2017-08-01

Microwave-Promoted Iminyl Radical Cyclizations for the Synthesis of Azaheterocycles and the Total Synthesis of Yaku'amide A

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A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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ABSTRACT

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Two different research projects are described in this dissertation. The first one focuses on microwave-promoted iminyl radical cyclization for the formation of azaheterocycles which are embedded within numerous pharmaceuticals and biologically active natural products (such as clindamycin, eletriptan, moxiflaxin, *etc*.). We are quite interested in this project because of the significance of nitrogen-containing heterocycles as pharmaceuticals and organocatalysts combined with the need for safe, simple, and economical means of constructing them. We have successfully developed an efficient one-step synthesis of 2-acylpyrroles and diastereoselective dihydropyrroles from readily available oxime ether substrates. This remarkably efficient and environmentally friendly methodology should be useful for rapid and easy preparation of potent drugs containing pyrrolidine ring systems.

The second project focuses on the total synthesis of yaku'amide A. The natural compound, isolated from a marine sponge in 2010, is a medium-sized peptide that contains bulky dehydroamino acids. It has an excellent IC_{50} value (14 ng/mL) against leukemia cells, making it a promising anticancer agent. Because of the unique anticancer profile, potent bioactivity, and limited supply, the natural product was attractive to us for an efficient synthesis and mechanistic investigation. We have devised more efficient strategies compared to Inoue's methods for the synthesis of bulky ΔAAs and their incorporation into peptides, which are innovative and will allow us to synthesize yaku'amide A rapidly and conveniently. A one-pot sequence consisting Martin sulfurane mediated *anti* dehydration, azide reduction, and O→N acyl transfer was developed for the construction of *E*- and *Z*-dehydroisoleucine-containing peptides. We also developed a three-step synthesis of N-terminal acyl group involving a one-pot indium-catalyzed cross-Claisen condensation/reduction from a known compound. The most hindered coupling reaction of pentapeptide acid and nanapeptide amine in the late stage is accomplished. Our total synthesis of yaku'amide A can be completed in 19 longest linear steps and 66 total steps. Further identification of yaku'amide A for elucidation of its biological target and mode of action will be explored, which will open up new avenues in the fight against cancer.

Keywords: iminyl radical cyclization, azaheterocycles, yaku'amide A, aminohydroxylation, dehydroamino acids, Martin sulfurane, *anti* dehydration

ACKNOWLEDGEMENTS

My dissertation would not have been possible without the financial support of the Jerald S. Bradshaw Organic Chemistry Fellowship, Graduate Research Fellowship, Christine Bireley Oliver Fellowship, and Simmons Center for Cancer Research Fellowship. I am especially indebted to the Department of Chemistry and Biochemistry at Brigham Young University for providing a wonderful research environment.

I would like to express my sincere gratitude to my advisor Professor Steven L. Castle for his continuous support of my Ph.D. study and related research, for his enthusiasm, motivation, patience, and immense knowledge. His wonderful guidance helped me in all the time of research in organic/medicinal chemistry and writing of this thesis. He has taught me more than I could ever give him credit for here. He has shown me, by his example, what a good scientist should be. Moreover, he has been supportive of my career goals and who worked actively to provide me with protected academic time to pursue those goals. His life philosophy has been a great influence on me as well.

I am grateful to each of my dissertation committee members (Professors Merritt B. Andrus, Daniel H. Ess, Joshua L. Price, and Matthew R. Linford) who have provided me with extensive personal and professional guidance and taught me a great deal about scientific research. I would like to thank Professor Merritt B. Andrus for his kindness and expertise in discussions on many tricky synthesis problems. I thank Professor Daniel H. Ess for his nice and patient training on calculation studies using the Gaussian 09 program. I thank Professors Joshua L. Price and Merritt B. Andrus for their wonderful help with my fellowship applications. Professors Matthew R. Linford, Paul B. Savage, David J. Michaelis, and Matt A. Peterson have been great sources of motivation.

It is a great experience to work with a number of wonderful lab-mates in the Castle Group during my graduate studies. I am especially thankful to Dr. Zhiwei Ma for his wonderful help and training for a lot of lab skills. He also accomplished impressive progress towards the total synthesis of yaku'amide A. Many thanks to Ph.D. candidate Ankur Jalan for his nice help in both research and life in general. He is also the only one who helped me and did a great job in both iminyl radical and yaku'amide A projects. Thanks to outstanding undergraduates Shi Luo, Aaron Kubosumi, Sia Im, Blake Christensen, and Kei Webber, whom I trained, for their help in either the iminyl radical or the yaku'amide A projects. I would like to thank all of the Castle group members for being together to fill the lab life with diligent work and liveliness. All of the lab-mates deserve my gratitude for their help in improving my poor spoken English.

Besides the Castle group, I would like to thank Dr. Shenglou Deng for his expertise and kindness in discussing the difficult synthetic problems I encountered in my projects. Thanks to Professor Scott R. Burt and Mr. Bruce J. Jackson for providing well-maintained NMR and MS facilities. I am also grateful to Janet Fonoimoana and Susan Mortensen for their wonderful help and support regarding to my graduate program and campus issues.

Last but not least, I would like to especially thank my wife Na Li, my parents Dingrun Cai and Fengxiang Yu, and my siblings Jiubiao Cai and Yinhong Cai for their endless love and tireless support all the time. Additionally, my wife is currently pregnant, and we are both excited to have our first baby.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

1 IMINYL RADICALS

The photochemical behavior of the carbon-nitrogen double bond was first studied in depth in 1977.[1] Studies of the N-O bond energies in acyloximes indicate that these bonds can easily undergo homolytic cleavage induced by ultraviolet light leading to iminyl radicals. The use of radicals has become a valuable tool in organic synthesis. In particular, nitrogen-centered radical cyclization (such as aminyl or iminyl radicals, Figure 1.1) is widely used as an efficient strategy for the synthesis of nitrogen heterocycles including pyrrolidines and piperidines.[2,3]

Figure 1.1 Aminyl and iminyl radicals

1.1 Methods for the generation of iminyl radicals

Different strategies have been explored for the formation of iminyl radicals. There are two common methods: the homolytic cleavage of N-X bonds which is a widely used method, and the use of radical addition to nitrile which is more limited. These two methods for the formation of iminyl radicals will be described in detail below.

1.1.1 Homolytic cleavage of N−X bonds

Oximes including Oxime esters (*O*-alkanoyl and O-aroyl oximes) and oxime ethers (*O*-alkyl and *O*-aryl oximes) are the most widely used precursors for the formation of iminyl radicals (Figure 1.2).[4-5] The N−O bonds in oximes are usually weak compared to the C−O and C=N bonds. The average bond energies of N−O, C−O, and C=N bonds are 53, 86, and 147 kcal/mol, respectively.[5] In contrast, the bond energies in *O*-phenyl oxime ethers are only 33−37 kcal/mol. Therefore, iminyl radicals can be easily formed via homolytic cleavage of N−O bonds in oximes by photochemical or thermal means.

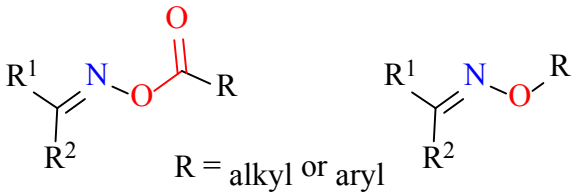
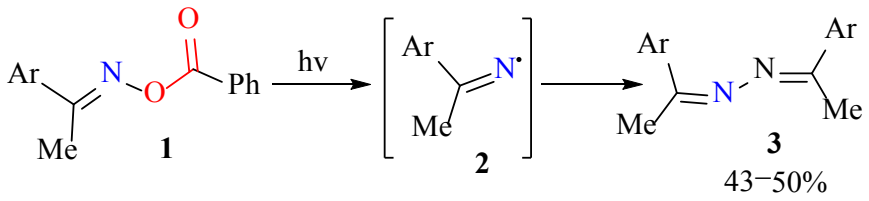


Figure 1.2 Oxime ester and oxime ether

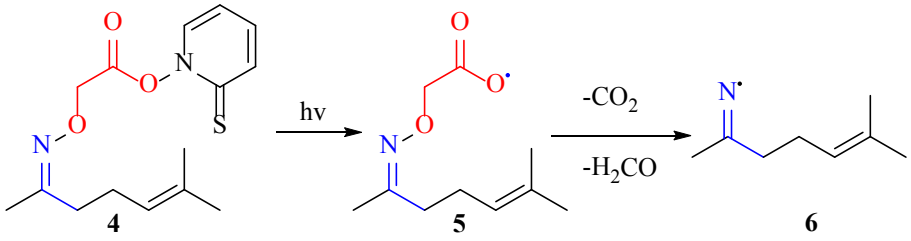
Interest has increased greatly in the photochemical formation of iminyl radicals since the 1990's. An early reaction involving the formation of iminyl radicals was the photolysis of oxime benzoates. As shown in Scheme 1.1, the homolytic cleavage of the N−O bond in the oxime benzoate (**1**) furnished a corresponding iminyl radical (**2**). Then, dimerization of the radical occurred to form the major product (**3**).[6]



Scheme 1.1 Dimerization of iminyl radical

A pioneering study from the group of Zard reported irradiation of a modified Barton ester **4**, which was prepared from *O*-carboxymethyl derivative of oxime ether was irradiated, to give the

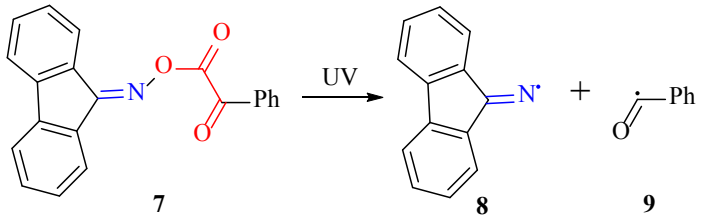
radical **5**. Then iminyl radical **6** was formed from **5** via decarboxylation and loss of formaldehyde (Scheme 1.2).[7]



4 **5** **6**

Scheme 1.2 O-carboxymethyl derivative of oxime

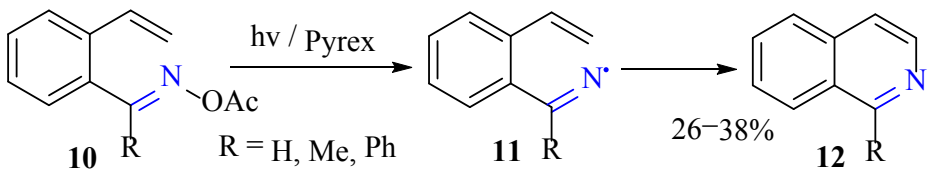
Bucher reported the cleavage of the N−O bond in 9-fluorenone oxime phenylglyoxylate induced by leptin.[8] The expected intermediates iminyl radical **8** and benzoyl radical **9** formed by losing CO_2 from the benzoylcarbonyloxyl radical, were detected using time-resolved EPR and FTIR (Scheme 1.3).



7 **8** **9**

Scheme 1.3 Photodissociation of an oxime glyoxalate

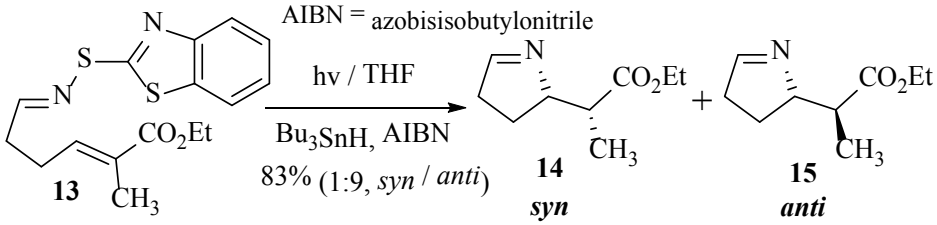
In 2006, Rodríguez first reported the formation of substituted isoquinolines in 26−38% yield by intramolecular cyclization between an iminyl radical and an olefin (Scheme 1.4).[9] Irradiation of 2-vinylbenzaldehyde *O*-acetyloxime ether **10** induced homolytic cleavage of the N−O bond, leading to the formation of iminyl radical **11**.



10 R **11** R **12** R

Scheme 1.4 Intramolecular iminyl radical cyclization

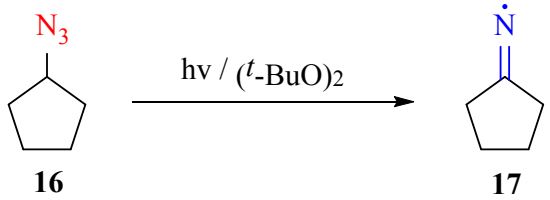
Although the homolytic cleavage of N-O bond in oximes or imines are most commonly used for the formation of iminyl radicals, N-S cleavage was also reported for this radical formation in 2001 by Landry's group.[10] As shown in Scheme 1.5, a sulfanyl imine was used as the precursor of iminyl radical. Irradiation of imine **13** in the presence of Bu_3SnH and AIBN induced the cleavage of the N−S bond and facilitated a tandem process of intramolecular iminyl radical cyclization/hydrogen atom transfer to give pyrrolines **14** and **15** with excellent yield and high diastereoselectivity.



Scheme 1.5 Homolytic cleavage of N−S bond

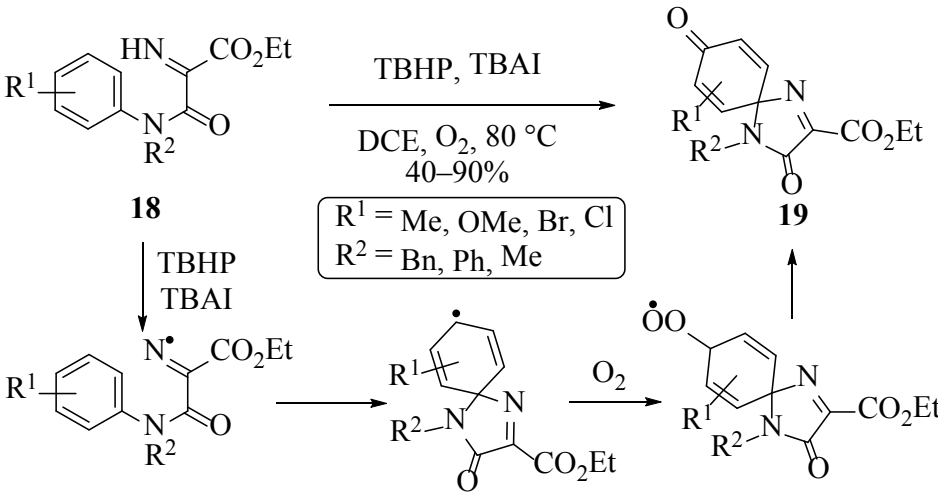
1.1.2 Radical addition to an unsaturated nitrogen derivative

Although the homolytic cleavage of N−O bonds is widely used for the formation of iminyl radicals, an alternative method was reported that involves addition of another radical species to an unsaturated nitrogen derivative (i.e., azide). This method was first reported by Winter's group in 1977.[11] As shown in Scheme 1.6, photochemical cleavage of the O−O bond in di-*tert*-butyl peroxide generated *tert*-butoxyl radicals, which reacted with secondary azide **16** to form iminyl radical **17** with loss of N_2.



Scheme 1.6 The formation of iminyl radical from a secondary azide

The combination of *tert*-butyl hydroperoxide (TBHP) and tetrabutylammonium iodide (TBAI) was reported to generate an iminyl radical from imine **18**. Yu found that the iminyl radical preferably undergoes 5-*exo* cyclization to give an azaspirocyclohexadienyl radical. The species is trapped with O_2 followed by oxidation to furnish azaspirocyclohexadienone **19** (Scheme 1.7).[12] In addition, a byproduct quinoxalin-2-one is isolated in some cases due to 6-*endo* cyclization.



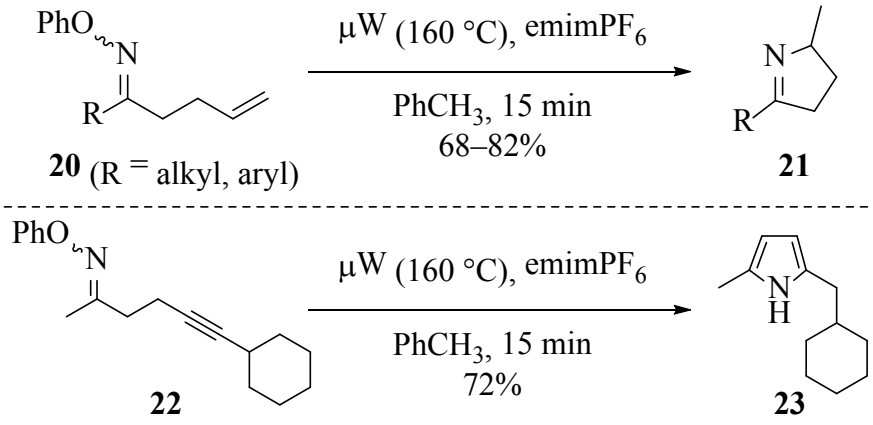
Scheme 1.7 TBHP/TBAI-mediated synthesis of azaspirocyclohexadienones

1.2 Synthesis of azaheterocycles via iminyl radical cyclization

Iminyl radicals have been shown to cyclize faster than aminyl radicals.[13] The favorable kinetics and the synthetic utility of the imino group make iminyl radical cyclization a remarkably useful transformation for the formation of heterocycles.[14]

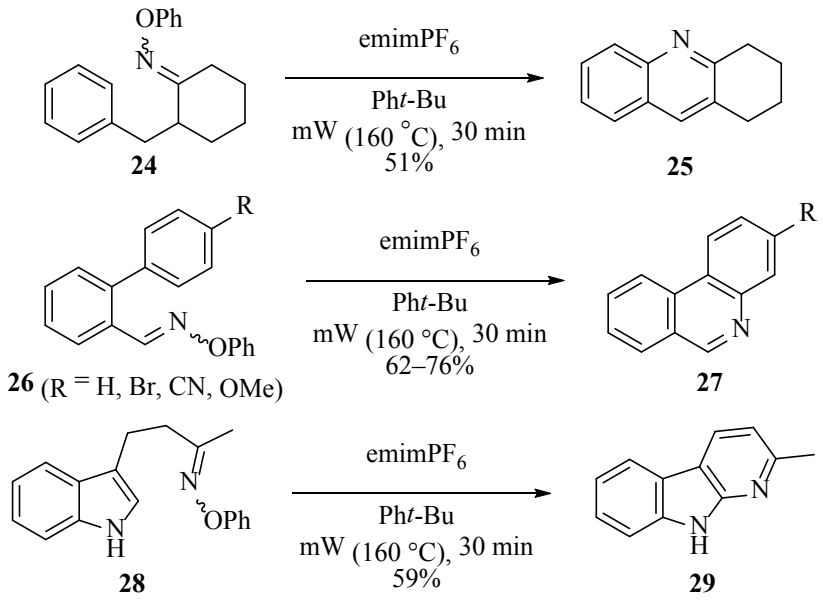
The pioneer Walton and co-workers have made several significant contributions to iminyl radical chemistry under microwave heating, which is mild, simple, and environmentally friendly.[15] Functionalized oxime ethers were used as a source of iminyl radicals in their reactions.[2] Walton first reported that alkene-containing *O*-phenyl oxime ethers **20** underwent 5-*exo* cyclization upon microwave heating in toluene to furnish dihydropyrroles **21** in 68%−82%

yields (Scheme 1.8). [16] The ionic liquid (emimPF_6, 1-Ethyl-3-methylimidazolium hexafluorophosphate) was employed in this cyclization to promote efficient microwave heating. A reasonable mechanistic pathway involves direct homolysis of the weak N–O bond generating an iminyl radical via a unimolecular process. This radical then cyclizes onto the terminal alkene. The resultant alkyl radical abstracts a hydrogen atom from toluene to afford the product. Interestingly, pyrrole **23** was formed via this transformation with alkyne-containing *O*-phenyl oxime **22**.



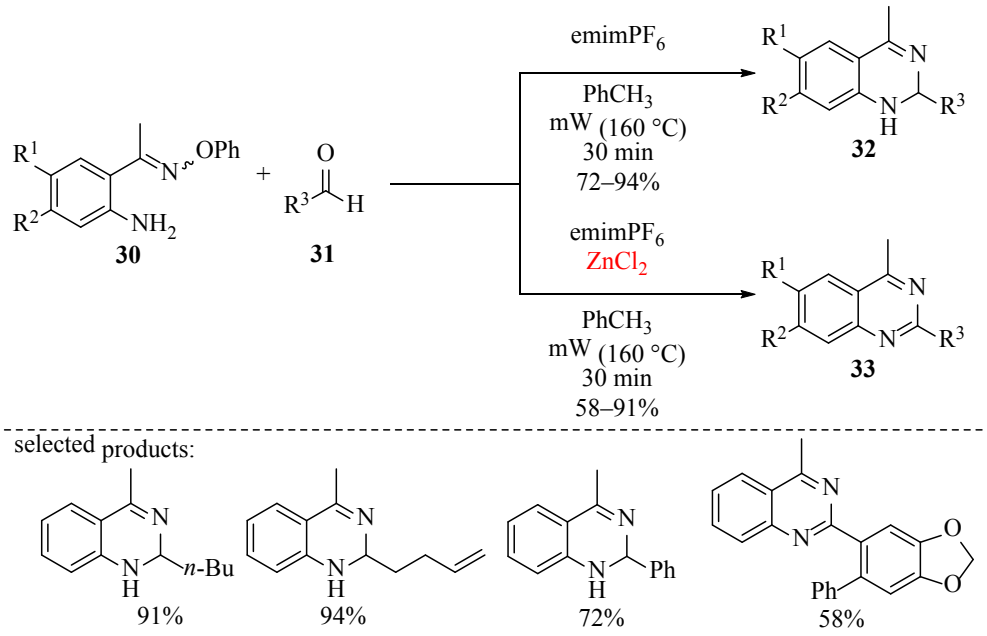
Scheme 1.8 Walton's iminyl radical cyclizations from corresponding oxime ethers

Walton's microwave-assisted thermolysis of *O*-phenyl oxime ethers could be applied to six-membered ring formations, forming a variety of polycyclic heteroaromatic ring systems (Scheme 1.9).[17] In this cyclization, *tert*-butylbenzene was used as the solvent instead of toluene because the presence of a hydrogen atom donor was not desired.



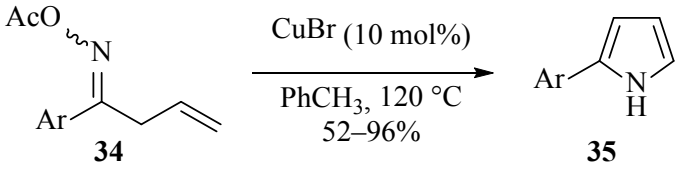
Scheme 1.9 Synthesis of heteroaromatic rings via iminyl radical cyclization

Moreover, Walton reported a convenient and mild microwave-based strategy for the preparation of dihydroquinazolines **32** involving annulation of anilines **30** and aldehydes **31** via iminyl radical cyclization (Scheme 1.10).[18] Interestingly, aromatization occurred to furnish quinazolines **33** when $ZnCl_2$ was added in the reaction mixture.



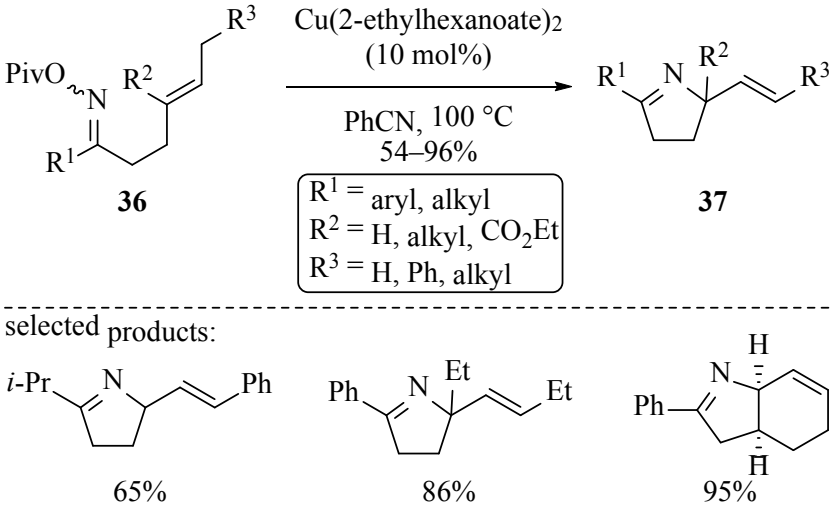
Scheme 1.10 Syntheses of dihydroquinazoline and quinazoline derivatives

Whereas most iminyl radical cyclizations that afford five-membered rings proceed via 5-*exo* pathway, Guan demonstrated the viability of the 5-*endo* process. Aryl-substituted ketoxime acetates **34** furnished 2-arylpyrroles **35** under CuBr catalysis (Scheme 1.11).[19] Both electron-donating and electron-withdrawing groups were tolerated on the aryl ring. The proposed mechanism of this cyclization involves the Cu(I) catalyst generating an iminyl radical from oxime ether **34**, which cyclizes via 5-*endo* ring closure. The cyclic radical intermediate is then oxidized to a cation by the resulting Cu(II) species and subsequently eliminated.



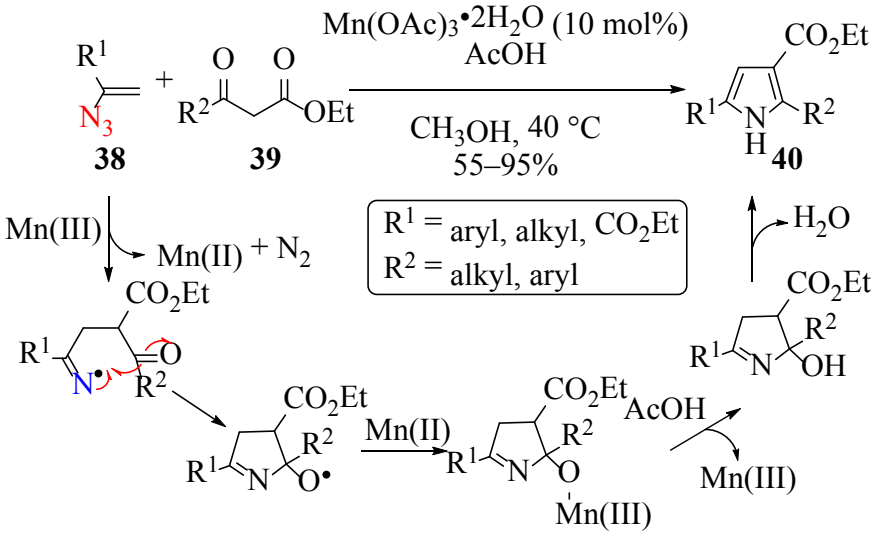
Scheme 1.11 Synthesis of 2-arylpyrrole via 5-*endo-trig* cyclization

Bower recently developed Heck-like cyclizations catalyzed by Cu(II) from oxime esters **36**, delivering dihydropyrroles **37** in 54 to 96% yields (Scheme 1.12).[20] Although the Pd-catalyzed process is believed to follow the typical Heck mechanism, mechanistic studies of the Cu-catalyzed reactions indicate the intermediacy of species with iminyl radical character.

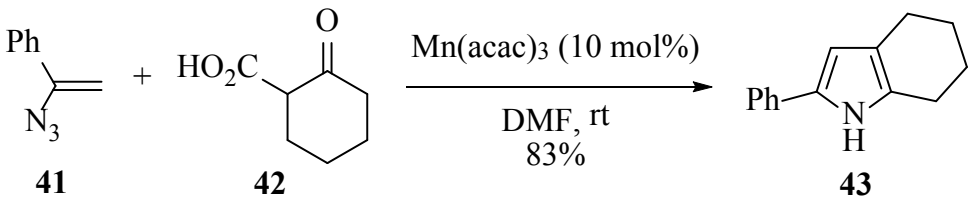


Scheme 1.12 Copper-catalyzed Heck-like cyclizations

Vinyl azides are also useful precursors for the formation of iminyl radicals.[21–22] Narasaka and Chiba reported a Mn(III)-catalyzed synthesis of polysubstituted pyrroles **40** based on the annulation of vinyl azides **38** and acetoacetic esters **39** (Scheme 1.13).[23] Presumably, addition to **38** of a radical derived from oxidation of **39** followed by loss of nitrogen furnished an iminyl radical. A possible pathway from this radical to **40** involves 5-*exo-trig* cyclization onto the ketone, reduction of the resulting oxygen-centered radical to a Mn(III)-alkoxide, then protonation followed by dehydration. Chiba subsequently developed Mn(III)-catalyzed decarboxylative annulation of vinyl azide **41** and β-keto acid **42** furnishing pyrrole **43** in 83% yield (Scheme 1.14).[24]

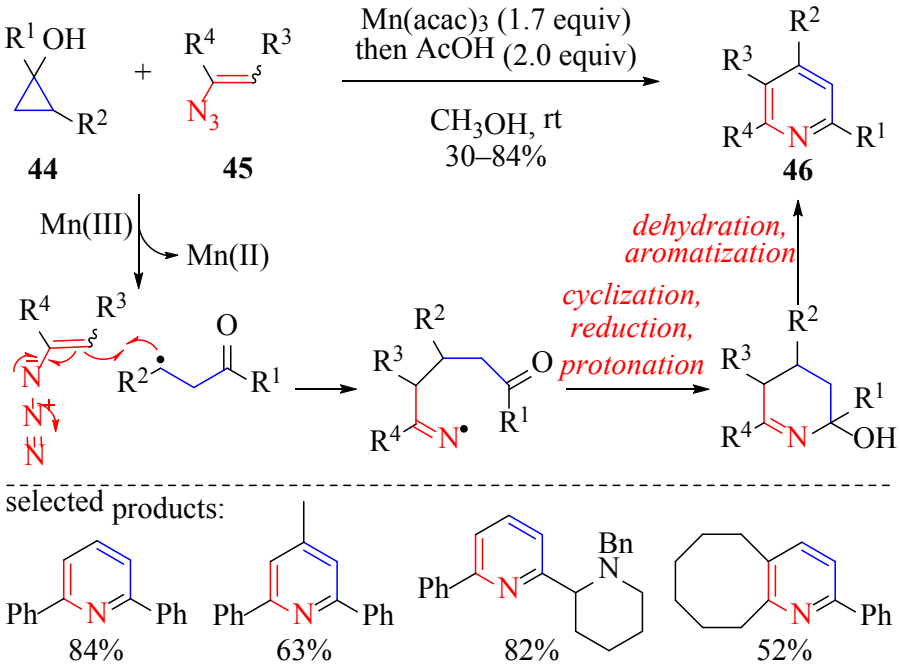


Scheme 1.13 Mn(III)-catalyzed pyrrole synthesis from vinyl azides and acetoacetic esters



Scheme 1.14 Mn(III)-catalyzed condensation of vinyl azide and β-keto acid

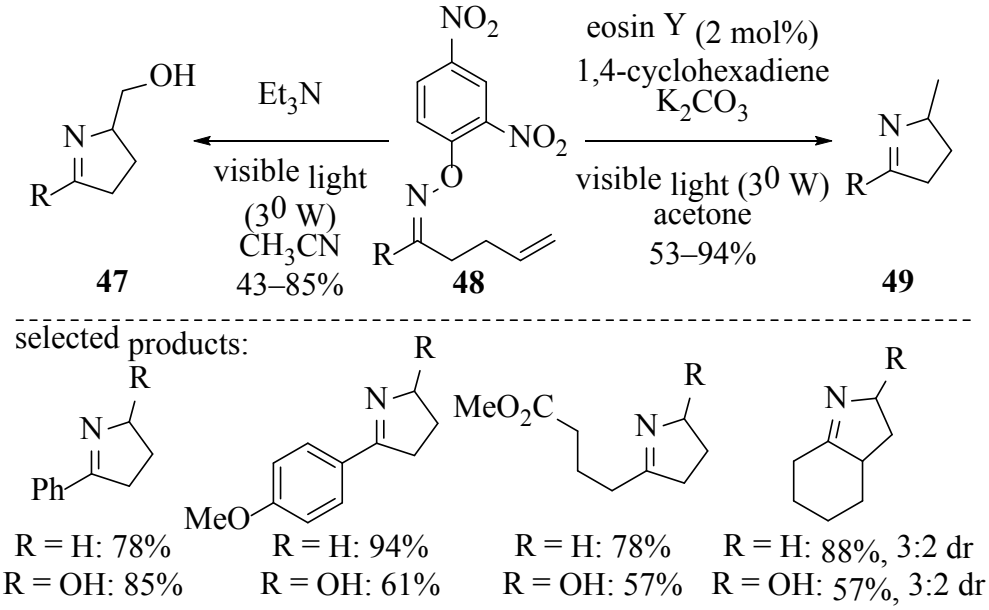
Chiba devised an efficient synthesis of polysubstituted pyridines **46** via a Mn(III)-catalyzed formal [3+3] annulation of cyclopropanols **44** and vinyl azides **45** (Scheme 1.15).[25−26] Whereas most reactions proceeded with stoichiometric amounts of the Mn(III) reagent, a catalytic protocol utilizing O_2 could be employed in some cases.[24] The proposed mechanistic pathway is shown in Scheme 15 and involves 6-*exo* cyclization of either an iminyl radical or an iminomanganese species onto the neighboring carbonyl group.



Scheme 1.15 [3+3] annulation mediated by $Mn(acac)_3$

Leonori developed two complementary light-mediated processes utilizing oxime ethers **48** as iminyl radical precursors (Scheme 1.16).[27] On the one hand, visible light irradiation of **48** in the presence of the organic dye eosin Y delivered dihydropyrroles **49** in 53−94% yields. Presumably, single-electron transfer (SET) from the excited state of eosin Y to **48** followed by fragmentation forms an iminyl radical, which then undergoes 5-*exo*-*trig* cyclization. On the other hand, Leonori found that irradiating **48** in the presence of Et_3N triggered an interesting and unexpected iminohydroxylation process, furnishing primary alcohols **47** in 43-85% yields. The

mechanism of this transformation is believed to involve light-mediated single-electron transfer from Et_3N to the substrate, and the oxygen atom in the products is thought to originate from a nitro group of the phenoxy moiety.



Scheme 1.16 Visible-light-promoted hydroiminations and iminohydroxylations

1.3 Conclusion

Strategies for efficient syntheses of a variety of useful aromatic and nonaromatic nitrogen-containing heterocycles via iminyl radical cyclizations were discussed in this chapter. Several different types of precursors including oximes and azides for the formation of iminyl radicals were also reported. The modern protocols for conducting these reactions are generally quite convenient and free of purification and toxicity issues that have plagued many traditional radical-based methods. The recent advances involving light-promoted iminyl radical cyclizations are interesting, and chemists should look forward to future developments in this promising area. Discoveries of practical nonphotochemical processes, particularly those promoted by microwaves or relatively inexpensive metal salts (e.g., copper or manganese), should attract

more attention and interest from the synthetic community. The enduring value of azaheterocycles in pharmaceuticals and medicinal chemistry combined with the need for safe, simple, and economical means of constructing them ensures that the remarkably efficient and environmentally friendly iminyl radical cyclizations will continue to grow in importance as the scope and utility of these methods expand.

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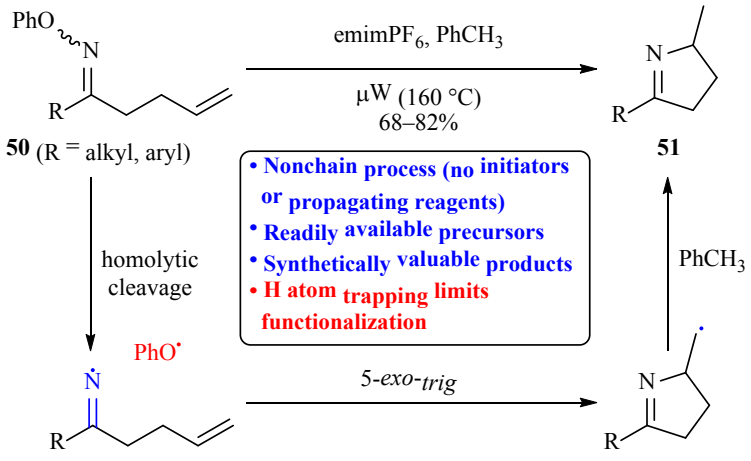
2 SYNTHESIS OF DIHYDROPYRROLES VIA MICROWAVE-PROMOTED IMINYL RADICAL CYCLIZATION

2.1 Introduction

Radical reactions are important because of their excellent functional group tolerance,[1,2] high degree of stereocontrol,[3,4] and ready incorporation into cascade transformations.[5,6] Nonetheless, most radical reactions require initiators (e.g. AIBN, benzoyl peroxide) and propagating reagents (e.g. Bu_3SnH, $(Me_3Si)_3SiH$) to commence and sustain chain reactions, which is a drawback. For example, most propagating reagents reduce a substrate by donation of a hydrogen atom, which limits the ability to introduce functional groups to the substrate. In addition, many initiators and propagating reagents are either explosive (e.g. AIBN), flammable, or toxic (e.g. Bu_3SnH). Whereas recent developments in photochemistry[7,8] do not require initiators and propagating reagents, the use of photoredox catalysts in these reactions causes turnover to be complicated, requiring either stoichiometric quantities of a sacrificial electron donor/acceptor or oxidation/reduction of a radical intermediate. In the latter case, elimination of the resulting cation[9] or protonation of the resulting anion[10] is typically rapid, thereby hindering further functionalization of the substrate. Additionally, commonly used photoredox catalysts are quite expensive ($Ru(bpy)_3Cl_2$: ca. \$90/g, $Ir(ppy)_2(dtbbpy)PF_6$: \$125/100 mg). Therefore, the development of practical radical processes without employing initiators, propagating reagents,

and photoredox catalysts would improve the field of organic synthesis by unlocking a host of functionalization opportunities.

In 2007, Walton and co-workers reported that *O*-phenyl oximes **50** undergo 5-*exo*-*trig* cyclizations upon microwave heating to furnish dihydropyrroles **51** in 68-82% yields (Scheme 2.1).[11] The proposed mechanism involves direct homolysis of the weak N–O bond (BDE = ca. 35 kcal/mol) under microwave heating,[12] generating an iminyl radical that cyclizes onto the terminal alkene. The resulting alkyl radical abstracts a hydrogen atom from toluene to deliver the product. We are quite interested in this reaction due to its lack of initiators and propagating reagents as well as its efficient and simple procedure. Moreover, the oxime ether substrates are easily prepared from corresponding ketones in a single step, and the dihydropyrrole adducts can be readily converted into valuable pyrrolidines which are embedded within numerous pharmaceutical and biological active natural products (e.g. clindamycin, eletriphtan, moxiflaxin, Figure 2.1). However, the use of toluene as both solvent and hydrogen atom source severely limits functionalization possibilities. To the best of our knowledge, the use of non-reducing conditions and further functionalization using other radical traps in the microwave-promoted iminyl radical cyclizations has not been investigated yet.



Scheme 2.1 Walton's iminyl radical cyclization

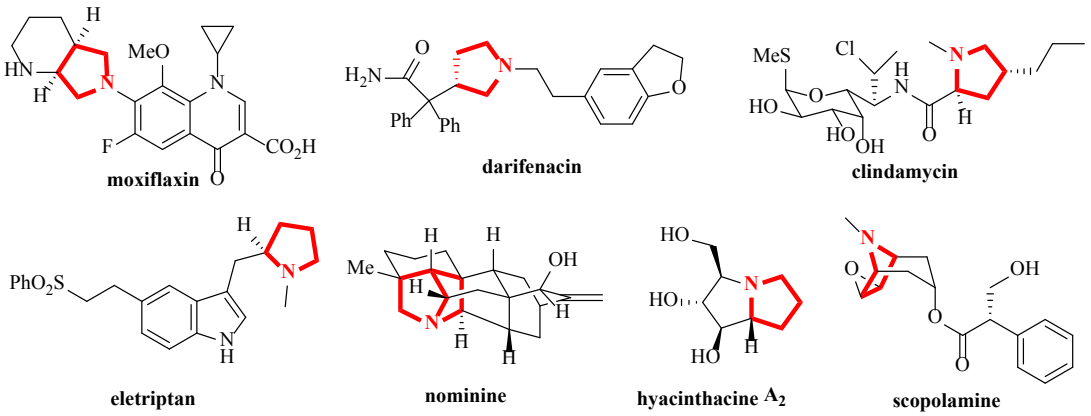
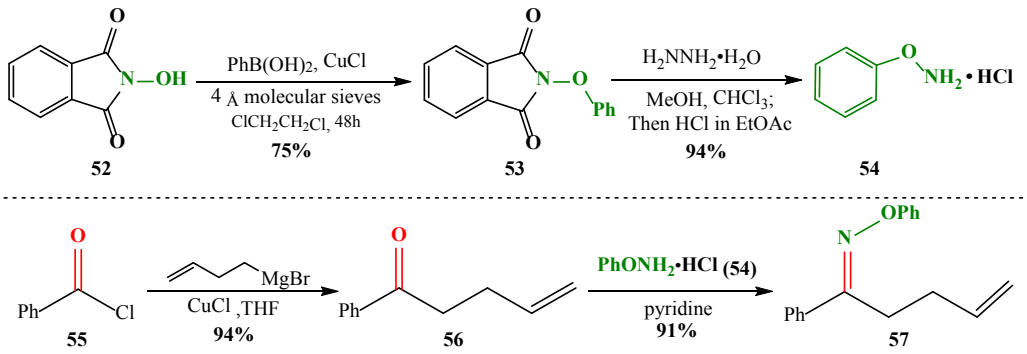


Figure 2.1 Pyrrolidine-containing pharmaceuticals and natural products

Therefore, our group is investigating the microwave-promoted iminyl radical reactions using different radical traps instead of hydrogen atom. In this Chapter, the formation of functionalized dihydropyrroles via highly diastereoselective iminyl radical cyclizations using TEMPO trapping will be discussed in detail.

2.2 Preparation of *O*-phenyl oxime ether

Alkenyl *O*-phenyl oxime ether **57** can be easily prepared in only two steps. As shown in Scheme 2.2, alkene-containing ketone **56** was prepared from benzoyl chloride **55** via nucleophilic addition with a Gilman reagent (organocopper reagent) in excellent yield.[13] Then, the corresponding ketone reacted with *O*-phenoxyamine hydrochloride (**54**) in pyridine to furnish **57** in 91% yield.[11] The primary amine **54** was prepared in two steps, which is a similar protocol as Gabriel amine synthesis.[14] *N*-hydroxyphthalimide **52** reacted with 3 equiv of phenylboronic acid, and 1 equiv of $Cu(OAc)_2$ at room temperature, forming *N*-phenoxyphthalimide **53** in 75% yield. Deprotection of **53** by treating with hydrazine monohydrate delivered *O*-phenoxylamine. After purification by flash chromatography, the free base oil was converted into a more stable HCl salt **54** by adding 4.0 M HCl in EtOAc.

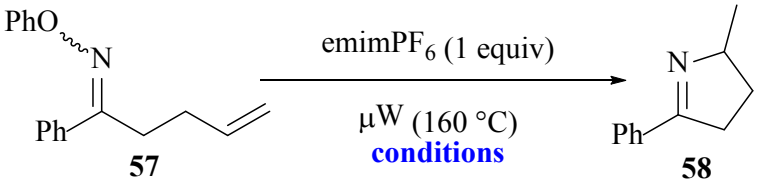


Scheme 2.2 Preparation of alkenyl *O*-phenyl oxime ether

2.3 Study with different solvents

In order to extend the scope of Walton's iminyl radical cyclization using other radical traps such as TEMPO, we first need to optimize the reaction using other solvents which could not function as a hydrogen atom donor. As shown in Table 2.1, the iminyl radical cyclization of alkenyl *O*-phenyl oxime ether **57** furnishing dihydropyrrole **58** was studied using different solvents under microwave heating (160 °C).

Table 2.1 Optimization of iminyl radical cyclization with different solvents



entry	H atom donor	solvent	yield
1	toluene	toluene	68%
2	toluene[a]	benzene	n.p.[c]
3	toluene[a]	DMF	n.p.
4	toluene[b]	*t*BuPh	66%
5	toluene[b]	$PhCF_3$	72%
6	toluene[b]	benzene	43%

[a]3 equiv toluene was added. [b]10 equiv toluene was added.
[c]n.p. means no product

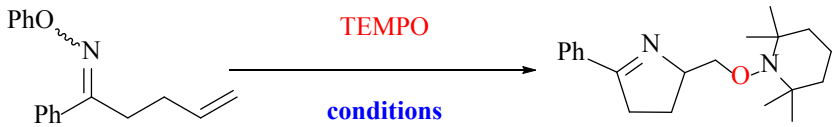
One equiv of ionic liquid 1-ethyl-3-methyl-*1H*-imidazol-3-ium hexafluorophosphate (emimPF_6) was added in this reaction in order to increase the polarity of the reaction mixture to facilitate efficient microwave heating (160 °C). No product was found using benzene or DMF as solvent with 3 equiv of toluene as hydrogen atom donor (Table 2.1, entry 2 and 3). However, desired product **58** was obtained in the presence of 10 equiv toluene with *t*-butylbenzene, trifluorotoluene, or benzene as solvent (Table 2.1, entries 4−6). Specifically, a 72% yield was obtained using trifluorotoluene as solvent, which is a higher yield than Walton's reaction using toluene (Table 2.1, entry 1).[11]

2.4 Radical trapping with TEMPO

We first studied the TEMPO trapping of iminyl radical cyclizations as shown in Table 2.2. The cyclization furnishing dihydropyrrole **59** did not work if using *t*-butylbenzene or trifluorotoluene as solvent under microwave irradiation at 160 °C even if 10 equiv of TEMPO was added (Table 2.2, entries 1−4). A possible reason was that TEMPO might have decomposed under high temperature (160 °C). Excitingly, the reaction worked quite well in the presence of 3.0 equiv TEMPO in trifluorotoluene under microwave irradiation at 98 °C for 15 min (Table 2.2, entry 5). The yield (98%) was unchanged when reducing the amount of TEMPO to 1.5 equiv (Table 2.2, entry 6). Since trifluorotoluene is a more polar solvent than toluene, we reasoned that the ionic liquid additive in the reaction might not be required. Indeed, microwave heating was efficient in its absence, leading to product **59** with yield unchanged (Table 2.2, entry 6). Additionally, a slightly less equiv of TEMPO (1.1 equiv) with longer reaction time (30 min) also favored the reaction in 92% yield (Table 2.2, entry 12). Conversion of **57** into **59** also proceeded with conventional heating in an oil bath, albeit with a longer reaction time (3 h) and a slightly

lower yield (Table 2.2, entry 13). Moreover, microwave irradiation with lower temperatures (90 °C or 80 °C) was studied as well; however, trace or no product was found (Table 2.2, entries 8−11).

Table 2.2 Iminyl radical cyclization with TEMPO trapping

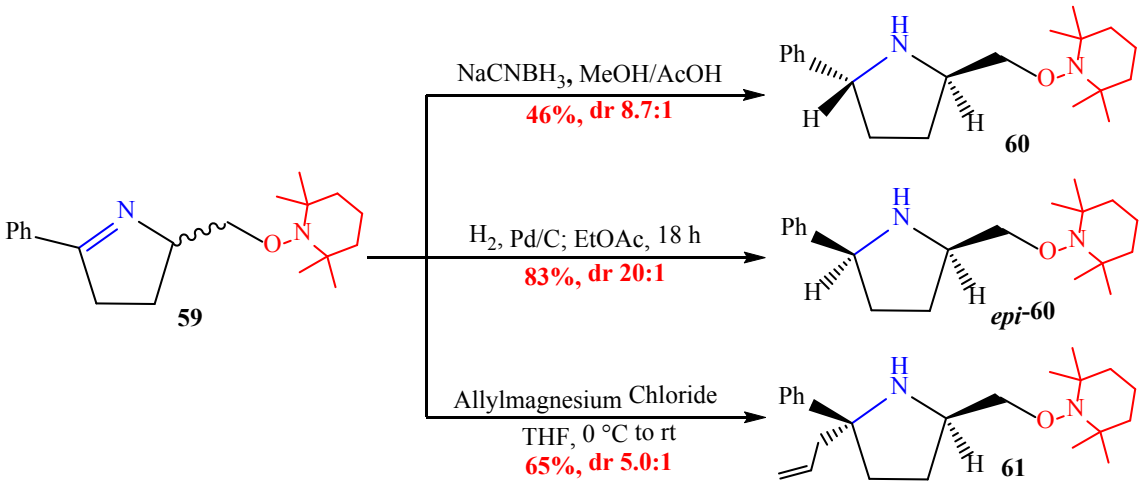


57 **59**

entry	solvent	emimPF$_6$ (equiv)	TEMPO (equiv)	temperature (°C)	time (min)	yield (%)
1	*t*BuPh	1.0	2.0	160	15	n.p.[a]
2	*t*BuPh	1.0	10.0	160	15	n.p.
3	PhCF$_3$	1.0	2.0	160	15	n.p.
4	PhCF$_3$	1.0	10.0	160	15	n.p.
5	PhCF$_3$	1.0	3.0	98	15	98
6	PhCF$_3$	1.0	1.5	98	15	98
7	PhCF$_3$	0	1.5	98	15	98
8	PhCF$_3$	0	1.5	90	15	trace
9	PhCF$_3$	0	1.5	90	30	trace
10	PhCF$_3$	0	1.5	80	15	n.p.
11	PhCF$_3$	0	1.5	80	30	n.p.
12	PhCF$_3$	0	1.1	98	30	92
13	PhCF$_3$	0	1.5	98	180[b]	84

[a]n.p. means no product. [b]conventional heating in an oil bath

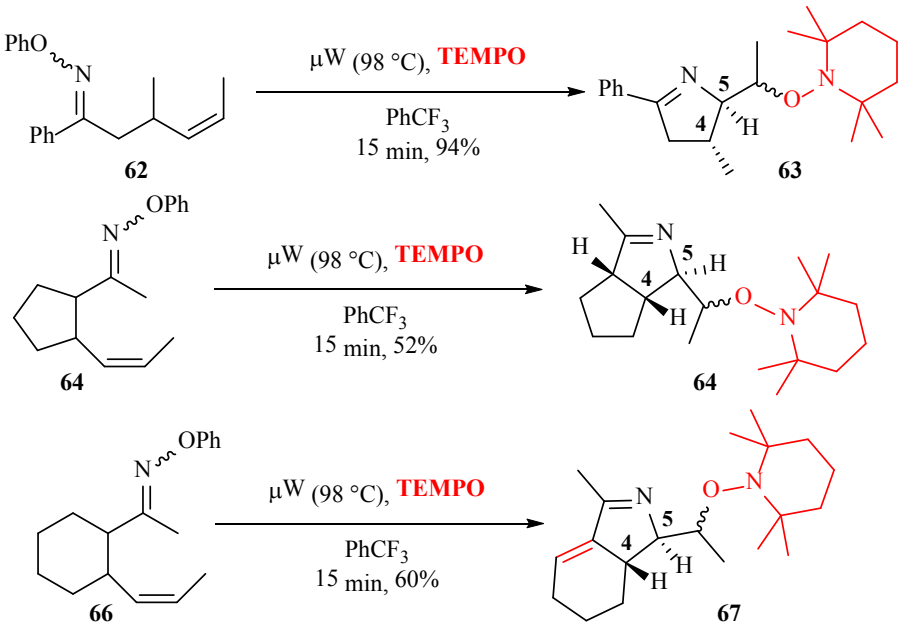
We then studied stereoselective functionalization of cycloadduct **59**. We have found that Grignard addition, catalytic hydrogenation, and hydride reduction proceeded with useful levels of diastereoselectivity (Scheme 2.4). Significantly, *trans*-pyrrolidine **60** and *cis*-pyrrolidine *epi*-**60** are accessible via catalytic hydride and hydrogenation in 43% and 83% yield with 8.7:1 and 20:1 dr, respectively. The ratio of diastereoselectivity was obtained using HPLC (solvent: 90/10, hexane/2-propanol).



Scheme 2.3 Stereoselective functionalization of dihydropyrrole **59**

2.5 Highly diastereoselective iminyl radical cyclization with TEMPO trapping

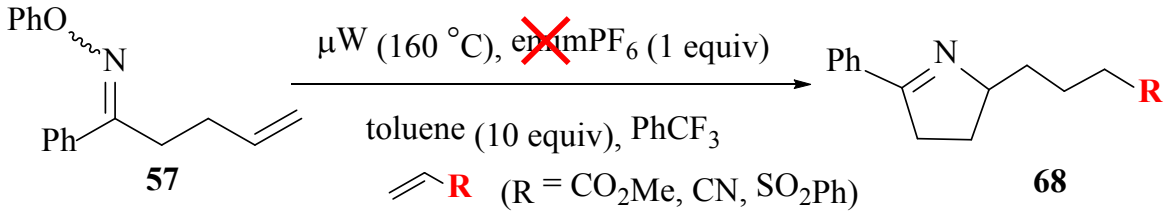
We then studied the prospects for stereoselective iminyl radical cyclizations using substituted *O*-phenyl oxime ethers, and our results obtained recently are encouraging. As shown in Scheme 2.4, *O*-phenyl oxime ethers **62**, **64**, and **66** were subjected to microwave irradiation in the presence of TEMPO afforded dihydropyrroles **63**, **65**, and **67** in good to excellent yields. Although the negligible levels of stereocontrol with respect to the exocyclic stereocenters were expected, excitingly, in each case the stereocenters (C4 and C5) on the newly formed dihydropyrrole rings were generated with complete diastereoselectivity. The substituents on C4 and C5 were in a *trans* relationship in all three examples as determined by NOESY studies. Interestingly, the dehydrogenation occurred in the cyclization of cyclohexane-containing substrate **66** and contrasted with the results obtained from cyclization of cyclopentane-containing substrate **64**. A hydrogen atom abstraction mediated by a TEMPO- or phenoxy-radical may play a role in this process. The failure of **64** to follow a similar pathway may be due to the increased ring strain caused by forming a radical in a 5-membered ring versus in a 6-membered ring.



Scheme 2.4 Highly diastereoselective iminyl radical cyclization

2.6 Other radical trapping agents

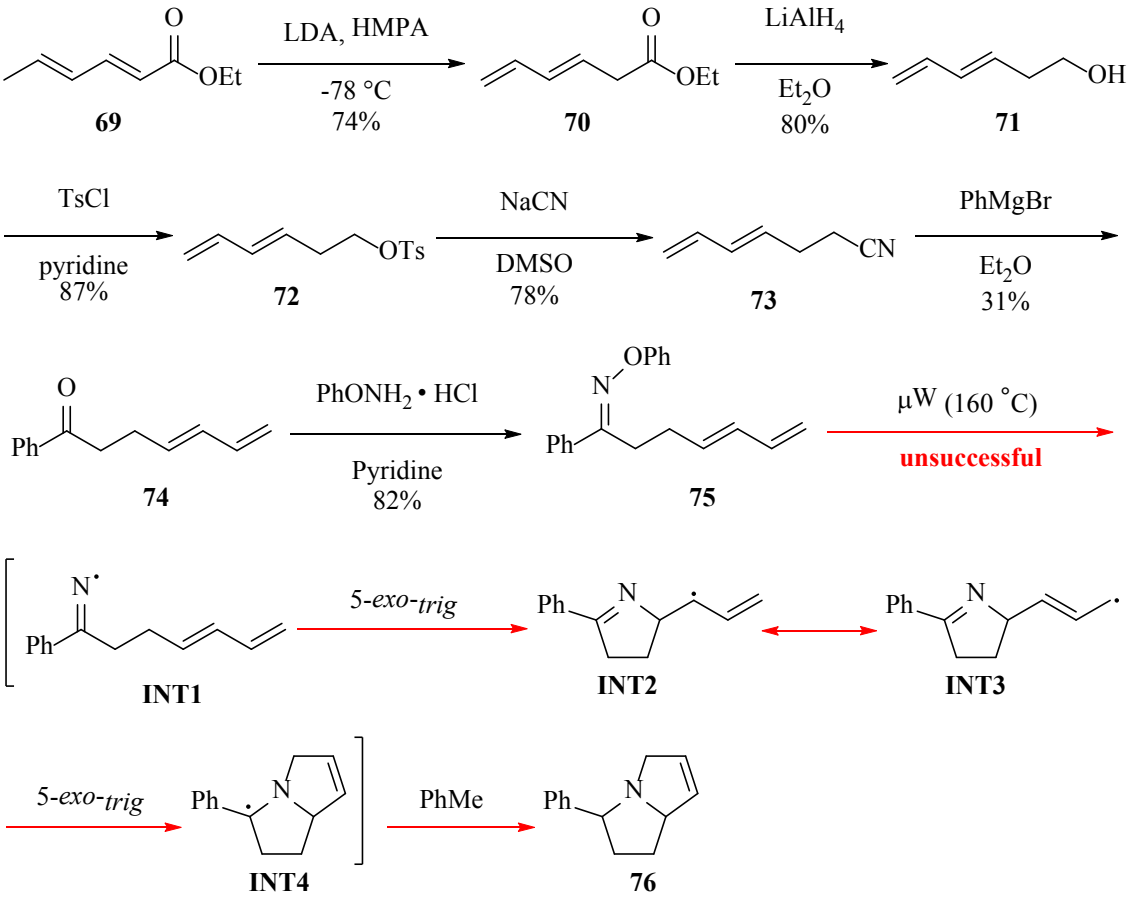
Electron-deficient alkenes as radical traps instead of TEMPO were studied. As shown in Scheme 2.5, *O*-phenyl oxime ether **57** in the presence of 3 equiv alkene and 10 equiv toluene in trifluorotoluene was treated under microwave heating. However, the reaction did not work and no product was found.



Scheme 2.5 Iminyl radical cyclization with ethyl acrylate trapping

Moreover, we tested an interesting cascade radical cyclization which was shown in Scheme 2.6. The iminyl radical precursor **75** was prepared in 7 steps from ethyl sorbate **69**. Subjection of **69** with LDA under -78 °C furnished the desire diene **70**.[15] Reduction of ethyl ester **70** using

lithium aluminium hydride ($LiAlH_4$) formed primary alcohol **71** in 80% yield. Cyanide **73** was obtained in two steps from alcohol **71** by treating with 4-toluenesulfonyl chloride (TsCl) followed by nucleophile substitution in the presence of NaCN.[16] Grignard addition of cyanide **73** in the presence of phenylmagnesium bromide provided ketone **74**,[17] and then treatment with *O*-phenoxyamine hydrochloride in pyridine delivered *O*-phenyl oxime ether **75**. Presumably, a bicyclic compound **76** could be formed via a cascade radical cyclization starting from iminyl radical (**INT1**) formed via homolysis of N−O bond under microwave heating. Unfortunately, the cascade cyclization was unsuccessful, as no desired product was found but an unknown dimer was detected by mass spectrometry.



Scheme 2.6 Cascade radical cyclization

2.7 Conclusion

We reported an efficient functionalized dihydropyrrole synthesis from *O*-phenyl oxime ethers via microwave-promoted iminyl radical cyclization using TEMPO trapping in excellent yields. In addition, highly diastereoselective iminyl radical cyclizations occurred from substituted *O*-phenyl oxime ethers, affording desired products in good to excellent yields. Moreover, studies of the iminyl radical cyclization using electron-deficient alkenes as radical trapping agents and a cascade radical cyclization were reported, although these reactions were unsuccessful. Therefore, the successful development of iminyl radical cyclization promoted by microwave with TEMPO trapping instead of hydrogen atom trapping will greatly extend the utility of this reaction.

2.8 References

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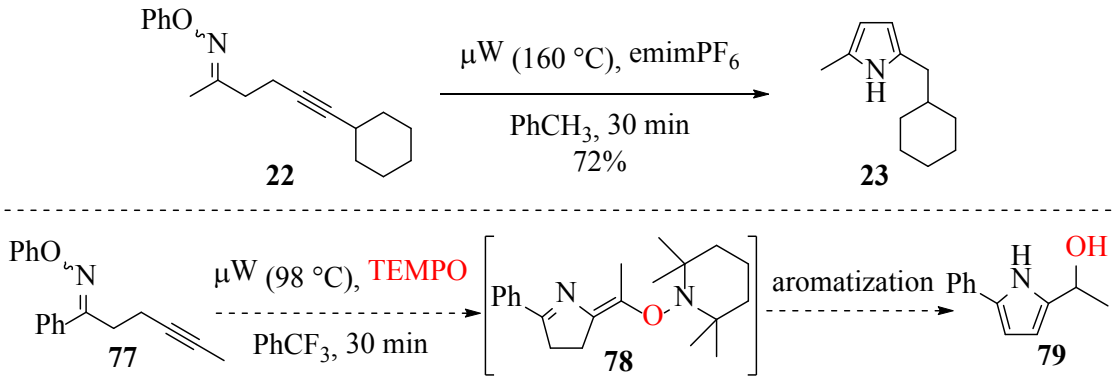
3 SYNTHESIS OF 2-ACYLPYRROLES VIA MICROWAVE-PROMOTED IMINYL RADICAL CYCLIZATION

In Chapter 2, we developed a powerful synthesis of functionalized dihydropyrroles from alkene-containing *O*-phenyl oxime ether via iminyl radical cyclization with TEMPO trapping promoted by microwave heating. Herein, a concise and efficient synthesis of 2-acylpyrroles from alkyne-containing *O*-phenyl oxime ethers via iminyl radical cyclization will be described in detail.[1]

3.1 Reaction optimization

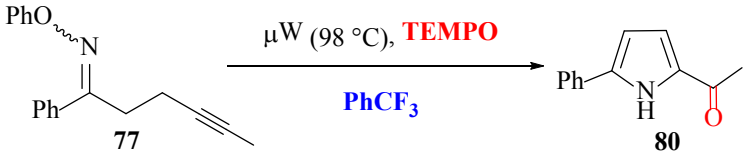
Besides the synthesis of dihydropyrroles via iminyl radical cyclizations (see Schemes 1.8 and 2.1), Walton and co-workers reported a synthesis of pyrrole **23** from alkyne-containing *O*-phenyl oxime ether **22** under microwave heating at 160 °C in 72% yield. Pyrrole **23** was formed due to isomerization and aromatization of the initially formed cycloadduct.[2] According to this synthesis and our successful development of cyclizations with TEMPO trapping, we proposed that a hydroxyl-containing pyrrole **79** could be formed from alkyne acceptor **77** via iminyl radical cyclization with TEMPO trapping followed by aromatization (see Scheme 3.1). If aromatization could be prevented, the resulting dihydropyrrole enol ether **78** would still be a valuable synthetic intermediate possessing numerous possibilities for further functionalization.



Scheme 3.1 Iminyl radcial cyclization with alkyne acceptor

Interestingly, neither dihydropyrrole enol ether **78** nor expected pyrrole **79** was found when the alkyne-containing *O*-phenyl oxime ether **77** was subjected to the conditions of our developed iminyl radical cyclization. After purification of the crude mixture using flash chromatography and analyzing its NMR spectrum, we found that an unexpected compound 2-acylpyrrole **80** was formed in moderate yield (Table 3.1, entry 1).[3] Optimization investigations showed that a good yield was obtained by adding two portions of 1.5 equiv of TEMPO (Table 3.1, entry 3).

Table 3.1 2-acylpyrrole synthesis via iminyl radcial cyclization with TEMPO trapping



entry	TEMPO (equiv)	time (h)	yield (%)
1	1.5	0.5	41
2	2.5	0.5	43
3[a]	3.0	1.0	83
4[b]	3.0	12	52

[a]1.5 equiv of TEMPO was added at the beginning of the reaction, and a second portion was added after 30 min. [b]reaction performed at 98 °C in an oil bath

Additionally, we studied the cyclization with TEMPO trapping under conventional conditions. Heating a reaction mixture of oxime ether **77** in the presence of 3 equiv of TEMPO in

$PhCF_3$ at 98 °C in an oil bath for 12 hours furnished the product **79** in a lightly lower yield (Table 3.1, entry 3). This study indicates that iminyl radical cyclization occurs efficiently and beneficially under microwave irradiation although not required. The microwave-specific acceleration is not operative because this effect has only been reported in cases where microwave-absorbing ionic or polar solutes are selectively heated in nonpolar solvents.[4,5] A microwave-absorbing polar solvent ($PhCF_3$) was employed in our reaction, therefore it is likely that the entire reaction mixture is heated in relatively uniform fashion upon microwave irradiation.

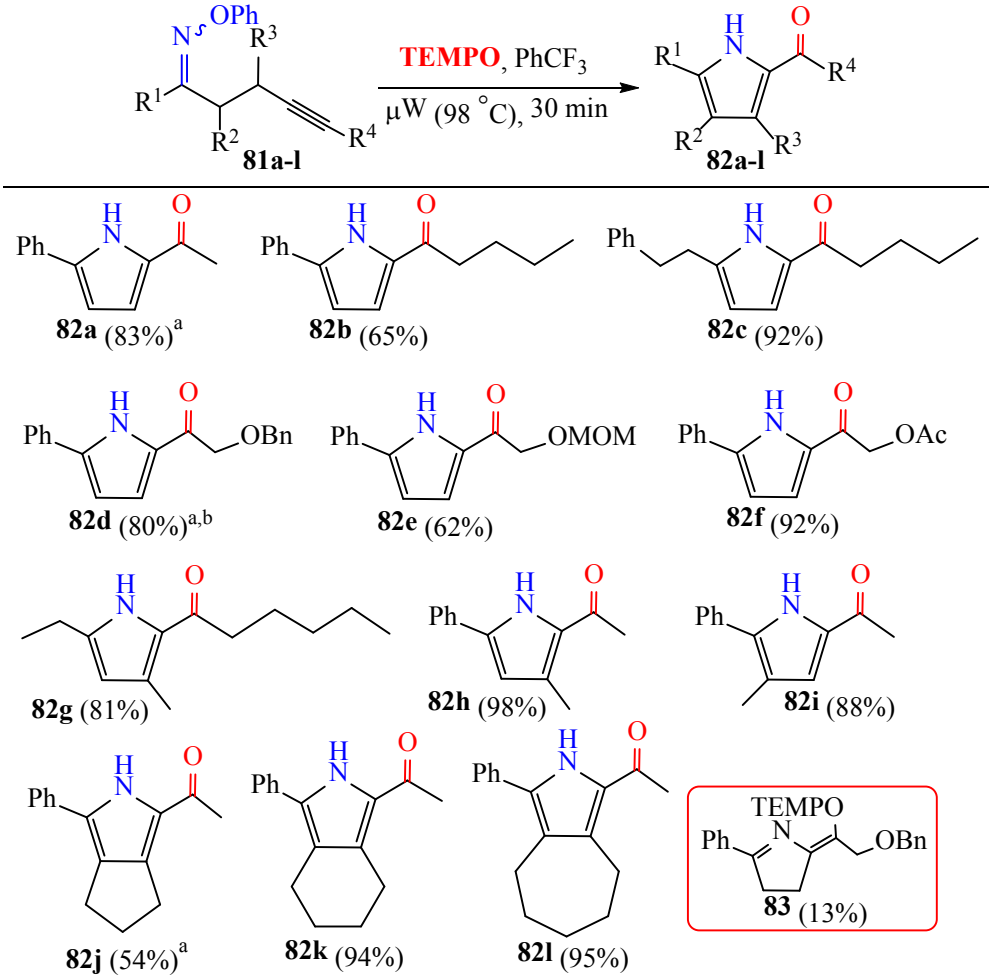
3.2 Scope of TEMPO-terminated iminyl radical cyclization

With optimized reaction conditions for the formation of 2-acylpyrrole **80**, we studied TEMPO-terminated microwave-promoted iminyl radical cyclizations of various alkyne-containing *O*-phenyl oxime ethers **81**. These oxime ethers were prepared via condensation of the corresponding ketones with *O*-phenoxyamine hydrochloride (**54**, see Scheme 2.2) in good to excellent yields. Details of these reactions and preparation of unknown ketones are provided in Chapter 6.

The TEMPO-terminated iminyl radical cyclization exhibited a broad substrate scope, furnishing a variety of polysubstituted 2-acylpyrroles (Scheme 3.2). While most of the iminyl radical cyclizations were performed by adding the entire 3.0 equiv of TEMPO in a single portion, the sequential addition of two 1.5 equiv portions afforded better yields in some cases (**82a**, **82d**, **82j**). Acyl groups larger than acetyl were shown to be easily installed (**82b**), and both aryl and alkyl groups were compatible at the C5 position (e.g. **82b** vs **82c**). Importantly, acyl groups containing alcohols protected with either base-labile (**82f**) or acid-labile (**82d** and **82e**) protecting groups were tolerated with the mild reaction conditions. Interestingly, in the formation of pyrrole

82d, a trace amount of TEMPO-containing dihydropyrrole enol ether **83** was also obtained, which could be the intermediate of this cyclization.

Besides the acyl group located at C2 and the alkyl or aryl group at C5 of the pyrrole, products with substituents at either C3 or C4 were obtained in excellent yields (**82g–i**). Moreover, cyclic substrates were also viable, delivering bicyclic pyrroles possessing fused five- (**82j**), six- (**82k**), and seven-membered rings (**82l**) in good to excellent yields.

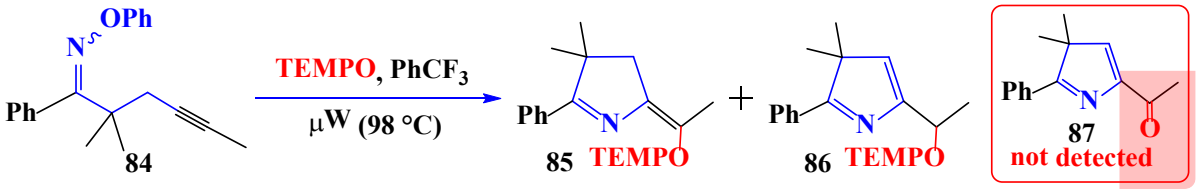


[a]TEMPO added in two 1.5 equiv portions, 60 min reaction time.
[b]13% of the dihydropyrrole enol ether **83** was also obtained

Scheme 3.2 Scope of 2-acylpyrrole formation via TEMPO-terminated iminyl radical cyclization

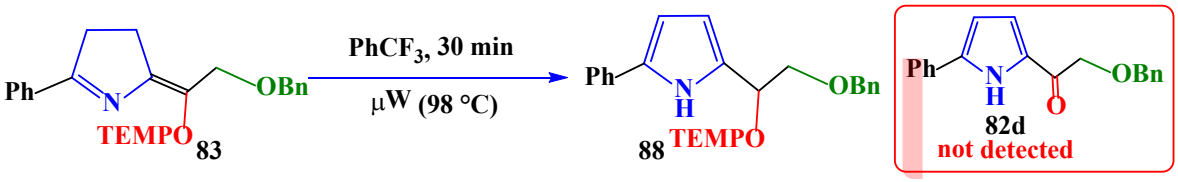
3.3 Mechanism investigation

In order to probe the mechanism of 2-acylpyrrole formation via TEMPO-terminated iminyl radical cyclization, we first conducted the radical cyclization of alkyne-containing *O*-phenyl oxime ethers **84** containing a quaternary carbon at C2 that is unable to form an aromatic pyrrole ring system. As shown in Scheme 3.3, this cyclization afforded a complex mixture that was not separable via flash chromatography. Analyzing the obtained mass spectrometry and ^{1}H NMR spectrum of the reaction mixture indicated the presence of TEMPO-containing dihydropyrrole enol ether **85** and its isomer **86**. Ketone **87**, which would have formed via fragmentation of **86**, was not detected.



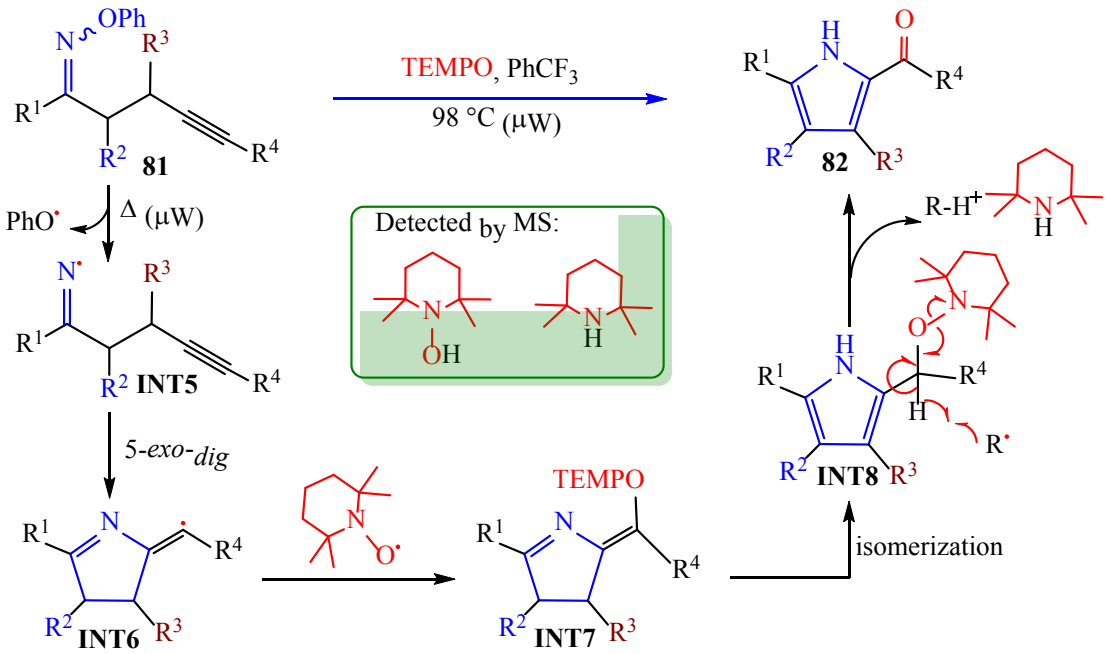
Scheme 3.3 Iminyl radical cyclization of alkyne **84**

We then subjected dihydropyrrole enol ether **83**, which was obtained as minor product in the course of synthesizing **82d**, to microwave irradiation in the absence of TEMPO. As shown in Scheme 3.4, TEMPO-containing pyrrole **88**, which was generated via isomerization, was visible in the ^{1}H NMR spectrum. However, 2-acylpyrrole **82d** was not detected from either mass spectrometry or ^{1}H NMR spectroscopy. These experimental results suggest that formation of an aromatic pyrrole ring system and the presence of radicals are both necessary to facilitate fragmentation and generate a ketone.



Scheme 3.4 Microwave heating of **83** without TEMPO

Therefore, as shown in Scheme 3.5, a plausible mechanism for the formation of 2-acylpyrroles **82** from alkyne-containing *O*-phenyl oxime ethers **81** was proposed. Homolytic cleavage of the N−O bond via microwave heating of *O*-phenyl oxime ethers **81** afforded iminyl radicals **INT5** along with a byproduct phenoxy radical. **INT5** underwent 5-*exo*-*dig* cyclization to deliver vinyl radical **INT6**, which was subsequently trapped by TEMPO to furnish enol ether **INT7**.[6,7] Then, isomerization of **INT7** provided pyrrole **INT8**. Presumably, the formation of a heteroaromatic ring system weakened the adjacent C−H bond sufficiently to facilitate a fragmentation triggered by abstraction of this hydrogen atom by a radical species. This radical species could be any of them that are present in the reaction mixture (e.g., TEMPO[8,9], phenoxy radical, or tetramethylpiperidinyl radical). The fragmentation proceeded via the homolytic cleavage of the N−O bond [10, 11] in **INT8** to provide 2-acylpyrrole **82** and the tetramethylpiperidinyl radical. The detection of *N*-hydroxytetramethylpiperidine and tetramethylpiperidine in the reaction mixture by mass spectrometry supports the proposed mechanism. In addition, the observation of enol ether **83** as a minor product in the synthesis of **82d** is consistent with this mechanism pathway, as is the unsuccessful formation of **87** from *O*-phenyl oxime ether **84** and the failure of **88** to undergo fragmentation in the absence of TEMPO.



Scheme 3.5 Proposed mechanism of TEMPO-terminated iminyl radical

3.4 Conclusion

Microwave-promoted iminyl radical cyclization terminated by trapping with TEMPO was developed for the synthesis of 2-acylpyrroles from alkyne-containing *O*-phenyl oxime ethers. The *O*-phenyl oxime ether substrates are easily prepared in a single step from corresponding ketones which are readily available using reported synthetic strategies. The formation of 2-acylpyrroles from alkyne radical acceptors is an efficient one step synthesis of these compounds in good to excellent yields. A plausible mechanism of the 2-acylpyrrole formation promoted by microwave irradiation was proposed, which involves isomerization and fragmentation.

Conventional syntheses of 2-acylpyrroles typically involve Friedel-Crafts acylatons[12,13] or Vilsmeier reactions.[14] Compared to these methods and others that are used for construction of substituted pyrroles,[15,16] this protocol developed in our laboratory is more attractive for its simple procedure and mild reaction conditions that tolerate the

presence of both acid- and base-labile functional groups. Additionally, toxic or hazardous reagents such as azo compounds, peroxides, and organotins are not required in this radical cyclization. Further investigations involving microwave-promoted iminyl radical reactions are currently ongoing in our laboratory.

3.5 References

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4 YAKU'AMIDE A AND B

4.1 Isolation, structure, and biological activity

Natural peptides bearing promising bioactivities play a significant role in medicine. Marine sponges were found containing a variety of polyketides and non-ribosomal peptides in recent years.[1] In 2010, Matsunaga and co-workers found that the *Ceratopsion* sponge obtained at a depth of 150 m at Yakushinsone in the East China Sea exhibited potent cytotoxicity.[2] Around 340 g (wet weight) *Ceratopsion* sponge was extracted with MeOH and $CHCl_3$/MeOH (1:1). Then H_2O was added, and extracted with $CHCl_3$ and *n*-BuOH. After extraction for three times, the residue was separated by ODS (C18 reverse phase) flash chromatography furnishing six fractions. The cytotoxic fraction was purified by reversed-phase HPLC (COSMOSIL $5C_{18}$-AR-II, 10 × 250 mm) with 60% *i*-PrOH/H_2O. The active fraction was further purified by the same condition to isolate two acyclic peptides yaku'amide A and B named after the collection site. The isolation paper[2] did not mention how many miligrams of yaku'amide A and B were obtained in total from 340 g (wet weight) sponge, but the SI of the paper mentioned that 0.2 mg of yaku'amide A and 0.1 mg of yaku'amide B were used for Marfey analysis and partial acidic hydrolysis.

Yaku'amide A and B have molecular formulas of $C_{83}H_{145}N_{15}O_{18}$ and $C_{84}H_{147}N_{15}O_{18}$, respectively as determined by HR-ESIMS. The initial structures of yaku'amide A and B were proposed according to extensive NMR spectroscopic analysis including ^{1}H, ^{13}C, COSY, TOCSY,

HMBC, and HMQC in conjunction with chemical degradations. Most of the stereocenters were established by analyzing NOESY data.

The originally proposed structures of yaku'amide A and B are shown in Figure 4.1, exhibiting fascinating molecular architecture including unique *N*-terminal acyl (NTA) and *C*-terminal amino groups (CTA). Additionally, they contain a wealth of *β*-hydroxyamino acid (*β*-OHAA) and α,β-dehydroamino acid (ΔAA) residues. Specifically, both yaku'amide A and B contain three *β*-OHAA residues including (2*S*, 3*R*)-hydroxyisoleucine (OHIle) and D- and L-hydroxyvaline (Val) along with four ΔAA residues including *Z*-ΔIle, *E*-ΔIle, and ΔVal. It is worth noting that the *Z*-ΔIle structure is unprecedented in natural products.[3] Moreover, the configuration of the stereocenter at the C4 position of the *N*-terminal acyl group was not assigned until a first total synthesis was reported by Inoue in 2013.[4]

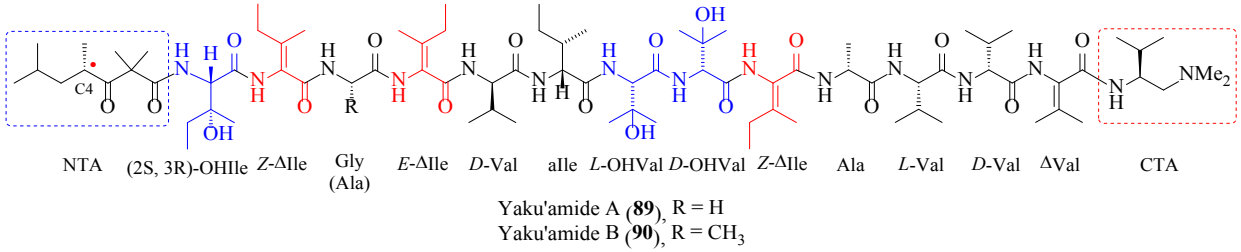


Figure 4.1 Initially proposed structure of Yaku'amide A and B

Preliminary biological studies revealed the potent anticancer activities of Yaku'amide A and B. These natural peptides were examined against P388 murine leukemia cells (JCRB17), and the IC_{50} values were 14 and 4 ng/mL, respectively. The inhibition profile of yaku'amide A towards a panel of 39 human cancer cell lines (JFCR39) including various types of human cancers[5,6] showed a unique profile compared to 38 anticancer drugs that have been examined in this panel.[7] The study indicates that yaku'amide A has a novel but unknown mode of action in its growth-inhibitory mechanism.

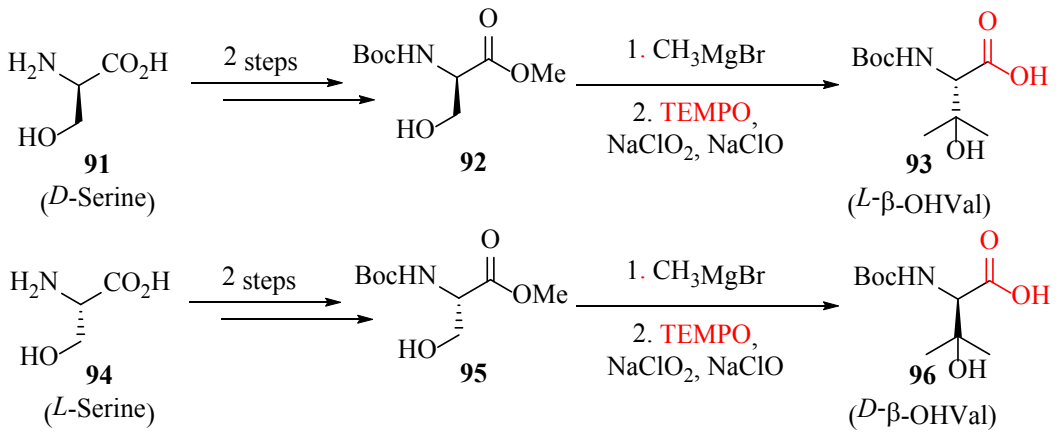
4.2 Inoue's total synthesis of Yaku'amide A

The complicated molecular architecture of yaku'amide A and B with a wealth of unusual amino acids, as discussed above, is quite challenging to synthesize. Especially difficult are the asymmetric constructions of the *β*-hydroxyamino acid ((2*S*,3*R*)-OHIle, D- and L-OHVal) and α,β-dehydroamino acid (*Z*-ΔIle, *E*-ΔIle, and ΔVal) residues. Herein, a recent total synthesis of yaku'amide A reported by Inoue's group will be described in detail.

4.2.1 Inoue's strategy for the synthesis of *β*-hydroxyamino acids (OHAA)

4.2.1.1 Synthesis of D- and L-*β*-OHVal

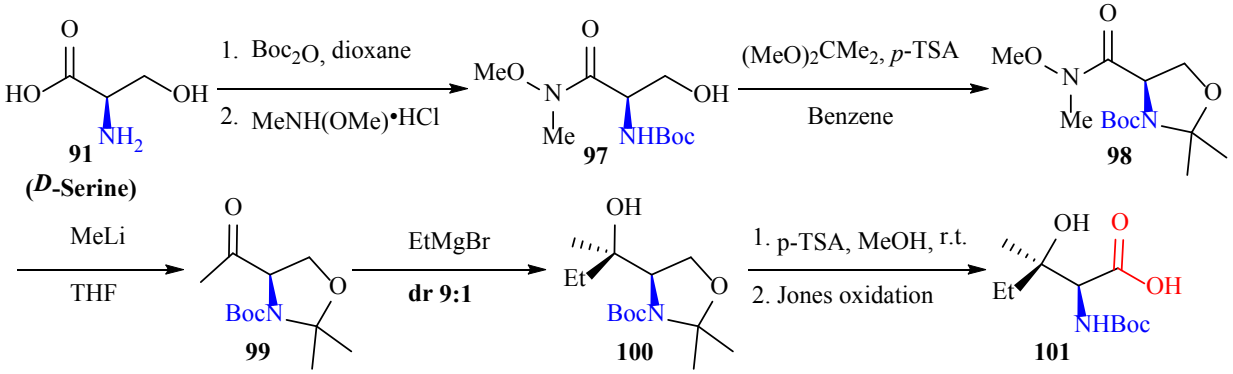
The previously reported asymmetric syntheses of *β*-OHVal and *β*-OHIle were employed in Inoue's synthesis of yaku'amide A. *N*-(*tert*-Butoxycarbonyl)-*L*-*β*-OHVal **93** was prepared in four steps from D-serine according to Lubell's synthesis.[8] As shown in Scheme 4.1, *N*-(*tert*-Butoxycarbonyl)-D-serine methyl ester **92** obtained in two steps from D-Serine **91** was subjected to excess methylmagnesium bromide. This furnished a diol, which was oxidized in one step to afford the carboxylic acid **93**. *N*-(*tert*-Butoxycarbonyl)-D-*β*-OHVal **96**, the enantiomer of **93**, was prepared in a similar fashion from L-Serine **94**.



Scheme 4.1 Syntheses of Boc-protected L- and D-*β*-OHVal from **91** and **94**

4.2.1.2 Synthesis of (2*S*, 3*R*)-OHIle

The preparation of (2*S*,3*R*)-OHIle in Inoue's total synthesis employed a 7-step protocol from D-Serine developed by Guanti and co-workers.[9] As shown in Scheme 4.2, Weinreb amide **98** was obtained from D-Serine **91** in three steps.[10] Compound **98** condensed with methyllithium to provide the key methyl ketone **99**. Grignard addition using ethylmagnesium bromide to the ketone **99** afforded tertiary alcohol **100** with high diastereoselectivity (dr 9:1). The steric effects of the cyclic *N*-*tert*-Butoxycarbonyl-*N*,*O*-isopropylidene moiety promoted the high diastereoselectivity of the Grignard addition, delivering the desired isomer **100**. Then, subsequent acetonide cleavage with *p*-toluenesulfonic acid (*p*-TSA) followed by Jones oxidation afforded *N*-*tert*-Butoxycarbonyl-(2*S*,3*R*)-OHIle **101**.



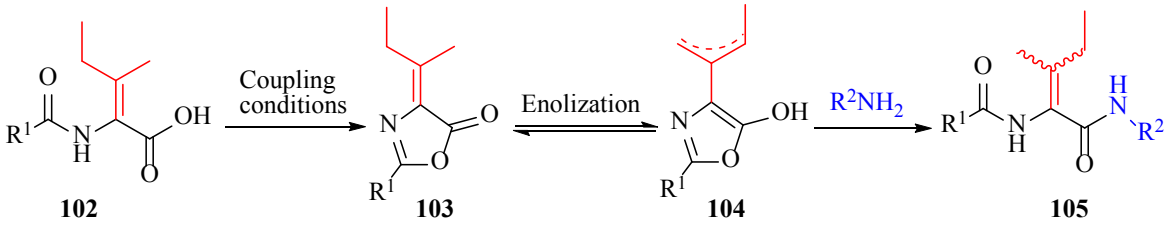
Scheme 4.2 Guanti's synthetic strategy of (2*S*,3*R*)-*β*-OHIle

4.2.2 Inoue's strategy for the synthesis of *Z*- and *E*-ΔIle-containing subunits

4.2.2.1 Prior strategy of ΔIle synthesis

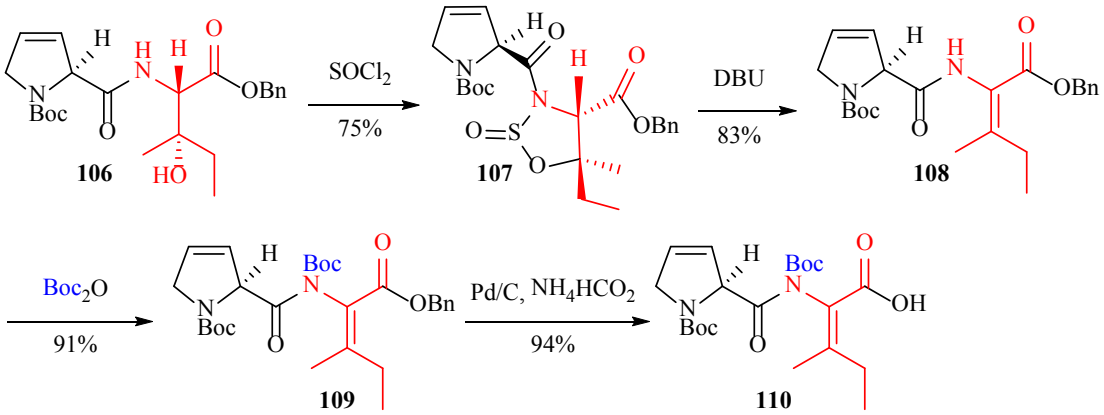
Yaku'amide A contains both *Z*- and *E*-ΔIle which are quite challenging to construct stereoselectively due to the existence of isomerization via azlactone formation. As shown in Scheme 4.3, the unprotected *Z*-ΔIle-containing carboxylic acid **102** could easily convert into azlactone **103** under coupling conditions, then enolized to deliver intermediate **104**. Subsequent

coupling with an amine would afford isomerized product **105** as a mixture of *Z- and E*-ΔIle-containing dipeptides.



Scheme 4.3 Isomerization of dehydroisoleucine via enolization of Azlactone

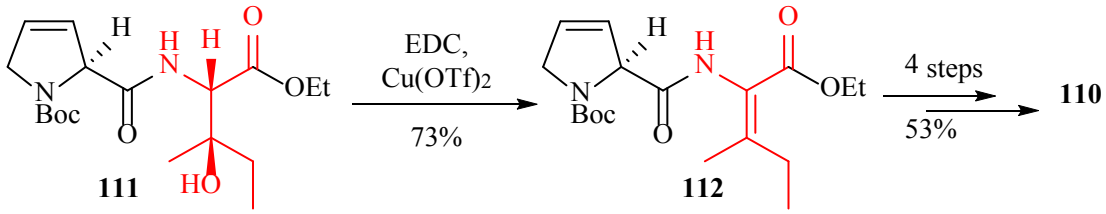
Stereoselective constructions of *E*-ΔIle have been achieved by two research groups in the course of synthesizing the phomopsins. Wandless and co-workers developed a two-step synthesis for the construction of an *E*-ΔIle derivative.[11] As shown in Scheme 4.4, the *E*-ΔIle derivative **108** was formed via the DBU-promoted E2 reaction of a cyclic sulfamidite intermediate **107** which was prepared by subjection of *β*-OHIle-containing dipeptide **106** to $SOCl_2$. In order to prevent the formation of an azlactone, the amide nitrogen must be protected. Thus, their target product *E*-ΔIle-containing carboxylic acid **110** used for coupling reaction with amine was prepared in two steps from **108** involving a Boc protection of the amide nitrogen.



Scheme 4.4 Wandless's synthesis of *E*-ΔIle

In 2009, Joullié and co-workers reported a Cu(II)-catalyzed *syn* elimination of *β*-OHIle derivative **111** in the presence of EDC, furnishing *E*-ΔIle-containing ester **112** in good yield

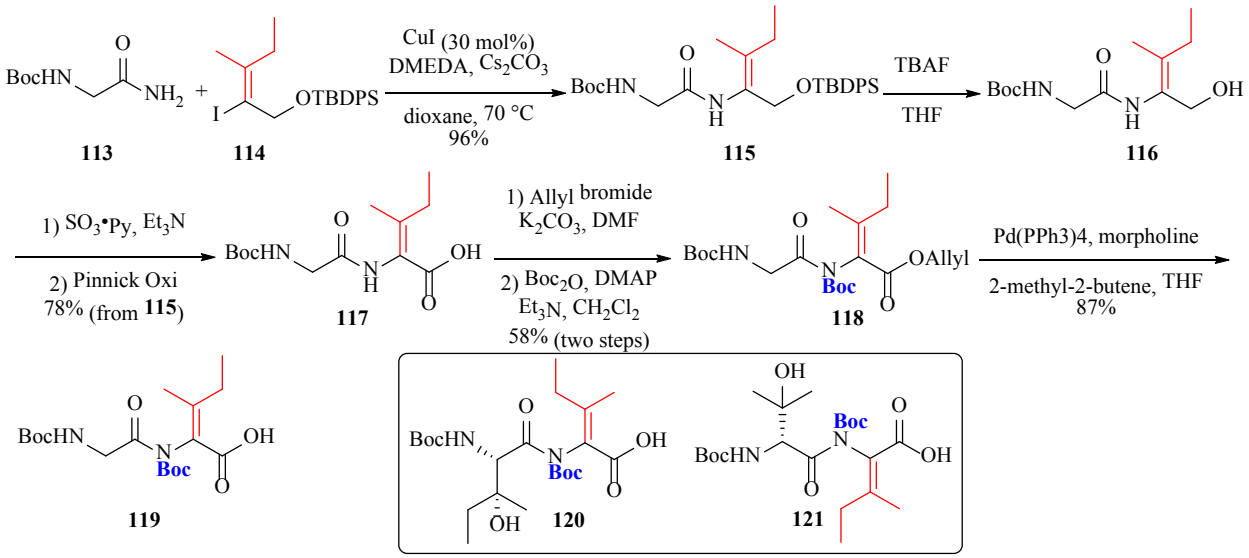
(Scheme 4.5).[12] Dipeptide **110**, a key intermediate for the synthesis of phomopsin A and B,[13] was prepared in four steps including Boc protection of the amide nitrogen.



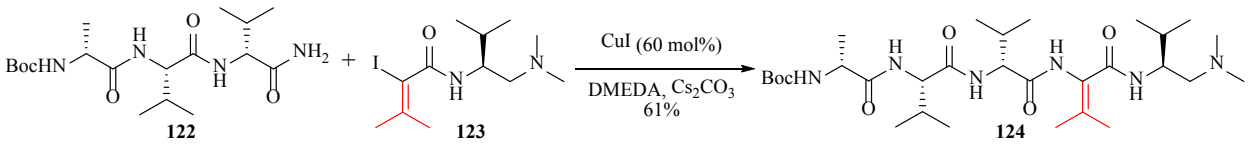
Scheme 4.5 Joullié's synthesis of *E*-ΔIle

4.2.2.2 Inoue's Cu-catalyzed cross-coupling reaction

Inoue and co-workers developed a Cu-catalyzed cross-coupling reaction based on Buchwald's method[14,15] to afford *Z*- and *E*-ΔIle-containing peptides in the course of their yaku'amide A synthesis. Scheme 4.7 shows the synthesis of *E*-ΔIle-containing carboxylic acid **119**, which is one of the key subunits for the synthesis of yaku'amide A. The synthetic route was started from the primary amide **113** which was coupled with vinyl iodide **114** using catalytic CuI in the presence of DMEDA and Cs_2CO_3. This afforded *E*-ΔIle-containing primary alcohol **115** with a TBDPS protecting group. The vinyl iodide **114** was prepared in three steps from the commercially available reagent ethyl 2-pentynoate. Deprotection of the TBDPS group using TBAF followed by oxidation reactions delivered carboxylic acid **117**. According to Wandless and Joullié's work, the *E*-ΔIle-containing carboxylic acid **117** cannot be used directly for the following coupling reaction since isomerization would occur via enolization of azlactone. Thus, Boc protection of the amide nitrogen bond is required, and was accomplished in three steps, furnishing desired compound **119** in 50% yield. This 7-step protocol was also employed for the preparation of the other two subunits **120** and **121**, both containing a *Z*-ΔIle residue. In addition, *C*-terminal pentapeptide **124** was synthesized in 61% yield via the Cu-catalyzed cross-coupling reaction of enamide **122** and vinyl iodide **123** (Scheme 4.7).



Scheme 4.6 Inoue's synthesis of *Z*- and *E*-ΔIle-containing dipeptides



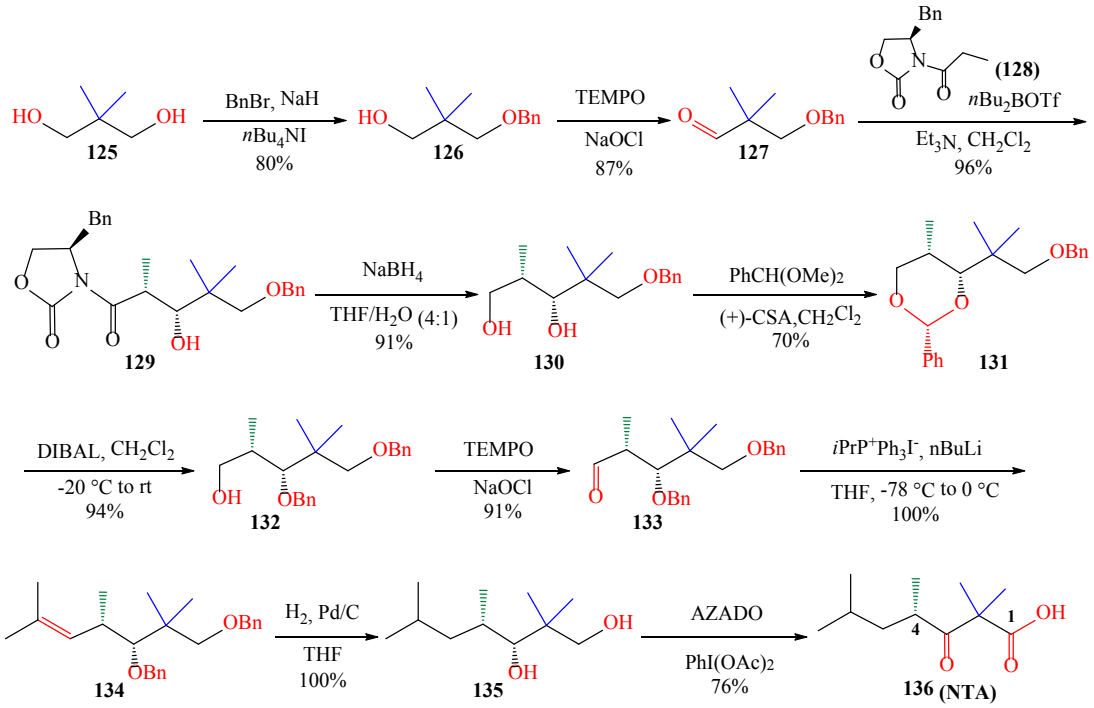
Scheme 4.7 Synthesis of *C*-terminal pentapeptide **124**

4.2.3 Inoue's synthesis of *N*-terminal acyl group (NTA)

The configuration at the C4 position of the N-terminal acyl group (NTA) in the structure of yaku'amide A was not determined in the original isolation work.[2] Inoue and co-workers synthesized both enantiomers of the NTA, and assigned the *S*-configuration to the NTA in their synthesis of yaku'amide A.

The synthetic route to the NTA with the desired *S*-configuration at the C4 position is shown in Scheme 4.8. A commercially available diol **125** was used as the starting material. One of the hydroxyl groups in **125** was protected as a benzyl ether (Bn), affording alcohol **126**. This compound was oxidized using TEMPO and NaOCl to deliver aldehyde **127**. The Evans asymmetric aldol reaction was employed to selectively deliver the key compound **129** with desired stereochemistry. Aldehyde **127** was subjected to the boron enolate of (*R*)-(−)-4-benzyl-3-

propionyl-2-oxazolidinone (**128**) to afford the *syn*-aldol adduct **129**. Reductive cleavage of the chiral auxiliary converted **129** into a diol **130** with excellent yield. Diol **130** was subjected to the sequence of protecting group manipulation, carbon-chain elongation using a Wittig reaction, and oxidation to afford the *N*-terminal carboxylic acid **136**. It is worth noting that the mild reaction conditions using AZADO-PhI(OAc)$_2$ in the final step successfully oxidized diol **135** to *β*-keto carboxylic acid **136** in one pot with high yield, and byproducts with C4-epimerization or C1-decarboxylation was not detected.

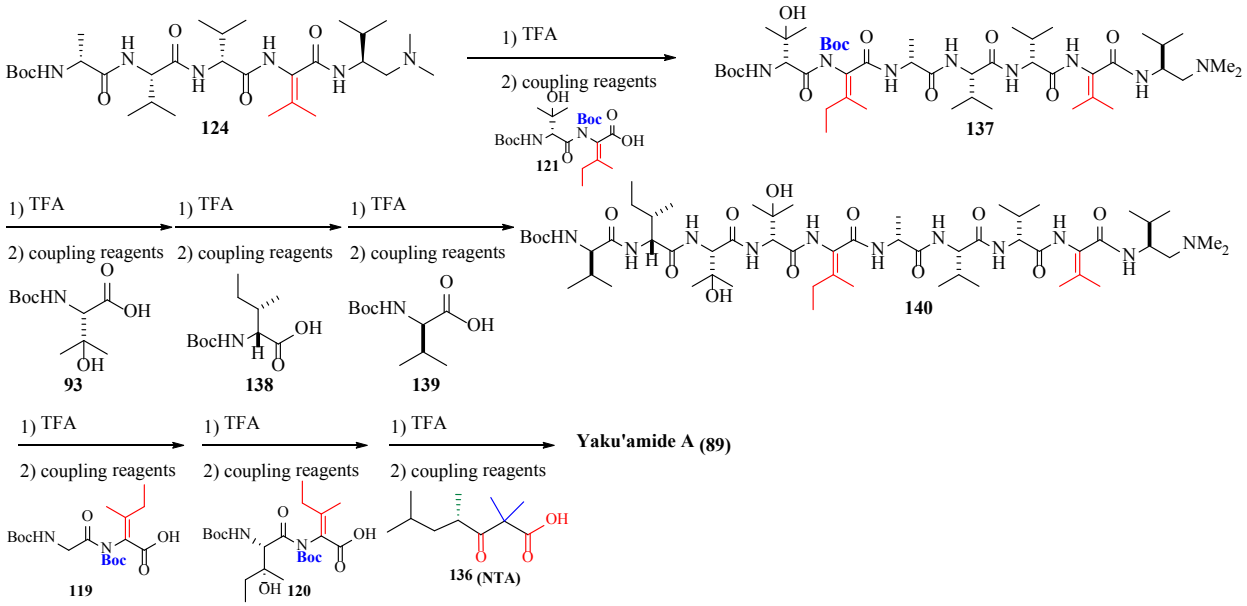


Scheme 4.8 Inoue's synthesis of the N-terminal acyl group **136**

4.2.4 Late-stage couplings of yaku'amide A synthesis

All required key subunits including *β*-OHAAs, *α*, *β*-ΔAAs, and the NTA were prepared, and employed in late-stage coupling reactions to complete the total synthesis of yaku'amide A. The most common "right-to-left" peptide synthetic strategy was employed in Inoue's synthesis of yaku'amide A.

Scheme 4.9 shows Inoue's peptide chain elongation strategy with continuous coupling reactions in the late stage. The Boc group of the *C*-terminal pentapeptide **124** was cleaved in the presence of trifluoroacetic acid (TFA), and the resulting amine was coupled to *Z*-ΔIle-containing dipeptide **121** to afford the heptapeptide **137**. Six iterations of a deprotection-coupling sequence were performed to install all other key fragments, delivering the originally proposed structure of yaku'amide A. In these hindered coupling reactions, two different types of coupling systems were used including PyBop−HOAt−*i*-Pr_2NEt and COMU−2,4,6-collidine. In summary, the originally proposed structure of yaku'amide A was synthesized by Inoue's group in 25 longest linear steps and 86 total steps. The configuration at the C4 position of NTA was also assigned in their work by comparison with the NMR spectrum of isolated natural compound combined with the results of bioassays.

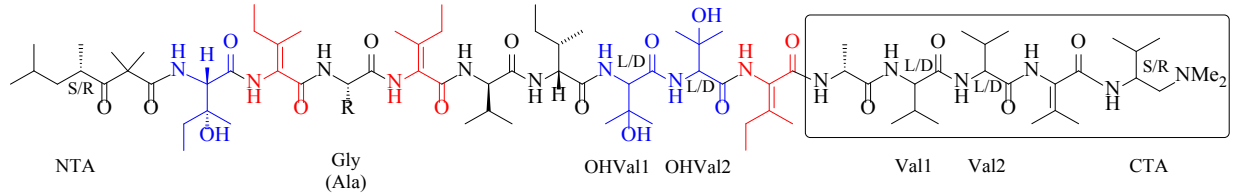


Scheme 4.9 Late-stage couplings for the construction of yaku'amide A

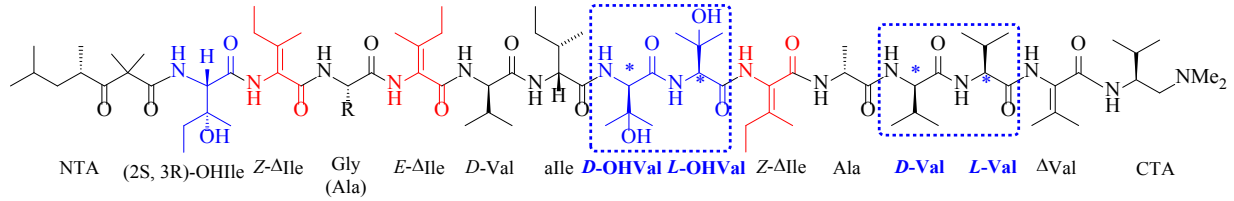
4.3 Structure revision of Yaku'amide A and B

In the course of the synthesis of yaku'amide B, Inoue and co-workers were found that the structure of the synthesized yaku'amide B was different compared to the isolated one, and the

originally proposed structures of yaku'amide A and B (**89** and **90**) were proved incorrect.[16] The structural information of natural yaku'amide B was obtained by applying the highly sensitive Marfey's analysis of the compound and its fragments. Inoue and co-workers first synthesized all possible isomers (8 in total) of the C-terminal pentapeptide with three different stereocenters. After comparing the C-terminal pentapeptide fragment obtained from natural yaku'amide B, they found that the correct configurations of Val1, Val2, and CTA are (*D*)-Val, (*L*)-Val, and (*S*)-CTA, respectively. In a similar way, the configurations of OHVal1 and OHVal2 were corrected as *D*- and *L*-, respectively (instead of *L*- and *D*- configurations). Therefore, the structural revision and total synthesis of revised yaku'amide A and B were reported in 2015 by the combination of natural compound degradation, mass spectrometry, chromatographic analyses, and chemical synthesis. As shown in Figure 4.2, the revised structures of yaku'amide A and B have the neighboring *L*- and *D*-*β*-OHVal and *L*- and *D*-Val residues were switched, relative to the originally proposed structures.



Yaku'amide A (**proposed structure**, **89**), R = H, OHVal1=*L*-OHVal, OHVal2=*D*-OHVal, Val1=*L*-Val, Val2=*D*-Val, (*S*)-CTA
Yaku'amide B (**proposed structure**, **90**), R = CH_3, OHVal1=*L*-OHVal, OHVal2=*D*-OHVal, Val1=*L*-Val, Val2=*D*-Val, (*S*)-CTA



Yaku'amide A (**revised structure**, **141**), R = H
Yaku'amide B (**revised structure**, **142**), R = CH_3

Figure 4.2 Structure revision of Yaku'amide A and B

4.4 Conclusion

A brief story of two natural tetradecapeptides yaku'amide A and B was described including their isolation, proposed structures, preliminary biological studies, structural revisions, and recent syntheses work. The first total syntheses of the two natural products by Inoue's group involved a highly efficient Cu(I)-catalyzed cross-coupling reaction to access both *Z*- and *E*-ΔIle-containing residues and a 10-step protocol to the construction of *N*-terminal acyl group. However, the total synthesis is not efficient and quite lengthy (25 longest linear steps and 86 total steps). Specifically, it suffers from lengthy preparation of *β*-OHAAs and inefficient functional group manipulations in the construction of ΔAA residues including their backbone amide protection. Therefore, the development of a more efficient and practical synthesis of yaku'amide A becomes significant and urgent in order to obtain this extremely scarce but potent anticancer agent in good amounts for its further biological studies. In the following chapter, our research efforts aimed at this target will be described in detail.

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5 TOTAL SYNTHESIS OF YAKU'AMIDE A

Yaku'amide A (**141**, Figure 5.1), isolated from a marine sponge in 2010, is a medium-sized peptide that contains the bulky dehydroamino acids (ΔAAs) dehydrovaline (ΔVal), *E*- and *Z*-dehydroisoleucine (ΔIle). It has an excellent IC_{50} value (14 ng/mL) against leukemia cells, making it a promising anticancer agent. Notably, its anticancer profile in the JFCR39 panel of cancer cell lines is different from that of known anticancer drugs, indicating that it acts by a novel but unknown mode of action. However, its natural supply is extremely limited, and a recent synthesis by Inoue is lengthy mainly due to the synthetic challenge of *E*- and *Z*-ΔIle residues as a result of their stereochemistry, greatly hindering further studies of its anticancer properties. The remarkable characteristics of yaku'amide A such as unique anticancer profile, potent bioactivity, and limited supply evoke our keen interest for an efficient synthesis of the natural product and investigation of its mode of action.

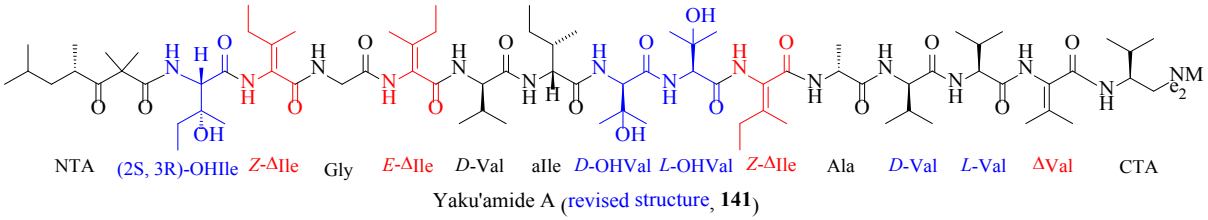


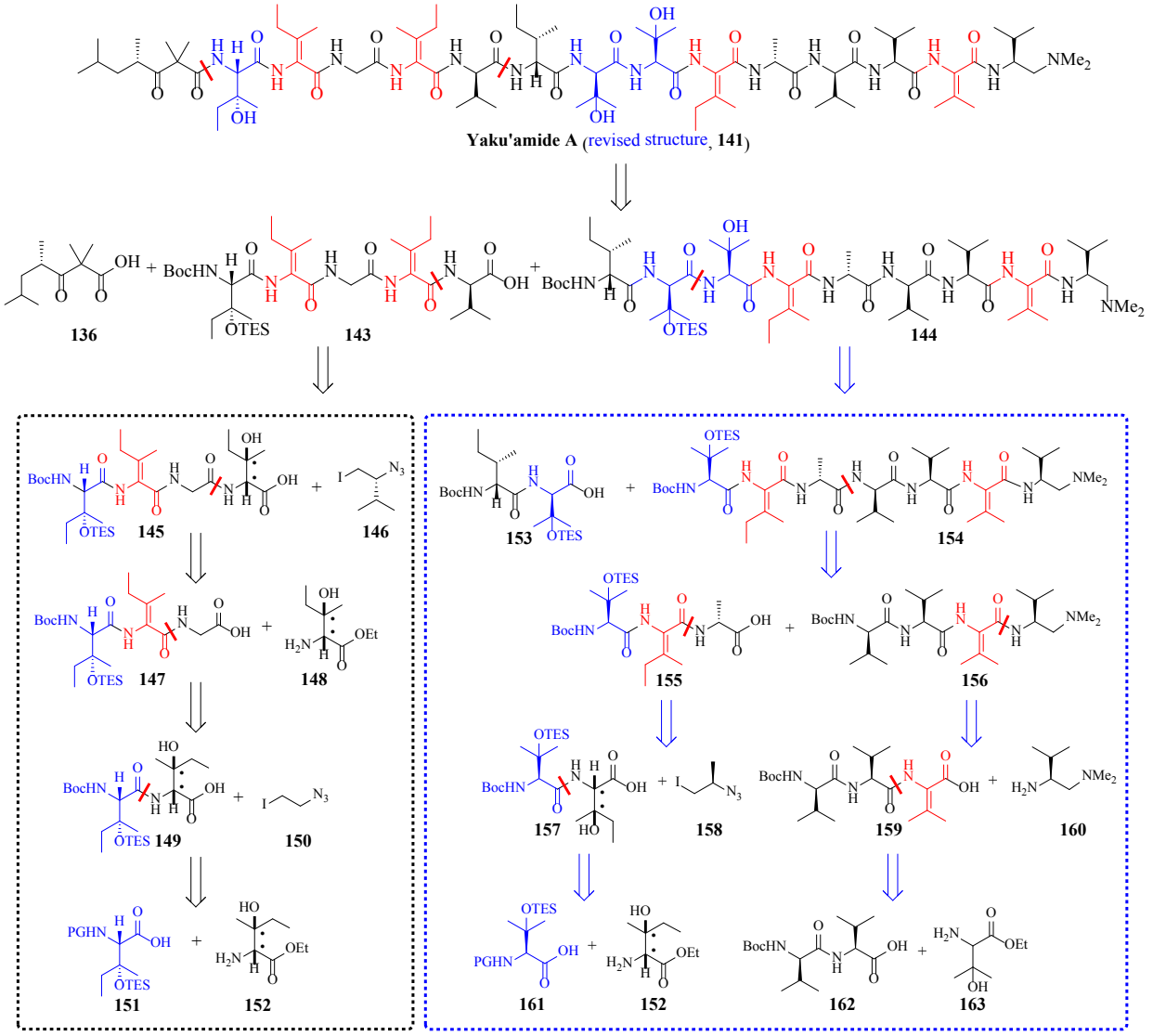
Figure 5.1 Structure of yaku'amide A

5.1 Retrosynthetic analysis

We successfully developed more efficient syntheses of *β*-hydroxyamino acids (*β*-OHAAs) and ΔAAs in the course of yaku'amide A synthesis by employing base-free OsO_4-catalyzed aminohydroxylation[1] and a sequence including *anti* dehydration, azide reduction, and O→N acyl transfer.[2] Our retrosynthetic analysis of yaku'amide A (revised structure, **141**) was designed according to our developed methodology work, and is shown in Scheme 5.1. The natural peptide **141** is disconnected at the two indicated amide bonds to reveal three key subunits: an *N*-terminal acyl group (NTA) **136**, a left-hand pentapeptide **143** and a right-hand nonapeptide **144**. We planned to attach the NTA with its sensitive ketone group in the final step by following Inoue's precedent.[3,4] The NTA would be prepared via Myers' asymmetric alkylation[5] followed by a Mukaiyama-type aldol reaction,[6] Which would be more efficient with less synthetic steps compared to Inoue's route.[3] The *E*- and *Z*-ΔIle residues would be the most challenging components of **141** to construct. Thus we divided the remainder of the structure into a smaller subunit possessing both *E*- and *Z*-ΔIle residues (**143**) and a larger subunit possessing only one *Z*-ΔIle residue (**144**). We believed that this strategy would maximize synthetic convergence because a comparable number of linear steps should be required to access each subunit. According to our initial studies, Boc and TES groups would be employed for protection of the amine and hydroxyl groups, respectively.

The construction of the left-hand pentapeptide **143** containing both *E*- and *Z*-ΔIle residues was projected to involve two dehydration–azide reduction–O→N acyl transfer sequences. The carboxylic acid **143** can be prepared from oxidation of the corresponding primary alcohol which would be prepared from tetrapeptide **145** and a chiral azido iodide **146** via the dehydration–azide reduction–O→N acyl transfer sequence. The tetrapeptide **145** would be accessible by coupling

an acid **147** with a racemic amine **148** obtained from a *cis*-enoate via our developed aminohydroxylation. Scission of tripeptide **147** at the indicated amide bond revealed dipeptide **149** and glycine surrogate **150**. The dipeptide **149** would be easily prepared from (2*S*,3*R*)-OHIle derivative **151** and racemic amine **152** (epimer of **148**) which would be prepared from a *trans*-enoate via aminohydroxylation.



Note: Stereocenters marked by asterisks possess the indicated relative stereochemistry. PG in **151** and **161** means protecting group

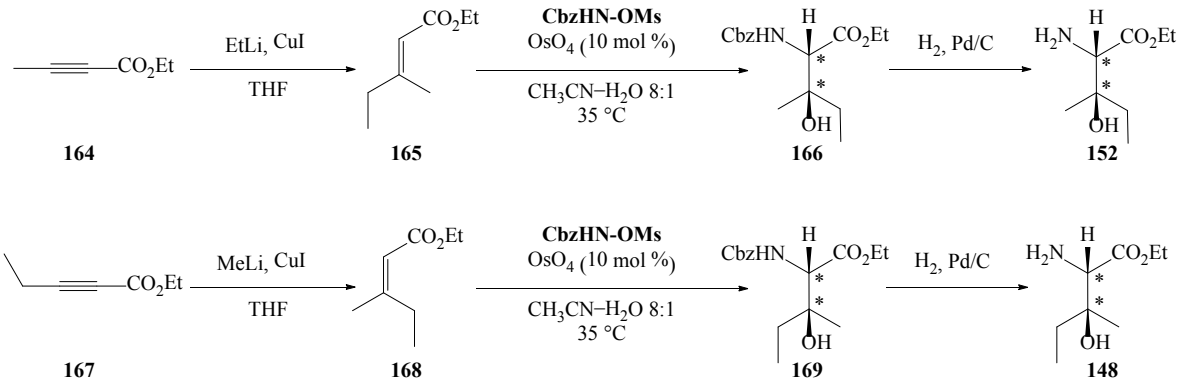
Scheme 5.1 Retrosynthetic Analysis

Inspection of nonapeptide **144** indicated that it would be obtained from dipeptide **153** and heptapeptide **154**. Dipeptide **153** would be prepared via coupling of D-OHVal derivative with Boc-D-*allo*-Ile which is a commercially available reagent. Further scission of heptapeptide **154** revealed the two smaller subunits tripeptide **155** and tetrapeptide **156**. The *Z*-ΔIle-containing tripeptide **155** can be prepared by combining aninohydroxylation with a three-step sequence involving *L*-OHVal derivative **161** and amine **152**. We proposed to employ the azlactone formation–ring opening chemistry[1] to construct the *C*-terminal tetrapeptide **156**, which involves the scission of *C*-terminus of ΔVal to deliver **159** and a known amine **160**.[7] The tripeptide **159** would be synthesized via straightforward coupling of the dipeptide **162** and a racemic amine **163**.

5.2 Synthetic strategy for the construction of β-OHAAs and ΔAAs

5.2.1 Synthesis of β-OHAAs

According to our retrosynthetic analysis, the D-OHVal, L-OHVal, and (2*S*,3*R*)-OHIle derivatives are to be used as starting materials for the synthesis of our key subunits dipeptide **153**, tripeptide **155**, and pentapeptide **143**, respectively. These *β*-OHAA derivatives can be prepared via base-free OsO_4-catalyzed aminohydroxylation developed by Zhiwei Ma and co-workers as shown in Scheme 5.2.[1]



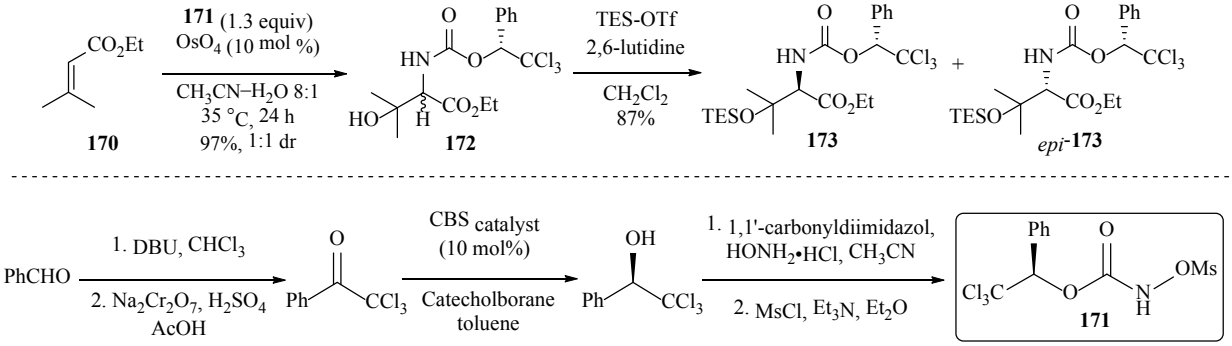
Notes: stereocenters marked by asterisks indicate relative stereochemistry

Scheme 5.2 Preparation of racemic amines **148** and **152** via regioselective aminohydroxylation

Regioselective aminohydroxylation of *trans* trisubstituted alkene **165** catalyzed by 10 mol% of OsO_4 afforded **166**. Then, subsequent hydrogenation using Pd/C under 500 Psi H_2 cleaved Cbz protecting group, delivering a racemic mixture of amine **152** with the amino and hydroxyl groups in a *cis* relationship. The isomer **148** can be prepared in a similar fashion from *cis* alkene **168** in two steps as well. These amines **148** and **152** will be used for the formation of *E*-ΔIle and *Z*-ΔIle, respectively.

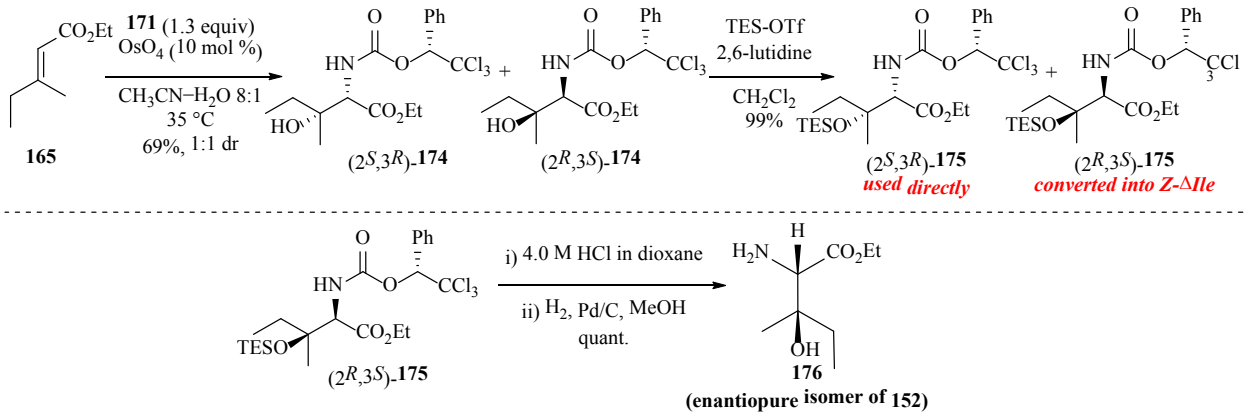
While efforts to develop an enantioselective base-free aminohydroxylation leading to enantioenriched *β*-OHAA derivatives were unsuccessful, we devised a strategy for the synthesis of D- and L-*β*-OHVal derivatives **173** and *epi*-**173** by using chiral nitrogen source reagents.[8] As shown in Scheme 5.3, base-free aminohydroxylation of ethyl 3,3-dimethylacrylate (**170**) with Lebel's carbamate **171**[9] furnishes **172** in 97% yield. The chiral mesyloxycarbamate **171** can be prepared in a 5-step sequence from benzaldehyde developed by Lebel and co-workers. TES protection of **172** provided a mixture including both D-*β*-OHVal derivative **173** and L-*β*-OHVal derivative *epi*-**173** in 87% yield. The mixture of **173** and *epi*-**173** can be separated by flash chromatography using 10−50% CH_2Cl_2 in hexanes gradient elution. The less polar compound found in early fractions was determined to be D-β-OHVal derivative **173** by conversion into a

known compound and measurement of its optical rotation. [10] Thus the more polar compound found in latter fractions was L-β-OHVal derivative *epi*-**173**. Compounds **173** and *epi*-**173** will be used for the synthesis of dipeptide **153** and tripeptide **155**, respectively.



Scheme 5.3 Synthesis of *D*- and *L*-*β*-OHVal derivative **173** and *epi*-**173**

The *β*-OHIle derivative **175** can be obtained using the same strategy involving aminohydroxylation of *E*-enoate **165** in the presence of chiral mesyloxycarbamate **171** followed by TES protection (Scheme 5.4). The resulting mixture includes (2*S*,3*R*)-**175** and (2*R*,3*S*)-**175** which are separable by flash chromatography using 10−50% CH_2Cl_2 in hexanes gradient elution. The desired isomer (2*S*,3*R*)-**175**, used as starting material for the synthesis of pentapeptide **143**, is the more polar isomer that was found in latter fractions.[11] The undesired and less polar isomer (2*R*,3*S*)-**175** found in early fractions could be converted into amine **176** in a one-pot reaction. The chiral compound **176** is an enantiopure isomer of **152**, which is used for the construction of *Z*-ΔIle.

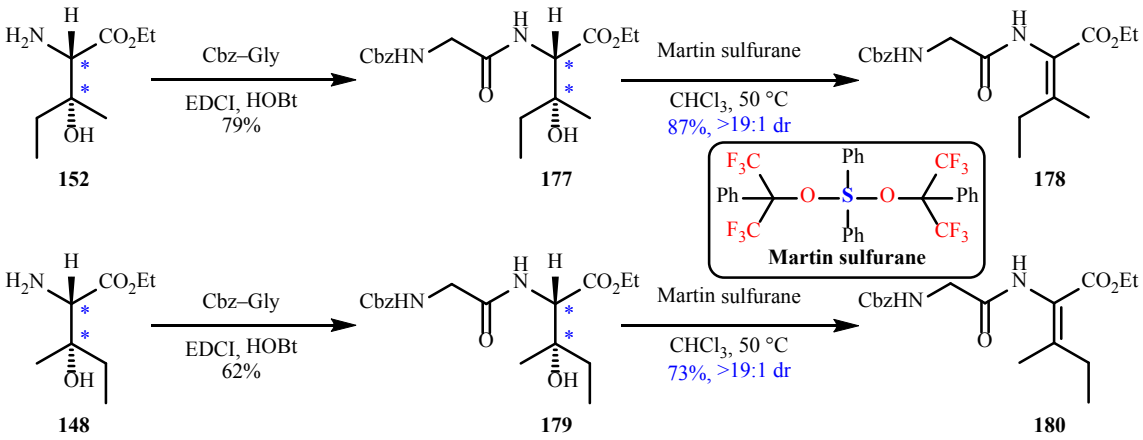


Scheme 5.4 Synthesis of *β*-OHIle derivative (2*S*, 3*R*)-**175**

5.2.2 The construction of Z- and E-ΔIle-containing peptides

5.2.2.1 Stereospecific anti dehydration mediated by Martin sulfurane

Initial attempts at generating *Z*- and *E*-ΔIle by employing the Wandless protocol ($SOCl_2$ and DBU)[12] for the dehydration of tertiary alcohols delivered moderate levels of selectivity (4−8:1 dr). Excitingly, the Martin sulfurane dehydrating agent mediated the reaction with unexpectedly high stereoselectivity. This protocol was developed by Zhiwei Ma.[13] Scheme 5.5 shows our model study of the dehydration reactions. Racemic amine **152**, obtained via regionselective aminohydroxylation of *E*-enoate **165**, was coupled with carbobenzyloxy (Cbz) protected glycine, furnishing a dipeptide **177**. Subjection of the tertiary alcohol **177** to Martin sulfurane in $CHCl_3$ afforded *Z*-ΔIle-containing dipeptide **178** as a single detectable isomer (>19:1 dr). *E*-ΔIle-containing dipeptide **180** as the product of clean *anti* dehydration was prepared in a similar fashion from **148**. No minor isomers were visible by ^1H NMR spectroscopy.



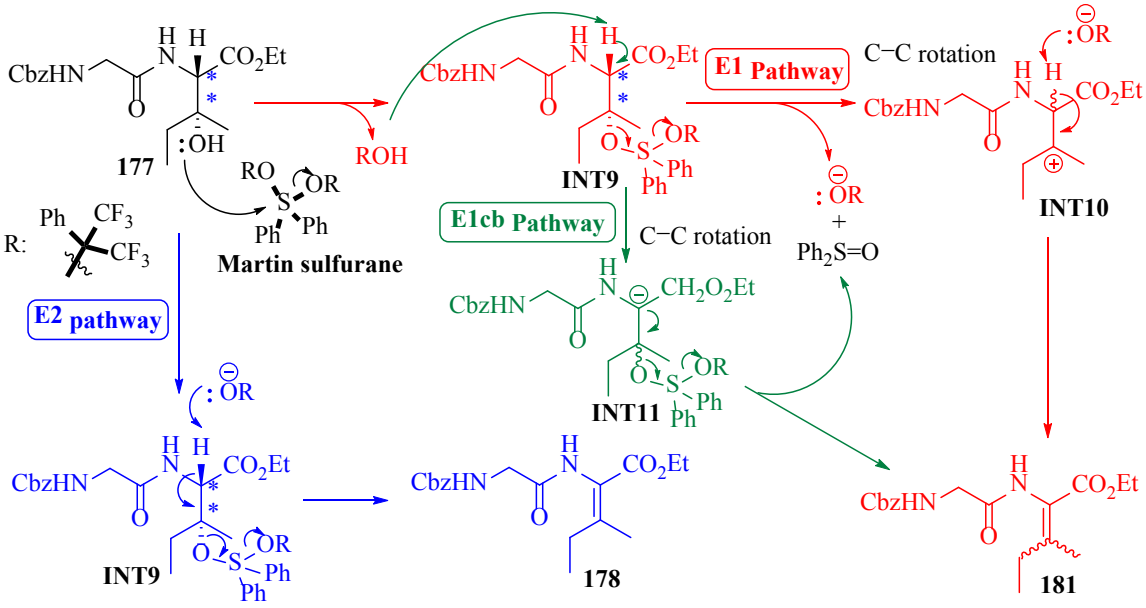
152 **177** **178** **148** **179** **180**

Notes: stereocenters marked by asterisks indicate relative stereochemistry

Scheme 5.5 *Anti* dehydration mediated by Martin sulfurane

The highly stereoselective dehydration mediated by Martin sulfurane surprised us because dehydrations of tertiary alcohols with this reagent were reported to proceed by an E1-like mechanisms.[14,15] All three possible pathways for Martin sulfurane dehydration of tertiary alcohol **177** are shown in Scheme 5.6. The tertiary alcohol **177** reacts with Martin sulfurane to form intermediate **INT9** and one equivalent of $(CF_3)_2PhCOH$. The intermediate **INT9** is the key species from which the E1, $E1_{cb}$, and E2 pathways diverge. In the E1 pathway, carbocation **INT10** would be formed from **INT9** by heterolytic cleavage of the C−O bond, which involves loss of $(CF_3)_2PhCO^-$ and diphenyl sulfoxide. The planar structure of the carbocation **INT10** could easily rotate via the δ C−C bond, which would subsequently deliver the isomerized product **181** via the hydrogen abstraction facilitated by the presence of $(CF_3)_2PhCO^-$. The $E1_{cb}$ pathway undergoes an opposite process compared to the E1 pathway. *β*-hydrogen abstraction would be performed from **INT9** first, furnishing carbanion **INT11**. Then, cleavage of the C−O bond in the structure of **INT11** by loss of $(CF_3)_2PhCO^-$ and diphenyl sulfoxide could form isomerization product **181** due to the C−C bond rotation of carbanion. Compared to these stepwise pathways, a concerted process involving simultaneous hydrogen abstraction and C−O

bond cleavage forms a product **178** via E2 pathway. A*nti* dehydration in E2 pathway is preferred because of the steric effects, affording product **178** stereoselectively.

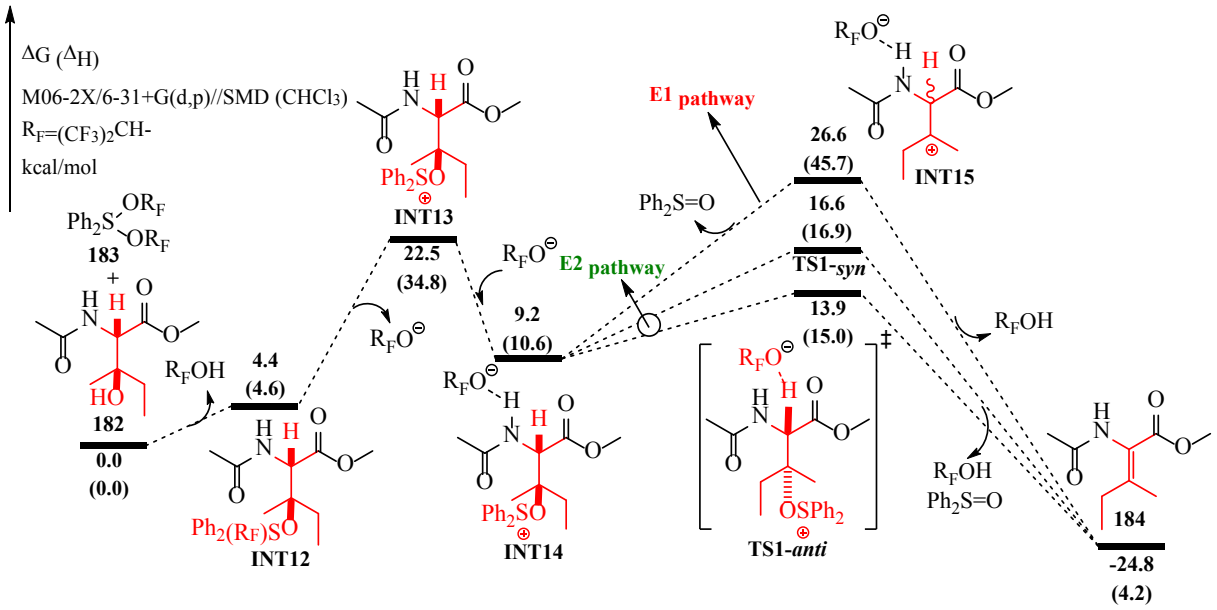


Notes: stereocenters marked by asterisks indicate relative stereochemistry

Scheme 5.6 Three possible pathways for Martin sulfurane mediated dehydration

According to our experimental results, the detected highly stereoselectivite *anti* dehydration of the tertiary alcohol facilitated by Martin sulfurane strongly suggested an E2 pathway, which was much less common[16] than its typical E1-like mechanism. This prompted us to utilize density functional calculations (Gaussian 09 program[17]) to test E1, $E1_{cb}$, and E2 pathways for our *anti* dehydration (The calculation work was conducted with the help of Professor Daniel H. Ess).

The DFT computed energy surface for dehydration of a model tertiary alcohol **182** and sulfurane **183** (slightly simplified structures of **177** and Martin sulfurane) is shown in Scheme 5.7. M06-2X/6-31+G(d,p) theory[18] was employed because it provides accurate E2 transition state barriers.[19] Calculations for geometry optimization and normal-mode frequency were performed in $CHCl_3$ using the SMD implicit solvent model.[20]



Scheme 5.7 DFT computed energy surface for dehydration

Tertiary alcohol **182** reacts with sulfurane **183** affording intermediate **INT12** by loss of an equivalent of $(CF_3)_2CHOH$, which is endergonic by 4.4 kcal/mol. Subsequent loss of an alkoxide $(CF_3)_2CHO^-$ delivers intermediate **INT13** that contains a good leaving group (Ph_2S^+O-). Complete cleavage of the $(CF_3)_2CHO^-$ from **INT12** requires 22.5 kcal/mol of free energy, thus the alkoxide may not actually leave the solvation sphere of **INT13**. This was confirmed by the successful location of the intermediate **INT14**, requiring only 4.8 kcal/mol of free energy from **INT12**, which is stabilized by hydrogen bonding between the alkoxide and the amide. **INT14** is the key intermediate from which the E1, $E1_{cb}$, and E2 pathways diverge. In the E1 pathway, loss of diphenyl sulfoxide (Ph_2SO) from **INT14** affords carbocation **INT15**, which requires 26.6 kcal/mol of free energy. The carbocation retains a hydrogen bond to the alkoxide ($(CF_3)_2CHO^-$), which was located via geometry optimization using DFT calculation. The carbocation without hydrogen bonding is endergonic by more than 50 kcal/mol of free energy. These high thermodynamic free energies provide strong evidence against an E1 pathway for this tertiary alcohol dehydration.

Then, we searched for possible $E1_{cb}$ and E2 transition states from **INT14**. **TS1-*anti*** is the lowest energy transition state with 13.9 kcal/mol of activation free energy. As shown in Figure 5.2, while the breaking C1−H bond (1.34 Å) and the new forming O1−H bond (1.26 Å) are both highly advanced, the C2−O2 bond is only stretched by 0.03 Å. The normal-mode vibration analysis for the transition structure (**TS1-*anti***) did not show significant motion in the bond of C2−O2. The characteristics of the structure of **TS1-*anti*** indicate that it is either an $E1_{cb}$ transition state or a highly asynchronous E2 transition state.

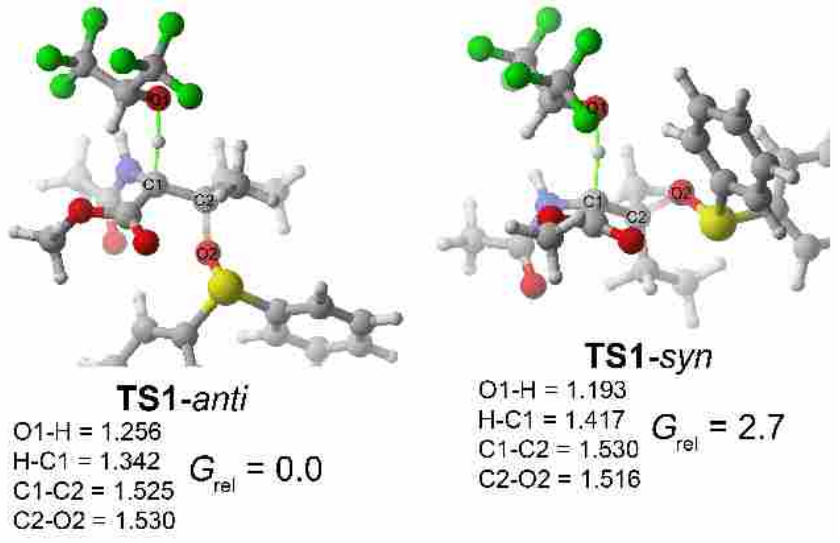


Figure 5.2 DFT calculated *anti* and *syn* E2 transition states (M06-2X/6-31+G(d,p)//SMD ($CHCl_3$); distances reported in Å; some groups partially obscured for clarity)

According to our IRC (intrinsic reaction path) calculations, no additional intermediate (carbanion) was found between **TS1-*anti*** and alkene **184** (Figure 5.3). The entire potential energy landscape was obtained by scanning the C1−H bond (length from 1.2−1.8 Å) and the C2−O2 bond (lengths from 1.5−2.5 Å) of **TS1-*anti*** (Figure 5.4).[21] This energy landscape did not show any local minimum for a carbanion intermediate except **TS1-*anti***. Additionally, an $E1_{cb}$ transition state was not located via geometry optimization. Therefore, **TS1-*anti*** is best described

as a concerted but highly asynchronous E2 transition state. A similar transition state in the elimination of 2-aryl-3-chloro-2-*R*-propanols was found by Yamataka.[22]

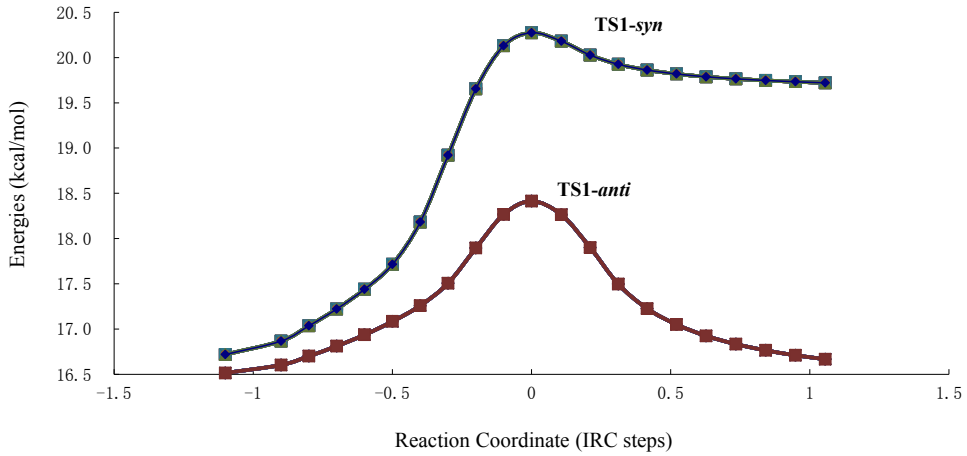


Figure 5.3 IRC plots of **TS1-*anti*** and **TS1-*syn***

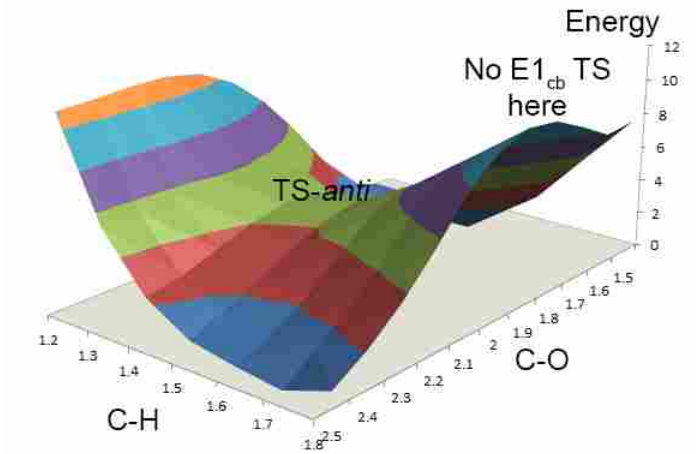
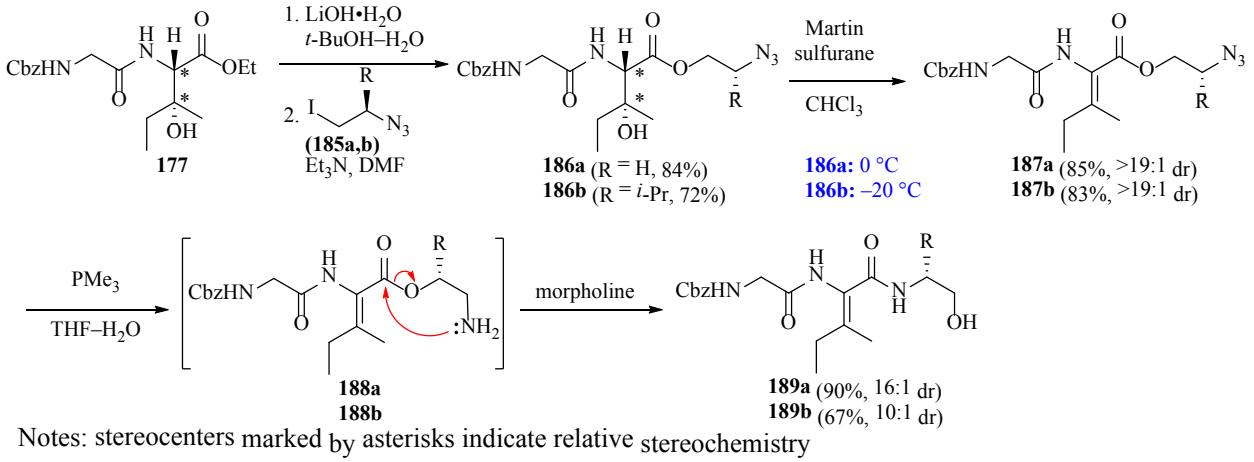


Figure 5.4 Energy landscape of **TS1-*anti*** with C−H bond length from 1.2−1.8 Å and C−O bond lengths from 1.5−2.5 Å

The observed stereoselectivity in the dehydration reaction is the result of an *anti* transition state that is lower energy than any of the possible *syn* transition states. **TS1-*syn*** is the *syn* transition state with lowest energy (Figure 5.2). The activation free energy ($\Delta G^{\ddagger}$) for **TS1-*anti*** is 13.9 kcal/mol, which is 2.7 kcal/mol lower than **TS1-*syn*** (16.6 kcal/mol). These calculation results are qualitatively in accordance with the high stereoselectivity for the Martin sulfurane mediated dehydration of **177** reported in Scheme 5.5.

5.2.2.2 Strategy for the construction of Z- and E-ΔIle-containing peptides

In order to avoid lengthy synthesis route requiring amide protection to preserve the alkene stereochemistry, other strategies involving Staudinger ligation,[23] thioacid-base couplings,[24] and $B(OCH_2CF_3)_3$[25] for elaboration of **178** were studied. However, saponification turned out to be sluggish and accompanied by alkene isomerization (ca. 2:1).[26] Fortunately, this problem was solved via a sequence including alkylation, *anti* dehydration, and a tandem reduction/O→N acyl transfer that was developed by Zhiwei Ma.[2] Scheme 5.8 shows a model study for the stereoselective synthesis of *Z*-ΔIle-containing tripeptide **189a** and **189b**. The racemic ester was treated with LiOH to afford a carboxylic acid. This acid reacted with azido iodides **185a** and **185b** to form **186a** and **186b**. The alkylative esterification was required in order to avoid nonselective dehydration. Iodides **21a** and **21b** served as surrogates for the simplest (Gly) and bulkiest amino acids (Val) coupled to the C-termini of bulky ΔAAs in yaku'amide A (Figure 5.1). Stereoconvergent *anti* dehydration of tertiary alcohols **186a** and **186b** mediated by Martin sulfurane afforded *Z*-ΔIle-containing dipeptides **187a** and **187b** as single detectable isomers. Staudinger reduction of azides **187a** and **187b** delivered primary amines **188a** and **188b**. Then, an amine base (morpholine) was added to the reaction mixture to trigger O→N acyl transfer,[27] furnishing tripeptides **189a** and **189b** with negligible amounts of alkene isomerization. This synthesis is also applicable for the construction of *E*-ΔIle-containing tripeptides.[12] Therefore, this sequence is efficient for the highly stereoselective construction of both *Z*- and *E*-ΔIle-containing peptides, and could be employed in our total synthesis of yaku'amide A.



Notes: stereocenters marked by asterisks indicate relative stereochemistry

Scheme 5.8 Synthesis of *Z*-ΔIle-containing tripeptide **189a** and **189b**

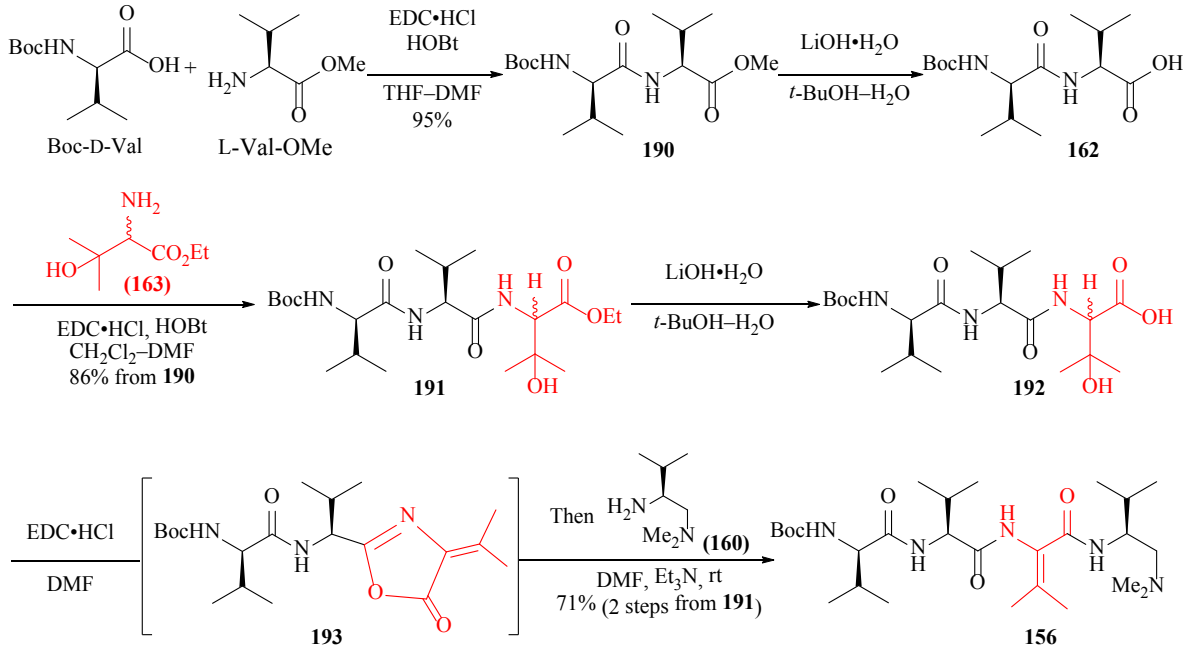
5.3 Synthesis of the right-hand nonapeptide

Right-hand nonapeptide **154** could be prepared from three smaller subunits including dipeptide **153**, tripeptide **155,** and tetrapeptide **156** (See Scheme 5.1). Herein, the synthetic route for the construction of nonapeptide **154** will be described.

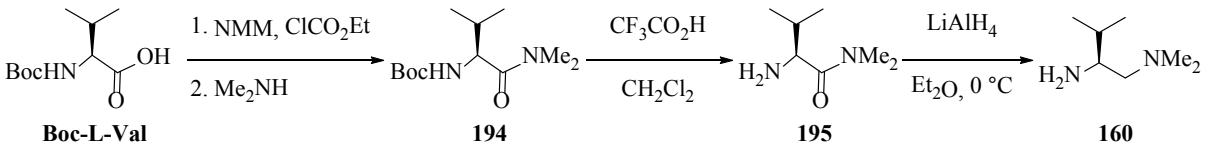
5.3.1 Synthesis of the right-hand tetrapeptide 156

As described in our retrosynthesis of yaku'amide A (Scheme 5.1), the right-hand tetrapeptide **156** would be the simplest subunit to prepare because it only contains one ΔVal residue instead of *Z*- or *E*-ΔIle. The construction of tetrapeptide **156** in the absence of alkene stereochemistry is rapid and efficient, as shown in Scheme 5.9, by employing the peptides with *C*-terminal ΔAAs to form azlactones under coupling conditions.[3,12,28] Commercially available reagents Boc-D-Val and L-Val-OMe were coupled in the first step using EDC and HOBt as coupling reagents, affording dipeptide **190** in 95% yield. Hydrolysis of the ester **190** and subsequent coupling with racemic β-OHVal derivative **163** furnished tripeptide **191** as an inconsequential mixture of diastereomers. The racemic amine **163** was prepared from ethyl 3,3-

dimethylacrylate (**170**) via base-free regioselective aminohydroxylation followed by Cbz deprotection.[1] Saponification of **191** was followed by subjection of the intermediate carboxylic acid **192** to EDC·HCl, which functioned to both activate the acid and dehydrate the tertiary alcohol. This process triggered spontaneous formation of azlactone **193**, then addition of chiral amine **160** to the reaction mixture promoted azlactone ring opening, furnishing the right-hand tetrapeptide **156** in 71% from compound **191**. The known chiral amine **160** was prepared from Boc-L-Val in four steps, as reported by Pedrosa and co-workers (Scheme 5.10).[29]



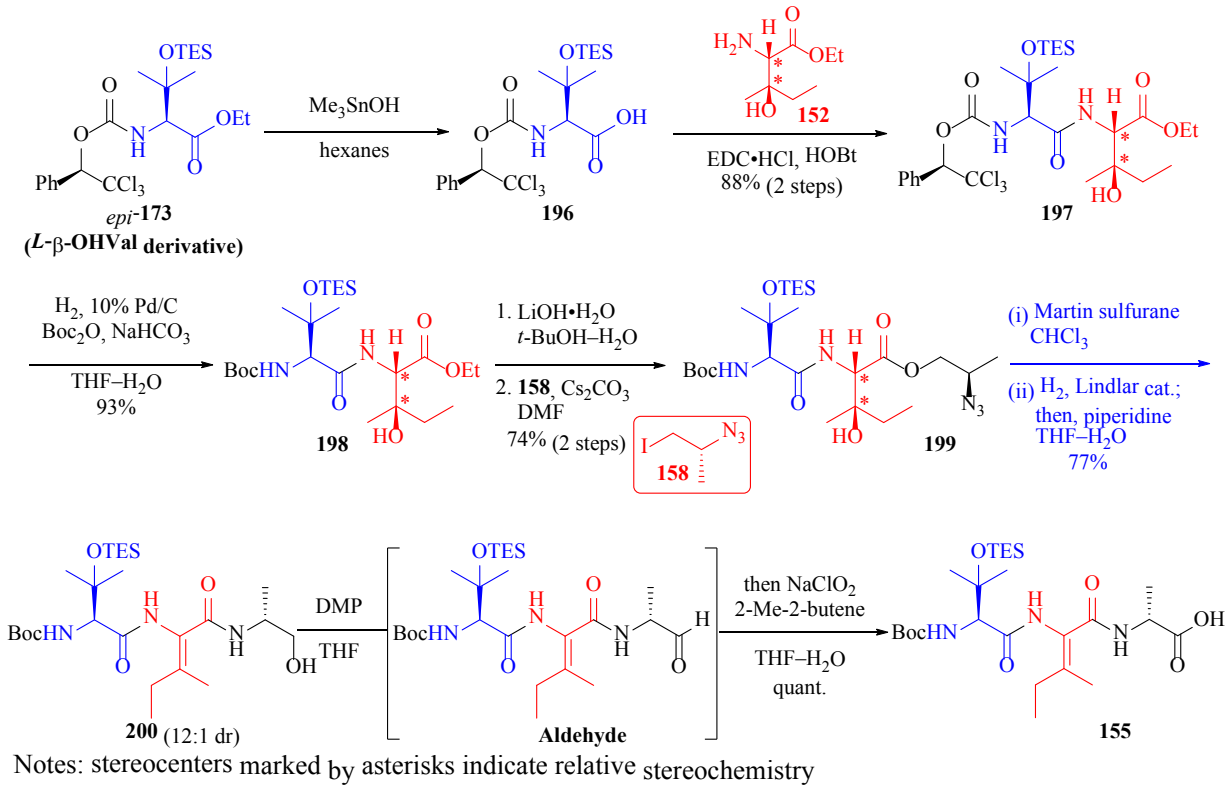
Scheme 5.9 Synthesis of right-hand tetrapeptide **156**



Scheme 5.10 Preparation of chiral amine **160**

5.3.2 Synthesis of the tripeptide 155

Tripeptide **155** was constructed from *L*-β-OHVal derivative *epi*-**173** as outlined in Scheme 5.11. It was challenging to selectively cleave the ester moiety of *epi*-**173** since the chiral carbamate moiety is a base-labile protecting group. Eventually, we accomplished selective cleavage using Me_3SnOH[30] in hexanes at 70 °C for 3 days. Lower (60 °C) or higher temperature (>80 °C) led to reaction incompletes or decomposition. The carboxylic acid obtained from *epi*-**173** was coupled with racemic β-OHIle derivative **152** to afford dipeptide **197** in 88% yield from *epi*-**173**. The subsequent hydrolysis and alkylation steps (*vide infra*) require basic conditions, which could cleave the chiral carbamate protecting group. Accordingly, the chiral carbamate moiety was exchanged for a more robust Boc protecting group under hydrogenolysis conditions in the presence of Boc_2O, furnishing compound **198**. It is worth noting that $NaHCO_3$ was added to this reaction in order to prevent the cleavage of the TES ether. Hydrolysis of the ethyl ester of **198** and subsequent alkylation with enantiopure azido iodide **158** delivered β-azidoethyl ester **199** in 74% yield. Cs_2CO_3 was found the most effective weak base in this alkylation reaction. Other bases such as Et_3N promoted an undesired retroaldol side reaction because the product (**199**) or starting material (**198**) contains the β-OHIle residue. Notably, extra drying of DMF and Cs_2CO_3 would increase the yield of the alkylation (DMF obtained from solvent system was dried using activated molecular sieves overnight; Cs_2CO_3 was dried via heating under high vacuum).



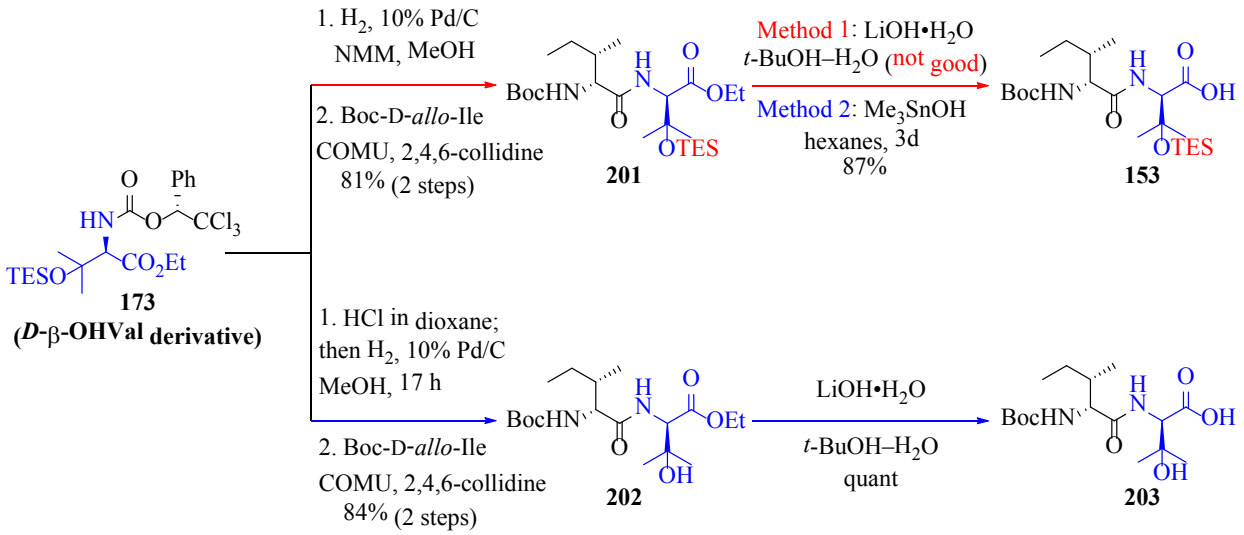
Scheme 5.11 Synthesis of tripeptide **155**

After some optimization, we developed an efficient one-pot reaction of our dehydration/ azide reduction/O→N acyl transfer sequence (see Scheme 5.8). Subjection of **199** to Martin sulfurane in $CHCl_3$ promoted facile and stereoconvergent *anti* dehydration. The $CHCl_3$ used as solvent in this reaction was dried and neutralized with a mixture of activated molecular sieves and dried K_2CO_3. The pre-treatment of $CHCl_3$ is the key for the success of the *anti* dehydration mediated by Martin sulfurane. This process for the treatment of $CHCl_3$ is also applied in the following synthesis involving this *anti* dehydration (*vide infra*). Upon completion of the dehydration, the $CHCl_3$ was evaporated, and THF−H_2O (10:1) was added in the same reaction vial, which set the stage for azide reduction via Lindlar hydrogenation under H_2 balloon. Piperidine (0.8 equiv) was then added directly to the reaction mixture once the reduction completed, triggering O→N acyl transfer and affording *Z*-ΔIle-containing tripeptide **200** in 77%

yield with 12:1 dr. The trace amounts of the undesired *E*-isomer are probably generated during the reduction or the acyl transfer process since no minor isomers were visible in the ^{1}H NMR spectrum of the crude dehydration product. This one-pot protocol was simpler and gave a better yield than our originally published process that employed PMe_3 to reduce the azide and morpholine to trigger the O→N acyl transfer.[2] Then, one-pot Dess−Martin/Pinnick oxidation was employed in the last step to deliver the carboxylic acid **155**, which was used directly in a subsequent peptide coupling.

5.3.3 Synthesis of dipeptides with or without TES protection

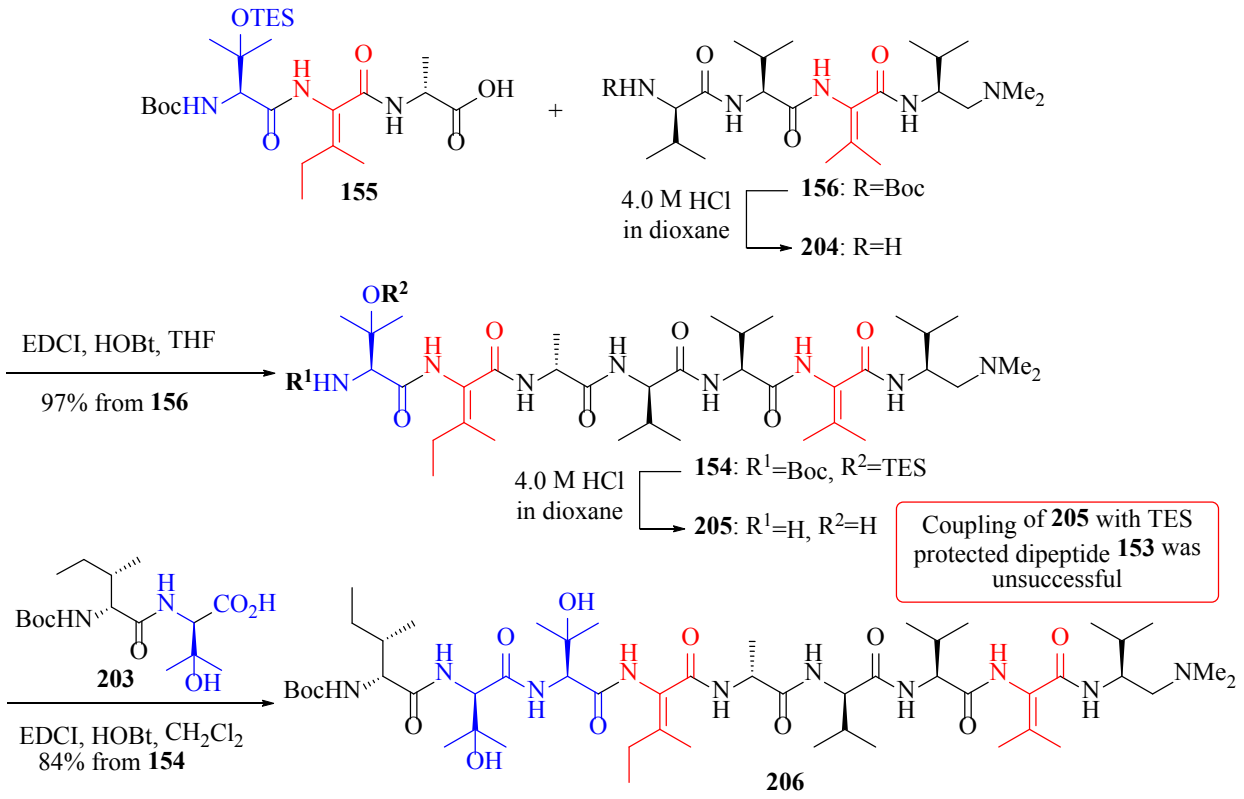
The D-β-OHVal derivative **173** was used for dipeptide synthesis. As shown in Scheme 5.12, the TES protected dipeptide **153** was prepared in three steps. The chiral carbamate was removed via hydrogenolysis using 10% Pd/C under H_2 (500 PSI). The resulting amine was coupled with Boc-D-*allo*-Ile, furnishing dipeptide **201** in 81% yield. We first tried using $LiOH{\cdot}H_2O$ for saponification to afford carboxylic acid **153**. The reaction could not complete due to the presence of the TES protecting group. In contract, Me_3SnOH was efficient for the cleavage of the ethyl ester of **201**, delivering carboxylic acid **153**. The TES protected dipeptide **153** was studied for peptide coupling to construct nonapeptide **144** (*vide infra*). However, the coupling reaction turned out to be unsuccessful mainly because of the steric hindrance. We then developed the synthesis of dipeptide **203** without TES protection also from **173** in 3 steps. A one-pot reaction was performed to remove both TES and chiral carbamate groups, and subsequent coupling with Boc-D-*allo*-Ile delivered dipeptide **202**. The following saponification was successful using $LiOH{\cdot}H_2O$, affording dipeptide **203** in quantitative yield.



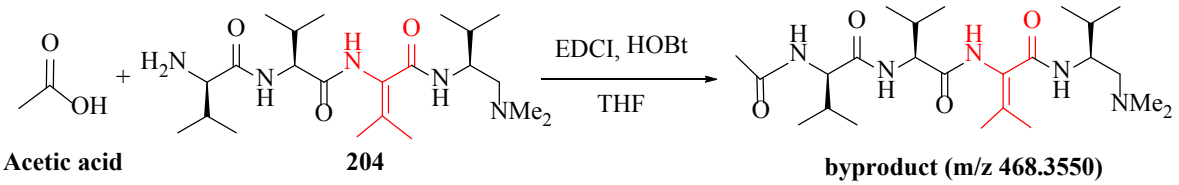
Scheme 5.12 Synthesis of dipeptides with or without TES protected

5.3.4 Construction of nonapeptide

The prepared intermediates dipeptide **203**, tripeptide **155**, and tetrapeptide **156** were elaborated into nonapeptide **206** as shown in Scheme 5.13. The Boc protecting group was easily removed by treating with 4.0 M HCl in CH_2Cl_2, affording the corresponding amine **204**. Preliminary studies of the following coupling reaction for the construction of heptapeptide **154** found an undesired compound formed as the major product. The byproduct was first detected from MS with m/z=468.3550. The byproduct has similar polarity as the desired product (heptapeptide **154**), and it is quite difficult to separate them via flash chromatography. The byproduct was formed via coupling of tetrapeptide amine **204** with acetic acid (Scheme 5.14). The side coupling reaction was a nuisance: it consumed our precious starting materials, it was quite difficult to separate because of similar polarity to the desired product, and it reduced the reaction yield.



Scheme 5.13 Synthesis of nonapeptide **206**



Scheme 5.14 Side reaction in the presence of acetic acid

The trace amount of acetic acid presented in the reaction was presumably introduced from ethyl acetate. Ethyl acetate is commonly used for extractions, column chromatography (EtOAc/Hexanes), or dissolving products for transfer to another vial or flask. In order to avoid this side reaction, ethyl acetate was not used in any processes for preparation of starting materials (both acid and amine). In this particular case for heptapeptide synthesis, EtOAc was replaced by $CHCl_3$ for extraction in the work-up of the Pinnick oxidation for the synthesis of carboxylic acid **155** (Scheme 5.11). The tetrapeptide **156** was azeotropically distilled using toluene (three times)

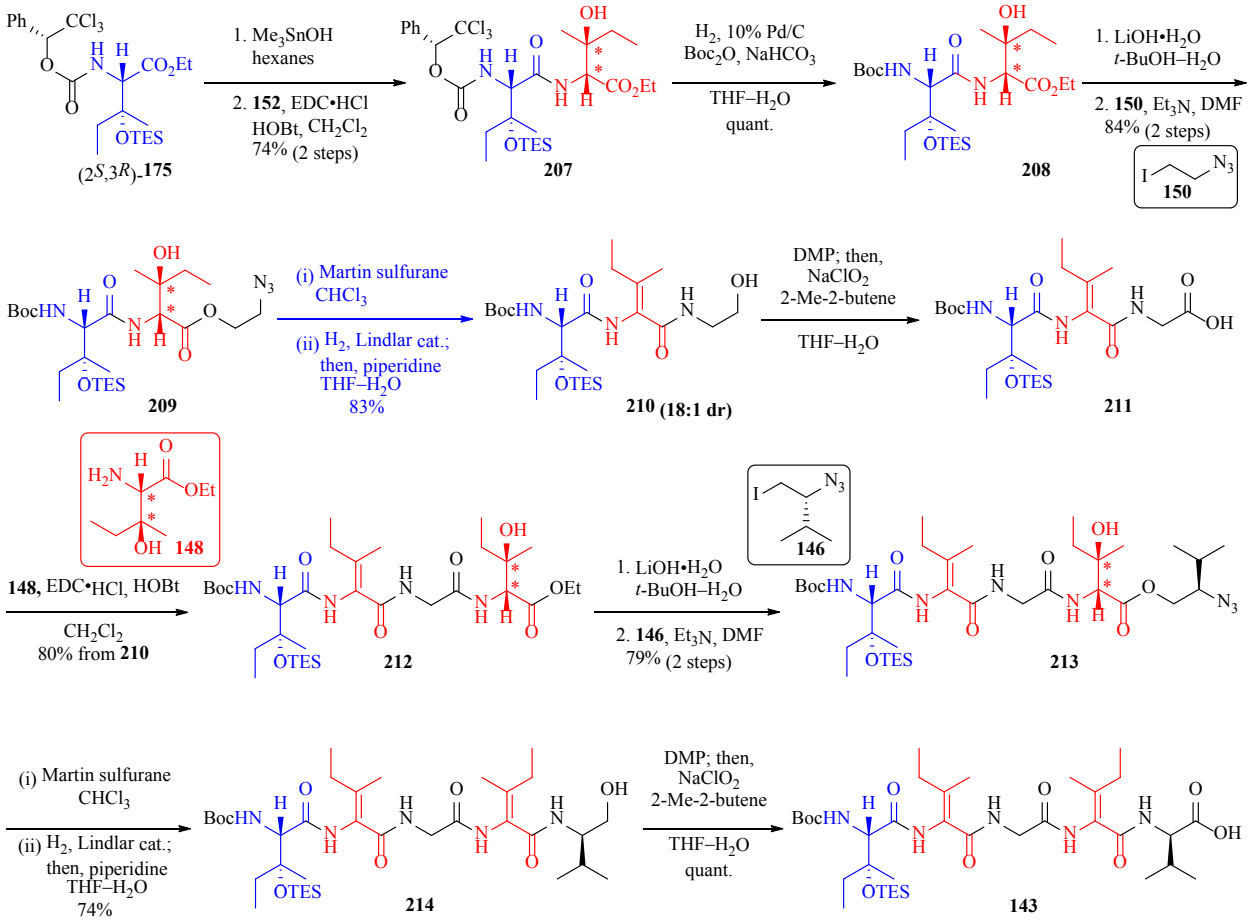
in order to remove the trace amounts of acetic acid that existed in compound **156**. This process was also applied in later coupling reactions in order to avoid a similar side coupling reaction.

In the absence of acetic acid in the starting materials, coupling of the amine **204** with carboxylic acid **155** furnished heptapeptide **154**. A 97% yield was finally obtained for this one-pot reaction from tetrapeptide **156**. Then, subjection of **156** (azeotropically distilled in order to remove the trace amount of acetic acid) to 4.0 M HCl in CH_2Cl_2 cleaved the Boc and TES protecting groups simultaneously. The resulting amine **205** was subsequently coupled with dipeptide **203** using CH_2Cl_2 as solvent, affording nonapeptide **206** in excellent yield (coupling with TES protected dipeptide **153** was found unsuccessful).

5.4 Synthesis of left-hand pentapeptide

The left-hand pentapeptide **143** containing both *Z*- and *E*-ΔIle moiety is the most difficult subunit of yaku'amide A to synthesize. As outlined in Scheme 5.15, the synthesis of **143** started with Me_3SnOH-promoted hydrolysis of *β*-OHIle derivative (2*S*,3*R*)-**175**. The resulting carboxylic acid was coupled with racemic amine **152**, furnishing dipeptide **207** as an inconsequential 1:1 mixture of diastereomers. The transformation of **207** into β-azidoethyl ester **209** proceeded by a three-step protocol in similar fashion to the conversion of **197** into **199** (See Scheme 5.11), with the exception that the alkylation gave the best results by using with Et_3N instead of Cs_2CO_3. The *β*-azidoethyl ester **209** underwent facile stereoconvergent *anti* dehydration followed by azide reduction/O→N acyl transfer, affording tripeptide **210** in excellent yield and high diastereoselectivity (18:1 dr). Then, one-pot Dess−Martin/Pinnick oxidation delivered carboxylic acid **211**, which was coupled with racemic β-OHIle derivative **148** (the diastereomer of **152**, see Scheme 5.2) to form tetrapeptide **212** in 80% yield (from **210**).

The sequence of reactions employed to convert **208** into **211** proceeded smoothly to transform **212** into the targeted pentapeptide **143**. The obtained pentapeptide **143** was used directly in a subsequent late-stage peptide coupling.



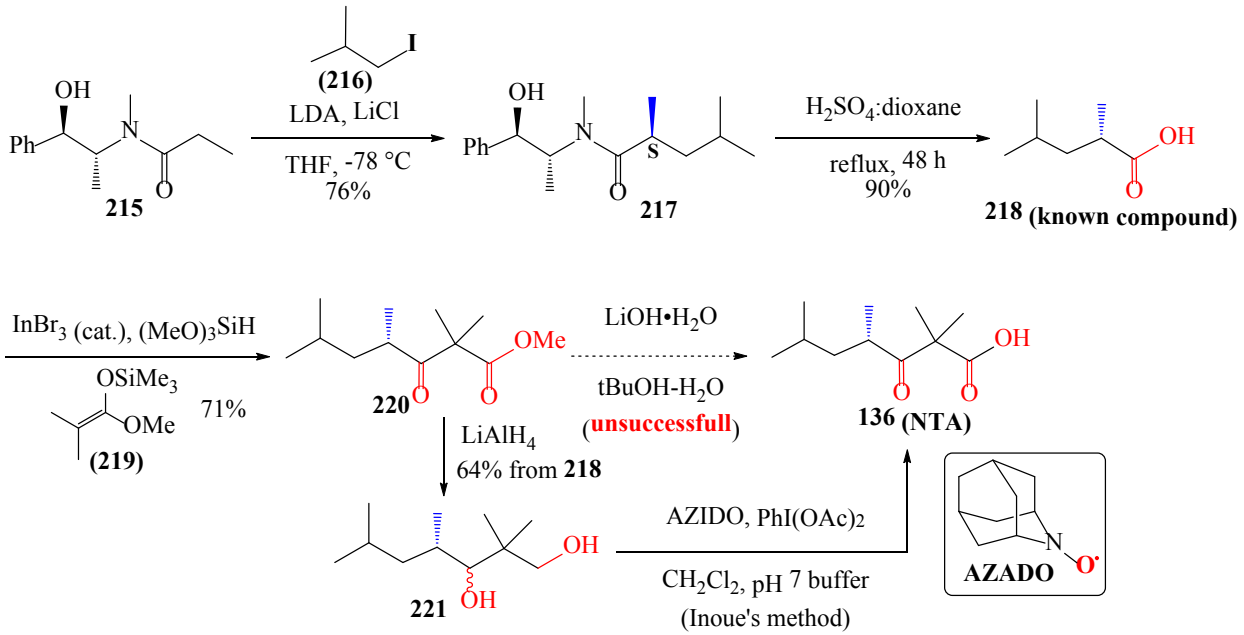
Notes: stereocenters marked by asterisks indicate relative stereochemistry

Scheme 5.15 Synthesis of pentapeptide **143**

5.5 Synthesis of N-terminal acyl group (NTA)

Our strategy for the construction of the N-terminal acyl (NTA) group is shown in Scheme 5.16. The chiral amide (1*R*,2*R*)-**215**[31] reacted with 1-iodo-2-methylpropane (**216**) via Myers asymmetric alkylation to afford a known chiral amide **217**[32], and one additional stereocenter with *S*-configuration was introduced. The chiral auxiliary pseudoephedrine was cleavaged in the presence of concentrated sulfuric acid in refluxing dioxane, generating carboxylic acid **218** in 90%

yield.[33] Then an indium-catalyzed cross-Claisen condensation[34] with a ketene silyl acetal (**219**) was performed, providing β–ketoester **220** in good yield. Attempts to hydrolyze the ester **220** to afford NTA **136** directly were unsuccessful, as the product decomposed. Alternatively, reduction of the *β*–ketoester **220** in the same pot afforded diol **221** smoothly, which then oxidized to generate the NTA according to Inoue's method (AZADO and $PhI(OAc)_2$). Therefore, our synthesis of NTA was accomplished in only two steps from a known compound **218**, which is a much more efficient sequence than Inoue's 10-step synthesis (see Scheme 4.8).

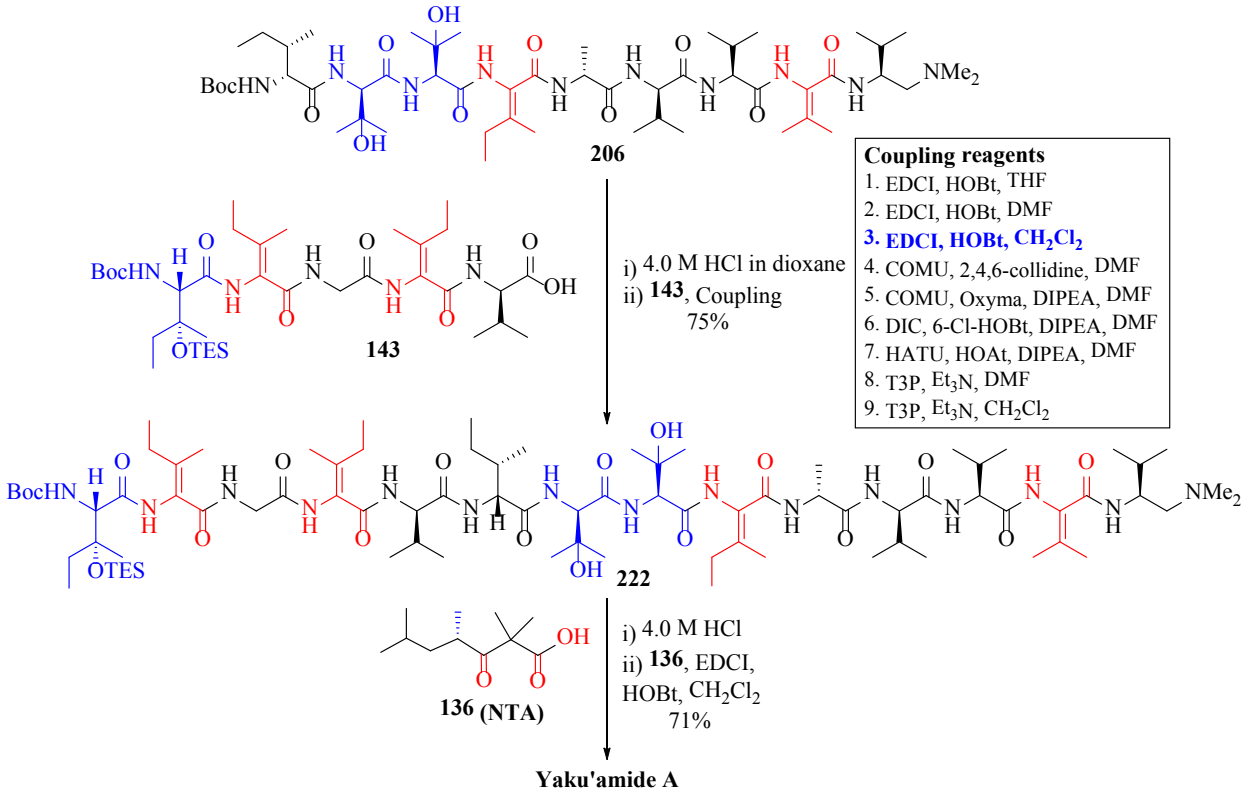


Scheme 5.16 Four-step protocol for the synthesis of NTA from a known compound **217**

5.6 Late-stage peptide coupling

All prepared key subunits set the stage for the late-stage peptide couplings as outlined in Scheme 5.17. Coupling of nonapeptide amine (afforded from **206** in acidic condition) with pentapeptide acid **143** turned out to be quite challenging because of the steric hindrance. A series of coupling reagents in different solvents were tested, we were finally pleased to find that reagents EDCI and HOBt in CH_2Cl_2 facilitated the bulky coupling reaction quite well (75%

yield). Reaction in THF or DMF using EDCI and HOBt was found unsuccessful. The conformations of the bulky nonapeptide and pentapeptide in the less-polar solvent CH_2Cl_2 may favor the hindered coupling reaction. Additionally, this coupling reaction also worked using DIC and 6-Cl-HOBt, but a low yield (<10%) with many unknown impurities was obtained. The Boc and TES groups were removed from tetradecapeptide **222** in 4.0 M HCl, and coupling of the resulting amine with NTA **136** afforded the targeted peptide yaku'amide A in 71% yield.



Scheme 5.17 Late-stage coupling for the construction of the final target yaku'amide A

5.7 Biological investigation

The bioactivities of yaku'amide A will be evaluated in the near future by the Oncology Chemistry group (Executive Director Greg Vite) at Bristol-Myers Squibb by screening against a panel of 12 cancer cell lines representing several tissue types. Toxicity to noncancerous cells will also be evaluated by screening against a standard fibroblast cell line. Some simiplified analogues

will be synthesized and tested for their anticancer activities alongside yaku'amide A. The simplified yaku'amide A analogue that most closely matches the activity pattern of yaku'amide A will then be synthesized in larger quantities to enable exploration of its target and mode of action.

5.8 Conclusion

The total synthesis of yaku'amide A (revised structure) is described in this chapter. Three β-OHAA residues (D- and L-*β*-OHVal and (2*S*,3*R*)-OHIle derivatives) in Yaku'amide A were prepared in only two steps via base-free OsO_4-catalyzed aminohydroxylation with chiral mesyloxycarbamate. Stereoselective syntheses of *Z*- and *E*-ΔIle containing peptides were achieved via a sequence of Martin sulfurane mediated *anti* dehydration, azide reduction, and O→N acyl transfer. This one-pot sequence was successfully applied to the synthesis of our key subunits left-hand pentapeptide **143** and tripeptide **155**, which contain both *Z*- and *E*-ΔIle residues and Z-ΔIle residue, respectively. Moreover, a more efficient synthesis of the N-terminal group was developed in only three steps from a known compound. Late-stage peptide couplings were achieved in excellent yields although some of them are quite challenging. Our total synthesis of Yaku'amide A was accomplished in 16 longest linear steps and 62 total steps. This represents a substantial reduction in step count relative to the Inoue synthesis (25 longest linear steps and 86 total steps). The biological properties and mode of action of yaku'amide A will be studied in the near future.

5.9 References

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6 EXPERIMENTAL SECTION

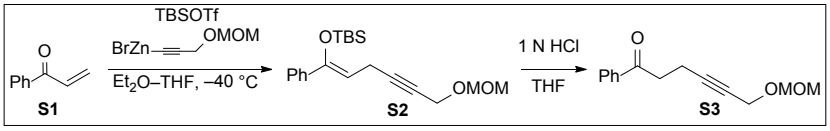
6.1 General Experimental Details

N,N-Dimethylformamide, dichloromethane, diethyl ether, methanol, tetrahydrofuran, and pyridine were dried by passage through a solvent drying system containing cylinders of activated alumina.[1] Chloroform was dried by activated molecular sieves Other solvents and reagents were purchased from commercial vendors and used without purification. Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were acquired on a 500 MHz spectrometer with chloroform (7.27 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), dd (doublet of doublets), dt (doublet of triplets), tt (triplet of triplets), qd (quartet of doublets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were acquired on a 500 MHz spectrometer operating at 125 MHz with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques. Microwave-promoted reactions were carried out by irradiating sealed reaction mixtures inside a CEM Discover S-Class microwave reactor that was set at 300 W.

6.2 Experimental procedures and spectral data

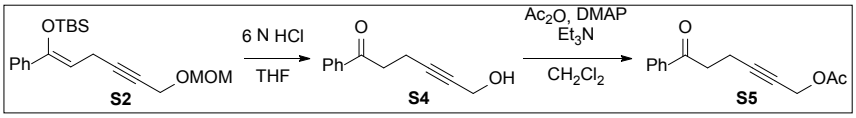
6.2.1 Synthesis of ketone precursors to *O*-phenyl oxime ethers

(note: all ketones not shown in this section are known compounds that were synthesized according to literature procedures)



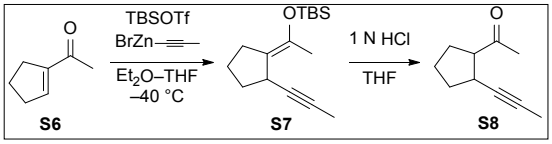
6-(Methoxymethoxy)-1-phenylhex-4-yn-1-one (S3). A solution of 3-(methoxymethoxy) prop-1-yne (114.1 mg, 1.14 mmol, 1.5 equiv) in anhydrous Et_2O (2.4 mL) at –40 °C under Ar was treated with *n*-butyllithium (1.57 M in hexane, 730 μL, 1.14 mmol, 1.5 equiv) and zinc bromide (1.0 M in THF, 1.14 mL, 1.14 mmol, 1.5 equiv). The mixture was stirred at rt under Ar for 20 min, then cooled to –40 °C and treated with a solution of phenyl vinyl ketone (**S1**, 100.3 mg, 0.759 mmol, 1.0 equiv) in anhydrous THF (1.1 mL) followed by TBS-OTf (260 μL, 299 mg, 1.13 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 3 h, then treated with sat aq $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude silyl enol ether **S2**.

Crude **S2** was treated with 1 N HCl (3 mL) and THF (3 mL), and the resulting mixture was stirred at rt for 3 h. Sat aq $NaHCO_3$ (6 mL) was added to neutralize the reaction, and it was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (25 mL of SiO_2, 2–5% EtOAc in hexanes gradient elution) afforded **S3** (82.1 mg, 0.353 mmol, 47% from **S1**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.70 (s, 2H), 4.20 (t, *J* = 2.1 Hz, 2H), 3.38 (s, 3H), 3.25 (t, *J* = 7.4 Hz, 2H), 2.70–2.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 136.5, 133.3, 128.7 (2C), 128.0 (2C), 94.7, 85.6, 76.0, 55.5, 54.7, 37.7, 13.6; IR (film) ν_{max} 2931, 2237, 1686, 1597, 1449, 1360, 1207, 1180, 1046 cm^{-1}; HRMS (ESI) *m/z* 233.1162 (MH^+, $C_{14}H_{16}O_3H^+$ requires 233.1178).



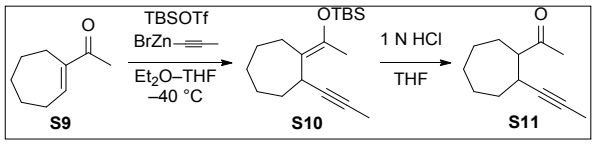
6-Oxo-6-phenylhex-2-yn-1-yl acetate (S5). A solution of crude silyl enol ether **S2** (prepared as described above from **S1** (73.4 mg, 0.555 mmol, 1.0 equiv) and 3-(methoxymethoxy)prop-1-yne (84.1 mg, 0.840 mmol, 1.5 equiv)) in THF (3.0 mL) and H_2O (2.0 mL) was treated with 6 N HCl (5.0 mL) and heated at 55 °C for 8 h. The mixture was then poured into brine (8.0 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (25 mL of SiO_2, 0.5–5% MeOH in CH_2Cl_2 gradient elution) afforded 6-hydroxy-1-phenylhex-4-yn-1-one (**S4**, 37.9 mg, 0.201 mmol, 36% from **S1**).

A solution of **S4** (32.1 mg, 0.171 mmol, 1.0 equiv) and Ac_2O (50 µL, 54 mg, 0.53 mmol, 3.1 equiv) in anhydrous CH_2Cl_2 (1.2 mL) at 0 °C under Ar was treated with Et_3N (71 µL, 52 mg, 0.51 mmol, 3.0 equiv) and DMAP (2.1 mg, 0.017 mmol, 0.1 equiv). The mixture was stirred at 0 °C for 5 min and at rt for 1.5 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (5 mL) and H_2O (5 mL), then extracted with Et_2O (3 × 6 mL). The combined organic layers were washed with 1 N HCl (4 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 10–20% EtOAc in hexanes gradient elution) afforded **S5** (37.2 mg, 0.162 mmol, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 4.66 (t, J = 2.0 Hz, 2H), 3.25 (t, J = 7.4 Hz, 2H) 2.71–2.66 (m, 2H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7, 170.4, 136.4, 133.3, 128.7 (2C), 128.0 (2C), 86.3, 74.5, 52.7, 37.5, 20.8, 13.6; IR (film) ν_{max} 2923, 2360, 2342, 1742, 1686, 1225, 1024 cm^{-1}; HRMS (ESI) *m/z* 231.1009 (MH^+, $C_{14}H_{14}O_3H^+$ requires 231.1021).



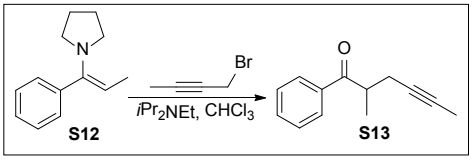
1-(2-(Prop-1-yn-1-yl)cyclopentyl)ethan-1-one (S8). A solution of $ZnBr_2$ (1.0 M in THF, 2.5 mL, 2.5 mmol, 1.25 equiv) in anhydrous Et_2O (6 mL) at –40 °C under Ar was treated with 1-propynylmagnesium bromide (0.5 M in THF, 5.0 mL, 2.5 mmol, 1.25 equiv), and the mixture was stirred at rt for 20 min. The formed alkynylzinc reagent was then cooled to –40 °C and treated with a solution of 1-acetyl-1-cyclopentene (**S6**, 230 μL, 220 mg, 1.99 mmol, 1.0 equiv) in anhydrous Et_2O (4.0 mL) followed by TBS-OTf (570 μl, 656 mg, 2.48 mmol, 1.24 equiv). The resulting mixture was stirred at 0 °C under Ar for 3 h, then treated with sat aq $NaHCO_3$ (12 mL) and extracted with Et_2O (3 × 12 mL). The combined organic layers were washed with brine (12 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude silyl enol ether **S7**.

Crude **S7** was treated with 1 N HCl (6.0 mL) and THF (6.0 mL), and the resulting mixture was stirred at rt for 3 h. Sat aq $NaHCO_3$ (10 mL) was added to neutralize the reaction, and it was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (70 mL of SiO_2, 3–5 % EtOAc in hexanes gradient elution) afforded **S8** (189.4 mg, 1.26 mmol, 63% from **S6**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.11–3.04 (m, 1H), 2.98–2.91 (m, 1H), 2.24 (s, 3H), 2.12–2.03 (m, 1H), 1.93–1.84 (m, 2H), 1.82–1.77 (m, 1H), 1.75 (d, J = 2.4 Hz, 3H), 1.72–1.64 (m, 1H), 1.62–1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.1, 79.1, 78.5, 56.5, 33.8, 33.7, 30.2, 25.3, 23.6, 3.5; IR (film) ν_{max} 2961, 2251, 1711, 1360, 1172 cm^{-1}; HRMS (ESI) *m/z* 151.1119 (MH^+, $C_{10}H_{14}OH^+$ requires 151.1123).



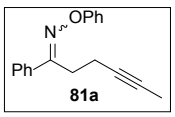
1-(2-(Prop-1-yn-1-yl)cycloheptyl)ethan-1-one (S11). A solution of $ZnBr_2$ (1.0 M in THF, 2.7 mL, 2.7 mmol, 1.26 equiv) in anhydrous Et_2O (6.8 mL) at –40 °C under Ar was treated with 1-propynylmagnesium bromide (0.5 M in THF, 5.4 mL, 2.7 mmol, 1.26 equiv), and the mixture was stirred at rt for 20 min. The formed alkynylzinc reagent was then cooled to –40 °C and treated with a solution of 1-acetyl-1-cycloheptene[2] (**S9**, 296.4 mg, 2.14 mmol, 1.0 equiv) in anhydrous Et_2O (4.5 mL) followed by TBS-OTf (620 μL, 714 mg, 2.70 mmol, 1.26 equiv). The resulting mixture was stirred at 0 °C under Ar for 3 h, then treated with sat aq $NaHCO_3$ (12 mL) and extracted with Et_2O (3 × 12 mL). The combined organic layers were washed with brine (12 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude silyl enol ether **S10**.

Crude **S10** was treated with 1 N HCl (6.5 mL) and THF (6.5 mL), and the resulting mixture was stirred at rt for 3 h. Sat aq $NaHCO_3$ (12 mL) was added to neutralize the reaction, and it was extracted with EtOAc (3 × 12 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (75 mL of SiO_2, 3–5 % EtOAc in hexanes gradient elution) afforded **S11** (153.5 mg, 0.861 mmol, 40% from **S9**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.19–3.14 (m, 1H), 2.49 (dt, J = 10.5, 3.4 Hz, 1H), 2.20 (s, 3H), 1.95–1.81 (m, 3H), 1.79 (d, J = 2.6 Hz, 3H), 1.78–1.66 (m, 3H), 1.61–1.51 (m, 3H), 1.48–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.5, 79.1, 79.0, 56.8, 33.9, 32.1, 28.2, 27.6, 26.3, 25.1, 24.6, 3.6; IR (film) ν_{max} 2923, 1711, 1446, 1353, 1178 cm^{-1}; HRMS (ESI) *m/z* 179.1434 (MH^+, $C_{12}H_{18}OH^+$ requires 179.1436).



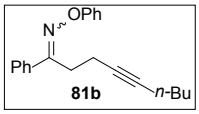
A solution of 1-bromo-2-butyne (68 μL, 103 mg, 0.78 mmol) and *i*Pr_2NEt (130 μL, 96 mg, 0.75 mmol) in $CHCl_3$ (1.0 mL) was treated with freshly prepared 1-(1-phenylprop-1-en-1-yl)pyrrolidine[3] (**S12**, ca. 70% purity, 201.1 mg, 0.75 mmol). The resulting mixture was refluxed for 12 h, then treated with 1N HCl (1.5 mL) and stirred at 65 °C for 4 h. The resulting biphasic mixture was extracted with diethyl ether (3 × 6 mL), and the combined organic layers were washed with water (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (18 mL of SiO_2, 0–5 % EtOAc in hexanes gradient elution) afforded **S13** (122.4 mg, 0.657 mmol, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 3.64 (h, *J* = 7.0 Hz, 1H), 2.64–2.51 (m, 1H), 2.41–2.29 (m, 1H), 1.76 (t, *J* = 2.6 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.8, 136.1, 133.0, 128.6 (2C), 128.4 (2C), 77.1, 76.9, 40.7, 22.8, 17.4, 3.5; IR (film) ν_{max} 2973, 2359, 1683, 1448, 1199 cm^{-1}; HRMS (ESI) *m/z* 187.1151 (MH^+, $C_{13}H_{14}OH^+$ requires 187.1123).

6.2.2 Synthesis of *O*-phenyl oxime ethers



1-Phenylhex-4-yn-1-one *O*-phenyl oxime (81a). A solution of *O*-phenyl hydroxylamine hydrochloride[4] (288.3 mg, 1.98 mmol, 1.5 equiv) in anhydrous pyridine (5.4 mL) under Ar at rt was treated with 1-phenylhex-4-yn-1-one[5] (227.7 mg, 1.32 mmol, 1.0 equiv). The resulting mixture was stirred at rt for 16 h, then poured into H_2O (12 mL) and extracted with

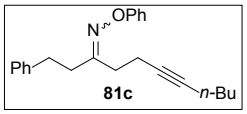
EtOAc (3 × 12 ml). The combined organic layers were washed with sat aq $CuSO_4$ (12 mL) to remove traces of pyridine, dried ($NaSO_4$), and concentrated *in vacuo*. Flash chromatography (30 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81a** (254.7 mg, 0.967 mmol, 73%) as a colorless oil that was a 3.2:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) 7.85–7.79 (m, 2H), 7.52–7.42 (m, 3H), 7.39–7.33 (m, 2H), 7.32 and 7.19 (2d, J = 7.2 and 7.7 Hz, 2H), 7.06 and 7.02 (2t, J = 7.1 and 7.3 Hz, 1H), 3.17 and 2.89 (2t, J = 7.6 and 7.3 Hz, 2H), 2.57–2.51 and 2.50–2.42 (2m, 2H), 1.80 and 1.74 (2t, J = 2.4 and 2.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.2 and 159.9, 159.5 and 159.4, 134.9, 129.8, 129.3 and 129.2 (2C), 128.6 and 128.2 (2C), 127.8 and 126.8, 122.3 and 122.0 (2C), 114.9 and 114.7 (2C), 77.8 and 77.6, 76.9, 35.2 and 27.2, 16.4, 3.4; IR (film) ν_{max} 3060, 2917, 2361, 1593, 1490, 1214 cm^{-1}; HRMS (ESI) *m/z* 264.1373 (MH^+, $C_{18}H_{17}NOH^+$ requires 264.1388).



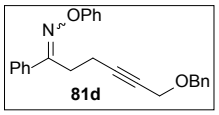
81b

1-Phenylnon-4-yn-1-one *O*-phenyl oxime (81b). Subjection of 1-phenylnon-4-yn-1-one[5] (36.6 mg, 0.171 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (10 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81b** (43.7 mg, 0.143 mmol, 84%) as a colorless oil that was a 2.1:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83–7.79 (m, 1H), 7.49–7.39 (m, 4H), 7.37–7.32 (m, 2H), 7.30 and 7.18 (2d, J = 7.6 and 7.7 Hz, 2H), 7.05 and 7.00 (2t, J = 7.1 and 7.3 Hz, 1H), 3.16 and 2.88 (2t, J = 7.7 and 7.5 Hz, 2H), 2.56 and 2.46 (2tt, J = 7.7, 2.2 Hz and 7.6, 2.2 Hz, 2H), 2.15 and 2.09 (2tt, J = 6.8, 2.3 Hz and 6.8, 2.3 Hz, 2H), 1.49–1.31 (m, 4H), 0.91–0.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3 and 159.8, 159.5 and 159.4, 135.0 and 133.1, 129.7 and 129.3 (2C), 129.2 and 129.1, 128.5 and 128.2 (2C), 127.8 and 126.9 (2C), 122.2 and 122.0, 114.9 and 114.7 (2C), 81.6, 78.4, 35.3 and 31.0, 31.1 and 27.3, 21.9, 18.4, 16.5 and 16.4,

13.6; IR (film) ν_{max} 2930, 2359, 1593, 1490, 1214, 1023 cm^{-1}; HRMS (ESI) *m/z* 306.1867 (MH^+, $C_{21}H_{23}NOH^+$ requires 306.1858).

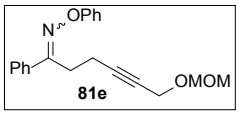


1-Phenylundec-6-yn-3-one *O*-phenyl oxime (81c). Subjection of 1-phenylundec-6-yn-3-one[6] (24.7 mg, 0.102 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (8 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81c** (27.7 mg, 0.0831 mmol, 82%) as a colorless oil that was a 1:1 mixture of isomers: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.28 (m, 4H), 7.27–7.22 (m, 3H), 7.20 and 7.14 (2d, *J* = 7.8 and 7.8 Hz, 2H), 7.04–6.98 (m, 1H), 2.99 and 2.93 (2t, *J* = 8.0, 8.0 Hz, 2H), 2.80 and 2.74 (2t, *J* = 7.9, 8.0 Hz, 2H), 2.70 and 2.54–2.43 (t and m, *J* = 7.3 Hz, 4H), 2.21–2.09 (m, 2H), 1.50–1.34 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.6 and 162.5, 159.5 and 159.4, 141.3 and 141.0, 129.2 (2C), 128.5 (2C), 128.4 and 128.3 (2C), 126.3 and 126.1, 121.9 and 121.8, 114.7 and 114.6 (2C), 81.4 and 81.2, 78.7 and 78.5, 36.6 and 34.4, 32.2 and 32.0, 31.3 and 31.1, 29.0, 22.0 and 21.9, 18.4, 16.0 and 15.7, 13.6; IR (film) ν_{max} 2930, 2360, 1591, 1489, 1213, 1072 cm^{-1}; HRMS (ESI) *m/z* 334.2143 (MH^+, $C_{23}H_{27}NOH^+$ requires 334.2171).

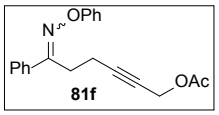


6-(Benzyloxy)-1-phenylhex-4-yn-1-one *O*-phenyl oxime (81d). Subjection of 6-(benzyloxy)-1-phenylhex-4-yn-1-one[6] (37.5 mg, 0.135 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (18 mL of SiO_2, 3–5% EtOAc in hexanes gradient elution) afforded **81d** (35.6 mg, 0.964 mmol, 72%) as a colorless oil that was a 6.1:1 mixture of isomers: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.86–7.77 (m,

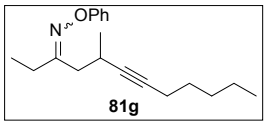
2H), 7.49 and 7.45–7.40 (d and m, J = 8.0 Hz, 4H), 7.38–7.28 and 7.17 (m and d, J = 7.9 Hz, 8H), 7.06 and 7.00 (2t, J = 7.1 and 7.2 Hz, 1H), 4.58 and 4.51 (2s, 2H), 4.16 and 4.10 (2t, J = 2.0 and 2.0 Hz, 2H), 3.21 and 2.94 (2t, J = 7.7 and 7.6 Hz, 2H), 2.66 and 2.58 (2tt, J = 7.7, 2.0 Hz and 7.5, 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 159.4, 137.6, 134.8, 129.9, 129.3 and 129.2 (2C), 128.6 (2C), 128.4 and 128.3 (2C), 128.1 and 128.0 (2C), 127.9 and 127.8, 126.8 (2C), 122.4 and 122.1, 114.8 and 114.7 (2C), 85.4, 77.2, 71.5 and 71.4, 57.6, 34.7 and 26.7, 16.4; IR (film) ν_{max} 3062, 2360, 1653, 1489, 1351, 1214, 1072 cm^{-1}; HRMS (ESI) *m/z 370*.1780 (MH^+, $C_{25}H_{23}NO_2H^+$ requires 370.1807).



6-(Methoxymethoxy)-1-phenylhex-4-yn-1-one *O*-phenyl oxime (81e). Subjection of 6-(methoxymethoxy)-1-phenylhex-4-yn-1-one (**S3**, 33.2 mg, 0.143 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (12 mL of SiO_2, 5–10% EtOAc in hexanes gradient elution) afforded **81e** (36.9 mg, 0.114 mmol, 80%) as a colorless oil that was a 4.7:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83–7.77 (m, 2H), 7.46–7.41 (m, 3H), 7.38–7.33 (m, 2H), 7.30 and 7.18 (2d, J = 7.6 and 7.8 Hz, 2H), 7.06 and 7.01 (2t, J = 7.2 and 7.3 Hz, 1H), 4.70 and 4.65 (2s, 2H), 4.21 and 4.15 (2t, J = 2.0 and 2.0 Hz, 2H), 3.37 (s, 3H), 3.20 and 2.92 (2t, J = 7.8 and 7.5 Hz, 2H), 2.65–2.61 and 2.58–2.54 (2m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 159.4 and 159.3, 134.7 and 133.0, 129.9, 129.3 and 129.2 (2C), 128.6 and 128.3 (2C), 127.8 and 126.8 (2C), 122.4 and 122.1, 114.8 and 114.7 (2C), 94.7 and 94.6, 85.3 and 85.2, 76.7 and 76.6, 55.5, 54.6 and 54.5, 34.7 and 26.7, 16.4; IR (film) ν_{max} 2946, 2236, 1592, 1490, 1214, 1150, 1072 cm^{-1}; HRMS (ESI) *m/z* 324.1603 (MH^+, $C_{20}H_{21}NO_3H^+$ requires 324.1600).

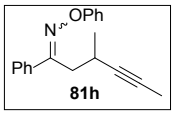


6-(Phenoxyimino)-6-phenylhex-2-yn-1-yl acetate (81f). Subjection of 6-oxo-6-phenylhex-2-yn-1-yl acetate (**S5**, 27.7 mg, 0.120 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (25 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81f** (35.1 mg, 0.109 mmol, 91%) as a colorless oil that was a 1.7:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81–7.77 (m, 1H), 7.50–7.41 (m, 4H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.32–7.28 (m, 2H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.06 and 7.01 (2t, *J* = 7.2 and 7.3 Hz, 1H), 4.66 and 4.60 (2t, *J* = 2.2 and 2.1 Hz, 2H), 3.20 and 2.92 (2t, *J* = 7.8 and 7.4 Hz, 2H), 2.63 and 2.57 (2tt, *J* = 7.8, 2.2 Hz and 7.6, 2.1 Hz, 2H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4 and 170.3, 159.6 and 159.4, 159.3 and 159.1, 134.7 and 132.9, 129.9 and 129.34, 129.30 and 129.2 (2C), 128.6 and 128.3 (2C), 127.8 and 126.8 (2C), 122.4 and 122.1, 114.8 and 114.7 (2C), 85.9 and 85.8, 75.2 and 75.1, 52.7 and 52.6, 34.5 and 26.5, 20.8, 16.4 and 16.3; IR (film) ν_{max} 2938, 2238, 1744, 1591, 1216, 1024 cm^{-1}; HRMS (ESI) *m/z* 322.1455 (MH^+, $C_{20}H_{19}NO_3H^+$ requires 322.1443).

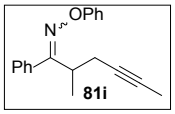


5-Methyldodec-6-yn-3-one *O*-phenyl oxime (81g). Subjection of 5-methyldodec-6-yn-3-one[5] (34.7 mg, 0.179 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (12 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81g** (49.8 mg, 0.174 mmol, 98%) as a colorless oil that was a 2.0:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (t, *J* = 7.4 Hz, 2H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 3.00–2.92 and 2.91–2.82 (2m, 1H), 2.75–2.69 and 2.44–2.38 (2m, 1H), 2.60–2.47 (m, 3H), 2.20–2.10 (m, 2H), 1.53–1.44 (m, 2H), 1.38–1.30 (m, 4H), 1.27–1.16 (m, 6H), 0.96–0.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 and 164.0, 159.6 and

159.5, 129.2 (2C), 121.7 and 121.6, 114.6 (2C), 83.6 and 83.4, 81.3 and 81.2, 41.1 and 36.2, 31.0, 28.7 and 28.6, 23.7 and 23.5, 22.4, 22.2, 21.9 and 21.4, 18.7, 14.0, 10.7 and 10.5; IR (film) ν_{max} 2932, 2360, 1592, 1489, 1211 cm^{-1}; HRMS (ESI) *m/z* 286.2149 (MH^+, $C_{19}H_{27}NOH^+$ requires 286.2171).

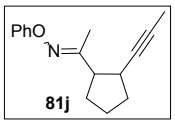


3-Methyl-1-phenylhex-4-yn-1-one *O*-phenyl oxime (81h). Subjection of 3-methyl-1-phenylhex-4-yn-1-one[5] (29.6 mg, 0.159 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (12 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81h** (39.1 mg, 0.141 mmol, 89%) as a colorless oil that was a 1.4:1 mixture of isomers: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87–7.75 (m, 1H), 7.49–7.40 (m, 4H), 7.37–7.28 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.05 and 7.01 (2t, *J* = 7.2, 7.3 Hz, 1H), 3.19 and 2.88 (2dd, *J* = 10.4, 7.7 and 10.9, 7.7 Hz, 1H), 3.07 and 2.74 (2dd, *J* = 10.2, 7.5 and 10.6, 7.1 Hz, 1H), 2.99–2.91 and 2.70–2.57 (2m, 1H), 1.77 and 1.67 (2d, *J* = 2.2, 2.3 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.9 and 159.8, 159.5 and 159.4, 135.4 and 133.2, 129.6 and 129.3, 129.2 and 129.1 (2C), 128.4, 128.2 and 127.9 (2C), 127.1, 122.2 and 122.0, 114.9 and 114.8 (2C), 82.6 and 82.3, 77.2 and 76.9, 42.7 and 34.5, 24.0 and 23.8, 21.3 and 20.9, 3.5 and 3.4; IR (film) ν_{max} 2968, 2360, 1593, 1490, 1216 cm^{-1}; HRMS (ESI) *m/z* 278.1575 (MH^+, $C_{19}H_{19}NOH^+$ requires 278.1545).

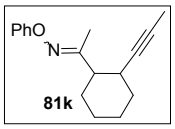


2-Methyl-1-phenylhex-4-yn-1-one *O*-phenyl oxime (81i). Subjection of 2-methyl-1-phenylhex-4-yn-1-one (**S13**, 23.7 mg, 0.127 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (15 mL of SiO_2, 1–5% EtOAc

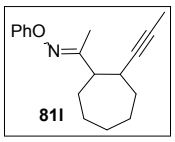
in hexanes gradient elution) afforded **81i** (29.3 mg, 0.106 mmol, 83%) as a colorless oil that was a 1.9:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.56 (m, 1H), 7.52–7.39 (m, 3H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.35–7.25 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.04 and 6.99 (2t, *J* = 7.2 and 7.2 Hz, 1H), 3.64 and 3.02 (2h, *J* = 7.2 and 7.0 Hz, 1H), 2.68–2.62 and 2.35–2.29 (2m, 1H), 2.57–2.51 (m, 1H), 1.82 and 1.75 (2t, *J* = 2.4 and 2.4 Hz, 3H), 1.42 and 1.32 (2d, *J* = 7.1 and 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.1 and 164.0, 159.5 and 159.3, 135.6 and 133.4, 129.2 and 129.14, 129.12 and 128.8 (2C), 128.3 and 128.1 (2C), 128.0 and 127.6 (2C), 122.2 and 121.9, 114.8 and 114.7 (2C), 77.3 and 77.2, 77.1, 40.1 and 35.9, 24.0 and 23.3, 17.9 and 17.0, 3.5; IR (film) ν_{max} 2918, 2359, 1594, 1490, 1215 cm^{-1}; HRMS (ESI) *m/z* 278.1543 (MH^+, $C_{19}H_{19}NOH^+$ requires 278.1545).



1-(2-(Prop-1-yn-1-yl)cyclopentyl)ethan-1-one *O*-phenyl oxime (81j). Subjection of 1-(2-(prop-1-yn-1-yl)cyclopentyl)ethan-1-one (**S8**, 38.6 mg, 0.257 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (25 mL of SiO_2, 3–5% EtOAc in hexanes gradient elution) afforded **81j** (47.2 mg, 0.196 mmol, 76%) as a colorless oil that was a 4.6:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (t, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 3.50 and 2.86 (2q, *J* = 8.6 and 8.0 Hz, 1H), 3.38–3.32 and 3.08–3.01 (2m, 1H), 2.12 and 2.10 (2s, 3H), 2.07–1.90 (m, 3H), 1.89–1.81 (m, 2H), 1.76 (d, *J* = 2.4 Hz, 3H), 1.68–1.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3 and 162.4, 159.7 and 159.5, 129.2 (2C), 121.8 and 121.5, 114.9 and 114.6 (2C), 80.5 and 79.7, 78.4, 49.9 and 43.4, 34.4, 33.4 and 33.2, 27.3 and 26.8, 23.6 and 23.5, 19.2 and 15.3, 3.6; IR (film) ν_{max} 2960, 2871, 1595, 1490, 1214, 1159 cm^{-1}; HRMS (ESI) *m/z* 242.1526 (MH^+, $C_{16}H_{19}NOH^+$ requires 242.1545).

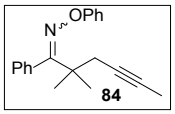


1-(2-(Prop-1-yn-1-yl)cyclohexyl)ethan-1-one *O*-phenyl oxime (81k). Subjection of 1-(2-(prop-1-yn-1-yl)cyclohexyl)ethan-1-one[5] (31.0 mg, 0.189 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (25 mL of SiO_2, 3–5% EtOAc in hexanes gradient elution) afforded **81k** (47.6 mg, 0.186 mmol, 99%) as a colorless oil that was a 6.7:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.4 Hz, 2H), 7.20 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.29 and 2.40 (2dt, J = 12.7, 3.3 Hz and 12.1, 3.3 Hz, 1H), 3.19 and 3.01 (2 br s, 1H), 2.07 (s, 3H), 1.94–1.87 (m, 2H), 1.82 (d, J = 2.4 Hz, 3H), 1.78–1.69 (m, 2H), 1.61–1.52 (m, 2H), 1.33–1.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.4, 159.7, 129.2 and 129.1 (2C), 121.8 and 121.5, 114.9 and 114.7 (2C), 79.2, 79.0, 47.1 and 40.2, 32.1 and 32.0, 31.4 and 29.8, 25.8, 24.5, 21.5 and 21.3, 18.3 and 13.5, 3.6; IR (film) ν_{max} 2932, 2362, 1594, 1490, 1212, 1158, 1023 cm^{-1}; HRMS (ESI) *m/z* 256.1680 (MH^+, $C_{17}H_{21}NOH^+$ requires 256.1701).



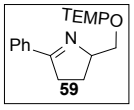
1-(2-(Prop-1-yn-1-yl)cycloheptyl)ethan-1-one *O*-phenyl oxime (81l). Subjection of 1-(2-(prop-1-yn-1-yl)cycloheptyl)ethan-1-one (**S11**, 31.6 mg, 0.177 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (20 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **81l** (34.7 mg, 0.129 mmol, 73%) as a colorless oil that was a 5.7:1 mixture of isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.9 Hz, 2H), 7.19 (d, J = 7.7 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 3.49–3.45 and 2.63–2.59 (2m, 1H), 3.09–3.05 and 3.02–2.96 (2m, 1H), 2.13 and 2.10 (2s, 3H), 2.02–1.89 (m, 2H), 1.84 (d, J = 2.4 Hz, 3H), 1.82–1.76 (m, 3H), 1.73–1.63 (m, 3H), 1.62–1.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125

MHz) δ 165.9 and 164.9, 159.6 and 159.4, 129.2 (2C), 121.8 and 121.6, 114.8 (2C), 80.0 and 79.9, 79.3 and 79.0, 51.8 and 48.7, 34.4, 34.2, 28.0 and 27.4, 27.0 and 26.9, 26.3, 24.9 and 24.6, 17.8 and 13.2, 3.6; IR (film) ν_{max} 2924, 2360, 1594, 1489, 1213 cm^{-1}; HRMS (ESI) *m/z* 270.1875 (MH^+, $C_{18}H_{23}NOH^+$ requires 270.1858).



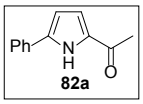
2,2-Dimethyl-1-phenylhex-4-yn-1-one *O*-phenyl oxime (84). Subjection of 2,2-dimethyl-1-phenylhex-4-yn-1-one[5] (35.4 mg, 0.177 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (20 mL of SiO_2, 1–5% EtOAc in hexanes gradient elution) afforded **84** (34.5 mg, 0.118 mmol, 67%) as a colorless oil that was a single isomer of undetermined configuration about the C=N bond: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.39 (m, 3H), 7.28–7.18 (m, 4H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 2.39 (q, *J* = 2.4 Hz, 2H), 1.85 (t, *J* = 2.4 Hz, 3H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 159.6, 133.4, 129.0 (2C), 128.0, 127.9 (2C), 127.4 (2C), 121.7, 114.6 (2C), 78.3, 76.3, 41.5, 30.7, 25.8 (2C), 3.6; IR (film) ν_{max} 3059, 2970, 2919, 1594, 1490, 1213, cm^{-1}; HRMS (ESI) *m/z* 292.1679 (MH^+, $C_{20}H_{21}NOH^+$ requires 292.1701).

6.2.3 Iminyl radical cyclizations

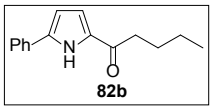


2,2,6,6-Tetramethyl-1-((5-phenyl-3,4-dihydro-2*H*-pyrrol-2-yl)methoxy) piperidine (59). An oven-dried microwave reaction vessel was charged with 1-phenylpent-4-en-1-one *O*-phenyl oxime[7,8] (**57**, 21.6 mg, 0.0859 mmol, 1.0 equiv), TEMPO (20.1 mg, 0.129 mmol, 1.5 equiv), and trifluorotoluene (0.86 mL). The vessel was sealed under an Ar atmosphere and subjected to microwave irradiation (300 W) for 15 min at 98 ºC. The mixture was cooled to rt

and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0.5–5% MeOH in CH_2Cl_2 gradient elution) afforded **59** (24.4 mg, 0.0776 mmol, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, *J* = 3.9 Hz, 2H), 7.46–7.38 (m, 3H), 4.45 (br s, 1H), 4.09 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.98 (t, *J* = 5.1 Hz, 1H), 3.08–2.93 (m, 2H), 2.20–2.11 (m, 1H), 2.09–2.01 (m, 1H), 1.59–1.34 (m, 6H), 1.22 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 134.7, 130.3, 128.4 (2C), 127.7 (2C), 79.1, 72.3, 59.9 (2C), 39.6, 35.4 (2C), 33.2, 33.0, 25.9, 20.3, 20.0, 17.1; IR (film) ν_{max} 2931, 1616, 1450, 1373, cm^{-1}; HRMS (ESI) *m/z* 315.2461 (MH^+, $C_{20}H_{30}N_2OH^+$ requires 315.2436).

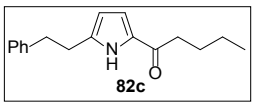


1-(5-Phenyl-1*H*-pyrrol-2-yl)ethan-1-one (82a). An oven-dried microwave reaction vessel was charged with *O*-phenyl oxime **81a** (20.4 mg, 0.0775 mmol), TEMPO (18.2 mg, 0.116 mmol, 1.5 equiv), and trifluorotoluene (0.8 mL). The vessel was sealed under an Ar atmosphere and subjected to microwave irradiation (300 W) for 30 min at 98 ºC. The mixture was treated with additional TEMPO (18.2 mg, 0.116 mmol, 1.5 equiv) and irradiated by microwaves for 30 additional min at 98 °C. The mixture was then cooled to rt and concentrated *in vacuo*. Flash chromatography (15 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82a** (11.9 mg, 0.0642 mmol, 83%) as a colorless powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (br s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.97 (dd, *J* = 3.1, 2.4 Hz, 1H), 6.58 (dd, *J* = 3.3, 2.8 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.6, 138.2, 132.5, 130.9, 129.1 (2C), 128.2, 125.0 (2C), 118.2, 108.3, 25.3; IR (film) ν_{max} 3300, 2360, 1634, 1470, 1273 cm^{-1}; HRMS (ESI) *m/z* 186.0898 (MH^+, $C_{12}H_{11}NOH^+$ requires 186.0919).



82b

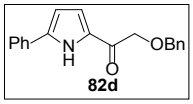
1-(5-phenyl-1*H*-pyrrol-2-yl)pentan-1-one (82b). An oven-dried microwave reaction vessel was charged with *O*-phenyl oxime **81b** (17.6 mg, 0.0576 mmol), TEMPO (27.0 mg, 0.173 mmol, 3.0 equiv), and trifluorotoluene (0.6 mL). The vessel was sealed under an Ar atmosphere and subjected to microwave irradiation (300 W) for 30 min at 98 ºC. The mixture was cooled to rt and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82b** (9.9 mg, 0.044 mmol, 76%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.43 (br s, 1H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.97 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.58 (dd, *J* = 4.2, 2.9 Hz, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.74 (p, *J* = 7.6 Hz, 2H), 1.43 (h, J = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.9, 137.9, 132.4, 131.0, 129.1 (2C), 128.1, 124.9 (2C), 117.4, 108.2, 37.6, 27.6, 22.6, 13.9; IR (film) ν_{max} 3322, 2360, 1638 cm^{-1}; HRMS (ESI) *m/z* 228.1382 (MH^+, $C_{15}H_{17}NOH^+$ requires 228.1388).



82c

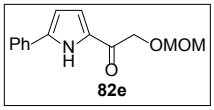
1-(5-Phenethyl-1*H*-pyrrol-2-yl)pentan-1-one (82c). Subjection of *O*-phenyl oxime **81c** (11.7 mg, 0.0351 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (8 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82c** (8.2 mg, 0.032 mmol, 92%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (br s, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 6.82 (dd, *J* = 3.7, 2.6 Hz, 1H), 6.01 (t, *J* = 3.2 Hz, 1H), 2.96 (s, 4H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.69 (p, *J* = 7.6 Hz, 2H), 1.39 (h, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.4, 140.7, 139.2, 131.0, 128.6 (2C), 128.3 (2C), 126.4, 116.7, 108.6, 37.4, 35.4,

29.7, 27.6, 22.6, 13.9; IR (film) ν_{max} 3261, 2951, 2359, 1623, 1496, 1203, 1054 cm^{-1}; HRMS (ESI) *m/z* 256.1711 (MH^+, $C_{17}H_{21}NOH^+$ requires 256.1701).



82d

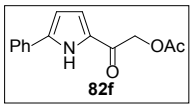
2-(Benzyloxy)-1-(5-phenyl-1*H*-pyrrol-2-yl)ethan-1-one (82d). Subjection of *O*-phenyl oxime **81d** (11.3 mg, 0.0306 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (5 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82d** (4.7 mg, 0.016 mmol, 53%) and **83** (1.4 mg, 0.0032 mmol, 11%). For **82d**: yellow powder, ^1H NMR ($CDCl_3$, 500 MHz) δ 9.68 (br s, 1H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.46–7.37 (m, 6H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.10 (dd, *J* = 3.1, 2.4 Hz, 1H), 6.58 (dd, *J* = 3.3, 2.7 Hz, 1H), 4.71 (s, 2H), 4.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.2, 137.2, 130.7, 129.1 (3C), 128.6 (2C), 128.3, 128.1 (4C), 125.0 (2C), 118.5, 108.6, 77.2, 73.6; IR (film) ν_{max} 3315, 2923, 2359, 1653, 1265, 1078, 1018 cm^{-1}; HRMS (ESI) *m/z* 292.1345 (MH^+, $C_{19}H_{17}NO_2H^+$ requires 292.1338). For **5**: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (d, *J* = 6.7 Hz, 2H), 7.50–7.41 (m, 5H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.34–7.31 (m, 1H), 5.11 (s, 2H), 4.97 (s, 2H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 1.50–1.41 (m, 4H), 1.35–1.30 (m, 2H), 1.15 (s, 6H), 1.13 (s, 6H); HRMS (ESI) *m/z* 433.2875 (MH^+, $C_{28}H_{36}N_2O_2H^+$ requires 433.2855).



82e

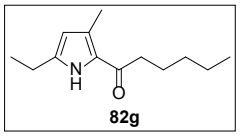
2-(Methoxymethoxy)-1-(5-phenyl-1*H*-pyrrol-2-yl)ethan-1-one (82e). Subjection of *O*-phenyl oxime **81e** (10.2 mg, 0.0315 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (12 mL of SiO_2, 0–5% MeOH in CH_2Cl_2 gradient elution) afforded **82e** (4.8 mg, 0.020 mmol, 62%) as a white film: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.60 (br s, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.06 (dd, *J* = 4.2, 2.4 Hz, 1H), 6.60 (dd, *J* = 4.2, 2.7 Hz, 1H), 4.81 (s, 2H), 4.67 (s,

2H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6, 138.6, 130.7, 130.0, 129.2 (2C), 128.4, 125.0 (2C), 118.0, 108.6, 96.7, 69.1, 55.8; IR (film) ν_{max} 3307, 2943, 2360, 1649, 1469, 1042 cm^{-1}; HRMS (ESI) *m/z* 246.1141 (MH^+, $C_{14}H_{15}NO_3H^+$ requires 246.1130).



82f

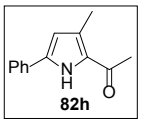
2-Oxo-2-(5-phenyl-1*H*-pyrrol-2-yl)ethyl acetate (82f). Subjection of *O*-phenyl oxime **81f** (11.9 mg, 0.0370 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (12 mL of SiO_2, 10–30% EtOAc in hexanes gradient elution) afforded **82f** (8.3 mg, 0.034 mmol, 92%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.47 (br s, 1H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.03 (dd, *J* = 3.9, 2.4 Hz, 1H), 6.61 (dd, *J* = 3.8, 2.7 Hz, 1H), 5.15 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.3, 170.5, 139.0, 130.6, 129.22, 129.20 (2C), 128.6, 125.1 (2C), 117.8, 108.7, 65.0, 20.7; IR (film) ν_{max} 3303, 1744, 1645, 1228 cm^{-1}; HRMS (ESI) *m/z* 244.0954 (MH^+, $C_{14}H_{13}NO_3H^+$ requires 244.0974).



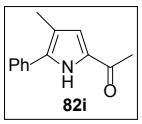
82g

1-(5-Ethyl-3-methyl-1*H*-pyrrol-2-yl)hexan-1-one (82g). Subjection of *O*-phenyl oxime **81g** (16.4 mg, 0.0575 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (10 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82g** (9.7 mg, 0.047 mmol, 81%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (br s, 1H), 5.85 (d, *J* = 2.7 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 1.77–1.69 (m, 2H), 1.40–1.34 (m, 4H), 1.25 (t, *J* = 7.7 Hz, 3H), 0.92 (t, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.0, 139.9, 128.2, 127.4, 111.0, 39.5, 31.8, 24.4, 22.6,

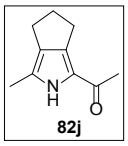
20.8, 14.5, 14.0, 13.1; IR (film) ν_{max} 3269, 2953, 2360, 1619, 1491 cm^{-1}; HRMS (ESI) *m/z* 208.1715 (MH^+, $C_{13}H_{21}NOH^+$ requires 208.1701).



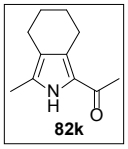
1-(3-Methyl-5-phenyl-1*H*-pyrrol-2-yl)ethan-1-one (82h). Subjection of *O*-phenyl oxime **81h** (12.5 mg, 0.0451 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (12 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82h** (8.8 mg, 0.044 mmol, 98%) as a colorless powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.35 (br s, 1H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 2.8 Hz, 1H), 2.49 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.4, 136.2, 130.9, 130.1, 129.1 (2C), 128.6, 128.1, 124.8 (2C), 111.2, 27.9, 14.5; IR (film) ν_{max} 3311, 2360, 1636, 1448, 1271 cm^{-1}; HRMS (ESI) *m/z* 200.1053 (MH^+, $C_{13}H_{13}NOH^+$ requires 200.1075).



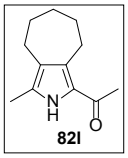
1-(4-Methyl-5-phenyl-1*H*-pyrrol-2-yl)ethan-1-one (82i). Subjection of *O*-phenyl oxime **81i** (12.7 mg, 0.0458 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (12 mL of SiO_2, 10–20% EtOAc in hexanes gradient elution) afforded **82i** (8.0 mg, 0.040 mmol, 88%) as a white powder: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.17 (br s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.4, 135.2, 131.9, 130.7, 128.9 (2C), 127.8, 127.0 (2C), 119.5, 118.7, 25.2, 12.5; IR (film) ν_{max} 3307, 1461, 1263, 1184 cm^{-1}; HRMS (ESI) *m/z* 200.1065 (MH^+, $C_{13}H_{13}NOH^+$ requires 200.1075).



1-(3-Methyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrol-1-yl)ethan-1-one (82j). Subjection of *O*-phenyl oxime **81j** (20.2 mg, 0.0837 mmol) to the procedure described above for the synthesis of **81a** with purification by flash chromatography (10 mL of SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded **82j** (7.0 mg, 0.0429 mmol, 51%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (br s, 1H), 2.88 (t, J = 7.3 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.40 (p, J = 7.2 Hz, 2H), 2.33 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.0, 139.6, 130.5, 127.6, 123.5, 30.8, 27.7, 26.2, 24.3, 12.2; IR (film) ν_{max} 3242, 2955, 1624, 1278, 1069 cm^{-1}; HRMS (ESI) *m/z* 164.1102 (MH^+, $C_{10}H_{13}NOH^+$ requires 164.1075).



1-(3-Methyl-4,5,6,7-tetrahydro-2*H*-isoindol-1-yl)ethan-1-one (82k). Subjection of *O*-phenyl oxime **81k** (25.3 mg, 0.0991 mmol) to the procedure described above for the synthesis of **81b** with purification by flash chromatography (10 mL of SiO_2, 5–20% EtOAc in hexane gradient elution) afforded **82k** (16.5 mg, 0.0931 mmol, 94%) as a white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (br s, 1H), 2.81 (t, J = 6.2 Hz, 2H), 2.42 (t, J = 6.1 Hz, 2H), 2.36 (s, 3H), 2.17 (s, 3H), 1.84–1.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.0, 130.9, 128.7, 126.7, 119.8, 27.5, 24.3, 23.4, 23.0, 21.3, 11.2; IR (film) ν_{max} 3269, 2939, 1613, 1434, 1277 cm^{-1}; HRMS (ESI) *m/z* 178.1232 (MH^+, $C_{11}H_{15}NOH^+$ requires 178.1232).



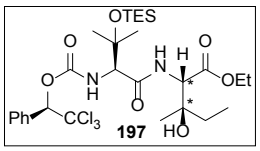
1-(3-Methyl-2,4,5,6,7,8-hexahydrocyclohepta[c]pyrrol-1-yl)ethan-1-one (82l). Subjection of *O*-phenyl oxime **81l** (11.7 mg, 0.0434 mmol) to the procedure described above for

the synthesis of **81b** with purification by flash chromatography (12 mL of SiO_2, 10–20% EtOAc in hexanes gradient elution) afforded **82l** (7.9 mg, 0.041 mmol, 95%) as a yellow powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.67 (br s, 1H), 2.91 (t, J = 5.4 Hz, 2H), 2.49 (t, J = 5.6 Hz, 2H), 2.45 (s, 3H), 2.19 (s, 3H), 1.88–1.82 (m, 2H), 1.72–1.66 (m, 2H), 1.63–1.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.8, 133.7, 130.3, 126.5, 125.2, 32.8, 28.7, 28.4, 28.1, 27.5, 25.8, 11.3; IR (film) ν_{max} 3311, 2918, 2360, 2342, 1616, 1496, 1420, 1273 cm^{-1}; HRMS (ESI) *m/z* 192.1386 (MH^+, $C_{12}H_{17}NOH^+$ requires 192.1388).

6.2.4 Calculation details for the study of stereospecific E2 dehydration

All structures were optimized with Gaussian 09.[9] Minima and transition states were verified to have zero and one negative vibrational frequencies. Enthalpies and free energies are reported at 298 K in solution. Solvent effects were included using the SMD solvent model for $CHCl_3$. Zero-point energies were left unscaled. No volume corrections were added to the solution free energy. XYZ coordinates are reported in Å units. Absolute energies are reported in Hartrees.

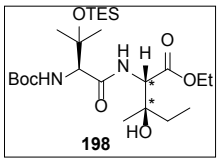
6.2.5 The synthesis of Yaku'amide A



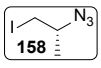
Ethyl (2*R,3*S**)-3-hydroxy-3-methyl-2-((*S*)-3-methyl-2-((((*R*)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)-3-((triethylsilyl)oxy)butanamido)pentanoate (197)**. A suspension of *epi*-**173** (94.0 mg, 0.178 mmol) and Me_3SnOH (81.0 mg, 0.448 mmol, 2.5 equiv) in hexanes (8 mL, pretreated with Na_2SO_4 for 6 h) under Ar was stirred at 60 °C for 48 h. The solvent was concentrated *in vacuo*, and the residue was treated with Et_2O (10 mL). The mixture was filtered through Celite, (washed with 60 mL of Et_2O), and the filtrate was

concentrated *in vacuo* to afford the crude acid as a colorless oil that was used directly in the next step without further purification.

A solution of the crude acid in anhydrous CH_2Cl_2 (2.5 mL) at 0 °C under Ar was treated with amine **152**[10] (35.1 mg, 0.200 mmol, 1.1 equiv), HOBt (ca. 20% H_2O content, 45.2 mg, 0.268 mmol, 1.5 equiv), and EDC•HCl (51.0 mg, 0.266 mmol, 1.5 equiv). The resulting mixture was stirred at 0 °C under Ar for 2 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (2 mL) and H_2O (2 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (6 × 4 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–1.5% MeOH in CH_2Cl_2 gradient elution) afforded **197** (102.8 mg, 0.157 mmol, 88%) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, minor rotamers present, data for major rotamer of each diastereomer) δ 7.61 (d, J = 7.5 Hz, 2H), 7.44–7.34 (m, 3H), 7.32 and 7.17 (2d, J = 8.1 and 8.4 Hz, 1H), 6.28 and 6.26 (2s, 1H), 6.07 and 6.01 (2d, J = 7.8 and 6.8 Hz, 1H), 4.61 and 4.47 (2d, J = 8.6 and 8.3 Hz, 1H), 4.28–4.19 (m, 2H), 4.17 and 4.09 (2d, J = 7.9 and 7.1 Hz, 1H), 2.62 and 2.58 (2s, 1H), 1.61–1.58 (m, 2H), 1.35–1.10 (m, 12H), 1.05–0.88 (m, 12H), 0.75–0.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6 and 171.2, 170.0 and 169.6, 154.6 and 154.5, 133.3 and 133.2, 129.63, 129.56 (2C), 127.8 (2C), 99.5, 83.5, 76.1 and 75.6, 74.2 and 73.6, 64.0 and 63.2, 61.6 and 61.5, 58.6 and 58.4, 31.6 and 31.4, 27.4 and 27.1, 26.6 and 25.4, 23.6 and 23.4, 14.1, 7.9 and 7.8, 7.0 (3C), 6.4 (3C); IR (film) ν_{max} 3356, 2957, 2877, 1734, 1666, 1506, 1373, 1202, 1059, 1021 cm^{-1}; HRMS (ESI) *m/z* 655.2139 (MH^+, $C_{28}H_{45}Cl_3N_2O_7SiH^+$ requires 655.2140).



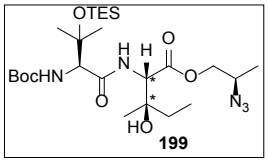
Ethyl (2*R,3*S**)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanamido)-3-hydroxy-3-methylpentanoate (198)**. A suspension of carbamate **197** (83.7 mg, 0.128 mmol) in a mixture of THF (1.5 mL) and sat aq $NaHCO_3$ (0.8 mL) was treated with 10% Pd/C (10 mg, 0.12 wt equiv) and Boc_2O (29.0 mg, 0.133 mmol, 1.04 equiv) sequentially at rt under Ar. The resulting mixture was stirred at rt under H_2 (100 psi) for 15 h, diluted with H_2O (3 mL), and extracted with EtOAc (5 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–1.5% MeOH in CH_2Cl_2 gradient elution) afforded **198** (60.1 mg, 0.119 mmol, 93%) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 and 7.14 (2 br s, 1H), 5.45 (br s, 1H), 4.62 and 4.49 (2d, J = 8.4 and 8.4 Hz, 1H), 4.29–4.16 (m, 2H), 4.14 and 4.04 (2 br s, 1H), 2.75 and 2.65 (2 br s, 1H), 1.60–1.53 (m, 2H), 1.45 and 1.44 (2s, 9H), 1.37 and 1.35 (2s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.20 and 1.19 (2s, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.95–0.91 (m, 3H), 0.72–0.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 171.3 and 170.9, 156.1, 80.0 and 79.7, 76.4 and 75.5, 74.2 and 73.7, 63.7 and 62.6, 61.5 and 61.4, 58.5 and 58.2, 31.5 and 31.4, 28.3 (3C), 27.6, 27.2 and 26.7, 23.6 and 23.4, 14.2 and 14.1, 7.9 and 7.8, 7.0 (3C), 6.5 (3C); IR (film) ν_{max} 3373, 2976, 2877, 2361, 1725, 1664, 1501, 1367, 1164, 1051 cm^{-1}; HRMS (ESI) *m/z* 505.3311 (MH^+, $C_{24}H_{48}N_2O_7SiH^+$ requires 505.3309).



(*R*)-2-azido-1-iodopropane (158). A solution of (*R*)-(–)-2-amino-1-propanol (222 μL, 214 mg, 2.85 mmol), K_2CO_3 (386.7 mg, 2.80 mmol), and $CuSO_4$•$5H_2O$ (7.7 mg, 0.031 mmol) in H_2O (9 mL) and MeOH (18 mL) at rt under Ar was treated with a solution of TfN_3 in CH_2Cl_2 (prepared according to the procedure of Lundquist and Pelletier,[11] ca. 0.42 M, 13.3 mL, ca. 5.6

mmol). The resulting mixture was stirred at rt for 48 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude azido alcohol was used in the next step without further purification.

A solution of PPh_3 (931 mg, 3.55 mmol) in anhydrous CH_2Cl_2 (30 mL) at rt under Ar was treated with imidazole (520 mg, 7.64 mmol) followed by I_2 (1.44 g, 5.67 mmol), stirred for 5 min, then treated dropwise with the crude azido alcohol. The resulting mixture was refluxed for 48 h, cooled to rt, and treated with sat aq Na_2SO_3 (20 mL). It was stirred until the color changed from black to yellow, at which time the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (100 mL of SiO_2, 0−0.5% EtOAc in hexanes gradient elution) afforded **158** (449 mg, 2.13 mmol, 75% over 2 steps) as a light yellow oil: $[\alpha]^{25}_D$ −29 (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.65–3.56 (m, 1H), 3.28–3.18 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 57.8, 19.9, 9.7; IR (film) ν_{max} 2922, 2851, 2105, 1261 cm^{-1}.

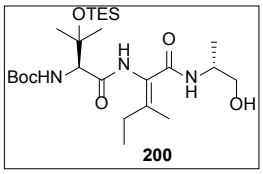


199

(*R*)-2-azidopropyl (2*S,3*R**)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanamido)-3-hydroxy-3-methylpentanoate (199).** A solution of ester **198** (21.3 mg, 0.0422 mmol) in *t*-BuOH (400 μL) and H_2O (150 μL) at 0 °C was treated with LiOH•H_2O (8.8 mg, 0.210 mmol, 5.0 equiv), then stirred at rt for 3 h. The resulting mixture was acidified to pH 4~5 by the addition of 2 N HCl, diluted with H_2O (2 mL), and extracted with EtOAc (2 × 6 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*.

The crude carboxylic acid (17.5 mg, 0.0367 mmol, 87%) was used directly without further purification.

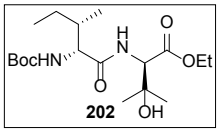
A solution of the crude carboxylic acid (17.5 mg, 0.0367 mmol) and iodide **158** (15.5 mg, 0.0735 mmol, 2.0 equiv) in anhydrous DMF (600 μL) at rt under Ar was treated with Cs_2CO_3 (9.6 mg, 0.0295 mmol, 0.80 equiv). The resulting mixture was stirred at 80 °C under Ar for 16 h, diluted with H_2O (2 mL), and extracted with EtOAc (6 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–1% MeOH in CH_2Cl_2 gradient elution) afforded **199** (15.5 mg, 0.0277 mmol, 75%; 66% from **198**) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 and 7.16 (2 br s, 1H), 5.48 and 5.43 (2 br s, 1H), 4.63 and 4.51 (2d, J = 7.8 Hz and 8.1 Hz, 1H), 4.19–4.01 (m, 3H), 3.85–3.74 (m, 1H), 2.56 and 2.45 (2 br s, 1H), 1.67–1.54 (m, 2H), 1.45 (s, 9H), 1.37 and 1.35 (2s, 3H), 1.34–1.31 (m, 3H), 1.29 and 1.28 (2s, 3H), 1.24 and 1.23 (2s, 3H), 0.98 (t, J = 7.8 Hz, 9H), 0.96–0.91 (m, 3H), 0.72–0.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3 and 171.0, 170.5, 156.1, 79.9 and 79.8, 76.3 and 75.6, 74.0 and 73.6, 67.8 and 67.4, 63.7 and 62.6, 58.7 and 58.4, 55.7 and 55.5, 31.6 and 31.5, 28.3 (3C), 27.5 and 27.2, 26.7 and 25.4, 23.7 and 23.4, 16.1 and 15.9, 7.9 and 7.8, 7.0 (3C), 6.4 (3C); IR (film) ν_{max} 3410, 2976, 2360, 2120, 1670, 1507, 1367, 1163 cm^{-1}; HRMS (ESI) *m/z* 560.3468 (MH^+, $C_{25}H_{49}N_5O_7SiH^+$ requires 560.3480).



200

***tert*-Butyl ((6*R*,12*R*,*Z*)-9-(butan-2-ylidene)-3,3-diethyl-13-hydroxy-5,5,12-trimethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-6-yl)carbamate (200)**. A solution of alcohol **199** (22.5 mg, 0.0402) in anhydrous $CHCl_3$ (300 μL) at 0 °C under Ar was

treated dropwise with a solution of Martin sulfurane (54.1 mg, 0.0804 mmol, 2.0 equiv) in anhydrous $CHCl_3$ (600 μL). The resulting mixture was stirred at 0 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. The residue was dissolved in THF (1.0 mL) and H_2O (100 μL), then treated with Lindlar catalyst (217.1 mg). The resulting suspension was stirred at rt under H_2 (1 atm) for 20 h, at which point reduction of the azide was complete as evidenced by MS. The H_2 was replaced by Ar (1 atm), piperidine (110 μL, 94.8 mg, 1.11 mmol, 28 equiv) was added to the mixture, and it was stirred at rt for 24 h. The mixture was then treated with sat aq $NaHCO_3$ (5 mL) and extracted with EtOAc (5 × 6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 0–4% MeOH in CH_2Cl_2 gradient elution) afforded **200** (16.8 mg, 0.0326 mmol, 81%, 12:1 dr) as a white film: $[\alpha]^{25}_D$ +16.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (s, 1H), 6.32 (br s, 1H), 5.45 (br s, 1H), 4.16–4.09 (m, 1H), 4.05 (d, *J* = 5.5 Hz, 1H), 3.81–3.73 (m, 1H), 3.49–3.41 (m, 2H), 2.18–2.08 (m, 2H), 1.99 (s, 3H), 1.45 (s, 9H), 1.37 (s, 3H), 1.31 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.67 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 166.6, 156.5, 140.9, 124.1, 80.5, 75.8, 66.5, 63.7, 48.0, 28.3 (3C), 27.3, 26.7, 26.3, 17.7, 16.7, 11.7, 7.0 (3C), 6.5 (3C); IR (film) ν_{max} 3265, 2924, 2854, 1649, 1517, 1367, 1170, 1051 cm^{-1}; HRMS (ESI) *m/z* 516.3441 (MH^+, $C_{25}H_{49}N_3O_6SiH^+$ requires 516.3469).

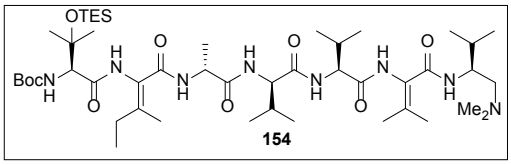


202

Ethyl (*R*)-2-((2*R*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylpentanamido)-3-hydroxy-3-methylbutanoate (202). A suspension of **173** (86.2 mg, 0.164 mmol) in EtOH–EtOAc (1:1, 4.0 mL) was treated with 10% Pd/C (8.6 mg, 0.1 wt equiv) at rt under Ar, and the resulting mixture was stirred at rt under H_2 (500 psi) for 3 d. The mixture

was filtered through Celite (2.0 mL, rinsed with 25 mL of EtOAc) and concentrated *in vacuo*. The crude amine was used directly without further purification.

A solution of the crude amine in anhydrous THF (4 mL) at 0 °C under Ar was treated sequentially with Boc-D-*allo*-Ile (56.8 mg, 0.246 mmol, 1.5 equiv), EDC•HCl (47.0 mg, 0.245 mmol, 1.5 equiv), and HOBt (ca. 20% H_2O content, 41.4 mg, 0.245 mmol, 1.5 equiv). The resulting mixture was stirred at 0 °C under Ar for 4 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (2 mL) and H_2O (2 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 6 mL), and the combined organic layers were washed with brine (4 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (15 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **202** (55.7 mg, 0.149 mmol, 91% over 2 steps) as a colorless oil: $[\alpha]^{25}_D$ +16.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.81 (d, *J* = 7.1 Hz, 1H), 5.02 (d, *J* = 7.4 Hz, 1H), 4.52 (d, *J* = 8.8 Hz, 1H), 4.28–4.20 (m, 2H), 4.12 (dd, J = 8.4, 2.9 Hz, 1H), 2.93 (br s, 1H), 1.96 (br s, 1H), 1.45 (s, 11H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 171.1, 155.9, 80.1, 72.0, 61.6, 59.9, 58.5, 37.0, 28.3 (3C), 26.72, 26.66, 26.2, 14.4, 14.1, 11.6; IR (film) ν_{max} 3338, 2978, 1655, 1535, 1367, 1025, 865, 756 cm^{-1}; HRMS (ESI) *m/z* 375.2491 (MH^+, $C_{18}H_{34}N_2O_6H^+$ requires 375.2495).



154

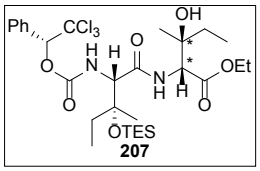
***tert*-Butyl ((4*S*,10*S*,13*R*,16*R*,22*S*,*Z*)-19-(butan-2-ylidene)-25,25-diethyl-4,10,13-triisopropyl-2,16,23,23-tetramethyl-6,9,12,15,18,21-hexaoxo-7-(propan-2-ylidene)-24-oxa-2,5,8,11,14,17,20-heptaaza-25-silaheptacosan-22-yl)carbamate (154)**. A solution of tetrapeptide **156** (14.0 mg, 0.0266 mmol) in anhydrous CH_2Cl_2 (200 μL) at

0 °C under Ar was treated with HCl (4.0 M in dioxane, 60 μL, 0.24 mmol, 9.0 equiv). The resulting mixture was stirred at rt for 1.5 h, then treated with Et_3N (300 μL) and concentrated *in vacuo*. The crude amine was used directly in the coupling with **7** without further purification.

A solution of alcohol **200** (17.8 mg, 0.0345 mmol) in anhydrous THF (800 μL) at rt under Ar was treated with the Dess–Martin periodinane (29.3 mg, 0.0691 mmol, 2.0 equiv). The resulting mixture was stirred at rt under Ar for 2 h, then diluted with H_2O (800 μL) and treated with NaH_2PO_4 (6.2 mg, 0.0517 mmol, 1.5 equiv), $NaClO_2$ (ca. 20% H_2O content, 11.7 mg, 0.103 mmol, 3.0 equiv), and 2-methyl-2-butene (183 μL, 121 mg, 1.73 mmol, 50 equiv). The resulting mixture was stirred vigorously at rt for 20 h, treated with sat aq K_2CO_3 (3 mL), and extracted with CH_2Cl_2 (6 × 10 mL). The combined organic layers were washed with brine (6 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude carboxylic acid **155** was used directly in the next step without further purification.

A solution of crude carboxylic acid **7** (ca. 0.0345 mmol. 1.3 equiv) in anhydrous THF (500 μL) at 0 °C under Ar was treated with HOBt (ca. 20% H_2O content, 8.7 mg, 0.0515 mmol, 1.9 equiv) and EDC•HCl (9.9 mg, 0.0516 mmol, 1.9 equiv). The resulting mixture was stirred at 0 °C under Ar for 20 min, then treated with a solution of the crude tetrapeptide amine (ca. 0.0266 mmol) in THF (200 μL) and stirred at rt for 3 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (3.0 mL) and extracted with $CHCl_3$ (6 × 6 mL). The combined organic layers were washed with brine (6 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (12 mL of SiO_2, 1.5–6% MeOH in $CHCl_3$ with 1% Et_3N gradient elution) afforded **154** (24.3 mg, 0.0259 mmol, 97%) as a white solid: $[\alpha]^{25}_D$ +68 (*c* 0.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 500 MHz, 353.15 K, ca. 4.0:1 mixture of rotamers) δ 8.79 (br s, 2H), 7.69–7.56 (m, 2H), 7.42 and 7.36 (2d, J = 7.6, 7.1 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 5.96 and 5.88 (2 br s, 1H),

4.41–4.31 (m, 1H), 4.28–4.15 (m, 2H), 4.09 and 4.05 (2d, J = 8.6, 8.3 Hz, 1H), 3.86–3.75 (m, 1H), 2.38–2.30 (m, 2H), 2.20 and 2.15 (2s, 6H), 2.13–2.02 (m, 4H), 1.94 and 1.93 (2s, 3H), 1.92 and 1.89 (2s, 3H), 1.84–1.76 (m, 1H), 1.65 (s, 3H), 1.40 (s, 9H), 1.30 (d, J = 6.4 Hz, 6H), 1.28–1.21 (m, 3H), 0.99–0.91 (m, 15H), 0.90–0.83 (m, 12H), 0.81 (d, J = 6.8 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz, data for major rotamer) δ 172.4, 171.7, 171.4, 170.8, 169.8, 165.6, 155.8, 140.3, 134.2, 126.1, 124.7, 78.8, 74.8, 71.2, 63.7, 61.0, 58.4, 51.5, 48.7, 45.7 (2C), 31.2, 30.4, 30.3, 28.6 (3C), 28.0, 26.8, 21.0, 20.6, 19.9, 19.8, 19.7, 18.8, 18.6, 18.4, 18.0, 17.9, 17.7, 12.1, 7.4 (3C), 6.5 (3C); IR (film) ν_{max} 3307, 2961, 2927, 2348, 1671, 1534, 1370, 1308, 1201, 1174, 1133, 1039 cm^{-1}; HRMS (ESI) *m/z* 937.6509 (MH^+, $C_{47}H_{88}N_8O_9SiH^+$ requires 937.6522).

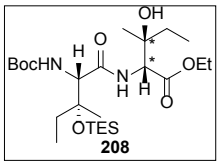


207

Ethyl (2*R,3*S**)-3-hydroxy-3-methyl-2-((2*S*,3*R*)-3-methyl-2-((((*R*)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)-3-((triethylsilyl)oxy)pentanamido)pentanoate (207)**. A suspension of *(2S,3R)*-**175** (109 mg, 0.201 mmol) and Me_3SnOH (100.0 mg, 0.553 mmol, 2.7 equiv) in hexane (10 mL, pretreated with Na_2SO_4 for 6 h) was stirred at 60 °C under Ar for 72 h. The solvent was concentrated *in vacuo*, and the residue was treated with Et_2O (10 mL). The mixture was filtered through Celite, (washed with 60 mL of Et_2O), and the filtrate was concentrated *in vacuo* to afford the crude acid (125.8 mg) as a colorless oil that was used directly in the next step without further purification.

A portion of the crude acid prepared above (97 mg, ca. 0.155 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL), cooled to 0 °C under Ar, and treated with amine **152**[10] (30 mg, 0.171 mmol, 1.1 equiv), HOBt (ca. 20% H_2O content, 39.2 mg, 0.232 mmol, 1.5 equiv), and EDC•HCl

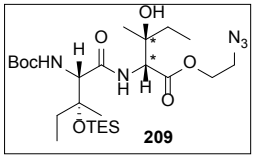
(44.6 mg, 0.233 mmol, 1.5 equiv). The resulting mixture was stirred at 0 °C under Ar for 3 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (4 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **207** (77.3 mg, 0.115 mmol, 74% from **207**) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, minor rotamers present, data for major rotamer of each diastereomer) δ 7.61 (d, *J* = 6.9 Hz, 2H), 7.46–7.34 (m, 3H), 7.24 and 7.12 (2d, *J* =8.3 and 8.3 Hz, 1H), 6.28 and 6.26 (2s, 1H), 6.00 and 5.94 (2d, *J* = 8.0 and 7.2 Hz, 1H), 4.60 and 4.51 (2d, *J* = 8.6 and 8.2 Hz, 1H), 4.29–4.15 (m, 3H), 2.62 and 2.59 (2 br s, 1H), 1.58–1.53 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 and 1.24 (2s, 3H), 1.21 and 1.20 (2s, 3H), 0.99 (t, *J* = 7.8 Hz, 9H), 0.96–0.90 (m, 3H), 0.87–0.81 (m, 3H), 0.73–0.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5 and 171.3, 170.1 and 169.8, 154.5 and 154.3, 133.32 and 133.25, 129.7, 129.6 (2C), 127.9 (2C), 99.5, 83.5, 78.5 and 78.1, 74.2 and 73.7, 61.9, 61.5, 58.3, 32.5 and 31.8, 31.5 and 31.4, 23.9 and 23.6, 23.4, 14.1, 8.6 and 8.5, 7.9, 7.1 (3C), 6.6 (3C); IR (film) ν_{max} 3428, 2964, 2360, 1736, 1546, 1380, 1062 cm^{-1}; HRMS (ESI) HRMS (ESI) *m/z* 669.2293 (MH^+, $C_{29}H_{47}Cl_3N_2O_7SiH^+$ requires 669.2296).



208

Ethyl (2*R,3*S**)-2-((2*S*,3*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)pentanamido)-3-hydroxy-3-methylpentanoate (208).** A suspension of carbamate **207** (84.9 mg, 0.127 mmol) in THF–sat aq $NaHCO_3$ (2:1, 2.3 mL) was treated sequentially with 10% Pd/C (10 mg, 0.12 wt equiv) and Boc_2O (29.0 mg, 0.133 mmol, 1.05 equiv). The resulting mixture was stirred at rt under H_2 (100 psi) for 15 h, diluted with H_2O (1

mL) and sat aq $NaHCO_3$ (1 mL), and extracted with EtOAc (5 × 3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded a quantitative yield of **208** (theoretical yield = 65.7 mg) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (s, 1H), 5.42 and 5.36 (2 br s, 1H), 4.61 and 4.52 (2d, J = 8.4 and 8.6 Hz, 1H), 4.29–4.10 (m, 3H), 2.73 and 2.71 (2 br s, 1H), 1.60–1.50 (m, 4H), 1.45 and 1.44 (2s, 9H), 1.32 (t, J = 9.9 Hz, 3H), 1.30 (t, J = 7.3 Hz, 3H), 1.20 and 1.18 (2s, 3H), 1.03–0.85 (m, 15H), 0.74–0.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5 and 171.4, 171.1 and 170.6, 156.0 and 155.9, 79.9 and 79.7, 78.7 and 78.0, 74.2 and 73.8, 61.6, 61.4, 58.4 and 58.1, 32.8 and 31.8, 31.44 and 31.40, 28.3 (3C), 24.1 and 24.0, 23.5 and 23.4, 14.1, 8.7 and 8.6, 7.8, 7.1 (3C), 6.7 and 6.6 (3C); IR (film) ν_{max} 3358, 2973, 2878, 2283, 1736, 1662, 1508, 1413, 1166, 1059 cm^{-1}; HRMS (ESI) *m/z* 519.3458 (MH^+, $C_{25}H_{50}N_2O_7SiH^+$ requires 519.3466).

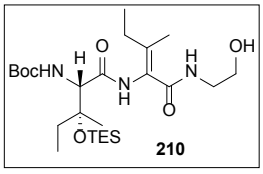


209

2-Azidoethyl (2*R,3*S**)-2-((2*S*,3*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)pentanamido)-3-hydroxy-3-methylpentanoate (209)**. A solution of **208** (31.0 mg, 0.0598 mmol) in *t*-BuOH–H_2O (3:1, 670 μL) at 0 °C was treated with LiOH•H_2O (12.5 mg, 0.298 mmol, 5.0 equiv), then stirred at rt for 3 h. The resulting mixture was acidified to pH 4~5 with 2N HCl, diluted with H_2O (1.5 mL), and extracted with EtOAc (6 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid was used directly in the next step without further purification.

A solution of the crude acid and iodide **150**[10] (24.0 mg, 0.122 mmol, 2.0 equiv) in anhydrous DMF (500 μL) at rt under Ar was treated with Et_3N (24 μL, 17 mg, 0.17 mmol, 2.9 equiv). The resulting mixture was stirred at 80 °C under Ar for 15 h, diluted with EtOAc (4 mL), and washed

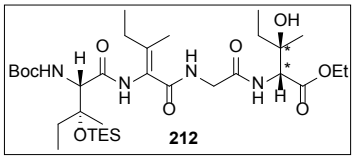
with H_2O (2 × 1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–1.5% MeOH in CH_2Cl_2 gradient elution) afforded **209** (27.0 mg, 0.0482 mmol, 84% from **208**) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (br s, 1H), 5.41 and 5.36 (2 br s, 1H), 4.63 and 4.52 (2d, J = 7.8 and 8.3 Hz, 1H), 4.35–4.25 (m, 2H), 4.19 and 4.12 (2 br s, 1H), 3.62–3.56 and 3.55–3.49 (2m, 2H), 2.52 and 2.46 (2 br s, 1H), 1.60–1.51 (m, 4H), 1.45 (s, 9H), 1.35 and 1.33 (2s, 3H), 1.24 and 1.23 (2s, 3H), 1.02–0.92 (m, 12H), 0.91–0.86 (m, 3H), 0.74–0.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 170.7, 155.9, 80.0 and 79.8, 78.6 and 78.0, 74.1 and 73.7, 63.4 and 63.3, 61.6 and 61.4, 58.6 and 58.2, 49.5, 32.8 and 31.9, 31.5, 28.3 (3C), 24.1 and 24.0, 23.6 and 23.5, 8.7 and 8.6, 7.9, 7.1 (3C), 6.7 and 6.6 (3C); IR (film) ν_{max} 3423, 2966, 2878, 2105, 1655, 1509, 1366, 1061 cm^{-1}, HRMS (ESI) *m/z* 560.3471 (MH^+, $C_{25}H_{49}N_5O_7SiH^+$ requires 560.3480).



210

***tert*-Butyl ((5*R*,6*S*,*Z*)-9-(butan-2-ylidene)-3,3,5-triethyl-13-hydroxy-5-methyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-6-yl)carbamate (210)**. A solution of **209** (25.2 mg, 0.0450 mmol) in anhydrous $CHCl_3$ (150 μL) was treated dropwise at 0 °C with a solution of Martin sulfurane (60.6 mg, 0.0901 mmol, 2.0 equiv) in anhydrous $CHCl_3$ (300 μL). The resulting mixture was stirred at 0 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. The residue was dissolved in THF (750 μL) and H_2O (50 μL), then treated with Lindlar catalyst (230 mg). The resulting suspension was stirred at rt under H_2 (1 atm) for 15 h, at which point reduction of the azide was complete as evidenced by MS. The H_2 was replaced by Ar (1 atm), piperidine (50 μL, 43.1 mg, 0.506 mmol, 11 equiv) was added to the mixture, and it was stirred at rt for 24 h. The mixture was then treated with sat aq NH_4Cl (0.5 mL) and H_2O (1.5 mL),

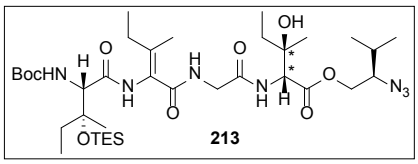
and extracted with EtOAc (6 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (6 mL of SiO_2, 0–4% MeOH in CH_2Cl_2 gradient elution) afforded **210** (19.2 mg, 0.0372 mmol, 83%, 18:1 dr) as a white film: $[\alpha]^{25}_D$ –4.1 (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (s, 1H), 6.85 (br s, 1H), 5.39 (br s, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 3.73 (br s, 2H), 3.53–3.26 (m, 3H), 2.13 (q, *J* =7.5 Hz, 2H), 2.04 (s, 3H), 1.75–1.60 (m, 2H), 1.46 (s, 9H), 1.35 (s, 3H), 1.04 (t, *J* = 8.0 Hz, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.92 (t, *J* =7.5 Hz, 3H), 0.68 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 167.0, 156.6, 143.3, 123.4, 80.8, 77.7, 75.7, 61.8, 42.8, 33.2, 28.3 (3C), 27.2, 24.4, 17.8, 11.7, 8.9, 7.1 (3C), 6.7 (3C); IR (film) ν_{max} 3317, 2919, 2850, 1686, 1522, 1248 cm^{-1}; HRMS (ESI) *m/z* 516.3480 (MH^+, $C_{25}H_{49}N_3O_6SiH^+$ requires 516.3469).



212

Ethyl (5*R*,6*S*,15*R,*Z*)-9-(butan-2-ylidene)-6-((*tert*-butoxycarbonyl)amino)-3,3,5-triethyl-15-((*R**)-2-hydroxybutan-2-yl)-5-methyl-7,10,13-trioxo-4-oxa-8,11,14-triaza-3-silahexadecan-16-oate (212)**. A solution of alcohol **210** (14.5 mg, 0.0281 mmol) in anhydrous THF (1.0 mL) at rt under Ar was treated with the Dess–Martin periodinane (23.8 mg, 0.0561 mmol, 2.0 equiv). The resulting mixture was stirred at rt under Ar for 2 h, then diluted with H_2O (300 μL) and treated with 2-methyl-2-butene (150 μL, 99.3 mg, 1.42 mmol, 50 equiv), NaH_2PO_4 (5.1 mg, 0.043 mmol, 1.5 equiv), and $NaClO_2$ (ca. 20% H_2O content, 9.5 mg, 0.084 mmol, 3.0 equiv). The resulting mixture was stirred at rt for 16 h, treated with sat aq NH_4Cl (3.0 mL), and extracted with EtOAc (6 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid **211** was used directly in the next step without further purification.

The crude acid **211** was dissolved in anhydrous THF (1.4 mL), cooled to 0 °C under Ar, and treated with amine **148**[10] (7.4 mg, 0.042 mmol, 1.5 equiv), HOBt (ca. 20% H_2O content, 7.1 mg, 0.042 mmol, 1.5 equiv), and EDC•HCl (8.1 mg, 0.042 mmol, 1.5 equiv). The resulting mixture was stirred at rt under Ar for 4 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (5 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–5% MeOH in CH_2Cl_2 gradient elution) afforded **212** (15.4 mg, 0.0224 mmol, 80% from **210**) as a white film that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, minor rotamers present, data for major rotamer of each diastereomer) δ 7.74 and 7.52–7.47 (br s and m, 1H), 7.62 (br s, 1H), 7.05 (br s, 1H), 5.54 (br s, 1H), 4.69 and 4.66 (2d, J = 9.3 and 9.4 Hz, 1H), 4.32–4.07 (m, 4H), 3.98–3.90 (m, 1H), 3.88–3.78 (m, 1H), 2.21–2.11 (m, 2H), 2.08 and 2.04 (2s, 3H), 1.71–1.60 (m, 4H, partially obscured by H_2O), 1.45 (s, 9H), 1.35 (s, 3H), 1.31–1.24 (m, 6H), 1.20 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H), 1.00 (t, J = 7.8 Hz, 9H), 0.95–0.84 (m, 3H), 0.68 (q, J = 6.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3 and 171.2, 170.6 and 170.5, 169.4 and 169.3, 165.3 and 165.2, 156.9 and 156.8, 143.6, 123.3 and 122.9, 81.0 and 80.8, 77.9, 74.5, 62.1 and 62.0, 61.1 and 61.0, 58.9 and 58.7, 43.2, 32.8, 32.0 and 31.9, 28.3 and 28.2 (3C), 27.2, 24.3, 23.3 and 23.2, 18.0 and 17.8, 14.11 and 14.08, 11.7, 8.8, 8.4 and 8.3, 7.1 (3C), 6.7 (3C); IR (film) ν_{max} 3404, 2923, 2852, 2360, 1655, 1522, 1460, 1376, 1247, 1168, 1069, 1015 cm^{-1}; HRMS (ESI) HRMS (ESI) *m/z* 687.4349 (MH^+, $C_{33}H_{62}N_4O_9SiH^+$ requires 687.4364).

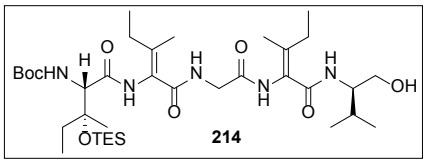


213

(*R*)-2-Azido-3-methylbutyl (5*R*,6*S*,15*R,*Z*)-9-(butan-2-ylidene)-6-((*tert*-butoxycarbonyl)amino)-3,3,5-triethyl-15-((*R**)-2-hydroxybutan-2-yl)-5-methyl-7,10,13-trioxo-4-oxa-8,11,14-triaza-3-silahexadecan-16-oate (213)**. A solution of **36** (8.4 mg, 0.012 mmol) in *t*-BuOH–H_2O (3:1, 400 μL) at 0 °C was treated with LiOH•H_2O (2.6 mg, 0.062 mmol, 5.1 equiv), then stirred at rt for 3 h. The resulting mixture was acidified to pH 6~7 with 1N HCl, diluted with H_2O (2.0 mL), and extracted with EtOAc (6 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid was used directly in the next step without further purification.

A solution of the crude acid and iodide **146**[10] (8.8 mg, 0.037 mmol, 3.0 equiv) in anhydrous DMF (400 μL) at rt under Ar was treated with Et_3N (5.1 μL, 3.7 mg, 0.037 mmol, 3.0 equiv). The resulting mixture was stirred at 80 °C under Ar for 15 h, diluted with EtOAc (6 mL), and washed with H_2O (2 × 1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 1–3% MeOH in CH_2Cl_2 gradient elution) afforded **213** (7.9 mg, 0.010 mmol, 84% from **212**) as a colorless oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, minor rotamers present, data for major rotamer of each diastereomer) δ 7.82 and 7.72 (d and br s, *J* = 8.2 Hz, 1H), 7.70–7.65 and 7.54 (m and br s, 1H), 6.90 (br s, 1H), 5.47 and 5.37 (2 br s, 1H), 4.76 (d, *J* = 9.4 Hz, 1H), 4.42–4.24 (m, 2H), 4.17–4.07 (m, 3H), 3.97 and 3.74 (2dd, *J* = 17.3, 5.3 Hz and 17.3, 5.0 Hz, 1H), 3.56 and 3.45 (2 br s, 1H), 2.19–2.11 (m, 2H), 2.02 and 1.99 (2s, 3H), 1.87–1.80 (m, 1H), 1.75–1.66 (m, 4H, partially obscured by H_2O), 1.45 (s, 9H), 1.35 (s, 3H), 1.22 and 1.20 (2s, 3H), 1.06 (t, *J* = 6.7 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 9H), 0.96–0.79 (m, 12H), 0.68 (q, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2 and 170.7, 170.1 and 169.9, 169.4 and 169.2, 165.7 and 165.3, 156.3, 139.7,123.7,

80.7, 77.7, 74.6, 66.7 and 66.4, 62.1 and 61.8, 59.2, 56.0, 43.1 and 41.1, 33.1, 31.9 and 31.8, 30.1 and 29.8, 28.2 (3C), 27.1 and 26.9, 25.4 and 24.3, 23.2, 22.4, 19.5, 18.1 and 17.9, 11.7 and 11.6, 8.8 and 8.7, 8.5 and 8.4, 7.1 (3C), 6.7 (3C); IR (film) ν_{max} 3348, 2923, 2852, 2101, 1665, 1553, 1462, 1379, 1250, 1168, 1080, 1012 cm^{-1}; HRMS (ESI) *m/z* 770.4840 (MH^+, $C_{36}H_{67}N_7O_9SiH^+$ requires 770.4848).



214

***tert*-Butyl ((5*R*,6*S*,9*Z*,15*E*,18*R*)-9,15-di(butan-2-ylidene)-3,3,5-triethyl-18-(hydroxymethyl)-5,19-dimethyl-7,10,13,16-tetraoxo-4-oxa-8,11,14,17-tetraaza-3-silaicosan-6-yl)carbamate (214)**. A solution of **213** (14.6 mg, 0.0190 mmol) in anhydrous $CHCl_3$ (200 μL) was treated dropwise at 0 °C with a solution of Martin sulfurane (25.5 mg, 0.0379 mmol, 2.0 equiv) in anhydrous $CHCl_3$ (400 μL). The resulting mixture was stirred at 0 °C under Ar for 1.5 h, warmed to rt, and concentrated *in vacuo*. The residue was dissolved in THF (600 μL) and H_2O (60 μL), then treated with Lindlar catalyst (172.1 mg). The resulting suspension was stirred at rt under H_2 (1 atm) for 15 h, at which point reduction of the azide was complete as evidenced by MS. The H_2 was replaced by Ar (1 atm), piperidine (50 μL, 43.1 mg, 0.506 mmol, 26.7 equiv) was added to the mixture, and it was stirred at rt for 24 h. The mixture was then treated with sat aq $NaHCO_3$ (1.0 mL) and H_2O (1.5 mL), and extracted with EtOAc (6 × 3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 2–6% MeOH in CH_2Cl_2 gradient elution) afforded **214** (9.4 mg, 0.0129 mmol, 68%, >8:1 dr) as a white film: $[\alpha]^{25}_D$ –16.8 (*c* 0.50, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz, minor rotamers present, data for major rotamer) δ 8.31 (s, 1H), 7.64 (s, 1H), 7.55 (s, 1H), 6.57 (d, *J* = 8.8 Hz, 1H), 5.43 (br s, 1H), 3.98 (s, 1H), 3.84-3.80 (m, 2H), 3.71

(t, J = 5.0 Hz, 1H), 3.57 (t, J = 5.0 Hz, 1H), 3.43 (t, J = 5.0 Hz, 1H), 2.52 (t, J = 6.2 Hz, 3H), 2.23–2.13 (m, 2H), 2.11 (s, 3H), 1.95–1.83 (m, 2H), 1.79 (s, 3H), 1.73–1.62 (m, 4H), 1.46 (s, 9H), 1.32 (s, 3H), 1.26 (s, 3H), 1.12 (t, J = 7.3 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H), 1.03–0.88 (m, 12H), 0.68 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 168.4, 166.0, 165.4, 157.2, 146.3, 145.6, 123.0, 122.0, 81.4, 63.2, 62.8, 62.0, 57.5, 42.9, 33.3, 31.3, 29.3, 28.3 (3C), 27.2, 26.5, 25.5, 24.5, 19.5, 18.1, 13.0, 11.7, 8.8, 7.1 (3C), 6.7 (3C); IR (film) ν_{max} 3339, 2956, 2853, 2360, 2343, 1655, 1523, 1367, 1165, 1070, 1016 cm^{-1}; HRMS (ESI) *m/z* 726.4810 (MH^+, $C_{36}H_{67}N_5O_8SiH^+$ requires 726.4837).

6.3 References

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6.4 XYZ coordinates obtained from Gaussian 09 calculations

182

Electronic Energy= -708.634693114

Electronic and Zero-Point Energy= -708.368889

Enthalpy= -708.351638

Free Energy= -708.412089

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C	-1.35478100	-0.22594200	0.09221600
C	2.03897500	1.46042100	-0.64284400
C	-0.30445200	2.39823800	-0.40481100
O	-1.66062700	-0.37924400	1.25724300
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183

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Electronic and Zero-Point Energy=-2438.904283

Enthalpy=-2438.873246

Free Energy=-2438.967954

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F	-2.17213900	-0.60354600	2.40140200

F	-0.40269300	-1.68764200	1.79404800
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C	0.36305400	1.95141600	-1.03174800
C	-0.13526300	1.63573600	-2.29149700
C	0.85279200	3.21856800	-0.72689100
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C	0.32230200	3.90562300	-2.98310600
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184

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Electronic and Zero-Point Energy= -631.968098

Enthalpy= -631.952123

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H	-1.10370200	3.97896200	0.41917500
H	0.38905100	3.97249400	-0.52720700
H	-1.10828600	3.33585900	-1.24681100
O	2.21459700	0.41419500	-0.28622300
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H	3.57552500	0.69156400	1.25797100
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H	-3.46494800	-1.25964900	-2.52500600

H	-1.85371100	-0.56053400	-2.75845400
H	-2.03859000	-2.30731100	-2.55738400
C	-0.01558000	-0.31236300	-0.14357300

INT13

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Electronic and Zero-Point Energy= -2357.743362

Enthalpy= -2357.705039

Free Energy= -2357.815537

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C	-0.46618000	-1.61326400	0.97043100
C	0.21638500	-2.76442000	0.59274300
C	-1.40422700	-1.62213800	2.00207700
C	-0.05952200	-3.95720600	1.26260600
H	0.95677300	-2.72540400	-0.19760800
C	-1.65439300	-2.81493900	2.67483800
H	-1.93065500	-0.71159800	2.27259800
C	-0.98760600	-3.98355100	2.30128200
H	0.46339800	-4.86299900	0.97243600
H	-2.37189100	-2.83082900	3.48973200
H	-1.19079500	-4.91355400	2.82350300

C	-0.06344600	1.19640000	1.25987400
C	-0.62421600	2.44086600	0.98887900
C	0.64627600	0.94873100	2.43068700
C	-0.45439900	3.46866900	1.91696400
H	-1.18090500	2.60960600	0.07174100
C	0.78677500	1.97789600	3.35808500
H	1.09625700	-0.02268400	2.60282100
C	0.24439000	3.23746300	3.10007200
H	-0.87208800	4.44936200	1.71063300
H	1.33207000	1.79439200	4.27859200
H	0.36936700	4.03880200	3.82186700
C	2.70092000	-0.00999900	-0.61289700
C	2.58404300	-0.68387400	-1.98990200
F	3.59247800	-0.36000000	-2.81795400
F	1.43815200	-0.38705500	-2.63061500
F	2.60926000	-2.01977800	-1.84099500
C	-5.54705200	-1.49412900	-0.00765000
O	-6.12427100	-1.62792900	-1.08450100
N	-4.60821700	-0.53695000	0.20625600
H	-4.12646300	-0.51085900	1.09594100
C	-2.67401800	-0.07826000	-1.26327900
C	-4.14575300	1.79287500	-0.39353400
C	-2.68340700	-1.58890300	-1.58446400
C	-2.16319200	0.75865500	-2.42968300
O	-4.16580900	2.72325200	-1.16982200
H	-3.62150000	-1.80596300	-2.10935400
H	-2.72784900	-2.13287500	-0.63432000
H	-2.18204900	1.82420700	-2.19269700

H	-1.13731000	0.47736100	-2.68410800
H	-2.78725700	0.59022200	-3.31357900
O	-1.94180000	0.22427600	-0.05414900
C	-5.80867100	-2.41247300	1.16123800
H	-5.46634200	-1.99617300	2.11134600
H	-6.87706600	-2.62795900	1.21399500
H	-5.28021600	-3.35411200	0.97908100
O	-4.12761200	1.93949600	0.93040700
C	-4.12307700	3.28952100	1.41279500
H	-5.08674900	3.76238300	1.20780100
H	-3.95415200	3.21842400	2.48628700
H	-3.32588600	3.86145200	0.93448400
C	-1.52546200	-2.11703000	-2.43220400
H	-1.58786400	-3.20795500	-2.48950100
H	-1.56111500	-1.72771300	-3.45370000
H	-0.54071200	-1.87049800	-2.02439500
C	-4.11600300	0.33358800	-0.83547100
H	-4.77936300	0.23827200	-1.69889600
H	3.72774100	-0.23617700	-0.27663600

$Ph_2S^+O(CH(CF_3)_2)$

Electronic Energy= -1569.09663529

Electronic and Zero-Point Energy= -1568.655056

Enthalpy= -1568.627145

Free Energy= -1568.712930

O	-0.02694500	-0.56349500	0.45169800

S	-1.33403700	-0.05014400	1.25599400
C	-2.23031700	0.80627400	-0.03028600
C	-1.75325300	0.84277600	-1.33338100
C	-3.40969200	1.43246400	0.36936500
C	-2.50898900	1.53588700	-2.27960400
H	-0.80888600	0.37705900	-1.59343200
C	-4.14885900	2.11313000	-0.59410000
H	-3.74777500	1.39851700	1.40212300
C	-3.69892800	2.16324800	-1.91472000
H	-2.15602200	1.58456200	-3.30481300
H	-5.06944100	2.61156800	-0.30876800
H	-4.27670700	2.70041900	-2.66035600
C	-2.25422000	-1.56104700	1.43719600
C	-2.49837500	-1.97735200	2.74490600
C	-2.65322500	-2.30736100	0.32597400
C	-3.16767500	-3.18417000	2.94527300
H	-2.17666000	-1.37540300	3.59079500
C	-3.31075600	-3.51164300	0.54501200
H	-2.45141700	-1.95771200	-0.68302300
C	-3.56623000	-3.94666100	1.84950500
H	-3.37180800	-3.52489000	3.95493000
H	-3.62719300	-4.11177700	-0.30180700
H	-4.08308200	-4.88785000	2.00923700
C	2.41617600	0.24927200	-1.91619400
O	1.23390200	0.53235800	-2.09439000
N	2.94279300	0.20151900	-0.66620800
H	3.93161900	0.02183300	-0.56050000
C	1.29978700	-0.56979000	1.12382300

C	1.43192700	1.87319600	0.33895200
C	1.85939000	-1.95038200	0.77767700
C	1.18170800	-0.35886500	2.62935200
O	0.36052800	2.11259000	0.85643700
H	2.92567900	-1.94881600	1.03530100
H	1.79729300	-2.07167700	-0.30845900
H	0.91133100	0.66926800	2.88318300
H	0.45649000	-1.04470500	3.07678700
H	2.15449800	-0.57740000	3.07915900
C	3.35960100	-0.03654900	-3.05444000
H	2.88615000	-0.74798800	-3.73401300
H	3.52286300	0.89543100	-3.60360200
H	4.32296800	-0.42853000	-2.72342800
O	2.12695700	2.75618100	-0.35961500
C	1.47957700	4.01986100	-0.58598000
H	1.30300000	4.52680400	0.36465400
H	2.16752200	4.59374200	-1.20385200
H	0.53345100	3.86236900	-1.10882200
C	1.15292600	-3.11045000	1.47161800
H	1.53651700	-4.05818300	1.08512200
H	1.31524700	-3.10711600	2.55321000
H	0.07404000	-3.09047800	1.28195700
C	2.18984000	0.55594900	0.51558800
H	2.94132200	0.76980900	1.28598200

INT15

Electronic Energy= -2358.22455721

Electronic and Zero-Point Energy= -2357.732951

Enthalpy= -2357.694607

Free Energy= -2357.807165

O	-1.87292900	-0.07109300	0.20921300
S	-3.10047500	-0.25661500	-0.81747100
C	-0.71679600	0.80040700	-0.16914000
C	-0.55940100	1.66254300	1.08334100
C	-1.02817600	1.64248900	-1.39943400
H	-0.39870400	0.98965800	1.93158100
H	-1.52209400	2.16265300	1.24402100
H	-1.15045400	1.03354000	-2.29918700
H	-1.92115800	2.25780000	-1.23992400
H	-0.18895700	2.32074100	-1.57165400
C	0.56716500	2.69261300	1.00458000
H	0.72443700	3.13652000	1.99177500
H	1.51492000	2.24840200	0.68181900
H	0.31841400	3.50675400	0.31635600
C	0.52913900	-0.09404400	-0.44225600
H	1.18005200	0.50237500	-1.09688200
O	3.39825500	1.07821900	-0.05553300
C	4.60123600	1.37086700	0.45713200
H	5.23639200	2.04157600	-0.16142100
C	4.46054100	2.11495300	1.79755200
C	5.45525900	0.10298600	0.63643800
F	3.87715800	3.31222200	1.59548500
F	3.68225400	1.45132300	2.67522400
F	5.62915100	2.36397000	2.42743300

F	4.87508000	-0.80058300	1.45078100
F	6.69132900	0.33368200	1.13081900
F	5.63104600	-0.50382500	-0.55119800
C	0.18653800	-1.33525100	-1.26543000
O	-0.85564200	-1.50031200	-1.87141800
O	1.20155800	-2.18385000	-1.32140700
C	0.97358900	-3.38874100	-2.06440000
H	0.74489700	-3.15555200	-3.10629300
H	1.90204800	-3.95274000	-1.99392300
H	0.14935400	-3.95002200	-1.61782500
N	1.35904700	-0.39392800	0.69825200
H	2.29141800	0.09433600	0.66725600
C	1.06601100	-1.39072900	1.54902500
O	0.03030900	-2.06305100	1.44770700
C	2.07997100	-1.66479600	2.63002200
H	2.69340900	-2.51795700	2.32270900
H	2.73388800	-0.81066100	2.80914800
H	1.55390600	-1.93612900	3.54727400
C	-3.63985100	-1.90490000	-0.36441200
C	-4.90663100	-2.29463000	-0.79905300
C	-2.78938900	-2.74281100	0.34403500
C	-5.33527400	-3.58380000	-0.49865700
H	-5.55174000	-1.61408500	-1.34890200
C	-3.24531500	-4.02943900	0.63716100
H	-1.80841100	-2.40344000	0.66475800
C	-4.50623600	-4.44859600	0.21926700
H	-6.31784700	-3.90936000	-0.82422800
H	-2.60164900	-4.69992500	1.19797900

H	-4.84763500	-5.45221400	0.45337200
C	-4.36875200	0.75487500	-0.08018200
C	-4.96649900	1.70585900	-0.90433000
C	-4.71044800	0.60713900	1.26553900
C	-5.94942400	2.53355500	-0.36084300
H	-4.67301800	1.80142100	-1.94662600
C	-5.68216400	1.44837700	1.79336400
H	-4.22320600	-0.14429600	1.88142100
C	-6.30017300	2.40490300	0.98097800
H	-6.43109000	3.27883100	-0.98512800
H	-5.96133800	1.35826400	2.83809600
H	-7.06014200	3.05572200	1.40217300

$Ph_2S=O$

Electronic Energy= -936.440997585

Electronic and Zero-Point Energy= -936.253719

Enthalpy= -936.241076

Free Energy= -936.294652

S	0.00675500	1.24885400	-0.99003900
C	-1.35174800	0.21511900	-0.40021600
C	-1.94804300	-0.67652900	-1.28590100
C	-1.79312300	0.35387300	0.91338900
C	-3.00032600	-1.47405700	-0.83252000
H	-1.60537200	-0.74598900	-2.31532100
C	-2.84804700	-0.44143500	1.35261300
H	-1.32008500	1.07954300	1.57006400

C	-3.44696800	-1.35604800	0.48232300
H	-3.47601800	-2.17504900	-1.51134800
H	-3.20539700	-0.34776600	2.37351400
H	-4.27050200	-1.97240000	0.82983100
C	1.35814700	0.31065400	-0.22884700
C	2.02307900	0.88654200	0.84599500
C	1.73144600	-0.92751600	-0.74826600
C	3.08163100	0.19122200	1.43275300
H	1.70949000	1.86229300	1.20541800
C	2.78899200	-1.61214800	-0.15344400
H	1.20668400	-1.35800600	-1.59835500
C	3.46176500	-1.05411900	0.93608500
H	3.60894000	0.62774400	2.27553900
H	3.09158100	-2.57932000	-0.54307500
H	4.28738400	-1.59049200	1.39377200
O	-0.06649900	2.55177900	-0.21513400

TS1-*anti*

Electronic Energy= -2358.21418429			
Electronic and Zero-Point Energy= -2357.726936			
Enthalpy= -2357.688543			
Free Energy= -2357.801063			
O	-1.91345000	0.16744500	0.70774500
S	-2.76607600	0.13897800	-0.64944900
C	-0.56264400	0.88366600	0.75033100
C	-0.62533200	1.58335600	2.10697500

C	-0.46292600	1.87885500	-0.40077400
H	0.37951300	1.97149400	2.31242000
H	-0.83141500	0.82190600	2.86594800
H	-0.30434600	1.37687600	-1.35812700
H	-1.34715500	2.52228100	-0.46364200
H	0.40444700	2.51701400	-0.20879500
C	-1.65356800	2.70601700	2.20280700
H	-1.71565400	3.06372000	3.23444200
H	-1.38952100	3.56191000	1.57495800
H	-2.65186000	2.35948600	1.91208200
C	0.56582500	-0.14018700	0.69240300
H	1.63182000	0.58528100	0.31881500
O	2.70862700	1.21828800	0.19184800
C	3.43293300	0.58532400	-0.76823400
H	2.89059500	-0.23723100	-1.27767100
C	3.81135600	1.56691500	-1.88091700
C	4.67574000	-0.07191100	-0.15599800
F	2.69762600	2.06216100	-2.44784600
F	4.52380100	2.61207800	-1.43256700
F	4.53066600	0.99337800	-2.86630000
F	5.50260100	0.81346400	0.42249100
F	5.40394600	-0.76685300	-1.05161600
F	4.29893500	-0.94054200	0.79931600
C	0.36694900	-1.18628900	-0.32142700
O	-0.38849300	-1.09229800	-1.28518600
O	1.14562500	-2.26730600	-0.14676300
C	1.01453200	-3.29083400	-1.13540200
H	1.32385900	-2.92114100	-2.11680200

H	1.67366900	-4.09630400	-0.81299700
H	-0.01843400	-3.64383100	-1.18860700
N	1.08681200	-0.62439700	1.94716400
H	2.02553400	-0.32906200	2.18866000
C	0.52155800	-1.59488500	2.70023600
O	-0.58602300	-2.06996000	2.44332800
C	1.33696800	-2.08202400	3.87418400
H	2.16286200	-1.41310000	4.12552200
H	0.68195000	-2.20185300	4.73932900
H	1.74579800	-3.06511300	3.62020000
C	-3.35513500	-1.55398900	-0.64980600
C	-4.32387800	-1.88221600	-1.59611900
C	-2.82131800	-2.47731200	0.23966900
C	-4.78295100	-3.19571700	-1.63999000
H	-4.71768100	-1.13753100	-2.28353800
C	-3.29816400	-3.78808500	0.17694400
H	-2.05619900	-2.18760300	0.95674700
C	-4.27117500	-4.14613100	-0.75394800
H	-5.53822700	-3.47481300	-2.36766700
H	-2.89811600	-4.52696700	0.86432600
H	-4.63204300	-5.16920700	-0.79404500
C	-4.23348600	1.03129700	-0.17201000
C	-4.54360500	2.16410100	-0.92160800
C	-4.98852500	0.63944200	0.93535800
C	-5.65257300	2.92644600	-0.55233500
H	-3.93495000	2.44927700	-1.77565300
C	-6.08459800	1.41456400	1.29518600
H	-4.71799500	-0.24656300	1.50359600

C	-6.41480300	2.55286700	0.55198600
H	-5.91256800	3.81044200	-1.12514000
H	-6.68332600	1.13252300	2.15511600
H	-7.27470800	3.15009800	0.83902900

TS1-*syn*

Electronic Energy= -2358.21121779

Electronic and Zero-Point Energy= -2357.723800

Enthalpy= -2357.685477

Free Energy= -2357.796204

S	-3.67446300	-0.00364200	0.97889100
C	-2.90553700	-0.53156100	2.51117200
C	-3.74067800	-0.58862000	3.62491000
C	-1.56089400	-0.87196300	2.55510200
C	-3.20174100	-1.02327200	4.83213400
H	-4.78788500	-0.30317200	3.56046500
C	-1.04352300	-1.30955300	3.77599800
H	-0.92419400	-0.78752500	1.67781400
C	-1.85649000	-1.38859500	4.90477300
H	-3.83292100	-1.07207900	5.71349900
H	0.00513500	-1.58159300	3.83704700
H	-1.44075000	-1.73006800	5.84763300
C	-4.64331500	-1.45783200	0.60339500
C	-4.02222400	-2.69408700	0.42202100
C	-6.02267700	-1.29436700	0.50782900
C	-4.81685400	-3.79514700	0.12572100

H	-2.94297000	-2.78881400	0.50548500
C	-6.80742000	-2.41347300	0.22498600
H	-6.47747400	-0.31624100	0.64157800
C	-6.20487200	-3.65436800	0.03156900
H	-4.35474800	-4.76528400	-0.02544500
H	-7.88460100	-2.30834800	0.14692800
H	-6.81746600	-4.52113600	-0.19643600
C	-0.26068400	3.63836800	-1.68902200
O	-1.21347900	4.30259200	-1.28484300
N	-0.06404000	2.34213000	-1.32945100
H	0.75422800	1.87889700	-1.70455100
C	-0.88192500	1.62137100	-0.38386600
H	-0.00541900	0.59230600	0.04243800
C	-2.08163900	0.92462200	-1.02846200
C	-1.16032700	2.33380100	0.85635200
C	-3.27132100	1.83183000	-1.34470200
C	-1.64096800	0.11787100	-2.24330800
O	-2.15297500	2.14778900	1.56146800
H	-2.86299600	2.63768300	-1.96260400
H	-3.60532300	2.32072500	-0.42423100
H	-0.75045100	-0.47268900	-2.00840900
H	-1.40850000	0.79329500	-3.07090400
O	-2.47947700	-0.18654800	-0.07626500
C	0.78520300	4.23172100	-2.60444300
H	1.48519700	3.49025100	-2.99590500
H	0.28391100	4.73497700	-3.43423100
H	1.34487000	4.98703100	-2.04472100
O	-0.15892700	3.13740300	1.26086900

C	-0.34829500	3.78390000	2.51941500
H	0.57719300	4.32629100	2.71350400
H	-1.18718000	4.48311100	2.46676800
H	-0.53045500	3.05263900	3.31022400
O	0.85645000	-0.18320200	0.32506600
C	3.18139700	0.11064000	-0.03030900
F	4.29445500	0.76200400	0.35586300
F	3.01575100	0.36581500	-1.34211700
F	3.43048500	-1.20162100	0.08727900
C	1.93474500	0.55106100	0.73737700
C	2.12267200	0.42456600	2.25113700
F	3.14013000	1.17059000	2.72058700
F	2.34559800	-0.84136100	2.64462600
F	1.00950300	0.84314000	2.87353600
H	1.83078800	1.63614200	0.55162600
C	-4.43844900	1.16218700	-2.07231600
H	-4.18614800	0.92676800	-3.11006000
H	-4.75423000	0.22504800	-1.59900200
H	-5.30462100	1.82993800	-2.08616700
H	-2.43867200	-0.55888600	-2.55804600

INT16

Electronic Energy= -1421.72241222

Electronic and Zero-Point Energy= -1421.425375

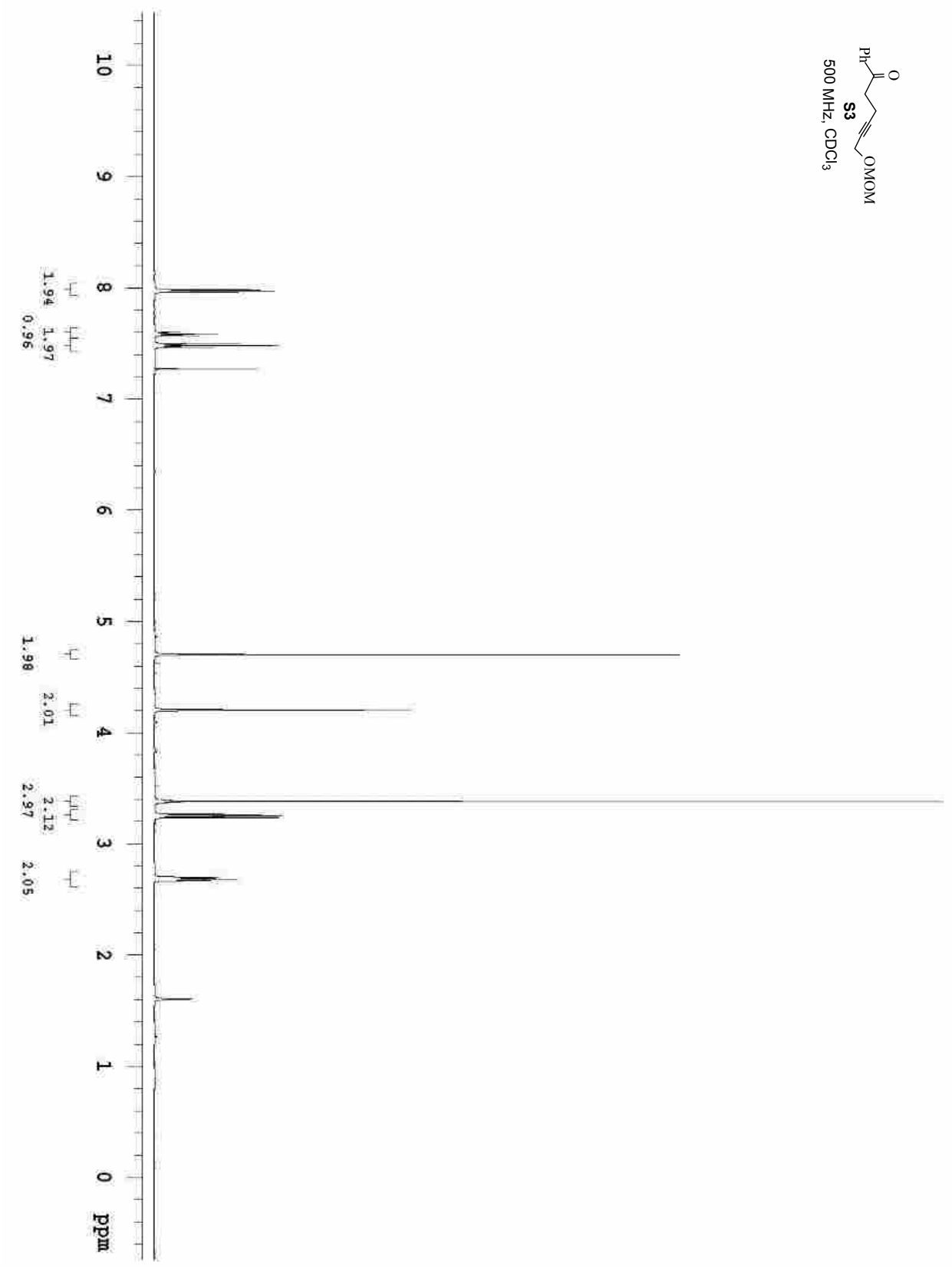
Enthalpy= -1421.398432

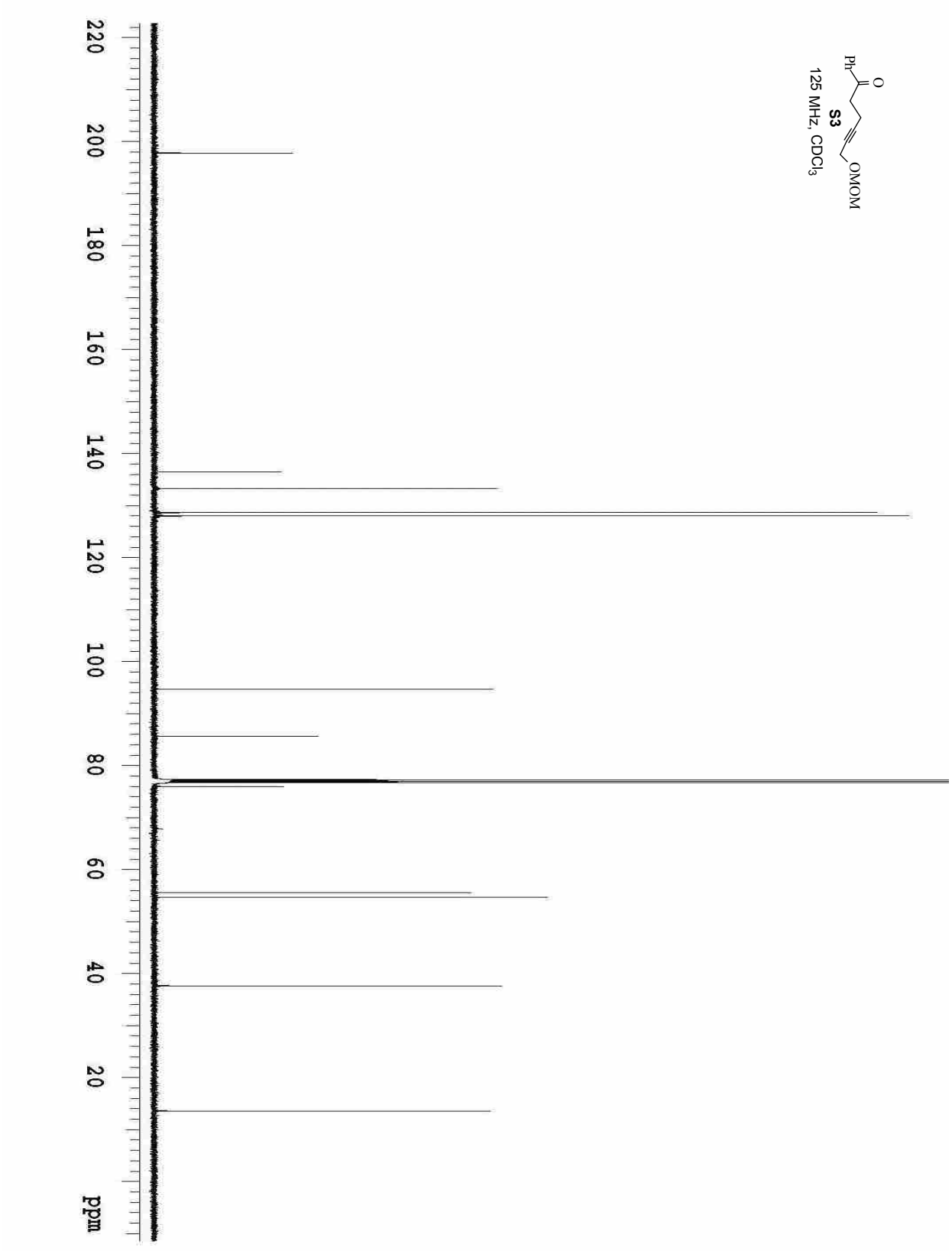
Free Energy= -1421.485537

C	-0.29247100	1.00081600	-0.30085300
C	-0.43979900	1.60465100	1.00866600
C	-1.08348000	1.49661100	-1.41835200
H	-0.23702400	0.89405700	1.81042800
H	-1.41518200	2.08274700	1.11785500
H	-0.62701600	1.33736000	-2.39547600
H	-1.99132900	0.86327700	-1.37930000
H	-1.40589900	2.52835700	-1.25814900
C	0.68278900	2.70801700	1.02390600
H	0.67113000	3.13841200	2.02728900
H	1.66962800	2.28226700	0.82101900
H	0.46434700	3.49153900	0.29513500
C	0.76023700	-0.02865800	-0.54021600
H	1.45056400	0.46746000	-1.25168200
O	3.49473600	1.13712200	-0.02031200
C	4.69098400	1.43564200	0.51494300
H	5.33156900	2.10219100	-0.09867200
C	4.51490500	2.18614700	1.84578300
C	5.53526000	0.16783800	0.72109800
F	3.89239500	3.36088300	1.62463000
F	3.74826700	1.50533700	2.72099200
F	5.66826800	2.47648100	2.48011300
F	4.91780800	-0.73457500	1.50921800
F	6.74783200	0.39746700	1.26543600
F	5.75392500	-0.43572500	-0.46050300
C	0.19221700	-1.25059700	-1.30912800
O	-0.90108400	-1.30417000	-1.81808500
O	1.10726000	-2.20012900	-1.36785700

C	0.69456300	-3.42108200	-2.00570300
H	0.42548700	-3.22807000	-3.04597300
H	1.55636800	-4.08300500	-1.94844700
H	-0.15520000	-3.84727400	-1.46848500
N	1.54311300	-0.38867900	0.59889500
H	2.49873700	0.08446500	0.60303400
C	1.05021200	-1.28922000	1.47685400
O	-0.09398300	-1.73997100	1.34532200
C	1.97299100	-1.71249300	2.58710000
H	2.53672000	-2.58985600	2.25297400
H	2.68431100	-0.92558200	2.84440500
H	1.38223200	-1.99159900	3.46050300

6.5 ^{1}H and ^{13}C NMR spectra

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O
OMOM
S3
125 MHz, CDCl3
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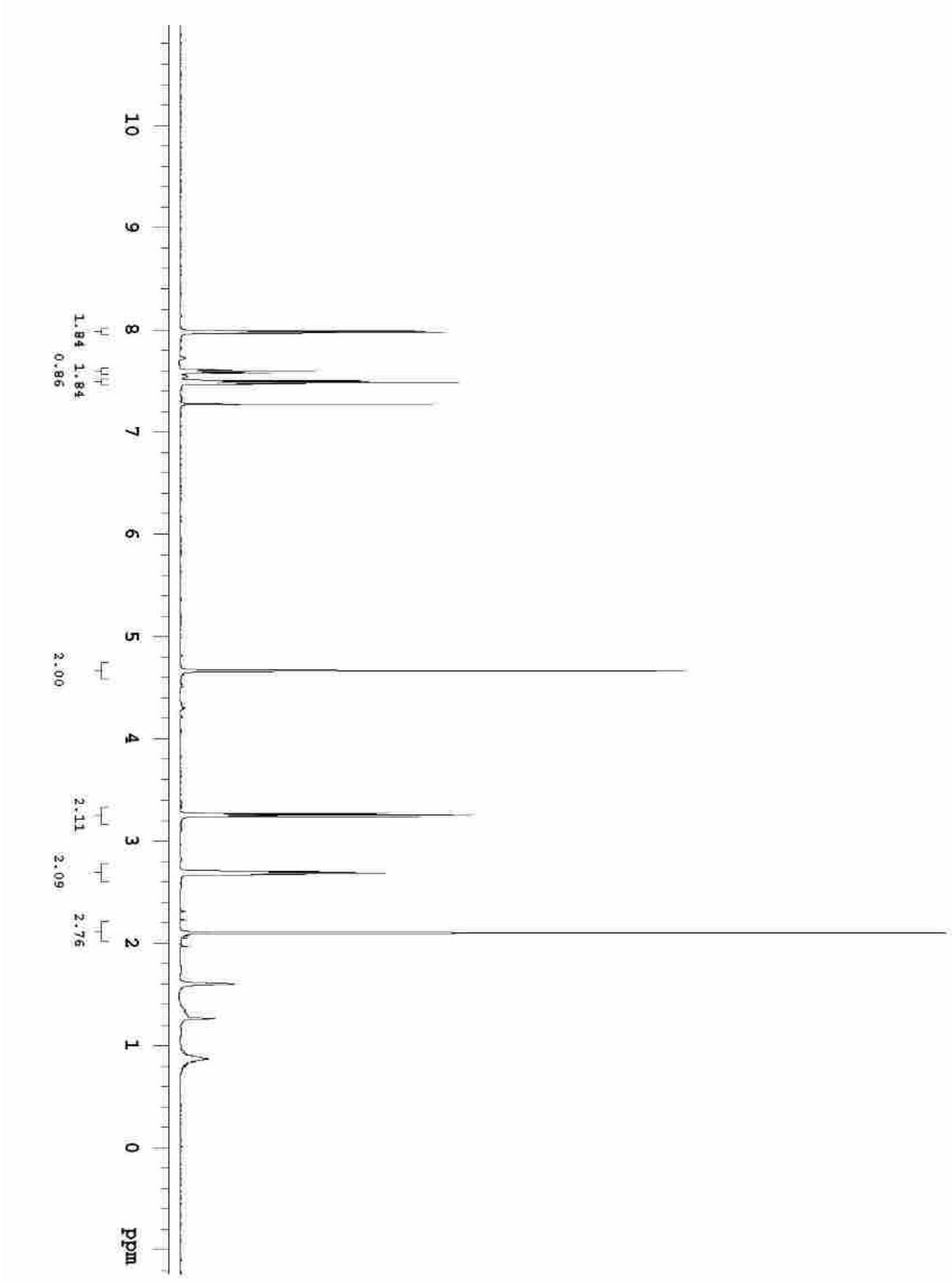
200
180
160
140
120
100
80
60
40
20
ppm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9
8
7
6
5
4
3
2
1
0
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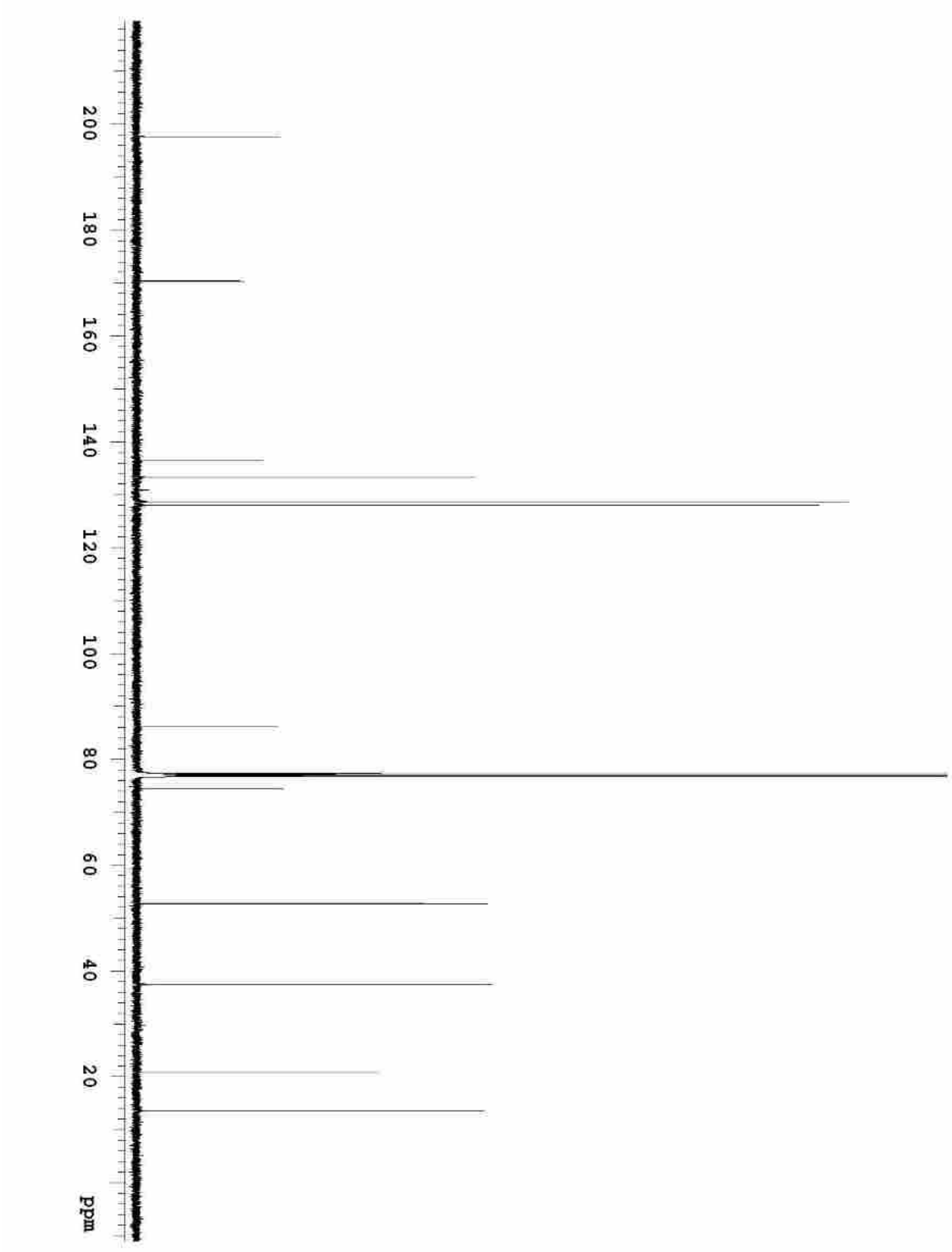
0.86
2.00
2.11
2.09
2.76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180
160
140
120
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80
60
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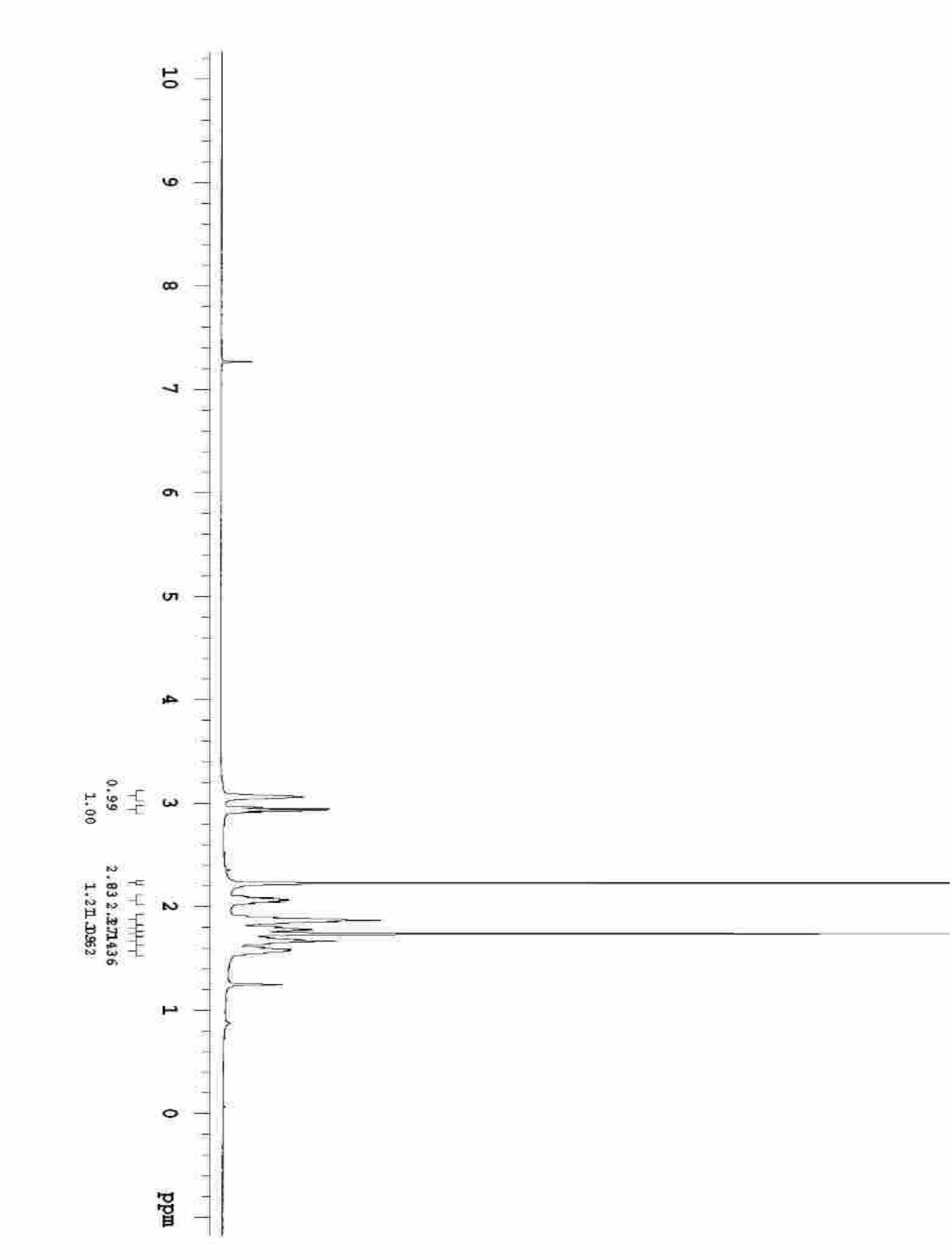
20
ppm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6
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1.27
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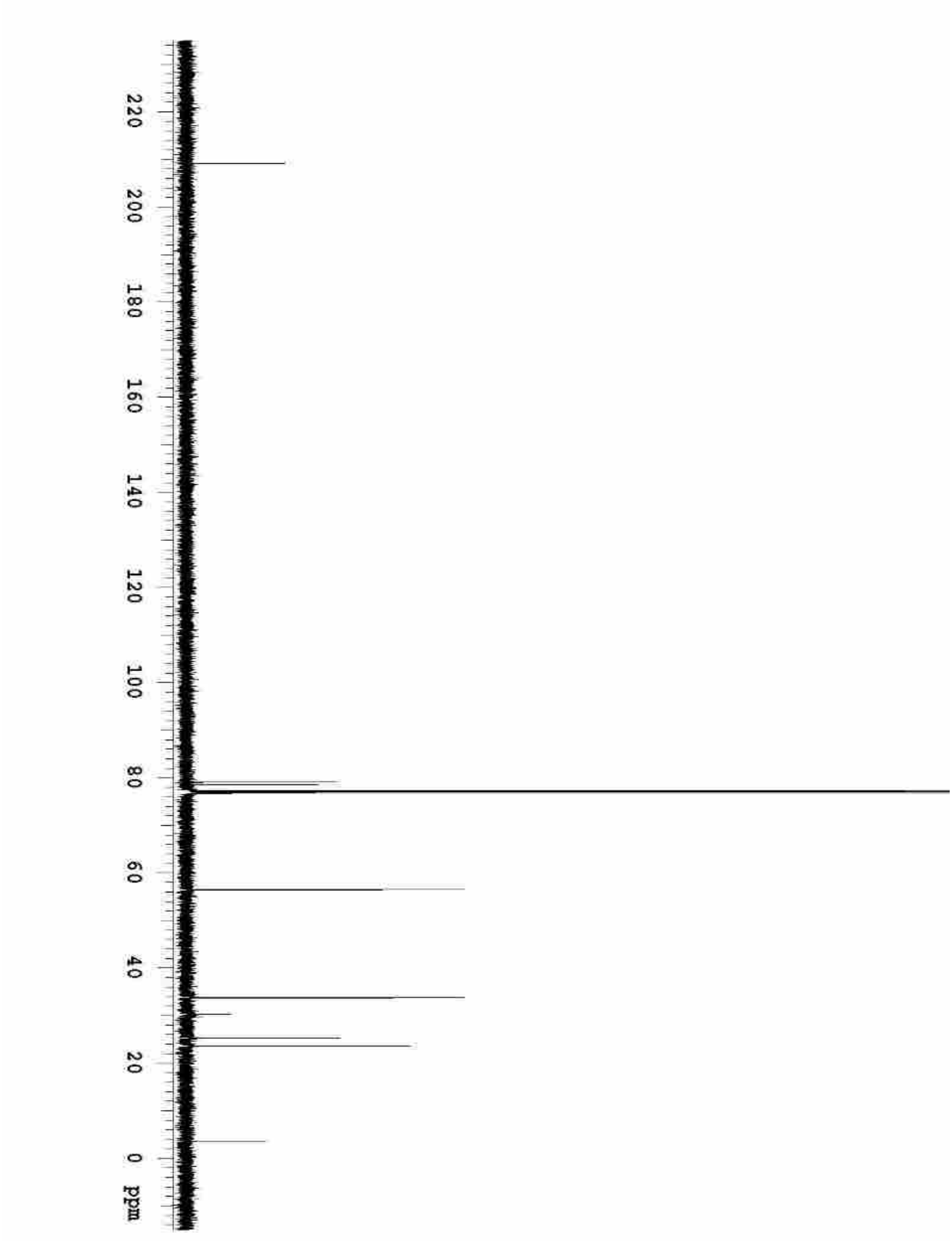
1.00
1.62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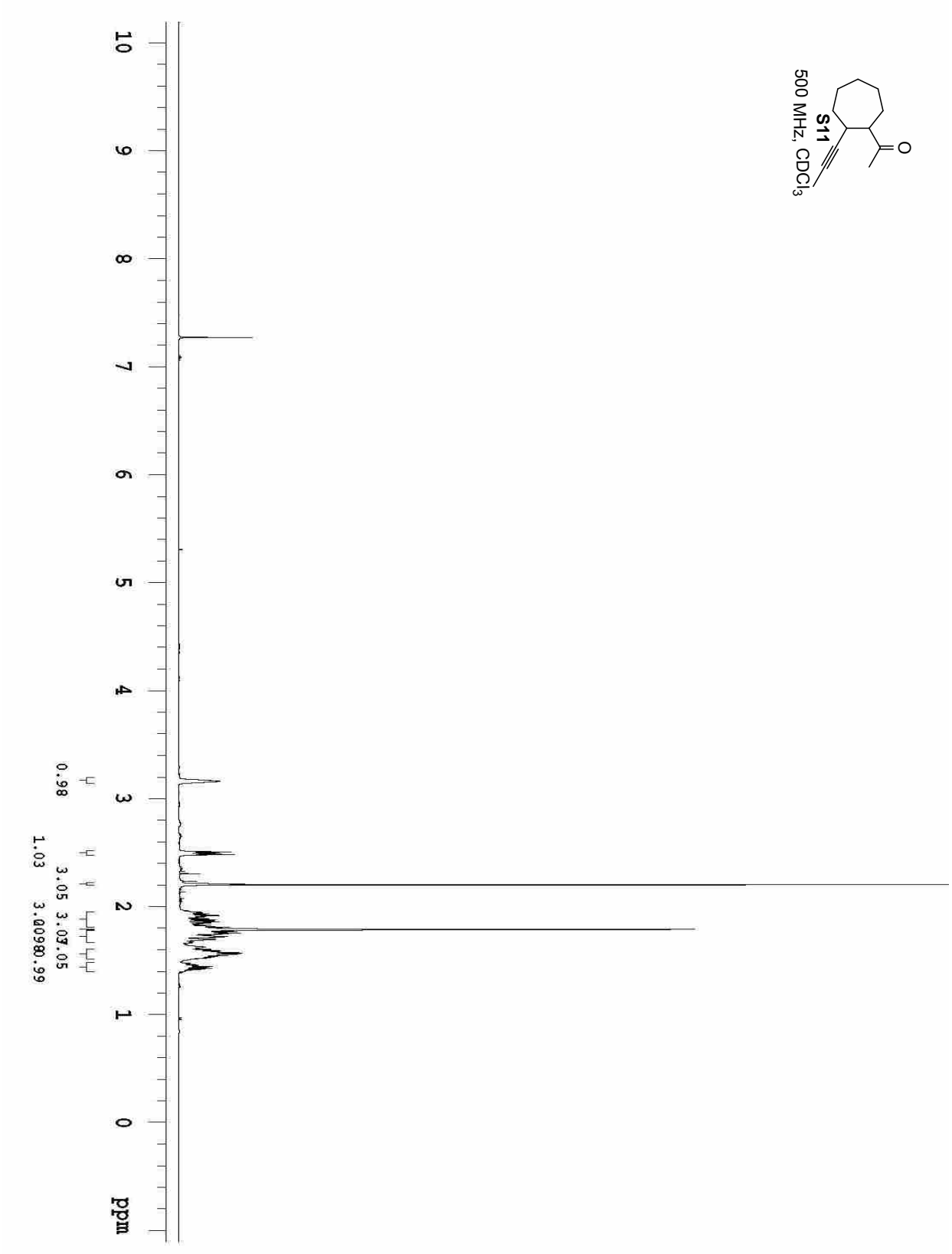
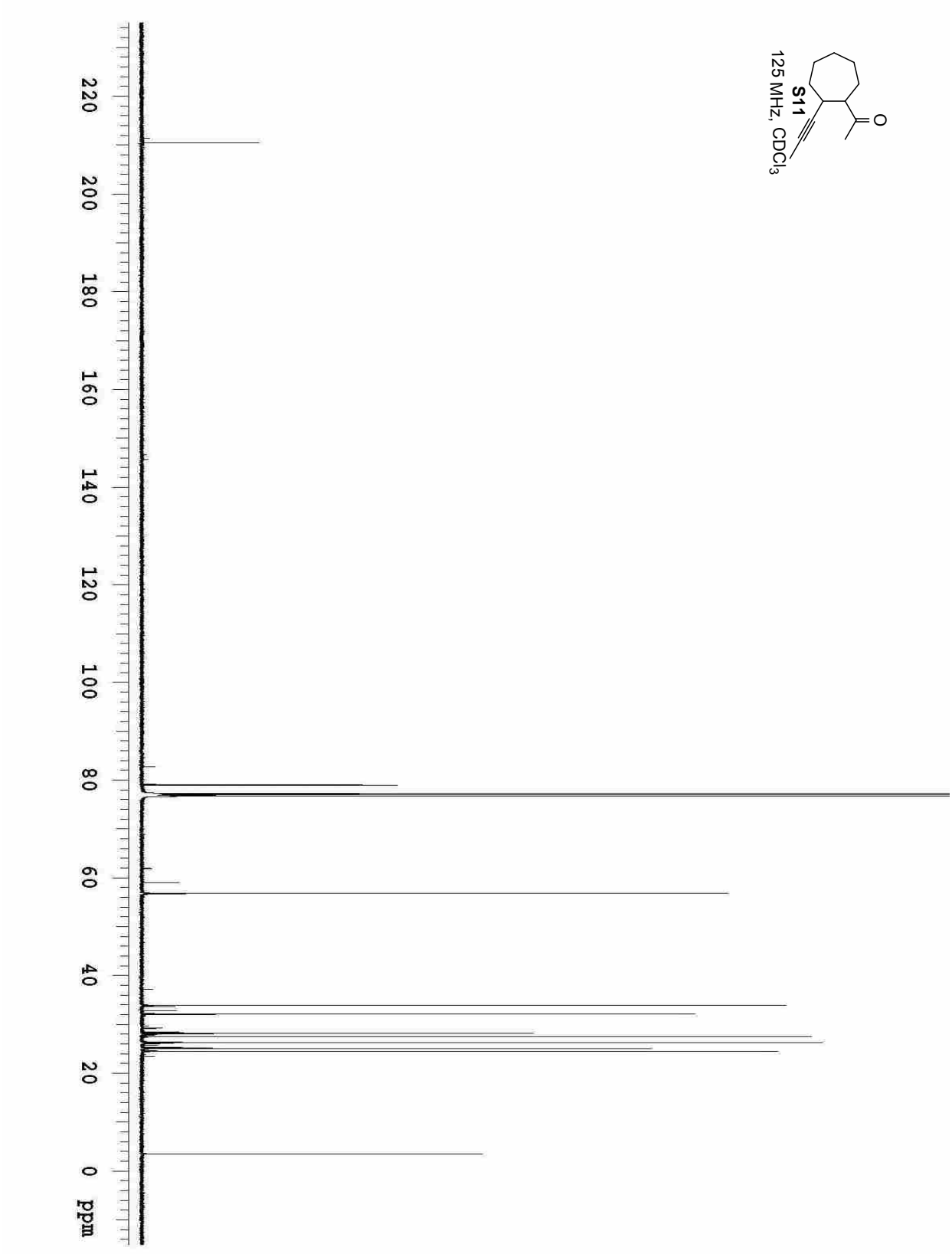
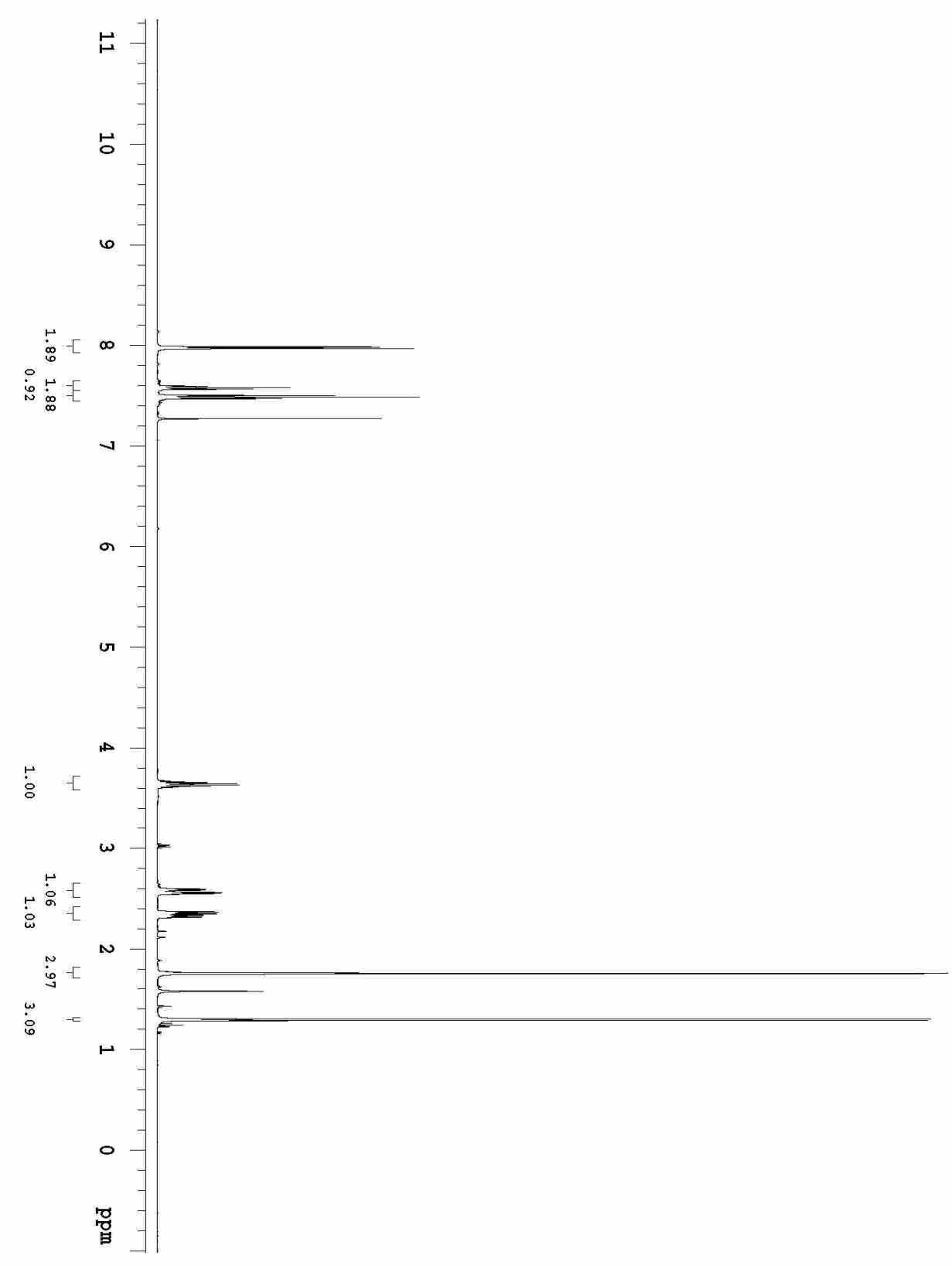
140
120
100
80
60
40
20
0
ppm


S11
500 MHz, CDCl3
O
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
3.05
3.03
7.05
1.03
3.00
9
8.99


S11
125 MHz, CDCl3
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm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10
9
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7
6
5
4
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ppm
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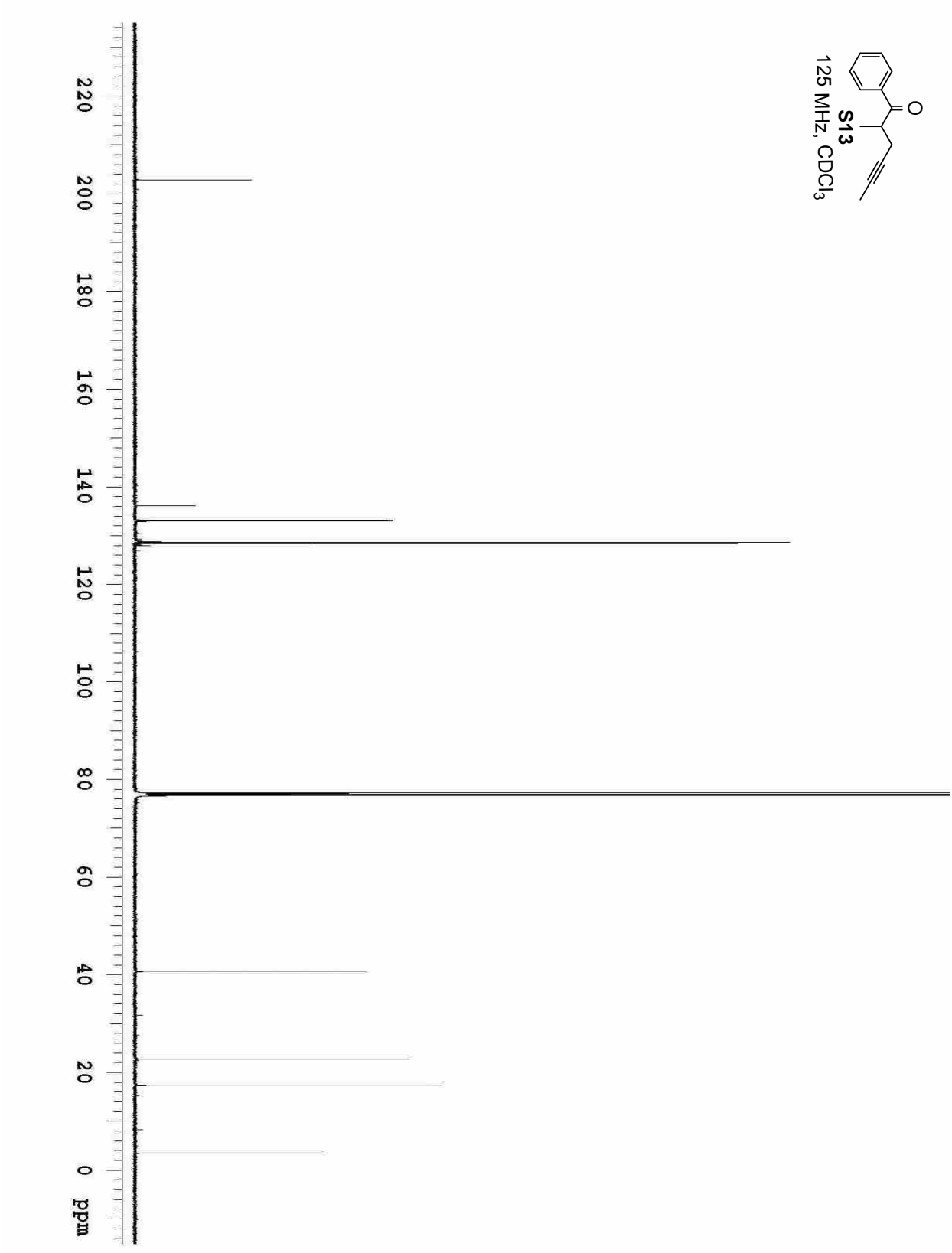
0.92
1.00
1.06
1.03
2.97
3.09


O
S13
125 MHz, CDCl3
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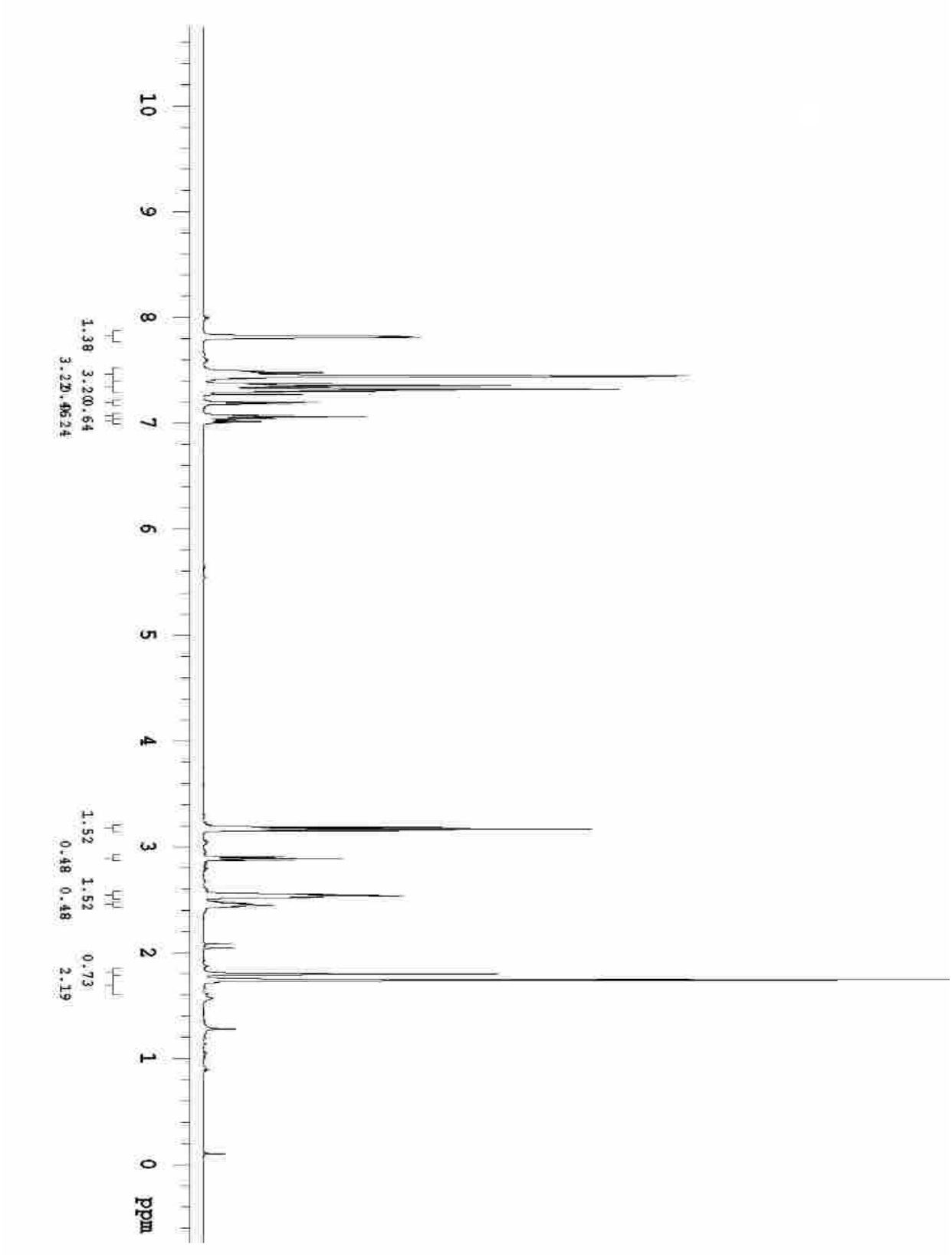
200
180
160
140
120
100
80
60
40
20
0
ppm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9
8
7
6
5
4
3
2
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0
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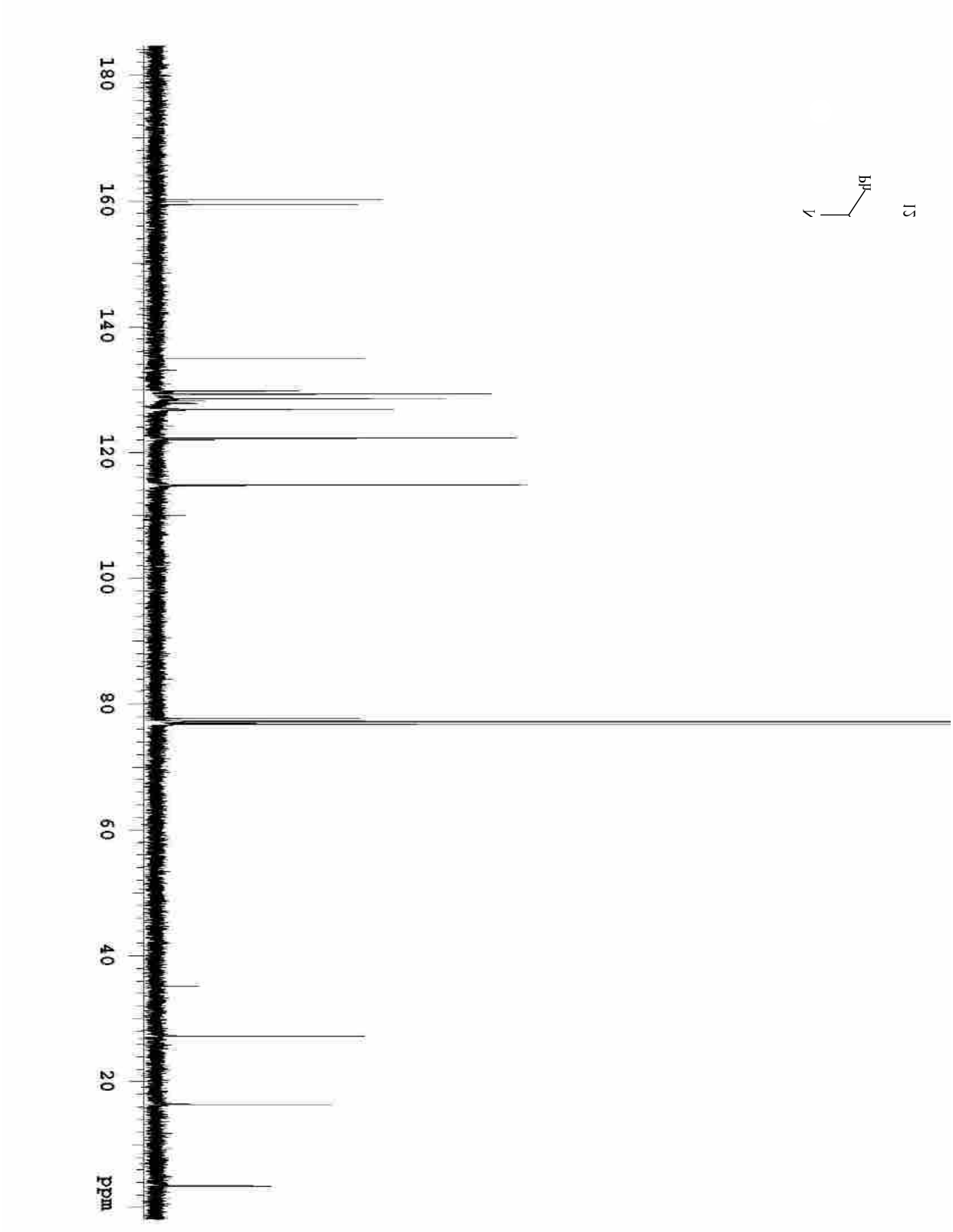
3.20.64
3.20.4624
1.52
1.52
0.48
0.48
0.73
2.19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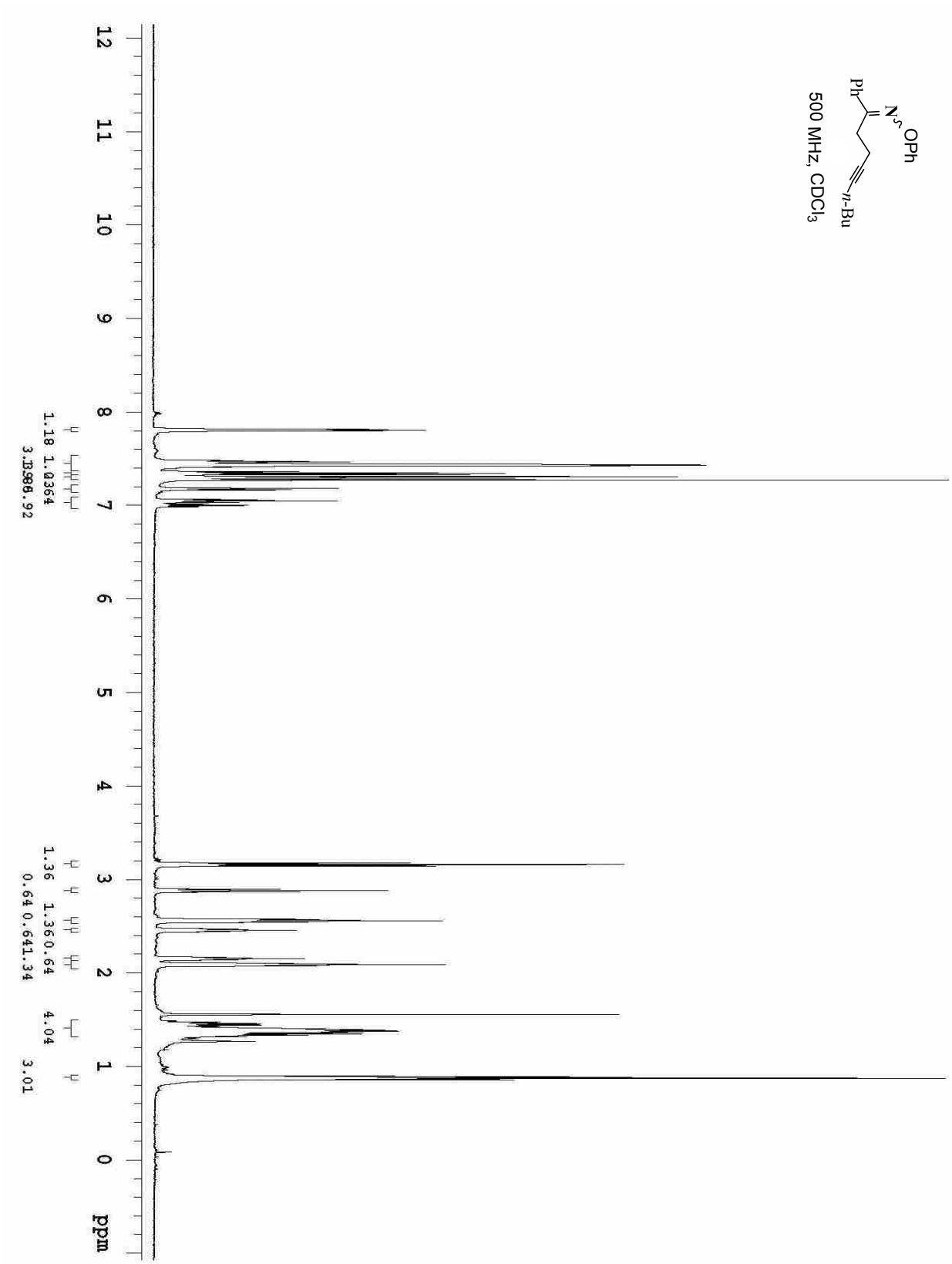
160
140
120
100
80
60
40
20
ppm


Ph
N
OPh
n-Bu
500 MHz, CDCl3
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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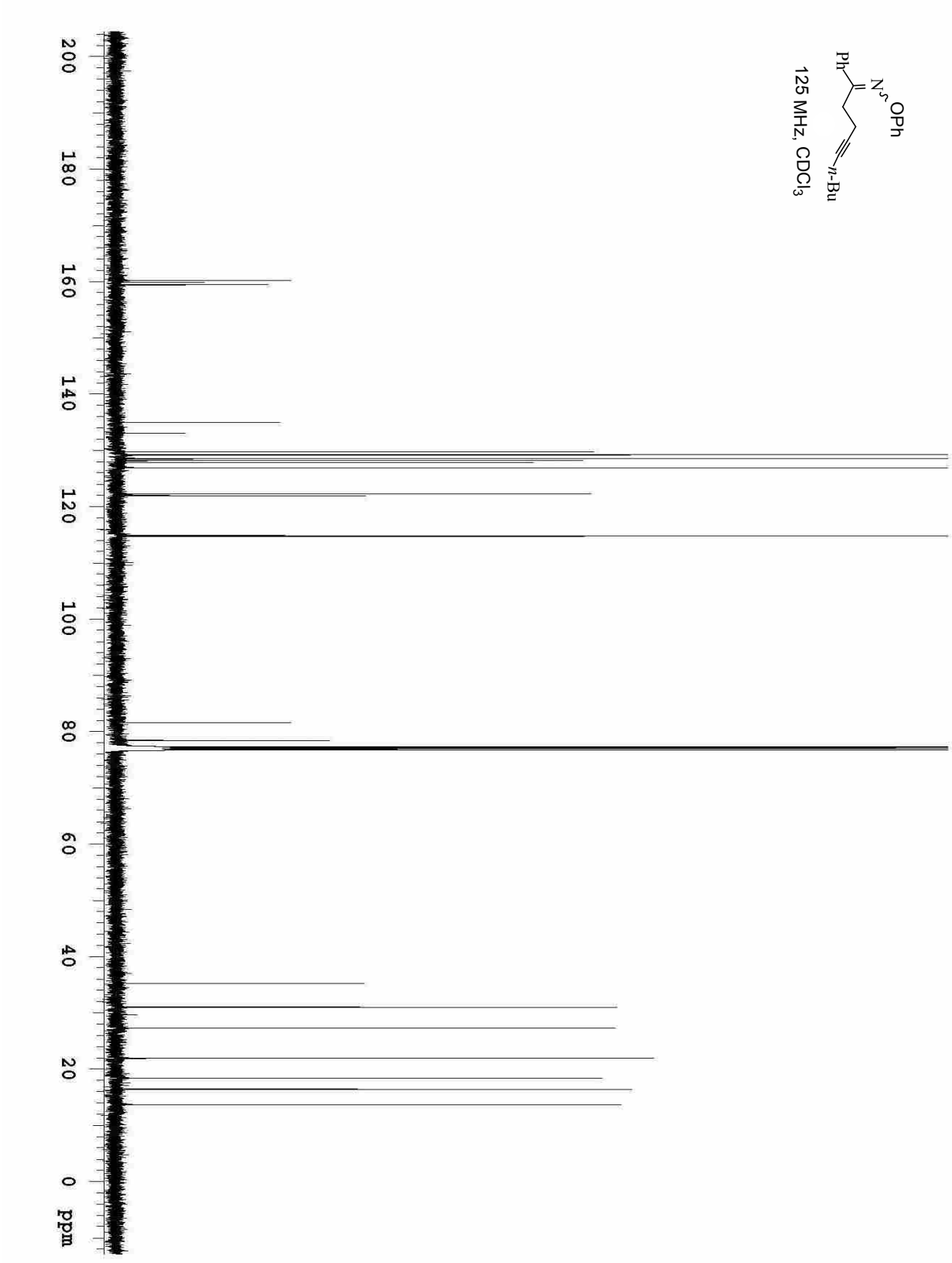
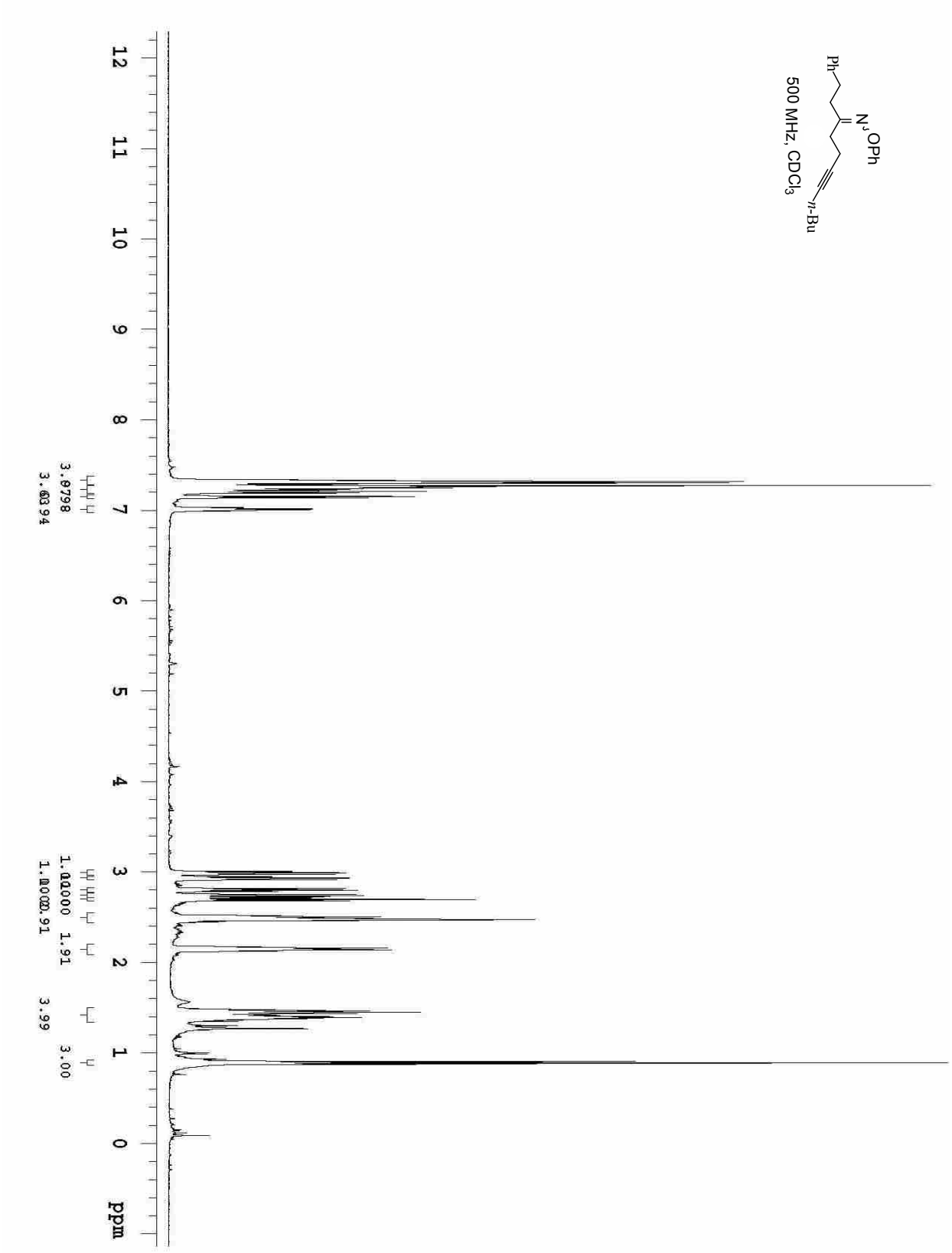
3.13 3.00 6.92
1.36 1.36 0.64
0.64 0.64 1.34
4.04
3.01


125 MHz, CDCl3
Ph
N
OPh
n-Bu
200
180
160
140
120
100
80
60
40
20
0
ppm


Ph
N
OPh
n-Bu
500 MHz, CDCl3
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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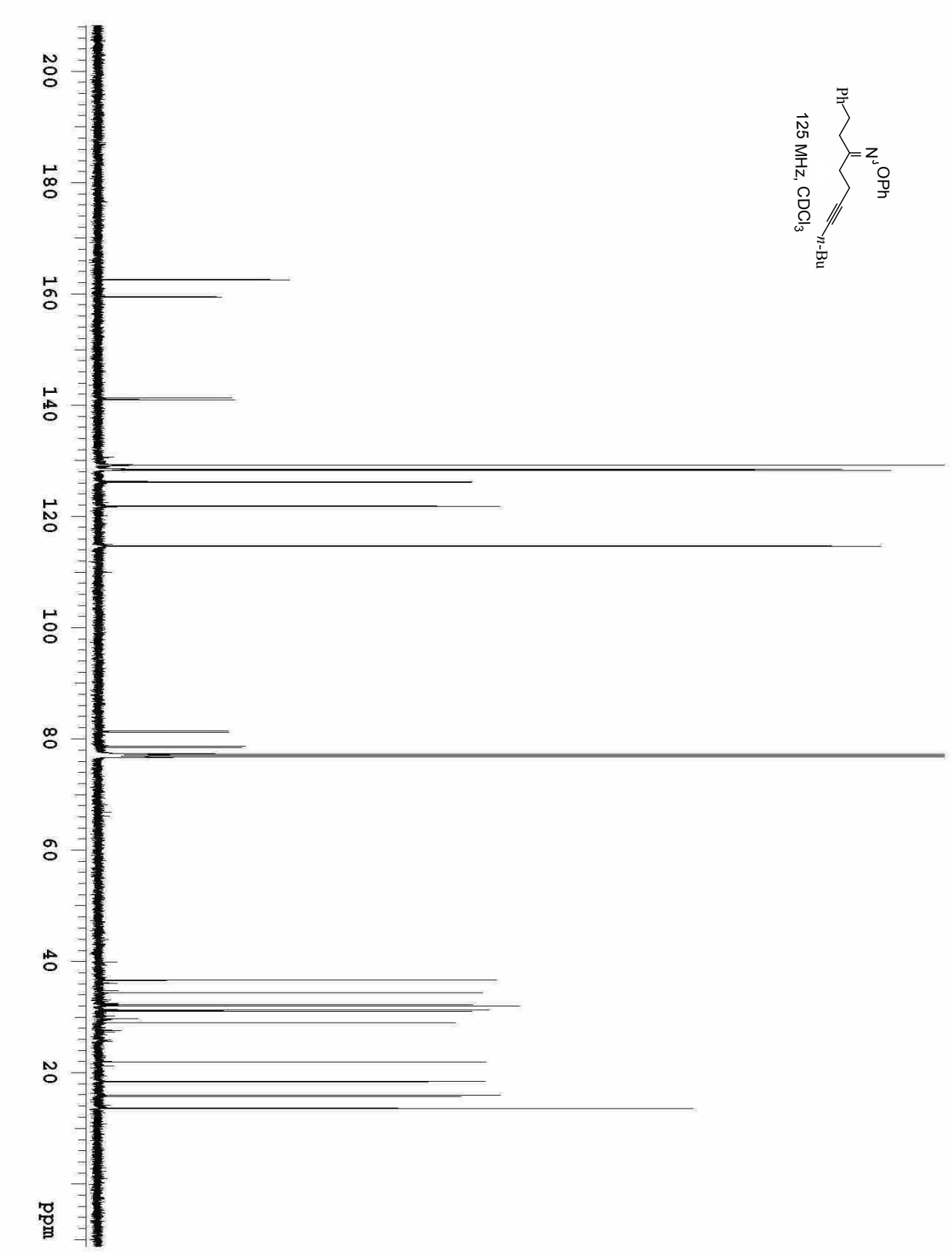
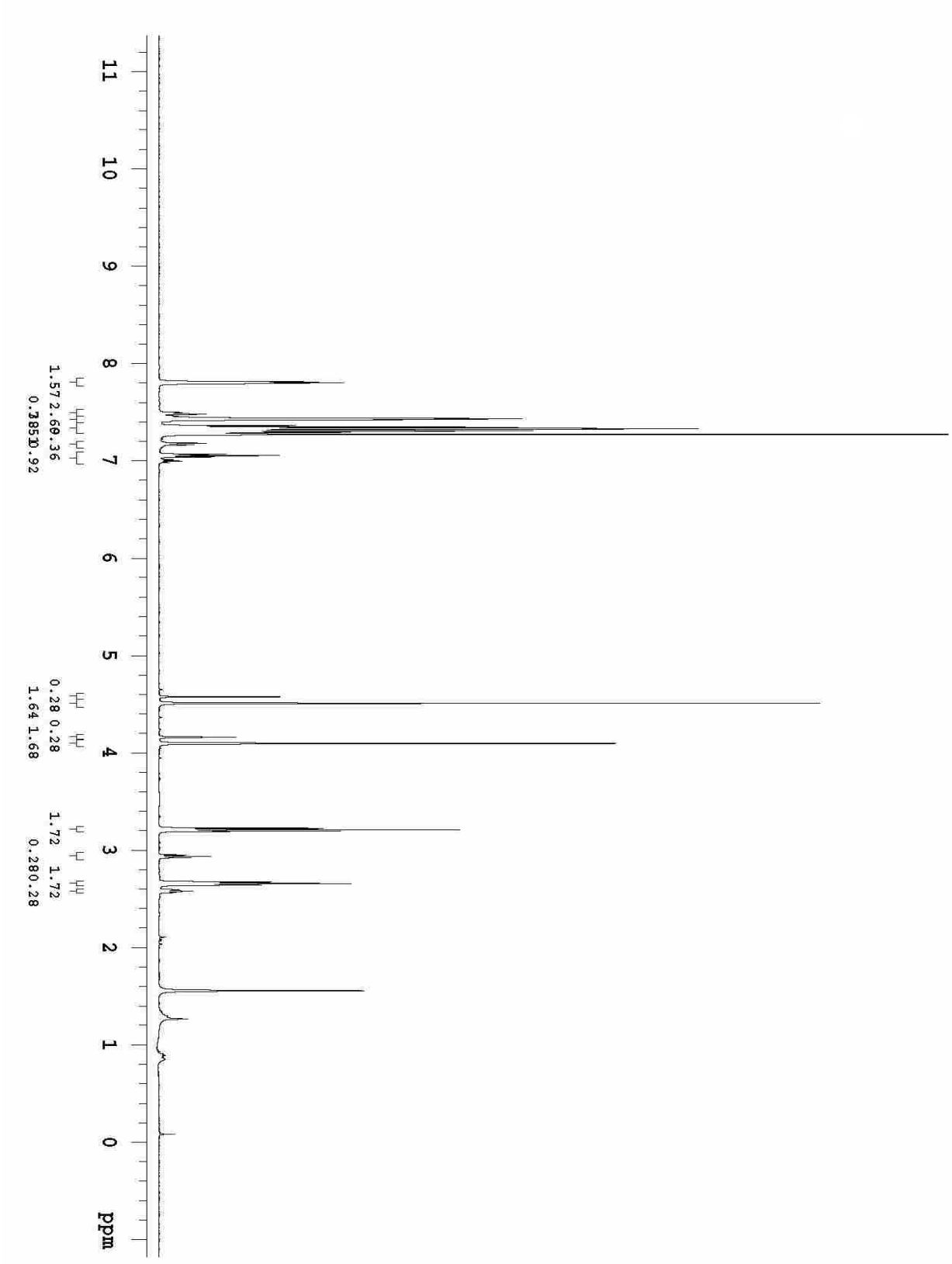
3.6394
1.0000
1.9144
1.9100
3.9991
3.00


Ph
N
OPh
n-Bu
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm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10
9
8
7
6
5
4
3
2
1
0
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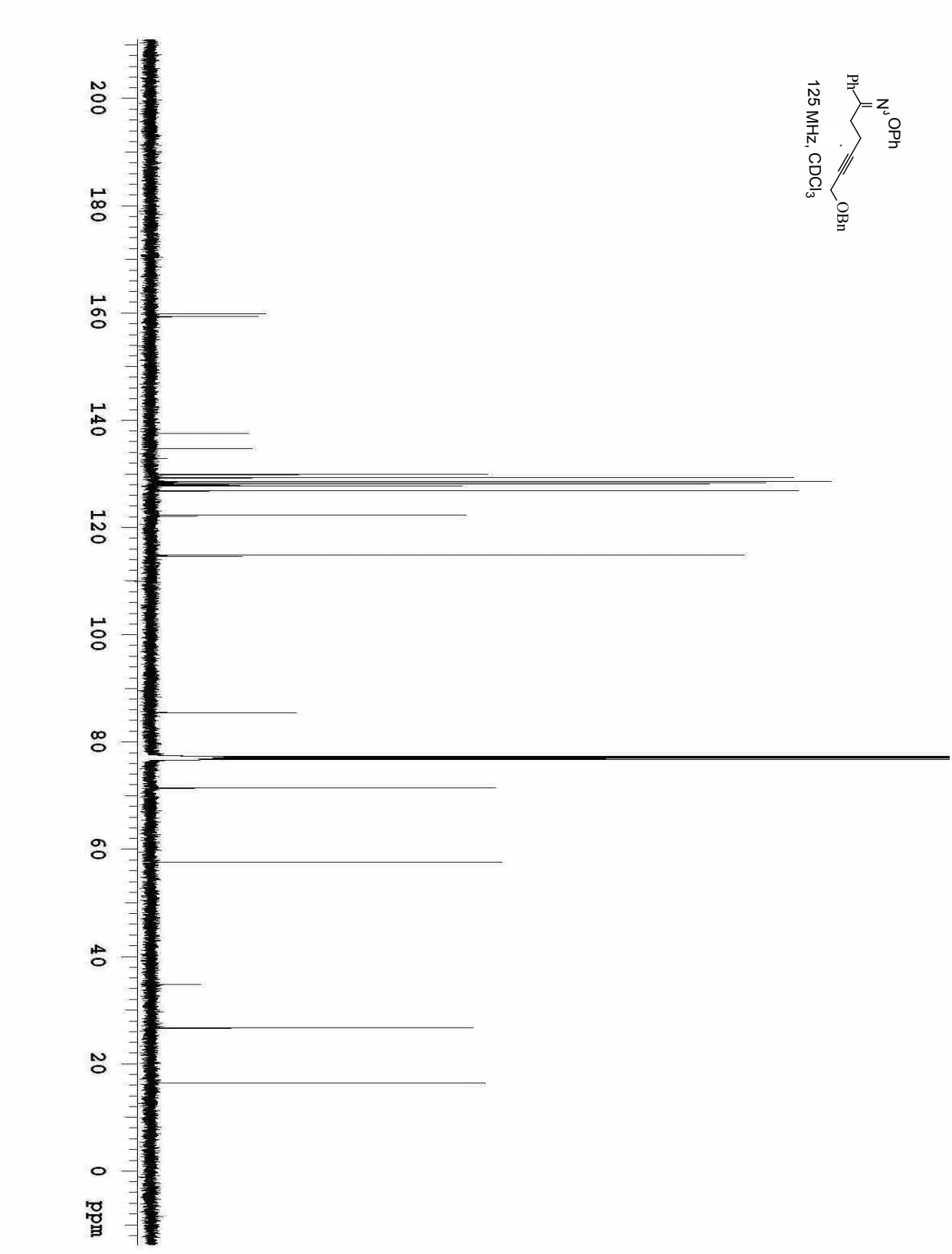
1.57 2.69 0.36
0.28 0.28
1.64 1.68
1.72 1.72
0.28 0.28


125 MHz, CDCl3
Ph
N3
OPh
OBn
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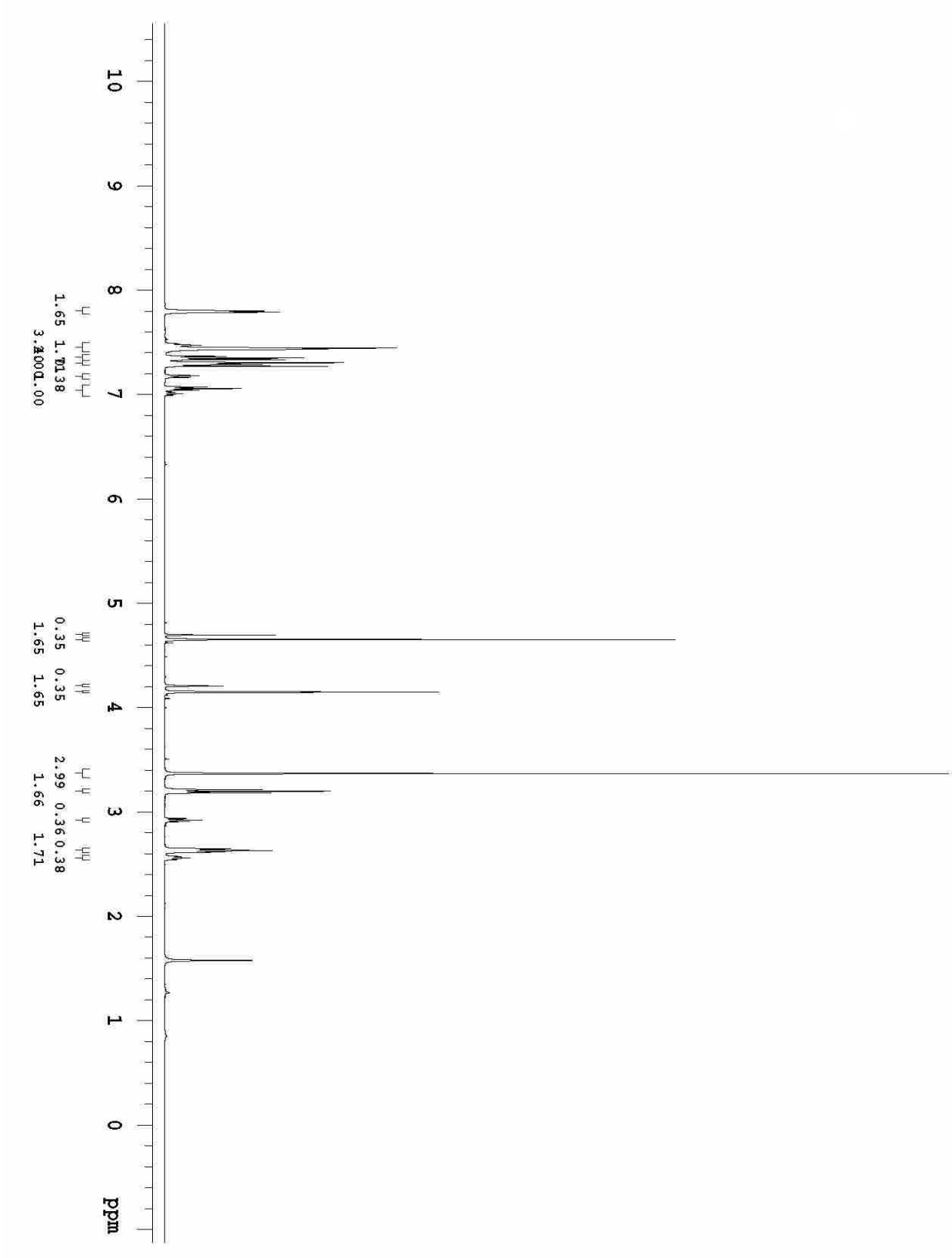
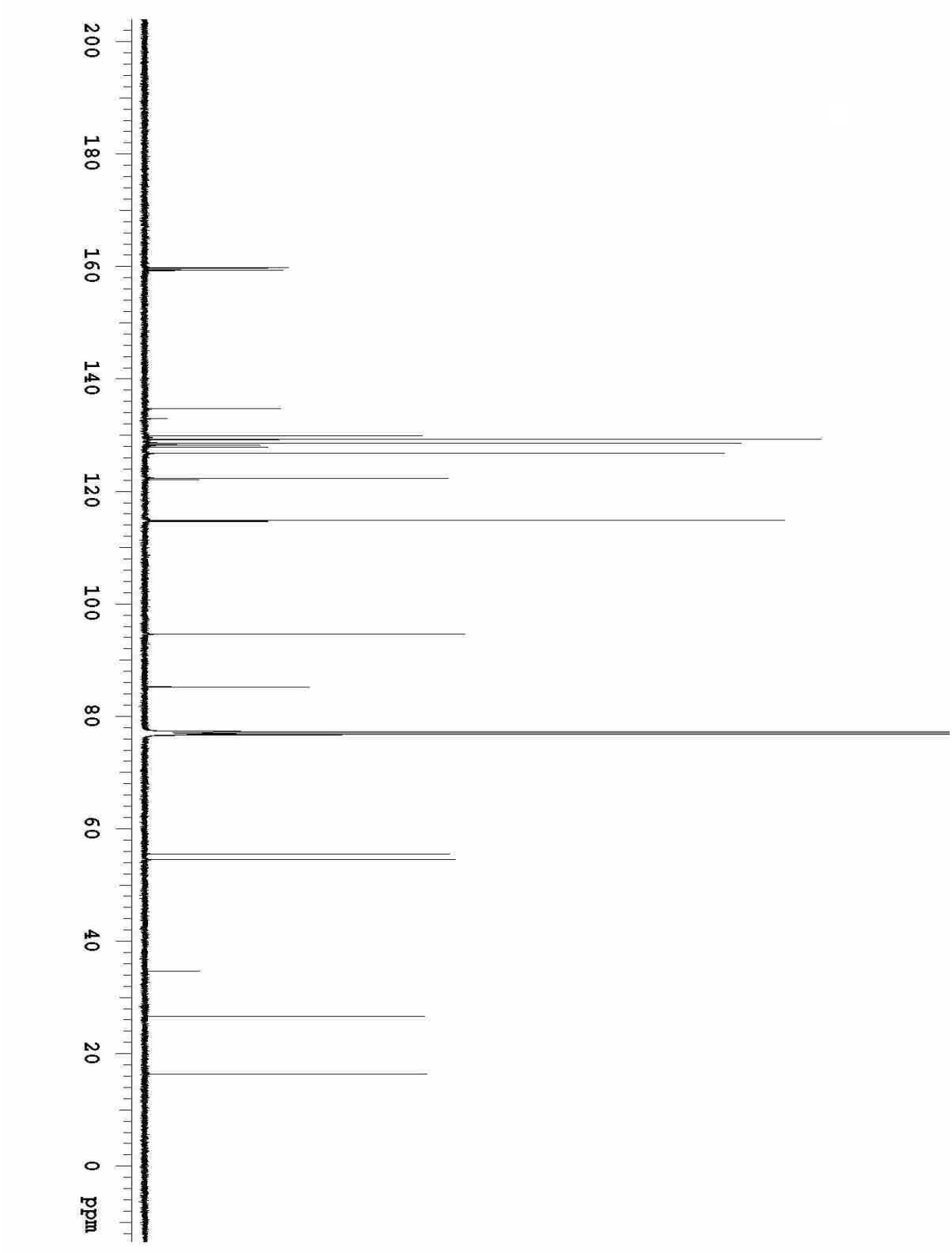
180
160
140
120
100
80
60
40
20
0
ppm


10
9
8
7
6
5
4
3
2
1
0
ppm
1.65 1.71 3.38 1.00
0.35 0.35
1.65 1.65
2.99 0.36 0.38
1.66 1.71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180
160
140
120
100
80
60
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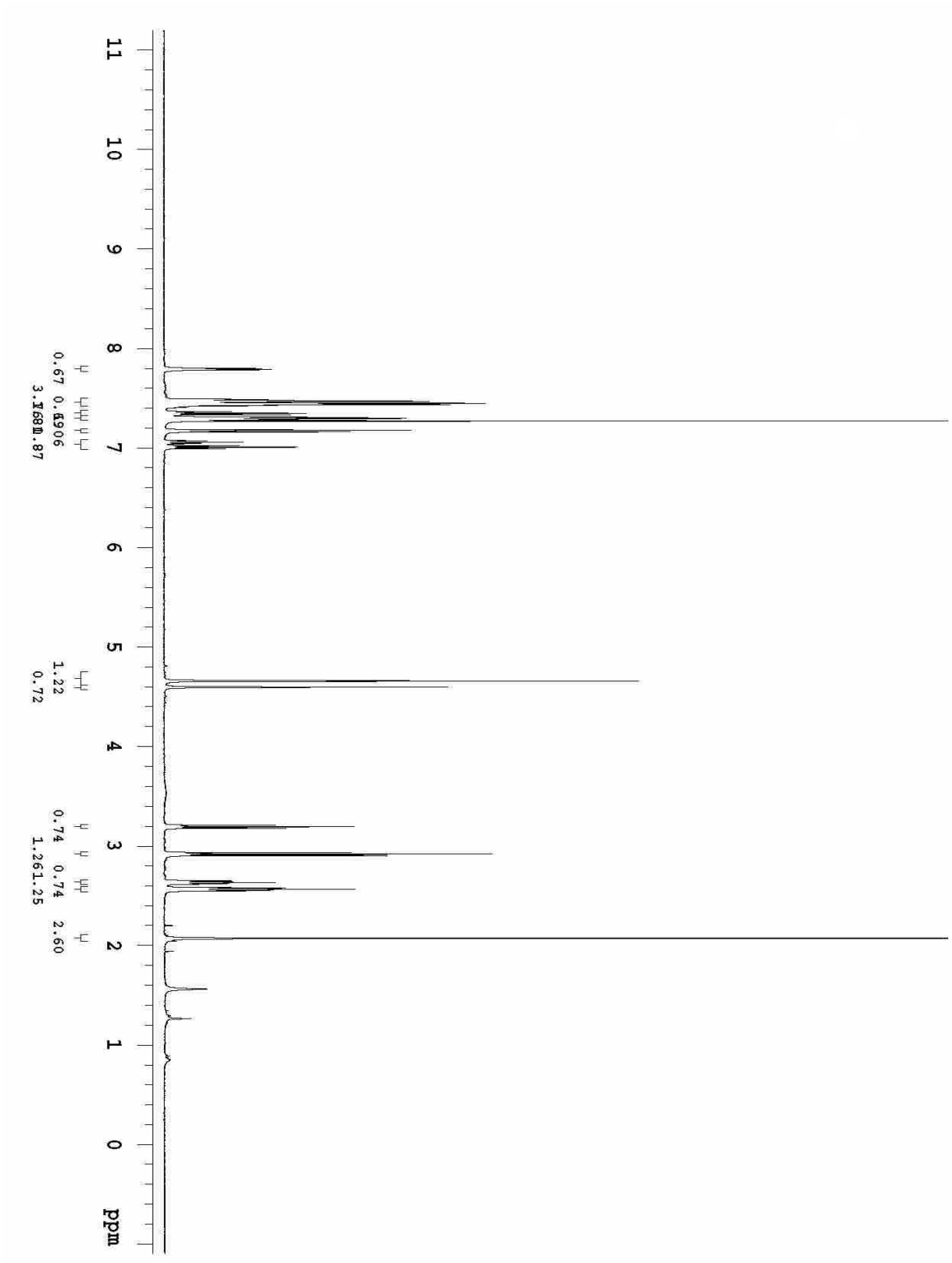
20
0
ppm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10
9
8
7
6
5
4
3
2
1
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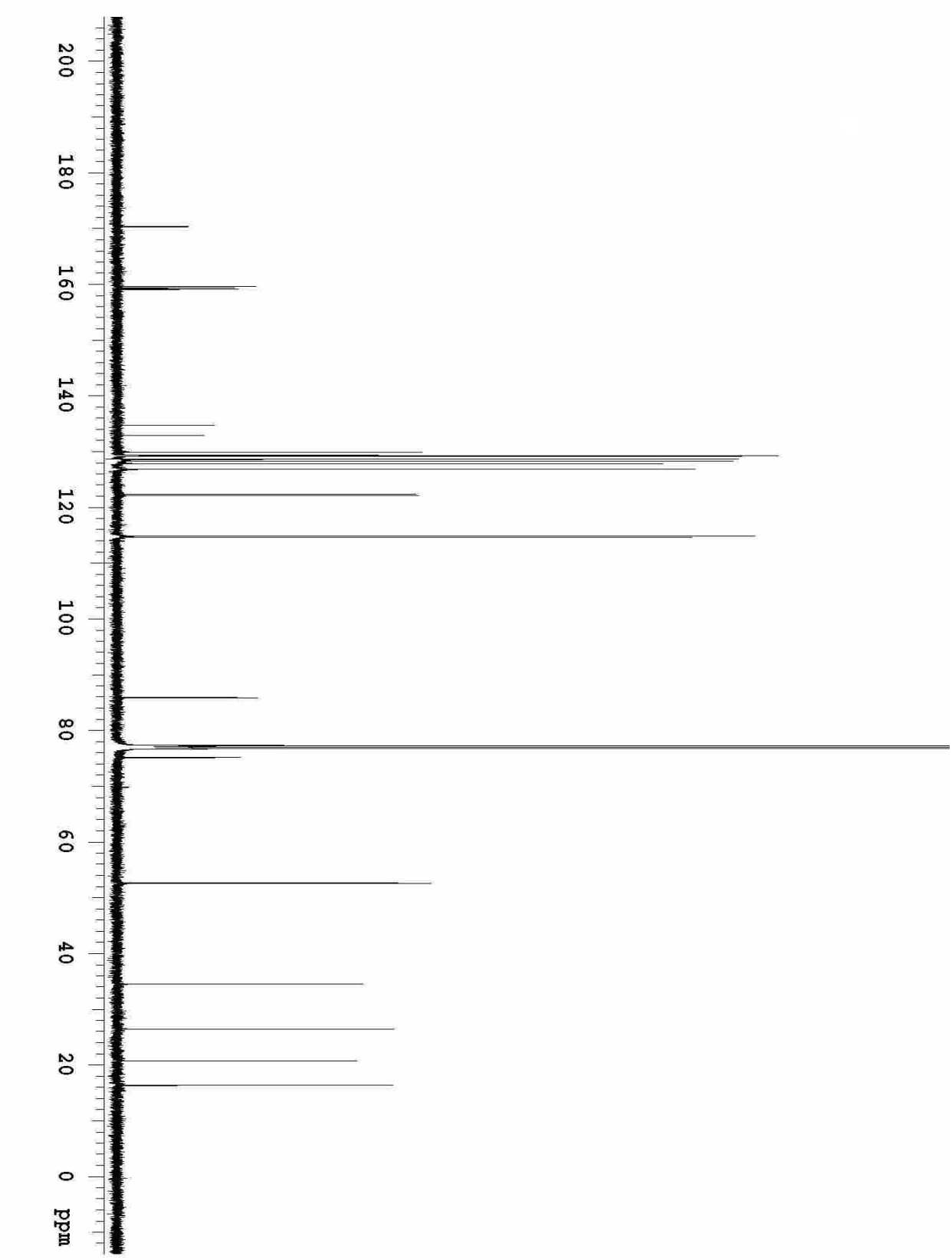
3.76 3.87
1.22
0.72
0.74 0.74 2.60
1.26 1.25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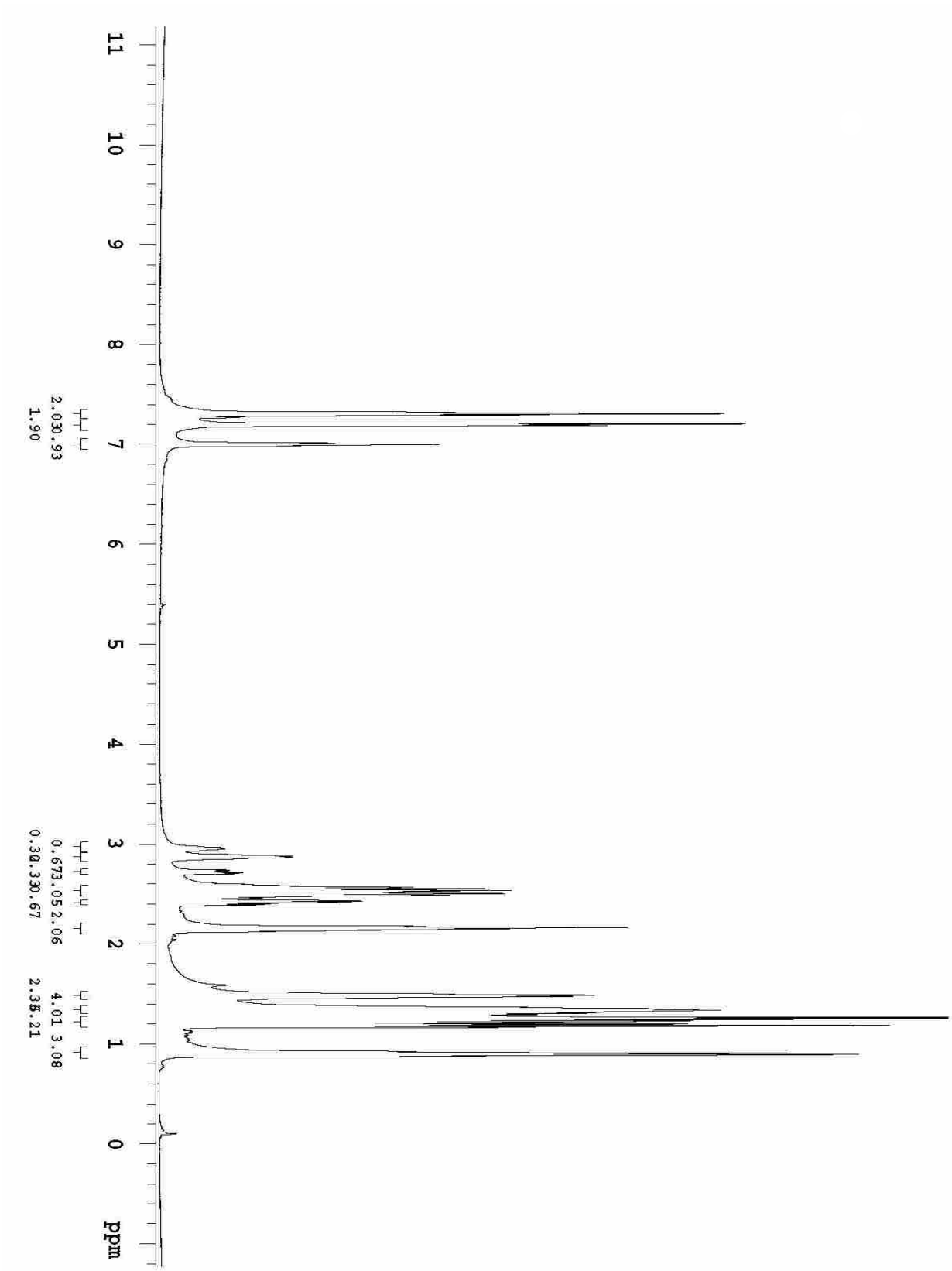
160
140
120
100
80
60
40
20
0
ppm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9
8
7
6
5
4
3
2
1
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ppm
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2.06
0.30
0.33
0.67
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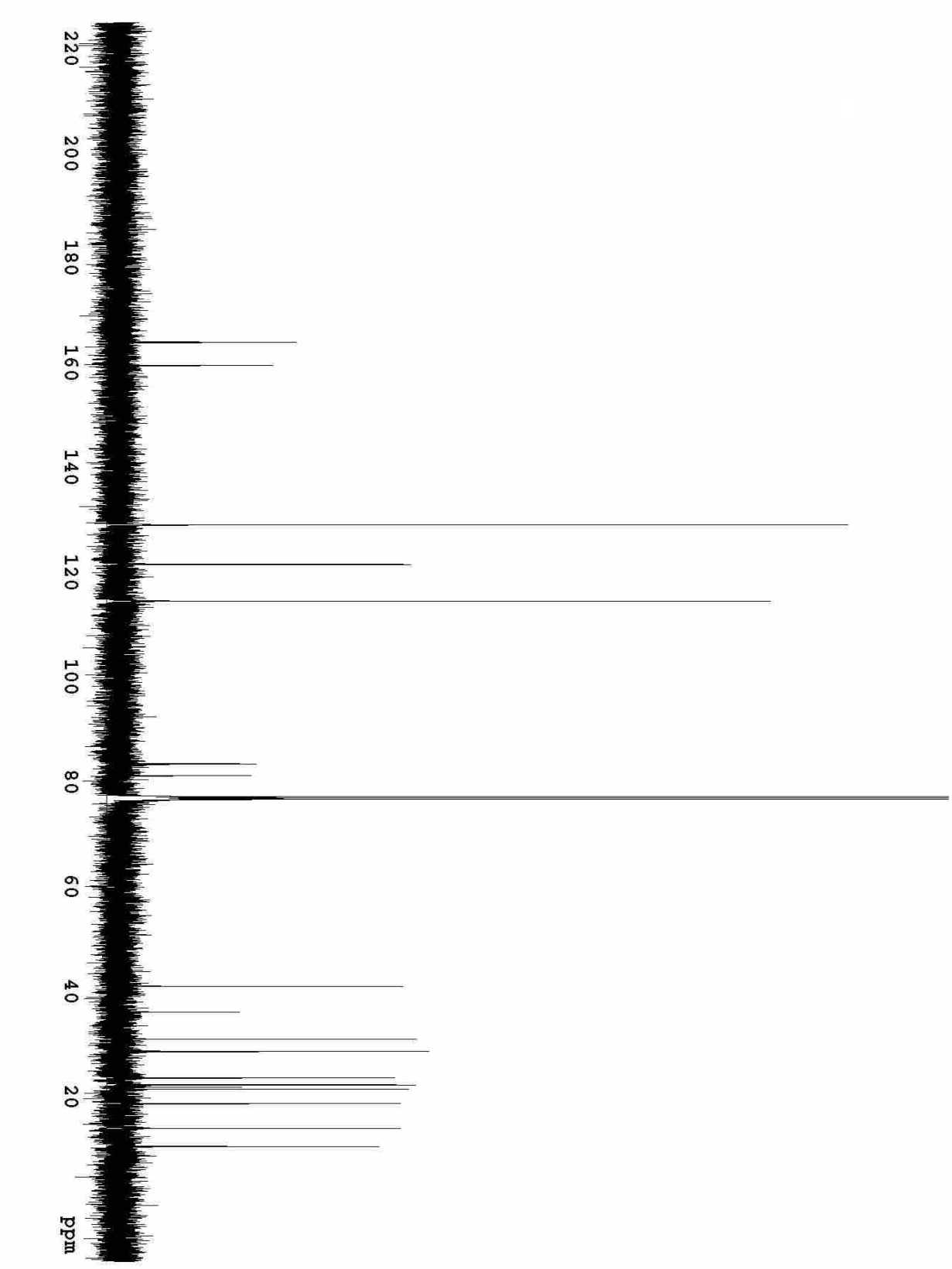
3.08
2.35
5.21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140
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100
80
60
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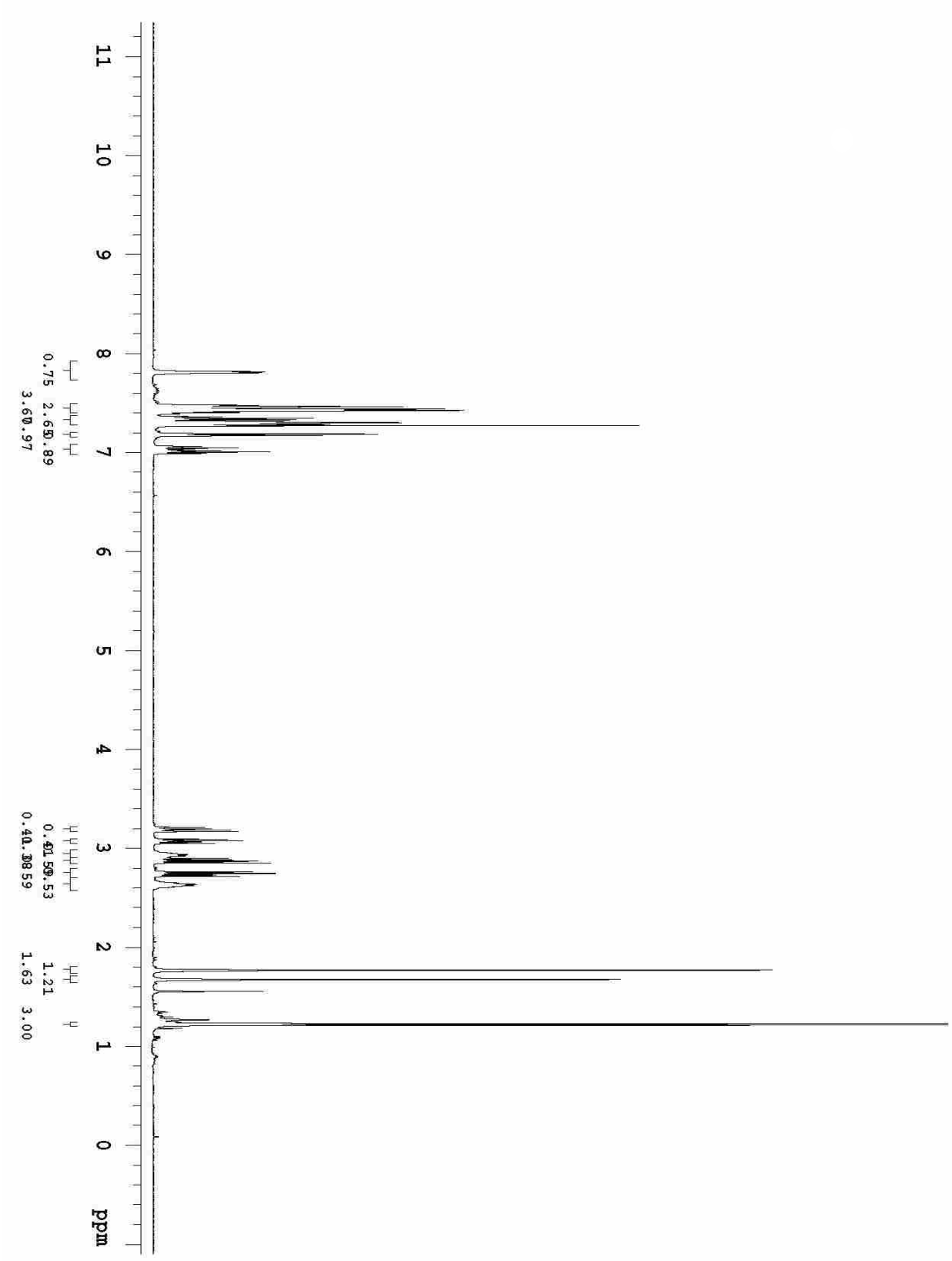
20
ppm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9
8
7
6
5
4
3
2
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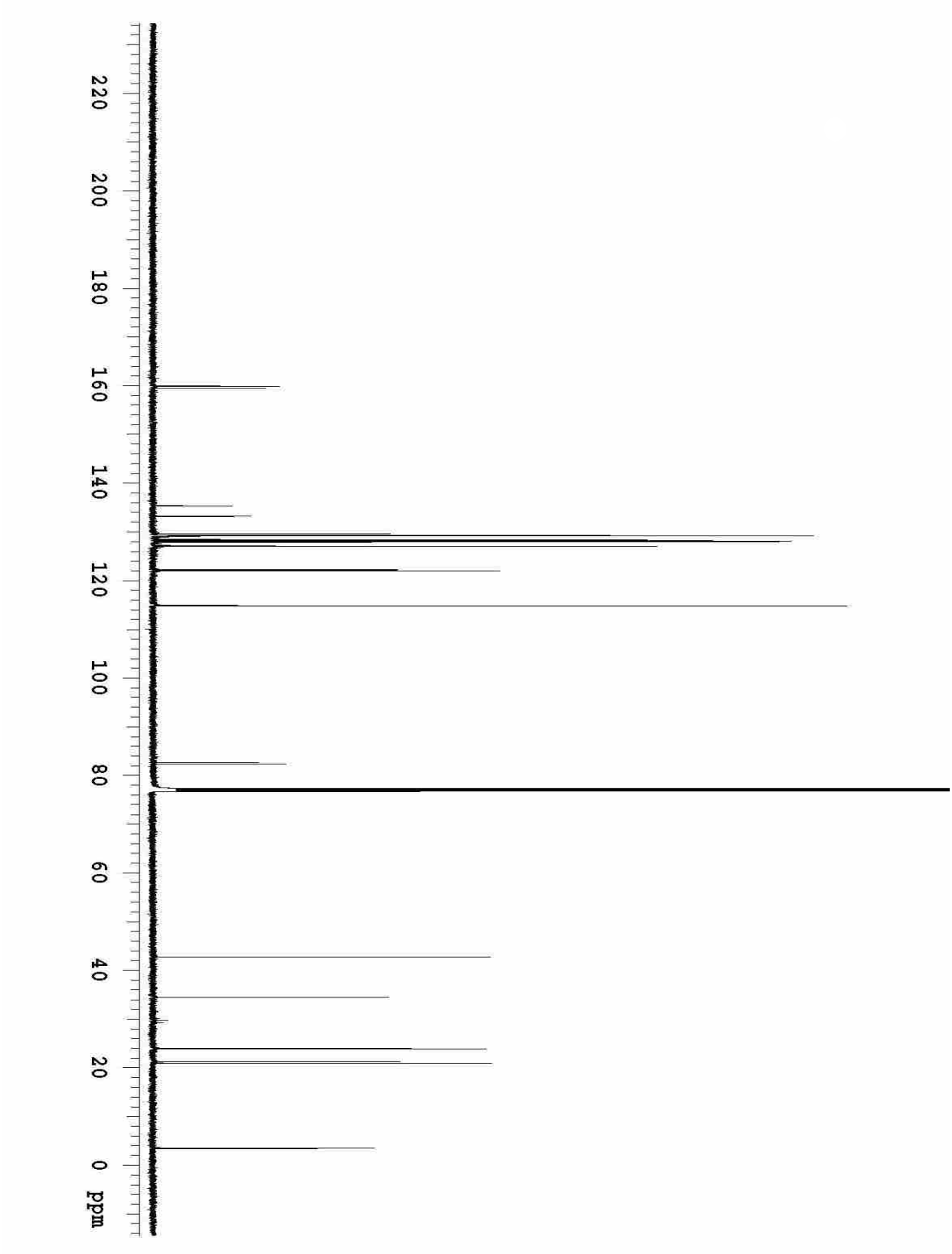
0.40 1.59 0.53
0.40 1.58 0.59
1.21
1.63 3.00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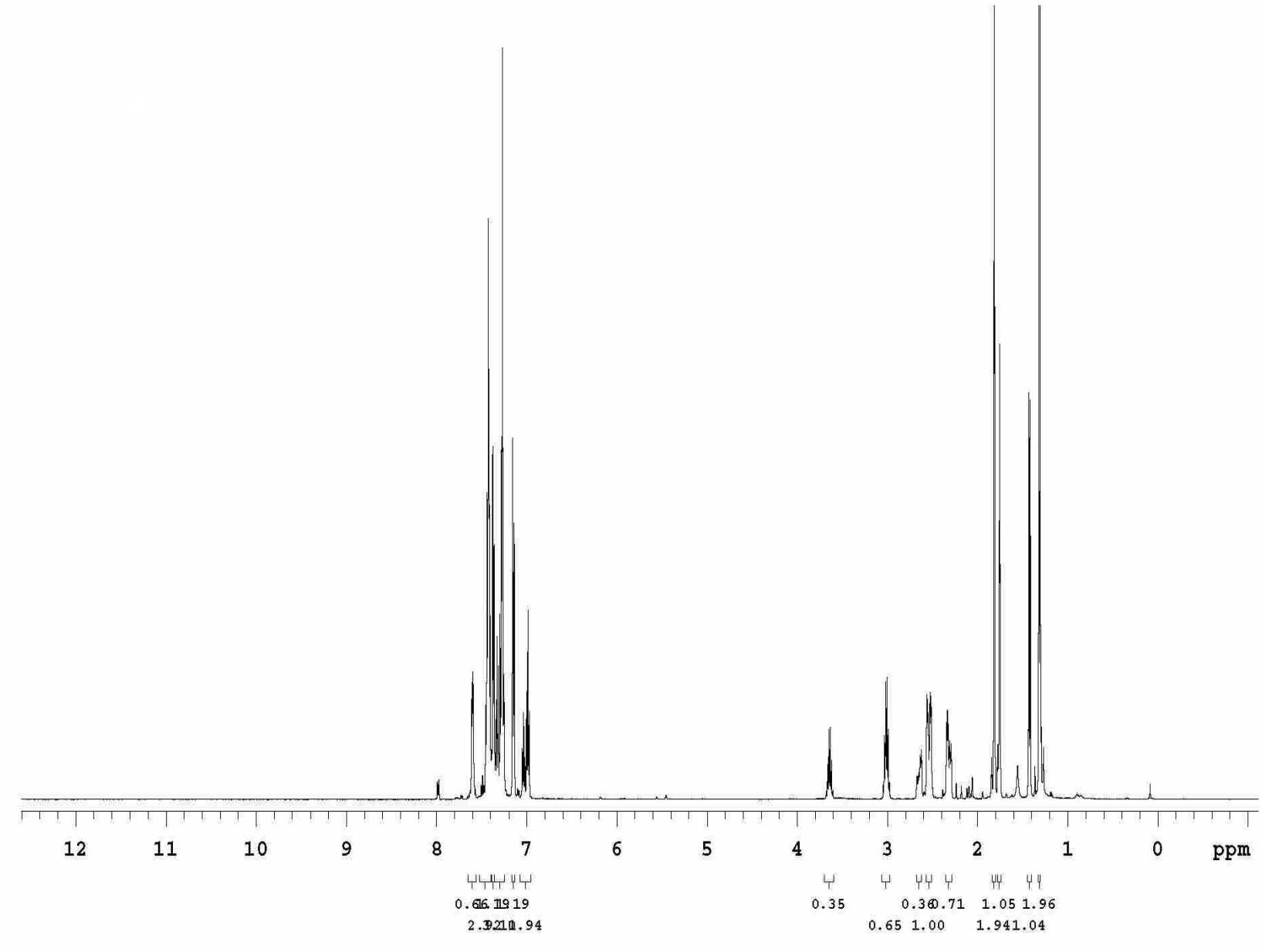
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8
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6
5
4
3
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0
ppm
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0.65
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0.71
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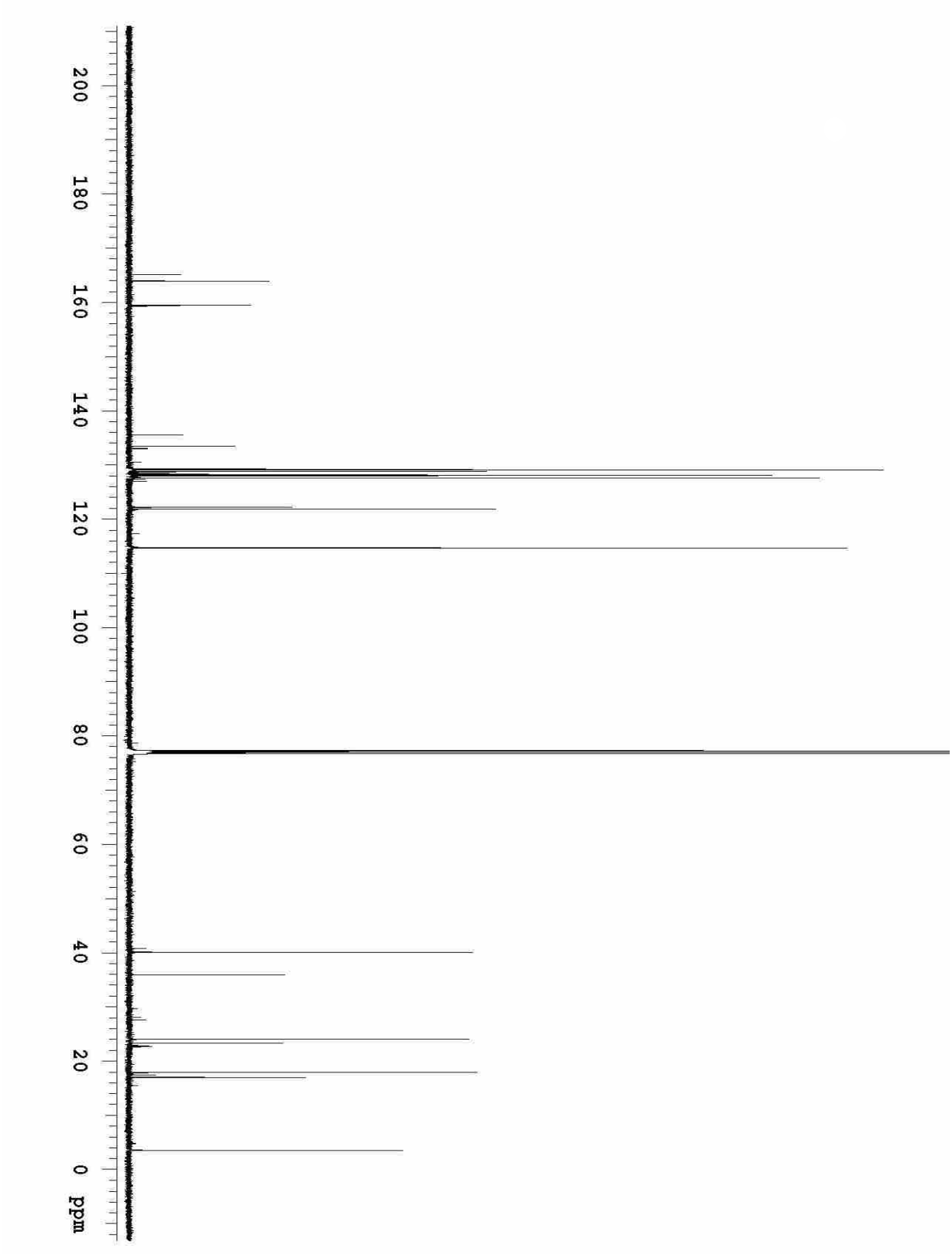
1.94
1.04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140
120
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80
60
40
20
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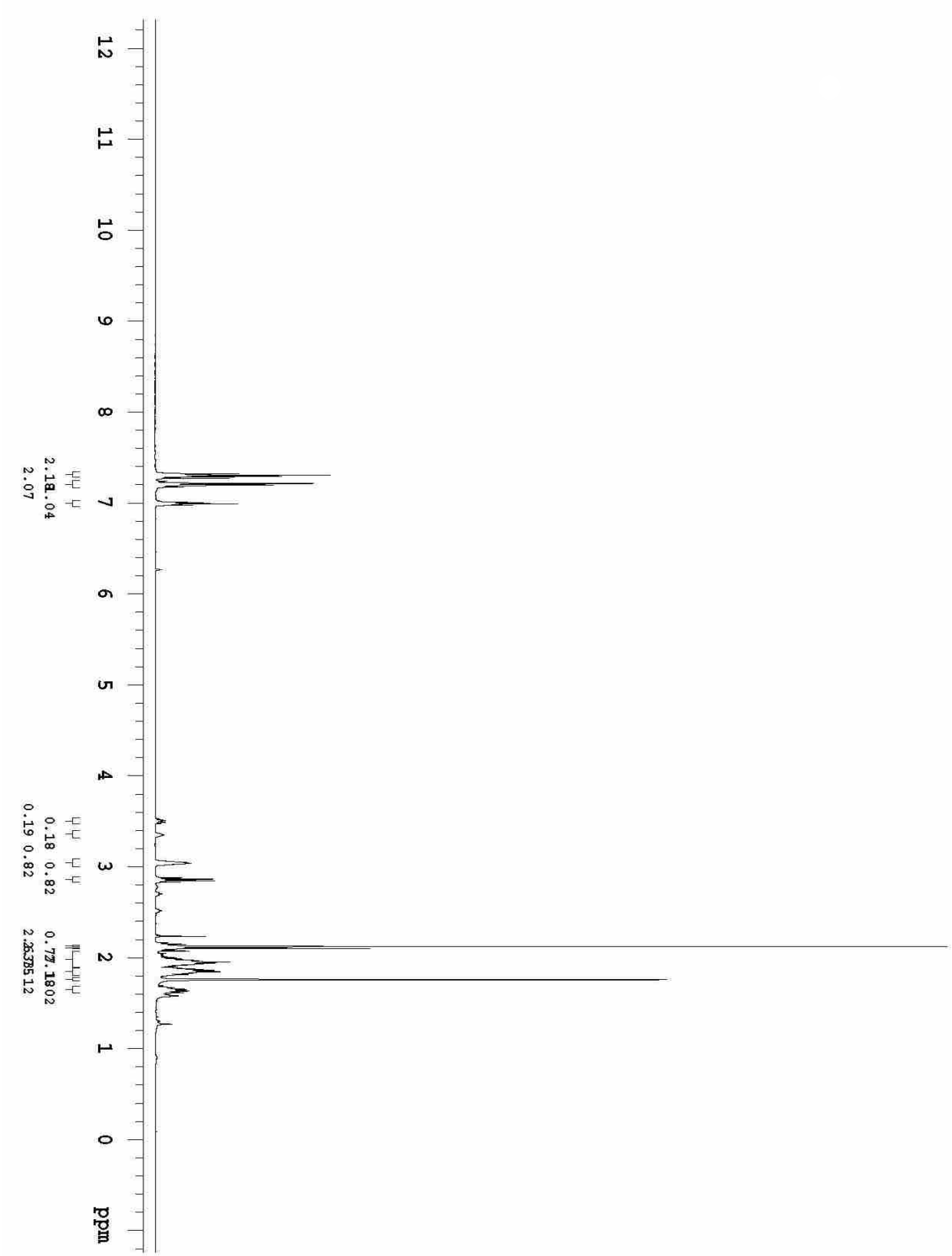
ppm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10
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8
7
6
5
4
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2
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2.07
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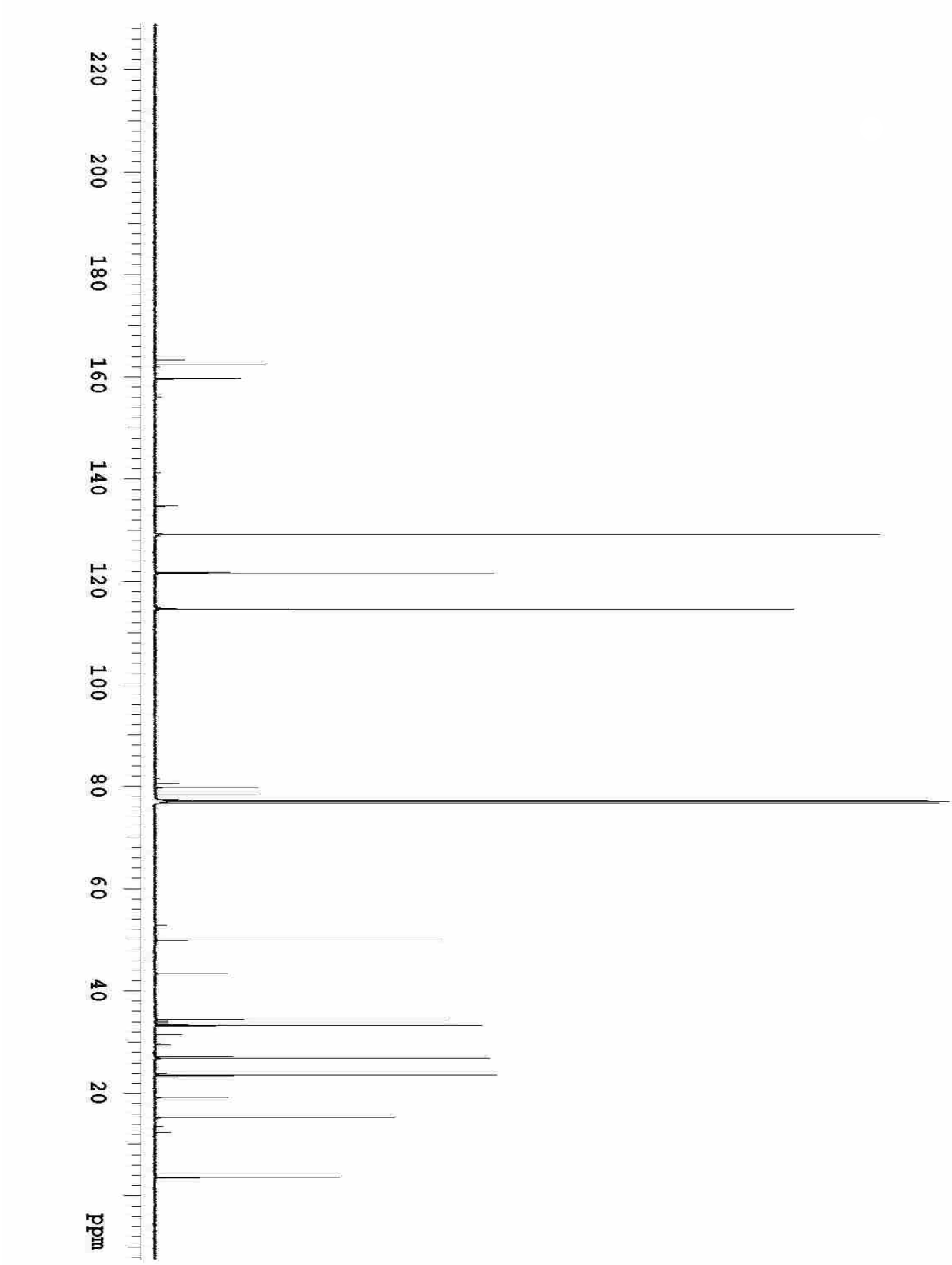
0.19 0.82
0.77 1.80
2.53 5.12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140
120
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80
60
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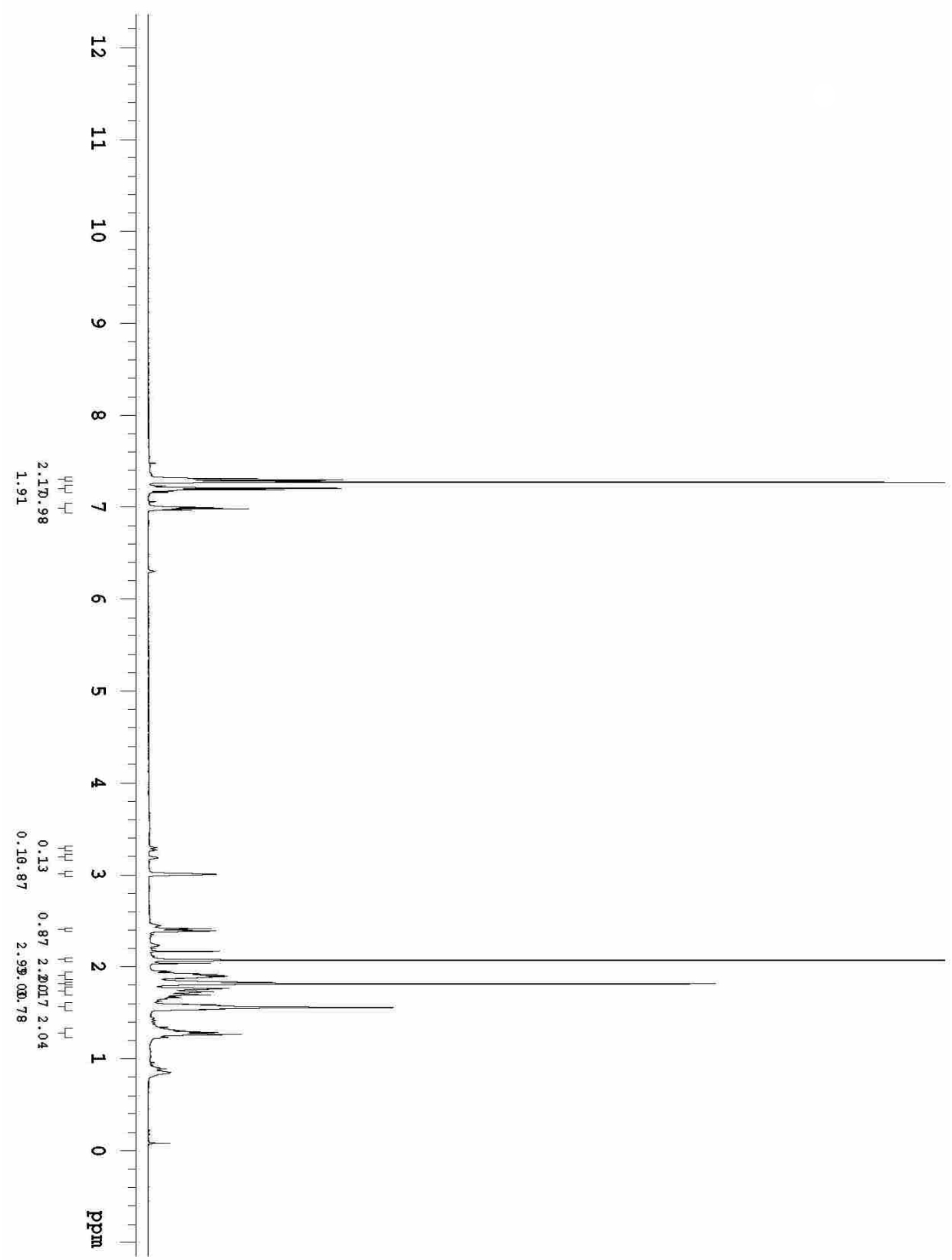
20
ppm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8
7
6
5
4
3
2
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0
ppm
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0.87
2.00
2.04
0.10
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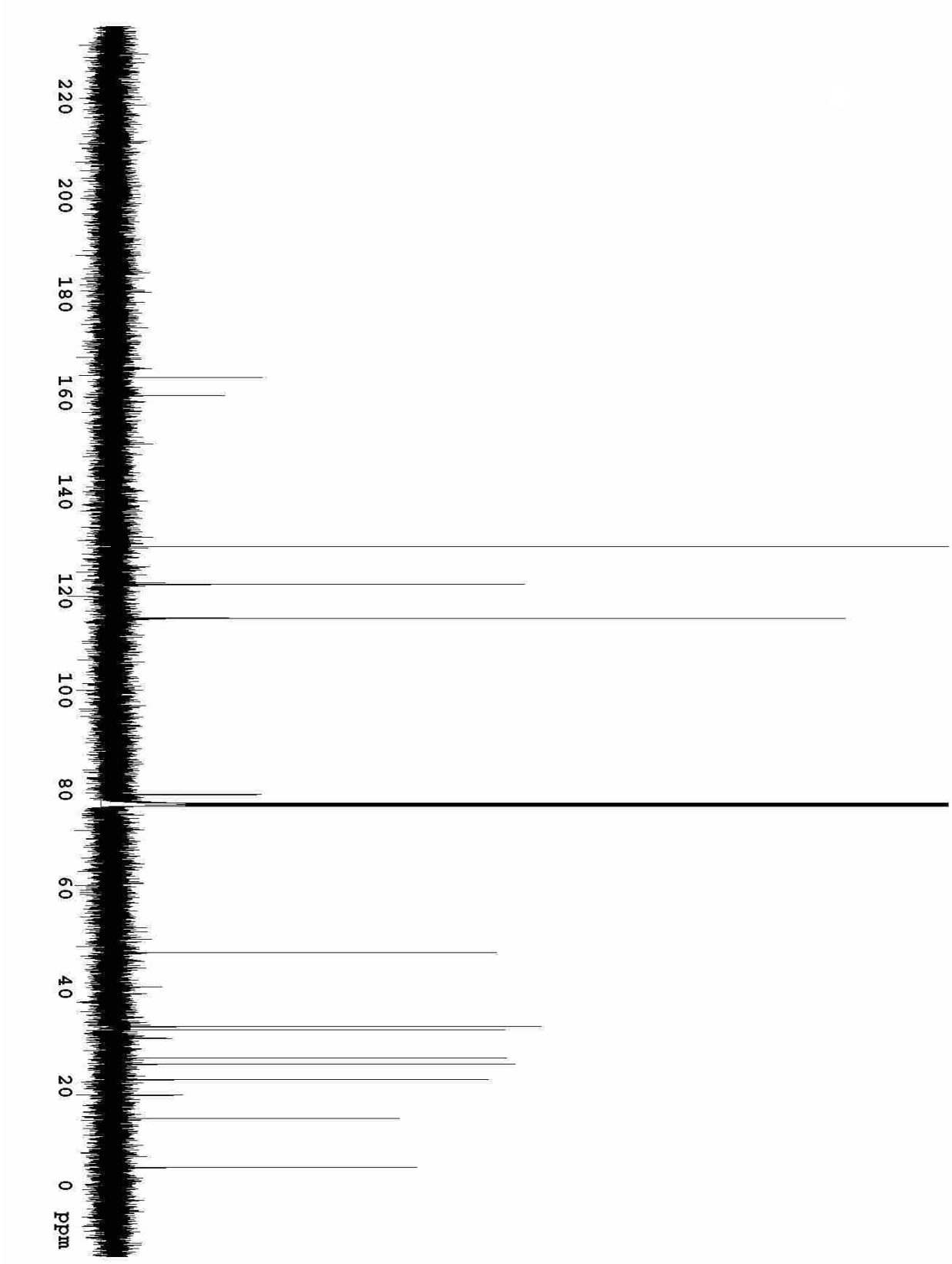
2.99
3.00
0.78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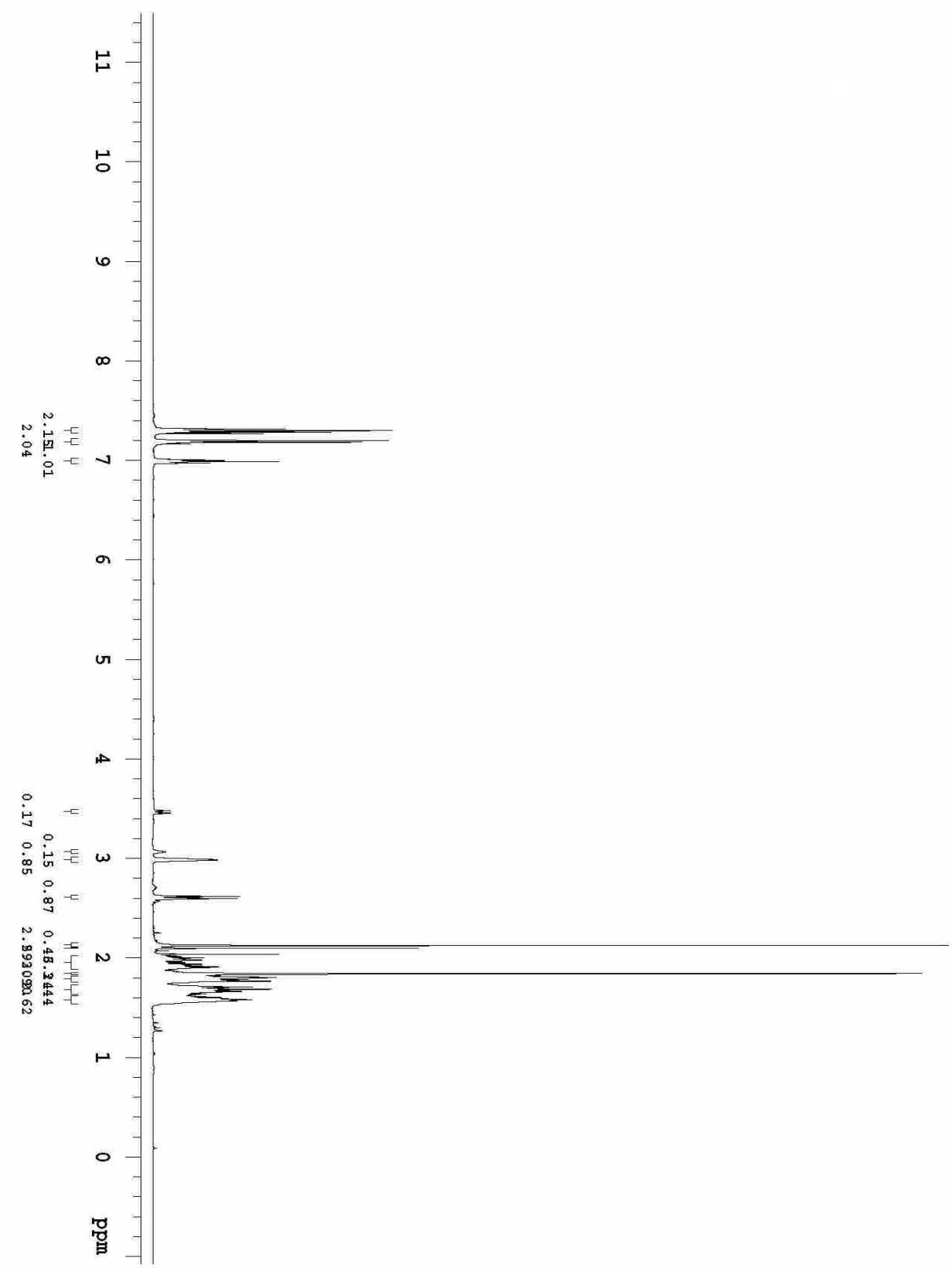
160
140
120
100
80
60
40
20
0 ppm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3444
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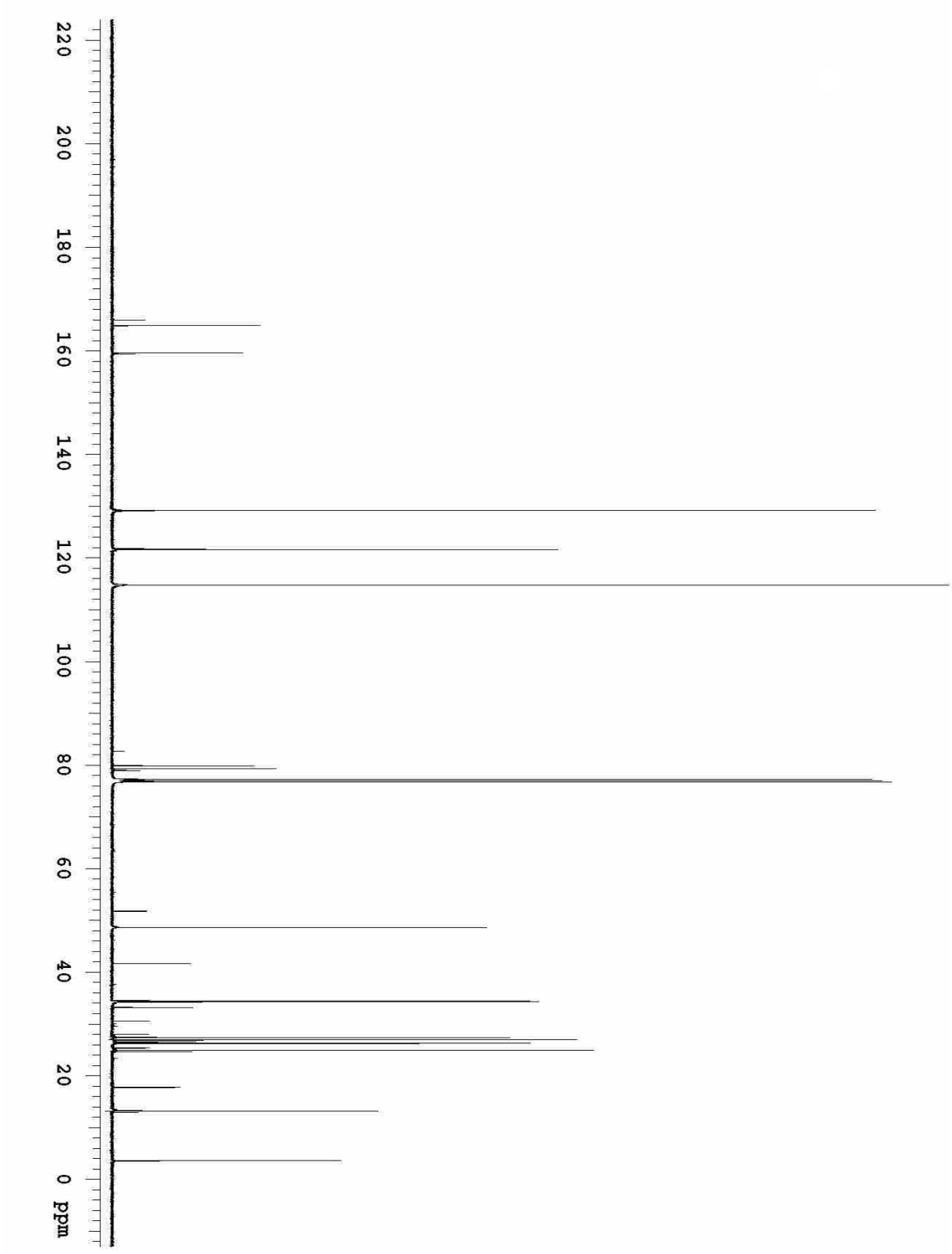
0.85
2.89
2090.62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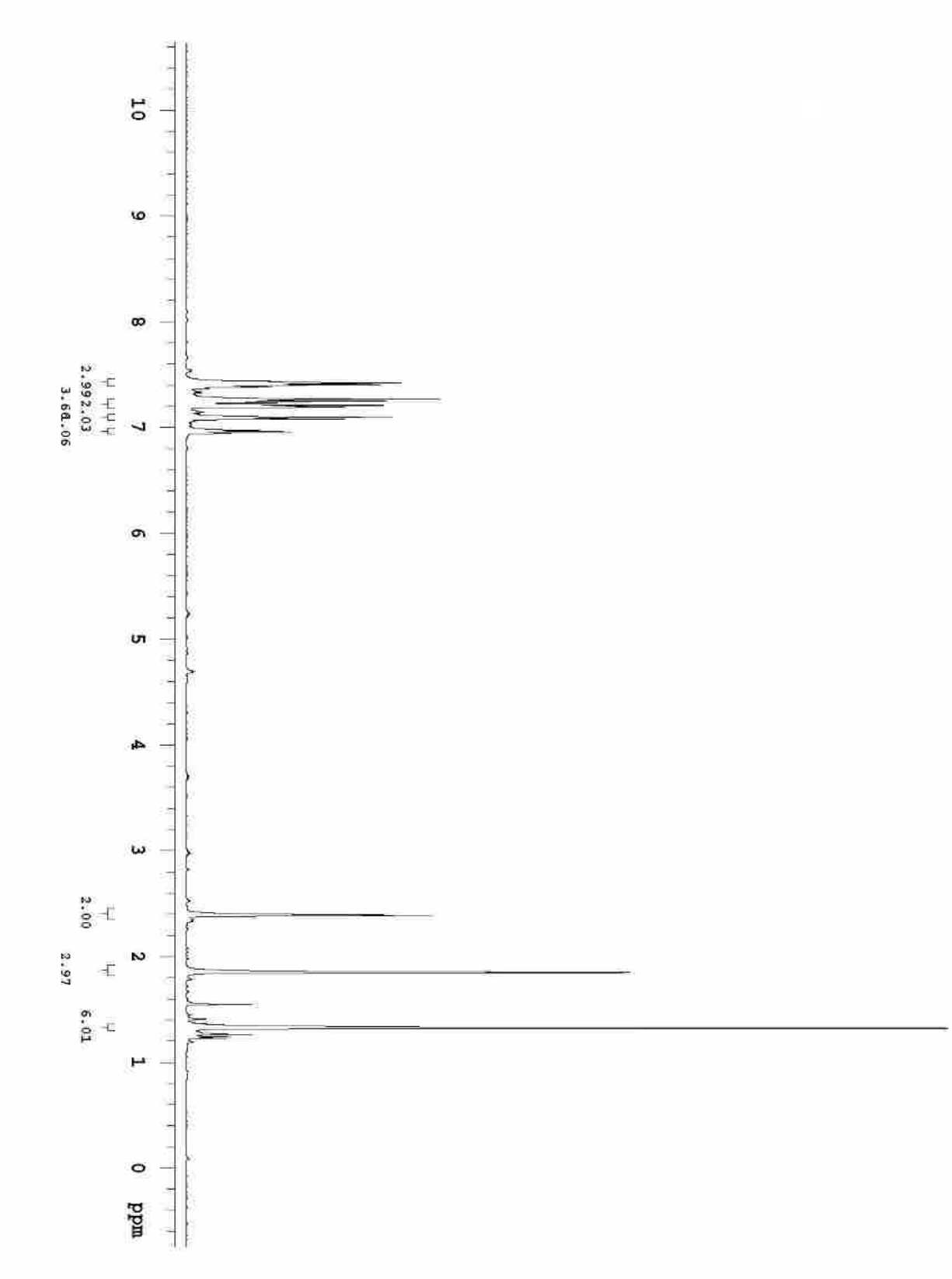
120
100
80
60
40
20
0 ppm


10
9
8
7
6
5
4
3
2
1
0
ppm
2.99
2.03
3.68
2.00
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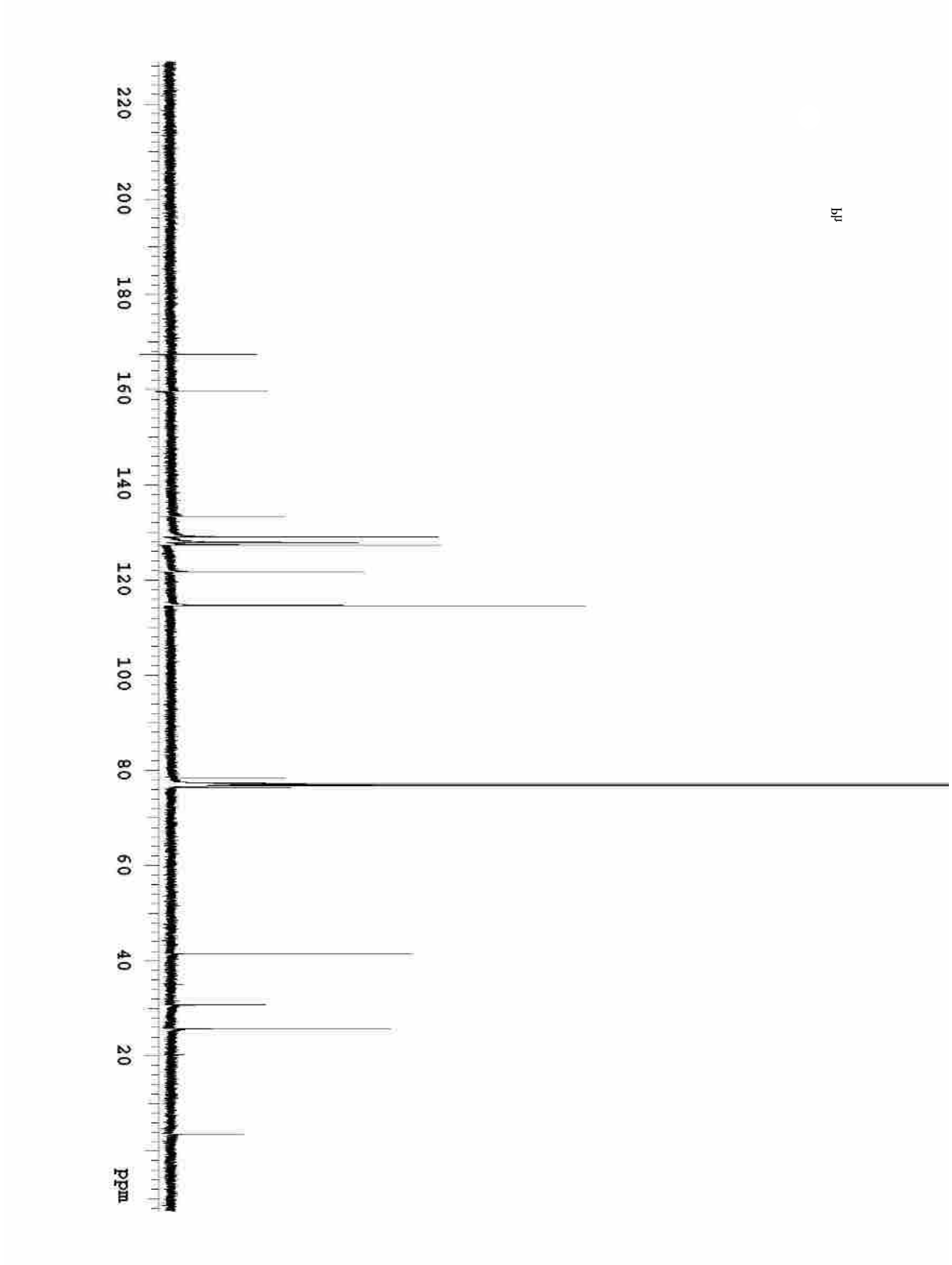
6.01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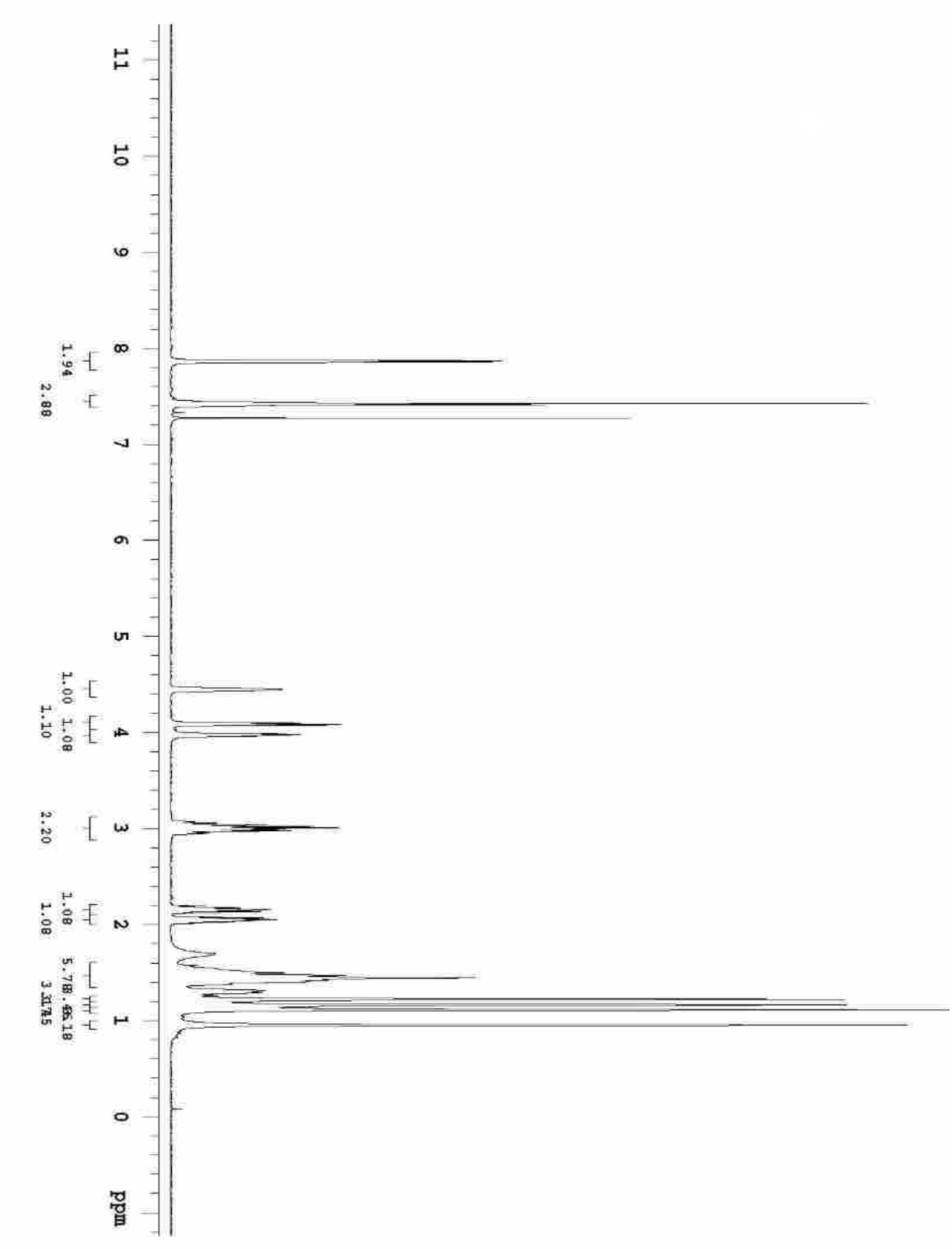
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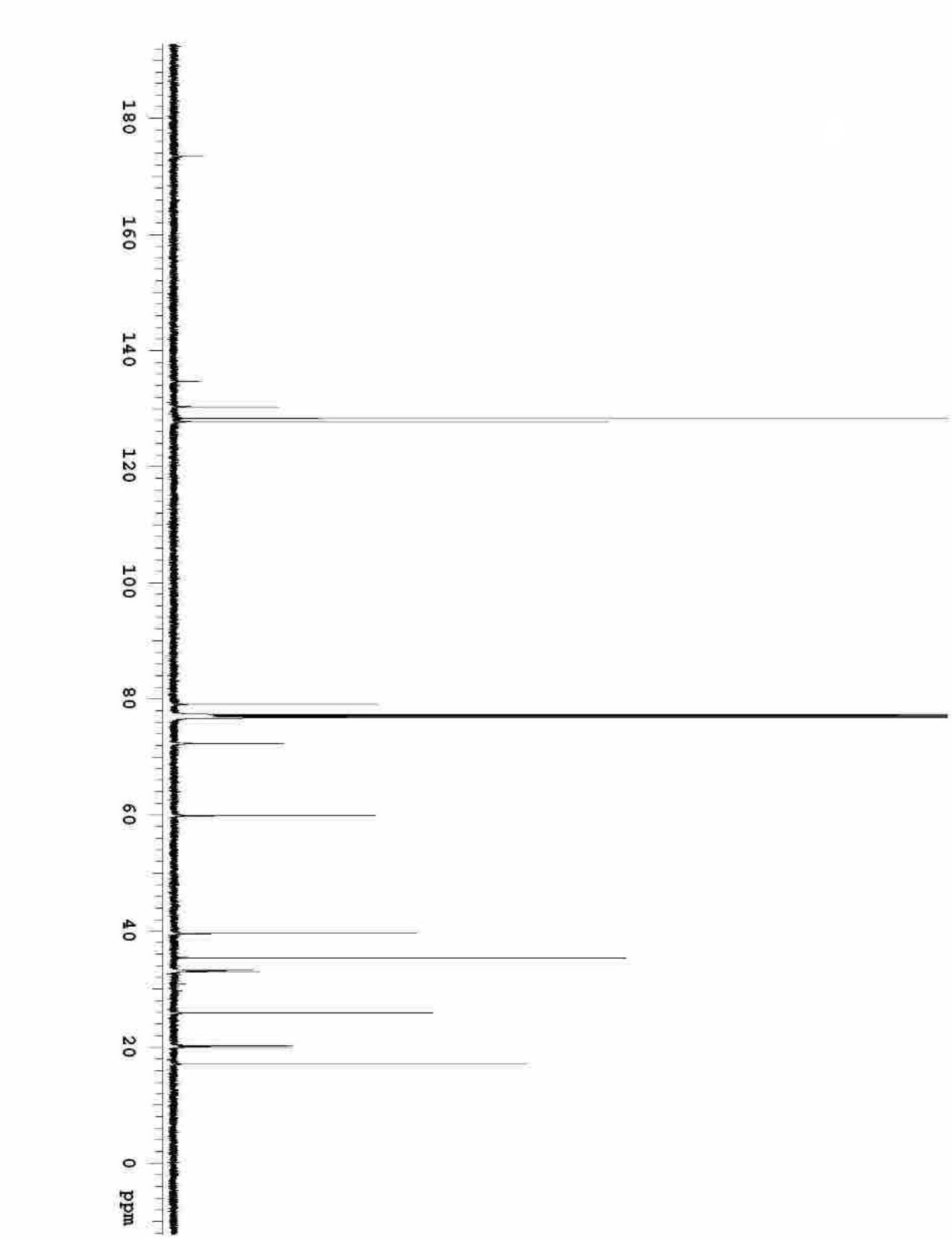
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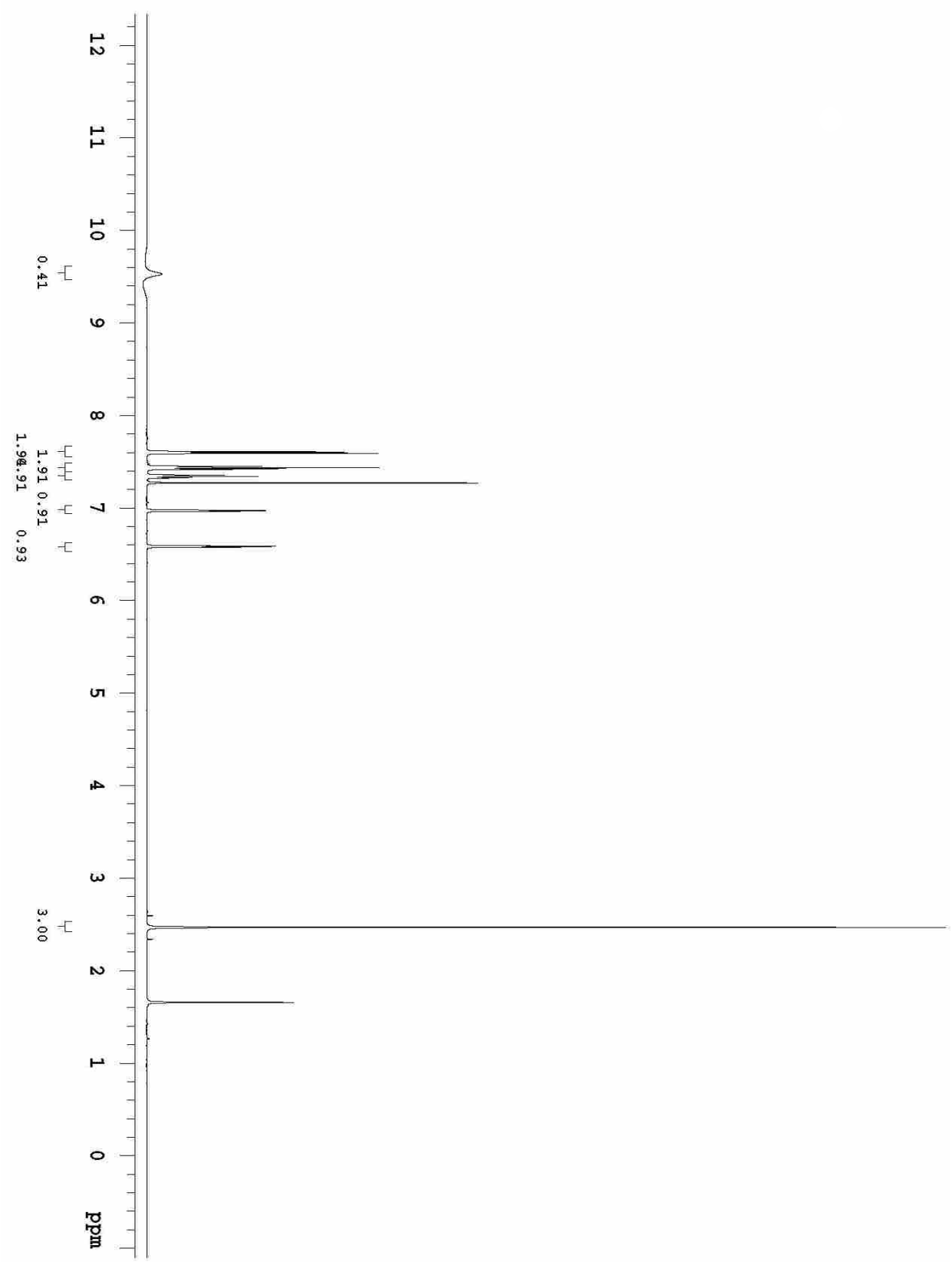
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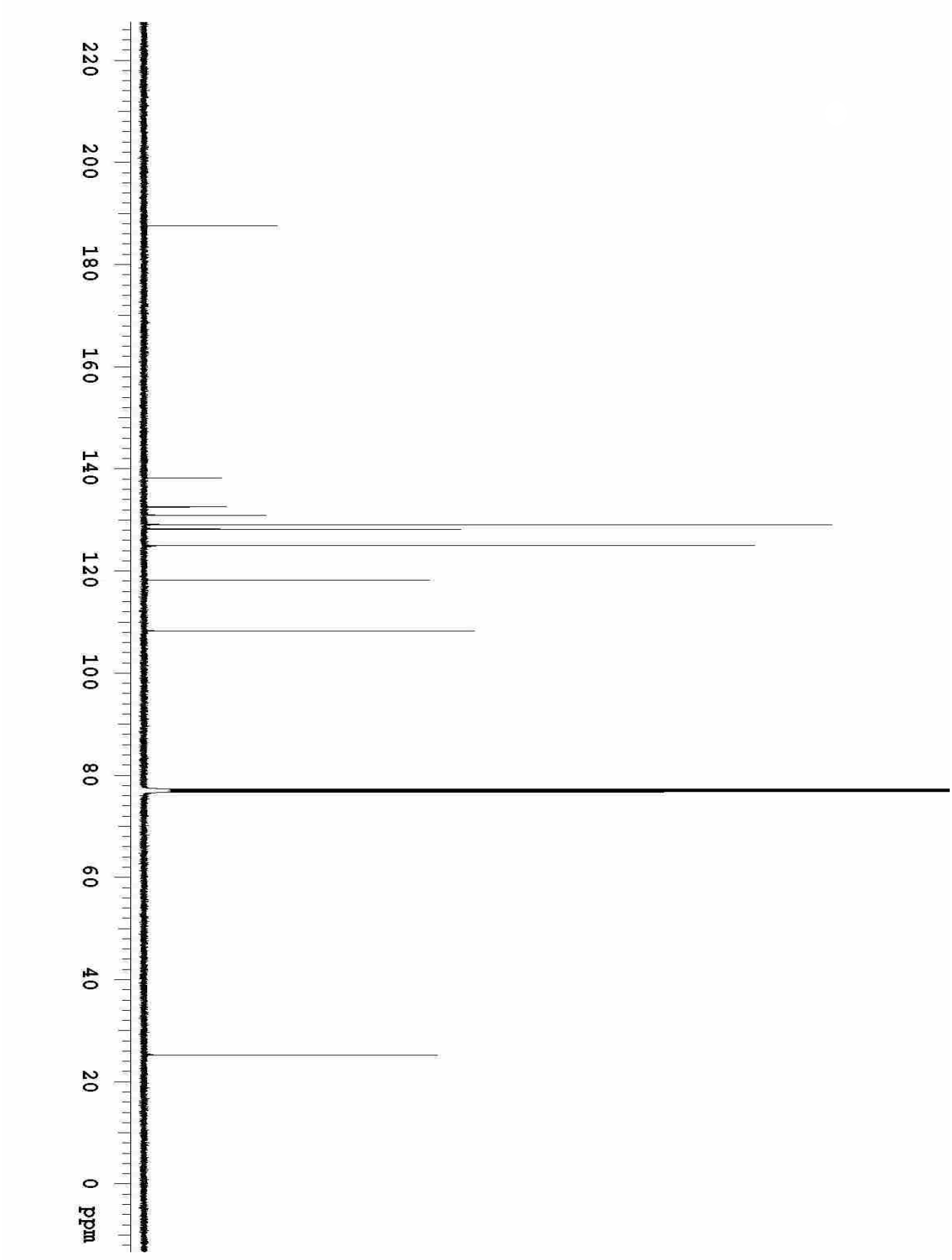
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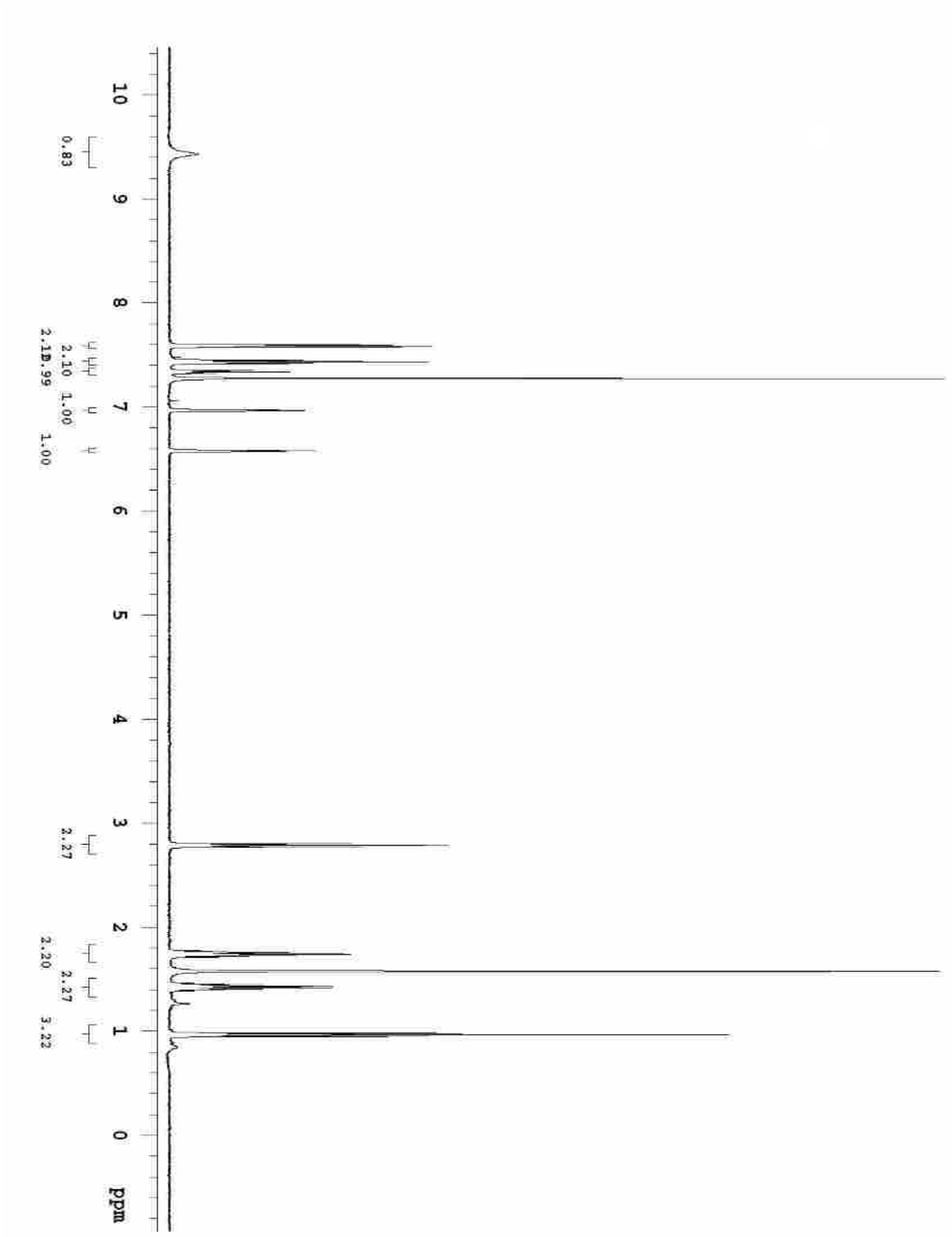
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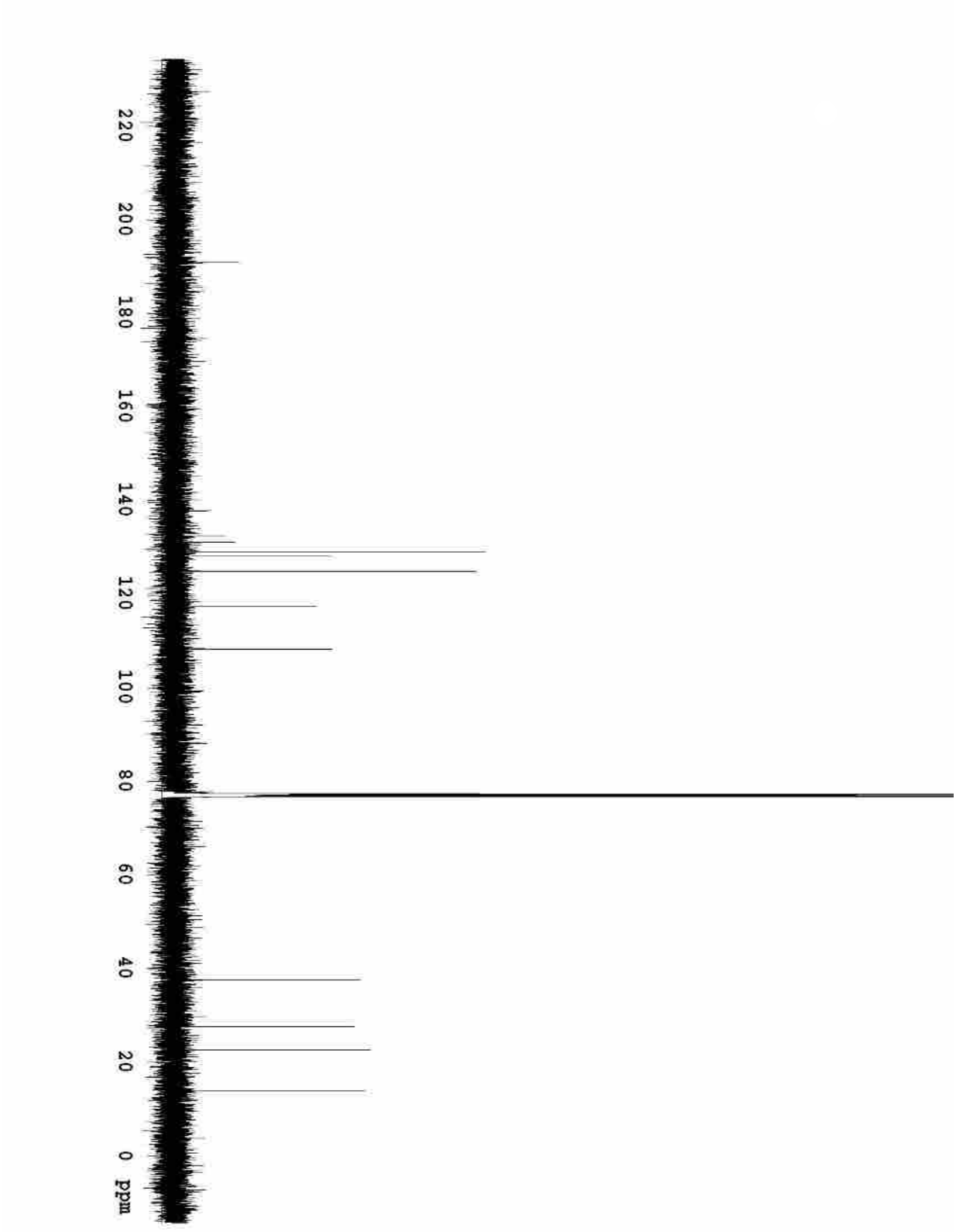
1.00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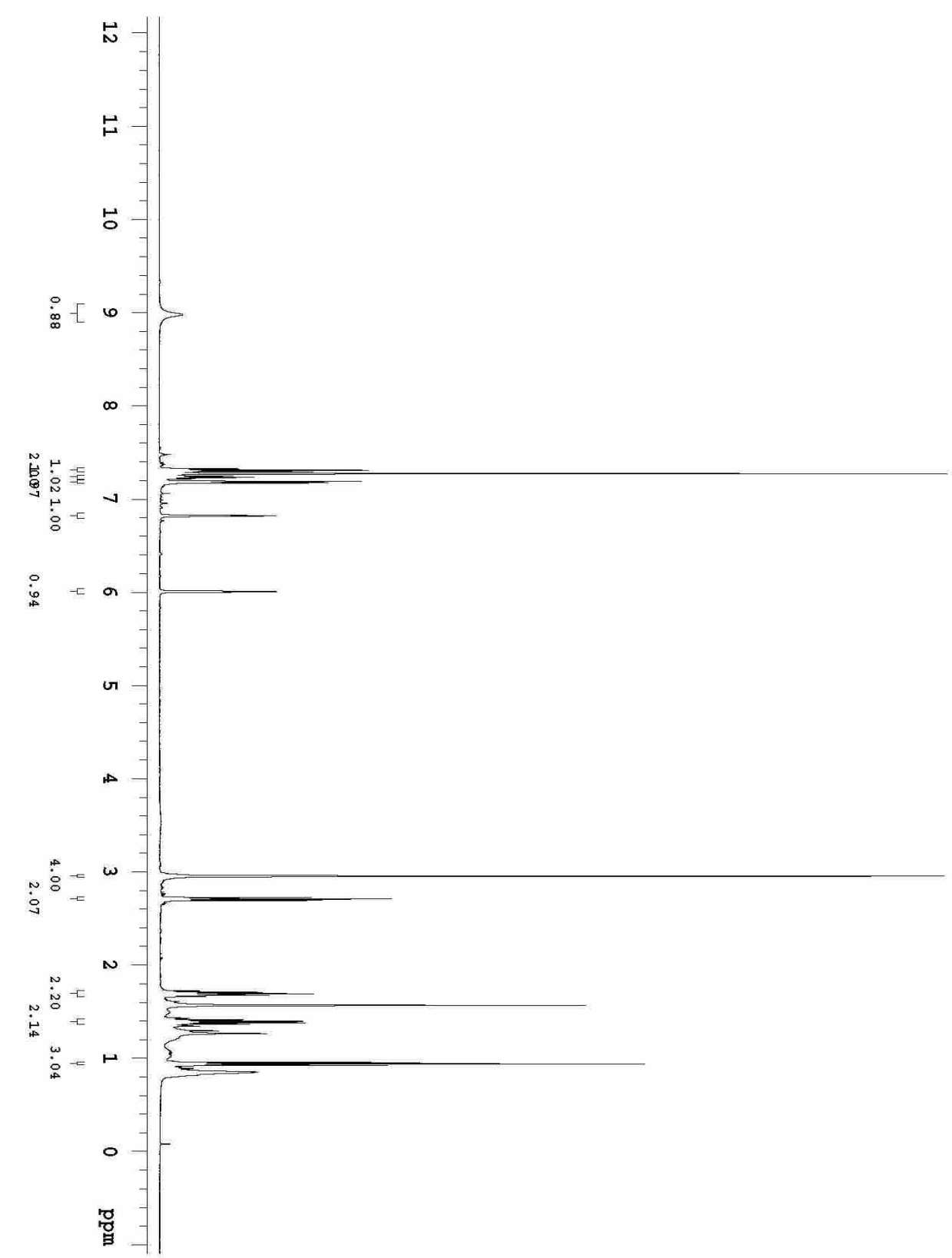
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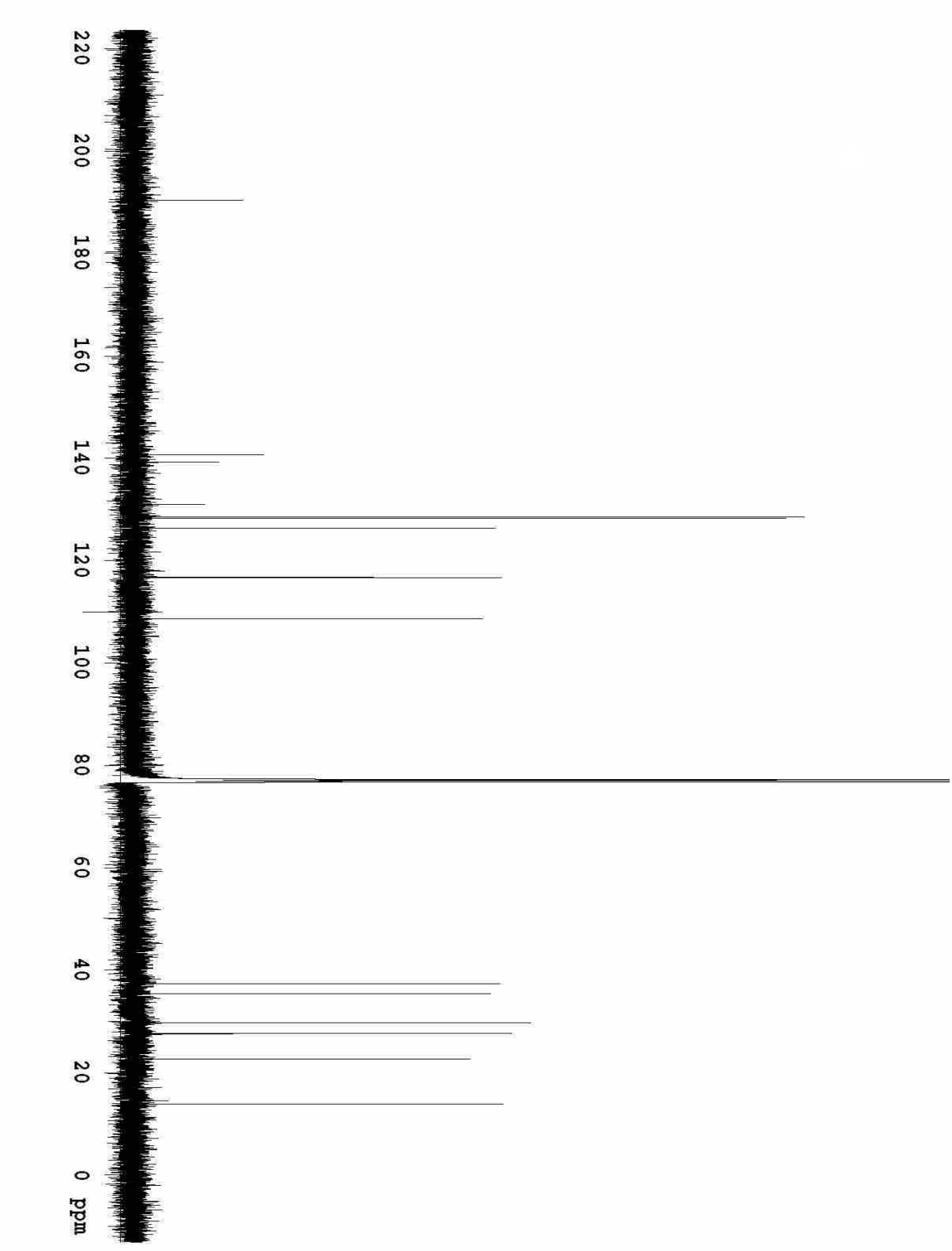
2.14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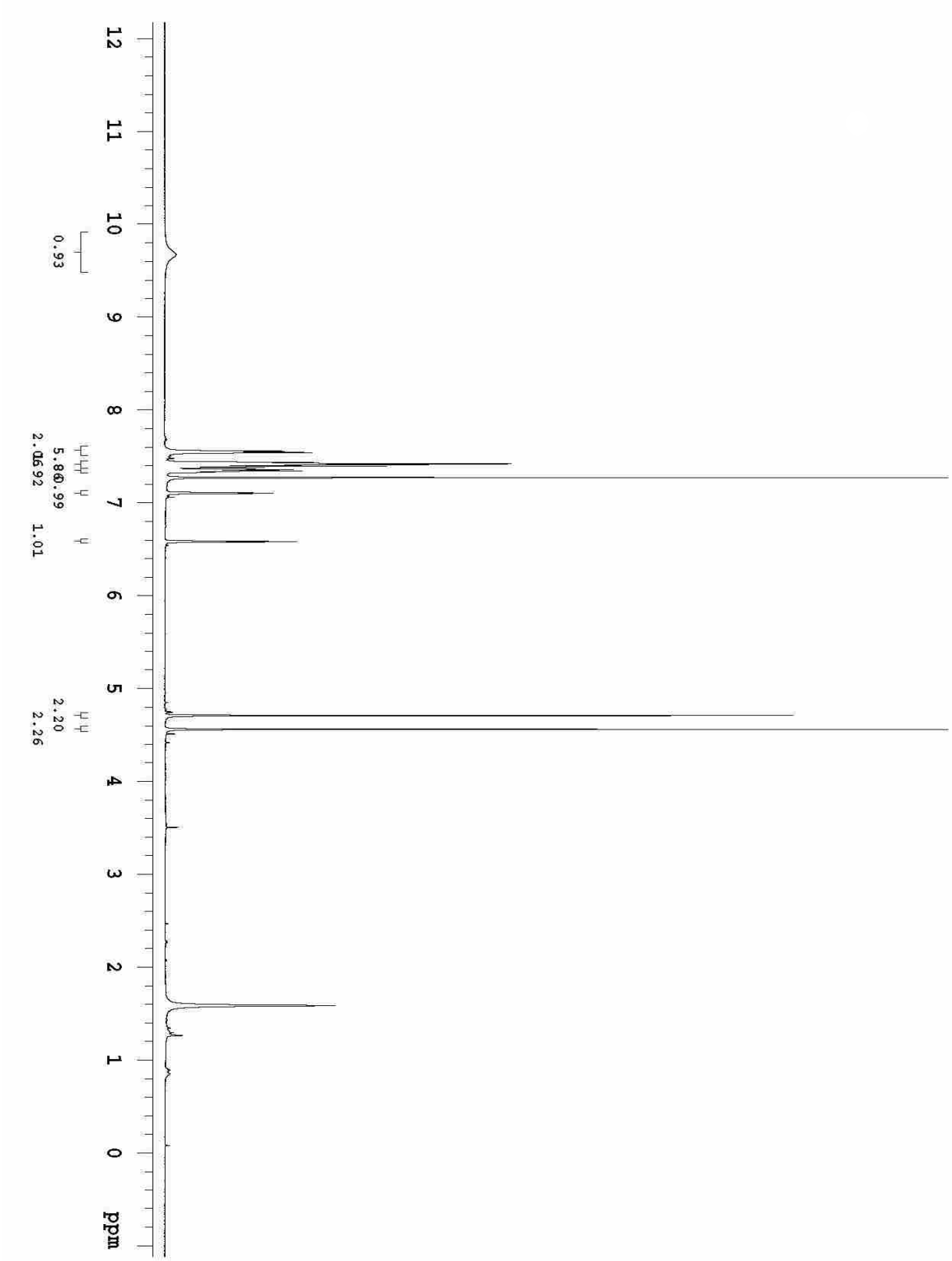
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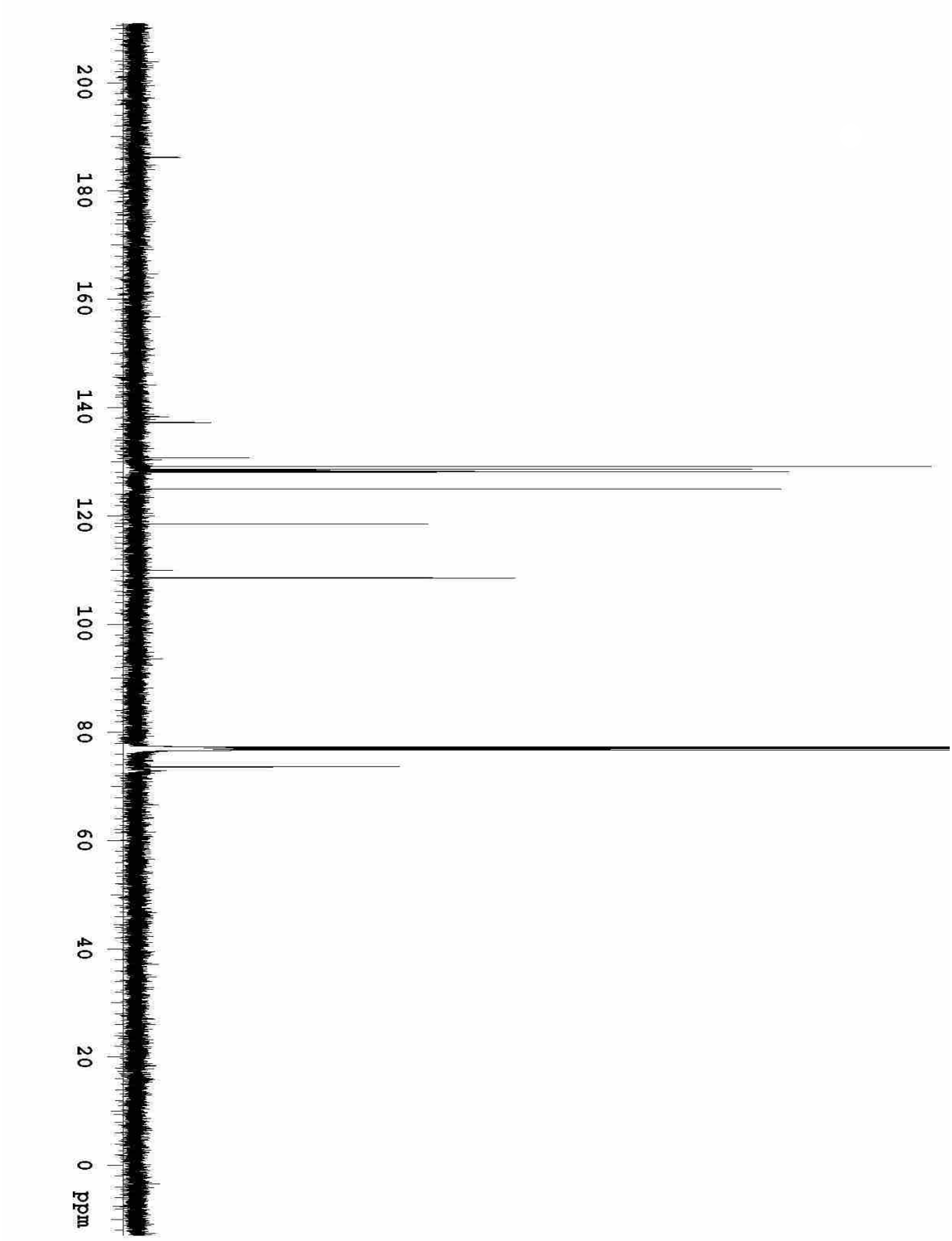
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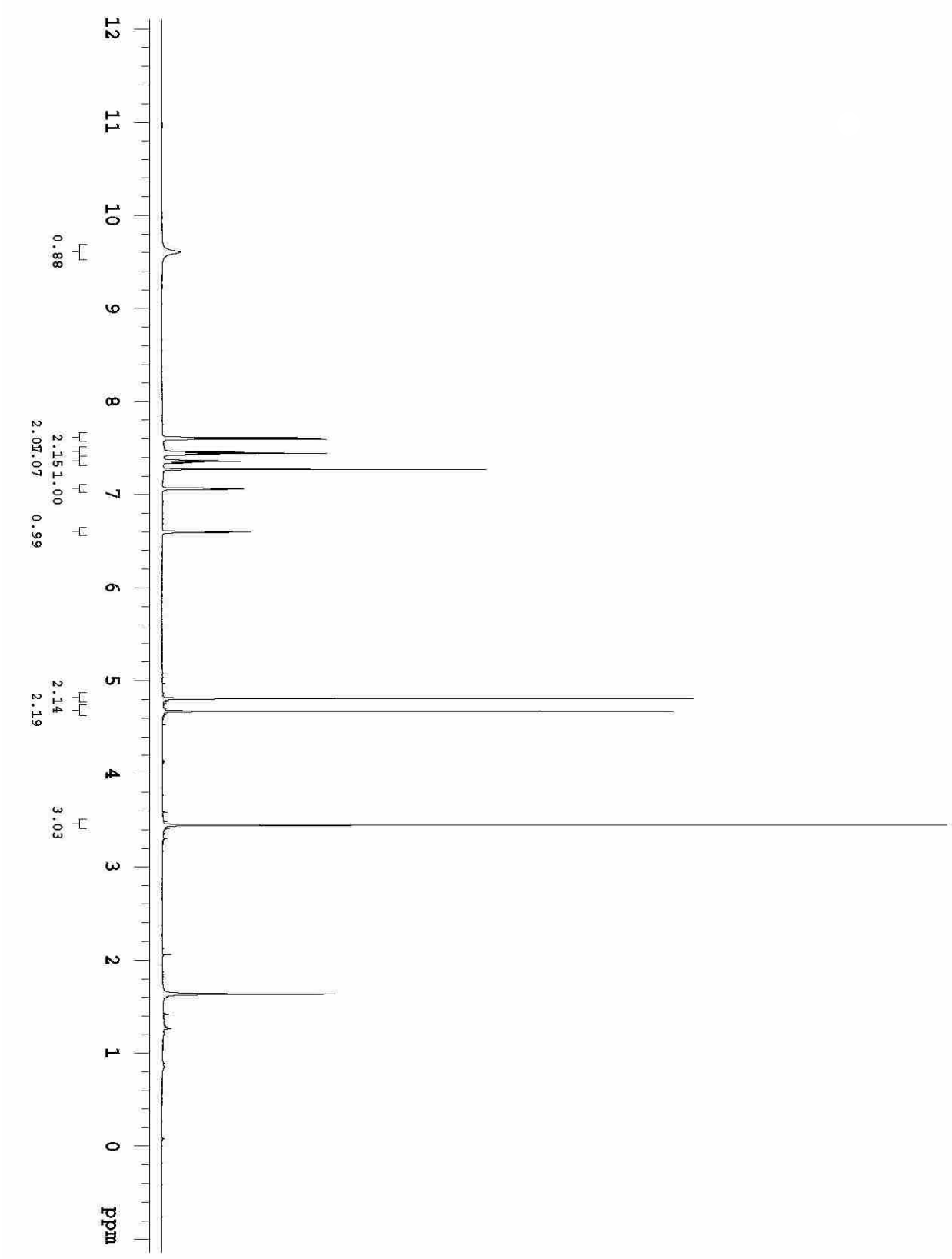
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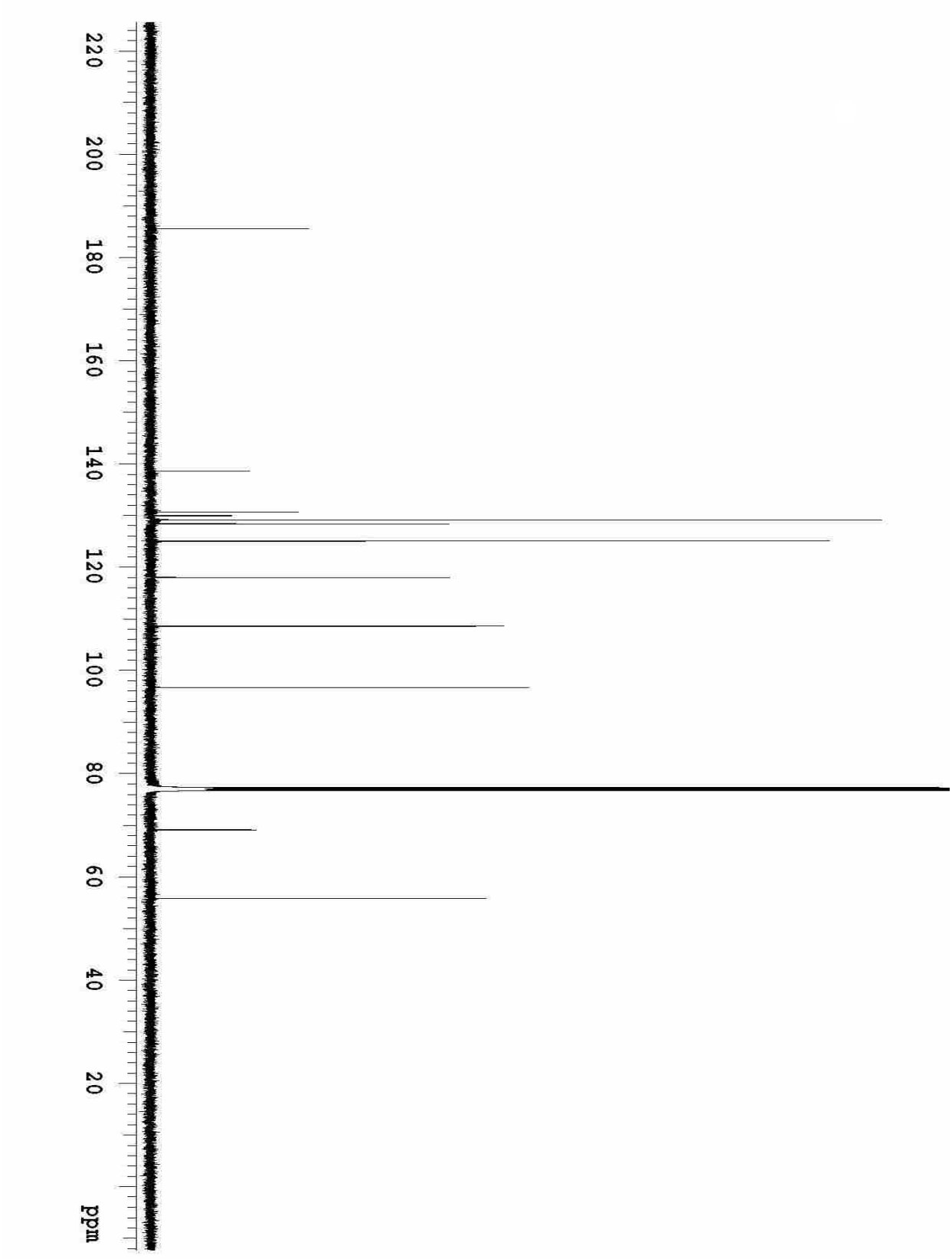
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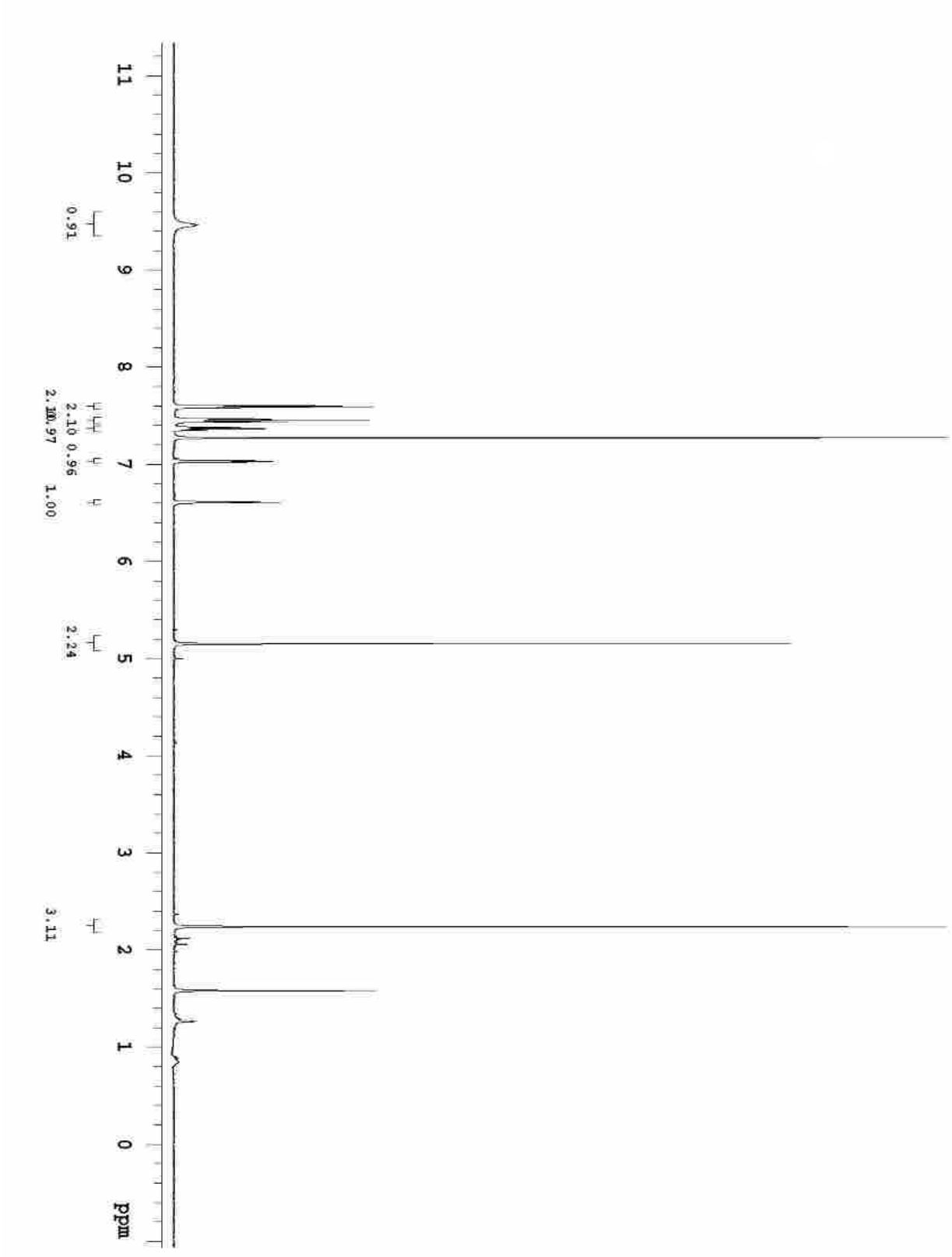
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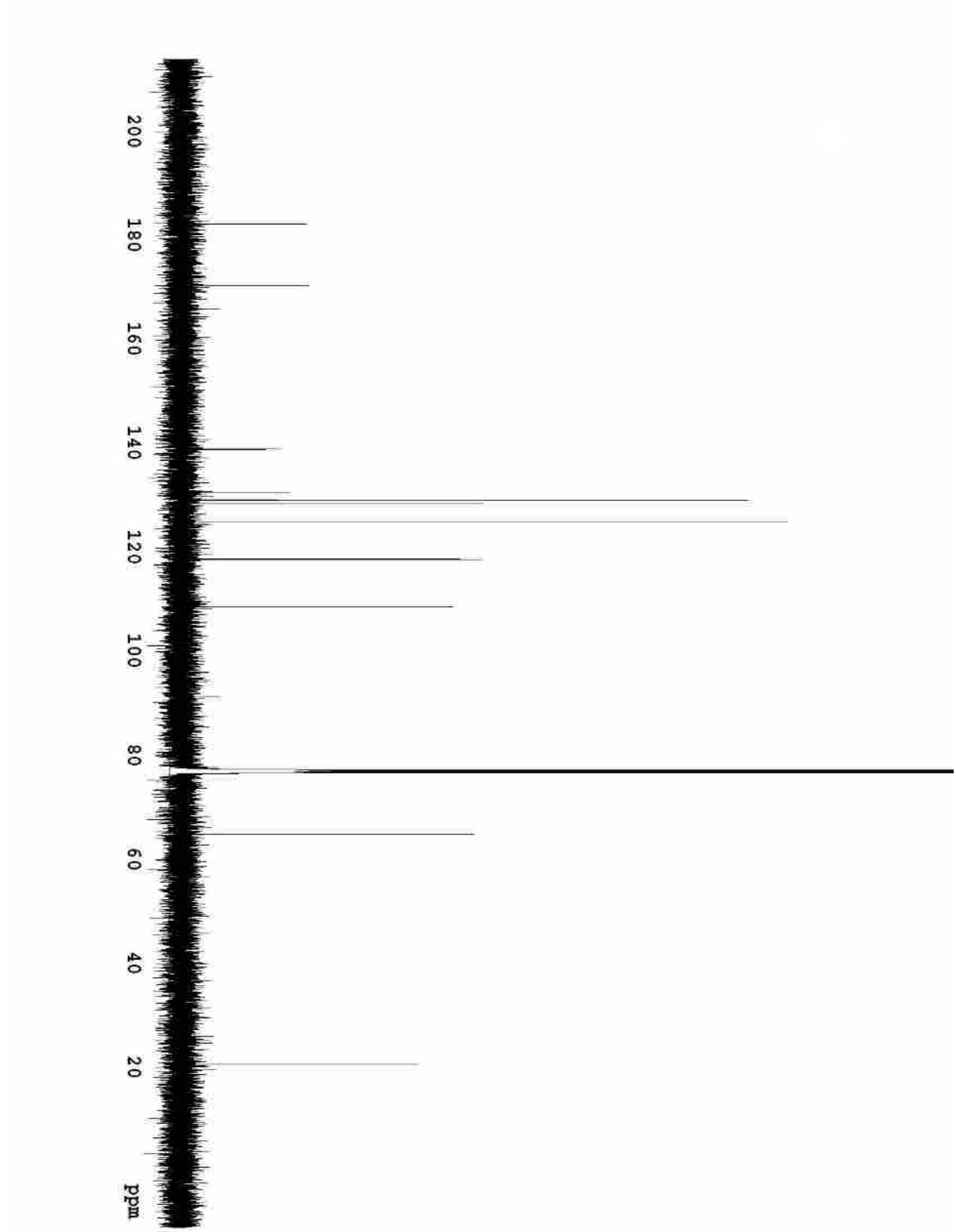
3.11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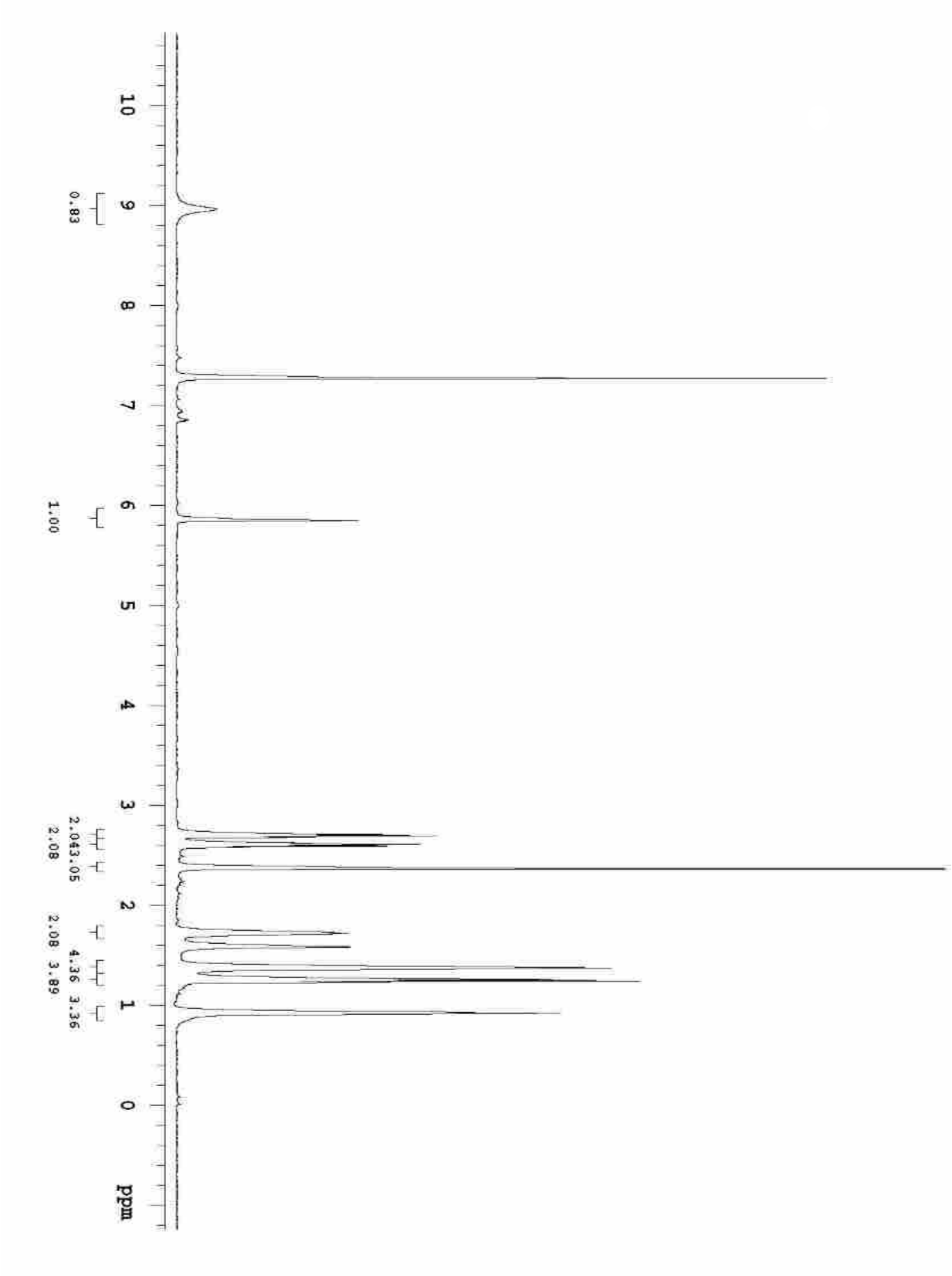
ppm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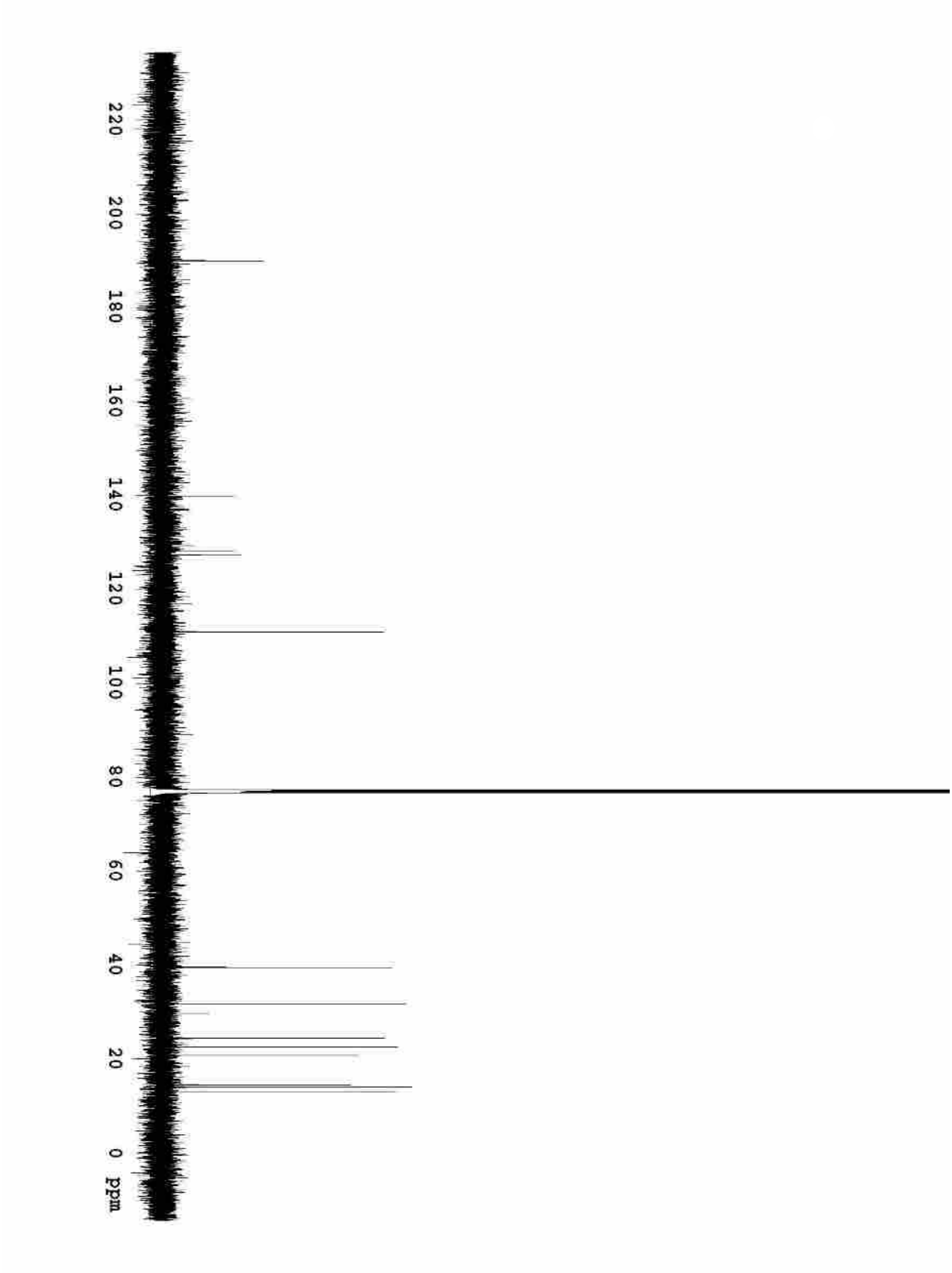
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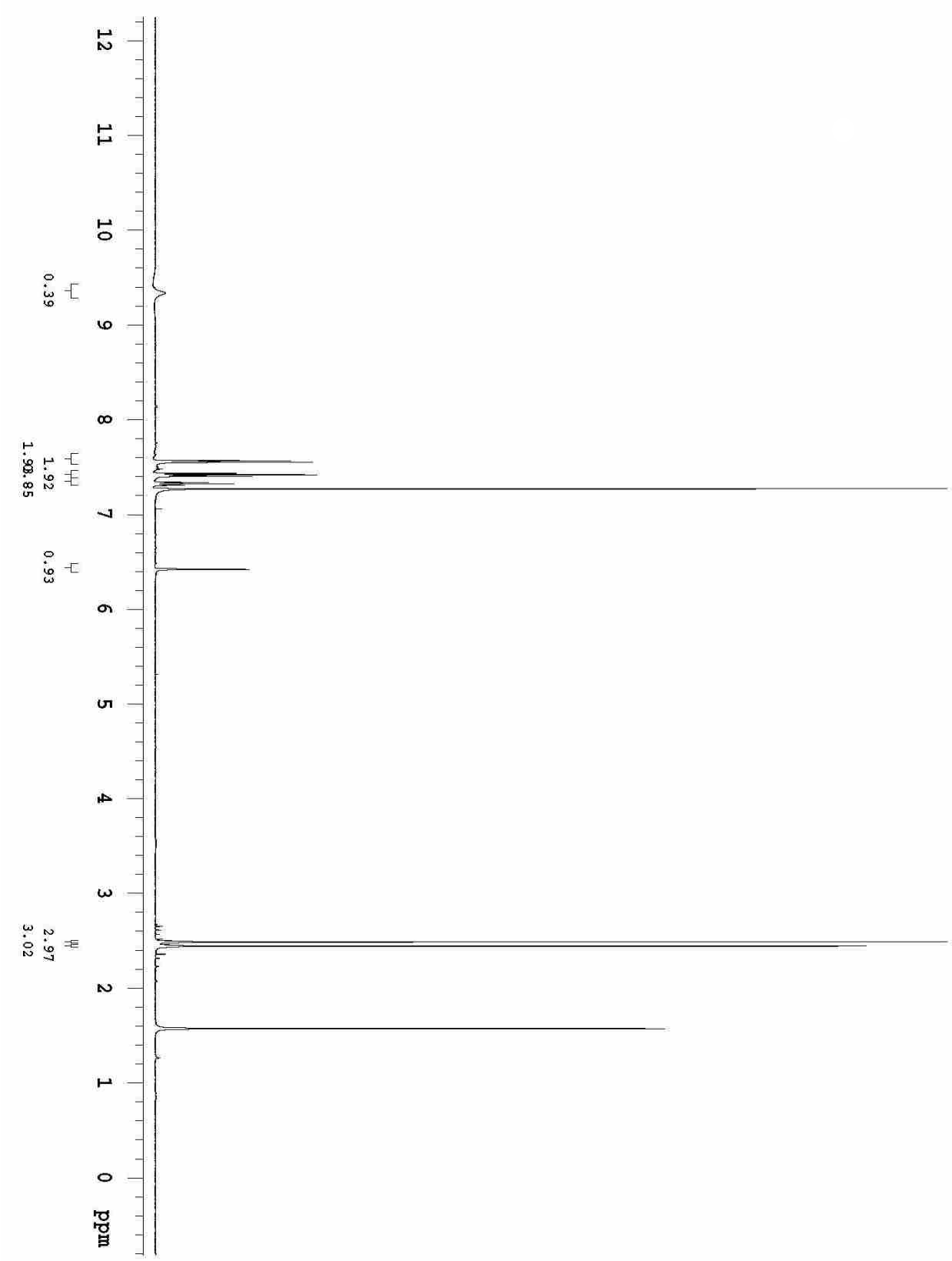
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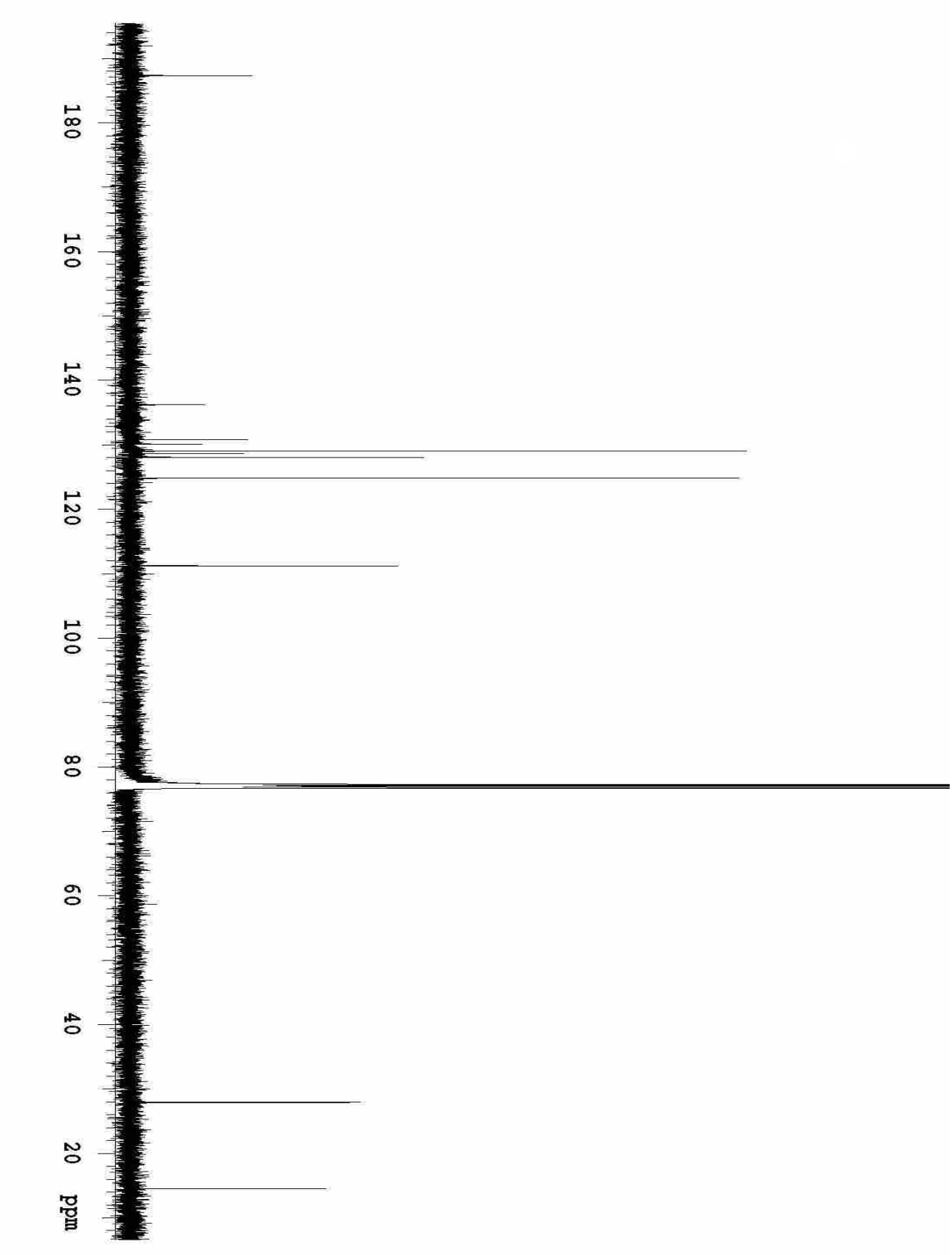
3.02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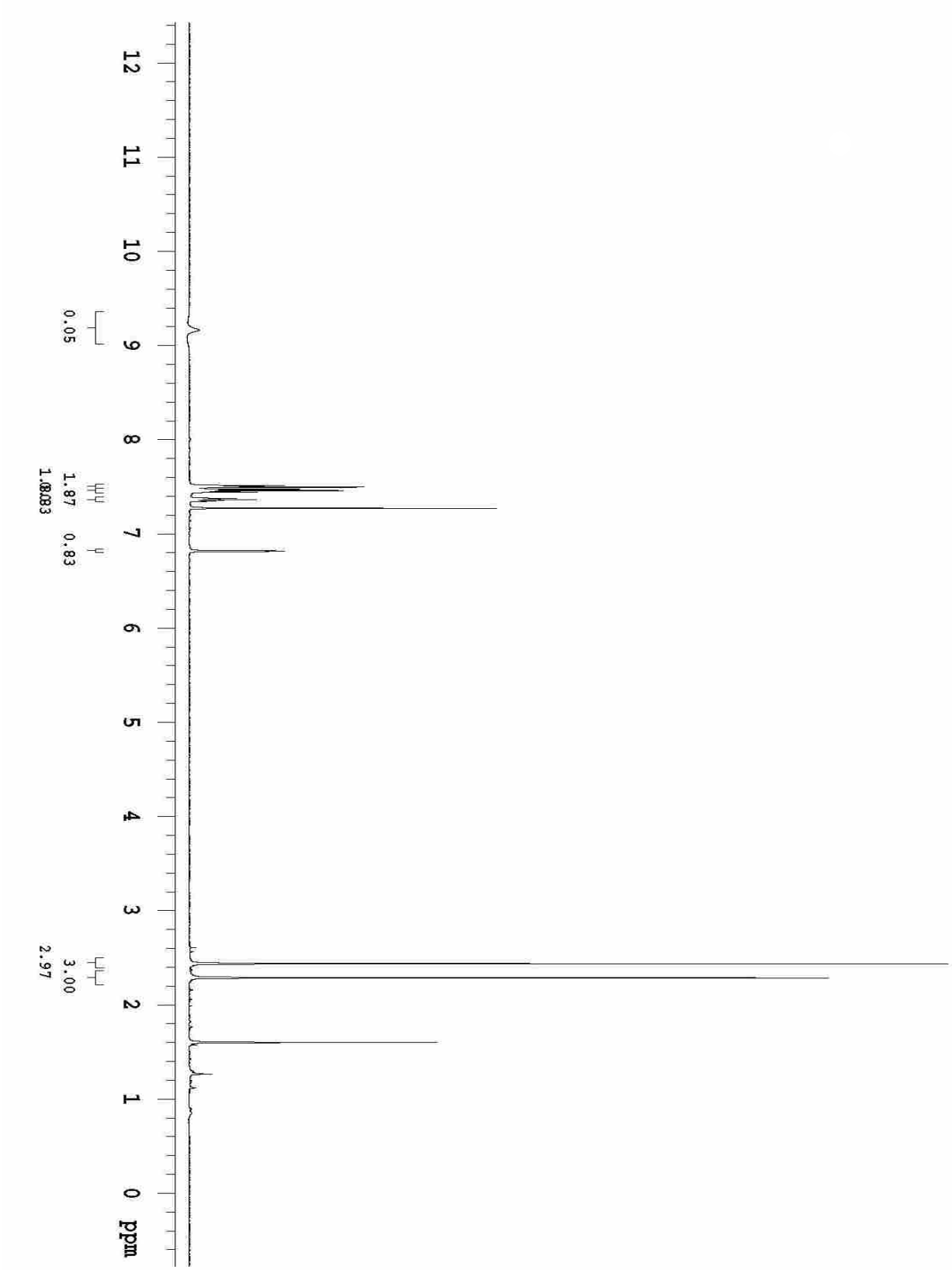
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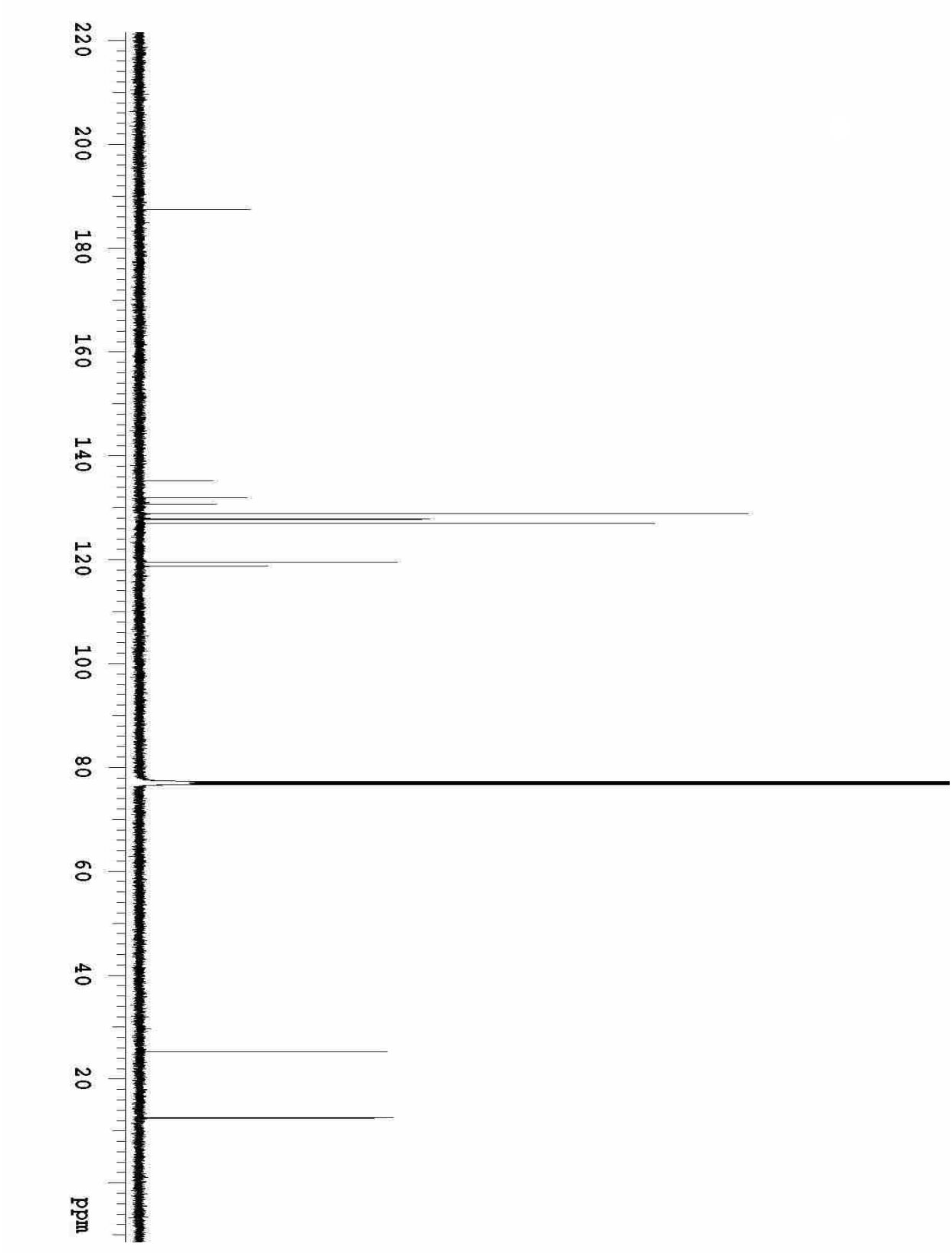
2.97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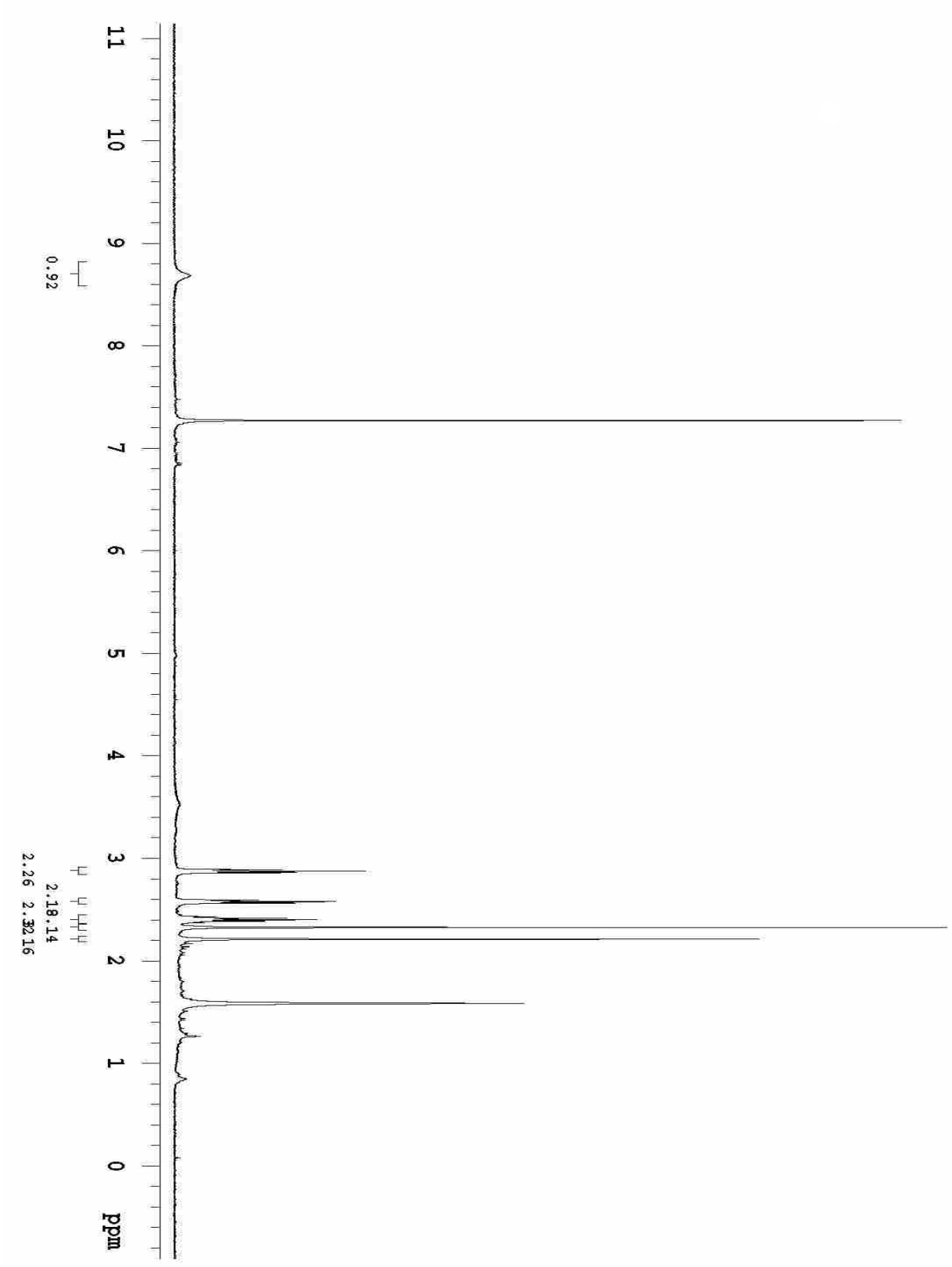
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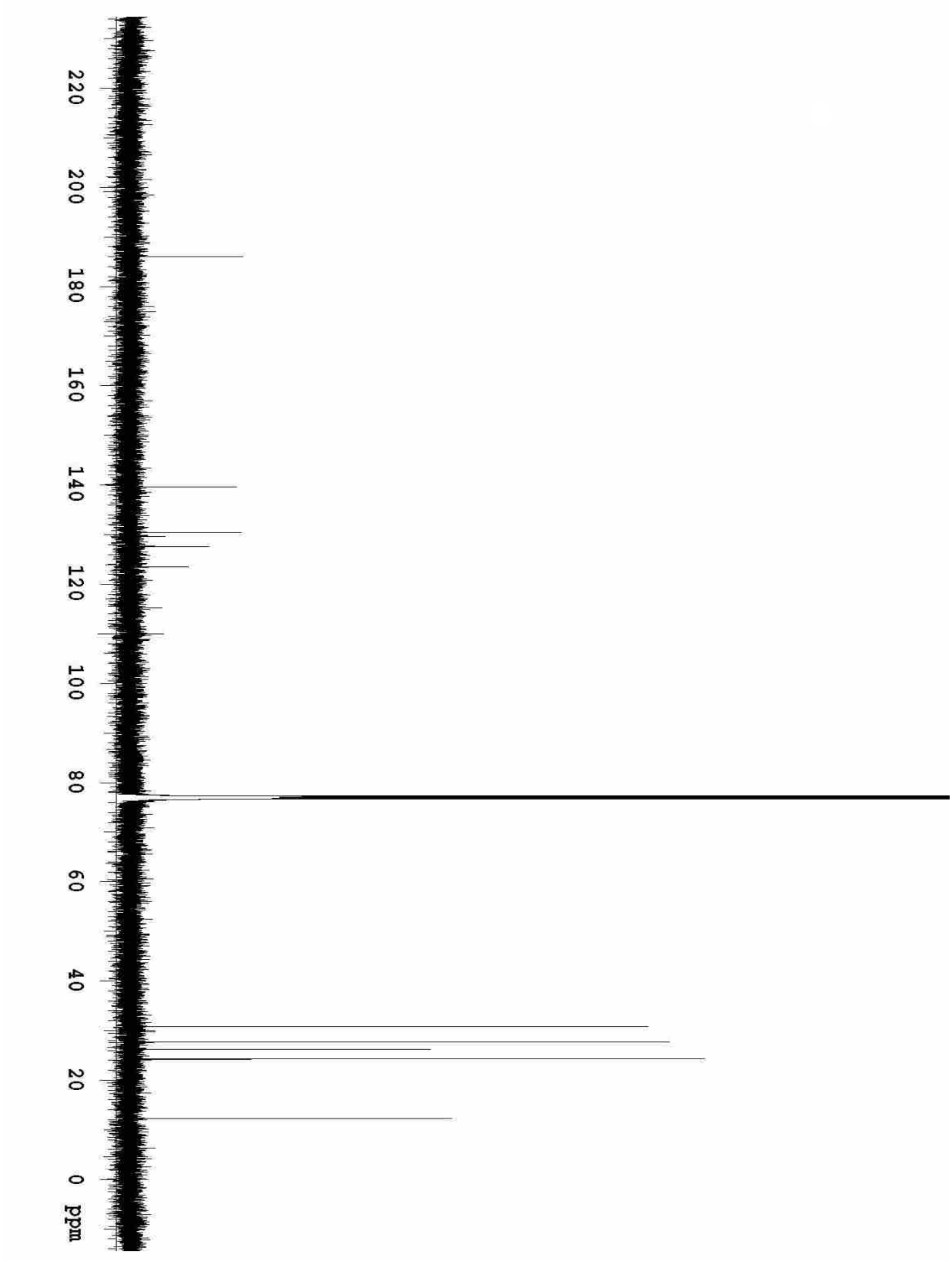
16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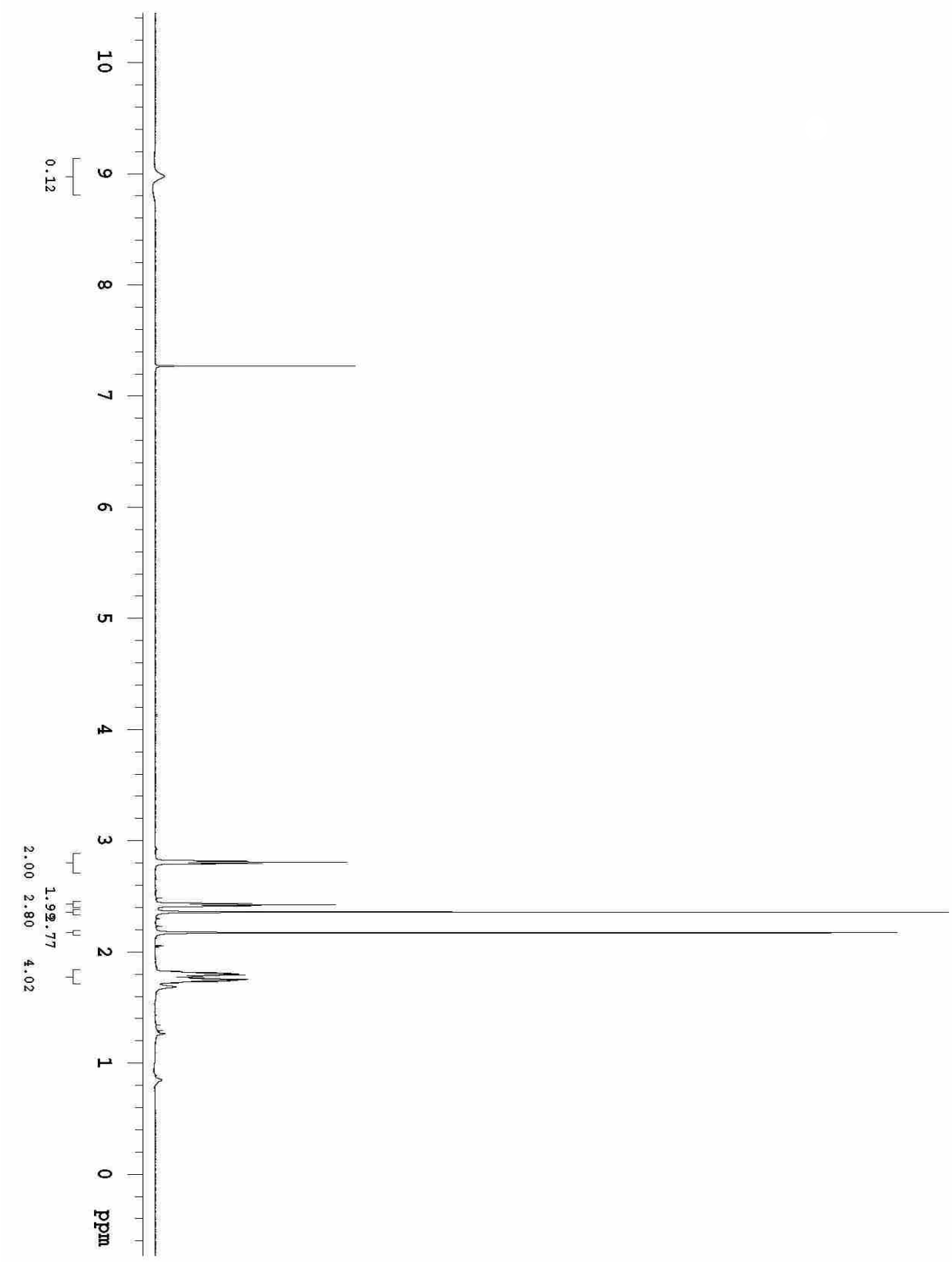
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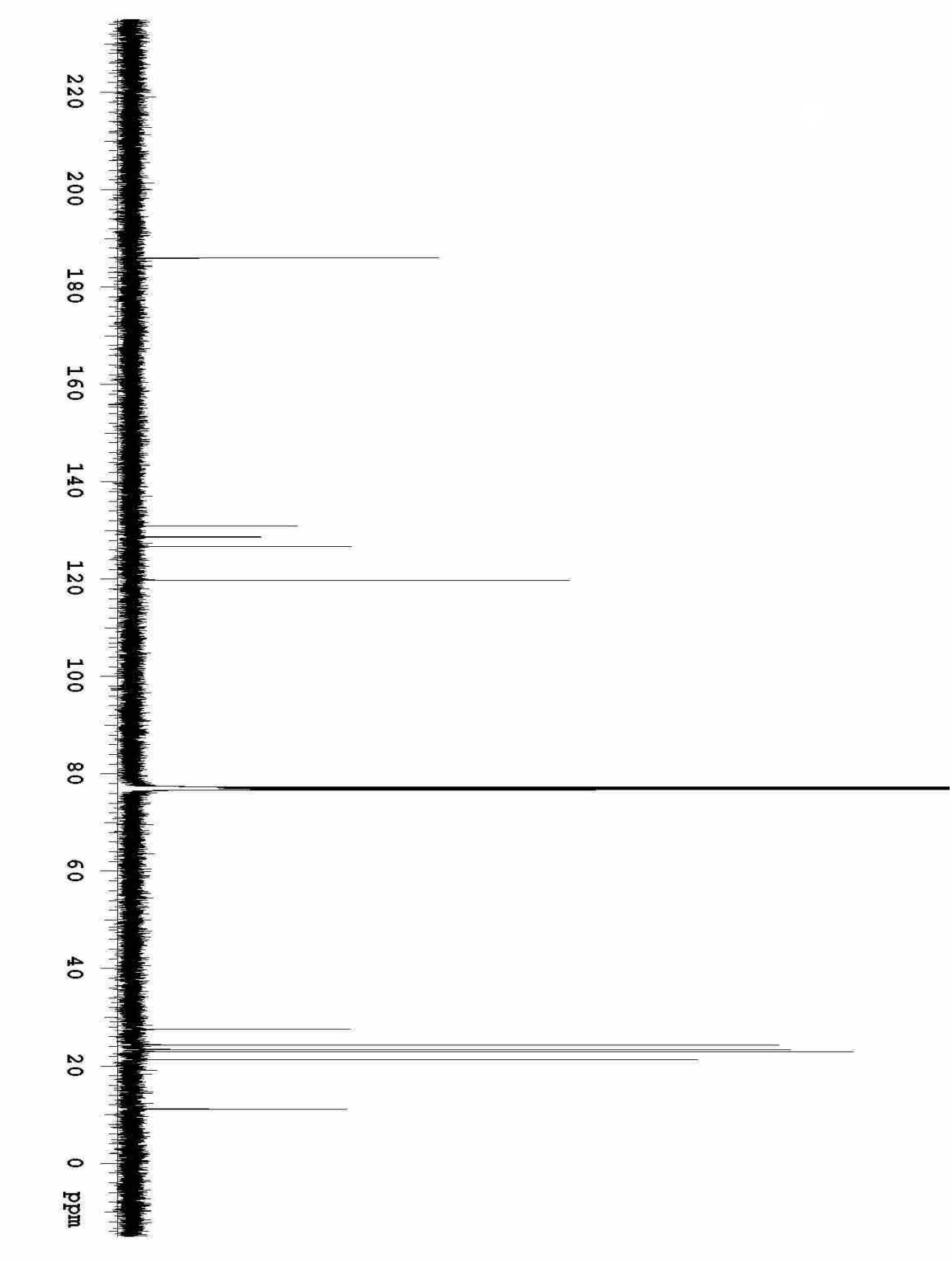
4.02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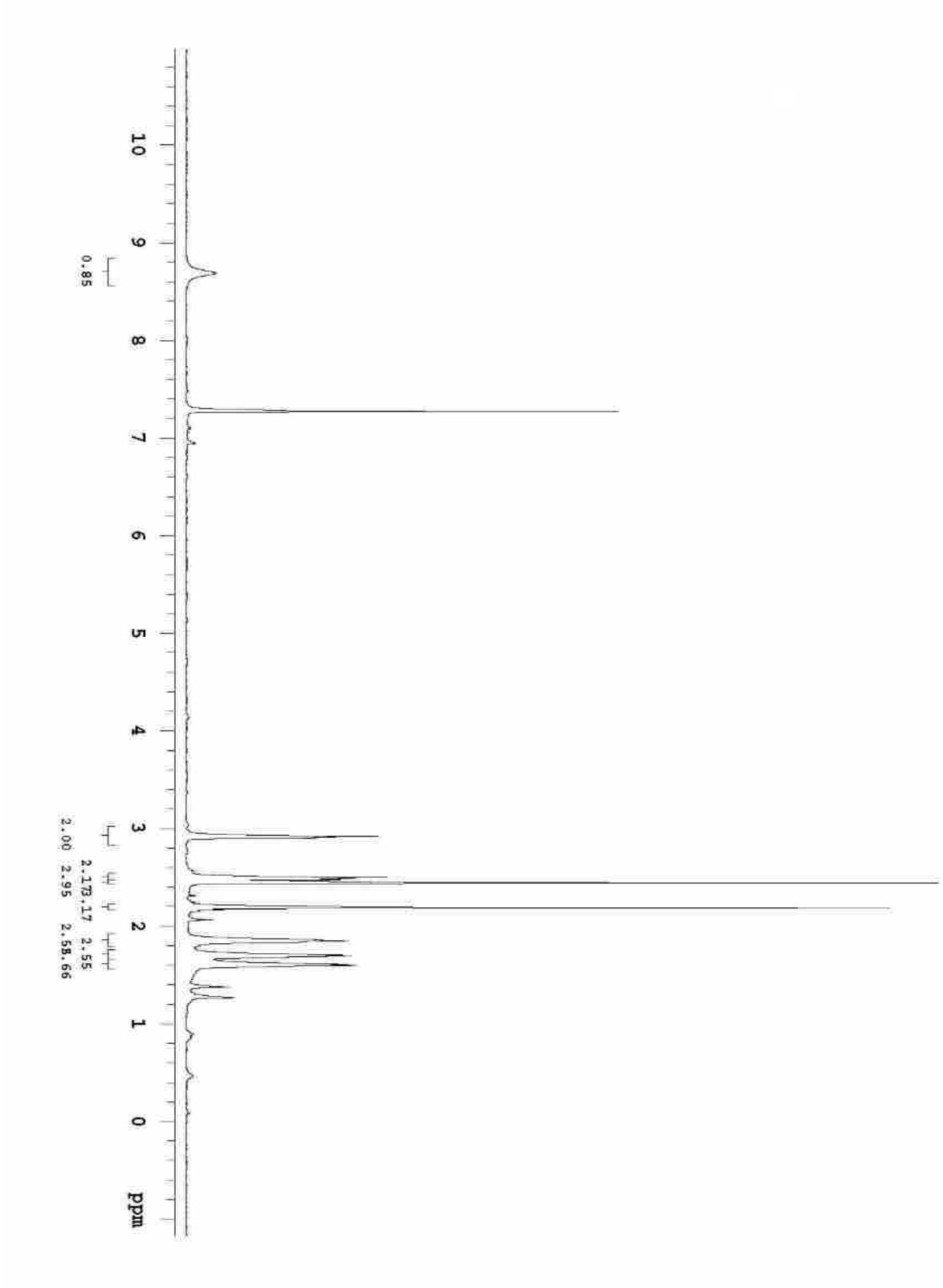
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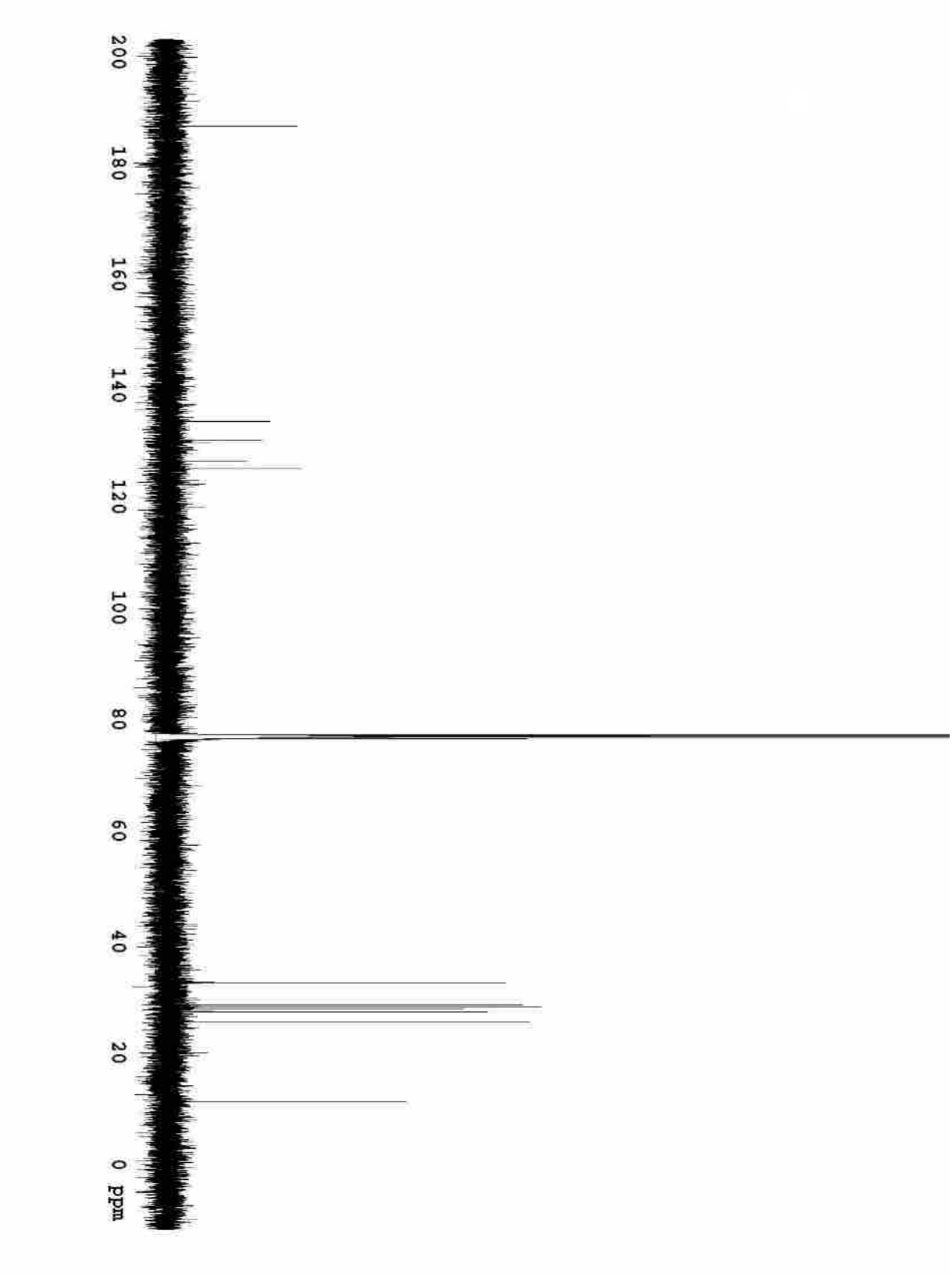
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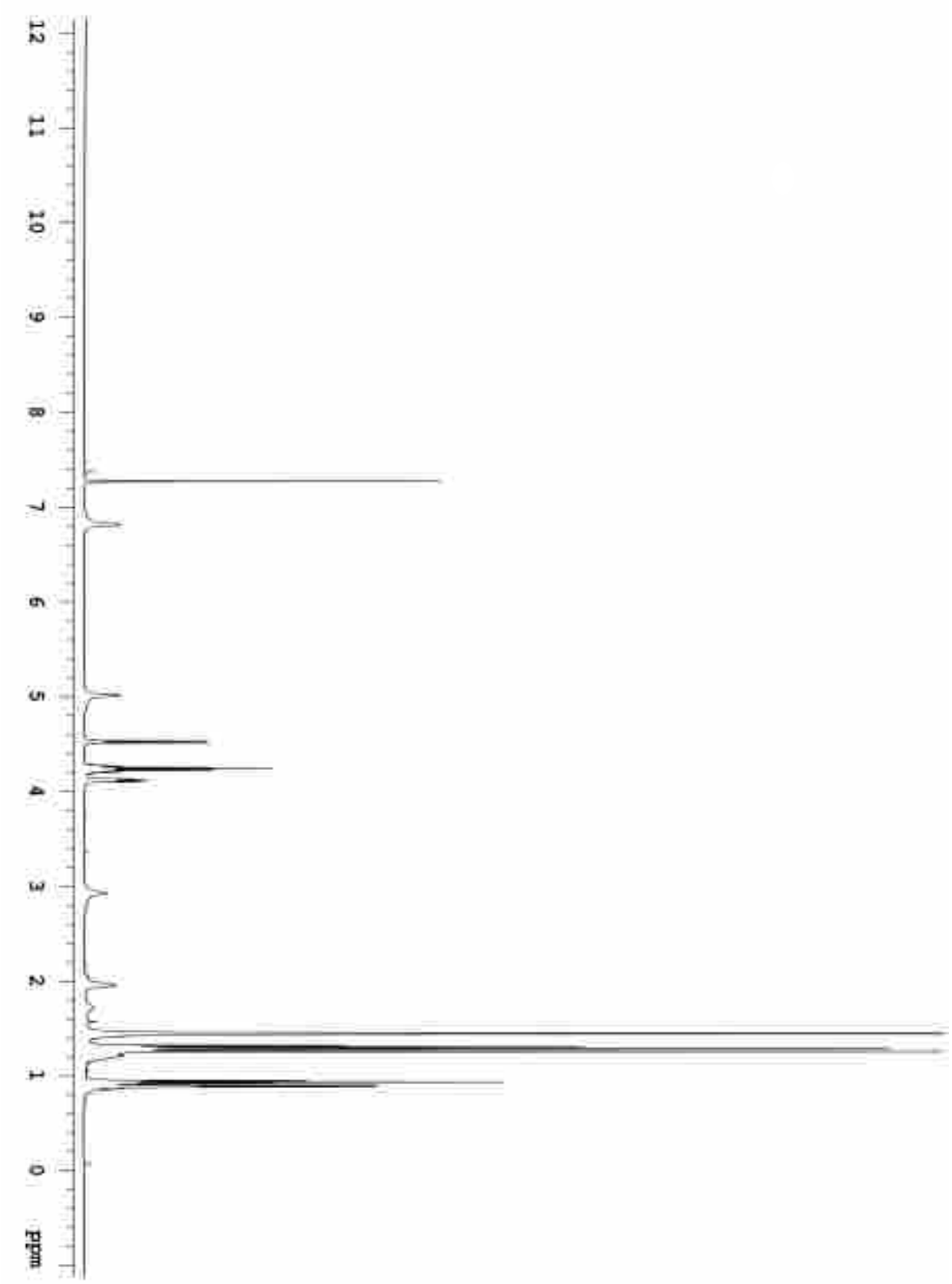
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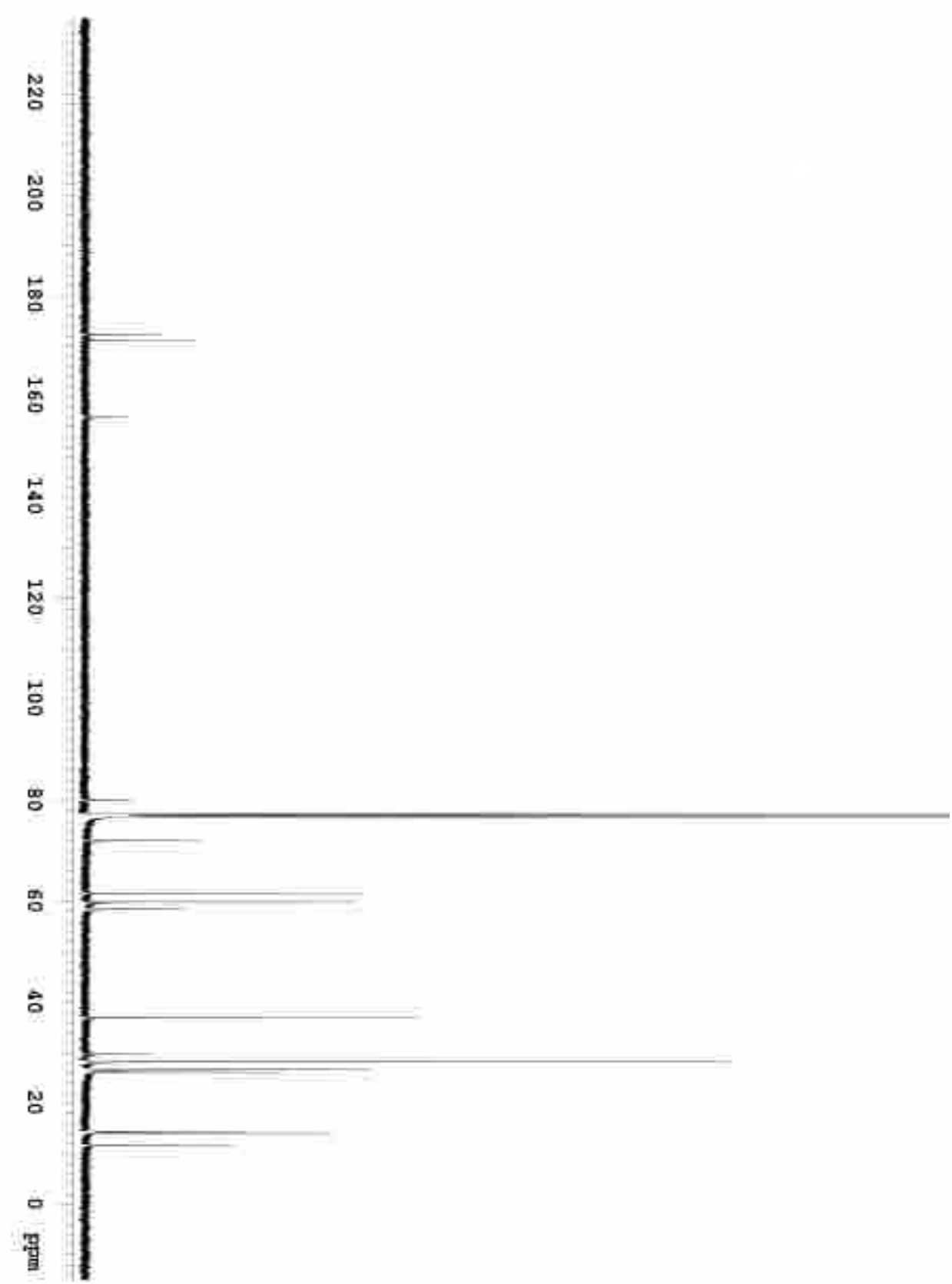
ppm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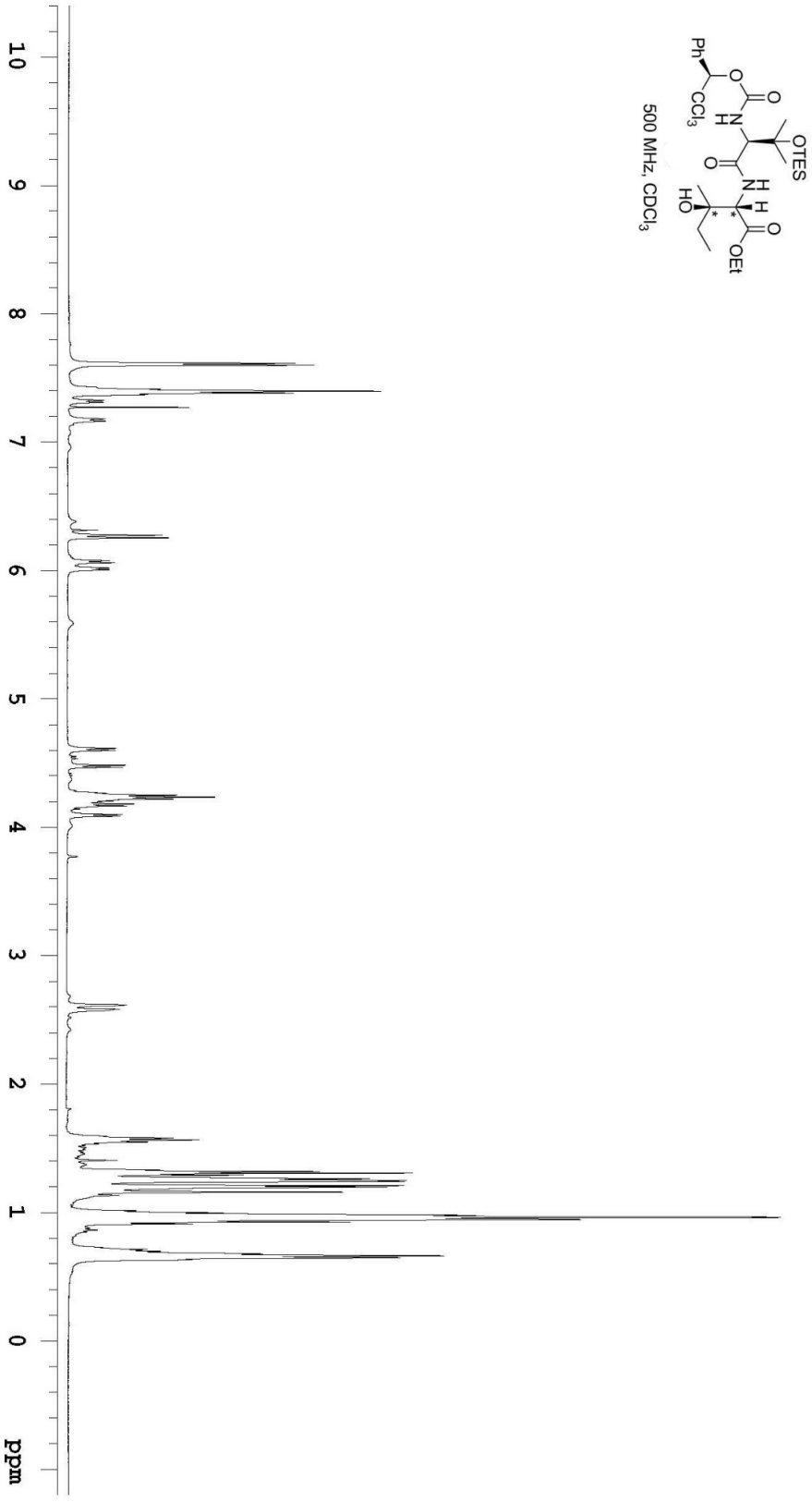
500 MHz, CDCl3
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CCl3
OTES
OEt
HO
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2
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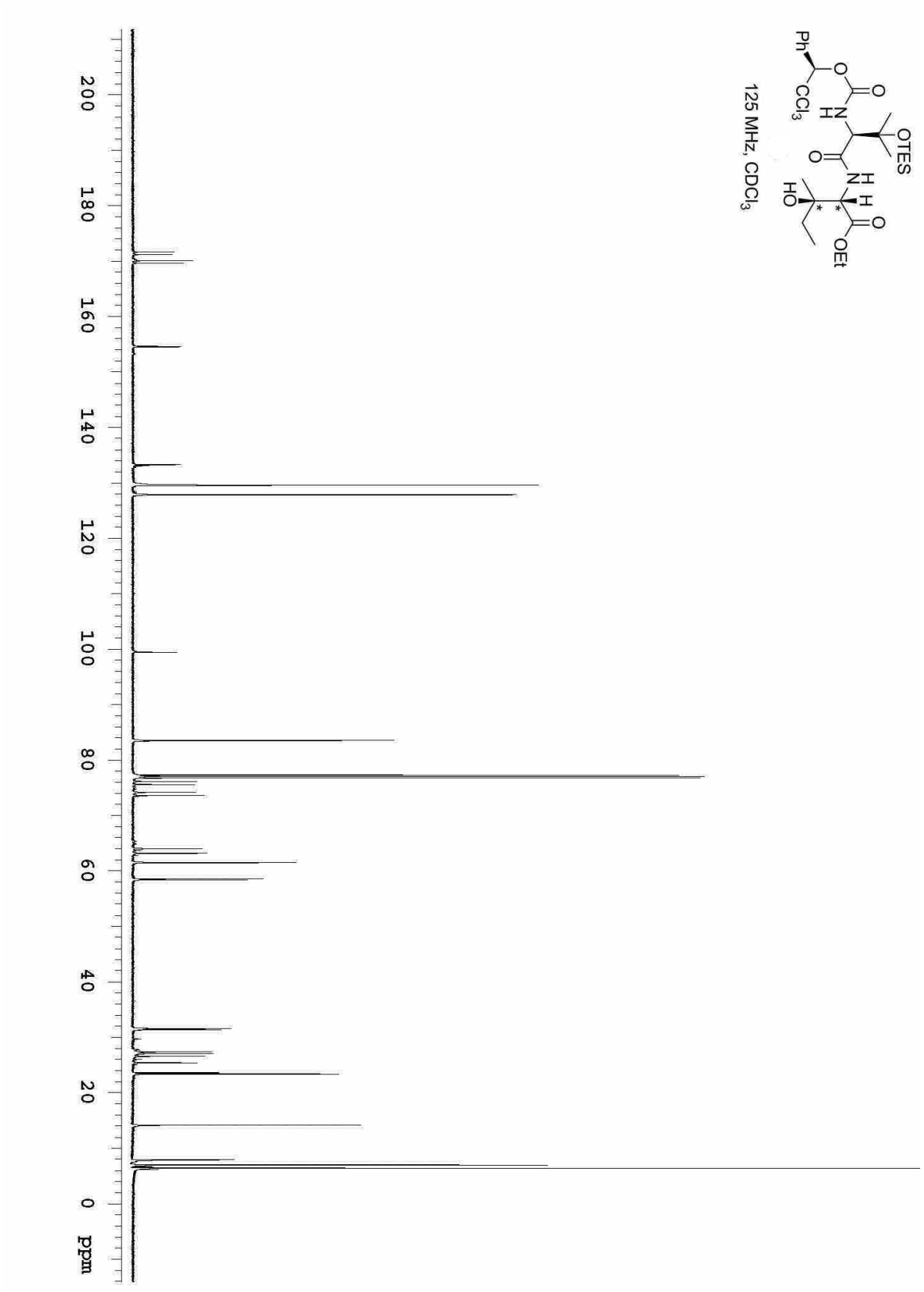
125 MHz, CDCl3
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Ph
CCl3
OEt
HO
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180
160
140
120
100
80
60
40
20
0
ppm

500 MHz, CDCl3
S4
BocHN
OTES
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H
HO
O
OEt
10
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6
5
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2
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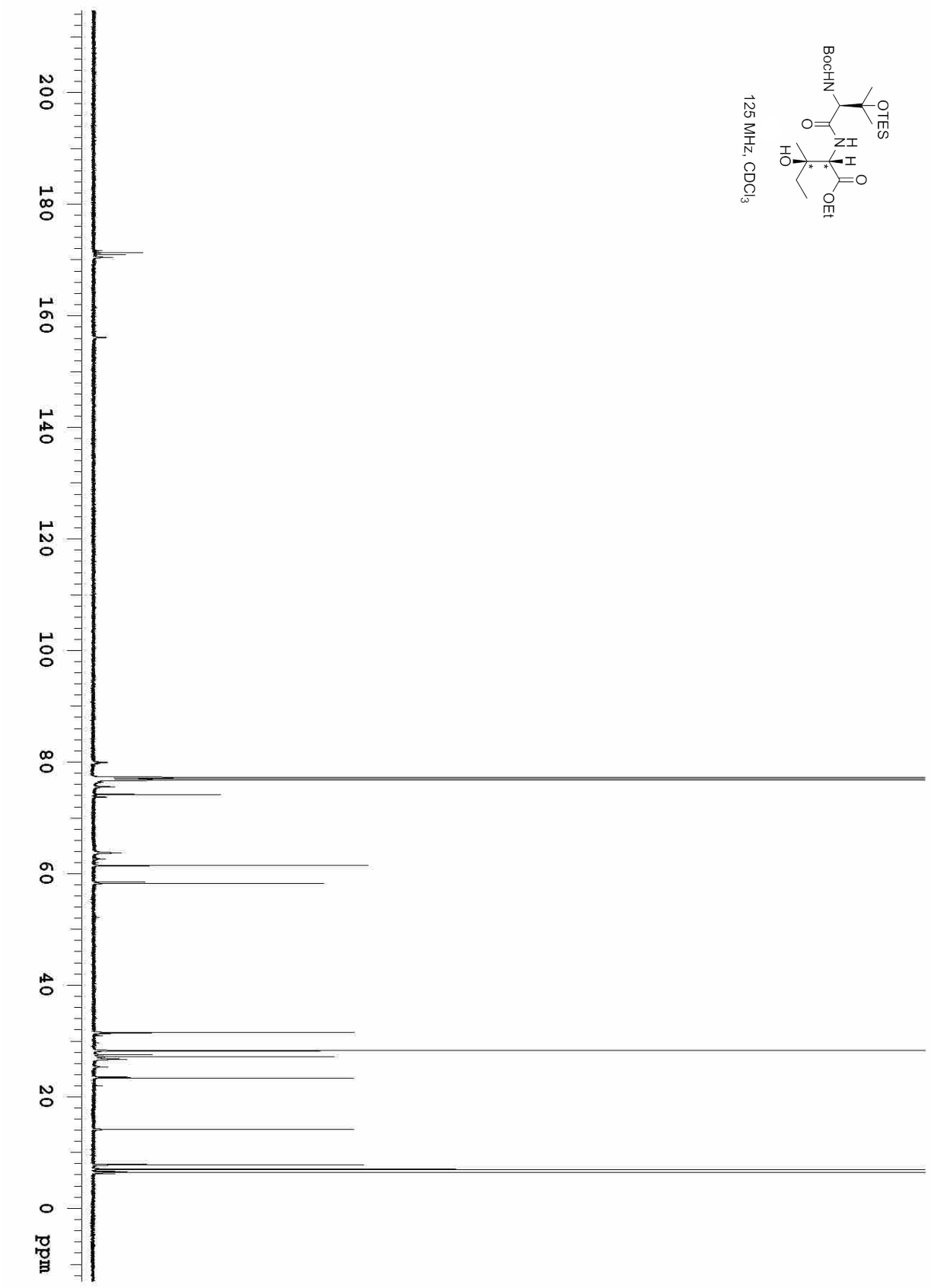
ppm


125 MHz, CDCl3
BocHN
OTES
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H
HO
O
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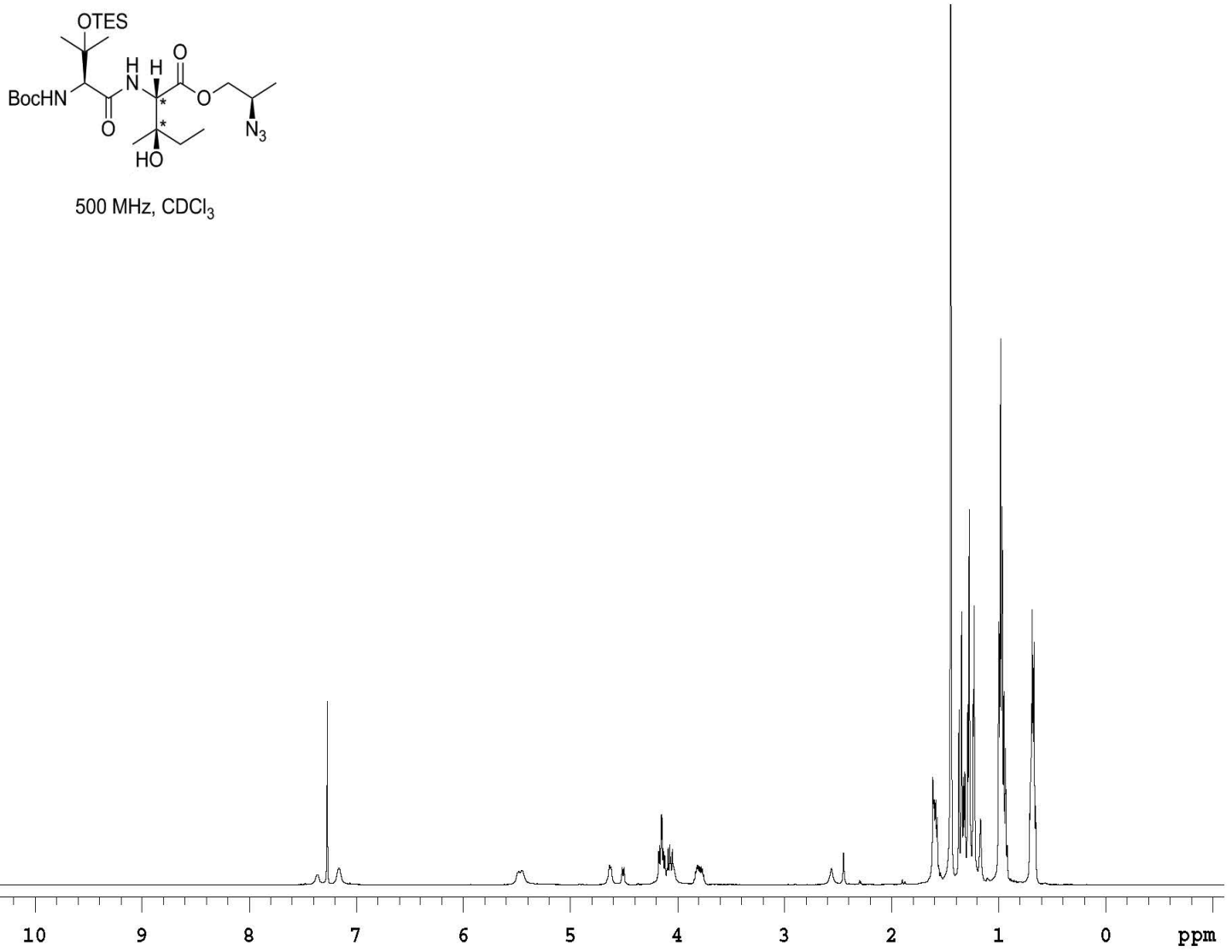
OTES
BocHN
H
N
H
O
O
O
O
*
*
HO
N3
500 MHz, CDCl3
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6
5
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2
1
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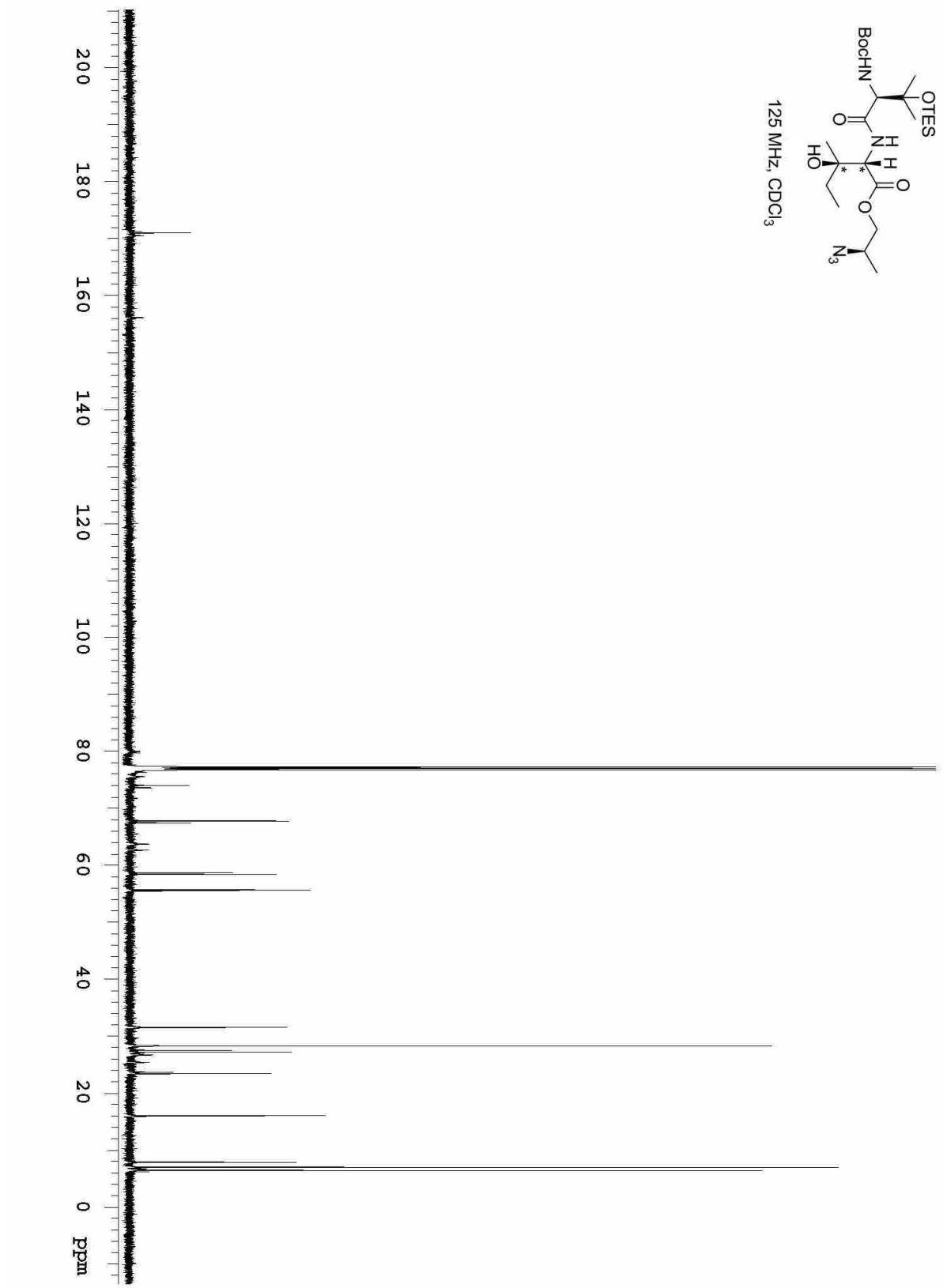
ppm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BocHN
OTES
HO
N3
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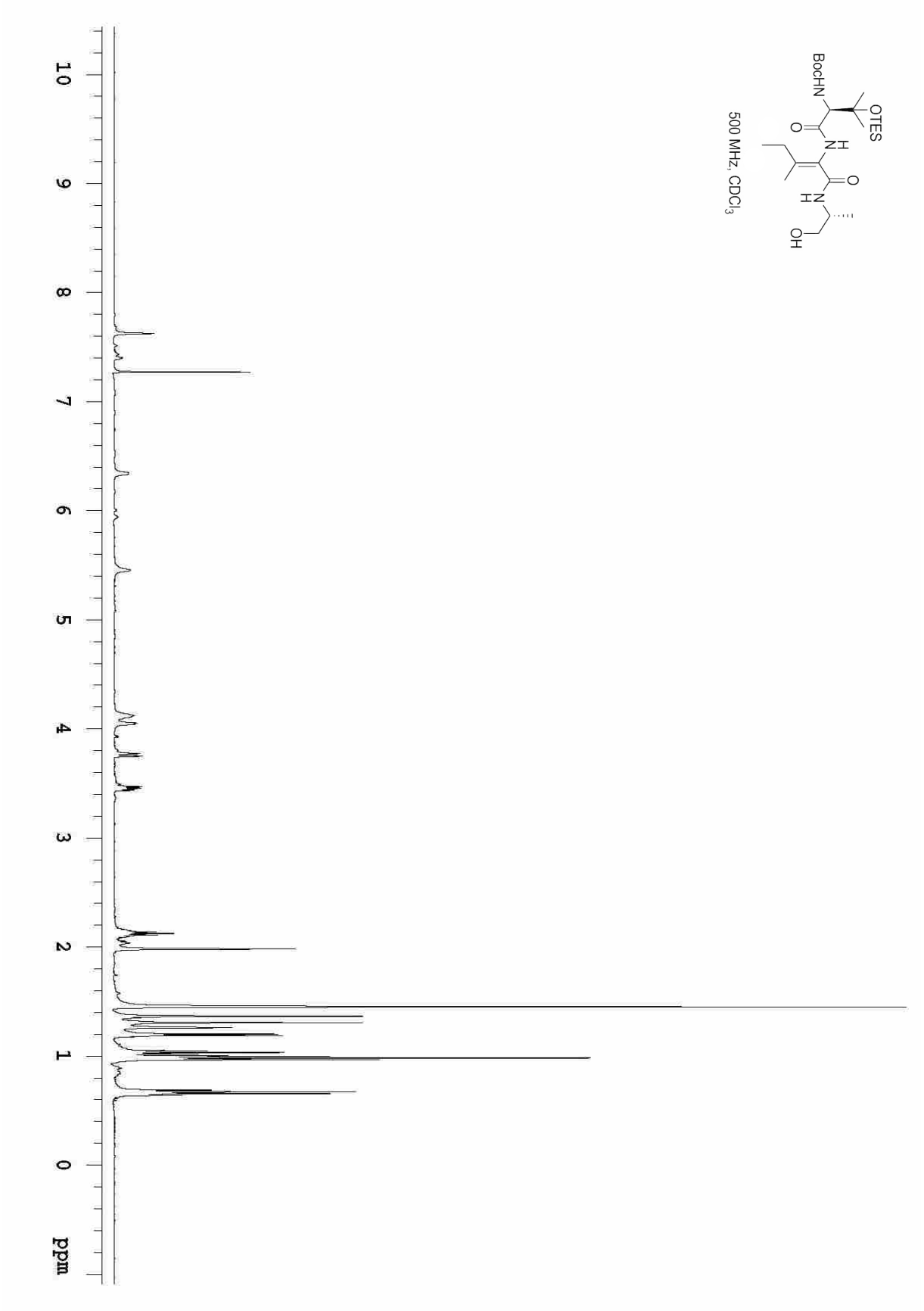
BocHN
OTES
O
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OH
500 MHz, CDCl3
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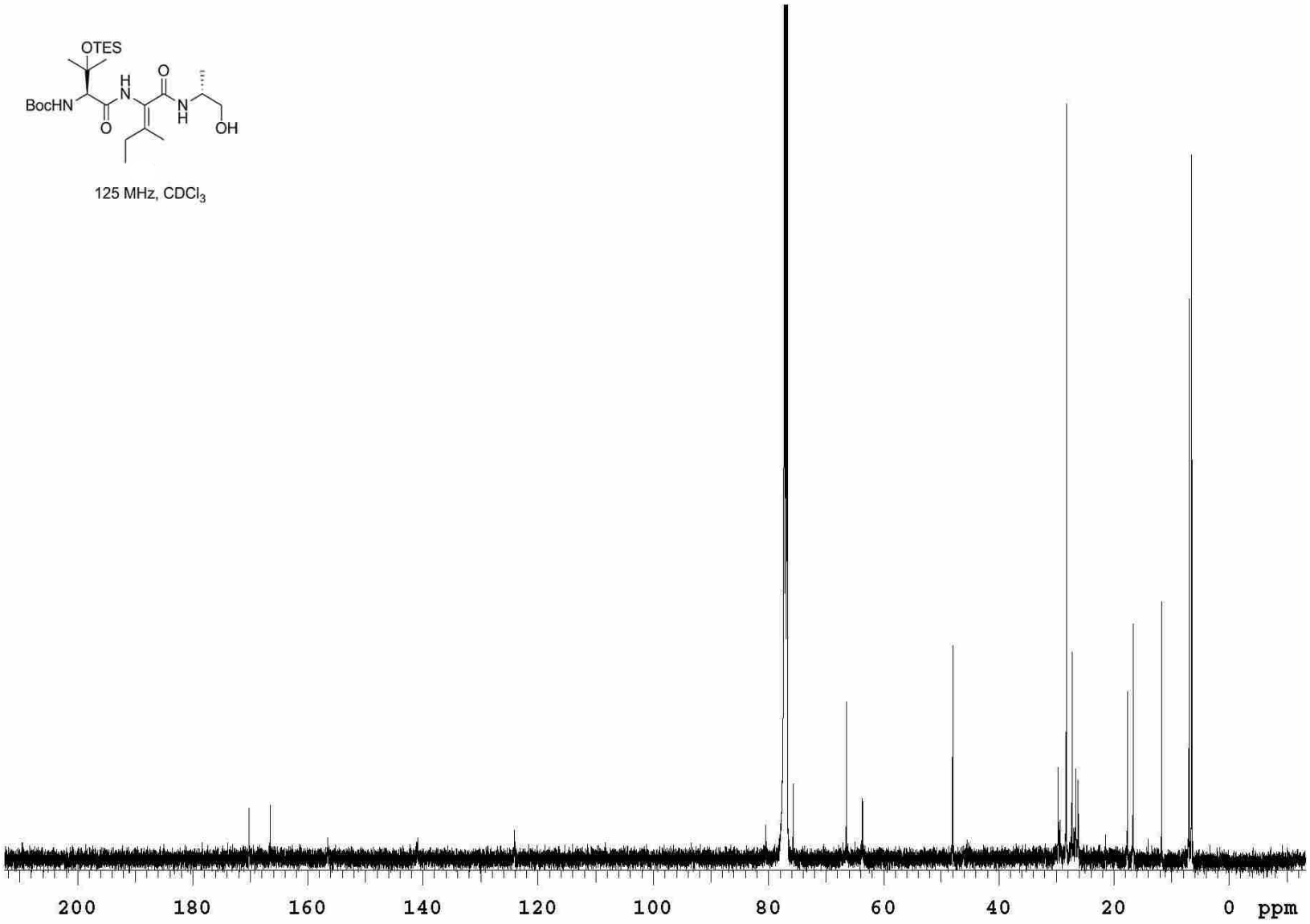
OTES
BocHN
H
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O
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OH
125 MHz, CDCl3
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20
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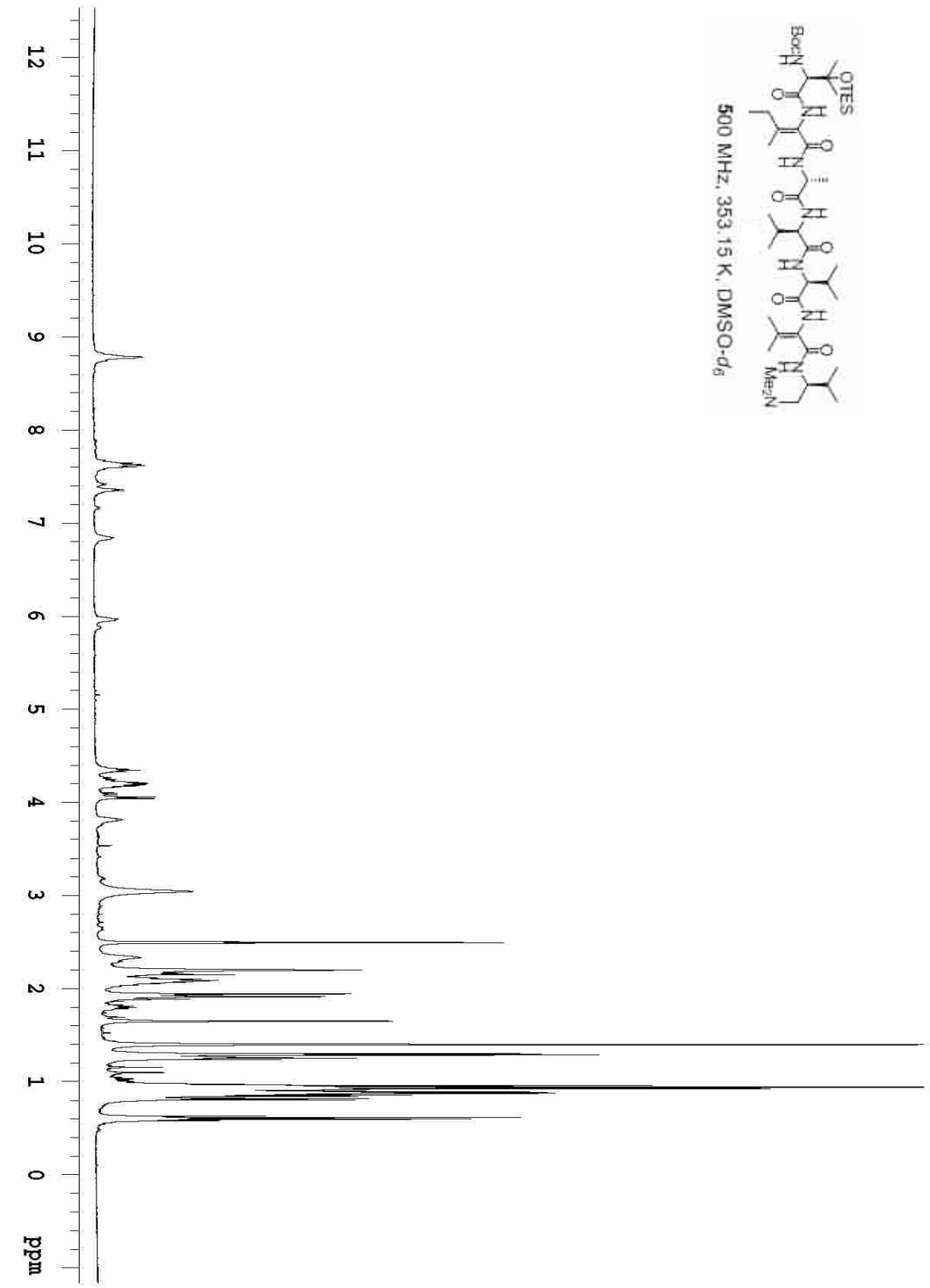
ppm


OTES
BocHN
Me2N
500 MHz, 353.15 K, DMSO-d6
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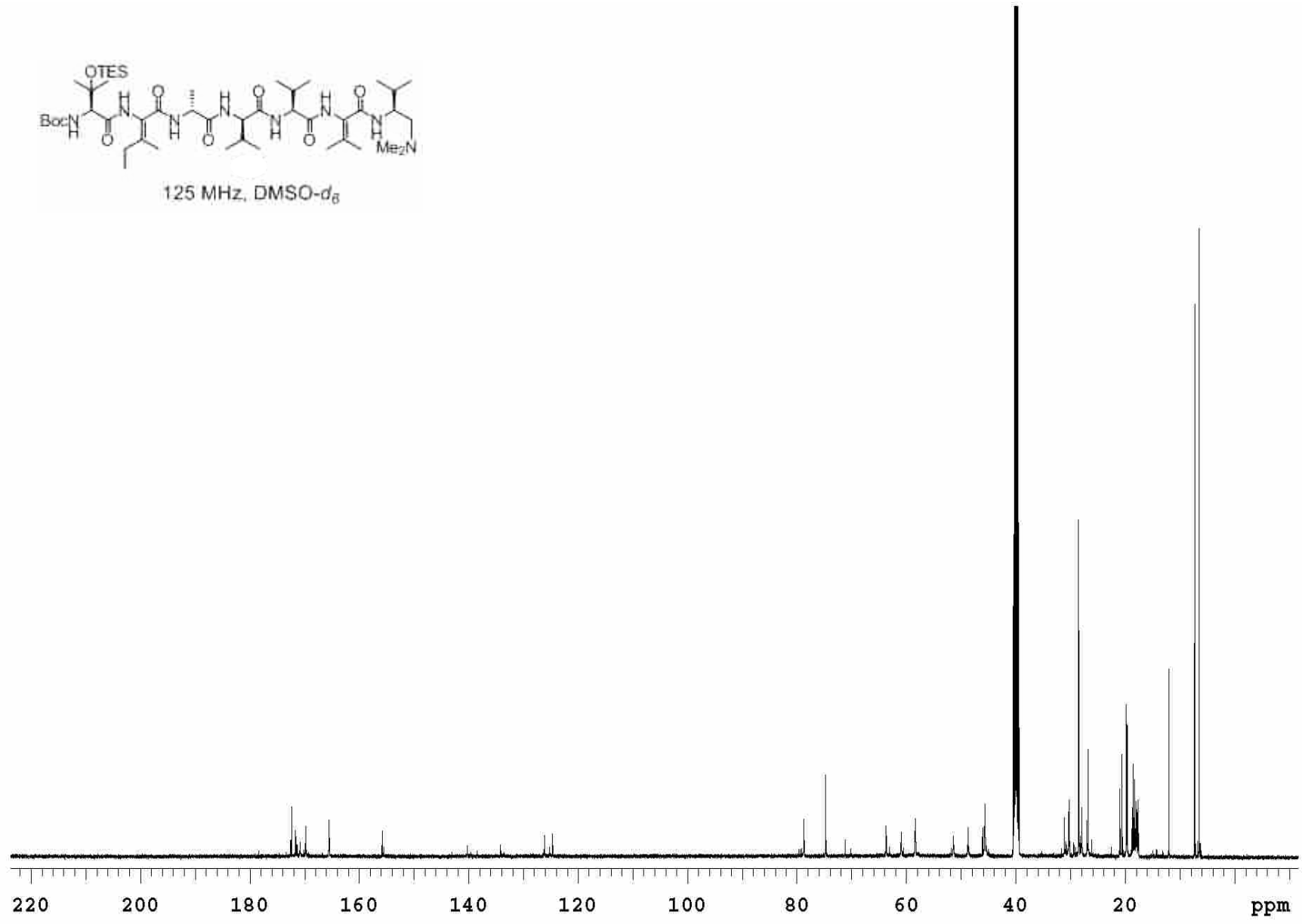
ppm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Boc
Me2N
125 MHz, DMSO-d6
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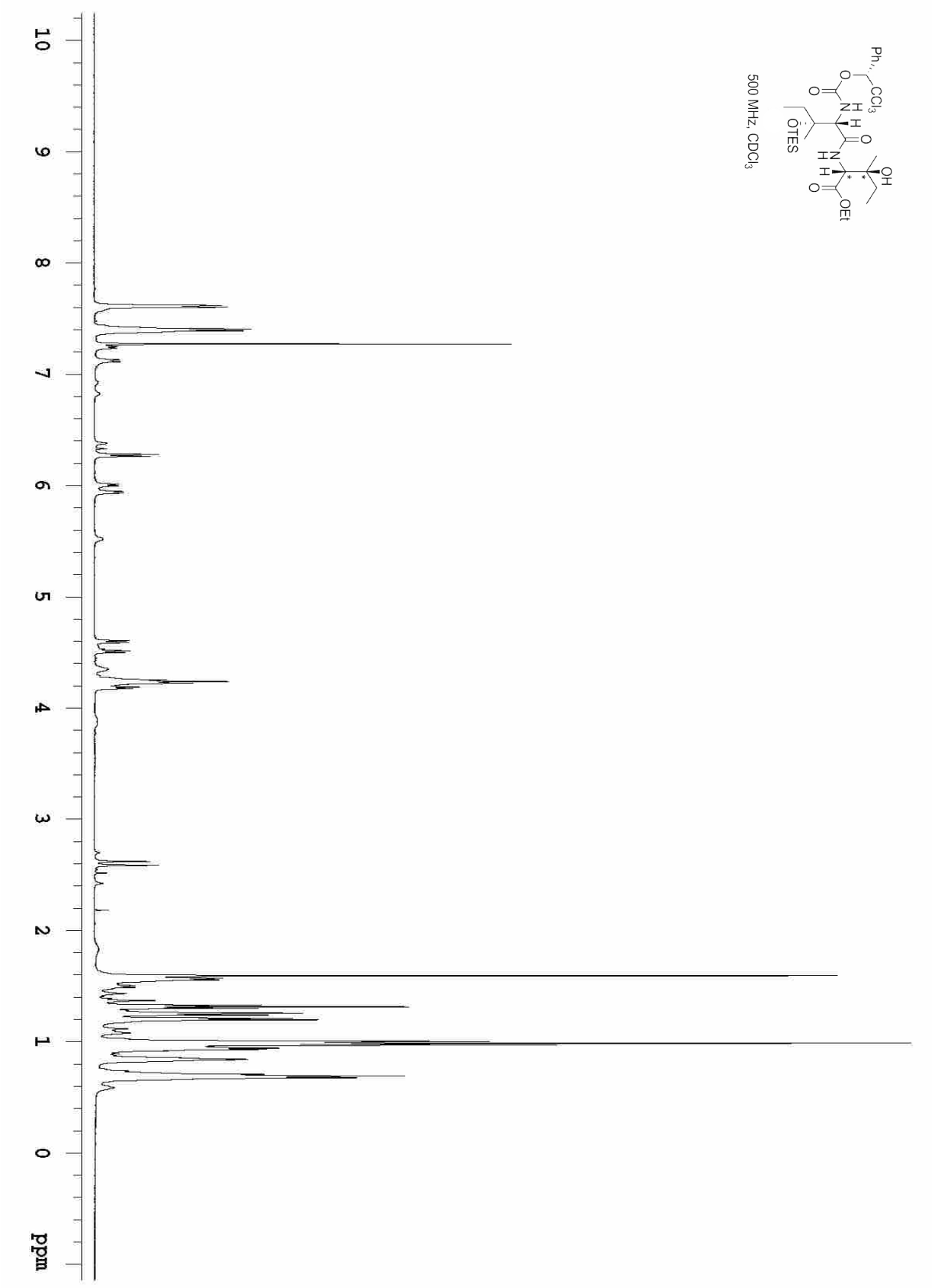
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OEt
OH
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6
5
4
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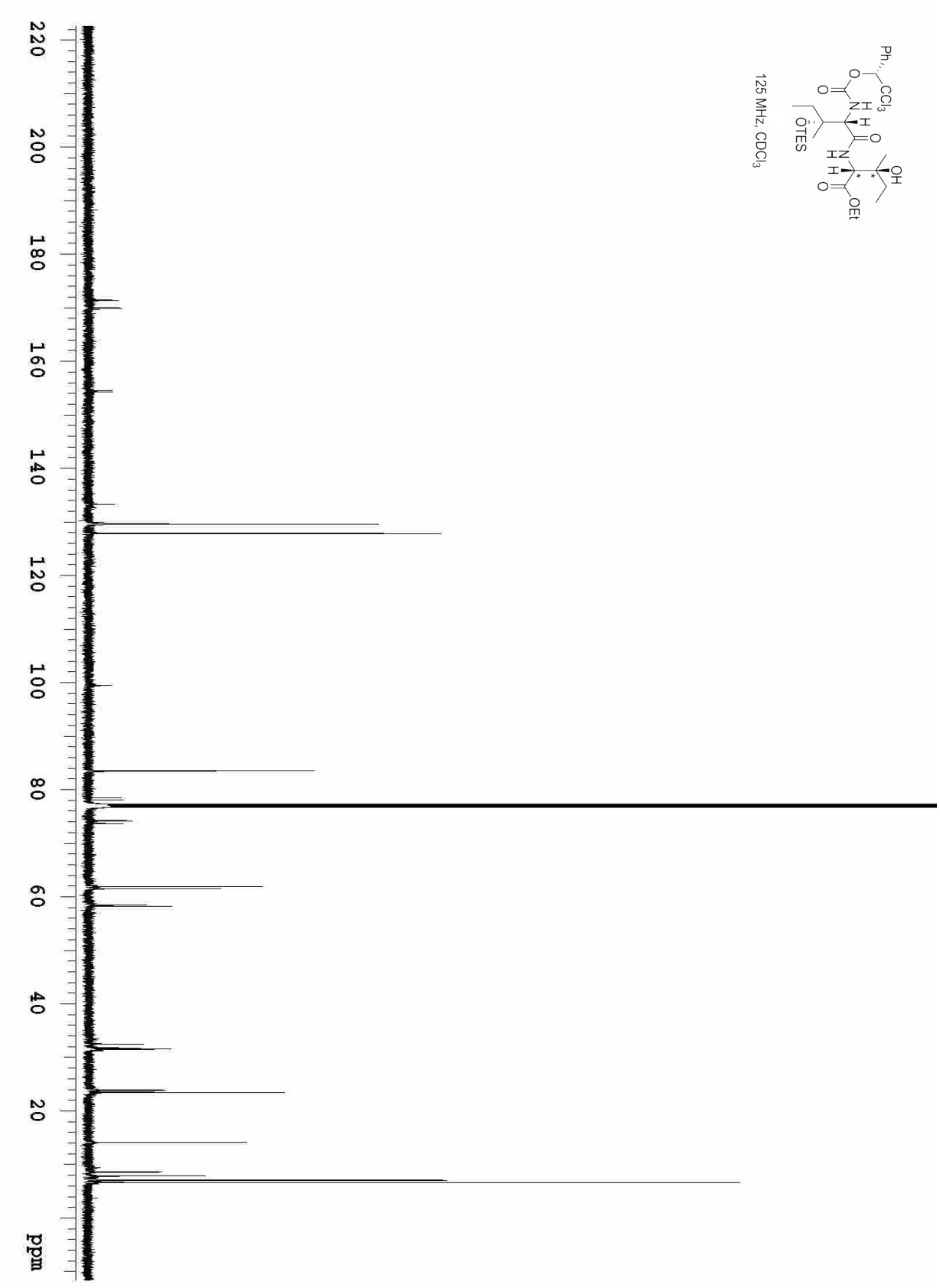
2
1
0
ppm


125 MHz, CDCl3
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120
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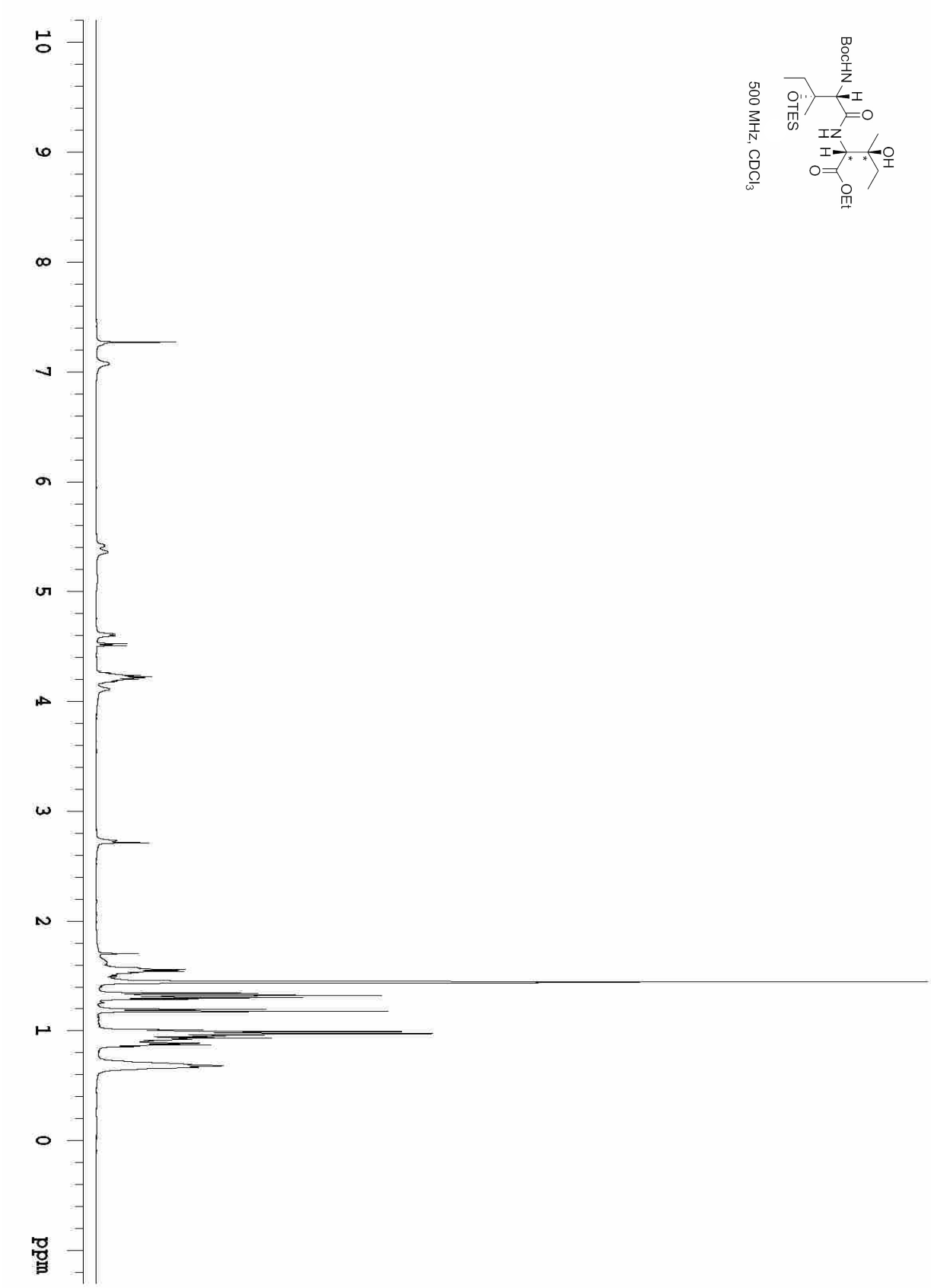
80
60
40
20
ppm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OTES
N
H
H
O
OEt
OH
500 MHz, CDCl3
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7
6
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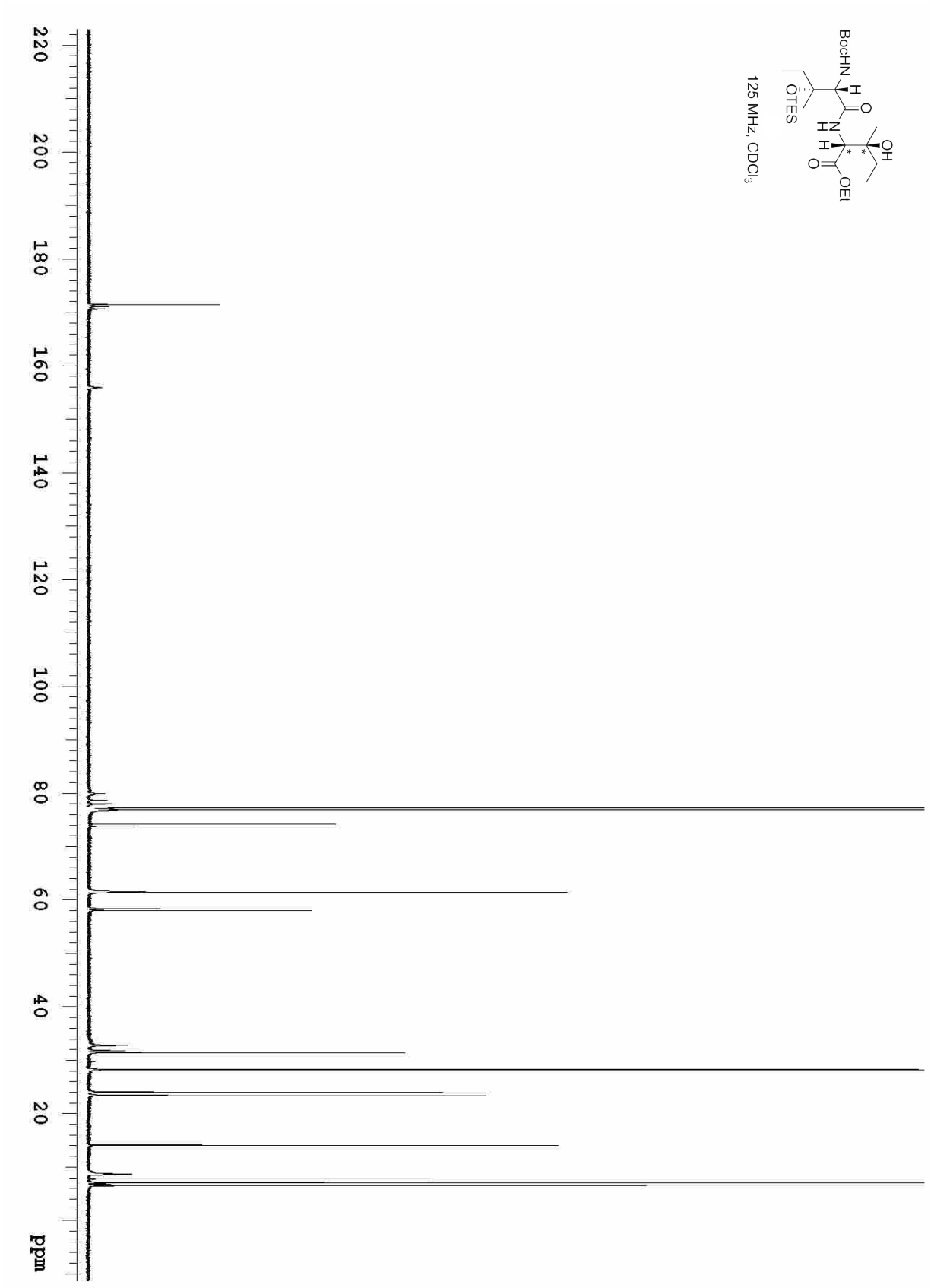
3
2
1
0
ppm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OTES
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OH
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200
180
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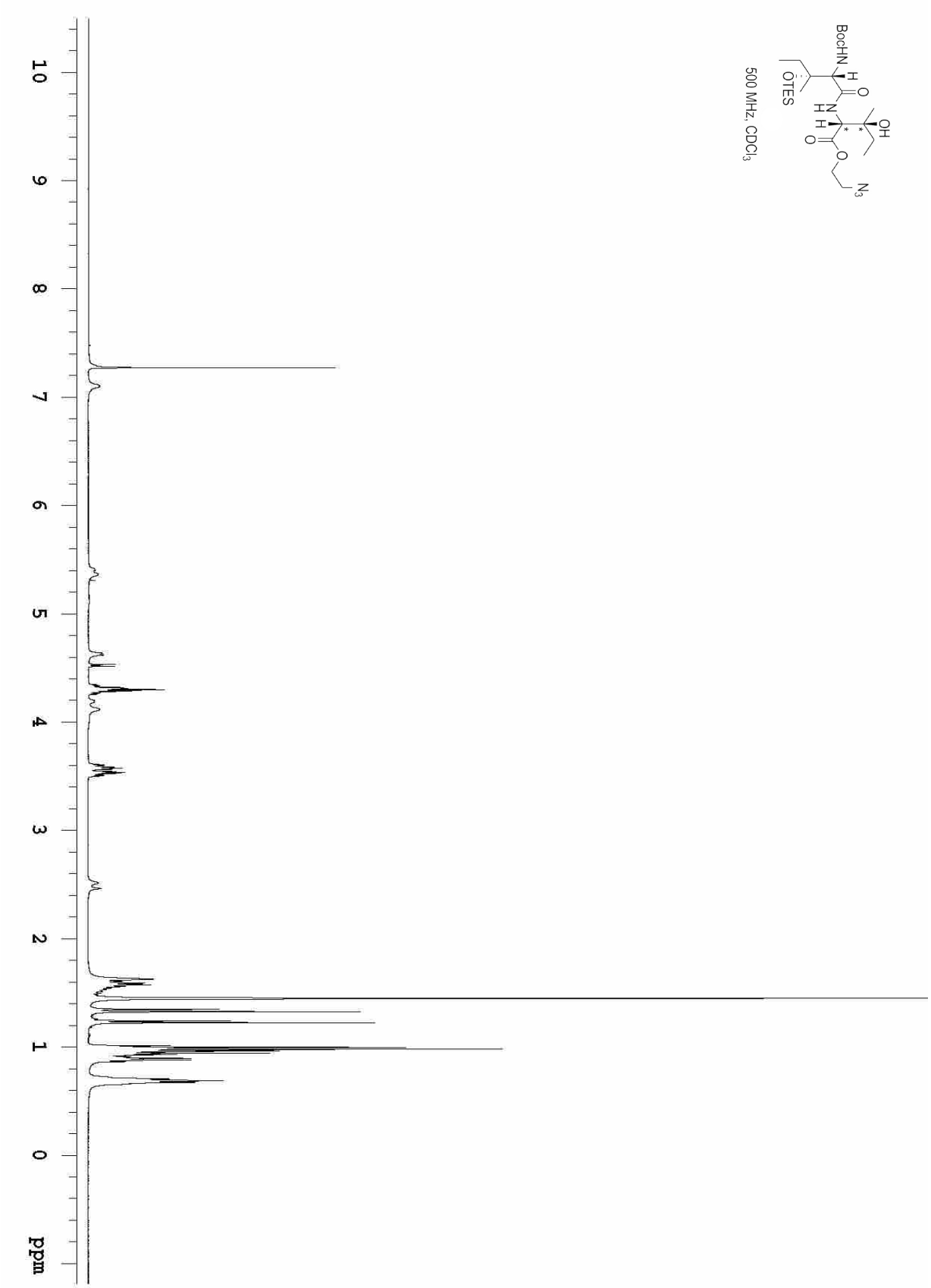
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2
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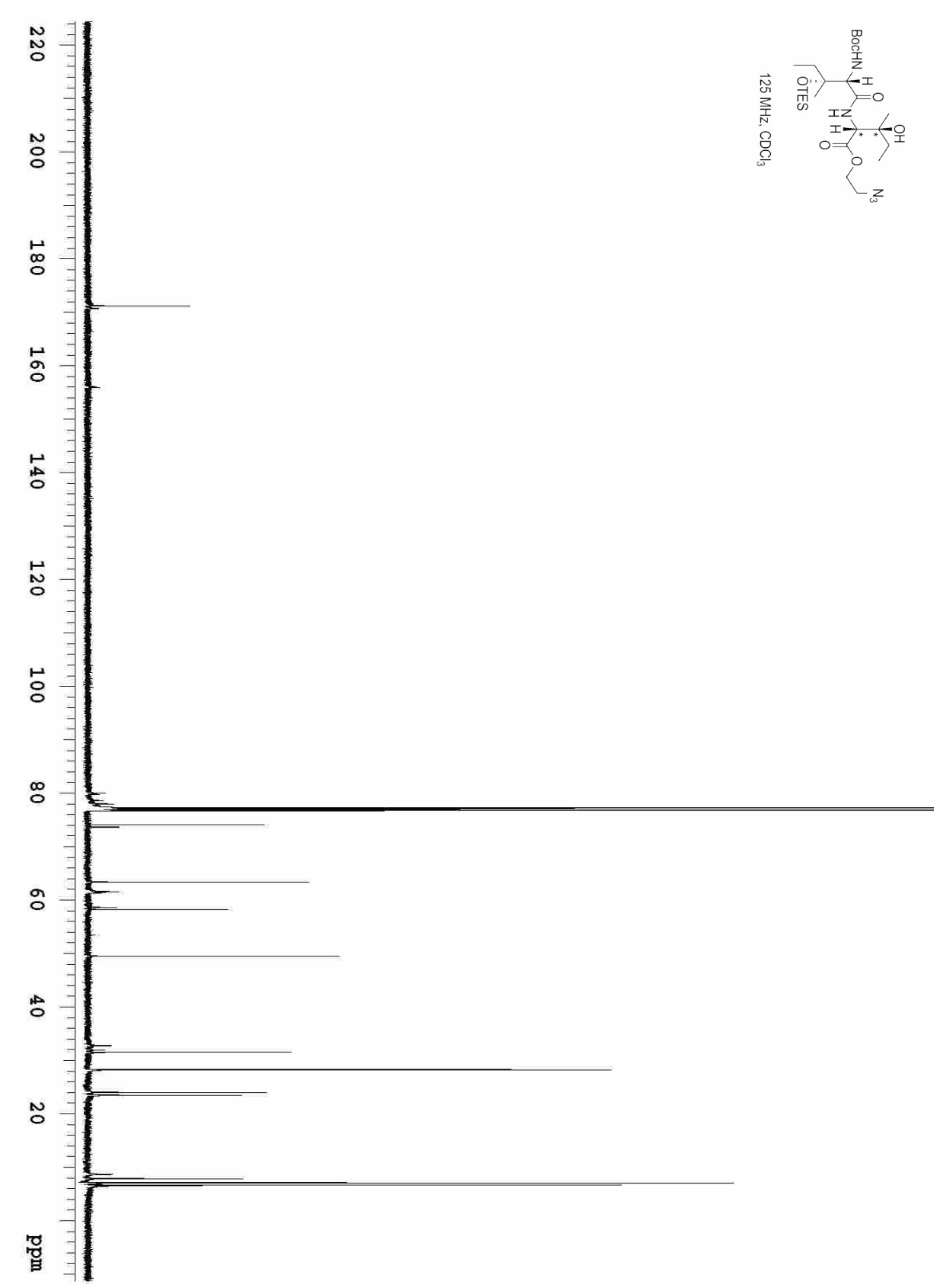
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OTES
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N3
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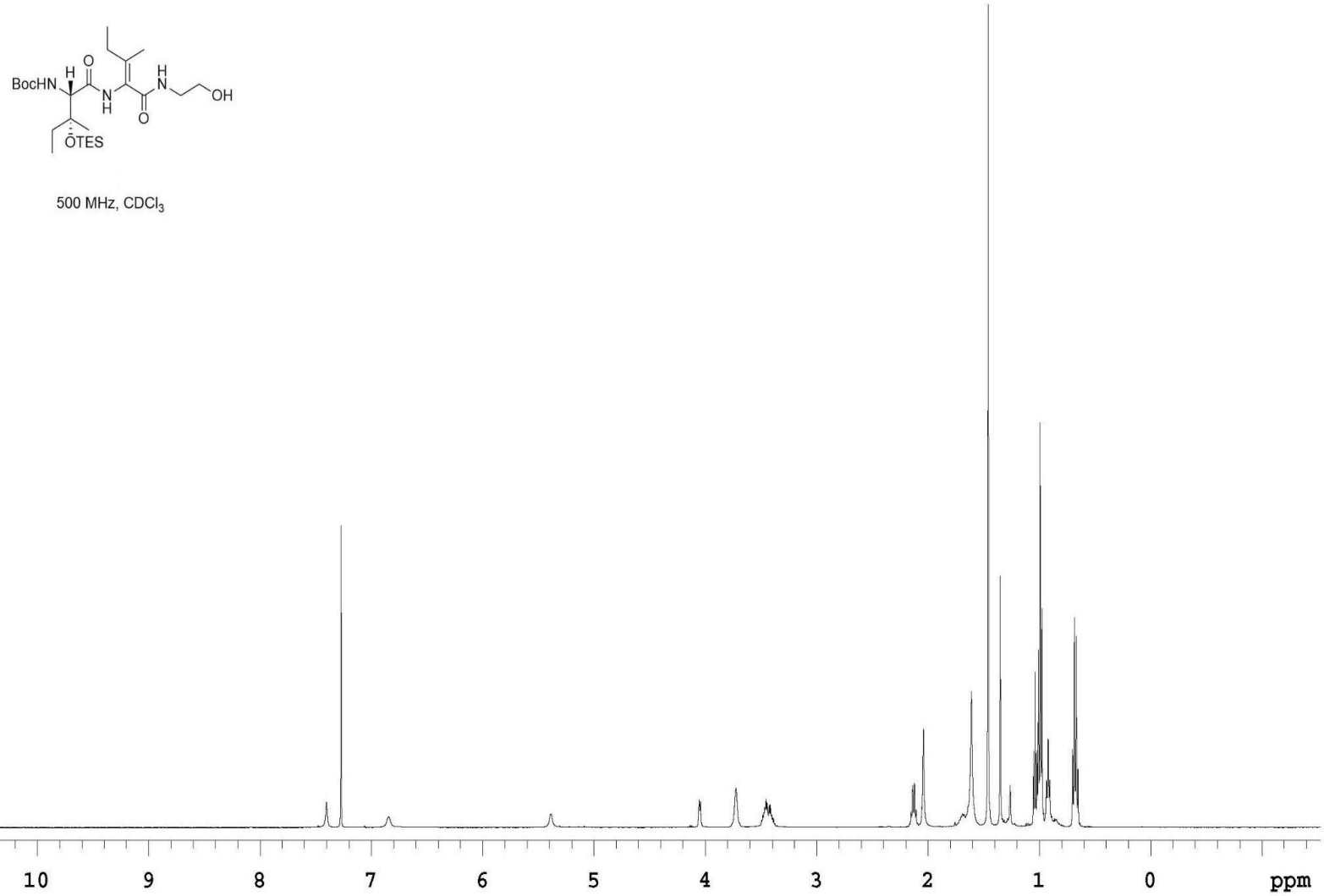
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500 MHz, CDCl3
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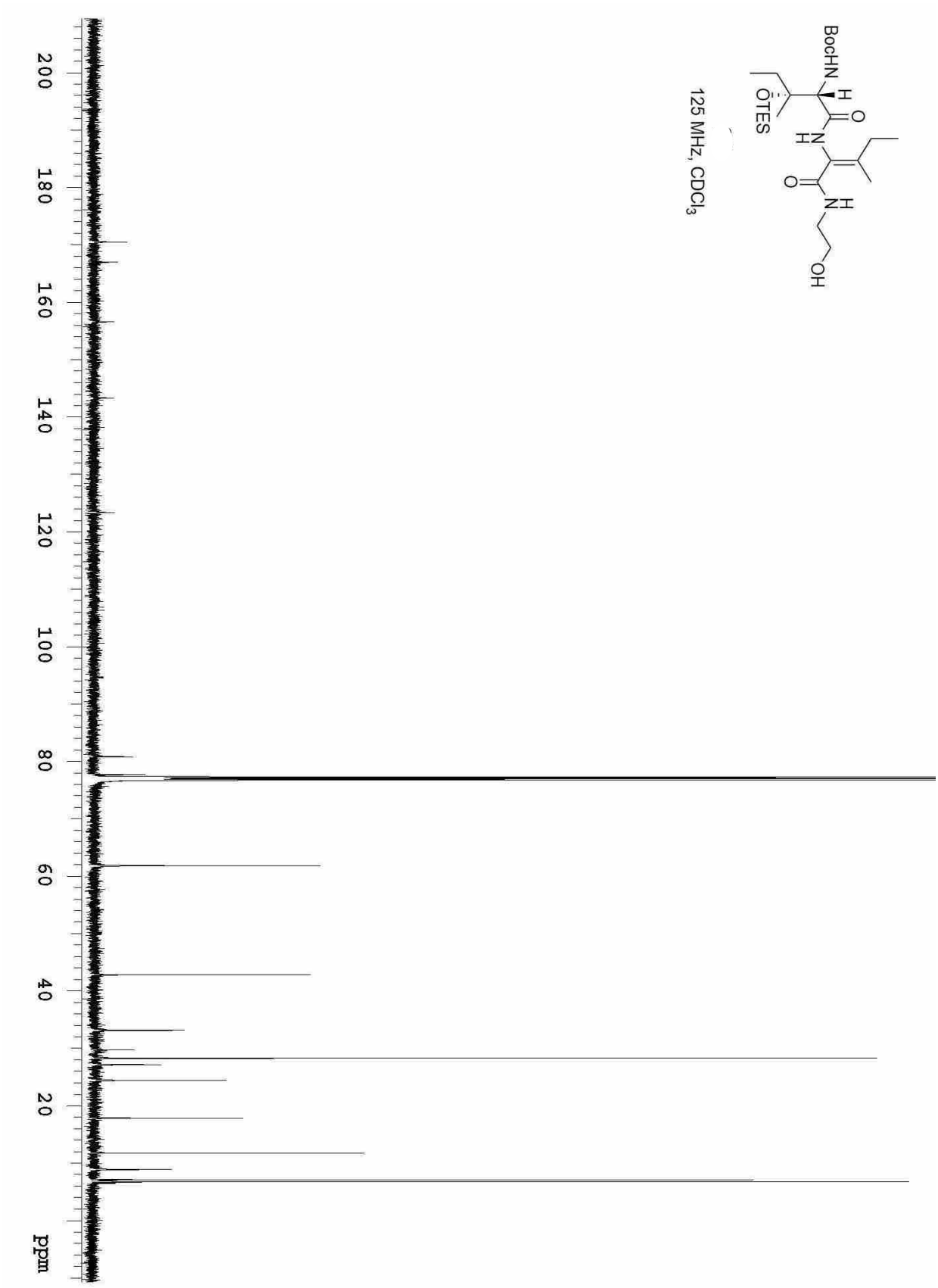
125 MHz, CDCl3
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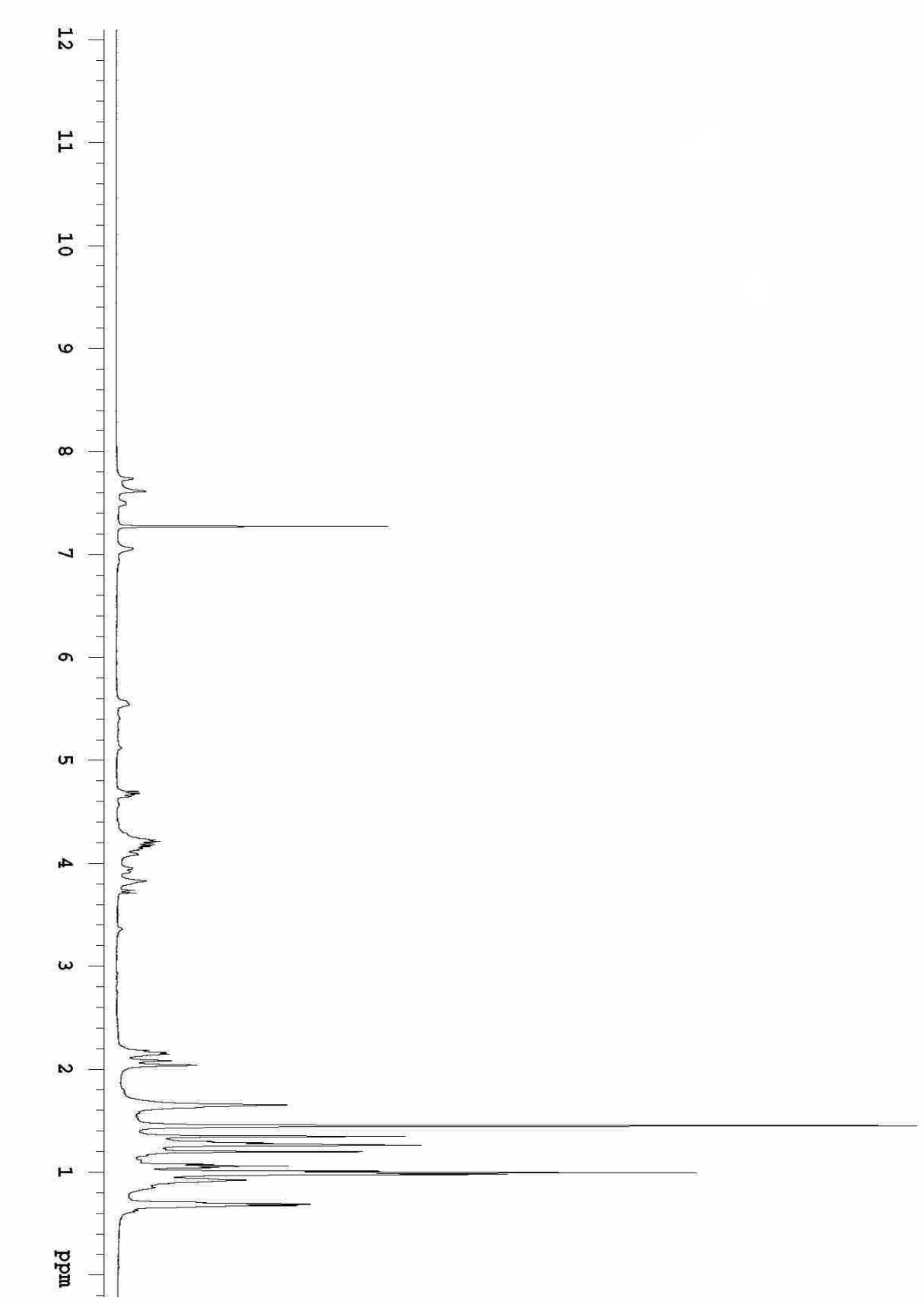
12
11
10
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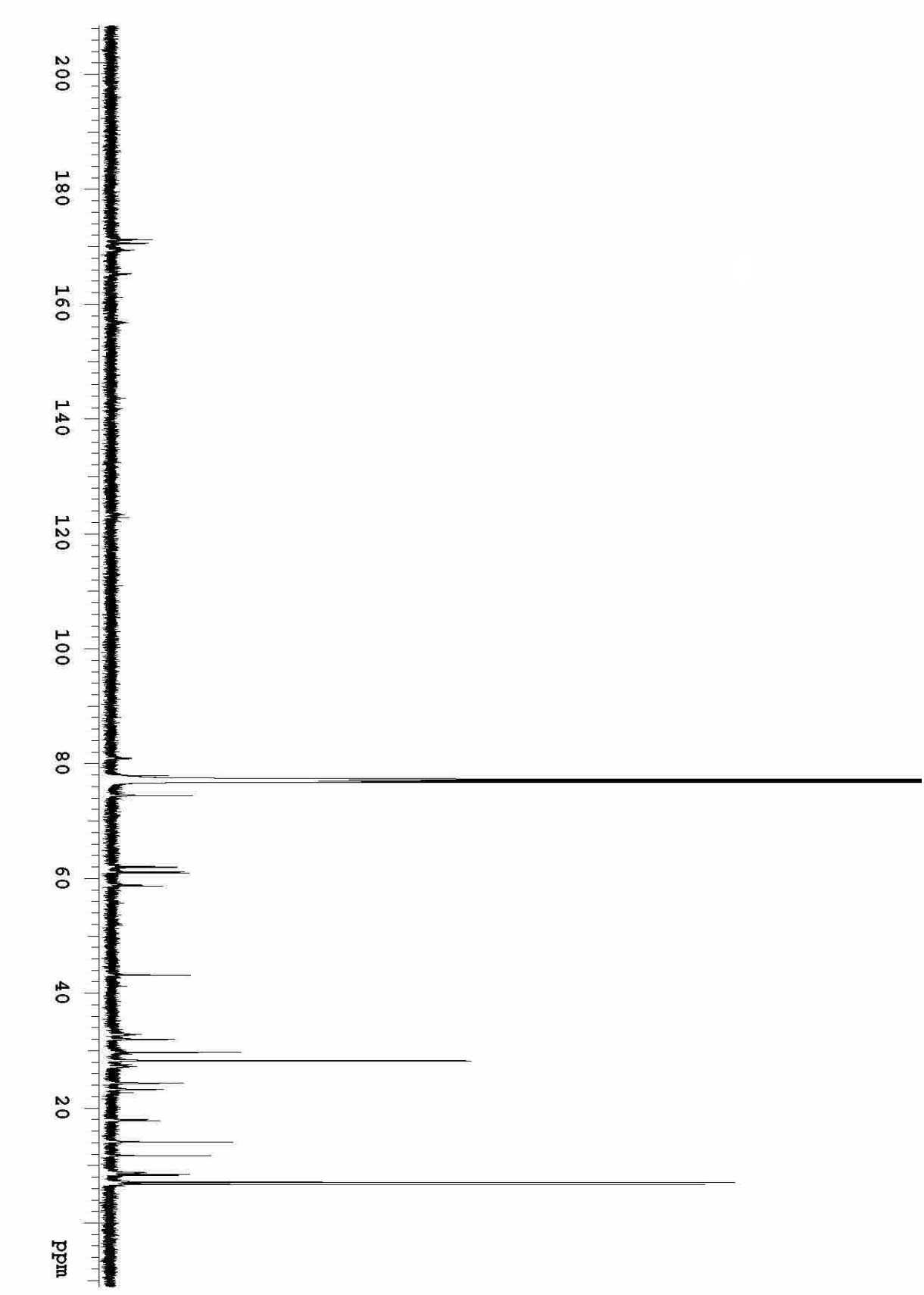
8
7
6
5
4
3
2
1
ppm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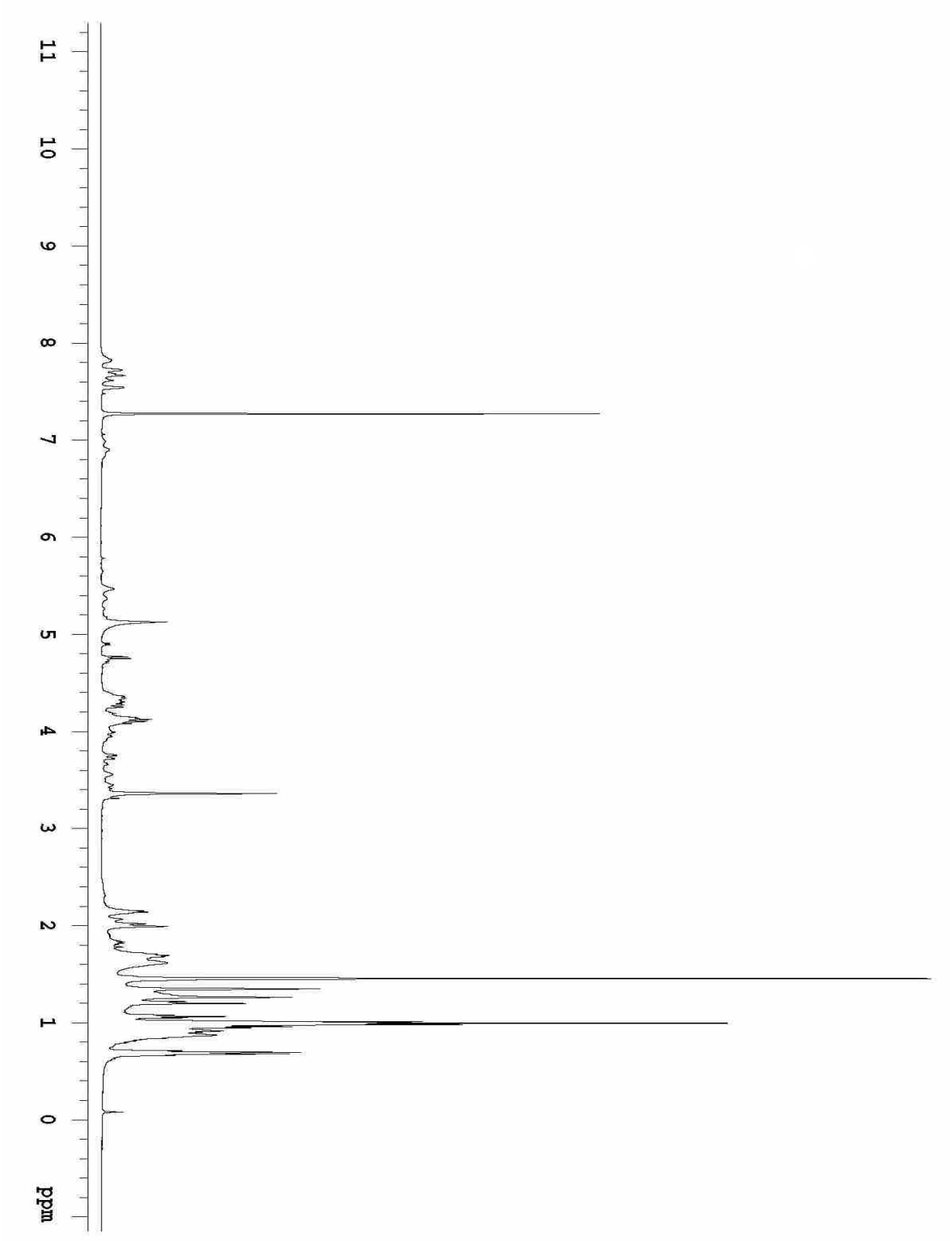
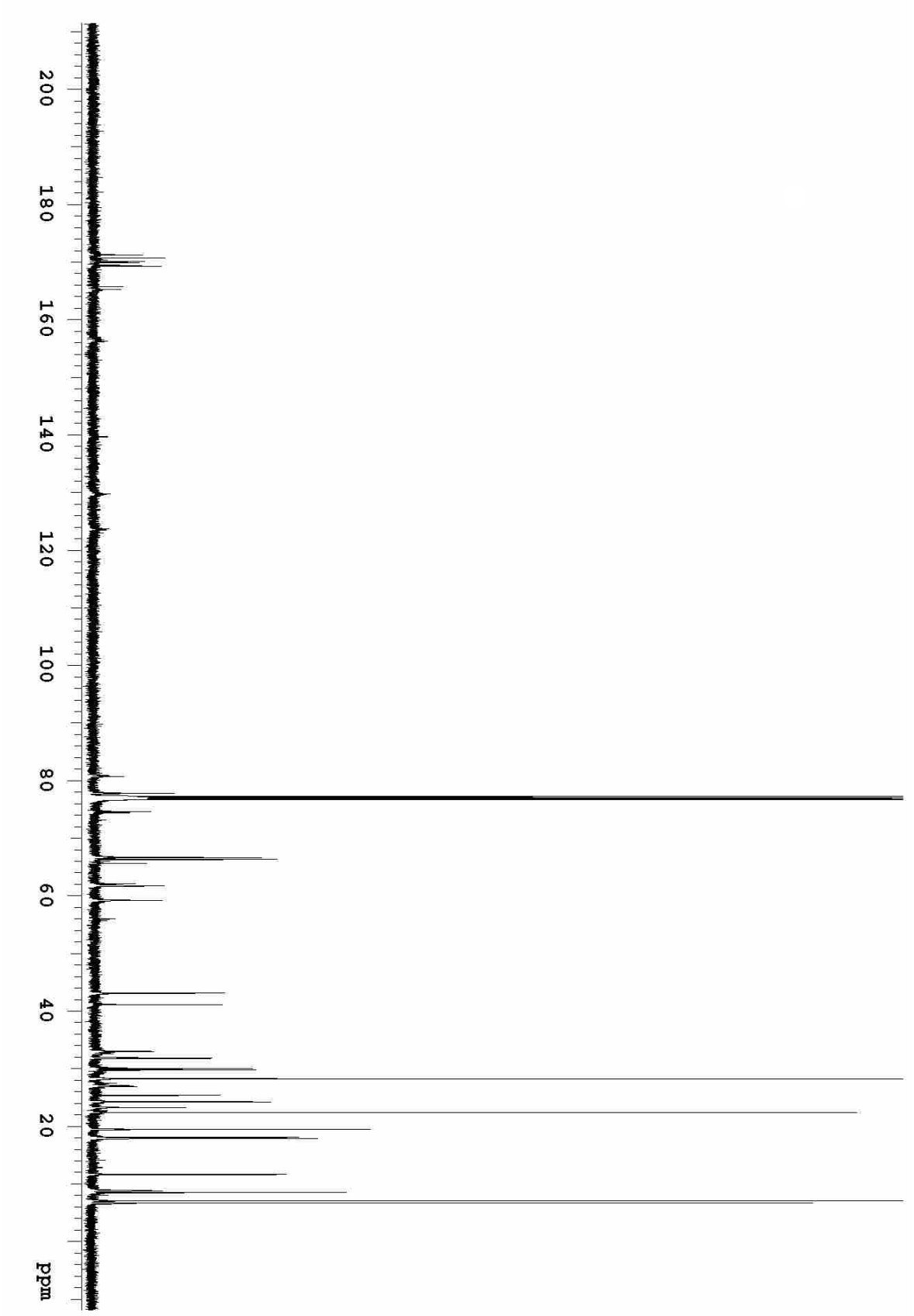
160
140
120
100
80
60
40
20
ppm


11
10
9
8
7
6
5
4
3
2
1
0
wdd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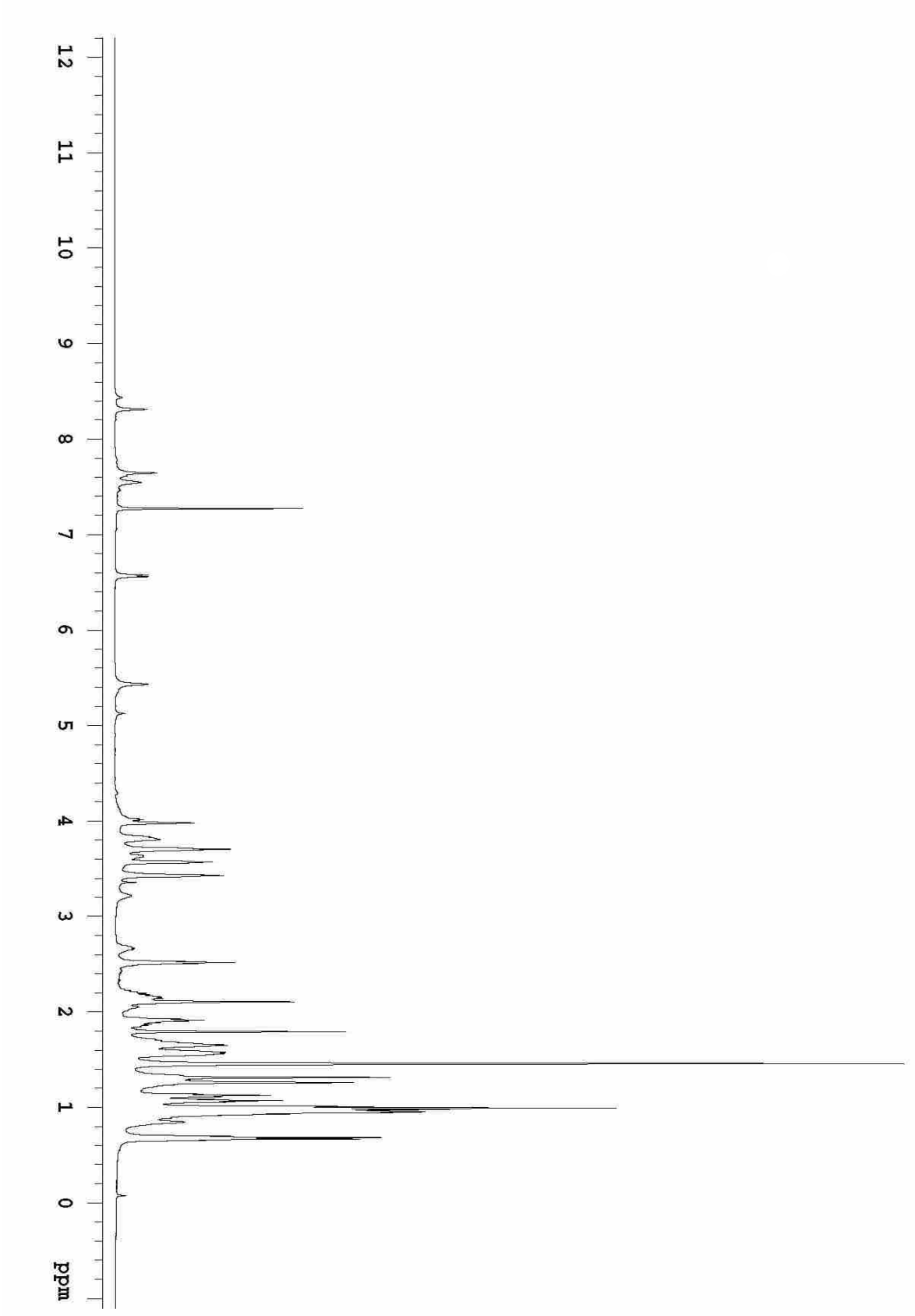
180
160
140
120
100
80
60
40
20
ppm


12
11
10
9
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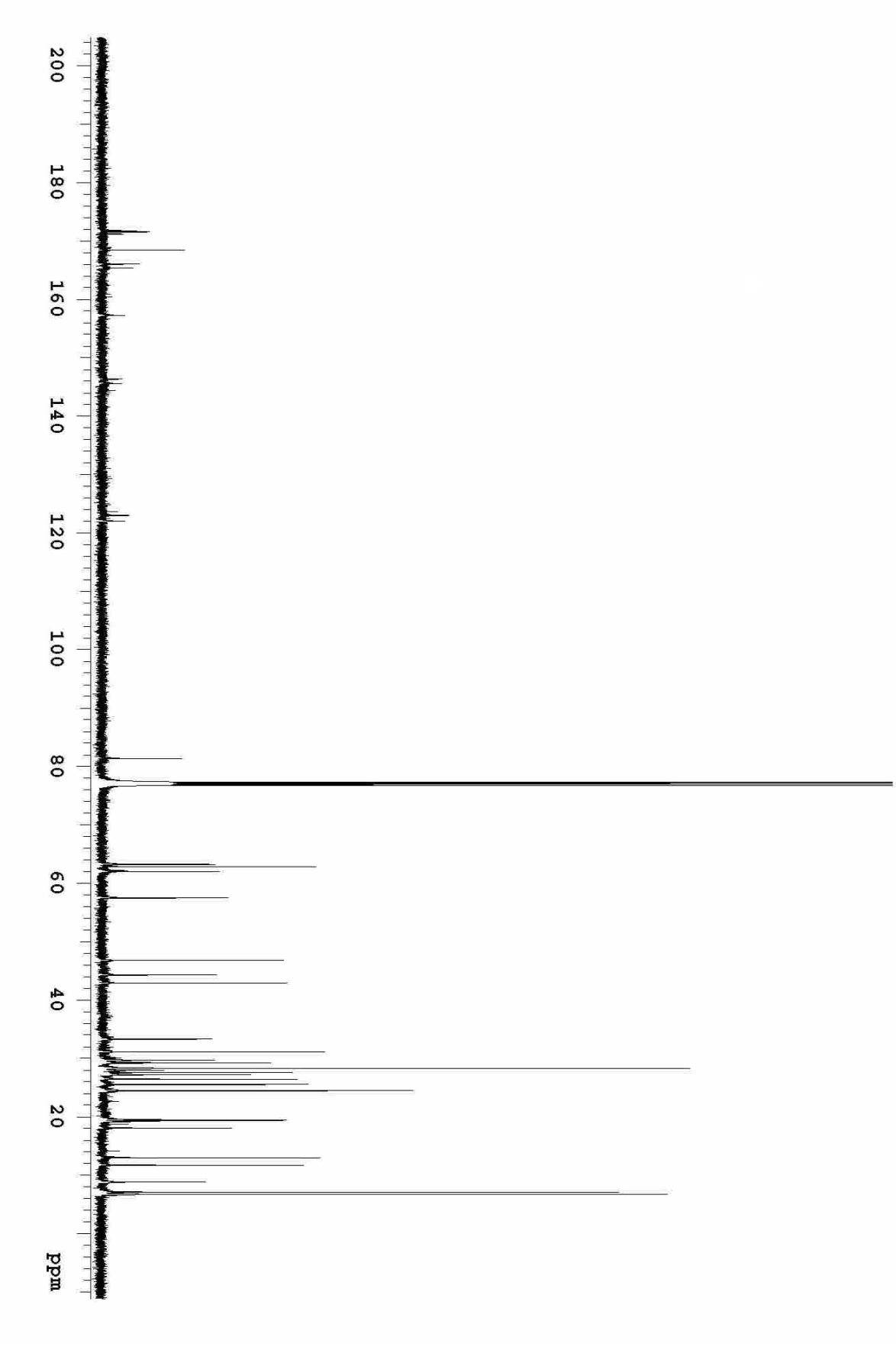
7
6
5
4
3
2
1
0
ppm


200
180
160
140
120
100
80
60
40
20
ppm