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I The tandem chain extension-acylation reaction II
Synthesis of papyracillic acid A: Application of the
tandem homologation-acylation reaction III
Synthesis of tetrahydrofuran-based
peptidomimetics

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I. THE TANDEM CHAIN EXTENSION-ACYLATION REACTION

**II. SYNTHESIS OF PAPYRACILLIC ACID A: APPLICATION OF THE
TANDEM HOMOLOGATION-ACYLATION REACTION**

III. SYNTHESIS OF TETRAHYDROFURAN-BASED PEPTIDOMIMETICS

BY

Carley Meredith Spencer

B.A., Connecticut College, 2008

DISSERTATION

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

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in

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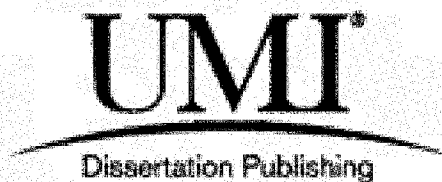
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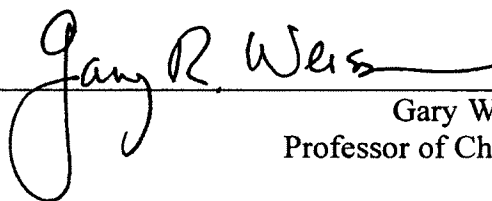


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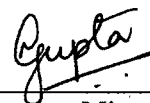
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DEDICATION

This dissertation is dedicated to my parents, John and Lisa Spencer.

*Without their endless support and encouragement I would not have gotten to where I am
today.*

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LIST OF ABBREVIATIONS

Bn	Benzyl
Boc	<i>t</i> -Butyloxycarbonyl
CAN	Ceric Ammonium Nitrate
CDI	Carbonyldiimidazole
Cbz	Carbobenzyloxy
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
LDA	Lithium Diisopropylamide
Me	Methyl
MOM	Methoxymethyl
Ph	Phenyl
PMB	<i>p</i> -Methoxybenzyl
TBDMS	<i>t</i> -Butyldimethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl

ABSTRACT

I. THE TANDEM CHAIN EXTENSION-ACYLATION REACTION

II. SYNTHESIS OF PAPYRACILIC ACID A: APPLICATION OF THE TANDEM HOMOLOGATION-ACYLATION REACTION

III. SYNTHESIS OF TETRAHYDROFURAN-BASED PEPTIDOMIMETICS

by

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A zinc-mediated tandem chain extension-acylation reaction was successfully developed. This reaction was optimized with the use of β -keto esters, amides, and imides as well as a variety of acylating agents. The tandem homologation-acylation reaction was successfully applied towards the total synthesis of papyracillic acid A.

Use of a tandem chain extension-aldol reaction, followed by a reductive cyclization, allowed for the synthesis of tetrahydrofuran-based peptidomimetics. A variety of amino acid derived β -keto imides and aldehydes were used during the initial tandem homologation-aldol reaction. High diastereocontrol was achieved during

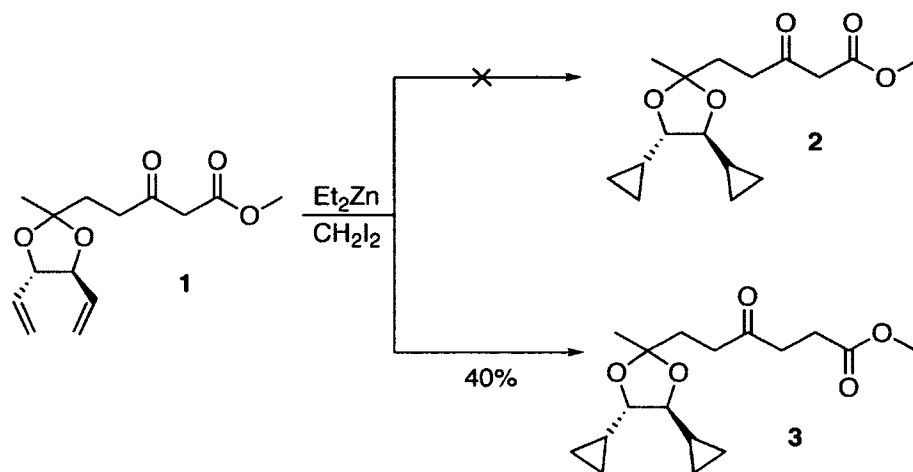
reductive cyclization when a *cis* relationship was present between the substituents on the tetrahydrofuran ring. Use of β -keto imides during the chain extension reaction was important as they led to the formation of the required *anti*-aldol products.

CHAPTER I

INTRODUCTION

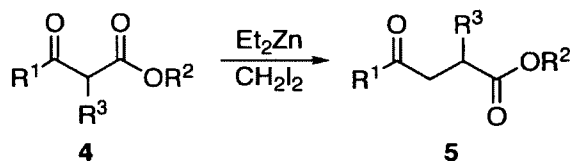
Zinc Carbenoid-Mediated Chain Extension Reaction

In 1997, Brogan and Zercher reported the discovery of a mild and efficient zinc carbenoid-mediated homologation reaction in which β -keto esters were converted to their γ -keto homologues.¹ In an attempt to synthesize intermediate **2** through cyclopropanation of the terminal olefins of ketal **1**, Brogan and Zercher discovered an unanticipated side product **3** in which an additional methylene unit had been inserted between the carbonyls forming a γ -keto ester (**Scheme 1**). This homologation was mediated by the same zinc-carbenoid used under standard Furukawa-modified Simmons-Smith cyclopropanation conditions.^{2,3}



Scheme 1: Discovery of the zinc-mediated chain extension reaction

This zinc-carbenoid mediated homologation was applied to simplified substrates in an attempt to elucidate the scope of the reaction. A variety of β -keto esters was subjected to a 1:1 mixture of diethylzinc and diiodomethane, which resulted in clean conversions in good yields to their respective γ -keto esters (**Table 1**). In general, the chain extension reaction tolerates bulky groups as well as those containing olefins. The ability to obtain olefin-containing γ -keto esters indicates that the chain extension reaction is more rapid than cyclopropanation of both electron rich (**4g**) and electron poor (**4h**) olefins. The low yield of compound **5i** revealed a reduced efficiency in the homologation of α -substituted γ -keto esters, possibly due to their increased steric bulk.



Entry	Starting Material	R ¹	R ²	R ³	Yield %
1	4a	Me	Me	H	81%
2	4b	Me	<i>t</i> -Bu	H	74%
3	4c	<i>i</i> -Pr	Et	H	68%
4	4d	<i>t</i> -Bu	Me	H	71%
5	4e	Ph	Et	H	58%
6	4f	Ph(CH ₂) ₂ -	Et	H	73%
7	4g	CH ₂ =CH(CH ₂) ₂ -	Me	H	74%
8	4h	PhCH=CH-	Me	H	68%
9	4i	Me	Me	Me	26%

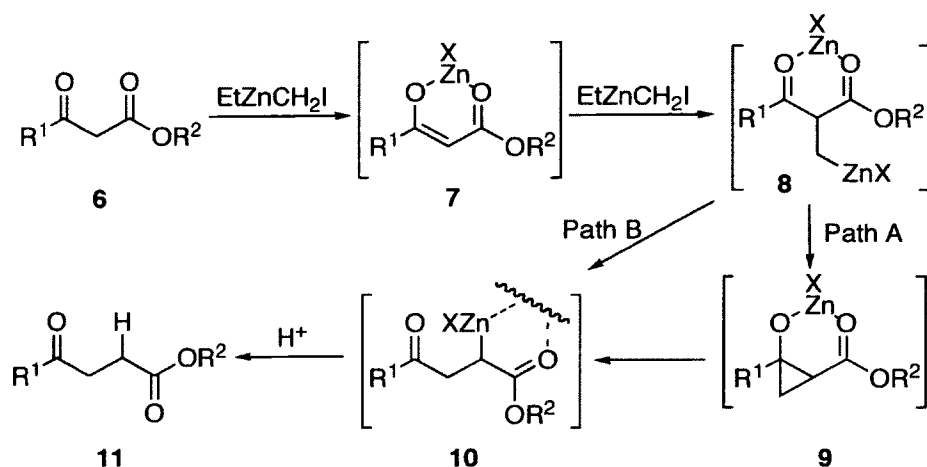
Table 1: Homologation of β -keto esters

Both experimental and computational methods^{4, 5} have been used to study the mechanism of this homologation reaction (**Scheme 2**). On the basis of these studies, the following mechanistic description has been proposed. Initially, one of the methylene protons α to the ester is removed resulting in the formation of zinc-enolate **7**. The deprotonation is performed by the ethyl residue of either diethylzinc or of the zinc carbenoid, as the formation of ethane has been observed by NMR studies.⁴ This enolate is then alkylated by zinc carbenoid, which provides homoenolate **8**.

From this point, there are two possible pathways by which the homologation can proceed. In pathway A, intramolecular cyclization of the homoenolate into the more electrophilic carbonyl affords a donor-acceptor cyclopropane (**9**). Fragmentation of this cyclopropane would afford zinc-enolate **10**. The donor-acceptor cyclopropane is a proposed mechanistic intermediate for related reactions,⁶⁻¹⁰ however spectroscopic

analysis of the zinc-mediated chain extension reaction failed to reveal this intermediate suggesting that this intermediate, if formed, is very short lived. Computational studies, in which the opening of the donor-acceptor cyclopropane is predicted to proceed with an energy barrier of 3-4 kcal/mol, are consistent with the short life of these proposed intermediates. Recent computations identified an alternate pathway in which homoenolate **8** is directly converted to zinc-enolate **10** (Path B).⁵

This zinc enolate (**10**) is thought to be the resting state of the reaction and appears similar to a Reformatsky-type intermediate.¹¹ The low reactivity of this organometallic intermediate is consistent with the oligomeric nature of the intermediate in solution.¹² Addition of a mild acid quenches the reaction and provides the desired γ -keto ester.

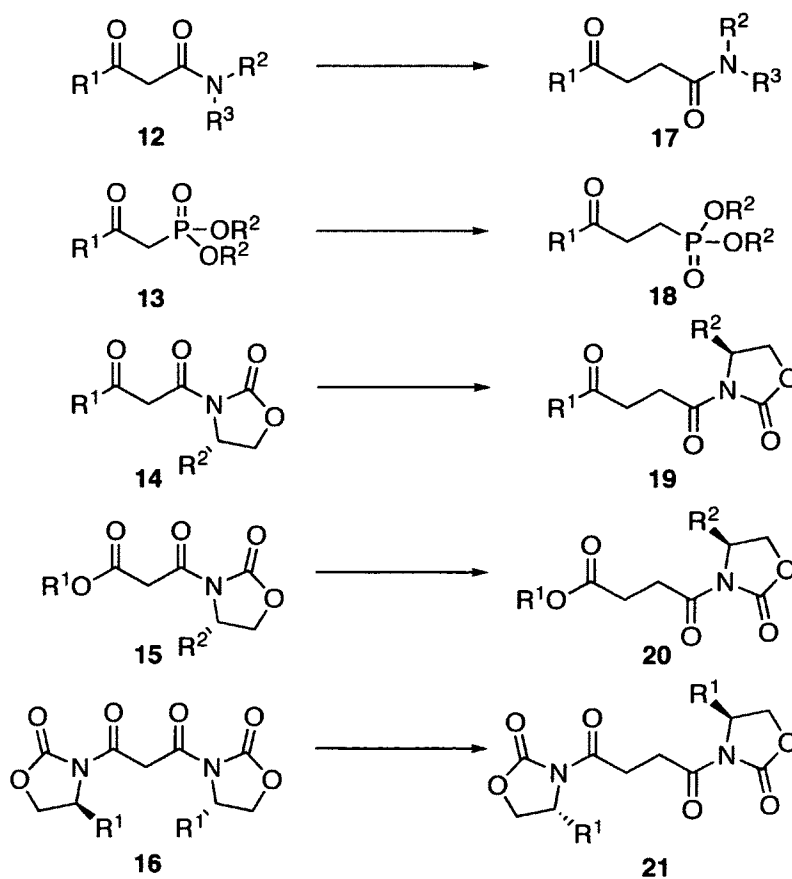


Scheme 2: Mechanistic pathway of the zinc-mediated chain-extension reaction

Since the initial report,¹ the zinc-mediated homologation reaction has been shown to tolerate a variety of functional groups, as well as to be amenable to tandem reactions.

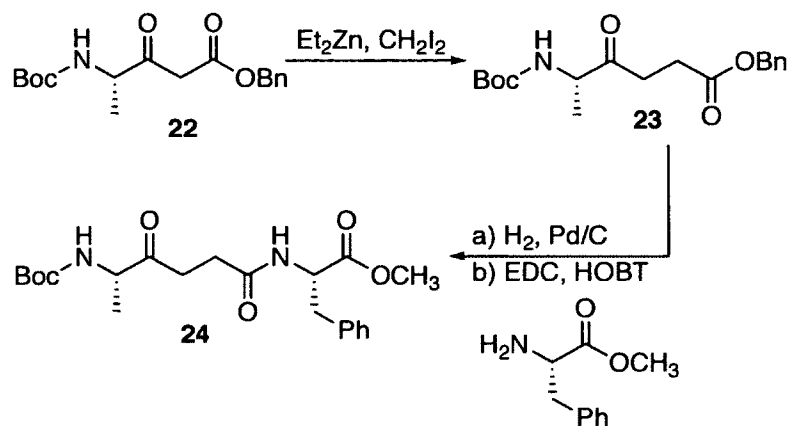
Various β -ketone-containing compounds have been shown to be suitable starting materials, and the ability to selectively functionalize both the α - and β -positions of the γ -keto product has been developed. Upon ring opening of intermediate **9**, anionic character is generated regioselectively, adjacent to the carboxylic acid derivative, which would be difficult to accomplish through direct deprotonation of a γ -keto ester. Addition of an electrophile to this zinc enolate allows for functionalization of this α -site. In addition, the proposed mechanism demonstrates incorporation of a methylene unit, originating from the zinc carbenoid, at the position β to the ester. Use of a substituted carbenoid allows for regioselective incorporation of functionality at the β -site. Use of 1,1-diiodoethane and α,α -diiodotoluene have allowed for incorporation of a β -methyl or β -phenyl group respectively. Details of these variations will be described below in greater depth.

The scope of the β -keto carbonyl starting materials capable of undergoing the zinc-mediated homologation reaction has been shown to include β -keto amides (**12**),¹³ β -keto phosphonates (**13**),¹⁴ β -keto imides (**14**),¹⁵⁻¹⁷ α -carboxyester imides (**15**),^{18, 19} and β -diimides (**16**) (Scheme 3).¹⁸ β -Keto compounds **12** - **16** can be cleanly converted to their corresponding homologues within 30 – 60 minutes, while β -diimides require slightly longer reaction times and produce more complex reaction mixtures.



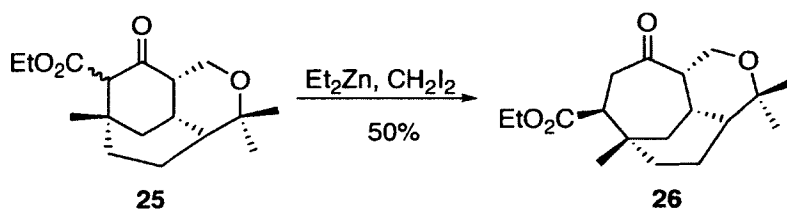
Scheme 3: Scope of β -keto carbonyls capable of undergoing zinc-mediated homologation

Subjection of amino acid derived β -keto esters, amides, and imides to the chain-extension reaction conditions has allowed for the facile synthesis of ketomethylene peptide mimetics (**Scheme 4**).²⁰⁻²² Ketomethylene mimetics are compounds that replace the amide bond of a natural peptide with a hydrolytically stable ketone. Their hydrolytic stability has allowed for their use in protease inhibition.^{23, 24} The ability to obtain a ketomethylene backbone in one step from its easily prepared β -keto ester homologue makes the zinc-mediated chain extension a synthetically powerful tool.



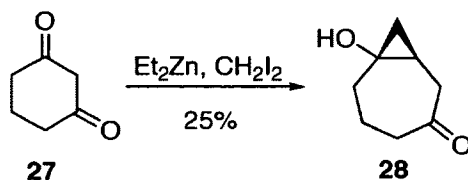
Scheme 4: Synthesis of the ketomethylene peptide mimetic

The zinc-mediated chain extension reaction has also been used as a key step in the synthesis of vibsane-type diterpenes. Williams and co-workers used chain extension reaction conditions to transform compound **25** to the ring-expanded homologue **26** (Scheme 5).²⁵ This reaction proceeded in good yield in spite of the α -substitution of the starting β -keto ester, which was previously shown to be a limitation of the chain extension reaction.



Scheme 5: Ring-expansion in the synthesis of vibsane-type diterpenes

Chain extension of β -diketones has resulted in slightly different results than those of other β -keto carbonyls. In the original report by Brogan and Zercher, the reaction of compound **27** with zinc carbenoid resulted in the formation of a γ -keto cyclopropanol (**Scheme 6**).¹



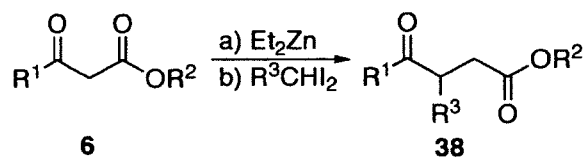
Scheme 6: Chain extension-cyclopropanation of β -diketone

This chain extension-cyclopropanation reaction has since been demonstrated on a variety of β -diketone starting materials.²⁶ The proposed reaction mechanism is similar to the homologation of β -keto esters; however, the zinc-intermediate **34** appears to react with a third equivalent of carbenoid to form a homoenolate (**35**) (**Scheme 7**). This homoenolate undergoes intramolecular cyclization to form cyclopropoxide **36**. Upon addition of a mild acid, the cyclopropoxide is protonated to yield a γ -keto cyclopropanol.

backbone. The ability to add functionality during the homologation reaction is, therefore, a synthetically powerful tool.

Functionalization of the β -position of the 1,4-dicarbonyl backbone has been accomplished through the use of substituted carbenoids derived from diethylzinc and a *gem*-diiodoalkane. There are a number of methods for the synthesis of *gem*-diiodoalkanes.^{28, 29} Subjecting benzaldehyde to trimethylsilyliodide at room temperature results in the formation of α,α -diiodotoluene.³⁰ 1,1-Diiodoethane may be synthesized through exposure of 1,1-dichloroethane to ethyl iodide and catalytic aluminum chloride.³¹ An alternative preparation of 1,1-diiodoethane is available in which acetaldehyde is first converted to its corresponding hydrazone, then treated with iodine in the presence of triethylamine.³²

Carbenoids derived from both 1,1-diiodoethane and α,α -diiodotoluene have been used to homologate both β -keto esters and β -keto amides (**Table 2**).³³ Incorporation of the β -substituent proceeded efficiently and in good yields when the zinc enolate was formed prior to the addition of the diiodoalkane. In some instances, a second portion of carbenoid was required for complete conversion to the γ -keto carbonyl. This is likely due to decomposition of the substituted carbenoid, which undergoes chain extension more slowly than the reaction utilizing diiodomethane.



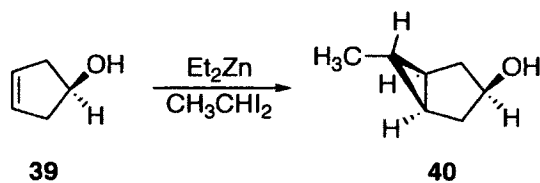
Entry	Starting Material	R ¹	R ²	R ³	% Yield
1	6a	Me	Me	Me	76
2	6b	Me	<i>t</i> -Bu	Me	88
3	6c	<i>t</i> -Bu	Me	Me	82
4	6d	Me	CH ₂ CH=CH ₂	Me	74
5	6e	Ph	Et	Me	84
6	6f	Me	Bn	Me	80
7	6g	Me	Me	Me	67
8	6h	Me	-(CH ₂) ₄ -	Me	74
9	6i	Me	Me	Ph	74
10	6j	Me	<i>t</i> -Bu	Ph	44

Table 2: Homologation using substituted carbenoids

Incorporation of a β -substituent during the homologation reaction results in the formation of a new stereocenter. Lin attempted to control the enantioselectivity of the reaction by introducing a chiral ligand into the reaction; however, a racemic mixture was obtained.¹⁶ Lin also attempted to control diastereoselectivity through the use of a chiral β -keto imide, but a 1:1 mixture of diastereomers was obtained.

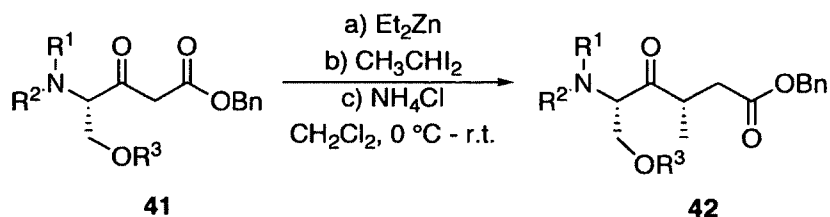
Homoallylic alcohols have been shown to provide high stereocontrol during cycloaddition reactions with methyl-substituted zinc carbenoid. For instance, cyclopropanation of 3-cyclopenten-1-ol (**39**) with methyl-substituted zinc-carbenoid resulted in exclusive formation of *exo*-6-methyl-*cis*-3-hydroxybicyclo[3.1.0]hexane (**40**)

out of four possible isomers (**Scheme 8**). It is believed that the mechanism of this cyclopropanation involves complexation of the zinc carbenoid to the hydroxyl group prior to cyclopropanation, allowing for a stereoselective ethylidene transfer to the most accessible face of the alkene.³⁴



Scheme 8: Stereocontrol of homoallylic alcohol **39** during zinc-carbenoid mediated cyclopropanation reaction

Mazzone exploited this homoallylic-directing effect by employing L-serine-derived β -keto esters in the chain extension reactions.³⁵ Exposure of L-serine-derived β -keto esters to substituted carbenoid resulted in a range of diastereomeric ratios of the β -methylated γ -keto esters (**Table 3**). High diastereoselectivity could be achieved, as seen in the homologation of compounds **41a-c**. When the hydroxyl functionality was restricted as with compound **41e**, all diastereocontrol was lost. This result suggests that the Lewis acid base interaction is important for high diastereoselectivity; however, more research is needed to understand the role that the oxygen is playing.



Entry	Starting Material	R ¹	R ²	R ³	dr
1	41a	Boc	H	Bn	20:1 ^{a,b}
2	41b	Boc	H	TBDMS	20:1 ^b
3	41c	Boc	H	MOM	15:1 ^a
4	41d	-C(O)OCH ₃	H	Et	3:1 ^a
5	41e	Boc			1:1 ^b

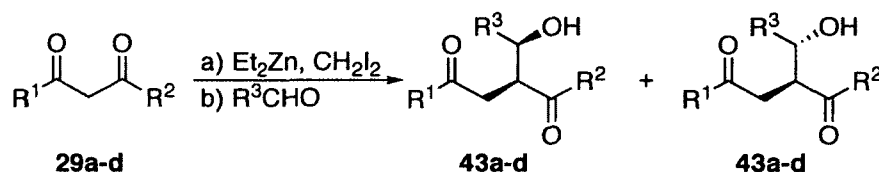
Table 3: Diastereoselective synthesis of β -methyl- γ -keto esters (^aDiastereomeric ratio was obtained from Bruker Top Spin line fit program, ^bDiastereomeric ratio was obtained from MestReNova line fit program)

Functionalization of the α -Position of the γ -Keto Backbone

Functionalization of the α -position may be achieved through the addition of an electrophile to organometallic intermediate **10**, which contains anionic character on the carbon α to the less electrophilic carbonyl. Addition of an electrophile allows the intermediate to be trapped, converting a 1,3-dicarbonyl to an α -substituted 1,4-dicarbonyl in a one-pot reaction.

Addition of an aldehyde or ketone to organometallic intermediate (**10**) results in the formation of the corresponding aldol products with high diastereoselectivity (**Table 4**). Treatment of β -keto esters and amides to the tandem chain extension-aldol reaction conditions has shown to favor the formation of *syn* aldol products. This high

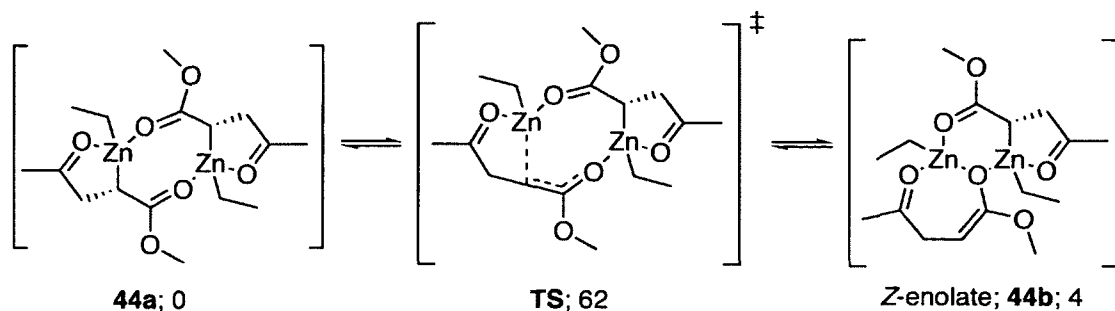
diastereoselectivity for zinc enolate reactions is unprecedented as Reformatsky reactions have rarely exceeded 50% de.³⁶



Entry	Starting Material	R ¹	R ²	R ³	Yield %	syn:anti
1	29a	<i>t</i> -Bu	OMe	Ph	97	12:1
2	29b	<i>t</i> -Bu	OMe	Ar	61	9:1
3	29c	Ar	OEt	Ar	57	7:1
4	29d	Me	OMe	<i>t</i> -Bu	85	>20:1
5	29e	Me	OMe	Ph	61	15:1
6	29f	Me	NPhMe	Me	46	3:1

Table 4: Diastereoselectivity in the tandem-chain extension aldol reaction

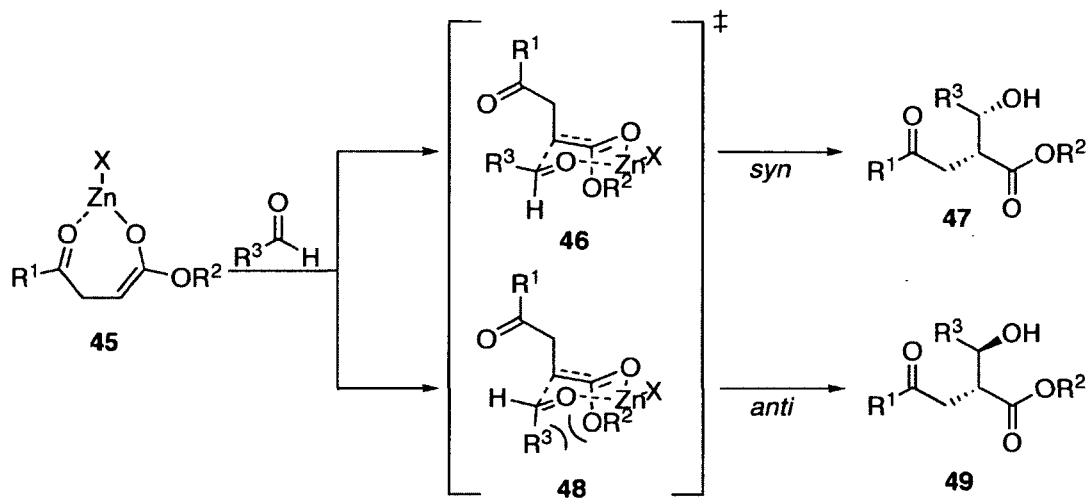
Recent computational studies suggest that the dimeric organometallic intermediate seen in the zinc-mediated chain extension reaction exists in equilibrium between a keto tautomer and the energetically similar *Z*-enolate (**Scheme 9**). All attempts to calculate the energy of the *E*-enolate resulted in the immediate relaxation to the more stable *Z*-enolate. Additionally, calculations support the assertion that upon addition of an aldehyde to the reaction mixture, the aldol reaction proceeds through a six-membered closed transition state.¹²



Scheme 9: Keto-to-enol tautomerization of dimeric organometallic intermediate **44**

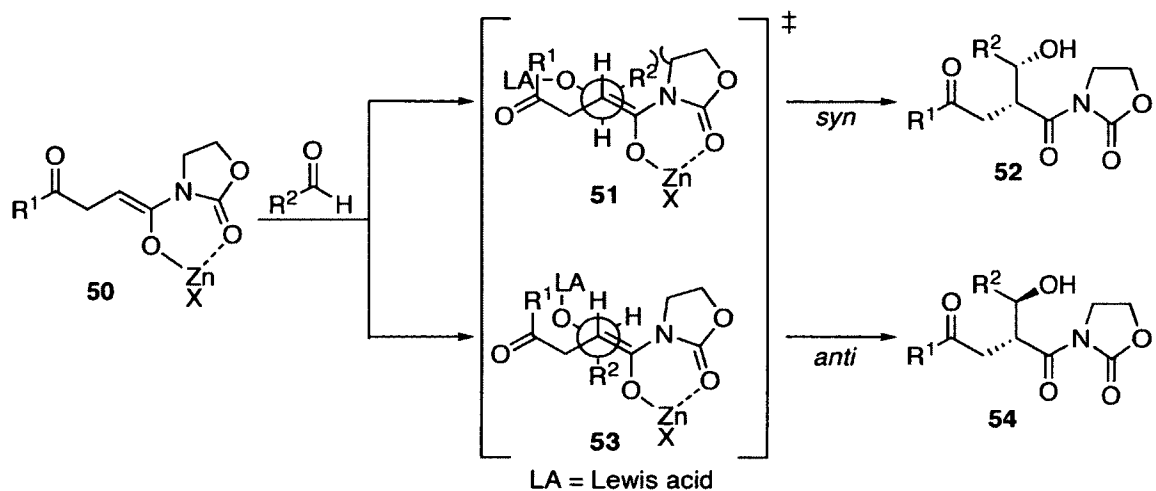
(Given numbers are Gibbs free energies relative to **44a** in kJ/mol)

The Zimmerman-Traxler model has been used to predict stereochemistry for aldol reactions that proceed through six-membered closed transition states. While the organometallic intermediate of the chain extension reaction is believed to be present as a dimer in solution, the Zimmerman-Traxler remains relevant to predict the stereochemistry of the aldol reaction.³⁷ The stereochemical outcome of the aldol reaction between *Z*-enolate **44b** and an aldehyde depends on the facial selectivity of the aldehyde (**Scheme 10**). When the aldehyde approaches with the R-group in a pseudo-equatorial position (**46**), the *syn*-isomer is obtained. When the aldehyde approaches with its R-group in a pseudo-axial position (**47**), the *anti* product is obtained. Having the R group of the aldehyde in a pseudo-axial position creates a 1,3-diaxial interaction making the *anti*-product less favorable. The high *syn*-selectivity of the tandem chain-extension aldol reaction is consistent with this model.



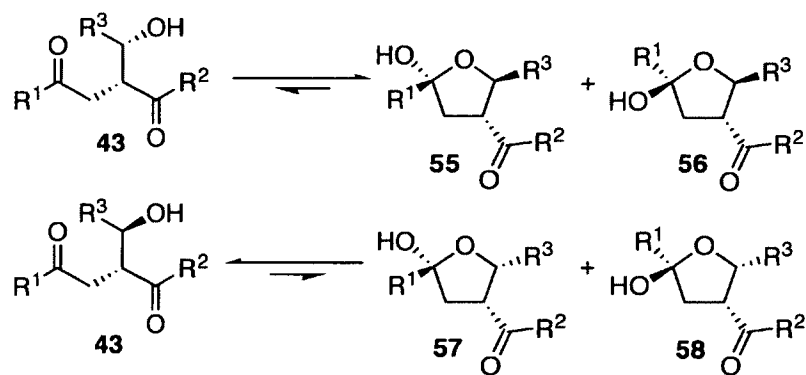
Scheme 10: Zimmerman-Traxler model for Z-enolate

Tandem chain extension-aldol reactions with β -keto imides strongly favor the formation of *anti*-aldol products. This result is consistent with an open transition state model in which an equivalent of Lewis acid chelates between the two oxygen atoms of the imide and a second equivalent of Lewis acid activates the aldehyde (**Scheme 11**).³⁸ In this open transition state model, attack of the enolate on one face of the aldehyde leads to a steric interaction between the R group of the aldehyde and the imide. Attack of the enolate on the opposite face of the aldehyde minimizes this steric interaction making the *anti*-product more favorable.



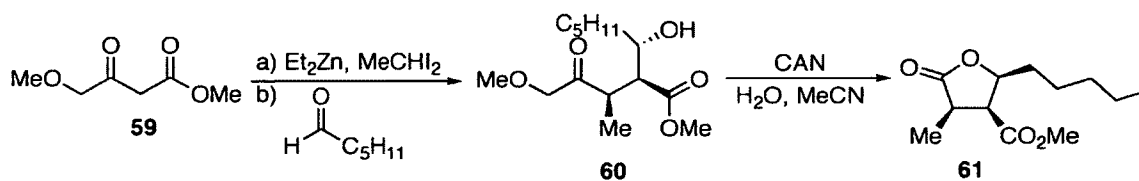
Scheme 11: Open transition state of *Z*-enolate

Analysis of the diastereoselectivity in the tandem homologation-aldol reaction can be difficult due to an equilibrium that exists between both the open and closed (hemiketal) forms of each diastereomer (**Scheme 12**). The *syn*-aldol products exist predominantly as the closed hemiketal isomers; whereas *anti*-aldol products typically contain less of the hemiketal forms. These preferences may be rationalized by steric interactions between the carbonyl and R^3 -substituent.



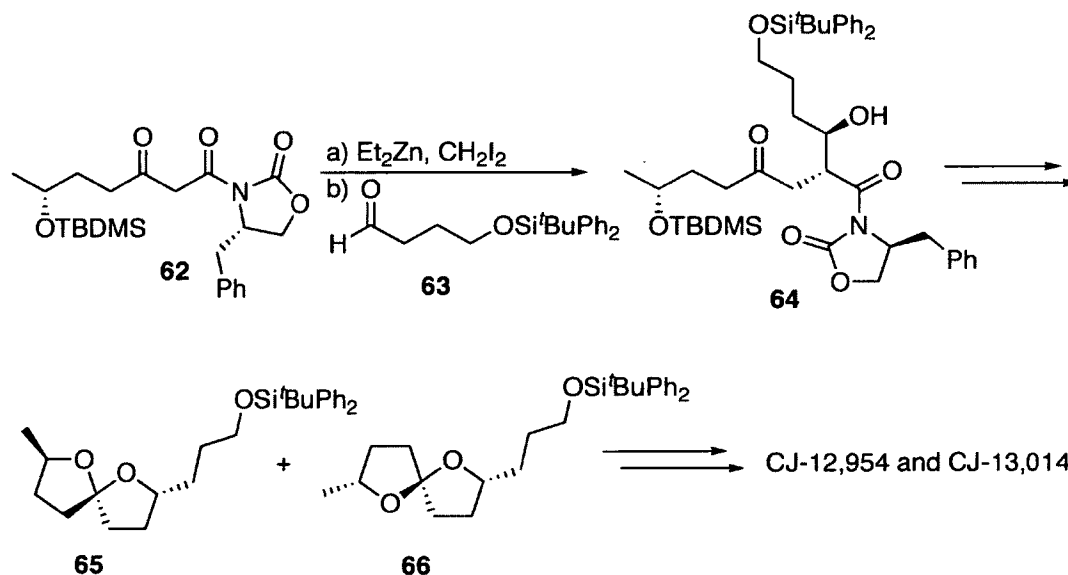
Scheme 12: Equilibrium between open chain and closed hemiketal isomers

A method discovered by Lin allows selected hemiketals formed in the tandem homologation-aldol reaction to be transformed into substituted γ -lactones via an oxidative cleavage in which ceric ammonium nitrate (CAN) is proposed to chelate to the hemiketal oxygen.¹⁶ Jacobine showed that it is possible to target the paraconic acid family of natural products through this methodology.^{39, 40} Paraconic acids are trisubstituted γ -butyrolactones that have drawn interest due to their antibiotic and antitumor properties.⁴¹ In order to synthesize these compounds through the zinc-mediated chain extension chemistry, both the α - and β -positions of the γ -keto ester need to possess substituents. Jacobine accomplished the synthesis of a phaseolinic acid derivative by performing a tandem chain extension-aldol reaction using a substituted carbenoid followed by CAN-oxidation to form the substituted γ -butyrolactone (**Scheme 13**). This was the first example of a tandem chain extension reaction performed while using substituted carbenoid. The incorporation of a β -substituent before trapping the aldehyde gave an unanticipated result. In tandem chain extension-aldol reactions starting from a β -keto ester, the major product is normally the *syn*-aldol product. Jacobine noted that the presence of a β -methyl substituent led to the formation of the *anti*-aldol product as the major isomer. In other words, the β -stereocenter controlled facial selectivity on the enolate and biased facial selectivity of the aldehyde.



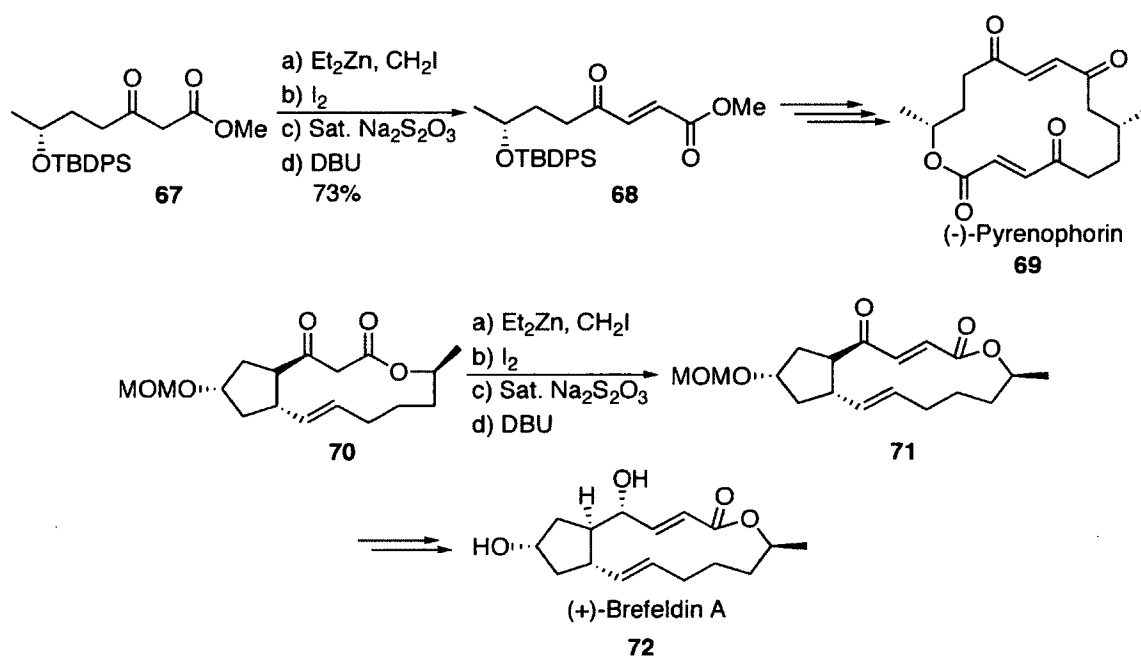
Scheme 13: Synthesis of phaseolinic acid derivative

The tandem chain extension-aldol reaction has also been applied towards the formal synthesis of CJ-12,954 and CJ-13,014.^{4, 42} A tandem chain extension-aldol reaction followed by spirocyclization allows access to the spiroketal cores of the advanced intermediates of the two natural products (**Scheme 14**). Conversion of these intermediates to the natural products would be possible by application of the strategy outlined by Brimble and co-workers.⁴³



Scheme 14: Formal synthesis of CJ-12,954 and CJ-13,014 through the chain extension-spirocyclization reaction

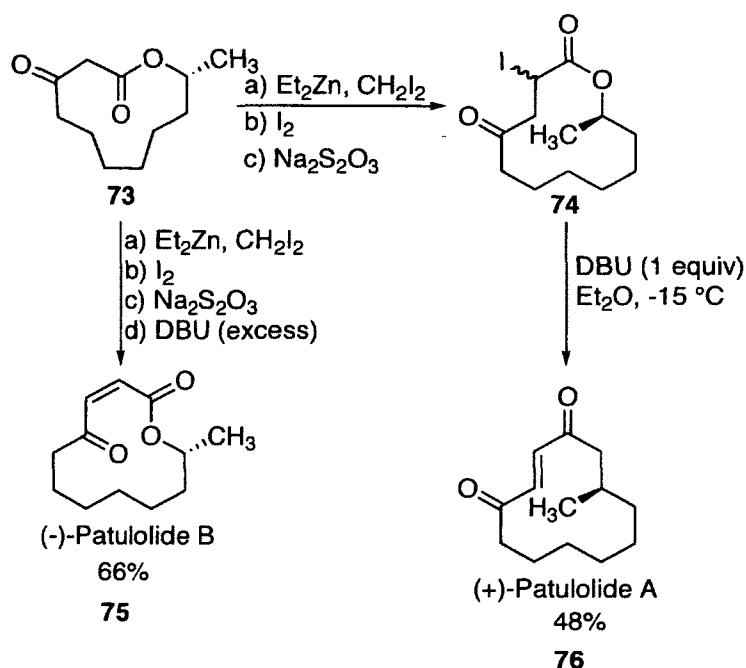
Incorporation of a halogen at the α -position of a γ -keto carbonyl followed by elimination provides access to α,β -unsaturated γ -keto carbonyls.⁴⁴ The development of this tandem chain extension-oxidation-elimination reaction has led to the formal syntheses of (-)-Pyrenophorin⁴⁵ and (+)-Brefeldin A.¹⁶



Scheme 15: Formal synthesis of (-)-Pyrenophorin and (+)-Brefeldin A

The tandem chain extension-oxidation-elimination reaction has also been applied to the total synthesis of (+)-Patulolide A and (\pm)-Patulolide B (Scheme 16).⁴⁶ The synthesis of these natural products demonstrated the applicability of the homologation-oxidation-elimination reaction to macrocyclic β -keto lactones. In addition, the olefin

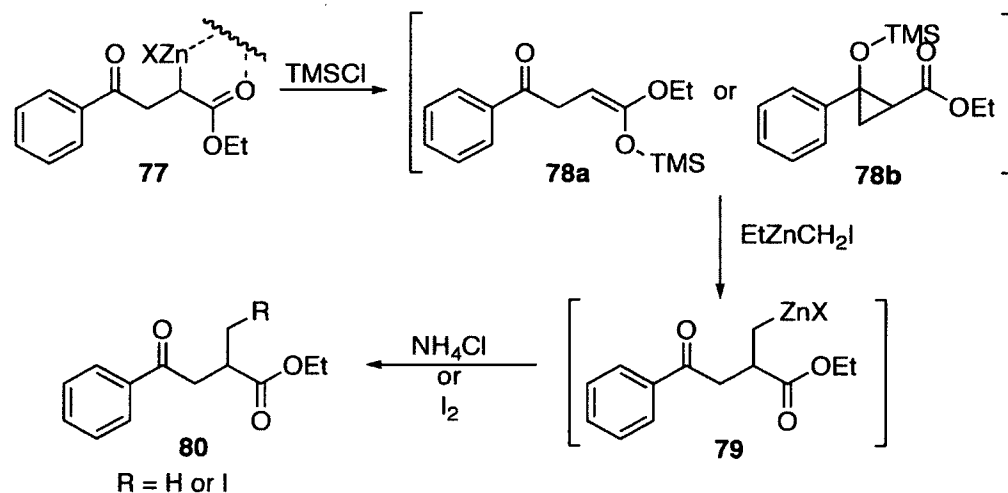
stereochemistry was influenced by use of kinetic or thermodynamic control in the elimination reaction.



Scheme 16: Total synthesis of Patulolide A and B

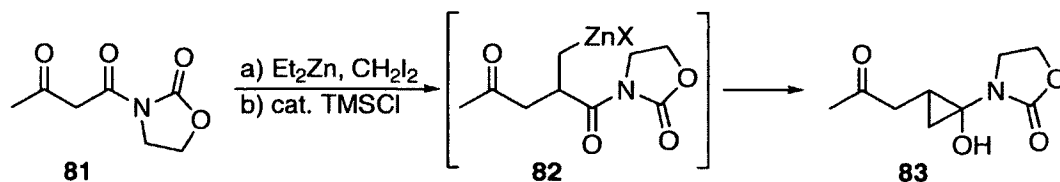
Another set of tandem reactions allows for the synthesis of α -methylated⁴⁷⁻⁴⁹ and α -iodomethylated^{50, 51} γ -keto carbonyls. Addition of a Lewis acid such as trimethylsilylchloride (TMSCl) appears to promote fragmentation of the dimeric zinc-enolate **77**. This fragmentation results in the formation of an activated nucleophile capable of reacting with another equivalent of zinc-carbenoid. Anionic character of the newly formed homoenolate (**79**) may be quenched with a mild acid to form α -methylated γ -keto carbonyls or with iodine to form α -iodomethylated γ -keto carbonyls (**Scheme 17**). Formation of α -iodomethylated γ -keto carbonyls introduces a handle that has been shown

to be capable of being further manipulated, through both cross coupling reactions and nucleophilic displacement of the iodide.^{50, 51}



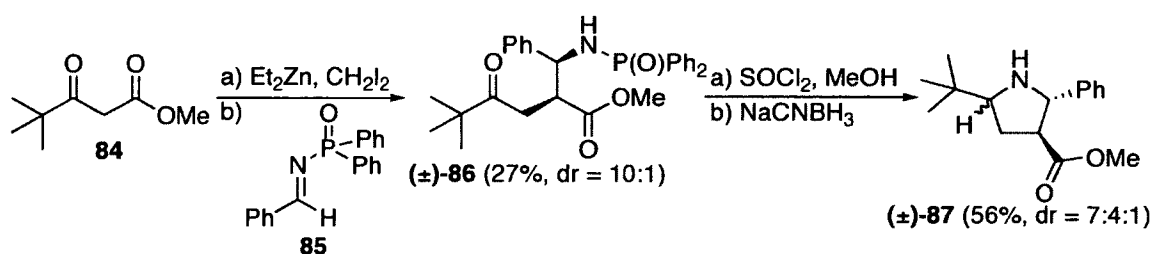
Scheme 17: Synthesis of α -methylated or α -iodomethylated γ -keto ester

An interesting byproduct seen in the tandem chain extension-methylation reaction of some β -keto imides was the corresponding γ -keto cyclopropanol **83** (Scheme 18).^{16, 50} The mechanism for its formation is believed to involve attack of the homoenolate **82** into the imide carbonyl before the reaction is quenched. This reaction mechanism is believed to be similar to the tandem homologation cyclopropanation reaction of β -diketones. Formation of these cyclopropanol compounds is not observed with β -keto esters or amides; however, the imide functionality, which is a better electrophile than either an ester or amide, is able to react in a similar fashion to the β -diketones.



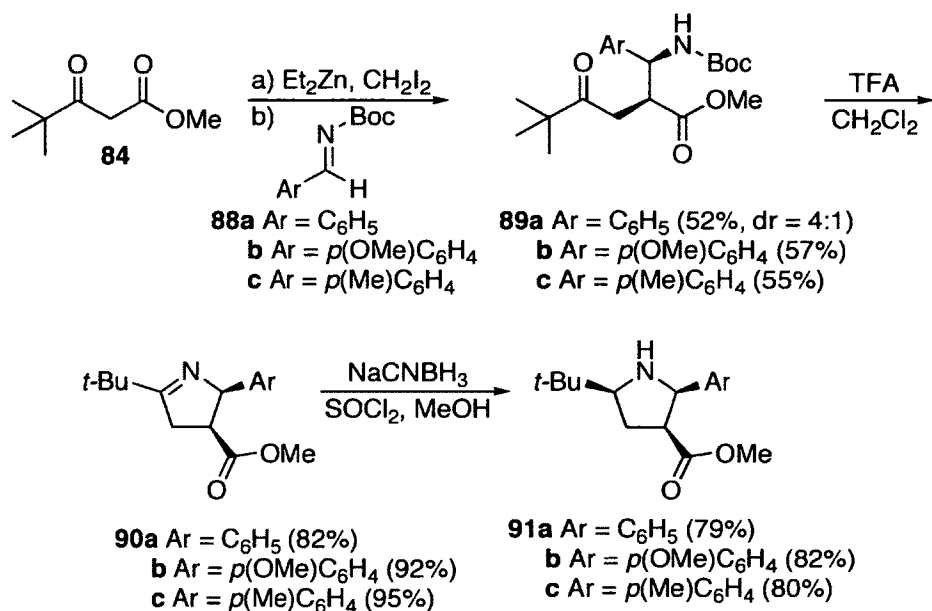
Scheme 18: Synthesis of cyclopropanol **83** under chain extension-methylation reaction conditions

One of the more recently developed tandem homologation reactions involved the use of activated imines. Jacobine developed the tandem chain extension-Mannich reaction as a method to target the synthesis of β -proline derivatives.^{39, 52} The reaction between the organometallic intermediate and *N*-phosphinoylimine **85** resulted in the formation of β -amino acid **86**, albeit in modest yield. A one-pot protocol was developed to synthesize β -proline derivatives through deprotection of the phosphinoyl group and subsequent reduction of the resulting cyclic imine (**Scheme 19**).



Scheme 19: Tandem chain extension-imine capture reaction with diphenylphosphinoyl imine **85**

The tandem chain extension-imine capture reaction of the organometallic enolate with the more reactive Boc-activated aryl imines proceeds more rapidly and in higher yields than those achieved with diphenylphosphinoyl imine. Deprotection of the β -amino acid was effected through exposure to trifluoroacetic acid (TFA). The resulting cyclic imine could then be reduced to the corresponding β -proline derivative by treatment with sodium cyanoborohydride (NaCNBH₃) (Scheme 20).



Scheme 20: Tandem chain extension-imine capture reaction with Boc-activated imines

It was noted that the nitrogen-protecting group controls the diastereoselectivity of the chain extension-imine capture reaction. The complementary diastereocontrol seen between the phosphinoyl imines and Boc-protected imines allows for the synthesis of either *anti* or *syn* β -proline derivatives, respectively. In addition, control of the absolute

stereochemistry of the β -proline derivatives through the homologation of a chiral β -keto imide is possible.

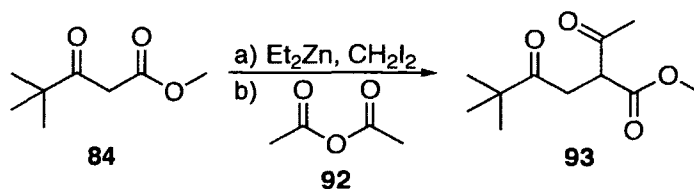
Use of tandem zinc-mediated chain extension reactions has been developed as an efficient and facile method of synthesizing substituted 1,4-dicarbonyl compounds. The ability to control diastereoselectivity in the incorporation of functional groups has proven useful in targeted synthesis. The expansion of the chain extension methodology to an even wider range of products continues to be a focal point of current research.

CHAPTER II

THE TANDEM CHAIN EXTENSION-ACYLATION REACTION

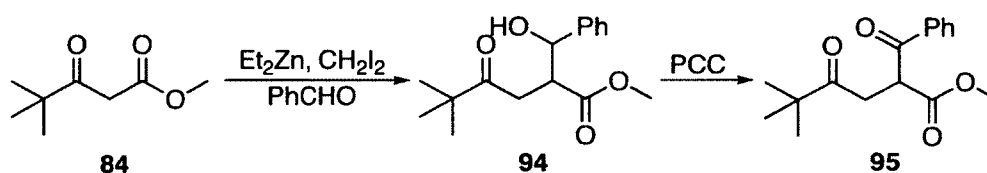
Discovery of the Tandem Homologation-Acylation Reaction

Jacobine recently reported that the chain extension methodology could be used to trap anhydrides in a tandem chain extension-acylation reaction.³⁹ Methyl pivaloylacetate (**84**) was subjected to zinc carbenoid followed by treatment with acetic anhydride. An α -acylated γ -keto ester **93** was efficiently produced (**Scheme 21**).



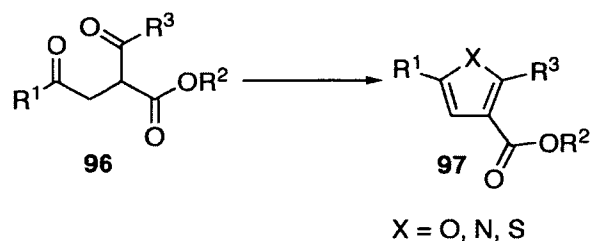
Scheme 21: First example of the tandem chain extension-acylation reaction

Taddei and co-workers previously synthesized a similar α -acylated γ -keto ester through a tandem homologation-aldol reaction followed by oxidation of the aldol product to the corresponding tricarbonyl compound (**Scheme 22**).⁵³ A number of oxidizing agents were examined and it was found that pyridinium chlorochromate (PCC) was generally required for complete conversion. Direct conversion of β -keto esters to their α -acylated γ -keto ester counterparts offers an advantage to the Taddei approach, since a synthetic step is avoided and the use of a toxic oxidizing agent, PCC, is not required.



Scheme 22: Synthesis of α -acylated γ -keto esters by tandem chain extension-aldol followed by oxidation

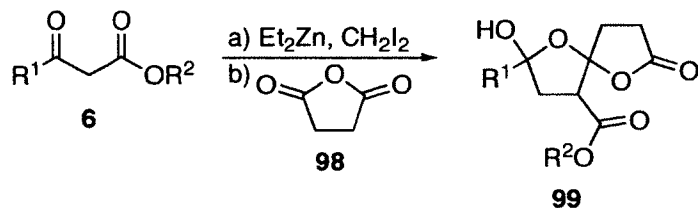
Use of a Paal-Knorr synthesis allows for the conversion of the α -acylated γ -keto carbonyl products to highly functionalized furans, pyrroles, and thiophenes (**Scheme 23**). These heterocycles are of synthetic interest as they are found abundantly in natural products and have found wide use in pharmaceuticals as well as materials science.⁵⁴⁻⁵⁸ Use of the tandem chain extension-acylation reaction to form the precursor for heterocycle formation is attractive, since the chain extension methodology allows for substitution to be controlled at every position of the heterocycle.



Scheme 23: Paal-Knorr synthesis of highly functionalized heterocycles

Tandem Chain Extension-Acylation with Cyclic Anhydrides

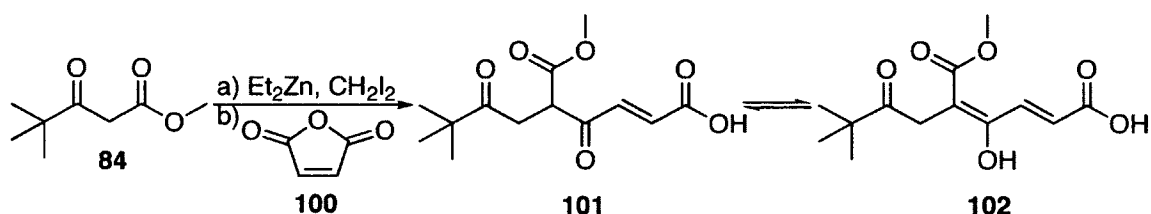
Initial investigations into the scope of the tandem chain extension-acylation reaction performed by Mazzone made use of cyclic anhydrides as acylating agents.³⁵ Cyclic anhydrides were used in an attempt to target a spiroketal ring system, a common motif found in natural products (**Scheme 24**).⁵⁹



Scheme 24: Synthesis of spiroketal **99** through the tandem chain extension-acylation reaction

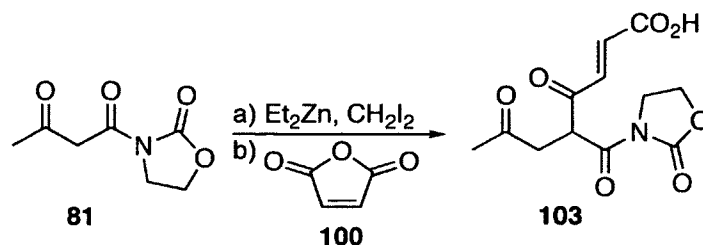
Mazzone began by subjecting methyl pivaloylacetate to chain extension reaction conditions and then treating the intermediate with maleic anhydride. This gave rise to a mixture of products. Analysis of the crude reaction mixture by ¹H and ¹³C NMR showed the main product to be the α -acylated γ -keto ester, in which the double bond of maleic

anhydride had undergone isomerization to the more thermodynamically stable *E*-alkene (Scheme 25). This identification was made through the measurement of the dominant alkene coupling constants in the ^1H NMR spectrum. A 3J coupling constant of 15.8 Hz was observed, which is consistent with that of an *E*-alkene.⁶⁰ The acylated product existed as a mixture of both the keto and enol tautomers. The relatively high concentration of the enol tautomer was most likely due to an extended conjugation between the ester and carboxylic acid.



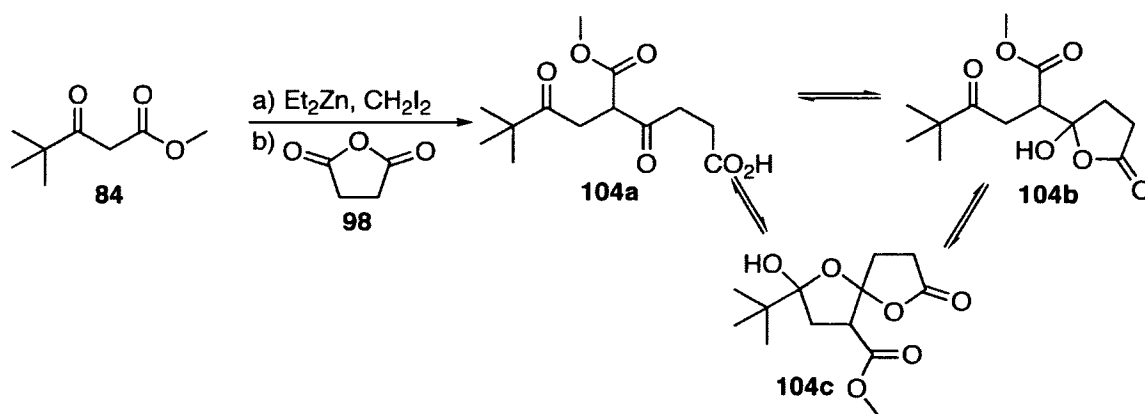
Scheme 25: Tandem chain extension-acylation of methyl pivaloylacetate using maleic anhydride

Mazzone also investigated alternative starting β -keto carbonyls.³⁵ Treatment of a more sterically bulky β -keto imide with the same tandem homologation-acylation reaction conditions did not prevent isomerization of the initial *Z*-alkene. Upon analysis of the crude reaction mixture an alkene 3J coupling constant of 15.8 Hz was observed, suggesting that steric bulk plays no role in preventing isomerization (Scheme 26).



Scheme 26: Tandem chain extension-aldol reaction of β -keto imide **81** with maleic anhydride **100**

Next, Mazzone studied the use of an aliphatic cyclic anhydride since it removed the possibility of double bond isomerization. Exposure of methyl pivaloylacetate to zinc carbenoid followed by treatment with succinic anhydride resulted in the formation of the α -acylated γ -keto ester in equilibrium with two other isomeric compounds, including the desired spiro-ketal (**104**) (**Scheme 27**). This result demonstrated the ability to obtain a spiro-ketal under tandem chain extension-acylation conditions.

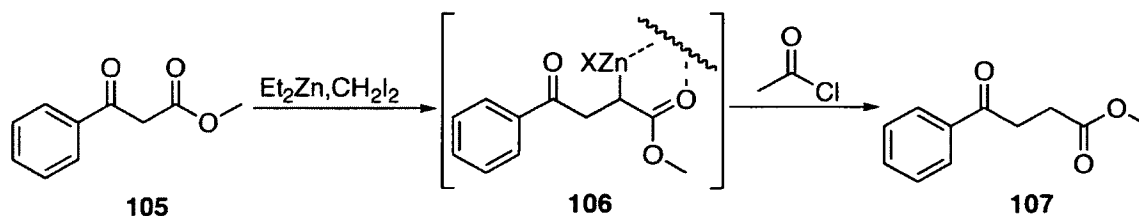


Scheme 27: Tandem chain extension acylation with succinic anhydride

While Mazzone was able to show that cyclic anhydrides can be trapped by the zinc-enolate formed during the chain extension reaction, the ability for the acylation products to exist as multiple isomers made purification and analysis difficult. General yields of the acylation reaction, as well as the ability to use a broader range of acylating agents, were not investigated by Mazzone.

Expansion of Methodology

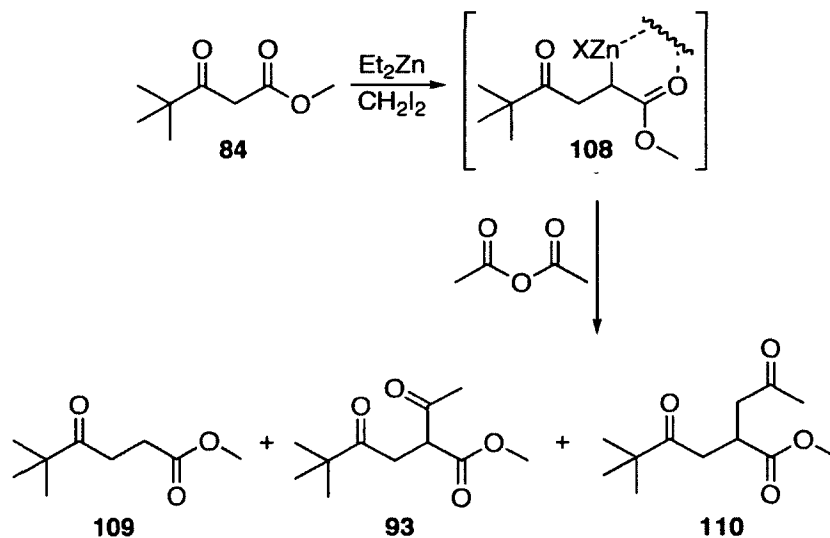
Our initial studies into the more general scope of the tandem chain extension-acylation reaction included the use of acid chlorides as possible acylating agents. Treatment of methyl benzoylacetate (**105**) with zinc carbenoid followed by addition of acetyl chloride resulted in the formation of unsubstituted γ -keto ester **107** (**Scheme 28**). The lack of α -acylated product was believed to result from protonation of organometallic intermediate **106** via acidic impurities in the acid chloride. Additionally, intermediate **106** could have been quenched by deprotonation of acetyl chloride. This would result in the formation of both unsubstituted γ -keto ester **107** as well as a ketene derived from the acid chloride.



Scheme 28: Tandem chain extension-acylation using an acid chloride acylating agent

Protonation of intermediate **106** when using an acid chloride turned focus back to the use of anhydrides as the acylating agent of choice. Optimization of the acylation reaction conditions demonstrated that order of addition and the stoichiometry of reagents played important roles in minimizing the formation of unwanted byproducts. Treatment of methyl pivaloylacetate with three equivalents of carbenoid followed by the addition of acetic anhydride led to the formation of three products: γ -keto ester **109**, the desired acylated product (**93**), as well as a further homologue of the acylation product (**110**) (**Table 5**). Formation of compound **110** was most likely due to the homologation of the β -keto ester formed in the initial chain extension-acylation reaction.

The formation of β -keto ester **93** introduced an acidic proton capable of quenching intermediate **108**, thereby providing the first by-product, γ -keto ester **109**. Once the acylated product **93** is deprotonated, the enolate can react with another equivalent of carbenoid, producing the second by-product (**110**). The yield of the desired acylated product was greatly improved upon treatment of methyl pivaloylacetate with three equivalents of diethylzinc, followed by one equivalent of diiodomethane and finally 1.5 equivalents of acetic anhydride. The first equivalent of diethylzinc deprotonated methyl pivaloylacetate (**84**), while a second equivalent reacted with diiodomethane to effect homologation to the γ -keto ester. Formation of only one equivalent of carbenoid prevented further homologation of compound **93**. The third equivalent of diethylzinc was used to deprotonate the acidic proton on compound **93**, preventing the organometallic intermediate **108** from being quenched before acylation was able to take place.

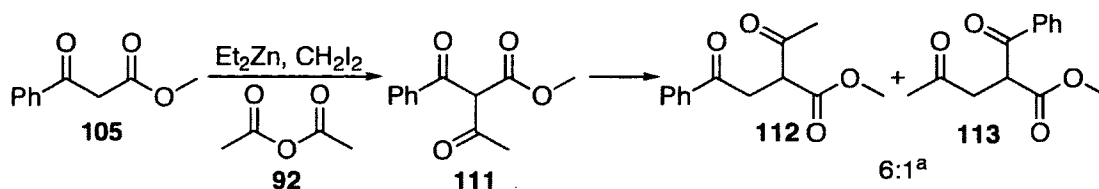


Entry	Et_2Zn (equiv)	CH_2I_2 (equiv)	Anhydride (equiv)	109(%) ^a	93(%) ^a	110(%) ^a
1	3	3	1	30	24	46
2	3	1	1.5	17	83	0
3 ^b	4	4	1	28	11	61

Table 5: Optimization of tandem homologation acylation reaction using methyl pivaloylacetate (^a Relative abundance using relative integrations from ¹H NMR analysis of the crude reaction mixtures; ^b Diethylzinc and methyl pivaloylacetate were stirred for 10 min prior to adding diiodomethane)

Treatment of methyl pivaloylacetate with four equivalents of carbenoid followed by the addition of acetic anhydride demonstrated that it is possible to bias the tandem chain extension-acylation reaction toward the formation of the further homologated product **110**. The double chain extension reaction was further investigated by St. Jean, who demonstrated that double chain extended products were most easily obtained when using an acylating agent with little steric bulk.⁶¹ In addition, the second homologation can be accomplished with bulkier acyl groups by resubjecting the α -acylated γ -keto ester to zinc carbenoid.

Order of addition of the reagents also plays a role in minimizing unwanted byproducts. When acetic anhydride was added to the homologation reaction of methyl benzoylacetate before the initial chain extension reaction took place, a regioisomer of the acylated γ -keto ester was observed (**Scheme 29**). The formation of two isomers may be explained by the formation of compound **111** prior to homologation. Compound **111** contains two β -keto esters, both capable of undergoing homologation. By ensuring that the starting β -keto ester has chain-extended before addition of the anhydride, the formation of the undesired regioisomer is avoided.

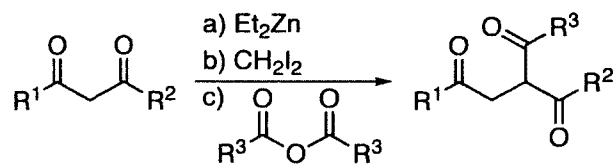


Scheme 29: Formation of a regioisomer during the tandem chain extension-acylation reaction (^aRelative integrations from ¹H NMR analysis of the crude reaction mixture)

Upon optimization of the tandem homologation acylation reaction conditions, a range of β -keto carbonyl substrates and acylating agents were used to examine their impact of the efficiency of the reaction (**Table 6**). Of the acylating agents used to trap the organometallic intermediate, benzoic anhydride and isobutyric anhydride provided higher yields than acetic anhydride. It is possible that bulkier acylating agents slow the deprotonation of the acylated products, thereby preventing the quenching of the organometallic intermediate and conversion to the double chain extended product. This is

consistent with the results seen by St. Jean, which showed slower formation of double chain extended products containing bulky R groups.

Use of a range of β -keto esters demonstrated that the presence of bulky or aromatic substituents on the ketone or ester do not hinder the efficiency of the acylation reaction. Use of a β -keto amide in the tandem acylation reaction also proved to be efficient in the production of an α -acylated γ -keto amide. When β -keto imide **120** (entry 11) was subjected to tandem chain extension-acylation reaction conditions, the γ -keto homologue was obtained as a 6:1 mixture of diastereomers in a combined yield of 80%. Reduced yields were observed in the tandem homologation-acylation reactions of allyl acetoacetate and *t*-butyl acetoacetate. These reduced yields may be explained by Lewis acid-catalyzed decomposition of the esters.

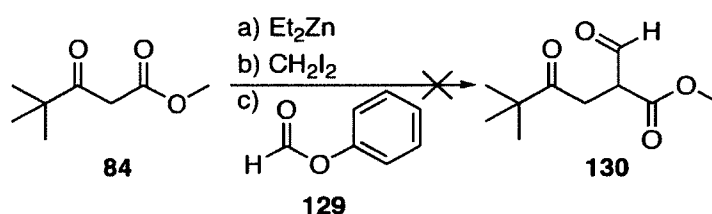


Entry	Starting Material	R ¹	R ²	R ³	Product	Yield (%)
1	84	<i>t</i> -Bu	OMe	Me	93	63
2	84	<i>t</i> -Bu	OMe	<i>i</i> -Pr	117	80
3	84	<i>t</i> -Bu	OMe	Ph	95	95
4	117	Me		Me	118	36
5	117	Me		Ph	119	51
6	118	Me	OAllyl	Me	120	44
7	118	Me	OAllyl	Ph	121	73
8	105	Ph	OMe	Me	112	55
9	105	Ph	OMe	Ph	122	51
10	119	Me	NPhMe	Ph	123	62
11	120			Ph	124	80

Table 6: Scope of the tandem chain extension-acylation reaction

Phenyl formate was used as an acylating agent during the tandem homologation acylation reaction in an attempt to obtain an α -formylated γ -keto ester (**Scheme 30**). Upon exposure of methyl pivaloylacetate to zinc carbenoid and subsequent treatment with phenyl formate, ¹H NMR analysis showed consumption of all starting material; however, none of the desired product was present. It is possible that the α -formylated γ -keto ester was synthesized and was too reactive under the tandem chain extension-

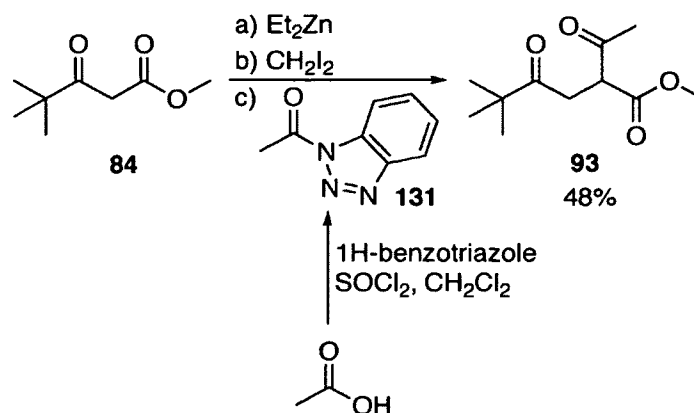
acylation reaction conditions, undergoing further chemistry and preventing compound **130** from being isolated.



Scheme 30: Tandem chain extension-formylation

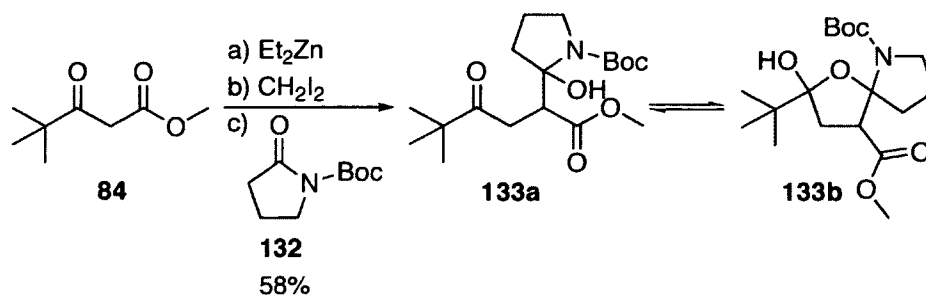
One drawback to using an anhydride as an acylating agent is that half of the corresponding carboxylic acid is sacrificed. If the tandem homologation-acylation reaction were to be used in a longer synthetic pathway, avoiding this sacrifice would be desirable. Even though acid chlorides were shown to be ineffective acylating agents, an activated carboxylic acid was proposed to be an acylating agent that would circumvent the inefficiency of the anhydride.

Benzotriazole-activated carboxylic acids are easily prepared through treatment of a carboxylic acid with 1H-benzotriazole and thionyl chloride (**Scheme 31**). The activated products are usually obtained as solids with clean conversion, which makes them easy to handle. Addition of benzotriazole-activated acetic acid to the intermediate zinc enolate resulted in the formation of the α -acylated γ -keto ester in a slightly reduced yield (48%) as compared to that obtained when using acetic anhydride. Benzotriazole activation of carboxylic acids, therefore, provides a useful alternative to the use of anhydrides generated from precursor carboxylic acids.



Scheme 31: Tandem homologation acylation with activated acetic anhydride

Similar to the cyclic anhydrides that were used by Mazzone to target a spiro-ketal core, the use of a Boc-protected lactam was proposed to allow access to an azaspiro-fused ring system. Treatment of methyl pivaloylacrylate under tandem chain extension-acylation reaction conditions in which Boc-pyrrolidine (**132**) was used as an acylating agent resulted in the formation of α -acylated γ -keto ester (**Scheme 32**). The acylated product (**133**) was isolated as a mixture of two isomers in an 80% yield.



Scheme 32: Tandem chain extension-acylation using a cyclic imide

In summary, the tandem chain extension-acylation reaction is an efficient reaction. A variety of both starting β -keto substrates and acylating agents are tolerated, allowing access to a vast array of α -acylated γ -keto carbonyls and spiro-fused ring systems. Future application of this reaction could involve the synthesis of highly substituted aromatic heterocycles.

CHAPTER III

SYNTHESIS OF PAPYRACILLIC ACID A: APPLICATION OF THE TANDEM HOMOLOGATION-ACYLATION REACTION

Papyracillic Acid Family of Natural Products

Papyracillic acid A was isolated from the ascomycete fungus *Lachnum papyraceum* in 1996.⁶² The structure of papyracillic acid A was determined to contain a spiro-fused acetal core with structural similarities to penicillic acid, a classical mycotoxin (Figure 1). Both of these natural products exist in equilibrium with open-chained isomers. Papyracillic acid A has been reported to exist as a 1:1:2:4 mixture of isomers.

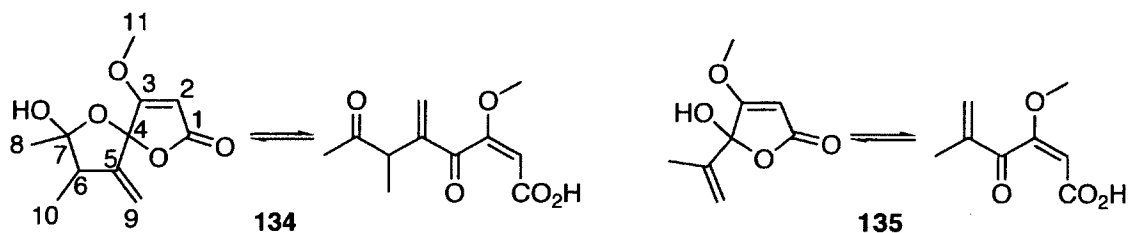
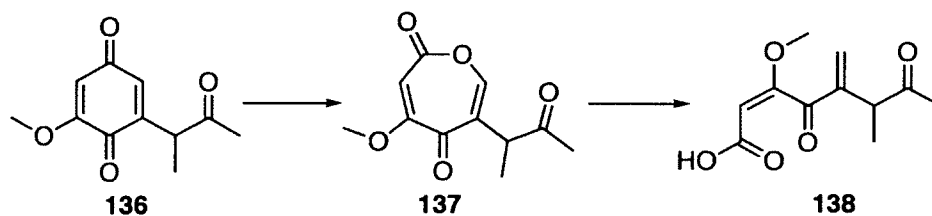


Figure 1: Structural comparison of papyracillic acid A (134) and penicillic acid (135)

Due to the structural similarities between papyracillic acid A and penicillic acid, it has been proposed that the biosynthetic pathways could be similar as well. The last steps of penicillic acid formation makes use of a Bayer-Villiger type oxidation of a benzoquinone intermediate followed by a ring opening.^{63, 64} While it has yet to be isolated from *L. papyraceum*, compound **136** has been proposed as a biosynthetic intermediate in the formation of papyracillic acid A. Oxidation to seven-membered lactone **137** followed by ring opening and reductive elimination would yield papyracillic acid in the same manner as penicillic acid (Scheme 33).



Scheme 33: Proposed biosynthetic pathway for the formation of papyracillic acid A

More recently, papyracillic acid A was obtained in very high yield from *Ascochyta agropyrina* var. *nana*, a strain of a fungus isolated from diseased leaves of the perennial weed quack grass.⁶⁵ Papyracillic acid was shown to have phytotoxic activity against its host plant, quack grass, as well as against other non-host plants. This phytotoxicity suggests a potential application of papyracillic acid as a natural herbicide. In addition to phytotoxic activity, papyracillic acid has been reported to have antimicrobial and cytotoxic activity. The bioactivity appears dependent on papyracillic acid's ability to act as an electrophile. Nucleophiles, such as amino acids are suggested to attack through conjugate addition at either C-3 in the lactone ring, or the α,β -unsaturated

ketone in the open-chain form. Shan and co-workers proposed that the α,β -unsaturated ketone present in the open-chain form, rather than the unsaturated lactone, is responsible for papyracillic acid A's biological activity.⁶⁶

Two other derivatives of papyracillic acid were isolated from *Microphaeropsis sp*, an endophytic fungus extracted from the branch of the tree *Larix decidua* found in Hjerting, Denmark. Neither of these compounds, papyracillic acid B and C, contain the α,β -unsaturated ketone found in the open-chain form of papyracillic acid A (**Figure 2**). Therefore, while the biological activity of these two new members of the papyracillic acid family has yet to be studied, it appears unlikely that they will have similar biological relevance.

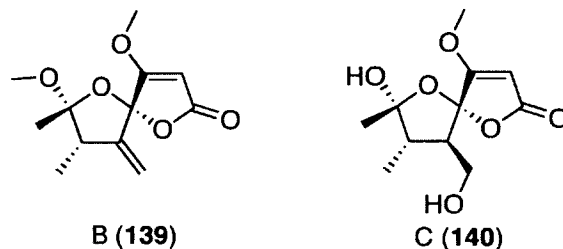


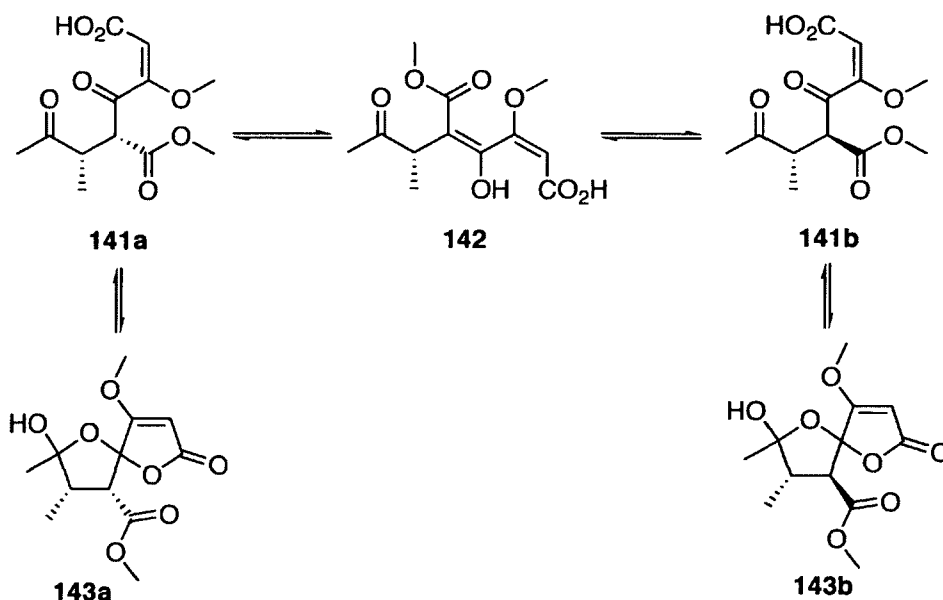
Figure 2: Papyracillic acid B (139) and C (140)

Previous Synthesis of Papyracillic Acids

Recently, Mazzone reported the total synthesis of 4-*epi*-papyracillic acid C and papyracillic acid B.^{35, 67} The key step in the synthesis of these two compounds was the formation of the spirofused cyclic ketal core of the papyracillic acids. Installation of this spirofused ketal was accomplished through the combination of two variations of the chain extension reaction. The first variation made use of the tandem chain extension-acylation

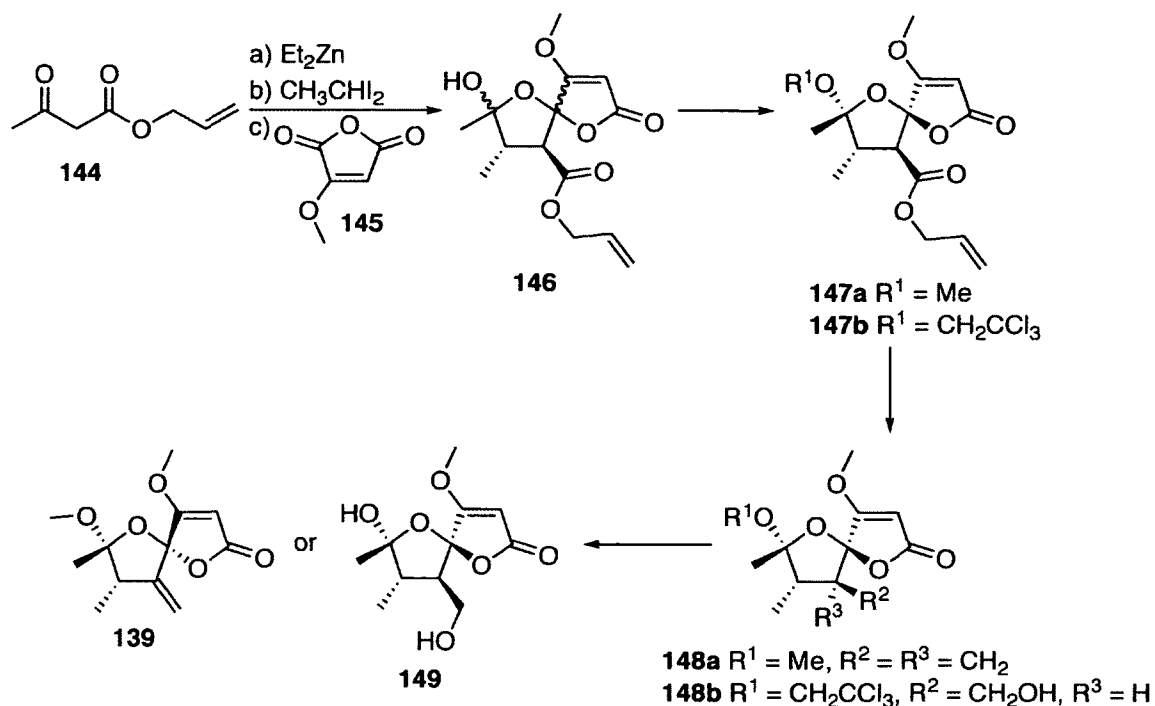
reaction, using 3-methoxymaleic anhydride as the acylating agent. As described earlier, tandem chain extension-acylation reactions using maleic anhydride resulted in a *Z*- to *E*-isomerization, preventing formation of the spiro-ketal core present in the papyracillic acids. In contrast, reaction with 3-methoxymaleic anhydride resulted in products containing a *Z*-alkene. The retention of the *Z*-alkene could be explained by the presence of the methoxy group, which provides the opportunity for facile interconversion of the *Z*- and *E*-alkenes, facilitating closure to the required spiro-ketal.

Mazzone's approach to the papyracillic acid core also made use of a methyl-substituted carbenoid, allowing for incorporation of the C10 methyl-substituent found in the spiro-fused ketal backbone of the papyracillic acids. Synthesis of the spiro-fused ketal found in the papyracillic acids was the second example of a tandem chain extension reaction being used with a substituted carbenoid. Jacobine's synthesis of a phaseolinic acid derivative revealed that incorporation of a methyl group at the β -position has a stereodirecting influence on the facial selectivity of the zinc-enolate in an aldol reaction.³⁹ If a similar facial selectivity was operative for the acylation reaction, a *cis*-stereochemical relationship between the methyl group and the ester would be generated. Unexpectedly, a *trans*-stereochemical relationship between these two functional groups was observed through a ¹H NMR coupling constant ($^3J = 12.3$ Hz) and was confirmed by X-ray crystallographic analysis. Studies performed by Mazzone indicated that an equilibrium between the kinetic *cis*-isomer and the thermodynamic *trans*-isomer (Scheme 34) was established. It was hypothesized that equilibration involved epimerization via the enol of the α -stereocenter of the open-chained isomer 142.



Scheme 34: Equilibrium between *cis*- and *trans*-isomers of spiro-fused ketal core

Due to the existence of interconverting isomers of the hemiketal, Mazzone converted hemiketal **146** to a mixed ketal in order to facilitate handling. In the case of papyracillic acid B, the methyl ketal was required for the product; however, during her synthetic approach to *epi*-papyracillic acid C, the methyl ketal proved difficult to deprotect, leading to the use of a trichloroethyl protecting group. Conversion to the hydroxymethyl substituent of **148b** and the *exo*-cyclic alkene present in **148a** required selective reduction of the ester functionality. This selectivity was accomplished through the use of an allyl ester. Deallylation followed by reduction of an activated carboxylic acid resulted in the formation of the desired hydroxymethyl spirofused ketal. Deprotection of the trichloroethyl acetal furnished 4-*epi*-papyracillic acid C, while conversion of the hydroxymethyl group to an *exo*-cyclic double bond resulted in the formation of papyracillic acid B (**Scheme 35**).

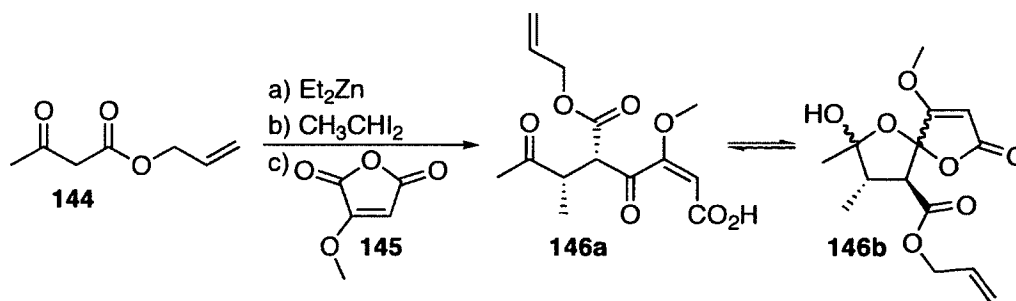


Scheme 35: Synthesis of papyracillic acid B (**139**) and 4-*epi*-papyracillic acid C (**149**)

Synthesis of Papyracillic Acid A

Papyracillic acid A contains the *exo*-cyclic double bond found in papyracillic acid B, as well as the hemiketal found in papyracillic acid C. Mazzone had not reported efforts directed toward the synthesis of papyracillic acid A, which is the member of the papyracillic acid family with the most intriguing biological activity. A synthetic strategy targeting papyracillic acid A, therefore, was proposed to make use of lessons learned in the earlier synthetic approaches. The synthetic approach to papyracillic acid A began with the tandem chain extension-acylation reaction between allyl acetoacetate and methyl

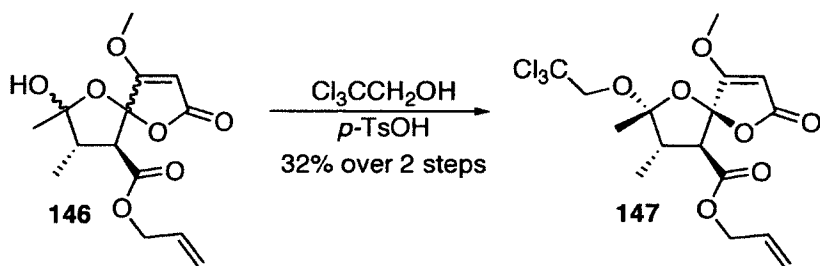
substituted carbenoid followed by treatment with 3-methoxymaleic anhydride (**Scheme 36**). The reaction mixture was stirred for 24 hours to allow for isomerization to the *trans* product (**146b**). The equilibrium studies performed by Mazzone demonstrated that a 24-hour time period allows for conversion of the *cis* product to the *trans* product, similar to hemiketal **143b**. Analysis of the crude reaction mixture by ^1H NMR spectroscopy revealed a doublet at 3.40 ppm with a 3J coupling constant of 12.4 Hz. This resonance corresponds to the proton α to the ester and suggests a *trans*-relationship between the methyl substituent and the ester of hemiketal **146b**. This result is consistent with the trend in ^1H NMR and X-ray crystallography data observed by Mazzone, who proved the major product of the tandem chain extension-acylation of methyl acetoacetate and 3-methoxymaleic anhydride to have the same *trans*-relationship.



Scheme 36: Concise synthesis of spiro-fused ketal core of papyracillic acid A

Exposure of hemiketal **146b** to 2,2,2-trichloroethanol with catalytic *p*-toluenesulfonic acid (*p*-TsOH) followed by column chromatography resulted in the isolation of the major ketal diastereomer in 32% yield over two steps (**Scheme 37**). The trichloroethyl protecting group was chosen as it has been reported to be a protecting

group for hemiketals capable of being deprotected through a mild, selective, non-acidic reaction via a zinc-insertion-elimination reaction.⁶⁸ The chemoselectivity of the eventual deprotection step was important, since other functionalities present in papyracillic acid could be sensitive to alternate deprotection reaction conditions.

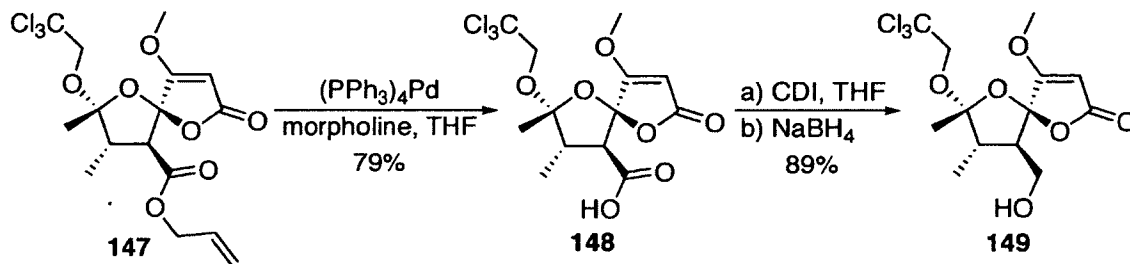


Scheme 37: Protection of hemiketal **146** as a trichloroethyl ketal

The spirocenter of ketal **147** was assigned as having R stereochemistry. This assignment was made based on the similarity of the ¹H NMR data to Mazzone's ¹H NMR data of ketal **147a**. Mazzone obtained a crystal structure of ketal **147a**, which allowed for the assignment of the relative stereochemistry. This stereochemistry was further confirmed later in the synthetic pathway when a crystal structure was obtained for ketal **159** (**Figure 3**), as discussed below.

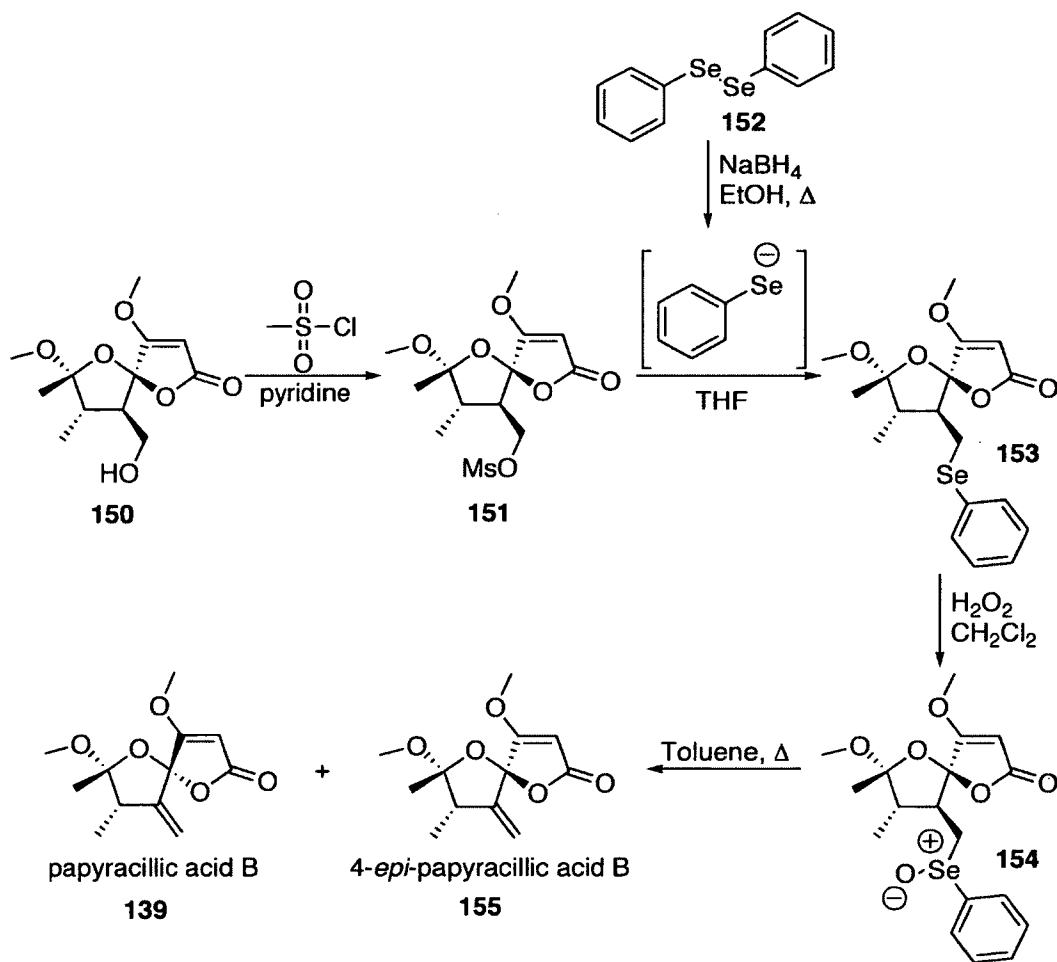
The next step in the synthesis of papyracillic acid A was the deallylation of the ester functionality. Incorporation of an allyl functionality allowed for the selective conversion to the corresponding carboxylic acid without affecting the lactone. Treatment of ketal **147** with catalytic tetrakis(triphenylphosphine)palladium(0) resulted in the efficient conversion to the corresponding carboxylic acid (**148**) in 79% yield (**Scheme 38**). Activation of the carboxylic acid with carbonyldiimidazole (CDI) followed by

treatment with sodium borohydride allowed for efficient reduction in a one-pot procedure, producing the alcohol (**149**) in 89% yield.



Scheme 38: Deallylation and reduction of ester **147**

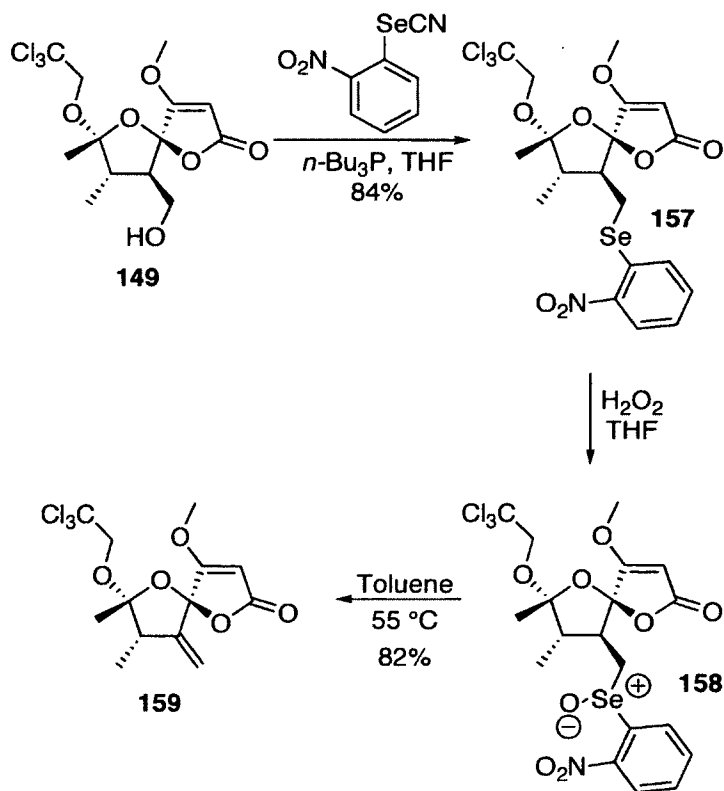
In the synthesis of papyracillic acid B, Mazzone attempted a number of methods to convert the hydroxymethyl functionality to the required *exo*-cyclic alkene. The method used to access papyracillic acid B involved activation of alcohol **150** as the mesylate (**Scheme 39**). The mesylate was then displaced by a selenium anion, obtained through treatment of diphenyl diselenide with sodium borohydride. Exposure of the resulting selenide (**153**) to hydrogen peroxide and subsequent heating in refluxing toluene produced the *exo*-cyclic alkene.



Scheme 39: Mazzone's conversion of hydroxymethyl functionality to *exo*-cyclic alkene

In an attempt to shorten the synthetic pathway in the formation to papyracillic acid A, conversion to the *exo*-cyclic alkene was attempted through the use of a Grieco reaction.^{69, 70} The Grieco reaction converts an alcohol to the corresponding alkene through an intermediate aryl selenide. The presence of a substituent on the β or γ carbons of primary alkyl phenyl selenoxides, such as in the case of compound **154**, tend to result in low yields of terminal alkenes. A method that has been shown to greatly increase the

ability of the selenoxide to undergo elimination is the addition of an electron-withdrawing group on the aromatic selenide. Treatment of alcohol **149** with *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine resulted in the formation of selenide **157** in 84% yield within 30 minutes (Scheme 40). Oxidation of the selenide was accomplished through addition of 30% hydrogen peroxide. The resulting selenoxides were not isolated, but rather gently heated in toluene to effect elimination to the terminal alkene **159**.



Scheme 40: Synthesis of *exo*-cyclic alkene **159** through the Grieco elimination

During the synthesis of papyracillic acid B, Mazzone observed epimerization of the spiroketal center during elimination of the selenoxide in refluxing toluene. This was rationalized to occur through fragmentation of the spiro-fused ketal to reveal a 3°, allylic, oxocarbenium ion. Energy differences between the two spiroketal epimers were expected to be small, which was confirmed with in a 1:1 mixture of isomers of papyracillic acid B.

During the selenoxide elimination of compound **158**, the reaction was maintained at a lower temperature of 55 °C in the hope of preventing a similar epimerization. Analysis of ¹H NMR spectrum of the crude reaction mixture showed clean conversion to a single diastereomer of compound **159**. Slow evaporation from ethyl acetate afforded a crystal suitable for X-ray crystal analysis (**Figure 3**).⁷¹ The crystal structure analysis confirmed the relative stereochemistry at C4 to be the opposite of that seen in the natural product. The same spiroketal stereochemistry was found by Mazzone in the major product formed in the tandem chain extension-acylation reaction (**146**) in the approach to papyracillic acid B and papyracillic acid C.

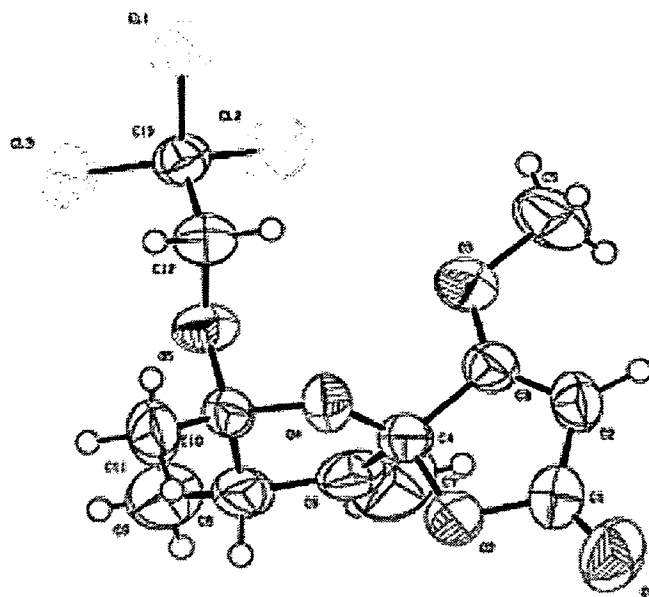


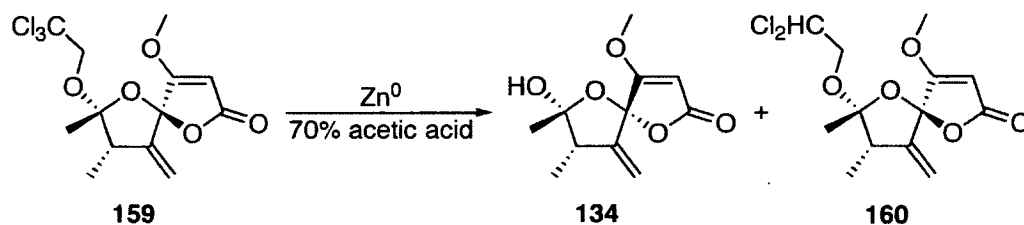
Figure 3: X-Ray crystal structure of spiroketal **159**

The final step required for the synthesis of papyracillic acid **A** was the deprotection of trichloroethyl ketal **159**, which would form the required hemiketal. During the synthesis of papyracillic acid **C**, Mazzone attempted the deprotection of the trichloroethyl ketal through a number of different methods.³⁵ A protocol specifically reported for the deprotection of trichloroethyl ketals makes use of freshly activated zinc dust in refluxing ethyl acetate or tetrahydrofuran.⁶⁸ Application of this method yielded only starting material as seen by ¹H NMR analysis of the crude reaction mixture.

An alternative method for the deprotection of trichloroethyl groups, reported by Marinier *et al.*, makes use of granular zinc in 70% acetic acid.⁷² Application of this method by Mazzone resulted in the production of 4-*epi*-papyracillic acid **C** in a 40% yield. Analysis of the ¹H NMR spectrum of the crude reaction mixture revealed the desired hemiketal (**149**) and dichloroethyl ketal to be present in a 1:1 ratio. While this

result demonstrates that protonation of the zinc anion competes with the elimination reaction, formation of the hemiketal did complete the synthesis of 4-*epi*-papyracillic acid C.

Deprotection of trichloroethyl ketal **159** in the synthesis of papyracillic acid A was attempted using the same acetic acid-mediated zinc insertion-elimination reaction (Scheme 41). Exposure of ketal **159** to freshly activated zinc dust in 70% acetic acid for 16 hours produced papyracillic acid A (**134**) in 27% yield, with the reduced dichloroethyl ketal **160** observed as the major product of the reaction.



Scheme 41: Zn-mediated deprotection of trichloroethyl ketal **159** in acetic acid

Analysis of the ¹H NMR spectrum of the purified hemiketal **134** showed a mixture of three isomers in a 1:1:2 ratio. This ratio was obtained by comparing the integrations of the three singlets representing the methoxy group at 3.94, 3.90, and 3.88 ppm. This ratio of isomers does not match that reported for papyracillic acid A in the literature, which reports a 1:1:2:4 mixture of four papyracillic acid isomers, but with no detailed NMR data.^{62, 65, 73} Support for the synthesis of papyracillic acid A came from analysis of the ¹³C NMR spectrum, which showed a resonance consistent for a hemiketal at 111.7 ppm. Slow evaporation from ethyl acetate afforded a crystal suitable for X-ray

crystal analysis (**Figure 4**)⁷⁴ The crystal structure analysis confirmed the formation of papyracillic acid A. The crystal structure demonstrated that epimerization of the spirofused stereocenter had occurred. This is easily explained by the equilibration between the open and closed forms of the hemiacetal under the acidic reaction conditions utilized in the zinc-mediated deprotection. Due to the presence of multiple isomers in solution, it is possible that the *R* stereochemistry of the spiro-fused center of ketal **159** is also present. Selective crystallization of the isomer containing *S* stereochemistry has led to its designation as the natural product, however the other isomers remain to be identified.

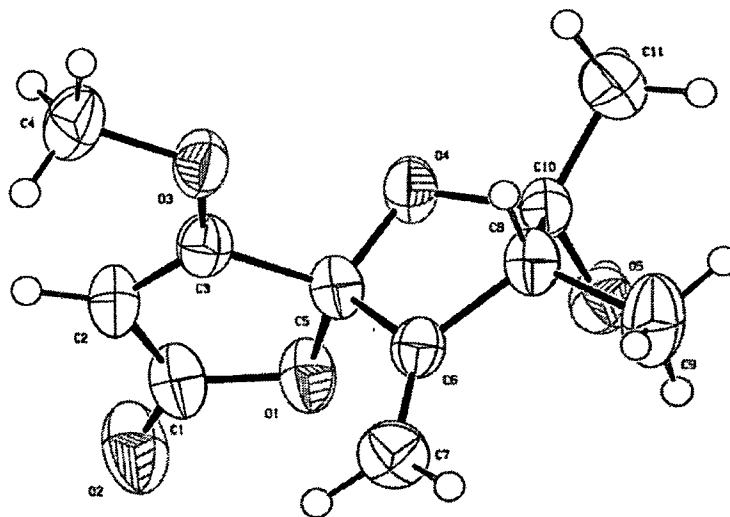
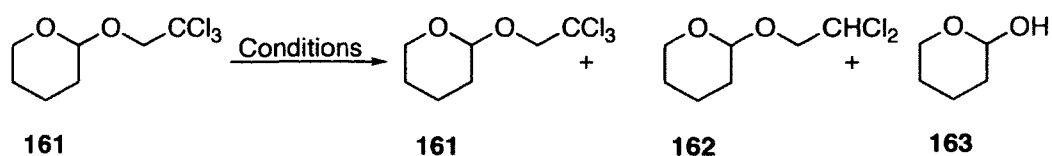


Figure 4: X-Ray crystal structure of papyracillic acid A

In an attempt to increase the yield of the trichloroethyl deprotection, alternative routes were investigated. A model trichloroethyl acetal was prepared by stirring 3,4-dihydropyran in dichloromethane with 2,2,2-trichloroethanol and K-10 montmorillonite

clay.⁷⁵ The resulting acetal **161** was used in a number of deprotection attempts. In a recent report by Zhang and coworkers, non-activated zinc dust and ammonium chloride (NH₄Cl) in refluxing acetonitrile was used to deprotect a 2,2,2-trichloroethyl group at the anomeric position of carbohydrates.⁷⁶ When trichloroacetal **161** was subjected to these deprotection conditions, only starting material was returned. The reaction was attempted again, using freshly activated zinc dust. Analysis of the crude reaction material by ¹H NMR spectroscopy showed a 10:1 mixture of starting material **161** and the dichloroethyl acetal **162** (Table 7).

In a return to the acetic acid-mediated protocol, trichloroethyl acetal **161** was stirred with activated zinc (20 mesh) in a 70% solution of glacial acetic acid in dioxane. It was hoped that replacing water with dioxane would help slow protonation and allow more of the eliminated product to be formed. After stirring the reaction mixture for eight hours, only starting material was recovered. Following a similar deprotection protocol, trichloroethyl acetal **161** was stirred at room temperature with activated zinc dust and sodium acetate in acetic acid for three hours. Analysis of the crude reaction mixture by ¹H NMR spectroscopy showed a 2:2:3 mixture of starting material, dichloroethyl acetal **162**, and the desired hemiacetal **163**.

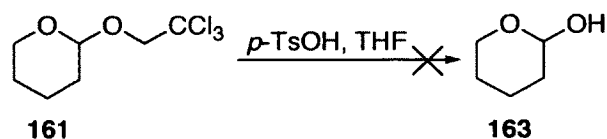


Zn ⁰	Additive	Solvent	161:162:163
dust ^a	NH ₄ Cl	Acetonitrile	100:0:0
dust ^b	NH ₄ Cl	Acetonitrile	90:10:0
granular ^c	Dioxane	Acetic acid	100:0:0
dust ^b	Sodium acetate	Acetic acid	30:30:40

Table 7: Attempted insertion-elimination deprotections of trichloroethyl group (^aNon-activated, ^bActivated by washing with 3 N HCl for 45 min, filtered, washed with 3 N HCl, water, ethanol, ether, dried under reduced pressure (5 mmHg) at 77 °C over P₂O₅, ^cActivated by washing with 3 N HCl for 45 min, filtered, washed with 3 N HCl, water, ethanol, ether, dried under reduced pressure (0.5 mmHg))

Even though formation of the dichloroethyl acetal **162** was still competing with formation of the desired hemiacetal, deprotection of trichloroethyl ketal **159** with zinc and sodium acetate in acetic acid was attempted. Upon analysis of the ¹H NMR spectrum, the major product was determined to be the dichloroethyl ketal rather than papyracillic acid A.

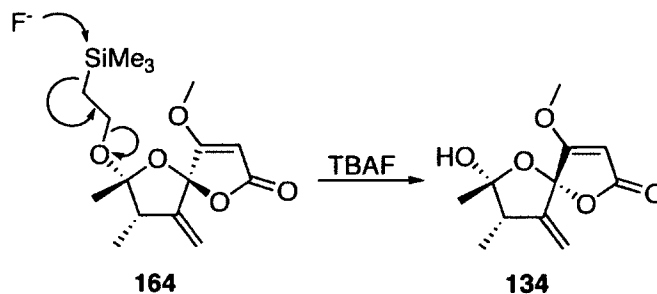
At this point, hydrolysis was explored in an effort to identify a suitable method for the removal of the trichloroethyl-protecting group. In an attempt to remove the trichloroethyl protecting group, acetal **161** was stirred at room temperature with *p*-TsOH and water in THF (**Scheme 42**). After 2 days, only starting material was observed by TLC. At this point it was determined that an alternative protecting group would be required to effect efficient deprotection to papyracillic acid A.



Scheme 42: Attempted hydrolysis of trichloroethyl ketal **161**

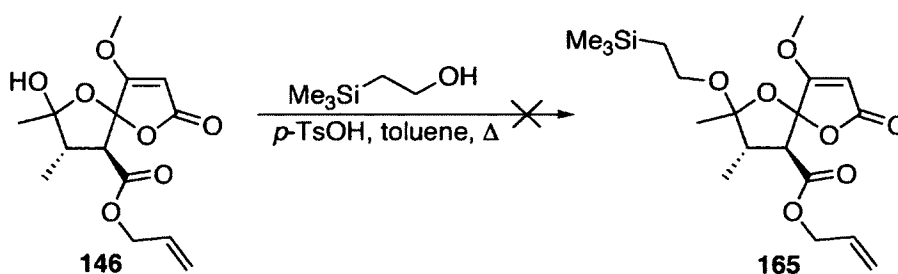
2-(Trimethylsilyl)ethyl Protecting Group

The 2-(trimethylsilyl)ethyl protecting group was an attractive protecting group as it has been reported to be easily cleaved through the use of boron trifluoride diethyl etherate in dichloromethane at 0 °C.⁷⁷ Since one of the previously attempted trichloroethyl deprotection methods involved stirring ketal **159** under these same reaction conditions, deprotection of the 2-(trimethylsilyl)ethyl group was anticipated to proceed chemoselectively with no decomposition of any of the other functionality in the molecule. Alternatively, tetrabutylammonium fluoride (TBAF) could be used as a source of a fluoride ion. Fluoride would preferentially attack the silicon atom, eliminating an equivalent of ethylene to form the desired hemiketal (**Scheme 43**).



Scheme 43: Proposed deprotection of the 2-(trimethylsilyl)ethyl protecting group

An initial attempt at synthesizing 2-(trimethylsilyl)ethyl ketal **165** was performed by exposing tandem chain extension-acylation product **146** to 2-(trimethylsilyl)ethanol and *p*-TsOH in toluene (Scheme 44). After stirring at room temperature for 2 days, TLC showed only starting material. The reaction was heated to reflux, but after heating for another 24 hours, again no change was seen by TLC.



Scheme 44: Attempted 2-(trimethylsilyl)ethyl protection of hemiketal **146**

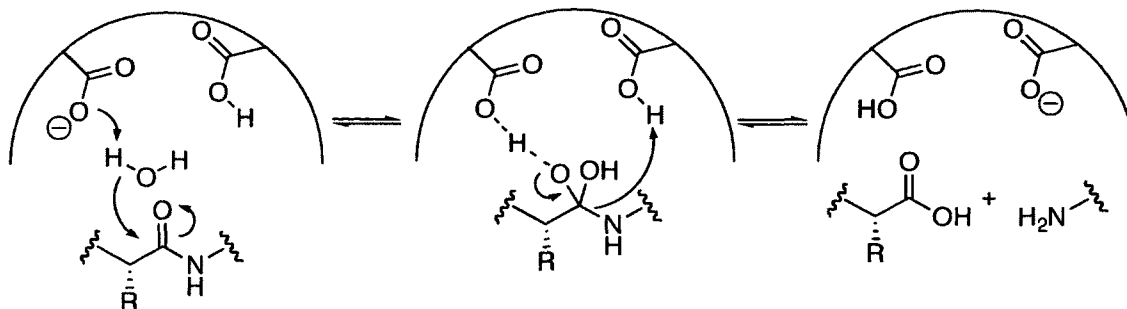
In summary, the tandem chain extension-acylation reaction was successfully applied to the synthesis of papyracillic acid A in 7 steps in 4% overall yield. It is possible that this overall yield could be increased through the use of a 2-(trimethylsilyl)ethyl protecting group in place of the trichloroethyl protecting group, as the deprotection is predicted to be more higher yielding.

CHAPTER IV

SYNTHESIS OF TETRAHYDROFURAN-BASED PEPTIDOMIMETICS

Introduction to Peptide Mimetics

Proteases are a class of enzymes that promote hydrolytic cleavage of peptide bonds with high selectivity and efficiency. They are classified by the varying amino acid residues acting as their active site participants and can be classified into two broad classes based on their mechanism of action.⁷⁸ The first class of protease enzymes makes use of an activated water molecule to initiate hydrolysis of a peptide substrate. In the case of zinc metalloproteinases activation of this water molecule is achieved by a zinc cation. In the case of aspartate proteases, such as HIV-1 protease, this activation is achieved by the two aspartyl residues found in the enzyme's active site (**Scheme 45**).⁷⁹ The second class of protease enzymes initiates peptide hydrolysis through attack by a nucleophilic amino acid residue, forming an ester or thioester acyl intermediate. Before nucleophilic attack, this amino acid residue is activated by a second amino acid side chain, such as histidine.⁸⁰ The resulting acyl-enzyme intermediate is eventually hydrolyzed by a water molecule, activated by active site functionality.



Scheme 45: Aspartic protease-mediated hydrolysis of peptide bond

While proteases are involved in many critical physiological reactions such as digestion, blood clotting, and immune response, they also aid in viral replication. Selective protease inhibitors, therefore, have great potential in drug design. One of the main strategies developing protease inhibitors has focused on the use of peptide isosteres.

The term isostere was introduced in 1919 by Langmuir to describe molecules containing the same number of atoms and valence electrons.⁸¹ Since the introduction of the concept of isosteres, the definition has been broadened. In medicinal chemistry, bioisosterism has been used to describe the application of isosterism to modify biological activity.⁸² Bioisosteres describe compounds that are related in structure and have similar antagonistic properties.⁸³ Isosteres can be classified as either classical or non-classical. Classical isosteres follow a more rigid steric and electronic definition, while one of the distinguishing characteristics of non-classical isosteres is that they do not have the same number of atoms as the molecule they are mimicking.

Bioisosteric replacement of an amide group has been an area that has received considerable attention due to its implications in peptide chemistry and in the development

of peptide mimetics. When developing peptide isosteres, a number of factors must be considered including structural concerns such as bond angles, functionality and stereochemistry of side chains, hybridization of the amide mimic, as well as the hydrogen bonding capability.

When the amide nitrogen of a peptide bond (**166**) is replaced with a methylene unit, the resulting compound is referred to as a ketomethylene isostere (**Figure 5**). An advantage of the ketomethylene isostere is that the ketone, just as with the amide bond of compound **166**, is able to accept a nucleophile and adopt a tetrahedral geometry, yet the ketone is hydrolytically stable. While ketomethylene isosteres have been successfully used for protease inhibition,^{84, 85} an important distinction between the ketomethylene and amide groups must be considered. Amide resonance is responsible for restricted rotation around the amide bond of a natural peptide and biases its ground state geometry to a conformation that has a high affinity for the active site of a targeted protease. Incorporation of a methylene unit removes the amide resonance and introduces free rotation that makes the ketomethylene isostere less likely to adopt the geometry needed to bind in the enzyme's active site.⁸⁶

Another type of peptide isostere that has found successful application in protease inhibition is the hydroxyethylene isostere (**168**).^{78, 87} Hydroxyethylene isosteres have been developed to mimic the tetrahedral intermediate formed during hydrolytic cleavage of the peptide bond. These isosteres maintain both hydrolytic stability and the ability to hydrogen-bond in the enzyme's active site; however, free rotation about the carbon-carbon bond impacts their ability to closely mimic the amide bond. In the case of cyclopropane isosteres, stereochemical rigidity is mandated.⁸⁸ While this rigidity can be

viewed as mimicking the amide bond, all hydrogen-bonding capability is lost, which would be expected to result in decreased binding affinities.

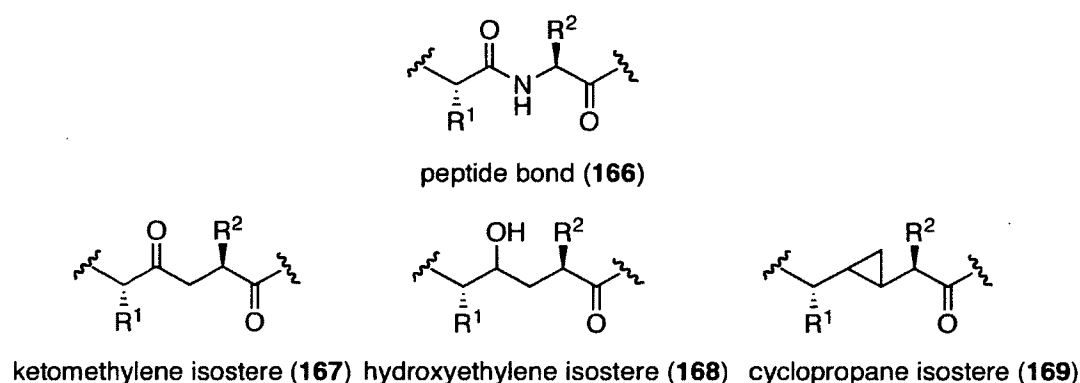


Figure 5: Isosteric replacement of amide bond

While these three classes of peptide isosteres have found utility in protease inhibition, they all lack certain desirable structural features. A series of compounds that may better mimic natural peptides are both the embedded hemiketal **170**, and the embedded tetrahydrofuran **171** isosteres (**Figure 6**). In both of these structures, a hydrolytically stable, sp^3 -hybridized, oxygen-containing functional group replaces the amide bond. In this way they are similar to the hydroxyethylene isosteres and are able to mimic the tetrahedral intermediate observed during hydrolysis of the natural peptide. In addition, the cyclic nature of these compounds allows for a restricted rotation about the carbon-carbon bond, which more closely mimics the amide bond.

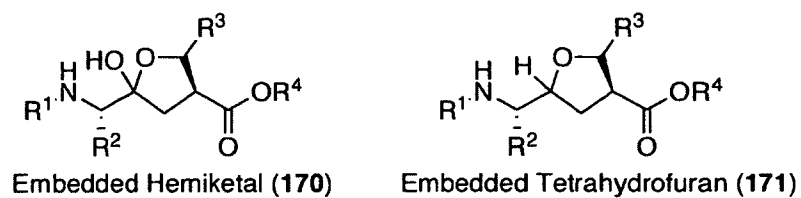
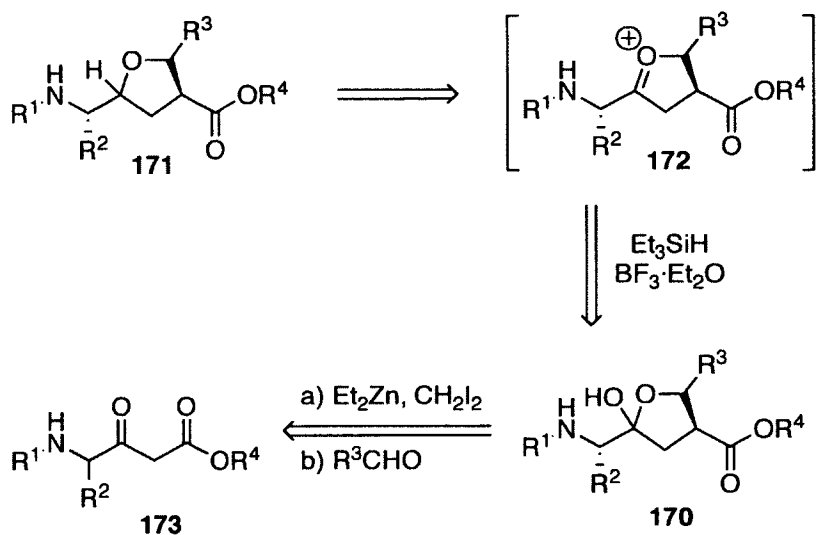


Figure 6: Novel heterocyclic peptide isosteres

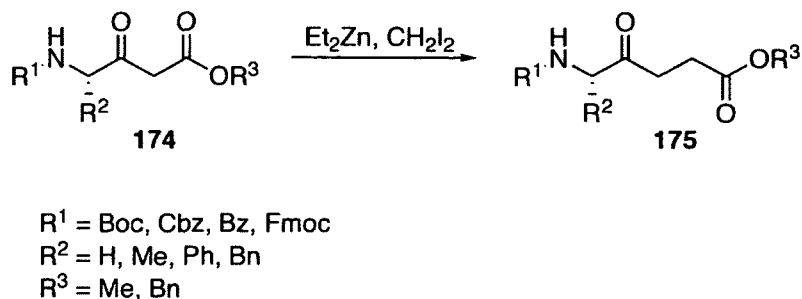
The synthesis of an embedded tetrahydrofuran isostere could be achieved through reduction of an embedded hemiketal (**Scheme 46**). Use of triethylsilane and boron trifluoride diethyl etherate would allow for initial formation of an oxocarbenium ion, followed by hydride addition to form the tetrahydrofuran ring. The embedded hemiketal isostere would be easily synthesized through the use of a tandem chain extension-aldol reaction of the appropriate amino acid derived β -keto ester. Use of the tandem chain extension-aldol reaction with a variety of starting β -keto carbonyls and aldehydes has the potential for the easy preparation of a wide range of these two novel isosteres.



Scheme 46: Synthetic route for the synthesis of embedded hemiketal and tetrahydrofuran isosteres

Previous Syntheses of Substituted Tetrahydrofurans

Previous work in the Zercher group has focused on the use of amino acid-derived systems in the zinc carbenoid-mediated chain extension reaction as an approach to peptide isosteres (Scheme 47).²² A variety of *N*-protected amino acid-derived β -keto esters were synthesized in order to establish the efficiency of the chain extension reaction. It was determined that a wide range of protecting groups was tolerated, and that the efficiency of the reaction was not dependent upon the starting amino acid. Epimerization of the amino acid stereocenter was shown not to occur under zinc-mediated chain extension reaction conditions.

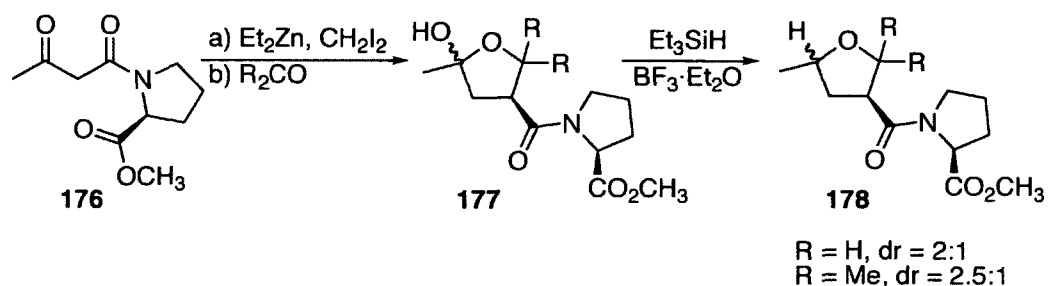


Scheme 47: Chain extension of amino acid derived β -keto esters

While mono-protected amino acids are tolerated in the chain extension reaction, the moderately acidic NH-amide proton would most likely quench the organometallic intermediate thereby preventing opportunities for further functionalization of the γ -keto backbone through tandem reaction methods. Bis-protection of the amino acid N-terminus has been shown to allow for the application of tandem chain extension reactions. When an alanine-derived β -keto ester (**174**) was subjected to a tandem chain extension-aldol reaction using formaldehyde as the electrophile, the aldol products were generated as an approximately 1:1 ratio of diastereomers.²⁰ This result suggests that the amino acid stereocenter was too far removed to influence the facial selectivity of the intermediate enolate.

Use of a proline-derived β -keto amide in the tandem chain extension-aldol reaction using benzaldehyde as the electrophile resulted in the formation of the *syn* aldol product with greater than 95% diastereoselectivity.¹⁶ Conversion of tandem chain extension-aldol products **177** to tetrahydrofurans **178** has been shown to proceed efficiently, albeit with modest diastereocontrol (**Scheme 48**).⁸⁹ Facial selectivity in the

hydride addition to an intermediate oxocarbenium ion is poor when a single stereocenter is present on the tetrahydrofuran backbone.



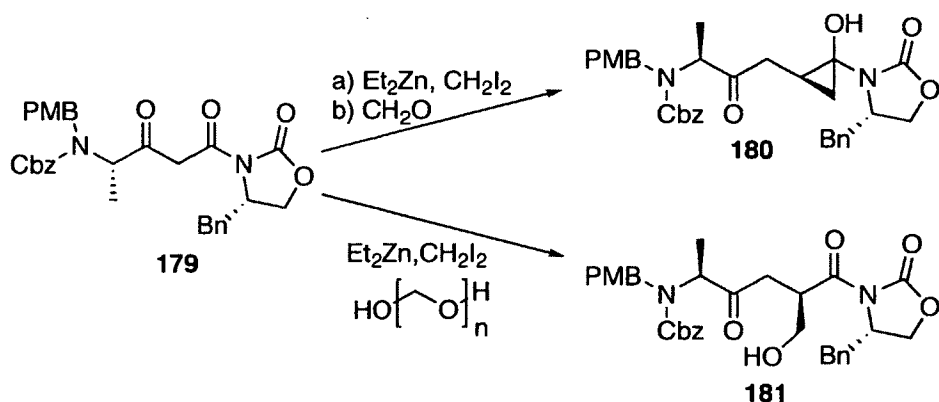
Scheme 48: Synthesis of substituted tetrahydrofurans through tandem homologation aldol reaction of chiral β -keto amide

While use of a proline-based chiral auxiliary allowed for stereocontrol in the aldol reaction and the triethylsilane reduction, application of the chain extension-aldol-reduction sequence to the stereocontrolled synthesis of dipeptide mimetics would have additional value if both the N-terminus and the C-terminus were available for further modification. The N-terminus of a dipeptide mimic would be accessible from an amino acid starting material with appropriate protection. Access to the C-terminus by hydrolysis of a proline amide would require harsh reaction conditions, which if performed in the presence of amino acid functionality may lead to epimerization of the amino acid stereocenter. Alternatively, higher diastereoselectivity in the tandem chain extension-aldol reaction could be available from a β -keto imide.¹⁵ Another benefit of using a β -keto imide in the tandem chain extension-aldol reaction is the formation of the *anti*-aldol product. The hemiketal isomer of the *anti*-aldol product possesses a *cis*-relationship between the imide and aldehyde-derived R-group (**Scheme 12**), which suggests one face

of the hemiketal would be more sterically crowded. This steric hindrance would be expected to bias hydride addition into the intermediate oxocarbenium ion during reduction to the tetrahydrofuran.

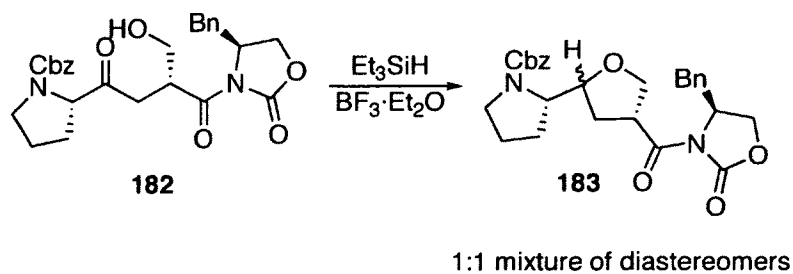
Evans' chiral auxiliaries, derived from amino acids, have found wide use in asymmetric synthesis.^{90, 91} Previous use of a chiral β -keto imide in the stereocontrol of a tandem chain extension-aldol reaction demonstrated the potential of amino acid-derived β -keto imides in the synthesis of peptide isosteres.¹⁵ An important benefit of the Evans auxiliaries is their ability to be easily hydrolyzed under mild reaction conditions, allowing for the opportunity to functionalize the C-terminus of a targeted peptide mimic.

Previous work by Lin demonstrated the successful synthesis of an amino acid-derived β -keto imide through a modified Claisen condensation reaction, with no epimerization of the amino acid stereocenter. Lin subjected this β -keto imide (**179**) to tandem chain extension-aldol reaction conditions using paraformaldehyde as the electrophile. When the β -keto imide was exposed to zinc-carbenoid prior to the addition of paraformaldehyde, a cyclopropane byproduct (**180**) was formed instead of the desired aldol product **181** (Scheme 49).¹⁶ Formation of this cyclopropane was presumably a result of alkylation by excess carbenoid, followed by cyclization into the imide carbonyl. Lin avoided the formation of this byproduct through addition of paraformaldehyde to the carbenoid mixture prior to the addition of the starting β -keto imide. Under these modified reaction conditions, aldol product **181** was isolated as the major product without formation of the undesired cyclopropane.



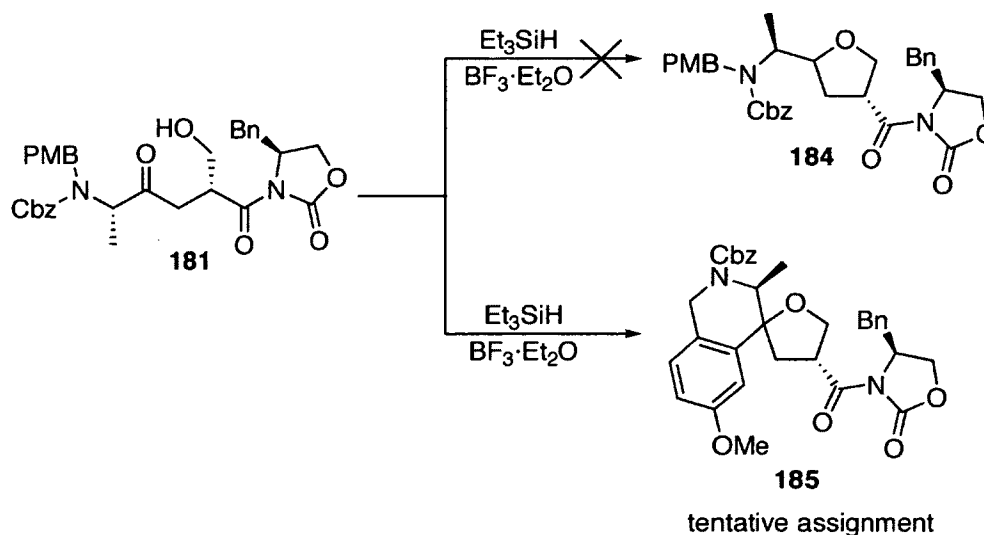
Scheme 49: Order of addition during the tandem chain extension-aldol reaction of β -keto imide **179**

Once the tandem chain extension-aldol reaction was shown to be applicable to the synthesis of amino acid derived γ -keto imides, conversion to the substituted tetrahydrofuran was attempted. Lin successfully synthesized tetrahydrofuran **183** as a 1:1 mixture of diastereomers through a triethylsilane reduction of aldol product **182** (**Scheme 50**). This result suggested that the proline stereocenter did not influence the stereoselectivity of the reduction of the hemiketal.



Scheme 50: Synthesis of substituted tetrahydrofuran **183**

When Lin subjected (*S*)-alanine derived β -keto imide **181** to tandem homologation-aldol reaction conditions followed by triethylsilane reduction, an unexpected byproduct (**185**) was obtained rather than the desired tetrahydrofuran **184** (Scheme 51). This byproduct was not unambiguously identified, but it was presumed to be formed though an intramolecular Friedel-Crafts reaction between the oxocarbenium ion and the PMB protecting group. It was proposed that synthesis of this byproduct could be avoided through addition of the triethylsilane into the reaction mixture prior to addition of the Lewis acid.



Scheme 51: Lin's attempted synthesis of substituted tetrahydrofuran **184**

The PMB protecting group has been used in the tandem chain extension-aldol reaction of β -keto imides for multiple reasons. As previously mentioned, diprotection of the N-terminus of amino acid substrates like **181** is required to avoid quenching the zinc-

enolate intermediate. The PMB protecting group is able to withstand zinc-mediated chain extension reaction conditions. Additionally, the PMB group can be efficiently and selectively removed from the amine, providing access for manipulation of the N-terminus following the homologation reaction.

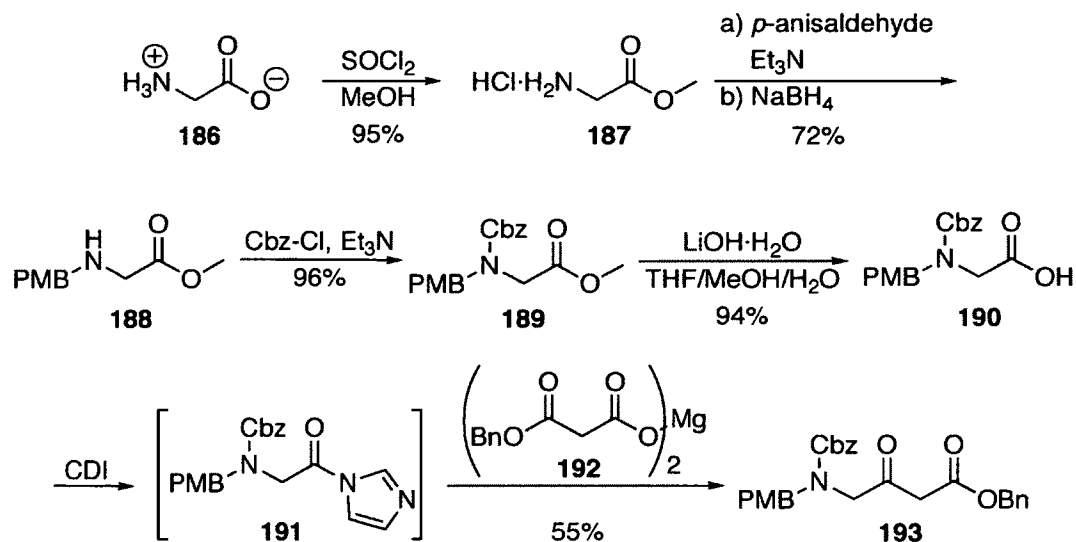
The general strategy that targets dipeptides with embedded tetrahydrofurans had been shown to be successful, albeit with a limited number of amino acid-derived starting materials. Formaldehyde had been the only electrophile incorporated during the tandem chain extension-aldol reaction with amino acid-derived β -keto imide starting materials.¹⁶ Investigation into the use of alternative amino acid derived systems and a broader range of electrophiles was needed to more fully understand the scope and utility of this synthetic approach to the novel peptide isosteres.

Utility of *p*-Methoxybenzyl Protecting Group

To test our ability to synthesize substituted tetrahydrofurans through a triethylsilane mediated reduction of substrates that possessed a PMB protecting group, a model β -keto ester was prepared (Scheme 52). Due to the high solubility of glycine in water, the methyl ester (**187**) was prepared prior to protection. Protection with a PMB group was effected through reductive amination.⁹² The resulting secondary amine (**188**) was then converted to the carbamate (**189**) through carbobenzyloxy (Cbz) protection.⁹³ Saponification of the methyl ester through exposure to potassium hydroxide⁹⁴ afforded the diprotected amino acid.

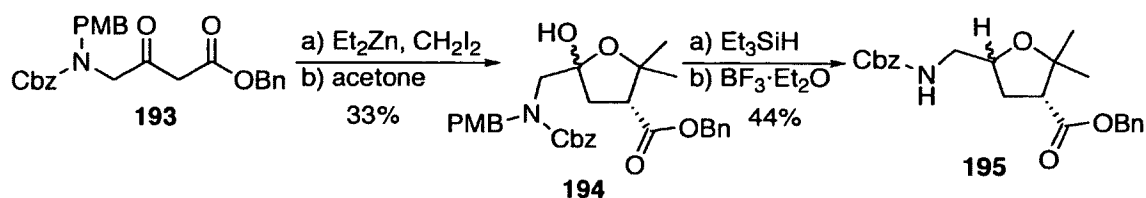
Conversion of an amino acid to the corresponding β -keto ester can be achieved through the use of the Masamune-Brooks reaction.⁹⁵ *N,N*-Protected glycine **190** was

activated with carbonyldiimidazole, generating acyl imidazole intermediate **191**. This intermediate was transferred to a solution of the magnesium salt of monobenzylmalonate **192**. Upon purification, the glycine derived β -keto ester **193** was obtained in 55% yield.



Scheme 52: Synthesis of an amino acid derived β -keto ester

Subjection of β -keto ester **193** to tandem chain extension-aldol reaction conditions using acetone as the electrophile resulted in the formation of hemiketal **194** in 33% yield. Hemiketal **194** was treated with 4 equivalents of triethylsilane at -78°C followed by addition of boron trifluoride diethyl etherate and allowed to stir for 22 h, while warming to room temperature, giving rise to tetrahydrofuran derivative **195** as a 1:1 mixture of diastereomers (**Scheme 53**). In addition to reduction to the tetrahydrofuran ring, ^1H NMR analysis revealed that the PMB group had been removed.

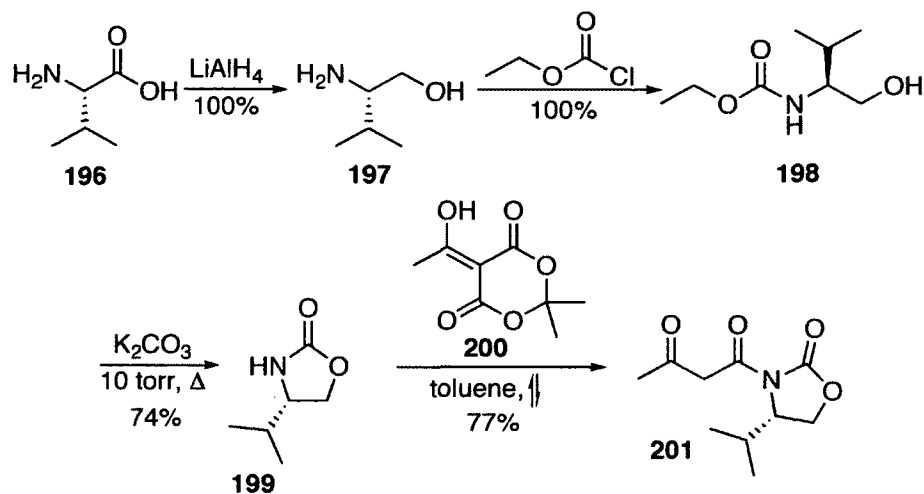


Scheme 53: Utility of the PMB protecting group during the synthesis of a tetrahydrofuran derivative

The absence of a Friedel-Crafts alkylation byproduct similar to that observed by Lin (**185**) indicated that the PMB-protecting group would be suitable for the synthesis of a wider variety of tetrahydrofuran derivatives. Removal of the PMB protecting group under triethylsilane reduction reaction conditions was unanticipated, but prevention of its removal by shortening the reaction time and maintaining a reduced temperature was proposed.

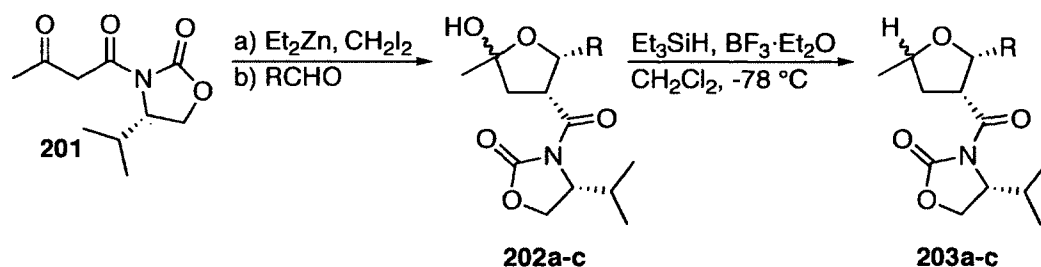
Model β -Keto Imide

All previous attempts at synthesizing tetrahydrofuran derivatives from β -keto imides used formaldehyde as the electrophile during the initial tandem chain extension-aldol reaction.¹⁶ To test this methodology with other aldehydes, simple β -keto imide **201** was prepared as a model substrate (**Scheme 54**). Synthesis of chiral β -keto imide **201** began with the formation of a L-valine derived oxazolidinone **99**.^{96, 97} This chiral oxazolidinone was then reacted with acylated Meldrum's acid **200** in refluxing toluene to yield a β -keto imide in 77% yield.



Scheme 54: Synthesis of a simple chiral β -keto imide

Exposure of the resulting β -keto imide to tandem chain extension-aldol reaction conditions with three different aldehydes gave rise to the corresponding hemiketals **202a-c** in good yield, and high diastereoselectivity (**Table 8**). Triethylsilane reduction of the purified aldol products resulted in the formation of tetrahydrofuran derivatives **203a-c**. The diastereoselectivity seen in the formation of these tetrahydrofuran derivatives was higher than those seen previously. Use of a β -keto imide in the tandem chain extension-aldol reaction results in the formation of anti-aldol products.⁹⁸ The hemiketal isomers of these products have a *cis* relationship between the imide and R functionality rather than the *trans* relationship seen in the hemiketals formed from *syn*-selective aldol reactions involving ester and amide starting materials. Having both functional groups on the same side of the five-membered ring appears to bias addition of the hydride into the opposite face of the oxocarbenium ion formed during the reduction.



Entry	R	202 yield (%)	Diastereomeric ratio of 203	203 yield (%)
1a	<i>t</i> -Bu	40	6:1	94
2b	Ph	63	8:1	64
3c	C ₄ H ₉	18	8:1	69

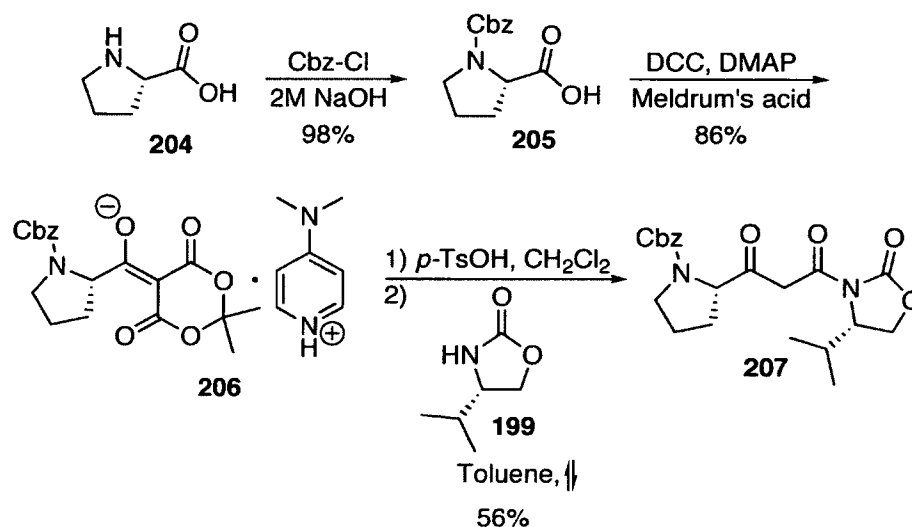
Table 8: Synthesis of substituted tetrahydrofurans from simple β -keto imide

Amino Acid-Derived β -Keto Imides

Once it was determined that tetrahydrofuran derivatives could be prepared with high diastereoselectivity, the next step was to apply this same methodology to amino acid-derived β -keto imides. Three representative primary and secondary amino acids were chosen as starting materials for the methodological study. L-Proline was selected, as it was a secondary amino acid containing an aliphatic side chain. L-Phenylalanine was selected as a primary amino acid containing an aromatic side chain. Glycine, which contains no side chain, was chosen as a third amino acid to investigate the influence of the amino acid stereocenter on the diastereoselectivity of the triethylsilane reduction.

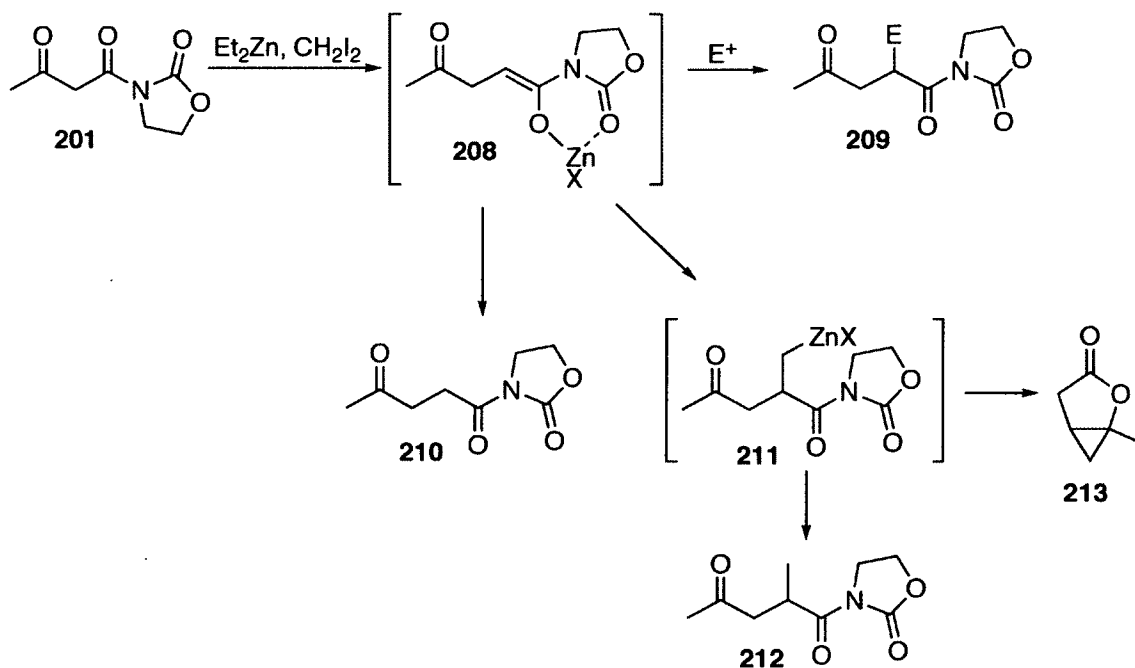
The first amino acid studied was L-proline. Synthesis of a proline derived β -keto imide began with Cbz protection (**Scheme 55**). The protected amino acid **205** was subjected to a *N,N*-dicyclohexylcarbodiimide (DCC) coupling with Meldrum's acid,

forming the Meldrum's acid adduct **206** in 83% yield. Exposure of this adduct to L-valine-derived oxazolidinone **199** in boiling toluene resulted in the formation of proline derived β -keto imide **207** as a single diastereomer.



Scheme 55: Synthesis of Cbz-derived β -keto imide

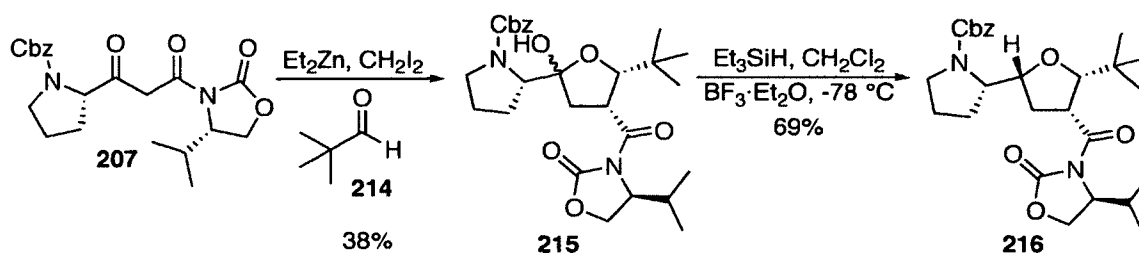
β -Keto imides are more reactive than β -keto esters and amides under zinc carbenoid-mediated chain extension reaction conditions. Previous studies of the exposure of β -keto imides to zinc carbenoid for extended reaction times have resulted in the identification of two major by-products, α -methylated γ -keto imide (**212**) and bicyclic lactone **213** (Scheme 56).^{35, 99}



Scheme 56: Byproducts observed during the tandem chain extension of a β -keto imide

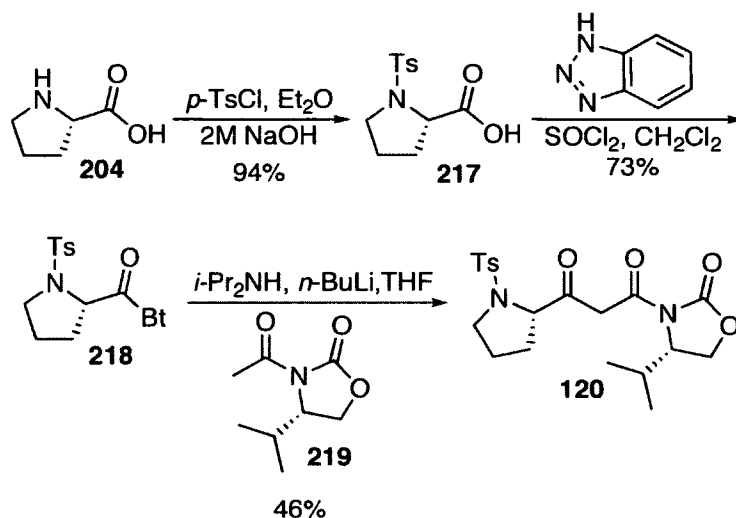
In an attempt to reduce the amount of unwanted byproducts formed in the tandem chain extension aldol reaction of β -keto imide **207**, the electrophile was added to the carbenoid prior to addition of the imide. The amount of carbenoid used in the reaction was limited to 2.5 equivalents. Conversion of β -keto imide **207** to hemiketal **215** was accomplished through the use of a tandem chain extension-aldol reaction using pivaldehyde as an electrophile (**Scheme 57**). Exposure of the purified aldol product to triethylsilane followed by addition of boron trifluoride diethyl etherate resulted in the formation of substituted tetrahydrofuran **216** in 69% yield. Analysis of the ^1H NMR spectrum was complicated by the presence of rotameric forms of compound **216**; however, it appeared as though only a single configurational diastereomer was formed. Addition of the hydride was predicted to occur on the face opposite to the imide and *t*-

butyl groups due to their steric bulk. This prediction was confirmed by NOESY NMR data for similar tetrahydrofuran derivatives and will be discussed below.



Scheme 57: Synthesis of substituted tetrahydrofuran **216**

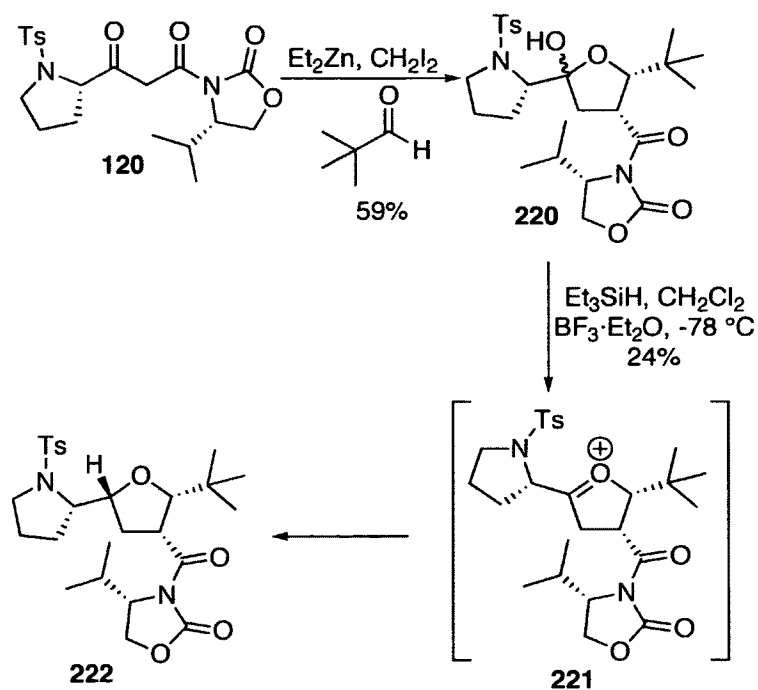
Synthesis of β -keto imides through the use of a Meldrum's acid adduct can be challenging, since the presence of moisture results in the formation of a methyl ketone byproduct. In order to avoid formation of this byproduct, β -keto imide **120** was synthesized through the use of a mixed Claisen reaction. Benzotriazole-activated carboxylic acid **218** was reacted with the lithium enolate of acylated oxazolidinone **219** to afford β -keto imide in 46% yield.



Scheme 58: Synthesis of β -keto imide **120**

β -Keto imide **120** was subjected to the tandem chain extension-aldol reaction using pivaldehyde as an electrophile (**Scheme 59**). Pivaldehyde was added just prior to the addition of the β -keto imide in order to prevent the formation of any unwanted byproducts. The purified aldol product was treated with triethylsilane and $BF_3 \cdot Et_2O$ at $-78^\circ C$ for 1 h to afford tetrahydrofuran derivative **222**. Analysis of the crude reaction mixture showed a single observable diastereomer of the tetrahydrofuran derivative **222**, which once again confirmed the high diastereoselectivity of this reduction.

While the triethylsilane reduction proceeded very cleanly with high mass recovery, a significant amount of material was lost during purification by preparative thin layer chromatography, resulting in an isolated yield of only 24%. Repetition of this reaction and purification through an alternative method, such as flash chromatography, is predicted to result in a much higher yield.



Scheme 59: Synthesis of substituted tetrahydrofuran **222**

In order to establish the stereochemistry of the tetrahydrofuran, NMR investigations were undertaken. A COSY NMR experiment was performed to assign each proton resonance in the ^1H NMR spectrum. A NOESY NMR experiment was performed to show a NOE correlation between protons on the tetrahydrofuran ring (**Figure 7**). These correlations suggest that a *cis*-relationship exists between all of the substituents of the tetrahydrofuran ring. This is consistent with the predicted model in which the imide and R-group, installed stereoselectively during the tandem chain extension-aldol reaction, bias the addition of the hydride to the top face of the oxocarbenium ion **221** during the reduction.

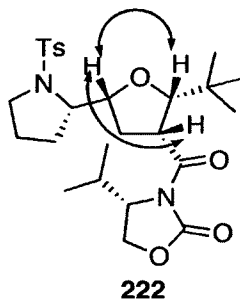
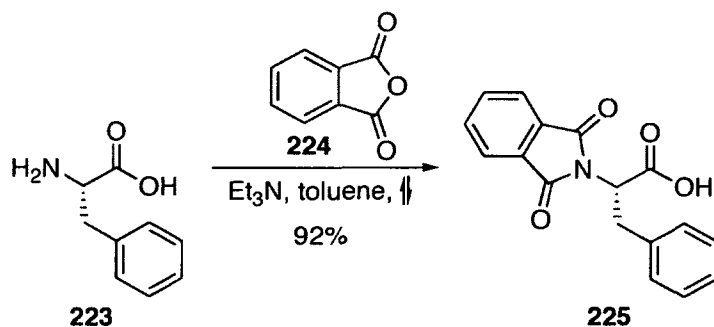


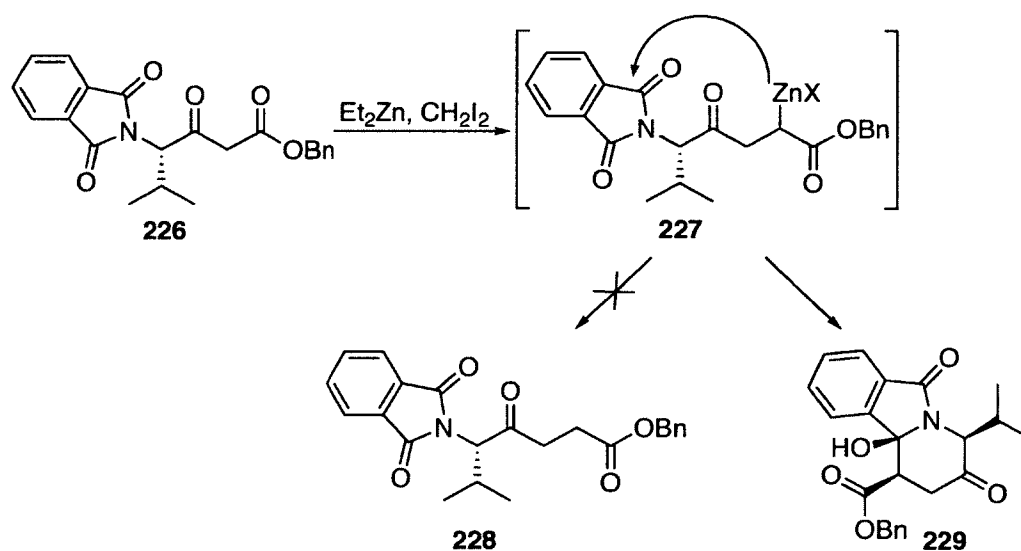
Figure 7: NOESY correlations between protons on the tetrahydrofuran ring

Based on the successful results observed during the reductive cyclization of the proline-derived systems, other amino acid-derived systems were investigated. L-Phenylalanine was chosen as an example of a primary amino acid. Di-protection of the N-terminus of L-phenylalanine can be accomplished in one step by stirring with phthalic anhydride and triethylamine in refluxing toluene (**Scheme 60**). The phthalimide protecting group was chosen since its symmetry avoids the appearance of rotameric forms.



Scheme 60: Phthalimide protection of L-phenylalanine

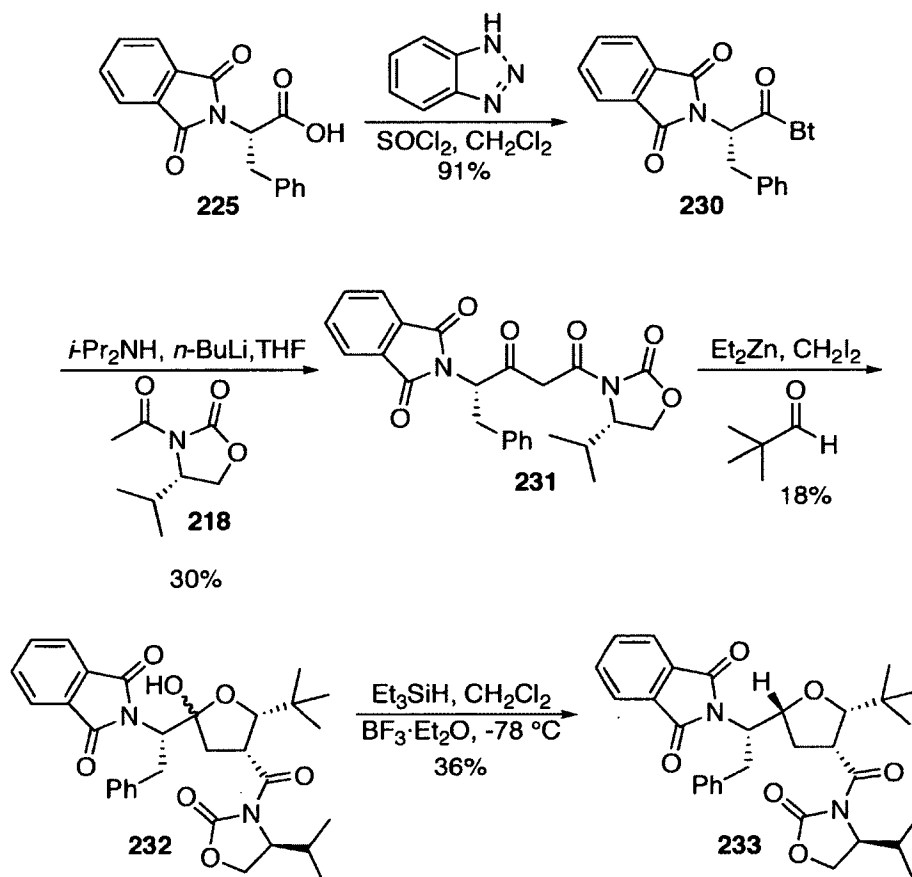
Phthalimide-protected β -keto ester **226** was prepared previously by Lin. When exposed to chain extension reaction conditions, a tricyclic byproduct (**229**) was formed instead of the expected γ -keto ester **228** (Scheme 61).¹⁶ Formation of this byproduct appears to be due to attack of the zinc-enolate into one of the phthalimide carbonyl groups.



Scheme 61: Chain extension of β -keto ester **226**

Since addition of pivaldehyde to the carbenoid before the addition of a β -keto imide was shown to avoid α -methylation of the zinc-enolate (Scheme 49), it was proposed that cyclization into the phthalimide protecting group could also be avoided by early introduction of the electrophilic aldehyde. β -Keto imide **231** was prepared through the use of a mixed Claisen reaction, in which benzotriazole-activated phenylalanine **230** was added to the enolate of an acylated oxazolidinone **218** (Scheme 62). The purified β -keto imide was subjected to the tandem chain extension-aldol reaction, which afforded

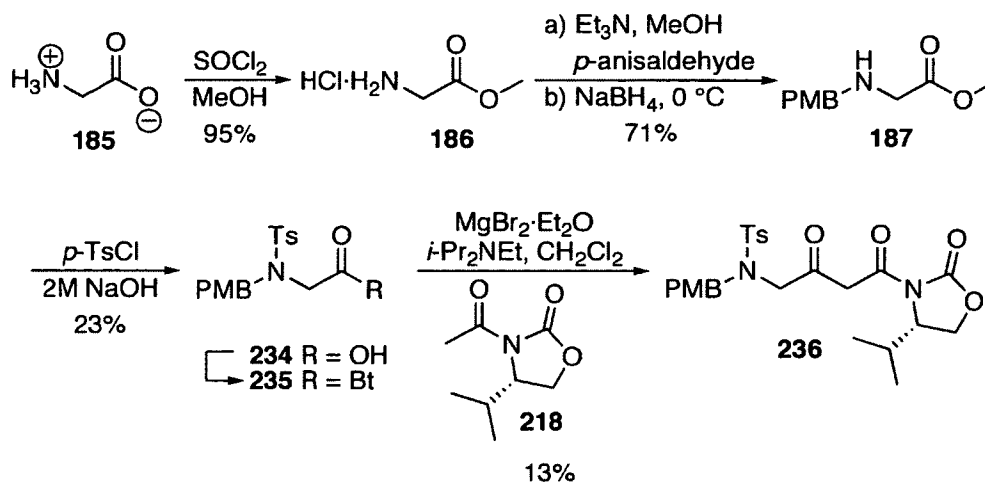
the aldol product in 18% yield. Triethylsilane reduction of the purified aldol product resulted in the synthesis of **233**, a single diastereomer of the substituted tetrahydrofuran as determined by ^1H NMR.



Scheme 62: Synthesis of embedded tetrahydrofuran **233**

In order to probe the effect of the amino acid stereocenter on the diastereoselectivity of the triethylsilane reduction, a glycine-derived β -keto imide was prepared (**Scheme 63**). Diprotected glycine **234** was prepared through a three-step process. Glycine was first converted to the methyl ester so as to reduce its water

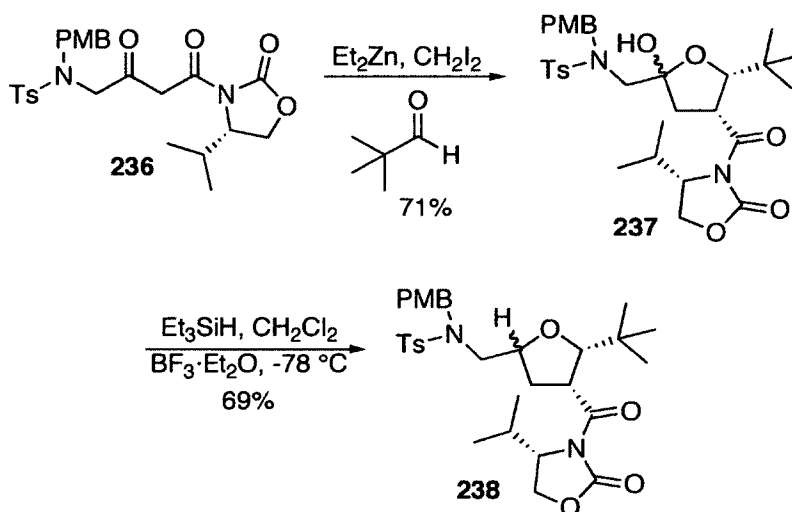
solubility and allow for easier handling during protection of its N-terminus. Diprotection was achieved through an initial reductive amination with *p*-anisaldehyde followed by treatment with *p*-TsCl in excess 2M NaOH. The excess 2M NaOH in the second protection step allowed for simultaneous saponification of the methyl ester. Diprotected glycine **234** was activated with benzotriazole and then converted to β -keto imide **236** through a modified mixed Claisen reaction.



Scheme 63: Synthesis of glycine derived β -keto imide **236**

Exposure of β -keto imide **236** to tandem chain extension-aldol reaction conditions, again using pivaldehyde as the electrophile, gave rise to hemiketal **237** in 71% yield (**Scheme 64**). This hemiketal was then treated with triethylsilane and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C to afford substituted tetrahydrofuran **238** as a 2:1 mixture of diastereomers. The diastereomeric ratio was calculated based on the integrations of the methoxy protons at 3.80 and 3.79 ppm. Unlike the result seen by Lin, the diastereoselectivity of this reductive cyclization suggests that the amino acid adjacent to the oxocarbenium ion does play a

role in biasing the facial selectivity of the intermediate oxocarbenium ion. In addition, it is possible that the presence of less hindered protecting groups blocked access to the top face of the oxocarbenium ion, resulting in the lower diastereocontrol. Subjection of a phenylalaine-derived β -keto imide, protected with both PMB and Ts protecting groups, to the same synthetic strategy may shed light on the influence of these bulky protecting groups.



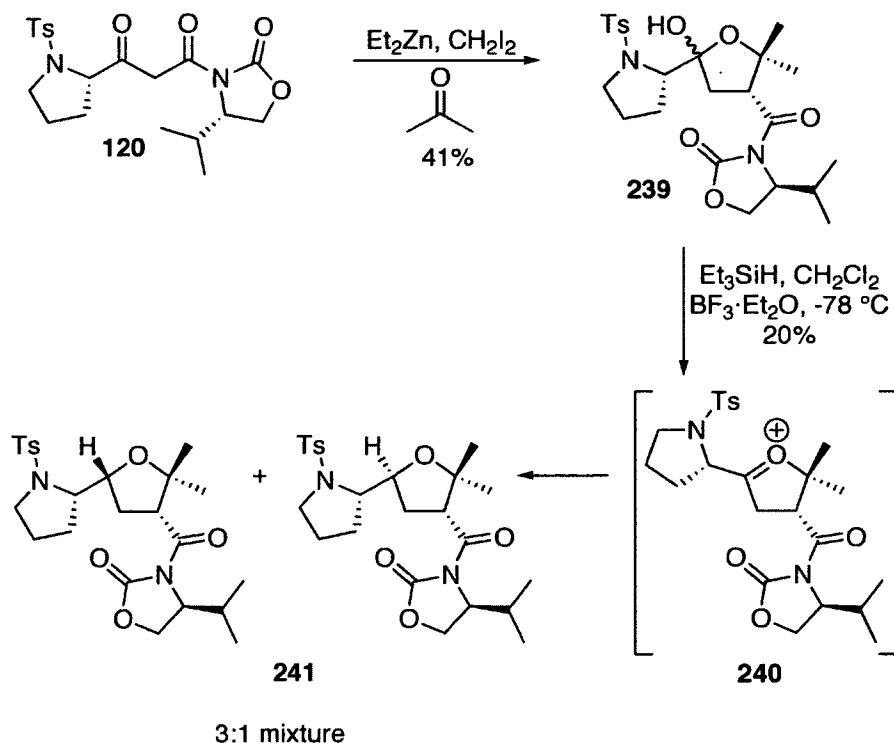
Scheme 64: Synthesis of embedded tetrahydrofuran **238**

The successful synthesis of a variety of amino acid derived tetrahydrofuran derivatives supports the utility of the tandem chain extension-aldol reaction as a route to embedded tetrahydrofuran isosteres. The *cis* relationship between the imide and aldehydic functional groups appears to bias addition of a hydride to the opposite face of the intermediate oxocarbenium ion.

Alternate Aldehydes and Ketones as Electrophiles

The next step in developing this methodology was to make use of aldehydes and ketones other than pivaldehyde. Due to ease of preparation, β -keto imide **120** was chosen as a starting material for these studies.

The first electrophile used to study this methodology was acetone. Acetone was chosen to probe the effect of having substitution on both faces of the five membered ring during the triethylsilane reduction. The tandem chain extension-aldol reaction between β -keto imide **120** and acetone resulted in the formation of aldol product **239** (Scheme 65). When this hemiketal was exposed to triethylsilane and boron trifluoride diethyl etherate at $-78\text{ }^{\circ}\text{C}$, an intermediate oxocarbenium ion, in which both faces of the five membered ring possessed substituents, was proposed to form. A 3:1 mixture of tetrahydrofuran diastereomers was calculated from the ^1H integrations of the methyl groups on the tetrahydrofuran ring at 1.26 and 1.24 ppm. This reduced diastereocontrol is expected, as hydride addition would encounter substituents on both faces of the tetrahydrofuran ring rather than on only one face, as is the case when an aldehyde is used as the electrophile.



Scheme 65: Synthesis of substituted tetrahydrofuran **241**

Use of benzaldehyde as an electrophile during the tandem chain extension-aldol reaction would allow for the incorporation of a phenylalanine-like side chain. This benzyl side chain has been previously incorporated into three different hydroxyethylene isosteres: Crixivan, Norvir, and Lopinavir (**Figure 8**).¹⁰⁰⁻¹⁰⁴ These three hydroxyethylene isosteres have been used successfully as HIV-protease inhibitors. Due to the similarities between hydroxyethylene isosteres and tetrahydrofuran-containing isosteres, it was desired to incorporate the benzyl functionality into a tetrahydrofuran derivative.

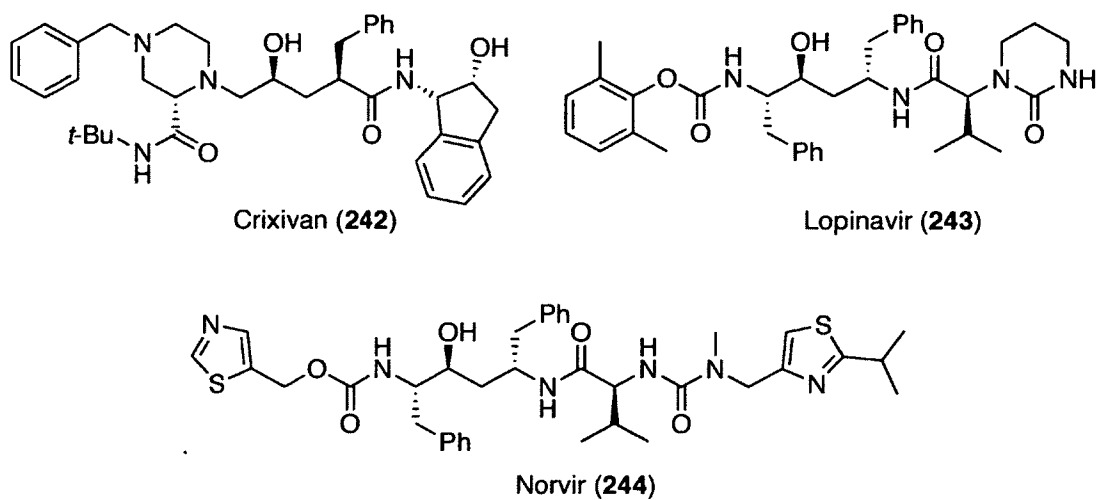
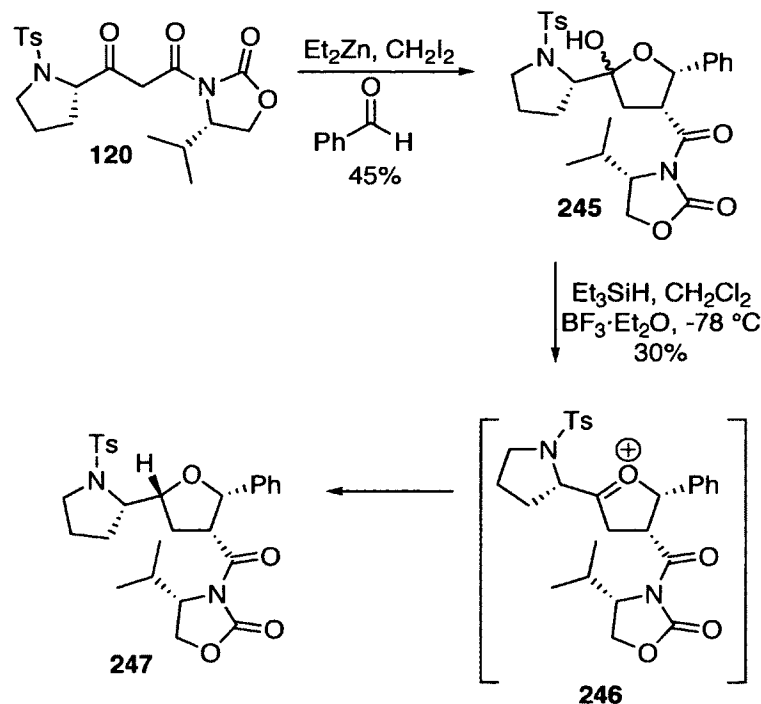


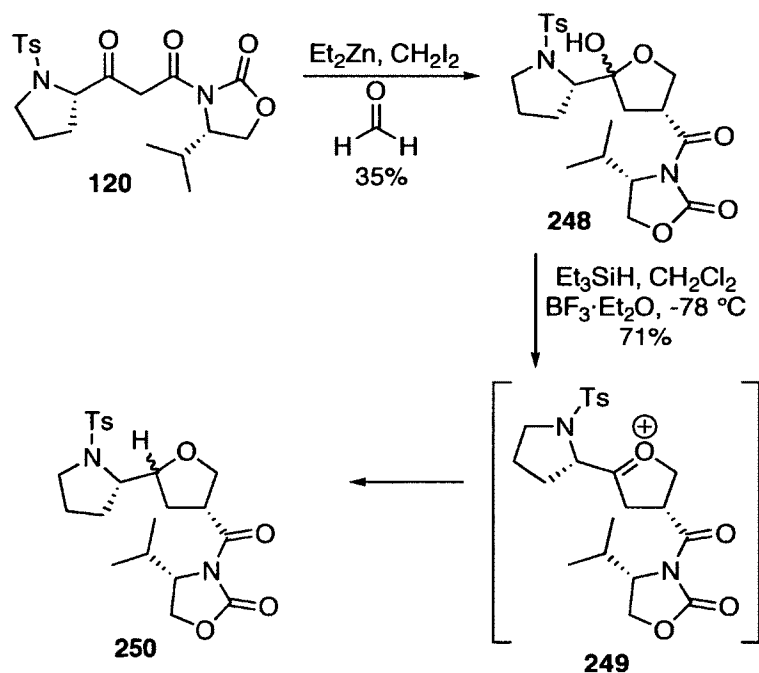
Figure 8: Hydroxyethylene isosteres

Treatment of β -keto imide **120** to the optimized tandem chain extension aldol reaction conditions with benzaldehyde acting as the electrophile resulted in the formation of *anti*-aldol product **245**. Exposure of the purified hemiketal to triethylsilane and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in the formation of the corresponding tetrahydrofuran derivative **247** as a single diastereomer in 30% yield.



Scheme 66: Synthesis of tetrahydrofuran derivative **247**

A tandem chain extension reaction was performed on β -keto imide **120** with formaldehyde in an attempt to incorporate a serine-type side chain as well as to probe the diastereoselectivity of the reduction with only one stereocenter present on the tetrahydrofuran ring. Due to the gaseous nature of formaldehyde, paraformaldehyde, a polymeric form of formaldehyde, was used in the reaction. The hemiketal (**248**) formed during this reaction was subjected to triethylsilane reduction, which resulted in the formation of tetrahydrofuran **249** in 71% yield. Analysis of the ^1H NMR spectrum of the crude reaction mixture showed a 1.4:1 mixture of diastereomers. This low diastereoselectivity corresponds to the results observed by Lin (**Scheme 50**) in studies using formaldehyde, as well as to the results obtained in the reductive cyclization of compound **239** (**Scheme 65**), which used acetone in the aldol reaction.



Scheme 67: Synthesis of tetrahydrofuran derivative **250**

Conclusion

Use of the tandem chain extension-aldol reaction starting from amino acid derived β -keto imides provides easy access to the corresponding *anti*-aldol products. These compounds are cleanly converted to the corresponding tetrahydrofuran derivatives in good yield through the use of triethylsilane and boron trifluoride diethyl etherate. When an aldehyde is used as an electrophile during the tandem chain extension-aldol reaction, the resulting substitution pattern leads to high diastereocontrol during reductive cyclization. The role of the amino acid adjacent to the oxocarbenium ion in the stereochemical outcome of the triethylsilane reduction is unclear. Use of an *L*-amino acid introduces a *S* stereocenter α to the oxocarbenium ion. Through the use of the Felkin-Ahn

model,¹⁰⁵ hydride addition is predicted to be biased toward the *re*-face of the intermediate oxocarbenium ion. This influence appears to be mismatched with the influence of the steric bulk of the functional groups on the tetrahydrofuran ring, which would direct the hydride addition to the *si*-face of the same oxocarbenium ion. Never the less, application of the tandem homologation-aldol reaction followed by triethylsilane reduction to a β -keto imide derived from a *D*-amino acid may help shed light on the role of the amino acid stereocenter.

CHAPTER V

GENERAL EXPERIMENTAL SECTION

Solvents

Anhydrous solvents, dichloromethane, tetrahydrofuran, toluene, and methanol, were obtained from an Innovative Technology Inc. Solvent Delivery System prior to use by passing through drying agent with nitrogen pressure.

Reagents

Unless otherwise noted, all reagents were obtained from commercial sources and used as received. β -Keto esters, aldehydes, and amines were dried, distilled, and stored over 3 Å sieves in a desiccator.

Reactions

Reaction glassware and magnetic stir bars were stored in an oven at 200 °C prior to use. Sigma-Aldrich Natural Rubber Septa and Teflon coated magnetic stir bars were used

unless otherwise noted. Nitrogen gas was introduced into reaction vessels through a Tygon® tube with a needle or gas inlet adapter.

Chromatography

Flash column chromatography was performed using Silica-P Flash Silica Gel with 40-63 μm particle size. Mobile phases were freshly prepared. Preparative chromatography was performed through the use of Analtech Uniplate Silica Gel GF 1000 microns with UV 254 glass-backed plates. Thin layer chromatography (TLC) analysis was conducted on glass-backed Silica Gel 60 Å 250 μm thickness with fluorescent indicator. TLC plates were visualized under UV light and through the use of anisaldehyde, phosphomolybdic acid, or potassium permanganate stain. Unless otherwise stated, TLC solvent systems were identical to the mobile phase used for column chromatography.

Spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy was conducted using a Varian *Mercury* spectrometer operating at 500 or 400 MHz for ^1H and at 126 or 100 MHz for ^{13}C spectroscopy. All ^1H resonances were reported relative to a TMS (δ 0 ppm) reference. All ^{13}C resonances were referenced to CDCl_3 (δ 77.16 ppm) or TMS (δ 0 ppm). Infrared (IR) spectroscopy was conducted using a Thermo Nicolet iS10 FTIR using a diamond ATR probe. Diastereomeric ratios were calculated from integrations obtained by applying a MestReNova line fit simulation in the ^1H spectra.

DETAILED EXPERIMENTAL SECTION

Methyl 2-acetyl-5,5-dimethyl-4-oxohexanoate (93)

Method A: An oven-dried, 50-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and a nitrogen gas inlet was charged with dichloromethane (20 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added to the flask via syringe in one portion. Methyl pivaloylacetate (0.16 g, 0.16 mL, 1 mmol) was added to the solution via syringe and allowed to stir for 5 min before the slow addition of diiodomethane (0.08 mL, 1 mmol) over 30 seconds. The solution was stirred for 1 h before the addition of acetic anhydride (0.07 mL, 1 mmol) in one portion via syringe. The reaction was stirred for 2 h then quenched with saturated ammonium chloride. Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a mobile phase of 8:1 hexane – ethyl acetate ($R_f = 0.15$) to afford 136 mg (63%) of the title compound as a clear oil.

Method B: An oven-dried, 50-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and a nitrogen gas inlet was charged with dichloromethane (20 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.51 mL, 5 mmol) was added

to the flask via syringe in one portion. Methyl pivaloylacetate (0.16 g, 0.16 mL, 1 mmol) was added to the solution via syringe and allowed to stir for 10 min before the drop-wise addition of diiodomethane (0.08 mL, 1 mmol). The solution was stirred for 1 h before the addition of benzotriazole-activated acetic acid (**131**) (242 mg, 1.5 mmol) in dichloromethane (2 mL) in one portion via syringe. The solution was stirred for 17 h at room temperature before being quenched with saturated ammonium chloride. Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a mobile phase of 20% diethyl ether in hexane ($R_f = 0.15$), to afford 102 mg (48%) of the title compound as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 3.98 (dd, $J = 8.4, 5.6$ Hz, 1 H), 3.69 (s, 3H), 3.19 (dd, $J = 18.5, 8.4$ Hz, 1H), 2.98 (dd, $J = 18.5, 5.6$ Hz, 1H), 2.32 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 213.8, 206.5, 174.9, 52.2, 44.2, 37.7, 35.5, 30.1, 26.4; IR (neat) ν 2969, 1743, 1702, 1479, 1435, 1397, 1362, 1249, 1148 cm^{-1} .

2-(Methoxycarbonyl)-5,5-dimethyl-1-phenyl-1,4-hexanedione (95)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of methyl pivaloylacetate **84** (0.16 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 5 min

before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting solution was allowed to stir for 45 min while warming to room temperature. Benzoic anhydride (0.34 g, 1.5 mmol) dissolved in dichloromethane (2 mL) was added at room temperature and stirred for 1 h. The reaction was quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with hexane – ethyl acetate (6:1) ($R_f = 0.21$), to afford the title compound **95** as a clear oil in 95% (261 mg) yield. ^1H NMR (500 MHz, CDCl_3) δ 8.04 (d, $J = 8.0$ Hz, 2H), 7.59 (m, 1H), 7.49 (t, $J = 7.9$ Hz, 2H), 4.94 (dd, $J = 7.7, 6.1$ Hz, 1H), 3.67 (s, 3H), 3.33 (dd, $J = 18.3, 7.8$ Hz, 1H), 3.23 (dd, $J = 18.3, 6.1$ Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 213.1, 195.0, 170.0, 136.1, 133.7, 129.0, 128.9, 52.8, 48.6, 44.1, 36.8, 26.5; IR (neat) ν 2969, 2872, 1739, 1685, 1448, 1275, 1232 cm^{-1} .

Methyl 2-acetyl-4-oxo-4-phenylbutanate (112)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of methyl benzoylacetate **105** (0.18 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 10

min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting solution was allowed to stir for 1 h while warming to room temperature. Acetic anhydride (0.11 mL, 1.5 mmol) was added at room temperature and stirred for 2 h. The reaction was quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 30%, 40%, 50% diethyl ether in hexane ($R_f = 0.36$, 50% diethyl ether in hexane), to afford 125 mg (50%) of the title compound **112** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 7.99 (m, 2H), 7.57, (tt, $J = 7.4, 1.3$ Hz, 1H), 7.46 (m, 2H), 4.24 (dd, $J = 8.2, 5.6$ Hz, 1H), 3.77 (s, 3H), 3.73 (dd, $J = 18.4, 8.2$ Hz, 1H), 3.53 (dd, $J = 18.4, 5.6$ Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 202.3, 197.1, 169.4, 136.0, 133.6, 128.7, 128.2, 53.7, 52.8, 37.5, 30.3; IR (neat) ν 3005, 2954, 2923, 2851, 1741, 1716, 1682, 1597, 1449, 1358, 1263, 1168, 1001, 754 cm^{-1} .

1-((S)-4-Isopropyl-2-oxooxazolidin-3-yl)-3-((S)-1-tosylpyrrolidin-2-yl)propane-1,3-dione (120)

An oven-dried, 250-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry tetrahydrofuran (150 mL) and cooled to 0 °C in an ice-water bath. Diisopropylamine (2.8 mL, 20 mmol) was added, followed by the slow addition of 2.5M *n*-butyl lithium (8 mL, 20 mmol). The

solution was stirred for 15 min to allow for formation of lithium diisopropylamine (LDA), then cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice-acetone bath. Acylated oxazolidinone **219** (3.71 g, 20 mmol) was dissolved in tetrahydrofuran (20 mL) then slowly added to the LDA solution via syringe pump over 100 min. Benzotriazole-activated proline **218** (3.71 g, 10 mmol) was dissolved in tetrahydrofuran (40 mL) and added to the reaction mixture then allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 h. The reaction was quenched with 3M hydrochloric acid (10 mL) then extracted with ethyl acetate (3 x 20 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a viscous yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 40% ethyl acetate in hexane ($R_f = 0.28$) to yield β -keto imide **120** (1.93 g, 46%) as a light yellow, viscous oil. ^1H NMR (500 MHz, CDCl_3) δ 7.72 (d, $J = 8.6$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 4.58 (d, $J = 17.3$ Hz, 1H), 4.48 (dt, $J = 8.2, 3.7$ Hz, 1H), 4.33 (m, 1H), 4.30 (d, $J = 8.7$ Hz, 1H), 4.23 (dd, $J = 9.1, 3.0$ Hz, 1H), 4.14 (m, 1H), 3.54 (ddd, $J = 10.3, 7.3, 5.0$ Hz, 1H), 3.27 (dt, $J = 9.8, 7.6$ Hz, 1H), 2.50 (septet of doublets, $J = 7.2, 3.6$ Hz, 1H), 2.44 (s, 1H), 2.24 (m, 3H), 1.88 (ddd, $J = 15.2, 10.5, 7.2$ Hz, 1H), 1.67 (m, 1H), 1.53 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 204.2, 166.8, 154.3, 144.1, 133.6, 129.9, 127.8, 67.3, 63.7, 58.5, 49.6, 48.4, 29.0, 28.3, 24.6, 21.6, 17.9, 14.5; IR (neat) ν 2965, 1774, 1724, 1699, 1389, 1334, 1211, 1158 cm^{-1} .

Methyl 2-(isobutyryl)-5,5-dimethyl-4-oxohexanoate (121)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20

mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of methyl pivaloylacetate **84** (0.16 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 10 min before the slow addition, over 30 sec, of diiodomethane (0.09 mL, 1.1 mmol) via syringe. The resulting solution was allowed to stir for 1 h while warming to room temperature. Isobutyric anhydride (0.25 mL, 1.5 mmol) was added to the solution via syringe and allowed to stir for 3 h. The reaction was quenched with saturated ammonium chloride (2 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 15%, 20%, 30%, diethyl ether in hexane ($R_f = 0.43$, 30% diethyl ether in hexane) to afford 194 mg (80%) of the title compound **121** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 4.21 (dd, $J = 8.2, 5.7$ Hz, 1H), 3.72 (s, 3H), 3.20 (dd, $J = 18.3, 8.2$ Hz, 1H), 2.99 (dd, $J = 18.3, 5.7$ Hz, 1H), 2.93 (septet, $J = 6.9$ Hz, 1H), 1.18 (d, $J = 7.1$, 3H), 1.17 (s, 9H), 1.12 (d, $J = 6.8$, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 213.1, 208.5, 170.0, 52.7, 51.4, 44.1, 41.0, 35.9, 26.6, 18.8, 18.0; IR (neat) ν 2971, 2875, 1743, 1704 cm^{-1} .

***tert*-Butyl 2-acetyl-4-oxopentanoate (122)**

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3

mmol) was added via syringe in one portion followed by the addition of *tert*-butyl acetoacetate **117** (0.16 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 10 min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting solution was allowed to stir for 1 h while warming to room temperature. Acetic anhydride (0.11 mL, 1.5 mmol) was added at room temperature and stirred for 3 h. The reaction was quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient of 2%, 5%, 7%, 10%, 15%, 20%, 25% diethyl ether in hexane ($R_f = 0.18$, 25% diethyl ether in hexane), to afford 107 mg (50%) of the title compound **122** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 3.94 (dd, $J = 8.2, 5.7$ Hz, 1H), 3.09 (dd, $J = 18.5, 8.3$ Hz, 1H), 2.90 (dd, $J = 18.5, 5.7$ Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 205.9, 202.8, 167.9, 82.5, 54.9, 41.7, 30.2, 29.9, 28.0; IR (neat) ν 2979, 2934, 1737, 1712, 1368, 1257, 1141 cm^{-1} .

***tert*-Butyl 2-benzoyl-4-oxopentanoate (123)**

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of *t*-butyl

acetoacetate **117** (0.18 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 5 min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting solution was allowed to stir for 30 min while warming to room temperature. Benzoic anhydride (0.34 g, 1.5 mmol) was added to the solution via syringe and allowed to stir for 2 h. The reaction was quenched with saturated ammonium chloride (2 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a mobile phase of hexane – ethyl acetate (6:1) ($R_f = 0.21$) to afford 128 mg (73%) of the title compound **123** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 8.02 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 4.81 (dd, $J = 7.7, 6.1$ Hz, 1H), 3.20 (dd, $J = 18.2, 7.7$ Hz, 1H), 3.09 (dd, $J = 18.2, 6.1$ Hz, 1H), 2.24 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 205.8, 195.1, 168.4, 136.4, 133.5, 129.0, 128.7, 82.54, 50.1, 42.2, 30.1, 27.9; IR (neat) ν 2979, 1737, 1721, 1688, 1369, 1249, 1148 cm^{-1} .

Allyl 2-acetyl-4-oxopentanoate (124)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of allyl acetoacetate **118** (0.14 g, 0.14 mL, 1 mmol). The solution was stirred at 0 °C for 5 min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting

solution was allowed to stir for 30 min while warming to room temperature. Acetic anhydride (0.11 mL, 1.5 mmol) was added to the solution via syringe and allowed to stir for 2 h. The reaction was quenched with saturated ammonium chloride (2 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 25%, 30% diethyl ether in hexane ($R_f = 0.15$, 30% diethyl ether in hexane) to afford 87 mg (44%) of the title compound **124** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 5.90 (ddt, $J = 17.2, 10.4, 5.8$ Hz, 1H), 5.33 (dq, $J = 17.2, 1.5$ Hz, 1H), 5.27 (dq, $J = 10.4, 1.2$ Hz, 1H), 4.64 (dt, $J = 5.8, 1.4$ Hz, 2H), 4.06 (dd, $J = 8.3, 5.7$ Hz, 1H), 3.16 (dd, $J = 18.3, 8.3$ Hz, 1H), 2.97 (dd, $J = 18.5, 5.7$ Hz, 1H), 2.37 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 205.7, 202.2, 168.6, 131.4, 119.3, 66.4, 53.8, 41.7, 30.3, 29.8; IR (neat) ν 3005, 1742, 1712, 1359, 1261, 1158, 934 cm^{-1} .

2-(Allyloxycarbonyl)-1-phenyl-1,4-pentanedione (125)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of allyl acetoacetate **118** (0.14 g, 0.14 mL, 1 mmol). The solution was stirred at 0 °C for 5 min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting

solution was allowed to stir for 30 min while warming to room temperature. Benzoic anhydride (0.34 g, 1.5 mmol) dissolved in dichloromethane (2 mL) was added at room temperature and stirred for 2.5 h. The reaction was quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 25% diethyl ether in hexane ($R_f = 0.15$, 25% diethyl ether in hexane), to afford 143 mg (55%) of the title compound **125** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 8.03 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 5.78 (ddt, $J = 17.2, 9.6, 5.6$ Hz, 1H), 5.20-5.15 (m, 2H), 4.95 (dd, $J = 7.2, 6.5$ Hz, 1H), 4.57 (dt, $J = 5.6, 1.3$ Hz, 2H), 3.24 (dd, $J = 18.3, 7.4$ Hz, 1H), 3.17 (dd, $J = 18.3, 6.4$ Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 205.4, 194.6, 169.0, 135.9, 133.8, 131.4, 129.0, 128.8, 118.6, 66.2, 48.7, 42.4, 29.9; IR (neat) ν 3064, 2949, 1737, 1716, 1682, 1269, 1155 cm^{-1} .

Methyl 2-benzoyl-4-oxo-4-phenylbutanoate (126)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of methyl benzoylacetate **105** (0.18 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 5 min

before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting solution was allowed to stir for 1 h while warming to room temperature. Benzoic anhydride (0.3396 g, 1.5 mmol) was dissolved in dichloromethane (2 mL) and added to the solution and allowed to stir for 2 h. The reaction was quenched with saturated ammonium chloride (2 mL) and diluted with saturated sodium chloride (10 mL). The solution was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with hexane – dichloromethane (2:3) ($R_f = 0.24$), to afford 185 mg (62%) of the title compound **126** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 8.10 (m, 2H), 8.00 (m, 2H), 7.61 (m, 1H), 7.57 (m, 1H), 7.50 (m, 2H), 7.46 (m, 2H), 5.15 (dd, $J = 7.6, 6.1$ Hz, 1H), 3.83 (dd, $J = 18.2, 7.6$ Hz, 1H), 3.74 (dd, $J = 18.2, 6.0$ Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 197.0, 194.8, 169.9, 136.2, 136.2, 133.8, 133.7, 129.1, 128.9, 128.8, 128.4, 53.0, 48.7, 38.5; IR (neat) ν 3343, 2954, 2923, 2853, 1738, 1680, 1596, 1448, 1274, 1274 cm^{-1} .

2-Benzoyl-*N,N*-dimethyl-4-oxopentanamide (127)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of *N,N*-dimethylacetoacetamide **119** (0.10 g, 0.12 mL, 1 mmol). The solution was stirred at 0 °C for 5 min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via

syringe. The resulting solution was allowed to stir for 30 min while warming to room temperature. Benzoic anhydride (0.34 g, 1.5 mmol) dissolved in dichloromethane (2 mL) was added via syringe at room temperature turning the solution a bright yellow color. The reaction was stirred for 2 h before being quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 30%, 40%, 50%, 60%, 70% ethyl acetate in hexane ($R_f = 0.13$, 1:1 ethyl acetate - hexane), to afford 199 mg (80%) of the title compound **127** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 7.95 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H) 5.08 (dd, $J = 8.0, 5.1$ Hz, 1H), 3.23 (dd, $J = 17.7, 8.0$ Hz, 1H), 3.02 (s, 3H), 2.97 (s, 3H), 2.94 (dd, $J = 17.8, 5.1$ Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 205.8, 195.9, 169.0, 135.5, 133.8, 129.1, 128.5, 47.9, 42.5, 37.6, 36.1, 30.3; IR (neat) ν 2931, 1715, 1692, 1636, 1396, 1263, 1166 cm^{-1} .

2-Benzoyl-1-((S)-4-isopropyl-2-oxooxazolidin-3-yl)-4-((S)-1-tosylpyrrolidin-2-yl)butane-1,4-dione (128)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (17 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion. β -Keto imide **120** (0.42 g, 1 mmol) (see

formation of **217** – **218** for the formation of **120**) was dissolved in dichloromethane (3 mL) then added to the solution via syringe. The solution was stirred at 0 °C for 5 min before the slow addition, over 30 sec, of diiodomethane (0.08 mL, 1 mmol) via syringe. The resulting solution was allowed to stir for 1 h while warming to room temperature. Benzoic anhydride (0.34 g, 1.5 mmol) dissolved in dichloromethane (2 mL) was added via syringe at room temperature. The reaction was stirred for 1 h before being quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford a 6:1 mixture of diastereomers as a yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 10%, 15%, 20%, 30% 40%, 50%, 60%, ethyl acetate in hexane ($R_f = 0.35$, 1:1 ethyl acetate - hexane), to afford 287 mg (53%) of the title compound **128** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 8.01 (m, 2H), 7.67 (m, 2H), 7.59 (m, 1H), 7.50 (m, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 5.86 (dd, $J = 11.7, 2.5$ Hz, 1H), 4.44 (dt, $J = 8.3, 2.9$ Hz, 1H), 4.32 (t, $J = 9.0$ Hz, 1H), 4.23 (dd, $J = 9.2, 2.8$ Hz, 1H), 3.91 (dd, $J = 9.0, 6.1$ Hz, 1H), 3.60 (dt, $J = 12.7, 6.3$ Hz, 1H), 3.48 (dd, $J = 18.6, 11.7$ Hz, 1H), 3.27 – 3.20 (m, 2H), 2.52 (septet of doublets, $J = 7.1, 4.0$ Hz, 1H), 2.43 (s, 3H), 2.17 (m, 1H), 1.99 (m, 1H), 1.93 (m, 1H), 1.54 (m, 1H), 0.94 (t, $J = 6.7, 6\text{H}$); ^{13}C NMR (126 MHz, CDCl_3) δ 208.0, 197.2, 169.4, 154.2, 144.3, 134.7, 133.8, 133.0, 129.1, 128.9, 127.9, 67.7, 63.8, 60.5, 58.7, 50.0, 49.8, 37.0, 30.4, 28.4, 24.9, 21.7, 18.1, 14.6; IR (neat) ν 2963, 1774, 1703, 1389, 1342, 1205, 1159 cm^{-1} .

1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)ethanone (131)

An oven-dried, 250-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry dichloromethane (75 mL). 1-*H*-Benzotriazole (7.15 g, 60 mmol) was added as a solid. Thionyl chloride (1.1 mL, 15 mmol) was added via syringe and stirred at room temperature for 30 min. Acetic acid (0.86 mL, 15 mmol) was added via syringe and stirred for 2 h. The resulting solution was filtered and the filtrate was washed with 2M sodium hydroxide (3 x 75 mL), dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to afford 1.81 g (75%) of the title compound **131** as a white solid. (m.p. 46.2 – 47.5 °C) (Lit. 49-51 °C)¹⁰⁶; ¹H NMR (500 MHz, CDCl₃) δ 8.28 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.65 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 7.51 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 3.01 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.7, 146.4, 131.1, 130.5, 126.3, 126.1, 120.2, 114.5, 23.3; IR (neat) ν 1735, 1484, 1448, 1378, 1287, 1207, 1074 cm⁻¹.

***tert*-Butyl 2-oxopyrrolidine-1-carboxylate (132)¹⁰⁷**

An oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry acetonitrile (20 mL). 2-Pyrrolidinone (0.76 mL, 10 mmol) was added to the flask followed by the addition of di-*tert*-butyl dicarbonate (2.62 g, 12 mmol) and dimethylaminopyridine (0.13 g, 1 mmol). The solution was stirred at room temperature for 2 h then concentrated by rotary evaporation. The residue was dissolved in ethyl acetate (20 mL) and washed with water (10 mL), and saturated sodium chloride (10 mL). The organic layer was dried over

anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a clear oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.30$) to yield 1.85 g (100%) of the title compound **132** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 3.75 (ddd, $J = 7.3, 6.8, 0.8$ Hz, 2H), 2.51 (ddd, $J = 8.4, 7.8, 1.0$ Hz, 2H), 2.00 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 150.3, 82.8, 46.5, 33.0, 28.1, 17.5; IR (neat) ν 2979, 2360, 1780, 1748, 1709, 1366, 1297, 1250, 1146 cm^{-1} .

6-*tert*-Butyl-4-methyl-2-(*tert*-butyl)-2-hydroxy-1-oxa-6-azaspiro[4.4]nonane-4,6-dicarboxylate (133)

An oven-dried, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL) via syringe and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.31 mL, 3 mmol) was added via syringe in one portion followed by the addition of methyl pivaloylacetate **84** (0.16 g, 0.16 mL, 1 mmol). The solution was stirred at 0 °C for 10 min before the slow addition, over 30 sec, of diiodomethane (0.09 mL, 1.1 mmol) via syringe. The resulting solution was allowed to stir for 2 h while warming to room temperature. 1,1-Dimethylethyl 2-oxo-1-pyrrolidinecarboxylate (0.26 mL, 0.28 g, 1.5 mmol) was added at room temperature and stirred for 3 h. The reaction was quenched with saturated ammonium chloride (2 mL). Saturated sodium chloride (10 mL) was added to the solution and the organic layer was removed. The remaining aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate (ca 2 g), filtered, and concentrated via rotary evaporation (20 mmHg,

20 °C) to afford a viscous yellow oil. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 30% diethyl ether in hexane ($R_f = 0.17$, 30% diethyl ether in hexane), to afford 227 mg (64%) of the title compound **133** as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 4.44 (dd, $J = 12.6, 7.5$ Hz, 1H), 3.71 (s, 3H), 3.56 (m, 1H), 3.35 (dt, $J = 13.9, 7.0$ Hz, 1H), 2.82 (m, 1H), 2.58 (t, $J = 6.6$ Hz, 1H), 2.49 (t, $J = 12.6$ Hz, 1H), 2.05 (dd, $J = 12.6, 7.5$ Hz, 1H), 1.97-1.79 (m, 2H), 1.48 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.6, 154.5, 108.6, 100.6, 81.2, 52.0, 48.0, 46.4, 37.5, 36.9, 36.5, 28.6, 25.4, 21.7; IR (neat) ν 3398, 2971, 1744, 1701, 1515, 1366, 1249, 1166 cm^{-1} .

3-Methoxyfuran-2,5-dione (3-methoxymaleic anhydride) (145)¹⁰⁸

An oven-dried 100-ml round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with dry methanol (50 mL). Dimethylacetylenedicarboxylate (3.7 mL, 4.3 g, 30 mmol) was added in one portion. Triethylamine (2.4 mL, 1.7 g, 17 mmol) was added to the reaction drop wise via syringe to produce a deep amber solution. The reaction was stirred for 2.5 h then concentrated by rotary evaporation (20 mmHg, 25 °C) to yield dimethyl 2-methoxybut-2-enedioate as a dark orange oil (5.3 g, 100%). The product did not require further purification and was carried on as a mixture of *E*- and *Z*-isomers in a 2:1 ratio. ^1H NMR (400 MHz, CDCl_3) *E*-isomer: δ 6.19 (s, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H). *Z*-isomer δ 5.21 (s, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) *E*-isomer: δ 164.8, 163.3, 154.9, 107.8, 57.1, 51.9. *Z*-isomer: δ 166.3, 164.0, 162.6, 93.2, 61.2, 53.0; IR (neat) ν 2954, 1717, 1628, 1435, 1370, 1261, 1209, 1171, 1144, 1030 cm^{-1} .

A 300-mL round-bottomed flask was equipped with a magnetic stir bar and charged with dimethyl 2-methoxybut-2-enedioate and methanol (90 mL). A 4 N aqueous potassium hydroxide solution (80 mL) was added to the reaction and allowed to stir for 20 h at room temperature. The resulting solution was cooled to 0 °C in an ice-water bath then acidified to pH 2 with 10 M hydrochloric acid solution, and extracted with diethyl ether (5 × 150 mL). The combined organics were dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation (20 mmHg, 25 °C) to afford 2-methoxybut-2-enedioic acid as a white solid (3.7 g, 85%). The product did not required further purification and was carried on as a mixture of *E*- and *Z*-isomers in a 2:1 ratio. ¹H NMR (400 MHz, acetone-d₆) *E*-isomer: δ 6.17 (s, 1H), 3.93 (s, 3H), *Z*-isomer: δ 5.34 (s, 1H), 3.81 (s, 3H); ¹³C NMR (100 MHz, acetone-d₆) δ 165.8, 164.6, 162.8, 154.7, 107.4, 91.8, 59.9, 56.3, 50.4, 48.9; IR (neat) ν 2957, 1689, 1403, 1269, 1221, 1113 cm⁻¹.

An oven-dried, 25-mL, round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and nitrogen gas inlet was charged with 2-methoxybut-2-enedioic acid (0.88 g, 6.0 mmol). Thionyl chloride (13 mL) was added directly to the flask via syringe producing a gaseous evolution. The solution was stirred at room temperature for 1 h before being heated to reflux for 18 h. The solvent was removed by distillation under reduced pressure (4 mmHg, 25 °C) to afford a yellow solid. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane (*R_f* = 0.3) to afford 498 mg of the title compound **145** as an off white solid (65%). (m.p. 152 – 155 °C; Lit. 152 – 155 °C)¹⁰⁸; ¹H NMR (400 MHz, CDCl₃) δ

5.79 (s, 1H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.8, 161.7, 160.6, 98.7, 60.4; IR (neat) ν 3129, 1855, 1765, 1640, 1455, 1439, 1341, 1219 cm^{-1} .

Allyl (3S,4S)-2-hydroxy-9-methoxy-2,3-dimethyl-7-oxo-1,6-dioxaspiro[4.4]non-8-ene-4-carboxylate (146)

An oven-dried, 100-mL, round-bottomed flask, equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet, was charged with dry dichloromethane (60 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.77 mL, 7.5 mmol) was added in one portion via an oven-dried needle. Allyl acetoacetate **144** (0.41 mL, 3 mmol) was added and stirred for 10 min before the dropwise addition of 1,1-diiodoethane (0.76 mL, 7.5 mmol). The reaction was stirred for 30 min while warming to room temperature then cooled back to 0 °C. A second portion of diethylzinc (0.77 mL, 7.5 mmol) was added and stirred for 10 min. 1,1-Diiodoethane (0.76 mL, 7.5 mmol) was slowly added and the reaction was stirred for another 3 h while warming to room temperature. A solution of 3-methoxymaleic anhydride (410 mg, 3.2 mmol) in dichloromethane (4 mL) was slowly added to the reaction mixture then stirred at room temperature for 1 day. The reaction was quenched with 3N hydrochloric acid (30 mL) and extracted with ethyl acetate (5 x 20 mL). The organic layers were washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a brown, viscous oil (0.97 g, ~100% of expected mass recovery). The title compound was carried on without further purification. Characteristic resonances for the major isomer of hemiketal **146b**: ^1H NMR (500 MHz, CDCl_3) δ 5.28 (s, 1H), 4.00 (s, 3H), 3.48 (d, J = 12.4 Hz, 1H), 2.75 – 2.65 (m, 1H), 1.61 (s, 3H), 1.21 (d, J = 6.7 Hz, 3H); All carbon

resonances for the crude product mixture: ^{13}C NMR (126 MHz, CDCl_3) δ 177.1, 167.1, 131.3, 119.7, 108.4, 107.6, 98.8, 95.1, 90.8, 66.6, 65.9, 61.5, 60.6, 54.4, 43.2, 42.8, 37.0, 26.2, 21.5, 16.7, 14.3, 12.2; IR (neat) ν 3424, 2983, 1743, 1646, 1454, 1374, 1279, 1250, 1206 cm^{-1} .

(2R,3S,4S,5R)-Allyl 9-methoxy-2,3-dimethyl-7-oxo-2-(2,2,2-trichloroethoxy)-1,6-dioxaspiro[4.4]non-8ene-4-carboxylate (147)

An oven-dried, 100-mL, round-bottom flask equipped with a magnetic stir bar, rubber septum, and calcium sulfate drying tube was charged with crude hemiketal **146** (2.84 g, 3 mmol) and toluene (30 mL). 2,2,2-Trichloroethanol (0.43 mL, 0.67 g, 4.5 mmol) was added via syringe followed by the addition of *p*-toluene sulfonic acid (49 mg, 0.28 mmol) as a solid. The solution was stirred at room temperature for 2 days. The reaction mixture was then concentrated by rotary evaporation yielding a viscous black oil. The crude product was purified by flash chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 22.5%, 25% ethyl acetate in hexane to afford the title mixed ketal **147** as a white solid (0.39 g, 32%). (R_f = 0.23, 20% ethyl acetate in hexane); (m.p. 106.4-107.2 $^\circ\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ 5.83 (ddt, J = 17.2, 11.9, 6.0 Hz, 1H), 5.29 (m, 1H), 5.25 (m, 1H), 5.14 (s, 1H), 4.61 (ddt, J = 13.0, 5.7, 1.2 Hz, 1H), 4.54 (ddt, J = 13.0, 6.1, 1.4 Hz, 1H) 4.16 (d, J = 10.4 Hz, 1H), 4.07 (d, J = 10.4 Hz, 1H) 3.95 (s, 3H), 3.56 (d, J = 12.3 Hz, 1H), 2.79 (dq, J = 13.3, 6.7, 1H), 1.60 (s, 3H), 1.26 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 168.5, 166.9, 131.4, 119.3, 109.9, 107.3, 96.7, 90.7, 74.5, 66.2, 59.8, 53.9, 44.6, 20.7, 11.8; IR (neat) ν 3126, 2988, 2942, 2884, 1786, 1745, 1648, 1457, 1372, 1300 cm^{-1} .

(2R,3S,4S,5R)-9-Methoxy-2,3-dimethyl-7-oxo-2-(2,2,2-trichloroethoxy)-1,6-dioxaspiro[4.4]non-ene-4-carboxylic acid (148)

An oven-dried, 10-mL, round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with allyl ester **147** (0.39 g, 0.93 mmol) and dry tetrahydrofuran (8 mL). Morpholine (0.08 mL, 0.08 g, 0.94 mmol) was added in one portion via syringe. Tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.09 mmol, 10 mol%) was added as a solid and allowed to stir at room temperature for 3 h. The reaction was quenched with 1 N hydrochloric acid (8 mL), then extracted with ethyl acetate (4 x 8 mL). The pooled organics were washed with 1 N hydrochloric acid (2 x 8 mL), dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation to yield a viscous orange oil. The crude product was dissolved in dichloromethane (10 mL) and extracted with saturated sodium bicarbonate (4 x 10 mL). The aqueous layer was cooled to 0 °C in an ice-water bath and acidified to pH 2 with 10 N hydrochloric acid. The acidified solution was extracted with ethyl acetate (5 x 30 mL). The pooled organics were washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation to afford the title compound **148** as a white solid (279 mg, 79%). (R_f = 0.0-0.2 streak, 1:1 ethyl acetate-hexane); (m.p. 188.5 – 188.9 °C, decomposition); ^1H NMR (500 MHz, CDCl_3) δ 5.17 (s, 1H), 4.15 (d, J = 10.4 Hz, 1H), 4.06 (d, J = 10.4 Hz, 1H), 3.96 (s, 3H), 3.59 (d, J = 12.3 Hz, 1H), 2.76 (dq, J = 12.8, 6.8 Hz, 1H), 1.60 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 171.0, 168.9, 109.9, 107.1, 96.7, 90.9, 74.6, 59.9, 53.6, 44.6, 20.8, 11.7; IR (neat) ν 3128, 2990, 2941, 1788, 1754, 1649, 1457, 1390, 1375 cm^{-1} .

(5R,7R,8S,9R)-9-(hydroxymethyl)-4-methoxy-7,8-dimethyl-7-(2,2,2-trichloroethoxy)-1,6-dioxaspiro[4.4]non-3-en-2-one (149)

An oven-dried, 10-mL, round-bottom flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with carboxylic acid **148** (129 mg, 0.34 mmol) and tetrahydrofuran (4 mL). Carbonyldiimidazole (60 mg, 0.36 mmol) was added as a solid in one portion and stirred at room temperature for 2 h. The reaction was cooled to 0 °C in an ice-water bath and sodium borohydride (45 mg, 1.1 mmol) was added as a solid in one portion. The reaction was stirred for 35 min until TLC analysis indicated consumption of starting material ($R_f = 0.0 - 0.2$ streak) and production of product ($R_f = 0.23$) eluting with a 1:1 ethyl acetate-hexane mobile phase. A solution of 1N hydrochloric acid (5 mL) was added cautiously at 0 °C and extracted with ethyl acetate (3 x 5 mL). The pooled organics were washed with saturated sodium bicarbonate (2 x 5 mL), dried over anhydrous sodium sulfate, vacuum filtered, and concentrated by rotary evaporation (20 mmHg, 25 °C) to yield a foamy white solid (0.11 g, 89%) which did not require further purification. (m.p. 118.5 – 120.3 °C); ^1H NMR (500 MHz, CDCl_3) δ 5.11 (s, 1H), 4.16 (d, $J = 10.4$ Hz, 1H), 4.07 (d, $J = 10.4$ Hz, 1H), 3.91 (s, 3H), 3.75 (d, $J = 5.4$, 2H), 2.78 (dt, $J = 12.4, 5.4$ Hz, 1H), 2.35 (dq, $J = 12.4, 6.7$ Hz, 1H), 1.58 (s, 3H), 1.18 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.6, 169.1, 109.8, 109.6, 96.9, 89.9, 74.6, 59.7, 59.0, 50.0, 44.1, 21.1, 11.3; IR (neat) ν 3451, 2939, 1767, 1647, 1457 cm^{-1} .

(5R,7R,8S,9S)-4-Methoxy-7,8-dimethyl-9-(((2-nitrophenyl)selenanyl)methyl)-7-(2,2,2-trichloroethoxy)-1,6-dioxaspiro[4.4]non-3-en-2-one (157)

A 20-mL scintillation vial equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with alcohol **149** (127 mg, 0.15 mmol) and tetrahydrofuran (0.7 mL). 2-Nitrophenyl selenocyanate (92 mg, 0.21 mmol) was added as a solid in one portion turning the solution orange. A 10 wt% solution of tri-*n*-butylphosphine in hexane (809 mg, 0.21 mmol) was added dropwise via syringe turning the reaction dark brown. The reaction was stirred for 30 min until TLC analysis indicated consumption of starting material ($R_f = 0.23$) and production of product ($R_f = 0.55$) eluting with a 1:1 ethyl acetate-hexane mobile phase. The reaction mixture was concentrated by rotary evaporation (20 mmHg, 25 °C) to afford an orange-brown solid. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 30% ethyl acetate in hexane to afford the title compound **157** as a yellow solid (161 mg, 84%). ($R_f = 0.19$, 30% ethyl acetate in hexane); (m.p. 142-148 °C); ^1H NMR (500 MHz, CDCl_3) δ 8.24 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.55 (ddd, $J = 8.6, 7.2, 1.5$ Hz, 1H), 7.47 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.35 (ddd, $J = 8.3, 7.2, 1.3$ Hz, 1H), 5.06 (s, 1H), 4.12 (d, $J = 10.4$ Hz, 1H), 4.03 (d, $J = 10.4$ Hz, 1H), 3.84 (s, 3H), 3.09 (m, 1H), 2.90 (m, 2H), 2.26 (m, 1H), 1.56 (s, 3H), 1.25 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.9, 169.1, 147.5, 134.0, 132.3, 129.5, 126.5, 126.1, 109.2, 108.7, 96.8, 91.0, 74.4, 59.6, 48.5, 47.4, 21.9, 21.3, 11.4; IR (neat) ν 2938, 1770, 1645, 1590, 1512, 1331, 1010, 885 cm^{-1} .

(5R,7R,8S)-4-methoxy-7,8-dimethyl-9-methylene-7-(2,2,2-trichloroethoxy)-1,6-dioxaspiro[4.4]non-3-en-2-one (159)

A 20-mL scintillation vial equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with selenide **157** (161 mg, 0.29 mmol) in tetrahydrofuran (3 mL) and cooled to 0 °C in an ice-water bath. A 30% aqueous solution of hydrogen peroxide (0.33 mL, 2.9 mmol) was added drop-wise via syringe. The reaction was stirred for 1 h while warming to room temperature. TLC analysis indicated that starting material was still present ($R_f = 0.54$, 50% ethyl acetate in hexane) so the reaction was cooled back to 0 °C and another aliquot of hydrogen peroxide (0.15 mL, 1.5 mmol) was slowly added. The reaction was allowed to stir at room temperature for 1 h. The addition of hydrogen peroxide (0.15 mL, 1.5 mmol) at 0 °C was repeated and the reaction mixture was allowed to stir at room temperature for another hour at which point TLC showed consumption of starting material and the presence of selenoxide **158** ($R_f = 0.26$, 50% ethyl acetate in hexane). The reaction was quenched with saturated sodium bicarbonate (1.5 mL) and extracted with diethyl ether (4 x 5 mL). The combined organics were dried over Na_2SO_4 , vacuum filtered, and concentrated by rotary evaporation. The resulting yellow residue was suspended in toluene (25 mL) and gently heated to 55 °C. After 2 h, TLC analysis showed consumption of the intermediate selenoxide (**158**) so the reaction mixture was cooled to room temperature and washed with 1M sodium hydroxide (1 x 10 mL) to remove the selenic acid byproduct. The organic layer was dried over Na_2SO_4 , vacuum filtered, and concentrated by rotary evaporation to yield a yellow solid. The crude residue was purified by flash column chromatography on silica, eluting with a mobile phase of 25% ethyl acetate in hexane ($R_f = 0.28$), to afford 82 mg (82%) of the title compound **159**

as a pale yellow solid. (m.p. 130 – 132 °C); ¹H NMR (500 MHz, CDCl₃) δ 5.24 (s, 1H), 5.16 (dt, *J* = 3.0, 0.8 Hz, 1H), 5.12 (dt, *J* = 3.1, 0.8 Hz, 1H), 4.11, 4.10 (ABq, *J* = 10.8 Hz, 2H), 3.92 (s, 3H), 2.94 (app tq, *J* = 6.8, 3.8, 3.4 Hz, 1H), 1.65 (s, 3H), 1.25 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 176.3, 168.9, 147.7, 109.7, 109.6, 108.0, 96.8, 91.5, 74.8, 59.7, 46.4, 21.6, 10.1; IR (neat) ν 3514, 2990, 2940, 1773, 1645, 1389, 1372, 1200 cm⁻¹.

(5S,7R,8S)-7-hydroxy-4-methoxy-7,8-dimethyl-9-methylene-1,6-dioxaspiro[4.4]non-3-en-2-one (papyracillic acid A) (134)

A 20-mL scintillation vial, equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet, was charged with trichloroethyl ketal **159** (10 mg, 0.03 mmol) in 70% acetic acid (0.75 mL). Freshly activated zinc granular 20 mesh (22 mg) was added in one portion and the heterogeneous solution was stirred vigorously for 16 h at room temperature. The aqueous solution was extracted with ethyl acetate (4 x 1 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation to afford a light yellow residue. The crude product was purified by flash column chromatography on silica, eluting with 30% ethyl acetate in hexane (*R_f* = 0.23) to afford the papyracillic acid A (**134**) as a white solid (2 mg, 27%) in a 1:1:2 mixture of isomers. ¹H and ¹³C NMR data reported for only the major hemiketal isomer: ¹H NMR (500 MHz, CDCl₃) δ 5.30 (d, *J* = 2.9 Hz, 1H), 5.27 (d, *J* = 2.7 Hz, 1H), 5.09 (s, 1H), 3.88 (s, 3H), 2.77 - 2.71 (m, 1H), 1.60 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 177.9, 169.9, 148.2, 111.7, 111.1, 107.3, 91.3, 88.7, 59.9, 47.6, 25.1, 24.6, 11.2, 10.6; IR (neat) ν 2953, 2923, 2854, 1765, 1643, 1461, 1365 cm⁻¹.

2-(2,2,2-Trichloroethoxy)-tetrahydro-2*H*-pyran (161)

An oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (25 mL), K-10 montmorillonite clay (503 mg), and 2,2,2-trichloroethanol (1.9 mL, 20 mmol). 3,4-Dihydro-2*H*-pyran (2.7 mL, 30 mmol) was dissolved in dichloromethane (9 mL) and added to the reaction mixture dropwise over 5 min. The reaction was stirred at room temperature for 30 min then filtered to remove the K-10 clay. The filtrate was concentrated by rotary evaporation to afford a clear oil. The crude product was purified by flash chromatography on silica, eluting with a gradient mobile phase of 2%, 4%, 6%, 8%, and 10% ethyl acetate in hexane ($R_f = 0.49$) to yield 2.7 g (59%) of the title compound **161** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.94 (t, $J = 3.3$ Hz, 1H), 4.29 (d, $J = 11.6$ Hz, 1H), 4.10 (d, $J = 11.6$ Hz, 1H), 3.91 (m, 1H), 3.59 (m, 1H), 1.89 (m, 1H), 1.80 – 1.76 (m, 2H), 1.69 – 1.55 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 99.4, 97.3, 79.5, 62.3, 30.2, 25.5, 18.8; IR (neat) ν 2943, 2871, 1454, 1441, 1262, 1202, 1130, 1034 cm^{-1} .

Methyl glycine hydrochloride (187)¹⁰⁹

An oven-dried 250-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with dry methanol (200 mL) and glycine (1.50 g, 20 mmol). The solution was cooled to 0 °C in an ice-water bath and thionyl chloride (1.7 mL, 24 mmol) was slowly added via syringe. The resulting solution was allowed to stir overnight while warming to room temperature. The reaction mixture was

concentrated by rotary evaporation to yield a white solid. The crude product was dissolved in a minimum of methanol and triturated with diethyl ether. The resulting precipitate was isolated by vacuum filtration to afford the title ester (**187**) as a white solid (2.38 g, 95%). (m.p. 167.1 – 167.8); ^1H NMR (500 MHz, D_2O - acetone reference) δ 3.94 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, D_2O) δ 169.3, 54.0, 40.7; IR (neat) ν 3373, 3012, 2882, 2686, 2634, 1744, 1584, 1495, 1438, 1257 cm^{-1} .

Methyl 2-(4-methoxybenzylamino)acetate (188)

A dry, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry methanol (30 mL) and the methyl ester of glycine (**187**) (2.51 g, 20 mmol), then cooled to 0 °C in an ice-water bath. Triethylamine (2.79 mL, 20 mmol) was added to the flask and allowed to stir for 10 min. *p*-Anisaldehyde (2.43 mL, 20 mmol) was added and stirred for 18 h while warming to room temperature. The reaction was cooled back to 0 °C and sodium borohydride was carefully added in small portions. The reaction mixture was stirred at 0 °C for 2 h then at room temperature for 1 h. The reaction mixture was acidified to pH 2 with 1M sodium bisulfate. The aqueous layer was washed with diethyl ether (30 mL). The ether layer was back extracted with 1M sodium bisulfate (2 x 30 mL). The combined aqueous layers were neutralized using sodium carbonate then extracted with diethyl ether (3 x 30 mL). The ether layers were pooled, dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation to afford the title ester **188** as a colorless oil (2.98 g, 71%). (R_f = 0.44, 1:1 ethyl acetate - hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.25 – 7.22 (m, 2H), 6.87 – 6.84 (m, 2H), 3.78 (s, 3H), 3.72 (s, 2H), 3.71 (s, 3H), 3.39 (s, 2H), 2.11

(s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.9, 158.8, 131.5, 129.5, 113.8, 55.2, 52.6, 51.7, 49.7; IR (neat) ν 3012, 2882, 2687, 2635, 1742, 1585, 1556, 1497, 1458, 1437, 1424, 1401, 1244 cm^{-1} .

Methyl 2-(((benzyloxy)carbonyl)(4-methoxybenzyl)amino)acetate (189)

A dry 50-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with dichloromethane (16 mL) and ester **188** (750 mg, 3.6 mmol) then cooled to 0 °C in an ice-water bath. Triethylamine (0.56 mL, 4.0 mmol) was added followed by the addition of benzylchloroformate (0.58 mL, 4.0 mmol). The reaction was allowed to stir at 0 °C for 1.5 h then at room temperature for another 30 min. The reaction mixture was washed with water (5 mL) then 0.5N hydrochloric acid (5 mL). The remaining organics were dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a yellow oil. The crude reaction mixture was purified by flash column chromatography on silica, eluting with a mobile phase of 25% ethyl acetate in hexane ($R_f = 0.15$) to afford the title compound **189** as a clear oil (1.2 g, 96%) as a mixture (1:1) of rotamers. ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.29 (m, 10H), 7.19 (d, $J = 8.7$ Hz, 2H), 7.1 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 5.22 (s, 2H), 5.18 (s, 2H), 4.54 (s, 2H), 4.53 (s, 2H), 3.95 (s, 2H), 3.86 (s, 2H), 3.78 (s, 6H), 3.71 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.19, 170.17, 159.33, 159.28, 156.6, 156.4, 136.6, 136.5, 129.8, 129.2, 128.81, 128.76, 128.60, 128.56, 128.2, 128.1, 128.0, 127.9, 114.1, 67.8, 67.6, 55.4, 52.2, 52.1, 51.1, 50.7, 47.6, 47.3; IR (neat) ν 2952, 2837, 1749, 1699, 1612, 1512, 1434, 1231, 1173, 1119 cm^{-1} .

2-(((Benzyloxy)carbonyl)(4-methoxybenzyl)amino)acetic acid (190)

A 100-mL round-bottomed flask was charged with starting ester **189** (409 mg, 1.2 mmol) in a 1:1:1 solution of tetrahydrofuran, methanol, and water (51 mL). Lithium hydroxide monohydrate (320 mg, 7.8 mmol) was added and the reaction was stirred at room temperature for 1 h. The reaction was quenched with 1N hydrochloric acid (40 mL) and extracted with dichloromethane (3 x 50 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 368 mg of the title compound **190** as a colorless oil (94%) as a mixture of rotamers. ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.28 (m, 10H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.23 (s, 2H), 5.19 (s, 2H), 4.54 (s, 2H), 4.52 (s, 2H), 3.98 (s, 2H), 3.90 (s, 2H), 3.79 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 173.8, 159.3, 156.8, 156.5, 136.4, 136.3, 133.0, 132.9, 129.8, 129.2, 128.8, 128.5, 128.2, 128.1, 128.0, 127.8, 127.1, 114.2, 114.0, 68.0, 67.8, 64.9, 55.3, 50.9, 50.7, 47.5, 46.9; IR (neat) ν cm⁻¹.

Benzyl 4-(((benzyloxy)carbonyl)(4-methoxybenzyl)amino)-3-oxobutanoate (193)

An oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry tetrahydrofuran (15 mL). Diprotected glycine **190** (0.60 g, 1.8 mmol) and carbonyldiimidazole (1.21 g, 2.4 mmol) were added to the flask and allowed to stir for approximately 15 min. A separate oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet and charged with monobenzylmalonate (1.21 g, 6.2 mmol) in dry tetrahydrofuran (30 mL). The solution was cooled to 0 °C in an ice-

water bath before adding dibutyl magnesium (3.2 mL, 3.2 mmol, 1M in heptanes), stirring until the solution was no longer cloudy, then warming to room temperature. The acyl imidazole solution was transferred via cannula into the magnesium malonate solution. The reaction was stirred for 48 h before being quenched with 1M hydrochloric acid (30 mL) and extracted with diethyl ether (3 x 50 mL). The organic layers were pooled, washed with a 5% solution of sodium bicarbonate (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation to afford a viscous yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.20$) to yield 364 mg (43%) of the title β -keto ester **193** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.26 (m, 10H), 7.13 (d, $J = 8.3$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 6.83 (d, $J = 8.3$ Hz, 1H), 6.80 (d, $J = 8.6$ Hz, 1H), 5.20 (s, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 5.08 (s, 1H), 4.47 (s, 1H), 4.44 (s, 1H), 4.08 (s, 1H), 4.00 (s, 1H), 3.78 (s, 3H), 3.46 (s, 1H), 3.32 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 198.4, 198.3, 166.7, 166.5, 161.4, 159.3, 156.58, 156.25, 136.40, 135.26, 129.93, 129.87, 129.33, 128.77, 128.73, 128.69, 128.65, 128.60, 128.56, 128.5, 128.4, 128.3, 128.13, 128.07, 128.06, 128.0, 114.2, 114.0, 68.0, 67.9, 67.4, 55.7, 55.4, 55.3, 51.2, 50.8, 46.6, 46.4. IR (neat) ν 3033, 2955, 2836, 1699, 1612, 1513, 1455, 1229, 1175 cm^{-1} .

(3*R*,5*S*)-Benzyl 5((((benzyloxy)carbonyl)(4-methoxybenzyl)amino)methyl)-5-hydroxy-2,2-dimethyltetrahydrofuran-3-carboxylate (194)

An oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry dichloromethane

(25 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.43 mL, 4.2 mmol) was added in one portion via an oven-dried needle. Diiodomethane (0.34 mL, 4.2 mmol) was slowly added via syringe and stirred for 10 min. β -Keto ester **193** (0.39 g, 0.85 mmol) was added to the reaction mixture and stirred at 0 °C. After 2 h, no starting material was still present by TLC, so another aliquot of both diethylzinc (0.21 mL, 2 mmol) and diiodomethane (0.17 mL, 2 mmol) were added to the solution. The reaction was stirred for 1.5 h at 0 °C then freshly distilled acetone (0.12 mL, 1.7 mmol) was added. The reaction was stirred for 18 h while warming to room temperature before being quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a clear oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 30% ethyl acetate in hexane ($R_f = 0.23$) to yield 0.15 g (33%) of a rotameric mixture of the title hemiketal **194** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.32 (m, 10H), 7.19 – 7.08 (m, 2H), 6.86 – 6.79 (m, 2H), 5.26 – 5.03 (m, 4H), 4.79 – 4.37 (m, 2H), 3.79 (m, 3H), 3.60 – 3.23 (m, 2H), 2.93 – 1.97 (m, 4H), 1.63 – 0.79 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 159.1, 159.0, 157.8, 136.6, 136.3, 135.7, 135.1, 130.0, 129.9, 129.8, 129.3, 129.1, 128.9, 128.8, 128.7, 128.63, 128.58, 128.5, 128.3, 128.2, 128.1, 128.0, 114.2, 114.1, 114.0, 106.8, 105.3, 84.3, 83.3, 68.0, 67.7, 67.5, 66.7, 55.4, 54.4, 53.1, 52.4, 51.5, 51.0, 50.6, 39.3, 38.6, 37.8, 30.7, 29.7, 25.6, 24.6; IR (neat) ν 2929, 1697, 1512, 1455, 1229, 1174 cm^{-1} .

Benzyl **(((4R)-4-((S)-4-isopropyl-2-oxooxazolidine-3-carbonyl)-5,5-dimethyltetrahydrofuran-2-yl)methyl)carbamate (195)**

An oven-dried, 50-mL, round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with hemiketal **194** (153 mg, 0.29 mmol) in dichloromethane (10 mL) and cooled to – 78 °C in a dry ice-acetone bath. Triethylsilane (0.19 mL, 1.2 mmol) was slowly added to the reaction via syringe followed by the dropwise addition of boron trifluoride diethyl etherate (0.11 mL, 0.92 mmol). The reaction was stirred at -78 °C for 1 h then at room temperature for 21 h. The reaction was quenched with saturated sodium bicarbonate (5 mL) and extracted with diethyl ether (3 x 15 mL). The combined organics were washed with saturated sodium chloride (15 mL), dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to afford a mixture of diastereomers in a 1.3:1 ratio as a viscous yellow oil. The crude reaction material was purified by flash column chromatography on silica, eluting with a mobile phase of 10:1 hexane-ethyl acetate.

Diastereomer **195a** was isolated as a clear oil in 28 mg, 25%. ($R_f = 0.09$, 10:1 hexane – ethyl acetate); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.39-7.30 (m, 10H), 5.15, 5.10 (ABq, $J = 12.2$ Hz, 2H), 5.10*, 5.09* (ABq, $J = 12.4$ Hz, 2H), 5.04 (br t, $J = 5.6$, 1H), 4.24 – 4.20 (m, 1H), 3.39 (ddd, $J = 13.6, 6.1, 3.7$ Hz, 1H), 3.19 (dt, $J = 12.3, 6.1$ Hz, 1H), 2.81 (t, $J = 8.9$ Hz, 1H), 2.53 (dt, $J = 16.9, 8.5$ Hz, 1H), 1.89 (ddd, $J = 14.7, 9.0, 5.5$ Hz, 1H), 1.39 (s, 3H), 1.04 (s, 3H) ; $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 171.7, 156.8, 136.6, 135.8, 128.8, 128.7, 128.6, 128.5, 128.3, 82.9, 75.6, 66.9, 66.8, 53.5, 45.5, 31.2, 29.0, 22.9; IR (neat) ν 3339, 3033, 2974, cm^{-1} .

* App br s. Chemical shifts were found in MestReNova by applying an exponential of - 2.10 with a Gaussian of 1.00.

Diastereomer **195b** was isolated as a clear oil in 22 mg, 19%. ($R_f = 0.06$, 10:1 hexane – ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.29 (m, 10H), 5.27 (t, $J = 5.5$ Hz, 1H) 5.14, 5.11 (ABq, $J = 12.2$ Hz, 2H), 5.11, 5.09 (ABq, $J = 14.7$ Hz, 2H), 4.12 – 4.07 (m, 1H), 3.52 (ddd, $J = 13.9, 6.4, 3.3$ Hz, 1H), 3.25 (dt, $J = 13.8, 5.9$ Hz, 1H), 2.92 (t, $J = 8.9$ Hz, 1H), 2.19 – 2.10 (m, 2H), 1.35 (s, 3H), 1.08 (3H) ; ^{13}C NMR (126 MHz, CDCl_3) δ 172.2, 156.7, 136.8, 135.7, 128.8, 128.7, 128.63, 128.56, 128.19, 128.18, 82.5, 75.9, 66.69, 66.66, 53.8, 45.0, 31.8, 28.6, 25.1; IR (neat) ν 3334, 2974, 1723, 1525, 1455, 1383, 1251, 1161 cm^{-1} .

***L*-Valinol (197)⁹⁶**

An oven-dried, 3-necked, round-bottomed flask was equipped with a mechanical stirrer, reflux condenser, glass stopper, and nitrogen gas inlet. The flask was charged with tetrahydrofuran (250 mL) and cooled to 0 °C in an ice-water bath. Lithium aluminum hydride (7.6 g, 200 mmol) was added to the flask followed by slow addition of *L*-valine (11.7 g, 100 mmol). The solution was heated to reflux for 4 h then cooled to room temperature. The reaction was carefully quenched with a 2M aqueous solution of sodium hydroxide (30 mL) then heated at reflux for another 1 h. The solution was filtered and the lithium salts were washed with boiling tetrahydrofuran (2 x 100 mL). The combined filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford *L*-valinol as a colorless oil (9.9 g, 96%). The product was carried on

without further purification. ^1H NMR (400 MHz, CDCl_3) δ 3.64 (dd, $J = 10.6, 3.7$ Hz, 1H), 3.32 (dd, $J = 10.7, 8.6$ Hz, 1H), 2.58 (ddd, $J = 8.6, 6.3, 3.7$ Hz, 1H), 2.33 (br s, 2H), 1.60 (octet, $J = 6.8$ Hz, 1H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 64.6, 58.5, 31.5, 19.4, 18.5; IR (neat) ν 3287, 2958, 2873, 1586, 1467, 1387, 1369, 1049 cm^{-1} .

Ethyl (*S*)-1-hydroxy-3-methylbutan-2-ylcarbamate (198**)⁹⁷**

A 250-mL round-bottomed flask was charged with a 1:1 solution of tetrahydrofuran – water (140 mL). *L*-Valinol (9.2 g, 89 mmol) was added to the flask along with sodium bicarbonate (37.4 g, 446 mmol). Ethyl chloroformate (9.5 mL, 100 mmol) was added to the solution and stirred at room temperature for 1.5 h. The reaction was extracted with ethyl acetate (3 x 150 mL). The organic layers were pooled, washed with water (150 mL) then saturated sodium chloride (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford the title carbamate **198** as a clear oil (13.6 g, 78%). The product was carried on without further purification. ^1H NMR (500 MHz, CDCl_3) δ 4.96 (br s, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.69 (m, 1H), 3.63 (m, 1H), 3.48 (m, 1H), 2.74 (br s, 1H), 1.86 (heptet, $J = 7.4$ Hz, 1H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.6, 64.0, 61.1, 58.6, 29.4, 19.6, 18.6, 14.7; IR (neat) ν 3321, 2961, 2875, 1688, 1534, 1467, 1370, 12451076, 1051 cm^{-1} .

(S)-4-Isopropylloxazolidin-2-one (199)⁹⁷

A 100-mL round bottomed flask was equipped with a magnetic stir bar, and short-path distillation head. The flask was charged with ethyl carbamate **198** (12.6 g, 71 mmol) and potassium carbonate (59 mg, 0.42). The reaction was heated to 120 – 130 °C under reduced pressure (ca. 10 mmHg) until gas evolution has ceased. The reaction was allowed to cool to room temperature to afford a white solid. The crude product was recrystallized from diethyl ether to yield 6.8 g (74%) of the title compound **99** as a white crystalline solid. (m.p. 73.4 – 73.7 °C); ¹H NMR (400 MHz, CDCl₃) δ 6.82 (br s, 1H), 4.44 (t, *J* = 8.7 Hz, 1H), 4.10 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.62 (dddd, *J* = 8.7, 7.2, 6.3, 1.0 Hz, 1H), 1.73 (octet, *J* = 6.7 Hz, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.6, 68.7, 58.5, 32.8, 18.1, 17.8; IR (neat) ν₃₂₆₂, 2974, 2961, 2914, 2874, 1744, 1720, 1471, 1403, 1385, 1242, 1089 cm⁻¹.

(S)-1-(4-Isopropyl-2-oxooxazolidin-3-yl)butane-1,3-dione (201)

An oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, reflux condenser and nitrogen gas inlet. The flask was charged with acylated Meldrum's acid (**200**)¹¹⁰ (1.26 g, 6.8 mmol) in toluene (25 mL). (S)-4-Isopropylloxazolidin-2-one (**199**) (0.88 g, 6.8 mmol) was added as a solid and the reaction was heated to reflux for 1 h. Once cooled to room temperature, the reaction mixture was concentrated by rotary evaporation to yield a yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 30% ethyl acetate in hexane (*R_f* = 0.2) to afford the title compound **199** as a white solid (1.12 g, 77%). (m.p. 54-56 °C); ¹H NMR (500 MHz, CDCl₃) *major keto tautomer* δ 4.47 (dt, *J* = 8.4, 3.7 Hz, 1H), 4.30 (t,

$J = 9.0$ Hz, 1H), 4.24 (dd, $J = 9.1, 3.0$ Hz, 1H), 4.11 (d, $J = 16.5$ Hz, 1H), 3.97 (d, $J = 16.5$ Hz, 1H), 2.46 (doublet of septets, $J = 7.1, 3.8$ Hz, 1H), 2.28 (s, 3H), 0.93 (t, $J = 7.0$ Hz, 6H) ^{13}C NMR (126 MHz, CDCl_3) *major tautomer* δ 201.1, 166.4, 154.4, 63.7, 58.4, 51.5, 30.1, 28.4, 17.9, 14.6; IR (neat) ν 2966, 1770, 1723, 1698, 1389, 1365, 1324, 1306, 1211, 1187, 1061 cm^{-1} .

(4*S*)-3-((2*S*,3*R*)-2-(*tert*-Butyl)-5-hydroxy-5-methyltetrahydrofuran-3-carbonyl)-4-isoprpyloxazolidin-2-one (202a)

An oven-dried 25-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (8mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.13 mL, 1.25 mmol) was added via oven-dried needle. 1,1-Diodomethane (0.10, 1.25 mmol) was added in a dropwise manner via syringe. The reaction was stirred for 10 min before the addition of pivaldehyde (0.11 mL, 1 mmol), followed by the immediate addition of β -keto imide **201** (106 mg, 0.5 mmol) dissolved in dichloromethane (2 mL). The reaction was stirred for 2 h before being quenched with saturated aqueous ammonium chloride (3 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation to afford a light yellow oil. The crude reaction mixture was purified by flash column chromatography on silica, eluting with a mobile phase of 30% ethyl acetate in hexane ($R_f = 0.19$) to afford the title compound **202a** as a clear oil (63 mg, 40%). ^1H NMR (500 MHz, CDCl_3) *major diastereomer* δ 4.90 (s, 1H), 4.57 (ddd, $J = 11.2, 5.2, 2.2$ Hz, 1H), 4.53 (dt, $J = 8.5, 3.5$

Hz, 1H), 4.31 (t, $J = 9.1$ Hz, 1H), 4.23 (dd, $J = 9.2, 3.3$ Hz, 1H), 4.12 (d, $J = 5.2$ Hz, 1H), 2.34 (septet of doublets, $J = 7.0, 3.9$ Hz, 1H), 2.16 (dd, $J = 13.5, 11.2$ Hz, 1H), 2.01 (dd, $J = 13.5, 2.2$ Hz, 1H), 1.54 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.92 (s, 9H), 0.87 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) *major diastereomer* δ 178.8, 153.6, 105.0, 90.9, 63.3, 58.6, 43.7, 42.1, 34.4, 28.6, 26.1, 25.5, 18.0, 14.8; IR (neat) ν 3421, 2961, 2875, 1780, 1702, 1672, 1388, 1196 cm^{-1} .

(4*S*)-3-((2*S*,3*R*)-5-Hydroxy-5-methyl-2-phenyltetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (202b)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (8 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.13 mL, 1.25 mmol) was added in one portion via an oven-dried needle. Diiodomethane (0.10 mL, 1.25 mmol) was added in a dropwise manner and stirred for 15 min. Benzaldehyde (0.06 mL, 0.6 mmol) was added to the solution, immediately followed by the addition of β -keto imide **201** (107 mg, 0.5 mmol) in dichloromethane (2 mL). The reaction was stirred at 0 °C for 1 h before it was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum filtered, and concentrated by rotary evaporation to afford a yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 40% ethyl acetate in hexane ($R_f = 0.17$) to yield 106 mg (63%) of a mixture of isomers of the title compound **202b** as a white solid. (m.p 117 – 119 °C); ^1H NMR (500 MHz, CDCl_3) δ 7.49 – 7.34 (m, 5H), 4.71 (ddd, $J = 10.8, 8.8, 3.5$

Hz, 1H), 4.64 (t, $J = 8.9$ Hz, 1H), 4.42 (ddd, $J = 8.2, 3.9, 2.2$ Hz, 1H), 4.37 (t $J = 8.5$ Hz, 1H), 4.23 (dd, $J = 8.7, 2.2$ Hz, 1H), 3.36 (d, $J 8.9$ Hz, 1H), 3.06 (dd, $J 18.4, 10.9$ Hz, 1H), 2.31 (m, 1H), 2.03 (s, 3H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.80 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 206.5, 174.9, 171.1, 155.4, 141.8, 128.8, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 126.8, 126.5, 126.4, 126.1, 126.0, 105.6, 104.7, 84.0, 82.9, 81.5, 73.2, 63.8, 63.7, 63.4, 63.4, 63.0, 59.4, 58.9, 58.9, 58.7, 58.6, 48.3, 46.9, 45.7, 44.6, 44.2, 43.8, 42.6, 40.5, 40.2, 29.9, 29.5, 29.01, 28.95, 28.5, 28.4, 26.9, 26.8, 26.7, 18.2, 18.1, 17.94, 17.89, 14.9, 14.8, 14.6, 14.2, 13.9; IR (neat) ν 3477, 2964, 1774, 1693, 1385, 1364, 1301, 1201 cm^{-1} .

(4*S*)-3-((2*R*,3*R*)-5-hydroxy-5-methyl-2-pentyltetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (202c)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (8 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.12 mL, 1.2 mmol) was added in one portion via an oven-dried needle. Diiodomethane (0.10 mL, 1.2 mmol) was added in a dropwise manner and stirred for 15 min. Hexanal (0.07 mL, 0.53 mmol) was added to the solution, immediately followed by the addition of β -keto imide **201** (102 mg, 0.48 mmol) in dichloromethane (2 mL). The reaction was stirred at 0 °C for 1 h before it was quenched with saturated ammonium chloride (3 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum filtered, and concentrated by rotary evaporation to afford a light yellow oil. The crude

product was purified by flash chromatography on silica, eluting with a mobile phase of 40% ethyl acetate in hexane ($R_f = 0.16$) to yield 29 mg (18%) of a mixture of isomers of the title compound **202c** as a colorless oil. ^1H (500 MHz, CDCl_3) δ 4.49 (m, 1H), 4.44 (m, 1H), 4.37 (m, 1H), 4.33 – 4.28 (m, 2H), 4.27 – 4.23 (m, 3H), 3.14 (ddd, $J = 18.3, 10.9, 2.5$ Hz, 1H), 2.70 (dt, $J = 18.3, 3.7$ Hz, 1H), 2.48 (d, $J = 9.7$ Hz, 1H), 2.42 – 2.31 (m, 3H), 2.22 (m, 1H), 2.18 – 2.13 (m, 3H), 1.71 – 1.59 (m, 4H), 1.43 – 1.24 (m, 15H), 0.97 – 0.85 (m, 22H); ^{13}C NMR (126 MHz, CDCl_3) δ 207.0, 177.1, 175.1, 174.8, 155.0, 154.4, 153.6, 105.4, 105.1, 83.6, 83.0, 82.3, 73.0, 71.8, 63.8, 63.4, 59.2, 58.7, 47.3, 43.9, 43.4, 41.6, 40.6, 35.7, 35.3, 34.5, 33.0, 31.7, 31.7, 29.9, 29.7, 29.0, 28.4, 26.7, 25.7, 25.2, 25.2, 22.6, 22.6, 18.0, 17.9, 15.0, 14.7, 14.01, 13.99; IR (neat) ν 3452, 2958, 2931, 2873, 1777, 1697, 1386, 1301, 1202, 1101 cm^{-1} .

(S)-3-((2S,3R,5S)-2-(tert-Butyl)-5-methyltetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (203a)

A 20-mL scintillation vial equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with hemiketal **202a** (48 mg, 0.15 mmol) and dichloromethane (6 mL). The vial was cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.10 mL, 0.6 mmol) was added to the vial followed by the addition of boron trifluoride diethyl etherate (0.06 mL, 0.45 mmol). The reaction was stirred at -78 °C for 45 min before being quenched with saturated sodium bicarbonate (1 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation to afford the title compound as a 6:1

mixture of diastereomers. The crude product was purified by flash column chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.40$) to afford 42 mg (94%) of the title compound **202a** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 4.47 (dt, $J = 8.4, 3.4$ Hz, 1H), 4.27 (t, $J = 9.1$ Hz, 1H), 4.21 (dd, $J = 9.1, 3.1$ Hz, 1H), 4.14 – 4.09 (m, 1H), 4.08 (d, $J = 7.1$ Hz, 1H), 2.34 (septet of doublets, $J = 7.0, 3.7$ Hz, 1H), 1.95 (ddd, $J = 12.5, 6.0, 4.4$ Hz, 1H), 1.83 (ddd, $J = 12.5, 10.7, 9.1$ Hz, 1H), 1.24 (d, $J = 6.1$ Hz, 3H), 0.92 (d, $J = 7.1$ Hz, 3H), 0.91 (s, 9H), 0.86 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.5, 153.9, 90.1, 74.4, 63.1, 58.6, 43.2, 40.4, 33.7, 28.4, 25.9, 20.3, 18.1, 14.7; IR (neat) ν 2962, 2872, 1774, 1696, 1481, 1466, 1385, 1362, 1203 cm^{-1} .

(S)4-Isopropyl-3-((2S,3R,5S)-5-methyl-2-phenyltetrahydrofuran-3-carbonyl)oxazolidin-2-one (203b)

A 20-mL scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (3 mL) and hemiketal **202b** (28 mg, 0.14 mmol) then cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.05 mL, 0.32 mmol) and boron trifluoride diethyl etherate (0.03 mL, 0.24 mmol) were added to the vial in order then stirred at -78 °C for 45 min. The reaction was quenched with saturated sodium bicarbonate (1.5 mL) and diluted with saturated sodium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a white solid. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 25% ethyl acetate in hexane (R_f

= 0.25) to yield 16 mg (64%) of the title tetrahydrofuran **203b** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.40 - 7.30 (m, 2H), 7.30 - 7.16 (m, 3H), 5.35 (d, *J* = 9.4 Hz, 1H), 4.54 (td, *J* = 9.4, 8.3 Hz, 1H), 4.20 - 4.05 (m, 3H), 4.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 2.32 (m, 1H), 2.15 (ddd, *J* = 12.1, 8.1, 4.9 Hz, 1H), 1.54 (septet of doublets, *J* = 6.9, 2.9 Hz, 1H), 1.48 (d, *J* = 5.9 Hz, 3H), 0.64 (d, *J* = 7.1 Hz, 3H), 0.10 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.6, 153.9, 138.7, 128.5, 128.3, 128.2, 82.7, 75.3, 63.4, 59.0, 49.4, 37.5, 28.6, 19.9, 18.3, 14.2; IR (neat) ν 2967, 2874, 1773, 1694, 1384, 1364, 1301, 1203 cm⁻¹.

(*S*)-4-Isopropyl-3-((2*R*,3*R*,5*S*)-5-methyl-2-pentyltetrahydrofuran-3-carbonyl)oxazolidin-2-one (203c)

A 20-mL scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The vial was charged with dichloromethane (4 mL) and hemiketal **202c** (29 mg, 0.09 mmol) then cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.06 mL, 0.35 mmol) and boron trifluoride diethyl etherate (0.03 mL, 0.26 mmol) were added in order then stirred at -78 °C for 1 h. The reaction was quenched with saturated sodium bicarbonate (5 mL) and extracted with dichloromethane (3 x 5mL). The organic layers were pooled, dried over anhydrous sodium sulfate, gravity-filtered, and concentrated to afford a clear oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 15% ethyl acetate in hexane (*R*_f = 0.17) to yield 19 mg (69%) of a mixture of isomers of tetrahydrofuran **203c** as a colorless oil. ¹H NMR (500 MHz, C₆D₆) δ 4.66 – 4.10 (m, 5H), 3.95 – 3.74 (m, 3H), 3.39 – 3.33 (m, 2H), 3.22 – 3.16 (m, 2H), 2.29 – 2.16 (m, 2H), 2.10 (m, 1H), 1.95 – 1.65 (m,

5H), 1.57 – 1.53 (m, 2H), 1.41 – 1.35 (m, 2H), 1.34 (d, $J = 6.0$ Hz, 3H), 1.29 – 1.25 (m, 8H), 1.22 – 1.14 (m, 3H), 0.86 – 0.83 (m, 6H), 0.63 – 0.59 (m, 3H), 0.54 – 0.50 (m, 4H), 0.41 – 0.37 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 173.7, 172.5, 154.0, 95.3, 83.4, 82.7, 80.8, 75.5, 75.0, 74.7, 62.6, 58.9, 58.3, 50.1, 48.9, 47.4, 38.8, 38.2, 37.1, 36.0, 35.4, 33.0, 32.3, 28.7, 27.1, 26.4, 23.0, 21.3, 20.6, 17.9, 17.6, 14.6, 14.3; IR (neat) ν 2960, 2930, 2872, 1777, 1696, 1464, 1385, 1300, 1203 cm^{-1} .

(S)-1((Benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (205)

L-Proline (5.76 g, 50 mmol) was dissolved in aqueous 2 M NaOH (45 mL) and cooled to 0°C. Benzylchloroformate (8 mL) was added dropwise in five portions alternating with 2 M NaOH (5 x 4 mL). The solution was then allowed to stir at 0°C for one h then at room temperature overnight. The reaction mixture was washed with diethyl ether (3 x 20 mL) then acidified to pH = 2 with 3M HCl. The solution was then extracted with ethyl acetate (5 x 20 mL). The organic layers were washed with H_2O , dried over Na_2SO_4 , filtered, and concentrated under vacuum (30 mmHg, then 1 mmHg). The title compound **205** was isolated as a clear, colorless oil as a mixture of rotamers (12.20 g, 98% yield) ^1H NMR (500 MHz, CDCl_3): δ = 11.56 (br s, 2H), 7.37 – 7.25 (m, 10 H), 5.20 (d, $J = 12.4$ Hz, 1H), 5.14 (d, $J = 12.4$ Hz, 3H), 4.43 (dd, $J = 8.9, 3.7$ Hz, 1H), 4.37 (dd, $J = 8.9, 3.7$ Hz, 1H), 3.65 – 3.57 (m, 2H), 3.55 – 3.42 (m, 2H), 2.29 (m, 1H), 2.22 – 2.14 (m, 2H), 2.10 (m, 1H), 2.03 – 1.84 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.4, 176.9, 155.8, 154.5, 136.5, 136.4, 128.6, 128.5, 128.2, 128.03, 127.97, 127.7, 67.6, 67.2, 59.3, 58.7, 47.0, 46.7, 31.0, 29.6, 24.4, 23.5; IR (neat) ν 2981, 1700, 1416, 1357, 1174 cm^{-1} .

4-(Dimethylamino)pyridin-1-ium (S)-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methanoate (206)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with Cbz-proline **205** (2.50 g, 10 mmol) and dichloromethane (11 mL) then cooled to 0 °C in an ice-water bath. *N,N*-dicyclohexylcarbodiimide (2.06 g, 10 mmol), Meldrum's acid (1.44 g, 10 mmol), and 4-dimethylaminopyridine (1.22 g, 10 mmol) were added to the flask and allowed to stir at room temperature for 18 h. The reaction mixture was filtered and concentrated under vacuum to afford the title compound as a yellow oil (4.28 g, 86%). The product was carried on without further purification. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (d, *J* = 7.4 Hz, 2H), 7.18 (m, 2H), 7.13 (m, 2H), 7.07 (m, 1H), 6.55 (d, *J* = 7.5 Hz, 2H), 5.61 (dd, *J* = 8.7, 3.4 Hz, 1H), 5.07 (d, *J* = 12.9 Hz, 1H), 4.92 (d, *J* = 12.9 Hz, 1H), 3.65 (m, 1H), 3.57 (m, 1H), 3.16 (s, 6H), 2.48 (m, 1H), 1.97 (m, 1H), 1.88 – 1.81 (m, 3H), 1.61 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 196.4, 166.4, 156.9, 155.5, 141.6, 137.4, 128.5, 128.2, 127.3, 127.2, 127.1, 106.4, 101.2, 87.3, 66.1, 64.5, 48.0, 40.0, 31.8, 26.5, 26.4, 23.1; IR (neat) ν 3468, 2937, 1694, 1641, 1601, 1556, 1387, 1320, 1206 cm⁻¹.

(S)-Benzyl 2-(3-((S)-4-isopropyl-2-oxooxazolidin-3-yl)-3-oxopropanoyl)pyrrolidine-1-carboxylate (207)

A 100-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with DMAP salt **206** (3.96 g, 8 mmol) and dichloromethane (60 mL). *p*-Toluenesulfonic acid (2.07 g, 12 mmol) was added to the

flask along with 4 Å molecular sieves. The reaction was stirred at room temperature for 1 h before being diluted with diethyl ether (40 mL) and cooled to 0 °C in an ice-water bath. The solution was filtered then concentrated by rotary evaporation. The residue was dissolved in toluene (60 mL). Chiral oxazolidinone **199** (1.04 g, 8 mmol) was added to the solution along with 4 Å molecular sieves. The solution was heated to reflux for 2.5 h. The reaction mixture was then cooled to room temperature, filtered, and concentrated via rotary evaporation to yield a yellow oil. The crude product was purified by flash column chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.16$) to afford the title compound as a clear oil, as a mixture of carbamate rotamers (1.80 g, 56%). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.37 – 7.29 (m, 10H), 5.20 - 5.06 (m, 4H), 4.47 – 4.46 (m, 3H), 4.40 (dd, $J = 8.7, 4.3$ Hz, 1H), 4.29, (t, $J = 8.9$ Hz, 2H), 4.22 (m, 4H), 4.10, 4.05 (ABq, $J = 16.9$ Hz, 2H), 3.65 – 3.48 (m, 4H), 2.49 – 2.39 (m, 2H), 2.31 – 2.22 (m, 2H), 2.20 – 2.16 (m, 1H), 2.12 – 2.03 (m, 1H), 2.02 – 1.93 (m, 2H), 1.91 – 1.84 (m, 2H), 0.94 – 0.91 (m, 12H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.4, 203.3, 166.5, 166.3, 155.4, 154.5, 154.3, 154.2, 136.6, 136.3, 128.6, 128.5, 128.3, 128.13, 128.06, 127.9, 68.6, 67.4, 67.2, 65.4, 65.2, 63.6, 63.2, 58.5, 48.4, 47.8, 47.4, 46.9, 32.6, 29.6, 28.4, 28.3, 24.4, 23.6, 18.0, 17.6, 14.7, 14.6; IR (neat) ν 2962, 1775, 1696, 1448, 1389, 1353, 1326, 1266, 1210, 1108 cm^{-1} .

(2S)-Benzyl 2-((4R,5S)-5-(tert-butyl)-2-hydroxy-4-((S)-4-isopropyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate (215)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (9

mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.11 mL, 1.1 mmol) was added to the flask followed by the dropwise addition of diiodomethane (0.09 mL, 1.1 mL) via syringe. The solution was stirred at 0 °C for 10 min before the addition of pivaldehyde (0.07 mL, 0.66 mmol) and β -keto imide **207** (177 mg, 0.44 mmol). The reaction was stirred for 1 h before being quenched with saturated ammonium chloride (2 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a viscous yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.14$) to yield 84 mg (38%) of hemiketal **215** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.28 (m, 5H), 5.16 – 5.10 (m, 2H), 4.51 – 4.40 (m, 2H), 4.30 – 4.06 (m, 4H), 3.61 (br s, 1H), 3.36 (m, 1H), 2.51 – 2.13 (m, 4H), 1.99 – 1.75 (m, 3H), 0.92 – 0.85 (m, 15H); ^{13}C NMR (126 MHz, CDCl_3) 153.5, 136.8, 128.6, 128.0, 107.4, 91.9, 90.1, 67.2, 63.30, 63.28, 58.74, 58.71, 47.7, 34.4, 28.7, 27.7, 26.0, 25.4, 18.2, 18.0, 14.9; IR (neat) ν cm^{-1} .

(S)-Benzyl 2-((2R,4R,5S)-5-(tert-butyl)-4-((S)-4-isopropyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate (216)

An oven-dried, 10-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. Dichloromethane (5 mL) and hemiketal **215** (81 mg, 0.16 mmol) were added to the flask and cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.10 mL, 0.64 mmol) and boron trifluoride diethyl etherate (0.06 mL, 0.48 mmol) were added to the solution in that order and allowed to stir at -78 °C for 1 h. The

reaction was quenched with saturated sodium bicarbonate (2 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation (20 mmHg, 20 °C) to afford a yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 25% ethyl acetate in hexane ($R_f = 0.20$) to yield 51 mg (69%) of substituted tetrahydrofuran **216** as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.29 (m, 5H), 5.19 – 5.06 (m, 2H), 4.44 (m, 1H), 4.26 (t, $J = 9.0$ Hz, 1H), 4.23 – 4.09 (m, 4H), 4.01 (d, $J = 6.6$ Hz, 1H), 3.58 (m, 1H), 3.39 (m, 1H), 2.33 (septet of doublets, $J = 6.8, 3.1$ Hz, 1H), 2.18 – 1.78 (m, 6H), 0.91 (d, $J = 7.1$ Hz, 3H), 0.88 (s, 9H), 0.85 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 186.7, 174.0, 153.8, 137.1, 128.5, 128.0, 127.9, 89.6, 80.9, 66.9, 63.1, 58.6, 47.4, 43.5, 42.5, 34.8, 33.9, 28.5, 28.3, 25.8, 18.1, 14.7; IR (neat) ν cm^{-1} .

(S)-1-tosylpyrrolidine-2-carboxylic acid (217)

A 100-mL round-bottomed flask was charged with L-proline (2.31 g, 20 mmol) and 2M sodium hydroxide (20 mL) then cooled to 0 °C in an ice-water bath. *p*-Toluenesulfonyl chloride (4.03 g, 20 mmol) dissolved in diethyl ether (20 mL) was slowly added to the round-bottomed flask then allowed to stir at room temperature for 18 h. The aqueous layer was extracted with diethyl ether (4 x 20 mL). The combined organics were then dried over magnesium sulfate, filtered, and concentrated under vacuum to afford the title compound **217** as a white solid (4.68 g, 94%). The product was used without further purification. (m.p. 75 – 79 °C); ^1H NMR (500 MHz, CDCl_3) δ 7.78 – 7.76 (m, 2H), 7.36 – 7.34 (m, 2H), 4.27 (dd, $J = 8.4, 3.7$ Hz, 1H), 3.53 (ddd, $J = 9.8, 6.6, 3.9$ Hz, 1H), 3.26

(m, 1H), 2.45 (s, 3H), 2.16 (m, 1H), 2.00 – 1.90 (m, 2H), 1.76 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.5, 144.3, 134.2, 130.0, 127.8, 60.6, 49.1, 30.6, 24.8, 21.7; IR (neat) ν 3561, 3480, 3315, 2966, 2899, 26.11, 2534, 1742, 1688, 1624, 1597, 1331, 1154, 1135 cm^{-1} .

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)((*S*)-1-tosylpyrrolidin-2-yl)methanone (218)

Into an oven-dried, 100-mL round-bottomed flask, equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet, 1*H*-1,2,3-benzotriazole (7.15 g, 60 mmol) and anhydrous dichloromethane (75 mL) were mixed. Thionyl chloride (1.1 mL, 15 mmol) was added to the solution via syringe and allowed to stir for 30 min. (*S*)-1-tosylpyrrolidine-2-carboxylic acid (217) was added to the flask turning the solution from yellow to clear. After stirring for 2 h the resulting white reaction mixture was filtered. The filtrate was washed with 2M sodium hydroxide (3 × 75 mL) then dried over magnesium sulfate, filtered and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford 4.07 g (73%) of the title compound as a white solid. (m.p. 203.3 – 204.6); ^1H NMR (400 MHz, CDCl_3) δ 8.32 (m, 1H), 8.16 (dt, $J = 8.3, 0.9$ Hz, 1H), 7.88 – 7.78 (m, 2H), 7.70 (ddd, $J = 8.2, 7.1, 1.0$ Hz, 1H), 7.55 (ddd, $J = 8.2, 7.1, 1.0$ Hz, 1H), 7.37 – 7.34 (m, 2H), 5.81 (dd, $J = 9.0, 4.4$ Hz, 1H), 3.72 (ddd, $J = 9.6, 7.1, 5.1$ Hz, 1H), 3.43 (dt $J = 9.6, 7.0$ Hz, 1H), 2.44 (s, 3H), 2.38 (m, 1H), 2.23 – 2.04 (m, 2H), 1.85 (dtt, $J = 12.4, 7.1, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.6, 146.1, 144.0, 134.8, 131.3, 130.8, 129.9, 129.8, 127.6, 126.6, 120.3, 114.6, 60.6, 49.0, 31.9, 24.9, 21.6; IR (neat) 3099, 2984, 2880, 1744.0, 1597, 1340, 1160 cm^{-1} .

1-((*S*)-4-Isopropyl-2-oxooxazolidin-3-yl)-3-((*S*)-1-tosylpyrrolidin-2-yl)propane-1,3-dione (120)

An oven-dried, 250-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dry tetrahydrofuran (150 mL) and cooled to 0 °C in an ice-water bath. Diisopropylamine (2.8 mL, 20 mmol) was added, followed by the slow addition of 2.5M *n*-butyl lithium (8 mL, 20 mmol). The solution was stirred for 15 min to allow for formation of lithium diisopropylamine (LDA), then cooled to -78 °C in a dry ice-acetone bath. Acylated oxazolidinone **219** (3.71 g, 20 mmol) was dissolved in tetrahydrofuran (20 mL) then slowly added to the LDA solution via syringe pump over 100 min. Benzotriazole-activated proline **218** (3.71 g, 10 mmol) was dissolved in tetrahydrofuran (40 mL) and added to the reaction mixture then allowed to stir at -78 °C for 1 h. The reaction was quenched with 3M hydrochloric acid (10 mL) then extracted with ethyl acetate (3 x 20 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a viscous yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 40% ethyl acetate in hexane ($R_f = 0.28$) to yield β -keto imide **120** (1.93 g, 46%) as a light yellow, viscous oil. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.72 (d, $J = 8.6$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 4.58 (d, $J = 17.3$ Hz, 1H), 4.48 (dt, $J = 8.2, 3.7$ Hz, 1H), 4.33 (m, 1H), 4.30 (d, $J = 8.7$ Hz, 1H), 4.23 (dd, $J = 9.1, 3.0$ Hz, 1H), 4.14 (m, 1H), 3.54 (ddd, $J = 10.3, 7.3, 5.0$ Hz, 1H), 3.27 (dt, $J = 9.8, 7.6$ Hz, 1H), 2.50 (septet of doublets, $J = 7.2, 3.6$ Hz, 1H), 2.44 (s, 2H), 2.24 (m, 3H), 1.88 (ddd, $J = 15.2, 10.5, 7.2$ Hz, 1H), 1.67 (m, 1H), 1.53 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 204.2, 166.8, 154.3, 144.1, 133.6, 129.9, 127.8, 67.3, 63.7, 58.5, 49.6,

48.4, 29.0, 28.3, 24.6, 21.6, 17.9, 14.5; IR (neat) ν 2965, 1774, 1724, 1699, 1389, 1334, 1211, 1158 cm^{-1} .

(4S)-3-((2S,3R)-2-(tert-Butyl)-5-hydroxy-5-((S)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (220)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (15 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.15 mL, 1.5 mmol) was added to the flask, followed by the slow addition of diiodomethane (0.12 mL, 1.5 mmol) via syringe. The resulting solution was stirred for 10 min before adding pivaldehyde (0.07 mL, 0.6 mmol) then β -keto imide **120** (212 mg, 0.5 mmol). The reaction was stirred at 0 °C for an additional 1 h before being quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum filtered, and concentrated by rotary evaporation to afford a yellow solid. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 25% ethyl acetate in hexane ($R_f = 0.13$) to yield 155 mg (59%) of the title hemiketal **220** as a clear oil. *Data reported for the major isomer:* ^1H NMR (500 MHz, CDCl_3) δ 7.74 – 7.71 (m, 2H), 7.33 – 7.28 (m, 2H), 4.68 (m, 1H), 4.54 (m, 1H), 4.34 (t, $J = 9.2$ Hz, 1H), 4.23 (m, 1H), 4.07 – 4.02 (m, 2H), 3.46 – 3.34 (m, 2H), 2.92 (ddd, $J = 13.9, 11.3, 2.3$ Hz, 1H), 2.43 (s, 3H), 2.32 (m, 1H), 2.18 (m, 1H), 2.05 – 1.93 (m, 2H), 1.44 – 1.34 (m, 2H), 0.94 – 0.91 (m, 12H), 0.87 – 0.86 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 179.4, 153.4, 143.7,

135.0, 129.8, 127.7, 107.1, 91.2, 64.0, 63.3, 58.7, 49.9, 40.9, 40.0, 34.6, 28.7, 26.7, 25.4, 24.6, 21.6, 18.0, 14.9; IR (neat) ν 2962, 1777, 1698, 1667, 1387, 1341, 1201, 1159 cm^{-1} .

(S)-3-((2S,3R,5R)-2-(tert-butyl)-5-((S)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (222)

A 20-mL scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The vial was charged with hemiketal **220** (95 mg, 0.18 mmol) in dichloromethane (6 mL). The vial was cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice-acetone bath. Once cooled, triethylsilane (0.12 mL, 0.74 mmol) and boron trifluoride diethyl etherate (0.07 mL, 0.54 mmol) were added to the solution in order. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 45 min before being warmed to room temperature and quenched with saturated sodium bicarbonate (3 mL). The aqueous layer was extracted with diethyl ether (3 x 4 mL). The organic layers were pooled, washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford a single diastereomer as a white solid. The crude product was purified by preparative thin layer chromatography, eluting with a mobile phase of 1:2 hexane – diethyl ether ($R_f = 0.43$) to yield 22 mg (24%) of the title tetrahydrofuran **222** as a white solid. (m.p. $147.6 - 148.0\text{ }^{\circ}\text{C}$); ^1H NMR (500 MHz, C_6D_6) δ 7.70 (d, $J = 8.1\text{ Hz}$, 2H), 6.79 (d, $J = 8.0\text{ Hz}$, 2H), 4.77 (ddd, $J = 9.9, 6.3, 3.9\text{ Hz}$, 1H), 4.61 (ddd, $J = 11.2, 7.1, 4.2\text{ Hz}$, 1H), 4.49 (d, $J = 7.1\text{ Hz}$, 1H), 4.00 (dt, $J = 8.3, 3.4\text{ Hz}$, 1H), 3.95 (dt, $J = 8.7, 4.5\text{ Hz}$, 1H), 3.44 (dd, $J = 9.1, 3.0\text{ Hz}$, 1H), 3.37 (t, $J = 8.3\text{ Hz}$, 1H), 3.27 – 3.18 (m, 2H), 2.53 (ddd, $J = 12.7, 10.8, 9.4\text{ Hz}$, 1H), 2.21 – 2.13 (m, 2H), 1.90 (s, 3H), 1.65 (m, 1H), 1.45 (tt, $J = 13.8, 7.0$, 1H), 1.33 (tdt, $J = 12.8, 8.0, 8.0\text{ Hz}$, 1H), 1.04 (s, 9H), 0.97 (m, 1H), 0.56 (d, $J = 6.9\text{ Hz}$, 3H),

0.45 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, C_6H_6) δ 175.2, 154.0, 142.9, 135.6, 129.7, 128.2, 90.0, 80.9, 62.7, 60.9, 58.5, 50.3, 42.9, 34.5, 34.2, 28.6, 27.6, 26.1, 24.8, 21.1, 17.7, 14.5; IR (neat) ν 2958, 2873, 1774, 1694, 1386, 1342, 1203, 1159 cm^{-1} .

(*S*)-2-(1,3-Dioxoisindolin-2-yl)-3-phenylpropanoic acid (225)¹¹¹

A 50-mL, round-bottomed flask, equipped with a reflux condenser, and Dean-Stark trap was charged with toluene (30 mL). L-Phenylalanine (3.31 g, 20 mmol), phthalic anhydride (2.96 g, 20 mmol), and triethylamine (0.26 mL, 1.9 mmol) were added to the flask and heated at reflux for 2 h. The reaction was allowed to cool to room temperature before removing the volatile solvents via rotary evaporation. The crude solid was triturated from cold water (40 mL) and concentrated HCl (0.4 mL) then recrystallized from ethyl acetate (12 mL) and water (8 mL) to afford the title compound as a crystalline white solid (5.44 g, 92%). (m.p. 181.2 – 181.7 °C, Lit. 183 – 185 °C)¹¹¹; ^1H NMR (500 MHz, CDCl_3) δ 7.80-7.76 (m, 2H), 7.70-7.66 (m, 2H), 7.21-7.12 (m, 5H), 5.23 (dd, $J = 8.9, 7.7$ Hz, 1H), 3.59 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.8, 167.5, 136.5, 134.3, 131.6, 128.9, 128.7, 127.1, 123.7, 53.2, 34.5; IR (neat) 3252, 2925, 2871, 1771, 1742, 1693, 1394, 1217, 1199, 1100 cm^{-1} .

2-((*S*)-1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione (230)

An oven-dried, 100-mL round-bottomed flask, equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet, was charged with dichloromethane and cooled to 0 °C in an ice-water bath. 1*H*-1,2,3,-Benzotriazole (3.81 g, 32 mmol) was added to the flask

followed by thionyl chloride (1.1 mL, 15 mmol). The resulting yellow solution was allowed to stir for 30 min. Compound **225** was added to the flask turning the solution clear. After stirring for 5 h the reaction was quenched with 2M sodium hydroxide (40 mL). The organic layer was washed with 2M sodium hydroxide (2 × 40 mL) then dried over sodium sulfate, filtered and concentrated via rotary evaporation (20 mmHg, 20 °C) to afford 3.22 g (100%) of the title compound as a white solid. (R_f = 0.44, 1:1 hexane – ethyl acetate); (m.p. 109.3-112.0 °C); ^1H NMR (400 MHz, CDCl_3) δ 8.28 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.78 – 7.76 (m, 2H), 7.67-7.64 (m, 3H), 7.49 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.19-7.16 (m, 1H), 6.39 (dd, J = 10.1, 5.5 Hz, 1H), 3.90-3.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.35, 167.30, 145.8, 136.1, 134.3, 131.5, 131.3, 130.9, 129.3, 128.7, 127.2, 126.6, 123.7, 120.4, 114.5, 55.1, 35.0; IR (neat) 3065, 1776, 1743, 1713, 1381, 1365 cm^{-1} .

2-((*S*)-5-((*S*)-4-Isopropyl-2-oxooxazolidin-3-yl)-3,5-dioxo-1-phenylpentan-2-yl)isoindoline-1,3-dione (231**)**

An oven-dried, 100-mL, round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with tetrahydrofuran (30 mL) and cooled to 0 °C in an ice-water bath. Diisopropylamine (0.42 mL, 3 mmol) was added to the flask followed by the slow addition of 2.5M *n*-butyllithium (1.2 mL, 3 mmol). The solution was stirred for 15 min, forming lithium diisopropylamine (LDA), then cooled to -78 °C in a dry ice-acetone bath. A solution of acylated oxazolidinone **218** (523 mg, 3 mmol) in tetrahydrofuran (10 mL) was added to the LDA solution via syringe pump over 30 min. Benzotriazole-activated carboxylic acid **230** (595 mg, 1.5 mmol) was dissolved in

tetrahydrofuran (10 mL) and added to the enolate solution. The reaction was stirred at -78 °C for 30 min before being quenched with 1M hydrochloric acid (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic layers were pooled, washed with saturated sodium chloride (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a yellow oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 40% ethyl acetate in hexane ($R_f = 0.21$) to yield 200 mg (30%) of the title β -keto imide as a white solid (m.p. 148.6 – 149.2 °C). ^1H NMR (500 MHz, CDCl_3) δ 7.79 – 7.76 (m, 2H), 7.71 – 7.66 (m, 2H), 7.19 – 7.09 (m, 5H), 5.33 (dd, $J = 11.4, 5.2$ Hz, 1H), 4.47 (dt, $J = 8.4, 3.1$ Hz, 1H), 4.30 (t, $J = 9.1$ Hz, 1H), 4.22 (dd, $J = 9.1, 3.1$ Hz, 1H), 4.18, 4.05 (ABq, $J = 16.5$ Hz, 2H), 3.55 (dd, $J = 14.3, 5.2$ Hz, 1H), 3.47 (dd, $J = 14.3, 11.5$ Hz, 1H), 2.41 (septet of doublets, $J = 7.0, 3.1$ Hz, 1H), 0.91 (d, $J = 7.0$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 198.1, 167.6, 165.9, 154.4, 136.5, 134.4, 131.6, 129.0, 128.7, 127.0, 123.7, 63.8, 60.0, 58.5, 48.3, 33.6, 28.3, 18.0, 14.7; IR (neat) ν 2966, 1774, 1711, 1383, 1330, 1211 cm^{-1} .

2-((1*S*)-1-((4*R*,5*S*)-5-(*tert*-Butyl)-2-hydroxy-4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)-2-phenylethyl)isoindoline-1,3-dione (232)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (8 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.13 mL, 1.28 mmol) was added to the flask followed by the slow addition of diiodomethane (0.10 mL, 1.28 mmol). The resulting solution was stirred for 10 min before the addition of pivaldehyde (0.07

mL, 0.65) and β -keto imide **231** (192 mg, 0.43 mmol) in order. The reaction was stirred for an additional 2 h at 0 °C before being quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum-filtered, and concentrated by rotary evaporation to afford an off white oil. The crude product was purified by flash chromatography on silica, with a mobile phase of 35% ethyl acetate in hexane to yield 28 mg (12%) of hemiketal **232** as a mixture of isomers. (R_f = 0.42, 1:1 hexane – ethyl acetate); ^1H NMR (500 MHz, CDCl_3) *Data reported for the major diastereomer*: δ 7.82 (d, J = 7.1 Hz, 1H), 7.70 – 7.64 (m, 3H), 7.18 – 7.05 (m, 5H), 5.29 (br s, 1H), 4.73 (dd, J = 11.9, 4.3 Hz, 1H), 4.50 – 4.47 (m, 2H), 4.30 – 4.18 (m, 3H), 3.49 (dd, J = 14.3, 12.0 Hz, 1H), 3.13 (dd, J = 14.3, 4.4 Hz, 1H), 2.60 (ddd, J 13.5, 11.9, 1.7 Hz, 1H), 2.36 (septet of doublets, J = 6.9, 3.2 Hz, 1H) 2.11 (dd, J = 13.6, 4.3 Hz, 1H), 0.91 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.81 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) *All resonances*: δ 174.5, 170.8, 167.6, 153.7, 137.2, 134.1, 134.0, 131.6, 131.2, 128.9, 128.8, 128.5, 128.4, 126.6, 123.5, 123.2, 105.0, 91.1, 87.5, 63.2, 59.6, 58.7, 42.8, 42.7, 33.9, 33.7, 29.7, 28.3, 25.9, 25.5, 18.0, 14.6; IR (neat) ν 2964, 1777, 1713, 1385, 1208, 1059 cm^{-1} .

2-((*S*)-1-((2*R*,4*R*,5*S*)-5-(*tert*-Butyl)-4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)-2-phenylethyl)isoindoline-1,3-dione (233**)**

A 20-mL scintillation vial equipped with a small magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with hemiketal **232** (7 mg, 0.01 mmol) in dichloromethane (1 mL). The vial was cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.01 mL,

0.04 mmol) and boron trifluoride diethyl etherate (0.01 mL, 0.03 mmol) were added to the vial in sequence and allowed to stir for 45 min. The reaction was quenched with saturated sodium bicarbonate and extracted with diethyl ether (3 x 4 mL). The organic layers were pooled, washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford a clear residue. The crude product was purified by thin layer chromatography, eluting with a 1:1 ethyl acetate – hexane solution to yield the title compound as a colorless residue (1.9 mg, 36%). ¹H NMR (500 MHz, CDCl₂) δ 7.41 – 7.29 (m, 2H), 7.21 – 7.17 (m, 2H), 6.99 (dd, *J* = 8.3, 7.0 Hz, 2H), 6.91 – 6.85 (m, 1H), 6.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.06 (td, *J* = 9.2, 6.1 Hz, 1H), 4.83 (ddd, *J* = 12.0, 8.8, 4.8 Hz, 1H), 4.69 (ddd, *J* = 10.6, 6.5, 3.8 Hz, 1H), 4.36 (d, *J* = 6.5 Hz, 1H), 3.98 (dt, *J* = 8.6, 3.4 Hz, 1H), 3.63 (dd, *J* = 13.9, 11.9 Hz, 1H), 3.38 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.26 (t, *J* = 8.8 Hz, 1H), 2.85 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.23 – 1.98 (m, 3H), 0.95 (s, 9H), 0.49 (d, *J* = 6.9 Hz, 3H), 0.39 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.0, 168.5, 153.9, 137.5, 133.8, 131.9, 129.0, 128.6, 126.7, 123.2, 89.3, 63.2, 58.6, 57.0, 43.2, 37.0, 34.3, 33.9, 29.9, 28.4, 25.8, 18.1, 14.7; IR (neat) ν 2959, 1776, 1710, 1468, 1382, 1234, 1207, 1104 cm⁻¹.

2-(*N*-(4-Methoxybenzyl)-*N*-tosylamino)acetic acid (234)

A 100-mL round-bottomed flask was charged with methyl ester **187** (2.64 g, 12.6 mmol) in 2M sodium hydroxide (25 mL). The solution was cooled to 0 °C in an ice-water bath and *p*-toluenesulfonyl chloride (2.41 g, 12.6 mmol), dissolved in diethyl ether (13 mL), was slowly added. The reaction was stirred for 6 h before removing the ether layer. The remaining aqueous layer was washed with diethyl ether (2 x 10 mL) and acidified with

3M hydrochloric acid to pH 2. The acidified aqueous layer was extracted with diethyl ether (3 x 30 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford the carboxylic acid as a white solid (1.01 g, 23 %). (R_f = 0.23, 1:1 hexane – ethyl acetate); (m.p. = 136.8 – 137.8 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.82 – 7.74 (m, 2H), 7.37 – 7.30 (m, 2H), 7.18 – 7.11 (m, 2H), 6.89 – 6.80 (m, 2H), 4.40 (s, 2H), 3.91 (s, 2H), 3.80 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 159.6, 143.7, 136.7, 130.1, 129.7, 127.5, 126.6, 114.2, 55.3, 50.9, 46.2, 21.6; IR (neat) ν 2920, 2841, 1725, 1712, 1610, 1512, 1442, 1331, 1238 cm^{-1} .

2-(*N*-(4-methoxybenzyl)-*N*-tosylamino)-1-(1*H*-benzo[*d*][1,2,3]triazole-1-yl)ethanone (235)

A dry, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (12.5 mL) and 1*H*-benzotriazole (0.91 g, 7.6 mmol) and cooled to 0 °C in an ice-water bath. Thionyl chloride (0.14 mL, 1.9 mmol) was added to the solution and stirred at 0 °C for 30 min. Carboxylic acid **234** (0.66 g, 1.9 mmol) was added as a solid and stirred for 2 h. The reaction mixture was filtered and washed with 2M sodium hydroxide (3 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to yield 0.81 g (94%) of the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (dd, J = 8.3, 0.9 Hz, 1H), 8.10 (dd, J = 8.3, 0.9 Hz, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.67 (m, 1H), 7.52 (ddd, J = 8.2, 7.1, 1.0 Hz, 1H), 7.34 (dd, J = 7.8, 0.9 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H), 4.55 (s, 2H), 3.71 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, 167.4, 159.7, 146.0, 143.9, 136.8, 131.0,

130.8, 130.2, 129.9, 127.7, 126.6, 126.5, 120.4, 114.32, 114.28, 55.3, 51.5, 48.4, 21.7; IR (neat) ν 2930, 1611, 1597, 1513, 1304, 1250, 1153, 1091 cm^{-1} .

(S)-N-(4-(4-Isopropyl-2-oxooxazolidin-3-yl)-2,4-dioxobutyl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide (236)

An oven-dried, 100-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane (20 mL), benzotriazole-activated acid **235** (0.80 g, 1.8 mmol), and magnesium bromide diethyl etherate (0.42 g, 1.6 mmol). Acylated oxazolidinone **218** (0.26 g, 1.5 mmol) was added to the solution followed by the addition of Hunig's base (0.35 mL, 2mmol). The reaction was allowed to stir for 18 h before the addition of 1N hydrochloric acid (10 mL). The solution was stirred for an additional 5 min before being extracted with dichloromethane (3 x 10 mL). The organic layers were pooled, washed with saturated sodium bicarbonate (2 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford a white oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.22$) to yield 122 mg (13%) of the title β -keto imide **236** as a white solid. $^1\text{H NMR}$ $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.82 – 7.65 (m, 2H), 7.38 – 7.19 (m, 2H), 7.22 – 7.04 (m, 2H), 6.90 – 6.76 (m, 2H), 4.45 – 4.34 (m, 2H), 4.29 – 4.26 (m, 2H), 4.21 (dd, $J = 9.1, 3.1$ Hz, 1H), 4.16 – 4.06 (m, 1H), 3.96 (d, $J = 18.5$ Hz, 1H), 3.89 (d, $J = 13.6$ Hz, 1H), 3.78 (s, 3H), 3.72 (d, $J = 16.6$ Hz, 1H), 2.43 (s, 3H), 2.38 (septet of doublets, $J = 7.0, 3.8$ Hz, 1H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 198.8, 165.9, 159.7 154.2, 143.6, 136.6, 130.6, 129.7, 127.6, 126.9, 114.2, 63.7,

58.4, 55.4, 54.6, 51.4, 48.1, 28.2, 21.7, 18.0, 14.5; IR (neat) ν 2921, 1775, 1727, 1611, 1329, 1233, 1176 cm^{-1} .

***N*-(((4*R*,5*S*)-5-(*tert*-Butyl)-2-hydroxy-4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)methyl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**237**)**

An oven-dried, 25-mL, round bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged with dichloromethane and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.07 mL, 0.72 mmol) was added to the flask followed by the slow addition of diiodomethane (0.06 mL, 0.72 mmol) via syringe. The solution was stirred for 10 min before the addition of pivaldehyde (0.04 mL, 0.36 mmol) and β -keto imide **236** (0.122 g, 0.24 mmol) in order. The reaction was stirred at 0 °C for 1 h before being quenched with saturated ammonium chloride (3 mL). The aqueous layer was extracted with dichloromethane (3 x 5mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum-filtered, and concentrated by rotary evaporation to afford a light yellow oil.. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 25% ethyl acetate in hexane (R_f = 0.16) to yield 89 mg (71%) of hemiketal **237** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.65 (m, 2H), 7.29 – 7.24 (m, 2H), 7.05 – 7.01 (m, 2H), 6.78 - 6.71 (m, 2H), 5.15 (s, 1H), 4.64 – 4.54 (m, 2H), 4.52 – 4.41 (m, 2H), 4.32 – 4.28 (m, 1H), 4.24 – 4.20 (m, 2H), 3.78 – 3.76 (m, 3H; contains 2 singlets in a 2:1 ratio), 3.55 – 3.32 (m, 2H; contains an ABq J = 15.1 Hz, and br s in a 2:1 ratio), 2.43 – 2.42 (m, 3H contains 2 singlets in a 2:1 ratio), 2.39 – 2.23 (m, 2H), 1.90 – 1.69 (m, 1H; contains a dd, J = 13.8,

2.4 Hz, and a br s in a 2:1 ratio), 0.93 – 0.87 (m, 12H), 0.85 – 0.84 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.9, 173.5, 159.2, 153.5, 143.3, 137.9, 130.6, 129.7, 127.5, 113.8, 105.6, 90.6, 63.3, 58.8, 55.3, 51.4, 51.2, 41.12, 41.08, 34.2, 28.7, 25.6, 21.6, 18.0, 14.8; IR (neat) ν 3380, 2932, 1778, 1704, 1612, 1513, 1389, 1249 cm^{-1} .

***N*-(((2*R*,4*R*,5*S*)-5-(*tert*-Butyl)-4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)methyl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (238)**

A 20-scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The vial was charged with hemiketal **237** (66 mg, 0.13 mmol) and dichloromethane (5 mL) then cooled to $-78\text{ }^\circ\text{C}$ in a dry ice-acetone bath. Triethylsilane (0.08 mL, 0.52 mmol) and boron trifluoride diethyl etherate (0.05 mL, 0.39 mmol) were added in order and allowed to stir at -78 ° for 1 h before being quenched with saturated sodium bicarbonate (2 mL). The aqueous layer was extracted with diethyl ether (3 x 5 mL). The organic layers were pooled, washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford a white solid. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 20% ethyl acetate in hexane ($R_f = 0.2$) to yield 44 mg (69%) of substituted tetrahydrofuran **238** as a white solid. ^1H NMR (500 MHz, C_6D_6) δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 6.81 (m, 2H), 6.69 (d, $J = 8.6$ Hz, 2H), 4.66 (d, $J = 7.3$ Hz, 1H), 4.59 (d, $J = 14.5$ Hz, 1H), 4.50 (dt, 9.5, 7.4 Hz, 1H), 4.16 (ddd, $J = 8.2, 3.9, 2.5$ Hz, 1H), 3.98 (m, 1H), 3.96 (d, $J = 14.6$ Hz, 1H), 3.70 (dd, $J = 14.3, 7.2$ Hz, 1H), 3.47 (t, $J = 8.8$ Hz, 1H), 3.40 (dd, $J = 9.1, 2.6$ Hz, 1H), 3.26 (s, 3H), 3.02 (dd, $J = 14.3,$

5.6 Hz, 1H), 2.37 (ddd, $J = 12.6, 9.6, 6.2$ Hz, 1H), 2.23 (dd, $J = 13.2, 6.2$ Hz, 1H), 2.15 (septet of doublets, $J = 7.0, 4.0$ Hz, 1H), 1.90 (s, 3H), 0.91 (s, 9H), 0.55 (d, $J = 6.9$ Hz, 3H), 0.43 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 174.8, 174.2, 159.8, 154.0, 142.8, 138.2, 130.5, 130.3, 129.8, 114.3, 88.8, 78.5, 77.9, 63.0, 58.9, 54.7, 53.4, 52.0, 44.0, 34.7, 28.7, 25.8, 21.1, 17.7, 14.7; IR (neat) ν 2960, 2873, 1777, 1697, 1611, 1513, 1386, 1246, 1204, 1158 cm^{-1} .

(4*S*)-3-((3*R*)-5-Hydroxy-2,2-dimethyl-5-((*S*)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (239)

A flame-dried, 20-mL, scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The vial was charged with dichloromethane (3 mL) then cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.04 mL, 0.37 mmol) was added followed by the slow addition of diiodomethane (0.03 mL, 0.37 mmol) via syringe. The resulting solution was allowed to stir for 10 min before the addition of acetone (0.02 mL, 0.22 mmol), after which β -keto imide **120** (63 mg, 0.15 mmol) in dichloromethane (2 mL) was added. The reaction was stirred at 0 °C for 1 h before being quenched with saturated ammonium chloride (1 mL) and extracted with dichloromethane (3 x 5 mL). The organic layers were pooled, dried over anhydrous magnesium sulfate, vacuum-filtered, and concentrated by rotary evaporation to afford a white oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 5:1 hexane – ethyl acetate ($R_f = 0.09$) to yield 30 mg (41%) of hemiketal **239** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 8.2$ Hz, 2H), 7.35 – 7.27 (m, 2H), 4.53 – 4.43 (m, 1H), 4.34 (dd, $J = 9.2, 7.9$ Hz, 1H), 4.31 – 4.23 (m, 2H), 4.12 (q, $J = 7.2$ Hz,

1H), 4.02 (dd, $J = 8.5, 2.7$ Hz, 1H), 3.48 – 3.31 (m, 2H), 2.49 – 2.36 (m, 5H), 2.25 – 2.14 (m, 3H), 2.03 – 1.91 (m, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 154.0, 143.8, 135.2, 130.0, 127.9, 107.5, 86.2, 64.7, 63.6, 59.6, 50.6, 50.1, 38.5, 29.2, 28.6, 26.5, 26.4, 24.7, 21.8, 18.5, 14.8; IR (neat) ν 3299, 2964, 1746, 1692, 1642, 1480, 1391, 1242, 1160 cm^{-1} .

(4*S*)-3-((3*R*)-2,2-dimethyl-5-((*S*)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (241)

A 20-mL scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The vial was charged with dichloromethane (2 mL) and hemiketal **239** (31 mg, 0.06 mmol) then cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.04 mL, 0.24 mmol) then boron trifluoride diethyl etherate (0.02 mL, 0.18 mmol) were added to the vial and allowed to stir for 1 h at -78 °C then for an additional 3 h at room temperature. The reaction was quenched with saturated sodium bicarbonate (1 mL) then extracted with dichloromethane (3 x 2 mL). The organic layers were pooled, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford a clear oil. The crude product was purified by preparative thin layer chromatography, eluting with a mobile phase of 1:1 hexane – ethyl acetate ($R_f = 0.42$) to yield 5.6 mg (20%) of the title tetrahydrofuran **241** as a colorless residue. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (d, 8.2 Hz, 2H), 7.32 – 7.28 (m, 2H), 4.54 (ddd, $J = 8.5, 6.9, 3.3$ Hz, 1H), 4.48 (dt, $J = 8.3, 3.1$ Hz, 1H), 4.29 (dd, $J = 9.1, 8.3$ Hz, 1H), 4.26 – 4.19 (m, 2H), 3.86 (dt, $J = 8.6, 3.5$ Hz, 1H), 3.43 – 3.23 (m, 2H), 2.43 (s, 3H), 2.42 – 2.35 (m, 2H), 2.31 (ddd, $J = 13.1, 6.9, 4.0$ Hz, 1H), 1.90 (m, 1H), 1.78 (dddd, $J = 12.8, 7.7, 5.2, 3.6$ Hz, 1H), 1.66 (m, 1H), 1.53

(app dq, $J = 12.7, 8.4$ Hz, 1H), 1.43 (s, 3H), 1.23 (s, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.5, 154.1, 143.5, 135.2, 129.8, 127.8, 83.9, 81.5, 63.2, 62.2, 59.0, 50.7, 50.0, 32.2, 29.5, 28.6, 28.4, 21.7, 18.3, 14.7; IR (neat) ν 2964, 2924, 1774, 1693, 1384, 1342, 1202, 1158 cm^{-1} .

(4*S*)-3-((2*S*,3*R*)-5-Hydroxy-2-phenyl-5-((*S*)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (245)

An oven-dried, 50-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The flask was charged dichloromethane (10 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.15 mL, 1.5 mmol) was added to the flask via syringe. β -Keto imide **120** (211 mg, 0.5 mmol) was added to the solution and stirred for 10 min before the dropwise addition of diiodomethane (0.04 mL, 0.5 mmol) via syringe. The reaction was stirred at 0 °C for 1.5 h before the addition of benzaldehyde (0.08 mL, 0.75 mmol). The reaction was stirred for an additional 2.5 h and was then quenched with saturated ammonium chloride (3 mL) and diluted with saturated sodium chloride (10 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum filtered, and concentrated by rotary evaporation to afford a yellow oil. The crude product was purified by flash chromatography on silica, eluting with a gradient mobile phase of 2%, 5%, 7%, 10%, 12%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% ethyl acetate in hexane ($R_f = 0.28$, 50% ethyl acetate in hexane) to yield 123 mg (45%) of the title compound **245** as a mixture of isomeric forms. ^1H NMR (500 MHz, CDCl_3) δ 7.86 – 7.65 (m, 4H), 7.50 – 7.04 (m, 14H), 5.41 (d, $J = 6.8$ Hz, 1H), 5.06 (m, 1H), 4.79 (m, 1H), 4.41

– 4.19 (m, 4H), 4.17 – 4.05 (m, 4H), 4.01 (td, $J = 8.6, 8.0, 1.6$ Hz, 1H), 3.60 – 3.42 (m, 4H), 3.41 – 3.10 (m, 4H), 2.45 – 2.42 (m, 6H), 2.35 – 2.17 (m, 4H), 2.01 – 1.81 (m, 3H), 1.60 – 1.49 (m, 2H), 1.43 – 1.33 (m, 2H), 1.19 (m, 1H), 0.77 – 0.63 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 208.7, 175.7, 174.9, 172.1, 171.9, 155.1, 153.5, 153.1, 144.02, 143.95, 143.7, 141.5, 137.7, 137.6, 135.2, 129.9, 129.84, 129.81, 129.79, 128.77, 128.33, 128.28, 128.11, 128.09, 128.06, 127.7, 127.6, 126.7, 126.4, 107.8, 105.4, 84.9, 81.4, 67.3, 66.9, 65.4, 65.1, 63.7, 63.5, 63.2, 62.9, 59.2, 58.87, 58.85, 58.5, 50.1, 49.7, 49.5, 49.3, 46.8, 46.3, 44.5, 39.7, 39.5, 38.3, 32.8, 29.9, 29.7, 29.6, 28.8, 28.42, 28.36, 27.1, 25.9, 24.7, 24.63, 24.56, 21.59, 21.55, 18.15, 18.12, 18.0, 17.9, 14.7, 14.6, 14.0, 13.9; IR (neat) ν 3397, 2964, 1779, 1696, 1667, 1386, 1161 cm^{-1} .

(*S*)-4-Isopropyl-3-((2*S*,3*R*,5*R*)-2-phenyl-5-((*S*)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (247)

A 20-mL, scintillation vial equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet was charged with hemiketal **245** (26 mg, 0.05 mmol) in dichloromethane (2 mL). The vial was cooled to -78 °C in a dry ice acetone bath. Triethylsilane (0.03 mL, 0.2 mmol) and boron trifluoride diethyl etherate were added in order then allowed to stir for 1 h. The reaction was quenched with saturated sodium bicarbonate (3 mL) then extracted with dichloromethane (3 x 3 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation to afford a clear oil. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 35% ethyl acetate in hexane ($R_f = 0.24$) to yield 8 mg (30%) of substituted tetrahydrofuran **247** as a clear oil. ^1H NMR

(500 MHz, C₆D₆) δ 7.92 (d, J = 8.2 Hz, 2H), 7.67 – 7.61 (m, 2H), 7.17 (td, J = 7.3, 1.1 Hz, 2H), 7.09 (m, 1H), 6.89 (d, J = 7.6, 2H), 5.28 (d, J = 8.5 Hz, 1H), 4.80 (td, J = 8.6, 7.1 Hz, 1H), 4.38 (ddd, J = 8.1, 5.5, 2.2 Hz, 1H), 4.25 (dt, J = 9.5, 5.9 Hz, 1H), 3.81 (dt, J = 8.4, 2.6 Hz, 1H), 3.44 (ddd, 10.1, 7.7, 3.8 Hz, 1H), 3.35 (dd, J = 9.1, 2.3 Hz, 1H), 3.25 – 3.14 (m, 2H), 3.02 (ddd, J = 12.7, 9.4, 7.1 Hz, 1H), 2.34 (ddd, J = 13.4, 7.2, 3.7 Hz, 1H), 2.29 (m, 1H), 1.99 (s, 3H), 1.77 (m, 1H), 1.67 (septet of doublets, J = 7.0, 3.0 Hz, 1H), 1.30 (ddt, J = 12.1, 9.6, 7.9 Hz, 1H), 1.21 (m, 1H), 0.36 (d, J = 7.1 Hz, 3H), 0.04 (d, J = 6.9 Hz, 3H); ¹³C NMR (126 MHz, C₆D₆) δ 172.0, 153.7, 142.8, 139.0, 136.3, 129.7, 128.4, 128.3, 128.2, 127.9, 83.4, 81.1, 63.1, 62.5, 58.7, 49.4, 47.9, 34.0, 28.6, 27.1, 24.6, 21.1, 17.9, 14.2; IR (neat) ν 2962, 2875, 1776, 1694, 1386, 1363, 1342, 1206, 1160 cm⁻¹.

(4S)-3-((3R)-5-Hydroxy-5-((S)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)-4-isopropylloxazolidin-2-one (248)

An oven-dried, 2-necked, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, nitrogen gas inlet, and solid addition funnel. The flask was charged with dichloromethane (8 mL) and cooled to 0 °C in an ice-water bath. Neat diethylzinc (0.13 mL, 1.25 mmol) was added to the flask followed by the slow addition of diiodomethane (0.10 mL, 1.25 mmol) via syringe. The solution was stirred for 20 min before paraformaldehyde (198 mg) was added via the solid addition funnel. β -Keto imide **120** (211 mg, 0.5 mmol) was added and the solution was stirred at 0 °C for 2 h before being quenched with saturated ammonium chloride (3 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, vacuum filtered, and concentrated by rotary evaporation to afford a

foamy white solid. The crude product was purified by flash chromatography on silica, eluting with a mobile phase of 1:1 ethyl acetate – hexane ($R_f = 0.19$) to yield 82 mg (35%) of the title hemiketal **248** as a white solid. (m.p. 66 – 68 °C); ^1H NMR (500 MHz, CDCl_3) δ 7.75 – 7.69 (m, 2H), 7.35 – 7.31 (m, 2H), 4.61 – 4.18 (m, 5H), 4.15 – 3.77 (m, 2H), 3.63 – 3.08 (m, 3H), 2.59 – 2.39 (m, 4H), 2.34 – 2.12 (m, 1H), 1.99 – 1.81 (m, 2H), 1.58 – 1.26 (m, 2H), 0.97 – 0.87 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 209.1, 176.7, 174.2, 173.3, 154.6, 153.8, 144.1, 143.7, 130.0, 129.9, 129.8, 127.8, 127.77, 127.75, 127.66, 127.6, 127.5, 108.3, 107.1, 72.5, 70.1, 67.4, 67.1, 67.0, 66.0, 65.4, 64.8, 64.1, 63.8, 63.7, 61.5, 60.4, 60.2, 59.1, 58.9, 58.7, 56.5, 50.3, 49.7, 43.6, 42.9, 41.4, 37.5, 36.9, 36.5, 30.0, 28.8, 28.6, 28.4, 28.3, 27.1, 25.9, 24.7, 24.7, 24.5, 21.6, 21.1, 17.99, 17.96, 17.9, 15.0, 14.95, 14.8; IR (neat) ν 3507, 2964, 1774, 1697, 1387, 1340, 1204, 1158 cm^{-1} .

(4S)-4-Isopropyl-3-((3R)-5-((S)-1-tosylpyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (250)

A 20-mL, scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen gas inlet. The vial was charged with hemiketal **248** (38 mg, 0.08 mmol) in dichloromethane (3 mL) then cooled to -78 °C in a dry ice-acetone bath. Triethylsilane (0.05 mL, 0.32 mmol) then boron trifluoride diethyl etherate (0.03 mL, 0.24 mmol) were added to the vial via syringe. The resulting solution was stirred at -78 °C for 1 h before being quenched with saturated sodium bicarbonate (5 mL) then extracted with dichloromethane (3 x 5 mL). The organic layers were pooled, dried over anhydrous sodium sulfate, gravity filtered, and concentrated by rotary evaporation to afford a clear oil. The crude product was purified by flash chromatography on silica, eluting with a

mobile phase of 40% ethyl acetate in hexane ($R_f = 0.28$) to yield 26 mg (71%) of the title tetrahydrofuran **250** as a clear oil. ^1H NMR (500 MHz, C_6D_6) δ 7.75 – 7.67 (m, 2H), 7.36 – 7.30 (m, 2H), 4.48 (ddd, $J = 8.2, 3.9, 2.5$ Hz, 1H), 4.35 (dd, $J = 8.9, 8.3$ Hz, 1H), 4.29 – 4.15 (m, 3H), 4.00 (m, 1H), 3.95 (m, 1H), 3.79 (m, 1H), 3.36 (m, 1H), 3.16 (dt, $J = 10.7, 7.9$ Hz, 1H), 2.48 (m, 1H), 2.43 (s, 3H), 2.41 – 2.30 (m, 2H), 1.94 (m, 1H), 1.82 (m, 1H), 1.50 (ddt, $J = 15.5, 7.6, 3.7$ Hz, 1H), 1.29 (m, 1H), 0.93 (d, $J = 7.1$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.8, 154.2, 143.6, 135.0, 129.9, 127.7, 81.2, 70.2, 63.8, 62.5, 59.2, 49.3, 43.7, 32.2, 28.8, 27.2, 24.0, 21.7, 18.2, 15.1; IR (neat) ν 2964, 2875, 1777, 1698, 1387, 1342, 1302, 1245, 1207, 1159 cm^{-1} .

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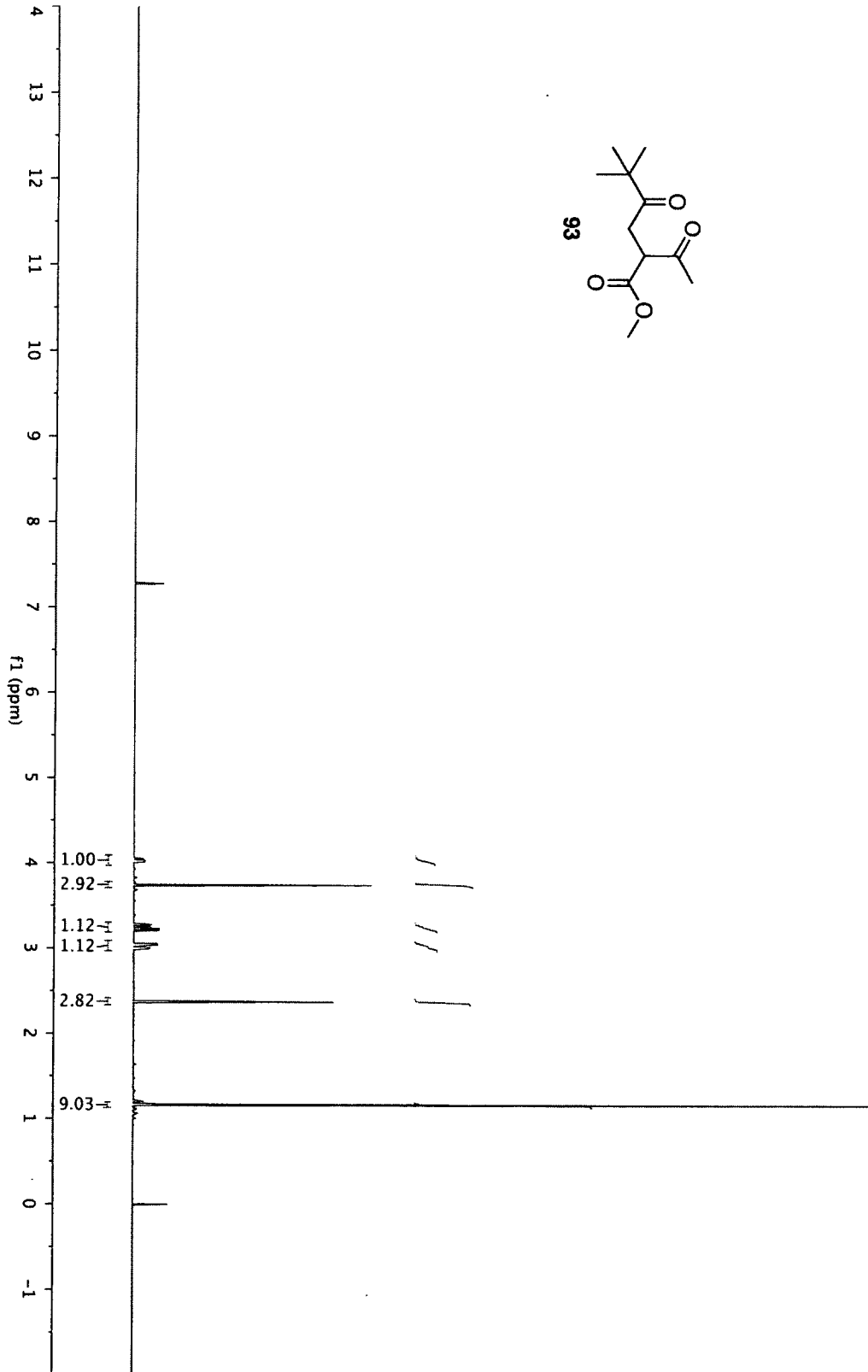
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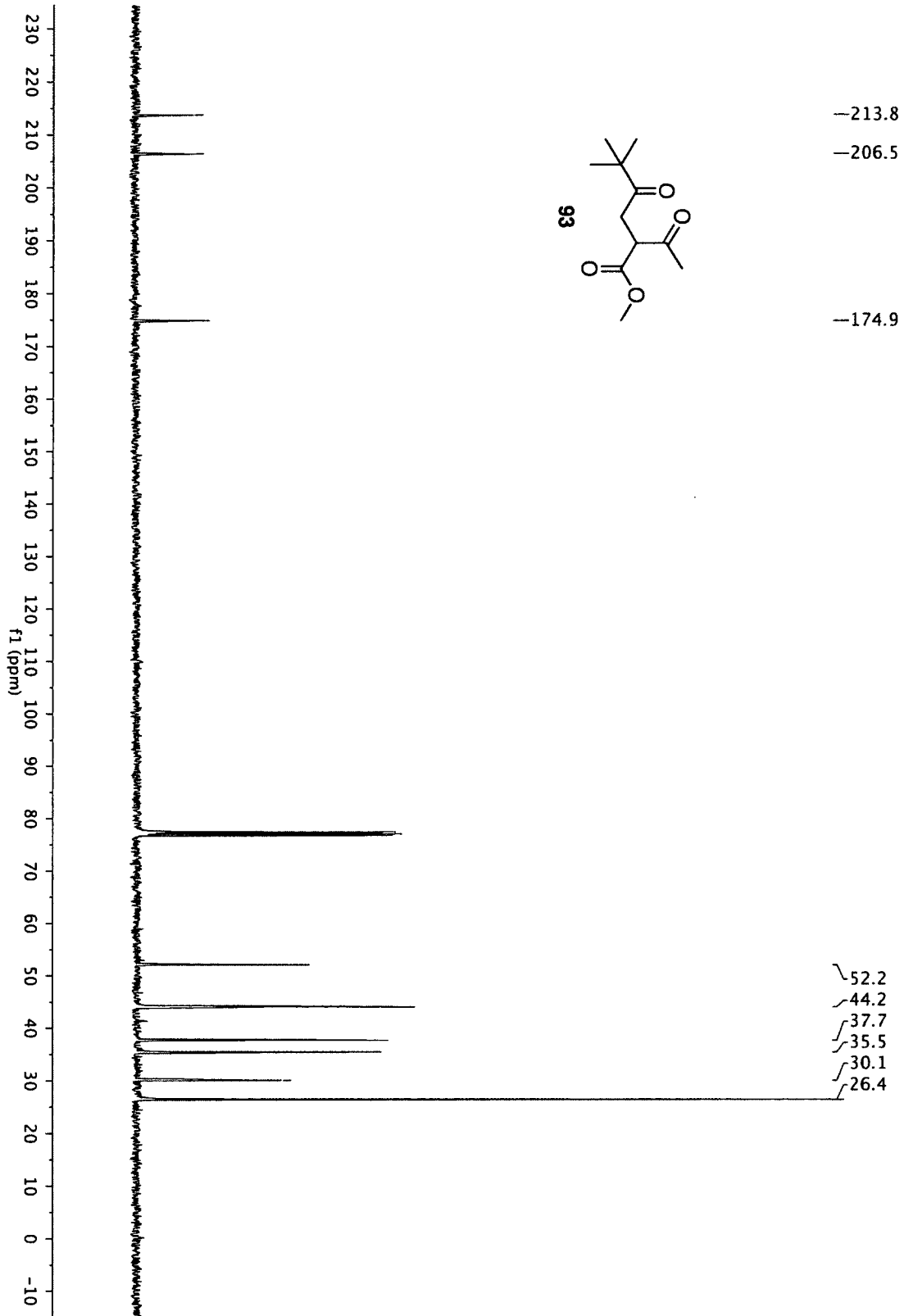
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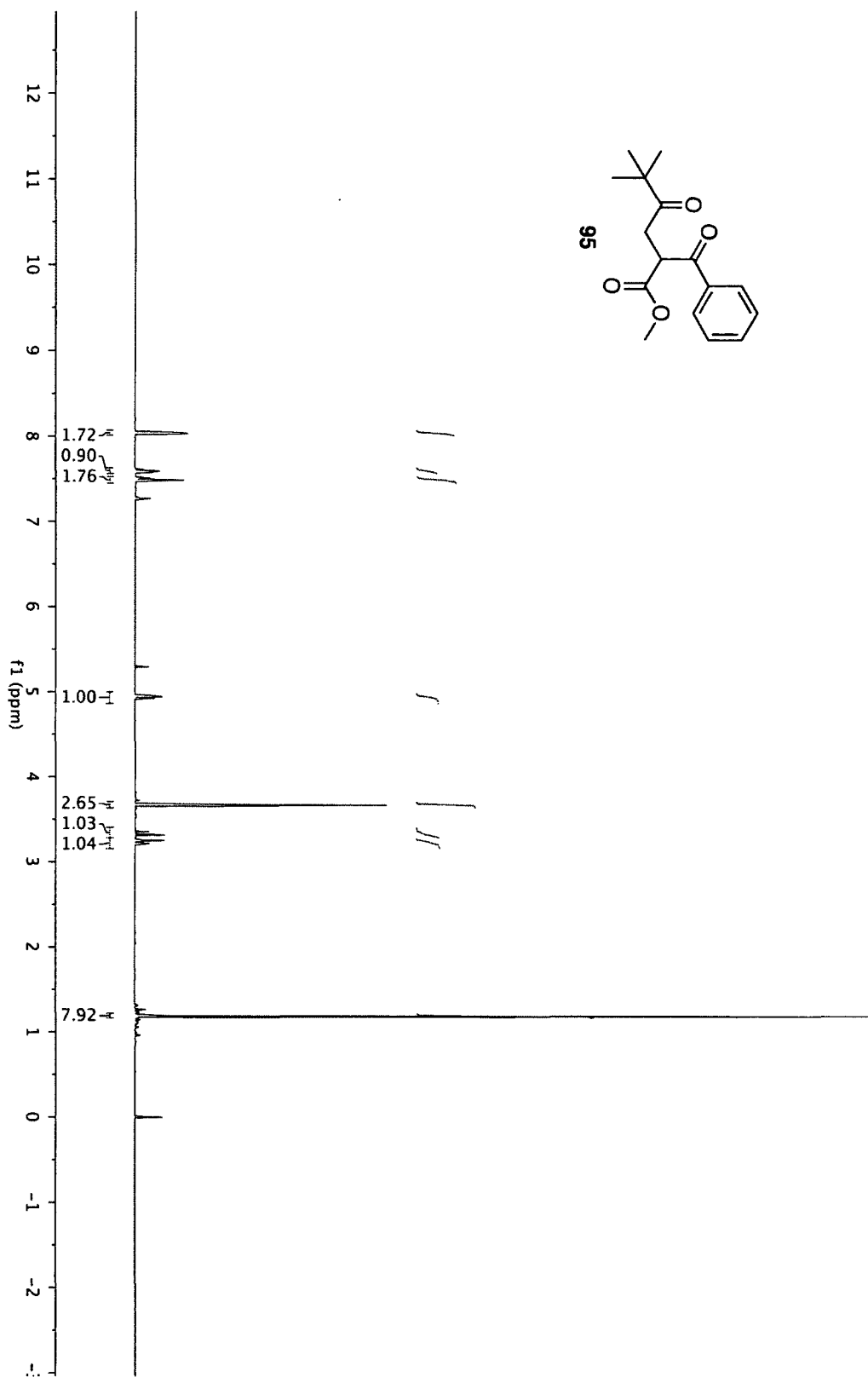
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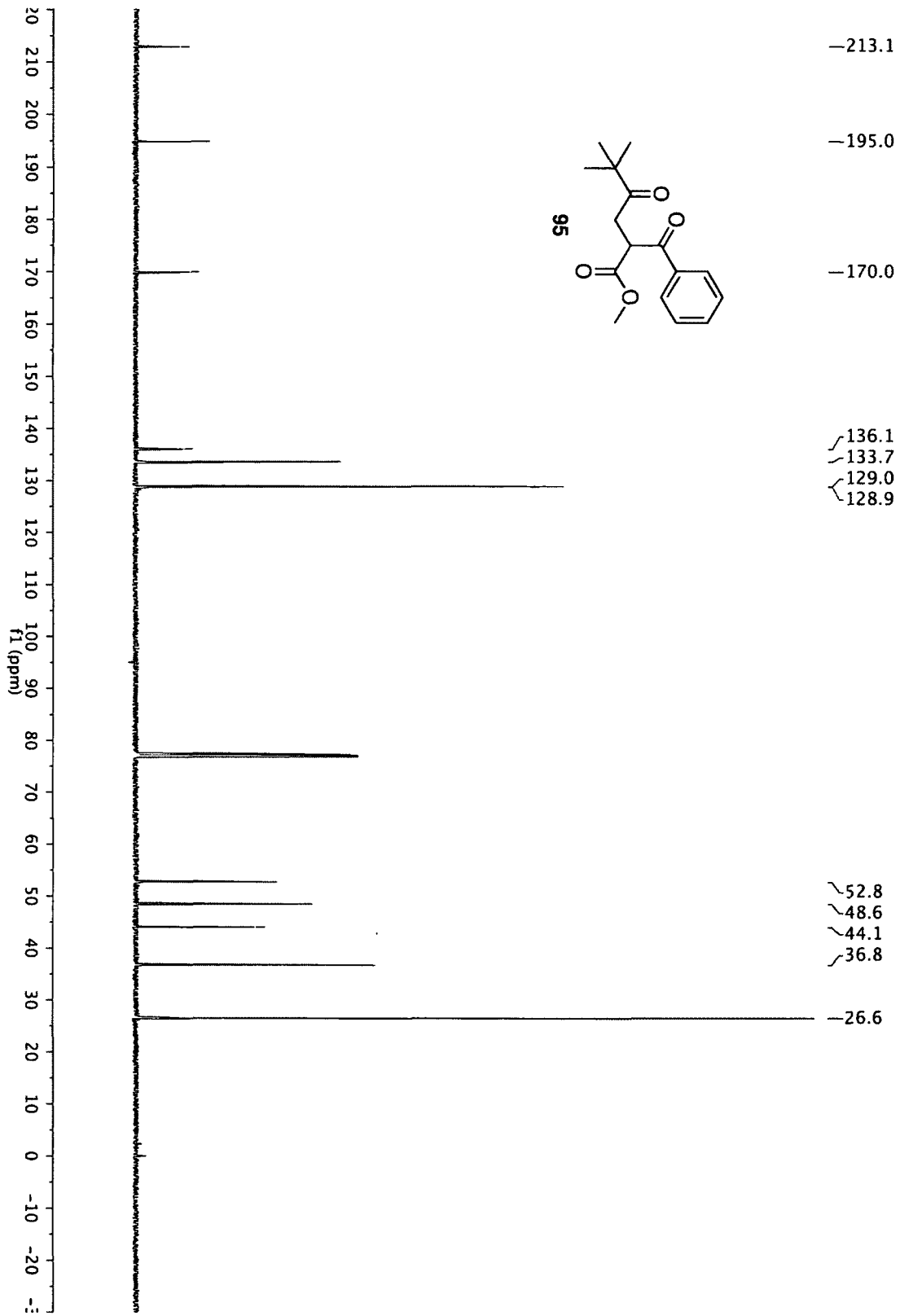
APPENDIX A.

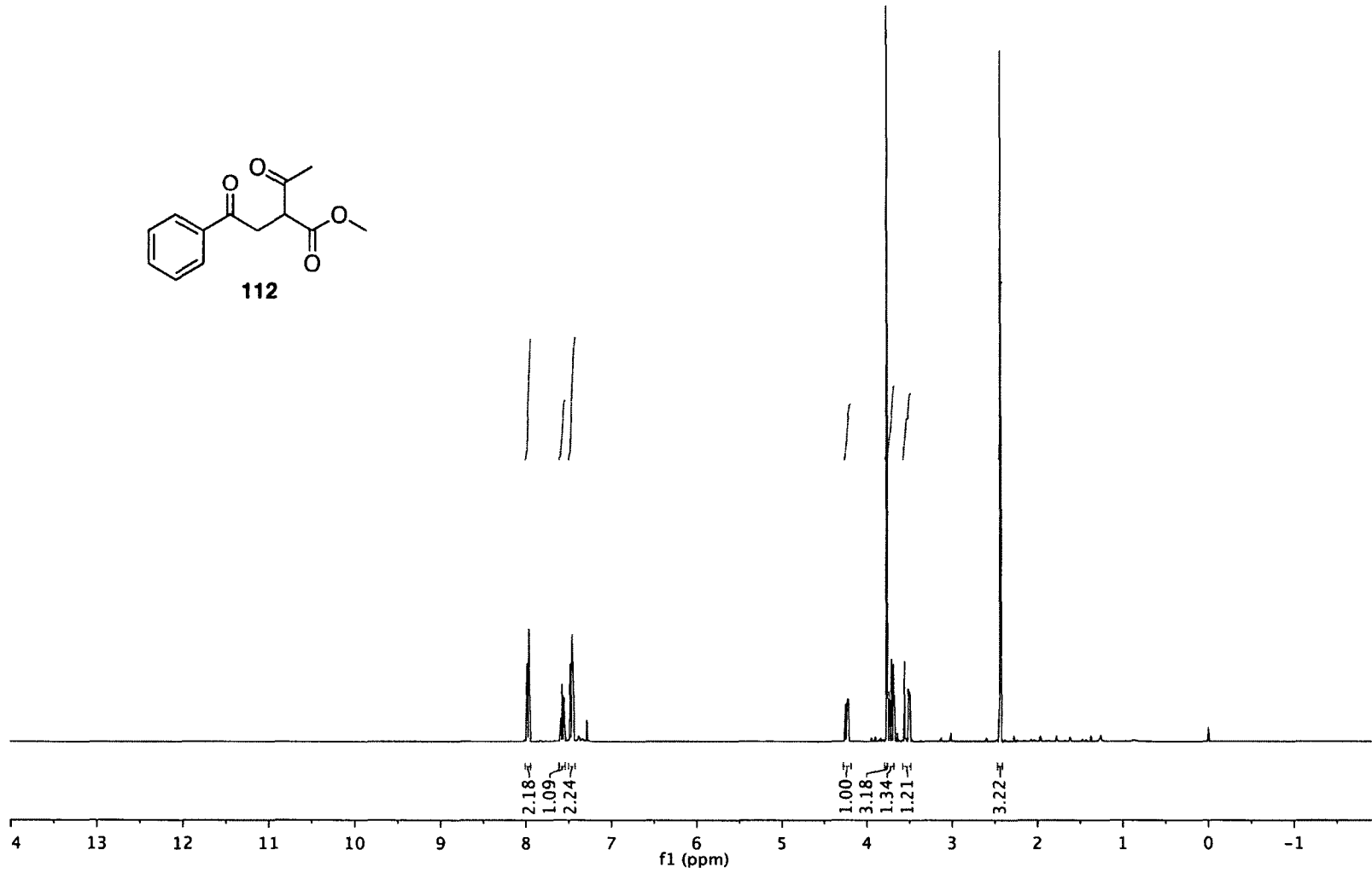
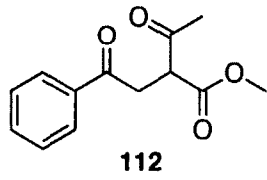
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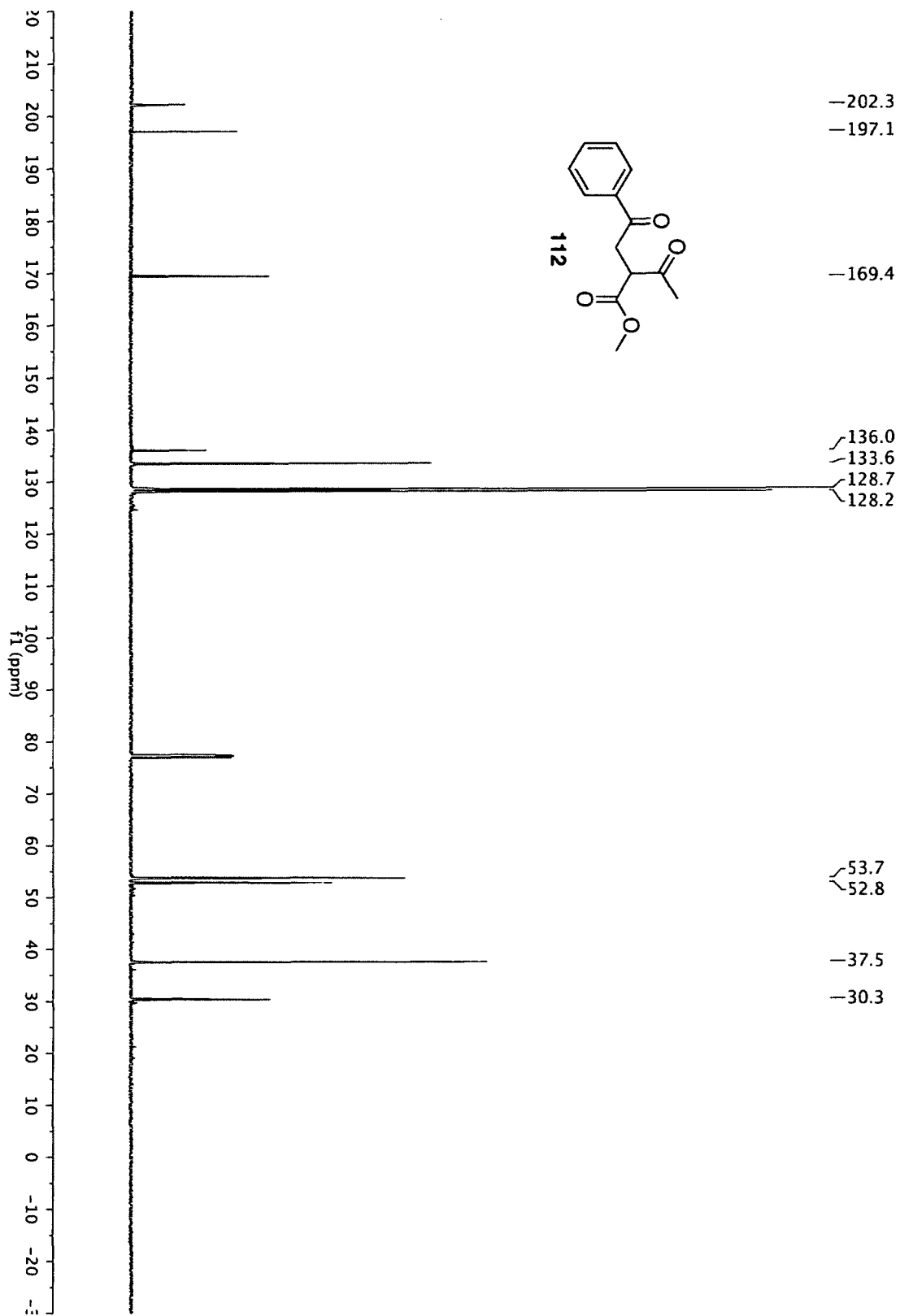


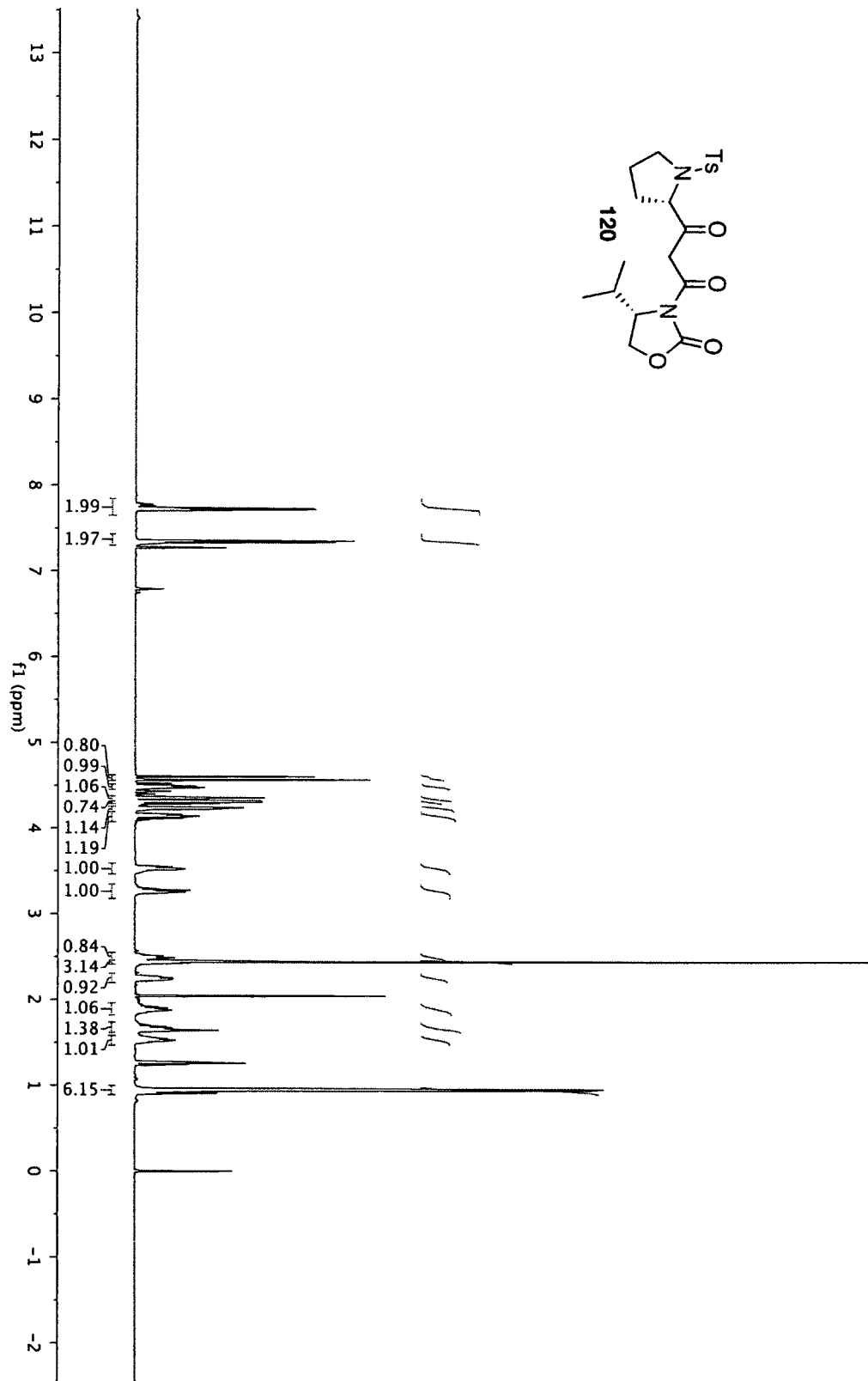


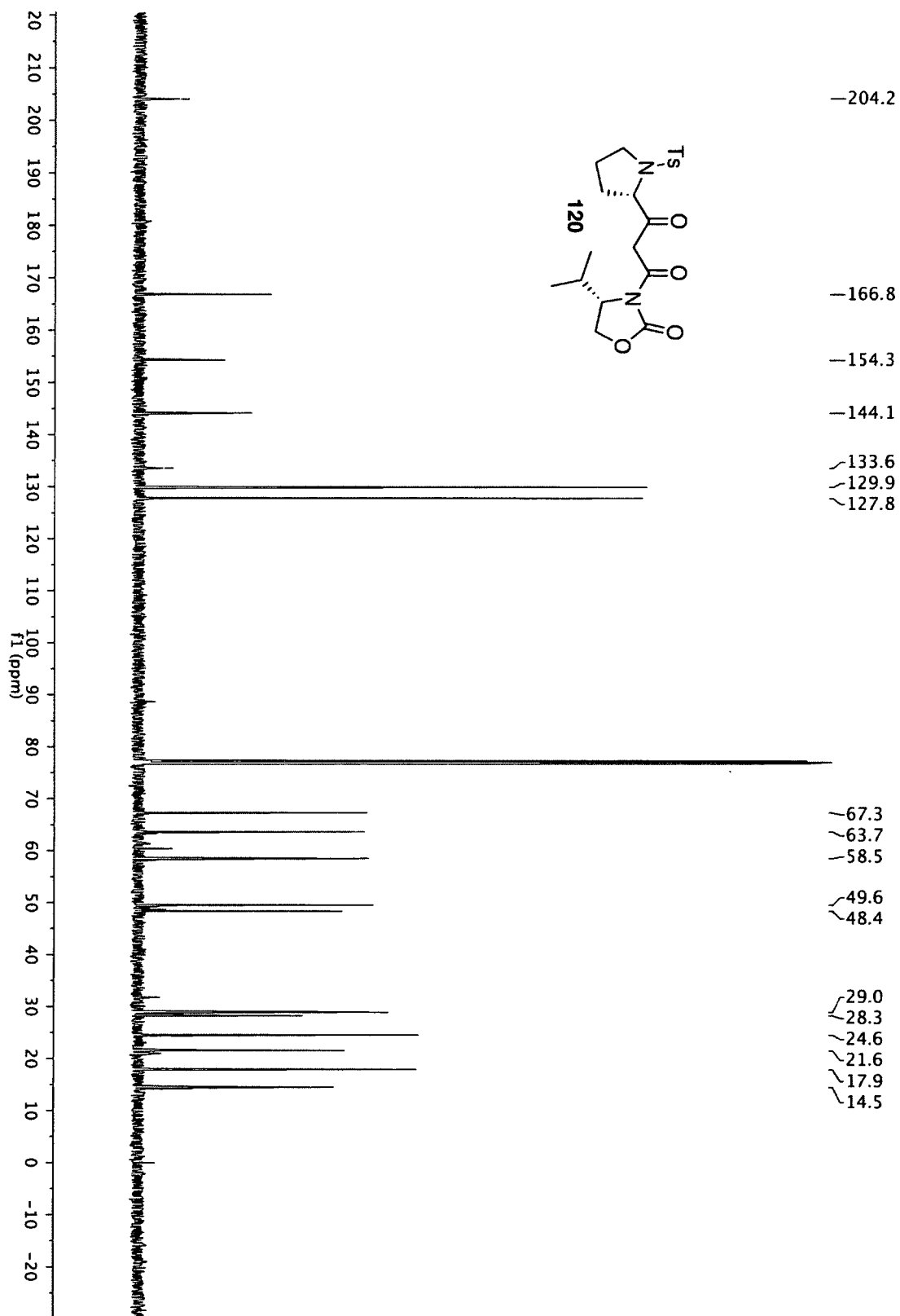


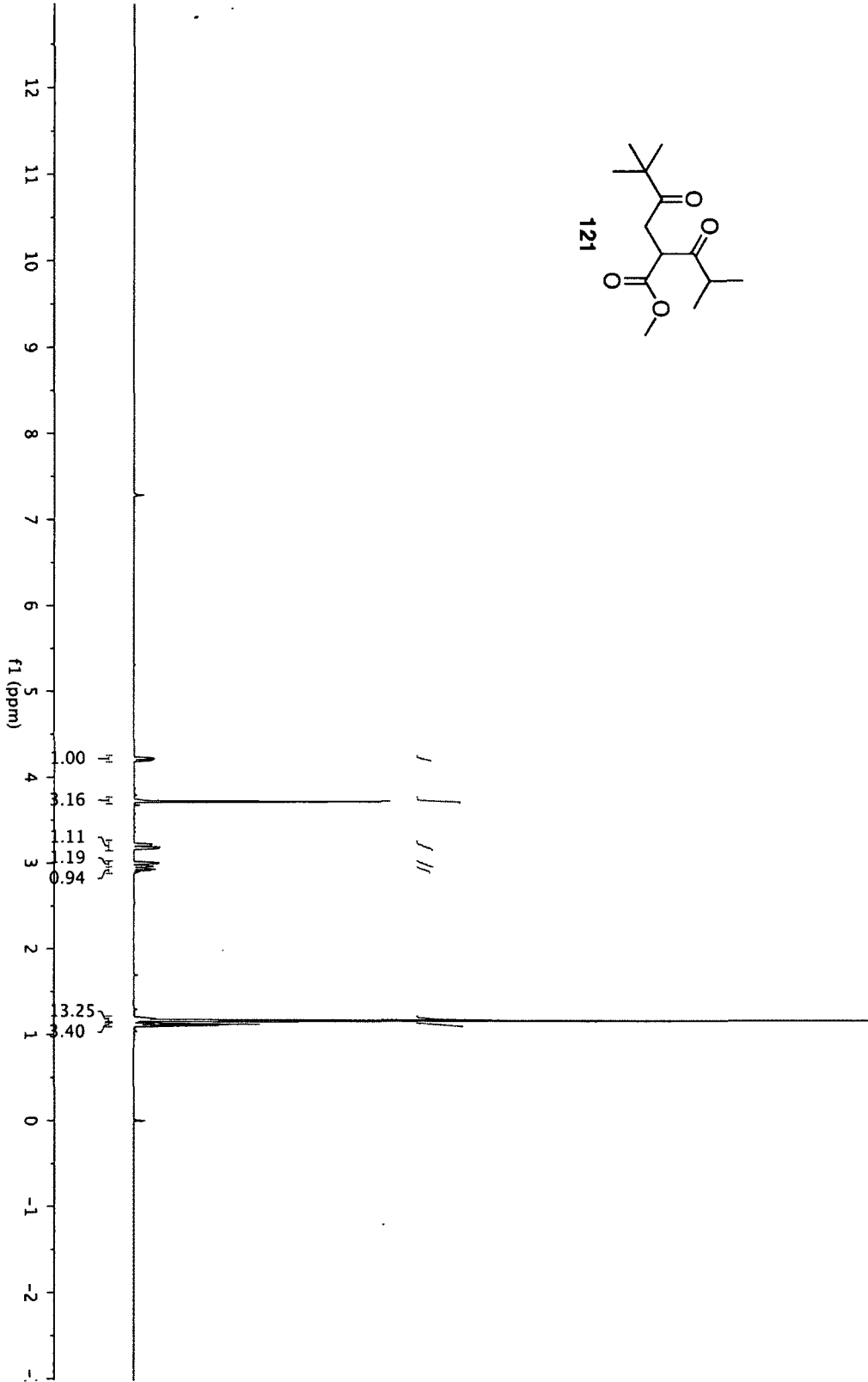
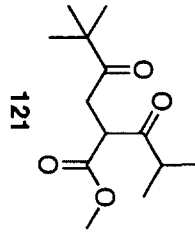


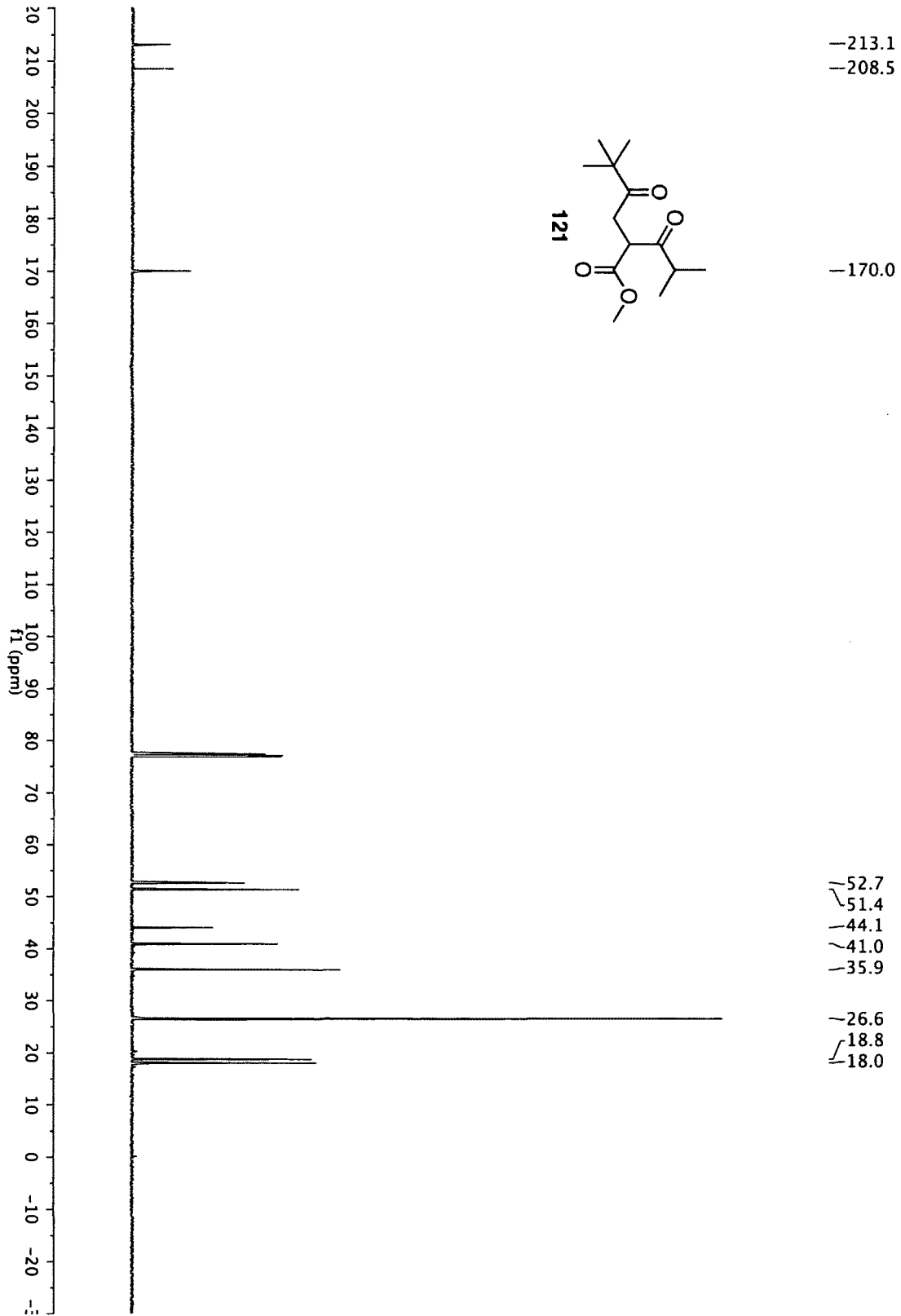


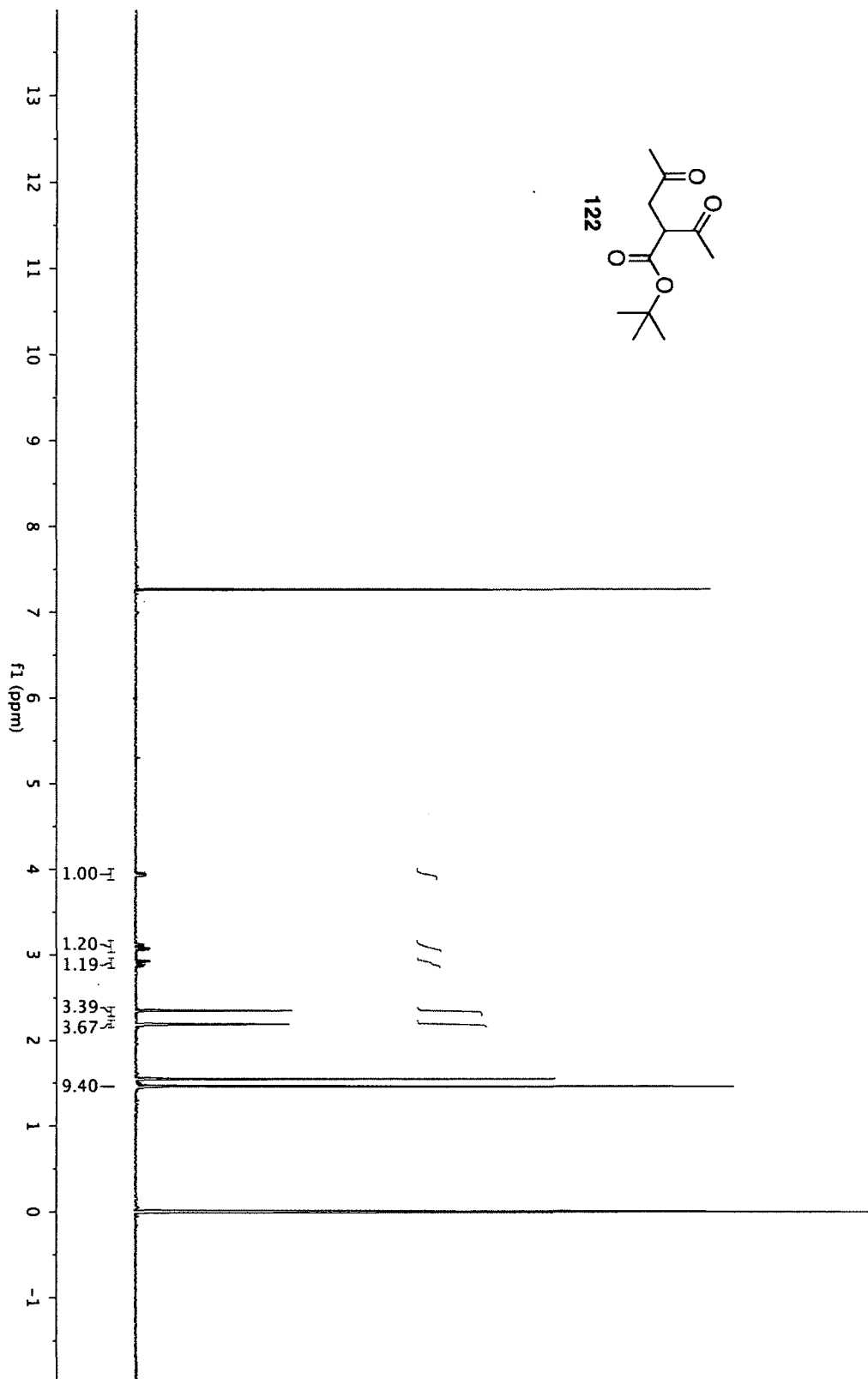


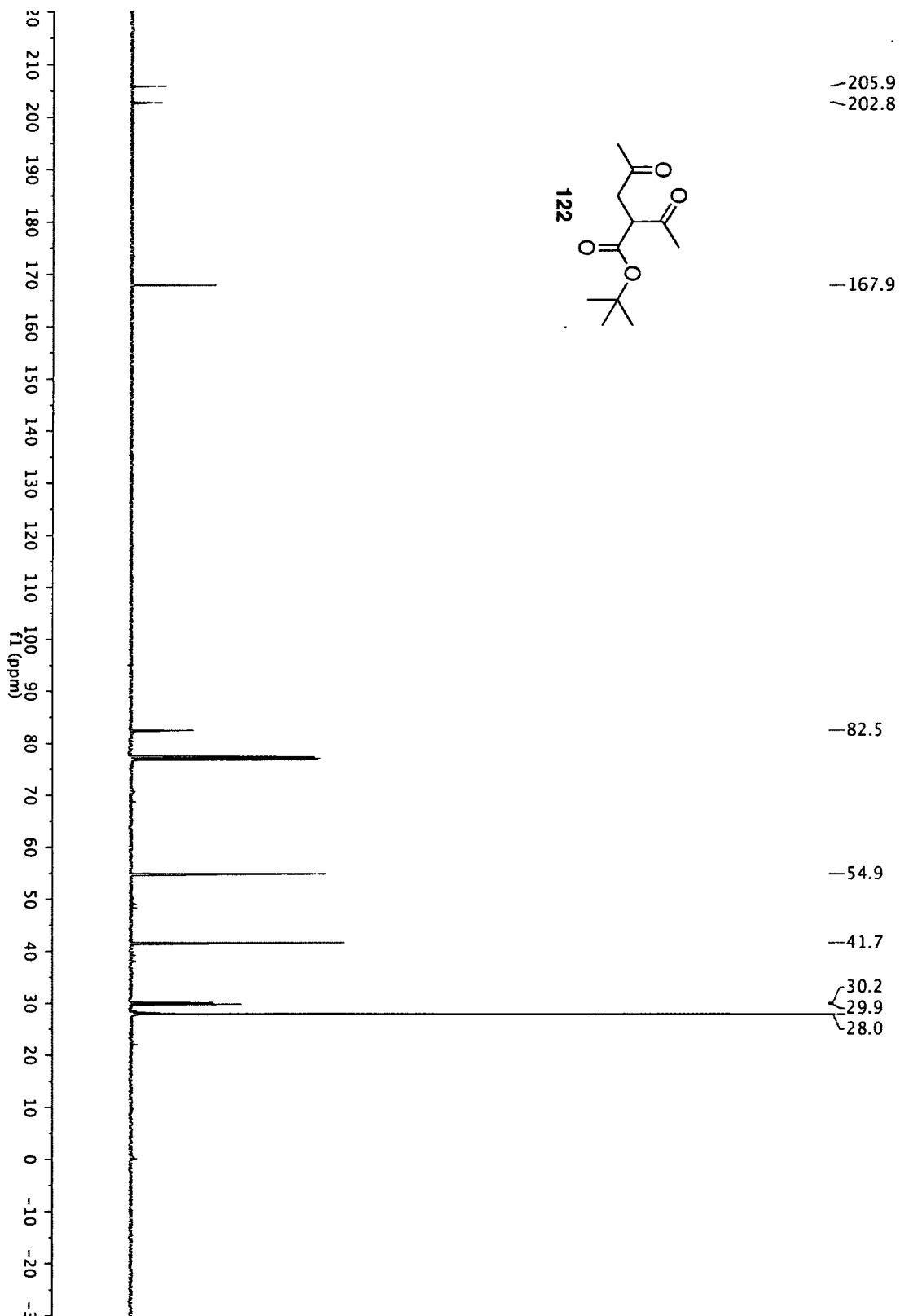


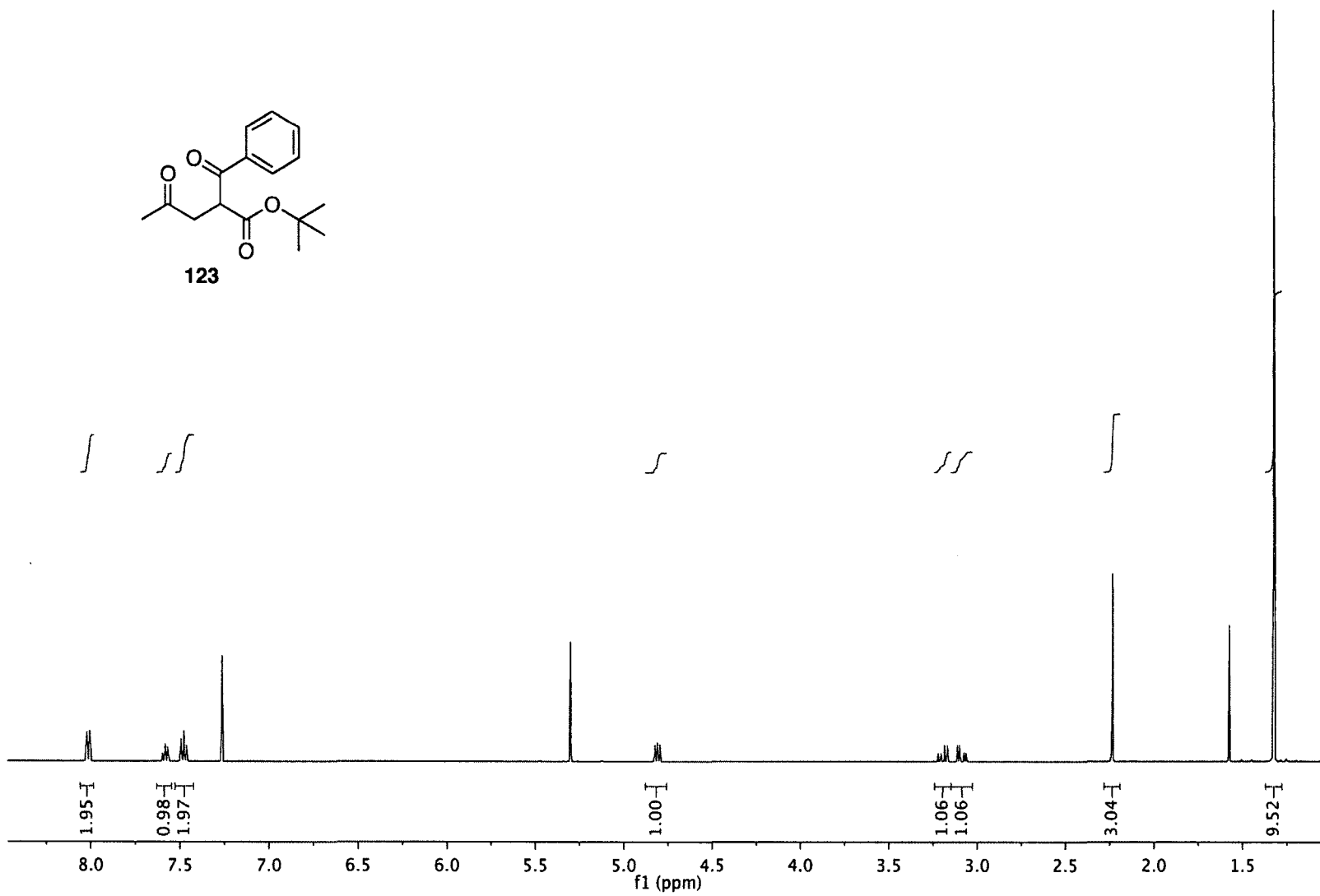
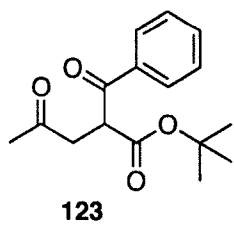


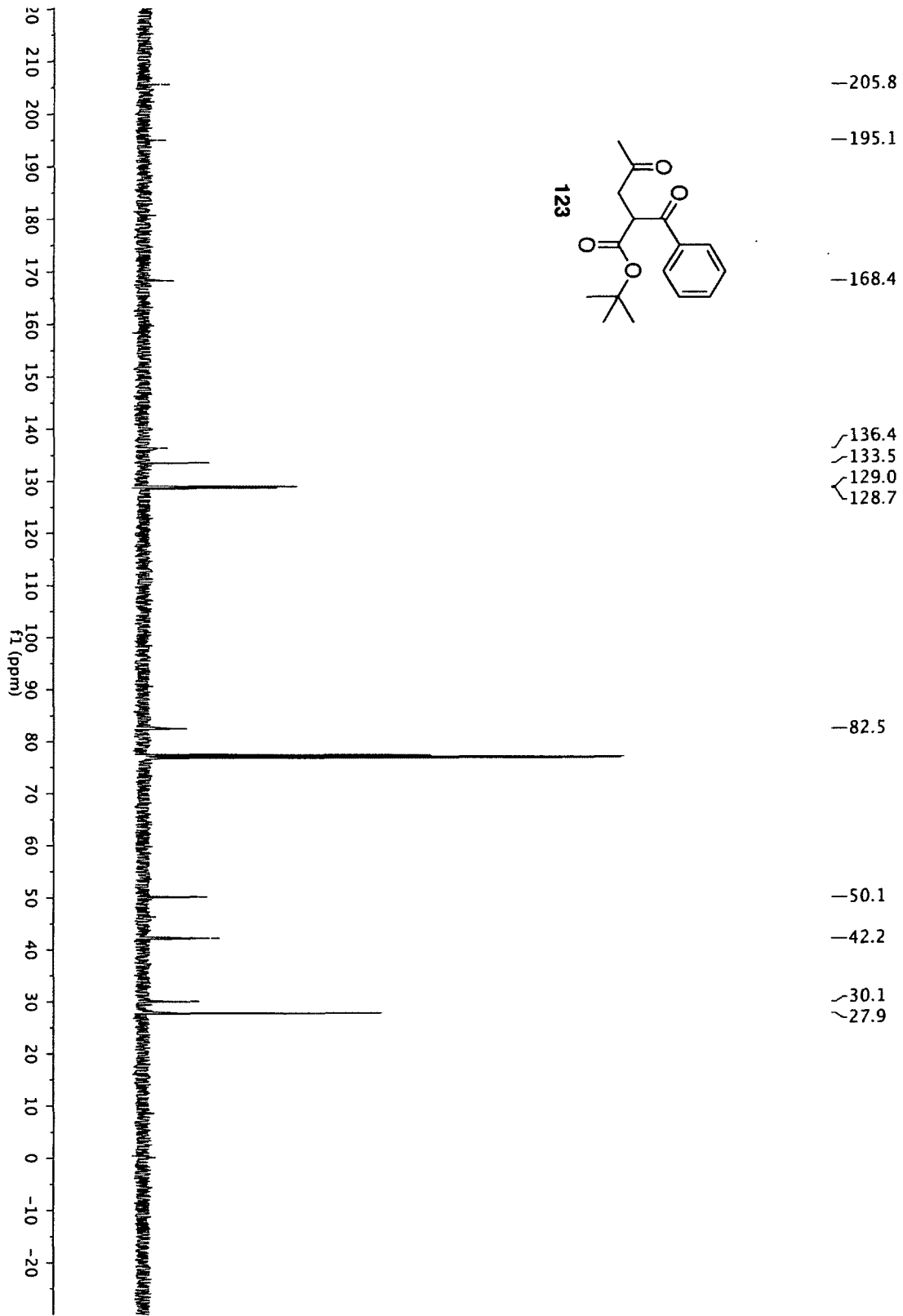


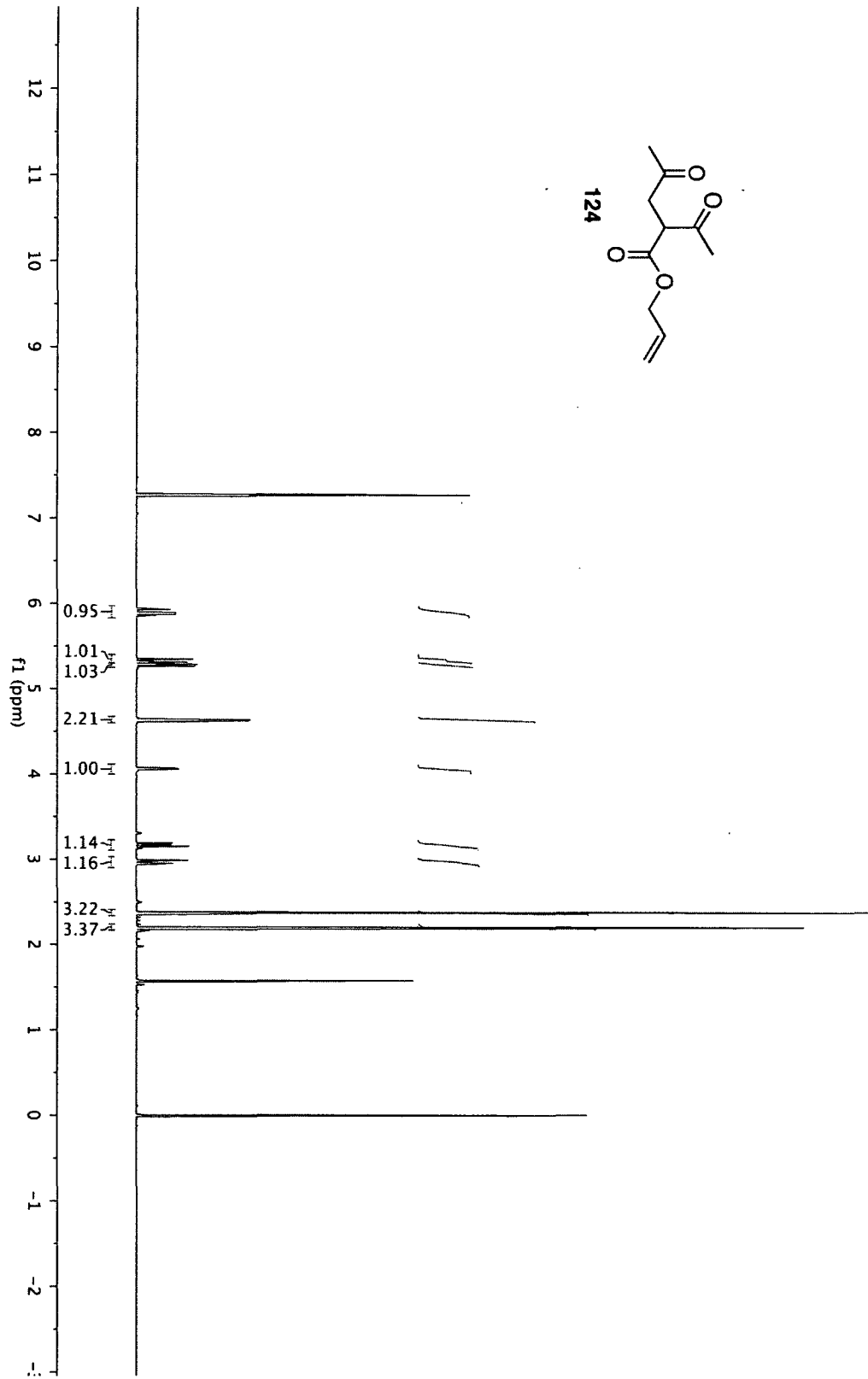


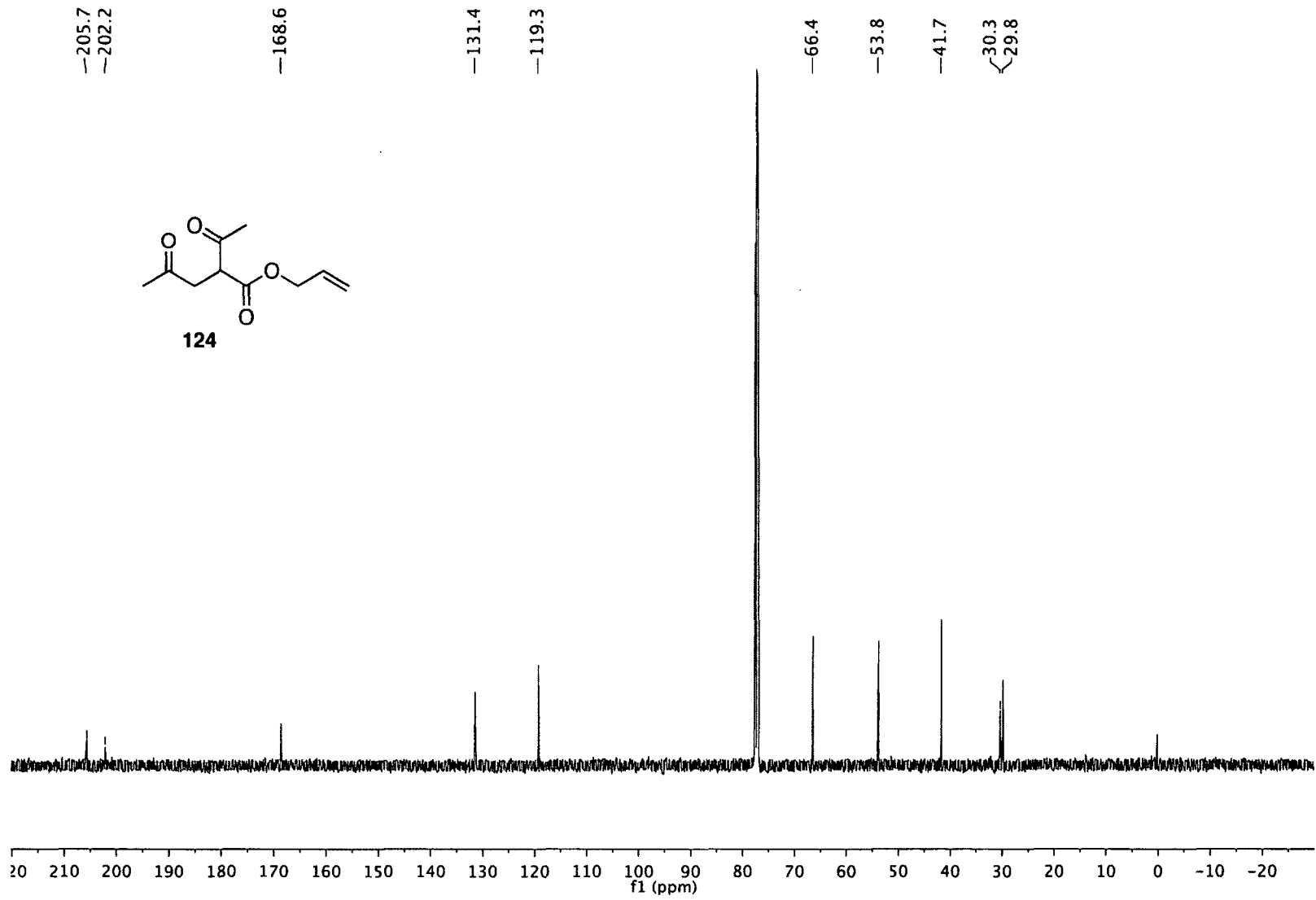


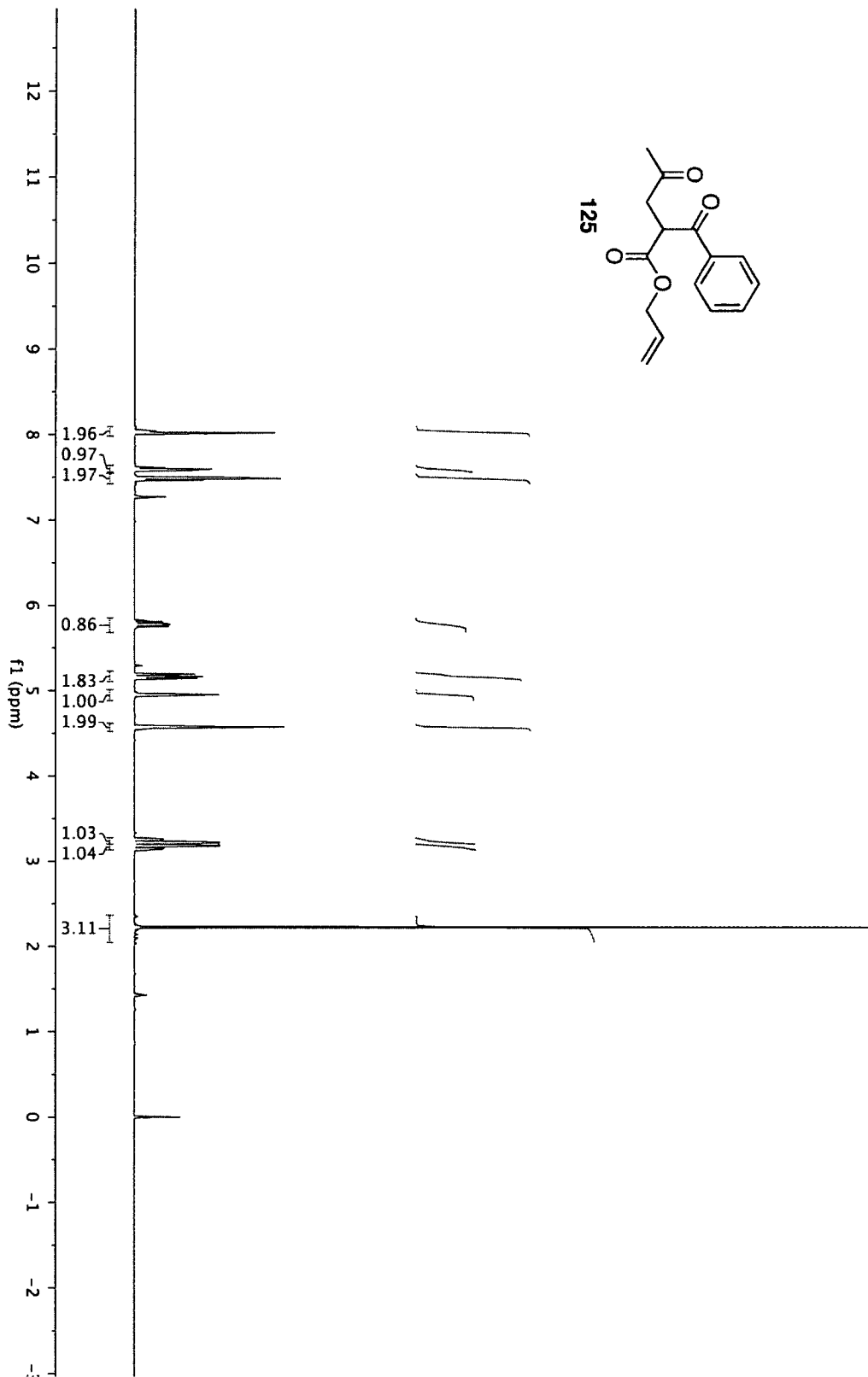


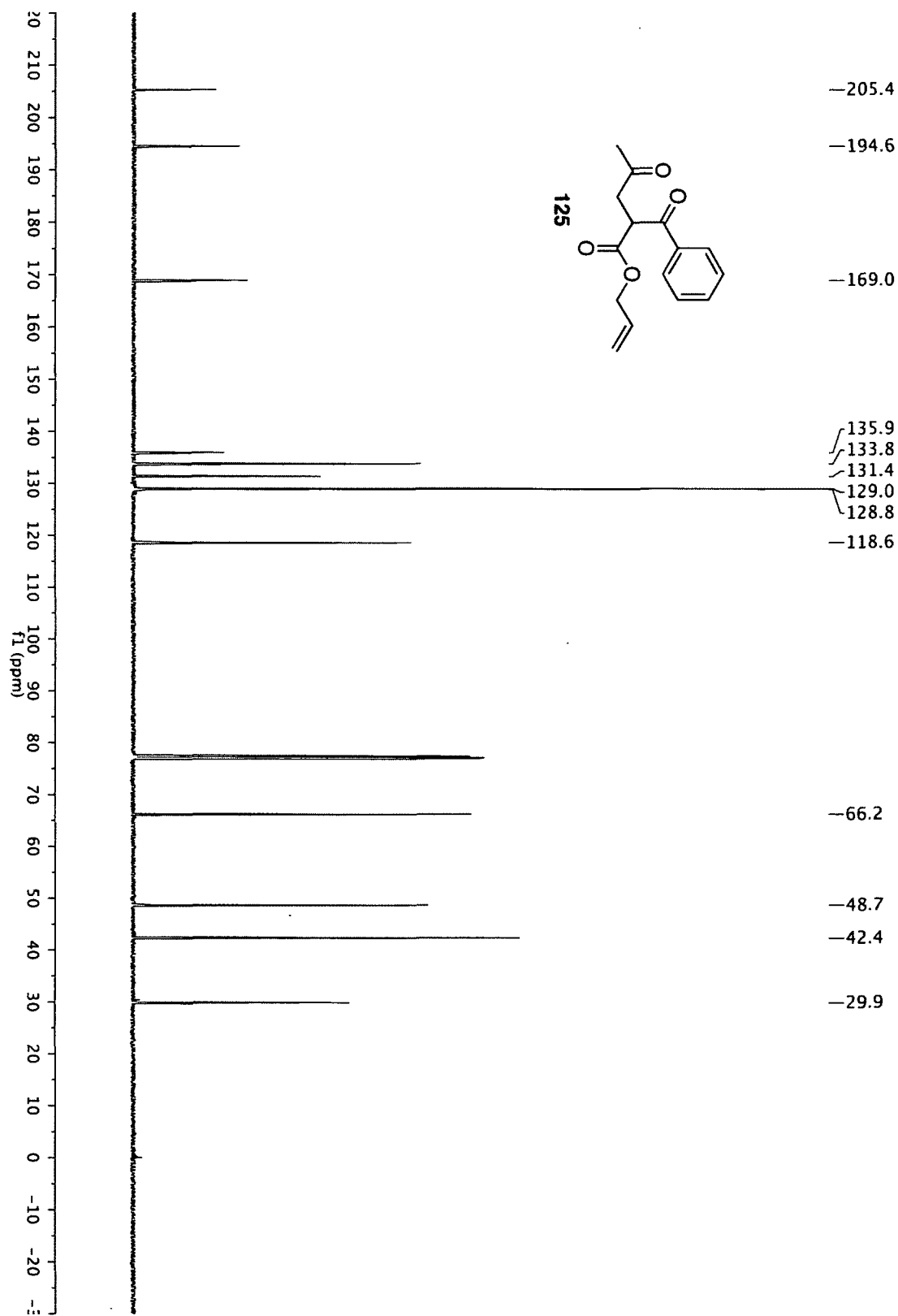


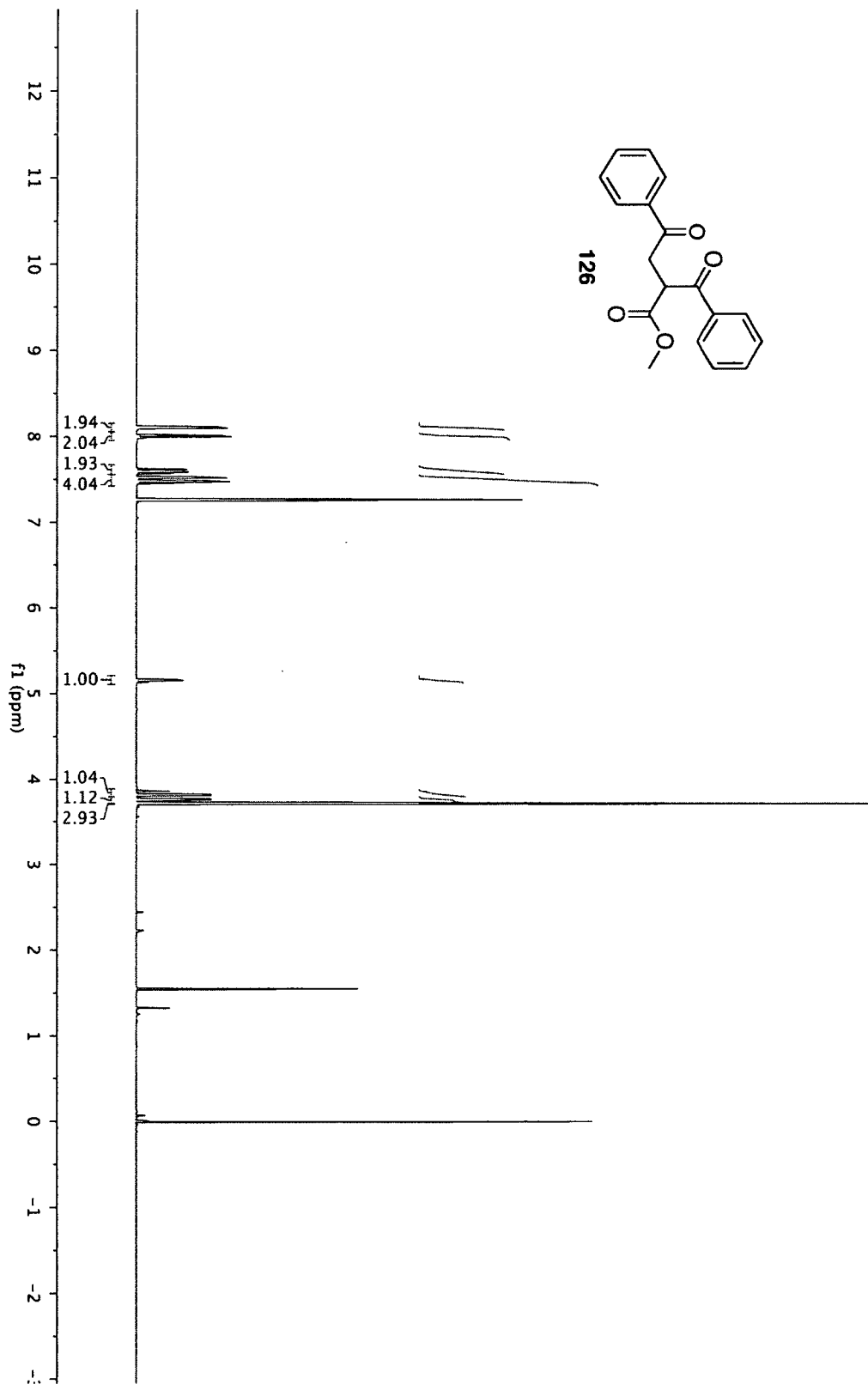


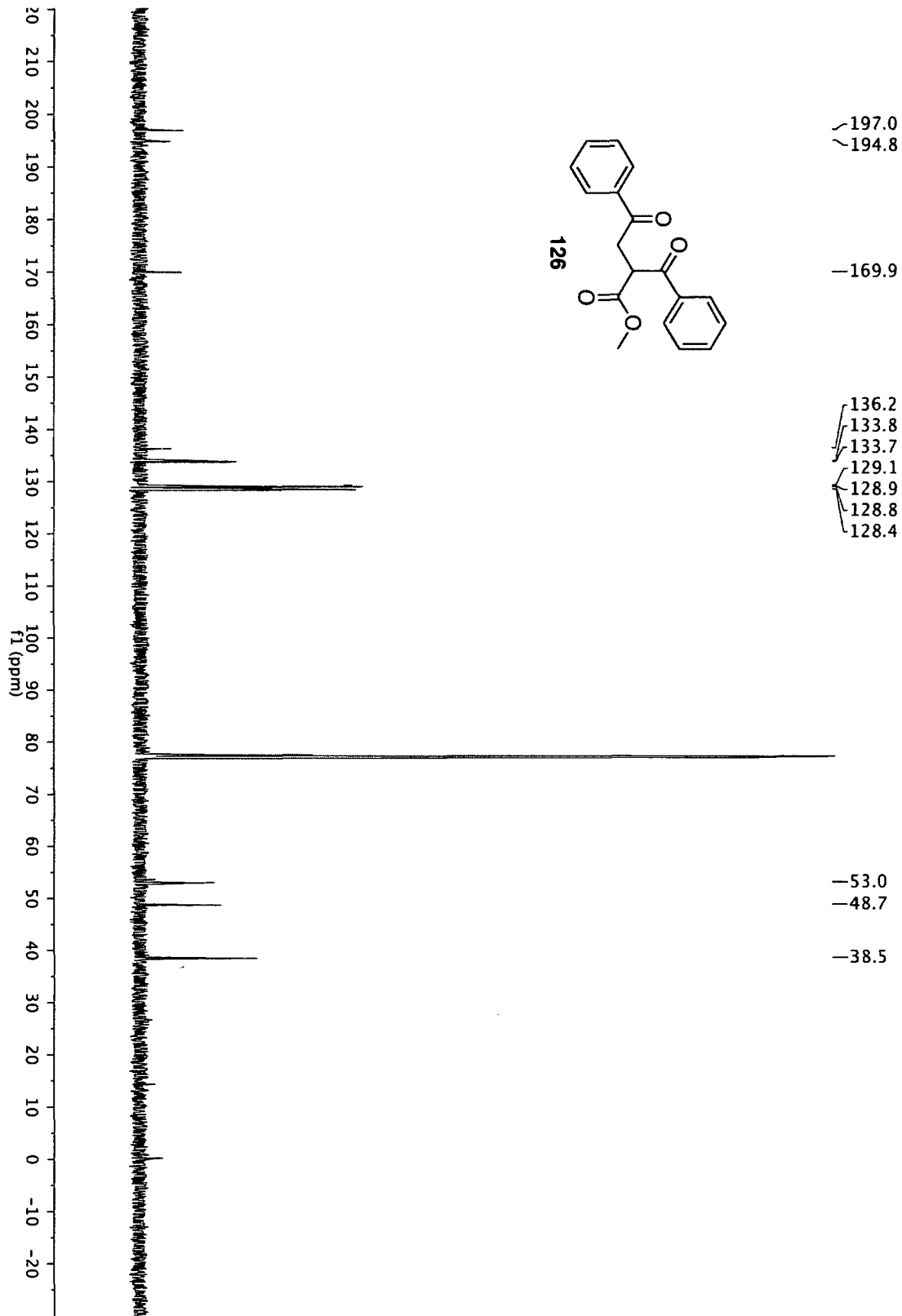


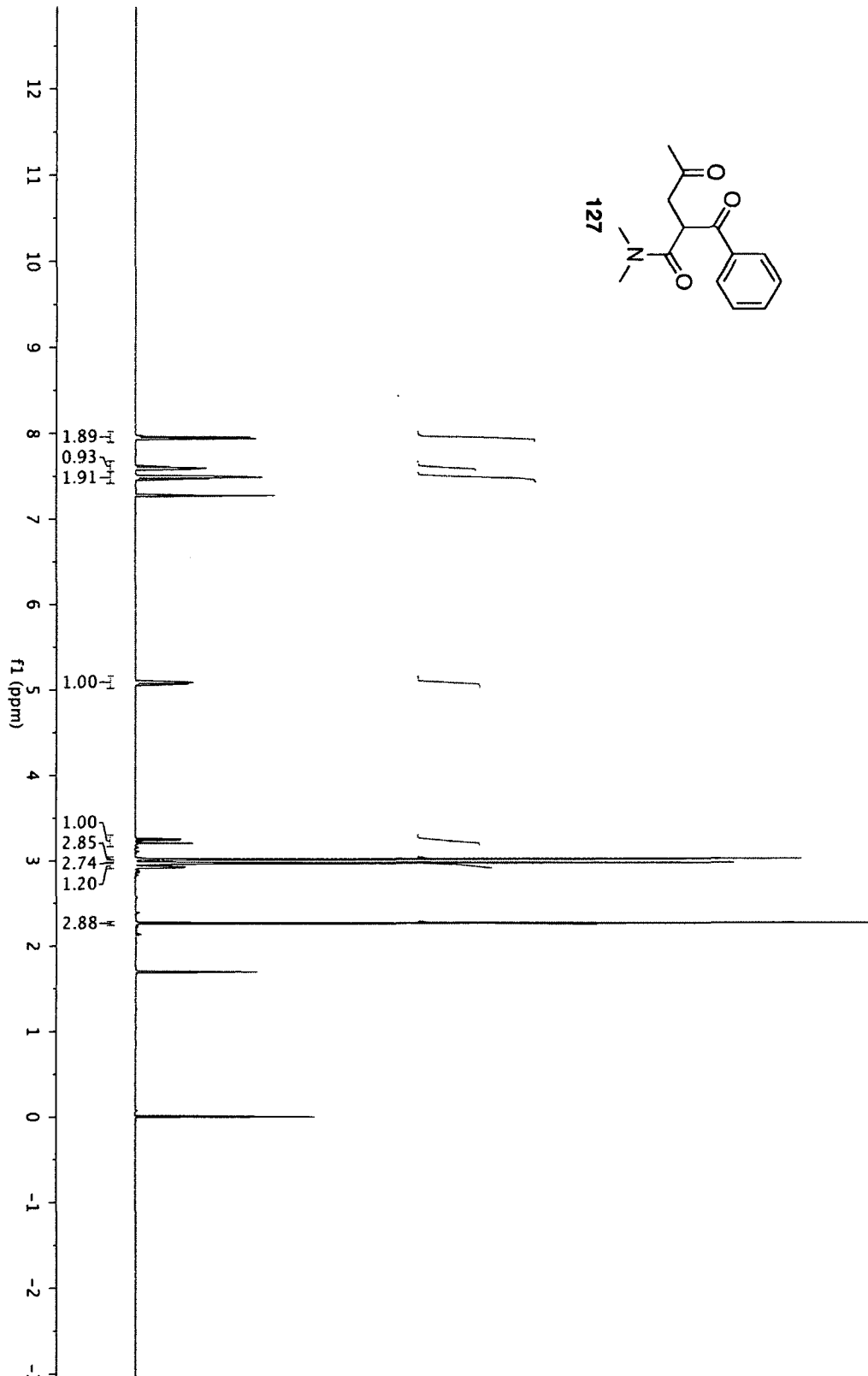


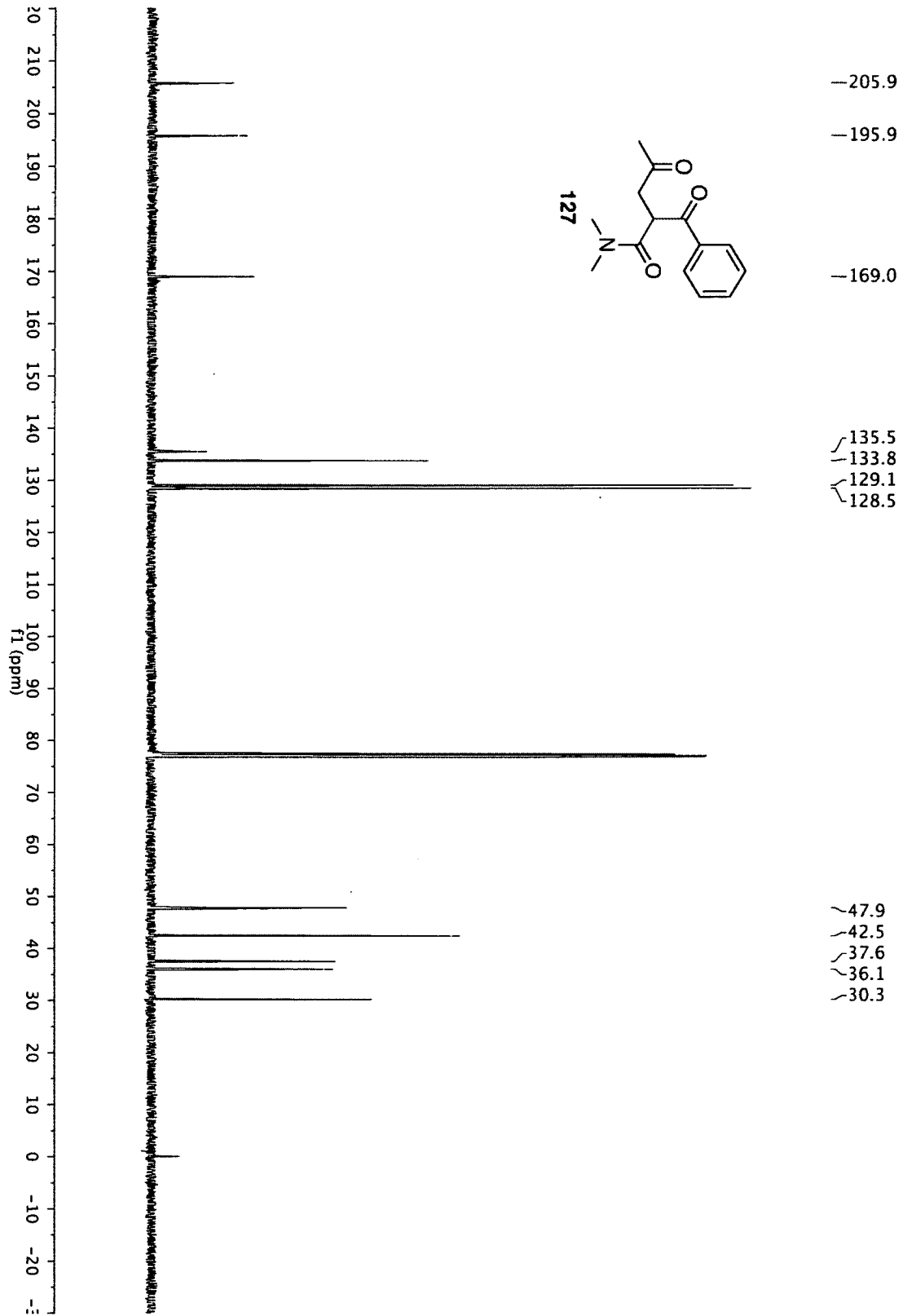


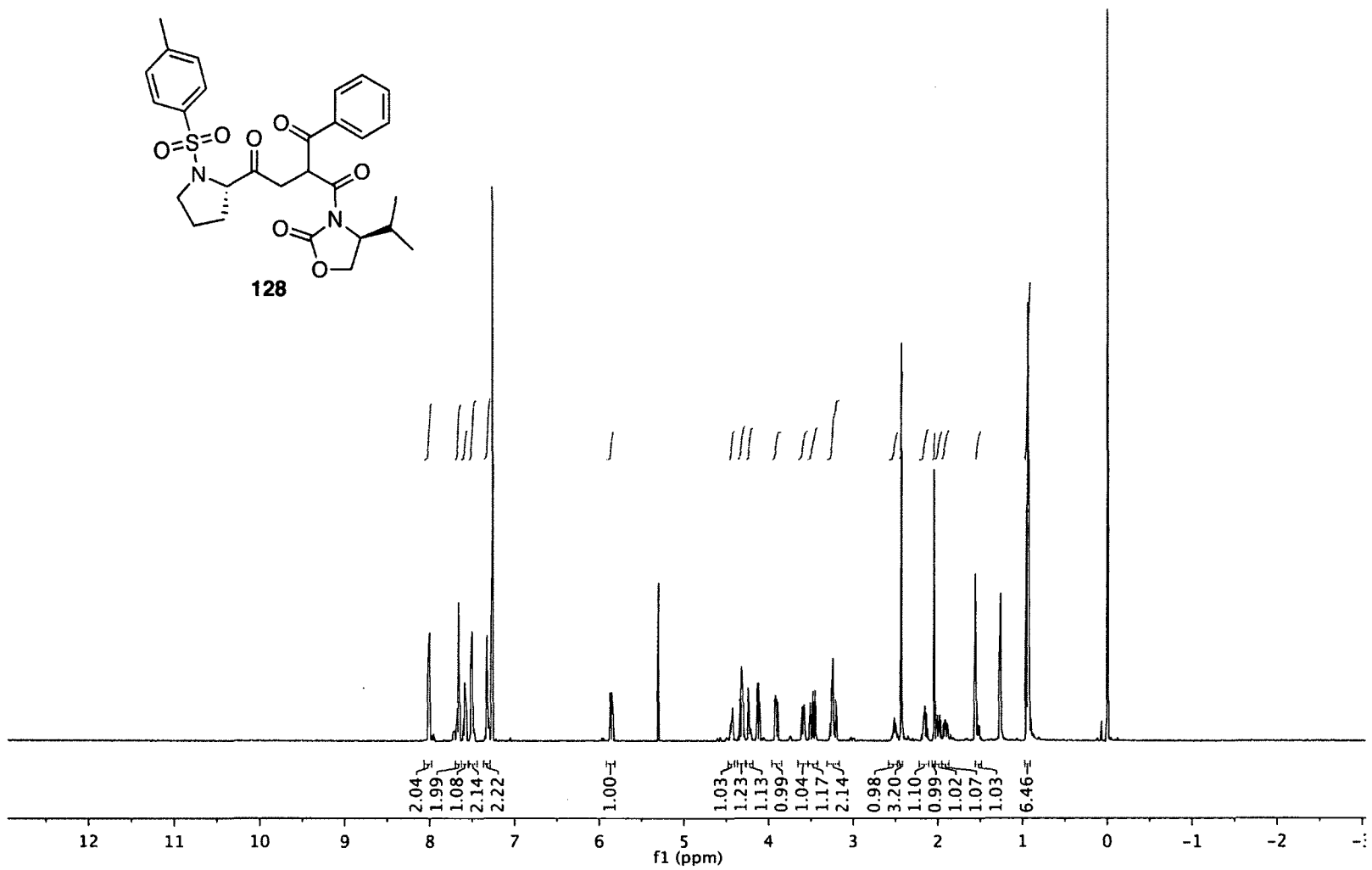
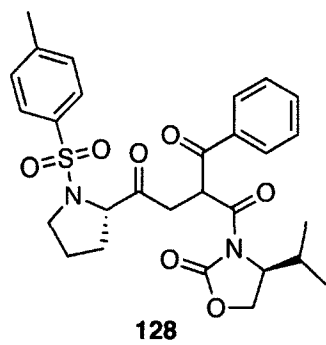


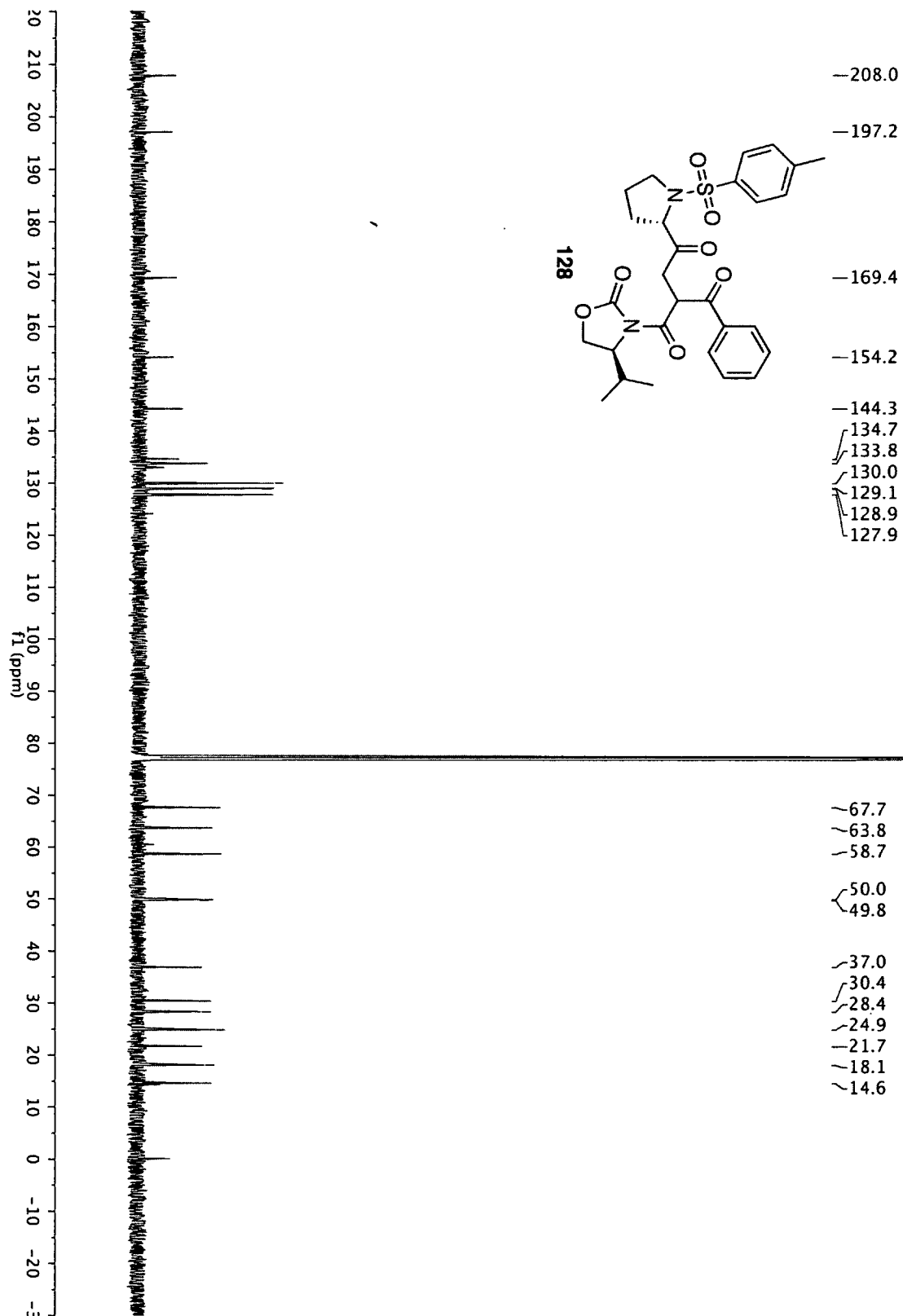


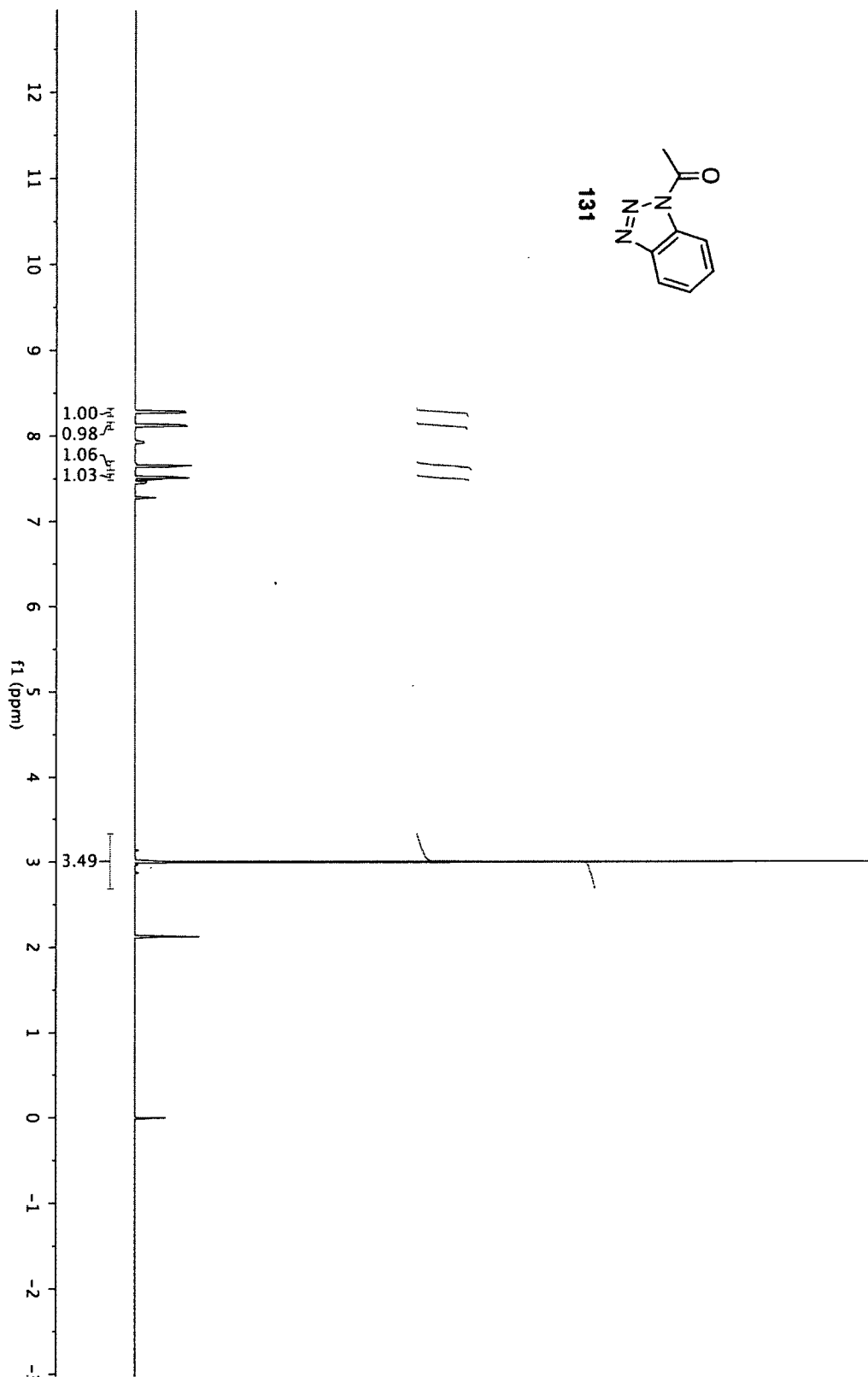


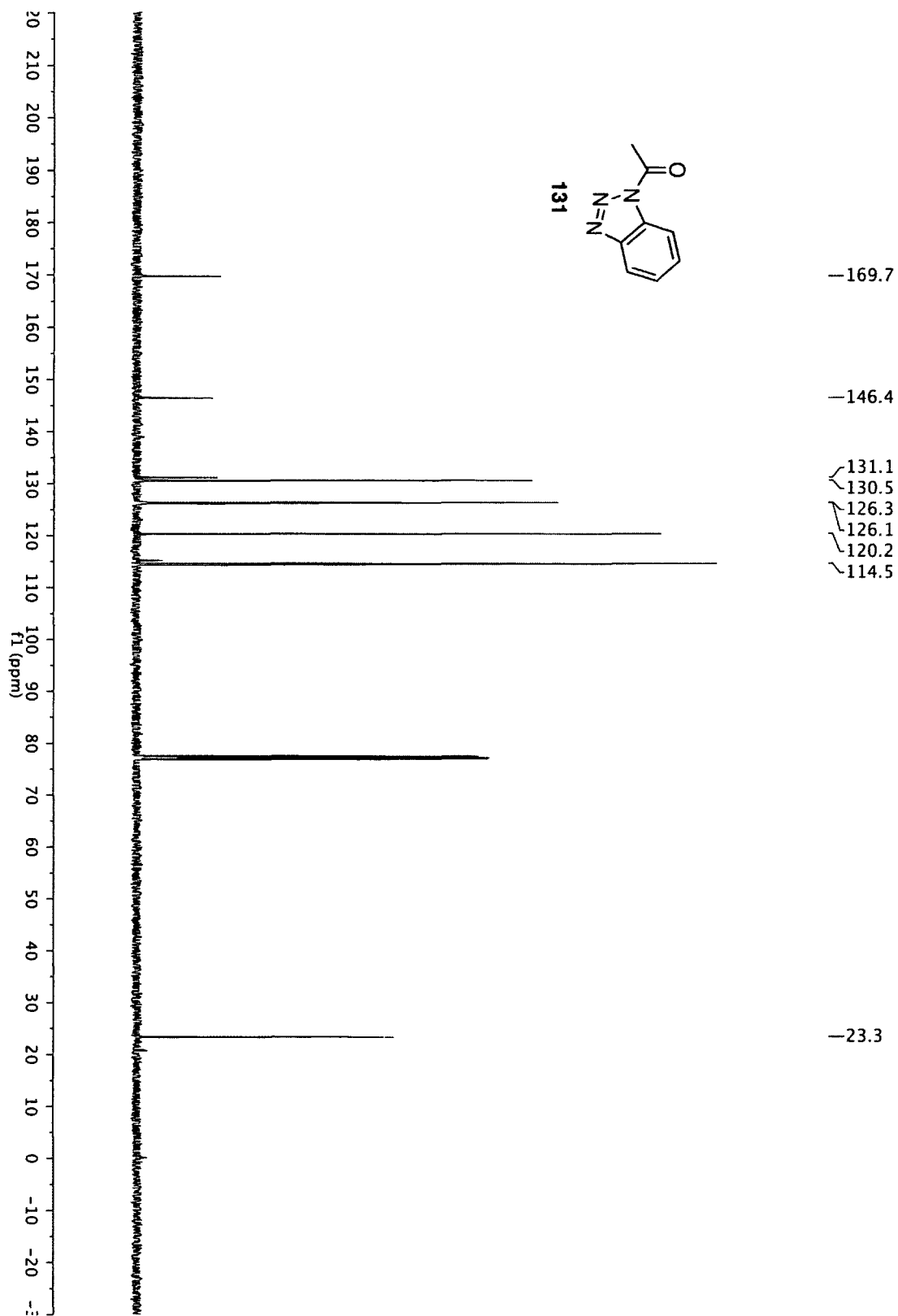


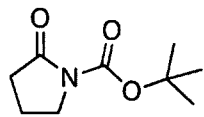




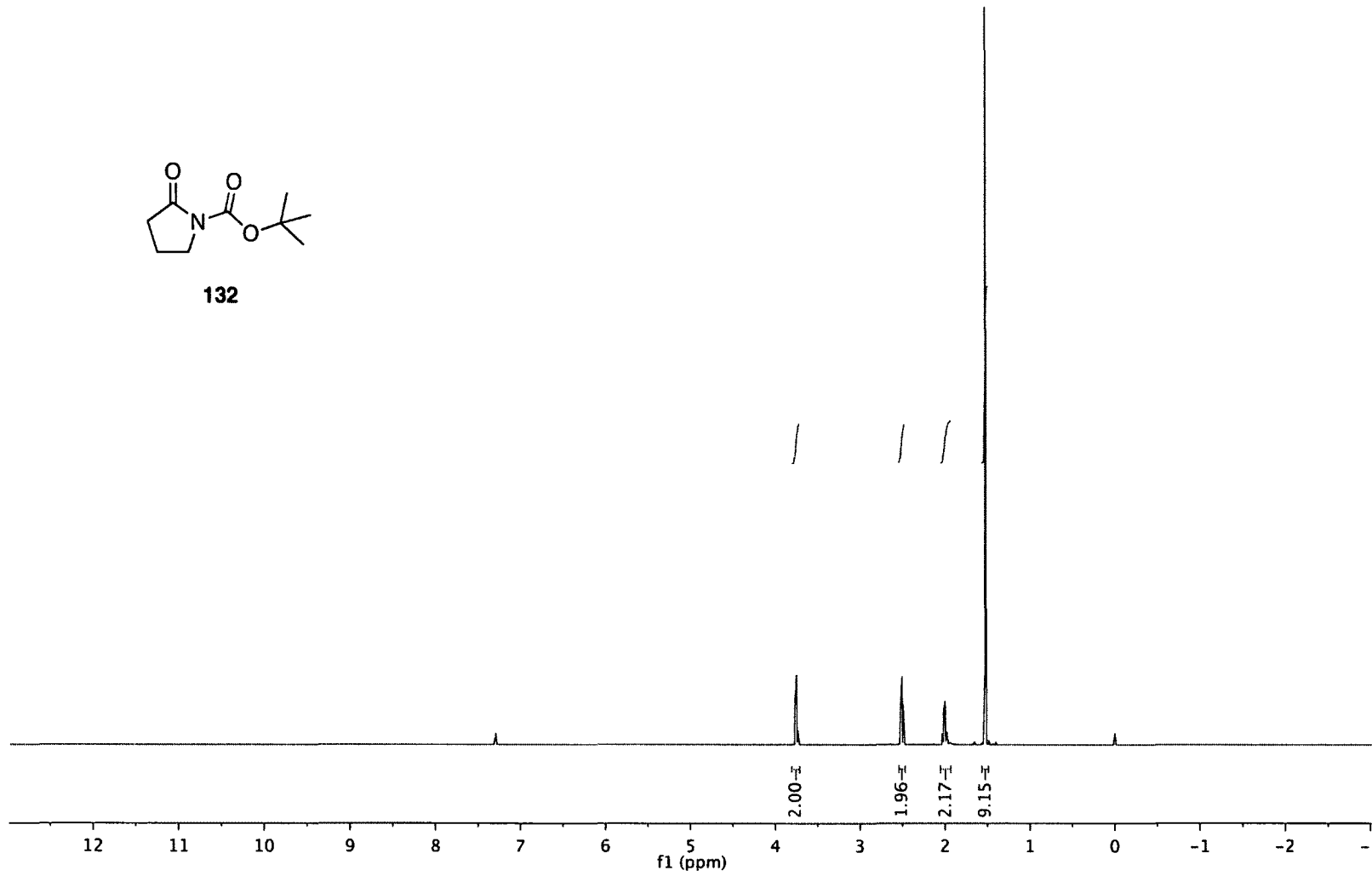


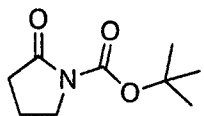




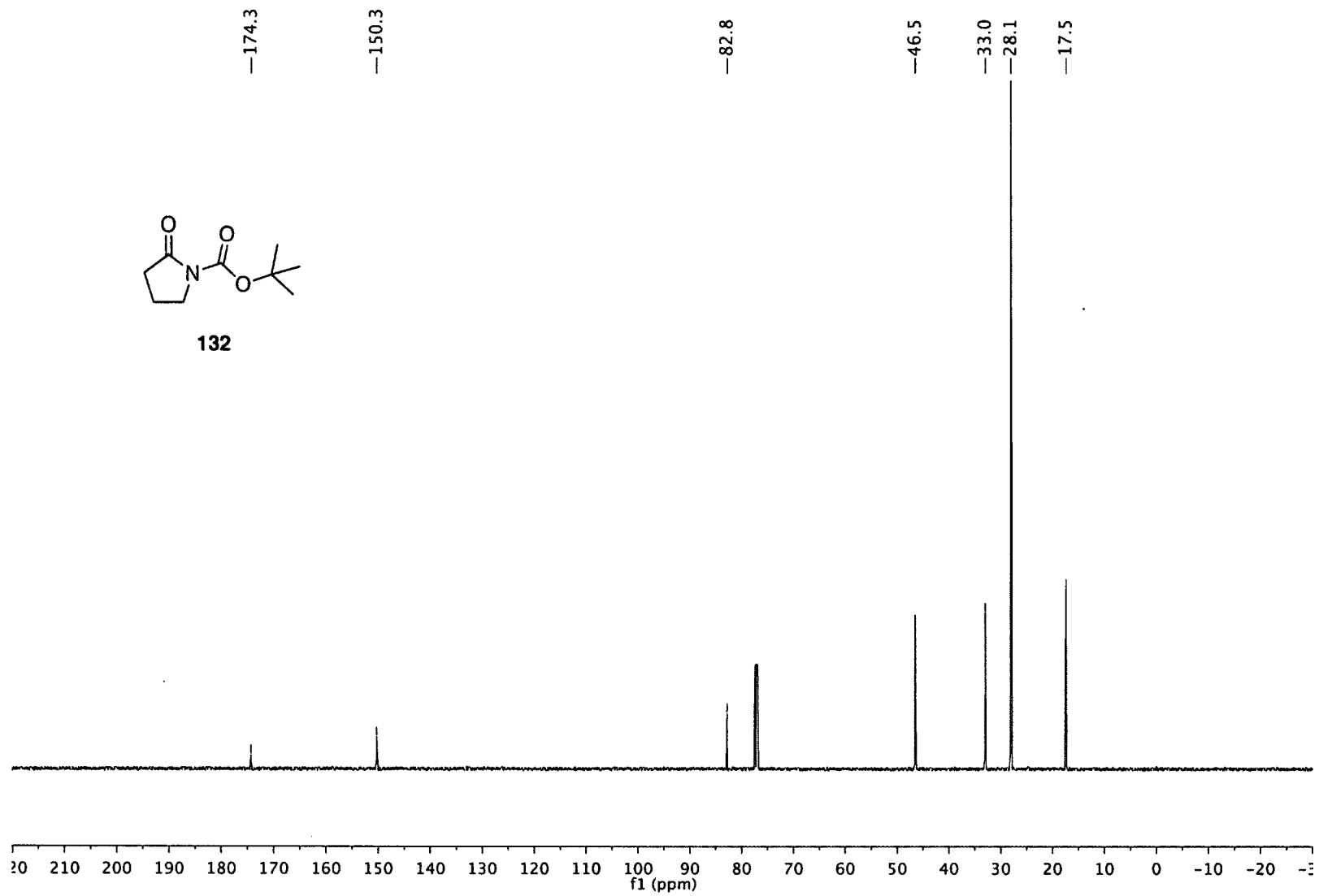


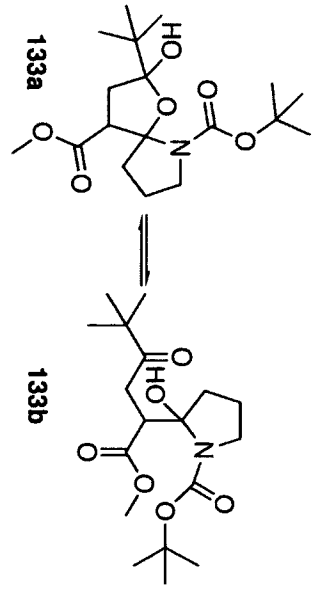
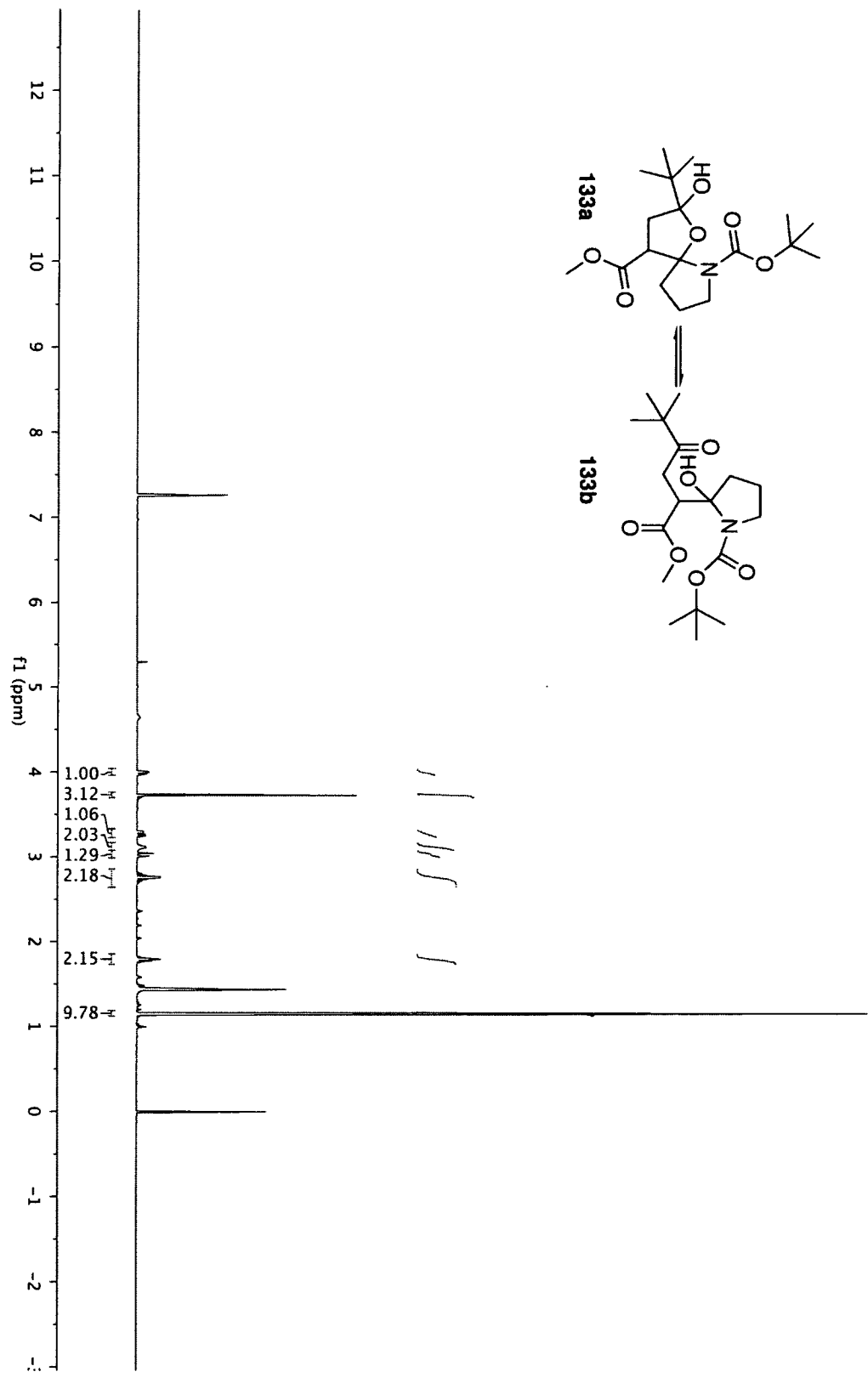
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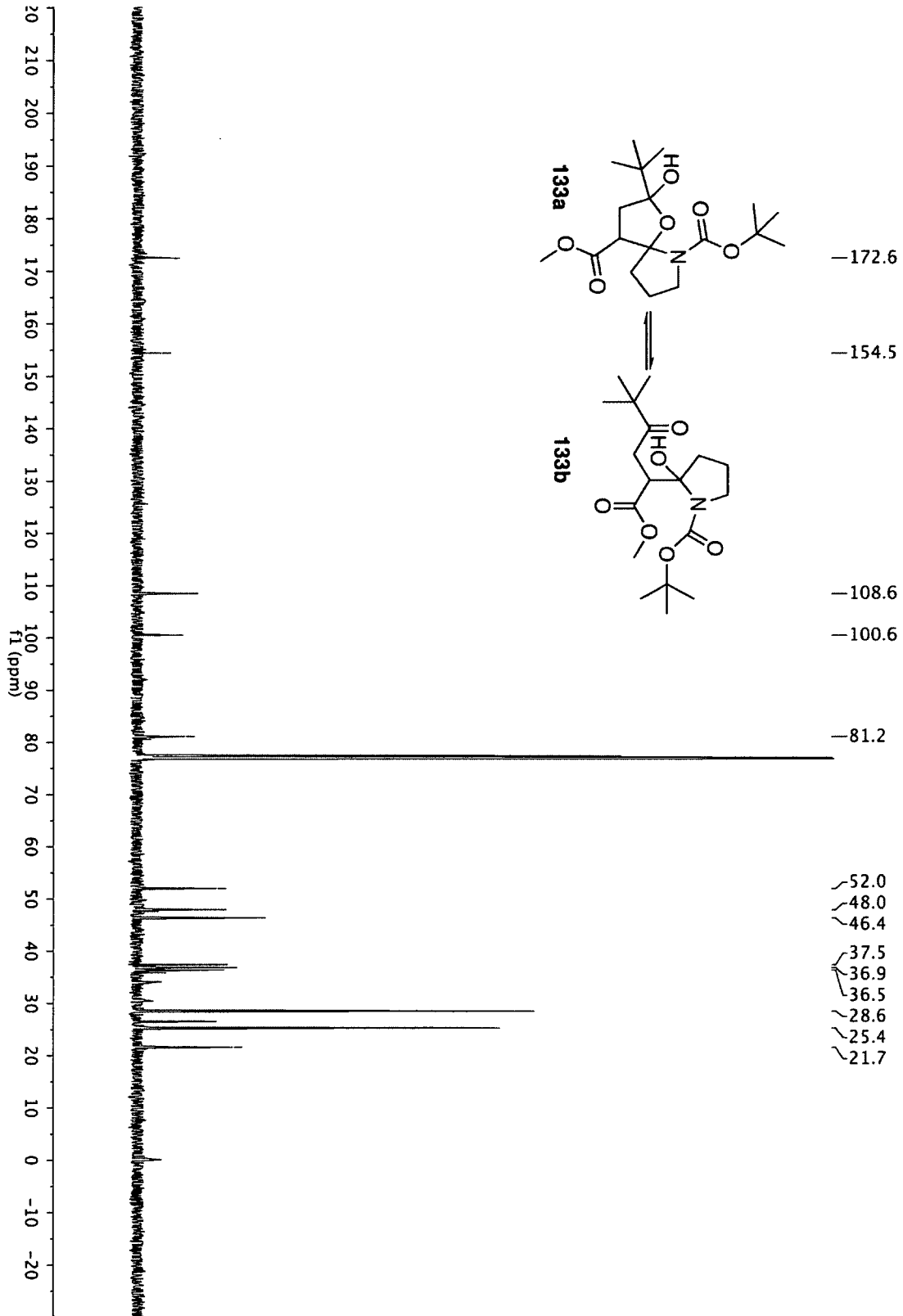


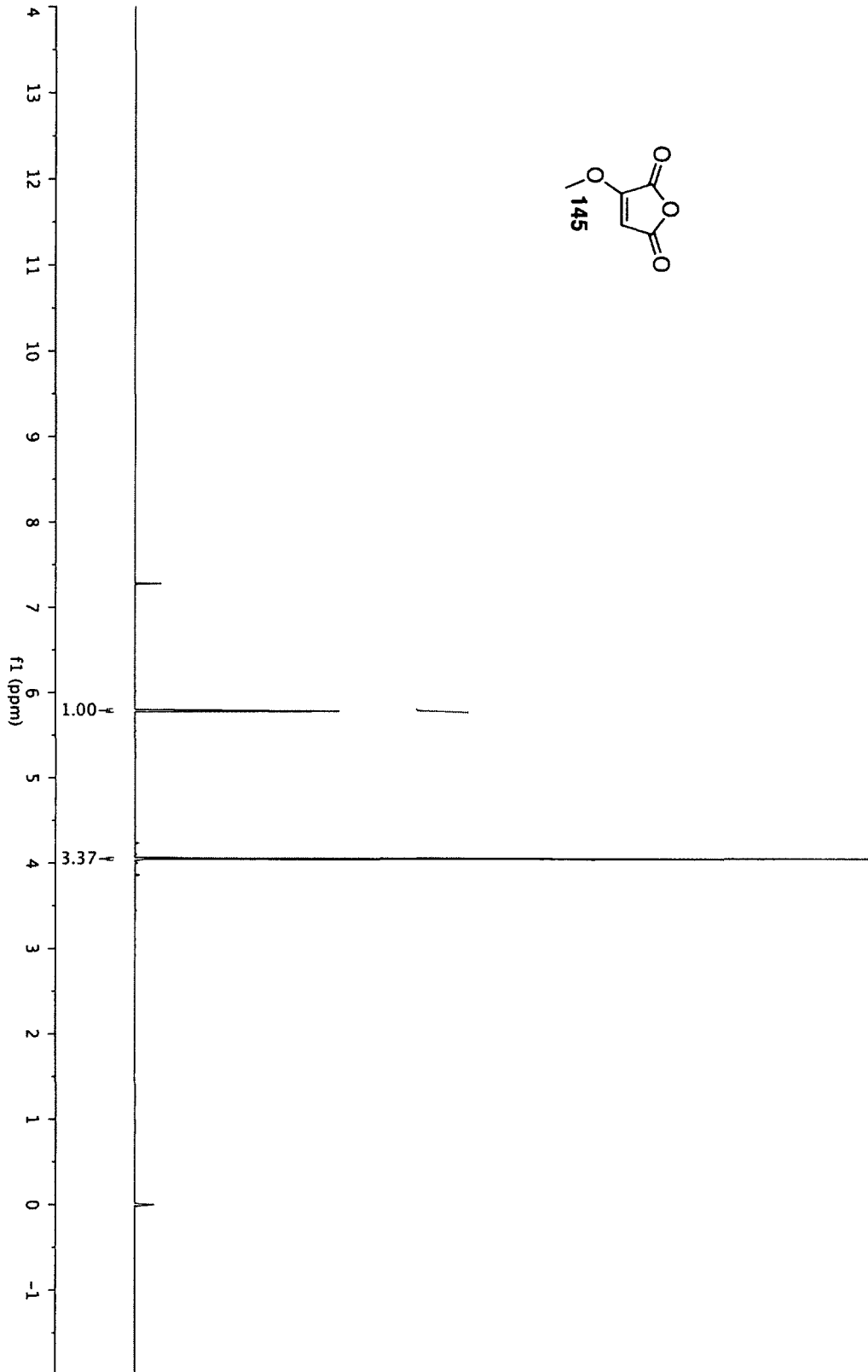


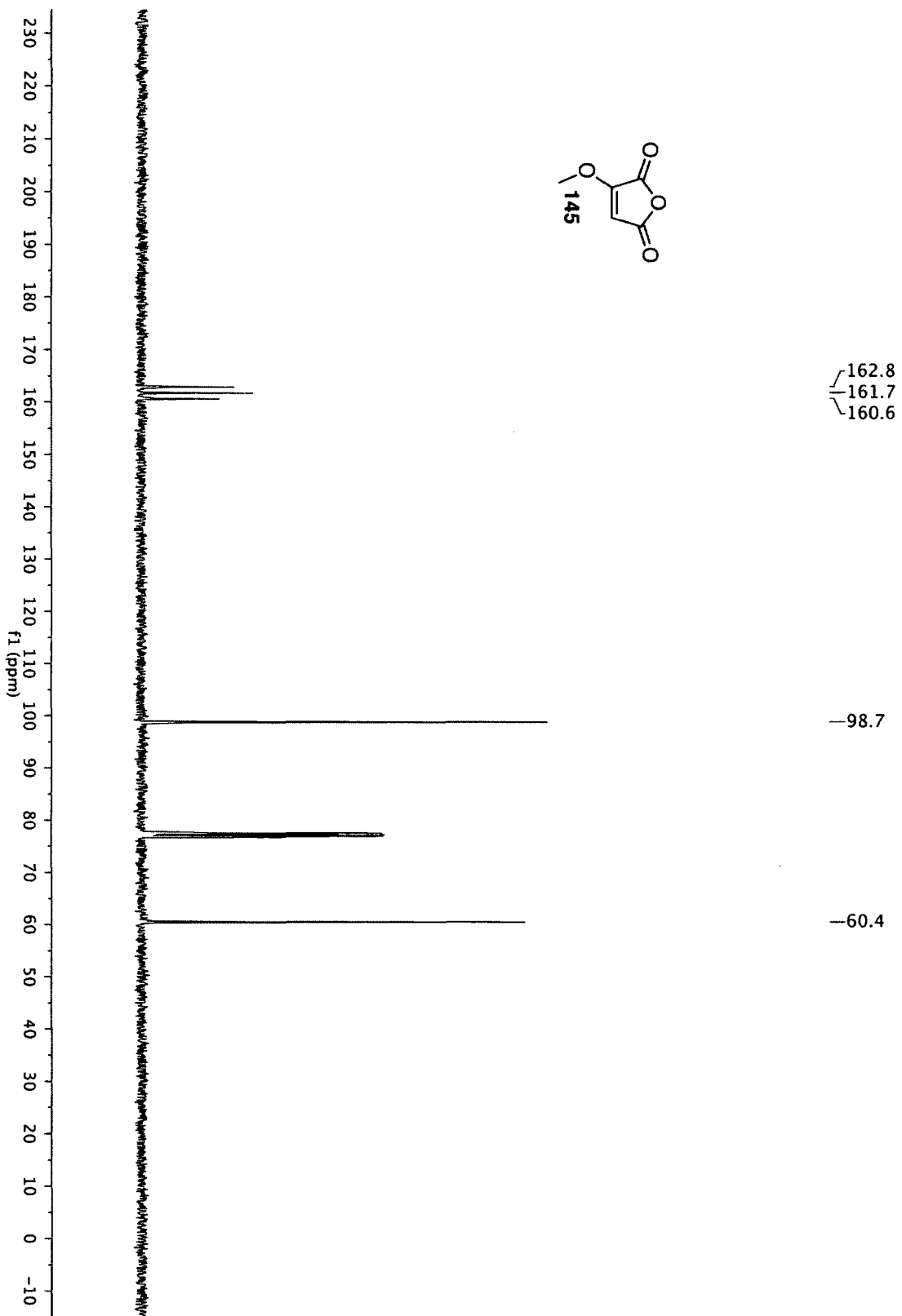
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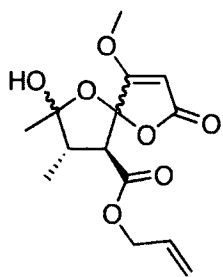




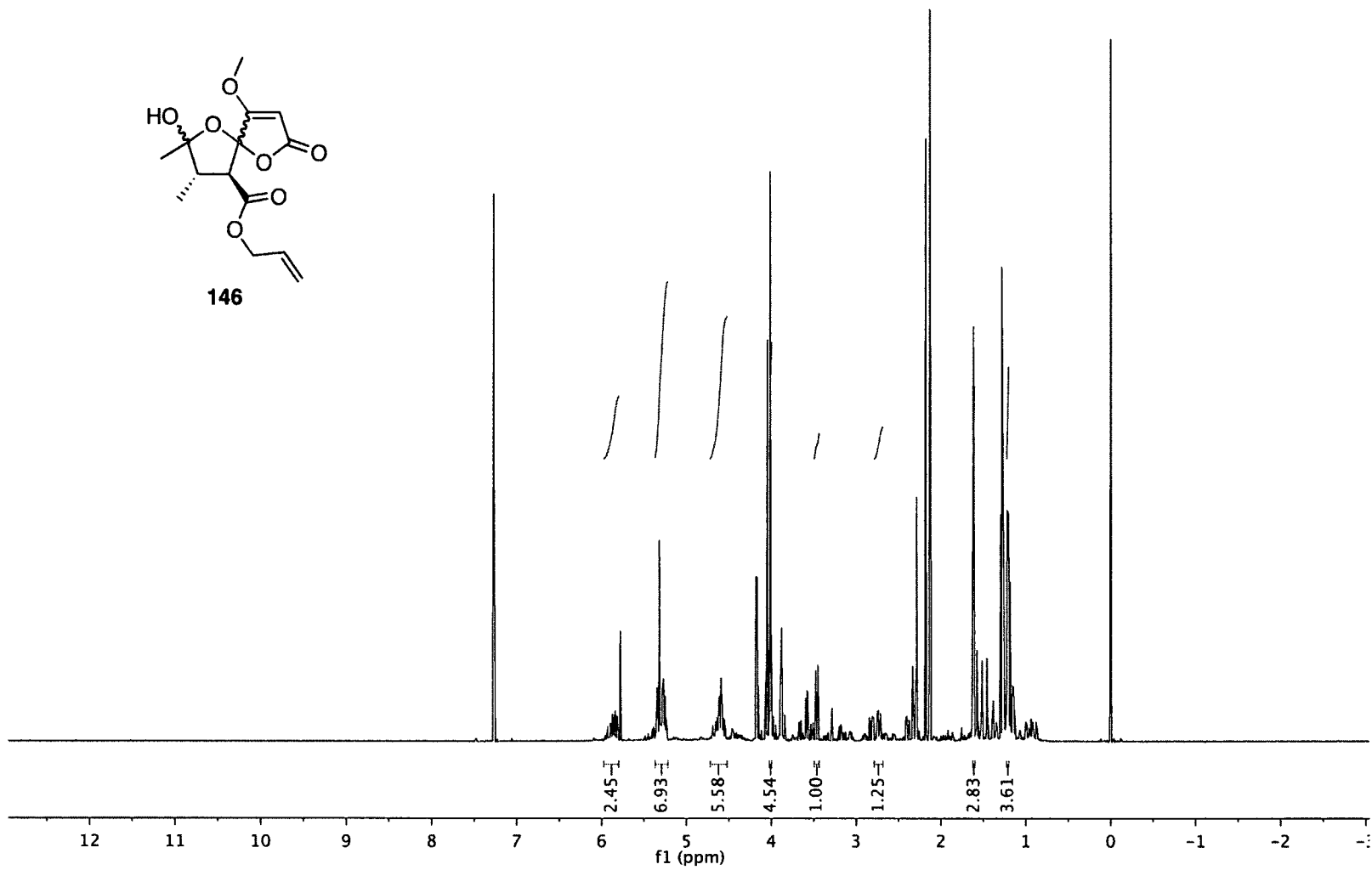


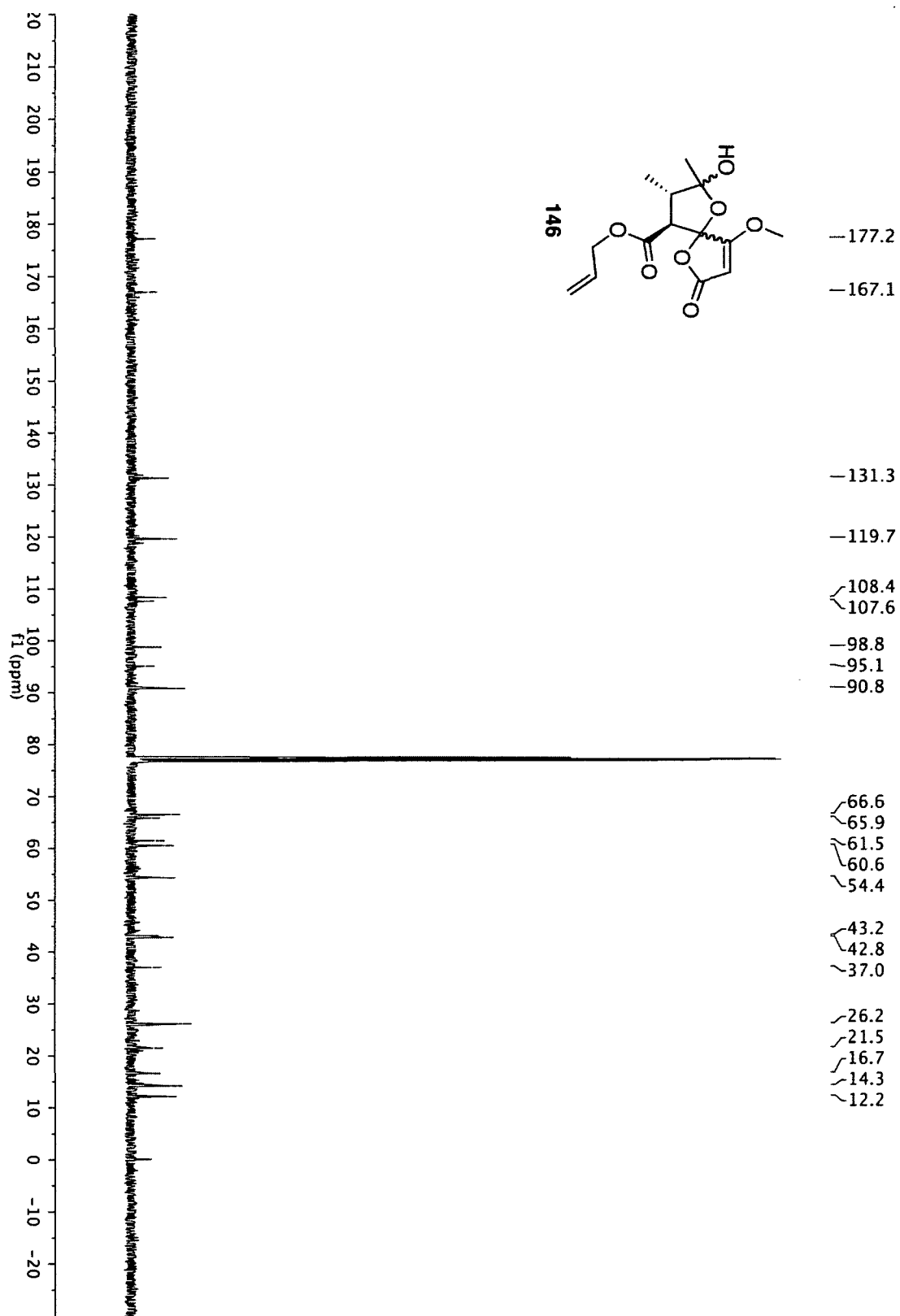


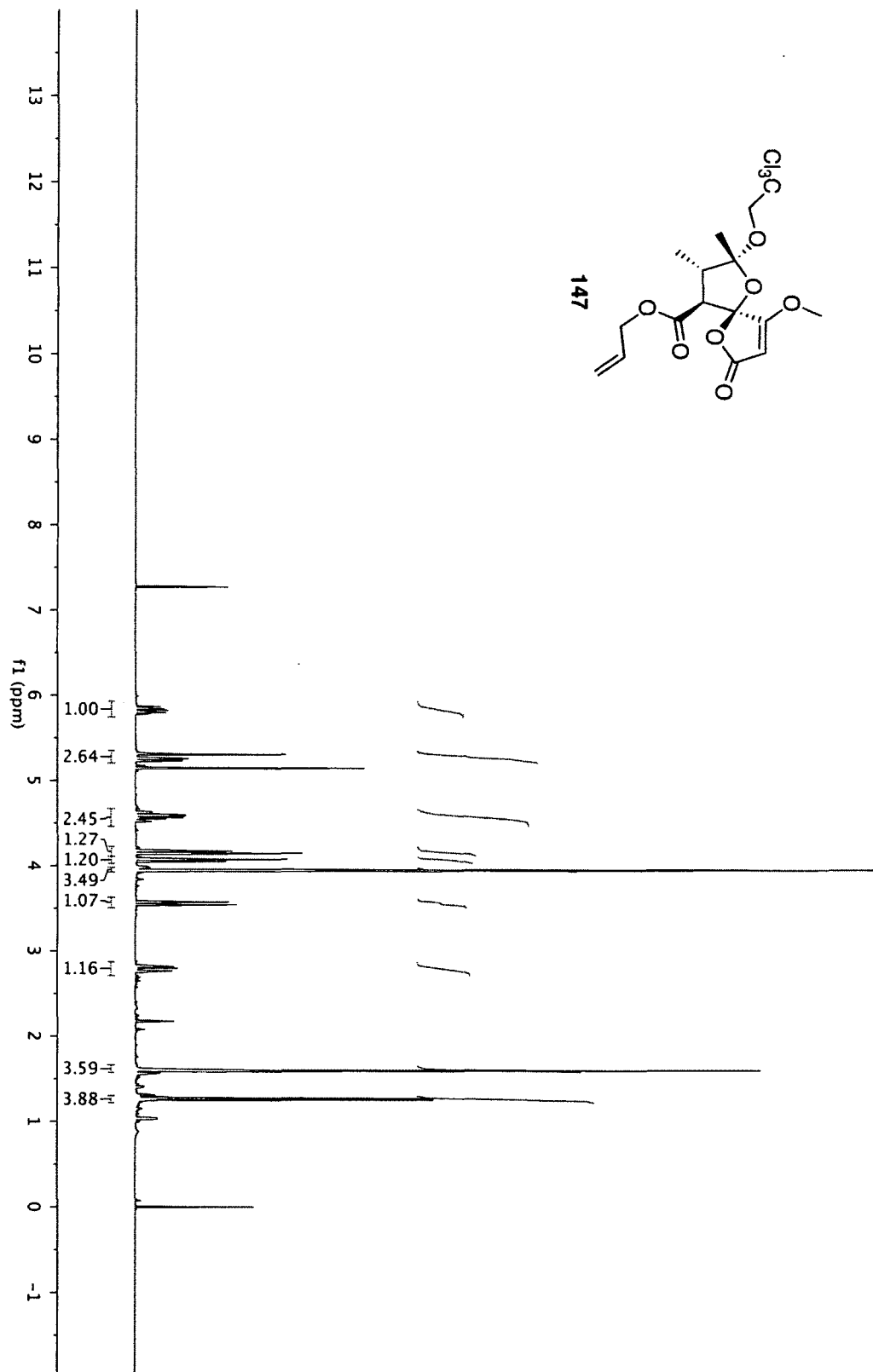


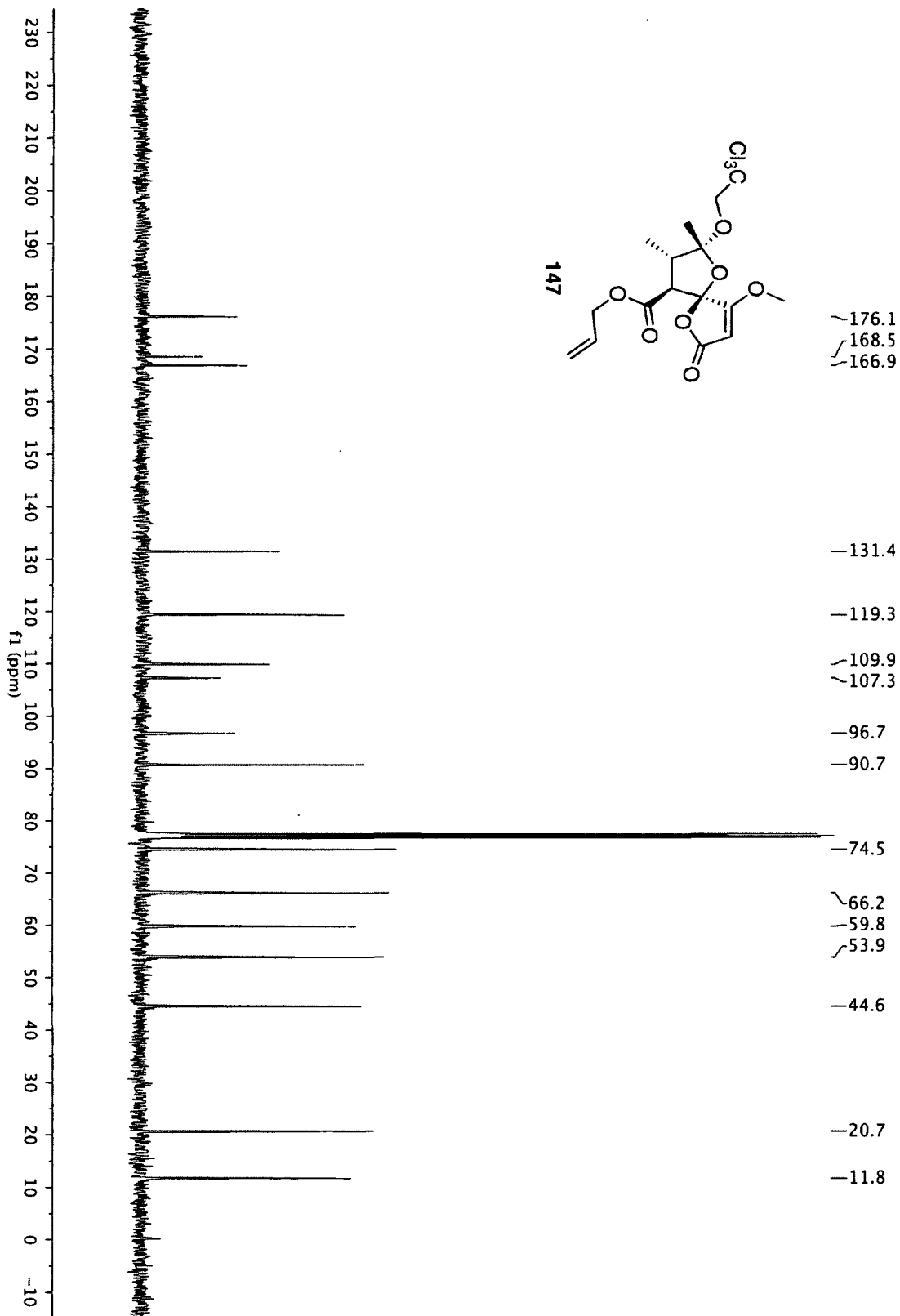


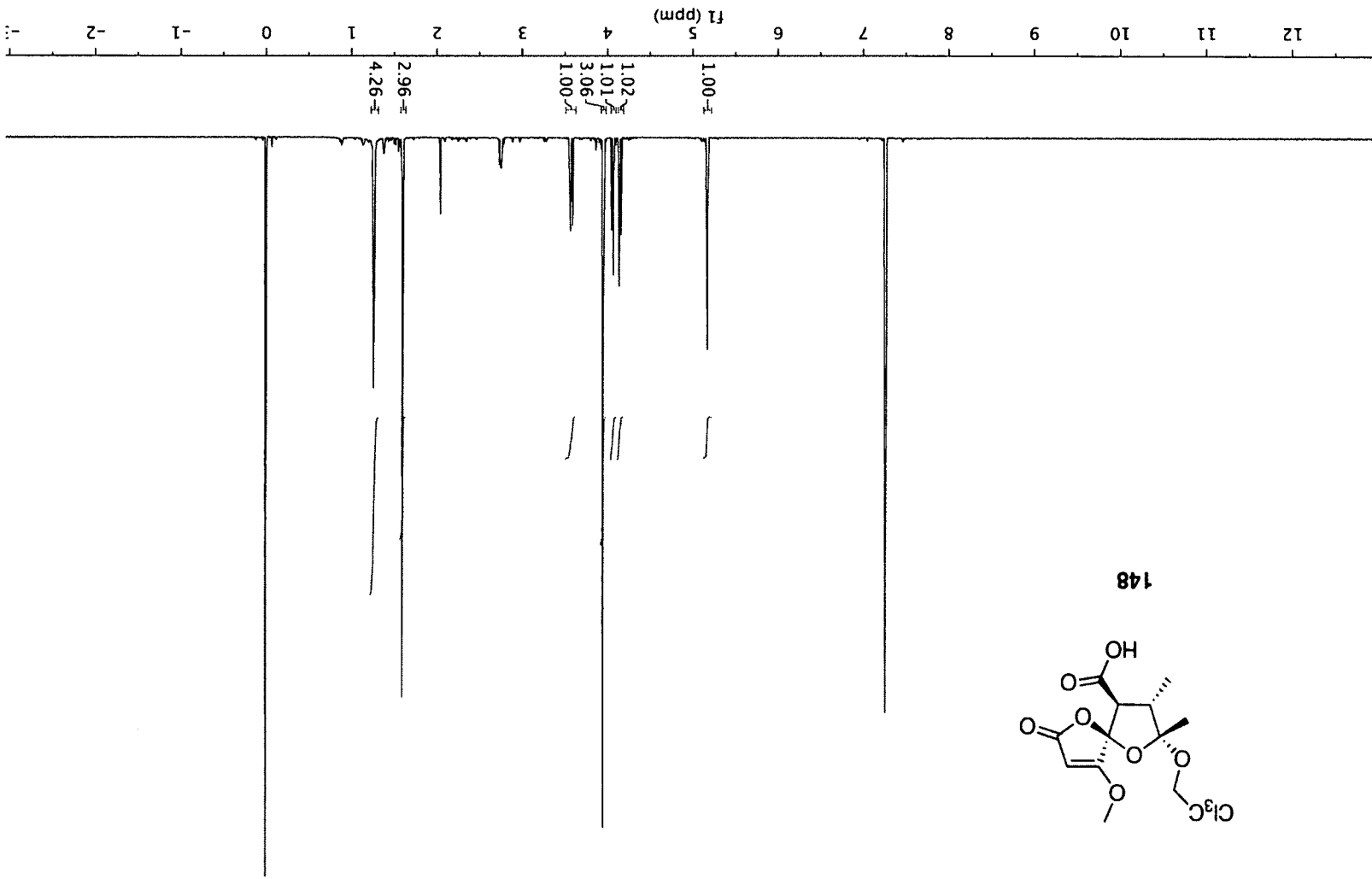
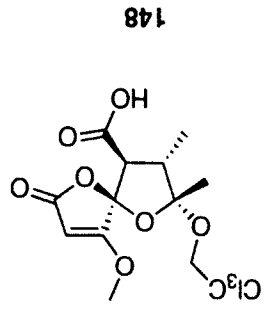
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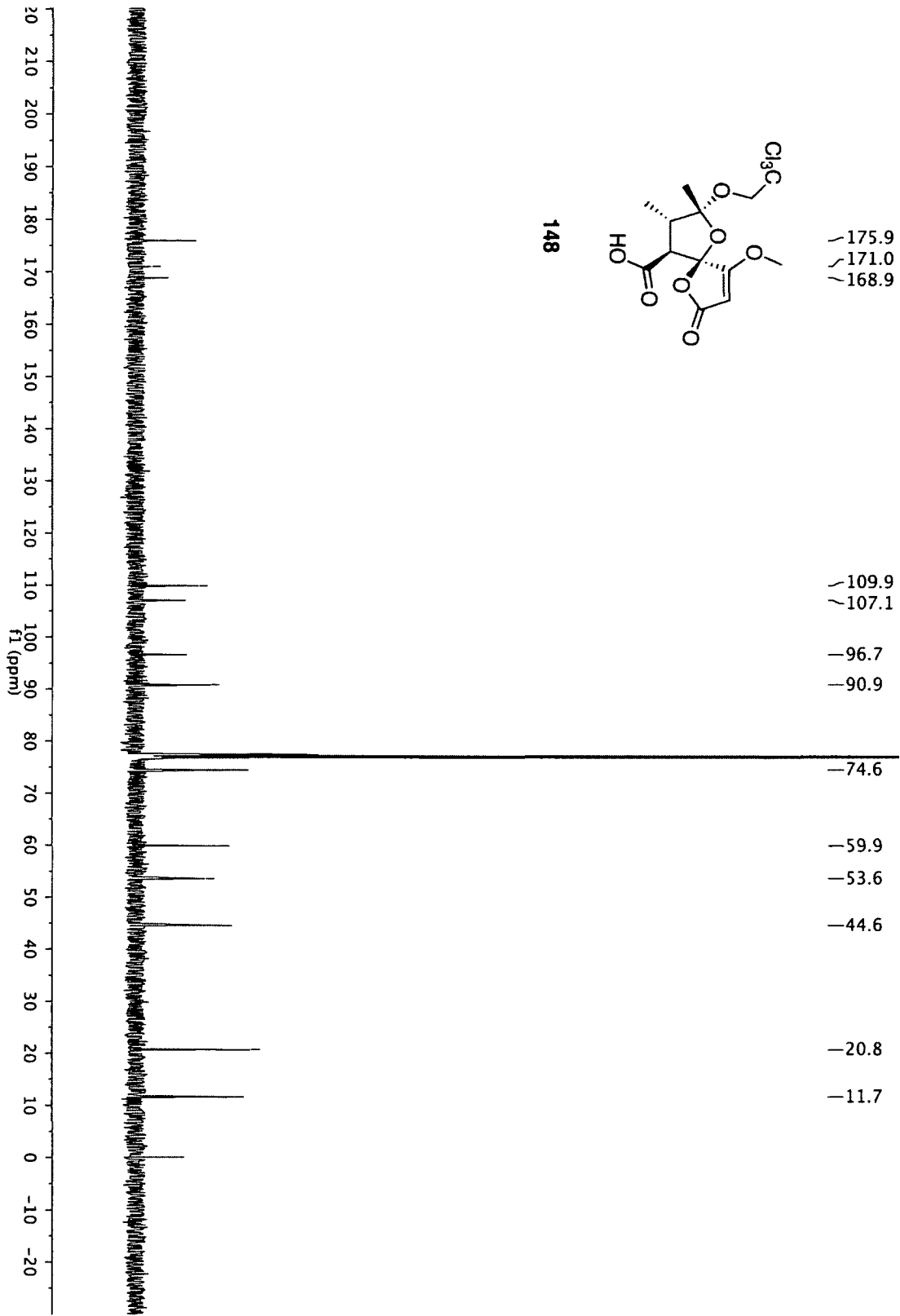


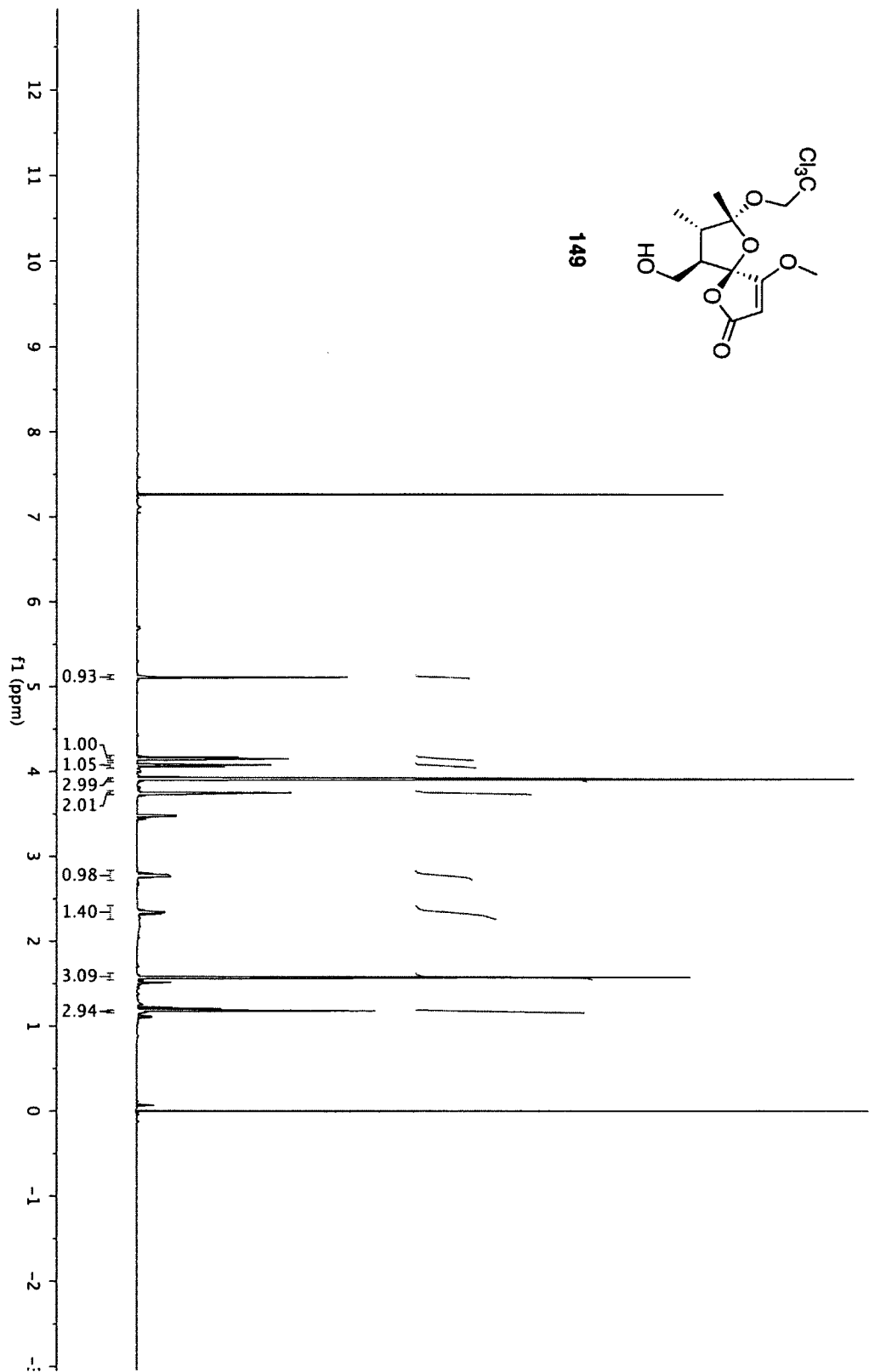


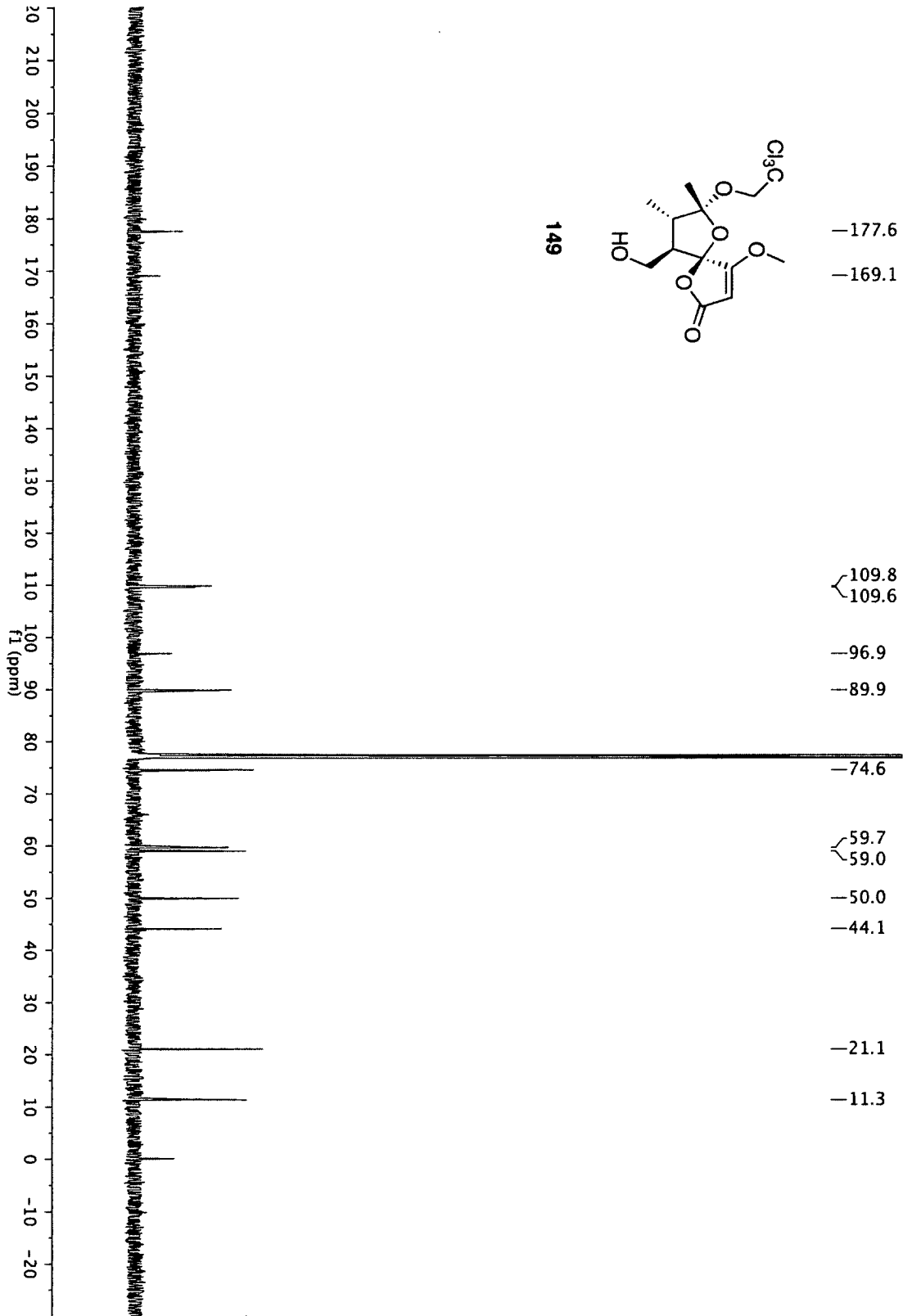


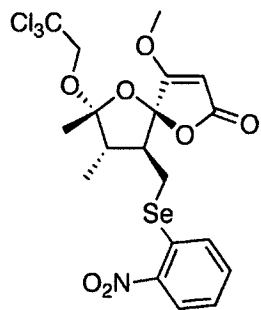




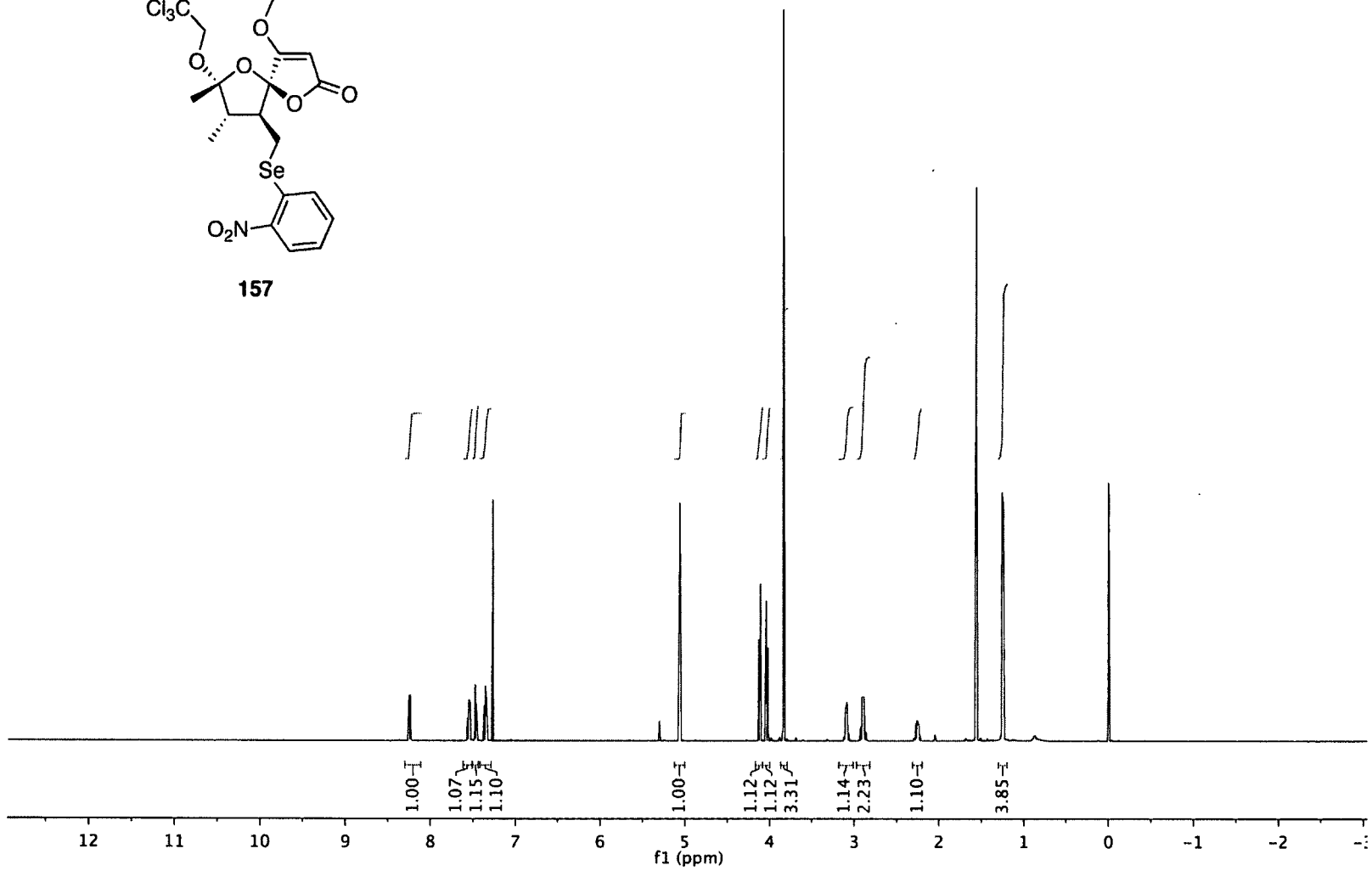


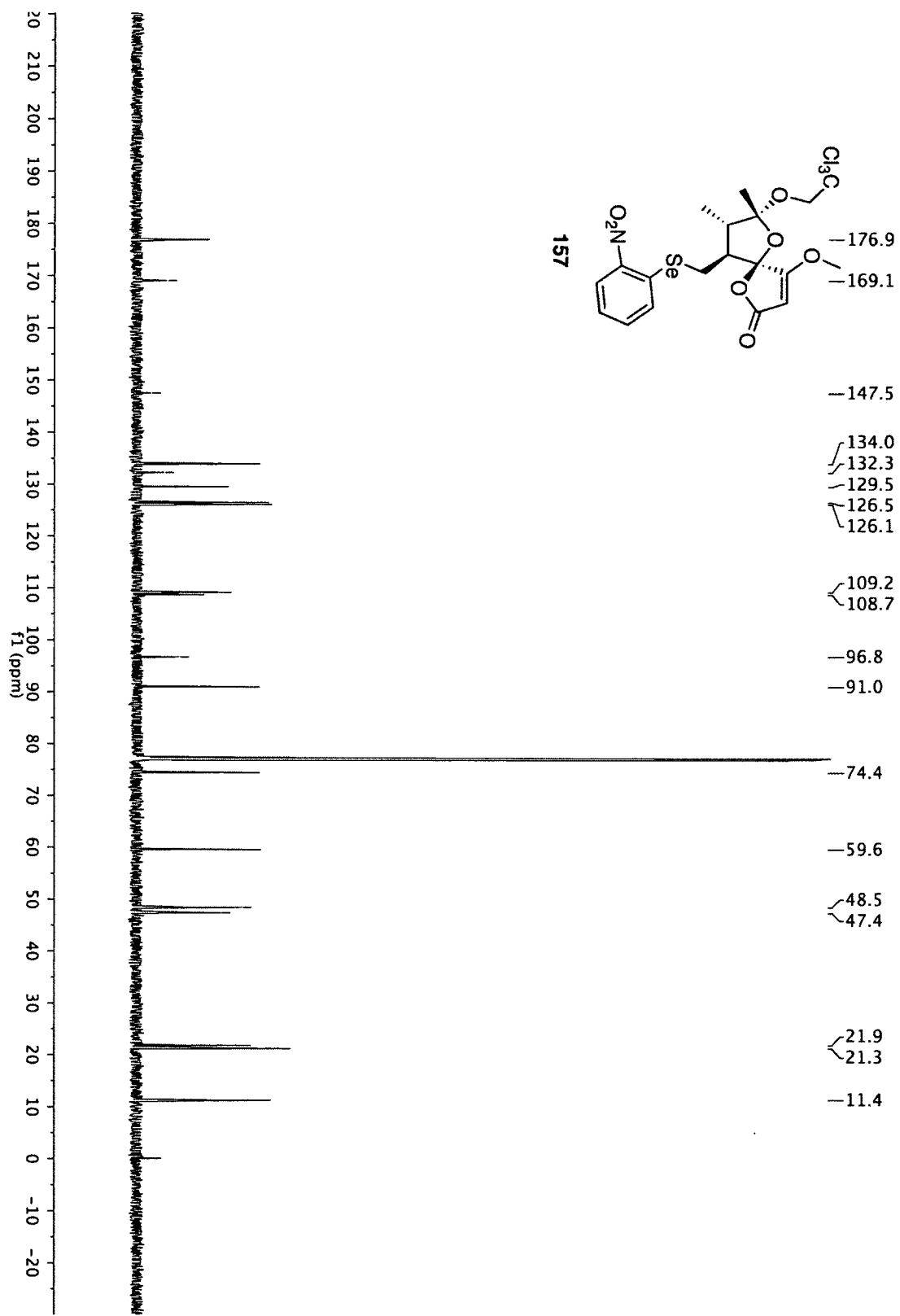


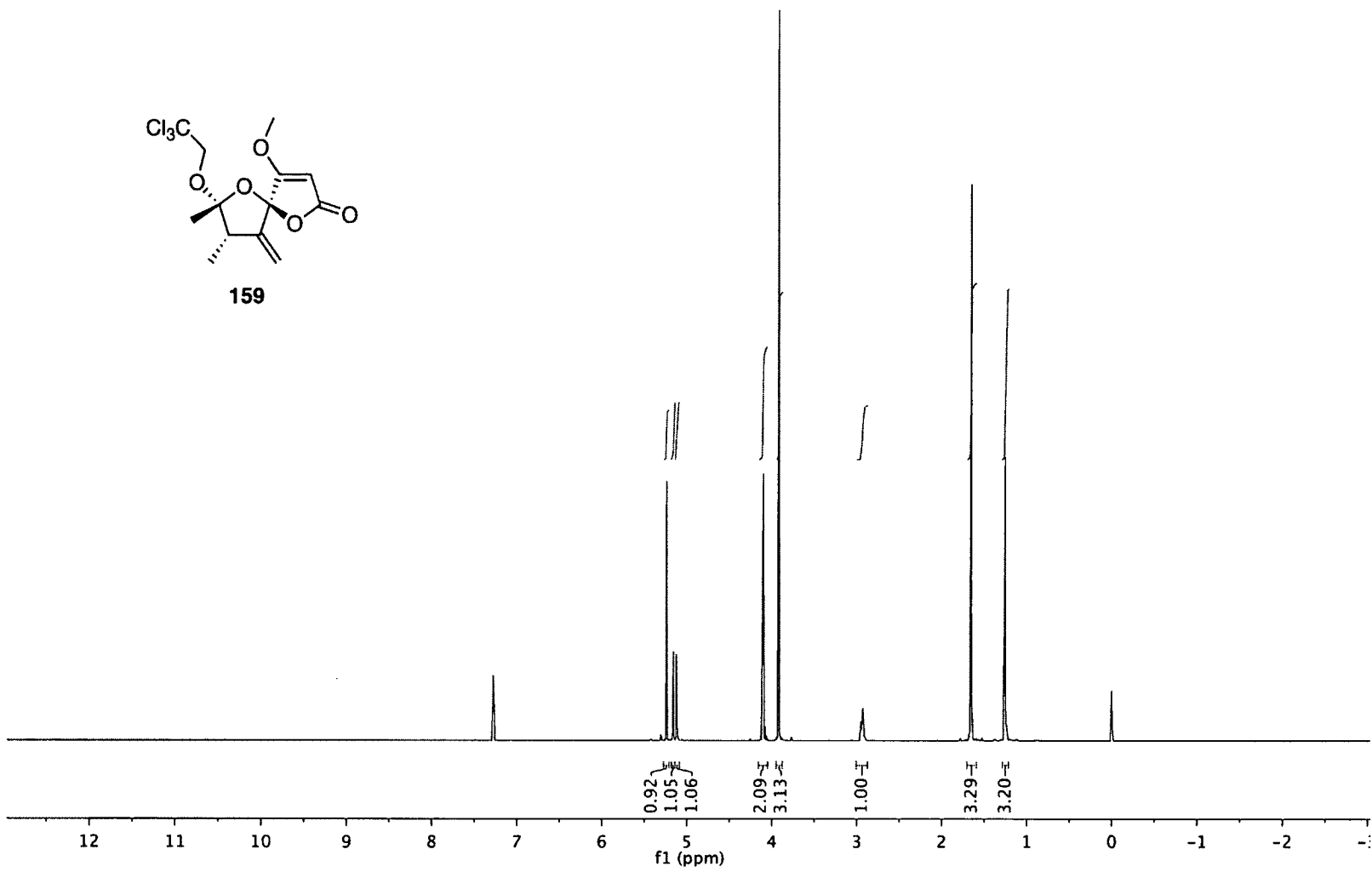
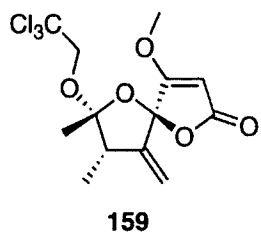


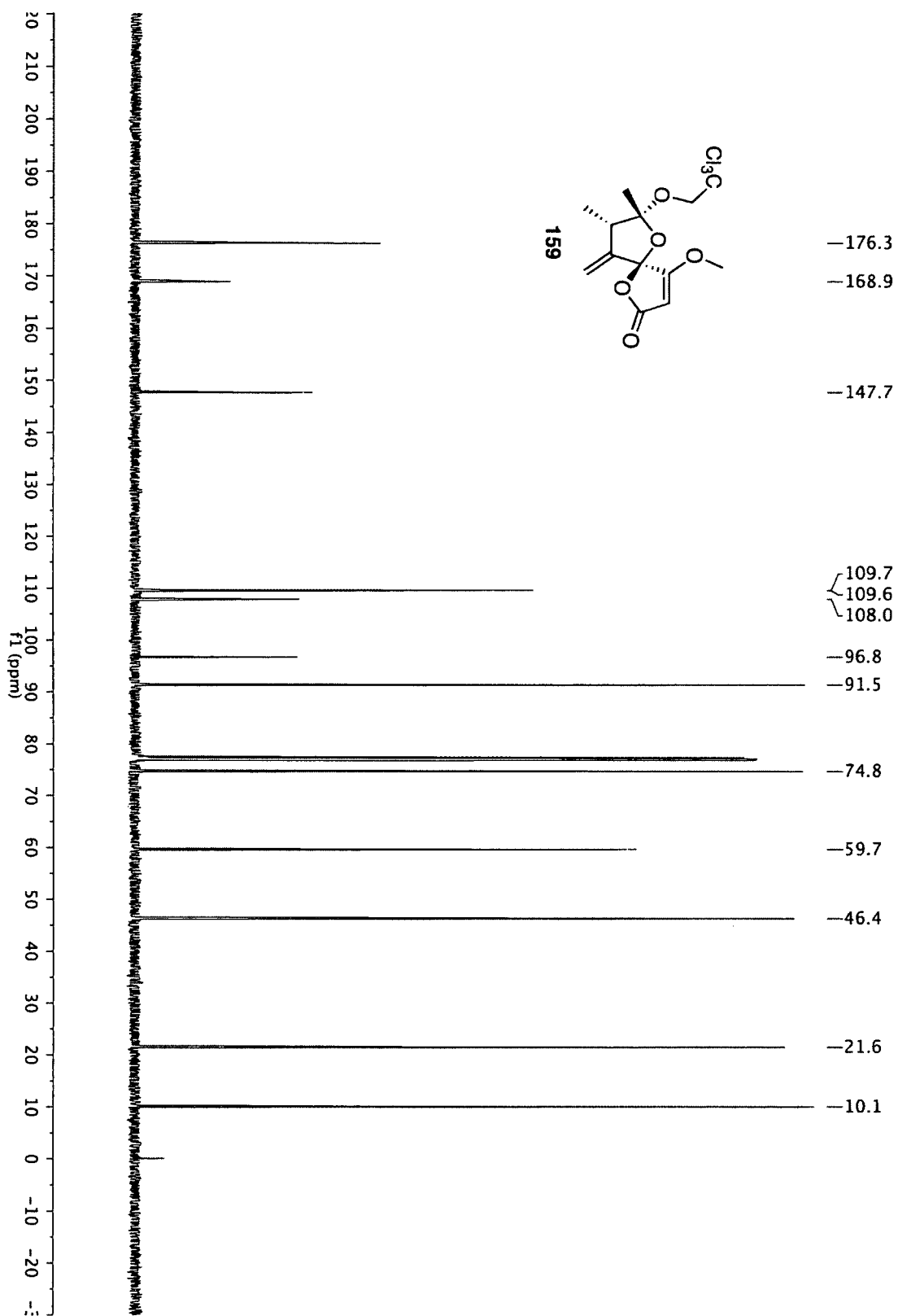


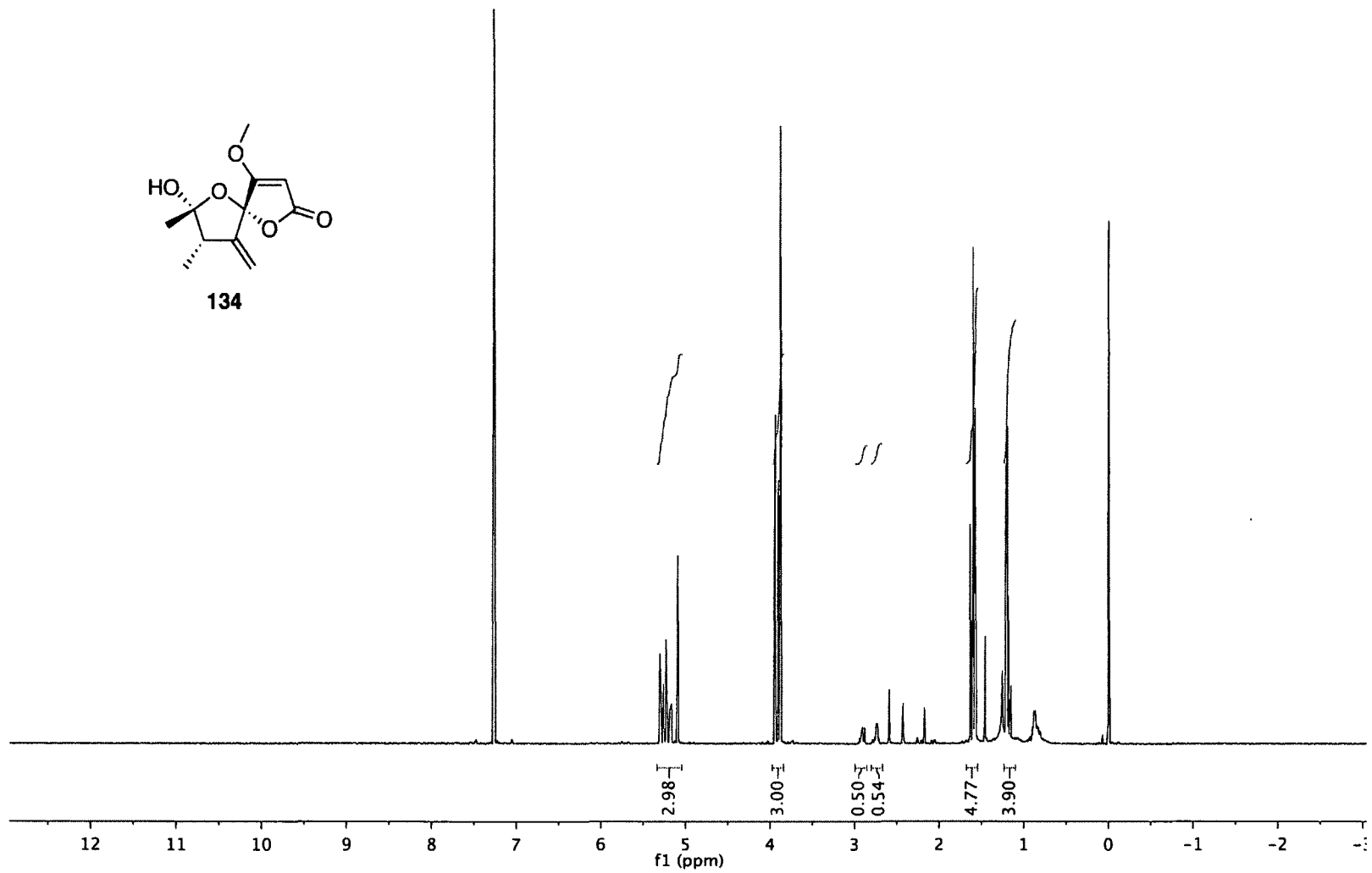
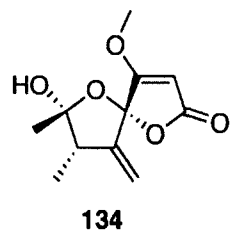
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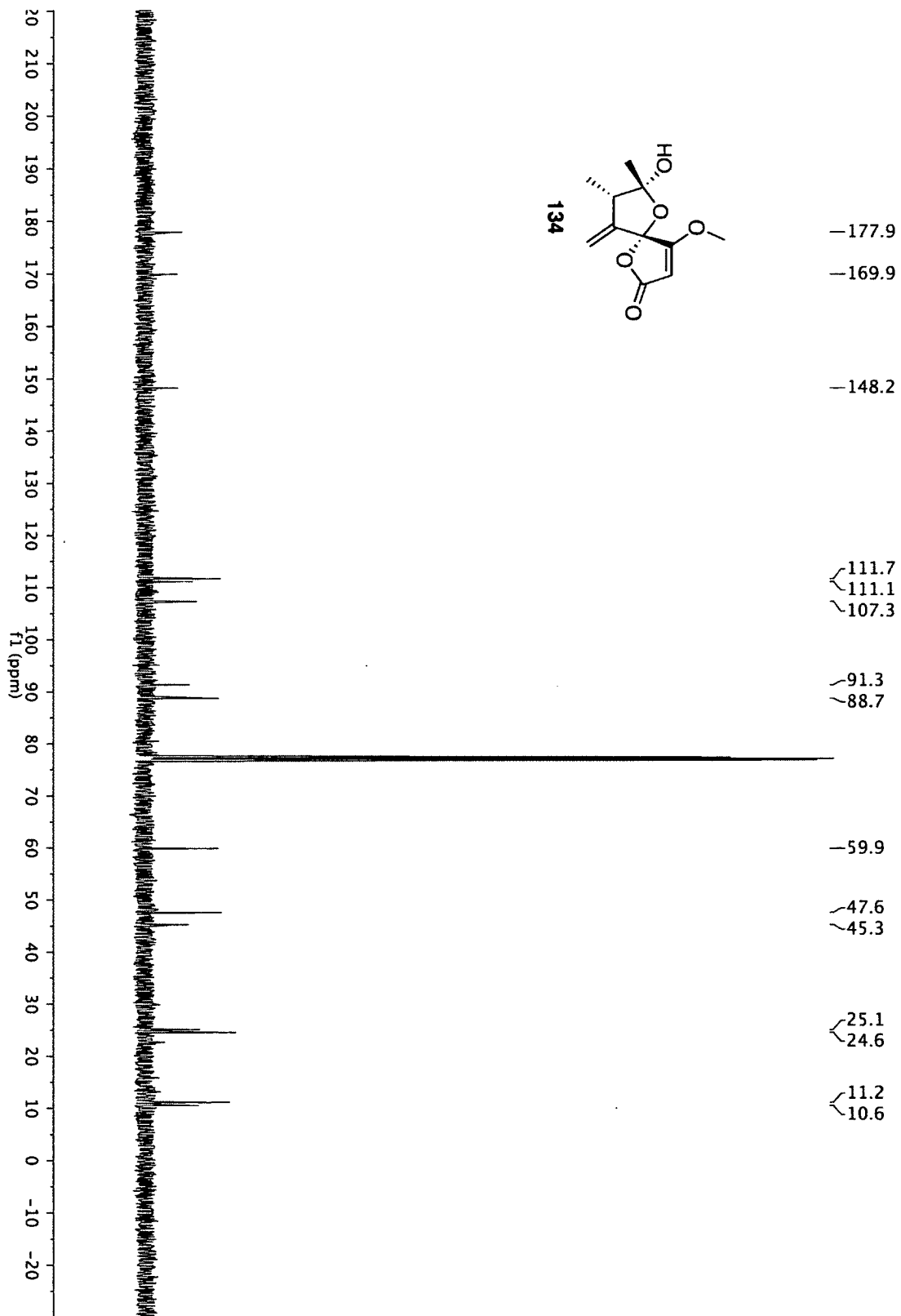


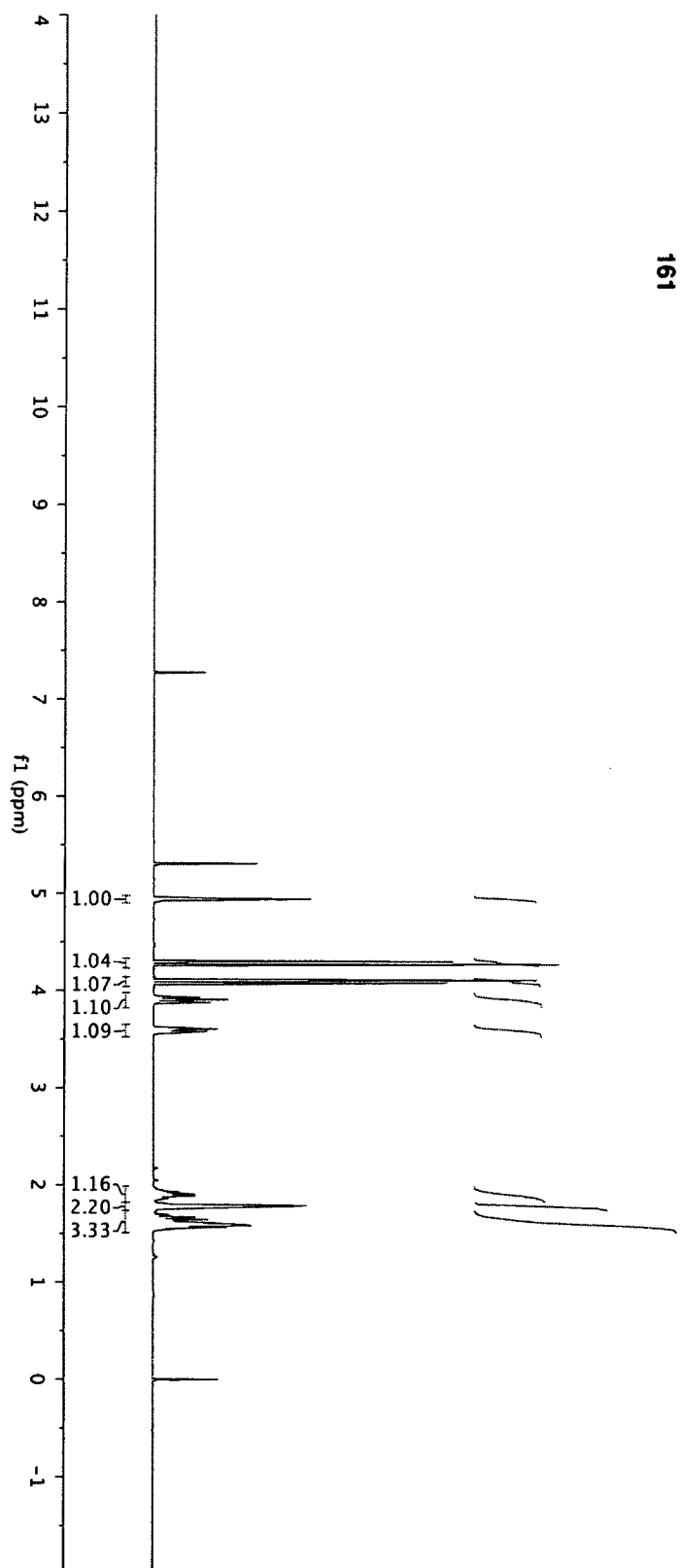
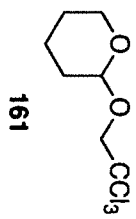


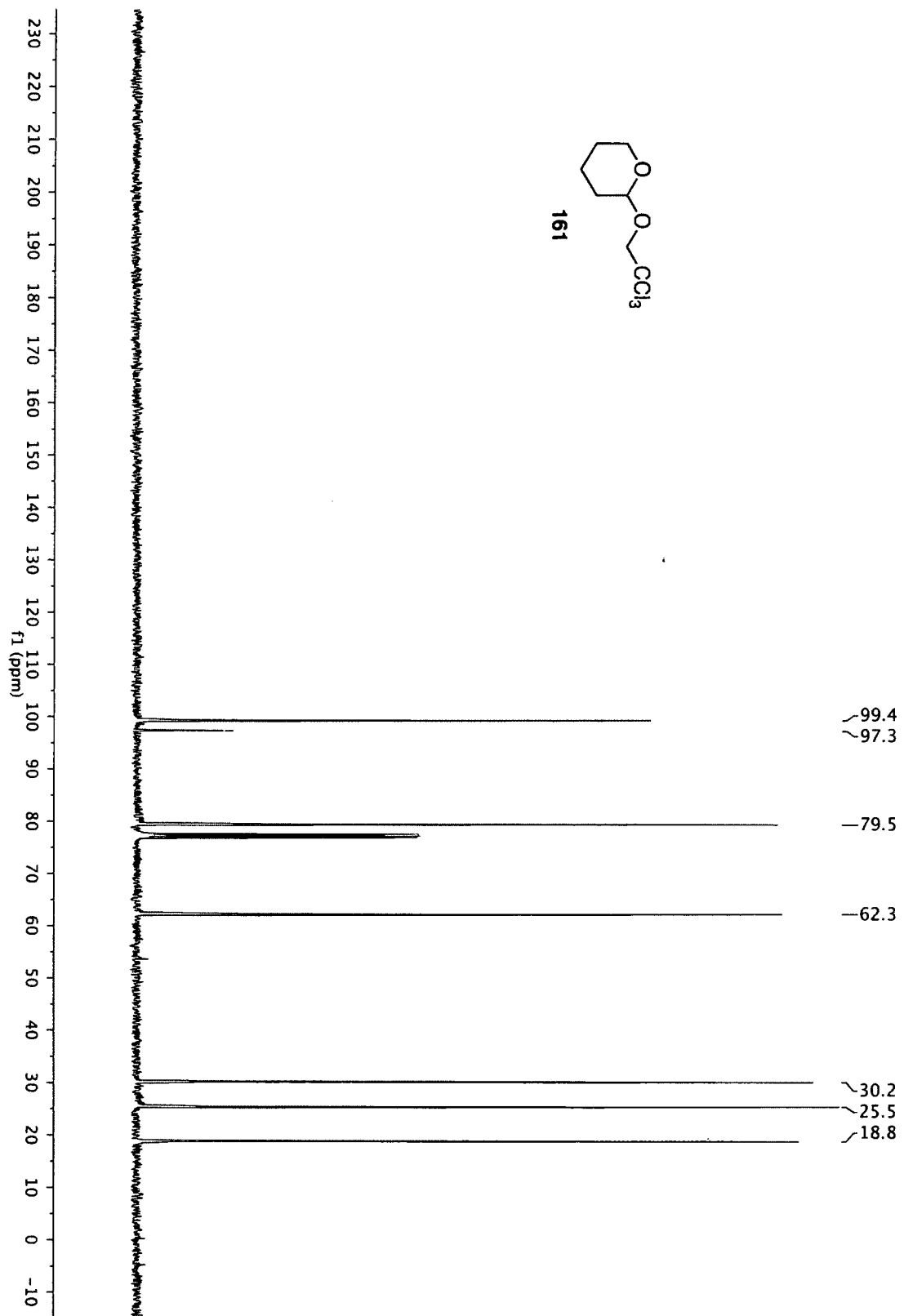


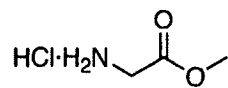




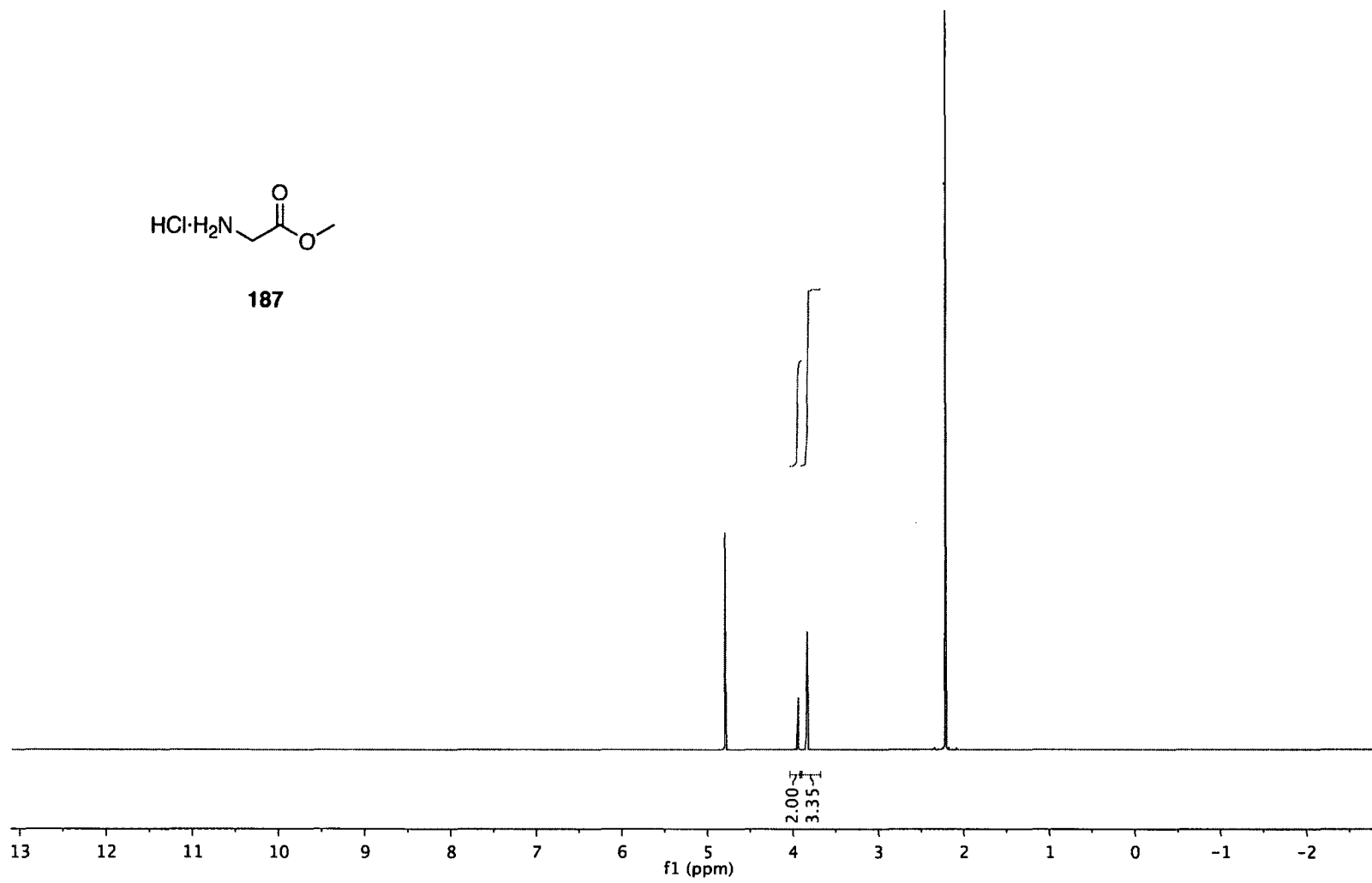


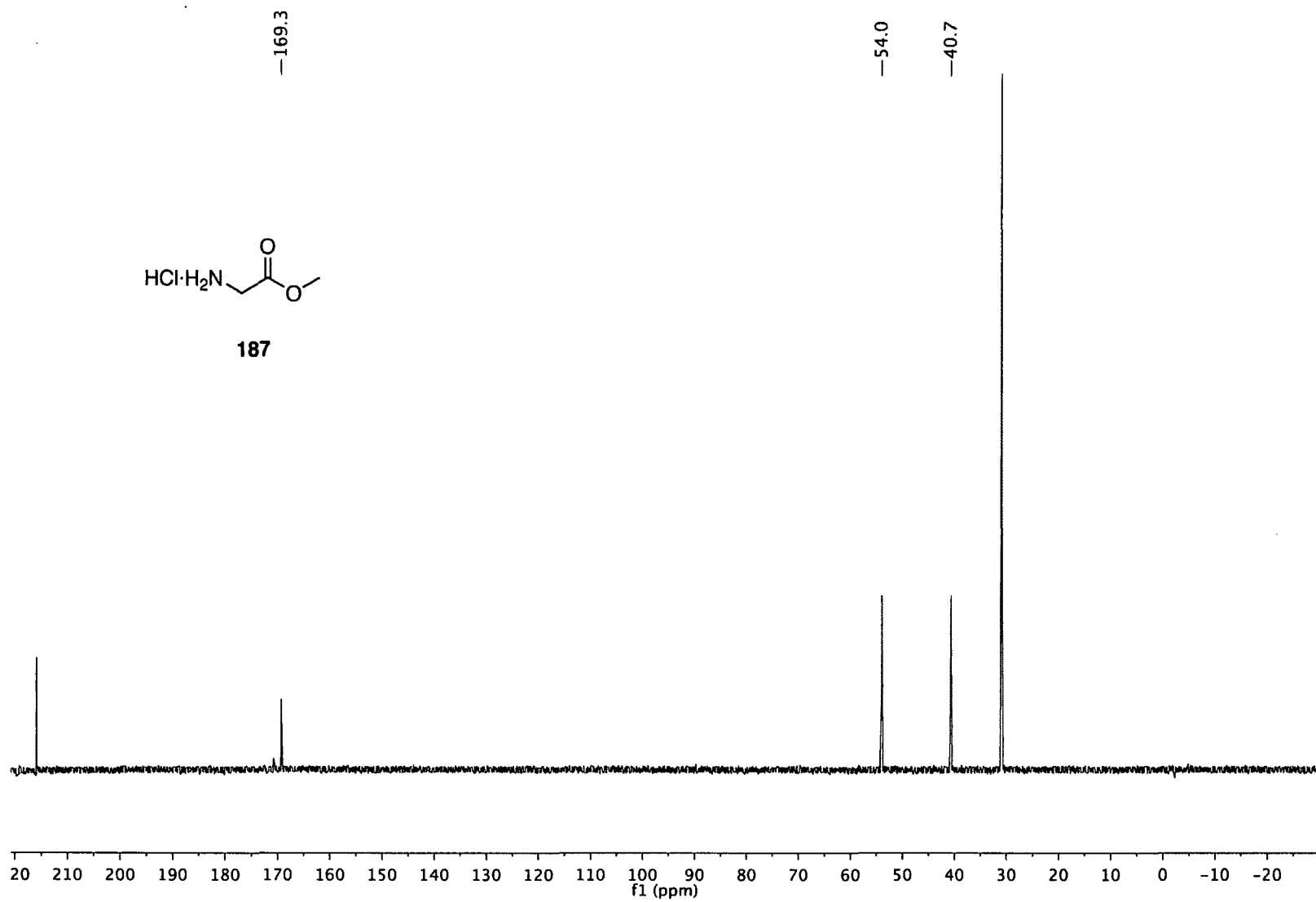


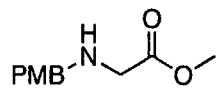




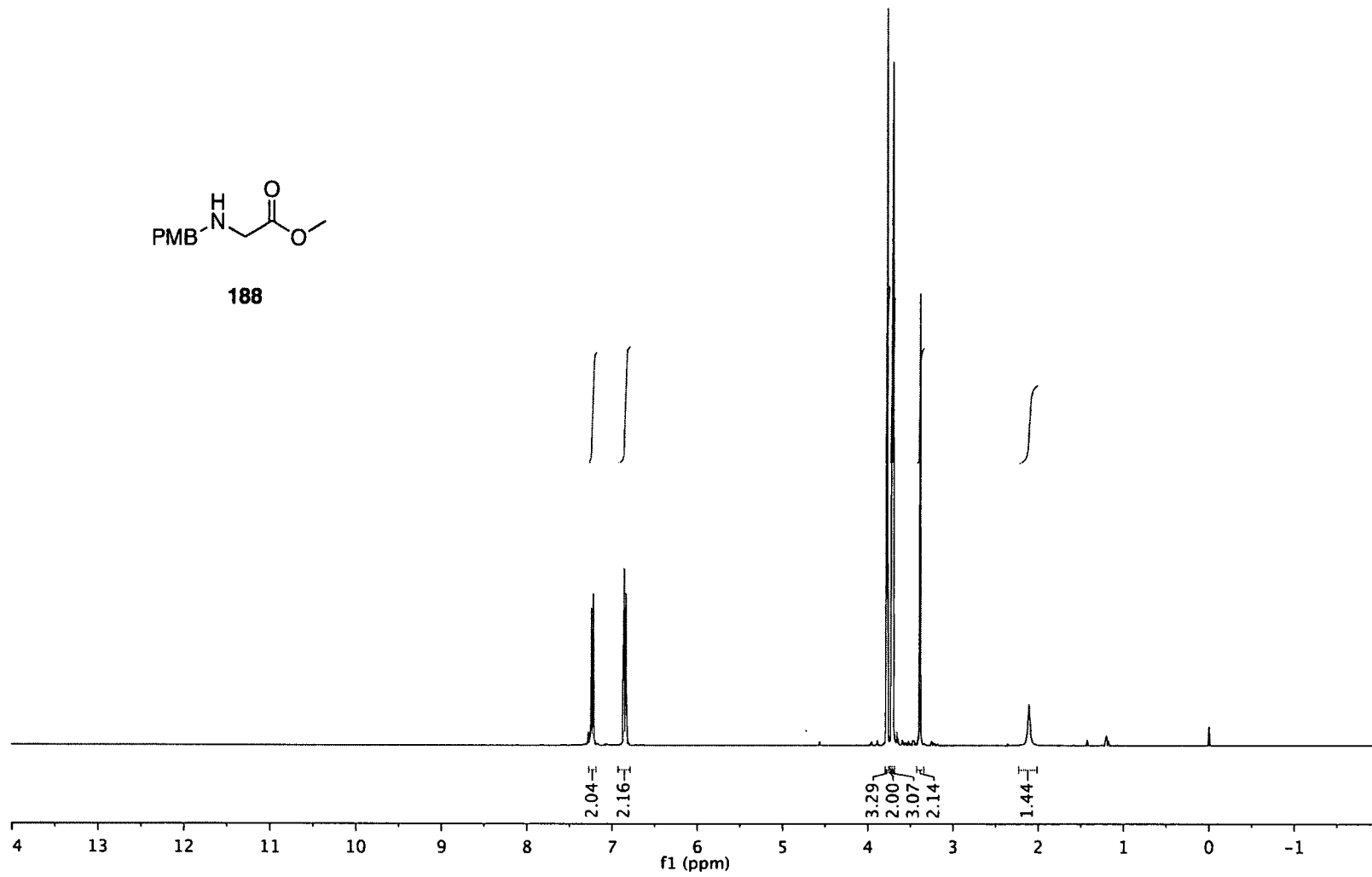
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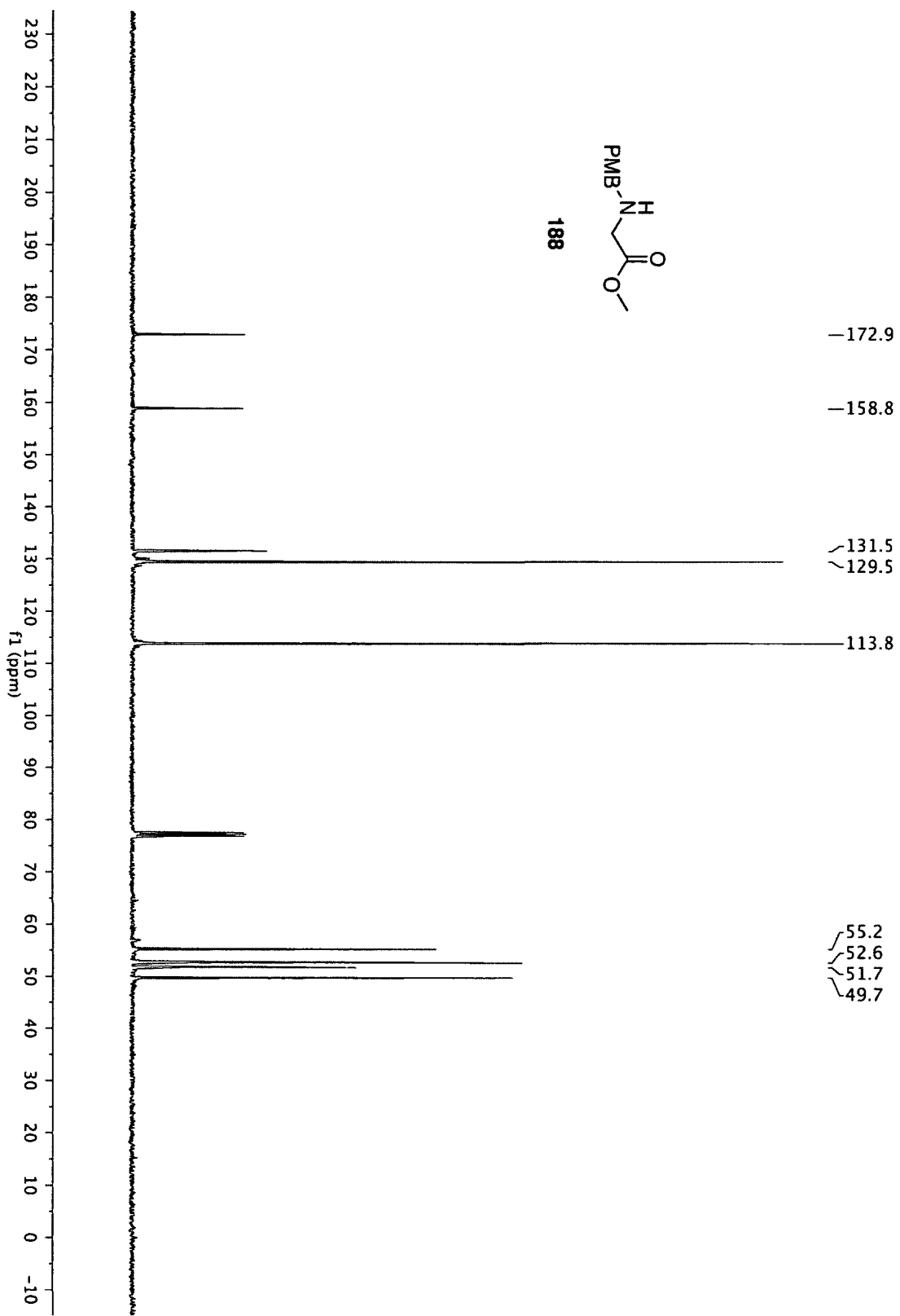


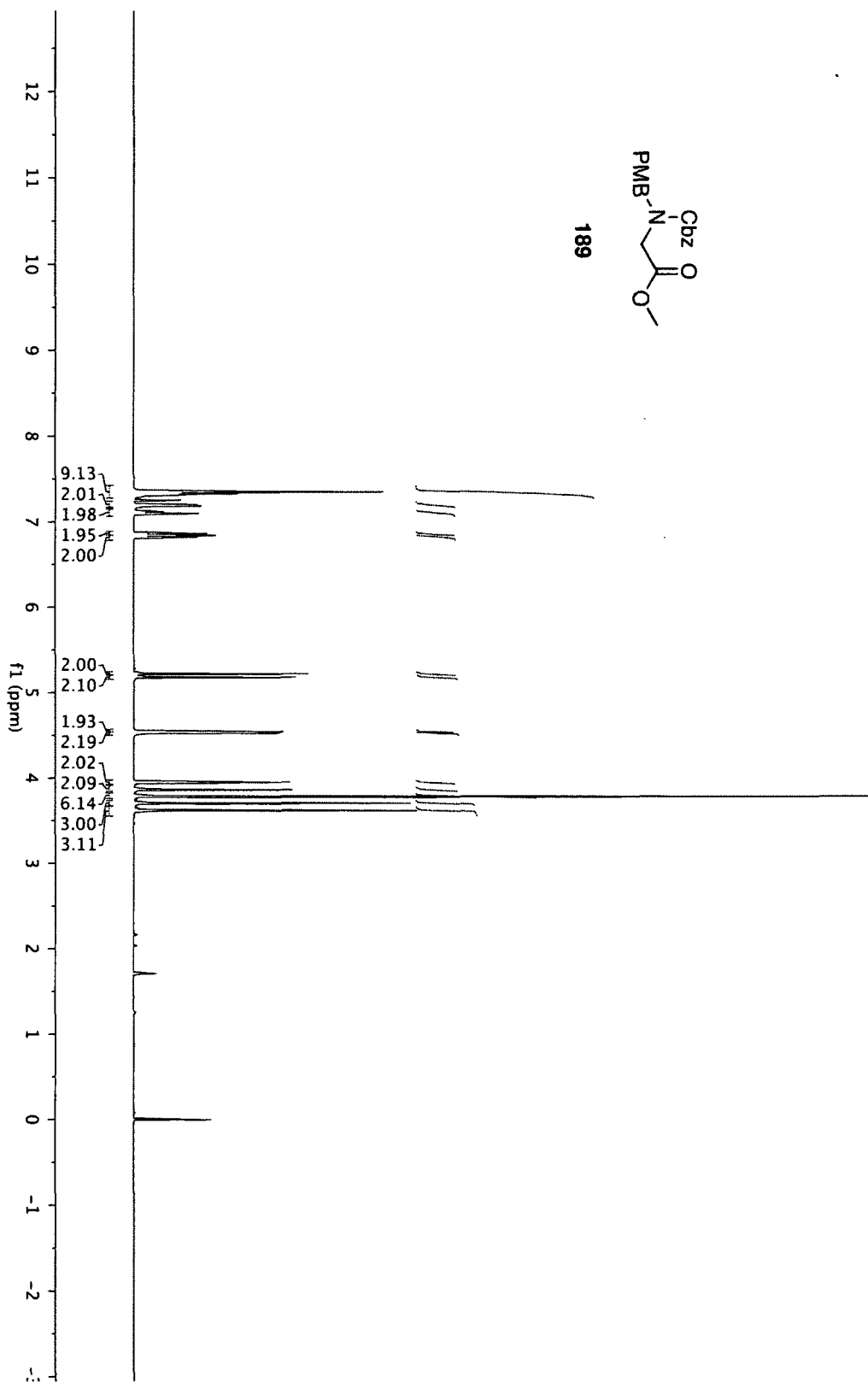


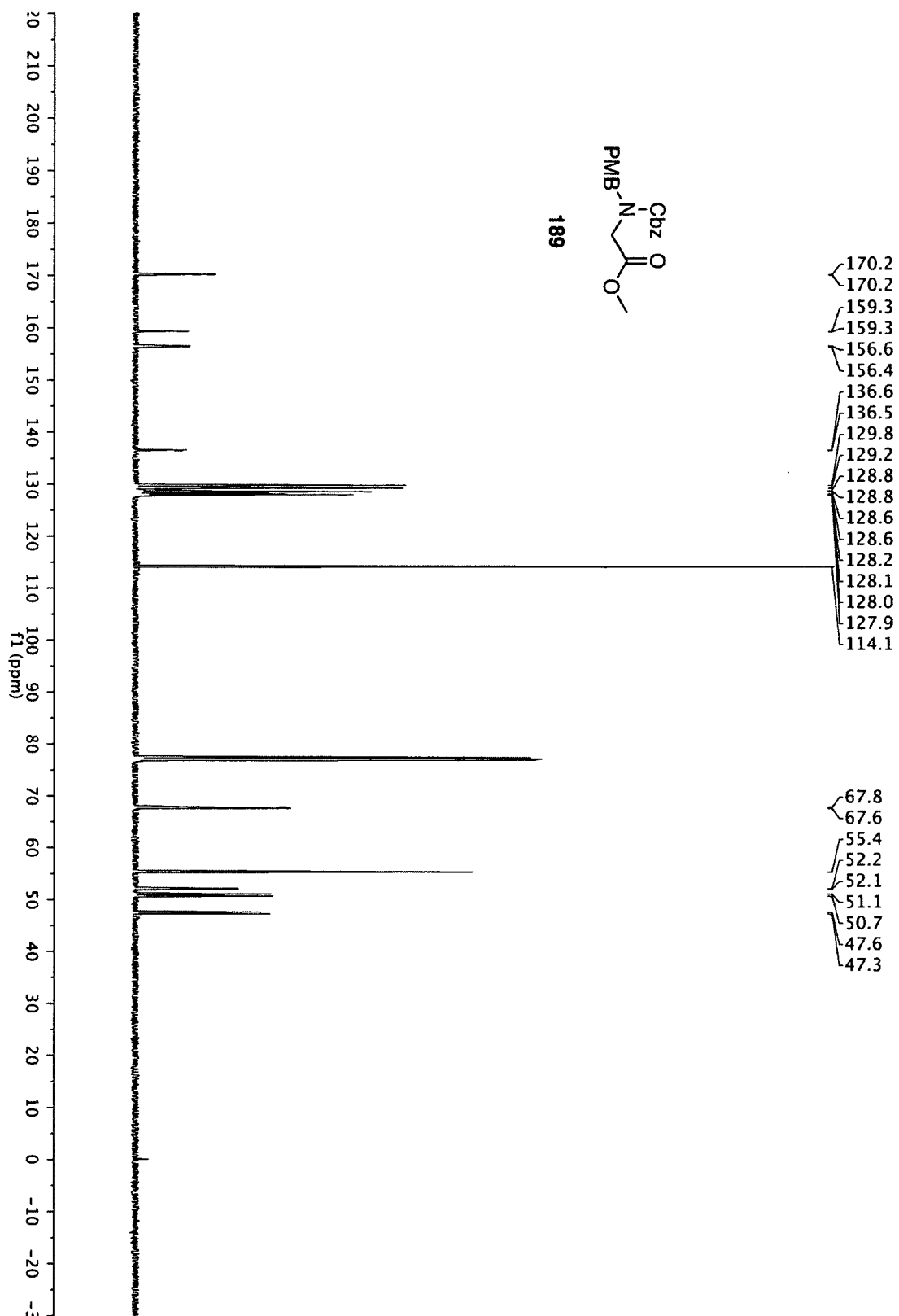


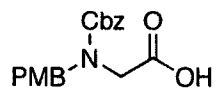
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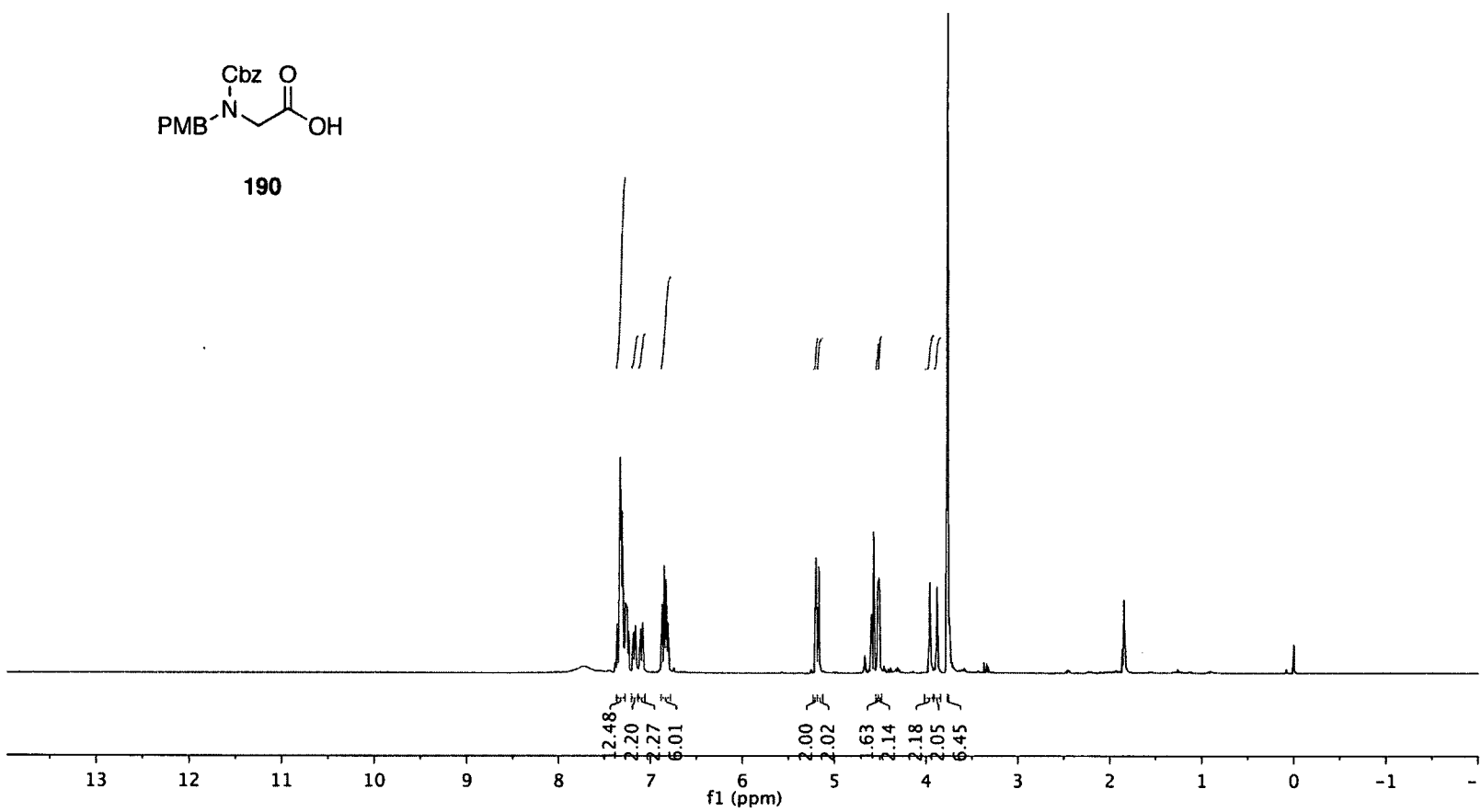


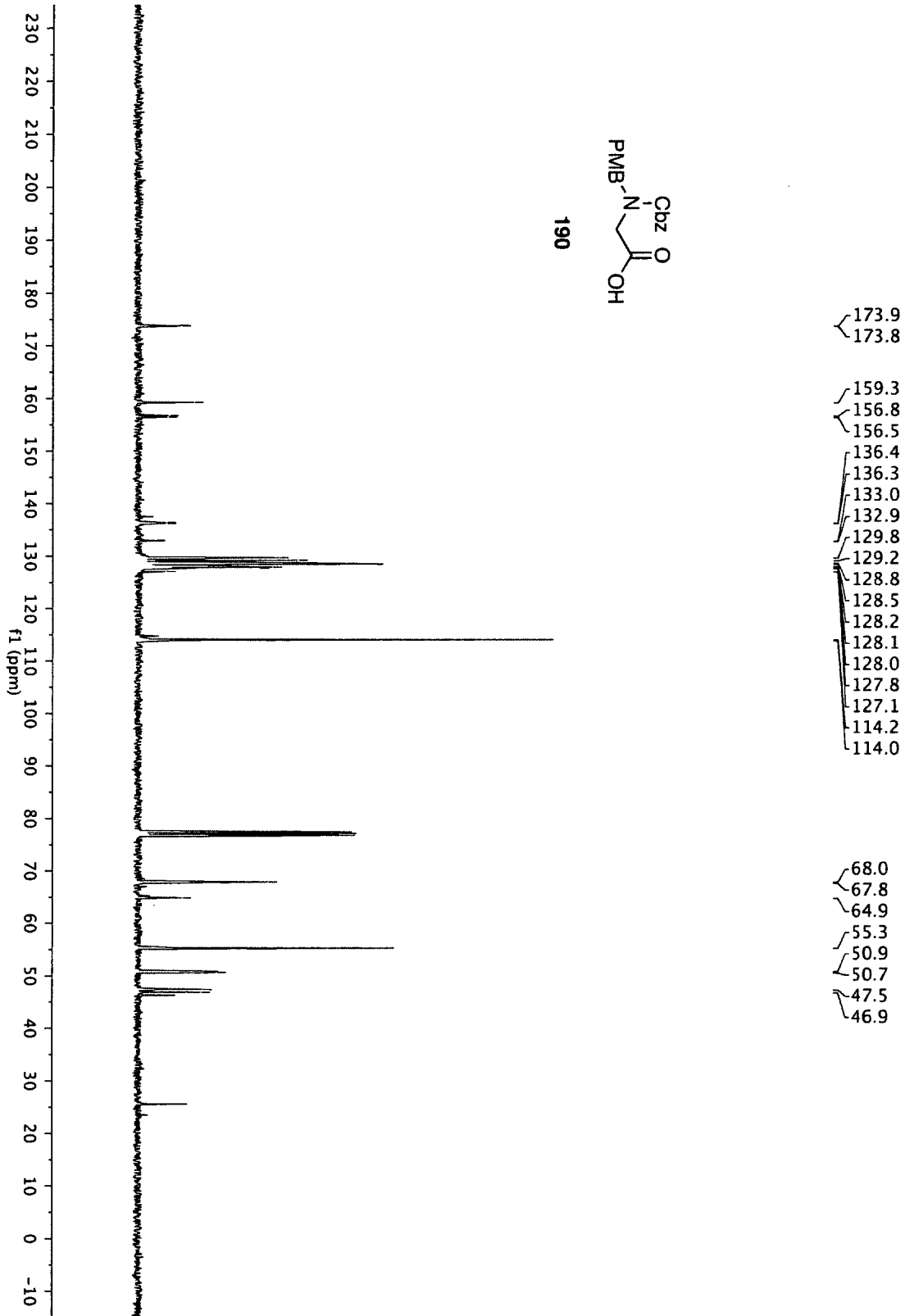


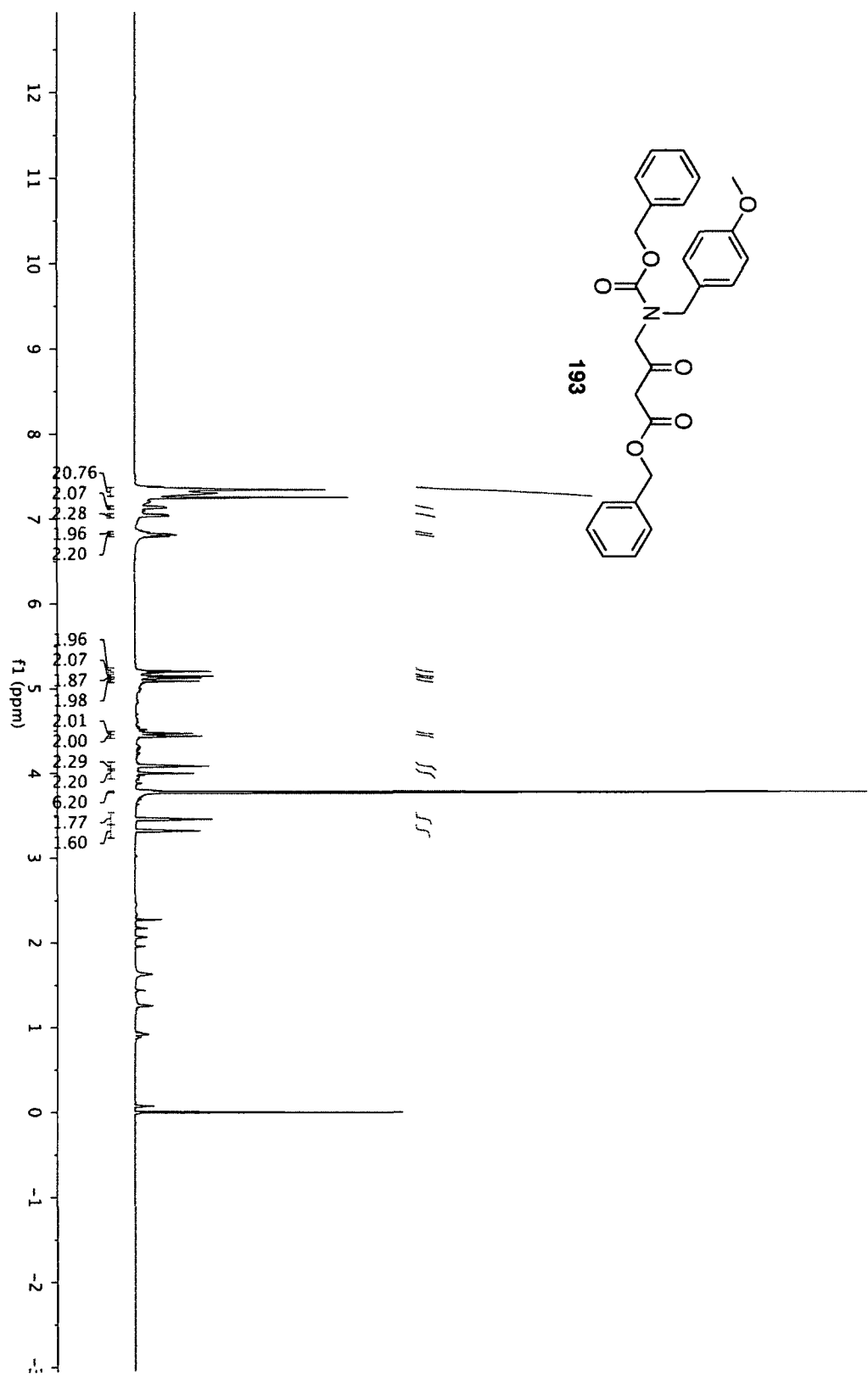


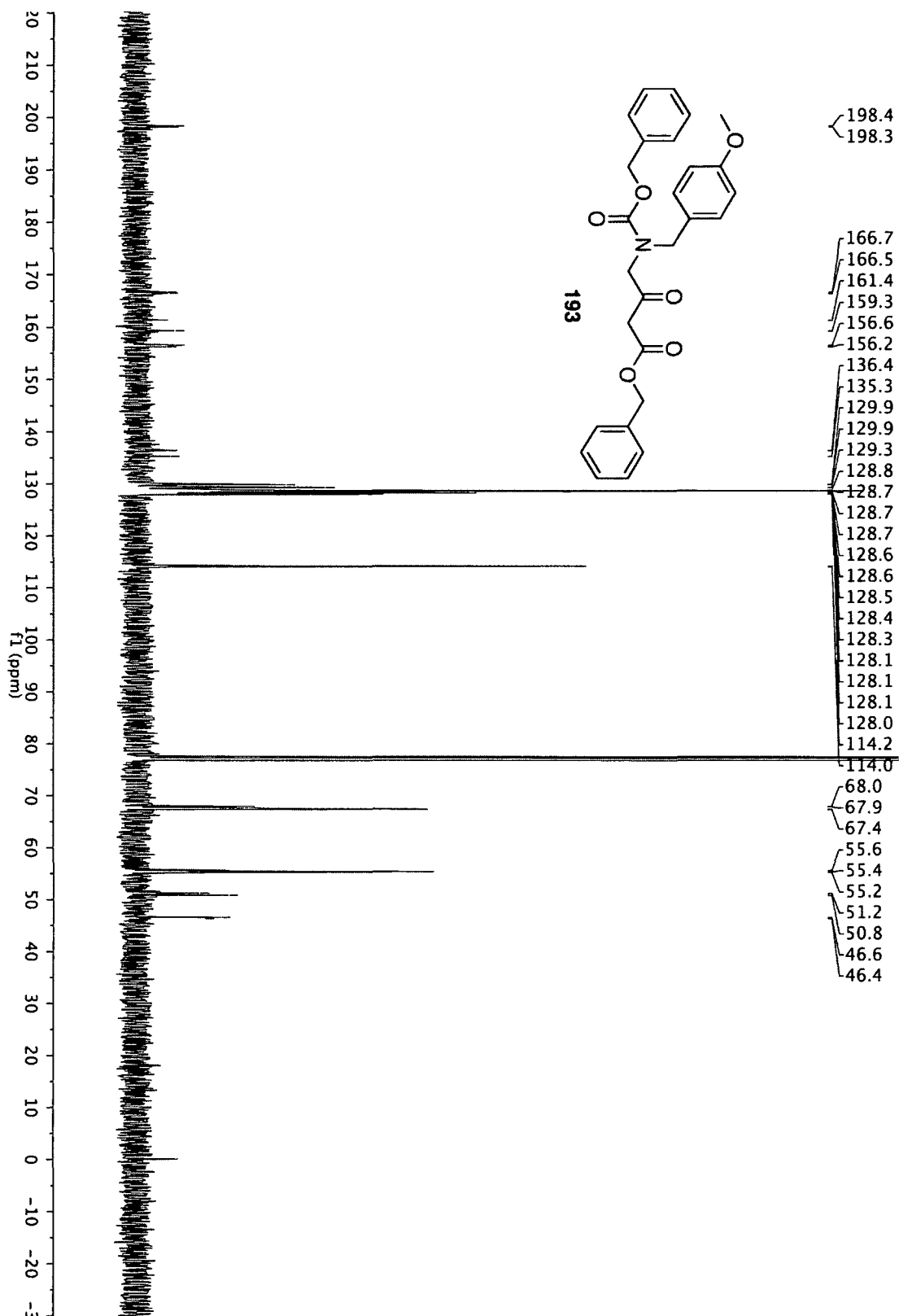


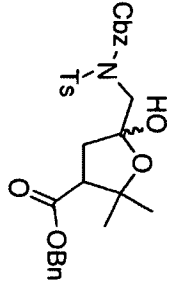
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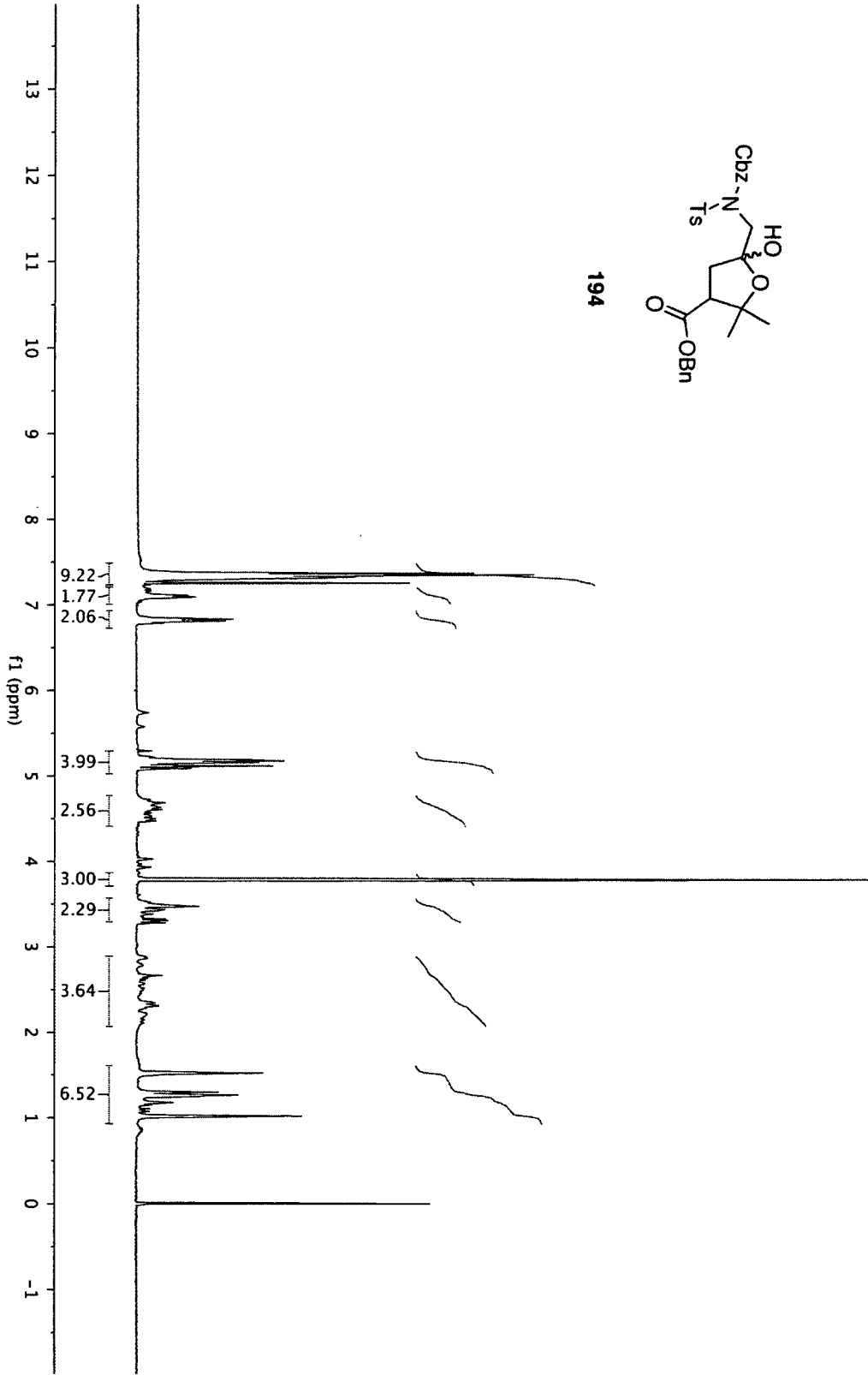


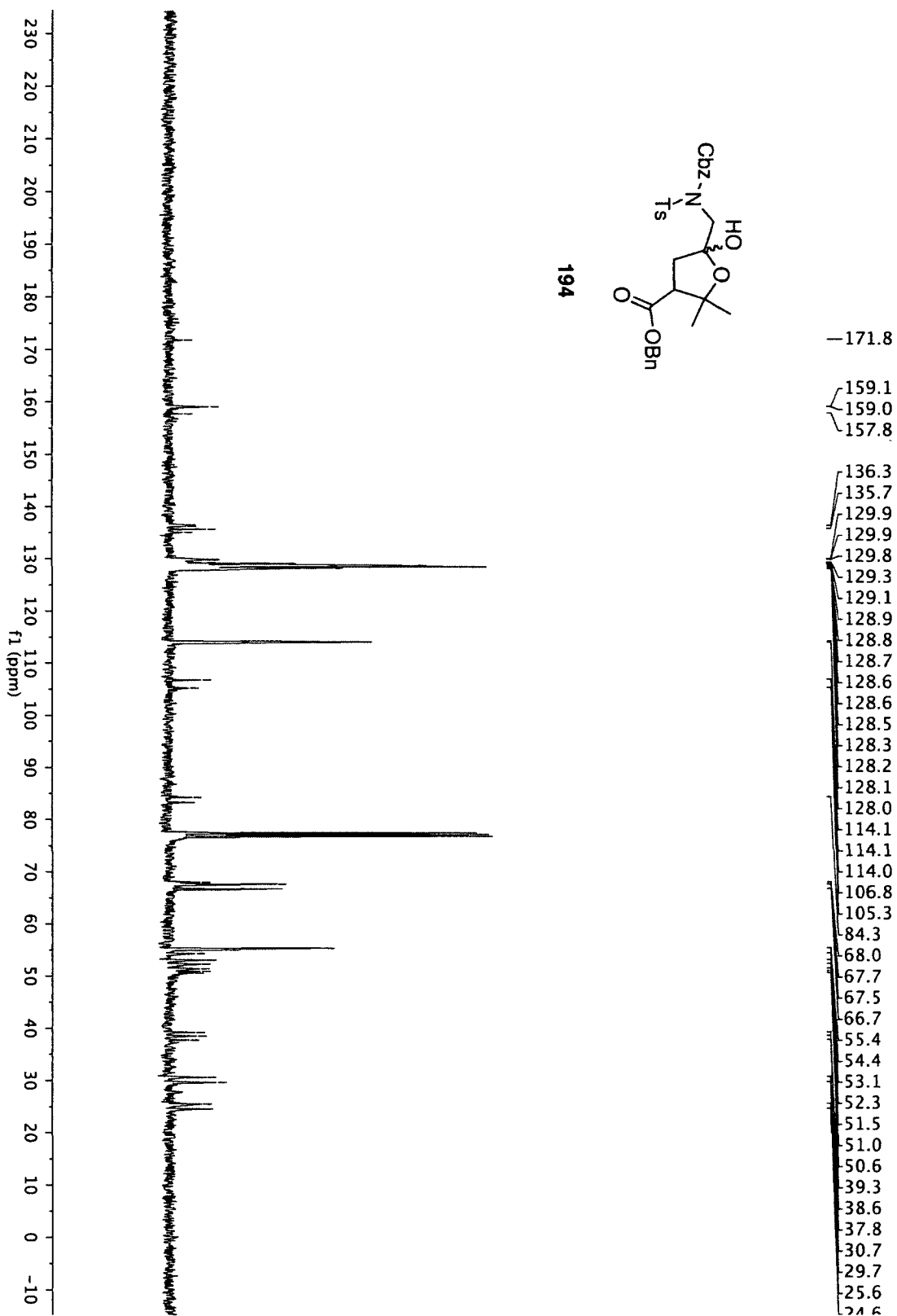


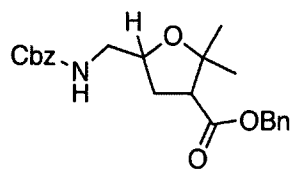




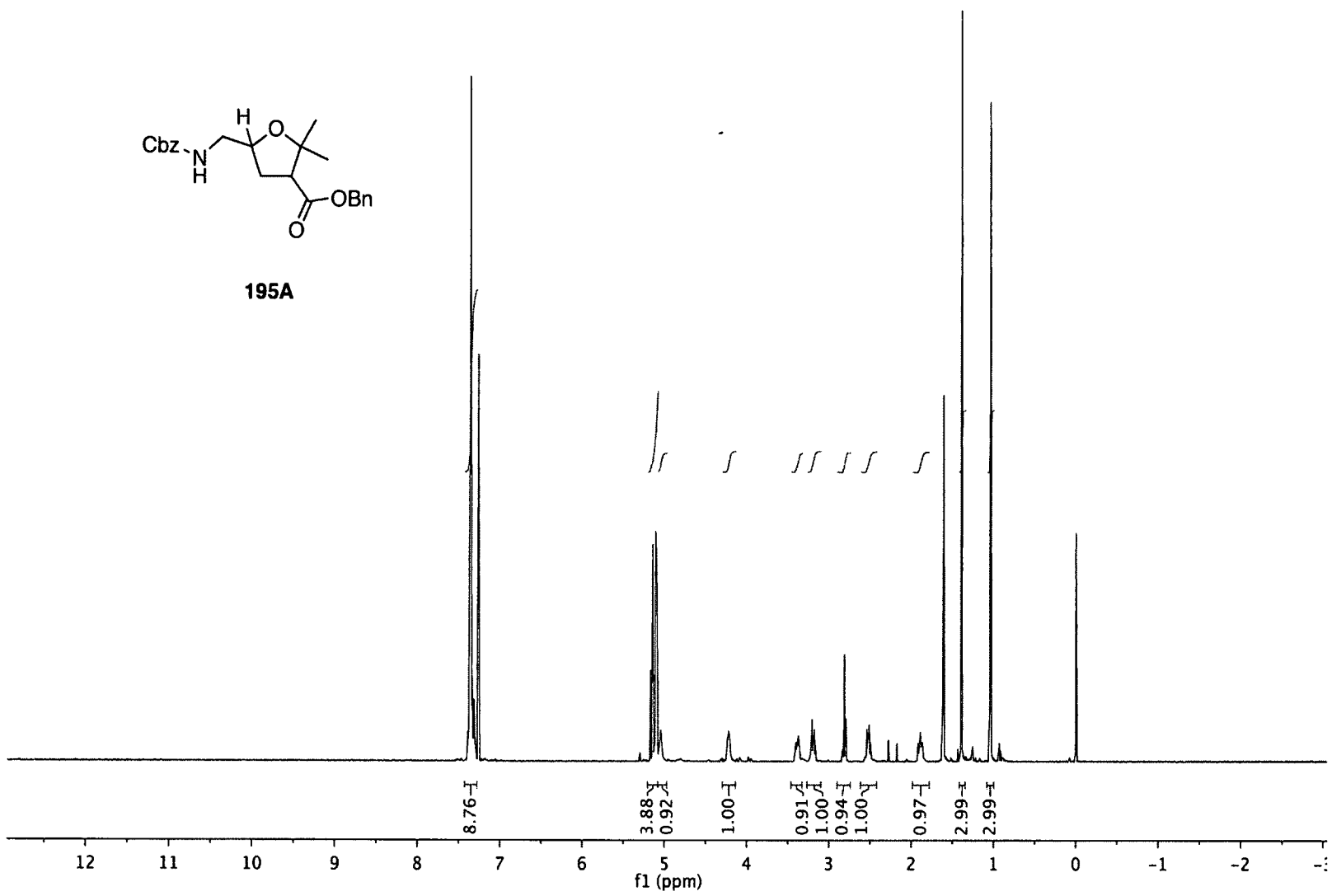
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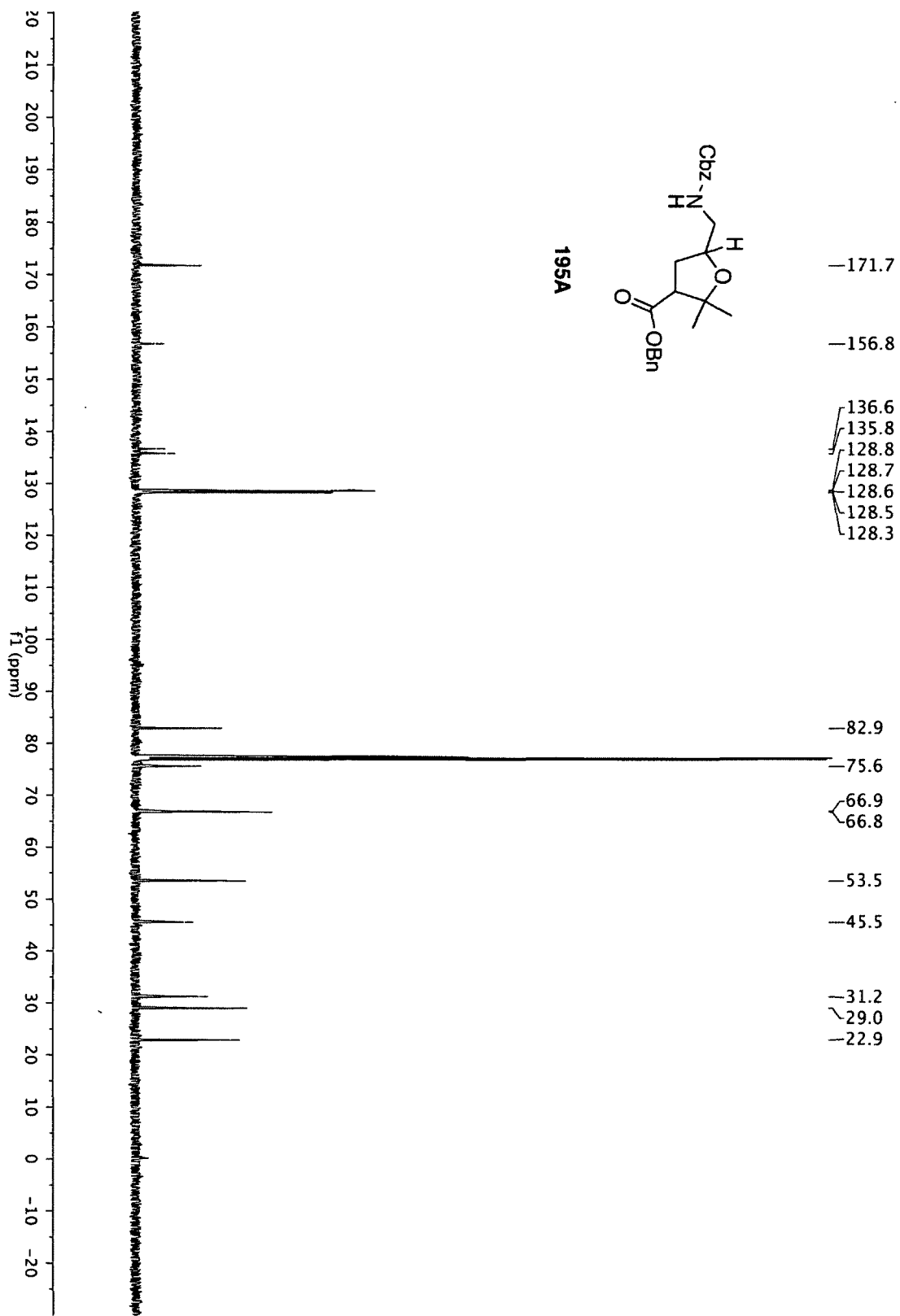


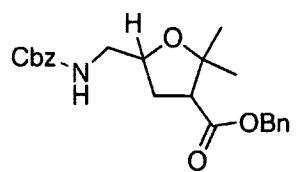




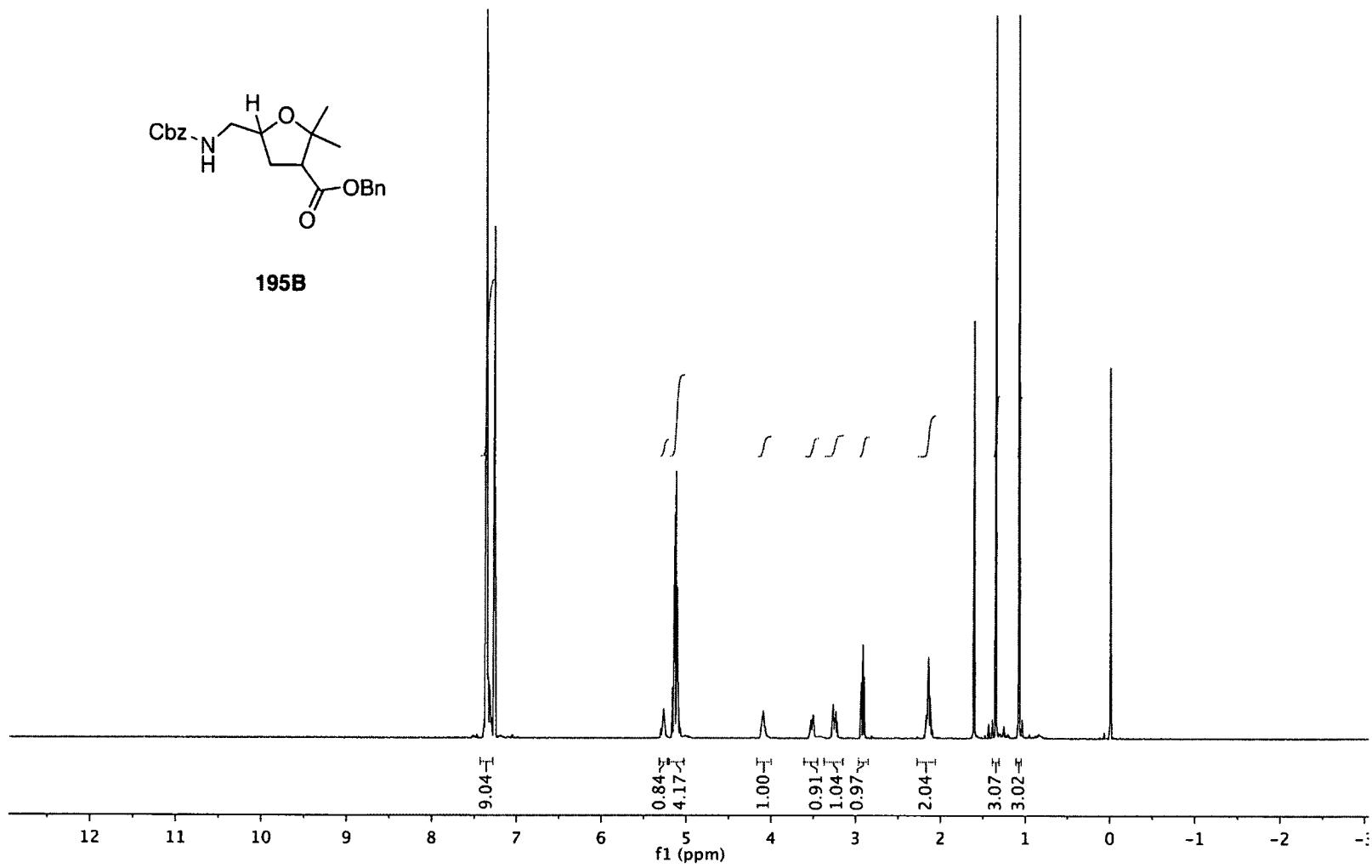
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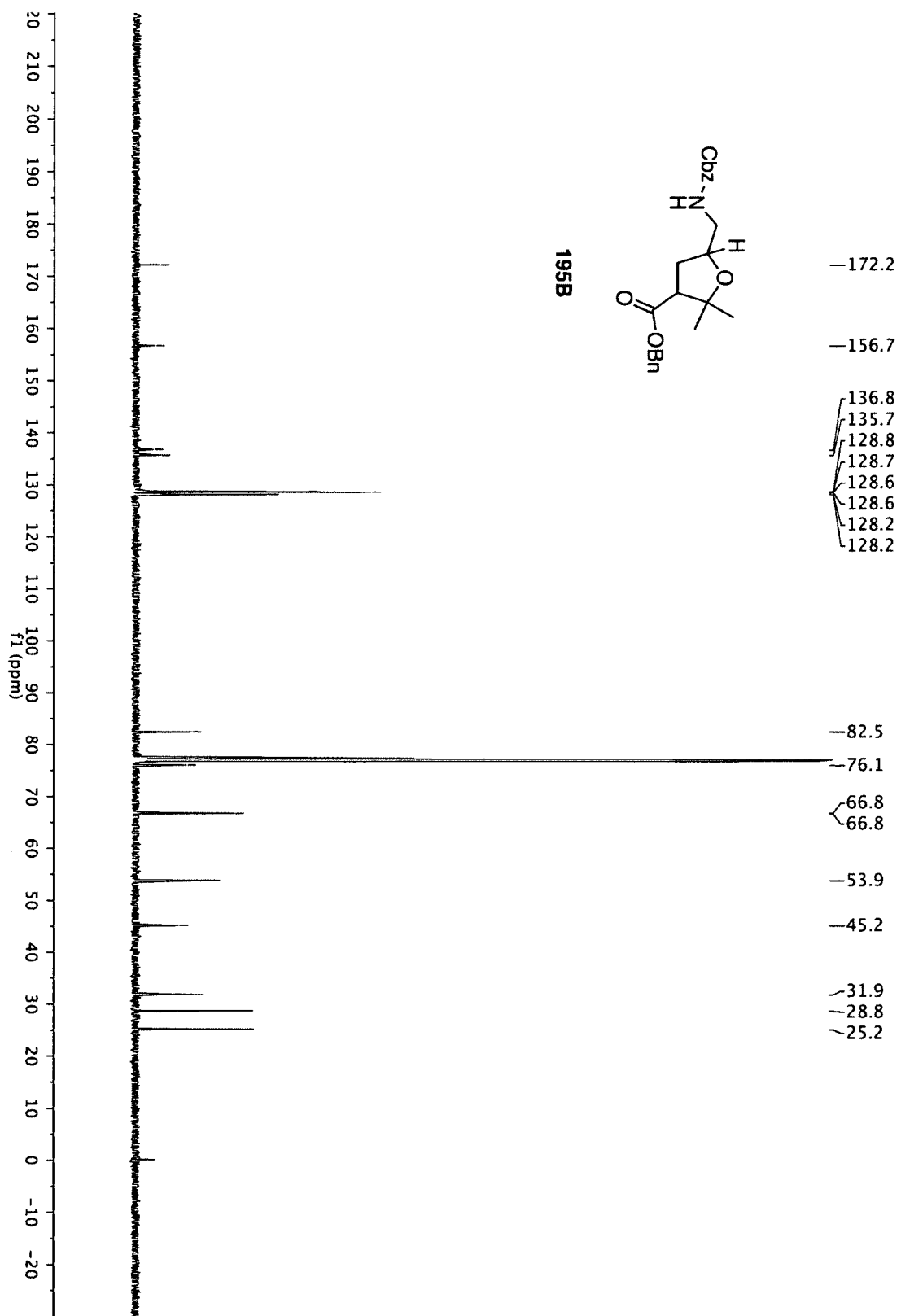


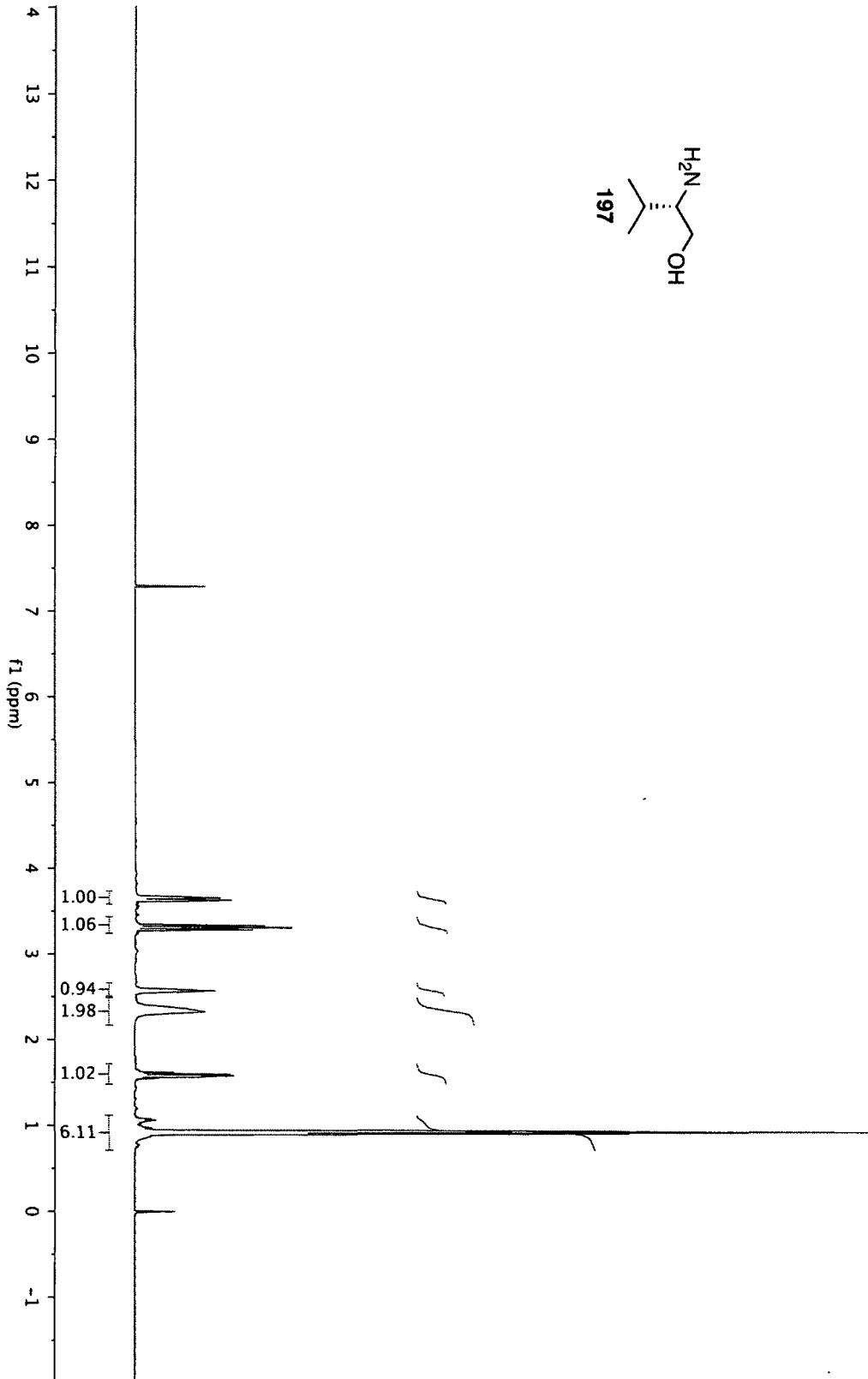
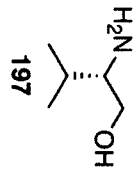


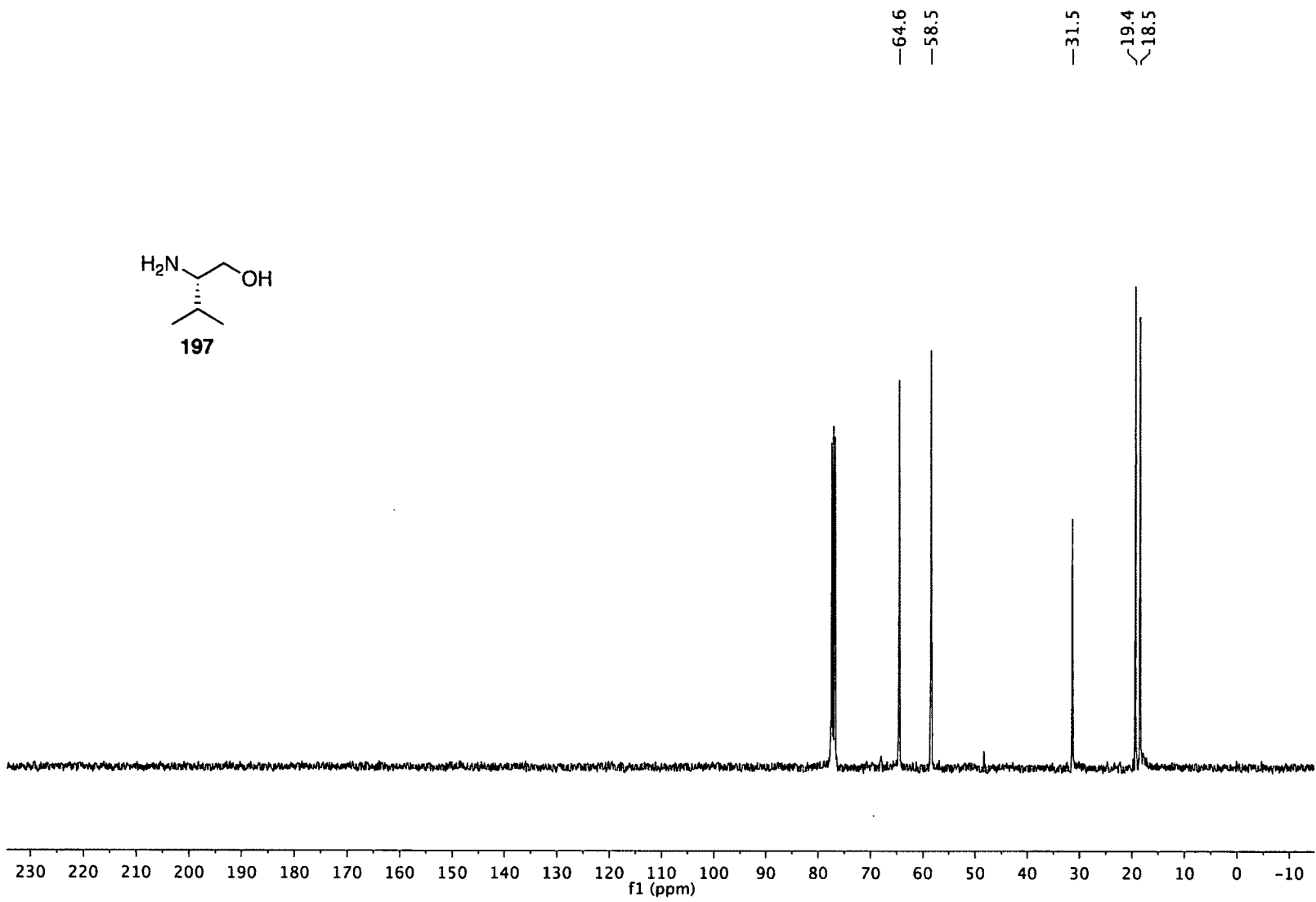
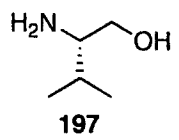


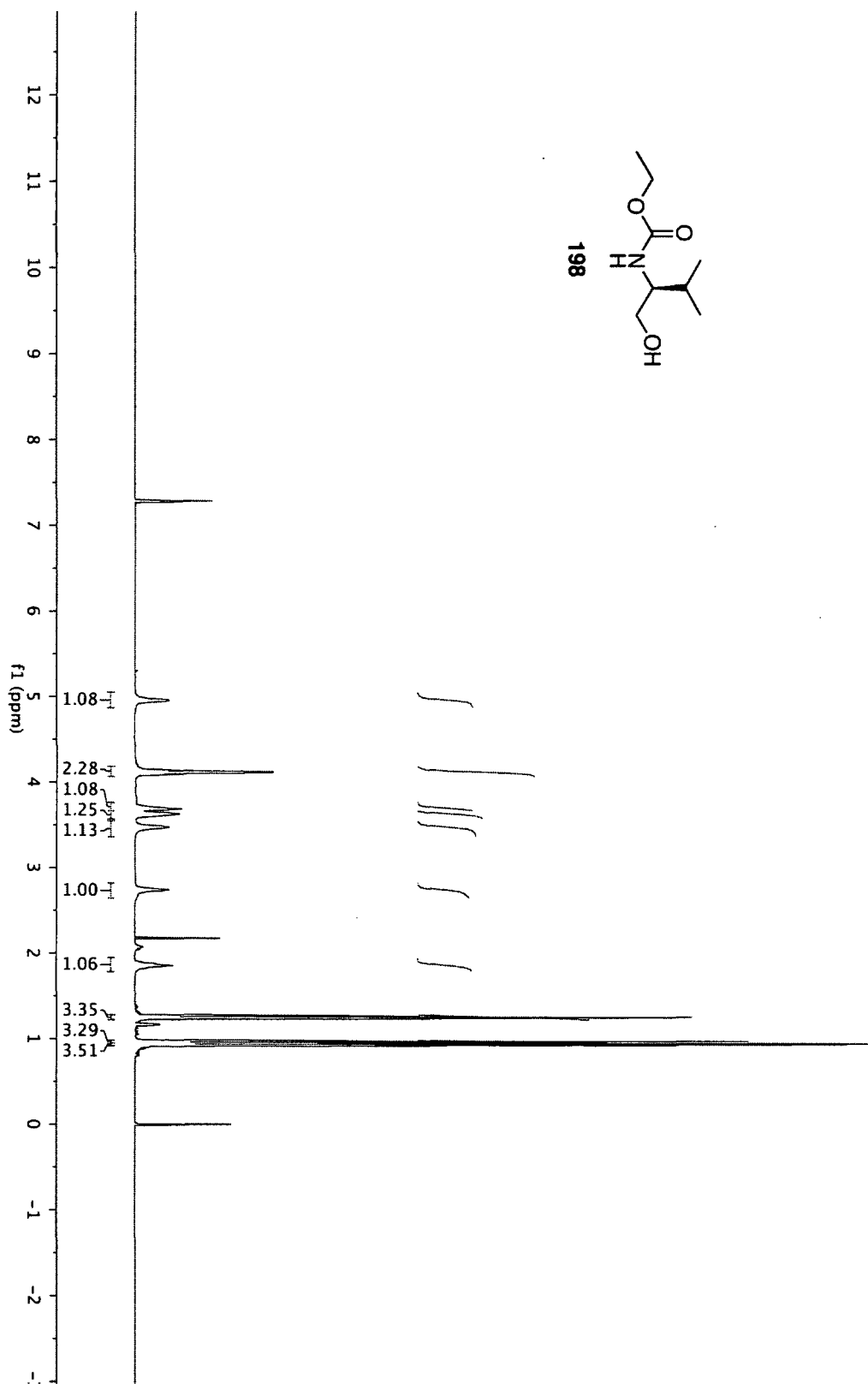
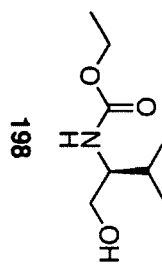
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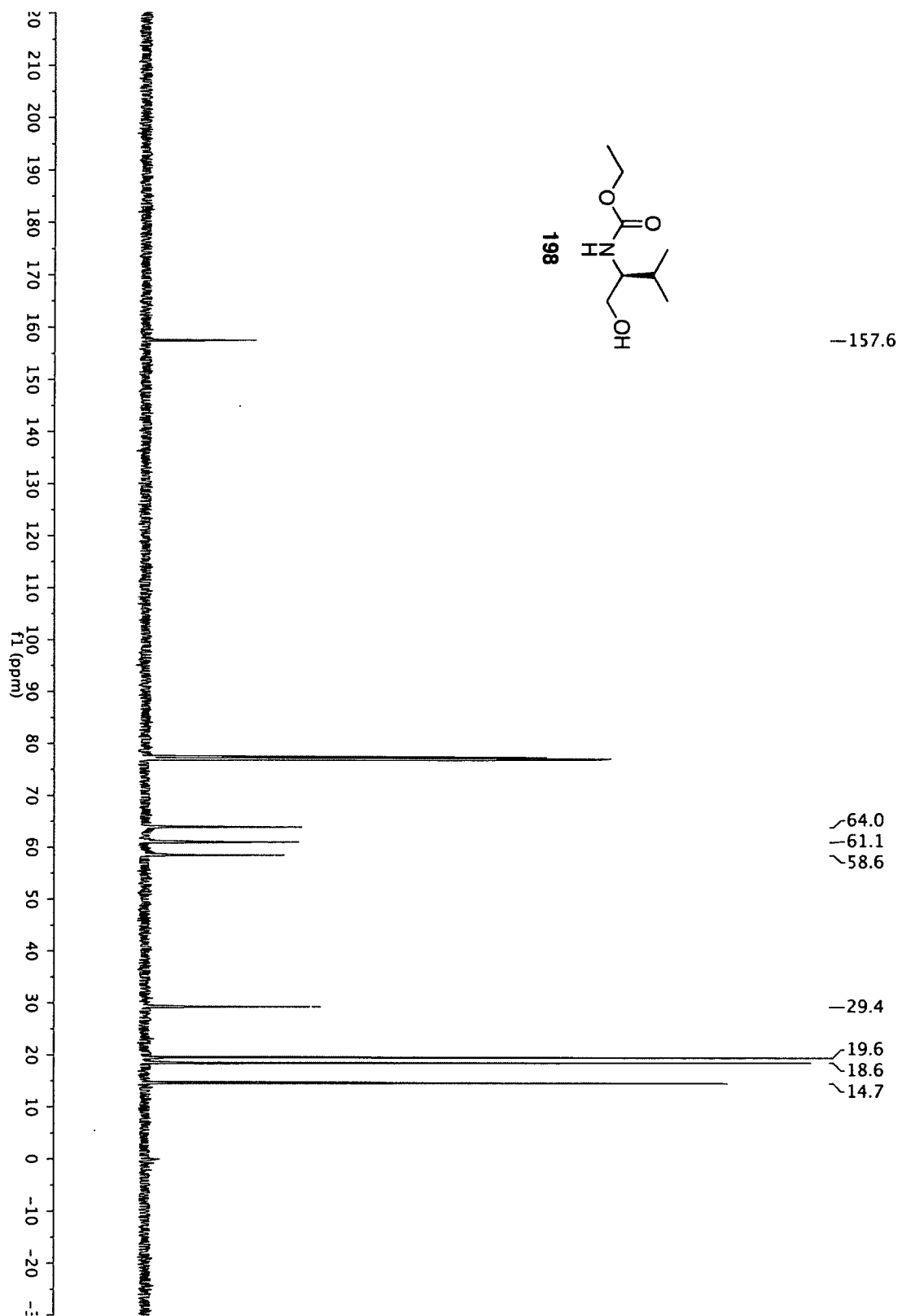


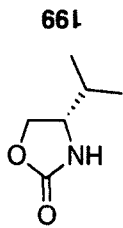
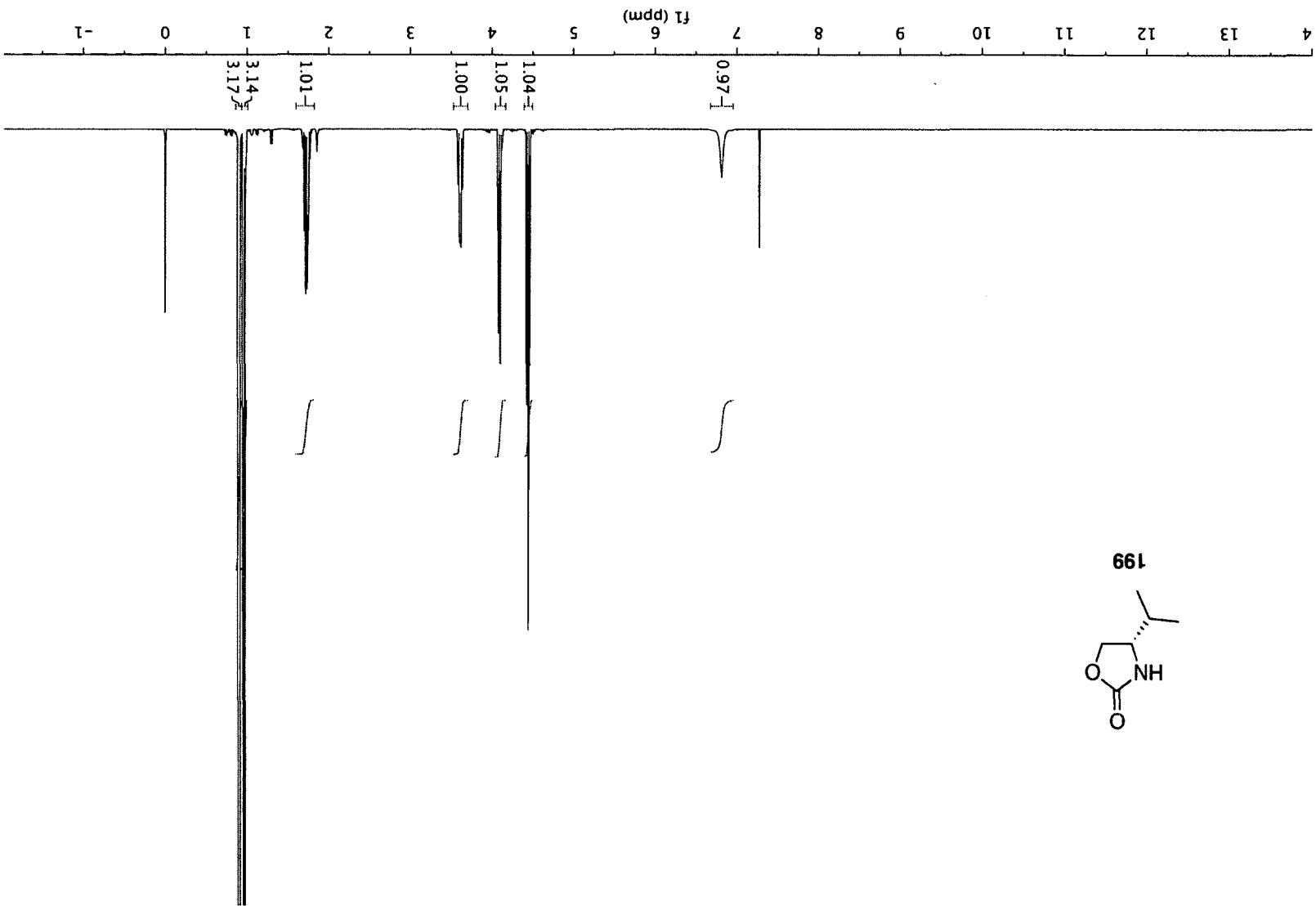


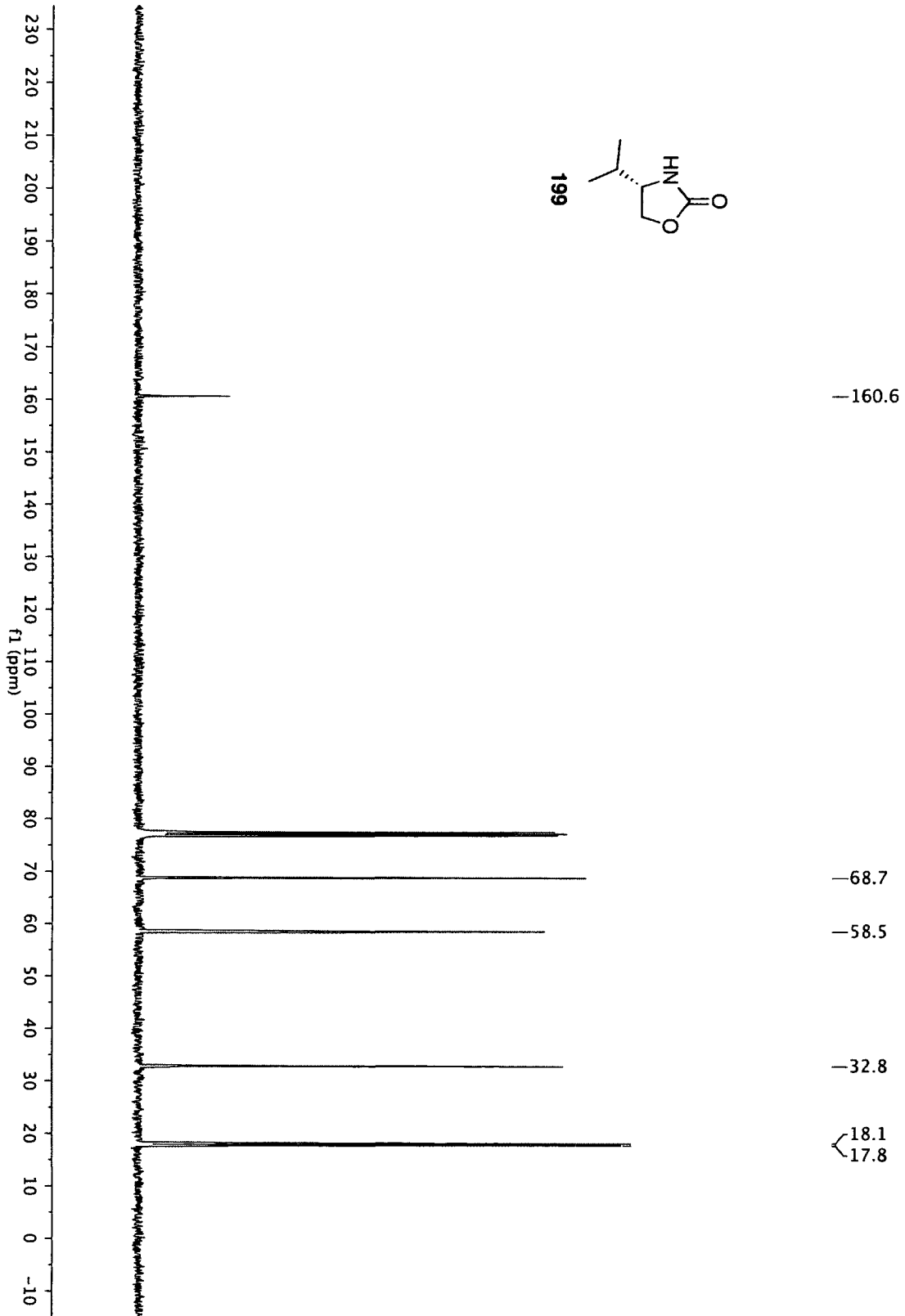


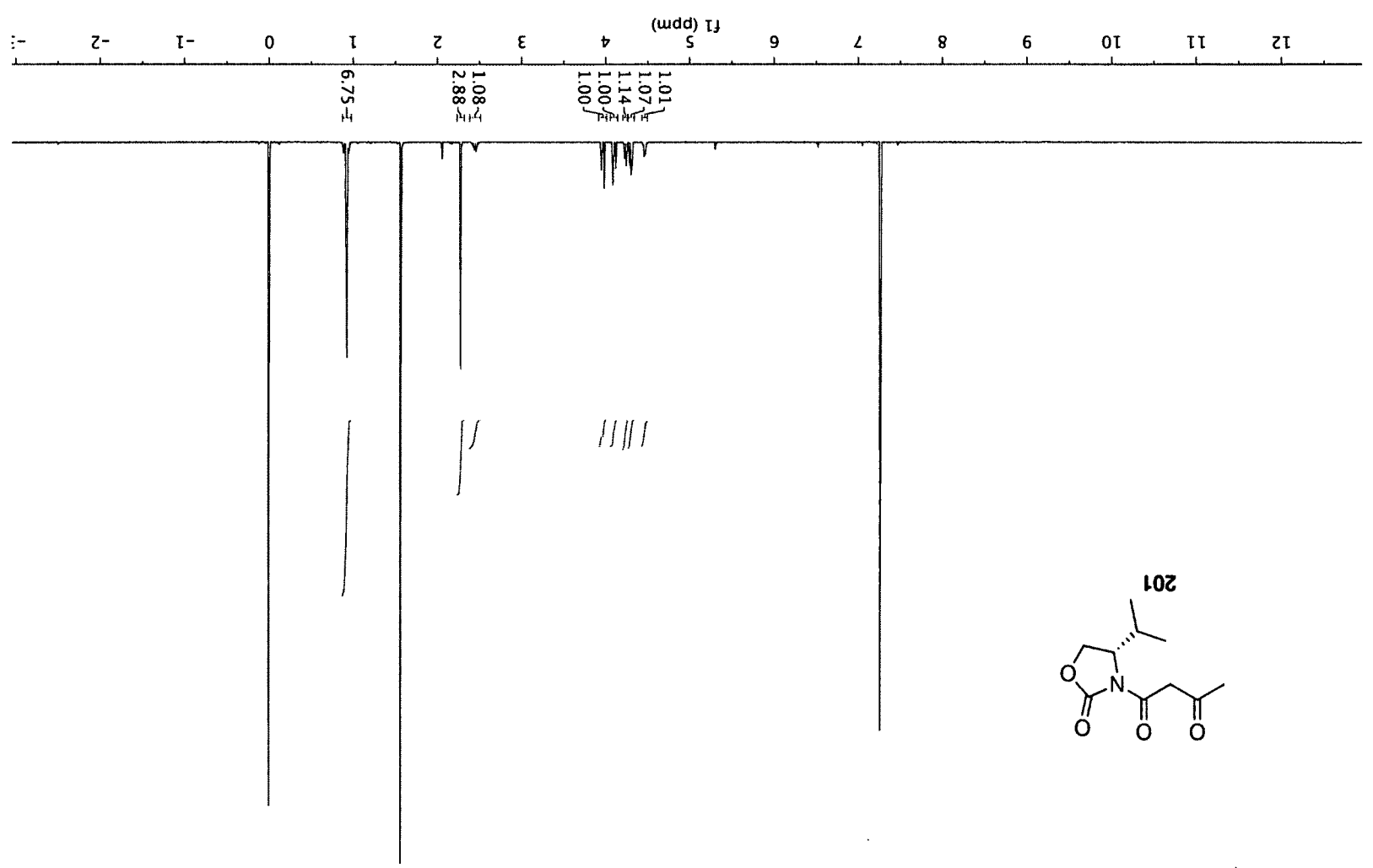
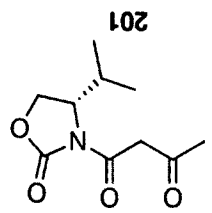


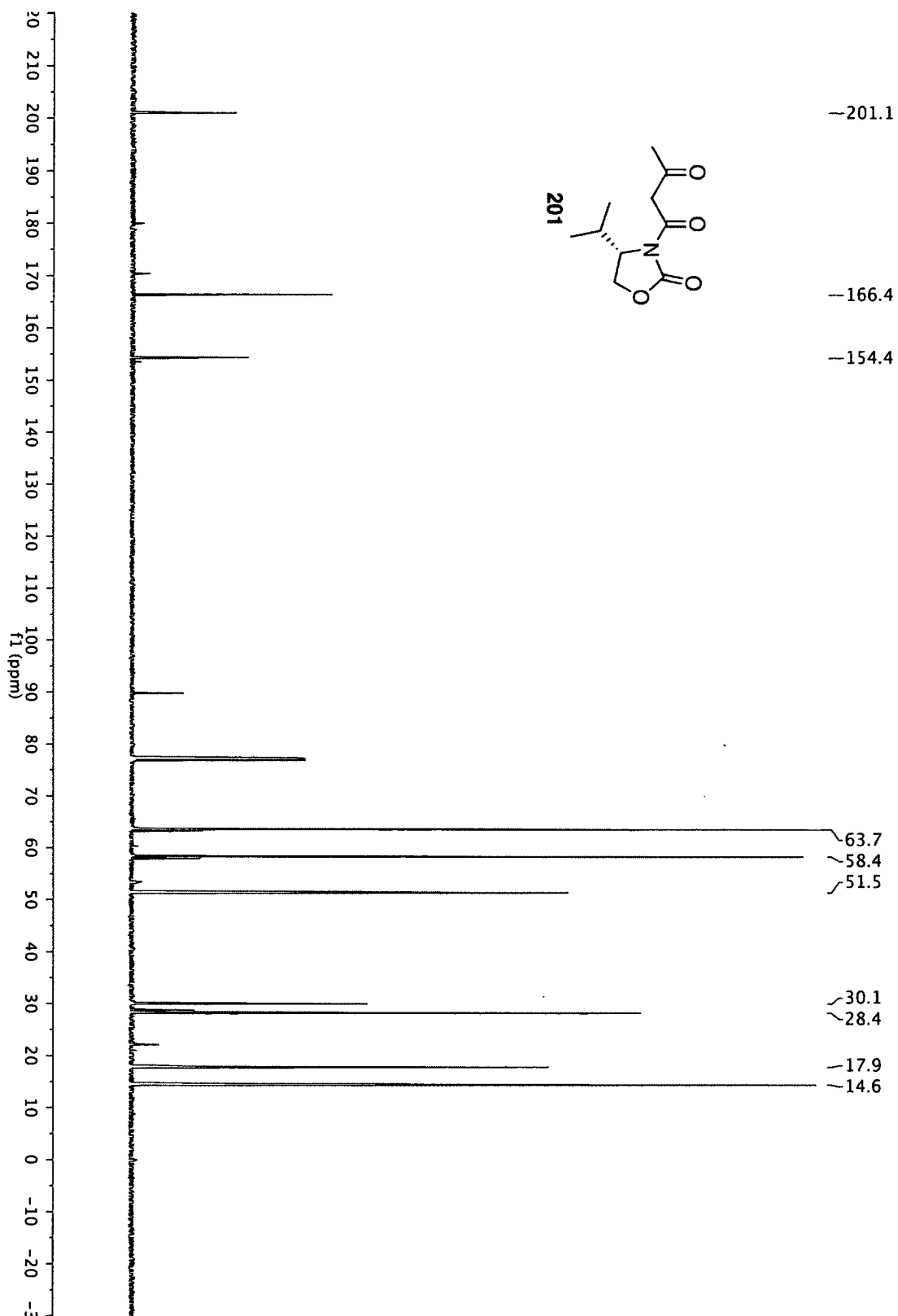


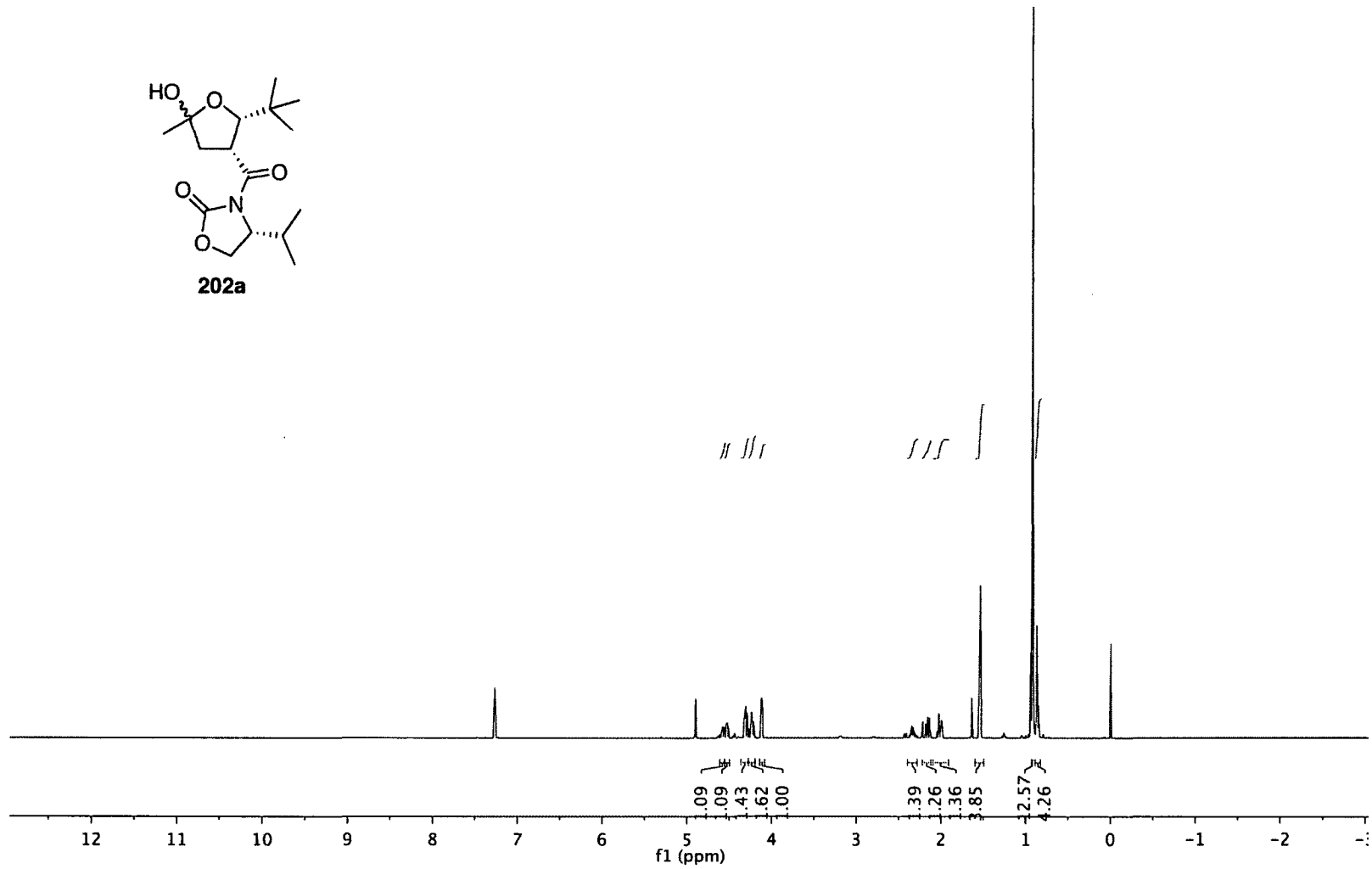
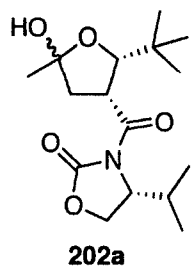


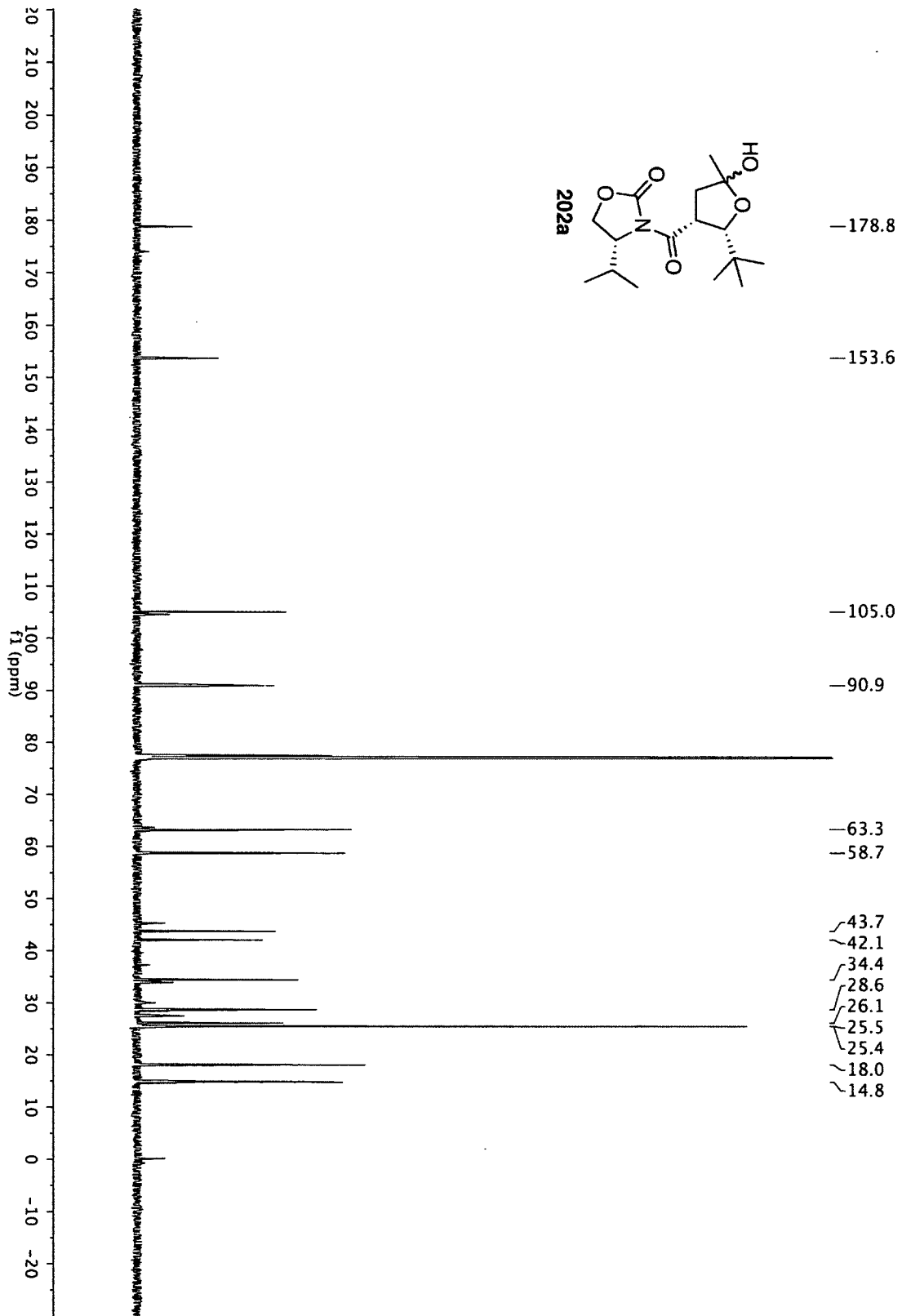


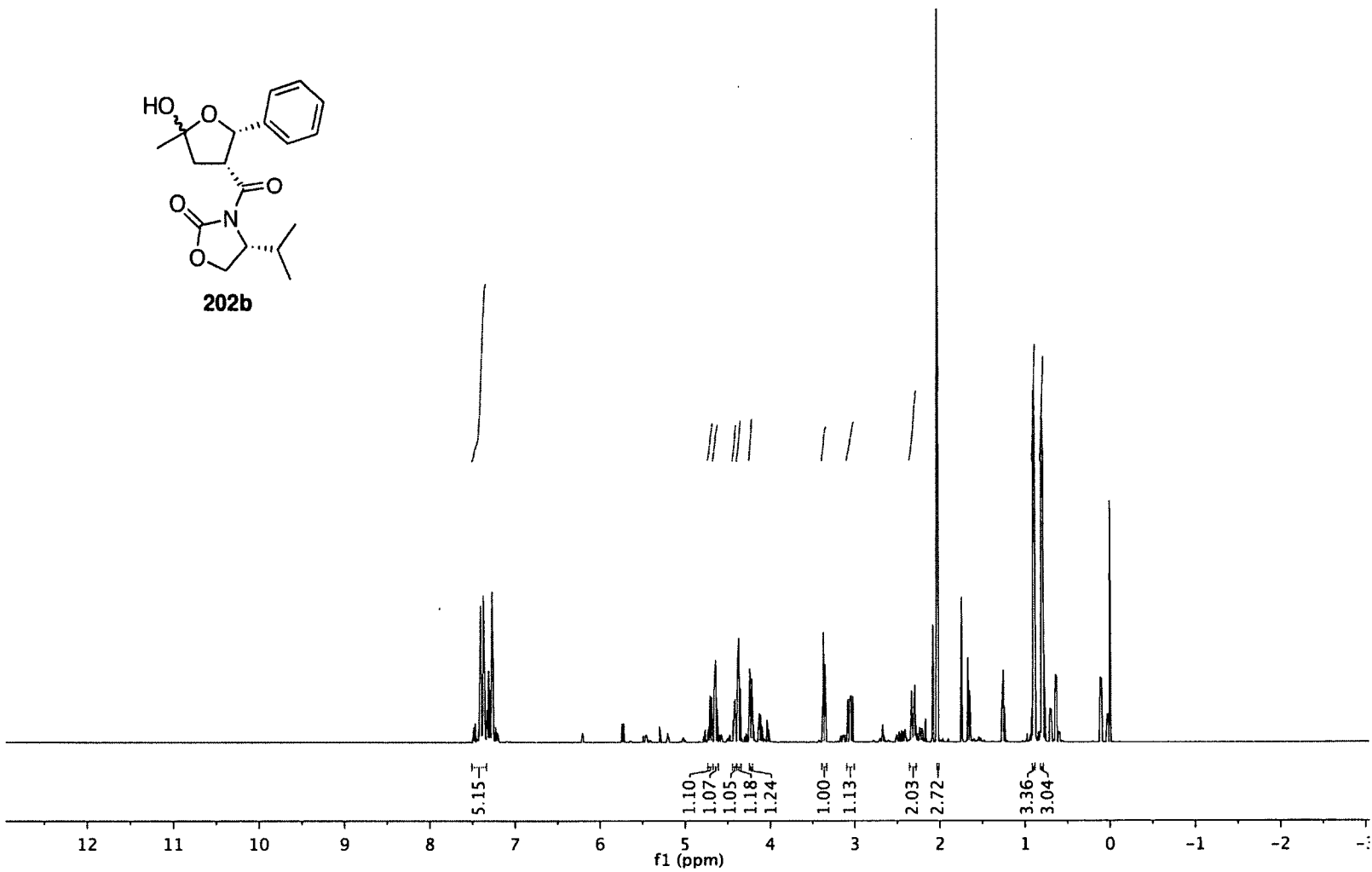
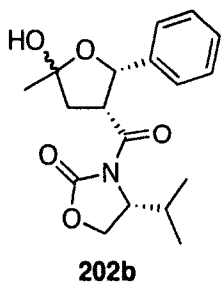


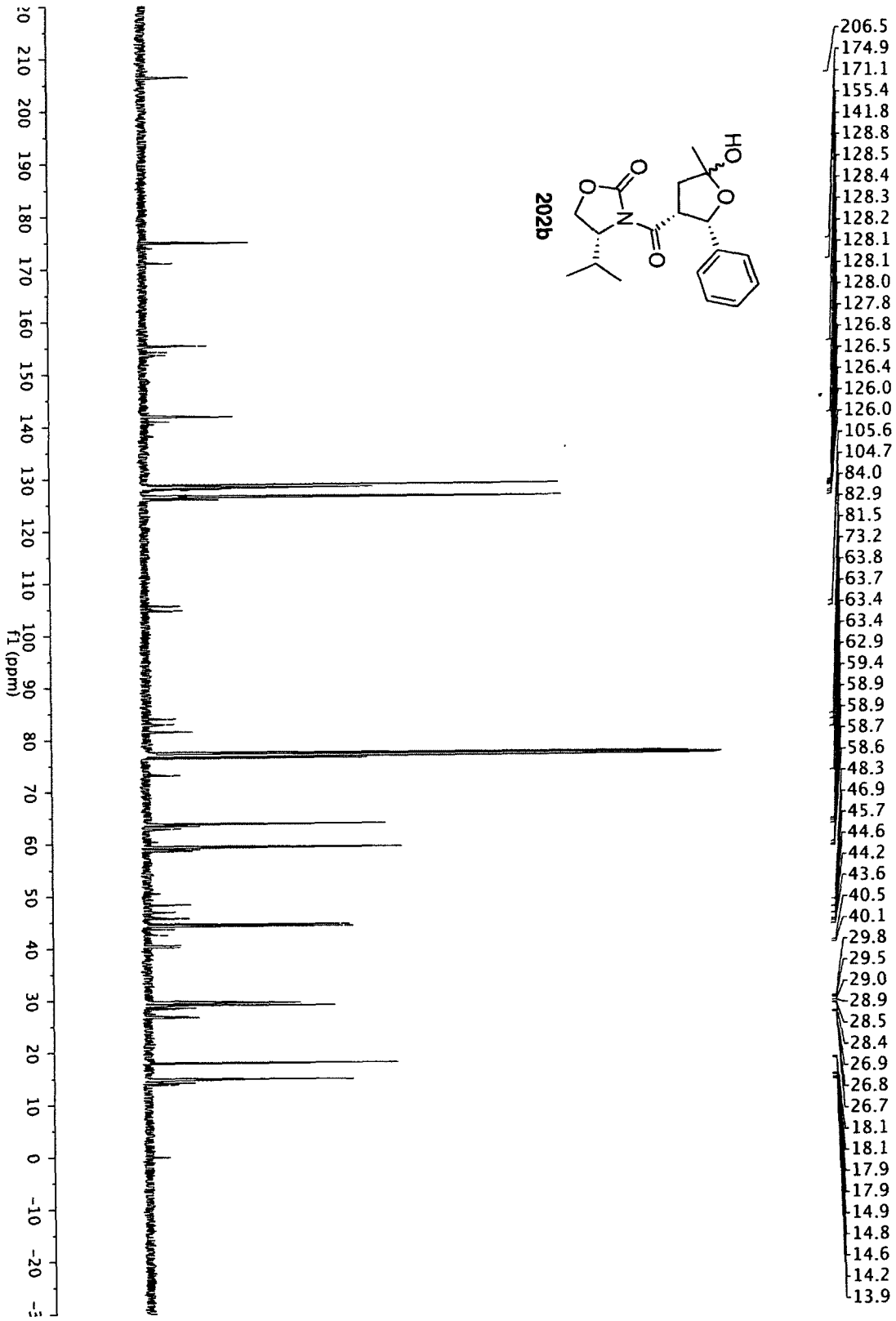


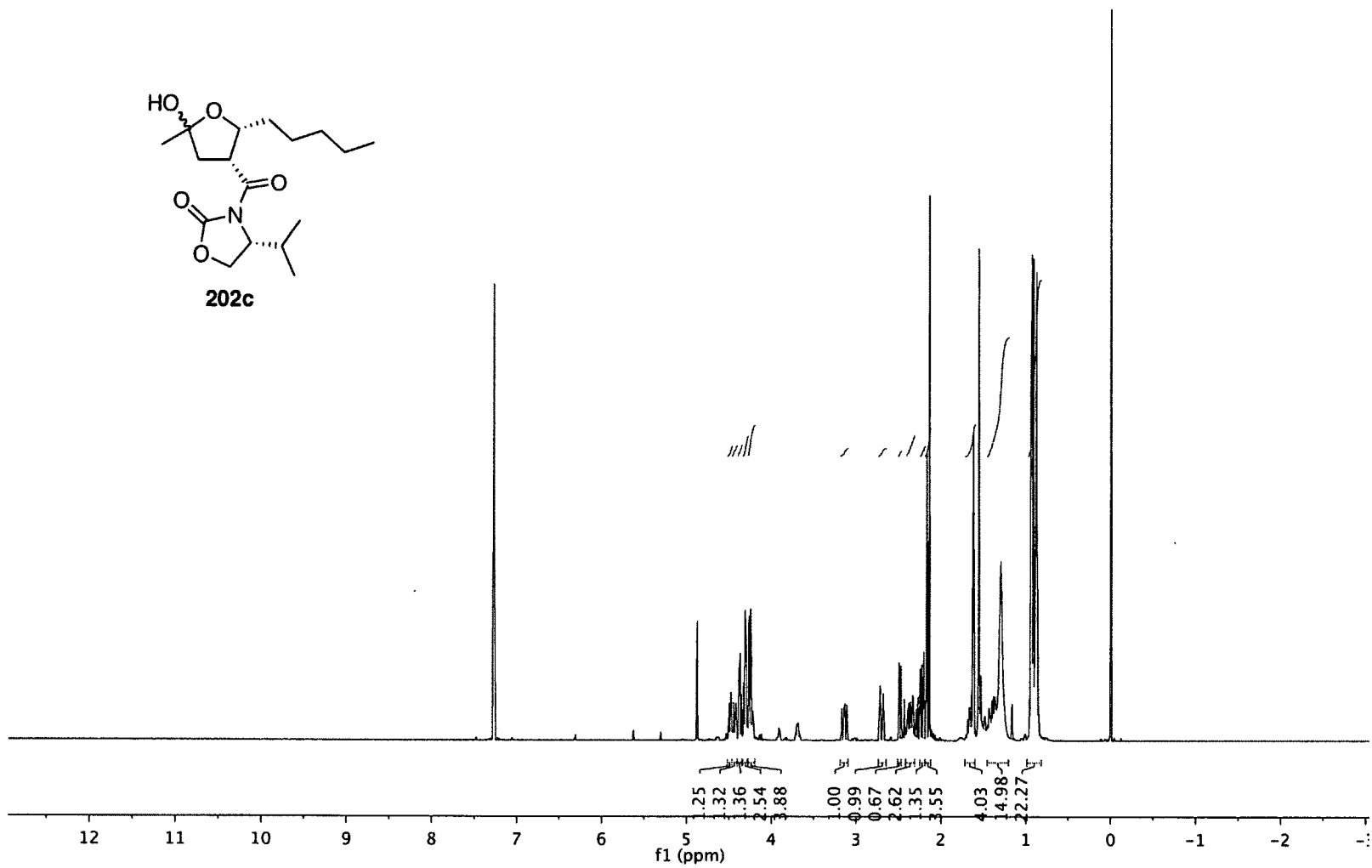
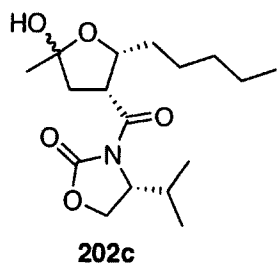


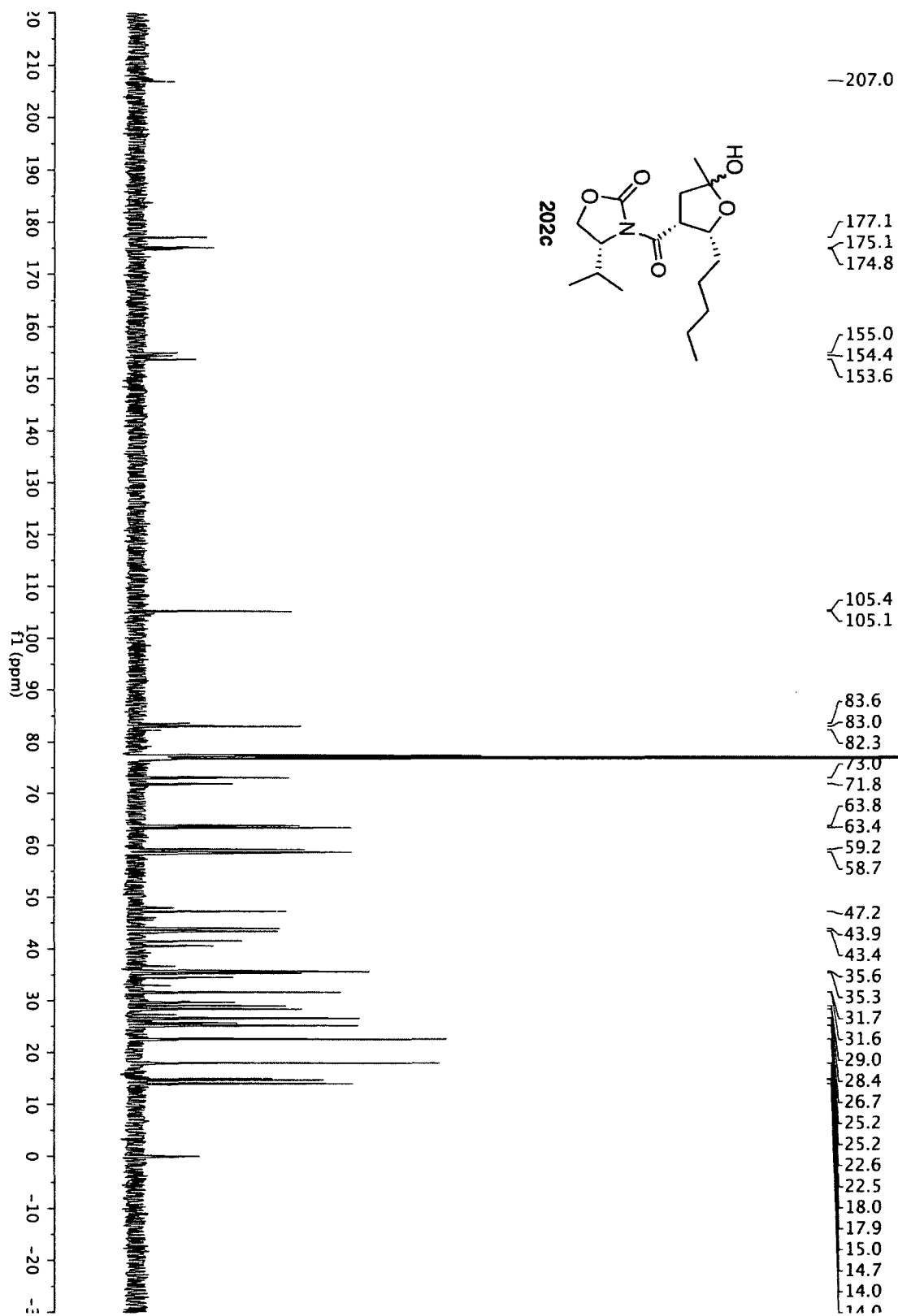


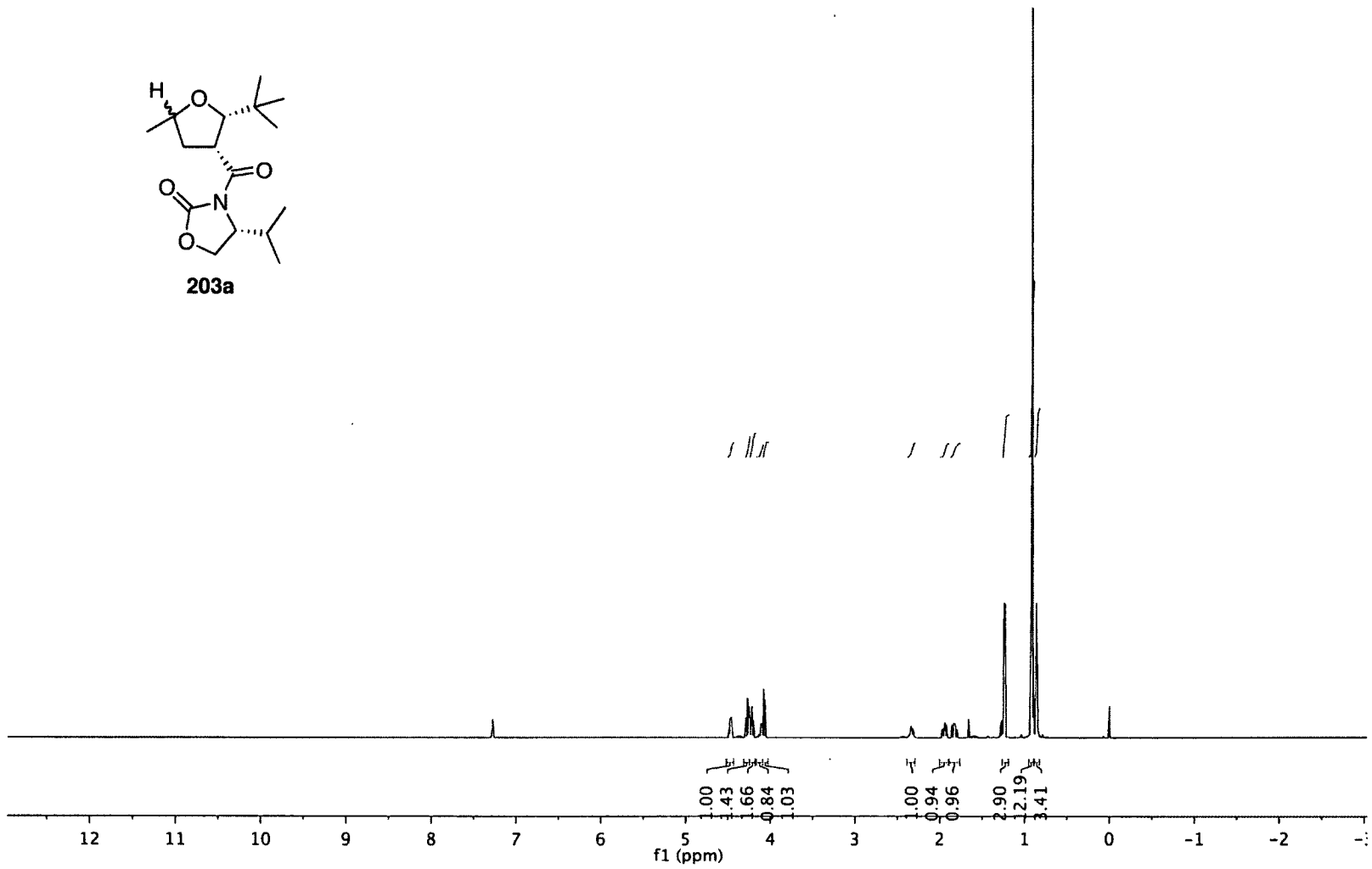
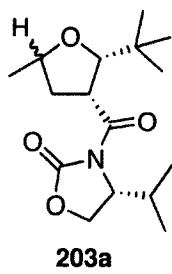


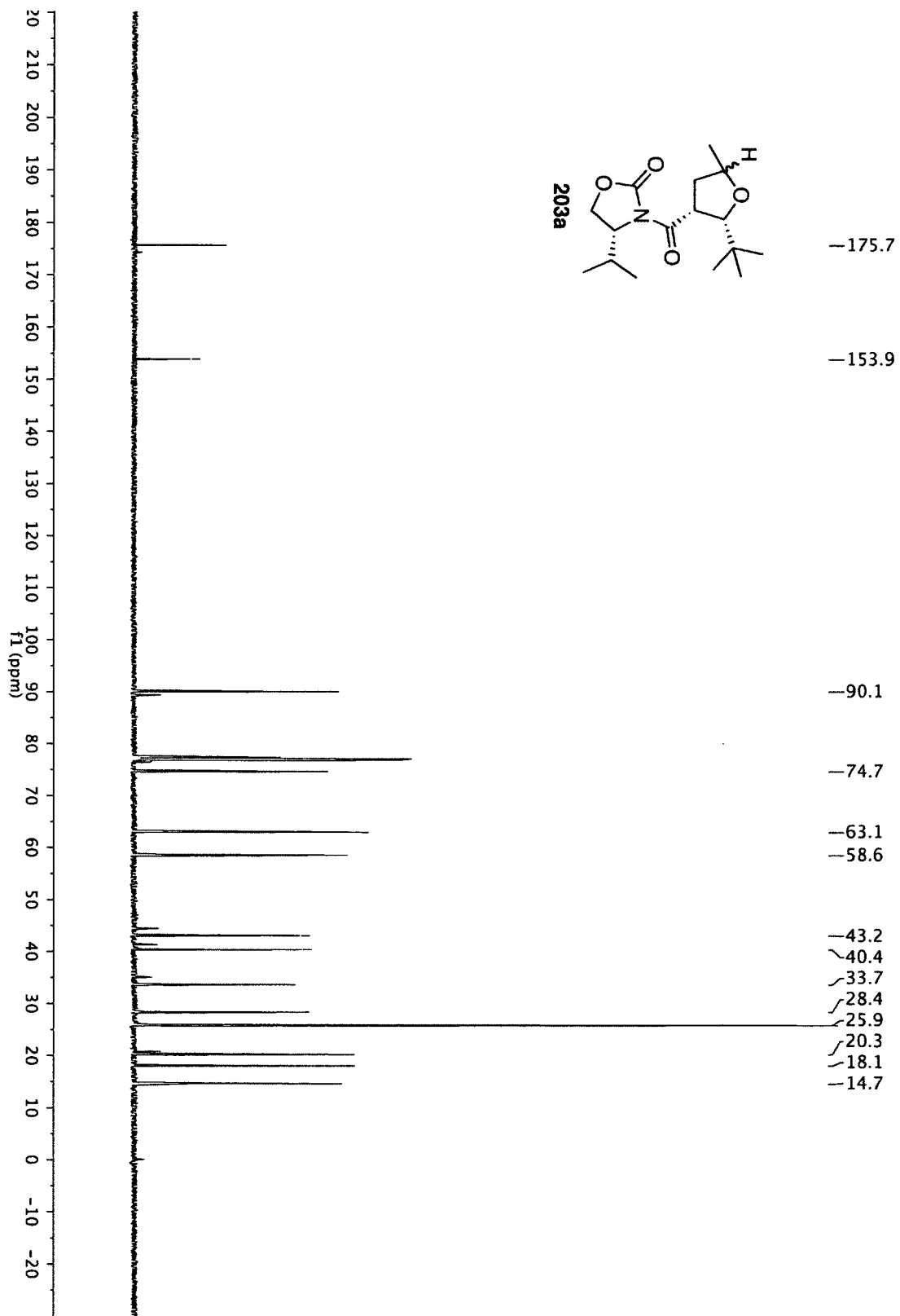


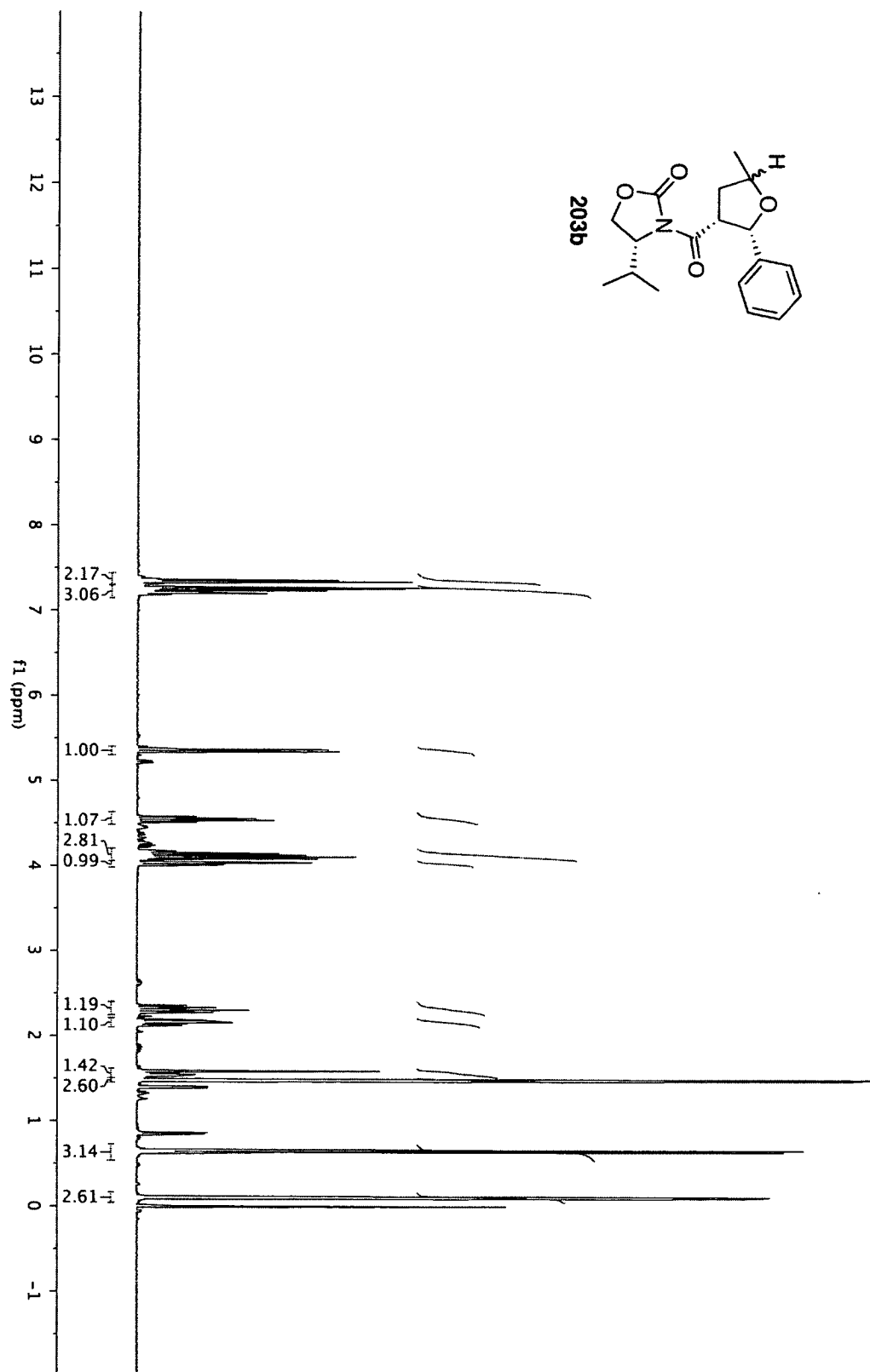


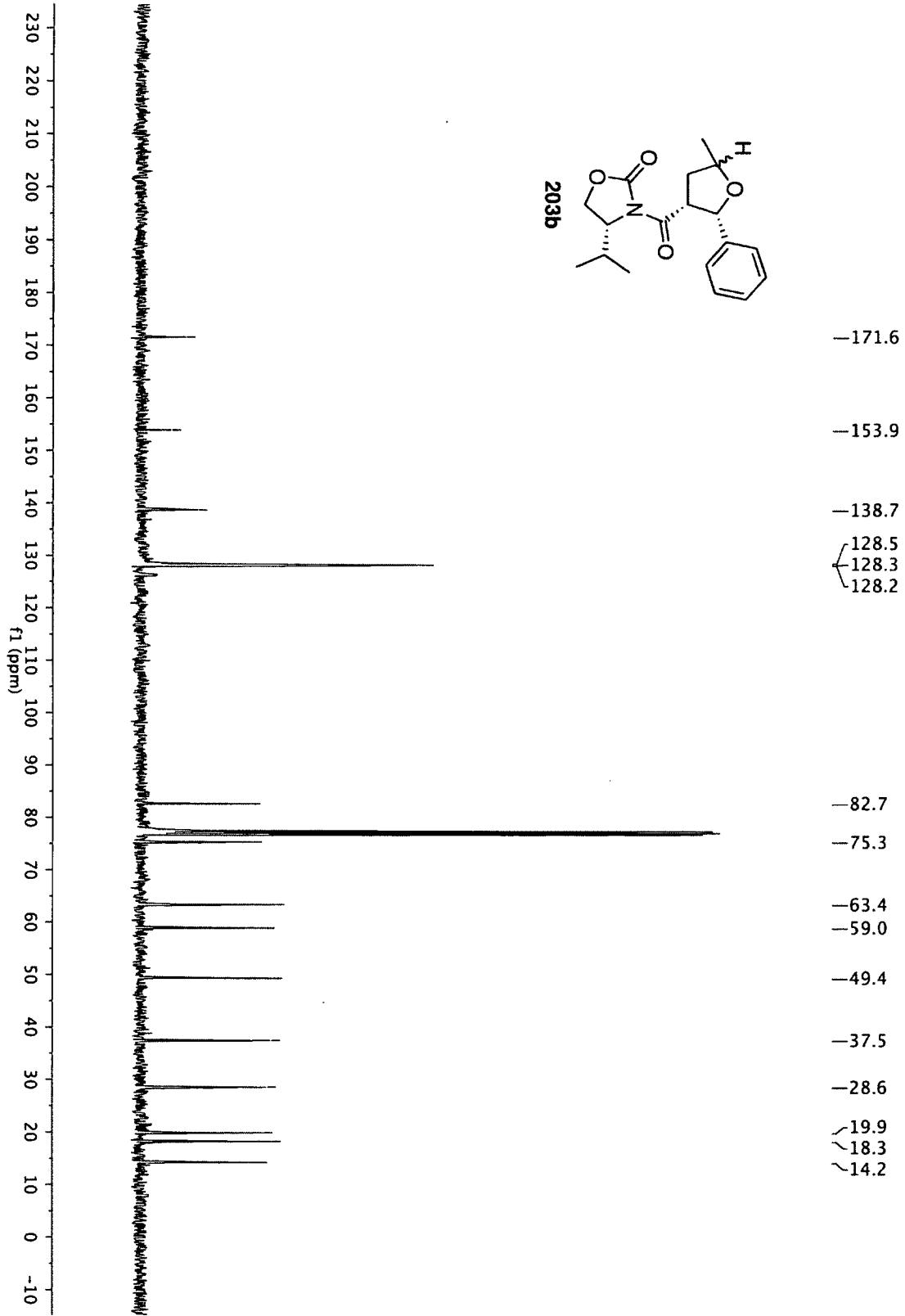


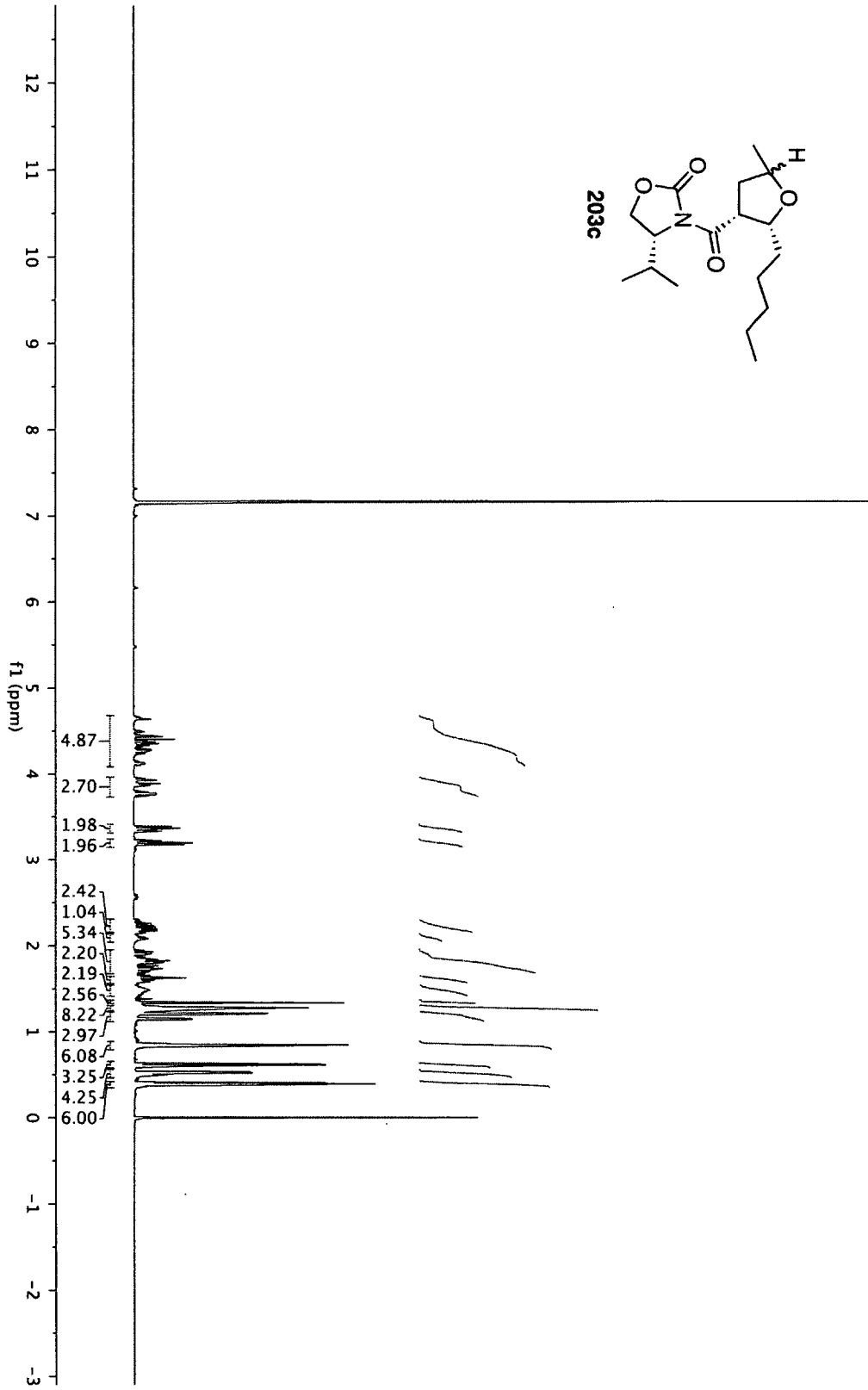


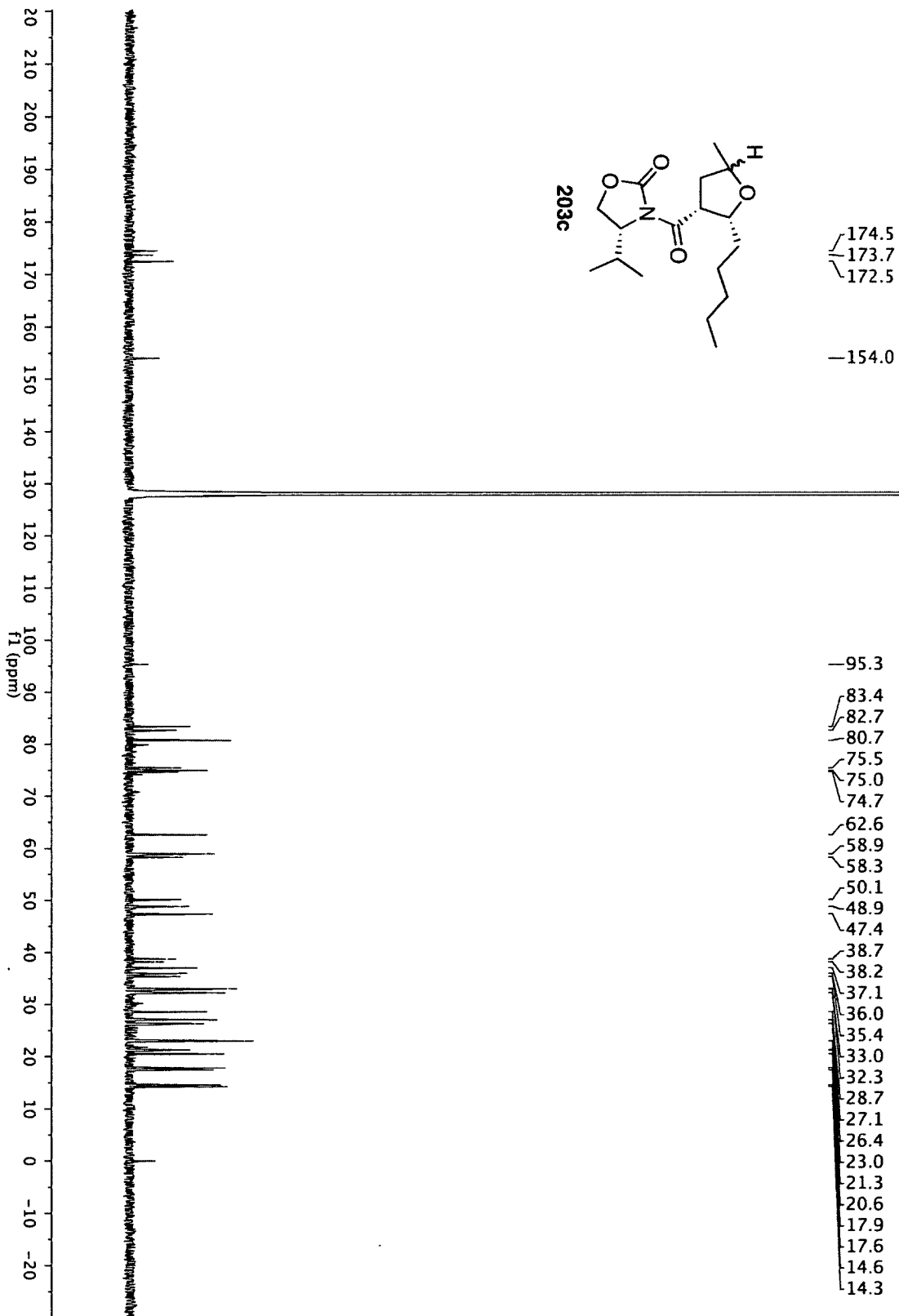


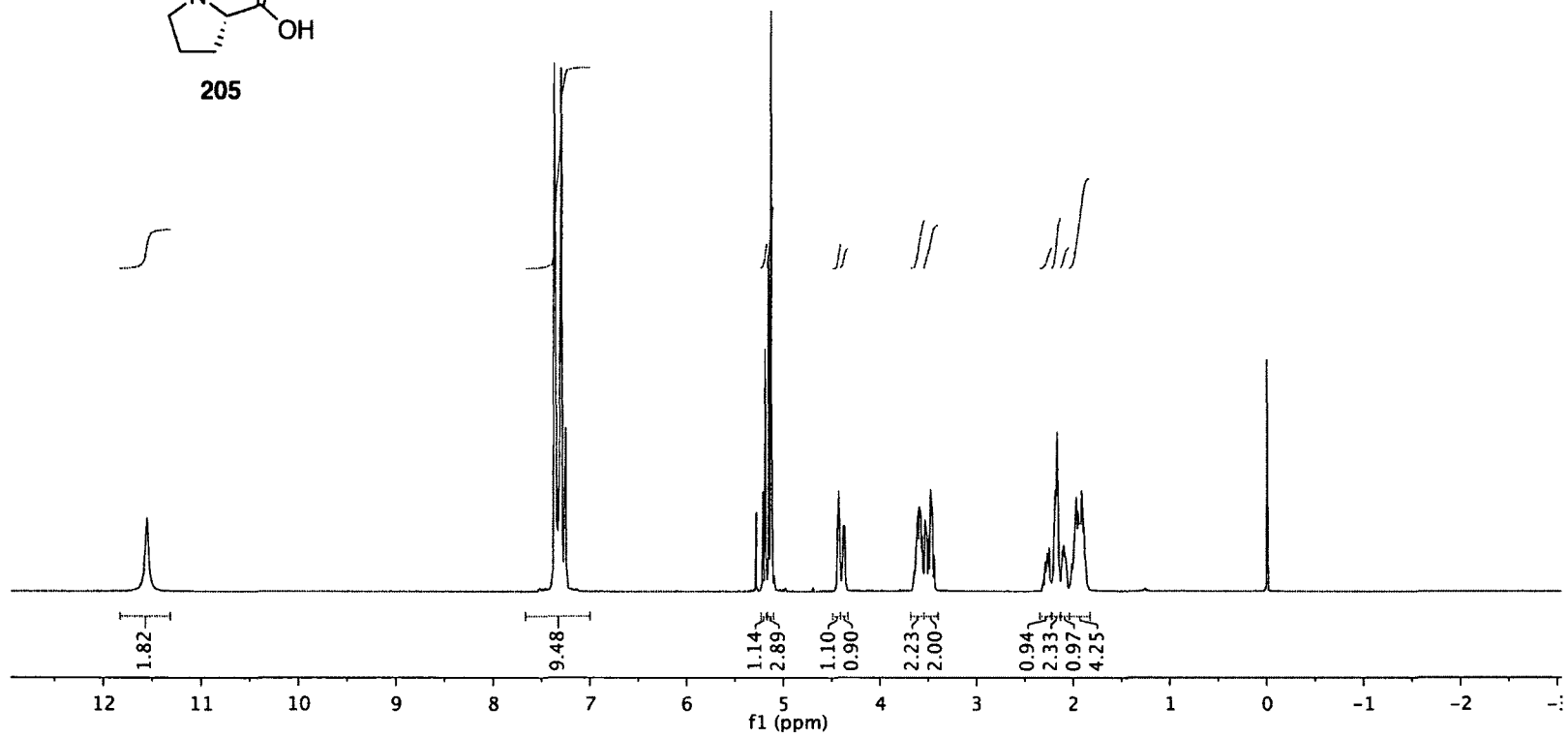
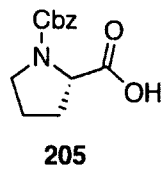


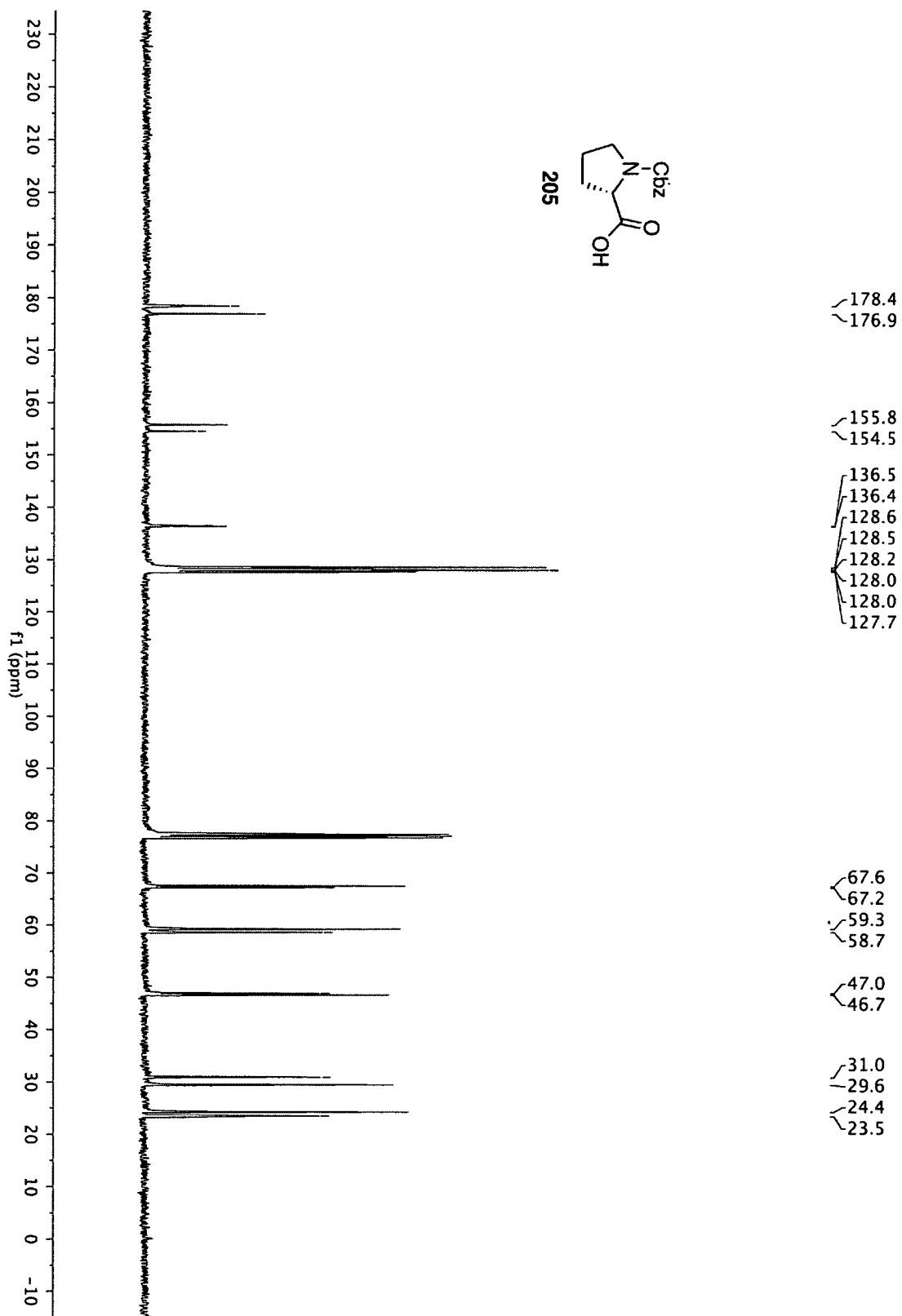


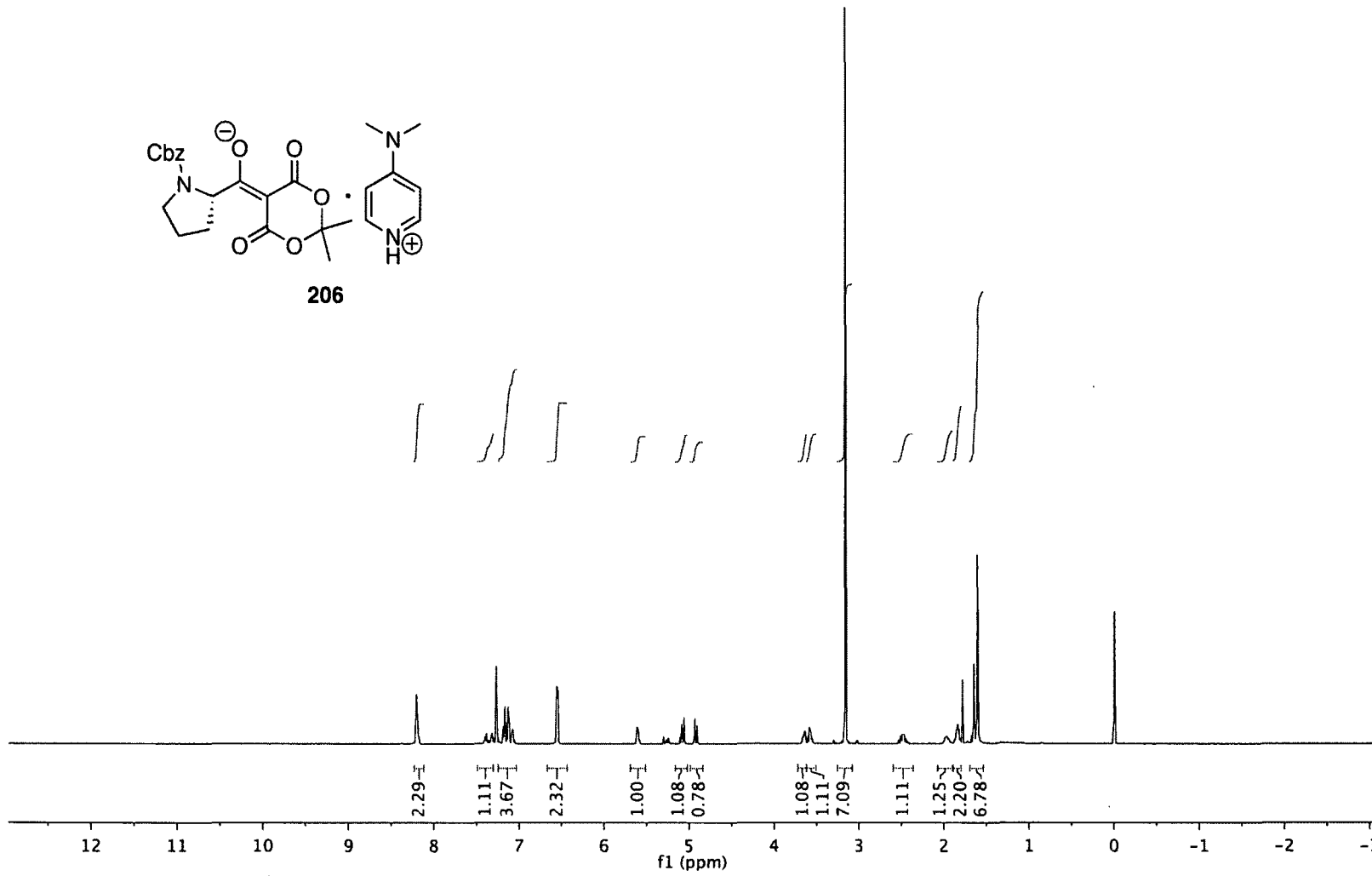
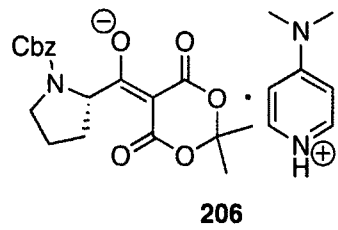


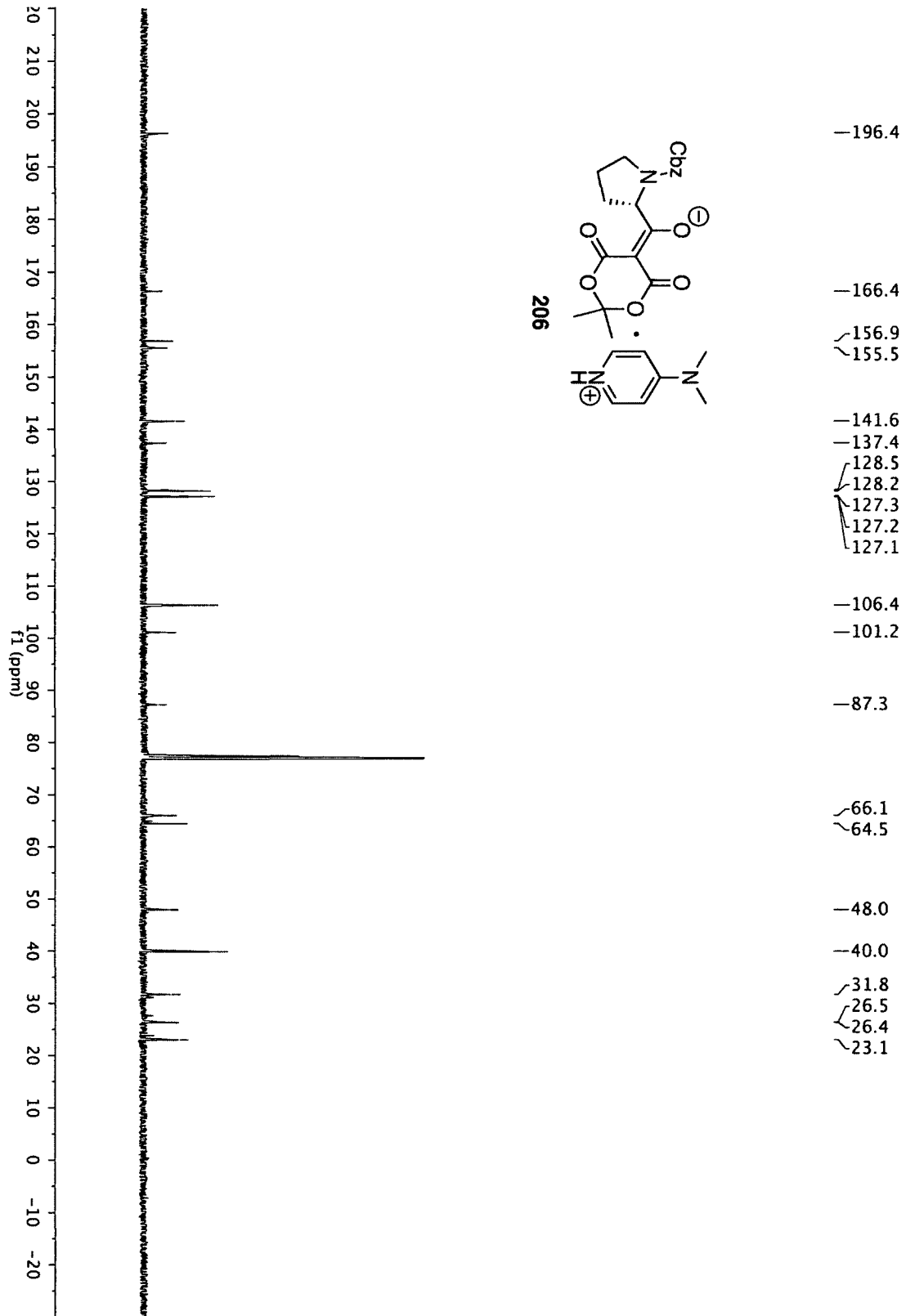


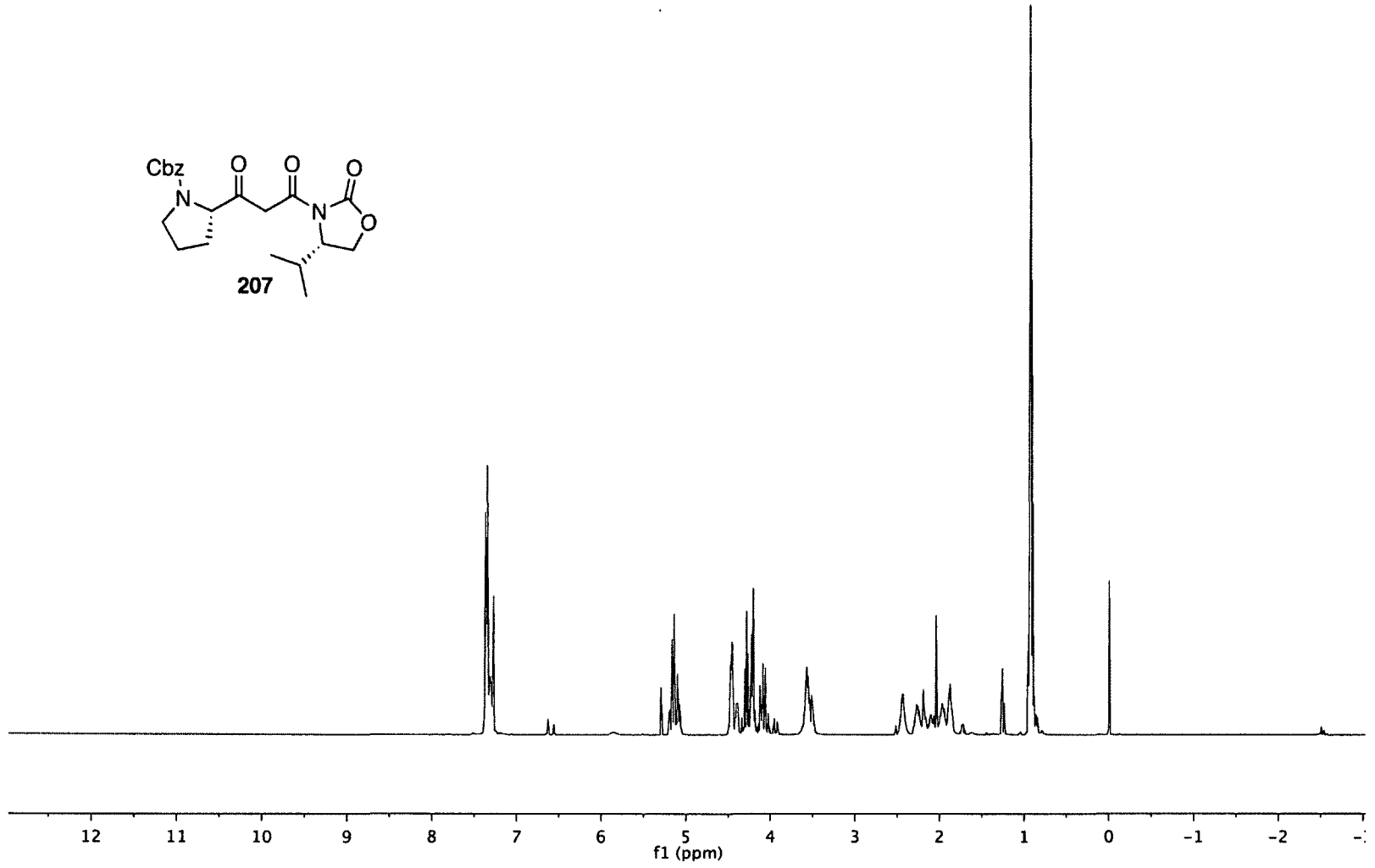
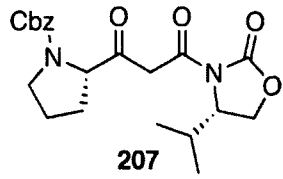


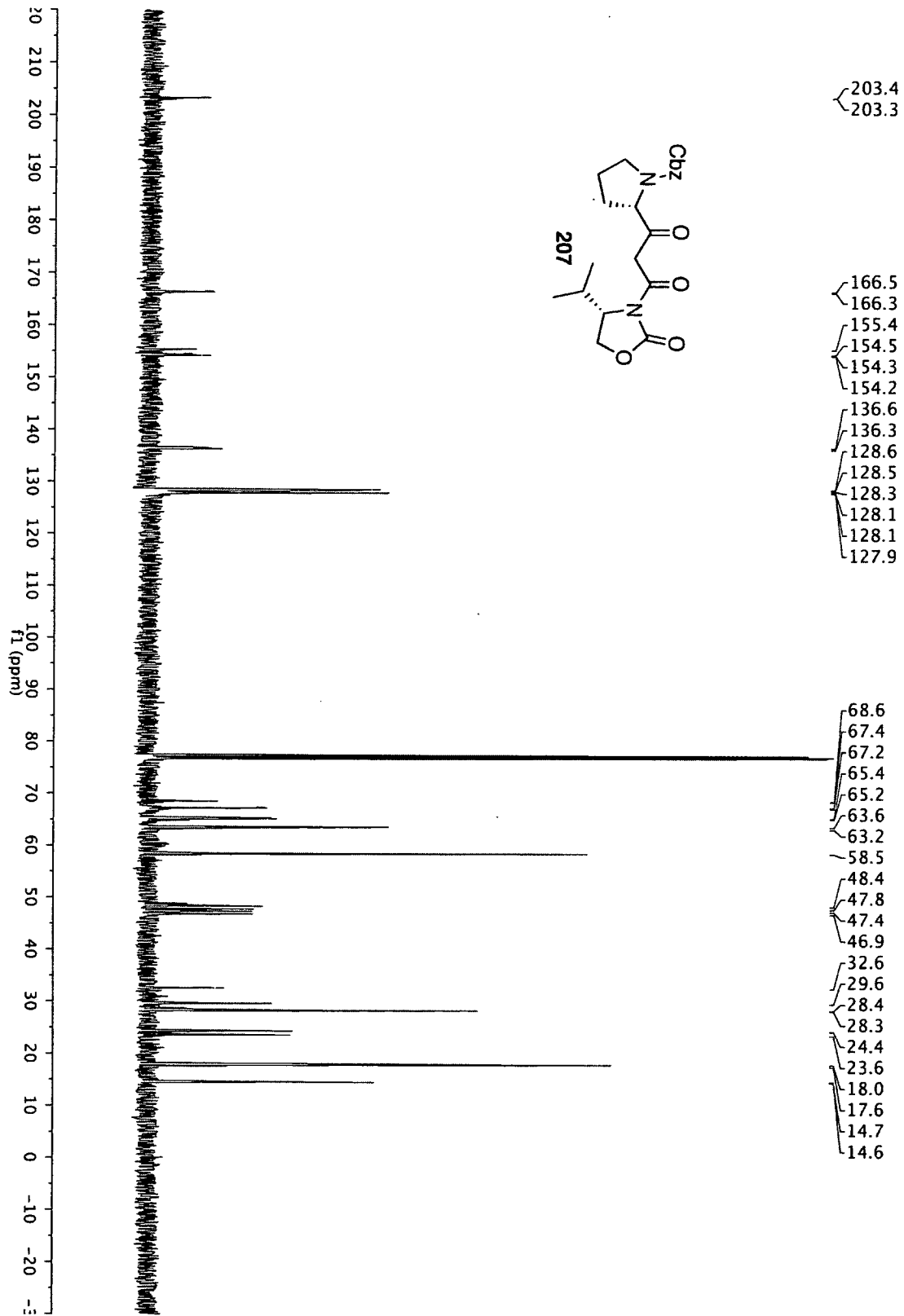


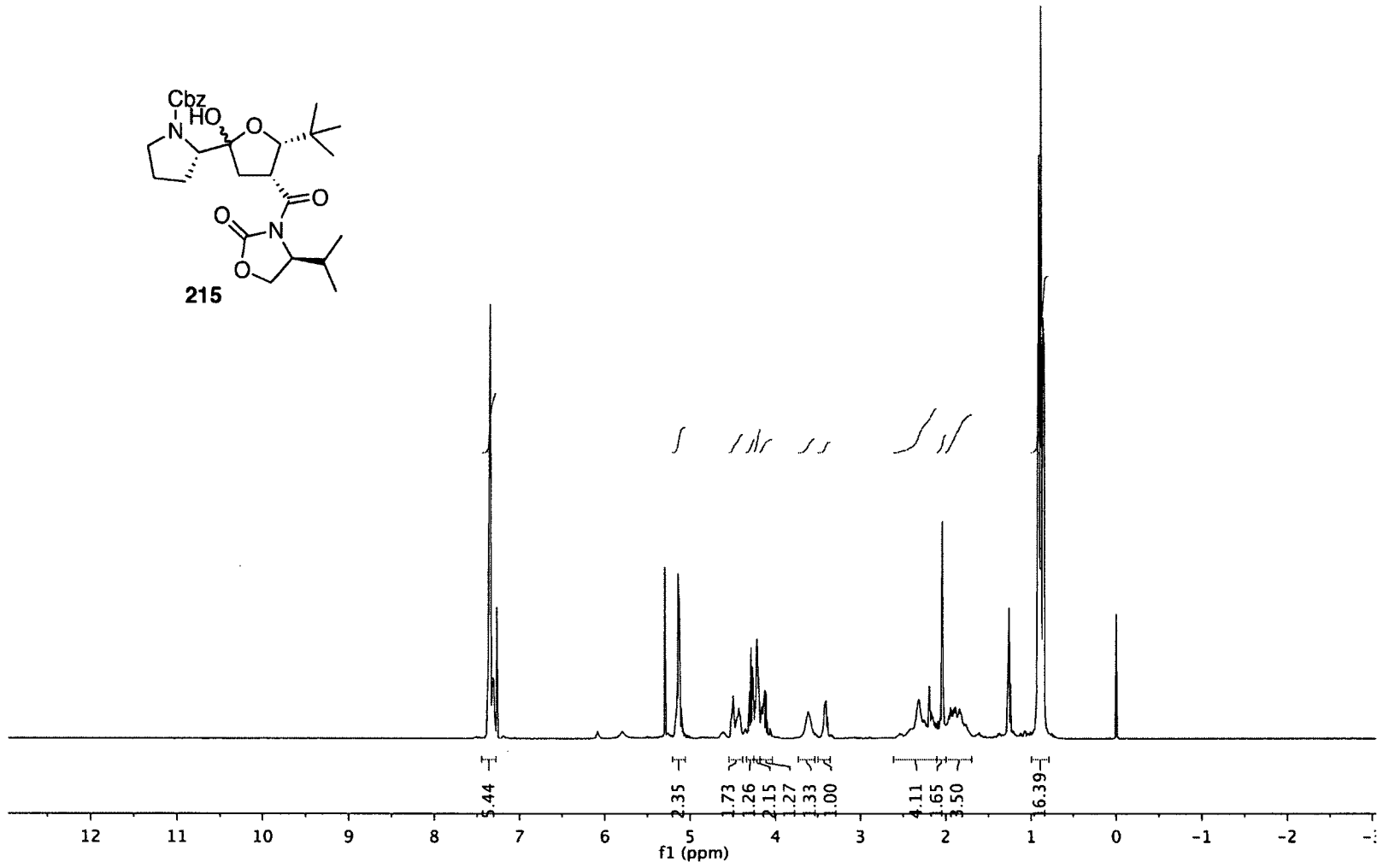
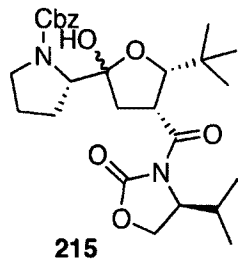


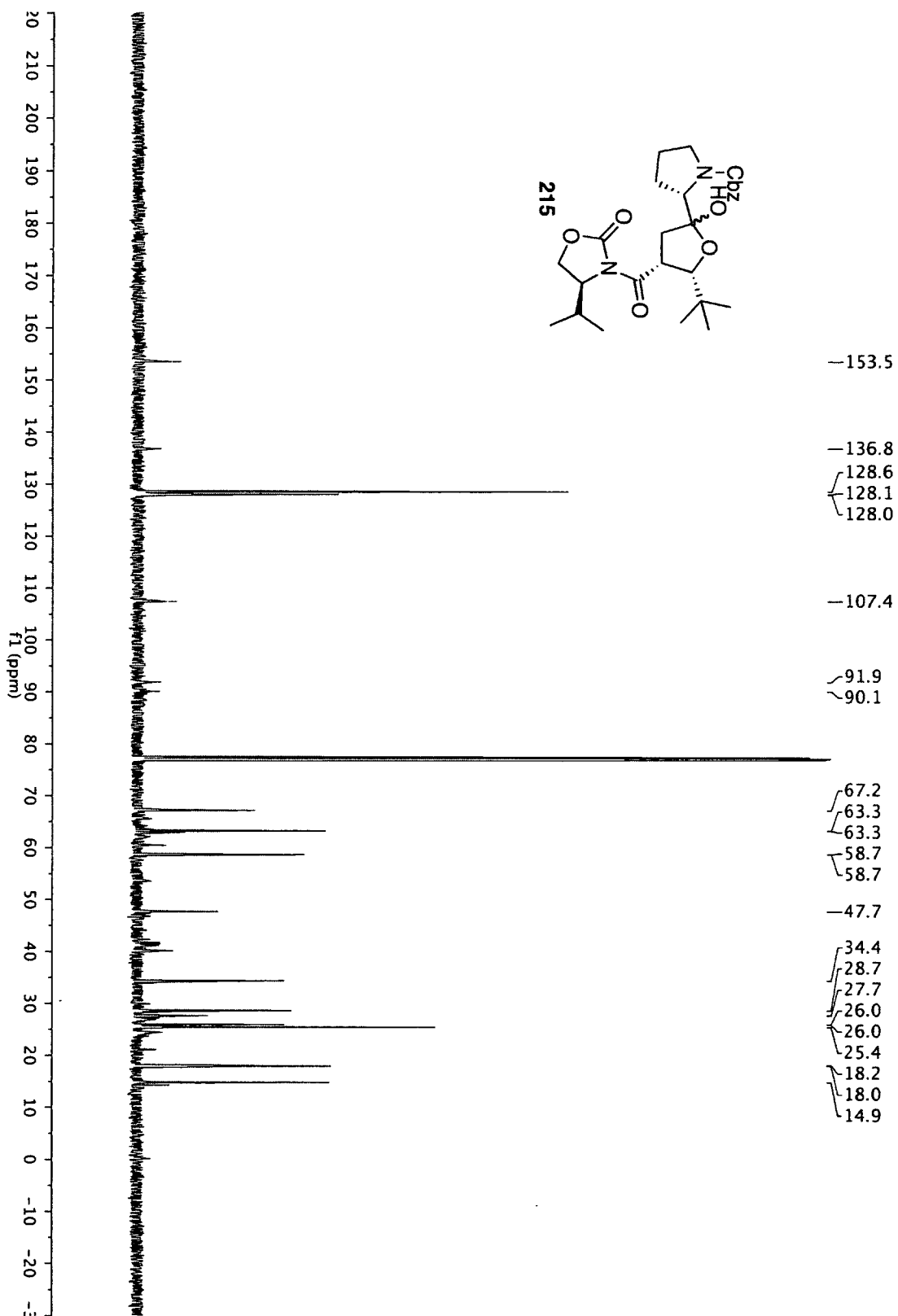


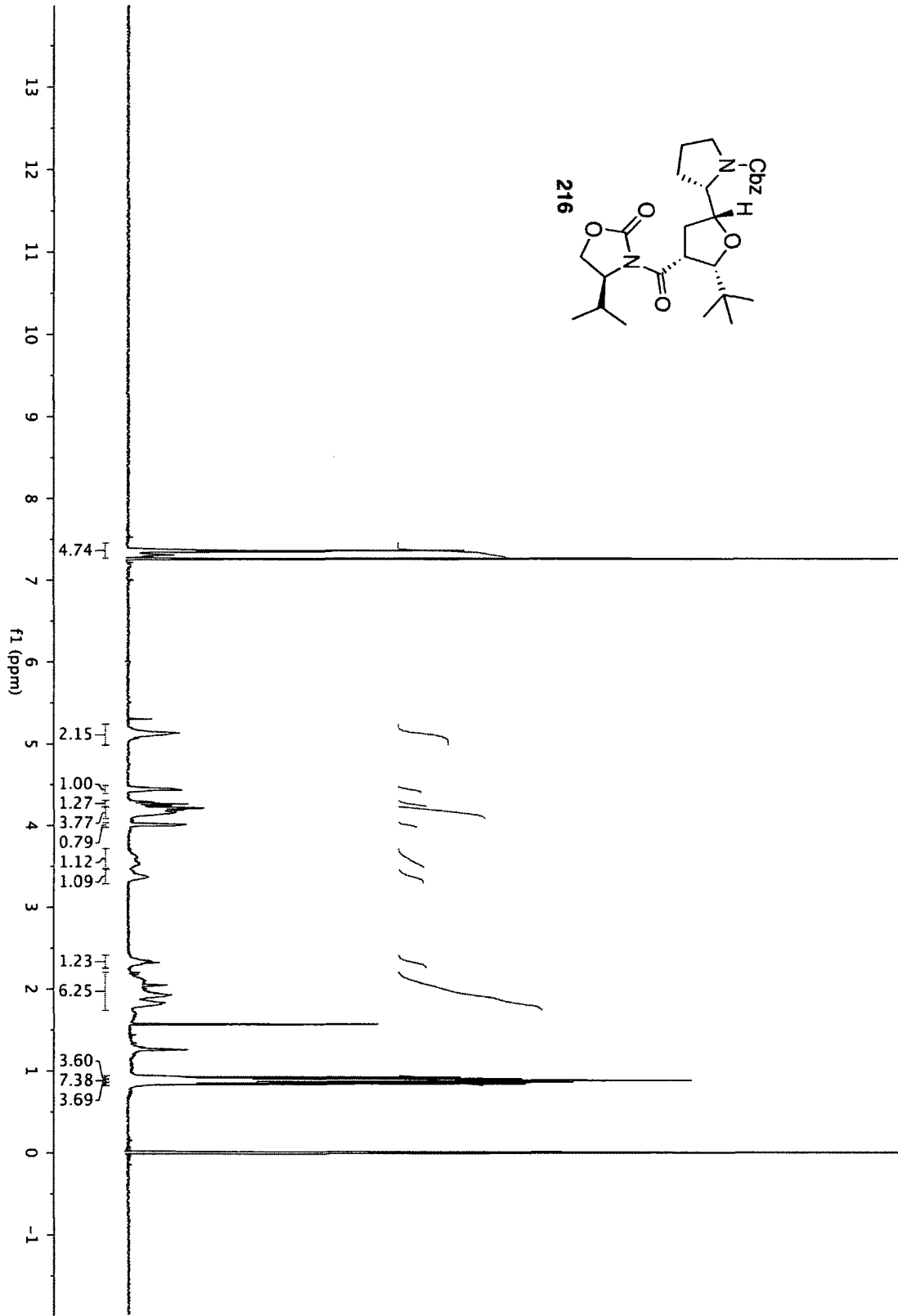


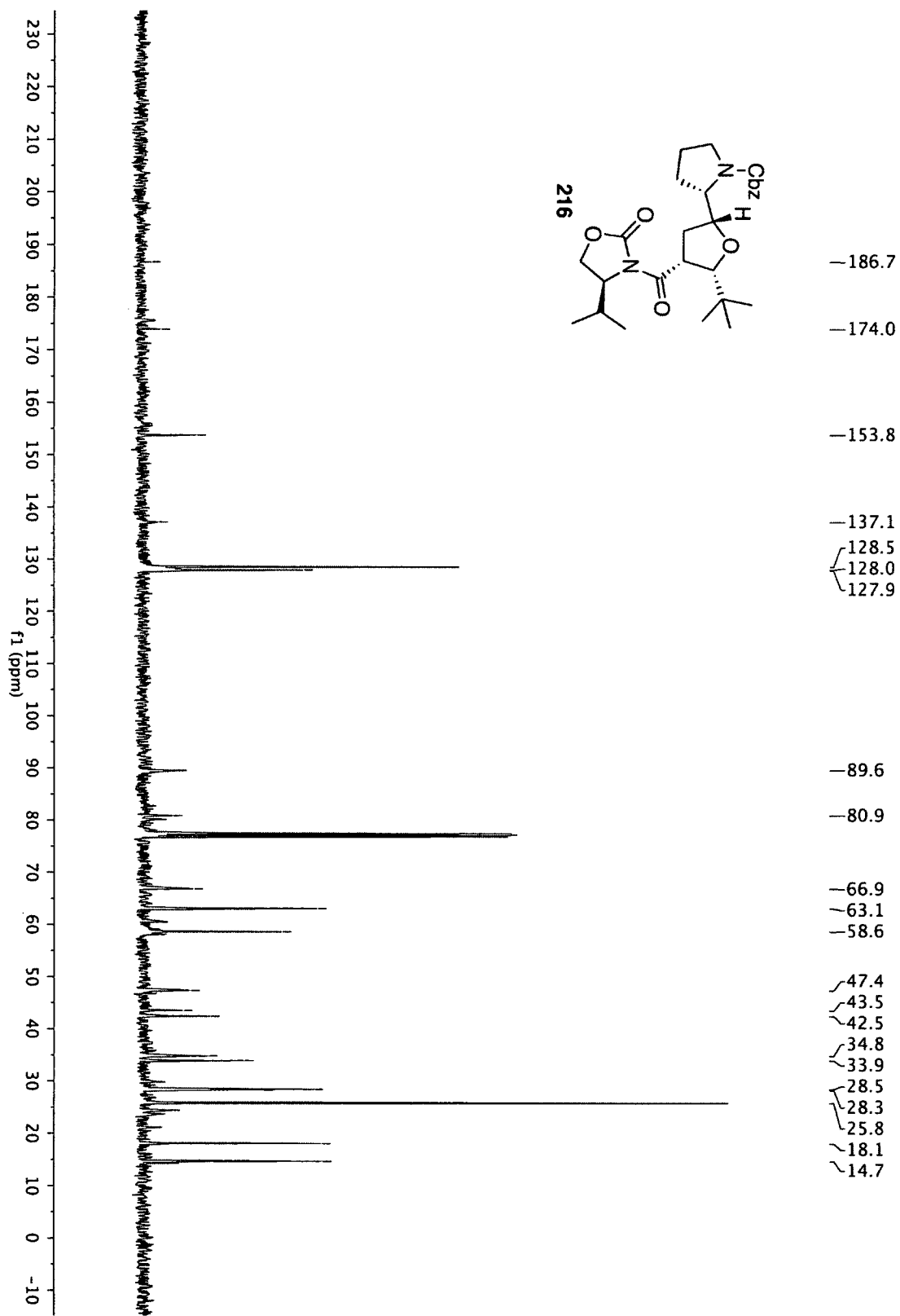


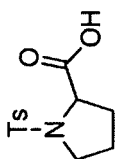




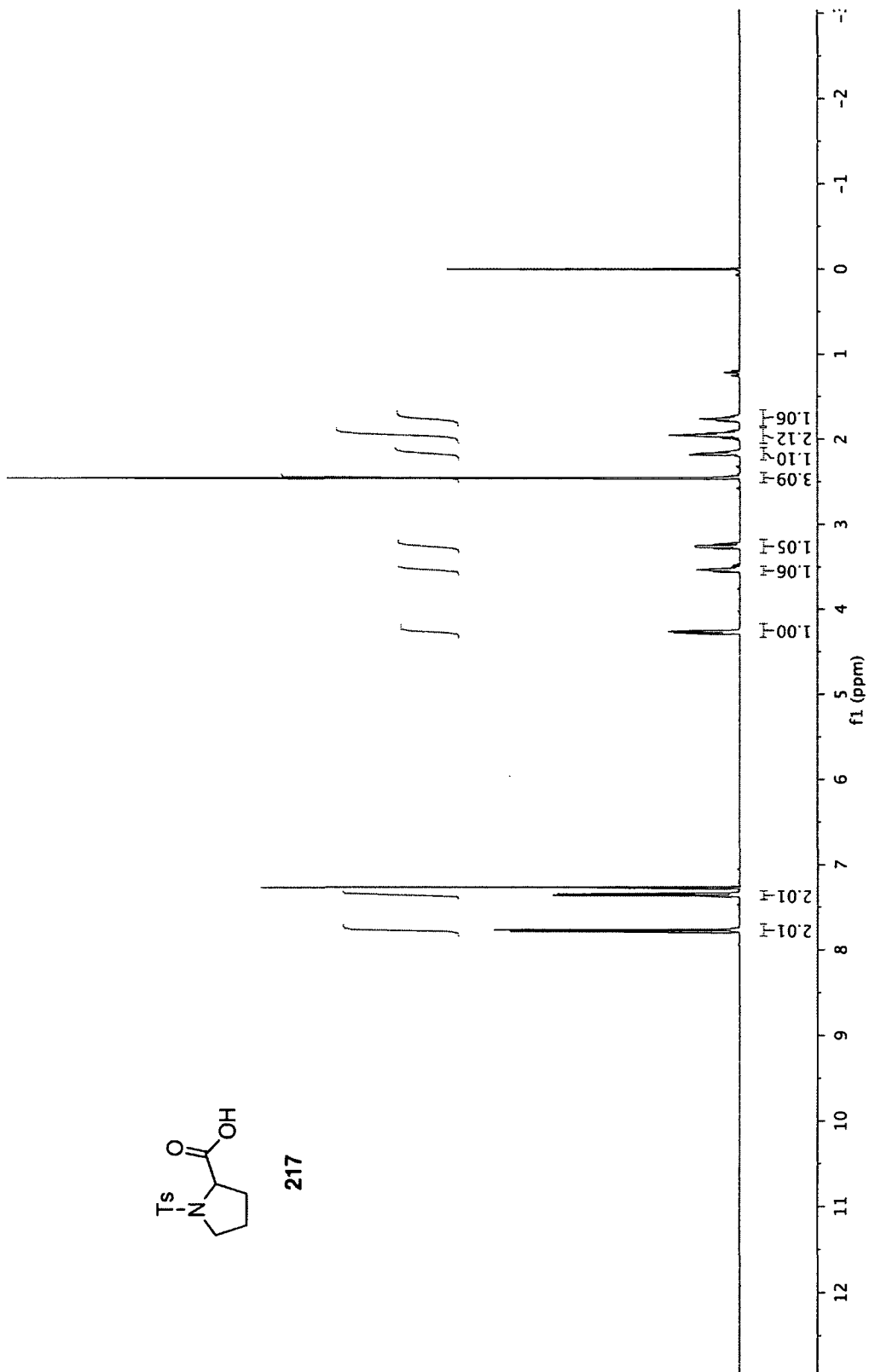


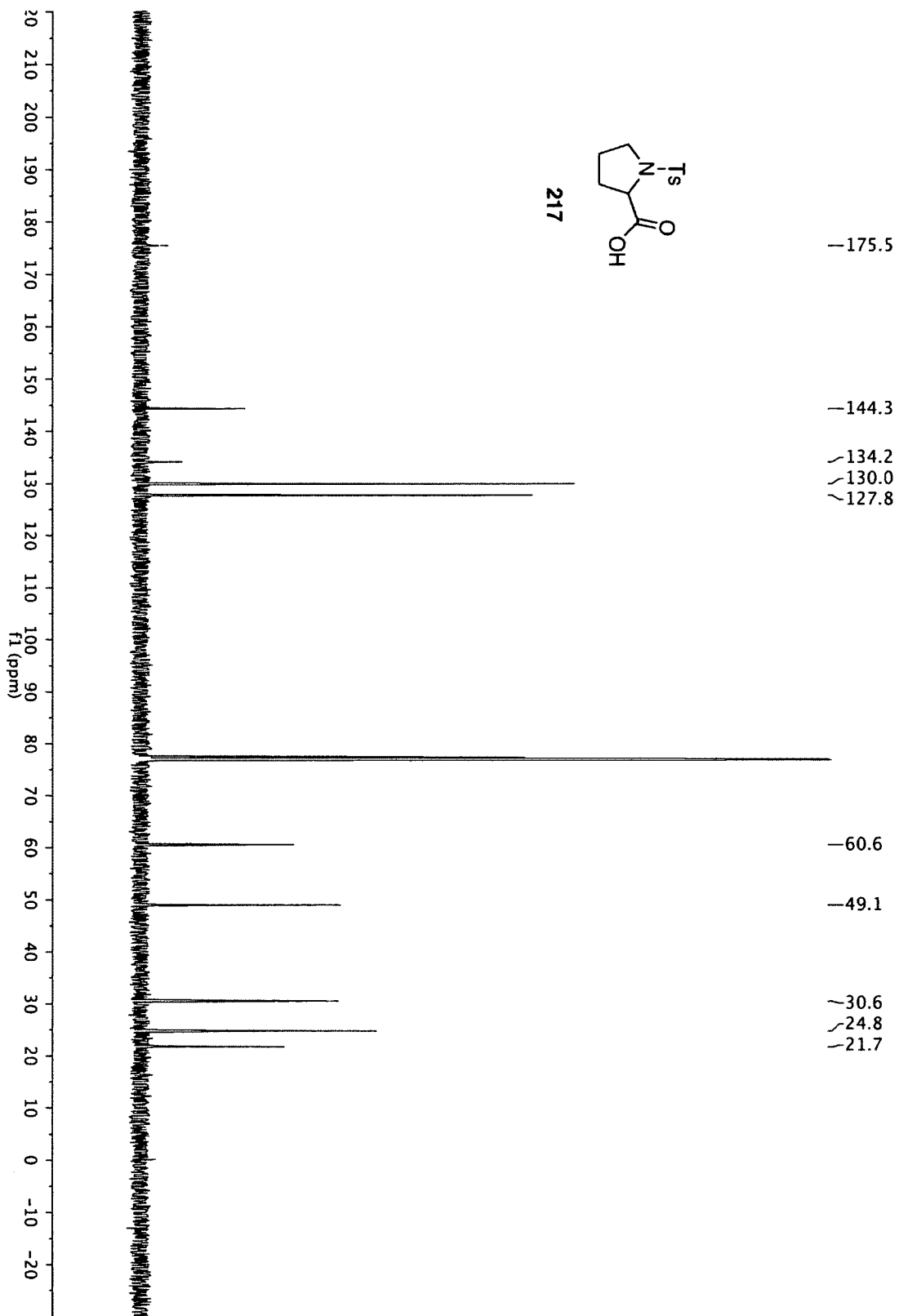


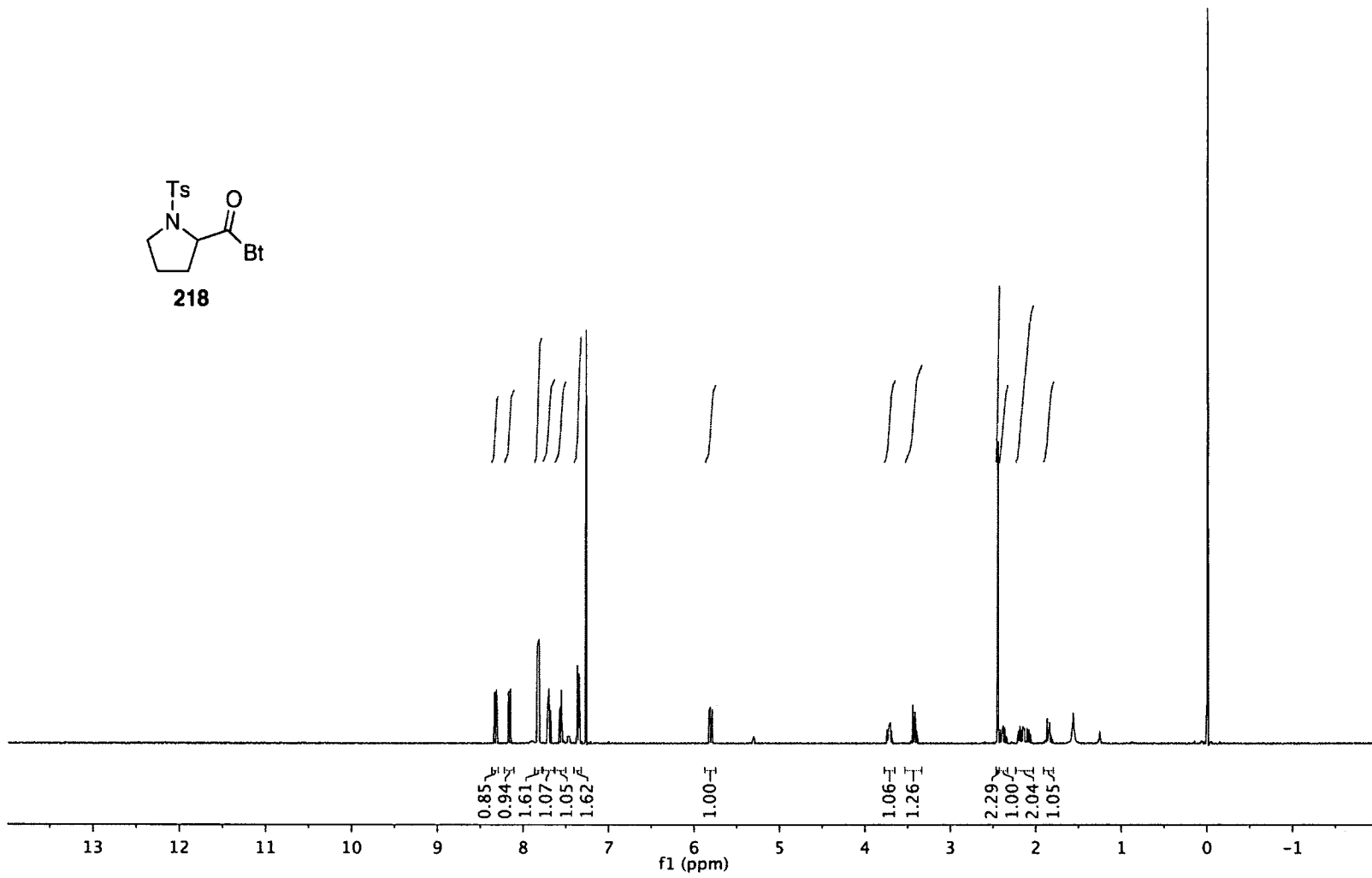
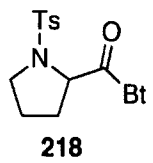


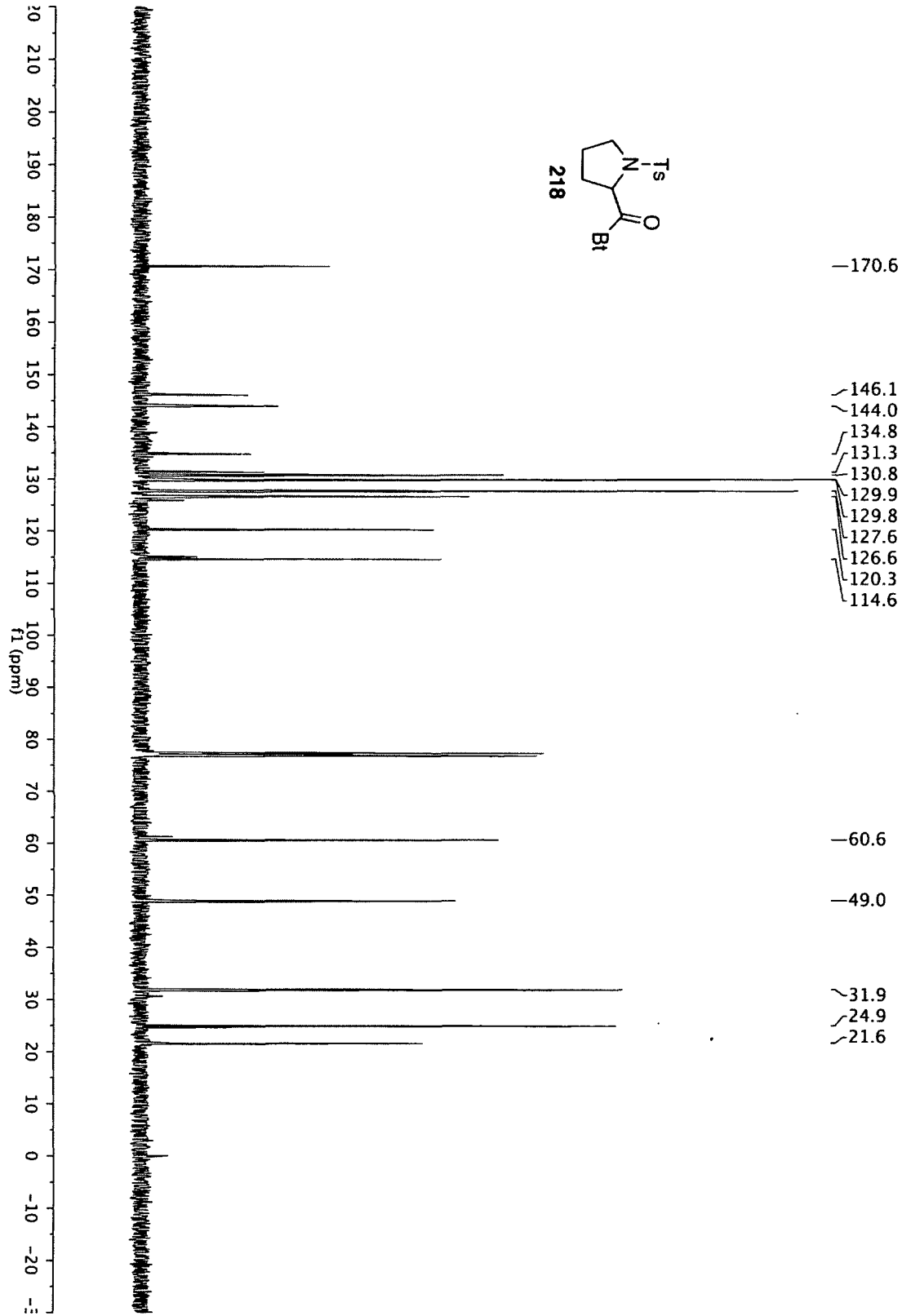


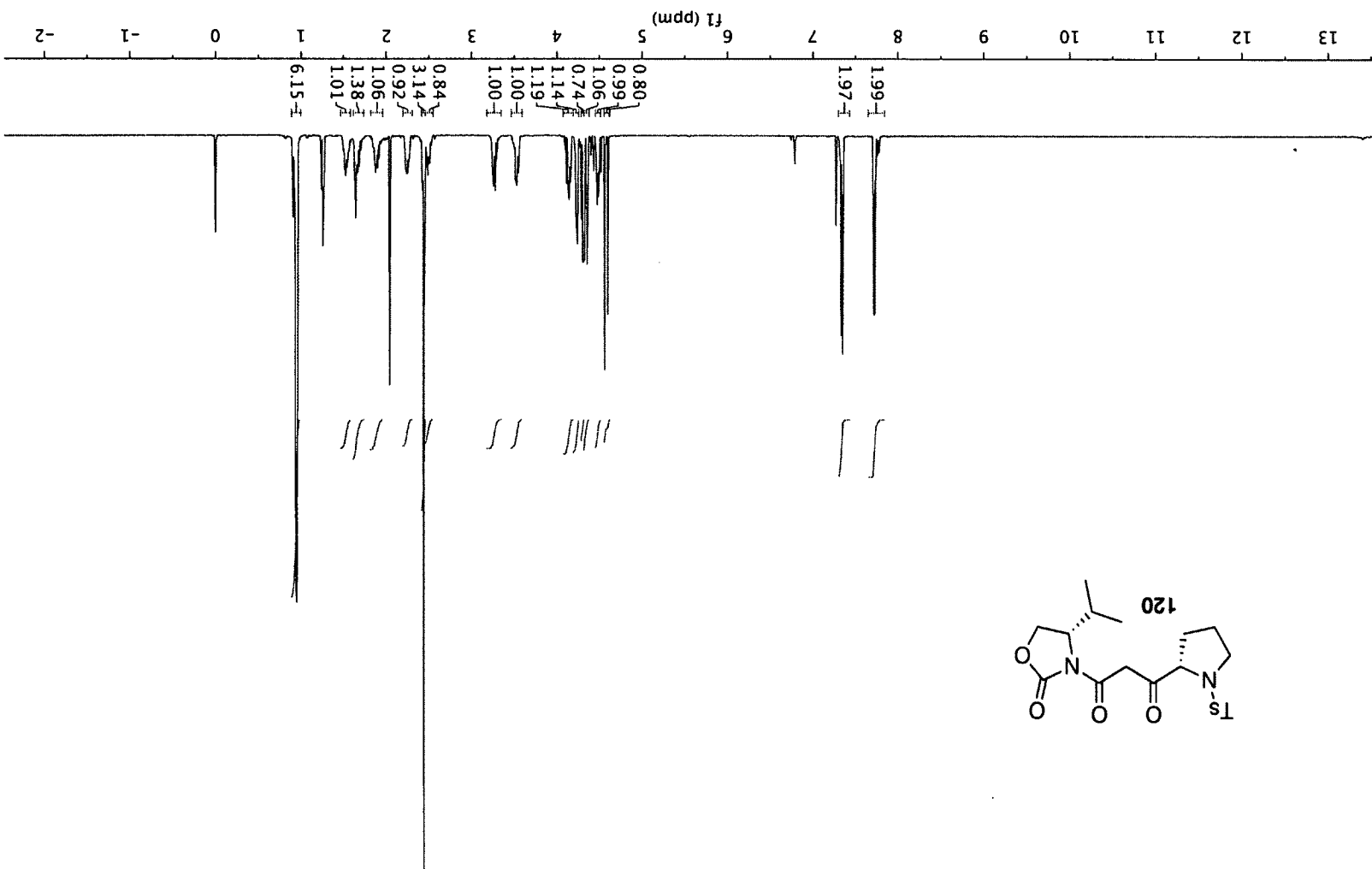
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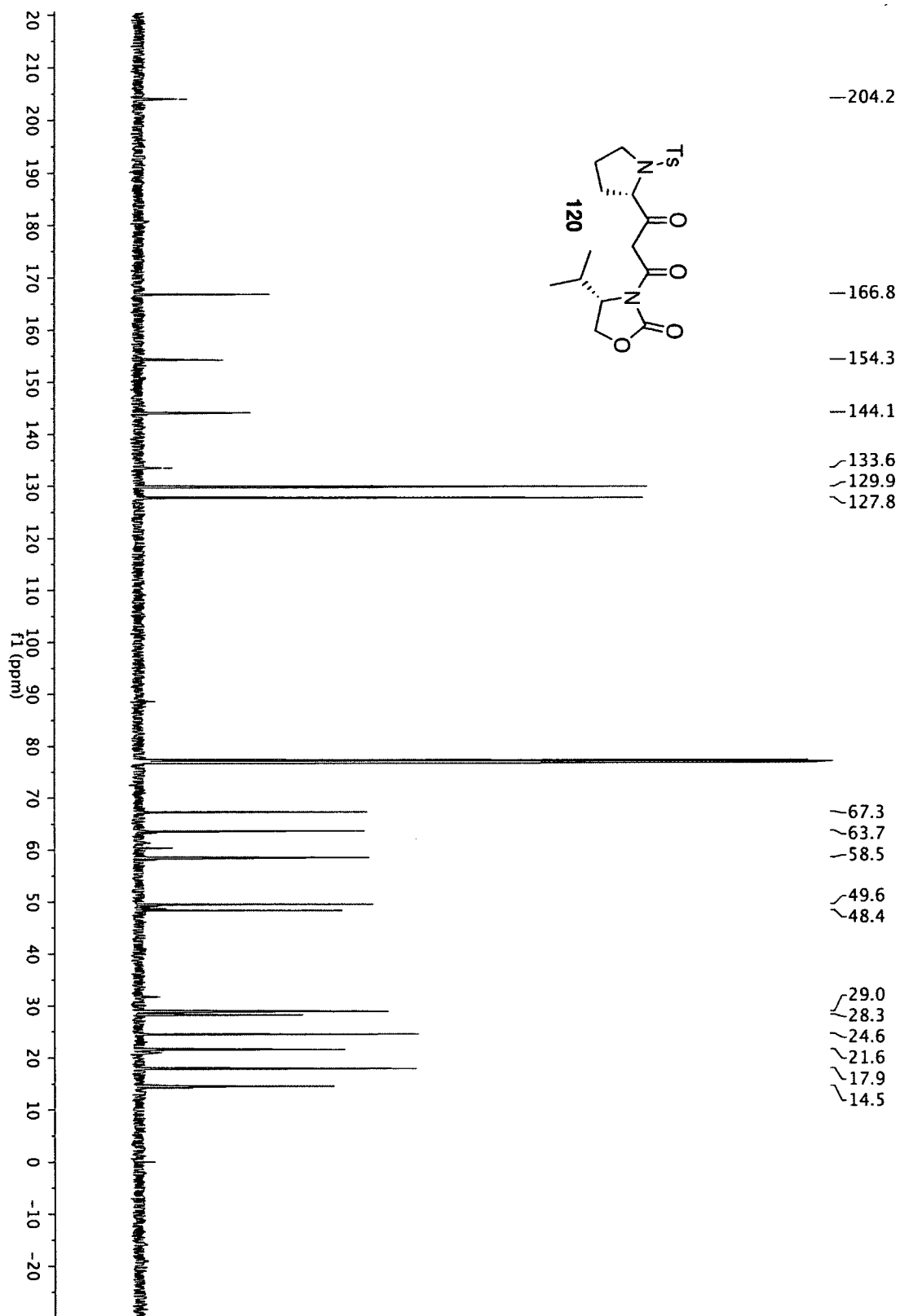


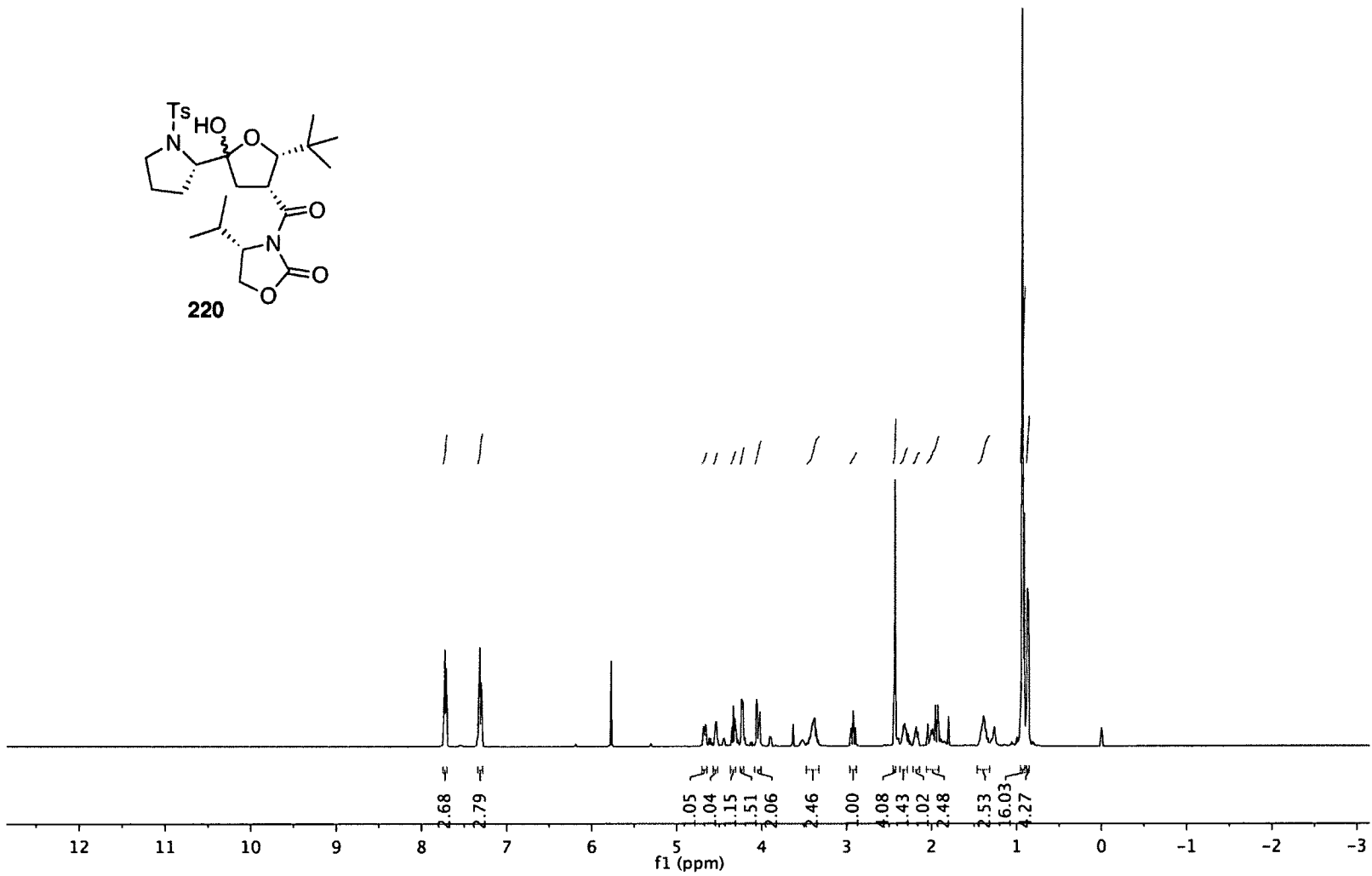
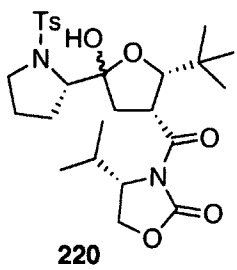


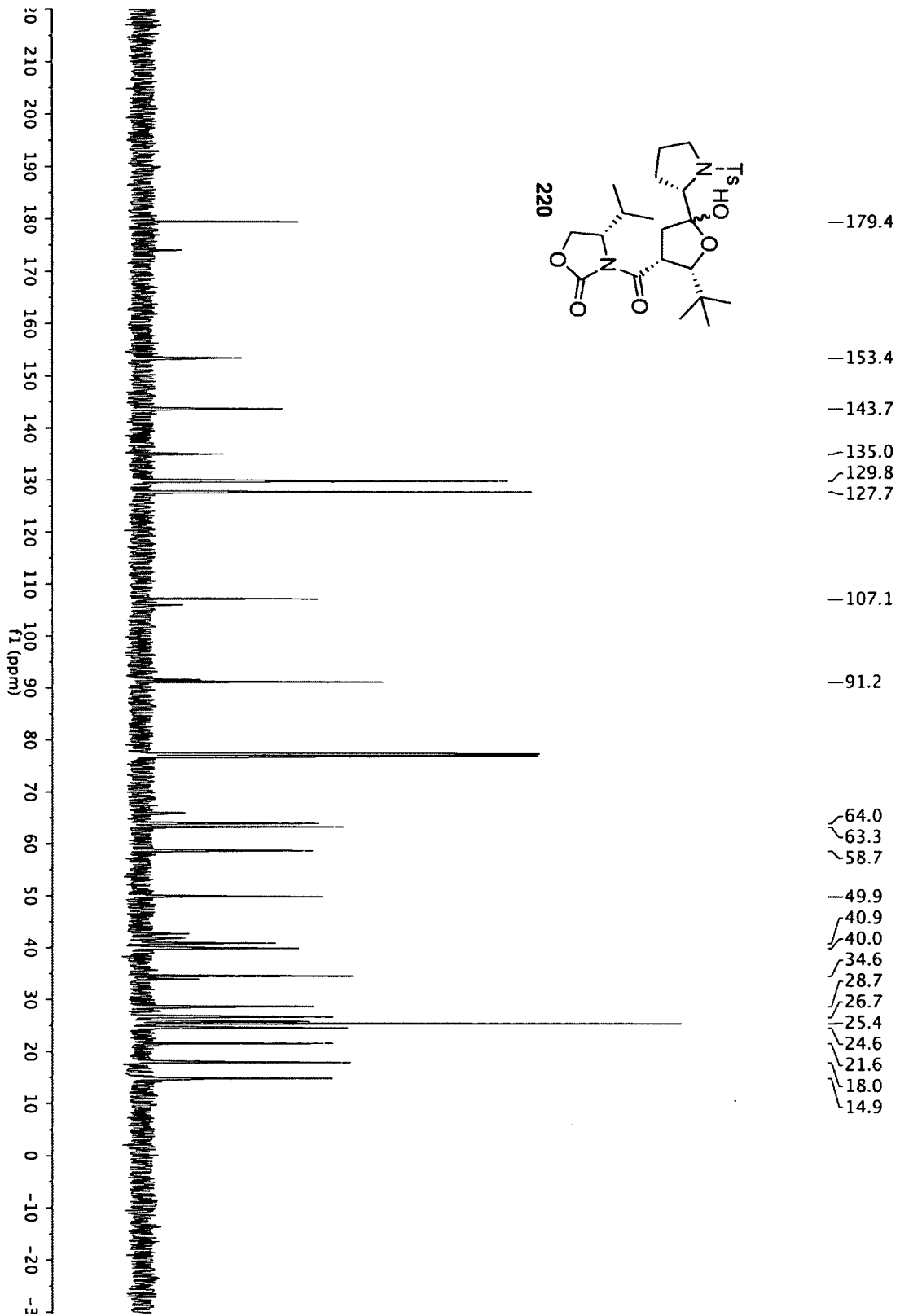


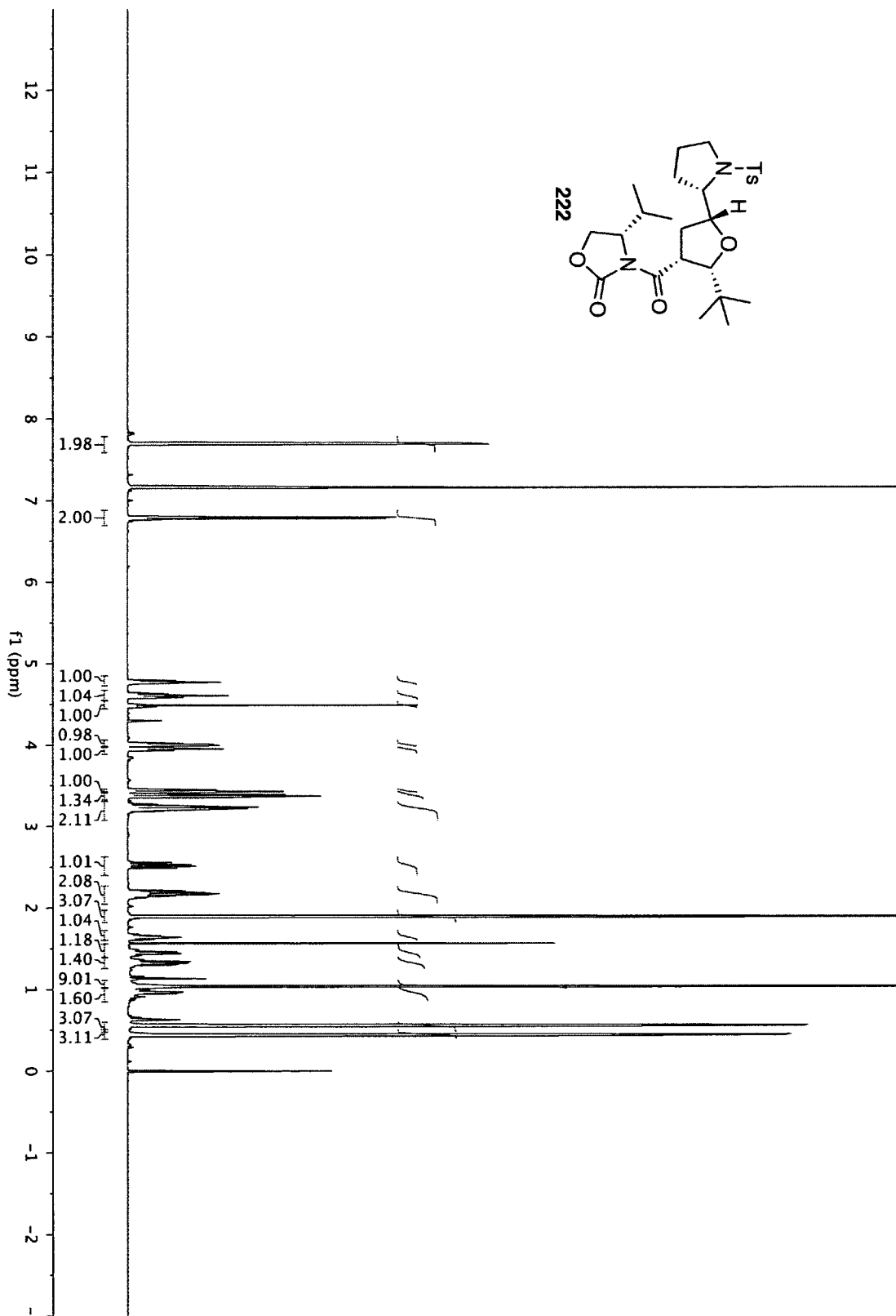


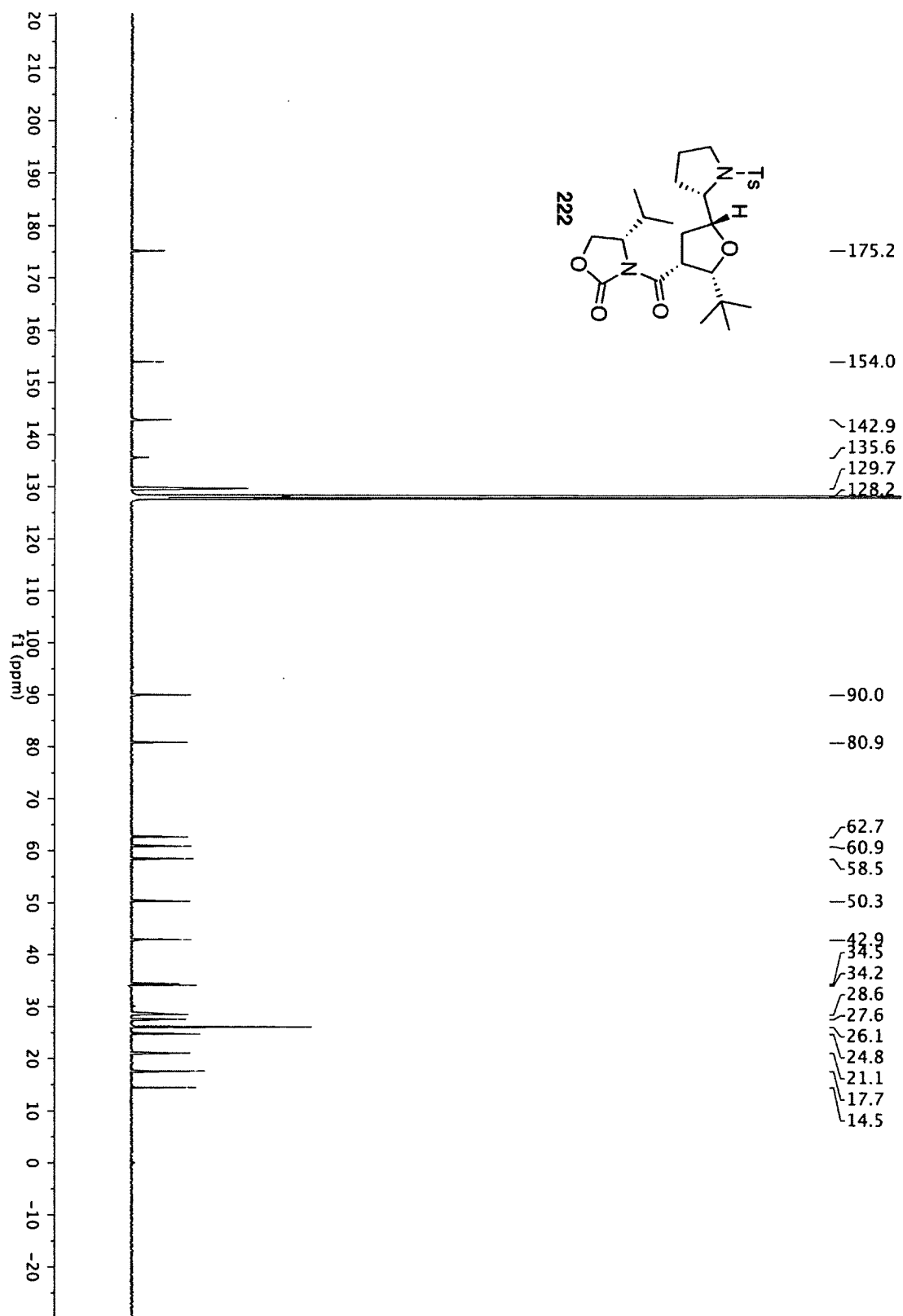


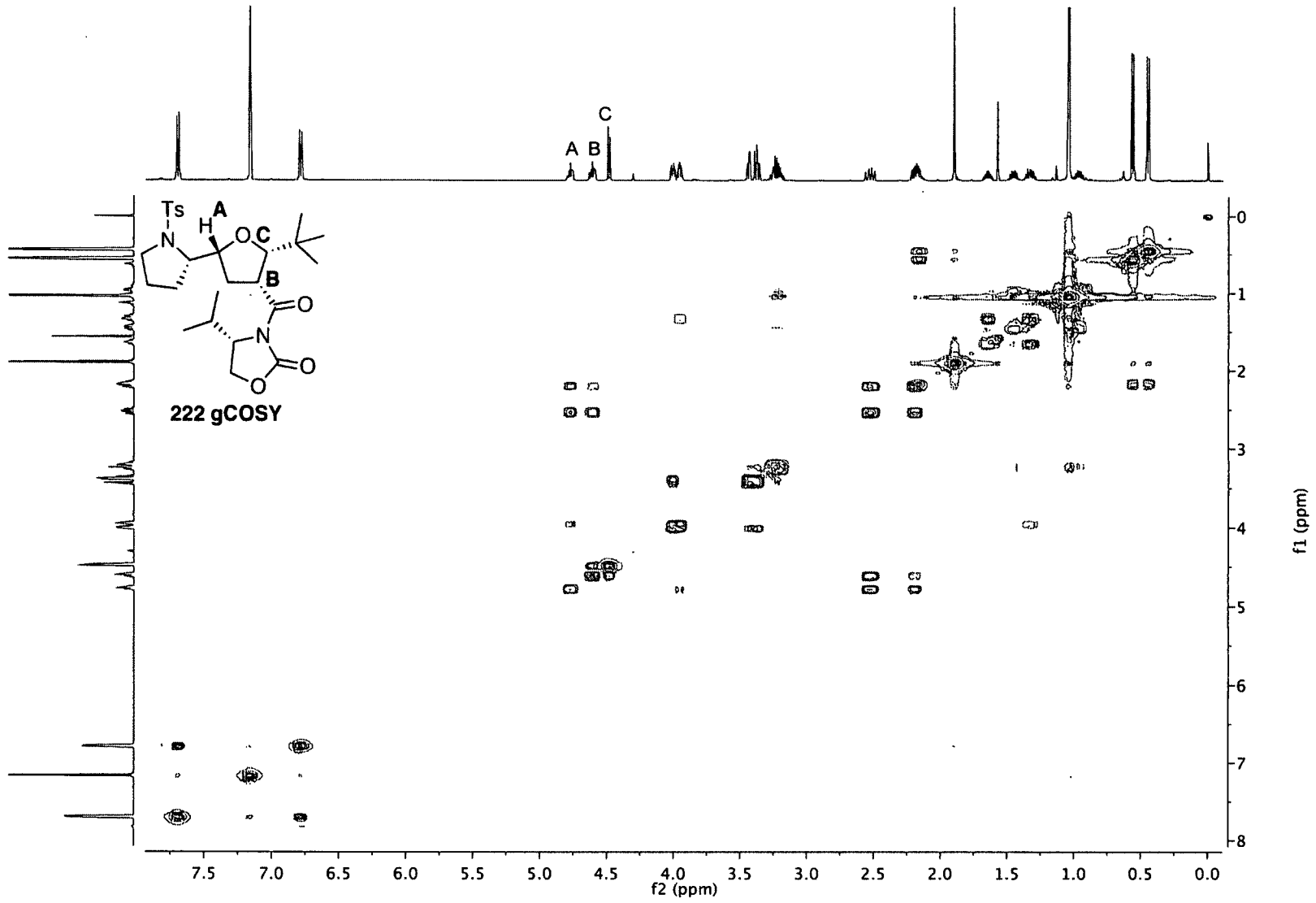


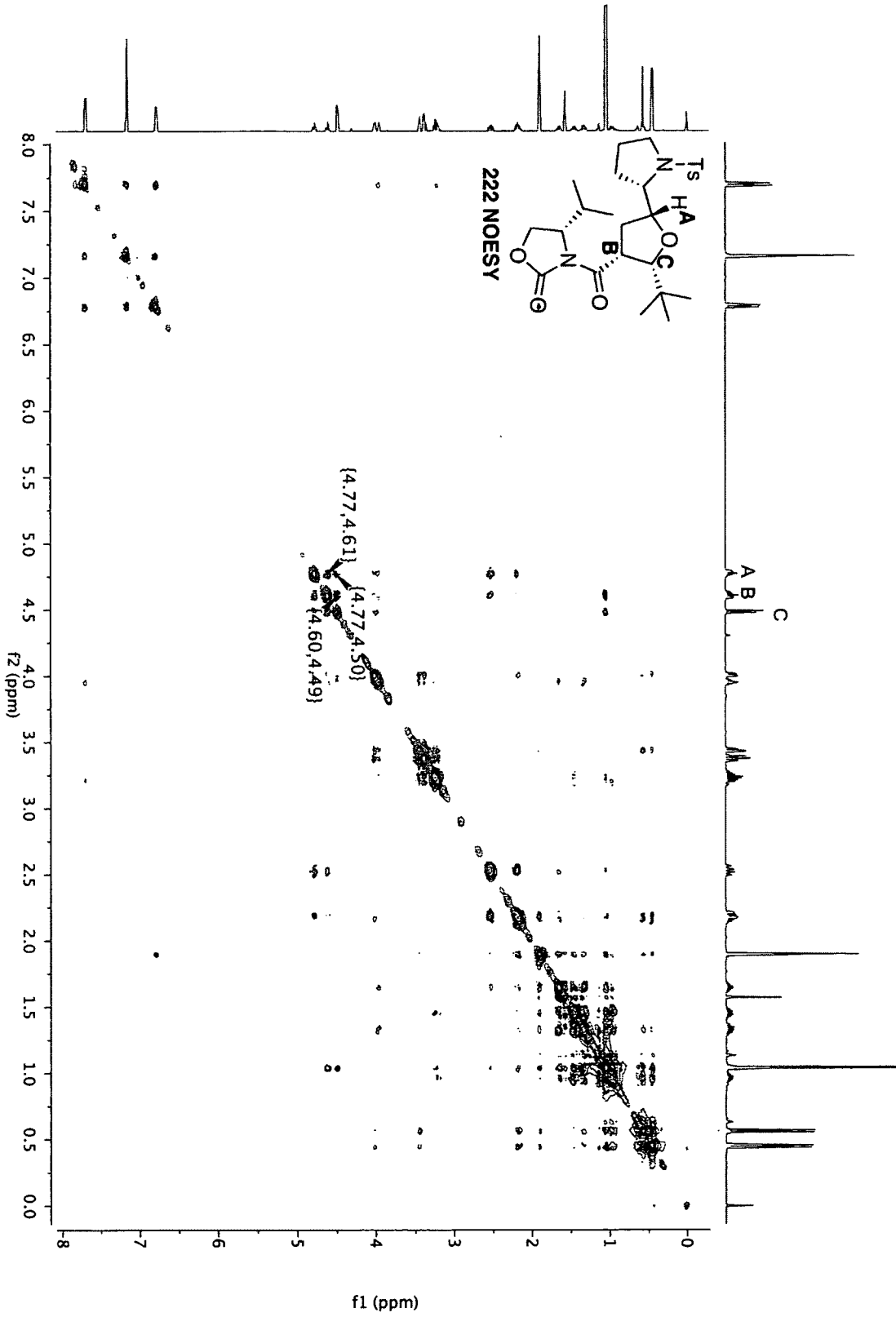


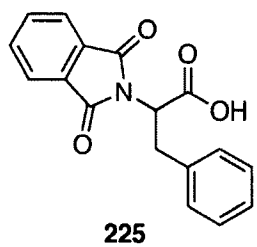




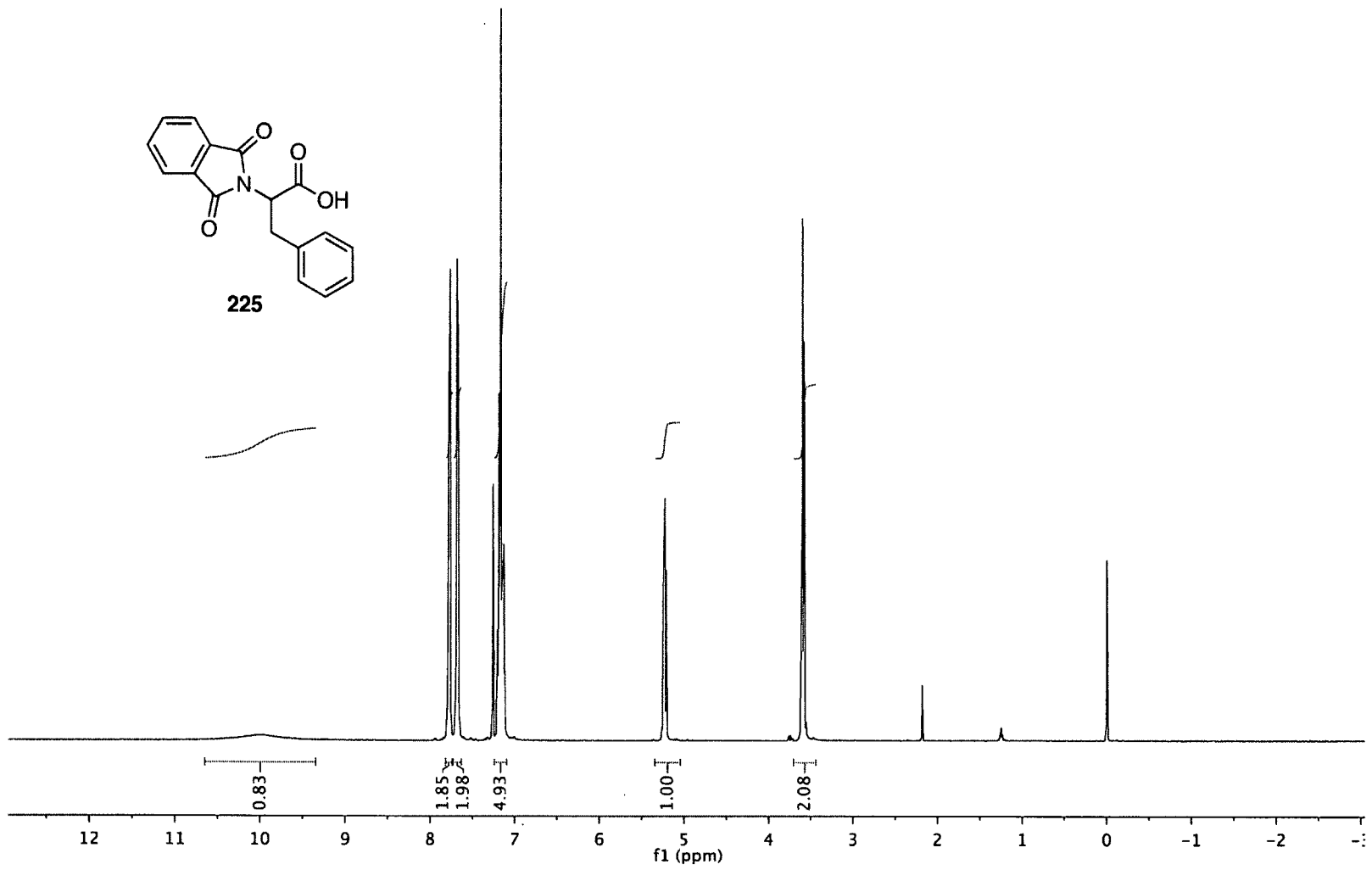


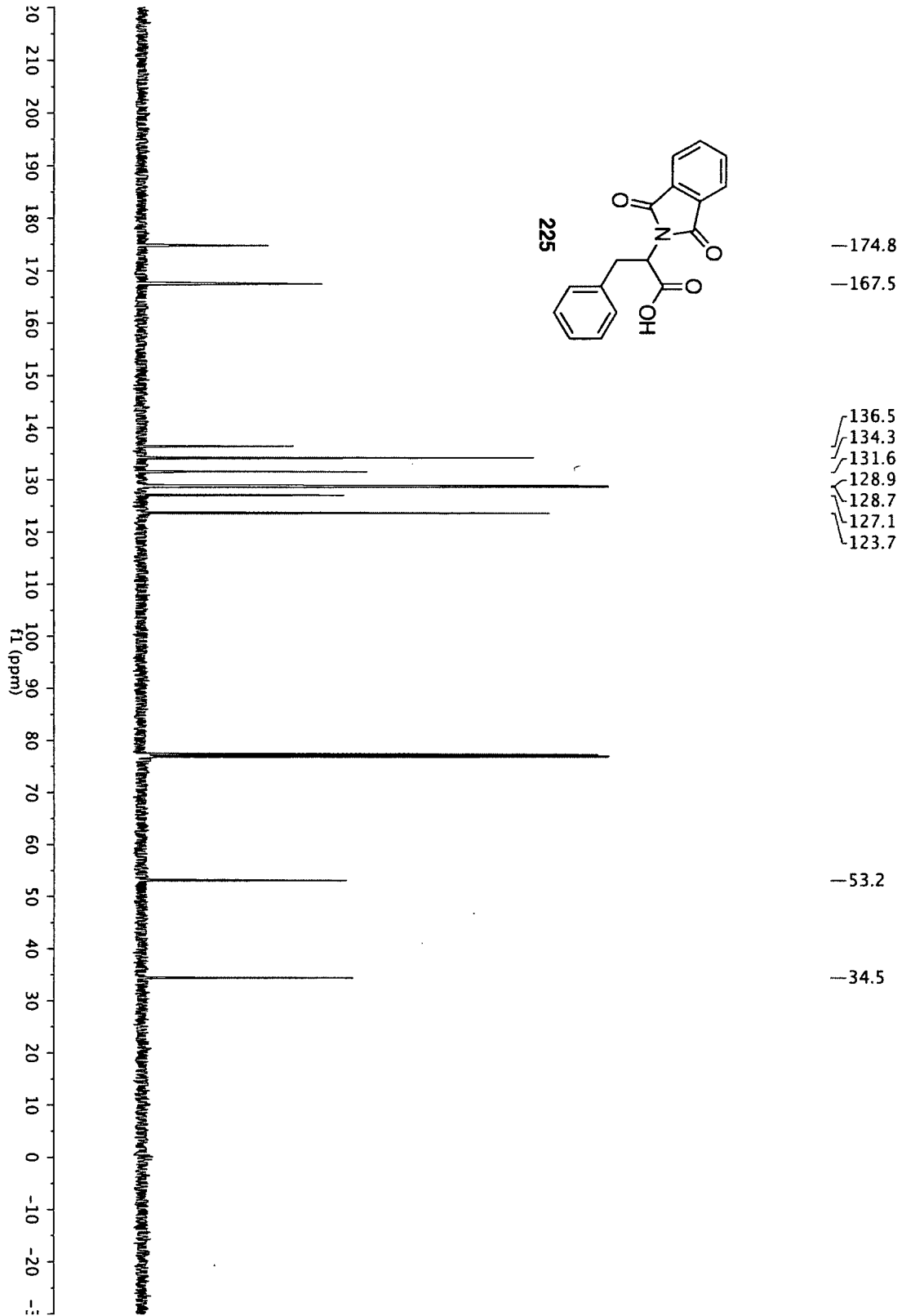


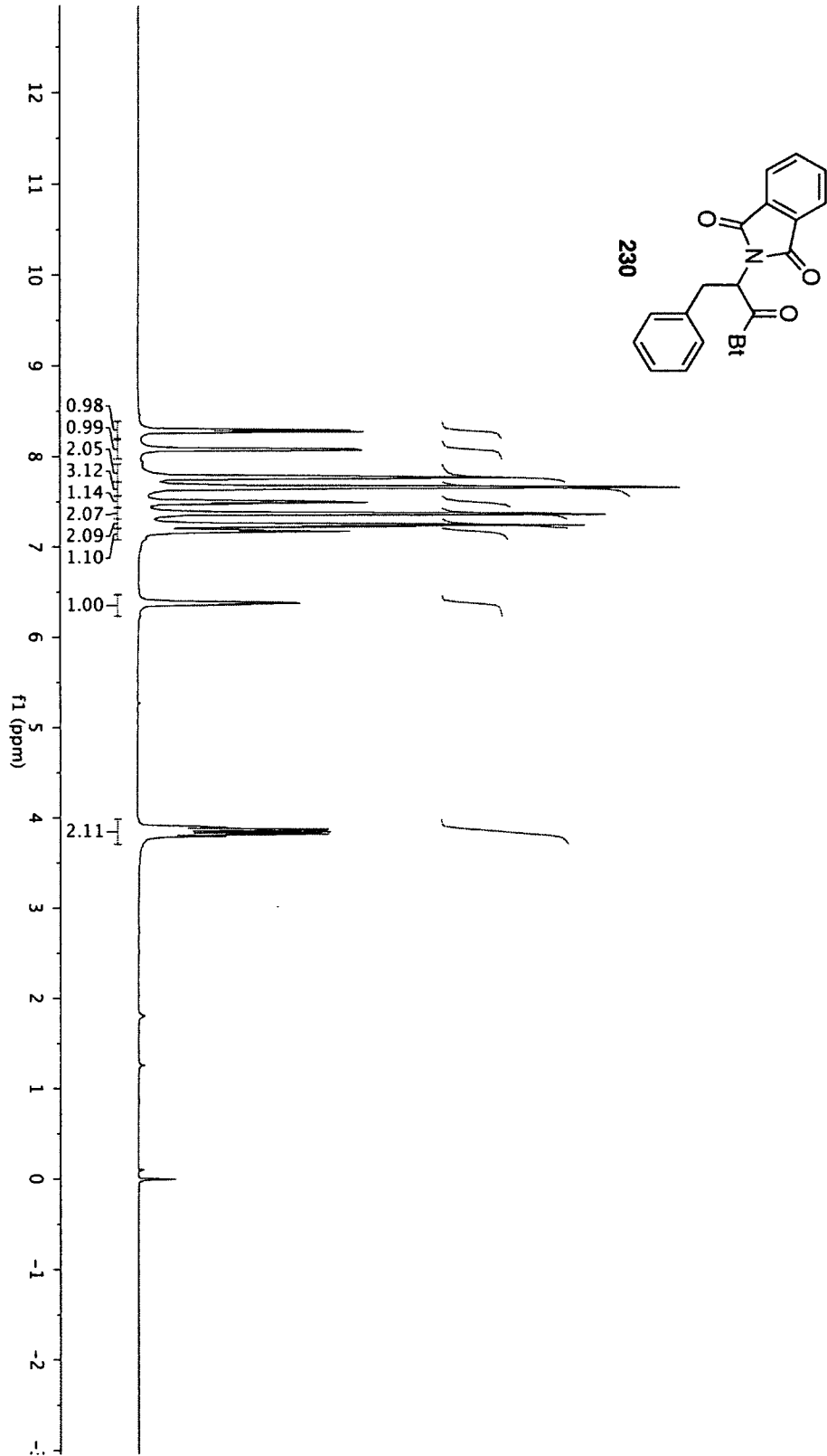


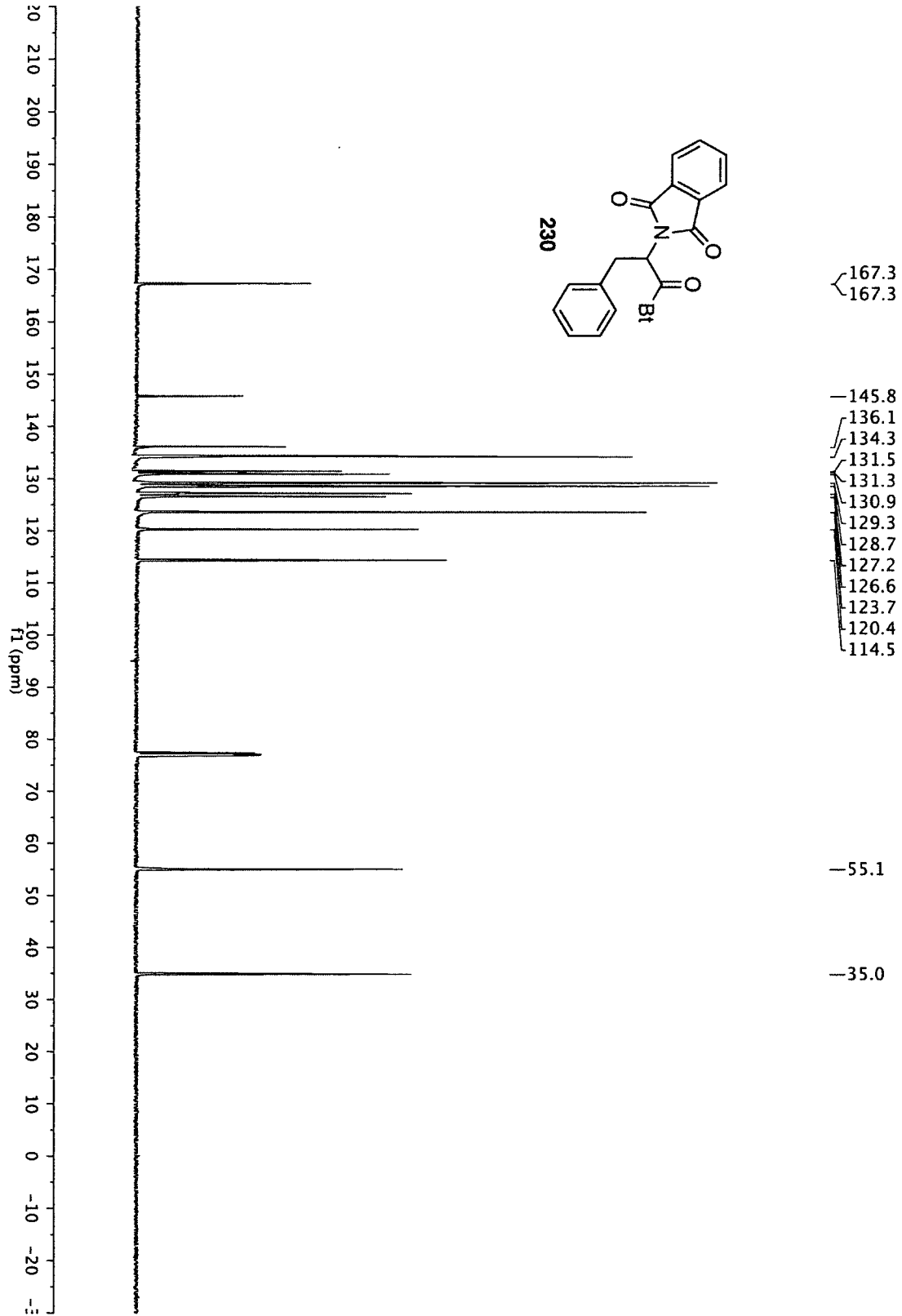


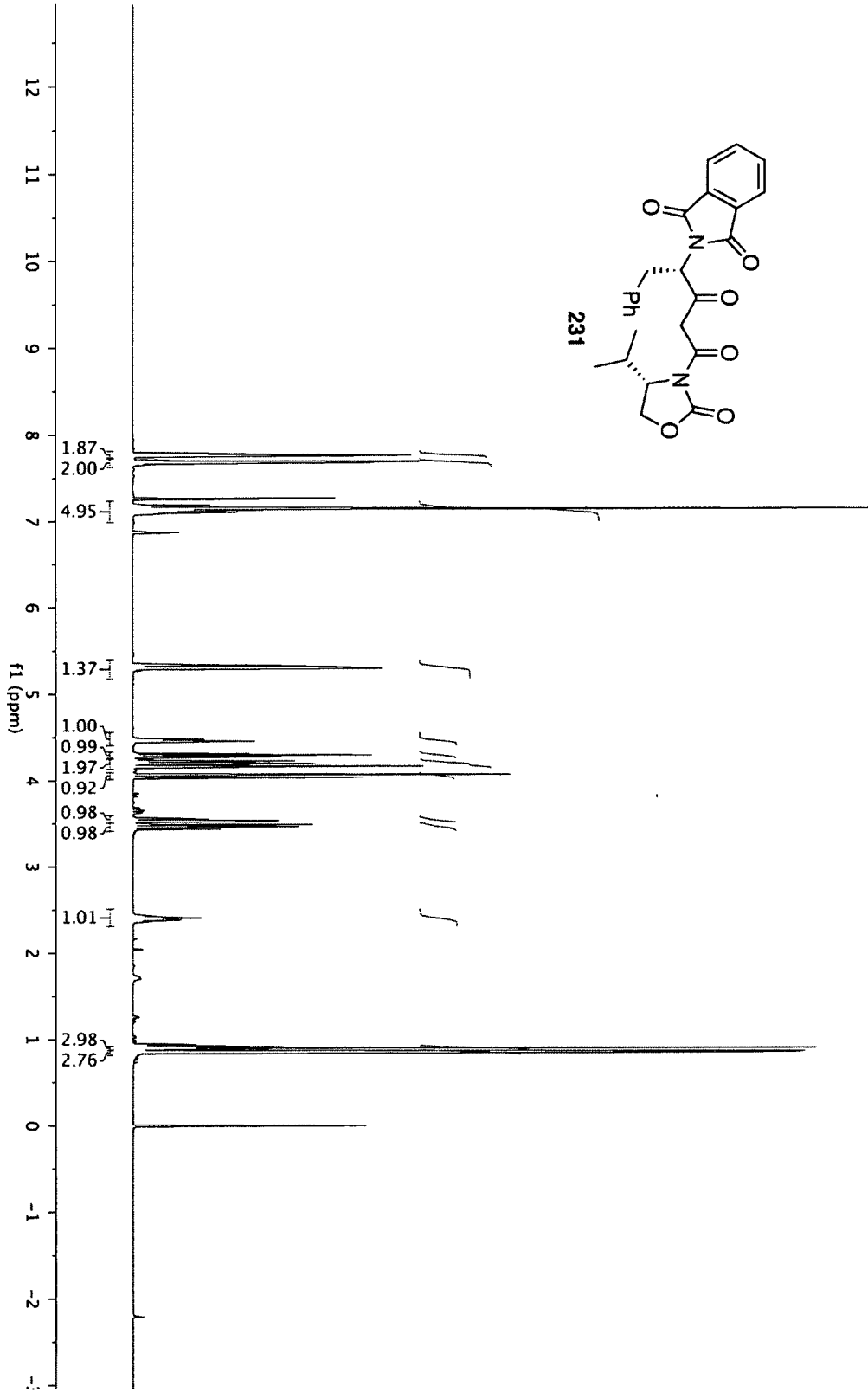
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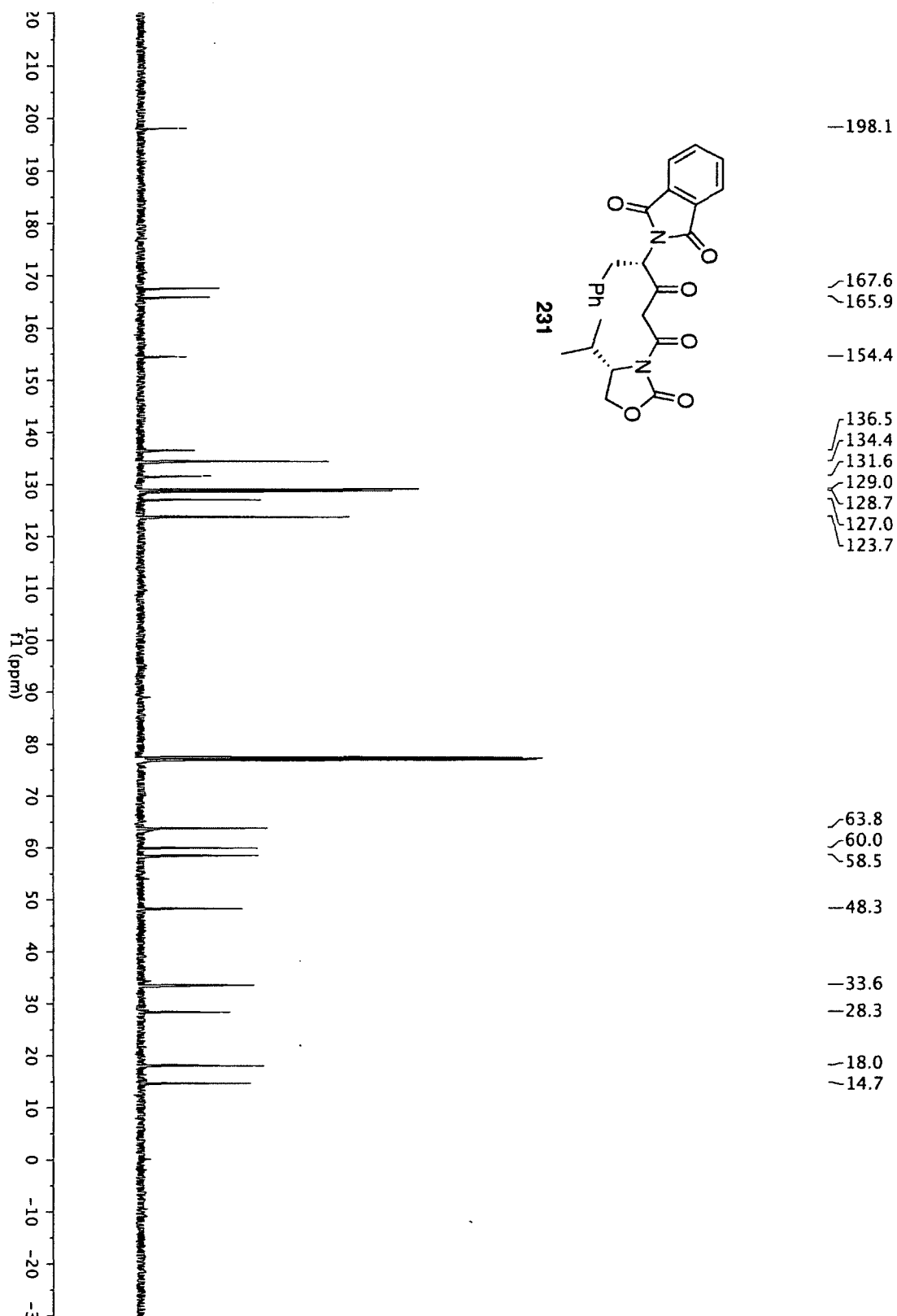


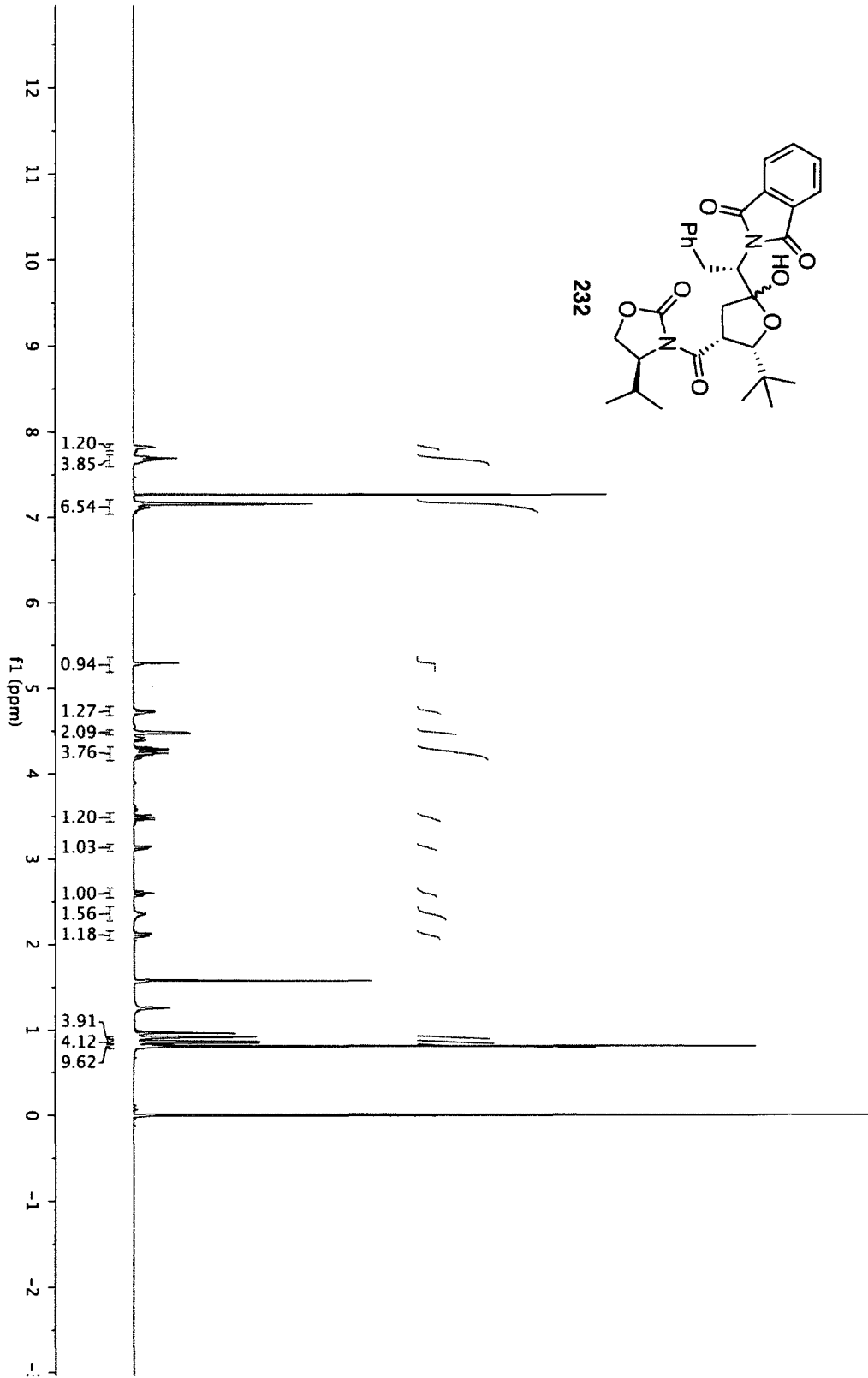


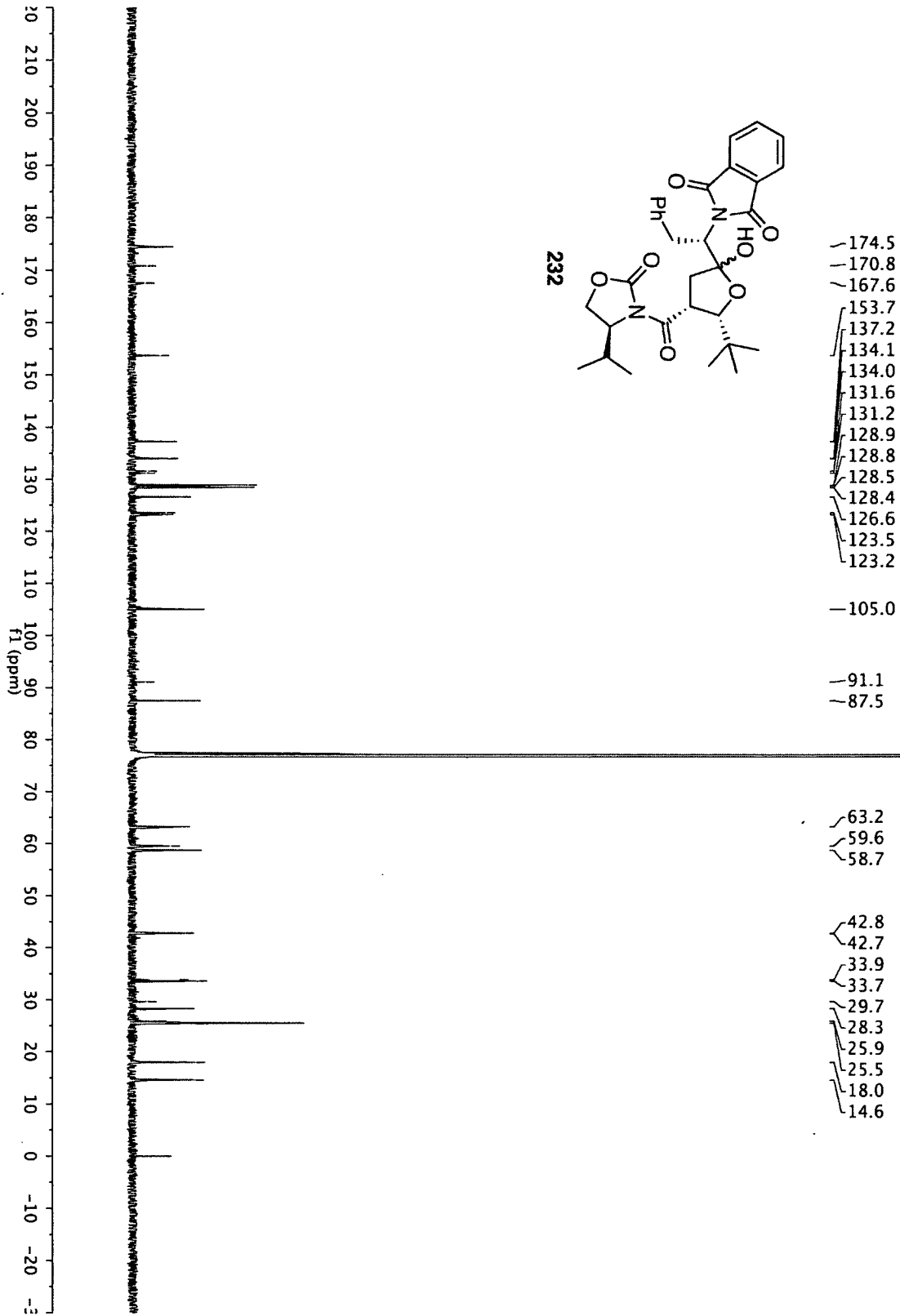


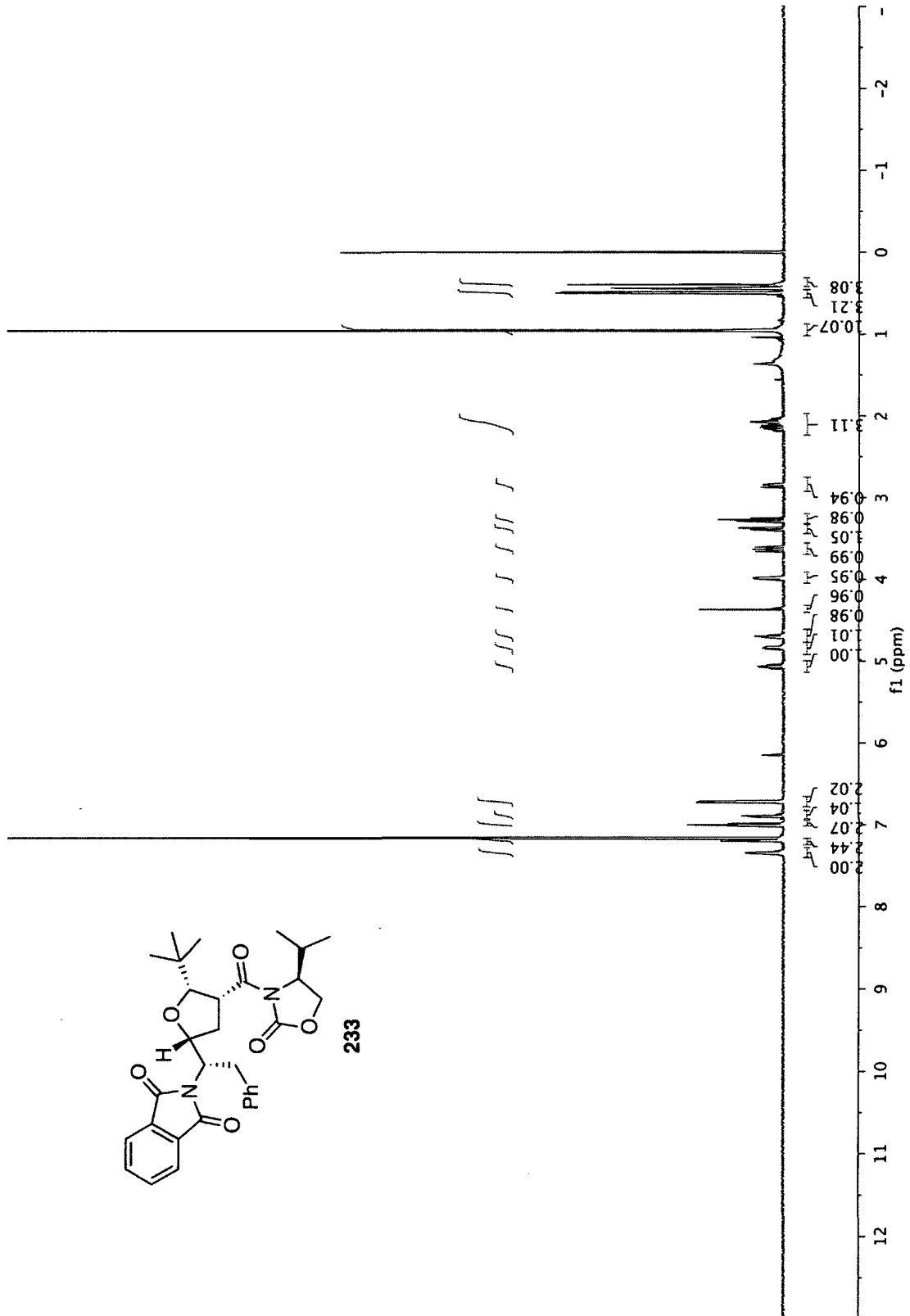
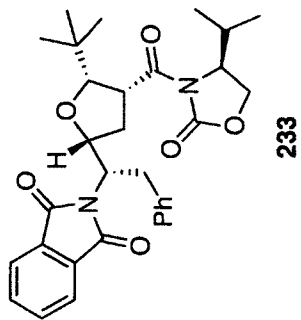


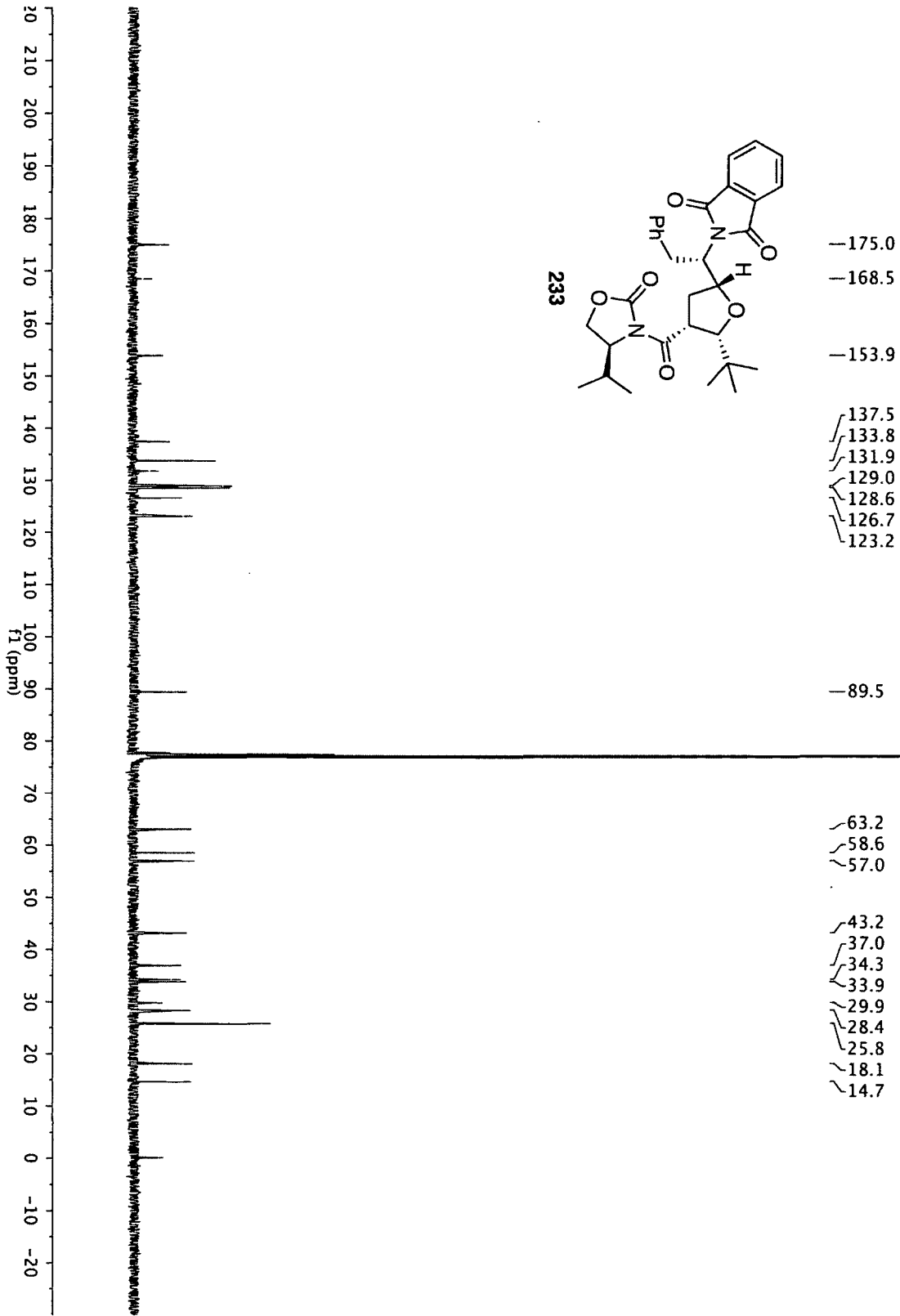


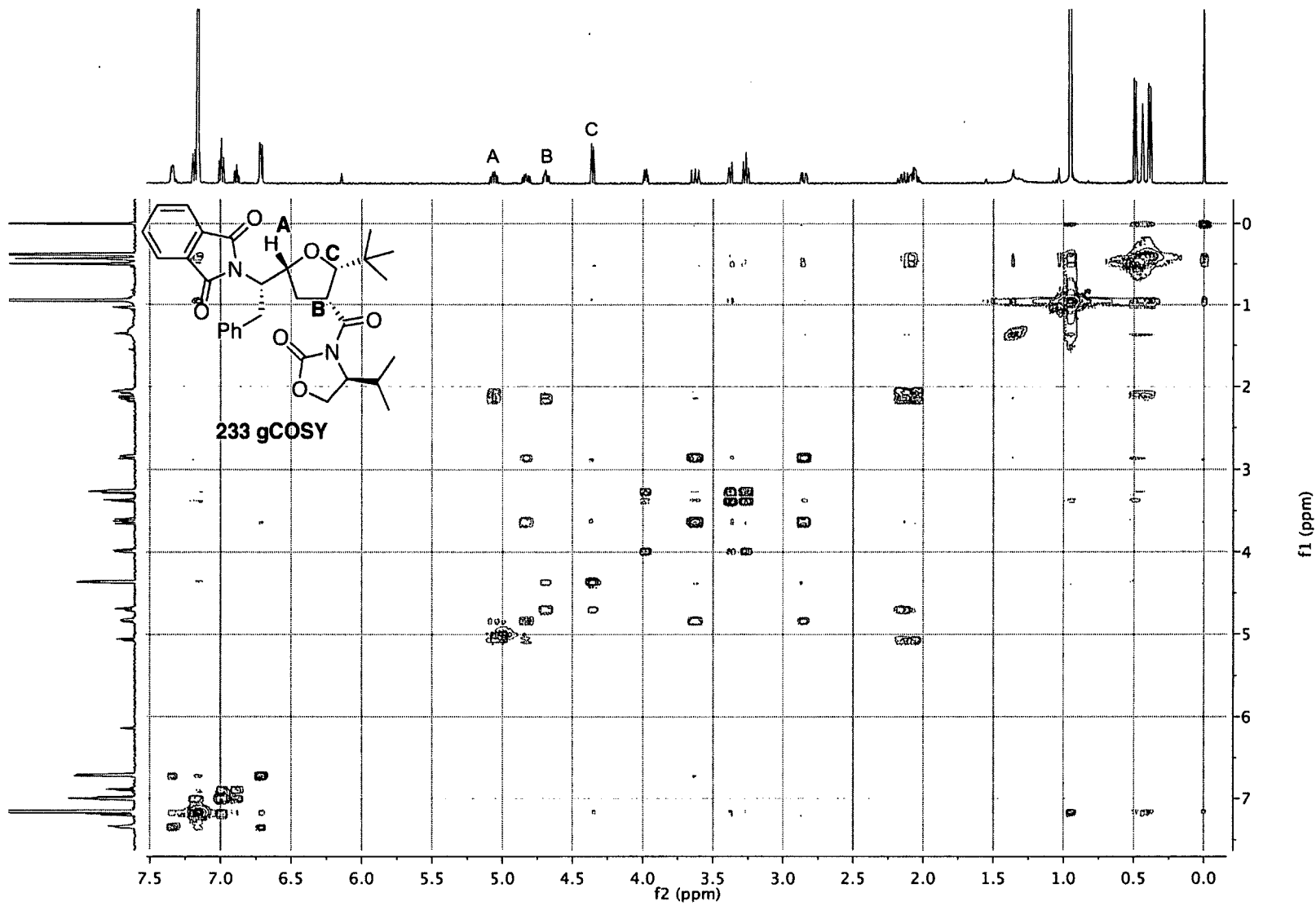


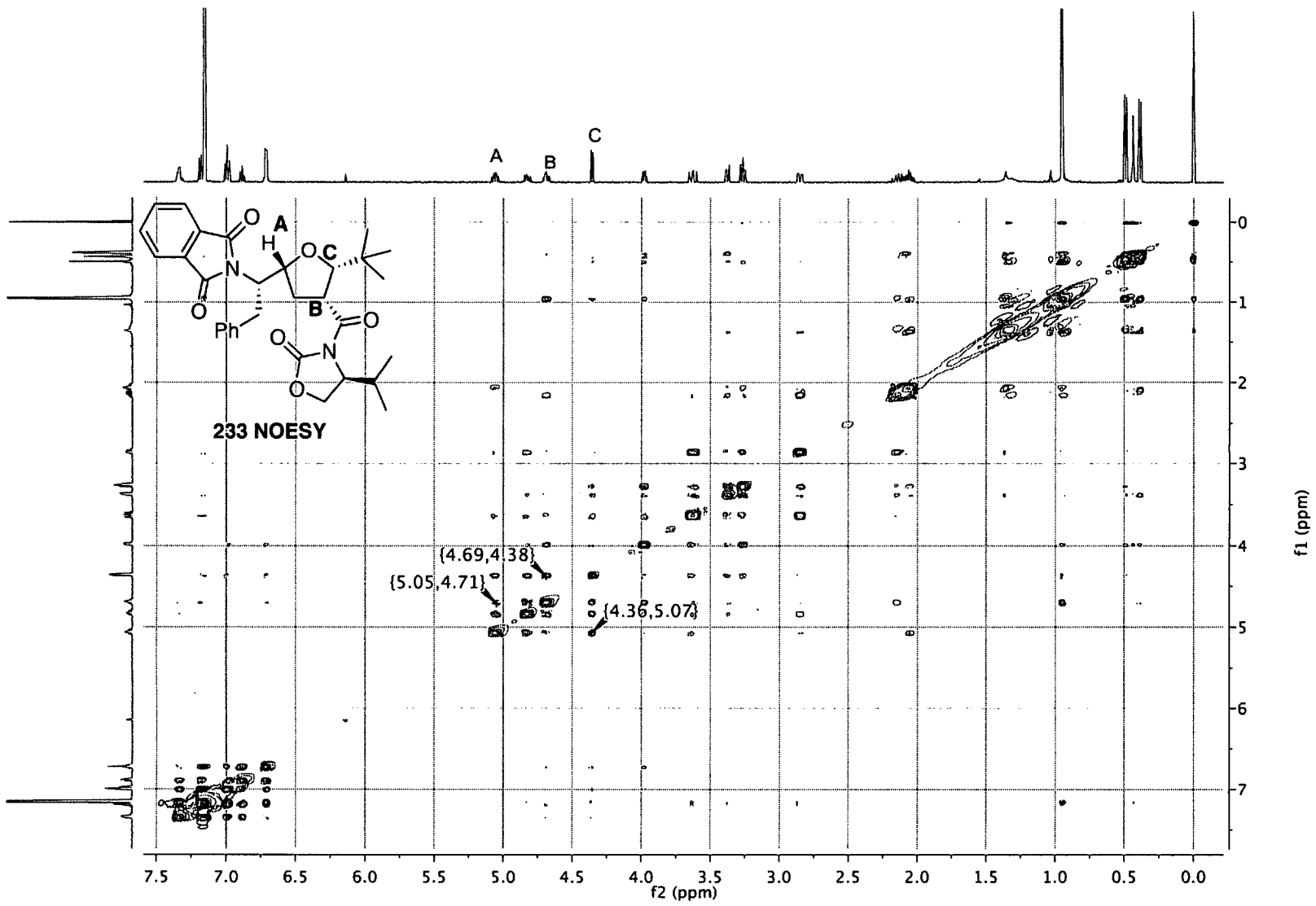


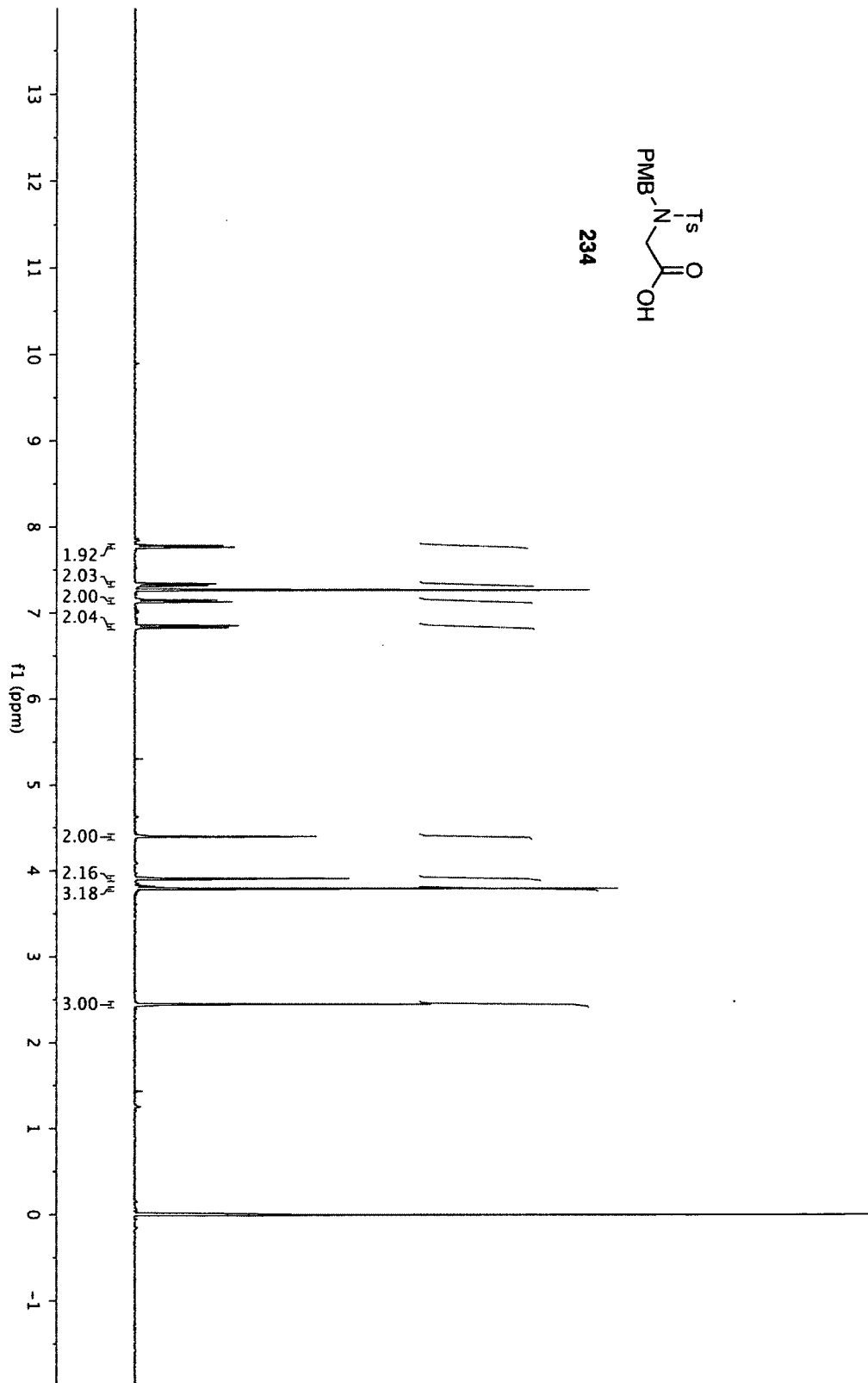


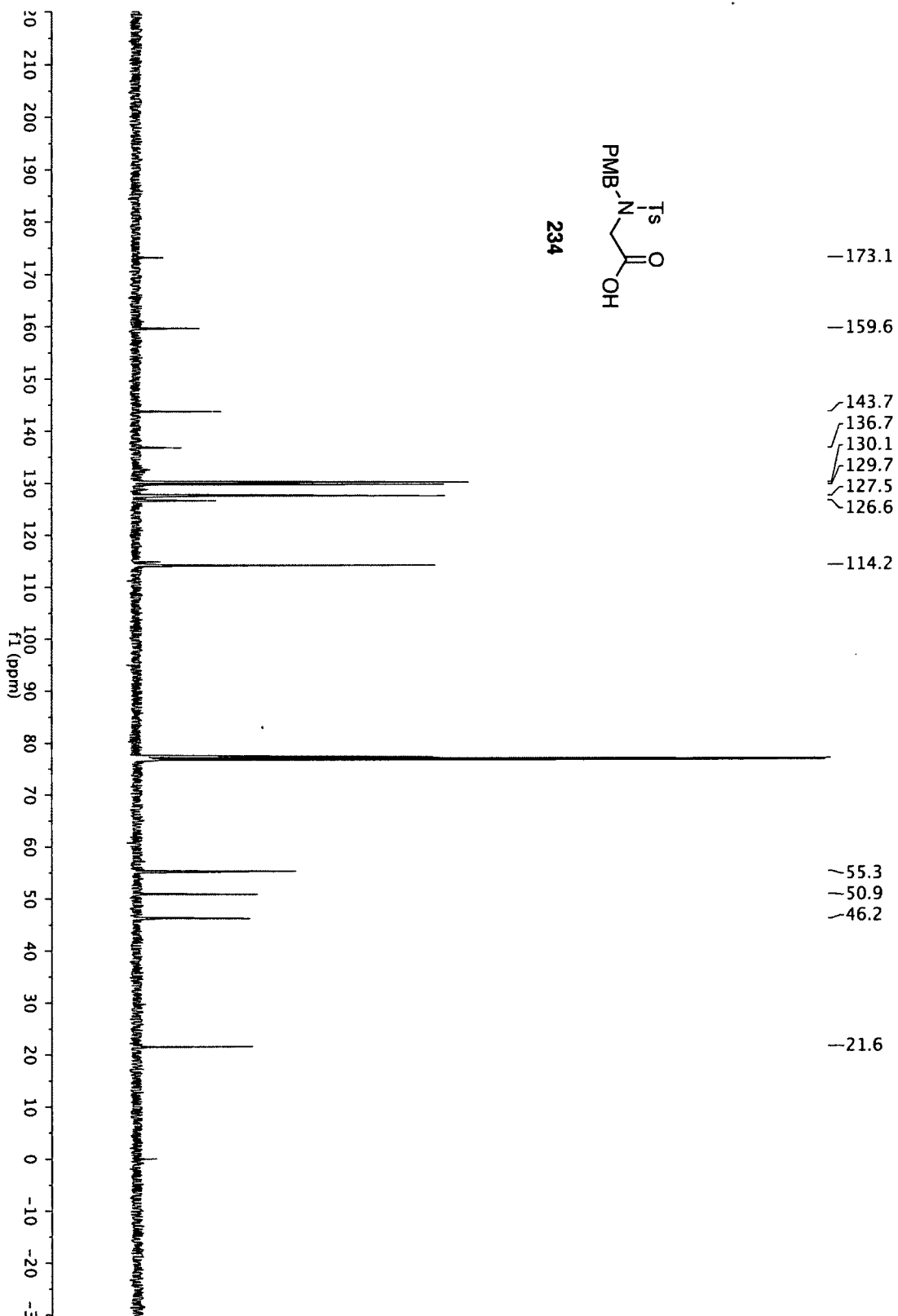


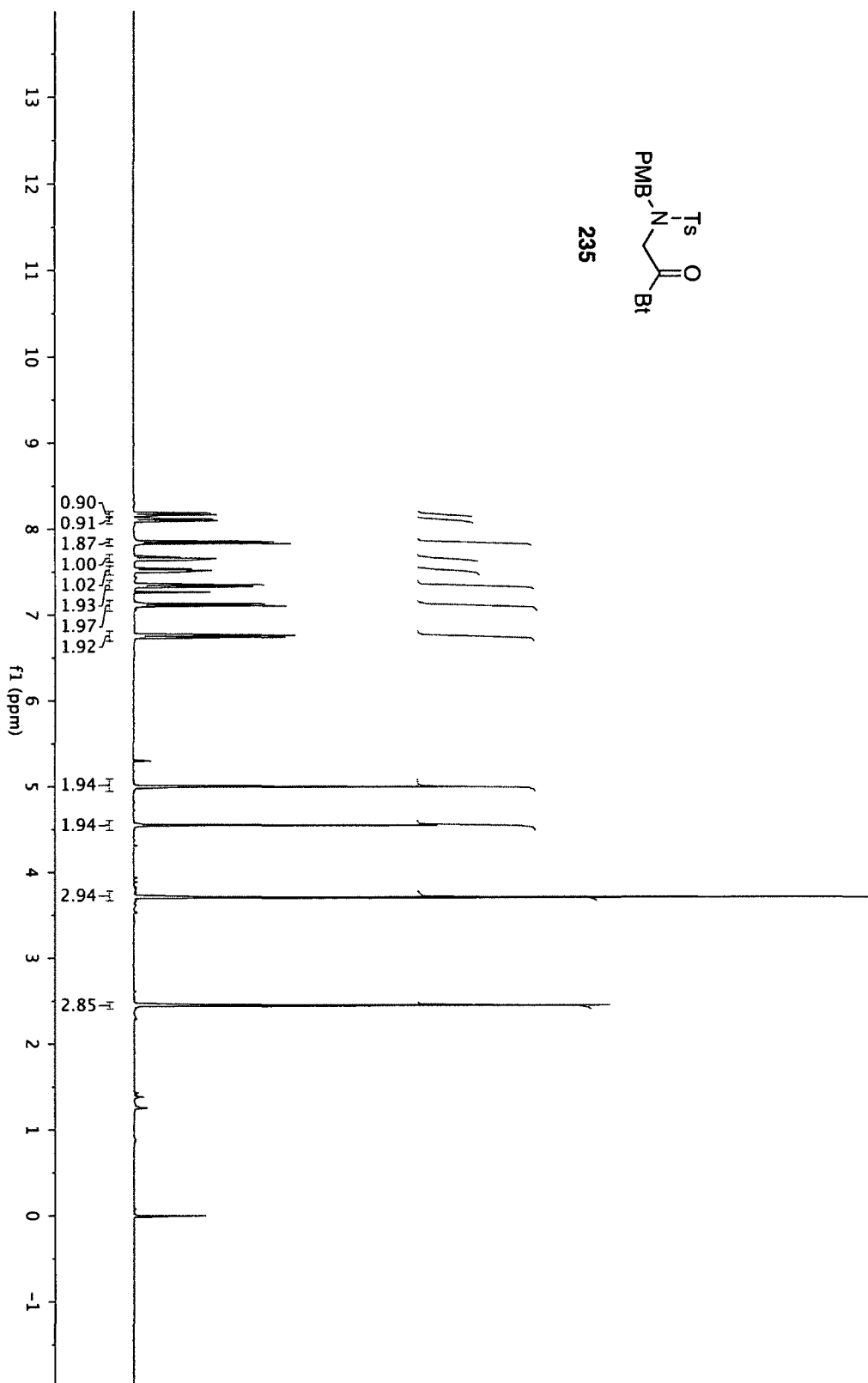


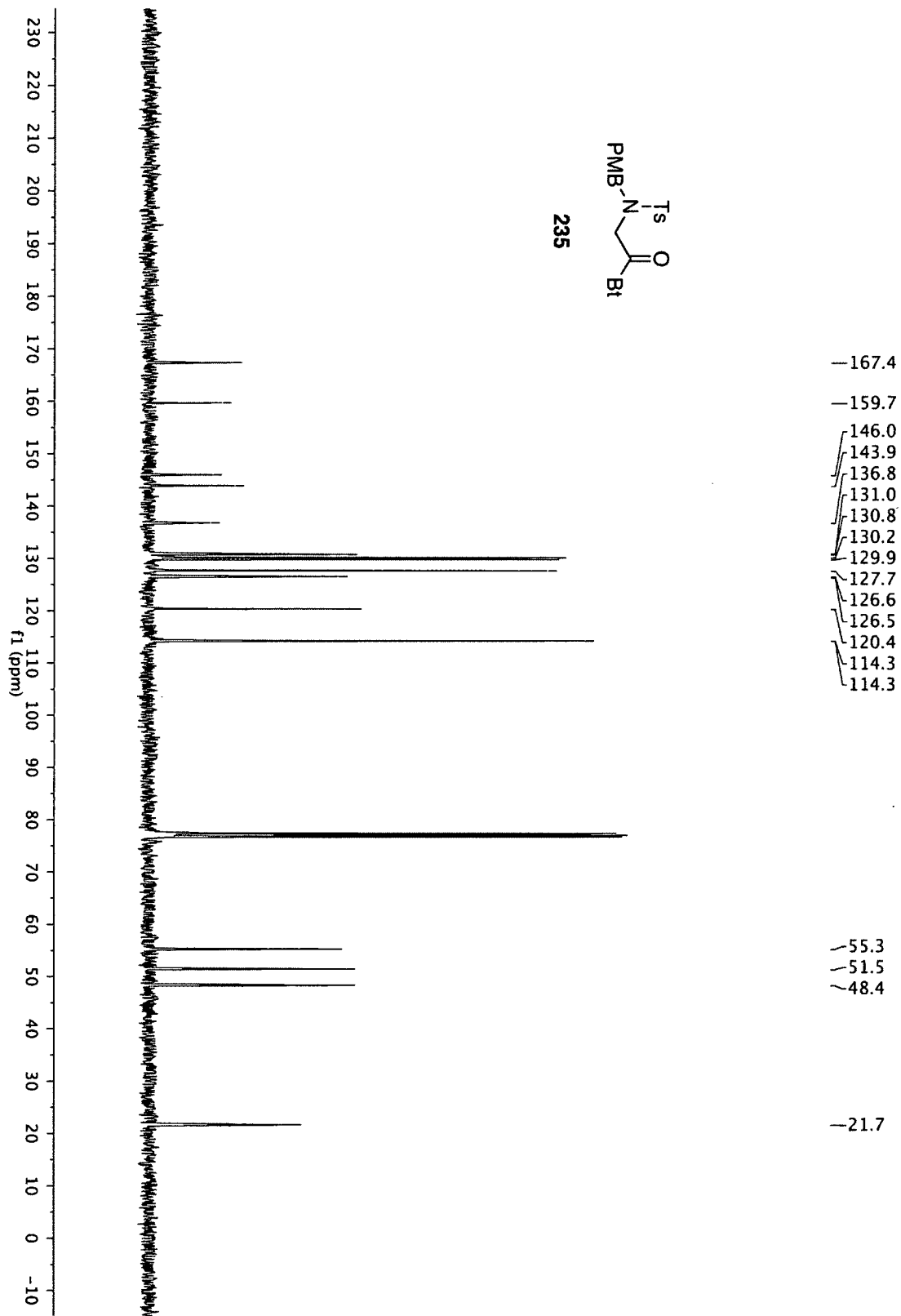


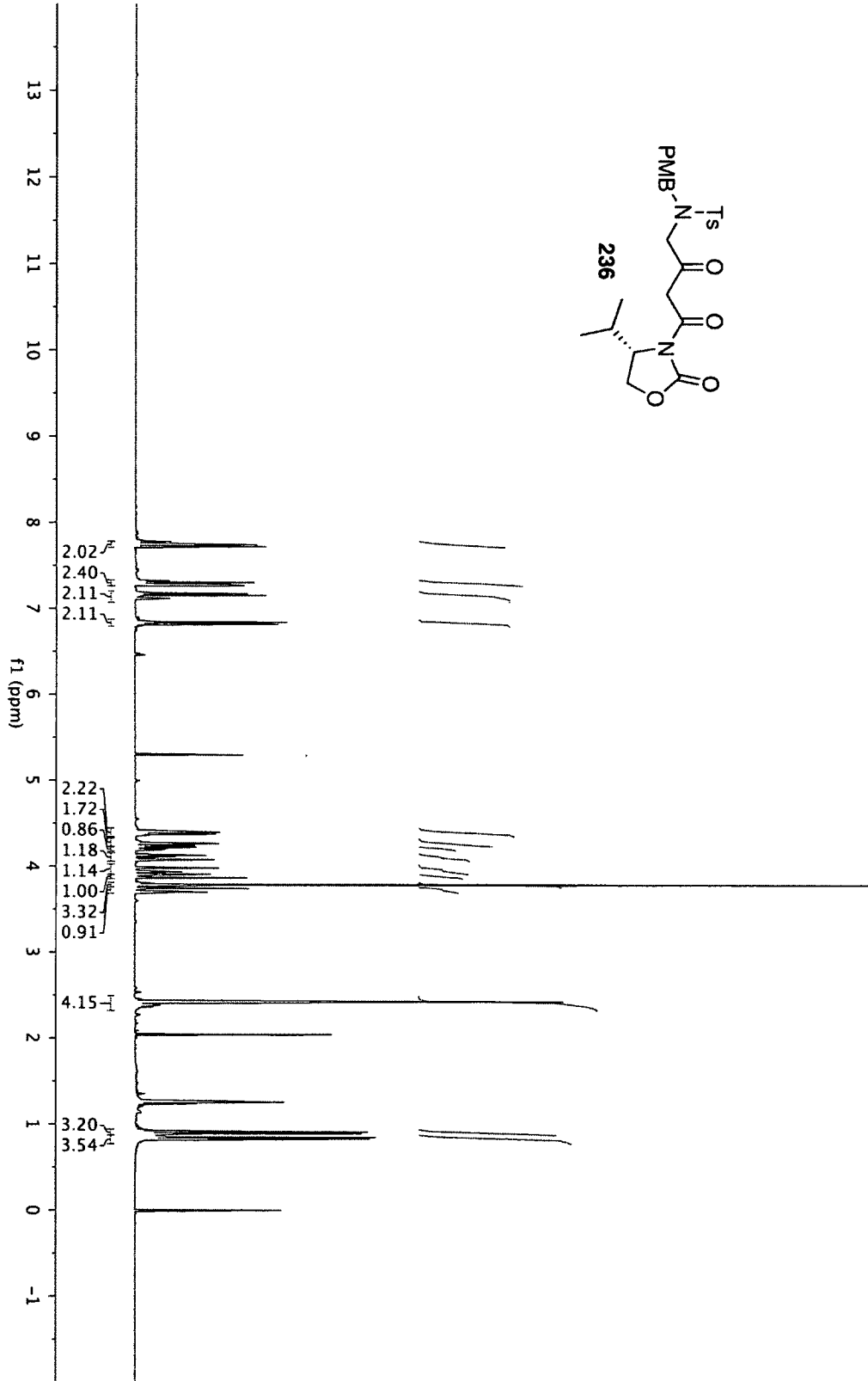


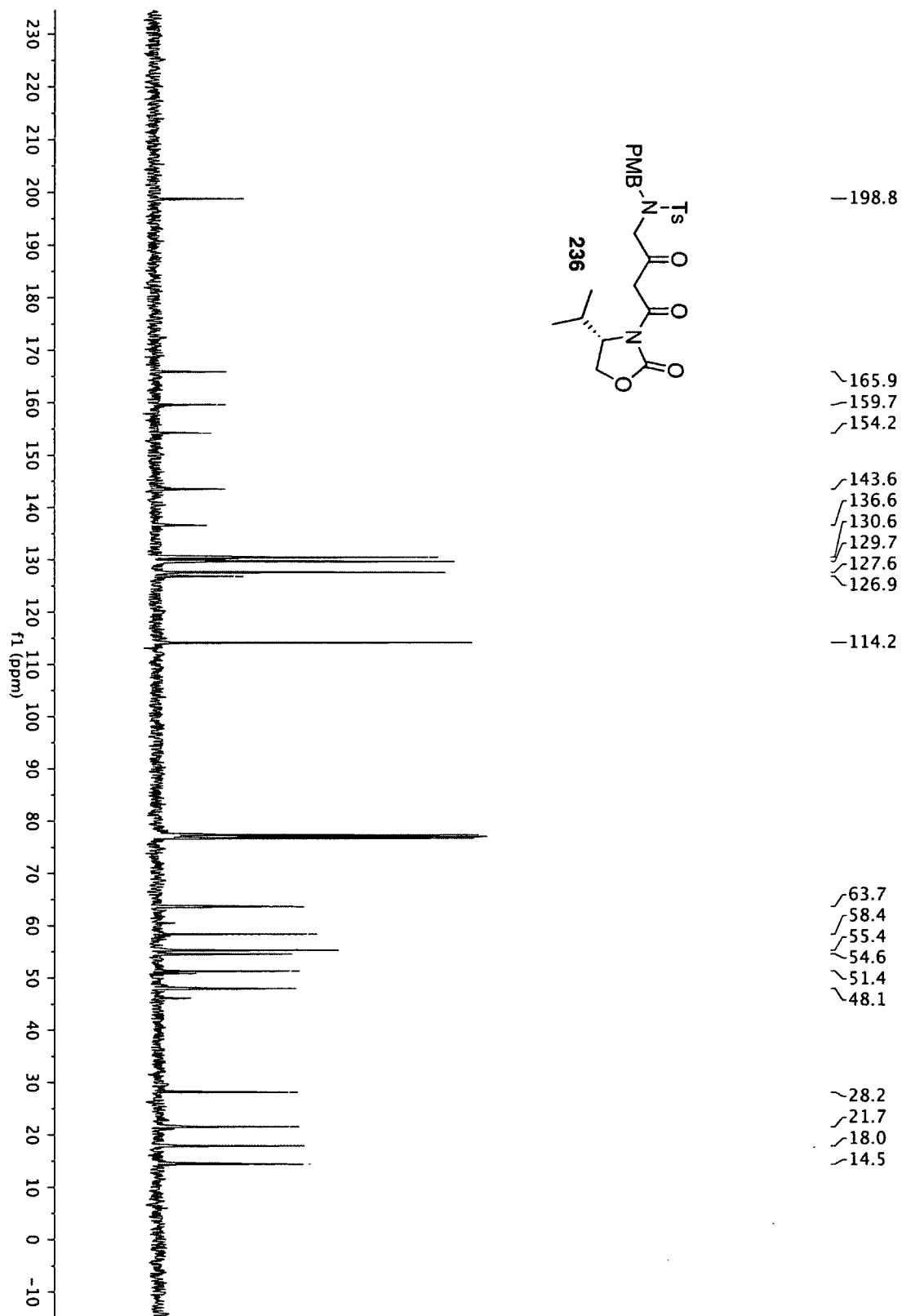


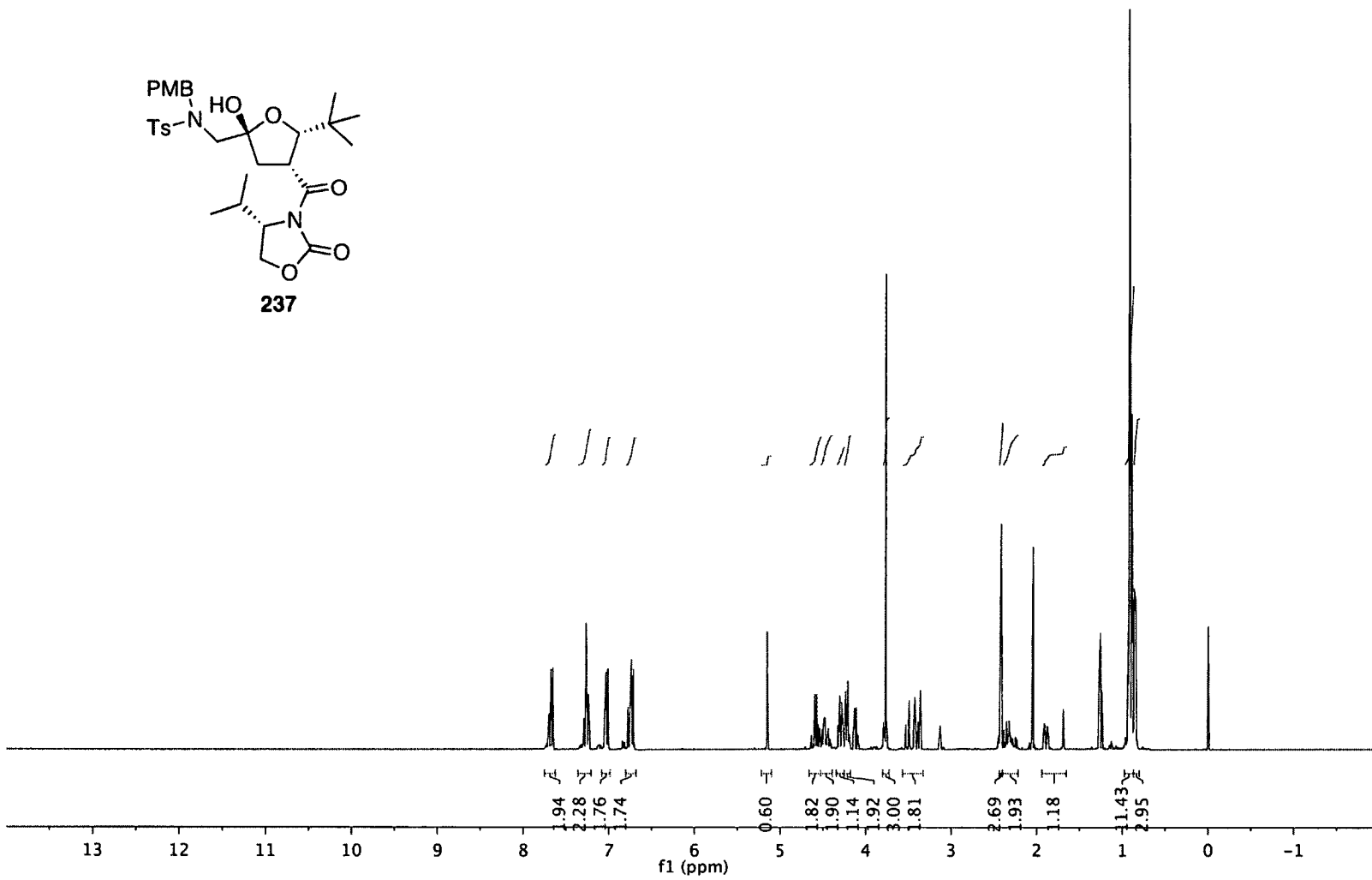
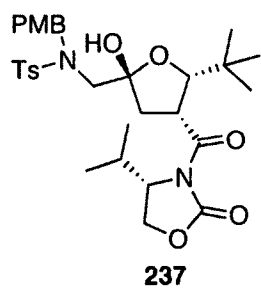


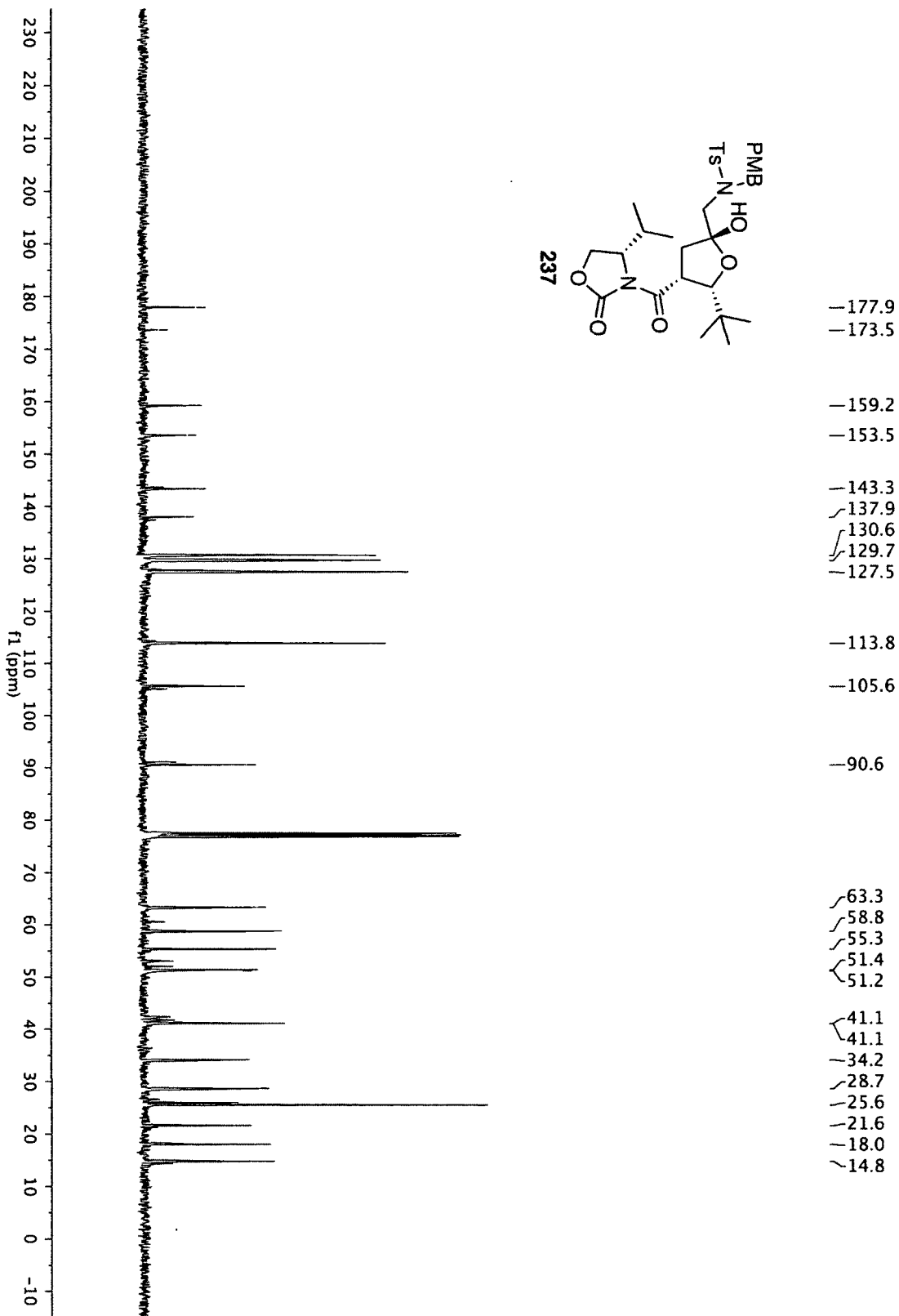


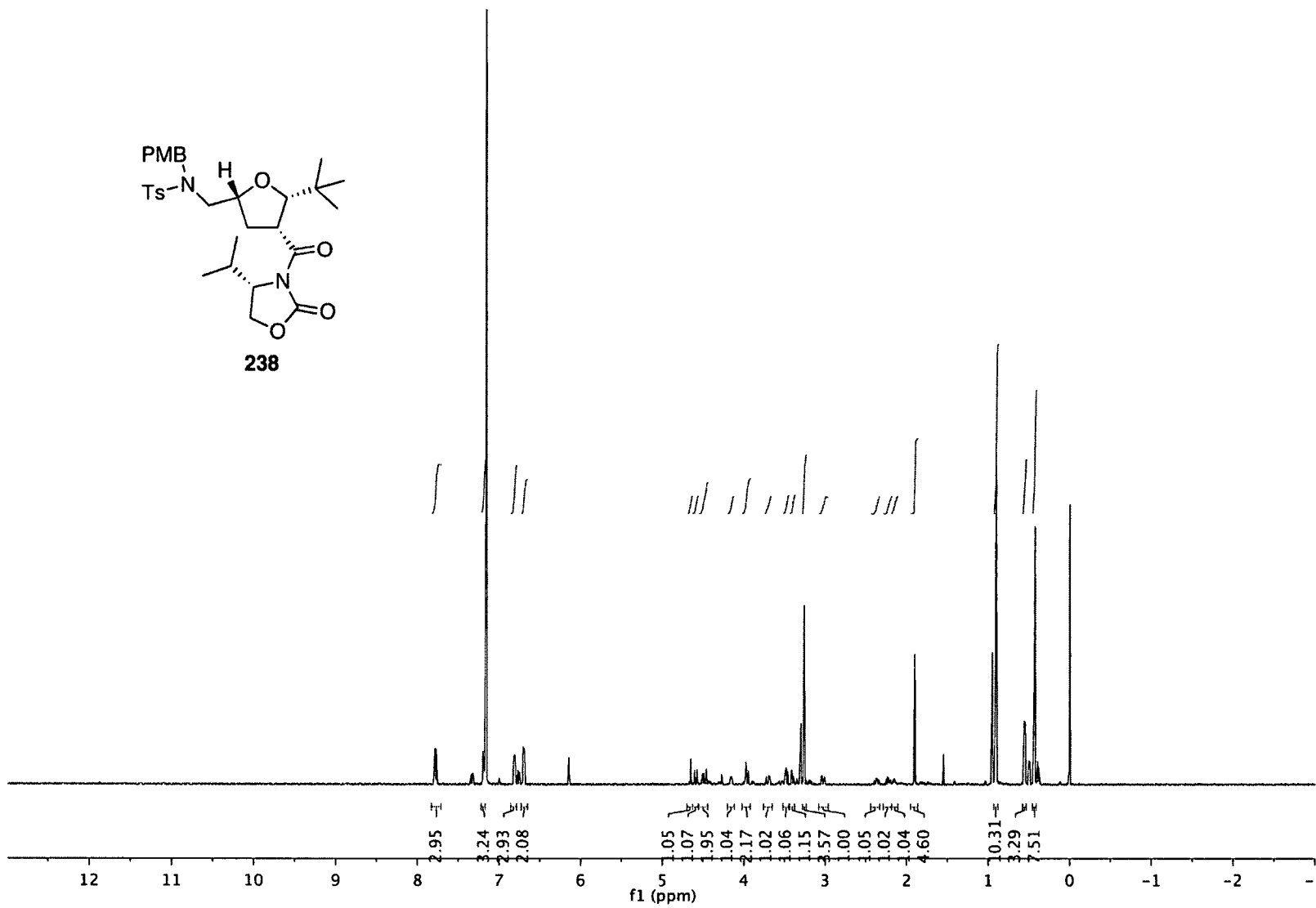
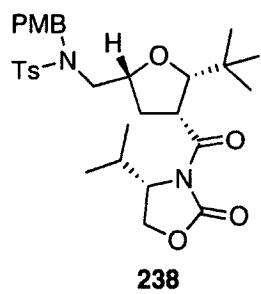


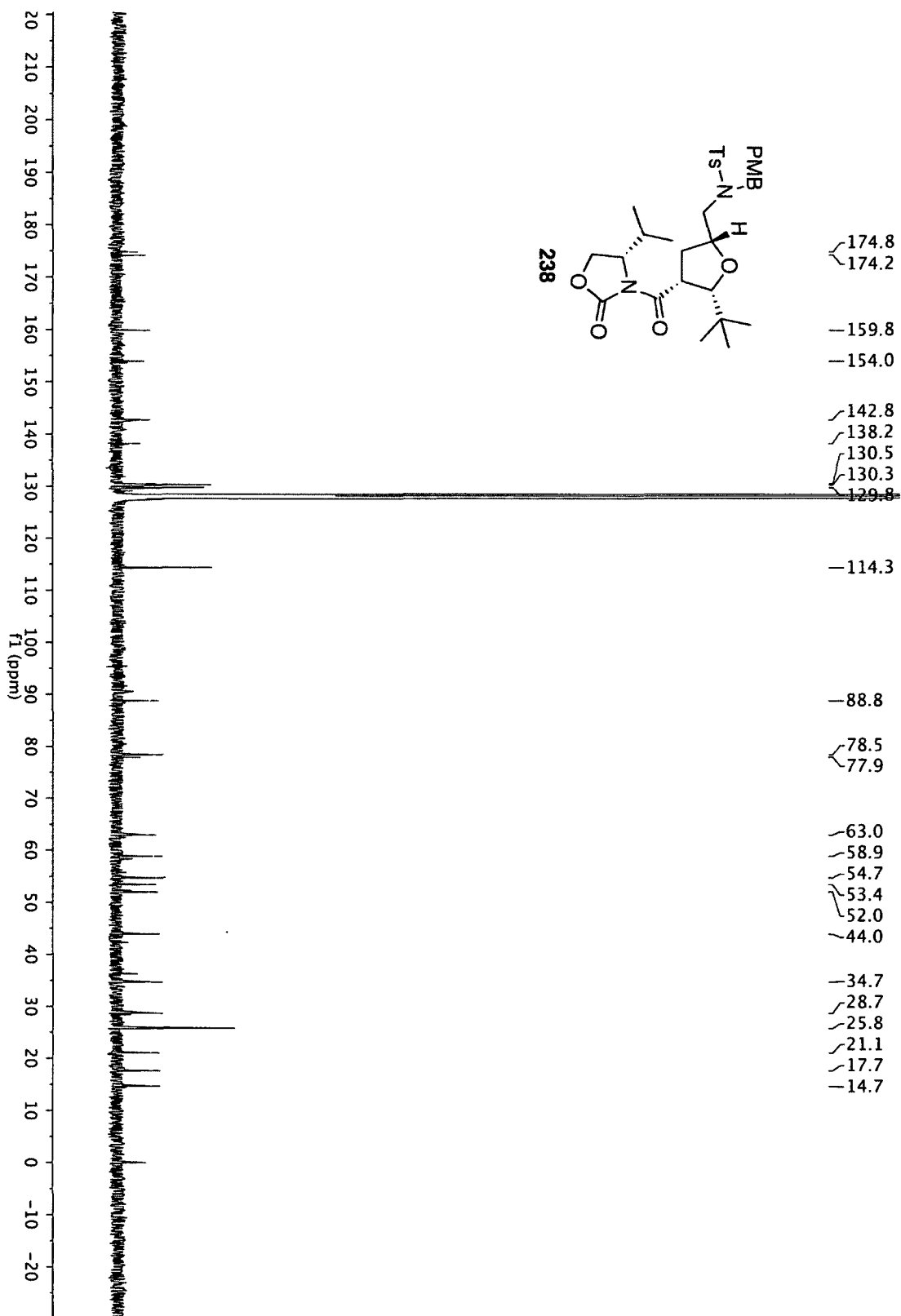




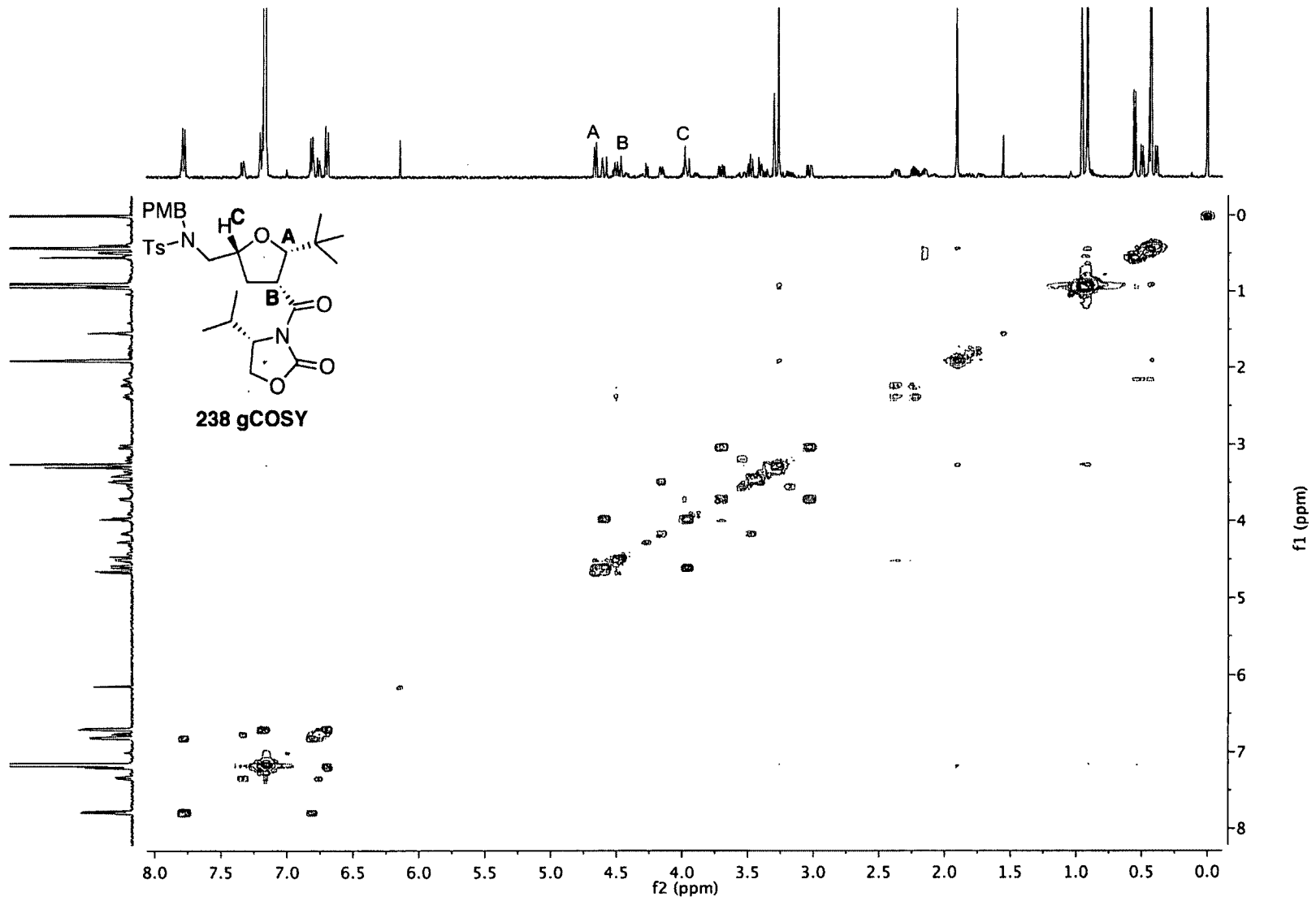


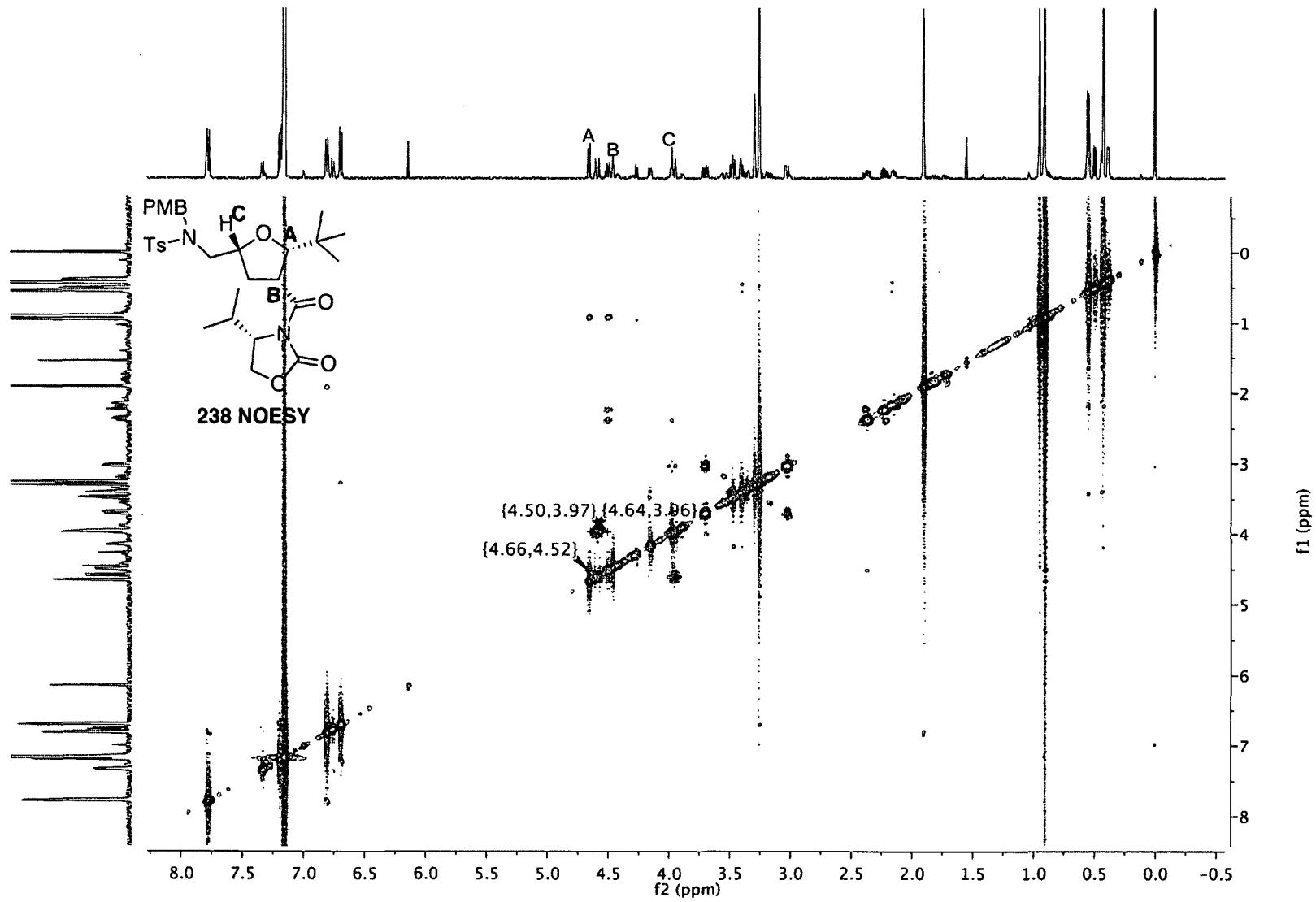


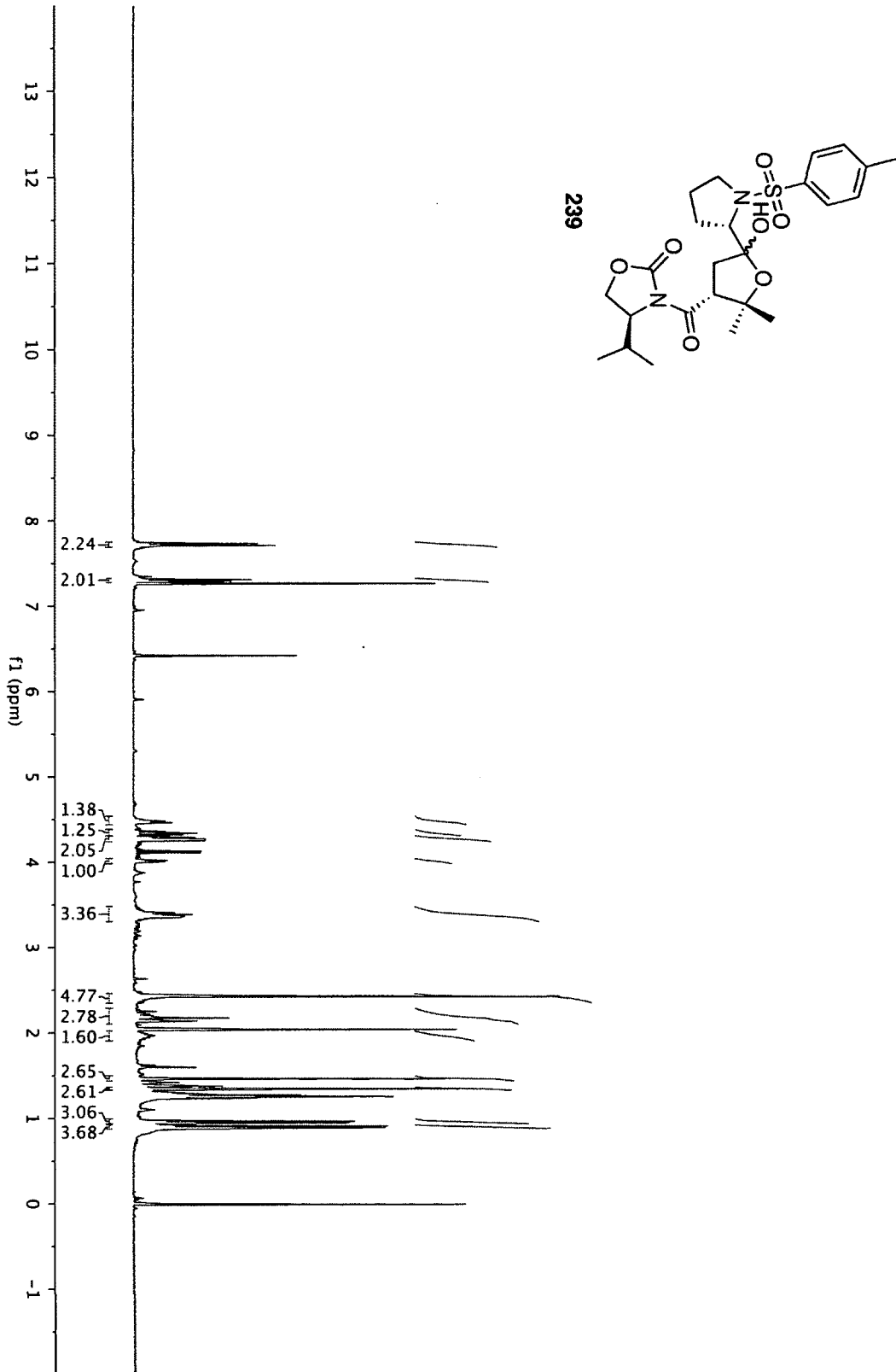


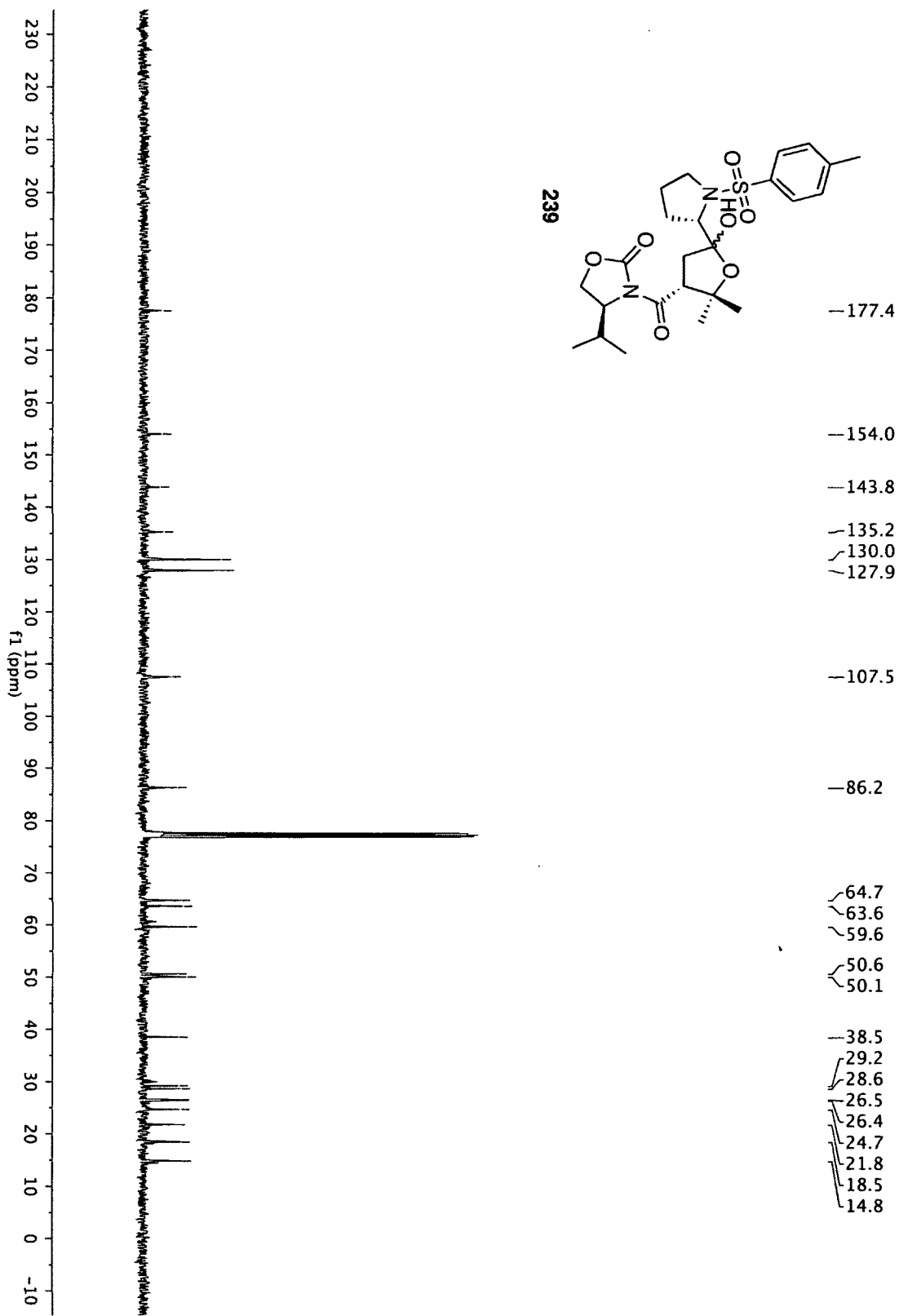


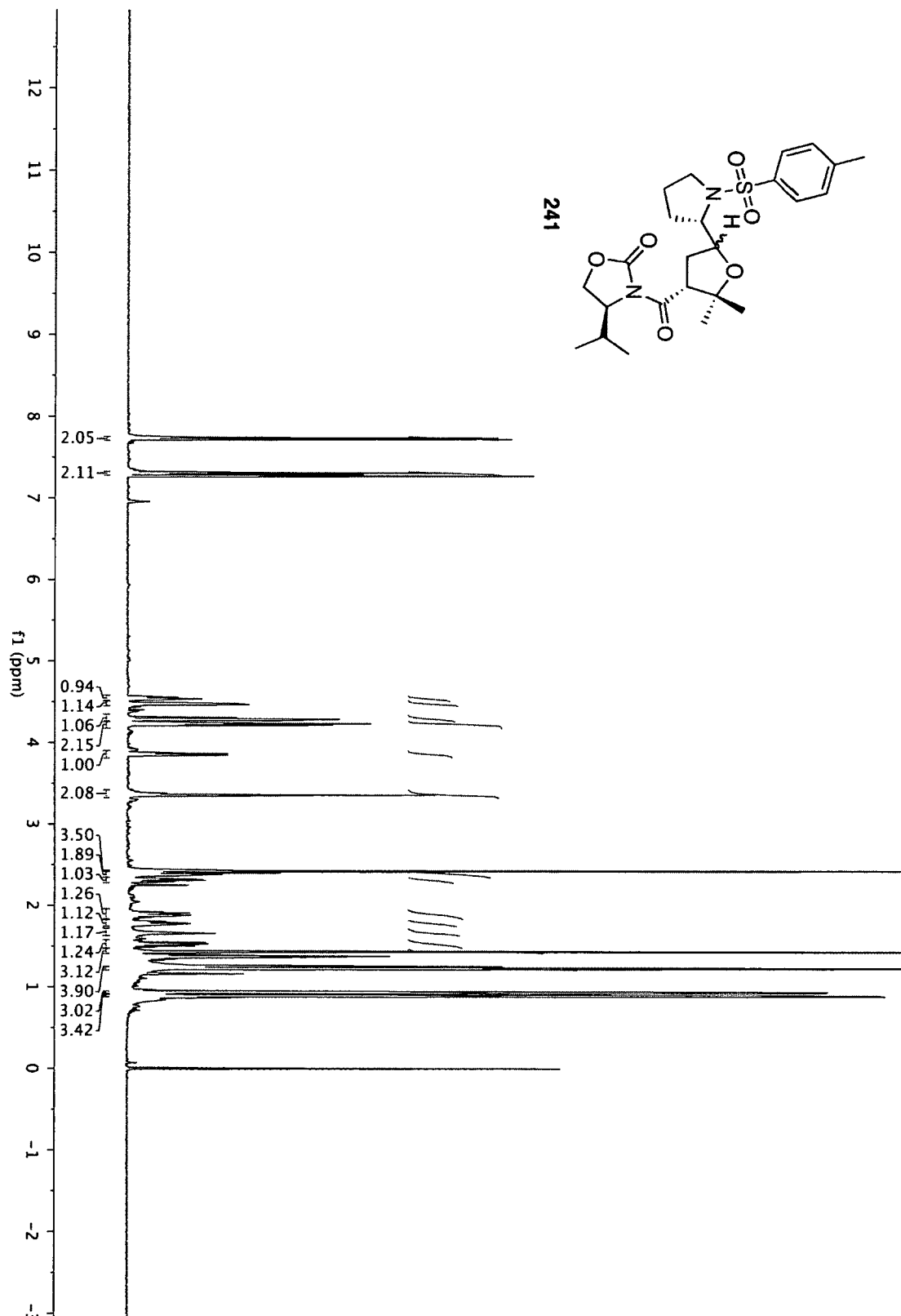
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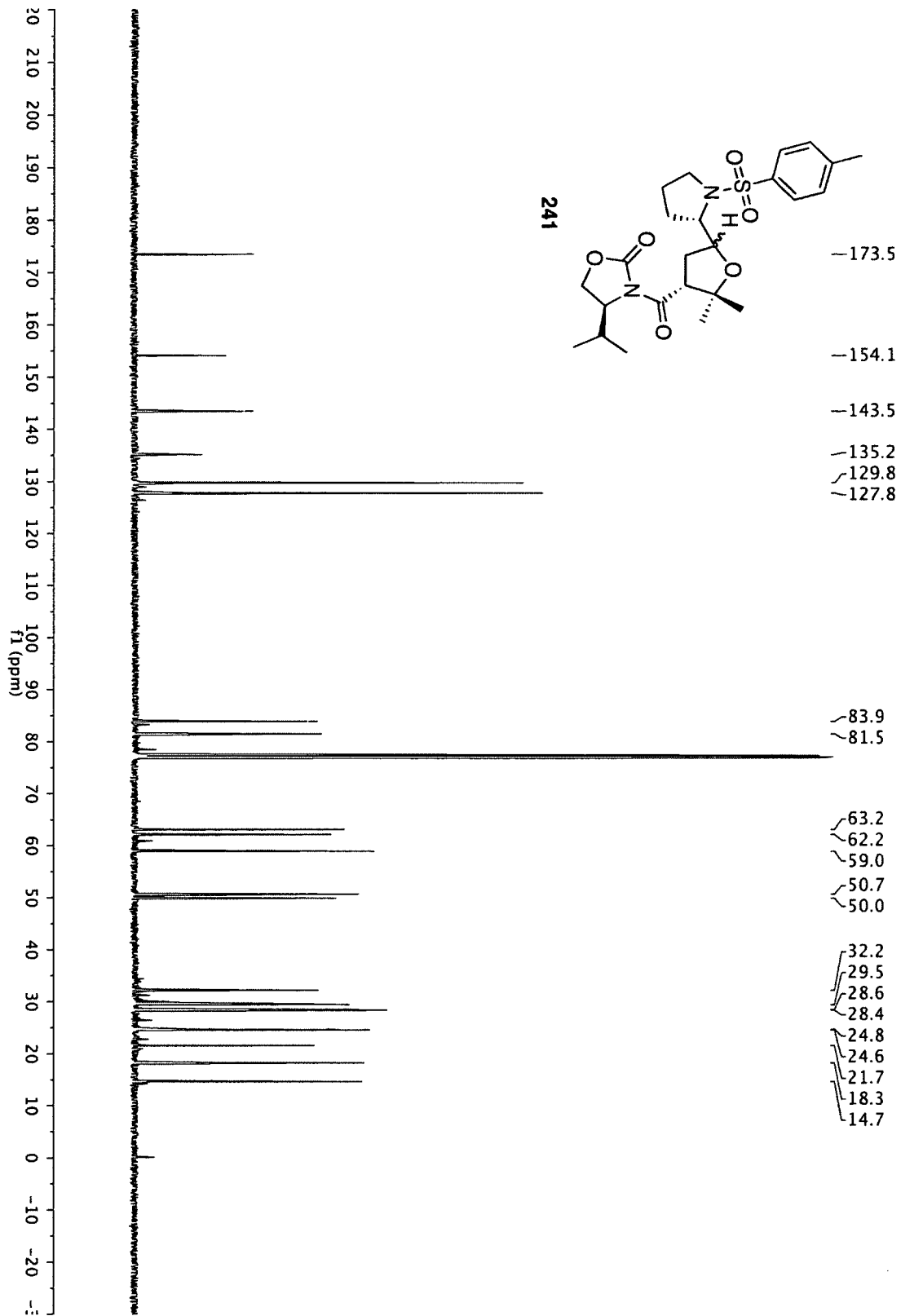


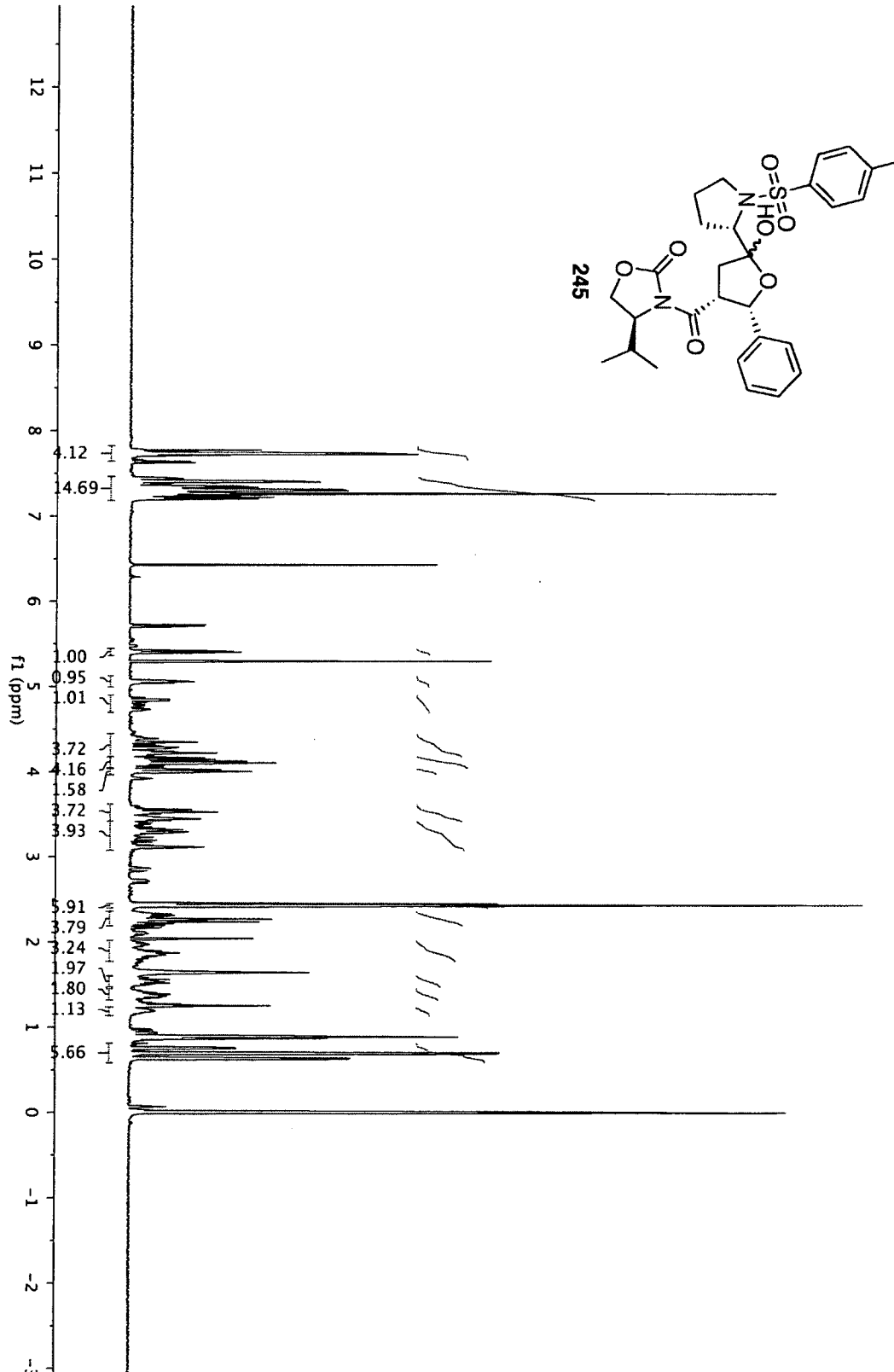


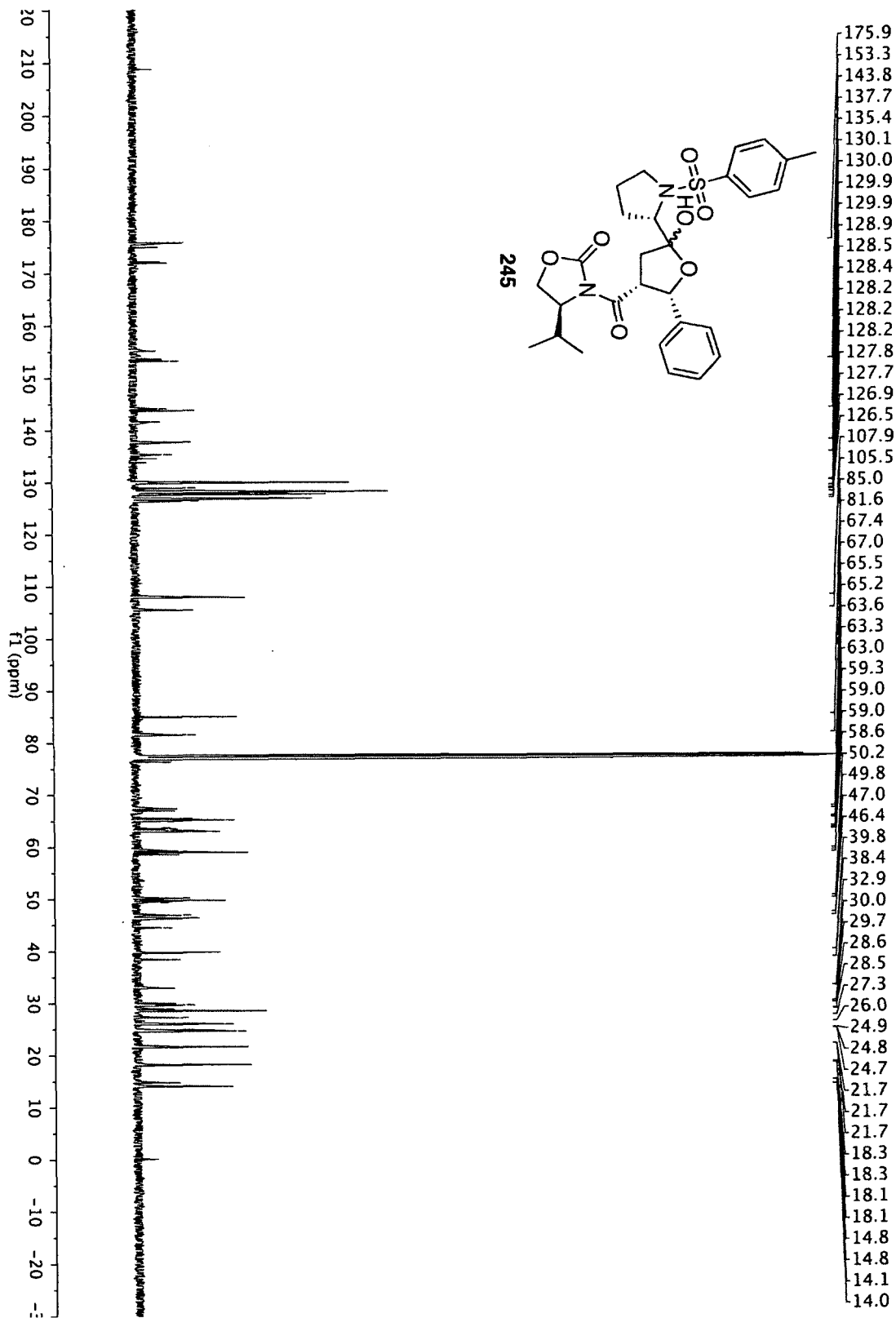


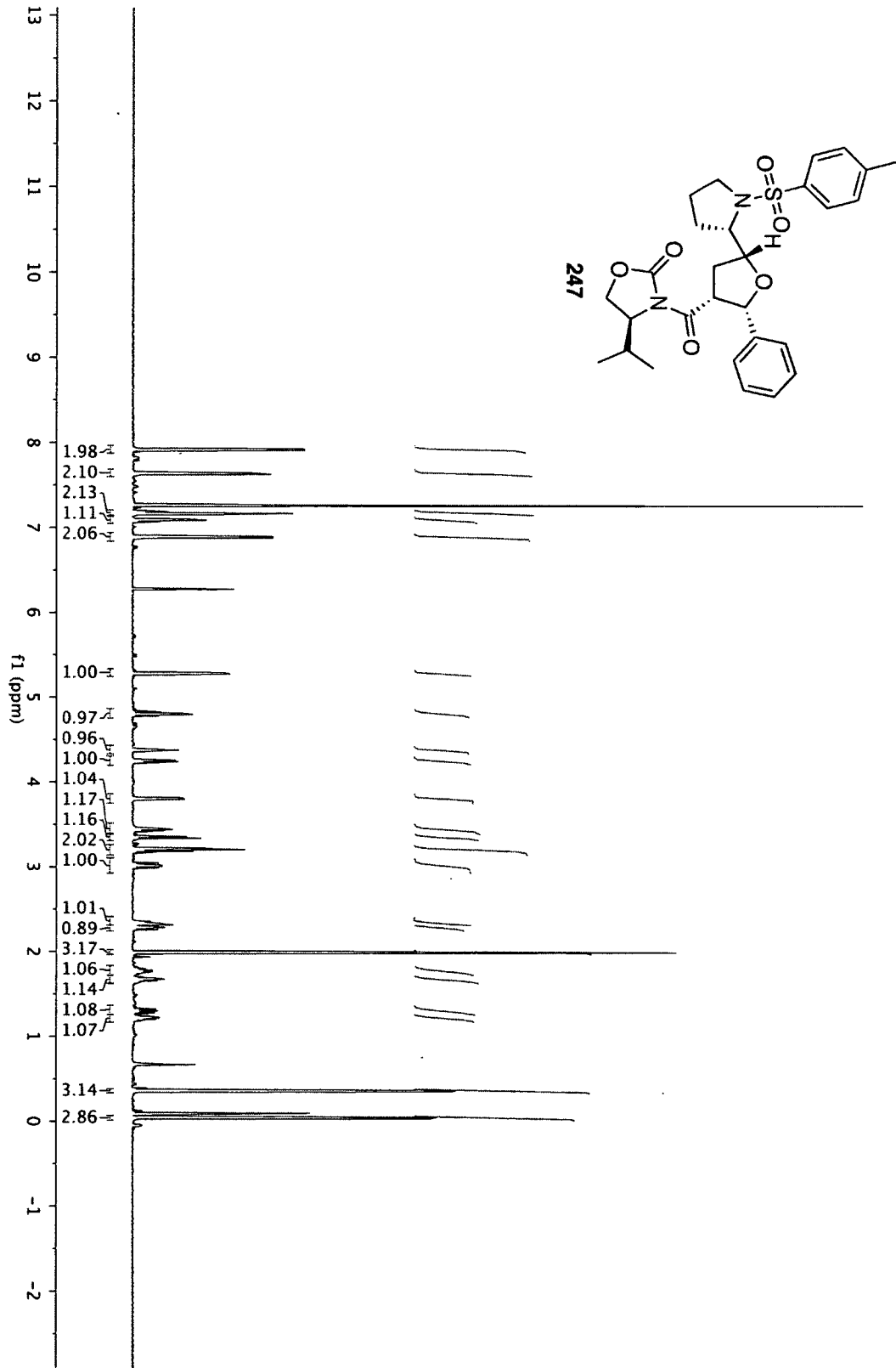


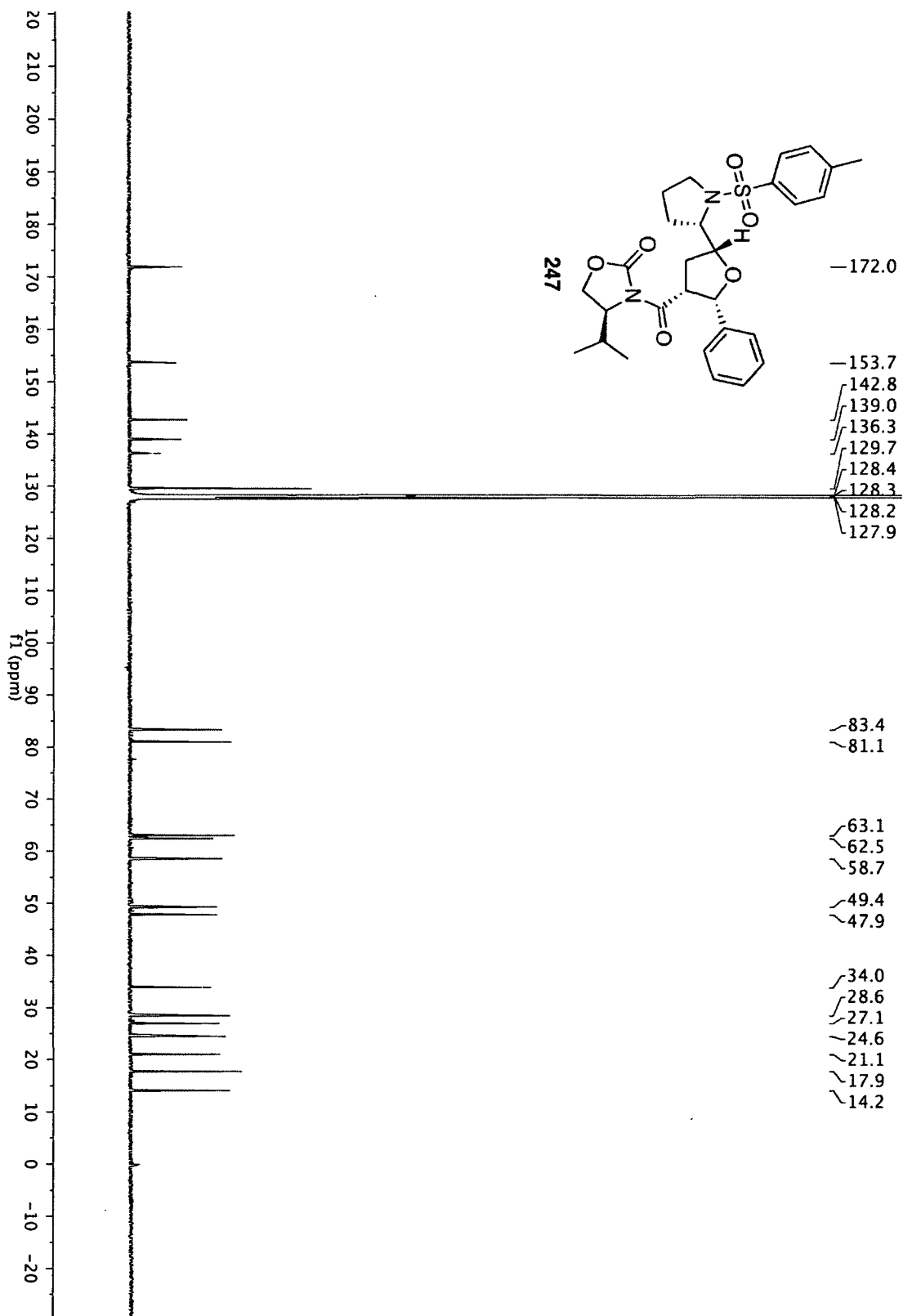


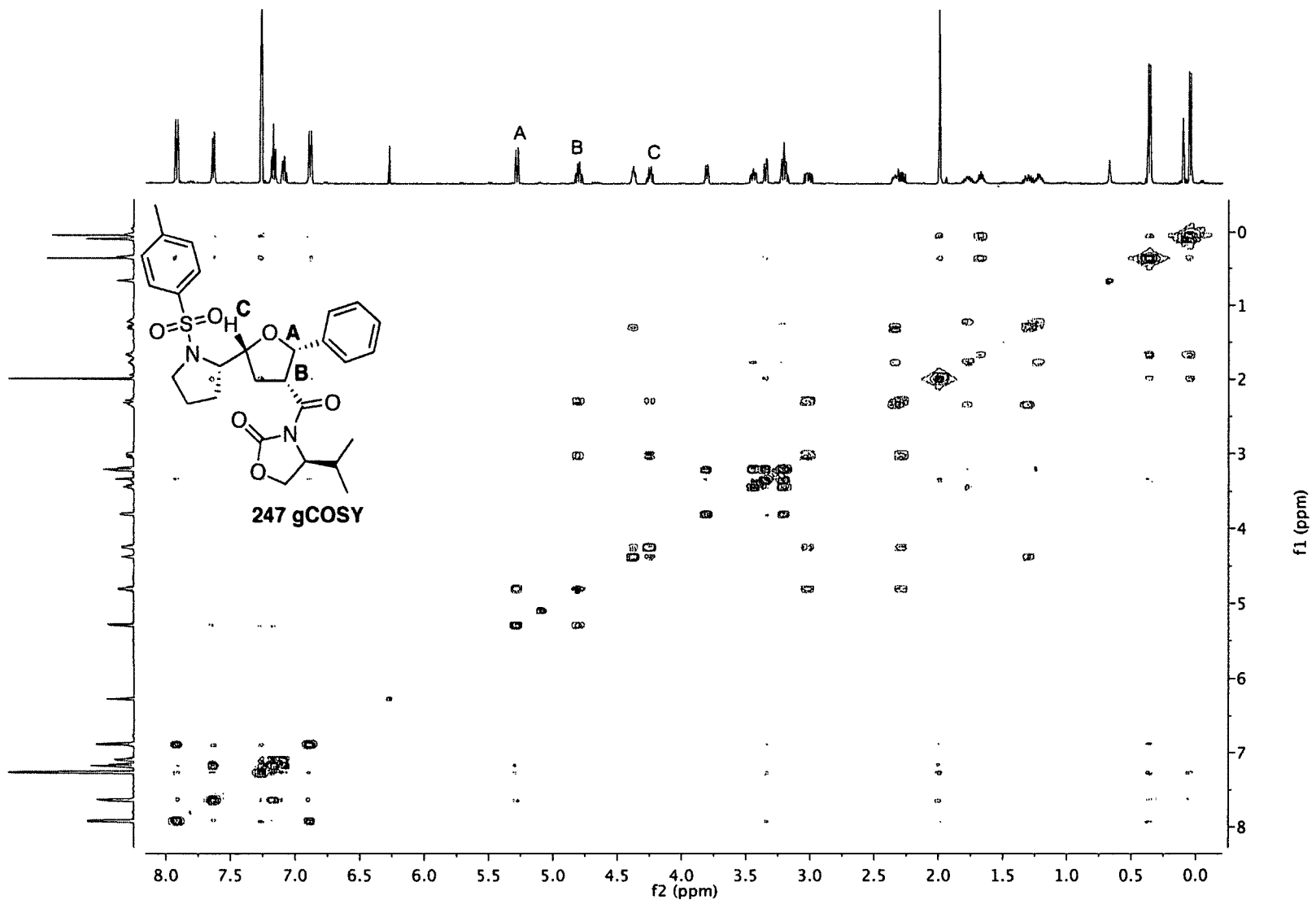


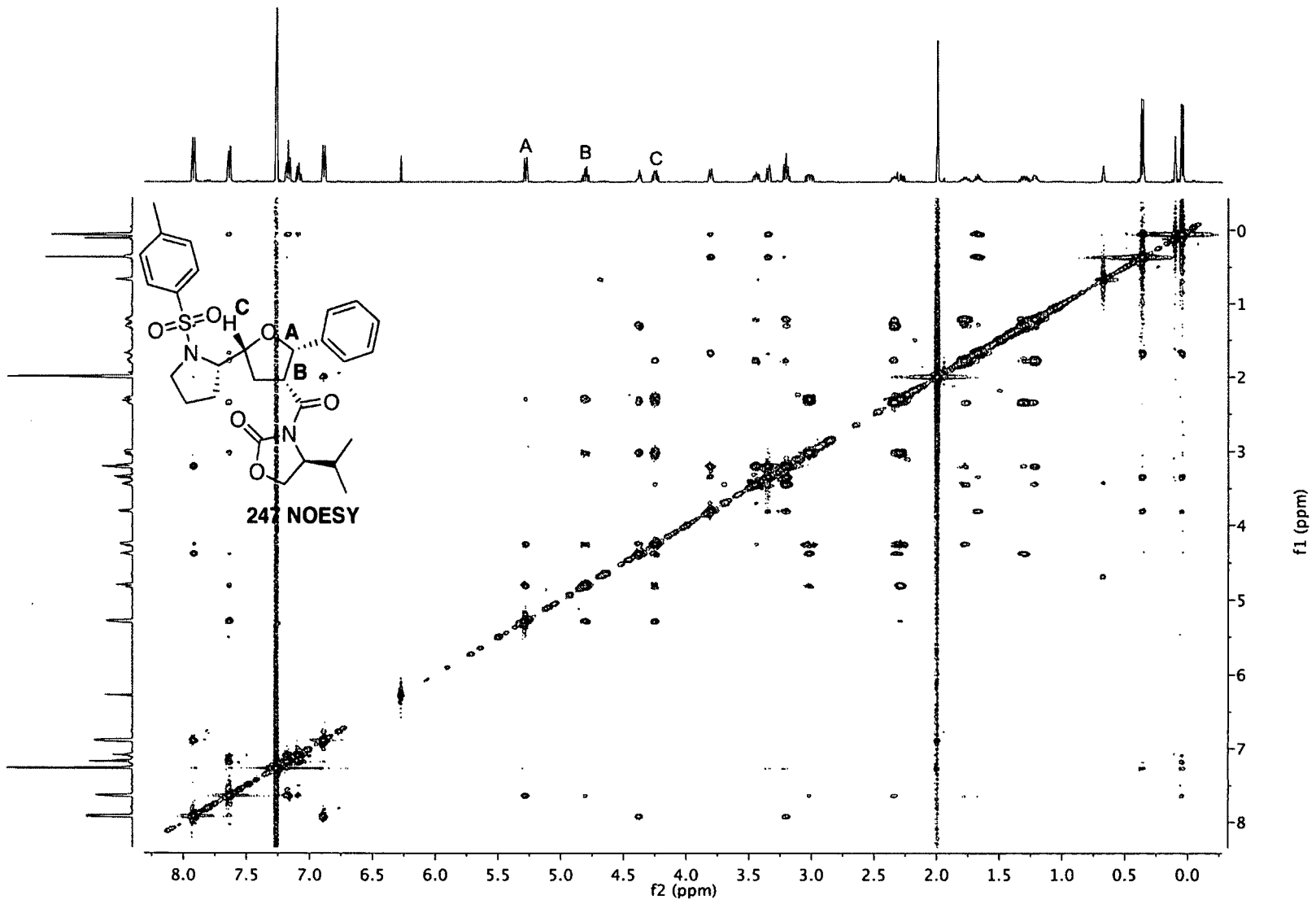


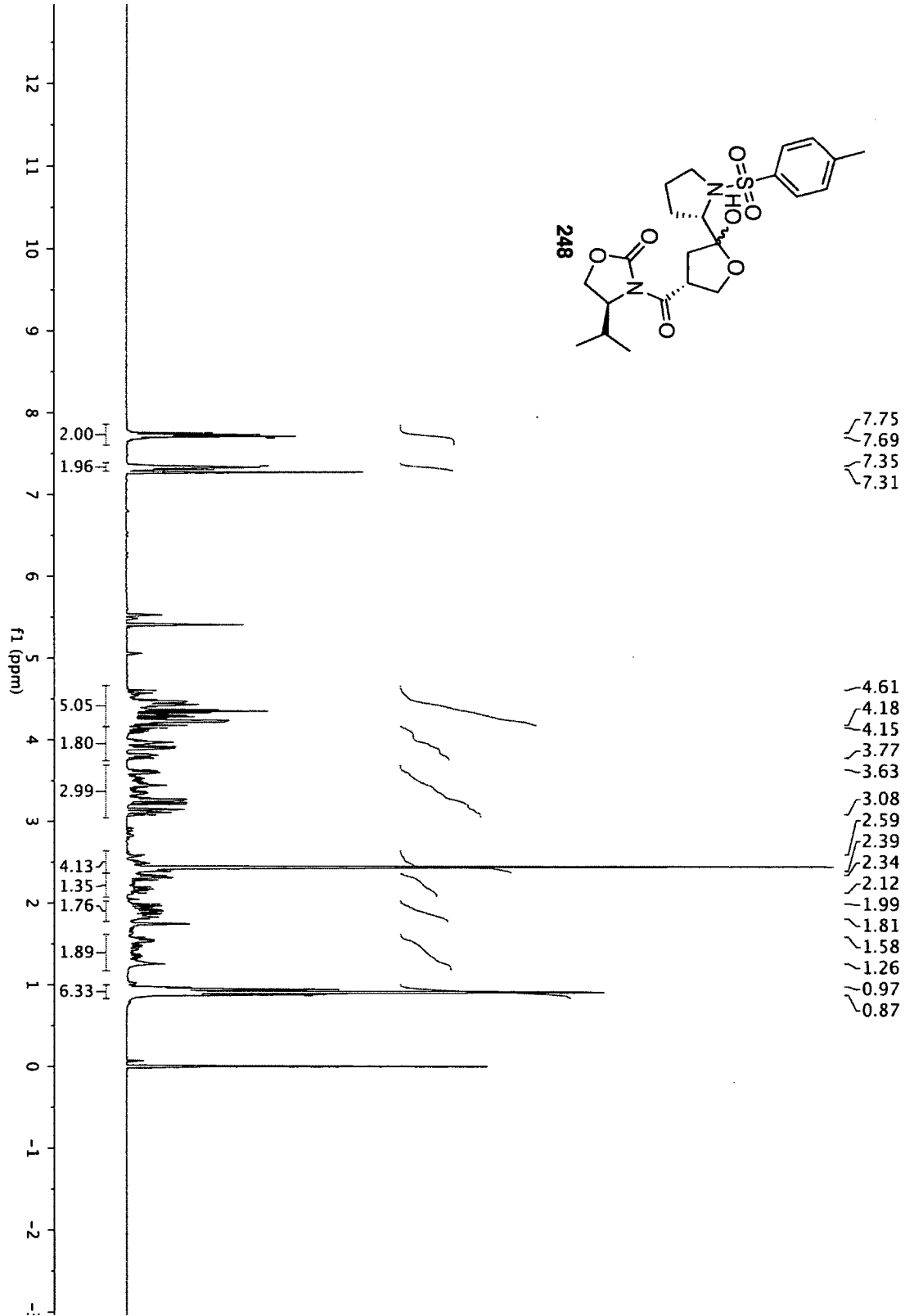


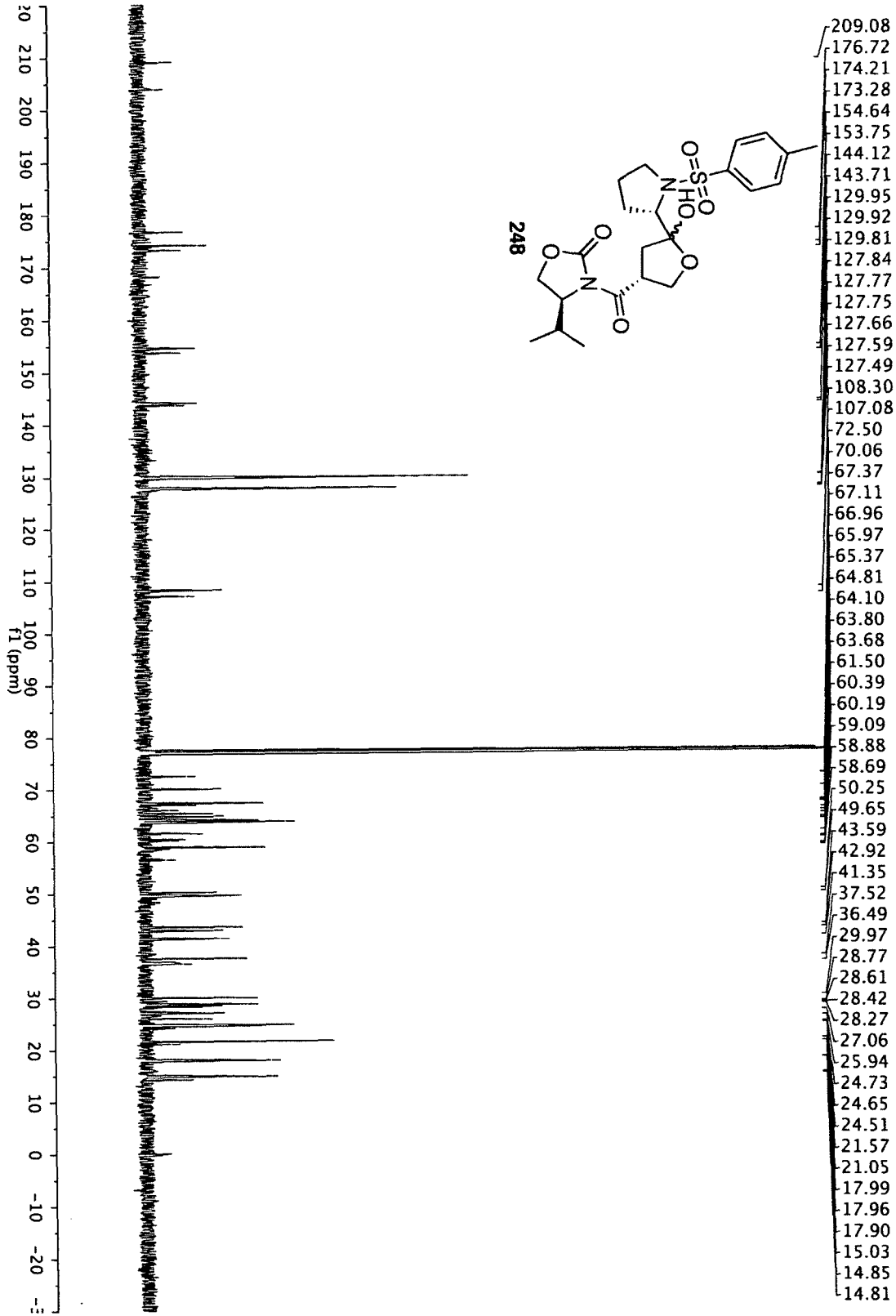


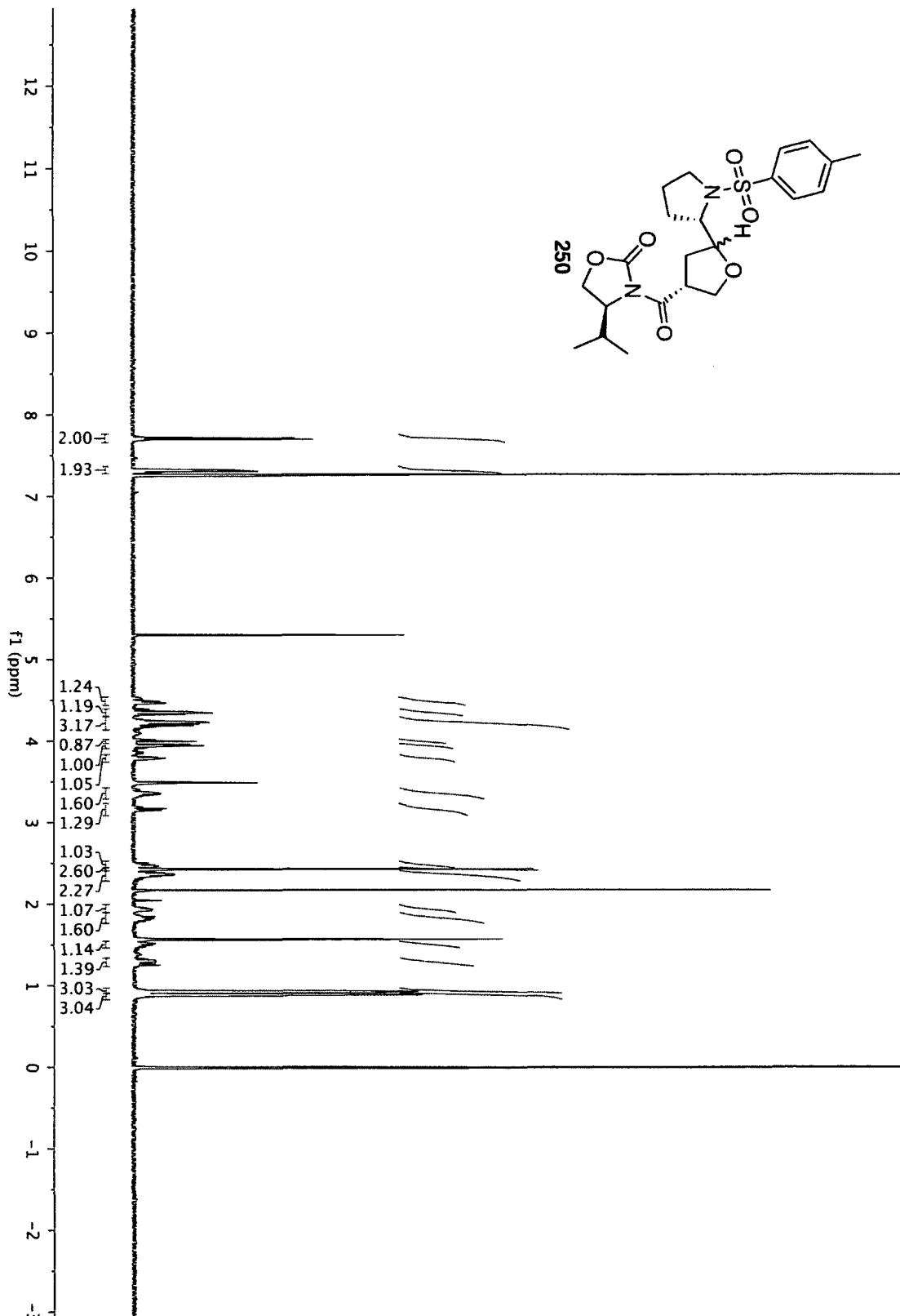


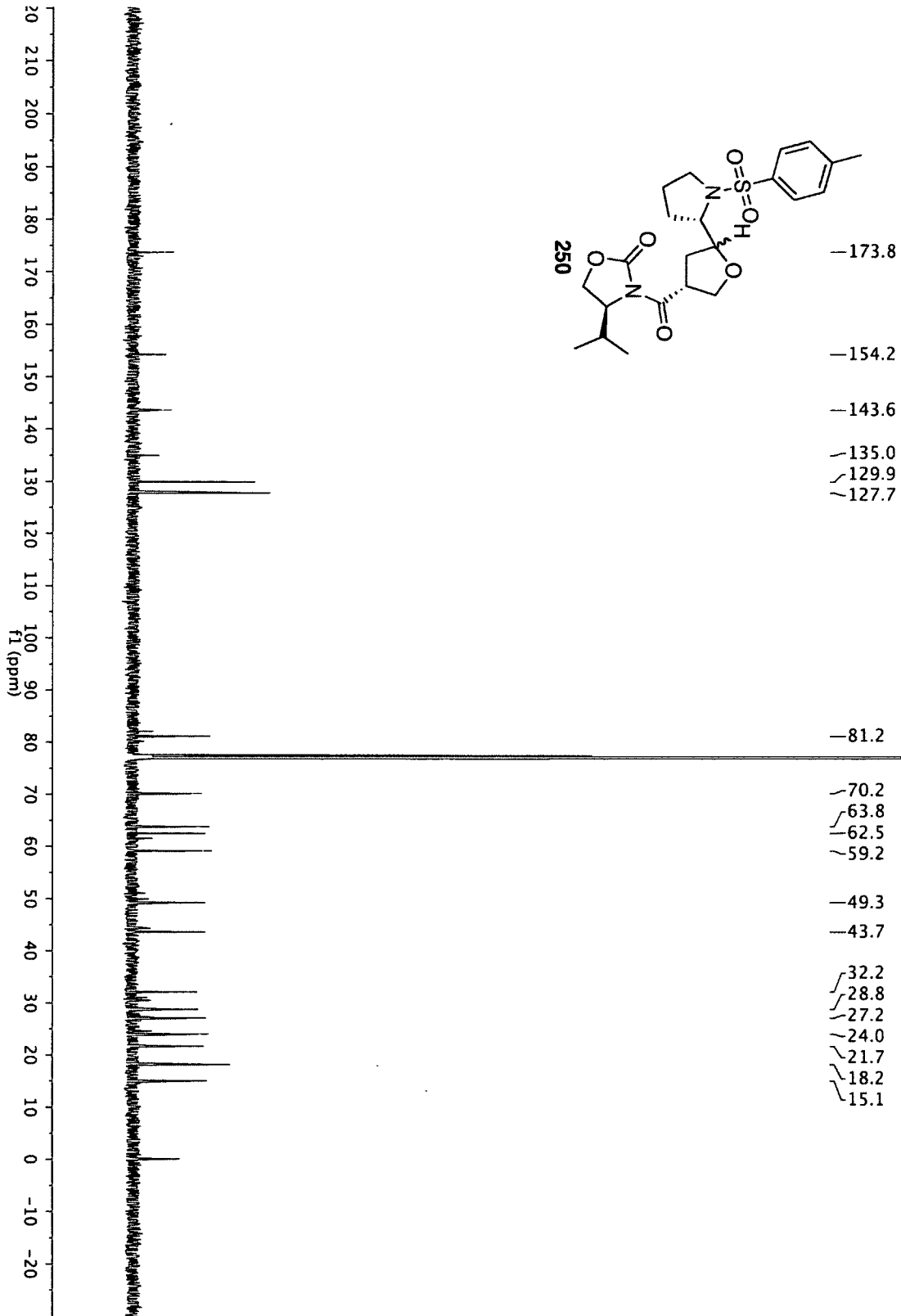






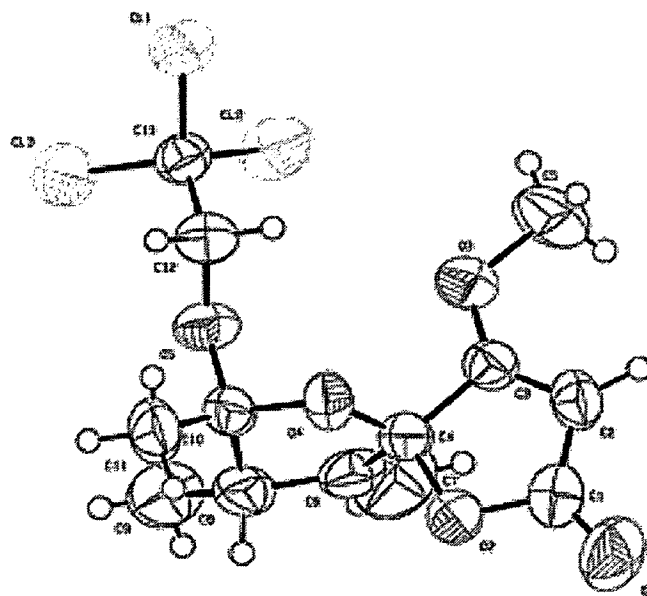
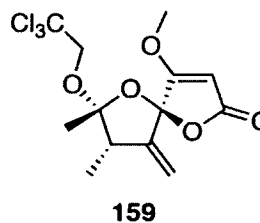




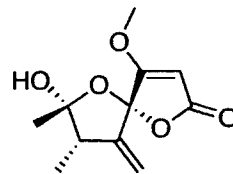


APPENDIX B.
Crystal Structures

(5*R*,7*R*,8*S*)-4-methoxy-7,8-dimethyl-9-methylene-7-(2,2,2-trichloroethoxy)-1,6-dioxaspiro[4.4]non-3-en-2-one (159)



(5S,7R,8S)-7-hydroxy-4-methoxy-7,8-dimethyl-9-methylene-1,6-dioxaspiro[4.4]non-3-en-2-one (papyracillic acid A)



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