UNIVERSITY OF CALIFORNIA, SAN DIEGO

Advancements in Isocyanide Based Multicomponent Reactions

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Chemistry

by

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2009

The Dissertation of Jerry Calhoun Isaacson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

2009

Dedicated to my loving, beautiful wife, Deborah.

I also wish to acknowledge Mrs. Shutey, Mr. McElroy,

Professor Eric Jacobsen, Professor Gary Procter, Professor Jim Davis,

Professor Yoshi Kobayashi,

and my Mom and Dad,

all of whom inspired and encouraged me to be a scientist.

Almost all commercially available isocyanides are volatile

and carry this repulsive odor…

The more long-term inhalation of isocyanides

is also said

to increase the intensity of dreams at night.

Alexander Dömling and Ivar Ugi

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List of Symbols and Abbreviations

Ac	acetate, acetyl
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
Bn	benzyl
Boc	tertiary-butoxycarbonyl
CAN	ceric ammonium nitrate
CSA	camphorsulfonic aci
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrum
Hz	hertz
i-Pr	isopropyl
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazane
MCR	multicomponent reaction
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram

MHz	megahertz
mL	milliliter
mmol	millimoles
MOM	methoxymethyl ether
Ms	methane sulfonyl or mesyl
MS	mass spectrum
MS 4Å	four angstrom molecular sieves
MsCl	methanesulfonyl chloride
NaHMDS	sodium hexamethyldisilazane
NaOEt	sodium ethoxide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Pd/C	palladium on charcoal
Ph	phenyl
PhH	benzene
PIFA	bis (trifluoroacetoxy)iodobenzene
Piv	trimethylacetate
PMB	*p*-methoxy benzyl
PPTS	pyridinium *p*-toluenesulfonic acid
rt	room temperature
TADDOL	(–)-trans-α, α '-(dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
TBAF	tetrabutyl ammonium fluoride
TBDPS	tertiary-butyl diphenyl silyl
TBS	tertiary-butyl dimethyl silyl
TBS-OTf	tertiary-butyl dimethyl silyl triflate
t-Bu	tertiary-butyl
*t*BuOK	potassium tertiary-butoxide
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropyl silyl
TLC	thin layer chromatography

TMS	trimethyl silyl
TMS-Cl	trimethyl silyl chloride
Ts	*p*-toluene sulfonyl or tosyl
U4C-3CR	Ugi four-center three-component condensation reaction
UV	ultraviolet
µL	microliter
µmol	micromoles

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Acknowledgements

First and foremost I must thank my advisor, Yoshi Kobayashi, whose sharp insight and unparalleled knowledge inspired me from the earliest days of my doctoral research. He made it clear from the beginning that we had a responsibility to always strive for the highest goals and work the best of our diligence. He always facilitated a lively and respectful exchange of ideas between colleagues in our group, using his intellect to keep conversations on strong scientific footing. I appreciate that Yoshi always let me explore my intellectual curiosities and asked the tough, poignant questions or gave suggestions at pivotal moments that kept me on the right path. Yoshi agreed with me often enough to keep me encouraged and disagreed enough to keep me on my toes.

I also want to thank all of my friends and family who supported me throughout my research program. Most importantly, my wife Deborah who in addition to always offering me sound advice and unwavering support, also kept me nourished by making me sandwiches every day! I also want to thank my parents, John Isaacson and Holly McCamant, my brothers Howard and Tommy and my sisters Jessica, Emily and, most vitally, Heather. Finally, my Uncle John T for the profound support he offered me throughout this endeavor.

Finally, in addition to the collaborators mentioned below I must thank Stephen Born as well as Mitchell Vamos, Matt Buller, Thong Nguyen, Janice Sindac and Yuan Liu for toiling along with me. Thanks to Dr. Yongxuan Su of the UCSD Mass Spectrometry facility and Professor Arnold Rheingold of the UCSD X-Ray Facility.

Chapter one contains material that was previously published in the paper: *Expeditious Access to Unprotected Pyroglutamic Acids*. Isaacson, Jerry; Gilley, Cynthia

B.; Kobayashi, Yoshihisa. *J. Org. Chem.* **2007**, *72*, 3913-3916. Dr. Gilley is graciously acknowledged for her contribution to this work.

Chapter two contains material that was previously published in the paper: *Total Synthesis of (±)-Dysibetaine.* Isaacson, Jerry; Loo, Mandy; Kobayashi, Yoshihisa. *Org. Lett*. **2008**, *10*, 1461-1463. Mandy Loo is graciously acknowledged for her contribution to this work.

Chapter three contains material that was previously published in the paper: *An Ugi Reaction in the Total Synthesis of (–)-Dysibetaine.* Isaacson, Jerry; Kobayashi, Yoshihisa. *Angew. Chem. Int. Ed.* **2009**, *48*, 1845-1848.

Chapter four contains material that has been submitted for publication: *Mild and Efficient One-Carbon Extension of Aldehydes.* Isaacson, Jerry; Goeser, Lauren M.; Olshansky, Lisa; Urbina, Armando; Kobayashi, Yoshihisa. *submitted.*. Ms. Goeser and Mr. Urbina are graciously acknowledged for their contribution to this work. This chapter also contains contributions from UCSD undergraduate researchers Lisa Olshanksy, Karen Lai, Allison Li, Philip Zhou and Kerem Ozboya.

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Publications

Expeditious Access to Unprotected Pyroglutamic Acids. Isaacson, Jerry; Gilley, Cynthia B.; Kobayashi, Yoshihisa. *J. Org. Chem.* **2007**, *72*, 3913-3916.

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ABSTRACT OF THE DISSERTATION

Advancements in Isocyanide Based Multicomponent Reactions

by

Jerry Calhoun Isaacson

Doctor of Philosophy in Chemistry

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Professor Yoshihisa Kobayashi, Chair

Isocyanide based multicomponent reactions, including the Ugi four-component and Passerini three-component reactions, offer chemists a powerful tool for quickly constructing complex molecules. A particular form of the Ugi reaction, in which two of the four reacting components are introduced into a single molecule, is useful for synthesizing cyclic products. Using a newly developed convertible isocyanide, known as indole isocyanide, in the Ugi reaction allowed for the mild synthesis of various pyroglutamic acids. This effort led first to a racemic total synthesis of the natural product

dysibetaine. A project to achieve the stereoselective synthesis of the same natural product led to the discovery of a unique Ugi reaction. Usually a carboxylic acid is one of the four reacting components in this reaction, however in this unusual case an ester acts as the carboxylic acid component. In addition to the natural product syntheses, a detailed explanation of the scope and mechanism of the new convertible indole isocyanide is presented. Finally, we reveal a new stereoselective, Brønsted-acid catalyzed Passerini-type reaction.

Chapter One

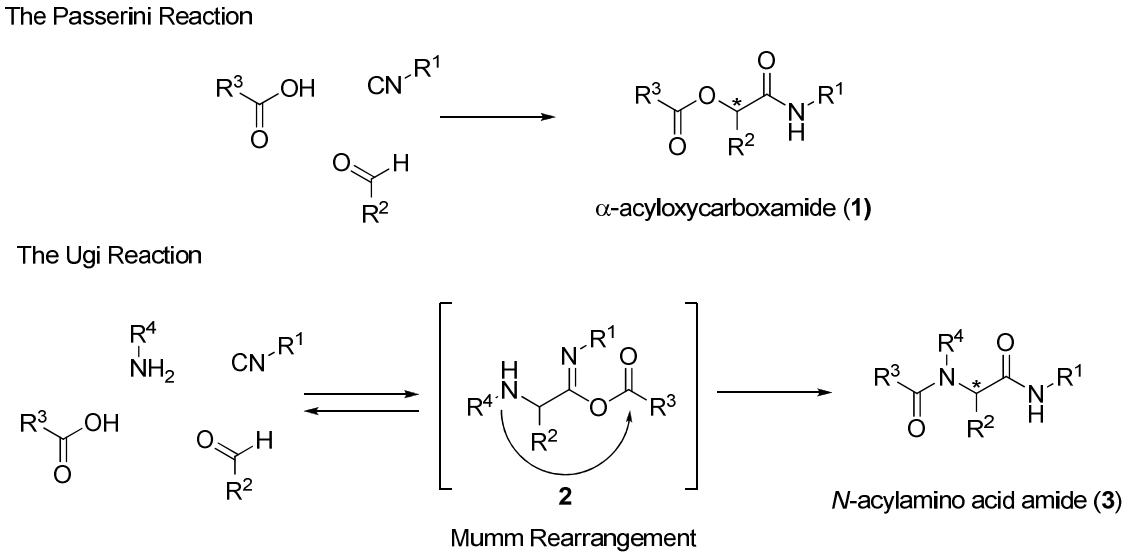
Expeditious Access to Various Pyroglutamic Acid Analogues

A. Introduction

Isocyanides are one of the most intriguing functional groups in organic chemistry. Owing mostly to their terminal carbon atom, these peculiar species, sometimes referred to as isonitriles, undergo or induce a broad range of transformations.[1] This unusual carbon center undergoes reactions with electrophiles and nucleophiles, and also participates in radical reactions[2] or can act as a ligand to metal centers.[3] The thing that sets the isocyanide apart most from other functional groups is its ready willingness to participate in multicomponent condensation reactions (MCRs). MCRs are useful because they bring together multiple, varied components in a single procedure, often producing multiple new bonds under very mild conditions. MCRs can be used to generate great diversity very rapidly and with minimal waste. The most commonly used isocyanide based MCRs are the Ugi and Passerini reactions.[2,4]

Mario Passerini was an early pioneer in the area of isocyanide based MCRs and developed the reaction that now bears his name almost a century ago.[5] In the event, an aldehyde or ketone reacts with the isocyanide and a carboxylic acid in order to form an α-acyloxyamide (**1**, Scheme 1.1) with a new stereocenter.[4] The reaction has excellent atom economy as every portion of the three components is incorporated into the product

and a new stereocenter is formed. Ivar Ugi entered the field many decades later and discovered that an amine could also be included, giving us a four-component reaction of a carbonyl component, a carboxylic acid, an amine and the isocyanide (Scheme 1.1). The reaction represents only a small variation on the Passerini reaction and the output is similar, however the Ugi reaction is much more widely used. Indeed, Ugi acknowledged that Passerini would easily have discovered the reaction himself if the intervening knowledge was at his disposal at that earlier date.[6] In the Ugi reaction the components combine reversibly to form the acylimidate (**2**). This intermediate undergoes irreversible Mumm rearrangement to form the product *N*-acylamino acid amide (**3**) with a new stereocenter.[4]

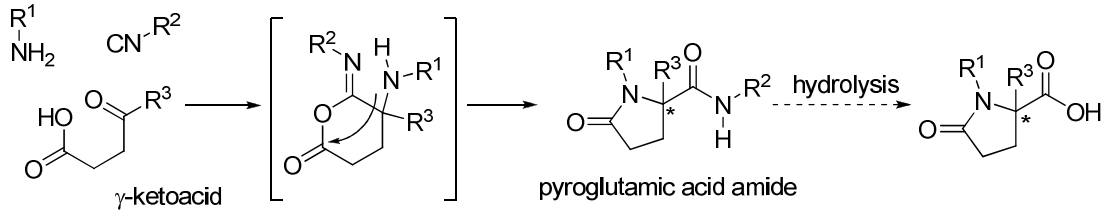


Scheme 1.1. The Ugi and Passerini Reactions.

The Ugi reaction is a powerful platform from which to embark for research because the combinations are endless. Ketones or aldehydes can participate as the

carbonyl component. Carboxylic acids may be substituted with water, CO_2, hydrogen sulfide, hydrogen selenide among others. Primary or secondary amines, ammonia or equivalents, as well as hydrazines and hydroxylamines are suitable amine components. The reaction can also be varied by incorporating two of the components into a single molecule, for example amino acids, cyclic imines or ketoacids. The Ugi reaction then yields cyclic products. Finally, the synthetic power of the Ugi reaction means that it often represents the shortest path to a given molecule. However, in order to arrive at the desired molecules it is often necessary to make further modifications of the Ugi products.[4]

These last two areas, the formation of cyclic Ugi products and subsequent modifications, combined to form an intriguing problem. The combination of a ketone and carboxylic acid into a single molecular backbone (for example a γ-ketoacid) affords the ability to quickly make cyclized products through the Ugi reaction, in this case pyroglutamic acid amides (Scheme 1.2). This specific combination has been reported by various groups.[7] We sought to exploit this reaction for the synthesis of biologically interesting molecules bearing the pyroglutamic acid moiety, but first we had to figure out how to carry out the necessary post-Ugi modifications because successful hydrolysis of the pyroglutamic acid amide to the corresponding acid had never been reported.



Scheme 1.2. Ugi reaction of a γ-ketoacid.

The use of multifunctional starting materials in the Ugi reaction offers an intriguing platform for natural product synthesis. By incorporating a ketone and carboxylic acid components of the Ugi four-component reaction, we can synthesize the pyroglutamic acid amide core structure, which is present in a number of natural products, such as those shown in Figure 1.1. All of these natural products contain some form of carboxylic acid derivative other than an amide – a β-lactone in the case of omuralide and a thioester in the case of lactacystin, for example – so post-Ugi reaction modifications of the amide moiety will be necessary if we hope to synthesize these molecules. A specially designed isocyanide, known as indole isocyanide, would help to overcome this problem.

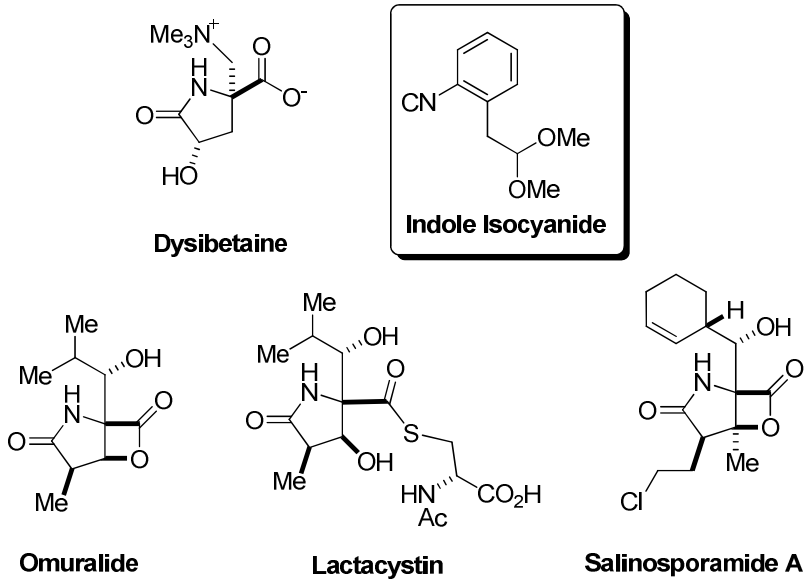


Figure 1.1. Pyroglutamic acid containing natural products and indole isocyanide.

Primary amines have been the most commonly used as the amine component in the Ugi reaction, however for these natural products to be synthesized most directly, ammonia or an equivalent must be used. A primary amine could be used with a plan to remove the protecting group and reveal the free amide at a later stage, however we wanted to synthesize these fully unprotected natural products more directly. No examples of using ammonia or equivalents in this particular variation of the Ugi reaction were previously reported, presenting another problem that we would have to solve.

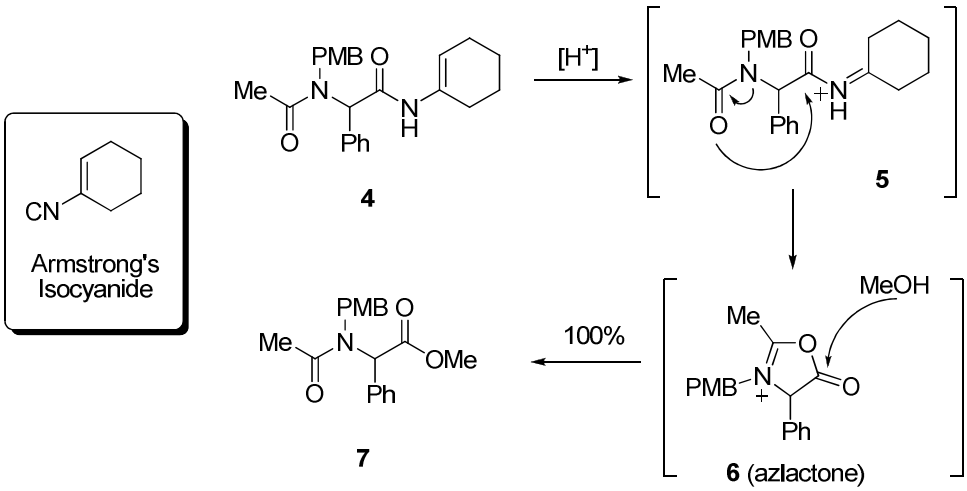
B. Convertible Isocyanides and the Ugi 4-Center 3-Component Reaction

1. Known Convertible Isocyanides for the Ugi Reaction

When the four components of the Ugi reaction are combined they react to form an N-acyl-α-amino acid amide (**1**, Scheme 1.1). In order to maximize the utility of this reaction it is sometimes necessary to make further modifications to the Ugi product.

Often the desire is to selectively convert one of the resulting amides to another carboxylic acid derivative or to unmask the free amine. This is inherently difficult since the two amides that result from the reaction should react similarly. A number of solutions to this problem have been devised, usually involving some type of intramolecular activation to facilitate selective cleavage. The two types of intramolecular activation that have had the most success are: (a) azlactone formation followed by opening by an external nucleophile; and (b) displacement of the amide bond by an internal nucleophile.

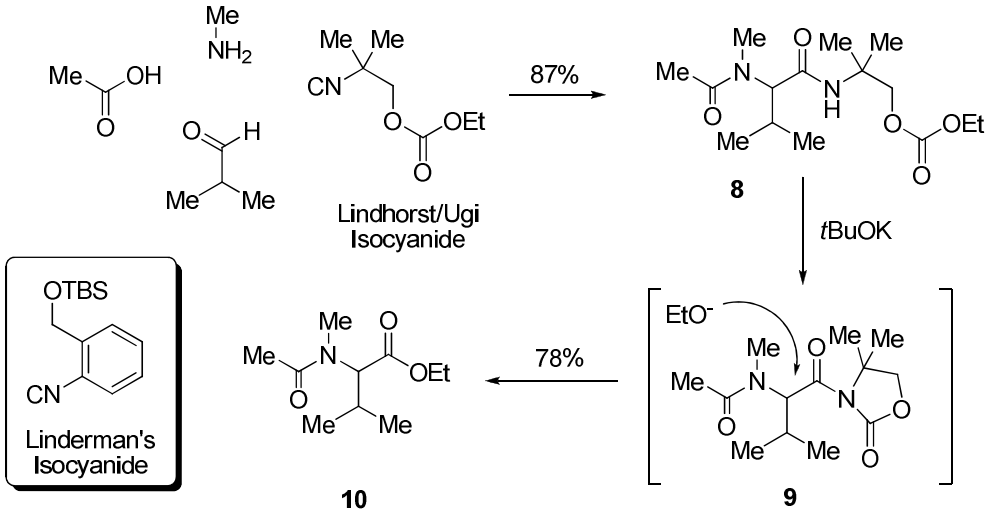
Armstrong's isocyanide uses the first type (a) of activation mentioned (Scheme 1.3).[8] After the Ugi reaction the resulting product (**4**) is treated with acid which causes the amide resulting from the isocyanide to become activated (**5**). The activated amide then reacts with the other amide in the molecule to form the azlactone intermediate **6**. A variety of nucleophiles, for example methanol, can be added to the azlactone to give the selectively cleaved methyl ester **7** in very good yield.



Scheme 1.3. Armstrong's convertible isocyanide and post-Ugi modifications.

The isocyanides shown in Scheme 1.4 utilize the second method (b) of activation. In these cases the isocyanide is specifically designed to react with the terminal amide of the Ugi product to enable its cleavage. The first example shown is the isocyanide developed by Ugi and Lindhorst.[9] The Ugi product **8** is treated with strong base to deprotonate the amide nitrogen and cause the formation of the *N*-acyl oxazolidinone **9**. The ethoxide ion released in the cyclization returns to cleave the amide bond and release the ethyl ester **10**. Various alcohols can be incorporated into the isocyanide.

Linderman's isocyanide is also shown in Scheme 1.4.[10] Treatment of an Ugi product derived from this isocyanide with acid causes the silyl ether to be deprotected. This reveals a nucleophilic oxygen atom that displaces the amide bond to form the more-readily cleavable ester via N–O acyl transfer reaction. These and other known convertible isocyanides would be the starting point for our search for a way to make pyroglutamic acid-containing molecules via the Ugi reaction.



Scheme 1.4. Lindhorst/Ugi and Linderman convertible isocyanides.

2. The Ugi 4-Center 3-Component Cyclization Reaction

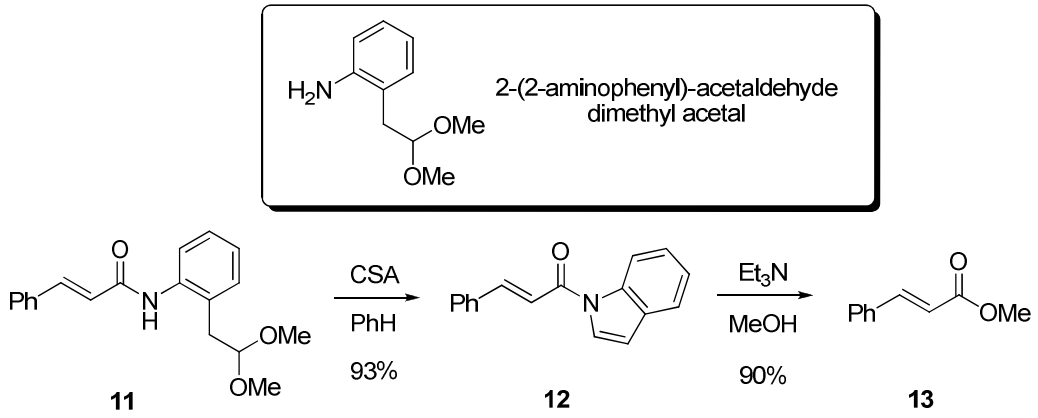
Ugi and his co-workers described intramolecular versions of their four-component reaction very soon after the reaction was initially discovered. They used this technology for the synthesis of a series of β-lactam containing Penicillin derivatives starting from β-amino acids.[11] Passerini also described the reaction of levulinic acid, which contains both a carboxylic acid and ketone, with isocyanides to form γ-lactones.[12] However, it was not until much later that this cyclic version of the Ugi reaction was finally tested. Various groups reported the successful synthesis of pyroglutamic acid-amides, in excellent yields and using very mild conditions, from levulinic acid derivatives. This reaction is known as the Ugi 4-center 3-component cyclization reaction (U4C-3CR) (Scheme 1.2).[7]

The U4C-3CR condensation has very strong potential to quickly assemble complex molecules. It allows the possibility of synthesizing α-substituted pyroglutamic acids derivatives without the need for alkylation, which usually requires the use of a strong base. The reaction creates a sterically hindered amide next to a new stereocenter. Incorporation of a ketone into a bi-functional molecule such as the γ-ketoacid greatly enhances the yield of Ugi products, while in general ketones do not react as well as aldehydes. Despite these advantages, however, this reaction was not widely used. This was surely in part because no good method existed for the conversion of the pyroglutamic amides to their corresponding carboxylic acids. After research was started in this area it became clear why that was the case, since the answer is not trivial.

This problem was initially explored by co-workers in our laboratory who were working towards the total synthesis of the pyroglutamic acid natural product omuralide.[13] They discovered very early that Armstrong's convertible isocyanide[8] would not provide a suitable answer to this problem because the pyroglutamic acid Ugi product is too strained to form the required azlactone intermediate. Testing of the Lindhorst-Ugi isocyanide[9] as well as other convertible isocyanides with a similar mode of action also failed. We believe that the amide is too sterically hindered due to the proximity of the fully substituted carbon atom at the α-position of the amide. It was therefore determined that a new mode of action, and a new convertible isocyanide, was needed.

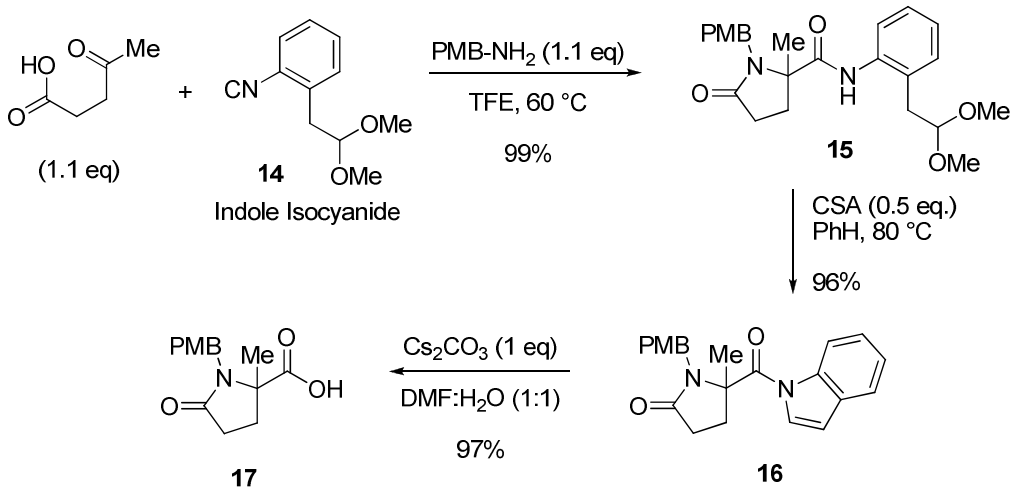
3. Introduction of Indole Isocyanide

Fortunately, the Fukuyama group had not long before published their account of a new protecting group for carboxylic acids.[14] In their research, they had used a specially derivatized amine, 2-(2-aminophenyl)-acetaldehyde dimethyl acetal, to form an anilide with the carboxylic acid in need of protection. After carrying out the desired chemistry, the protecting group could be cleaved under mild conditions via conversion to the corresponding *N*-acylindole. For example, cinnamic acid was coupled with the amine to form anilide **11** (Scheme 1.5). This anilide was heated with catalytic acid in benzene to form *N*-acylindole **12**. The activated intermediate **12** is stable and isolable, however when the anilide **11** is converted to **12** the character of the C–N bond is dramatically altered. The nitrogen lone pair is now participating in the indole aromatic system, so the C–N bond is weakened and **12** is readily cleaved to various other carboxylic acid derivatives. For example, treating **12** with a small amount of triethylamine in methanol readily affords the methyl ester **13**.



Scheme 1.5. Fukuyama's indole-inspired carboxylic acid protecting group.

We thought that it would be possible to incorporate this amine into a strategy for cleaving the pyroglutamic acid amides derived from the U4C-3CR reactions of levulinic acid derivatives. The concept was first proved by coworkers in our laboratory using levulinic acid itself and the isocyanide derived from Fukuyama's protecting group, 1-isocyano-2-(2,2-dimethoxyethyl)benzene, also known as indole isocyanide.[13] Scheme 1.6 shows the sequence by which levulinic acid and an *p*-methoxybenzylamine were reacted with indole isocyanide **14** to form the corresponding pyroglutamic acid anilide **15** in great yield as a racemic mixture. The Ugi product was treated with a catalytic amount of CSA in benzene with gentle heating to afford the *N*-acylindole **16**. Despite significant steric hinderance about the amide, this activated intermediate was readily cleaved to the corresponding carboxylic acid **17** using cesium carbonate in a mixture of DMF and water. When this general sequence was set we decided to make a series of pyroglutamic acids from the corresponding levulinic acid derivatives containing various functional groups and an additional stereocenter.



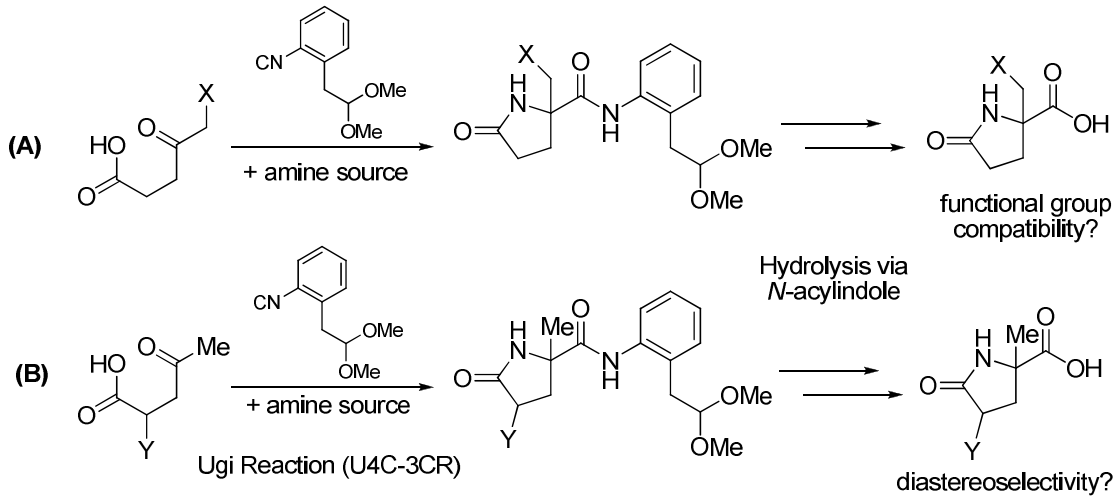
Scheme 1.6. Introduction of indole isocyanide as a convertible isocyanide.[13]

C. Synthesis of a Series of Pyroglutamic Acids

We set out to synthesize two series of pyroglutamic acids using the combination of the Ugi reaction and the cleavable indole isocyanide. The first goal with the two series would be to ensure that the pyroglutamic acids synthesized would be fully unprotected, meaning that in addition to the free carboxylic acid the amide nitrogen, which results from the amine component, should also be unprotected. We also wanted to see the effect on the Ugi reaction from the positioning of various substituents on the levulinic acid backbone prior to the U4C-3CR.

As seen in Scheme 1.7, we chose to define the two series by varying substituents in two places on the levulinic acid backbone. The first, series **A**, made by varying the X substituents, would place the substituents outside of the newly formed ring. The second, series **B**, made by varying the Y substituents, would allow us to test for the presence of substrate-controlled diastereoselectivity in the reaction. The first series, containing

substituents in the X position, is described in this section and the second series, with a discussion of diastereoselectivity for the reaction, is in the next section.

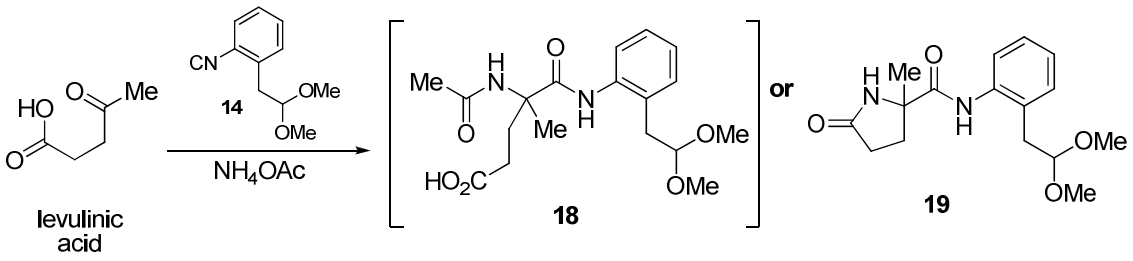


Scheme 1.7. Plan for two series of unprotected pyroglutamic acids.

1. Searching for an Ammonia Equivalent for the Ugi Reaction

There is a key difference between the reaction sequence shown in Scheme 1.6 and the first sequence we were currently planning (Scheme 1.7). While a primary amine such as allyl amine or *p*-methoxybenzyl amine had always been previously used in the reaction, we now sought to use ammonia or an ammonia equivalent as the necessary amine source. We wanted to obtain unprotected pyroglutamic acids because the natural products we wished to pursue are unsubstituted. Finding conditions for an ammonia equivalent would not only shorten the overall synthetic sequence. When a protecting group like *p*-methoxybenzyl is used for the amine harsh oxidative conditions, usually including ceric ammonium nitrate (CAN), are required for the deprotection.[15]

Various ammonia sources were tried in the U4C-3CR with levulinic acid and indole isocyanide. Ammonia in methanol and various salts of ammonium carboxylates and halides were tested. Ammonium acetate was found to be the best choice and 1,1,1,3,3,3-hexamethyl disilazane (HMDS) worked as well. We were initially worried that ammonium acetate would not work because of incorporation of the acetic acid into the products. Since acetic acid can participate in the Ugi reaction we were concerned that linear products such as **18** would form preferentially to the cylcized product **19** (Scheme 1.8). Fortunately, this outcome was never observed. We believe that the intramolecular relationship between the carboxylic acid and ketone in levulinic acid excludes the participation of acetic acid. Since ammonium acetate is a readily available and easy to handle crystalline solid we decided it would be a suitable ammonia source for the U4C-3CR.

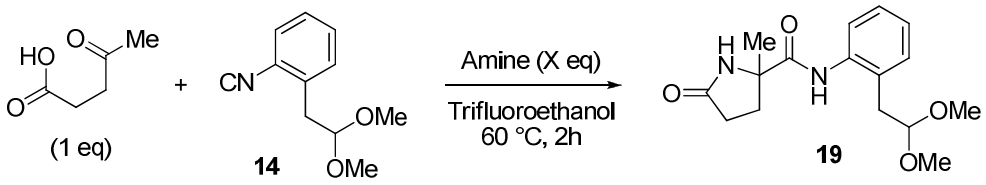


Scheme 1.8. Concern about incorporation of acetate into the Ugi product.

Previous experience showed that 2,2,2-trifluoroethanol (TFE) was the solvent of choice for this reaction. With all of the necessary components in hand the only thing left was to find the optimal procedure for carrying out the Ugi reactions. Levulinic acid was

reacted with indole isocyanide **14** and ammonium acetate in TFE in the ratios shown in Table 1.1 to form Ugi product **19**.[16]

Table 1.1. Optimization of the U4C-3CR with levulinic acid.



Entry	Amine	X eq	Isonitrile **14**	Yield (%)[a]
1	NH_4·OAc	1.1	1.1	61
2	NH_4·OAc	2	1.1	77
3	NH_4·OAc	2	2	82
4[b]	NH_4·OAc	2	1.1	84
5	HMDS[c]	2	1.1	72

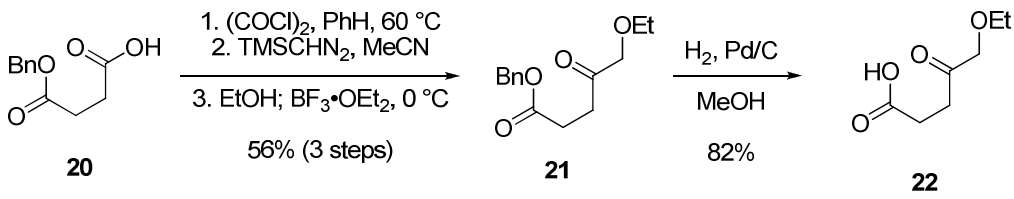
[a] Isolated yield (1 mmol scale). [b] MS4Å was added (20 mg/mmol).
[c]HMDS =Hexamethyldisilazane.

The first observation we were able to make while carrying out these experiments is that two equivalents of ammonium acetate improved the yield over only one equivalent but further excess did not help. Doubling the amount of isocyanide added improved the yield, but not dramatically (Entry 3). We did notice that hydration of the isocyanide to form the corresponding formanilide was a competing reaction and so decided to add 4Å molecular sieves, which did improve the yield. HMDS was also found to participate in the reaction (Entry 5), although ammonium acetate was chosen because of the higher yield. The ease of handling ammonium acetate, a stable, crystalline solid, was also a factor. Armed with an optimized Ugi reaction we set out to make the first set of

pyroglutamic acids, beginning with the synthesis of the necessary levulinic acid derivatives.

2. Synthesis of Linear Starting Materials

The first step in making a series of pyroglutamic acids was to develop a general way to quickly arrive at the necessary linear γ-ketoacids needed for the Ugi reactions. Fortunately, a few of the substituted levulinic acid derivatives that we were interested are commercially available, however not all. We found that the quickest route to certain of the necessary derivatives was to start with succinic anhydride. This readily available anhydride starting material is easily opened to the corresponding ester/acid **20** using a nucleophile such as benzyl alcohol (Scheme 1.9).



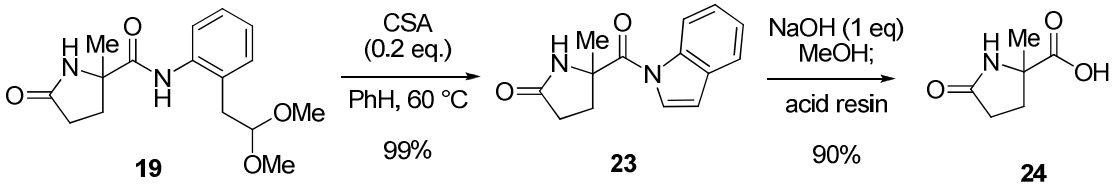
Scheme 1.9. TMS-diazomethane assisted synthesis of γ-ketoacid.

The carboxylic acid **20** is converted to the corresponding acid chloride and then treated with TMS-diazomethane. This yields a very unstable intermediate diazoketone that can quickly react with many acids and alcohols. In the example shown, treatment of the diazoketone with ethanol and $BF_3 \cdot OEt_2$ yields the corresponding ethyl ether **21**.[17] It is also possible to treat the diazoketone with hydrochloric or hydrobromic acid to obtain the corresponding halo-ketone. In most cases we chose to use the benzyl group as

protection for the ester because it can be removed easily under neutral (reductive) conditions, as was completed smoothly in this case to yield γ-ketoacid **22**.

3. Elaboration of the Ugi Products to Pyroglutamic Acids

Once the necessary γ-ketoacids were in hand, we were ready to bring them through the reaction sequence to make the various unprotected pyroglutamic acids. First, levulinic acid was submitted to the Ugi reaction as shown in Table 1.1. After the Ugi reaction the product **19** was treated with catalytic acid to form *N*-acylindole **23** (Scheme 1.10). Notably, we were able to show at this point that indole formation was successful despite the presence of the unprotected amide nitrogen (derived from ammonium acetate), which we feared might interfere with indole formation. **23** was hydrolyzed using sodium hydroxide in methanol to give the intermediate sodium salt which was immediately treated with acidic resin to give fully unprotected pyroglutamic acid **24**. Compound **24** had been previously prepared by a different method,[18] as was the corresponding methyl ester.[19]



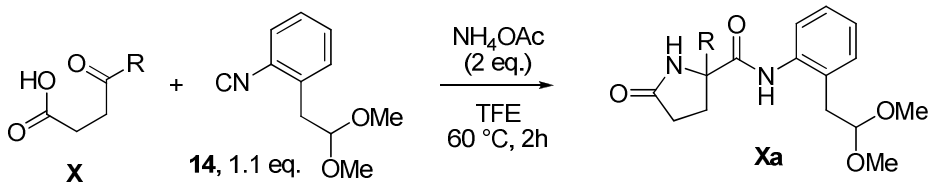
Scheme 1.10. Elaboration of Ugi product **19** to the corresponding acid.

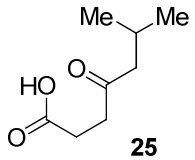
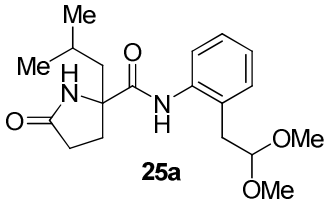
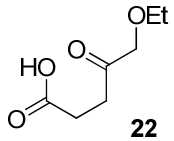
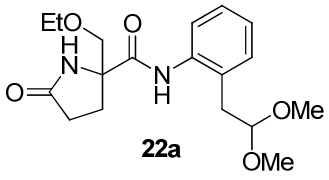
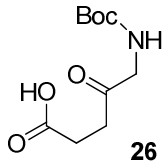
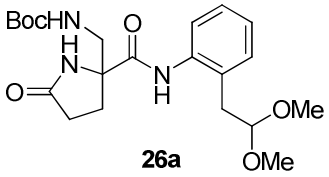
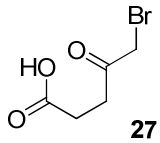
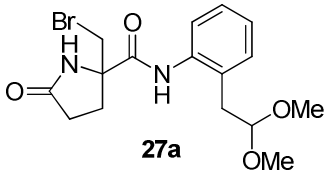
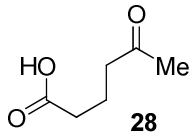
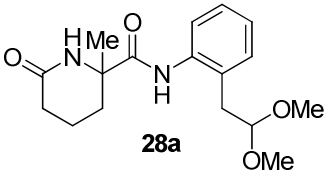
Because we were working with unprotected pyroglutamic acids it was necessary to develop new conditions for the hydrolysis step. The increased water solubility of the products left us unable to extract the hydrophilic product **24** from DMF as had been done

in the example shown in Scheme 1.6. Our plan was therefore to use sodium hydroxide in methanol, which gives the unprotected pyroglutamic acids very cleanly. The free acids are readily isolated by treating the intermediate sodium salts with acid resin and removing the resin by filtration followed by evaporation of methanol. In the actual event, we decided to isolate the various pyroglutamic acids as their methyl esters due to ease of handling and purification. The methyl ester of pyroglutamic acid **24**, (**24a**, see Experimental Section) was isolated in 90% yield using this procedure.

We finally undertook the full transformations for this series. The γ-ketoacids chosen are listed in Table 1.2 along with the yields for each step, the Ugi reaction, each of which was carried out according to the procedure just described.

Table 1.2. U4C-3CR of various γ-ketoacids with indole isocyanide.



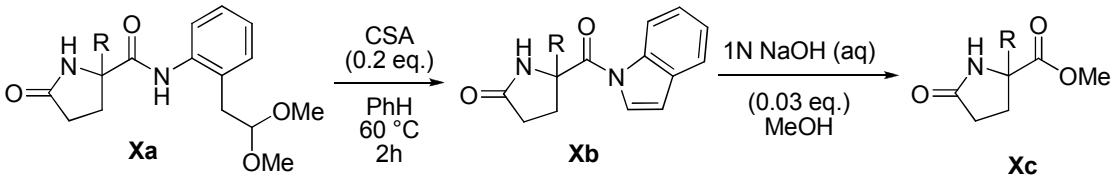
Entry	Substrate	Product	Yield (%)
1	 **25**	 **25a**	63%
2	 **22**	 **22a**	76%
3	 **26**	 **26a**	67%
4	 **27**	 **27a**	49%
5	 **28**	 **28a**	59%

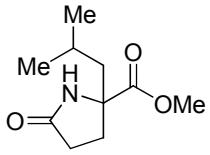
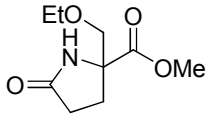
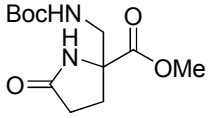
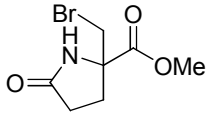
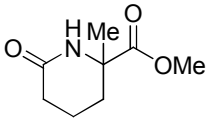
Compound **25** was chosen because we wanted to see the steric tolerance around the ketone beyond levulinic acid. We sought to determine the effect on yield in the Ugi product as well as the problems, if any, that would be associated with indole formation. While the Ugi product yield was mildly depressed, no problems were encountered with

indole formation. In addition, the Ugi product derived from **25** contains the full carbon backbone of the natural product lactacystin. Compound **25** was synthesized according to literature precedent.[20] Compounds **22**, **26**, and **27** were chosen because of the existence of a heteroatom in the α-position of the ketone. Compound **22** was synthesized as described above while **26**[21] and **27**[22] were synthesized according to literature precedents. We believe that the yield of **27a** was most likely lowered by slow nucleophilic displacement of the bromoketone by ammonia or another nucleophile during the Ugi reaction. Commercially available compound **28** is actually a δ-ketoacid and was ultimately used to synthesize homo-pyroglutamic acid methyl ester **28c** (Table 1.3). In this case the decrease in yield is assumed to be due to the fact that the Ugi reaction must proceed through a seven-membered acylimidate ring before Mumm rearrangement.

The Ugi products were all successfully converted to the corresponding *N*-acylindole intermediates as listed in Table 1.3. Yields shown are for two steps (**Xa-Xc**). Each *N*-acylindole was finally submitted to methanolysis conditions using a small, catalytic amount of sodium hydroxide in methanol to cleanly afford the methyl esters as shown. As was mentioned before, the *N*-acylindoles could also be hydrolyzed using sodium hydroxide to obtain the corresponding sodium carboxylates or free acids in excellent yield.

Table 1.3. Conversion of Ugi products to the methyl esters via *N*-acylindoles.



Entry	Substrate	Product	Yield (%)[a]
1	**25a**	 **25c**	86
2	**22a**	 **22c**	94
3	**26a**	 **26c**	98
4	**27a**	 **27c**	96
5[b]	**28a**	 **28c**	83

[a] Isolated yield of **Xc** (2 steps from **Xa**, 0.2-0.5 mmol scale).
[b] Homopyroglutamic acid.

One of the products shown, **28c**, was previously synthesized by another group using a different method.[23] The ethyl ester of compound **25c** was also previously constructed.[24]

D. Study of Diastereoselectivity in the U4C-3CR

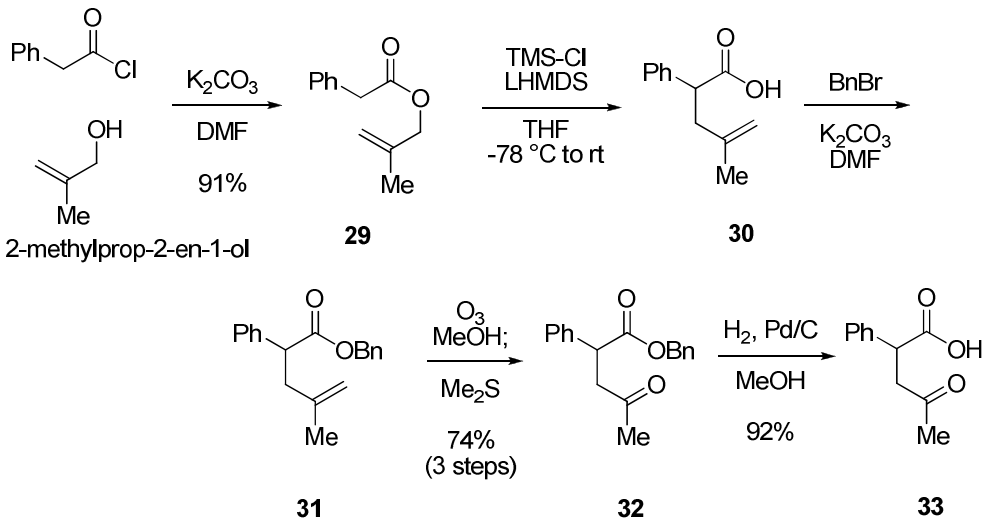
The second series of unprotected pyroglutamic acids that we chose to synthesize would test the substrate-controlled diastereoselectivity of the Ugi reaction. We hoped to

find some indication that varying the substitution pattern of the γ-ketoacid starting materials would show a corresponding variation in diastereoselectivity. Unfortunately no such pattern emerged. Developing methods to make this reaction more diastereoselective has always been one of our foremost goals, but one to which we have not found a general solution.

1. Synthesis of Linear Starting Materials – Chiral γ-Ketoacid

As with the previous series of pyroglutamic acids, we needed to start by synthesizing the necessary γ-ketoacid starting materials needed for the Ugi cyclizations. In addition to showing the usefulness of the Ugi reaction for this type of process, we also wished to develop a general method for making the starting materials. This was necessary because a general method for synthesizing substituted levulinic acid derivatives did not exist. Developing a standard method would not only enable us to quickly make various derivatives. We also hoped that by providing a facile, general method of making the starting materials, that other chemists would be encouraged to use this method.

We found that a series of reactions consisting of Ireland-Claisen rearrangement of an allyl ester followed by oxidative olefin cleavage via ozonolysis was the best sequence to prepare the various chiral γ-ketoacids. Scheme 1.11 outlines the synthesis of a γ-ketoacid by this method.



Scheme 1.11. Synthesis of a γ-ketoacid via Ireland-Claisen reaction and ozonolysis.

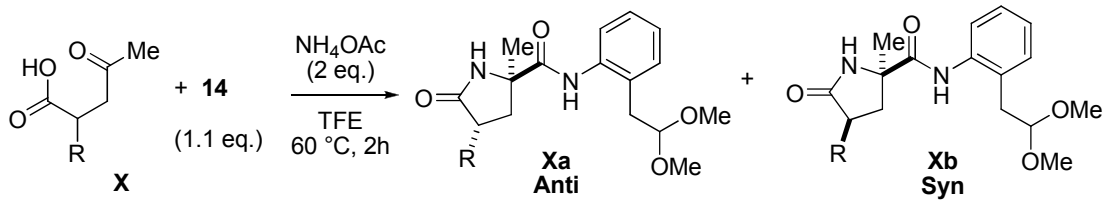
An acetic acid chloride substituted with the desired substituent, in this example it is a phenyl group, was coupled with commercially available 2-methyl-2-propenol according to literature precedent to give ester **29**.[25] Ireland-Claisen rearrangement was induced by the addition of TMS-Cl and then LHMDS at very low temperature, affording **30**.[26] The resulting carboxylic acid was immediately protected as the benzyl ester **31** and then purified. The exo-olefin of **31** was cleaved to the corresponding ketone **32** using ozonolysis.[27] Palladium-charcoal mediated hydrogenolysis of the benzyl ester cleanly yields the desired γ-ketoacid **33** which can be submitted to the U4C-3CR.

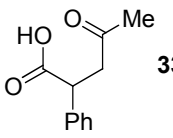
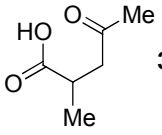
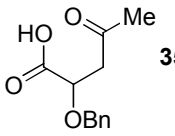
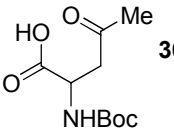
2. Substrate-Controlled Diastereoselectivity in the U4C-3CR

We submitted the second series of linear γ-ketoacids containing a chiral center to the U4C-3CR with a particular eye towards the diastereoselectivity of the resulting amino acid. Table 1.4 shows the yields and diastereomeric ratios of the various Ugi products. For the cases studied the two diastereomers were separable and the ratio shown was

determined by the isolated yield of each diastereomer. In each case the ratio shown is of the less polar to more polar compound indicated by TLC analysis on silica gel.

Table 1.4. Yield and diastereoselectivities in U4C-3CR for various chiral δ-ketoacids.



Substrate		Yield	Ratio Xa:Xb
	**33**	74%	1:1
	**34**	64%	1:1
	**35**	61%	2:3
	**36**	59%	3:2

The assignment of diastereomers is based on comparison with an X-ray crystal structure obtained for compound **33b**, which was more polar by TLC than **33a**, and was shown to be the *syn*-compound. In this case the *syn*-designation refers to the relationship

between the α-substituent and the resulting anilide on the γ-lactam ring. The ORTEP drawing for the X-ray structure of **33b** is shown in Figure 1.2.

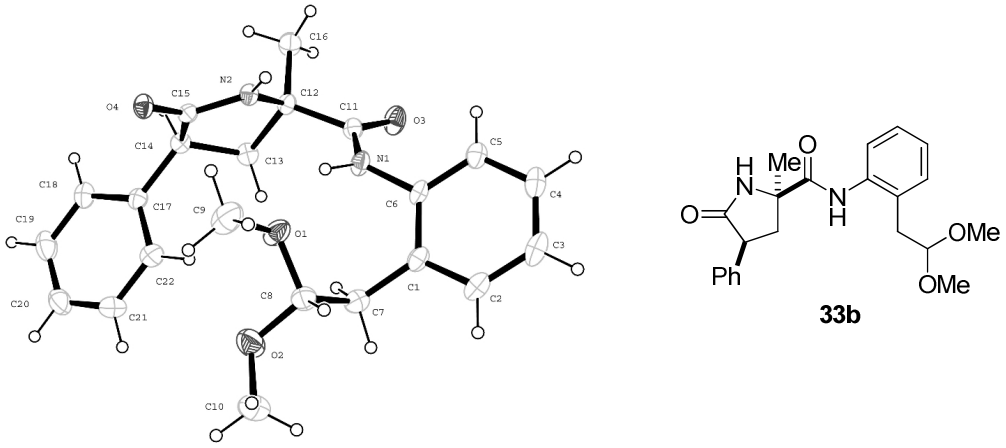


Figure 1.2. ORTEP drawing of the X-ray crystal structure of **33b**.

All of the δ-ketoacids tested participated in the Ugi cyclization reaction. The yields were modest but respectable, however the induced diastereoselectivities of the reaction offered no encouragement. We had hoped that the use of a bulky 'R' group like phenyl and the others shown would affect the diastereoselectivity of the reaction, but this was not the case.

E. Conclusions

This research was originally designed to probe the usefulness of the Ugi reaction for making unprotected pyroglutamic acids and that task was satisfactorily completed. We successfully developed a cleavable isocyanide for this problem that enabled the selective cleavage of a very hindered amide bond. This bond was easily converted into either the corresponding methyl ester or free carboxylic acid. The pyroglutamic acids

and esters we made were very hydrophilic. We were therefore able to develop special conditions for these types of compounds that employ water-free reaction conditions and purification procedures for ease of isolation.

Another important goal of the research just described was the incorporation of ammonia or an equivalent as the amine source for the Ugi reaction. We found that ammonium acetate participates as an ammonia equivalent without the formation of undesirable side products. Furthermore, we showed that even with the γ-lactam derived from this reaction is left unprotected that there is no interference with the formation and subsequent cleavage of the *N*-acylindole. Additionally, the incorporation of an ether, a protected amine and a halogen into the linear precursors did not cause any adverse side effects.

Unfortunately, we did not observe the type of substrate-induced diastereoselectivity that we hoped for when submitting chiral γ-ketoacids to the U4C-3CR. Although the various substrates reacted to form the Ugi products in reasonable yield, the diastereoselectivity was poor. This appears to be a problem that must be solved on a case-by-case basis, and one that would certainly continue to occupy our time going forward. With all of the lessons learned from this project now in hand, we next turned our sites towards the synthesis of the pyroglutamic acid natural product dysibetaine.

F. Acknowledgements

This chapter contains material that was previously published in the paper: *Expeditious Access to Unprotected Pyroglutamic Acids*. Isaacson, Jerry; Gilley, Cynthia B.; Kobayashi, Yoshihisa. *J. Org. Chem.* **2007**, *72*, 3913-3916. Dr. Gilley is graciously acknowledged for her contribution to this work.

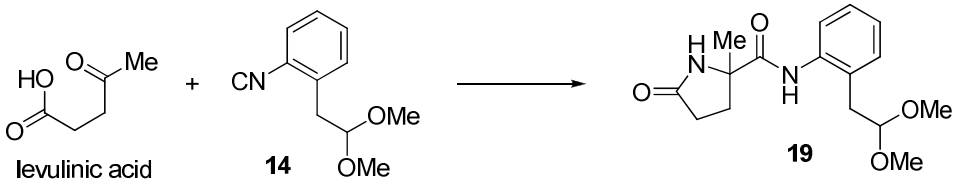
G. Experimental Section

1. Materials and Methods

All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. Tetrahydrofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), 2,2,2-trifluoroethanol (TFE), and acetone were purchased as reagent grade and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, br = broad. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnigan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or

fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]25D = (100 \cdot \alpha)/(l \cdot c)$, where the concentration c is in g/100 mL and the path length l is in decimeters.

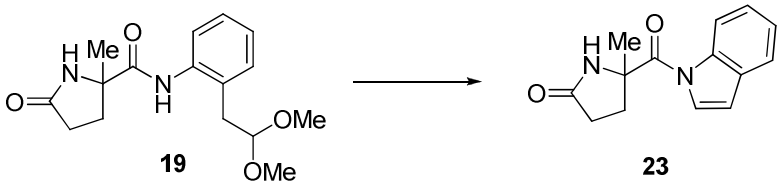
2. Procedures and Spectral Data



Scheme 1.12. Synthesis of **19**.

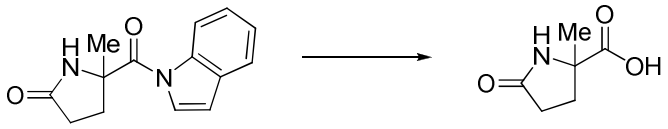
General Procedure for Ugi reaction (Preparation of **19**): Ammonium acetate (2.0 mmol) was added to levulinic acid (1.0 mmol) in 2,2,2-trifluoroethanol (2 ml) and the reaction was heated to 60 °C. After thirty minutes, 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**14**) (1.1 mmol) was added and the reaction continued to stir at 60 °C until the isonitrile was consumed according to TLC (about 2 hours). The reaction was removed from heat and the 2,2,2-trifluoroethanol was evaporated. The residue was diluted with water (10 mL) then extracted with ethyl acetate (2 x 15 mL). The combined organic portions were washed with brine (10 mL), dried over Na_2SO_4 then concentrated. Recovered 0.236 g (77%) Ugi product **19** as colorless solid after purification by silica gel column chromatography (100% EtOAc). Mp 142-143 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H),

7.11 (t, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 4.45 (t, *J* = 5.3 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.88 (dd, *J* = 3.8, 5.3 Hz, 2H), 2.58-2.44 (m, 3H), 2.19-2.14 (m, 1H), 1.62 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 178.0, 172.8, 136.3, 131.3, 128.5, 127.8, 125.5, 124.3, 106.8, 63.8, 54.8, 54.6, 37.3, 34.4, 30.5, 26.0.; HRMS $C_{16}H_{22}N_2O_4$: calculated: 306.1574, observed: 306.1579.



Scheme 1.13. Synthesis of **23**.

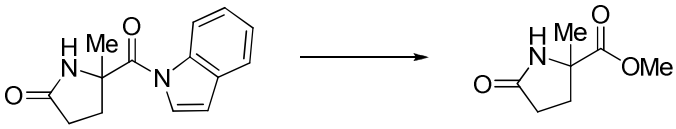
General Procedure for *N*-Acylindole Formation (Preparation of **23**): Camphorsulfonic acid (0.4 mmol) was added to the Ugi product **19** (2.0 mmol) in benzene (10 mL) and the reaction was heated to 60 °C for one hour. The reaction was washed with saturated $NaHCO_3$ (aq.) and brine. Dried over Na_2SO_4 then filtered and concentrated. Recovered 0.485 g (2.0 mmol) oil **23**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.79 (br, 1H), 6.70 (d, *J* = 3.6 Hz, 1H), 2.83-2.77 (m, 1H), 2.66-2.59 (m, 1H), 2.52-2.41 (m, 2H), 1.80 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 175.4, 172.1, 129.7, 128.5, 126.0, 124.6, 124.1, 121.1, 117.4, 110.6, 64.8, 33.3, 30.2, 28.2. HRMS $C_{14}H_{14}N_2O_2$: calculated: 242.1050, observed: 242.1053.



23 **24**

Scheme 1.14. Synthesis of **24**.

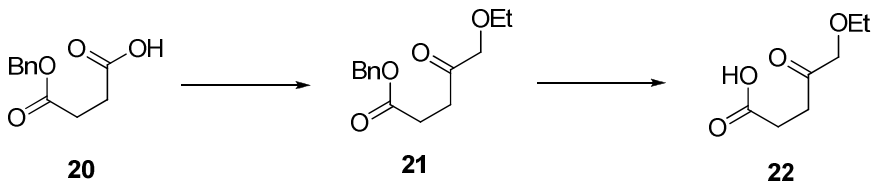
General Procedure for Hydrolysis of *N*-Acylindole (Preparation of 2-Methylpyroglutamic Acid **24**): 0.242 g (1.0 mmol) of **23** was dissolved in methanol (3 mL). Solid sodium hydroxide (1.0 mmol) was added and the reaction stirred until no starting material remained by TLC (about 1 hr). The reaction was concentrated and the sodium salt of the product was recrystallized from methanol/diethyl ether to yield 0.162 g (0.98 mmol) white solid. The sodium salt was treated with Amberlyst 15 in methanol and upon concentration 0.124 g (90% from **23**) of the free carboxylic acid **24** was recovered as a white solid, mp 144-145 °C (lit: 144-145 °C).[18] ^{1}H NMR (400MHz, CD_3OD) δ 8.15 (s, 1H), 2.48-2.37 (m, 3H), 2.07-1.99 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (100MHz, CD_3OD) 179.0, 176.4, 62.7, 32.6, 32.5, 24.1. HRMS $C_6H_9NO_3$: calculated: 143.0577, observed: 143.0575.



23 **24a**

Scheme 1.15. Synthesis of **24a**.

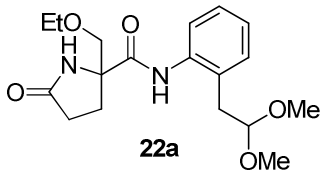
General Procedure for Methanolysis of *N*-Acylindole (Preparation of 2-Methylpyroglutamic Acid Methyl Ester **24a**): Aqueous sodium hydroxide (1N, 6 μmol) was added to crude *N*-acylindole **23** (1.0 mmol) dissolved in methanol (3 mL) and the reaction was stirred for one hour then concentrated. Purified by column chromatography (100% CH_2Cl_2 to 9:1 CH_2Cl_2:methanol). The combined fractions were dried over Na_2SO_4 and treated with activated charcoal (if necessary) then filtered and concentrated. Recovered 0.282 g (90%) white crystalline solid of methyl ester **24a**, mp 87-89 °C (lit 58-59 °C)[19]. ^{1}H NMR (400MHz, CD_3OD) δ 3.74 (s, 3H), 2.47-2.32 (m, 3H), 2.07-1.99 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (100MHz, CD_3OD) δ 178.9, 174.9, 62.8, 52.0, 32.5, 29.9, 24.1. HRMS $C_7H_{11}NO_3$: calculated: 157.0733, observed: 157.0736.



Scheme 1.16. Synthesis of **22**.

5-Ethoxy-4-Oxopentanoic Acid (**22**): Benzyl succinate **20** (6.3 mmol) was treated with oxalyl chloride (8.1 mmol, 1.3 eq.) in benzene (20 mL) and the reaction was heated to 60 °C for one hour after which time all volatile components were removed by vacuum. The crude acid chloride was dissolved in acetonitrile (15 mL) then (trimethylsilyl)diazomethane (2.0M solution in Et_2O, 6.3 mL, 2.0 eq.) was slowly added. After 30 minutes the reaction was cooled to 0 °C then ethanol (5 mL) was added followed by the careful addition of $BF_3{\cdot}OEt_2$ (1.16 mL, 1.5 eq.). After 1 hour the reaction

was diluted with water (50 mL) then extracted with ethyl acetate (2 x 20 mL). The combined organic portions were washed with brine (20 mL) then dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using 4:1 hexanes:ethyl acetate to yield benzyl 5-ethoxy-4-oxopentanoate **21** (3.5 mmol, 56%) as a clear oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 5.11 (s, 2H), 4.06 (s, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 2.79 (t, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 1.24 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 207.8, 172.7, 136.0, 128.8, 128.5, 128.4, 76.0, 67.4, 66.8, 33.7, 27.8, 15.3. HRMS $C_{14}H_{18}O_4$: calculated: 250.1200, observed: 250.1201. **(21)** (0.46 mmol) was dissolved in methanol (3 mL) and catalytic palladium on carbon (10% w/w, 5 mg) was added. The reaction was stirred under one atmosphere of H_2 for three hours then filtered through Celite and concentrated to yield **22** (0.38 mmol, 82%) as a clear oil. ^{1}H NMR (400MHz, CD_3OD) δ 4.16 (s, 1H), 3.55 (q, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 2.6 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100MHz, CD_3OD) δ 208.4, 175.1, 75.2, 66.9, 33.0, 27.1, 14.1. HRMS $C_7H_{12}O_4$: calculated: 160.0730, observed: 160.0728.

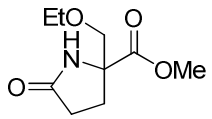


22a

Figure 1.3. Synthesis of **22a**.

(**22a**) mp 101-102 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H),

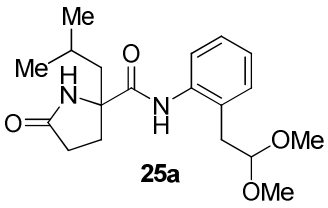
6.37 (s, 1H), 4.48 (dd, *J* = 4.4, 6.4 Hz, 1H), 4.02 (d, *J* = 8.8 Hz, 1H), 3.53-3.47 (m, 2H), 3.42 (s, 6H), 3.39 (d, *J* = 8.8 Hz, 1H), 2.97 (dd, *J* = 6.4, 14 Hz, 1H), 2.82 (dd, *J* = 4.4, 14 Hz, 1H), 2.52-2.36 (m, 3H), 2.11-2.06 (m, 1H), 1.14 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 177.4, 171.4, 136.1, 131.1, 128.6, 127.5, 125.4, 124.3, 106.1, 75.2, 67.0, 66.6, 54.4, 53.5, 36.8, 29.3, 28.7, 14.9. HRMS $C_{18}H_{26}N_2O_5$: calculated: 350.1836, observed: 350.1843.



22c

Figure 1.4. Synthesis of **22c**.

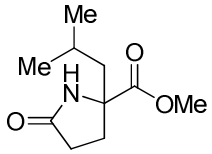
(**22c**) (oil) ^{1}H NMR (400MHz, CD_3OD) δ 3.76 (s, 3H), 3.55-3.49 (m, 4H), 2.38-2.26 (m, 3H), 2.15-2.13 (m, 1H), 1.16 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100MHz, CD_3OD) δ 178.9, 173.2, 74.8, 67.1, 66.8, 52.2, 29.6, 27.6, 14.3. HRMS $C_9H_{15}NO_4$: calculated: 201.0996, observed: 201.0995.



25a

Figure 1.5. Synthesis of **25a**.

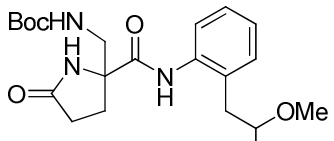
(**25a**) mp 129-131 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.33 (s, 1H), 4.48 (t, *J* = 5.3 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.88 (d, *J* = 5.3 Hz, 2H), 2.59-2.53 (m, 1H), 2.46-2.39 (m, 2H), 2.22-2.13 (m, 2H), 1.80-1.74 (m, 1H), 1.61 (dd, *J* = 6.2, 14.1 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 178.1, 172.8, 136.5, 131.5, 128.6, 127.9, 125.6, 124.4, 106.6, 66.7, 54.5, 54.4, 47.8, 37.2, 34.9, 29.7, 25.4, 24.4, 23.2. HRMS $C_{19}H_{28}N_2O_4$: calculated: 348.2044, observed: 348.2039.



25c

Figure 1.6. Synthesis of **25c**.

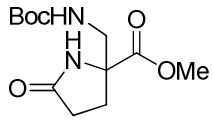
(**25c**) mp 81-84 °C. ^{1}H NMR (400MHz, CD_3OD) δ 3.74 (s, 3H), 2.45-2.31 (m, 3H), 2.12-2.05 (m, 1H), 1.85-1.69 (m, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100MHz, CD_3OD) δ 178.6, 174.7, 66.1, 52.0, 47.4, 32.0, 29.7, 24.7, 23.7, 22.1. HRMS $C_{10}H_{17}NO_3$: calculated: 199.1203, observed: 199.1199.



26a

Figure 1.7. Synthesis of **26a**.

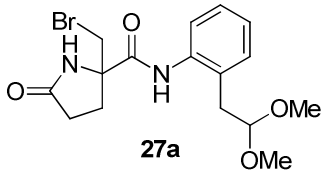
(**26a**) mp 83-86 °C. ^{1}H NMR (500MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.08 (s, 1H), 5.16 (s, 1H), 4.49 (t, *J* = 5.1 Hz, 1H), 3.58-3.48 (m, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 2.86 (d, *J* = 5.1 Hz, 2H), 2.50-2.39 (m, 3H), 2.14-2.12 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 178.3, 172.2, 157.5, 136.1, 131.5, 129.0, 127.7, 125.8, 124.4, 106.1, 80.4, 68.3, 54.3, 54.2, 48.0, 37.0, 30.7, 29.9, 28.5. HRMS $C_{21}H_{31}N_3O_6$: calculated: 421.2207, observed: 421.2213.



26c

Figure 1.8. Synthesis of **26c**.

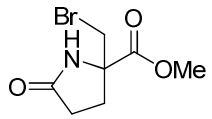
(**26c**) (oil) ^{1}H NMR (400MHz, CD_3OD) δ 3.75 (s, 3H), 3.48 (d, *J* = 14.1 Hz, 1H), 3.38 (d, *J* = 14.1 Hz, 1H), 2.40-2.14 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (100MHz, CD_3OD) δ 179.0, 173.2, 157.4, 79.4, 66.9, 52.2, 46.4, 29.5, 27.8, 27.5. HRMS $C_{12}H_{20}N_2O_5$: calculated: 272.1367, observed: 272.1367.



27a

Figure 1.9. Synthesis of **27a**.

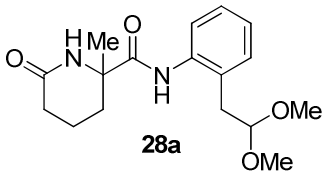
(**27a**) mp 130°C (dec). ^{1}H NMR (300MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.74 (s, 1H), 7.33-7.15 (m, 3H), 6.23 (s, 1H), 4.51 (t, *J* = 5.5 Hz, 1H), 4.19 (d, *J* = 7.5 Hz, 1H), 3.50 (d, *J* = 7.5 Hz, 1H), 3.45 (s, 3H), 3.44 (s, 3H), 3.01 (dd, *J* = 5.5, 13.8 Hz, 1H), 2.85 (dd, *J* = 5.5, 13.8 Hz, 1H), 2.66-2.52 (m, 3H), 2.30-2.25 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.8, 170.2, 136.1, 131.6, 129.0, 127.9, 126.1, 124.7, 106.5, 66.8, 54.7, 54.1, 39.2, 37.3, 32.0, 30.3. HRMS $C_{16}H_{21}BrN_2O_4$: calculated: 384.0679, observed: 384.0678.



27c

Figure 1.10. Synthesis of **27c**.

(**27c**) mp 92-94 °C. ^{1}H NMR (400MHz, CD_3OD) δ 3.85-3.71 (m, 2H), 3.80 (s, 3H), 2.51-2.21 (m, 4H); ^{13}C NMR (100MHz, CD_3OD) δ 178.8, 172.0, 66.6, 52.4, 37.4, 29.8, 29.6. HRMS $C_7H_{10}BrNO_3$: calculated: 234.9839, observed: 234.9835.

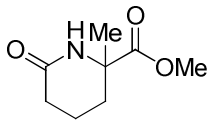


28a

Figure 1.11. Synthesis of **28a**.

(**28a**) mp 157-159 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H),

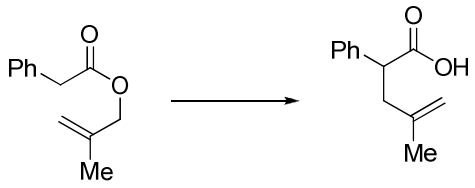
6.51 (s, 1H), 4.45 (t, *J* = 5.3 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 2.86 (d, *J* = 5.3 Hz, 2H), 2.49-2.37 (m, 3H), 1.87-1.80 (m, 2H), 1.65-1.59 (m, 1H), 1.57 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.8, 172.1, 136.4, 131.3, 128.8, 127.7, 125.7, 124.7, 106.6, 61.8, 54.9, 54.3, 37.3, 33.8, 31.3, 27.9, 18.6. HRMS $C_{17}H_{24}N_2O_4$: calculated: 320.1731, observed: 320.1728.



28c

Figure 1.12. Synthesis of **28c**.

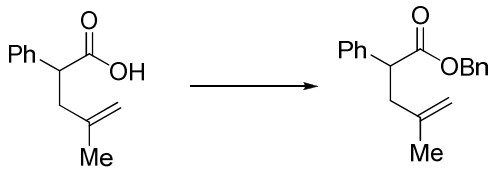
(**28c**) mp 98-100 °C. (lit: 98.5-99.5 °C) ^{1}H NMR (400MHz, CD_3OD) δ 3.74 (s, 3H), 2.31-2.19 (m, 3H), 1.86-1.82 (m, 1H), 1.74-1.61 (m, 2H), 1.47 (s, 3H); ^{13}C NMR (100MHz, CD_3OD) δ 174.9, 173.6, 59.9, 52.1, 32.4, 30.1, 25.3, 17.8. HRMS $C_8H_{13}NO_3$: calculated: 171.0890, observed: 171.0892.



29 **30**

Scheme 1.17. Synthesis of **30**.

(**30**) **29**[25] (0.855 g, 4.5 mmol) was dissolved in THF (10 mL) and cooled to -78 ˚C under N_2 atmosphere. LHMDS (6.35 mL, 1.06M in THF) was slowly added followed by freshly distilled TMS-Cl (0.86 mL, 6.7 mmol). After 1 hr the reaction was allowed to slowly warm to room temperature and was then heated to 60 ˚C for 1.5 hr. The reaction was removed from heat and cooled then extracted with 2x 1N NaOH (10 mL). The aqueous extracts were washed with EtOAc (10 mL) then carefully acidified with conc. HCl and extracted with 2 x EtOAc (15 mL). The combined organics were brined and dried over Na_2SO_4 then concentrated to give 0.942 g of **30** that was brought forward to the next step without further purification. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.76 (s, 1H), 4.72 (s, 1H), 3.82 (dd, *J* = 6.6, 8.8 Hz, 1H), 2.84 (dd, *J* = 8.8, 14.6 Hz, 1H), 2.45 (dd, *J* = 6.6, 14.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 179.3, 142.5, 138.3, 128.9, 128.2, 127.8, 112.7, 50.1, 41.0, 22.8. MS (negative mode) $C_{12}H_{14}O_2$: calculated: 190.10, observed: $[M - H]^-$ = 188.99.

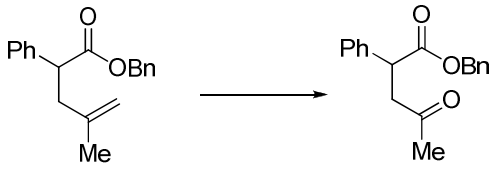


30 **31**

Scheme 1.18. Synthesis of **31**.

(**31**) **30** (0.942 g crude) was dissolved in DMF (15 mL) and K_2CO_3 (1.242 g, 9.0 mmol) was added followed by benzyl bromide (1.07 mL, 9.0 mmol). After 3 hours the reaction was diluted with H_2O (100 mL) then extracted with 3 x EtOAc (20 mL).

Combined organics were brined, dried over Na_2SO_4 and concentrated. Recovered 1.641 g of a mixture that contained **31** and excess benzyl bromide. The mixture was brought forward to the next step for ease of purification. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.23 (m, 10H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.74 (s, 1H), 4.69 (s, 1H), 2.87 (dd, *J* = 9.3, 14.7 Hz, 1H), 2.46 (dd, *J* = 6.3, 14.7 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 173.6, 142.8, 138.9, 136.1, 128.8, 128.7, 128.3, 128.20, 128.18, 127.6, 112.5, 66.7, 50.3, 41.5, 22.9. MS $C_{19}H_{20}O_2$: calculated: 280.15, observed: $[M + NH_4]^+ = 297.95$.

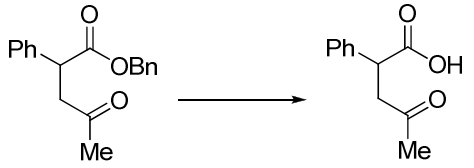


31 **32**

Scheme 1.19. Synthesis of **32**.

(**32**) **31** (1.641 g crude from the previous step) was dissolved in MeOH (20 mL) along with a trace amount of Sudan III indicator. The reaction was cooled to -78 ˚C and ozone was applied to the reaction until the red color of the indicator had disappeared, approximately 15 min. The reaction vessel was cleared with N_2 gas then dimethyl sulfide (1.64 mL, 22.5 mmol) was added and the reaction was allowed to warm to room temperature. After warming the reaction was concentrated and submitted to column chromatography (7:1 hexanes:EtOAc) and 0.941g of **32** (74% over 3 steps) as a golden oil were recovered. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.32-7.19 (m, 10H), 5.14 (d, *J* = 12.5

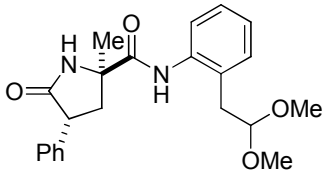
Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 4.17 (dd, *J* = 4.4, 10.3 Hz, 1H), 3.40 (dd, *J* = 10.3, 18.0 Hz, 1H), 2.74 (dd, *J* = 4.4, 18.0 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.3, 171.1, 138.2, 136.0, 129.1, 128.6, 128.2, 128.02, 127.95, 127.8, 66.9, 47.2, 46.5, 30.2. MS $C_{18}H_{18}O_3$: calculated: 282.13, observed: $[M + H]^+$ = 282.90.



32 **33**

Scheme 1.20. Synthesis of **33**.

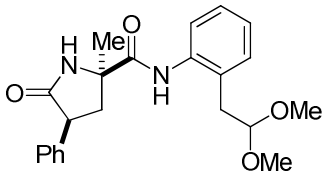
(**33**) **32** (0.391 g, 1.4 mmol) was dissolved in MeOH (10 mL) and a catalytic amount of Pd/C (10% w/w) was added. An H_2 balloon was applied and kept in place overnight after which time the reaction was cleared with N_2. After filtering through Celite, the reaction was concentrated to afford 0.244 g of **33** (92%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.37-7.22 (m, 5H), 4.12 (dd, *J* = 4.4, 10.2 Hz, 1H), 3.35 (dd, *J* = 10.2, 18.0 Hz, 1H), 2.73 (dd, *J* = 4.4, 18.0 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 206.4, 179.1, 137.6, 129.2, 128.1, 128.0, 46.8, 46.3, 30.1. MS (negative mode) $C_{11}H_{12}O_3$: calculated: 192.08, observed: $[M - H]^-$ = 190.90.



33a

Figure 1.13. Synthesis of **33a**.

(**33a**) ^{1}H NMR (500MHz, $CDCl_3$) δ 9.53 (s, 1H) 7.83 (d, *J* = 8.1 Hz, 1H), 7.37-7.13 (m, 8H), 6.55 (s, 1H), 4.48 (t, *J* = 5.4 Hz, 1H), 3.87 (dd, *J* = 8.7, 11.6 Hz, 1H) 3.43 (s, 3H), 3.42 (s, 3H), 3.15 (dd, *J* = 8.7, 13.2 Hz, 1H) 2.91 (dd, *J* = 1.2, 5.4 Hz, 2H), 2.24 (dd, *J* = 11.6, 13.2 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 178.2, 172.9, 138.1, 136.4, 131.5, 129.1, 128.7, 128.1, 127.9, 127.6, 125.6, 124.4, 107.1, 61.8, 54.9, 54.7, 47.3, 42.2, 37.2, 25.5. MS $C_{22}H_{26}N_2O_4$: calculated: 382.19, observed: $[M + Na]^+$ = 405.10.

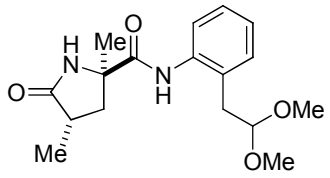


33b

Figure 1.14. Synthesis of **33b**.

(**33b**) ^{1}H NMR (500MHz, $CDCl_3$) δ 9.48 (s, 1H) 7.76 (d, *J* = 8.1 Hz, 1H), 7.34-7.10 (m, 8H), 6.58 (s, 1H), 4.42 (t, *J* = 5.2 Hz, 1H), 3.88 (t, *J* = 9.1 Hz, 1H) 3.37 (s, 3H), 3.31 (s, 3H), 2.82 (dq, *J* = 5.2, 14.1 Hz, 2H), 2.75-2.65 (m, 2H), 1.70 (s, 3H); ^{13}C NMR

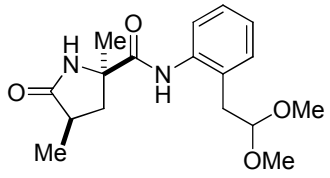
(75MHz, $CDCl_3$) δ 177.9, 172.9, 138.2, 136.4, 131.5, 129.0, 128.8, 128.5, 127.9, 127.6, 125.8, 124.5, 106.9, 61.7, 54.9, 54.6, 47.9, 44.5, 37.3, 26.2. MS $C_{22}H_{26}N_2O_4$: calculated: 382.19, observed: $[M + Na]^+ = 405.11$.



34a

Figure 1.15. Synthesis of **34a**.

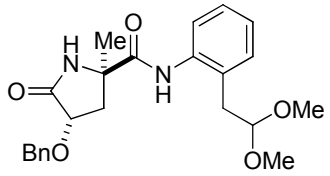
(**34a**) ^1H NMR (500MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.30-7.10 (m, 3H), 5.95 (s, 1H), 4.46 (t, *J* = 5.3 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 2.92-2.86 (m, 3H), 2.68-2.60 (m, 1H), 1.76 (dd, *J* = 11.1, 13.1 Hz, 1H), 1.62 (s, 3H), 1.23 (d, *J* = 5.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 180.2, 173.2, 136.4, 131.4, 128.6, 127.8, 125.6, 124.4, 106.8, 61.6, 54.7, 54.5, 43.8, 37.2, 36.2, 26.5, 15.7. MS $C_{17}H_{24}N_2O_4$: calculated: 320.17, observed: $[M + Na]^+ = 343.06$.



34b

Figure 1.16. Synthesis of **34b**.

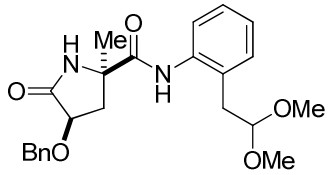
(**34b**) ^{1}H NMR (500MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.30-7.10 (m, 3H), 6.01 (s, 1H), 4.48 (t, *J* = 5.2 Hz, 1H), 3.45 (s, 3H), 3.43 (s, 3H), 2.89 (d, *J* = 5.3 Hz, 2H), 2.70-2.62 (m, 1H), 2.45 (dd, *J* = 8.9, 13.0 Hz, 1H), 2.13 (dd, *J* = 5.6, 13.0 Hz, 1H), 1.60 (s, 3H), 1.26 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 180.3, 173.3, 136.5, 131.5, 128.5, 127.9, 125.5, 124.3, 106.9, 61.6, 54.7, 54.6, 42.2, 37.2, 35.9, 25.4, 16.5. MS $C_{17}H_{24}N_2O_4$: calculated: 320.17, observed: $[M + Na]^+$ = 343.05.



35a

Figure 1.17. Synthesis of **35a**.

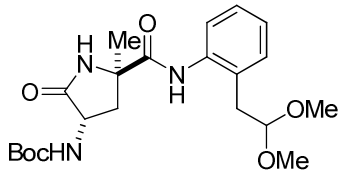
(**35a**) ^{1}H NMR (300MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.40-7.08 (m, 8H), 6.22 (s, 1H), 4.98 (d, *J* = 11.8 Hz, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.46 (t, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 7.9 Hz, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 2.94-2.82 (m, 3H), 2.13 (dd, *J* = 7.9, 13.2 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 175.8, 172.5, 137.6, 136.3, 131.5, 128.7, 128.6, 128.23, 128.17, 127.9, 125.7, 124.4, 106.8, 75.0, 72.7, 60.9, 54.8, 54.4, 41.8, 37.2, 26.5. MS $C_{23}H_{28}N_2O_5$: calculated: 412.20, observed: $[M + Na]^+$ = 435.10.



35b

Figure 1.18. Synthesis of **35b**.

(**35b**) ^{1}H NMR (300MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.31-7.07 (m, 8H), 6.24 (s, 1H), 4.87 (d, *J* = 11.8 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.41 (t, *J* = 5.3 Hz, 1H), 4.15 (dd, *J* = 4.5, 7.3 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.88 (dd, *J* = 5.3, 14.1 Hz, 1H), 2.73 (dd, *J* = 5.3, 14.1 Hz, 1H), 2.62 (dd, *J* = 4.5, 13.8 Hz, 1H), 2.37 (dd, *J* = 7.3, 13.8 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 175.7, 172.8, 137.6, 136.5, 131.3, 129.0, 128.6, 128.1, 128.0, 127.7, 125.4, 124.4, 107.0, 75.7, 72.4, 61.5, 54.8, 54.4, 41.5, 36.8, 26.1. MS $C_{23}H_{28}N_2O_5$: calculated: 412.20, observed: $[M + Na]^+$ = 435.17.

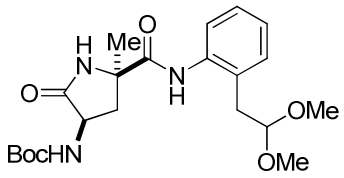


36a

Figure 1.19. Synthesis of **36a**.

(**36a**) ^{1}H NMR (500MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.27-7.09 (m, 3H), 5.32-5.27 (m, 1H), 4.48-4.41 (m, 2H), 3.42 (s, 6H), 2.91-2.76 (m, 3H), 2.27 (dd, *J* = 10.2, 12.1 Hz, 1H), 2.04-1.95 (m, 1H), 1.61 (s, 3H), 1.42 (s, 9H); ^{13}C NMR

(75MHz, $CDCl_3$) δ 176.0, 172.3, 155.8, 136.3, 131.3, 128.5, 127.9, 125.7, 124.4, 107.6, 80.3, 61.1, 55.0, 51.8, 43.0, 37.2, 28.5, 26.4. MS $C_{21}H_{31}N_3O_6$: calculated: 421.22, observed: $[M + Na]^+ = 444.05$.



36b

Figure 1.20. Synthesis of **36b**.

(**36b**) ^1H NMR (500MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H), 7.31-7.09 (m, 3H), 5.31 (d, *J* = 6.5 Hz, 1H), 4.47-4.39 (m, 2H), 3.44 (s, 3H), 3.37 (s, 3H), 3.17 (dd, *J* = 8.7, 12.1 1H), 2.88 (dq, *J* = 6.5, 27.8 Hz, 2H), 2.04-1.94 (m, 1H), 1.64 (s, 3H) 1.43 (s, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.3, 172.0, 168.7, 136.3, 131.5, 128.5, 128.0, 125.6, 124.3, 107.0, 80.3, 60.4, 54.8, 54.7, 51.6, 41.5, 37.2 ,28.5, 25.7. MS $C_{21}H_{31}N_3O_6$: calculated: 421.22, observed: $[M + Na]^+ = 444.08$.

H. References and Notes

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Chapter Two

Racemic Total Synthesis of Dysibetaine

featuring Ugi 4-Center-3-Component Condensation Reaction

A. Introduction

(–)-Dysibetaine is a pyroglutamic acid natural product originally isolated by Sakai and coworkers in the late 1990s.[1] It is a member of a group of natural products that were isolated from the Micronesian sponge *Dysidea Herbacea* that includes dysiherbaine[2] and dysibetaine PP[3] (Figure 2.1).

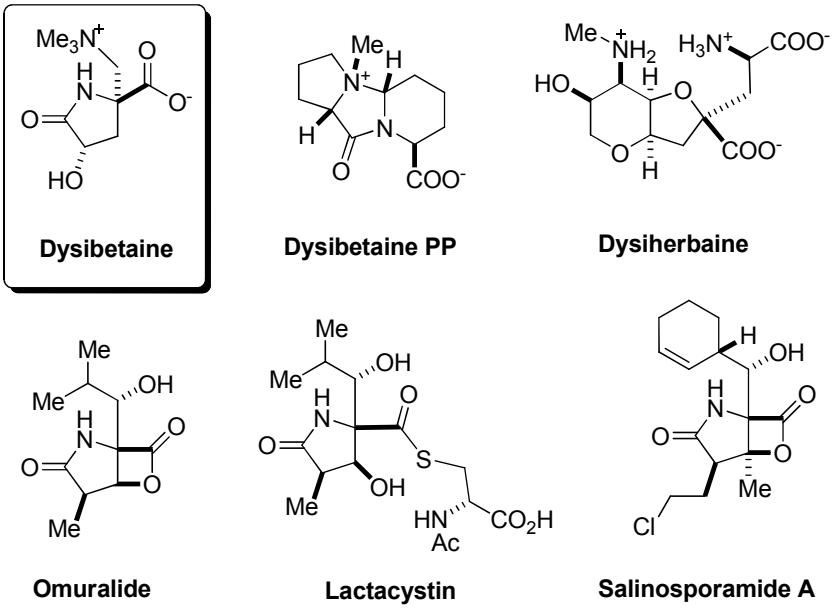


Figure 2.1. Dysibetaine and related natural products.

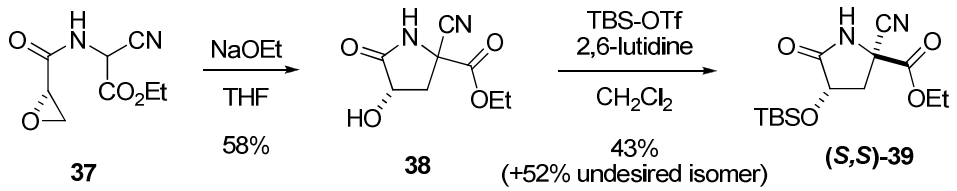
Also shown in Figure 2.1 are pyroglutamic acid containing natural products lactacystin[4] and salinosporamide A[5] both of which have interesting biological properties. Omuralide,[4] which is believed to be derived form lactacystin, has also shown strong biological activity. Many of us have therefore hoped that dysibetaine might also show good biological activity. In their initial report, Sakai and coworkers described biological studies conducted by injecting dysibetaine intracerebrally into mice and observed convulsive behavior. Although this is a possible sign that dysibetaine acts on the mice' glutamate receptors and central nervous system, no follow up studies were ever published, likely indicating no significant biological activity.

B. History of Dysibetaine

The unique structural complexity of dysibetaine has drawn many different groups to synthesize or attempt[6] to synthesize the molecule. Despite being small in size, dysibetaine remains a challenging target. The final molecule is zwitterionic, making special handling important. A carbon framework of only six atoms supports an alcohol, lactone, carboxylate and quaternary amine. Finally, there are two stereocenters that must be set appropriately. The various synthetic approaches provide a testament to the complexity of this tiny molecule.

Snider and Gu were the first to complete a total synthesis of dysibetaine and were therefore the first to assign the proper absolute configuration for the natural product.[7] They took a very straightforward pathway to the natural product (Scheme 2.1). Gylcidamide **37** was produced by coupling (*S*)-glycidic acid with ethyl amino(cyano)acetate, which is available in one step from commercially available materials. Compound **37** was then treated with sodium ethoxide in THF to yield the

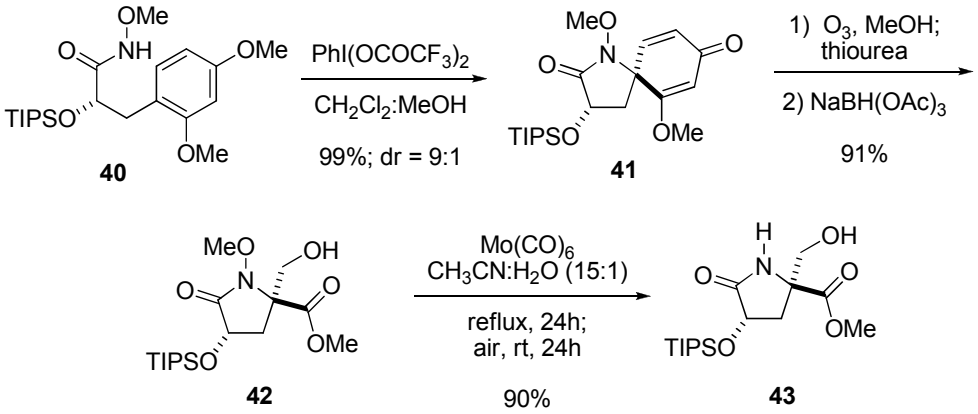
cylcized pyroglutamic ester **38** as a mixture of diastereomers. TBS protection of the resulting secondary alcohol allowed the diastereomers to be separated to give the desired diastereomer **39** in 42% yield plus the undesired isomer in 52% yield. TBS deprotection and functional group manipulations afforded the natural product, which was eventually synthesized in 8 steps and 20% overall yield from commercially available materials. Comparison of the optical rotations from their first synthetic compounds and the natural materials revealed to them that they had originally made the unnatural enantiomer and that the natural product is actually (*S,S*)-dysibetaine. They therefore went back to the beginning and completed the sequence shown in Scheme 2.1 to arrive at the properly configured natural product.



Scheme 2.1. Key step in Snider's total synthesis of (–)-dysibetaine.

Wardrop and co-workers presented a fascinating synthesis of dysibetaine.[8] They sought to apply a nitrenium ion cyclization/cleavage strategy they had developed in their laboratory to this natural product (Scheme 2.2). The cyclization commenced from intermediate **40** and was induced by hypervalent iodine species phenyliodine bis(trifluoroacetate), or PIFA, to give the cylcized product **41**. The nitrenium ion cyclization was coupled with dienone cleavage as part of the group's retrosynthetic plan. From **41** exhaustive, oxidative carbon-carbon bond cleavage followed by reduction gave

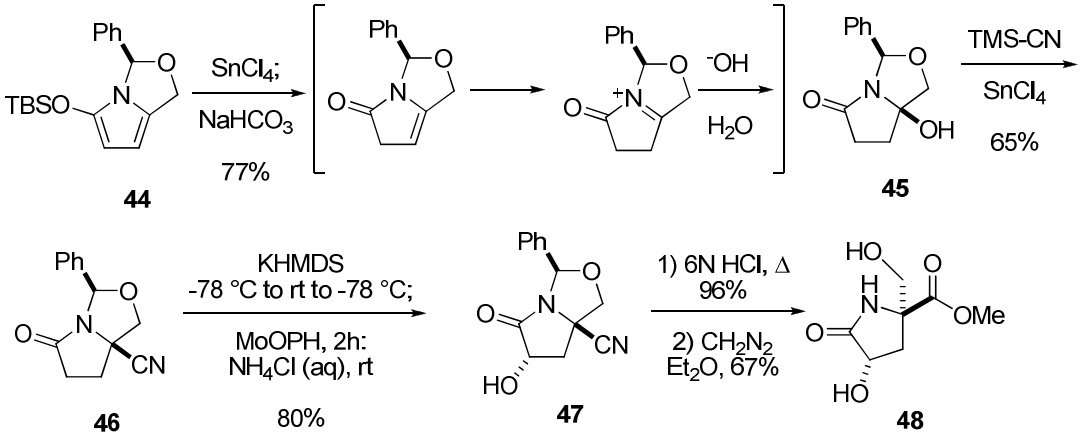
rise to compound **42**. The next important step was cleavage of the N-O bond, which had been necessary for the cyclization. This was achieved by treating **42** with $Mo(CO)_6$ in acetonitrile and water. Advanced intermediate **43** was then carried forward through the necessary functional group manipulations to reach the natural product in 15 steps and 11% overall yield.



Scheme 2.2. Key steps in Wardrop's total synthesis of (–)-dysibetaine.

The Langlois group approached the natural product from compound **44**, which was synthesized in six steps from commercially available materials (Scheme 2.3). Upon successive treatment with strong Lewis acid and by aqueous base intermediate **44** is hydrolyzed to **45**. The final hydroxide addition step takes place stereospecifically due to the chiral directing group.[9] The hydroxide in **45** is readily substituted with cyanide to form **46**. The group then extensively studied the stereoselective hydroxylation of **46** and related compounds in order to install the necessary secondary alcohol, and were able to arrive at hydroxylated intermediate **47** using the conditions shown. The benzylidene acetal was hydrolyzed with strong acid and the intermediate was methylated with

diazomethane to obtain pyroglutamic ester **48**. From this advanced intermediate they were able to substitute the primary alcohol after activation as the mesylate and performed the final functional group manipulations needed to reach (–)-dysibetaine. The natural product was synthesized in 16 steps on the longest linear sequence with about 2% yield from commercially available materials.

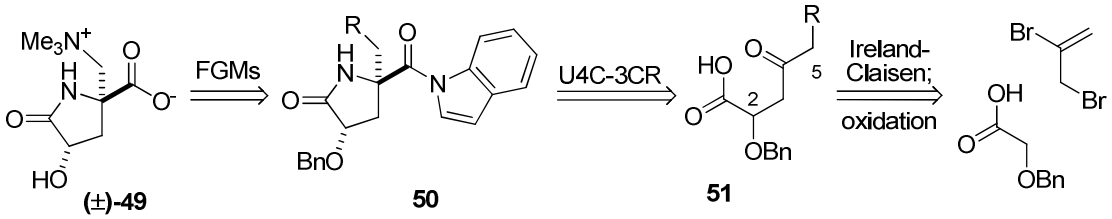


Scheme 2.3. Key steps in Langlois's total synthesis.

C. Retrosynthetic Plan

The first step towards our total synthesis of dysibetaine was the retrosynthetic plan. We looked initially at existing technologies that were readily available in our laboratory. We knew already that the combination of the convertible indole isocyanide and a levulinic acid derivative can react with ammonium acetate to afford the unprotected pyroglutamic amide in the Ugi 4-center-3-component condensation reaction (U4C-3CR).[10] The convertible isocyanide would eventually allow this amide to be selectively cleaved to the corresponding carboxylic acid. Substitution of a levulinic acid derivative

at C5 with a heteroatom such as nitrogen or oxygen still allows the Ugi reaction to proceed (Scheme 2.4). Finally, we knew that substitution at C2 is tolerated in the U4C-3CR, affording products in reasonable yield, but that little or no diastereoselectivity was observed. We hoped that the additional steric bulk at the C5 position would lead to enhanced stereoselectivity. That question and the overall tolerance of the U4C-3CR to the extra substituents we needed would be questions we would have to explore during the synthesis.



Scheme 2.4. Retrosynthetic analysis for (±)-dysibetaine.

Although our eventual goal from the beginning was to complete a stereoselective synthesis of (–)-dysibetaine, we initially started with the racemic synthesis. Starting from the natural product **49**, the retrosynthesis[11] leads through a series of known functional group manipulations to the *N*-acylindole intermediate **50**. The "R" group in **50** would have to be nitrogen or another substitutable heteroatom in order to allow for eventual quaternary amine formation. From **50**, the retrosynthesis proceeds from the U4C-3CR to the linear precursor and levulinic acid derivative **51**. Again using a reaction sequence that was familiar to our laboratory, we envisioned that **51** could be synthesized from commercially available 2,3-dibromopropene and benzyloxyacetic acid via a sequence of

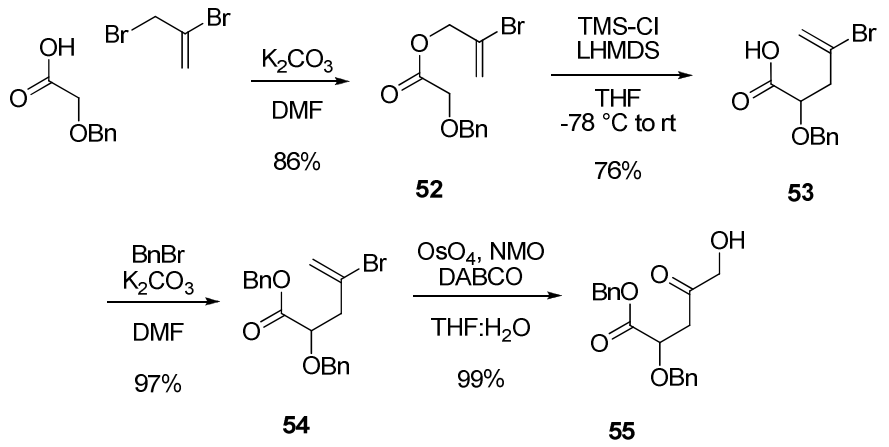
ester formation and then Ireland-Claisen rearrangement. This would be followed by osmium-mediated dihydroxylation of the bromo-olefin to reveal the ketone and alcohol.

With the retrosynthetic plan in hand, we began the total synthesis of (±)-dysibetaine. It should be noted that Mandy Loo, then a UCSD undergraduate researcher in our laboratory, carried out the initial investigations into this total synthesis.

D. Synthesis of Linear Ugi Precursors and Study of Diastereoselectivity

1. Synthesis of Linear Precursors for the Ugi Reaction

The total synthesis of (±)-dysibetaine began with an ester formation reaction as we coupled commercially available 2,3-dibromopropene and benzyloxyacetic acid to form **52** (Scheme 2.5). Ireland-Claisen rearrangement was affected by treating **52** with TMS-Cl and LHMDS in THF at very low temperature then allowing the reaction to warm to ambient temperature.[12] The resulting carboxylic acid, **53**, was immediately transformed to the corresponding benzyl ester **54**. The benzyl ester was chosen because it can be cleaved under mild, neutral conditions in the final step before the Ugi reaction. Once the purified benzyl ester **54** was in hand it was easily oxidized using the Upjohn method to give **55**.[13] The bromo-olefin was specifically chosen because the dihydroxylation reaction installs both the ketone and alcohol functionalities in a single step.



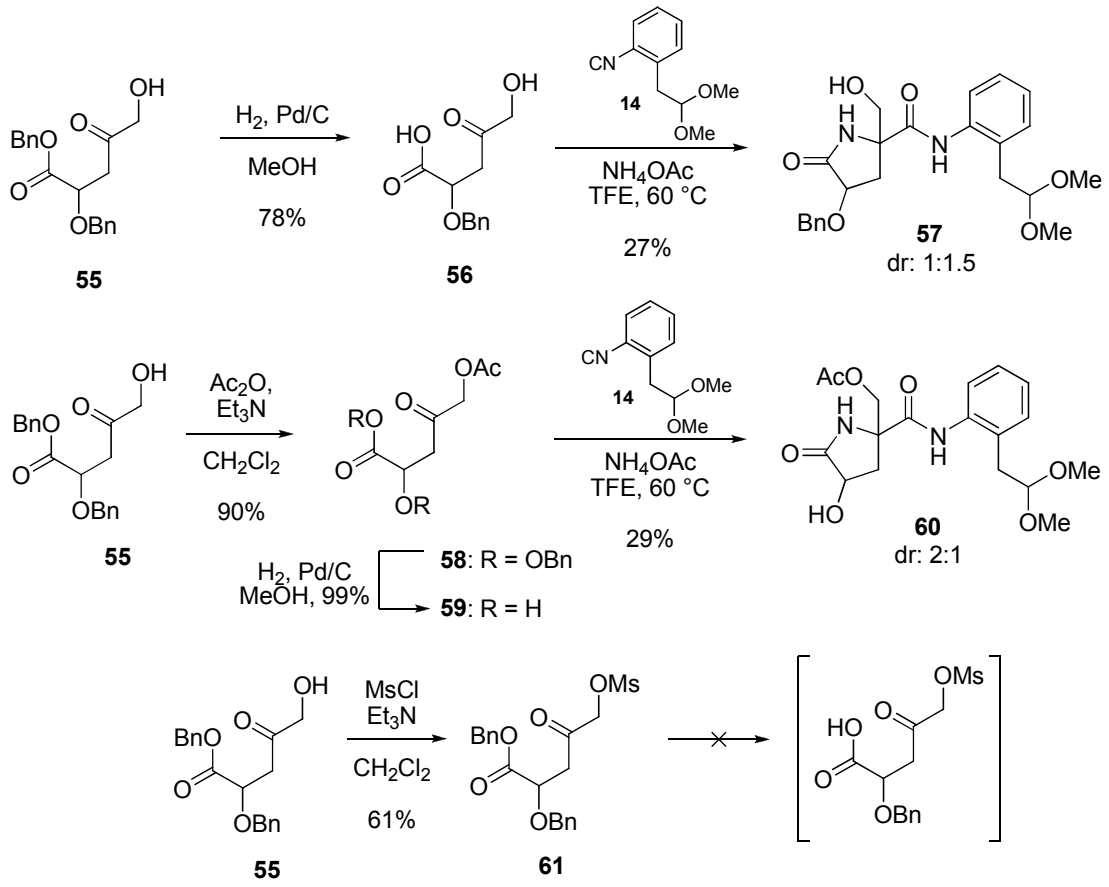
Scheme 2.5. First steps in the total synthesis of dysibetaine.

At this point in the synthesis we had to determine the best protecting group regimen for the two alcohols present in **55**. We wanted to find a combination that would give high yield and the best possible diastereoselectivity in the Ugi cyclization reaction. In the end, however, the choice was made much easier for us because most of the combinations tested led to unacceptably low yields.

2. Testing the U4C-3CR of γ-Ketoacid and Studies of Diastereoselectivity

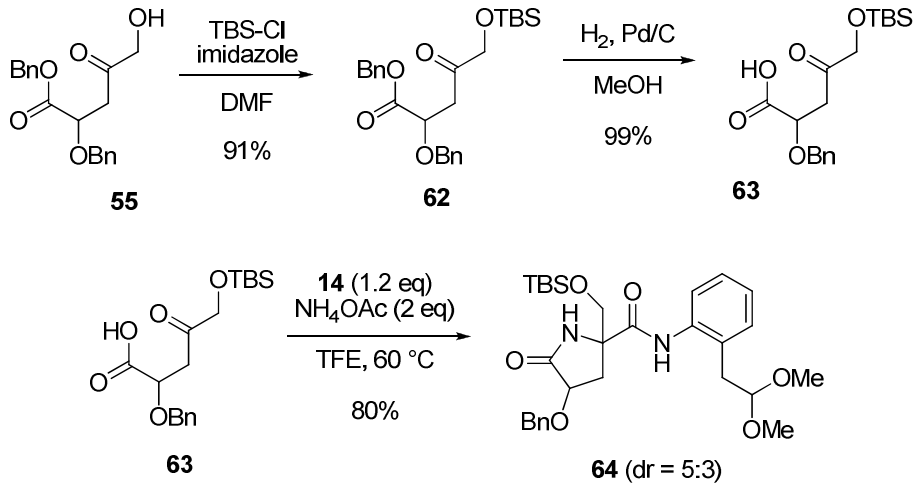
The initial attempt at the Ugi reaction was made from the γ-ketoacid derived directly from **55**, with the primary alcohol unprotected (Scheme 2.6). Thus linear precursor **56** was submitted to the same conditions for the U4C-3CR that we had previously developed to give Ugi product **57**, but it was obtained in only 27% yield. The two diastereomers were separated and the more polar compound, according to TLC analysis on silica gel, was major. The low yield may have been due to interference by the free alcohol with the desired reaction pathway. We also tested the Ugi reaction using a precursor **59** with the secondary alcohol unprotected and primary alcohol protected as

acetate, which was obtained in two steps from **55** via **58** as shown. This γ-ketoacid gave similarly unsatisfactory yield of Ugi product **60**. In this case the diastereomers were not separable but the ratio was determined by NMR. Along these same lines, we tried to incorporate mesylate as a protecting group for the primary alcohol **61**. Unfortunately, we were never able to successfully isolate the δ-ketoacid to try the Ugi reaction as it seemed to decompose under various ester cleavage conditions.



Scheme 2.6. Initial attempts at the U4C-3CR.

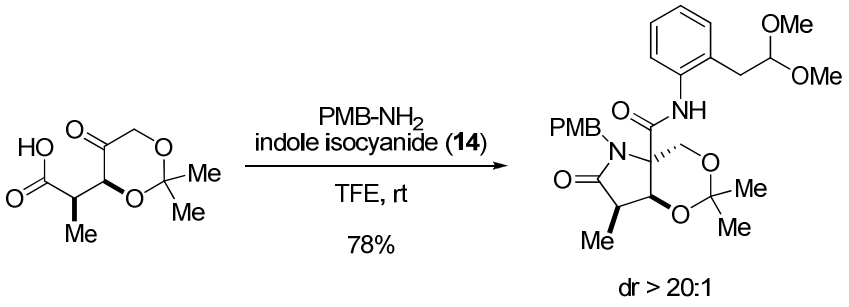
We next protected primary alcohol in **55** as TBS ether **62** as shown in Scheme 2.7. After the protection step the benzyl ester was readily cleaved by hydrogenolysis using short reaction time to preserve the benzyl ether. When linear γ-ketoacid **63** was subjected to the Ugi reaction the product **64** was obtained in much more acceptable yield. Unfortunately, the ratio of the inseparable diastereomers was found to be a very underwhelming 5:3. We also tested the more bulky TBDPS protecting group for the primary alcohol in the hope that the diastereoselectivity would be affected, but no real difference was seen between the groups.



Scheme 2.7. Progress on the path towards dysibetaine.

At this point we reviewed all of the U4C-3CR reactions with these and similar substrates and determined that the problem of controlling the diastereoselectivity is not one with a clear, general solution. In the course of a colleague's research towards the total synthesis of omuralide a diastereoselective Ugi reaction was discovered (Scheme 2.8).[14] The selectivity in this case was controlled by placing the ketone of the γ-ketoacid

into a six-membered dioxanone ring. Unfortunately, this was additional evidence that a diastereoselective reaction is very difficult. Furthermore, there is no plausible way to make such a ring that conforms to the backbone of dysibetaine. The range of selectivities in most Ugi reactions tested varied only a small amount from 1:1. We therefore decided to go forward along the best available path according to yield.

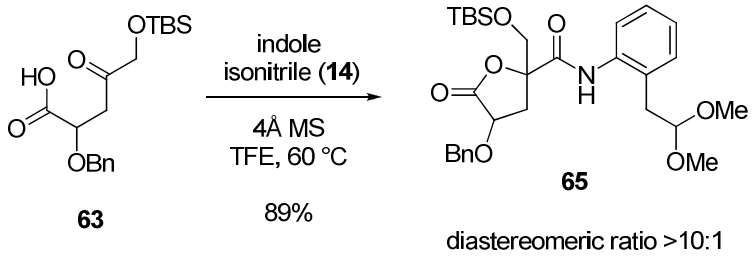


Scheme 2.8. A stereoselective Ugi reaction in the total synthesis of omuralide.

3. Good Diastereoselectivity in the Passerini Reaction of γ-Ketoacid

In the face of our difficulties the diastereoselectivity of the U4C-3CR of γ-ketoacids, the corresponding Passerini reaction starting from the same levulinic acid derivative actually proceeds with excellent diastereoselectivity to give the lactone analogue of the pyroglutamic acid product. The Passerini adduct is a common byproduct during the Ugi reaction so we submitted the γ-ketoacid precursor **63** to the cyclization reaction while omitting the amine source (Scheme 2.9). This is the standard condition for the Passerini reaction.[15] The Passerini product **65** formed in good yield and with greater than 10:1 selectivity (stereochemistry undetermined). We were able to form the *N*-acylindole from **65** but unfortunately we were never able to selectively cleave the *N*-

acylindole to an ester or carboxylic acid without opening the lactone despite deeper investigations into that reaction.

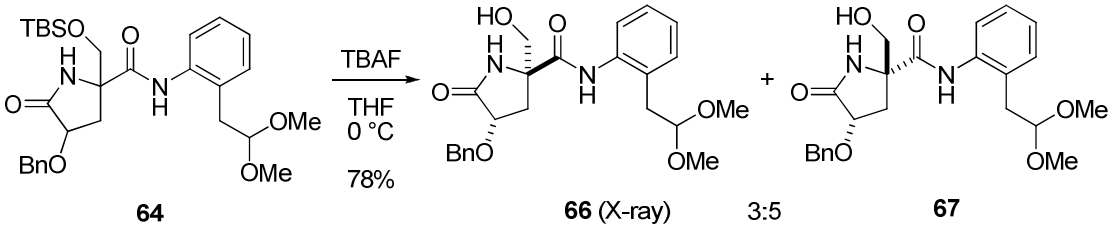


Scheme 2.9. Passerini reaction of δ-ketoacid **60** shows good diastereoselectivity.

E. Completion of the Racemic Total Synthesis of Dysibetaine

We now had in hand a reliable method to reach the desired Ugi product from commercially available materials and turned our attention towards the final two phases of the racemic total synthesis of dysibetaine. The first phase would involve the separation of diastereomers and selective amide cleavage facilitated by the use of indole isocyanide.

1. Separation and Determination of Diastereomers



Scheme 2.10. TBS deprotection and separation of diastereomers.

From the Ugi product **64** it was necessary to deprotect the silyl ether in order to separate the two diastereomers (Scheme 2.10). Doing so revealed a ratio of 5:3 in favor of the undesired diastereomer **67**. The relative stereochemistry of **66** was determined by X-ray crystallography and the X-ray crystal structure is shown in Figure 2.2.

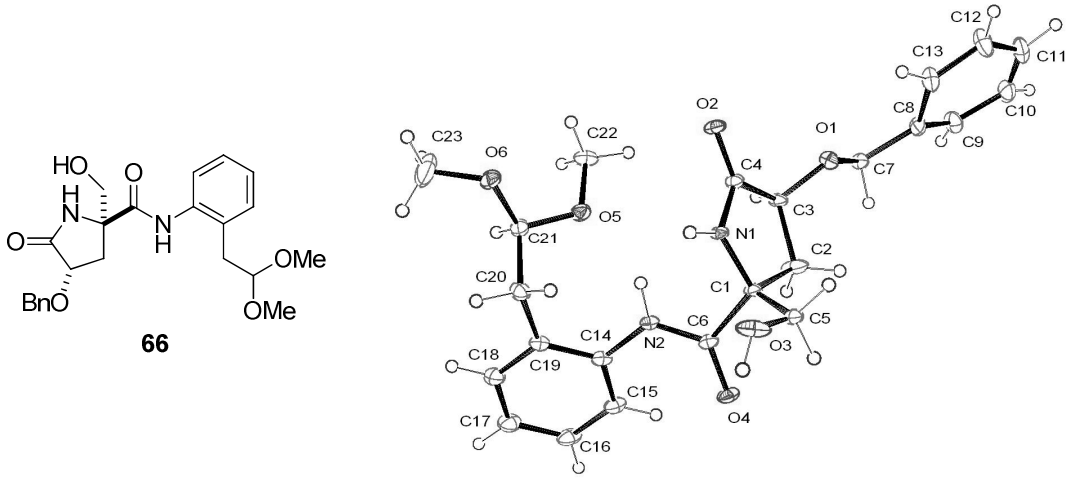
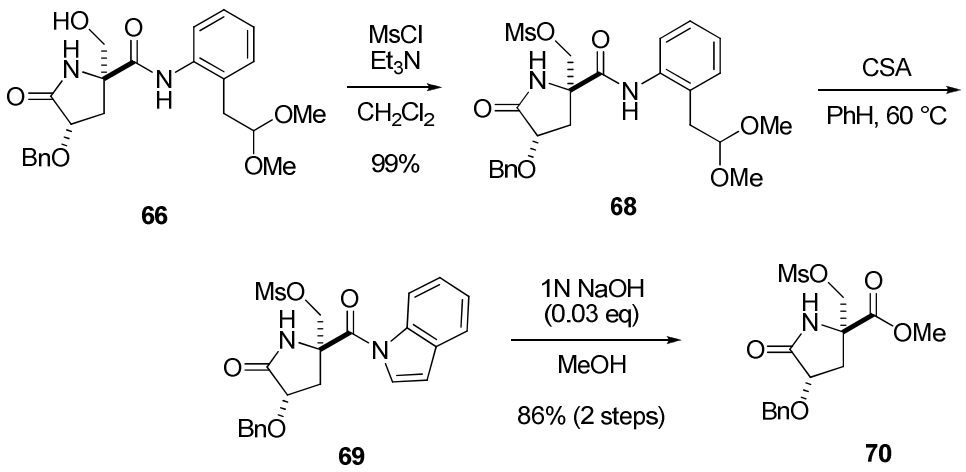


Figure 2.2. ORTEP drawing of the X-ray crystal structure of **66**.

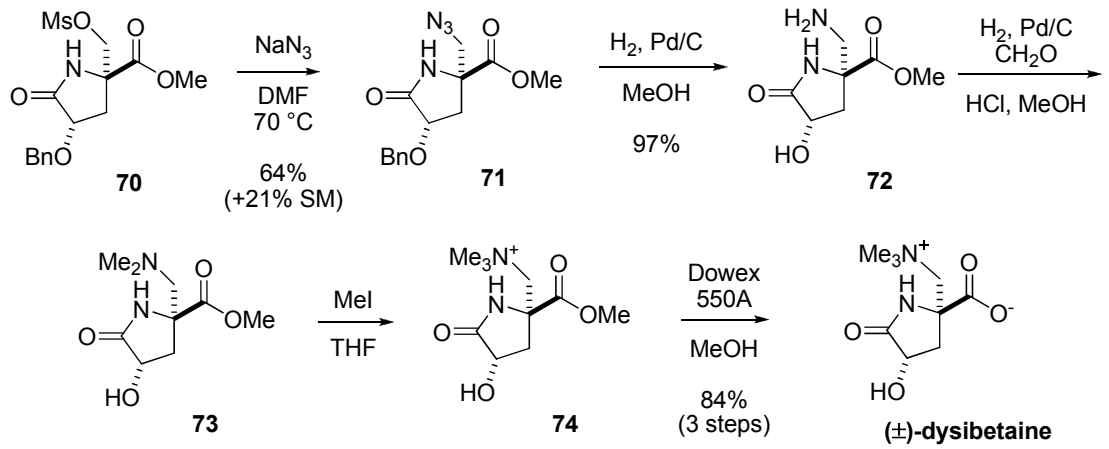
Proceeding with the desired stereoisomer, **66**, the primary alcohol was converted for substitution to the mesylate **68** in high yield (Scheme 2.11). The resulting compound was then treated with a catalytic amount of acid in benzene with gentle heating in order to afford *N*-acylindole **69**. This intermediate was finally treated with a very small amount of aqueous sodium hydroxide in methanol to yield methyl ester **70**. This two step sequence was carried out in accordance with our previous research.[16] With this compound in hand we could turn our attention to the final functional group manipulations needed to complete the natural product.



Scheme 2.11. Selective cleavage of *N*-acylindole to the methyl ester.

2. Completion of the Total Synthesis of (±)-Dysibetaine

The next step towards the completion of the natural product was to introduce the necessary nitrogen functionality. Mesylate **70** was therefore treated with sodium azide in DMF with heating to afford azide **71** (Scheme 2.12) in 64% yield plus 21% recovered starting material, which could be recycled into the reaction. Despite screening various conditions, the reaction never went to completion, likely due to the very demanding steric environment surrounding the leaving group. Our original goal in this synthesis was to reach the Ugi reaction expeditiously, but at this point we realized it may have been better to take a few extra steps to include nitrogen in the linear levulinic acid derivative before the Ugi reaction. Doing so would have allowed us to avoid the difficult substitution of the mesylate at a very hindered position. Although we went forward with this reaction in its current state, the incorporation of nitrogen before the Ugi reaction would be a key consideration in the stereocontrolled synthesis.

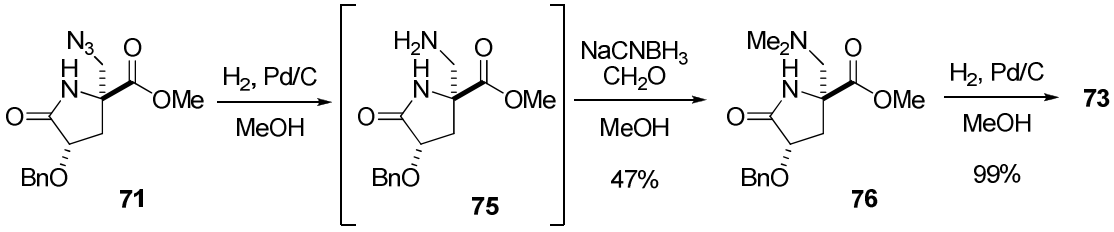


Scheme 2.12. Completion of (±)-dysibetaine.

The azide in **71** was reduced to the corresponding amine under hydrogen atmosphere using palladium/charcoal catalysis. The reductive conditions also led to the cleavage of the benzyl ether protecting group to give **72** in good yield. With this intermediate we could now intercept the work of other groups who had previously worked on this molecule. Specifically, the Langlois synthesis[9] went through this exact intermediate, however all syntheses to date have employed the same end game developed by Snider and Gu.[7] **72** was submitted to Clarke-Eschweiler methylation conditions using formaldehyde and palladium charcoal under acidic conditions and, contrary to previous reports, which had used very high pressure, only a single atmosphere of hydrogen pressure was required to give dimethylamine **73**. The amine was quaternized by treatment with an excess of iodomethane in THF to yield **74**. This final intermediate was treated with basic ion-exchange resin in refluxing methanol to afford the racemic natural product (±)-dysibetaine in 84% yield over the last three steps. Interestingly, we found that when **73** was allowed to sit for a few days a small amount converted on its own to

the natural product, possibly through intramolecular methyl-transfer from the ester to the amine.

During the course of this total synthesis we also examined other possible end-game strategies. For example, we attempted a sodium cyanoborohydride-mediated reductive amination to introduce the dimethyl amine moiety. So, the azide in intermediate **71** was reduced quickly using palladium/charcoal conditions so as to conserve the benzyl ether. Without isolation the crude **75** was then submitted to sodium cyanoborohydride-mediated reductive amination, affording dimethyl amine **76** in only 47% yield over the two steps. Unfortunately, the balance of the mass was not recovered. Intermediate **76** was again reduced, this time for a longer time period to allow the cleavage of the benzyl ether to intercept with intermediate **73**.



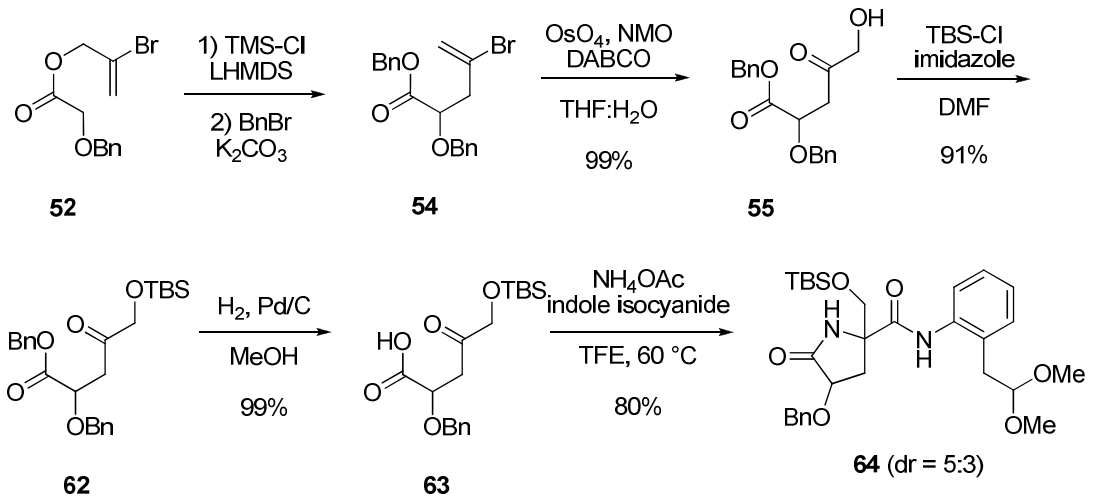
Scheme 2.13. Alternative end-game.

We had originally pursued this path for two reasons. First, previous syntheses had employed very high pressure for the reductive amination of **72** to **73** (Scheme 2.12). We tried this alternative to avoid the high pressure reaction, but the yield was not satisfactory. In the end it was a moot point because we discovered that the Clarke-Eschweiller methylation actually proceeds well employing only atmospheric H_2 pressure.

F. Conclusion

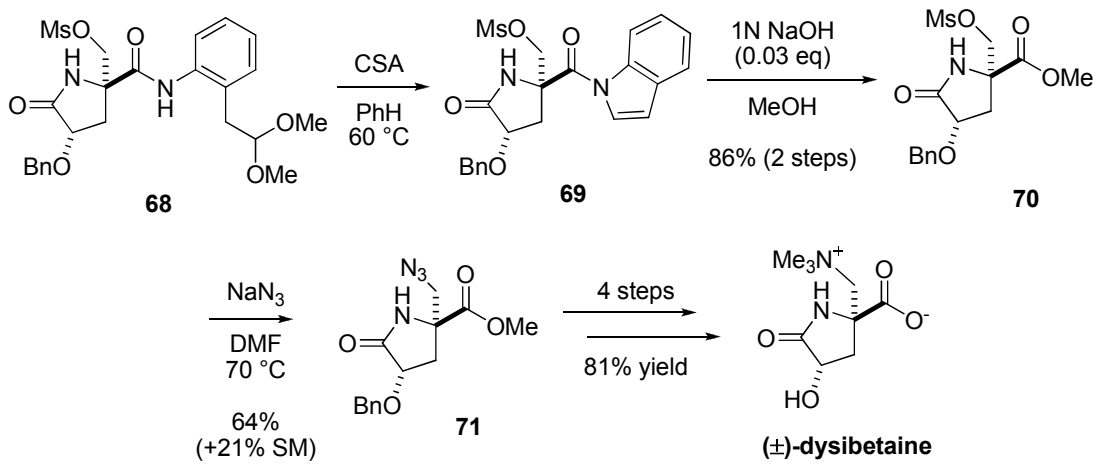
We thus completed a racemic total synthesis of the natural product dysibetaine in 16 steps and 9% overall yield from commercially available materials. This was the first application of our convertible indole isocyanide to the total synthesis of a natural product and showed that the designed experiments worked well in the presence of various functional groups. Although we continued to struggle with the problem of diastereoselectivity in the U4C-3CR, we were pleasantly surprised to find that the Passerini reaction afforded γ-lactones with excellent stereoselectivity. Finally, we presented a synthesis that overall uses very mild conditions.

The key aspects of this total synthesis are summarized, beginning in Scheme 2.14. The linear γ-ketoacid was synthesized from ester **52** using the following key steps: (a) Ireland-Claisen rearrangement, followed by benzyl ester formation, to form intermediate **54**; (b) dihydroxylation of the bromo-olefin in **54** to easily introduce the ketone and alcohol moieties in **55**. After TBS protection of the resulting primary alcohol, palladium/charcoal mediated hydrogenolysis of the benzyl ester in **62** set the stage for the Ugi 4-center 3-component condensation of γ-ketoacid **63** with ammonia and indole isocyanide **14** to give the cylcized product **64**. Amazingly, this Ugi condensation reaction allowed the formation of key carbon-carbon bonds, including the fully substituted carbon center, under mild conditions in a one-pot reaction with no waste.



Scheme 2.14. Summary of key steps leading to the U4C-3CR.

Another key aspect of this synthesis, shown in Scheme 2.15, is the selective, mild cleavage of one of two amide bonds present in the Ugi product. By using the specifically designed indole isocyanide, we were able to achieve this cleavage at a late stage, as intermediate **68** was heated with a catalytic amount of CSA in benzene to form *N*-acylindole **69**. Now properly activated, this amide bond was cleaved at room temperature using only a catalytic amount of base to form methyl ester **70**. This method of activation and cleavage is a nice contrast to the harsh conditions that are usually required to cleave the amide C–N bond.



Scheme 2.15. Selective amide bond cleavage and completion of (±)-dysibetaine.

One of the crucial trouble spots in this synthesis came from the reaction of **70** to **71** (Scheme 2.15). The difficulty of substituting the mesylate leaving group with azide next to a very hindered, fully substituted carbon center became apparent. Despite forcing conditions, the reaction never went to completion. In the future we would seek to incorporate all of the required functionalities into the linear precursor prior to the Ugi reaction. From intermediate **71** we arrived at the natural product through a series of straight-forward functional group manipulations.

We believe that this work represents an interesting use of the Ugi reaction in target-oriented synthesis and demonstrates that this is a reliable method for obtaining pyroglutamic acid natural products. We next turned our focus towards the completion of a stereoselective version of dysibetaine, which was already underway. We would continue to work on improving the diastereoselectivity of the U4C-3CR. Beyond that, two key goals for the stereoselective synthesis would be to arrive at the necessary chiral γ-ketoacid Ugi precursor in enantiomerically pure form efficiently and to incorporate the

amine into this precursor before the U4C-3CR in order to avoid a difficult substitution at the neopentyl position.

G. Acknowledgements

This chapter contains material that was previously published in the paper: *Total Synthesis of (±)-Dysibetaine.* Isaacson, Jerry; Loo, Mandy; Kobayashi, Yoshihisa. *Org. Lett*. **2008**, *10*, 1461-1463. Mandy Loo is graciously acknowledged for her contribution to this work.

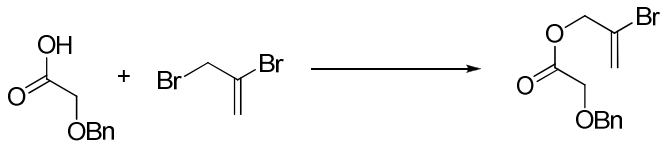
H. Experimental Section

1. Materials and Methods

All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. Tetrahydrofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), 2,2,2-trifluoroethanol (TFE), and acetone were purchased as reagent grade and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal

reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnigan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]25D = (100\cdot\alpha)/(l\cdot c)$, where the concentration c is in g/100 mL and the path length l is in decimeters.

2. Procedures and Spectral Data

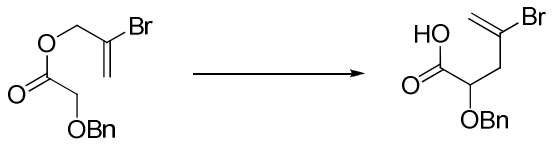


52

Scheme 2.16. Synthesis of **52**.

2-Bromoallyl 2-(benzyloxy)acetate (52) Benzyloxyacetic acid (11.3 mmol) was dissolved in DMF (20 mL). K_2CO_3 (16.9 mmol) was added at once followed by slow addition of freshly distilled 2,3-dibromopropene (11.3 mmol). After stirring at room temperature for two hours the reaction was washed with water (15 mL, w/back

extraction) and brine (15 mL) then dried over Na_2SO_4 and concentrated to give essentially pure **52** in 86% yield as a clear oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 5.93-5.91 (m, 1H), 5.67-5.66 (m, 1H), 4.80 (s, 2H), 4.66 (s, 2H), 4.18 (s, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.7, 137.2, 130.2, 128.8, 128.3, 126.0, 120.0, 73.7, 68.0, 67.2. HRMS $C_{12}H_{13}BrO_3$: calcd 284.0043, obsd 284.0046.

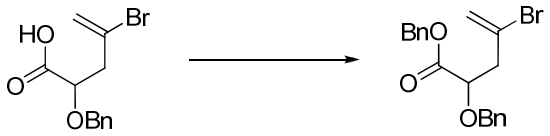


52 **53**

Scheme 2.17. Synthesis of **53**.

2-(Benzyloxy)-4-bromopent-4-enoic acid (53) A solution of **52** (4.3 mmol) in THF (15 mL) was cooled to -78 °C under N_2 atmosphere. Freshly distilled TMS-Cl (6.4 mmol) was carefully added. After five minutes, LHMDS (6.03 mL, 1.06 M in THF) was added and the reaction was allowed to stir at the same temperature for 30 minutes after which time the cold bath was removed. After the reaction reached room temperature it was diluted with EtOAc (15 mL) and extracted 3 x 15 mL water. The combined aqueous portions were adjusted to pH 3-5 by the careful addition of 1.0M citric acid (aq.) and then extracted with 3 x 15 mL EtOAc. The combined organic portions were washed with brine (20 mL) then dried over Na_2SO_4 and concentrated to afford **53** in 76% yield, which was used without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.77-5.75 (m, 1H), 5.57 (d, J = 1.8 Hz, 1H), 4.77 (d, J = 11.3 Hz, 1H), 4.60 (d, J = 11.3

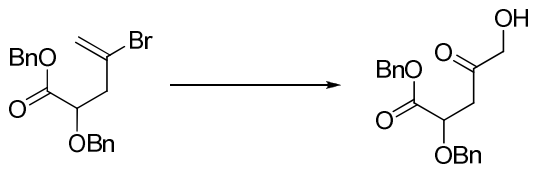
Hz, 1H), 4.35 (dd, *J* = 4.9, 8.2 Hz, 1H), 2.96-2.87 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.6, 136.9, 128.8, 128.44, 128.43, 128.2, 120.9, 75.7, 73.6, 44.8. HRMS $C_{12}H_{13}BrO_3$: calcd 284.0043, obsd 284.0045.



53 **54**

Scheme 2.18. Synthesis of **54**.

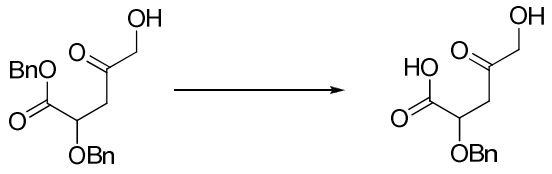
Benzyl 2-(Benzyloxy)-4-bromopent-4-enoate (54) Benzyl bromide (3.9 mmol) was added to **53** (3.2 mmol) and K_2CO_3 (4.8 mmol) in 15 mL DMF. After stirring for three hours the reaction was diluted with water (90 mL) and extracted with 3 x 15 mL EtOAc. Combined organic portions were washed with 20 mL brine then dried over Na_2SO_4 and concentrated. The crude oil was purified by column chromatography (5:1 hexanes:EtOAc) to give **54** in 97% yield as a golden oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.39-7.26 (m, 10H), 5.67-5.66 (m, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 5.21 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.31 (dd, *J* = 5.8, 7.5 Hz, 1H), 2.96-2.86 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.6, 137.3, 135.6, 128.9, 128.73, 128.66, 128.62, 128.5, 128.4, 128.2, 120.6, 76.2, 73.2, 67.1, 44.9. HRMS $C_{19}H_{19}BrO_3$: calcd 374.0512, obsd 374.0514.



54 **55**

Scheme 2.19. Synthesis of **55**.

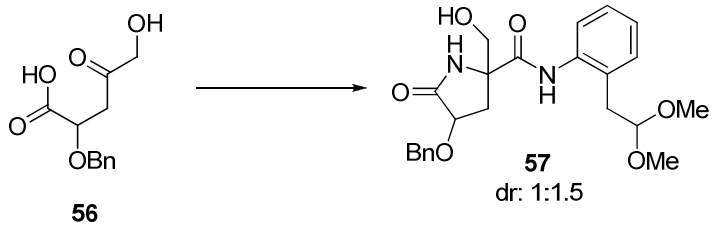
Benzyl 2-(Benzyloxy)-5-hydroxy-4-oxopentanoate (55) A solution of **54** (0.38 mmol) in THF:H_2O (10:1, 9 mL) was treated with NMO (1.1 mmol), OsO_4 (4% w/w sol'n in H_2O, 0.04 mmol) and a catalytic amount of DABCO. After stirring overnight the reaction was diluted with 20 mL water and extracted with 2 x 15 mL EtOAc. The combined organic portions were washed with 2 x $NaHSO_3$ (aq.) then brine (15 mL). Dried over Na_2SO_4, concentrated and purified by column chromatography (2:1 hexanes:EtOAc) to give **55** as a clear oil in 99% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40-7.25 (m, 10H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.52-4.47 (m, 2H), 4.23 (d, J = 4.9 Hz, 2H), 2.98-2.78 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 206.5, 171.3, 137.0, 135.4, 128.9, 128.8, 128.71, 128.66, 128.5, 128.4, 74.1, 73.5, 69.3, 67.4, 41.5. HRMS $C_{19}H_{20}O_5$: calcd 327.1227, obsd 327.1224.



55 **56**

Scheme 2.20. Synthesis of **56**.

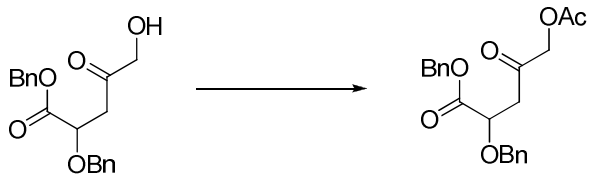
(56) A catalytic amount of Pd/C (10% w/w) was added to **55** (25 mg, 0.08 mmol) in MeOH (4 mL) and H_2 was applied to the reaction. After 45 minutes the reaction vessel was cleared with N_2 and the reaction was filtered through Celite, rinsing with MeOH. Upon concentration **56** (14.0 mg, 78%) was recovered as a clear oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.40 (m, 5H), 6.25 (br, 1H), 4.78 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.50-4.47 (m, 1H), 4.29-4.19 (m, 2H), 2.94-2.82 (m, 2H). MS $C_{12}H_{14}O_5$: calcd 238.08, obsd $[M + H]^+ = 239.03$.



Scheme 2.21. Synthesis of **57**.

(57) 56 (0.0140g, 0.06 mmol) was mixed with NH_4OAc (9.0 mg, 0.12 mmol) in TFE (1mL) and heated to 60 ˚C with stirring. After 15 minutes indole isocyanide **14** (12.4 mg, 0.06 mmol) was added. After 4 hrs the reaction was removed from heat and concentrated. Prep TLC (100% EtOAc) afforded the product as a separable mixture of diastereomers: less polar **57a** (2.3 mg, 9%) and more polar **57b** (4.4 mg, 18%). **57a** ^{1}H NMR (500MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.38-7.14 (m, 8H), 6.53 (s, 1H), 4.98 (d, *J* = 11.8 Hz, 1H), 4.75 (d, *J* = 11.8 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.28-4.24 (m, 2H), 3.65 (d, *J* = 10.9 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 2.89 (dd, *J* = 5.6, 14.1 Hz, 1H), 2.78 (dd, *J* = 4.8, 14.0 Hz, 1H), 2.71 (dd, *J* = 8.3, 13.9 Hz, 1H), 2.09 (dd, *J*

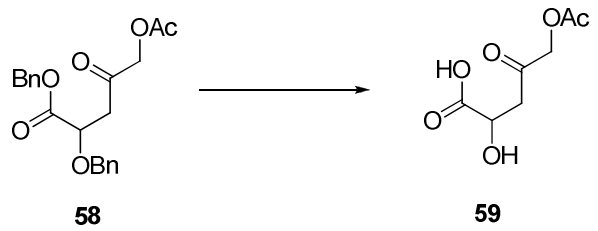
= 7.4, 13.9 Hz, 1H). MS $C_{23}H_{28}N_2O_6$: calcd 428.19, obsd $[M + Na]^+$ = 451.12. **57b** ^{1}H NMR (500MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.32-7.11 (m, 8H), 6.70 (s, 1H), 4.89 (d, *J* = 11.8 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.41 (t, *J* = 5.1 Hz, 1H), 4.14-4.11 (m, 2H), 3.60 (d, *J* = 11.0 Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 2.86 (dd, *J* = 4.9, 14.2 Hz, 1H), 2.79 (dd, *J* = 5.6, 13.8 Hz, 1H), 2.46 (dd, *J* = 7.8, 14.2 Hz, 1H), 2.39 (dd, *J* = 4.7, 14.1 Hz, 1H). MS $C_{23}H_{28}N_2O_6$: calcd 428.19, obsd $[M + H]^+$ = 428.16.



55 **58**

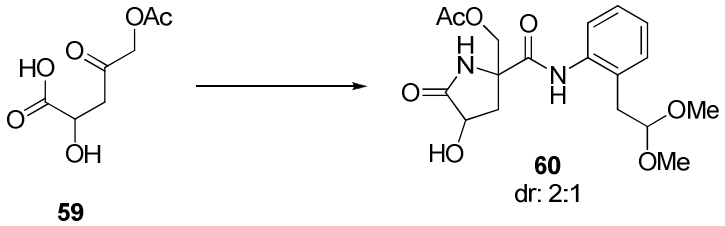
Scheme 2.22. Synthesis of **58**.

(58) Acetic anhydride (0.078 mL, 0.83 mmol), triethylamine (0.116 mL, 0.83 mmol) and a catalytic amount of DMAP were added to **55** (91 mg, 0.28 mmol) in DCM (5 mL). After 1 hr of stirring the reaction was washed with aq NH_4Cl (5 mL) and brine (5 mL) then dried over Na_2SO_4 and concentrated. Column chromatography (4:1 hexanes:EtOAc) afforded **58** (92 mg, 90%) as a clear oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.40-7.28 (m, 10H), 5.21 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.65 (q, *J* = 9.7 Hz, 2H), 4.52-4.49 (m, 2H), 2.92 (dd, *J* = 8.4, 16.5 Hz, 1H), 2.84 (dd, *J* = 4.5, 16.5 Hz, 1H), 2.15 (s, 3H). MS $C_{21}H_{22}O_6$: calcd 370.14, obsd $[M + H]^+$ = 370.98.



Scheme 2.23. Synthesis of **59**.

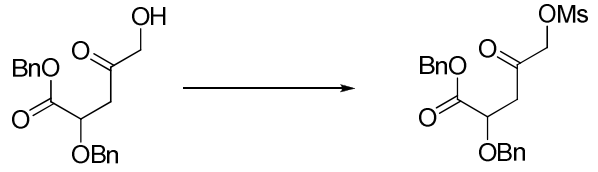
(59) A catalytic amount of Pd/C (10% w/w) was added to **58** (92 mg, 0.25 mmol) in MeOH (4 mL) and H_2 was applied to the reaction. After 75 minutes the reaction vessel was cleared with N_2 and the reaction was filtered through Celite, rinsing with MeOH. Upon concentration **59** (47 mg, 99%) was recovered as a clear oil. This unstable intermediate was brought immediately forward to the next step.



Scheme 2.24. Synthesis of **60**.

(60) NH_4OAc (0.038g, 0.50 mmol) was added to **59** (0.25 mmol) in TFE (1 mL) and heated to 60 ˚C with stirring. After 1 hr indole isocyanide **14** (71 mg, 0.37 mmol) was added. After 3 hrs the reaction was removed from heat and diluted w/H_2O (10 mL). Extracted with EtOAc (2 x 10 mL) which was then brined, dried over Na_2SO_4 and concentrated. Column chromatography (100% EtOAc) gave the product **60** (27 mg, 29%) as an inseparable mixture of diastereomers. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.54-

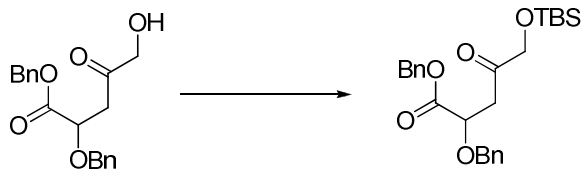
9.50 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.43-7.10 (m, 4H), 4.68-4.39 (m, 3H), 4.25-4.04 (m, 2H), 3.43-3.36 (m, 6H), 2.92-2.81 (m, 2H), 2.67 (dd, J = 8.4, 13.9 Hz, 1H), 2.35 (dd, J = 7.0, 13.9 Hz, 1H), 2.15-2.03 (m, 3H). MS $C_{18}H_{24}N_2O_7$: calcd 380.16, obsd $[M + Na]^+$ = 403.14.



55 **61**

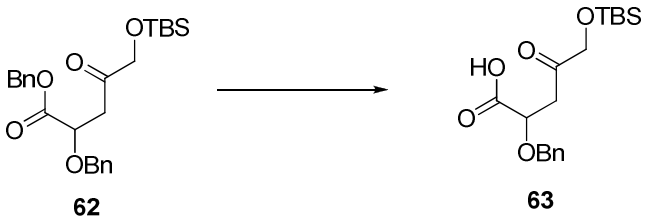
Scheme 2.25. Synthesis of **61**.

(61) Triethylamine (0.039 mL, 0.28 mmol) then methanesulfonyl chloride (0.0136 mL, 0.18 mmol) were added to **55** (46 mg, 0.14 mmol) in DCM (3mL). After 2 hrs of stirring an additional portion of methanesulfonyl chloride (0.04 mmol) was added. After stirring for an additional 18 hrs the reaction was removed from stirring and concentrated. After prep TLC (5:2 hexanes:EtOAc) the product **61** was recovered (35 mg, 61%) as a golden oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.40-7.46 (m, 10H), 5.20 (q, J = 12.2 Hz, 2H), 4.78 (d, J = 1.5 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.52-4.46 (m, 2H), 3.11 (s, 3H), 2.95-2.82 (m, 3H). MS $C_{20}H_{22}O_7S$: calcd 406.11, obsd $[M + H]^+$ = 406.04.



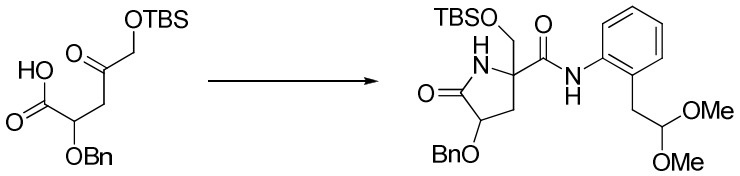
Scheme 2.26. Synthesis of **62**.

Benzyl 2-(Benzyloxy)-5-(tert-butyldimethylsilyloxy)-4-oxopentanoate (62) TBS-Cl (3.7 mmol) was added to a solution of **55** (2.8 mmol) and imidazole (7.1 mmol) in 10 mL DMF. After stirring overnight the reaction was diluted with 80 mL water and extracted with 2 x 20 mL EtOAc. The combined organics were washed with 15 mL brine then dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (6:1 hexanes:EtOAc) to afford **62** as an oil in 91% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H), 5.22 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.55-4.50 (m, 2H), 4.16 (s, 2H), 3.05-2.88 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 207.2, 172.0, 137.4, 135.7, 128.9, 128.7, 128.6, 128.54, 128.50, 128.2, 74.1, 73.5, 69.9, 67.1, 41.8, 26.0, 18.5, 5.29, 5.31. HRMS $C_{25}H_{34}O_5Si$: calcd 442.2170, obsd 442.2181.



Scheme 2.27. Synthesis of **63**.

2-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4-oxopentanoic acid (63) A catalytic amount of Pd/C (10% w/w) was added to **62** (1.4 mmol) in 5 mL MeOH. The reaction was stirred under hydrogen (1 atm) for 35 minutes then filtered over celite and concentrated to yield pure **63** in 99% yield. The unstable acid was immediately brought forward to the next step. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.77 (d, J = 10.7 Hz, 1H), 4.59 (d, J = 10.7 Hz, 1H), 4.51 (t, J = 6.3 Hz, 1H), 4.16 (s, 2H), 3.08-2.80 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H). HRMS $C_{18}H_{28}O_5Si$: calcd 352.1701, obsd 352.1698.

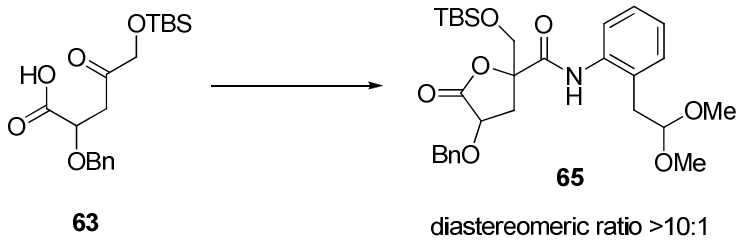


63 **64** (dr = 5:3)

Scheme 2.28. Synthesis of **64**.

4-(Benzyloxy)-2-((*tert*-butyldimethylsilyloxy)methyl)-*N*-(2-(2,2-dimethoxyethyl)phenyl)-5-oxopyrrolidine-2-carboxamide (64) **63** (2.1 mmol) was dissolved in 5 mL 2,2,2-trifluoroethanol and a few 4Å molecular sieves were added. NH_4OAc (4.1 mmol) was added followed immediately by **14** (2.5 mmol) and the reaction was heated to 60 °C until there was no **14** remaining by TLC after which time the reaction was decanted to remove the molecular sieves then concentrated. The crude mixture was purified by column chromatography (2:1 hexanes:EtOAc) to give **64** as an oil in 86% yield as a mixture of diastereomers: ^{1}H NMR (300MHz, $CDCl_3$) δ 9.59, 9.51 (s, 1H), 7.78-7.73 (m, 1H), 7.39-7.11 (m, 8H), 6.38, 6.27 (s, 1H), 4.99-4.69 (m, 2H),

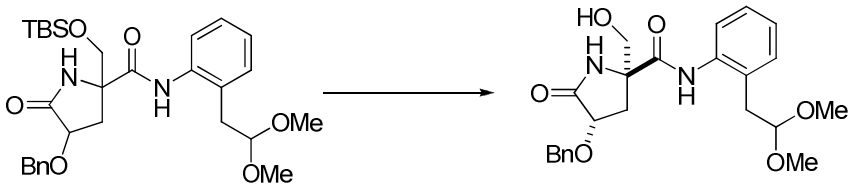
4.49-4.08 (m, 3H), 3.58-3.35 (m, 7H), 2.92-2.69 (m, 2H), 2.47-2.27 (m, 1H), 2.05-1.96 (m, 1H), 0.85 (s, 9H), 0.07-0.03 (m, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 175.43, 175.36, 171.1, 171.0, 137.54, 137.51, 136.3, 136.4, 131.5, 131.4, 128.8, 128.7, 128.63, 128.58, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 125.7, 125.5, 124.35, 124.28, 106.31, 106.26, 75.0, 74.0, 72.6, 72.3, 69.3, 68.8, 66.1, 65.1, 54.21, 54.17, 54.1, 53.8, 36.76, 36.68, 26.01, 25.99, 18.5, 18.4, -5.24, -5.25, -5.30, -5.33. HRMS $C_{29}H_{42}N_2O_6Si$: calcd 542.2807, obsd 542.2811.



Scheme 2.29. Synthesis of **65**.

(65) Indole isocyanide **14** (1.59 mmol) was added to **63** (1.06 mmol) and 4Å MS in 3 mL TFE. The reaction was heated to 60 ˚C for three hours then removed from heat and allowed to stir an additional 18 hrs. The reaction was concentrated and purified by column chromatography (5:1 H:E) to give **65** (0.512 g, 89%) as an inseparable mixture of diastereomers (dr = 10:1). ^{1}H NMR (300MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.38-7.09 (m, 8H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.51 (t, *J* = 5.4 Hz, 1H), 4.31 (t, *J* = 9.0 Hz, 1H), 4.10 (d, *J* = 11.1 Hz, 1H), 3.87 (d, *J* = 11.1 Hz, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.93-2.81 (m, 3H), 2.32 (dd, *J* = 9.2, 13.4 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.5, 168.7, 136.9,

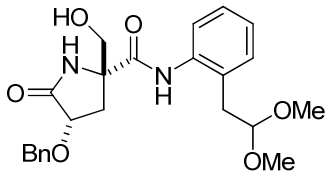
135.9, 131.6, 128.82, 128.80, 128.5, 128.4, 127.8, 125.8, 124.1, 105.6, 86.4, 72.7, 67.2, 54.2, 53.5, 37.1, 34.1, 29.9, 26.0, 18.5, -5.17, -5.22. HRMS $C_{29}H_{41}NO_7Si$: calcd 543.2647, obsd 543.2639.



Scheme 2.30. Synthesis of **66**.

4-Benzyloxy-*N*-(2-(2,2-dimethoxyethyl)phenyl)-2-(hydroxymethyl)-5-oxopyrrolidine-2-carboxamide (66) A solution of **64** (0.98 mmol) in THF was cooled to 0 °C and TBAF (1.1 mL, 1.0M in THF) was added. After 15 minutes 15 mL of saturated NH_4Cl (aq.) was added and the layers were separated. Aqueous layer was extracted with 15 mL EtOAc. The organic layer was brined, dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (1:3 hexanes:EtOAc to 100% EtOAc) to give solid **66** in 29% yield along with the undesired diastereomer **67** in 49% yield. **(66)**: MP = 79-83 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.38-7.12 (m, 8H), 6.77 (s, 1H), 4.96 (d, *J* = 11.8 Hz, 1H), 4.74 (d, *J* = 11.8 Hz, 1H), 4.43 (dd, *J* = 4.9, 5.7 Hz, 1H), 4.28-4.20 (m, 2H), 3.62 (dd, *J* = 6.4, 10.9 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.95-2.67 (m, 3H), 2.10-2.04 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.1, 171.8, 137.5, 136.0, 131.5, 129.1, 128.7,

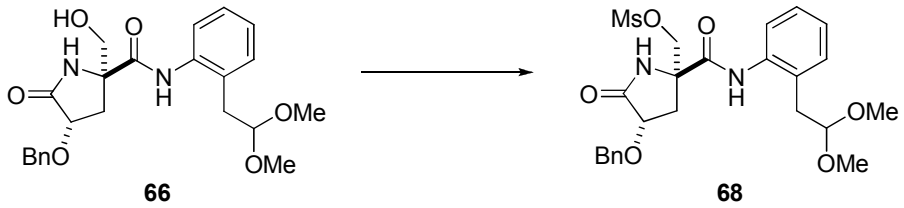
128.3, 128.2, 127.8, 126.0, 124.7, 106.7, 74.2, 72.6, 67.8, 65.4, 54.8, 54.7, 37.0, 36.2. HRMS $C_{23}H_{28}N_2O_6$: calcd 428.1942, obsd 428.1939.



67

Figure 2.3. Synthesis of **67**.

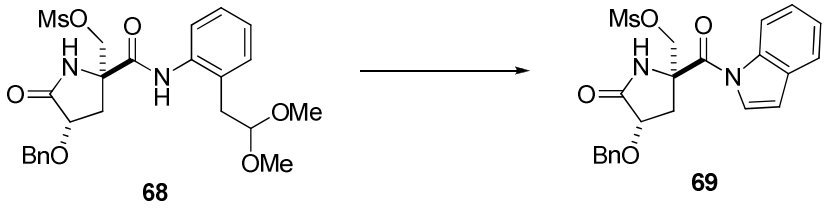
(67) ^{1}H NMR (400MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.30-7.11 (m, 8H), 6.97 (s, 1H), 4.88 (d, *J* = 11.8 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.39 (t, *J* = 5.3 Hz, 1H), 4.13-4.08 (m, 2H), 3.60 (d, *J* = 11.3 Hz, 1H), 3.40 (s, 3H), 3.30 (s, 3H), 3.22 (s, 1H), 2.81 (d, *J* = 5.4 Hz, 1H), 2.45 (dd, *J* = 7.7, 14.2 Hz, 1H), 2.37 (dd, *J* = 4.8, 14.2 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 176.3, 171.8, 137.6, 136.2, 131.4, 129.1, 128.6, 128.1, 128.0, 127.8, 125.8, 124.5, 107.0, 75.1, 72.5, 67.4, 65.9, 54.9, 54.8, 36.8, 36.5. MS $C_{23}H_{28}N_2O_6$: calcd 428.19, obsd $[M + Na]^+$ = 451.18.



66 **68**

Scheme 2.31. Synthesis of **68**.

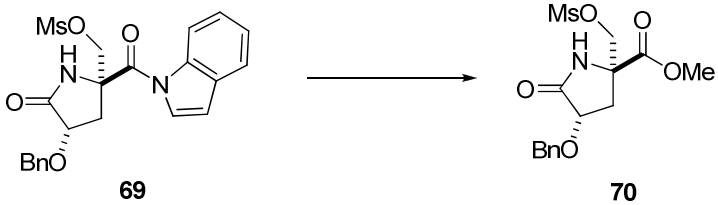
(4-Benzyloxy-2-[2-(2,2-dimethoxyethyl)phenylcarbamoyl]-5-oxopyrrolidin-2-yl)methyl methanesulfonate (68) Methanesulfonyl chloride (0.60 mmol) was carefully added to **66** (0.46 mmol) and Et_3N (2.3 mmol) in 5 mL CH_2Cl_2. After one hour the reaction was washed with 5 mL water then 5 mL brine. Dried over Na_2SO_4 and concentrated to afford **68** as a foam in 99% yield. ^{1}H NMR (500MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.70 (d, *J* = 5.0 Hz, 1H), 7.37-7.13 (m, 8H), 6.60 (s, 1H), 4.98 (d, *J* = 11.9 Hz, 1H), 4.82 (d, *J* = 10.0 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.48 (t, *J* = 5.1 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 4.22 (dd, *J* = 6.7, 7.9 Hz, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 3.02 (s, 3H), 2.94-2.71 (m, 3H), 2.15-2.11 (m, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 175.3, 169.4, 137.3, 135.8, 131.7, 129.1, 128.8, 128.335, 128.326, 127.9, 126.2, 124.4, 106.4, 73.5, 73.1, 72.7, 63.3, 54.55, 54.51, 37.5, 37.1, 36.6. HRMS $C_{24}H_{30}N_2O_8S$: calcd 506.1717, obsd 506.1723.



Scheme 2.32. Synthesis of **69**.

[4-(Benzyloxy)-2-(1H-indole-1-carbonyl)-5-oxopyrrolidin-2-yl]methyl methanesulfonate (69) A solution of **68** (0.18 mmol) in benzene (3 mL) was treated with CSA (0.04 mmol) and heated to 60 °C for one hour. The reaction was washed with 5 mL $NaHCO_3$ (aq.) and 5 mL brine then dried over Na_2SO_4 and concentrated to afford

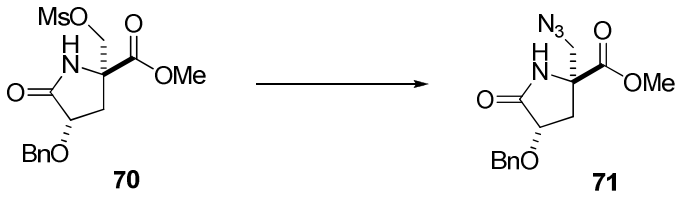
69 as foam. The crude material was pure by NMR and was therefore brought directly to the next step. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.4 Hz, 1H), 7.89 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 3.9 Hz, 1H), 7.37-7.26 (m, 7H), 6.68 (d, *J* = 3.9 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 10.4 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 10.4 Hz, 1H), 4.13-4.10 (m, 1H), 2.89 (s, 3H), 2.85-2.78 (m, 1H), 2.45 (dd, *J* = 2.6, 14.4 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.1, 168.3, 137.3, 136.7, 129.8, 128.8, 128.4, 128.3, 126.2, 125.0, 123.9, 121.3, 117.4, 111.5, 74.3, 72.9, 72.7, 66.1, 37.7, 36.5. HRMS $C_{22}H_{22}N_2O_6S$: calcd 442.1193, obsd 442.1201.



Scheme 2.33. Synthesis of **70**.

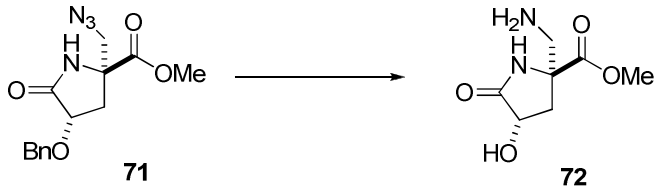
Methyl-4-Benzyloxy-2-[(methylsulfonyloxy)methyl]-5-oxopyrrolidine-2-carboxylate (70) **69** (0.18 mmol) was dissolved in 3 mL MeOH and NaOH (1N aq., 0.009 mmol) was added. After two hours the reaction was concentrated then purified by column chromatography (1:1 hexanes:EtOAc) to afford **70** as a white solid in 86% yield over two steps. MP = 134-138 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 7.10 (s, 1H), 4.94 (d, *J* = 11.8 Hz, 1H), 4.69 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 10.0 Hz, 1H), 4.32 (d, *J* = 10.0 Hz, 1H), 4.12 (m, 1H), 3.80 (d, *J* = 0.7 Hz, 3H), 3.02 (d, *J* = 0.7 Hz, 3H), 2.60-2.53 (m, 1H), 2.12-2.06 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.7, 171.1,

137.4, 128.7, 128.31, 128.27, 73.9, 72.7, 72.3, 62.6, 53.7, 37.8, 35.4. HRMS $C_{15}H_{19}NO_7S$: calcd 357.0877, obsd 357.0871.



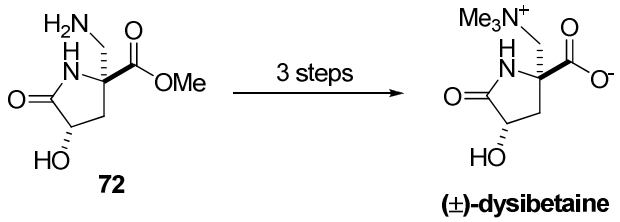
Scheme 2.34. Synthesis of **71**.

Methyl 2-Azidomethyl-4-(benzyloxy)-5-oxopyrrolidine-2-carboxylate (71) Sodium azide (1.7 mmol) was added to **70** (0.17 mmol) in 1 mL DMF and the reaction was heated to 60 °C for 24 hr after which time the reaction was poured into 10 mL water and extracted with 2 x 10 mL EtOAc. The combined organic portions were washed with 10 mL brine then dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography to provide **71** as an oil in 64% yield along with 21% recovered **70**. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 6.98 (s, 1H), 4.97 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.8 Hz, 1H), 4.13 (dd, J = 5.9, 8.0 Hz, 1H), 3.87 (d, J = 12.2 Hz, 1H), 3.79 (s, 3H), 3.57 (d, J = 12.2 Hz, 1H), 2.59-2.52 (m, 1H), 2.08-2.02 (m, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.9, 172.1, 137.6, 128.7, 128.3, 128.2, 74.3, 72.7, 63.2, 58.2, 53.6, 36.4. HRMS $C_{14}H_{17}N_4O_4$: calcd 305.1244, obsd 305.1249.



Scheme 2.35. Synthesis of **72**.

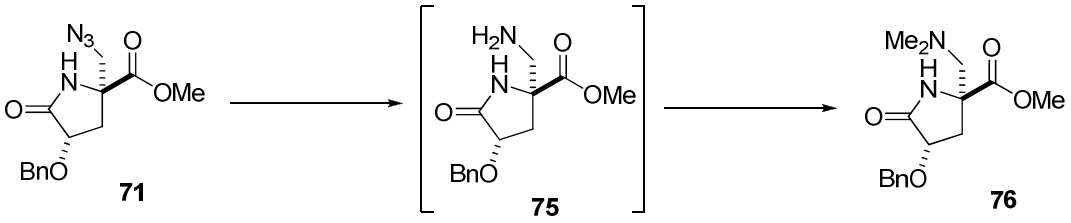
Methyl 2-(Aminomethyl)-4-hydroxy-5-oxopyrrolidine-2-carboxylate (72) Pd/C (10% w/w) was added to **71** (0.08 mmol) in 3 mL MeOH and the reaction was stirred under hydrogen (1 atm) overnight then filtered through celite, rinsed with MeOH, and concentrated to afford **72** in 97% yield as a clear oil. ^{1}H NMR (300MHz, D_2O) δ 4.33 (t, *J* = 8.4 Hz, 1H), 3.62 (s, 3H), 2.96 (d, *J* = 13.8 Hz, 1H), 2.85 (d, *J* = 13.8 Hz, 1H), 2.65 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.84 (dd, *J* = 13.7, 8.5 Hz, 1H); ^{13}C NMR (100MHz, CD_3OD) δ 178.0, 173.5, 68.6, 64.4, 52.1, 48.0, 37.8. HRMS $C_9H_{16}N_2O_4$: calcd 188.0792, obsd 188.0789.



Scheme 2.36. Synthesis of (±)-dysibetaine **(49)**.

(±)-Dysibetaine (49) **72** was submitted to the same three step procedure used by the Langlois group[3a] to afford **(±)-49** in 84% yield over three steps**.** ^{1}H NMR (400MHz, D_2O) δ 4.18 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.88 (d, *J* = 14.0 Hz, 1H), 3.58 (d, *J* = 14.0 Hz,

1H), 3.04 (s, 9H), 2.50 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.83 (dd, *J* = 14.0, 5.5 Hz); ^{13}C NMR (100MHz, D_2O, CD_3OD at δ 49.0 as internal standard.) δ 179.7, 177.0, 73.1, 69.1, 64.2, 55.6, 42.4. ESI-MS $C_9H_{16}N_2O_4$: $[M + H]^+$ = 217.24, $[M + Na]^+$ = 239.15. HRMS $C_9H_{16}N_2O_4$: calcd 215.1026, obsd 215.1026.



Scheme 2.37. Synthesis of **76**.

(76) H_2 gas was applied to **71** (0.06 mmol) and a catalytic amount of Pd/C (10% w/w) stirring in 2mL MeOH. After 40 minutes, when the starting material was gone by TLC, the reaction vessel was cleared with N_2 gas and the reaction was filtered through celite, rinsing with 1 mL MeOH to give intermediate **75** in solution. Formalin solution (0.042 mL, 0.57 mmol) was added followed by sodium cyanoborohydride (14.3 mg, 0.23 mmol). After 6 hours 1M HCl (1mL) was added and the reaction was diluted with 10 mL H_2O. Washed with 10 mL EtOAc then added enough 1N NaOH to make the solution basic. Extracted with 2 x 10 mL EtOAc; the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford **76** (82 mg, 47%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 6.42 (s, 1H), 4.98 (d, *J* = 11.8 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.09 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 2.93 (d, *J* = 13.5 Hz, 1H), 2.64-2.56 (m, 2H), 2.24 (s, 6H), 1.99 (dd, *J* = 7.1, 13.5 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$)

δ 174.6, 173.8, 137.8, 128.7, 128.2, 128.1, 74.4, 72.6, 67.5, 63.6, 53.0, 47.5, 37.6. MS $C_{16}H_{22}N_2O_4$: calcd 306.16, obsd $[M + Na]^+ = 329.13$.

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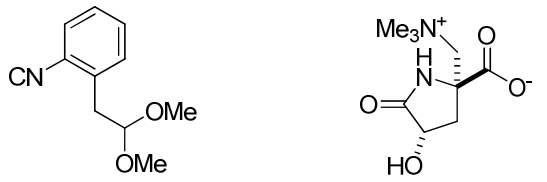
Chapter Three

Enantioselective Total Synthesis of (–)-Dysibetaine

A. Introduction and Retrosynthesis

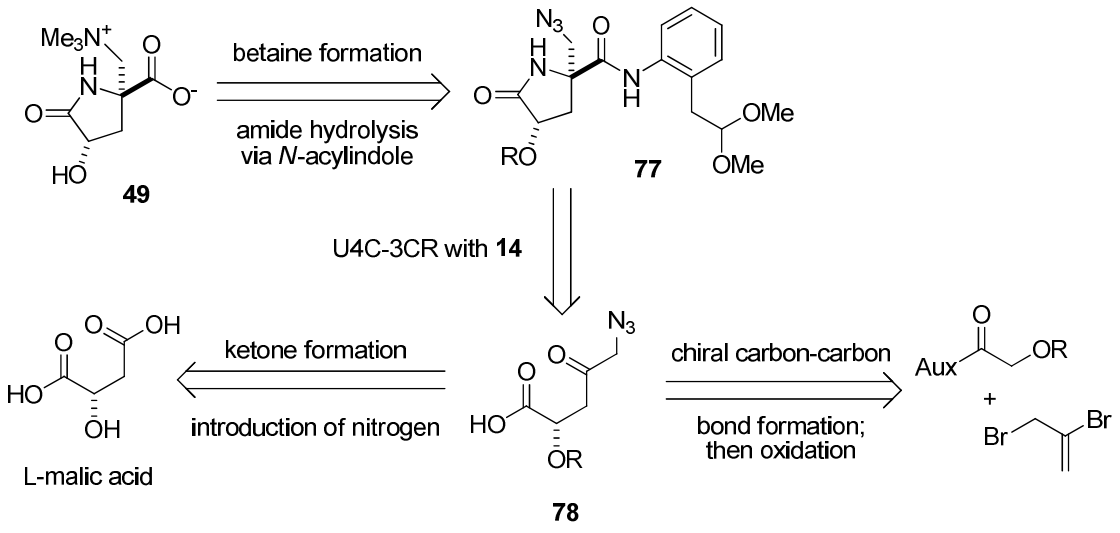
The ultimate goal of our studies using the convertible indole isocyanide **14** in the synthesis of pyroglutamic acids was the stereoselective total synthesis of (–)-dysibetaine (**49**, Figure 3.1).[1] Although our research efforts were initially focused on the racemic total synthesis of dysibetaine,[2] we could now shift towards this underlying goal. While progressing towards the racemic natural product we were trying various methods to install the necessary stereocenter. The racemic natural product was finished first but along the way developments in each pathway spurred advancements in the other. We originally set out to synthesize a chiral γ-ketoacid that would participate in the Ugi 4-center 3-component condensation reaction (U4C-3CR), but in the end we discovered a new reaction pathway in which an ester actually acts as the carboxylic acid component in the Ugi reaction.



indole isocyanide (**14**) (–)-dysibetaine (**49**)

Figure 3.1. Indole isocyanide and (–)-dysibetaine.

The retrosynthetic plan for the stereoselective synthesis of **(–)-49** is very similar to that used for the racemic synthesis and is outlined in Scheme 3.1. From the natural product the final functional group manipulations needed for betaine formation as well as indole-assisted, selective amide cleavage lead to the Ugi product **77**. We decided that the amine must be incorporated into the linear precursor of the Ugi reaction so later substitution reaction would not be necessary. This led us naturally back to the γ-ketoacid **78** which we believed could be synthesized in two ways. We hoped **78** could be derived from the chiral pool material L-malic acid, also known as apple acid, because this material contains the necessary stereocenter and is sufficiently oxidized. We held open, as an alternative, the possibility of deriving **78** from some type of asymmetric carbon-carbon bond forming event, most likely through the use of a chiral auxiliary. Initial steps were taken down each path to explore the best possible route.



Scheme 3.1. Retrosynthetic analysis for (–)-dysibetaine.

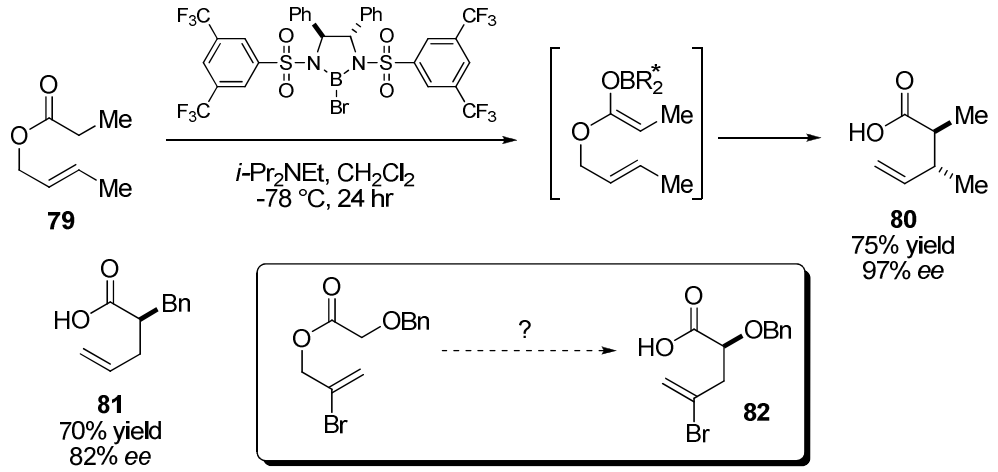
B. Initial Studies into Chiral γ-Ketoacid Synthesis

We saw two general pathways to synthesize the necessary chiral γ-ketoacid that would lead to dysibetaine through the Ugi reaction. One choice would be to use some sort of chiral auxiliary or chiral catalyst to set the necessary stereocenter through a carbon-carbon bond forming event. The other, more desirable, possibility was to start with a compound from the chiral pool. We pursued both options vigorously and ultimately we were able to use the readily available L-malic acid as the starting point for our synthesis.

1. Attempts Towards Chiral γ-Ketoacid via Carbon-Carbon Bond Forming Reaction

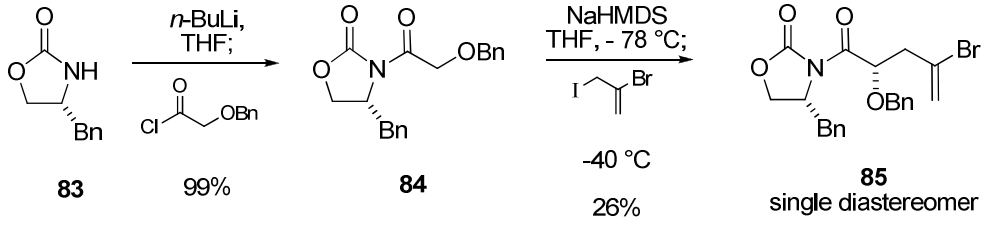
While designing our stereoselective synthesis of dysibetaine the most obvious choice for setting the chiral center was a modified version of the Ireland-Claisen rearrangement used in the racemic synthesis.[2,3] This would allow us to simply plug this reaction into the previous sequence for the molecule. We first reviewed the possibility of using achiral starting materials and inducing chirality using a chiral boron enolate. This method was pioneered by E. J. Corey and coworkers[4] and used in the total synthesis of *β*-Elemene and Fuscol.[5] As shown in Scheme 3.2, Corey and coworkers were able to transform ester **79** into **80** in good yield and high *ee* using the chiral bromoborane shown to induce stereochemistry through the boron-enolate. We would need chiral acid **82** for our synthesis, however most of the examples shown had more substitution, similar to **79**. The most similar example was product **81**, which suffered from reduced *ee* and, moreover, none of the examples shown contained oxygen in the α-position of the ester, as

in our case. Unsure if this method would be compatible with our substrate, we decided instead to first explore the use of chiral auxiliaries.



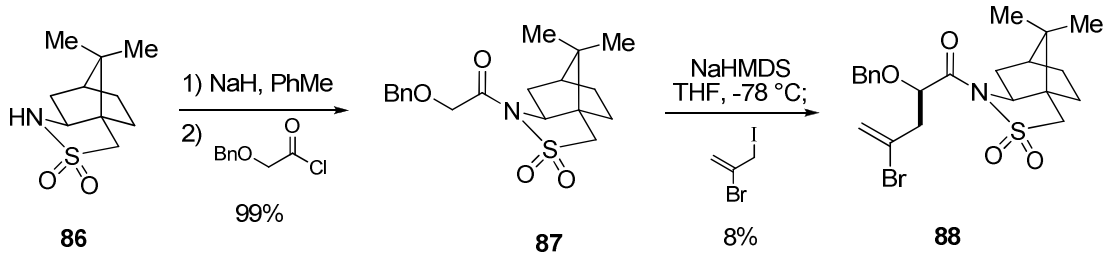
Scheme 3.2. Corey's stereoselective Ireland-Claisen rearrangement.

In our first attempt we chose to use the Evans chiral auxiliary for the carbon-carbon bond forming reaction as outlined in Scheme 3.3.[6] Chiral oxazolidinone **83** was coupled with commercially available benzyloxyacetyl chloride according to established procedure[7] to give **84**[8] in high yield. We hoped to couple **84** with 2-bromo-3-iodopropene to yield chiral **85**. After screening various bases and reaction conditions it seemed that the product did form as a single diastereomer, but we were only able to achieve a modest 26% yield. Furthermore, when this compound was taken a few more steps along the path towards the natural product significant difficulty was encountered in removing the chiral auxiliary. Although this problem would likely have been overcome, the low yield for the alkylation step provided a strong disincentive to exploring this pathway.



Scheme 3.3. Early attempts at chiral carbon-carbon bond formation.

We next decided to try the camphorsultam chiral auxiliary developed by Oppolzer and coworkers.[9] Coupling of the chiral auxiliary **86** to benzyloxyacetyl chloride to form previously known compound **87** was smooth (Scheme 3.4).[10] However, we were only ever able to achieve 8% yield of the alkylated product **88** with undetermined selectivity.

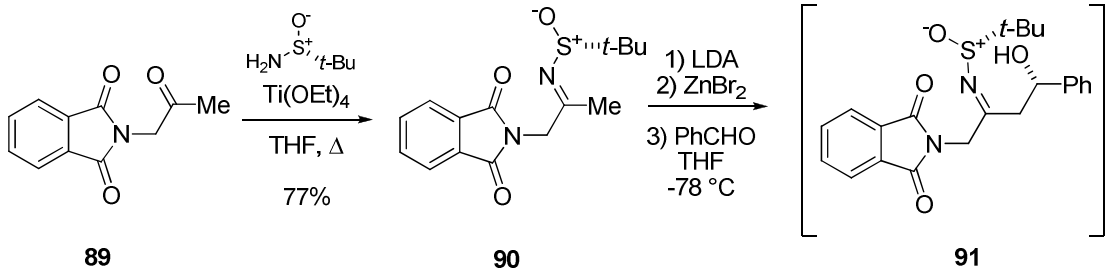


Scheme 3.4. Camphorsultam as a chiral auxiliary for carbon-carbon bond formation.

Throughout all of the attempts with both chiral auxiliaries it seemed like the electrophile was a problem. 2-bromo-3-iodopropene was made fresh and distilled before use but usually developed a highly colored impurity soon after distillation. An additional problem is that we are working with nucleophiles containing the –OBn group at the α-

position, while most of the published examples contained only alkyl substituents in this postion.

We additionally explored a sulfur-based chiral auxiliary recently introduced by Ellman and co-workers to form the necessary chiral carbon-carbon bond.[11] An *N*-sulfinyl imine is used in the reaction and the stereochemistry is controlled by the sulfur-stereocenter. In this case, chloroacetone and potassium phthalate were coupled to give previously synthesized **89** (Scheme 3.5).[12] Ketone **89** was treated with the chiral sulfinyl amine and dehydrated with $Ti(OEt)_4$ to give the corresponding sulfinimide **90**.[13] Using LDA and $ZnBr_2$ we attempted to couple **90** with benzaldehyde to form **91**. We envisioned a ruthenium catalyzed oxidation of the phenyl ring to the corresponding carboxylic acid. Unfortunately, despite repeated attempts, we were unable to get any products from this reaction. In the original report, Ellman used only acetophenone as the ketone and there were no examples of alkyl ketones such as **89**. This may explain the lack of reactivity in our case.

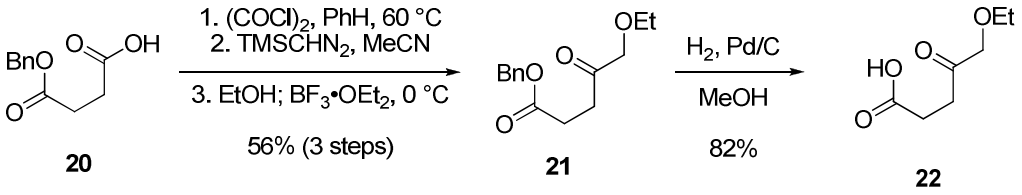


89 **90** **91**

Scheme 3.5. Failed carbon-carbon bond forming with sulfoxide chiral auxiliary.

2. Initial Attempts Towards Chiral γ-Ketoacid from L-Malic Acid

At the same time that we were experimenting with the various chiral auxiliaries, we also hoped to derive the necessary γ-ketoacid from the readily available chiral material L-malic acid. We knew from previous experience that TMS-diazomethane can be a powerful reagent for the one-carbon extension of carboxylic acids to ketones.[14] We had previously used the method to elaborate succinic anhdyride into the corresponding γ-ketoacid **22** containing an ethyl ether (Scheme 3.6).[15] We thought this would be a good way to elaborate L-malic acid into the Ugi precursor needed for dysibetaine.

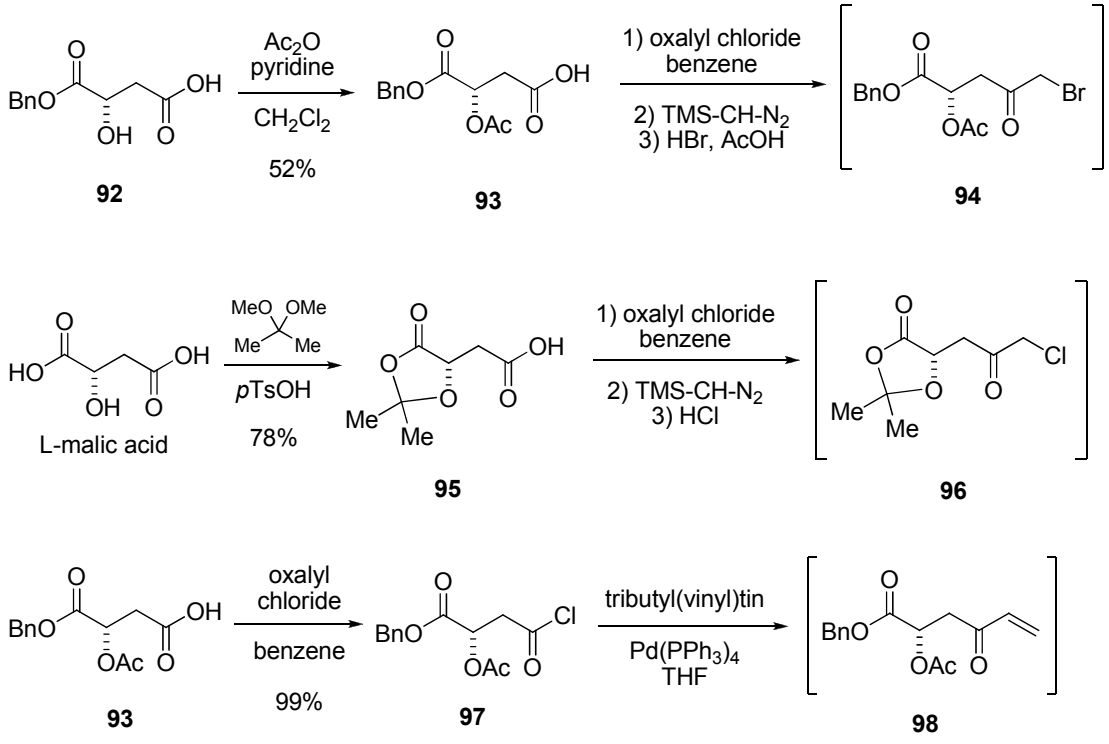


Scheme 3.6. TMS-diazomethane-assisted synthesis of γ-ketoacid.

As an initial foray into this area we followed literature precedent to arrive at compound **92** in a single step from L-malic acid (Scheme 3.7).[16] Previous work indicated that participation of the secondary alcohol with the diazoketone intermediate might lead to side reactions.[17] We therefore protected the alcohol as the acetate **93** in the hope that this would facilitate the ketone formation reaction. Unfortunately we were never able to successfully reach the desired ketone **94** using this method. Some material was isolated but the identity was never determined unequivocally. Undaunted, we decided to tie the ester and secondary alcohol together using an acetonide protecting group as in **95** (Scheme 3.7).[18] We hoped that this would sterically restrain the alcohol as well as

deactivate it electronically. Still, however, we were never able to isolate any ketone like **96**.

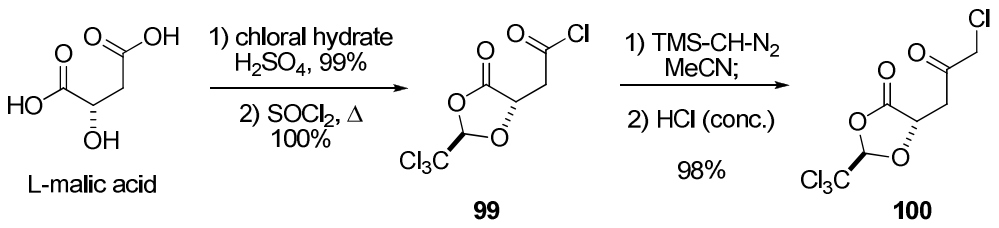
Next, we attempted the palladium-mediated coupling of tributyl(vinyl)tin with acid chloride **97**, derived from intermediate **93**.[19] We tested various catalysts, and tried vinyltrimethylsilane as well, but again were never able to isolate the ketone **98**. We believe that the secondary alcohol present in the molecule, despite protection, was the culprit in interfering with these reactions. The one-carbon extension of this acid to the corresponding ketone was successful and uneventful when using simpler substrates, but completely unsuccessful when starting with L-malic acid.



Scheme 3.7. Failed ketone formation from L-malic acid.

Finally we discovered that another group had overcome this same problem by using the strongly electron-withdrawing chloral protecting group (Scheme 3.8).[20] Treating L-malic acid with the hydrate of chloral under strongly acidic conditions led to the protection of the alcohol and the proximal carboxylic acid. The introduction of the chloral group created a new stereocenter, and the molecule was isolated as a single diastereomer, as shown. Treatment of the resulting mono-acid with refluxing thionyl chloride afforded the acid chloride **99** without affecting the chloral protecting group. We reacted the acid chloride with TMS-diazomethane in acetonitrile to form the corresponding diazoketone *in-situ*. This reactive intermediate was captured with hydrochloric acid to give ketone **100**.

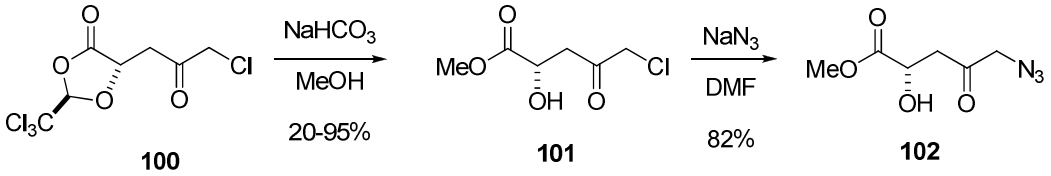
Relieved that we had discovered a reliable route to the chiral ketone, we were finally able to turn our attention towards elaborating this molecule into the necessary Ugi precursor. The next challenge would be the removal of the chloral protecting group. From there we would seek to introduce the amine functionality and then find a suitable γ-ketoacid for the U4C-3CR.



Scheme 3.8. Successful formation of chloro-ketone **100**.

3. Testing Chiral γ-Ketoacids Derived from L-Malic Acid in the U4C-3CR

Not surprisingly, the elaboration of ketone **100** into a suitable γ-ketoacid precursor for the Ugi reaction was not as straightforward as it initially seemed. The chloral protecting group has most commonly been used to protect diols,[21] not an α-hydroxycarboxylic acid as in the present case. The most common method for deprotection involves zinc/acetic acid reduction to remove the chlorines followed by hydrolysis. Unfortunately, the reductive conditions are not compatible with the chloroketone that we just painstakingly formed. We therefore explored the deprotection of the chloral group of **100** using methanol and a variety of bases to form the corresponding α-hydroxyester **101** (Scheme 3.9). This was a tricky reaction to monitor because the starting material disappeared immediately by TLC but an unidentified intermediate formed before converting to the product **101**. We experimented with adding ethylene glycol to the reaction mixture with the idea that it would capture any free chloral that might be present, but this seemed to have little effect. Although good yields of **101** were sometimes obtained, they were not reproducible, possibly due to a competing retro-aldol reaction, and this was found to be a very unreliable reaction.

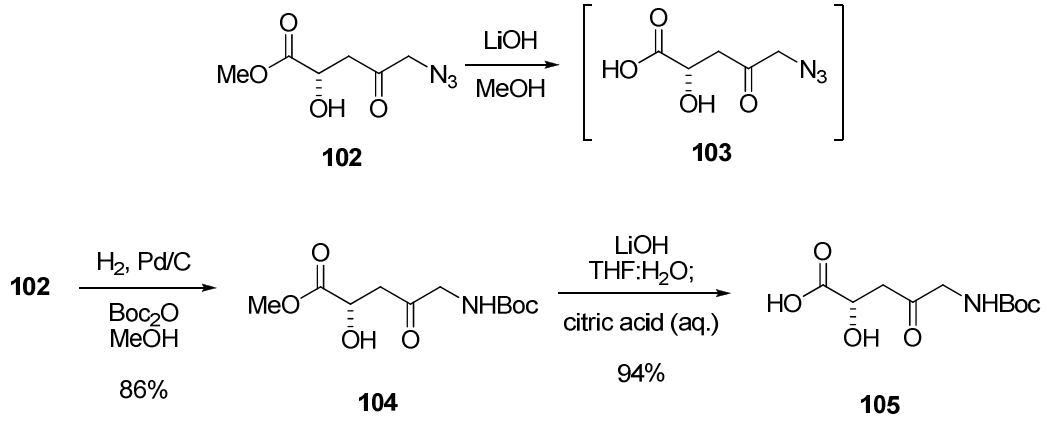


Scheme 3.9. Methanolysis of **100** and conversion to azide **102**.

Undaunted by this problem, we pushed a large amount of material through to intermediate **101** and began examining the best way to reach the desired γ-ketoacid. The

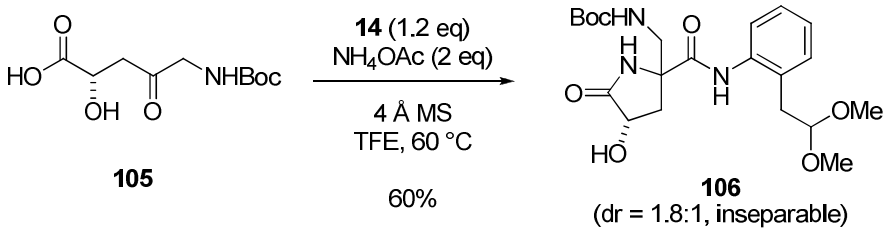
chlorine in **101** was successfully substituted with sodium azide to give **102**. We saw the introduction of nitrogen at this step, before cyclization, as being a crucial part of this synthesis. It is also worth noting that we attempted to protect the secondary alcohol in **102** under various, sometimes forcing conditions but were not able to successfully introduce a MOM group, or benzyl ether. We believe that a competing retro-aldol pathway may again be the culprit in these unsuccessful reactions. A silyl ether was introduced using TBS-OTf but in unsatisfactory yield. The secondary alcohol was therefore left unprotected.

Azide **102** was treated with lithium hydroxide in methanol in an attempt to synthesize γ-ketoacid **103** (Scheme 3.10). We were not able to isolate this γ-ketoacid, a result consistent with previous attempts to incorporate azide into this type of molecule. This may be because the α-ketoazide moiety was not compatible with the strong base used. The azide **102** was therefore reduced in the presence of Boc-anhydride to give the protected amine **104**. With the Boc-protected amine in place, the methyl ester in **104** was then successfully cleaved using lithium hydroxide as the base to give γ-ketoacid **105** in good yield.



Scheme 3.10. Synthesis of amine-containing chiral γ-ketoacid **102**.

When the linear precursor **105** was submitted to the Ugi 4-center 3-component condensation reaction conditions the cyclization did occur, eventually giving a 60% yield of **106** as a 1.8:1 mixture of inseparable diastereomers (Scheme 3.11). While this yield was reasonable enough to carry forward, it was disappointing as a key step. The problem was aggravated, though, because we were never able to separate the two diastereomers using chromatography despite testing a variety of protection regimes at various subsequent steps. We felt that we had arrived at a point of impasse and this project was pushed to the back burner for a while, but a breakthrough awaited us.



Scheme 3.11. U4C-3CR reaction of chiral γ-ketoacid **105**.

C. Unique Ugi Reaction of an Activated Ester

1. Initial Discovery

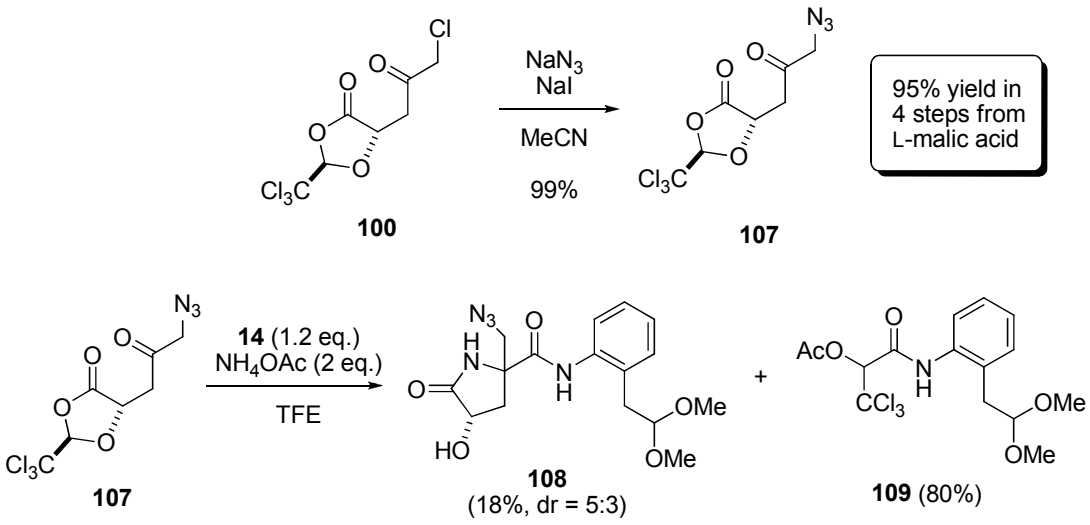
As you can see, we put in a considerable amount of effort towards preparing a viable chiral γ-ketoacid for use in the Ugi 4-center 3-component cyclization reaction. Unfortunately, the sequence to arrive at the desired molecules was too long, many of the steps were suspect, and ultimately this path led us to a dead end. If any one of the multiple problems we faced were easily remedied we might have pushed forward stubbornly along this path towards a stereoselective synthesis of dysibetaine. Fortunately

we decided to take step back and wondered if the chloral protecting group, which had proven to be quite promiscuous, might have another surprise in store for us.

Due to these continuing problems with arriving at a suitable Ugi product in acceptable yield, we decided to try submitting the chloral protected α-hydroxyester directly to the Ugi reaction. First, though, it was very important that we incorporate the amine functionality into the linear backbone before cyclization. For our more direct pursuit of a suitable Ugi product we started by converting **100** to the corresponding azide **107** in great yield using sodium azide in acetonitrile with sodium iodide as a catalyst (Scheme 3.12). We initially followed conditions that had been previously published[20] to reach **107**, but unsatisfactory yields led us to use the conditions shown. Following this pathway we arrived at enantiomerically pure **107** in four operationally simple steps and in 95% overall yield from L-malic acid.

We then submit the γ-keto*ester* **107** directly to the conditions of the U4C-3CR, using ammonium acetate as the amine source and indole isocyanide **14**, with TFE as the solvent. We were very pleasantly surprised to see that, in fact, the Ugi product **108** did form, albeit in very low yield. The diastereomeric ratio was found to be 3:5 for the inseparable diastereomers. In addition to the Ugi product, the major product formed was determined to be the Passerini adduct (**109**) of chloral (which was released during the multicomponent reaction of **107**), acetic acid (from ammonium acetate) and indole isocyanide **14**. We had hoped to see the Ugi reaction directly from γ-ketoester **107** but were unable to determine if that is what happened from the current data – the ester may have been deprotected to the free carboxylic acid *in-situ*. Although disappointing, this

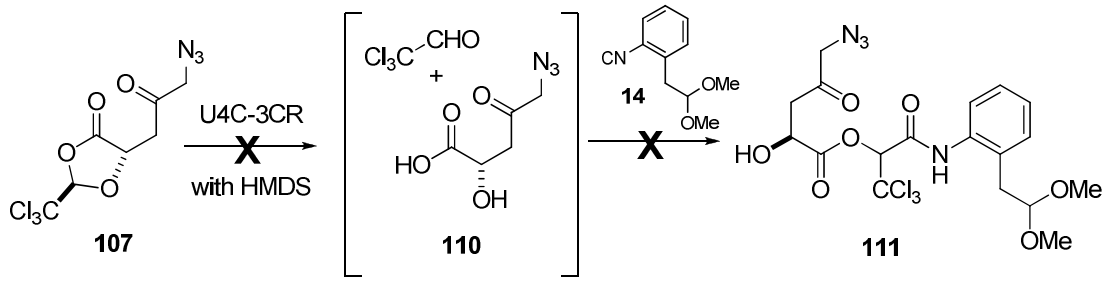
result was not particularly surprising because the Passerini reaction of an aldehyde, carboxylic acid and isocyanide should be much faster than the Ugi reaction of a ketone.



Scheme 3.12. Initial observations in the Ugi reaction of γ-ketoester **107**.

Our earlier work,[12] as well as the work of another group,[22] had revealed that 1,1,1,3,3,3-hexamethyldisilazane (HMDS) could also function as an ammonia equivalent in the Ugi and related reactions. The Passerini adduct **109** cannot form if acetic acid, which was present only as the counter ion for ammonia, is not present. So, we hoped that the yield of the Ugi product **108** would be greatly improved by the use of HMDS as an ammonia equivalent because the isocyanide would not be consumed by the preferential reaction with chloral. Although using HMDS completely suppressed the formation of **109**, the desired product **108** still formed in low yield (22%), so we clearly needed to improve this reaction. The fate of the balance of the starting material **107** was not determined and no other major side products derived from **107** were detected.

Mechanistically, however, this reaction gave us great insight. We now knew that **110** (Scheme 3.13), the unprotected form of γ-ketoester **107**, is not an intermediate in the reaction. If carboxylic acid **110** was present we would expect to detect formation of the Passerini adduct **109** that would be form between indole isocyanide **14**, chloral and **110**.



Scheme 3.13. Evidence that the U4C-3CR happens directly from γ-ketoester **107**.

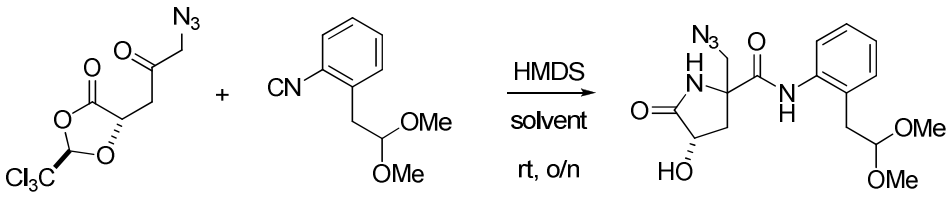
2. Optimization of Reaction Conditions

In order to include our interesting new Ugi reaction in a successful synthesis of (–)-dysibetaine it was clear that we would need to improve the yield. The first step we took was to screen various solvents. We screened the typical range of organic solvents including THF, acetonitrile, dichloromethane as well as a variety of alcohols, acetic acid and water. These experiments revealed that in addition to TFE only 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was conducive to the reaction, and in fact it proved to be the best choice.

Next we would attempt to optimize the ratios of the various reactants to see if the yield could be improved. We saw a striking result when we varied the amount of the amine component, HMDS, that was used in the reaction. When TFE was used as the

solvent the yield of **108** decreased as the number of equivalents of HMDS were increased (Table 3.1). We observed the opposite effect when HFIP was used as the solvent.

Table 3.1. Effect of changing the amount of the amine component (HMDS) while varying the solvent between TFE and HFIP.



107 (1 eq) **14 (1 eq)** **108**

Solvent	eq. HMDS	Yield of **108**
F_3C OH TFE	1	33%
	2	29%
	3	21%
	4	17%
OH F_3C CF_3 HFIP	1	25%
	2	40%
	3	52%
	4	59%

These results are not entirely inconsistent with our earlier studies on **100**. When attempting the deprotection via methanolysis of **100** (Scheme 3.9) we observed that **100** was very prone to decomposition – most likely by the nucleophilic solvent used. Since HMDS is weakly basic it may have increased the propensity of TFE to decompose the starting material **107**. As mentioned above, we believe the most likely pathway for decomposition to be partial solvolysis of the chloral protecting group followed be retro-aldol reaction.

Because of the presence of the additional electron-withdrawing trifluoromethyl group in HFIP the solvent is only very weakly nucleophilic, perhaps even non-

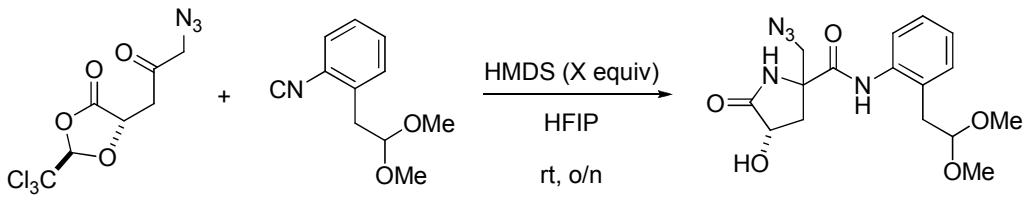
nucleophilic.[23] We believe that the additional equivalents of HMDS added when HFIP was the solvent only helped drive the reaction forward towards the formation of **108** rather than decomposing the starting material **107**. The difference between these two solvents also gave us insight into the mechanism, as discussed below.

Now that we had the best available solvent we tried to optimize the reaction conditions to get the best possible yield. In all of the early experiments that were performed, the indole isocyanide **14** was never fully consumed. TLC analysis indicated that the starting material **107** was consumed but the isocyanide persisted even after prolonged stirring. Furthermore, the isocyanide **14** is available in five sometimes laborious steps from commercially available materials while the Ugi precursor **107** is made more readily in only four steps and up to 95% yield overall. The combination of these factors led us to carry out the optimization experiments always using the isocyanide **14** as the limiting reagent. We also knew from the solvent studies (Table 3.1) that when HFIP is the solvent increasing the amount of HMDS tended to increase the yield.

Using these thoughts as a starting point, a series of small scale experiments was carried out to begin to determine the optimal ratios of starting materials. Table 3.2 outlines the first set of experiments as various ratios of **107** and HMDS were tested. Entries 1-4 show the effects when one equivalent of isocyanide **14** and one equivalent of **107** are treated with increasing amounts of HMDS. The yield increases with increasing HMDS up to about four equivalents, at which point the yield levels off and further increasing the amount of HMDS has, if anything, a deleterious effect. Since 59% (Entry 2) is still not a satisfactory yield, we next experimented using one equivalent of isocyanide with two equivalents of **107** and increasing amounts of HMDS. As can be

seen from Entries 5-7, the yield plateaus around 78% despite increasing from six to eight equivalents of HMDS.

Table 3.2. Testing various ratios of reactants for the synthesis of **108**.

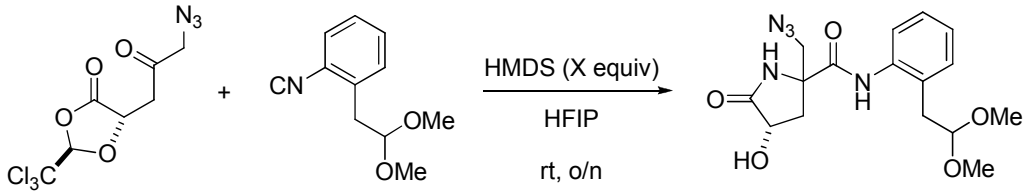


107 (X equiv) **14** (1 equiv) **108**

Entry	Equiv **107**	Equiv HMDS	Yield of **108**
1	1	2	40%
2	1	4	59%
3	1	6	59%
4	1	8	54%
5	2	4	63%
6	2	6	78%
7	2	8	79%

With the completion of these experiments we were clearly closing in on the best possible reaction condition for the formation of **108** from chiral γ-ketoester **107** and isocyanide **14**. Table 3.3 outlines the next steps we took, with more slight variations of the ratios of reactants. Entry 2 was the best in terms of both yield and amount of reactants that were needed so these were the ratios finally used in the total synthesis of the natural product.

Table 3.3. Final optimization of Ugi reaction conditions.



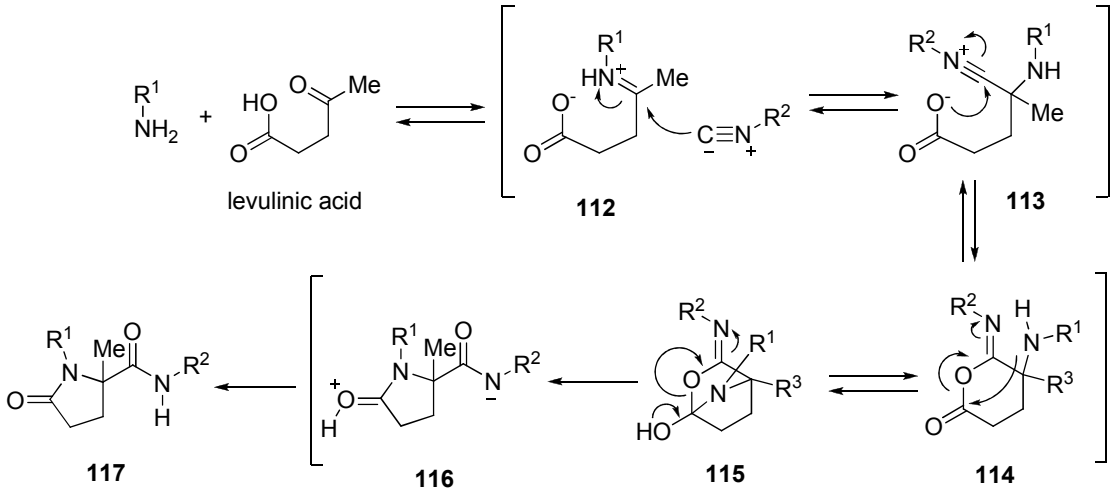
107 (X equiv) **14** (1 equiv) **108**

Entry	Equiv **107**	Equiv HMDS	Yield of **108**
1	1.5	4.5	78%
2	1.5	6	85%
3	1.5	7.5	58%
4	1.75	7	70%
5	1.75	8.75	69%

3. Mechanistic Hypothesis

In the course of investigating the unusual Ugi reaction of γ-ketoester **107** with indole isocyanide **14** to form **108**, we naturally wondered about the mechanism. The generally accepted mechanism for the Ugi reaction, specifically the U4C-3CR is mapped out for the case of levulinic acid with a primary amine and generic isocyanide in Scheme 3.14.[24] It is believed that the first step in the reaction is Brønsted-acid (in this case the carboxylic acid) catalyzed dehydration of the ketone to form an activated iminium species, **112**. This intermediate is then attacked by the isocyanide to form intermediate **113**, in which the isocyanide carbon atom is immediately attacked by the carboxylate ion. The intermediate thus formed, **114**, contains an acylimidate, a very strong acylating reagent which quickly acylates the amine in a process known us Mumm rearrangement[25] to give the cylcized product **115**. All of the processes that have taken place up until this

stage are believed to be reversible. It is not until the Mumm rearrangement is finalized, with the conversion of bicyclic intermediate **115** to intermediate **116**, that the process becomes irreversible. A final proton transfer to relieve all charges yields the pyroglutamic acid amide **117**.

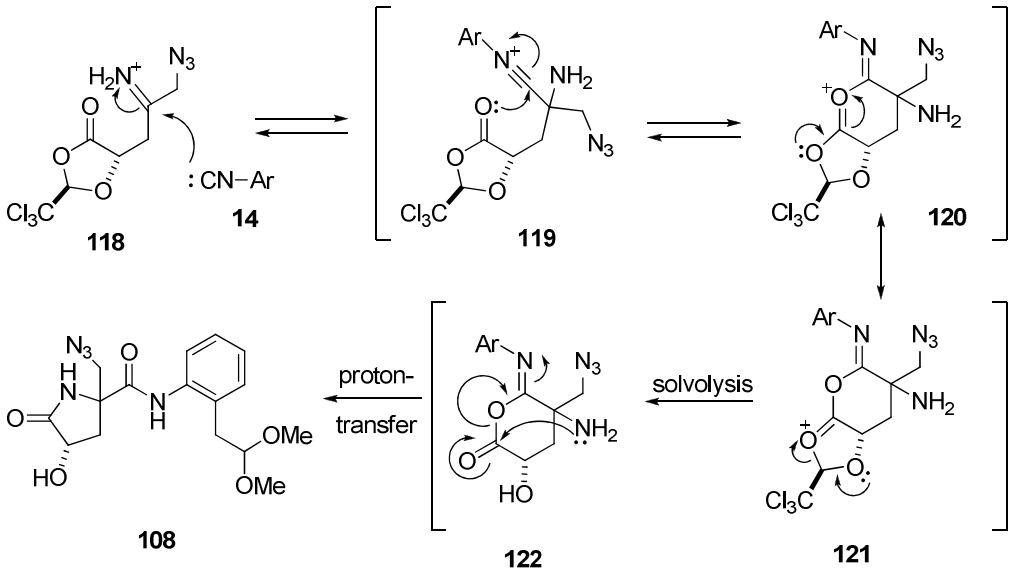


Scheme 3.14. Generally accepted mechanism for U4C-3CR.

Understanding the usual mechanism makes the current case more puzzling. The Ugi reaction is believed to be catalyzed by Brønsted acid but in this case an ester acts as the acid component so no acid is present. It was initially plausible that some sort of *in-situ* deprotection of the ester led subsequently to the Ugi reaction. However we strongly believe that the evidence presented in Table 3.1 discounts this hypothesis. The increase in yield using the non-nucleophilic HFIP seems to rule out a mechanism involving nucleophilic attack of the solvent on the ester in **107**. Furthermore, no Passerini product arising from chloral, isocyanide **14** and the carboxylic acid form of **107** (**110**, Scheme

3.13) was ever detected, further evidence that the Ugi reaction proceeded directly from the ester.

We therefore propose the mechanism laid out in Scheme 3.15. Chiral γ-ketoester **107** reacts with HMDS and HFIP to form the first intermediate, ketimine **118**, which reacts with indole isocyanide to form **119**. We believe the ester now interacts directly with the isocyanide carbon atom to form the cyclic intermediate **120**. The activation of the ester now causes the chloral protecting group to become very labile, as shown in the resonance structures **120** and **121**. All of the intermediate steps up to **121** are considered to be reversible. Solvolysis of the protecting group yields intermediate **122** and finally Mumm rearrangement completes the Ugi reaction to give the product **108**. It is worth mentioning that when γ-ketoester **107** was treated with the isocyanide in the absence of the amine source, HMDS, that the corresponding lactone analogue of pyroglutamic acid **108** was formed; the Passerini reaction did not occur.

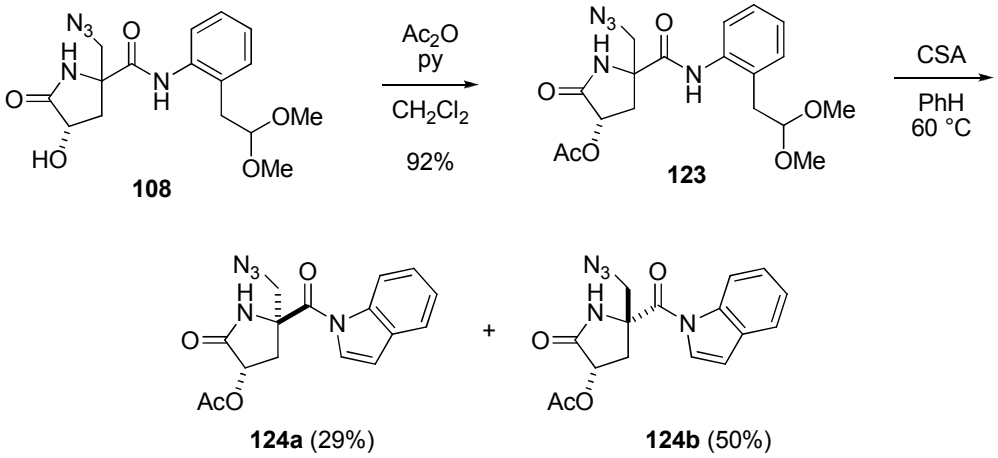


Scheme 3.15. Proposed mechanism for the formation of **108** from **118**.

The chloral protecting group was originally chosen as a strongly deactivating protecting group to inhibit the intramolecular participation of thusly protected alcohol with a diazoketone intermediate. It is therefore quite remarkable that the same protecting group allowed the participation of the ester group in a very unusual Ugi reaction. This serendipitous reaction allowed us to reach the desired Ugi product much more expeditiously than was possible following a conventional route. We felt well prepared at this point to move forward to the completion of the natural product.

D. Completion of the Total Synthesis of (–)-Dysibetaine

With a straightforward pathway to the Ugi product readily available we were ready to focus on the elaboration of **108** to the natural product (–)-dysibetaine. We initially proceeded directly forward from **108** to the corresponding *N*-acylindole but discovered that it was not possible to separate the diastereomers at any subsequent step. We therefore proceeded by acetylating the free alcohol to form **123**, which was treated with catalytic acid and heated in benzene to afford the *N*-acylindole **124** as a mixture of diastereomers (Scheme 3.16). At this point it was possible to separate the diastereomers to give **124a** (29% from **123**) and **124b** (50% from **123**).



Scheme 3.16. Determination of diastereoselectivity for the U4C-3CR.

X-ray of the major diastereomer **124b** revealed that, as was the case during the racemic synthesis, the minor diastereomer was the one required to reach the natural product. An ORTEP drawing of the X-ray crystal structure of **124b** is included in Figure 3.2.

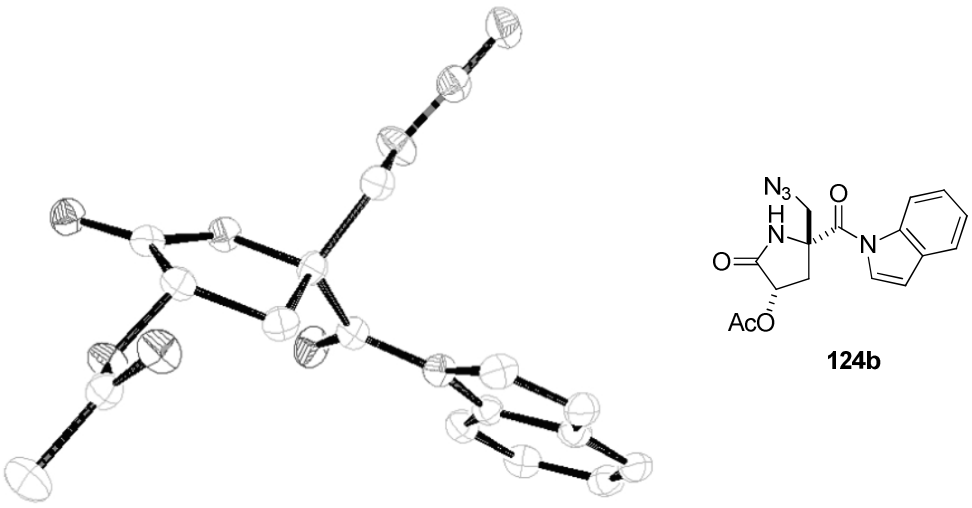
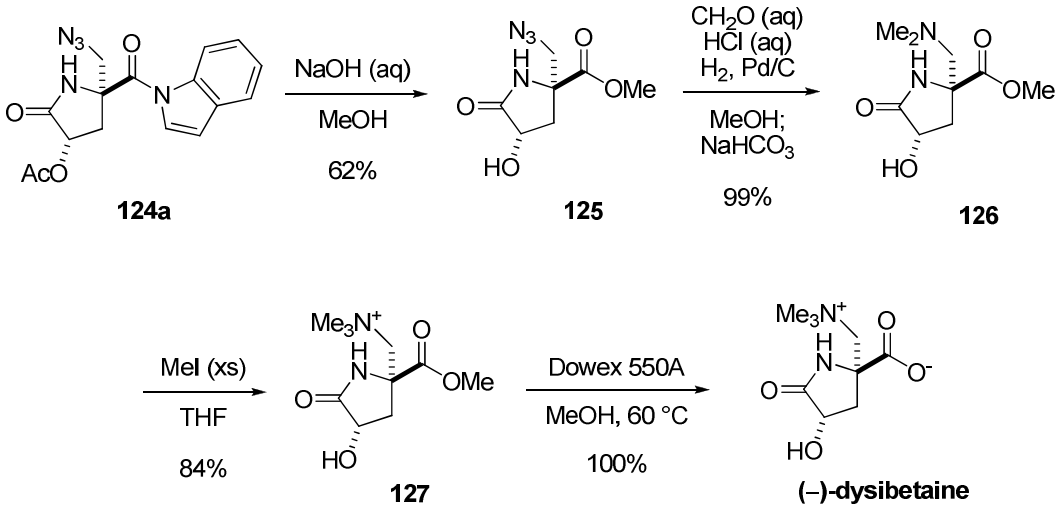


Figure 3.2. ORTEP drawing of **124b**.

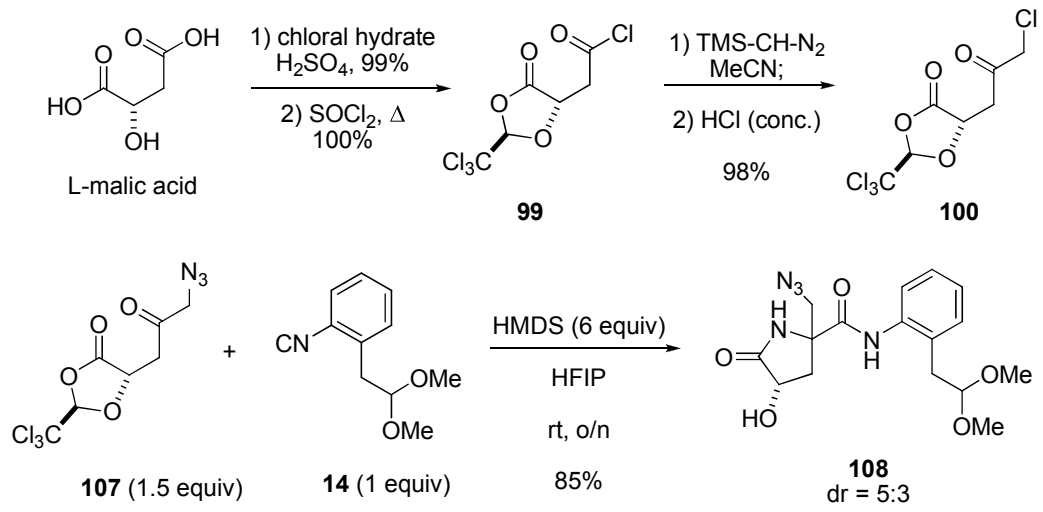
We proceeded by treating **124a** with a catalytic amount of sodium hydroxide in methanol (Scheme 3.17). As a testament to the ease of amide cleavage when indole isocyanide is used, TLC analysis indicated that the amide bond was fully cleaved within a few minutes while the acetate ester group was removed much more slowly. Having selectively cleaved this single amide bond we thus arrived at methyl ester **125** which was ready for final elaboration to the final product. Previous syntheses suggested we approach the dimethyl amine in a stepwise fashion via reduction of the azide in **125** and subsequent Clarke-Eschweiller methylation under high pressure.[26] We found, however, that these steps were easily completed in one under H_2 at atmospheric pressure to afford **126** in great yield. The resulting dimethyl amine of **126** was quaternized using excess methyl iodide to give **127** which was hydrolyzed with basic anion-exchange resin to give (–)-dysibetaine in accordance with literature precedent. The spectral properties of the synthetic material showed a close correlation to the published properties of the natural product as well as with our own previous work.



Scheme 3.17. Completion of the natural product (–)-dysibetaine.

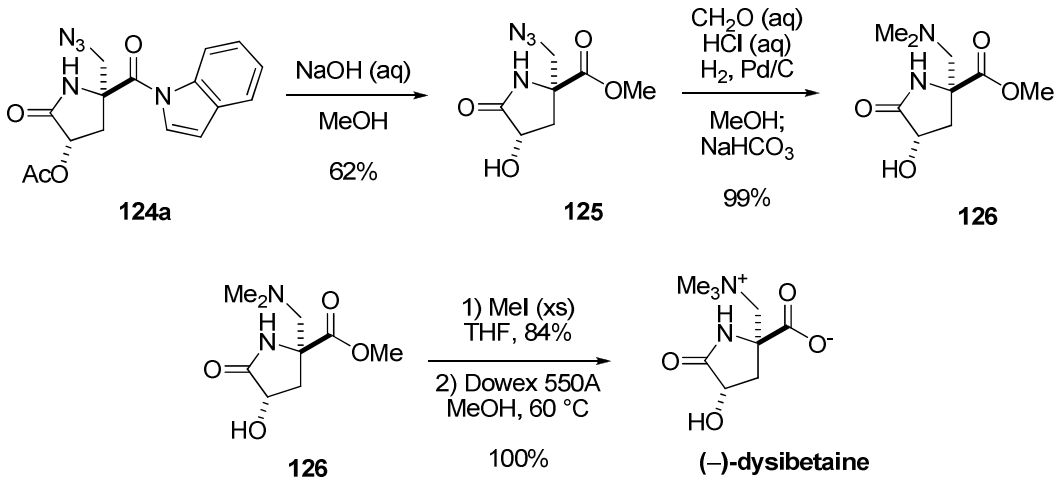
E. Summary

The stereoselective total synthesis of (–)-dysibetaine was completed in 12 steps on the longest linear sequence and in just 11 steps and 11% overall yield from L-malic acid. The key developments that made this synthesis possible are outlined in Scheme 3.18. We were able to use the chiral pool compound L-malic acid as the source of the necessary chiral center and this widely available material was successfully converted into ketone **100** in just three steps and excellent yield by way of acid chloride **99**. The introduction of the chloral protecting group was necessary for the TMS-diazomethane mediated ketone formation reaction.



Scheme 3.18. Key developments in the total synthesis of (–)-dysibetaine.

After conversion of the chlorine in **100** to the corresponding azide **107**, we were able to proceed directly to the U4C-3CR. This was very advantageous for multiple reasons: (a) we successfully introduced nitrogen into the linear backbone before cyclization; (b) the Ugi reaction was reached in a very short number of steps; and (c) we never successfully isolated an azide-containing γ-ketoacid, so the ability to submit the γ-ketoester directly to the reaction was also key. After discovering this unique Ugi reaction, wherein an ester acts as the carboxylic acid component, we successfully developed conditions for the reaction of **107** with HMDS as the amine source and indole isocyanide **14** to yield **108** with a good yield.



Scheme 3.19. Summarizing key steps in the end-game for (–)-dysibetaine.

Although it is a very routine reaction for us at this point, it is still remarkable that we were able to selectively cleave the *N*-acylindole amide bond in **124a** using mild conditions and without affecting the other amide present in the molecule to afford methyl ester **125** (Scheme 3.19) Indeed, TLC indicated that this activated amide bond even cleaved faster than the acetate ester protecting group for the secondary alcohol. Because we had incorporated the azide into the molecule prior to the Ugi reaction the remaining functional group transformations were straightforward. We found that the azide could be reduced and the resulting amine dimethylated in one pot under atmospheric H_2 pressure. From there, completion of the natural product (–)-dysibetaine was readily completed in just 11 steps and 11% overall yield from L-malic acid.

F. Conclusion

The Ugi reaction is a powerful platform on which to build complex total syntheses. There are many advantages brought about by using a strategy based around the Ugi reaction, including: (a) extremely mild reaction conditions that do not require

stoichiometric activating agents nor catalysts so sensitive functionalities are preserved without protection; (b) efficient coupling between the various components with a single equivalent of water as the only by-product makes this an environmentally friendly approach; and (c) four components with various functional groups combine to form a biologically interesting α-amino acid derivative with a new stereocenter.

While many different groups have harnessed the advantages of the Ugi reaction, critical problems remain unsolved. The biggest of these problems is the issue of stereoselectivity in the Ugi reaction. Efforts to induce stereochemistry into the Ugi reaction have been mostly unsuccessful, and most successful cases reported have been highly substrate specific.[24] We chose to use the Ugi 4-center 3-component reaction of γ-ketoacids as a platform to study diastereoselectivity in the Ugi reaction.

We thought that the U4C-3CR of γ-ketoacids would be a fruitful area of research because two of the reacting centers are tied into one molecule. This restricts the freedom of movement of the various components as they react, which we hoped might lead to greater selectivity. Tying of two components together also allowed us to study the U4C-3CR with a ketone as the carbonyl component. It is desirable to use a ketone as the carbonyl component in the reaction because a fully substituted stereocenter is created in the product. In standard four-component Ugi reactions ketones are generally not very reactive, but they are more reactive in the U4C-3CR. Finally, the products of this type of reaction are pyroglutamic acid derivatives, which are attractive targets from a biological standpoint.

During the course of our efforts, we were not able to find a general solution to the problem of stereoselectivity in the U4C-3CR. Our laboratory had success in the case of

the Ugi reaction that led to the formal total synthesis of omuralide, when the ketone moiety was part of a dioxanone ring. Unfortunately, this example proved the rule that the only real solution so far to the problem of stereoselectivity in the Ugi reaction is substrate specific. It is interesting that the analogous Passerini reaction, wherein no amine was used, gave very good selectivity. This result certainly lends weight to the general agreement[24] that the Passerini and Ugi reactions, despite their similarities, operate according to different reaction mechanisms.

Despite the obstacles encountered thus far, we remain devoted to developing a general solution to the problem of stereoselectivity in isocyanide based multicomponent reactions. One possibility that is currently under investigation in our laboratory is the use of a different U4C-3CR in which the amine and ketone are tied together in a single molecule to make cyclic ketimines and aldimines that can enter into the Ugi reaction. There is evidence[27] to suggest that stereoselectivity may be induced in this type of Ugi reaction due to the cyclic nature of the starting material and we hope to exploit this idea for natural product synthesis.

In addition to the efforts just described, throughout the total synthesis of (–)-dysibetaine we were exploring other ways to induce stereochemistry in multicomponent reactions. We also continued our work to expand the usefulness of these reactions by creating methods for further elaboration of the products thus derived. The results of that research, which include the use of indole isocyanide as a convertible isocyanide for the Passerini reaction and a new entry into stereoselective isocyanide based MCRs – specifically a Brønsted acid catalyzed stereoselective Passerini-type reaction – are described in the next chapter.

G. Acknowledgements

This chapter contains material that was previously published in the paper: *An Ugi Reaction in the Total Synthesis of (–)-Dysibetaine.* Isaacson, Jerry; Kobayashi, Yoshihisa. *Angew. Chem. Int. Ed.* **2009**, *48*, 1845-1848.

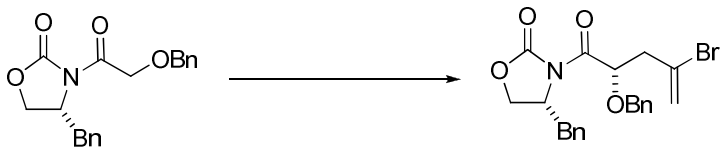
H. Experimental Section

1. Materials and Methods

All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. Tetrahydrofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), 2,2,2-trifluoroethanol (TFE), and acetone were purchased as reagent grade and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnigan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]25D = (100\cdot\alpha)/(l\cdot c)$, where the concentration c is in g/100 mL and the path length l is in decimeters.

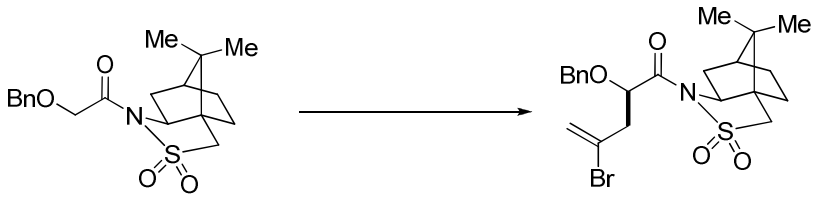
2. Procedures and Spectral Data



Scheme 3.20. Synthesis of **85**.

(85) NaHMDS (2.51 mL, 1.0M solution in THF) was cooled to -78 ˚C under N_2 atmosphere. **84** (0.545 g, 1.7 mmol) in THF (10 mL) was slowly added and the reaction was allowed to stir for 20 minutes after which time 2-bromo-3-iodopropene (2.068 g, 8.4 mmol) in THF (1.5 mL) was slowly added. The reaction was allowed to warm to -40 ˚C where it was maintained for 16 hours before being quenched with aq. NH_4Cl (20 mL). After warming to room temperature the reaction was extracted with EtOAc (2 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4 and

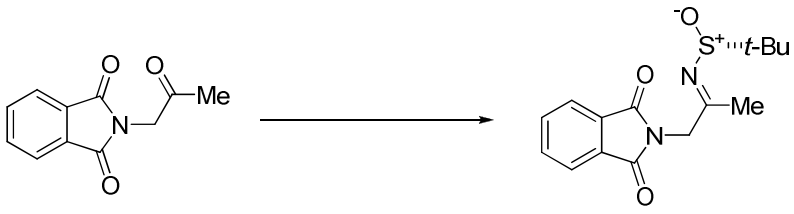
concentrated. Submitted to column chromatography (4:1 hexanes:EtOAc) to recover **85** (0.194 g, 26%) as a golden oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.17 (m, 10H), 5.79 (s, 1H), 5.58 (s, 1H), 5.43 (dd, *J* = 4.2, 8.5 Hz, 1H), 4.66-4.55 (m, 3H), 4.21-4.16 (m, 2H), 3.24 (dd, *J* = 3.3, 13.5 Hz, 1H), 2.97 (dd, *J* = 4.2, 14.7 Hz, 1H), 2.86 (dd, *J* = 8.5, 14.7 Hz, 1H), 2.75 (dd, *J* = 9.5, 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 153.1, 137.5, 135.1, 129.7, 129.3, 128.7, 128.6, 128.21, 128.18, 127.7, 120.7, 75.4, 73.5, 67.1, 55.3, 44.1, 38.0. MS $C_{22}H_{22}BrNO_4$: calcd 443.07, 445.07, obsd $[M + H]^+$ = 443.92, 445.92.



Scheme 3.21. Synthesis of **88**.

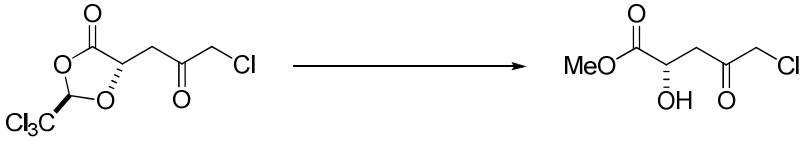
(88) Compound **87** in THF (2 mL) was slowly added to NaHMDS (0.62 mL, 1.0M in THF) stirring in THF (5 mL) at -78 ˚C under N_2 atmosphere. After 30 minutes, 2-bromo-3-iodopropene (0.509 g, 0.62 mmol) in THF (1.5 mL) was added. After two hours the cold bath was removed and aq NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (2 x 10 mL) which was then brined, dried over Na_2SO_4 and concentrated. Column chromatography (4:1 to 3:1 hexanes:EtOAc) afforded the starting material **87** (64 mg, 43%) and free camphorsultam (13 mg, 15%) along with the product **88** (16 mg, 8%). . ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.17 (m, 10H), 5.79 (s, 1H), 5.58

(s, 1H), 5.43 (dd, *J* = 4.2, 8.5 Hz, 1H), 4.66-4.55 (m, 3H), 4.21-4.16 (m, 2H), 3.24 (dd, *J* = 3.3, 13.5 Hz, 1H), 2.97 (dd, *J* = 4.2, 14.7 Hz, 1H), 2.86 (dd, *J* = 8.5, 14.7 Hz, 1H), 2.75 (dd, *J* = 9.5, 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 137.5, 128.5, 128.4, 128.3, 128.0, 120.7, 72.8, 65.3, 53.3, 50.6, 49.1, 48.1, 44.9, 44.8, 38.4, 33.0, 26.7, 21.0, 20.1. MS $C_{22}H_{28}BrNO_4S$: calcd 481.09, 483.09, obsd $[M + H]^+$ = 482.01, 484.01.



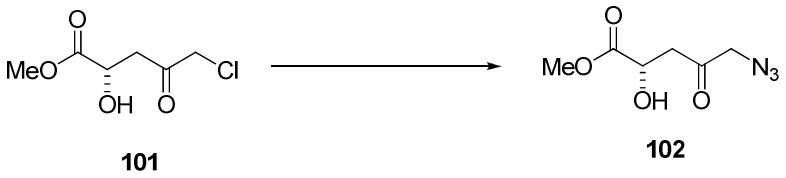
Scheme 3.22. Synthesis of **90**.

(90) Starting material **89** was dissolved in THF (2 mL) under N_2 atmosphere then $Ti(OEt)_4$ (0.146 mL, 0.66 mmol) and R-(+)-2-methyl-2-propanesulfinamide (0.040 g, 0.33 mmol) were added. The reaction was heated to 60 ˚C for 3 hours then allowed to cool to room temperature. Brine (2 mL) was added and the reaction was stirred vigorously. Filtered through Celite, rinsing well with EtOAc. Brine (5 mL) was added and the layers were separated. The EtOAc layer was dried over Na_2SO_4 and concentrated then submitted to column chromatography (1:1 hexanes:EtOAc) to afford **90** (0.078 g, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 3.0, 5.4 Hz, 2H), 7.74 (dd, *J* = 3.0, 5.4 Hz, 2H), 4.52 (d, *J* = 17.7 Hz, 1H), 4.43 (d, *J* = 17.7 Hz, 1H), 2.42 (s, 3H), 0.99 (s, 9H). MS $C_{15}H_{18}N_2O_3S$: calcd 306.10, obsd $[M + H]^+$ = 306.98.



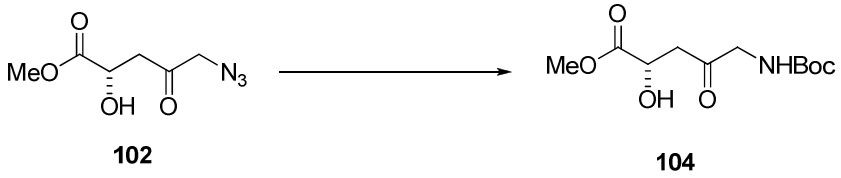
Scheme 3.23. Synthesis of **101**.

(101) Typical procedure: **100** (0.650 g, 2.2 mmol) was dissolved in MeOH (5 mL) then ethylene glycol (0.37 mL, 0.44 mmol) and $NaHCO_3$ (0.037 g, 0.44 mmol) were added. The reaction was allowed to stir overnight then diluted with EtOAc (5 mL) and hexanes (5 mL) and decanted from insoluble materials. Concentration and column chromatography (3:2 hexanes:EtOAc) afforded **101** (0.292 g, 74%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (dd, *J* = 4.1, 6.2 Hz, 1H), 4.13 (s, 2 H), 3.81 (s, 3H), 3.15 (dd, *J* = 4.1, 17.3 Hz, 1H), 3.04 (dd, *J* = 6.2, 17.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 174.1, 67.8, 56.1, 53.0, 44.0. MS $C_6H_9ClO_4$: calcd 180.02, obsd $[M + H]^+$ = 180.98.



Scheme 3.24. Synthesis of **102**.

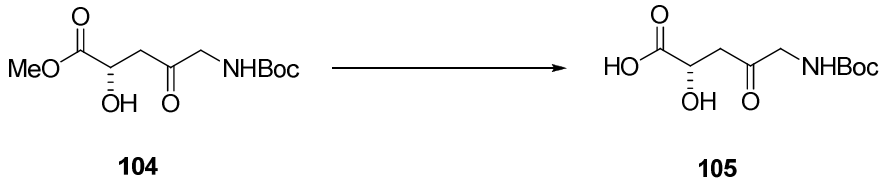
(102) Sodium azide (0.065 g, 0.10 mmol) was added to **101** (0.173 g, 0.96 mmol) stirring in 3 mL DMF. After 20 hours of stirring the reaction was poured into half-saturated aq NaCl (30 mL) then extracted with EtOAc (2 x 10 mL). Combined organics were brined, dried over Na_2SO_4 and concentrated to afford **102** (0.146 g, 82%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (dt, *J* = 4.4, 6.2 Hz, 1H), 4.00 (s, 2 H), 3.81 (s, 3H), 3.19 (d, *J* = 4.7 Hz, 1H), 2.99 (dd, *J* = 4.1, 16.9 Hz, 1H), 2.88 (dd, *J* = 6.2, 16.9 Hz, 1H). MS $C_6H_9N_3O_4$: calcd 187.06, obsd $[M + H]^+$ = 187.94.



102 **104**

Scheme 3.25. Synthesis of **104**.

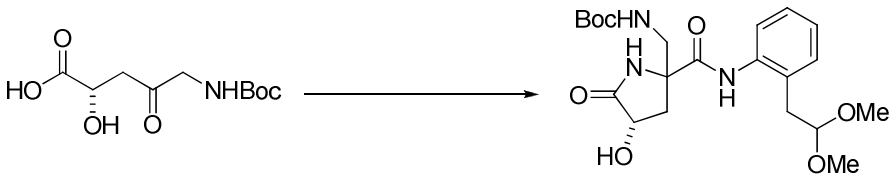
(104) Boc anhydride (0.98 g, 4.5 mmol) and a catalytic amount of Pd/C (10% w/w) were added to **102** (0.336 g, 1.8 mmol) in MeOH (5 mL) and H_2 was applied to the reaction. After 3 hrs the reaction vessel was cleared with N_2 gas and the reaction was filtered through Celite and concentrated. Column chromatography afforded **104** (0.397 g, 85%) as a golden oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 1H), 4.53 (t, *J* = 4.6 Hz, 1H), 4.03 (d, *J* = 5.0 Hz, 2 H), 3.78 (s, 3H), 3.35 (br, 1H), 2.96 (dd, *J* = 4.1, 16.7 Hz, 1H), 2.86 (dd, *J* = 6.5, 16.7 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 174.1, 155.9, 80.3, 67.0, 53.1, 51.2, 43.6, 28.5. MS $C_{11}H_{19}NO_6$: calcd 261.12, obsd $[M + Na]^+$ = 284.02.



104 **105**

Scheme 3.26. Synthesis of **105**.

(105) $LiOH{\cdot}H_2O$ (0.0724g, 1.7 mmol) was added to **104** (0.376 g, 1.4 mmol) in THF:H_2O (5 mL, 4:1) and the reaction stirred for 45 minutes. Poured into H_2O (5 mL) and washed with EtOAc (5 mL). The aqueous portion was acidified with citric acid then extracted with EtOAc (2 x 10 mL). Combined organics were brined, dried over Na_2SO_4 and concentrated to afford free acid **105** as a clear oil. This unstable intermediate was brought directly forward to the next step.

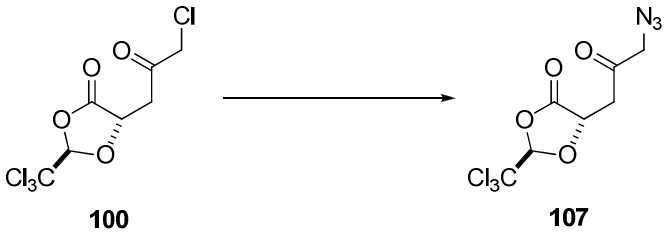


105 **106**
(dr = 1.8:1, inseparable)

Scheme 3.27. Synthesis of **106**.

(106) 105 (0.293 g, 1.2 mmol) was stirred in TFE (3 mL) and a few 4Å molecular sieves were added. NH_4OAc (0.183 g, 2.4 mmol) and isocyanide **14** (0.295 g, 1.5 mmol) were added and the reaction was heated to 60 ˚C for 1.5 hrs then removed from heat and poured into H_2O (15 mL). Extracted with EtOAc (2 x 10 mL) which was then brined,

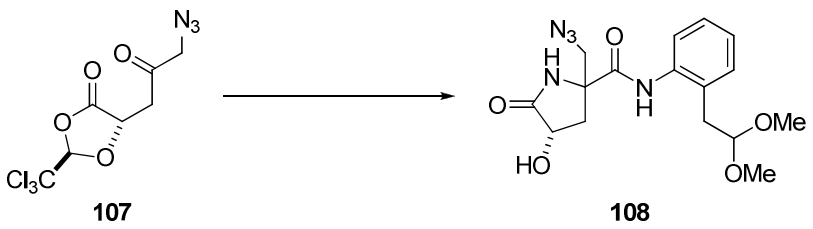
dried over Na_2SO_4 and concentrated. Column chromatography (100% EtOAc) of the crude material afforded the white foam **106** (0.308 g, 60%) as an inseparable mixture of diastereomers (dr = 1.8:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70, 9.61 (s, 1H), 7.79-7.72 (m, 1H), 7.45 (s, 1H), 7.29-7.10 (m, 3H), 5.32 (br, 1H), 4.47-4.39 (m, 1H), 3.62-3.48 (m, 1H), 3.42-3.35 (m, 8H), 3.01-2.79 (m, 2H), 2.56-2.52 (m, 1H), 2.37-2.34 (m, 1H), 1.40, 1.39 (s, 9H). MS $C_{21}H_{31}N_3O_7$: calcd 437.22, obsd $[M + Na]^+$ = 460.18.



100 **107**

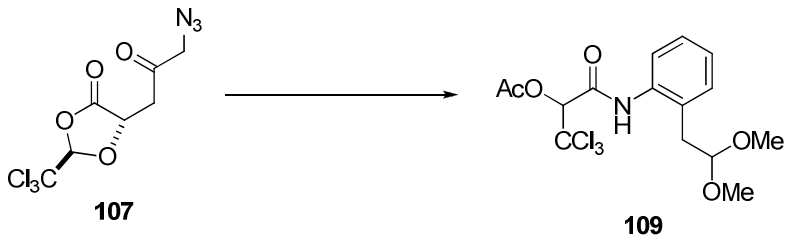
Scheme 3.28. Synthesis of **107**.

(107) To a solution of **100** (synthesized in 3 steps from L-malic acid, 98% yield, 0.100 g, 0.34 mmol)[20] in acetonitrile (2.5 mL) was added a mixture of NaI (51 mg, 0.34 mmol) and NaN_3 (0.044 g, 0.68 mmol) and the reaction stirred at room temperature for 1.5 hours. Diluted with EtOAc (10 mL) then washed with water (5 mL) and brine (5 mL). The organic portion was dried over sodium sulfate and concentrated to yield **107** (0.102 g, 99%) as a white solid. $[\alpha]_D^{22.0^\circ}$ +22.2 (c 0.55, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (d, *J* = 1.8 Hz, 1H), 4.88 (td, *J* = 3.7, 1.8 Hz, 1H), 4.03 (s, 2H), 3.29 (dd, *J* = 4.1, 18.8, 1H), 3.08 (dd, *J* = 4.1, 18.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 170.6, 105.4, 97.8, 70.6, 57.6, 41.0; IR ν_{max} (film)/cm^{-1}: 2104, 1814, 1731, 1280, 1204, 1173, 1120, 1040. HRMS $C_7H_6Cl_3N_3O_4Na$: calcd 323.9316, obsd 323.9309.



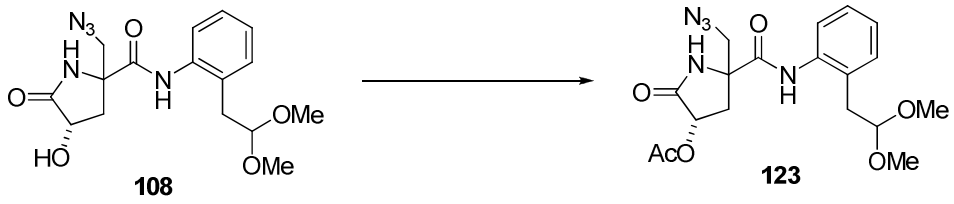
Scheme 3.29. Synthesis of **108**.

(108) To a solution of **107** (30.0 mg, 0.10 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (0.5 mL) was added 1,1,1,3,3,3-hexamethyldisilazane (84 μL, 0.4 mmol) immediately followed by convertible isocyanide **14**, (12.6 mg, 0.07 mmol). The reaction stirred overnight after which time the solvent was removed by vacuum and the residue purified by column chromatography (100% EtOAc) to yield solid **108** (20.3 mg, 85%) as a mixture of diastereomers (dr = 1.7:1 based on ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.72 (t, *J* = 8.7 Hz, 1H), 7.57, 7.41 (s, 1H), 7.30-7.71 (m, 3H), 4.54-4.43 (m, 2H), 4.32 (br, 1H), 4.22-4.00 (m, 1H), 3.55-3.45 (m, 1H), 3.42-3.37 (m, 6H), 2.94-2.81 (m, 2H), 2.64-2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 178.1, 170.0, 169.9, 136.0, 135.9, 131.53, 131.52, 129.0, 128.9, 128.0, 127.9, 126.2, 126.0, 124.7, 124.5, 107.2, 106.8, 68.8, 68.5, 64.1, 64.0, 58.0, 57.4, 55.0, 54.9, 54.8, 54.6, 38.9, 38.5, 37.2, 37.0. HRMS $C_{16}H_{21}N_5O_5Na$: calcd 386.1435, obsd 386.1440.



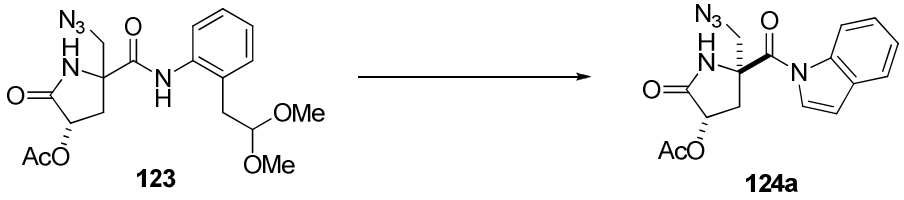
Scheme 3.30. Synthesis of **109**.

(109) To a solution of **107** (20.0 mg, 0.07 mmol) in 2,2,2-trifluoroethanol (1.0 mL) was added NH_4OAc (10.2 mg, 0.13 mmol) immediately followed by convertible isocyanide **14**, (12.6 mg, 0.07 mmol). The reaction was allowed to stir overnight after which time the reaction was diluted with EtOAc (5 mL) then washed with water (5 mL) and brine (5 mL). The organic portion was dried over sodium sulfate and concentrated then purified by preparatory TLC (100% EtOAc) to yield solid **108** (5.6 mg, 18%) and **109** (25.7 mg, 80%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H) 7.85 (d, J = 8.1, 1H), 7.31 – 7.11 (m, 3H), 5.83 (s, 1H), 4.44 (t, J = 4.7 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 2.96 - 2.82 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 161.0, 135.8, 131.4, 128.5, 128.0, 126.0, 124.4, 107.7, 95.6, 81.3, 55.4, 55.2, 37.4, 20.7. IR ν_{max} (film)/cm^{-1}: 3297, 2937, 1767, 1698, 1589, 1523, 1454, 1196, 1069. HRMS $C_{15}H_{18}Cl_3NO_5Na$: calcd 420.0143, obsd 420.0147.



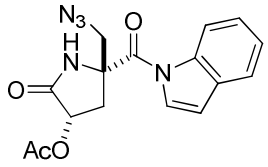
Scheme 3.31. Synthesis of **123**.

(123) To a solution of **108** (85 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.226 mL, 2.30 mmol) followed by acetic anhydride (0.221 mL, 2.80 mmol). The reaction was allowed to stir for 24 hours and was then washed with 1M HCl (2 x 5 mL) with back-extraction. The combined organic portions were washed with $NaHCO_3$ (10 mL) and brine (10 mL) then dried over Na_2SO_4 and concentrated. Purified by column chromatography (hexanes:EtOAc = 1:2) to yield the oil **109** (87 mg, 92%) as a mixture of diastereomers (dr = 1.7:1 based on ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60, 9.58 (s, 1H), 7.95, 7.87 (br, 1H), 7.74-7.71 (m, 1H), 7.28-7.09 (m, 3H), 5.49, 5.36 (m, 1H), 4.46-4.41 (m, 1H), 4.20-3.98 (m, 1H), 3.63-3.46 (m, 1H), 3.42-3.35 (m, 6H), 2.97-2.68 (m, 3H), 2.30-2.20 (m, 1H), 2.12-2.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 173.7, 170.2, 170.1, 169.82, 169.79, 136.0, 135.8, 131.6, 131.5, 129.0, 128.9, 127.94, 127.91, 126.2, 126.0, 124.6, 124.3, 107.0, 106.9, 69.8, 69.1, 64.2, 63.9, 57.5, 57.2, 54.77, 54.76, 54.7, 54.6, 37.10, 37.06, 36.9, 36.5, 20.92, 20.89. HRMS $C_{18}H_{23}N_5O_6Na$: calcd 428.1541, obsd 428.1542.



Scheme 3.32. Synthesis of **124a**.

(124a) To a solution of **123** (85.0 mg, 0.20 mmol) in benzene (5 mL) was added CSA (10.0 mg, 0.04 mmol). The reaction was heated to 60 ˚C for 1.5 hrs then removed from heat and cooled. Washed with $NaHCO_3$ (5 mL) and brine (5 mL) then dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes:EtOAC = 2:1) to yield the two diastereomers **124a** (20.5 mg, 29%) and **124b** (35.5 mg, 50%) as solids. Desired diastereomer (**124a**): $[\alpha]_D^{21.3^\circ}$ +24.4 (c 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.2 Hz, 1H), 7.93 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.39-7.29 (m, 3H), 6.71 (d, *J* = 3.8 Hz, 1H), 5.30 (dd, *J* = 4.7, 8.9 Hz, 1H), 4.09 (d, *J* = 12.8 Hz, 1H), 3.79 (d, *J* = 12.8 Hz, 1H), 3.15 (dd, *J* = 8.9, 14.6 Hz, 1H), 2.39 (dd, *J* = 4.7, 14.6 Hz, 1H), 2.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.4, 168.7, 136.7, 129.8, 126.4, 125.1, 123.6, 121.3, 117.5, 111.7, 69.7, 66.4, 59.0, 36.1, 21.0; IR ν_{max} (film)/cm^{-1}: 2111, 1724, 1452, 1335, 1228. HRMS $C_{18}H_{16}N_5O_4$: calcd 342.1197, obsd 342.1203.

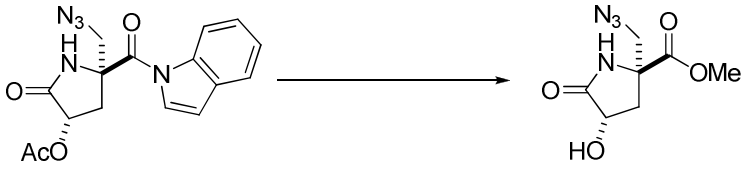


124b

Figure 3.3. Synthesis of **124b**.

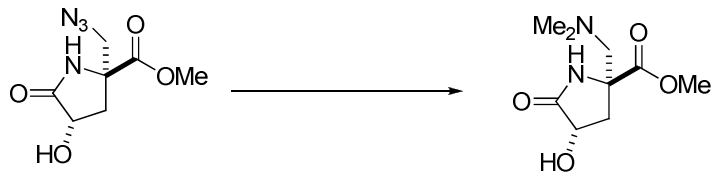
(124b) Major diastereomer: $[\alpha]_D^{22.3^\circ}$ -6.4 (c 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 7.58 -7.29 (m, 4H), 6.72 (dd, *J* = 3.9, 0.7 Hz, 1H), 5.51 (dd, *J* = 7.9, 8.9 Hz, 1H), 3.91 (d, *J* = 12.6 Hz, 1H), 3.84 (d, *J* = 12.6 Hz,

1H), 3.13 (dd, *J* = 8.9, 13.7 Hz, 1H), 2.49 (dd, *J* = 7.9, 13.7 Hz, 1H), 2.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.5, 168.5, 136.6, 129.9, 126.3, 125.1, 123.6, 121.3, 117.5, 111.7, 69.8, 65.1, 58.3, 37.1, 20.9; IR ν_{max} (film)/cm^{-1}: 2110, 1701, 1452, 1338, 1229.



Scheme 3.33. Synthesis of **125**.

(125) To a solution of **124a** (45.7mg, 0.13 mmol) in MeOH (3 mL) was added 1M NaOH (6.7 μL, 0.007 mmol) and the reaction was stirred for 36 hrs after which time the reaction was removed from stirring and concentrated. The crude material was purified by column chromatography (100% CH_2Cl_2 then 5% MeOH in CH_2Cl_2) to yield **125** (17.7 mg, 62%) as an oil. $[\alpha]_D^{21.5^\circ}$ -24.5 (c 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.32 (t, *J* = 8.4 Hz, 1H), 3.86 (d, *J* = 12.6 Hz, 1H), 3.78 (s, 3H), 3.54 (d, *J* = 12.6 Hz, 1H), 2.65 (dd, *J* = 8.4, 13.3 Hz, 1H), 1.97 (dd, *J* = 8.4, 13.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.9, 172.4, 68.4, 62.6, 56.5, 52.4, 37.4; IR ν_{max} (film)/cm^{-1}: 3254 (br, OH), 2109, 1706, 1436, 1280, 1225, 1115. HRMS $C_7H_{10}N_4O_4Na$: calcd 237.0594, obsd 237.0591.



125 **126**

Scheme 3.34. Synthesis of **126**.

(126) Pd/C (10% w/w) was added to a solution of **125** (11.5 mg, 0.0537 mmol), formaldehyde (37% aq; 0.537 mmol) and 1N HCl (53.7 μL) in MeOH (3 mL). H_2 gas (balloon pressure) was applied and the reaction was stirred for 18 hrs at room temperature after which time the reaction was neutralized and dried with a small amount of $NaHCO_3$ (s) then filtered through celite and concentrated to yield **126** (11.5 mg, 99%). $[\alpha]_D^{20.0^\circ}$ -28.1 (c 1.5, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 4.38 (t, *J* = 7.6, 1H), 3.84 (s, 3H), 3.68 (d, *J* = 14.0 Hz, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 2.94 (s, 6H), 2.83 (dd, *J* = 7.6, 13.6 Hz, 1H), 2.13 (dd, *J* = 7.6, 13.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.6, 173.4, 89.9, 68.7, 65.1, 64.3, 46.7, 38.8; IR ν_{max} (film)/cm^{-1}: 3233 (br, OH), 2949, 2830, 2779, 1705, 1281, 1085. HRMS $C_9H_{17}N_2O_4$: calcd 217.1183, obsd 217.1186.

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Chapter Four

Extended Use of Indole Isocyanide in Multicomponent Reactions

A. Introduction

Isocyanide based multicomponent reactions (MCRs) have been a valuable tool for chemists seeking to quickly create complex molecules from simple starting materials. The Ugi reaction is a four-component condensation of an aldehyde or ketone, a carboxylic acid, an amine and an isocyanide that provides an *N*-acylamino acid containing a new stereogenic center at the α-carbon. It allows for the quick construction of peptides, β-lactams, pyroglutamic acids and other biologically interesting molecules. The Passerini reaction, between aldehydes or ketones, carboxylic acids and isocyanides readily furnishes α-acyloxyamides, also with a new stereocenter.[1] These reactions may rightly be viewed as prototypes because of the degree of variation that is allowed in the different components. Cyclized products are obtained most readily by incorporating more than one of the components into a single molecule. However, a wide variety of heterocycles are also available through the incorporation of carefully chosen components designed to allow facile post-MCR modifications.[1,2]

Despite the depth and breadth of research that has been conducted in the field of isocyanide based MCRs, fertile ground remains for patient cultivation. The biggest unsolved problem with isocyanide based MCRs is the difficulty encountered when trying

to induce stereoselectivity in the reactions. A secondary problem that has interested our laboratory is the need to make useful post-MCR modifications to the products thus obtained. During the course of our research into the synthesis of the pyroglutamic acid natural product dysibetaine, we grappled with these two problems. Concerning the second problem, we have both used the indole isocyanide in a variety of Ugi reactions to explore its scope and mechanism and we have successfully employed the new indole isocyanide as a convertible isocyanide for the Passerini reaction. Finally, we have made a new entry into stereoselective MCRs by developing a catalytic, asymmetric Passerini-type reaction catalyzed by BINOL-derived chiral Brønsted acids.

B. Scope and Mechanism of Indole Isocyanide in Isocyanide Based MCRs

1. The Mechanisms of Convertible Isocyanides in Post-Ugi Modification

The original focus of our research was attempting to use the Ugi reaction for the synthesis of pyroglutamic acid containing natural products such as omuralide and dysibetaine (Figure 4.1). During the course of these syntheses it became clear that a new convertible isocyanide would be needed because existing convertible isocyanides did not allow for the necessary post-Ugi modifications for these substrates (see Chapter 1).

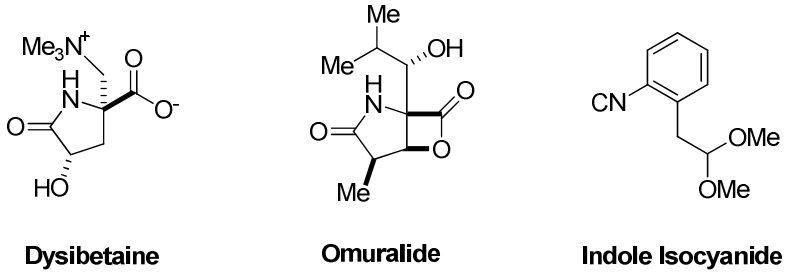
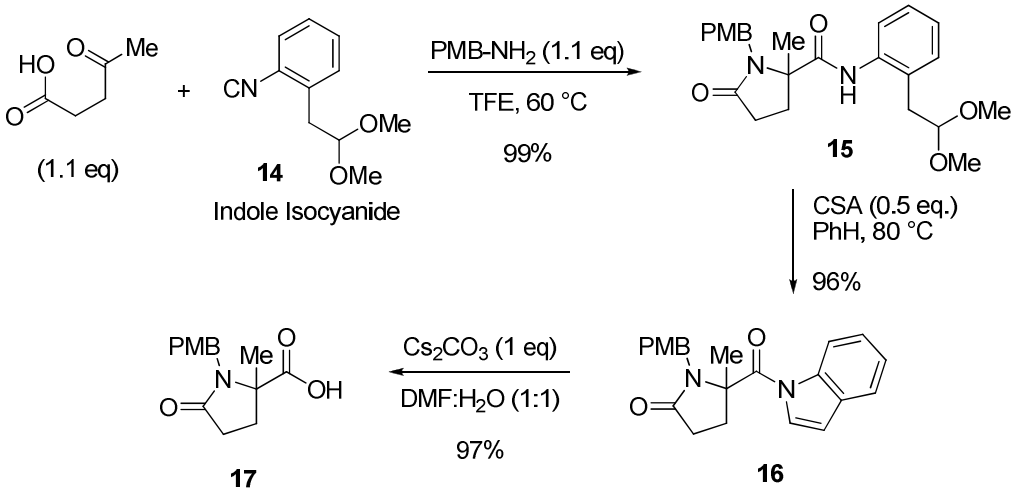


Figure 4.1. Pyroglutamic acid natural products and indole isocyanide.

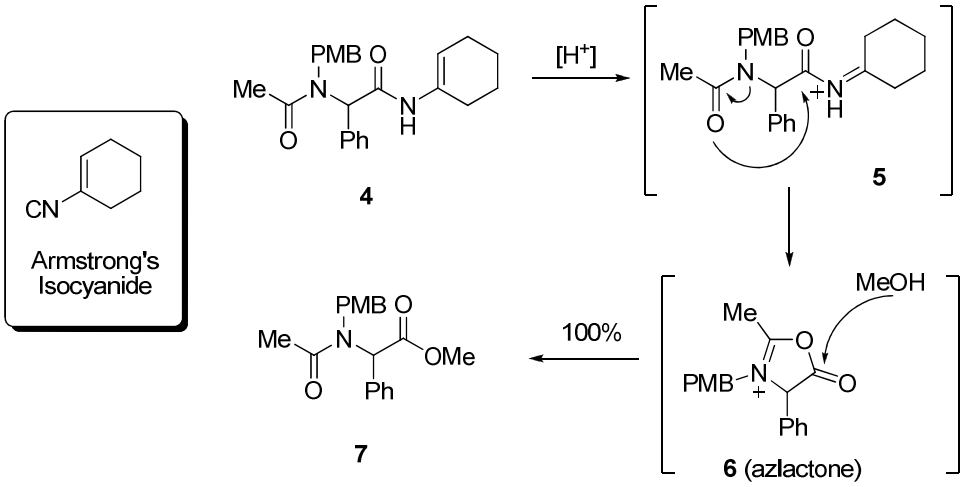
As previously discussed in Chapter 1, the Ugi reaction between a γ-ketoacid, such as levulinic acid, an amine and an isocyanide yields a pyroglutamic acid anilide[3] (**15**, Scheme 4.1). Using the convertible indole isocyanide **14** in this type of Ugi 4-center 3-component condensation reaction (U4C-3CR) allows for the selective cleavage of one of the two amides in the product molecule.[4] Treatment of anilide **15** with a catalytic amount of camphorsulfonic acid (CSA) in benzene with gentle heating affords *N*-acylindole **16**. The formation of indole changes the character of the amide C–N bond, making it very vulnerable to attack by an external nucleophile. Treatment of *N*-acylindole **16** with base as shown affords the pyroglutamic acid **17**.[5]



Scheme 4.1. Synthesis of pyroglutamic acid **17** via U4C-3CR using isocyanide **14**.

The first convertible isocyanide that we unsuccessfully tested for this reaction was Armstrong's isocyanide, which allows for the selective cleavage of *C*-terminal amide via formation of an azlactone intermediate (Scheme 4.2).[6] The Ugi product **4** is treated with acid which causes an intramolecular reaction in which the *N*-terminal amide oxygen

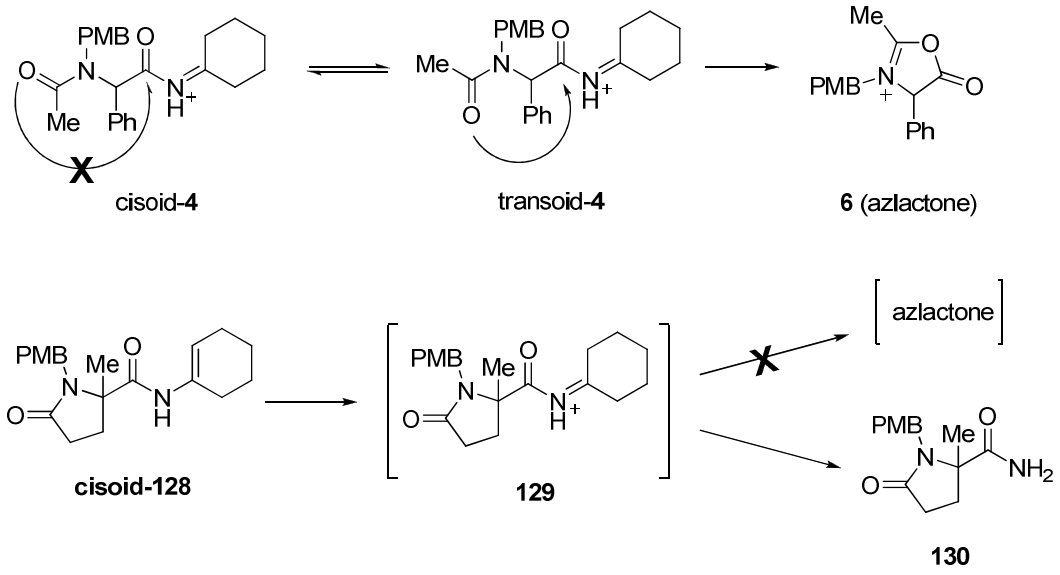
attacks the carbonyl carbon of the *C*-terminal amide to form azlactone **6.** The azlactone **6** contains a highly activated acylimidate moiety which is readily attacked by an external nucleophile, in this case methanol, affording the methyl ester **7**.



Scheme 4.2. Mechanism of action for Armstrong's convertible isocyanide.

There is a particular reason that pyroglutamic acid amides derived from Armstrong's isocyanide will not undergo azlactone formation. The linear Ugi product **4** is in equilibrium between the cisoid isomer and transoid isomer (Scheme 4.3). Cisoid-**4** can not react to form azlactone **6** because the reacting atoms are held too far away from each other. Transoid-**4**, on the other hand, contains a geometry that puts the reacting centers in close proximity and allows for azlactone formation. In the case of the pyroglutamic acid **128** that would be derived from levulinic acid and Armstrong's isocyanide, the conformation is locked into the cisoid-configuration because of the existence of the five-membered ring.

The inability of the *N*-terminal amide to interact with the *C*-terminal amide in pyroglutamic acid amide **128** makes azlactone formation impossible for this substrate. **128** is activated by acid to form acyliminium ion **129**. Instead of azlactone formation, **129** was converted to the corresponding carboxamide **130** by methanolysis. Indole isocyanide was therefore a necessary choice of convertible isocyanide for the selective activation and cleavage of the *C*-terminal amide. However, we also wondered how the convertible indole isocyanide would react in cases other than the pyroglutamic acid amide.

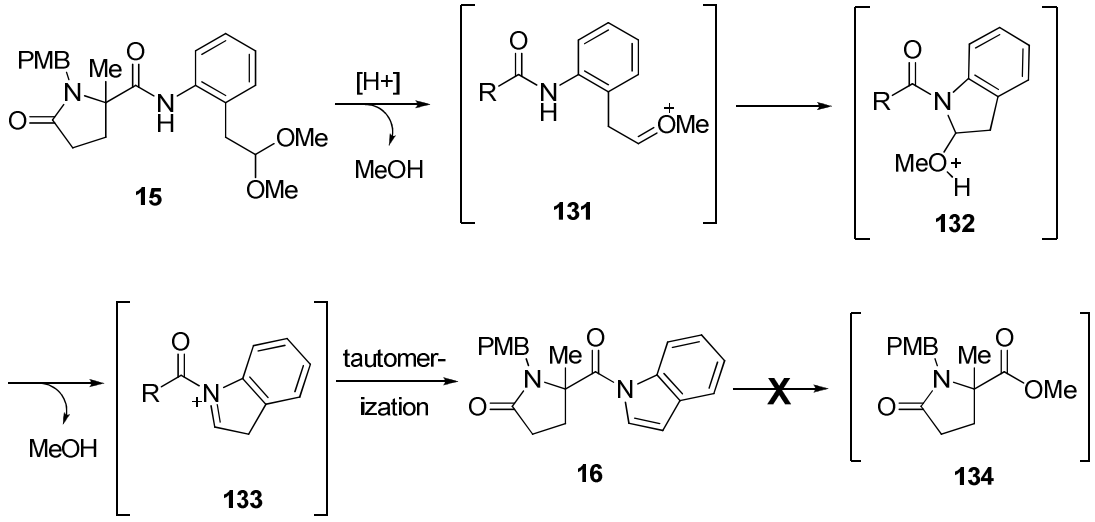


Scheme 4.3. Azlactone can not form from pyroglutamic acid amide.

2. Mechanism of Indole Formation and Cleavage with Indole Isocyanide

Before moving on to consider how the cleavable indole isocyanide would behave in various Ugi reactions, it is important to consider the mechanism of indole formation in the case of the pyroglutamic acid amide (**15** → **16**, Scheme 4.1). When the Ugi product

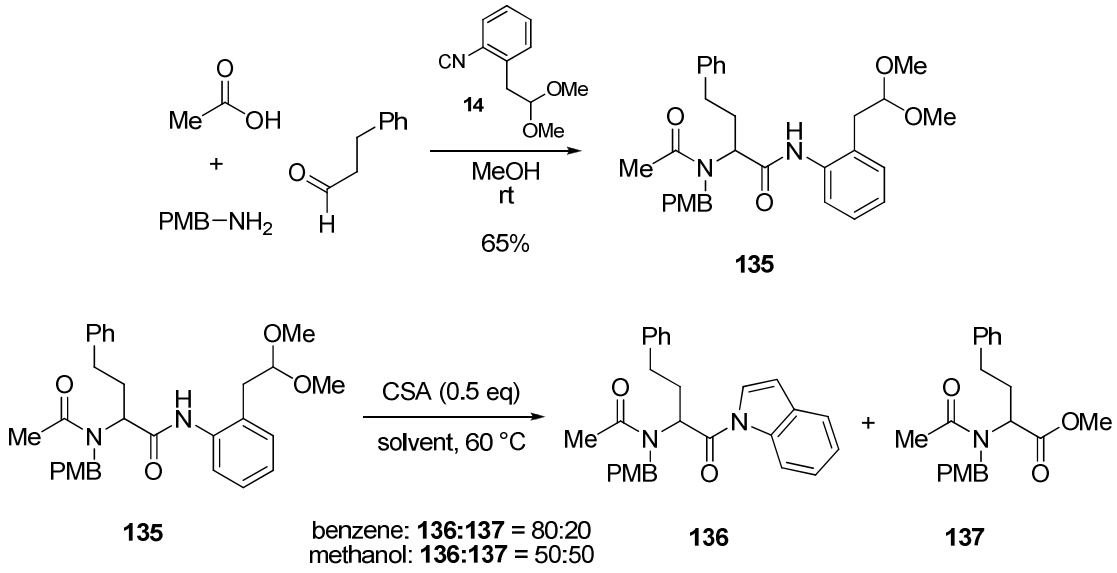
15 derived from levulinic acid and indole isocyanide is treated with acid, the dimethyl acetal is activated to form intermediate **131** (Scheme 4.4). Cyclization of the amide nitrogen onto the activated aldehyde provides intermediate **132** which finally loses methanol to give *N*-acylindole **16** after tautomerization of intermediate **133**. In this process the activating acid is catalytic as two equivalents of methanol are produced and finally the acid catalyst is regenerated. It should be noted that the methyl ester **134** was never recovered directly from the *N*-acylindole formation reaction. Indeed, treating the *N*-acylindole **16** with various acids in methanol yields no reaction and the starting material is recovered. It is only when **16** is treated with base that the methyl ester or other carboxylic acid derivatives are formed.



Scheme 4.4. Mechanism of *N*-acylindole formation.

With this understanding of the mechanism in mind, we next synthesized the linear Ugi product **135** derived from hydrocinnamaldehyde, acetic acid, *p*-methoxybenzyl amine and isocyanide **14** (Scheme 4.5). We then subjected **135** to the standard condition

for indole formation, which is to heat it with a catalytic amount of camphorsulfonic acid (CSA) in benzene. Surprisingly, in addition to the expected *N*-acylindole product **136**, which was recovered in 80% yield, we also recovered methyl ester **137** in 20% yield. This clearly means that some of the methanol that is released as part of the indole formation is reacting further to form the methyl ester. It is unclear exactly how this happens since we know the *N*-acylindole should not be cleaved with methanol under acidic conditions. We therefore submitted **135** to the indole formation using methanol as solvent and recovered 50% of **136** and 50% of **137**. These results confirm that a mechanism other than the normal reaction mechanism outlined in Scheme 4.4 is operating in this case.

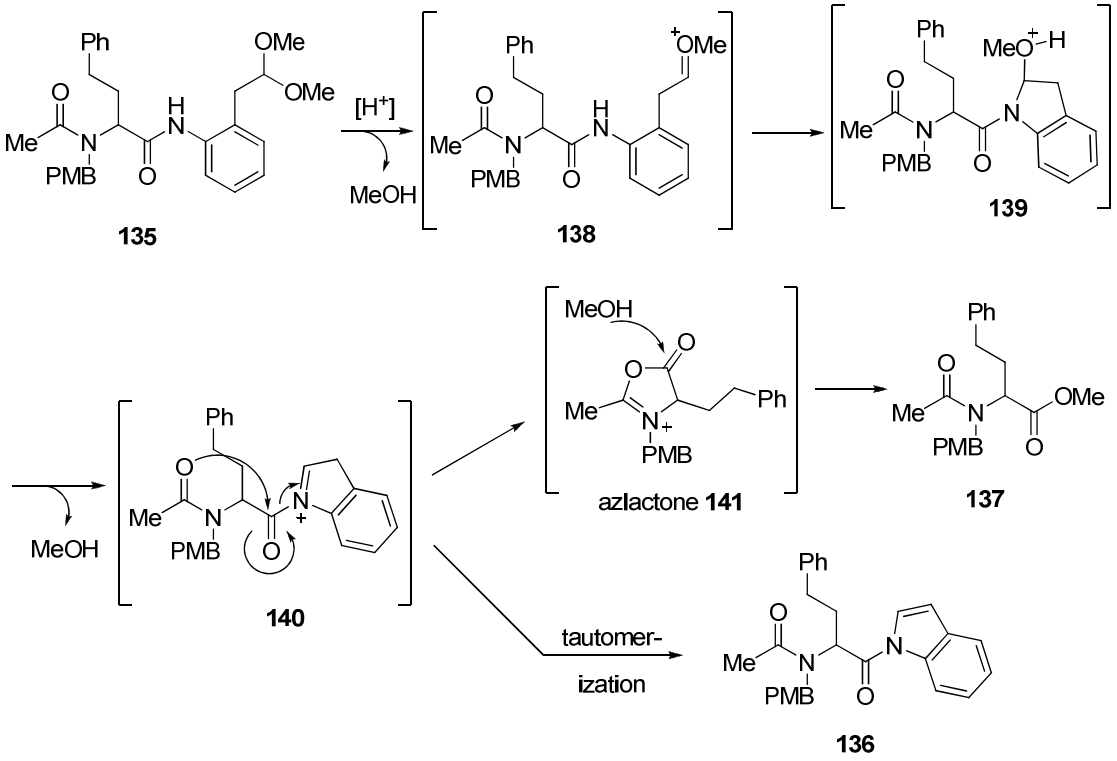


Scheme 4.5. Indole isocyanide in the 4-component Ugi reaction.

In order to determine how the methyl ester **137** can form under the reaction conditions shown, we had only to look back to Armstrong's convertible isocyanide. The mode of reactivity for that isocyanide is outlined in Scheme 4.2. The key to this

mechanism is the formation of azlactone intermediate **6** which is readily opened by an external nucleophile. An intermediate in the formation of indole, **137**, (Scheme 4.6) is analogous to the activated, azlactone intermediate of Armstrong's isocyanide. When the indole isocyanide is used as a convertible isocyanide for the Ugi reaction with a linear substrate, an azlactone intermediate **141** can alternatively form, leading to methyl ester **137**.

The mechanism for the azlactone formation and subsequent methanolysis using indole isocyanide is outlined in Scheme 4.6. When the Ugi product **135** is treated with catalytic acid the indole formation process begins. Activation of the dimethyl acetal leads to the activated **138** which then cyclizes to form **139**. From this intermediate, the *C*-terminal amide nitrogen pushes electrons to release methanol and forms intermediate **140** which is analogous to the activation of Armstrong's isocyanide (**5**, Scheme 4.2). At this point **140** will follow one of two reaction pathways, the first of which is tautomerization to form *N*-acylindole **136**. The other possibility is that the the *N*-terminal amide now attacks the activated *C*-terminal amide to form azlactone **141**. Analogous with Armstrong's isocyanide, this azlactone is readily opened by methanol to afford methyl ester **137** and regenerate the acid catalyst. When benzene was used as the solvent the methanol released from indole formation was sufficient to cause 20% formation of **137**, but when methanol was used as solvent the yield increased to 50%.

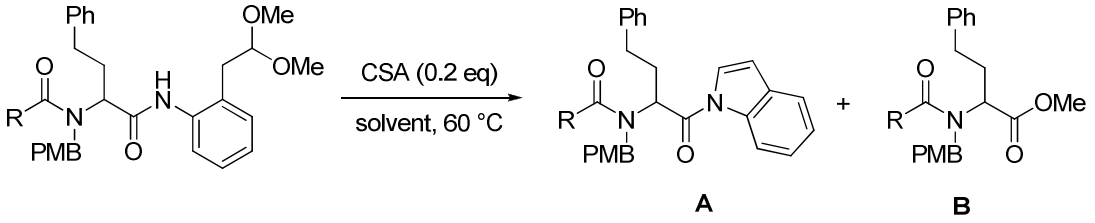


Scheme 4.6. Mechanism of azlactone formation with indole isocyanide.

3. Substrate-Determined Differences in *N*-Acylindole Formation

Through the previous series of reactions we discovered that Ugi products derived from indole isocyanide and four separate components react differently than Ugi products derived from a γ-ketoacid. Instead of exclusively forming the *N*-acylindole, some of the material forms the azlactone and subsequently the methyl ester, such as **137**. The nucleophilicity of the *N*-terminal amide should affect the extent to which the azlactone forms versus *N*-acylindole. We therefore decided to vary the carboxylic acid component, and thereby the nucleophilicity of the resulting amide, in the Ugi reaction and submit the various Ugi products to the indole formation conditions. The results of this series of experiments are outlined in Table 4.1.

Table 4.1. Ratio of *N*-acylindole to methyl ester with various acid components.



Entry	R =	solvent	yield **A**	yield **B**
1	-Me	benzene	80%	20%
2	-Me	methanol	50%	50%
3	-H	benzene	72%	-
4	-H	methanol	no reaction	no reaction
5	$-CF_3$	benzene	94%[a]	-
6	$-CF_3$	methanol	99%[a]	-

[a]Reaction run at room temperature.

When using trifluoroacetic acid as the carboxylic acid component in the Ugi reaction, we expected that the nucleophilicity of the resulting triflouroacetate-protected amide would be decreased. In practice this turned out to be the case, and methyl ester product **B** was not isolated in the case where R = $-CF_3$. While we had usually used heating to 60 ˚C to form the *N*-acylindole, when the trifluoroacetyl group was present heating led to decomposition. Fortunately, running these reactions at room temperature allowed us to isolate the *N*-acylindole products in good yield.

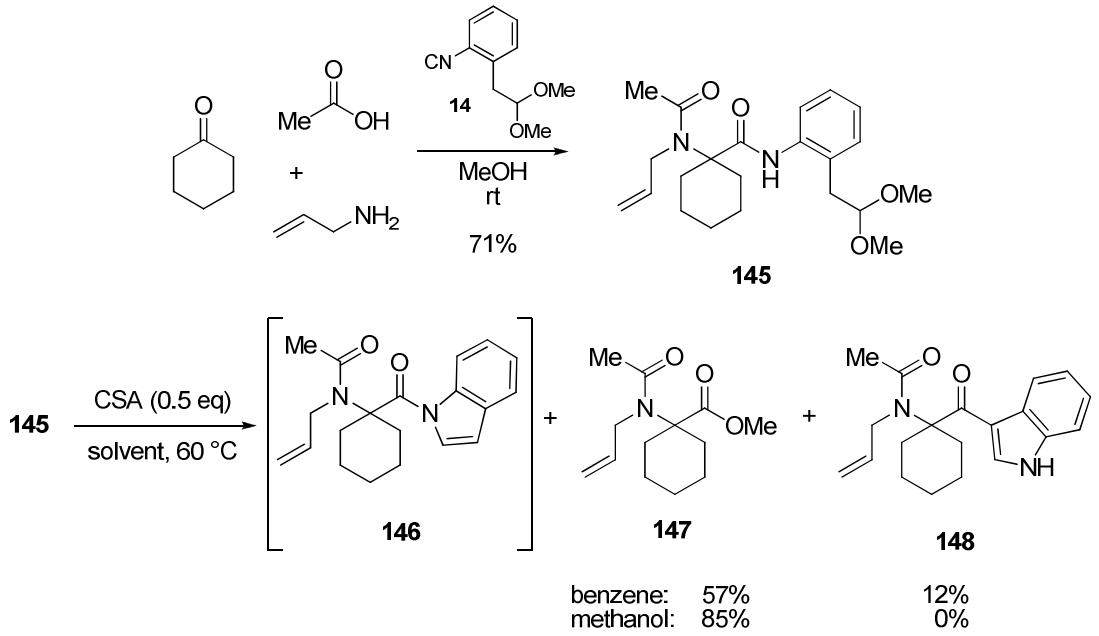
Using formic acid as the carboxylic acid component led to more inconclusive results. Interestingly, when the formamide Ugi products were submitted to the *N*-acylindole formation conditions with methanol as the solvent no reaction occurred and starting material was recovered. The *N*-acylindole did form when the Ugi product was

treated with CSA in benzene, although unknown side reactions – most likely due to the acid-promoted deprotection of the formamide – led to a depressed yield. Triflouroacetic acid is therefore the best choice when using indole isocyanide in the Ugi reaction. First, the strong electron-withdrawing properties of this protecting group suppress azlactone formation. Perhaps more importantly, though, the trifluoroacetamide protecting group is removed much more readily than a standard acetamide, meaning that a wider range of post-Ugi modifications is available when trifluoroacetic acid is chosen.

Considering the results of the experiments just performed, where aldehydes acted as the carbonyl component in the Ugi reaction, there was one more possibility we wanted to try. In the case of the pyroglutamic acid amides, the locked cisoid confirmation of the cyclic amide made azlactone formation impossible. In the cases where we used aldehydes as the carbonyl component in the Ugi reaction, the products had free rotation and could form either the azlactone or the *N*-acylindole. The final possibility would be to test an intermediate case where *N*-terminal amide and *C*-terminal amide of the Ugi product are held more closely together. We imagined that this would encourage the formation of the azlactone and resultant methyl ester products.

In order to test this hypothesis we chose the ketone cyclohexanone as the carbonyl component for the Ugi reaction. Our belief was that the Thorpe-Ingold effect[7] would force the *N*-terminal and *C*-terminal amides close to one another in space. Consequently, cyclohexanone was condensed with acetic acid, allyl amine and isocyanide **14** to afford Ugi product **145** in reasonable yield (Scheme 4.7). **145** was then submitted to the *N*-acylindole formation conditions and we discovered another surprising result. First, we were happy to see that our hypothesis was correct because when cyclohexanone was used

as the carbonyl component the *N*-acylindole product **146** did not form at all. When benzene was used as the solvent we recovered the methyl ester **147** as the major product in 57% yield, but also the C3-substituted indole **148** in 12% yield. When **145** is converted to the azlactone form, one equivalent of indole and two equivalents of methanol are released. We believe product **148** formed as the result of the nucleophilic indole, instead of methanol, attacking the azlactone intermediate. When methanol was used as the solvent **147** was formed exclusively.

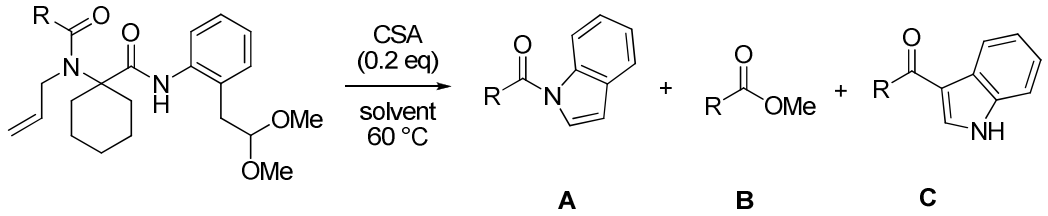


Scheme 4.7. Cyclohexanone derived Ugi product and attempts to form *N*-acylindole.

When we varied the acid component in the four-component Ugi reaction including an aldehyde the product distributions varied, as described in Table 4.1. We therefore decided to make the same modification to the current scheme and make a series

of cyclohexanone-derived Ugi products by varying the acid component. The results of these experiments are shown in Table 4.2.

Table 4.2. Ratio of products from cyclohexanone derived Ugi products with various acid components.



A **B** **C**

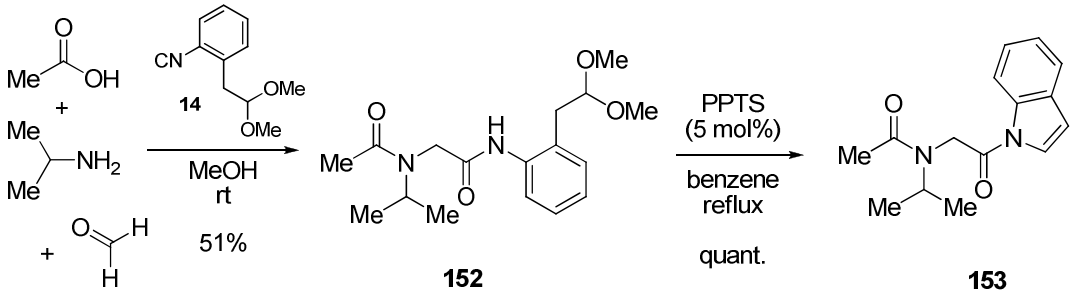
Entry	R =	solvent	yield **A**	yield **B**	yield **C**
1	-Me	benzene	-	57%	12%
2	-Me	methanol	-	85%	0%
3	-H	benzene	-	67%	-
4	-H	methanol	-	no reaction	no reaction
5	$-CF_3$	benzene	91%[a]	-	-
6	$-CF_3$	methanol	94%[a]	-	-

[a]Reaction run at room temperature.

The results of these experiments were consistent with those obtained when an aldehyde was used as the carbonyl component in the Ugi reaction (Table 4.1). The use of formic acid as the carboxylic acid component in the Ugi reaction yielded no reaction when we attempted to form the *N*-acylindole intermediate. The use of trifluoroacetic acid as the carboxylic acid source, however, allowed for almost quantitative recovery of the *N*-acylindole product **A**. While the use of acetic acid and formic acids as the carboxylic acid source in the Ugi reaction led to mixed results, side reactions were suppressed when trifluoroacetic acid was the acid component, and we believe this acid is a good choice when indole isocyanide is used in the Ugi reaction.

4. Another Application of Indole Isocyanide for the Ugi Reaction

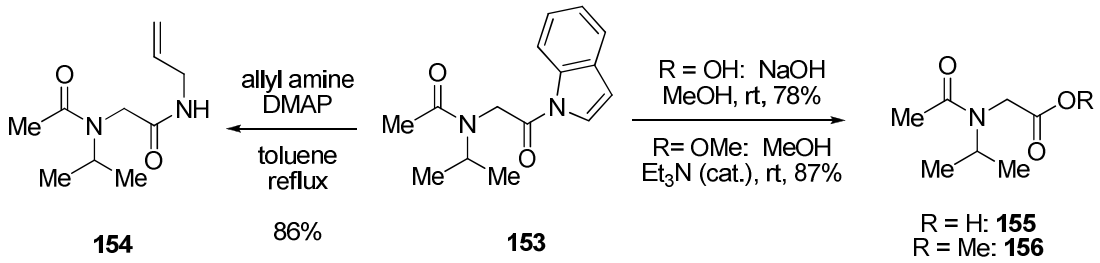
During the course of our investigations into the use of the convertible indole isocyanide in the Ugi reaction, and after our initial publication of the use of the isocyanide for making pyroglutamic acids, the Wessjohann group reported on the application of indole isocyanide to MCRs.[8] As described in Scheme 4.8, acetic acid, isopropyl amine and formaldehyde were condensed with isocyanide **14** to afford Ugi product **152**. They then treated the Ugi product with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene to afford *N*-acylindole **153**. We believe that the choice of PPTS, a weaker acid than CSA, enabled this group to isolate the *N*-acylindole **153** without forming of the corresponding methyl ester. It is possible that in the presence of the weaker acid catalyst indole formation is faster than azlactone formation.



Scheme 4.8. Wessjohann's synthesis of *N*-acylindole **153**.

After successful isolation of **153** the Wessjohann group proceeded with further modifications as outlined in Scheme 4.9. Treating **153** with allyl amine and DMAP in refluxing toluene afforded diamide **154**. Similarly, sodium hydroxide in methanol

afforded carboxylic acid **155** and by using a catalytic amount of triethylamine in methanol they were able to isolate methyl ester **156**.

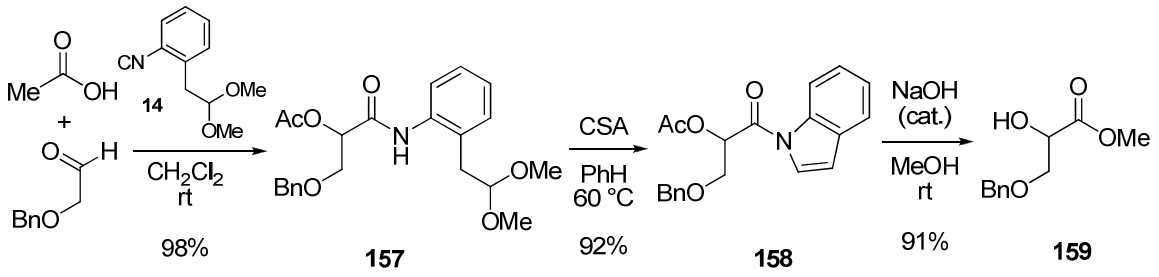


154 **153**

Scheme 4.9. Conversion of **153** to various carboxylic acid derivatives by Wessjohan.

5. Indole Isocyanide as a Convertible Isocyanide for the Passerini Reaction

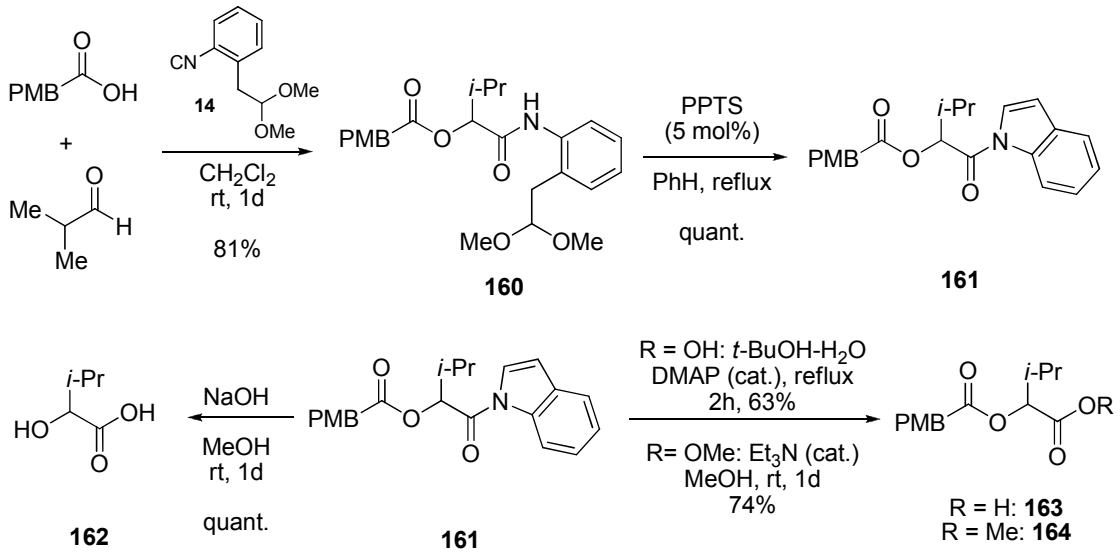
Until the introduction of indole isocyanide, there was not a readily available method for the conversion of the α-acyloxycarboxamides derived from the Passerini reaction to the corresponding carboxylic acid derivatives. Because the Passerini product contains only the *C*-terminal amide, no azlactone can form so convertible isocyanides such as the Armstrong isocyanide won't work. Furthermore, it is difficult to preserve the more labile ester functionality that is formed as a result of the Passerini reaction. Using indole isocyanide **14** as the isocyanide in the Passerini reaction opens a range of possibilities for post-MCR modification that were not previously available. Our first foray into this area was formation of the Passerini adduct **157** by condensing benzyloxyacetaldehyde with acetic acid and indole isocyanide **14** (Scheme 4.10).



Scheme 4.10. Our synthesis of Passerini adduct **157** and subsequent methanolysis.

The Passerini product **157** was cleanly converted to the corresponding *N*-acylindole **158**. This intermediate was readily transformed to the free-alcohol methyl ester compound **159**. While we were pleased with this result, the acetate ester was cleaved in addition to the *N*-acylindole and it is desirable to selectively cleave the indole while leaving the acetate ester in place.

Around the same time that we were considering this reaction the Wessjohann group published their earlier mentioned paper on the use of **14** as a convertible isocyanide. They showed an example using the convertible isocyanide in the Passerini reaction when *p*-methoxyphenylacetic acid and isobutyraldehyde were treated with convertible isocyanide **14** to give the Passerini product **160** (Scheme 4.11). Treatment of **160** with a catalytic amount of PPTS in refluxing benzene afforded *N*-acylindole **161** in quantitative yield. **161** was converted into various other derivatives. Both the ester and amide were cleaved using sodium hydroxide to afford **162**. More usefully, they showed conditions where indole was released without cleavage of the ester, to afford α-acyloxycarboxylic acid **163** and ester **164**.



Scheme 4.11. Indole isocyanide in the Passerini reaction by Wessjohann.

We felt that with this published account the Wessjohann group had adequately solved the issues associated with using **14** as a convertible isocyanide in the Passerini reaction. We therefore decided to put this problem on the shelf and focus our efforts on the elusive stereoselective isocyanide-based MCR. What we didn't realize at the time was that these efforts would lead us back to a slightly modified version of the Passerini reaction, as discussed below.

C. History of Stereoinduction in the Ugi and Passerini Reactions

Isocyanide based MCRs are very powerful reactions for multiple reasons. They usually involve very mild reaction conditions and all or almost all of the atoms from the original starting materials are incorporated into the final product. Complex molecules can be constructed expeditiously by bringing together various components with complexity already built in. Finally they create products with new stereocenters, and the molecules are often of biological interest, for example the Ugi reaction is a very efficient

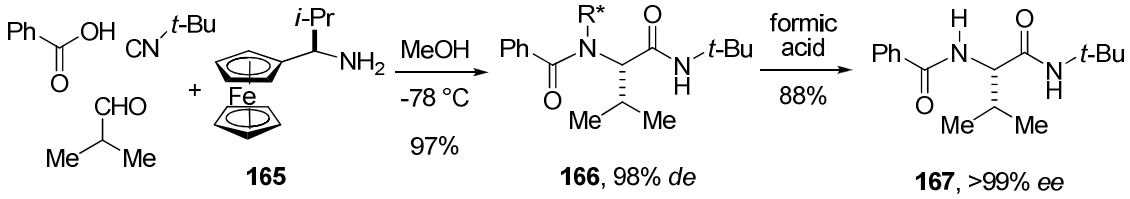
means of generating α-amino acids. Unfortunately, the large drawback of isocyanide based MCRs is that it is very difficult to control the stereochemical outcome of the reactions. Many approaches to this problem have been tested and most solutions found tend to be substrate dependent, although a few have proven to be more general. Before describing our own efforts towards a catalytic, stereoselective Passerini-type reaction, we present the following brief history of stereocontrol in the Ugi and Passerini reactions.

1. Stereocontrol in the Ugi Reaction

Ivar Ugi suggested soon after the discovery of the reaction that now bears his name that the best way to induce stereochemistry into the reactions would be to use chiral starting materials. Naturally, then, each of the four components of the Ugi reaction – the carboxylic acid, amine, isocyanide and carbonyl compound – have all been tested as possible chirality-inducing substrates. In the Ugi reaction, it has been found that only chiral amines are able to reliably induce diastereoselectivity during the Ugi reaction. The first amines successfully employed for the stereoselective Ugi reaction were α-substituted phenethylamines; however these amines are not readily cleaved from the rest of the Ugi product after the condensation.[9] As mentioned above, one of the keys to the success of MCRs in a larger synthetic strategy is the ability to make post-condensation modifications to the molecules. In the case of chirality-inducing amines, they also had to be successfully cleaved to the corresponding free amine, with removal of the chiral auxiliary, after the condensation.

There are two well-recognized methods of using readily-cleaved chiral amines in the stereoselective Ugi reaction. The first is the use of chiral α-ferrocenylamines and the second is the use of glycosylamines and other sugar-derived chiral auxiliaries. The first

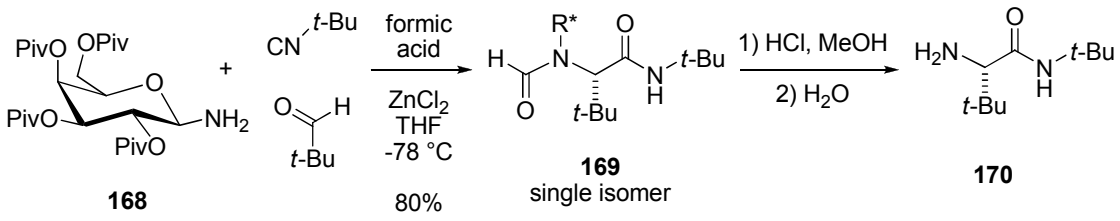
of these approaches, which was pioneered by Ugi and coworkers, is outlined in Scheme 4.12.[10] Chiral α-ferrocenylisobutylamine **165** is condensed with isobutyraldehyde, benzoic acid and *t*-butyl isocyanide to form *N*-benzoyl-*N*-[(*R*)-α-ferrocenylisobutyl]-(*S*)-valine *tert*-butylamide **166**. For best results the chiral amine and aldehyde are pre-mixed to promote imine formation before addition of the carboxylic and isocyanide. The Ugi product **166** was obtained in 97% yield and 98% *de*. Interestingly, in this particular case the rates of cleavage of the chiral auxiliary for the two diastereomers were significantly different. Cleavage of the desired isomer (*R*,*S*)-**166** was faster than the undesired isomer (*R*,*R*)-**166**, which allowed them to recover valine derivative **167** in greater than 99% *ee*.



Scheme 4.12. Ugi's cleavable α-ferrocenylamine for the stereoselective Ugi reaction.

The use of chiral α-ferrocenylamines is not perfect, of course. In the present case the use of the *enantiomer* of **165** as the chiral amine did not lead to the enantiomer of **166** but rather to a 4:1 mixture of diastereomers favoring **166**. Furthermore, while concentrated formic acid was a suitable reagent for cleavage of the chiral auxiliary in this case, it can lead to decomposition of sensitive functional groups or racemization of the desired stereocenter.[1b] By using sugar-derived chiral auxiliaries researchers were able to develop more mild cleavage conditions.

These sugar-derived chiral auxiliaries were first introduced by Kunz and co-workers when they employed galactopyranosylamine **168** (Scheme 4.13) as a chiral amine for the Ugi reaction.[11] The use of a Lewis acid such as zinc (II) chloride is necessary to hold the reacting partners in a rigid conformation to allow for the diastereoselective reaction. In the particular case shown, when **168** was used as the amine source with the very hindered pivaldehyde and *t*-butyl isocyanide the product **169** formed as a single isomer. After removal of the formyl protecting group using acid conditions, the glycosyl bond is destabilized and therefore the chiral auxiliary **R*** is removed upon treatment with water to afford free amine **170**. The chiral auxiliary can be recovered and converted back into **168**.

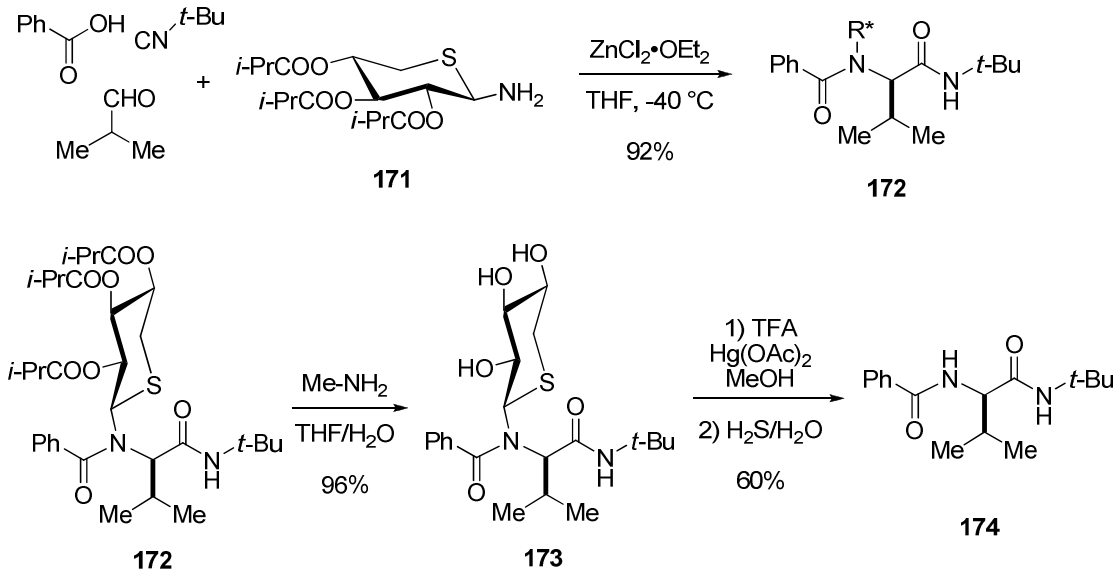


168 **169** single isomer **170**

Scheme 4.13. Kunz and coworkers' sugar-derived chiral amine in the Ugi reaction.

This approach was quickly picked up by Ugi and co-workers, who tested a wide variety of sugar-derived chiral auxiliaries[12] and were eventually able to engineer a xylopyranose derivative **171** (Scheme 4.14) that showed a high degree of diastereoselectivity in all cases tested.[13] Furthermore, the amine is in the anomeric position which allows for very easy cleavage. In a typical example, amine **171** would be pre-condensed with isobutyraldehyde and zinc (II) chloride then cooled to -40 ˚C before

being treated with benzoic acid and *t*-butyl isocyanide. The resulting Ugi product **172** was obtained in good yield. In all of the examples shown, diastereoselectivities greater than 90% were obtained. The Ugi product **172** was treated with methylamine to remove the acyl protecting groups on the xylopyranose ring. This allowed for easy recrystallization so that the final products could be obtained with high enantiomeric excess. The de-acylated chiral auxiliary is easily removed using a dilute solution of trifluoroacetic acid in methanol along with mercury (II) acetate. The chiral auxiliary can be recovered and recycled back to amine **171** in a four step procedure. In contrast to Kunz's amine, the thiosugar is cleaved in the mercury-mediated reaction without having to first deprotect the benzamide.



Scheme 4.14. Ugi's entry into sugar-derived chiral amines for the Ugi reaction.

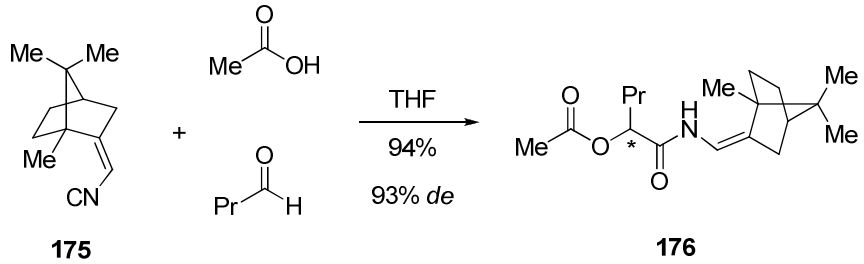
Clearly this method has drawbacks, most notably the use of mercury for the cleavage of the chiral auxiliary. Of course, every method has advantages and

disadvantages, and in the case of the Ugi reaction the availability of a diverse range of chiral auxiliaries is useful. Having a deep toolbox of reactions allows for ease in the selection of conditions that are compatible with the particular molecules at hand. There are other examples of successful chiral induction in the Ugi reaction. Notably, methods exist for the synthesis of peptides in which successive amino acids can be added with varying degrees of selectivity in the newly formed stereocenter.[1] However, other than the chiral amines such as those just described there are not many other choices for stereoinduction in the Ugi reaction. Researchers have had more luck inducing stereochemistry in the three-component Passerini reaction.

2. Stereoinduction in the Passerini Reaction

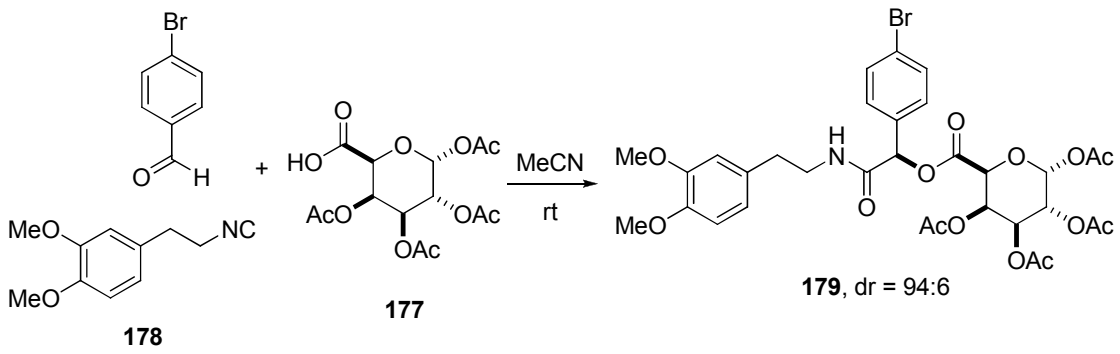
Unlike its close analogue the Ugi reaction, the Passerini reaction has been a fruitful area of research for chemists trying to synthesize optically active products. The varying range of solutions that have been found to this problem further illuminate the understanding that mechanisms of these two similar reactions are actually very different. When considering the Passerini reaction, it is possible for both the isocyanide and the carboxylic acid component to induce stereochemistry to some degree. Furthermore, a chiral Lewis-acid catalyzed version of the Passerini reaction in which water acts as the carboxylic acid component is known.

A chiral isocyanide derived from camphor was successfully employed as a chirality-inducing agent in the Passerini three-component condensation (Scheme 4.15). Chiral isocyanide **175** was condensed with acetic acid and butyraldehyde in THF to afford Passerini adduct **176**.[14] The diastereoselectivity of the reaction was good with 93% *de*.



Scheme 4.15. Bock and Ugi's stereoselective Passerini reaction of chiral isocyanide.

In another stark contrast to the Ugi reaction, it has also been found that chiral carboxylic acids can lead to high diastereoselectivity in the Passerini reaction.[15] Fully acylated galactose derivative **177** was condensed with *p*-bromobenzaldehyde and isocyanide **178** to afford Passerini adduct and **179** with good diastereoselectivity (Scheme 4.16). The chiral carboxylic acid is readily cleaved using sodium hydroxide. This reaction is definitely substrate-dependent, for example when *o*-tolyl isocyanide was used the diastereomeric ratio was barely greater than 1:1. Nonetheless, this reaction does provide access to stereochemically enriched mandelamides, which are medicinally interesting compounds.[1b]

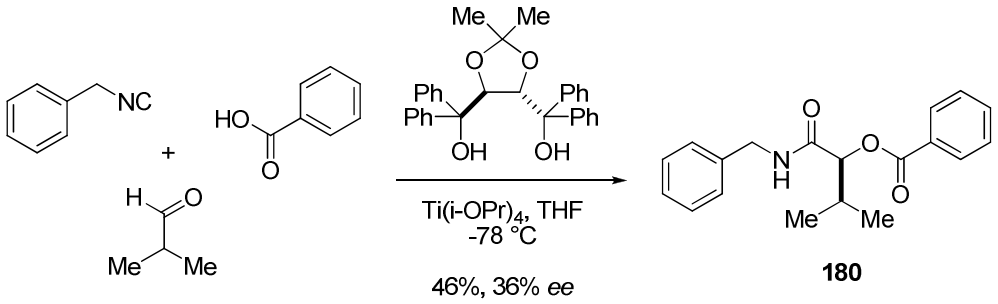


Scheme 4.16. Lamberth's chiral acid for stereoinduction in the Passerini reaction.

Instead of using a chiral component to control the stereochemical outcome of a multicomponent reaction, it would be preferable to use some sort of catalyst. Due to the difficulty of synthesizing optically active starting materials, it is advantageous in stereocontrolled reactions for the stereochemical information to come from an external source such as a chiral catalyst. Ideally the catalyst is used in only very small amounts relative to the chemical reactants. In this way, the chirality of the catalyst is greatly amplified, eliminating the need for stoichiometric amounts of a chiral auxiliary. For the Passerini reaction this sort of catalytic stereoinduction has been achieved by two groups who took distinct approaches.

The first group to approach this problem was that of Dömling and coworkers.[16] A key consideration for this group was that the integrity of the three-component coupling be conserved. In other words, they wanted to use the same components – a carboxylic acid, carbonyl component and isocyanide – in the condensation as are usually used. This allows for very diverse products to be synthesized quickly. A combination of titanium (IV) isopropoxide as the Lewis acid and TADDOL as the chiral ligand provided moderate selectivity in the Passerini reaction, as described in Scheme 4.17. When benzyl

isocyanide, isobutyraldehyde and benzoic acid were subjected to the conditions shown, the product **180** was isolated in 46% yield but with only 36% *ee*. For all of the examples shown the *ee*'s were moderate, ranging from 32-44%. Part of the difficulty with stereocontrol in this reaction is that the three starting materials are able to condense with one another even without the catalyst present. Schreiber and coworkers also submitted an entry in this area using a copper (II)-pybox Lewis acid/ligand combination.[17] They achieved high levels of stereoinduction only when using aldehydes that contained chelating heteroatoms at the α-position.

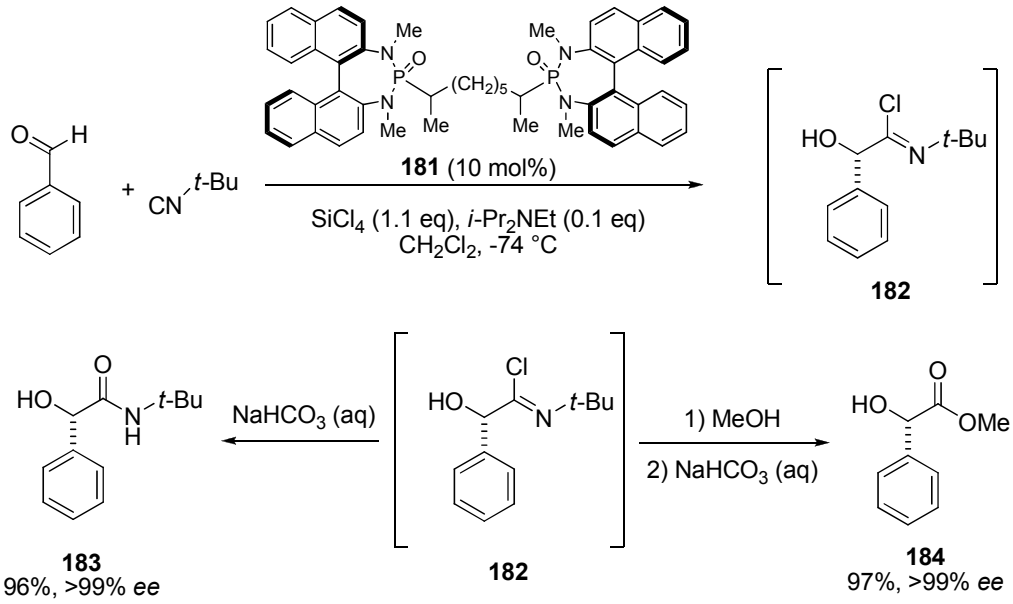


Scheme 4.17. Dömling's Lewis-acid mediated chiral Passerni reaction.

Denmark and Fan reported the first catalytic, asymmetric version of a Passerini-type reaction, which was also the first report where isocyanides were effective nucleophiles in a catalytic, stereoselective reaction.[18] In this case the reaction is not the classical Passerini reaction but rather a slightly modified version in which water formally acts as the carboxylic acid component in the reaction. A Lewis acid is necessary to activate the incorporation of water into the product via an intermediate imidoyl chloride, and a chiral ligand (**181**, Scheme 4.18) was used to induce stereochemistry. The products

of this type of reaction are α-hydroxyamides. While this means that the products derived from this reaction are less diverse than if the standard Passerini reaction was used, it is a worthwhile tradeoff since the products can be obtained with high levels of selectivity.

As described in Scheme 4.18, the aldehyde is mixed at a very low temperature and treated with $SiCl_4$ as the Lewis acid. The chiral catalyst, which is formed by the coordination of the Lewis-basic ligand **181** to $SiCl_4$, is also present. In order to achieve the best selectivities they added the isocyanide, along with Hünig's base, slowly over the course of four hours. The intermediate product **182** is an imidoyl chloride and is obtained in solution at the end of the addition. At this point there are two different choices of work-up procedure, depending on the desired product. If the reaction is simply quenched with saturated aqueous sodium bicarbonate the amide **183** is obtained with excellent *ee*. Imidoyl chloride **182** can also be treated first with methanol to form an intermediate imidoyl-ester before quenching with sodium bicarbonate, in which case the methyl ester **184** is isolated in high yield and again with very high *ee*.



Scheme 4.18. Denmark and Fan's enantioselective Passerini-type reaction.

It is necessary to use *t*-butyl isocyanide in this reaction if the best selectivity is to be achieved since less hindered isocyanides gave products with lower *ee*. Aromatic aldehydes worked best in the reaction, however there were examples of aliphatic aldehydes. The ability to obtain esters in addition to the usual amide from this procedure definitely makes it more attractive from a synthetic standpoint. The ester is much more readily converted to other useful functionalities. On the other hand, the imidoyl chloride intermediate is very reactive and could lead to side reactions if more complex molecules are used. The protection regime in such cases would have to be carefully considered. Nonetheless, this is a very attractive method for the construction of α-hydroxyamides and esters.

Until this research was published a few years ago, there were no catalytic asymmetric versions of isocyanide based MCRs, so this was definitely a nice

advancement. It is yet another important tool among many that might be used to quickly generate stereo-enriched materials quickly from simple achiral starting materials. Although no perfect solution remains to the problem of stereoinduction in the Ugi and Passerini reactions, a wide array of solutions exist and different solutions will surely continued to be used for particular problems. We would consider all of these precedents when attempting to make our own entry into this area.

D. Stereoselective, Brønsted Acid-Catalyzed Passerini-Type Reaction

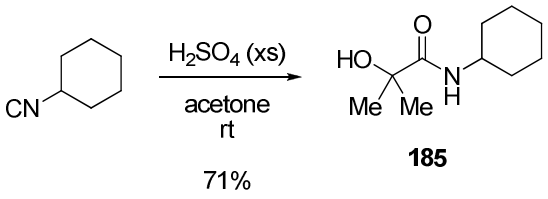
Denmark and Fan used a Passerini-type reaction where water is incorporated into the product instead of a carboxylic acid component as a platform to develop a stereoselective isocyanide based multicomponent reaction. However, they were not the first to envision the use of water in this reaction. The use of Lewis acids in this type of Passerini reaction was known and well developed before that time.[19] Another version of this Passerini-type reaction was also known, in which Brønsted acids acted as the activating agent to allow water to act as the carboxylic acid component, but this version of the reaction was not as well developed. With the advent of a new class of chiral, BINOL-derived Brønsted acid catalysts,[20] we decided to re-examine this type of Passerini reaction. We hoped to develop a suitable procedure to use Brønsted acids as the catalysts for a Passerini-type reaction and then apply these new catalysts to induce stereochemistry.

We already knew that indole isocyanide was a convertible isocyanide for the Passerini reaction so we hoped to extend its use to show the broad utility this reagent brings to reactions where one-carbon elongation of an aldehyde is desired. Before detailing our efforts in this area we will briefly discuss the history of the particular

Passerini-type reaction as well as the currently known uses for BINOL-derived Brønsted acid catalysts. Combining the convertible indole isocyanide with the Brønsted acid catalyzed Passerini-type reaction led to a new entry into stereoselective isocyanide-based MCRs as well as a convenient, one-pot method for the extension of aldehydes to α-hydroxycarboxylic acids and their derivatives.

1. The Classical Brønsted Acid Catalyzed Passerini-Type Reaction

Although it has been known for quite some time, the Brønsted acid catalyzed Passerini reaction in which water acts as the carboxylic acid component was mostly neglected by organic chemists. While the standard Passerini reaction brings together three diverse components in equimolar amounts, the Brønsted-acid catalyzed version usually used large excess of either the carbonyl component, a strong mineral acid, or both. The reaction was first introduced by Hagedorn and Eholzer.[21] In their version of this Passerini reaction, outlined in Scheme 4.19, the carbonyl component was used as solvent. In a typical example, cyclohexylisocyanide was stirred in acetone and then an excess amount of aqueous sulfuric acid was added. The resulting α-hydroxyamide **185** was isolated in 71% yield.



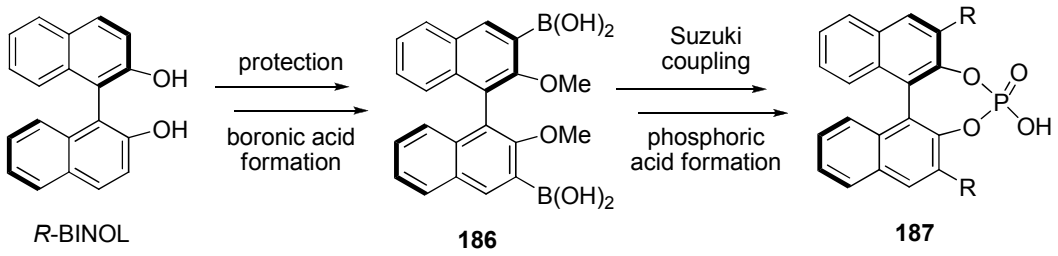
Scheme 4.19. Early example of a Brønsted-acid catalyzed Passerini-type reaction.

In the few other times that this reaction was mentioned in the literature, it was usually as a side reaction observed in the course of some other research.[22] A few examples do exist of using the reaction for preparative purposes, and in those cases hydrochloric acid[23] and hydrobromic acid[24] were also used, as were aqueous solvent conditions.[25] Usually, this reaction depends on the carbonyl component, in this case acetone, being available as a solvent. Furthermore, the products thus derived are not readily converted to any further products. It is likely for these reasons, not to mention the use of excess strong acid, that this reaction was only rarely exploited. We felt that the existence of the convertible indole isocyanide, if successfully deployed in this type of reaction, would lead to a much more useful reaction sequence since the products will be readily converted into various carboxylic acid equivalents via the *N*-acylindole.

2. BINOL-Derived, Chiral Brønsted Acid Catalysts for Organic Synthesis

There was another factor driving our desire to develop a more useful Brønsted-acid catalyzed Passerini-type reaction. During the last decade, a new class of chiral Brønsted acids has been developed as catalysts for various organic transformations.[20] Of these catalysts, a particular group derived from BINOL have proven to be particularly useful. The first examples of the use of this type of catalyst were reported in close proximity to one another by the groups of Terada[26] and Akiyama.[27] The procedure used to make these catalysts starting from BINOL, along with some representative examples, is outlined in Scheme 4.20.[27] Enantiomerically pure (*R*)-BINOL is elaborated through a sequence of protection, *o*-bromination and then boronic acid formation to intermediate **186**. From this common intermediate, a variety of catalysts can be made. Suzuki coupling introduces to bulky, usually aryl groups into position to create the steric

environment needed for the stereoselective reaction to take place. After Suzuki coupling it is necessary to deprotect the two phenols. Introduction of the phosphoric acid moiety provides **187** with the rigidity it needs by locking the conformation of the molecule. The phosphoric acid portion of **187** is also the Brønsted acid catalyst.



Scheme 4.20. Akiyama's synthesis of BINOL-derived phosphoric acid catalysts.

Many different catalysts containing a variety of –R groups have been reported as successful stereoselective catalysts. Akiyama and Terada each reported an array of catalysts that they tested and more have been reported since. The first two catalysts which gave high enantioselectivities are shown in Figure 4.2. The reactions are discussed in detail below.

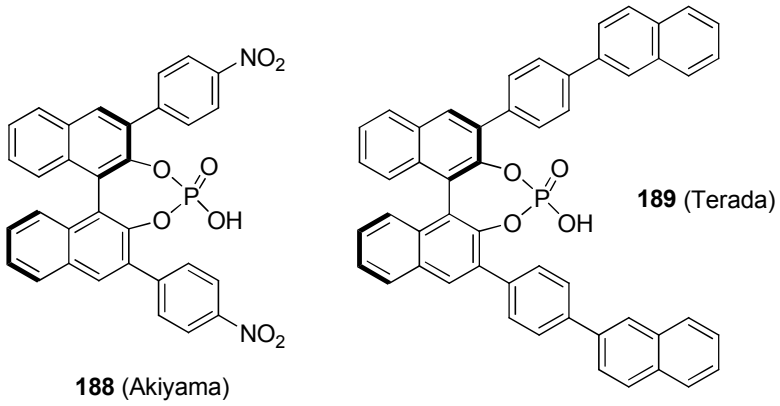
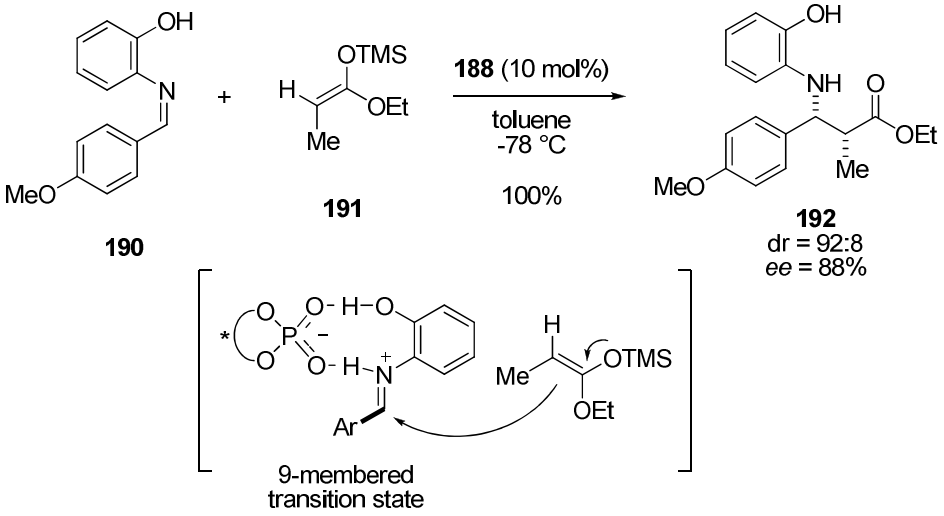


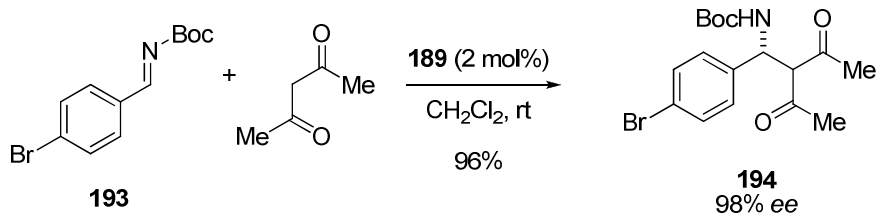
Figure 4.2. Akiyama and Terada's first successful BINOL-derived catalysts.

The first report of successful Brønsted acid catalysis with a BINOL-derived chiral phosphoric acid, from the Akiyama group, was an indirect Mannich reaction (Scheme 4.21).[27] Pre-condensed aryl aldimine **190** was treated with ketene silyl acetal **191** in the presence of catalyst **188**. The aryl aldimine **190** is derived from derived from 2-hydroxyaniline. The resulting product **192** was formed in a 92:8 *syn:anti* ratio with 88% *ee*. The enantioselectivities for the reactions shown ranged from 81% *ee* to 96% *ee*. This group has written convincingly about the necessity of using 2-hydroxyaniline as an extra coordinating site.[28] They invoke a nine-membered transition state, as shown, in which the hydroxyl group is necessary for the desired selectivity. While this is a very reasonable explanation for the observed selectivity, other groups have reported stereoselective reactions without specifically using 2-hydroxyanline.



Scheme 4.21. Akiyama's indirect Mannich reaction catalyzed by **188**.

Shortly after Akiyama's initial publication, the Terada group published their first report of a direct Mannich reaction between N-Boc derived, aryl aldimines and 1,3 diketones.[26] As described in Scheme 4.22, pre-formed aryl aldimine **193** was treated with acetoacetone in the presence of catalyst **189**. The product **194** was recovered in good yield with a high degree of selectivity. This report is different from Akiyama's work in many different ways. Most notably, there is no hydrogen-bond donor implicated as necessary by Akiyama and coworkers. Furthermore, the reactions were run with lower catalyst loading and at room temperature. While these reactions are not directly comparable since they yield different types of products, using a small amount of catalyst without special concern for temperature is generally desirable.



Scheme 4.22. Terada's direct Mannich reaction catalyzed by phosphoric acid **189**.

Following these two initial reports, a steady stream of publications have described expanded uses for these catalysts. Most of the reactions reported to date employ imines as the electrophilic component.[29] Other interesting applications have been described, however, including Diels-Alder type reactions[30] and asymmetric reduction of pyridines.[31] By contrast, there have been very few reports of using these catalysts to activate reactions of aldehydes and ketones directly. Notably, Terada and coworkers reported an aza-ene

type reaction of glyoxylates,[32] and the Rueping group has reported a stereoselective Nazarov cyclization.[33] We felt after looking at these examples that the BINOL-derived phosphoric acid catalysts that they might be applied to a Brønsted-acid catalyzed Passerini type reaction.

E. A Stereoselective Passerini-Type Reaction Using a Convertible Isocyanide

1. Introduction

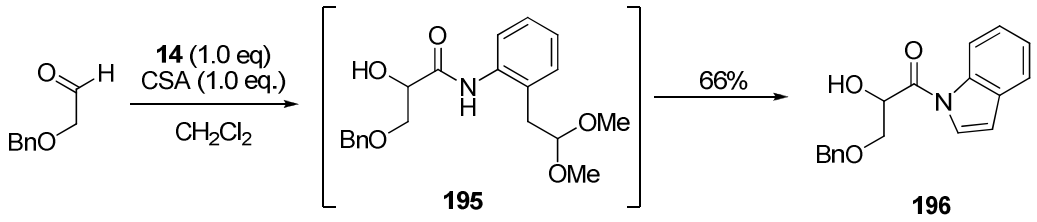
In order to achieve a Brønsted acid catalyzed Passerini-type reaction between isocyanides, aldehydes and water it was necessary to overcome a few obstacles. First, we had to devise a modernized protocol for this reaction in which only a catalytic amount of Brønsted acid would be needed. Next, we would have to test and see if this protocol was applicable for use with the chiral phosphoric acid catalysts that are available. Finally, we would have to discover the optimum procedure for both yield and selectivity. After working through these steps, a very useful Passerini-type reaction was developed. Despite trying various reaction conditions and substrates, high enantiomeric excess was not achieved. However, we were able to achieve moderate stereoselectivity and make a new entry into stereoselective isocyanide-based multicomponent reactions.

2. Designing a Brønsted Acid Catalyzed Passerini-Type Reaction

We began the process of designing a better Brønsted acid catalyzed Passerini-type reaction by setting out the most basic parameters we hoped to follow. First, it was important that the reactants be used in equimolar amounts. Next, we wanted to use only a catalytic amount of Brønsted acid. Finally, the reaction would require an aprotic solvent. This is necessary for the hydrogen-bonded framework that allows for the enantioselective

reaction to take place.[28] We didn't imagine this would be a problem because the Passerini reaction is usually run in dichloromethane.

Taking these parameters into account, we selected reaction conditions and tried the reaction. The first experiment conducted was actually surprisingly successful and is outlined in Scheme 4.23. Benzyloxyacetaldehyde was mixed with one equivalent of indole isocyanide **14** in dichloromethane and the reactants were treated with one equivalent of camphorsulfonic acid (CSA) without addition of water. We were happy to see that soon after the acid was added a new product began to form. The reaction was monitored by TLC analysis on silica gel and the initial product was very polar relative to the isocyanide **14**. After a few minutes a second, much less polar product began to appear by TLC and eventually the initial product disappeared. It was later determined that the Passerini-type product, α-hydroxyanilide **195**, was initially formed but under the acidic reaction conditions the anilide cyclized to form *N*-acylindole **196**.

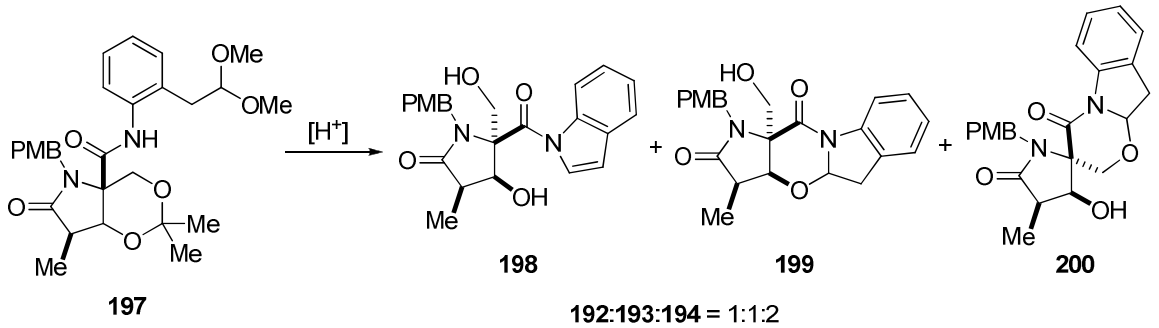


Scheme 4.23. Our first attempt at the Brønsted acid catalyzed Passerini-type reaction.

We were pleased but not surprised to discover that the Passerini-type adduct **195** formed quite easily. We were very surprised, however, that *N*-acylindole **196** formed under the same reaction conditions. It was previously believed that heating was

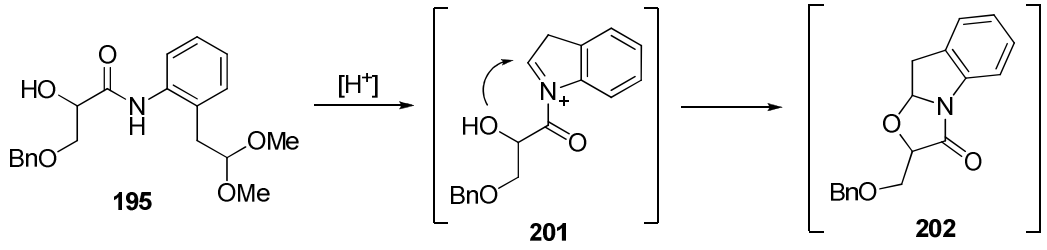
necessary to complete the cyclization, and we had furthermore never tried the reaction in dichloromethane. Of course, this is a very pleasant outcome for us because cyclization to form the *N*-acylindole is the planned next step for this convertible isocyanide. This result cuts one step from any synthesis using this protocol and, as will be described below, opened the door for some interesting chemistry using very mild conditions. It should also be noted that the α-hydroxyanilide **195** could be isolated if the reaction was conducted and quenched at 0 ˚C or if a weaker acid such as phosphoric acid is used.

It was not a foregone conclusion that this reaction would be successful. We had already successfully formed *N*-acylindole from standard Passerini products, for example the conversion of **157** to **158** (Scheme 4.10). However, in that case the α-hydroxyl group is protected as acetate. During the formal total synthesis of omuralide that was conducted in our laboratory we found that two hydroxyl groups near the site of *N*-acylindole formation led to the formation of side products. As described in Scheme 4.24, when compound **197** was treated with CSA to form *N*-acylindole, three products were actually recovered. In addition the desired compound **198**, most of the starting material was converted to one of two mixed acetals, either **199** or **200**.



Scheme 4.24. A problem with *N*-acylindole formation during omuralide synthesis.

Based on this result, we were unsure if the products derived from the Passerini-type reaction would successfully form *N*-acylindole. When the product **195** is submitted to the *N*-acylindole formation conditions, one step in the mechanism is compound **201** (Scheme 4.25). It is possible that the free alcohol in this molecule can react intramolecularly to form mixed acetal **202**. Fortunately, we never observed in products of this type so we were able to move on without worry.

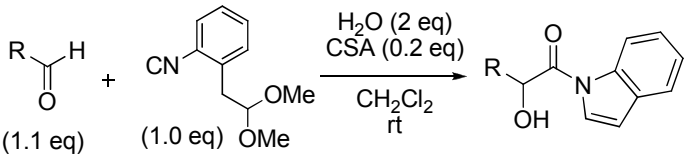


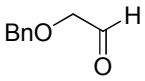
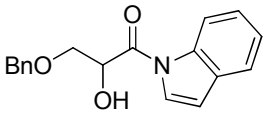
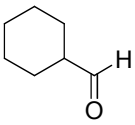
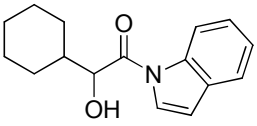
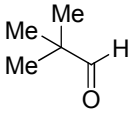
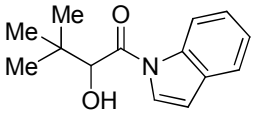
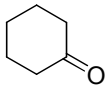
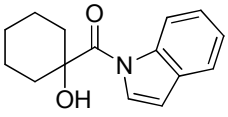
Scheme 4.25. Possible but unrealized issue with *N*-acylindole formation.

Before going forward it was necessary to optimize the reaction conditions to improve the yield. Although we had originally relied on the assumption that small amounts of water are present in reagent-grade dichloromethane, we found that the yield was improved if two equivalents of water were added to the reaction. This is logical since water is acting as the third component in this reaction. We also found that a very small amount of acid catalyst (CSA) was necessary for the Passerini-type reaction itself, as little as 1% at room temperature. However more acid was necessary for concomitant indole formation, and 20% was found to be optimum in most cases. We decided to use a slight excess of the aldehyde to ensure that all of the isocyanide, which can be difficult to

remove from the products, was consumed. Using these conditions we quickly synthesized a variety of α-hydroxy-*N*-acylindoles as described in Table 4.3.

Table 4.3. Passerini-type reaction of indole isocyanide with aldehydes and ketones.



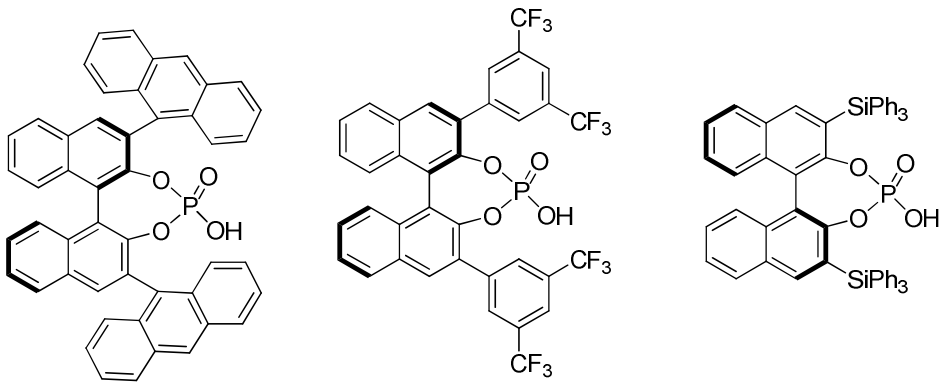
Entry	Substrate	Yield	Product
1		93%	 **196**
2		98%	 **203**
3		86%	 **204**
4		98%	 **205**

Importantly, this Passerini-type reaction affords versatile one-carbon extended products containing the *N*-acylindole. This moiety is readily converted into a variety of other carboxylic acid derivatives and alternatively can be reduced using mild conditions. As you can see from the table, an aldehyde containing a heteroatom at the α-position posed no problem (Entry 1). More highly substituted aldehydes also participated in the

reaction with good yields (Entries 2 and 3). We also found that cyclohexanone is a particularly good substrate for this reaction. Surprisingly, though, neither cyclopentanone nor cycloheptanone participated in the reaction. The reason is unclear. Aromatic aldehydes were also unreactive in the current scheme, however we later discovered that only certain isocyanides, most notably *t*-butyl isocyanide, undergo any type of Passerini reaction with aromatic aldehydes. All of the isocyanides tested in the Passerini-type reaction led to the formation of α-hydroxyamides, as described below.

3. Attempted Optimization of Conditions for the Enantioselective Reaction

Armed with a simple and useful procedure for the Brønsted acid catalyzed Passerini-type condensation of aldehydes, isocyanides and water, we turned our attention to the asymmetric version of the reaction. We would use BINOL-derived chiral phosphoric acids as the catalysts for the stereoselective reaction. We began by attempting to synthesize a series of these catalysts according to literature precedent.[27] Although this had been described as a straightforward process, we did not find that to be the case. We found that the *o*-bromination of the BINOL-derivatives was difficult and had further trouble with the successful Suzuki coupling. Fortunately, although they were not initially available, during the course of this research many of these catalysts became available commercially. In light of this, we directed our attention to the catalysts shown in Figure 4.3.

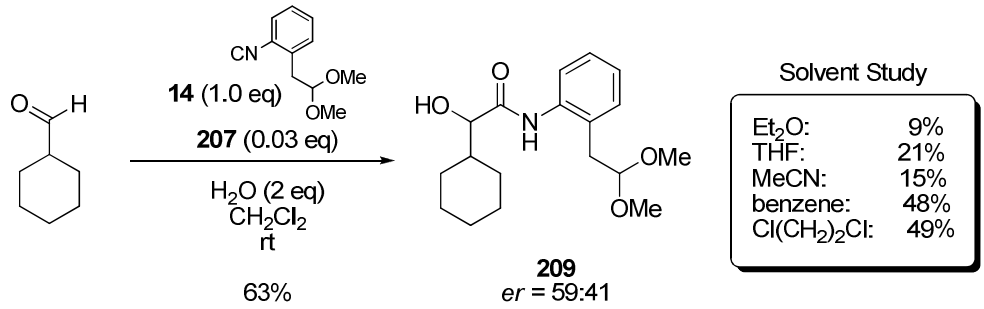


(*R*)-206 (*R*)-207 (*S*)-208

Figure 4.3. Some commercially available phosphoric acid catalysts.

The first of these catalysts that was available to use was **207**, which is substituted with 3,5-bis-trifluoromethyl substituted benzene rings. After an early screen of various aldehydes, we decided to use cyclohexanecarboxaldehyde in combination with indole isocyanide **14** to test various reaction parameters. This substrate was chosen because of its steric bulk and because it was the best of the early aldehydes tested in terms of enantioselectivity. Even though the level of selectivity was low, we believed it could be improved. The first thing that we noticed when using these phosphoric acid catalysts is that although the Passerini reaction was successful, affording **209**, further conversion to the corresponding *N*-acylindole did not happen with this catalyst under the given conditions (Scheme 4.26). This is presumably due to the weaker strength of phosphoric acid (H_3PO_4: pKa = 2.12) relative to CSA (H_2SO_4: pKa = –3.0). When CSA was used as the catalyst for this reaction, the Passerini-type reaction itself proceeded with very little catalyst, and it was only *N*-acylindole formation that required up to 0.2 equivalents of catalyst to be used. Since the *N*-acylindole would not form regardless of how much

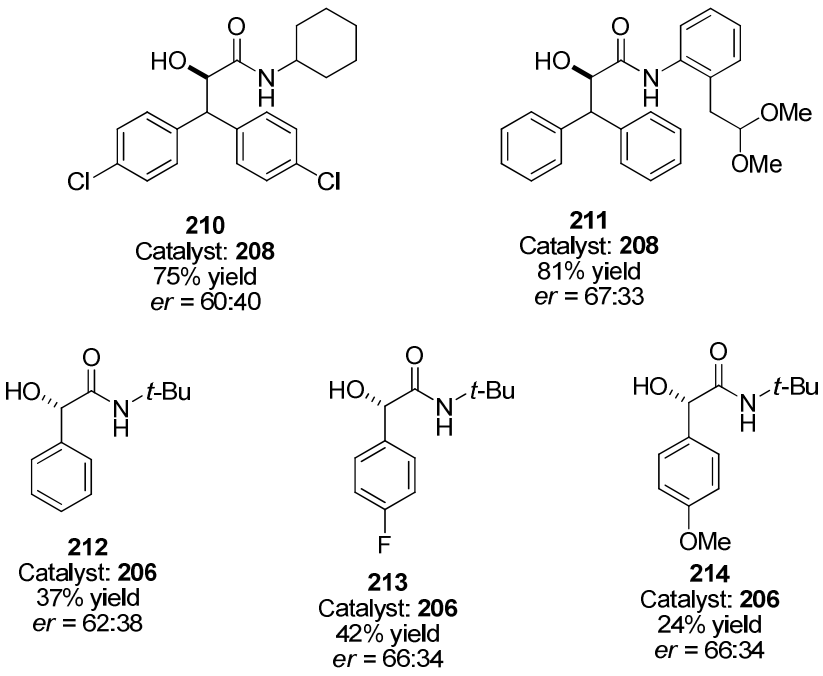
phosphoric acid catalyst was used, much lower catalyst loading is possible in the present case. The enantiomeric ratios for all products tested were determined by chiral HPLC analysis.



Scheme 4.26. Initial studies for enantioselective Passerini-type reaction.

After finding suitable conditions for this reaction the next step we took was a solvent study. As shown in Scheme 4.26, the yield was depressed when different aprotic solvents were tested. More importantly, the selectivity when these solvents were used was also decreased. The next step we took was to test the reaction at low temperature, because that is usually a step that can be taken in catalytic, enantioselective reactions to improve the selectivity. Unfortunately, we found that catalytic activity was almost non-existent at lower temperatures. Beginning at -78 ˚C we found that there was essentially no reaction, and the same was true at -40 ˚C. When the reactions were tested at -10 ˚C the yield began to improve, but the enantioselectivity never improved over the level that was achieved at room temperature. Since both yield and selectivity seemed to be optimum at ambient temperatures, we settled on this procedure and began testing a variety of substrates and catalysts to see if better selectivity could be achieved.

We next embarked on a course of submitting as many combinations of aldehydes and isocyanides as possible to the Passerini-type reaction. The main limiting factor in these experiments was the availability of the catalysts. Despite being commercially available, they are very expensive and due to their popularity they were often back-ordered. We nonetheless tested a diverse field of combinations. One thing that we discovered in the course of this research is that aromatic aldehydes will participate in the reaction of *t*-butyl isocyanide is used. Figure 4.4 shows the products that were synthesized with the best selectivities, as well as the catalyst that was used in each case.



210
Catalyst: **208**
75% yield
er = 60:40

211
Catalyst: **208**
81% yield
er = 67:33

212
Catalyst: **206**
37% yield
er = 62:38

213
Catalyst: **206**
42% yield
er = 66:34

214
Catalyst: **206**
24% yield
er = 66:34

Figure 4.4. Yield and *er* for some α-hydroxyamides from the Passerini-type reaction.

The procedure used to synthesize the compounds shown was the same as that outlined for the synthesis of **209** in Scheme 4.26. All of the cases shown contain bulky

substituents in the α-position of the aldehyde, which makes sense because greater selectivity should be achieved with increasing steric bulk. The stereochemistry for compound **211** was determined by comparison with a readily-accessible, known derivative, as reported in the next section, and the other assignments were made by analogy. We were surprised with the results when we used trimethylacetaldehyde, which worked in the CSA-catalyzed reaction to give product **204** (Table 4.3), because we hoped the extra steric bulk would lead to increased selectivity. While this aldehyde did participate in the phosphoric acid catalyzed reaction, very little stereoselectivity was observed.

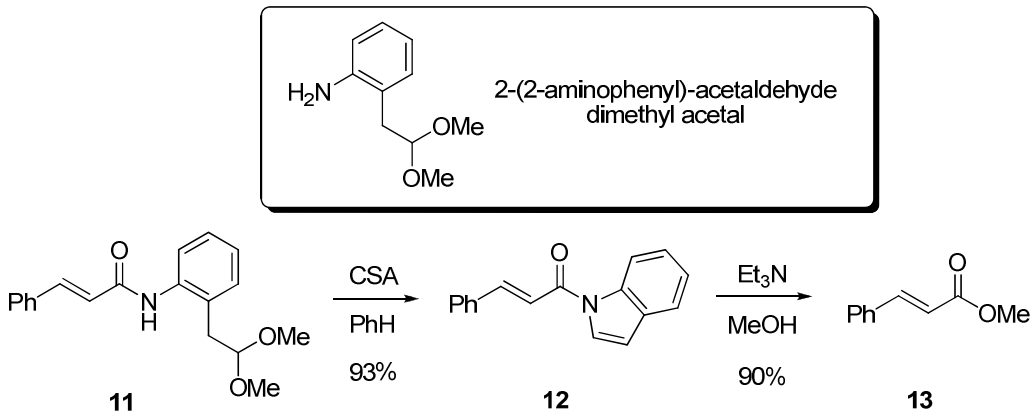
t-Butyl isocyanide successfully reacted with aromatic aldehydes to give products **212**, **213** and **214**. The presence of the electron-withdrawing fluorine atom in **213** increased the yield of the Passerini-type reaction relative to benzaldehyde (product **212**) and the *p*-methoxy group present in **214** led to a decreased yield. We believe the yield of products **212**, **213** and **214** might be improved with higher catalyst loading, although we were not able to test this hypothesis due to an insufficient supply of catalyst. We had hoped that through the variation of temperature and solvent, as well as by testing different catalysts, that a high degree of enantioselectivity would be observed in these reactions. At this time, the examples shown in Figure 4.4 are the best we obtained. We are still hopeful that testing of a broader range of catalysts will yield better enantioselectivities under the present conditions.

This protocol was tested, with variations, in the Ugi reaction as well. The only difference being that in addition to the other components, an amine is also present for the Ugi reaction. Despite testing various solvents and amines, we never isolated any Ugi-

type α-aminoamides analogous to the Passerini-type products α-hydroxyamides. This is consistent with the results of other groups who have worked in this area. One particular problem is that the amine, which is a base, may quench the catalyst. Though disappointing, our failure to apply this or a similar protocol to the Ugi reaction was not particularly surprising because it is widely believed that the two reactions, despite their similarities, actually operate according to distinct mechanisms.

4. Extension and Application of the Passerini-Type Reaction

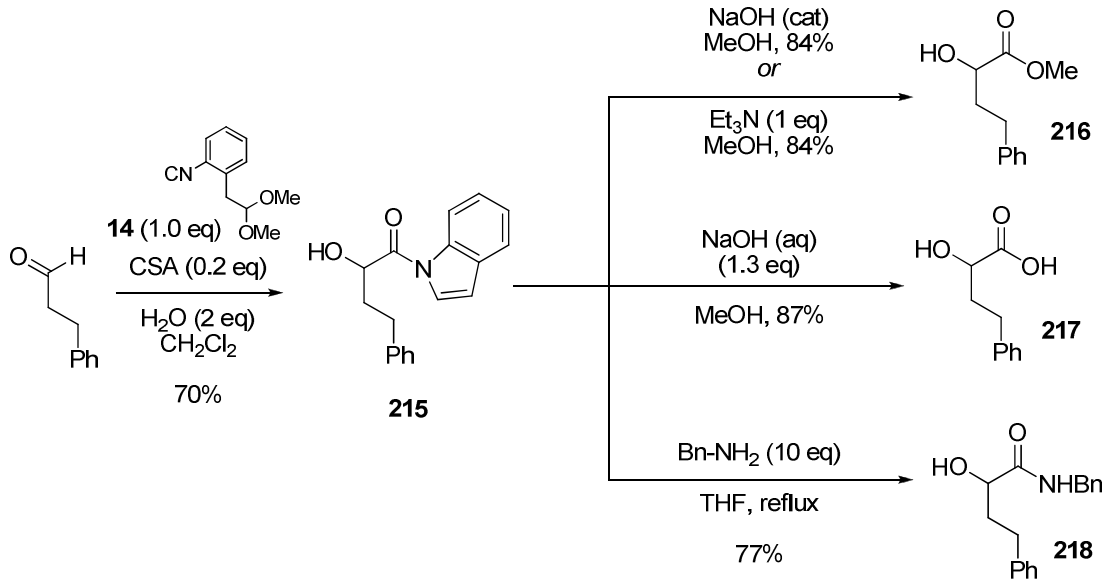
The final step for us in the development of the Brønsted acid catalyzed Passerini-type reaction is to show why it is useful in the broader context of organic synthesis. As was discussed in Chapter 1, Fukuyama and coworkers were the first to introduce the particular protecting group for carboxylic acid that uses an anilide that is easily converted to *N*-acylindole using an attached aldehyde masked as the acetal form (Scheme 4.27).



Scheme 4.27. Fukuyama's indole-inspired carboxylic acid protecting group.

In order to ensure that the products derived from our Passerini-type reaction were suitable for the subsequent transformations, we synthesized Passerini-type adduct **215**

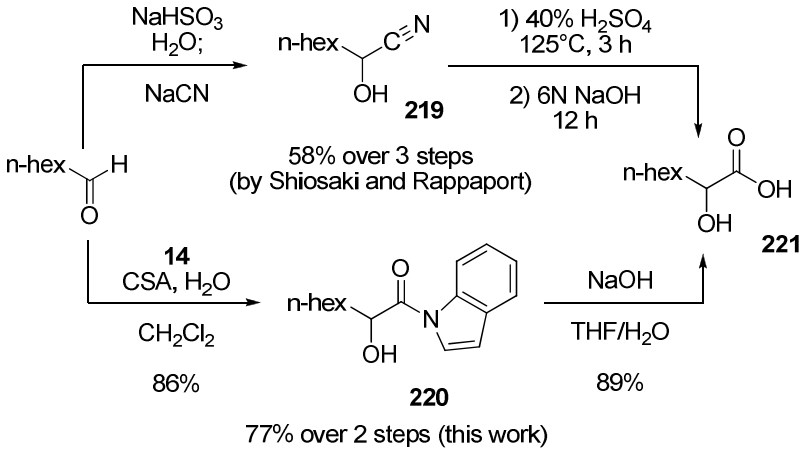
from dihydrocinnamaldehyde, water and **14** using CSA as the catalyst (Scheme 4.28). This product was transformed without incident to the corresponding methyl ester **216** using methanol as solvent and either catalytic sodium hydroxide or triethylamine as the base. Adding an excess of sodium hydroxide led to the free α-hydroxyacid **217**. Finally, **215** was converted to the amide **218** simply by refluxing it in THF with benzylamine. This reaction may seem superfluous at first glance because it could be argued that the amine should simply be converted to the corresponding isocyanide and fed into the Passerini reaction itself. This is not always a viable option, however, due to availability of material and the difficulty of making isocyanides from certain amines – especially chiral amines.[1]



Scheme 4.28. Conversion of Passerini-type adduct **215** to other useful products.

The ease with which the *N*-acylindole derived from the Passerini-type reaction is cleaved to other useful products opens many possibilities for its use. For example, the

common method for one-carbon extension of an aldehyde to the corresponding α-hydroxycarboxylic acid derivative is the cyanohydrin method. In a typical example, Shiosaki and Rappaport reported the synthesis of α-hydroxyacid **221** from heptaldehyde (Scheme 4.29).[34] The first step is cyanohydrin formation, which is followed by hydrolysis to the corresponding carboxylic acid. As is usually required, the cyanohydrin intermediate **219** was boiled in sulfuric acid to first give the carboxamide and then stirred in highly concentrated sodium hydroxide to give the acid in 58% yield over 3 steps. Using the Passerini-type reaction we arrived at **221** in two steps and 77% yield from heptaldehyde via *N*-acyl indole **220**; only 1.2 equivalents of sodium hydroxide were needed for the hydrolysis step. The difference in harshness between the two sets of conditions could hardly be more marked. Additionally, in Passerini sequence both reactions were completed in relatively short time compared to the cyanohydrin method so the products can be obtained more rapidly.

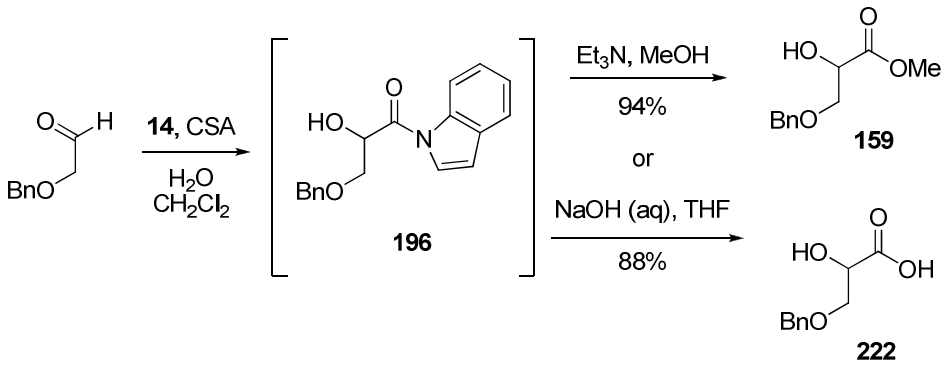


Scheme 4.29. The cyanohydrin method versus the Passerini-type reaction.

This reaction sequence is also a nice alternative to cyanohydrin formation because it avoids the use of highly toxic cyanide-containing reagents. Also, in many cases it has been reported that the cyanohydrin intermediate is difficult to isolate. If a chemist desired to extend a molecule containing a variety of different functional groups then the current method would be much more likely to succeed while keeping those functional groups intact, and the yield would likely be better as well. This strategy might also be useful in the late stages of a total synthesis where a specific and selective cleavage reaction is needed, as was demonstrated with the total synthesis of dysibetaine in Chapters 2 and 3. Of course, due to the relative difficulty of obtaining indole isocyanide versus a cyanide source, this may not be the best choice in all cases, especially if large amounts of a readily available aldehyde need to be fed into the sequence. However, this method does provide a nice substitute pathway since there are not very many alternatives for this transformation.

In order to maximize the utility of this reaction sequence, we wanted to combine all of the steps into a one-pot procedure. Happily, we succeeded in finding the necessary conditions for the this conversion of an aldehyde to the corresponding one-carbon elongated α-hydroxycarboxylic acid or ester. As described in Scheme 4.30, benzyloxyacetaldehyde was submitted to the standard condition for the Passerini-type reaction and was allowed to stir until TLC analysis indicated that conversion of the starting aldehyde and intermediate anilide to **196** was completed. After that time the next set of reagents were added to give the corresponding products. When methanol and triethylamine were added the methyl ester **159** was obtained in great yield and when a slight excess of aqueous sodium hydroxide in THF were added we were able to isolate

the free carboxylic acid **222**. Both of these transformations could be completed within the course of a day, which is another nice advantage over the cyanohydrin method.

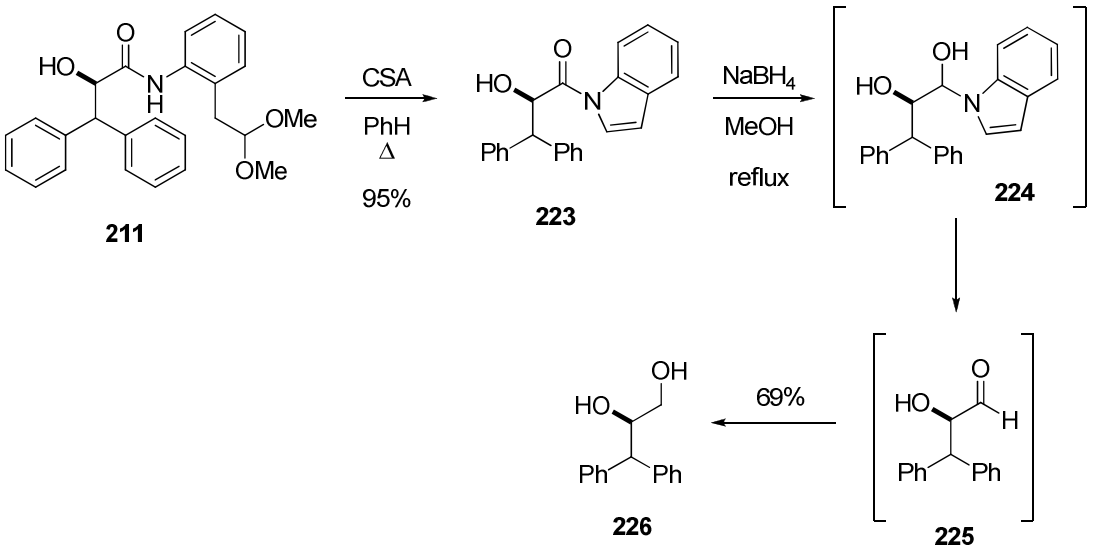


Scheme 4.30. One-pot conversion of aldehyde to one-carbon extended acid or ester.

Another advantage of the *N*-acylindole is that is easily reduced. Usually when we think about reducing an amide to the corresponding alcohol we imagine that it will take refluxing conditions and a strong reducing agent such as lithium aluminum hydride. However, α-hydroxy-*N*-acylindole products derived from these reactions are readily reduced to the corresponding diols using only sodium borohydride. Another amide or carboxylic acid derivative moiety contained in a compound of interest could be preserved while moving forward with the reduction of the *N*-acylindole to the corresponding diol.

An example of this process is shown in Scheme 4.31. Enantio-enriched product **211** from the Passerini reaction using a BINOL-derived chiral catalyst was converted to the corresponding *N*-acylindole **223** using the standard protocol. **223** was then reduced with sodium borohydride in methanol at reflux. In this reaction the *N*-acylindole **223** is first reduced to the intermediate hemi-aminal **224**. While the initial reduction proceeded

at room temperature, heating was necessary to decompose the hemi-aminal intermediate to the corresponding aldehyde **225**, which is immediately reduced under the reaction conditions to the corresponding alcohol. In the case of **226** we arrived at a compound that was previously described in the literature[35] and were therefore able to determine the absolute stereochemistry of the product.



Scheme 4.31. Sodium borohydride reduction of *N*-acylindole.

Considering this reaction sequence you can see that the Passerini-type reaction followed by reduction with sodium borohydride is also a suitable alternative to commonly used chemistry. The most common choice for a chemist who wished to convert an aldehyde into the corresponding one-carbon extended diol would be a sequence of Wittig-olefination followed by dihydroxylation. The olefination reaction usually requires strong base and the olefination reagent would react not only with aldehydes but also any ketones present in the molecule. The Passerini-type reaction uses

much milder conditions and furthermore is much faster for aldehydes than ketones and therefore selective between the two. The second step, dihydroxylation, is not compatible if other olefins or low-oxidation state sulfur atoms are present in the molecule. The Passerini-type reaction avoids all of these problems and is therefore a very effective, orthogonal choice of reaction sequence if a one-carbon extended diol is desired.

F. Summary

In this chapter delved into all of the possibilities that were presented by the discovery of the new cleavable indole isocyanide for the Ugi multicomponent condensation reaction. We examined the mechanism of action for other convertible isocyanides and the sometimes variant behavior if indole isocyanide with different components in the Ugi reaction. From this examination came a deeper understanding of the mechanism of action in post-Ugi reaction modifications for indole isocyanide. Specifically, we discovered that when open chain Ugi products are used an azlactone intermediate forms, leading by solvolysis to the direct formation of products other than the desired, versatile *N*-acylindole. This problem can be overcome by using TFA as the acid component in the Ugi reaction. Our goal in these pursuits was to define the limits of usability for this interesting isocyanide. We hope that giving a thorough definition of the usefulness of this isocyanide will encourage other chemists to use it in their own projects and syntheses.

Because of its unique mode of action, indole isocyanide is also an ideal choice of convertible isocyanide for the Passerini reaction. Before this isocyanide was introduced there was no isocyanide available that would lead to practical, selective cleavage of the amide derived from the reaction. Since harsh conditions were required to cleave the

amide, the Passerini reaction was not usually considered if carboxylic acids or esters were needed starting from an aldehyde via one-carbon extension. However with the introduction of this reagent we believe the Passerini reaction will be seen in a new light. The introduction of a one-pot procedure for the conversion of aldehydes to one-carbon extended α-hydroxycarboxylic acid derivatives will also be an attractive tool for other synthetic chemists since this conversion usually takes many steps and requires harsh reagents.

The ultimate goal for any reaction is, of course, to be able to employ it for the construction of stereochemically pure products with excellent chemical yield and minimum waste. We surveyed the history of stereoinduction in isocyanide based multicomponent-reactions in order to familiarize ourselves with the possibilities in this area. Then we experimented and explored all of the possibilities we could imagine in an attempt to make our own entry into this field. The timing of the release of a new series of chiral Brønsted acid catalyst derived from BINOL was very fortuitous for our efforts. We used the intersection of a long-known but little utilized version of the Passerini reaction with these new catalysts to discover a new method for the stereoselective Passerini-type reaction in which water acts as the carboxylic acid component. With the range of chiral Brønsted acid catalysts currently available we were unable to achieve the desired level of stereoinduction. However, we are hopeful that this problem will be solved and enantioselectivity in this reaction will be improved when a broader range of catalysts is screened. Nonetheless, the reaction at hand is a rare entry into the area of stereoselective reaction of isocyanides.

G. Conclusion

The research described herein was originally inspired by a desire to use the Ugi reaction to construct pyroglutamic acid-containing natural products. From that platform we followed an arc of discovery that led eventually to two separate syntheses of the natural product dysibetaine. As we followed this path, however, those syntheses inspired other projects and pathways for development. While the total synthesis of natural products is a lengthy, time-consuming effort, that effort bore fruit at surprising points all along the way. Those intermittent successes – tasty snacks – were important nourishment for the more arduous journey.

The total synthesis of dysibetaine was made possible by the development of a cleavable isocyanide, indole isocyanide, for the Ugi reaction. This isocyanide has a different method of action than other known cleavable isocyanides and we were therefore able to use it to selectively cleave pyroglutamic acid amides to the corresponding carboxylic acid derivatives with surprising ease. The success of our research was based on our insistence that this tool be developed for as many uses as possible. Once we had used indole isocyanide as the solution to our particular problem we let scientific curiosity take over. From that point we were able to develop a series of useful applications for this reagent. Throughout the process we kept in mind our higher goals of research in organic chemistry – completion of interesting natural products and the development of stereoselective methods – and doing so allowed us to achieve some satisfaction on the way to these ideals.

H. Acknowledgements

This chapter contains material that has been submitted for publication: *Mild and Efficient One-Carbon Extension of Aldehydes.* Isaacson, Jerry; Goeser, Lauren M.;

Urbina, Armando; Kobayashi, Yoshihisa. *submitted.*. Ms. Goeser, Ms. Olshanksy and Mr. Urbina are graciously acknowledged for their contribution to this work. This chapter also contains contributions from UCSD undergraduate researchers Karen Lai, Allison Li, Philip Zhou and Kerem Ozboya.

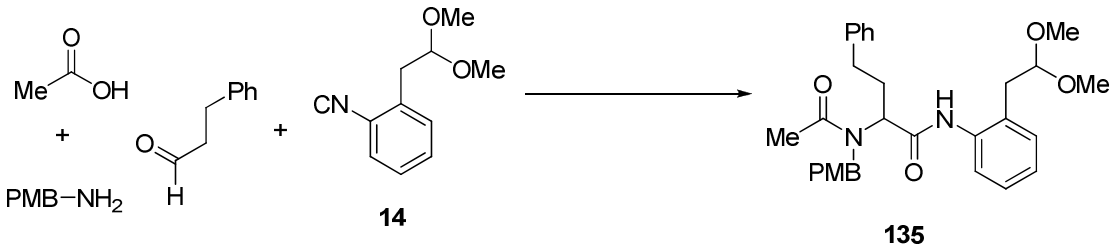
I. Experimental Section

1. Materials and Methods

All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. Tetrahydrofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), 2,2,2-trifluoroethanol (TFE), and acetone were purchased as reagent grade and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnigan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]25D = (100\cdot\alpha)/(l\cdot c)$, where the concentration c is in g/100 mL and the path length l is in decimeters.

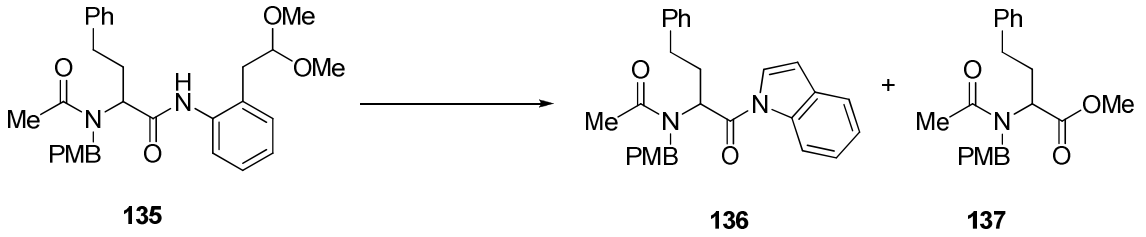
2. Procedures and Spectral Data



Scheme 4.32. Synthesis of **135**.

(135) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.34-6.99 (m, 10H), 6.85 (d, J = 8.7 Hz, 2H), 5.20 (dd, J = 6.8, 7.8 Hz, 1H), 4.68 (d, J = 17.4 Hz, 1H), 4.60 (d, J = 17.4 Hz, 1H), 4.48 (t, J = 5.2 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H), 2.91 (d, J = 5.4 Hz, 2H), 2.77-2.30 (m, 4H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.1, 159.1, 141.3, 136.6, 131.3, 130.4, 129.6, 128.7, 128.6,

127.7, 127.6, 126.3, 125.2, 124.2, 114.5, 106.6, 58.3, 55.6, 54.8, 54.5, 49.3, 36.9, 33.0, 30.8, 22.6. MS $C_{30}H_{36}N_2O_5$: calcd 504.26, obsd $[M + Na]^+ = 527.35$.



Scheme 4.33. Synthesis of **136** and **137**.

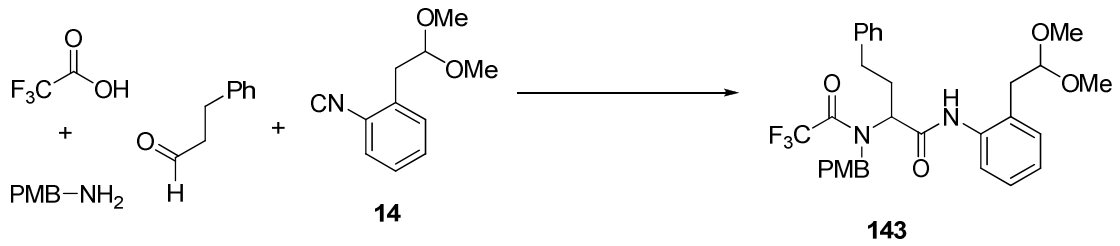
(136) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.11 (m, 1H), 7.69 (d, *J* = 3.8 Hz, 1H), 7.52-7.49 (m, 1H), 7.31-7.17 (m, 7H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 3.7 Hz, 1H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.20 (t, *J* = 7.3 Hz, 1H), 4.54 (d, *J* = 17.2 Hz, 1H), 4.46 (d, *J* = 17.2 Hz, 1H), 3.53 (s, 3H), 2.81-2.71 (m, 1H), 2.65-2.56 (m, 1H), 2.45-2.36 (m, 1H), 2.18-2.09 (m, 1H), 2.13 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.3, 158.8, 141.1, 135.7, 130.9, 128.7, 128.6, 128.0, 127.1, 126.4, 125.5, 125.1, 124.1, 120.7, 116.8, 114.0, 110.1, 55.3, 54.5, 47.9, 32.3, 30.9, 22.4. MS $C_{28}H_{28}N_2O_3$: calcd 440.21, obsd $[M + H]^+ = 441.05$.

(137) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.11 (m, 1H), 7.69 (d. *J* = 3.8 Hz, 1H), 7.30-7.04 (m, 2H), 6.88-6.67 (m, 2H), 6.60 (d, *J* = 3.8 Hz, 1H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.20 (t, *J* = 7.2 Hz, 1H), 4.56-4.44 (m, 2H), 3.53 (s, 3H), 3.38 (s, 3H), 2.80-2.72 (m, 1H), 2.64-2.57 (m, 1H), 2.45-2.35 (m, 1H), 2.108-2.09 (m, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.3, 158.8, 141.1, 135.7, 131.5, 130.9, 128.7, 128.6, 128.0,

127.9, 127.1, 126.4, 125.5, 125.1, 124.1, 120.7, 118.9, 116.8, 116.5, 114.0, 110.1, 106.8, 55.3, 54.5, 54.2, 47.9, 36.7, 32.3, 30.9, 22.4, 22.3. MS $C_{21}H_{25}NO_4$: calcd 355.18, obsd $[M + H]^+ = 336.11$.

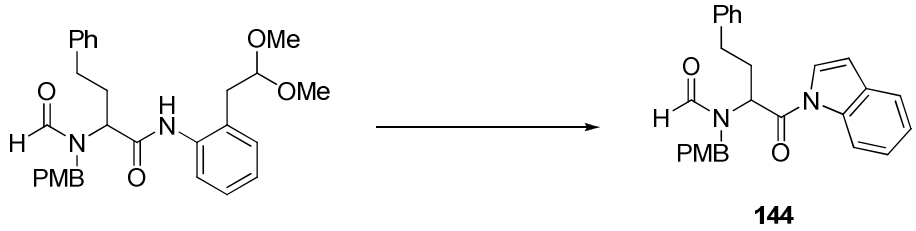
Scheme 4.34. Synthesis of **142**.

(142) ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotomers: δ 9.04, 8.99 (s, 1H), 8.43, 8.37 (s, 1H), 7.69, 7.66 (d, *J* = 8.1 Hz, 1H), 7.32-6.98 (m, 10H), 6.86-6.78 (m, 2H), 4.96 (t, *J* = 7.3 Hz, 1H), 4.70-4.40 (m, 2H), 3.94 (dd, *J* = 5.5, 9.5 Hz, 1H), 3.77, 3.75 (s, 3H), 3.38, 3.37 (s, 3H), 3.33 (s, 3H), 2.91-2.68 (m, 2H), 2.63-2.32 (m, 3H), 2.15-1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 168.1, 164.1, 163.5, 159.7, 159.5, 141.1, 140.3, 136.5, 136.3, 131.4, 130.6, 129.6, 128.8, 128.6, 127.8, 127.6, 126.6, 126.3, 125.5, 125.3, 124.2, 124.1, 114.5, 114.2, 106.7, 106.4, 62.0, 56.8. MS $C_{29}H_{34}N_2O_5$: calcd 490.25, obsd $[M + Na]^+ = 513.34$.



Scheme 4.35. Synthesis of **143**.

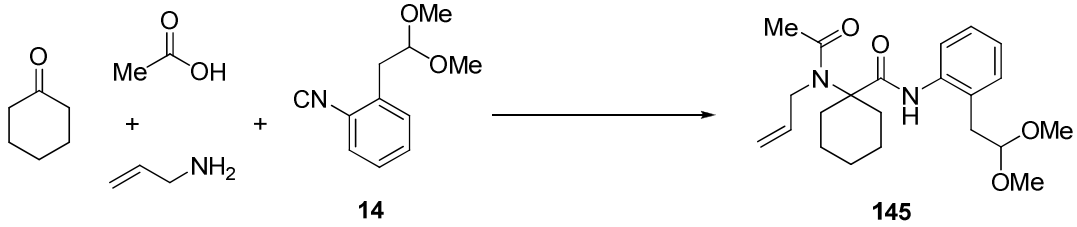
(143) ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotomers: δ 9.12-8.92 (m, 1H), 7.68-7.60 (m, 1H), 7.35-6.72 (m, 12H), 5.20-5.02 (m, 1H), 4.72-4.42 (m, 2H), 3.80-3.75 (m, 3H), 3.43-3.29 (m, 6H), 3.01-2.31 (m, 4H), 2.16-1.90 (m, 2H), 1.33-1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 167.2, 166.6, 159.8, 159.1, 141.3, 140.7, 140.4, 136.7, 136.4, 136.0, 131.3, 130.3, 129.7, 128.8, 128.7, 128.6, 127.6, 126.5, 126.4, 125.9, 125.5, 124.6, 124.5, 114.5, 114.2, 106.7, 106.6, 61.0, 55.5, 54.6, 54.1, 54.0, 36.7, 36.6, 35.9, 32.8, 32.7, 32.3, 31.7, 30.5. MS $C_{30}H_{33}F_3N_2O_5$: calcd 558.23, obsd $[M + Na]^+$ = 581.31.



Scheme 4.36. Synthesis of **144**.

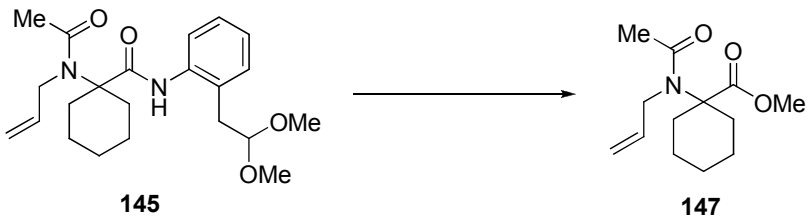
(144) ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotomers: δ 8.52, 8.35 (s, 1H), 8.15-8.13 (m, 1H), 7.51-7.47 (m, 2H), 7.31-7.16 (m, 6H), 7.07-7.03 (m, 1H), 6.90 (d, *J* =

8.6 Hz, 2H), 6.58-6.43 (m, 3H) 5.84 (t, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 15.5 Hz, 1H), 4.30 (d, *J* = 15.5 Hz, 1H), 3.58, 3.52 (s, 3H), 2.75-2.67 (m, 1H), 2.61-2.54 (m, 1H), 2.45-2.32 (m, 1H), 2.19-2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 163.3, 159.4, 140.9, 135.6, 130.8, 130.2, 129.1, 128.9, 128.7, 127.0, 126.5, 125.1, 125.0, 124.2, 120.7, 116.9, 113.9, 110.1, 55.2, 53.1, 48.4, 32.1, 30.5. MS $C_{27}H_{26}N_2O_3$: calcd 426.19, obsd $[M+H]^+$ = 427.07.



Scheme 4.37. Synthesis of **145**.

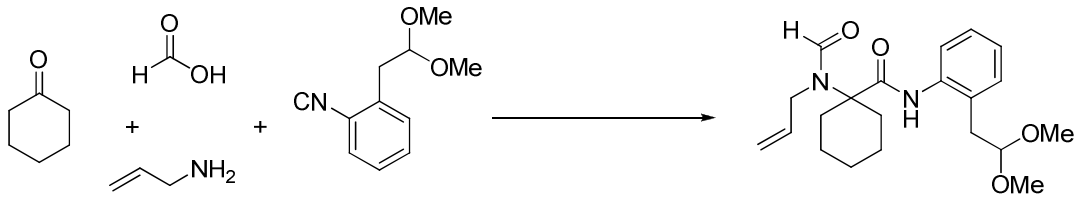
(145) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.22-7.01 (m, 3H), 5.98-5.89 (m, 1H), 5.33 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.44-4.41 (m, 1H), 4.09 (d, *J* = 4.9 Hz, 2H), 3.38 (s, 6H), 2.96 (d, *J* = 5.5 Hz, 2H), 2.50 (d, *J* = 10.7 Hz, 2H), 2.11 (s, 3H), 1.83-1.64 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.2, 137.3, 135.7, 131.0, 128.9, 127.4, 125.2, 124.8, 117.2, 107.5, 65.9, 54.9, 47.7, 36.6, 33.5, 25.9, 24.1, 23.1. MS $C_{22}H_{32}N_2O_4$: calcd 388.24, obsd $[M + Na]^+$ = 411.30.



145 **147**

Scheme 4.38. Synthesis of **147**.

(147) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92-5.83 (m, 1H), 5.45-5.40 (m, 1H), 5.26-5.22 (m, 1H), 3.99-3.97 (m, 2H), 3.69 (s, 3H), 2.28 (d, *J* = 12.0 Hz, 2H), 2.06 (s, 3H), 1.68-1.42 (m, 6H), 1.24-1.11 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 171.6, 135.1, 117.0, 64.5, 52.0, 47.0, 32.7, 25.6, 23.1, 22.8. MS $C_{13}H_{21}NO_3$: calcd 239.15, obsd $[M + H]^+$ = 240.01.

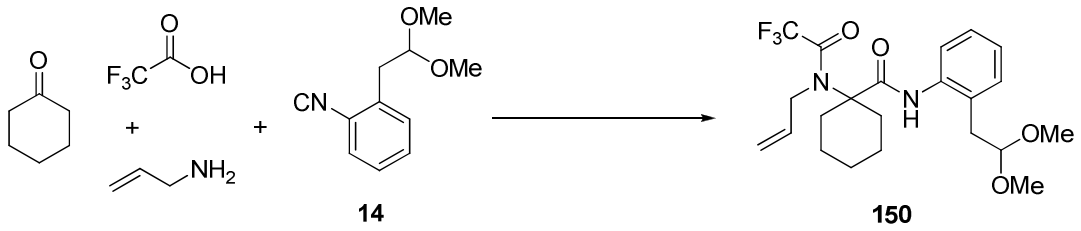


14 **149**

Scheme 4.39. Synthesis of **149**.

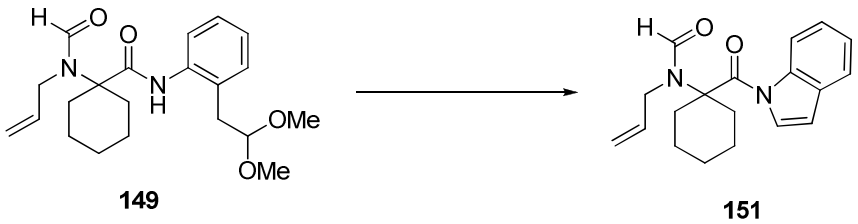
(149) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br, 1H), 8.57 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.26-7.06 (m, 3H), 5.91-5.81 (m, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.42 (t, *J* = 5.4 Hz, 1H), 3.99 (d, *J* = 6.2 Hz, 2H), 3.37 (s, 6H), 2.82 (d, *J* = 5.4 Hz, 2H), 2.2-2.22 (m, 2H), 2.05-1.99 (m, 2H), 1.69-1.46 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 162.4, 136.5, 134.0, 131.3, 128.6, 127.8, 125.5, 124.4, 117.7,

106.9, 66.8, 54.6, 45.6, 37.0, 33.4, 25.4, 22.3. MS $C_{21}H_{30}N_2O_4$: calcd 374.22, obsd $[M + Na]^+$ = 397.28.



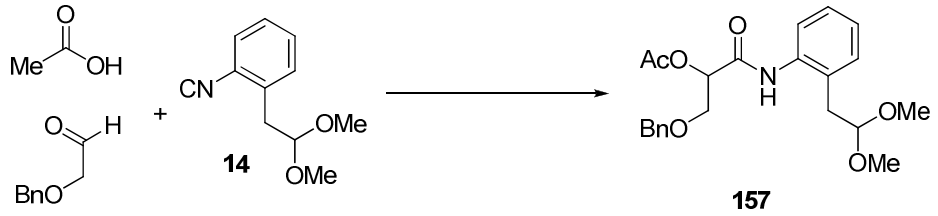
Scheme 4.40. Synthesis of **150**.

(150) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.27-7.06 (m, 3H), 6.00-5.90 (m, 1H), 5.34 (d, *J* = 17.0 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 4.49-4.45 (m, 1H), 4.25 (d, *J* = 4.9 Hz, 2H), 3.41-3.40 (m, 6H), 3.00-2.98 (m, 2H), 2.61-2.57 (m, 2H), 1.87-1.64 (m, 6H), 1.37-1.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.7, 136.9, 135.6, 131.2, 129.2, 127.6, 125.3, 118.1, 107.2, 68.3, 54.5, 46.79 46.76, 36.5, 32.5, 25.7, 23.0. MS $C_{22}H_{29}F_3N_2O_4$: calcd 442.21, obsd $[M + Na]^+$ = 465.26.



Scheme 4.41. Synthesis of **151**.

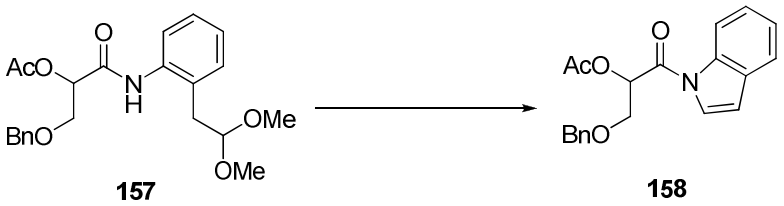
(151) ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotomers: δ 8.62-8.47 (m, 1H), 8.52, 8.10 (s, 1H), 7.56-7.24 (m, 4H), 6.60-6.52 (m, 1H), 6.01-5.80 (m, 1H), 5.43-5.34 (m, 1H), 5.23-5.08 (m, 1H), 4.15-4.12 (m, 1H), 4.05-4.02 (m, 1H), 2.62-2.52 (m, 2H), 2.02-1.63 (m, 6H), 1.36-1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 163.7, 162.2, 136.8, 133.2, 129.7, 125.8, 125.5, 124.9, 124.4, 123.7, 121.1, 120.6, 119.8, 118.8, 11.7, 117.3, 110.0, 108.5, 68.3, 65.8, 48.4, 45.3, 35.5, 33.2, 25.6, 25.3, 23.1, 22.8. MS $C_{19}H_{22}N_2O_2$: calcd 310.17, obsd $[M + NH^4]^+$ = 328.01.



Scheme 4.42. Synthesis of **157**.

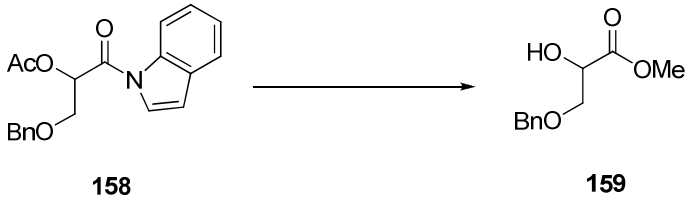
(157) Benzyloxyacetaldehyde (0.211 mL, 1.5 mmol) was stirred in CH_2Cl_2 (3 mL) then acetic acid (0.086 mL, 1.5 mmol) and isocyanide **14** (0.287g, 1.5 mmol) were added and the reaction was allowed to stir at room temperature for 16 hrs. The reaction was concentrated and purified by column chromatography (4:1 to 2:3 hexanes:EtOAC) to afford **157** (0.588g, 98%) as a golden oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.34-7.10 (m, 8H), 5.49 (dd, *J* = 3.1, 5.1 Hz, 1H), 4,58 (d, *J* = 4.4 Hz, 2H), 4.40 (t, *J* = 5.5 Hz, 1H), 4.00 (dd, *J* = 5.1, 10.9 Hz, 1H), 3.92 (dd, *J* = 3.1, 10.9 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.90 (dd, *J* = 5.5, 14.0 Hz, 1H), 2.81 (dd, *J* = 5.5, 14.0 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 166.5, 138.0, 136.2,

131.2, 128.6, 128.5, 128.0, 127.9, 127.8, 125.5, 124.4, 107.5, 73.9, 73.6, 69.9, 55.0, 54.9, 37.0, 21.2. MS $C_{22}H_{27}NO_6$: calcd 401.18, obsd $[M + Na]^+ = 424.25$.



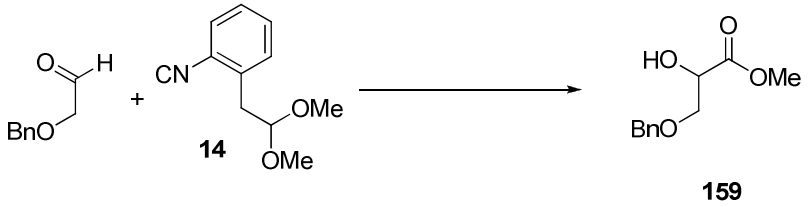
Scheme 4.43. Synthesis of **158**.

(158) CSA (0.016 g, 0.07 mmol) was added to **157** (0.141g, 0.35 mmol) in benzene (4 mL) and the reaction was heated to 60 ˚C. After 2.5 hrs the reaction was removed from heat and washed with aq. NaHCO3 (5 mL) and brine (5 mL). After drying over Na_2SO_4 the reaction was concentrated to afford pure **158** (0.109g, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.2 Hz, 1H), 7.58-7.20 (m, 9H), 6.65 (d, *J* = 3.8 Hz, 1H), 5.88 (t, *J* = 5.5 Hz, 1H) 4.57 (s, 2H), 3.95 (d, *J* = 5.5 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.6, 137.3, 136.0, 130.5, 128.7, 128.2, 127.9, 125.7, 124.5, 124.4, 121.1, 117.0, 110.5, 73.8, 72.2, 68.9, 20.8. MS $C_{20}H_{19}NO_4$: calcd 337.13, obsd $[M + Na]^+ = 337.99$.



Scheme 4.44. Synthesis of **159**.

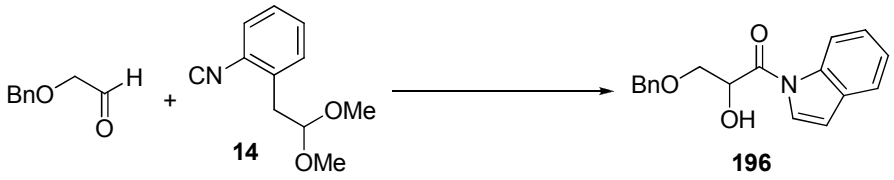
(159) From **158**: The starting material **158** (0.051g, 0.15 mmol) was stirred in methanol (3 mL) then 1N aq. NaOH (0.0045 mL, 0.005 mmol) was added. After stirring for 24 hours the quenched with aq. NH_4Cl (1 mL) then concentrated. Diluted with brine and extracted with EtOAC (2 x 5 mL). The combined organic portions were then dried over Na_2SO_4 and concentrated. Purified by preparative TLC (2:1 hexanes:EtOAc) to recover **159** (0.029g, 91%) as a colorless oil.



Scheme 4.45. One-pot synthesis of **159**.

One-pot conversion of aldehyde to one-carbon extended α-hydroxyester (Preparation of **159**): Water (0.0036 mL, 0.20 mmol), CSA (0.0046g, 0.02 mmol) and then isocyanide **14** (0.0191g, 0.10 mmol) were added to benzyloxyacetaldehyde (0.0162 mL, 0.11 mmol) in CH_2Cl_2 (1 mL) and the reaction progress was monitored by TLC (1:1 hexanes:EtOAc). After about 6 hrs, when conversion of all material the *N*-acylindole intermediate was complete, methanol (1 mL) and triethylamine (0.0418 mL, 0.30 mmol) were added and there action was allowed to stir overnight. After 16 hours the reaction was concentrated and purified by preparatory TLC (2:1 hexanes:EtOAc) to afford **159** (0.0198g, 94%) as a colorless oil. (^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.61

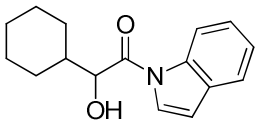
(d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.33 (br, 1H), 3.79 (s, 3H), 3.75 (d, *J* = 3.4 Hz, 2H), 3.13, (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.3, 137.9, 128.7, 128.0, 127.9, 73.7, 71.5, 71.1, 52.9. HRMS $C_{11}H_{14}O_4$: $[M + Na]^+$ = calcd 233.0784, obsd 233.0788.



Scheme 4.46. One-pot synthesis of **196**.

General Procedure for the Brønsted-acid catalyzed Passerini-type reaction (Preparation of **196**): Water (0.0036 mL, 0.20 mmol), CSA (0.0046g, 0.02 mmol) and then isocyanide **14** (0.0191g, 0.10 mmol) were added to benzyloxyacetaldehyde (0.0162 mL, 0.11 mmol) in CH_2Cl_2 (1 mL) and the reaction progress was monitored by TLC (1:1 hexanes:EtOAc). When the reaction was completed, after 6 hrs, it was diluted with CH_2Cl_2 (5 mL) then washed with aq. $NaHCO_3$ (5 mL) and brine (5 mL). After drying over Na_2SO_4 the reaction was concentrated and purified by preparatory TLC (3:1 hexanes:EtOAc) to afford **196** as a golden oil (0.0274g, 93%). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.42-7.16 (m, 8H), 6.64 (d, *J* = 3.8 Hz, 1H) 5.04-5.01 (m, 1H), 4.55 (d, *J* = 3.8 Hz, 2H), 3.84 (d, *J* = 3.7 Hz, 2H) 3.74 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.3, 137.5, 136.0, 130.5, 128.7,

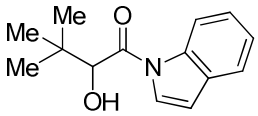
128.1, 127.8, 125.8, 124.7, 124.3, 121.2, 117.0, 110.6, 73.7, 72.2, 70.8. HRMS $C_{18}H_{17}NO_3$: $[M + Na]^+$ = calcd 318.1101, obsd 318.1104.



203

Figure 4.5. Synthesis of **203**.

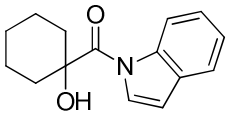
(203) ^{1}H NMR (400MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H) 7.42-7.30 (m, 3H), 6.71 (d, *J* = 3.8 Hz, 1H), 4.72 (dd, *J* = 3.0, 7.7 Hz, 1H) 3.39 (d, *J* = 7.7 Hz, 1H) 1.83-1.07 (m, 11H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.5, 135.9, 130.5, 125.8, 124.6, 124.0, 121.3, 116.9, 110.6, 74.9, 43.1, 30.2, 26.6, 26.1, 26.0, 25.8. HRMS $C_{16}H_{19}NO_2$: $[M + H]^+$ = calcd 258.1489, obsd 258.1493.



204

Figure 4.6. Synthesis of **204**.

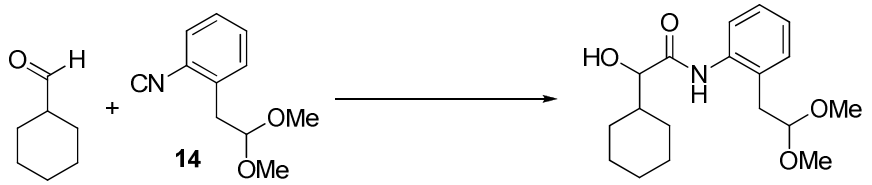
(204) ^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.2 Hz, 1H), 7.61-7.57 (m, 1H), 7.47 (d, *J* = 3.9 Hz, 1H), 7.42-7.29 (m, 2H), 6.68 (d, *J* = 3.9 Hz, 1H), 4.61 (s, 1H), 3.35 (s, 1H), 1.02 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.7, 135.8, 130.8, 125.6, 125.2, 124.6, 121.3, 117.1, 110.0,77.4, 37.1, 26.3. HRMS $C_{14}H_{17}NO_2$: $[M + Na]^+$ = calcd 254.1152, obsd 254.1156.



205

Figure 4.7. Synthesis of **205**.

(205) ^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.2 Hz, 1H), 8.29 (d, *J* = 3.9 Hz, 1H), 7.57-7.53 (m, 1H), 7.36-7.24 (m, 2H), 6.58 (d, *J* = 3.9 Hz, 1H), 2.56 (s, 1H), 2.14-2.02 (m, 2H), 1.98-1.88 (m, 2H), 1.78-1.65 (m, 4H), 1.43-1.26 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 175.1, 136.8, 130.1, 127.6, 125.2, 124.1, 120.7, 117.3, 108.7, 77.1, 35.8, 25.4, 21.6. HRMS $C_{15}H_{17}NO_2$: $[M + Na]^+$ = calcd 266.1152, obsd 266.1154.

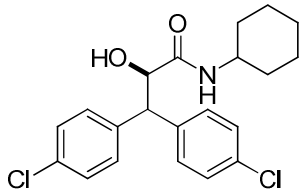


209

Scheme 4.47. Synthesis of **209**.

General procedure for the stereoselective Passerini-type reaction (Preparation of **209**): Water (0.0036 mL, 0.20 mmol), isocyanide **14** (0.0191 g, 0.10 mmol) and cyclohexanecarboxaldehyde (0.0133 mL, 0.11 mmol) were stirred in CH_2Cl_2 (1 mL) at rt then the desired catalyst is added. In this case (*R*)-**207** (95% purity, 0.0024g, 0.003 mmol) was added and the reaction was allowed to stir for 18 hrs. It was then diluted with

CH_2Cl_2 (5 mL) and washed with aq. $NaHCO_3$ (5 mL) and brine (5 mL). After drying over Na_2SO_4 the reaction was concentrated and purified by preparatory TLC (1:1 hexanes:EtOAc) to afford **209** as a white solid (0.020g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.89 (dd, *J* = 0.7, 8.0 Hz, 1H), 7.27 (dt, *J* = 1.6, 7.4 Hz, 1H), 7.18 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.10 (dt, *J* = 1.1, 7.4 Hz, 1H), 4.47 (t, *J* = 5.3 Hz, 1H), 4.07 (d, *J* = 2.4 Hz, 1H), 3.414 (s, 3H) 3.409 (s, 3H), 3.04 (br, 1H), 2.90 (d, *J* = 5.3 Hz, 2H), 1.90-1.58 (m, 6H), 1.42-1.09 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 136.5, 131.4, 128.1, 127.9, 125.2, 123.9, 106.8, 76.6, 54.7, 54.6, 42.6, 37.1, 29.8, 26.7, 26.3, 26.2. MS $C_{18}H_{27}NO_4$: calcd 321.19, obsd $[M - H]^-$ = 320.25. The enantiomeric ratio (59:41) was determined by chiral HPLC: major enantiomer – 1.623 min.; minor enantiomer – 1.884 min. Heptane and MeOH/EtOH (50:50); 2-70% Heptane in 5 min.; 5.5 min. method; 2.5 mL/min. Chiralpak IB 4.6x100 mm.

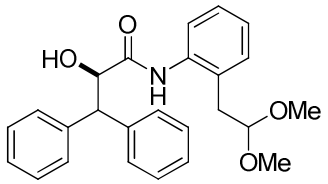


210

Figure 4.8. Synthesis of **210**.

(210) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (m, 8H), 6.19 (d, *J* = 8.4 Hz, 1H), 4.63 (br, 1H), 4.60 (d, *J* = 3.5 Hz, 1H), 3.67-3.57 (m, 1H), 3.00 (br, 1H), 1.76-1.51 (m, 5H), 1.34-0.78 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 139.806, 139.798, 137.2, 133.4, 133.1, 131.3, 130.1, 129.0, 128.8, 74.7, 52.5, 48.1, 32.9, 25.6, 24.9, 24.805,

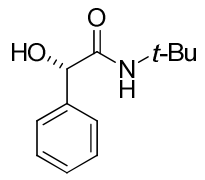
24.800. MS $C_{21}H_{23}Cl_2NO_2$: calcd 391.11, obsd [M + H]+ = 392.15. The enantiomeric ratio (60:40) was determined by chiral HPLC: major enantiomer – 2.256 min.; minor enantiomer – 2.100 min. Heptane and MeOH/EtOH (50:50); 2-70% Heptane in 5 min.; 5.5 min. method; 2.5 mL/min. Chiralpak IA 4.6x100 mm.



211

Figure 4.9. Synthesis of **211**.

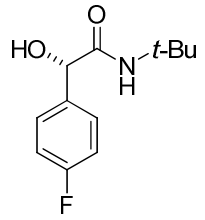
(211) ^{1}H NMR (300MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.39-7.04 (m, 11H), 4.93 (dd, *J* = 3.2, 6.4 Hz, 1H), 4.84 (d, *J* = 2.6 Hz, 1H), 4.35 (t, *J* = 4.9 Hz, 1H), 3.32 (s, 3H), 3.25 (s, 3H), 3.18 (d, *J* = 6.4 Hz, 1H), 2.65 (dd, *J* = 4.9, 13.9 Hz, 1H), 2.53 (dd, *J* = 5.5, 13.9 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.4, 141.8, 139.2, 136.3, 131.3, 130.1, 128.9, 128.84, 128.83, 128.71, 128.70, 128.54, 128.53, 127.7, 127.3, 127.0, 125.3, 124.1, 106.5, 75.5, 54.7, 54.0, 53.7, 36.6. HRMS $C_{25}H_{27}NO_4$: [M + Na]+ = calcd 428.1832, obsd 428.1838. The enantiomeric ratio (67:33) was determined by chiral HPLC: major enantiomer – 2.246 min.; minor enantiomer – 2.391 min. Heptane and MeOH/EtOH (50:50); 2-70% Heptane in 5 min.; 5.5 min. method; 2.5 mL/min. Chiralpak IA 4.6x100 mm.



212

Figure 4.10. Synthesis of **212**.

(212) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 5.82 (br, 1H), 4.89 (s, 1H), 3.72 (br, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.1, 129.2, 128.8, 127.1, 74.4, 51.8, 28.9. MS $C_{12}H_{17}NO_2$: calcd 207.13, obsd [M + H]+ = 208.03. The enantiomeric ratio (62:38) was determined by chiral HPLC: major enantiomer – 1.593 min.; minor enantiomer – 1.761 min. Heptane and MeOH/EtOH (50:50); 2-70% Heptane in 5 min.; 5.5 min. method; 2.5 mL/min. Chiralcel OJ-H 4.6x100 mm.

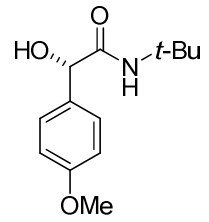


213

Figure 4.11. Synthesis of **213**.

(213) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.09-7.01 (m, 2H), 5.93 (br, 1H), 4.87 (s, 1H), 3.77 (br, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 164.2, 136.0, 128.9, 128.8, 116.2, 115.9, 73.7, 51.8, 28.9. MS $C_{12}H_{16}FNO_5$: calcd

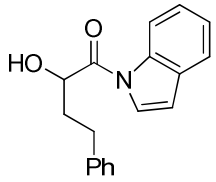
225.12, obsd [M + H]+ = 226.00. The enantiomeric ratio (66:34) was determined by chiral HPLC: major enantiomer – 1.744 min.; minor enantiomer – 1.614 min. Heptane and MeOH/EtOH (50:50); 2-70% Heptane in 5 min.; 5.5 min. method; 2.5 mL/min. Chiralpak IA 4.6x100 mm.



214

Figure 4.12. Synthesis of **214**.

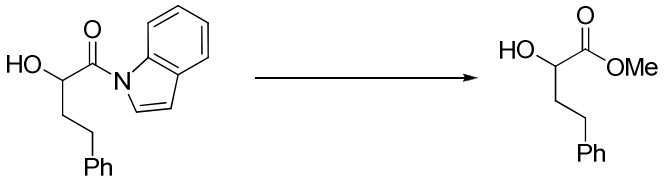
(214) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 6.93-6.87 (m, 2H), 5.80 (br, 1H), 4.85 (s, 1H), 3.81 (s, 3H), 3.63 (br, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 160.0, 134.8, 128.5, 114.5, 74.0, 55.5, 51.7, 28.9. MS $C_{13}H_{19}NO_3$: calcd 237.14, obsd $[M + H]^+$ = 237.92. The enantiomeric ratio (66:34) was determined by chiral HPLC: major enantiomer – 1.664 min.; minor enantiomer – 1.795 min. Heptane and MeOH/EtOH (50:50); 2-70% Heptane in 5 min.; 5.5 min. method; 2.5 mL/min. Chiralpak IA 4.6x100 mm.



215

Figure 4.13. Synthesis of **215**.

(215) ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (br, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.39-7.02 (m, 8H), 6.63 (d, *J* = 3.8 Hz, 1H), 4.81-4.77 (m, 1H) 3.48 (d, *J* = 7.6 Hz, 1H), 2.94-2.90 (m, 2H), 2.22-2.16 (m, 1H), 2.07-1.98 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.9, 140.8, 135.9, 130.5, 129.0, 128.9, 126.6, 125.8, 124.6, 123.6, 121.3, 116.8, 110.9, 69.4, 37.9, 31.4. MS $C_{18}H_{17}NO_2$: calcd 279.13, obsd [M + H]+ = 280.10.

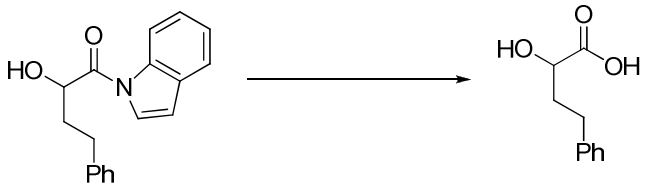


215 **216**

Scheme 4.48. Synthesis of **216**.

(216) Procedure A: 1N aq. NaOH (0.0050 mL, 0.005 mmol) was added to **215** (0.045g, 0.16 mmol) in methanol (3 mL). After 40 minutes the reaction was concentrated and purified by preparatory TLC (3:1 hexanes:EtOAc) to afford **216** (0.026g, 84%) as an oil.

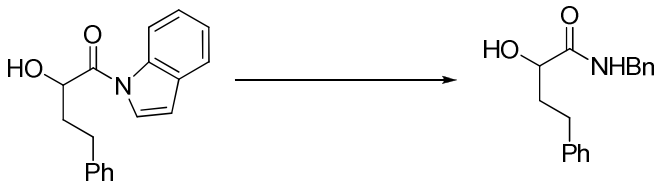
Procedure B: Triethylamine (0.0264 mL, 0.19 mmol) was added to **215** (0.054g, 0.19 mmol) in methanol (3 mL). After 3 hrs the reaction was concentrated and purified by preparatory TLC (3:1 hexanes:EtOAc) to afford **216** (0.031g, 84%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.23-7.18 (m, 3H), 4.22-4.19 (m, 1H), 3.75 (s, 3H), 2.88 (d, *J* = 5.0 Hz, 1H), 2.82-2.72 (m, 2H), 2.16-2.10 (m, 1H), 2.00-1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 141.2, 128.8, 128.7, 126.3, 69.9, 52.8, 36.1, 31.2. MS $C_{11}H_{14}O_3$: calcd 194.09, obsd $[M + H]^+$ = 195.03.



215 **217**

Scheme 4.49. Synthesis of **217**.

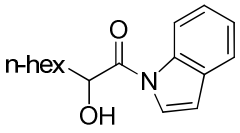
(217) 1N aq NaOH (0.284 mL, 0.28 mmol) was added to **215** (0.061g, 0.22 mmol) and the reaction was allowed to stir. TLC indicated that the methyl ester formed first before converting to the product. After 18 hrs the reaction was concentrated and then purified by acid-base extraction to afford **217** (0.034g, 87%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.27-7.14 (m, 5H), 4.09 (dd, *J* = 4.0, 8.0 Hz, 1H), 2.74 (t, *J* = 8.0 Hz, 2H), 2.09-2.02 (m, 1H), 1.95-1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 141.6, 128.4, 128.34, 128.26, 69.7, 36.2, 31.2. MS $C_{10}H_{12}O_3$: calcd 180.08, obsd $[M - H]^-$ = 179.17.



215 **218**

Scheme 4.50. Synthesis of **218**.

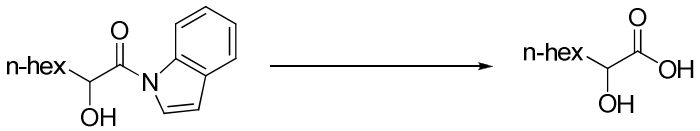
(218) Benzyl amine (0.152 mL, 1.4 mmol) was added to **215** (0.039g, 0.14 mmol) in THF (2 mL) and the reaction was heated to reflux for 4.5 hrs. After cooling the reaction was diluted with EtOAc (5 mL) and washed with 1N aq HCl (2 x 5 mL). The acid washes were back-extracted with EtOAc (5 mL). The combined organic portions were washed with aq $NaHCO_3$ (5 mL) and brine (5 mL) then dried over Na_2SO_4 and concentrated. Purification by preparatory TLC afforded **218** (0.029g, 77%) as a solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.15 (m, 10H), 7.02 (t, *J* = 5.4 Hz, 1H), 4.48-4.33 (m, 2H), 4.14 (dd, *J* = 3.1, 7.9 Hz, 1H), 3.51 (br, 1H), 2.80-2.68 (m, 2H), 2.24-2.11 (m, 1H), 2.04-1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 141.4, 138.1, 129.0, 128.77, 128.75, 128.0, 127.8, 126.3, 71.8, 43.4, 36.7, 31.5. MS $C_{17}H_{19}NO_2$: calcd 269.14, obsd $[M + H]^+ = 270.13$.



220

Figure 4.14. Synthesis of **220**.

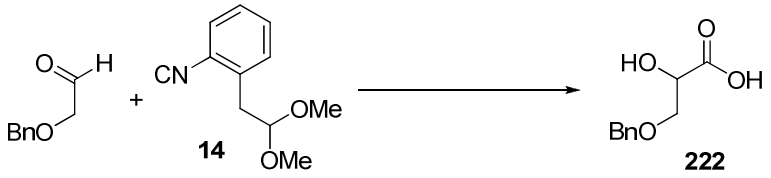
(220) ^{1}H NMR (400MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.45-7.30 (m, 3H) 6.71 (d, *J* = 3.8 Hz, 1H), 4.87 (br, 1H), 3.47 (d, *J* = 6.8 Hz, 1H), 1.96-1.87 (m, 1H), 1.76-1.67 (m, 1H), 1.60-1.47 (m, 2H), 1.40-1.23 (m, 6H), 0.90-0.85 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.1, 135.9, 130.4, 125.8, 124.6, 123.8, 121.3, 116.9, 110.8, 70.6, 36.2, 31.9, 29.2, 25.2, 22.8, 14.3. HRMS $C_{16}H_{21}NO_2$: calcd 259.16, obsd $[M + H]^+$ = 260.13.



220 **221**

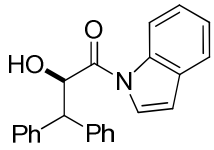
Scheme 4.51. Synthesis of **221**.

(221) 1N aq NaOH (0.203 mL, 0.20 mmol) was added to **220** (0.044 g, 0.17 mmol) in THF (1 mL). After stirring for 2.5 hrs the reacting was diluted with EtOAc (5 mL) then extracted with dilute aq NaOH (2 x 5 mL). The aqueous portions were acidified with citric acid then extracted with EtOAc (2 x 5 mL). Combined organics were washed with brine (5 mL) then dried over Na_2SO_4 and concentrated to afford **221** (0.024g, 89%) as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 4.27 (dd, *J* = 4.2, 7.6 Hz, 1H), 4.01-3.94 (m, 1H), 1.88-1.81 (m, 1H), 1.73-1.66 (m, 1H), 1.50-1.38 (m, 2H), 1.37-1.25 (m, 6H), 0.91-0.85 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 180.3, 70.5, 34.4, 31.8, 29.1, 24.9, 22.8, 14.3. MS $C_8H_{16}O_3$: calcd 160.11, obsd $[M - H]^-$ = 159.17.



Scheme 4.52. Synthesis of **222**.

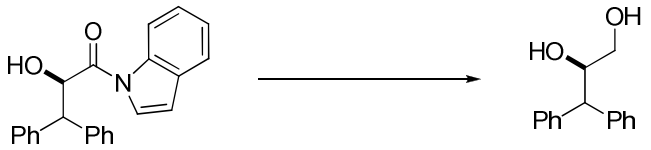
One-pot conversion of aldehyde to one-carbon extended α-hydroxycarboxylic acid (Preparation of **222**): Water (0.0036 mL, 0.20 mmol), CSA (0.0046g, 0.02 mmol) and then isocyanide **14** (0.0191g, 0.10 mmol) were added to benzyloxyacetaldehyde (0.0162 mL, 0.11 mmol) in CH_2Cl_2 (1 mL) and the reaction progress was monitored by TLC (1:1 hexanes:EtOAc). After about 6 hrs, when conversion of all material the *N*-acylindole intermediate was complete, THF (1 mL) and 1N aq. NaOH (0.200 mL, 0.20 mmol) were added and the reaction was allowed to stir for an additional six hours. The reaction was then diluted with H_2O (5 mL) and washed with EtOAc (2 x 5 mL). Combined EtOAc portions were back-extracted with dilute aq. NaOH (5 mL). The combined aqueous portions were then acidified with citric acid and extracted with EtOAc (2 x 5 mL). The combined organics were then washed with brine (5 mL) and dried over Na_2SO_4. Removal of solvents under reduced pressure afforded **222** (0.0125g, 64%) as a clear oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.60 (d, J = 2.5 Hz, 2H), 4.38 (t, J = 4.2 Hz, 1H), 3.80 (dq, J = 4.2, 9.9 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.2, 137.3, 128.8, 128.3, 128.1, 74.0, 71.0, 70.4. HRMS $C_{11}H_{14}O_4$: $[M + Na]^+$ = calcd 219.0628, obsd 219.0631.



223

Figure 4.15. Synthesis of **223**.

(223) ^{1}H NMR (400MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.8 Hz, 1H), 7.62-7.59 (m, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.41-7.22 (m, 9H), 7.05-7.03 (m, 2H), 6.69 (d, *J* = 3.8 Hz, 1H), 5.64 (dd, *J* = 3.1, 8.2 Hz, 1H), 4.54 (d, *J* = 3.3 Hz, 1H), 3.37 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.2, 141.3, 138.0, 129.9, 128.9, 128.8, 128.5, 127.6, 127.3, 125.9, 124.7, 123.7, 121.3, 116.8, 111.0, 73.0, 55.4. HRMS $C_{23}H_{19}NO_2$: $[M + Na]^+$ = calcd 364.1308, obsd 364.1313.



223 **226**

Scheme 4.53. Synthesis of **226**.

(226) **223** (16.2 mg, 0.05 mmol) in 2 mL methanol was treated with $NaBH_4$ (3.6mg, 0.09 mmol). The reaction stirred at reflux for one hour and was then quenched with acetone and concentrated, but not to dryness. Poured into brine (10 mL) and extracted with EtOAc (2 x 10 mL). Purification by preparatory TLC (2:1 hexanes:EtOAc) afforded **226** (7.5 mg, 69%) as a solid. ^{1}H NMR (400MHz, $CDCl_3$) δ

7.42-7.18 (m, 10H), 4.49-4.44 (m, 1H), 4.04 (d, J = 9.6 Hz, 1H), 3.64 (dd, J = 3.0, 11.4 Hz, 1H), 3.47 (dd, J = 6.3, 11.4 Hz, 1H), 2.12 (br, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 141.5, 141.2, 129.2, 129.0, 128.8, 128.4, 127.3, 127.1, 74.2, 64.9, 55.1. HRMS $C_{15}H_{16}O_2$: $[M + Na]^+$ = calcd 251.1043, obsd 251.1044.

J. References and Notes

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Appendix

A. ^{1}H and ^{13}C Spectra

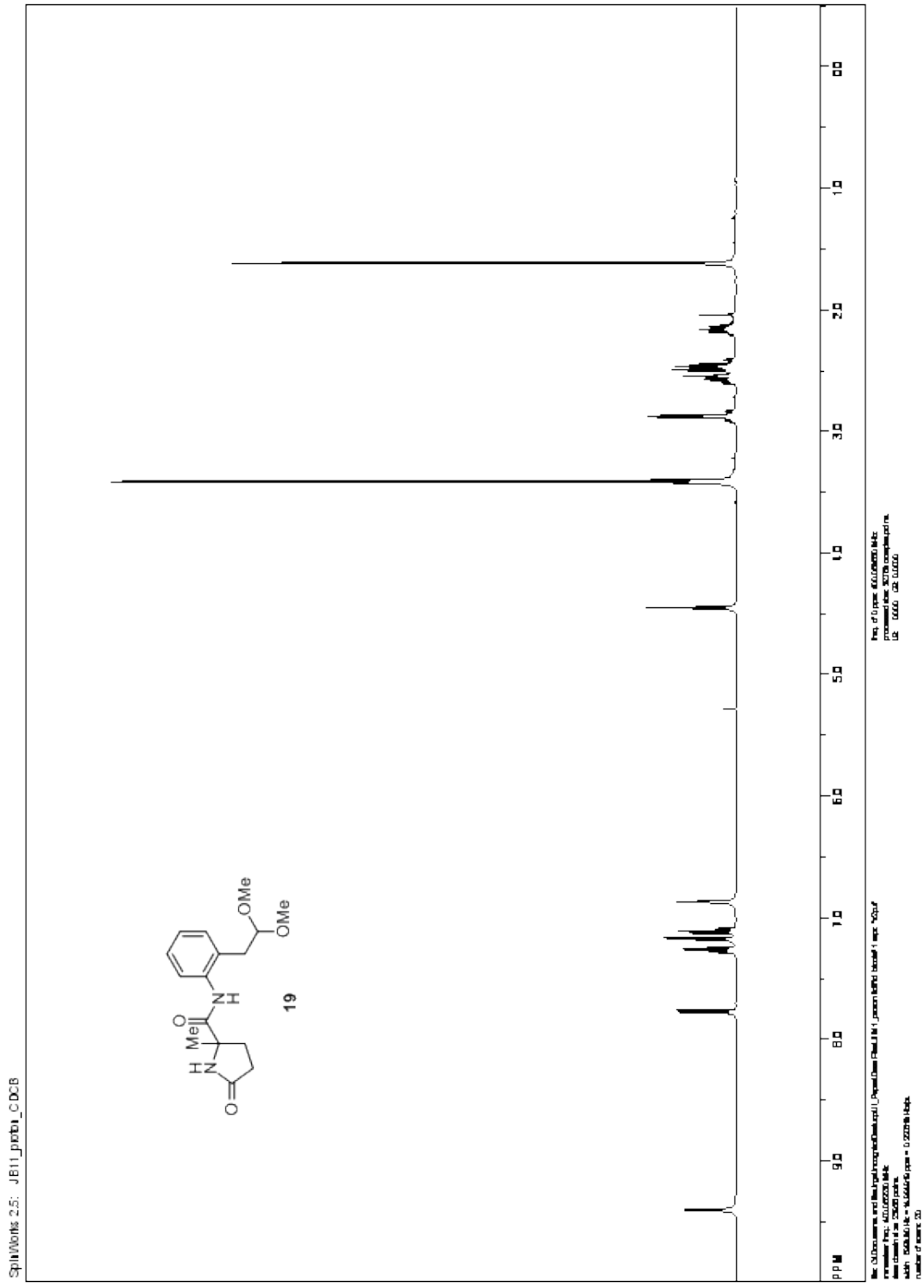

Figure A.1. ^{1}H Spectrum of **19**.

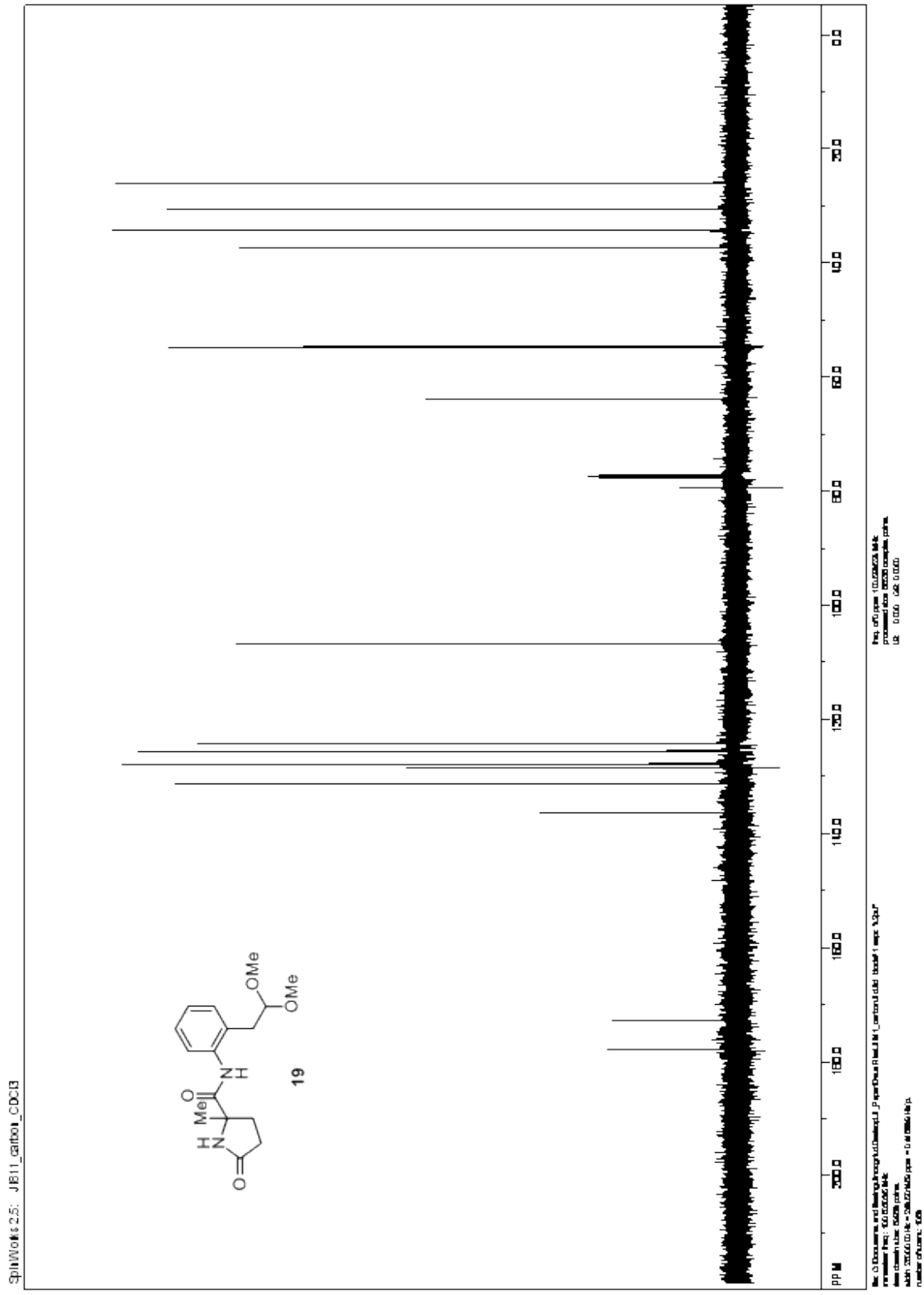

Figure A.2. ^{13}C Spectrum of **19**.

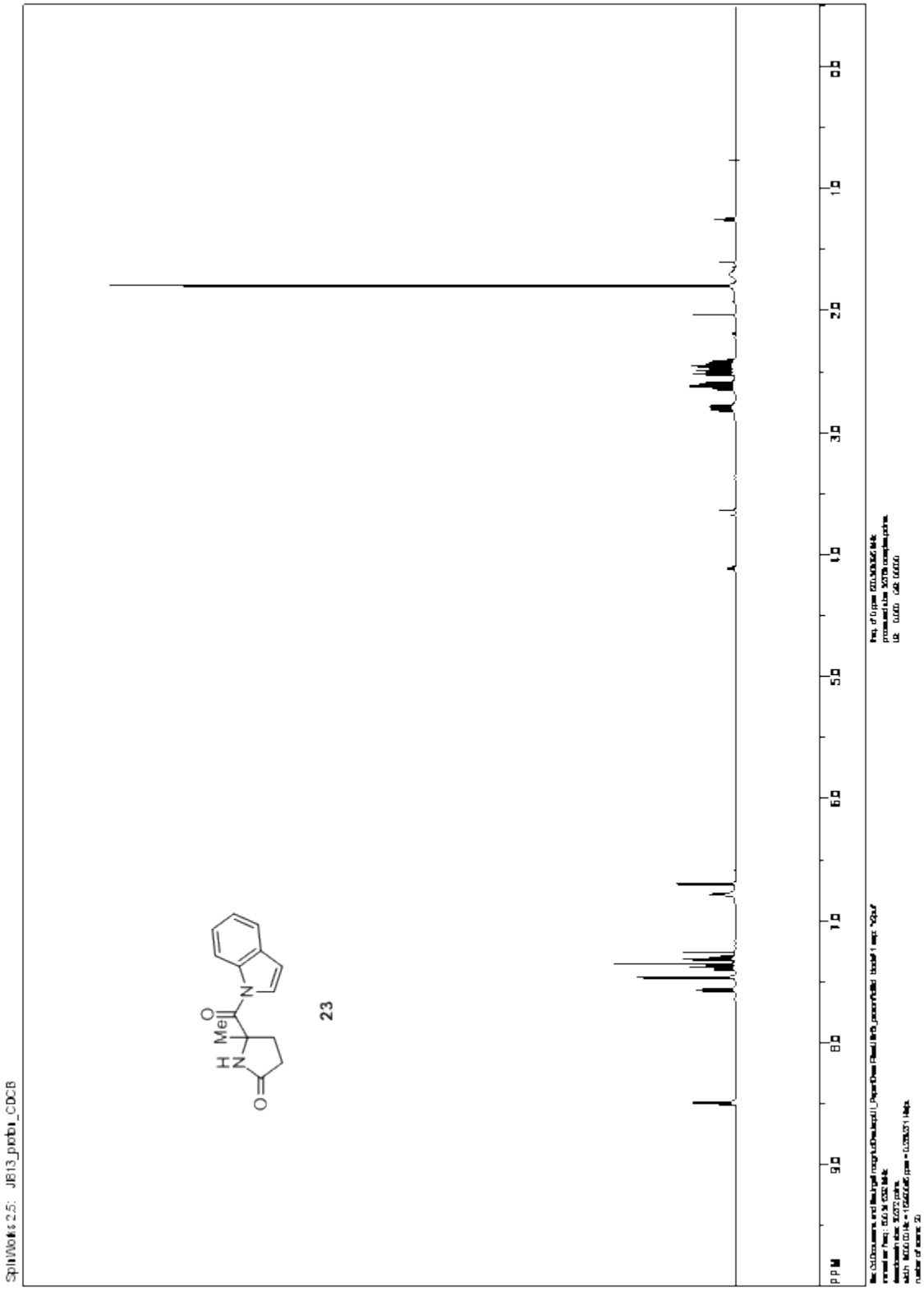

Figure A.3. ^{1}H Spectrum of **23**.

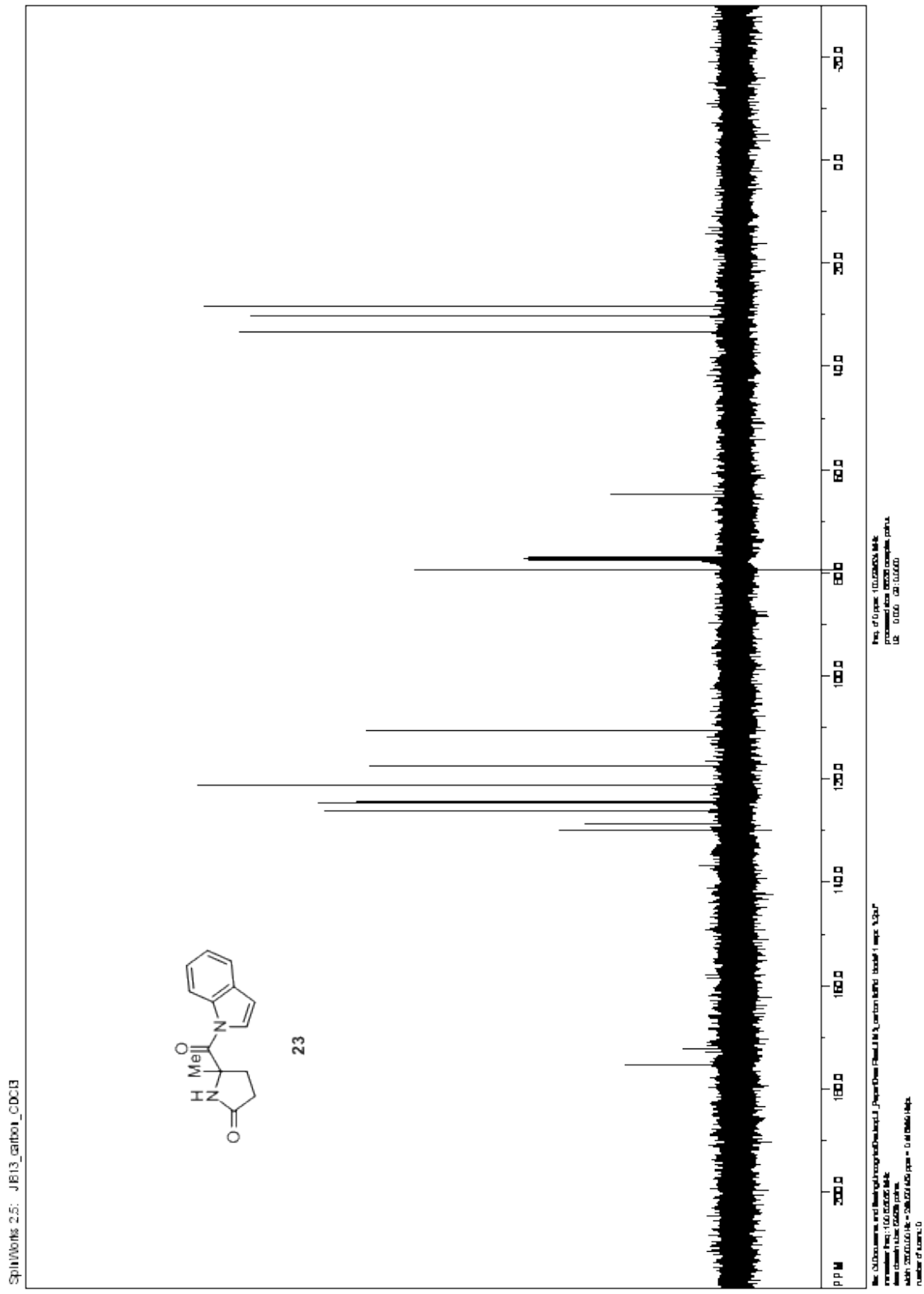

Figure A.4. ^{13}C Spectrum of **23**.

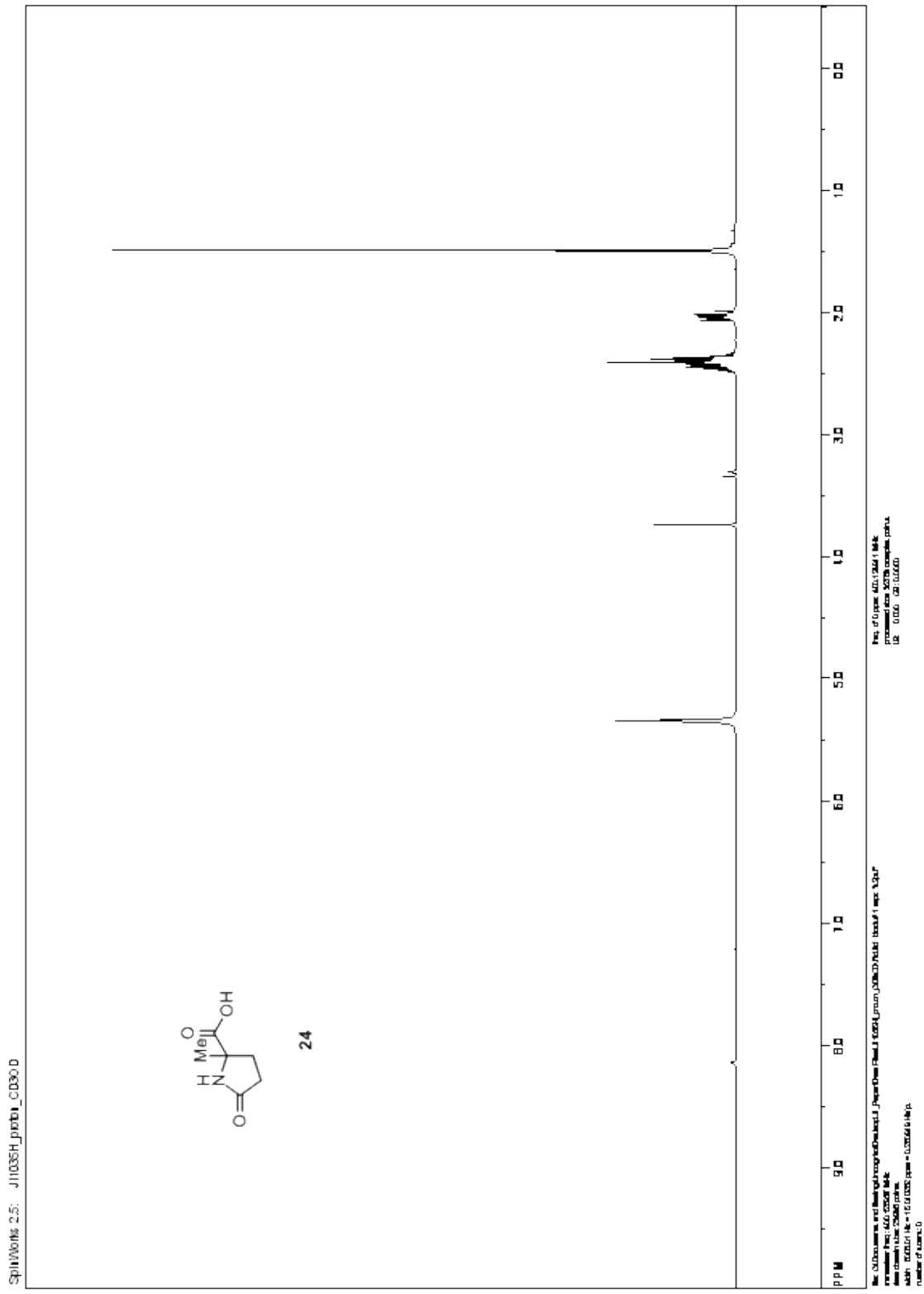

Figure A.5. ^{1}H Spectrum of **24**.

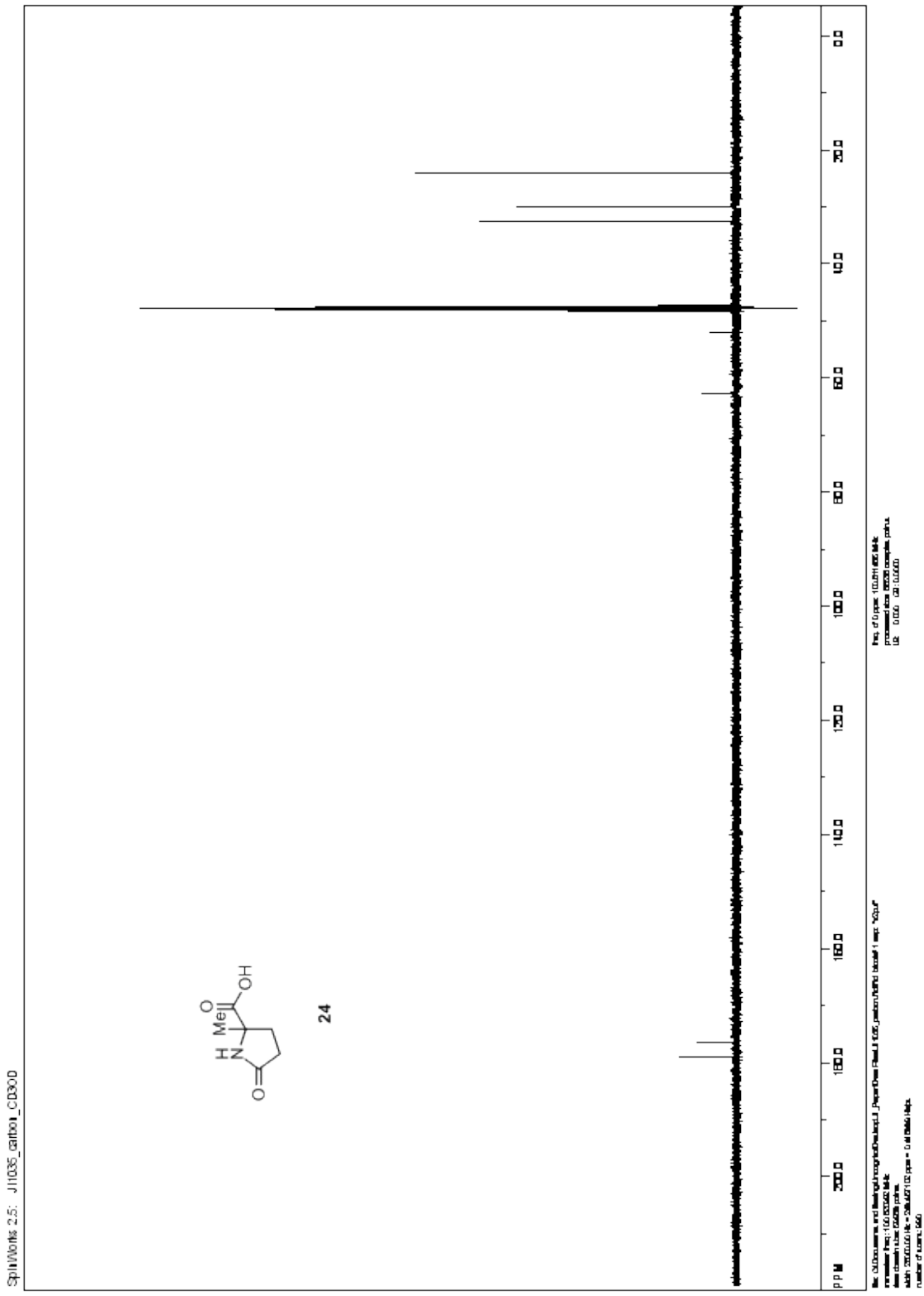

Figure A.6. ^{13}C Spectrum of **24**.

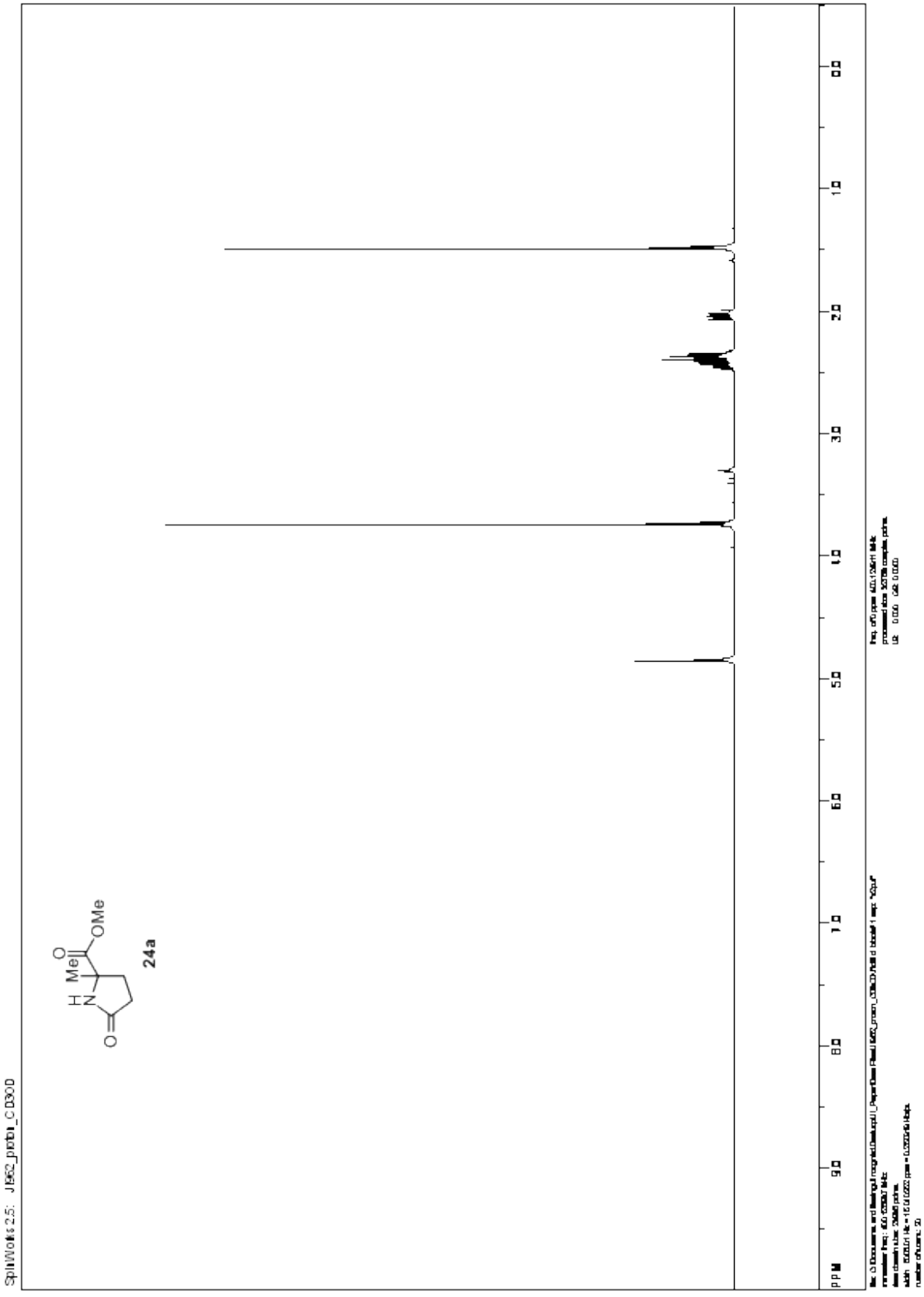

Figure A.7. ^{1}H Spectrum of **24a**.

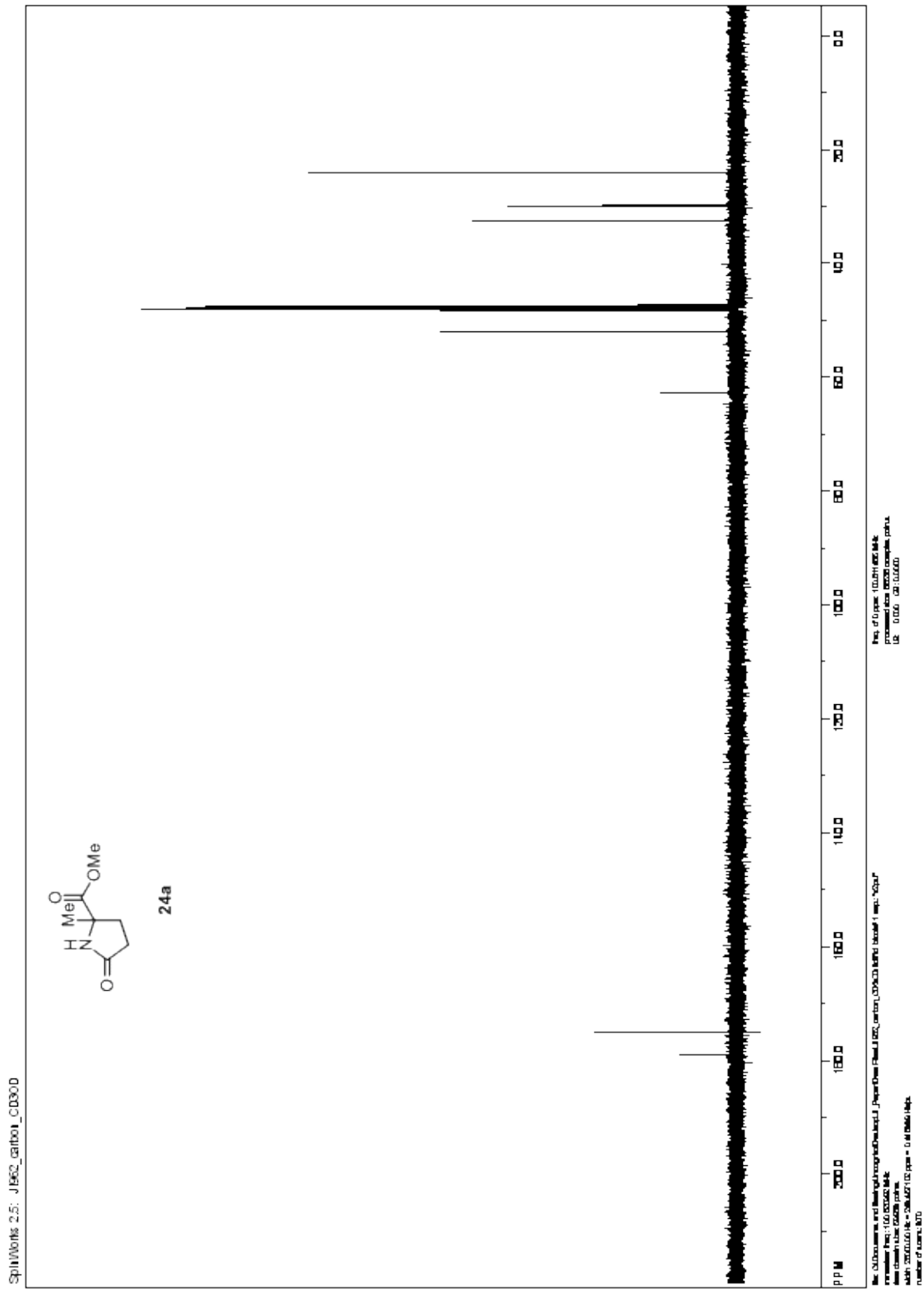

Figure A.8. ^{13}C Spectrum of **24a**.

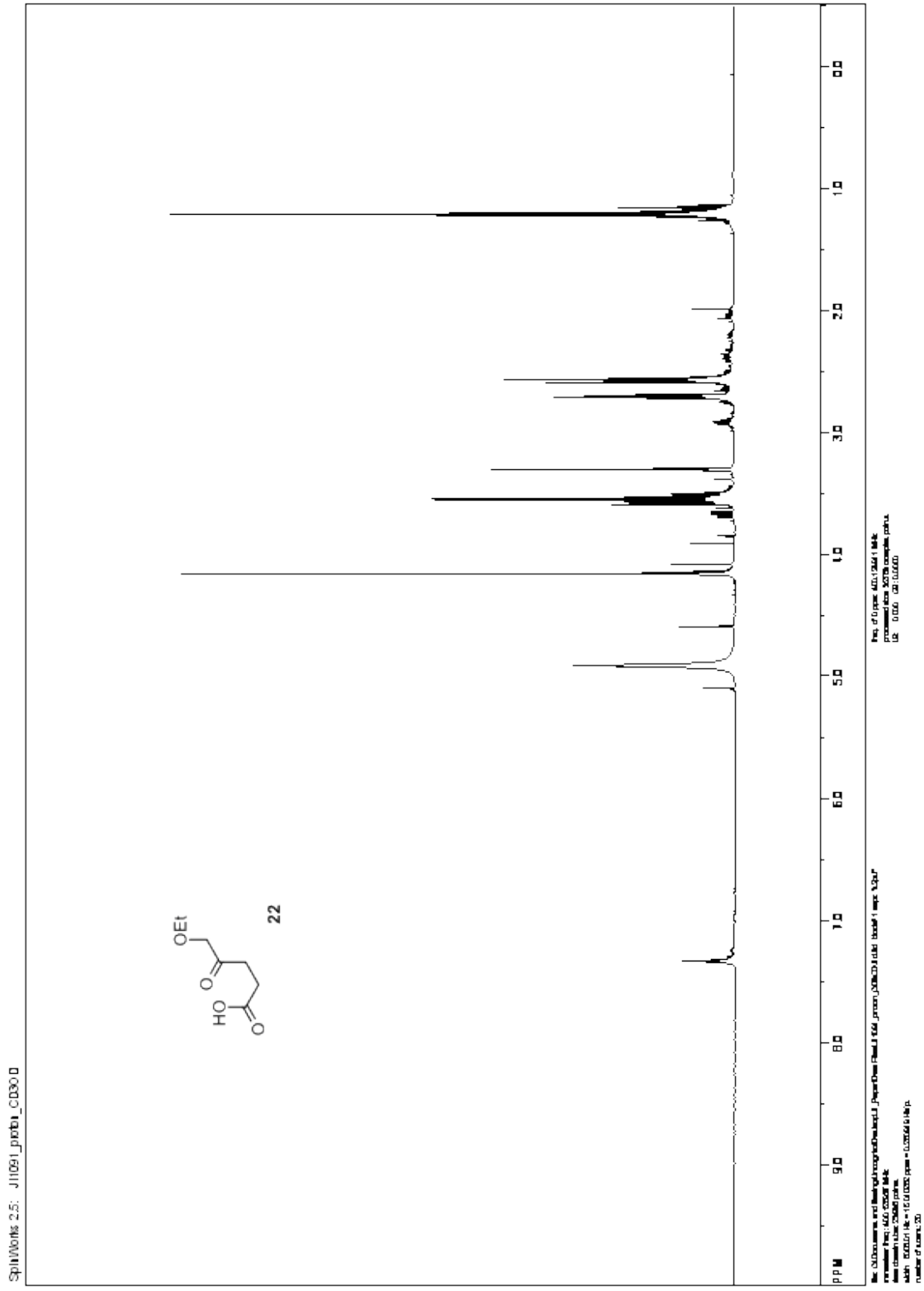

Figure A.9. ^{1}H Spectrum of **22**.

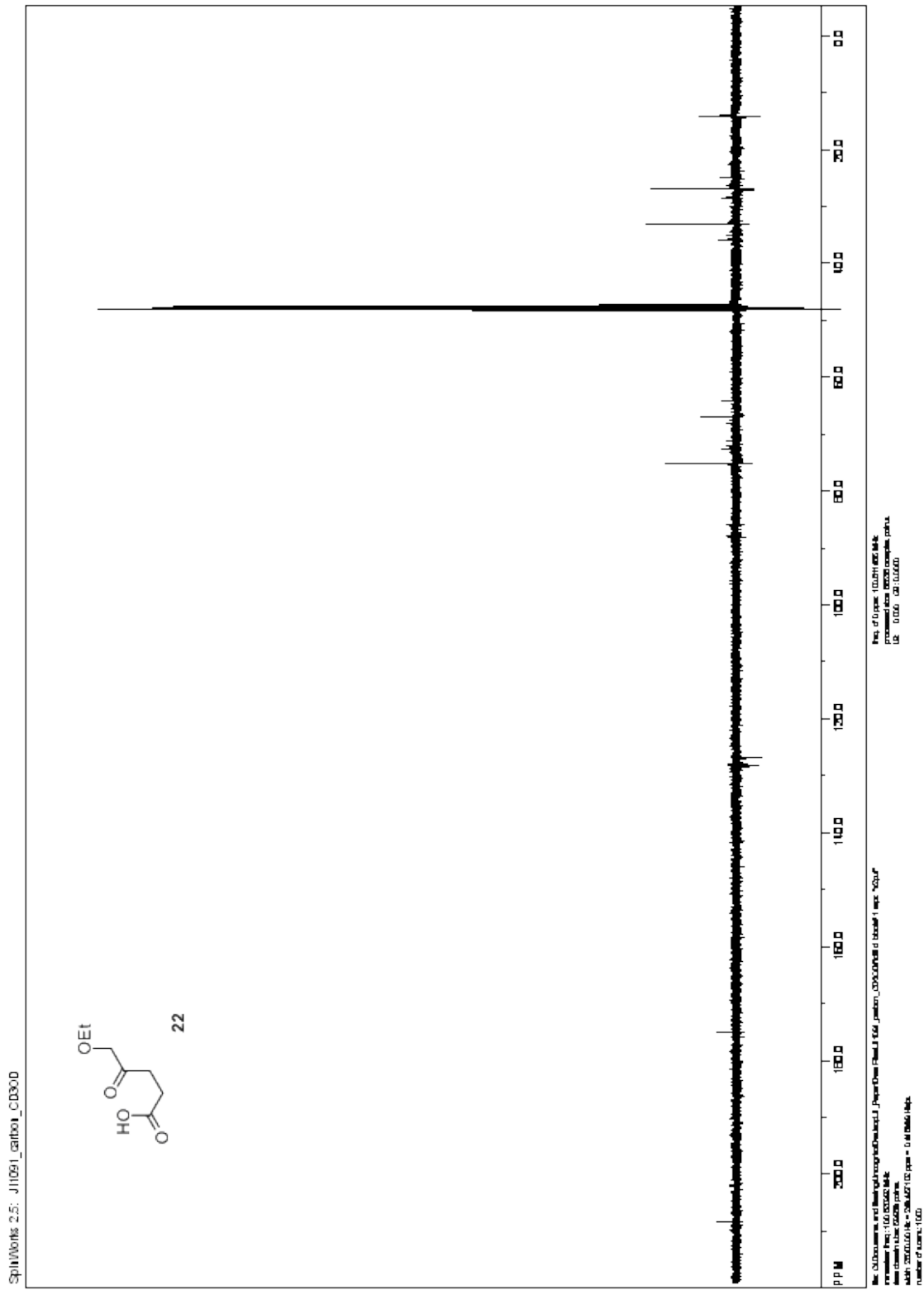

Figure A.10. ^{13}C Spectrum of **22**.

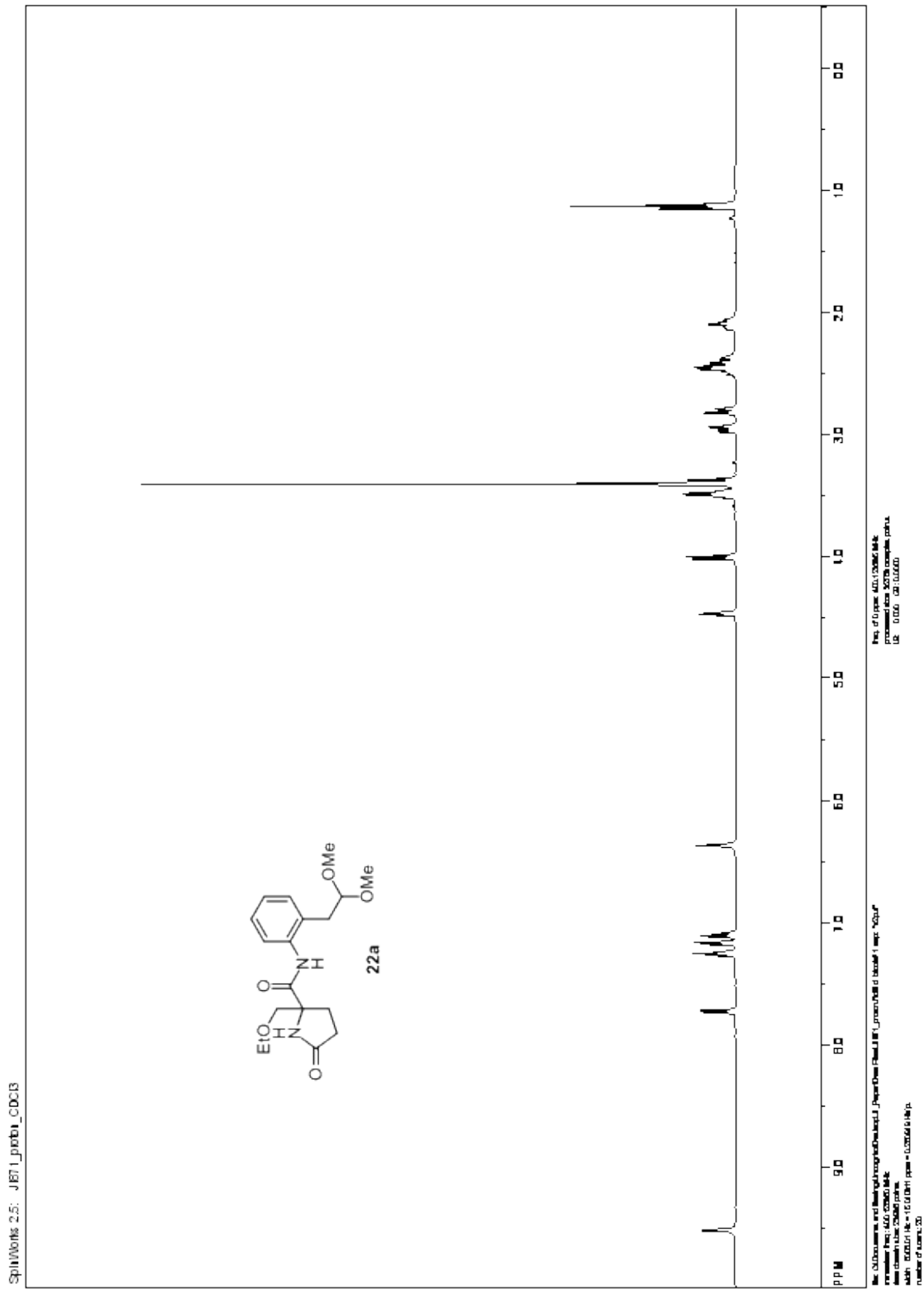

Figure A.11. ^{1}H Spectrum of **22a**.

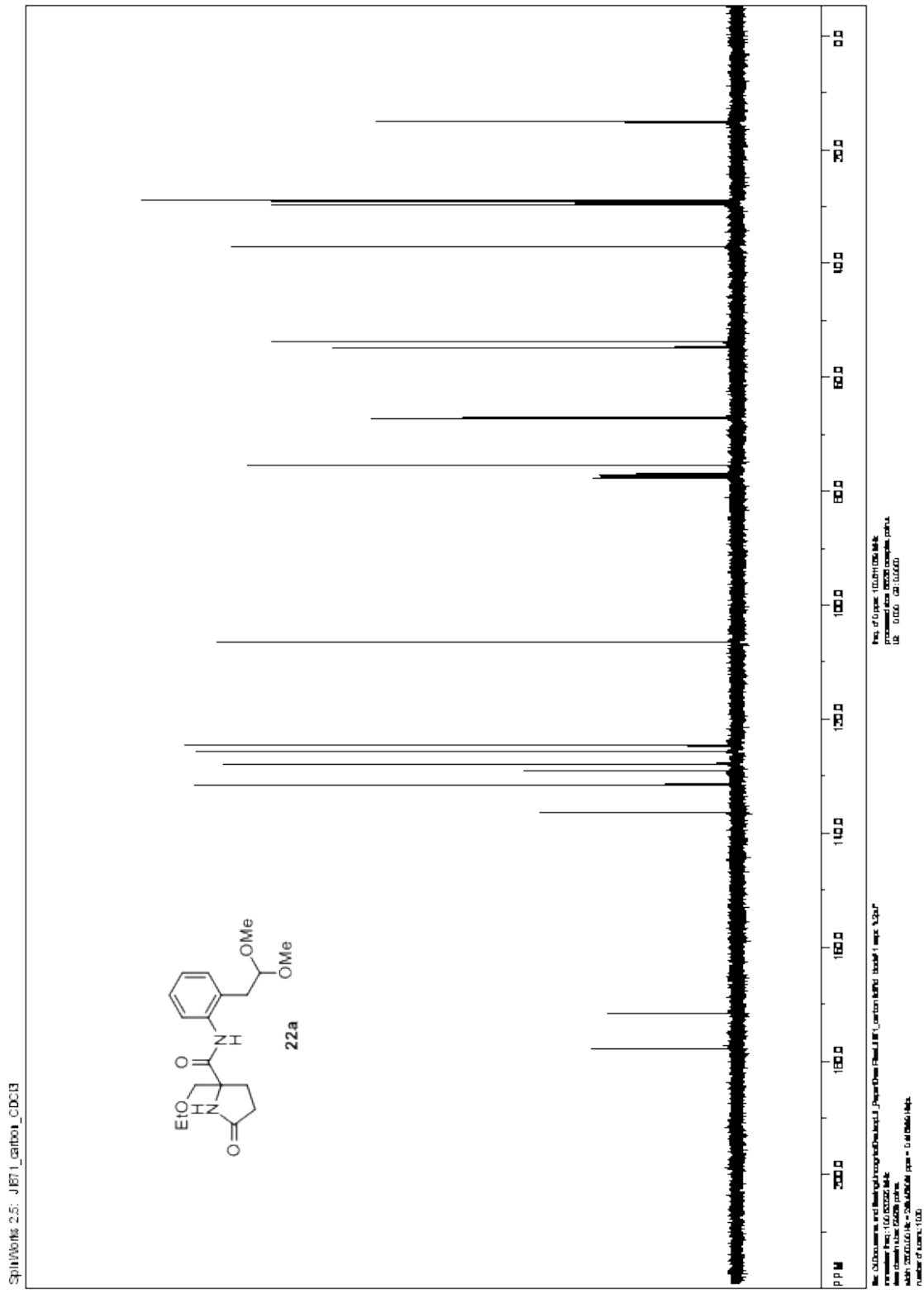

Figure A.12. ^{13}C Spectrum of **22a**.

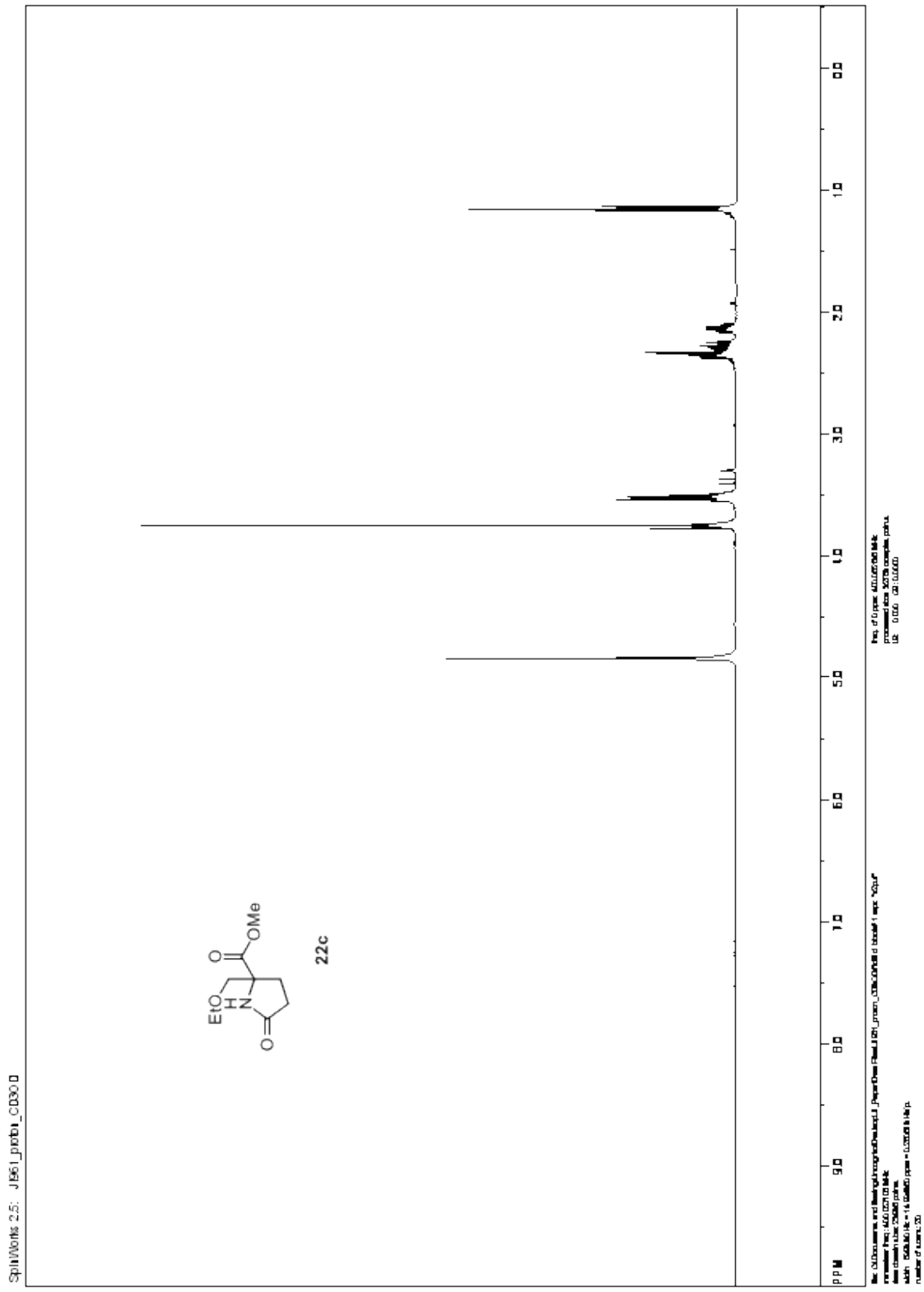

Figure A.13. ^{1}H Spectrum of **22c**.

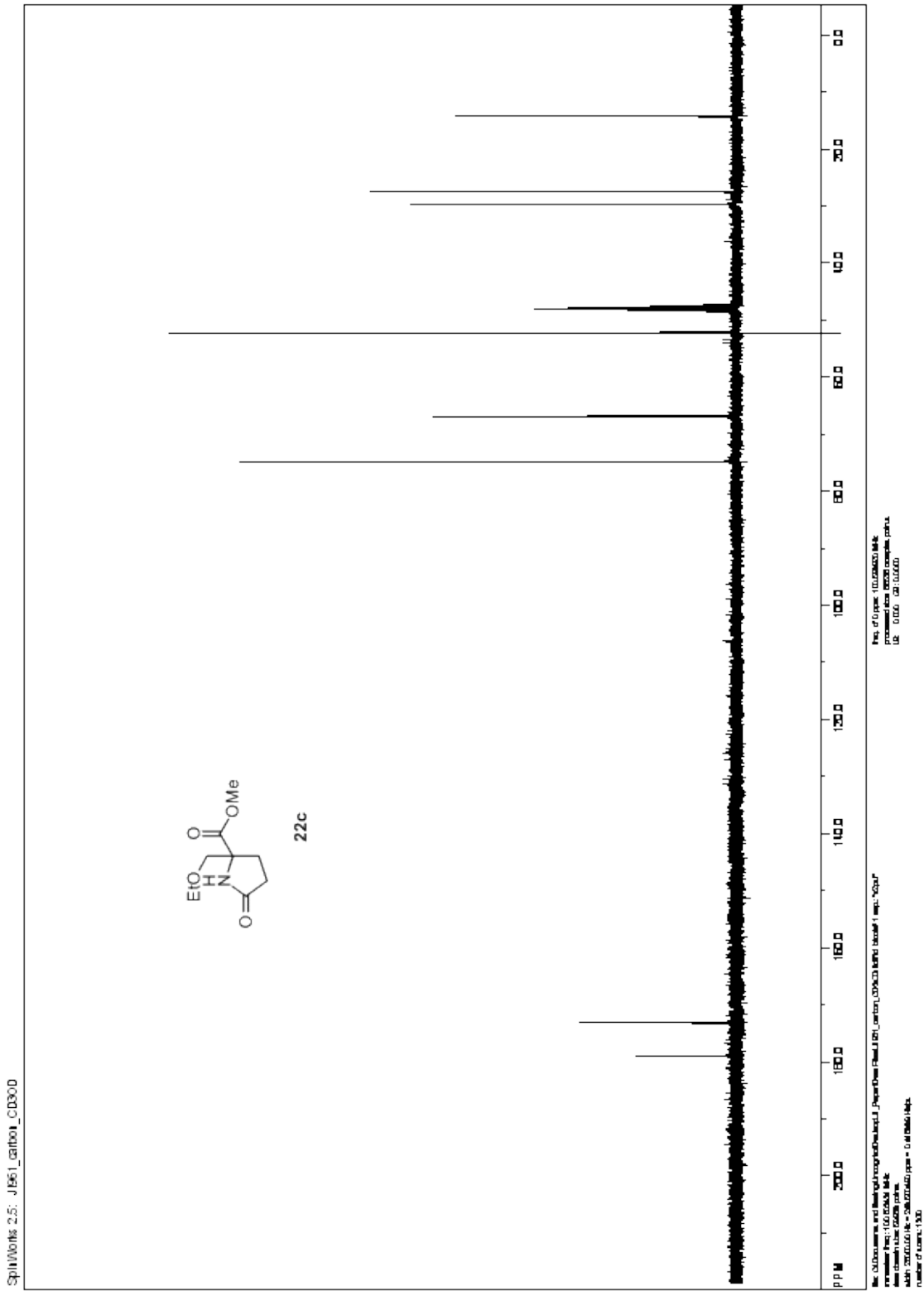

Figure A.14. ^{13}C Spectrum of **22c**.

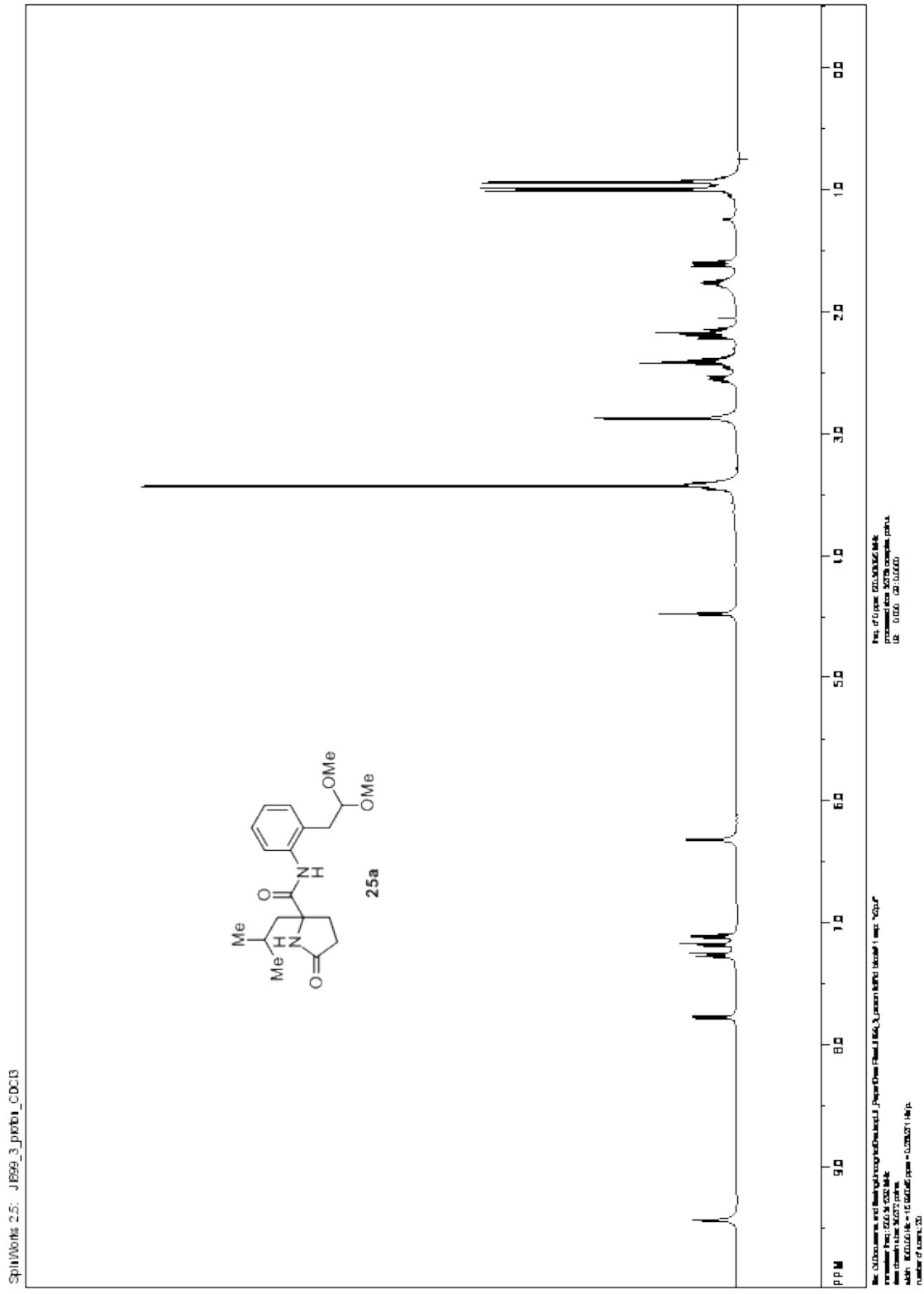

Figure A.15. ^{1}H Spectrum of **25a**.

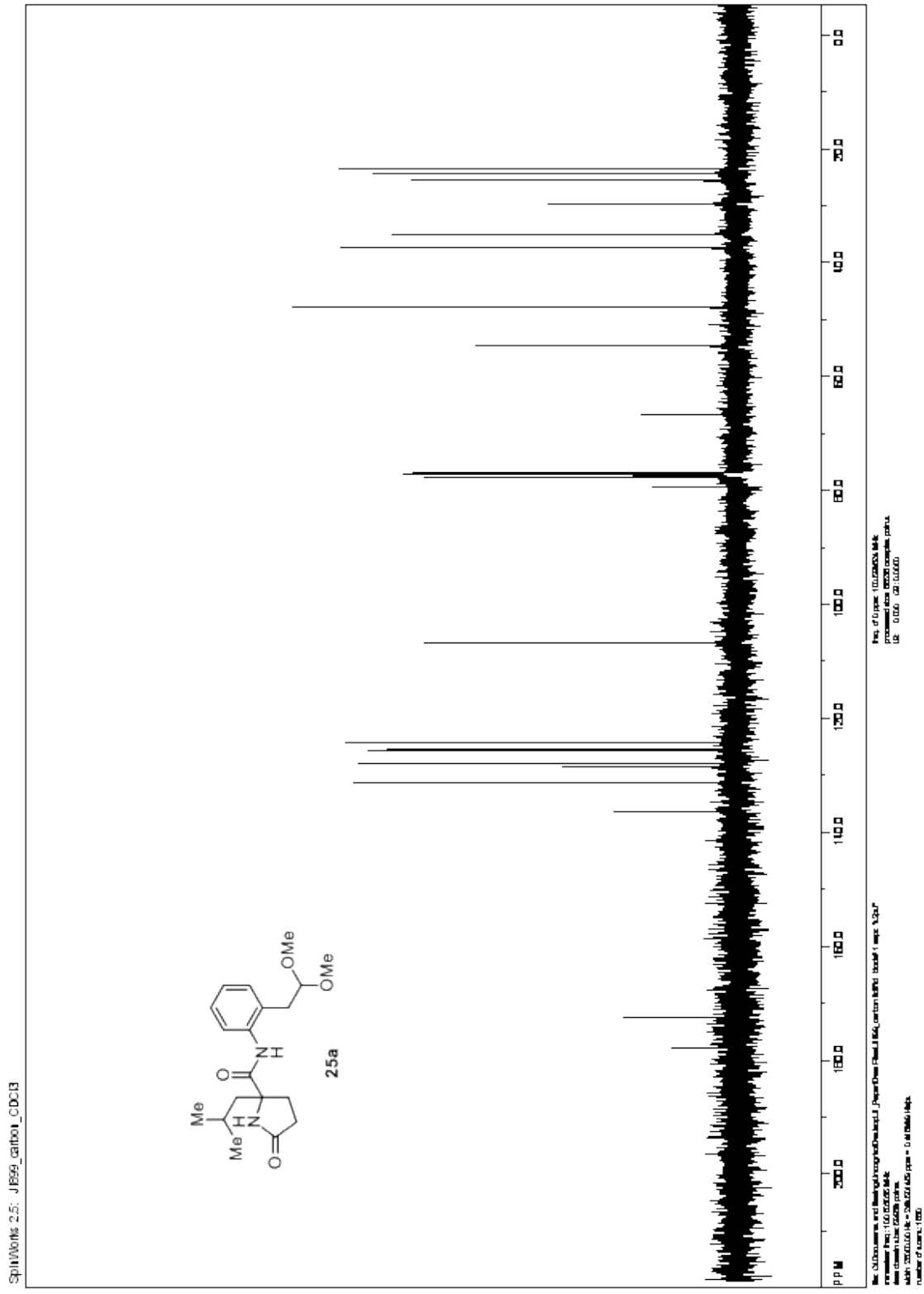

Figure A.16. ^{13}C Spectrum of **25a**.

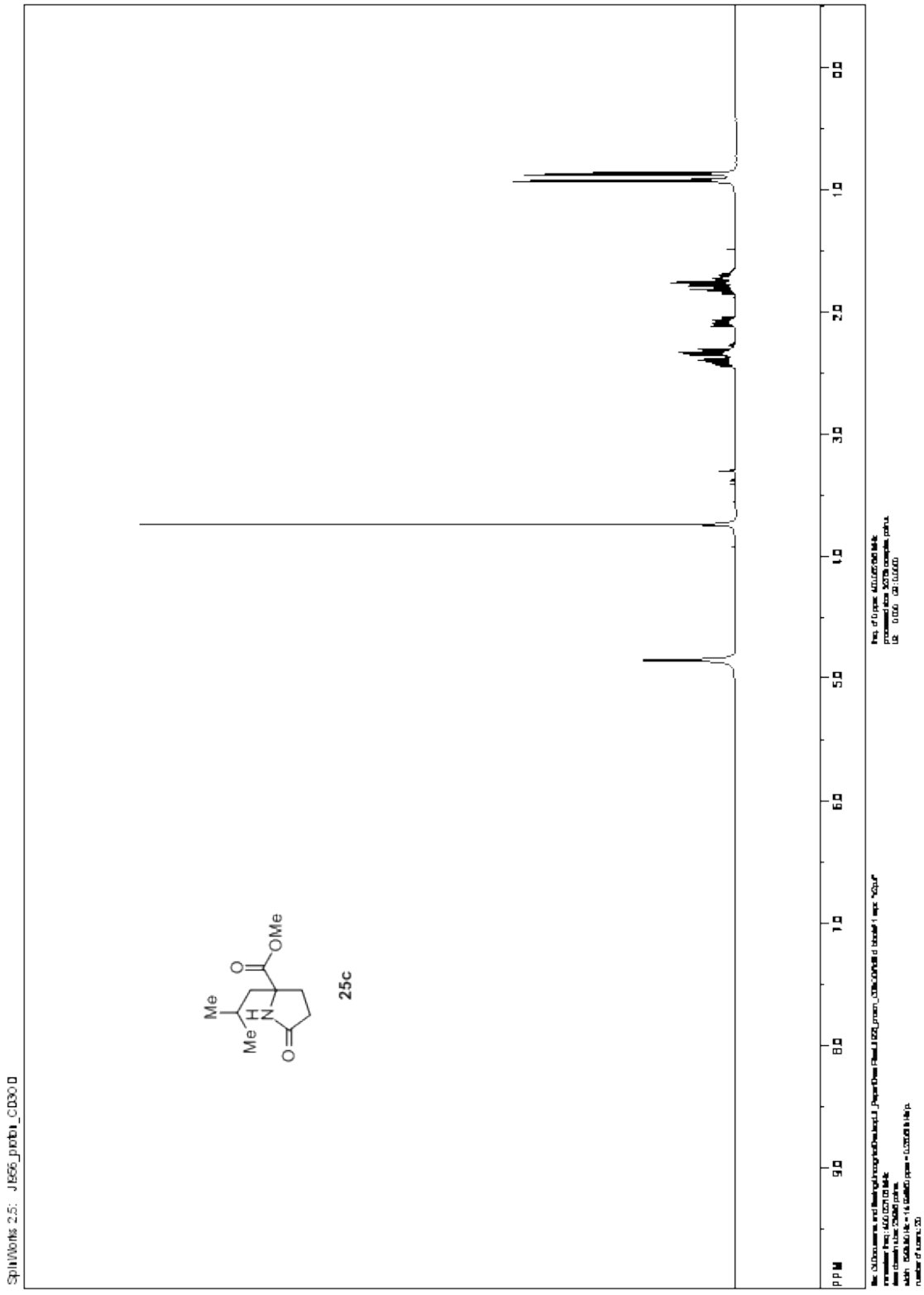

Figure A.17. ^{1}H Spectrum of **25c**.

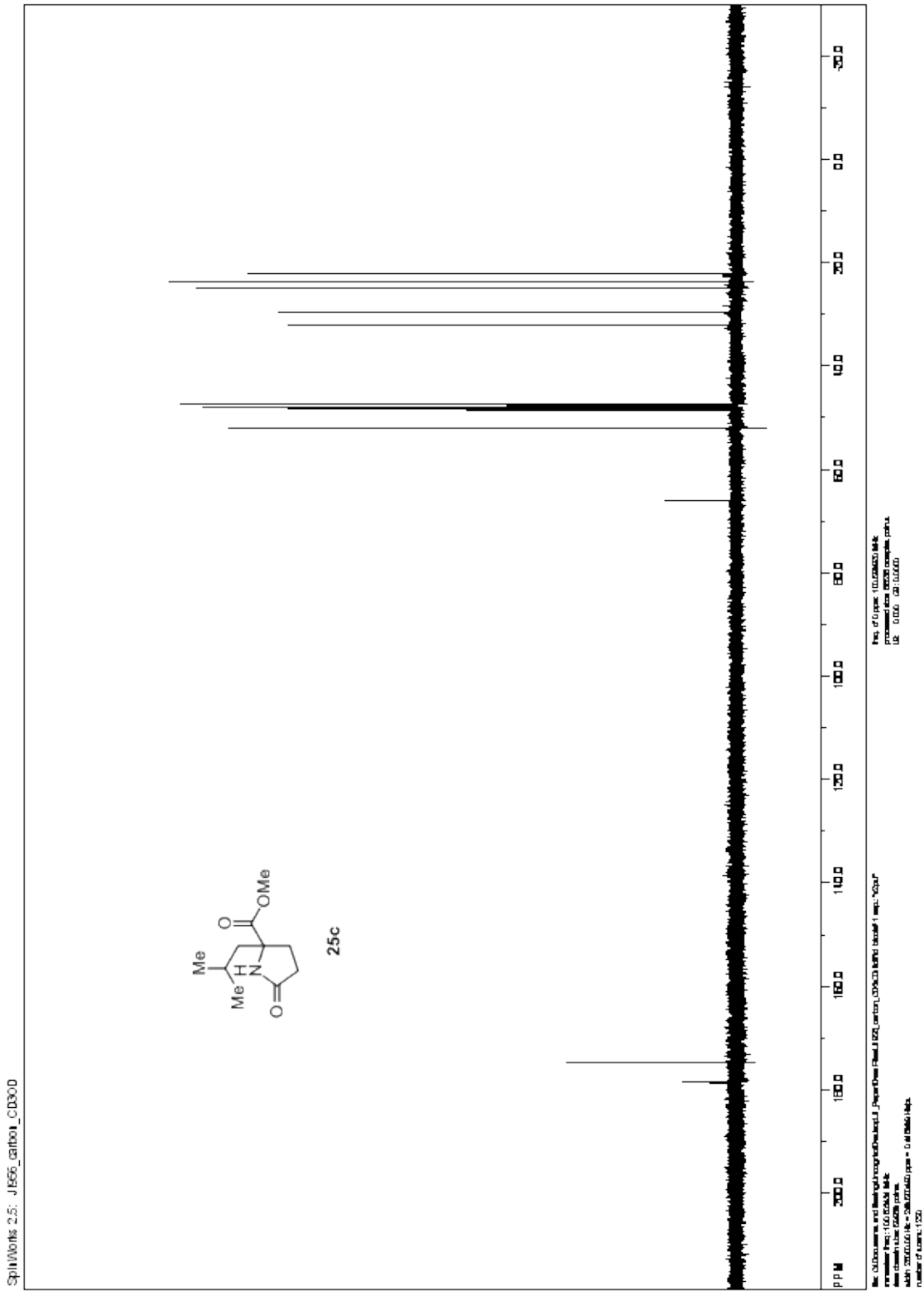

Figure A.18. ^{13}C Spectrum of **25c**.

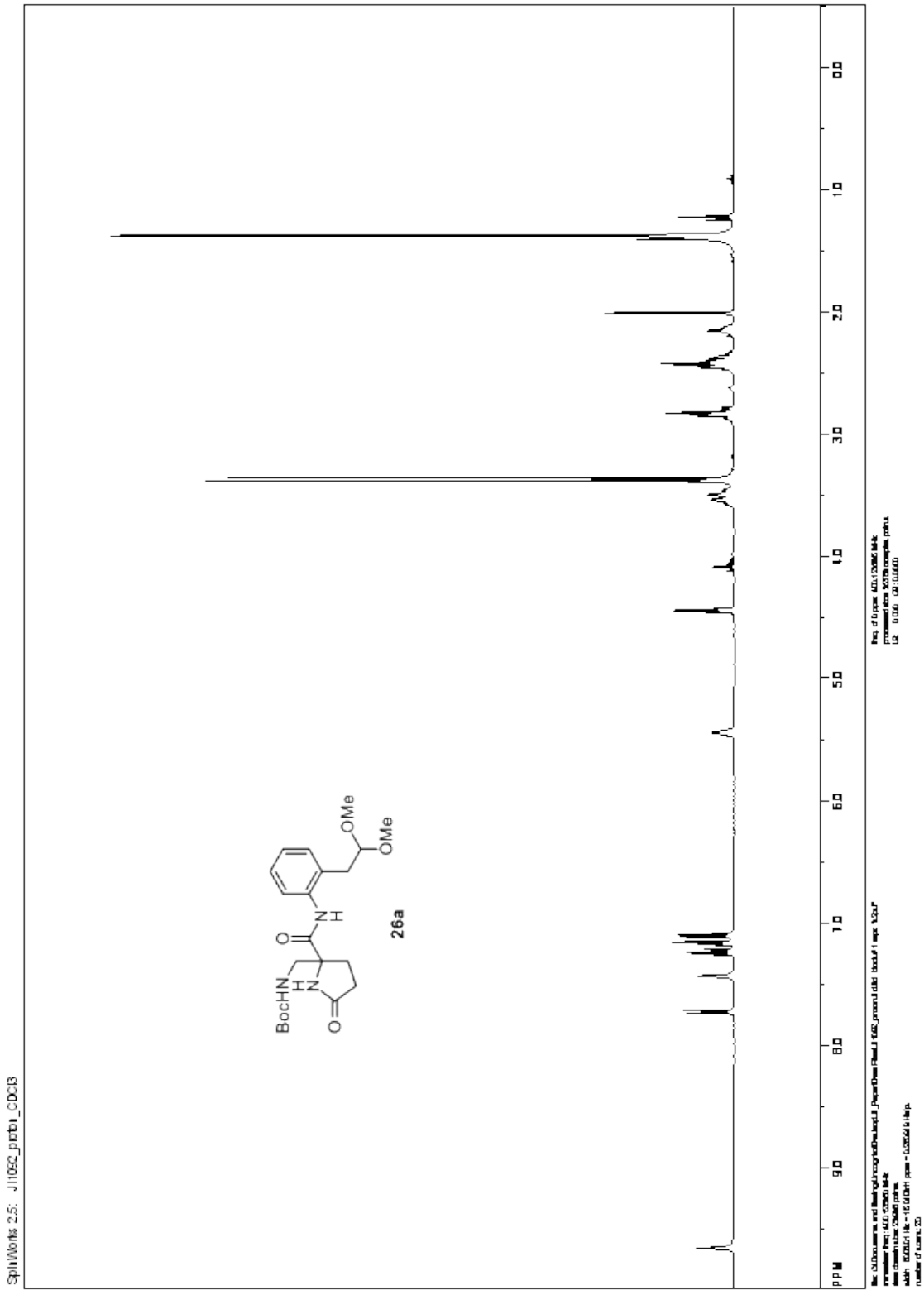

Figure A.19. ^{1}H Spectrum of **26a**.

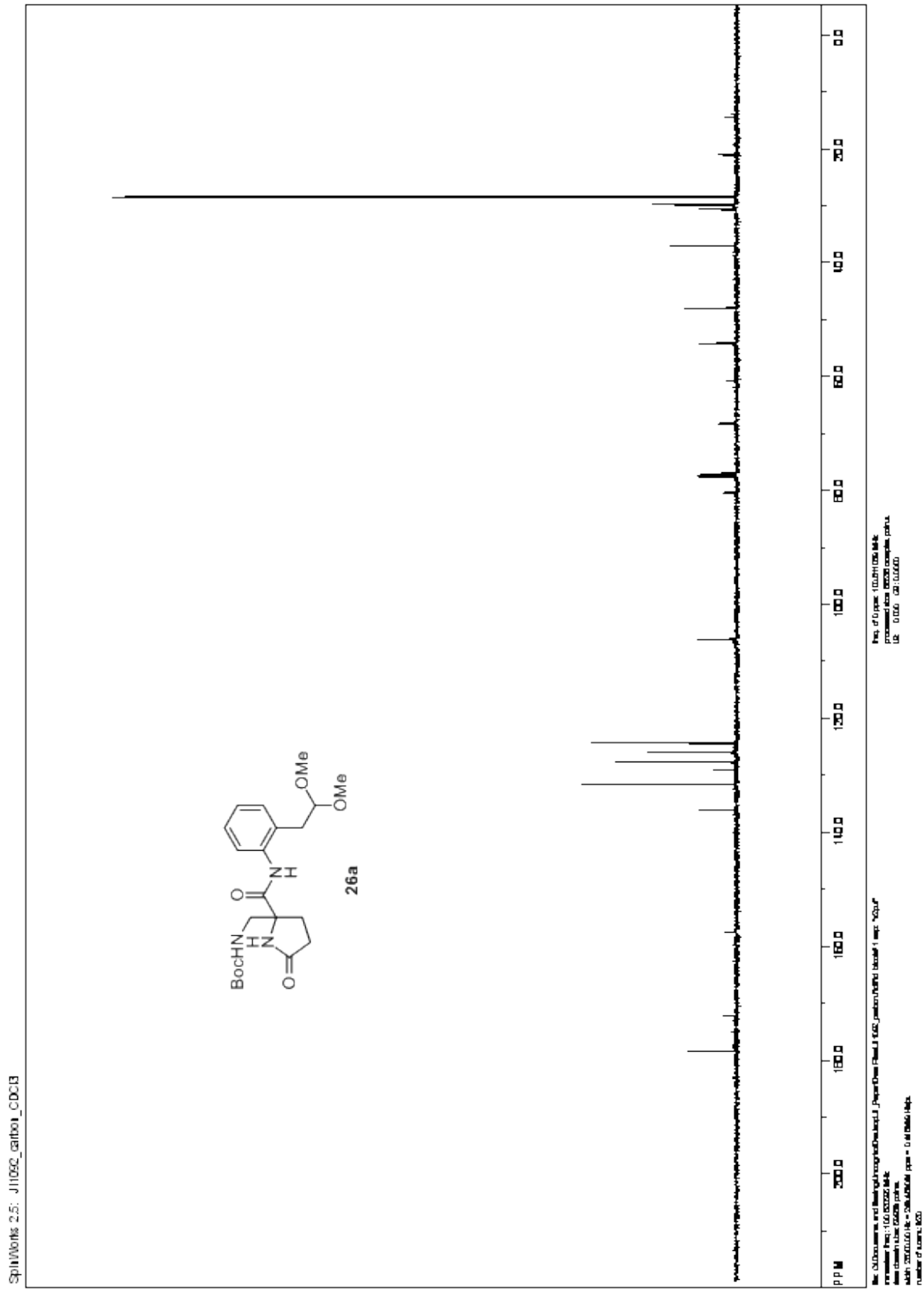

Figure A.20. ^{13}C Spectrum of **26a**.

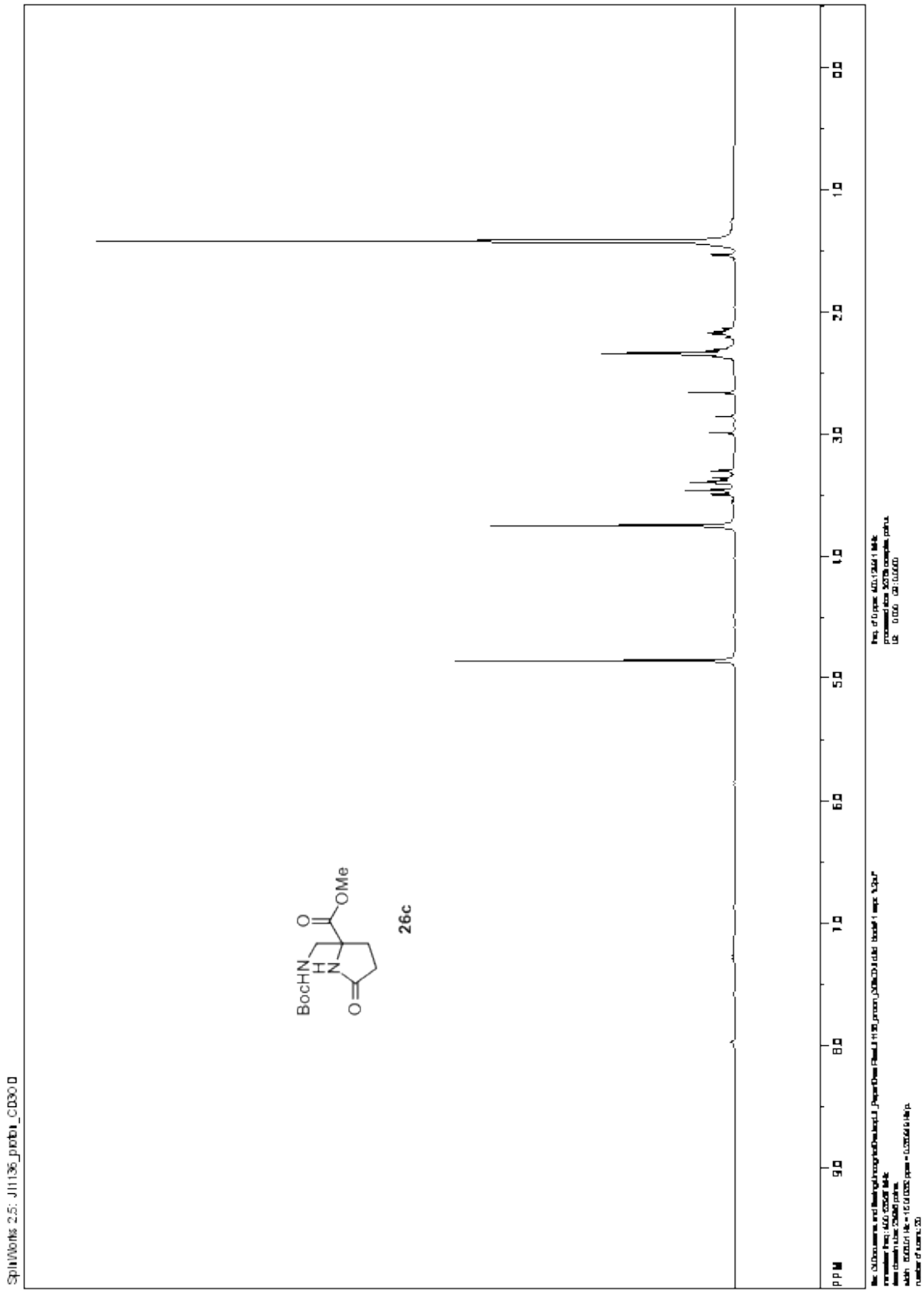

Figure A.21. ^{1}H Spectrum of **26c**.

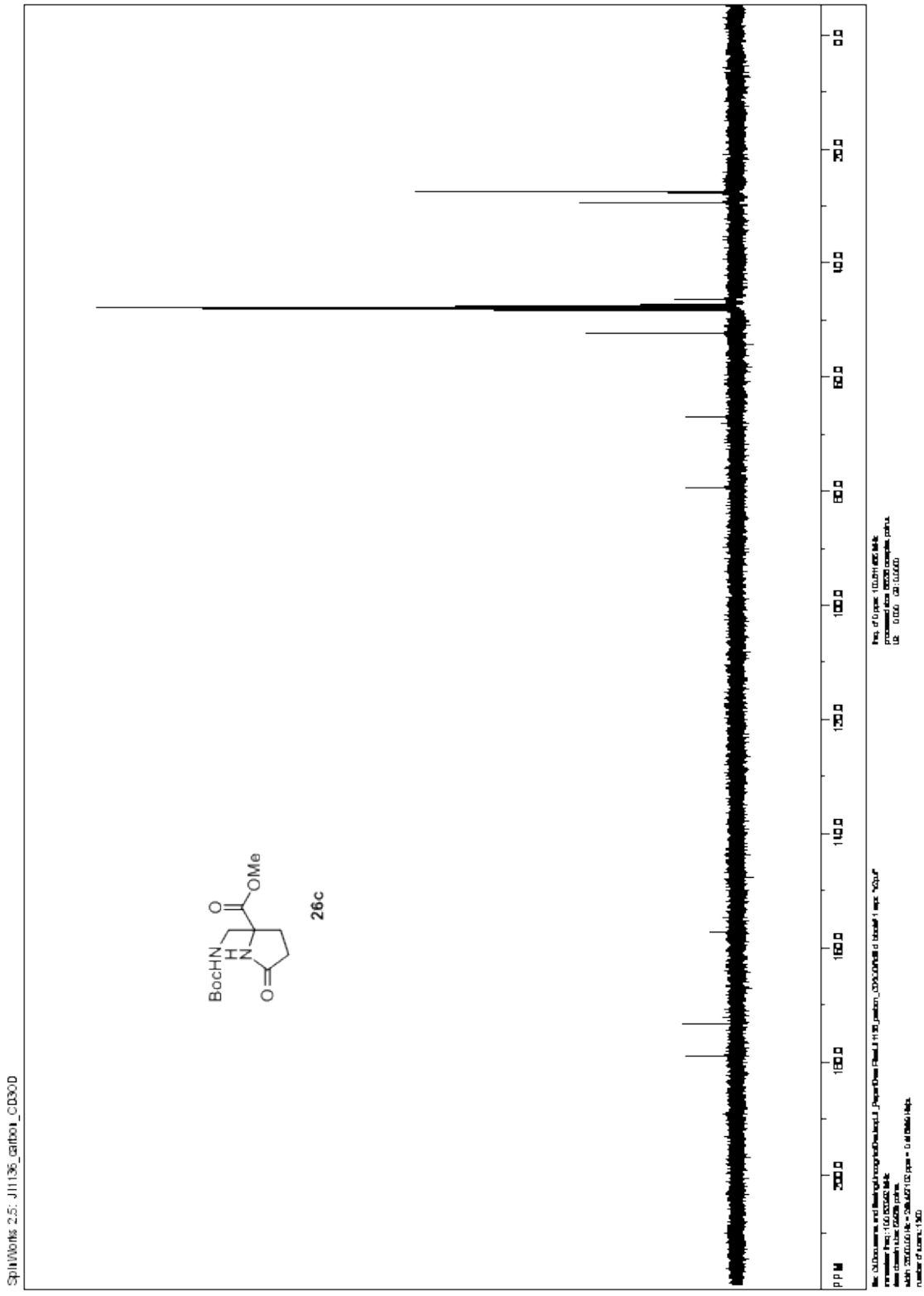

Figure A.22. ^{13}C Spectrum of **26c**.

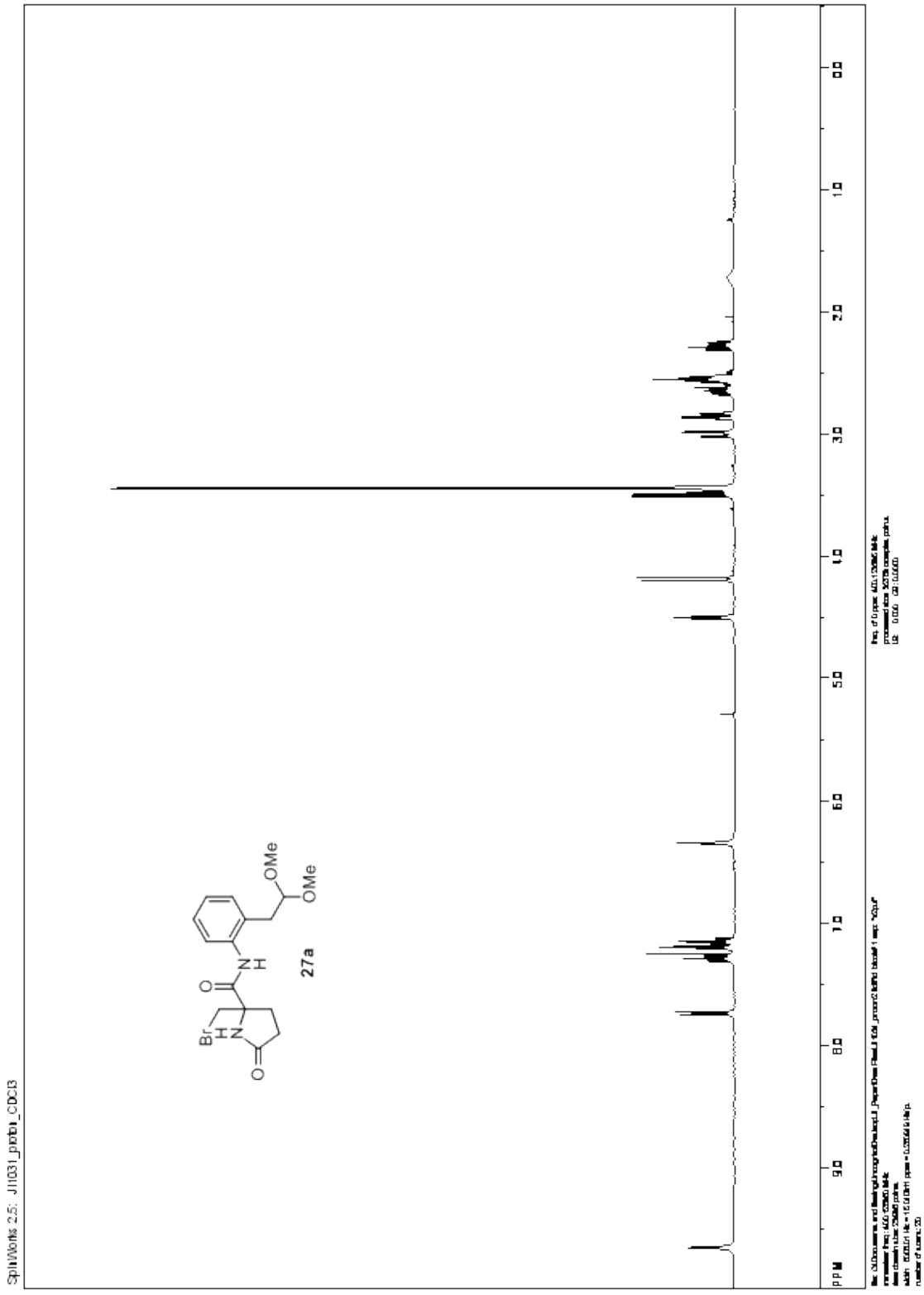

Figure A.23. ^{1}H Spectrum of **27a**.

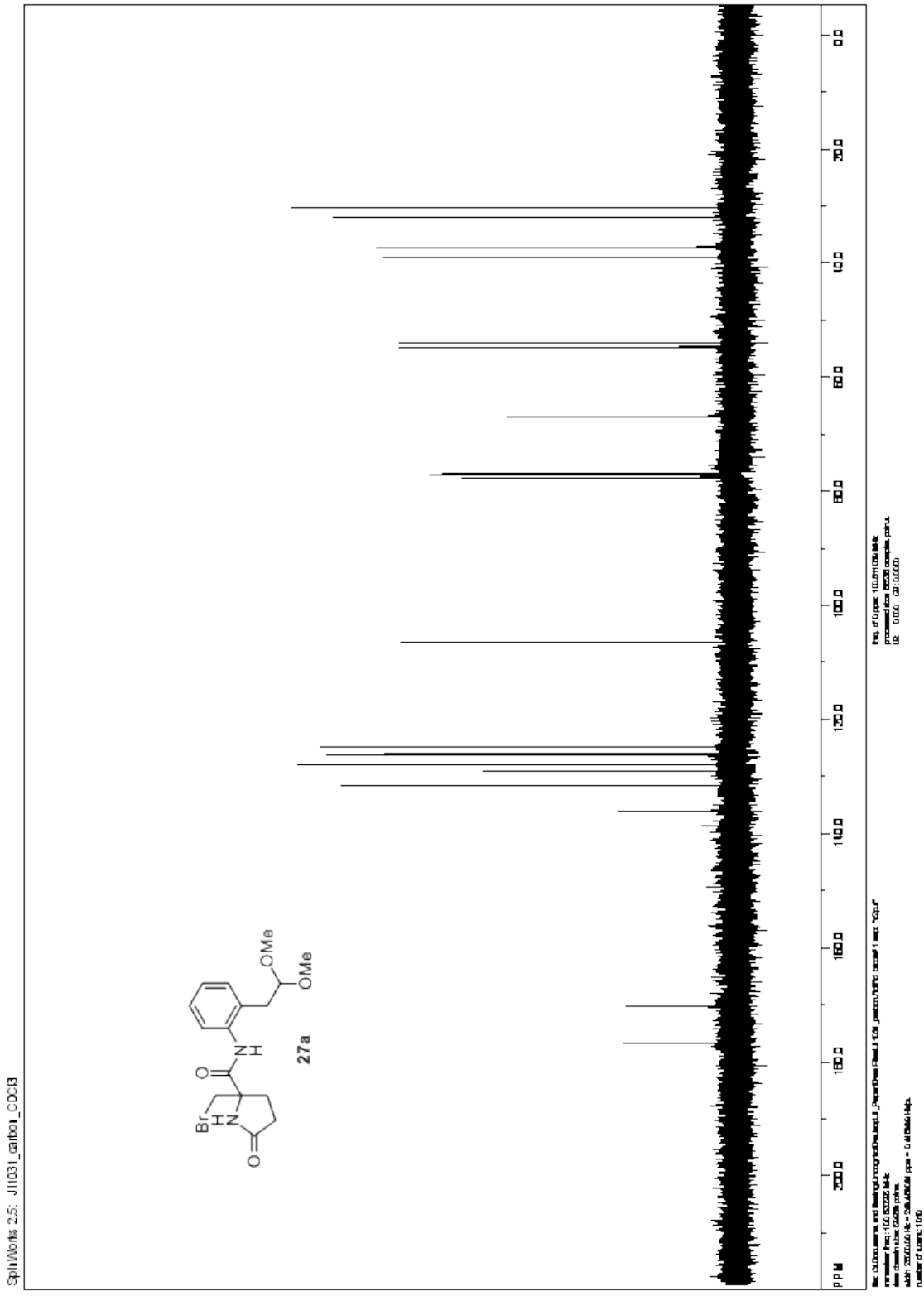

Figure A.24. ^{13}C Spectrum of **27a**.

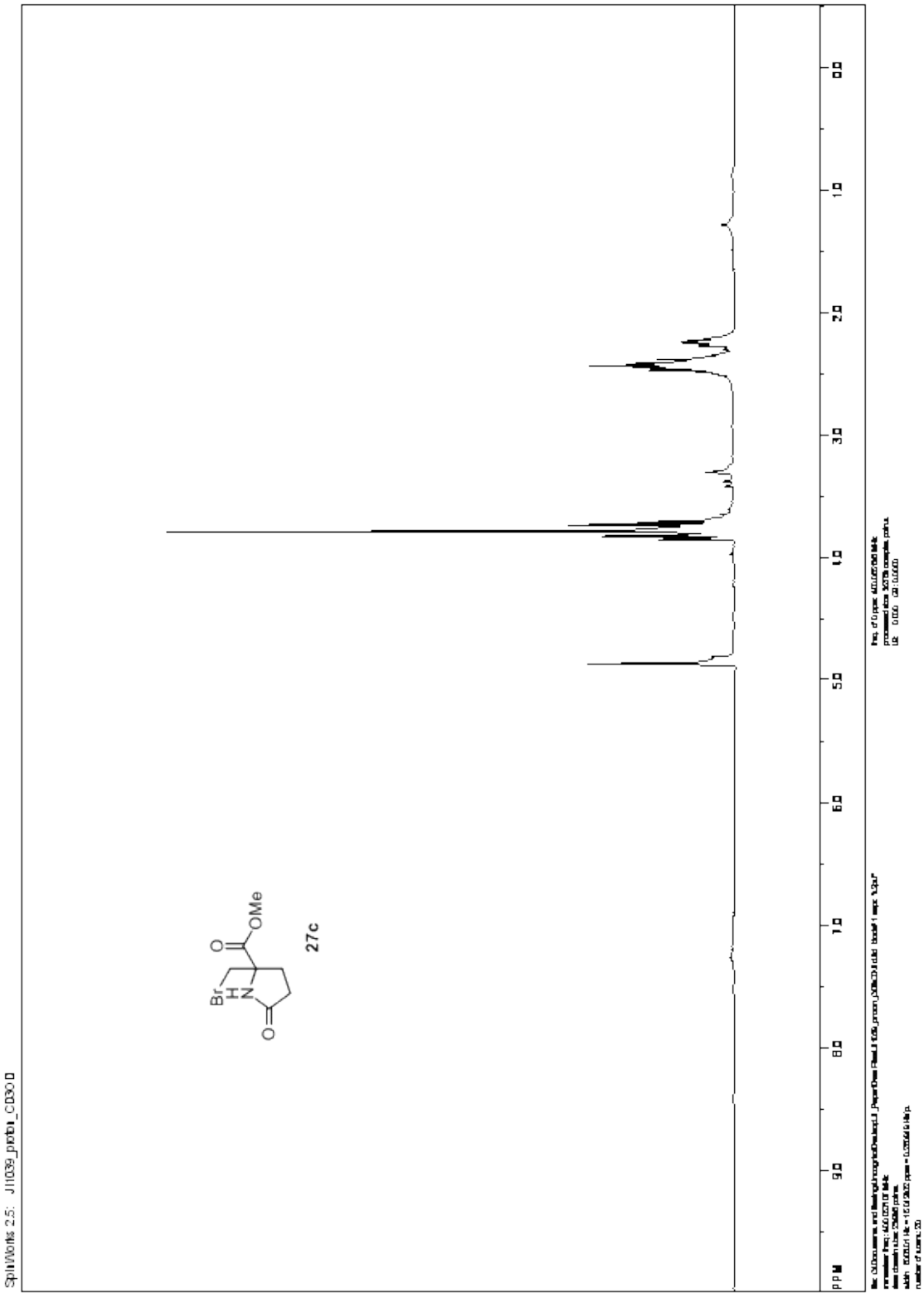

Figure A.25. ^{1}H Spectrum of **27c**.

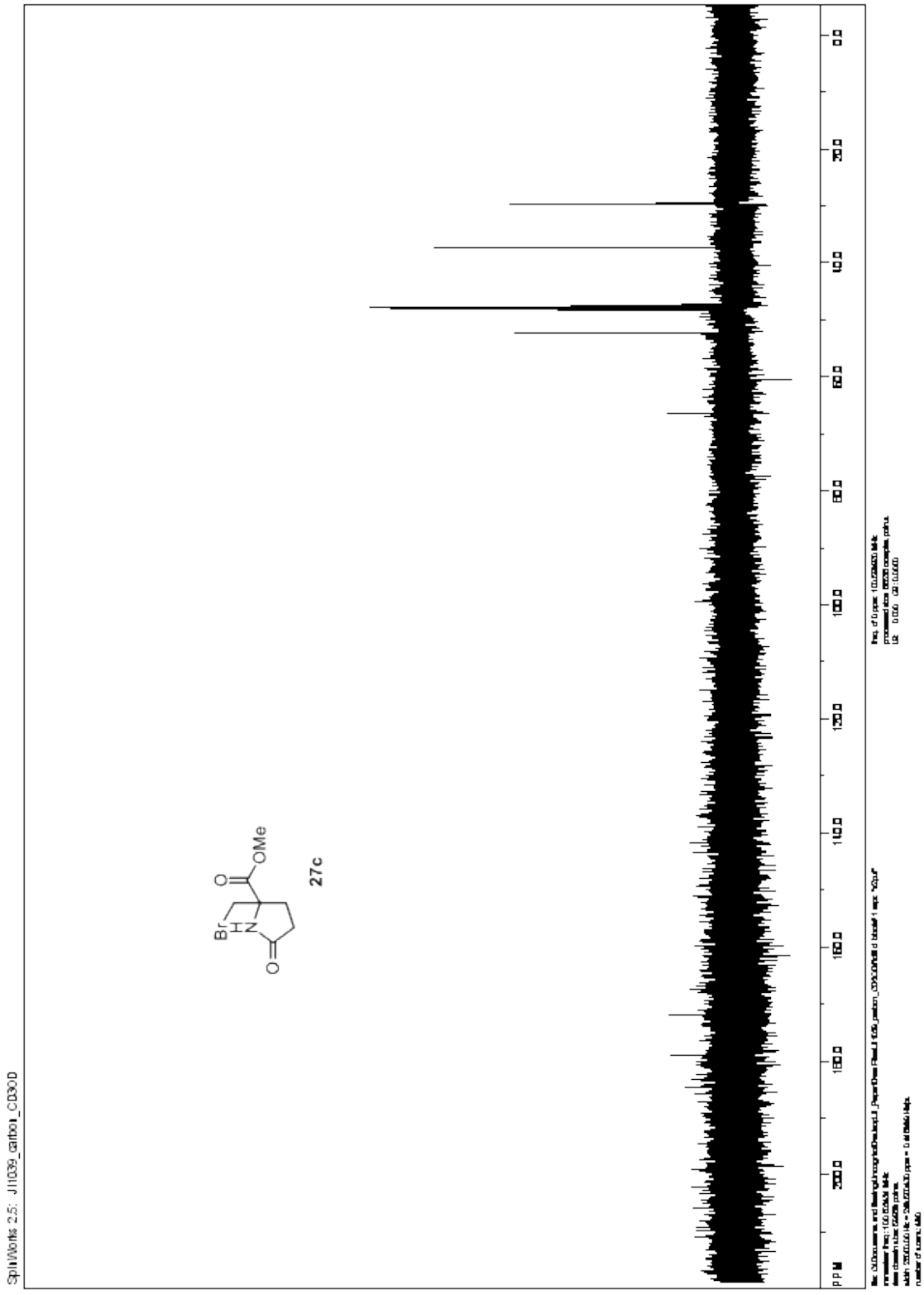

Figure A.26. ^{13}C Spectrum of **27c**.

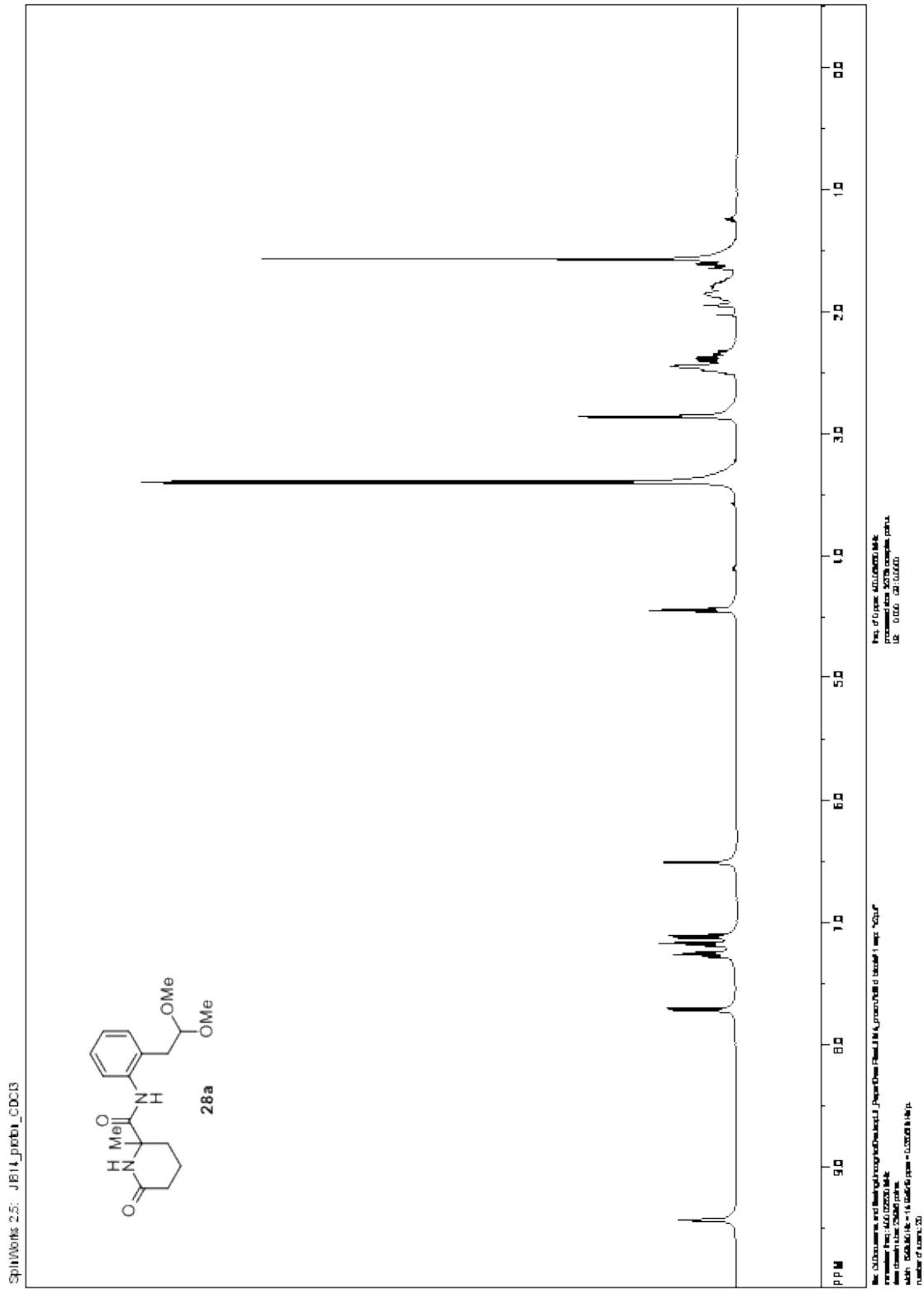

Figure A.27. ^{1}H Spectrum of **28a**.

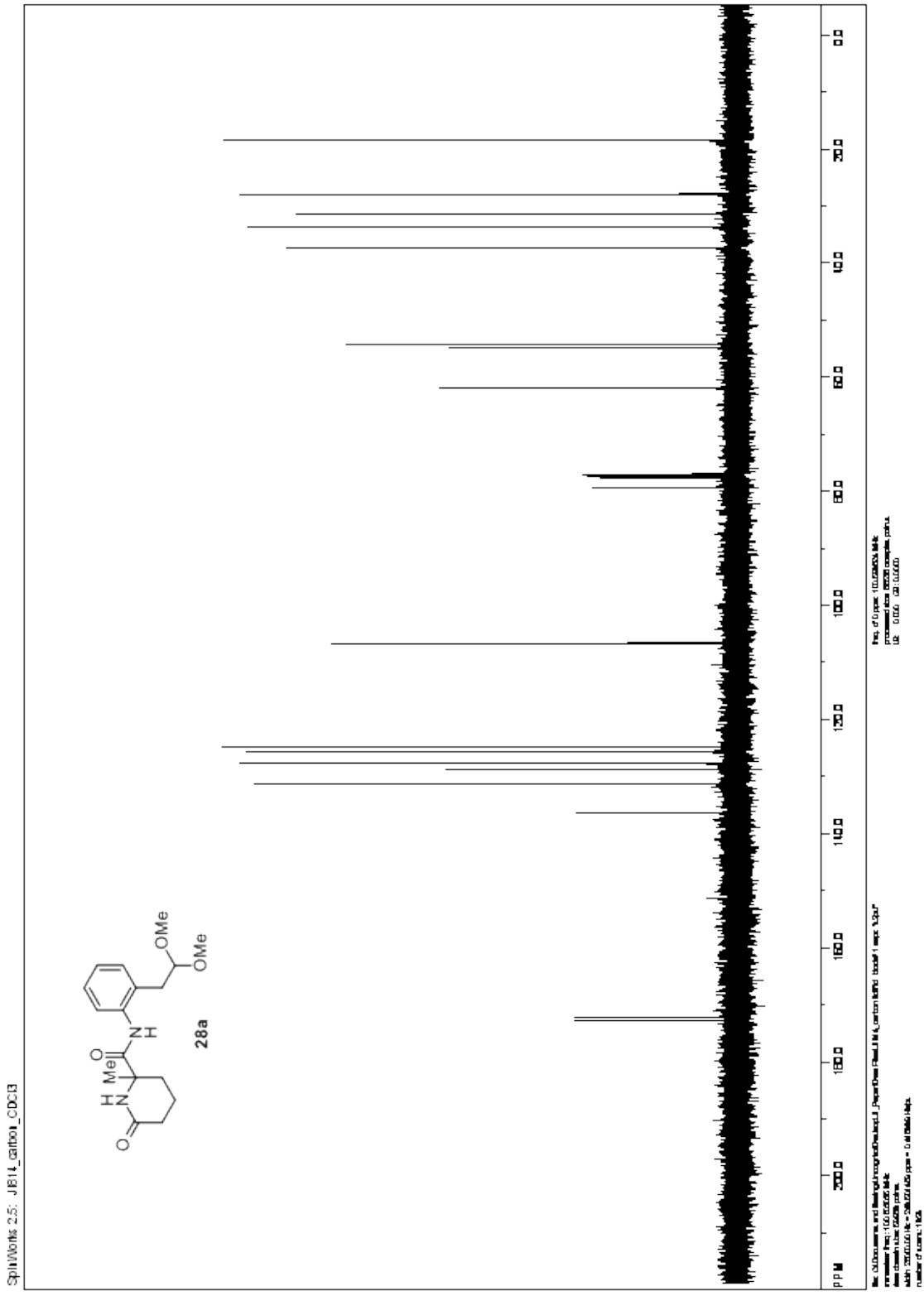

Figure A.28. ^{13}C Spectrum of **28a**.

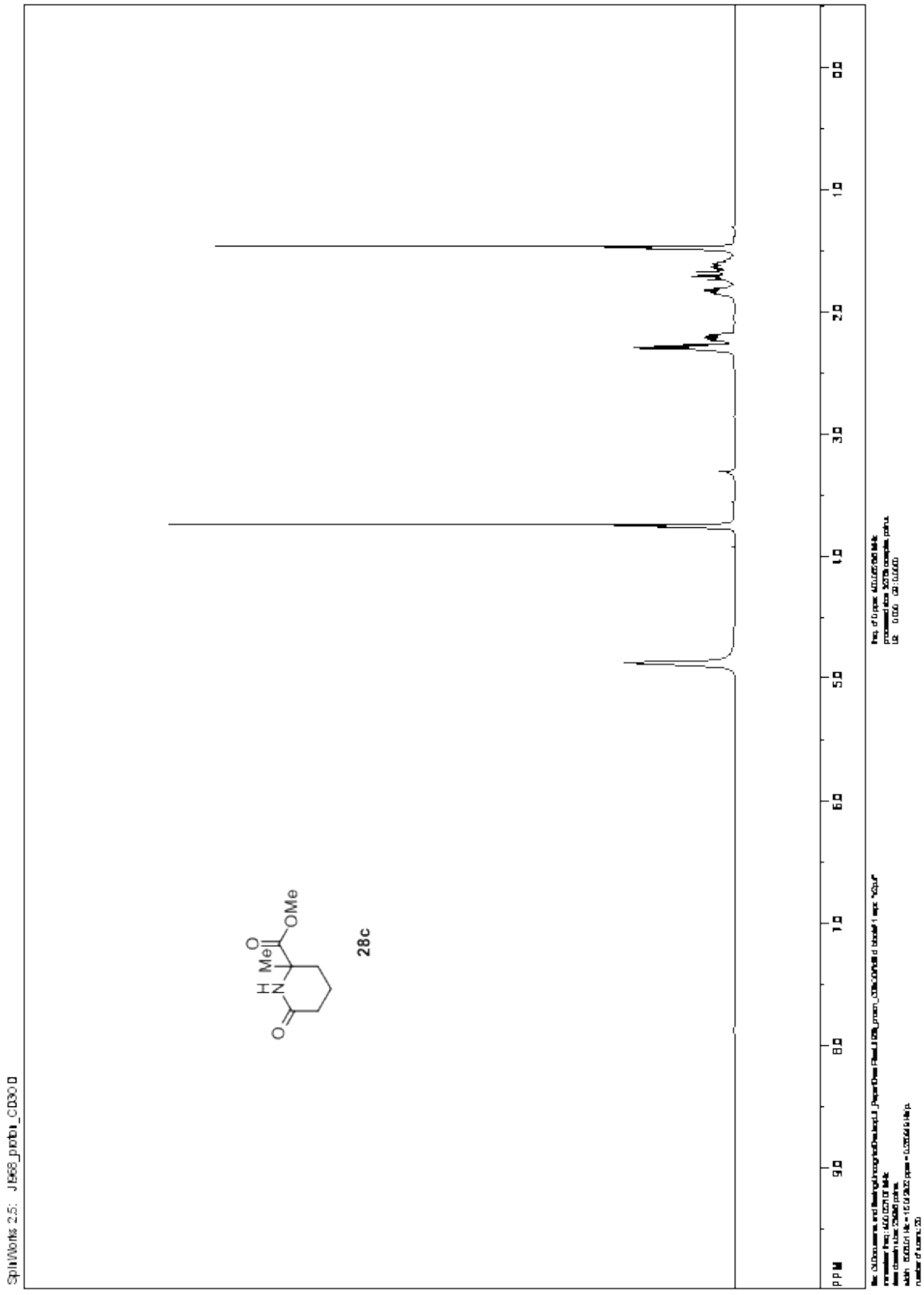

Figure A.29. ^{1}H Spectrum of **28c**.

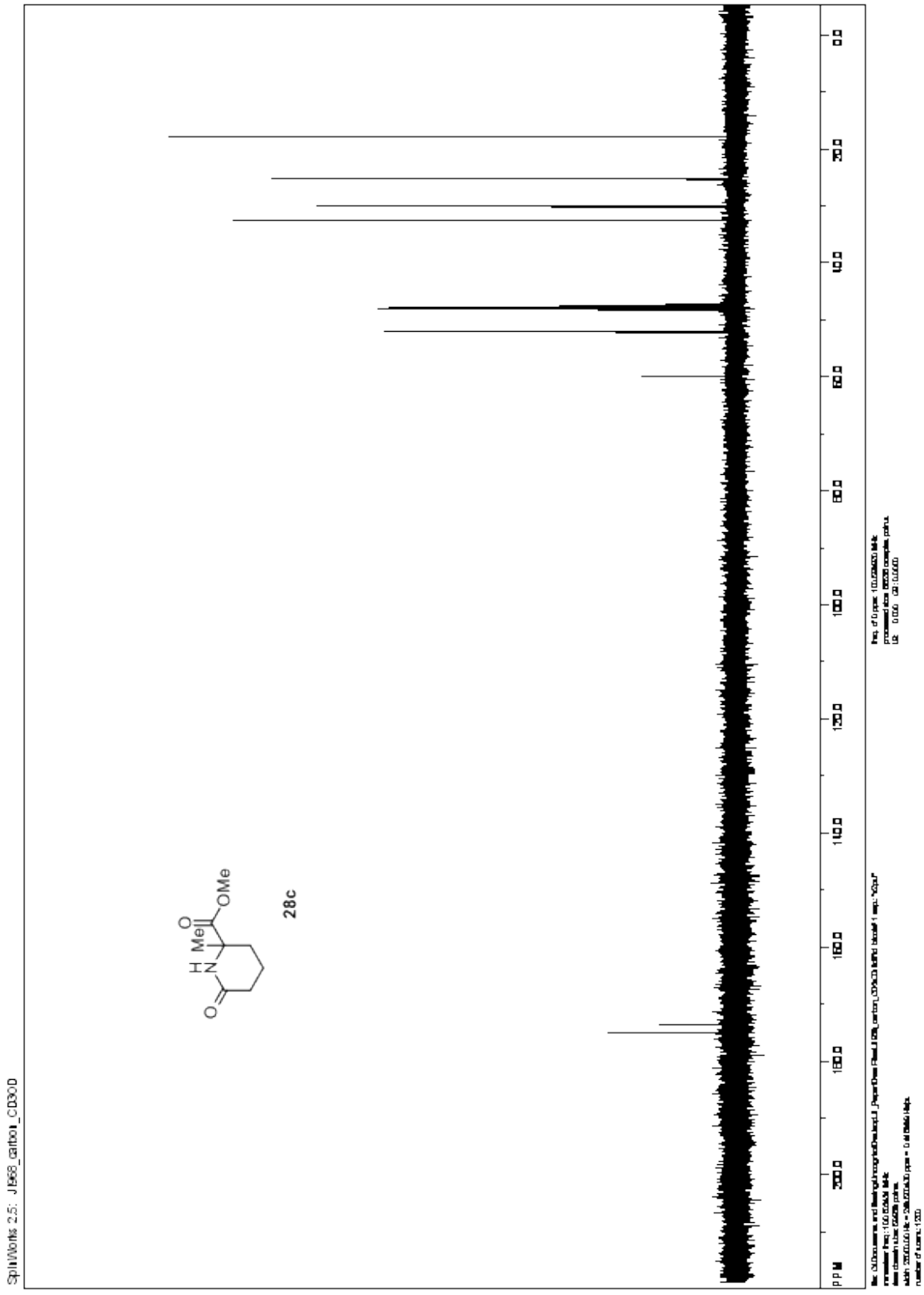

Figure A.30. ^{13}C Spectrum of **28c**.

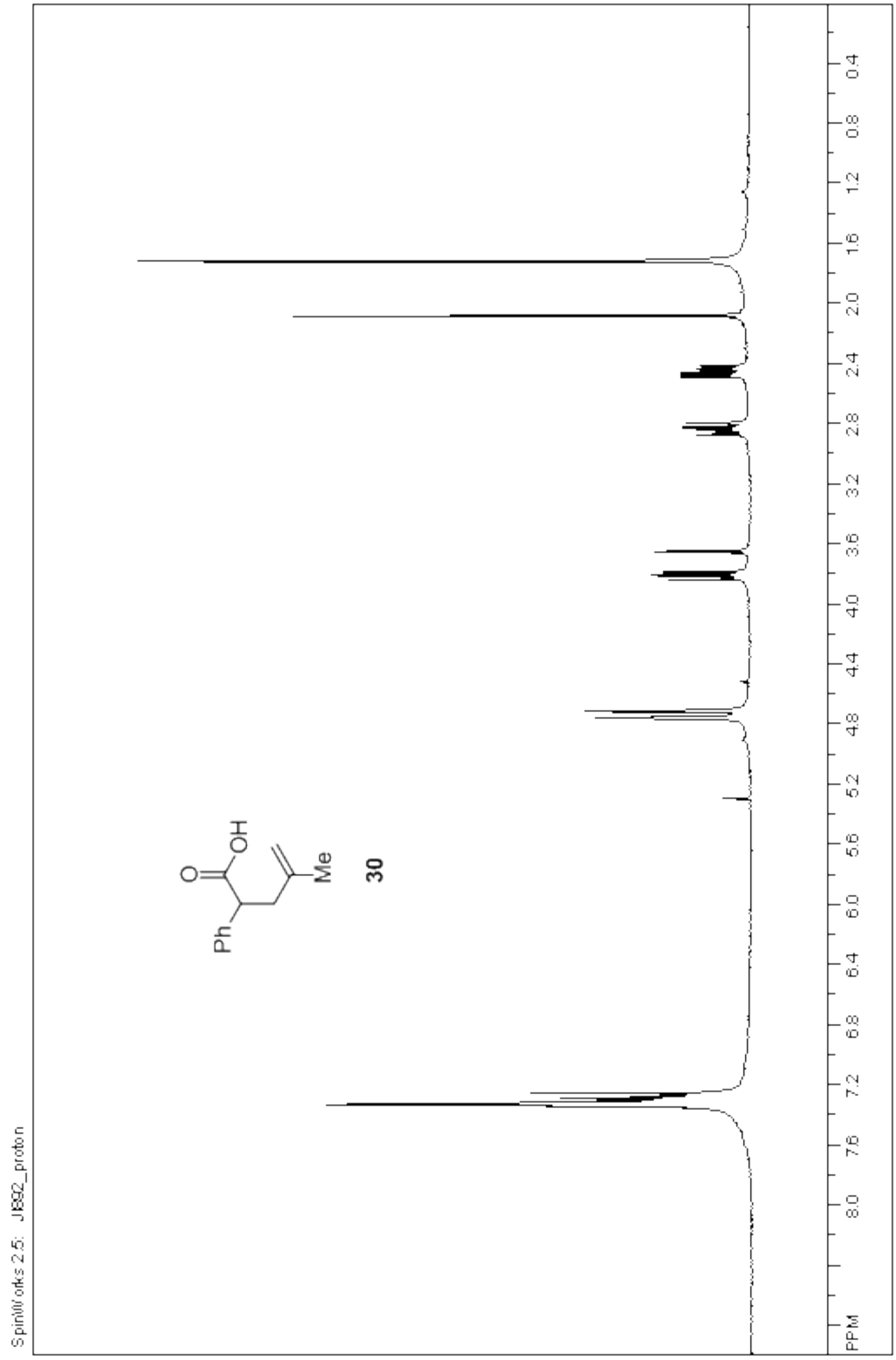

Figure A.31. ^{1}H Spectrum of **30**.

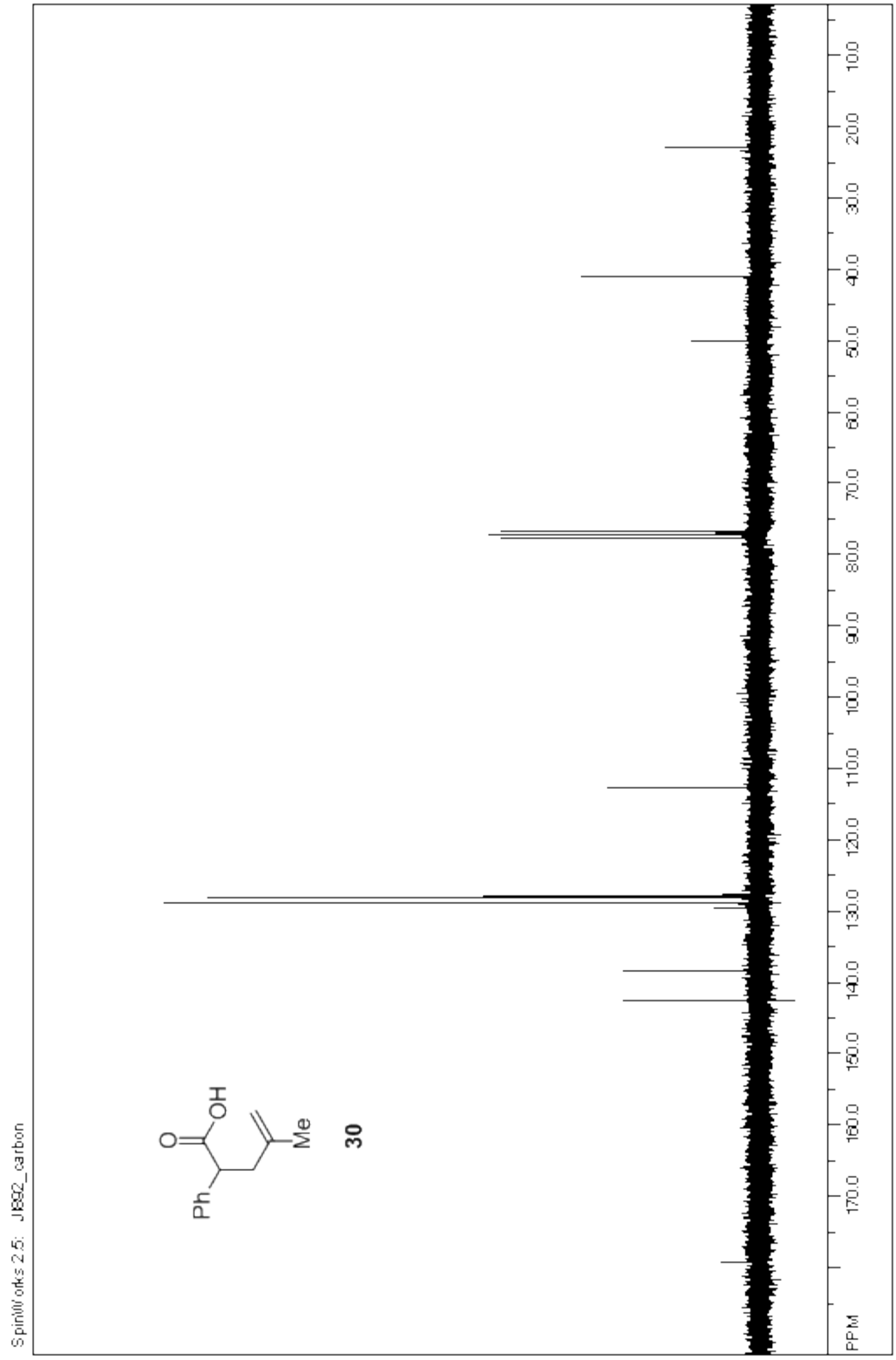

Figure A.32. ^{13}C Spectrum of **30**.

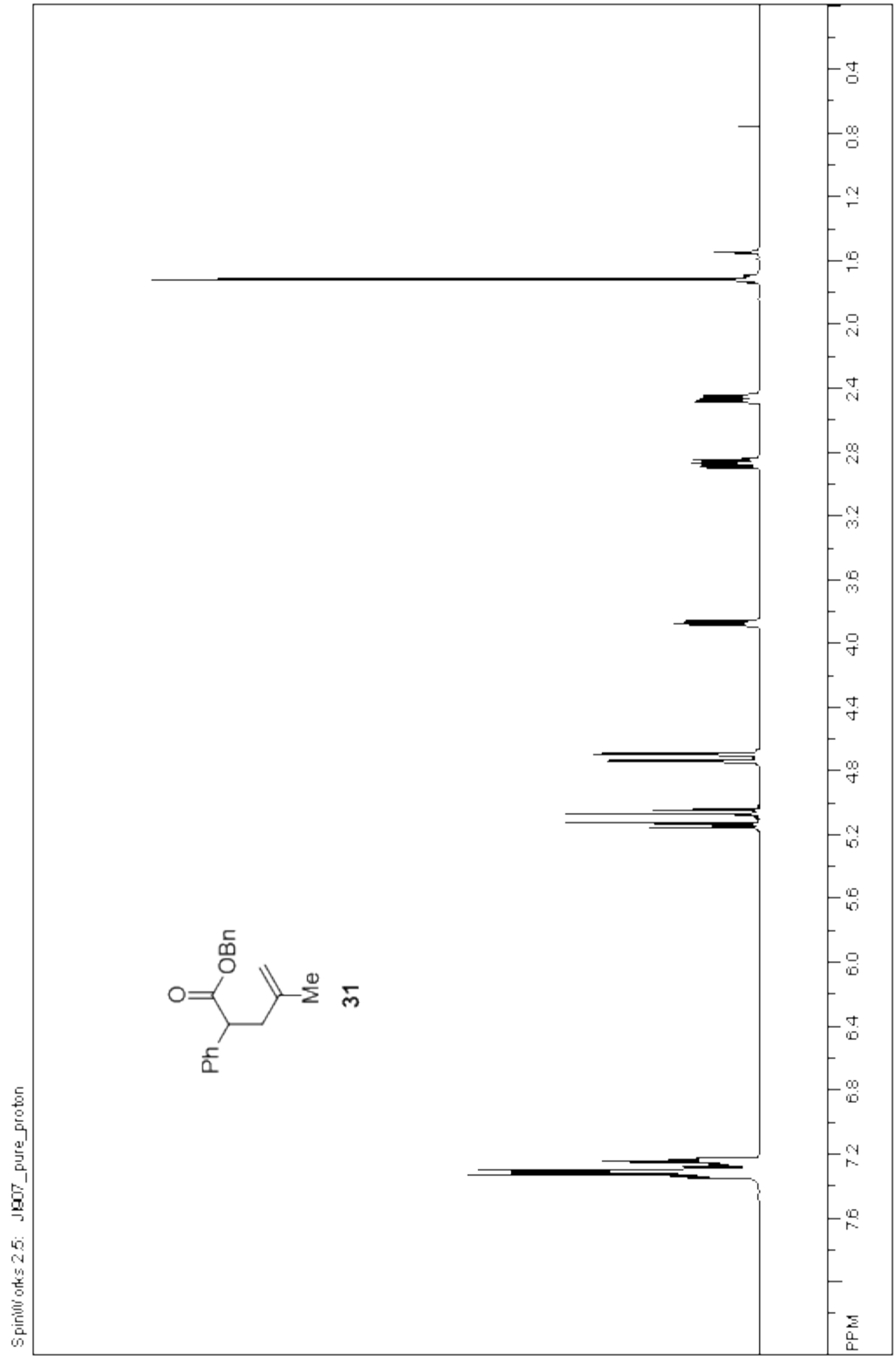

Figure A.33. ^{1}H Spectrum of **31**.

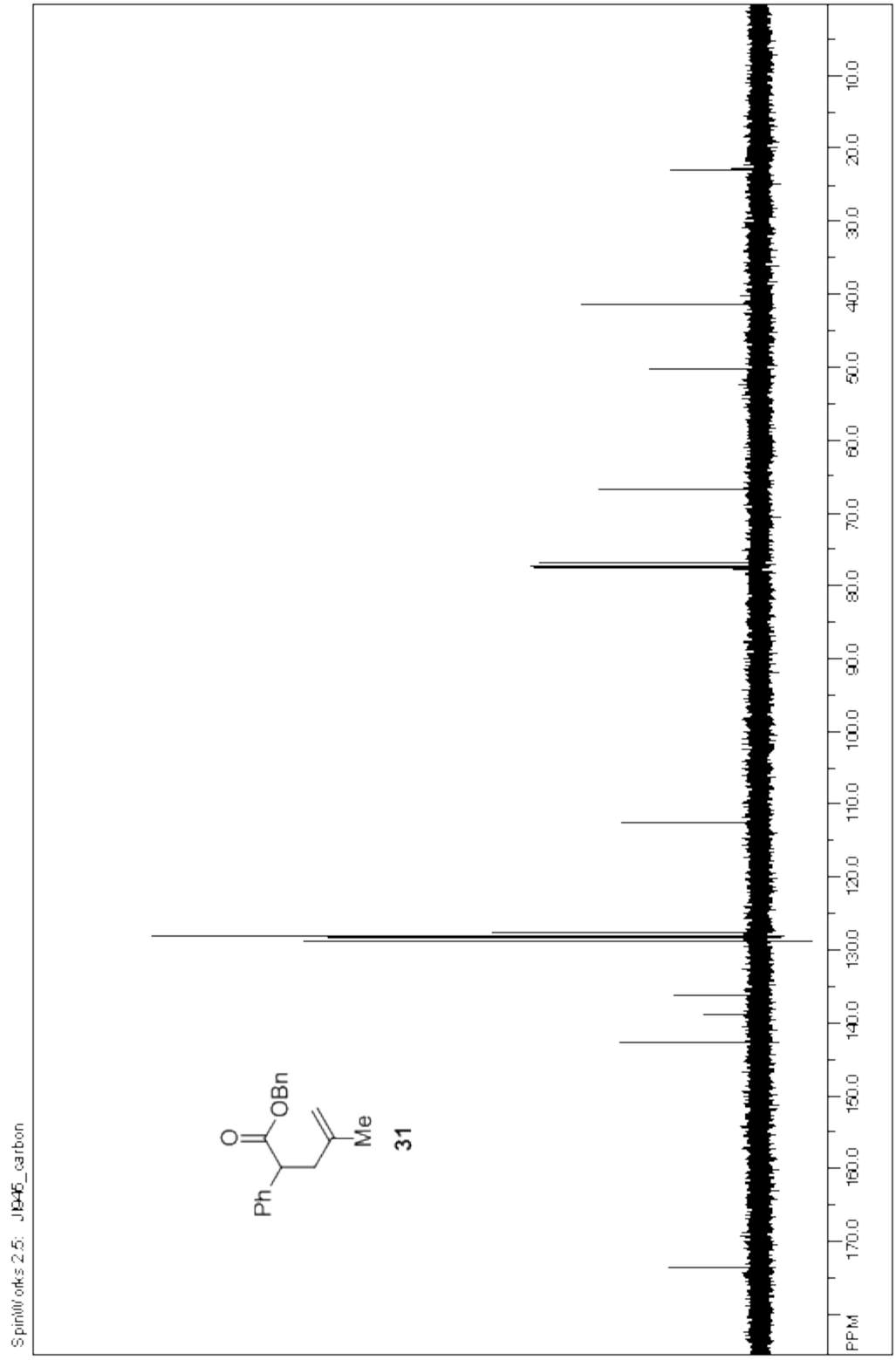

Figure A.34. ^{13}C Spectrum of **31**.

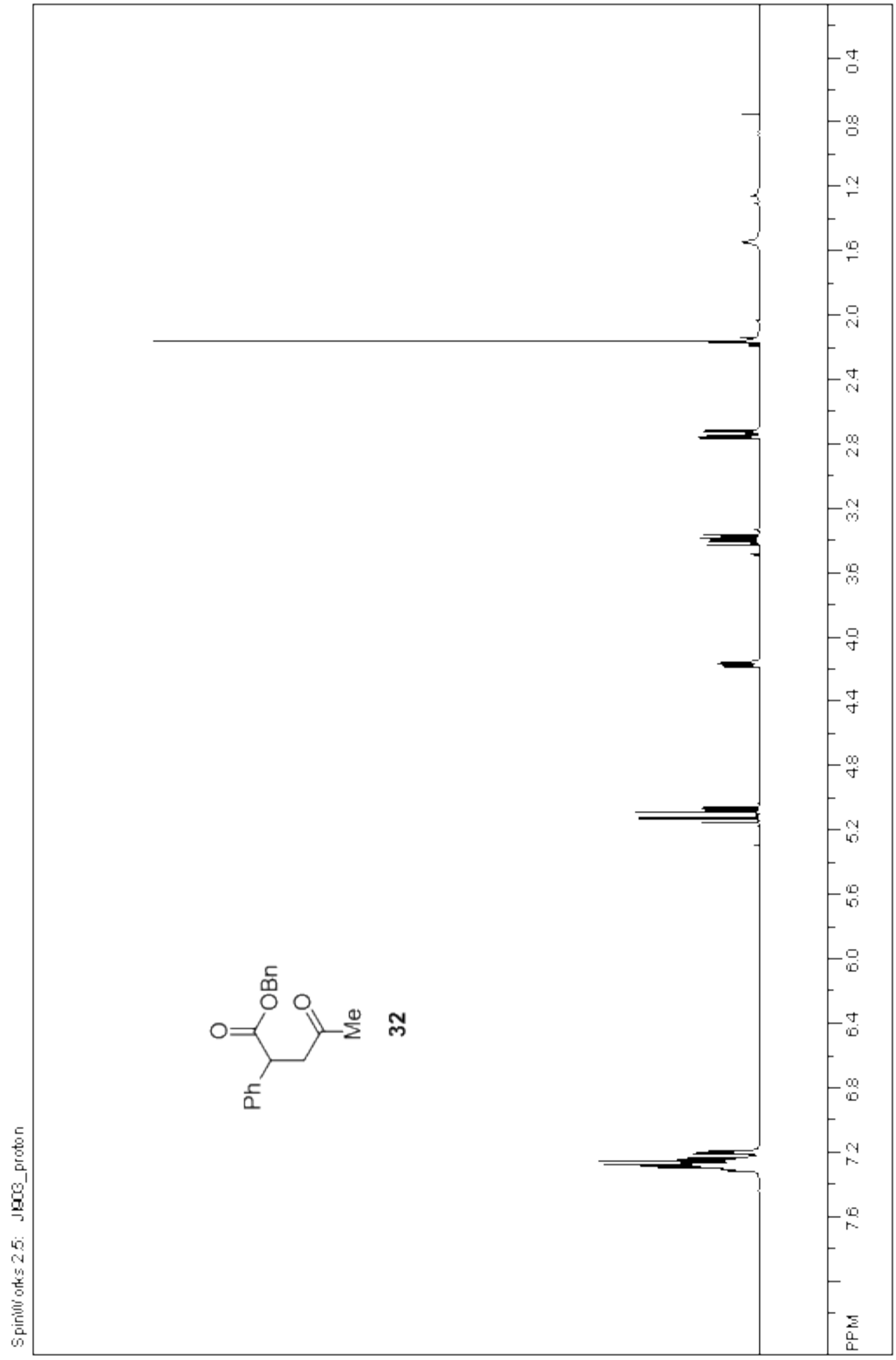

Figure A.35. ^{1}H Spectrum of **32**.

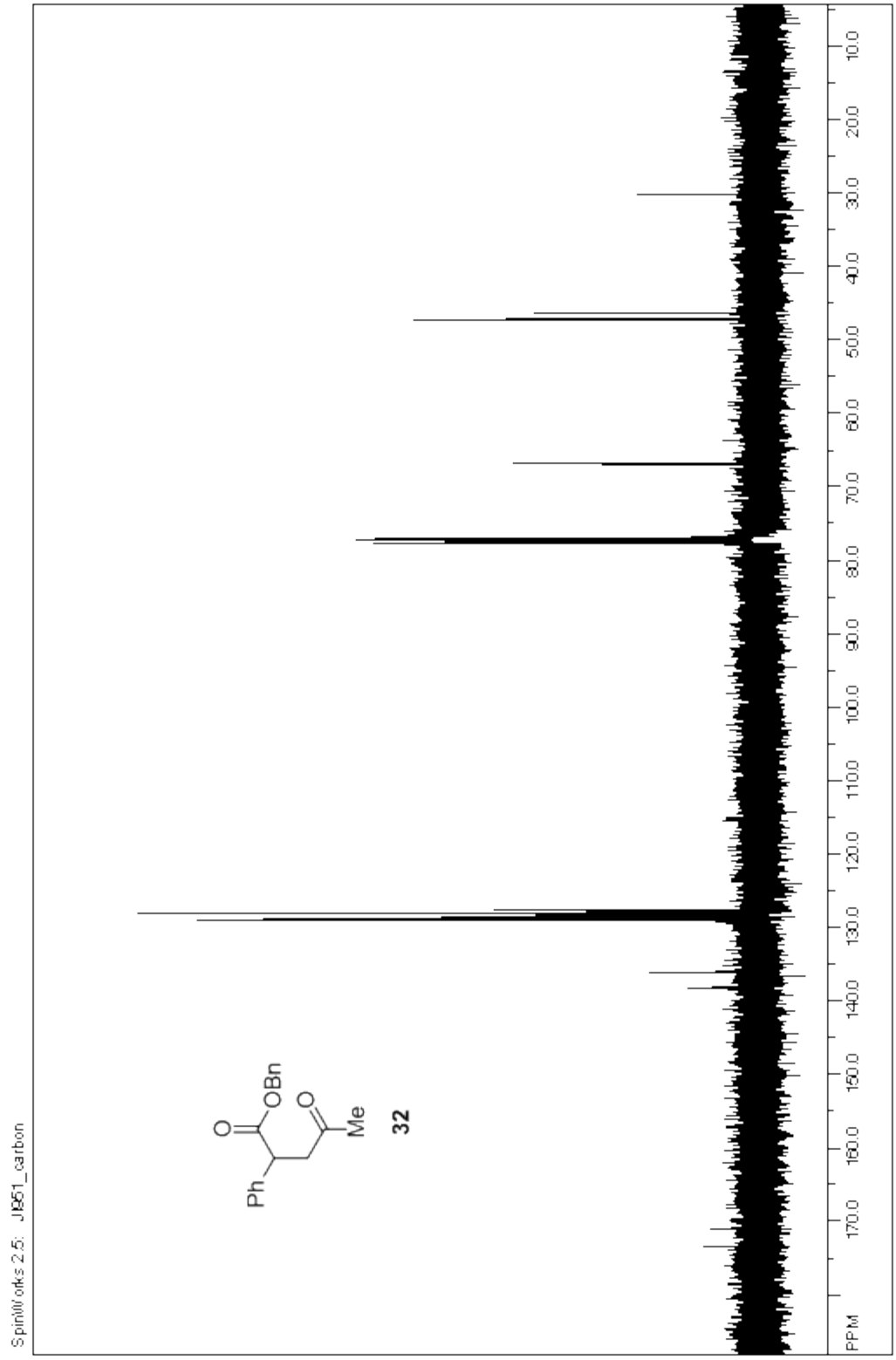

Figure A.36. ^{13}C Spectrum of **32**.

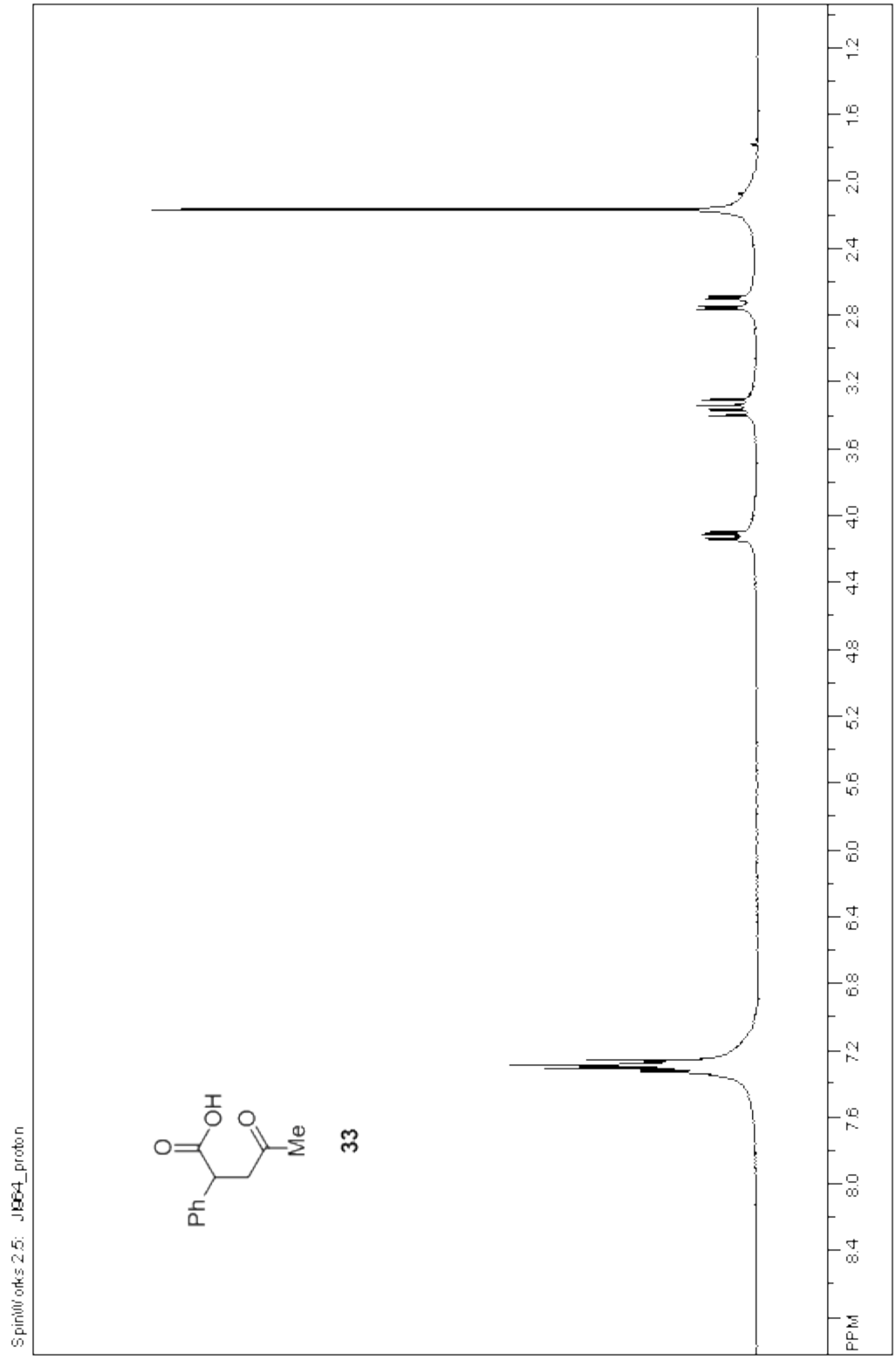

Figure A.37. ^{1}H Spectrum of **33**.

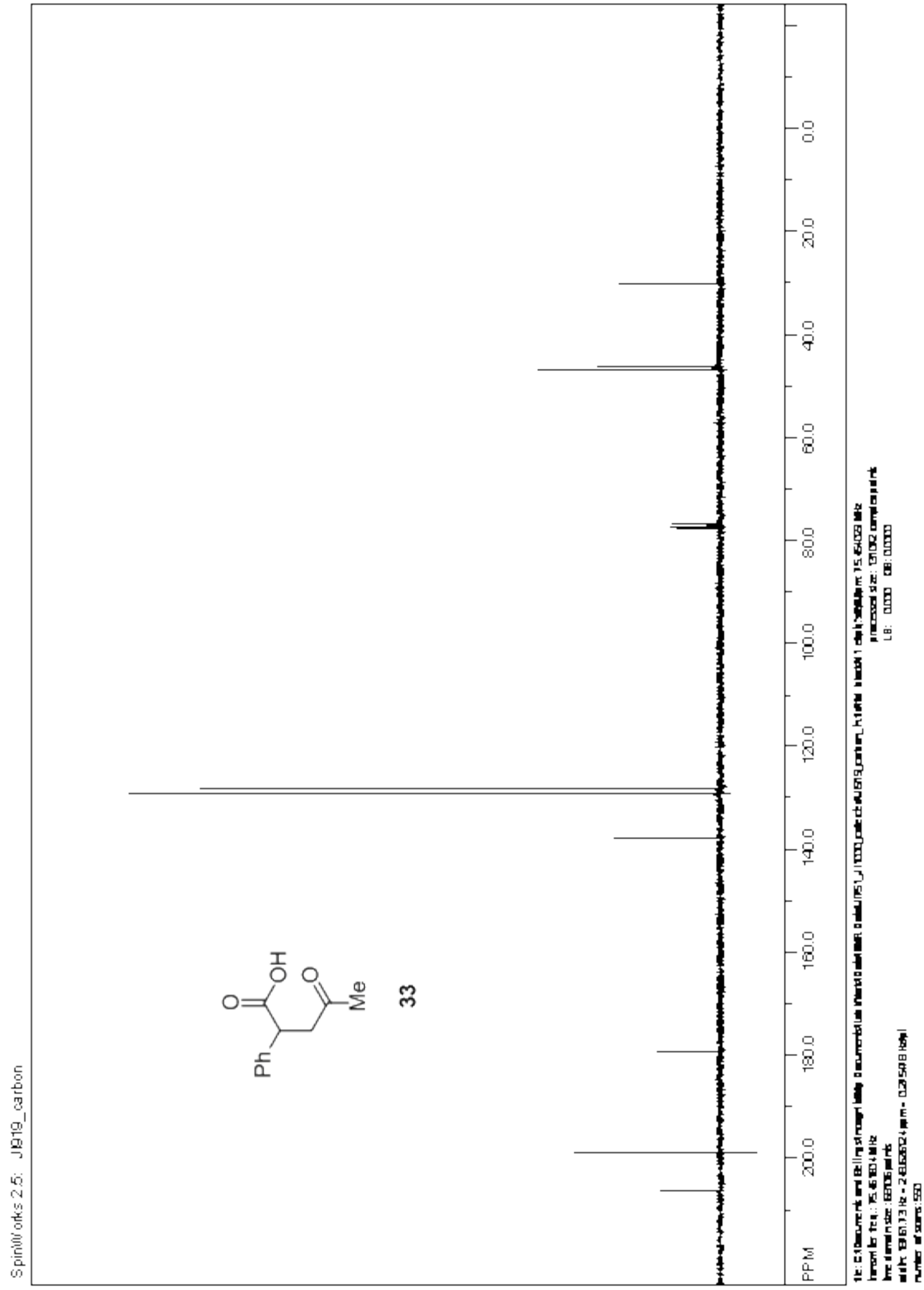

Figure A.38. ^{13}C Spectrum of **33**.

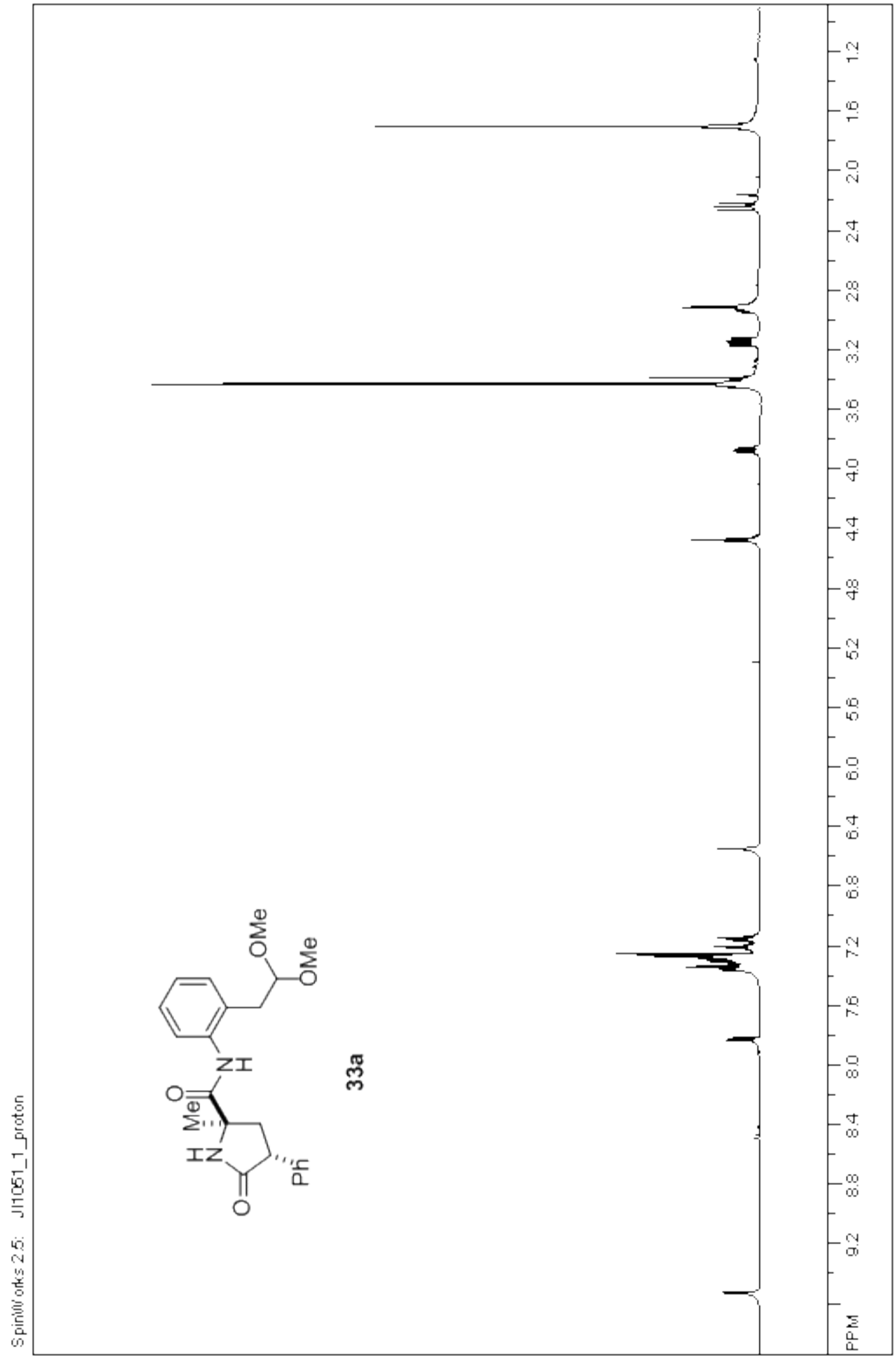

Figure A.39. ^{1}H Spectrum of **33a**.

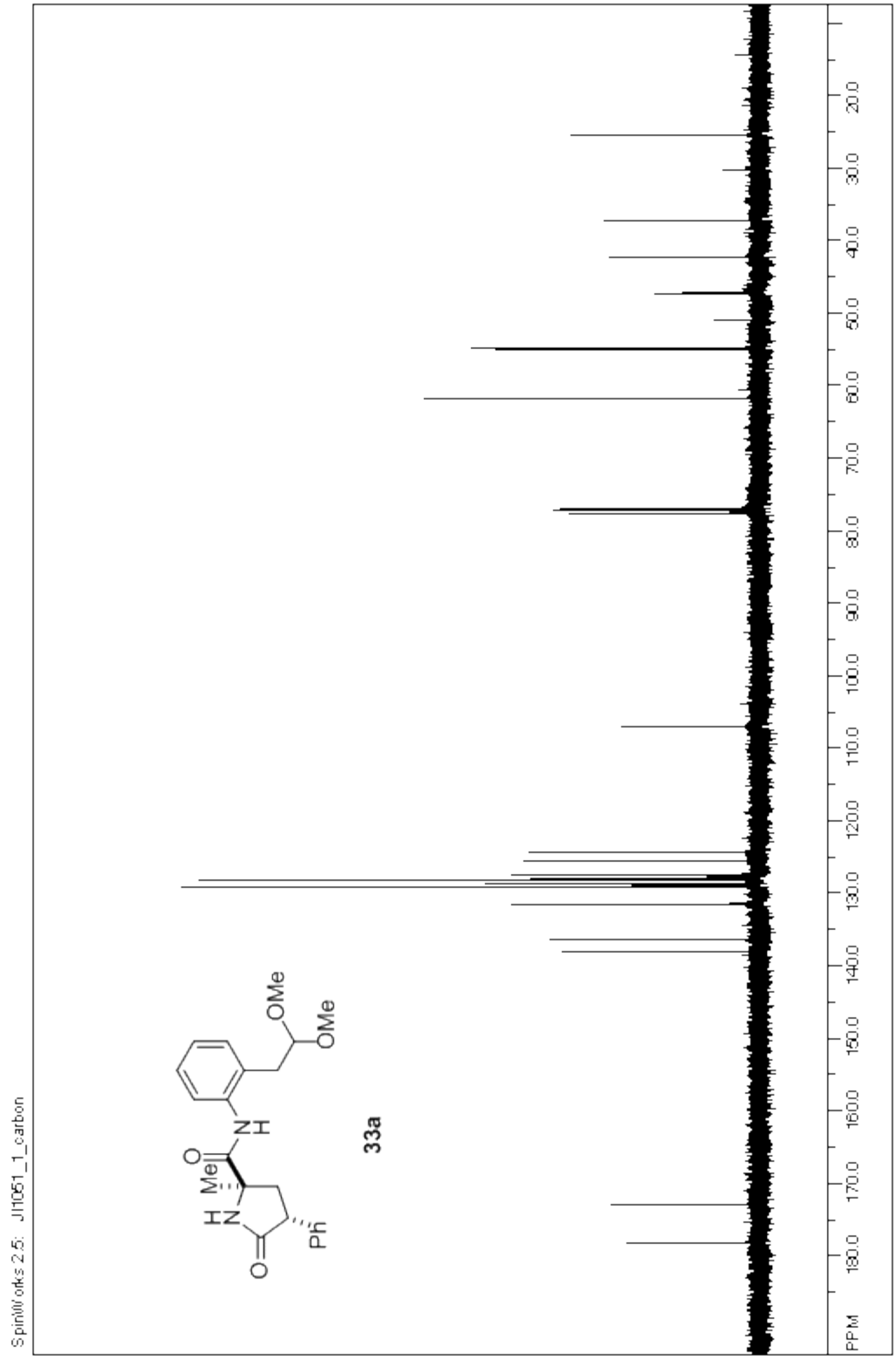

Figure A.40. ^{13}C Spectrum of **33a**.

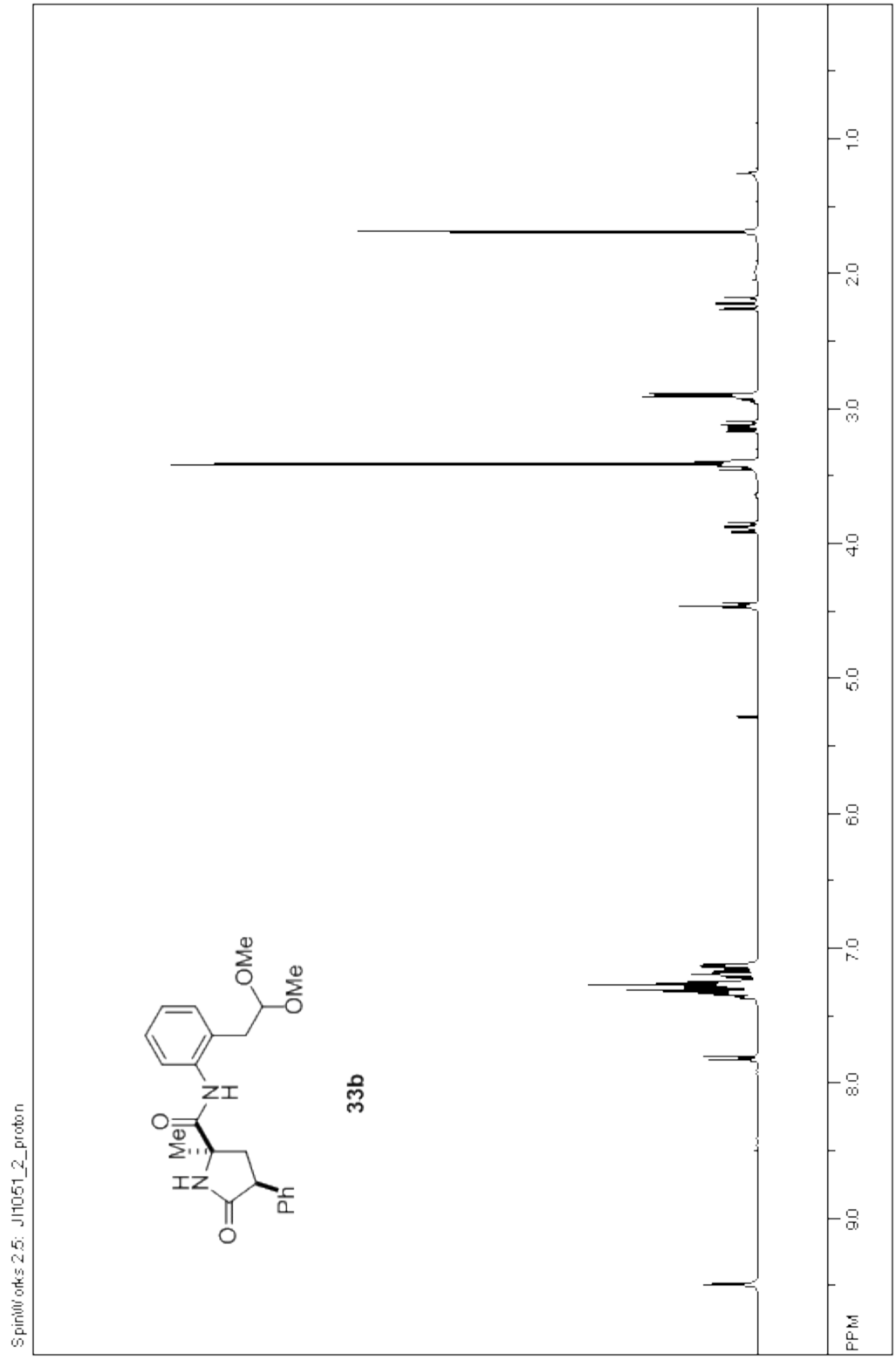

Figure A.41. ^{1}H Spectrum of **33b**.

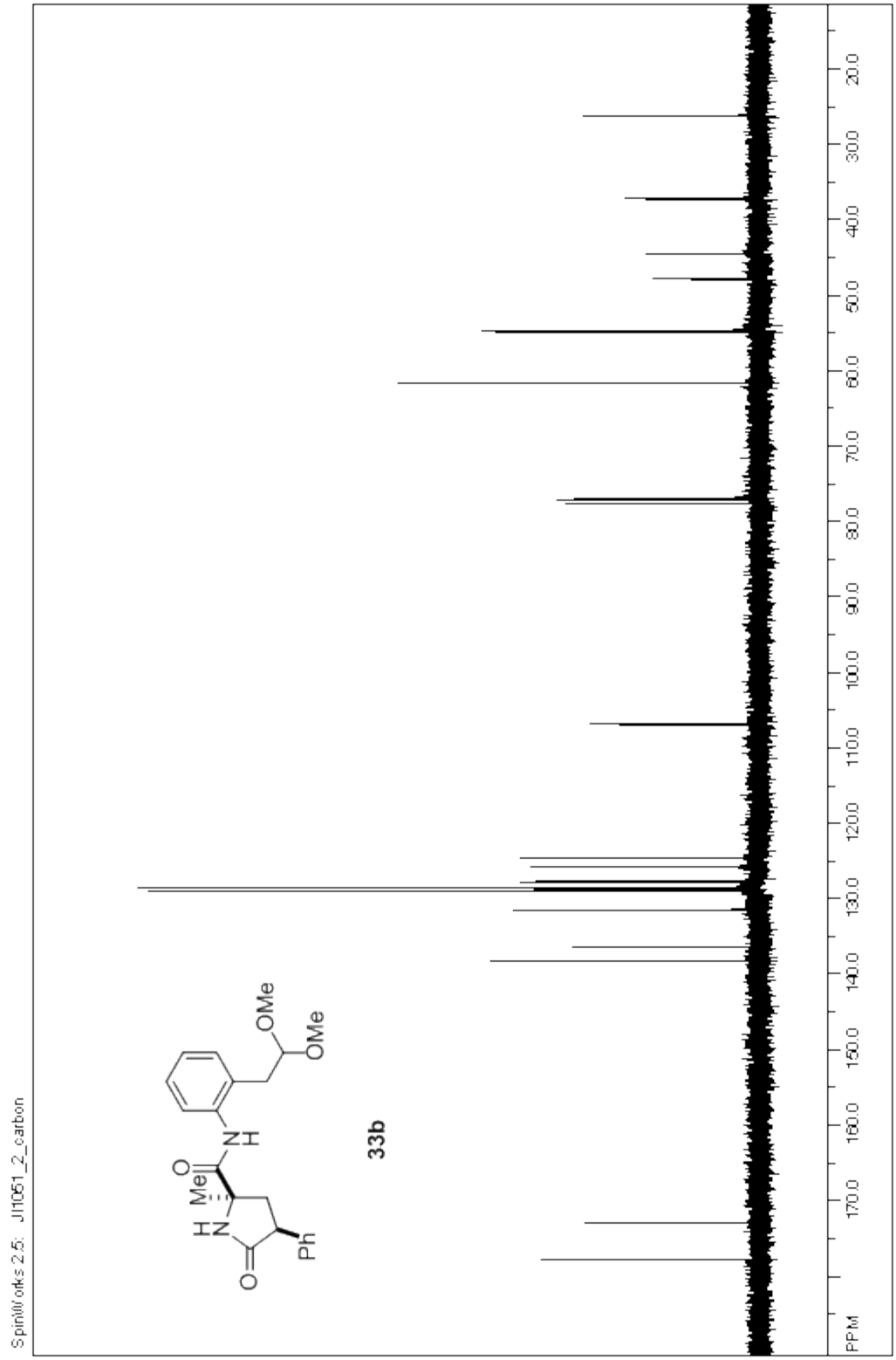

Figure A.42. ^{13}C Spectrum of **33b**.

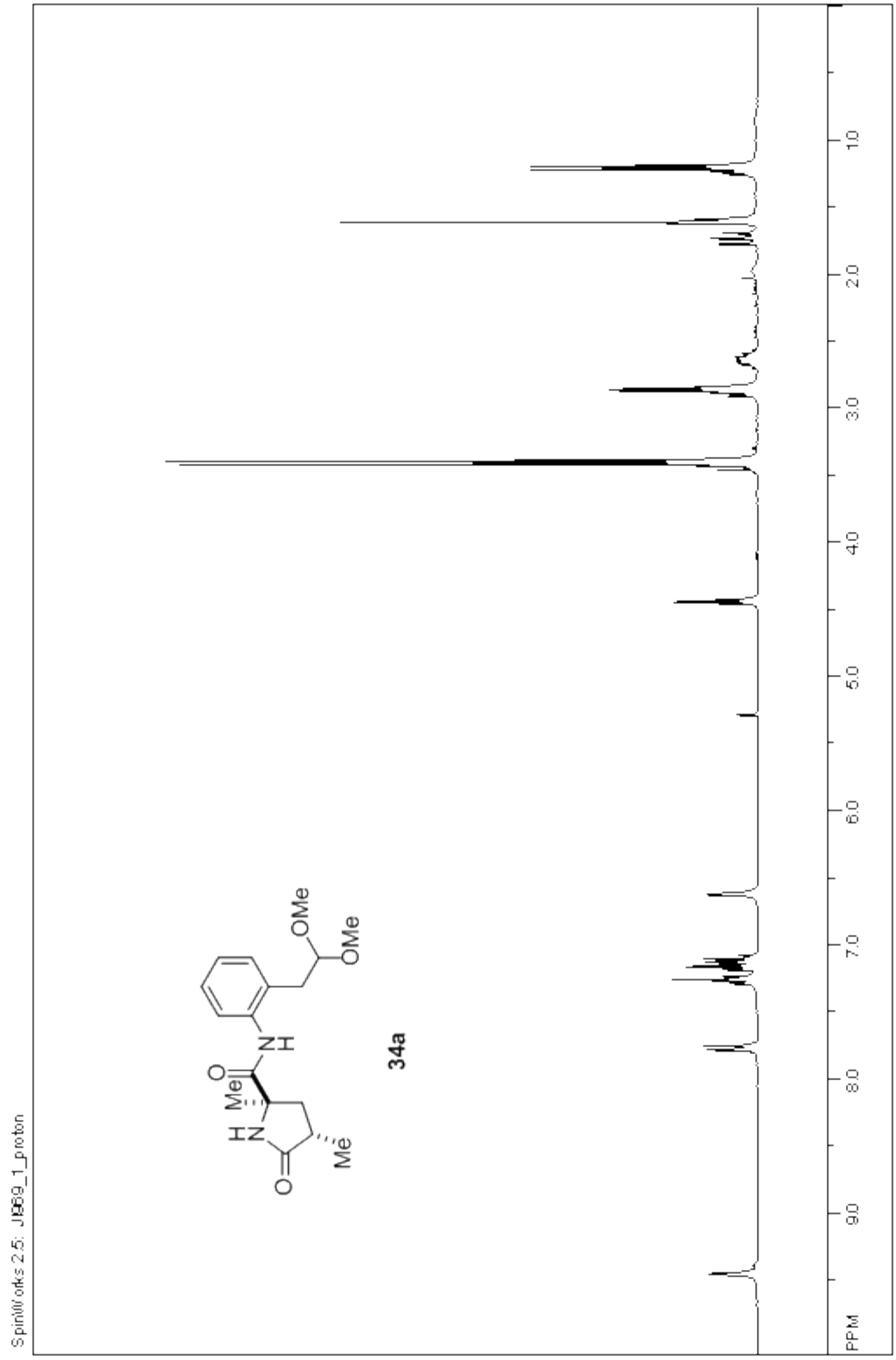

Figure A.43. ^{1}H Spectrum of **34a**.

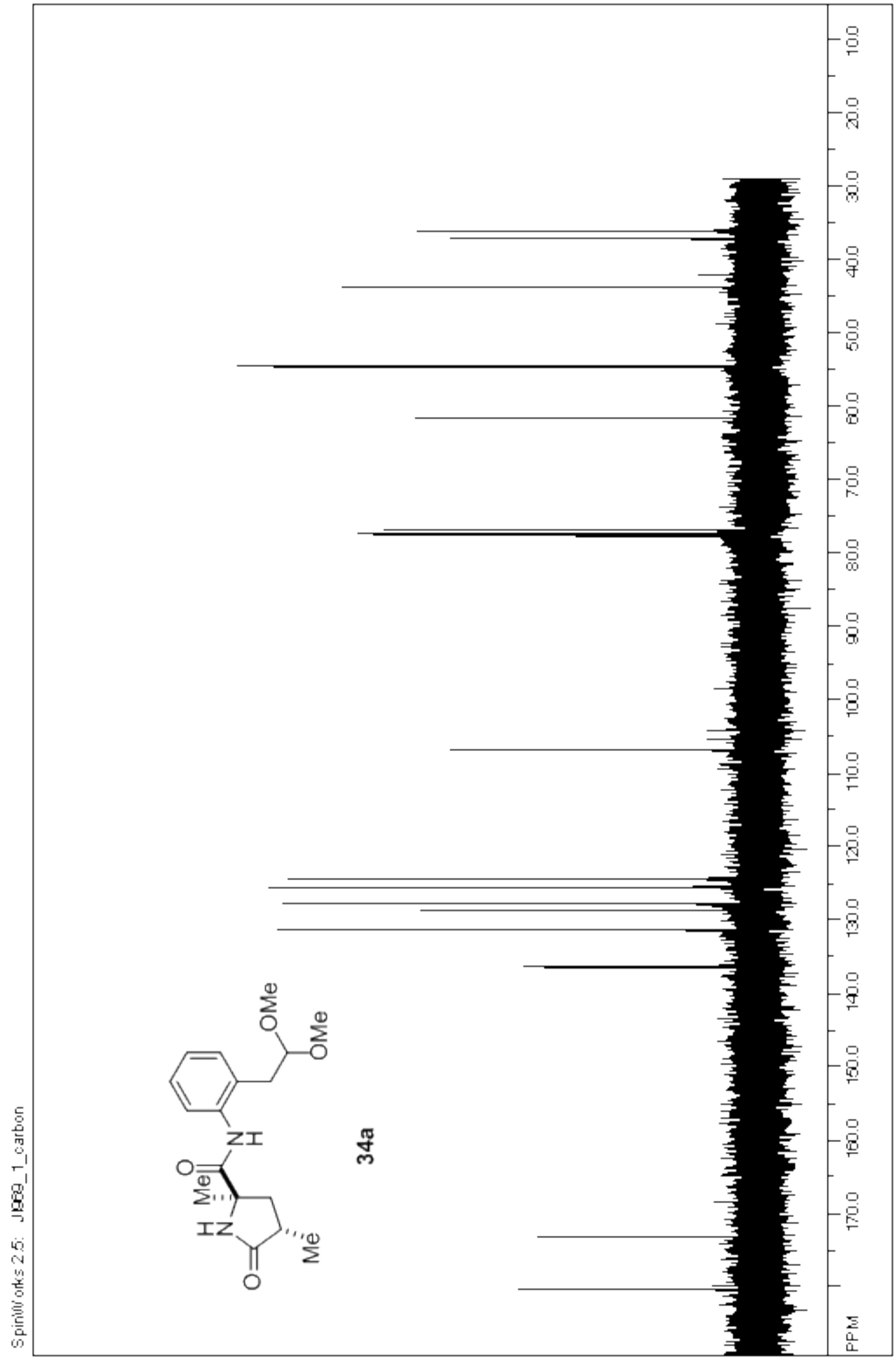

Figure A.44. ^{13}C Spectrum of **34a**.

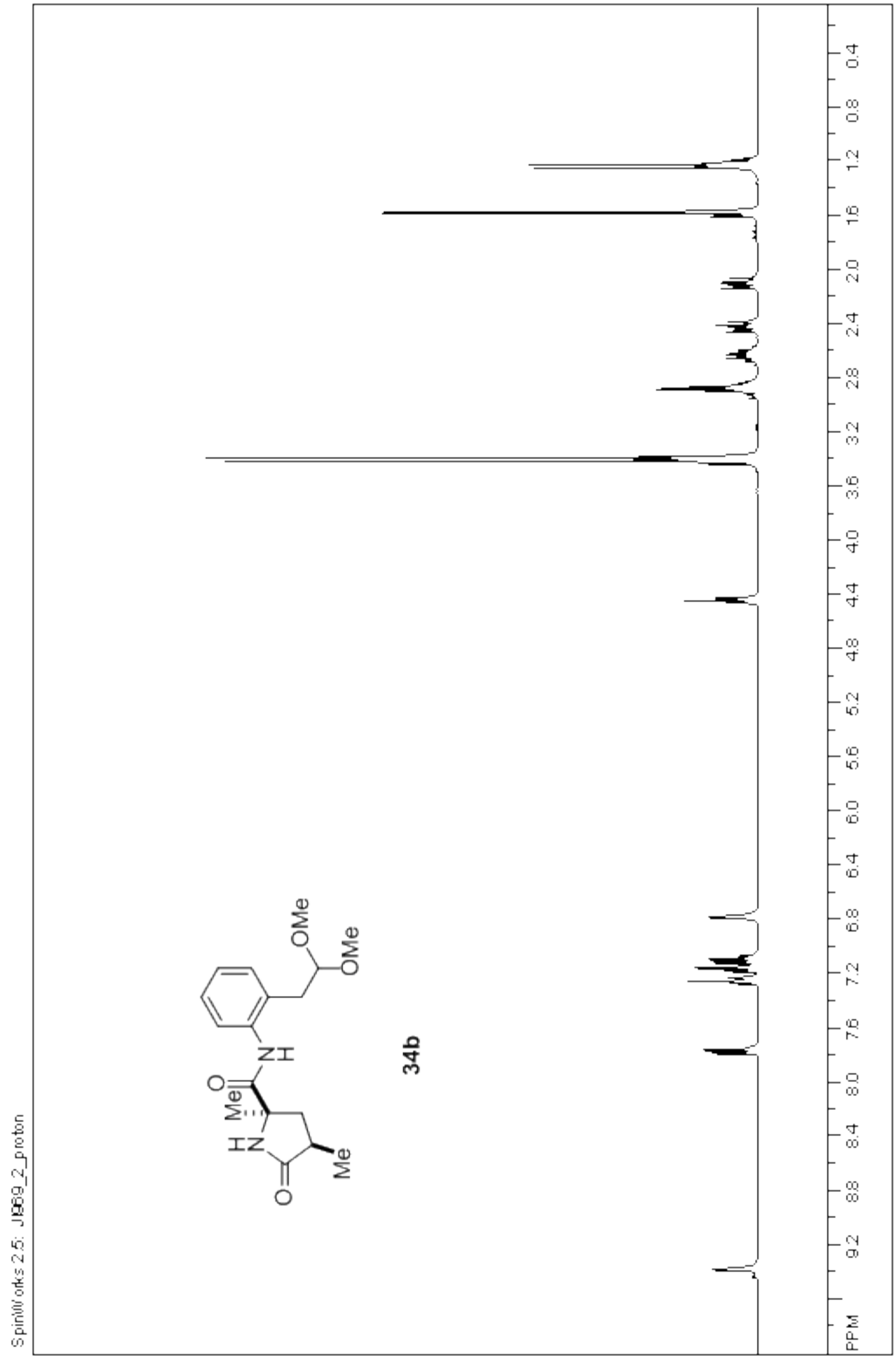

Figure A.45. ^{1}H Spectrum of **34b**.

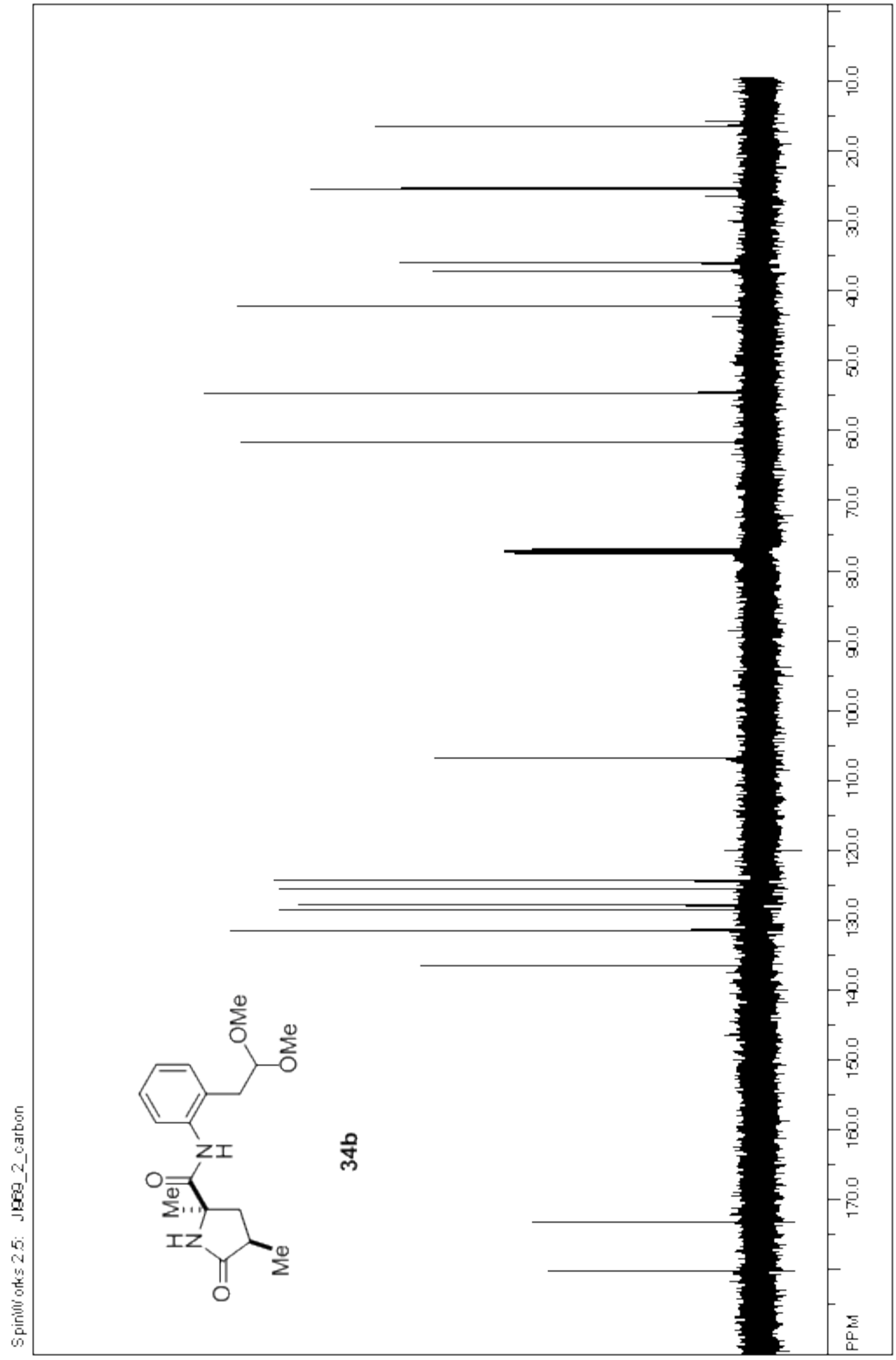

Figure A.46. ^{13}C Spectrum of **34b**.

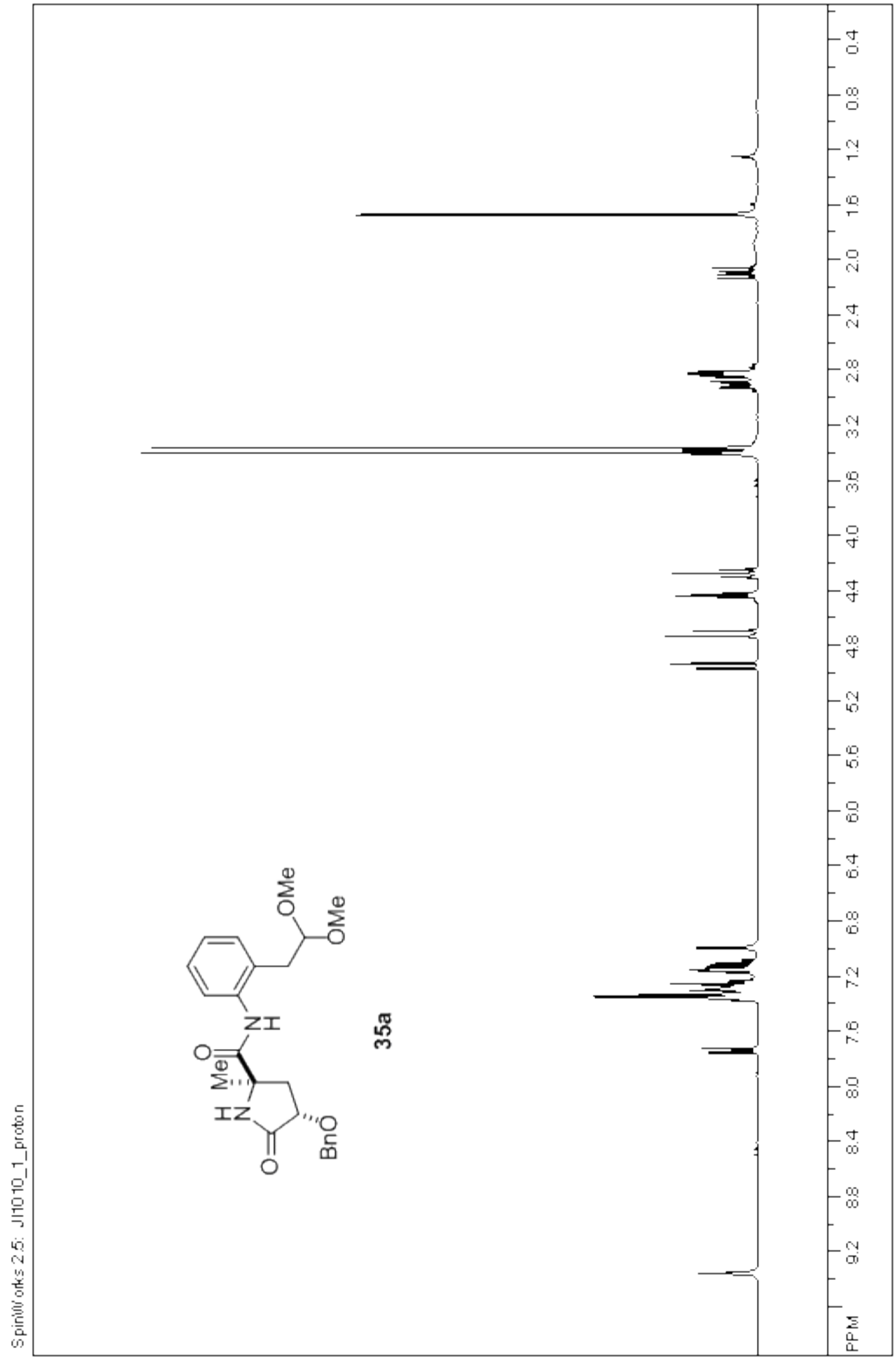

Figure A.47. ^{1}H Spectrum of **35a**.

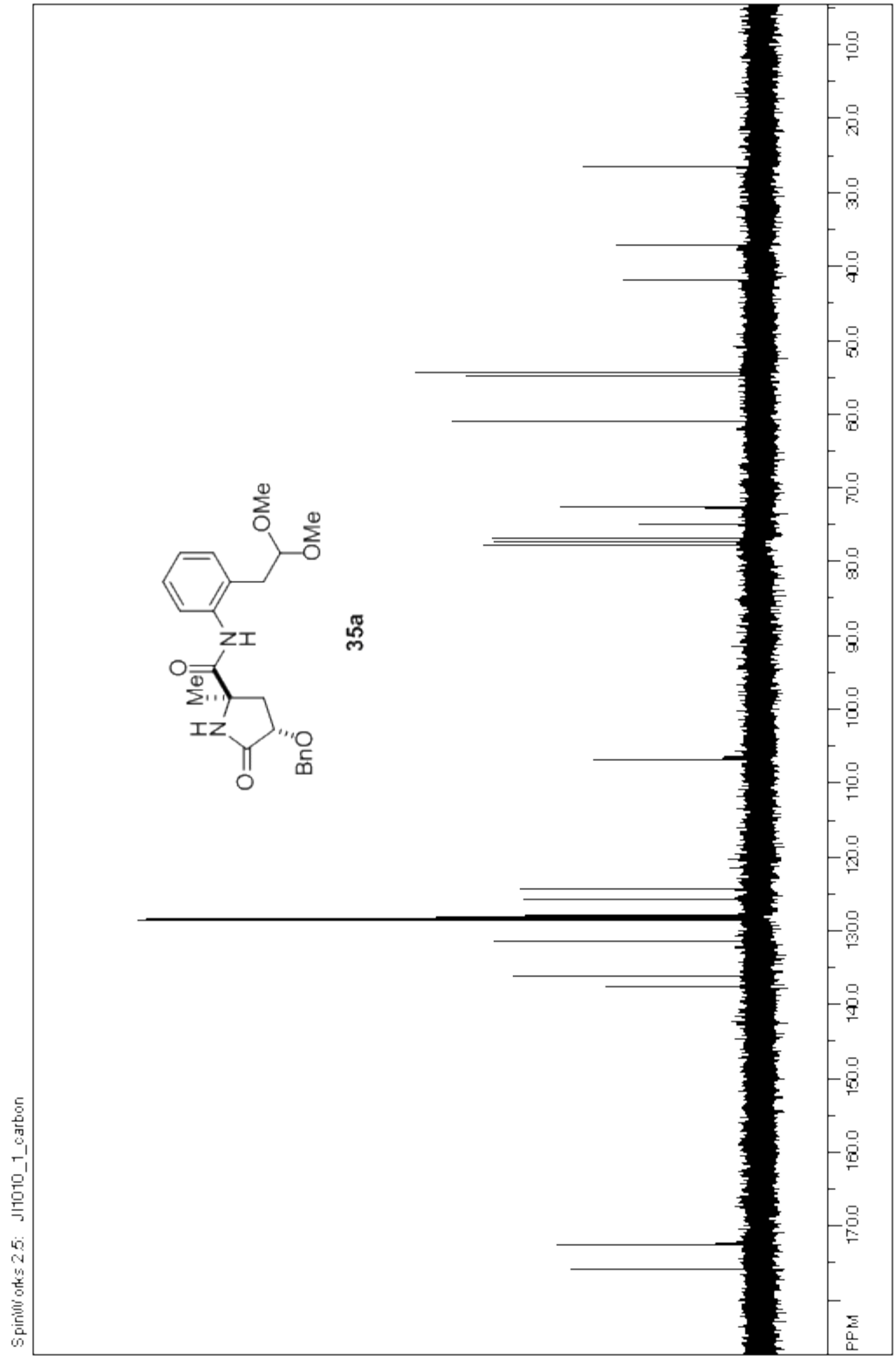

Figure A.48. ^{13}C Spectrum of **35a**.

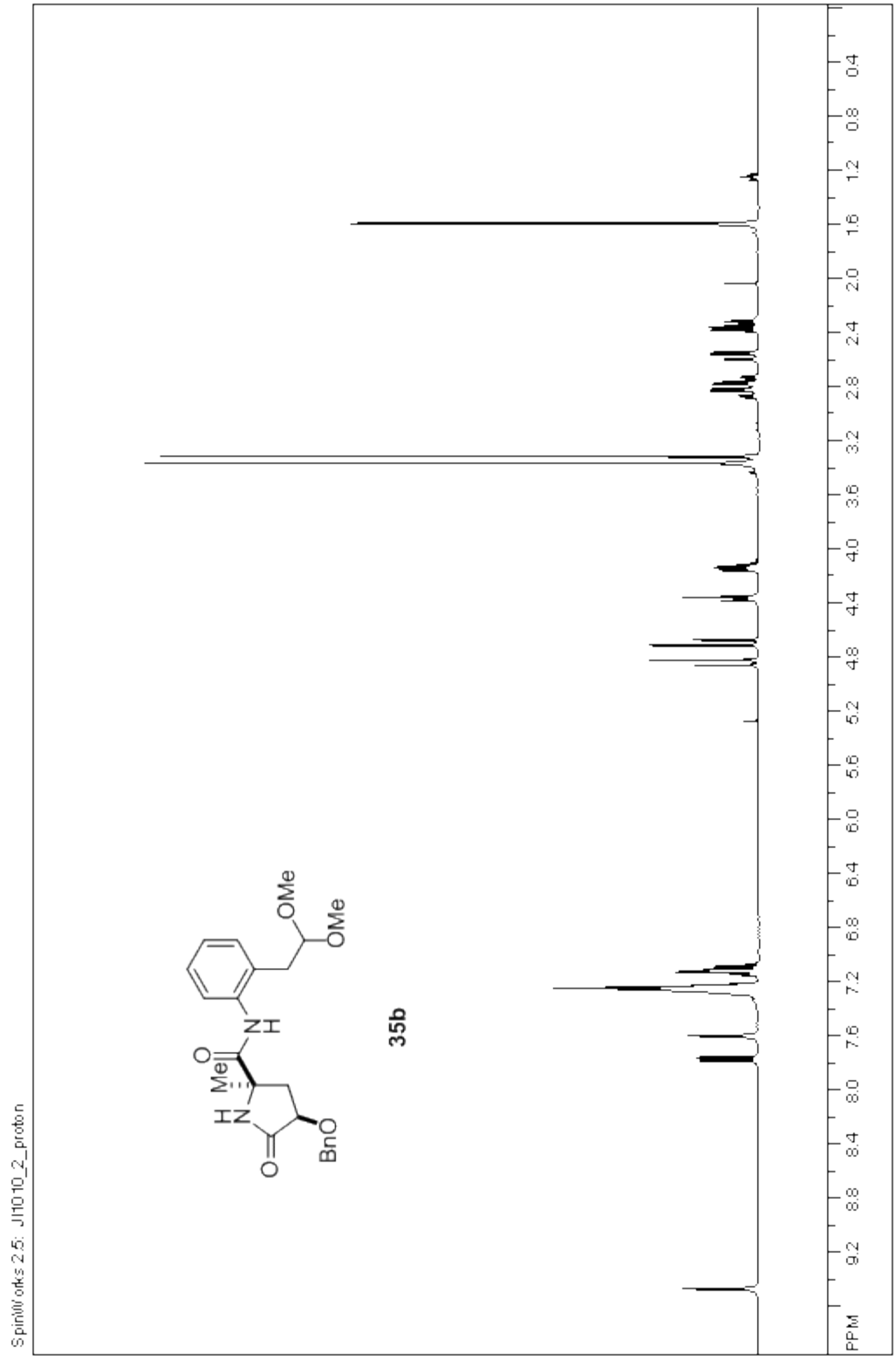

Figure A.49. ^{1}H Spectrum of **35b**.

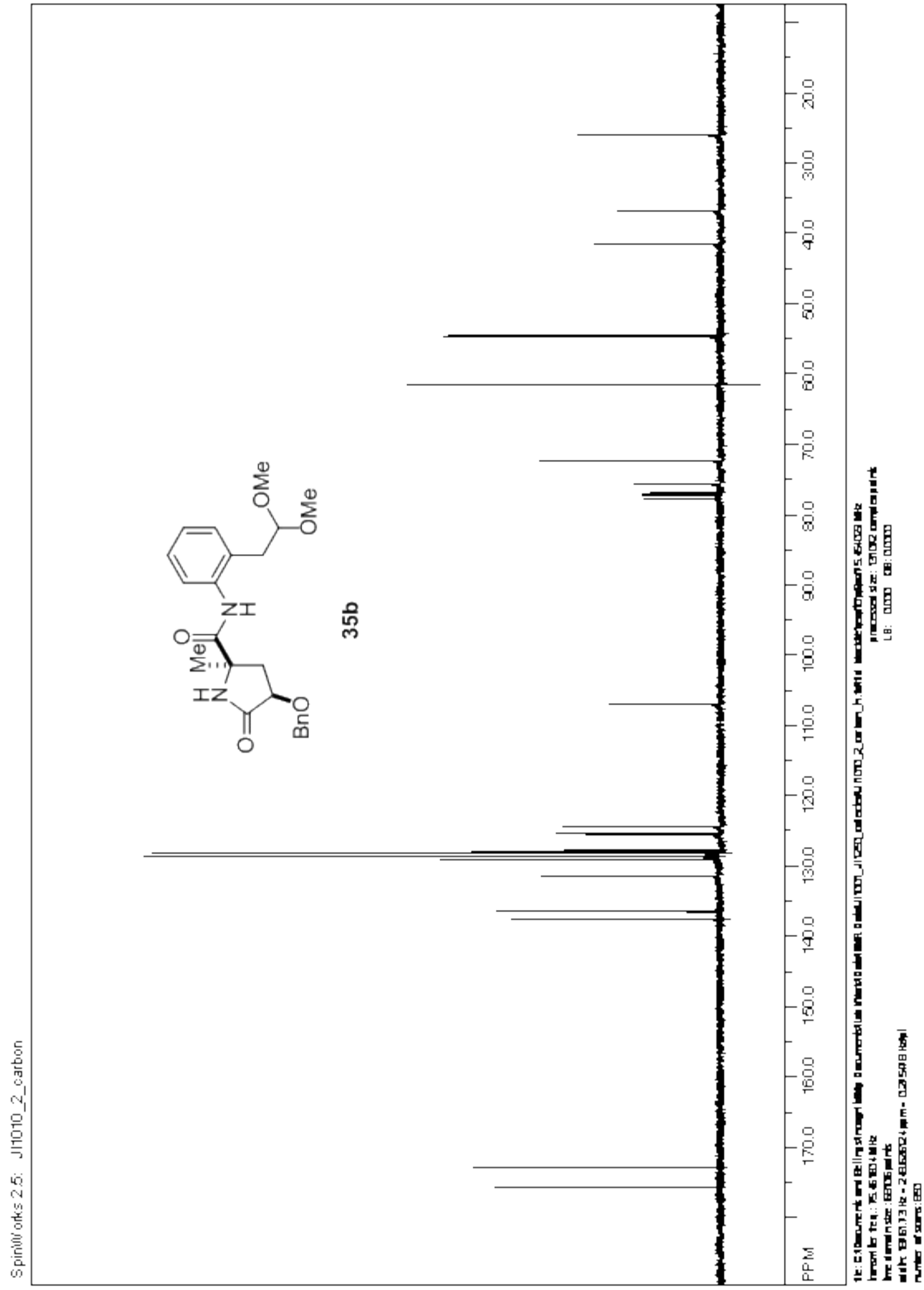

Figure A.50. ^{13}C Spectrum of **35b**.

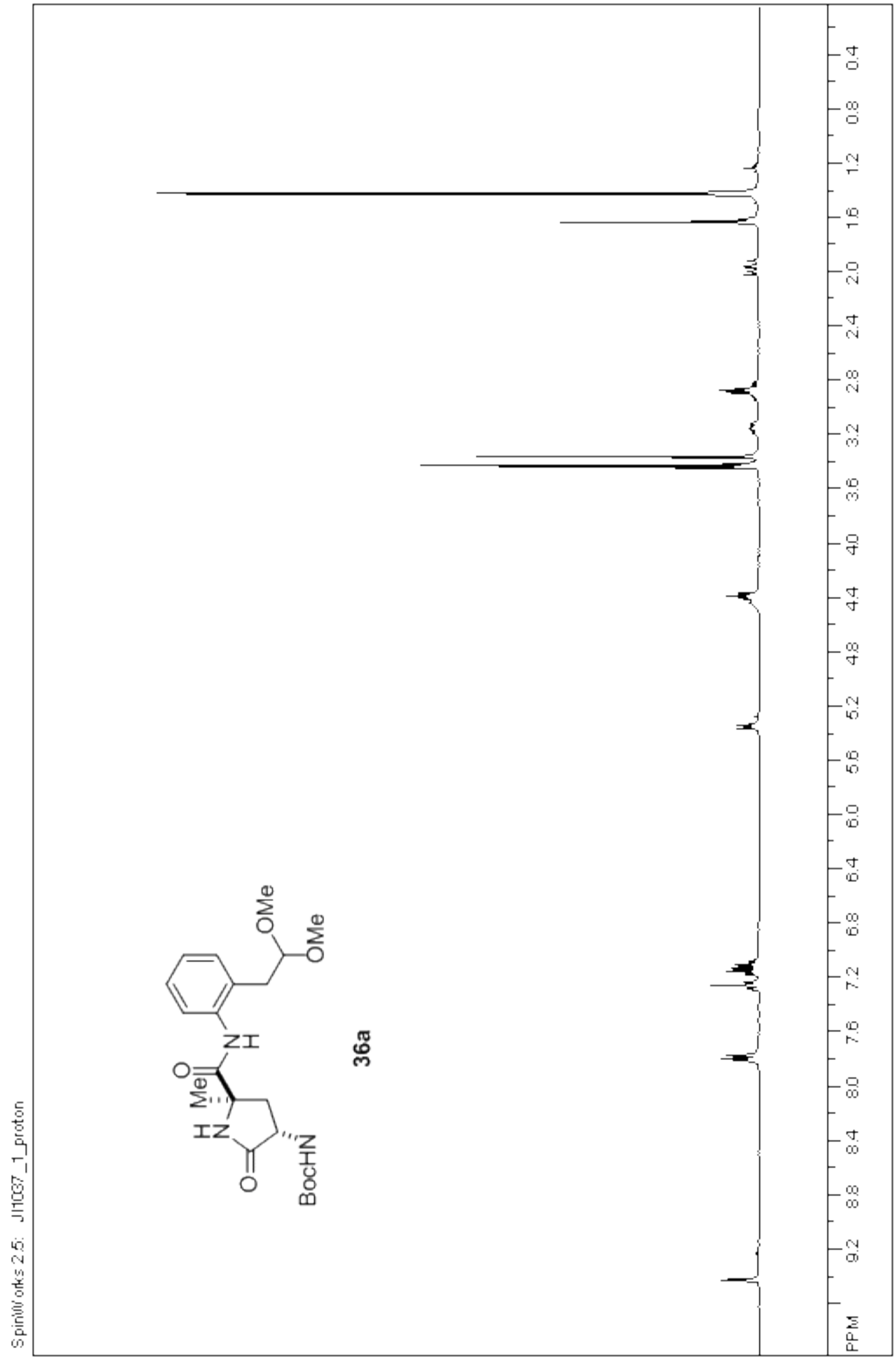

Figure A.51. ^{1}H Spectrum of **36a**.

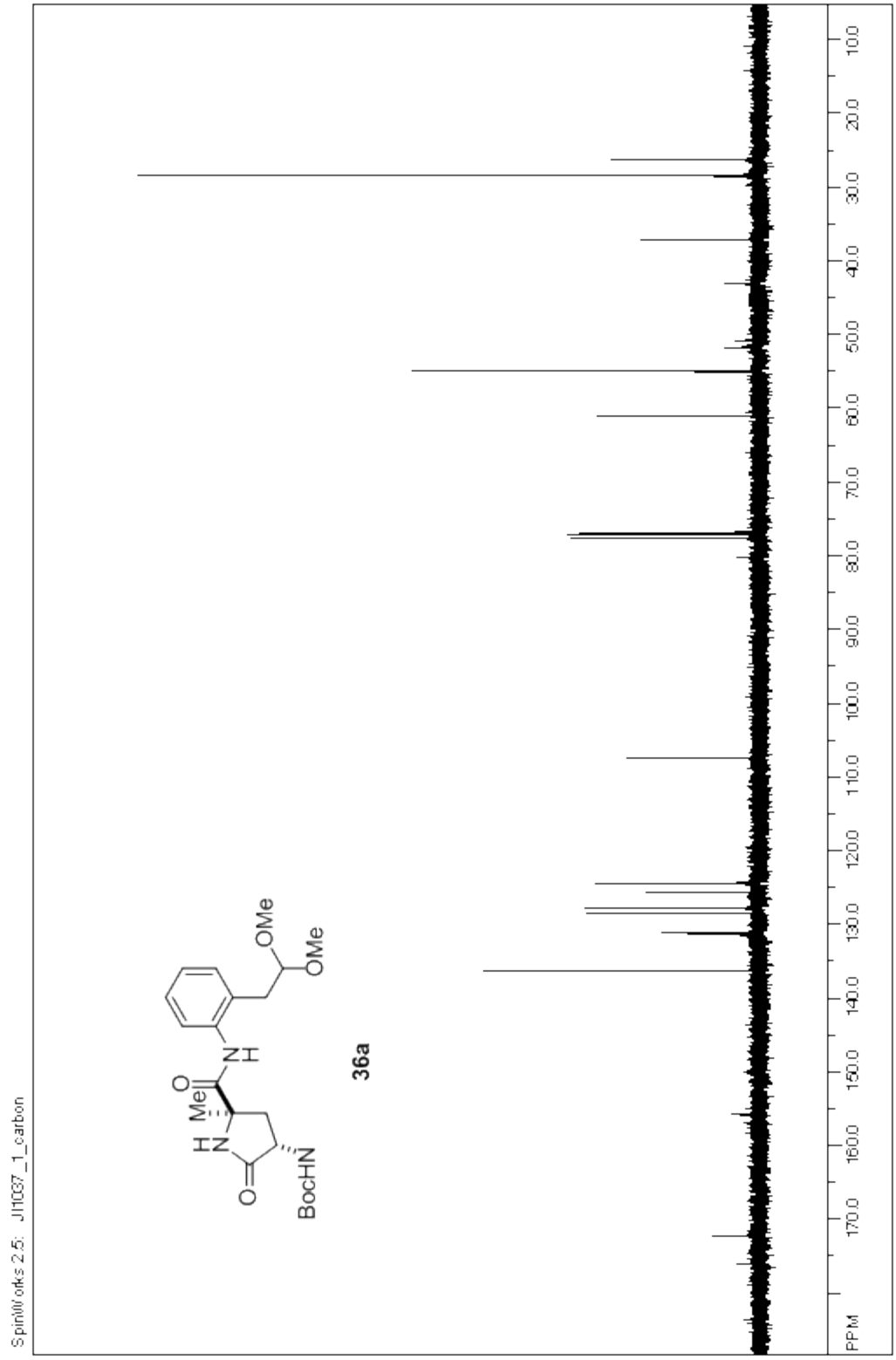

Figure A.52. ^{13}C Spectrum of **36a**.

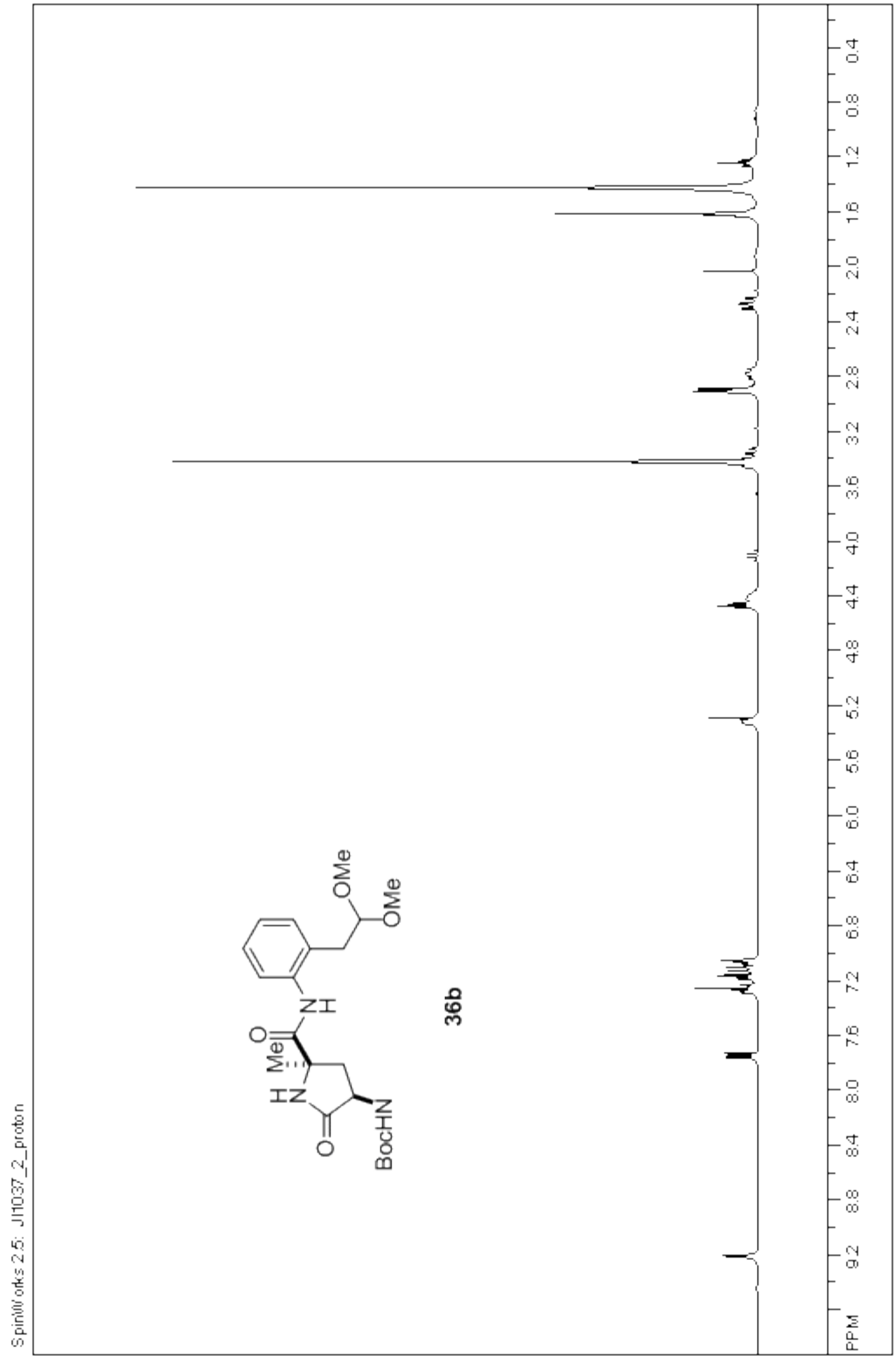

Figure A.53. ^{1}H Spectrum of **36b**.

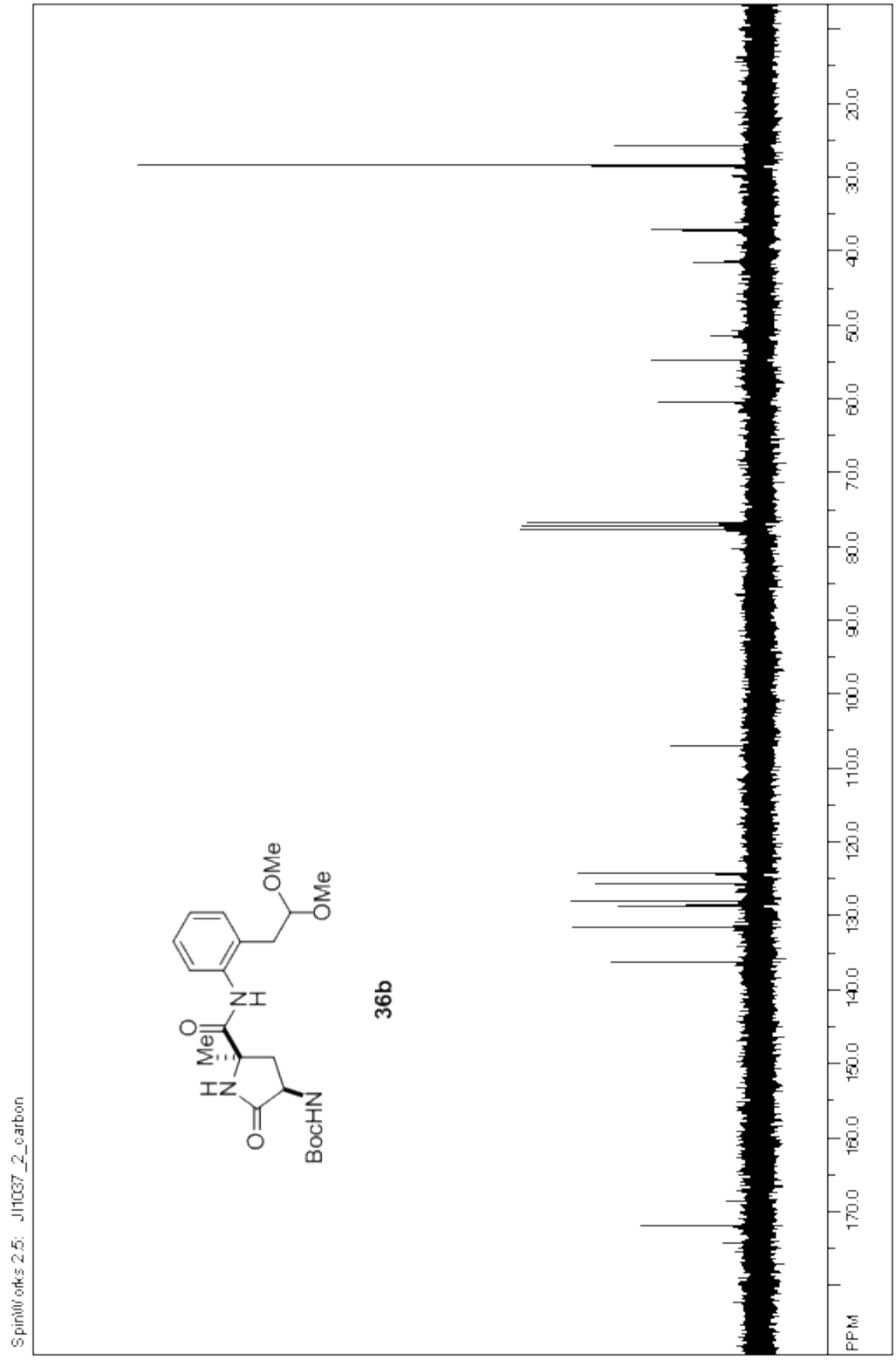

Figure A.54. ^{13}C Spectrum of **36b**.

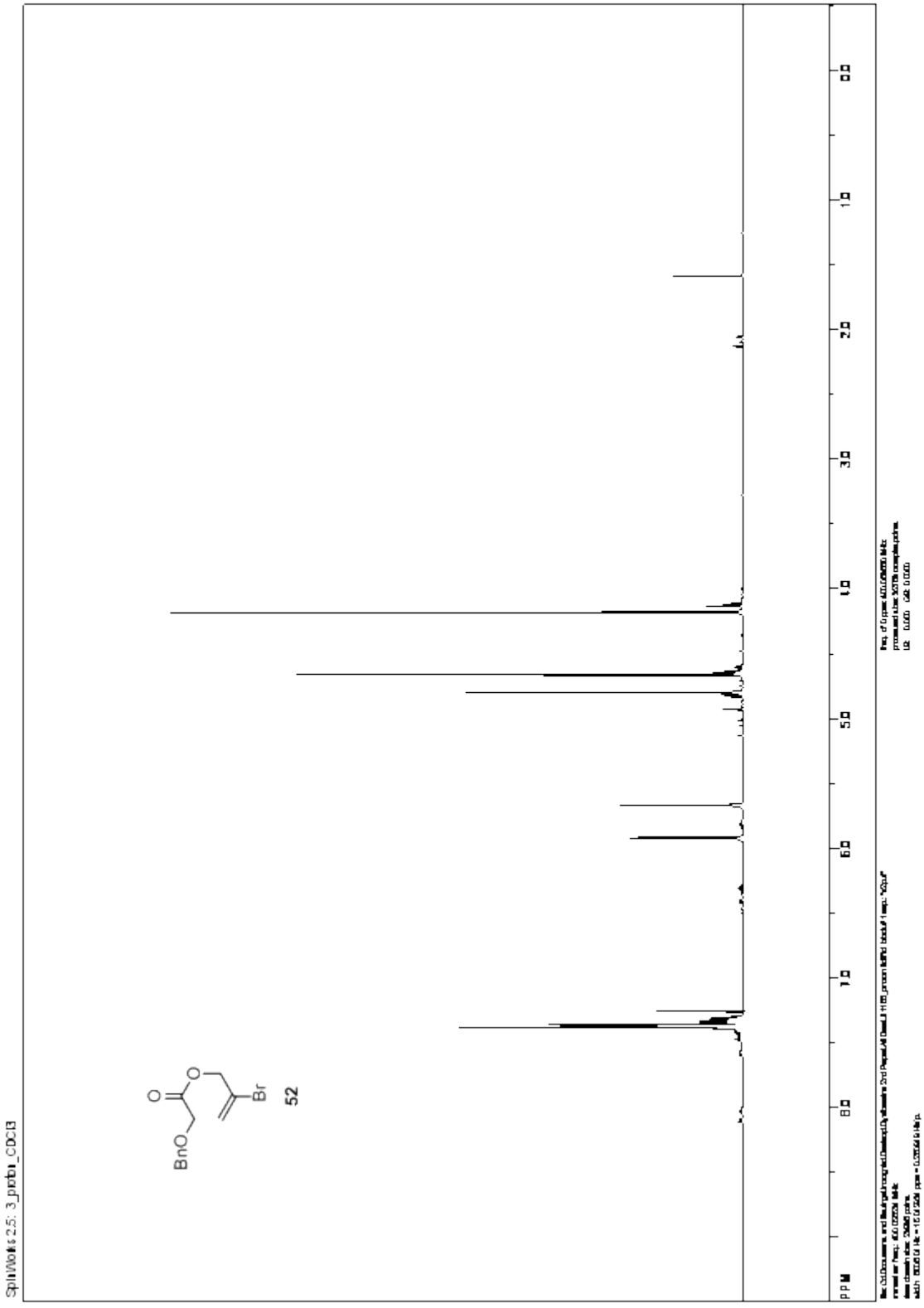

Figure A.55. ^{1}H Spectrum of **52**.

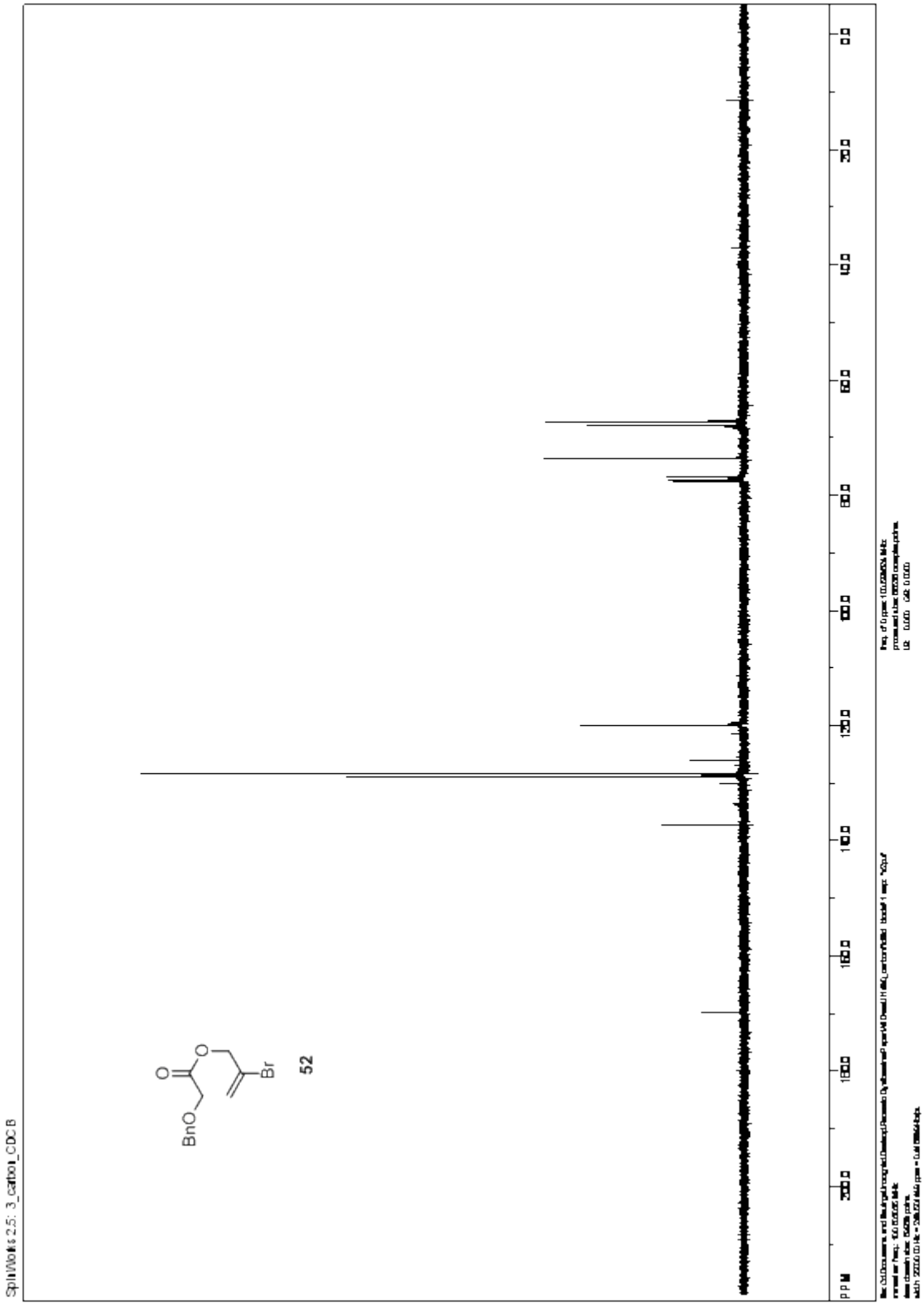

Figure A.56. ^{13}C Spectrum of **52**.

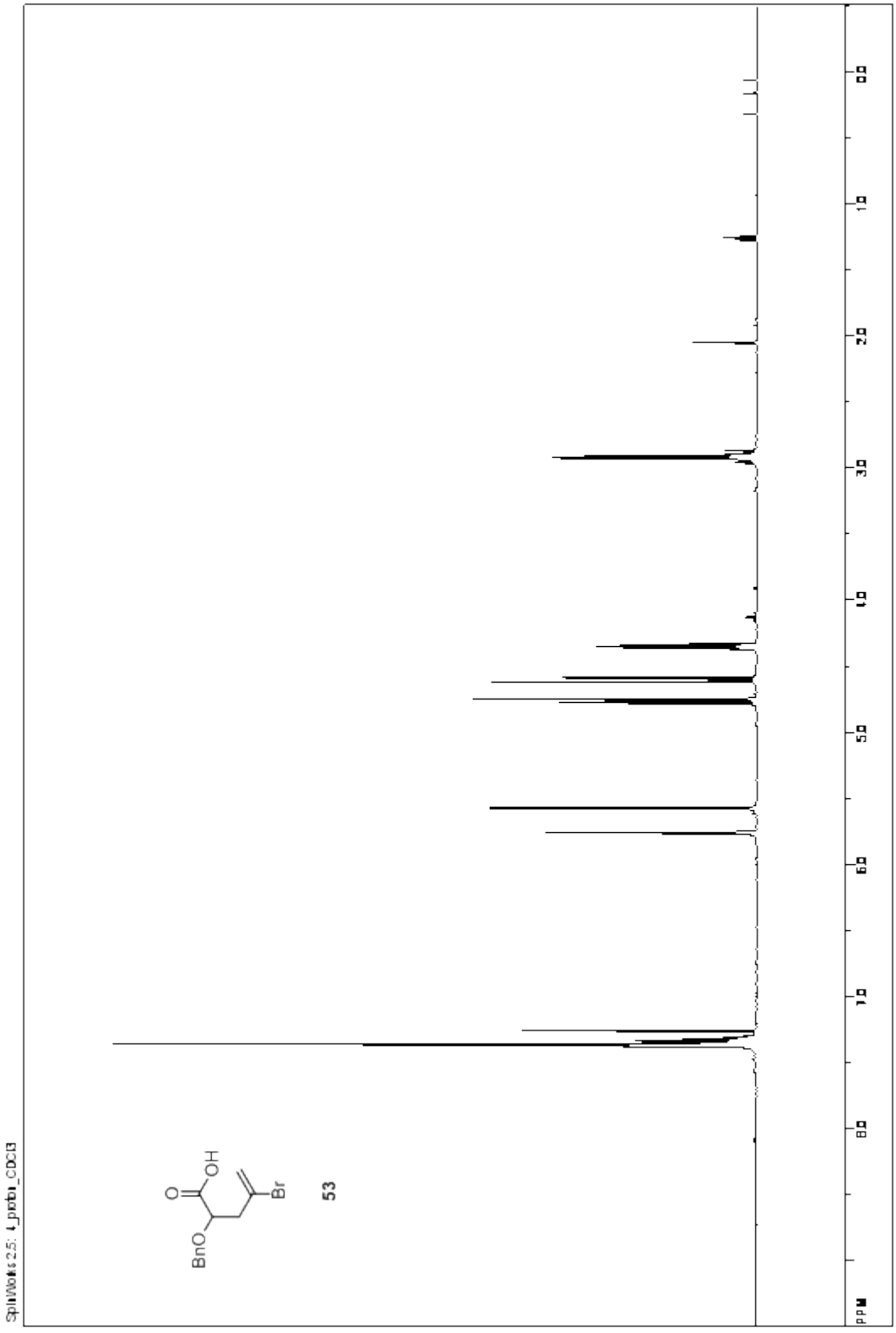

Figure A.57. ^{1}H Spectrum of **53**.

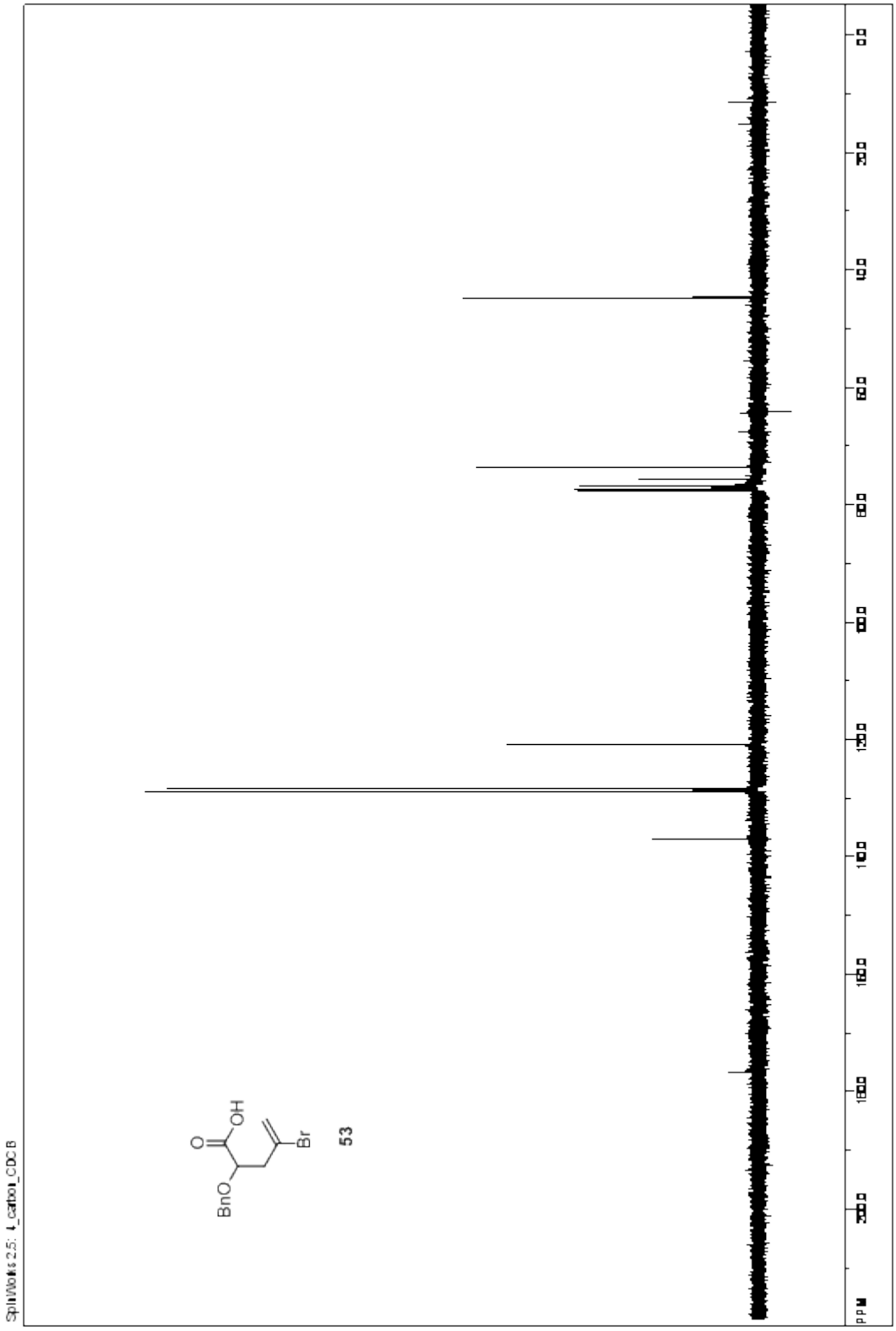

Figure A.58. ^{13}C Spectrum of **53**.

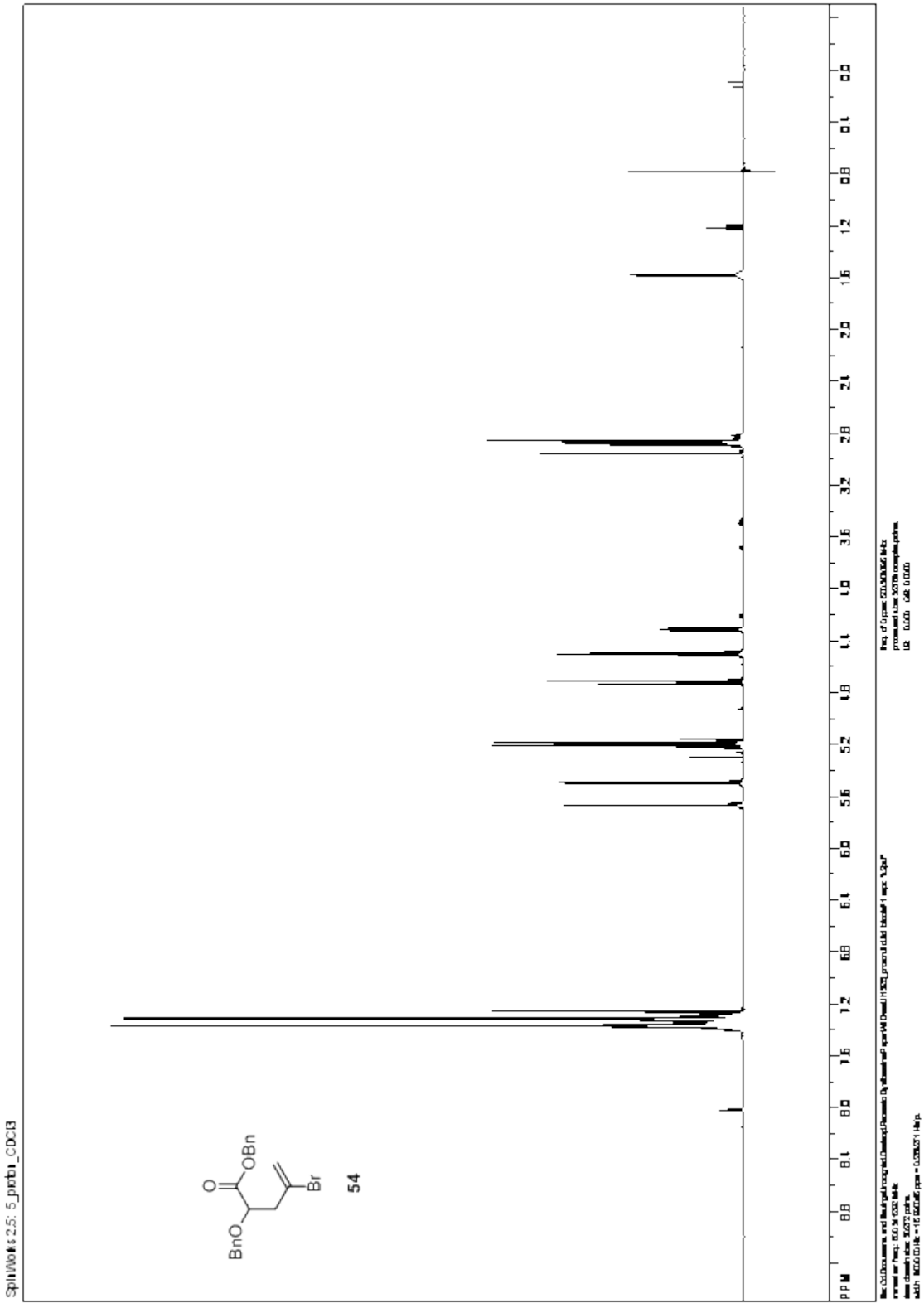

Figure A.59. ^{1}H Spectrum of **54**.

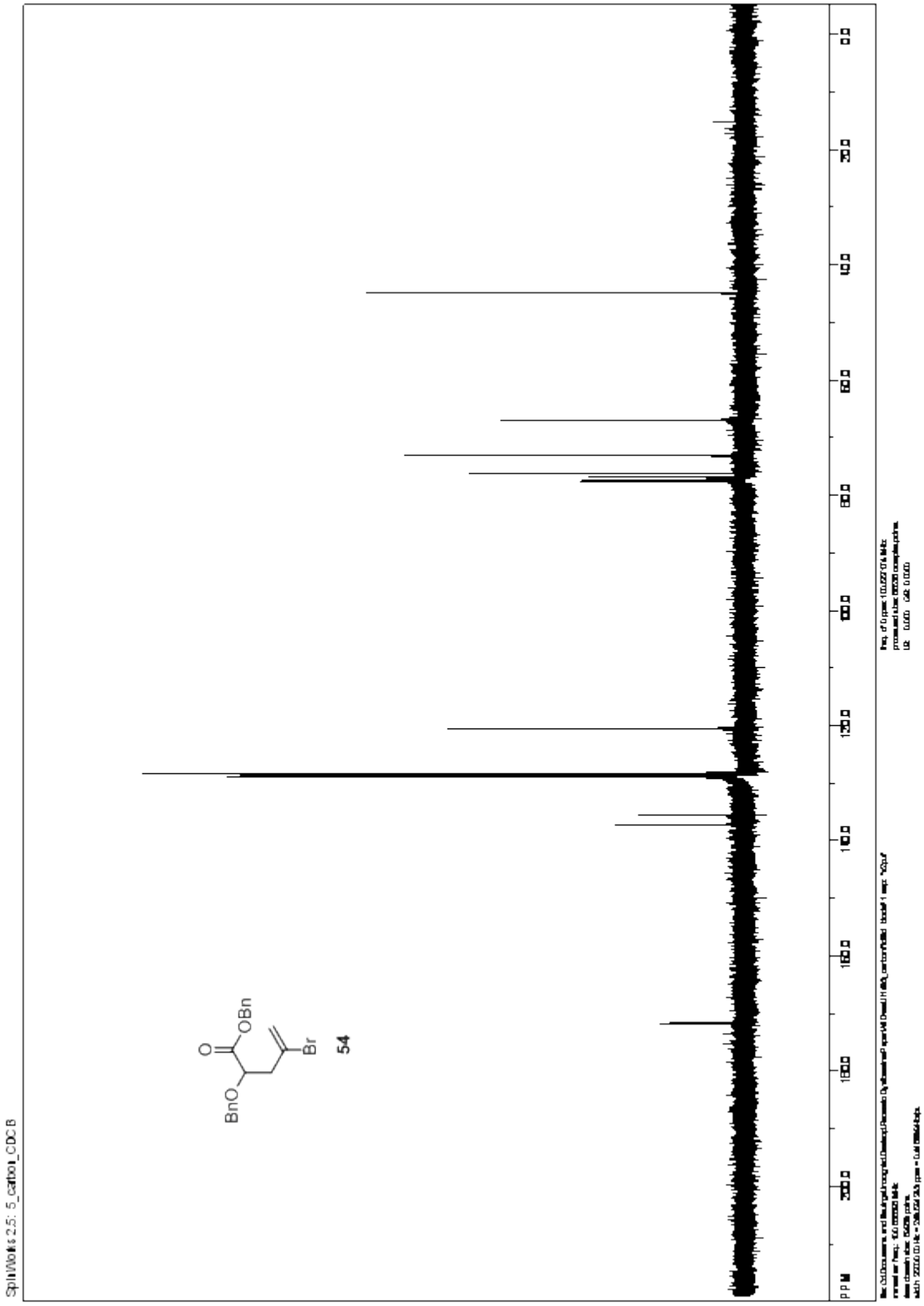

Figure A.60. ^{13}C Spectrum of **54**.

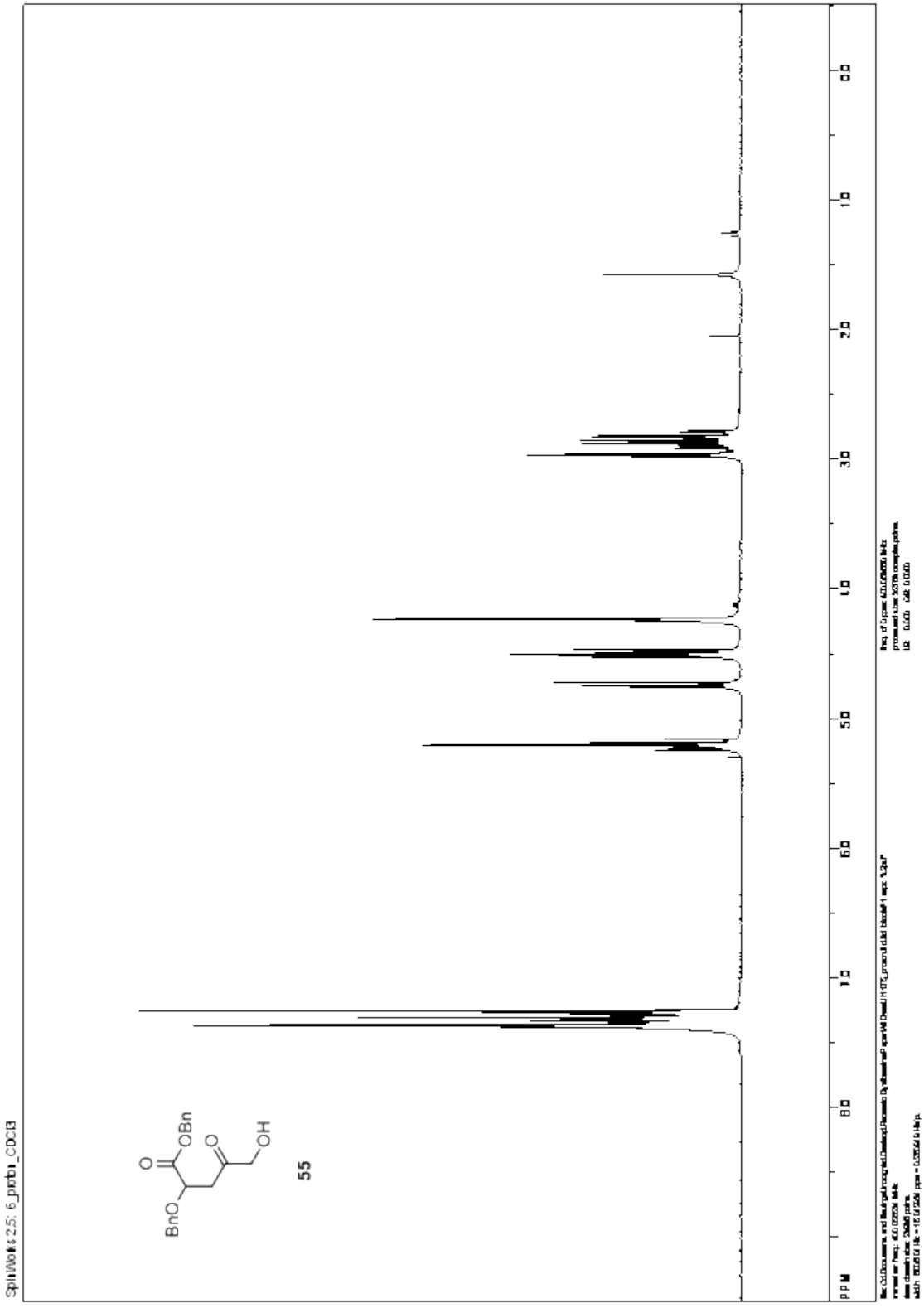

Figure A.61. ^{1}H Spectrum of **55**.

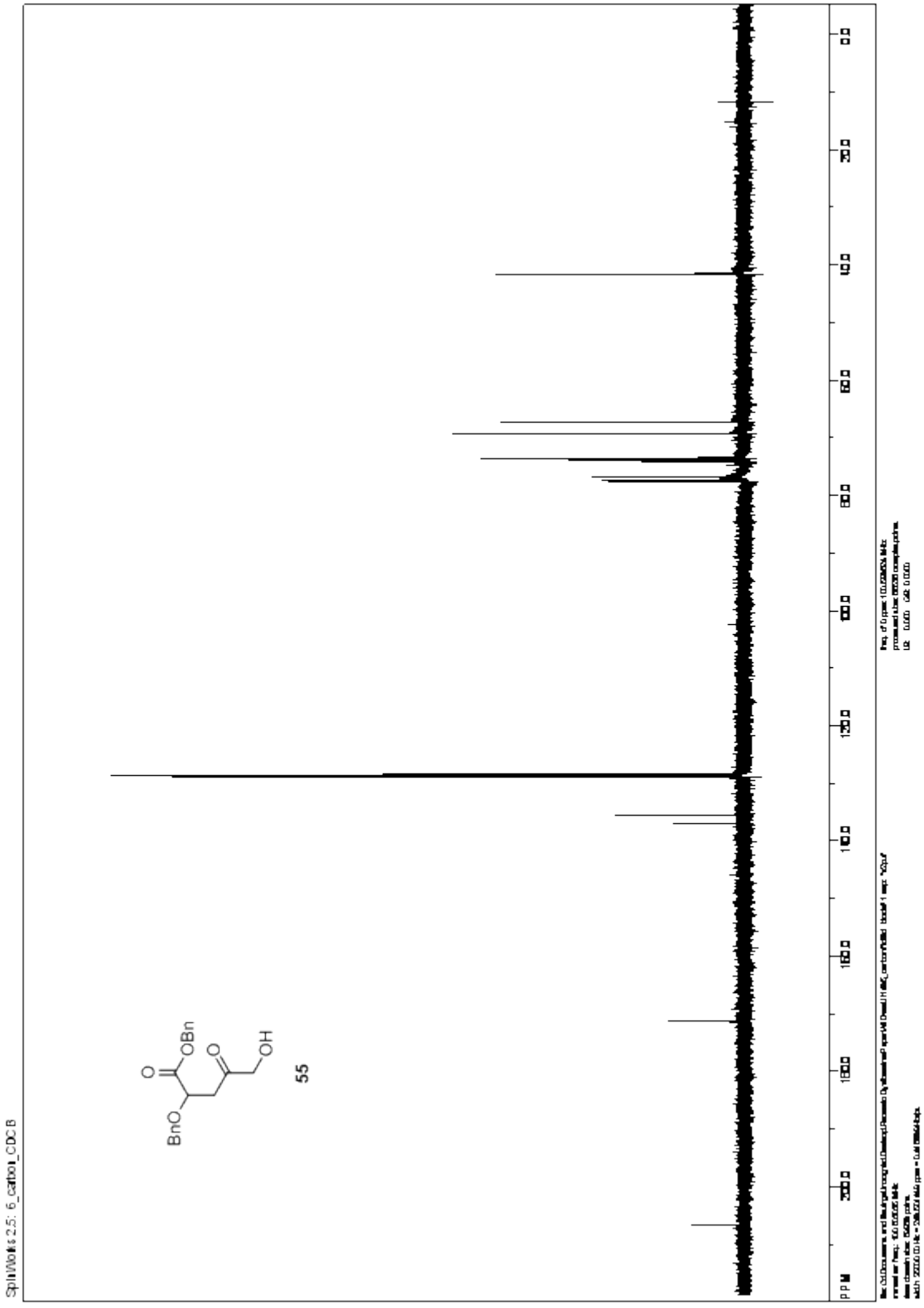

Figure A.62. ^{13}C Spectrum of **55**.

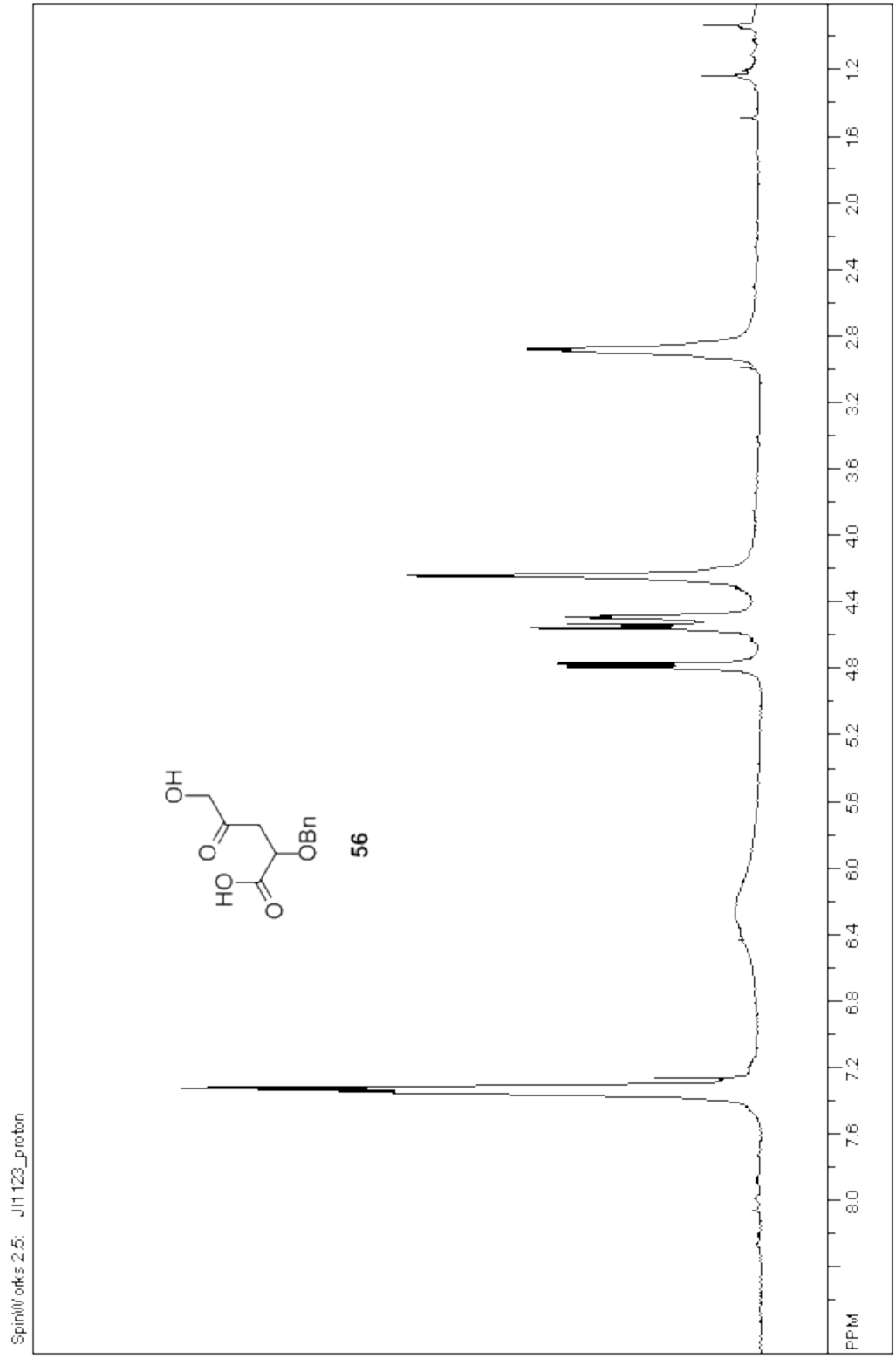

Figure A.63. ^{1}H Spectrum of **56**.

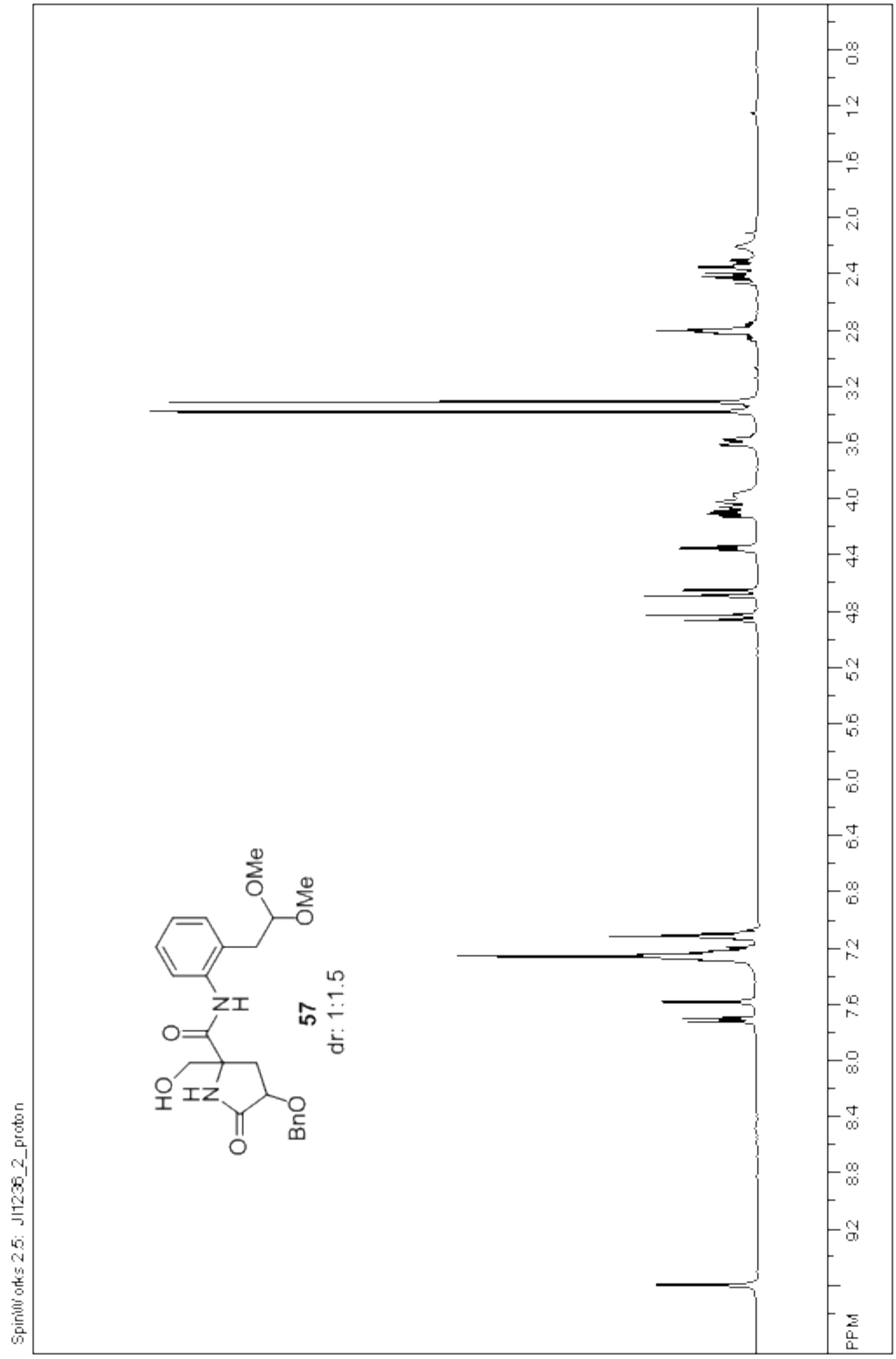

Figure A.64. ^{1}H Spectrum of **57**.

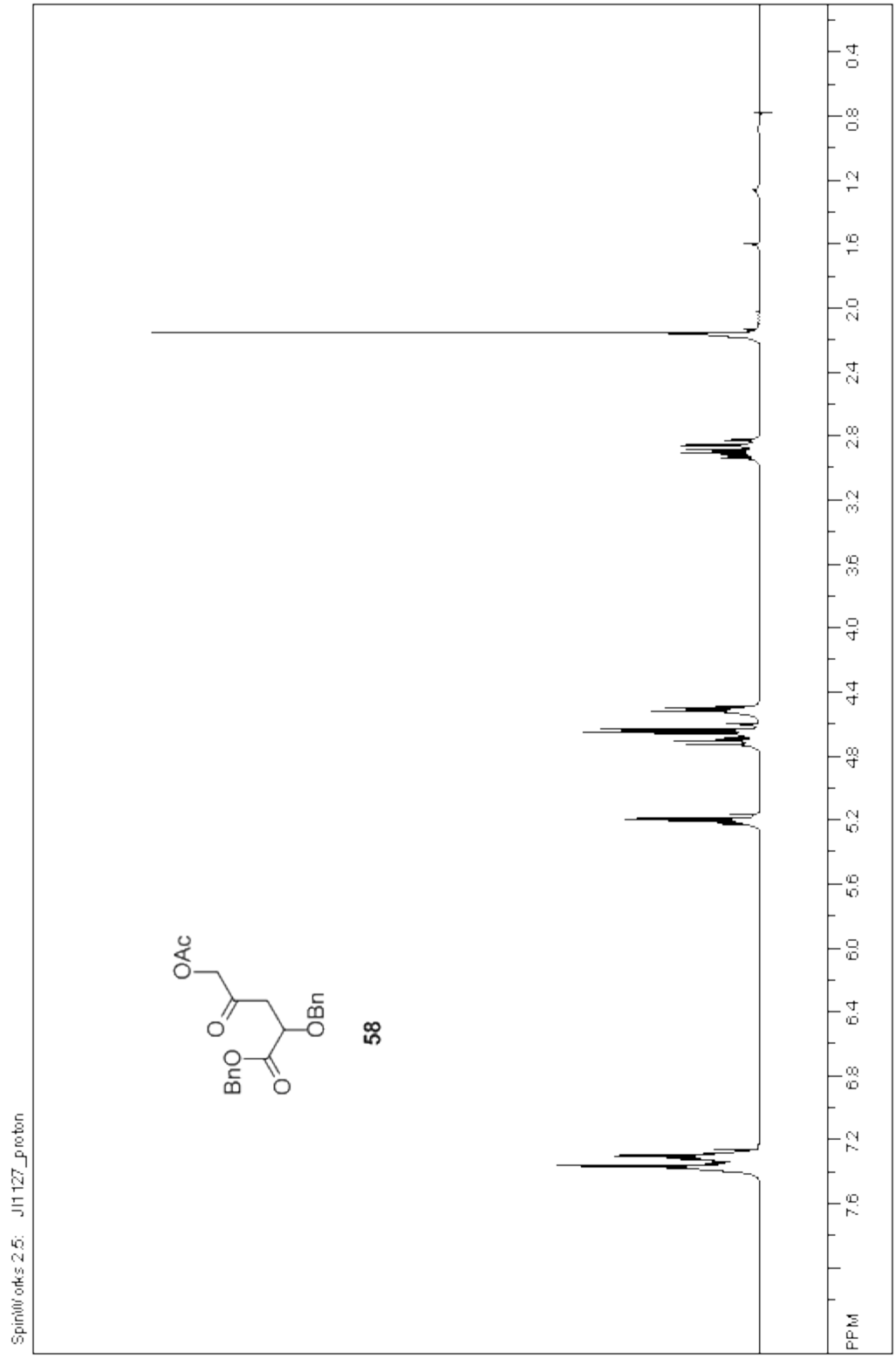

Figure A.65. ^{1}H Spectrum of **58**.

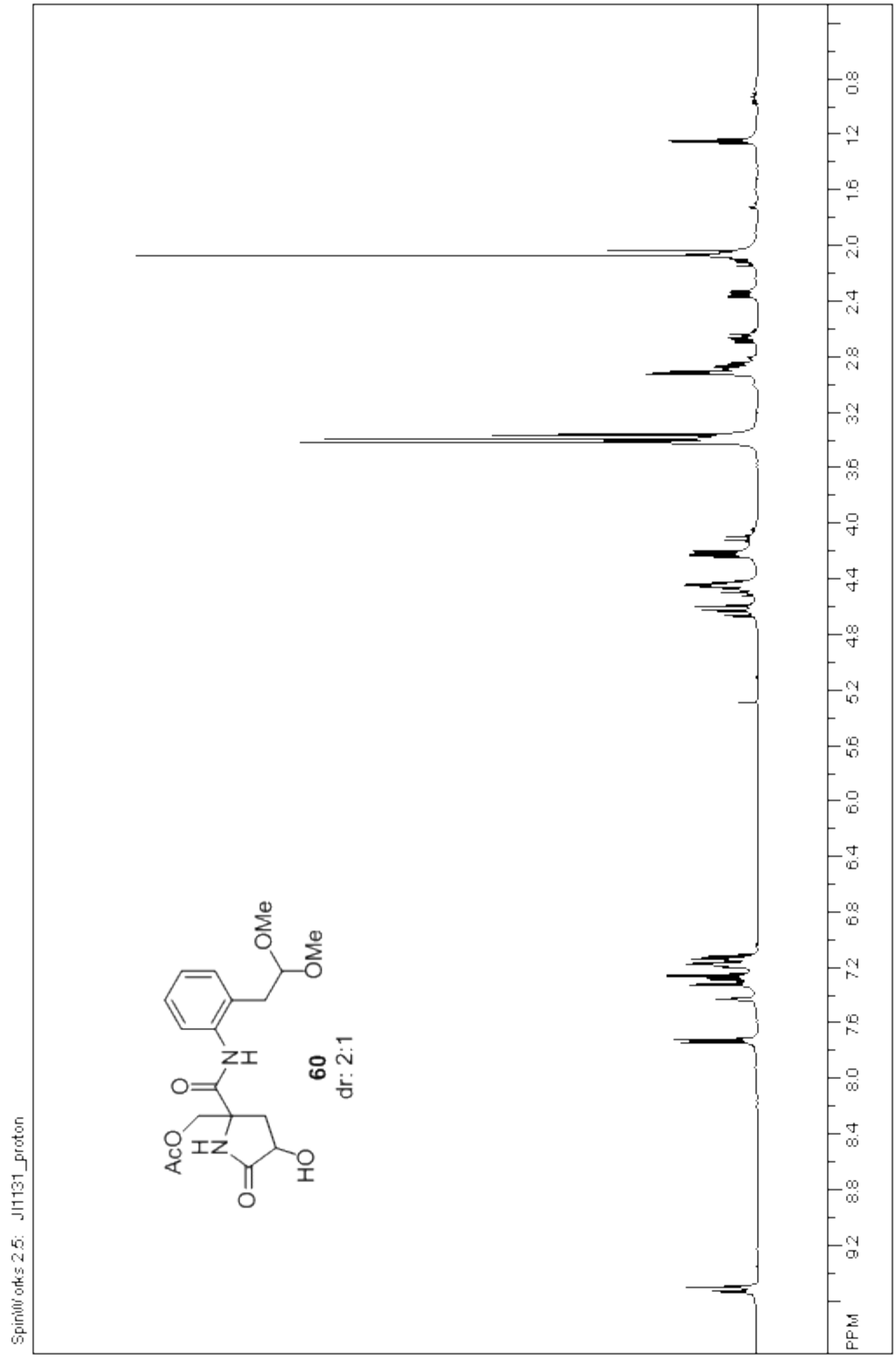

Figure A.66. ^{1}H Spectrum of **60**.

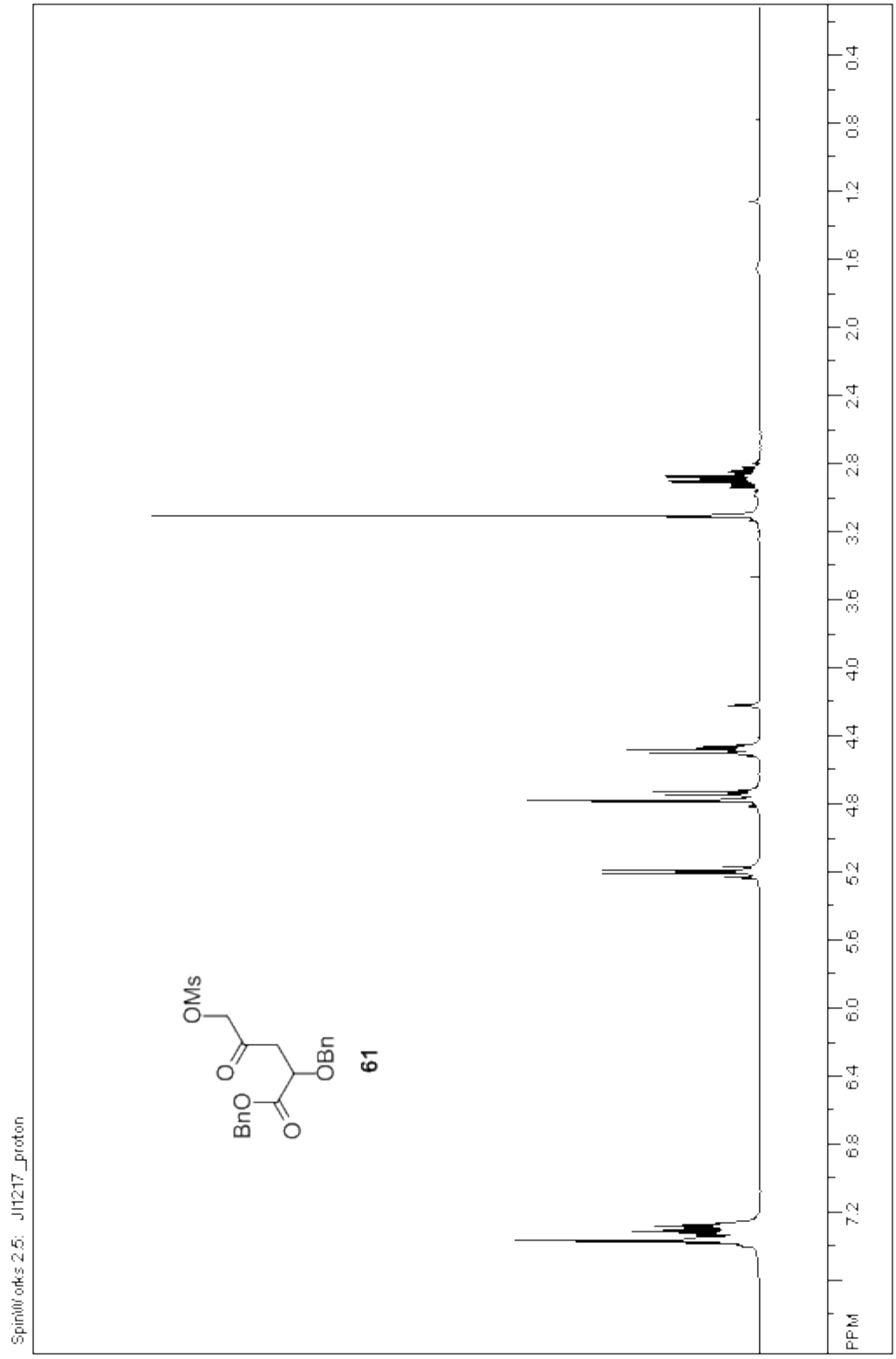

Figure A.67. ^{1}H Spectrum of **61**.

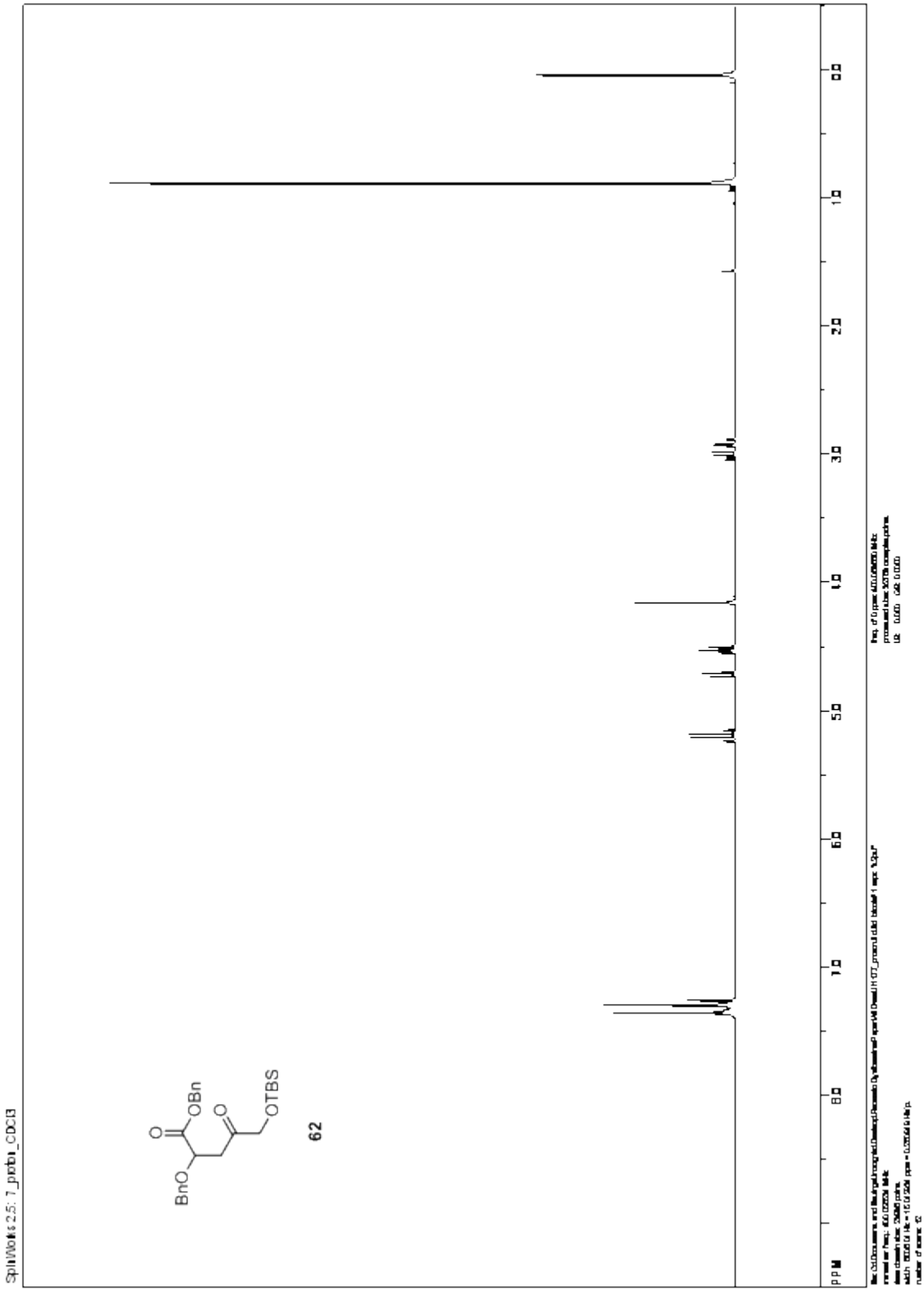

Figure A.68. ^{1}H Spectrum of **62**.

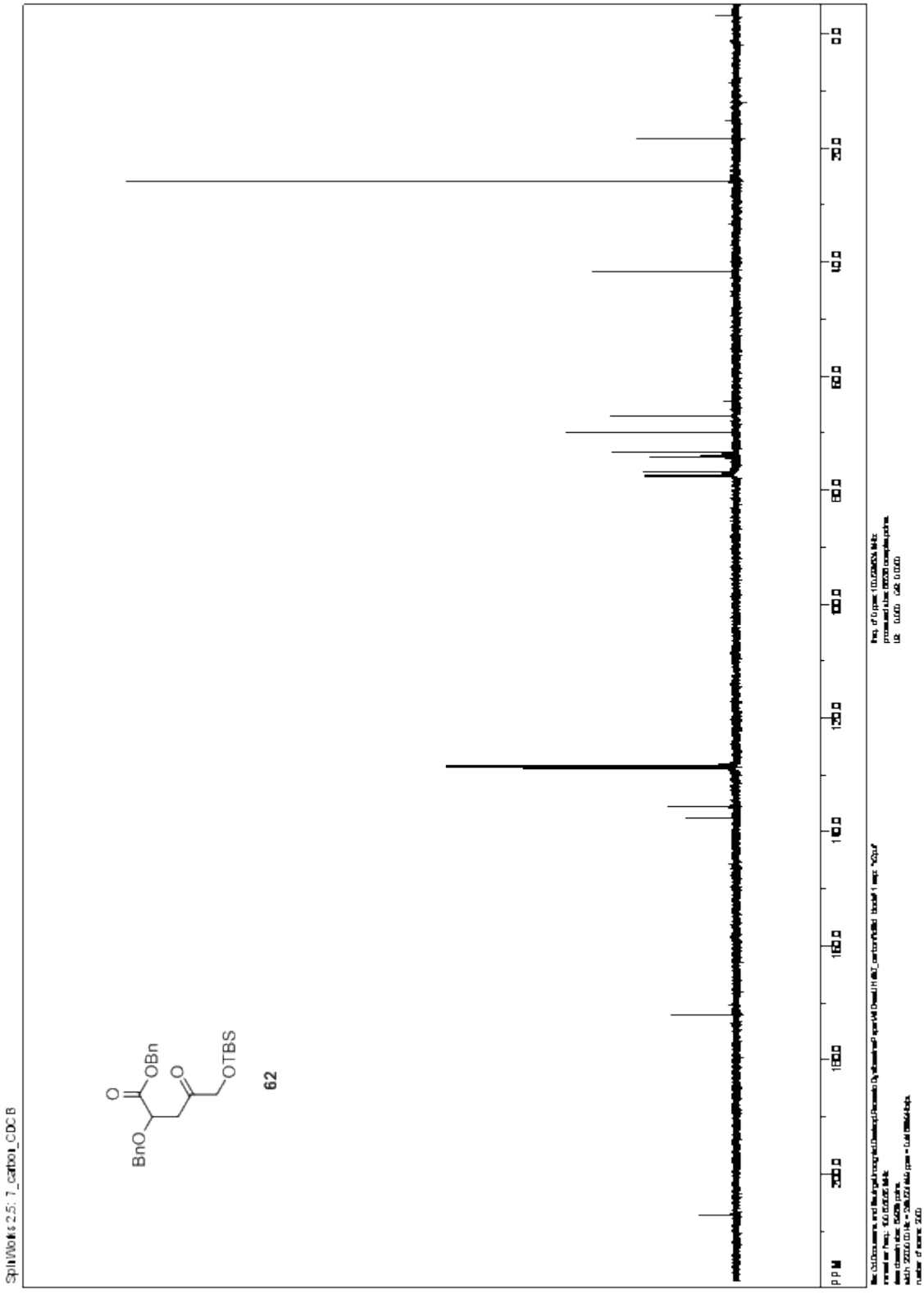

Figure A.69. ^{13}C Spectrum of **62**.

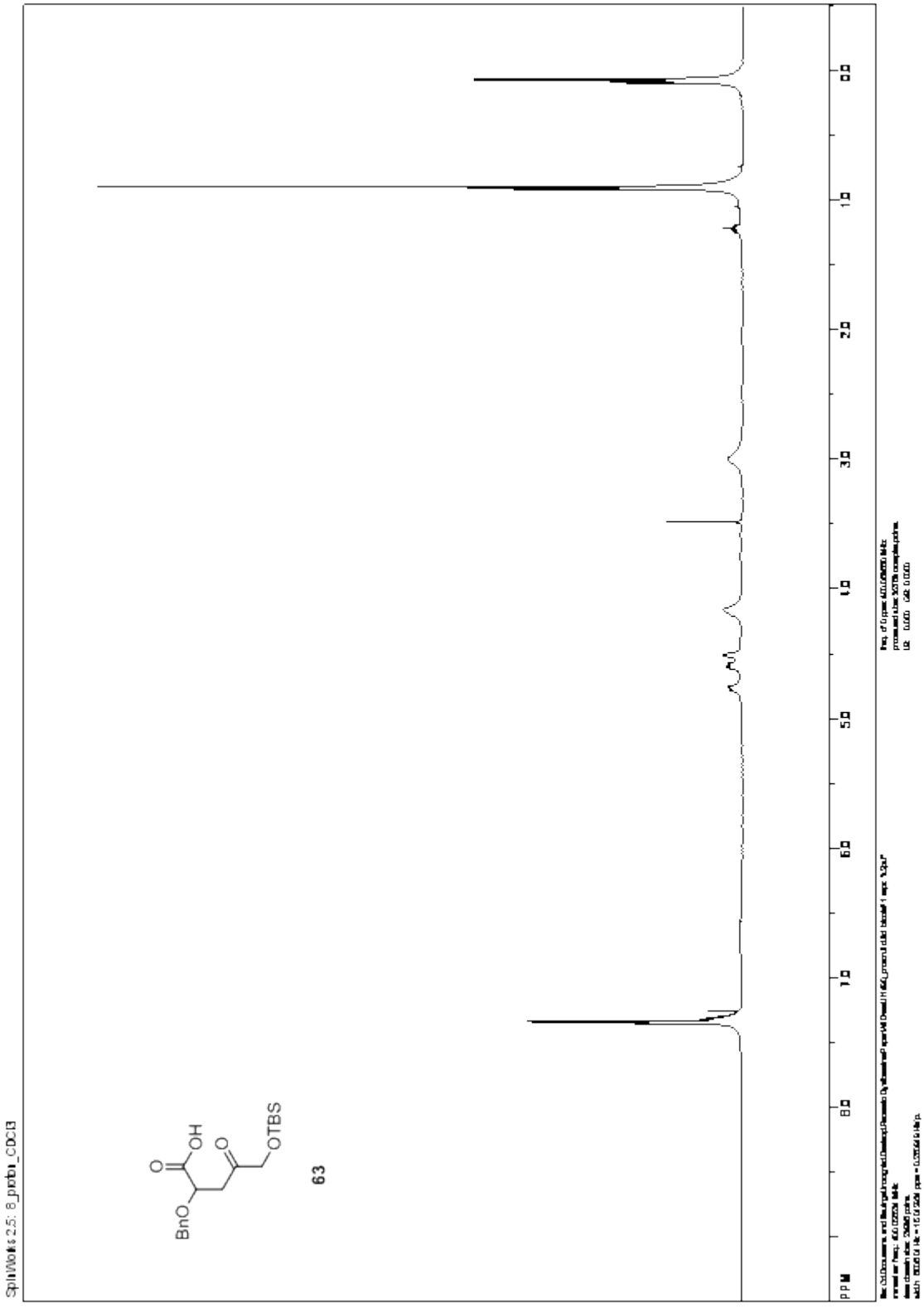

Figure A.70. ^{1}H Spectrum of **63**.

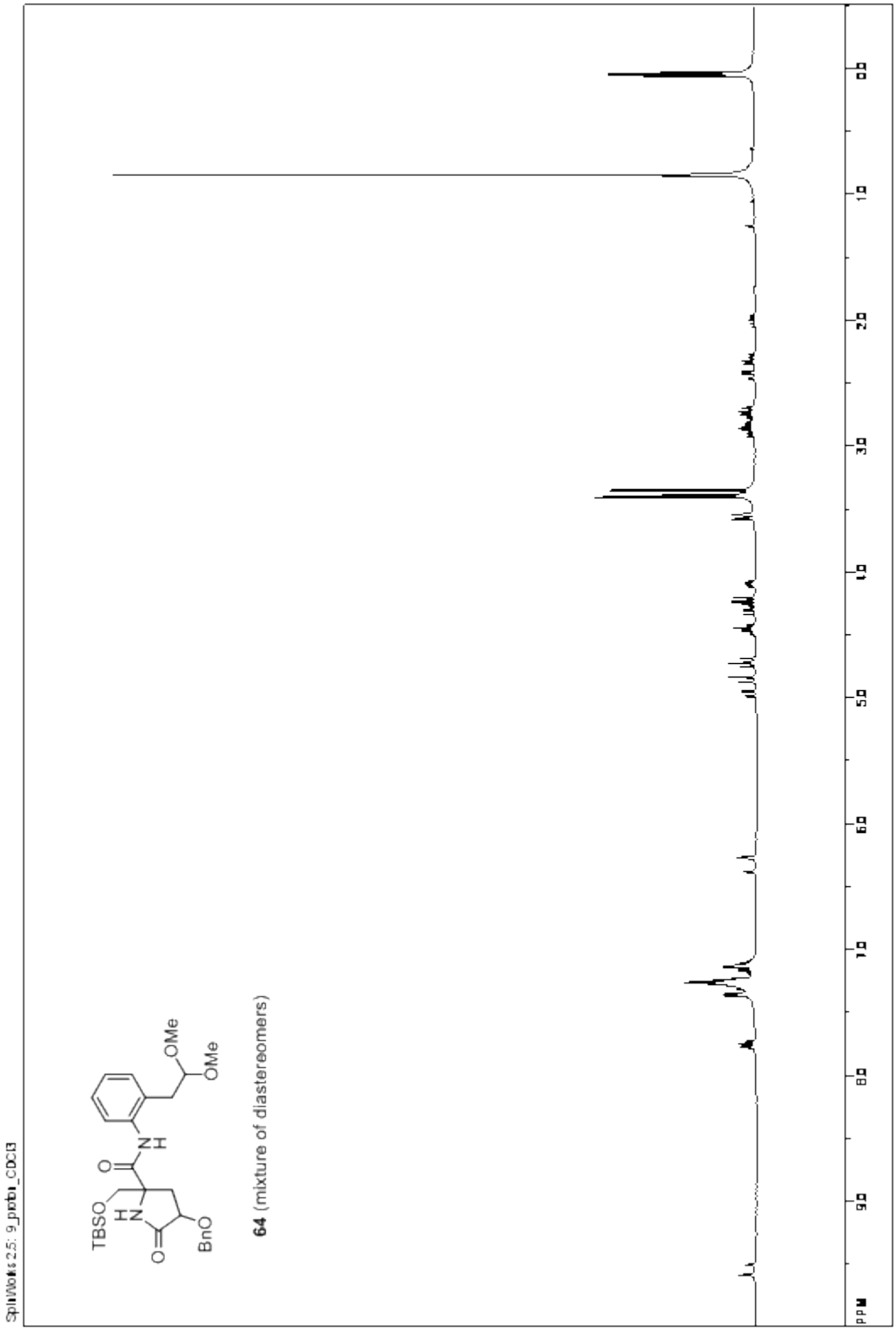

Figure A.71. ^{1}H Spectrum of **64**.

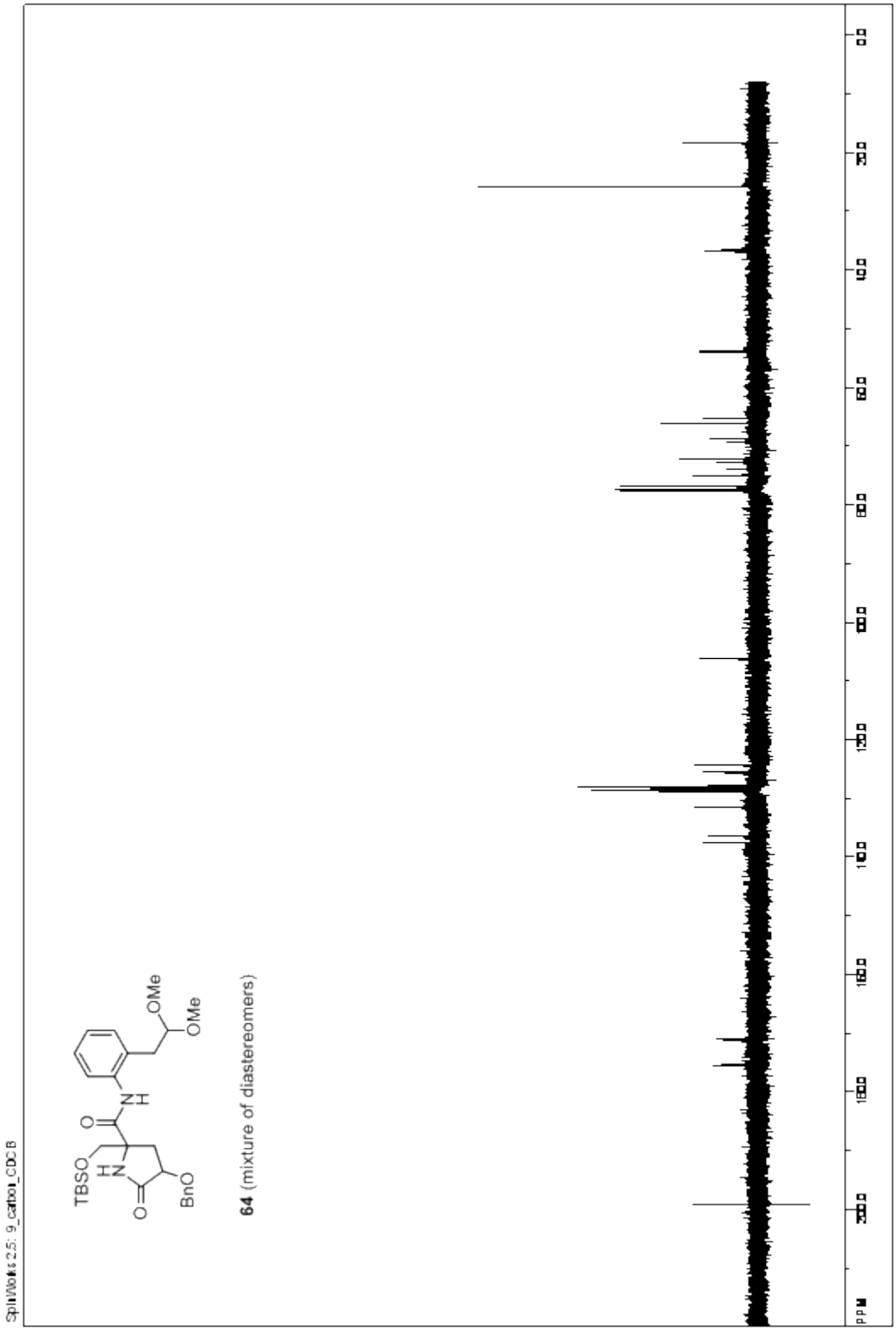

Figure A.72. ^{13}C Spectrum of **64**.

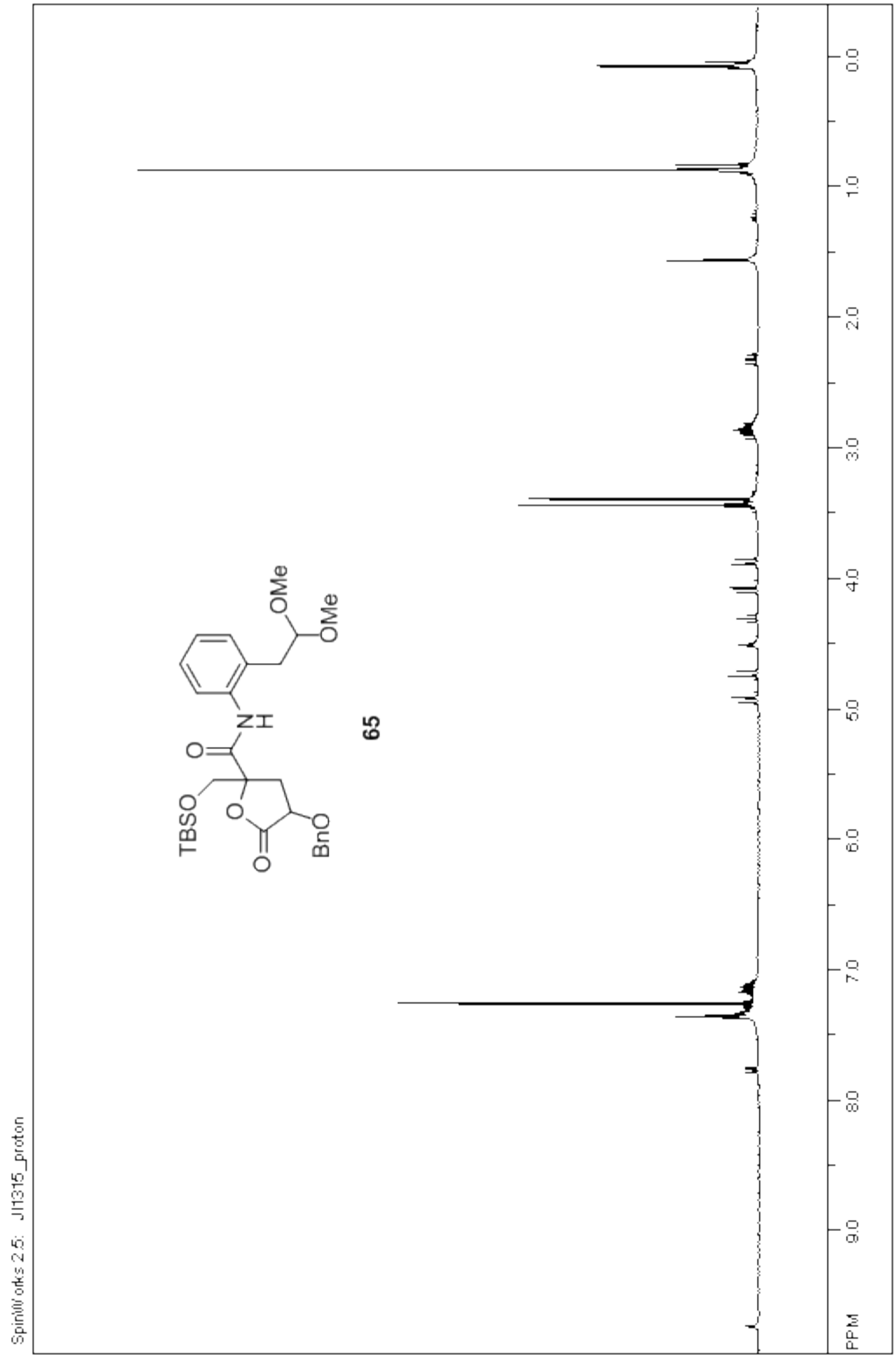

Figure A.73. ^{1}H Spectrum of **65**.

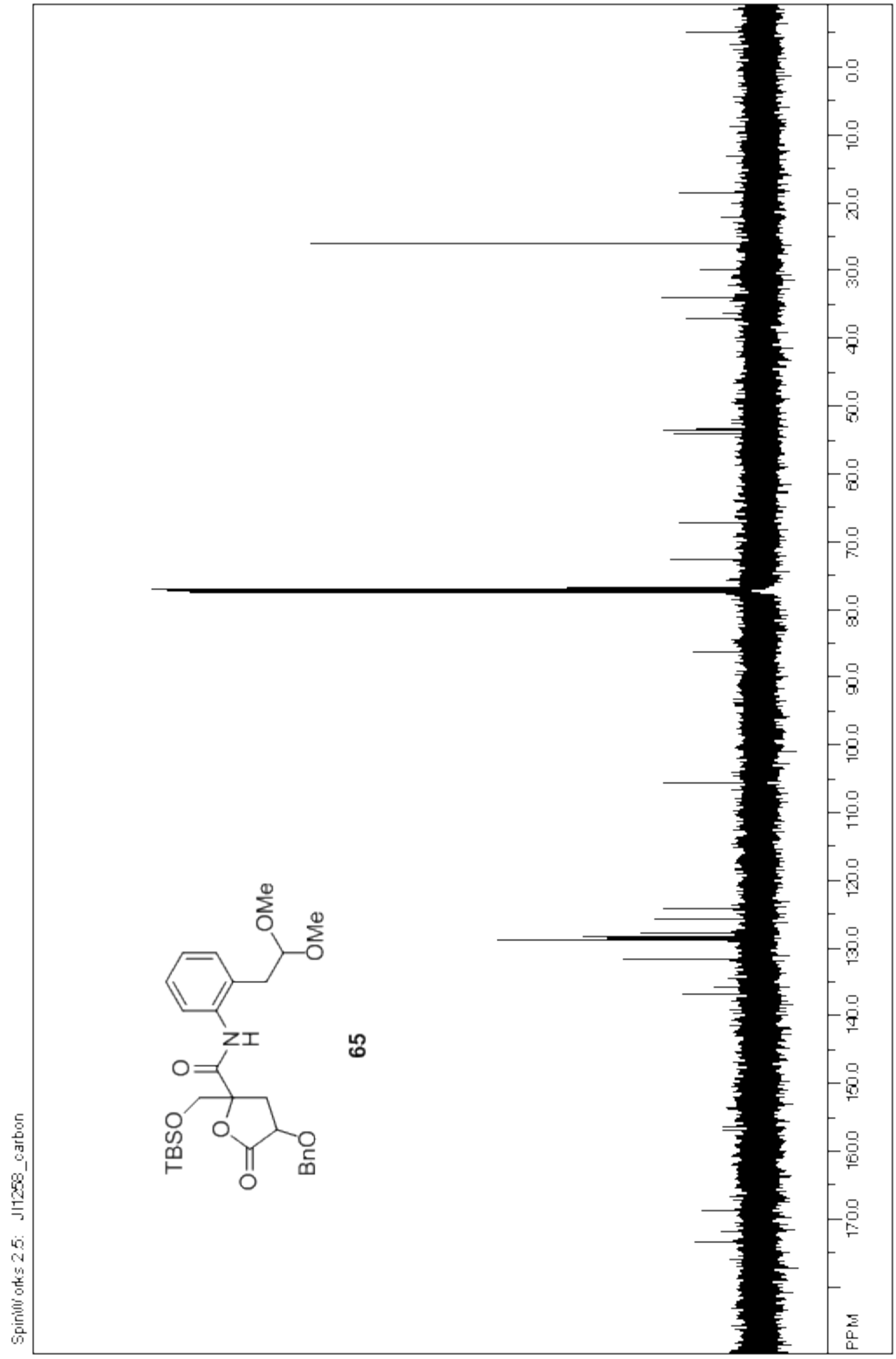

Figure A.74. ^{13}C Spectrum of **65**.

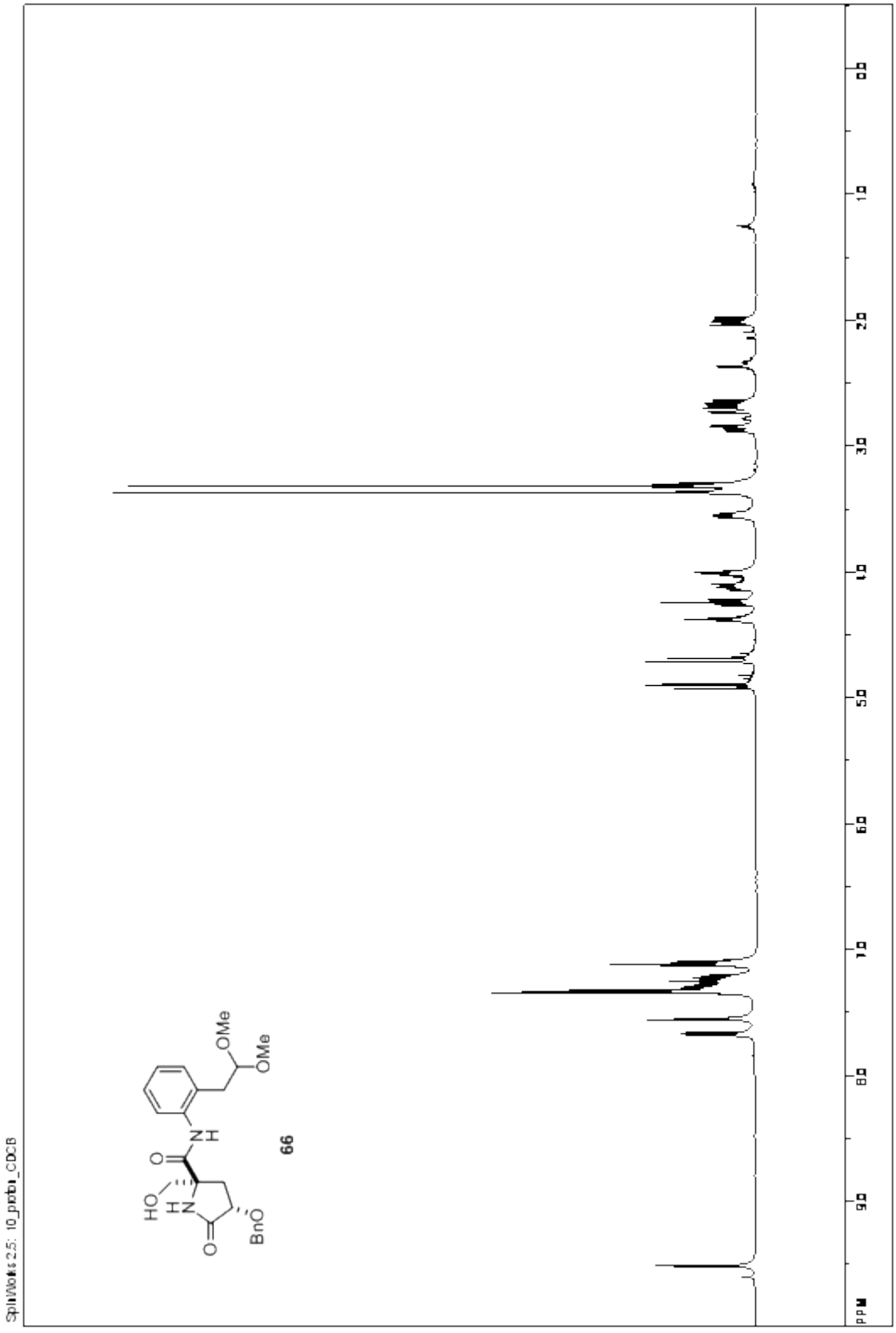

Figure A.75. ^{1}H Spectrum of **66**.

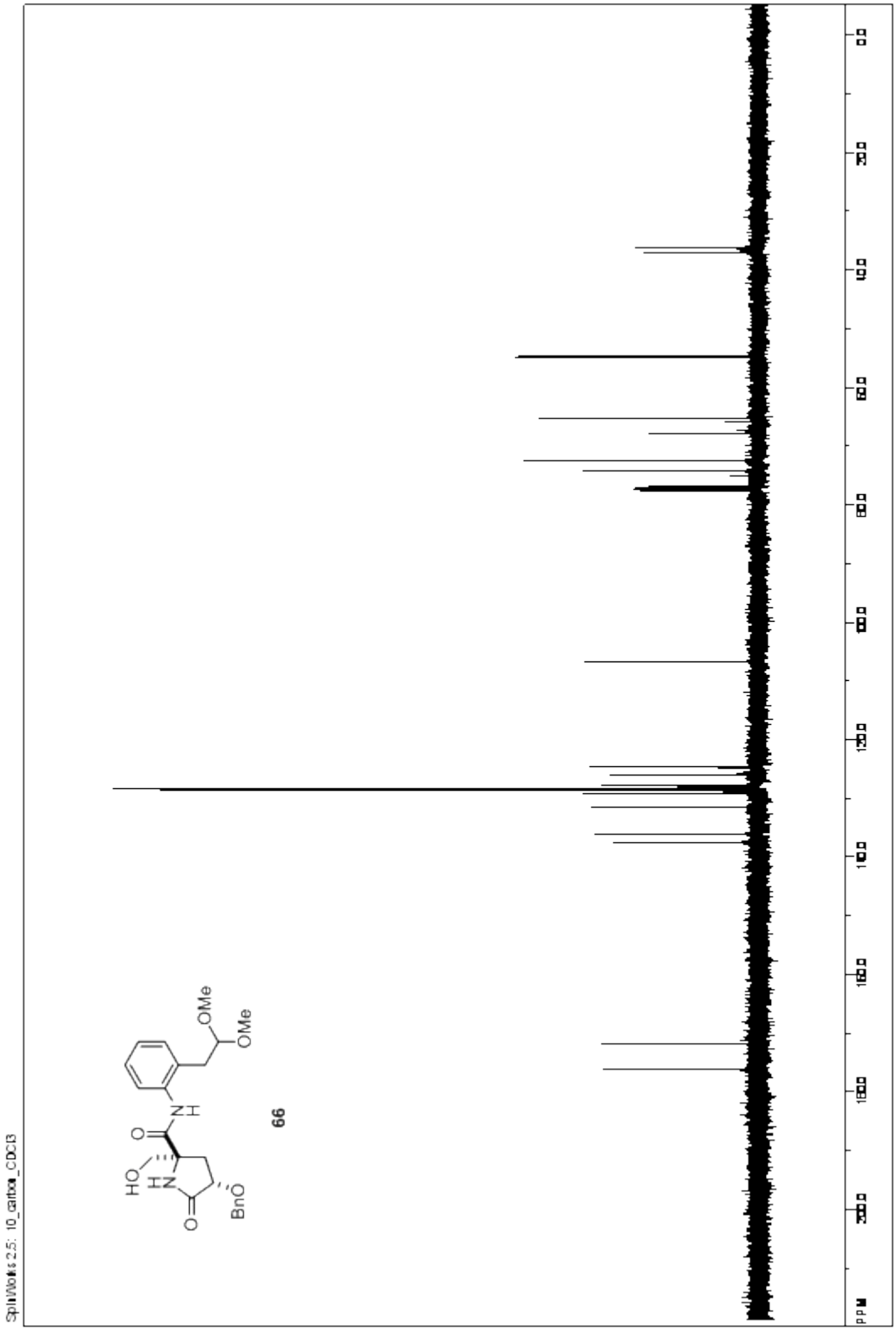

Figure A.76. ^{13}C Spectrum of **66**.

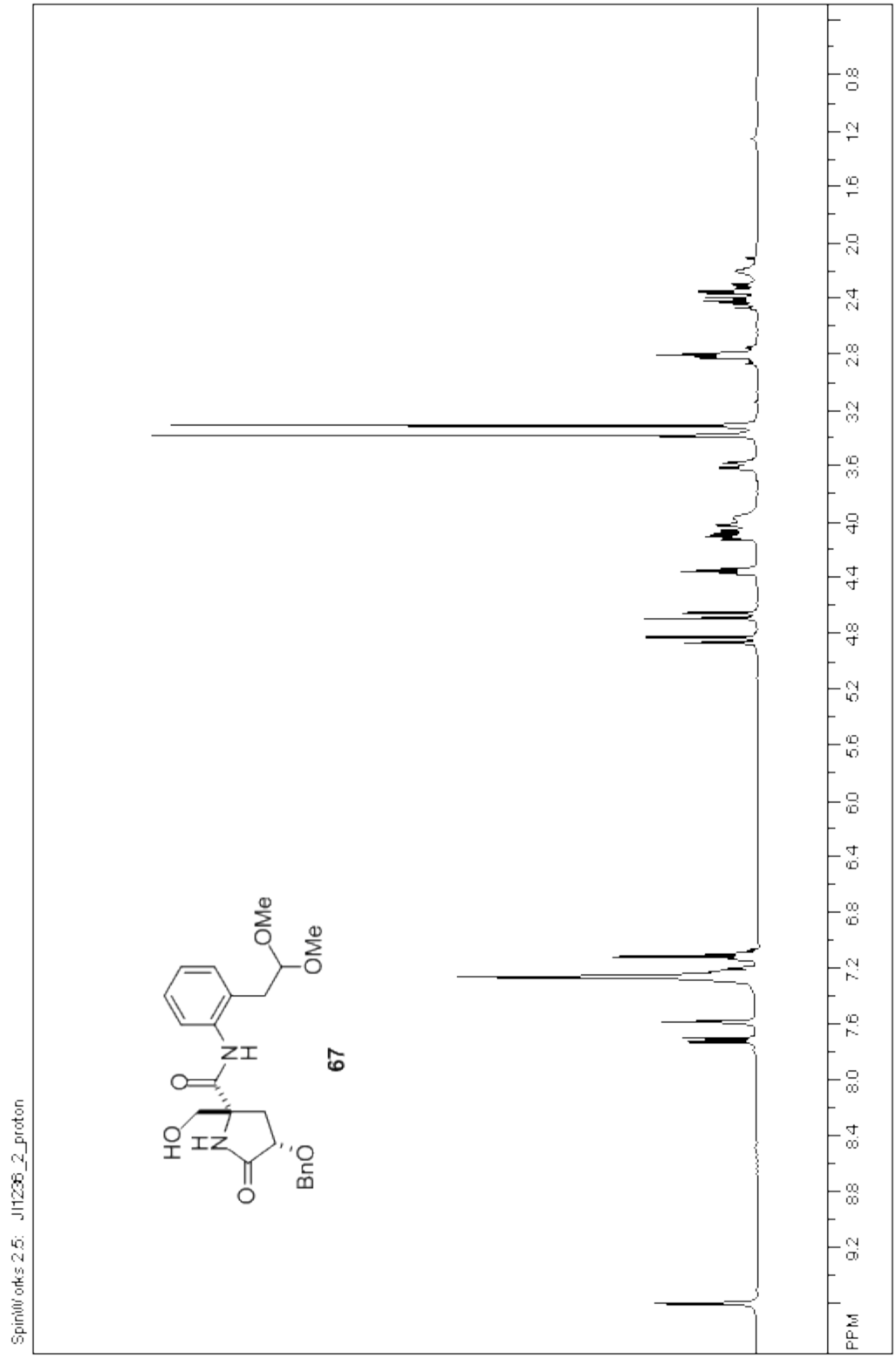

Figure A.77. ^{1}H Spectrum of **67**.

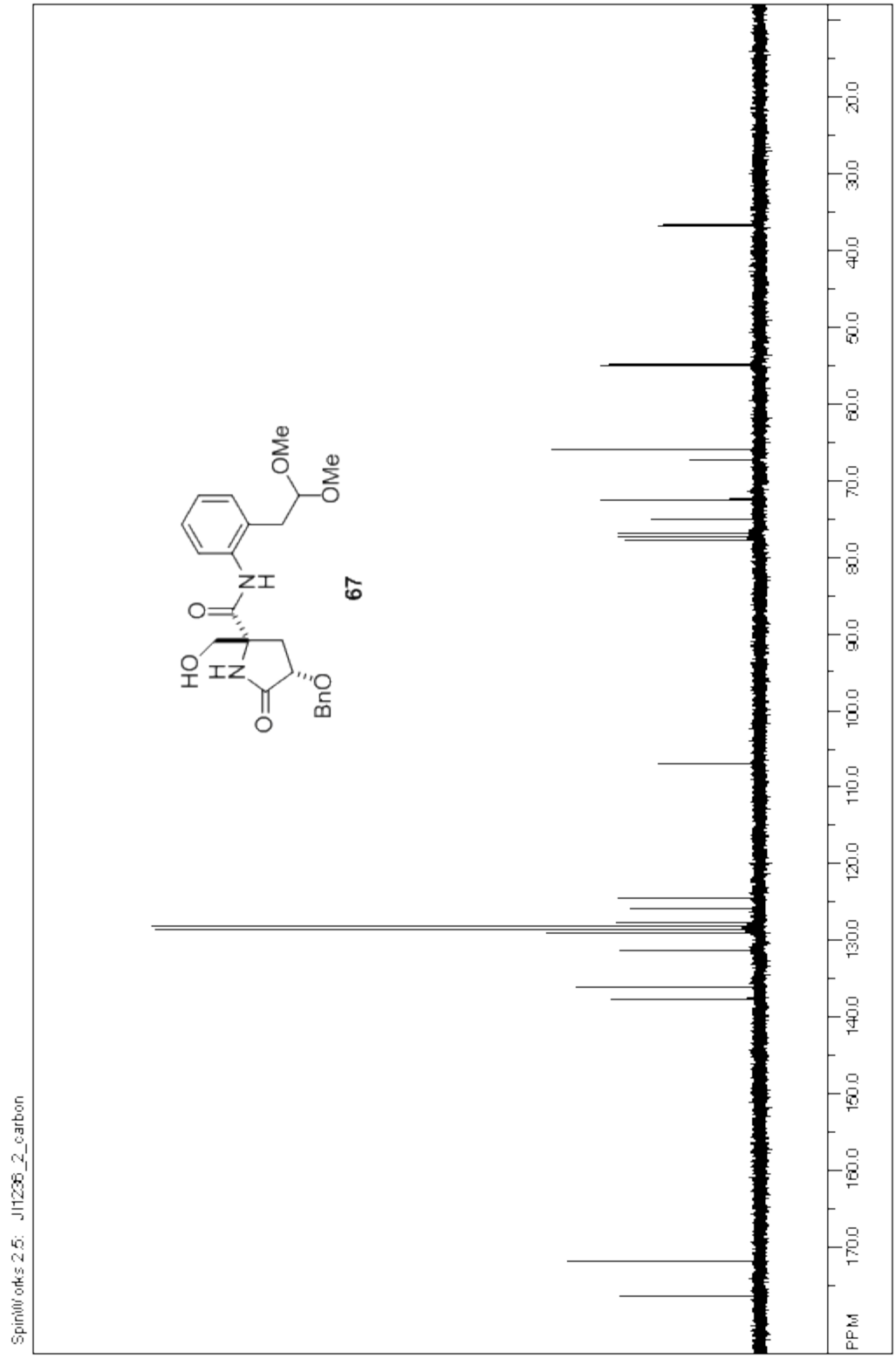

Figure A.78. ^{13}C Spectrum of **67**.

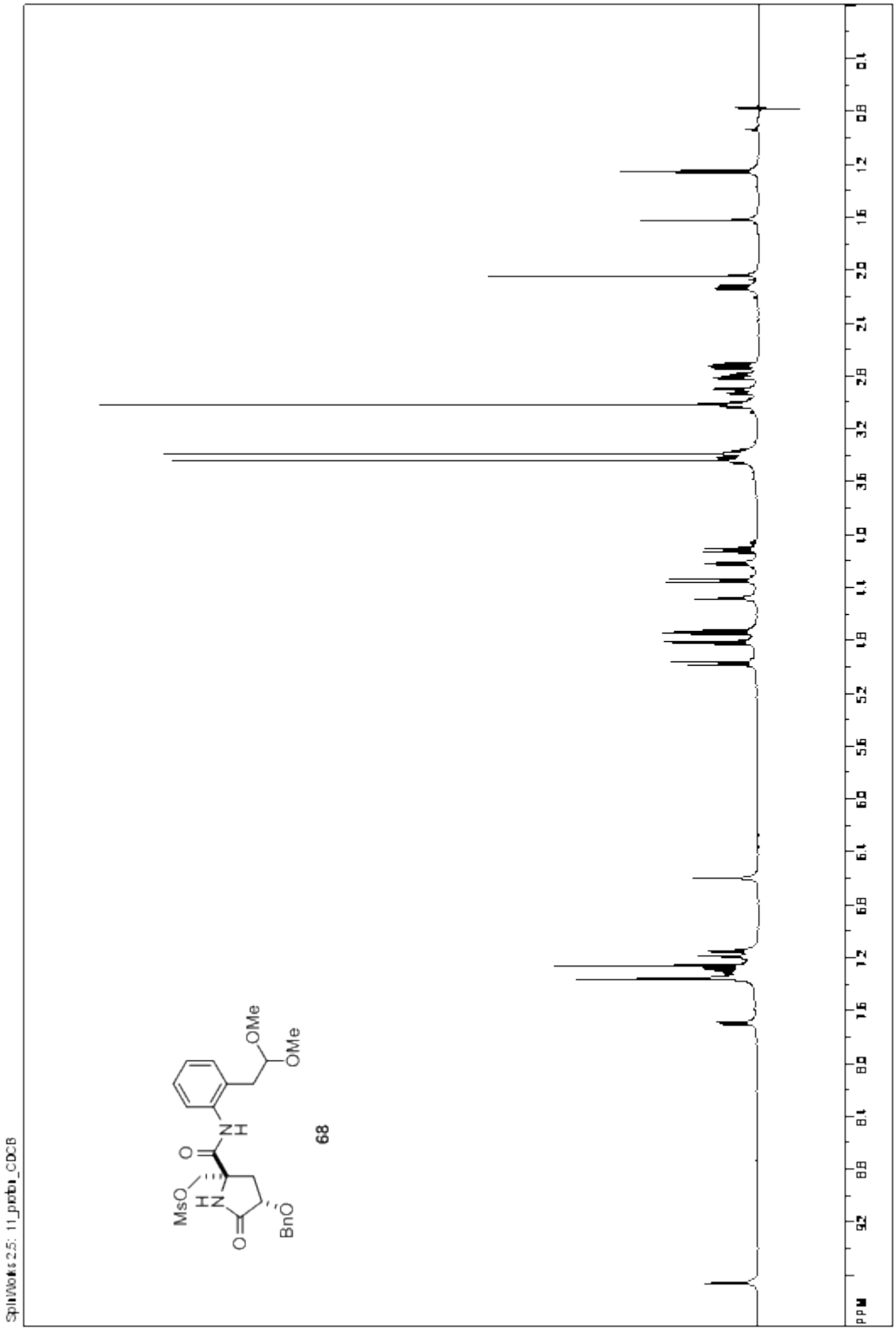

Figure A.79. ^{1}H Spectrum of **68**.

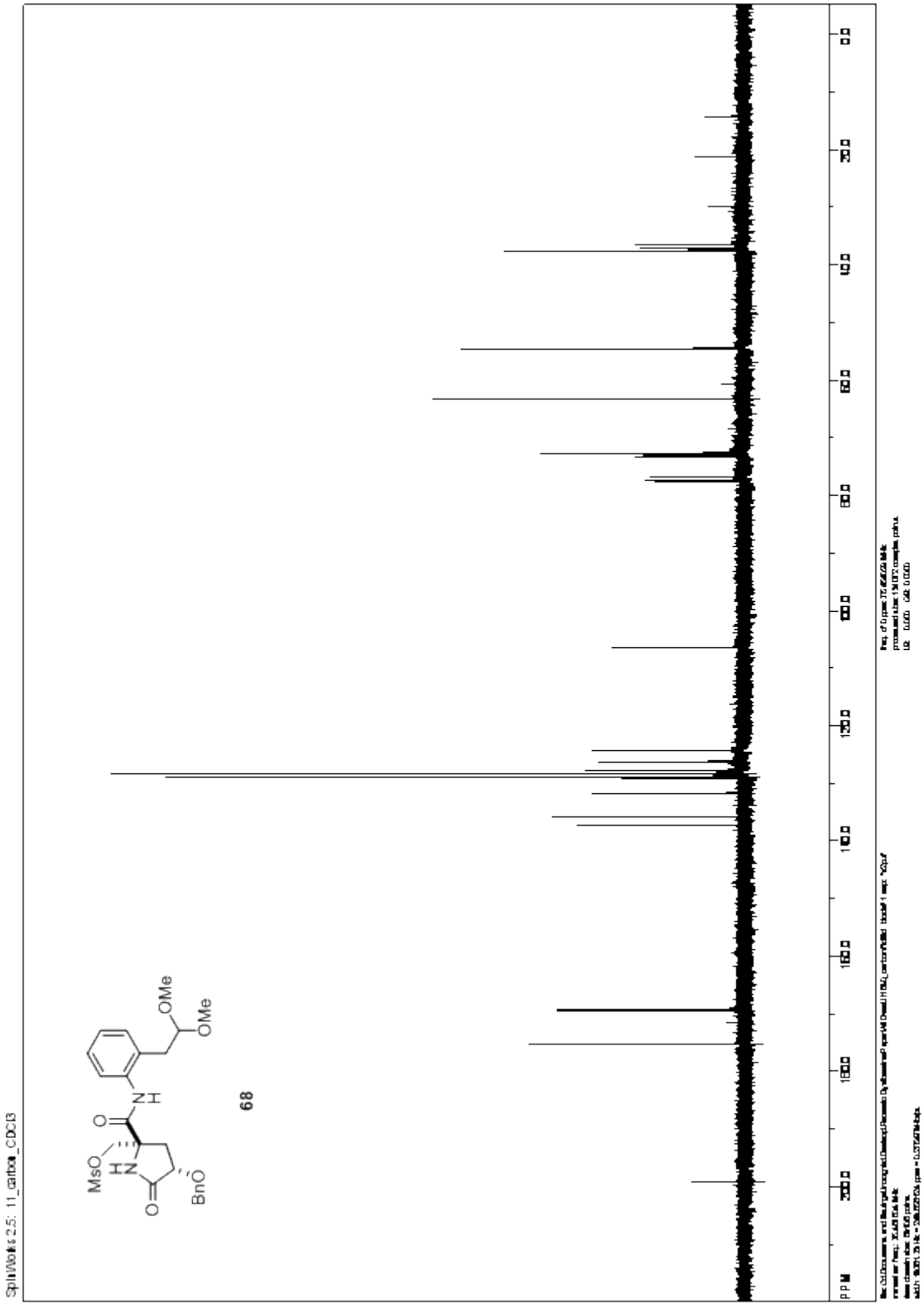

Figure A.80. ^{13}C Spectrum of **68**.

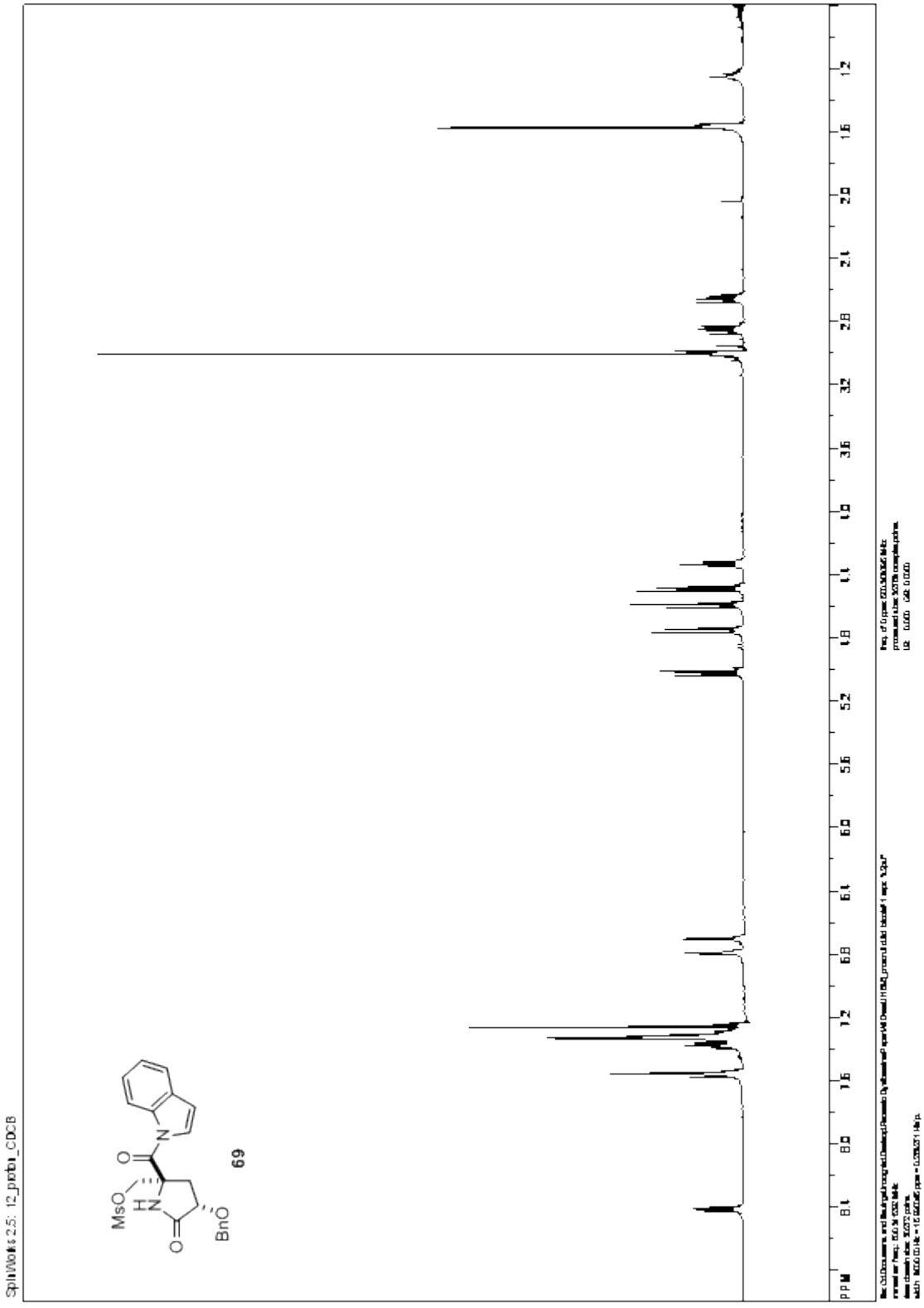

Figure A.81. ^{1}H Spectrum of **69**.

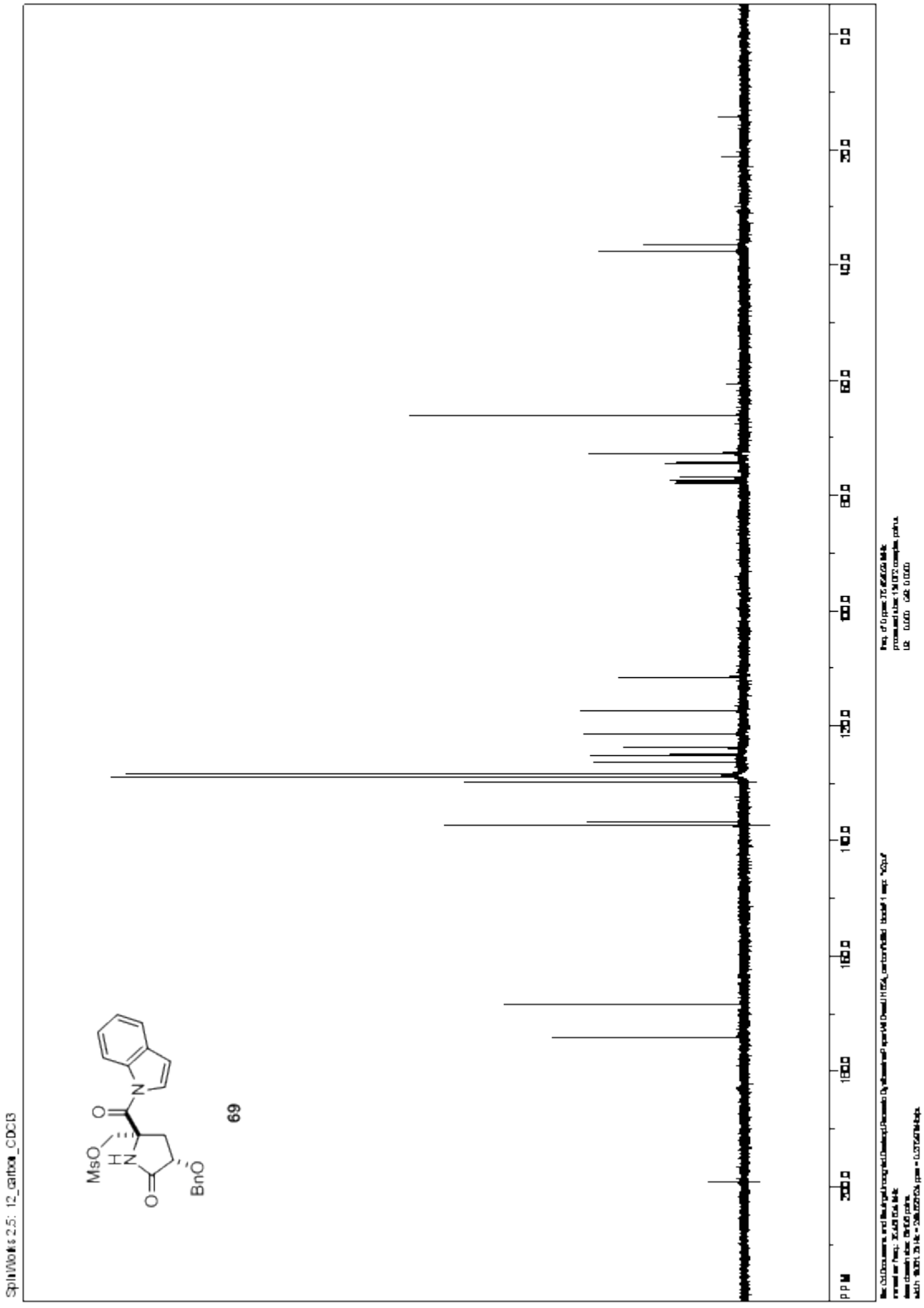

Figure A.82. ^{13}C Spectrum of **69**.

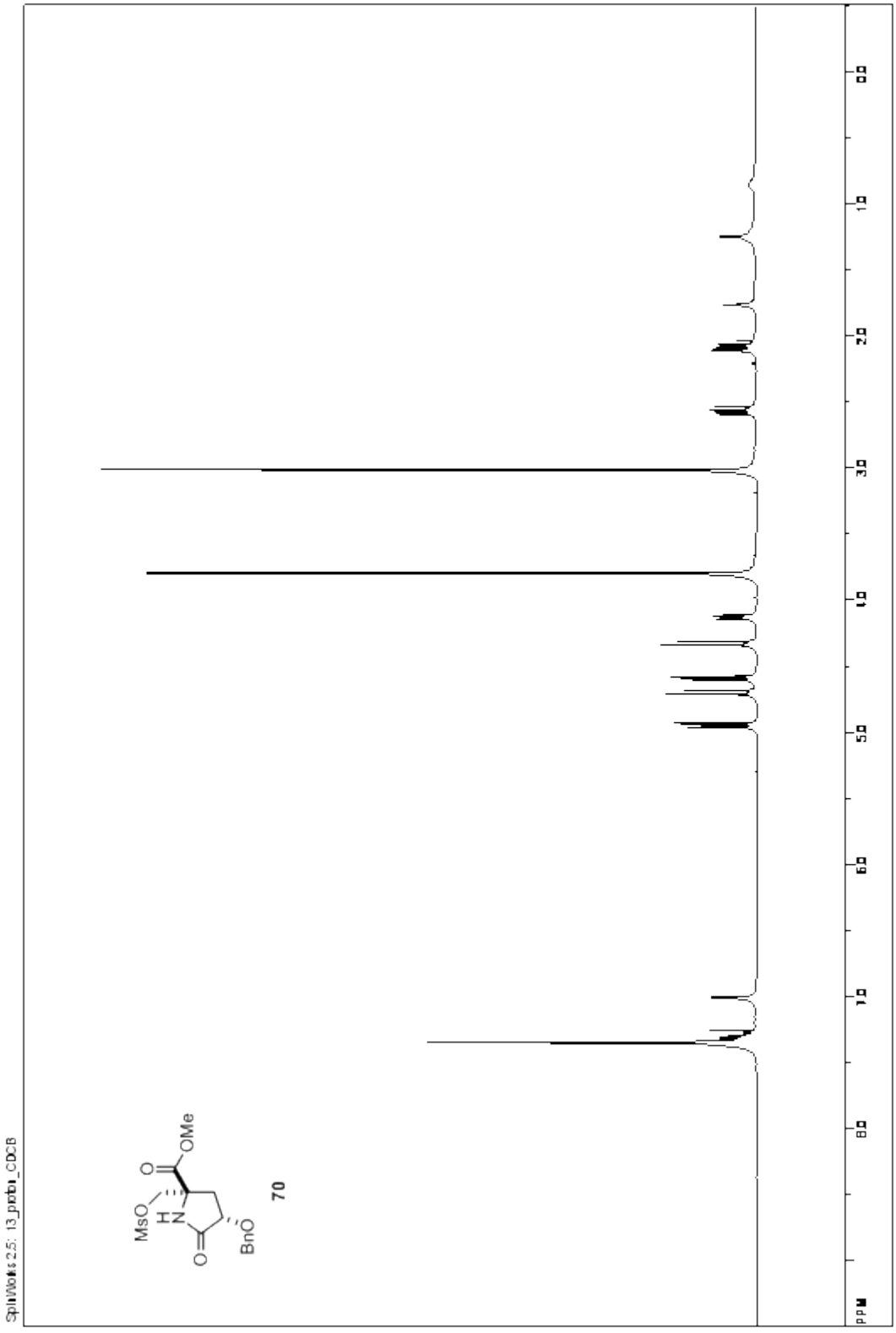

Figure A.83. ^{1}H Spectrum of **70**.

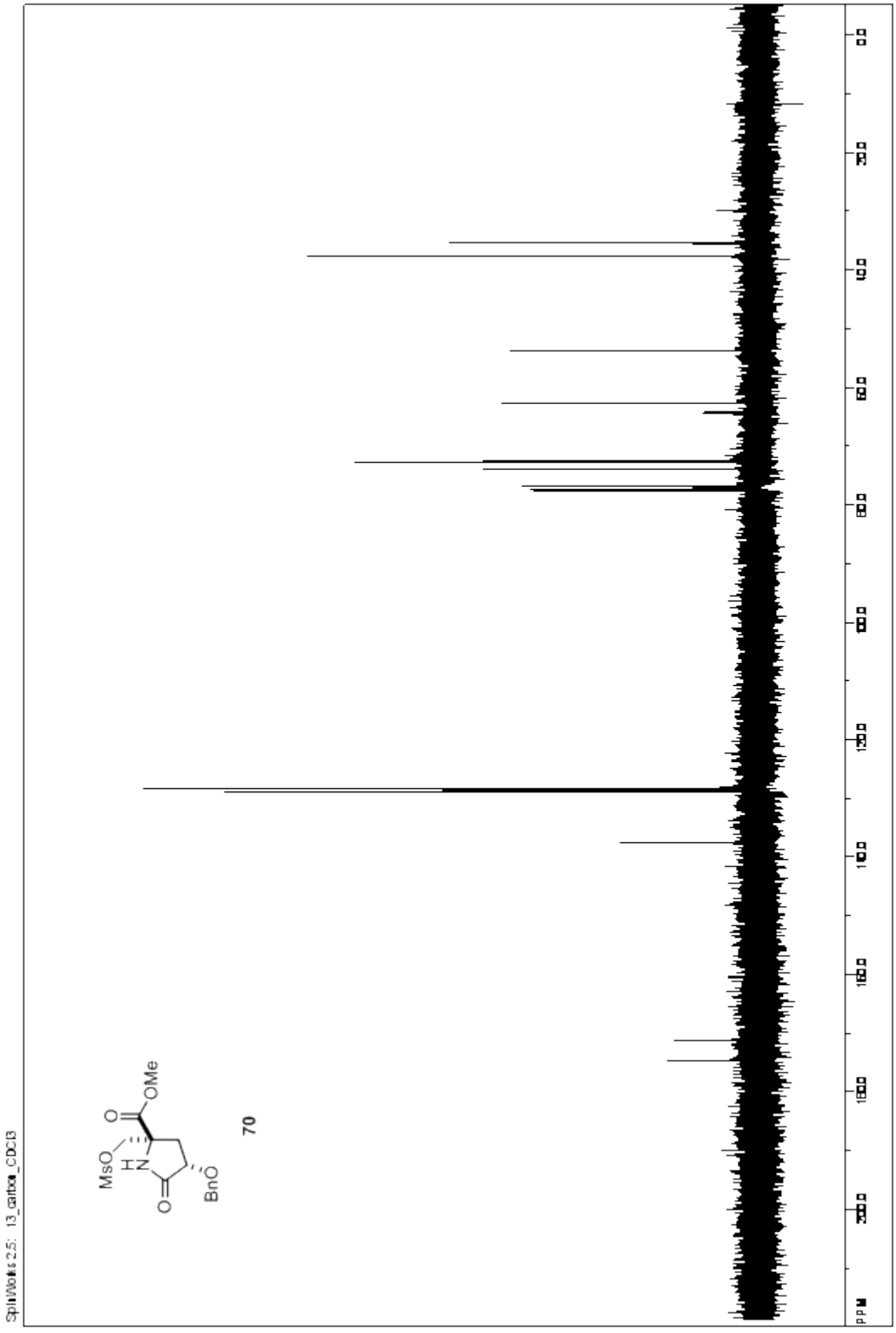

Figure A.84. ^{13}C Spectrum of **70**.

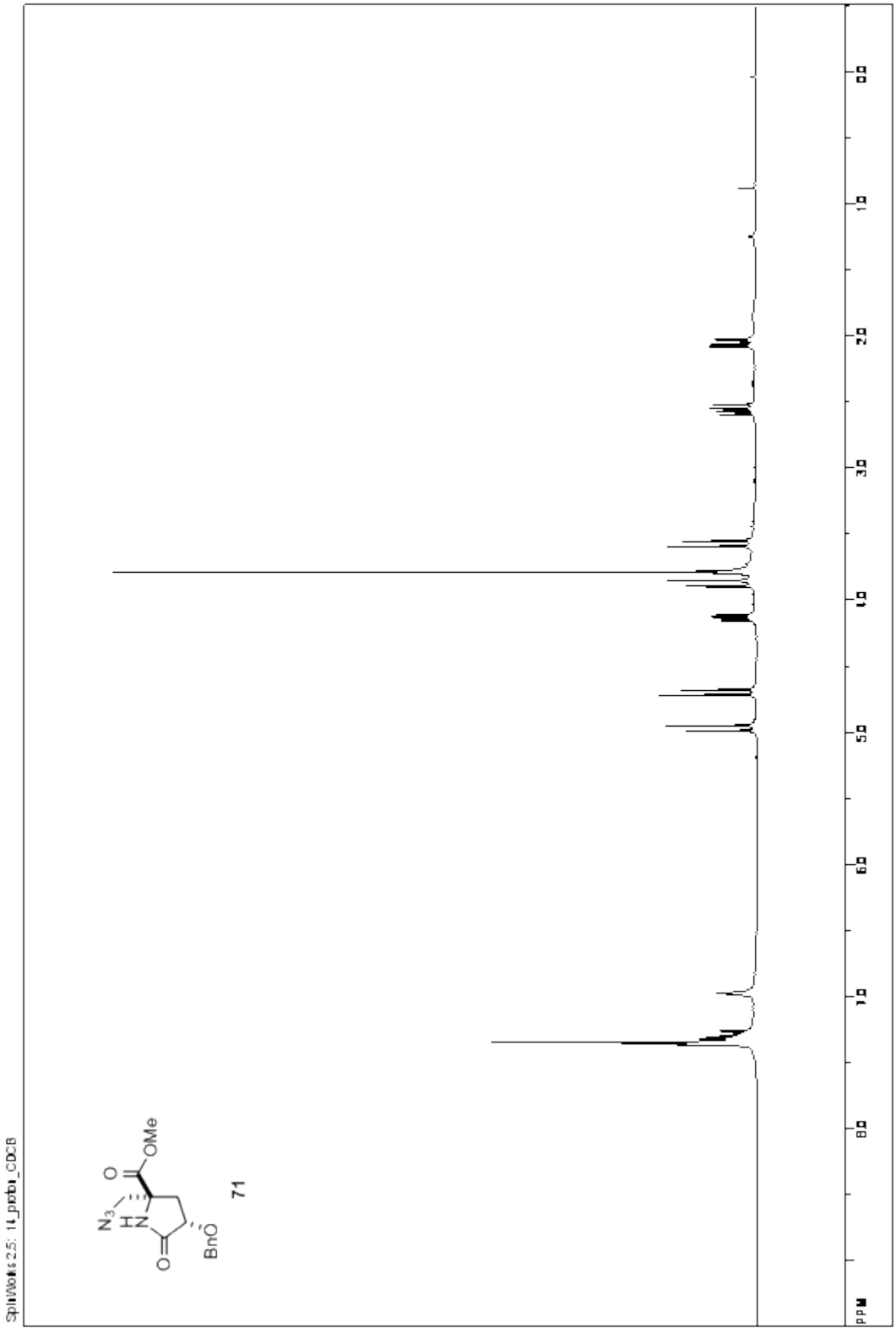

Figure A.85. ^{1}H Spectrum of **71**.

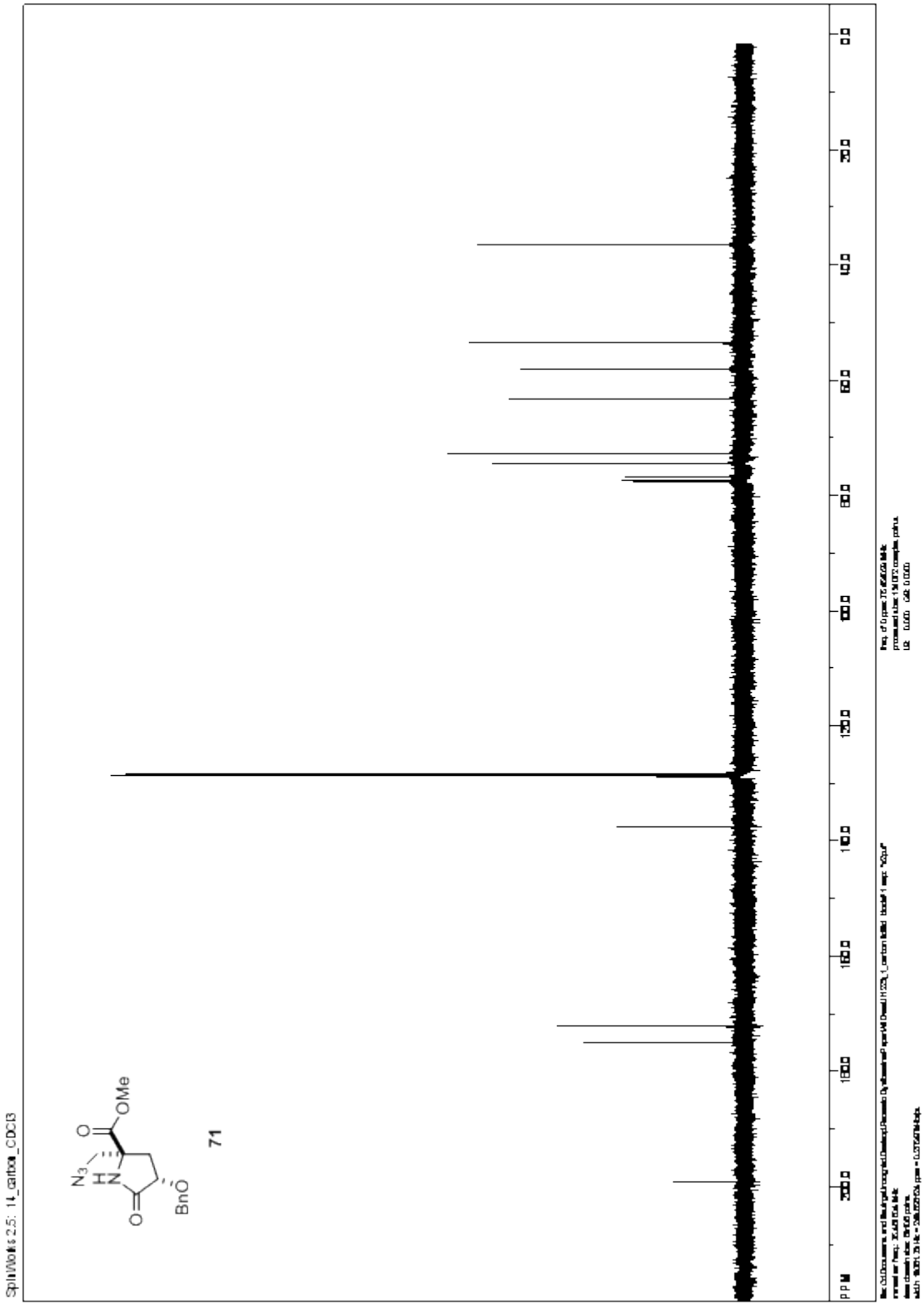

Figure A.86. ^{13}C Spectrum of **71**.

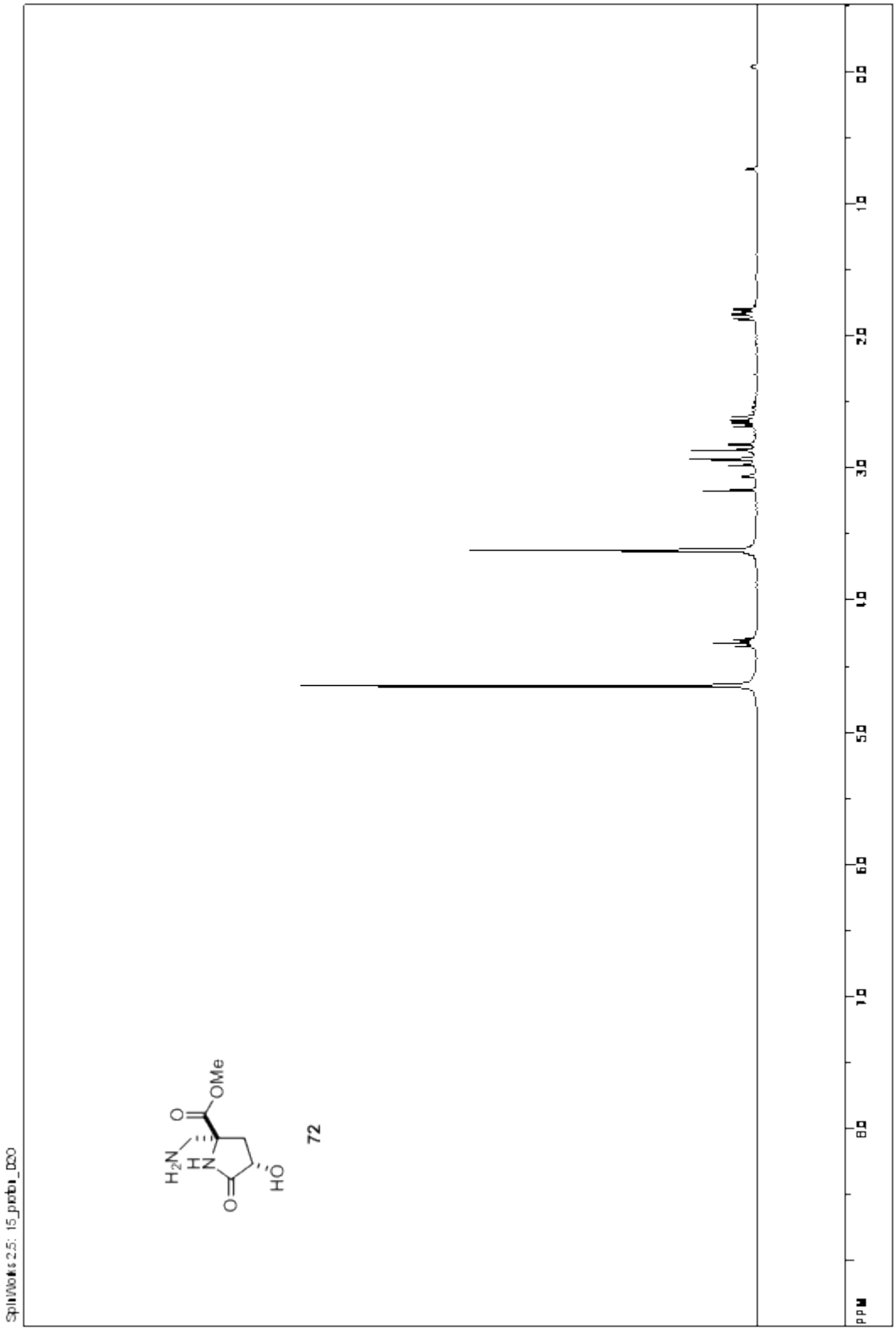

Figure A.87. ^{1}H Spectrum of **72**.

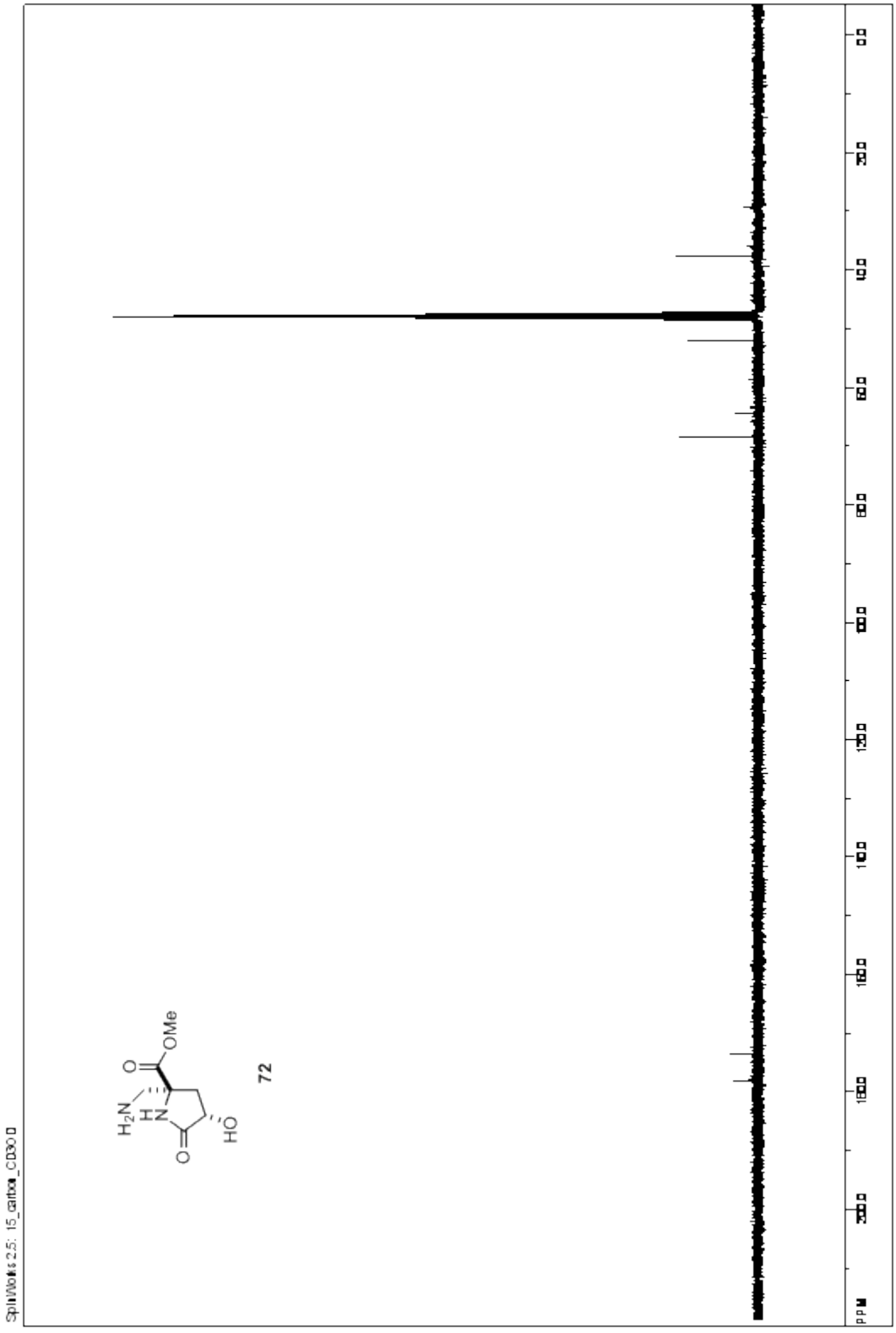

Figure A.88. ^{13}C Spectrum of **72**.

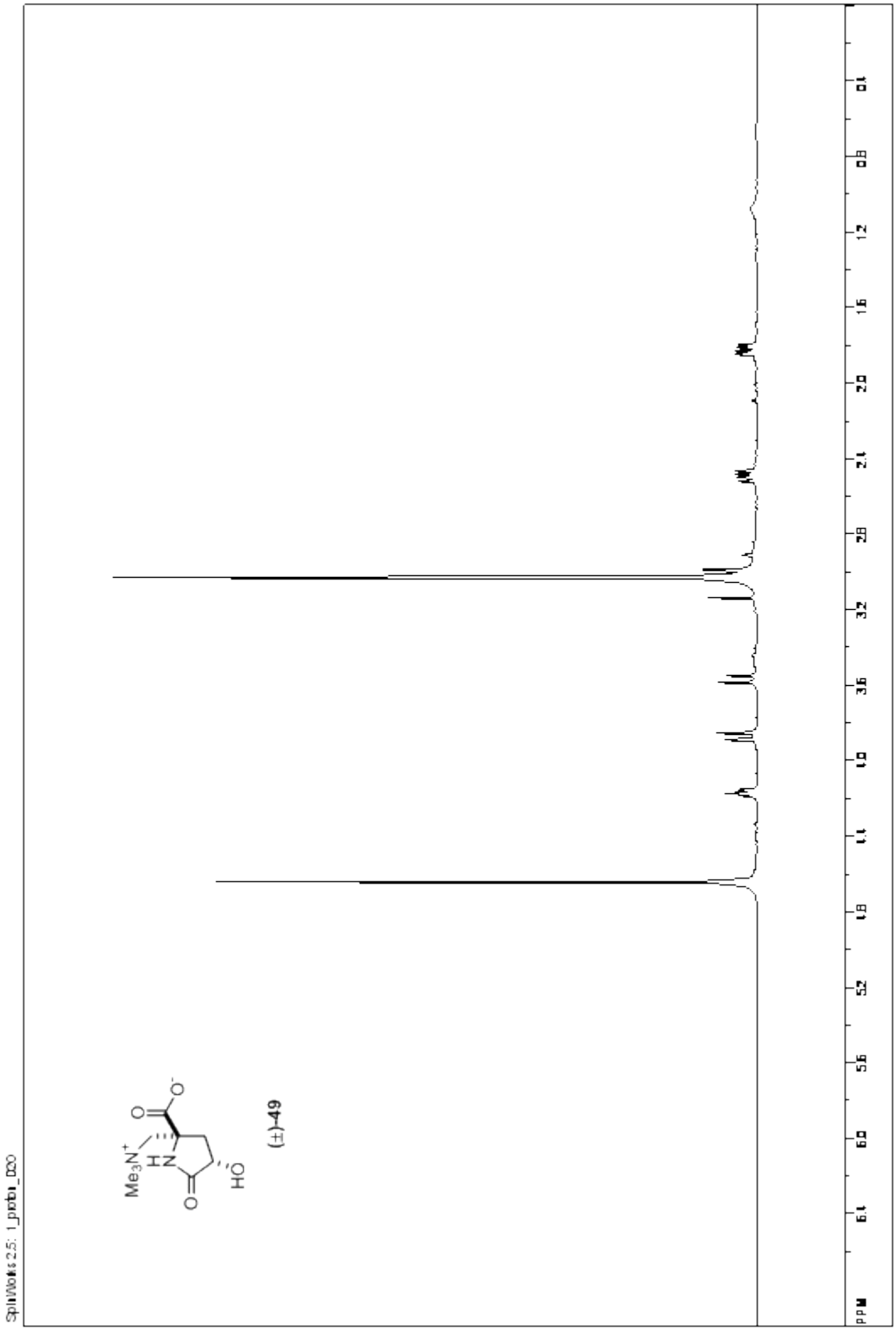

Figure A.89. ^{1}H Spectrum of **49**.

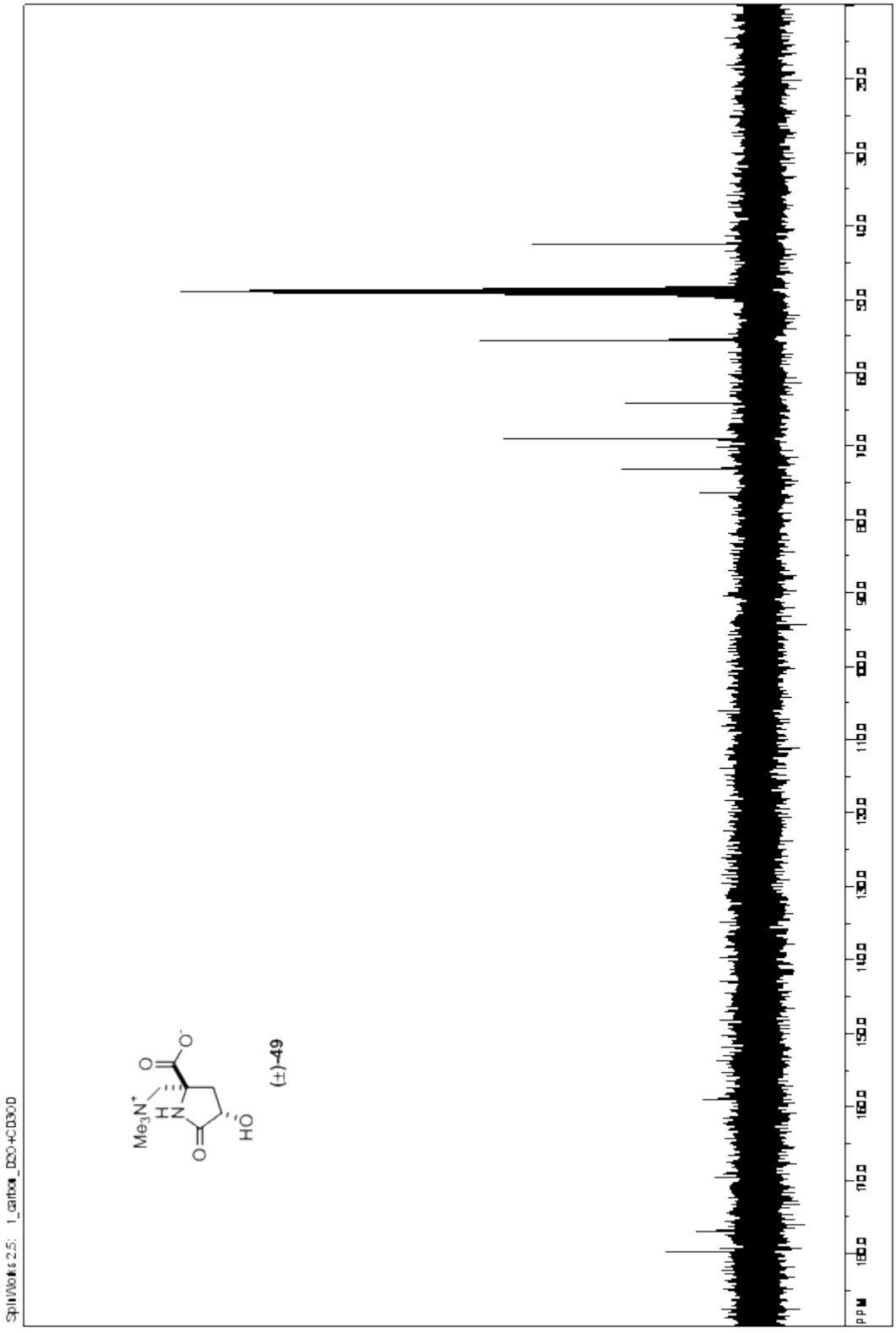

Figure A.90. ^{13}C Spectrum of **49**.

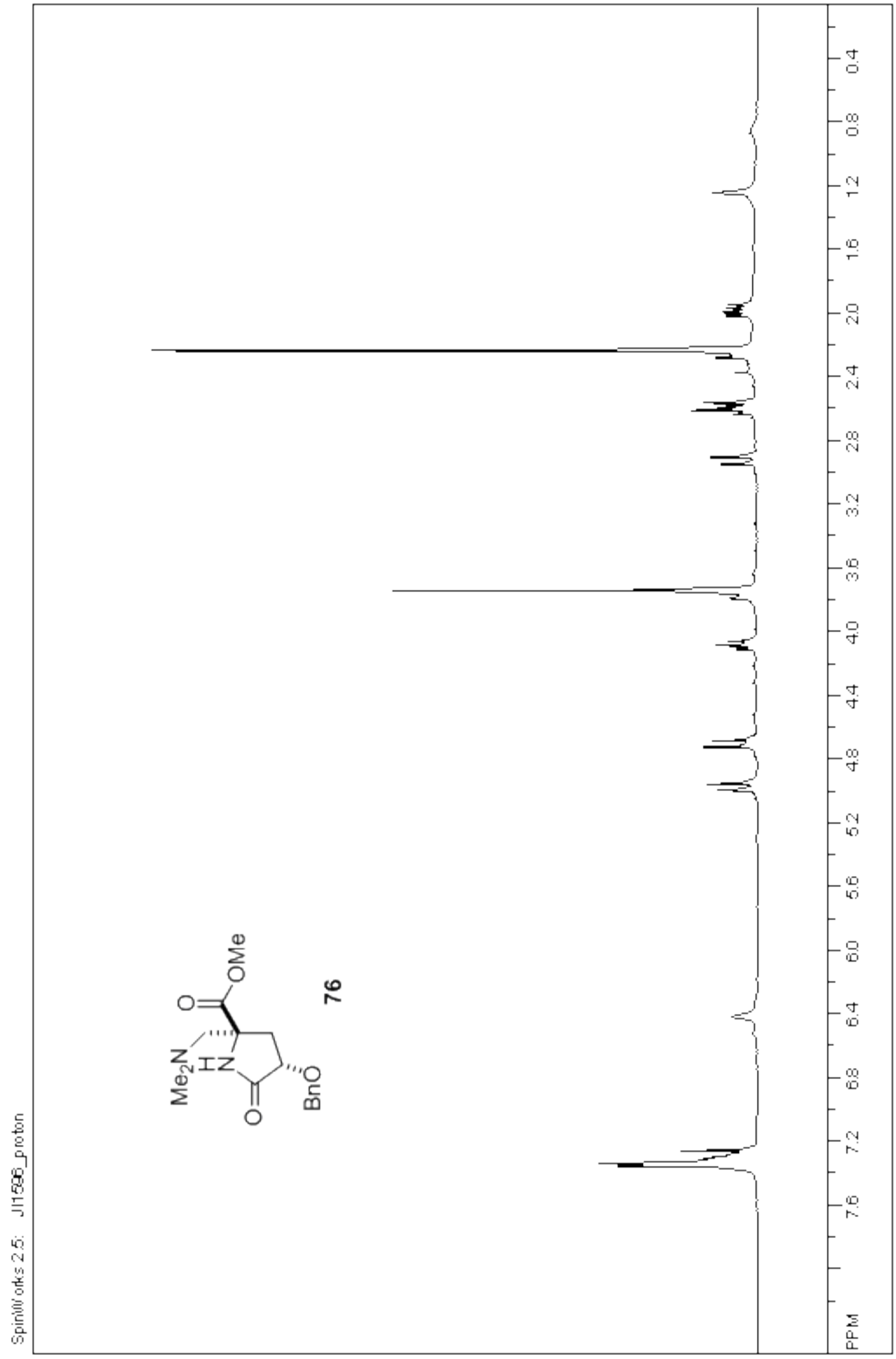

Figure A.91. ^{1}H Spectrum of **76**.

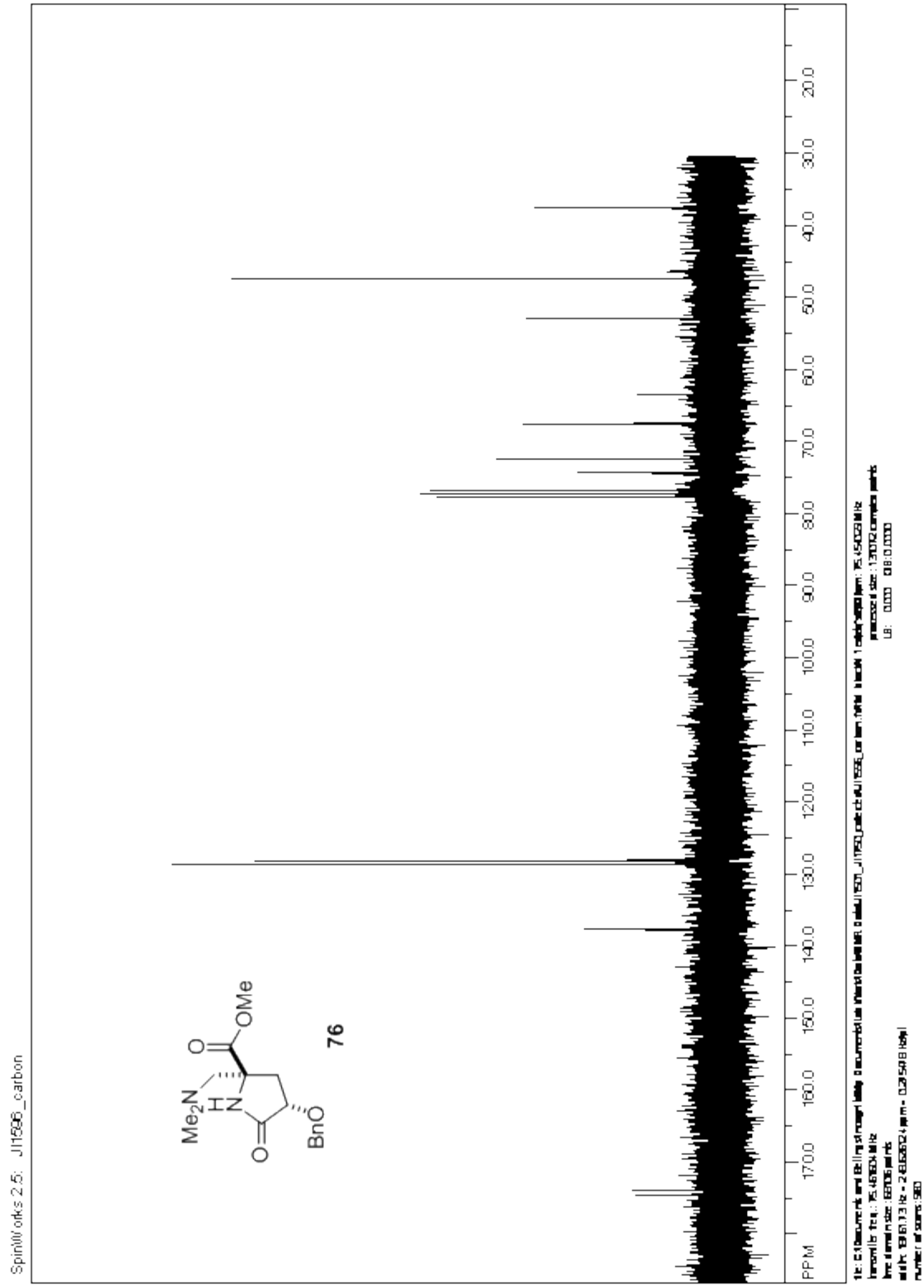

Figure A.92. ^{13}C Spectrum of **76**.

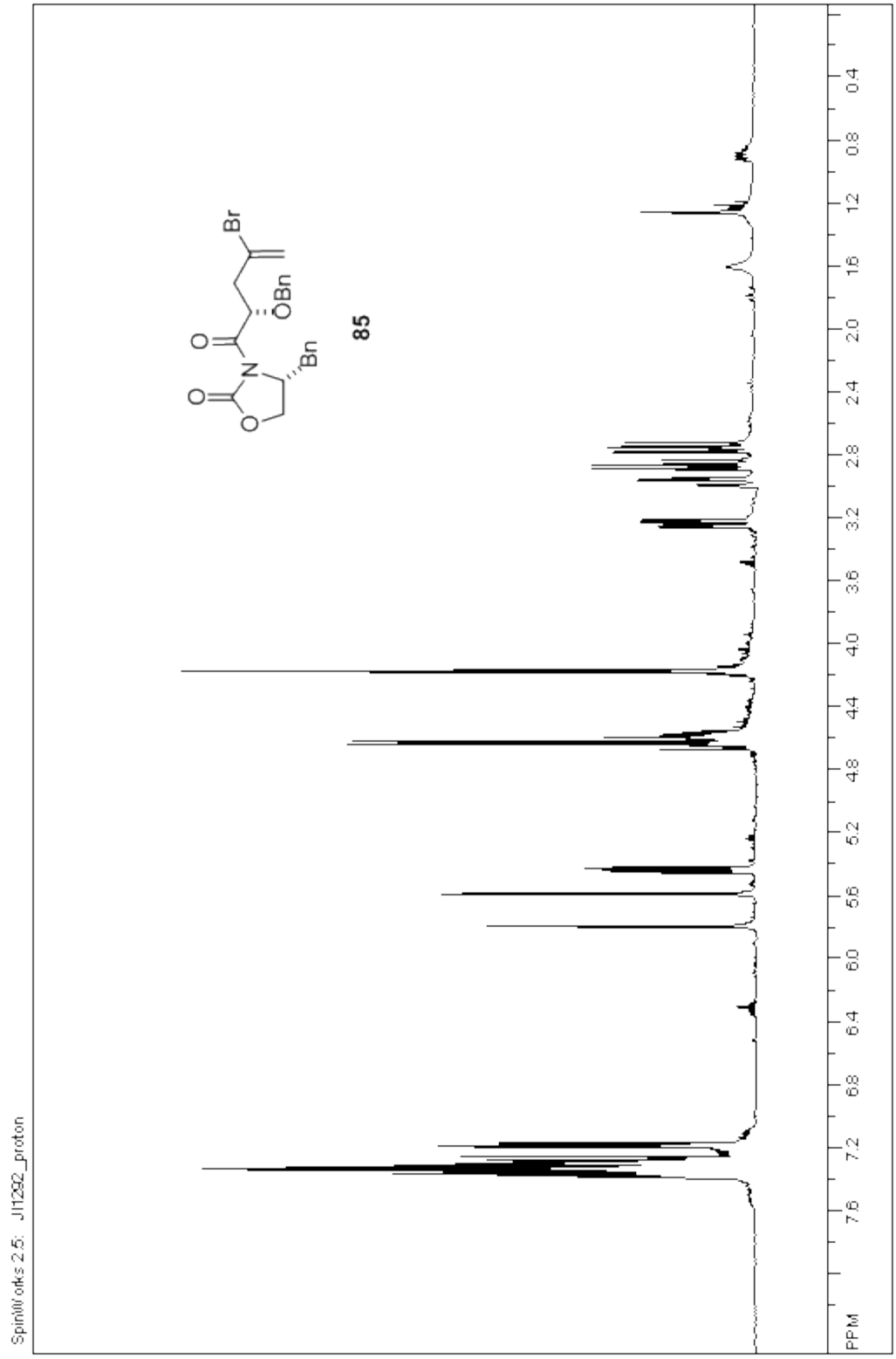

Figure A.93. ^{1}H Spectrum of **85**.

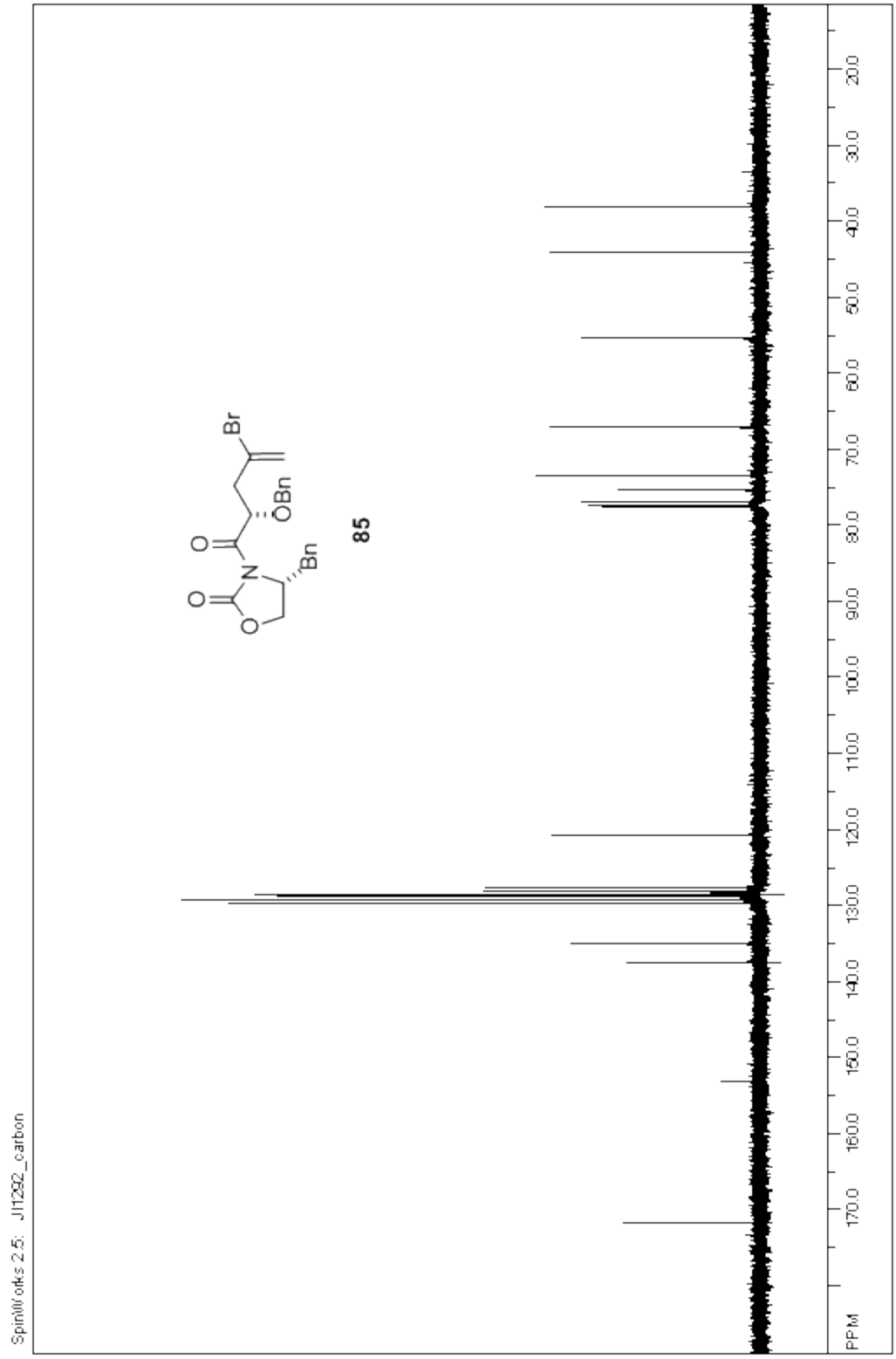

Figure A.94. ^{13}C Spectrum of **85**.

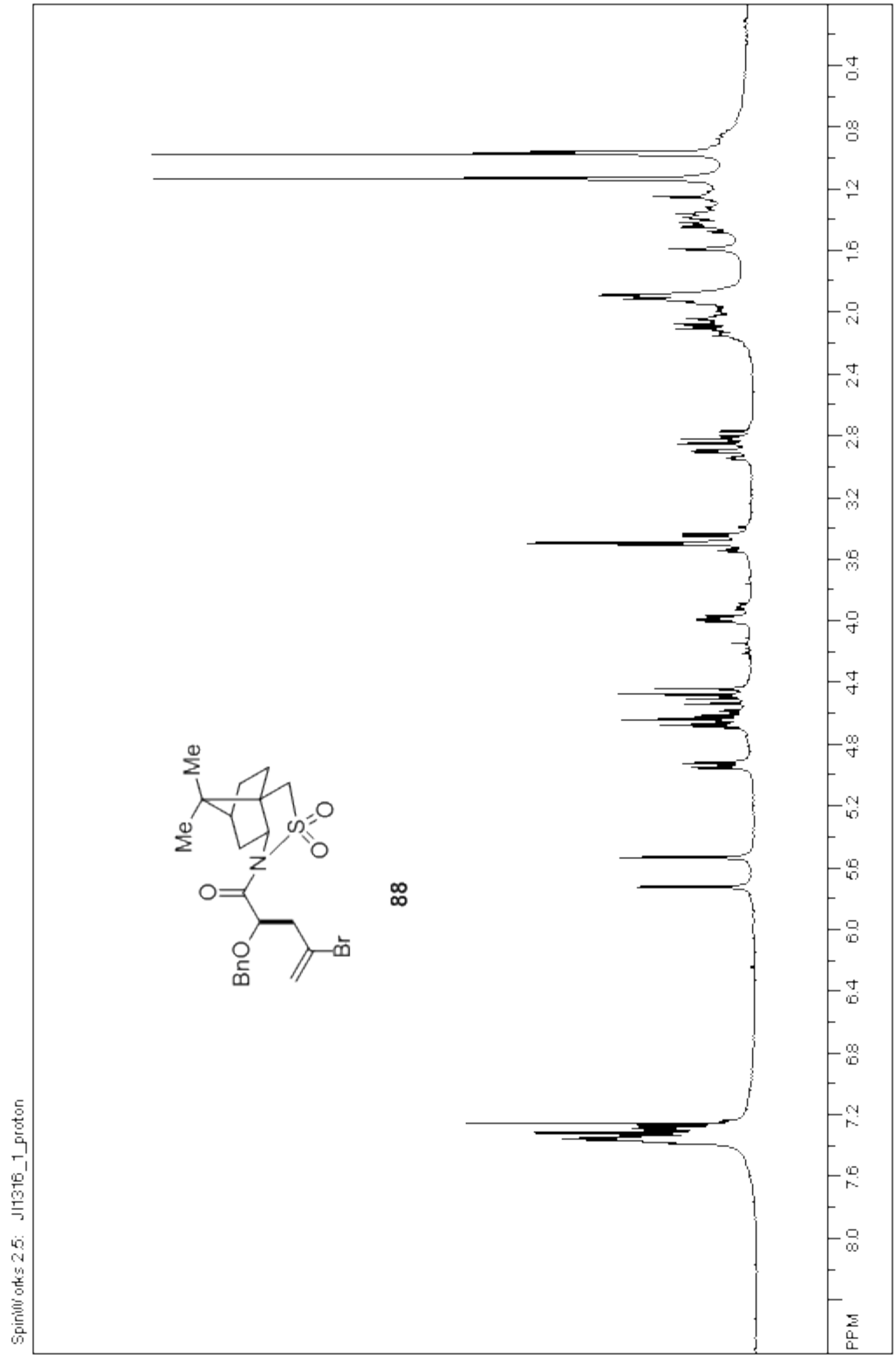

Figure A.95. ^{1}H Spectrum of **88**.

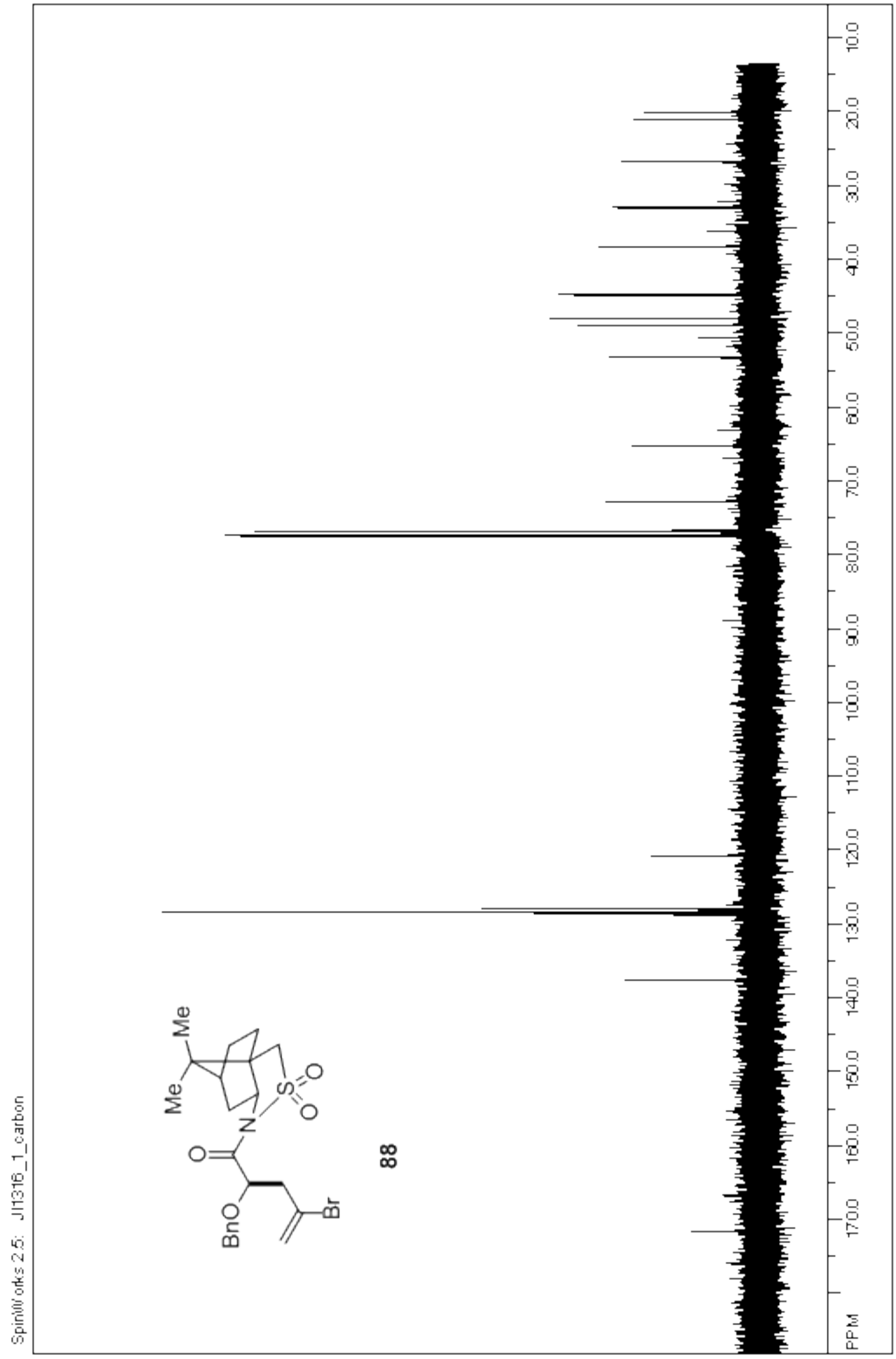

Figure A.96. ^{13}C Spectrum of **88**.

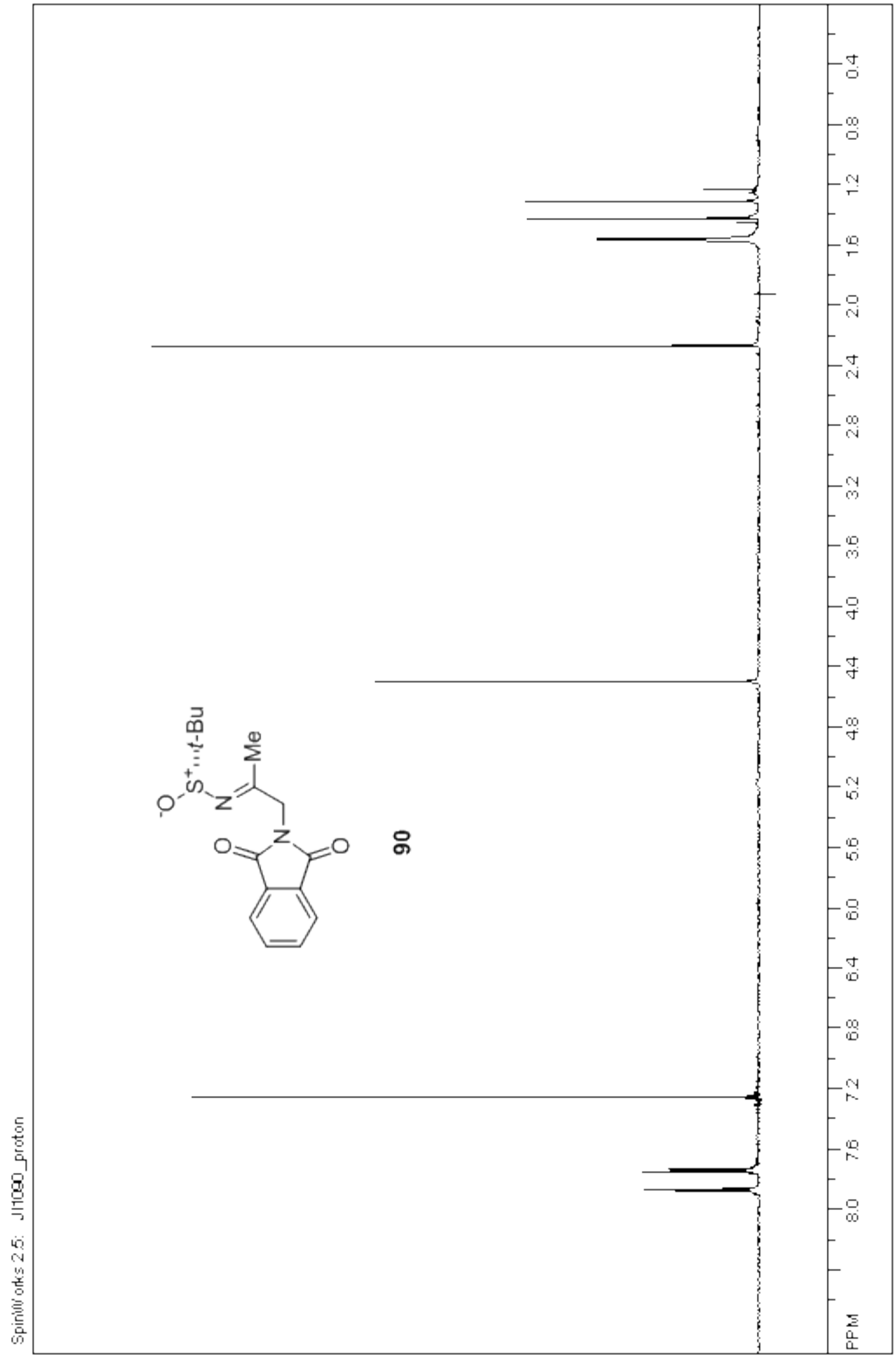

Figure A.97. ^{1}H Spectrum of **90**.

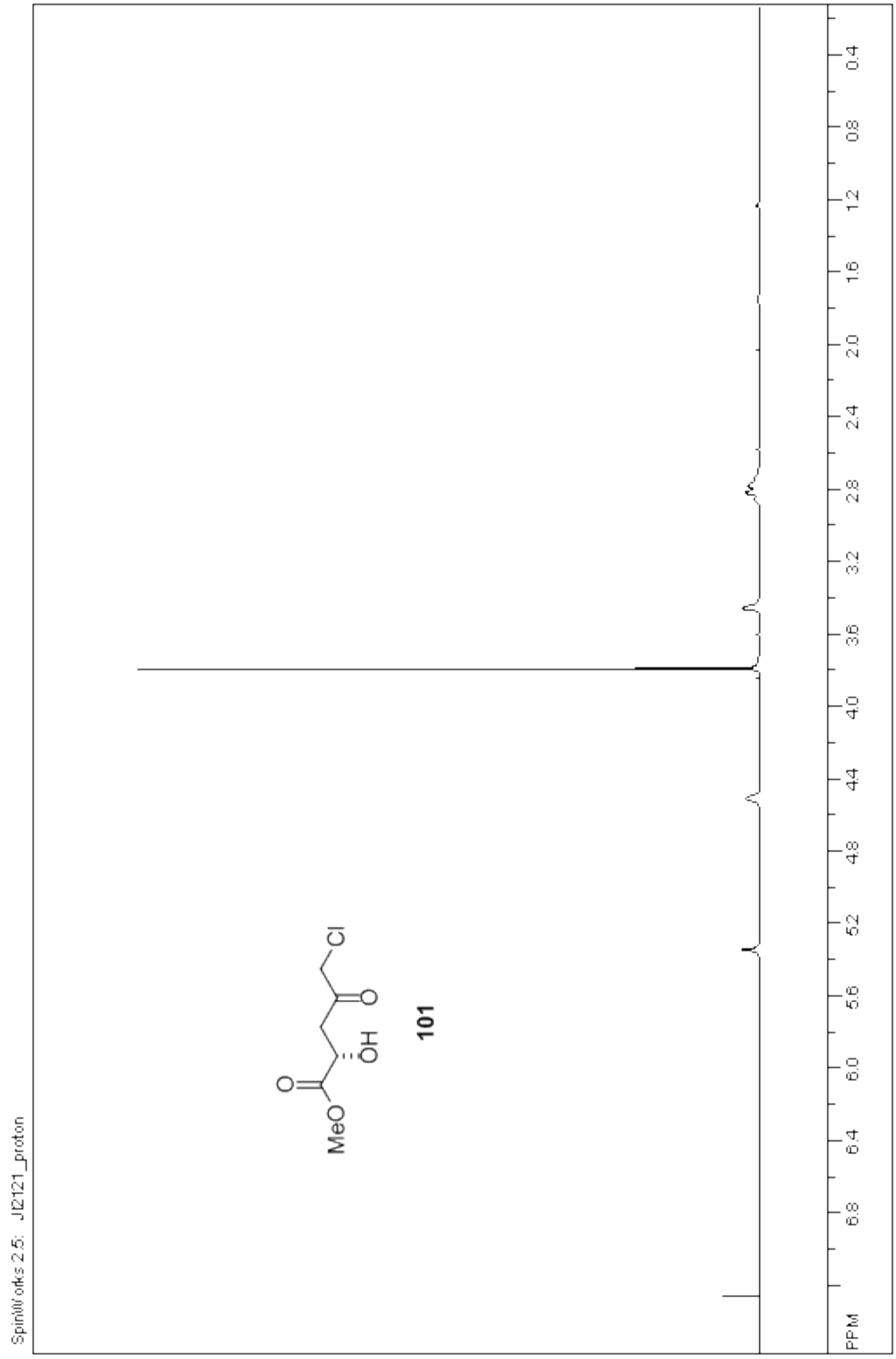

Figure A.98. ^{1}H Spectrum of **101**.

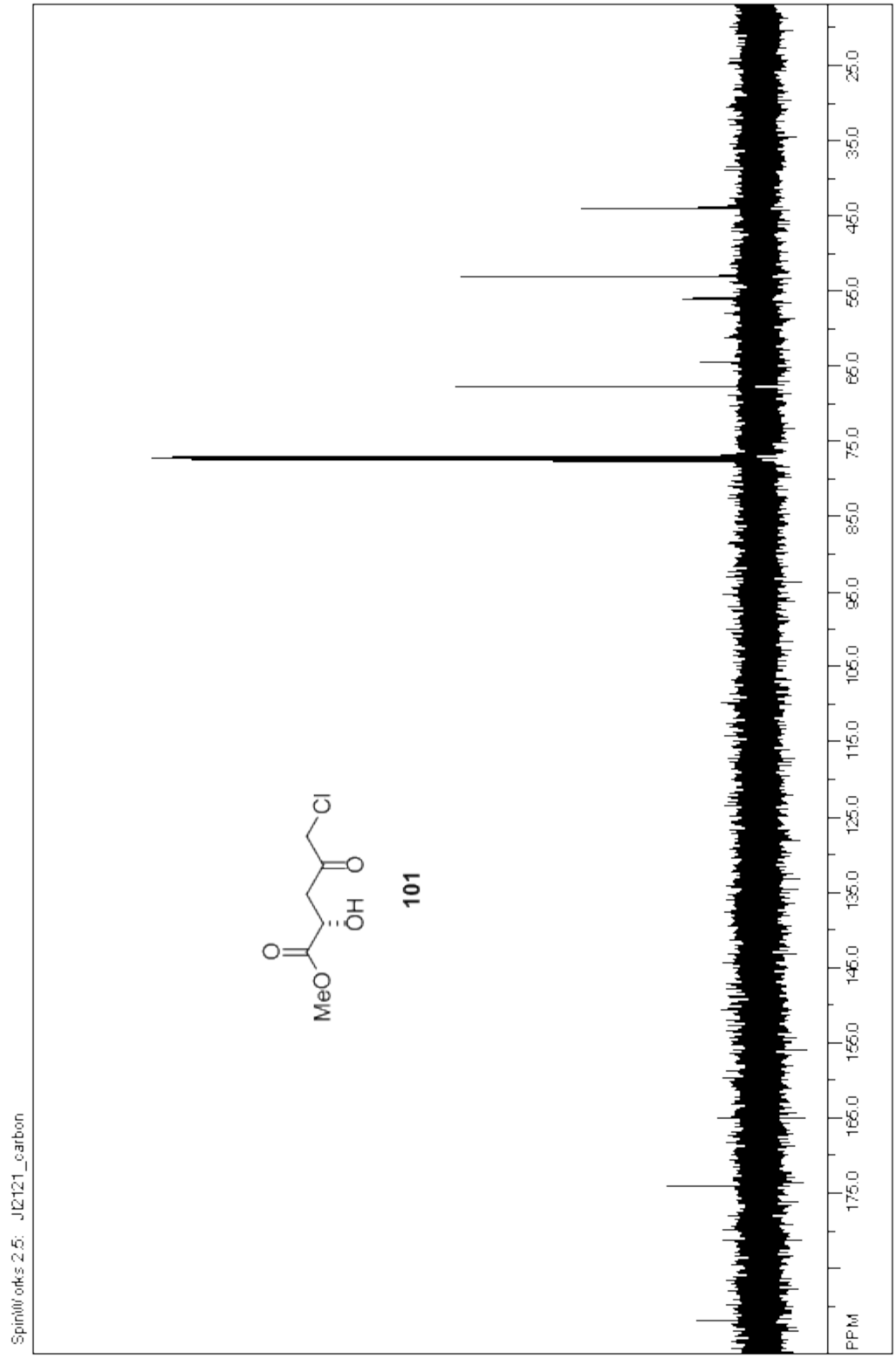

Figure A.99. ^{13}C Spectrum of **101**.

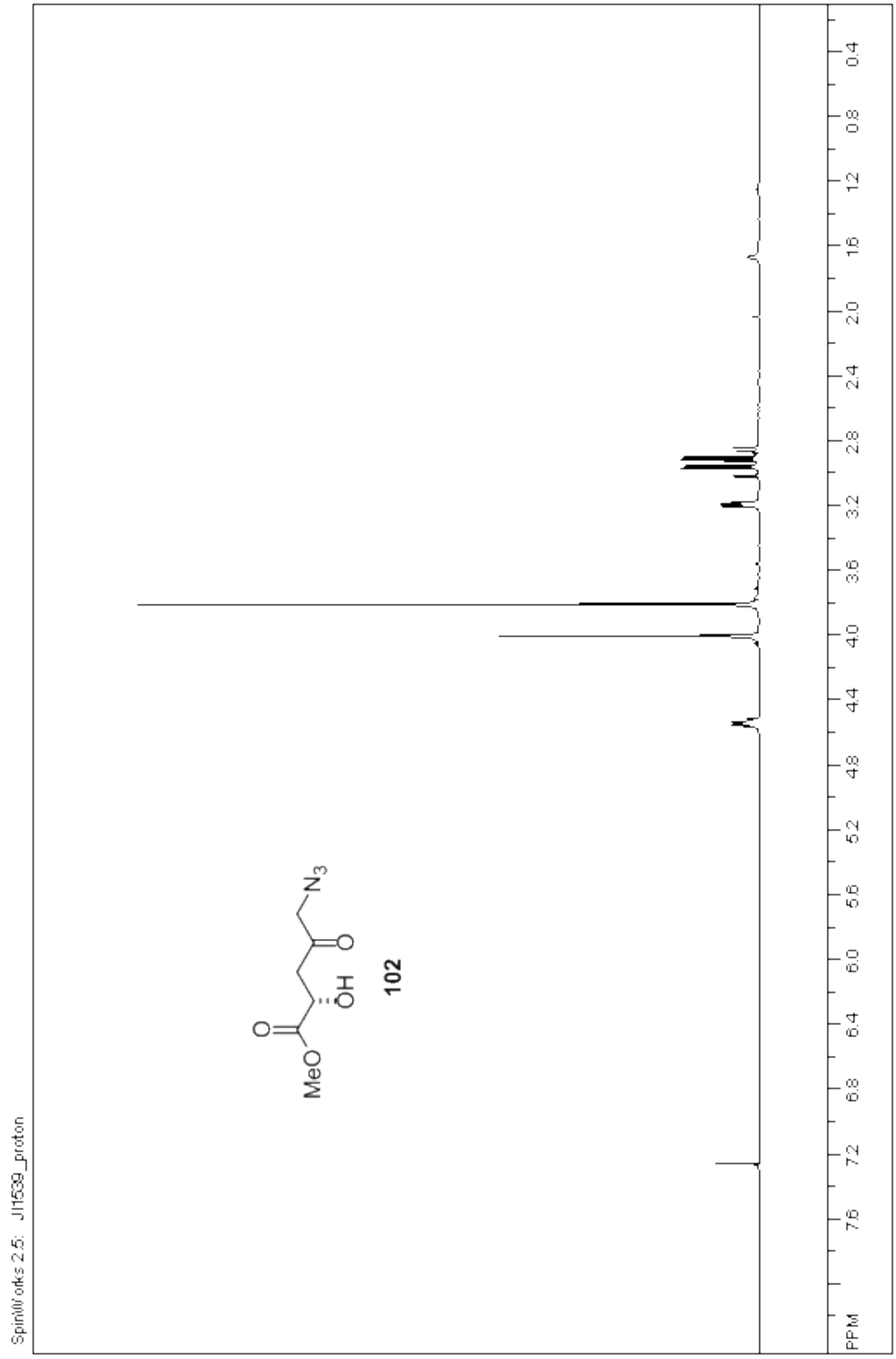

Figure A.100. ^{1}H Spectrum of **102**.

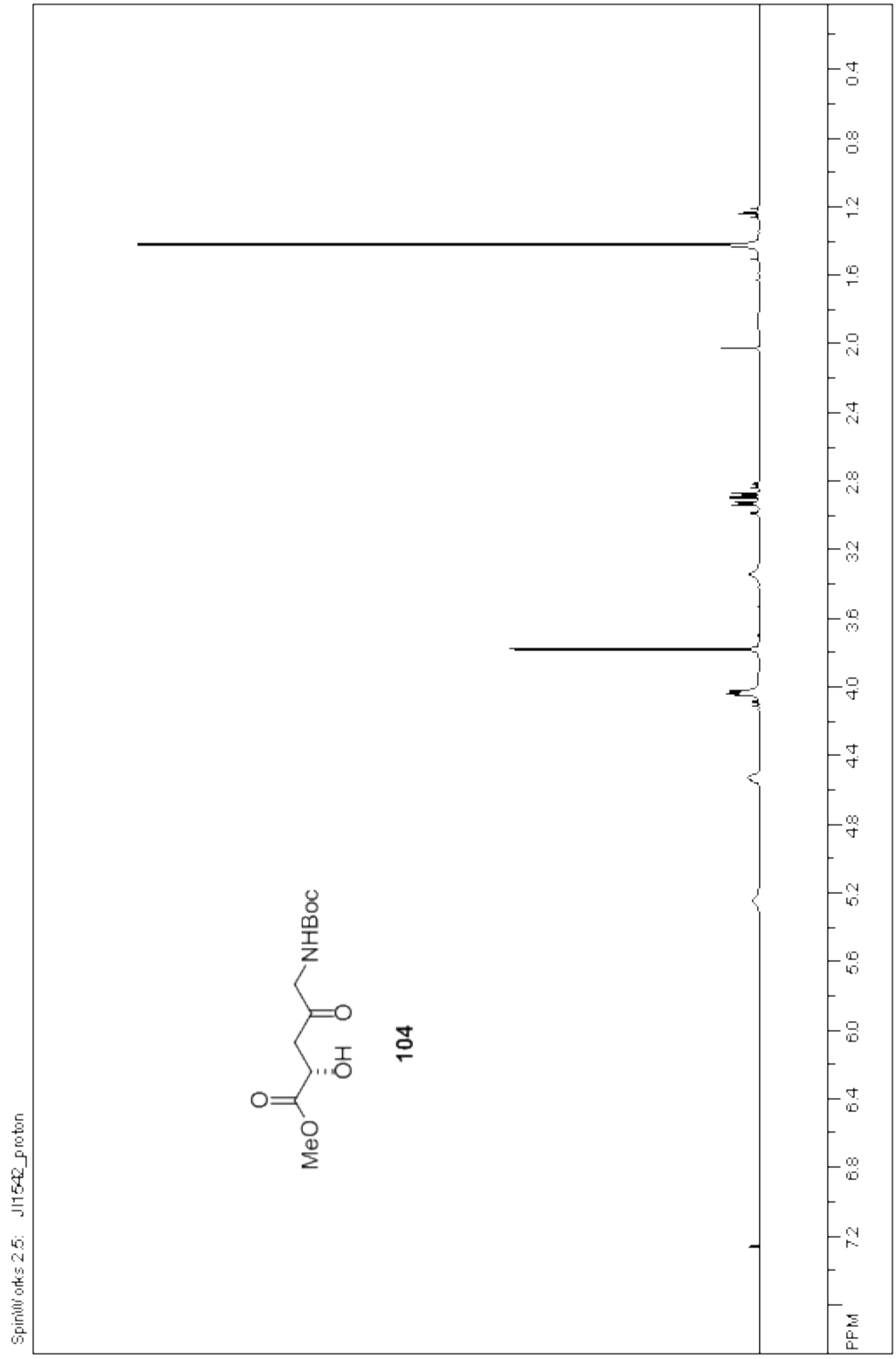

Figure A.101. ^{1}H Spectrum of **104**.

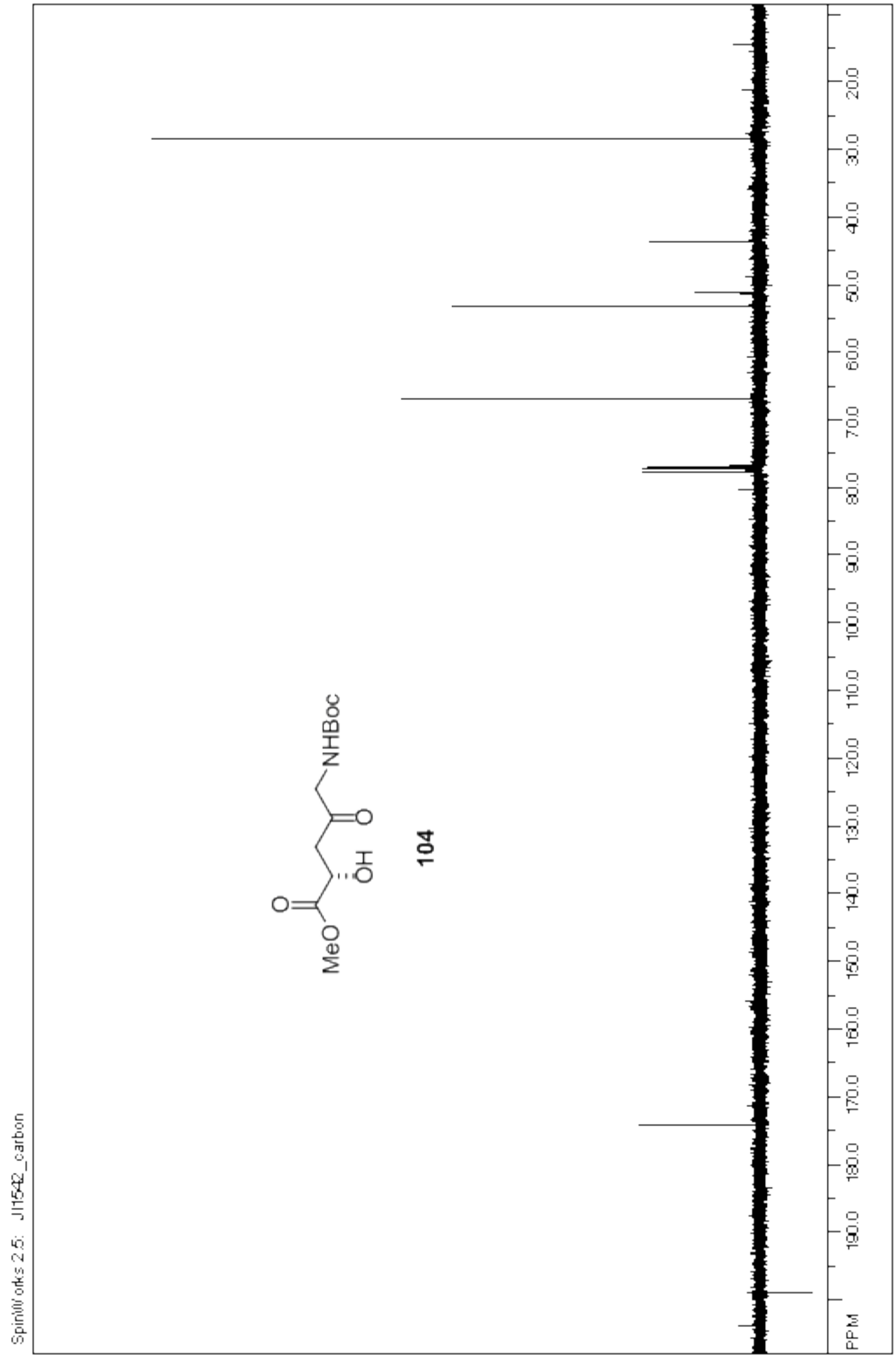

Figure A.102. ^{13}C Spectrum of **104**.

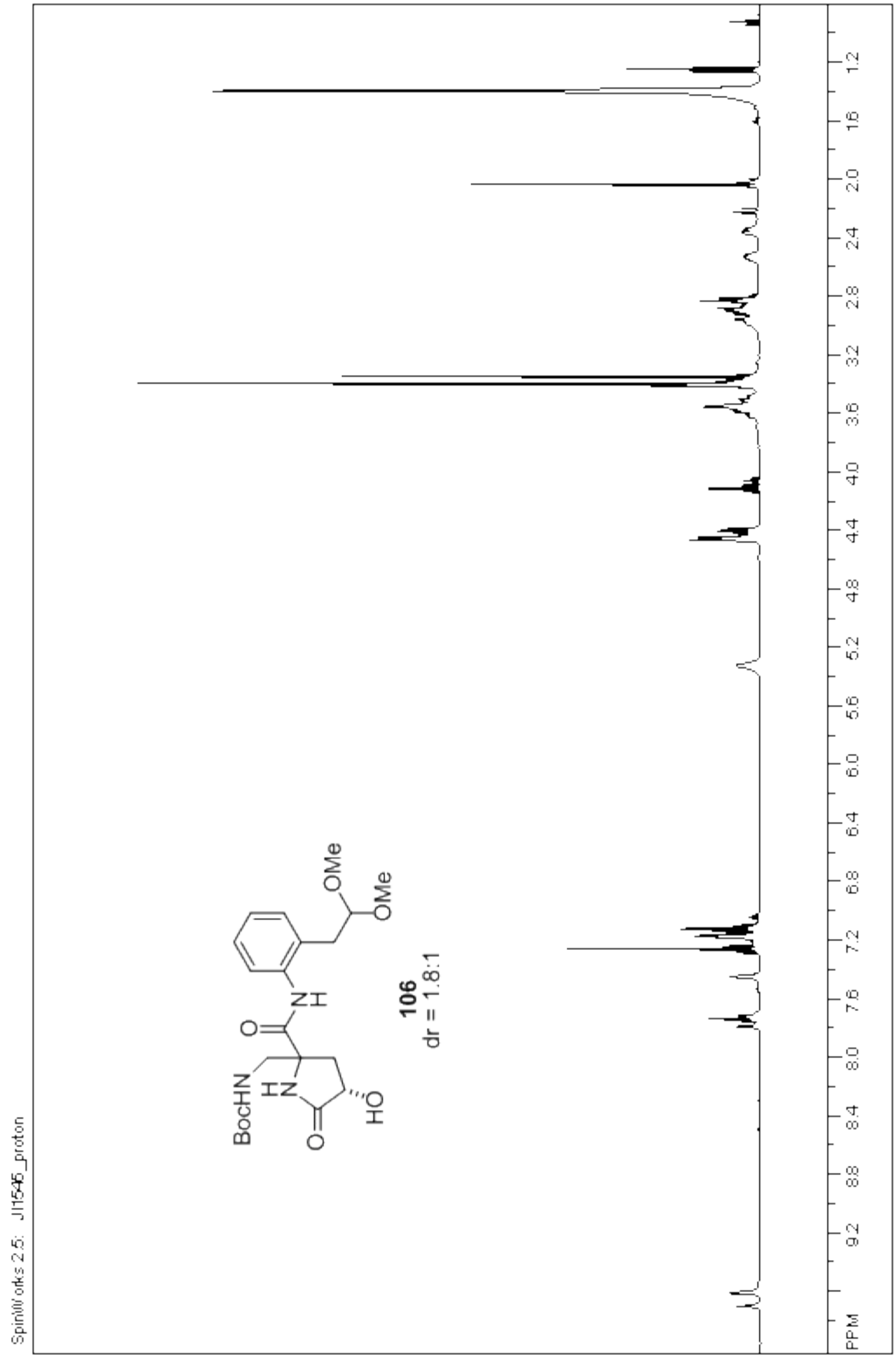

Figure A.103. ^{1}H Spectrum of **106**.

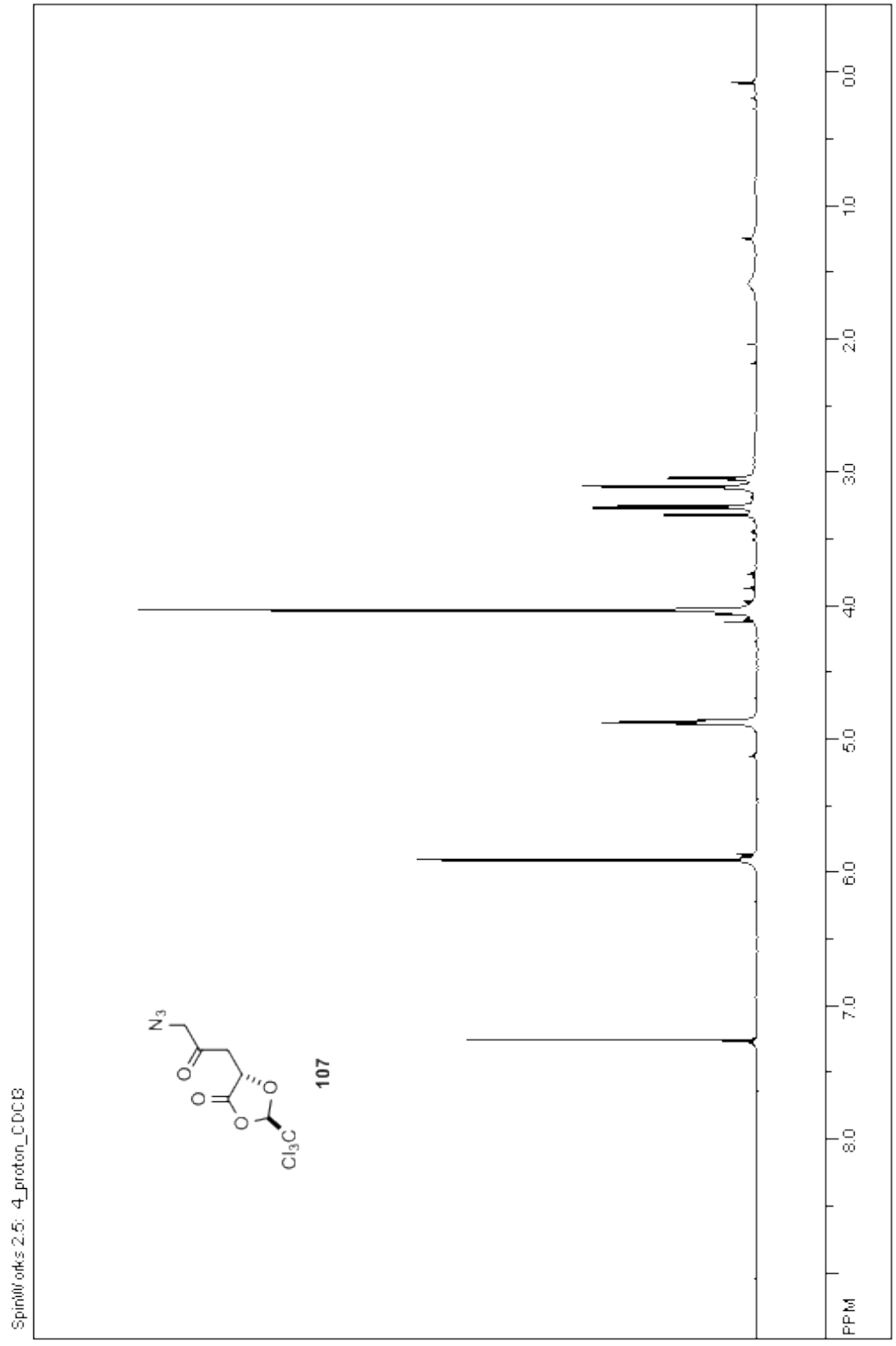

Figure A.104. ^{1}H Spectrum of **107**.

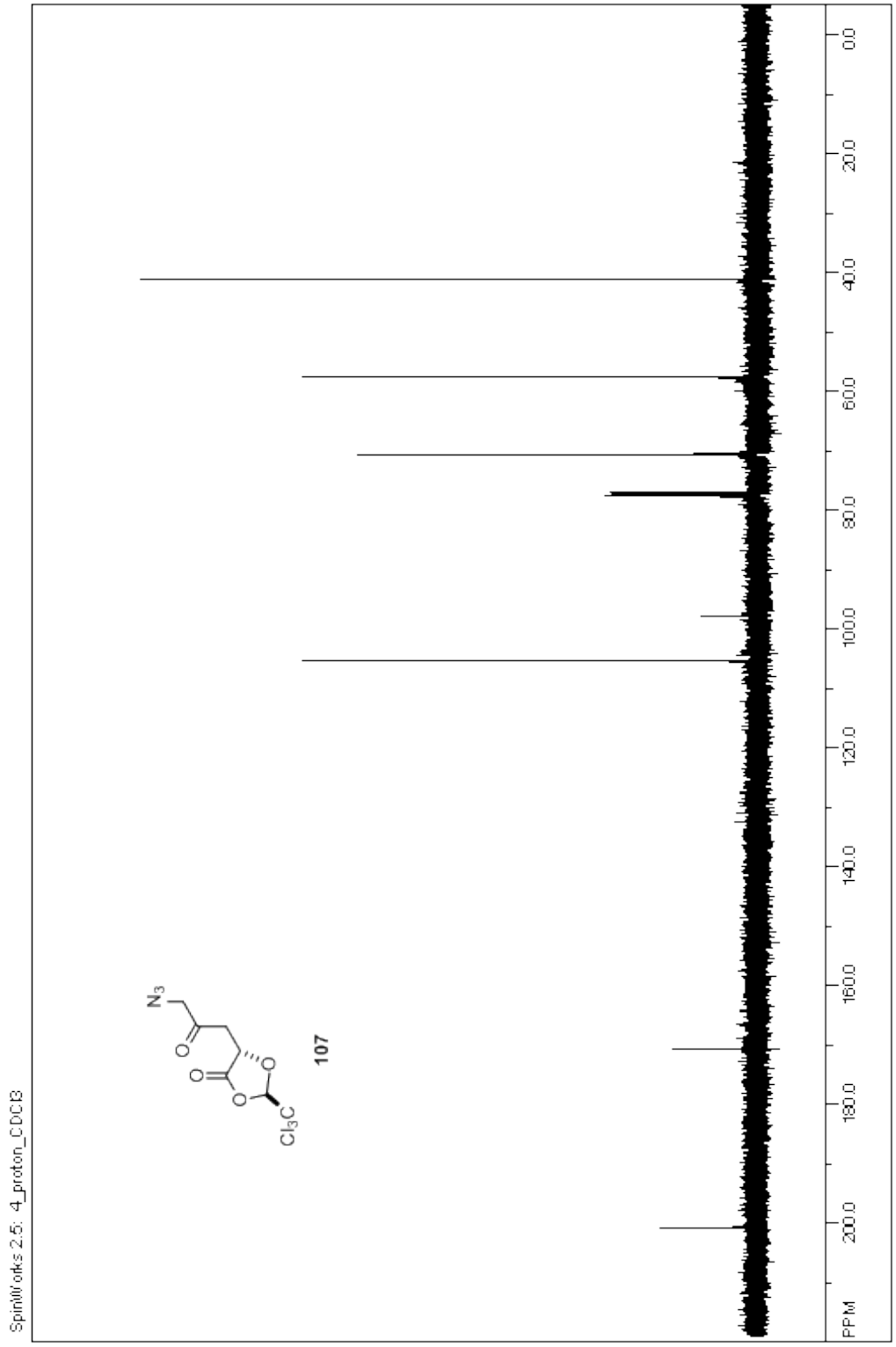

Figure A.105. ^{13}C Spectrum of **107**.

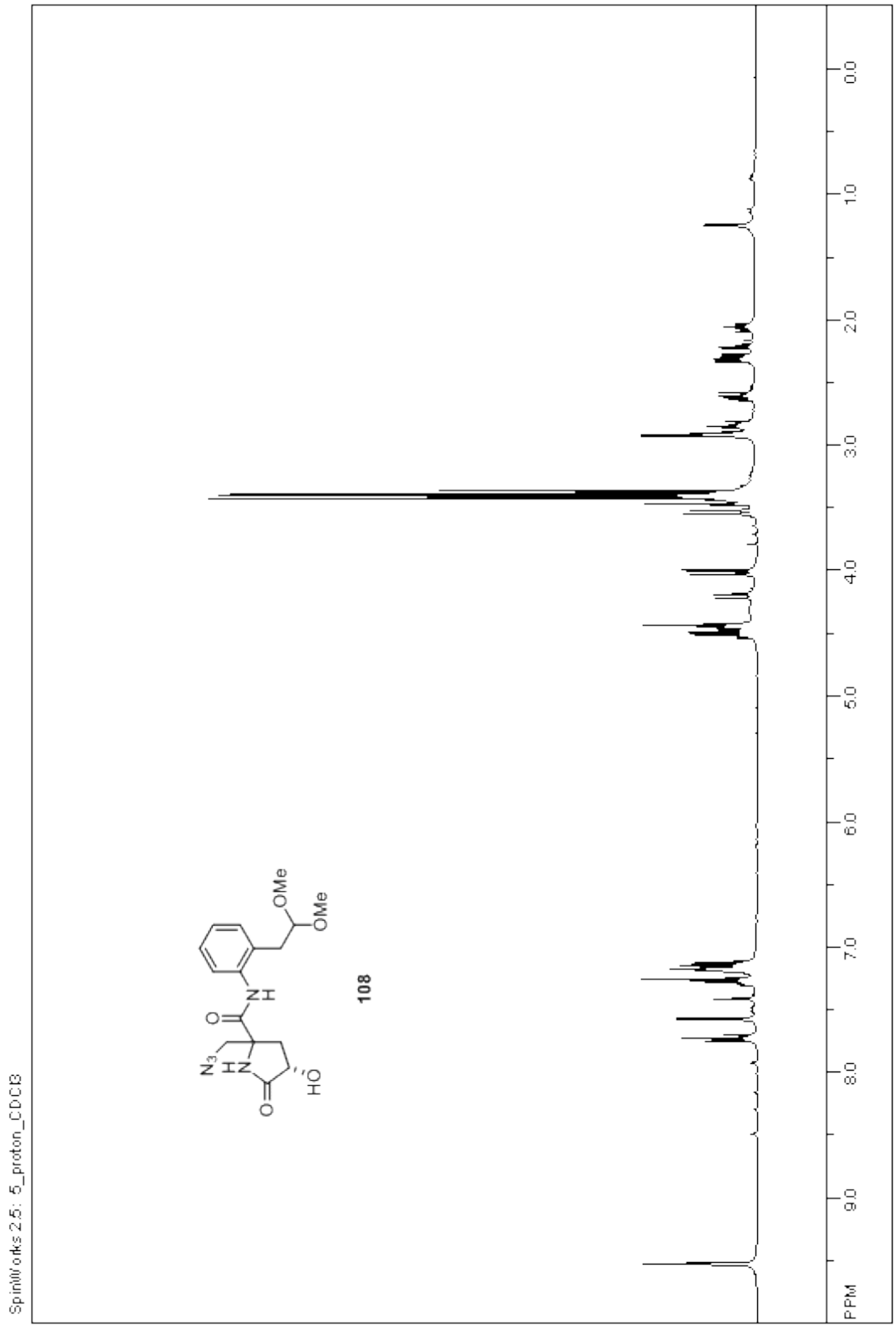

Figure A.106. ^{1}H Spectrum of **108**.

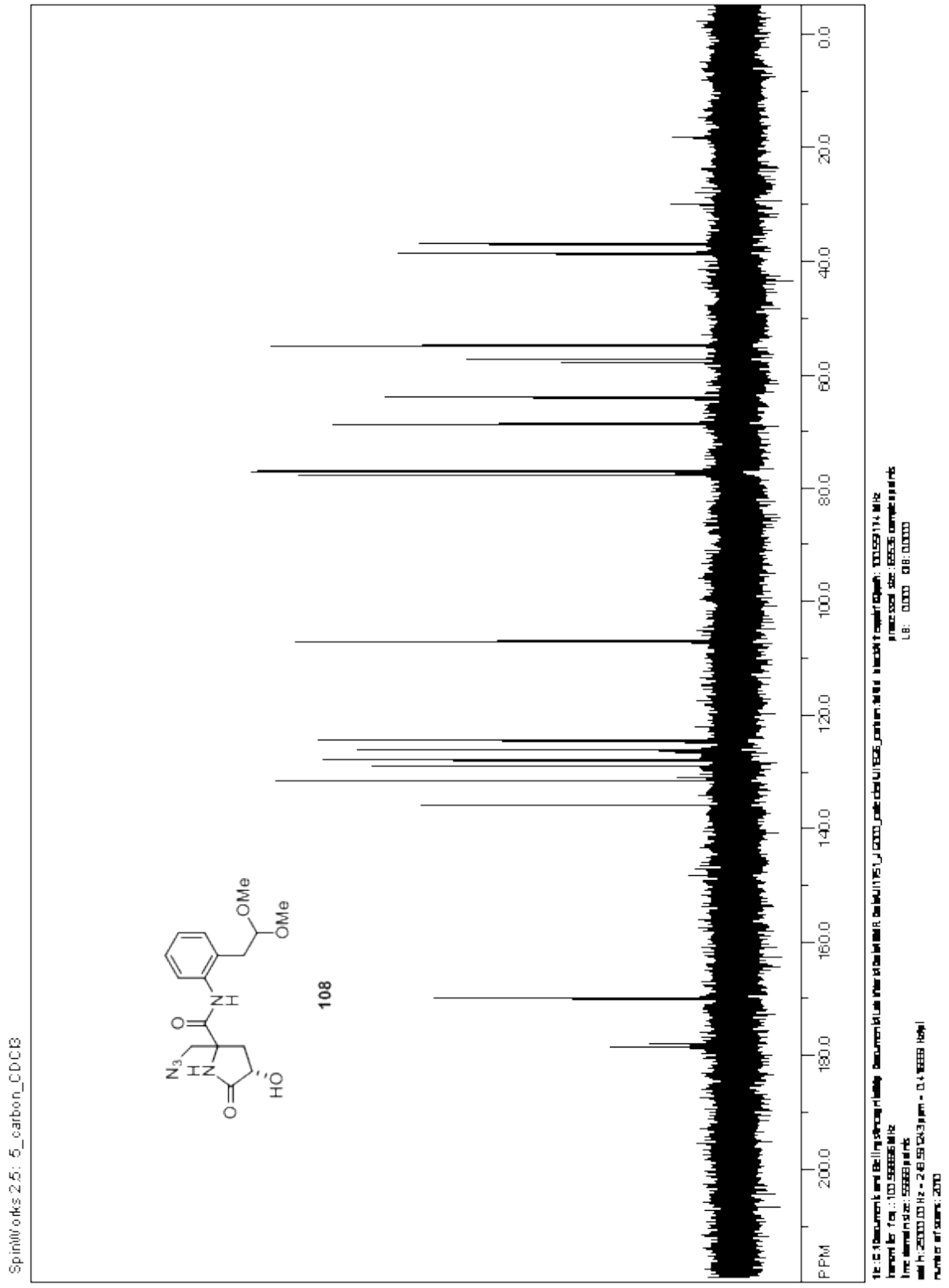

Figure A.107. ^{13}C Spectrum of **108**.

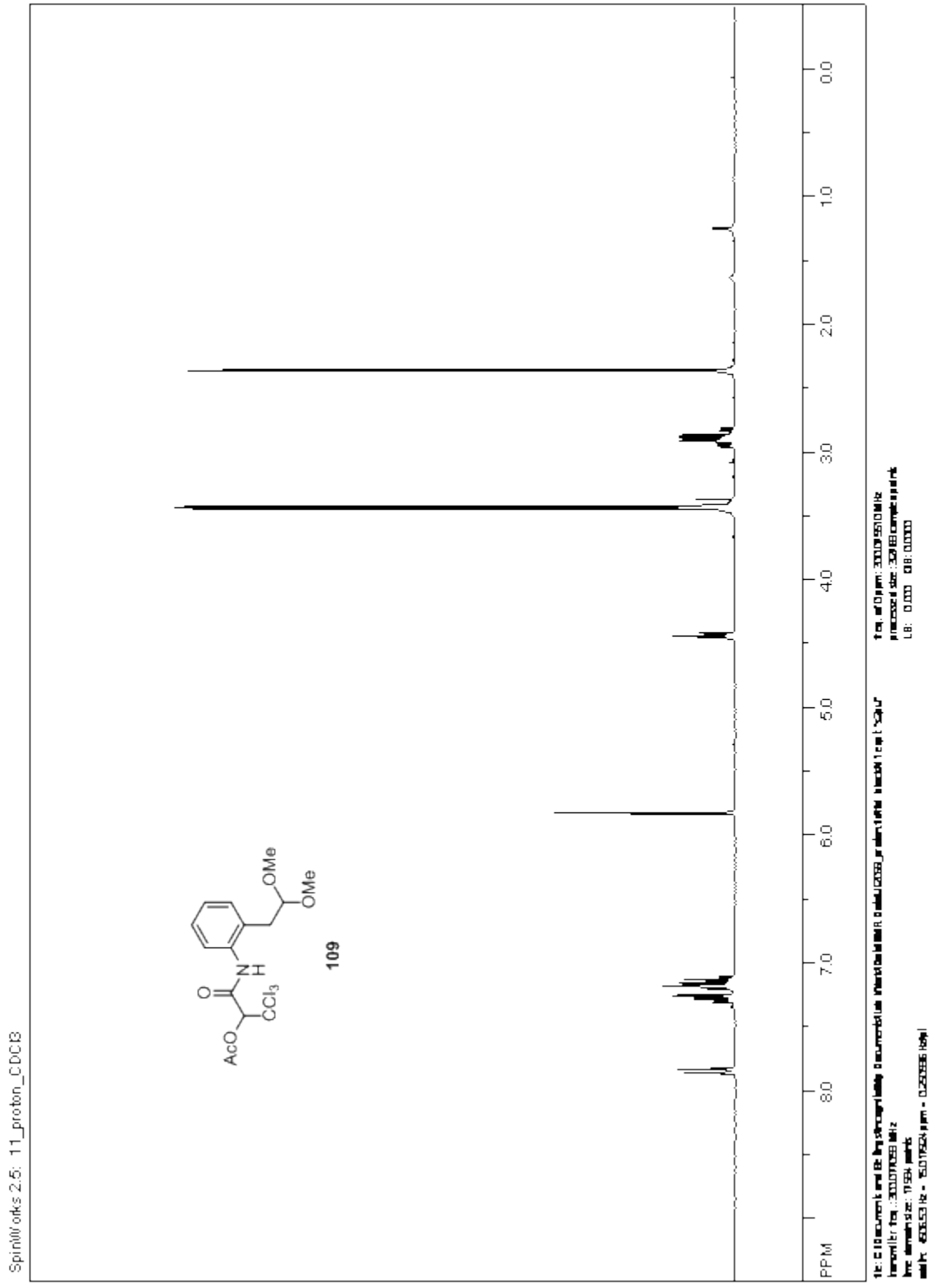

Figure A.108. ^{1}H Spectrum of **109**.

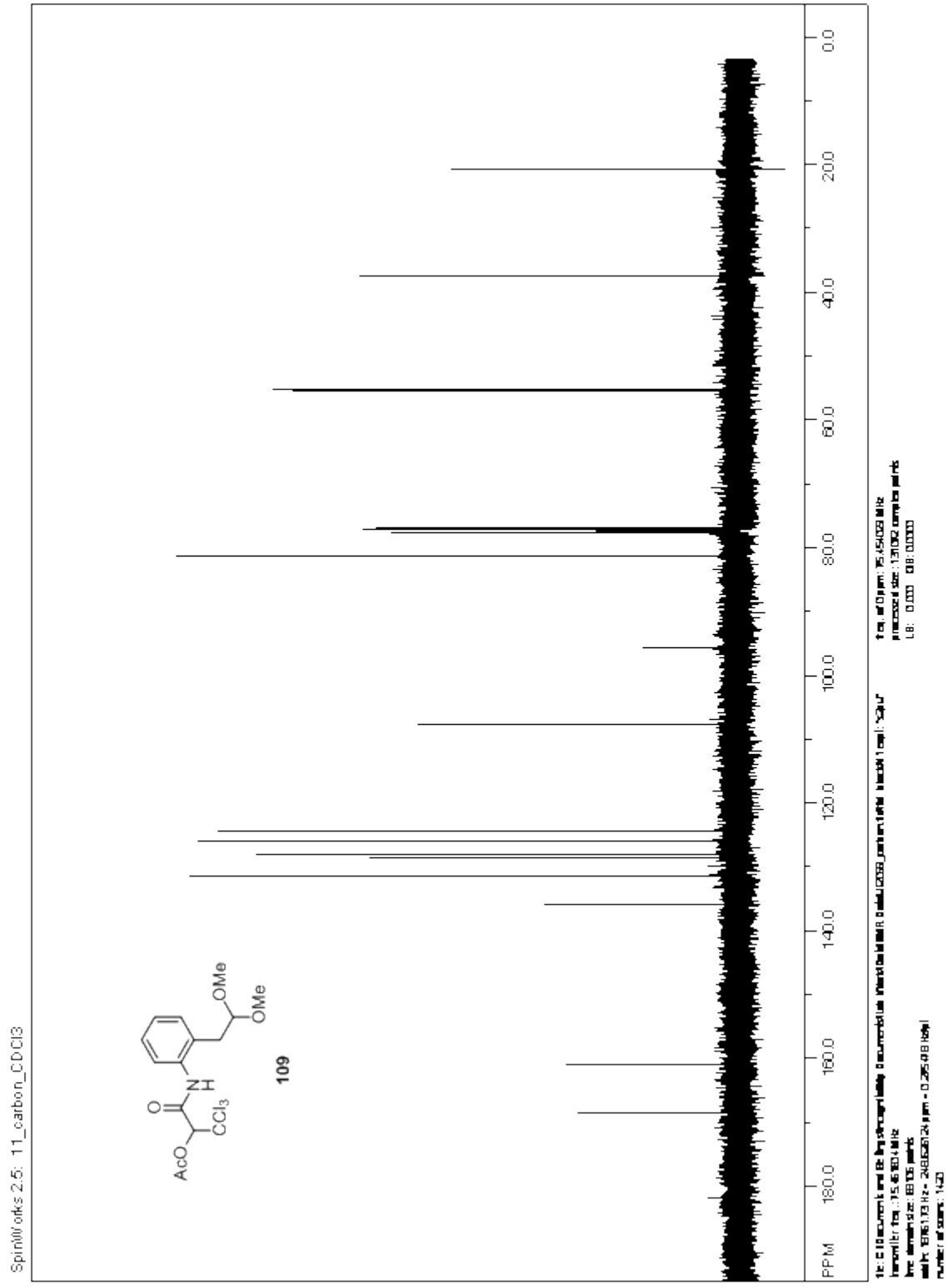

Figure A.109. ^{13}C Spectrum of **109**.

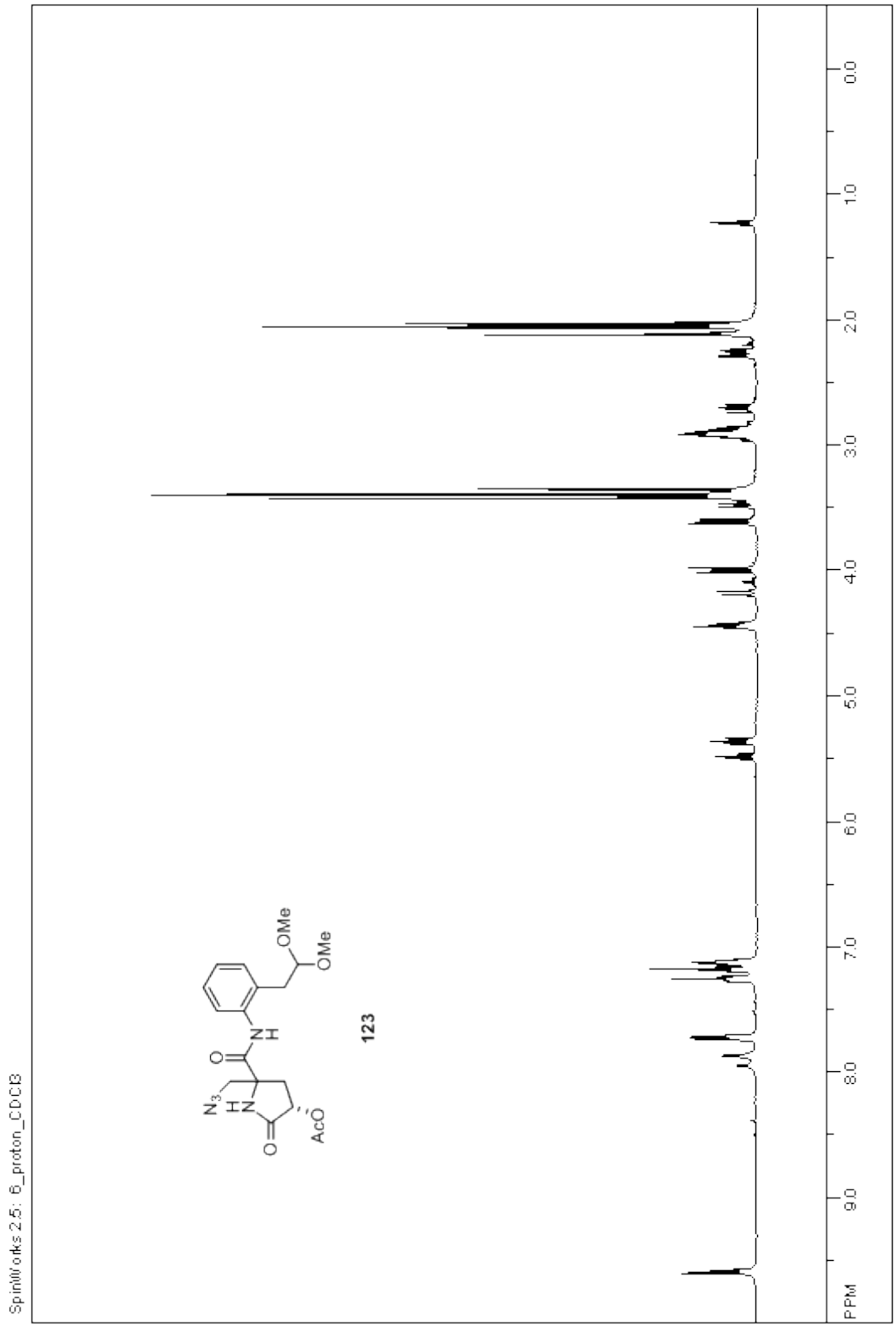

Figure A.110. ^{1}H Spectrum of **123**.

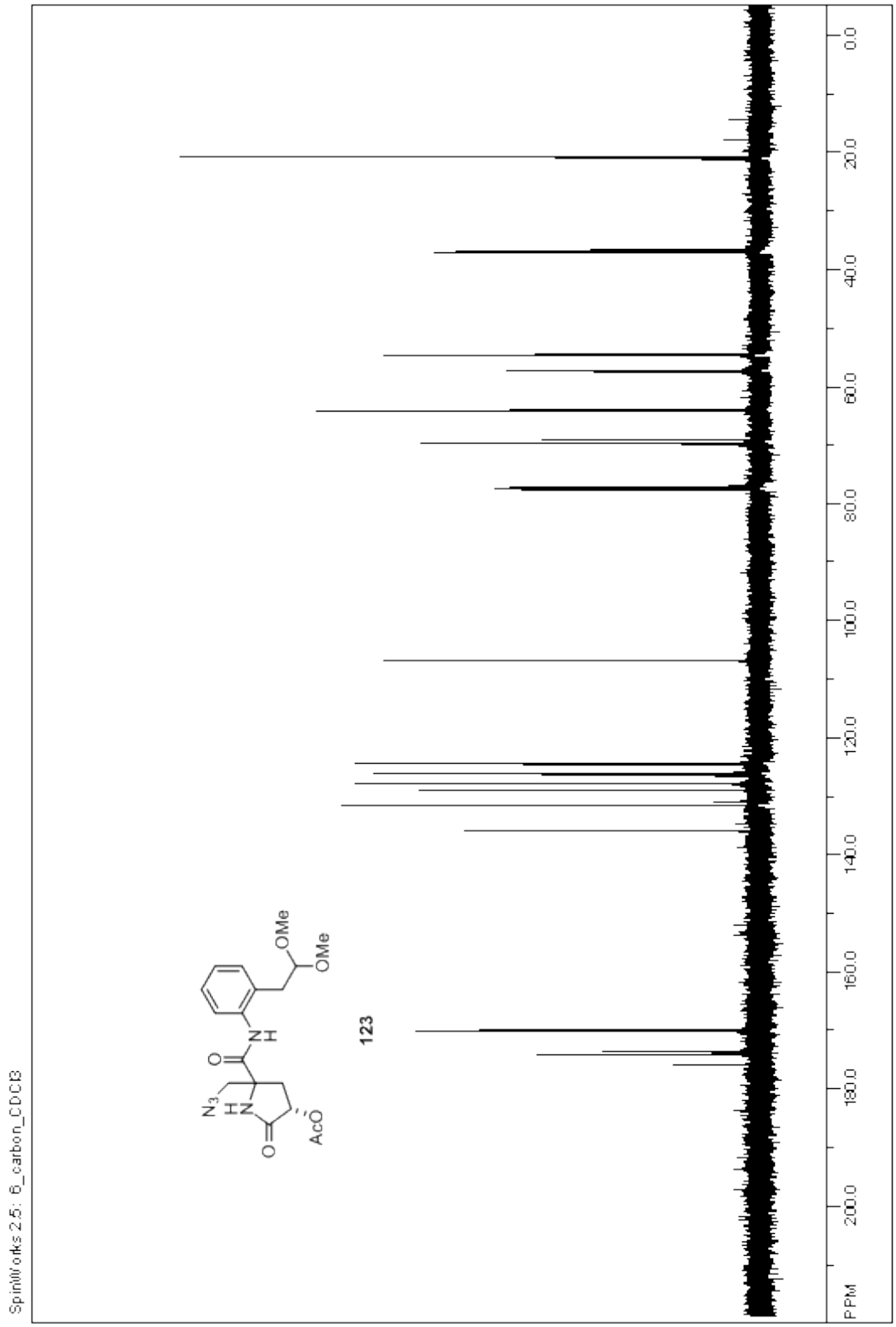

Figure A.111. ^{13}C Spectrum of **123**.

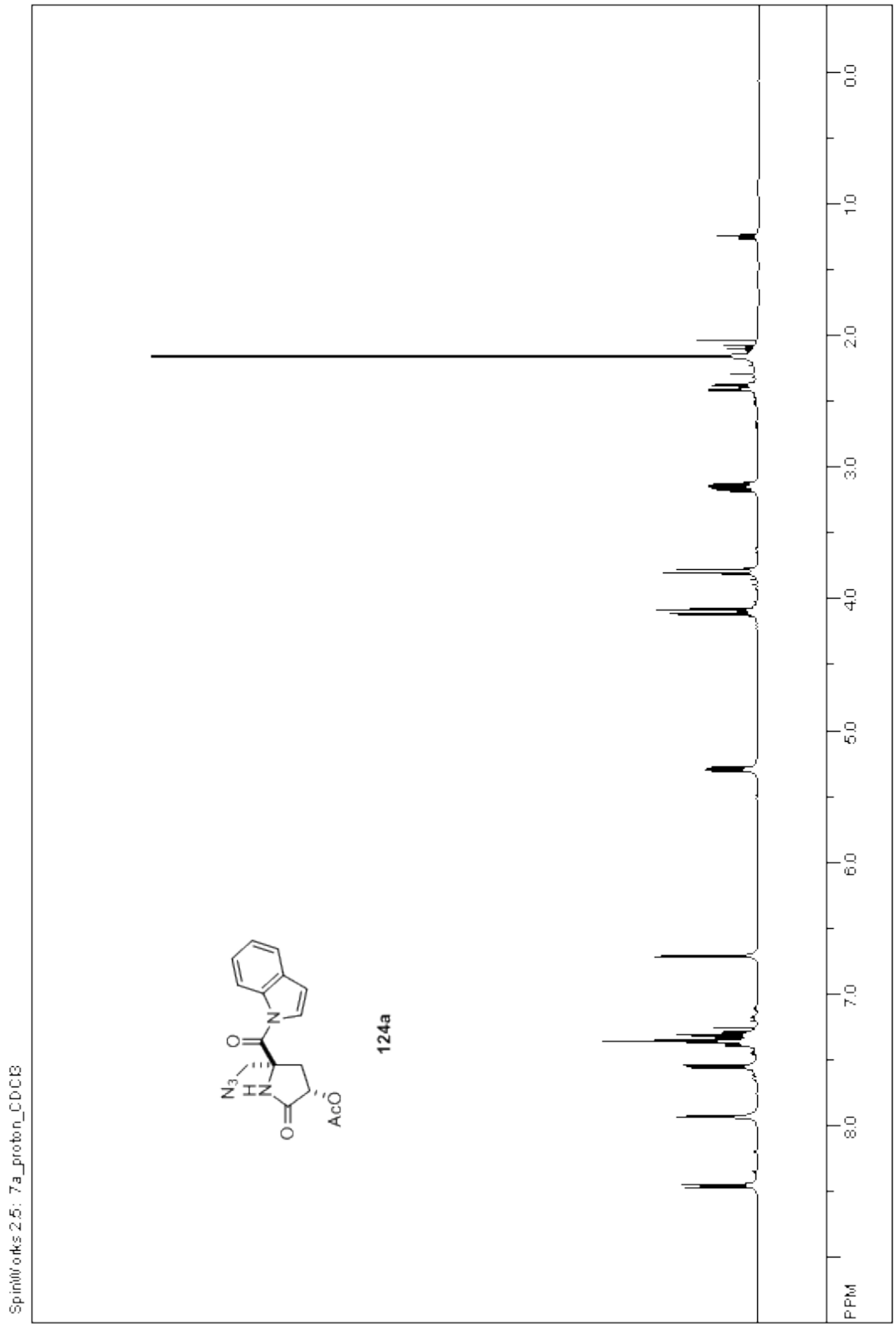

Figure A.112. ^{1}H Spectrum of **124a**.

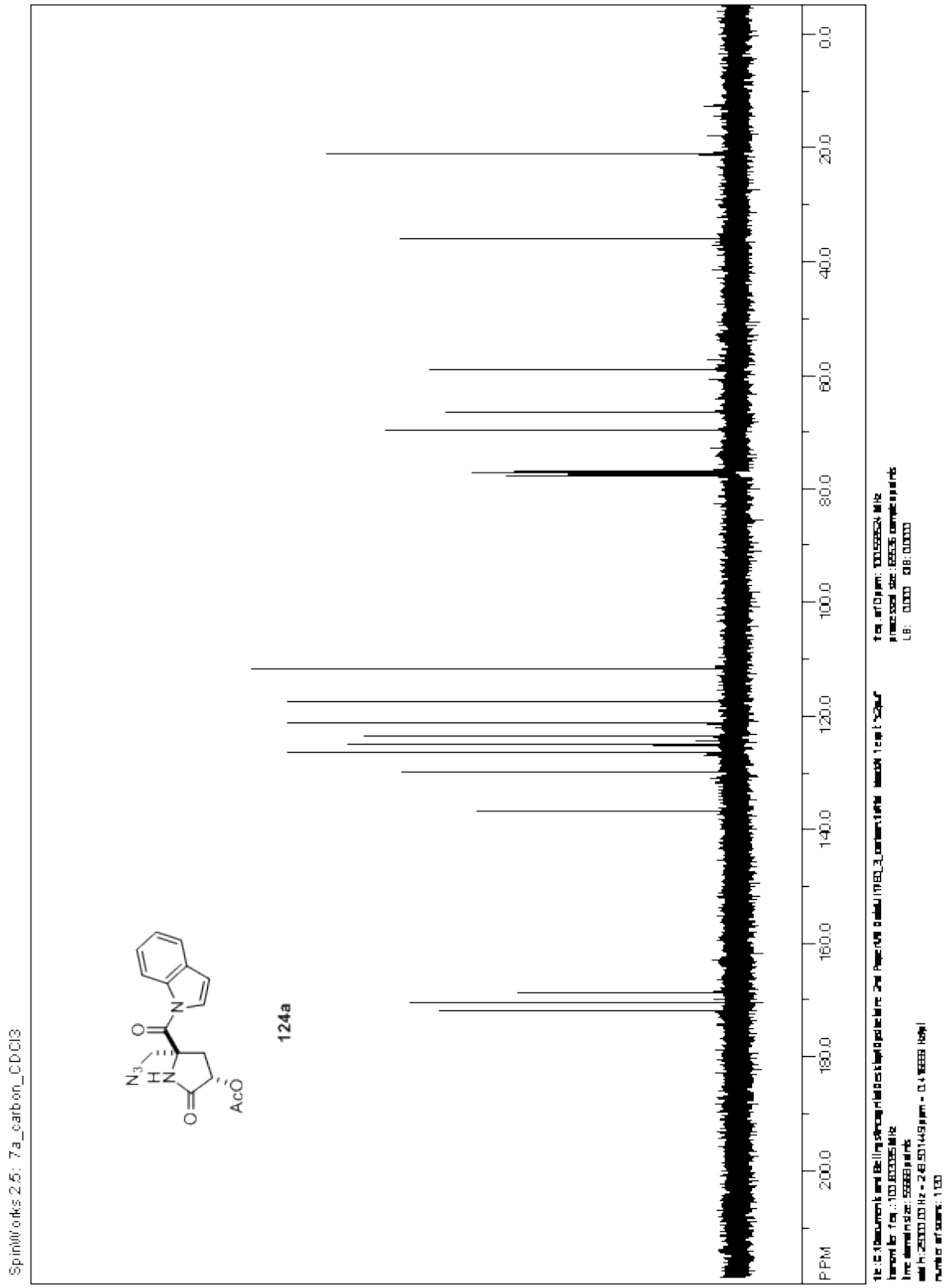

Figure A.113. ^{13}C Spectrum of **124a**.

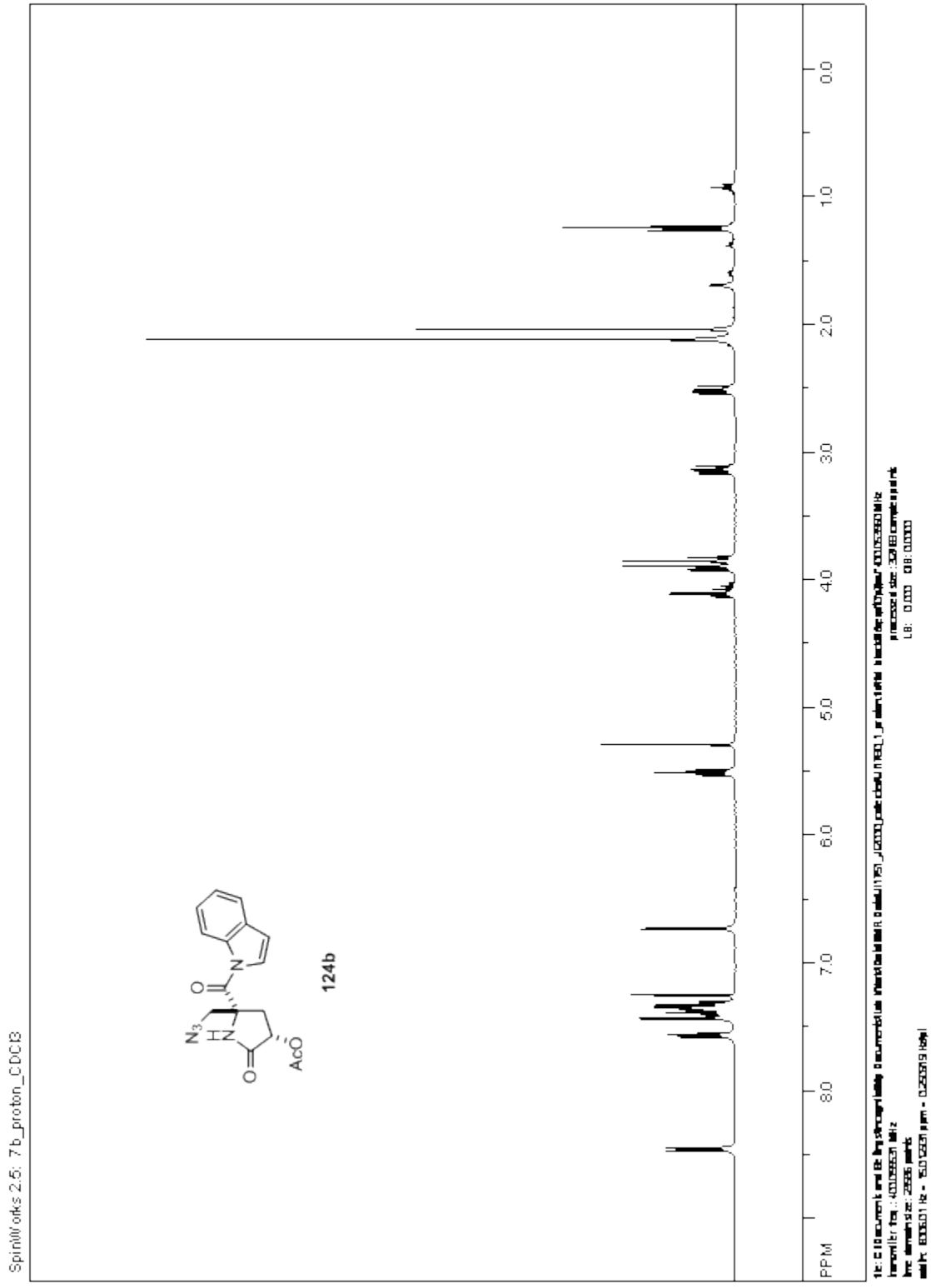

Figure A.114. ^{1}H Spectrum of **124b**.

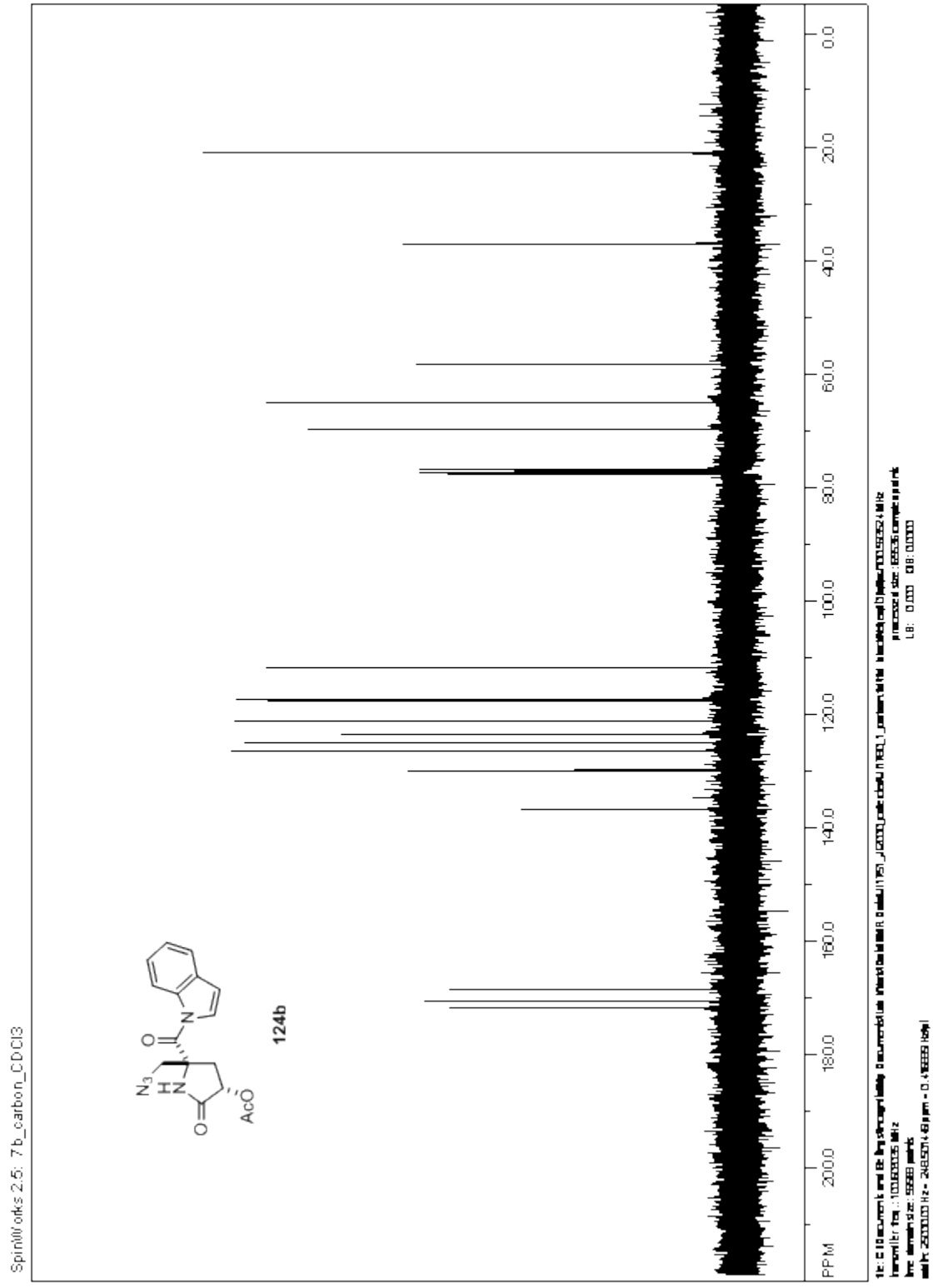

Figure A.115. ^{13}C Spectrum of **124b**.

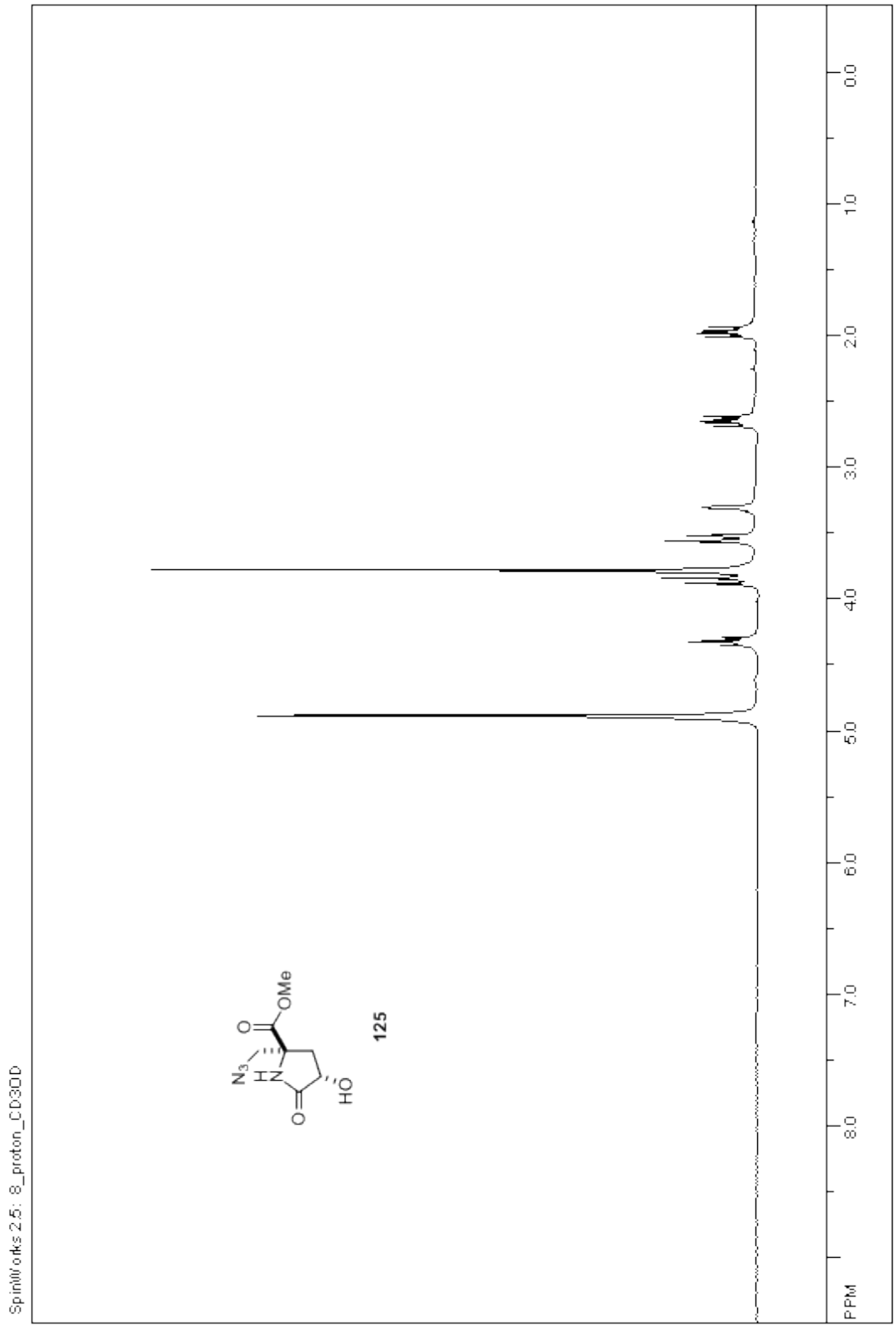

Figure A.116. ^{1}H Spectrum of **125**.

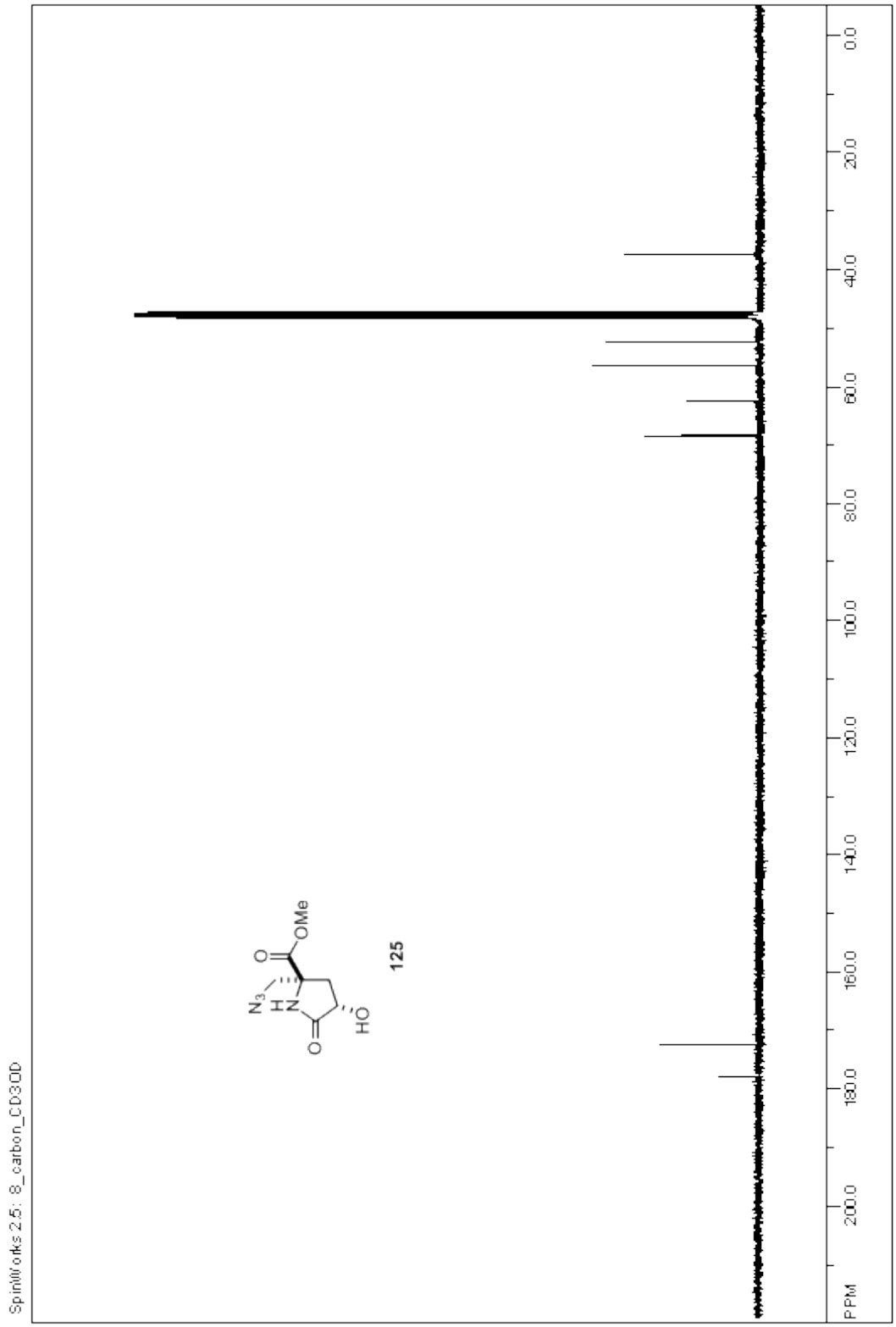

Figure A.117. ^{13}C Spectrum of **125**.

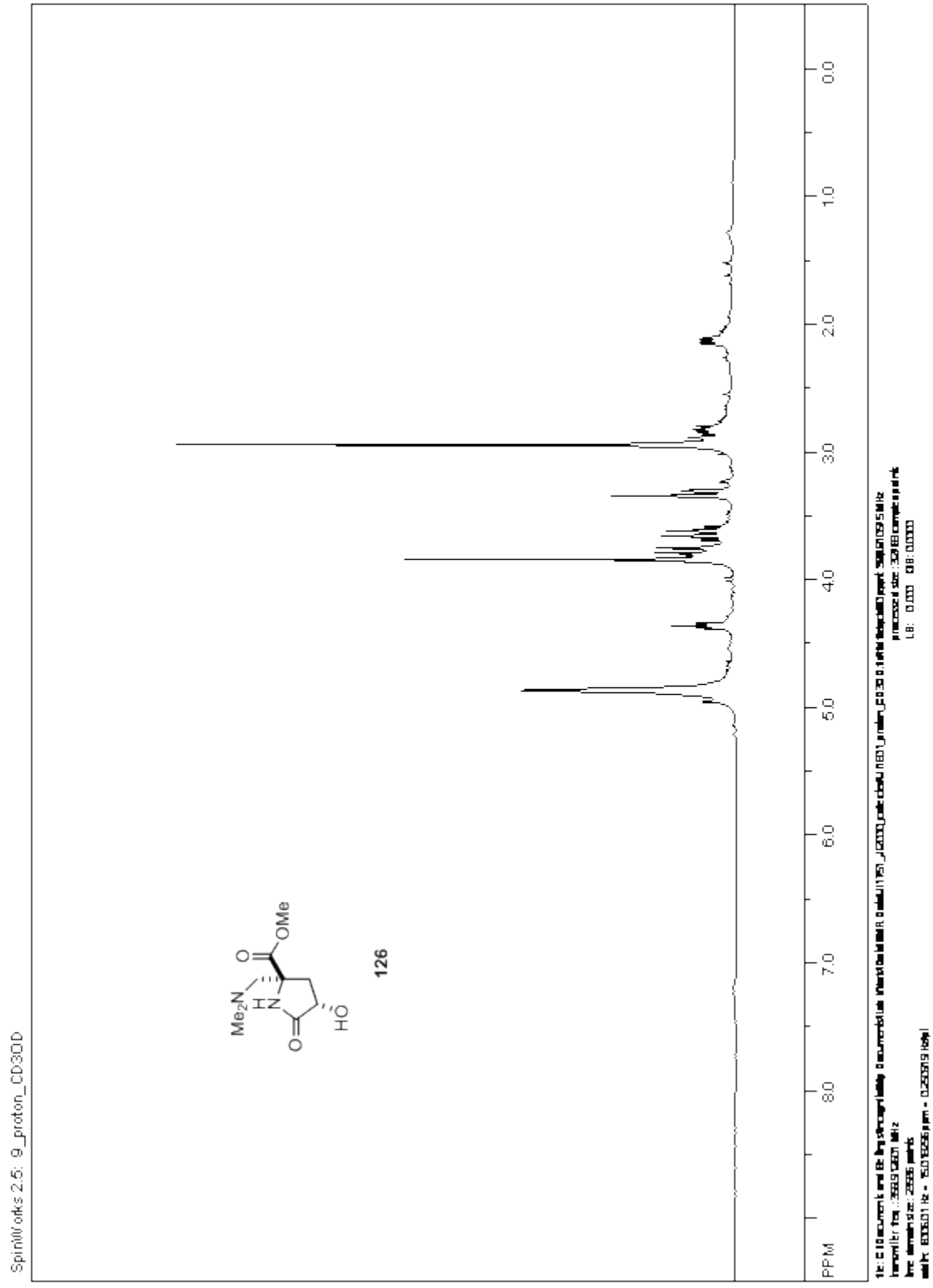

Figure A.118. ^{1}H Spectrum of **126**.

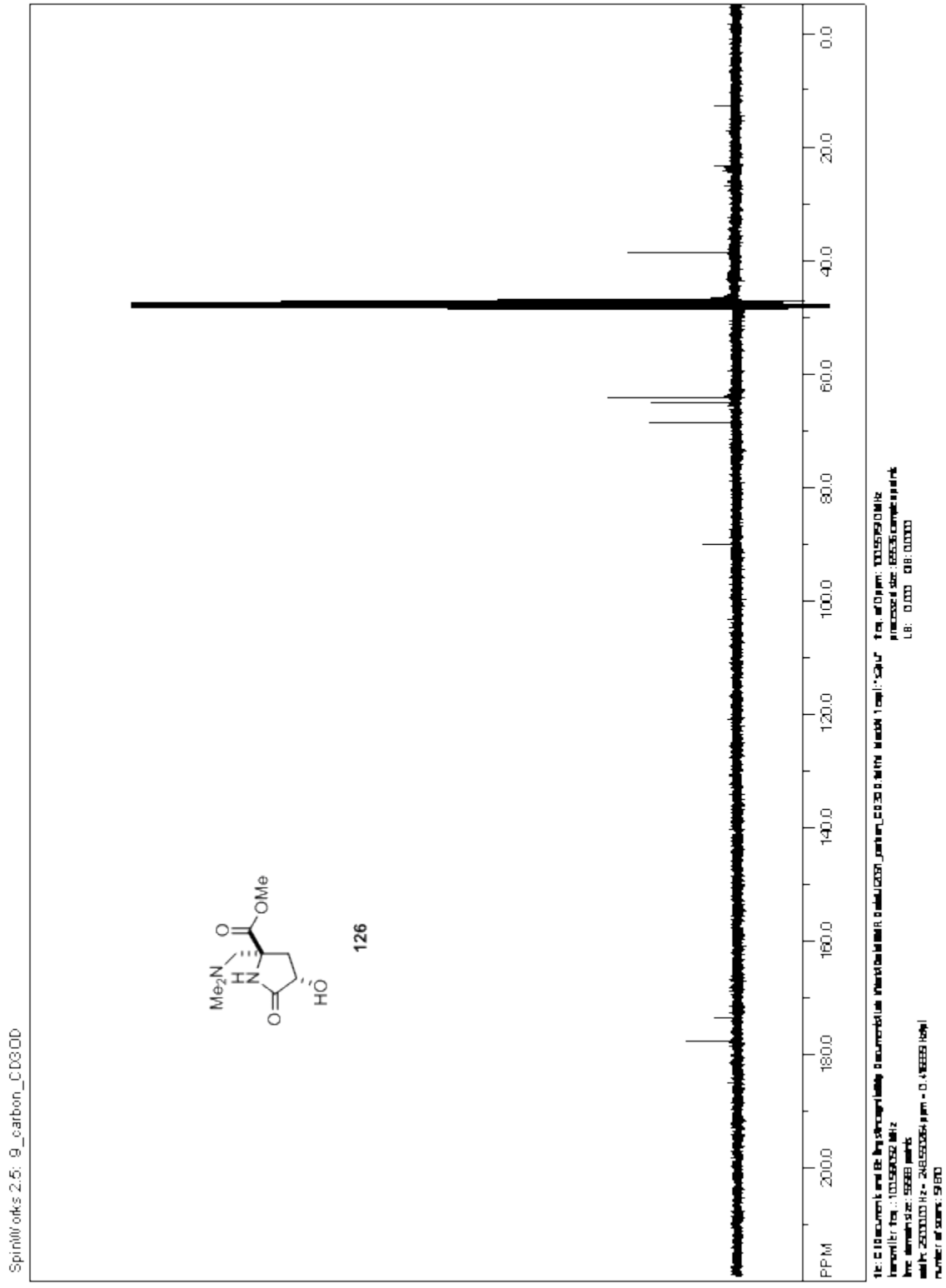

Figure A.119. ^{13}C Spectrum of **126**.

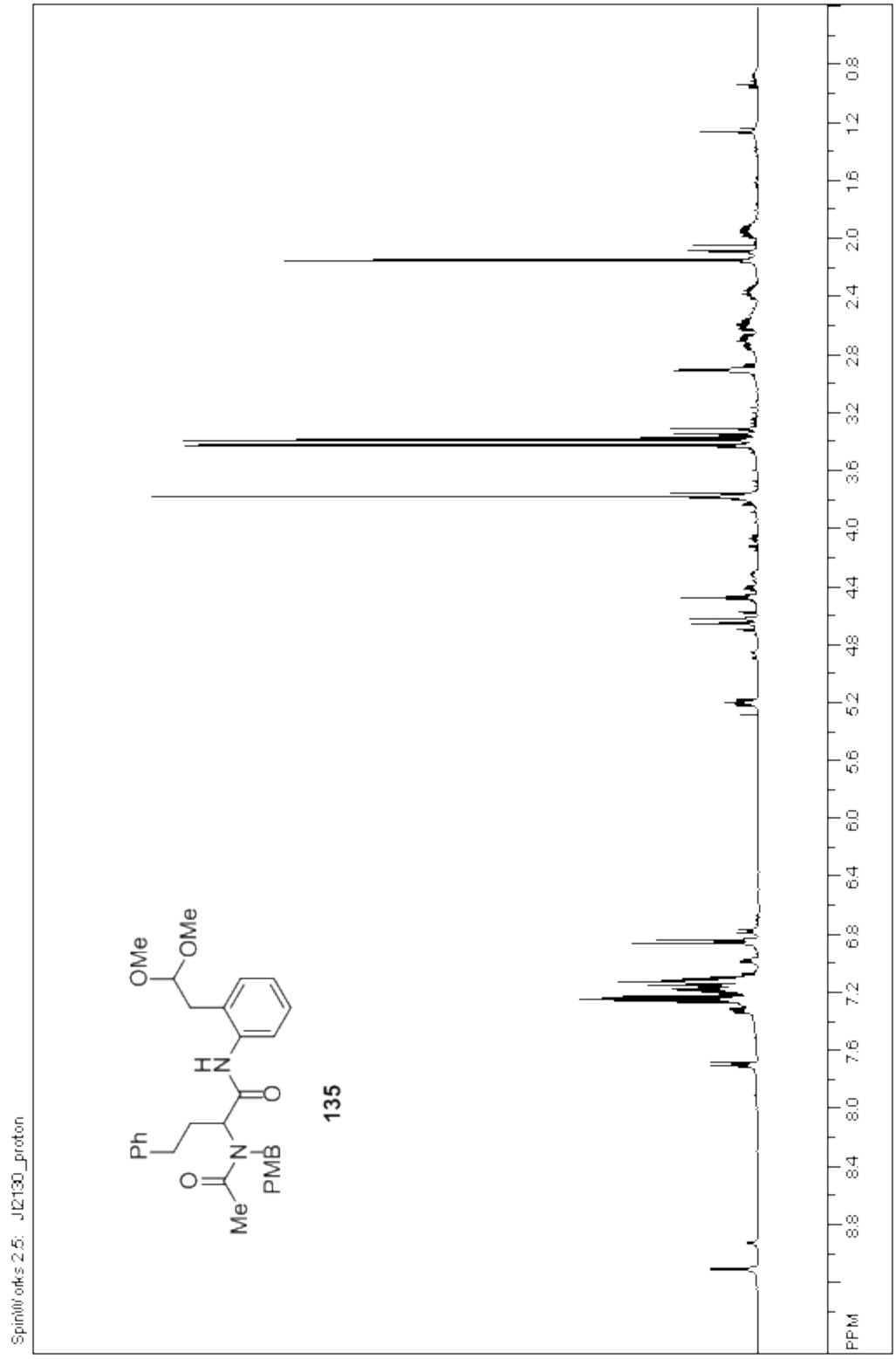

Figure A.120. ^{1}H Spectrum of **135**.

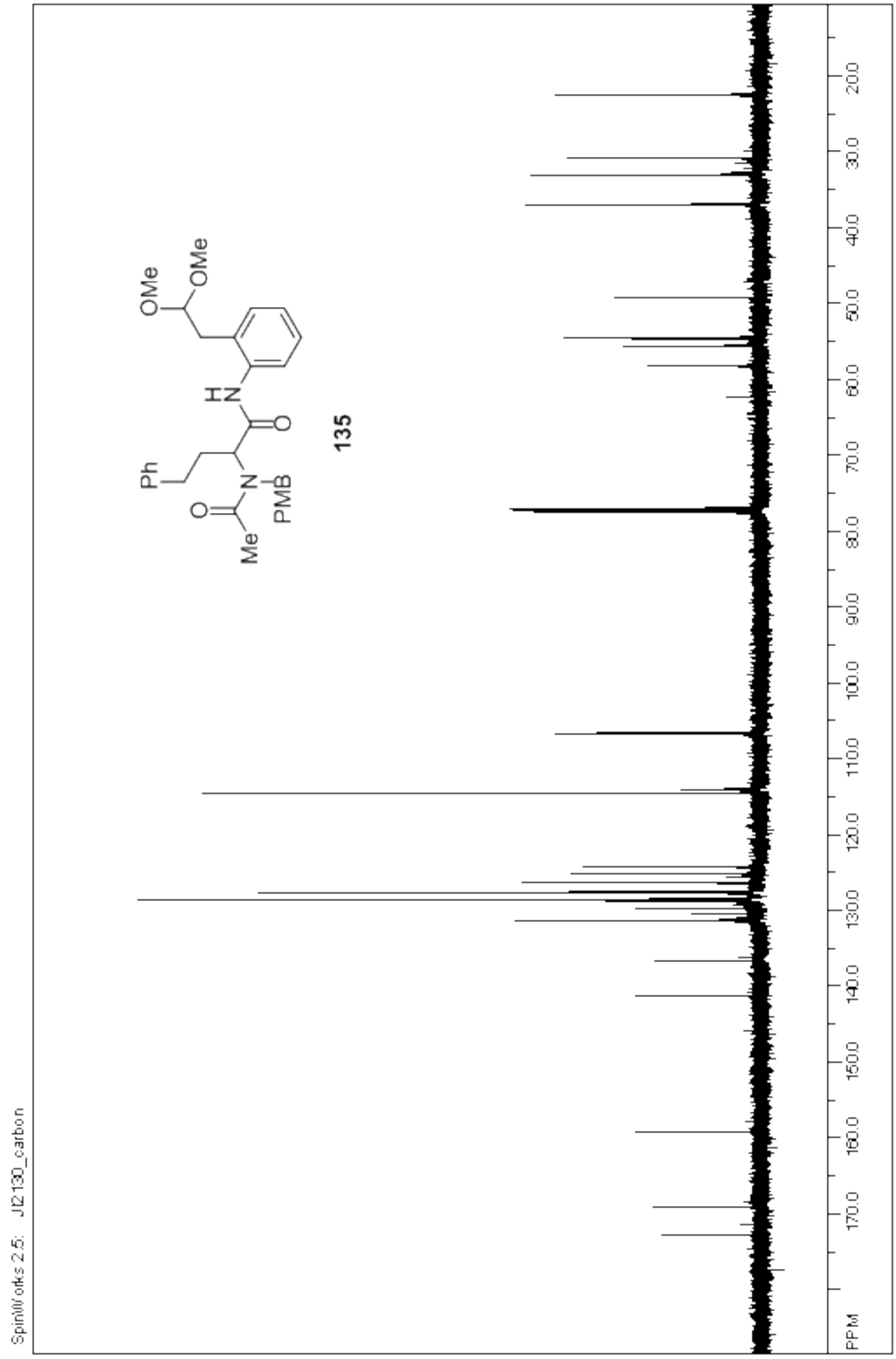

Figure A.121. ^{13}C Spectrum of **135**.

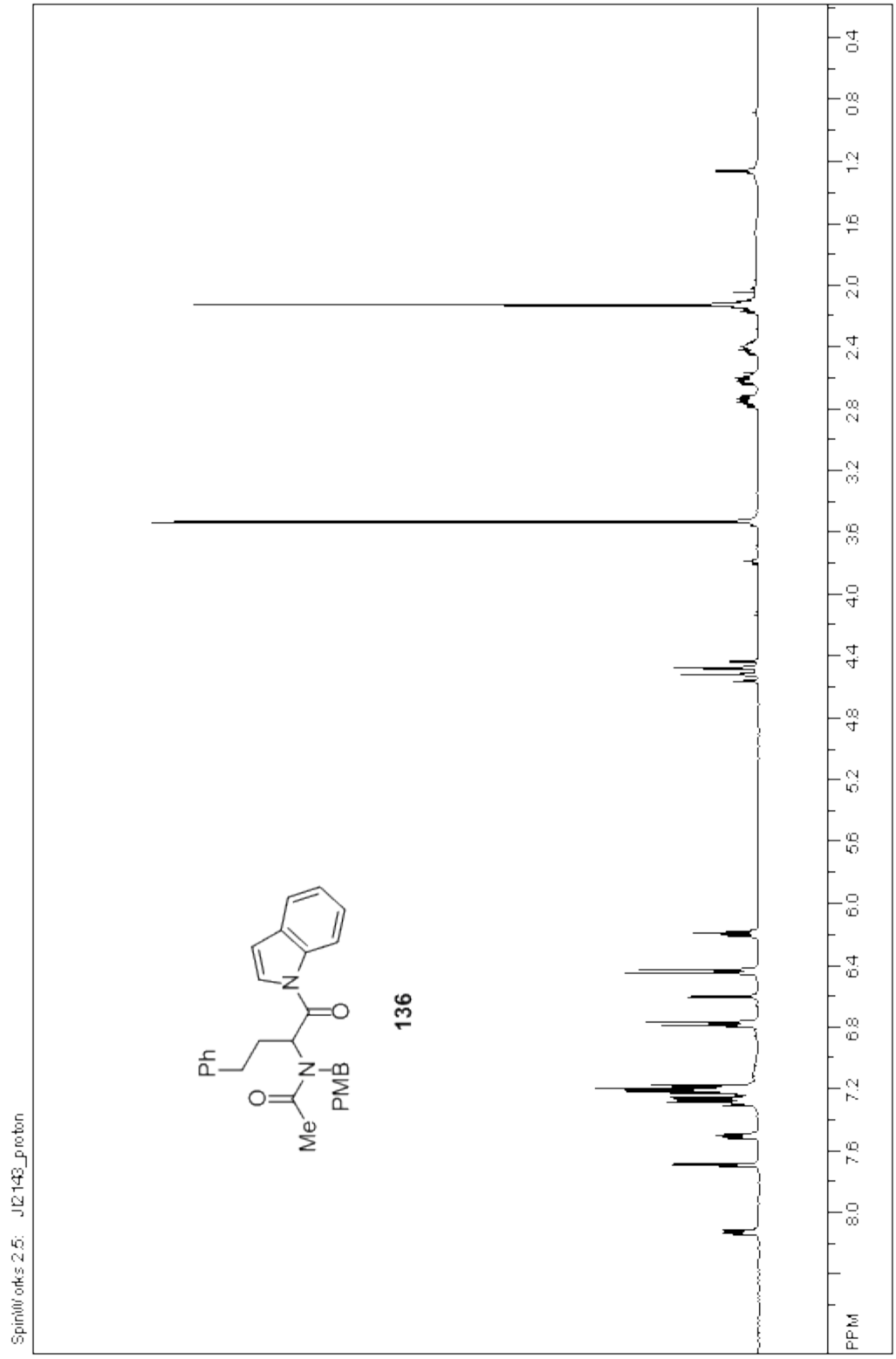

Figure A.122. ^{1}H Spectrum of **136**.

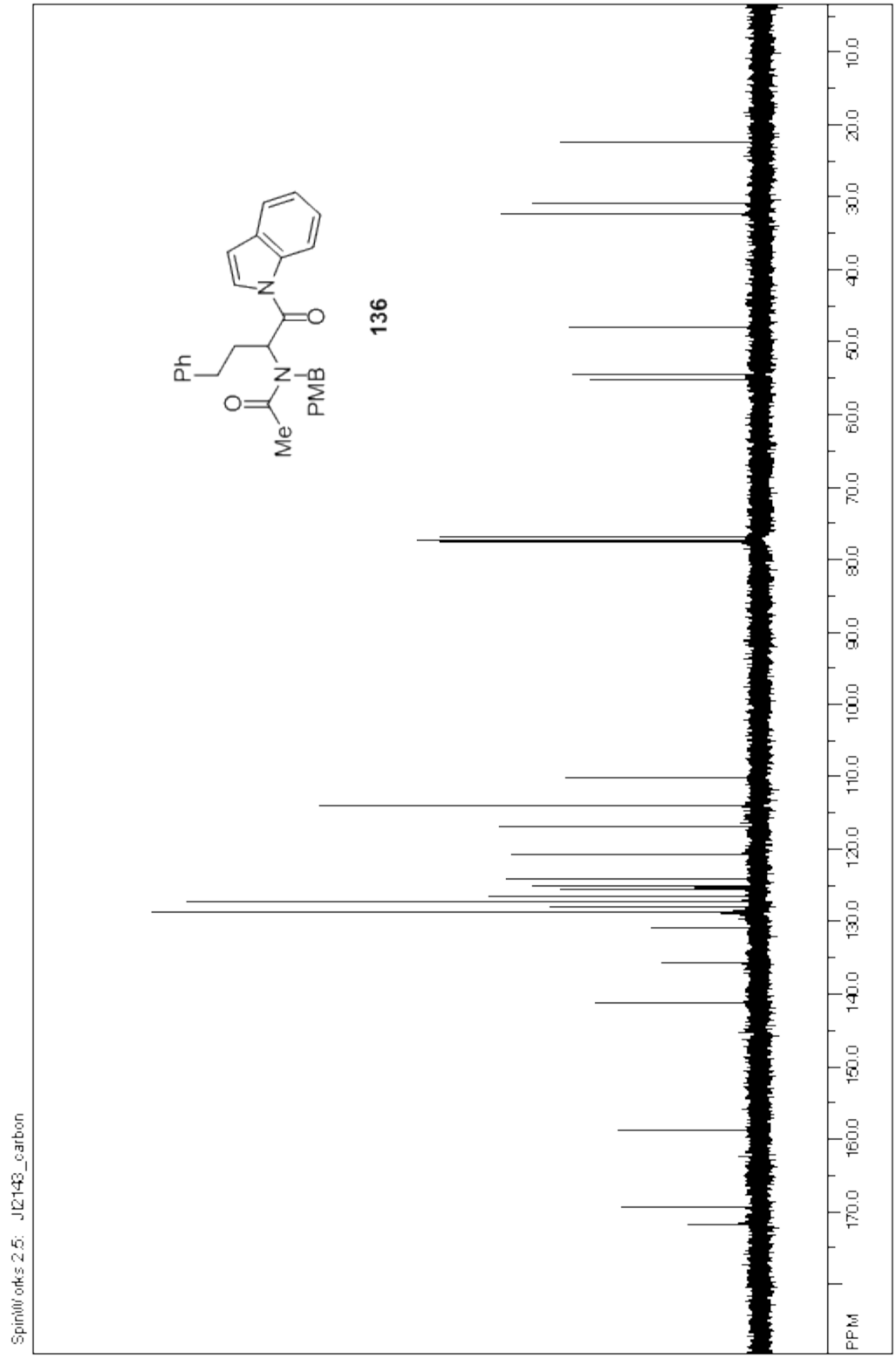

Figure A.123. ^{13}C Spectrum of **136**.

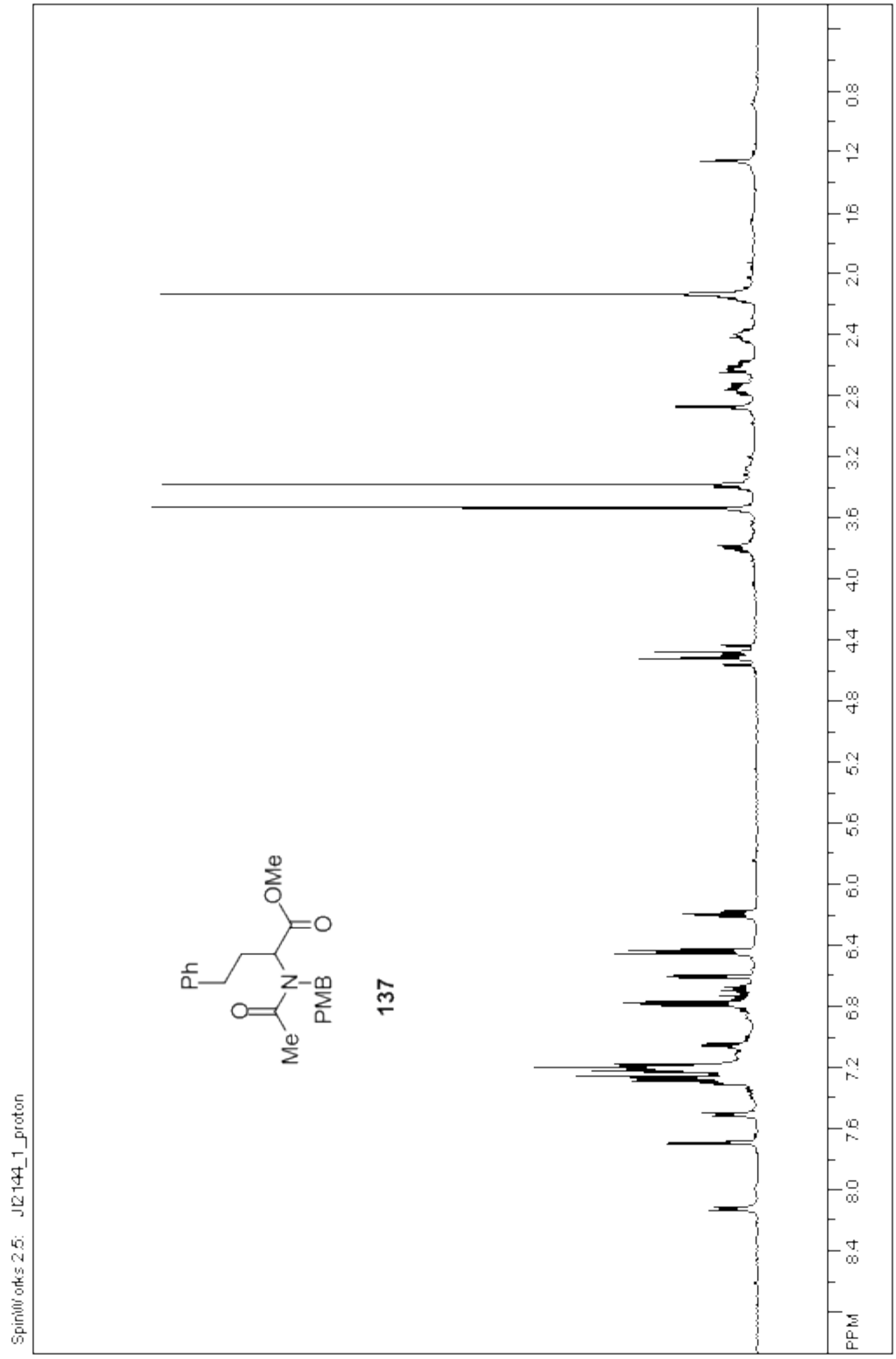

Figure A.124. ^{1}H Spectrum of **137**.

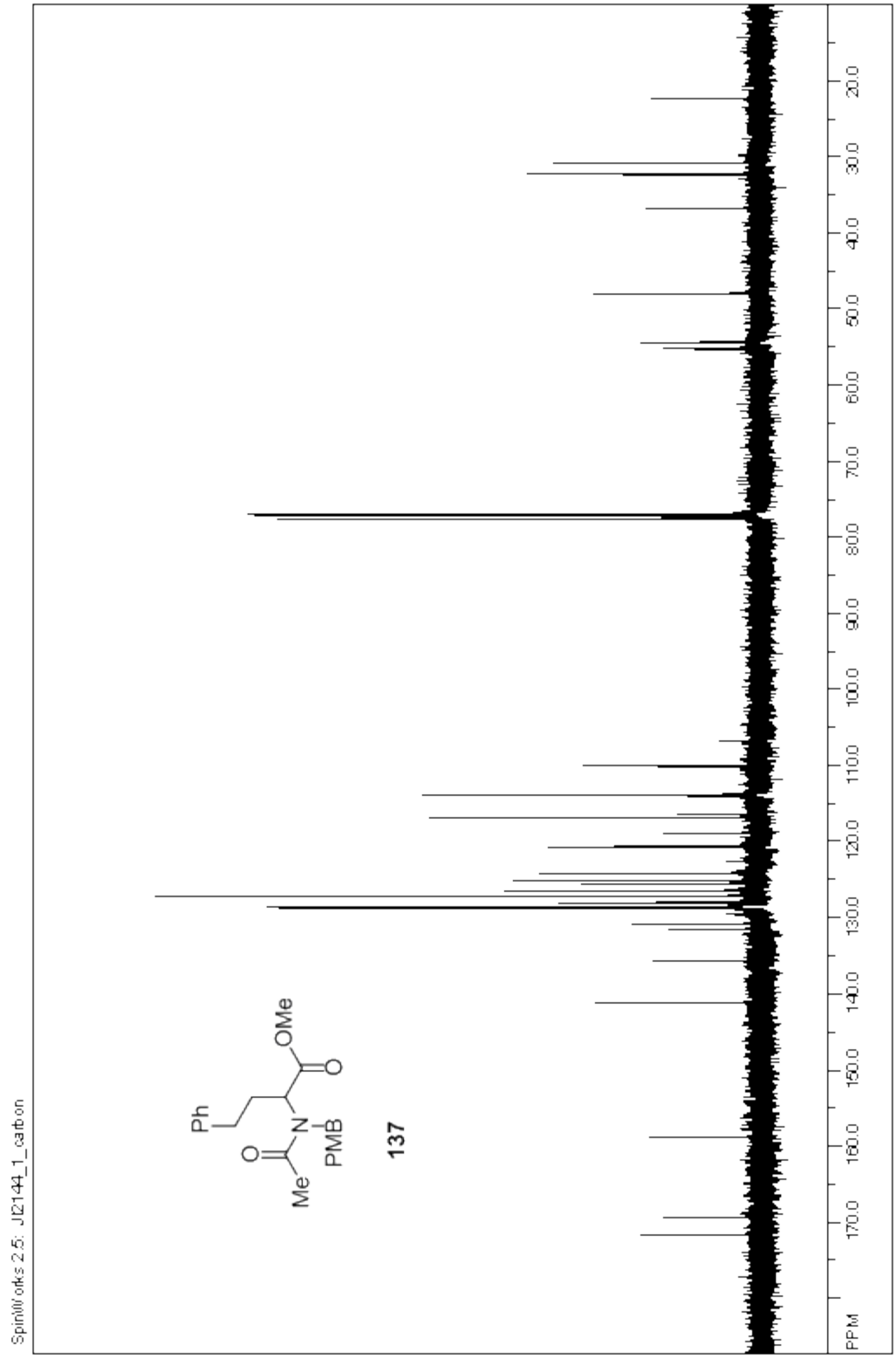

Figure A.125. ^{13}C Spectrum of **137**.

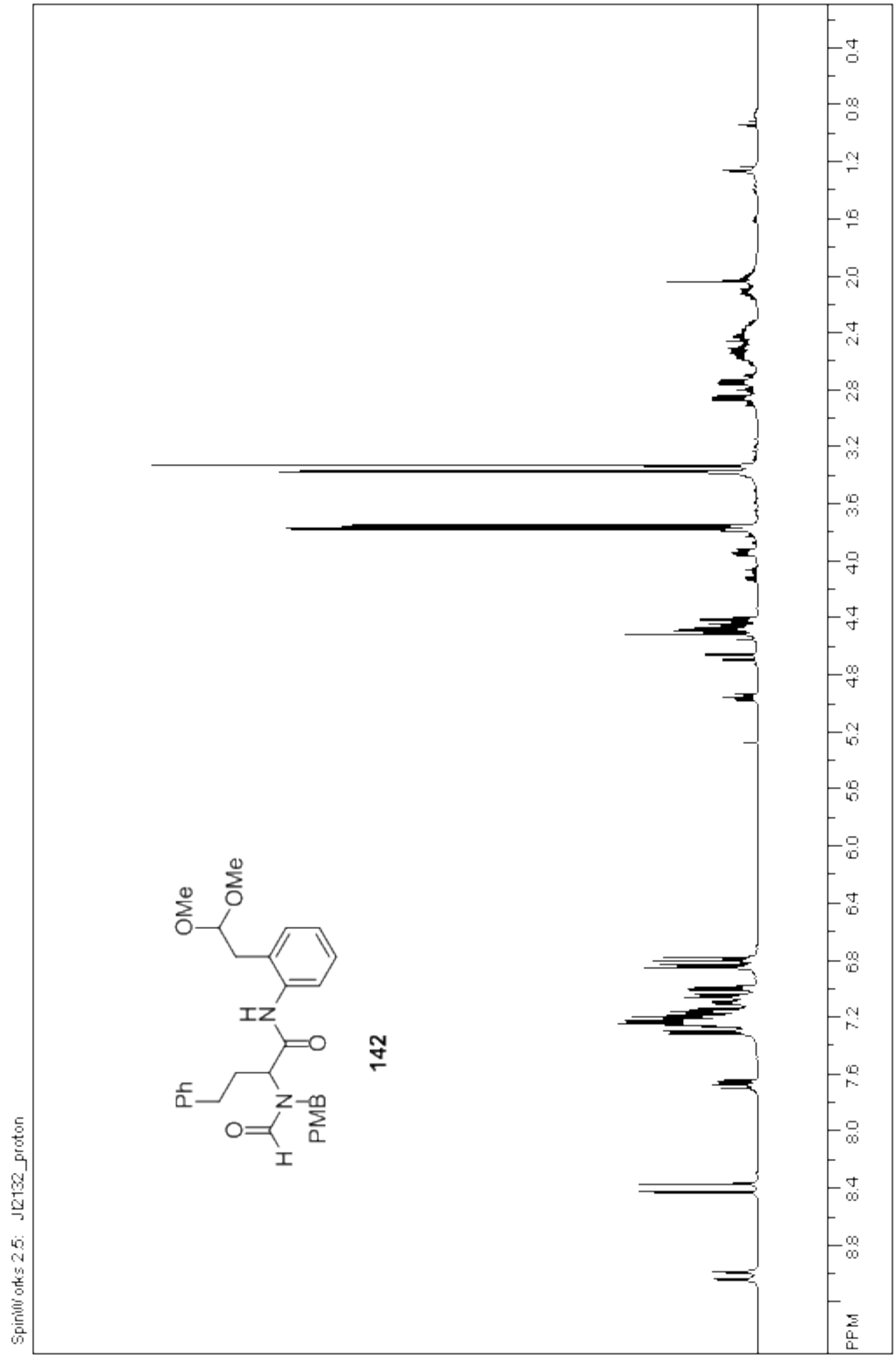

Figure A.126. ^{1}H Spectrum of **142**.

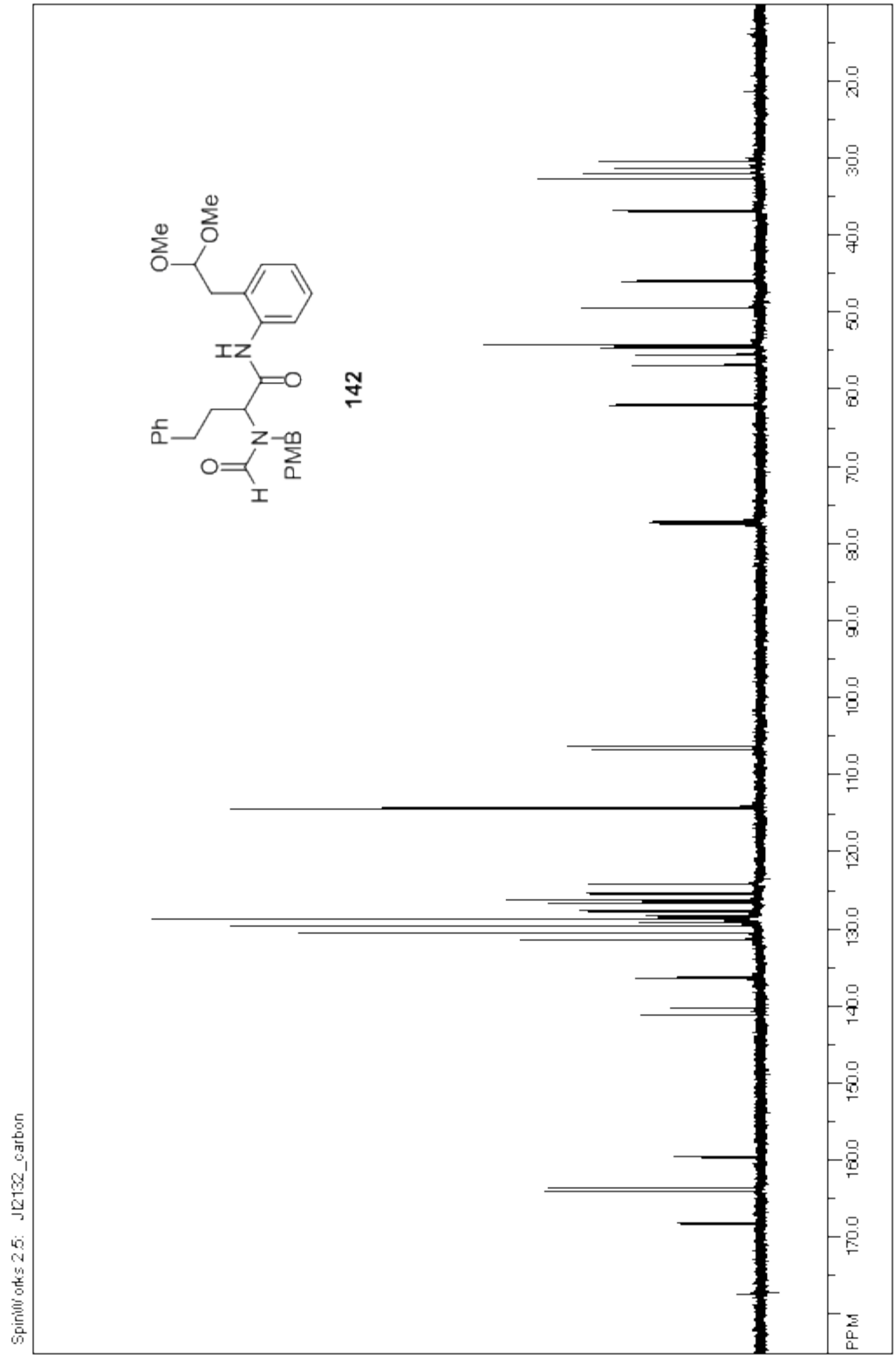

Figure A.127. ^{13}C Spectrum of **142**.

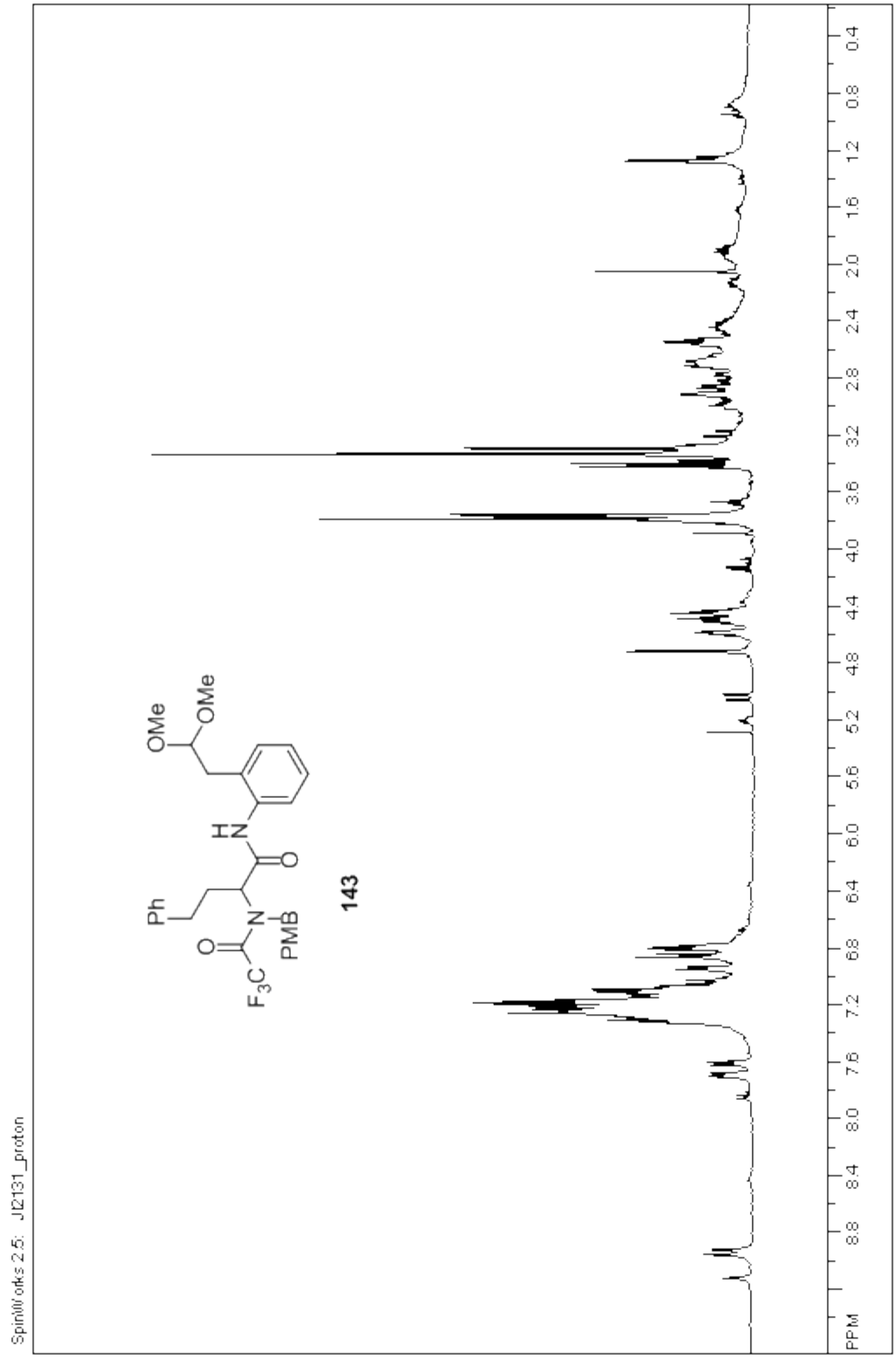

Figure A.128. ^{1}H Spectrum of **143**.

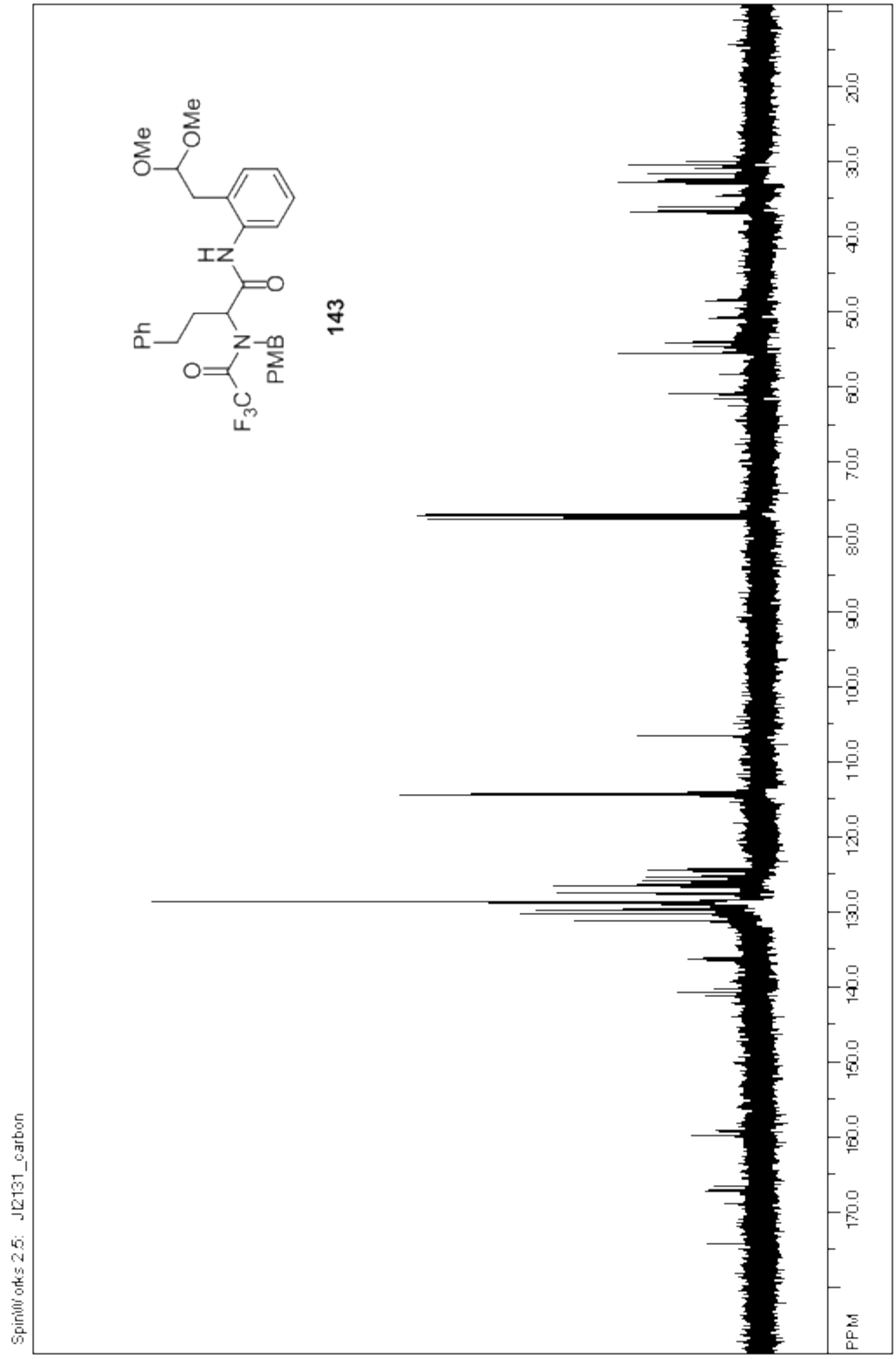

Figure A.129. ^{13}C Spectrum of **143**.

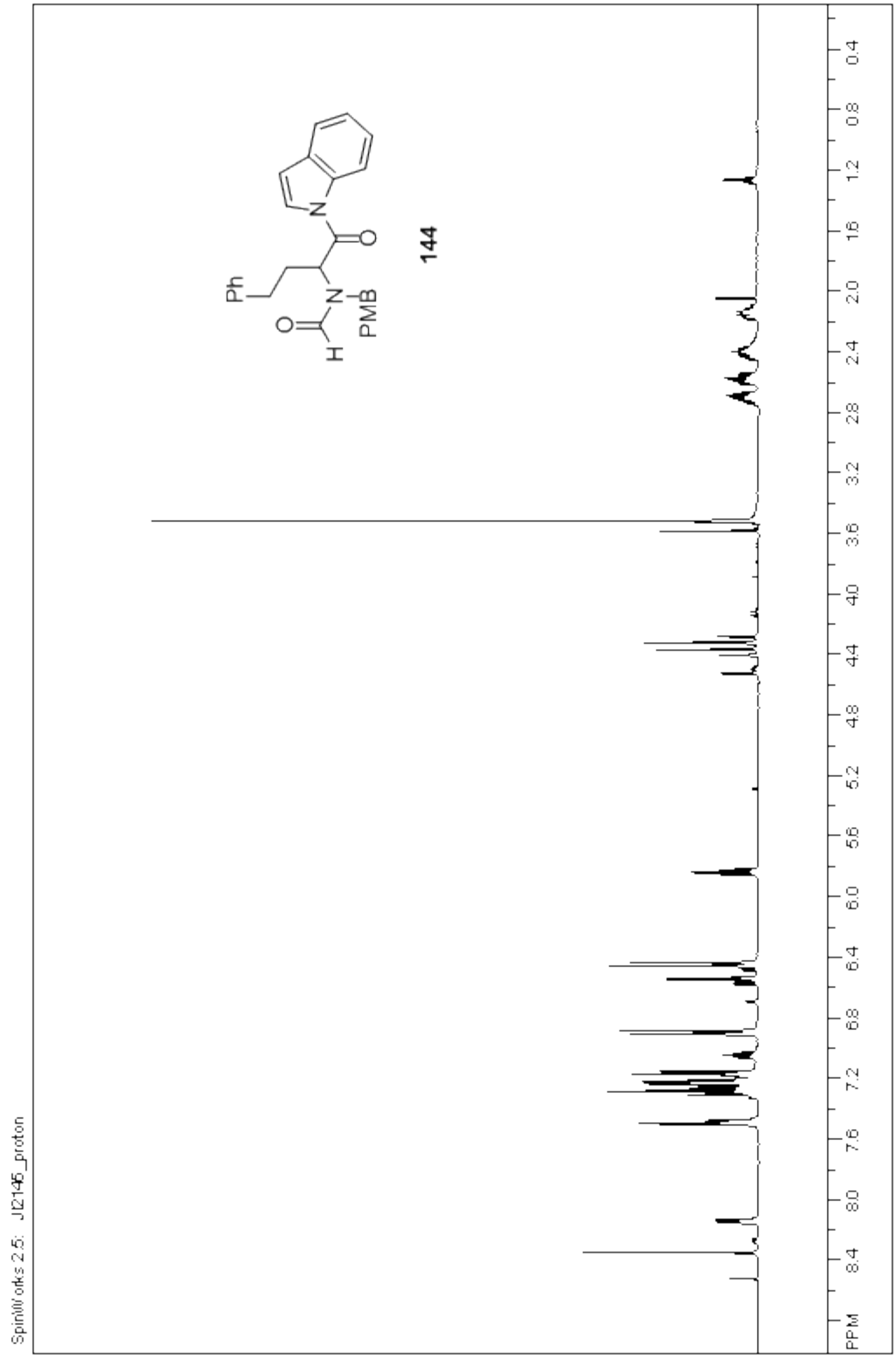

Figure A.130. ^{1}H Spectrum of **144**.

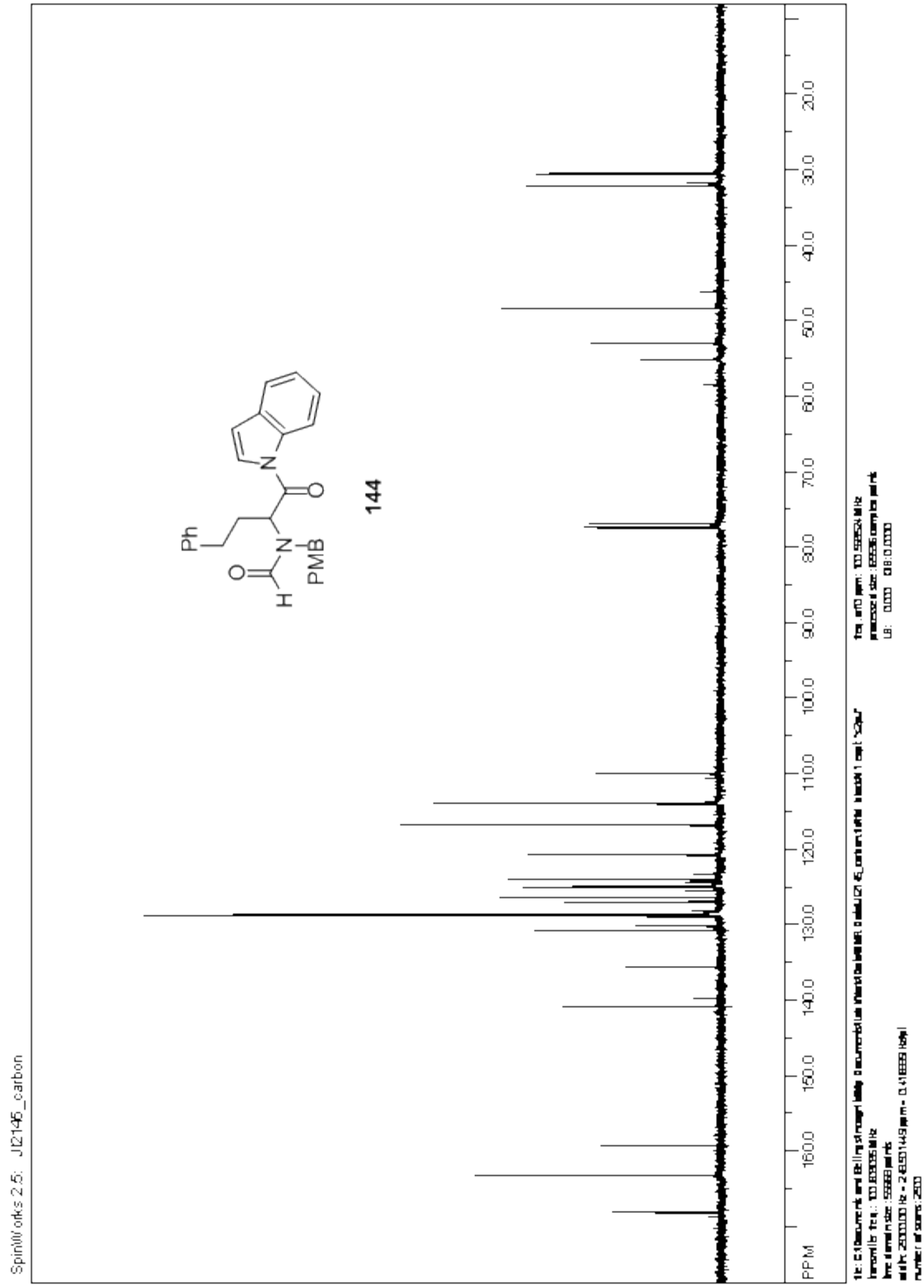

Figure A.131. ^{13}C Spectrum of **144**.

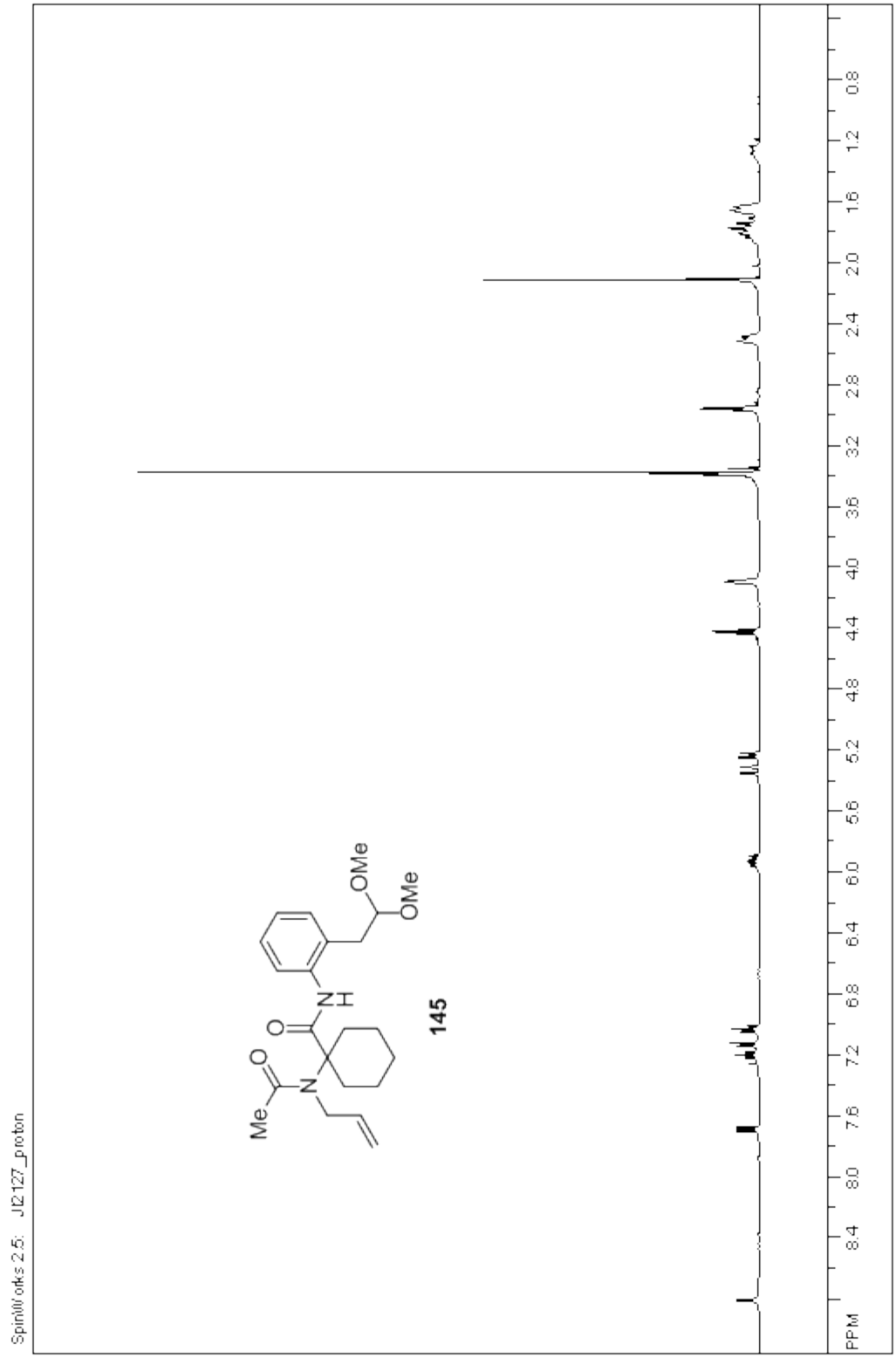

Figure A.132. ^{1}H Spectrum of **145**.

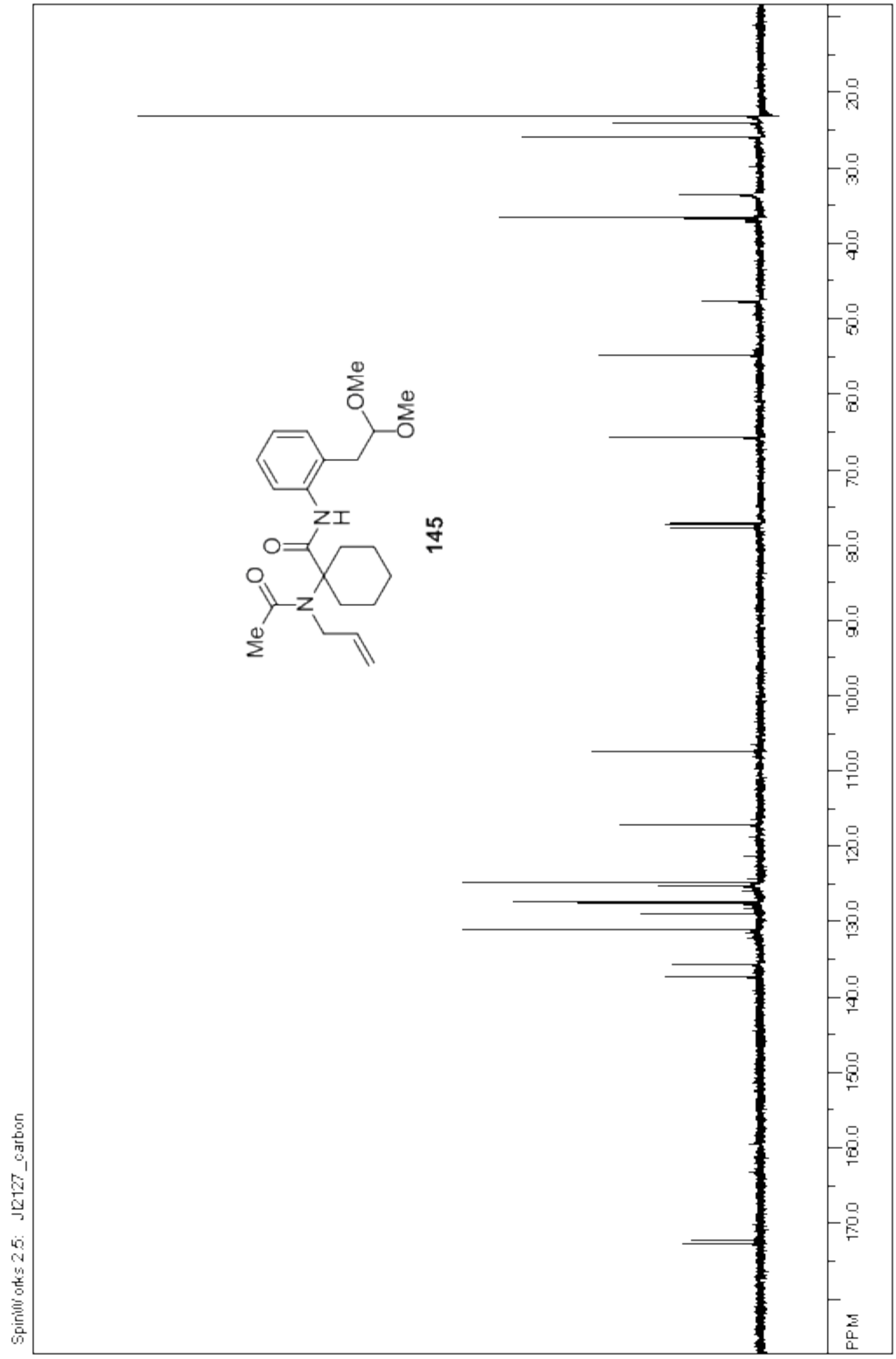

Figure A.133. ^{13}C Spectrum of **145**.

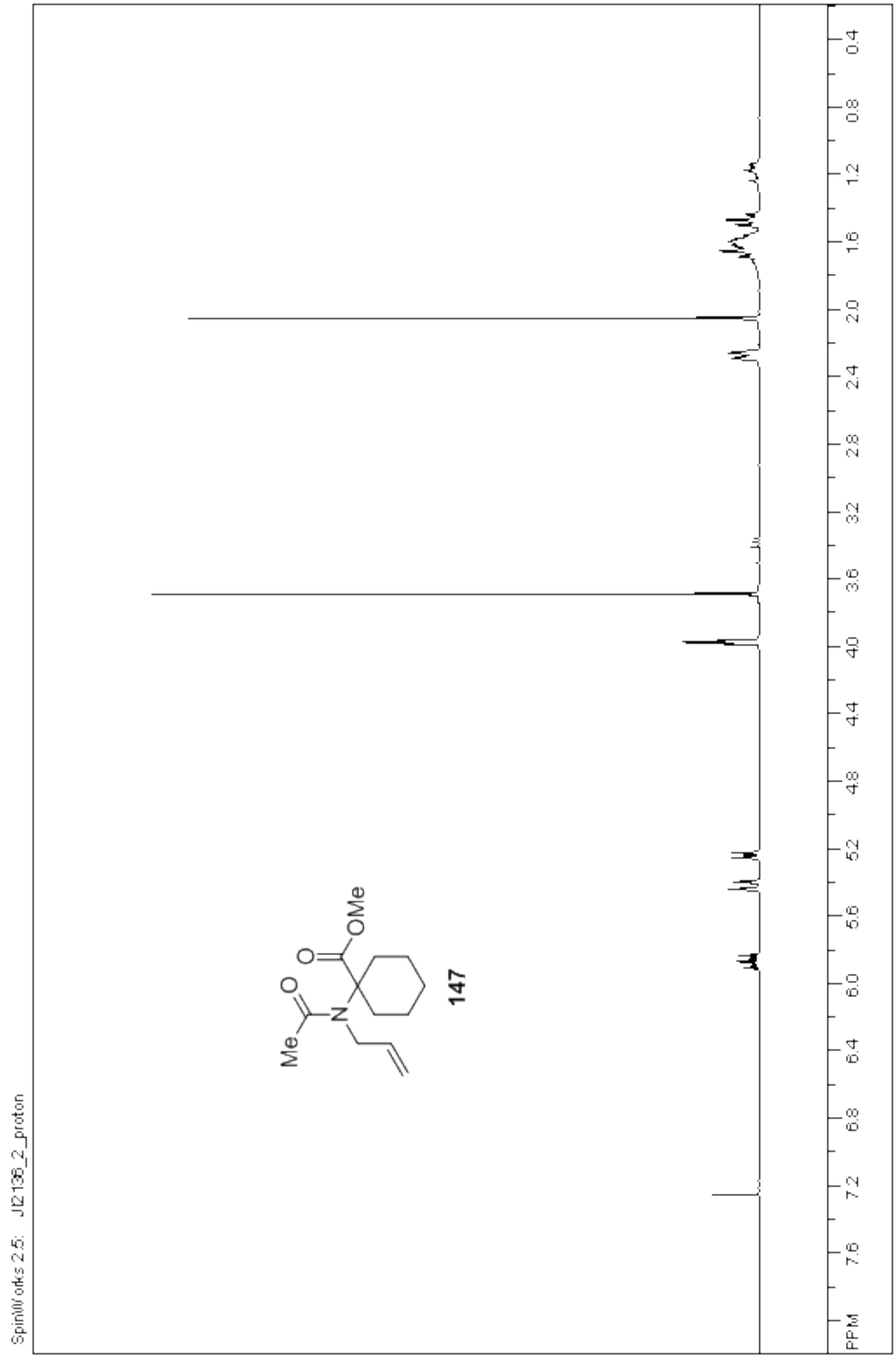

Figure A.134. ^{1}H Spectrum of **147**.

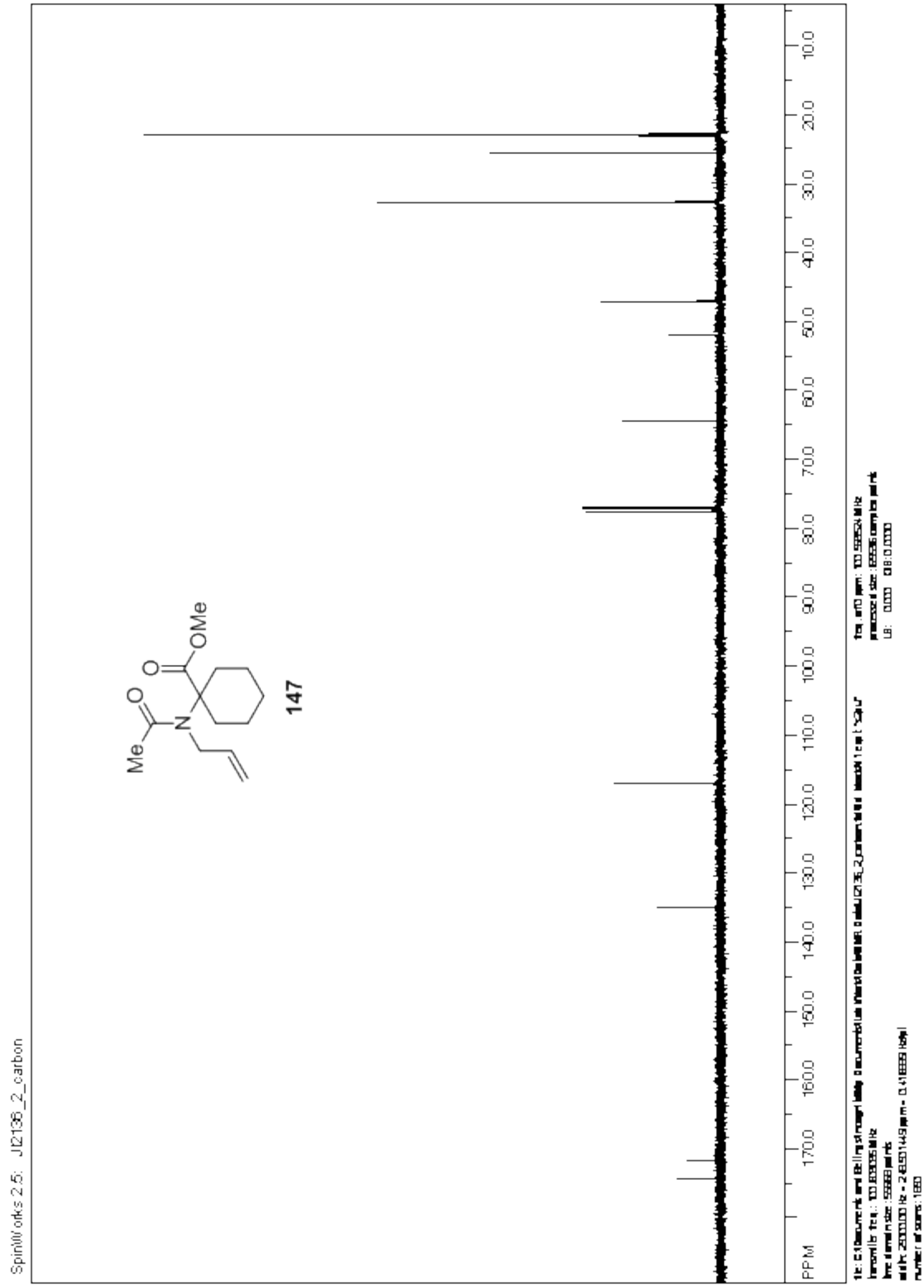

Figure A.135. ^{13}C Spectrum of **147**.

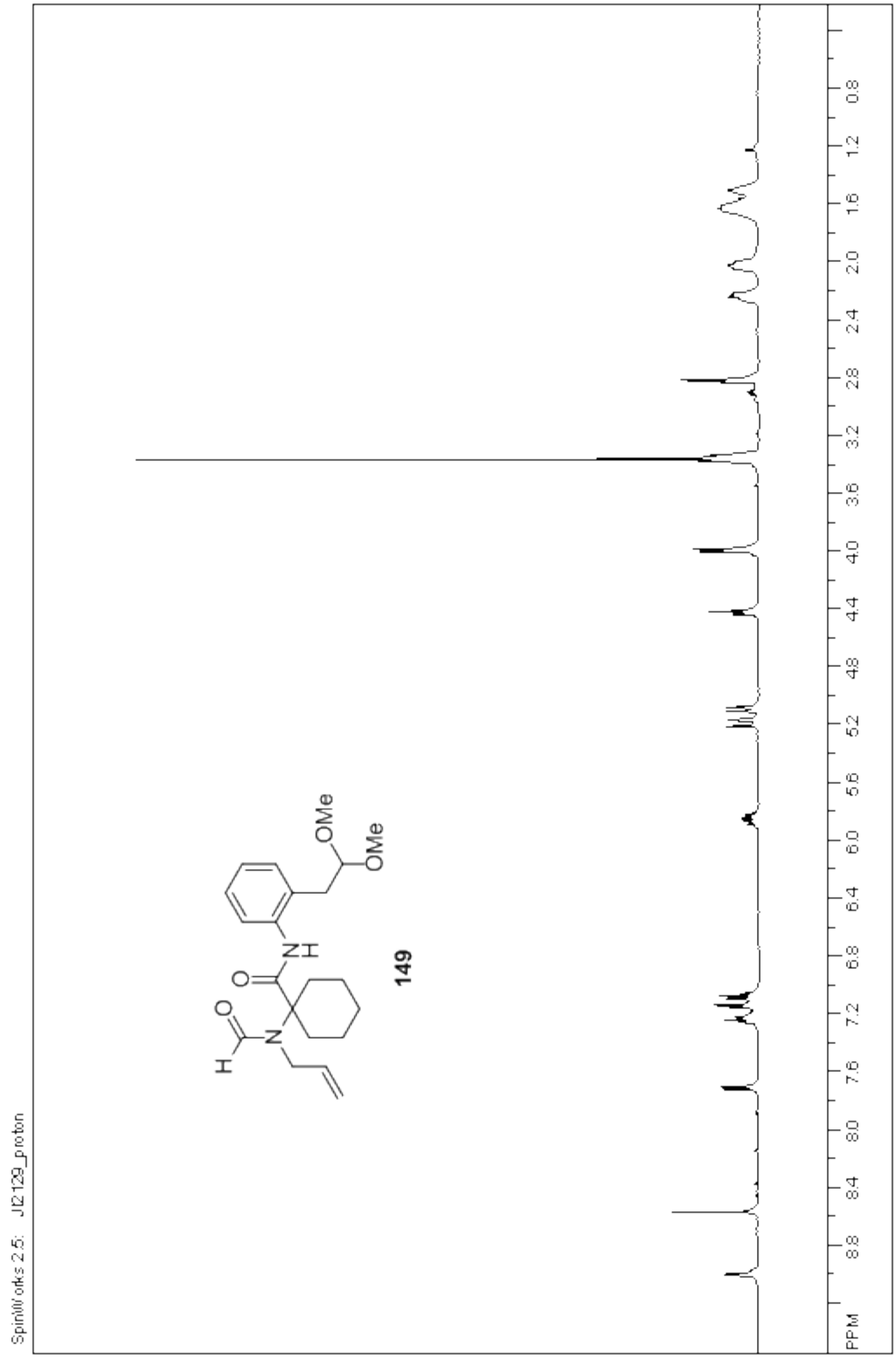

Figure A.136. ^{1}H Spectrum of **149**.

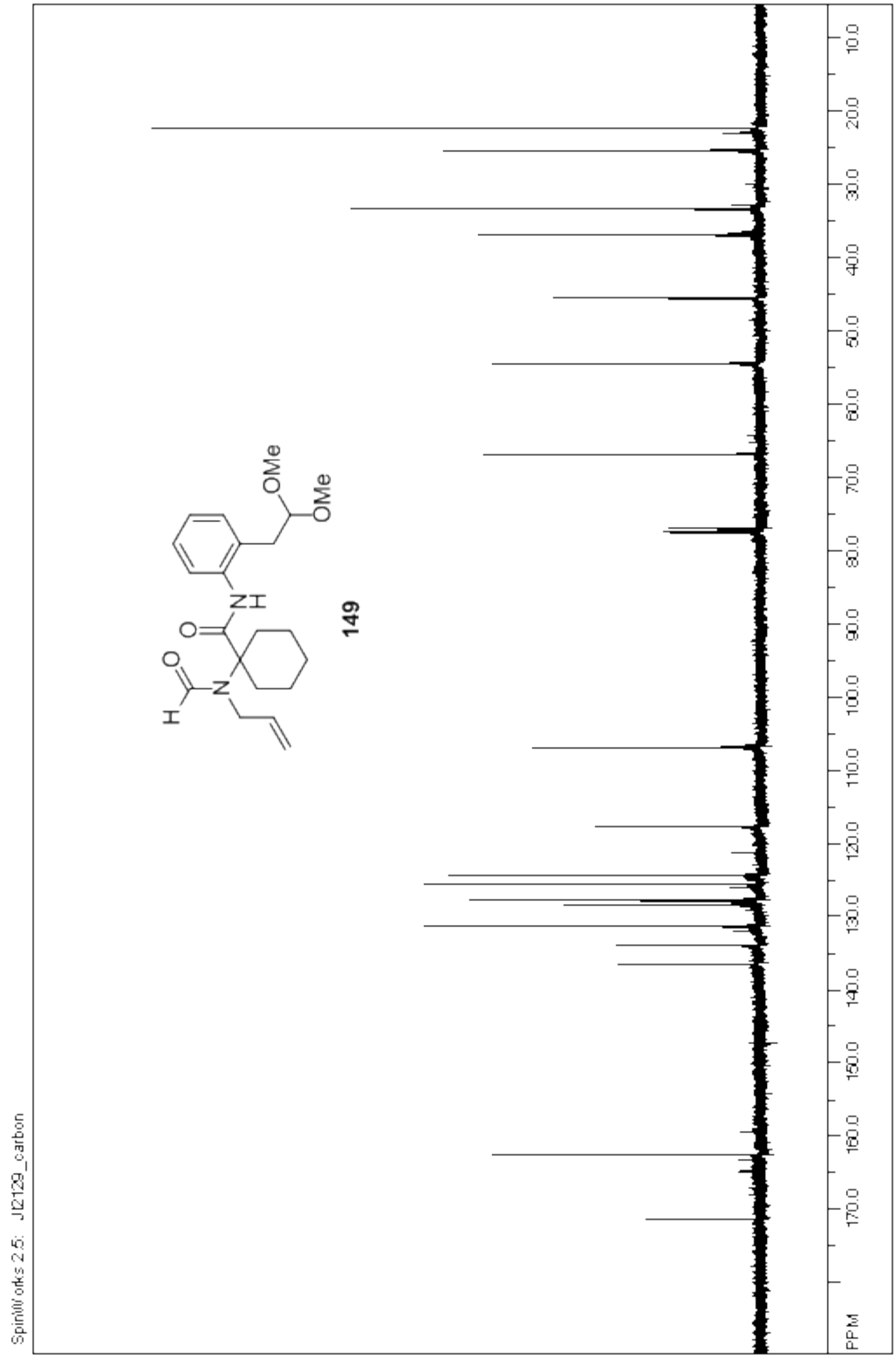

Figure A.137. ^{13}C Spectrum of **149**.

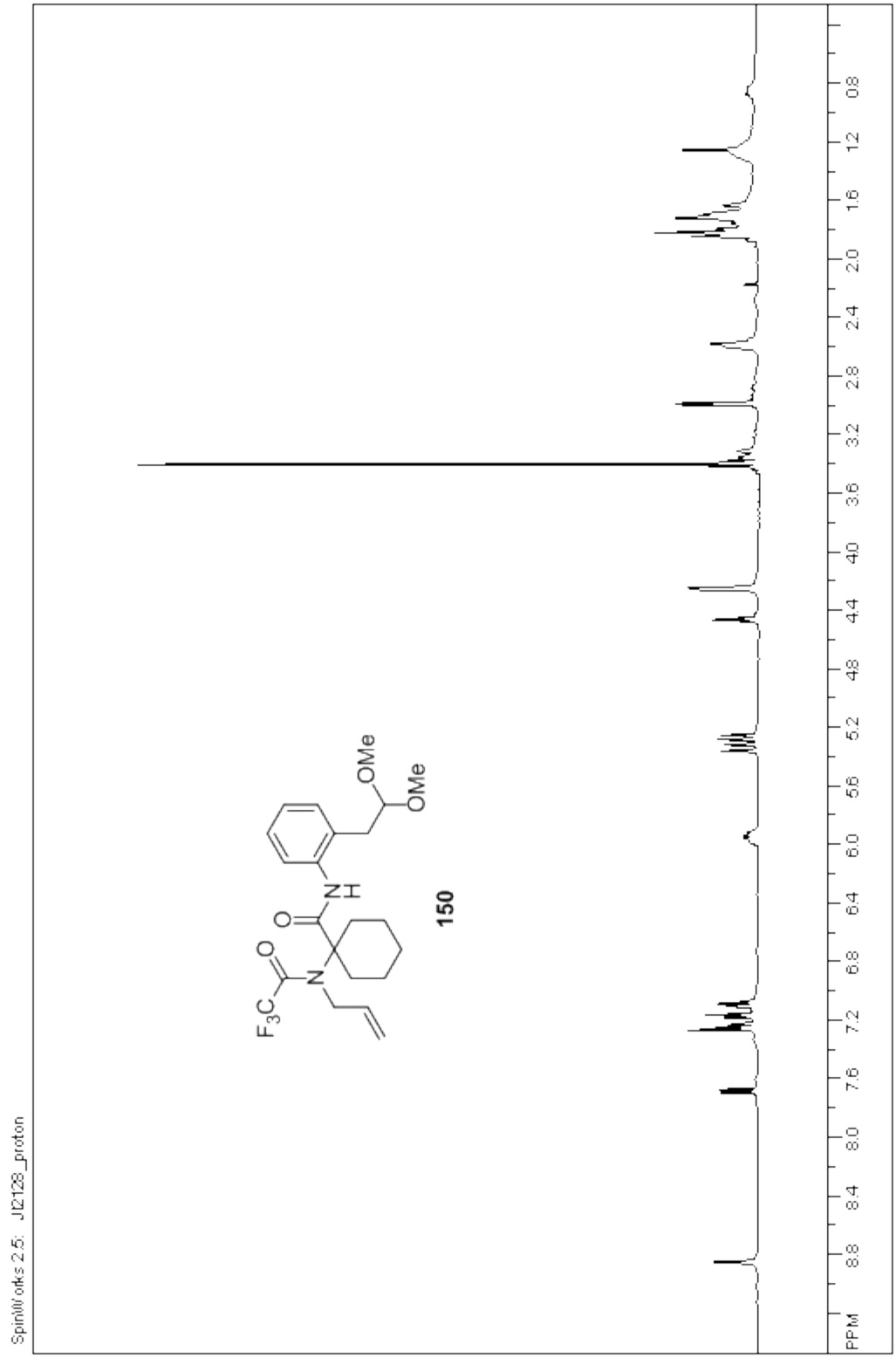

Figure A.138. ^{1}H Spectrum of **150**.

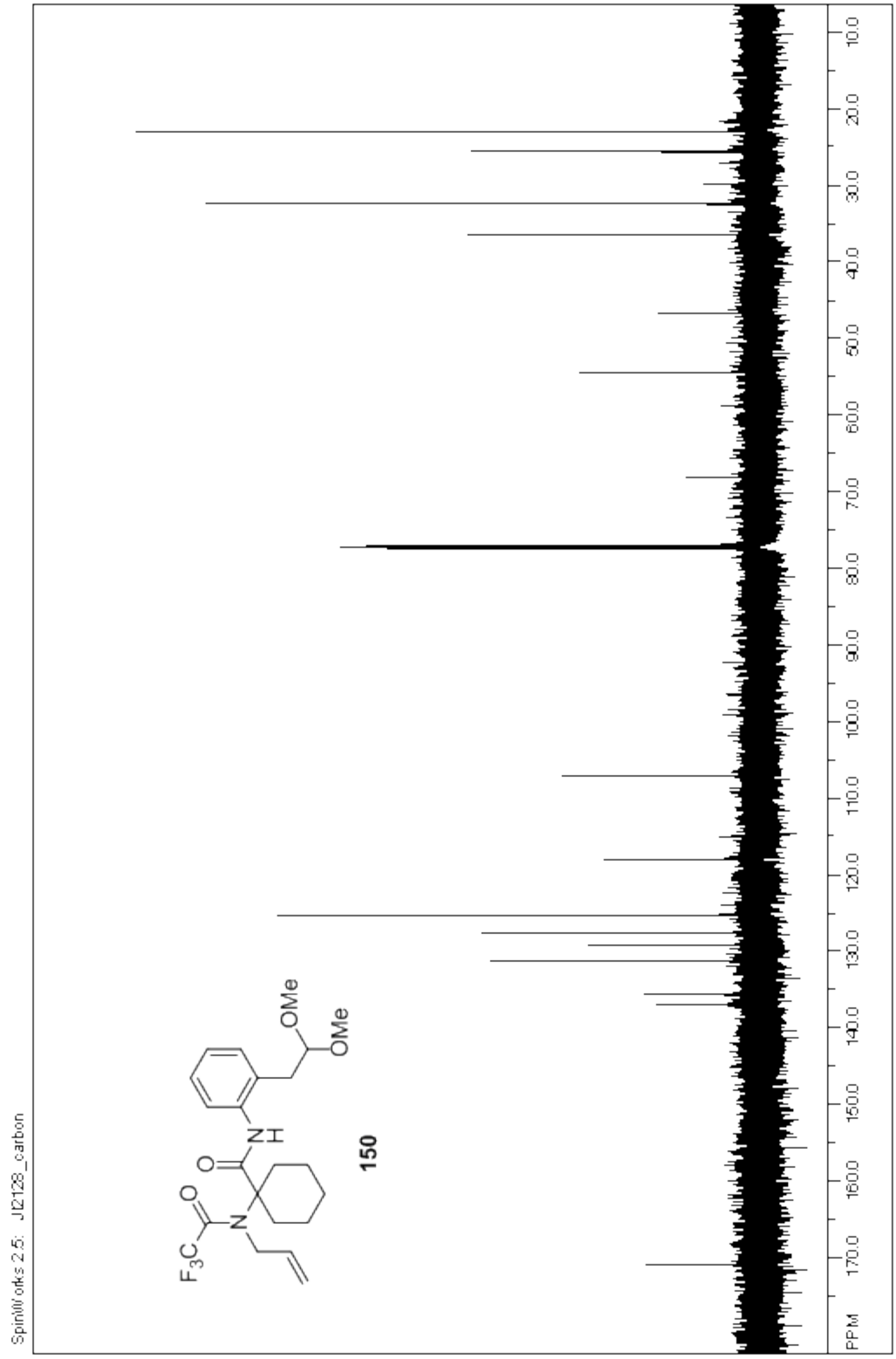

Figure A.139. ^{13}C Spectrum of **150**.

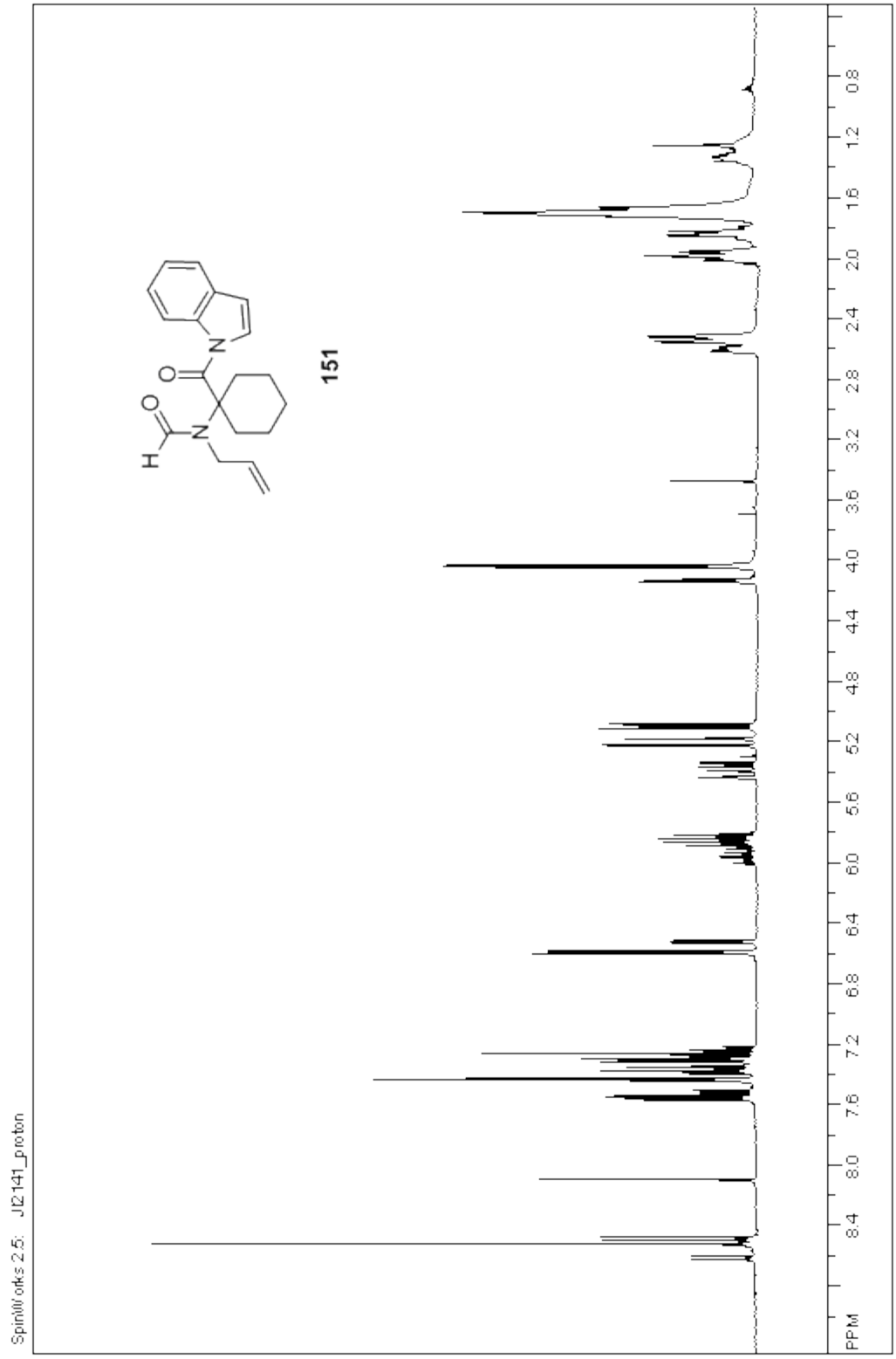

Figure A.140. ^{1}H Spectrum of **151**.

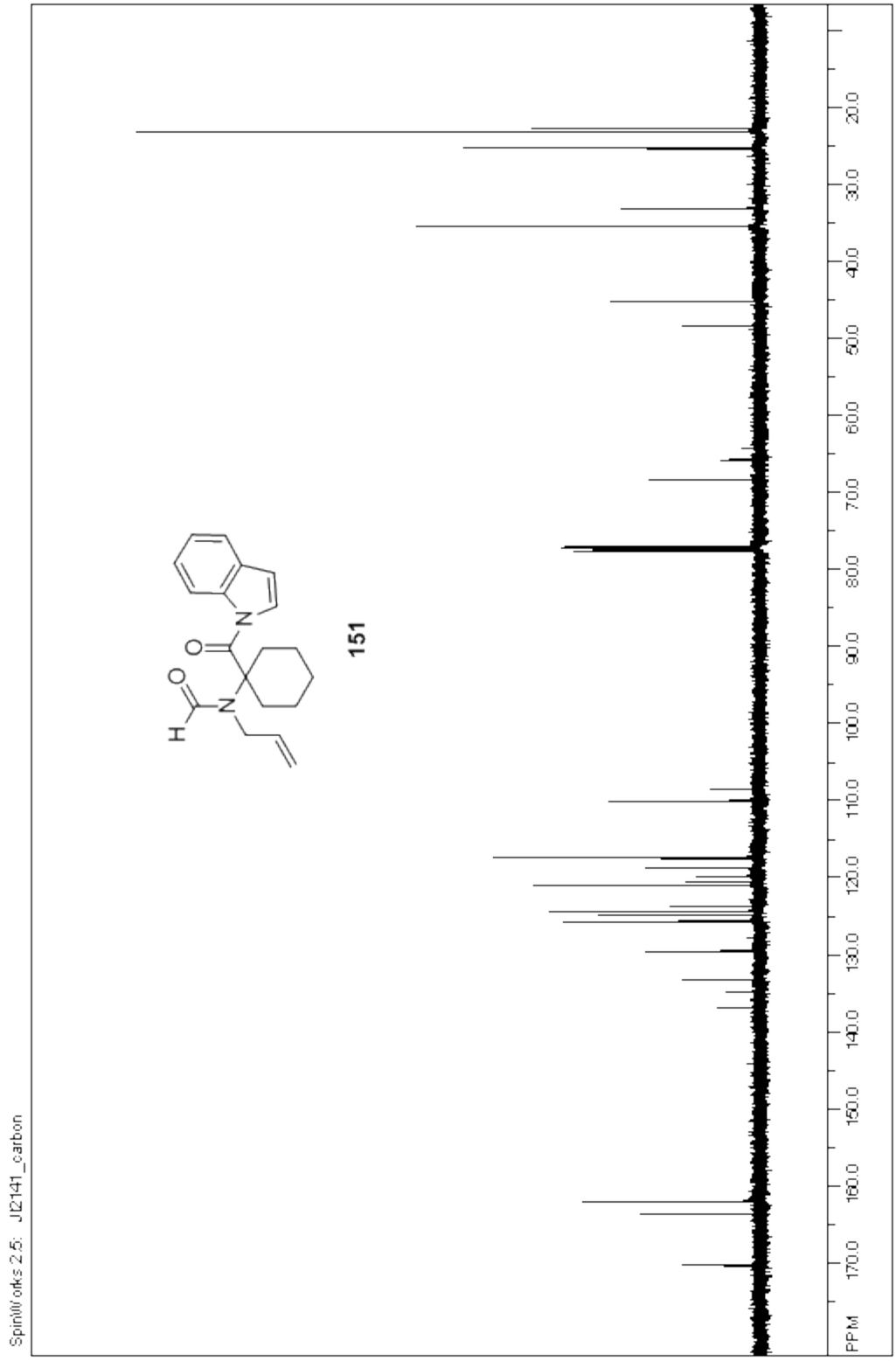

Figure A.141. ^{13}C Spectrum of **151**.

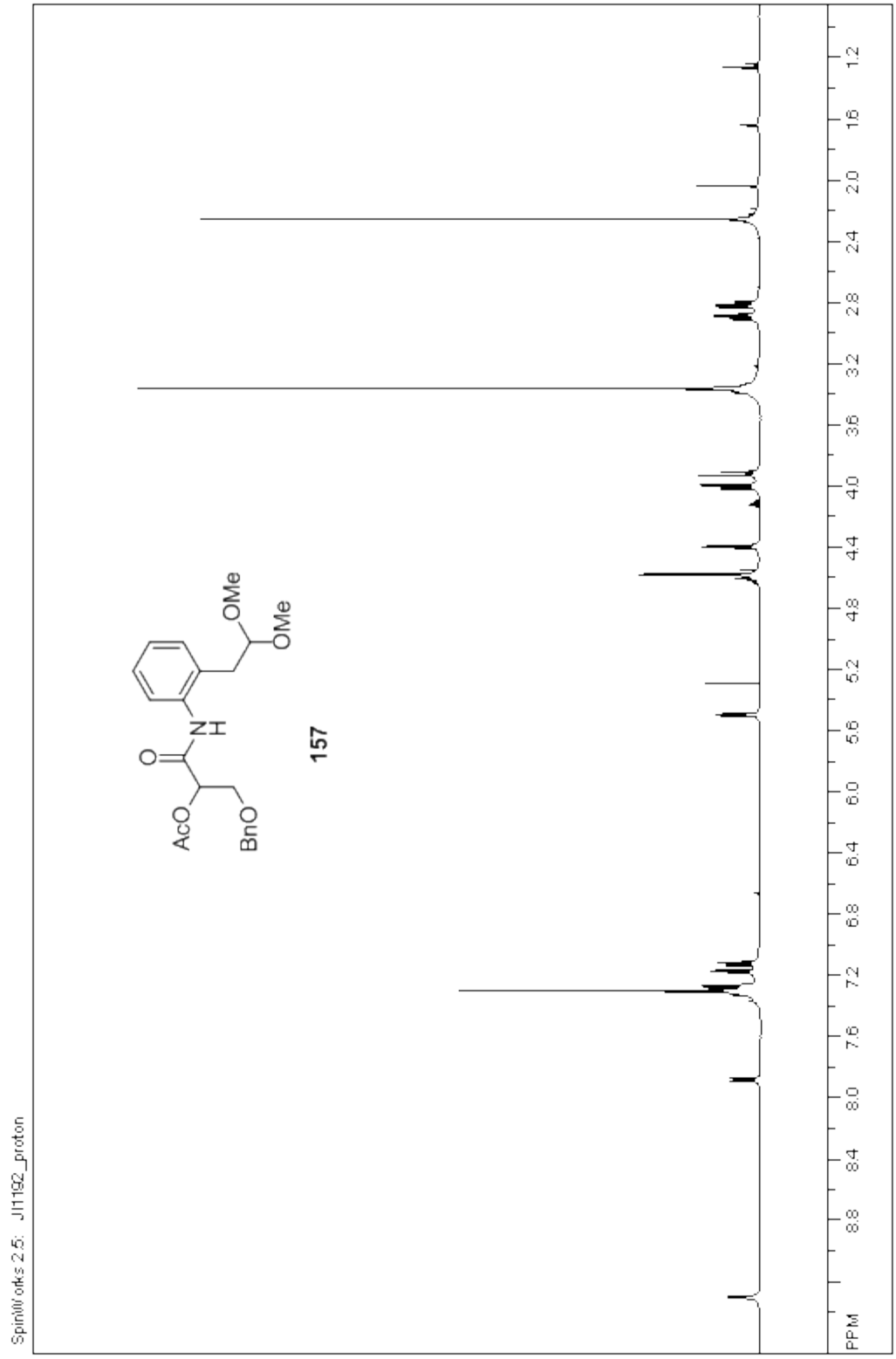

Figure A.142. ^{1}H Spectrum of **157**.

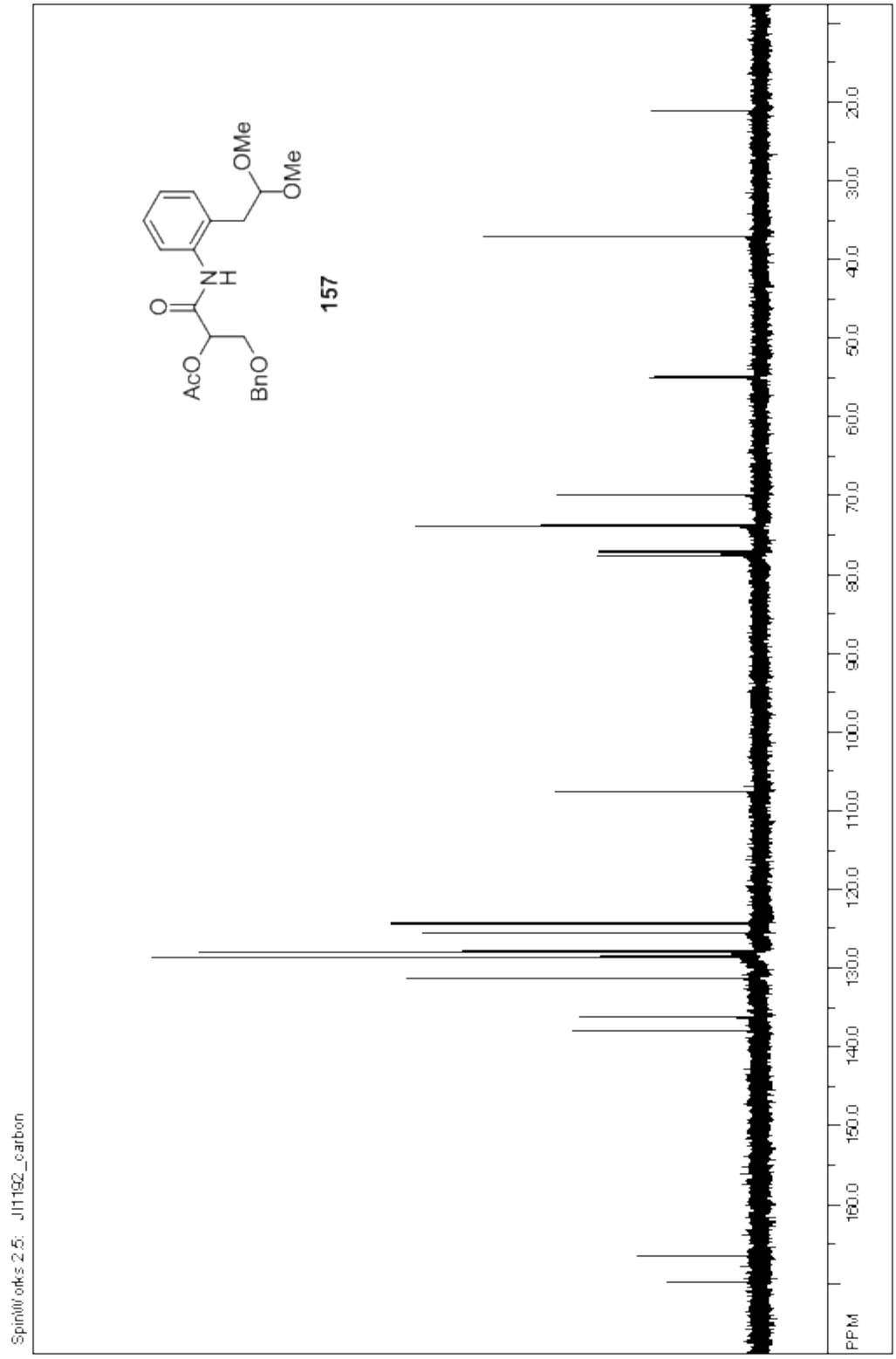

Figure A.143. ^{13}C Spectrum of **157**.

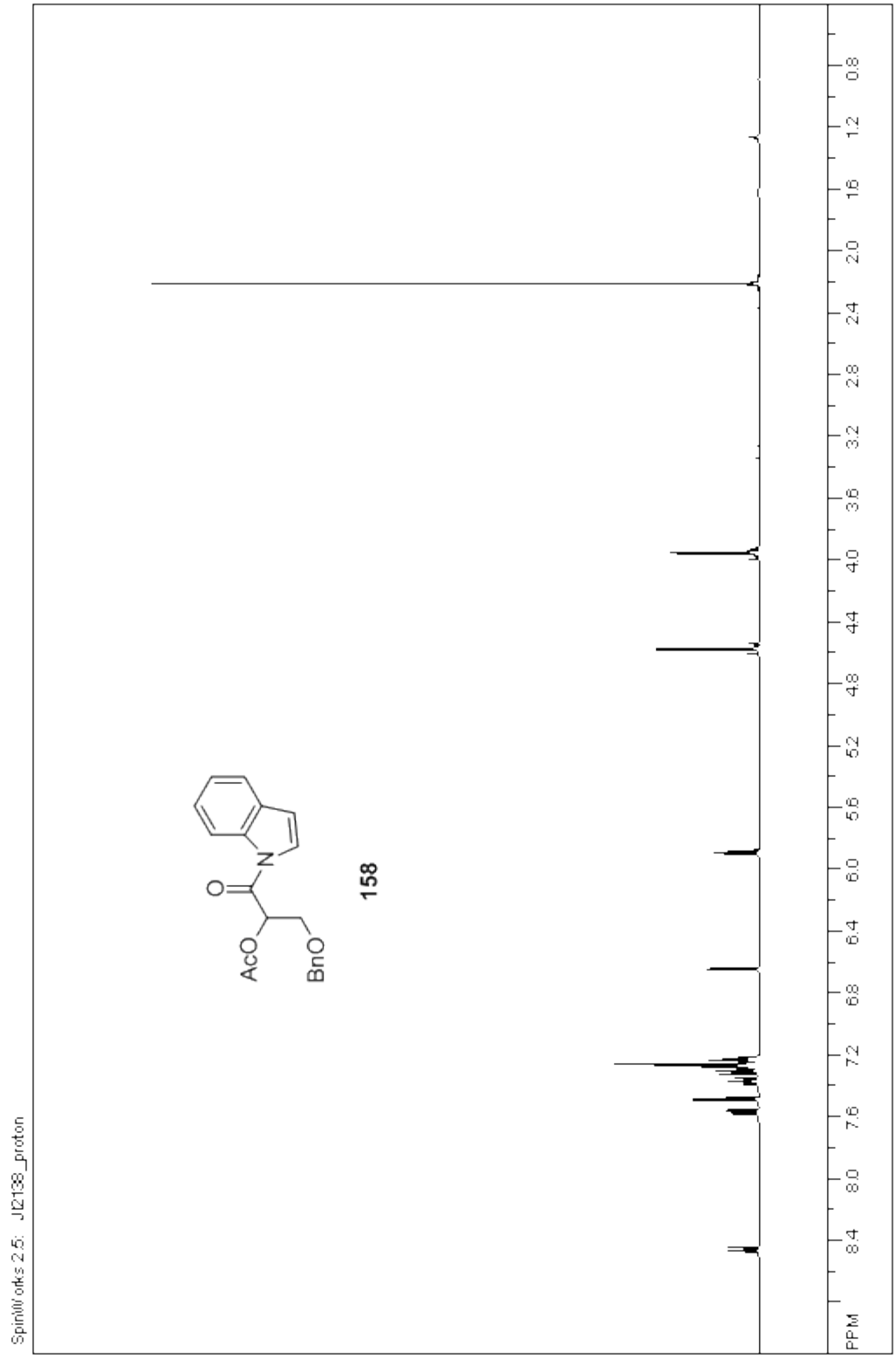

Figure A.144. ^{1}H Spectrum of **158**.

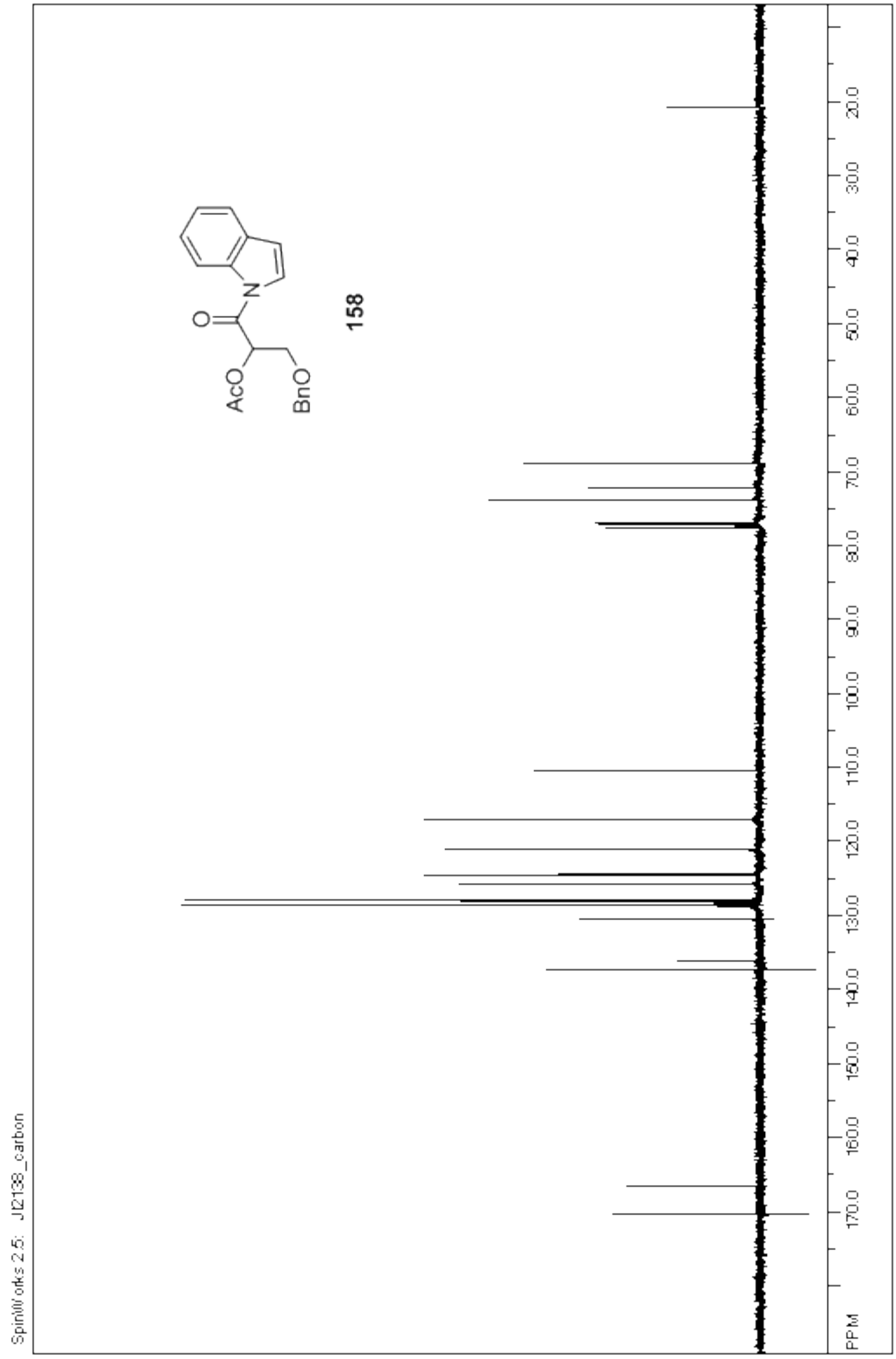

Figure A.145. ^{13}C Spectrum of **158**.

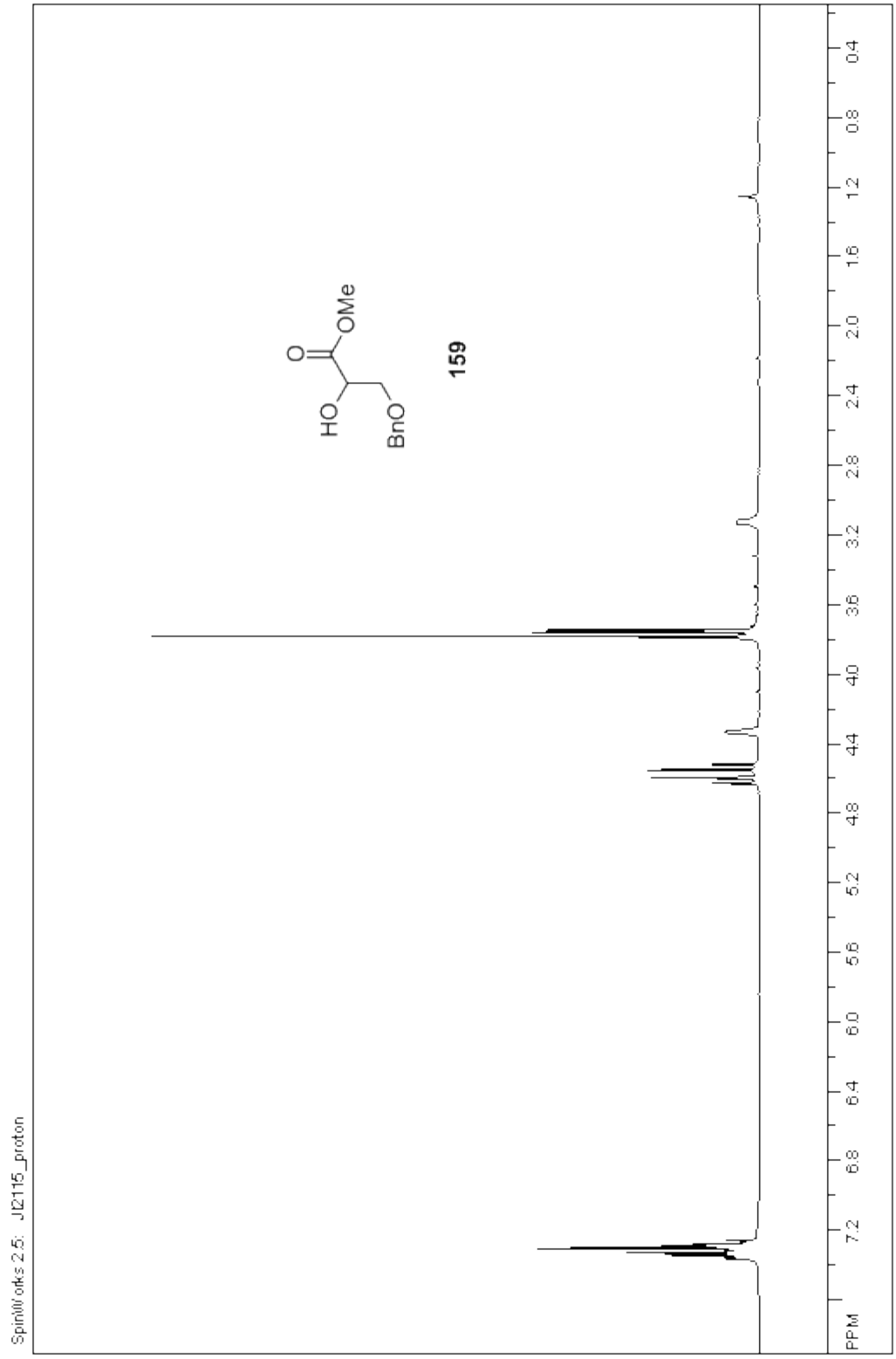

Figure A.146. ^{1}H Spectrum of **159**.

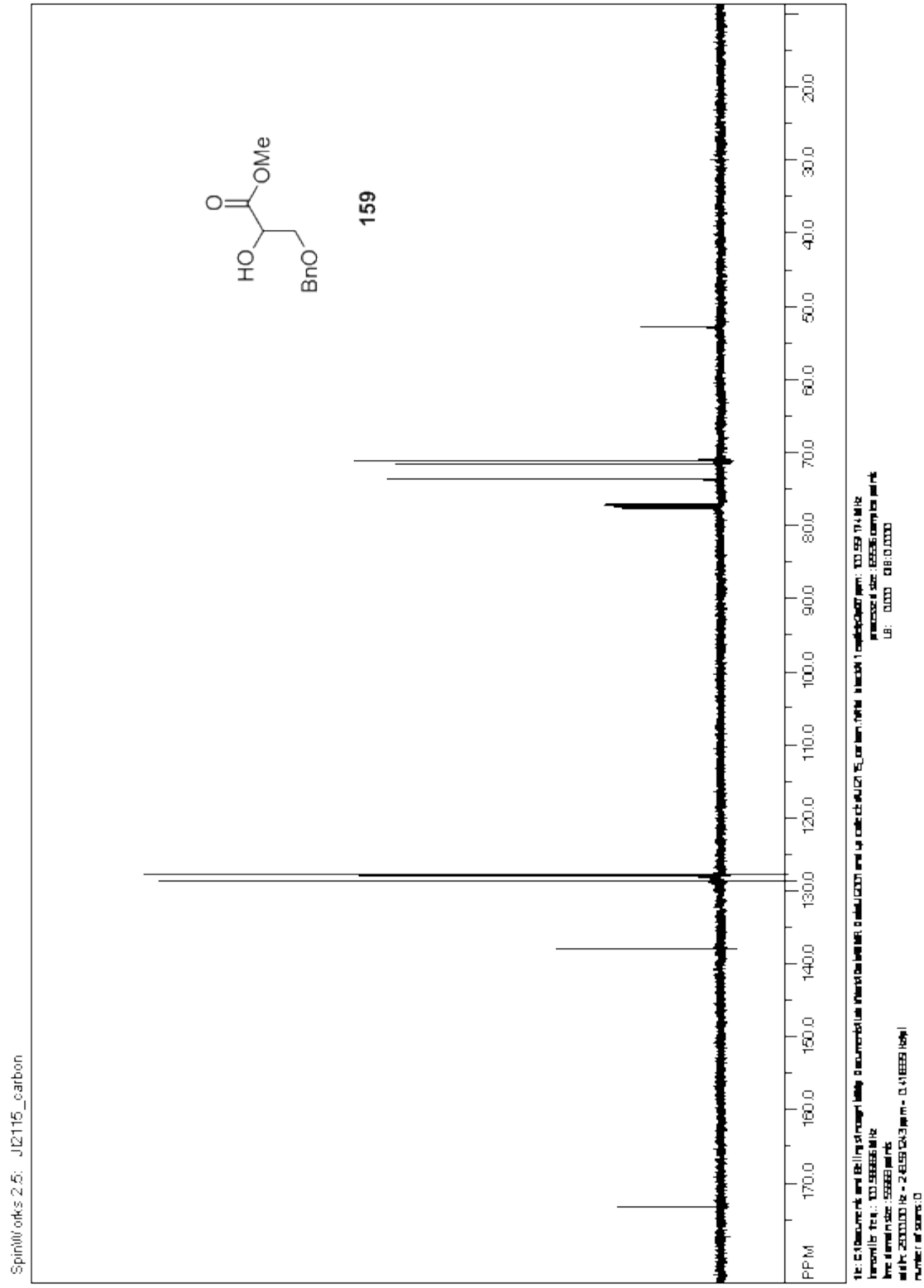

Figure A.147. ^{13}C Spectrum of **159**.

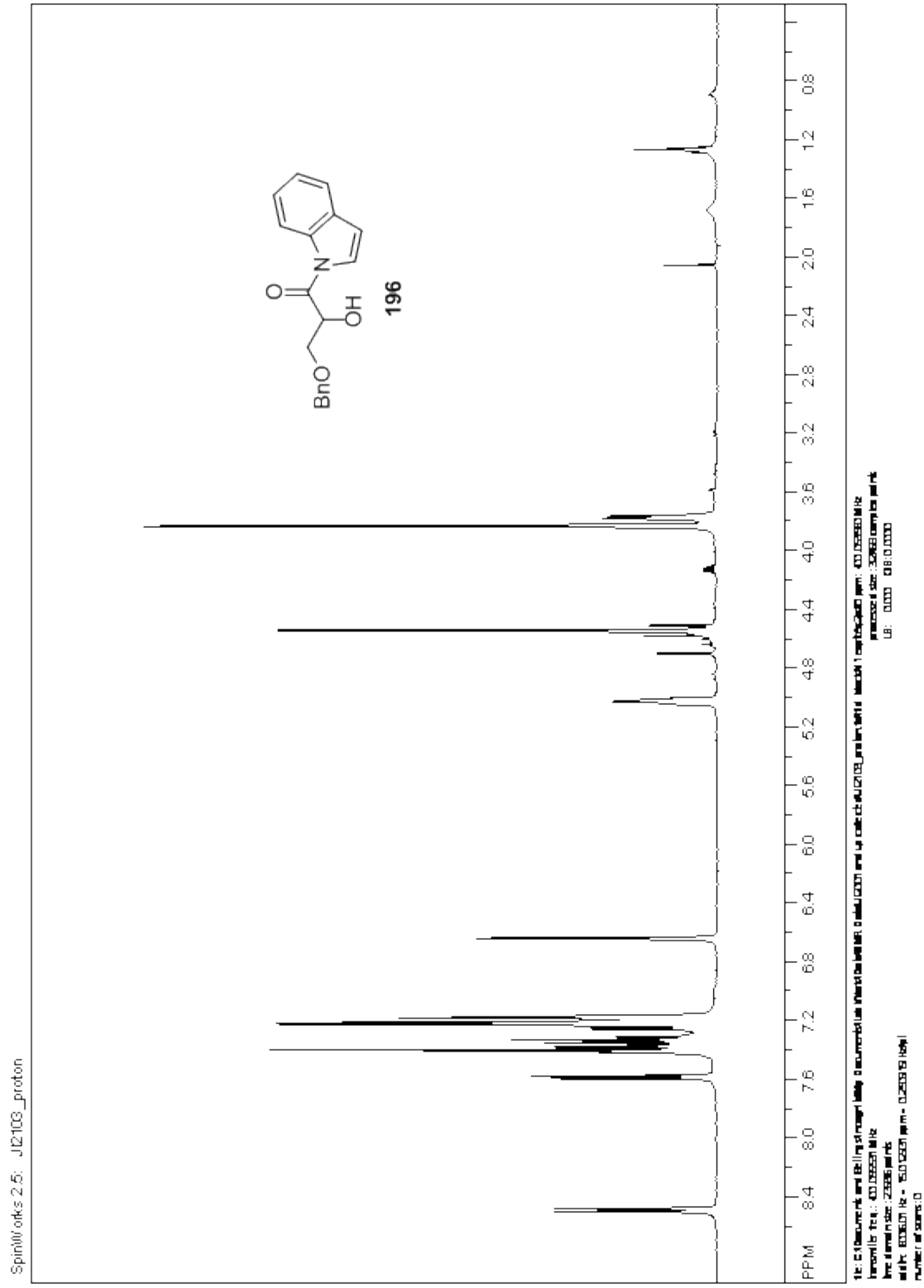

Figure A.148. ^{1}H Spectrum of **196**.

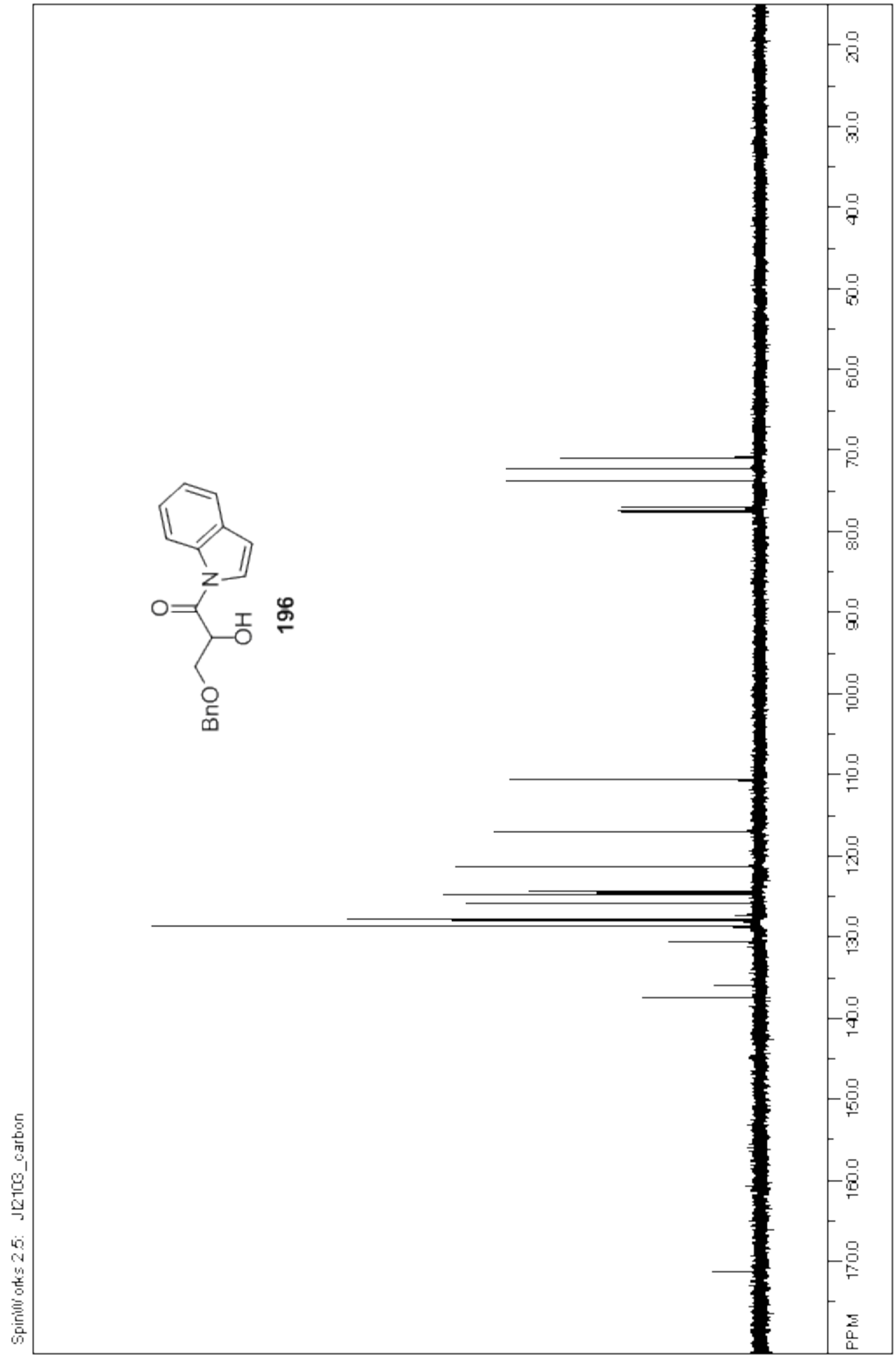

Figure A.149. ^{13}C Spectrum of **196**.

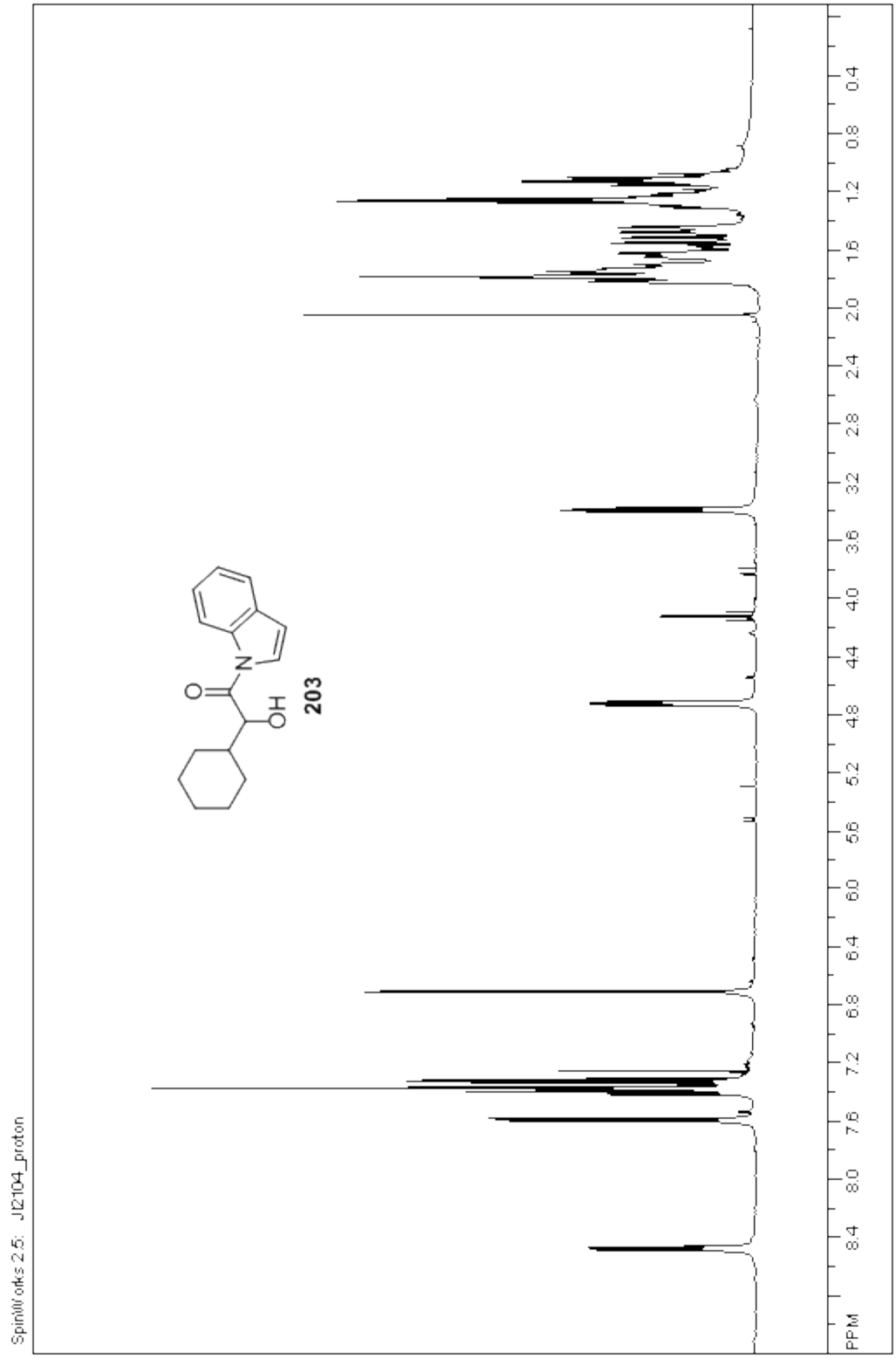

Figure A.150. ^{1}H Spectrum of **203**.

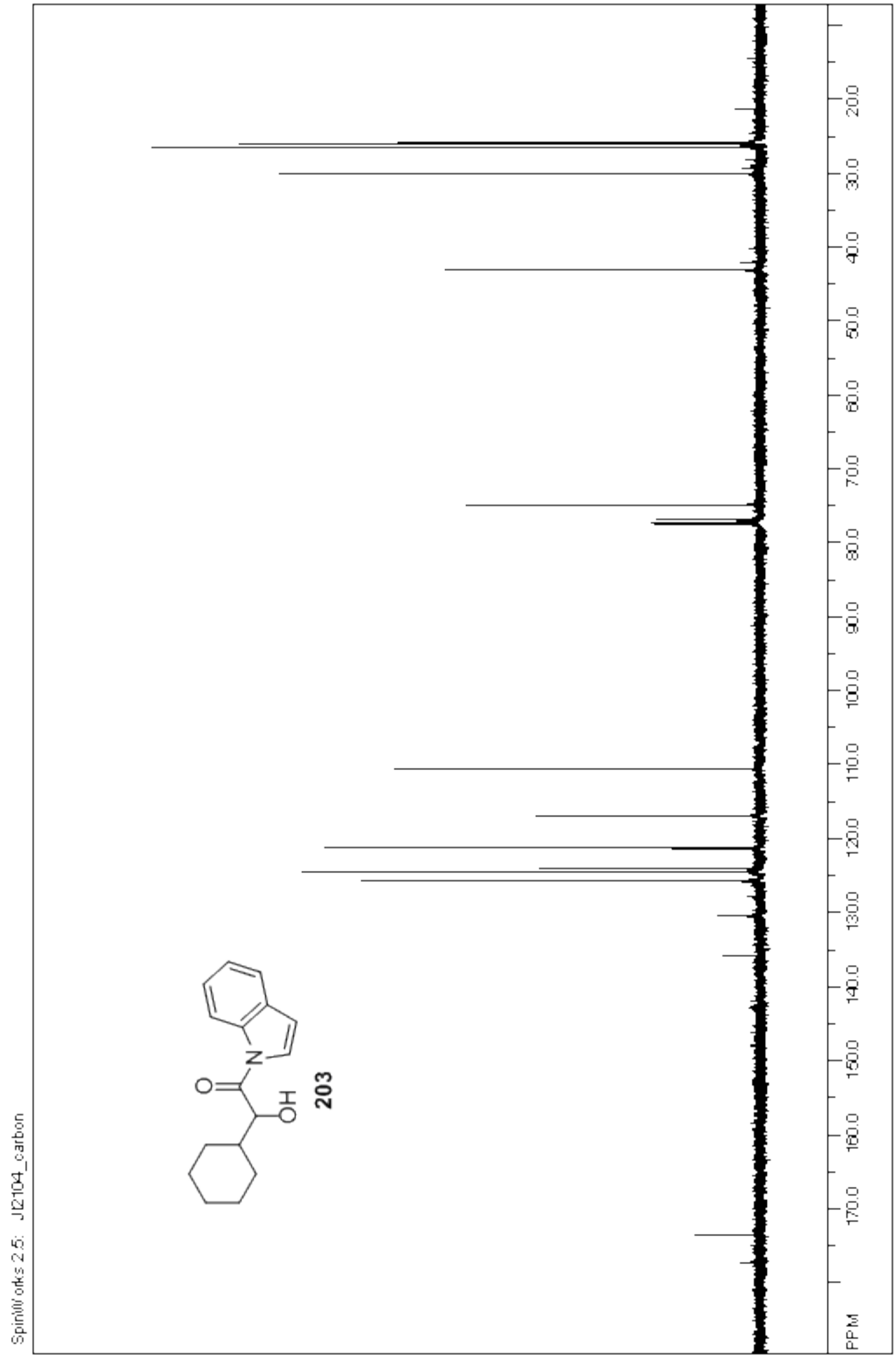

Figure A.151. ^{13}C Spectrum of **203**.

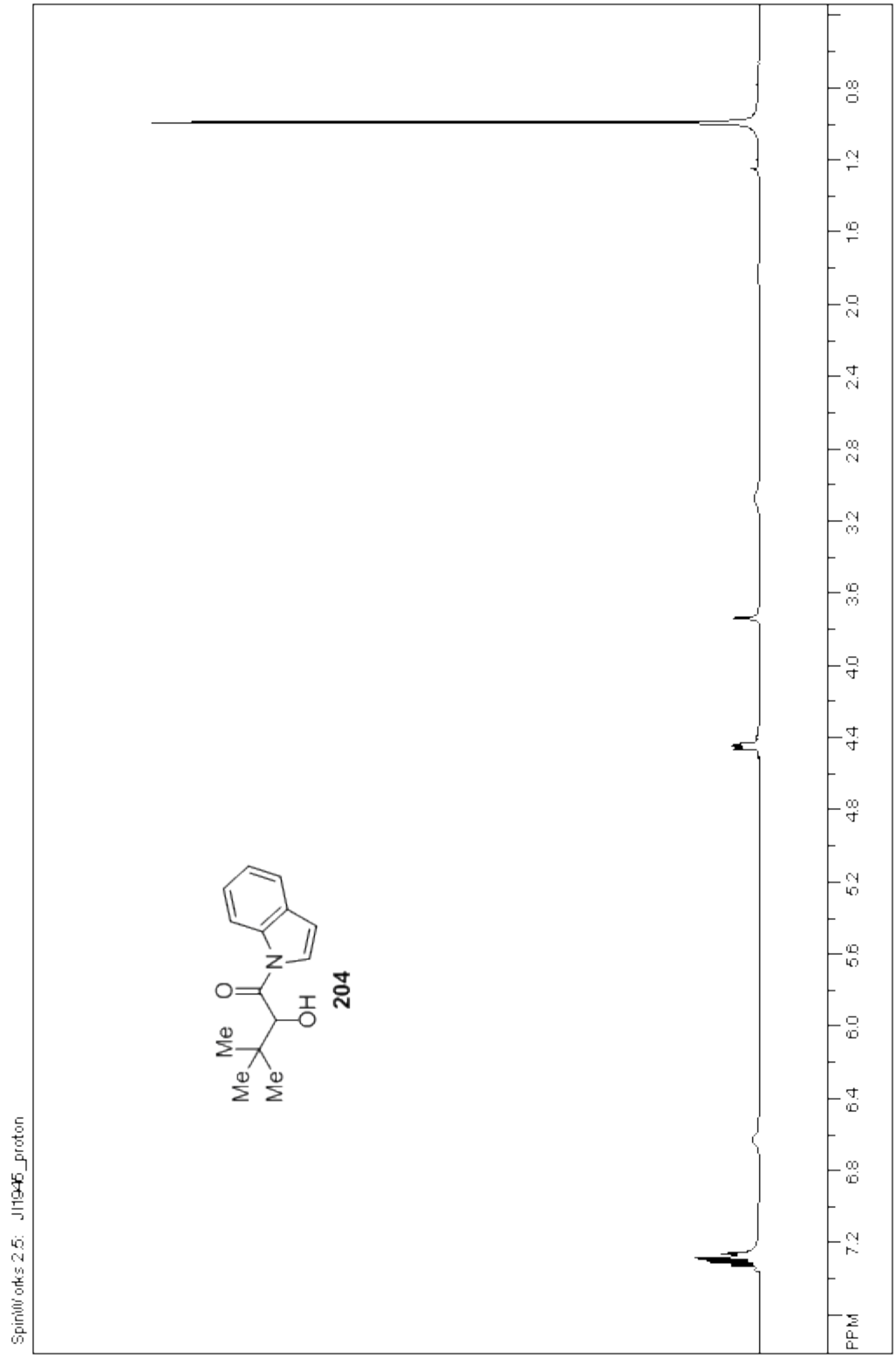

Figure A.152. ^{1}H Spectrum of **204**.

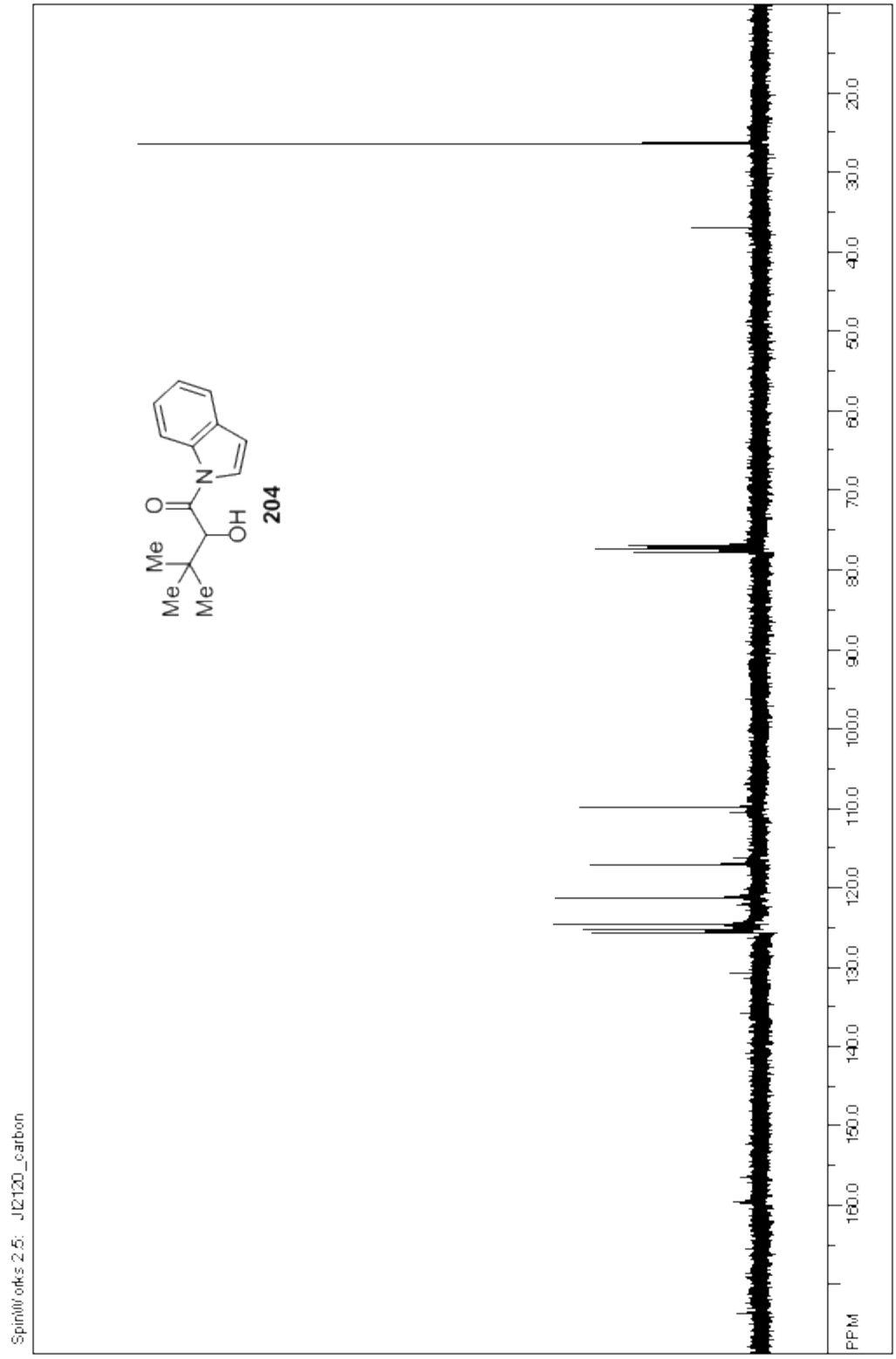

Figure A.153. ^{13}C Spectrum of **204**.

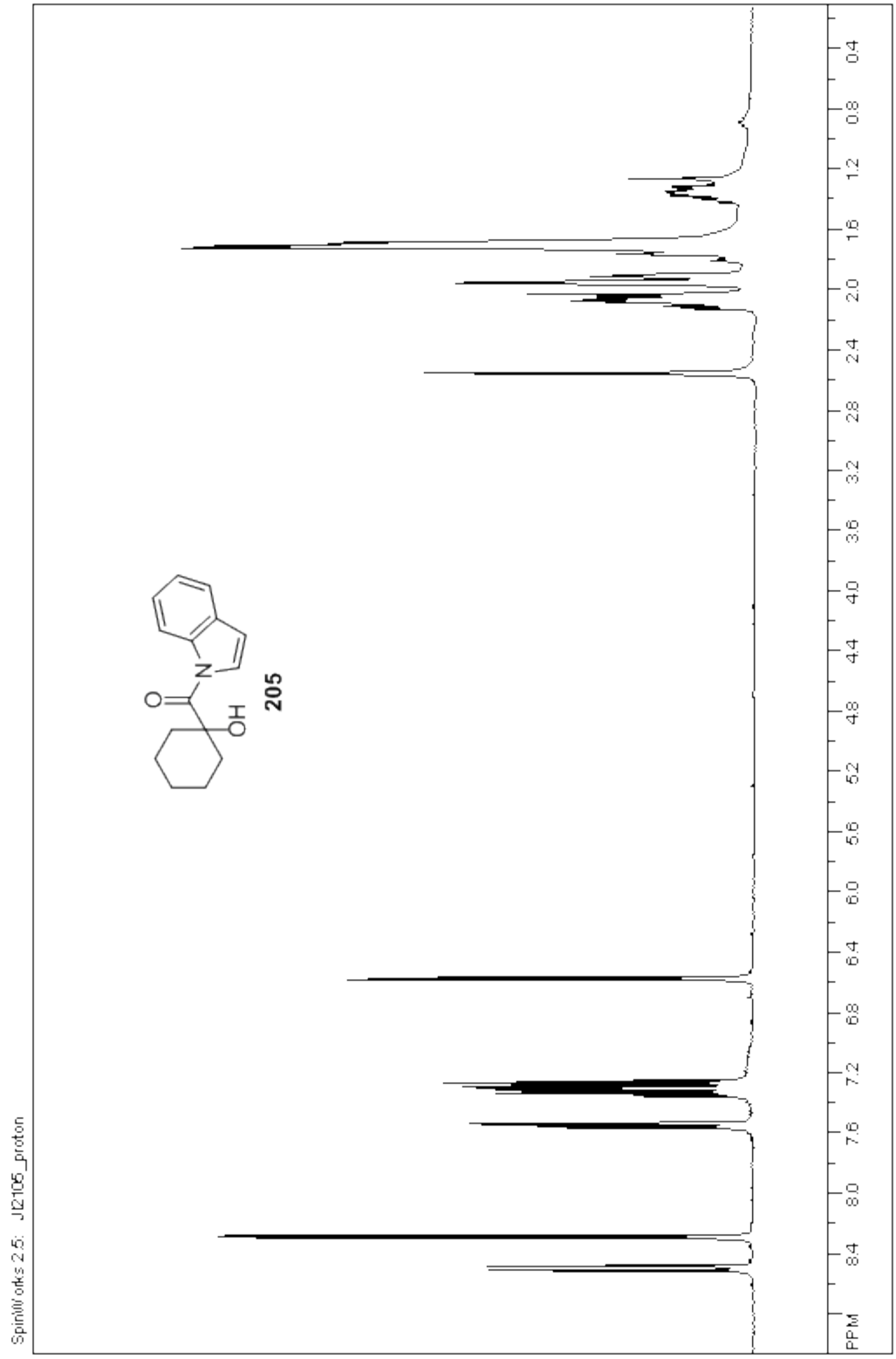

Figure A.154. ^{1}H Spectrum of **205**.

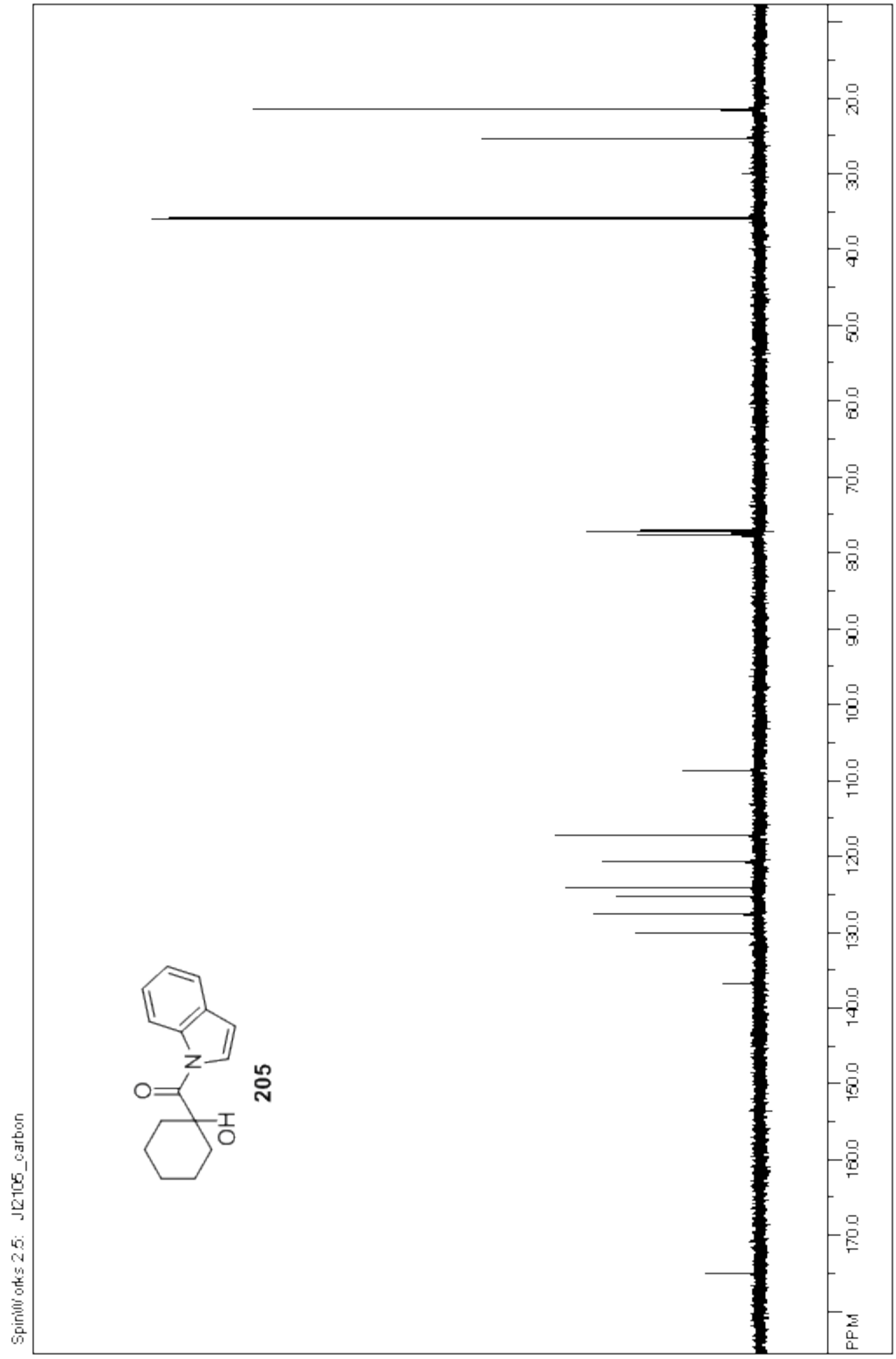

Figure A.155. ^{13}C Spectrum of **205**.

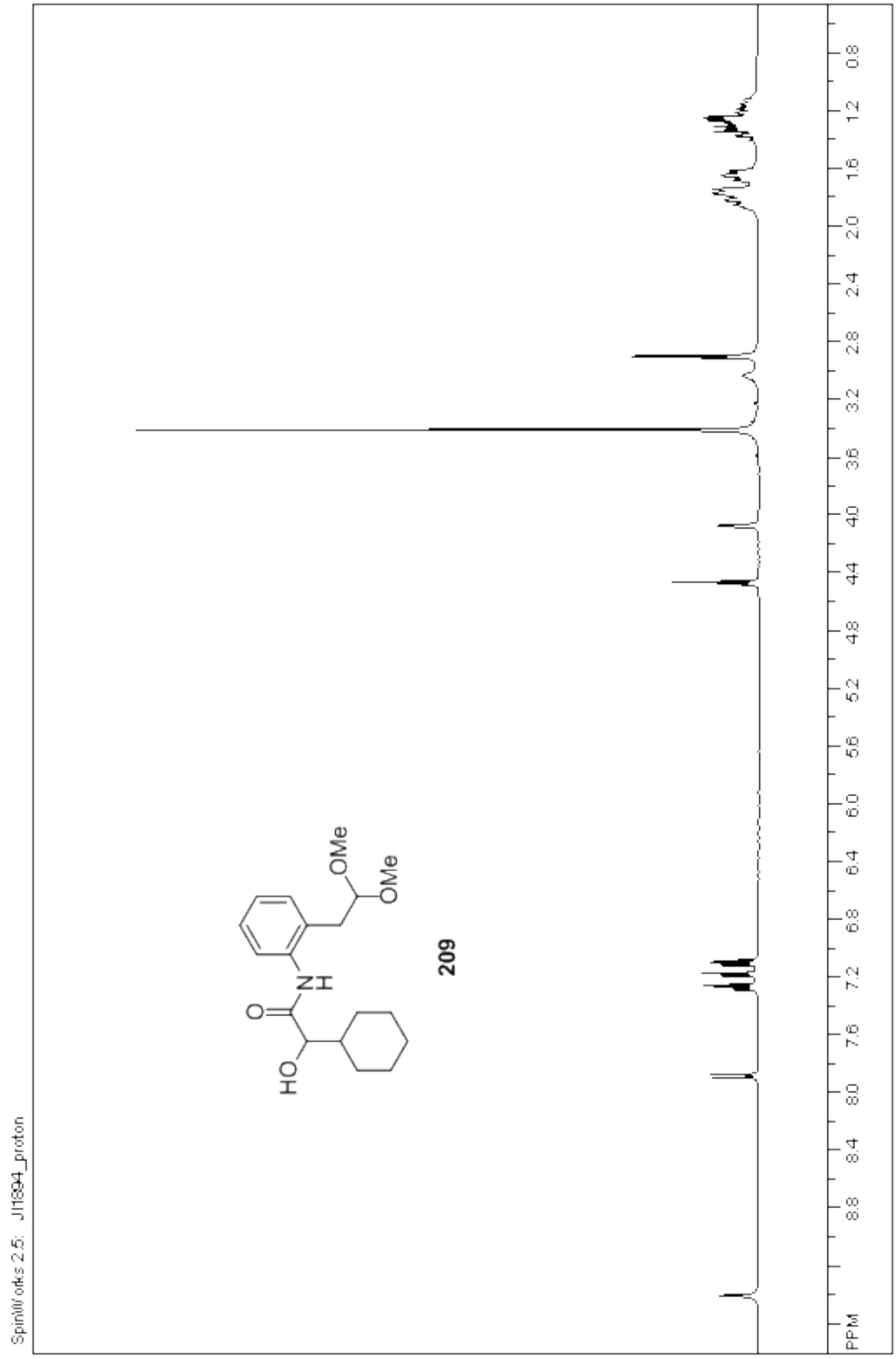

Figure A.156. ^{1}H Spectrum of **209**.

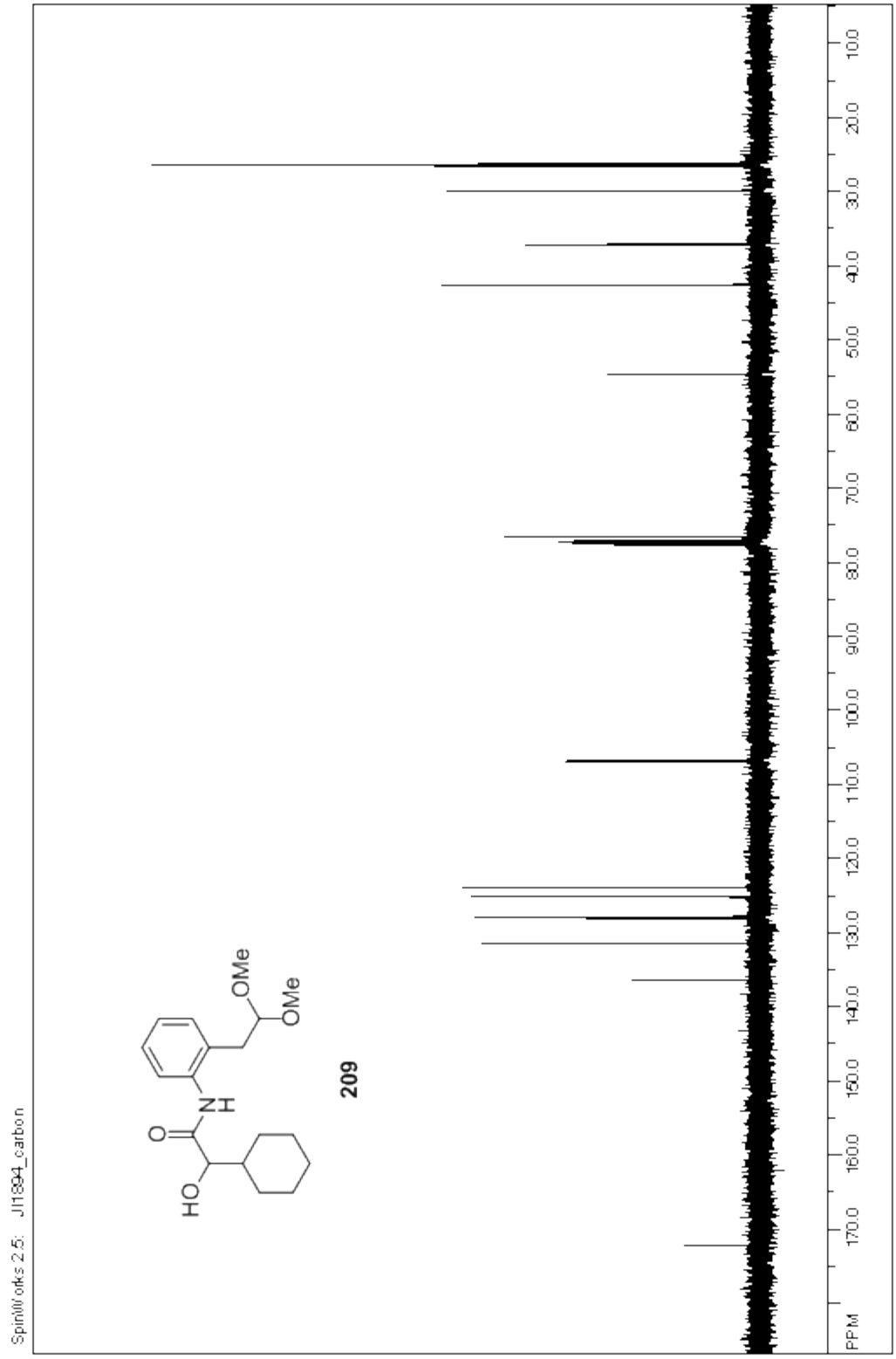

Figure A.157. ^{13}C Spectrum of **209**.

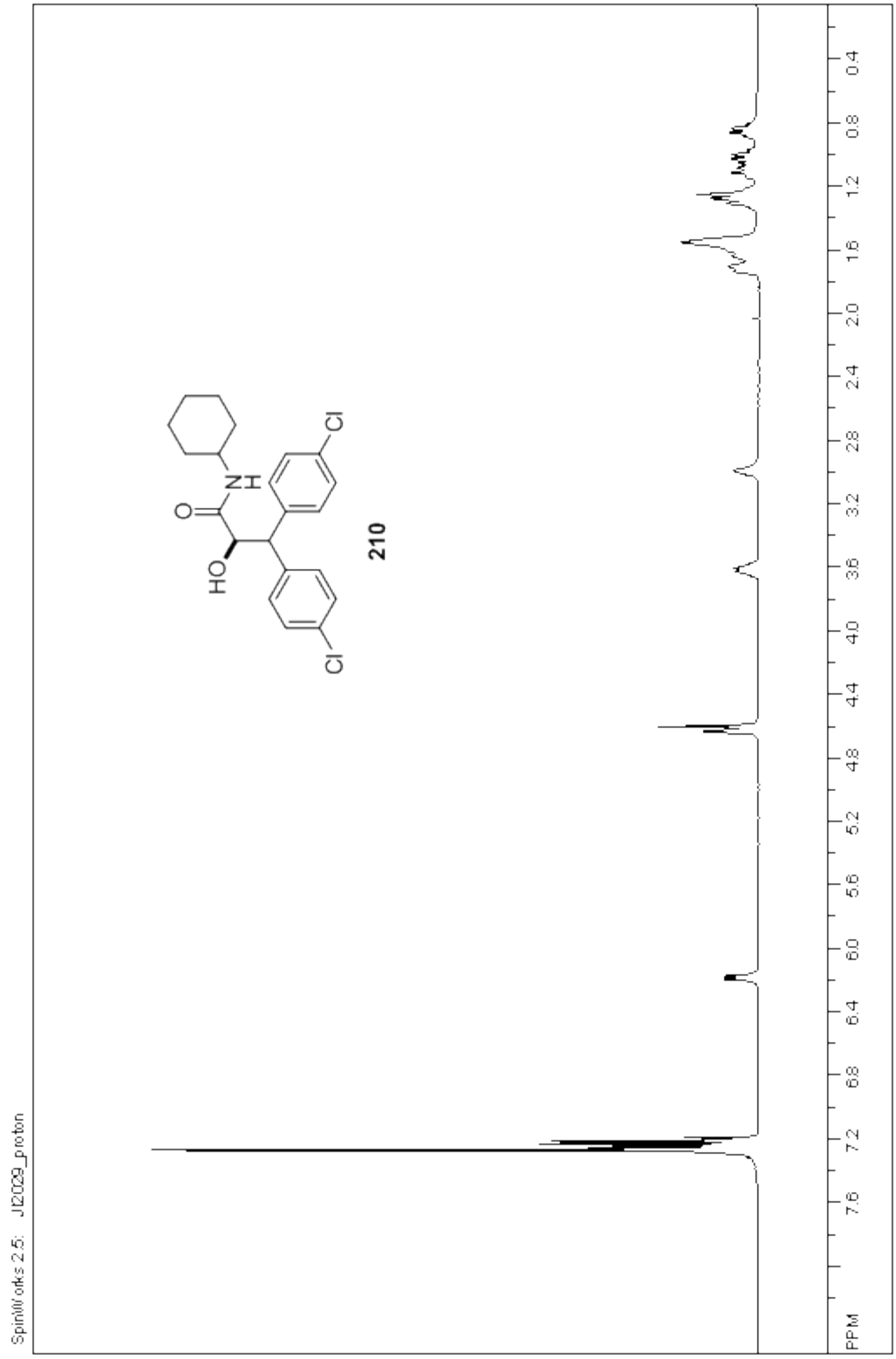

Figure A.158. ^{1}H Spectrum of **210**.

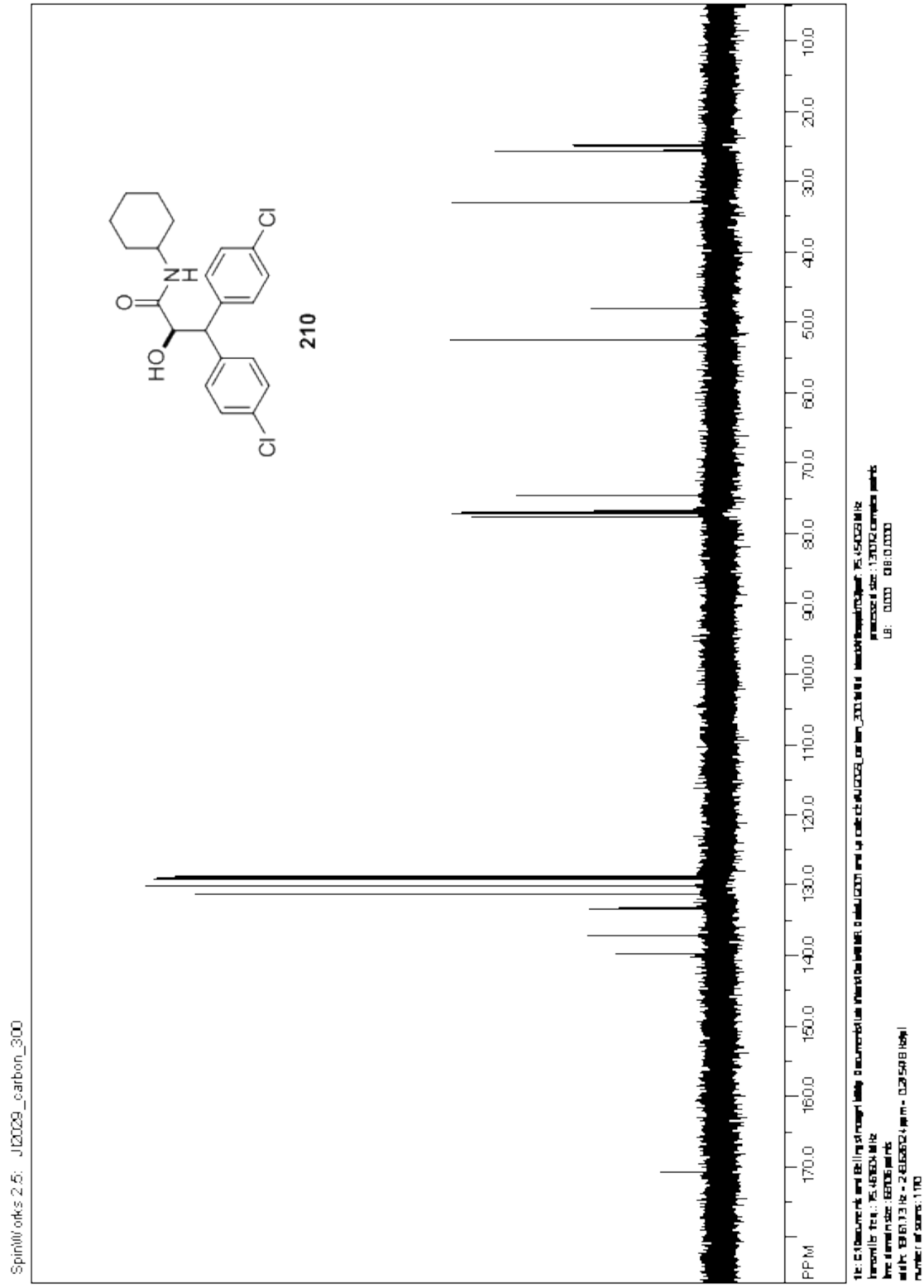

Figure A.159. ^{13}C Spectrum of **210**.

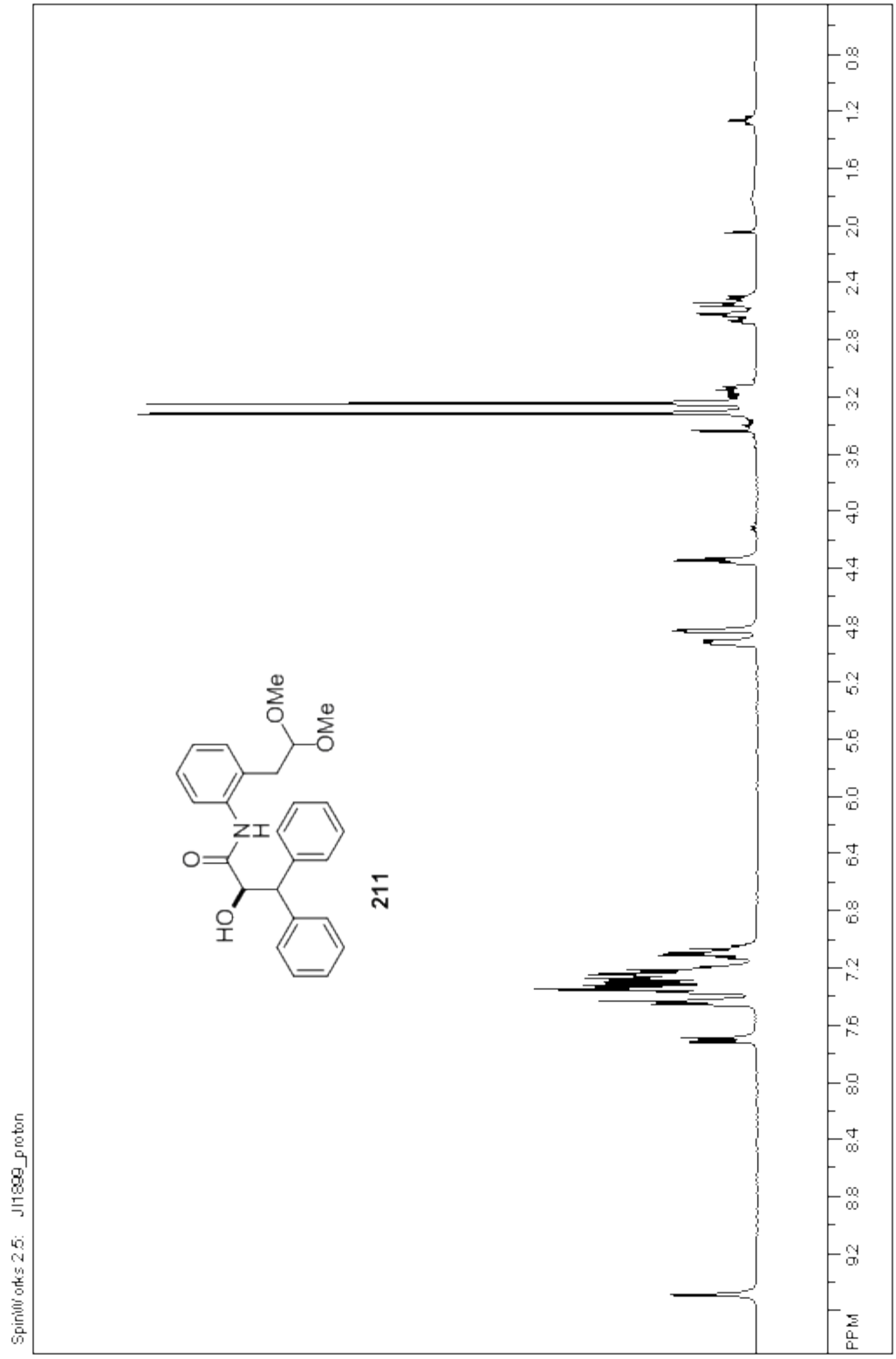

Figure A.160. ^{1}H Spectrum of **211**.

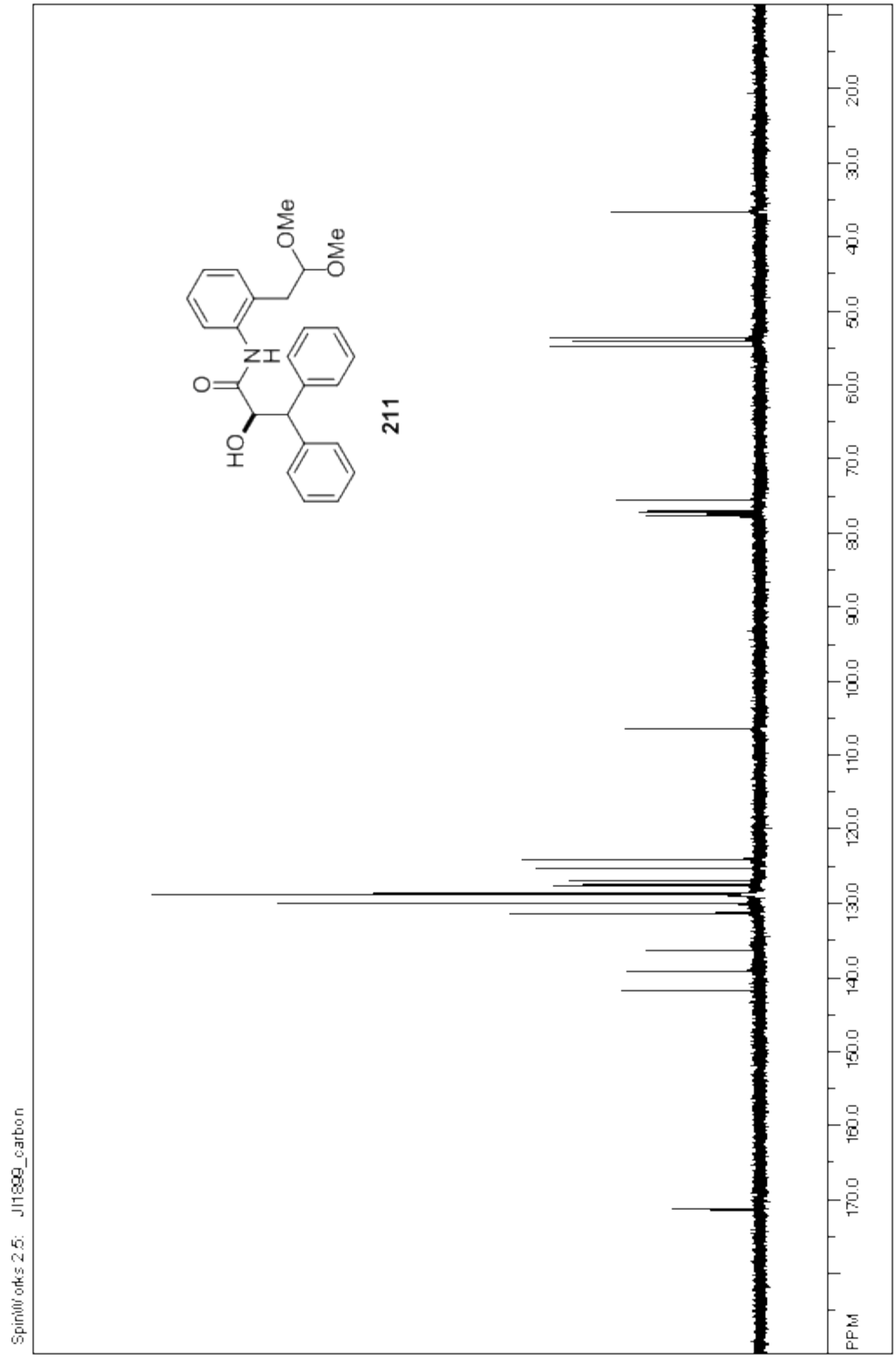

Figure A.161. ^{13}C Spectrum of **211**.

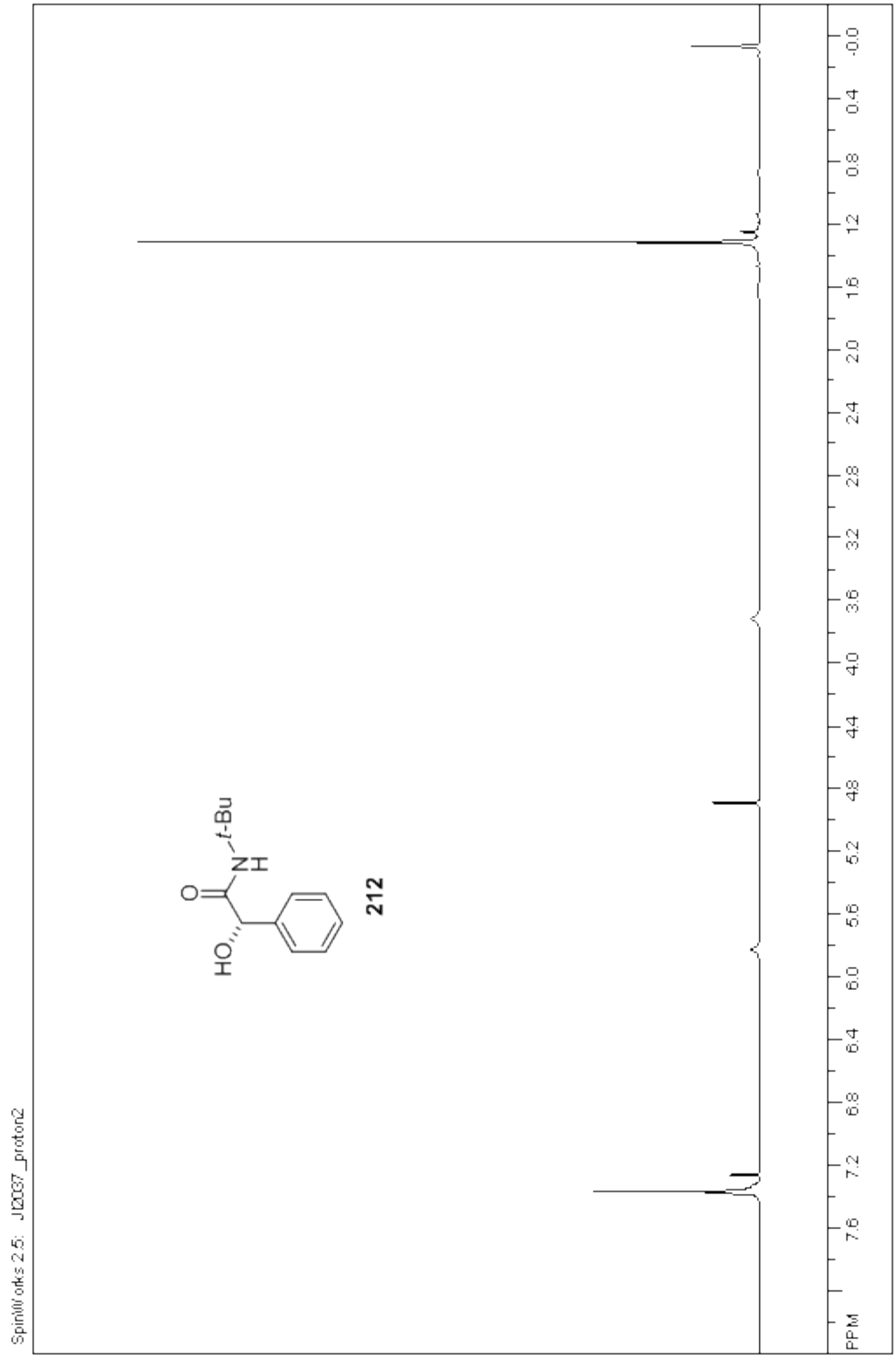

Figure A.162. ^{1}H Spectrum of **212**.

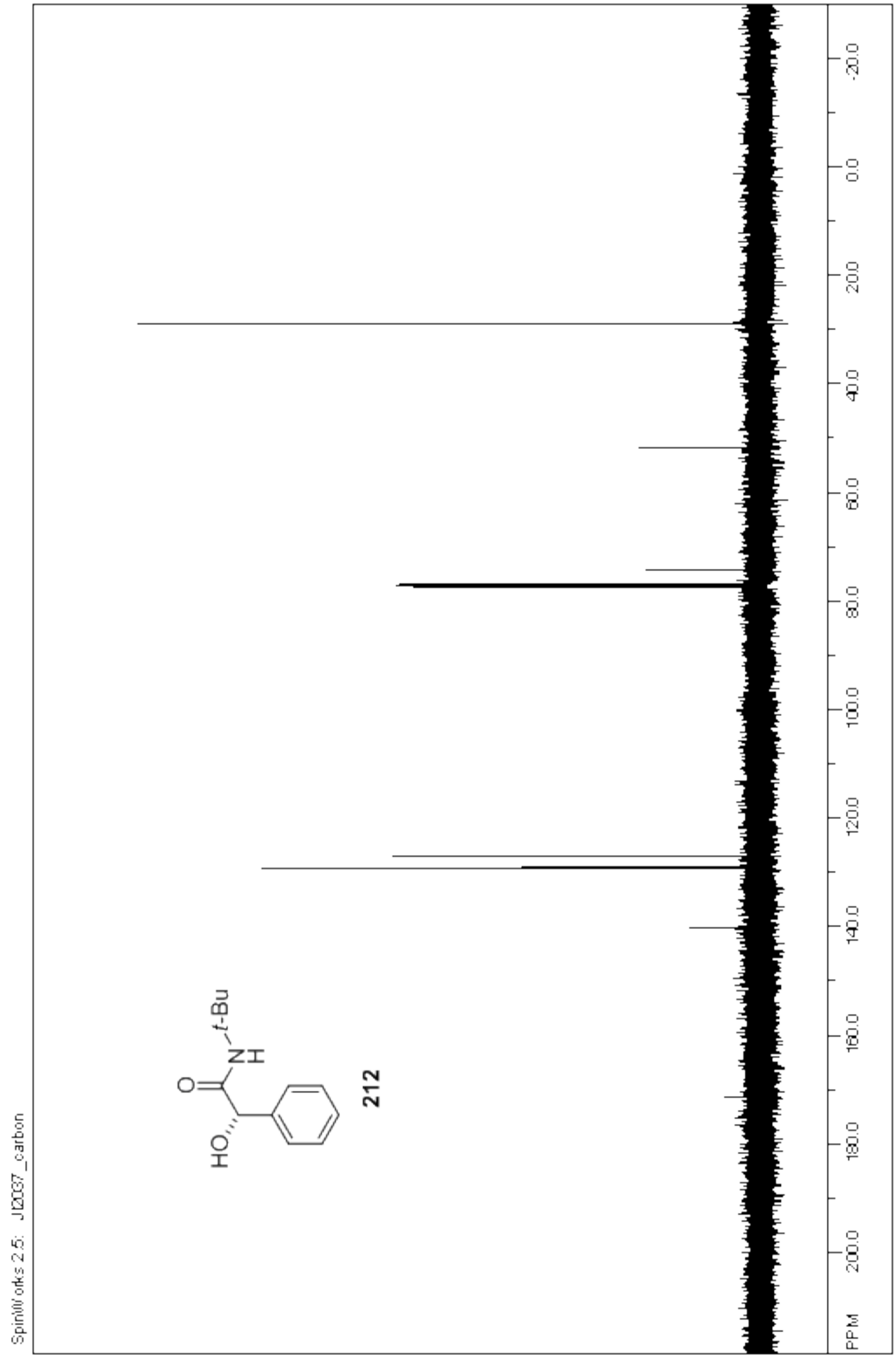

Figure A.163. ^{13}C Spectrum of **212**.

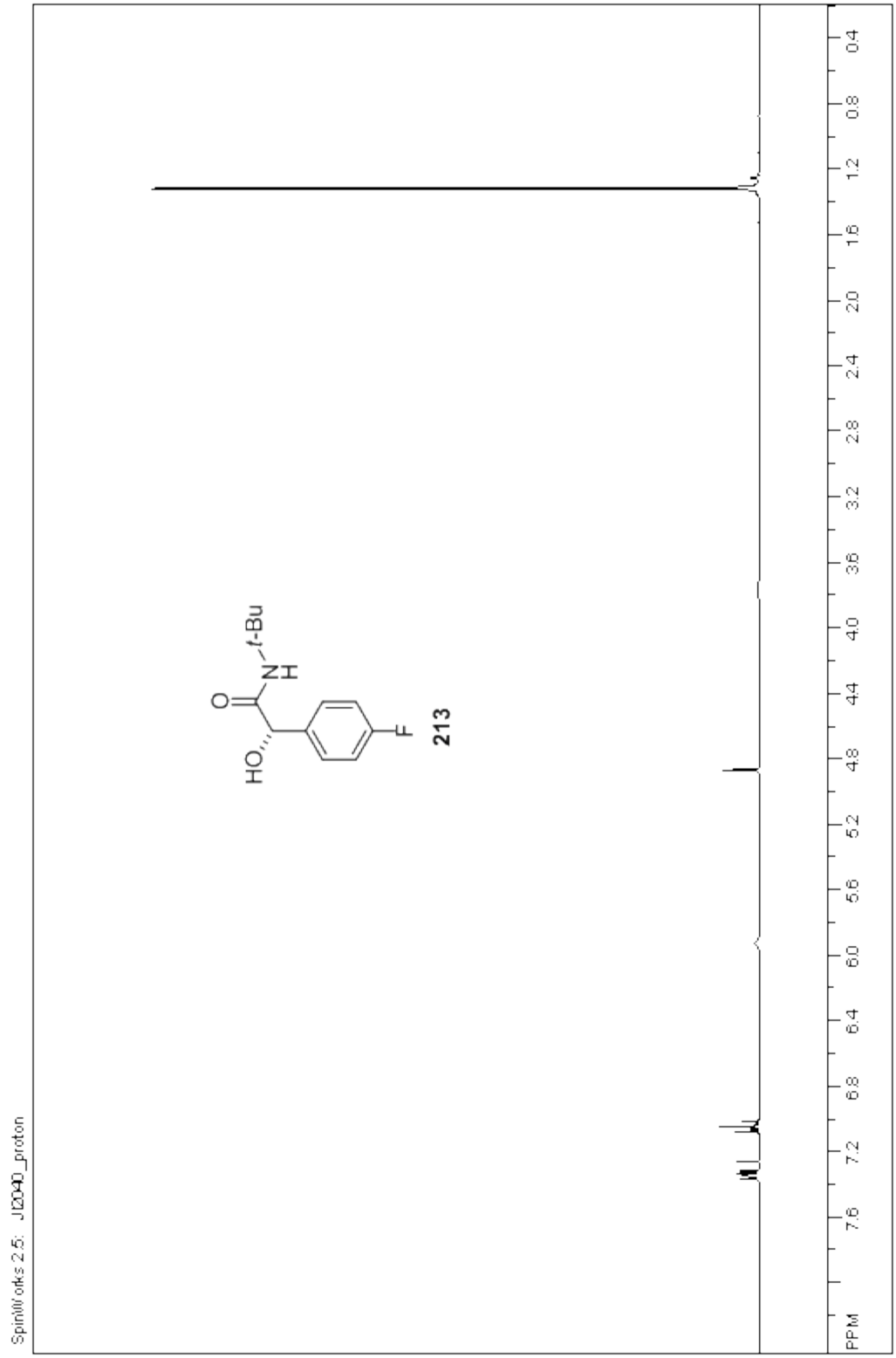

Figure A.164. ^{1}H Spectrum of **213**.

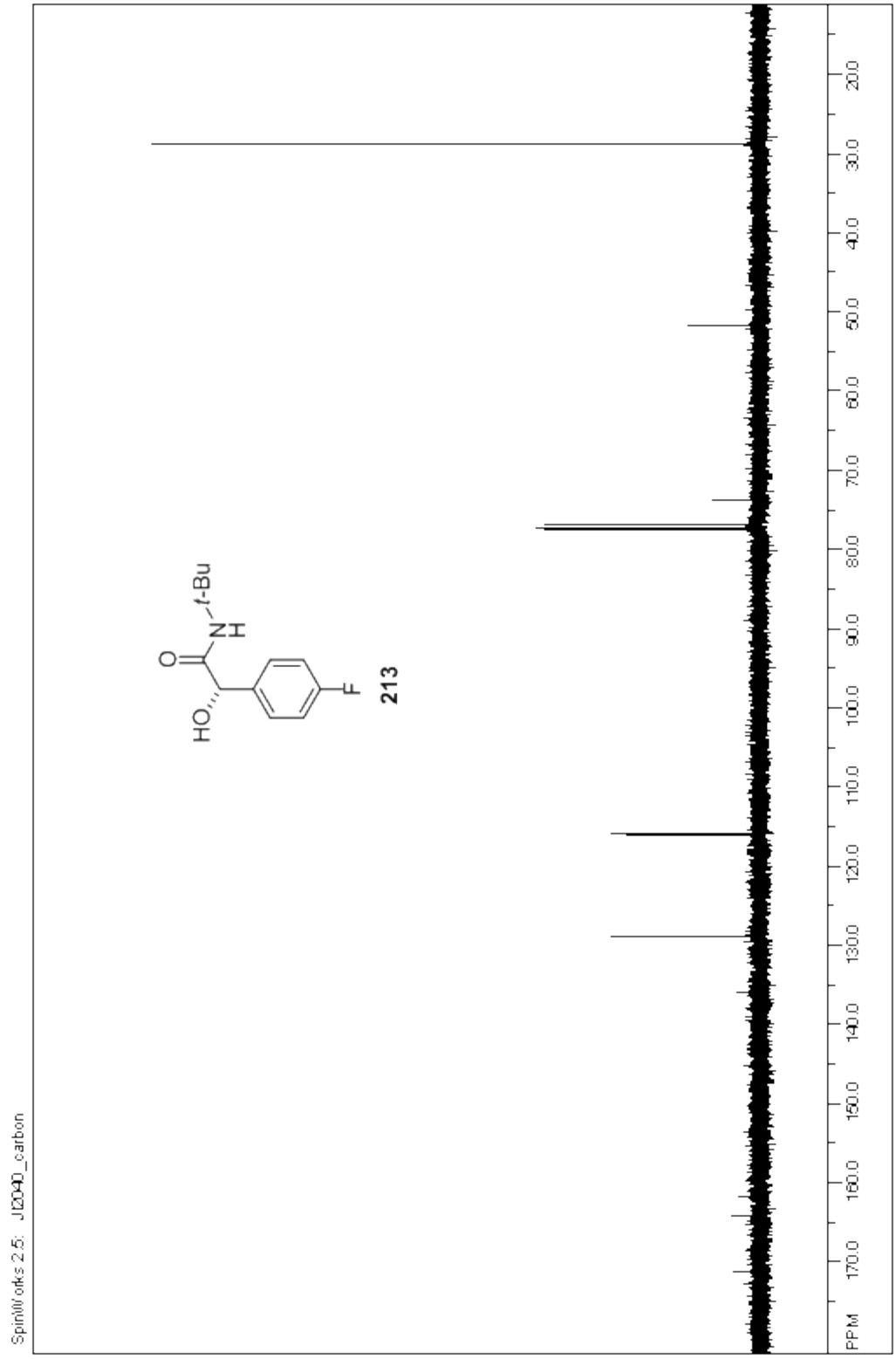

Figure A.165. ^{13}C Spectrum of **213**.

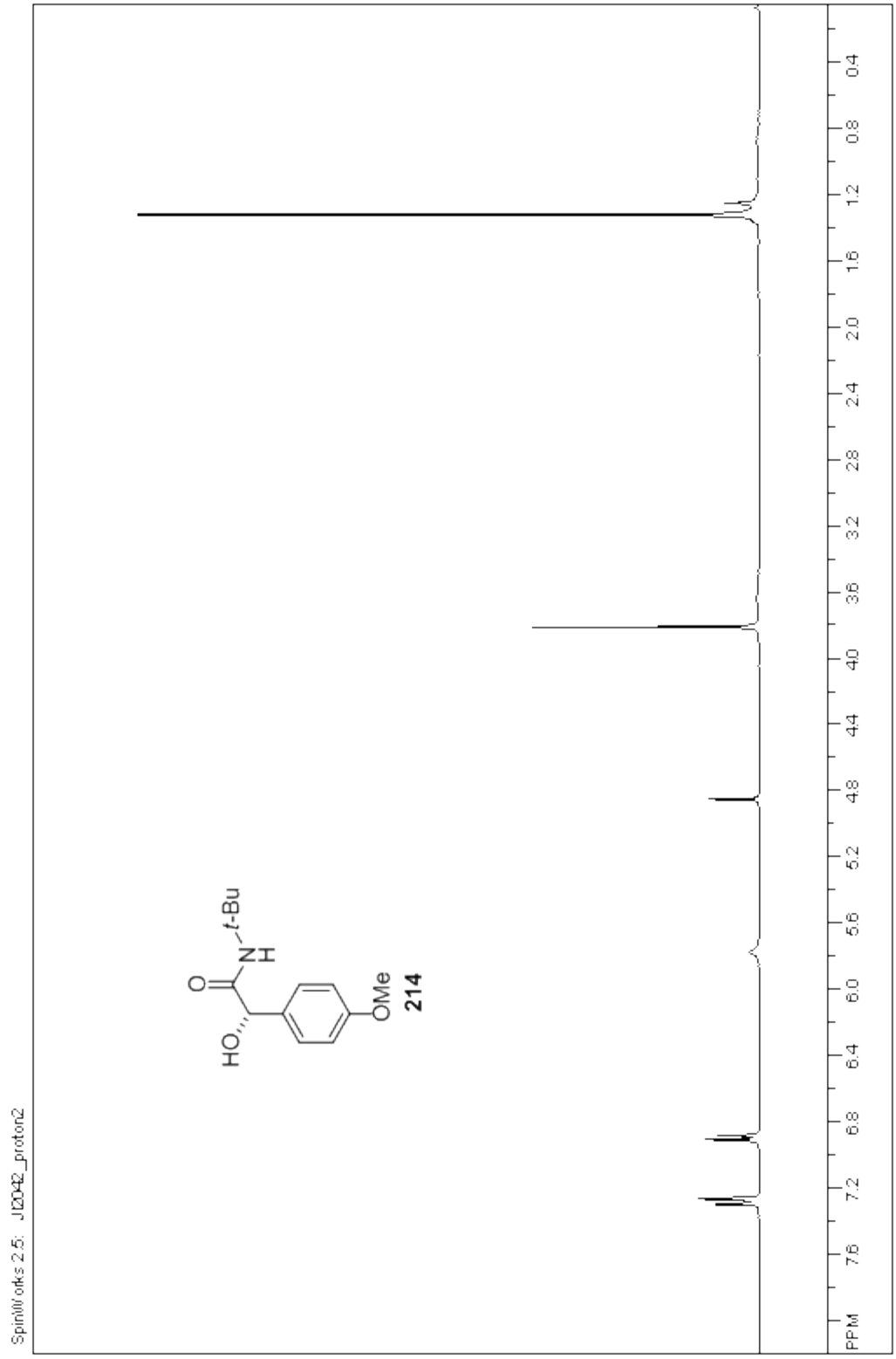

Figure A.166. ^{1}H Spectrum of **214**.

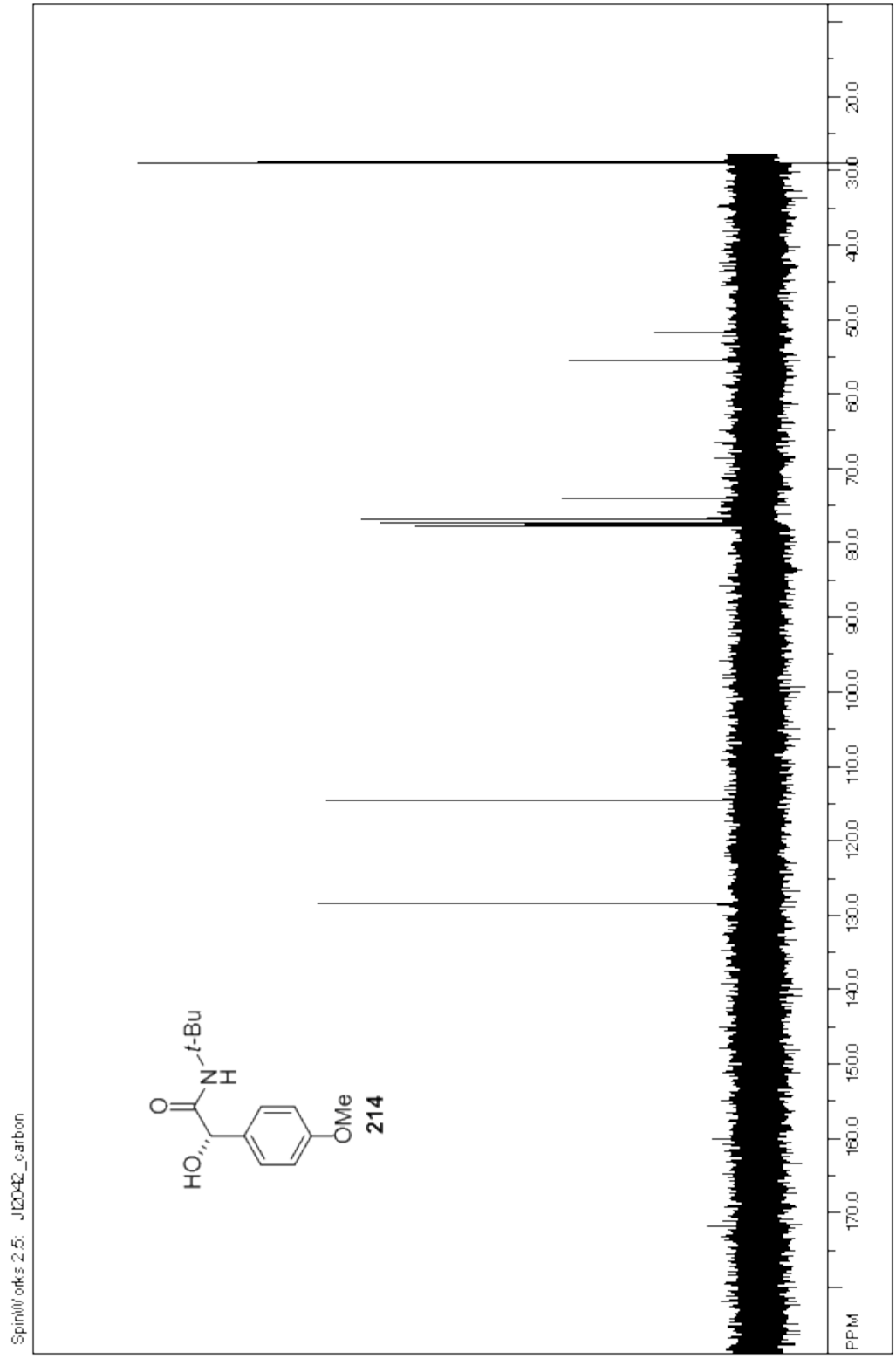

Figure A.167. ^{13}C Spectrum of **214**.

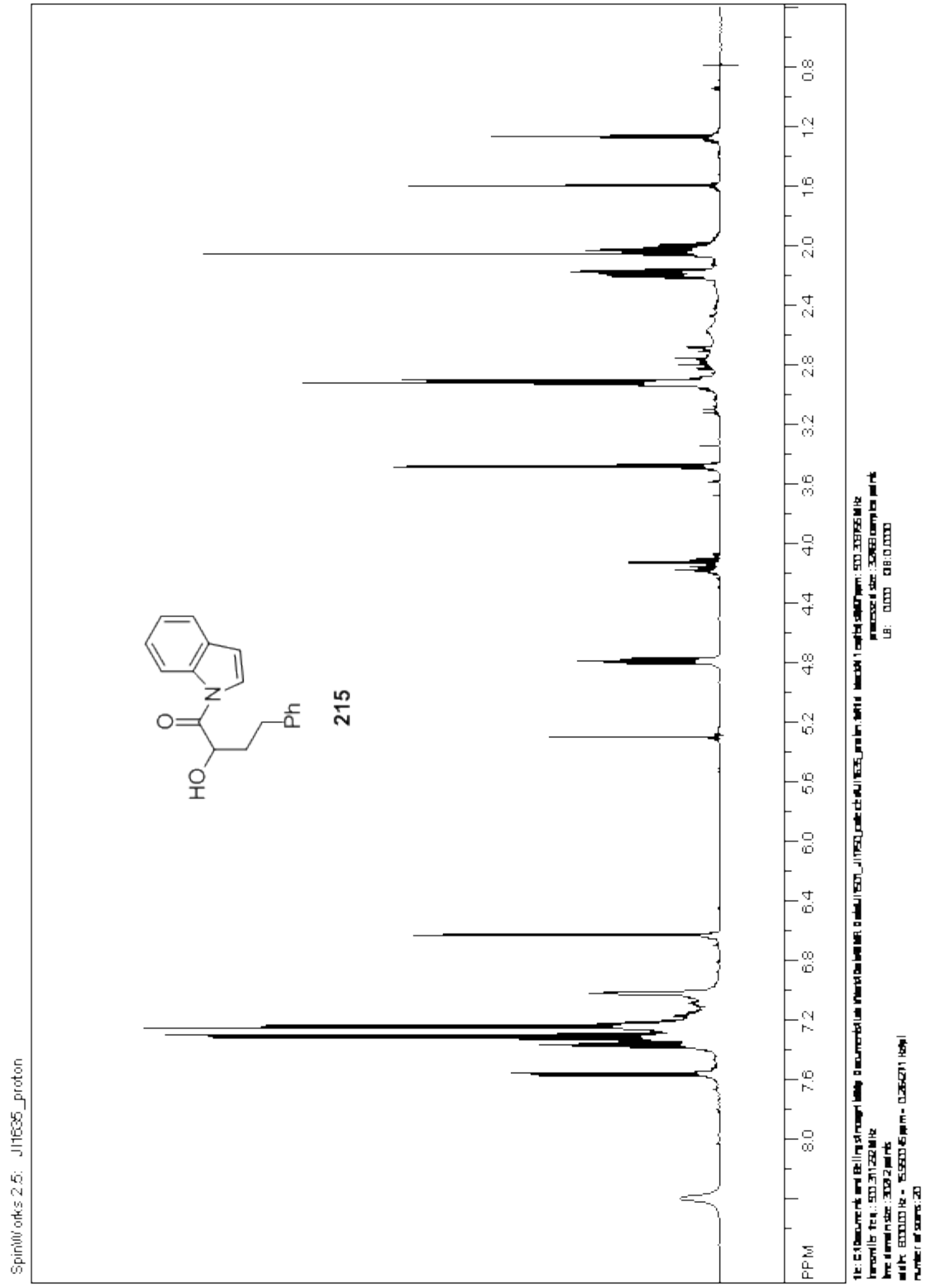

Figure A.168. ^{1}H Spectrum of **215**.

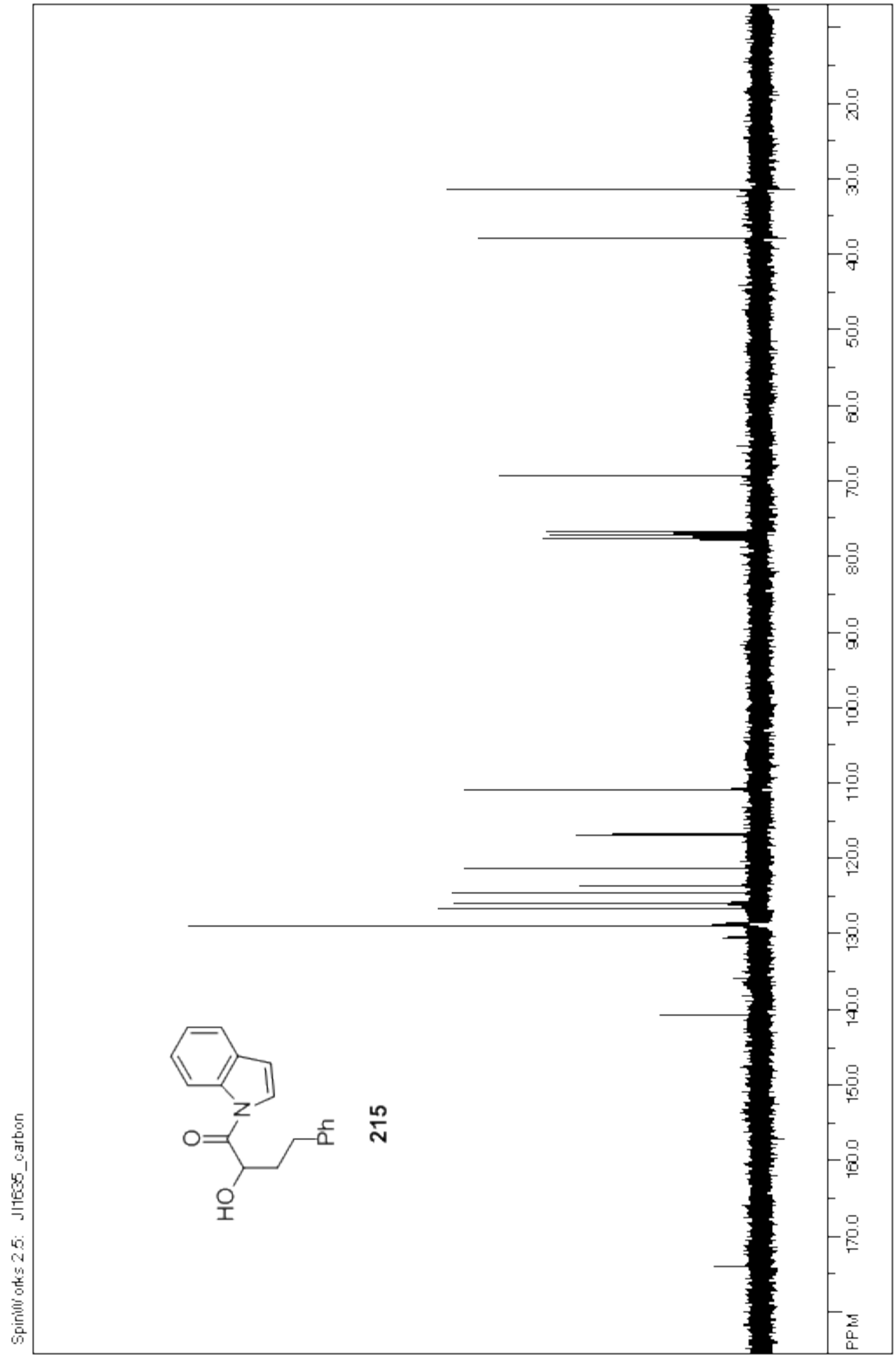

Figure A.169. ^{13}C Spectrum of **215**.

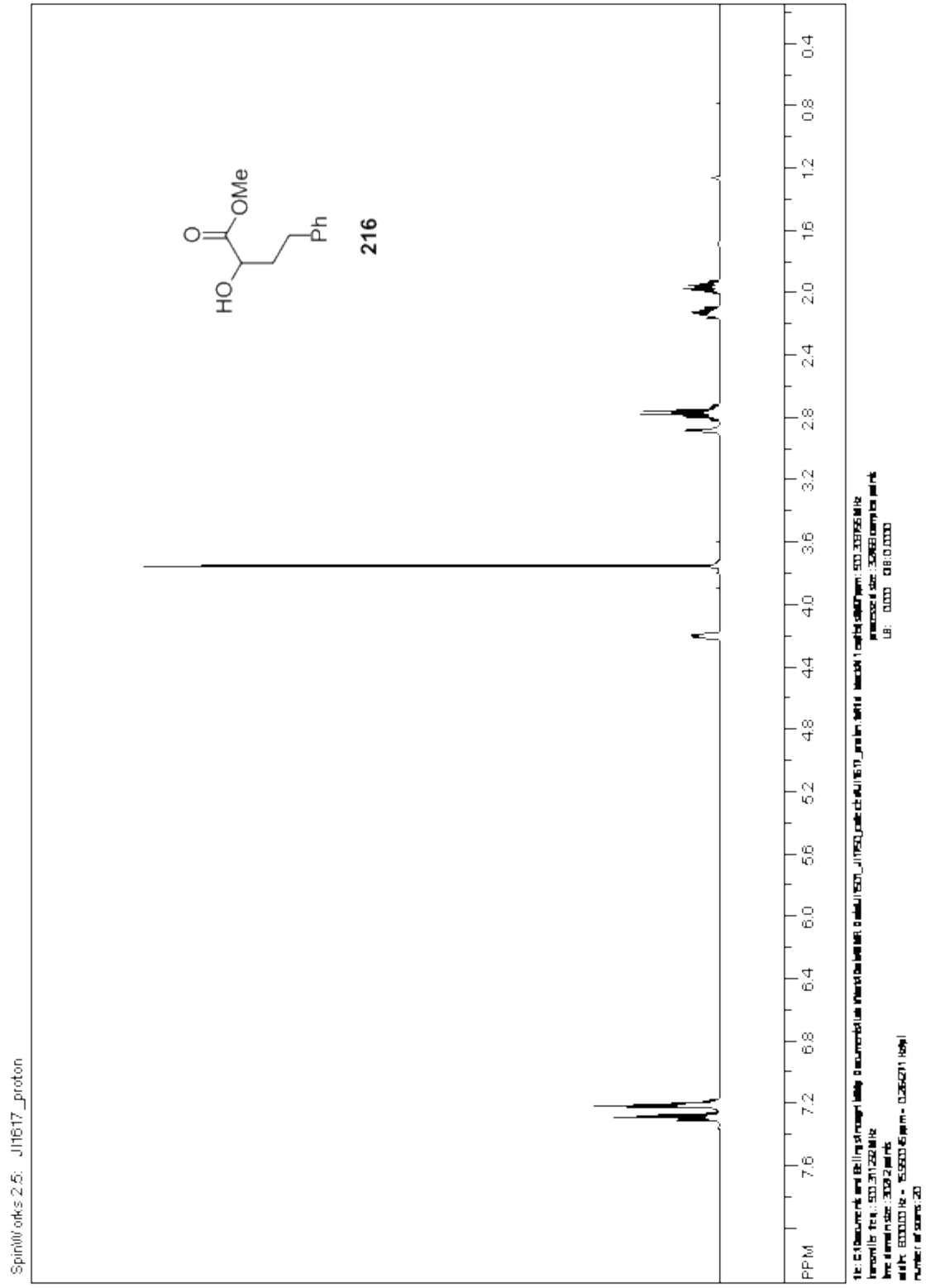

Figure A.170. ^{1}H Spectrum of **216**.

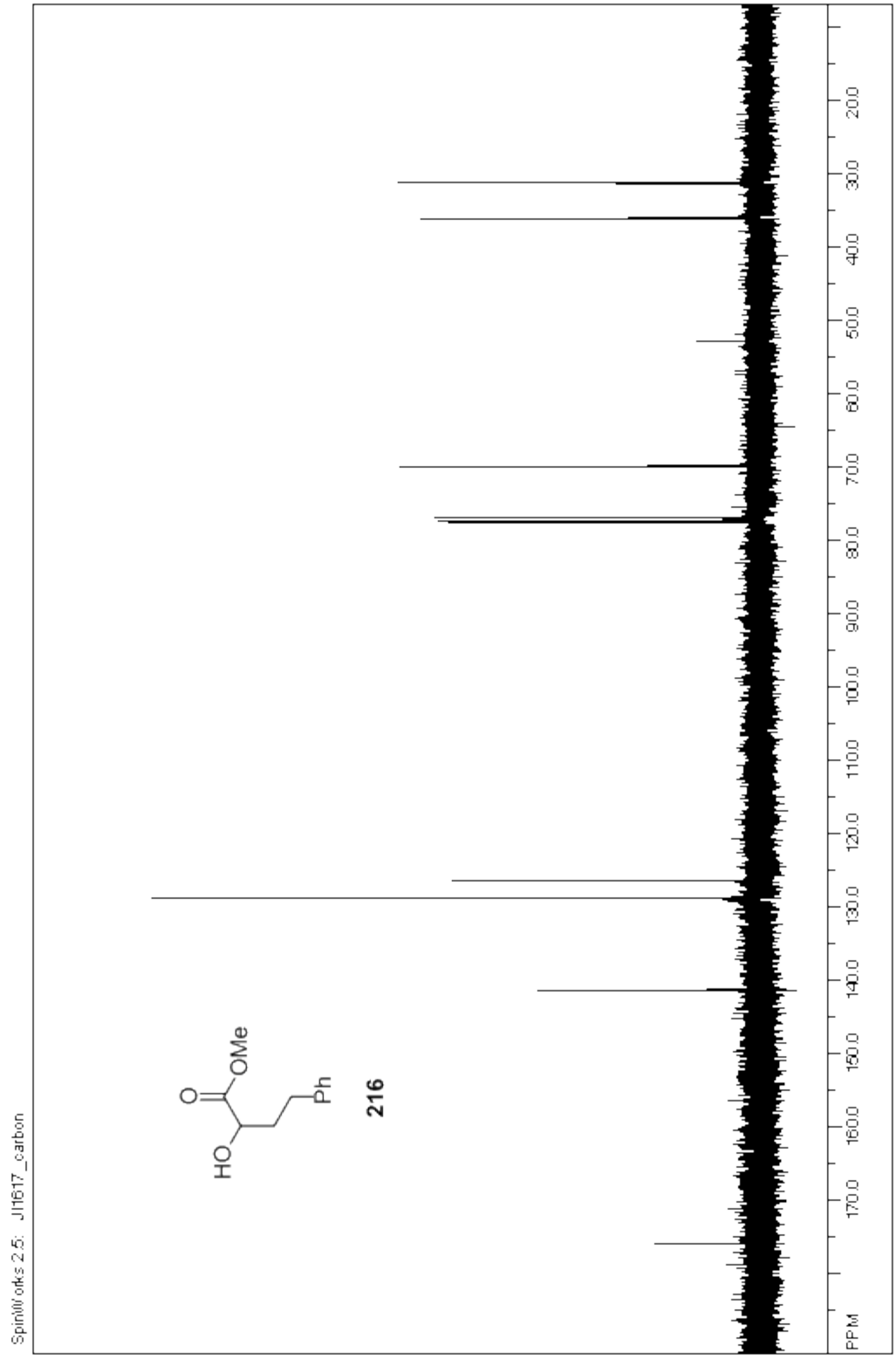

Figure A.171. ^{13}C Spectrum of **216**.

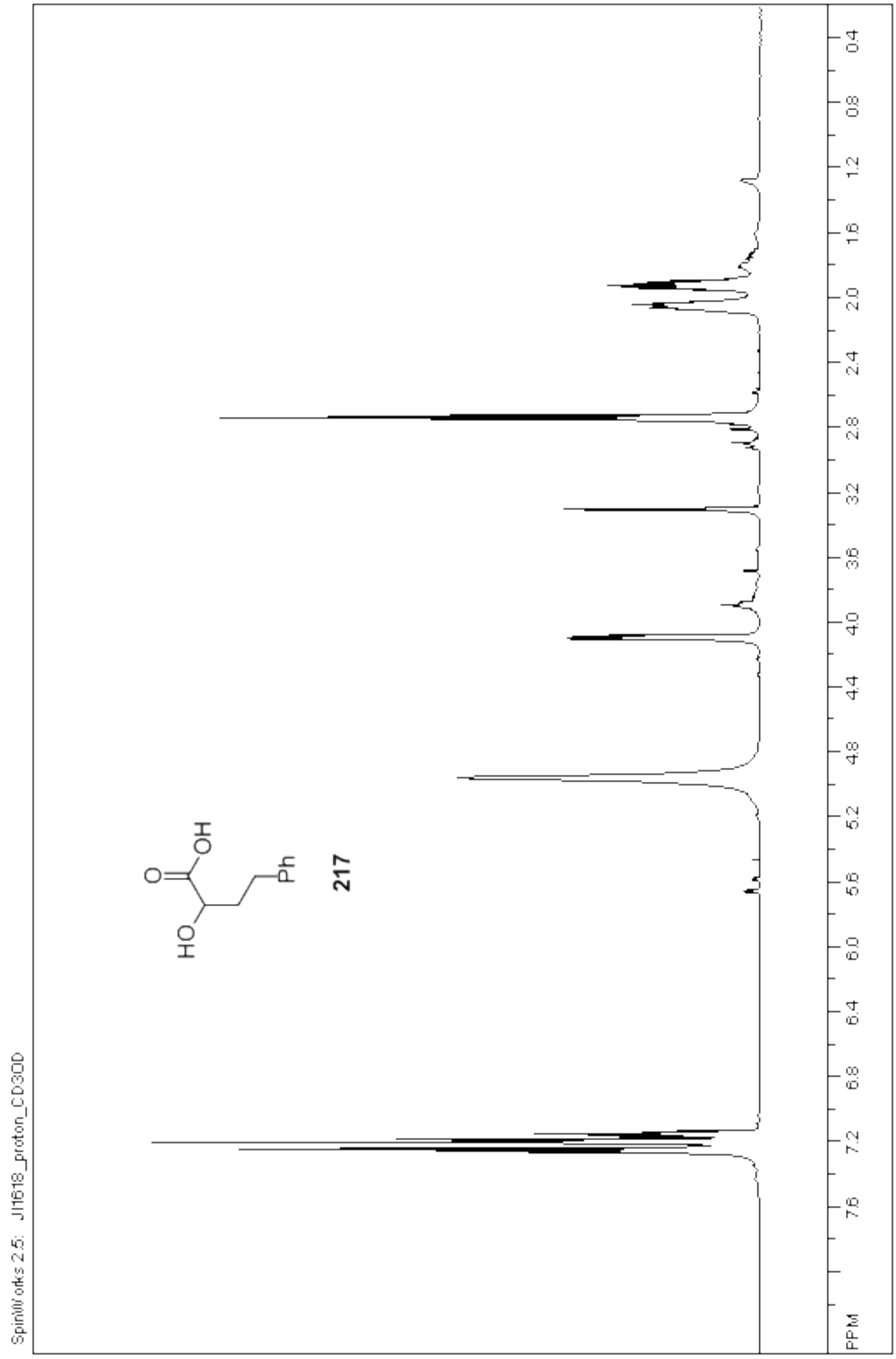

Figure A.172. ^{1}H Spectrum of **217**.

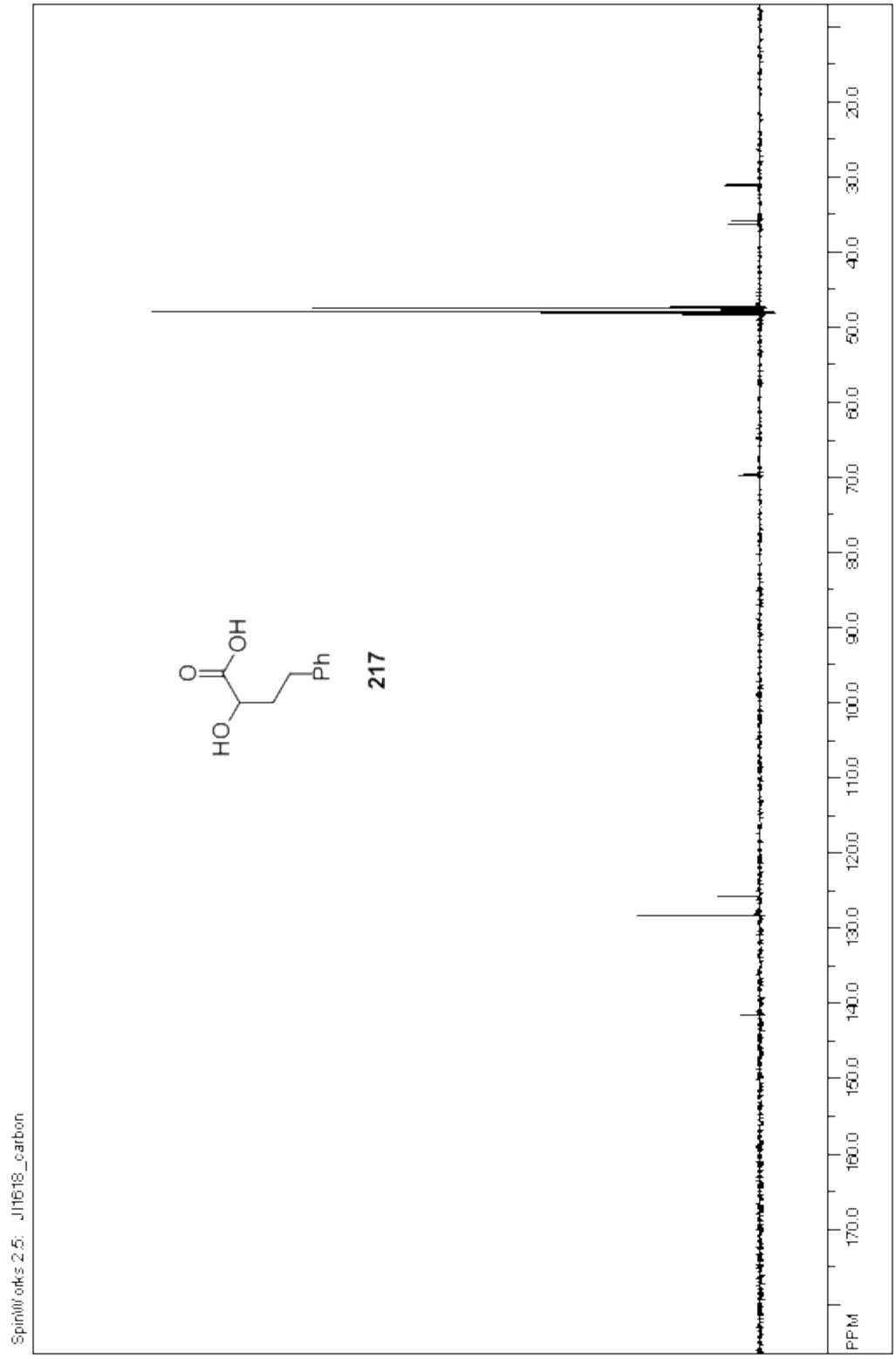

Figure A.173. ^{13}C Spectrum of **217**.

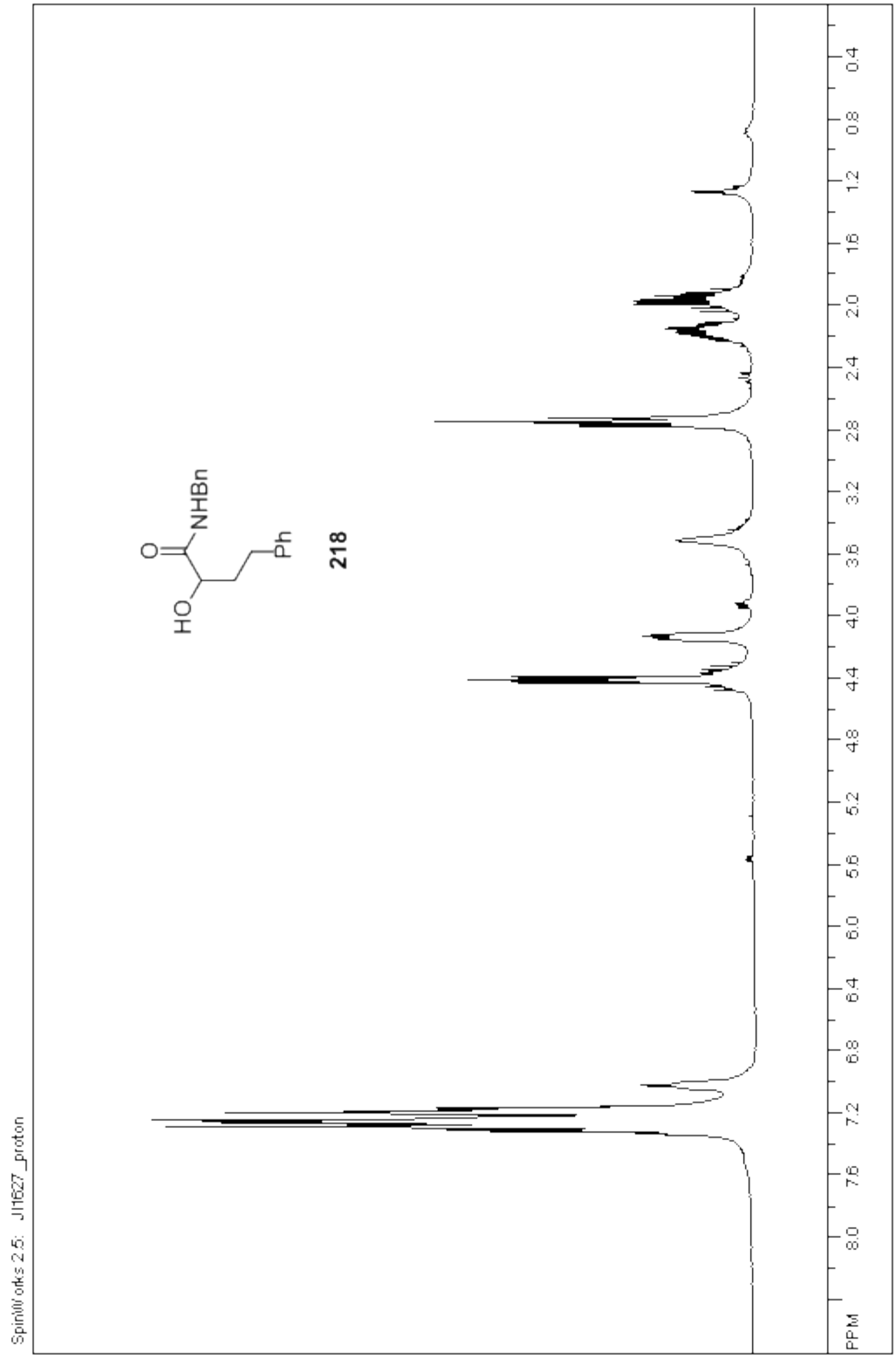

Figure A.174. ^{1}H Spectrum of **218**.

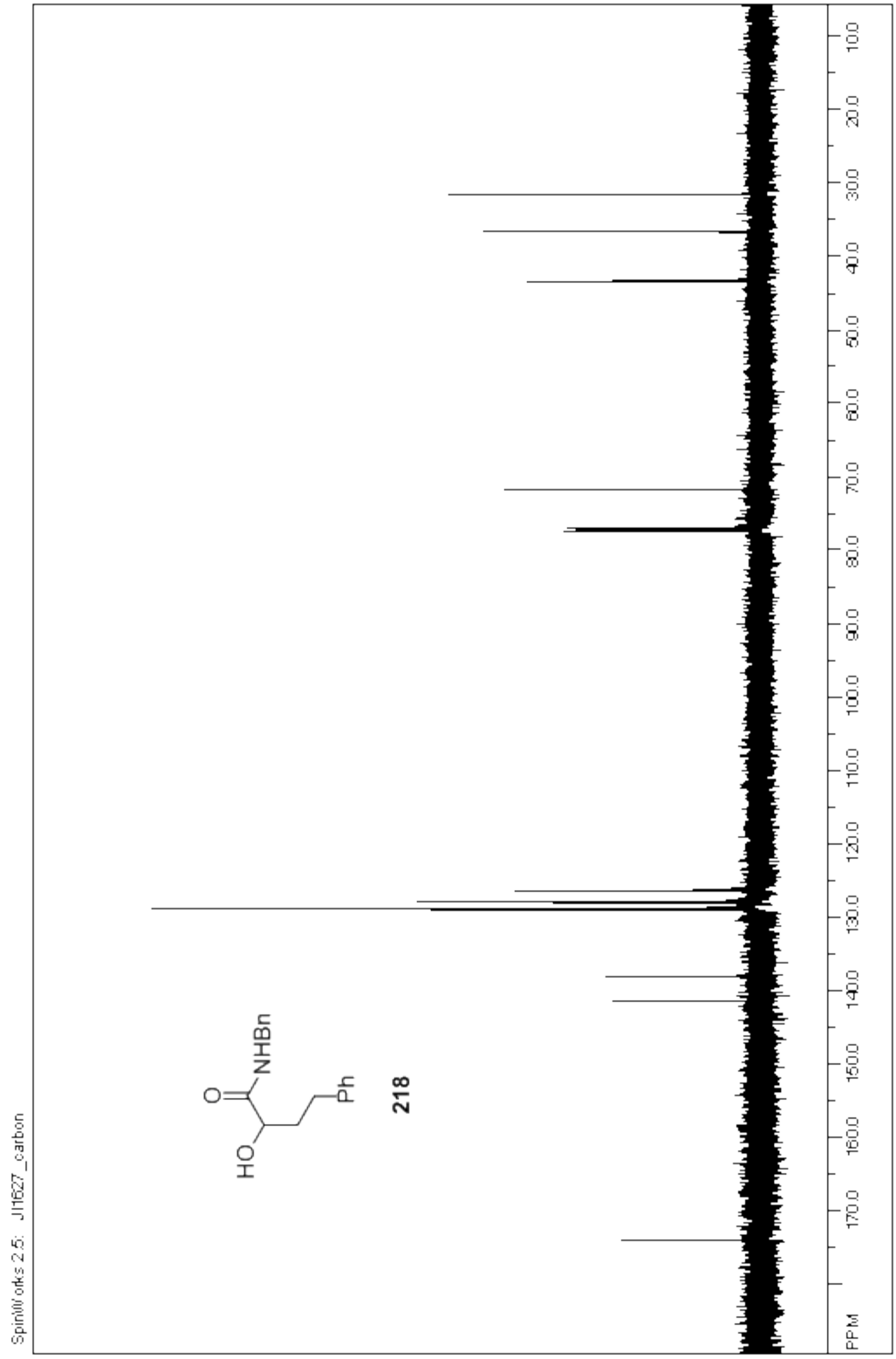

Figure A.175. ^{13}C Spectrum of **218**.

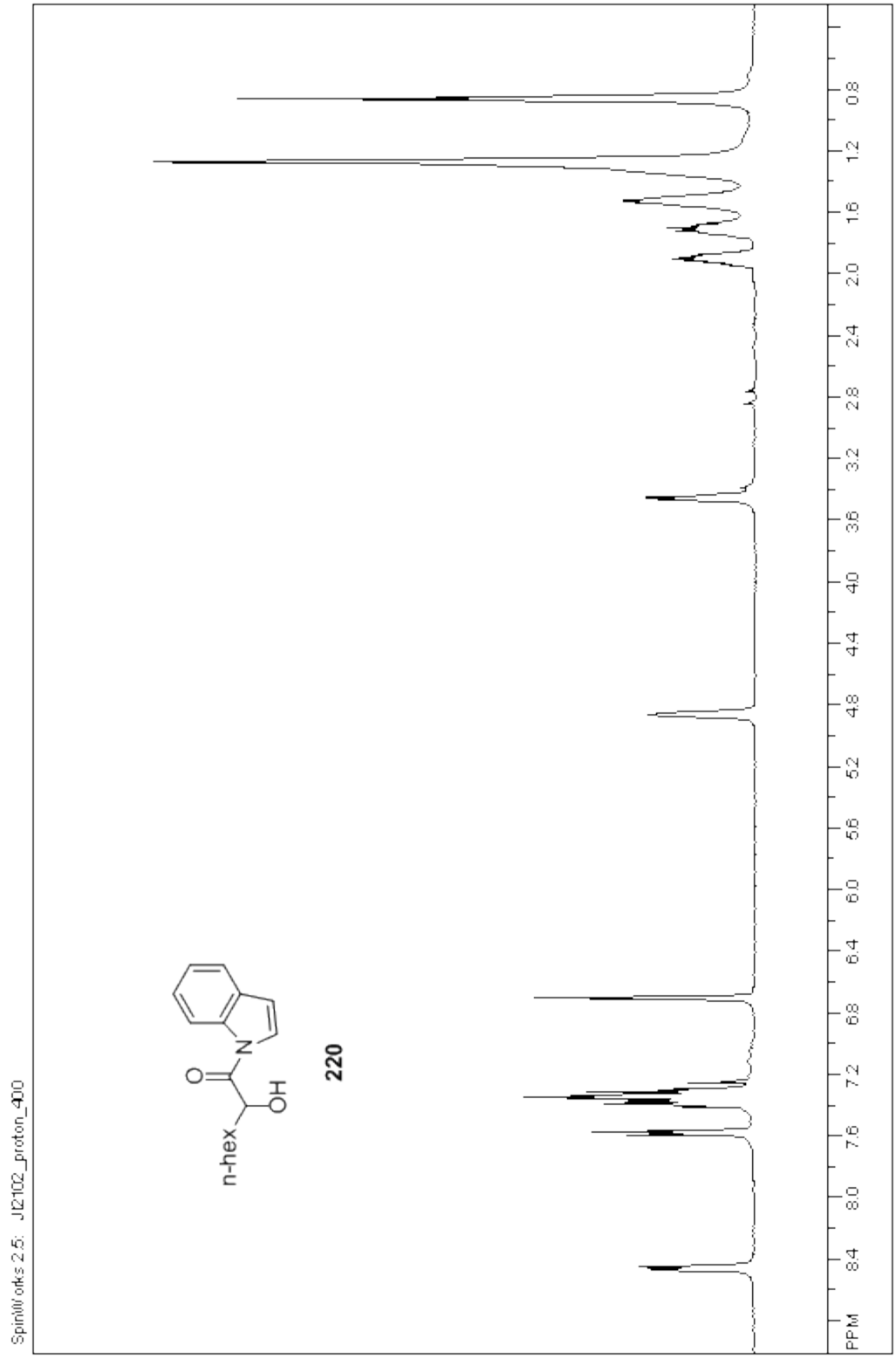

Figure A.176. ^{1}H Spectrum of **220**.

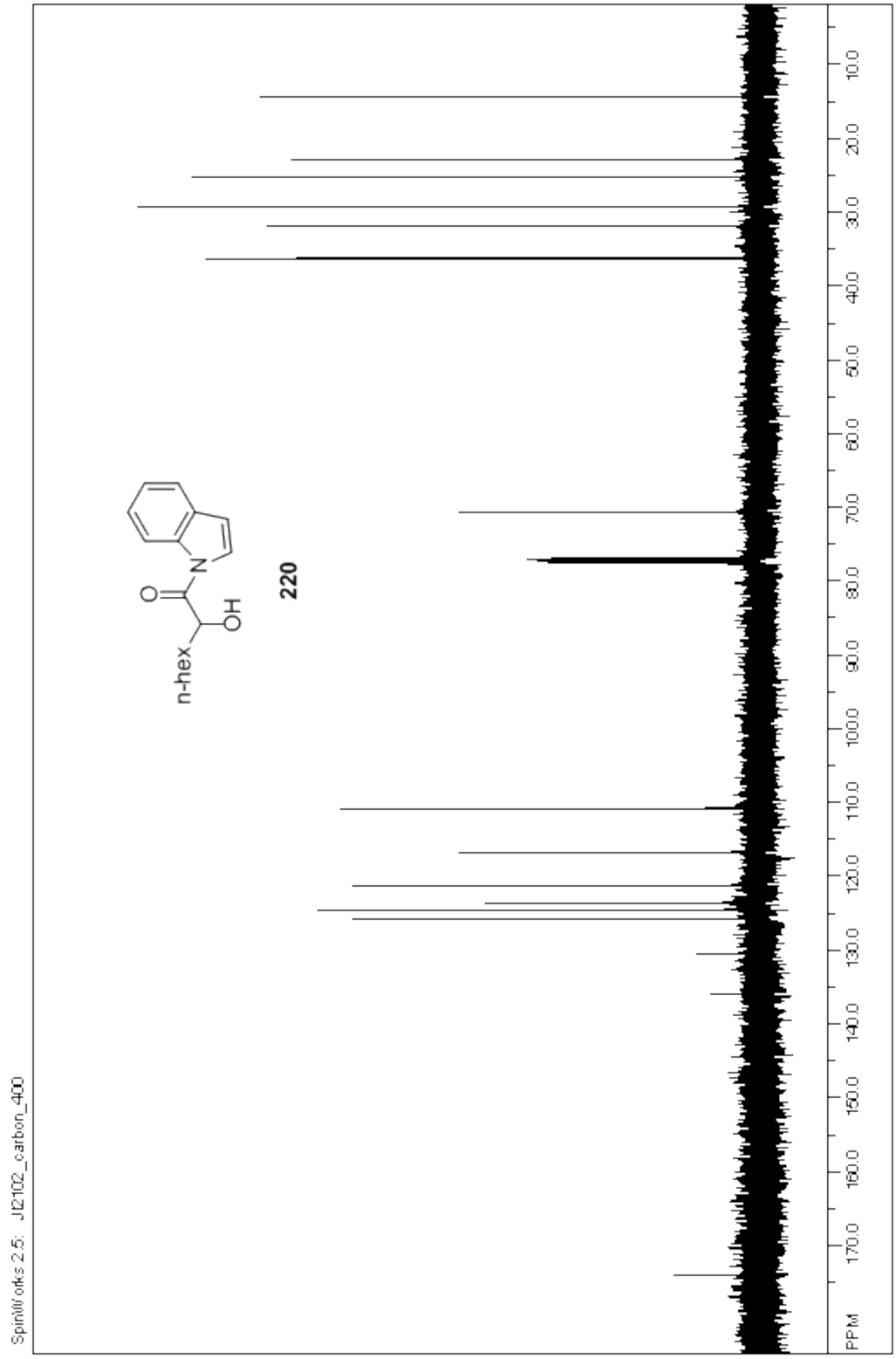

Figure A.177. ^{13}C Spectrum of **220**.

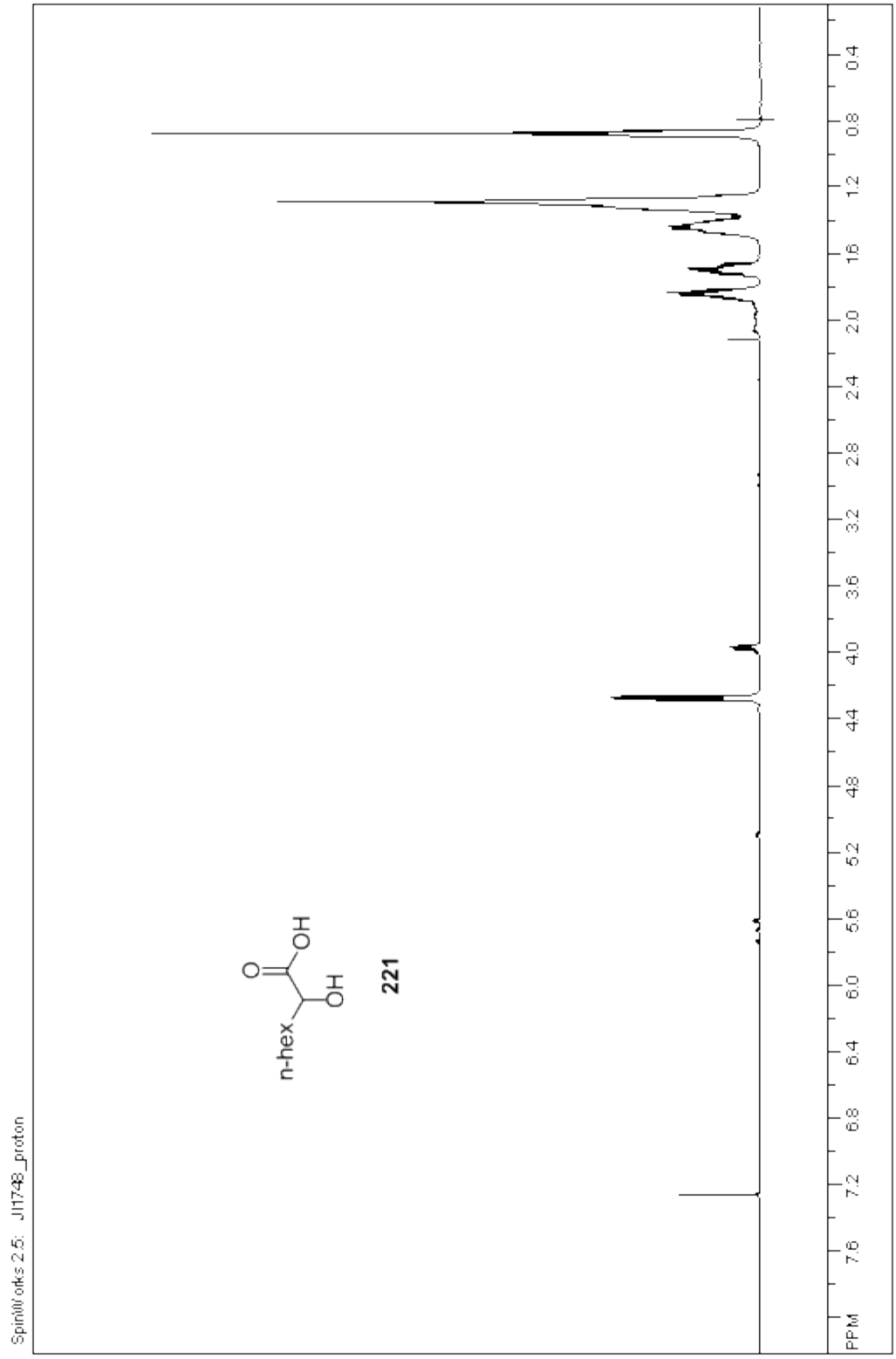

Figure A.178. ^{1}H Spectrum of **221**.

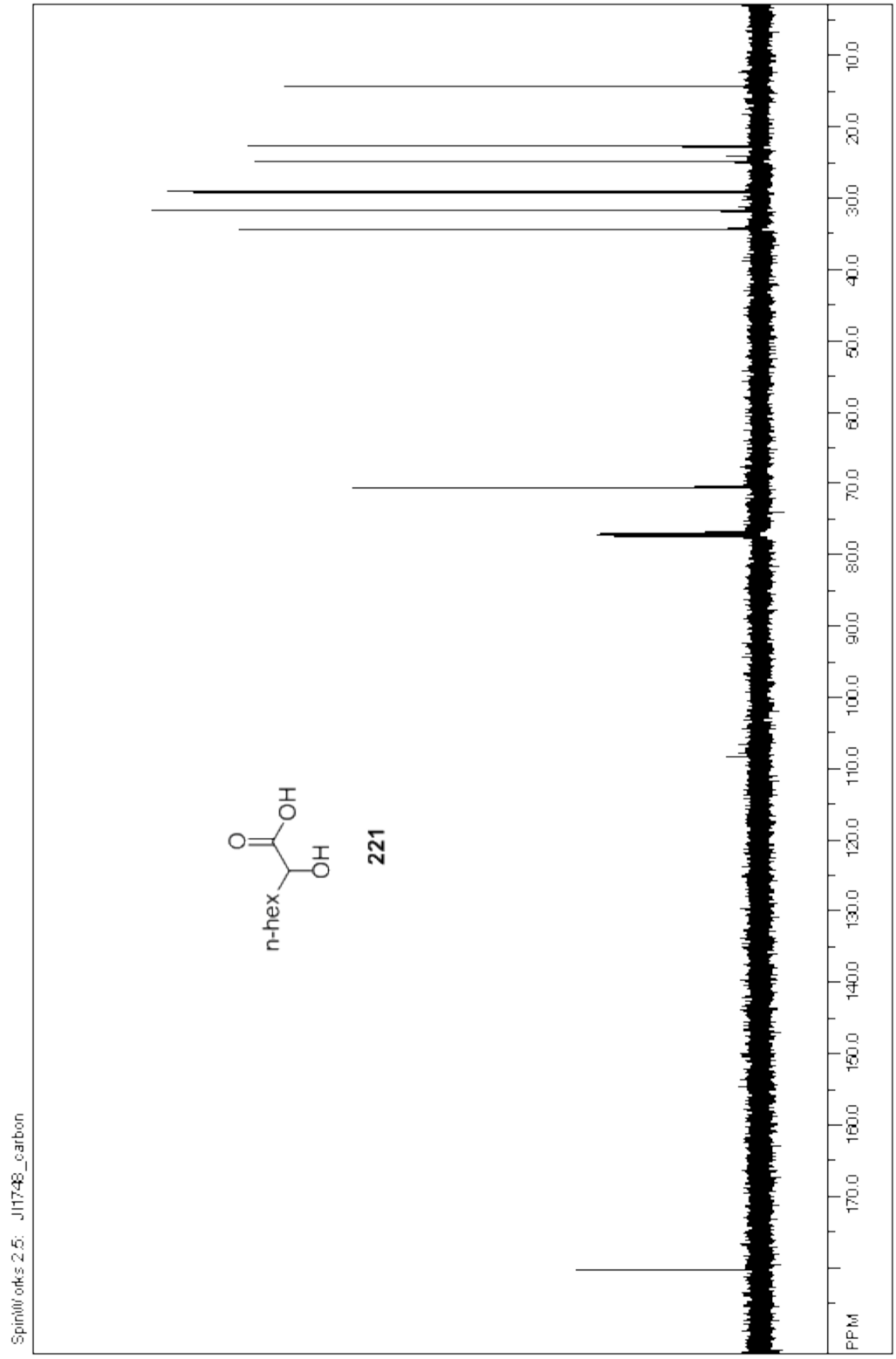

Figure A.179. ^{13}C Spectrum of **221**.

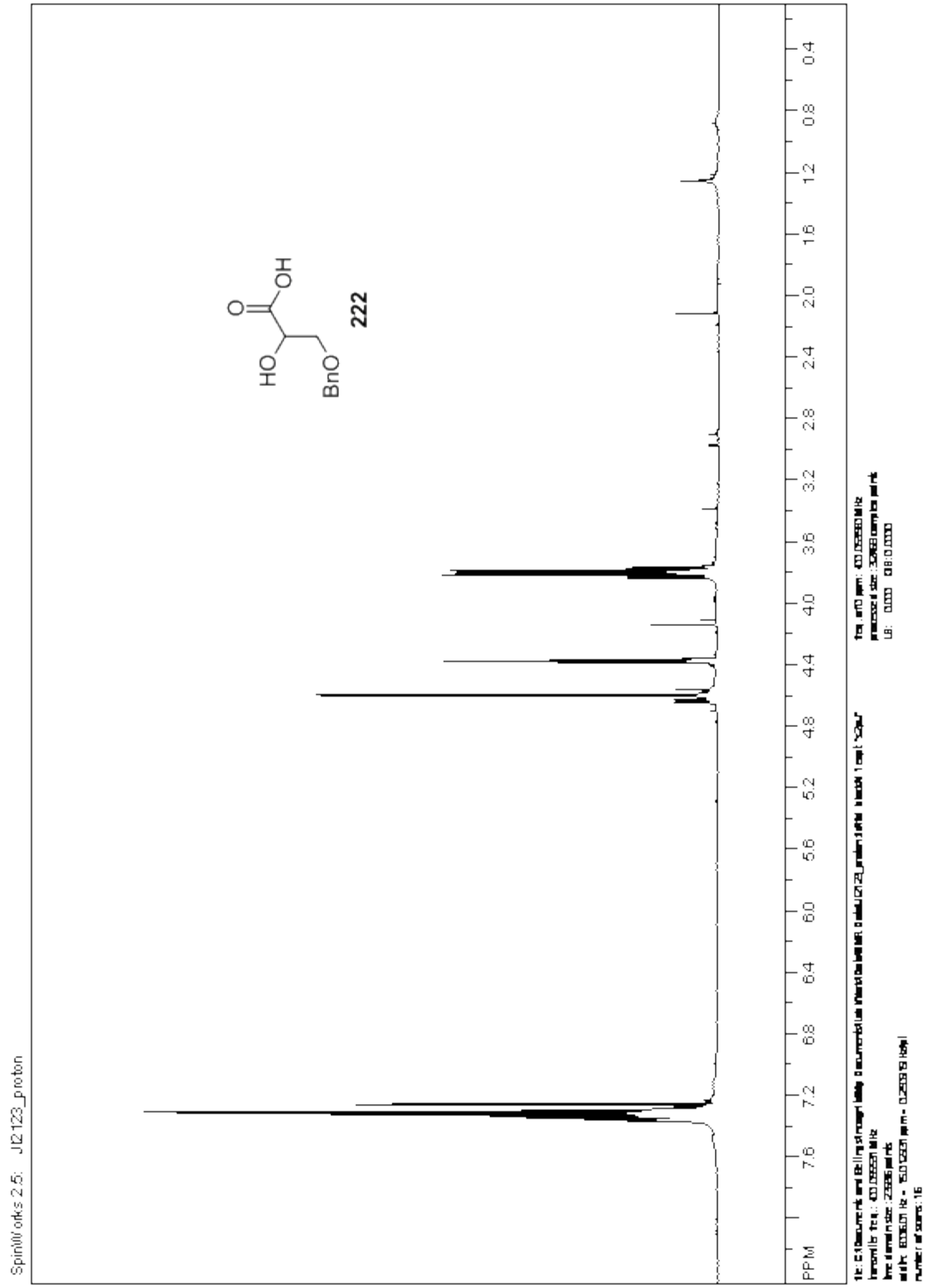

Figure A.180. ^{1}H Spectrum of **222**.

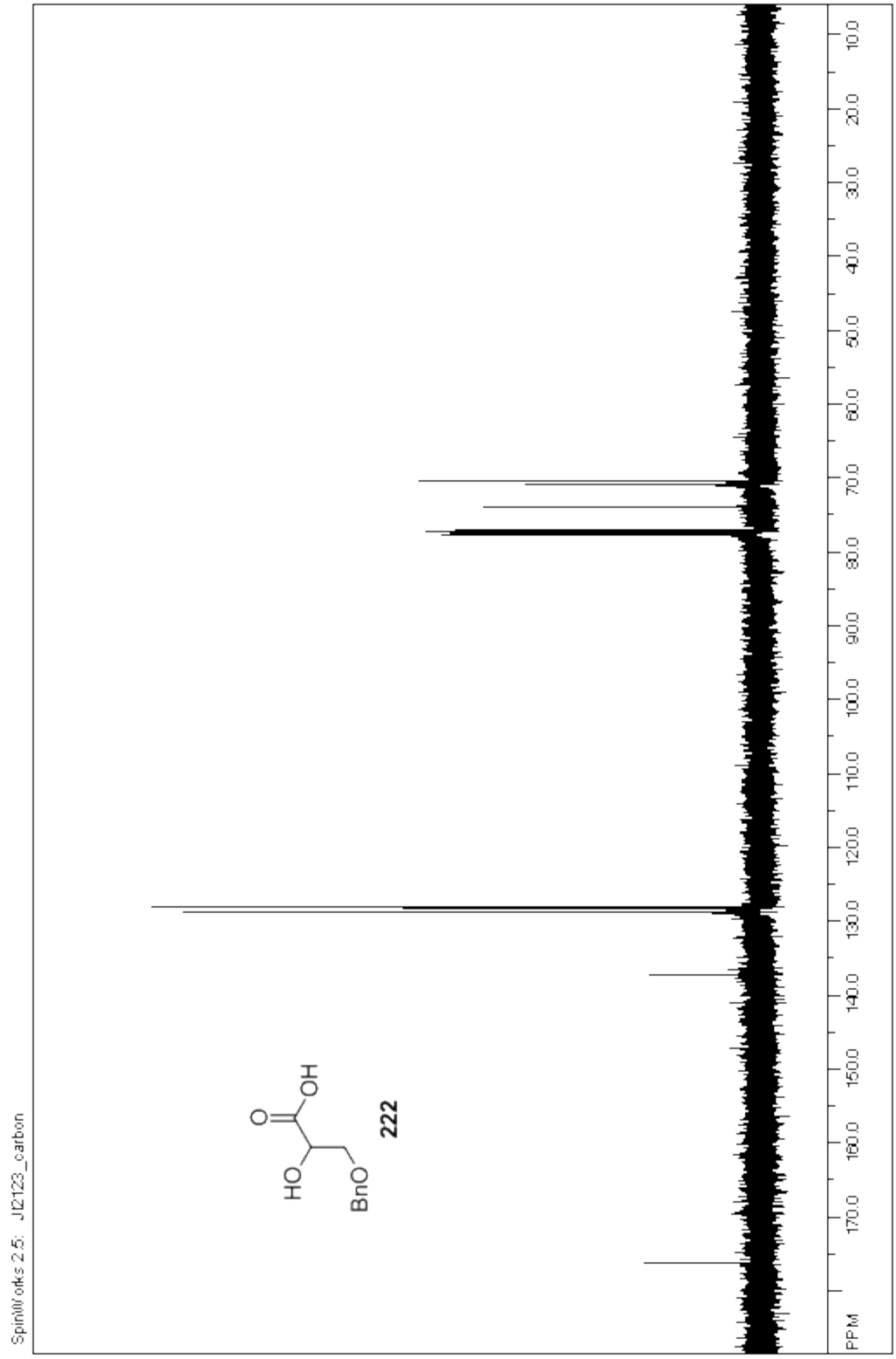

Figure A.181. ^{13}C Spectrum of **222**.

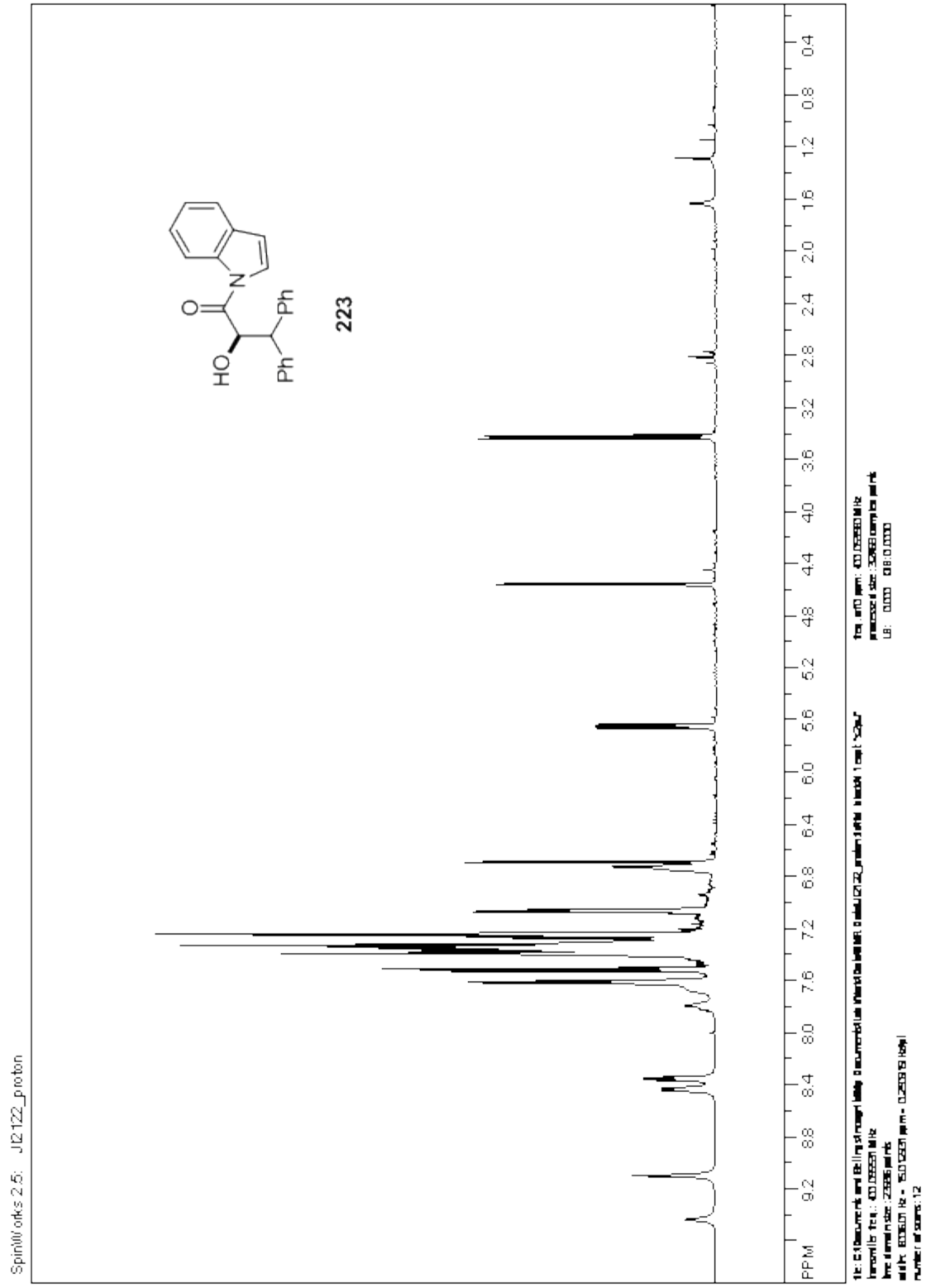

Figure A.182. ^{1}H Spectrum of **223**.

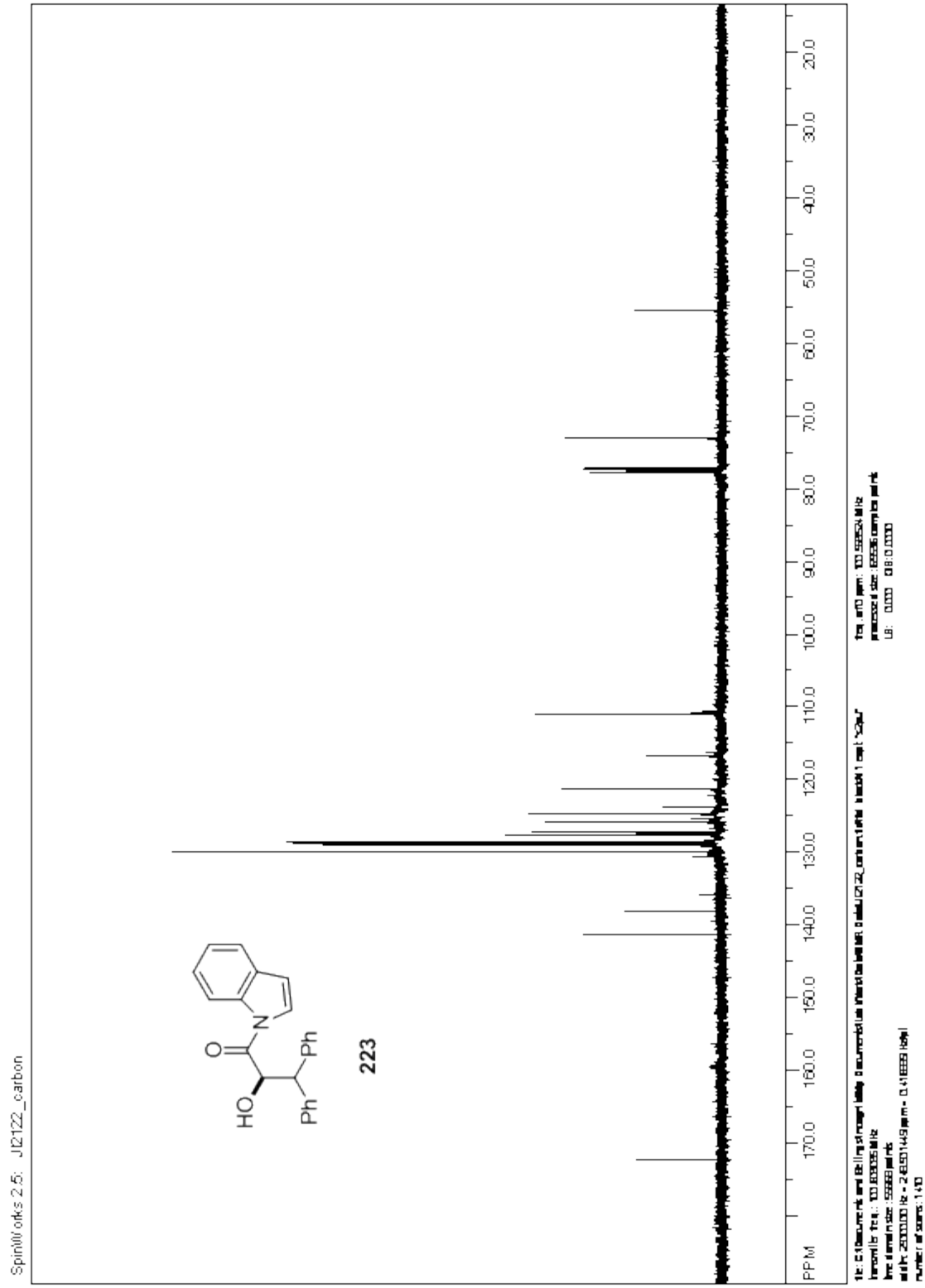

Figure A.183. ^{13}C Spectrum of **223**.

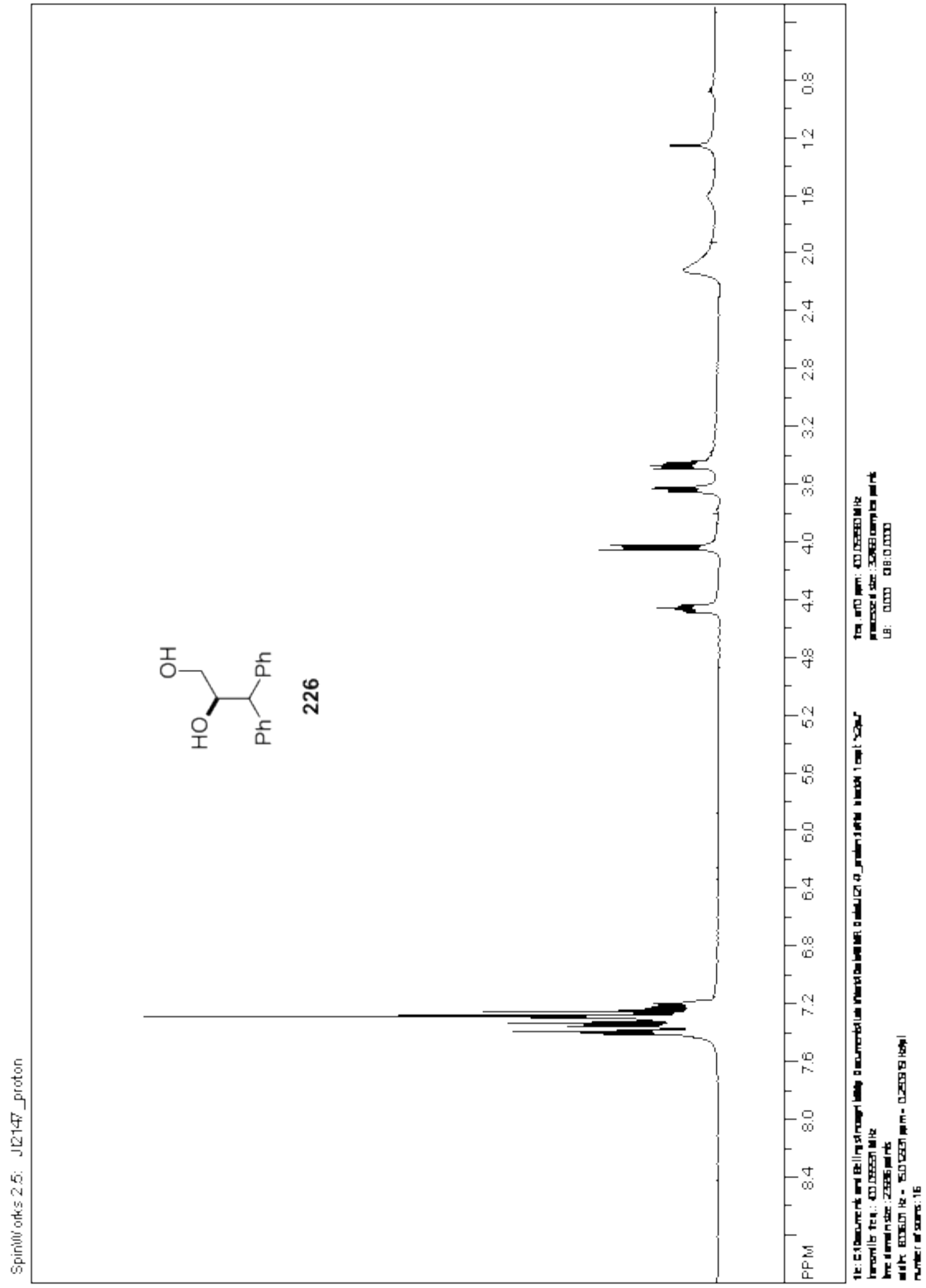

Figure A.184. ^{1}H Spectrum of **226**.

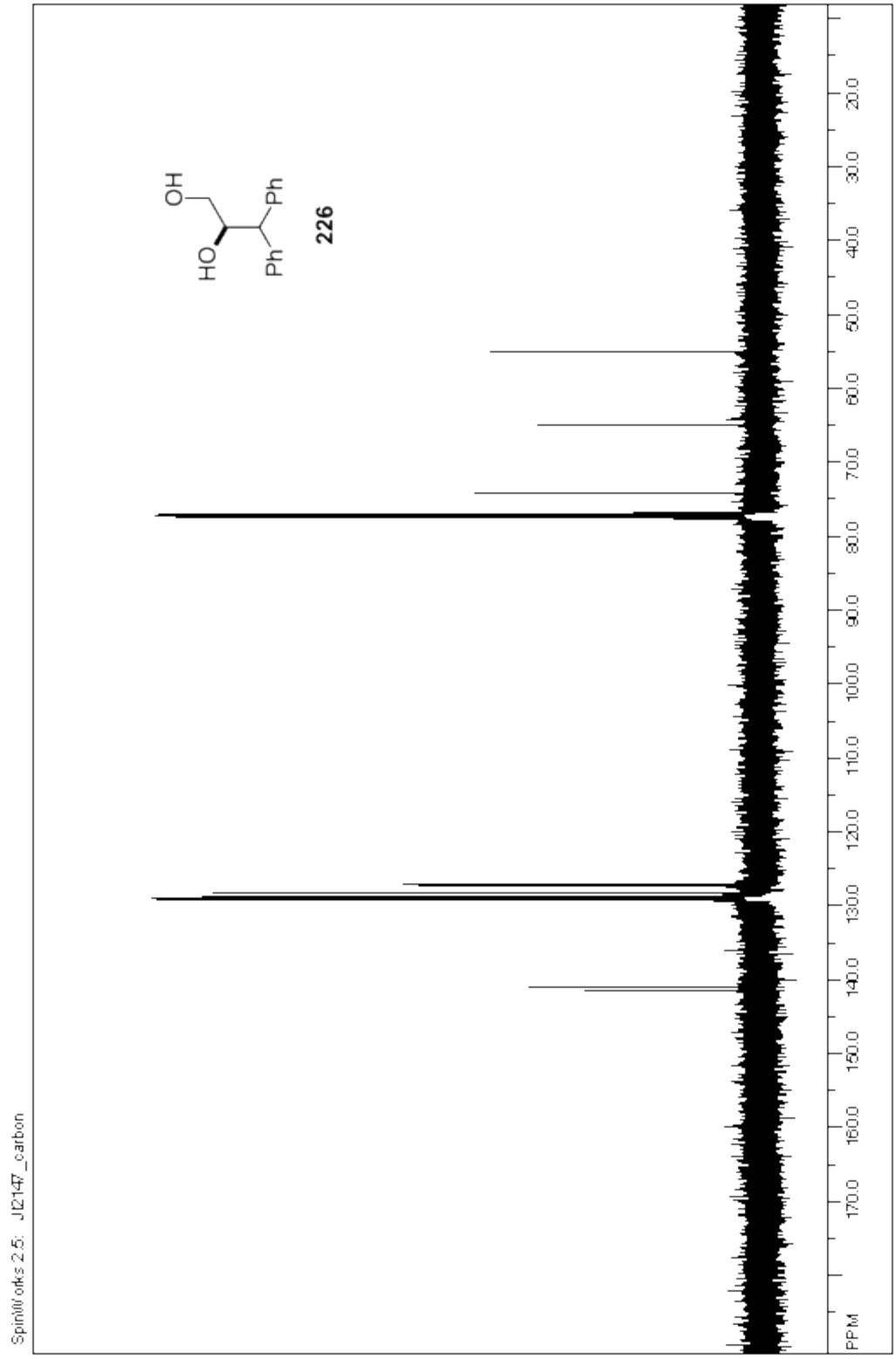

Figure A.185. ^{13}C Spectrum of **226**.

B. X-Ray Crystal Data

1. X-Ray Crystal Data for Chapter 1

A colorless plate 0.17 x 0.17 x 0.05 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 208(2) K using a single phi scan. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.3°. Data collection was 100.0% complete to 25.00° in □. A total of 16404 reflections were collected covering the indices, -12<=*h*<=22, -13<=*k*<=11, -22<=*l*<=22. 3631 reflections were found to be symmetry independent, with an R_{int} of 0.0425. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be Pbca (No. 61). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Crystal data and structure refinement for kob06.

X-ray ID	kob06	
Sample/notebook ID	JI-965-2	
Empirical formula	C22 H26 N2 O4	
Formula weight	382.45	
Temperature	208(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 18.480(2) Å	α= 90°.
	b = 11.7538(16) Å	β= 90°.
	c = 18.948(3) Å	γ = 90°.
Volume	4115.8(10) $Å^3$	
Z	8	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	1632	
Crystal size	0.17 x 0.17 x 0.05 mm^3	
Crystal color/habit	colorless plate	
Theta range for data collection	2.15 to 25.03°.	
Index ranges	-12<=h<=22, -13<=k<=11, -22<=l<=22	
Reflections collected	16404	
Independent reflections	3631 [R(int) = 0.0425]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9958 and 0.9857	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3631 / 0 / 256	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1076	
R indices (all data)	R1 = 0.0654, wR2 = 0.1151	
Largest diff. peak and hole	0.180 and -0.198 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for kob06. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3987(1)	-4262(2)	6008(1)	36(1)
C(2)	4147(1)	-5411(2)	6064(1)	46(1)
C(3)	4199(1)	-6104(2)	5480(1)	51(1)
C(4)	4087(1)	-5656(2)	4819(1)	47(1)
C(5)	3932(1)	-4513(2)	4743(1)	40(1)
C(6)	3888(1)	-3820(2)	5330(1)	33(1)
C(7)	3907(1)	-3536(2)	6661(1)	42(1)
C(8)	4568(1)	-2865(2)	6881(1)	43(1)
C(9)	5357(1)	-1422(2)	6461(1)	66(1)
C(10)	4693(2)	-2830(2)	8118(1)	72(1)
C(11)	3273(1)	-2116(2)	4851(1)	32(1)
C(12)	3309(1)	-812(2)	4861(1)	30(1)
C(13)	2890(1)	-332(2)	5501(1)	35(1)
C(14)	3303(1)	746(2)	5701(1)	30(1)
C(15)	4067(1)	481(2)	5455(1)	27(1)
C(16)	3030(1)	-328(2)	4166(1)	41(1)
C(17)	3250(1)	1106(2)	6464(1)	32(1)
C(18)	3025(1)	2189(2)	6637(1)	42(1)
C(19)	2953(1)	2520(2)	7334(1)	57(1)
C(20)	3107(1)	1781(2)	7864(1)	65(1)
C(21)	3350(2)	707(2)	7701(1)	67(1)
C(22)	3424(1)	368(2)	7004(1)	51(1)
N(1)	3781(1)	-2629(1)	5248(1)	36(1)
N(2)	4041(1)	-407(1)	5015(1)	28(1)
O(1)	4705(1)	-2050(1)	6359(1)	50(1)
O(2)	4438(1)	-2271(1)	7513(1)	61(1)
O(3)	2804(1)	-2618(1)	4525(1)	48(1)
O(4)	4617(1)	1011(1)	5618(1)	34(1)

Bond lengths [Å] and angles [°] for kob06.

C(1)-C(2)	1.386(3)	C(11)-C(12)	1.534(3)
C(1)-C(6)	1.397(3)	C(12)-N(2)	1.463(2)
C(1)-C(7)	1.510(3)	C(12)-C(16)	1.525(3)
C(2)-C(3)	1.377(3)	C(12)-C(13)	1.546(3)
C(2)-H(2)	0.9400	C(13)-C(14)	1.526(3)
C(3)-C(4)	1.375(3)	C(13)-H(13A)	0.9800
C(3)-H(3)	0.9400	C(13)-H(13B)	0.9800
C(4)-C(5)	1.381(3)	C(14)-C(17)	1.510(3)
C(4)-H(4)	0.9400	C(14)-C(15)	1.520(3)
C(5)-C(6)	1.381(3)	C(14)-H(14)	0.9900
C(5)-H(5)	0.9400	C(15)-O(4)	1.232(2)
C(6)-N(1)	1.422(2)	C(15)-N(2)	1.336(2)
C(7)-C(8)	1.513(3)	C(16)-H(16A)	0.9700
C(7)-H(7A)	0.9800	C(16)-H(16B)	0.9700
C(7)-H(7B)	0.9800	C(16)-H(16C)	0.9700
C(8)-O(1)	1.400(2)	C(17)-C(18)	1.379(3)
C(8)-O(2)	1.409(3)	C(17)-C(22)	1.379(3)
C(8)-H(8)	0.9900	C(18)-C(19)	1.384(3)
C(9)-O(1)	1.425(3)	C(18)-H(18)	0.9400
C(9)-H(9A)	0.9700	C(19)-C(20)	1.357(4)
C(9)-H(9B)	0.9700	C(19)-H(19)	0.9400
C(9)-H(9C)	0.9700	C(20)-C(21)	1.376(4)
C(10)-O(2)	1.402(3)	C(20)-H(20)	0.9400
C(10)-H(10A)	0.9700	C(21)-C(22)	1.385(3)
C(10)-H(10B)	0.9700	C(21)-H(21)	0.9400
C(10)-H(10C)	0.9700	C(22)-H(22)	0.9400
C(11)-O(3)	1.218(2)	N(1)-H(1)	0.8700
C(11)-N(1)	1.345(2)	N(2)-H(2A)	0.8700

C(2)-C(1)-C(6)	117.47(19)	C(3)-C(2)-H(2)	119.0
C(2)-C(1)-C(7)	120.51(19)	C(1)-C(2)-H(2)	119.0
C(6)-C(1)-C(7)	122.00(17)	C(4)-C(3)-C(2)	119.7(2)
C(3)-C(2)-C(1)	121.9(2)	C(4)-C(3)-H(3)	120.2

C(2)-C(3)-H(3)	120.2	O(3)-C(11)-C(12)	121.38(17)
C(3)-C(4)-C(5)	119.9(2)	N(1)-C(11)-C(12)	114.30(16)
C(3)-C(4)-H(4)	120.1	N(2)-C(12)-C(16)	111.32(15)
C(5)-C(4)-H(4)	120.1	N(2)-C(12)-C(11)	111.55(15)
C(6)-C(5)-C(4)	120.1(2)	C(16)-C(12)-C(11)	110.36(15)
C(6)-C(5)-H(5)	119.9	N(2)-C(12)-C(13)	100.81(14)
C(4)-C(5)-H(5)	119.9	C(16)-C(12)-C(13)	111.85(16)
C(5)-C(6)-C(1)	120.85(18)	C(11)-C(12)-C(13)	110.65(15)
C(5)-C(6)-N(1)	120.06(18)	C(14)-C(13)-C(12)	104.32(15)
C(1)-C(6)-N(1)	119.00(17)	C(14)-C(13)-H(13A)	110.9
C(1)-C(7)-C(8)	116.13(17)	C(12)-C(13)-H(13A)	110.9
C(1)-C(7)-H(7A)	108.3	C(14)-C(13)-H(13B)	110.9
C(8)-C(7)-H(7A)	108.3	C(12)-C(13)-H(13B)	110.9
C(1)-C(7)-H(7B)	108.3	H(13A)-C(13)-H(13B)	108.9
C(8)-C(7)-H(7B)	108.3	C(17)-C(14)-C(15)	114.30(15)
H(7A)-C(7)-H(7B)	107.4	C(17)-C(14)-C(13)	115.92(15)
O(1)-C(8)-O(2)	107.02(17)	C(15)-C(14)-C(13)	102.59(14)
O(1)-C(8)-C(7)	107.99(16)	C(17)-C(14)-H(14)	107.9
O(2)-C(8)-C(7)	110.75(18)	C(15)-C(14)-H(14)	107.9
O(1)-C(8)-H(8)	110.3	C(13)-C(14)-H(14)	107.9
O(2)-C(8)-H(8)	110.3	O(4)-C(15)-N(2)	125.62(17)
C(7)-C(8)-H(8)	110.3	O(4)-C(15)-C(14)	125.83(16)
O(1)-C(9)-H(9A)	109.5	N(2)-C(15)-C(14)	108.52(15)
O(1)-C(9)-H(9B)	109.5	C(12)-C(16)-H(16A)	109.5
H(9A)-C(9)-H(9B)	109.5	C(12)-C(16)-H(16B)	109.5
O(1)-C(9)-H(9C)	109.5	H(16A)-C(16)-H(16B)	109.5
H(9A)-C(9)-H(9C)	109.5	C(12)-C(16)-H(16C)	109.5
H(9B)-C(9)-H(9C)	109.5	H(16A)-C(16)-H(16C)	109.5
O(2)-C(10)-H(10A)	109.5	H(16B)-C(16)-H(16C)	109.5
O(2)-C(10)-H(10B)	109.5	C(18)-C(17)-C(22)	118.37(19)
H(10A)-C(10)-H(10B)	109.5	C(18)-C(17)-C(14)	120.35(18)
O(2)-C(10)-H(10C)	109.5	C(22)-C(17)-C(14)	121.28(18)
H(10A)-C(10)-H(10C)	109.5	C(17)-C(18)-C(19)	121.0(2)
H(10B)-C(10)-H(10C)	109.5	C(17)-C(18)-H(18)	119.5
O(3)-C(11)-N(1)	124.28(18)	C(19)-C(18)-H(18)	119.5

C(20)-C(19)-C(18)	120.4(2)	C(21)-C(22)-H(22)	119.9
C(20)-C(19)-H(19)	119.8	C(11)-N(1)-C(6)	126.83(16)
C(18)-C(19)-H(19)	119.8	C(11)-N(1)-H(1)	116.6
C(19)-C(20)-C(21)	119.3(2)	C(6)-N(1)-H(1)	116.6
C(19)-C(20)-H(20)	120.3	C(15)-N(2)-C(12)	114.35(15)
C(21)-C(20)-H(20)	120.3	C(15)-N(2)-H(2A)	122.8
C(20)-C(21)-C(22)	120.7(2)	C(12)-N(2)-H(2A)	122.8
C(20)-C(21)-H(21)	119.6	C(8)-O(1)-C(9)	114.28(16)
C(22)-C(21)-H(21)	119.6	C(10)-O(2)-C(8)	113.91(18)
C(17)-C(22)-C(21)	120.2(2)		
C(17)-C(22)-H(22)	119.9		

Anisotropic displacement parameters ($Å^2$ x 10^3)for kob06. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	27(1)	31(1)	50(1)	4(1)	0(1)	-4(1)
C(2)	38(1)	35(1)	63(1)	12(1)	-4(1)	-4(1)
C(3)	39(1)	28(1)	87(2)	1(1)	-3(1)	1(1)
C(4)	40(1)	34(1)	68(2)	-11(1)	3(1)	-4(1)
C(5)	36(1)	35(1)	49(1)	-3(1)	1(1)	-5(1)
C(6)	27(1)	26(1)	46(1)	2(1)	-2(1)	-4(1)
C(7)	42(1)	42(1)	43(1)	7(1)	2(1)	2(1)
C(8)	49(1)	40(1)	39(1)	4(1)	-6(1)	5(1)
C(9)	62(2)	60(2)	76(2)	19(1)	-27(1)	-21(1)
C(10)	100(2)	70(2)	45(1)	8(1)	-11(1)	-14(2)
C(11)	28(1)	33(1)	35(1)	-2(1)	-1(1)	-2(1)
C(12)	25(1)	29(1)	35(1)	1(1)	-4(1)	-1(1)
C(13)	25(1)	39(1)	41(1)	-2(1)	1(1)	1(1)
C(14)	27(1)	28(1)	36(1)	1(1)	-1(1)	4(1)
C(15)	28(1)	24(1)	30(1)	3(1)	-1(1)	0(1)
C(16)	43(1)	39(1)	42(1)	3(1)	-11(1)	3(1)
C(17)	25(1)	33(1)	38(1)	-1(1)	5(1)	-2(1)
C(18)	34(1)	37(1)	54(1)	-7(1)	2(1)	-1(1)
C(19)	53(2)	51(2)	66(2)	-24(1)	13(1)	-6(1)
C(20)	73(2)	74(2)	47(1)	-21(1)	21(1)	-30(2)
C(21)	92(2)	70(2)	38(1)	9(1)	6(1)	-18(2)
C(22)	67(2)	42(1)	43(1)	2(1)	3(1)	-1(1)
N(1)	39(1)	25(1)	45(1)	1(1)	-14(1)	-4(1)
N(2)	24(1)	27(1)	34(1)	-1(1)	1(1)	2(1)
O(1)	51(1)	46(1)	52(1)	16(1)	-20(1)	-14(1)
O(2)	81(1)	55(1)	46(1)	-4(1)	-13(1)	15(1)
O(3)	43(1)	39(1)	64(1)	-2(1)	-20(1)	-8(1)
O(4)	29(1)	32(1)	42(1)	-7(1)	2(1)	-4(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for kob06.

	x	y	z	U(eq)
H(2)	4221	-5726	6514	55
H(3)	4312	-6879	5534	61
H(4)	4115	-6127	4419	56
H(5)	3858	-4206	4291	48
H(7A)	3767	-4032	7054	51
H(7B)	3508	-3001	6583	51
H(8)	4990	-3377	6935	51
H(9A)	5332	-1016	6906	99
H(9B)	5416	-882	6079	99
H(9C)	5765	-1941	6468	99
H(10A)	4465	-3570	8155	107
H(10B)	4578	-2381	8532	107
H(10C)	5213	-2924	8084	107
H(13A)	2389	-154	5373	42
H(13B)	2888	-877	5892	42
H(14)	3115	1377	5407	36
H(16A)	3027	496	4190	61
H(16B)	2542	-601	4082	61
H(16C)	3343	-572	3784	61
H(18)	2918	2710	6275	50
H(19)	2797	3261	7442	68
H(20)	3047	2001	8337	77
H(21)	3467	197	8065	80
H(22)	3594	-367	6899	61
H(1)	4075	-2186	5479	44
H(2A)	4426	-717	4835	34

2. X-Ray Crystal Data for Chapter 2

A colorless block 0.12 x 0.12 x 0.10 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 0.5°. Data collection was 98.7% complete to 67.00° in □. A total of 11370 reflections were collected covering the indices, -7<=*h*<=8, -13<=*k*<=13, -16<=*l*<=16. 3970 reflections were found to be symmetry independent, with an R_{int} of 0.0544. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P-1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Crystal data and structure refinement for kob11.

X-ray ID	kob11	
Sample/notebook ID	JI-1236-1	
Empirical formula	C23 H28 N2 O6	
Formula weight	428.47	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.3653(4) Å	α= 95.528(4)°.
	b = 11.5496(7) Å	β= 90.616(4)°.
	c = 13.7255(9) Å	γ = 107.472(4)°.
Volume	1107.56(12) $Å^3$	
Z	2	
Density (calculated)	1.285 Mg/m^3	
Absorption coefficient	0.769 mm^{-1}	
F(000)	456	
Crystal size	0.12 x 0.12 x 0.10 mm^3	
Crystal color/habit	colorless block	
Theta range for data collection	3.24 to 68.19°.	
Index ranges	-7<=h<=8, -13<=k<=13, -16<=l<=16	
Reflections collected	11370	
Independent reflections	3970 [R(int) = 0.0544]	
Completeness to theta = 67.00°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9271 and 0.9134	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3970 / 0 / 335	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0424, wR2 = 0.1218	
R indices (all data)	R1 = 0.0519, wR2 = 0.1415	
Largest diff. peak and hole	0.229 and -0.349 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for kob11. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-3572(2)	2514(1)	4683(1)	20(1)
C(2)	-2864(3)	1390(2)	4419(2)	42(1)
C(3)	-681(2)	1863(1)	4503(1)	22(1)
C(4)	-220(2)	3243(1)	4660(1)	19(1)
C(5)	-4812(2)	2709(2)	3860(1)	30(1)
C(6)	-4714(2)	2368(1)	5614(1)	20(1)
C(7)	347(2)	377(1)	3567(1)	20(1)
C(8)	998(2)	76(1)	2568(1)	27(1)
C(9)	1235(3)	-1046(2)	2310(1)	33(1)
C(10)	1824(3)	-1359(2)	1397(2)	44(1)
C(11)	2674(9)	-592(4)	841(3)	39(1)
C(12)	2753(8)	603(4)	1105(3)	43(1)
C(13)	1988(8)	934(3)	1972(3)	32(1)
C(11A)	1711(8)	-499(4)	636(3)	35(1)
C(12A)	1197(6)	549(3)	875(3)	35(1)
C(13A)	763(7)	848(3)	1829(3)	27(1)
C(14)	-4442(2)	2994(2)	7402(1)	23(1)
C(15)	-5765(2)	1967(2)	7700(1)	28(1)
C(16)	-6372(3)	1976(2)	8651(1)	36(1)
C(17)	-5632(3)	3001(2)	9312(1)	39(1)
C(18)	-4308(3)	4014(2)	9011(1)	34(1)
C(19)	-3703(2)	4048(2)	8057(1)	24(1)
C(20)	-2310(2)	5198(2)	7763(1)	27(1)
C(22)	1843(2)	4151(2)	7160(1)	31(1)
N(1)	-1822(2)	3528(1)	4808(1)	18(1)
N(2)	-3762(2)	2995(1)	6439(1)	21(1)
O(1)	182(2)	1580(1)	3639(1)	23(1)
O(2)	1398(2)	3966(1)	4674(1)	22(1)
O(3)	-5155(2)	3842(1)	4038(1)	38(1)
O(4)	-6361(2)	1696(1)	5574(1)	27(1)

O(5)	1(2)	4335(1)	7120(1)	27(1)
C(21)	-236(2)	5207(2)	7832(1)	26(1)
O(6)	1065(2)	6347(1)	7729(1)	29(1)
C(23)	1728(6)	7090(3)	8596(2)	73(1)
C(21A)	-236(2)	5207(2)	7832(1)	26(1)
O(6A)	219(6)	5228(4)	8742(3)	29(1)
C(23A)	812(12)	6385(7)	9307(5)	44(2)

Bond lengths [Å] and angles [°] for kob11.

C(1)-N(1)	1.4531(19)	C(13)-H(13)	0.9500
C(1)-C(5)	1.521(2)	C(11A)-C(12A)	1.385(6)
C(1)-C(6)	1.532(2)	C(11A)-H(11A)	0.9500
C(1)-C(2)	1.553(2)	C(12A)-C(13A)	1.386(5)
C(2)-C(3)	1.534(2)	C(12A)-H(12A)	0.9500
C(2)-H(2A)	0.9900	C(13A)-H(13A)	0.9500
C(2)-H(2B)	0.9900	C(14)-C(15)	1.390(2)
C(3)-O(1)	1.4087(18)	C(14)-C(19)	1.402(2)
C(3)-C(4)	1.5190(19)	C(14)-N(2)	1.4184(19)
C(3)-H(3)	1.0000	C(15)-C(16)	1.384(2)
C(4)-O(2)	1.2316(19)	C(15)-H(15)	0.9500
C(4)-N(1)	1.330(2)	C(16)-C(17)	1.384(3)
C(5)-O(3)	1.404(2)	C(16)-H(16)	0.9500
C(5)-H(5A)	0.9900	C(17)-C(18)	1.381(3)
C(5)-H(5B)	0.9900	C(17)-H(17)	0.9500
C(6)-O(4)	1.2260(19)	C(18)-C(19)	1.389(2)
C(6)-N(2)	1.349(2)	C(18)-H(18)	0.9500
C(7)-O(1)	1.4249(16)	C(19)-C(20)	1.508(2)
C(7)-C(8)	1.501(2)	C(20)-C(21)	1.526(2)
C(7)-H(7A)	0.9900	C(20)-H(20A)	0.9900
C(7)-H(7B)	0.9900	C(20)-H(20B)	0.9900
C(8)-C(9)	1.373(2)	C(22)-O(5)	1.4360(19)
C(8)-C(13)	1.384(4)	C(22)-H(22A)	0.9800
C(8)-C(13A)	1.455(4)	C(22)-H(22B)	0.9800
C(9)-C(10)	1.381(2)	C(22)-H(22C)	0.9800
C(9)-H(9)	0.9500	N(1)-H(1)	0.8800
C(10)-C(11)	1.252(5)	N(2)-H(2)	0.8800
C(10)-C(11A)	1.527(6)	O(3)-H(3A)	0.8400
C(10)-H(10)	0.95(3)	O(5)-C(21)	1.3852(19)
C(11)-C(12)	1.376(6)	C(21)-O(6)	1.397(2)
C(11)-H(11)	0.9500	C(21)-H(21)	1.0000
C(12)-C(13)	1.391(5)	O(6)-C(23)	1.389(3)
C(12)-H(12)	0.9500	C(23)-H(23A)	0.9800

C(23)-H(23B)	0.9800	C(23A)-H(23D)	0.9800
C(23)-H(23C)	0.9800	C(23A)-H(23E)	0.9800
O(6A)-C(23A)	1.422(8)	C(23A)-H(23F)	0.9800

N(1)-C(1)-C(5)	109.36(13)	O(1)-C(7)-H(7A)	109.8
N(1)-C(1)-C(6)	112.70(12)	C(8)-C(7)-H(7A)	109.8
C(5)-C(1)-C(6)	108.68(12)	O(1)-C(7)-H(7B)	109.8
N(1)-C(1)-C(2)	103.45(12)	C(8)-C(7)-H(7B)	109.8
C(5)-C(1)-C(2)	111.90(14)	H(7A)-C(7)-H(7B)	108.3
C(6)-C(1)-C(2)	110.71(14)	C(9)-C(8)-C(13)	111.6(2)
C(3)-C(2)-C(1)	106.25(13)	C(9)-C(8)-C(13A)	121.24(19)
C(3)-C(2)-H(2A)	110.5	C(13)-C(8)-C(13A)	36.6(2)
C(1)-C(2)-H(2A)	110.5	C(9)-C(8)-C(7)	120.46(15)
C(3)-C(2)-H(2B)	110.5	C(13)-C(8)-C(7)	124.58(19)
C(1)-C(2)-H(2B)	110.5	C(13A)-C(8)-C(7)	115.47(18)
H(2A)-C(2)-H(2B)	108.7	C(8)-C(9)-C(10)	122.19(19)
O(1)-C(3)-C(4)	107.38(12)	C(8)-C(9)-H(9)	118.9
O(1)-C(3)-C(2)	113.02(14)	C(10)-C(9)-H(9)	118.9
C(4)-C(3)-C(2)	104.53(12)	C(11)-C(10)-C(9)	123.4(3)
O(1)-C(3)-H(3)	110.6	C(11)-C(10)-C(11A)	31.6(3)
C(4)-C(3)-H(3)	110.6	C(9)-C(10)-C(11A)	114.2(2)
C(2)-C(3)-H(3)	110.6	C(11)-C(10)-H(10)	113.5(16)
O(2)-C(4)-N(1)	126.24(14)	C(9)-C(10)-H(10)	120.5(16)
O(2)-C(4)-C(3)	124.59(13)	C(11A)-C(10)-H(10)	123.4(16)
N(1)-C(4)-C(3)	109.14(13)	C(10)-C(11)-C(12)	116.8(4)
O(3)-C(5)-C(1)	110.87(13)	C(10)-C(11)-H(11)	121.6
O(3)-C(5)-H(5A)	109.5	C(12)-C(11)-H(11)	121.6
C(1)-C(5)-H(5A)	109.5	C(11)-C(12)-C(13)	120.9(4)
O(3)-C(5)-H(5B)	109.5	C(11)-C(12)-H(12)	119.5
C(1)-C(5)-H(5B)	109.5	C(13)-C(12)-H(12)	119.5
H(5A)-C(5)-H(5B)	108.1	C(8)-C(13)-C(12)	121.9(3)
O(4)-C(6)-N(2)	124.79(14)	C(8)-C(13)-H(13)	119.0
O(4)-C(6)-C(1)	119.86(13)	C(12)-C(13)-H(13)	119.0
N(2)-C(6)-C(1)	115.34(13)	C(12A)-C(11A)-C(10)	121.9(3)
O(1)-C(7)-C(8)	109.25(12)	C(12A)-C(11A)-H(11A)	119.0

C(10)-C(11A)-H(11A)	119.0	C(21)-C(20)-H(20A)	108.8
C(11A)-C(12A)-C(13A)	120.3(4)	C(19)-C(20)-H(20B)	108.8
C(11A)-C(12A)-H(12A)	119.9	C(21)-C(20)-H(20B)	108.8
C(13A)-C(12A)-H(12A)	119.9	H(20A)-C(20)-H(20B)	107.7
C(12A)-C(13A)-C(8)	117.8(3)	O(5)-C(22)-H(22A)	109.5
C(12A)-C(13A)-H(13A)	121.1	O(5)-C(22)-H(22B)	109.5
C(8)-C(13A)-H(13A)	121.1	H(22A)-C(22)-H(22B)	109.5
C(15)-C(14)-C(19)	120.72(15)	O(5)-C(22)-H(22C)	109.5
C(15)-C(14)-N(2)	121.06(15)	H(22A)-C(22)-H(22C)	109.5
C(19)-C(14)-N(2)	118.20(14)	H(22B)-C(22)-H(22C)	109.5
C(16)-C(15)-C(14)	120.08(16)	C(4)-N(1)-C(1)	115.83(12)
C(16)-C(15)-H(15)	120.0	C(4)-N(1)-H(1)	122.1
C(14)-C(15)-H(15)	120.0	C(1)-N(1)-H(1)	122.1
C(17)-C(16)-C(15)	119.99(17)	C(6)-N(2)-C(14)	127.31(13)
C(17)-C(16)-H(16)	120.0	C(6)-N(2)-H(2)	116.3
C(15)-C(16)-H(16)	120.0	C(14)-N(2)-H(2)	116.3
C(18)-C(17)-C(16)	119.51(17)	C(3)-O(1)-C(7)	112.49(11)
C(18)-C(17)-H(17)	120.2	C(5)-O(3)-H(3A)	109.5
C(16)-C(17)-H(17)	120.2	C(21)-O(5)-C(22)	114.25(13)
C(17)-C(18)-C(19)	122.05(17)	O(5)-C(21)-O(6)	110.54(14)
C(17)-C(18)-H(18)	119.0	O(5)-C(21)-C(20)	107.90(13)
C(19)-C(18)-H(18)	119.0	O(6)-C(21)-C(20)	113.40(15)
C(18)-C(19)-C(14)	117.62(16)	O(5)-C(21)-H(21)	108.3
C(18)-C(19)-C(20)	119.60(15)	O(6)-C(21)-H(21)	108.3
C(14)-C(19)-C(20)	122.79(14)	C(20)-C(21)-H(21)	108.3
C(19)-C(20)-C(21)	113.70(13)	C(23)-O(6)-C(21)	115.66(19)
C(19)-C(20)-H(20A)	108.8		

Anisotropic displacement parameters ($Å^2$ x 10^3)for kob11. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	12(1)	13(1)	32(1)	-3(1)	4(1)	1(1)
C(2)	17(1)	18(1)	87(2)	-10(1)	12(1)	3(1)
C(3)	16(1)	13(1)	36(1)	2(1)	8(1)	3(1)
C(4)	16(1)	15(1)	27(1)	2(1)	3(1)	4(1)
C(5)	16(1)	44(1)	22(1)	0(1)	3(1)	-1(1)
C(6)	16(1)	15(1)	28(1)	6(1)	1(1)	4(1)
C(7)	20(1)	12(1)	28(1)	1(1)	3(1)	5(1)
C(8)	31(1)	18(1)	26(1)	-1(1)	4(1)	0(1)
C(9)	37(1)	35(1)	34(1)	-1(1)	3(1)	21(1)
C(10)	38(1)	51(1)	41(1)	-18(1)	0(1)	18(1)
C(11)	51(3)	45(3)	24(2)	-8(2)	1(2)	22(2)
C(12)	70(4)	37(2)	24(2)	6(2)	11(2)	19(2)
C(13)	47(3)	25(2)	23(2)	1(1)	1(2)	12(2)
C(11A)	36(3)	42(2)	24(2)	-3(2)	7(2)	10(2)
C(12A)	47(3)	28(2)	28(2)	6(1)	14(2)	7(2)
C(13A)	31(3)	22(2)	28(2)	4(1)	9(2)	6(2)
C(14)	17(1)	29(1)	26(1)	9(1)	2(1)	7(1)
C(15)	20(1)	32(1)	30(1)	11(1)	0(1)	1(1)
C(16)	23(1)	46(1)	33(1)	18(1)	3(1)	-2(1)
C(17)	28(1)	58(1)	26(1)	11(1)	6(1)	2(1)
C(18)	25(1)	42(1)	30(1)	2(1)	6(1)	5(1)
C(19)	17(1)	28(1)	28(1)	6(1)	3(1)	7(1)
C(20)	28(1)	22(1)	31(1)	3(1)	8(1)	8(1)
C(22)	19(1)	38(1)	39(1)	14(1)	5(1)	10(1)
N(1)	13(1)	11(1)	28(1)	-1(1)	3(1)	2(1)
N(2)	15(1)	22(1)	26(1)	6(1)	3(1)	2(1)
O(1)	27(1)	13(1)	31(1)	5(1)	7(1)	8(1)
O(2)	13(1)	16(1)	37(1)	3(1)	3(1)	2(1)
O(3)	20(1)	51(1)	52(1)	32(1)	12(1)	14(1)
O(4)	17(1)	28(1)	30(1)	9(1)	1(1)	-3(1)

O(5)	19(1)	25(1)	36(1)	-1(1)	-2(1)	8(1)
C(21)	26(1)	23(1)	26(1)	3(1)	5(1)	0(1)
O(6)	27(1)	23(1)	31(1)	2(1)	4(1)	-2(1)
C(23)	94(3)	44(2)	46(2)	-13(2)	7(2)	-26(2)
C(21A)	26(1)	23(1)	26(1)	3(1)	5(1)	0(1)
O(6A)	32(3)	27(2)	27(2)	5(2)	-7(2)	5(2)
C(23A)	57(5)	37(4)	36(4)	-12(3)	-25(3)	15(3)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for kob11.

	x	y	z	U(eq)
H(2A)	-3355	767	4877	51
H(2B)	-3302	1020	3743	51
H(3)	-190	1553	5074	26
H(5A)	-4171	2675	3232	36
H(5B)	-6040	2047	3803	36
H(7A)	-900	-216	3675	24
H(7B)	1276	324	4074	24
H(9)	985	-1627	2775	40
H(11)	3238	-823	265	47
H(12)	3338	1209	690	51
H(13)	2149	1773	2160	38
H(11A)	2001	-689	-22	42
H(12A)	1141	1065	385	42
H(13A)	327	1534	1994	33
H(15)	-6254	1257	7250	34
H(16)	-7296	1280	8850	43
H(17)	-6031	3007	9968	47
H(18)	-3796	4710	9472	40
H(20A)	-2452	5905	8188	32
H(20B)	-2632	5298	7080	32
H(22A)	2821	4905	7036	46
H(22B)	1876	3491	6662	46
H(22C)	2088	3932	7810	46
H(1)	-1823	4284	4972	22
H(2)	-2588	3455	6373	26
H(3A)	-6221	3742	4287	57
H(21)	14	4964	8488	31
H(23A)	644	7194	8963	109
H(23B)	2542	7889	8445	109
H(23C)	2465	6712	8990	109

H(21A)	533	6012	7630	31
H(23D)	1912	6924	9012	67
H(23E)	1168	6284	9977	67
H(23F)	-234	6747	9323	67
H(10)	1960(40)	-2150(30)	1233(18)	68(8)

3. X-Ray Crystal Data for Chapter 3

A colorless plate 0.12 x 0.10 x 0.06 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 97.8% complete to 67.00° in θ. A total of 5938 reflections were collected covering the indices, -8<=*h*<=8, -7<=*k*<=7, -17<=*l*<=18. 2537 reflections were found to be symmetry independent, with an R_{int} of 0.0173. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2(1) (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Absolute Configuration of C10 ... S
Absolute Configuration of C13 ... S

Crystal data and structure refinement for kob13.

X-ray ID	kob13	
Sample/notebook ID	JI-1712-1	
Empirical formula	C16 H15 Cl N2 O4	
Formula weight	334.75	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.3355(4) Å	α= 90°.
	b = 6.7551(4) Å	β= 99.371(2)°.
	c = 15.6069(9) Å	γ = 90°.
Volume	763.03(8) $Å^3$	
Z	2	
Density (calculated)	1.457 Mg/m^3	
Absorption coefficient	2.425 mm^{-1}	
F(000)	348	
Crystal size	0.12 x 0.10 x 0.06 mm^3	
Crystal color/habit	colorless plate	
Theta range for data collection	2.87 to 68.25°.	
Index ranges	-8<=h<=8, -7<=k<=7, -17<=l<=18	
Reflections collected	5938	
Independent reflections	2537 [R(int) = 0.0173]	
Completeness to theta = 67.00°	97.8 %	
Absorption correction	Analytical	
Max. and min. transmission	0.8682 and 0.7596	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2537 / 1 / 210	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0218, wR2 = 0.0553	
R indices (all data)	R1 = 0.0222, wR2 = 0.0555	
Absolute structure parameter	0.086(10)	
Extinction coefficient	0.0074(6)	
Largest diff. peak and hole	0.159 and -0.190 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for kob13. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-4141(2)	3280(2)	7325(1)	19(1)
C(2)	-4362(2)	1989(3)	6662(1)	21(1)
C(3)	-3534(2)	2839(3)	5970(1)	20(1)
C(4)	-3343(2)	2146(3)	5143(1)	26(1)
C(5)	-2428(2)	3337(3)	4627(1)	31(1)
C(6)	-1704(2)	5161(3)	4925(1)	30(1)
C(7)	-1872(2)	5886(3)	5741(1)	24(1)
C(8)	-2800(2)	4686(3)	6254(1)	19(1)
C(9)	-2723(2)	6681(2)	7597(1)	16(1)
C(10)	-3264(2)	6772(2)	8515(1)	15(1)
C(11)	-2132(2)	5304(2)	9132(1)	18(1)
C(12)	-5386(2)	6494(2)	8514(1)	17(1)
C(13)	-6089(2)	8479(2)	8776(1)	16(1)
C(14)	-4379(2)	9748(3)	9052(1)	16(1)
C(15)	-8565(2)	10598(3)	8137(1)	17(1)
C(16)	-9283(2)	11765(3)	7340(1)	23(1)
N(1)	-3186(2)	4984(2)	7108(1)	17(1)
N(2)	-2914(2)	8767(2)	8850(1)	16(1)
O(1)	-1914(2)	8036(2)	7324(1)	24(1)
O(2)	-7092(1)	9480(2)	8017(1)	18(1)
O(3)	-4394(2)	11411(2)	9360(1)	21(1)
O(4)	-9194(1)	10625(2)	8803(1)	19(1)
Cl(1)	293(1)	5632(1)	9147(1)	23(1)

Bond lengths [Å] and angles [°] for kob13.

C(1)-C(2)	1.342(2)	C(10)-C(11)	1.530(2)
C(1)-N(1)	1.417(2)	C(10)-C(12)	1.5677(18)
C(1)-H(1)	0.9500	C(11)-Cl(1)	1.7895(14)
C(2)-C(3)	1.442(2)	C(11)-H(11A)	0.9900
C(2)-H(2)	0.9500	C(11)-H(11B)	0.9900
C(3)-C(8)	1.401(3)	C(12)-C(13)	1.516(2)
C(3)-C(4)	1.402(2)	C(12)-H(12A)	0.9900
C(4)-C(5)	1.386(3)	C(12)-H(12B)	0.9900
C(4)-H(4)	0.9500	C(13)-O(2)	1.4547(17)
C(5)-C(6)	1.391(3)	C(13)-C(14)	1.523(2)
C(5)-H(5)	0.9500	C(13)-H(13)	1.0000
C(6)-C(7)	1.389(2)	C(14)-O(3)	1.223(2)
C(6)-H(6)	0.9500	C(14)-N(2)	1.343(2)
C(7)-C(8)	1.393(2)	C(15)-O(4)	1.2049(17)
C(7)-H(7)	0.9500	C(15)-O(2)	1.3555(19)
C(8)-N(1)	1.4217(18)	C(15)-C(16)	1.494(2)
C(9)-O(1)	1.206(2)	C(16)-H(16A)	0.9800
C(9)-N(1)	1.389(2)	C(16)-H(16B)	0.9800
C(9)-C(10)	1.5485(19)	C(16)-H(16C)	0.9800
C(10)-N(2)	1.453(2)	N(2)-H(2A)	0.8800

C(2)-C(1)-N(1)	110.24(13)
C(2)-C(1)-H(1)	124.9
N(1)-C(1)-H(1)	124.9
C(1)-C(2)-C(3)	107.82(15)
C(1)-C(2)-H(2)	126.1
C(3)-C(2)-H(2)	126.1
C(8)-C(3)-C(4)	119.82(16)
C(8)-C(3)-C(2)	107.75(13)
C(4)-C(3)-C(2)	132.42(17)
C(5)-C(4)-C(3)	118.13(18)
C(5)-C(4)-H(4)	120.9
C(3)-C(4)-H(4)	120.9
C(4)-C(5)-C(6)	120.97(15)
C(4)-C(5)-H(5)	119.5
C(6)-C(5)-H(5)	119.5
C(7)-C(6)-C(5)	122.18(16)
C(7)-C(6)-H(6)	118.9
C(5)-C(6)-H(6)	118.9
C(6)-C(7)-C(8)	116.52(17)
C(6)-C(7)-H(7)	121.7
C(8)-C(7)-H(7)	121.7
C(7)-C(8)-C(3)	122.37(14)
C(7)-C(8)-N(1)	130.33(15)
C(3)-C(8)-N(1)	107.30(13)
O(1)-C(9)-N(1)	121.55(13)
O(1)-C(9)-C(10)	120.76(14)
N(1)-C(9)-C(10)	117.69(13)
N(2)-C(10)-C(11)	109.19(11)
N(2)-C(10)-C(9)	108.23(12)
C(11)-C(10)-C(9)	111.23(12)
N(2)-C(10)-C(12)	103.23(12)
C(11)-C(10)-C(12)	111.09(11)
C(9)-C(10)-C(12)	113.47(11)
C(10)-C(11)-Cl(1)	111.35(10)
C(10)-C(11)-H(11A)	109.4

Cl(1)-C(11)-H(11A)	109.4
C(10)-C(11)-H(11B)	109.4
Cl(1)-C(11)-H(11B)	109.4
H(11A)-C(11)-H(11B)	108.0
C(13)-C(12)-C(10)	105.95(12)
C(13)-C(12)-H(12A)	110.5
C(10)-C(12)-H(12A)	110.5
C(13)-C(12)-H(12B)	110.5
C(10)-C(12)-H(12B)	110.5
H(12A)-C(12)-H(12B)	108.7
O(2)-C(13)-C(12)	109.94(11)
O(2)-C(13)-C(14)	104.65(12)
C(12)-C(13)-C(14)	105.88(12)
O(2)-C(13)-H(13)	112.0
C(12)-C(13)-H(13)	112.0
C(14)-C(13)-H(13)	112.0
O(3)-C(14)-N(2)	127.22(15)
O(3)-C(14)-C(13)	124.67(15)
N(2)-C(14)-C(13)	108.01(14)
O(4)-C(15)-O(2)	123.56(14)
O(4)-C(15)-C(16)	125.32(15)
O(2)-C(15)-C(16)	111.13(11)
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(9)-N(1)-C(1)	128.74(12)
C(9)-N(1)-C(8)	124.34(13)
C(1)-N(1)-C(8)	106.90(13)
C(14)-N(2)-C(10)	116.17(13)
C(14)-N(2)-H(2A)	121.9
C(10)-N(2)-H(2A)	121.9
C(15)-O(2)-C(13)	117.16(10)

Anisotropic displacement parameters ($Å^2 x\ 10^3$)for kob13. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	16(1)	22(1)	0(1)	3(1)	0(1)
C(2)	17(1)	19(1)	27(1)	-2(1)	1(1)	0(1)
C(3)	16(1)	23(1)	21(1)	-2(1)	0(1)	4(1)
C(4)	22(1)	31(1)	24(1)	-8(1)	0(1)	4(1)
C(5)	27(1)	48(1)	18(1)	-7(1)	3(1)	7(1)
C(6)	27(1)	44(1)	20(1)	1(1)	6(1)	0(1)
C(7)	22(1)	27(1)	22(1)	2(1)	3(1)	0(1)
C(8)	16(1)	22(1)	17(1)	1(1)	2(1)	5(1)
C(9)	16(1)	16(1)	18(1)	1(1)	2(1)	-1(1)
C(10)	14(1)	15(1)	16(1)	-2(1)	2(1)	-2(1)
C(11)	15(1)	17(1)	21(1)	2(1)	2(1)	-3(1)
C(12)	14(1)	16(1)	23(1)	-1(1)	5(1)	-2(1)
C(13)	14(1)	16(1)	18(1)	0(1)	2(1)	1(1)
C(14)	17(1)	16(1)	16(1)	2(1)	4(1)	-1(1)
C(15)	14(1)	16(1)	21(1)	-1(1)	2(1)	-2(1)
C(16)	20(1)	26(1)	23(1)	4(1)	1(1)	2(1)
N(1)	18(1)	15(1)	18(1)	0(1)	4(1)	0(1)
N(2)	13(1)	15(1)	21(1)	-2(1)	4(1)	-4(1)
O(1)	32(1)	19(1)	22(1)	0(1)	9(1)	-7(1)
O(2)	16(1)	21(1)	16(1)	1(1)	3(1)	2(1)
O(3)	22(1)	15(1)	26(1)	-3(1)	6(1)	-1(1)
O(4)	17(1)	21(1)	21(1)	-1(1)	6(1)	-1(1)
Cl(1)	14(1)	21(1)	33(1)	5(1)	2(1)	0(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for kob13.

	x	y	z	U(eq)
H(1)	-4564	3080	7862	22
H(2)	-4958	739	6651	25
H(4)	-3826	895	4942	32
H(5)	-2293	2902	4062	37
H(6)	-1074	5936	4558	36
H(7)	-1379	7136	5939	29
H(11A)	-2485	3936	8947	22
H(11B)	-2415	5492	9726	22
H(12A)	-6022	6110	7929	21
H(12B)	-5603	5455	8933	21
H(13)	-6849	8345	9250	19
H(16A)	-10271	11021	6981	35
H(16B)	-8278	12006	7009	35
H(16C)	-9769	13033	7508	35
H(2A)	-1806	9302	8916	20