

THE EXPANSION AND OPTIMIZATION OF ZN(II)-MEDIATED INTRAMOLECULAR
METALLOAMINATION AND SUBSEQUENT CU(I)-CATALYZED
FUNCTIONALIZATION FOR THE CONSTRUCTION OF
PYRROLIDINES AND PIPERIDINES

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana

July 2023

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DEDICATION

This dissertation is dedicated to my wife, Tindall Ouverson.

Stay young, go dancing.

ACKNOWLEDGEMENTS

To Dr. Tom Livinghouse for his unending dedication to good science and technique of only the highest quality. May we all take pride in our work and make friends with our reactions. Excelsior.

To my committee members Dr. Mary Cloninger, Dr. Sharon Neufeldt, Dr. Michael Mock, and Dr. Christopher Lemon for helping me overcome synthetic and theoretical hurdles by offering both knowledge and advice throughout my time at Montana State University.

To my family for their unending love and support. I would not have been able to achieve this monumental task without them. My wife never once let me struggle alone. My parents never once failed to support me. My brothers never once failed to be the best friends a person could ever hope for.

To the great friends I have made through the graduate school experience. When I first arrived, I met Dr. Hunter Fausset, David Stephens, Matthew Kania, and Jacob Norman as part of my incoming cohort. I thank each of them for five years of meaningful friendship and mutual support. I also acknowledge the friends I met along the way, like Oliver Jackson, Jerome Lepeule, and William Robinson.

To my fellow Livinghouse lab members for their dedication to the craft and herculean support in editing manuscripts and presentations.

To the faculty members Brian Tripet, Kim Hilmer, Susan Crawley, Donald Smith, and Jesse Smith without whom none of us in the organic division could succeed.

I acknowledge the generous funding I received throughout my career from The National Institute of Health, Montana State University, and a mysterious Hawaiian coffee farmer.

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ABSTRACT

Nitrogen-containing heterocycles (azacycles) are ubiquitous in pharmaceutical agents. Their ability to moderate and modulate the activity of drugs in the body make them especially powerful, and thus sought after, synthetic targets. While the synthesis of many popular azacycles has been greatly improved in recent years, the production of pyrrolidines and piperidines has not received as much attention despite their standing as the 1st and 5th most common azacycles in FDA-approved drugs. The intramolecular Zn(II)-mediated metalloamination/cyclization of N,N-dimethylhydrazinoalkenes provides structurally diverse pyrrolidines and piperidines with the added advantage of a subsequent functionalization step, efficiently building molecular complexity in one reaction sequence. Herein, this method is optimized and improved by the addition of a new hydrazone reduction method, the inclusion of 1-bromoalkynes in the functionalization step, and multiple key discoveries in the reagents used to effect these transformations. Furthermore, preliminary results adding N,N-dimethylhydrazinoallenes as substrates for this powerful method are presented.

CHAPTER ONE

INTRODUCTION

1.1 Azacycles in Pharmaceuticals

Nitrogen-containing heterocycles (azacycles) are ubiquitous among natural, biologically active molecules. Azacycles are key components of essential nutrients, such as the B vitamins, essential metabolites, such as ATP and NADP, and essential neurotransmitters, such as serotonin. Furthermore, they form the very basis of life as part of every nucleotide. As a result, the azacyclic subunit has been under constant investigation, finding a wide set of applications across several disciplines.¹⁻⁶ Due to their tendency towards high bioactivity, azacycles have been central to the extensive research that encompasses all fields of pharmacology.¹⁻⁶ As a result, some 60% of small-molecule drugs approved by the FDA contain at least one azacycle, and this trend is increasing.⁷⁻¹⁰ So far for the decade of 2020 a majority of all newly approved drugs, small-molecule or otherwise, have contained this subunit (Figure 1.1).⁸⁻¹⁰

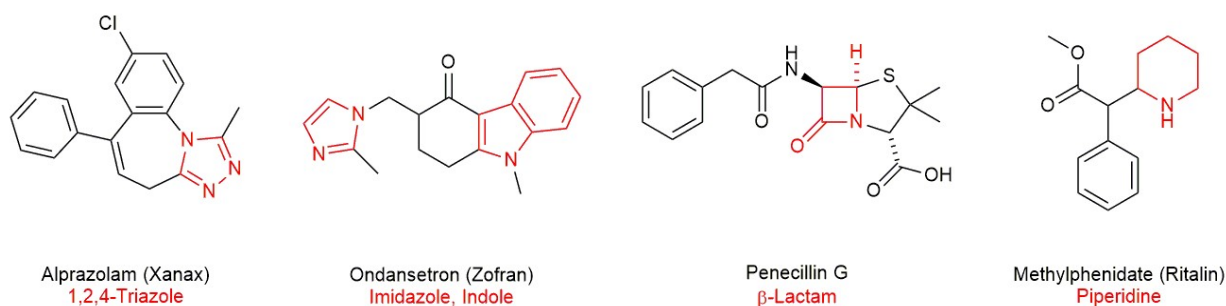


Figure 1.1 Examples of common azacyclic pharmaceuticals.

Azacycles are generally considered to be a biologically “privileged” moiety for drug discovery.¹⁻⁷ Nitrogen heterocycles can act as both an electron donor and an electron acceptor,

allowing them to participate in a vast array of intermolecular interactions of varying strength. It is from these intermolecular interactions that azacycles gain their ability to bind a multitude of biological targets with high affinity.¹⁻⁵ For instance, the growing prevalence of azacyclic anti-cancer agents can be mainly attributed to how well N-heterocycles bind to DNA, allowing them to interrupt cell growth and proliferation.^{2,6} In the laboratory, the application of nitrogen heterocycles enables fine tuning of the solubility, polarity, lipophilicity, and hydrogen bonding capacity of molecules of interest. By applying new nitrogen-containing subunits to known compounds, the ADME/tox profile of a drug candidate can be optimized for maximum effect at minimal dosage.¹⁻⁶

Saturated azacycles are the most common form found in pharmaceuticals.⁷ Since many piperidines and pyrrolidines can be accessed by relatively simple condensation reactions, they are the easiest to incorporate and modify. However, a heavy reliance still exists on the use of premade or naturally occurring piperidines and pyrrolidines as starting materials.^{1,2} Thus, synthetic methods that provide these structures have received considerable attention. Most of these new synthetic pathways have been heavily influenced by modern drug discovery methodologies. Industrial drug discovery initiatives often begin with the use of powerful neural networks that can identify the key structures to target and the most likely drug candidates to effectively target those structures.¹¹⁻¹⁵ These algorithms provide a general direction for the synthetic target, but many variations of the target molecule must be synthesized, purified, and tested for activity before lead compounds can be identified. Therefore, synthetic methods which provide azacyclic scaffolds are very useful for drug discovery.

To this end, a plethora of studies achieving highly impressive syntheses of popular azacyclic subunits such as imidazoles,¹⁶⁻¹⁸ β -lactams,¹⁹⁻²¹ and tetrazoles²²⁻²⁴ with great yields and functional group tolerance have been published in the last ten years. Pyrrolidines and piperidines are both in the top five most recurring azacycles in FDA approved small-molecule drugs.⁷ However, the production of pyrrolidine and piperidine scaffolds with similar utility is underdeveloped. The synthesis of complex pyrrolidines and piperidines is still carried out by mostly classical techniques that can take a double-digit number of steps while resulting in a single-digit yield.¹⁻⁴ Therefore, a synthetic method which provides functionalized pyrrolidine and piperidine scaffolds that can easily be further elaborated would help bridge this gap in medicinal science.

1.2 Synthesis of Pyrrolidines and Piperidines

1.2.1 Methods with No Organometallic Catalysis

The limited synthesis of pyrrolidines and piperidines can be achieved with simple organic reactions that require no organometallic catalysis via annulations and cycloadditions.²⁵⁻³⁰ Pyrrolidines can be prepared by an intramolecular Schmidt reaction using azido carboxylic acids,²⁶ while piperidines can be constructed by the reaction of an amine with an alkyl halide in a simple S_N2 reaction (Figure 1.2).²⁹

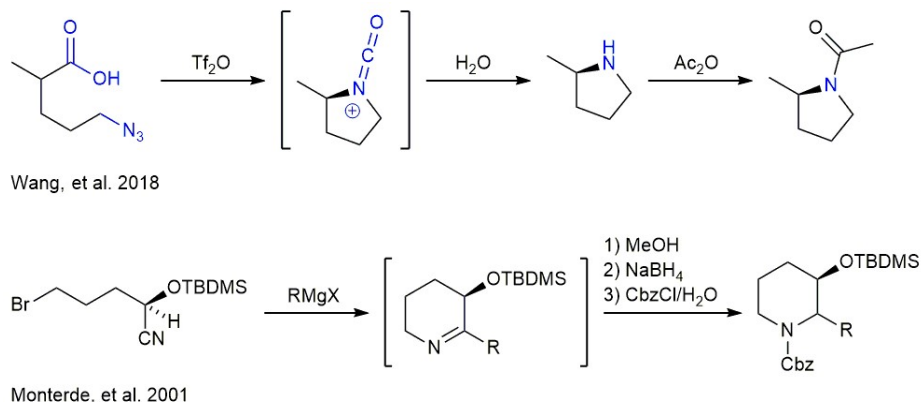


Figure 1.2 Noncatalytic routes to pyrrolidines and piperidines.^{26,29}

However, these classical routes generally require multiple steps, and the inclusion of strong acids and bases, reductions, and heating in these reactions limits their scope to only those substrates which can tolerate these harsher conditions. This often leads to an increase in the number of steps it takes to yield a useful azacyclic product from the reaction, as many protecting groups must be installed and removed throughout. Many studies which perform a total synthesis of a complex azacyclic product leave the formation of the desired azacycle as one of the last steps, making their modification as part of a drug discovery initiative much more difficult. (Figure 1.3).³¹⁻³³

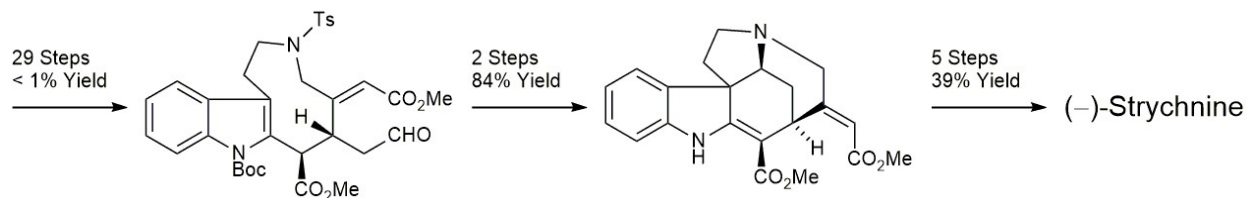


Figure 1.3 Total synthesis of (-)-Strychnine by Kaburagi, et al.³²

1.2.2 Ring-Closing Metathesis

Ring-closing metathesis (RCM) provides one alternative synthetic route to pyrrolidines and piperidines. Ring-closing metathesis reactions to form 5-membered heterocycles were first reported by Grubbs in 1992 with the aid of a Mo(VI) catalyst (Figure 1.4).³⁴

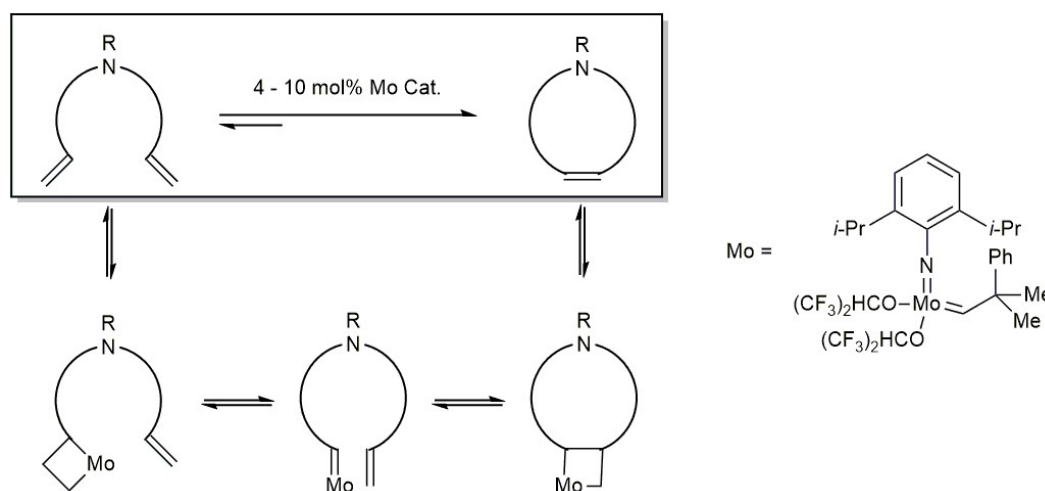


Figure 1.4 General mechanism for RCM formation of azacycles, demonstrated with Mo(VI).³⁴

This methodology has since been expanded upon to include the production of pyrrolidines by the functionalization of the resulting double bond.^{35,36} This method, however, has fallen out of use since the late 2000's. This is likely due to the reactions needed to reduce this double bond, which limits the scope and increases the total number of steps; a problem pointed out as early as 1997.³⁷ Furthermore, because a free amine nitrogen on the substrate can form a complex with a cross-metathesis catalyst, only tri-substituted and protected amine starting materials may be used in this reaction, further limiting the overall scope of the reaction. Because of these limitations, this method has only really found success in the production of iminosugars (Figure 1.5).^{35,36}

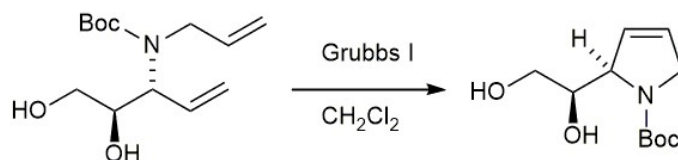


Figure 1.5 Enantioselective RCM formation of pyrrolines as the base for iminosugars.³⁶

While the production of piperidines using RCM is still widely used, this route suffers from the same issues as that of pyrrolidines, with recent studies demonstrating limited functional group tolerance.^{30,38,39} However, the proper application of RCM does make the formation of a difficult azacycle late into a total synthesis relatively trivial. While this defeats the purpose of a scaffold approach to drug synthesis, RCM has proven useful for the production of fused 6-membered azacycles such as quinolines or in the production of multicyclic alkaloids, such as those derived from Ergot (Figure 1.6).^{40,41}

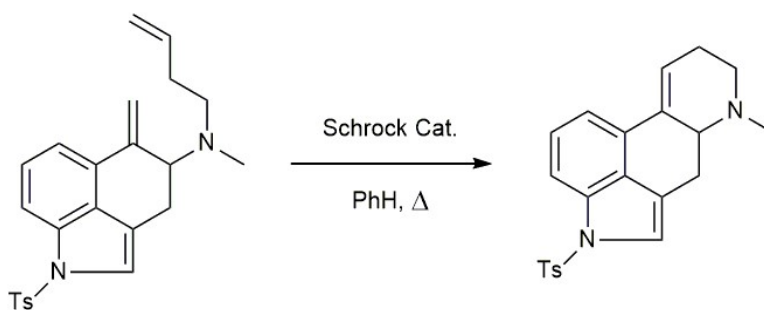


Figure 1.6 RCM formation of a tetrahydropiperidine in the synthesis of Ergoline derivatives.⁴⁰

1.2.3 Cycloadditions

By far the most common method for production of saturated heterocycles is via metal-catalyzed cycloadditions.³⁰ These reactions offer improvements to both the number of steps and yield of these synthetic routes while promoting desirable asymmetric reactions. 1,4-cycloadditions to form piperidines usually take advantage of the reactivity of three-membered

rings such as epoxides⁴² or mercurinium ions.⁴³ While these reactions can be as short as one step with very high diastereo- or even enantioselectivity, reaction conditions are harsh, can be toxic, and usually lack atom-efficiency (Figure 1.7).⁴³ 1,4-Cycloadditions can also be performed via radical mechanisms^{44,45} or Michael additions,⁴⁶ which limits the substrates only to those that will not undergo unwanted side reactions.

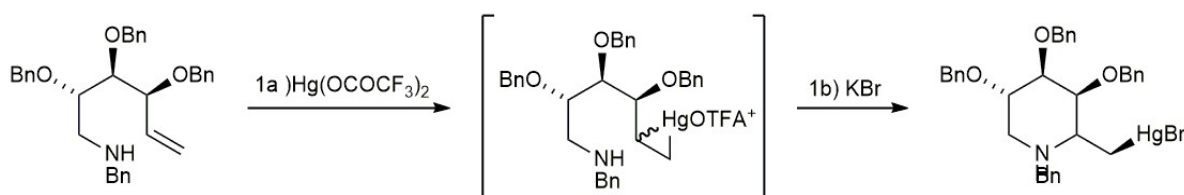


Figure 1.7 Use of a mercurinium ion to produce a piperidine.⁴³

The most common type of reaction for forming complex pyrrolidines and piperidines are those involving imines.³⁰ Imino and aza-Diels-Alder reactions have proven extremely useful for the production of piperidines. Imino Diels-Alder reactions have been very well studied and a wide variety of applications have been reported (Figure 1.8).^{47,48} These reactions require much less harsh reaction conditions, making them a highly attractive method. However, imino Diels-Alder reactions require a protected imine and are generally slow and lack selectivity.^{46,47} The aza-Diels-Alder is much less used, as competitive imine addition and tautomerization can easily lead to low conversions in increasingly slow reactions.^{49,50}

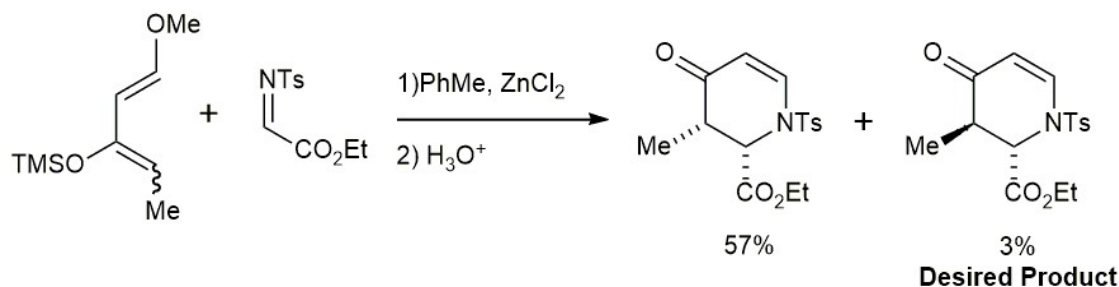


Figure 1.8 Imino Diels-Alder reaction for the synthesis of a piperidone, published as part of a larger total synthesis of Cylindrospermopsin.⁴⁷

The formation of pyrrolidines by 1,3-dipolar cycloadditions is similarly wide-spread. The transition metal-catalyzed asymmetric 1,3-dipolar cyclization of azomethine ylides is considered the most reliable method for the production of enantioenriched pyrrolidines.⁵¹⁻⁵³ The 1,3-dipolar cyclization of azomethine ylides is most commonly performed in the presence of Ag(I) or Cu(I) catalysts. The reaction can be tuned by the addition of phosphine ligands, with *ee* values generally above 90%, rendering this approach a particularly powerful synthetic tool (Figure 1.9).⁵⁴⁻⁵⁷



Figure 1.9 Umpolung synthesis of enantioselective pyrrolidines via 1,3-dipolar cycloaddition.⁵⁷

The 1,3-dipolar cyclization does, however, require proper pre-planning, as the identity of the substrate and the dipolarophile must be carefully considered for proper regiochemistry and activation.^{54,57} Substrates can isomerize, dipolarophiles are limited to those with electron-withdrawing groups, and the use of dipolarophiles more complex than simple alkenes can require

extensive catalyst screening and lead to decreased yields.⁵⁶ Therefore, while this strategy does produce enantioenriched products, the practical functionality of the final pyrrolidines depends upon the complexity of the starting materials. Furthermore, the reliance on electron-withdrawing esters means that most products require further reactions to remove these esters before they can be used as a scaffold for a pharmaceutical molecule (Figure 1.10).^{58,59}

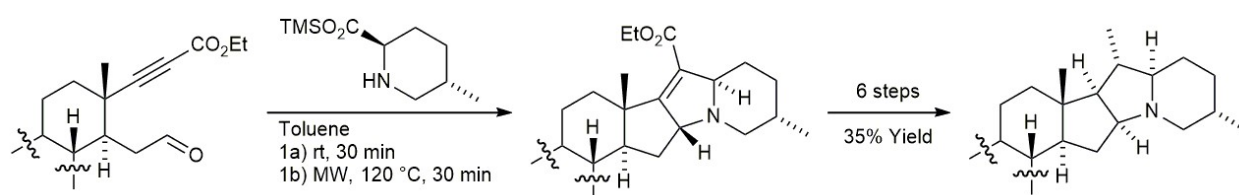


Figure 1.10 Formation and elaboration of a pyrroline in the total synthesis of Demissidine.⁵⁹

The Livinghouse research group has since improved upon some of these issues by employing an acylnitrilium ion as the substrate for intramolecular 2,3-cycloadditions.⁶⁰ Livinghouse, et al. demonstrated the usefulness of the acylnitrilium cation in the construction of Erythrinane derivatives where azomethine ylide cycloadditions had previously failed.⁶¹ Livinghouse also demonstrated the production of 2-acylpyrrolidines using this method in the production of (±)-Dendrobrine (Figure 1.11).⁶²

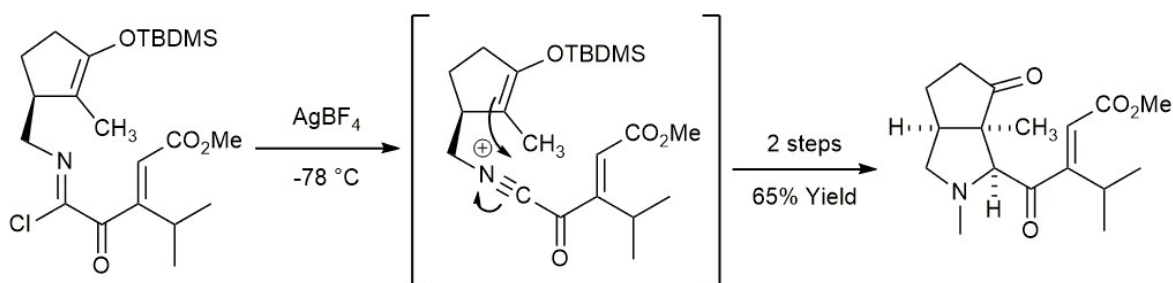


Figure 1.11 Formation of the key pyrrolidine via an acylnitrilium cation in the total synthesis of (±)-Dendrobrine.⁶²

1.2.4 Hydroamination Reactions

Intramolecular hydroaminations are regarded as the simplest and most straightforward route to saturated N-heterocycles.³⁰ Intramolecular hydroamination reactions typically encompass a metal-catalyzed migratory insertion of a metal-nitrogen bond into a site of unsaturation with a subsequent protonation (Figure 1.12).

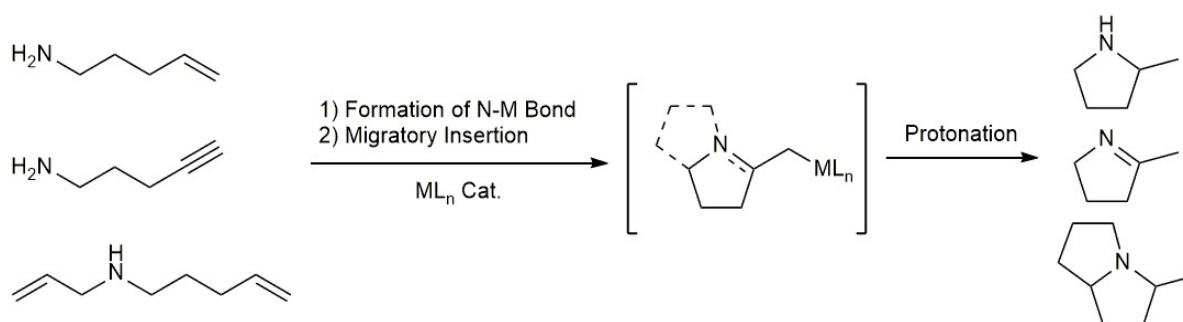


Figure 1.12 General mechanism of intramolecular hydroaminations resulting in five-membered azacycles.

Intramolecular hydroamination reactions can be performed with primary^{63,64} secondary,^{65,66} and tertiary amines,^{67,68} as well as azides,^{69,70} with good diastereoselectivity. Effective hydroamination reactions have been reported using metals from groups 2,⁷¹ 3,⁶³ 4,^{72,73} 8,^{69,70} 9,⁷⁴ 10,^{65,75} 11,^{76,77} and 12^{66,78} with a range from simple salts, such as FeI₂, to very complex chiral catalyst systems. These reactions, however, are comparable to RCM in that they afford very little increase in molecular complexity. Because the utility of the hydroamination reaction is only in the formation of a carbon-nitrogen bond, all desired functional groups must be installed before the cyclization, ultimately making this method no different from leaving the formation of the N-heterocycle until the end of a total synthesis (*vide supra*). Furthermore, if an

alkene is used, the resulting azacycle will have completely saturated bonds, making the product less useful as a drug scaffold.⁷⁹

1.3 Metalloamination

Hydroamination reactions have been expanded to include a concomitant functionalization of the carbon-metal bond that results from the migratory insertion step (Figure 1.13). The advantage that metalloamination offers in the ability to effect the formation of a new carbon-carbon bond by well-known organometallic reactions after the formation of the desired azacycle builds remarkable levels of molecular complexity in a one-pot reaction, making this an extremely attractive method for the production of pyrrolidine and piperidine scaffolds.

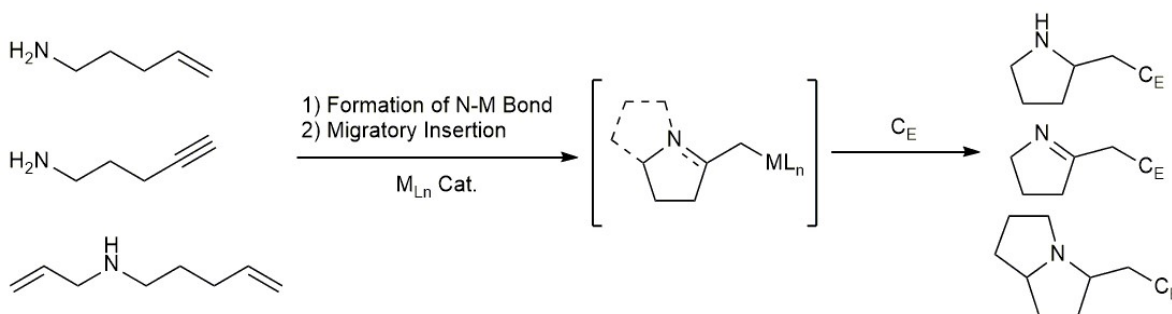


Figure 1.13 Intramolecular metalloamination/cyclization reactions trap the organometallic intermediate of an intramolecular hydroamination using a carbon electrophile (C_E).

Intramolecular metalloamination/cyclization reactions have been reported using Pd,^{65,80-88} Ru,^{89,90} Mn,⁹¹ Cu,^{77,92} Zn,^{66,78} Au,^{93,94} and Ti⁹⁵⁻⁹⁸ both catalytically and stoichiometrically. However, Pd catalysts are the most-well studied. Wolfe's group and Michael's group have done particularly outstanding work elucidating the mechanism of "aminopalladation" reactions with both Pd(0)⁸⁷ and Pd(II)⁸⁸ catalysts. They have demonstrated that metalloaminations generally

follow one of two pathways: either a metal-alkene complex is formed first which results in the anti-addition of the electrophile, or a metal-amide is formed first, which results in the syn-addition of the electrophile (Figure 1.14).^{87,88} Michael has specifically noted that one of the main factors contributing to which pathway is operative is the acidity of the amine as well as the acidity of the overall solution, as both contribute to the ability of the catalyst to form the amide complex required for syn-addition.⁸⁸ Varying degrees of this acidity trend have been reported for other metals as well,^{66,89,91,92,98} and a clear connection between formation and control of the metal-amide complex and the ability to control stereoselectivity has emerged (Figure 1.14).^{65,66,78,80-88} Employment of chiral ligands has been found to promote asymmetrical metalloaminations.¹⁰⁰⁻¹⁰²

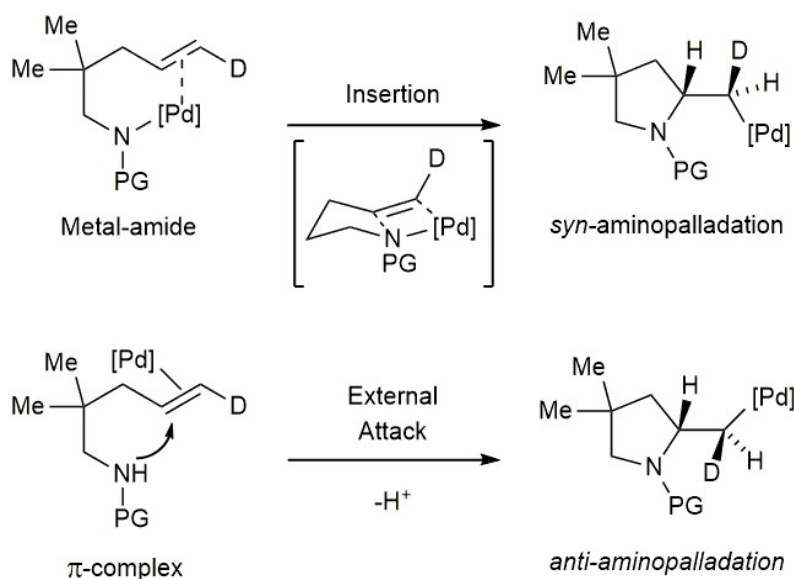


Figure 1.14 The stereochemical outcome of “aminopalladation” reactions depends upon whether the metal deprotonates the amine or complexes with the alkene first.⁸⁷

While the Pd catalyzed metalloamination is the most studied variant, it still relies upon the use of a rare, non-earth abundant metal, complex ligands, and, frequently, an amidation

reagent or base to activate the substrate. This issue was partially addressed by the Livinghouse lab in the 1990s when they first described the use of titanium complexes in metalloamination reactions.⁹⁵⁻⁹⁹ The group demonstrated the use of $\text{TiCl}_4(1,2\text{-DME})$ ^{98,99} and CpTiCl_3 ⁹⁵⁻⁹⁷ in the formation of metal-imide complexes with amines with a subsequent intramolecular 2,2-cycloaddition. This method was notably used in the total syntheses of Monomorine⁹⁶ and (+)-Preussin (Figure 1.15).⁹⁷

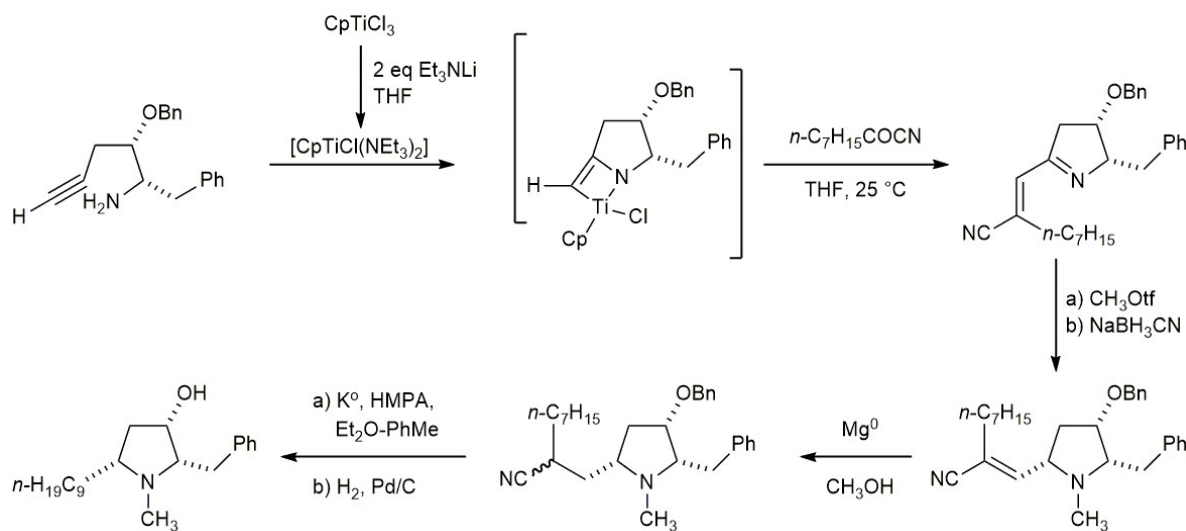


Figure 1.15 A Ti(IV)-mediated metalloamination/cyclization reaction as part of a total synthesis of (+)-Preussin.⁹⁷

In the 2000s, the labs of Blechert,¹⁰³ Zhou,¹⁰⁴ and Nakamura¹⁰⁵ independently showed that Zn(II) complexes were competent, cost-effective metalloamination/cyclization reagents. Furthermore, Nakamura demonstrated that the resulting organozinc reagents could be transmetallated with Pd(0) to effect subsequent cross-coupling reactions (Figure 1.16).¹⁰⁵

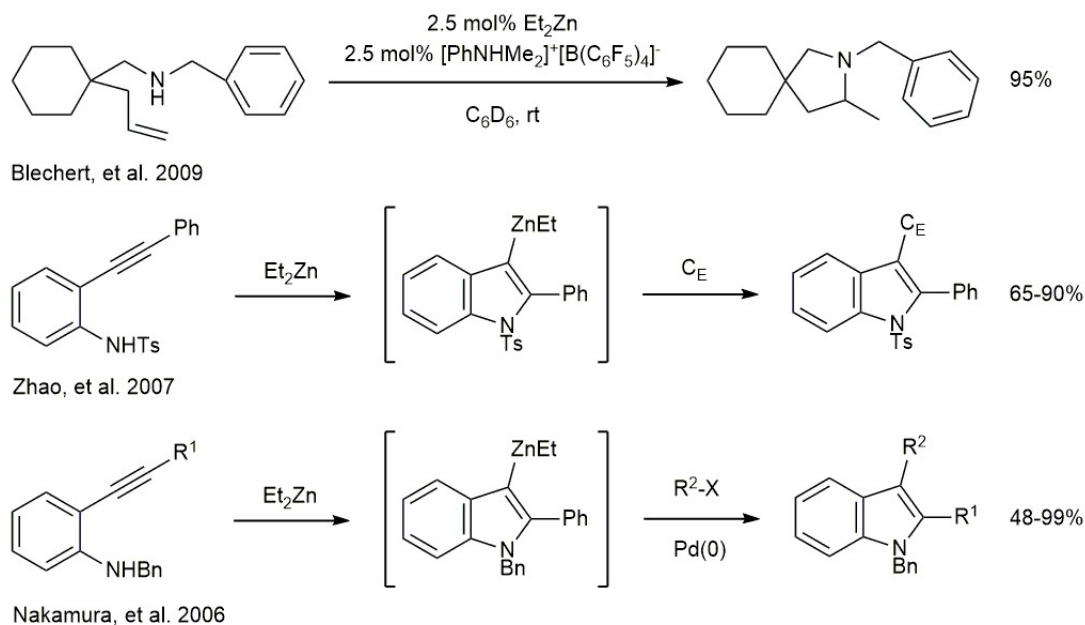


Figure 1.16 Examples of Zn(II)-mediated hydro- and metalloaminations.¹⁰³⁻¹⁰⁵

Inspired by these reports and the well-established reactivity of organozinc species,¹⁰⁶ the Livinghouse group demonstrated the facile formation of pyrrolidines and piperidines using a Zn(II)-mediated intramolecular metalloamination/cyclization reaction with a subsequent allylation utilizing $\text{CuCN}\cdot 2\text{LiCl}$ in 2014.¹⁰⁷ Livinghouse, et al. found that N,N-dimethylhydrazinoalkenes were particularly good substrates that readily metalated and cyclized to form a diverse range of saturated N-heterocycles with good diastereoselectivity without the need for exogenous ligands or activators. Unlike other reports, the Livinghouse group also found that, while Thorpe-Ingold acceleration could increase yields, it was not necessary for the reaction.^{107,108} Subsequent electrophilic functionalizations using a stoichiometric amount of $\text{CuCN}\cdot 2\text{LiCl}$ demonstrated that both allyl bromide and methallyl chloride are exceptional electrophiles for this transformation (Figure 1.18). Furthermore, transmetallation to $\text{Pd}(0)$ is also

facile, enabling subsequent functionalization with well-established Pd(0) cross-coupling reactions.¹⁰⁷

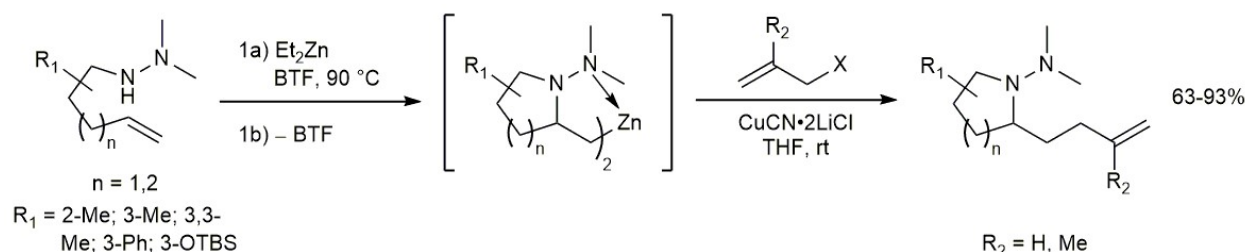


Figure 1.17 Zn(II)-mediated intramolecular metalloamination/cyclization of N,N-dimethylhydrazonealkenes with subsequent Cu(I)-mediated allylation.¹⁰⁷

By 2016, the reaction had been expanded to use 1,2-disubstituted alkenes as the migratory insertion partner for the Zn–N bond, notably producing highly functionalized pyrrolidines, exhibiting > 20:1 diastereoselectivity.¹⁰⁸ This study also demonstrated the use of vinylcyclopropanes as migratory insertion partners, leading to an “exceptionally facile cyclization with concomitant cleavage of the cyclopropane ring”, which performs a remote functionalization four carbons away from the newly formed pyrrolidine (Figure 1.18).¹⁰⁸

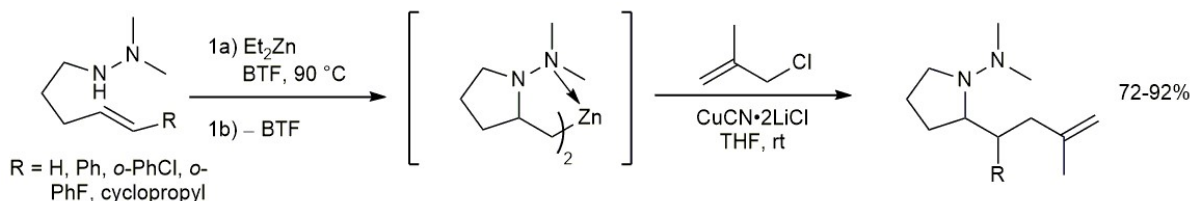


Figure 1.18 Zn(II)-mediated intramolecular metalloamination/cyclization of 1,2-disubstituted N,N-dimethylhydrazonealkenes with subsequent Cu(I)-mediated allylation.¹⁰⁸

In 2018, the group further expanded the scope of the electrophilic functionalization by demonstrating that the carbocupration could be made catalytic with as little as 5 mol% Cu(I) by changing the Cu(I) source from stoichiometric CuCN·2LiCl to 5 mol% CuCN·2LiBr admixed

with 1 equivalent of LiBr.¹⁰⁹ A number of the previously reported reactions were repeated using this catalytic system, which resulted in higher yields. The scope of this functionalization was also expanded to include methyl 2-(bromomethyl)acrylate (Figure 1.19) and propargyl bromide.¹⁰⁹

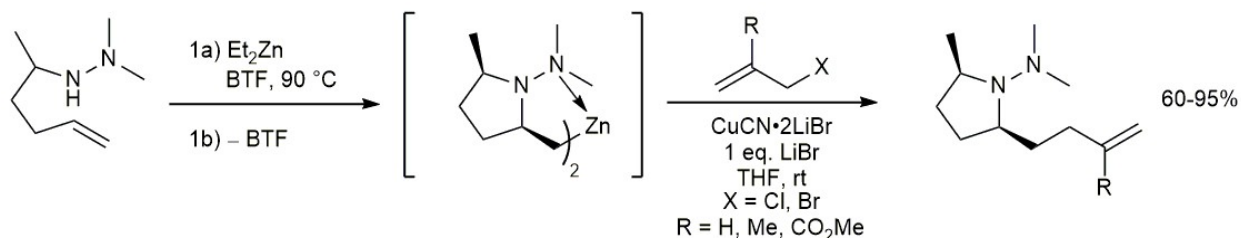


Figure 1.19 Zn(II)-mediated intramolecular metalloamination/cyclization of N,N-dimethylhydrazinoalkenes with subsequent LiBr-stabilized Cu(I)-catalyzed functionalization.¹⁰⁸

The diethylzinc-mediated intramolecular metalloamination/cyclization with subsequent functionalization of the organozinc intermediate has been demonstrated to be a versatile, cost-effective, and robust route to saturated azacycles.¹⁰⁷⁻¹⁰⁹ However, the method is still highly limited in scope and plagued by poor reaction conditions.

The production of the starting N,N-dimethylhydrazinoalkenes can be a lengthy process and previous methods for reducing the requisite hydrazone to the hydrazine starting materials were inadequate. For instance: reduction by LiAlH_4 often left a small amount of hydrazone in the purified product, and, due to its sensitivity to moisture, separating the hydrazine from this starting material was extremely difficult. Reduction by NaBH_3CN eliminates this starting material, but the toxicity and price of the reductant was of concern. Thus, a novel amine-borane reduction was developed.¹¹⁰ Using primary amines and a solution of borane methyl sulfide complex, a competent amine-borane reductant can be formed *in situ* for the complete reduction of N,N-dimethylhydrazones to the subsequent hydrazines in high yield. This method was

demonstrated to reduce the N,N-dimethylhydrazones derived from both ketones and aldehydes, including those with bulky groups, in excellent yield with no starting hydrazone remaining (Figure 1.20).¹¹⁰

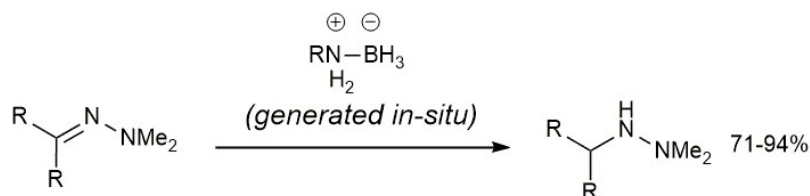


Figure 1.20 Reduction of N,N-dimethylhydrazones using amine-boranes generated *in situ*.¹¹⁰

While Cu(I)-catalyzed functionalization with allyl and propargyl electrophiles (a form of carbocupration) is facile, the catalyst system had remained untested in regards to Cu(I)-catalyzed cross-coupling reactions. Furthermore, because only allyl and propargyl electrophiles had been used, the only functional group provided by this method for the elaboration of the N-heterocyclic scaffolds was the alkene. Therefore, the use of 1-bromoalkynes as electrophiles for the Cu(I)-catalyzed functionalization step was investigated.^{111,112} Utilizing the same catalyst system of $\text{CuCN} \cdot 2\text{LiBr}$ admixed with 1 equiv. of LiBr, it was found that the cross-coupling of the azacyclic organozinc dimer derived from reaction of N,N-dimethylhydrazinoalkenes with diethyl zinc can be achieved in good to moderate yields. A range of 1-bromoalkynes bearing various functional groups (eg alkyl, silyl ethers, esters) all successfully couple to multiple substrates to produce synthetically useful amounts of propargyl piperidines and pyrrolidines (Figure 1.21).^{111,112}

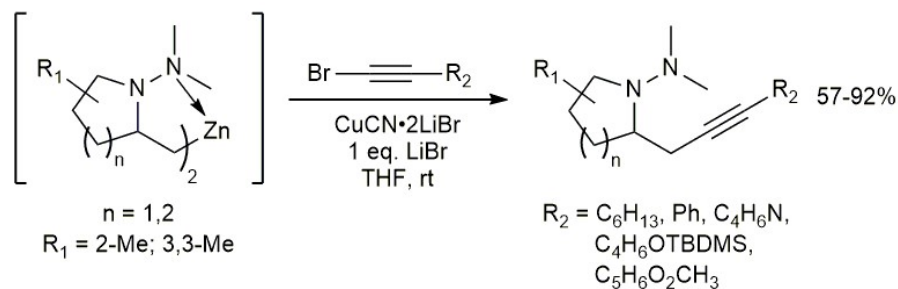


Figure 1.21 The cross-coupling of 1-bromoalkynes to the azacyclic organozinc intermediates derived from N,N-dimethylhydrazinoalkenes.¹¹¹⁻¹¹²

The Zn(II)-mediated metalloamination/cyclization reaction is highly sensitive to reaction conditions. The use of more polar or coordinating solvents can hinder the reaction greatly. Furthermore, exposure of the azacyclic organozinc intermediates to proton sources does not produce the expected hydroamination product, but leads to regeneration of the starting hydrazinoalkene. Herein, we report a number of optimizations and alternative zinc reagents to address these issues, as well as the preliminary results of using hydrazinoallenes as migratory insertion partners for the Zn–N bond.

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CHAPTER TWO

EFFICIENT REDUCTIONS OF DIMETHYLHYDRAZONES
USING PREFORMED AMINE BORANES

2.1 Contribution of Authors and Co-Authors

Manuscript in Chapter 2

Author: Christian Frabitore

Contributions: Performed experimental work. Writing and editing of manuscript.

Co-Author: Jérôme Lépeule

Contributions: Performed experimental work. Assisted in editing of manuscript.

Co-Author: Bradley Towey

Contributions: Original idea and preliminary experiments.

Co-Author: Tom Livinghouse

Contributions: Original idea. Writing and editing manuscript.

Co-Author: William C. Robinson

Contributions: Confirmed experimental work. Assisted in editing manuscript.

2.2 Manuscript Information

Christian Frabitore, Jérôme Lépeule, Bradley Towey, Tom Livinghouse, and William C.

Robinson

Synthetic Communications

Status of Manuscript:

☐ Prepared for submission to a peer-reviewed journal

☐ Officially submitted to a peer-reviewed journal

☐ Accepted by a peer-reviewed journal

☒ Published in a peer-reviewed journal

Taylor & Francis

Publication Date: January 17, 2022

Volume 52, 2022

DOI: 10.1080/00397911.2021.2008449

2.3 Abstract

A convenient method for the reduction of N,N-dimethylhydrazones using amine borane complexes generated *in-situ* is described. It was found that primary amine borane complexes performed exceedingly well at reducing N,N-dimethylhydrazones in as little as 1.1 equivalents, furnishing the corresponding air-sensitive hydrazine products in excellent yields.

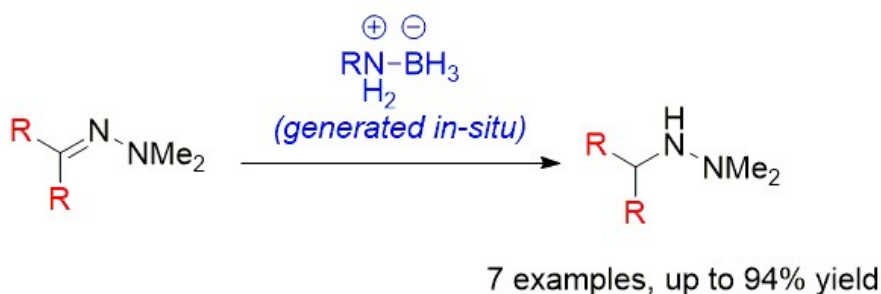


Figure 2.1 Graphical abstract for the *Synth. Comm.* manuscript.

2.4 Introduction

We have previously reported that N,N-dimethylhydrazinoalkenes are versatile intermediates for metalloamination/cyclization leading to direct electrophilic functionalization.¹⁻³ We have found that the reduction of precursor N,N-dimethylhydrazones using previously existing procedures is surprisingly tedious due to the extreme sensitivity of the product N,N-dimethylhydrazines to air exposure. Here we describe an exceptionally practical method for these reductions using primary amine boranes generated *in-situ*. The reduction of N,N-dimethylhydrazones to the corresponding hydrazines has most commonly been achieved by using LiAlH_4 , NaBH_4 , pyridine borane, and NaBH_3CN .⁴⁻⁶ NaBH_3CN and pyridine borane have been described as more selective toward the C=N π system than LiAlH_4 and NaBH_4 .⁴ The use of

NaBH₃CN suffers from both its toxicity and expense, whereas pyridine borane entails a relatively tedious work up. Alternatively, Casarini has described the use of dimethylamine borane with *p*-toluenesulfonic acid for the reduction of α,β -unsaturated hydrazones to provide allyl hydrazines.⁷ In addition, Perdicchia utilized trimethylamine borane and HCl gas for the reductions of hydrazones.⁸ More recent work has included the use of various tertiary amine boranes to reduce hydrazones and produce air stable hydrazine and hydrazide products. These methods, however, rely on the ability to trap the hydrazine product as a salt or to intercept it *in-situ* with an electrophile.^{9,10}

Amine boranes are relatively expensive, but can be readily generated from the parent amine and either borane-dimethyl sulfide (BMS) or borane-THF.¹¹⁻¹³ The objective of this study was to identify amine-boranes that could be prepared *in-situ*, immediately prior to the reduction of dimethylhydrazones, to facilitate high yield reductions to dimethylhydrazines (Figure 2.2).

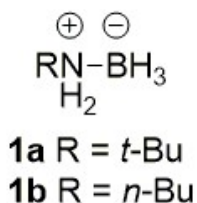


Figure 2.2 The general structure of the amine boranes used for the *in-situ* reduction of N,N-dimethylhydrazones.

2.5 Results and Discussion

The series of amines examined in this study comprised *n*-butylamine, *t*-butylamine, diethylamine, morpholine, dimethylethylamine, triethylamine, and pyridine. Aqueous solutions of alkylamines were not considered due to the rapid hydrolysis of BMS in the presence of water.

The reduction efficiencies of the corresponding amine boranes (prepared *in-situ*) were initially gauged with respect to their acid mediated reactions [using 1:5 (37%) HCl:MeOH (v/v)] with the N,N-dimethylhydrazone derived from 2-heptanone to provide dimethylhydrazine **2a** in the presence of methyl orange. It should be emphasized that cautious titrative addition of the acid was necessary to minimize premature hydrazone hydrolysis (Figure 2.3).

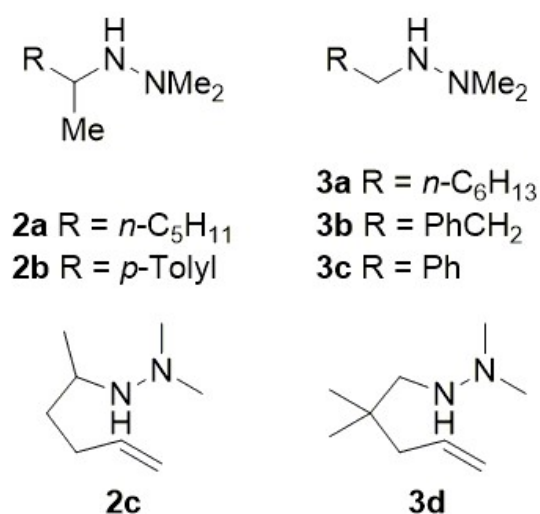


Figure 2.3 Structures of the N,N-dimethylhydrazine products prepared by the *in-situ* reduction of the corresponding N,N-dimethylhydrazones by amine borane complexes.

It was readily determined that both *t*-butylamine borane (**1a**) and *n*-butylamine borane (**1b**) were superior hydride sources to effect the desired reduction. Efficient reductions could be achieved with as little as 1.1 equiv. of **1a** or **1b** for the N,N-dimethylhydrazones of both 2-heptanone and 4-methylacetophenone (Table 2.1). Importantly, the reactant mixtures are air-sensitive *after basification*, and are facilitated by using Schlenk techniques. Borane adducts derived from the secondary amines diethylamine and morpholine were found to be inferior in that the reductions proved slower and the product N,N-dimethylhydrazine was contaminated

with 2-heptanol, resulting from premature hydrazine hydrolysis. The boranes derived from tertiary amines (e.g., Me₂NEt and Et₃N) were even less effective. Although pyridine borane was a competent reductant, the subsequent removal of the pyridine byproduct was more tedious than the aforementioned primary amines.

Table 2.1 Preparation of hydrazines **2a**, **2b**, and **2c** by reduction of the corresponding hydrazones using amine boranes **1a** and **1b**.

Hydrazine	Amine borane ^a	Equivalents	Yield(%)
2a	1a	3	88
		1.5	86
		1.1	83
	1b	3	86
		1.5	80
		1.1	84
2b	1a	3	87
		1.5	86
		1.1	90
	1b	3	90
		1.5	92
		1.1	94
2c	1a	1.5	71

^a Performed from the corresponding amine and BMS in-situ.

Amine borane complexes **1a** and **1b** were then tested for their capability to reduce hydrazines derived from aldehydes (**3a**, **3b**, and **3c**). Initial tests using 1.1 eq of amine borane resulted in incomplete reduction of the starting hydrazones. However, 1.5 eq of amine borane complex proved to be adequate for the reduction of all three aldehyde-derived hydrazones in good yield (Table 2.2).

Table 2.2 Synthesis of hydrazines **3a**, **3b**, **3c**, and **3d** by the reduction of the corresponding hydrazones with amine borane complexes **1a** and **1b**.

Hydrazine	Amine borane ^a	Yield(%)
3a	1a	80
	1b	80

3b	1a	87
	1b	87

3c	1a	94
	1b	94

3d	1a	83

^a All reactions performed with 1.5 eq of reactive amine borane complex.

Amine borane complex **1a** was then tested for its capability to reduce the N,N-dimethylhydrazone precursors of some examples of our previously described N,N-dimethylhydrazinoalkenes.¹⁻³ Using 1.5 eq of amine borane complex **1a** furnished N,N-dimethylhydrazinoalkenes **2c** and **3d** in good yield. It is especially noteworthy that these hydrazines were produced in high purity with no hydrazone precursor remaining, which was a major shortcoming of other previously existing procedures.

2.6 Conclusions

In conclusion, *t*-butylamine borane and *n*-butylamine borane, generated *in-situ*, are unusually effective reducing reagents at moderately low pH. These provide a cost-effective, and simple method for the reduction of N,N-dimethylhydrazones to the corresponding hydrazines. The use of these reagents for the reduction of related C=N π systems will be described in the future.

2.7 Appendices

All experimental and spectroscopic data can be found in the appendices.

2.8 Funding Information

Generous funding for this research was provided by the National Institute for General Medical Science [GM11694].

2.9 References

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CHAPTER THREE

COPPER(I)-CATALYZED CROSS-COUPPLING OF 1-BROMOALKYNES WITH N-
HETEROCYCLIC ORGANOZINC REAGENTS3.1 Author Contributions

Manuscript in Chapter 3

Author: Christian Frabitore

Contributions: Performed experimental work. Writing and editing of manuscript.

Co-Author: Jérôme Lépeule

Contributions: Confirmed experimental work. Assisted in editing manuscript.

Co-Author: Tom Livinghouse

Contributions: Original idea. Writing and editing manuscript.

3.2 Manuscript Information

Christian Frabitore, Jérôme Lépeule, and Tom Livinghouse

Molecules

Status of Manuscript:

☐ Prepared for submission to a peer-reviewed journal

☐ Officially submitted to a peer-reviewed journal

☐ Accepted by a peer-reviewed journal

☒ Published in a peer-reviewed journal

MDPI

Publication Date: July 17, 2022

Volume 27, 2022

DOI: 10.3390/molecules27144561

Figure 3.2 has been changed from the original manuscript. Additional information not in the original manuscript regarding this figure has been added on pg. 41-42.

3.3 Abstract

Nitrogen containing heterocycles represent a majority of FDA approved small molecule pharmaceuticals. Herein we describe a synthetic method to produce saturated N-heterocyclic drug scaffolds with an internal alkyne for elaboration. Treatment of N,N-dimethylhydrazinoalkenes with Et_2Zn followed by a Cu(I) catalyzed cross-coupling with 1-bromoalkynes affords piperidines and pyrrolidines in good yield. Five examples are reported and a proposed mechanism for the Cu(I) catalyzed cross-coupling is presented.

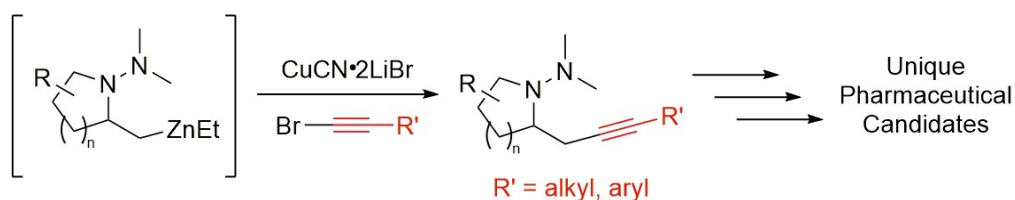


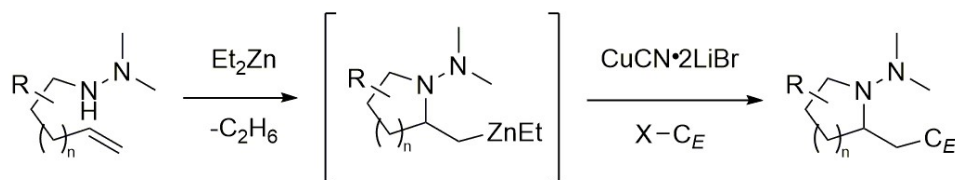
Figure 3.1. Graphical abstract for the *Molecules* manuscript.

3.4 Introduction

Nitrogen containing heterocycles are recognized as privileged scaffolds for pharmaceuticals due to their increased pharmacokinetics and bioavailability.¹⁻³ As such, N-heterocycles are present in nearly 59% of all FDA approved small molecule drugs and make up a plurality of newly approved drugs each year.⁴⁻⁶ Piperidines and pyrrolidines appear in the top five most common N-heterocycles in FDA approved drugs.¹ Industrial drug discovery initiatives often approach drug synthesis by creating large molecular libraries that can comprise hundreds of variations of one scaffold.^{7,8} The use of neural networks and powerful algorithms to identify better and more specific target compounds has helped narrow the scope of these libraries.⁸ However, each of these target compounds and their variants must be synthesized, purified, and assayed, which can take a

significant amount of time to achieve for even a single drug candidate. Therefore, a synthetic method that provides saturated N-heterocyclic drug scaffolds with common functional groups that can also easily be elaborated to make many variations of one target compound would be extremely useful to drug discovery.

We have previously reported one such method involving the use of Et_2Zn in a Zn(II) mediated metalloamination/cyclization cascade with subsequent electrophilic functionalization (Scheme 3.1).⁹⁻¹¹

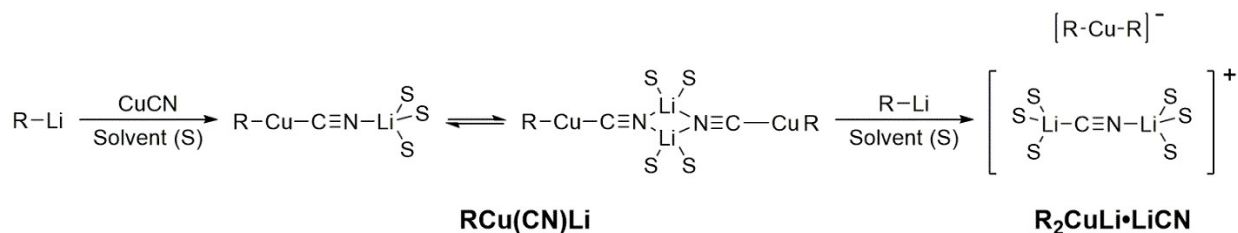


Scheme 3.1 Zn(II) -mediated metalloamination/cyclization with subsequent functionalization.⁹

Unlike previously reported methods, the Zn(II) mediated metalloamination/cyclization cascade does not rely on transient intermediates that limit the following functionalization to only those electrophiles which will react quickly and completely.¹²⁻²⁰ The Zn(II) cascade generates a stable organozinc intermediate that can readily be transmetallated, resulting in the formation of a diverse repository of scaffolds. Here we expand the scope of this method to the use of 1-bromoalkynes in Cu(I) catalyzed functionalizations.

The cross-coupling of 1-haloalkynes with organozinc reagents was first reported by Knochel.²¹ This initial report involved the coupling of alkyl organozincs with bromo- and iodoalkynes in the presence of catalytic $\text{CuCN} \cdot 2\text{LiCl}$ to produce internal alkynes in good yields. This original study demonstrated the usefulness of this method by its application to the synthesis of a pheromone derived from *Amathes c-nigra*.²¹

The copper/zinc reagents RCu(CN)ZnX formed during this reaction are not well characterized, but studies have elucidated the structure and reactivity of the related copper/lithium reagents of type RCu(CN)Li and $\text{R}_2\text{CuLi} \cdot \text{LiCN}$.²²⁻²⁶ Lower-order lithium cyanocuprates (RCu(CN)Li) are formed by the transmetallation of an alkyl lithium reagent with CuCN .^{22,23} Further treatment with an additional equivalent of alkyl lithium reagent forms the “higher-order” cyano-Gilman cuprate ($\text{R}_2\text{CuLi} \cdot \text{LiCN}$, Scheme 3.2).^{24,25} The cyano-Gilman cuprates also demonstrate an equilibrium between a homodimer, heterodimer, and mono-anionic unit depending upon concentrations of cyanide salt and solvent.²⁶



Scheme 3.2 Formation and structure of lower- and higher-order lithium cyanocuprates.

While the crystal structures of many representatives of both categories have been found, to our knowledge no crystal structure of the reagent RCu(CN)ZnX (Figure 3.2, **A**) has been reported. Therefore, it cannot be said with certainty whether the active reagent is of the lower- or higher-order cyanocuprates. Due to the large excess of R-Zn in the reaction mixture, the general catalytic cycle can be satisfactorily demonstrated and understood by representing the cyanocuprate as a mono-anionic, higher-order species (Figure 3.2, **B**),^{27,28} but it should be noted as well that zinc is a much less electropositive metal than lithium, so this cycle may also be envisioned using a lower-order cyanocuprate. Regardless of the exact structure of the cuprate and

identity of the cation, the 1-2 migratory insertion (Figure 3.2, **B**→**C**) and subsequent elimination (Figure 3.2, **C**→**D**) would proceed in a similar fashion.

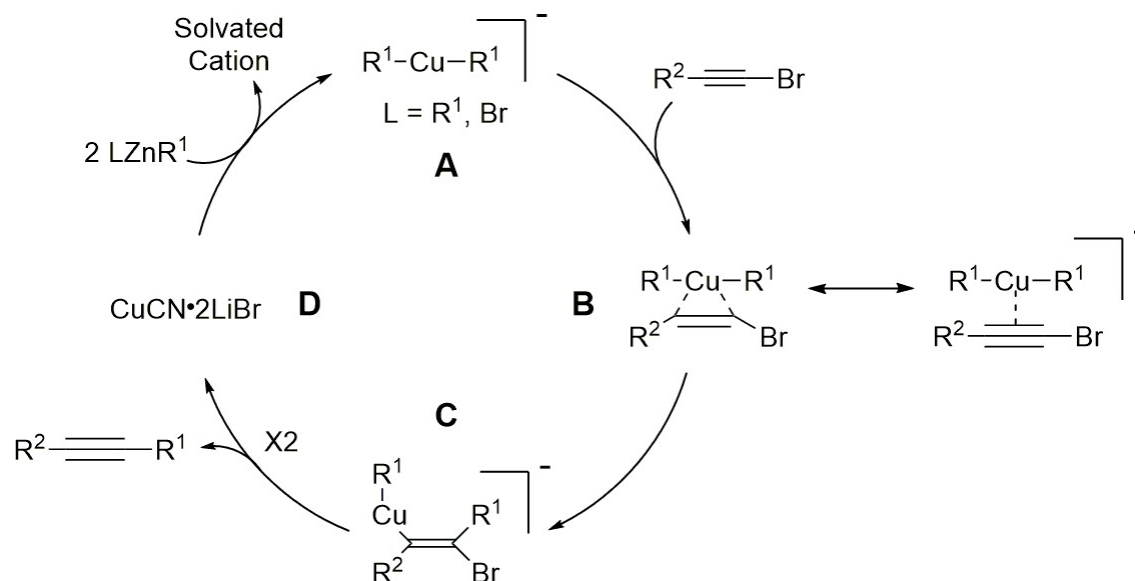


Figure 3.2 Proposed mechanism for the Cu(I)-catalyzed cross-coupling of 1-bromoalkynes with alkyl zinc reagents. Changed from original manuscript.²⁹

3.5 Results and Discussion

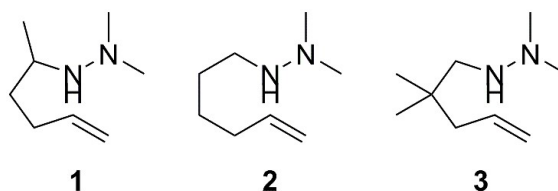


Figure 3.3 N,N-dimethylhydrazinoalkenes used in this study.

Our investigation commenced with N,N-dimethylhydrazinoalkenes **1** and **2**, which underwent metalloamination and cyclization as reported previously (see methods). These intermediates were treated with 1-bromo-1-octyne (2 equiv), $CuCN \cdot 2LiBr$ in THF (5 mol%), and LiBr in THF (1 equiv). This catalytic mixture has demonstrated a great stabilizing and accelerating effect in

our previous work with zincated intermediates of N,N-dimethylhydrazino alkenes.⁹ Isolation of the products was straightforward to afford **1a** and **2a** in good yields (Table 3.1). Product **3a** demonstrates that increased steric bulk on the N-heterocycle still leads to successful coupling. Having found success with these initial reactions, we moved forward to coupling with the more reactive 1-bromo-2-phenylethyne.

Table 3.1 Results of the cross-coupling of 1-bromo-1-octyne and 1-bromo-2-phenylethyne with N,N-dimethylhydrazinoalkenes **1**, **2**, and **3**.

$n = 1, 2$

1-Bromoalkyne	Product	Yield [%]
	 1a^a	77 ^b
	 2a	81 ^b
	 3a	58 ^b 76 ^c
	 1b^a	66 ^b
	 2b	72 ^b

^a Product obtained as racemic mixture. ^b 0.1 mmol N,N-dimethylhydrazinoalkene, 5 mol% CuCN·2LiBr, 1 equiv. LiBr. ^c 1.5 mmol N,N-dimethylhydrazinoalkene, 5 mol% of CuCN·2LiBr, 1 equiv. LiBr.

Knochel reported that similar Cu(I) catalyzed cross-couplings with 1-bromo-2-phenylethyne were difficult to control. Successful reactions with 1-bromo-2-phenylethyne took 1-4 hr at -76 °C to complete and increasing the temperature inevitably led to decreased yields.²¹ Diamine ligands can exert a stabilizing effect on copper catalysts.³⁰ These ligands also accelerate Cu(I) catalyzed cross-coupling reactions.³¹ With substrate **2** we found that utilizing 1 equivalent TMEDA as a Cu(I) ligand allowed the cross-coupling reaction with 1-bromo-1-octyne to be run at room temperature overnight with no issues, yielding 18 mg (72%) product **2a**. Cooling the reaction showed no improvement in yield. However, the coupling of **2** to 1-bromo-2-phenylethyne led to a decrease in yield of **2b** (6.1 mg, 25%) and lowering reaction temperature showed no improvement. The product mixture contained homocoupled diyne product and a Zn dimer of the cyclized substrate **2**. Related homocoupling reactions have been previously reported and the presence of base has been shown to be key to these reactions.³² Gratifyingly, we found that our previously reported conditions using 1 equivalent of LiBr allowed the alkynylation reactions of both **2a** and **2b** to be run at room temperature overnight with an increase in yield demonstrated in both products.⁹

3.6 Conclusions

The Cu(I) catalyzed cross-coupling of 1-bromoalkynes with the metalloamination intermediates derived from N,N-dimethylhydrazinoalkenes has been demonstrated. Of note, only the reactions which utilized 1-bromo-2-phenylethyne had diminished yields. This technique provides saturated N-heterocyclic pharmaceutical scaffolds containing a highly useful internal alkyne for further synthetic elaboration.

3.6 Appendices

All experimental and spectral data for this chapter can be found in the appendices.

3.7 Funding Information

Generous funding for this research was provided by the National Institute for General Medical Science [GM11694].

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CHAPTER FOUR

ON THE COPPER(I)-CATALYZED CROSS-COUPPLING OF 1-BROMOALKYNES WITH N-
HETEROCYCLIC ORGANOZINC REAGENTS. SUBSTRATE SCOPE
AND CATALYST EVALUATION

4.1 Author Contributions

Manuscript in Chapter 4

Author: Christian Frabitore

Contributions: Performed experimental work. Writing and editing of manuscript.

Co-Author: Tom Livinghouse

Contributions: Original idea. Writing and editing of manuscript.

4.2 Manuscript Information

Christian Frabitore and Tom Livinghouse

Synthesis

Status of Manuscript:

☐ Prepared for submission to a peer-reviewed journal

☐ Officially submitted to a peer-reviewed journal

☐ Accepted by a peer-reviewed journal

☒ Published in a peer-reviewed journal

Thieme

Publication Date: July 4, 2023

Volume 55, 2023

DOI: 10.1055/s-0042-1751467

4.3 Abstract

Nitrogen-containing heterocycles are ubiquitous in FDA approved small molecule pharmaceuticals. Herein, we expand on a novel synthetic method for the production of saturated N-heterocyclic pharmacophore motifs with an internal alkyne for elaboration. The treatment of N,N-dimethylhydrazinoalkenes with diethylzinc followed by a Cu(I) catalyzed cross coupling with 1-bromoalkynes affords piperidines and pyrrolidines in respectable yields. Functional group tolerance is demonstrated by the inclusion of heteroatom-bearing alkynes. Unexpectedly, the use of ethyl propiolate as the trapping electrophile led to selective N-functionalization with the formation of vinylogous urethanes. Alternative Cu(I) complexes were also evaluated as prospective catalysts. This synthetic protocol can readily be achieved on a preparative scale.

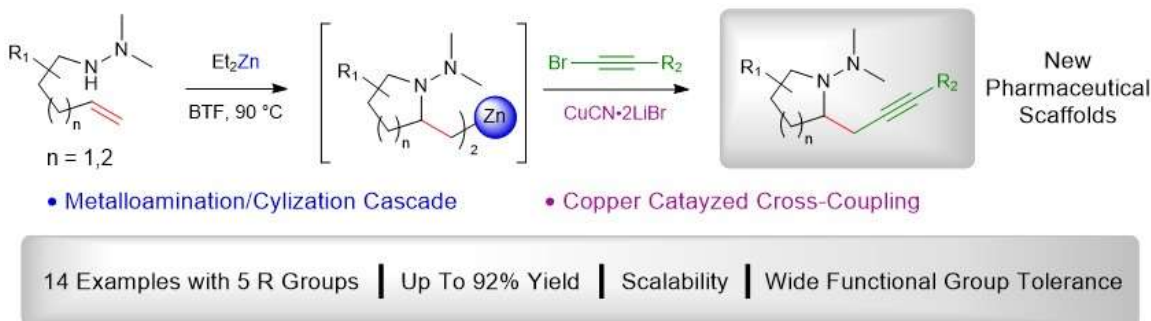
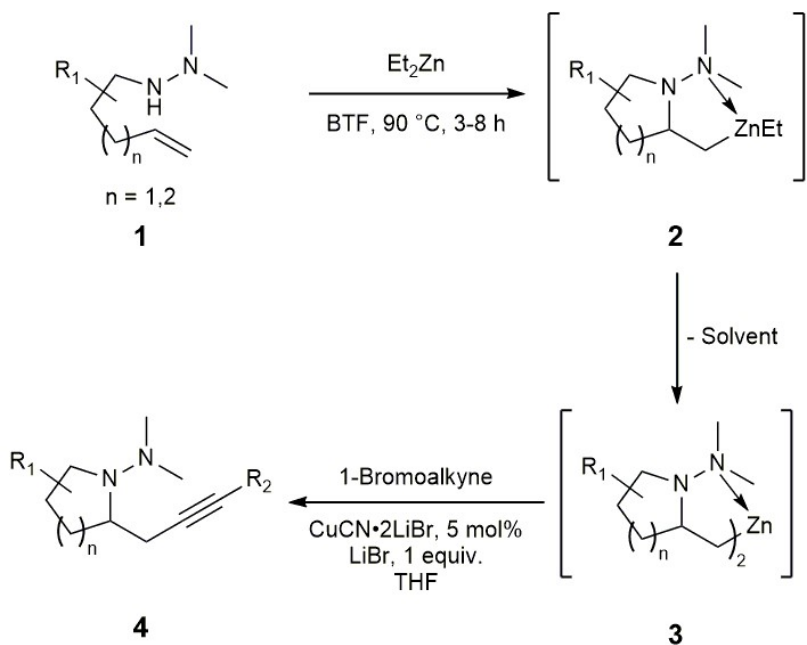


Figure 4.1 Graphical abstract for the *Synthesis* manuscript

4.4 Introduction

The FDA has approved thirty-one new drugs and combination therapies in 2022.¹ Of these thirty-one new pharmaceuticals, twenty-two are small molecules, eighteen of which contain N-heterocycles and twelve of which contain saturated N-heterocycles. N-heterocyclic small molecule motifs have formed the plurality of new pharmaceuticals approved by the FDA

for the entirety of this young decade.¹⁻³ N-heterocyclic compounds occupy this position since they are considered privileged scaffolds for medicinals due to their increased pharmacokinetics and bioavailability.⁴⁻⁶ Accordingly, a synthetic method that provides azacycles, which can be easily functionalized, would be useful for drug discovery.⁴⁻⁷ We have briefly described a synthetic method in this category, which involves the copper(I) catalyzed cross-coupling of 1-bromoalkynes with N-heterocyclic organozinc reagents derived from N,N-dimethylhydrazines bearing pendant alkenes.⁸ Here we provide a detailed account of this transformation, which encompasses the reaction scope, functional group tolerance, and show that this method can be readily adapted to a preparative scale (Scheme 4.1).



Scheme 4.1 Zn(II)-mediated metalloamination/cyclization and Subsequent Cu(I)-catalyzed 1-bromoalkyne cross-coupling.

The foregoing reaction sequence was developed with the aim of facilitating an efficient method for the rapid and convergent assembly of saturated N-heterocyclic (azacyclic) scaffolds.

The incorporation of alkyne appendages provides for the further elaboration of these to expedite the construction of more extensive molecular libraries.⁹

4.5 Results and Discussion

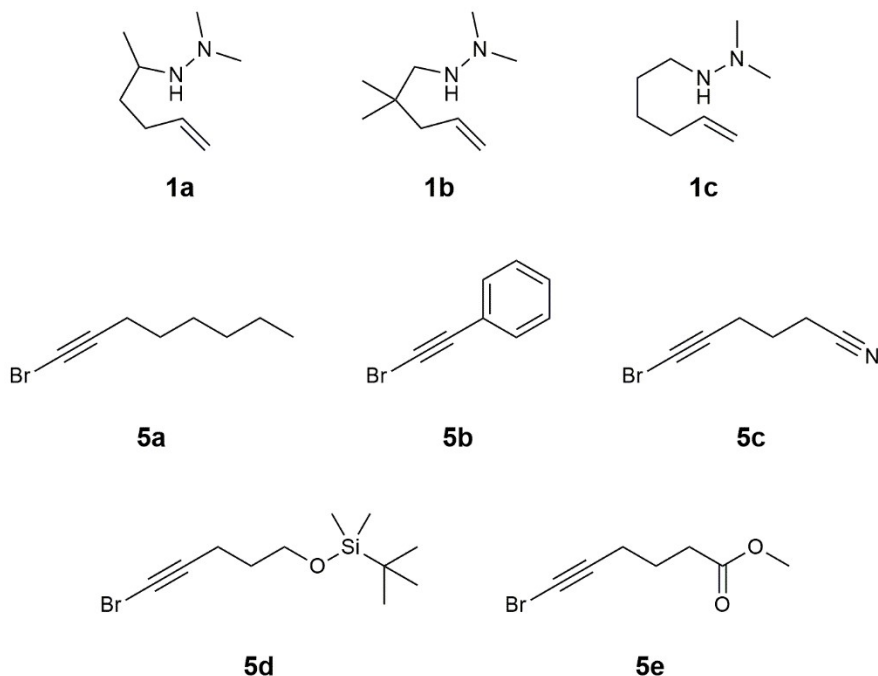
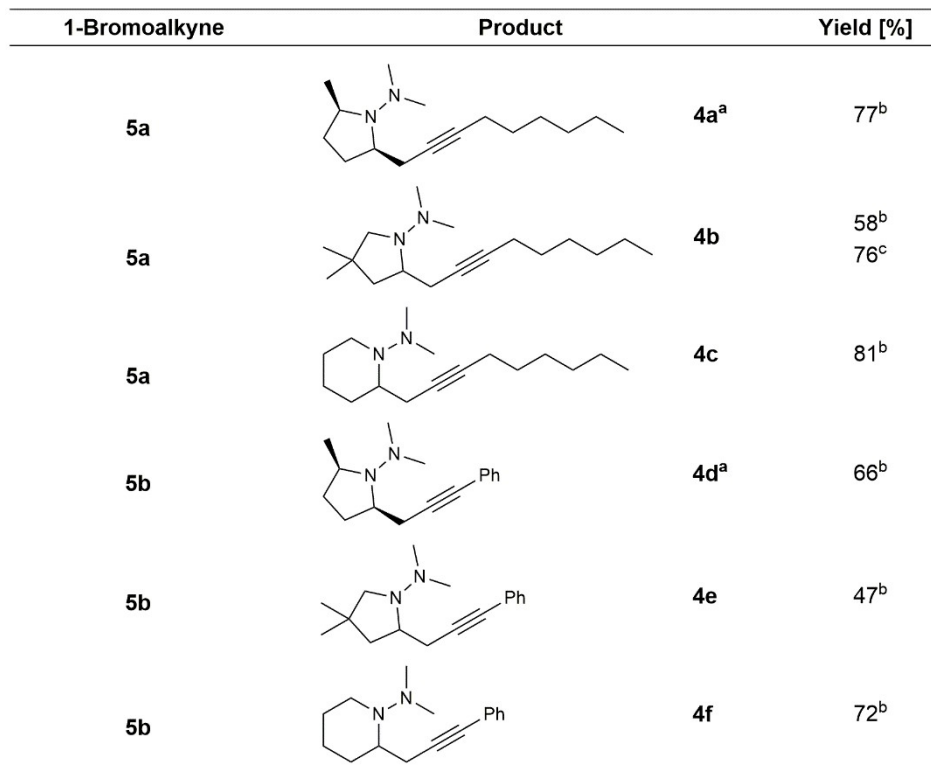


Figure 4.2 N,N-dimethylhydrazinoalkenes and 1-bromoalkynes used in this study.

We have previously shown that the metalloamination/cyclization of N,N-dimethylhydrazinoalkenes **1a-c** efficiently produces the corresponding N-heterocyclic organozinc intermediates (Figure 4.2).¹⁰⁻¹² Metalloamination/cyclization promoted by diethylzinc proceeded optimally at 90 °C when benzotrifluoride (BTF) was used as the reaction solvent, although toluene and even 1,2-DME can be substituted. In contrast, THF suppresses this process. In addition, 1.1 equiv of Et₂Zn is necessary for metalation since the remaining Zn–Et group in the post-cyclization intermediate **2** inefficiently deprotonates the starting hydrazine N–H.¹³ Since the remaining ethyl group in **2** would be expected to also engage in consumptive cross-coupling

with the intended 1-bromoalkyne electrophile, it was preemptively deleted by vacuum removal of the BTF solvent, thus driving the Schlenk equilibrium to provide **3** (Scheme 4.1). These bis(N-heterocyclic) organozinc reagents undergo cross-coupling with 1-bromoalkynes on a 0.1 mmol scale by treatment with 2 equiv. of the requisite 1-bromoalkyne, with CuCN·2LiBr (5 mol%), and LiBr (1 equiv.) to efficiently produce the corresponding alkynylated azacycles. For the alkynylation reaction, THF or Et₂O are ideal solvents. Alternatively, 1,4-dioxane can be used for alkynylations performed above its melting point. The scalability of alkynylation was demonstrated by preparing **4b** on a 1.5 mmol scale, using slightly altered reaction conditions (Table 4.1, entry 2).⁸



^c 1.5 mmol N,N-dimethylhydrazinoalkene, 3.0 mmol 1-bromoalkyne, 5 mol% CuCN·2LiBr, 1 equiv. LiBr, -76 °C

Our investigation of organozinc alkynylation were subsequently extended to substrates containing additional functional groups. To demonstrate the applicability of this reaction, 6-bromohex-5-yne nitrile (**5c**), [(5-bromopent-4-yn-1-yl)oxy](tert-butyl)dimethylsilane (**5d**) and methyl 6-bromohex-5-ynoate (**5e**) were intercepted with the bis(azacyclic) organozincs derived from N,N-dimethylhydrazinoalkenes **1a-c**. These cross-coupling reactions furnished the N-heterocyclic nitriles **4g-i**, silyl ethers **4j-l** and methyl esters **4m** and **4n** in good overall yields

(Table 4.2). We have previously shown that the addition of TMEDA as an auxiliary ligand for Cu(I)¹⁴⁻¹⁶ conferred faster reaction times albeit with lower overall product yields due to the production of homocoupled diynes.⁸ This was also noted with the formation of **4e** (Table 4.1) and with 1-bromoalkynes **5c** and **5d**. The use of TMEDA was therefore determined to be deleterious and was discontinued. In contrast, the addition of LiBr (1 equiv.) to reactions conducted in THF conferred a catalyst stabilizing effect, as noted previously.¹⁰

Table 4.2 Alkynylations employing 1-bromoalkynes **5c-e** with 0.1 mmol of N,N-dimethylhydrazinoalkenes **1a-c**.

1-Bromoalkyne	Product	Yield [%]	
5c		4g^a	91
5c		4h	56
5c		4i	82
5d		4j^a	66
5d		4k	57
5d		4l	74
5e		4m	39
5e		4n	92

^a Product obtained as a racemic mixture

For alkynylation reactions conducted on a preparative (1.5 mmol) scale, it was found that cross-coupling at room temperature resulted in side reactions leading to decreased yields.

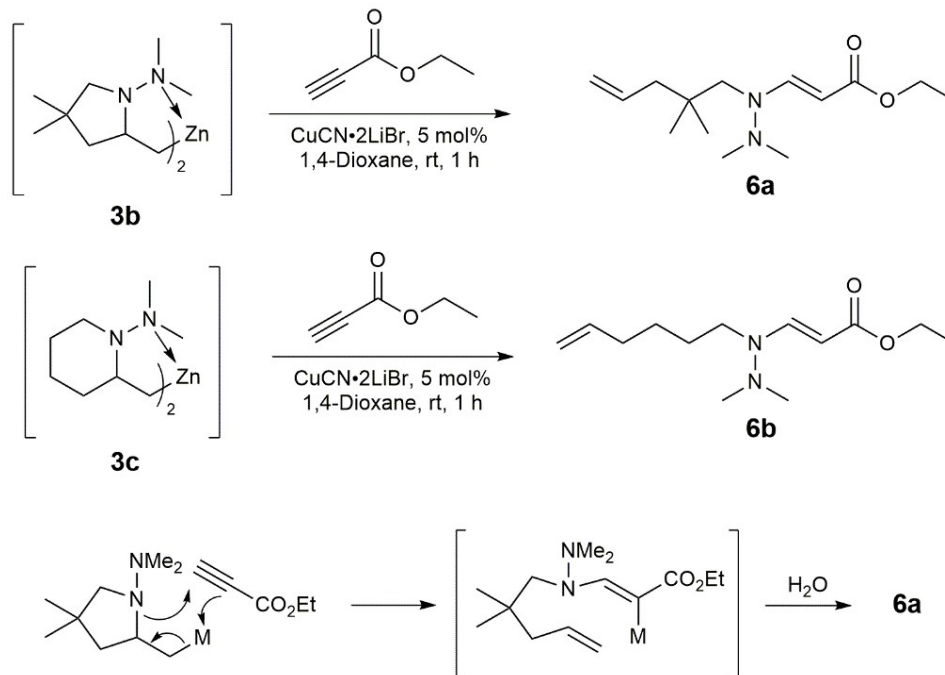
Knochel has shown that the Cu(I)-catalyzed cross-coupling of conventional organozinc

Reaction conditions:
1-Bromoalkyne, 1.33 equiv.
CuCN·2LiBr, 5 mol%
LiBr, 1 equiv.
THF, -78 °C
n = 1, 2 **3a-c** → **4a-o**

1-Bromoalkyne	Product	Yield [%]
5a	4a	45
	4b	76
	4c	55
5b	4d	67
	4e	48
	4f	62
5c	4g	62
	4h	63
	4i	44
5d	4j	84
	4k	72
	4l	84

The preparation of alkynylation products utilizing substrate **3a** was occasionally impacted by incomplete cross-coupling. Gas chromatographic analysis confirmed the presence of unreacted N,N-dimethylhydrazinoalkene **1a** in these cases. Alternative Cu(I) catalysts were therefore investigated. Copper(I) thiophene-2-carboxylate (CuTC), CuBr·P(OEt)₃, and [Cu(IPr)]Cl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) are Cu(I) complexes that have previously been demonstrated to activate carbon halogen bonds in cross-coupling reactions.¹⁸⁻²² Additionally, CuTC has been previously used to couple alkyllithium reagents with 1-bromoalkynes.¹⁹ These Cu(I) sources were evaluated as catalysts for the preparation of product **4a**. Unfortunately, these catalysts offered no obvious advantages as the overall product yield remained relatively unchanged.

Ethyl propiolate has previously been shown to serve as an efficient 1,4-acceptor for conventional organozinc iodides in the presence of *stoichiometric* CuCN·2LiCl.¹⁷ In an effort to utilize this alkynoate as the electrophilic component for C–Zn functionalization, it was found that treating intermediates **3a** and **3b** with ethyl propiolate (2 equiv, Et₂O or 1,4-dioxane, 10 °C) did not provide the anticipated products, but instead gave the vinylogous urethanes **6a** and **6b** via C–N bond formation in excellent yield. Conceivably, these products could have arisen by way of a cyclic transition state followed by hydrolytic protonation of the α -C–M bond as depicted in Scheme 4.2.



Scheme 4.2 Synthesis of vinylogous urethanes **6a** and **6b** and possible mechanism for their formation.

4.6 Conclusions

The Cu(I)-catalyzed cross-coupling of organozinc intermediates derived from N,N-dimethylhydrazinoalkenes with 1-bromoalkynes has been substantially expanded in the context of this investigation. Functional group-bearing 1-bromoalkynes have been shown to be compatible as electrophilic partners in cross-coupling. The use of LiBr as a catalyst adjuvant provides enhanced conversions and improved yields. Lowering the reaction temperature for cross-coupling facilitated the production of products on a preparative scale and in improved yields. This modified experimental protocol provides a stereocontrolled route to saturated N-heterocyclic assemblies possessing an internal alkyne, that may be synthetically altered for

subsequent structural modification. Unexpectedly, the use of ethyl propiolate as the electrophile led to N-C rather than C-C bond formation providing vinylogous urethanes as products.

4.7 Appendices

All experimental and spectral data for this chapter can be found in the appendices.

4.8 Funding Information

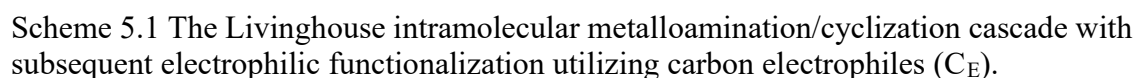
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5.1 Optimizing the Livinghouse Metalloamination and Electrophilic Functionalization



Initially inspired by the work of Blechert,¹ the Livinghouse group originally optimized a Zn(II)-mediated intramolecular metalloamination/cyclization reaction in toluene (Scheme 5.1).² The conversion of the starting N,N-dimethylhydrazinoalkene **1** to the azacyclic organozinc intermediate **2** could take up to 24 h to complete depending on the substrate. In 2018, Mickelsen, et al. examined how modulating the polarity and electron density of the aryl solvent could increase the rate of this metalloamination/cyclization.² Mickelsen discovered that chlorobenzene and thiophene shortened the reaction to 12 h and that benzo-trifluoride (BTF) shortened the overall reaction to 6 h. While this change did considerably accelerate the reaction, the use of BTF significantly increased the overall cost of the reagents. Furthermore, the subsequent functionalization of **2** to **3** must be carried out in THF. Thus, a solvent that would allow for both quick and complete metalloamination, as well as smooth electrophilic functionalization, was sought. 1,2-Dimethoxyethane (1,2-DME) has similar polarity to BTF ($\epsilon = 7.20$ and 9.18,

respectively), making it a possible replacement for the metalloamination step; and 1,2-DME has been used in the past to replace THF in organometallic reactions with both zinc^{3,4} and copper.⁵ Therefore, 1,2-DME was assessed as a possible substitute. The reaction of 2-(hex-5-en-1-yl)-1,1-dimethylhydrazine (**1-Me**) with Et₂Zn in 1,2-DME at 90 °C was found to afford the N-heterocyclic organozinc intermediate **4** in 22 h. **4** was then subjected to electrophilic functionalization, utilizing methallyl chloride under multiple catalyst systems to elucidate 1,2-DME's ability to replace THF for the functionalization step (Table 5.1)

Table 5.1 The electrophilic functionalization of the azacyclic organozinc intermediate **4** in 1,2-DME utilizing different catalyst systems.

Entry	Cu(I) Catalyst	Additive	Time ^a	% Conversion
1	CuCN·2LiBr	1 eq LiBr	10 h	>95%
2	CuCN·2LiBr	None	22 h	>95%
3	CuCN·2LiBr	1 eq HMPA	178 h	>95%
4	CuCN·2LiI	None	83 h	45%
5	CuCN·2LiI	1 eq LiI	81 h	40%
6	CuCN·2LiI	1 eq HMPA	345 h	>95%

^a Reactions were monitored until no change was apparent by ¹H NMR

The use of CuCN·2LiBr admixed with one equivalent of LiBr, the most efficient catalyst system reported by Mickelsen, et al. (Entry 1), produced a clean allylation in 1,2-DME in 10 h; the same time previously reported.² Mickelsen, et al. had also found that CuCN·2LiBr admixed

with one equivalent of LiBr performed a cleaner and faster functionalization than $\text{CuCN} \cdot 2\text{LiCl}$ admixed with one equivalent of LiCl.^{2,6} Entry 4 (Table 5.1) confirmed that continuing this trend to the iodine salts did not improve the performance of the system. The addition of HMPA to our catalyst system also proved less effective than Mickelsen's original system (Entries 3 and 6). Furthermore, as was previously demonstrated Although the metalloamination and functionalization steps were slower in 1,2-DME than the respective reactions in BTF and THF, the ability to use a single solvent for both steps is still considered highly practical.

Chelating diamine ligands are a well-known source of stabilization and acceleration for a range of Cu(I)-catalyzed functionalizations.^{7,8} Therefore, it was hypothesized that the application of chelating amine bases in the functionalization step may improve the rate and yield of the reaction (Table 5.2).

Table 5.2 The electrophilic functionalization of **4** in 1,2-DME utilizing chelating amine bases.

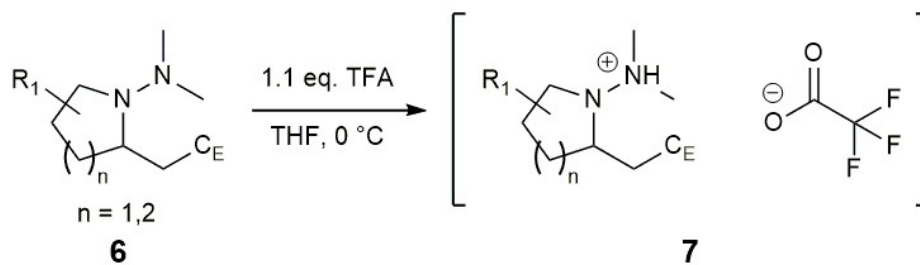
Reaction scheme: **4** $\xrightarrow[\text{Amine base, 1,2-DME, rt}]{\text{CuCN} \cdot 2\text{LiBr, 1 eq LiBr, Cl-CH}_2\text{-CH=CH}_2}$ **5**

Entry	Amine base	Time	% Conversion
1	Methylpiperazine	24 h	Decomposed
2	PMDTA	10 h	>95%
3	DMEDA	8 h	>95%
4	TMEDA	4 h	>95%

Tetramethylethylenediamine (TMEDA), dimethylethylenediamine (DMEDA), pentamethyldiethylenetriamine (PMDTA), and methylpiperazine were all tested as additives to the functionalization step. Apart from methylpiperazine (Entry 1), all tested amines improved the rate of reaction. The ability of TMEDA to accelerate the electrophilic functionalization of our organozinc intermediates was striking, completing the reaction in less than half the time reported in the 2018 study (Entry 4).² Reactions of various N,N-dimethylhydrazinoalkenes with allyl bromide, methallyl chloride, and propargyl chloride in the presence of TMEDA were thoroughly explored, and all examples experienced significant acceleration and resulted in good yields.

5.2 Optimizing the Work-Up of the Products of the Electrophilic Functionalization

The products of the Cu(I)-catalyzed allylations reported by the Livinghouse group are traditionally isolated as the mono-TFA salt by addition of 1.1 equivalents of TFA to the crude amine product (Figure 5.1).² TFA salts (**7**) are considered advantageous due to their low solubility in nonpolar solvents and their significantly higher boiling points, allowing flash chromatography to be replaced with a simple trituration and the azacyclic products to be dried completely by high vacuum with no possibility of product loss. However, when this purification method is applied to the products of TMEDA-accelerated functionalizations, the resulting products are impure. It was hypothesized that some side product forms during the TMEDA-accelerated functionalization that is not produced during those reported by Mickelsen, et al. As a result, TFA salts of the products made by the TMEDA-accelerated functionalization must be purified by different means.



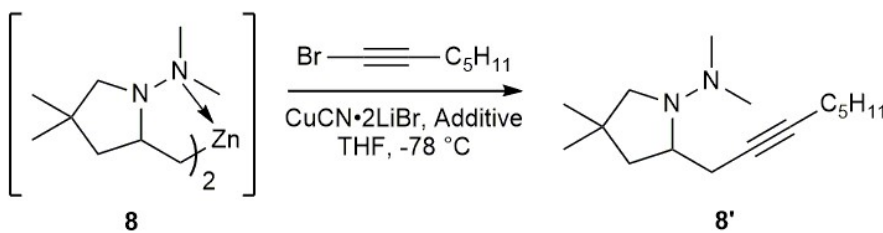
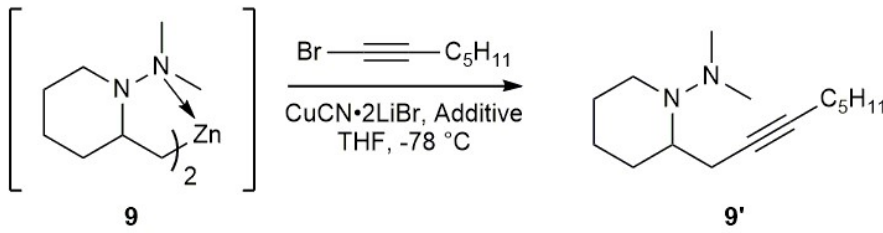
Scheme 5.2 Protonation of the cyclic amine products by TFA.

A similar issue is prevalent when using 1-bromoalkynes as the carbon electrophile, which can suffer from more complex reaction mixtures as the starting 1-bromoalkynes cannot be removed as easily. It was found that the highest yields for all carbon electrophiles can be obtained by purifying the free amines **6** using flash chromatography (See Chapter 4).

5.3 Chelating Amine Ligands for the Cu(I)-Catalyzed Cross-Coupling with 1-Bromoalkynes

TMEDA is an incredible stabilizing ligand in our Cu(I)-catalyzed functionalization reactions using allylic electrophiles, providing increased rates and yields over previously reported reactions. Consequently, the addition of TMEDA to the functionalization of azacyclic organozinc reagents **8** and **9** with 1-bromo-1-octyne was investigated (Table 5.3).

Table 5.3 The use of TMEDA in the Cu(I)-catalyzed cross-coupling of 1-bromo-1-octyne with N-heterocyclic organozinc intermediates **8** and **9**.

			
Entry	Additive	Time	yield
1	1 eq TMEDA	12 h	45%
2	1 eq TMEDA + 1 eq LiBr	12 h	44%
3	1 eq LiBr	18 h	58%
			
Entry	Additive	Time	yield
4	TMEDA	12 h	72%
5	1 eq TMEDA + 1 eq LiBr	12 h	72%
6	1 eq LiBr	18 h	81%

The addition of TMEDA to the alkylation improved reaction time and did not significantly impact the work-up (Entry 1 and 4). Furthermore, the inclusion of 1 equivalent of LiBr was shown to not affect the time of reaction or significantly impact the ^1H NMR spectrum of the reaction mixture in the presence of TMEDA (Entry 2 and 5). This result appeared to obviate the need for the LiBr additive deemed previously necessary.² While TMEDA does increase the rate of reaction, lower product yields are obtained. It has since been determined that the presence of TMEDA was catalyzing the formation of homocoupled diyne products in the reaction, demonstrated by GC/MS data.⁹ The consumption of the electrophile in this competing

reaction likely caused the reduction in yields from those obtained using Mickelsen's catalyst (Entry 3 and 6). Furthermore, it is known that the inclusion of TMEDA in Sonogashira-type cross-couplings causes similar issues.¹⁰ Subsequently, DMEDA, *trans*-1,2-diaminocyclohexane, and *trans*-1,2-dimethyldiaminocyclohexane, chelating amine ligands known to be advantageous in Cu(I) catalyzed reactions⁷ were also used and found to catalyze the formation of homocoupled diyne products as well.

5.4 Alternative Zn(II) Complexes for the Cu(I)-Catalyzed Cross-Coupling with 1-Bromoalkynes

As previously discussed, the alkynylation of N-heterocyclic organozinc intermediates of type **4** with more reactive 1-bromoalkynes, such as 2-phenyl-1-bromoethyne and 3-bromopropiolate, appear to proceed in uncontrolled exothermic reactions, as evidenced by the decomposition of the reactant mixture with consistently lower product yields (See Chapters 3 and 4). Several other Cu(I) catalysts for the alkynylation failed to control this exotherm or produce higher yields (Chapter 4). Adrian Smith also screened a variety of bidentate anionic 1,3-dicarbonyl and β -carbonyl-imine ligands for Zn(II)-metalloamination/cyclization to control reactivity and induce enantioselectivity, but the ligands tested universally resulted in lower product yields.¹² Furthermore, the work of Blechert¹ (*vide supra*) that served as inspiration for the very first Zn(II)-mediated metalloamination/cyclization in the Livinghouse lab¹¹ demonstrated that, in the presence of a dimethylanilinium tetrakis(pentafluorophenyl)borate activator, a cationic zinc catalyst was generated that readily effected the hydroamination of complex aminoalkenes (Figure 5.2).

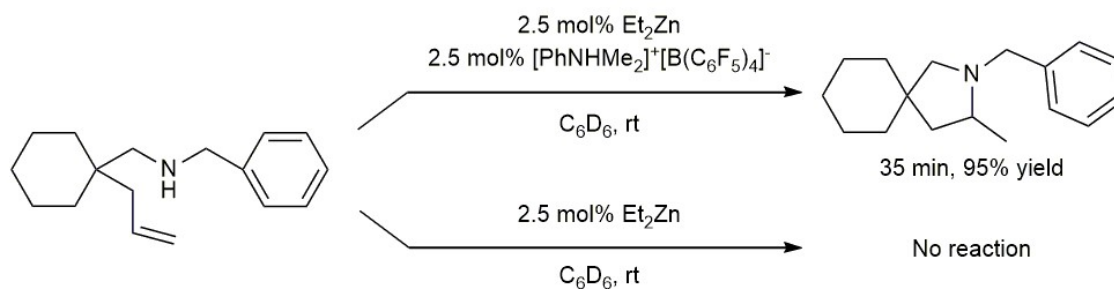
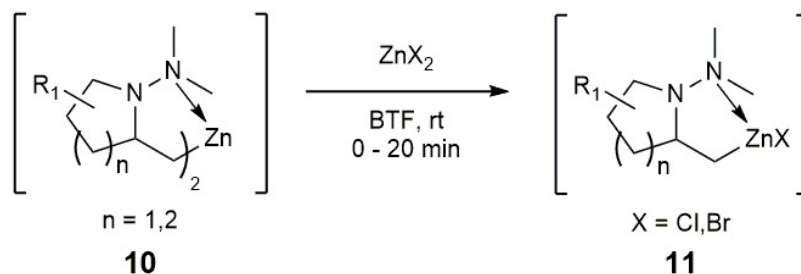


Figure 5.1 Hydroamination using catalytic Zn(II) with an activator.¹

With this previous work and the recent discovery of the detrimental effects of TMEDA on this cross-coupling (Table 5.3) in mind, we hypothesized that a less reactive Zn(II) complex may better moderate this exothermic reaction than ligands, additives, or alternate Cu(I) catalysts.

The Knochel group has found great success in producing difunctionalized alkynes in excellent yields using the so-called “highly functionalized” organometallic species $\text{RCu}(\text{CN})\text{ZnX}$ (R = alkynyl, X = Cl, Br).¹³ Knochel specifically notes that this organometallic species enables the smooth functionalization of 2-phenyl-1-bromoethyne at -78°C with very little degradation.¹³ In order to mirror these conditions, 1 equivalent of ZnX_2 (X = Cl, Br, I) was added to our Cu(I)-catalyzed cross-coupling of azacyclic organozinc intermediates of type **10** with 2-phenyl-1-bromoethyne with the intention of forming $\text{RCu}(\text{CN})\text{ZnX}$ *in-situ* (Scheme 5.2). The addition of the zinc halides did not change the overall reaction and did not improve yields. Furthermore, no evidence showing the formation of the desired highly functionalized organozinc intermediate was found via NMR spectroscopy.



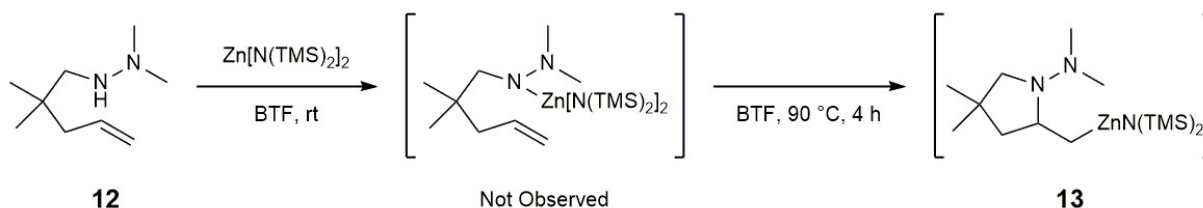
Scheme 5.3 Production of azacyclic zinc halides **11**.

Instead, the addition of ZnX_2 to the pre-formed N-heterocyclic organozinc dimer in BTf led to the instant and complete formation of the desired RZnX reagent **11** at room temperature (Scheme 5.3). The RZnX reagents **11** performed well in the Cu(I)-catalyzed cross-coupling using 2-phenyl-1-bromoethyne at -50°C , slowing the reaction rate and producing a much cleaner reaction mixture. However, the overall conversion to product ($\sim 30\%$, measured by ^1H NMR spectroscopy) is lower than that observed with the N-heterocyclic organozinc dimer (Chapter 4, Table 4.1, Entries 3-6). Diethyl ether and 1,2-DME as solvents for the cross-coupling improved conversions ($\sim 40\%$); however, product yields remained lower than those obtained using organozinc intermediates **10** in THF (Chapter 4). Despite these drawbacks, this new organozinc halide has recently been utilized in a Zn(II)-mediated metalloamination/cyclization that requires no heating and further explorations are under way.

5.5 Alternative Zn(II) Complexes for the Metalloamination/Cyclization

Both the Belchert and Knochel groups have reported the successful intramolecular metalloamination/cyclization of amine-bearing substrates by employing more electron-rich organozinc reagents.^{1,14} Furthermore, Zn(II) amides¹⁵ and Zn(II) N-heterocyclic carbenes¹⁶ have also been reported to be competent catalysts for the formation of C–N bonds. $\text{Zn}[\text{N}(\text{TMS})_2]_2$ has

been demonstrated by Hartwig to be an exceptional Zn(II) catalysts for C–N cross-couplings¹⁷ and has the added benefit of leading to a much more thermodynamically favored deprotonation of N,N-dimethylhydrazinoalkenes due to the formation of HMDS. Unfortunately, $\text{Zn}[\text{N}(\text{TMS})_2]_2$ does not complex with the hydrazine of **12** at room temperature, as expected from previous work in the group.² However, heating the reaction to 90 °C led to the full metalloamination/cyclization of the N,N-dimethylhydrazinoalkene **12** to azacyclic organozinc intermediate **13** without the observation of the intermediate metalation step (Scheme 5.4). Unfortunately, subsequent treatment of the N-heterocyclic organozinc **13** with our Cu(I) catalyst lead to the regeneration of **12**.



Scheme 5.4 Production of azacyclic organozinc intermediate **13** by reaction with $\text{Zn}[\text{N}(\text{TMS})_2]_2$

$\text{Zn}[\text{N}(\text{TMS})_2]_2$, however, has proven very useful for diagnostic use. Successful formation of a desired N-heterocyclic organozinc intermediate is very clear by the unique chemical shifts of the methylene-zinc hydrogen atoms by ^1H NMR spectroscopy and the production of HMDS as a byproduct. Furthermore, the lack of an observable metalation intermediate before metalloamination/cyclization may indicate that the metalation step is the rate-determining step, but further computational work is required to help further elucidate this relationship.

5.6 Conclusions

It was shown that the Cu(I)-catalyzed S_N2' type functionalizations previously reported by Mickelsen, et al. can be successfully carried out in a range of ethereal solvents, demonstrating its flexibility and robustness. Furthermore, readily available diamine ligands, and especially TMEDA, can greatly accelerate these reactions. The products of these diamine-accelerated reactions were unable to be isolated as TFA salts in high yield, necessitating the development of a new purification method that was easily adapted to the work with alkynyl products (see Chapters 3 and 4). It has also been demonstrated that careful control of reaction conditions when attempting functionalizations with especially reactive electrophiles is paramount, however, CuCN·2LiBr admixed with 1 equivalent of LiBr can enact these transformations with no alterations. While it has been found that less reactive Zn(II) complexes can moderate the rate of both the intramolecular metaloamination/cyclization and subsequent Cu(I)-catalyzed functionalization, these alternative complexes universally led to lower product conversions. However, the ability of zinc halides to moderate difficult reactions is a very promising concept that warrants further investigation.

5.7 Appendices

Experimental and spectral data of selected experiments can be found in the appendices.

5.8 References

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CHAPTER SIX

ALLENES AS C–N BOND ACCEPTORS IN ZN(II)-MEDIATED
INTRAMOLECULAR METALLOAMINATION/CYCLIZATION6.1 Introduction

Zn(II)-mediated intramolecular metalloamination/cyclization of N,N-dimethylhydrazinoalkenes established by the Livinghouse group has been demonstrated to be a highly useful method for the production of pharmaceutically relevant pyrrolidines and piperidines.¹⁻⁴ The two-step reaction has undergone a number of optimizations since 2014, which have ultimately improved the reaction rate, product yields, and scope of functionalizations. The current state of the art has proven to be capable of cyclizing a wide range of substrates and catalyzing functionalization of the organozinc intermediate with allylic, propargyl, and alkynyl electrophiles.¹⁻⁴ One drawback of this method is that, unlike previous work,^{5,6} the introduction of any proton source to the N-heterocyclic organozinc intermediate of the Zn(II)-mediated metalloamination/cyclization will result in the full reversal of the reaction back to N,N-dimethylhydrazinoalkene and not the expected hydroamination product (Figure 6.1).¹ Therefore, this method is acutely sensitive to air and moisture, and requires great care in its execution.

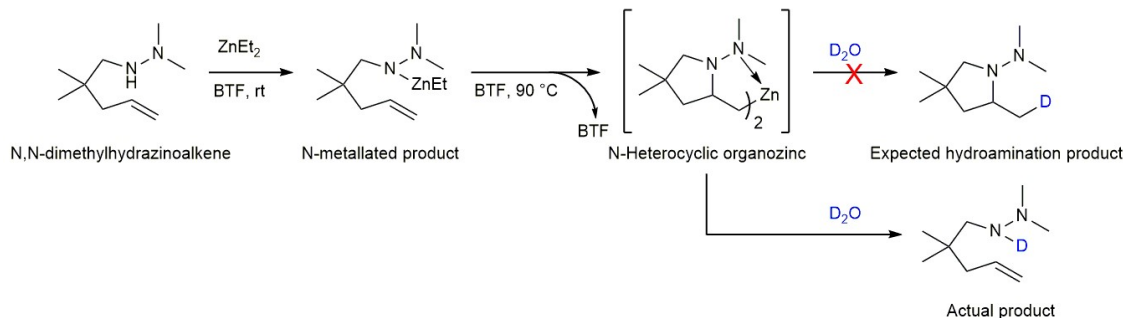
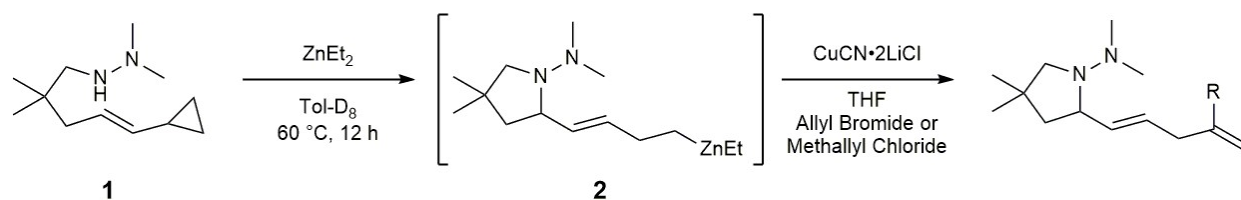


Figure 6.1 Treatment of azacyclic organozinc intermediates with D₂O.

In 2016, the Livinghouse group published the use of 1,2-disubstituted alkenes as the C–N bond acceptor in intramolecular metalloamination/cyclization reactions.² In this work, the group demonstrated the use of a vinylcyclopropane derived N,N-dimethylhydrazinoalkene, **1**, which was noted as being the most reactive of the disubstituted alkenes that were studied.² In his thesis, Mickelsen notes that this is the first and only example of an irreversible intramolecular metalloamination/cyclization that the group has described, since the cyclization step leads to an irreversible cyclopropyl scission in the formation of organozinc intermediate **2** that would make the reverse reaction highly unfavorable (Scheme 6.1).⁷



Scheme 6.1 Irreversible metalloamination/cyclization of (*E*)-2-(5-cyclopropyl-2,2-dimethyl-4-en-1-yl)-1,1-dimethylhydrazine with subsequent allylation.²

The ability to effect the metalloamination/cyclization irreversibly in a considerably thermodynamically favored reaction was envisioned to provide a pathway to add tri-substituted alkenes to the list of substrates, as well as the ability to affect “remote” functionalizations. To

investigate this possibility, seven additional vinylcyclopropyl-derived N,N-dimethylhydrazinoalkenes were prepared and thoroughly examined for their ability to cyclize via an intramolecular metalloamination. Unfortunately, a set of cyclopropyl-derived substrates that would cyclize was unable to be identified.⁷ One possible reason why these reactions failed was due to the overall steric hinderance inherent in the transition state of these cyclopropyl substrates. In order to effect the desired *syn*-addition of Zn–N across the C–C double bond, the cyclopropyl ring of the substrate would be in such a position as to cause severe steric strain (Figure 6.3). Inspired by earlier examples of allenes as migratory insertion partners in intramolecular cyclizations,^{8–10} we hypothesized that using N,N-dimethylhydrazinoallenes could affect similar irreversible metalloamination/cyclizations of the substrate while avoiding steric hinderance that likely prevented the vinylcyclopropyl derivatives from cyclizing (Figure 6.3).

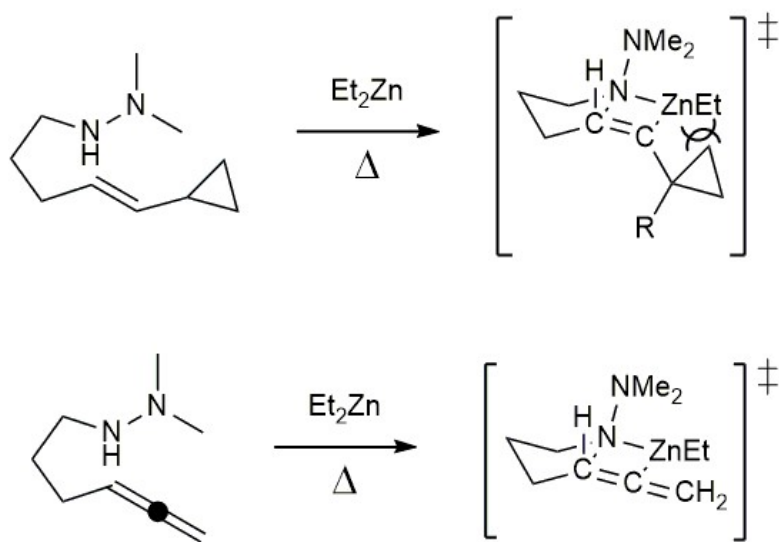
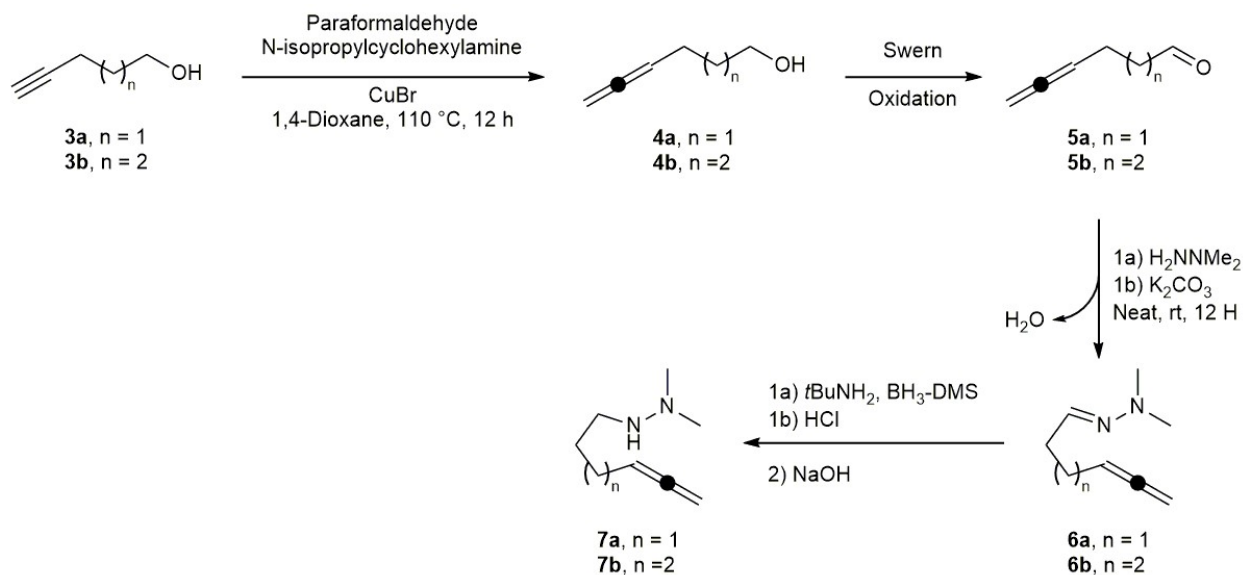


Figure 6.2 Proposed steric hinderance during the cyclization of cyclopropyl-derived substrates and the proposed transition state of a similar hydrazinoallene.

6.2 Synthesis and Initial Screening of N,N-Dimethylhydrazinoallenes

Initially a model N,N-dimethylhydrazinoallene that would form a pyrrolidine product was synthesized. Starting with 4-pentyn-1-ol, **3a**, a Crabbé homologation reaction affords hexa-4,5-dien-1-ol, **4a**.^{11,12} This alcohol is then converted to the corresponding aldehyde, **5a**, by Swern oxidation^{13,14} and condensed with N,N-dimethylhydrazine in the presence of drying agent to afford hydrazone **6a**. Utilizing our previously published amine-borane reduction method,¹⁵ the desired N,N-dimethylhydrazinoallene **7a** was synthesized and tested for cyclization using Et₂Zn (Scheme 6.1).



Scheme 6.2 Synthesis of N,N-dimethylhydrazinoallenes **7a** and **7b**.

The addition of 1.2 equivalents of Et₂Zn to 0.1 mmol of substrate **7a** with no heating leads to swift complexation, as evidenced by ¹H NMR spectroscopy. Subsequent heating at 40 °C for only 4 h results in near complete consumption of the allene peaks by NMR spectroscopy. This metalloamination/cyclization demonstrated that, like vinylcyclopropyl-derived substrates,

the allene appears to undergo exceptionally facile cyclization.^{2,7} Subsequent treatment of organozinc intermediate **8** with 10 equivalents of MeOH leads to the production of a complex product mixture. Separation of the mixture by column chromatography yielded starting material and the expected hydroamination product by ^1H and ^{13}C NMR spectroscopy (Figure 6.4).

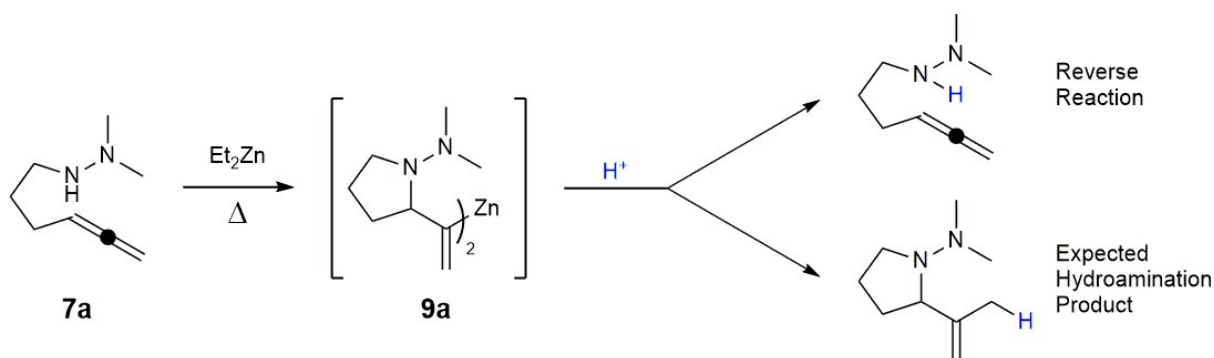
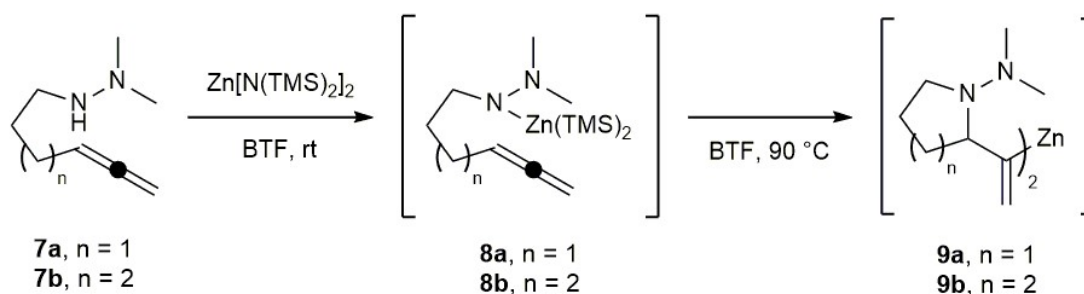


Figure 6.3 Identified products of the reaction of substrate **7a** with Et_2Zn .

This initial result provides significant support for our initial hypotheses. Not only was the metalloamination/cyclization able to be completed in only 4 h at lower temperatures than N,N-dimethylhydrazinoalkenes, but the organozinc intermediate **9a** could be treated with a proton source to produce the hydroamination product, which makes this reaction irreversible as with the previously reported vinylcyclopropyl-derived substrate.³ It should be noted, however, that these results are preliminary as both isolated products were obtained in < 10% yield (< 2 mg each).

The N,N-dimethylhydrazinoallene corresponding to a piperidine product can be produced by treating 5-hexyn-1-ol, **3b**, with the same reaction sequence as 4-pentyn-1-ol to produce the substrate **7b** (Scheme 6.1). Again, treatment with 0.1 mmol of **7b** with 1.2 equivalents of Et_2Zn at room temperature results in complete complexation of the substrate. Heating the reaction to 40 °C leads to the full consumption of 1 equivalent of Et_2Zn and production of 1 equivalent of

ethane, but does not also concurrently consume the allene peaks in the ^1H NMR spectrum. Furthermore, the ^1H NMR spectra recorded during the experiment only contained extremely broad peaks, making positive identification of the azacyclic organozinc intermediate, hypothesized to be **9b** (Figure 6.5), difficult at this early stage. Treatment of the unidentified intermediate with 5 equivalents of MeOH results in similarly low-quality NMR spectra and heterogeneous products. While reactions of **7b** in toluene gives similar results, the reaction in 1,2-DME does demonstrate some consumption of the allene peaks, but with similarly low-quality NMR spectra and a non-homogenous product.

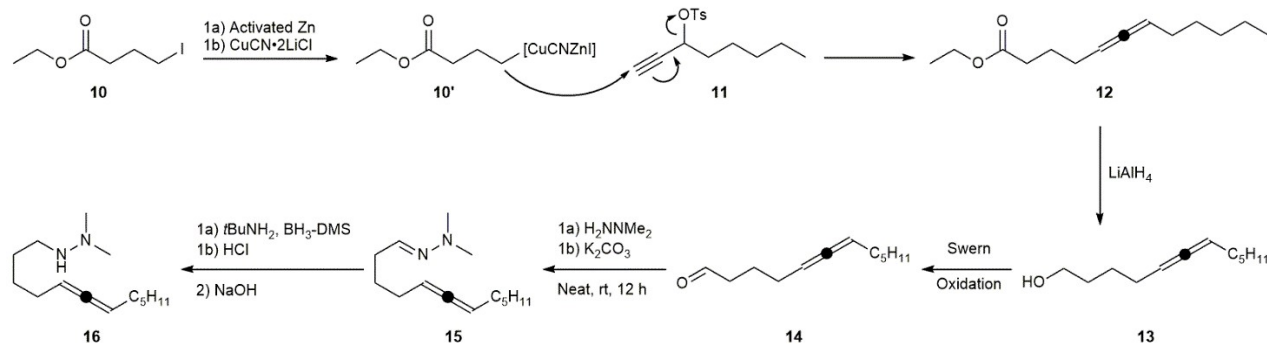


Scheme 6.3 Production of the azacyclic organozinc intermediates **9a** and **9b** expected from the intramolecular metalloamination/cyclization of **7a** and **7b**.

Having found previous success using $\text{Zn}[\text{N}(\text{TMS})_2]_2$ to moderate metalloamination/cyclization reactions (see Chapter 5), we hypothesized that the increased steric bulk and basicity of this Zn(II) source could aid in the metalloamination/cyclization of these substrates and improve product yields. The addition of 1.2 equivalents of the zinc reagent at room temperature to 0.1 mmol of both substrates **7a** and **7b** produces a small amount of metalated intermediate **8a** and **8b** and HMDS ($< 5\%$, ^1H NMR). Allowing the reactions to stand at room temperature and heating them to $40\text{ }^\circ\text{C}$ results in the very slow production of more metalated intermediate and HMDS. Heating the reactions to $90\text{ }^\circ\text{C}$ for 6 h causes the production

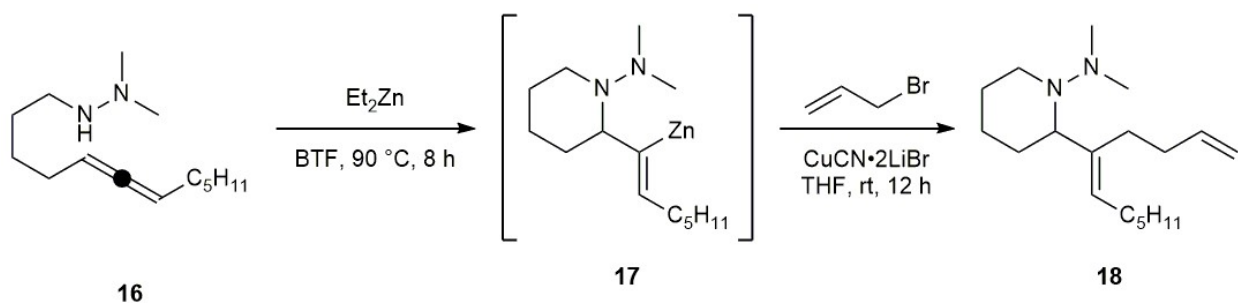
of the expected azacyclic organozinc intermediates **9a** and **9b** by ^1H NMR spectroscopy and the concomitant production of HMDS (Figure 6.5). However, upon treatment with 5 equivalents of acetic acid and work-up with EDTA, a complex mixture was observed in both cases, which could not be easily separated by chromatography. While $\text{Zn}[\text{N}(\text{TMS})_2]_2$ provides no obvious advantage in product yield, it is notable that this reagent is apparently able to affect the cyclization of substrate **7b**; which was not observed with Et_2Zn , and that both azacyclic organozinc intermediates **10a** and **10b** were able to be clearly observed by NMR spectroscopy.

Due to these results, it was hypothesized that the steric bulk of the substrate may indeed have a profound effect on the reaction. Therefore, 1,3-disubstituted N,N-dimethylhydrazinoallene **16** was synthesized and tested using the same reaction conditions.. Following the work of Bäckvall, dodecadiene ester **12** is produced via a Cu(I)-mediated $\text{S}_{\text{N}}2'$ reaction by first generating alkyl zinc reagent **10'**, and transmettaling with $\text{CuCN}\cdot 2\text{LiCl}$, which affects a carbocupration with 1-octyn-3-yl tosylate, **11**. Ester **12** is smoothly reduced to the corresponding alcohol **13**, then oxidized to the aldehyde **14**. Condensation with N,N-dimethylhydrazine and reduction by amine-borane gives N,N-dimethylhydrazinoallene **16** (Scheme 6.2).⁸



Scheme 6.4 Synthesis of 1,3-disubstituted N,N-dimethylhydrazinoallene **16**.

Reaction of **16** with Et_2Zn at room temperature overnight leads to complete consumption of Et_2Zn with concomitant production of stoichiometric ethane, but the allene remained unchanged in the ^1H NMR spectrum. Heating to $90\text{ }^\circ\text{C}$ for 4 h leads to nearly complete consumption of the allene peaks, however, the resulting intermediate **17** and the product of treatment of **17** with 5 equivalents of acetic acid are both heterogenous and give poor NMR spectra. Heating **16** directly to $90\text{ }^\circ\text{C}$ leads to complete consumption of Et_2Zn in 1 h, but the allene remains unchanged. Heating for a further 8 h consumes the allene, forming intermediate **17**, and subsequent treatment with acetic acid and work-up regenerated starting material and a complex mixture of products. The organozinc intermediate **17** was also treated with 5 mol% of $\text{CuCN}\cdot 2\text{LiBr}$ and 4 equivalents of allyl bromide, in order to affect allylation.⁴ Allowing **17** to react overnight at room temperature under these conditions results in partial consumption of the allyl bromide in the ^1H NMR spectrum with concurrent growth of new alkene resonances consistent with the expected allylation product **18** (< 20%, Scheme 6.3). Unfortunately, work-up results in another highly complex product mixture with multiple co-eluting species, making positive identification of the intended allylated product difficult.



Scheme 6.5 Reaction of **16** with Et_2Zn with subsequent allylation.

6.3 Conclusions

While intramolecular metalloamination/cyclizations of N,N-dimethylhydrazinoallenes have yet to produce good yields of the intended alkenyl products, the initial results of treating **7a**, **7b**, and **16** with multiple Zn(II) reagents to affect metalloamination/cyclization indicates that this method can likely be optimized. Our preliminary work with **7a**, **7b**, and **16** has demonstrated that the hydrazine of each complexes with Zn(II), are able to at least partially cyclize intramolecularly, and do so in faster rates than our previously reported N,N-dimethylhydrazinoalkenes. Preliminary results also demonstrate the azacyclic organozinc intermediate **9a** can be protonated to form the expected hydroamination product in an irreversible metalloamination/cyclization. These preliminary results bolster our hypotheses and demonstrate that improved yields likely can be obtained.

6.4 Appendices

All experimental and spectral data for this chapter can be found in the appendices.

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CHAPTER SEVEN

CONCLUSIONS AND FUTURE WORK

Throughout this manuscript, the utility, flexibility, and optimization of Zn(II)-mediated intramolecular metalloamination/cyclization reactions have been explored.

Nitrogen-containing heterocycles become increasingly important to the pharmaceutical industry every year due to their unusual ability to take part in a plethora of intermolecular interactions. Azacyclic drugs continue to be the front-runners of the pharmaceutical industry in effectiveness, sales, and scope. In light of this, synthetic methods which produce azacycles have been increasingly in demand, particularly those which provide these heterocycles with enhanced molecular complexity and atom economy. However, methods which provide saturated azacycles are lacking. Zn(II)-mediated intramolecular metalloamination/cyclization reactions provide one such method for the production of pyrrolidines and piperidines, with a focus on producing azacycles that can be easily elaborated as scaffolds for the production of complex pharmaceuticals.

Utilization of preformed primary amine-boranes for the reduction of N,N-dimethylhydrazones has proven to be an exceptionally useful method for the synthesis of the corresponding hydrazines. Using this method, N,N-dimethylhydrazones are reduced completely in 80-95% yield with no side-products and work-up of the reaction mixture is simple. This method is robust and easily adapted to any N,N-dimethylhydrazone, including N,N-dimethylhydrazonoalkynes and N,N-dimethylhydrazonoallenes, with the same efficiency. This new method has improved yields of the desired compounds, removed the issue of remaining

unreduced hydrazone prevalent when using LiAlH_4 , and has obviated the safety concerns inherent with LiAlH_4 and NaBH_3CN .

1-Bromoalkynes were successfully coupled with the azacyclic organozinc intermediates of intramolecular Zn(II) -mediated metalloamination/cyclizations using $\text{CuCN}\cdot 2\text{LiBr}$, the same Cu(I) catalyst reported previously. The cross-coupling reaction was effectively optimized and demonstrated to tolerate a full range of functional groups. The Cu(I) -catalyzed cross-coupling of 1-bromoalkynes to organozinc intermediates could also be readily achieved on a preparative scale, further demonstrating its utility. The addition of alkynes to our pyrrolidine and piperidine products serves as a useful handle for further synthetic elaboration, making them exceptional scaffolds for drug discovery. The importance of solvent was also demonstrated, as the alkynyl methyl ester tested was only able to be successfully coupled to our organozinc intermediates in diethyl ether, a departure from previous methods. Furthermore, we have observed the first instance of a direct N-C bond formation using these conditions in the production of vinylogous urethanes. This new cross-coupling could itself be further studied, however, future work should be done cautiously in light of this result and conditions should be carefully considered to limit the possibility of an unintended side-reaction.

Considerable work was undertaken to further optimize intramolecular Zn(II) -mediated metalloamination/cyclizations of N,N -dimethylhydrazinoalkenes. It was demonstrated that chelating diamine ligands greatly accelerate the Cu(I) -catalyzed $\text{S}_{\text{N}}2'$ allylation of the azacyclic organozinc intermediates. Particularly, the addition of one equivalent of TMEDA to the $\text{CuCN}\cdot 2\text{LiBr}$ catalyst can decrease reaction times from 12 h to 4 h. Attempts to find more suitable solvents for both the metalloamination and the subsequent functionalization have shown

that the reaction sequence itself is quite robust and can be adapted to multiple solvent systems. However, the previously reported BTF and THF system was vindicated as the optimal system for these reactions. Many new Zn(II) sources for the intramolecular metalloamination/cyclization were investigated and were universally found to promote similar metalloamination/cyclization reactions as Et₂Zn. While Et₂Zn remains the best Zn(II) source for this transformation, the desire to find less harsh reaction conditions and less reactive Zn(II) sources has already led to a set of exciting new discoveries: Zn[N(TMS)₂]₂ can be used as a diagnostic tool for the metalation and cyclization steps and RZnX species successfully slow the rate of highly exothermic functionalizations, affording cleaner product mixtures. Furthermore, optimizations stemming from this work may completely obviate our need to use pyrophoric Et₂Zn and high temperatures, leading to milder reaction conditions with even more cost-effective reagents.

Promising initial results have been obtained in the use of N,N-dimethylhydrazinoallenes as substrates for Zn(II)-mediated intramolecular metalloamination/cyclizations. Early experiments have successfully led to metalation of these new hydrazines with subsequent migratory insertion into the allene. Furthermore, this reaction was demonstrated to be irreversible and capable of forming the target hydroamination product, in contrast to previous studies involving alkene acceptors. While results remain limited in scope and low in yield, continued optimization for suitable conditions that could facilitate better conversions are under current investigation.

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APPENDICES

APPENDIX A

EXPERIMENTAL

Chapter Two Experimental

Materials and Methods

Oven- or flame-dried glassware was employed under nitrogen unless otherwise noted. All materials were used as received from commercial sources. Syntheses of hydrazones adapted from previously reported procedures.^{1,2} Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm) or potassium permanganate staining. Nuclear magnetic resonance (NMR) data was obtained from a Bruker AVANCE III HD NMR spectrometer equipped with an Ascend 500 (500 MHz) magnet. Infrared spectra (IR) were obtained from a JASCO FTIR-4100 or a Thermo Scientific iS5 FTIR with iD7 ATR attachment. High-resolution mass spectra (HRMS) were obtained from a Bruker MicroTOF with a Dart 100 – SVP 100 ion source or an Agilent 7890A/5975C TAD series GC/MSD.

Synthesis of Hydrazones

2-(2-Heptanylidene)-1,1-dimethylhydrazine (2a'). A 100 mL round-bottomed flask equipped with a magnetic stirring bar and an N₂ inlet was charged with 2-heptanone (12.5 mL, 90.0 mmol) and N,N-dimethylhydrazine (11.0 mL, 145 mmol). The reactant mixture was stirred at room temperature for 24 h. The resulting water layer was removed and KOH pellets (2 g) were added to the reaction mixture. The solution was stirred for an additional 12 hours then filtered through a pad of Celite. Excess N,N-dimethylhydrazine was removed in vacuo and the concentrate was purified by short path distillation from CaH₂ to provide 12.37 g (87%) of the title compound as a clear liquid. ¹H NMR (500 MHz, CDCl₃): δ 2.44, (s, 6H), 2.20 (t, *J* = 7.8 Hz, 2H) 1.95, (s, 3H), 1.55-1.48 (m, 2H), 1.37-1.27 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 168.0, 47.0, 39.0, 31.4, 26.7, 22.4, 16.4, 13.9; δ 169.6, 47.5, 31.9, 31.4, 26.1,

22.6, 22.4 13.9; **Note:** The peak doubling and integration is due to 4:1 *E* to *Z* isomer ratio.

HRMS Electrospray ionization (ESI) m/z calcd. for $C_9H_{14}N_2^+$: 156.16265, found: 156.200 (mass error $\Delta m = 239$ ppm).

1,1-Dimethyl-2-[1-(4-methylphenyl)ethylidene]hydrazine (**2b'**). A 100 mL flask equipped with a magnetic stirring bar and an N_2 inlet was charged with 4'-methylacetophenone (2.00 mL, 15.0 mmol), *N,N*-dimethylhydrazine (2.28 mL, 30.0 mmol), acetic acid (0.086 mL, 1.5 mmol) and anhydrous ethanol (30 mL). The mixture was refluxed for 12 h, dried over anhydrous sodium sulfate and filtered through a plug of silica. Concentration in vacuo afforded 2.35 g (89 %) of the title compound as a yellow oil. **1H NMR** (500 MHz, $CDCl_3$): δ 7.67 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 2.62 (s, 6H), 2.39 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 162.1, 139.2, 136.4, 128.9, 126.3, 47.3, 21.3, 15.4 **HRMS** Electrospray ionization (ESI) m/z calcd. for $C_9H_{14}N_2^+$: 176.13135, found: 176.100 (mass error $\Delta m = 178$ ppm).

2-Heptylidene-1,1-dimethylhydrazine (**3a'**).³ A 100 mL round- bottomed flask equipped with a magnetic stirring bar, and an N_2 inlet was charged in succession with heptanal (4.20 mL, 29.8 mmol), dichloromethane (20 mL), and *N,N*-dimethylhydrazine (4.60 mL, 60.5 mmol). The reactant mixture was stirred at room temperature for 12 h. The resulting mixture was dried with anhydrous magnesium sulfate and filtered through a pad of Celite. Concentration in vacuo followed by short path distillation from CaH_2 afforded 4.23 g (91%) of the title compound as a clear liquid. **1H NMR** (500 MHz, $CDCl_3$): δ 6.62 (dd, $J = 5.5, 10.7$ Hz, 1H), 2.69 (s, 6H), 2.22-

2.16 (m, 2H), 1.48-1.40 (m, 2H), 1.35-1.20 (m, 6H), 0.89-0.82 (m, 3H). ^{13}C NMR (500 MHz, CDCl_3): δ 139.6, 43.3, 33.1, 31.7, 28.8, 27.7, 22.5, 14.0; **Note:** The peak doubling and integration is due to 4:1 *E* to *Z* isomer ratio.

1,1-Dimethyl-2-(2-phenylethylidene)hydrazine (**3b'**).⁴ A 50 mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet was cooled to 0 °C and charged with phenylacetaldehyde (5.00 mL, 45.0 mmol) followed by the slow addition of N,N-dimethylhydrazine (7.30 mL, 90.0 mmol). The reactant mixture was allowed to warm up to room temperature and was stirred for 4 h. After completion of the reaction was confirmed by TLC, the resulting solution was dried over anhydrous magnesium sulfate and filtered through a plug of silica. Concentration in vacuo followed by short path distillation from CaH_2 afforded 6.43 g (88%) of the title compound as a clear liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.35 (t, J = 7.7 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.25 (d, J = 7.7 Hz, 1H), 6.73 (t, J = 5.6 Hz, 1H), 3.63 (d, J = 5.8 Hz, 2H), 2.81 (s, 6H). ^{13}C NMR (500 MHz, CDCl_3): δ 138.7, 136.7, 128.9, 128.6, 126.4, 43.3, 39.7; **IR**: 2986, 2952, 2854, 2816, 2771, 1602, 1512, 1466, 1358, 1007, 947, 814 cm^{-1} .

2-Benzylidene-1,1-dimethylhydrazine (**3c'**).⁵ A 250 mL round-bottomed flask equipped with a magnetic stirring bar, and an N_2 inlet was charged with benzaldehyde (3.2 g, 30 mmol), dichloromethane (60 mL), anhydrous magnesium sulfate (7.2 g, 60 mmol), and N,N-dimethylhydrazine (4.6 mL, 60 mmol). The reactant mixture was stirred at room temperature for 12 h. The resulting mixture was filtered through a pad of Celite. Concentration in vacuo followed by short path distillation from CaH_2 afforded 4.10 g (92%) of the title compound as a pale-

yellow liquid. **¹H NMR** (500 MHz, CDCl₃): δ 7.60 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 0.75 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 3.01 (s, 6H). **¹³C NMR** (500 MHz, CDCl₃): δ 136.9, 133.0, 128.5, 127.4, 125.7, 42.9.

5-Hexen-2-one-N,N-dimethylhydrazone (**4a'**).⁶ A 50 mL round-bottomed flask equipped with a magnetic stirring bar and an N₂ inlet was charged with 5-hexen-2-one (6.0 mL, 52 mmol) and N,N-dimethylhydrazine (5.0 mL, 65 mmol). The reactant mixture was stirred at room temperature for 12 h. The resulting water layer was removed and KOH pellets (2.0 g) were added to the reaction mixture. The solution was stirred for an additional 2 h then filtered through a pad of Celite. Excess N,N-dimethylhydrazine was removed in vacuo and the concentrate was purified by short path distillation from CaH₂ to provide 5.30 g (88%) of the title compound as a clear liquid. **¹H NMR** (500 MHz, CDCl₃): δ 5.74-5.61 (m, 1H), 4.96-4.78 (m, 2H), 2.48 (dt, *J* = 2.3, 8.2 Hz, 2H), 2.28 (s, 6H), 2.20-2.06 (m, 4H), 1.80 (s, 3H). **¹³C NMR** (500 MHz, CDCl₃): δ 168.5, 166.7, 114.9, 47.3, 46.9, 38.0, 40.0, 30.3, 30.3, 22.4, 16.5; **Note:** The peak doubling and integration is due to 4:1 *E* to *Z* isomer ratio.

2,2-Dimethyl-4-pentenal-N,N-dimethylhydrazone (**4b'**).⁶ A 20 mL round-bottomed flask equipped with a magnetic stirring bar and an N₂ inlet was charged with 2,2-dimethyl-4-pentenal⁷ (2.6 g, 23 mmol) and N,N-dimethylhydrazine (2.2 mL, 28 mmol). The reactant mixture was stirred at room temperature for 12 h. The resulting water layer was removed and KOH pellets (2.0 g) were added to the reaction mixture. The solution was stirred for an additional 2 h then filtered through a pad of Celite. Excess N,N-dimethylhydrazine was removed in vacuo and the

concentrate was purified by short path distillation from CaH₂ to provide 3.00 g (85%) of the title compound as a clear liquid. ¹H NMR (500 MHz, CDCl₃): δ 6.56 (s, 1H), 5.81 (ddt, *J* = 7.3, 10.7, 14.5 Hz, 1H), 5.08-4.97 (m, 2H), 2.71 (s, 6H), 2.16 (dt, *J* = 1.2, 7.3 Hz, 2H), 1.06 (s, 6H). ¹³C NMR (500 MHz, CDCl₃): δ 146.0, 135.3, 116.9, 46.0, 43.4, 37.1, 25.9.

Synthesis of Hydrazines

2-(2-Heptanyl)-1,1-dimethylhydrazine (2a). A 100 mL round-bottomed schlenk flask equipped with a magnetic stirring bar and an N₂ inlet was charged with *t*-butylamine (0.8 mL, 7.65 mmol) and dichloromethane (5 mL). The reactant mixture was cooled to 0 °C with stirring and BMS (0.75 mL, 10 M, 7.5 mmol) was added. The resulting solution was warmed to room temperature and stirred for 30 min. A solution of 2-(2-Heptanylidene)-1,1-dimethylhydrazine (**2a'**, 0.78 g, 5.0 mmol) and methyl orange (10 mg) in methanol (20 mL) was then added. The stirred reactant mixture was then cautiously titrated with a 1:5 HCl:MeOH (v/v) solution at room temperature until the solution maintained a pink/red color for 30 min. The volatiles were removed in vacuo leaving a pink/red residue. Aqueous sodium hydroxide (25% w/w) was added dropwise with stirring until a pH > 10 was achieved. With the exclusion of air, diethyl ether (25 mL) was added to the resulting aqueous solution with vigorous stirring followed by the addition of pentane (10 mL). The resulting aqueous layer was separated and extracted with ether (10 mL), and the combined organic layers were dried with anhydrous sodium sulfate. The volatiles were removed in vacuo and the resulting oil was distilled from CaH₂ to afford 0.71 g (89%) of 2-(2-Heptanyl)-1,1-dimethylhydrazine as a clear liquid. ¹H NMR (500 MHz, C₆D₆): δ 2.75 (sex, *J* = 6.1, 1H). 2.25 (s, 6H), 1.66 (s, 1H), 1.53-1.42 (m, 1H), 1.35-1.17 (m, 7H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.87 (t, *J* = 6.1 Hz, 3H). ¹³C NMR (500 MHz, C₆D₆): δ 52.1, 47.8, 35.8, 32.3, 25.5, 22.7,

19.5, 13.9; **IR** (Film): 3189, 2955, 2928, 2857, 2807, 2764, 1477, 1461, 1374, 1137, 1015, 895, 772, cm^{-1} . **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_9\text{H}_{22}\text{N}_2^+$: 159.1856, found: 159.1893 (mass error $\Delta m = 23.2$ ppm).

1,1-Dimethyl-2-[1-(4-methylphenyl)ethyl]hydrazine (**2b**). The title compound was prepared using the general procedure described for 2-(2-heptyl)-1,1-dimethylhydrazine, employing 1,1-dimethyl-2-[1-(4-methylphenyl)ethylidene]hydrazine (**2b'**, 0.882 g, 5.0 mmol) to furnish 1,1-dimethyl-2-[1-(4-methylphenyl)ethyl]hydrazine (0.80 g, 90%) as a yellow liquid. **¹H NMR** (500 MHz, C_6D_6): δ 7.28 (d, $J = 7.8$ Hz, 2H), 7.03 (d, $J = 7.8$ Hz, 2H), 3.87 (q, $J = 6.2$ Hz, 1H), 2.22 (s, 6H), 2.14 (s, 3H), 1.90 (s, 1H), 1.34 (d, $J = 6.2$ Hz, 2H). **¹³C NMR** (500 MHz, C_6D_6): δ 142.8, 135.9, 128.8, 127.0, 56.9, 47.6, 22.5, 20.7; **IR** (Film): 3193, 2976, 2946, 2840, 2807, 2765, 1515, 1473, 1446, 1362, 1106, 1091, 1017, 895, 818, 777, 733, cm^{-1} . **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_2^+$: 179.1543, found: 179.1566 (mass error $\Delta m = 12.8$ ppm).

2-Heptyl-1,1-dimethylhydrazine (**3a**). The title compound was prepared using the general procedure described for 2-(2-heptyl)-1,1-dimethylhydrazine, employing 2-heptylidene-1,1-dimethylhydrazine (**3a'**, 0.782 g, 5.0 mmol) to furnish 2-heptyl-1,1-dimethylhydrazine (0.63 g, 80%) as a clear liquid. **¹H NMR** (500 MHz, C_6D_6): δ 2.69 (t, $J = 7.0$ Hz, 2H), 2.25 (s, 6H), 1.60 (s, 1H), 1.48 (pen, $J = 7.5$ Hz, 2H), 1.36-1.16 (m, 8H), 0.87 (t, $J = 6.4$ Hz, 3H). **¹³C NMR** (500 MHz, C_6D_6): δ 48.6, 47.4, 31.9, 29.4, 28.8, 27.4, 22.7, 13.9; **IR** (Film): 3178, 2927, 2854, 2807,

2764, 1469, 1377, 1092, 1014, 885, 725, cm^{-1} . **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_9\text{H}_{22}\text{N}_2^+$: 159.1856, found: 159.1916 (mass error $\Delta m = 37.7$ ppm).

1,1-Dimethyl-2-(2-phenylethyl)hydrazine⁸ (3b). The title compound was prepared using the general procedure described for 2-(2-heptanyl)-1,1-dimethylhydrazine, employing 1,1-dimethyl-2-(2-phenylethylidene)hydrazine (**3b'**, 0.81 g, 5.0 mmol) to furnish 1,1-dimethyl-2-(2-phenylethyl)hydrazine (0.71 g, 87%) as a clear liquid. **¹H NMR** (500 MHz, C_6D_6): δ 7.17-7.09 (m, 4H), 7.05 (t, $J = 6.9$ Hz, 1H), 2.91 (t, $J = 7.5$ Hz, 2H) 2.75 (t, $J = 7.5$ Hz, 2H), 2.19 (s, 6H), 1.69 (s, 1H). **¹³C NMR** (500 MHz, C_6D_6): δ 140.8, 128.7, 128.2, 125.8, 50.1, 47.2, 35.3;

2-Benzyl-1,1-dimethylhydrazine (3c). The title compound was prepared using the general procedure described for 2-(2-heptanyl)-1,1-dimethylhydrazine, employing 2-benzylidene-1,1-dimethylhydrazine (**3c'**, 0.74 g, 5.0 mmol) to furnish 2-benzyl-1,1-dimethylhydrazine (0.71 g, 94%) as a clear liquid. **¹H NMR** (500 MHz, C_6D_6): δ 7.34 (d, $J = 7.43$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 7.10 (t, $J = 7.4$ Hz, 2H), 3.81 (s, 2H), 2.22 (s, 6H), 1.80 (s, 1H). **¹³C NMR** (500 MHz, C_6D_6): δ 140.0, 128.5, 128.0, 126.7, 53.1, 47.3; **IR**: 3182, 2980, 2945, 2837, 2807, 2765, 1471, 1452, 728, 695 cm^{-1} . **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_9\text{H}_{14}\text{N}_2^+$: 150.1157, found: 150.100 (mass error $\Delta m = 104.6$ ppm).

2-(Hex-5-en-2-yl)-1,1-dimethylhydrazine (4a). The title compound was prepared using the general procedure described for 2-(2-heptanyl)-1,1-dimethylhydrazine employing 5-hexen-2-one-N,N-dimethylhydrazone (**4a'**, 2.1 g, 15 mmol) to furnish 2-(Hex-5-en-2-yl)-1,1-dimethylhydrazine (1.50 g, 71%) as a clear oil. **¹H NMR** (500 MHz, C_6D_6): δ 5.78 (ddt, $J = 6.6$,

9.9, 17.0 Hz, 1H), 5.02 (dq, $J = 1.7, 17.0$ Hz, 1H), 4.95 (ddt, $J = 1.3, 1.7, 9.9$ Hz, 1H), 2.75 (sex $J = 5.4, 6.2$ Hz, 1H), 2.21 (s, 6H), 2.13-1.94 (m, 2H), 1.64-1.54 (m, 2H), 1.42-1.33 (m, 1H), 0.99 (d, $J = 6.2$ Hz, 3H). **^{13}C NMR** (500 MHz, C_6D_6): δ 139.0, 114.0, 51.4, 47.8, 34.8, 30.1, 19.3. **IR** (Film): 3184, 3078, 2977, 2946, 2842, 2809, 2766, 1641, 1478, 1450, 907 cm^{-1} . **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_8\text{H}_{18}\text{N}_2^+$: 143.1548, found: 143.1495 (mass error $\Delta m = 37.0$ ppm).

2-(2,2-Dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (**4b**). The title compound was prepared using the general procedure described for 2-(2-heptyl)-1,1-dimethylhydrazine employing 2,2-dimethyl-4-pentenal-*N,N*-dimethylhydrazone (**4b'**, 2.30 g, 15 mmol) to furnish 2-(2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (1.90 g, 83%) as a clear oil. **^1H NMR** (500 MHz, C_6D_6): δ 6.01-5.90 (m, 1H), 5.17-5.11 (m, 2H), 2.61-2.58 (m, 2H), 2.33 (s, 6H), 2.14 (dt, $J = 1.1, 7.5$ Hz, 2H), 1.72 (s, 1H), 1.00 (s, 6H). **^{13}C NMR** (500 MHz, C_6D_6): δ 135.8, 116.4, 58.6, 47.4, 44.7, 34.0, 25.5. **IR** (Film): 3075, 2952, 2906, 2869, 2836, 2807, 2765, 1638, 1474, 1448, 912 cm^{-1} . **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_9\text{H}_{20}\text{N}_2^+$: 157.1705, found: 157.1631 (mass error $\Delta m = 47.1$ ppm).

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Chapter Three Experimental

Materials and Methods

All materials were either prepared according to previous literature or purchased from commercial sources. N,N-dimethylhydrazinoalkene substrates **1–3** were synthesized by previously reported methods^{1,2} and stored in an inert atmosphere glovebox. All solvents were obtained from a JC Meyer solvent dispensing system. Inorganic salts were dried by heating under a high vacuum before use. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and were visualized with UV light (254 nm) or potassium permanganate staining. Nuclear magnetic resonance (NMR) data were obtained from a Bruker AVANCE III HD NMR spectrometer equipped with an Ascend 500 (500 MHz) magnet. High-resolution mass spectra (HRMS) were obtained from a Bruker MicroTOF with a Dart 100–SVP 100 ion source.

General Procedure for the Synthesis of Alkynyl N,N-Dimethylhydrazinoalkenes

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube was charged with benzonitrile (BTF, 0.4 mL), 2 M diethyl zinc in BTF (60 μ L, 0.12 mmol, 1.2 equiv), and the requisite N,N-dimethylhydrazinoalkene (0.1 mmol). To this was added a sealed 3 mm NMR calibration tube containing C₆D₆. The J. Young tube was placed in a 90 °C oil bath and the cyclization reaction was monitored by NMR (indicated by the recession of the alkene peaks) using BTF as an internal standard. Upon completion of the cyclization, the volatiles were removed in vacuo. The J. Young NMR tube was returned to the glovebox and was charged with THF (0.3 mL), the requisite 1-bromoalkyne (0.2 mmol), 0.5 M CuCN·2LiBr solution in THF (10

μL , 5 mol%), and 2 M LiBr in THF (50 μL , 0.1 mmol, 1 equiv). The reactant mixture was allowed to stand at room temperature overnight. The resulting solution was dispersed in diethyl ether (1 mL) and washed with an aqueous solution of 1:1 sat. NH_4OH /sat. NH_4SO_4 (3 x 1 mL). The combined aqueous washes were then back extracted with diethyl ether (2 x 1 mL) and the combined organic layers were concentrated in vacuo. The resulting crude product was dissolved in CH_2Cl_2 (1 mL), dispersed onto silica gel (50 mg), and dried in vacuo. This was purified by dry loading the resulting silica gel onto a silica gel plug and eluting with pentane. The product was then flushed from the silica gel using diethyl ether and concentrated in vacuo. The product could be further purified, if necessary, by column chromatography (15% ether/pentane for elution).

1-(N,N-dimethylamino)-2-(2-heptynyl)-5-methyl-2a-3,4-5a-tetrahydropyrrole (**1a**). The title compound was synthesized by the general procedure, affording 19.2 mg (77%) of the title compound as a clear to yellow oil. **$^1\text{H-NMR}$** (CDCl_3 , 500 MHz): δ 3.04 (dq, 1H, J = 8.2, 6.2 Hz), 3.02-2.95 (m, 1H), 2.55-2.49 (m, 1H), 2.48 (s, 6H), 2.19-2.13 (m, 2H), 2.10 (ddt, 1H, J = 16.2, 9.3, 2.4 Hz), 1.83 (dq, 1H, J = 12.4, 8.0 Hz), 1.78-1.70 (m, 1H), 1.64-1.55 (m, 1H), 1.53-1.45 (m, 2H), 1.44-1.25 (m, 7H), 1.13 (d, 3H, J = 6.2 Hz), 0.91 (t, 3H, J = 7.0 Hz). **$^{13}\text{C NMR}$** (CDCl_3 , 126 MHz): δ 80.87, 78.79, 59.34, 54.56, 41.37, 31.53, 30.48, 29.28, 28.67, 27.84, 26.41, 22.73, 22.15, 18.95, 14.21. **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{30}\text{N}_2$: 250.2409, found: 250.2415 (mass error Δm = 2.46 ppm).

1-(N,N-dimethylamino)-2-(2-heptynyl)-2a-3,4,5,6-pentahydropyridine (**2a**). The title compound was synthesized by the general procedure, affording 20.3 mg (81%) of the title

compound as a clear to yellow oil. **¹H NMR** (CDCl₃, 500 MHz): δ 2.99-2.94 (m, 1H), 2.91 (ddt, 1H, *J* = 16.4, 3.3, 2.5 Hz), 2.37-2.31 (ddt, 1H, *J* = 10.6, 9.0, 3.1 Hz), 2.29 (s, 6H), 2.17-2.10 (m, 3H), 2.05 (ddt, 1H, *J* = 16.4, 9.0, 2.5 Hz), 2.05-1.99 (m, 1H), 1.73-1.64 (m, 2H), 1.52-1.42 (m, 3H), 1.41-1.34 (m, 2H), 1.33-1.22 (m, 5H), 1.14 (qt, 1H, *J* = 13.2, 4.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz). **¹³C NMR** (CDCl₃, 126 MHz): δ 81.50, 78.92, 59.82, 42.90, 39.14, 32.32, 31.53, 29.35, 28.71, 26.34, 24.74, 23.79, 22.73, 19.06, 14.19. **HRMS** Electrospray ionization (ESI) *m/z* calcd. for C₁₆H₃₀N₂: 250.2409, found: 250.2412 (mass error Δ*m* = 1.00 ppm).

1-(N,N-dimethylamino)-2-(2-heptynyl)-4,4-dimethyl-2a-3,5-tetrahydropyrrole (3a). The title compound was synthesized by the general procedure, affording 15.3 mg (58%) of the title compound as a clear to yellow oil. **¹H NMR** (CDCl₃, 500 MHz): δ 2.85 (ddd, 1H, *J* = 8.9, 8.0, 3.3 Hz) 2.6 (d, 1H, *J* = 8.2 Hz), 2.62 (ddt, 1H, *J* = 16.2, 3.3, 2.4 Hz), 2.44 (d, 1H, *J* = 8.2 Hz), 2.35 (s, 6H), 2.15 (m, 2H), 2.09 (ddt, 1H, *J* = 16.2, 8.9, 2.4 Hz), 1.69 (dd, 1H, *J* = 8.0, 12.6 Hz), 1.52-1.45 (m, 2H), 1.44-1.36 (m, 3H), 1.36-1.25 (m, 4H), 1.12 (s, 3H), 1.05 (s, 3H), 0.91 (t, 3H, *J* = 7.1 Hz). **¹³C NMR** (CDCl₃, 126 MHz): δ 80.88, 78.73, 59.92, 54.30, 43.97, 40.46, 34.06, 31.54, 30.54, 29.40, 29.30, 28.67, 24.44, 22.75, 18.97, 14.21. **HRMS** Electrospray ionization (ESI) *m/z* calcd. for C₁₇H₃₂N₂: 264.2565, found: 264.2567 (mass error Δ*m* = 0.69 ppm).

1-(N,N-dimethylamino)-2-(3-phenyl-2-propynyl)-5-methyl-2a-3,4-5a-tetrahydropyrrole (1b). The title compound was synthesized by the general procedure, affording 16.0 mg (66%) of the title compound as a clear to yellow oil. **¹H NMR** (CDCl₃, 500 MHz): δ 7.44-7.40 (m, 2H), 7.32-7.25 (m, 3H), 3.15-3.06 (m, 2H), 2.77 (dd, 1H, *J* = 16.6, 3.7 Hz), 2.53 (s, 6H), 2.39 (dd, 1H,

$J = 16.6, 9.0$ Hz), 1.95-1.85 (m, 1H), 1.83-1.74 (m, 1H), 1.74-1.65 (m, 1H), 1.47-1.37 (m, 1H), (d, 3H, $J = 6.0$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 131.70, 128.29, 127.54, 124.36, 89.23, 81.15, 59.28, 54.29, 41.43, 30.60, 27.86, 26.93, 22.27. **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2$: 242.1783, found: 242.1784 (mass error $\Delta m = 0.48$ ppm).

1-(N,N-dimethylamino)-2-(3-phenyl-2-propynyl)-2a-3,4,5,6-pentahydropyridine (**2b**).

The title compound was synthesized by the general procedure, affording 17.4 mg (72%) of the title compound as a clear to yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 7.40-7.45 (m, 2H), 7.24-7.32 (m, 3H), 3.18 (dd, 1H, $J = 16.7, 3.5$ Hz), 2.99-3.05 (m, 1H), 2.48-2.55 (m, 1H), 2.36 (s, 6H), 2.36 (dd, 1H, $J = 16.6, 8.9$ Hz), 2.20 (ddd, 1H, $J = 12.3, 10.6, 2.5$ Hz), 2.08-2.15 (m, 1H), 1.69-1.78 (m, 2H), 1.47-1.58 (m, 1H), 1.34-1.44 (m, 1H), 1.15-1.26 (m, 1H). ^{13}C NMR (CDCl_3 , 126 MHz): δ 131.71, 128.27, 127.44, 124.55, 89.66, 81.78, 59.65, 42.93, 39.27, 32.52, 26.33, 24.75, 24.60. **HRMS** Electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2$: 242.1783, found: 242.1784 (mass error $\Delta m = 0.62$ ppm).

Procedure for Preparative Scale Synthesis of **3a**.

1-(N,N-dimethylamino)-2-(2-heptynyl)-4,4-dimethyl-2a-3,5-tetrahydropyrrole (**3a**). In an inert atmosphere glovebox, a 5 mm J. Young NMR tube was charged with 0.4 mL of benzotrifluoride, 300 μL of 2-(2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (1.5 mmol), and 185 μL of Et_2Zn (1.8 mmol, 1.2 equiv.). The J. Young tube was placed in a 90 °C oil bath and the cyclization reaction was monitored by No-D NMR (indicated by the recession of the alkene peaks) using BTF as an internal standard. Upon completion of the cyclization, the J. Yung tube was returned to the glovebox and the contents were transferred to a 10 mL Schlenk flask

equipped with a magnetic stirring bar, and a Schlenk adapter with a septum on the sidearm. The J. Young tube was rinsed with THF (3 x 0.5 mL), which was added to the Schlenk flask, and the flask was then removed from the glovebox. The volatiles were removed in vacuo and the resulting solids were redissolved in a preformed solution of 500 μ L of 1-bromo-1-octyne (3.125 mmol, 2.08 equiv.) in 1.5 mL of THF. The resulting solution was cooled to -78 °C and a preformed solution of 130 mg of LiBr (1.5 mmol, 1 equiv.) and 150 μ L of 0.5 M CuCN·2LiBr solution in THF (5 mol%) in 3 mL of THF was slowly added. The solution was allowed to warm to RT with stirring overnight. The reactant mixture was then dispersed in 5 mL of diethyl ether and washed with 1:1 sat. aqueous NH₄Cl : sat. aqueous NH₄OH solution (3 x 2 mL). The combined aqueous layers were back extracted with diethyl ether (2 x 2 mL). The combined organic layers were dried with brine and Na₂SO₄, concentrated in vacuo, and the volatile components were removed under high vacuum. The crude product was further purified by column chromatography using gradient elution (hexane to 20% EtOAc/hexane) to provide 293.1 mg (76%) of the title compound as a yellow oil. **¹H NMR** (CDCl₃, 500 MHz): δ 2.85 (ddd, 1H, J = 8.9, 8.0, 3.3 Hz) 2.6 (d, 1H, J = 8.2 Hz), 2.62 (ddt, 1H, J = 16.2, 3.3, 2.4 Hz), 2.44 (d, 1H, J = 8.2 Hz), 2.35 (s, 6H), 2.15 (m, 2H), 2.09 (ddt, 1H, J = 16.2, 8.9, 2.4 Hz), 1.69 (dd, 1H, J = 8.0, 12.6 Hz), 1.52-1.45 (m, 2H), 1.44-1.36 (m, 3H), 1.36-1.25 (m, 4H), 1.12 (s, 3H), 1.05 (s, 3H), 0.91 (t, 3H, J = 7.1 Hz). **¹³C NMR** (CDCl₃, 126 MHz): δ 80.88, 78.73, 59.92, 54.30, 43.97, 40.46, 34.06, 31.54, 30.54, 29.40, 29.30, 28.67, 24.44, 22.75, 18.97, 14.21. **HRMS** Electrospray ionization (ESI) m/z calcd. for C₁₇H₃₂N₂: 264.2565, found: 264.2567 (mass error Δm = 0.69 ppm).

General Procedure for the Synthesis of 1-Bromoalkynes (Adapted from Gao et al)³

To a 100 mL round bottomed flask equipped with a magnetic stirring bar was added acetone (30 mL) and the requisite 1-alkyne (12.5 mmol). To this solution was added AgNO₃ (0.213 g, 1.25 mmol) and, with vigorous stirring, N-bromosuccinimide (2.5 g, 14 mmol) was added in portions. The mixture was stirred at room temperature for 2 h when confirmed to be completed by TLC. The reactant mixture was diluted in pentane (75 mL) and filtered. The resulting solution was washed with water (2 x 25 mL) and the combined aqueous washes were back extracted with 1:1 diethyl ether/pentane (2 x 15 mL). The combined organic layers were dried with Na₂SO₄, filtered through a plug of silica gel, and concentrated in vacuo. The product can be further purified by vacuum distillation or flash column chromatography.

1-Bromo-1-octyne. The title compound was synthesized by the general procedure. Short path distillation in vacuo over CaH₂ afforded 2.10 g (89%) of the title compound as a clear liquid. . ¹H NMR (C₆D₆, 500 MHz): δ, 1.87 (t, 2H, *J* = 6.9 Hz), 1.19-1.27 (m, 2H), 1.10-1.19 (m, 4H), 1.00-1.08 (m, 2H), 0.80 (t, 3H, *J* = 7.2 Hz). ¹³C NMR (C₆D₆, 126 MHz): δ 80.81. 38.26, 31.53, 28.69, 28.50, 22.82, 19.80, 14.21. HRMS Data previously reported.⁴

1-Bromo-2-phenylethyne. The title compound was synthesized by the general procedure. Flash column chromatography with 1:1 ether/pentane afforded 2.24 g (99%) of the title compound as a clear liquid. ¹H NMR (C₆D₆, 500 MHz): δ 7.24-7.27 (m, 2H), 6.83-6.92 (m, 3H). ¹³C NMR (C₆D₆, 126 MHz): δ 132.28, 128.80, 128.55, 123.13, 80.73, 50.49. HRMS Data previously reported.⁴

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Chapter Four Experimental

Materials and Methods

All materials were either prepared according to previous literature or purchased from commercial sources. N,N-dimethylhydrazinoalkene substrates **1a-c** were synthesized by previously reported methods^{1,2} and stored in an inert atmosphere glovebox. All solvents were obtained from a JC Meyer solvent dispensing system. Inorganic salts were dried by heating under a high vacuum before use if necessary. Copper(I) thiophene-2-carboxylate,² CuBr·P(OEt)₃,³ [Cu(IPr)]Cl⁴ were prepared by previously reported methods. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and were visualized with UV light (254 nm) or potassium permanganate staining. Nuclear magnetic resonance (NMR) data were obtained from a Bruker AVANCE III HD NMR spectrometer equipped with an Ascend 500 (500 MHz) magnet. High-resolution mass spectra (HRMS) were obtained from a Bruker MicroTOF with a Dart 100–SVP 100 ion source.

0.1 mmol Scale Synthesis of Alkynyl N,N-Dimethylhydrazinoalkenes 4a-l; General Procedure

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube with a sealed 3 mm NMR calibration tube containing C₆D₆ was charged with benzotrifluoride (BTF, 0.4 mL), 2 M diethylzinc in BTF (60 μ L, 0.12 mmol, 1.2 equiv.), and the requisite N,N-dimethylhydrazinoalkene **1a-c** (0.1 mmol). The J. Young tube was placed in a 90 °C oil bath and the cyclization reaction was monitored by NMR (indicated by the recession of the alkene peaks), using BTF as an internal standard. Upon completion of the cyclization, the volatiles were removed in vacuo. The J. Young NMR tube was returned to the glovebox and was charged with THF (0.3 mL), the requisite 1-bromoalkyne **5a-d** (0.2 mmol), 0.5 M CuCN·2LiBr solution in THF (10 μ L, 5 mol%), and 2 M LiBr in THF (50 μ L, 0.1 mmol, 1 equiv.). The reactant mixture was allowed to stand at room temperature overnight. The resulting solution was dispersed in diethyl ether (1 mL) and washed with an aqueous solution of 1:1 sat. NH₄OH/sat. NH₄Cl (3 $\times$ 1 mL). The combined aqueous washes were then back-extracted with diethyl ether (2 $\times$ 1 mL) and the combined organic layers were concentrated in vacuo. The resulting crude product was dissolved in CH₂Cl₂ (1 mL), dispersed onto silica gel (50 mg), and dried in vacuo. This was purified by dry-loading the resulting silica gel onto a pad of silica gel and eluting with pentane. The product was then flushed from the silica gel using diethyl ether and concentrated in vacuo. The product could be further purified, if necessary, by column chromatography.

N,N,2-Trimethyl-5-(2-nonynyl)-1-pyrrolidinamine (4a)⁵

Yield: 19.2 mg (77%); colorless oil.

¹H NMR (CDCl₃, 500 MHz): δ 3.04 (dquin, 1H, J = 8.2, 6.2 Hz), 3.02–2.95 (m, 1H), 2.55–2.49 (m, 1H), 2.48 (s, 6H), 2.19–2.13 (m, 2H), 2.10 (ddt, 1H, J = 16.2, 9.3, 2.4 Hz), 1.83 (dq, 1H, J = 12.4, 8.0 Hz), 1.78–1.70 (m, 1H), 1.64–1.55 (m, 1H), 1.53–1.45 (m, 2H), 1.44–1.25 (m, 7H), 1.13 (d, 3H, J = 6.2 Hz), 0.91 (t, 3H, J = 7.0 Hz).

¹³C NMR (CDCl₃, 126 MHz): δ 80.87, 78.79, 59.34, 54.56, 41.37, 31.53, 30.48, 29.28, 28.67, 27.84, 26.41, 22.73, 22.15, 18.95, 14.21.

HRMS electrospray ionization (ESI) m/z calcd. for C₁₆H₃₀N₂: 250.2409, found: 250.2415 (mass error Δm = 2.46 ppm).

N,N,3,3-Tetramethyl-5-(2-nonynyl)-1-pyrrolidinamine (4b)⁵

Yield: 15.3 mg (58%); colorless oil.

¹H NMR (CDCl₃, 500 MHz): δ 2.85 (ddd, 1H, J = 8.9, 8.0, 3.3 Hz), 2.6 (d, 1H, J = 8.2 Hz), 2.62 (ddt, 1H, J = 16.2, 3.3, 2.4 Hz), 2.44 (d, 1H, J = 8.2 Hz), 2.35 (s, 6H), 2.15 (m, 2H), 2.09 (ddt, 1H, J = 16.2, 8.9, 2.4 Hz), 1.69 (dd, 1H, J = 8.0, 12.6 Hz), 1.52–1.45 (m, 2H), 1.44–1.36 (m, 3H), 1.36–1.25 (m, 4H), 1.12 (s, 3H), 1.05 (s, 3H), 0.91 (t, 3H, J = 7.1 Hz).

¹³C NMR (CDCl₃, 126 MHz): δ 80.88, 78.73, 59.92, 54.30, 43.97, 40.46, 34.06, 31.54, 30.54, 29.40, 29.30, 28.67, 24.44, 22.75, 18.97, 14.21.

HRMS electrospray ionization (ESI) m/z calcd. for C₁₇H₃₂N₂: 264.2565, found: 264.2567 (mass error Δm = 0.69 ppm).

N,N-Dimethyl-2-(2-nonynyl)-1-piperidinamine (4c)⁵

Yield: 20.3 mg (81%); pale yellow oil; $R_f = 0.30$ (5% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 2.99–2.94 (m, 1H), 2.91 (ddt, 1H, $J = 16.4, 3.3, 2.5$ Hz), 2.37–2.31 (ddt, 1H, $J = 10.6, 9.0, 3.1$ Hz), 2.29 (s, 6H), 2.17–2.10 (m, 3H), 2.05 (ddt, 1H, $J = 16.4, 9.0, 2.5$ Hz), 2.05–1.99 (m, 1H), 1.73–1.64 (m, 2H), 1.52–1.42 (m, 3H), 1.41–1.34 (m, 2H), 1.33–1.22 (m, 5H), 1.14 (qt, 1H, $J = 13.2, 4.0$ Hz), 0.88 (t, 3H, $J = 7.0$ Hz).

^{13}C NMR (CDCl_3 , 126 MHz): δ 81.50, 78.92, 59.82, 42.90, 39.14, 32.32, 31.53, 29.35, 28.71, 26.34, 24.74, 23.79, 22.73, 19.06, 14.19.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{30}\text{N}_2$: 250.2409, found: 250.2412 (mass error $\Delta m = 1.00$ ppm).

N,N,2-Trimethyl-5-(2-propynyl-3-phenyl)-1-pyrrolidinamine (4d)⁵

Yield: 16.0 mg (66%); pale yellow oil; $R_f = 0.23$ (10% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 7.44–7.40 (m, 2H), 7.32–7.25 (m, 3H), 3.15–3.06 (m, 2H), 2.77 (dd, 1H, $J = 16.6, 3.7$ Hz), 2.53 (s, 6H), 2.39 (dd, 1H, $J = 16.6, 9.0$ Hz), 1.95–1.85 (m, 1H), 1.83–1.74 (m, 1H), 1.74–1.65 (m, 1H), 1.47–1.37 (m, 1H), (d, 3H, $J = 6.0$ Hz).

^{13}C NMR (CDCl_3 , 126 MHz): δ 131.70, 128.29, 127.54, 124.36, 89.23, 81.15, 59.28, 54.29, 41.43, 30.60, 27.86, 26.93, 22.27.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2$: 242.1783, found: 242.1784 (mass error $\Delta m = 0.48$ ppm).

N,N,3,3-Tetramethyl-5-(2-propynyl-3-phenyl)-1-pyrrolidinamine (4e)

Yield: 12.1 mg (47%); pale yellow oil; R_f = 0.15 (10% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 7.44–7.38 (m, 2H), 7.32–7.25 (m, 3H), 3.04–2.93 (m, 1H), 2.87 (d, 1H, J = 16.7), 2.66 (d, 1H, J = 7.5 Hz), 2.48 (d, 1H, J = 8.1 Hz), 2.39 (s, 6H), 1.76 (dd, 1H, J = 12.1, 8.6 Hz), 1.51 (dd, 1H, J = 11.5, 8.6 Hz), 1.30 (d, 1H, J = 14.4 Hz), 1.17 (s, 3H), 1.08 (s, 3H), 0.10 (s, 6H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 131.57, 128.13, 127.36, 59.48, 54.00, 43.66, 40.39, 34.06, 30.42, 29.22, 24.87.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2$: 256.1939, found: 256.2000 (mass error Δm = 23.8 ppm).

N,N-Dimethyl-2-(2-propynyl-3-phenyl)-1-piperidinamine (4f)⁵

Yield: 17.4 mg (72%); pale yellow oil; R_f = 0.11 (10% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 7.40–7.45 (m, 2H), 7.24–7.32 (m, 3H), 3.18 (dd, 1H, J = 16.7, 3.5 Hz), 2.99–3.05 (m, 1H), 2.48–2.55 (m, 1H), 2.36 (s, 6H), 2.36 (dd, 1H, J = 16.6, 8.9 Hz), 2.20 (ddd, 1H, J = 12.3, 10.6, 2.5 Hz), 2.08–2.15 (m, 1H), 1.69–1.78 (m, 2H), 1.47–1.58 (m, 1H), 1.34–1.44 (m, 1H), 1.15–1.26 (m, 1H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 131.57, 128.13, 127.31, 124.39, 89.51, 81.64, 59.50, 42.78, 39., 32.38, 26.19, 24.61, 24.46.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2$: 242.1783, found: 242.1784 (mass error Δm = 0.62 ppm).

7-(2-N,N-Dimethylamino-3-methylpyrrolidinyl)-5-heptynenitrile (4g)

Yield: 21.2 mg (66%); colorless oil.

^1H NMR (CDCl_3 , 500 MHz): δ 3.06 (dquin, 1H, $J = 6.3, 7.9$ Hz), 2.94 (ddd, 1H, $J = 15.2, 8.2, 3.5$ Hz), 2.53 (t, 2H, $J = 7.2$ Hz), 2.51-2.46 (m, 1H), 2.48 (s, 6H), 2.35 (tt, 2H, $J = 6.6, 2.4$ Hz), 2.14 (ddt, 1H, $J = 16.3, 8.8, 2.5$ Hz), 1.84 (quin, 2H, 7.0 Hz), 1.83-1.71 (m, 2H), 1.60-1.53 (m, 1H), 1.40- 1.32 (m, 1H), 1.13 (d, 3H, $J = 6.0$ Hz).

^{13}C NMR (CDCl_3 , 126 MHz): δ 119.43, 81.01, 77.58, 77.25, 59.29, 53.99, 41.20, 30.35, 27.43, 25.80, 24.99, 22.10, 17.97, 16.03.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{23}\text{N}_3$: 233.1892, found: 233.2000 (mass error $\Delta m = 46.3$ ppm).

7-(2-N,N-Dimethylamino-4,4-dimethylmethylpyrrolidinyl)-5-heptynenitrile (4h)

Yield: 13.9 mg (56%); colorless oil; $R_f = 0.36$ (50% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 2.83 (ddd, 1H, $J = 16.4, 8.1, 3.4$), 2.60 (dt, 1H, $J = 17.3, 8.5$ Hz), 2.56 (ddt, 1H, $J = 16.4, 4.0, 1.8$ Hz), 2.51 (t, 2H, $J = 7.2$ Hz), 2.43 (d, 1H, $J = 7.8$), 2.36-2.31 (m, 8H), 2.13 (ddt, 1H, $J = 16.4, 8.5, 2.3$ Hz), 1.83 (quin, 2H, $J = 6.9$ Hz), 1.64 (dd, 1H, $J = 12.8, 8.1$ Hz), 1.38 (dd, 1H, $J = 12.5, 8.1$ Hz), 1.11 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 119.43, 80.91, 77.60, 59.47, 53.90, 43.59, 33.31, 30.39, 29.22, 25.01, 23.99, 17.99, 16.02, 1.01.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{25}\text{N}_3$: 247.2048, found: 247.2000 (mass error $\Delta m = 19.4$ ppm)

7-(2-N,N-Dimethylaminopiperidinyl)-5-heptynenitrile (4i)

Yield: 19.1 mg (82%); pale yellow oil; $R_f = 0.24$ (20% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 3.00 (d, 1H, $J = 10.2$ Hz), 2.81 (dq, 1H, $J = 16.4, 2.4$ Hz), 2.55 (t, 2H, $J = 7.5$ Hz), 2.40-2.34 (m, 3H), 2.32 (s, 6H), 2.19 (dddd, 1H, $J = 24.7, 8.1, 2.4, 1.8$ Hz), 1.94 (ddd, 1H $J = 13.0, 3.0, 0.9$ Hz), 1.86 (quin, 2H, $J = 6.9$ Hz), 1.77-1.68 (m, 2H), 1.48 (qt, 1H, $J = 12.6, 4.0$ Hz), 1.39-1.25 (m, 2H), 1.18 (qt, 1H, $J = 13.0, 4.0$ Hz).

^{13}C NMR (CDCl_3 , 126 MHz): δ 119.15, 81.17, 78.14, 77.23, 59.27, 42.71, 32.14, 26.16, 25.08, 24.55, 23.58, 18.10, 16.07, 1.02.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{23}\text{N}_3$: 233.1892, found: 233.2000 (mass error $\Delta m = 46.3$ ppm)

N,N,2-Trimethyl-5-[2-hexynyl-6-(tert-butyl)dimethylsiloxy]-1-pyrrolidinamine (4j)

Yield: 22.3 mg (66%); colorless oil $R_f = 0.38$ (10% ethyl acetate on hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 3.71 (t, 2H, $J = 6.7$ Hz), 3.04 (dsex, 1H, $J = 5.9, 1.7$), 3.01-2.94 (m, 1H), 2.53 (dq, 1H, $J = 2.5, 1.3$ Hz), 2.50 (dq, 1H, $J = 2.5, 1.6$ Hz), 2.48 (s, 6H), 2.34 (tt, 2H, $J = 7.1, 2.1$ Hz), 2.09 (dt, 1H, $J = 16.3, 9.5, 2.3$ Hz), 1.82 (dq, 1H, $J = 12.6, 8.2$ Hz), 1.78-1.72 (m, 1H), 1.70 (quin, 2H, $J = 6.5$ Hz), 1.62-1.55 (m, 1H), 1.36 (dq, 1H, $J = 11.9, 8.2$ Hz), 1.13 (d, 3H, $J = 6.1$ Hz), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 80.11, 78.82, 77.22, 61.80, 59.15, 54.40, 41.20, 32.17, 30.31, 27.72, 26.25, 25.96, 22.01, 18.36, 15.19, -5.31.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{38}\text{N}_2\text{OSi}$: 338.2753, found: 338.3000 (mass error $\Delta m = 73.0$ ppm).

N,N,3,3-Tetramethyl-5-[2-hexynyl-6-(tert-butyl)dimethylsiloxy]-1-pyrrolidinamine (4k)

Yield: 21.0 mg (56%); colorless oil $R_f = 0.62$ (20% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 3.71 (t, 1H, $J = 6.4$ Hz), 2.85 (ddd, 1H, $J = 17.1, 8.4, 3.5$ Hz), 2.62 (m, 2H), 2.44 (d, 1H, $J = 8.4$ Hz), 2.35 (s, 6H), 2.24 (tt, 2H, $J = 7.0, 2.5$ Hz), 2.07 (ddt, 1H, $J = 16.4, 9.2, 2.3$ Hz), 1.73-1.66 (m, 3H), 1.39 (dd, 1H, $J = 12.5, 8.1$ Hz), 1.12 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 80.11, 78.79, 77.22, 61.84, 59.74, 54.10, 43.89, 40.31, 33.93, 32.18, 30.39, 29.27, 25.98, 24.32, 18.37, 15.22, 5.29.

HRMS electrospray ionization (ESI) m/z calcd. $\text{C}_{20}\text{H}_{40}\text{N}_2\text{OSi}$: 352.2910, found: 352.3000 (mass error $\Delta m = 25.5$ ppm)

N,N-Dimethyl-2-[2-hexynyl-6-(tert-butyl)dimethylsiloxy]-1-piperidinamine (4l)

Yield: 25.1 mg (74%); pale yellow oil; $R_f = 0.39$ (10% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 3.71 (t, 2H, $J = 6.2$ Hz), 2.97 (ddd, 2H $J = 16.8, 2.8, 1.4$ Hz), 2.40-2.28 (m, 7H), 2.25 (tt, 2H, $J = 7.2, 2.4$ Hz), 2.15 (ddd, 1H $J = 12.4, 2.1, 1.4$ Hz), 2.10-2.01 (m, 2H), 1.76-1.66 (m, 4H), 1.49 (ddt, 1H $J = 25.1, 12.4, 3.8$ Hz), 1.28 (ddd, 1H, $J = 23.7, 13.4, 3.4$ Hz), 1.16 (ddt, 1H $J = 26.1, 13.4, 4.1$ Hz), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 80.74, 78.99, 77.23, 61.88, 59.63, 42.74, 39.25, 39.00, 32.20, 26.17, 25.97, 24.59, 23.61, 18.36, 18.30, 5.31.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{38}\text{N}_2\text{OSi}$: 338.2753, found: 338.3000 (mass error $\Delta m = 73.0$ ppm)

Synthesis of Alkynyl N,N-Dimethylhydrazinoalkenes 4m and 4n; General Procedure

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube with a sealed 3 mm NMR calibration tube containing C₆D₆ was charged with benzotrifluoride (BTF, 0.4 mL), 2 M diethylzinc in BTF (60 μ L, 0.12 mmol, 1.2 equiv.), and the requisite N,N-dimethylhydrazinoalkene **1b** or **1c** (0.1 mmol). The J. Young tube was placed in a 90 °C oil bath and the cyclization reaction was monitored by NMR (indicated by the recession of the alkene peaks), using BTF as an internal standard. Upon completion of the cyclization, the volatiles were removed in vacuo. The J. Young NMR tube was returned to the glovebox and was charged with diethyl ether (0.4 mL), **5e** (41 mg, 0.2 mmol), and a 0.5 M CuCN·2LiBr solution in diethyl ether (10 μ L, 5 mol%). The reactant mixture was cooled to -50 °C overnight. The resulting solution was dispersed in diethyl ether (1 mL) and washed with 0.5 M aqueous tetrasodium EDTA (1 mL). The resulting organic layer was dried with anhydrous Na₂SO₄, filtered through a plug of silica, and concentrated in vacuo. The product was purified by column chromatography.

Methyl 7-[1-(Dimethylamino)-4,4-dimethyl-2-pyrrolidinyl]-5-heptynoate (**4m**)

Yield: 10.8 mg (39%); colorless oil; R_f = 0.38 (10% ethyl acetate in hexane).

¹H NMR (CDCl₃, 500 MHz): δ 3.70 (s, 3H), 2.85 (qd, 1H, J = 8.6, 3.7 Hz), 2.63-2.57 (m, 2H), 2.47 (t, 2H, J = 7.6 Hz), 2.44 (d, 1H, J = 8.6 Hz), 2.35 (s, 6H), 2.24 (tt, 2H, J = 7.2, 2.5 Hz), 2.10 (ddt, 1H, J = 16.2, 9.0, 2.2), 1.82 (quin, 2H, J = 7.2 Hz), 1.68 (dd, 1H, J = 12.6, 7.9 Hz), 1.39 (dd, 1H, J = 12.6, 7.9 Hz), 1.12 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (CDCl_3 , 126 MHz): δ 173.87, 129.83, 59.65, 54.04, 51.52, 43.72, 40.32, 33.95, 32.89, 30.37, 29.25, 24.30, 18.32, 1.03.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_2$: 280.2151, found: 280.2000 (mass error $\Delta m = 53.9$ ppm).

Methyl 7-[1-(Dimethylamino)-2-piperidinyl]-5-heptynoate (**4n**)

Yield: 24.5 mg (92%); colorless oil; $R_f = 0.50$ (10% ethyl acetate in hexane).

^1H NMR (CDCl_3 , 500 MHz): δ 3.70 (s, 3H), 3.00 (dt, 1H, $J = 11.0, 3.3$ Hz), 2.90 (dq, 1H, $J = 16.4, 2.6$ Hz), 2.48 (t, 2H, $J = 7.5$ Hz), 2.40-2.33 (m, 1H), 2.32 (s, 6H), 2.26 (tt, 2H, $J = 7.0, 2.6$ Hz), 2.17 (ddt, 1H, $J = 18.3, 6.8, 2.6$ Hz), 2.12 (ddt, 1H, $J = 16.7, 8.7, 2.6$ Hz), 2.00 (dt, 1H, $J = 13.1, 2.8$ Hz), 1.83 (quin, 2H, $J = 7.3$ Hz), 1.76-1.67 (m, 2H), 1.49 (ddt, 1H, $J = 25.4, 12.7, 3.8$ Hz), 1.36-1.25 (m, 1H), 1.17 (ddt, 1H, $J = 26.4, 13.3, 4.0$ Hz).

^{13}C NMR (CDCl_3 , 126 MHz): δ 173.90, 79.91, 59.50, 51.52, 42.73, 32.95, 32.16, 26.16, 25.29, 24.58, 24.36, 23.62, 18.42, 18.42, 1.03.

HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_2$: 266.1994, found: 266.2000 (mass error $\Delta m = 2.3$ ppm).

Synthesis of Vinylogous Urethanes 6a and 6b; General Procedure

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube with a sealed 3 mm NMR calibration tube containing C_6D_6 was charged with benzotrifluoride (BTF, 0.4 mL), 2 M diethylzinc in BTF (60 μL , 0.12 mmol, 1.2 equiv.), and the requisite N,N-dimethylhydrazinoalkene **1b** or **1c** (0.1 mmol). The J. Young tube was placed in a 90 °C oil bath and the cyclization reaction was monitored by NMR (indicated by the recession of the alkene

peaks), using BTF as an internal standard. Upon completion of the cyclization, the volatiles were removed in vacuo. The J. Young NMR tube was returned to the glovebox and was charged with 1,4-dioxane (0.4 mL), ethyl propiolate (20.3 μ L, 0.2 mmol), and a 0.5 M CuCN $\cdot$ 2LiBr solution in diethyl ether (10 μ L, 5 mol%). The reactant mixture was allowed to stand at for 1 h. The resulting solution was dispersed in diethyl ether (1 mL) and washed with 0.5 M aqueous tetrasodium EDTA (1 mL). The resulting organic layer was dried with anhydrous Na₂SO₄, filtered through a plug of silica, and concentrated in vacuo. Remaining volatiles were removed under high vacuum (0.01 mmHg), yielding product with no further purification.

Ethyl (2E)-3-[1-(2,2-Dimethyl-4-pentenyl)-2,2-dimethylhydrazino]-2-propenoate (**6a**)

Yield: 21.1 mg (84%); pale yellow oil.

¹H NMR (CDCl₃, 500 MHz): δ 7.70 (d, 1H, J = 14.1 Hz), 5.85 (ddt, 1H, J = 17.1, 10.4, 7.4 Hz), 5.09 (d, 1H, J = 9.7 Hz), 5.06 (d, 1H, J = 17.8 Hz), 4.80 (d, 1H, J = 14.1 Hz), 4.16, (q, 2H, J = 7.4 Hz), 2.98 (s, 2H), 2.60 (s, 6H), 2.04 (d, 2H, J = 8.9 Hz), 1.29, (t, 3H, J = 7.4 Hz), 0.94 (s, 6H).

¹³C NMR (CDCl₃, 126 MHz): δ 169.24, 148.30, 134.80, 117.68, 87.14, 61.06, 59.29, 45.29, 43.90, 35.97, 25.59, 14.62.

HRMS electrospray ionization (ESI) m/z calcd. for C₁₄H₂₆N₂O₂: 254.1994, found: 254.2000 (mass error Δm = 2.36 ppm).

Ethyl (2E)-3-[1-(5-Hexenyl)-2,2-dimethylhydrazino]-2-propenoate (**6b**)

Yield: 22.6 mg (94%); pale yellow oil.

¹H NMR (CDCl₃, 500 MHz): δ 7.58 (d, 1H, *J* = 12.7 Hz), 5.81 (ddt, 1H, *J* = 16.8, 9.9, 6.5 Hz), 5.04 (dd, 1H, *J* = 17.2, 1.9 Hz), 4.99 (dd, 1H, *J* = 10.3, 1.9 Hz), 4.76 (d, 1H, *J* = 10.3 Hz), 4.15 (q, 2H, *J* = 7.2 Hz), 3.14 (dd, 2H, *J* = 8.8, 7.6 Hz), 2.55 (s, 6H), 2.10 (q, 2H, *J* = 7.6 Hz), 1.68-1.60 (m, 2H), 1.43 (quin, 2H, *J* = 7.6 Hz), 1.28 (t, 3H, *J* = 7.2 Hz).

¹³C NMR (CDCl₃, 126 MHz): δ 169.57, 149.10, 138.21, 114.98, 84.89, 58.96, 46.12, 44.00, 33.38, 27.65, 26.32, 14.65.

General Procedure for the Preparative Scale Synthesis of Alkynyl N,N-Dimethylhydrazinoalkenes

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube was charged with 0.4 mL of benzotrifluoride, 1.5 mmol of the requisite N,N-dimethylhydrazinoalkene **1a-c**,^{1,2} and 185 μL of Et₂Zn (1.8 mmol, 1.2 equiv.). The J. Young tube was placed in a 90 °C oil bath and the cyclization reaction was monitored by No-D NMR (indicated by the recession of the alkene peaks) using BTF as an internal standard. Upon completion of the cyclization, the J. Young tube was returned to the glovebox and the contents were transferred to a 10 mL Schlenk flask equipped with a magnetic stirring bar, and a Schlenk adapter with a septum on the sidearm. The J. Young tube was rinsed with THF (3 × 0.5 mL), which was added to the Schlenk flask, and the flask was then removed from the glovebox. The volatiles were removed in vacuo and the resulting solids were redissolved in a preformed solution of 2.0 mmol (1.33 equiv.) of the prerequisite 1-bromoalkyne **5a-d** in 1.5 mL of THF. The resulting solution was cooled to -78 °C and a preformed solution of 130 mg of LiBr (1.5 mmol, 1 equiv.) and 150 μL of 0.5 M CuCN·2LiBr solution in THF (5 mol%) in 3 mL of THF was slowly added. The solution was

allowed to warm to rt with stirring overnight. The reactant mixture was then dispersed in 5 mL of diethyl ether and washed with a 1:1 sat. aqueous NH_4Cl : sat. aqueous NH_4OH solution (3×2 mL). The combined aqueous layers were back-extracted with diethyl ether (2×2 mL). The combined organic layers were dried with brine and Na_2SO_4 , concentrated in vacuo, and the volatile components were removed under a high vacuum. The crude product was further purified by column chromatography (gradient elution using hexane to 20% ethyl acetate in hexane).

N,N,2-Trimethyl-5-(2-nonynyl)-1-pyrrolidinamine (4a). The title compound was synthesized by the general procedure, producing 161.5 mg (43%) of the title compound as a colorless oil. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 3.04 (dquin, 1H, $J = 8.2, 6.2$ Hz), 3.02–2.95 (m, 1H), 2.55–2.49 (m, 1H), 2.48 (s, 6H), 2.19–2.13 (m, 2H), 2.10 (ddt, 1H, $J = 16.2, 9.3, 2.4$ Hz), 1.83 (dq, 1H, $J = 12.4, 8.0$ Hz), 1.78–1.70 (m, 1H), 1.64–1.55 (m, 1H), 1.53–1.45 (m, 2H), 1.44–1.25 (m, 7H), 1.13 (d, 3H, $J = 6.2$ Hz), 0.91 (t, 3H, $J = 7.0$ Hz). $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz): δ 80.87, 78.79, 59.34, 54.56, 41.37, 31.53, 30.48, 29.28, 28.67, 27.84, 26.41, 22.73, 22.15, 18.95, 14.21. **HRMS** electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{30}\text{N}_2$: 250.2409, found: 250.2415 (mass error $\Delta m = 2.46$ ppm).

N,N,3,3-Tetramethyl-5-(2-nonynyl)-1-pyrrolidinamine (4b). The title compound was synthesized by the general procedure, producing 301.5 mg (76%) of the title compound as a colorless oil. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 2.85 (ddd, 1H, $J = 8.9, 8.0, 3.3$ Hz) 2.6 (d, 1H, $J = 8.2$ Hz), 2.62 (ddt, 1H, $J = 16.2, 3.3, 2.4$ Hz), 2.44 (d, 1H, $J = 8.2$ Hz), 2.35 (s, 6H), 2.15 (m, 2H), 2.09 (ddt, 1H, $J = 16.2, 8.9, 2.4$ Hz), 1.69 (dd, 1H, $J = 8.0, 12.6$ Hz), 1.52–1.45 (m, 2H),

1.44–1.36 (m, 3H), 1.36–1.25 (m, 4H), 1.12 (s, 3H), 1.05 (s, 3H), 0.91 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 80.88, 78.73, 59.92, 54.30, 43.97, 40.46, 34.06, 31.54, 30.54, 29.40, 29.30, 28.67, 24.44, 22.75, 18.97, 14.21. HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{32}\text{N}_2$: 264.2565, found: 264.2567 (mass error $\Delta m = 0.69$ ppm).

N,N-Dimethyl-2-(2-nonyl)-1-piperidinamine (4c). The title compound was synthesized by the general procedure, producing 206.6 mg (55%) of the title compound as a yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 2.99–2.94 (m, 1H), 2.91 (ddt, 1H, $J = 16.4, 3.3, 2.5$ Hz), 2.37–2.31 (ddt, 1H, $J = 10.6, 9.0, 3.1$ Hz), 2.29 (s, 6H), 2.17–2.10 (m, 3H), 2.05 (ddt, 1H, $J = 16.4, 9.0, 2.5$ Hz), 2.05–1.99 (m, 1H), 1.73–1.64 (m, 2H), 1.52–1.42 (m, 3H), 1.41–1.34 (m, 2H), 1.33–1.22 (m, 5H), 1.14 (qt, 1H, $J = 13.2, 4.0$ Hz), 0.88 (t, 3H, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 81.50, 78.92, 59.82, 42.90, 39.14, 32.32, 31.53, 29.35, 28.71, 26.34, 24.74, 23.79, 22.73, 19.06, 14.19. HRMS electrospray ionization (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{30}\text{N}_2$: 250.2409, found: 250.2412 (mass error $\Delta m = 1.00$ ppm).

N,N,2-Trimethyl-5-(2-propynyl-3-phenyl)-1-pyrrolidinamine (4d). The title compound was synthesized by the general procedure, producing 250.0 mg (67%) of the title compound as a yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 7.44–7.40 (m, 2H), 7.32–7.25 (m, 3H), 3.15–3.06 (m, 2H), 2.77 (dd, 1H, $J = 16.6, 3.7$ Hz), 2.53 (s, 6H), 2.39 (dd, 1H, $J = 16.6, 9.0$ Hz), 1.95–1.85 (m, 1H), 1.83–1.74 (m, 1H), 1.74–1.65 (m, 1H), 1.47–1.37 (m, 1H), (d, 3H, $J = 6.0$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 131.70, 128.29, 127.54, 124.36, 89.23, 81.15, 59.28, 54.29, 41.43, 30.60,

27.86, 26.93, 22.27. **HRMS** electrospray ionization (ESI) m/z calcd. for $C_{16}H_{22}N_2$: 242.1783, found: 242.1784 (mass error $\Delta m = 0.48$ ppm).

N,N,3,3-Tetramethyl-5-(2-propynyl-3-phenyl)-1-pyrrolidinamine (4e). The title compound was synthesized by the general procedure, producing 185.1 mg (4%8) of the title compound as a yellow oil. **1H NMR** ($CDCl_3$, 500 MHz): δ 7.44-7.38 (m, 2H), 7.32-7.25 (m, 3H), 3.04-2.93 (m, 1H), 2.87 (d, 1H, $J = 16.7$), 2.66 (d, 1H, $J = 7.5$ Hz), 2.48 (d, 1H, $J = 8.1$ Hz), 2.39 (s, 6H), 1.76 (dd, 1H, $J = 12.1, 8.6$ Hz), 1.51 (dd, 1H, $J = 11.5, 8.6$ Hz), 1.30 (d, 1H, $J = 14.4$ Hz), 1.17 (s, 3H), 1.08 (s, 3H), 0.10 (s, 6H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 131.57, 128.13, 127.36, 59.48, 54.00, 43.66, 40.39, 34.06, 30.42, 29.22, 24.87. **HRMS** electrospray ionization (ESI) m/z calcd. for $C_{17}H_{24}N_2$: 256.1939, found: 256.2000 (mass error $\Delta m = 23.8$ ppm)

N,N-Dimethyl-2-(2-propynyl-3-phenyl)-1-piperidinamine (4f). The title compound was synthesized by the general procedure, producing 363.6 mg (62%) of the title compound as a yellow oil. **1H NMR** ($CDCl_3$, 500 MHz): δ 7.40–7.45 (m, 2H), 7.24–7.32 (m, 3H), 3.18 (dd, 1H, $J = 16.7, 3.5$ Hz), 2.99–3.05 (m, 1H), 2.48–2.55 (m, 1H), 2.36 (s, 6H), 2.36 (dd, 1H, $J = 16.6, 8.9$ Hz), 2.20 (ddd, 1H, $J = 12.3, 10.6, 2.5$ Hz), 2.08–2.15 (m, 1H), 1.69–1.78 (m, 2H), 1.47–1.58 (m, 1H), 1.34–1.44 (m, 1H), 1.15–1.26 (m, 1H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 131.71, 128.27, 127.44, 124.55, 89.66, 81.78, 59.65, 42.93, 39.27, 32.52, 26.33, 24.75, 24.60. **HRMS** electrospray ionization (ESI) m/z calcd. for $C_{16}H_{22}N_2$: 242.1783, found: 242.1784 (mass error $\Delta m = 0.62$ ppm).

7-(2-N,N-Dimethylamino-3-methylpyrrolidinyl)-5-heptynenitrile (**4g**). The title compound was synthesized by the general procedure, producing 217.0 mg (62%) of the title compound as a colorless oil. **¹H NMR** (CDCl₃, 500 MHz): δ 3.06 (dquin, 1H, J = 6.3, 7.9 Hz), 2.94 (ddd, 1H, J = 15.2, 8.2, 3.5 Hz), 2.53 (t, 2H, J = 7.2 Hz), 2.51-2.46 (m, 1H), 2.48 (s, 6H), 2.35 (tt, 2H, J = 6.6, 2.4 Hz), 2.14 (ddt, 1H, J = 16.3, 8.8, 2.5 Hz), 1.84 (quin, 2H, 7.0 Hz), 1.83-1.71 (m, 2H), 1.60-1.53 (m, 1H), 1.40-1.32 (m, 1H), 1.13 (d, 3H, J = 6.0 Hz). **¹³C NMR** (CDCl₃, 126 MHz): δ 119.43, 81.01, 77.58, 77.25, 59.29, 53.99, 41.20, 30.35, 27.43, 25.80, 24.99, 22.10, 17.97, 16.03. **HRMS** electrospray ionization (ESI) m/z calcd. for C₁₄H₂₃N₃: 233.1892, found: 233.2000 (mass error Δm = 46.3 ppm)

7-(2-N,N-Dimethylamino-4,4-dimethylmethylpyrrolidinyl)-5-heptynenitrile (**4h**). The title compound was synthesized by the general procedure using ethyl acetate to extract the crude product in place of diethyl ether, producing 232.0 mg (63%) of the title compound as a colorless oil. **¹H NMR** (CDCl₃, 500 MHz): δ 2.83 (ddd, 1H, J = 16.4, 8.1, 3.4), 2.60 (dt, 1H, J = 17.3, 8.5 Hz), 2.56 (ddt, 1H, J = 16.4, 4.0, 1.8 Hz), 2.51 (t, 2H, J = 7.2 Hz), 2.43 (d, 1H, J = 7.8), 2.36-2.31 (m, 8H), 2.13 (ddt, 1H, J = 16.4, 8.5, 2.3 Hz), 1.83 (quin, 2H, J = 6.9 Hz), 1.64 (dd, 1H, J = 12.8, 8.1 Hz), 1.38 (dd, 1H, J = 12.5, 8.1 Hz), 1.11 (s, 3H), 1.04 (s, 3H). **¹³C NMR** (CDCl₃, 126 MHz): δ 119.43, 80.91, 77.60, 59.47, 53.90, 43.59, 33.31, 30.39, 29.22, 25.01, 23.99, 17.99, 16.02, 1.01. **HRMS** electrospray ionization (ESI) m/z calcd. for C₁₅H₂₅N₃: 247.2048, found: 247.2000 (mass error Δm = 19.4 ppm)

7-(2-N,N-Dimethylaminopiperidiny)-5-heptynenitrile (4i). The title compound was synthesized by the general procedure, producing 143.8 mg (41%) of the title compound as a yellow oil. **¹H NMR** (CDCl₃, 500 MHz): δ 3.00 (d, 1H, *J* = 10.2 Hz), 2.81 (dq, 1H, *J* = 16.4, 2.4 Hz), 2.55 (t, 2H, *J* = 7.5 Hz), 2.40-2.34 (m, 3H), 2.32 (s, 6H), 2.19 (dddd, 1H, *J* = 24.7, 8.1, 2.4, 1.8 Hz), 1.94 (ddd, 1H *J* = 13.0, 3.0, 0.9 Hz), 1.86 (quin, 2H, *J* = 6.9 Hz), 1.77-1.68 (m, 2H), 1.48 (qt, 1H, *J* = 12.6, 4.0 Hz), 1.39-1.25 (m, 2H), 1.18 (qt, 1H, *J* = 13.0, 4.0 Hz). **¹³C NMR** (CDCl₃, 126 MHz): δ 119.15, 81.17, 78.14, 77.23, 59.27, 42.71, 32.14, 26.16, 25.08, 24.55, 23.58, 18.10, 16.07, 1.02. **HRMS** electrospray ionization (ESI) *m/z* calcd. for C₁₄H₂₃N₃: 233.1892, found: 233.2000 (mass error Δ*m* = 46.3 ppm)

N,N,2-Trimethyl-5-[2-hexynyl-6-(tert-butyl)dimethylsiloxy]-1-pyrrolidinamine (4j). The title compound was synthesized by the general procedure, producing 365.7 mg (72%) of the title compound as a colorless oil. **¹H NMR** (CDCl₃, 500 MHz): δ 3.71 (t, 2H, *J* = 6.7 Hz), 3.04 (dsex, 1H, *J* = 5.9, 1.7), 3.01-2.94 (m, 1H), 2.53 (dq, 1H, *J* = 2.5, 1.3 Hz), 2.50 (dq, 1H, *J* = 2.5, 1.6 Hz), 2.48 (s, 6H), 2.34 (tt, 2H, *J* = 7.1, 2.1 Hz), 2.09 (dt, 1H, *J* = 16.3, 9.5, 2.3 Hz), 1.82 (dq, 1H, *J* = 12.6, 8.2 Hz), 1.78-1.72 (m, 1H), 1.70 (quin, 2H, *J* = 6.5 Hz), 1.62-1.55 (m, 1H), 1.36 (dq, 1H, *J* = 11.9, 8.2 Hz), 1.13 (d, 3H, *J* = 6.1 Hz), 0.91 (s, 9H), 0.07 (s, 6H). **¹³C NMR** (CDCl₃, 126 MHz): δ 80.11, 78.82, 77.22, 61.80, 59.15, 54.40, 41.20, 32.17, 30.31, 27.72, 26.25, 25.96, 22.01, 18.36, 15.19, -5.31. **HRMS** electrospray ionization (ESI) *m/z* calcd. for C₁₉H₃₈N₂OSi: 338.2753, found: 338.3000 (mass error Δ*m* = 73.0 ppm)

N,N,3,3-Tetramethyl-5-[2-hexynyl-6-(tert-butyl)dimethylsiloxy]-1-pyrrolidinamine (4k).

The title compound was synthesized by the general procedure, producing 380.0 mg (72%) of the title compound as a colorless oil. **¹H NMR** (CDCl₃, 500 MHz): δ 3.71 (t, 1H, J = 6.4 Hz), 2.85 (ddd, 1H, J = 17.1, 8.4, 3.5 Hz), 2.62 (m, 2H), 2.44 (d, 1H, J = 8.4 Hz), 2.35 (s, 6H), 2.24 (tt, 2H, J = 7.0, 2.5 Hz), 2.07 (ddt, 1H, J = 16.4, 9.2, 2.3 Hz), 1.73-1.66 (m, 3H), 1.39 (dd, 1H, J = 12.5, 8.1 Hz), 1.12 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H). **¹³C NMR** (CDCl₃, 126 MHz): δ 80.11, 78.79, 77.22, 61.84, 59.74, 54.10, 43.89, 40.31, 33.93, 32.18, 30.39, 29.27, 25.98, 24.32, 18.37, 15.22, 5.29. **HRMS** electrospray ionization (ESI) m/z calcd. C₂₀H₄₀N₂OSi: 352.2910, found: 352.3000 (mass error Δm = 25.5 ppm)

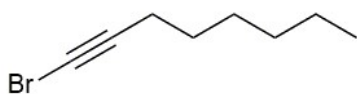
N,N-Dimethyl-2-[2-hexynyl-6-(tert-butyl)dimethylsiloxy]-1-piperidinamine (4l). The title compound was synthesized by the general procedure, producing 233.6 mg (46%) of the title compound as a yellow oil. **¹H NMR** (CDCl₃, 500 MHz): δ 3.71 (t, 2H, J = 6.2 Hz), 2.97 (ddd, 2H J = 16.8, 2.8, 1.4 Hz), 2.40-2.28 (m, 7H), 2.25 (tt, 2H, J = 7.2, 2.4 Hz), 2.15 (ddd, 1H J = 12.4, 2.1, 1.4 Hz), 2.10-2.01 (m, 2H), 1.76-1.66 (m, 4H), 1.49 (ddt, 1H J = 25.1, 12.4, 3.8 Hz), 1.28 (ddd, 1H, J = 23.7, 13.4, 3.4 Hz), 1.16 (ddt, 1H J = 26.1, 13.4, 4.1 Hz), 0.91 (s, 9H), 0.07 (s, 6H). **¹³C NMR** (CDCl₃, 126 MHz): δ 80.74, 78.99, 77.23, 61.88, 59.63, 42.74, 39.25, 39.00, 32.20, 26.17, 25.97, 24.59, 23.61, 18.36, 18.30, 5.31. **HRMS** electrospray ionization (ESI) m/z calcd. for C₁₉H₃₈N₂OSi: 338.2753, found: 338.3000 (mass error Δm = 73.0 ppm)

General Procedure for the Synthesis of 1-Bromoalkyne Electrophiles

A 100 mL round bottomed flask equipped with a magnetic stirring bar was charged with acetone (30 mL) and the requisite 1-alkyne (12.5 mmol). To this solution, AgNO₃ (0.213 g, 1.25

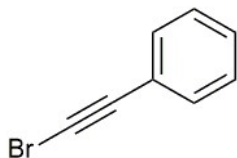
mmol) was added and, with vigorous stirring, N-bromosuccinimide (2.5 g, 14 mmol) was added in portions. The mixture was stirred at rt for 2 h when confirmed to be completed by TLC. The reactant mixture was diluted in pentane (75 mL) and filtered. The resulting solution was washed with water (2×25 mL) and the combined aqueous washes were back-extracted with 1:1 diethyl ether/pentane (2×15 mL). The combined organic layers were dried with Na_2SO_4 , filtered through a pad of silica gel, and concentrated in vacuo. The product could be further purified by vacuum distillation or flash column chromatography. Procedure adapted from Gao et al.⁶

1-Bromo-1-octyne (5a).



The title compound was synthesized by the general procedure. Short-path distillation in vacuo over CaH_2 furnished 2.10 g (89%) of the title compound as a clear liquid. $^1\text{H NMR}$ (C_6D_6 , 500 MHz): δ , 1.87 (t, 2H, $J = 6.9$ Hz), 1.19–1.27 (m, 2H), 1.10–1.19 (m, 4H), 1.00–1.08 (m, 2H), 0.80 (t, 3H, $J = 7.2$ Hz). $^{13}\text{C NMR}$ (C_6D_6 , 126 MHz): δ 80.81, 38.26, 31.53, 28.69, 28.50, 22.82, 19.80, 14.21. $^1\text{H NMR}$ and $^{13}\text{C NMR}$ spectra have been previously reported.^{2,6}

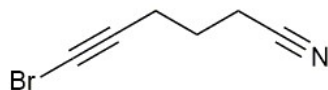
1-Bromo-2-phenylethyne (5b).



The title compound was synthesized by the general procedure. Flash column chromatography with 1:1 ether/pentane produced 2.24 g (99%) of the title compound as a clear to yellow liquid.

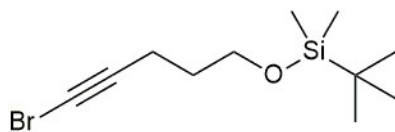
¹H NMR (C₆D₆, 500 MHz): δ 7.24–7.27 (m, 2H), 6.83–6.92 (m, 3H). **¹³C NMR** (C₆D₆, 126 MHz): δ 132.28, 128.80, 128.55, 123.13, 80.73, 50.49. ¹H NMR and ¹³C NMR spectra have been previously reported.^{2,6}

6-bromohex-5-ynenitrile (**5c**).

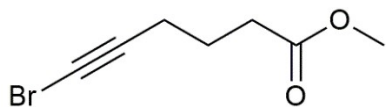


The title compound was synthesized by the general procedure. Flash column chromatography with 1:1 ether/pentane produced 2.13 g (99%) of the title compound as a clear liquid. **¹H NMR** (CDCl₃, 500 MHz): δ 2.52 (t, 2H, *J* = 6.8 Hz), 2.44 (t, 2H, *J* = 6.8 Hz), 1.91 (quin, 2H, *J* = 6.8 Hz). **¹³C NMR** (CDCl₃, 126 MHz): δ 118.91, 40.41, 24.25, 18.81, 16.16, 1.03. Spectra agree with previous literature.⁷

[(5-bromopent-4-yn-1-yl)oxy](tert-butyl)dimethylsilane (**5d**).



The title compound was synthesized by the general procedure. Flash column chromatography with hexane followed by ether furnished 2.91 g (84%) of the title compound as a clear liquid. **¹H NMR** (CDCl₃, 500 MHz): δ 3.70 (t, 2H, *J* = 6.3 Hz), 2.32 (t, 2H, *J* = 6.7 Hz), 1.73 (dquin, 2H, *J* = 6.0, 1.1 Hz), 0.92 (s, 9H), 0.08 (s, 6H). **¹³C NMR** (CDCl₃, 126 MHz): δ 79.99, 61.38, 37.67, 31.28, 25.92, 18.33, 16.13, 1.03, -5.36. Spectra agree with previous literature.⁸

methyl 6-bromo-5-hexynate (5e).

The title compound was synthesized by the general procedure. Short-path distillation in vacuo over CaH₂ furnished 2.53 g (99%) of the title compound as a clear liquid. ¹H NMR (CDCl₃, 500 MHz): δ 3.68 (s, 3H), 2.44 (t, 2H, *J* = 7.3), 2.29 (t, 2H, *J* = 6.8 Hz), 1.84 (quin, 2H, *J* = 7.3 Hz). ¹³C NMR (CDCl₃, 126 MHz): δ 173.38, 79.08, 51.59, 38.79, 32.68, 23.45, 19.11. Spectra agree with previous literature.¹⁹

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Chapter Five Experimental

Materials and Methods

All materials were either prepared according to previous literature or purchased from commercial sources. All solvents were obtained from a JC Meyer solvent dispensing system. Inorganic salts were dried by heating under a high vacuum before use if necessary. Nuclear magnetic resonance (NMR) data were obtained from a Bruker AVANCE NEO NMR spectrometer equipped with an Ascend 400 (400 MHz) magnet or a Bruker AVANCE III HD NMR spectrometer equipped with an Ascend 500 (500 MHz) magnet.

General Procedure for Cu(I)-Catalyst and Additive Screening Reaction

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube with a sealed 3 mm NMR calibration tube containing C₆D₆ was charged with benzotrifluoride (BTF, 0.4 mL), 2 M diethylzinc in BTF (60 μ L, 0.12 mmol, 1.2 equiv.), and 2-(hex-5-en-1-yl)-1,1-dimethylhydrazine (**1-Me**, 14.2 mg, 0.1 mmol). The J. Young tube was placed in a 90 °C oil bath and the metalloamination reaction was monitored by ¹H NMR (as indicated by the recession of the alkene peaks), using BTF as the internal standard. Upon completion of the formation of **4**, the volatiles were removed in vacuo. The J. Young NMR tube was returned to the glovebox and was charged with 1,2-DME (0.3 mL), methallyl chloride (39.3 μ L, 0.4 mmol), a Cu(I) catalyst (5 mol%) and, if desired, an additive (0.1 mmol). The reactant mixture was maintained at room temperature until no further reaction was observed by ¹H NMR. Percent conversion was calculated using the recession of the Zn–C methylene peaks using 1,2-DME as the internal standard. Spectroscopic data of product **5** has been previously reported.¹

General Procedure for Additive Screening in the Cu(I)-Catalyzed Cross-Coupling of 1-Bromoalkynes

In an inert atmosphere glovebox, a 5 mm J. Young NMR tube with a sealed 3 mm NMR calibration tube containing C₆D₆ was charged with benzotrifluoride (BTF, 0.4 mL), 2 M diethylzinc in BTF (60 μ L, 0.12 mmol, 1.2 equiv.), and N,N-dimethylhydrazinoalkene **8** or **9** (0.1 mmol). The J. Young tube was placed in a 90 °C oil bath and the metalloamination reaction was monitored by ¹H NMR (as indicated by the recession of the alkene peaks), using BTF as an internal standard. Upon completion of the metalloamination, the volatiles were removed in vacuo. The J. Young NMR tube was returned to the glovebox and was charged with THF (0.3 mL), 1-bromo-1-octyne (37.8 mg, 0.2 mmol), 0.5 M CuCN·2LiBr solution in THF (10 μ L, 5 mol%), and, if desired, additives (0.1 mmol each). The J. Young NMR tube was placed in a liquid nitrogen/isopropanol bath and allowed to warm to room temperature overnight. The resulting solution was dispersed in diethyl ether (1 mL) and washed with an aqueous solution of 1:1 sat. NH₄OH/sat. NH₄Cl (3 $\times$ 1 mL). The combined aqueous washes were then back-extracted with diethyl ether (2 $\times$ 1 mL) and the combined organic layers were concentrated in vacuo. The resulting crude product was dissolved in CH₂Cl₂ (1 mL), dispersed onto silica gel (50 mg), and dried in vacuo. This was purified by dry-loading the resulting silica gel onto a pad of silica gel and eluting with pentane. The product was then flushed from the silica gel using diethyl ether and concentrated in vacuo, providing azacycle **8'** or **9'**. The product could be further purified, if necessary, by column chromatography. Spectroscopic data of **8'** and **9'** have been previously reported.²

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Chapter Six Experimental

Materials and Methods

All materials were either prepared according to previous literature or purchased from commercial sources. Ethyl-4-iodobutyrate¹ and 1-octyn-3-yl tosylate² were prepared by previously reported methods. All solvents were obtained from a JC Meyer solvent dispensing system. Inorganic salts were dried by heating under a high vacuum before use if necessary. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and were visualized with UV light (254 nm) or potassium permanganate staining. Nuclear magnetic resonance (NMR) data were obtained from a Bruker AVANCE III HD NMR spectrometer equipped with an Ascend 500 (500 MHz) magnet.

Procedures for the Preparation of N,N-Dimethylhydrazinoallenes

Hexa-4,5-dien-1-ol (4a) The title compound was prepared via Crabbé homologation.^{3,4} To a 100 mL round-bottomed flask equipped with a magnetic stirring bar, jacketed condenser, and drying tube was added pent-4-yn-1-ol (2.56 g, 30.5 mmol), N-isopropylcyclohexylamine (10.2 mL, 61.0 mmol, 2 equiv.), and anhydrous 1,4-dioxane (50 mL). CuBr (1.46 g, 10.2 mmol, 0.3 equiv.) and paraformaldehyde (1.83 g, 61.0 mmol, 2 equiv.) were dispersed in the reactant mixture with stirring and the reactant mixture was heated at reflux at 110 °C for 12 h. The resulting mixture was filtered through a pad of celite and concentrated in vacuo. The crude product was dispersed

in diethyl ether (20 mL) and washed with 2 M aqueous HCl (5 mL). The aqueous layer was back-extracted with diethyl ether (3 x 5 mL) and the combined organic layers were neutralized with sat. aqueous NaHCO₃ (5 mL), washed with brine (5 mL), and dried with MgSO₄, to provide **4a** (1.60 g, 16.3 mmol, 53%). The resulting product could be purified by column chromatography utilizing gradient elution (hexanes to 1:1 ethyl acetate:hexanes) or by fractional distillation if necessary. ¹H NMR (CDCl₃, 500 MHz): δ 5.15 (quin, 1H, *J* = 6.7 Hz), 4.70 (dt, 2H, *J* = 3.4, 3.1 Hz), 3.71 (t, 2H, *J* = 6.5 Hz), 2.12 (dtd, 2H, *J* = 11.2, 7.0, 3.4 Hz), 1.72 (quin, 2H, *J* = 7.6 Hz), 1.44 (s, 1H). ¹³C NMR (CDCl₃, 126 MHz): δ 208.52, 89.42, 75.13, 62.28, 31.85, 24.45.

Hexa-4,5-dien-1-al (**5a**) To a 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet was added anhydrous CH₂Cl₂ (10 mL) and anhydrous DMSO (1.4 mL, 20.4 mmol, 2 equiv.). The resulting solution was cooled to -78 °C and oxalyl chloride (1.05 mL, 12.2 mmol, 1.2 equiv.) was added dropwise. After 10 min of stirring, alcohol **4a** (1.0 g, 10.2 mmol) in anhydrous CH₂Cl₂ (5 mL) was added to the reactant mixture. After an additional 30 min of stirring at -78 °C, Et₃N (7.1 mL, 51 mmol, 5 equiv.) was added and the reaction was allowed to warm to room temperature and stirred for an additional 1 h. Water (10 mL) was added to the resulting suspension and the layers were separated. The aqueous layer was back-extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic layers were washed with 2 M HCl (5 mL), of sat. aqueous NaHCO₃ (5 mL), and brine (5 mL), dried with Na₂SO₄, and concentrated in vacuo. The resulting crude product was distilled under high vacuum, affording **5a** (0.9 g, 9.3 mmol, 92%). ¹H NMR (CDCl₃, 500 MHz): δ 9.78 (s, 1H), 5.18 (quin, 1H, *J* = 6.2

Hz), 4.73 (dt, 2H, $J = 6.5, 3.6$ Hz), 2.57 (td, 2H, $J = 7.1, 1.2$ Hz), 2.33 (dtd, 2H, $J = 10.4, 7.1, 3.6$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 208.46, 201.2, 88.62, 76.40, 42.35, 20.53.

Hexa-4,5-dien-*N,N*-dimethylhydrazone (**6a**) A 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged with aldehyde **5a** (0.5 g, 4.5 mmol), and cooled to 0 °C whereupon *N,N*-dimethylhydrazine (0.41 mL, 5.4 mmol, 1.2 equiv.) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The water layer was removed and K_2CO_3 (0.2 g) was added to the reactant mixture and stirred for an additional 1 h. The resulting mixture was filtered and concentrated in vacuo. The crude product was purified by distillation from CaH_2 under vacuum to provide **6a** (0.19 g, 1.4 mmol, 31%) ^1H NMR (CDCl_3 , 500 MHz): δ 6.68 (t, 1H, $J = 5.6$ Hz), 5.16 (quin, 1H, $J = 6.7$ Hz), 4.70 (dt, 2H, $J = 6.7, 3.4$ Hz), 2.75 (s, 6H), 2.41-2.34 (m, 2H), 2.55-2.18 (m, 2H). ^{13}C NMR (CDCl_3 , 126 Hz): δ 208.63, 139.11, 89.20, 75.22, 43.33, 32.44, 26.49.

1,1-Dimethyl-2-(hexa-4,5-dien-1-yl)hydrazine (**7a**) Hydrazine **7a** was prepared from hydrazone **6a** (0.44 g, 3.2 mmol) using previously reported methods⁵ with no changes (0.36 g, 2.6 mmol, 81%). ^1H NMR (C_6D_6 , 500 MHz): δ 5.08 (quin, 1H, $J = 6.5$ Hz), 4.60 (dt, 2H, $J = 6.5, 3.3$ Hz), 2.65 (t, 2H, $J = 6.7$ Hz), 2.21 (s, 6H), 2.03 (dtd, 2H, $J = 11.5, 6.7, 3.3$ Hz), 1.57 (quin, 2H, $J = 6.7$ Hz), 1.59-1.54 (s, 1H). ^{13}C NMR (C_6D_6 , 126 MHz): δ 208.66, 90.04, 74.50, 47.72, 47.29, 28.14, 26.00.

Hepta-5,6-dien-1-ol (4b) The title compound was prepared via Crabbé homologation.^{3,4} To a 100 mL round-bottomed flask equipped with a magnetic stirring bar, jacketed condenser, and drying tube was added hex-5-yn-1-ol (3.00 g, 30.5 mmol), N-isopropylcyclohexylamine (10.2 mL, 61.0 mmol, 2 equiv.), and anhydrous 1,4-dioxane (50 mL). CuBr (1.46 g, 10.2 mmol, 0.3 equiv.) and paraformaldehyde (1.83 g, 61.0 mmol, 2 equiv.) were dispersed in the reactant mixture with stirring and the reactant mixture was heated at reflux at 110 °C for 12 h. The resulting product mixture was filtered through a pad of celite and concentrated in vacuo. The crude product was dispersed in diethyl ether (20 mL) and washed with 2 M aqueous HCl (5 mL). The aqueous layer was back-extracted with diethyl ether (3 x 5 mL) and the combined organic layers were neutralized with sat. aqueous NaHCO₃ (5 mL), washed with brine (5 mL), and dried with MgSO₄, yielding **4b** (1.43 g, 12.7 mmol, 41%). The resulting product could be purified by column chromatography utilizing gradient elution (hexanes to 1:1 ethyl acetate:hexanes) or by fractional distillation if necessary. ¹H NMR (CDCl₃, 500 MHz): δ 5.12 (quin, 1H, *J* = 6.4 Hz), 4.68 (dt, 2H, *J* = 6.5, 3.3), 3.68 (t, 2H, *J* = 6.5 Hz), 2.06 (dtd, 2H, *J* = 11.0, 7.0, 3.3 Hz), 1.67-1.60 (m, 2H), 1.55-1.48 (m, 2H). ¹³C NMR (CDCl₃, 126 MHz): δ 208.56, 89.75, 74.83, 62.80, 32.16, 27.94, 25.19.

Hepta-5,6-dien-1-al (5b) To a 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet was added anhydrous CH₂Cl₂ (10 mL) and anhydrous DMSO (1.4 mL, 20.4 mmol, 2 equiv.). The resulting solution was cooled to -78 °C and oxalyl chloride (1.05 mL, 12.2 mmol, 1.2 equiv.) was added dropwise. After 10 min of stirring, alcohol **5a** (1.14 g, 10.2 mmol) in anhydrous CH₂Cl₂ (5 mL) was added to the reactant mixture. After an

additional 30 min of stirring at -78 °C, Et₃N (7.1 mL, 51 mmol, 5 equiv.) was added and the reaction was allowed to warm to room temperature and stirred for an additional 1 h. Water (10 mL) was added to the resulting suspension and the layers were separated. The aqueous layer was back-extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic layers were washed with 2 M HCl (5 mL), sat. aqueous NaHCO₃ (5 mL), and brine (5 mL), dried with Na₂SO₄, and concentrated in vacuo. The resulting crude product was distilled under high vacuum, affording **5b** (1.1 g, 10.1 mmol, 99%). ¹H NMR (CDCl₃, 500 MHz): δ 9.77 (s, 1H), 5.08 (quin, 1H, *J* = 6.7 Hz), 4.69 (dt, 2H, *J* = 6.7, 3.4 Hz), 2.48 (td, 2H, *J* = 7.3, 1.5 Hz), 2.05 (dtd, 2H, *J* = 10.7, 7.0, 3.4 Hz), 1.77 (quin, 2H, *J* = 7.3 Hz). ¹³C NMR (CDCl₃, 126 MHz): δ 208.67, 202.35, 89.01, 75.23, 43.14, 27.46, 21.33.

Hepta-5,6-dien-*N,N*-dimethylhydrazone (**6b**) A 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged aldehyde **5b** (0.5 g, 4.5 mmol), and was cooled to 0 °C whereupon *N,N*-dimethylhydrazine (0.41 mL, 5.4 mmol, 1.2 equiv.) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The water layer was removed and K₂CO₃ (0.2 g) was added to the reaction mixture and stirred for an additional 1 h. The resulting mixture was filtered and concentrated in vacuo. The crude product was purified by distillation from CaH₂ under vacuum to provide **6b** (0.46 g, 3.0 mmol, 67%). ¹H NMR (CDCl₃, 500 MHz): δ 6.67 (t, 1H, *J* = 5.7 Hz), 5.23 (quin, 1H, *J* = 7.1 Hz), 4.69 (dt, 2H, *J* = 7.1, 3.7 Hz), 2.75 (s, 6H), 2.30 (dt, 2H, *J* = 5.7, 2.0 Hz), 2.07 (dtd, 2H, *J* = 10.1, 7.1, 3.4 Hz), 1.63 (quin, 2H, *J* = 7.7 Hz). ¹³C NMR (CDCl₃, 126 MHz): δ 208.61, 138.92, 89.65, 74.85, 43.40, 32.52, 27.76, 27.22.

1,1-Dimethyl-2-(hepta-5,6-dien-1-yl)hydrazine (7b) Hydrazine **7b** was prepared from hydrazone **6b** (0.46 g, 3.0 mmol) using previously reported methods⁵ with no changes (0.37 g, 2.4 mmol, 80%). ¹H NMR (C₆D₆, 500 MHz): δ 5.05 (quin, 1H, J = 6.8 Hz), 4.61 (dt, 2H, J = 6.8, 3.3 Hz), 2.64 (t, 2H, J = 6.8 Hz), 2.22 (s, 6H), 1.94 (dtd, 2H, J = 10.7, 7.0, 3.3 Hz), 1.53 (s, 1H), 1.51-1.39 (m, 4H). ¹³C NMR (C₆D₆, 126 MHz): δ 208.68, 90.05, 74.45, 48.27, 47.32, 28.28, 28.16, 26.93.

Dodeca-5,6-dienoic acid ethyl ester (12) The title product was prepared according to the procedure of Bäckvall.² A 50 mL Schlenk flask equipped with a magnetic stirring bar and an argon inlet was charged with powdered zinc (0.973 g, 14.85 mmol, 1.6 equiv.), anhydrous THF (3 mL), and 1,2-dibromoethane (97.5 mg, 0.53 mmol). The resulting suspension was heated under inert atmosphere with a heat gun for 30 s and then was allowed to cool to room temperature. Chlorotrimethylsilane (55 μ L, 0.45 mmol) was added to the suspension and the mixture was stirred for 15 min. A solution of ethyl-4-iodobutyrate (3.48 g, 14.35 mmol, 1.55 equiv.) in anhydrous THF (5 mL) was added to the suspension and the reactant mixture was stirred at 35 °C overnight. The resulting organozinc mixture was cooled to -10 °C and a solution of CuCN (0.92 g, 10.35 mmol, 1.12 equiv.) and LiCl (0.88 g, 20.75 mmol, 2.25 equiv.) in THF (20 mL) was added and stirred at 0 °C for 30 min. The resulting mixture was cooled to -40 °C and 1-octyn-3-yl tosylate (2.78 g, 9.23 mmol, 1 equiv.) was added dropwise. The reactant mixture was allowed to slowly warm to room temperature and stirred for an additional 1 h. The mixture was then dispersed in water (10 mL) and diethyl ether (10 mL), the resulting layers were separated, and the aqueous layer was back-extracted with diethyl ether (3 x 5 mL). The

combined organic layers were washed with water (5 mL) and brine (5 mL) and then dried with MgSO_4 . The crude product was then filtered through a pad of silica and concentrated in vacuo, affording ethyl ester **12** (1.77 g, 7.89 mmol, 85%) with no further purification. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 5.11 (dt, 1H, $J = 9.8, 6.4, 3.2$ Hz), 5.07 (dt, 1H, $J = 9.8, 6.4, 3.2$ Hz), 4.14 (q, 2H, $J = 7.1$ Hz), 2.35 (t, 2H, $J = 7.6$ Hz), 2.04 (qd, 2H, $J = 7.1, 3.1$ Hz), 1.99 (qd, 2H, $J = 7.1, 3.1$ Hz), 1.76 (quin, 2H, $J = 7.1$ Hz), 1.41 (quin, 2H, $J = 7.1$ Hz), 1.35-1.30 (m, 4H), 1.27 (t, 3H, $J = 7.1$ Hz). $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz): δ 204.03, 173.68, 91.47, 89.84, 60.21, 33.65, 31.33, 28.91, 28.89, 28.37, 24.38, 22.50, 14.25, 14.08.

Dodeca-5,6-dien-1-ol (**13**) The title product was prepared according to the procedure of Bäckvall.² A 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet was charged with lithium aluminum hydride (0.263 g, 6.9 mmol, 1.1 equiv.) and anhydrous diethyl ether (10 mL). The resulting suspension was cooled to 0 °C and ethyl ester **12** (1.41 g, 6.3 mmol) in anhydrous diethyl ether (10 mL) was added. The reactant mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and stirred for an additional 1 h. The suspension was cooled to 0 °C and the lithium aluminum hydride was carefully quenched by the addition of ethyl acetate and water. Enough 2 M aqueous HCl was added to the mixture to fully dissolve the solids and the layers were separated. The resulting aqueous layer was back-extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with sat. aqueous NaHCO_3 (5 mL) and brine (5 mL), dried with MgSO_4 , and concentrated in vacuo. The crude product was purified by column chromatography (20% ethyl acetate/hexanes for elution), providing alcohol **13** (1.10g, 6.0 mmol, 87%). $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 5.13-5.05 (m,

2H), 3.67 (t, 2H, $J = 6.8$ Hz), 2.08-1.95 (m, 4H), 1.68-1.59 (m, 2H), 1.54-1.46 (m, 2H), 1.45-1.37 (m, 3H), 1.36-1.28 (m, 4H), 0.90 (t, 3H, $J = 6.8$ Hz). ^{13}C NMR (CDCl_3 , 126 Hz): δ 203.88, 91.22, 90.52, 62.85, 32.20, 31.33, 28.96, 28.91, 28.72, 25.29, 22.52, 14.09.

Dodeca-5,6-dien-1-al (**14**) To a 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet was added anhydrous CH_2Cl_2 (5 mL) and anhydrous DMSO (0.73 mL, 10.6 mmol, 2 equiv.). The resulting solution was cooled to -78°C and oxalyl chloride (0.55 mL, 6.4 mmol, 1.2 equiv.) was added dropwise. After 10 min of stirring, alcohol **13** (0.972 g, 5.3 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to the reactant mixture. After an additional 30 min of stirring at -78°C , Et_3N (3.7 mL, 26.5 mmol, 5 equiv.) was added and the reaction was allowed to warm to room temperature and stirred for an additional 1 h. Water (10 mL) was added to the resulting suspension and the layers were separated. The aqueous layer was back-extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with 2 M HCl (5 mL), sat. aqueous NaHCO_3 (5 mL), and brine (5 mL) and then dried with Na_2SO_4 and concentrated in vacuo. The resulting crude product was distilled under vacuum, affording **14** (0.754 g, 4.2 mmol, 79%). ^1H NMR (CDCl_3 , 500 MHz): δ 9.80 (t, 1H, $J = 1.7$ Hz), 5.13 (dt, 1H, $J = 6.6, 6.6, 3.1$ Hz), 5.07 (dt, 1H, $J = 6.6, 6.6, 3.1$ Hz), 2.50 (dt, 2H, $J = 7.3, 1.7$ Hz), 2.05 (ddq, 2H, $J = 7.3, 2.9, 1.7$ Hz), 2.00 (dq, 2H, $J = 7.3, 2.9$ Hz), 1.78 (quin, 2H, $J = 7.3$ Hz), 1.41 (quin, 2H, $J = 7.3$ Hz), 1.35-1.30 (m, 4H), 0.91 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 204.09, 202.61, 91.68, 89.75, 43.23, 31.33, 28.90, 28.26, 22.51, 21.45, 14.09.

Dodeca-5,6-dien-*N,N*-dimethylhydrazone (**15**) A 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged aldehyde **14** (0.42 g, 2.3 mmol), and was cooled to 0 °C whereupon *N,N*-dimethylhydrazine (0.27 mL, 3.5 mmol, 1.5 equiv.) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The water layer was removed and K₂CO₃ (0.2 g) was added to the reactant mixture and stirred for an additional 1 h. The resulting mixture was filtered and concentrated in vacuo. The crude product was purified by distillation from CaH₂ under vacuum to provide **15** (0.453 g, 2.0 mmol, 89%). ¹H NMR (CDCl₃, 500 MHz): δ 6.67 (t, 1H, *J* = 5.5 Hz), 5.10 (quin, 2H, *J* = 4.7 Hz), 2.74 (s, 6H), 2.29 (dt, 2H, *J* = 7.4, 6.1 Hz), 2.08-2.02 (m, 2H), 2.02-1.96 (m, 2H), 1.61 (quin, 2H, *J* = 7.4 Hz), 1.41 (quin, 2H, *J* = 7.4 Hz), 1.36-1.29 (m, 4H), 0.91 (t, 3H, *J* = 6.9 Hz). ¹³C NMR (CDCl₃, 126 MHz): δ 203.93, 139.18, 91.26, 90.41, 43.41, 32.58, 31.33, 28.96, 28.92, 28.55, 27.38, 22.52, 14.11.

1,1-Dimethyl-2-(dodeca-5,6-dien-1-yl)hydrazine (**16**) Hydrazine **16** was prepared from hydrazone **15** (0.605 g, 2.7 mmol) using previously reported methods⁵ with no changes (0.459 g, 2.0 mmol, 76%). ¹H NMR (C₆D₆, 500 MHz): δ 5.18-5.10 (m, 2H), 2.68 (t, 2H, *J* = 6.4 Hz), 2.23 (s, 6H), 2.05-1.94 (m, 4H), 1.58-1.45 (m, 5H), 1.39 (quin, 2H, *J* = 7.4 Hz), 1.25 (s, 4H, *J* = 3.6 Hz), 0.86 (t, 3H, *J* = 7.0 Hz). ¹³C NMR (C₆D₆, 126 MHz): δ 204.19, 90.98, 90.95, 48.37, 47.34, 31.34, 29.12, 29.04, 29.00, 28.24, 27.10, 22.53, 13.93.

References

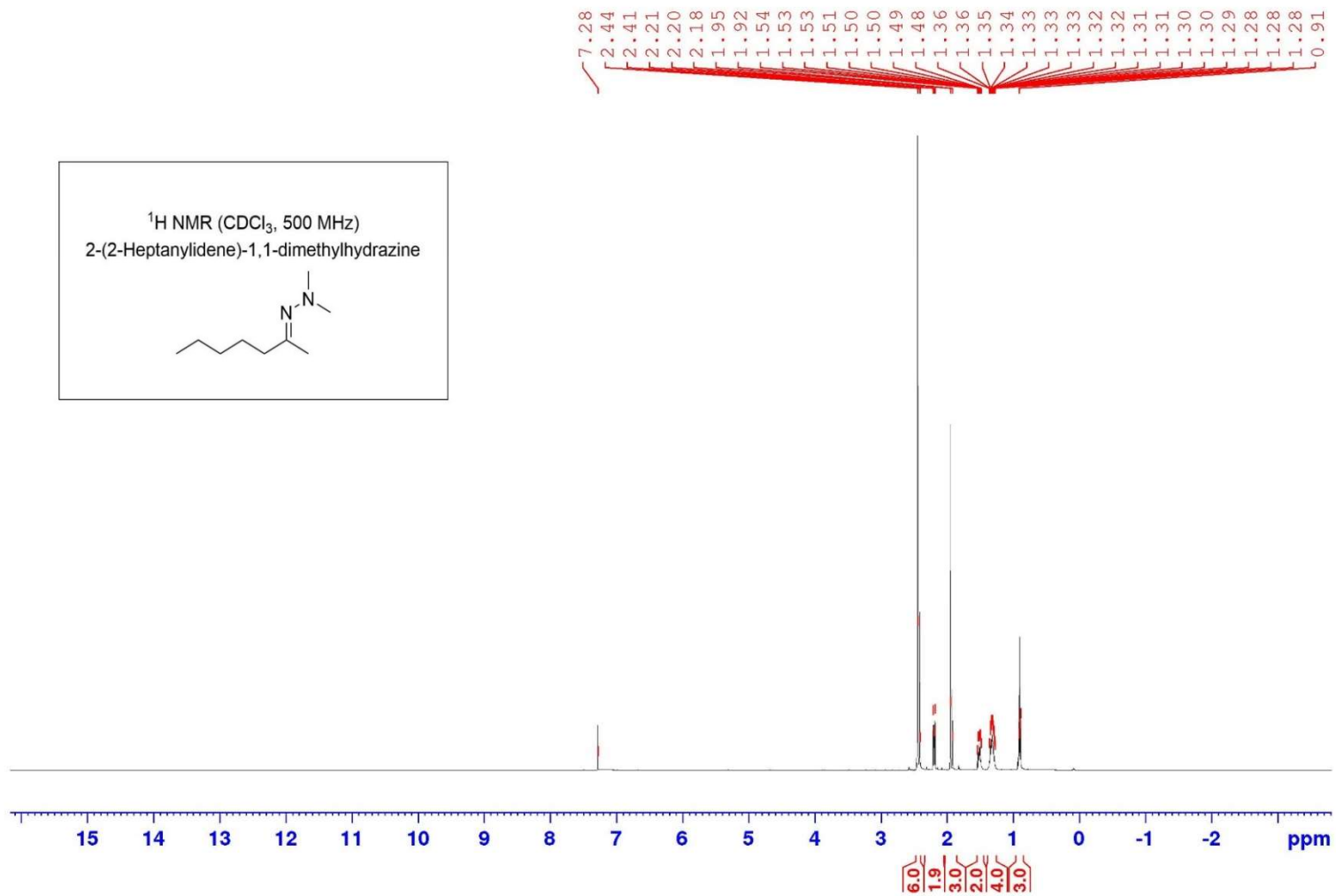
1. Ethyl-4-iodobutyrate was prepared from ethyl-4-chlorobutyrate by refluxing in acetone with sodium iodide. Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528.
2. Jonasson, C.; Horváth, A.; Bäckvall, J-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600-9609.

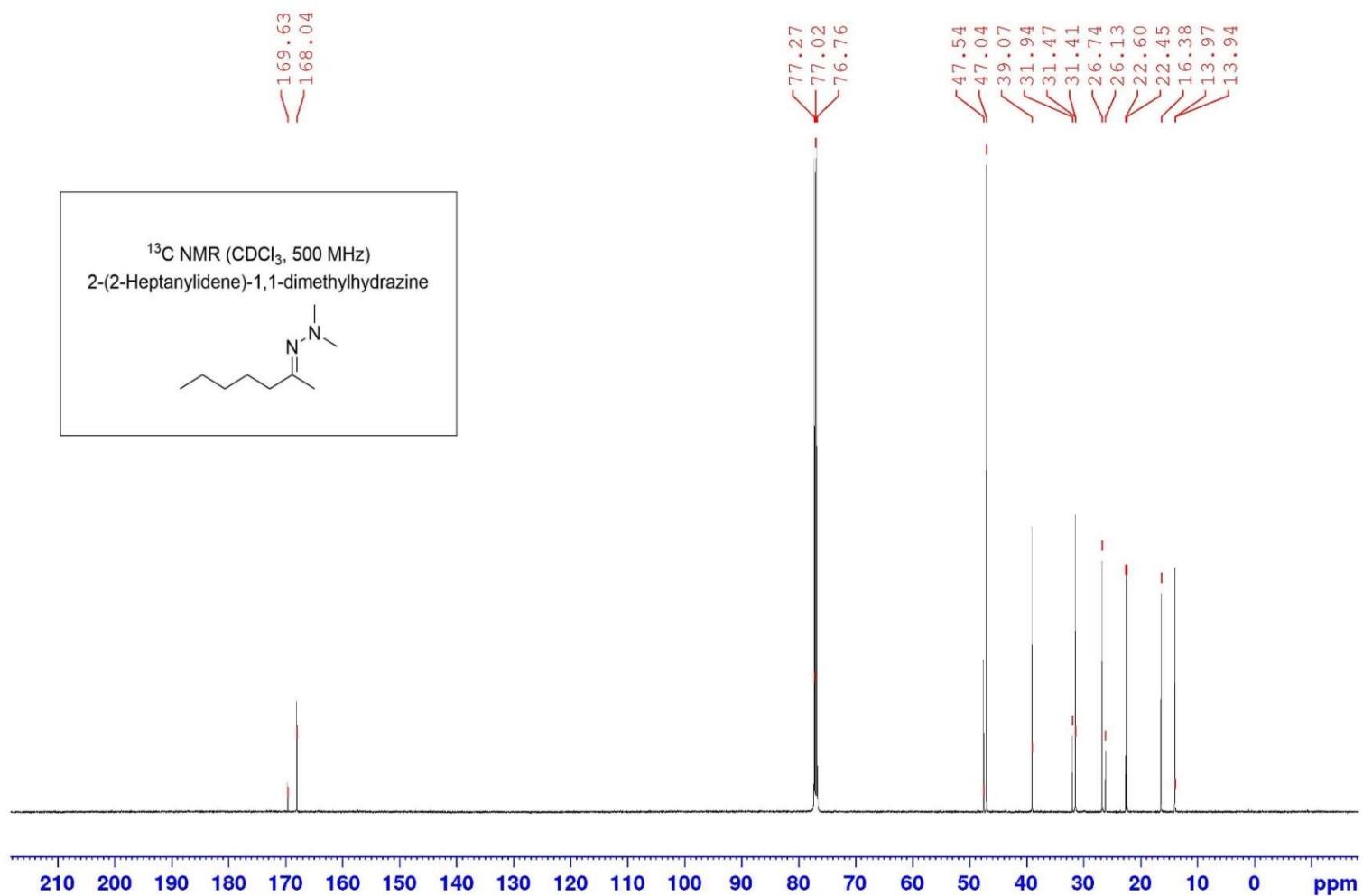
3. Crabbé, P.; Fillion, H.; André, D.; Lucie, J-L. *J. Chem. Soc., Chem. Commun.* **1979**, 19, 859-860.
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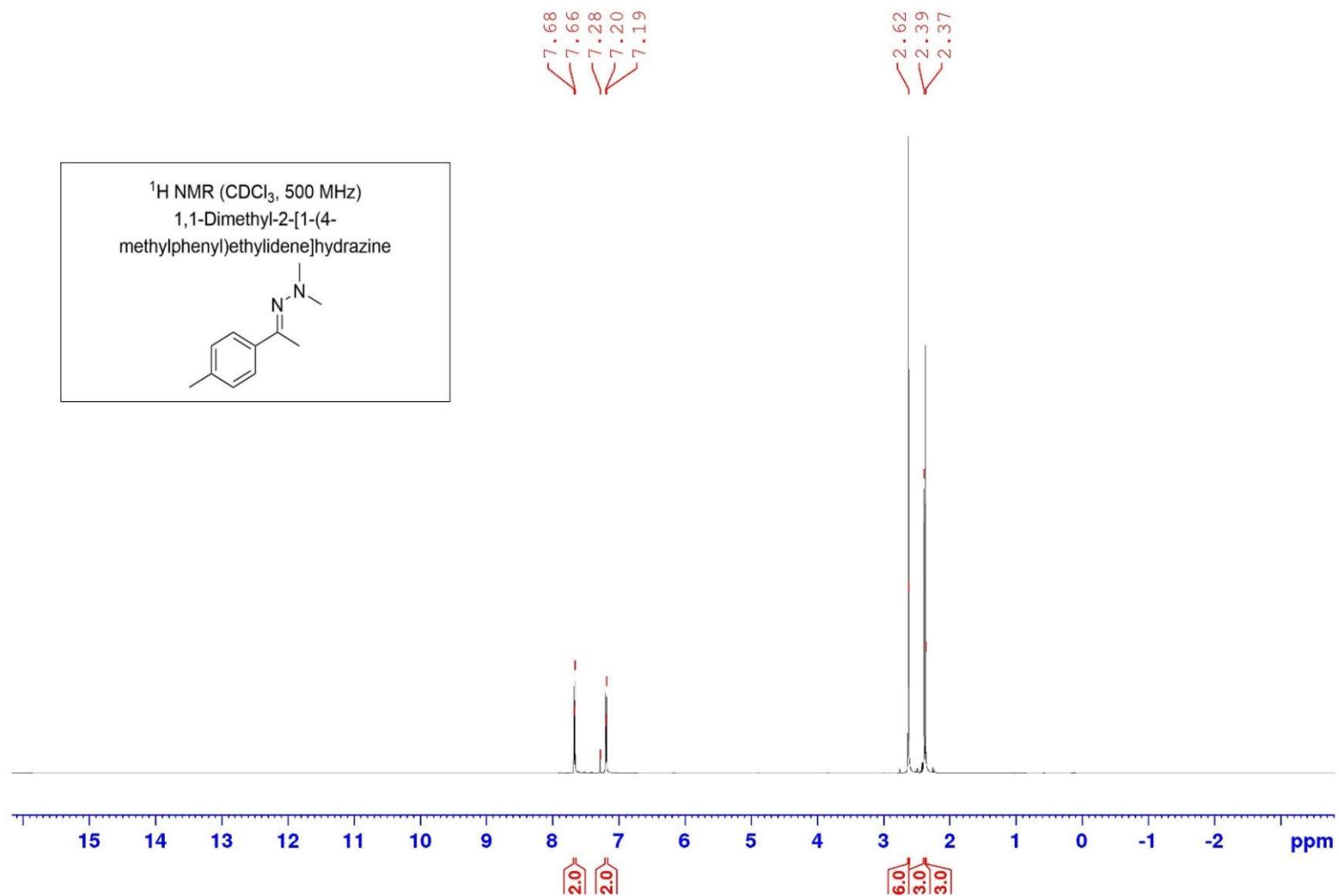
APPENDIX B

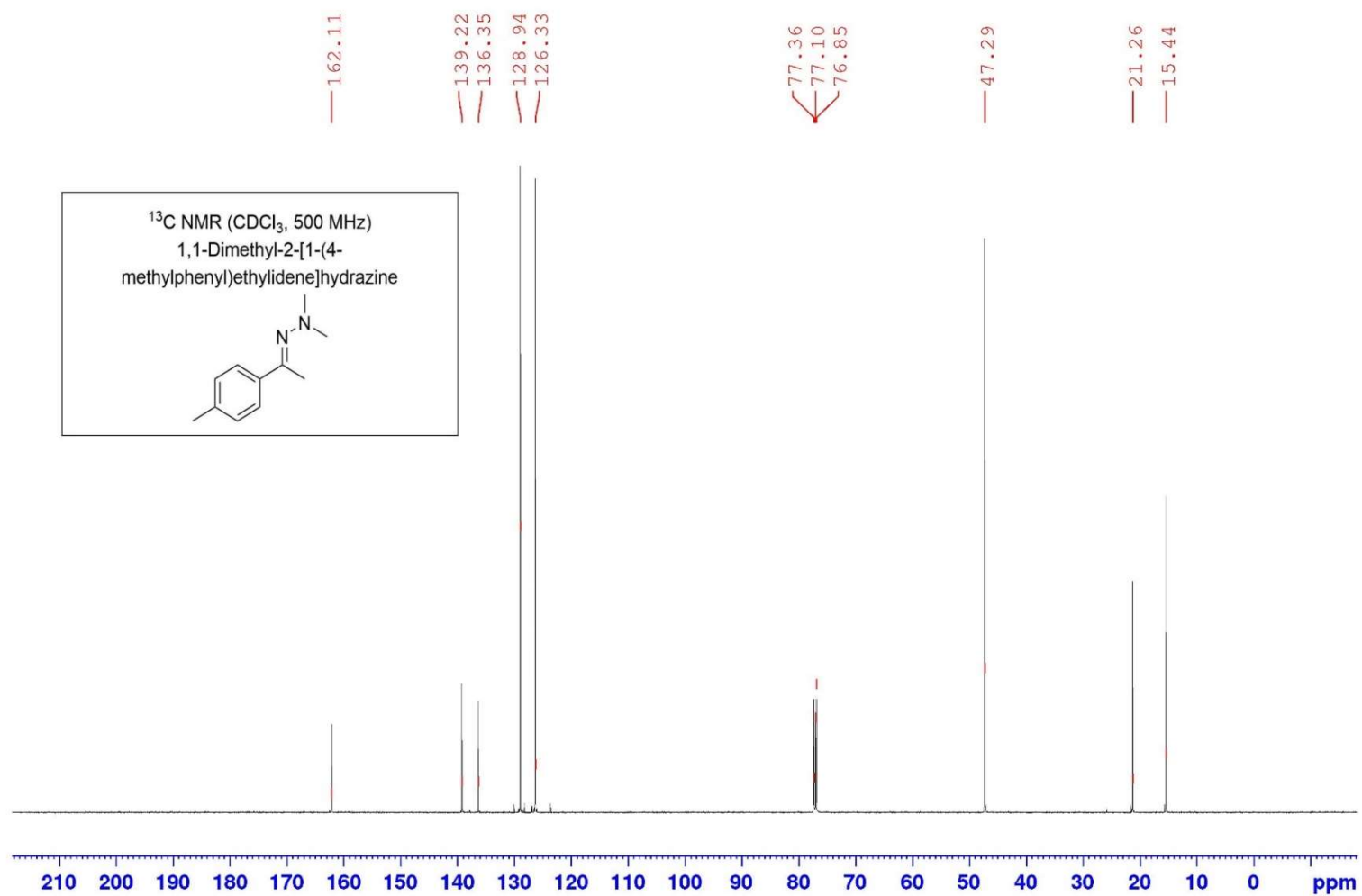
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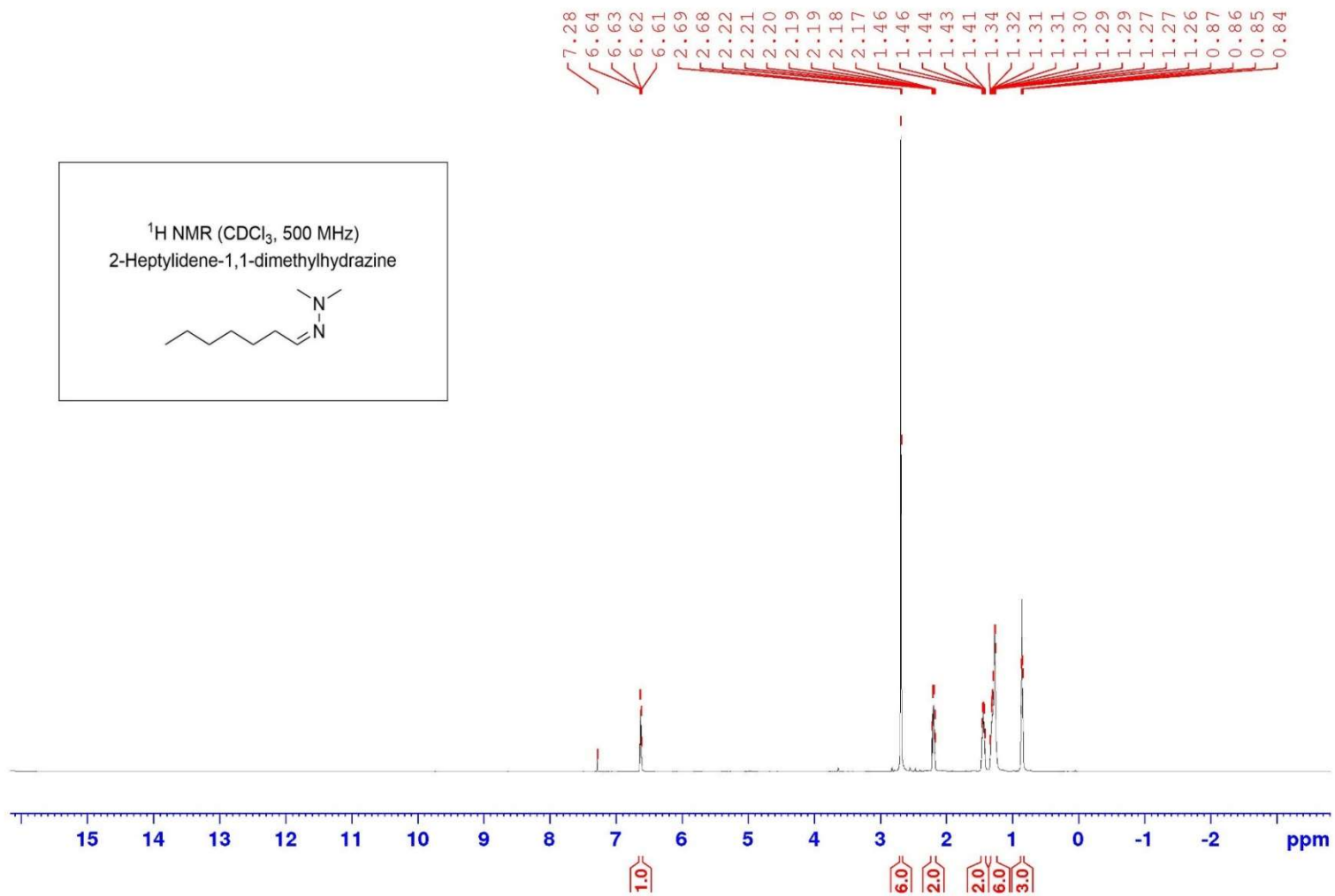
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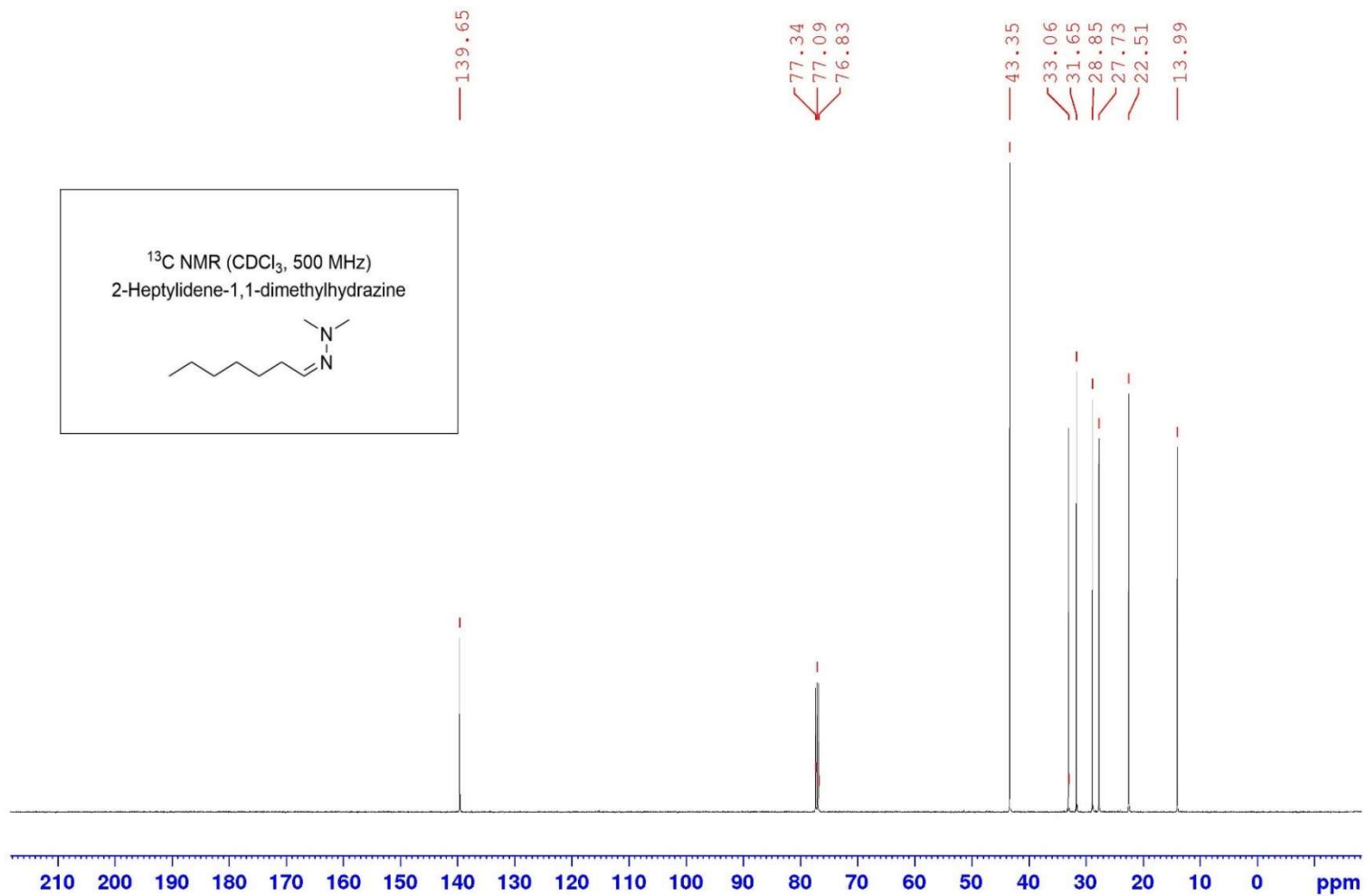


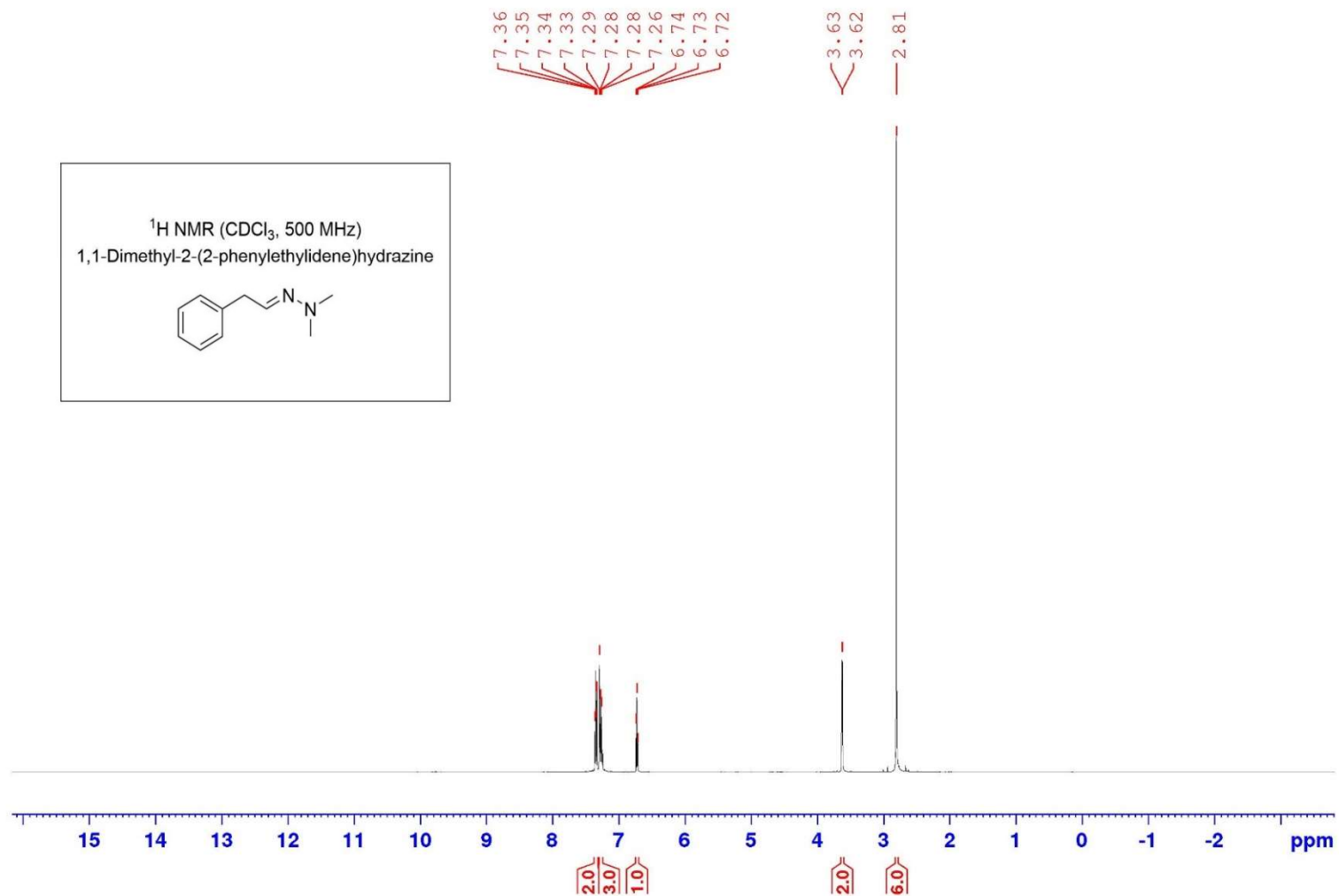


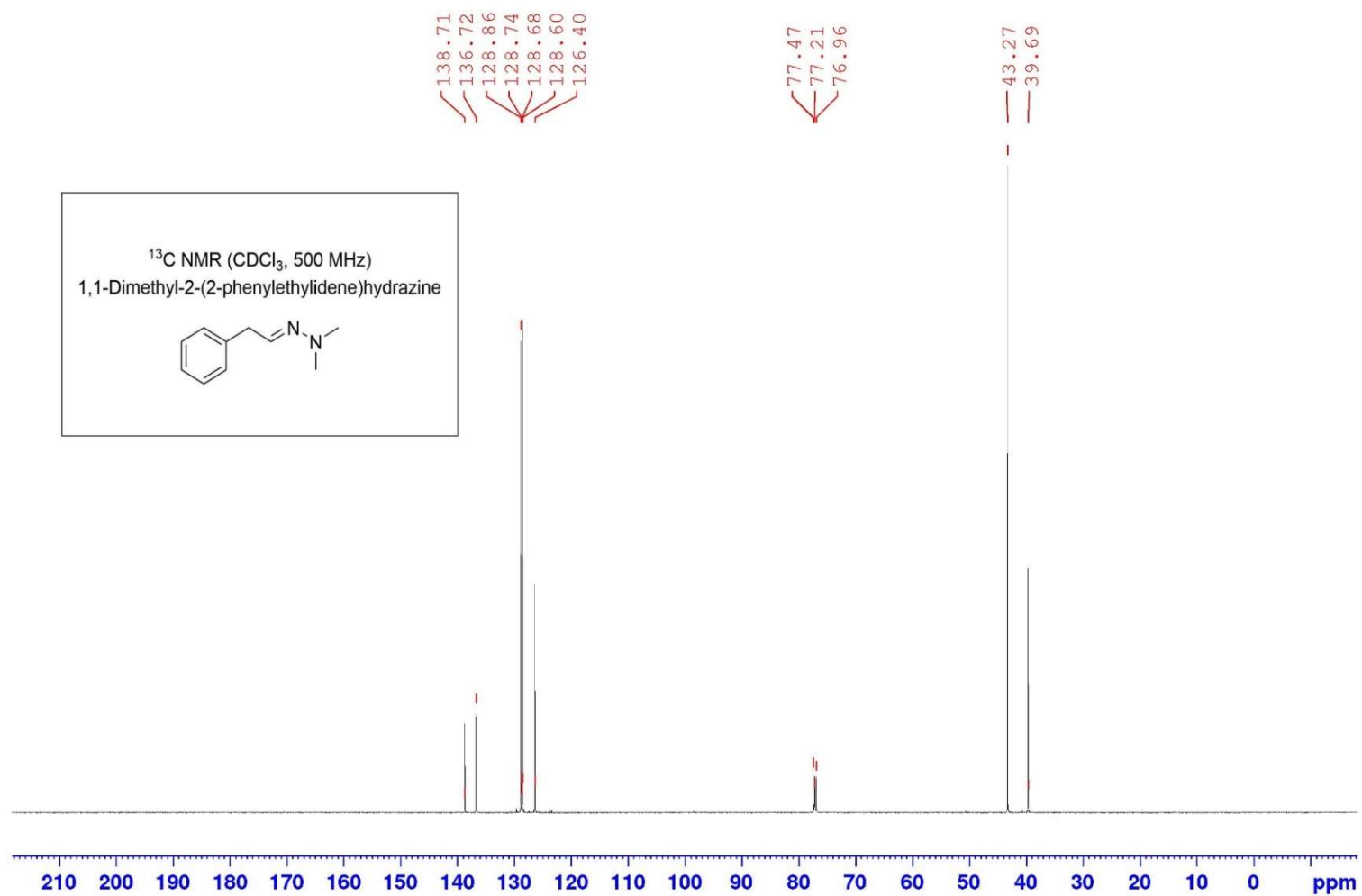


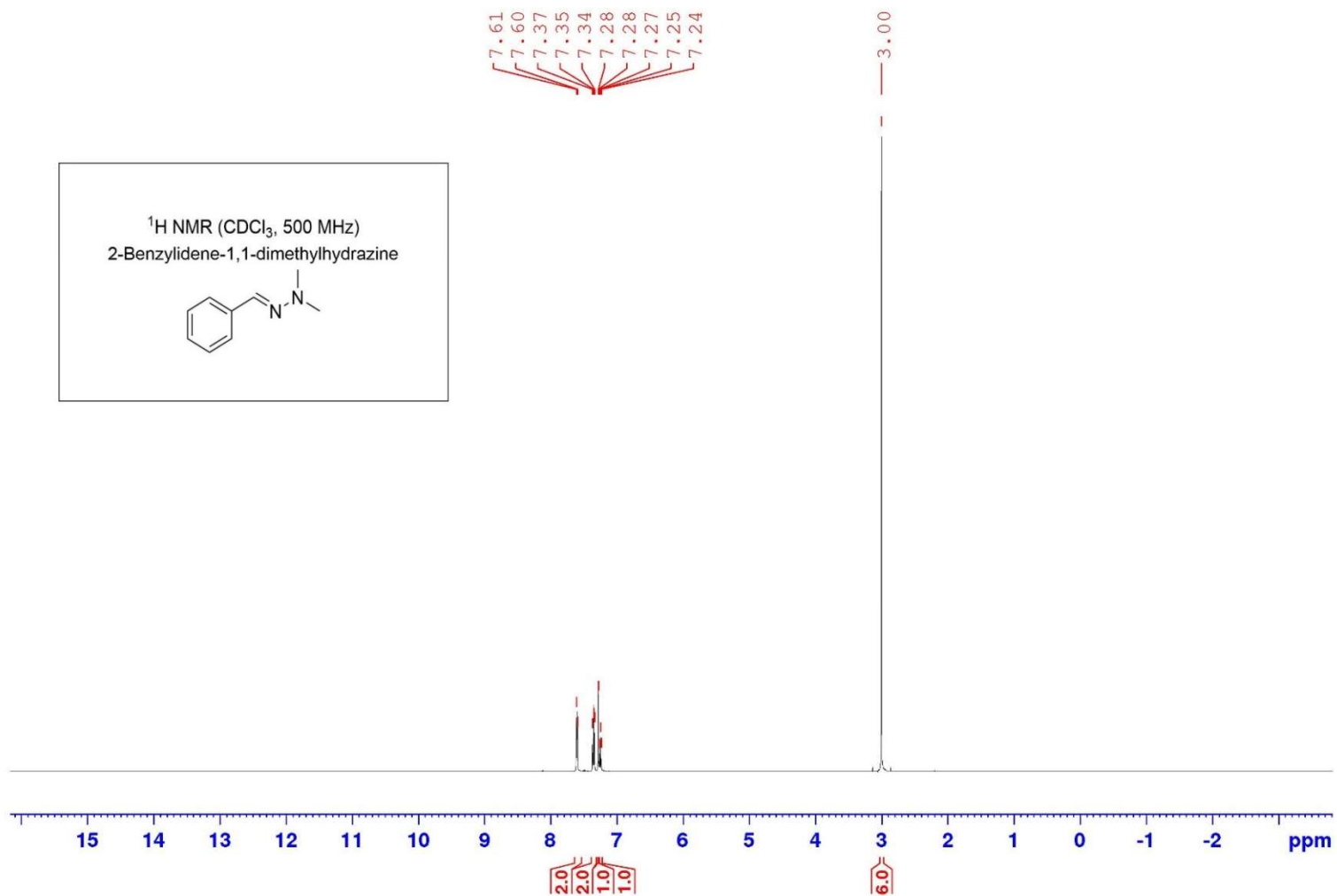


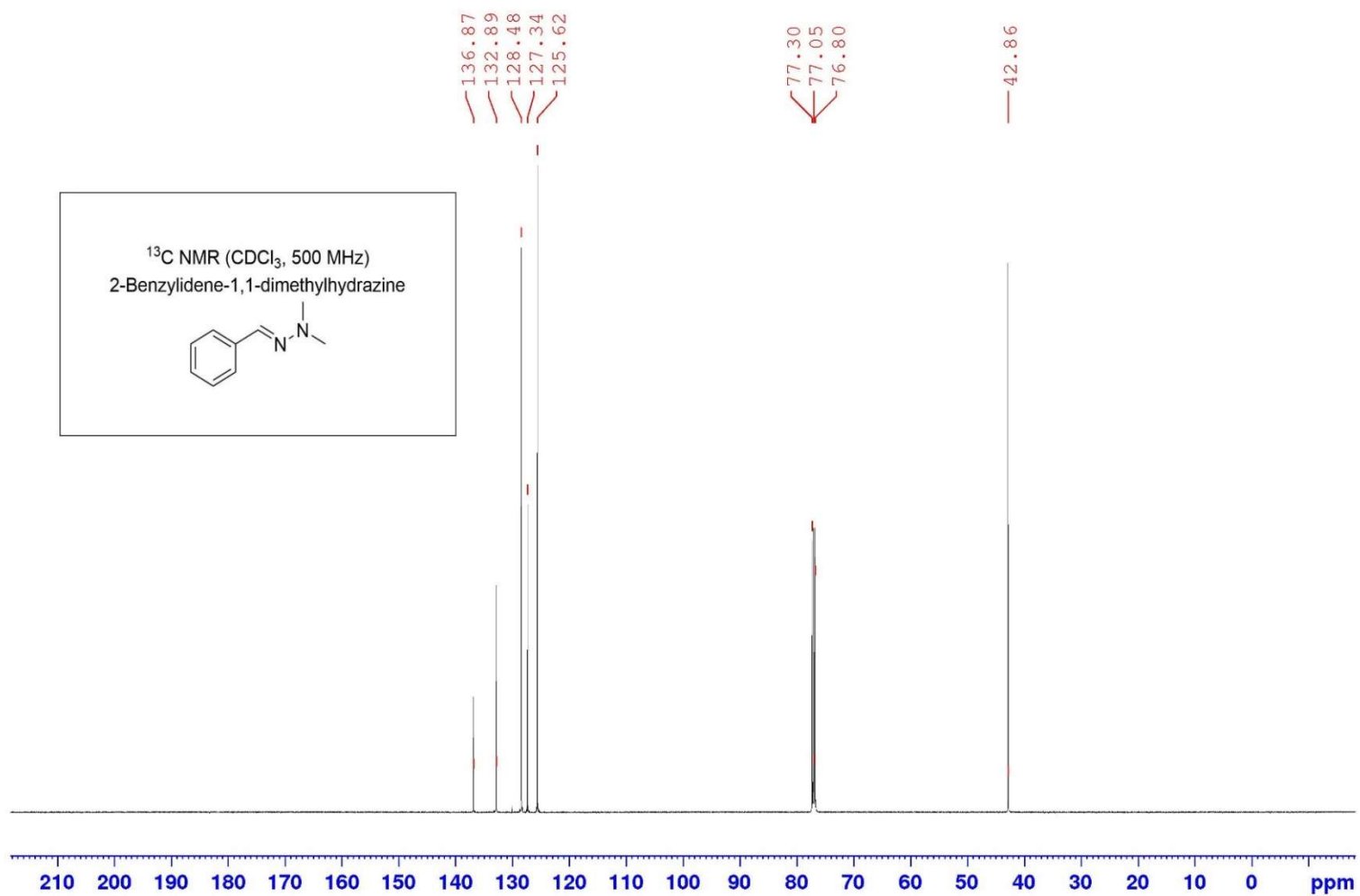


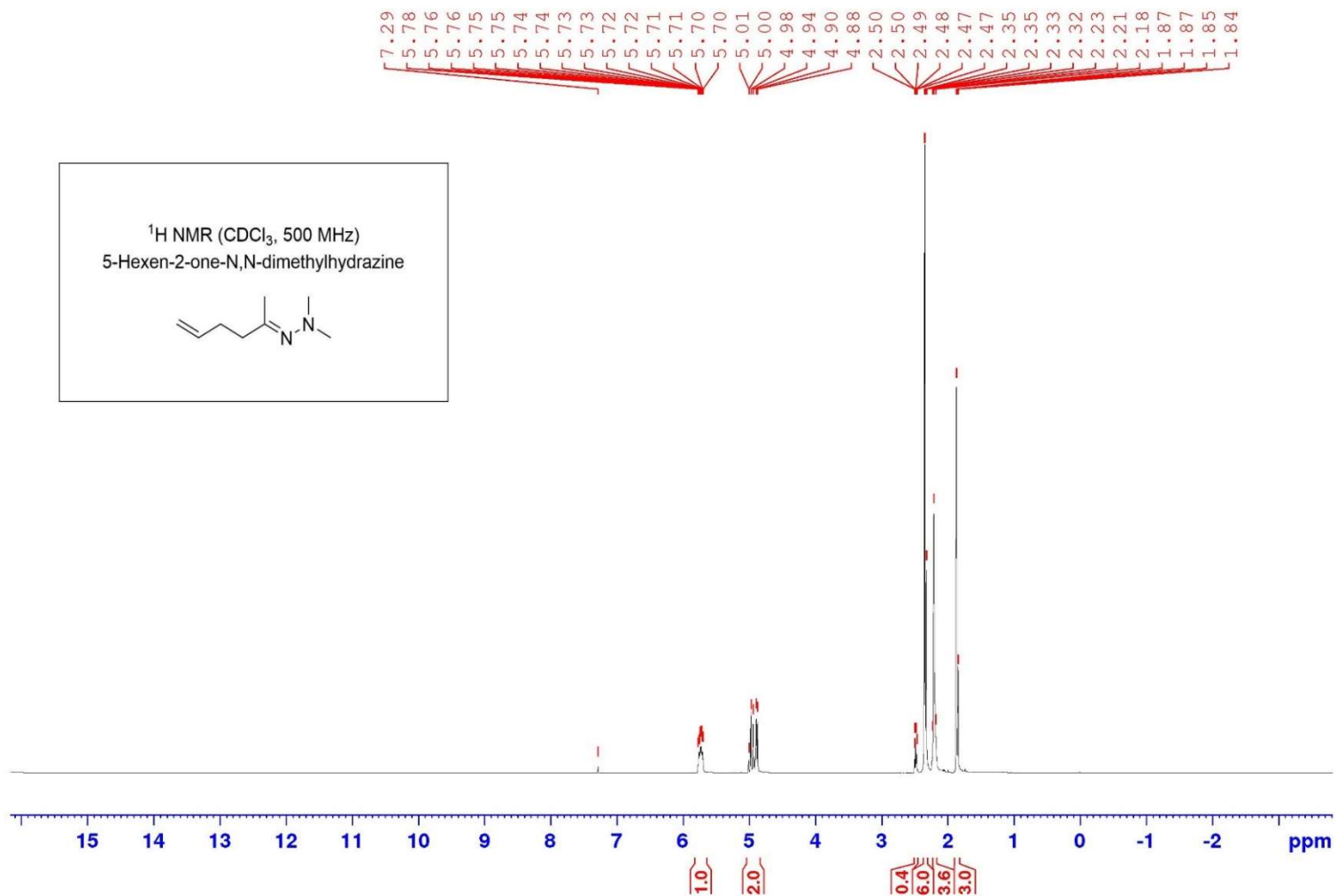


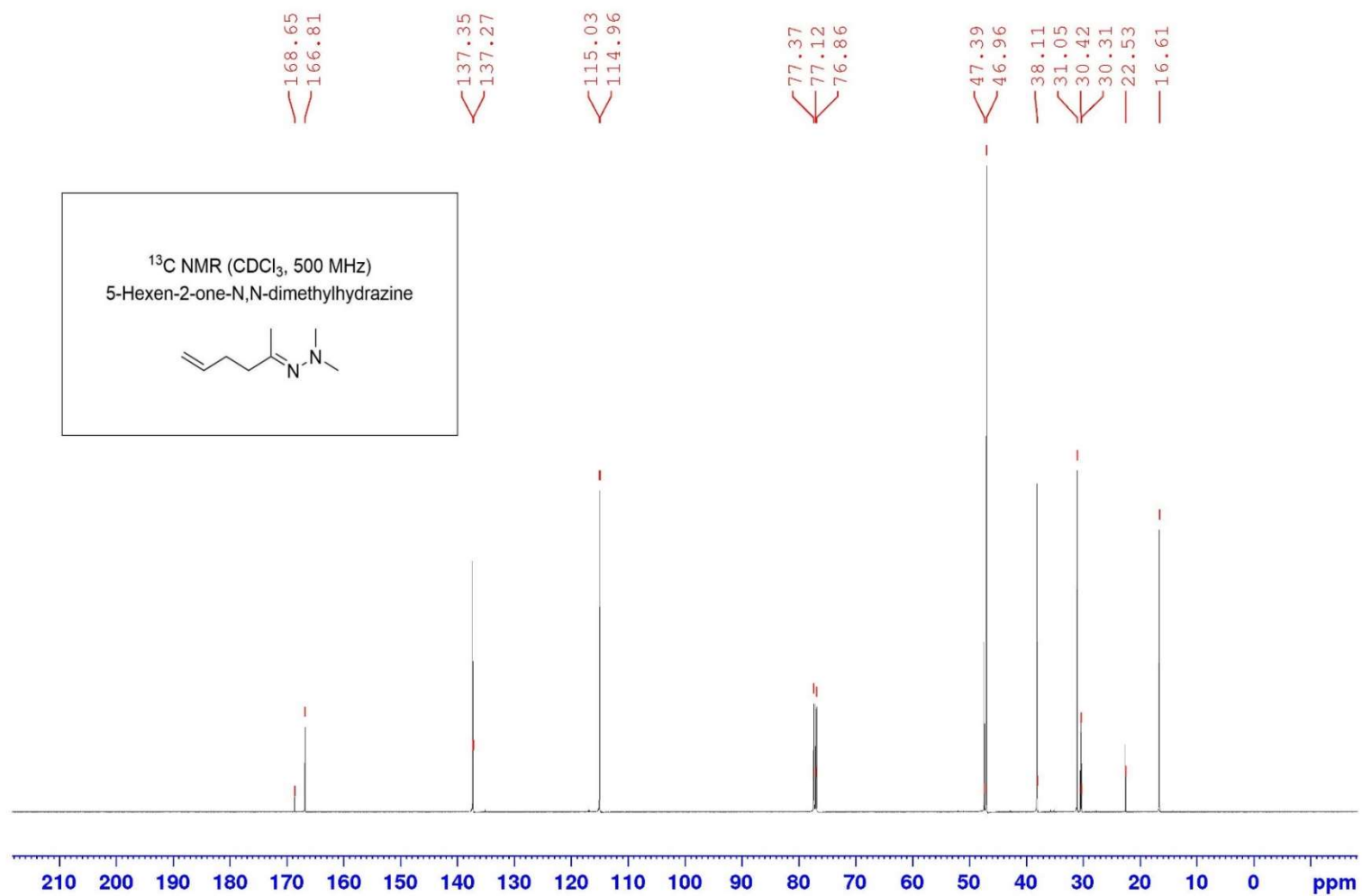


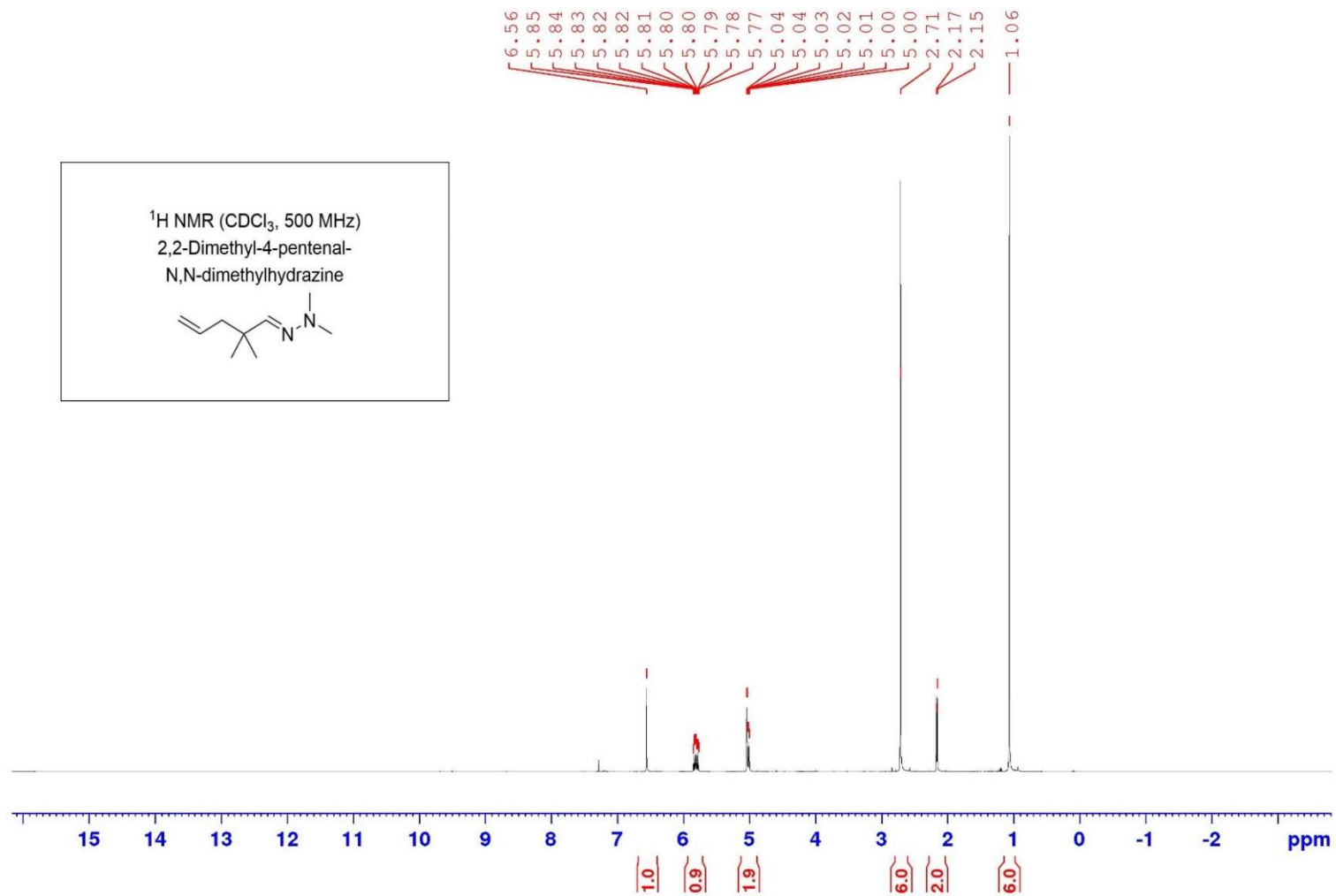


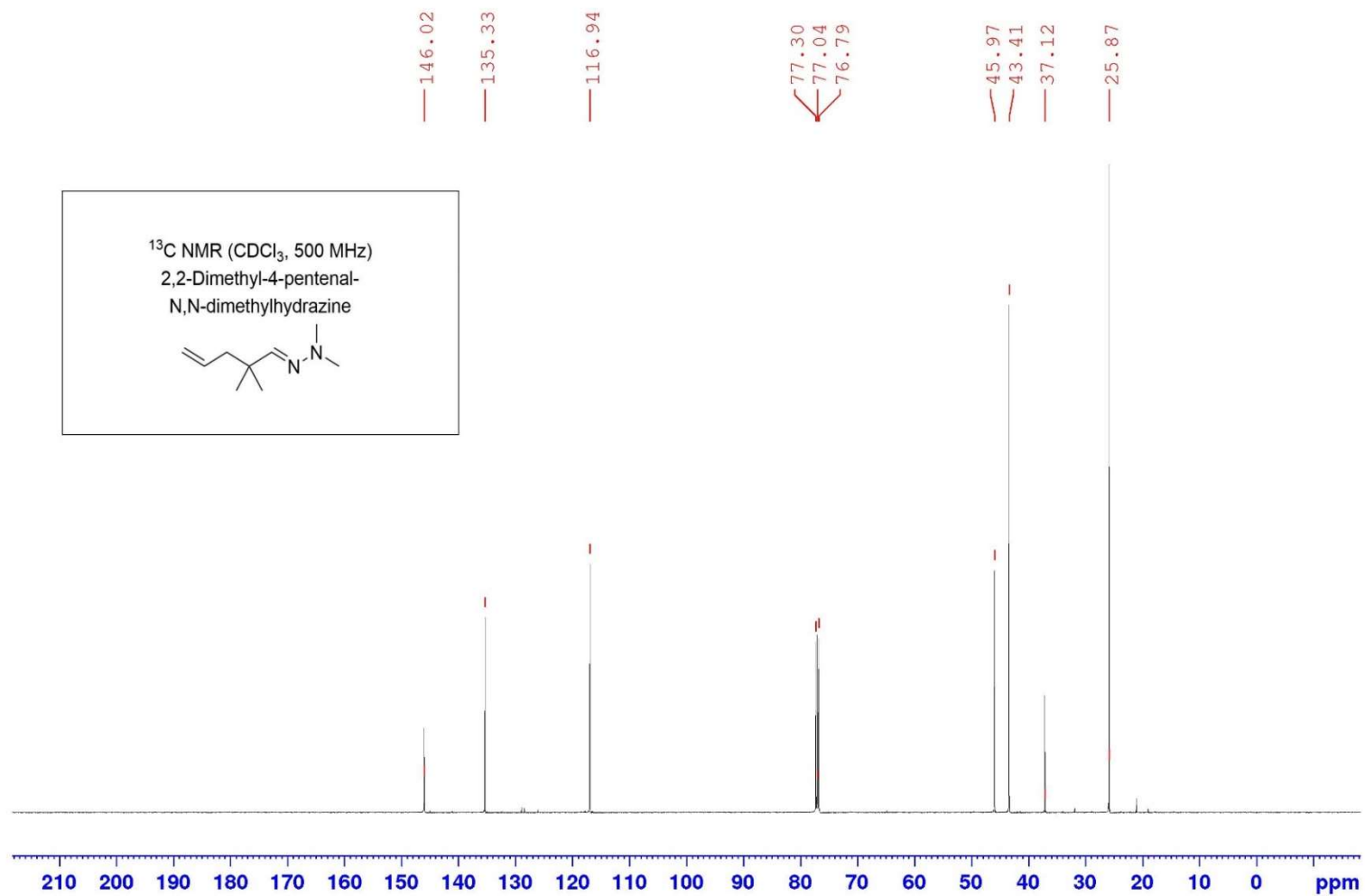


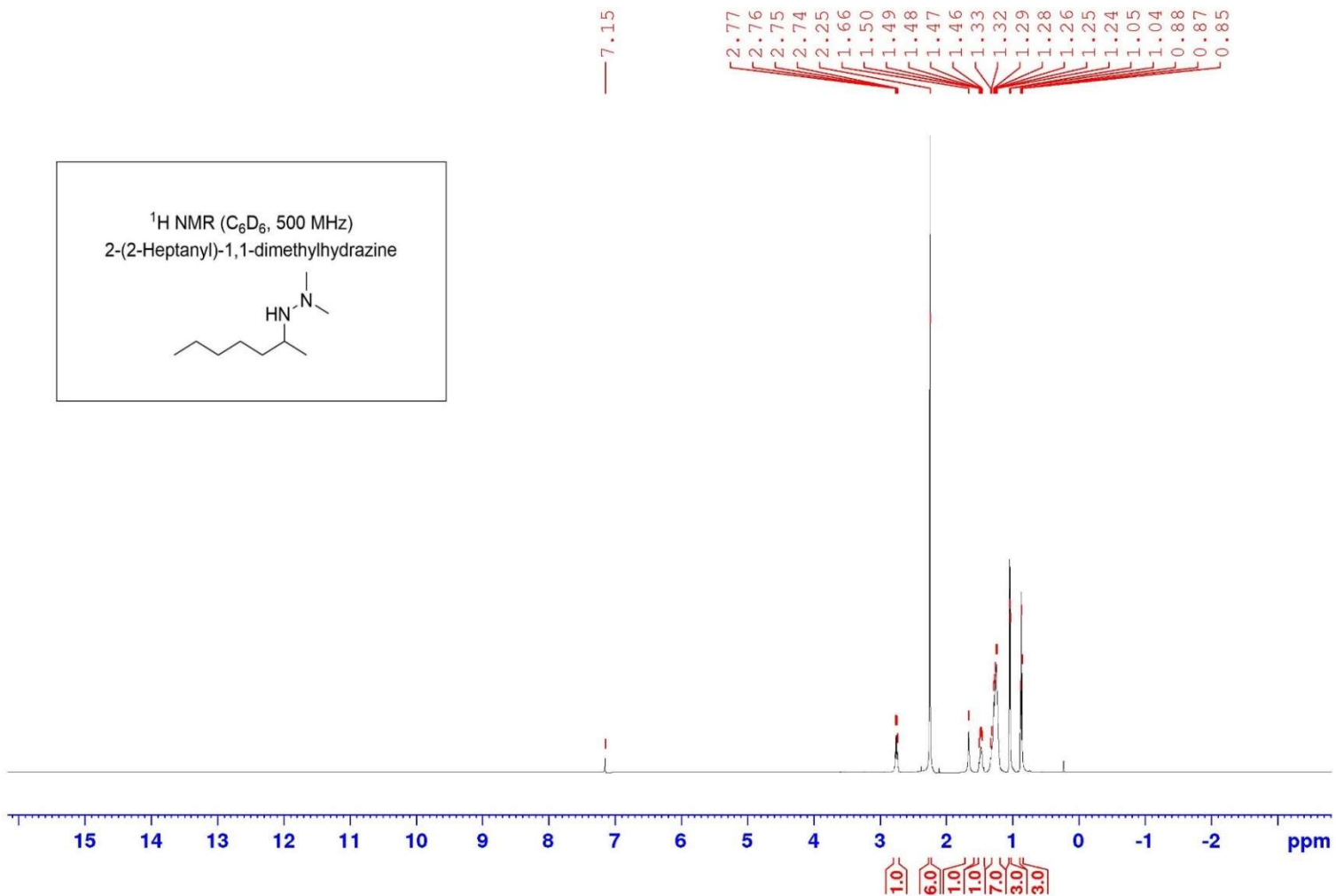
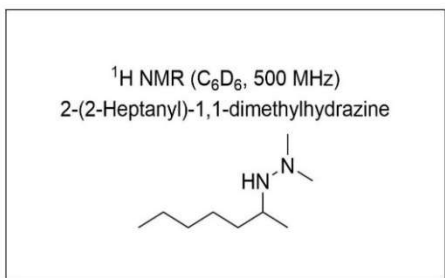


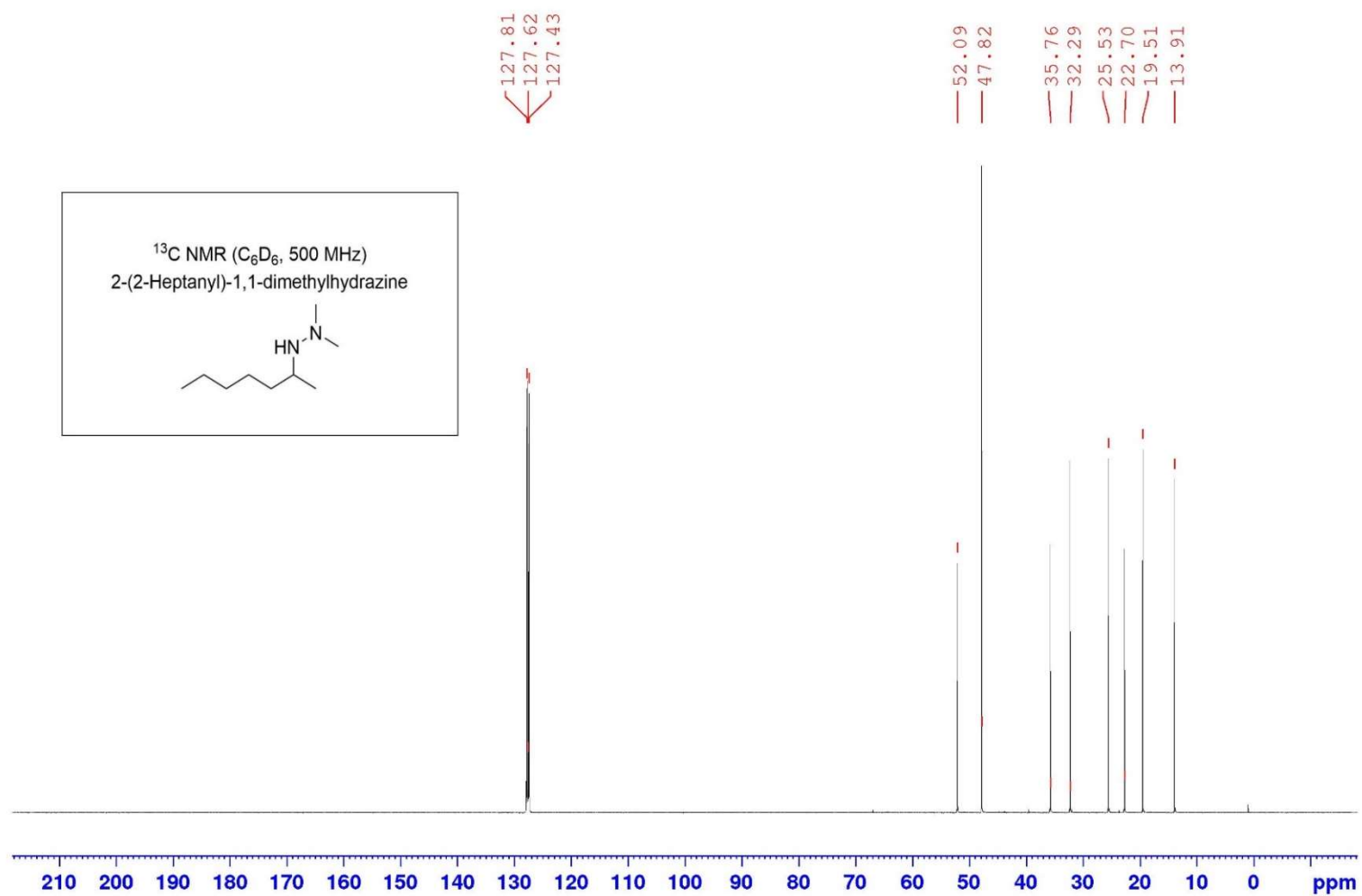


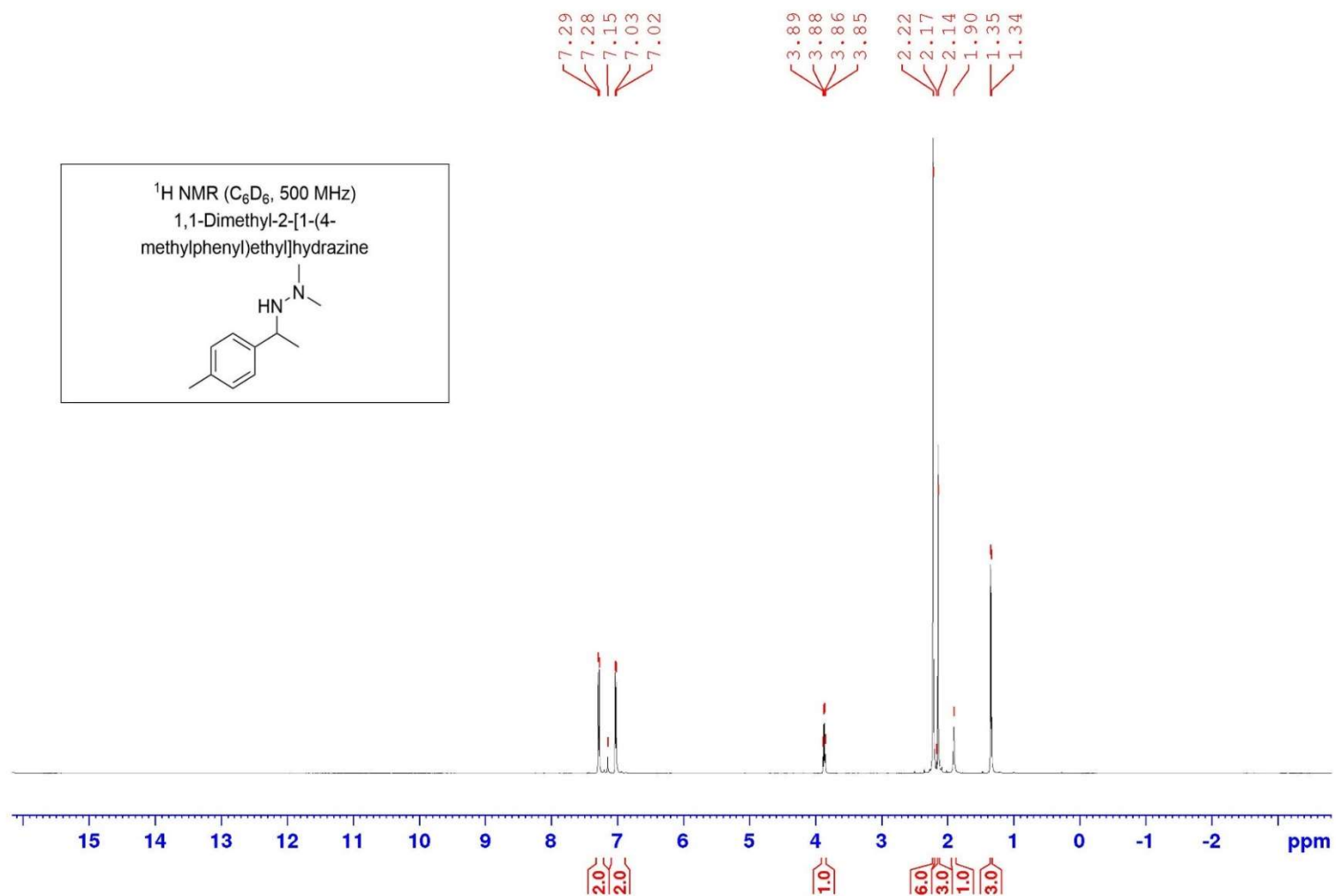


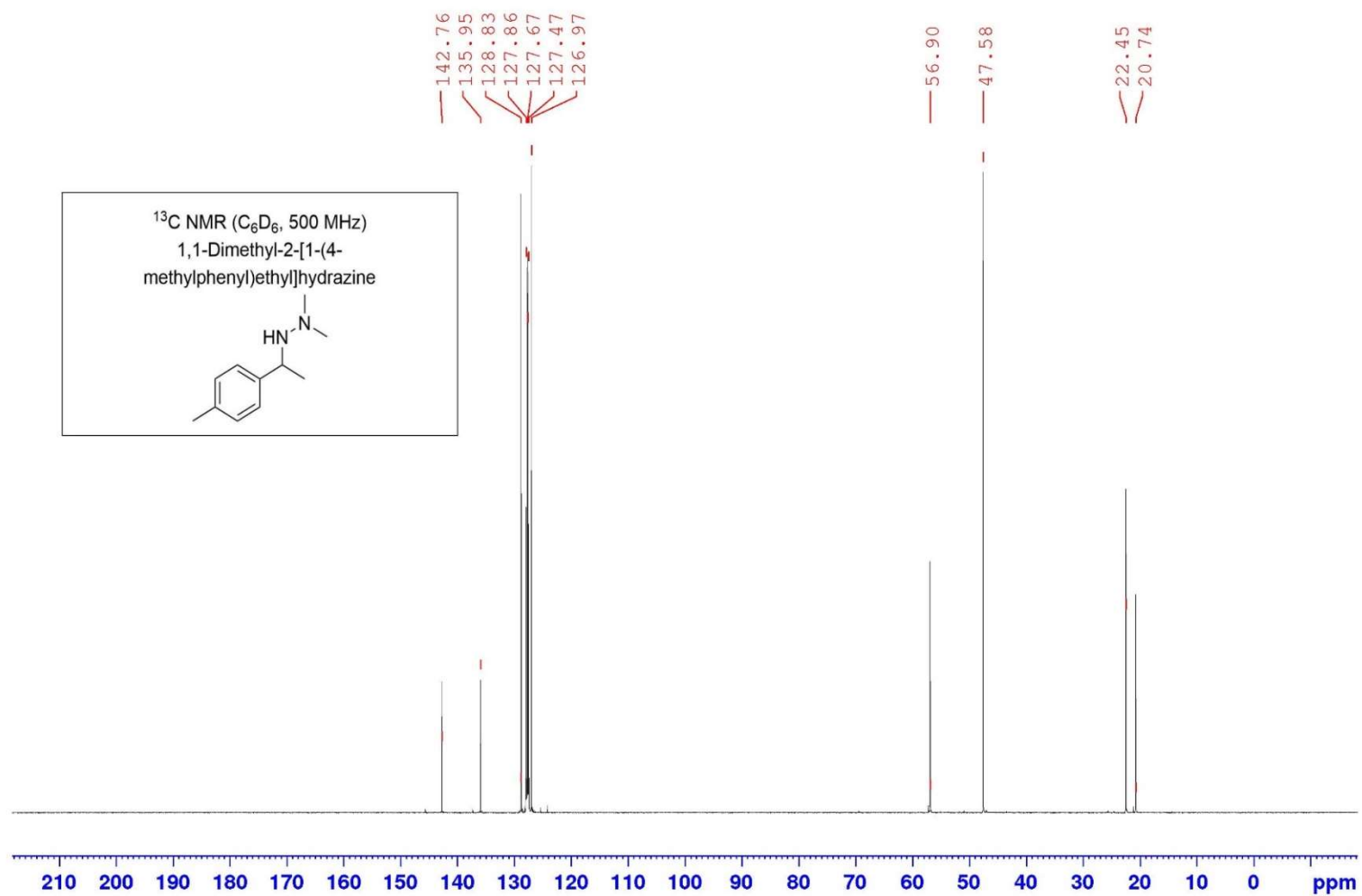




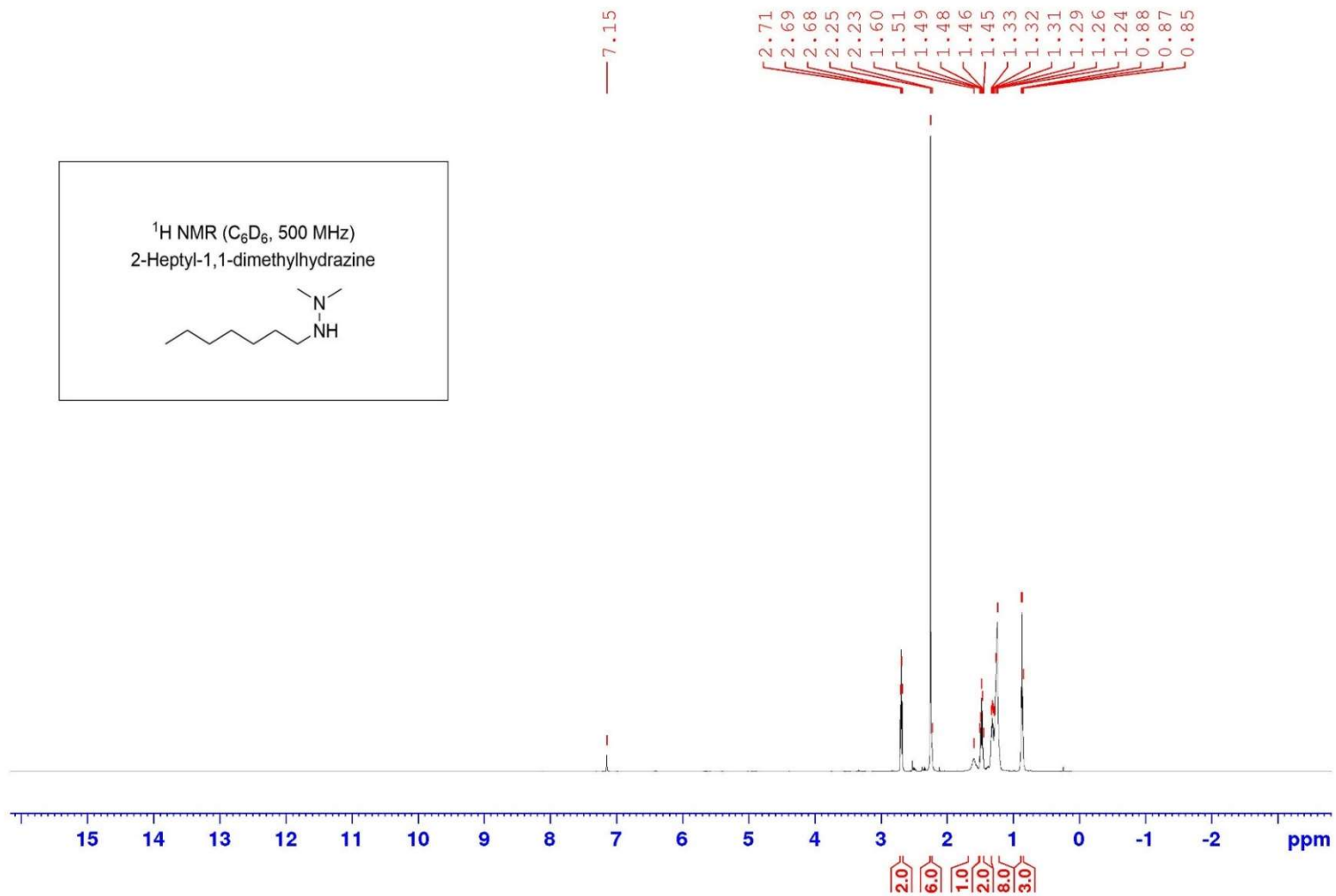
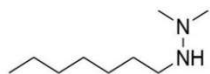


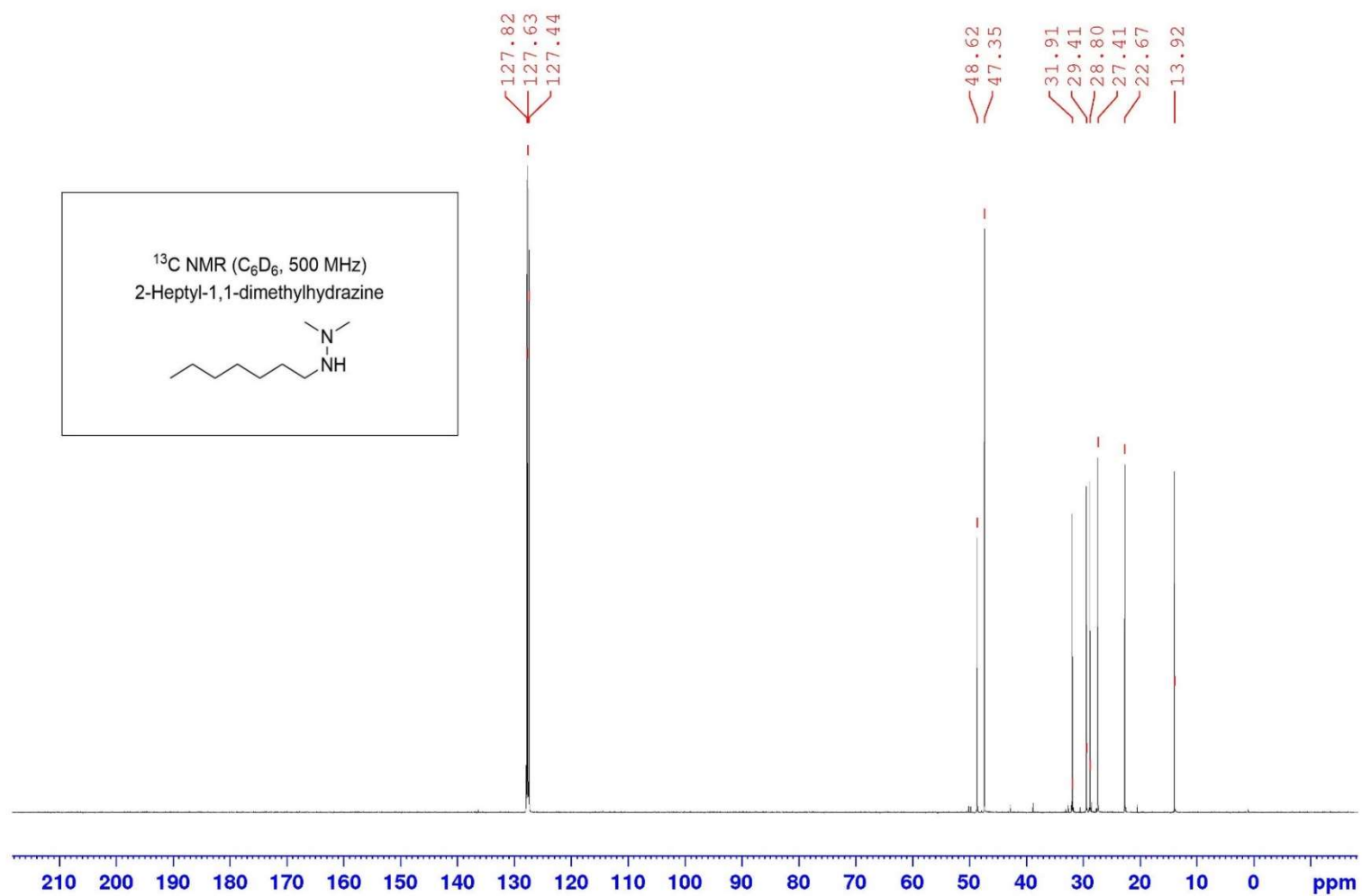


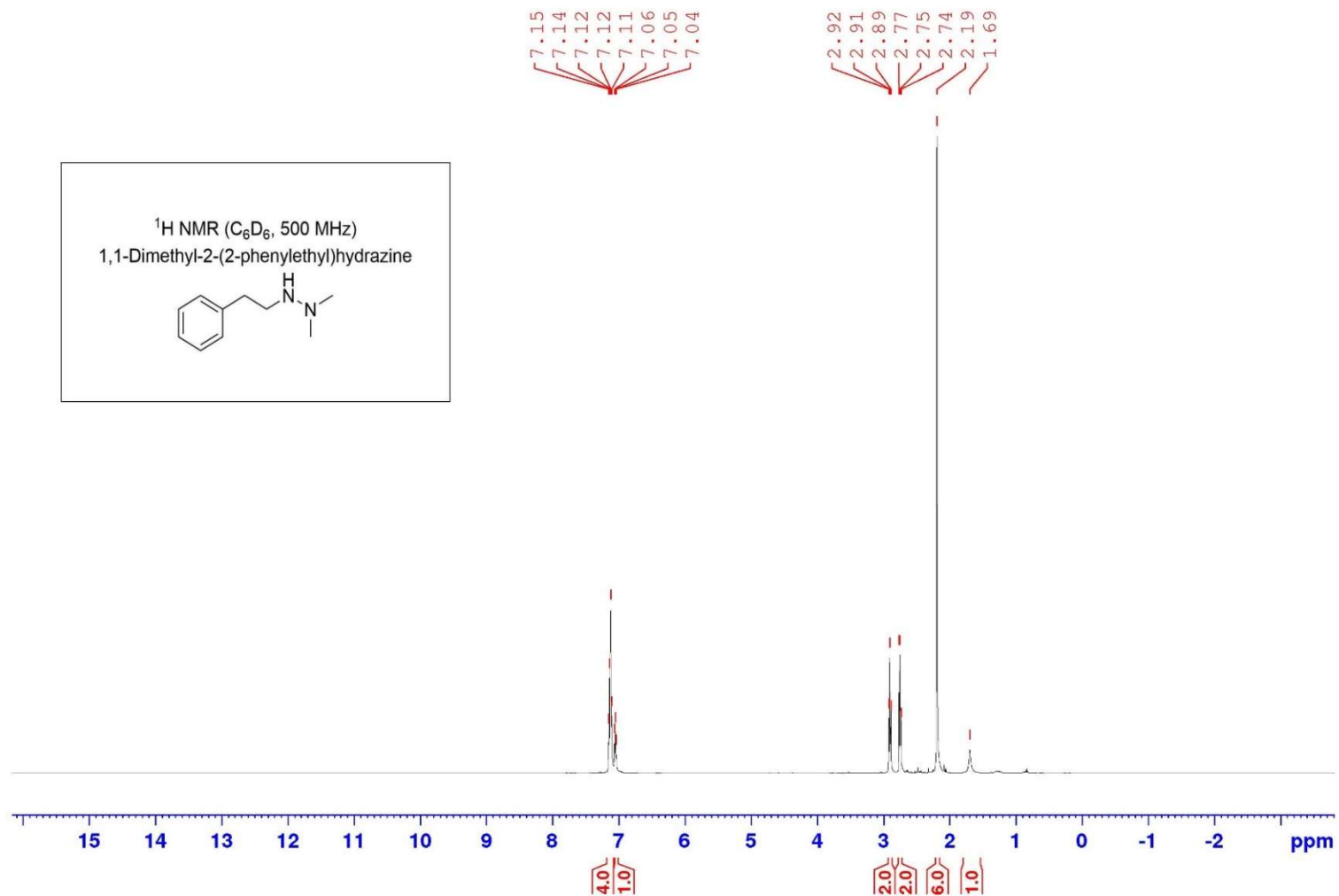


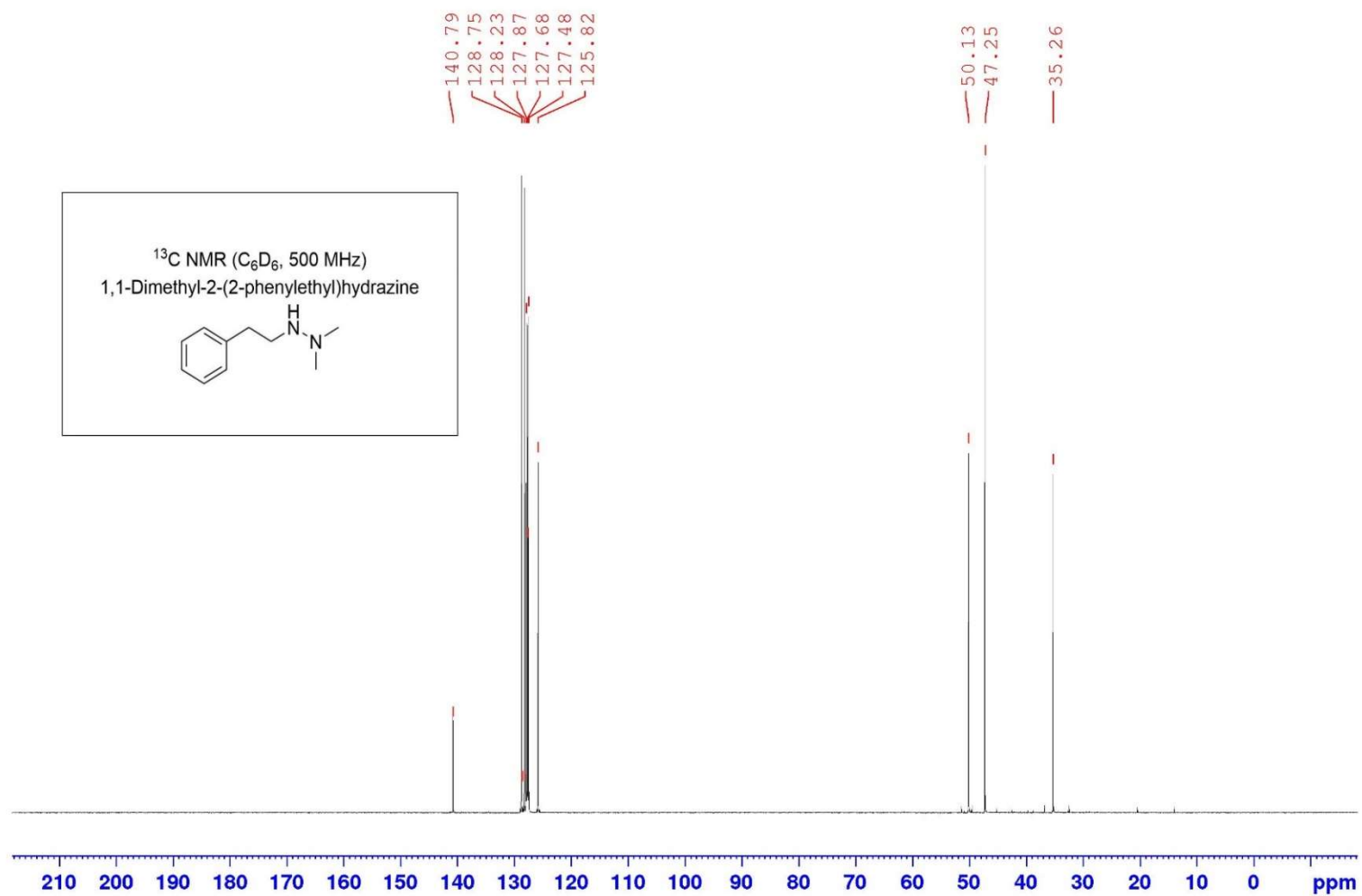


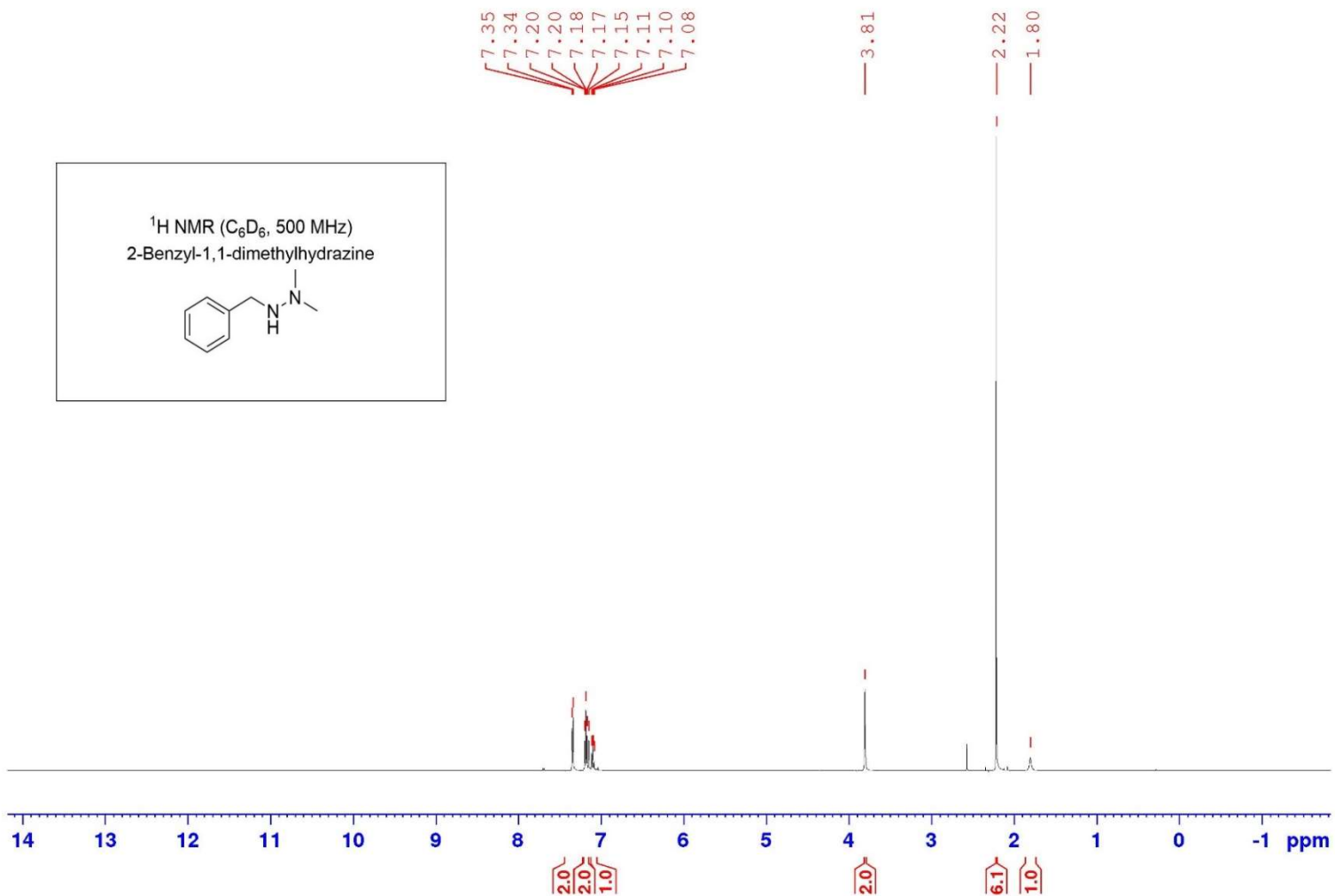
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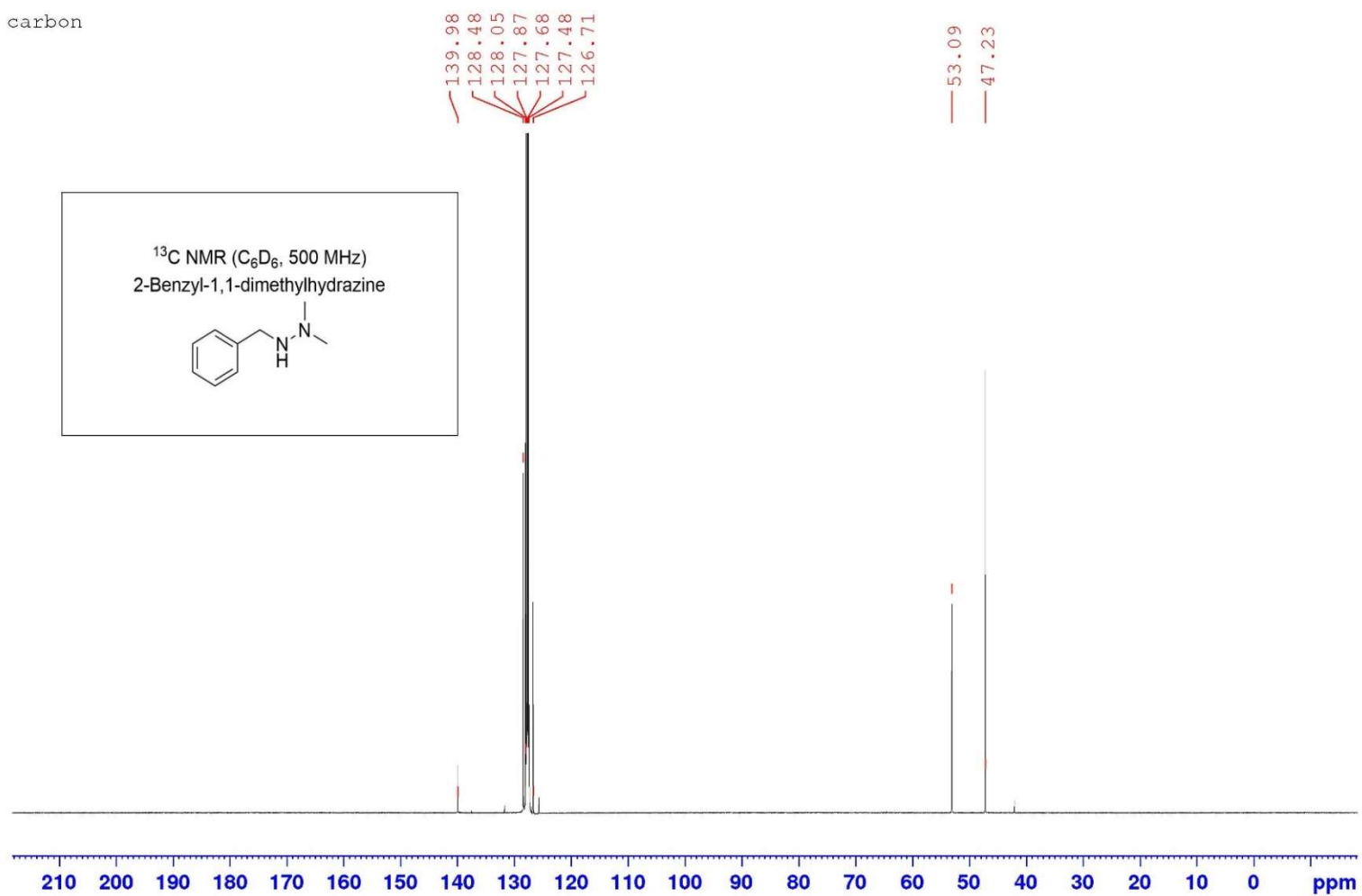


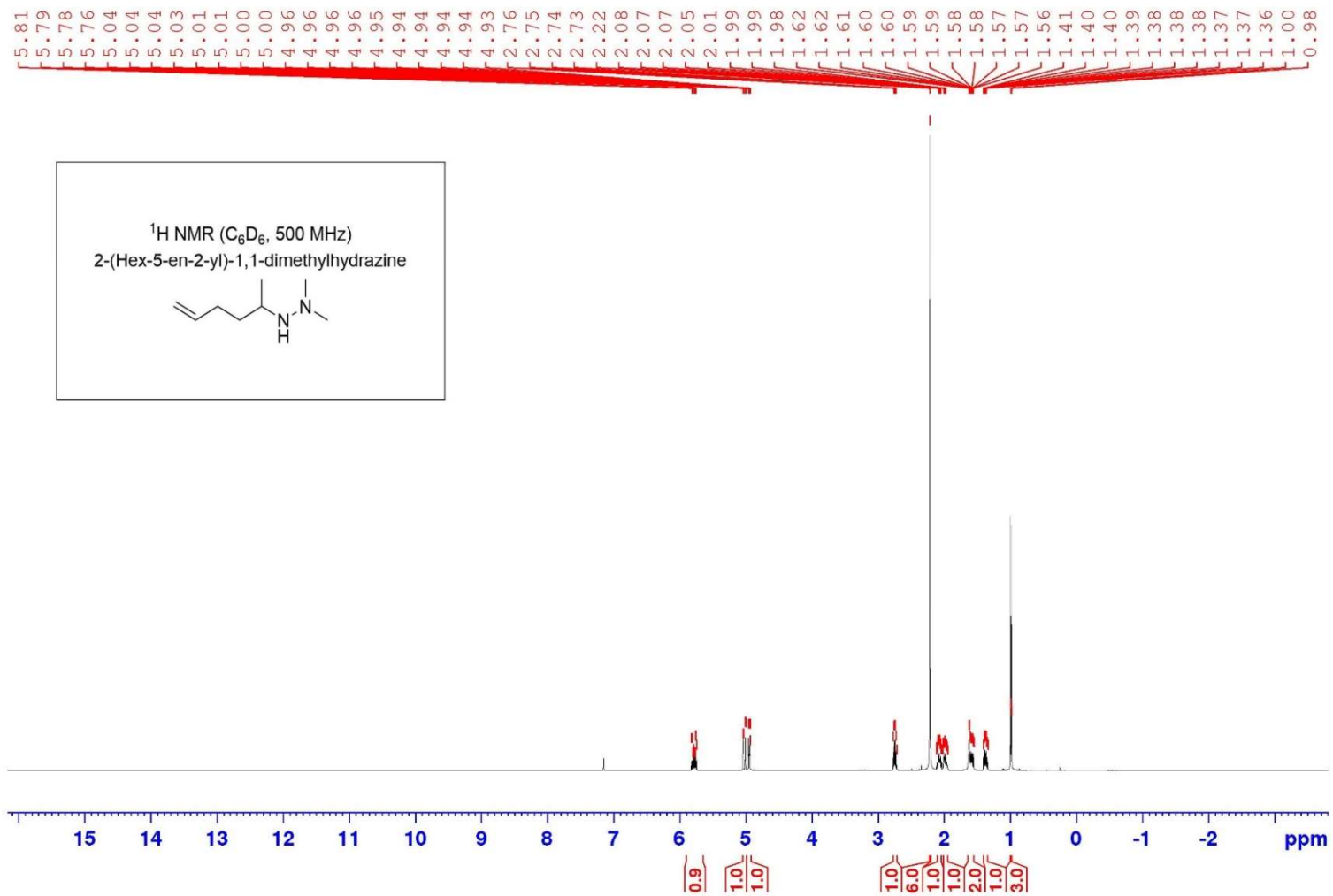


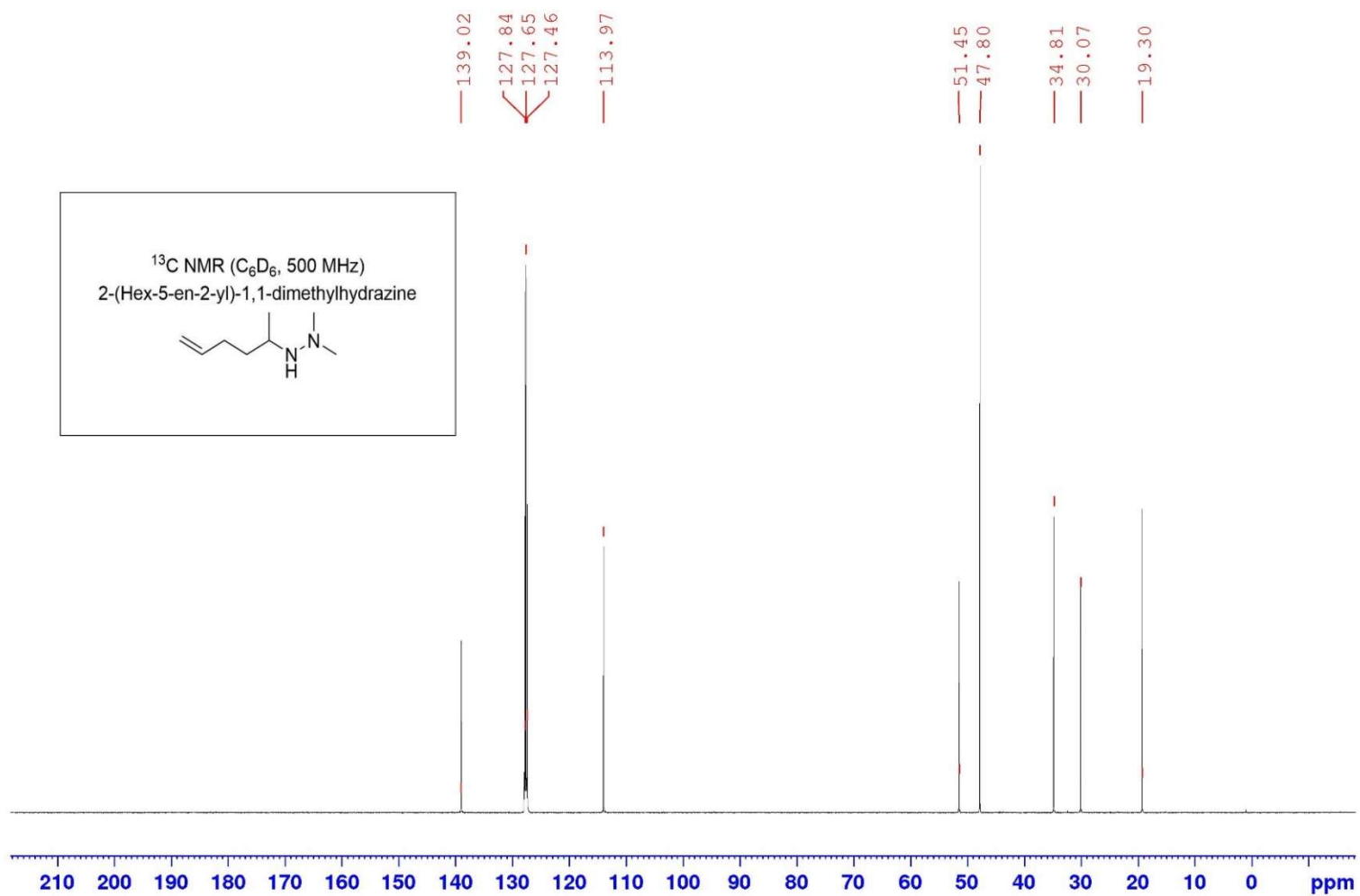


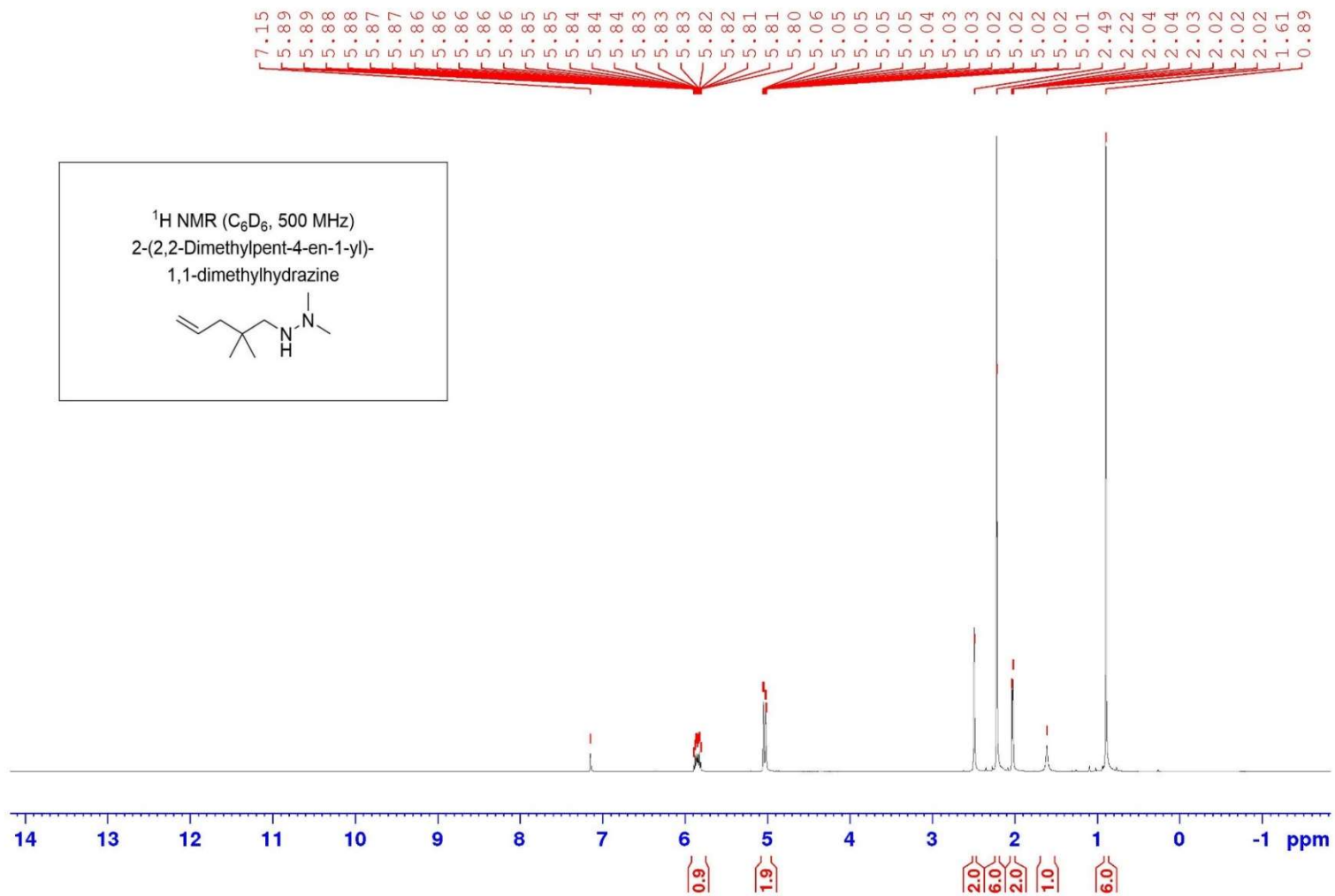


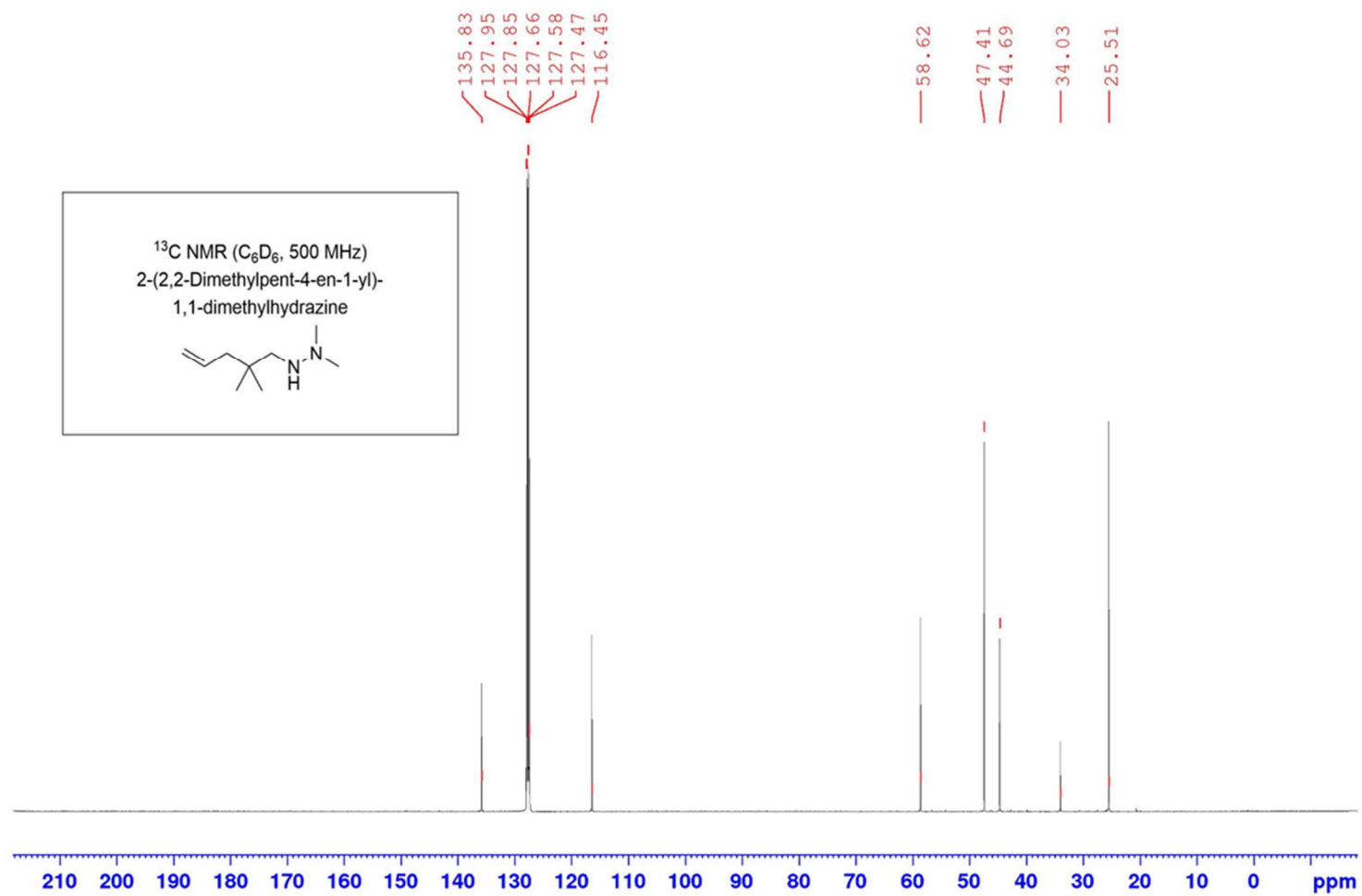
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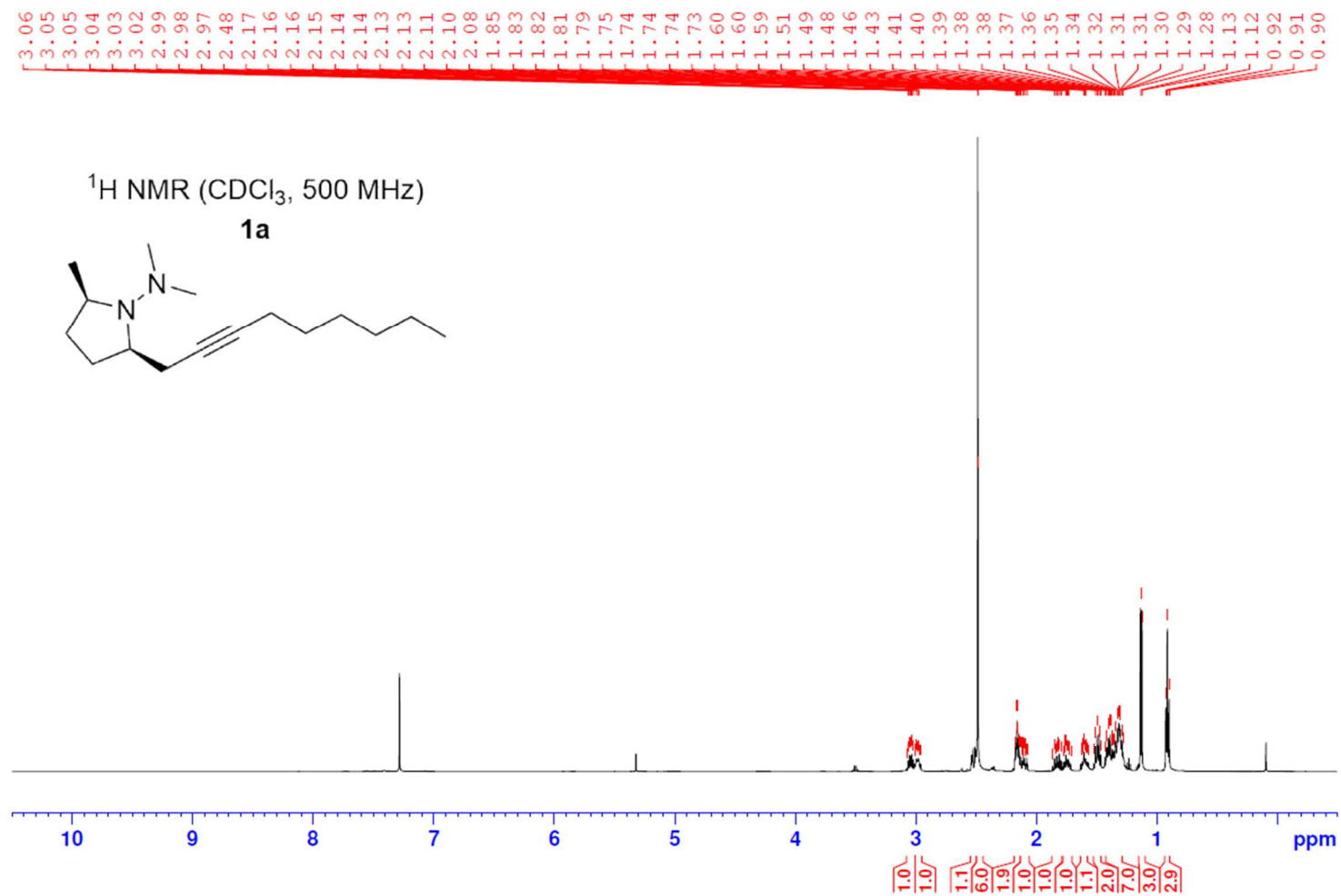


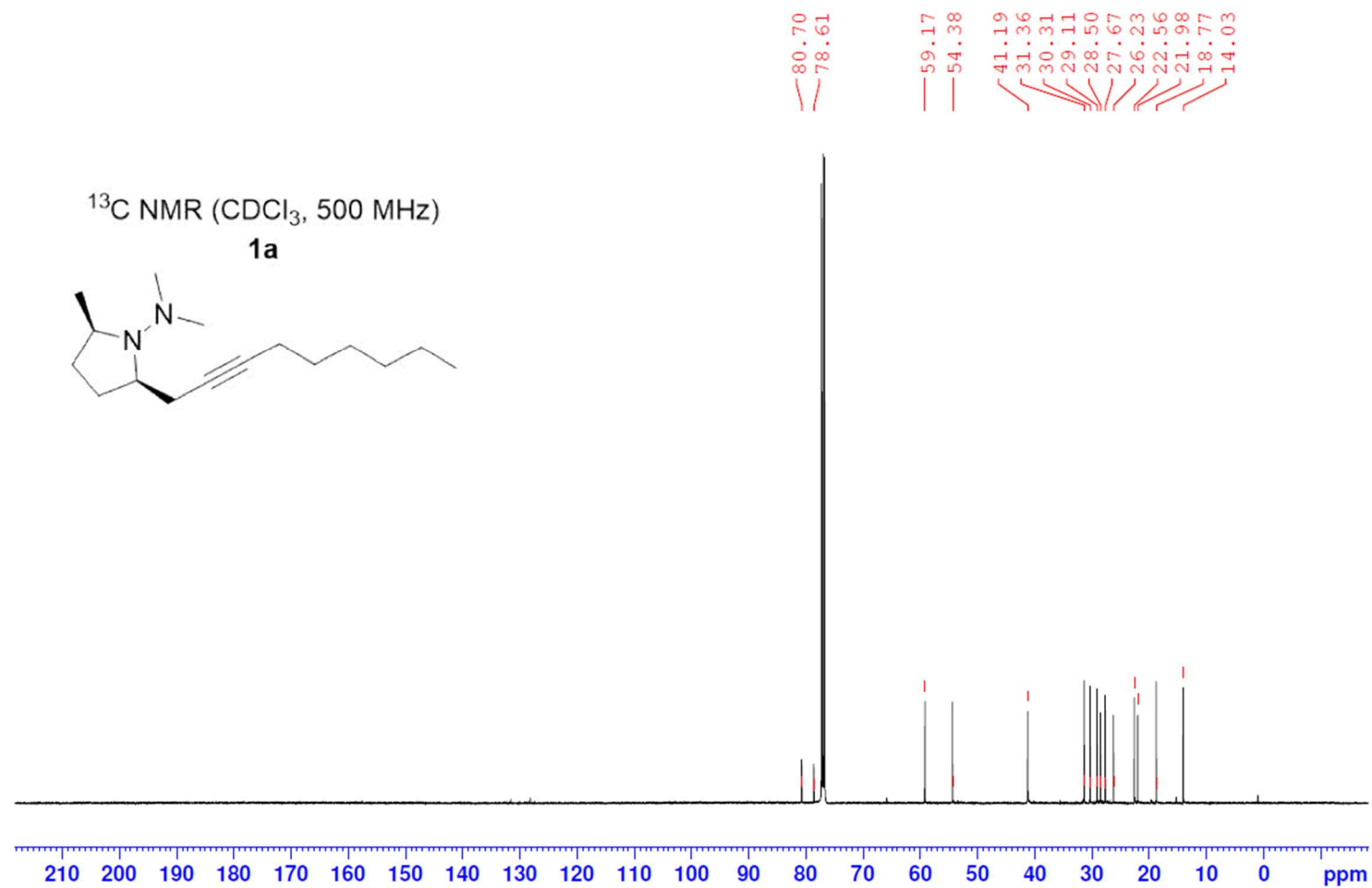


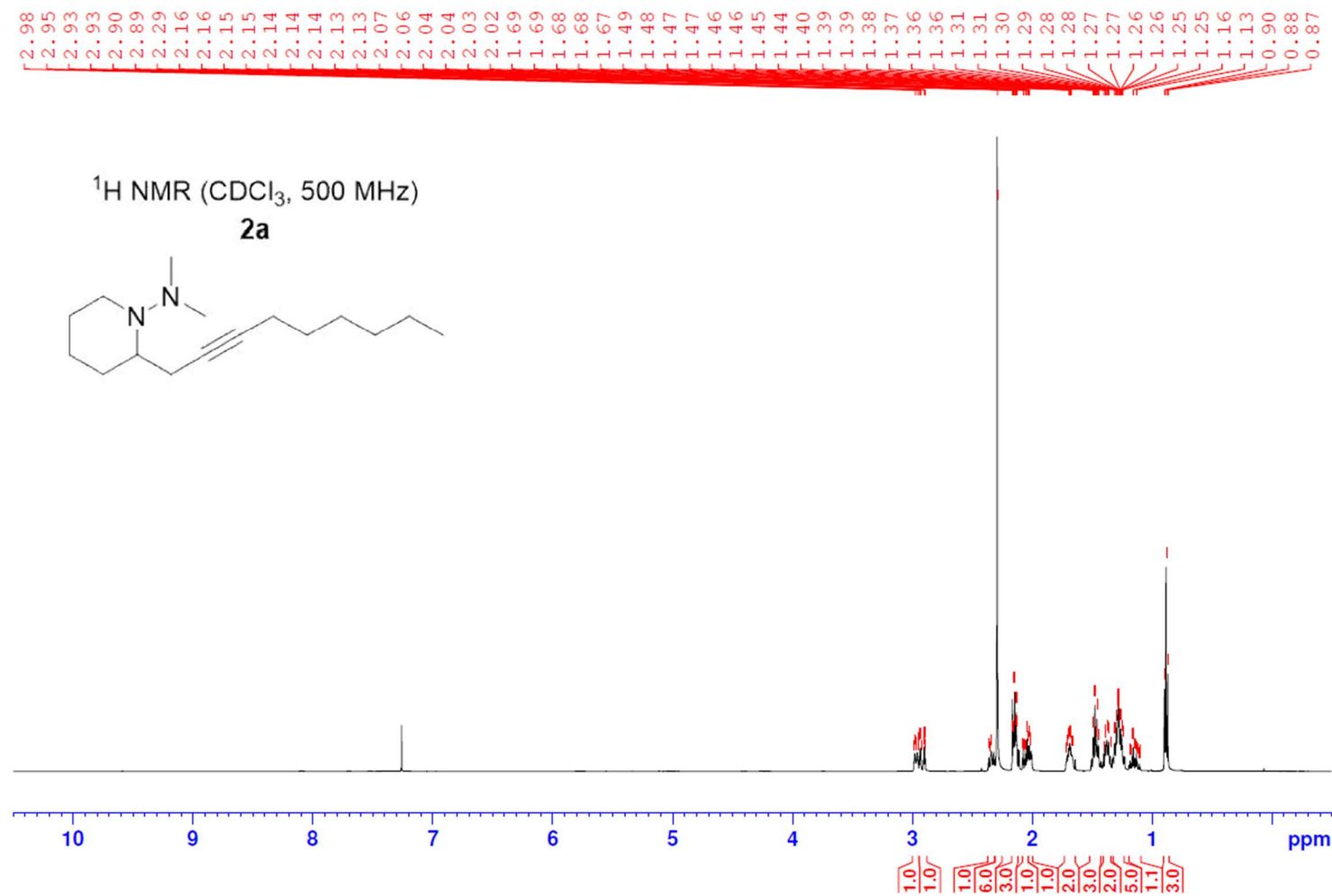


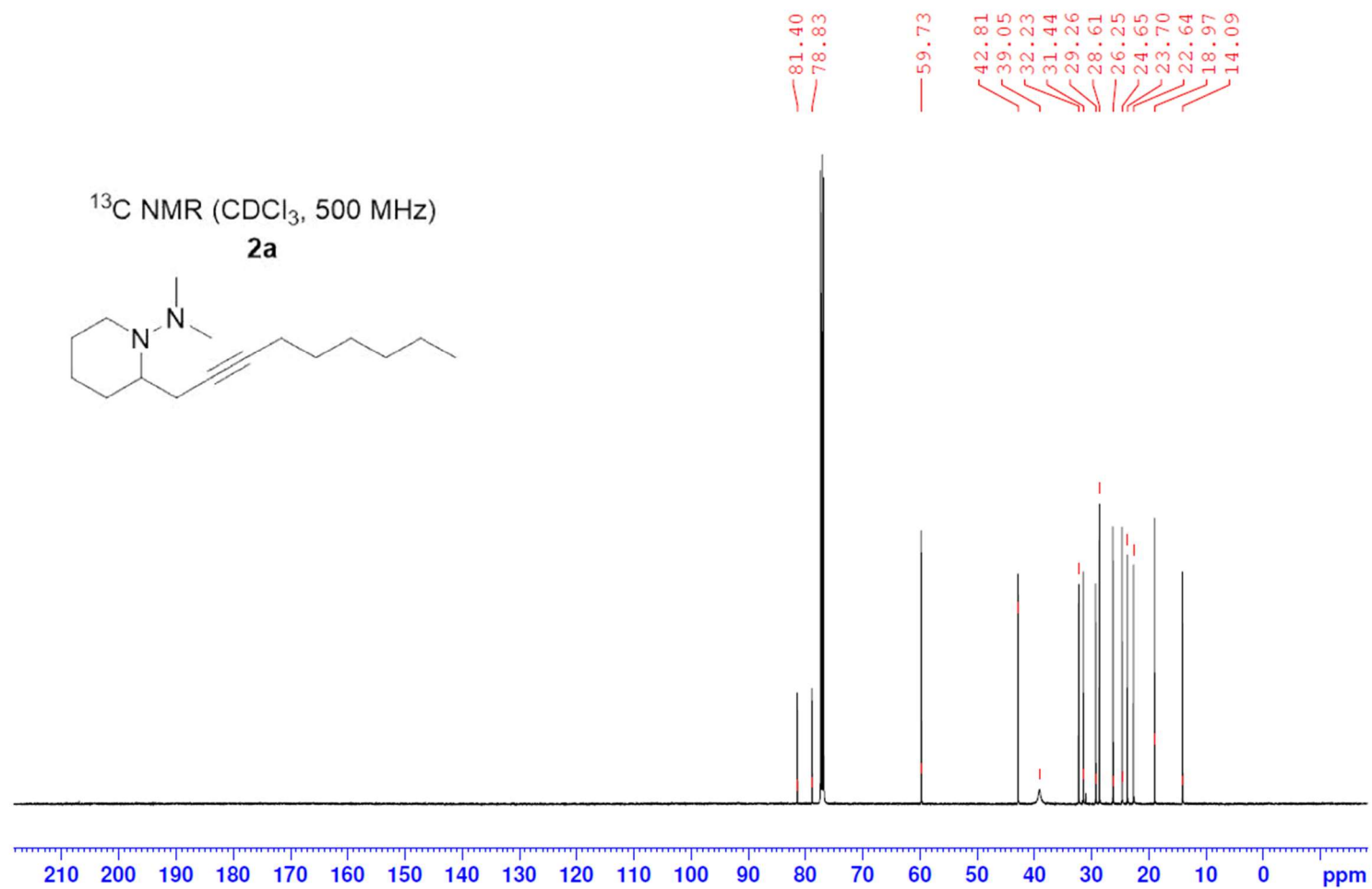


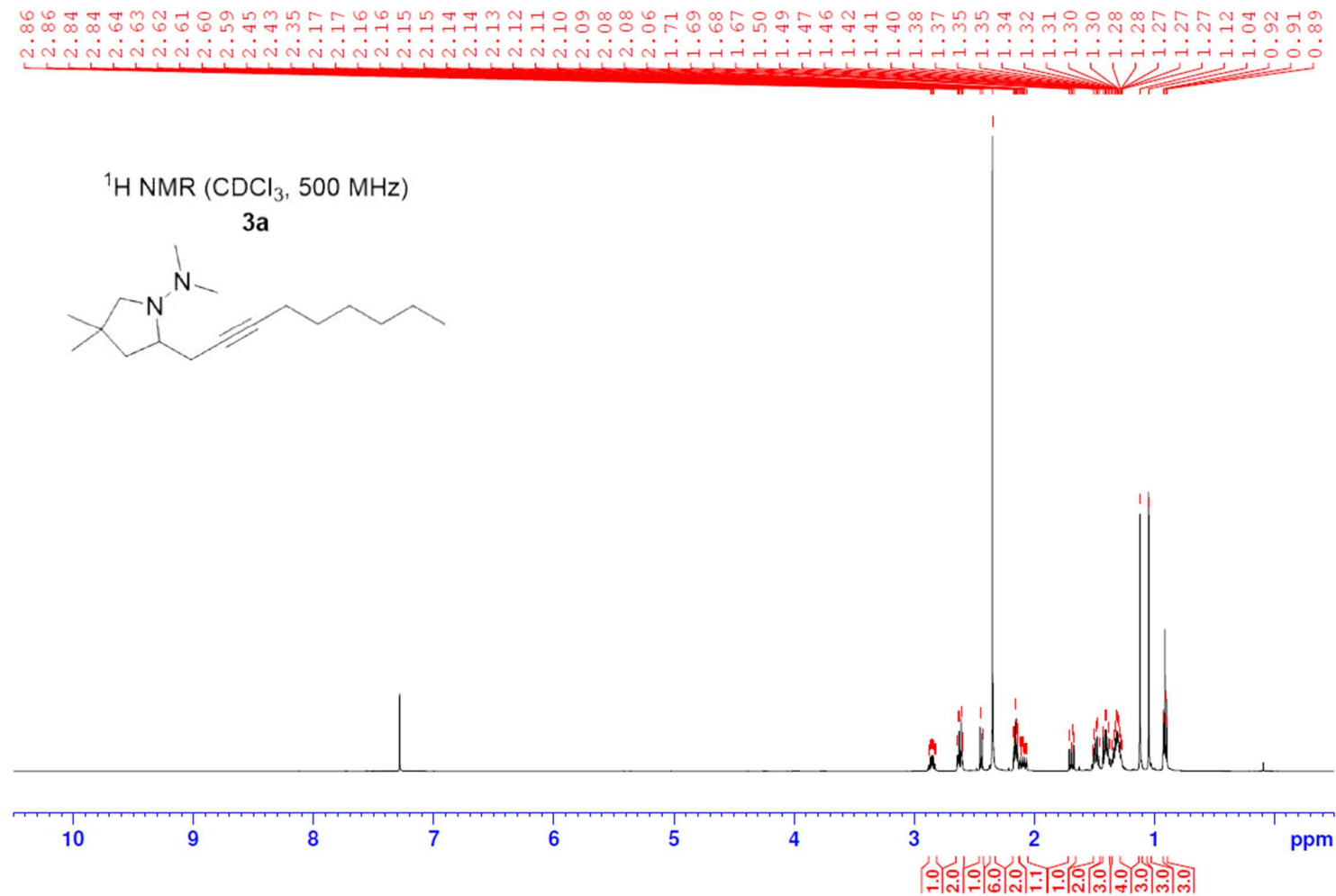
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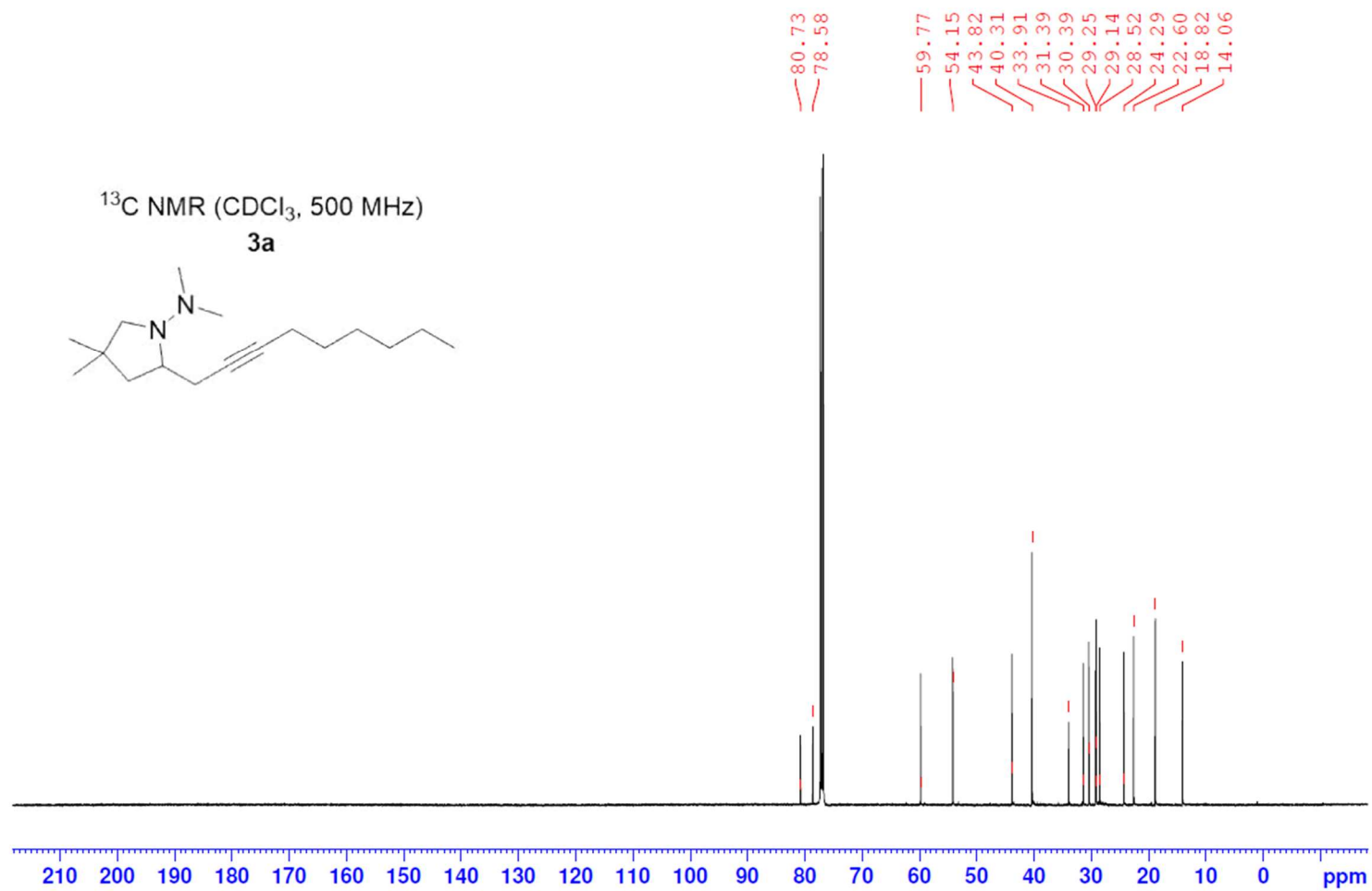


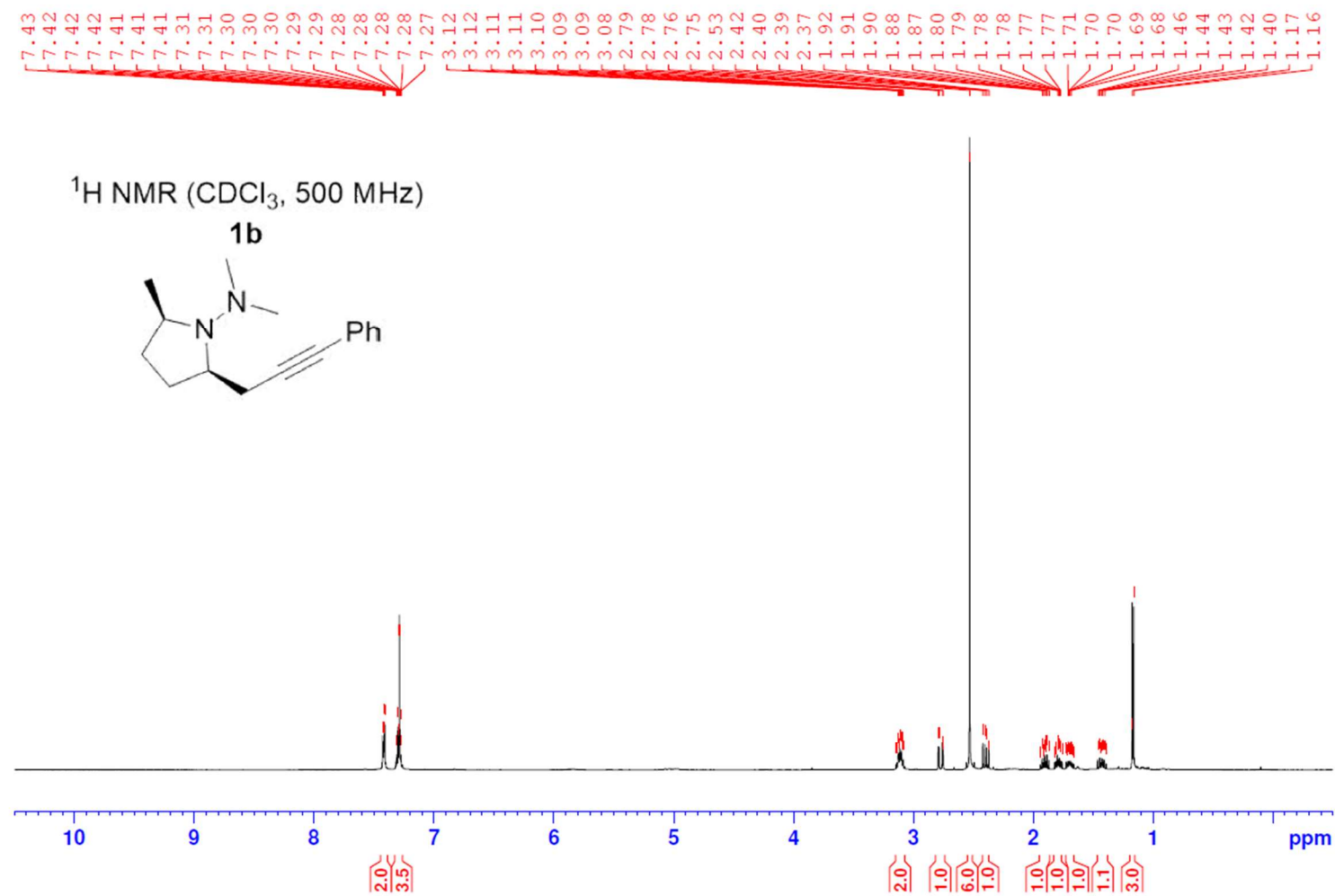


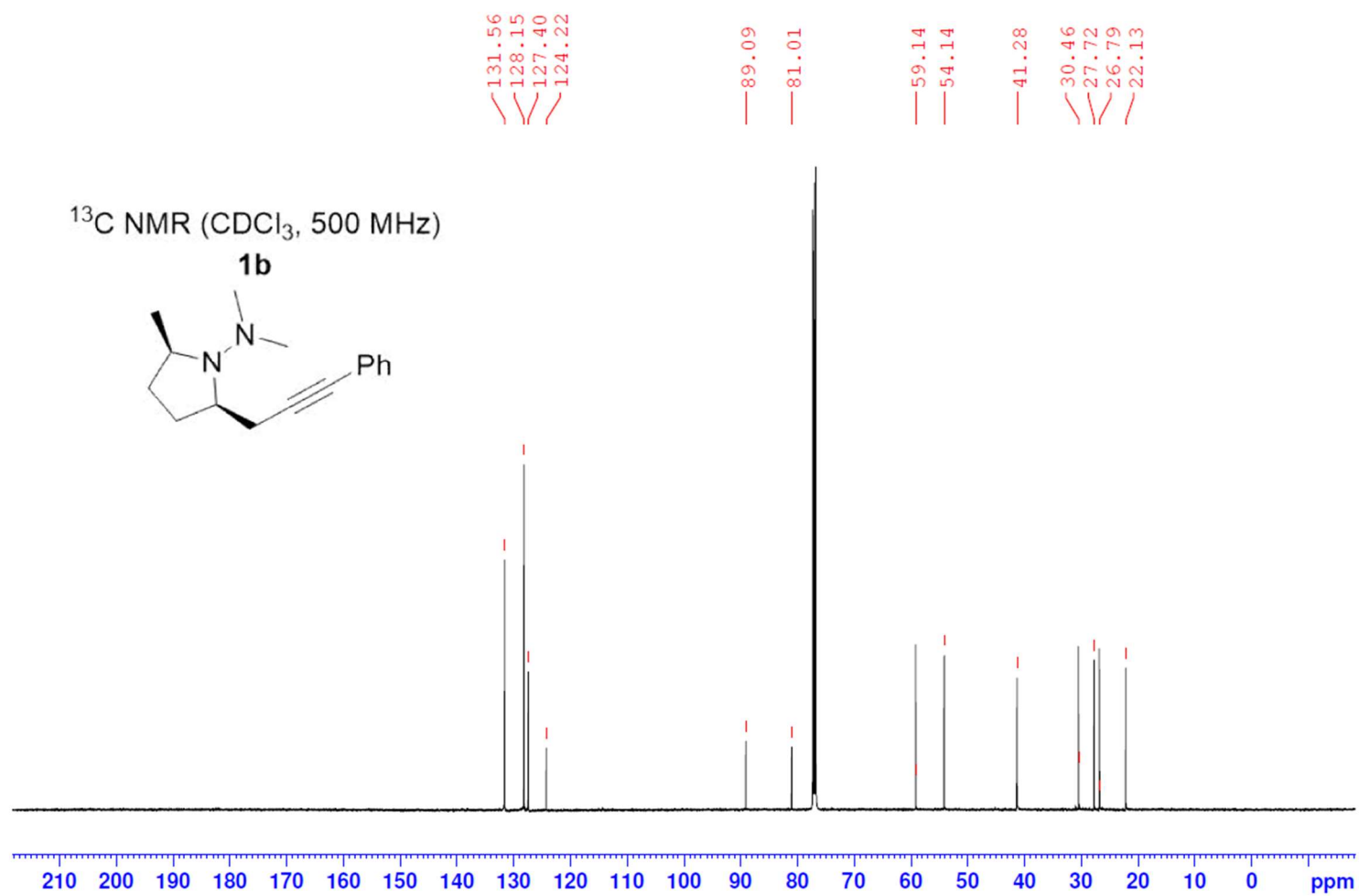


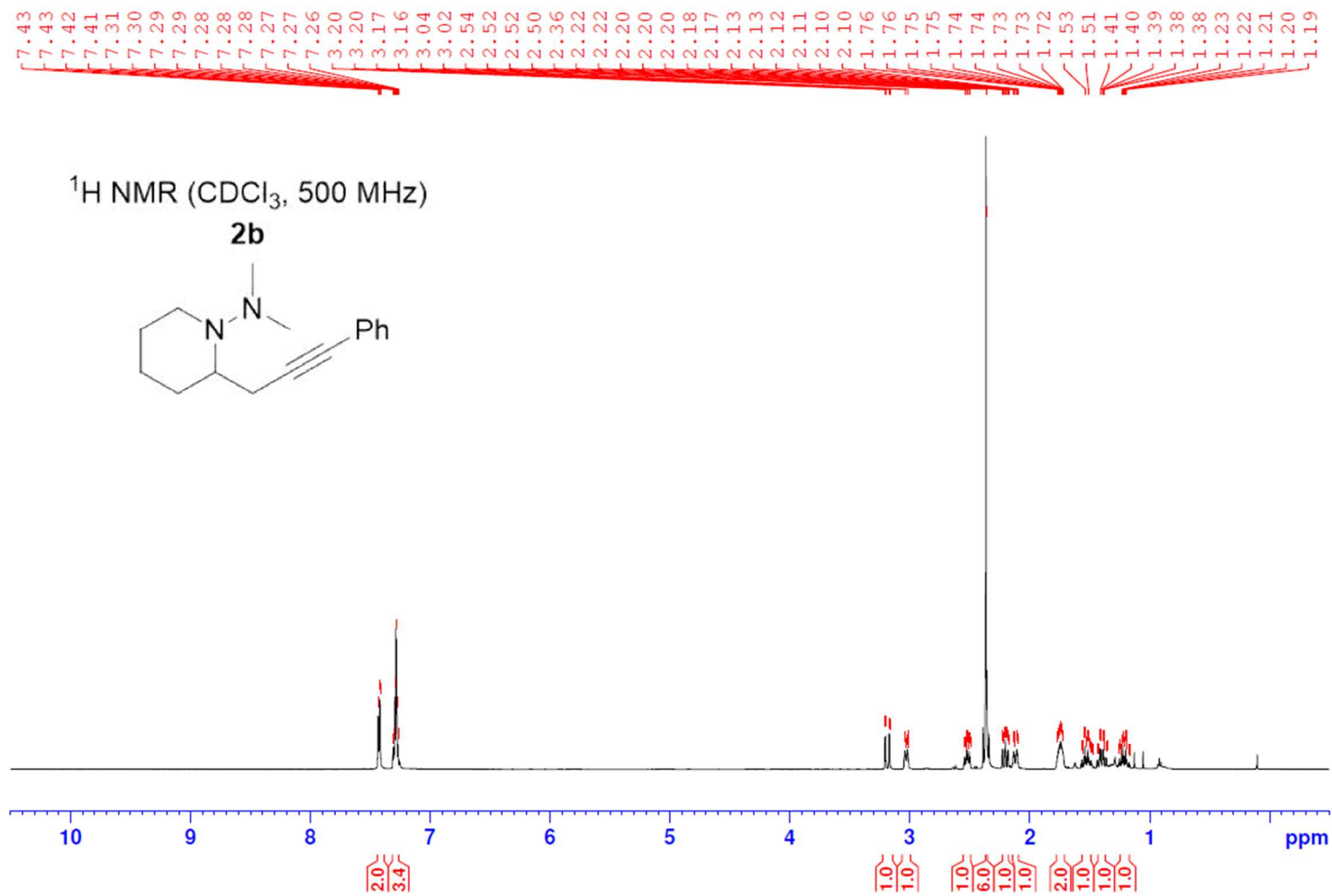


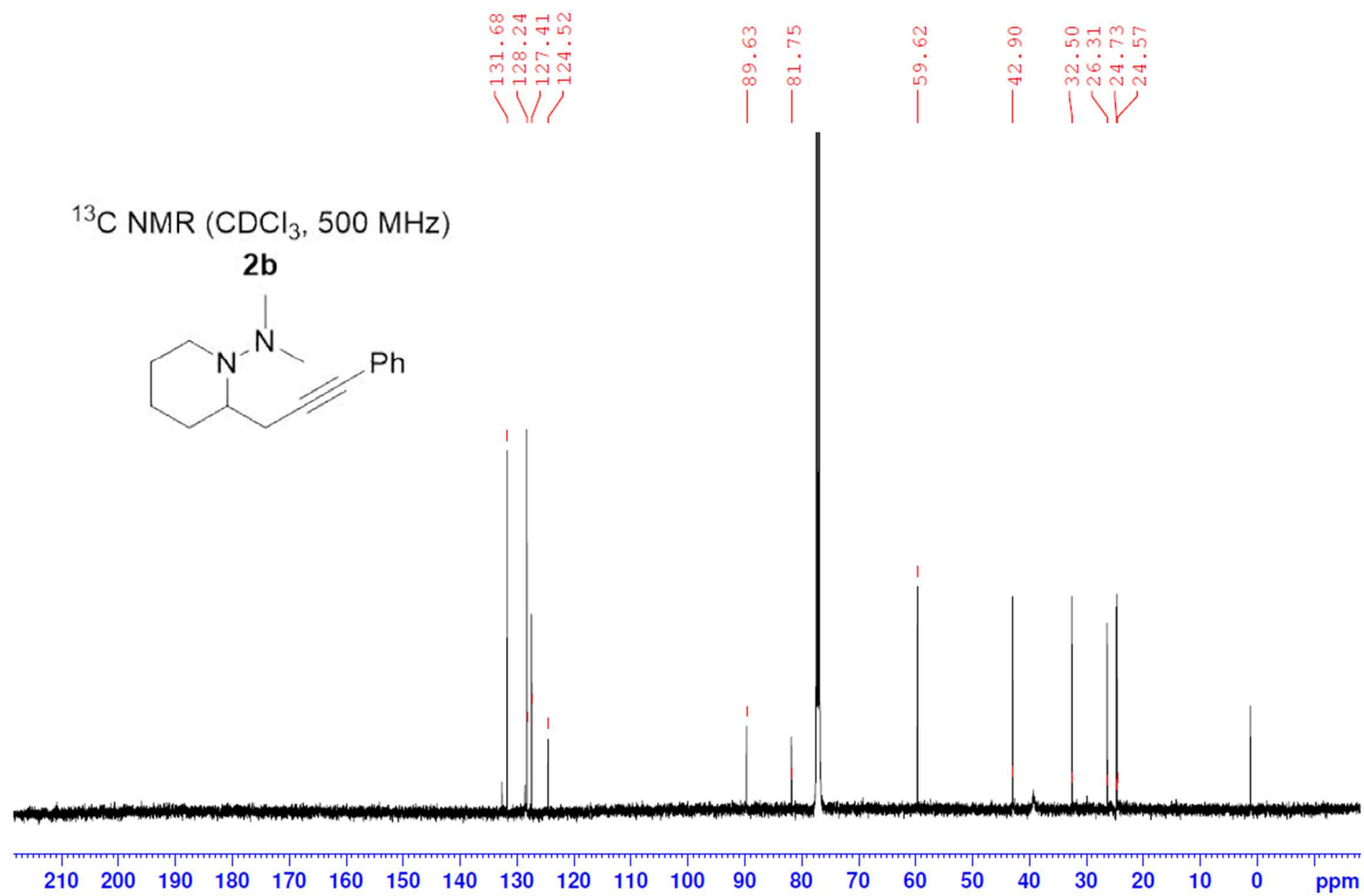


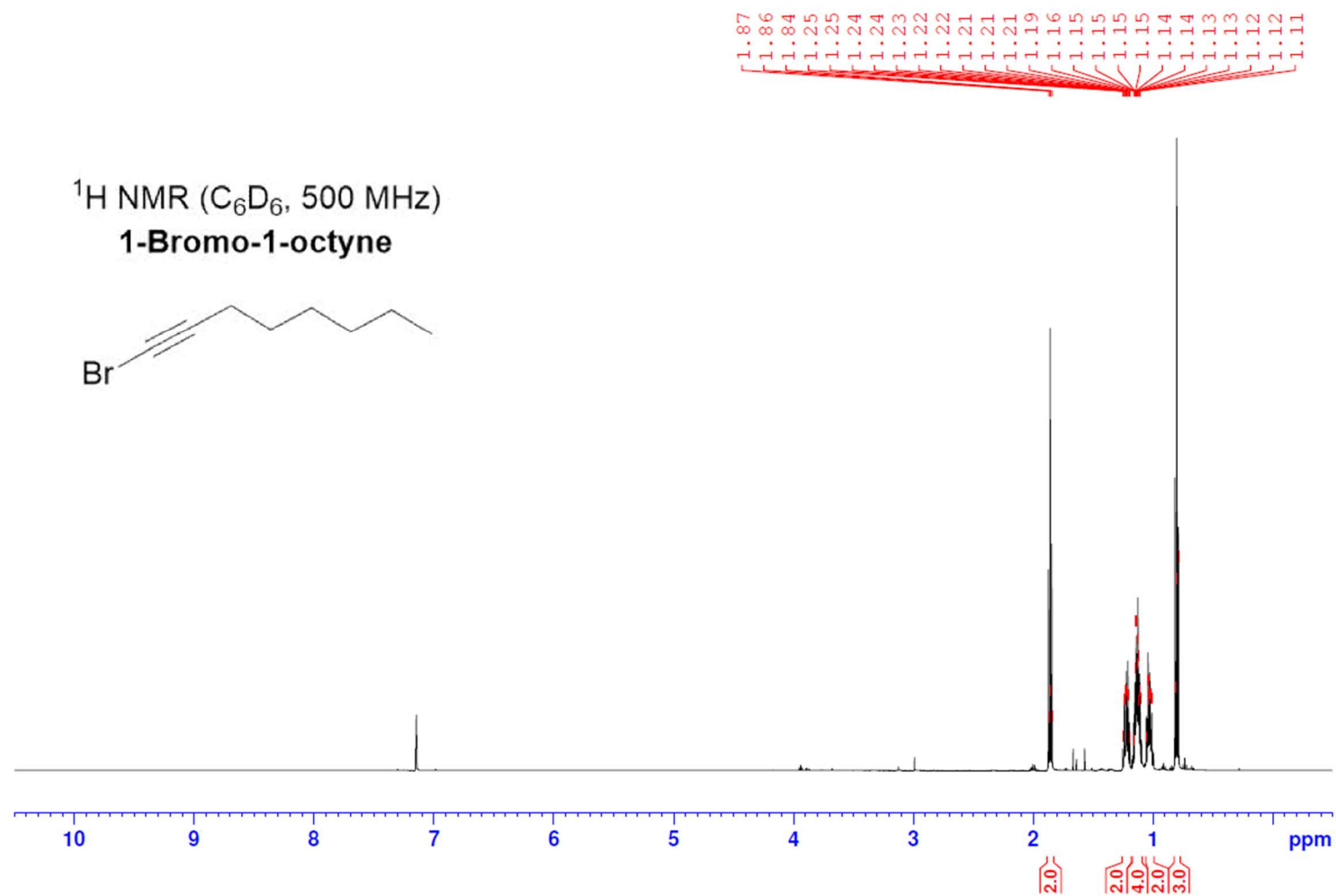


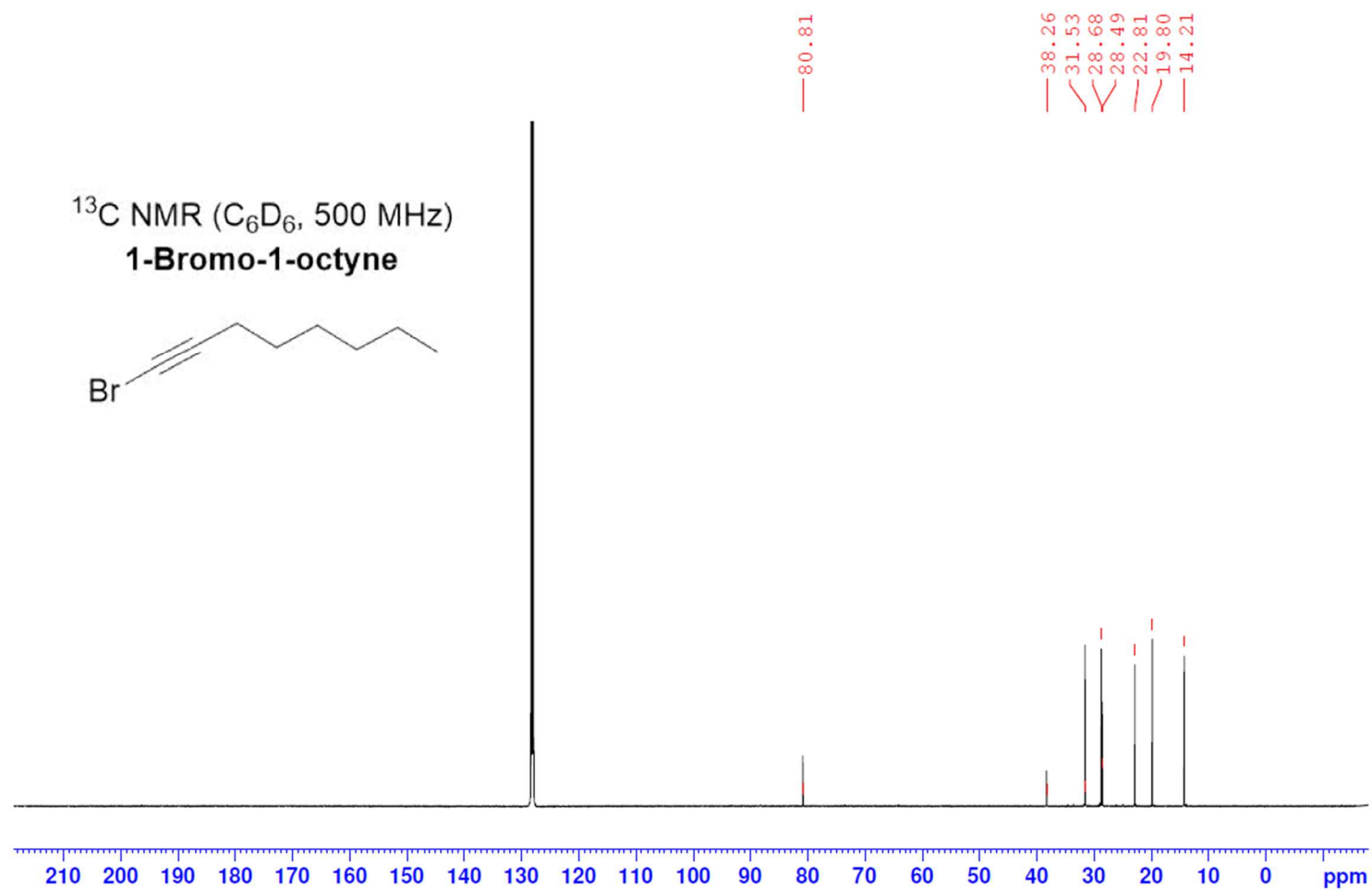


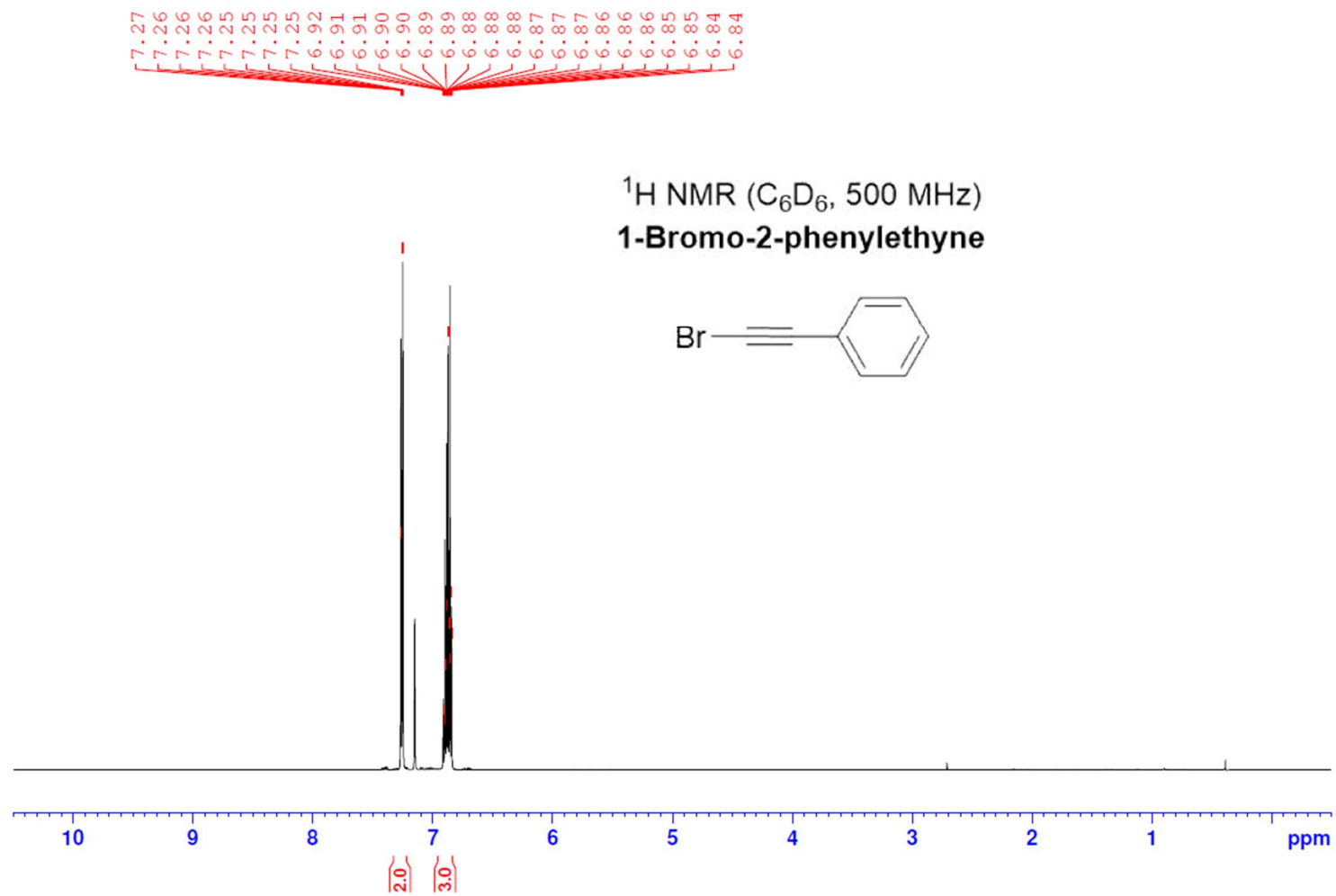


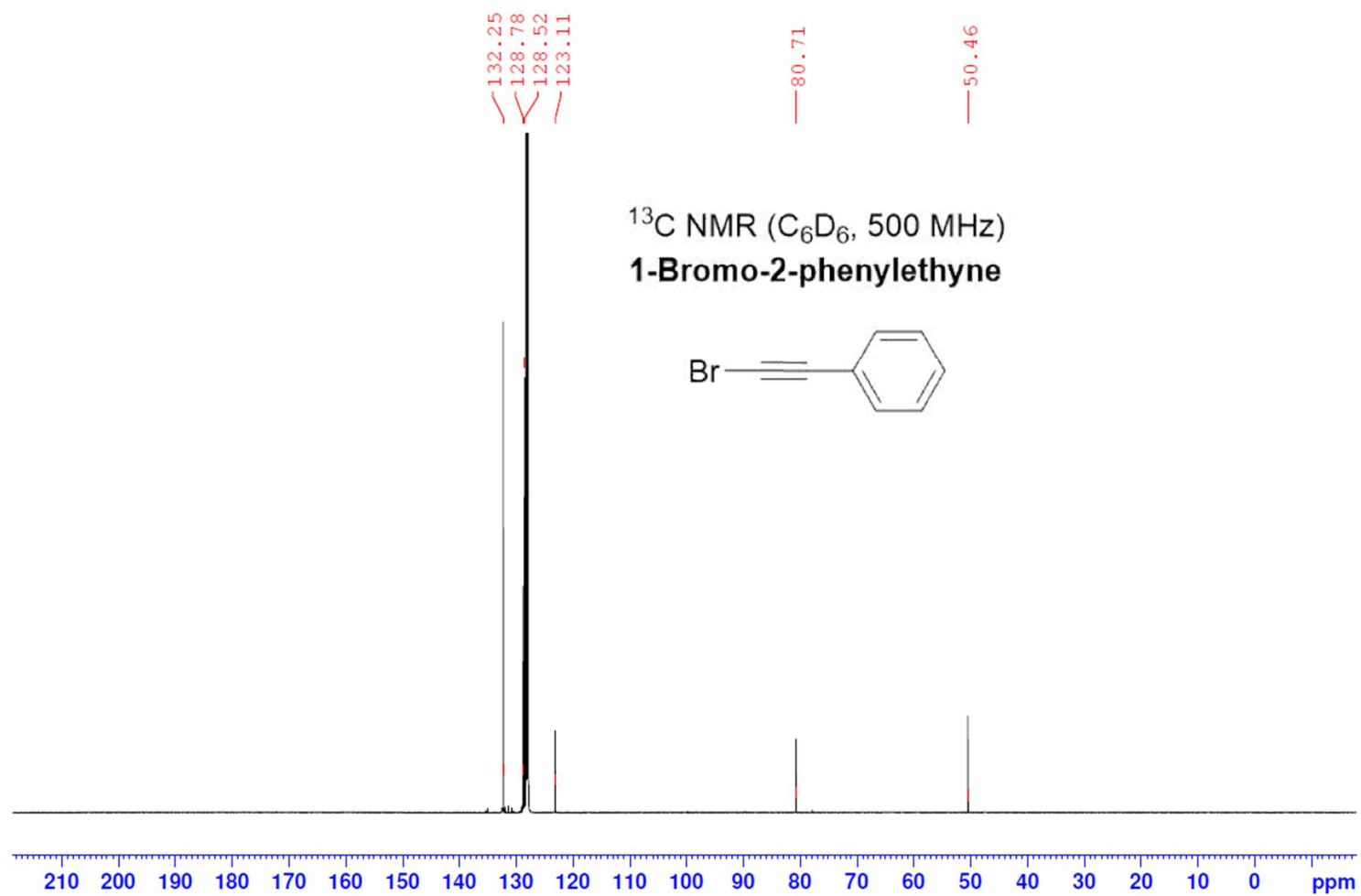




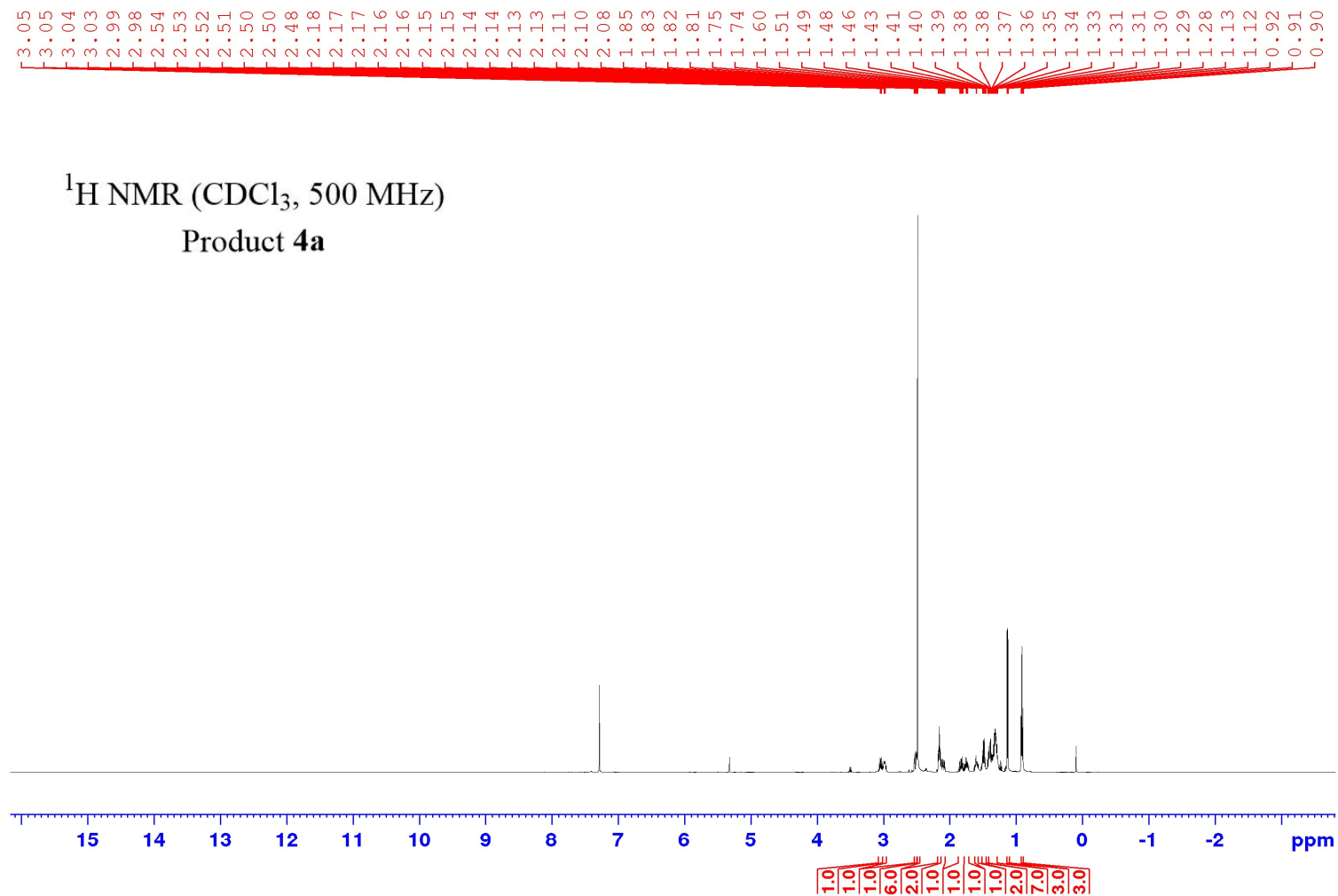


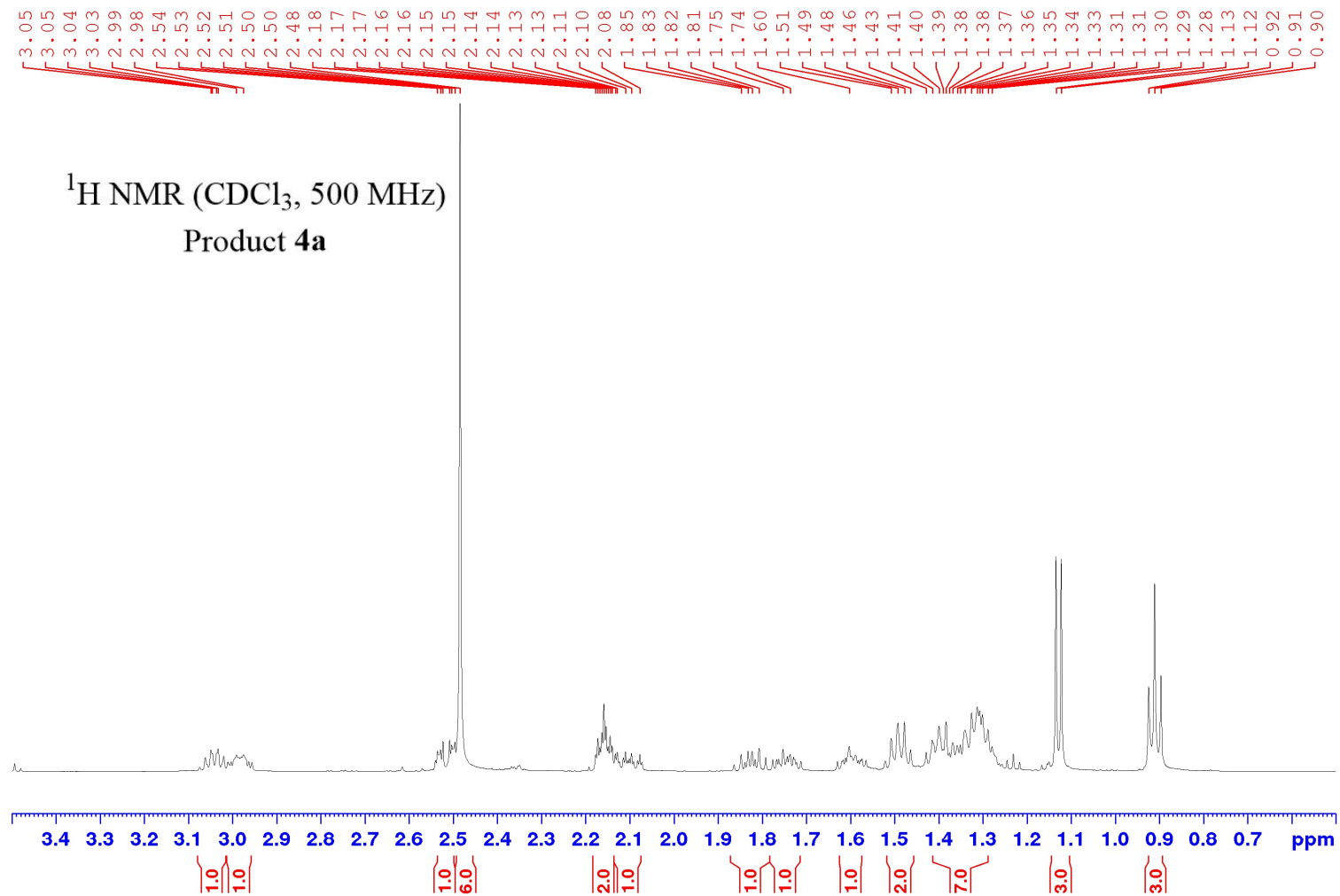


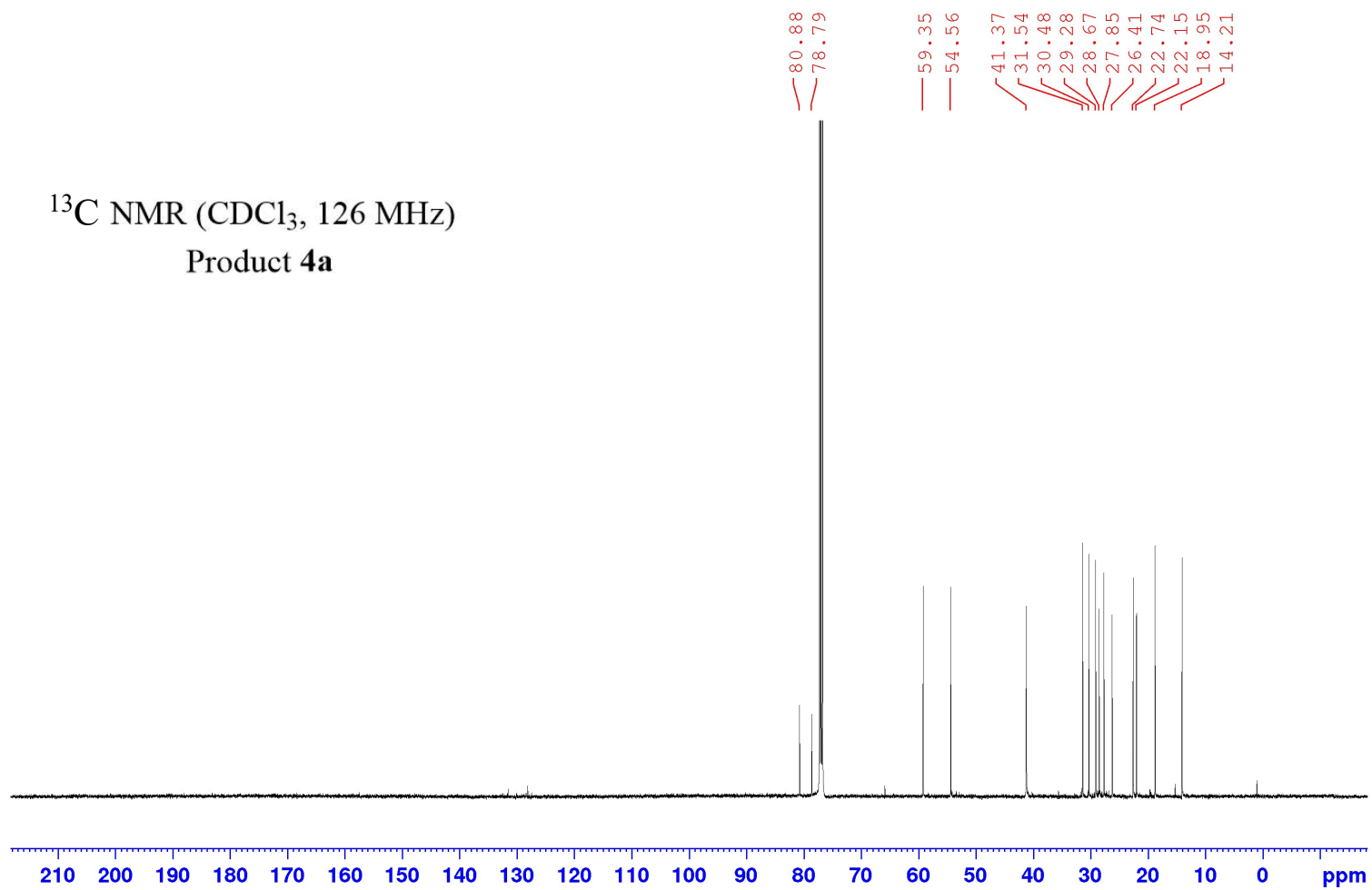


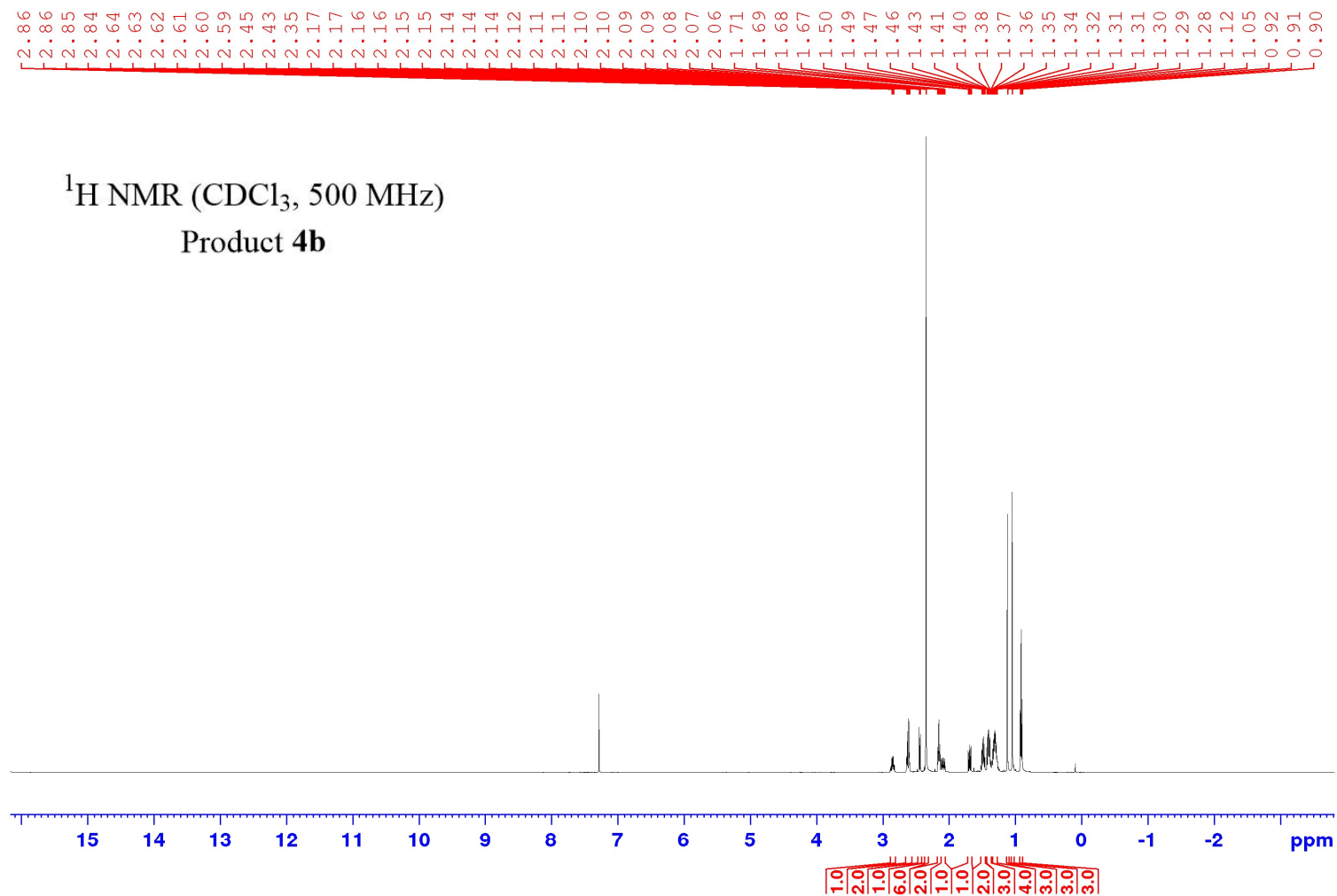


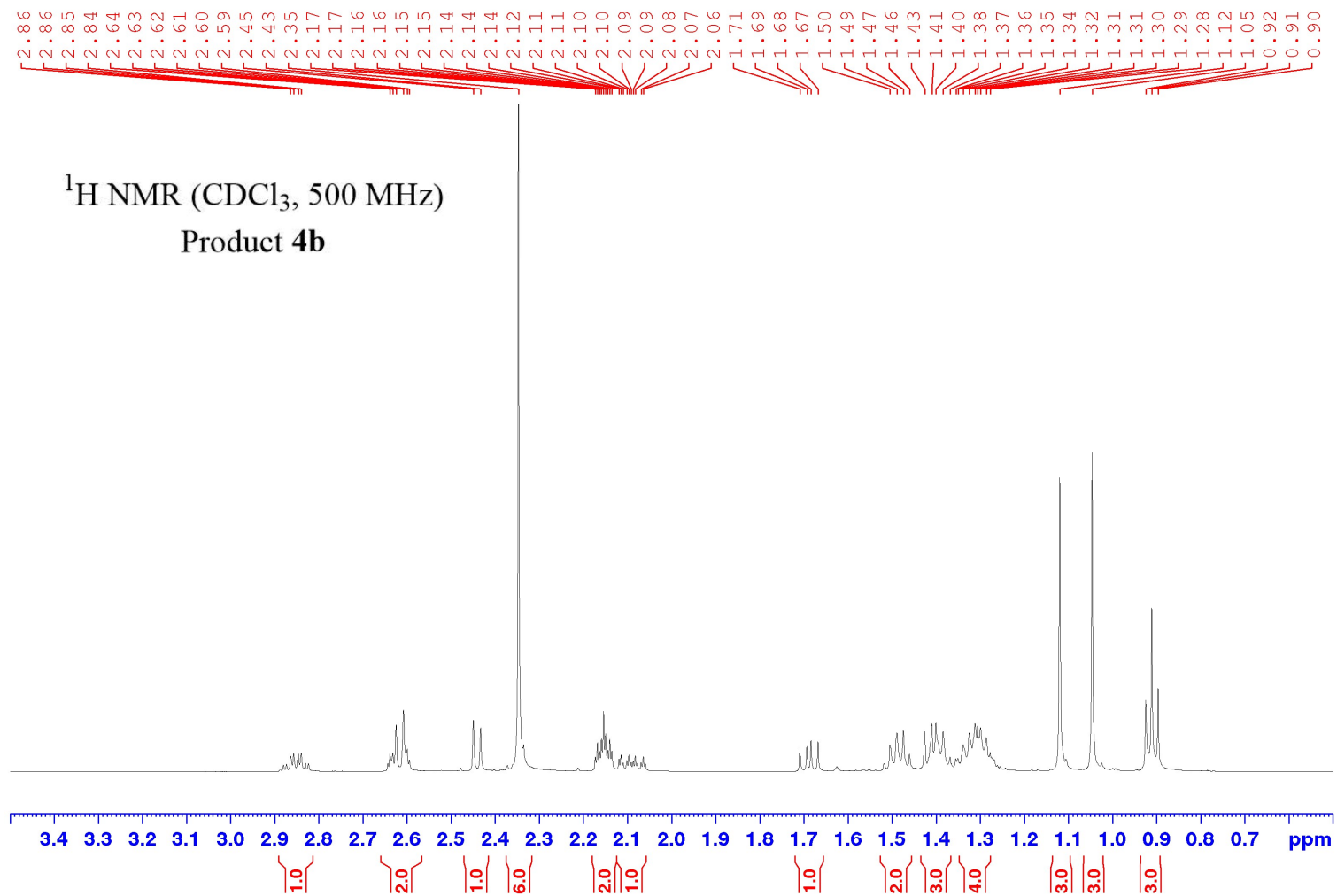
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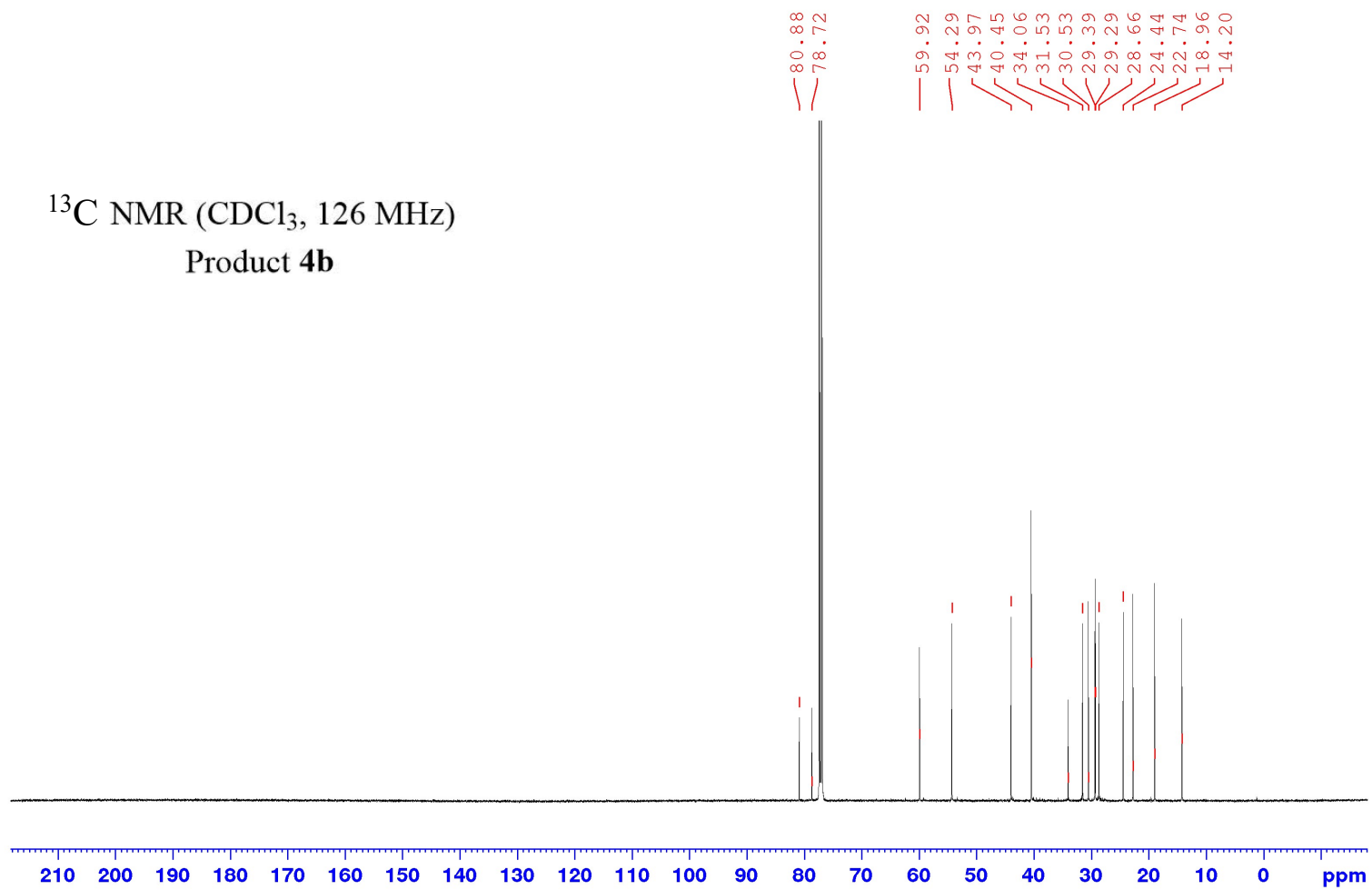


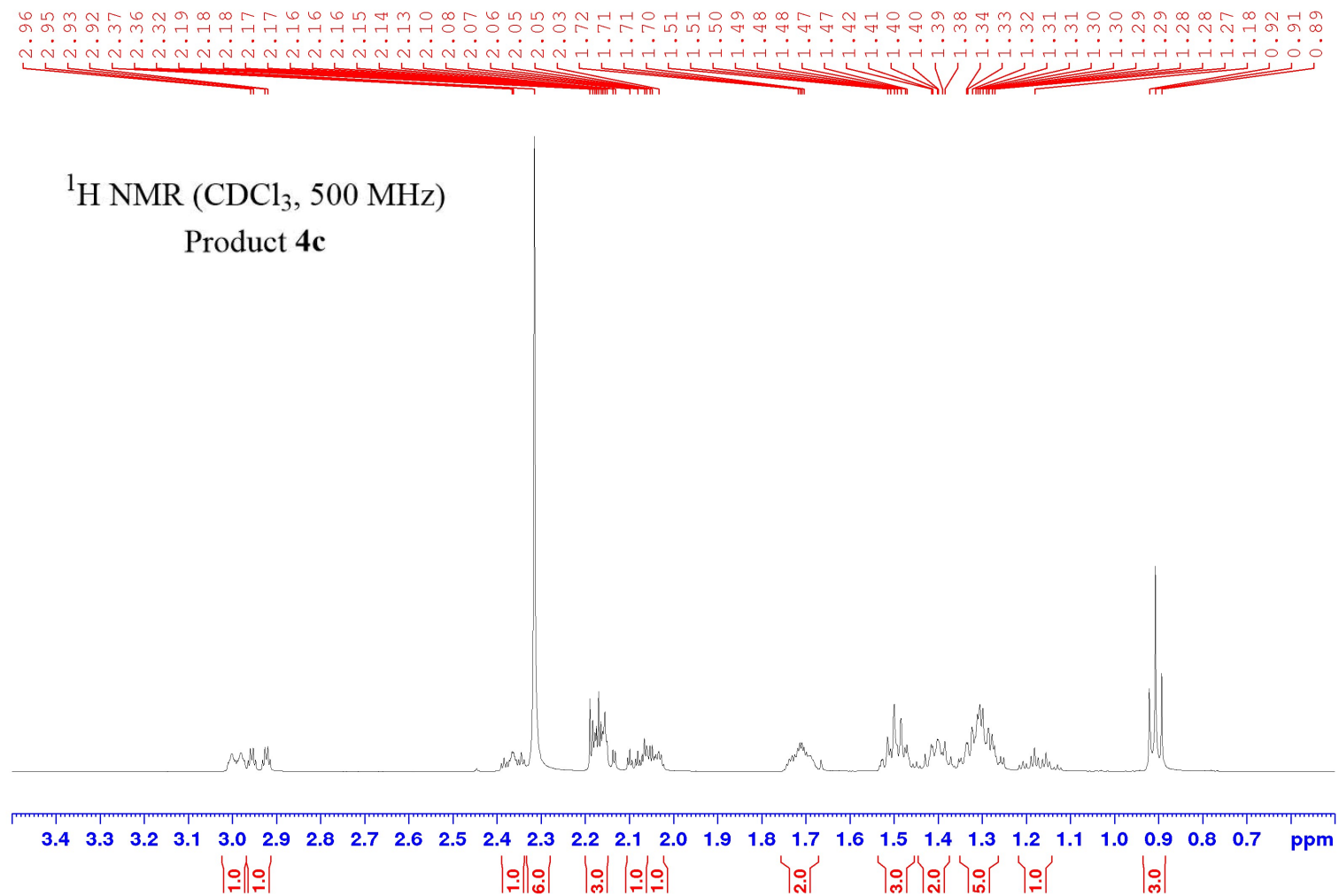


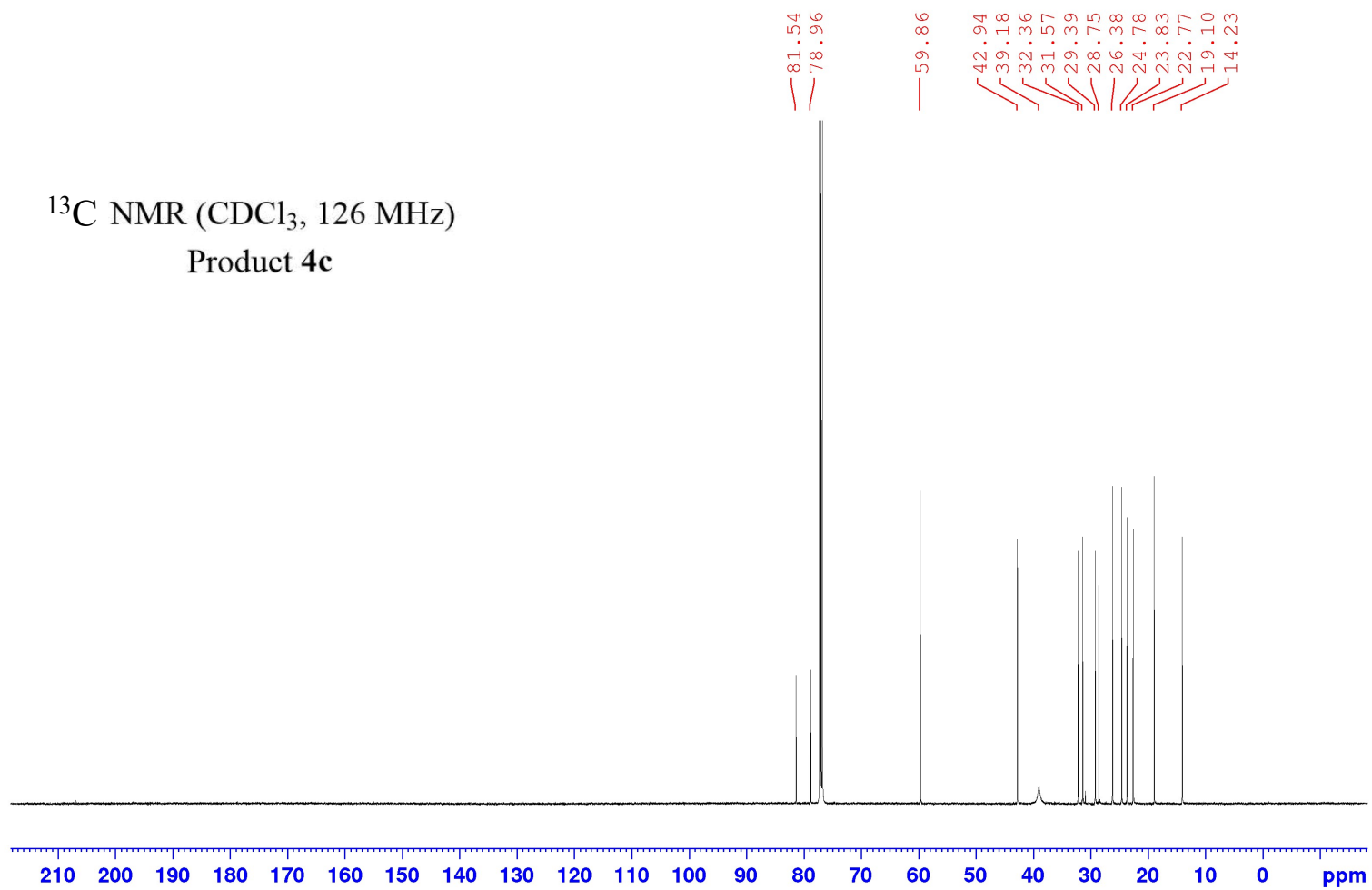


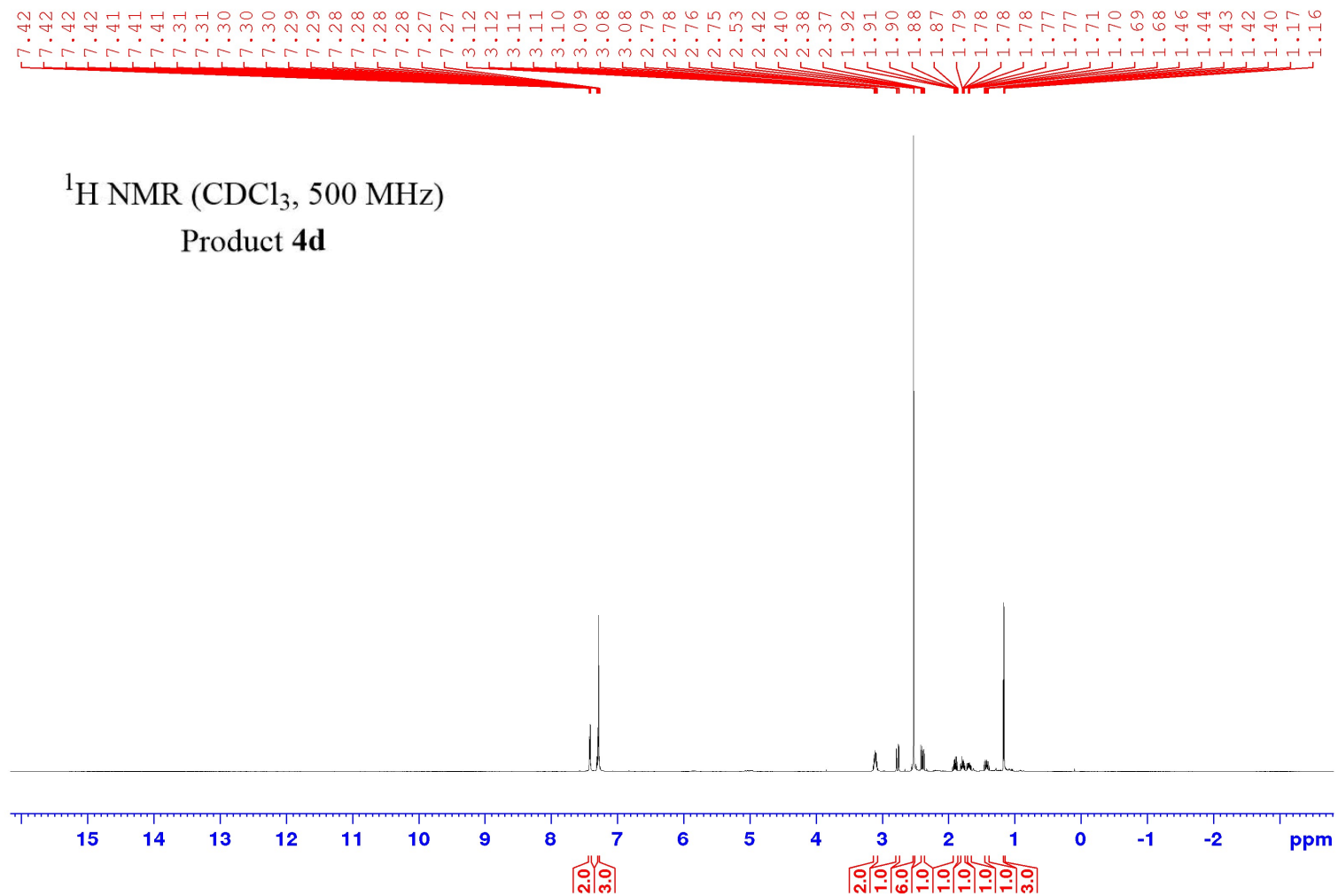


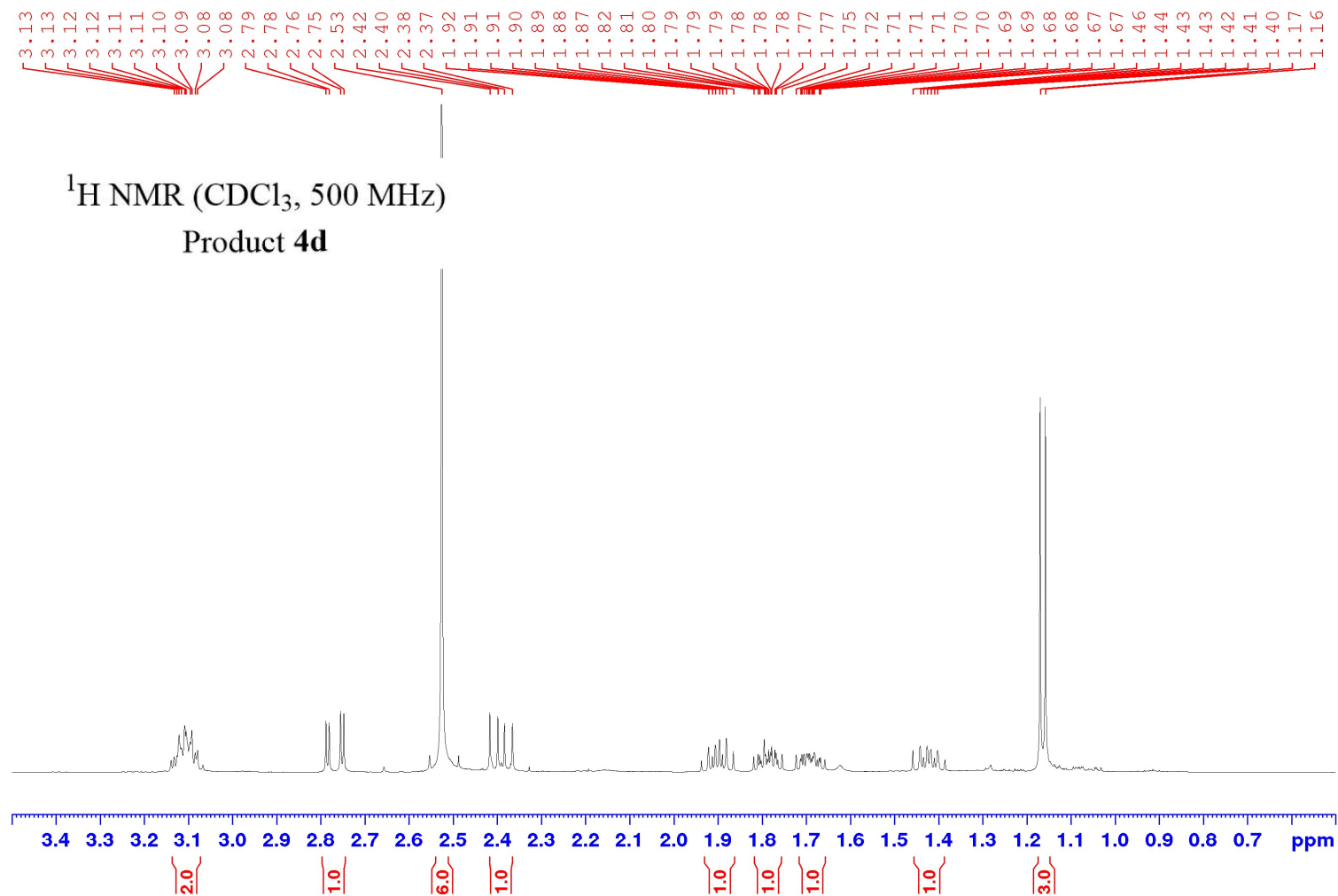


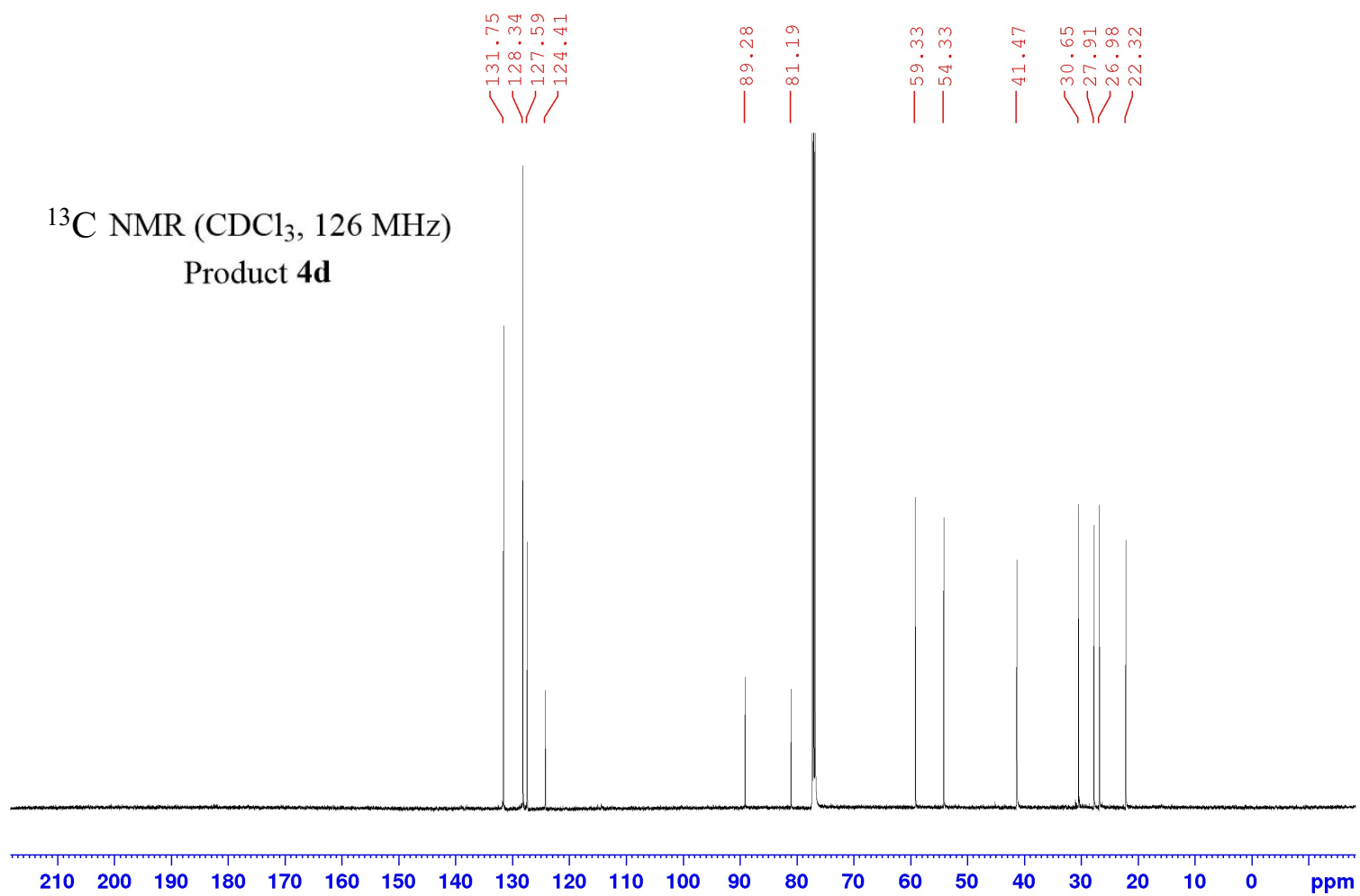


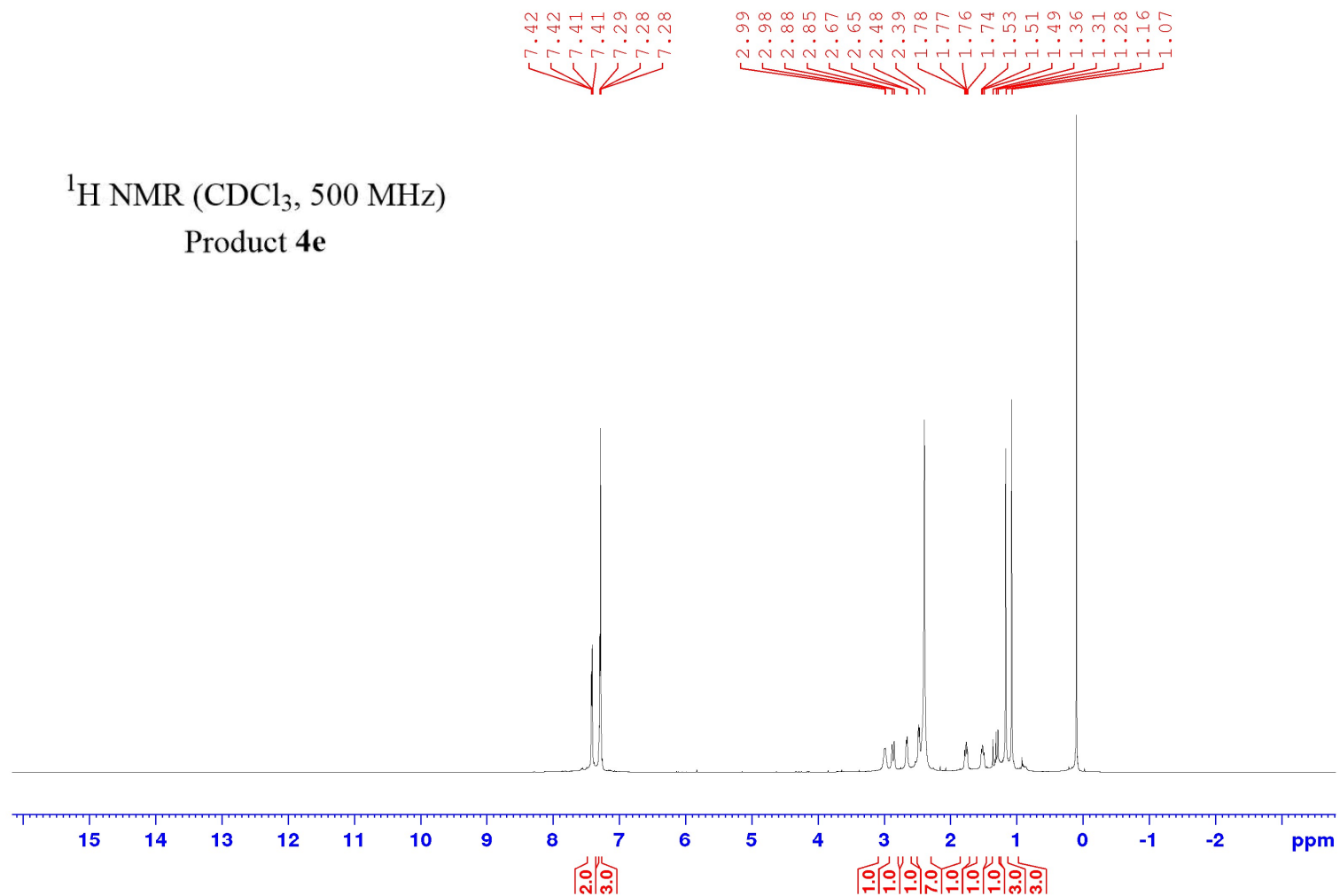


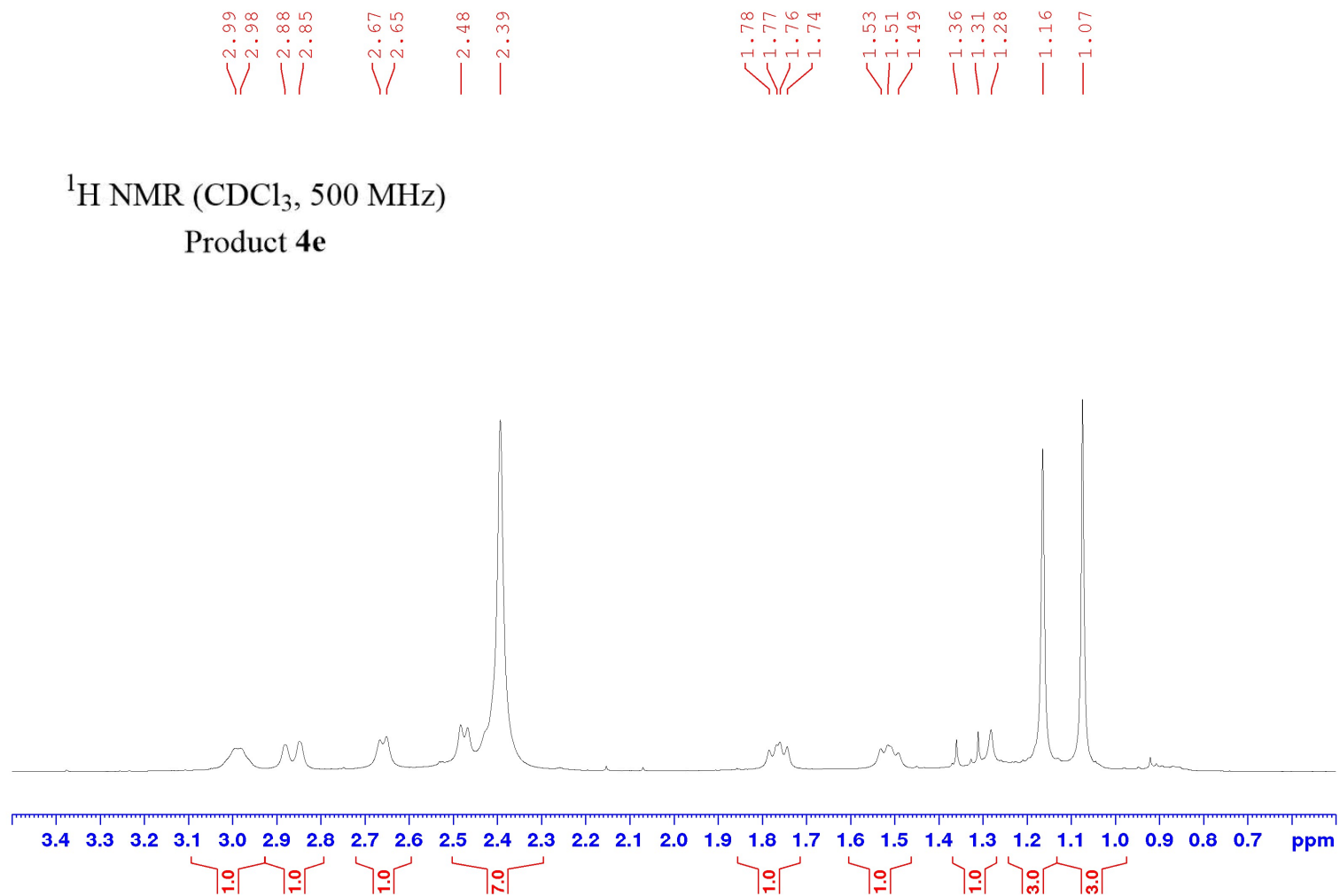


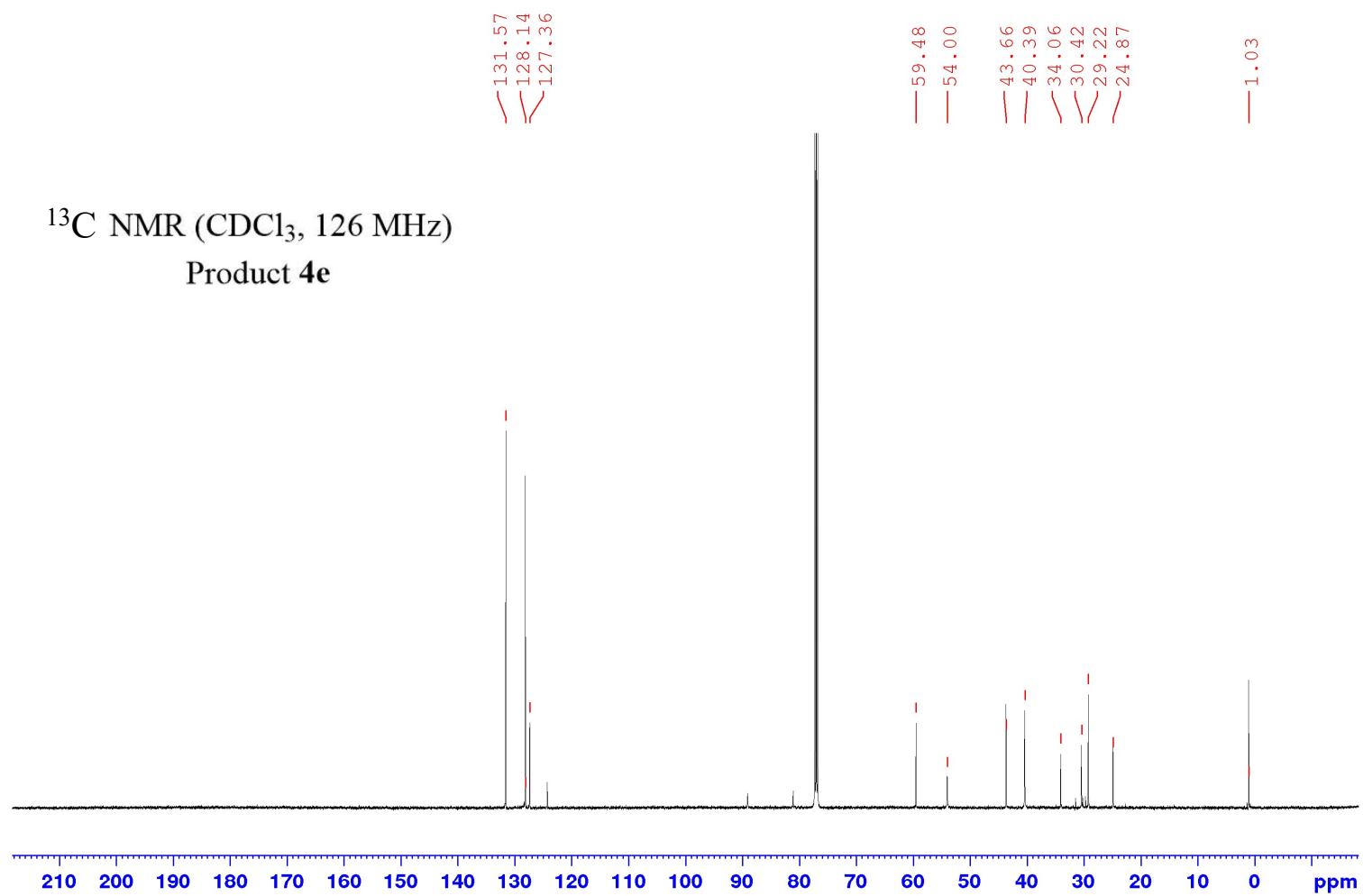


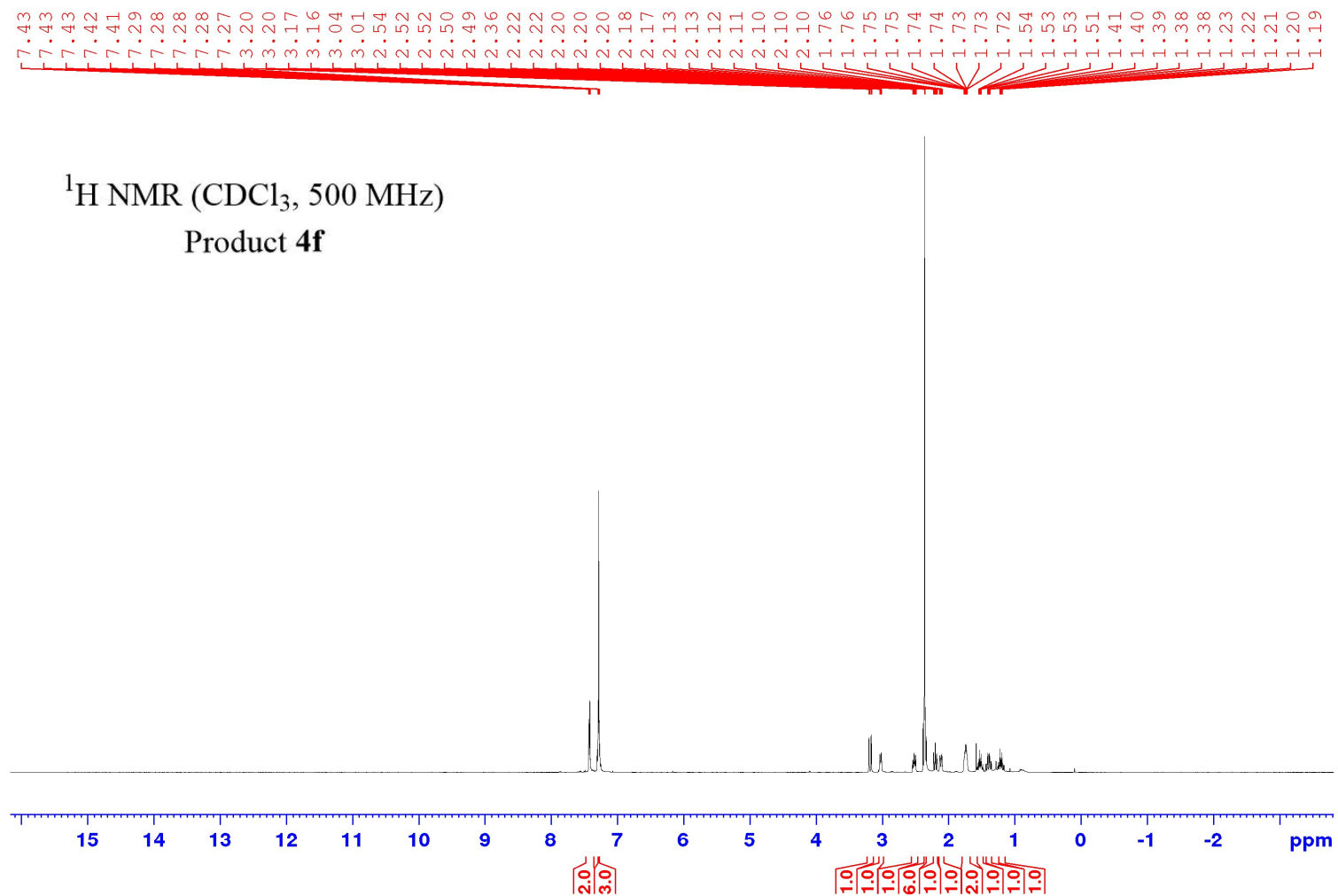


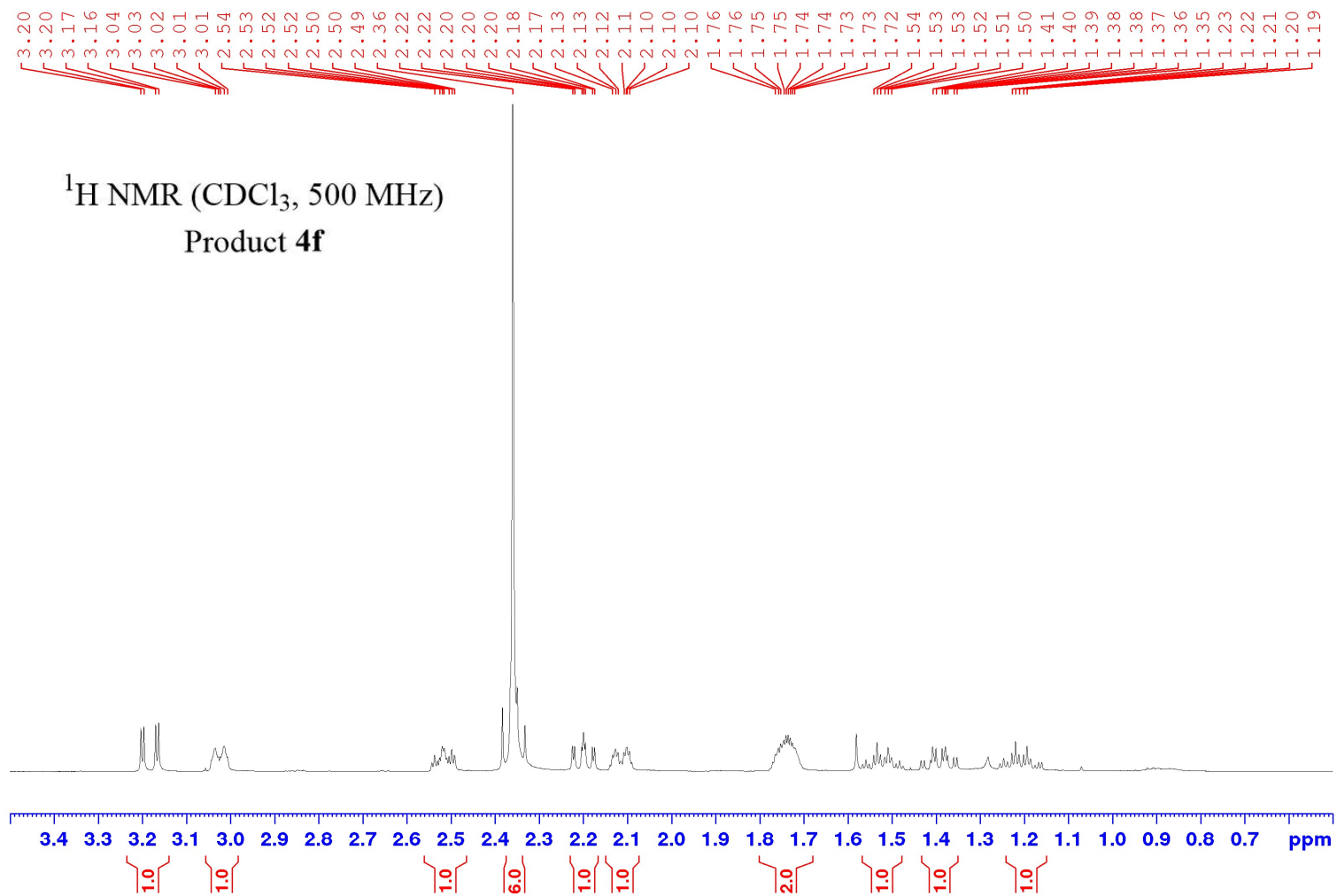


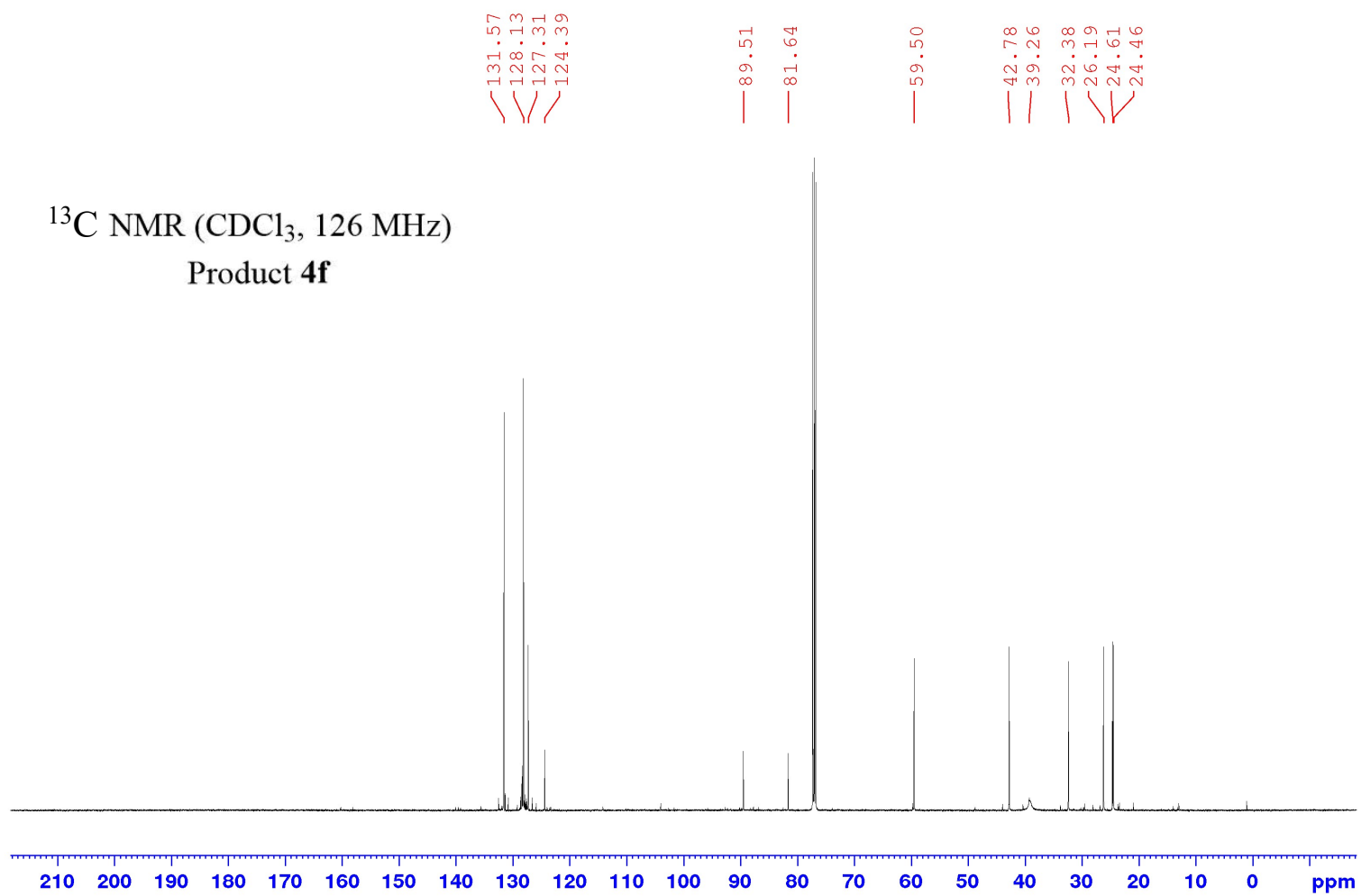


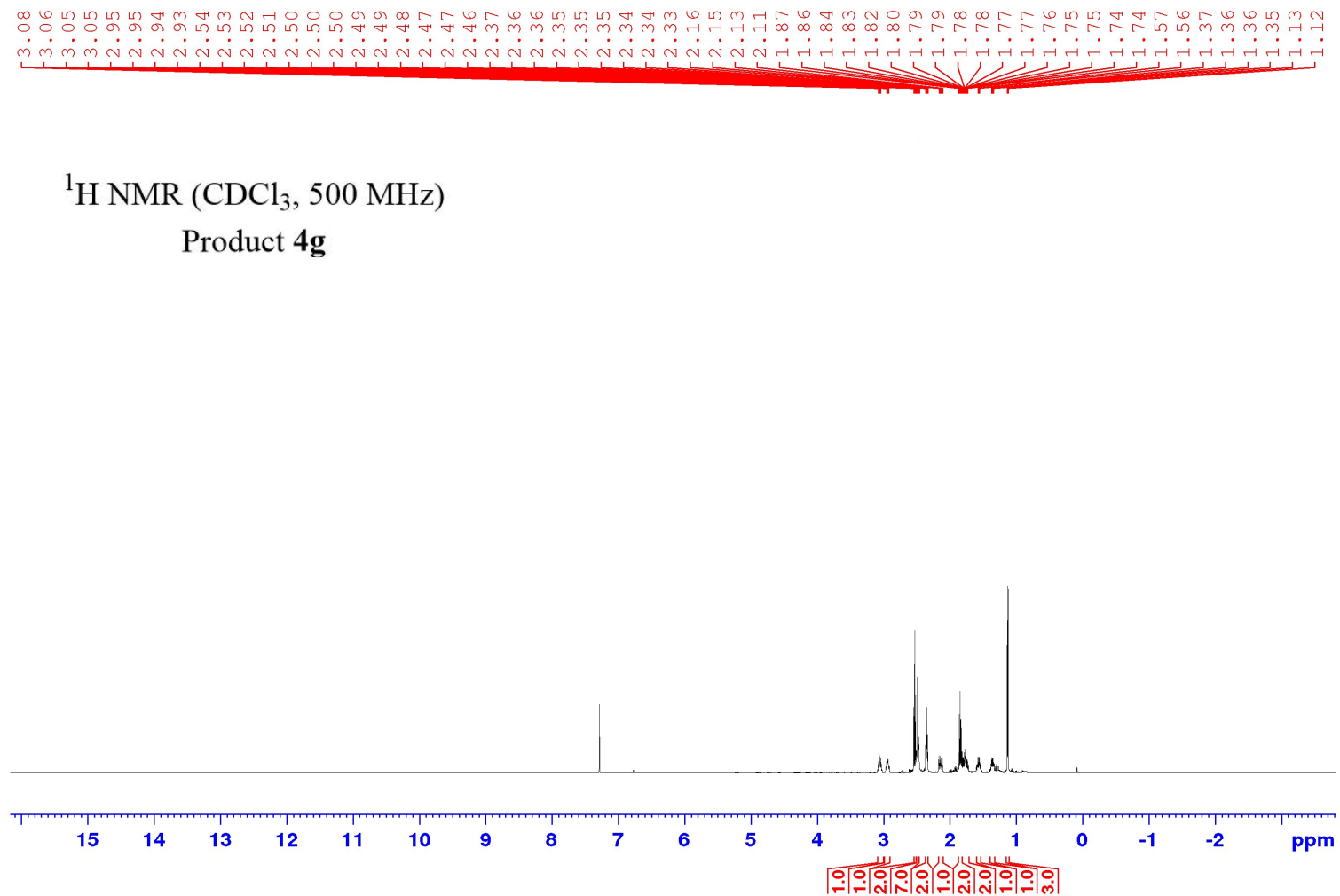


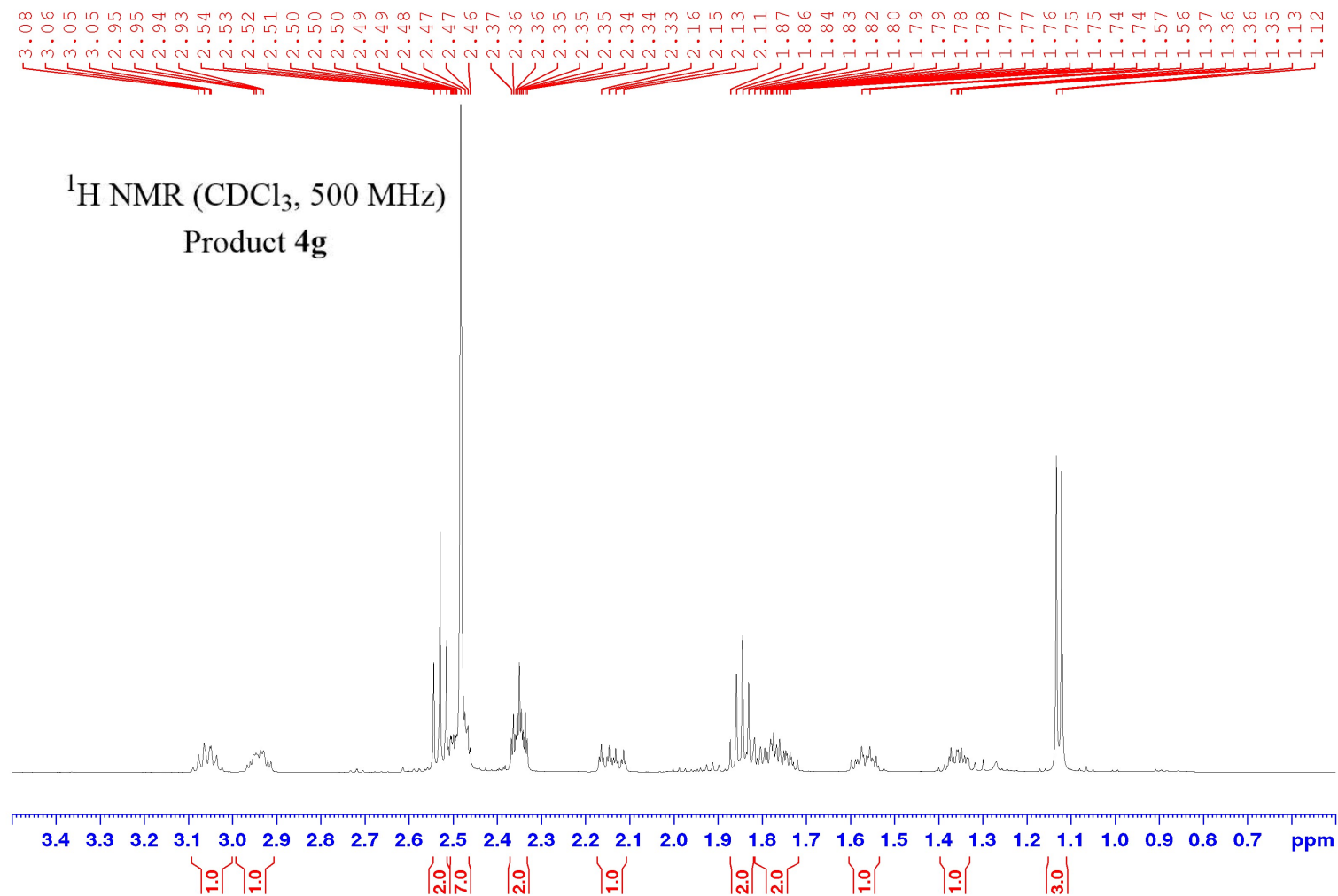


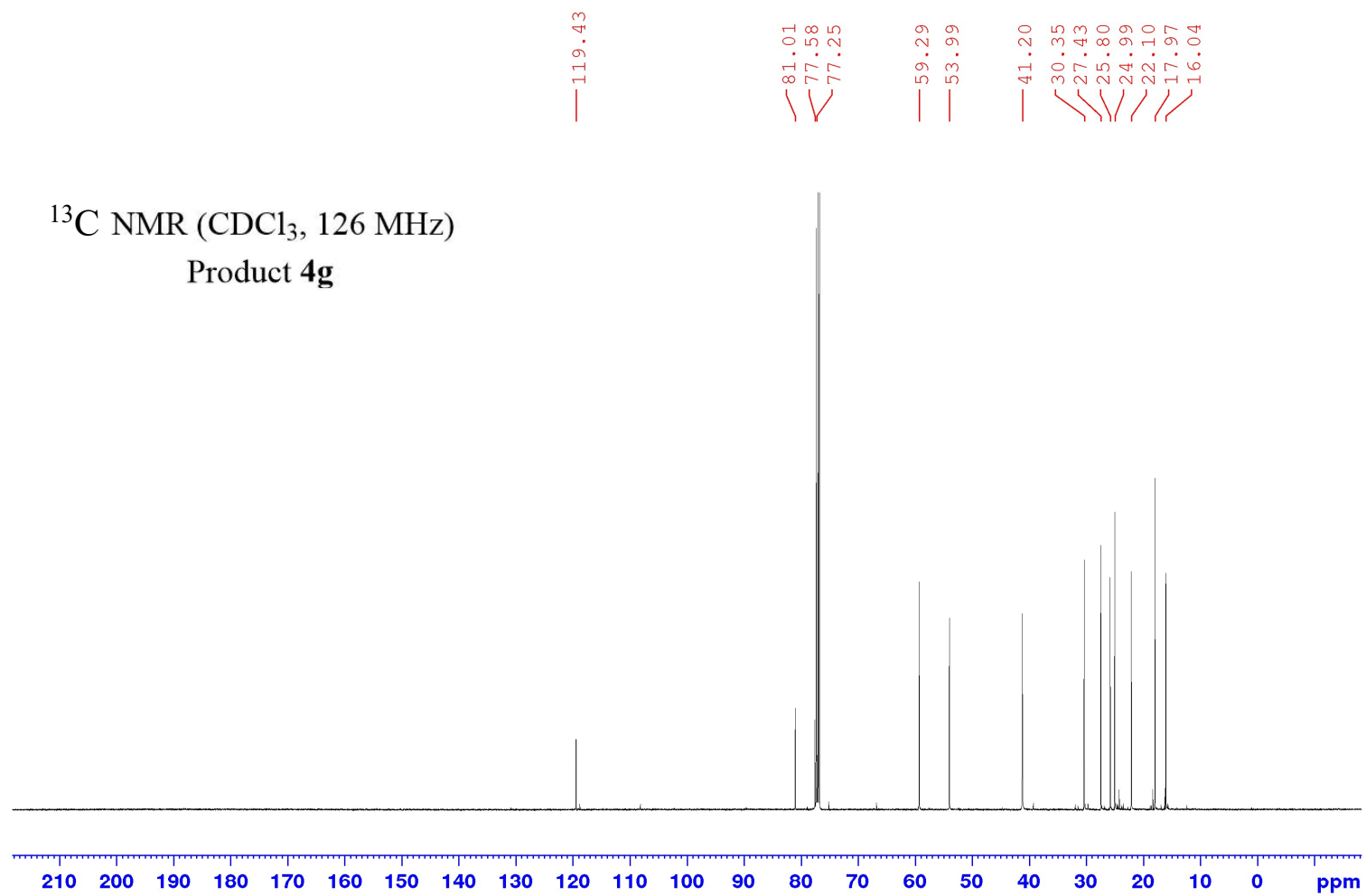


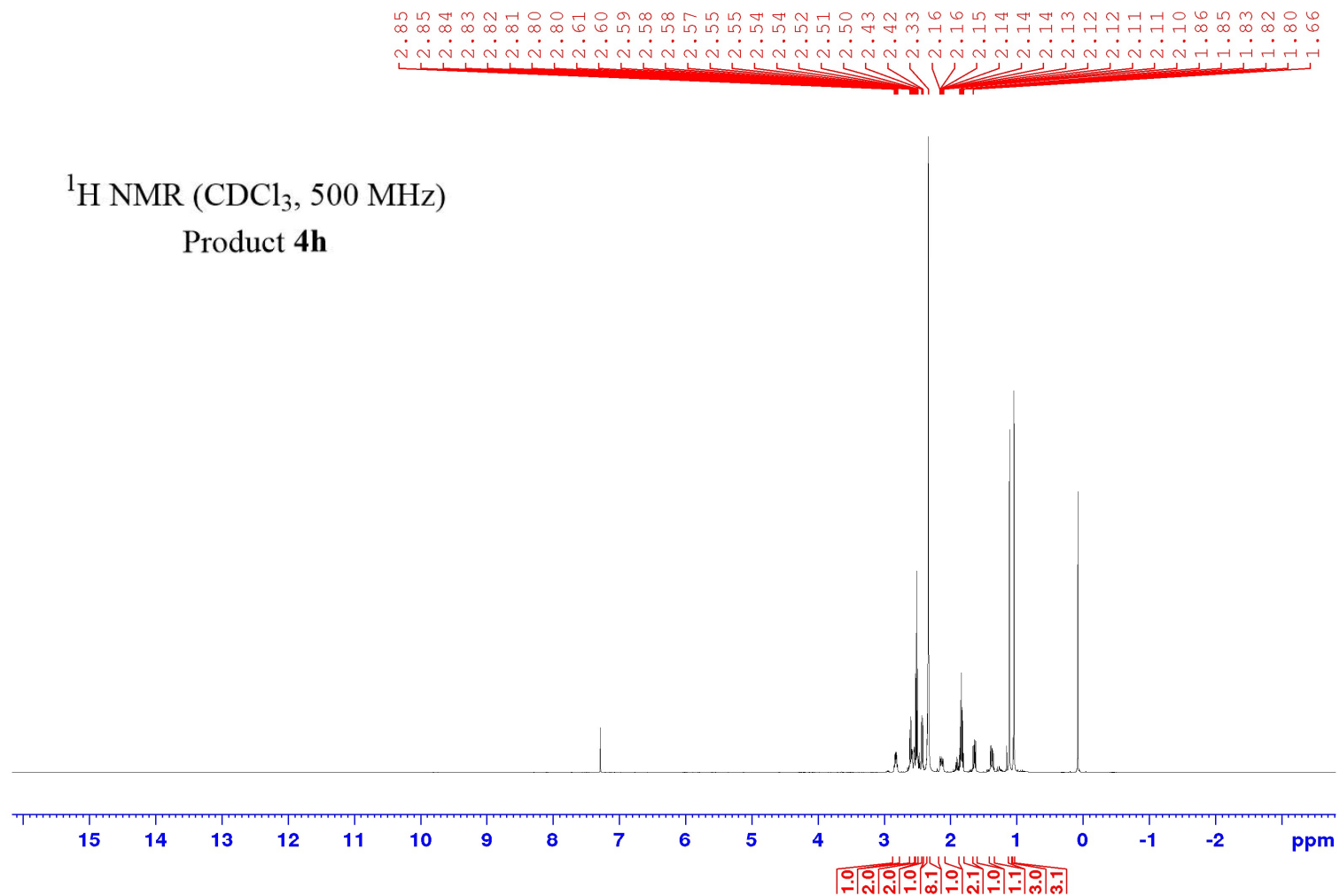


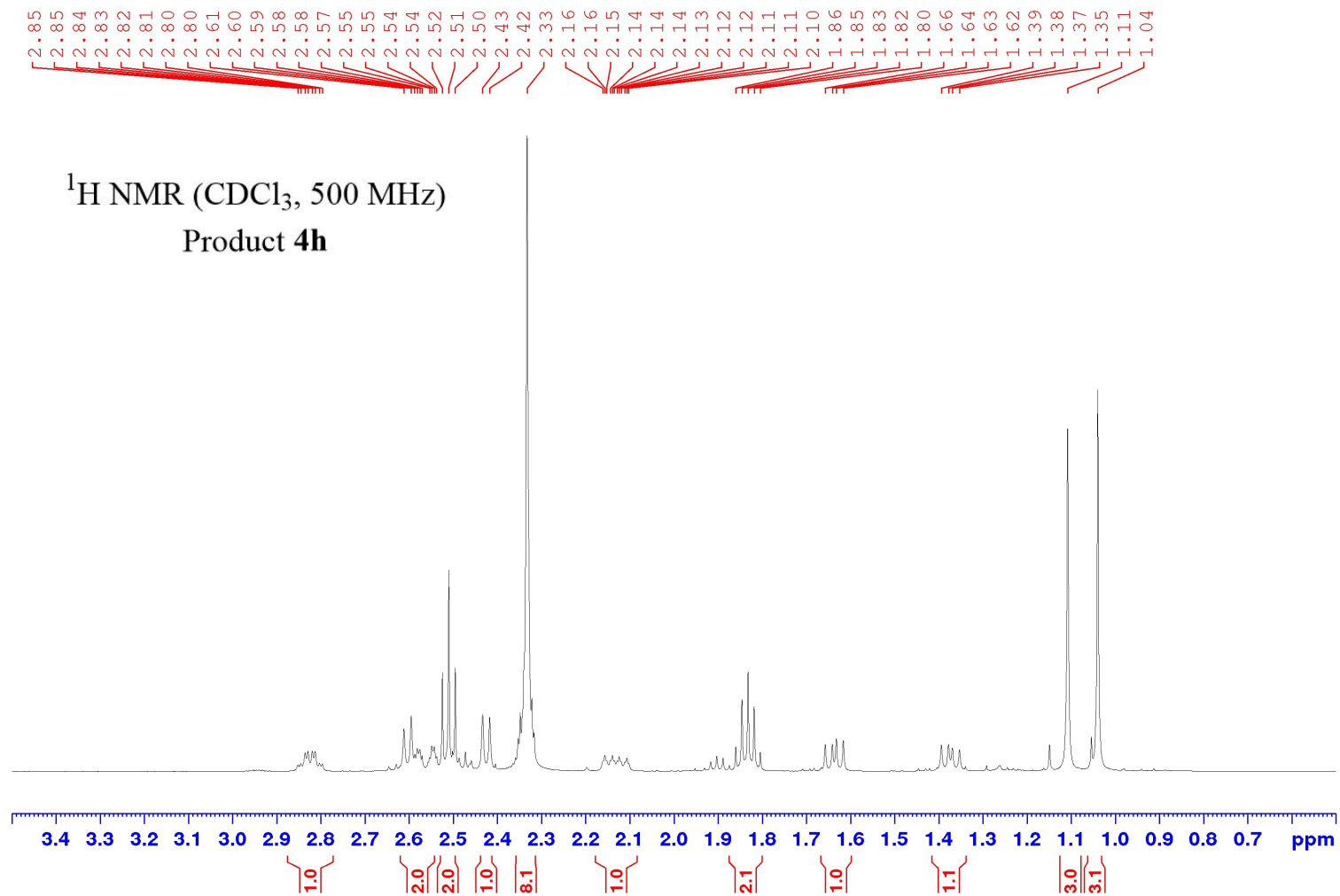


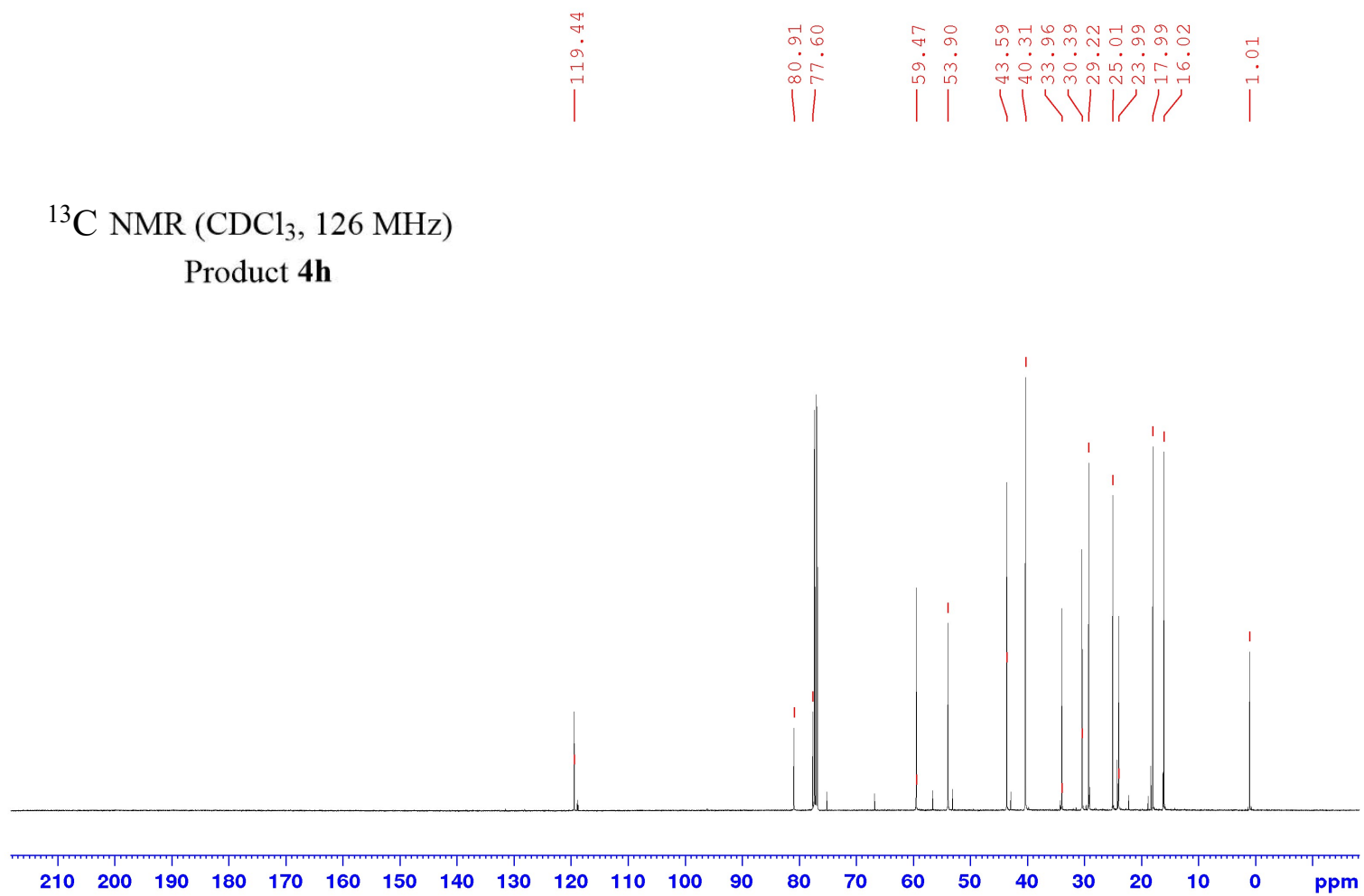


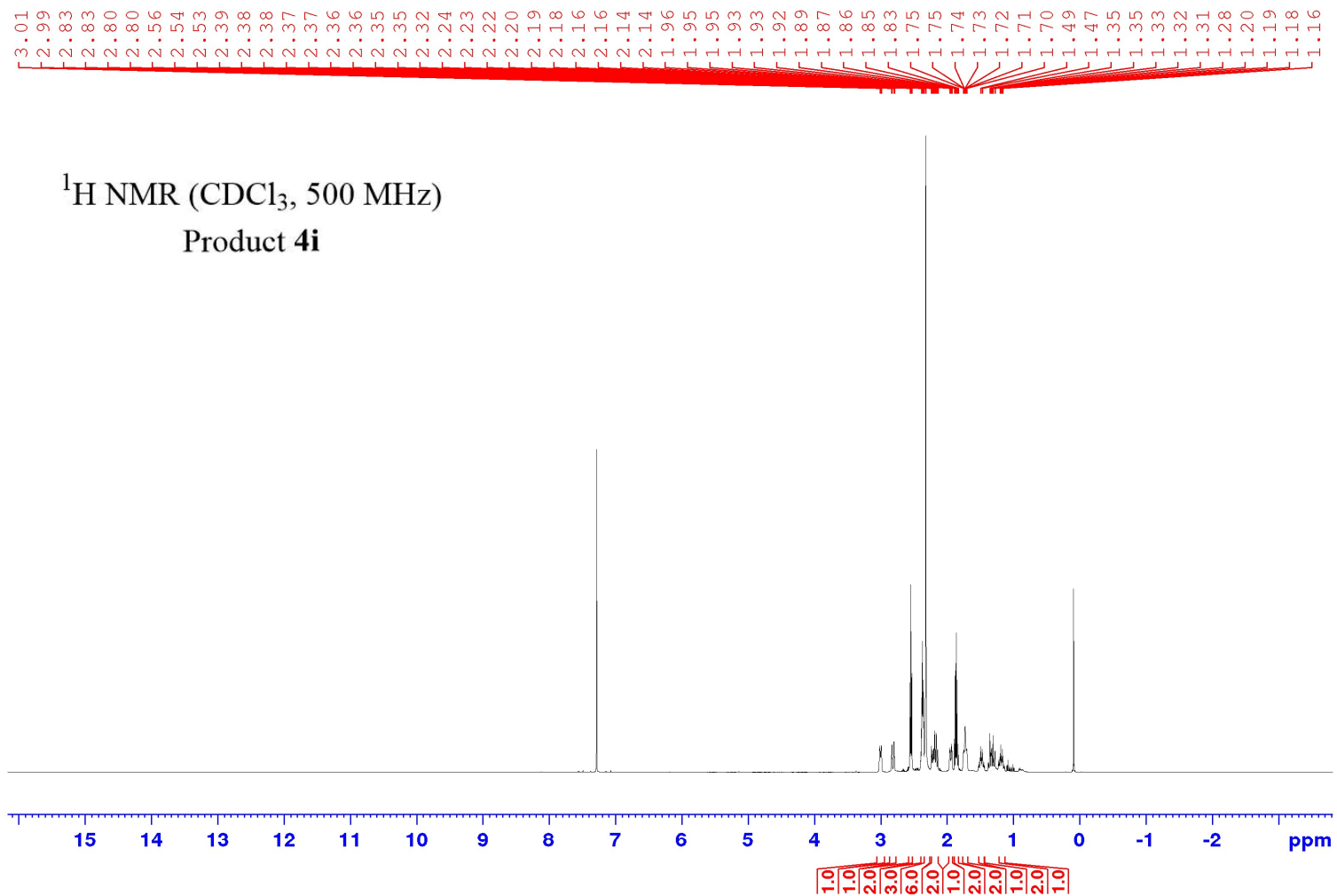


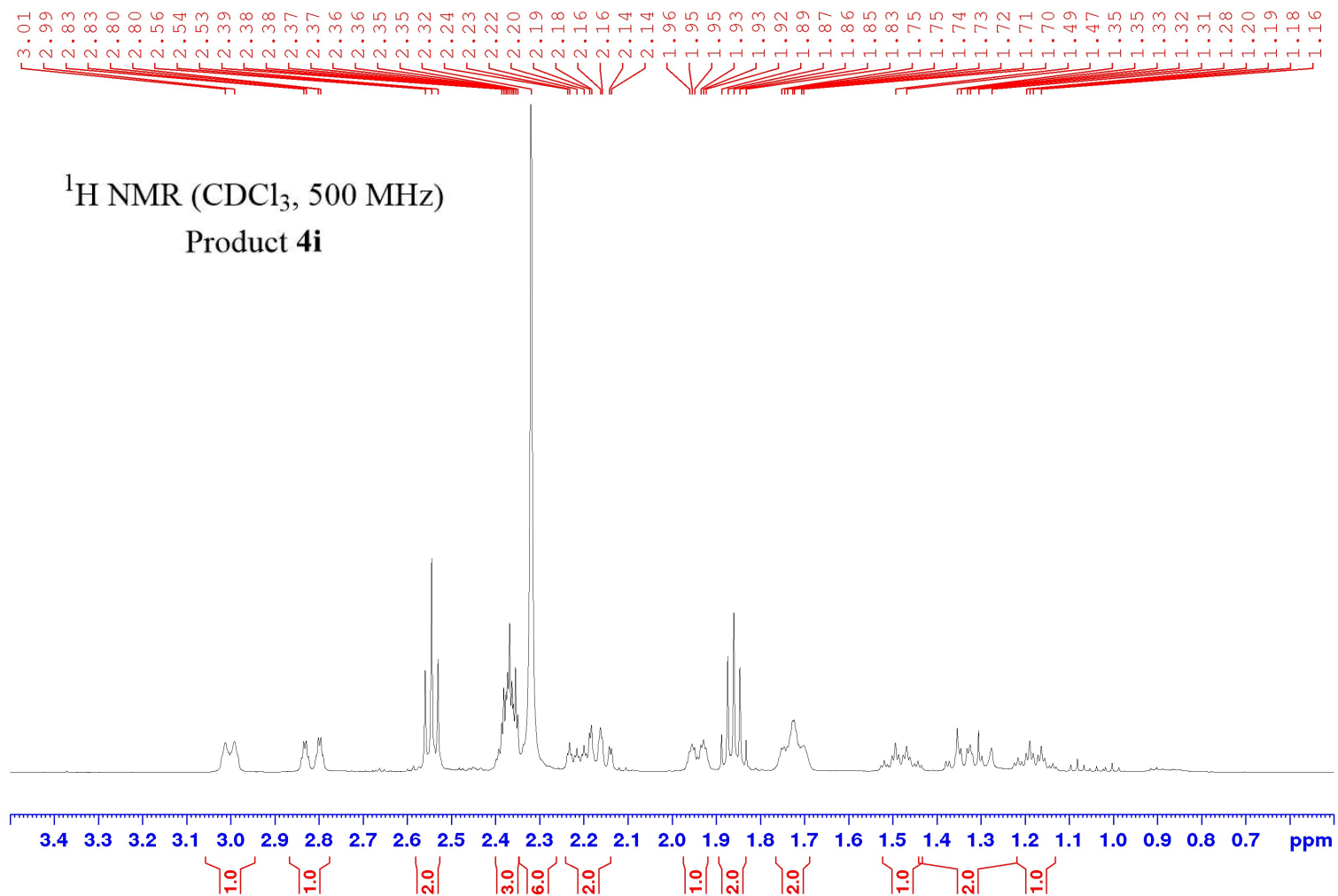


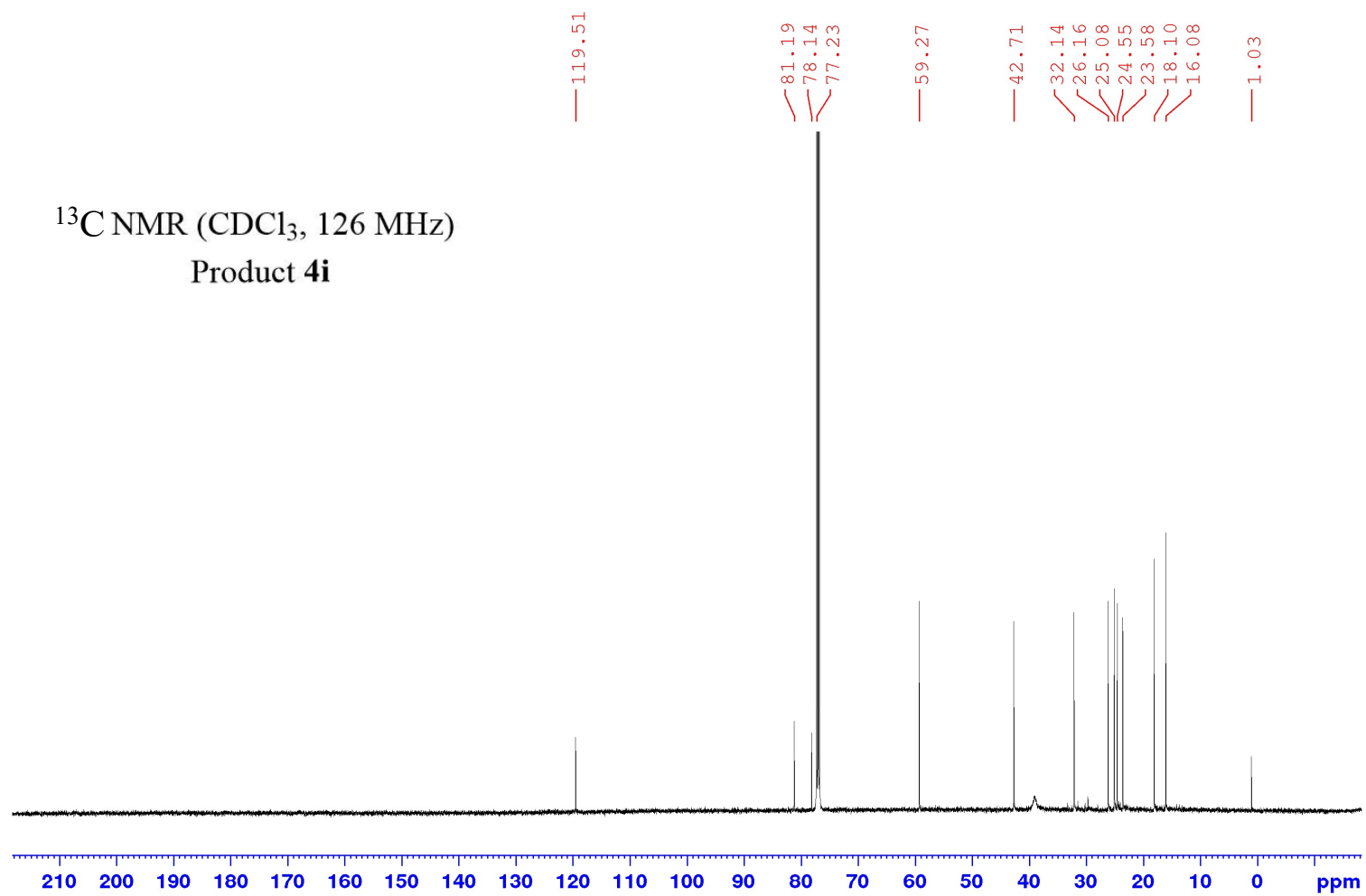


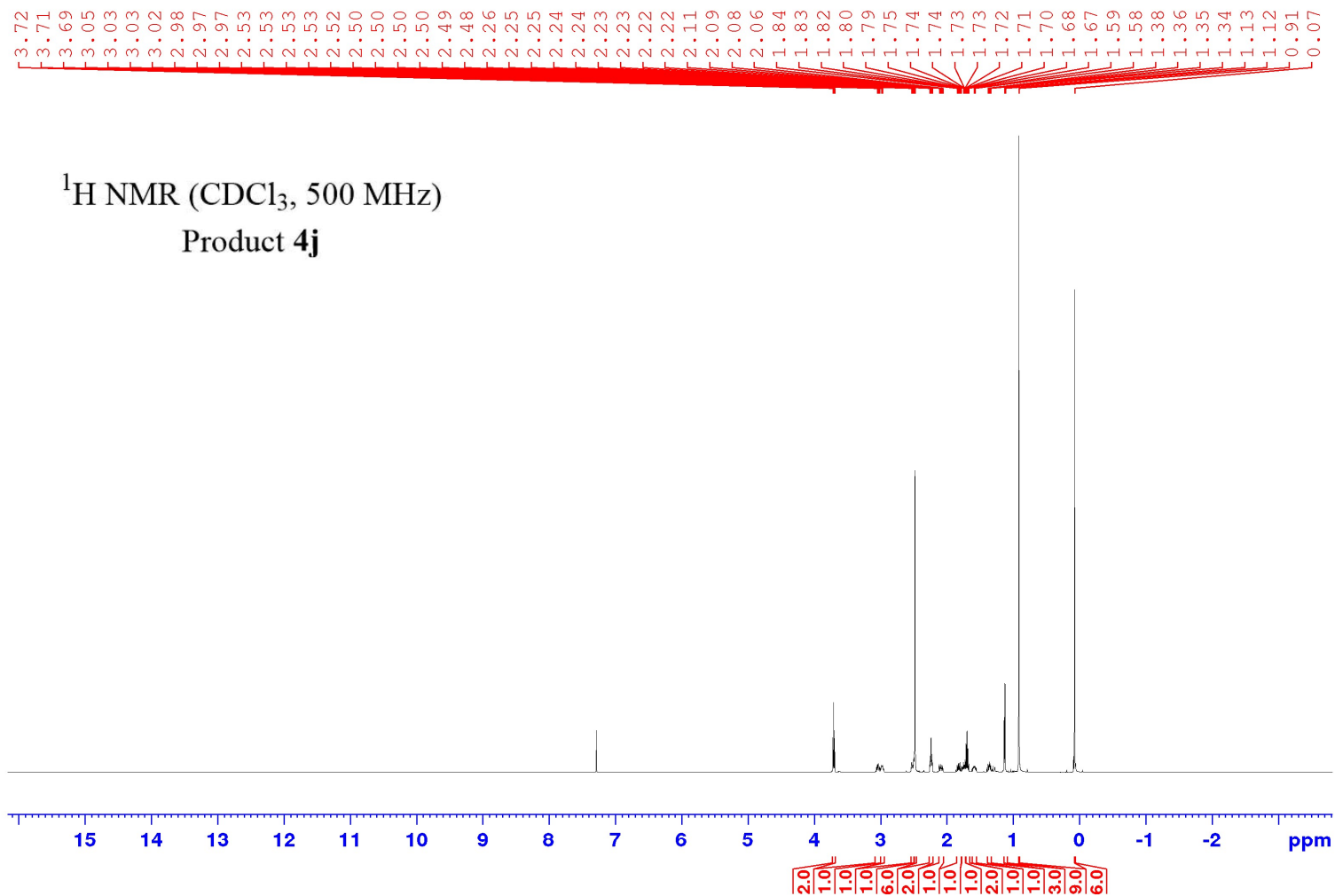


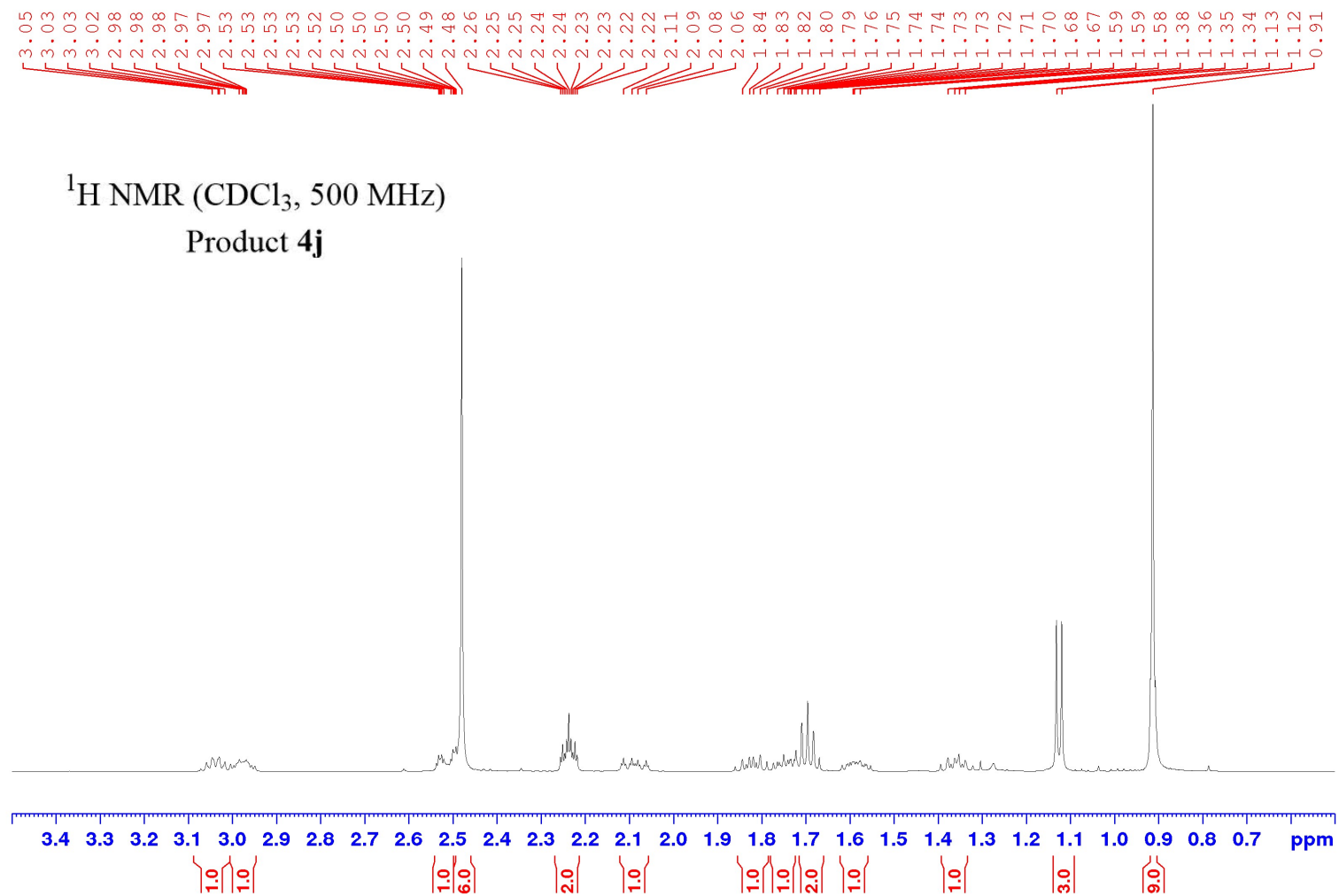


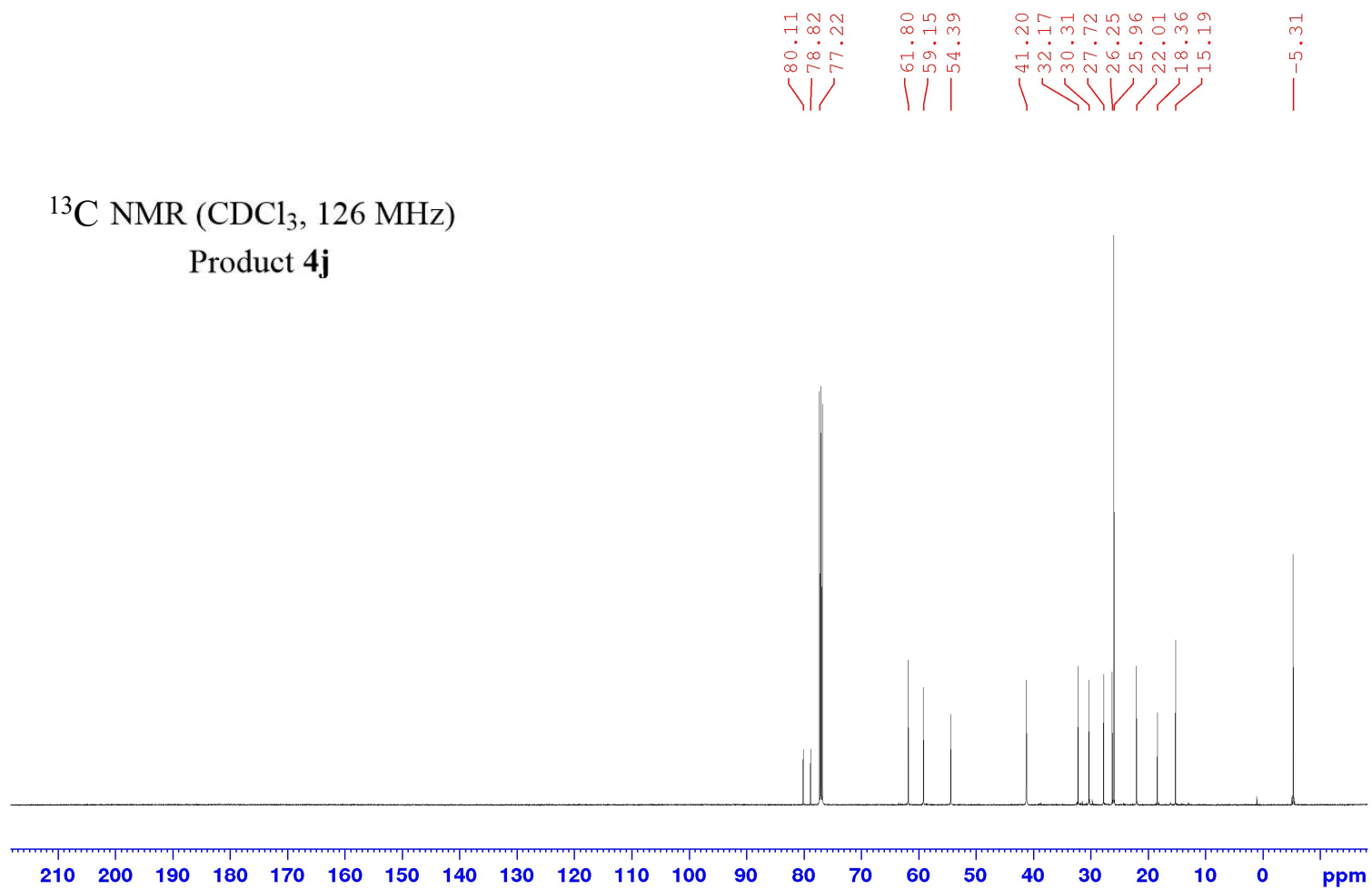








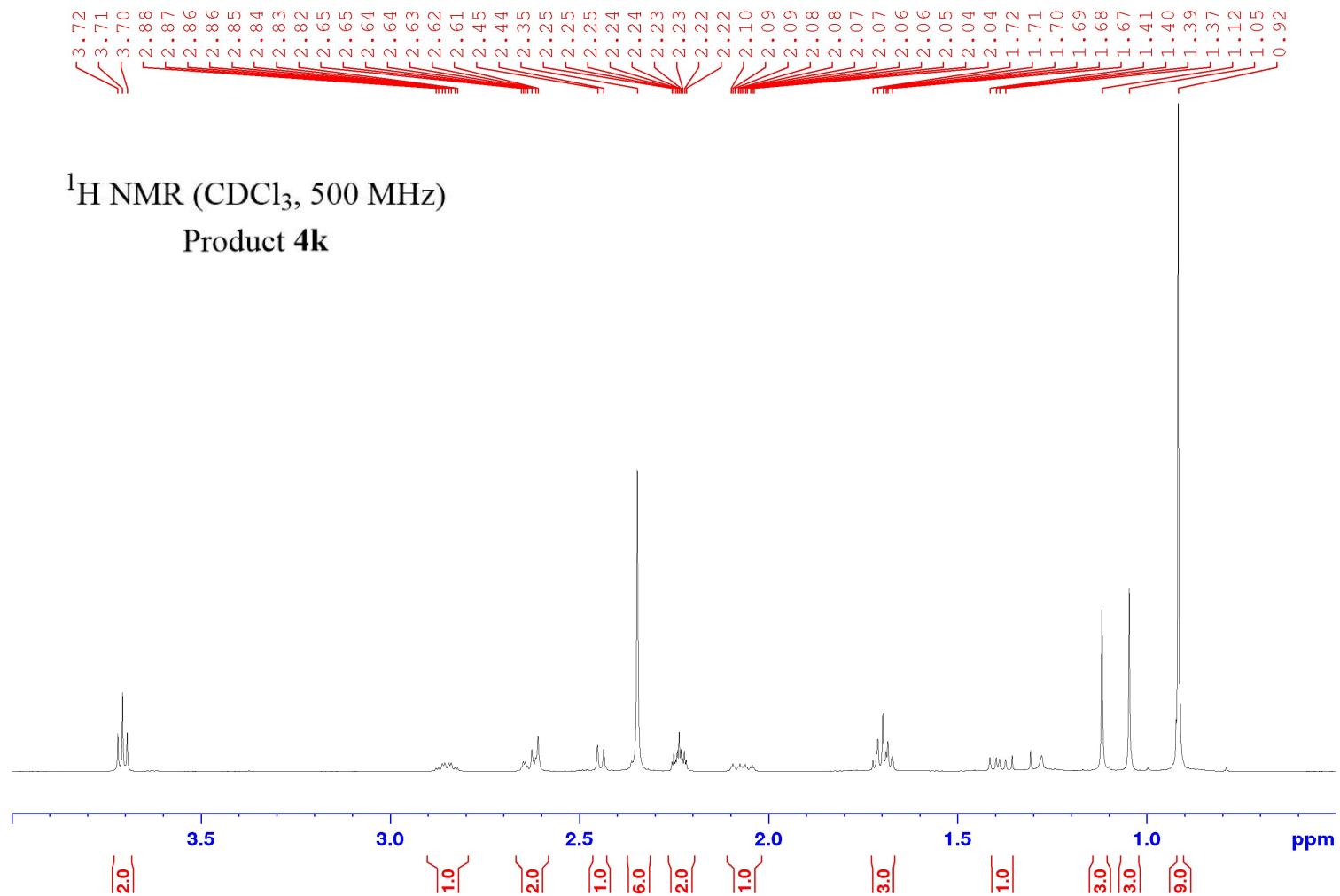


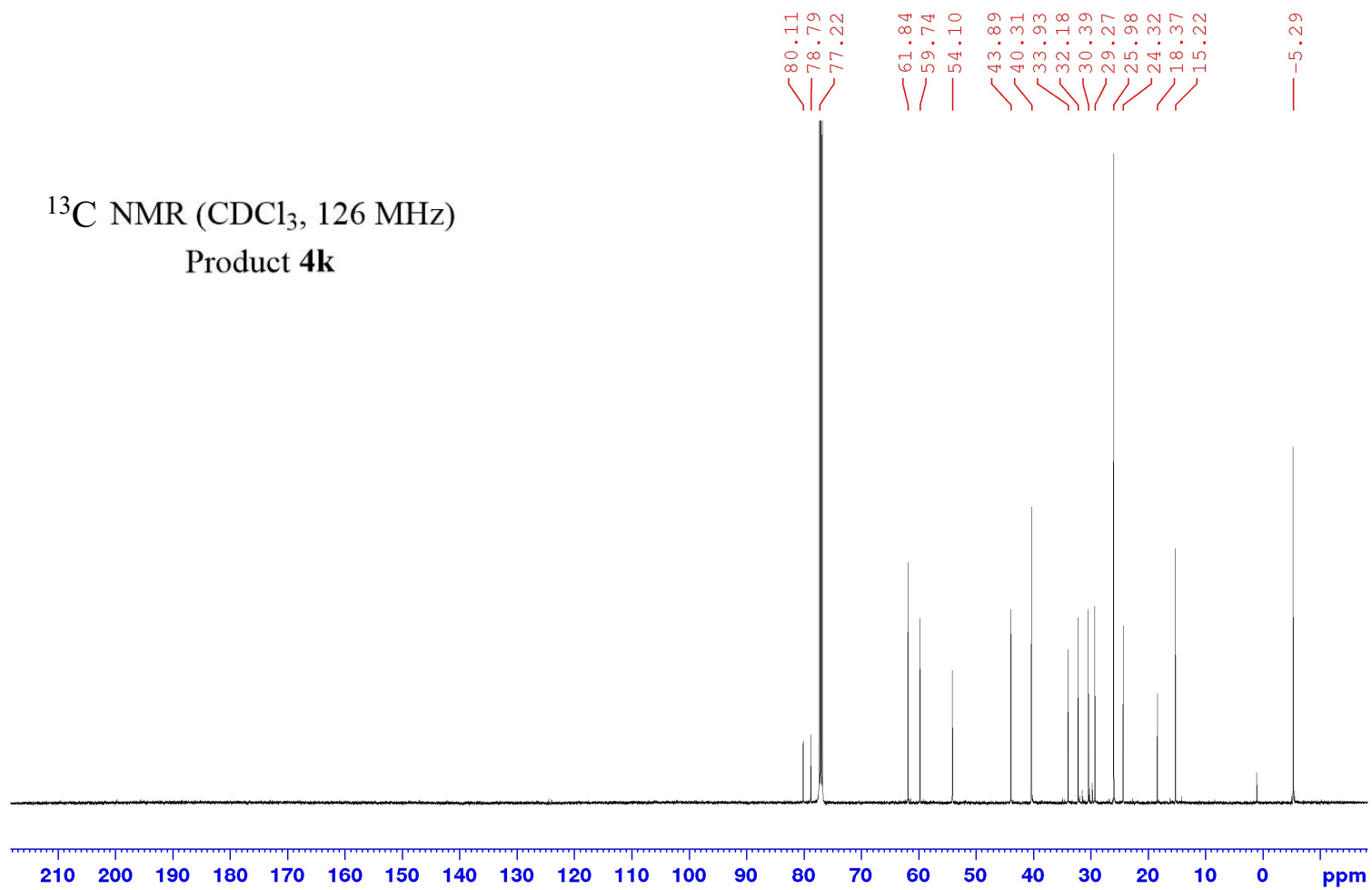


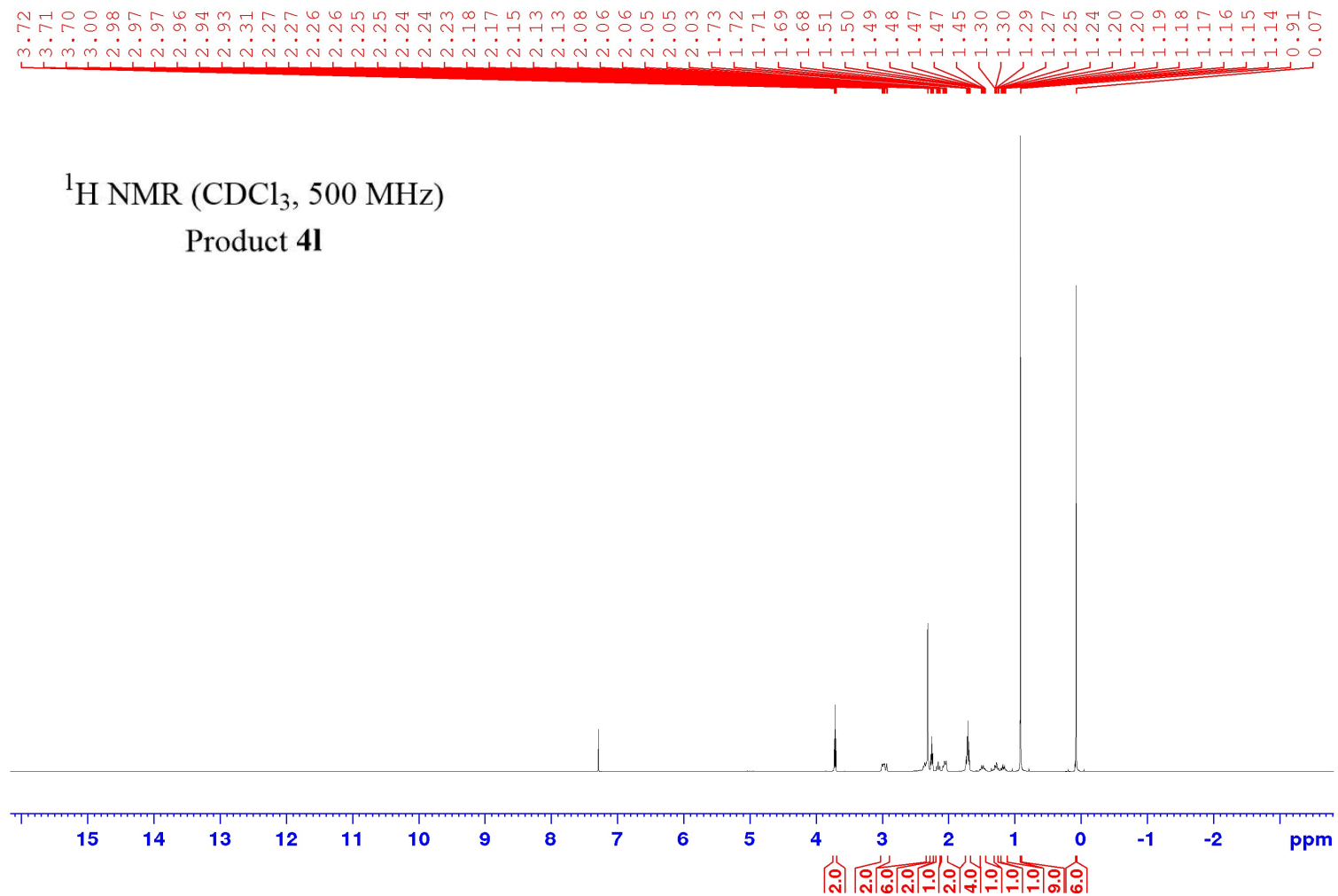
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Product **4k**

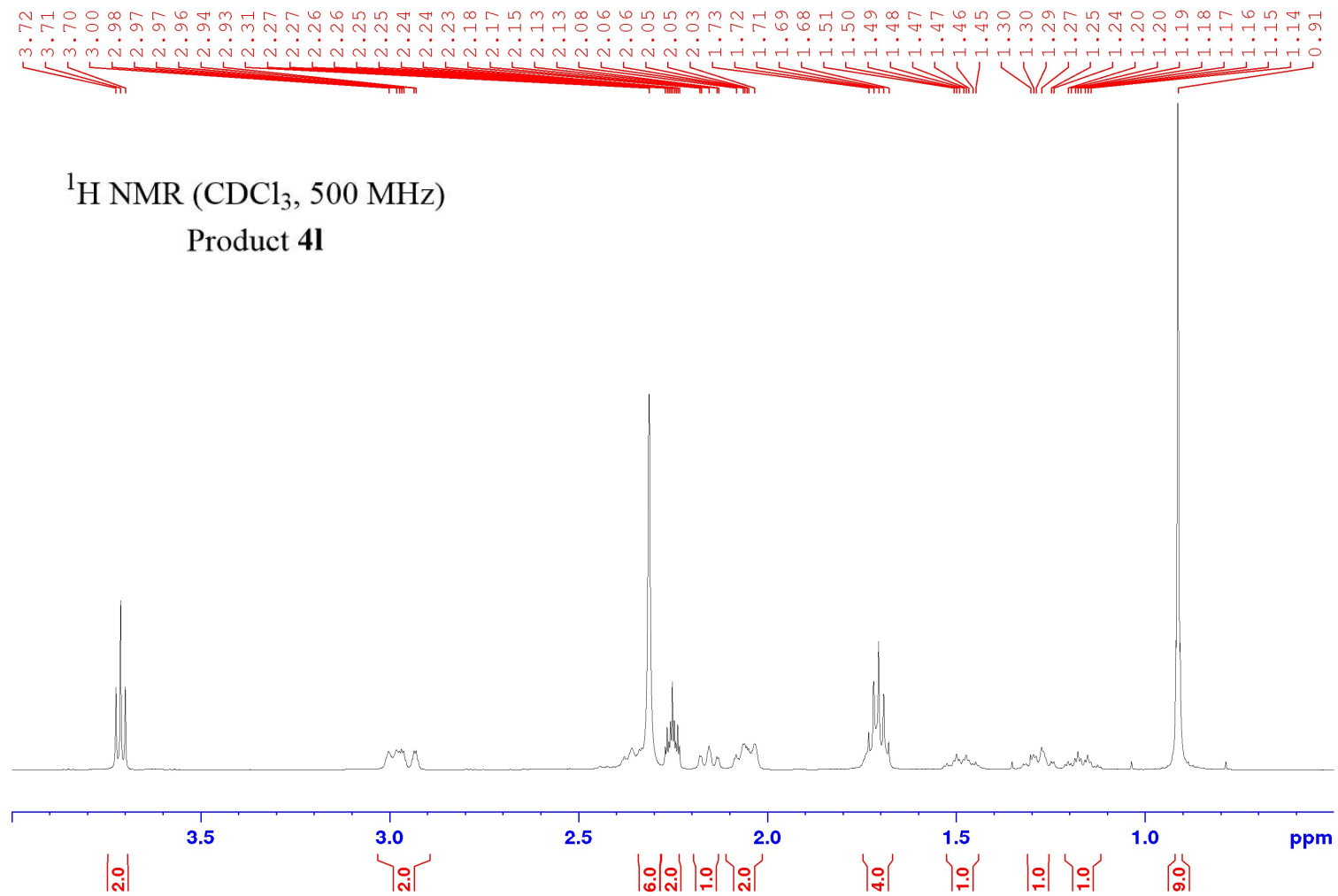
Chemical shifts (ppm): 3.72, 3.71, 3.70, 2.88, 2.87, 2.86, 2.86, 2.85, 2.84, 2.83, 2.82, 2.65, 2.65, 2.64, 2.64, 2.63, 2.62, 2.61, 2.45, 2.44, 2.35, 2.25, 2.25, 2.25, 2.24, 2.24, 2.23, 2.23, 2.22, 2.22, 2.10, 2.09, 2.08, 2.08, 2.07, 2.07, 2.06, 2.06, 2.05, 2.04, 2.04, 1.72, 1.71.

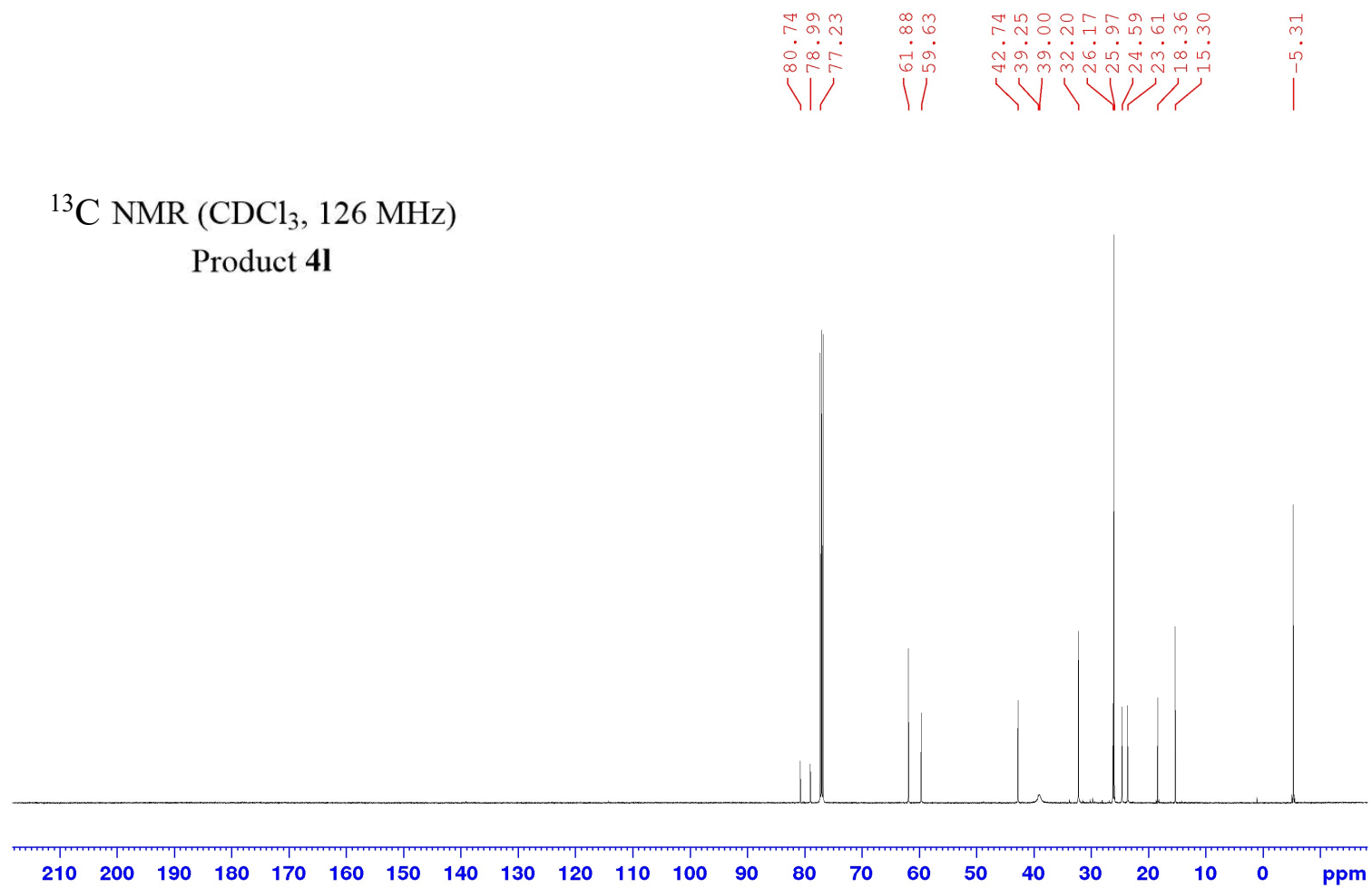
Integrations: 2.0, 1.0, 2.0, 1.0, 6.0, 2.0, 1.0, 3.0, 1.0, 3.0, 9.0, 6.0.

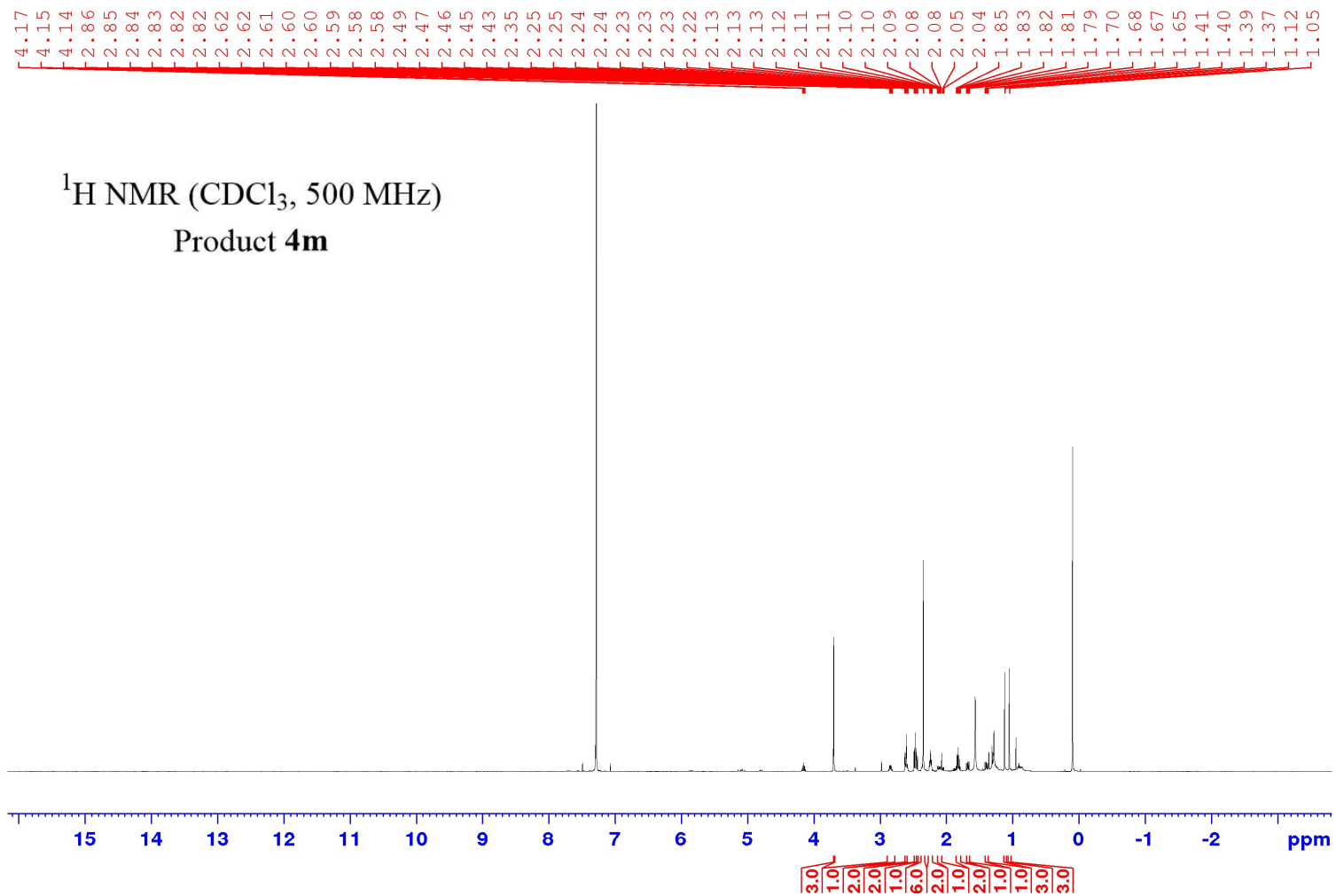


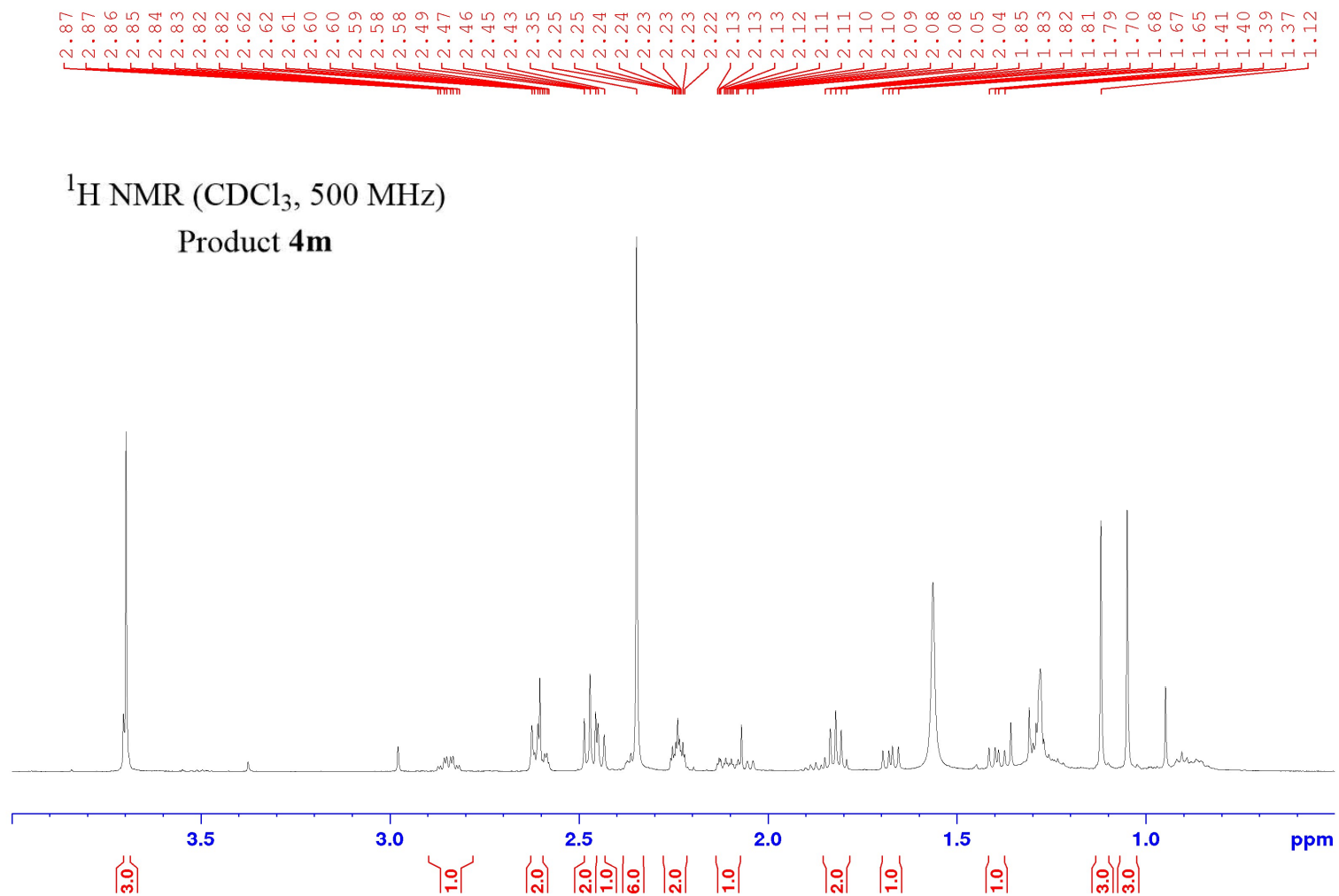


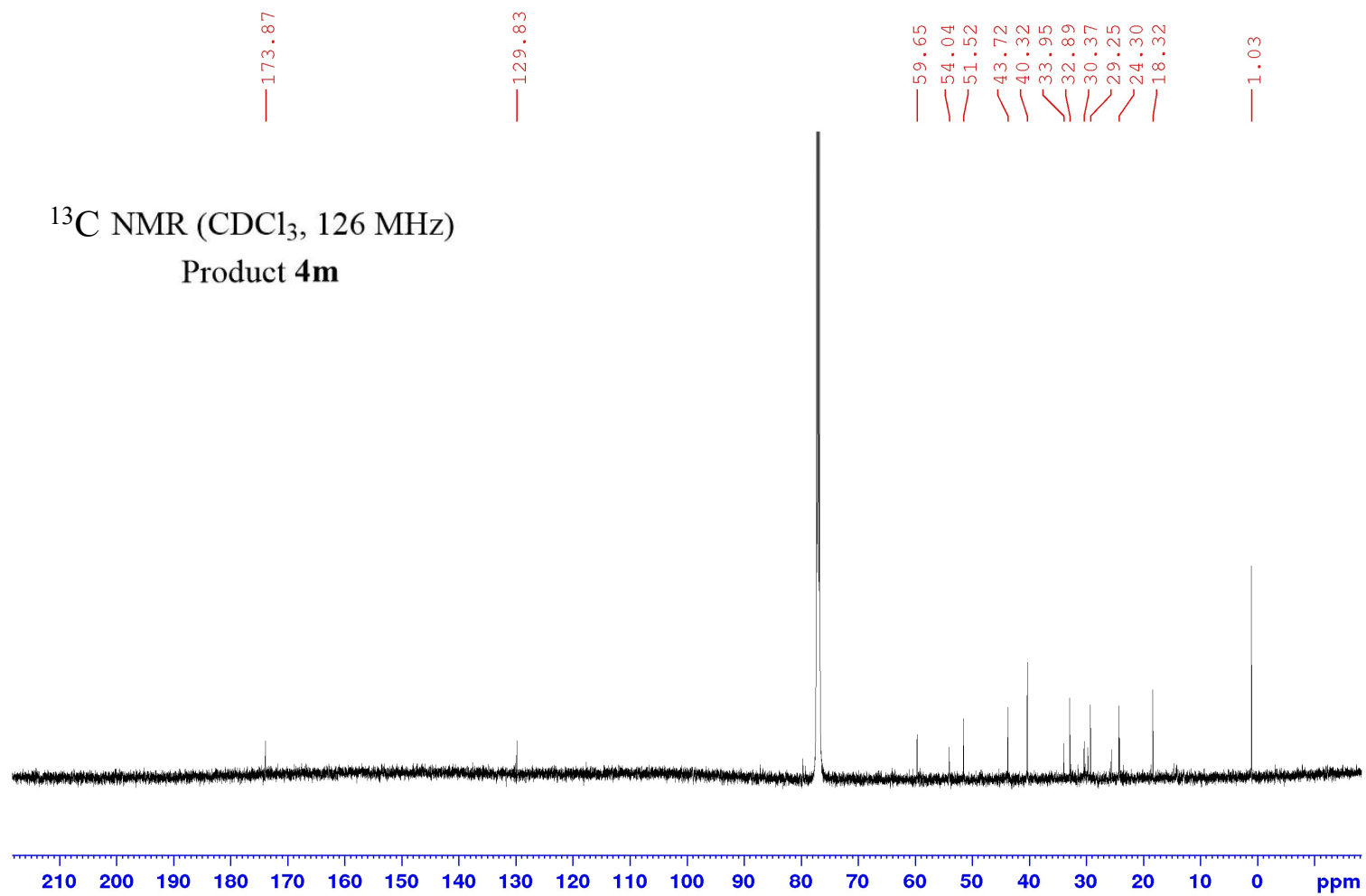


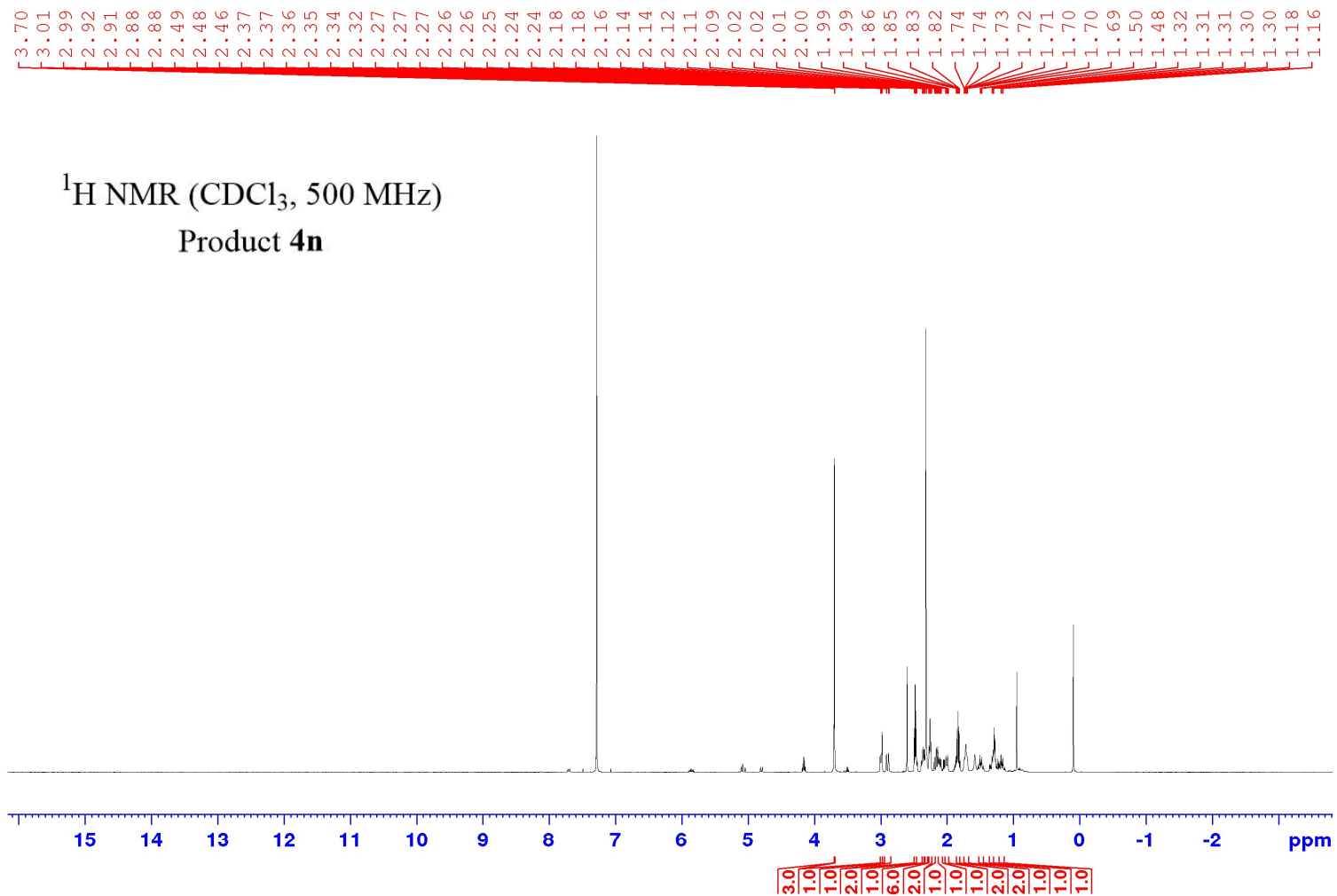


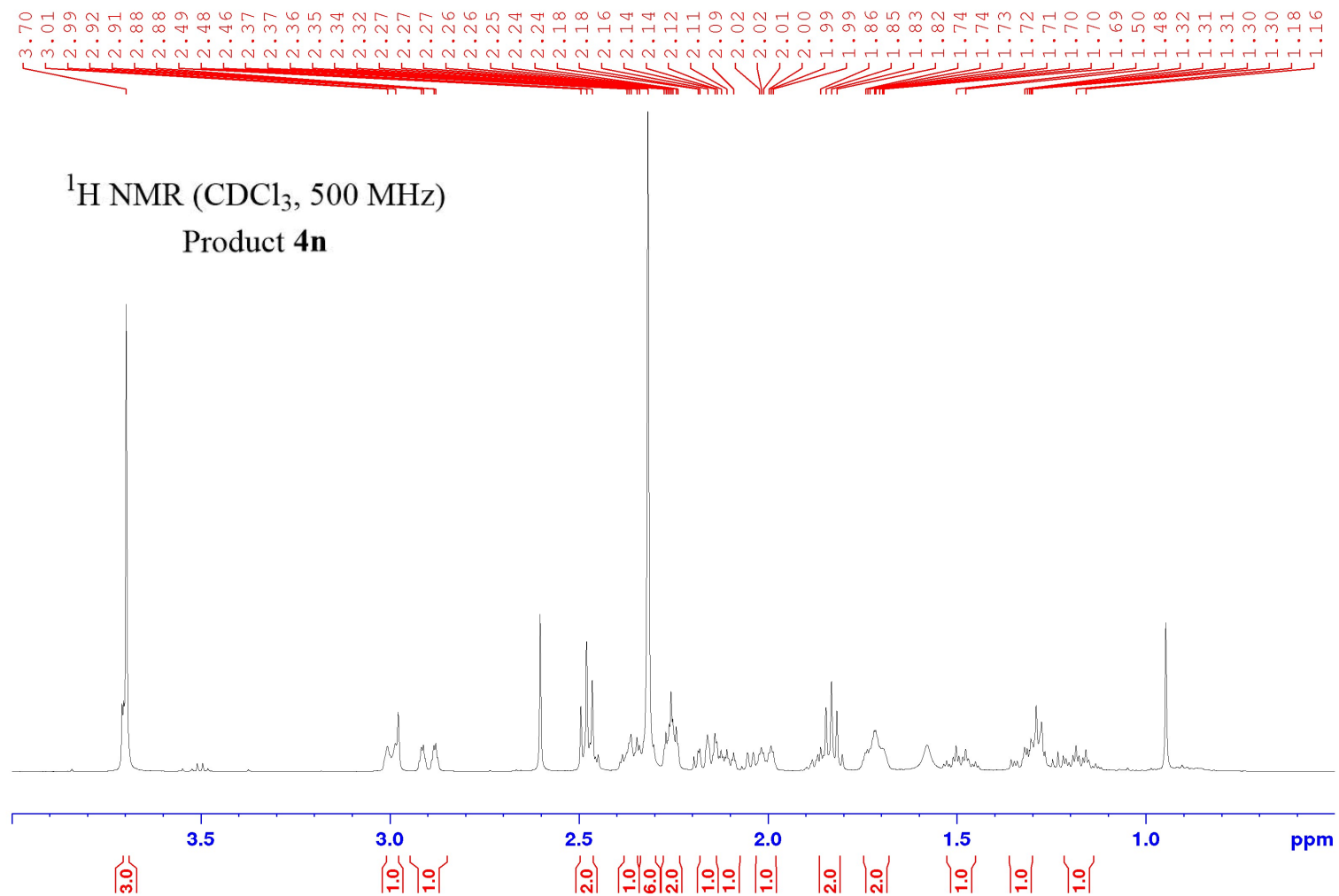






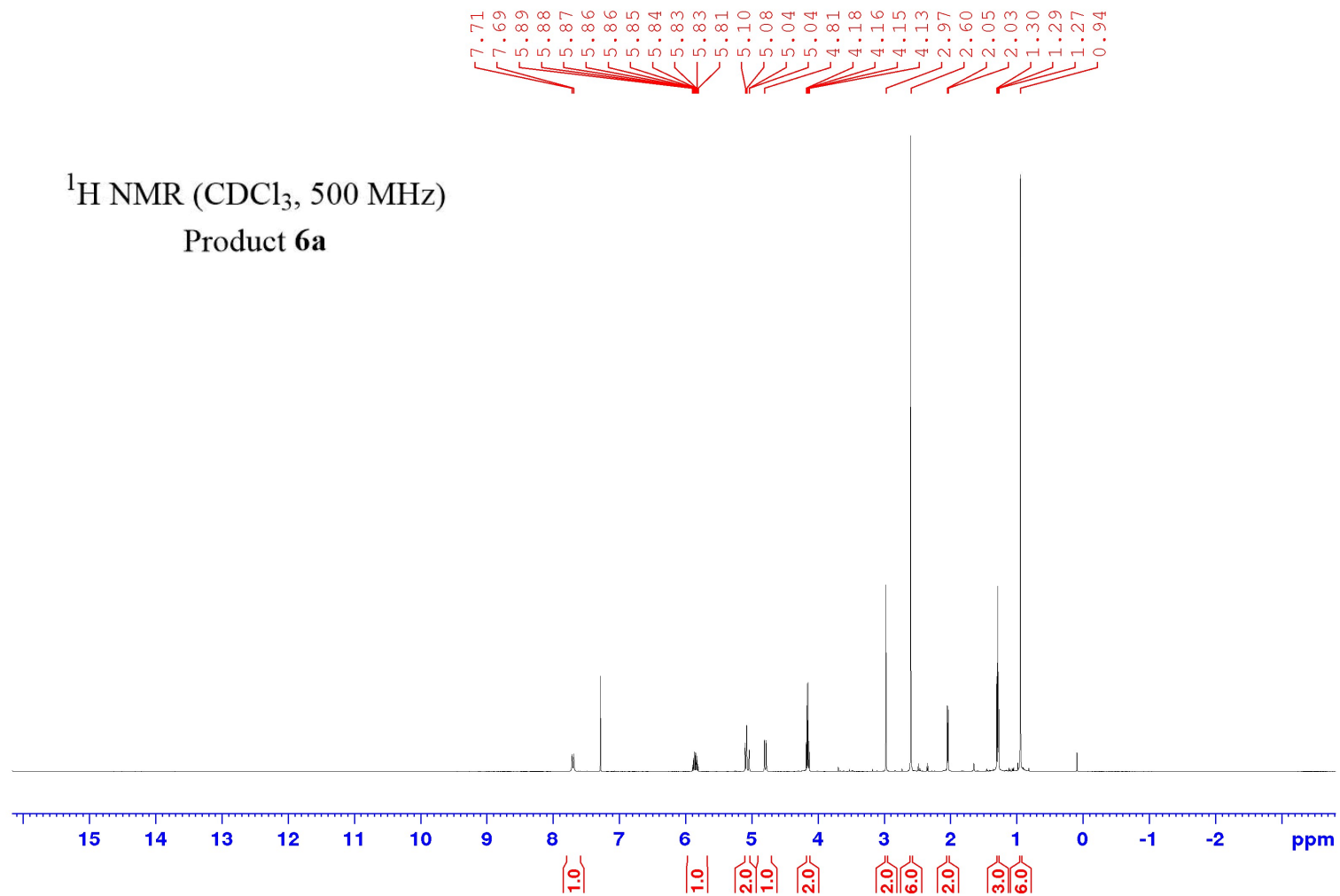


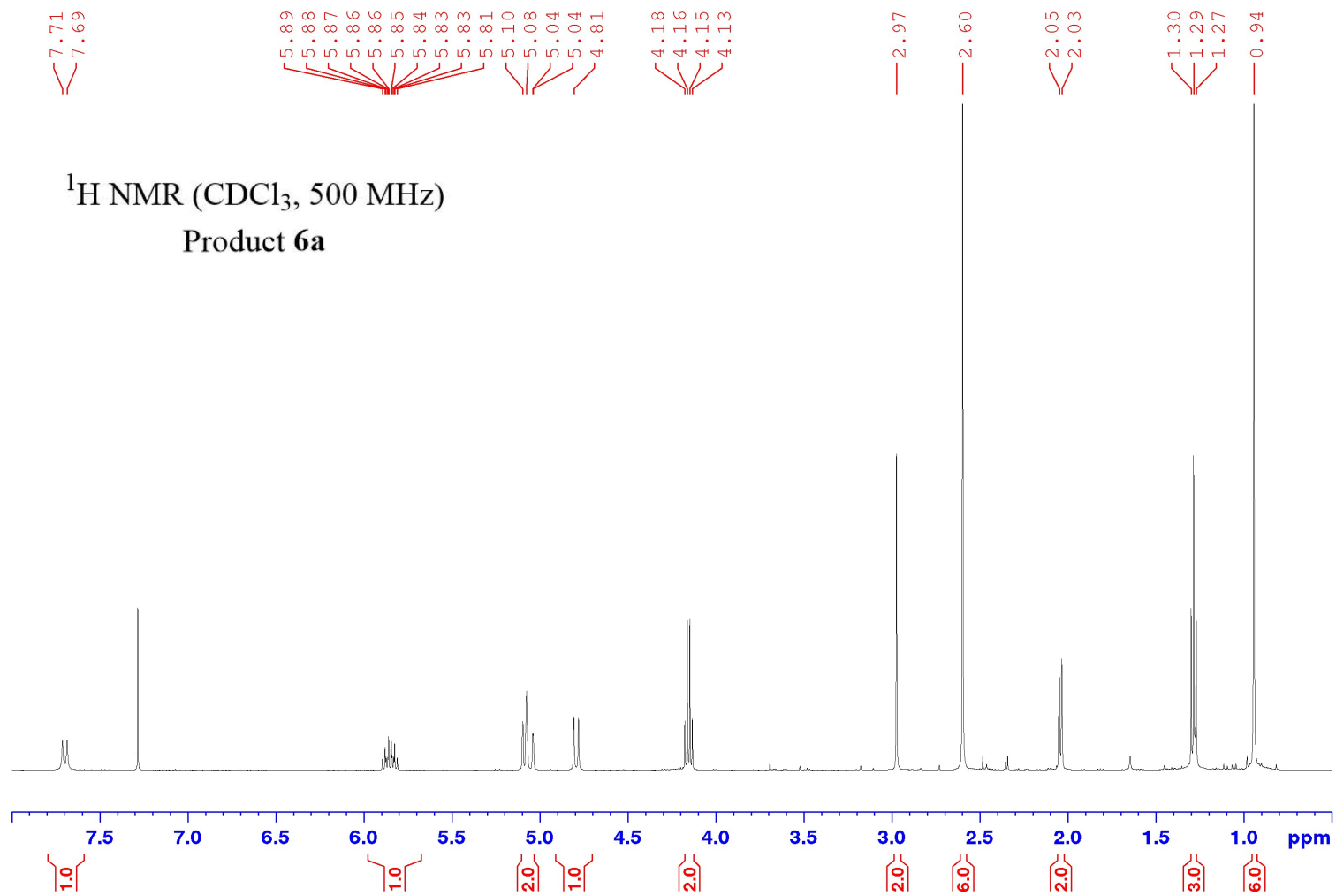


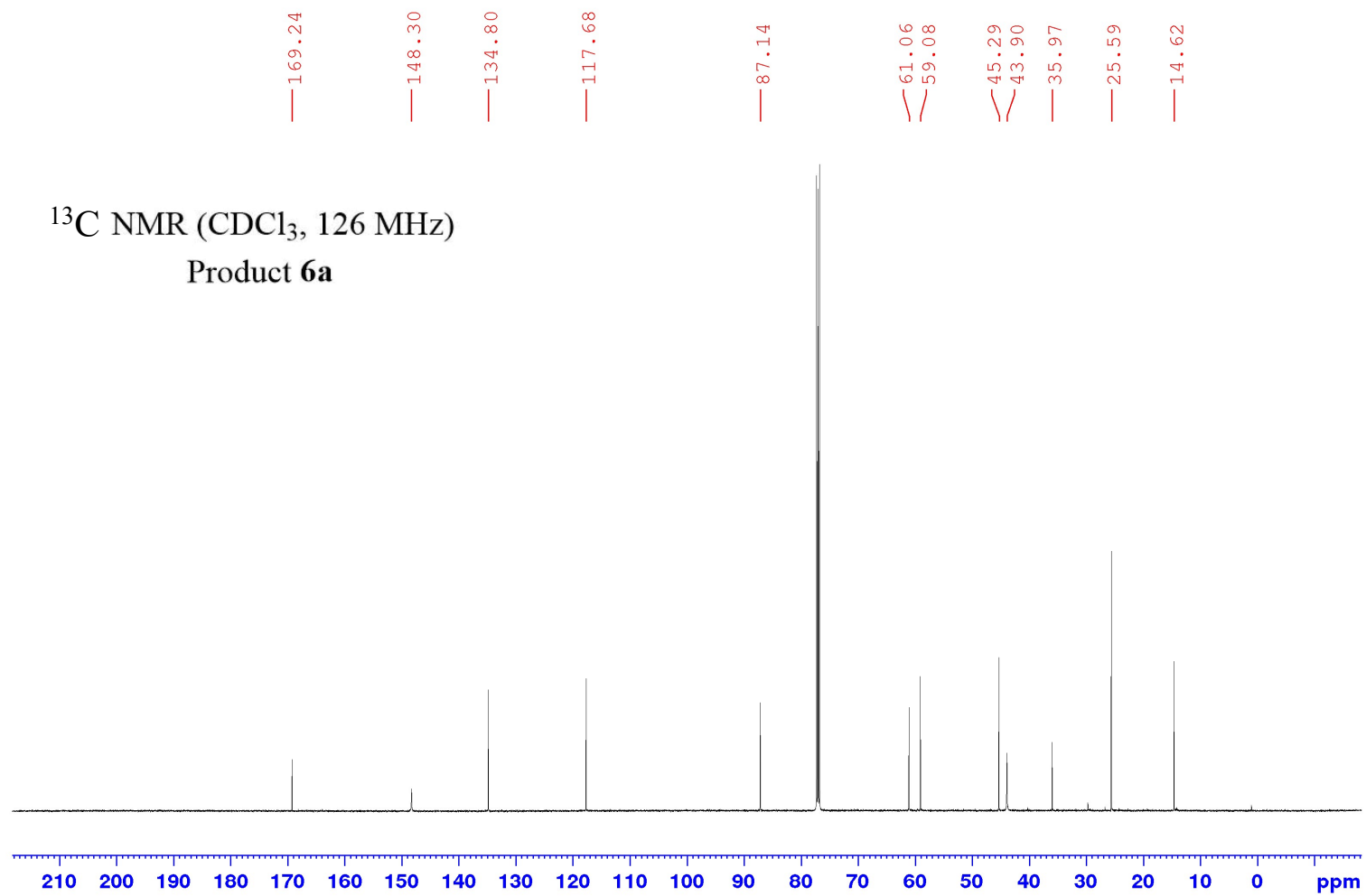


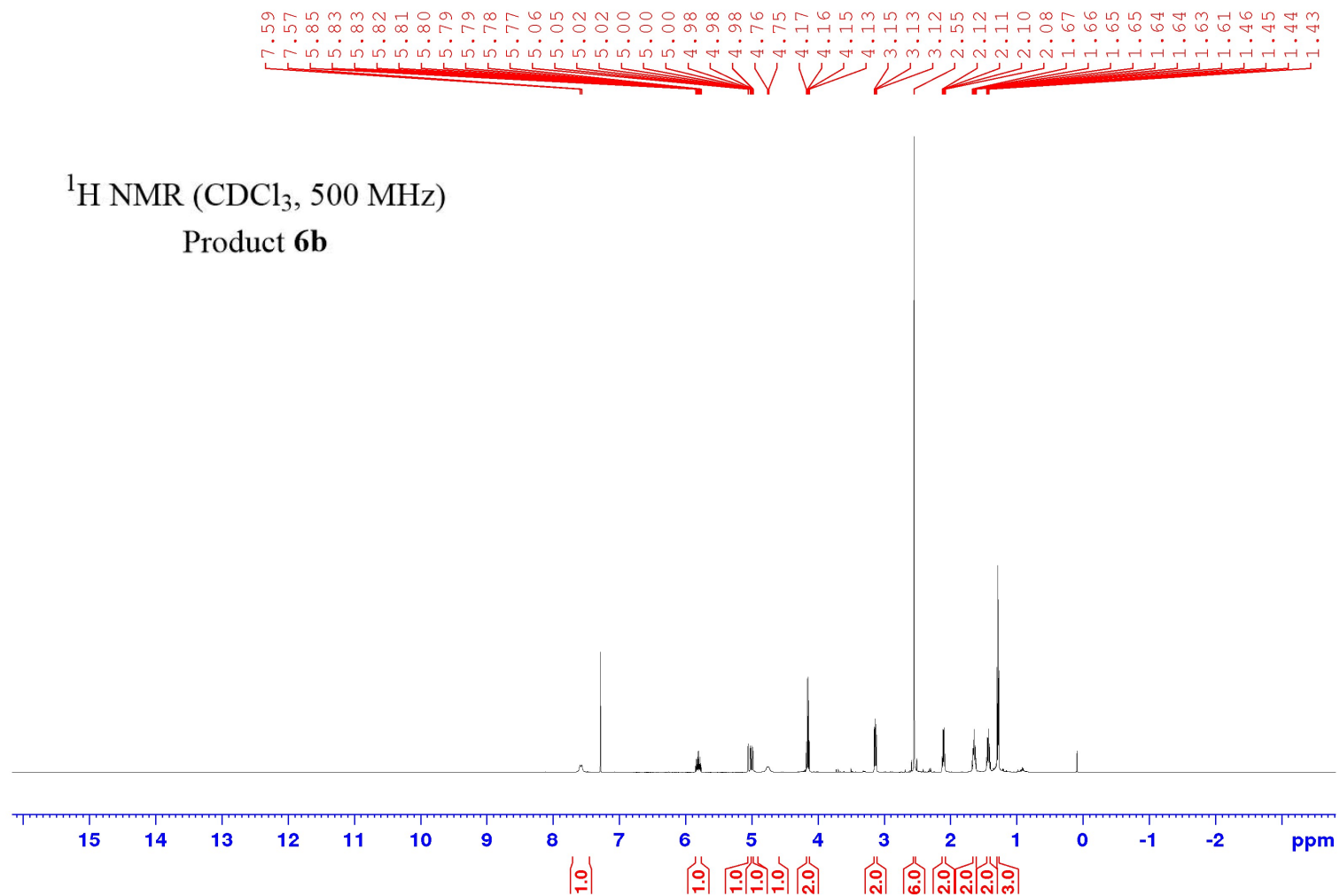
^{13}C NMR (CDCl_3 , 126 MHz)
Product **4n**

Chemical shift values (ppm): 173.90, 79.91, 59.50, 51.52, 42.73, 32.95, 32.16, 26.16, 25.59, 24.58, 24.36, 23.62, 18.42, 1.03.

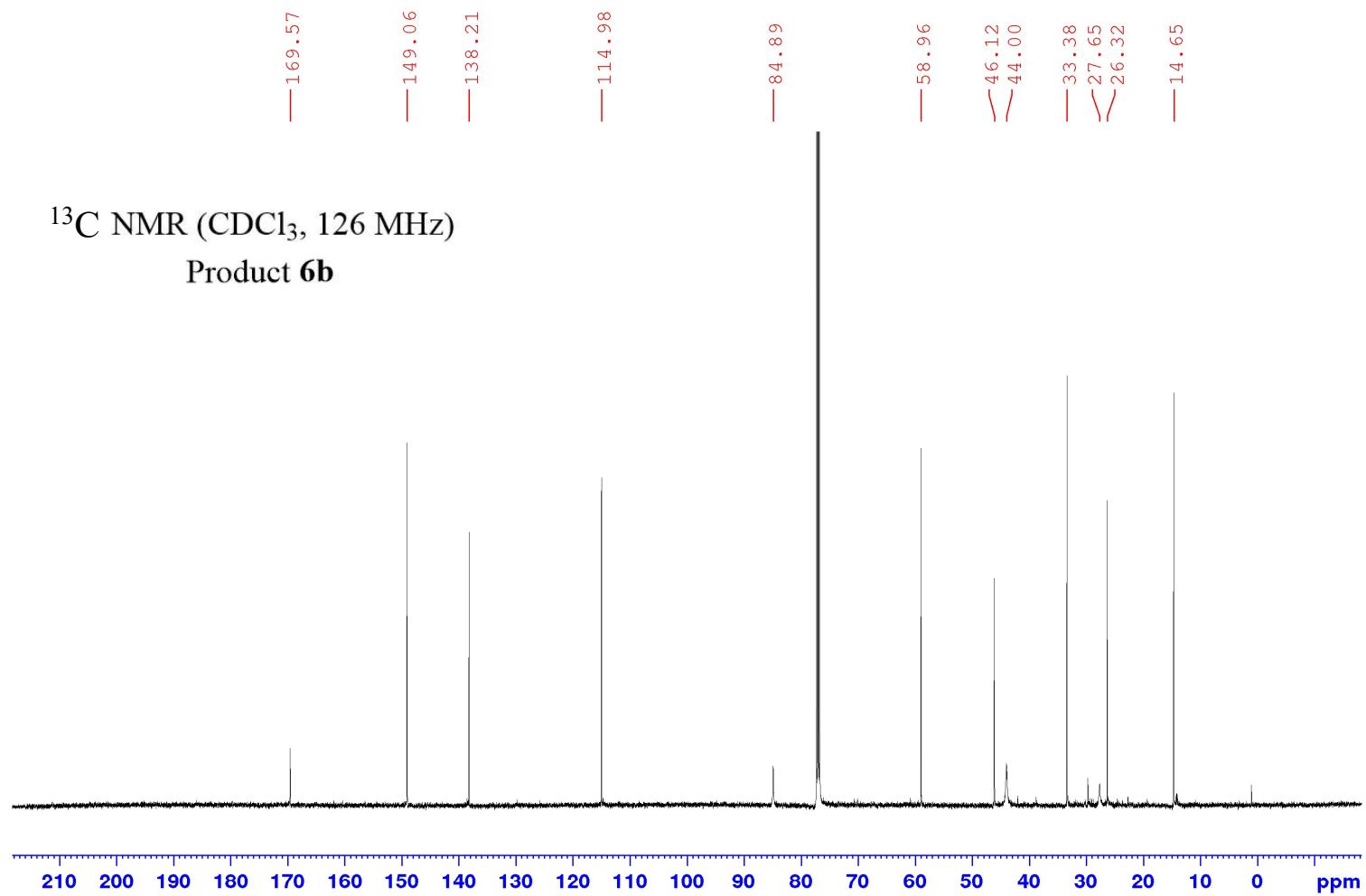












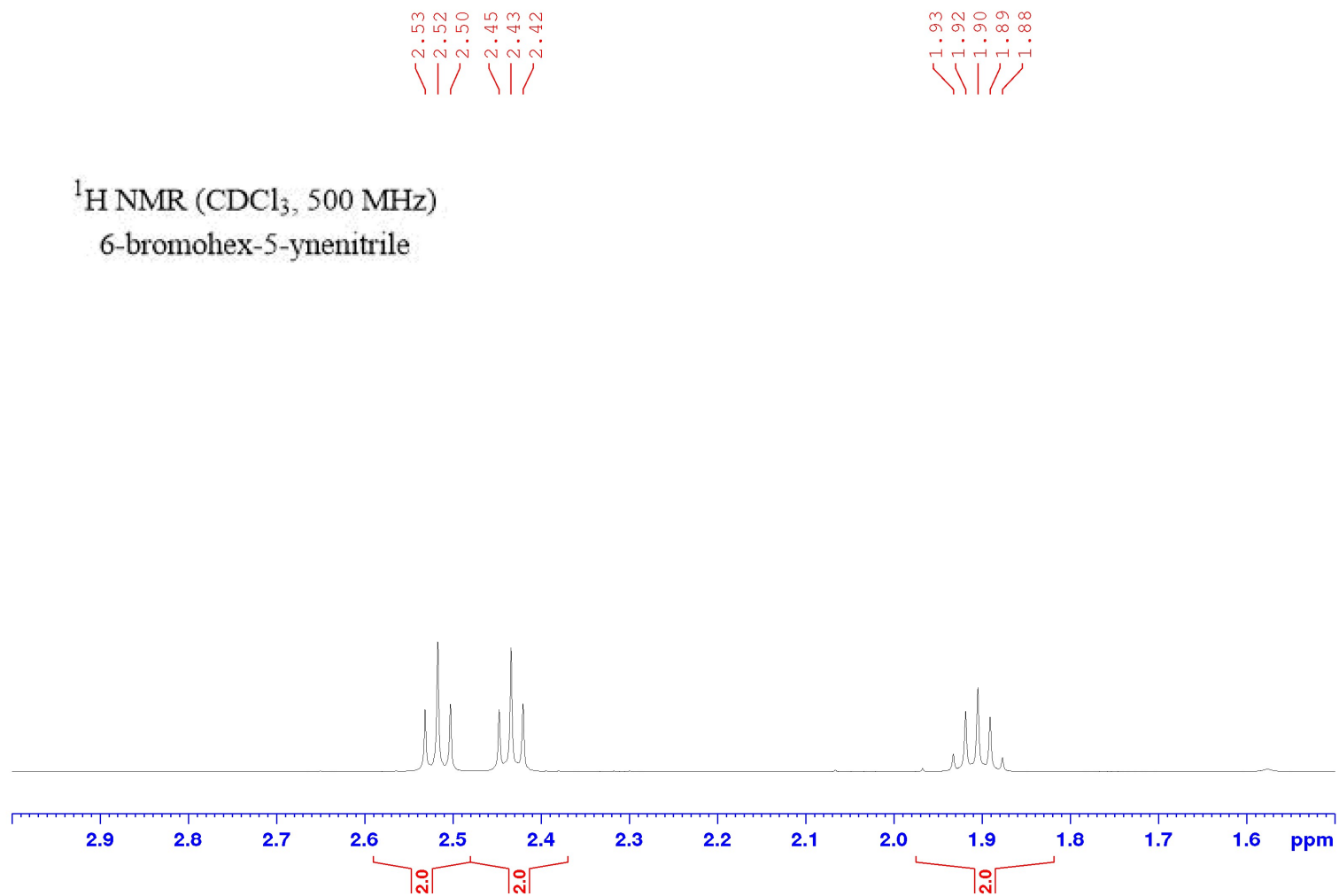
¹H NMR (CDCl₃, 500 MHz)

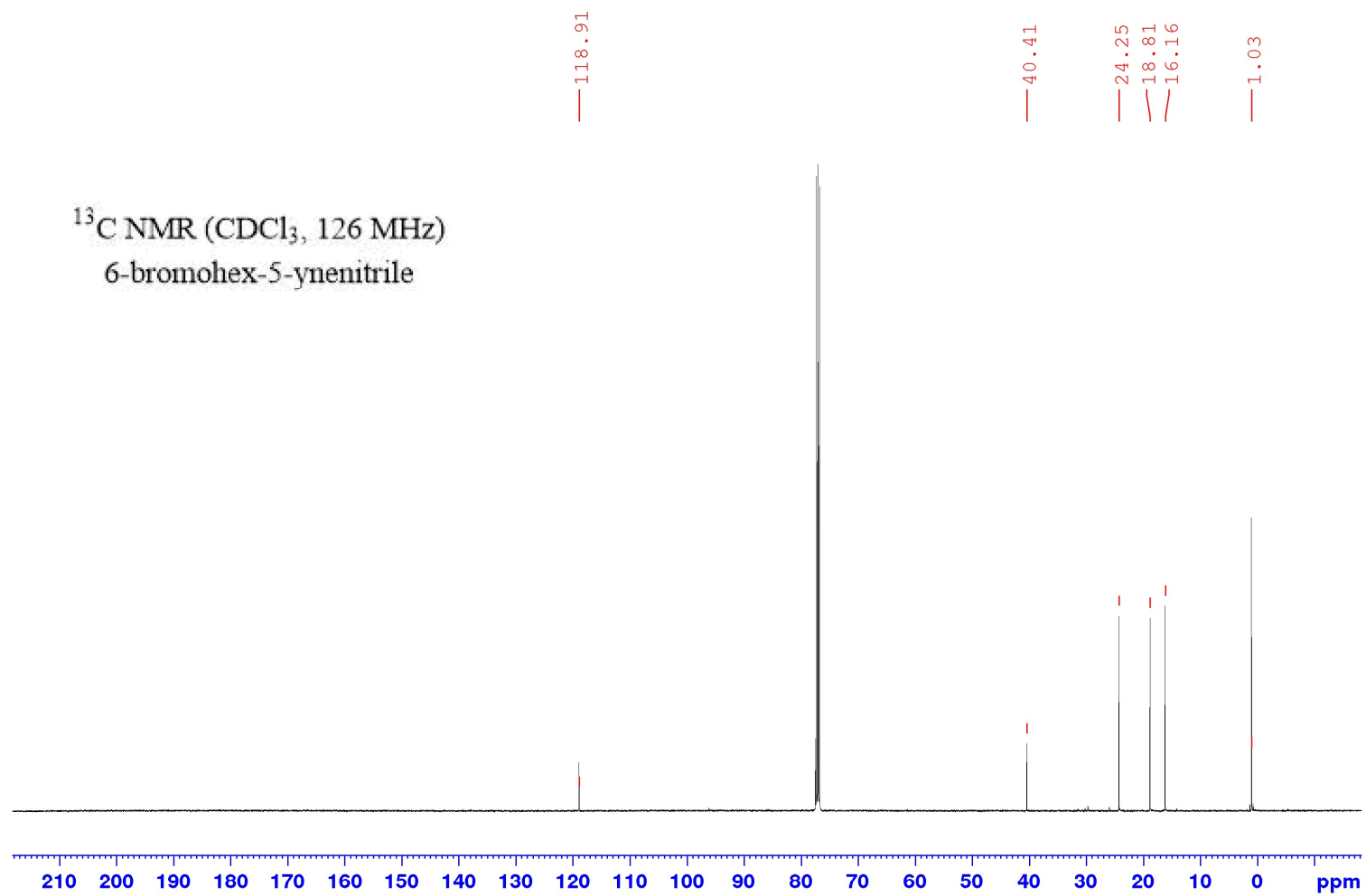
6-bromohex-5-ynenitrile

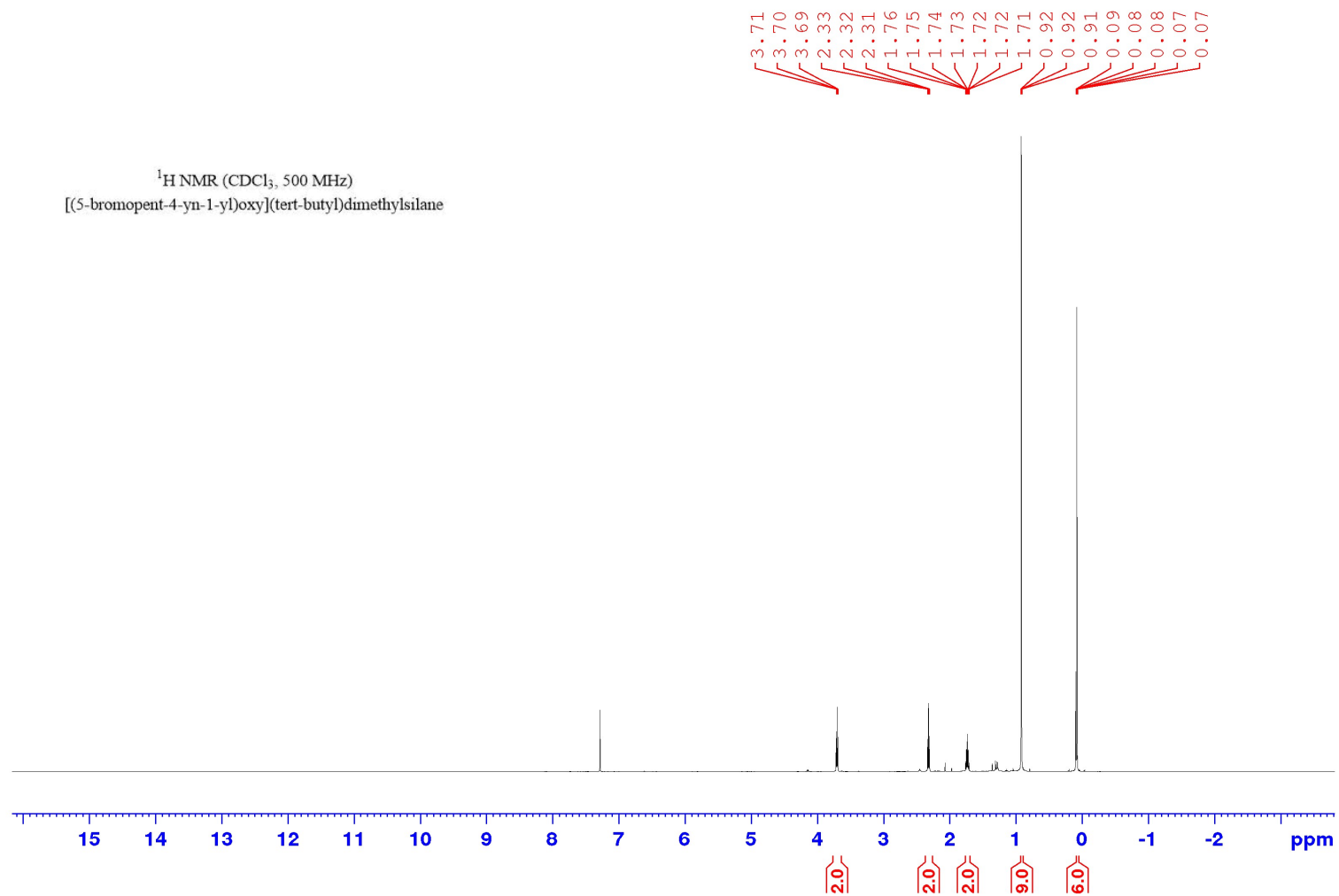
2.53
2.52
2.50
2.45
2.43
2.42
1.93
1.92
1.90
1.89
1.88

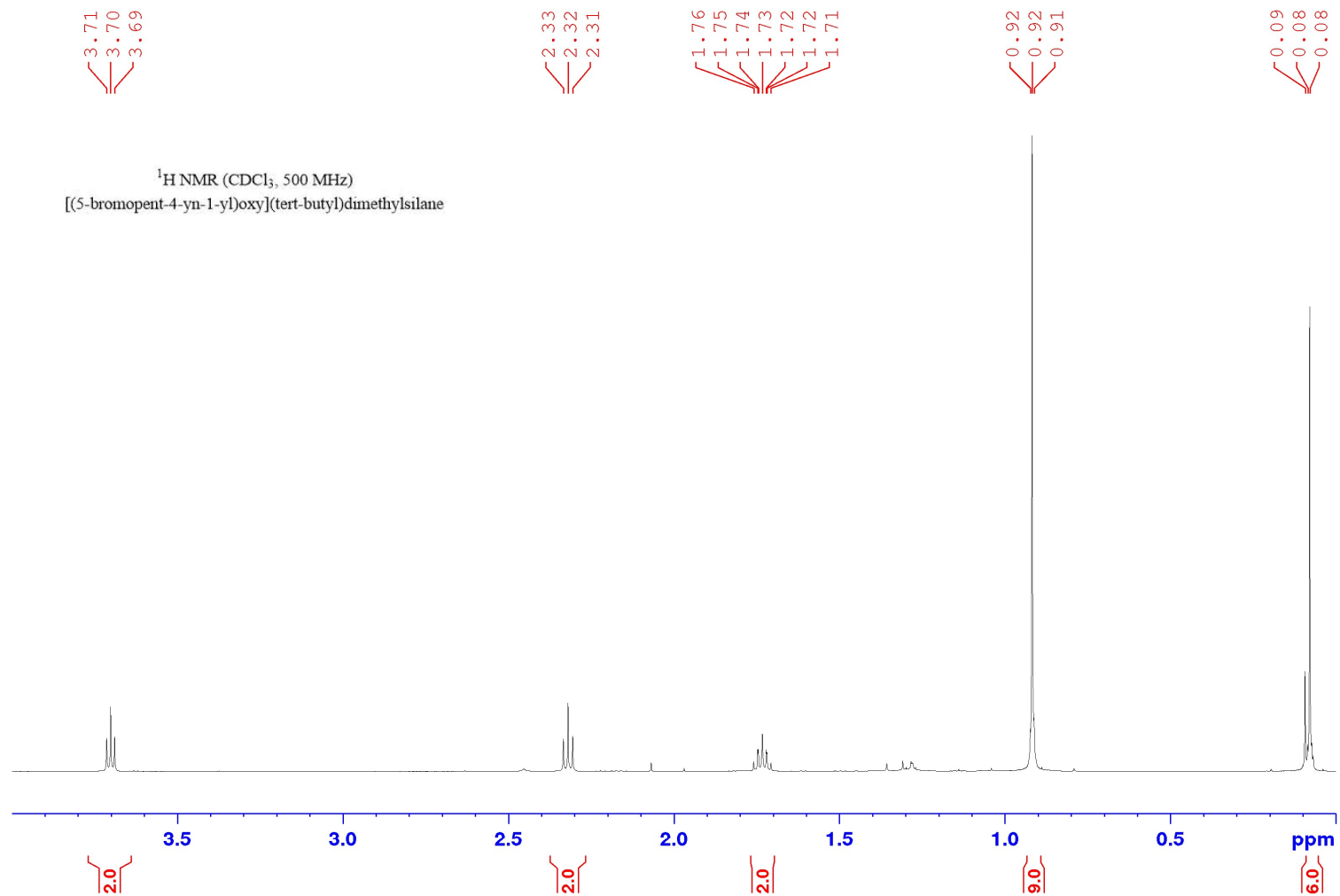
2.00
2.00
2.00
2.00
2.00

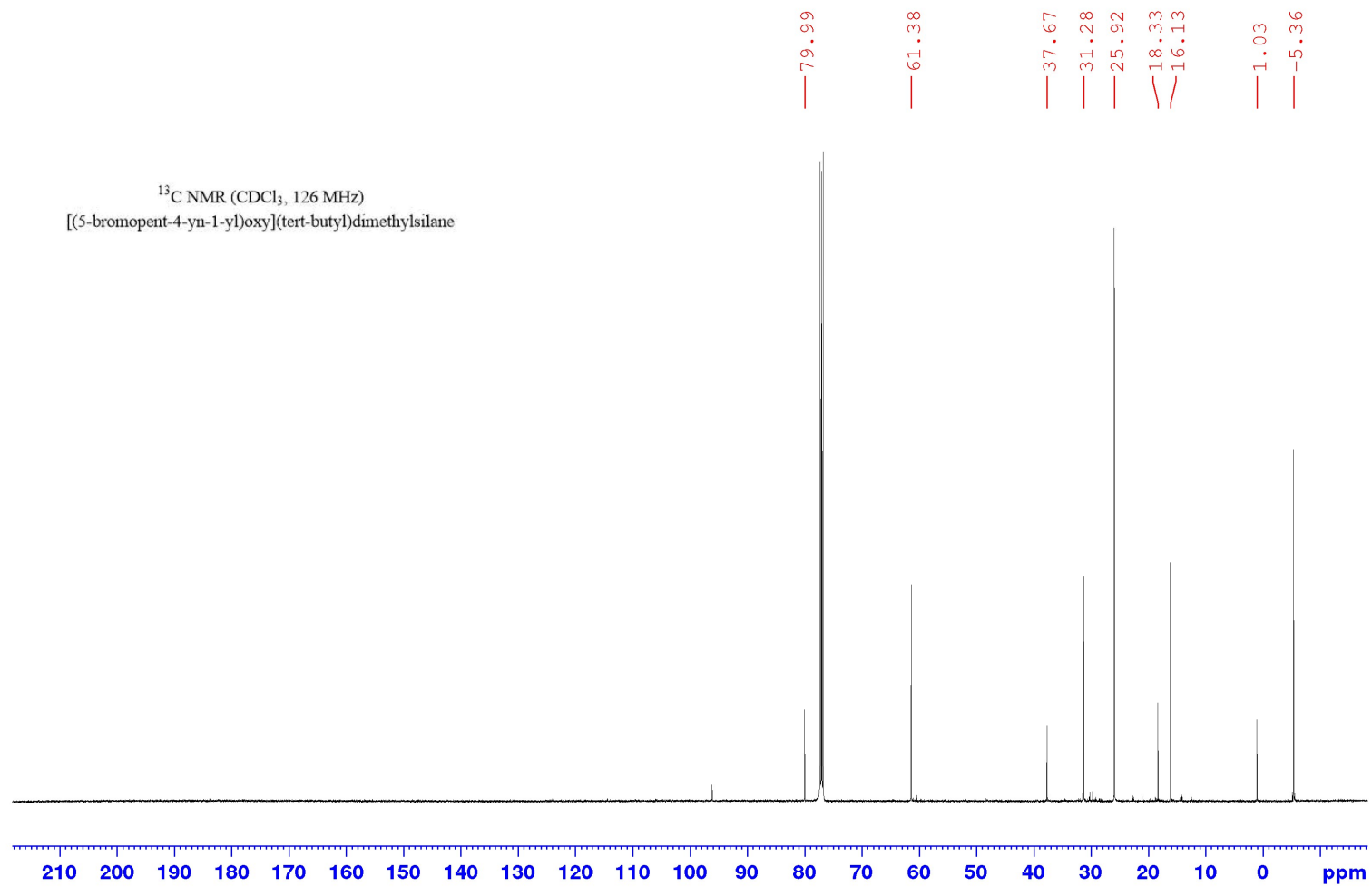
ppm

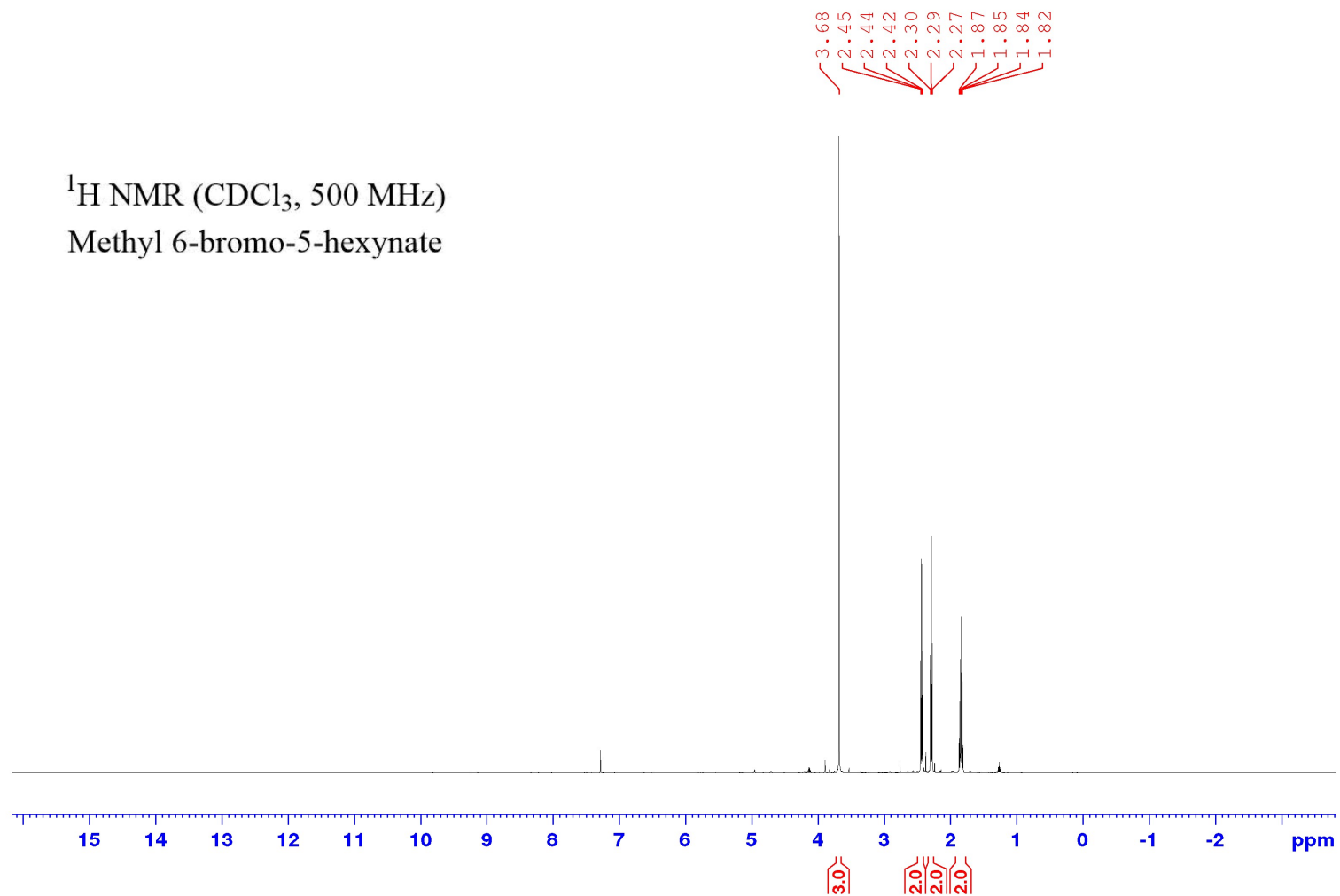


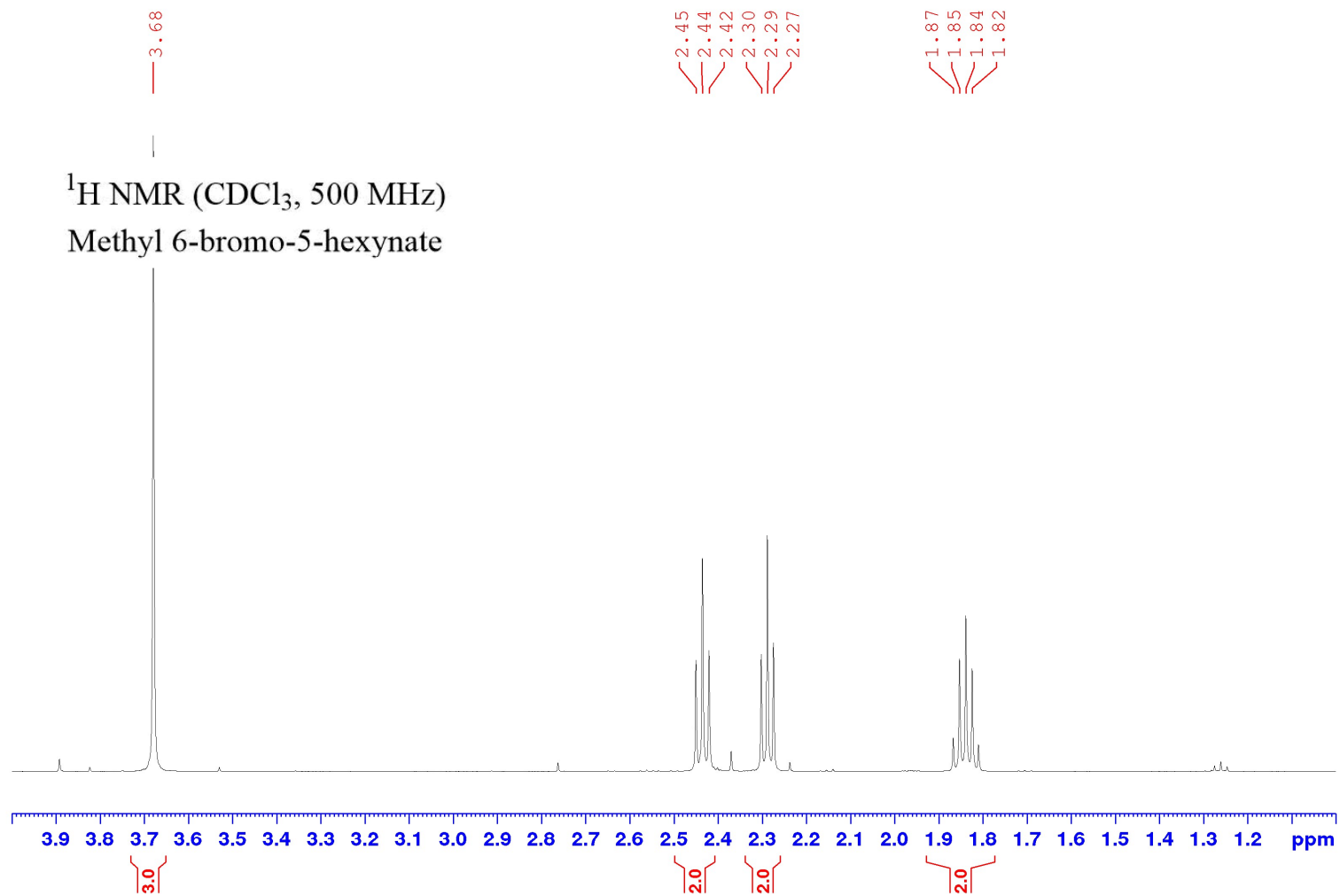


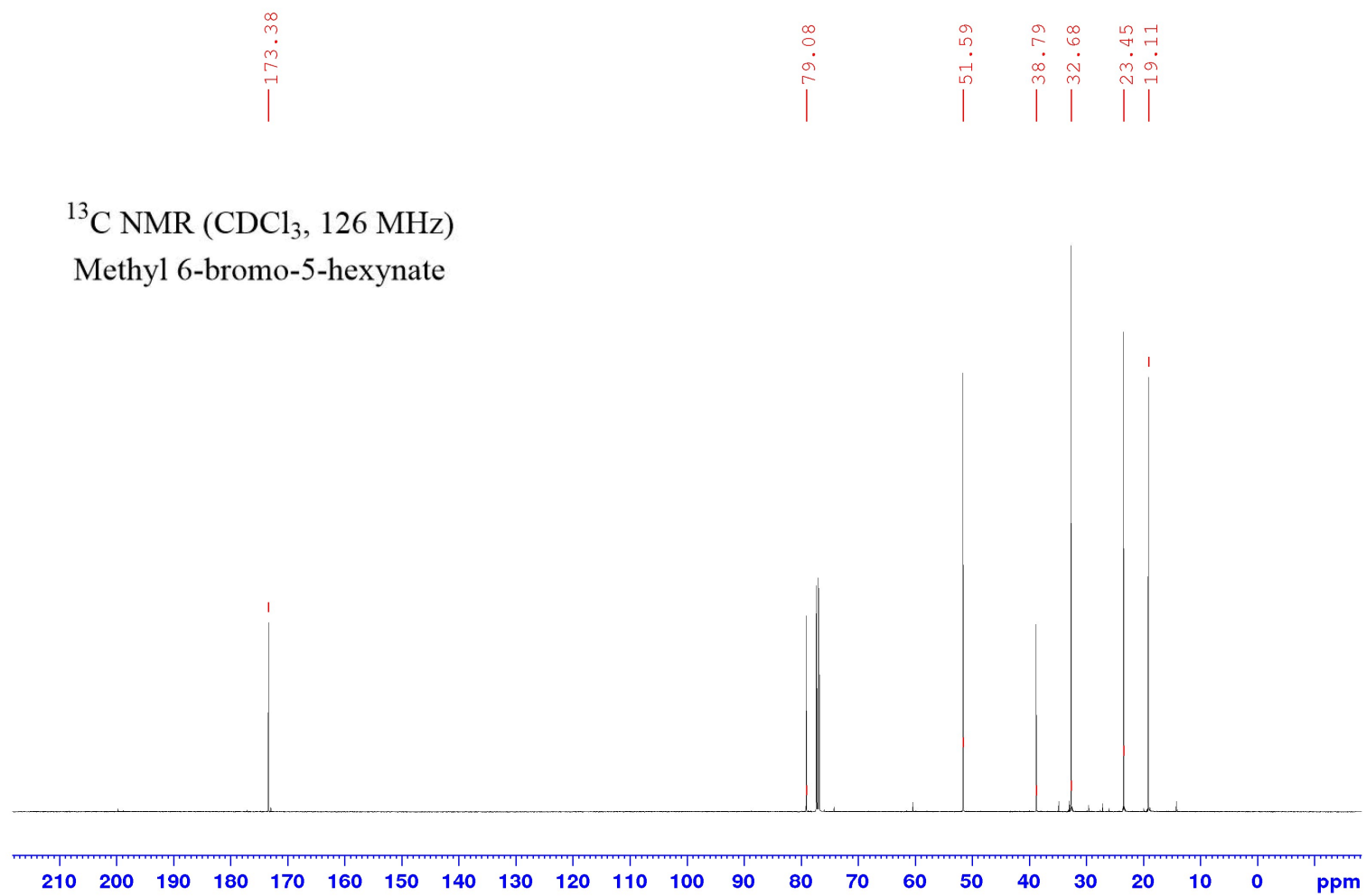




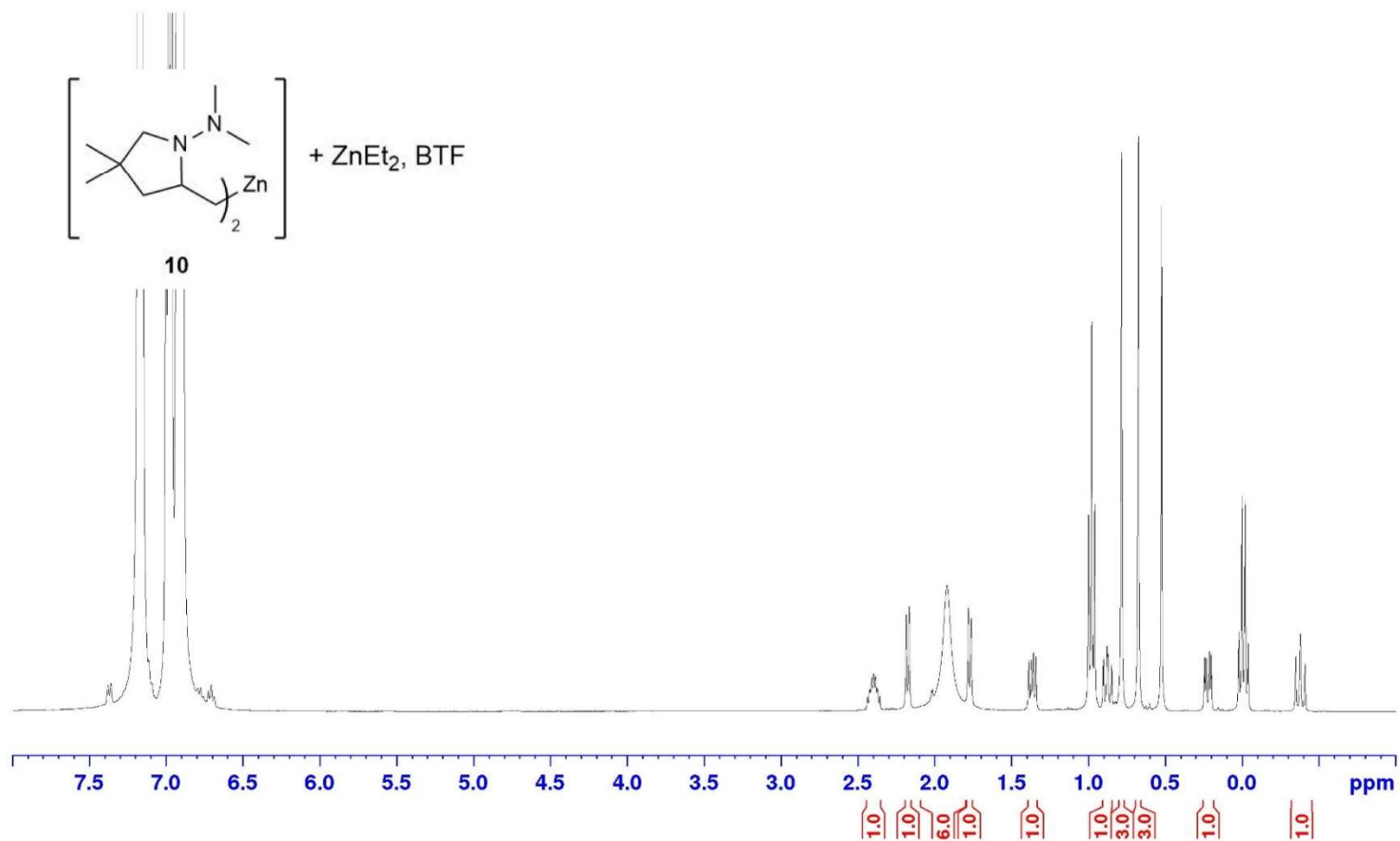


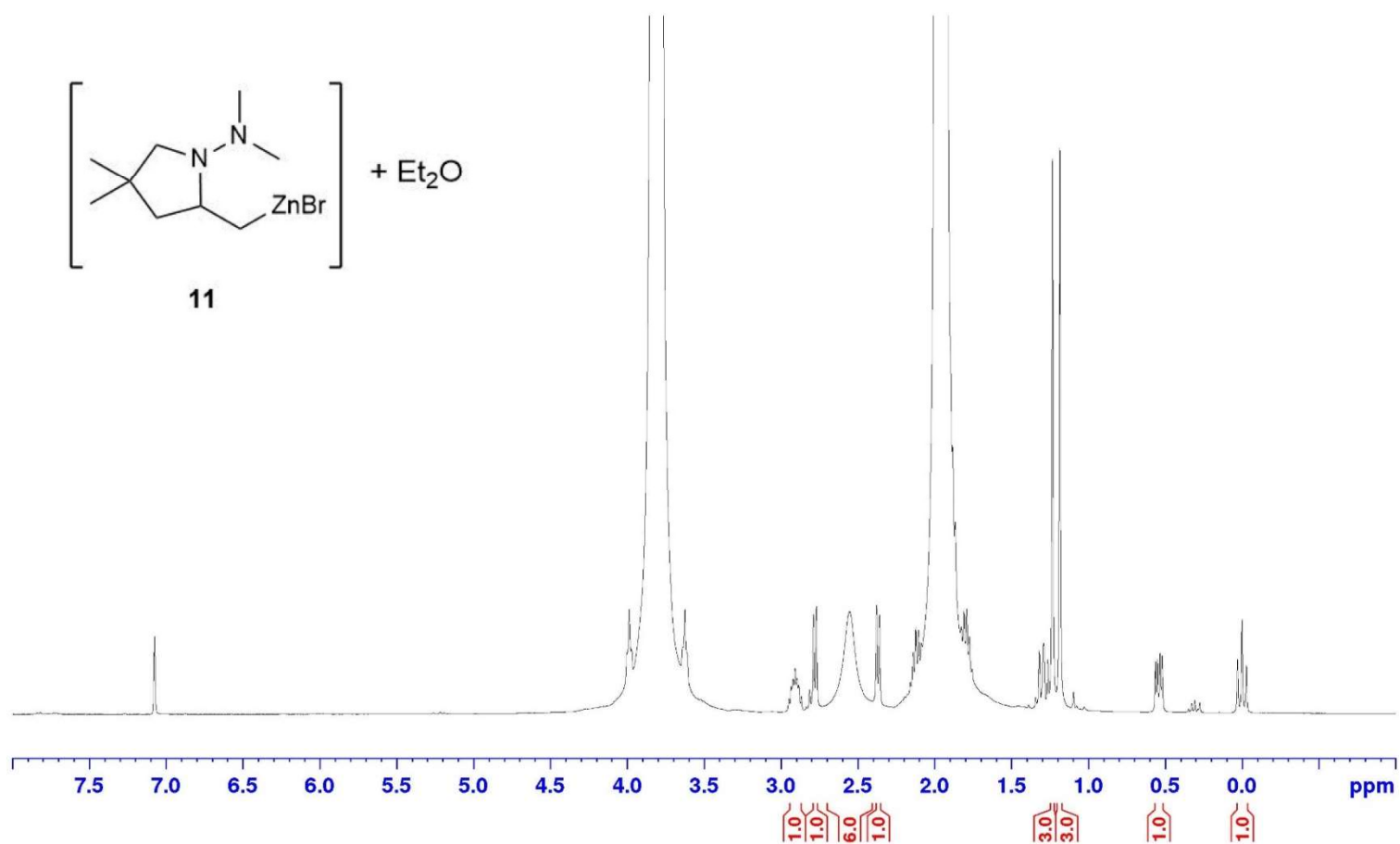


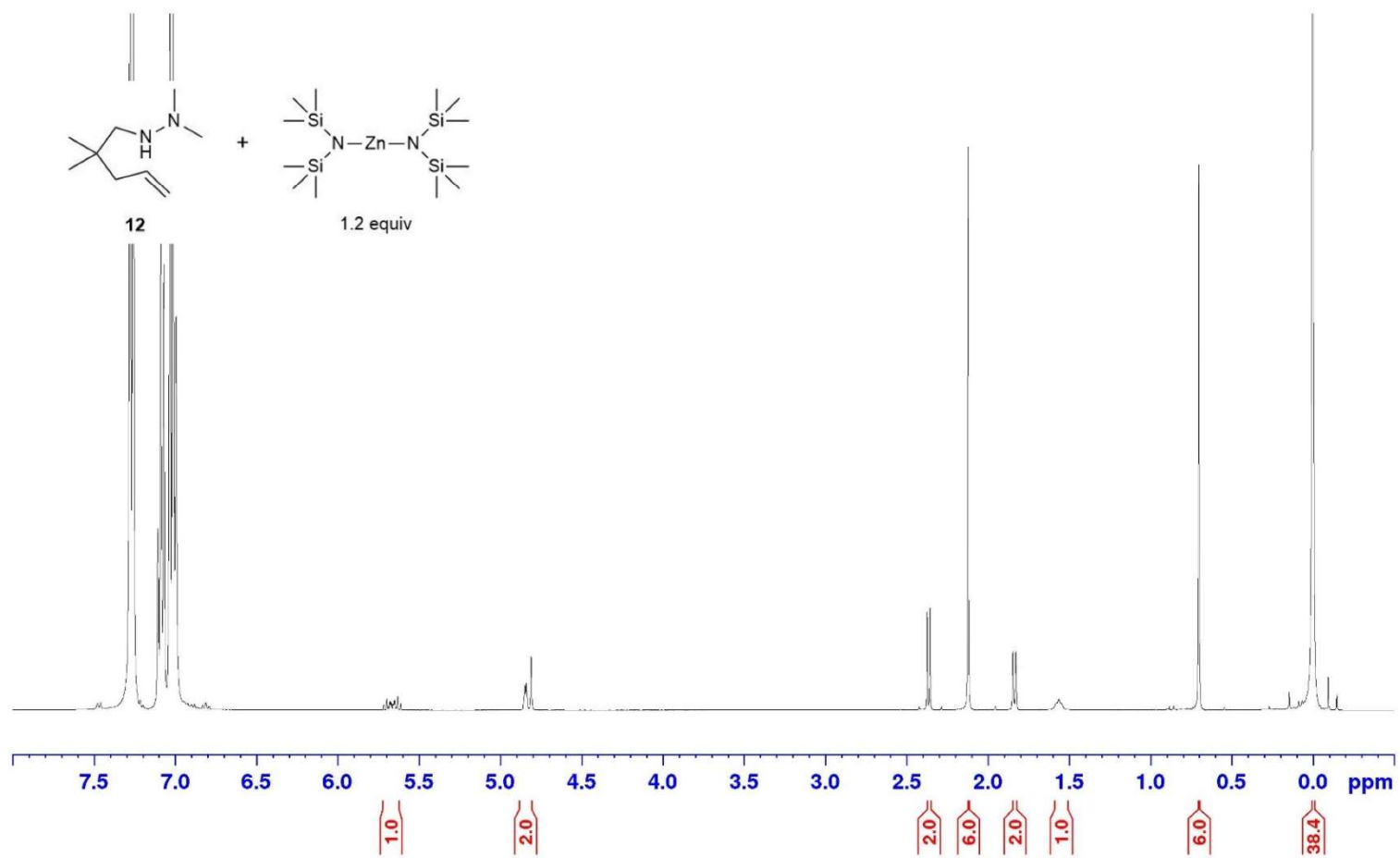


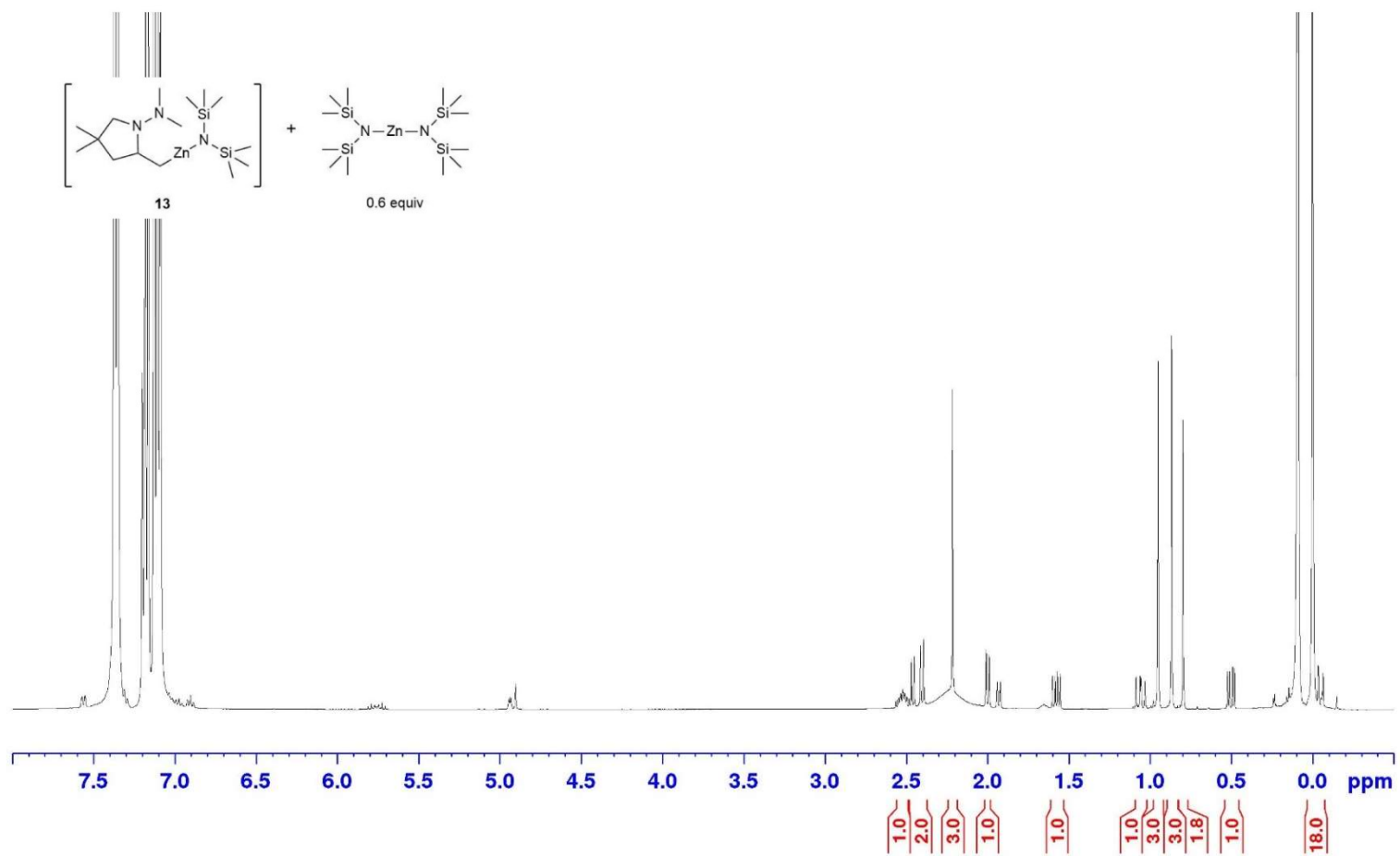


CHAPTER FIVE



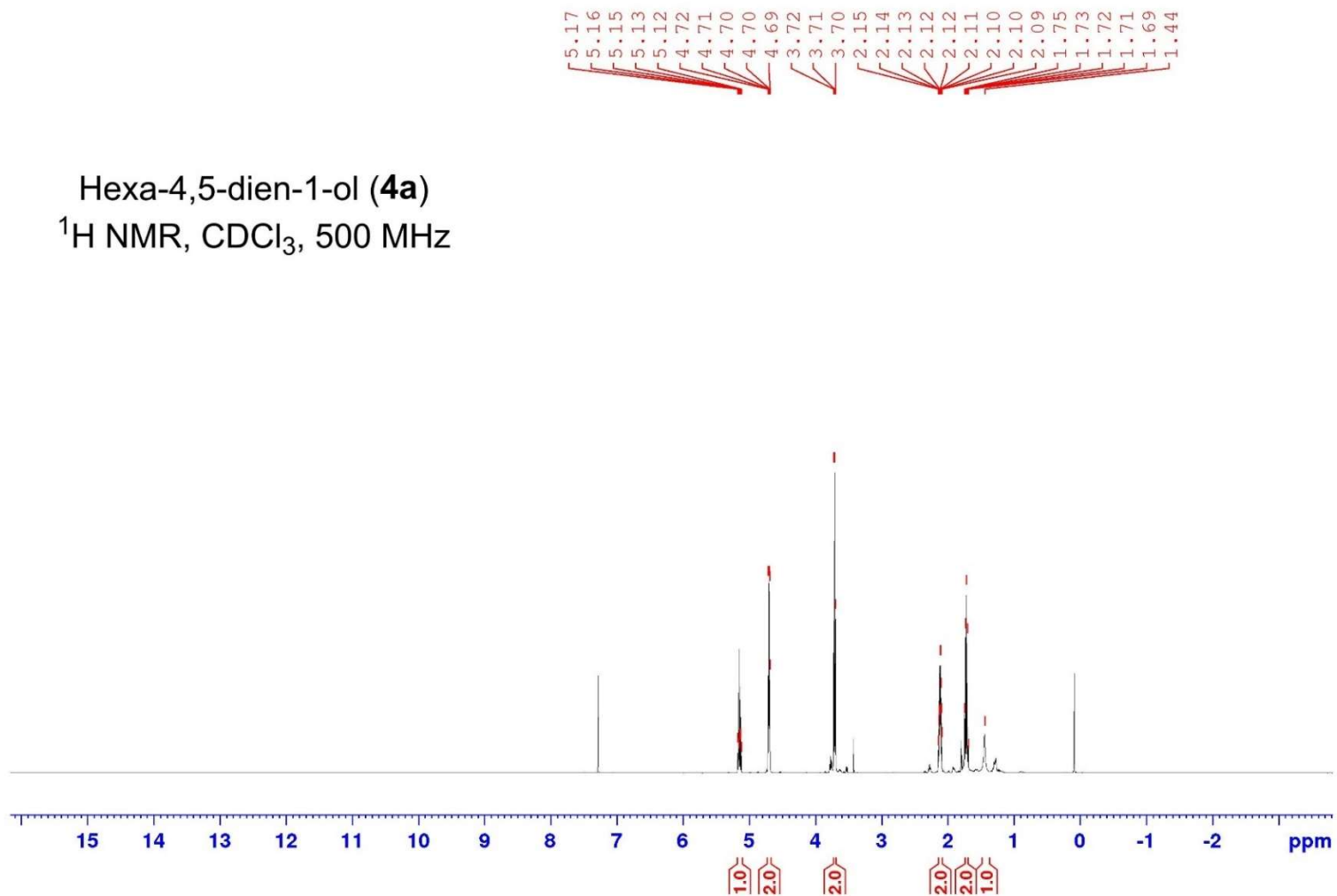


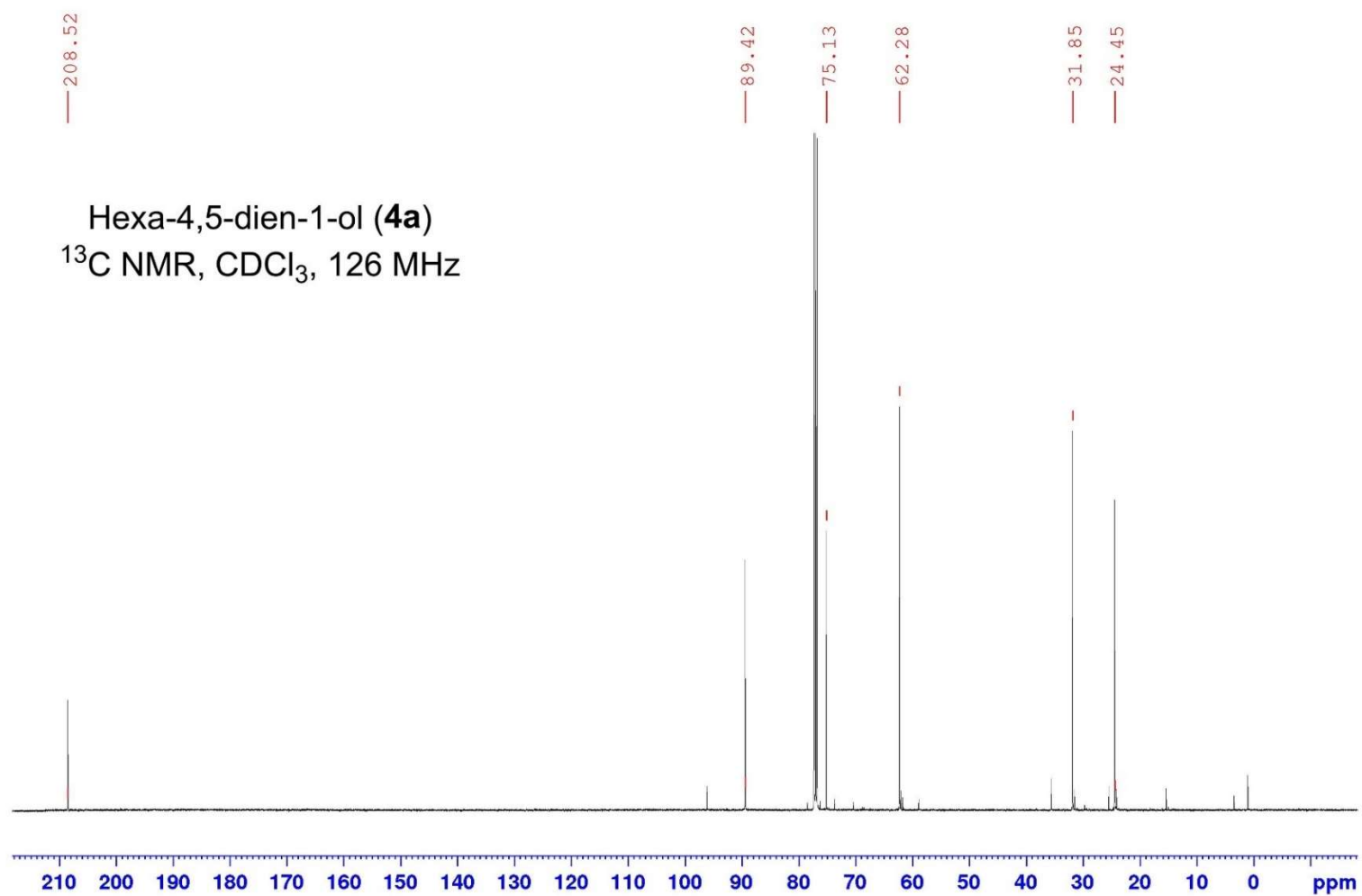


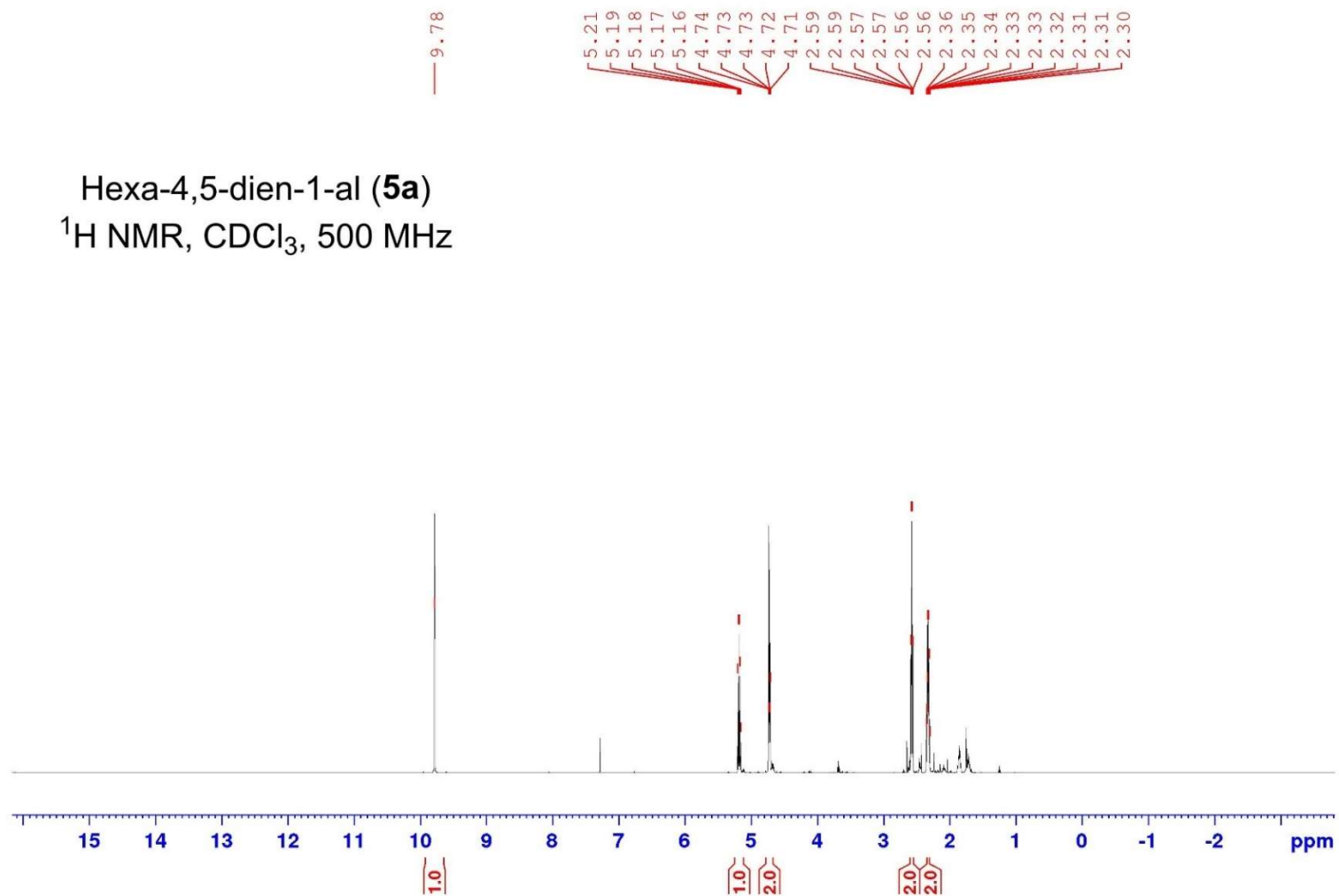


CHAPTER SIX

Hexa-4,5-dien-1-ol (**4a**)
 ^1H NMR, CDCl_3 , 500 MHz







— 208.46
— 201.82

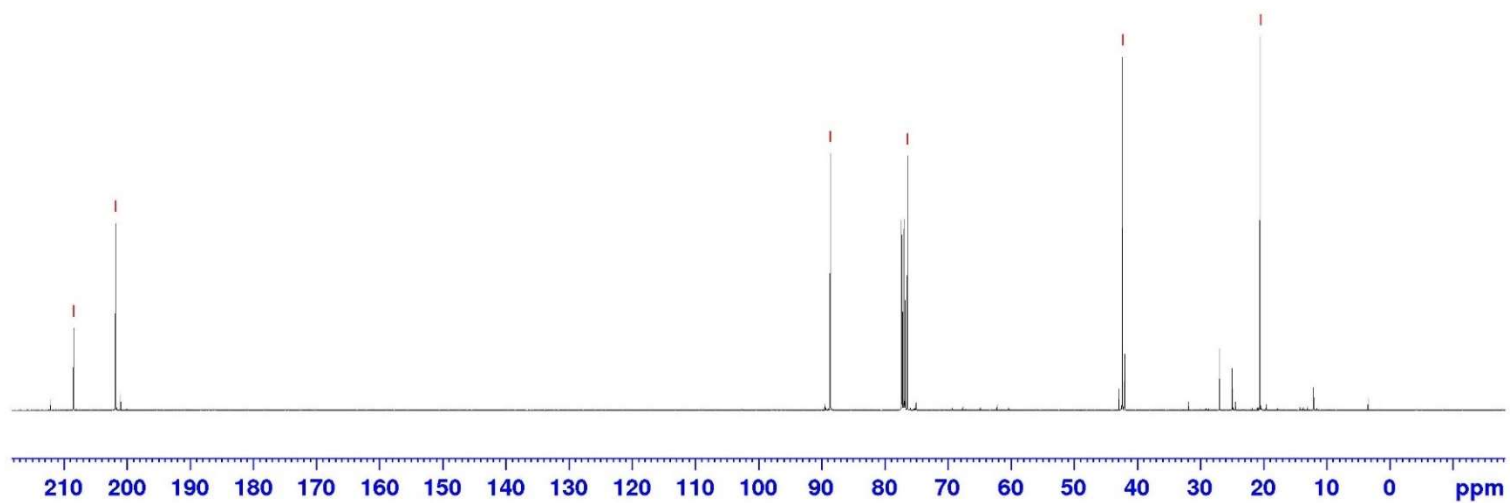
— 88.62

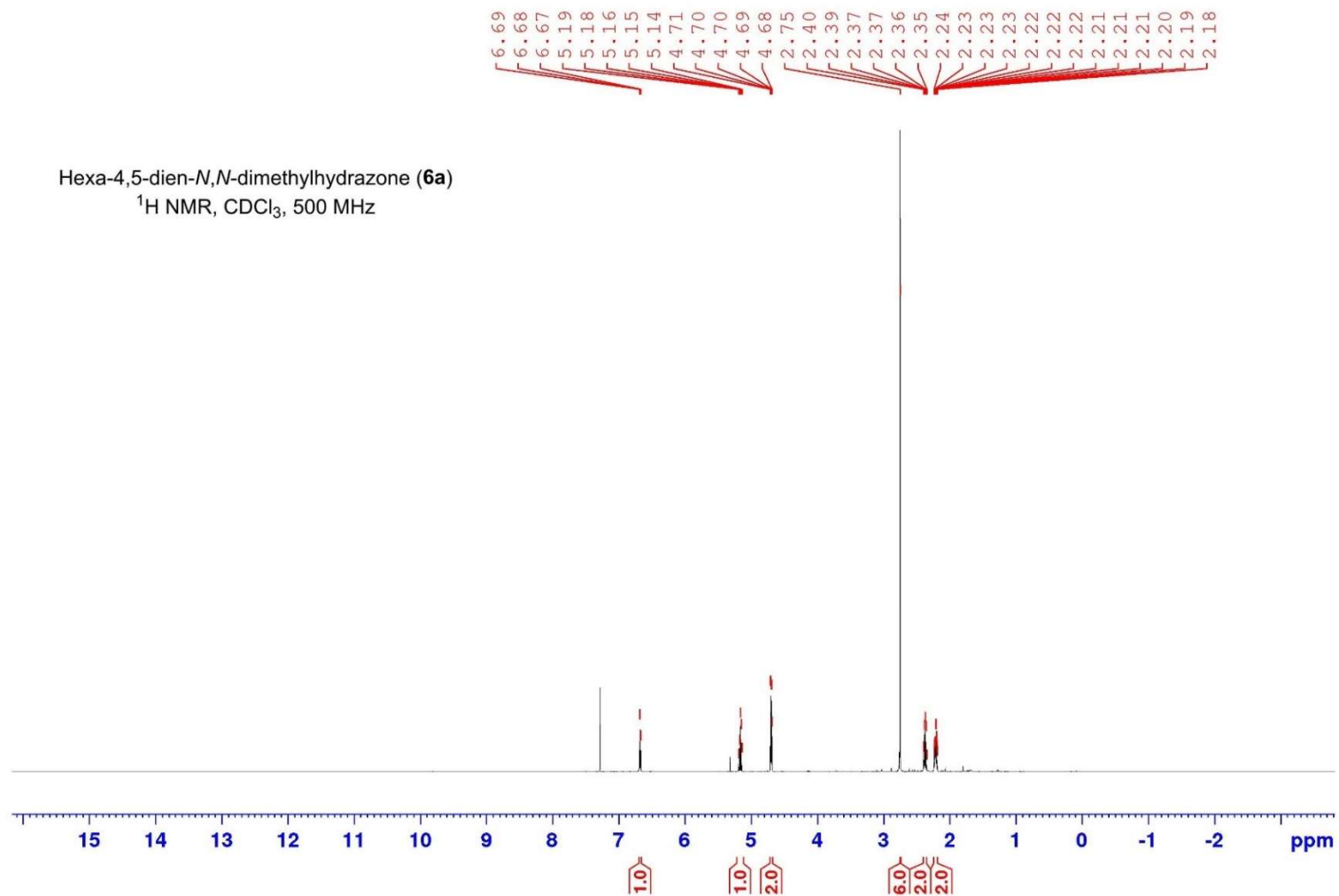
— 76.40

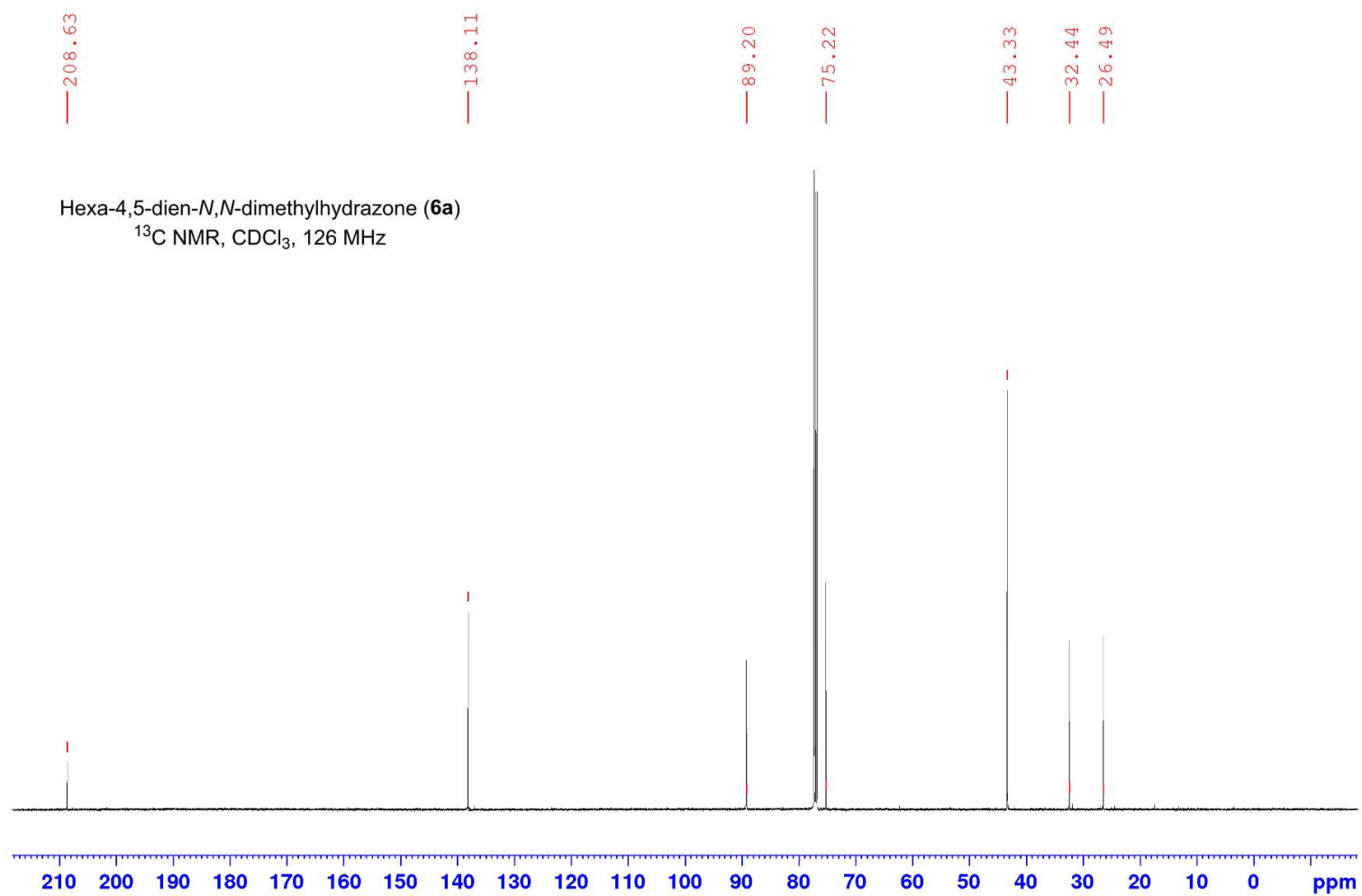
— 42.35

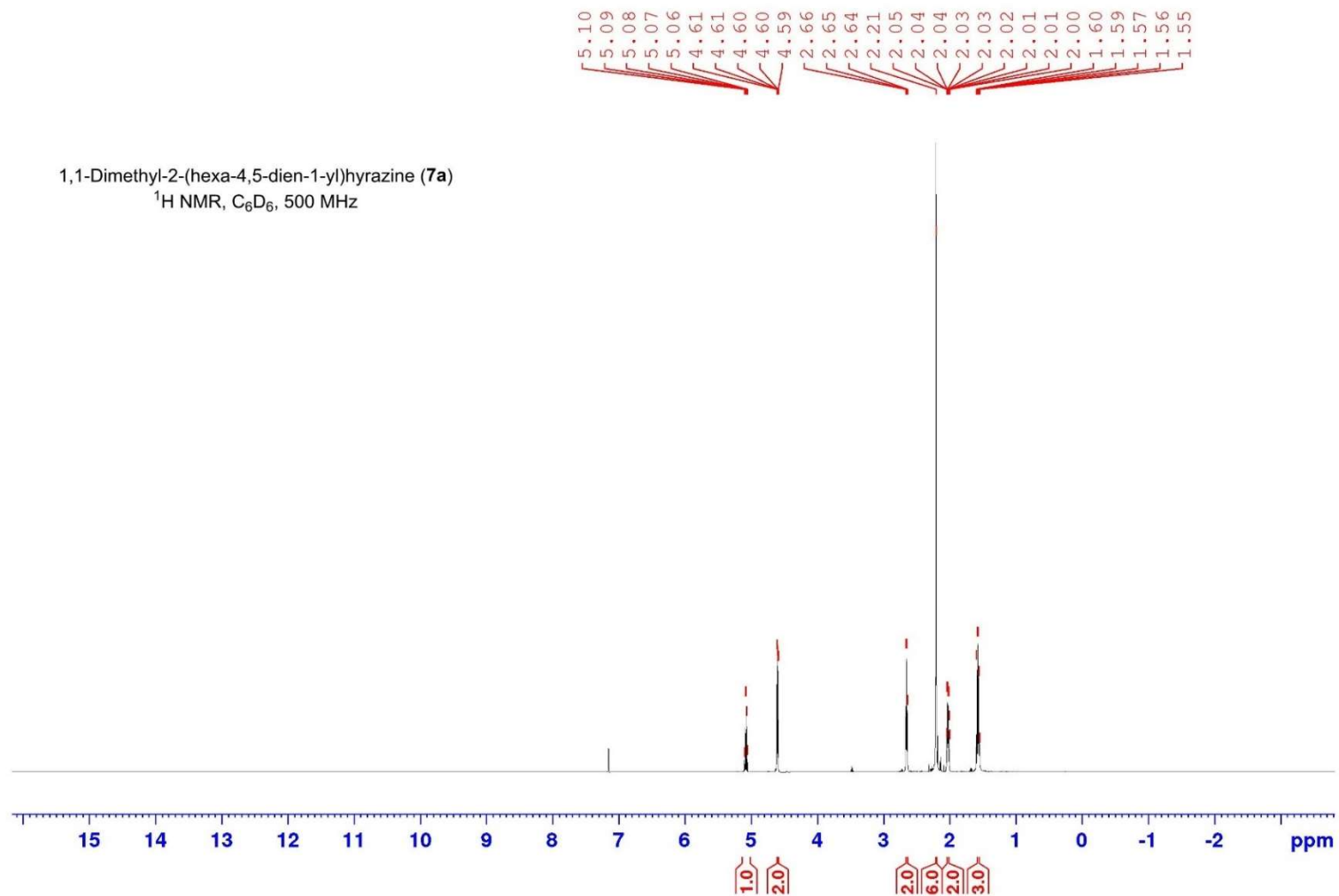
— 20.53

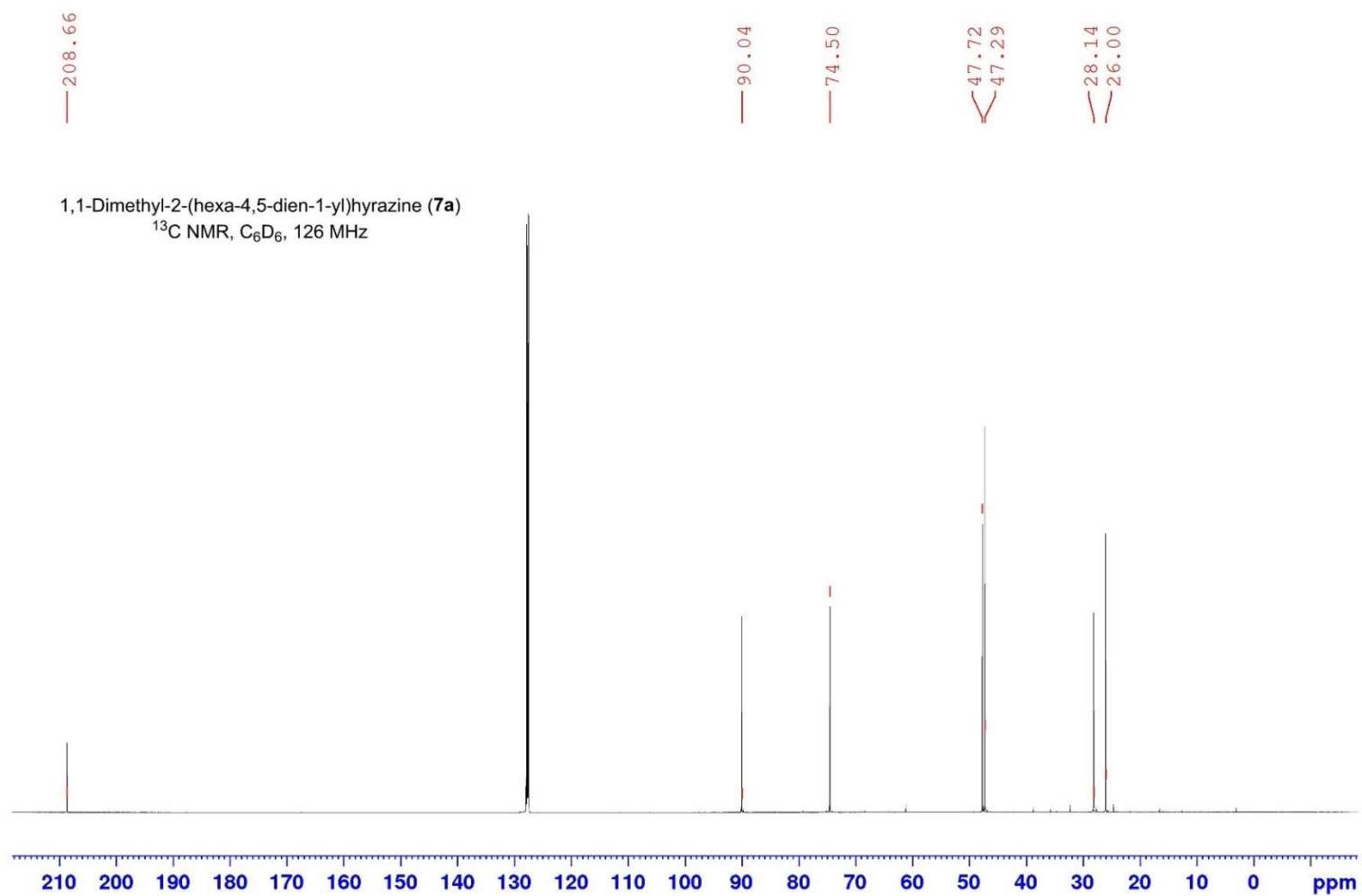
Hexa-4,5-dien-1-al (**5a**)
 ^{13}C NMR, CDCl_3 , 126 MHz



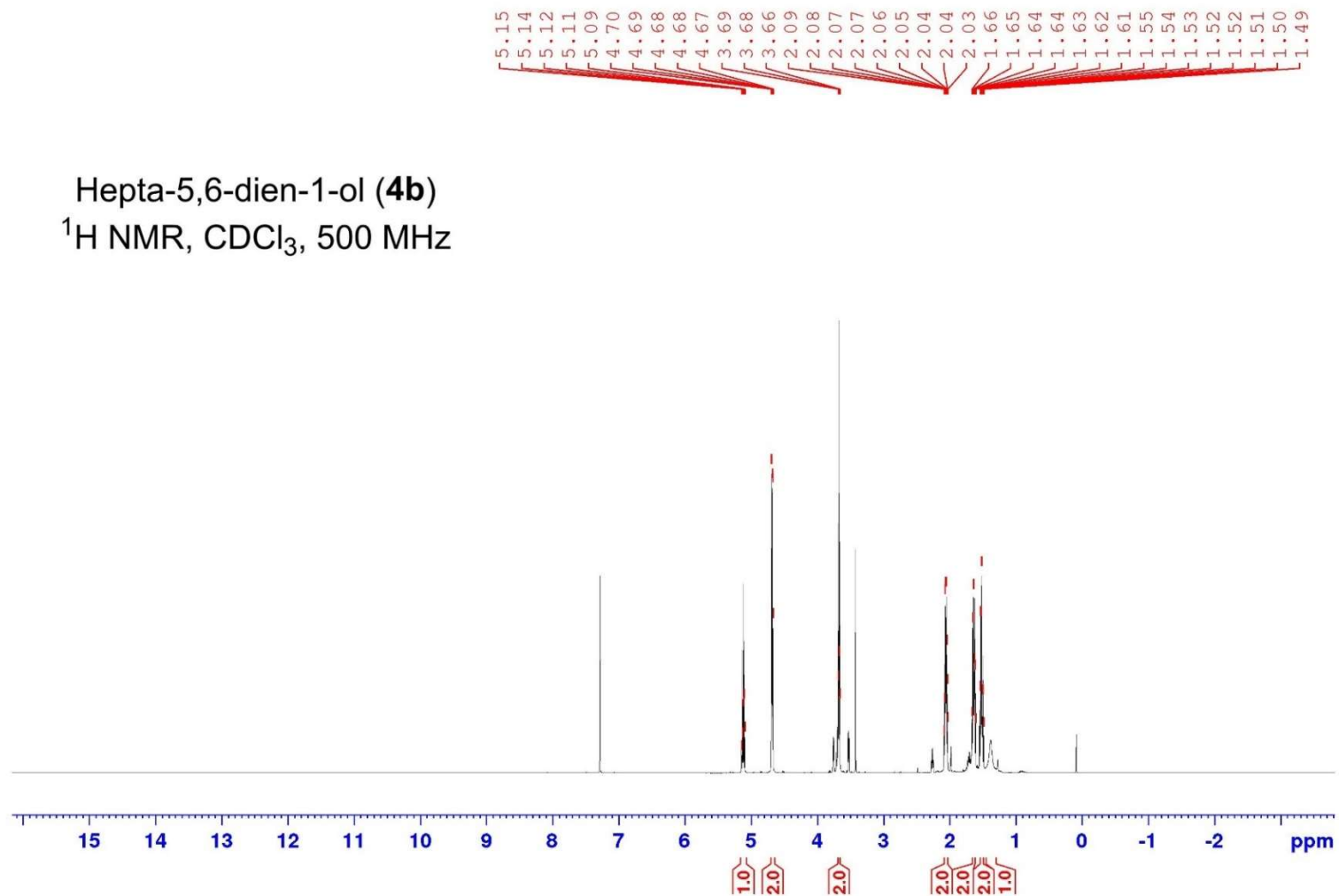


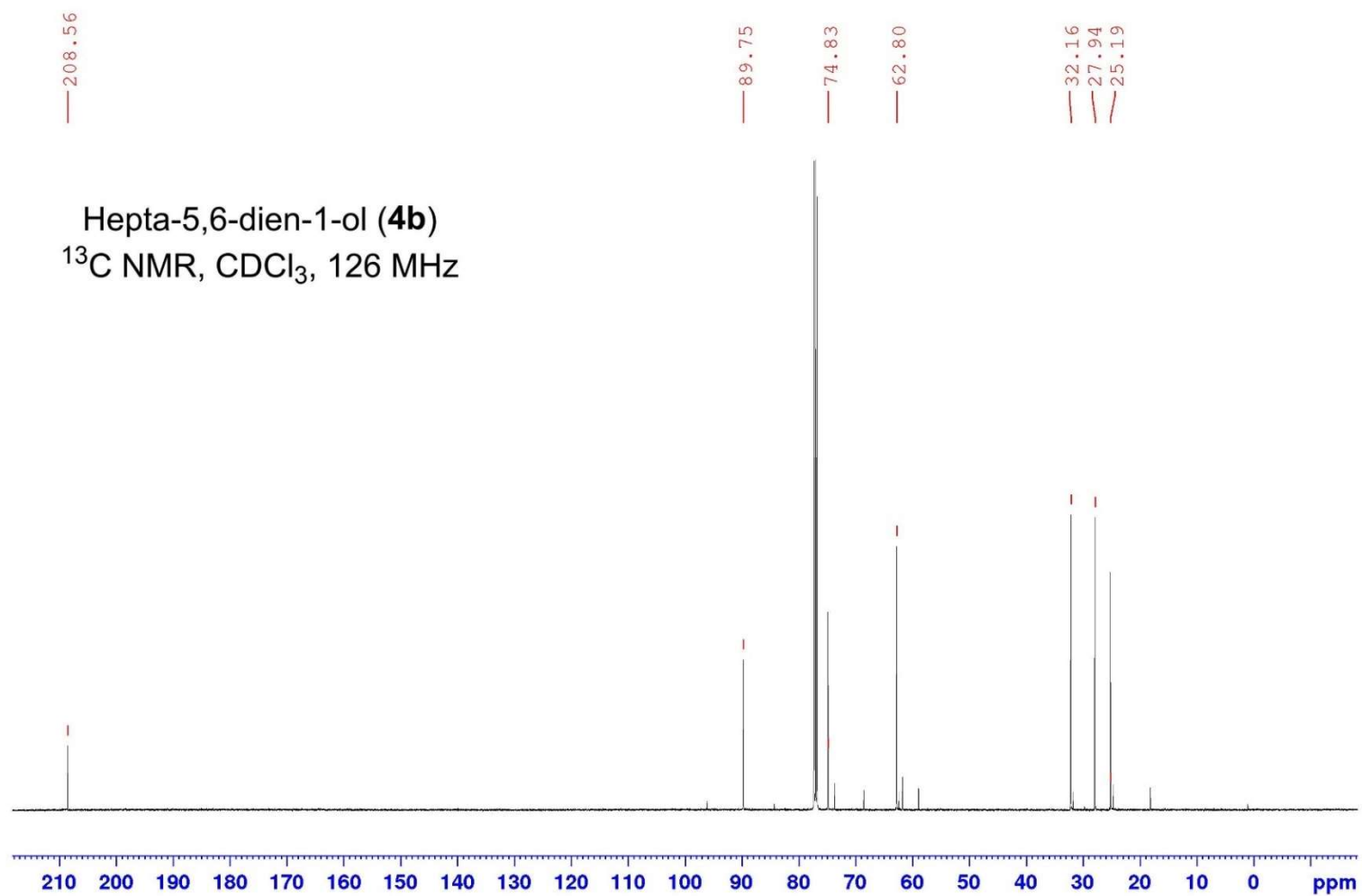




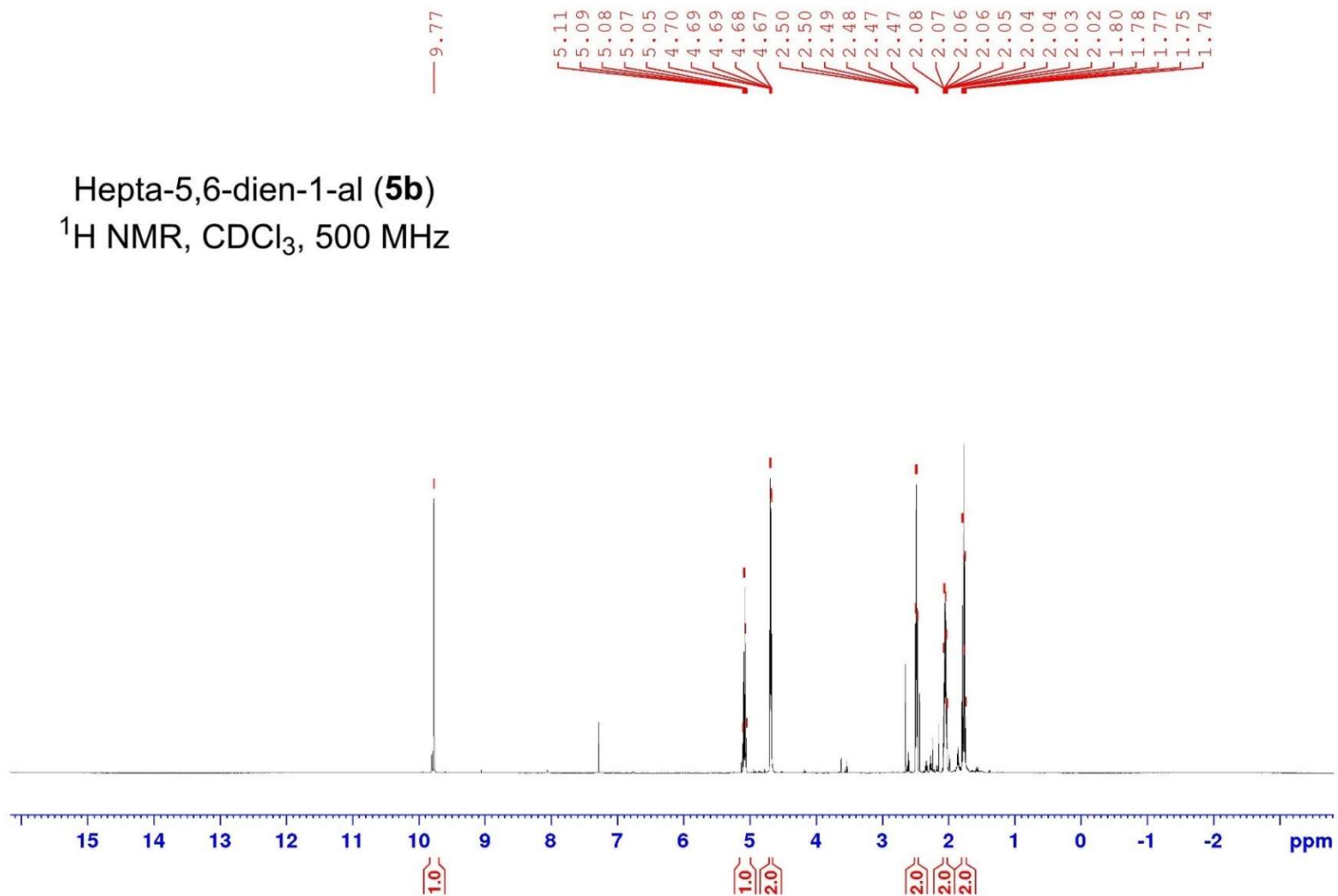


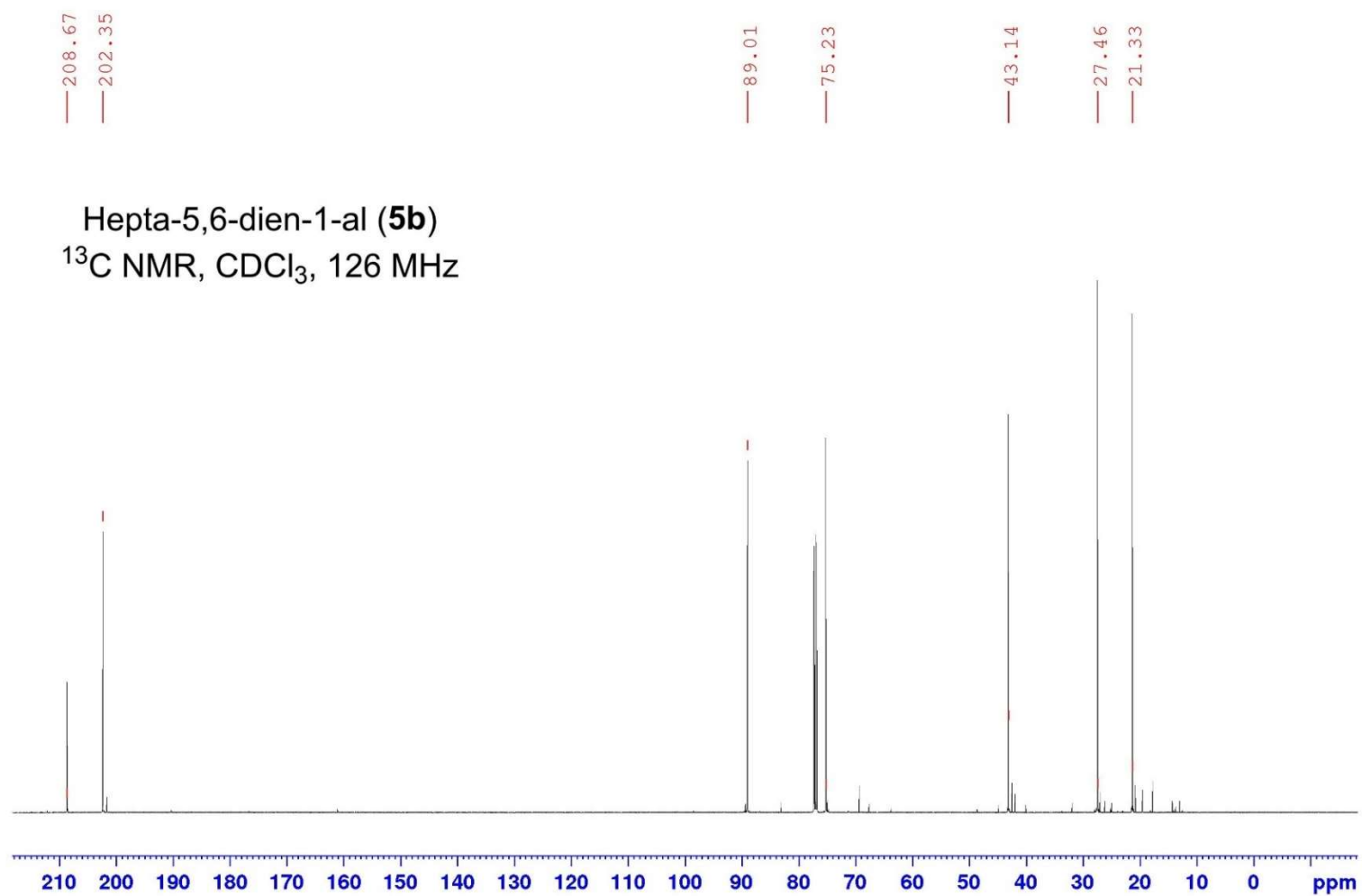
Hepta-5,6-dien-1-ol (**4b**)
¹H NMR, CDCl₃, 500 MHz

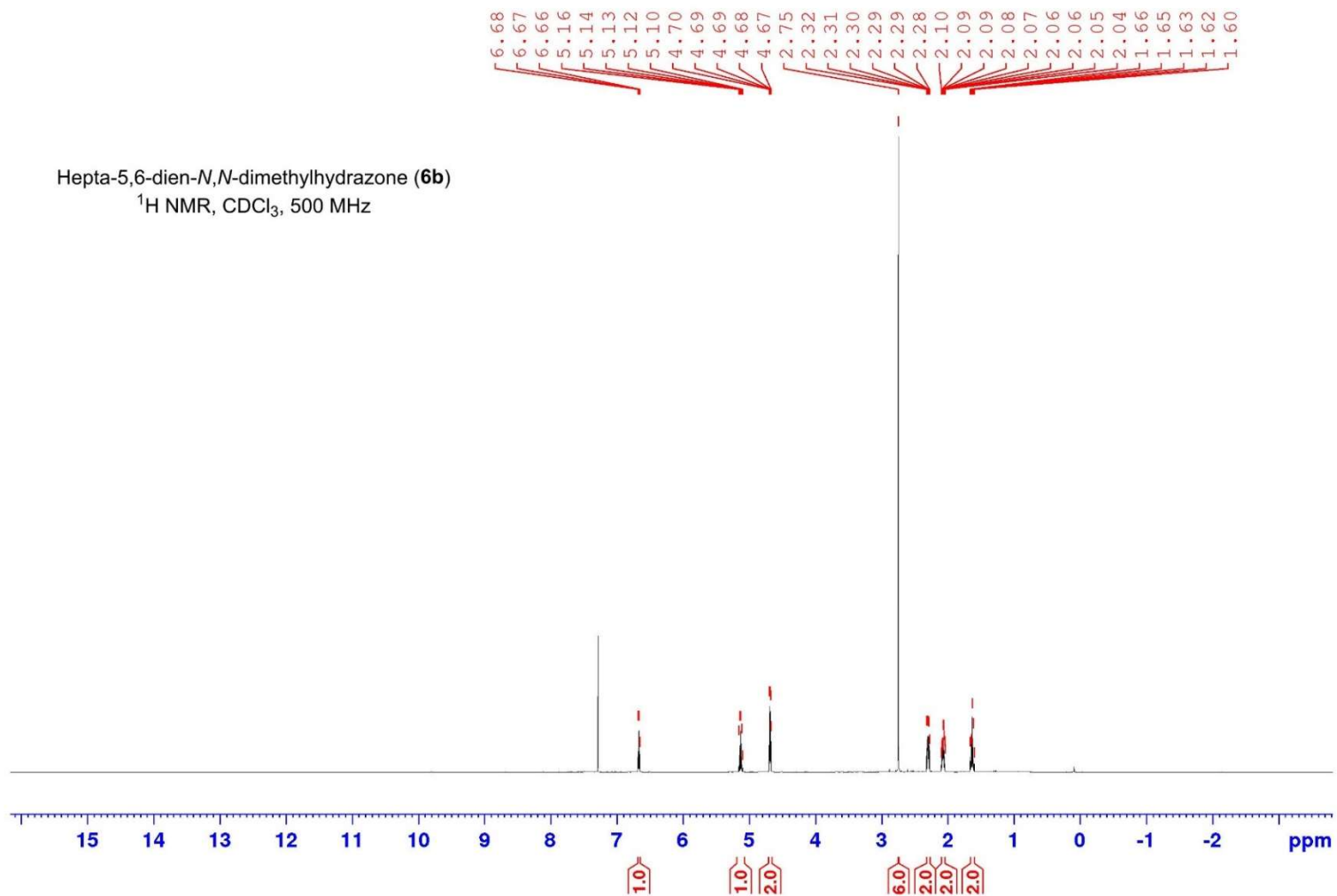


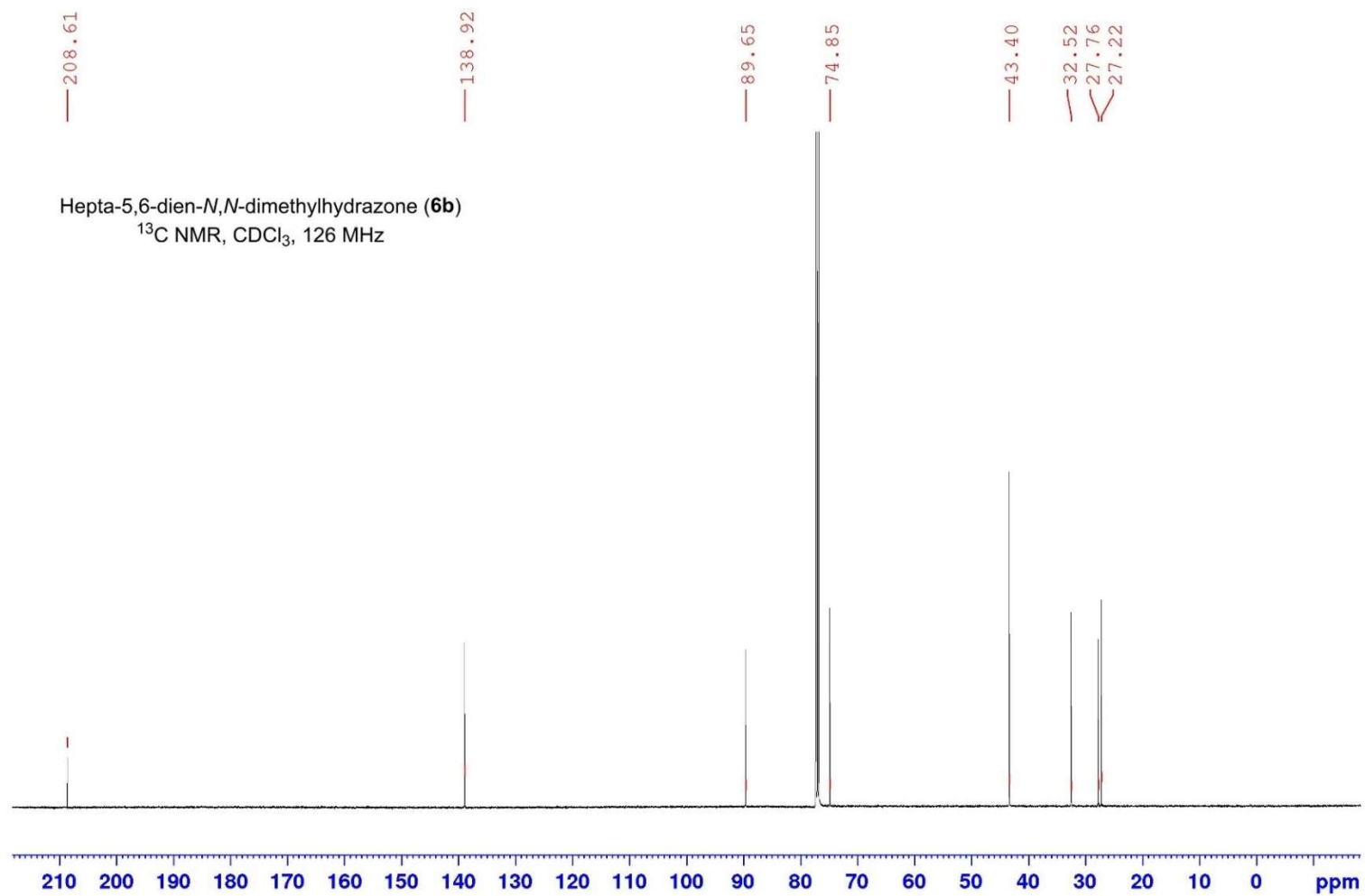


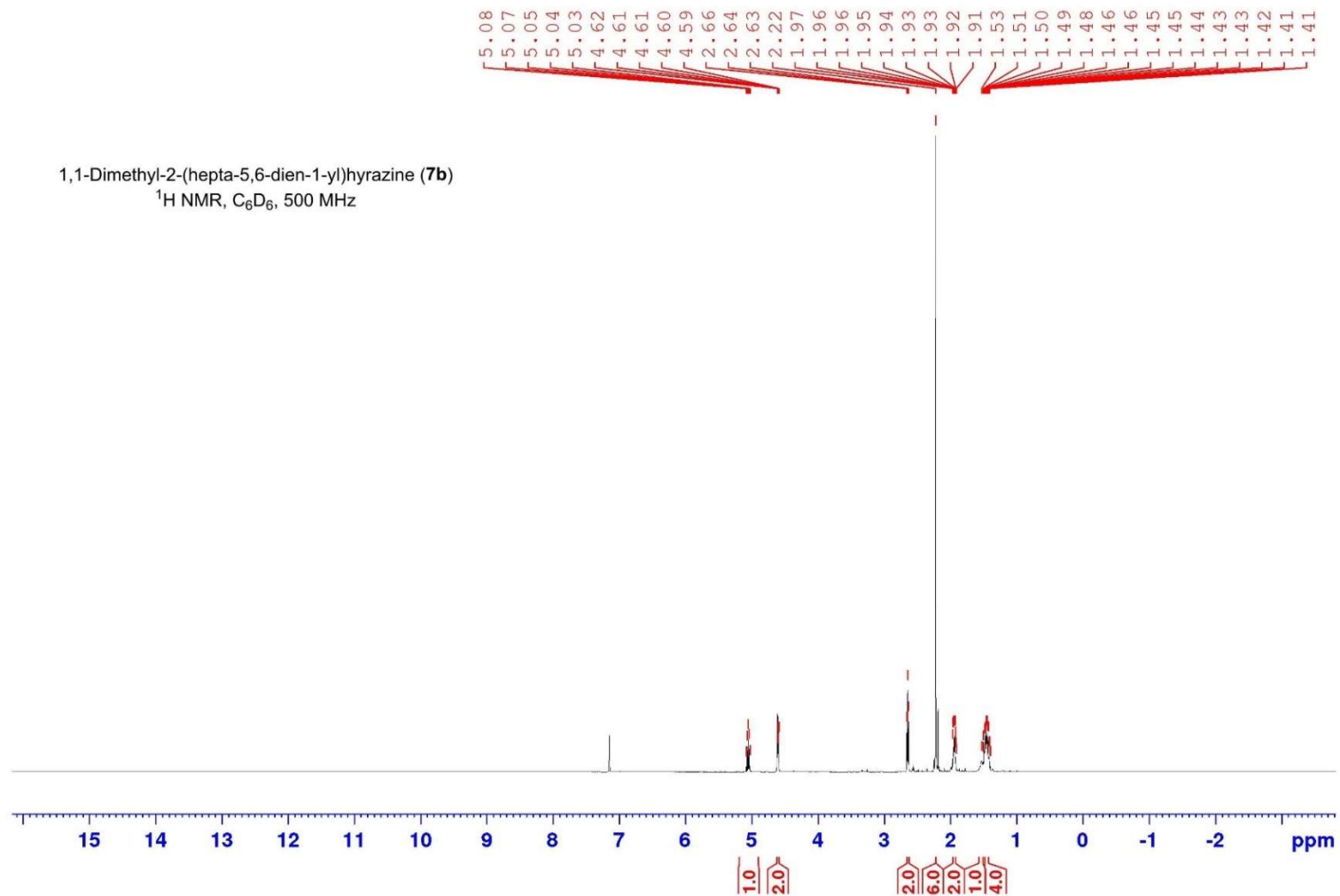
Hepta-5,6-dien-1-al (**5b**)
 ^1H NMR, CDCl_3 , 500 MHz

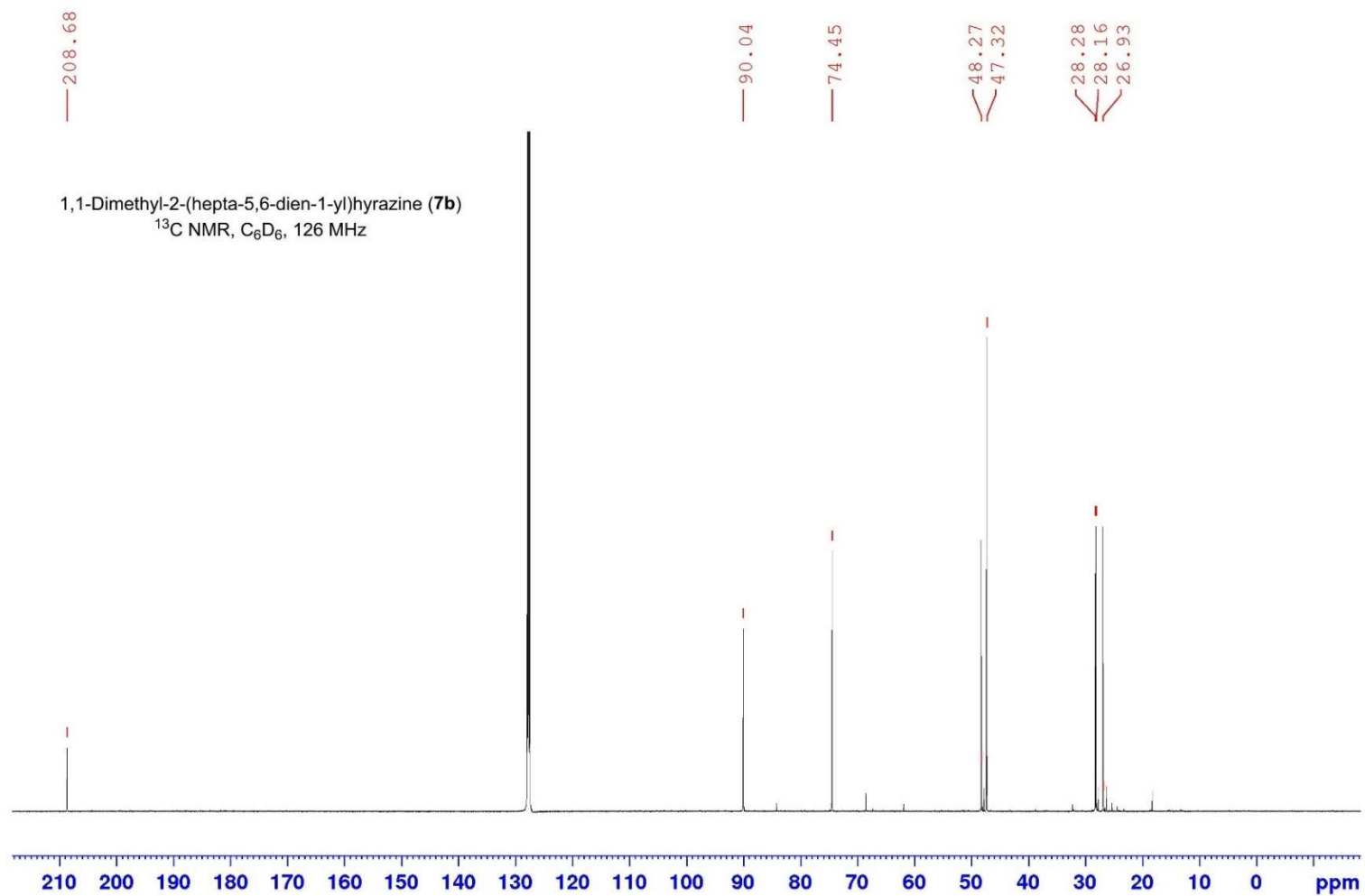


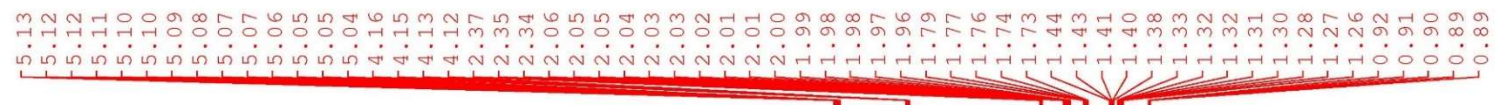






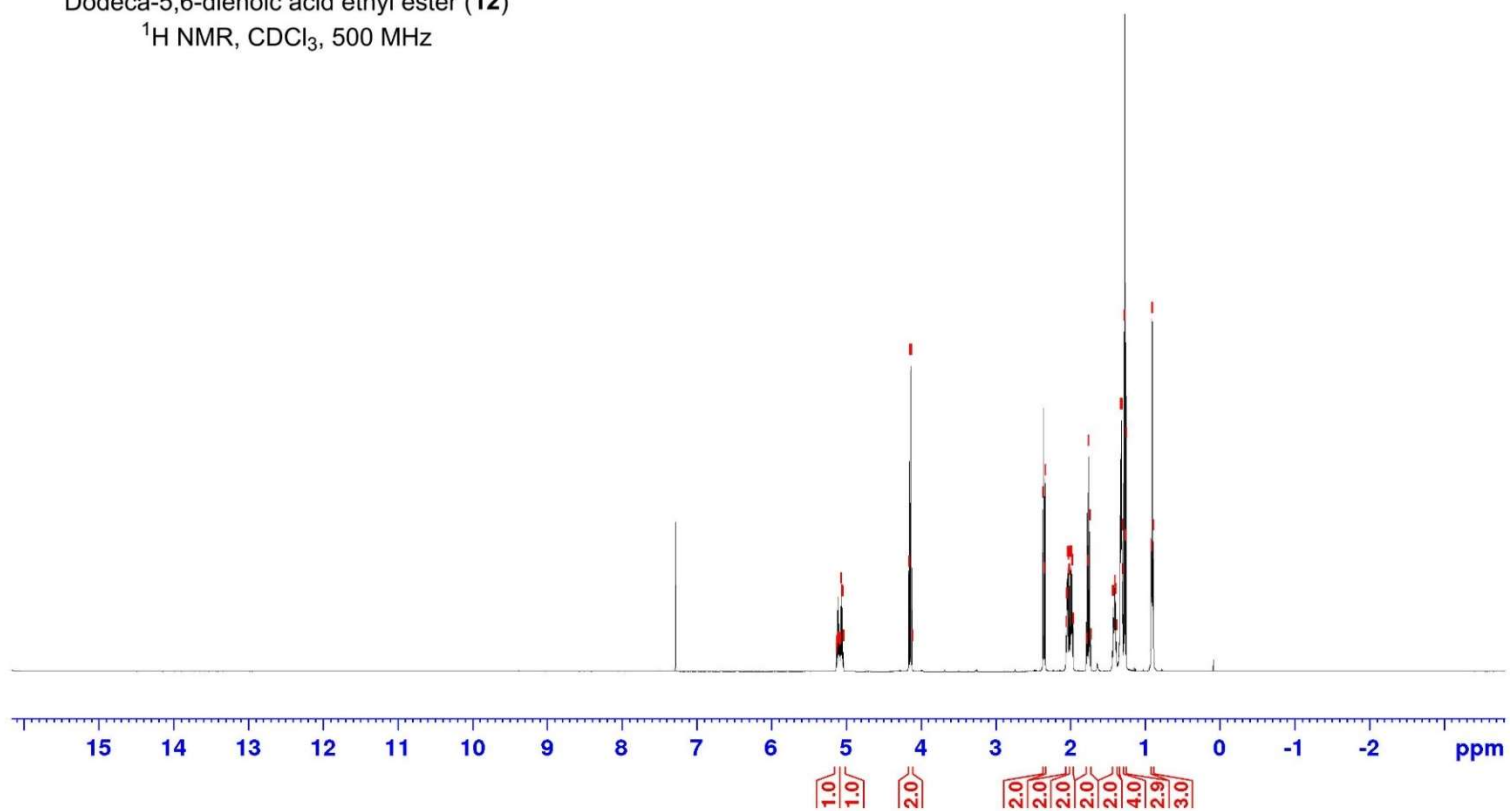


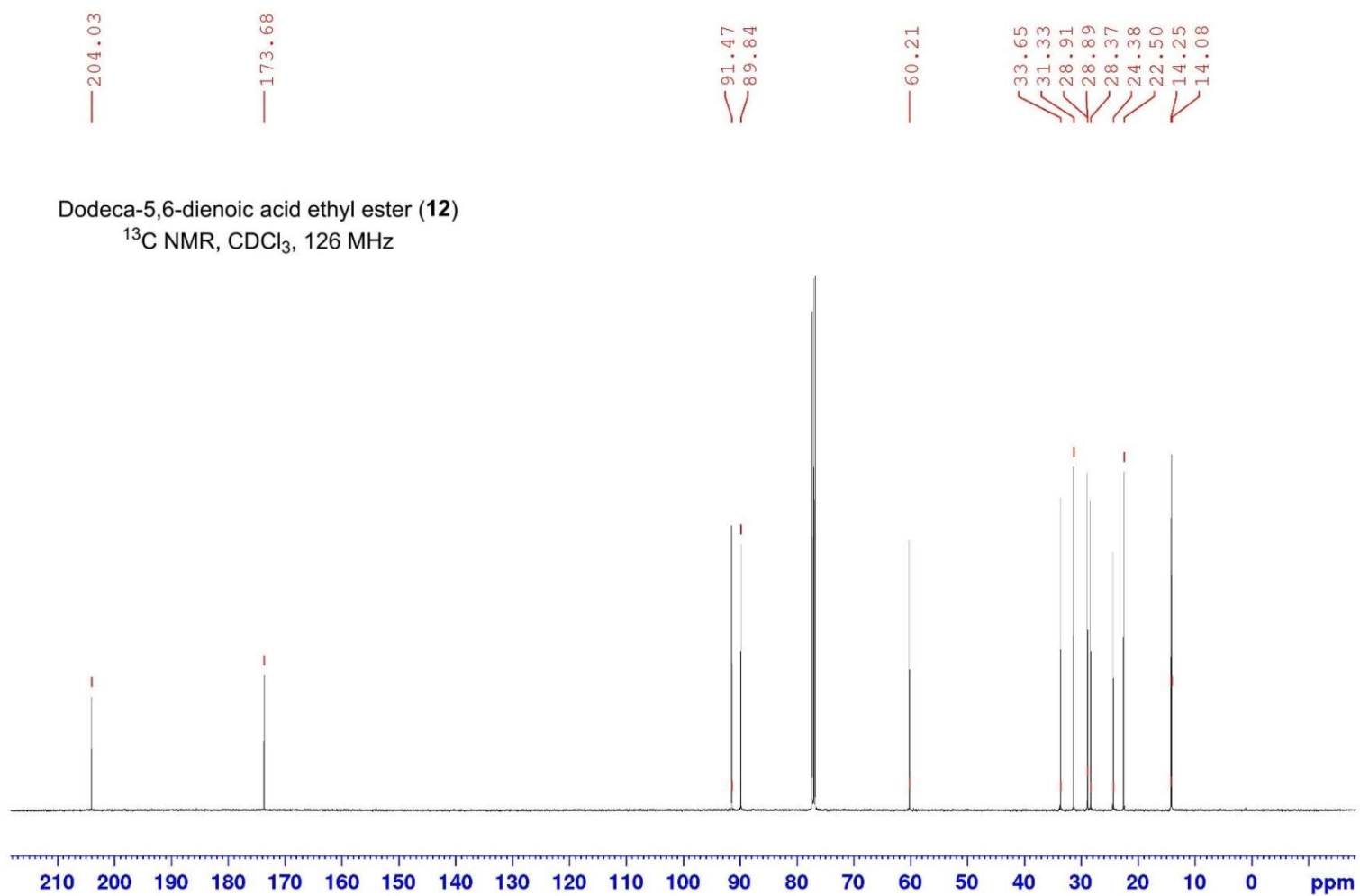


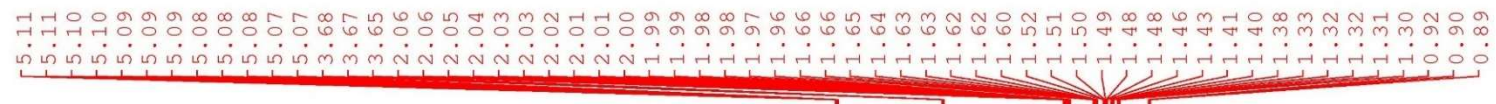


Dodeca-5,6-dienoic acid ethyl ester (**12**)

^1H NMR, CDCl_3 , 500 MHz







Dodeca-5,6-dien-1-ol (**13**)

^1H NMR, CDCl_3 , 500 MHz

