2015-07-01

Progress Towards 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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July 2015

ABSTRACT

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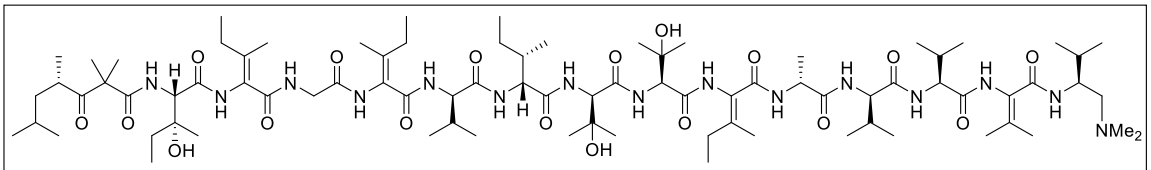
The synthetic progress towards yaku'amide A is described. The study leads to development of new synthetic methodologies. Base-free regioselective aminohydroxylation is convenient to deliver β-*tert*-hydroxyamino acids. A sequence consisting of alkylative esterification, Martin sulfurane mediated *anti* dehydration, a tandem azide reduction–O→N acyl transfer allows the rapid access of *E*- and *Z*-dehydroisoleucine-containing peptides from β-*tert*-hydroxyisoleucine derivatives. Those methods are effective in constructing complicated peptides and advanced subunits of yaku'amide A.



Yaku'amide A

Keywords: yaku'amide A, base-free regioselective aminohydroxylation, β-*tert*-hydroxy amino acids, dehydroamino acids, dehydroisoleucine, Martin sulfurane, *anti* dehydration, azide reduction, O→N acyl transfer.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my advisor Professor Steven L. Castle for his support, enthusiasm and patience in my development as an organic chemist. His insightful synthetic route of yaku'amide A has been great, highlighting the beauty of organic chemistry and motivating me to pursue higher goals in synthesis. His expertise in organic synthesis and dedication to the research are inspiring and teach me to work efficiently and diligently. His life philosophy has been a great influence on me as well.

I would like to thank Professors Merritt B. Andrus, Matt A. Peterson and David J. Michaelis for their kindness and expertise in discussions on dozens of tricky synthesis problems. Professor Paul B. Savage's philosophy of "becoming the one who knows their project the most in the world" has been encouraging me all the way through my graduate study. Professors Joshua L. Price and Roger G. Harrison have been great source of motivation.

During my graduate career, I have been fortunate to work with a number of impressive people. Dr. Brad M. Loertscher was the perfect example of how an organic chemist should be, and he trained me when I joined BYU with little synthesis experience. I am proud of the outstanding undergraduates Joseph M. Cardon and Shi Luo, whom I trained. They are reliable and self-motivated researchers, providing crucial intermediates to push the total synthesis forward. There is no doubt that they will have a bright future. Yu Cai and Ankur Jalan joined BYU after me, and they are great lab-mates for being professional in chemistry and joyful in life. Yu is working on the NTA synthesis and provides precious material to me. In addition, I am grateful for their help in my commute to the train station, especially Ankur, since I live 50 miles north of BYU. Good luck for them. 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 language.

Apart from the Castle group, I would like to thank Dr. Shenglou Deng for his expertise and kindness in discussing the problems I encountered in the project. Also, I am grateful for Yubo Li's technical help in chromatography as well as being a friend. In addition, I would like to thank Dr. Xiaobo Gu, Dr. Yong Wang, Dr. Yanshu Feng, Dr. Mark Acerson, Paul Laurence, Sara Mata and Paulo A. Machicao Tello for very helpful advices and discussions. It is fortunate to me to be able to work with those outstanding people on the same floor.

I would like to thank Department of Chemistry and Biochemistry (BYU) for providing a wonderful research environment as well as financial support, namely the Cancer research fellowship, Bradshaw graduate fellowship, Graduate study fellowship. I would like to acknowledge Professor Scott R. Burt and Mr. Bruce J. Jackson for providing well-maintained NMR and MS facilities.

At last, I would like to especially thank my wife Yun Ding, my parents Yaorong Li and Cuihua Ma for their endless love and tireless support during those difficult times. Also, I am grateful for the joy my daughter Sophia M. Ma brings to my life everyday. Without you all, this thesis would have been impossible.

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LIST OF ABBREVIATIONS AND ACRONYMS

Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
t-Bu or *t*Bu	*tert*-Butyl
Burgess Reagent	Methyl *N*-(triethylammoniumsulfonyl)carbamate
Cbz	Carbobenzyloxy
CH_2Cl_2	Dichloromethane
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
COSY	Correlation Spectroscopy (NMR)
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl Carbodiimide
DEPBT	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DIBAL	Diisobutylaluminum Hydride
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl Sulfoxide
dr	diastereomeric ratio
ee	Enantiomeric Excess
EDC or EDCI	1-Ethyl-3-(3-dimethylaminopropy)carbodiimide
EDCI•HCl	1-Ethyl-3-(3-dimethylaminopropy)carbodiimide Hydrochloride
HOAt	7-Aza-1-hydroxybenzotriazole
HOBt	1-Hydroxybenzotriazole
Hünig's Base	Diisopropylethylamine
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Proton detected Heteronuclear Multiquantum Coherence
IR	Infrared Spectroscopy
J	Coupling Constant (NMR)
LAH	Lithium Aluminum Hydride ($LiAlH_4$)
Lindlar Catalyst	Pd on $CaCO_3$/PbO
MS	Mass spectrometry
Ms	Methanesulfonyl (Mesyl, CH_3SO_2)
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
PhthN	Phthalimido
Ph	Phenyl
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
Rf	Retention Factor (chromatography)
TBAF	Tetra-*n*-butylammonium fluoride

TBDPS	*tert*-Butyldiphenylsilyl
TBS (TBDMS)	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Triflate (CF_3SO_2)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMG	1,1,3,3-Tetramethylguanidine
TPAP	Tetra-*n*-propylammonium Perruthenate
UV	Ultraviolet spectroscopy
*	Stereocenters marked by asterisks possess the indicated relative, not absolute stereochemistry

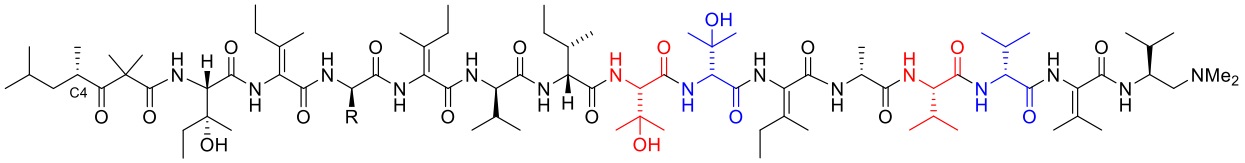
Chapter 1. YAKU'AMIDE A

1.1 Isolation and biological activity

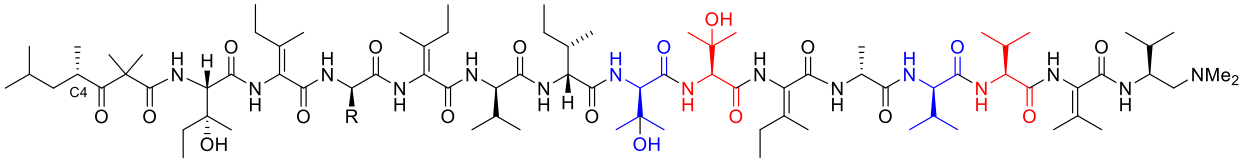
The acyclic peptides yaku'amide A and B were isolated from the *Ceratopsion* sponge collected at a depth of 150 m from the East China Sea, by Matsunaga et al. in 2010.[1] These linear tetradecapeptides feature unusual molecular architecture such as rare *N*-terminal acyl and *C*-terminal amino groups, and they are rich in α,β-dehydroamino acid (ΔAA) and β-hydroxyamino acid (β-OHAA) residues, including *Z*-dehydroisoleucine (ΔIle), *E*-ΔIle, and dehydrovaline (ΔVal, Figure 1.1). It is noteworthy that the *Z*-ΔIle structure was unprecedented in natural products. The initially proposed structures of the peptides were based on extensive nuclear magnetic resonance spectroscopic analysis (^{1}H, ^{13}C, COSY, HMBC, HMQC) and chemical degradations. The C-4 configuration of the *N*-terminal acyl subunit was undefined. In 2013, Inoue et al. synthesized the proposed structure of yaku'amide A and determined the C-4 S-configuration.[2] In June 2015, a new structure of the yaku'amides was determined by Inoue et al., which showed that the originally proposed sequence of the neighboring L- and D-β-OHVal and L- and D-Val residues were switched.[3] Possibly, the chemical degradation products were not characterized correctly during the original structure elucidation step. To simplify the naming, the originally determined structures will be represented as yaku'amide A' (**1**, Figure 1.1) and B' (**2**) and the corrected structures as yaku'amide A (**3**) and B (**4**) in this thesis.

Biological tests showed the potent anticancer activity of the yaku'amides. The IC_{50} values for yaku'amide A and B against P388 murine leukemia cells are 14 and 4 ng/mL, respectively. The inhibition profile of yaku'amide A towards a panel of 39 human cancer cell lines (JFCR39) is unique compared to 38 known anticancer drugs that have been tested in this panel. Thus, it is believed that yaku'amide A possesses a novel mode of action to kill cancer cells.

However, the isolation of this natural product in minute quantities (ca. 1 mg) hinders further detailed study to elucidate its anticancer mechanism. Therefore, it is vital to synthesize yaku'amide A in the lab for further anticancer studies.



Yaku'amide A' (**1**), R = H
Yaku'amide B' (**2**), R = CH_3



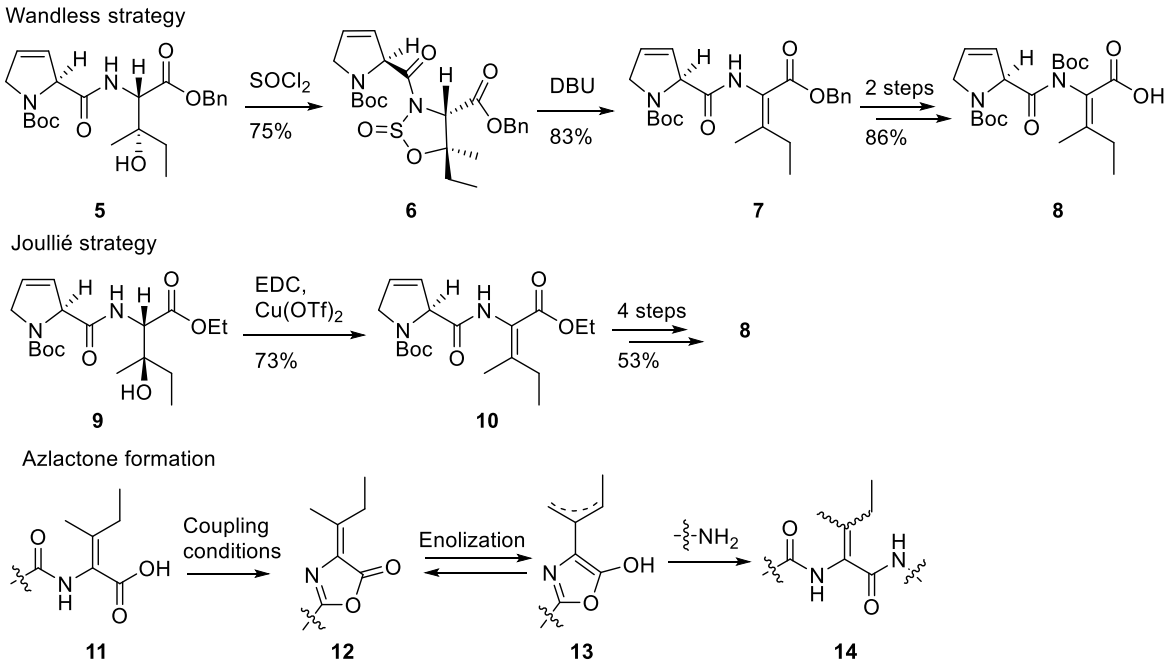
Yaku'amide A (**3**), R = H
Yaku'amide B (**4**), R = CH_3

Figure 1.1 Yaku'amide A' and B'; yaku'amide A and B.

1.2 Prior art for the synthesis of *Z*- and *E*-ΔIle

α,β-Dehydroisoleucine (ΔIle) is a key component of several bioactive peptide natural products.[4] The *E*-ΔIle-containing phomopsins have been the focus of several research groups, and significant effort has been devoted to achieving a stereoselective construction of *E*-ΔIle.[5] In their efforts toward the total synthesis of phomopsins, the Wandless and Joullié groups independently developed stereospecific dehydrations of β-hydroxyisoleucine (β-OHIle) derivatives for the construction of *E*-ΔIle. Wandless et al. devised a two-step protocol involving

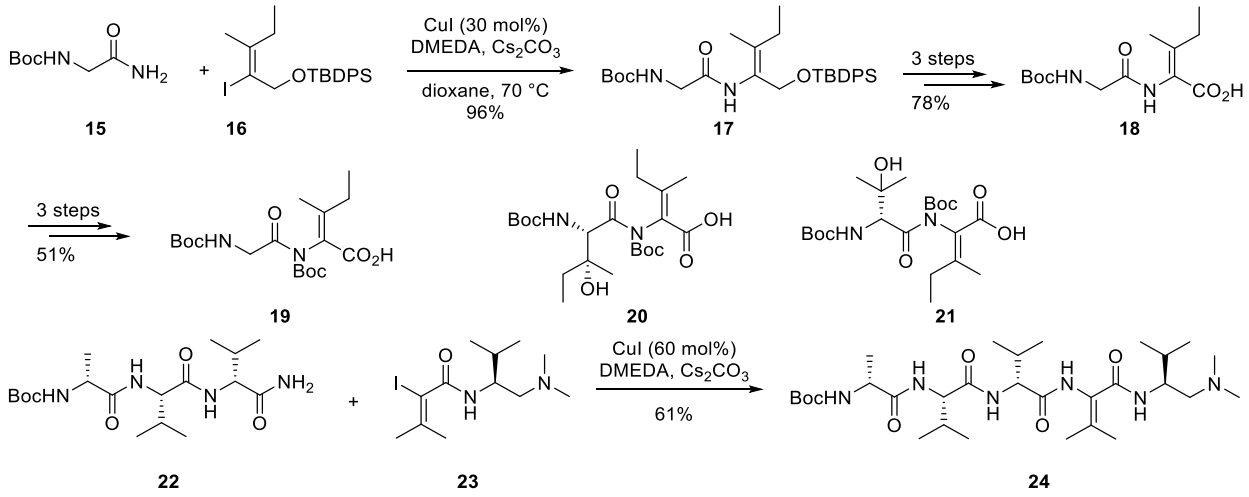
the DBU-promoted *anti* elimination of a cyclic sulfamidite intermediate **6** obtained from treatment of β-OHIle-containing dipeptide **5** with $SOCl_2$. Joullié et al. developed a $Cu(OTf)_2$-catalyzed and EDC-promoted *syn* elimination of β-OHIle derivative **9** (Scheme 1.1). Dipeptide **8** is a key component for the natural products phomopsin A and B.[6] During the course of converting the ΔIle-containing esters **7** and **10** to the carboxylic acid **8**, the backbone amide protection was performed by both groups to facilitate the peptide chain elongation without alkene isomerization. This extra protection step is mandatory due to the facile formation of an azlactone intermediate **12**, which is highly enolizable and leads to the alkene isomerized coupling product **14** (Scheme 1.1).[3]



Scheme 1.1 Prior art for ΔIle synthesis (Wandless and Joullié) and the azlactone formation.

In the course of synthesizing yaku'amide A', Inoue and co-workers innovatively utilized Buchwald's Cu-catalyzed cross-coupling to deliver the key dehydroamino acids.[7] The original reaction conditions were optimized to fuse alkenyl iodides and primary amides to construct *Z*-

and *E*-ΔIle as well as ΔVal.[2] For instance, primary amide **15** was coupled to vinyl iodide **16** under the DMEDA–Cs_2CO_3–30 mol % CuI conditions, exclusively delivering *E*-ΔIle containing dipeptide **17** (Scheme 1.2). However, possibly due to functional group incompatibilities, protected primary alcohols were used in the cross-coupling instead of the more convenient amides or esters. Upon TBDPS removal from **17**, the primary alcohol was released and further oxidized to carboxylic acid **18** via a SO_3·Py–Pinnick oxidation sequence. Based on the work of Wandless and Joullié, it is not surprising that the backbone amide of **18** was protected to effect an isomerization-free peptide coupling. Similarly, dipeptides **20** and **21** as well as pentapeptide **24** were delivered via this powerful transformation and used to synthesize yaku'amide A'. It is noteworthy that *C*-terminal pentapeptide **24** was constructed via the coupling of enamide **22** and peptide-like iodide **23**.



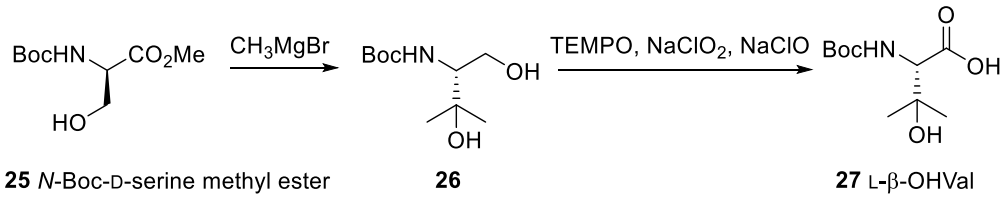
Scheme 1.2 Prior art for ΔIle synthesis (Inoue).

1.3 **Prior art for the synthesis of β-OHIle and β-OHVal**

Besides dehydroamino acids, β-hydroxyamino acids are the other key components of yaku'amide A. Previously, asymmetric syntheses of β-OHVal and β-OHIle have been achieved

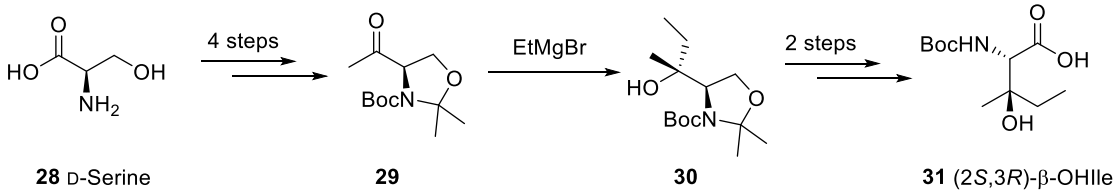
using chiral pool starting materials, which were employed in Inoue's synthesis of yaku'amide A' (vide infra).

Lubell et al. used a Grignard addition of methylmagnesium bromide to the commercially available *N*-(*tert*-Butoxycarbonyl)-D-serine methyl ester **25** followed by a one-step oxidation to convert the primary alcohol to the carboxylic acid L-β-OHVal **27** (Scheme 1.3).[8] The similar L-serine derivative can be used to deliver D-β-OHVal. Therefore, an enantioselective synthesis of both β-OHVal isomers can be achieved in 4 steps from the protected serine derivatives or in 8 steps from D- and L-serine.



Scheme 1.3 Prior art for L-β-OHVal synthesis.

Guanti et al. developed a 7-step protocol to access (2*S*,3*R*)-β-OHIle from D-Serine **28**.[9] The Grignard addition of ketone **29** constructed the stereocenter of the tertiary alcohol **30** with high diastereoselectivity due to chelation control (Scheme 1.4).

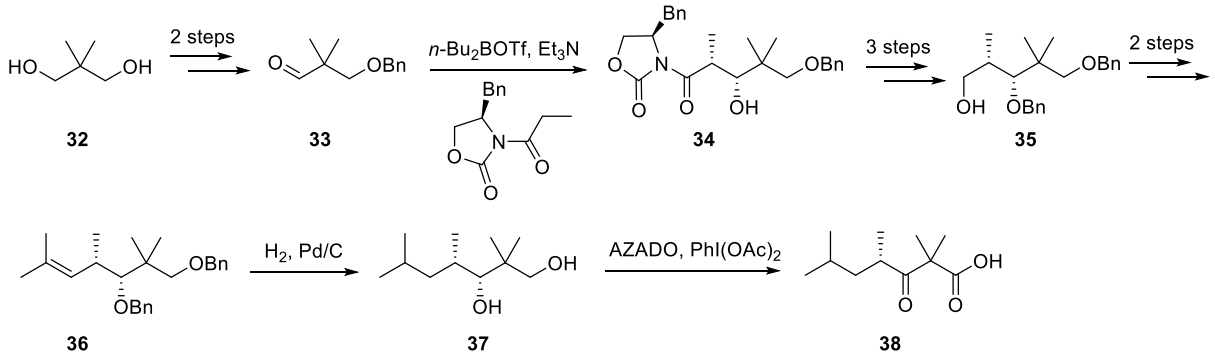


Scheme 1.4 Prior art for (2S,3R)-β-OHIle synthesis.

1.4 **Inoue's synthesis of yaku'amide A'**

To furnish yaku'amide A', Inoue et al. also developed a method to access both enantiomers of the *N*-terminal acyl group (NTA). To simplify the description, only the

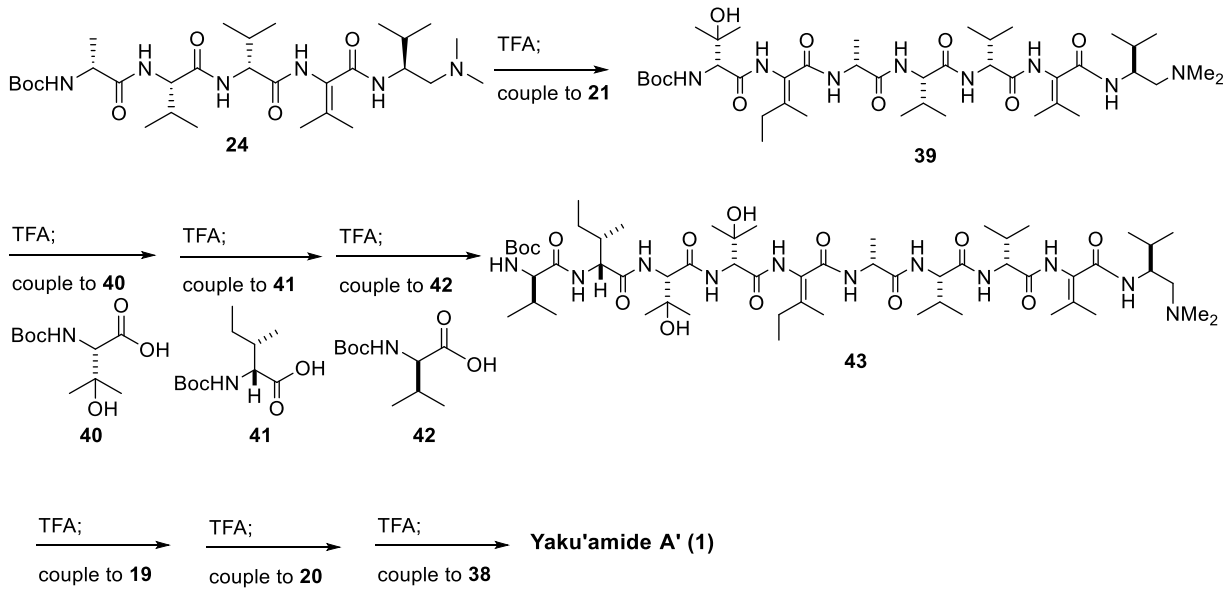
construction of NTA with correct C4-*S* stereochemistry will be discussed here. Evans asymmetric aldol reaction was utilized to selectively deliver the crucial C4 stereochemistry. Aldehyde **33** was obtained from diol **32** via monobenzylation and oxidation, which was reacted with the boron enolate of (*R*)-(–)-4-Benzyl-3-propionyl-2-oxazolidinone to deliver the *syn*-aldol adduct **34** (Scheme 1.5). Reductive cleavage of the chiral auxiliary successfully converted **34** into a diol. Via the combination of protecting group manipulation and carbon-chain elongation, diol **37** was obtained and further oxidized to the *N*-terminal carboxylic acid **38**. It is noteworthy that the mild AZADO−$PhI(OAc)_2$ conditions successfully oxidized **37** to β-ketone carboxylic acid **38** in one pot, without concomitant C4-epimerization or C1-decarboxylation.



Scheme 1.5 Inoue's synthetic route to the N-terminal acyl group.

The successful syntheses of all the required fragments of yaku'amide A set the stage to furnish the natural product. Inoue et al. utilized a "right-to-left" strategy to assemble those fragments due to the availability of the prepared starting materials (all fragments were ending with free carboxylic acids), which also lead to a relatively linear synthesis rather than a highly convergent synthesis. To start the peptide chain elongation process, the Boc group of the *C*-terminal pentapeptide **24** was cleaved and the resulting amine was coupled to dipeptide **21** to deliver the heptapeptide **39** (Scheme 1.6). Six sets of similar operations were able to install all the other fragments and deliver yaku'amide A'. The *C*-4 epimer of yaku'amide A' was prepared

in the same fashion. Spectral comparison of synthetic isomers to natural isolated yaku'amide A determined the *C*-4 S stereochemistry and verified the success of their total synthesis. It is interesting that the ^{1}H and ^{13}C NMR spectra of yaku'amide A' and yaku'amide A are apparently very similar, although they differ in configuration at four stereocenters. Two different coupling systems were used extensively in this project, namely PyBop−HOAt−*i*-Pr_2NEt and COMU−2,4,6-collidine, to eliminate the possible epimerization.



Scheme 1.6 Inoue's route to the total synthesis of yaku'amide A'.

1.5 **Conclusion**

Inoue's work features a highly efficient Cu(I)-catalyzed cross-coupling reaction and a novel route to synthesize the *N*-terminal acyl group. However, the efficiency of this pioneering work suffers from lengthy synthesis of β-OHAAs, inefficient functional group manipulations in the ΔAAs construction, and backbone amide protection. Thus, this work totals 86 steps with a 25-step longest linear sequence. There is a clear need for a more efficient synthesis of yaku'amide A.

To obtain this scarce but promising anticancer agent in a more practical fashion, development of a concise synthesis of *Z*- and *E*-ΔIle and β-OHAAs would be crucial and urgent. Therefore, we initiated research efforts in pursuit of an efficient and backbone amide protection-free stereoselective ΔIle synthesis.

1.6 **References**

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(3) (a) Personal communication between Professor Steven L. Castle and Professor Masayuki Inoue (June 2015); (b) Kuranaga, T.; Mutoh, H.; Sesoko, Y.; Goto, T.; Matsunaga, S.; Inoue, M. *J. Am. Chem. Soc.* **2015**, http://pubs.acs.org/doi/abs/10.1021/jacs.5b05550

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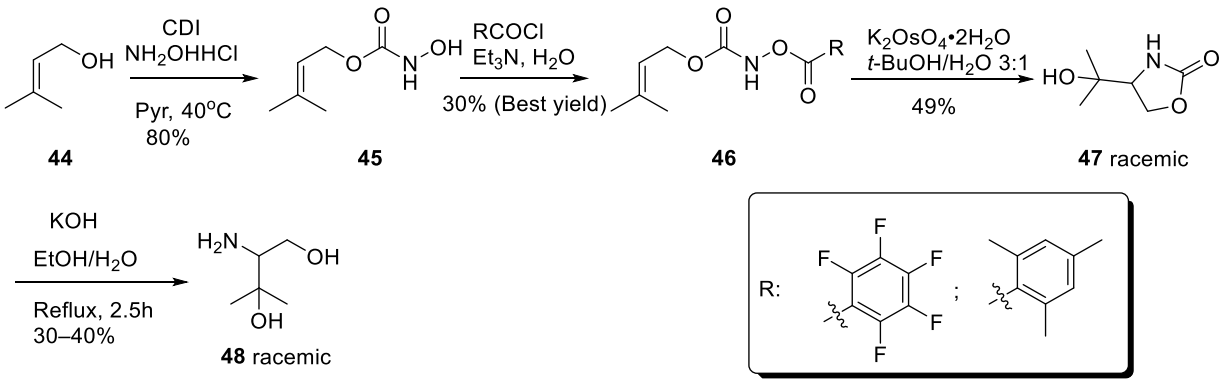
Chapter 2. REGIOSELECTIVE AMINOHYDROXYLATION

2.1 Introduction to aminohydroxylation methods

The unusual amino acid residues are the most challenging substructures incorporated in yaku'amide A, and the synthesis of those AAs dictates the efficiency of the total synthesis of the natural product. Wandless and Joullie's efforts in the ΔIle synthesis enlightened us to construct ΔAA residues via a similar dehydration of β-*tert*-OH amino acids (chapter 1). Among reported methods to synthesize β-*tert*-OH amino acids, the alkene oxyamination chemistry was chosen due to its straightforwardness.[1] The Sharpless aminohydroxylation is well-known for its wide application in asymmetric synthesis of β-OH 1,2-amino alcohols.[2] However, this protocol is not applicable to our project due to the scope limitation of mono- and disubstitued alkenes and the problem of regioselectivity.[3]

To overcome the common regioselectivity problem existing in the intermolecular oxyamination reactions, Donohoe et al. devised a tethered aminohydroxylation method to access β-OH amino acids with fully controlled regioselectivity via an intramolecular pathway.[4] This strategy was attempted in our lab on a trisubstituted allylic alcohol and delivered the desired product **48** (Scheme 2.1). However, multi-step operations were required to tether the nitrogen source to alkene **44** and then remove the tether after the aminohydroxylation. This problem combined with the low overall yield and the difficulty in the aqueous extraction of the polar amino diol **48** made us abandon this route.



Scheme 2.1 Investigation of tethered aminohydroxylation.

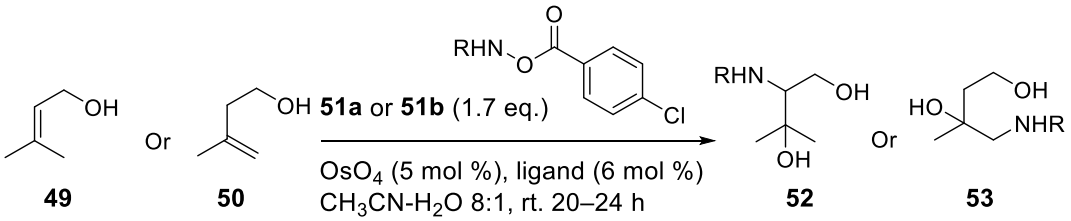
Recently, Luxenburger and co-workers developed a base-free aminohydroxylation method to access the β-OHAAs from mono- or disubstituted alkenes.[5] This method features an intermolecular regioselective *syn* addition of respective nitrogen source and hydroxyl group to the alkenes using a benzoyloxycarbamate. We envisioned the possibility of broadening the scope to the more challenging trisubstituted alkenes to deliver the β-*tert*-OHAAs that are present in yaku'amide A. We hypothesized that the bulkiness of the trisubstitued alkenes would act like a double-edged sword, bringing more steric hindrance but affording better regioselectivity to the aminohydroxylation reaction. The possible drawback could be circumvented via employing high catalyst loadings or higher reaction temperatures.

2.2 **Optimization of the aminohydroxylation conditions**

The study to verify our hypothesis was initiated with the aminohydroxylation of prenol **49**. The reaction was fully regioselective under Luxenburger's conditions (Table 2.1, entry 1).[6] Thus, we further explored the reaction conditions using the model substrates prenol **49** and isoprenol **50** to obtain optimum conditions. The trisubstituted alkene prenol was chosen since its aminohydroxylation product **52** can be used as a ΔVal precursor. The details of our investigation are shown in Table 2.1. There was no obvious reactivity difference between the CH_3CN–H_2O or

t-BuOH–H_2O solvent systems, so the former was chosen as a homogenous solvent system (entries 1 and 3). However, the *N*-Boc carbamate **51b** showed slightly better reactivity than *N*-Cbz (75% versus 63%, entries 2 and 3). Due to the isolation convenience of UV-active compounds, we chose the *N*-Cbz carbamate **51a** to perform our study. For the isoprenol **50**, initial yield obtained was only 30%, possibly due to the extreme bulkiness of one alkene terminus. Analysis of the crude reaction mixture revealed that the hydrolysis of the carbamate **51a** happened predominantly, delivering Cbz-NH_2 as the side product. Similar observations were made by Donohoe with tethered aminohydroxylations.[4d] To circumvent this problem, the use of base additives as ligands was explored and we were pleased to find that pyridine and DABCO both gave improved yields (entries 5–6). However, the use of other bases (i.e., NEt_3, DMAP, imidazole) did not induce any improvement, showing the significance of subtle changes in the ligand-promoted reactions.[7] Finally, we were pleased to find that simple heating brought significant improvement and delivered **53** in 85% yield (entry 7). Thus, the conditions of entry 7 were chosen as the standard to investigate the scope of the aminohydroxylation.

Table 2.1 Optimization of aminohydroxylation conditions.



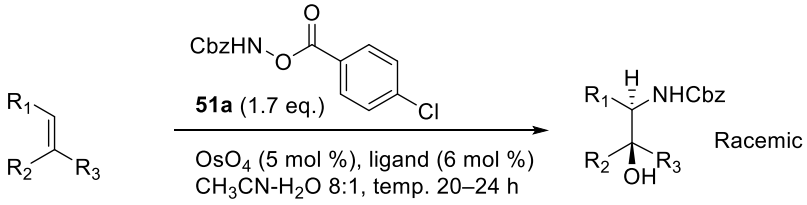
entry	alkene	R	ligand	product	yield
1[a]	**49**	Cbz (**51a**)	none	**52a**	63%
2	**49**	Cbz	none	**52a**	63%
3	**49**	Boc (**51b**)	none	**52b**	75%
4	**50**	Cbz	none	**53**	30%
5	**50**	Cbz	pyr	**53**	61%
6	**50**	Cbz	DABCO	**53**	59%
7[b]	**50**	Cbz	none	**53**	85%

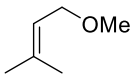
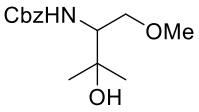
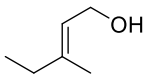
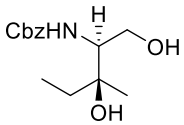
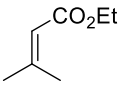
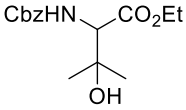
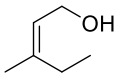
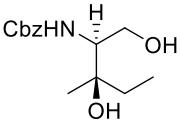
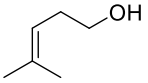
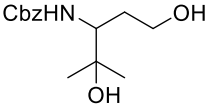
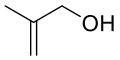
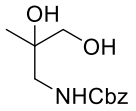
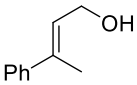
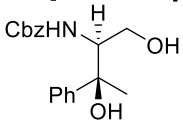
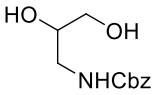
[a]*t*-BuOH–H_2O 6:1 was used as a solvent. [b]Reaction was performed at 35 °C.

2.3 **Investigation of the aminohydroxylation scope**

With the optimal aminohydroxylation conditions in hand, we evaluated the reaction with several di- or trisubstituted alkenes, including allylic or homoallylic alochols and an enoate (Table 2.2). Single regioisomers were obtained in good yields from aminohydroxylations of allylic ether **54**, enoate **56**, and homoallylic alcohol **58** (Table 2.2, entries 1−3). Aminohydroxylations of bulkier trisubstituted alkenes **60**, **62**, and **64** effected the single regioisomers with moderate yields (entries 4−6). This selectivity could be ascribed to the steric differences between the two alkene carbons. Consistent with the study on isoprenol **50**, conversion of methallyl alcohol **66** to the amino diol **67** happened smoothly at rt in good yield (entry 7). Aminohydroxylation of the monosubstituted alkene **68** predominantly delivered the amino diol **69** at 70% yield with 10% cogeneration of the meso isomer (entry 8). A 10 mol % loading of OsO_4 greatly improved the yields with several highly bulky substrates (entries 2, 5, and 6). The respective products **57**, **63**, and **65** can be used as precursors to ΔVal or ΔIle.

Table 2.2 Reaction scope of regioselective aminohydroxylation.



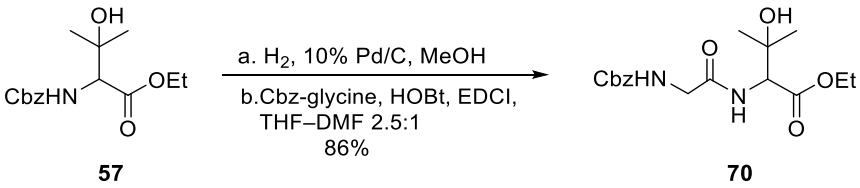
entry	alkene	product [temp., yield]	entry	alkene	product [temp., yield]
1			5		
	54	**55** [35 °C, 54%]		**62**	**63** [45 °C, 38% (55%)[b]]
2			6		
	56	**57** [35 °C, 54% (79%)[a]]		**64**	**65** [45 °C, 41% (59%)[b]]
3			7		
	58	**59** [35 °C, 58%]		**66**	**67** [rt, 62%]
4			8		
	60	**61** [35 °C, 46%]		**68**	**69** [rt, 70%[c]]

[a] 10 mol % OsO_4 was used. [b]10 mol % loading of OsO_4 was used at 35 °C.

[c] A 6.7:1 mixture of regioisomers was obtained.

2.4 **ΔVal-containing peptide synthesis**

With the success in the synthesis of β-OHAAs, we initiated the model study of ΔVal-containing peptide synthesis. β-OHVal **57** was converted to the respective amine via Pd/C catalyzed hydrogenolysis, and the amine was coupled to Cbz-glycine, delivering dipeptide **70** with overall yield of 80% (Scheme 2.2). Due to the robustness of the Cbz group, high pressures of hydrogen (450 PSI) were required to maintain a fast cleavage rate. Convenient accessible dipeptide **70** was chosen as the model compound to investigate the dehydration reactions.

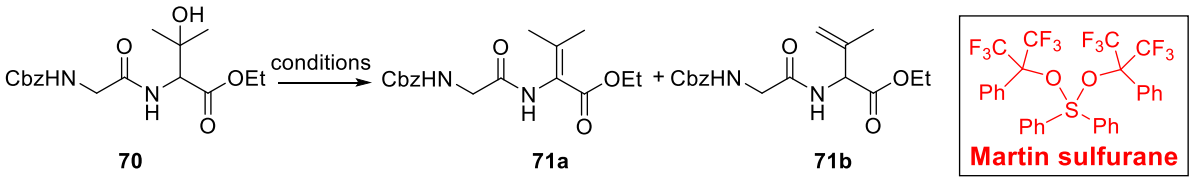


Scheme 2.2 Synthesis of dipeptide **70**.

To dehydrate the tertiary alcohol **70** regioselectively, we screened many conditions reported in the literature (more than 100 different variants), and the representative conditions and results are shown in Table 3. The beginning effort to convert the tertiary alcohol to a mesylate or tosylate was unsuccessful due to facile elimination in situ, delivering both the desired product **71a** and its regioisomer **71b** (entries 1–2, Table 2.3). Attempted one-pot elimination without separation of the intermediates gave similar results. Acetic anhydride related conditions delivered mono- or di-acylated products instead of any further elimination product, and these acetates could not be eliminated under TBAF or DBU conditions (entries 3–5). The Burgess dehydrating reagent gave both regioisomers as well, and attempts to decrease the temperature to improve the regioselectivity were unsuccessful (entry 6). Joullié's EDCI-promoted Copper(II) Lewis acid-catalyzed dehydration was appealing due to its high yielding and one-step operation.[8] However, the application of this method to our substrate was unsuccessful (entries 7–8). Significant effort was devoted to optimizing this method via screening different combinations of solvents, Lewis acids and temperatures, but the best yield we obtained was 30%. Also, this yield was difficult to reproduce (entries 9–10). The Mitsunobu-type conditions and Lewis acid-catalyzed dehydration conditions caused decomposition or returned the starting material (entries 11–14). Dehydrating reagents $SOCl_2$, SO_2Cl_2 and $POCl_3$ were also not able to deliver the desired product **71a** (entries 15–17). Interestingly, the Swern oxidation conditions delivered the elimination product at 21% yield (entry 18). Wandless conditions[9] delivered the desired ΔVal-

containing peptide **71a** at 47% yield (entry 19). Ultimately, we found Martin sulfurane (Table 2.3, shown in red) exhibited superior activity and delivered the dipeptide **71a** in 80% yield (entry 20).[10] This success demonstrates the feasibility of our proposed oxyamination–derivatization–dehydration sequence in producing the crucial ΔAA-containing peptides.

Table 2.3 Investigation of dehydration conditions.



entry	reaction condition	result
1	MsCl, NEt_3; DMAP or DBU or Pyr	**71a** and **71b**
2	Tf_2O, Pyr. CH_2Cl_2 -78 °C or 0 °C	**71a** and **71b**
3	Ac_2O, DMAP, NEt_3	*N*- and *O*-acylation product
4	Ac_2O, 100 °C	*O*-acylation product
5	$Sc(OTf)_3$, Ac_2O, 60 °C	*N*- and *O*-acylation product
6	Burgess's Reagent, -30 °C or 0 °C or rt	**71b**
7	EDC, $CuCl_2$, Toluene, 80 °C	Decomposition
8	EDC, $Cu(OTf)_2$, THF/ DMF, 60 °C	**71a** 33% (Not reproducible)
9	$Yb(OTf)_3$, EDC, THF, 70 °C	**71a** 30% (Not reproducible)
10	$Sc(OTf)_3$ or $La(OTf)_3$ or $Y(OTf)_3$, EDC, THF, 70 °C	Decomposition
11	I_2, PPh_3, CH_2Cl_2, rt or 60 °C	Decomposition
12	$BF_3.OEt_2$, CH_2Cl_2, rt	No reaction
13	$BF_3.THF$, CH_2Cl_2, rt	Decomposition
14	$CeCl_3 \cdot 7H_2O$, NaI, CH_3CN, rt or reflux	No reaction
15	$POCl_3$, Pyr or NEt_3, 0 °C or rt	Decomposition
16	$SOCl_2$, 2,6-lutidine, CH_2Cl_2	Sulfonamide intermediate
17	SO_2Cl_2, 2,6-lutidine, CH_2Cl_2	Decomposition
18	DMSO, $(COCl)_2$, -78 °C; TBAF	**71a** 21% (brsm: 32%)
19	$SOCl_2$, CH_2Cl_2, NEt_3, -78°C; DBU	**71a** 47%
20	Martin sulfurane, 50 °C, $CHCl_3$	**71a** 80%

2.5 Conclusion

During the course of synthesizing dehydroamino acids, a base-free regioselective aminohydroxylation method was developed, which allows rapid access to β-*tert*-OHAAs. The

application of this method was demonstrated via synthesizing a model ΔVal-containing dipeptide. The dehydration process was mediated by the Martin sulfurane dehydrating reagent. This progress set the stage for the investigation of a synthetic method to access ΔIle-containing peptides stereoselectively.

2.6 **References**

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(8) Shangguan, N.; Joullié, M. *Tetrahedron Lett.* **2009**, *50*, 6748–6750.

(9) Stohlmeyer, M. M.; Tanaka, H.; Wandless, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 6100–6101.

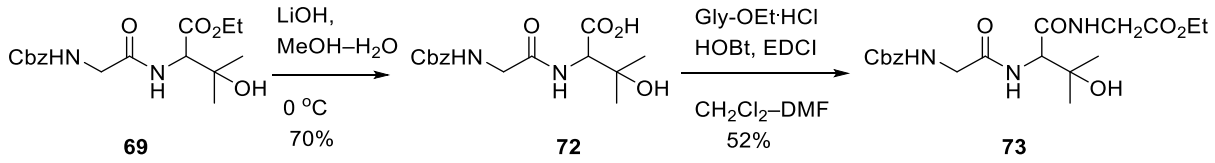
(10) Yokokawa, F.; Shioiri, T. *Tetrahedron Lett*. **2002**, *43*, 8679–8682.

Chapter 3. THE CONSTRUCTION OF ΔAA-CONTAINING TRIPEPTIDES

In Chapter 2, we demonstrated that the ΔVal-containing peptide can be accessed via dehydration of a β-OHVal-containing precursor using Martin sulfurane. In the following stage, we pursued a concise incorporation of tetrasubstituted dehydroamino acids into peptides.

3.1 Attempt of direct dehydration of tripeptide

With the successful synthesis of the ΔVal-containing dipeptide, we considered the possibility of direct dehydration of the tripeptide **73** containing β-OHVal as the middle segment was synthesized from ester **69** via a saponification–coupling sequence (Scheme 3.1).



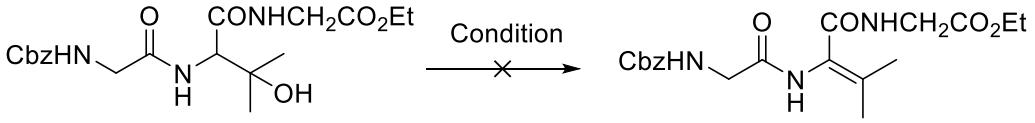
69 **72** **73**

Scheme 3.1 Synthesis of amide **73**.

The best dehydration conditions from Chapter 2 were tested on this more challenging substrate (Table 3.1). Disappointingly, EDCI-Lewis acid combinations did not deliver any detectable product, and only recovered starting material or decomposition was observed (Table 3.1, entries 1 and 2). The Wandless conditions were unsuccessful, as well as the $POCl_3$/Pyr conditions (entries 3 and 4). Various combinations of temperature and equivalents of the Martin sulfurane were screened, but all led to recovered starting material or decomposition (summarized

in entry 5).[1] Therefore, we abandoned the dehydration of β-hydroxy amino acids embedded in peptides and pursued other alternatives.

Table 3.1 Dehydration study of amide **73**.



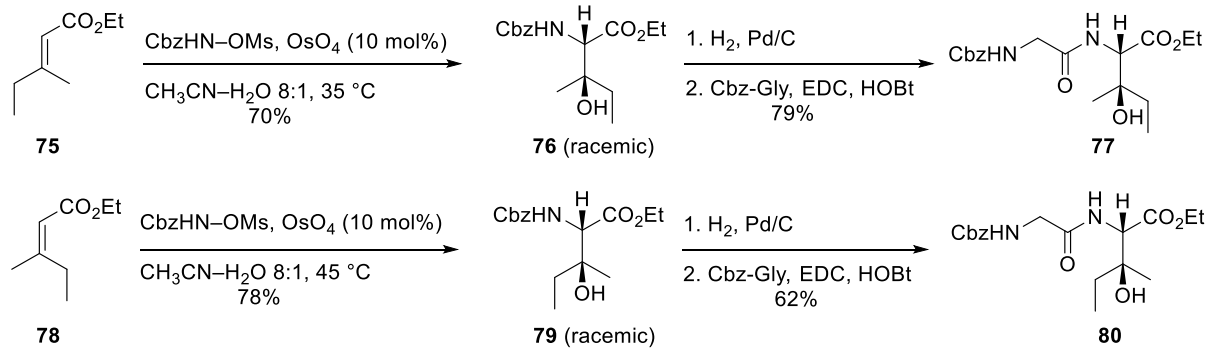
73 **74**

entry	condition	result
1	0.2–0.9 eq $Yb(OTf)_3$, EDC, 60 °C	Starting material
2	0.2–2.0 eq $Cu(OTf)_2$, EDC, 60 °C	Starting material or decomposition
3	i. $SOCl_2$, NEt_3, –78 °C; ii. DBU	Decomposition
4	$POCl_3$, Pyr. 0 °C to rt	Decomposition
5	1.0–3.3 eq Martin sulfurane, rt–80 °C	No reaction or decompostion

3.2 **Aminohydroxylation using a new benzyl mesyloxycarbamate**

The failure in the direct dehydration of **73** as well as pioneering efforts of Wandless and Joullié showed the importance of obtaining a ΔIle ester intermediate en route to ΔIle-containing peptides. Therefore, we focused on the development of a stereospecific dehydration of β-OHIle substrates **77** and **80**, which could be delivered via an aminohydroxylation–coupling sequence from alkenes **75** and **78** (Scheme 3.2).[2] Similar to the aminohydroxylation of isoprenol in Chapter 2, Cbz-NH_2 was obtained predominantly when benzyl *p*-chlorobenzoyloxycarbamate **51a** (Chapter 2) was used to aminohydroxylate the bulky and electron-deficient alkenes **75** and **78**. Herein, a new benzyl mesyloxycarbamate (CbzHN–OMs) was used that delivered aminohydroxylation adducts **76** and **79** with high efficiency and suppressed Cbz-NH_2 generation. The improved activity of CbzHN–OMs could be attributed to the decreased basicity of –OMs leaving group compared to the original 4-chlorobenzoyl group. A related phenomenon was observed by Donohoe and co-workers in their tethered aminohydroxylation work.[3] While the

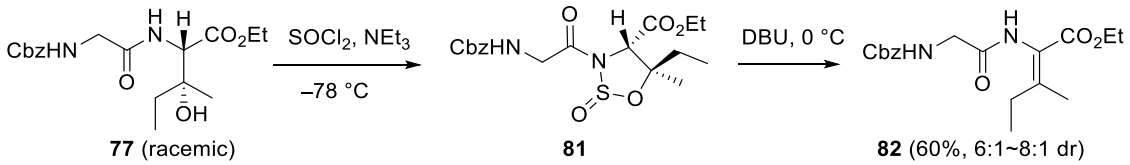
development of a stereoselective dehydration towards *Z*- and *E*-ΔIle was underway in our lab, McLeod group reported the advantageous reactivity of sulfonyloxycarbamates in base-free aminohydroxylations.[4] With the success of constructing **76** and **79**, the backbone elongation strategy used in the ΔVal synthesis worked without incident, affording the model dipeptides **77** and **80** in good yields.



Scheme 3.2 Synthesis of β-OHIle-containing dipeptides **77** and **80**.

3.3 **Investigation of the Wandless dehydration protocol**

Since the Martin sulfurane dehydrating reagent was well known for reacting via an E1-like mechanism with tertiary alcohols,[5] we were not expecting a stereoselective dehydration to occur with this reagent. During the dehydration study outlined in Chapter 2, the Wandless' $SOCl_2$–DBU 2-step protocol was the most promising method for delivering the ΔIle-containing peptides. Therefore, we used this method to pursue a backbone amide protection-free ΔIle synthesis. The moderate yield and stereoselectivity obtained on dehydration of **77** (Scheme 3.3) were not ideal but demonstrated the possibility of using this method for accessing ΔIle-containing peptides.



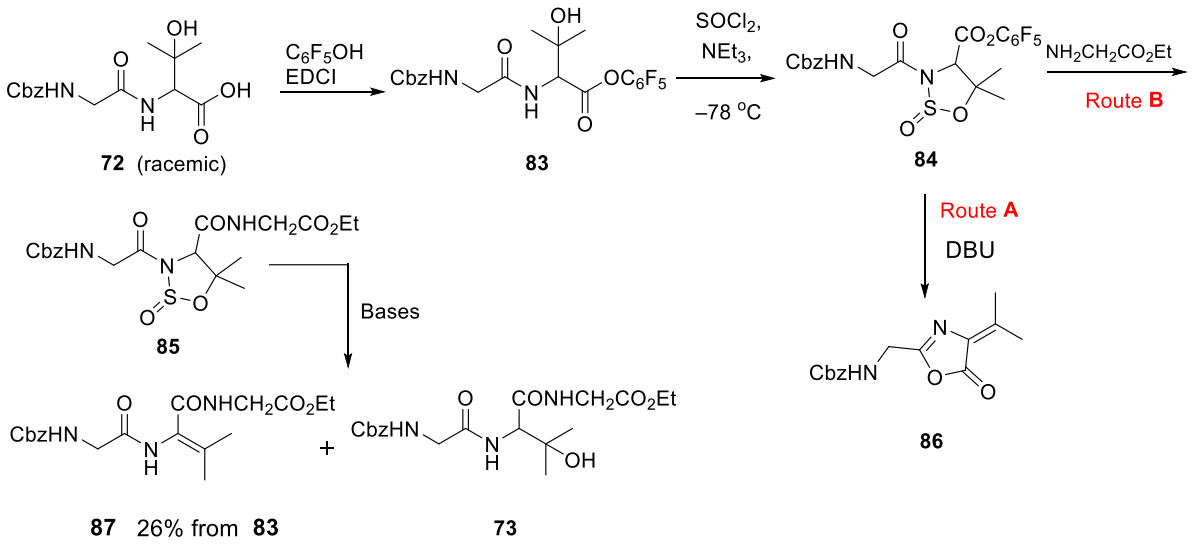
Scheme 3.3 *Anti* dehydration of tertiary alcohol **77** via Wandless method.

3.4 Broadening the Wandless protocol

With the positive results using Wandless chemistry, we considered the possibility of producing ΔIle-containing peptides via transamidation of an activated ester intermediate.

3.4.1 The investigation of pentafluorophenyl (C_6F_5) ester

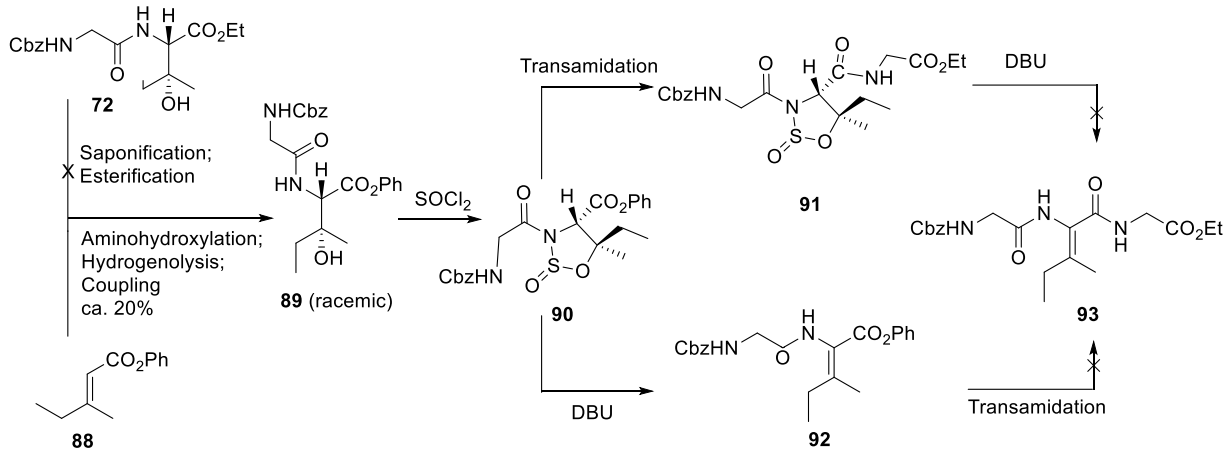
The pentafluorophenyl (C_6F_5) ester was chosen to test our proposal due to its application in amide bond construction.[6] From carboxylic acid **72**, pentafluorophenyl ester **83** was obtained via EDCI•HCl–pentafluorophenol conditions. It was further converted to the sulfamidite intermediate by treating with $SOCl_2$, and two routes were investigated. Route **A** was a dead end since direct elimination of the sulfamidite **84** produced the azlactone **86** exclusively. In Route **B**, sulfamidite **84** was treated with the free amine of glycine ethyl ester, delivering the advanced sulfamidite **85** via transamidation. Unfortunately, the following elimination afforded the desired product **83** and tertiary alcohol **73** as the side product. After screening various bases (TMG, DBU, DBN), the best yield obtained was 24% and the side product generation could not be circumvented. This result is not efficient enough for use in the future total synthesis of yaku'amide A.



Scheme 3.4 The investigation of transamidation via pentafluorophenyl ester.

3.4.2 **The investigation of phenyl ester**

To address the problem of the pentafluorophenyl ester cleavage during the elimination step, we switched to the more robust phenyl ester. We began with a similar saponification–coupling strategy to access the phenyl ester **89** from ester **72** (Scheme 3.5). However, various coupling conditions all led to dehydration of the tertiary alcohol or azlactone formation. Therefore, starting from alkene **88**, an aminohydroxylation–hydrogenolysis–coupling sequence delivered dipeptide **89** (Scheme 3.5). Subsequently, alcohol **89** was converted to sulfamidite **90**, setting the stage to test the transamidation–elimination sequence as well as the sequence with the reverse order. Disappointingly, azlactone was detected in both routes as well as significant decomposition of the starting material. Therefore, the phenyl ester chemistry was abandoned. The aminohydroxylation and Cbz cleavage steps were low yielding and only one attempt of this chemistry was performed, therefore, no exact yields were obtained for the reactions shown in Scheme 3.5 (This rule also applies to most of the investigative chemistry in the dissertation).



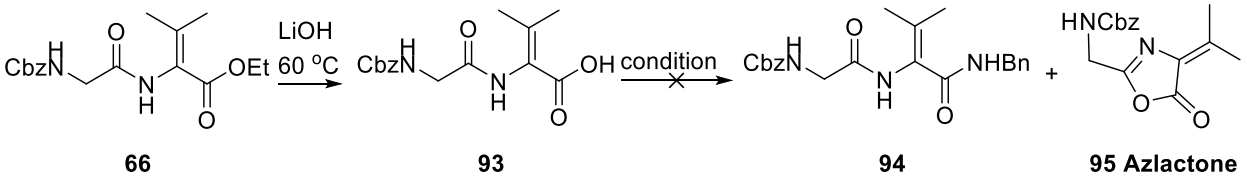
Scheme 3.5 The investigation of Wandless chemistry on phenyl esters.

3.5 **Attempts to elongate the dipeptide via carboxylic acid coupling**

With the failure to combine the Wandless elimination protocol with transamidation, we examined the possibility of fusing the carboxylic acid with an amine using nontraditional coupling conditions to avoid formation of the azlactone intermediate. Several newly reported coupling methods were investigated on our substrate. The $ZrCl_4$-catalyzed coupling reaction with no activated ester intermediate showed the possibility to effect isomerization-free coupling. Therefore, the carboxylic acid **93** was obtained via saponification of **66** and subjected to the coupling conditions. However, product was not detected and the azlactone formation was observed during heating (Table 3.2, entry 1).[7] In 2012, Ashfeld and co-workers reported a peptide coupling method via traceless Staudinger ligation (entry 2).[8] This method featured an O→N acyl transfer to deliver a key phosphite ylide intermediate, which could be hydrolyzed to deliver the amide. Unfortunately, attempts of this method were fruitless and the azlactone side product was formed again. Recently, Sheppard and co-workers developed a $B(OCH_2CF_3)_3$-catalyzed amination process.[9] The attempts with $B(OCH_2CF_3)_3$ resulted in formation of some amide **94** as evidenced by mass spectrometry. However, desired product could not be isolated

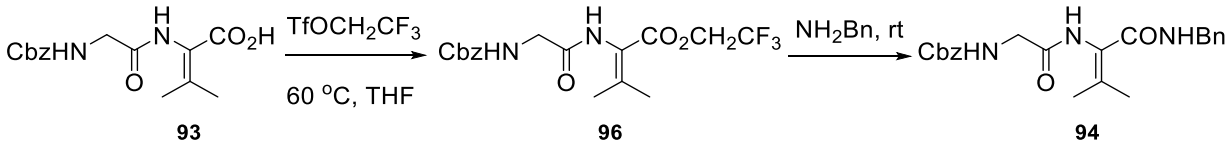
from SiO_2 purfication. NMR analysis of the crude reaction mixture also disclosed significant decomposition (entry 3).

Table 3.2 Non-traditional coupling study.



entry	condition	result
1	25 mol % $ZrCl_4$, NH_2Bn, 70 °C, 22 h	**95** with decomposition
2	BnN_3, $ClP(OEt)_2$, NEt_3, 1,4-dioxane, 80 °C	**95** with decomposition
3	$B(OCH_2CF_3)_3$, NH_2Bn, CH_3CN, 90 °C	Decompostion

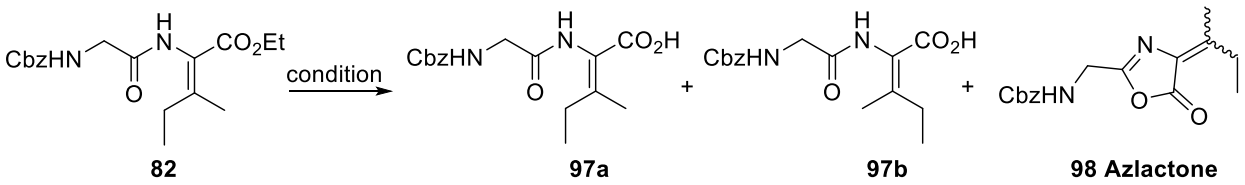
Furthermore, failure in applying the Wandless protocol to pentafluorophenyl ester **83** and phenyl ester **89** led us to conduct an alkylative esterification on the carboxylic acid **93** to form a 2,2,2-trifluoroethyl ester **96**. This attempt was successful and ester **96** was subsequently subjected to the transamination condition. The amide **94** was evidenced by mass spectrometry only when extra equivalents (>100 equiv) of benzyl amine were loaded into the reaction. Therefore, this is not practical for the future total synthesis due to the high cost of enantiomerically pure β-amino alcohols. In addition, the heavy base loading is a concern to cause azlactone formation or perform reversible conjugate addition to the alkene, and either pathway could lead to isomerization of the alkene.



Scheme 3.6 Transamidation of 2,2,2-trifluoroethyl ester.

During the meantime, the saponification of *Z*-ΔIle-containing **82** was tested and it turned out to be a slow process. Careful analysis of the crude reaction mixture via NMR and MS revealed that the hydrolysis process was accompanied by alkene isomerization (ca. 2:1 dr), azlactone formation, or both (Table 3.3). This observation was different from Joullie's report on isomerization-free hydrolysis of a similar substrate, showing that large reactivity variations could be caused by subtle structural differences.[10] Disappointingly, those side reactions were impossible to circumvent after thoroughly tuning of reaction conditions (Table 3.3). The best explanation might be the bulkiness of the ester allowing reversible enolization to happen via γ-deprotonation, which scrambled the ΔIle stereochemistry. Finally, this saponification–nontraditional coupling strategy was abandoned due to the inaccessibility of the crucial carboxylic acid intermediates.

Table 3.3 Investigation of the saponification of ester **82**.



82 **97a** **97b** **98 Azlactone**

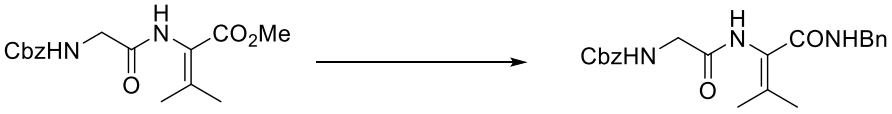
entry	condition	result (**97a** : **97b**)[a]
1	1.1 eq LiOH, EtOH–H_2O, 60 ºC, 3 h, then rt, 15 h	2:1
2	1.0 eq LiOH,THF–EtOH–H_2O, 60 ºC, 24–120 h	1:1
3	1.0 eq LiOH, EtOH–H_2O, 70 ºC, 6 h	2.5:1
4	1.0 eq LiOH, THF–EtOH–H_2O, 70 ºC, 3 h	1:1
5	1.5 eq LiOH, EtOH–H_2O, 60 ºC, 3 h	2:1
6	1.5 eq LiOH, THF–EtOH–H_2O, 60 ºC, 3 h	1.8:1
7	2.0 eq LiOH, EtOH–H_2O, 50 ºC, 2 h	1.8:1
8	2.0 eq LiOH, THF–EtOH–H_2O, 50 ºC, 2 h	1.8:1
9	0.95–2.0 eq LiOH, THF–MeOH–H_2O, 50 ºC, 2 h	2:1–1:1
10	3.3 eq LiOH, 10 eq H_2O, CH_3CN, rt, 72 h	No reaction
11	$CaCl_2$, NaOH, isopropanol–H_2O, rt, 24 h (40 ºC, 3 h)	**82** (**98** with **82**)
12	5 eq LiOH (1M in H_2O), MeOH, rt, 3 d	1:1 with **82**
13	NaOH, EtOH or Dioxane, rt, 24 h or 70 ºC, 1 h	**98** with **82**
14	4.5–7.0 eq Me_3SnOH, $(CH_2Cl)_2$, 80 ºC, 15 h	**98** with **82**
15	LiOOH	**82**
16	LiI, pyr. 130 ºC	Decomposition

[a] The ratio was determined by analysis of the NMR of crude reaction mixture.

3.6 **Transamidation of non-activated esters**

Due to the incapability of performing isomerization-free saponification, the direct transamidation method was considered and investigated. Similarly, the ΔVal-containing methyl ester **99** (Table 3.4) was synthesized via Martin sulfurane mediated dehydration, and subjected to two popular transamidation conditions. The trimethyl aluminum-catalyzed transamidation did not proceed at room termperature or decomposed upon being heated (entry 1). The direct transamidation only happened with large equivalents loading of benzyl amine (entry 2), which is similar to previously tested 2,2,2-trifluoroethyl ester **96** (Scheme 3.6). Therefore, this transamidation pathway via methyl ester was concluded as failure.

Table 3.4 Transamidation of methyl ester.

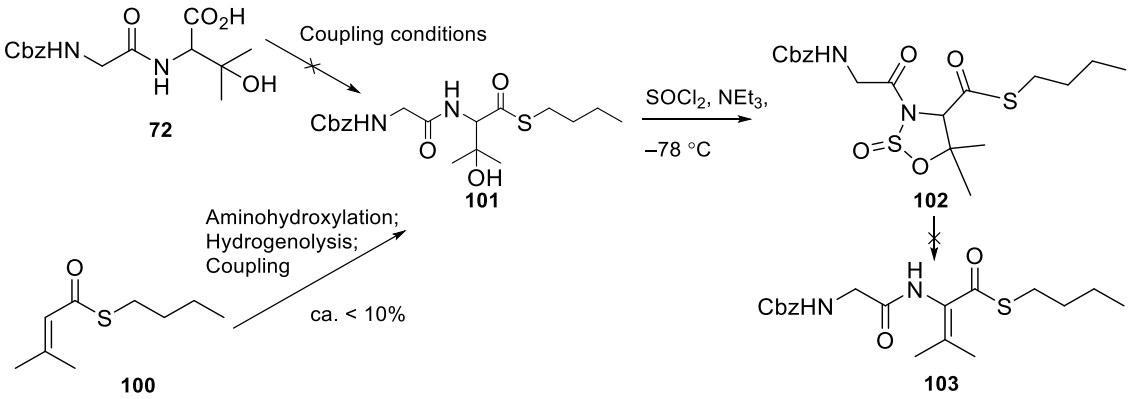


99 **94**

entry	reaction condition	result
1	$AlMe_3$, NH_2Bn, C_6H_5Cl, rt (50–80 °C)	**99** (Decomposition)
2	MeOH, NH_2Bn, rt, 3 d	**94**

3.7 **The attempts of performing thioester coupling chemistry**

Recently, Aimoto reported a thioester-mediated amide synthesis protocol,[11] and Inoue et al. utilized this strategy in the total synthesis of polytheonamide B.[12] Encouraged by the feasibility of this method in challenging coupling reactions as well as the utility of thioesters in amide bond formation,[13] we attempted to synthesize a thioester intermediate to investigate this indirect amide coupling pathway. However, the direct coupling from carboxylic acid **72** to thioester **101** was fruitless (Scheme 3.7). The longer aminohydroxylation–hydrogenolysis–coupling sequence delivered very minor amounts of alcohol **101** from alkene **100**. The low conversion was possibly caused by the incompatibility of the thioester moiety with the aminohydroxylation and hydrogenolysis conditions. Furthermore, the failure of the DBU-promoted elimination of sulfamidite **102** made us abandon this route as well.

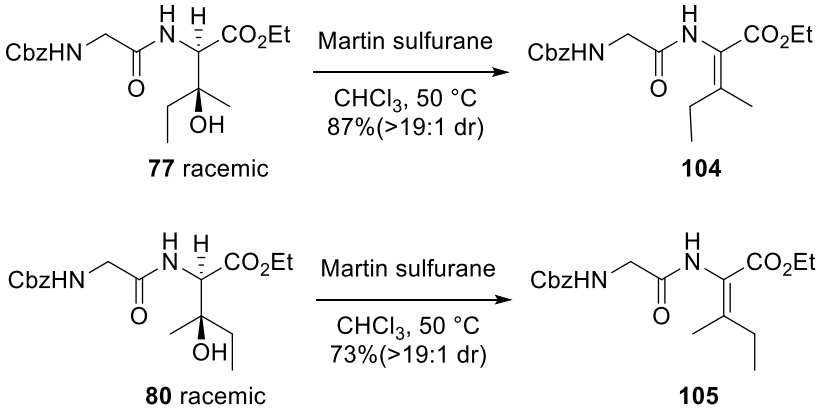


Scheme 3.7 The attempts of synthesizing alkene thioester **103**.

3.8 **Martin sulfurane dehydration**

Due to the fact that the Wandless protocol could not deliver high enough yields and stereoselectivities on our substrates, finding an efficient dehydration method with high selectivity was crucial and urgent to the total synthesis. We pursued useful dehydration method in parallel with an isomerization-free coupling pathway. With all possible known dehydration conditions tested, we decided to try Martin sulfurane dehydrating reagent, which we did not expect to be promising due to its propensity to promote E1 dehydration.[5] Surprisingly, we found that it delivered *Z*- and *E*-dehydroisoleucine-containing peptides **104** and **105** from the alcohols **77** and **80**, respectively, in high yields (Scheme 3.8). Crude NMR analysis of those stereoconvergent dehydration reactions showed that a single detectable isomer **104** or **105** was delivered from a pair of enantiomers (to the limits of detection by ^{1}H NMR), and both alkene isomers are complementary to each other. This one-step dehydration protocol is convenient and powerful, delivering the best yields and diastereomeric ratios among all the tested conditions. This success broadens the application of our aminohydroxylation method, delivering isomerically pure ΔIle-containing peptides in only four chemical transformations from enoates **75** and **77** (Scheme 3.2). Although the cost is relatively high ($50/g), Martin sulfurane can be conveniently synthesized

from inexpensive commercially available starting materials (<$3/g) following Martin's one-step protocol.[14]



Scheme 3.8 Martin sulfurane mediated dehydration of tertiary alcohols.

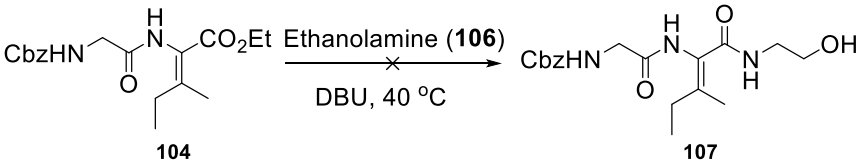
3.9 **Asynchronous E2 *anti* elimination**

This new tertiary alcohol dehydration method was exciting and such high diastereoselectivity cannot be explained by the commonly accepted E1 mechanism. Therefore, density functional calculations (Gaussian 09) were performed by Professor Daniel L. Ess, Yu Cai and Benjamin M. Kay to probe possible reaction pathways (E1, E2 and $E1_{cb}$). The M06-2X/6-31+G(d,p) level of theory was chosen for its accuracy in other E2 transition state barrier calculations.[15] Calculation shows that the E2-*anti* dehydration transition state has lower energy than the E1 carbocation intermediate and E2-*syn* dehydration transition state, and no E1cb transition state or carbanion intermediate was able to be located. These facts indicate that the dehydration proceeded via a highly asynchronous E2-*anti* transition state. [1]

3.10 **Recourse to the transamidation**

With this powerful dehydration method in hand and the experience we gained during the previous study, we reconsidered the transamidation strategy on ethyl ester **104** or **105**, which

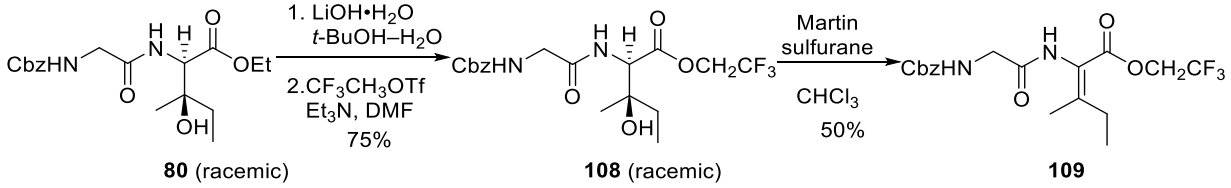
could be a most convenient transformation to incorporate ΔAAs into peptides. Recently, Costa and co-workers reported a DBU-catalyzed transamidation method from unactivated esters to amides.[16] Encouraged by their results, we used ester **104** to test the conditions, however, no conversion was observed under reported conditions (Scheme 3.9).



104 **107**

Scheme 3.9 Transamidation of ethyl ester **104**.

Pirrung and coworkers reported a transamidation employing ethanolamine via an esterification–O→N acyl transfer sequence and they proposed a novel mechanism.[17] The intramolecular hydrogen bonding between the amine and the alcohol of the ethanolamine makes the oxygen atom a better nucleophile to attack the mildly activated ester, effecting a transesterification process. A subsequent O→N acyl transfer would be driven by the formation of the more stable amide bond. To test this new chemistry, alkene **109** was produced via alkylative esterification–dehydration sequence with >20:1 dr from ester **80**.



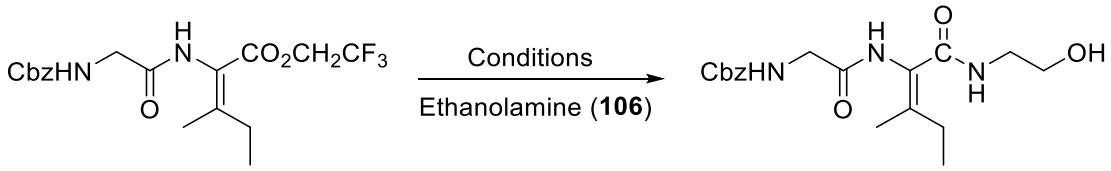
80 (racemic) **108** (racemic) **109**

Scheme 3.10 Synthesis of 2,2,2-trifluoroethyl ester **109**.

2,2,2-Trifluoroethyl ester **109** was subjected to the ethanolamine–toluene conditions, but no conversion of the ester **109** to amide **110** was detected (entry 1, Table 3.5). Using additives such as $NaHCO_3$, K_2CO_3, $CeCl_3$, or adjusting reaction conditions, such as switching to other solvent systems or increasing loading of the ethanolamine were fruitless (entries 2–5, 7–9).

Similar to previous observations, the transamidation occurred while excess ethanolamine (21 eqiv, entry 6, Table 3.5) was loaded into the system, delivering **110** with scrambled alkene stereochemistry as evidenced by NMR analysis of crude reaction mixtures. A reasonable explanation is that the large amount of amine promoted reversible conjugate addition to the alkene, thereby eroding the alkene integrity. Another possibility is that the basic conditions could promote azlactone formation, then subsequent ring opening delivered the product as alkene isomers. The ethanolamine–K_2CO_3–DMA combination also provided the transamidation product upon heating, and the alkene integrity was scrambled even with usage of 1.0 eq base, showing the challenge of performing such transformations on this delicate ester. Those observations excluded the application of this strategy to backbone protection-free ΔIle synthesis.

Table 3.5 Investigation of the hydrogen bonding involved transamidation.



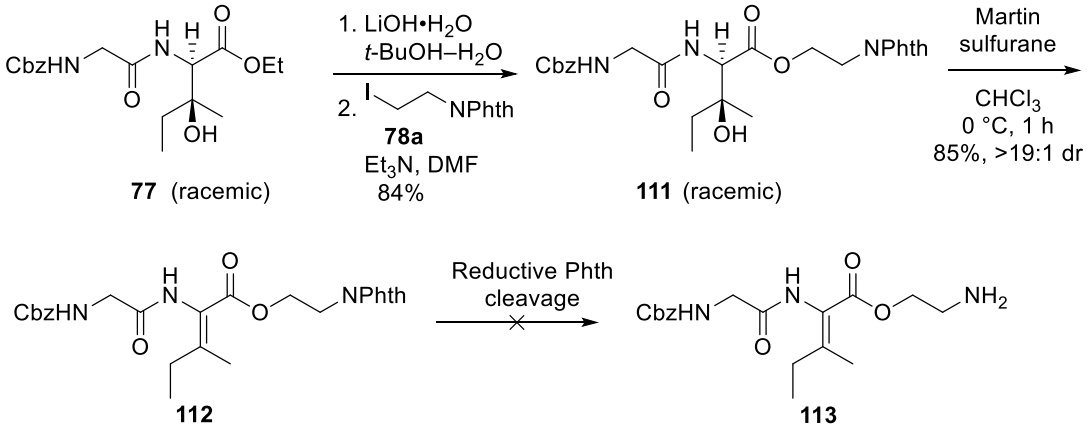
109 **110**

entry	conditions	result
1	3.0 eq , Toluene, rt or 70 ºC, 15 h	No reaction
2	3.0 eq **106**, $NaHCO_3$, toluene, 70 ºC, 15 h	No reaction
3	3.0 eq **106**, $NaHCO_3$, THF–H_2O, rt, 60 h	No reaction
4	1.0–6.0 eq **106**, Benezene, rt	No reaction
5	6.0 eq **106**, acetic acid, cyclohexane, rt	No reaction
6	21.0 eq **106**, cyclohexane, acetic acid, rt	**110** with scrambled alkene configuration
7	1.5 eq **106**, toluene, 50 ºC, 1.5 h	No reaction
8	1.0 eq **106**, $CeCl_3$, CH_2Cl_2, rt	Decomposition
9	1.0 eq **106,** K_2CO_3, DMA, 60 ºC	**110** with scrambled alkene configuration

3.11 **Advanced ester dehydration and O→N acyl transfer investigation**

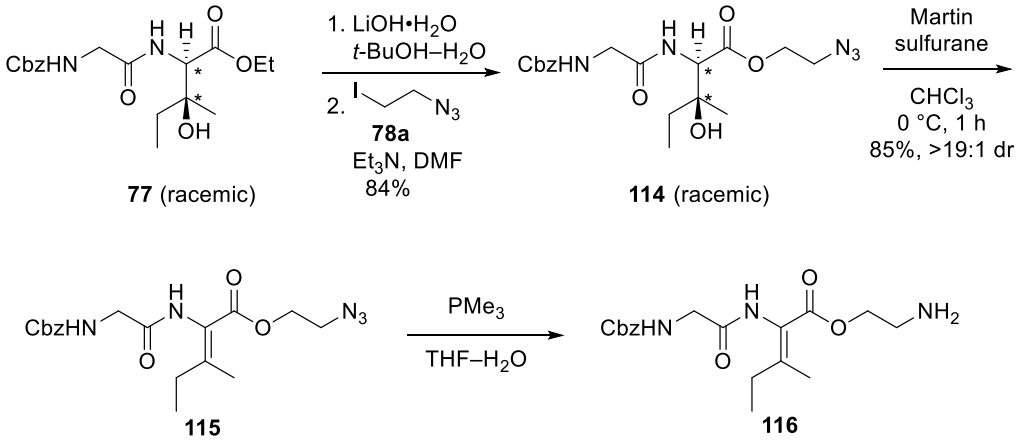
The lesson we learned from the previous ΔIle-containing peptide synthesis is that intermolecular couplings or transamidation processes cannot compete with the intramolecular azlactone formation (or possible intermolecular conjugate addition in certain cases). Either undesired pathway could cause the scrambling of the alkene integrity of ΔIle. To circumvent the azlactone formation, an activated ester should not be involved in the coupling process. However, to trigger an intermolecular transamidation to an unactivated ester, extra equivalents of free amine were required, and this in turn might promote the fatal reversible conjugate addition. Therefore, an intramolecular version of the transamidation, namely "O→N acyl transfer", was adapted and corresponding model compound **111** was synthesized (Scheme 3.11). The phthalimide acted as a masked amine, which could be deprotected to reveal the free amine. We hypothesized that O→N acyl transfer could be triggered to deliver the more stable amide bond under appropriate conditions, and hopefully this activated-ester-free intramolecular transamidation would not scramble the alkene configuration. Starting from ester **77**, the three-step sequence of saponification, alkylative esterification with glycine surrogate **78**, and Martin sulfurane dehydration proceeded smoothly and delivered ester **111** in >19:1 dr (Scheme 3.11). The glycine surrogate **78** represented the least hindered amino acid connected to the *C*-terminus of an ΔIle residue in yaku'amide A. The facile dehydration of *C*-terminal β-hydroxylamino acids during couplings was frequently observed in our previous studies, which necessitated this alkylative esterification step. Unfortunately, decomposition of the starting material occurred inevitably during the following phthalimide cleavage step.

Possibly, the unsaturated ester moiety of **111** cannot survive the basic hydrazine conditions, which are commonly used to cleave phthalimide.



Scheme 3.11 Investigation of O→N acyl transfer using NPhth as amine surrogate.

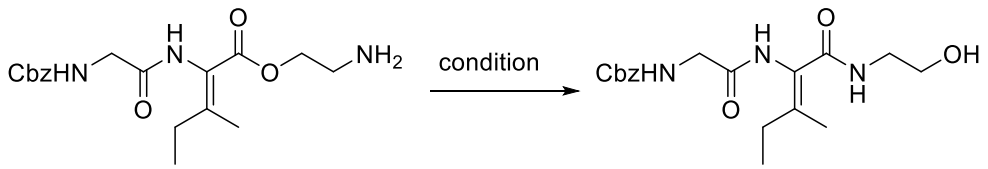
With the failure of Phthalimide deprotection as well as the success of dehydrating tertiary alcohol **111**, a new β-azido iodide **78a** was used as an alternative in the alkylating step and delivered the azido ester **114** (Scheme 3.12). This choice was based on the facile reduction of azides under mild Staudinger reduction conditions. Gratifyingly, the alkylation and Martin sulfurane mediated dehydration delivered alkene **115** with excellent results. Also, the crucial azide reduction proceeded smoothly with 3 equivalents of PMe_3 at 0 ºC. However, careful analysis of the crude NMR obtained after aqueous workup as well as the TLC (R_f value 0.0 under 10% MeOH/CH_2Cl_2 conditions, being sensitive to the Ninhydrin stain) disclosed that the ester **116** did not spontaneously rearrange to form the respective amide **117** (Table 3.6) automatically. Thus, further manipulation was required to trigger the O→N transfer process.



Scheme 3.12 Investigation of O→N acyl transfer using azide as amine surrogate.

To convert the amine **116** to amide **117**, the solvent effect was considered at first. Various solvent systems were screened but in vain (entries 2–8, Table 3.6). The mild base pyridine could not promote the acyl transfer chemistry either (entry 6). Fortunately $NaHCO_3$ in THF–H_2O promoted the acyl transfer chemistry and delivered the corresponding amide **117** in excellent yield and 6:1–9:1 dr (entry 1). In addition, we found that various organic bases could trigger the acyl transfer chemistry with different rates (entries 10–15), while some bases led to decomposition (entry 16) or isomerization (entry 17). We also observed that a reverse "N→O acyl transfer" could happen to amide **117** under acidic conditions. Ultimately, the use of morphline or piperidine afforded the ΔIle-containing peptide **117** in >10:1 dr (entries 10 and 13).

Table 3.6 Testing of the O→N acyl transfer process.



116 **117**

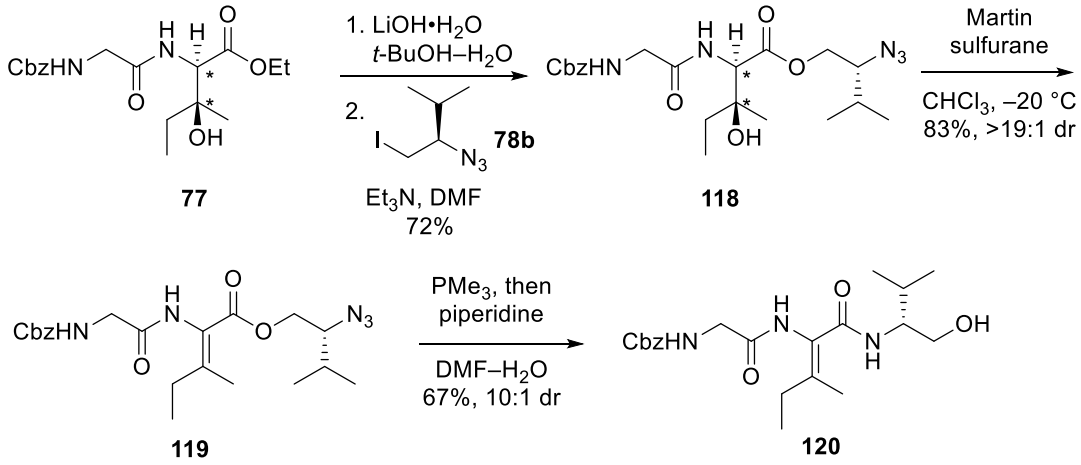
entry	condition[a]	result[b]
1	$NaHCO_3$, THF–H_2O, 24 h	80%, 6:1–9:1 dr
2	Tolene, 24–168 h:	No progress
3	THF, 24–168 h	No progress
4	THF, 50 °C, 14 h	Sluggish progress with isomerization
5	$CDCl_3$, 408 h	Half conversion to **117**
6	Benzene, 72 h	Sluggish progress
7	Pyr, 24–72 h	No progress
8	Toluene, 35 °C, 15 h	Sluggish progress with isomerization
9	Toluene, 50 °C, 14 h	Alkene isomerization
10	Silical gel, THF, 24 h	No progress
11	Piperidine, THF–H_2O, 24 h	67%, 11.5:1 dr
12	Piperidine, EtOAc–H_2O	Very sluggish progress
13	*N*-methylmorpholine, THF–H_2O, 60 h	Sluggish progress
14	Morpholine, THF–H_2O, 60 h	60%–90%, 10.5:1–16:1 dr
15	Morpholine, THF, MS 4Å, 15 h	Sluggish progress with decomposition
16	Morpholine, THF–H_2O, 40 °C, 15 h	60%, 6:1 dr
17	NEt_3, 48 h	Possible decomposition
18	*N,N,N'*-Trimethylethylenediamine, THF–H_2O, 24 h	2:1 dr

a: All reactions were performed at rt, unless marked with other temperature.
b: The dr is the intergration ratio in NMR between *Z*-ΔIle product and *E*-ΔIle side product.

3.12 **The synthesis of model peptide Cbz-Gly-*Z*-ΔIle-D-Valinol**

The success of the synthesis of Cbz-Gly-*Z*-ΔIle-Glycinol **117** was exciting and encouraged us to test the feasibility of this method with other ΔIle-containing model peptides. Very similarly, the ester **119** was obtained efficiently from ester **77** (Scheme 3.13). Here, the valine surrogate **78b** represented the most hindered amino acid connected to the *C*-terminus of ΔIle residue in yaku'amide A, which was assumed to be the most challenging substructure. The Martin

sulfurane dehydration happened smoothly with excellent yield and dr. Upon Staudinger reduction using PMe_3, the azide **119** was reduced to amine, and one-pot addition of base triggered the O→N acyl transfer and delivered amide **120** with minimal alkene isomerization. Interestingly, we observed the dr of the products from the O→N acyl transfer varied under THF–H_2O–morpholine and DMF–H_2O–piperidine conditions. Nonetheless, both combinations delivered usable results to be applied to total synthesis.



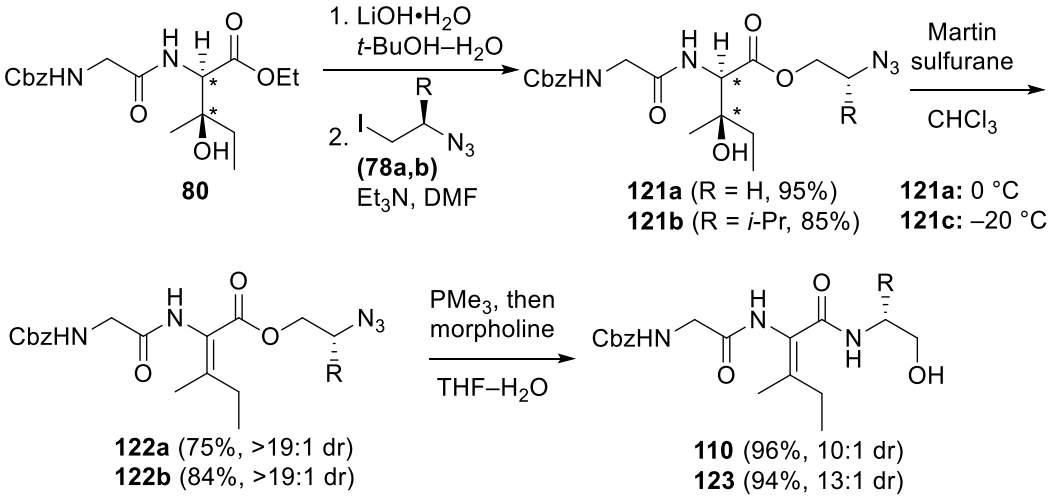
Note: Stereocenters marked by asterisks possess the indicated relative stereochemistry. (This rule works for all the chapters of this disseration.)

Scheme 3.13 Synthesis of the Cbz-Gly-*Z*-ΔIle-D-Valinol.

3.13 **The synthesis of *E*-ΔIle-containing model peptides**

In the following stage, we were curious to test the diastereoselectivity after the O→N acyl transfer reaction on *E*-ΔIle residue-containing peptides. Gratifyingly, this saponification–alkylative esterification–*anti* dehydration sequence worked equally well as the previous *Z*-ΔIle related synthetic sequence (Schemes 3.12 and 3.13). Isomerically pure alkenes **122a** and **122b** were obtained with high yields and subjected to Staudinger reduction and base-catalyzed

rearrangement conditions (Scheme 3.13). The *Z*-ΔIle-containing tripeptides **110** and **123** were obtained with high efficiency and minimal *E*-to-*Z* isomerization (>10:1 dr).

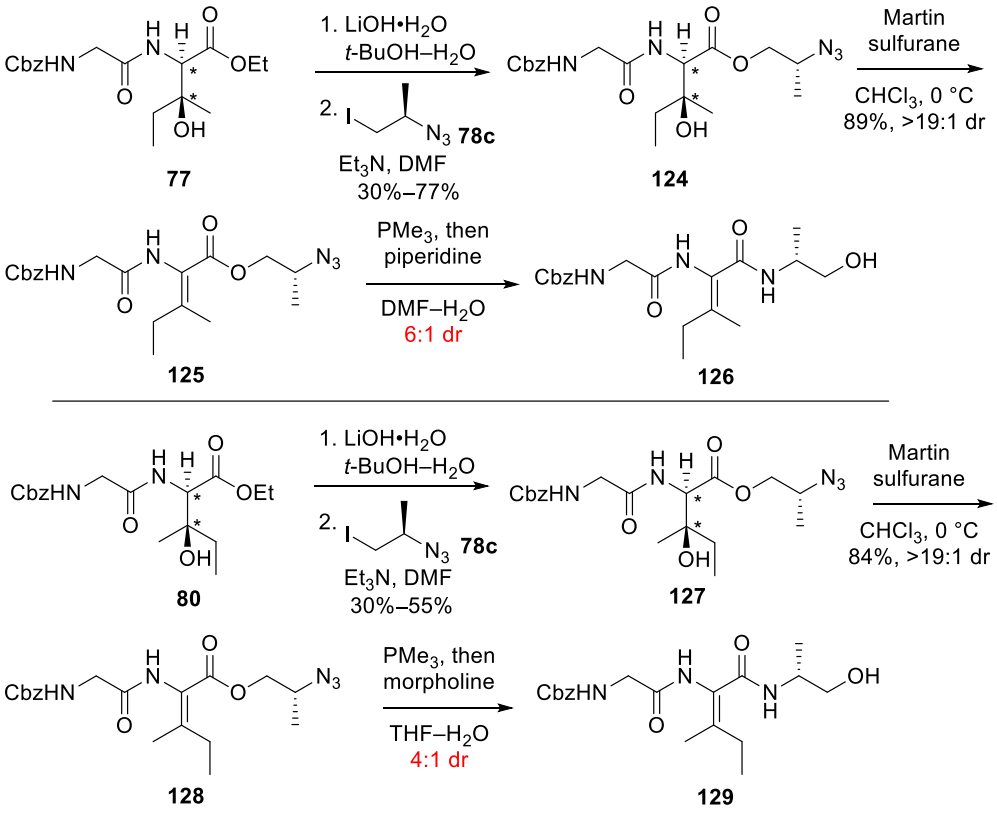


Scheme 3.14 Synthesis of the *E*-ΔIle-containing model peptides.

3.14 **The synthesis of *Z*(*E*)-ΔIle-Alaninol-containing model peptides**

With the successful incorporation of the least and most sterically hindered amino acids at the *C*-termini of the *E*- and *Z*-ΔIle-containing dipeptides, we tested the feasibility of this strategy to install an alanine residue to the C-terminus of ΔIle, which is also present in yaku'amide A. Surprisingly, different reactivity was observed during the course of incorporating this medium-sized residue (Scheme 3.15). The first variation happened in the alkylative esterification process: the standard β-azido iodide (**78c**)–NEt_3 conditions only delivered 30–60% yield after purification, instead of the 80–90% for the glycine and valine surrogates. The second variation was observed during the O→N acyl transfer process: 4:1–6:1 dr was obtained consistently. These interesting results are unusual compared to the results obtained during the synthesis of Gly and Val-containing substrates, which indicated that optimization of reaction conditions in the following total synthesis might be required. Unfortunately, we cannot find any compelling arguments to

explain this phenomenon except that the reactivity difference was caused by subtle structural changes.



Scheme 3.15 Synthesis of the Cbz-Gly-*Z*(*E*)-ΔIle-D-Alaninol.

3.15 **Conclusion**

We have developed a method of incorporating *E*- or *Z*-dehydroisoleucine(ΔIle) residues into peptides via a Martin sulfurane dehydration–Staudinger reduction–O→N acyl transfer sequence. The key transformation is an unusual Martin sulfurane mediated *anti* dehydration of β-OHAA derivatives. This highly efficient method did not require the backbone amide protection chemistry, which is necessary in all other known routes. The success of the model study set the stage for initiating the total synthesis of yaku'amide A.

3.16 **References**

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Chapter 4. PROGRESS TOWARDS THE SYNTHESIS OF YAKU'AMIDE A

With the success of the model study to deliver ΔIle-containing dipeptides, we initiated the total synthesis of yaku'amide A'.[1]

4.1 Retrosynthetic analysis

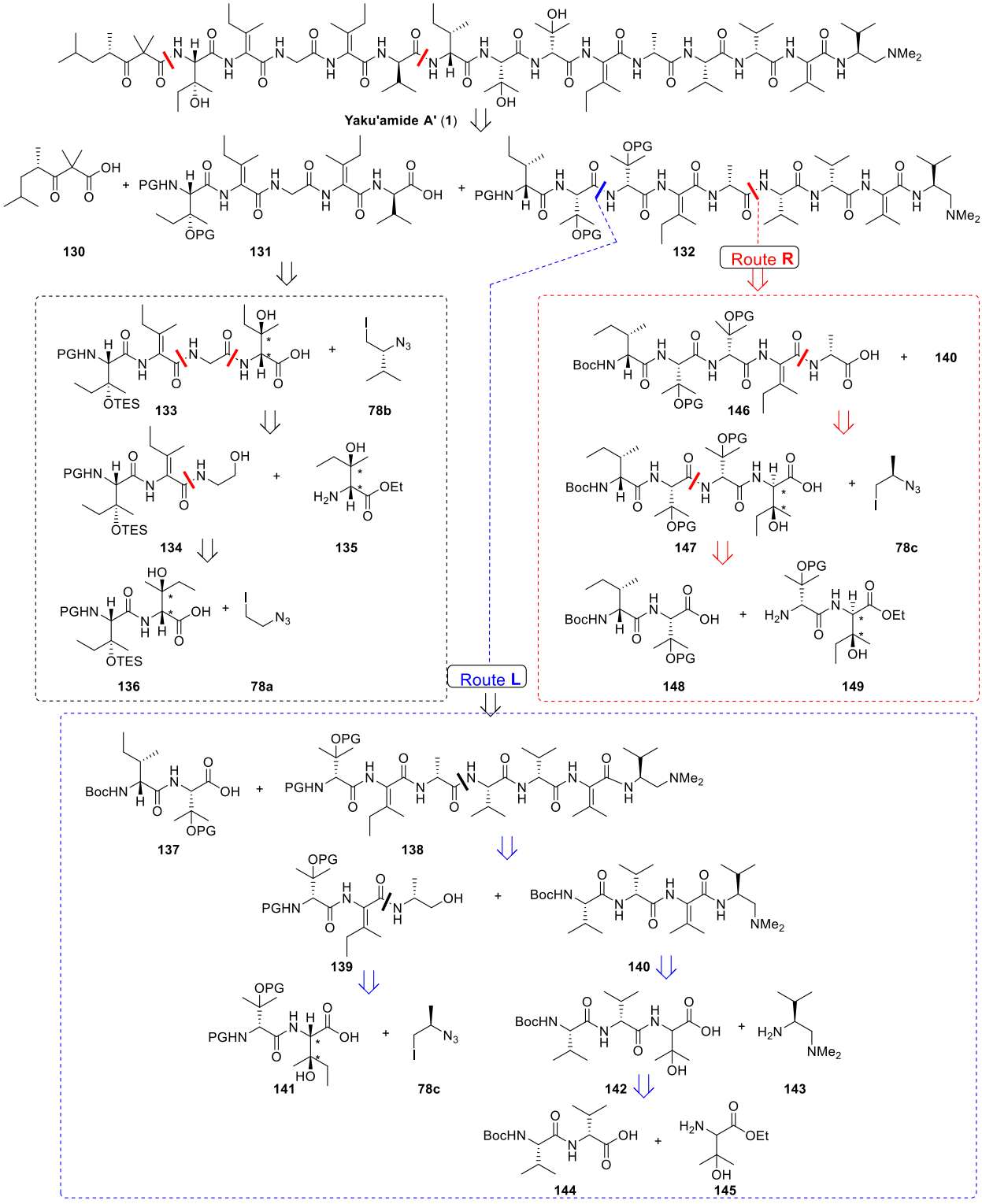
Our retrosynthesis of yaku'amide A' was designed to maximize synthetic convergence based on our O→N acyl transfer chemistry (Chapter 3). Retrosynthetically, **1** is disconnected at two key amide bonds producing three subunits: the *N*-terminus **130**, left-hand pentapeptide **131** and right-hand nonapeptide **132** (Scheme 4.1). The specific protecting groups (PGs) would be identified through experimentation.[2] In the long run, we plan to synthesize the *N*-terminal acyl group via Myer's alkylation[3] followed by a Mukaiyama-type aldol reaction.[4] Inoue's method,[5] although lengthy, would be suitable for quick access to the *N*-terminal acyl group. The construction of the left-hand pentapeptide **131**, containing a β-OHIle-*Z*-Δ-Ile-Gly-*E*-ΔIle-Val sequence, demands a linear synthesis as a result of two dehydration–azide reduction–O→N acyl transfer sequences. To access nonapeptide **132**, there are two possible key scissions at the peptide backbone, which lead to the routes **L** and **R**.

Further scission of those key subunits revealed several smaller intermediates. Scission of pentapeptide **131** revealed tetrapeptide **133** and valine surrogate **78b**. Peptide **133** was further divided into tripeptide **134** and racemic β-OH isoleucine **135**. An alkylation–dehydration–azide

reduction–O→N acyl transfer sequence can fuse dipeptide **136** and glycine surrogate **78a** together to deliver tripeptide **134**, and the *C*-terminus primary alcohol can be oxidized prior to coupling with racemic aminohydroxylation adduct **135** (synthesized in Chapter 3). Dipeptide **136** can be accessed via coupling of the optically active β-OHIle derivative with the racemic aminohydroxylation adduct. The synthesis of subunit **131** would cost most linear steps due to the presence of two ΔIle residues, and we expected it to be the most challenging part of the project.

To access nonapeptide **132** via route **L**, scission of the amide bond connecting the two β-OH-Val residues revealed the dipeptide **137** and heptapeptide **138**, which can be further divided into ΔIle-containing tripeptide **139** and *C*-terminal tetrapeptide **140** (Scheme 4.1). Peptide **139** can be obtained via a similar strategy to the one proposed for tripeptide **134**. Specifically, alkylation product from dipeptide **141** with alanine surrogate **78c** followed by the dehydration–azide reduction–O→N acyl transfer sequence can afford **139**. To synthesize the *C*-terminal tetrapeptide **140**, the ΔVal is the key fragment. Based on the observation of EDCI·HCl-promoted azlactone formation in our lab(vide infra), we proposed to apply the azlactone formation–azlactone ring opening chemistry to construct **140**, which enables the scission of *C*-terminus of ΔVal to deliver **142** and known amine **143**.[6] The tripeptide **142** can be provided straightforwardly via coupling of the dipeptide **144** and racemic aminohydroxylation adduct **145**.

Route **R** represents another possible means of constructing nonapeptide **132** as well. Fragments **146** and **140** are delivered from the first key scission of **132**. Further scission of **146** reveals tetrapeptide **147** and alanine surrogate **78c**, and the former could be accessed via coupling of dipeptides **148** and **149**.



Note: Stereocenters marked by asterisks possess the indicated relative stereochemistry. (This rule works for all the chapters of this dissertation.)

Scheme 4.1 Retrosynthetic Analysis.

4.2 **Synthesis of the right-hand nonapeptide**

In targeting the natural product, we chose the right-hand nonapeptide **132** (Scheme 4.1) as the first synthetic goal since it could be prepared in fewer linear steps than the left-hand pentapeptide **131**. Only one ΔIle residue is incorporated in **132**, rendering it easier to access than **131**.

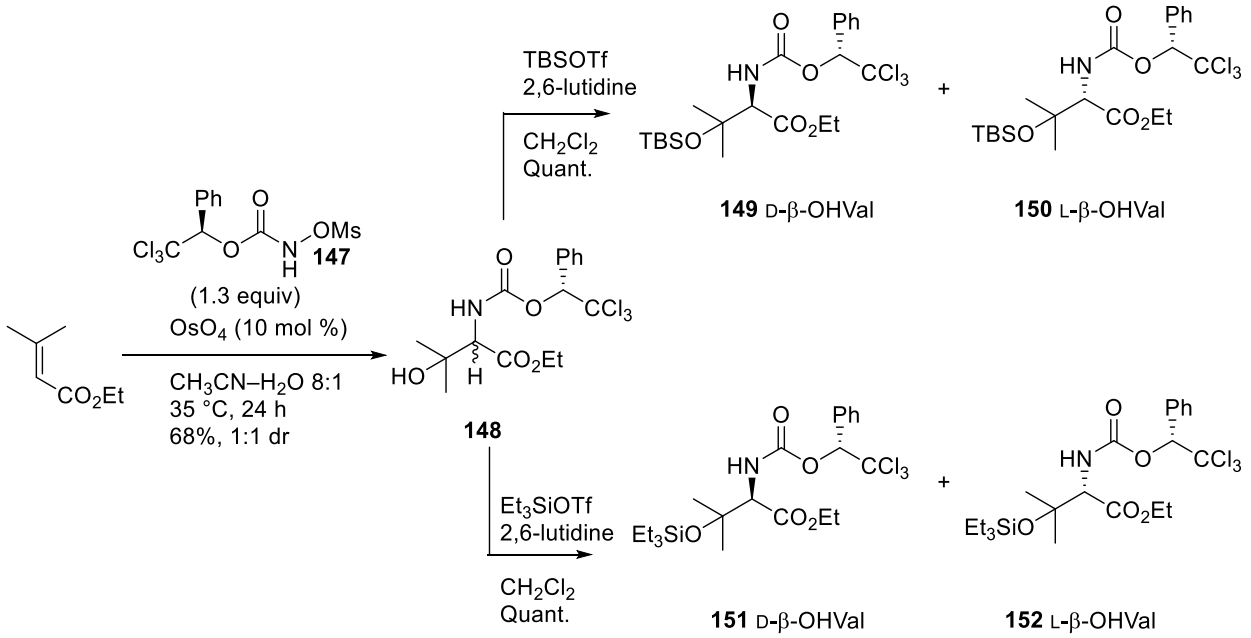
4.2.1 **Investigation of route R**

Of the two possible synthetic routes towards **132** (Scheme 4.1), we initially examined route **R**, which is more convergent. In addition, route **R** will require one less chromatographic separation of tertiary amine-containing intermediates than route **L,** and the purification of such compounds amines can be difficult and time-consuming.

4.2.1.1 **Synthesis of enantio-rich D- and L-β-OH Vals**

To access the β-OH amino acids enantioselectively, co-workers J. Jiang and J. M. Cardon had thoroughly investigated the asymmetric oxyamination. However, useful levels of enantioselectivity were not observed. Fortunately, they discovered a convenient alternative to access enantiomerically enriched β-OHAAs via aminohydroxylation employing Lebel's chiral mesyloxycarbamate **2** (Scheme 4.2).[7] The two diastereomers **148** (1:1 dr) generated via aminohydroxylation, were protected as silyl ethers, and then separated on silica gel. Three chromatographic separations were required to deliver 100 mg of each isomer (dr ≥10:1) from 1 g of the mixture (1:1 dr), providing sufficient material for testing synthetic routes.[8] The attempts to increase the separation efficiency via switching the silyl protecting group were fruitless. Similarly, we can access the desired (2*S*,3*R*)-β-OHIle using the same sequence. This

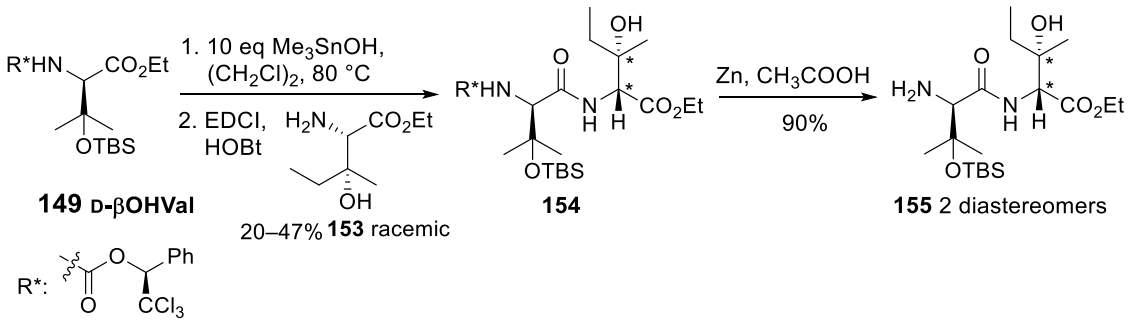
advantageous method enables production of both required β-OHVal isomers in two steps with the required functional groups protected.



Scheme 4.2 Aminohydroxylation employing Lebel's carbamate.

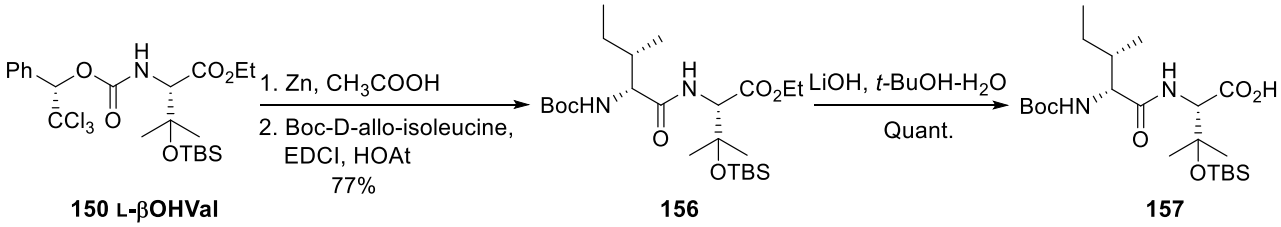
4.2.1.2 **Synthesis of β-OH containing dipeptides**

With success in accessing enatioenriched β-hydroxy amino acids, we began the synthesis of dipeptide **154**. Attempted saponification of ethyl ester **149** under traditional methods was problematic. The common basic hydrolysis conditions (eg., LiOH, NaOH, KOH) inevitably led to the cleavage of the chiral carbamate residue. In light of Nicoloau's work on mild hydrolysis of methyl esters using $SnMe_3OH$, we adapted these conditions and delivered the desired carboxylic acid from **149**.[9] However, subsequent coupling to the racemic amine **153** only afforded 20–47% yield from ester **149**, which may be caused by the inefficient hydrolysis of the robust ethyl ester. This method also suffers from a common disadvantage: ten or more equivalents loading of the toxic and expensive $SnMe_3OH$ is required to promote full conversion. Sufficient material was provided via this inefficient two-step protocol, which enabled the testing of subsequent reactions.



Scheme 4.3 Synthesis of dipeptide **155**.

To access the coupling partner of **155**, the chiral auxiliary of the ester **150** was reductively cleaved under Zn-AcOH conditions and coupling to Boc-D-allo-isoleucine delivered the dipeptide **154** in 77% yield (Scheme 4.4). The Zn–Acetic acid conditions require chromatographic purification to deliver the amine product after Celite filtration, which is inconvenient. The vulnerability of chiral auxiliary observed in the ethyl ester saponification process inspired us to test the LiOH–H_2O–*t*-BuOH conditions for cleavage of the chiral auxiliary. Disappointingly, although the amine product was present in mass spectrometry, following coupling to Boc-D-allo-isoleucine was not able to provide **156** with useful yields. Possibly, this low yielding transformation was the consequence of inefficient aqueous workup or base-promoted decomposition of the starting material. Therefore, this method was abandoned and the Zn-AcOH conditions were set as the standard chiral auxiliary cleavage conditions. Next, the LiOH-promoted hydrolysis revealed the free carboxylic acid **157** without incident.



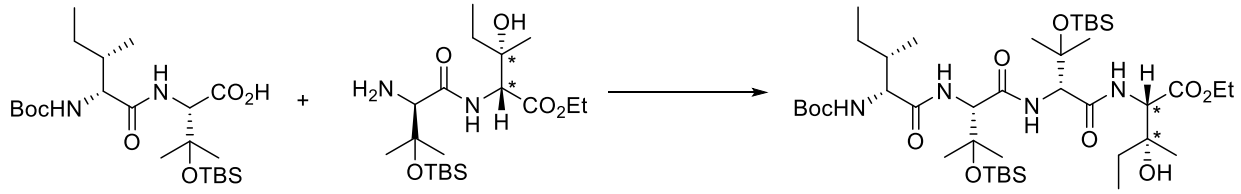
150 L-βOHVal **156** **157**

Scheme 4.4 Synthesis of dipeptide **157**.

4.2.1.3 **Synthesis of central pentapeptide**

With the two advanced dipeptides **155** and **157** in hand, we tested the coupling reaction to deliver the tetrapeptide **158**. EDCI–HOAt conditions were tested first due to their success in the synthesis of dipeptide **156** (Table 4.1). Surprisingly, this coupling reaction was extremely challenging. Attempts to tune the bases in EDCI–HOAT conditions were fruitless (entries 2–4). COMU–2,4,6-collidine conditions failed as well (entry 5). The DEPBT–NEt_3 combinations delivered milligram quantities of the product in 20% yield with concomitant decomposition (entry 1). The difficulty of this coupling may be caused by the bulkiness of the two *tert*-butyldimethylsilyl (TBS) protecting groups.

Table 4.1 Study of the tetrapeptide synthesis.

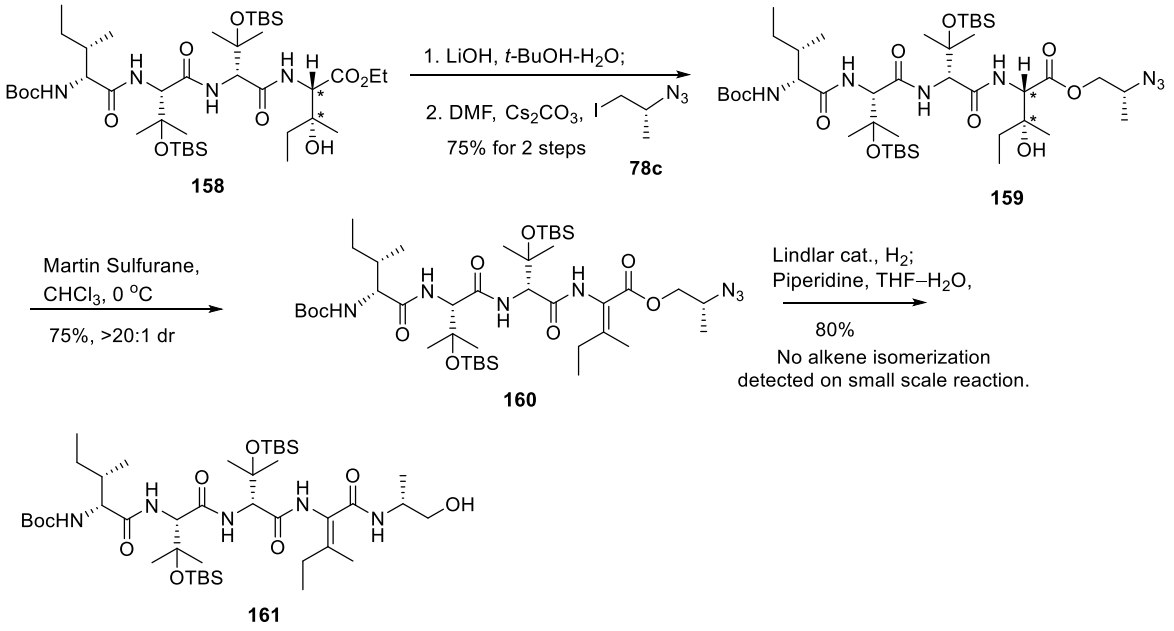


157 **155** 2 diastereomers **158**

entry	conditions	result
1	DEPBT, NEt_3, THF–DMF	20% with Decomposition (Not reproducible)
2	HOAt, EDCI, THF–DMF	Decomposition
3	HOAt, EDCI, Hunig's base, THF–DMF	Decomposition
4	HOAt, EDCI, Na_2CO_3, THF–DMF	Decomposition
5	COMU, 2,4,6-collidine, NEt_3, THF–DMF	Decomposition

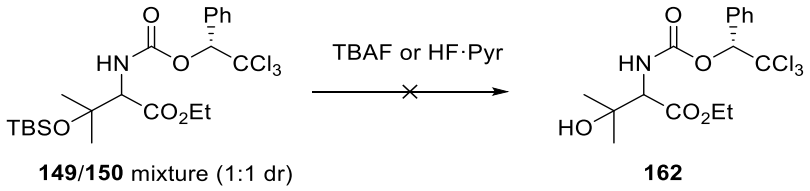
4.2.1.4 **Testing of the O→N acyl transfer chemistry**

With this precious tetrapeptide **158** in hand, we proceeded forward and tested the following reactions. The saponification–alkylative esterification progressed smoothly at 75% yield, and the following Martin sulfurane mediated dehydration delivered the required alkene **160** at excellent yield without observation of the other alkene isomer (Scheme 4.5). This advance set the stage to test the azide reduction–O→N acyl transfer chemistry. Azide reduction promoted by Lindlar catalyst (Sigma-Aldrich)–H_2 happened smoothly, and one-pot addition of piperidine delivered the pentapeptide in 80% yield. Careful analysis of the reaction mixture revealed that no isomerized product was detected, showing the feasibility of this chemistry with complicated intermediates. In this sequence of reactions, several modifications of the chemistry used in the model study were explored with good results. Cs_2CO_3 exhibited superior activity than the NEt_3 in the alkylation step and afforded excellent conversion, and the Lindlar catalyst–H_2 conditions successfully suppressed the isomerization possibly caused by the conjugate addition of PMe_3.



Scheme 4.5 Test of the O→N acyl transfer chemistry.

Since the bulkiness of the *tert*-OTBS were presumably hindering the tetrapeptide coupling reaction, we were concerned that their cleavage might be problematic. Therefore, the cleavage of –TBS were tested on a mixture of **149** and **150** (1:1 dr). Unfortunately, the common TBAF or HF·Pyr conditions did not promote silyl cleavage (Scheme 4.6). We were hesitant to apply stronger conditions, which might cause epimerization or decomposition of later stage intermediates. Afterwards, the less robust protecting group triethysilyl (–TES) was chosen to replace the –TBS group. Starting with the –TES-protected amino acids **151** and **152** (Scheme 4.2), we attempted to perform the route **R** but the synthesis of the respective tetrapeptide was problematic again. Finally, we abandoned route **R**.



Scheme 4.6 Attempts of TBS group cleavage.

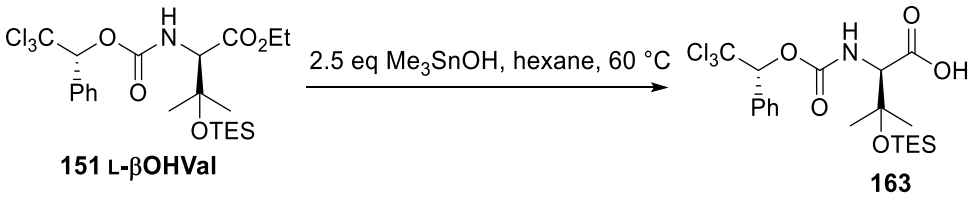
4.2.2 **Investigation of route L**

In the course of investigating route **R**, we gained valuable experience and lessons for the peptide coupling as well as the functional group transformations. With the failure of route **R**, we moved forward to investigate route **L**.

4.2.2.1 **Optimization of the Me_3SnOH hydrolysis reaction**

We reasoned the problematic hydrolysis–coupling sequence en route to **154** (Scheme 4.3). The inefficient hydrolysis required the use of large amount of Me_3SnOH, which was hard to completely remove via the acidic aqueous workup. The remaining Me_3SnOH or its derivative may be the culprit decreasing the efficiency of the coupling reaction. Since a large amount of

white precipitate was observed during the hydrolysis process in the standard $(CH_2Cl)_2$ media, we hypothesized that the poor solubility of Me_3SnOH possibly caused the inefficient transformation. Therefore, we finely tuned the parameters of hydrolysis of ester **151** (Scheme 4.7) by testing various solvents, gradually decreasing the Me_3SnOH loadings, and adjusting the reaction temperatures. Ultimately, we were pleased to find that 2–3 eq Me_3SnOH in hexane at 60 ^oC is the optimum condition, representing the lowest Me_3SnOH loading that can still furnish full conversion of starting material. This choice of solvent took advantage of the low polarity of our chiral ester **151**. In addition, to overcome the shortcomings of acidic aqueous workup (especially since the –TES protecting group is sensitive to acidic conditions), a Celite pad filtration of the reaction mixture followed by diethyl ether wash delivered the desired carboxylic acid **152** with high purity, which was used in the coupling reaction without chromatographic purification. To the best of our knowledge, this is the first time that the hexane–$SnMe_3OH$ combination was observed to promote ethyl ester hydrolysis with extremely low $SnMe_3OH$ loadings. This novel Celite filtration–workup can be employed to handle acid- or base-sensitive substrates.

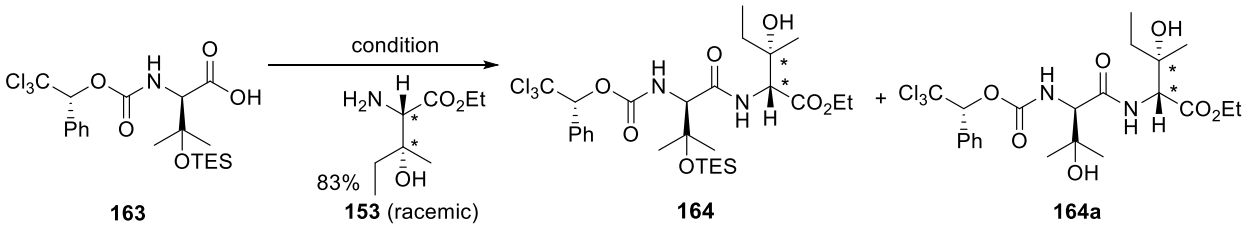


Scheme 4.7 Hydrolysis of the ester **151**.

4.2.2.2 **Optimization of the dipeptide coupling**

With high quality product from the hydrolysis reaction, the following coupling reaction was investigated and it turned out quite eventful. The TES group cleavage was often observed in the standard EDCI–HOBt coupling conditions (Table 4.2). Therefore, a detailed study was carried out to overcome this drawback, using the mass spectrometry to monitor the TES cleavage.[10]

Adjusting the loading of coupling reagents, switching the solvent from THF–DMF mixture to pure THF or DMF and varying the reaction time did not produce positive results (entries 1 and 3). Using $NaHCO_3$ as an additive directly led to the TES group cleavage (entry 2). Surprisingly, the DCC–HOBt–CH_2Cl_2 conditions gave superior results and **164** was the only detected product (entry 4). However, while DCC–HOBt were combined with THF or THF–DMF solvent system, the –TES cleavage product **164a** was observed again (entries 5–6). After careful analysis of those conditions, we concluded that the solvent might be the key to this coupling reaction. Rapidly, EDCI–HOBt–CH_2Cl_2 was tested and delivered **164** as single product with >80% yield with good reproducibility (entry 7). Due to difficulties in the removal of DCU side product from the reaction mixture (entry 4), we chose EDCI•HCl as the coupling reagent (entry 7).



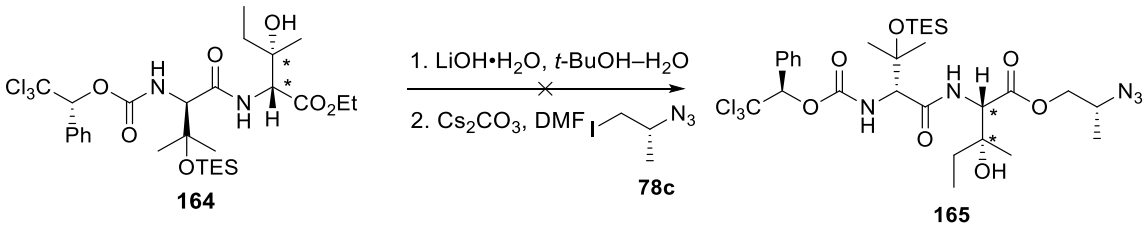
entry	coupling condition	result (the ratio of **164**:**164a** in MS)
1	EDCI, HOBt, THF–DMF, 3–15 h	Inconsistant, varies from 3:1 to 1**64** as single product
2	EDCI, HOBt, $NaHCO_3$, THF–DMF	Only 1**64a**
3	EDCI, HOBt, THF or DMF	Inconsistant, varies from 3:1 to 1**64** as single product
4	DCC, HOBt, CH_2Cl_2, 3 h	Only 1**64**, ca. 80%
5	THF, DCC, HOBt, 2.5 h	1.5:1
6	DCC, HOBt, THF–DMF, 15 h	Inconsistant, **164a** or **164** as the only product
7	EDCI, HOBt, CH_2Cl_2, 2 h	Only **164**, 83%, reproducible

Table 4.2 Optimization of dipeptide coupling.

4.2.2.3 **Protecting group switch and alkylation**

With the puzzle of dipeptide **164** solved, the following hydrolysis and alkylation sequence was tested. In contrast to the route **R** study, this sequence was quite eventful. Due to the liability towards inorganic bases, partial cleavage of the chiral auxiliary of **164** was consistently observed

during the hydrolysis and alkylation steps. Significant effort was taken to optimize this reaction, such as adjusting the temperatures, the amount of base, and changing solvents, but no positive result was obtained. Interestingly, dehydrovaline-like structural features were shown by NMR analysis of the crude mixture.

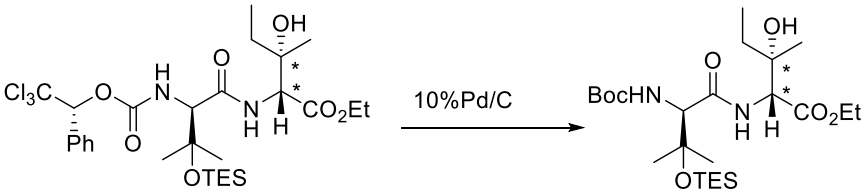


Scheme 4.8 Attempts to synthesis dipeptide with alanine surrogate.

Next, we considered using the less efficient strategy of switching the chiral auxiliary into a base-stable protecting group, which would add extra steps to the total synthesis. The *tert*-butyloxycarbonyl (Boc) group was chosen due to its robustness towards basic conditions as well as facile removal, and hopefully, its removal could happen concomitantly with the TES group cleavage. To maintain the efficiency of our synthesis, a one-pot conversion was investigated to effect the cleavage of the chiral auxiliary as well as installation of the Boc protecting group to the resulting amine intermediate. As expected, cleavage of the fragile TES group happened during the weakly acidic reaction conditions (Pd/C, Boc_2O without adding base, Table 4.3, entry 1). Attempts to use Na_2CO_3 or $NaHCO_3$ as basic additives were also not effective (entries 2 and 3). Employing a one-pot, 2-step conversion via cleaving the chiral auxiliary then adding Boc_2O–NEt_3 was unsuccessful (entry 4), and analysis of the amine intermediate obtained in the first step demonstrated the hydrogenolysis conditions can cause TES cleavage as well. Recently, Sajiki, Hirota and co-workers reported the advantage of using CH_3CN as the hydrogenolysis solvent in retaining the TES protecting group.[11] Unfortunately, CH_3CN did not bring any improvement in

suppressing TES cleavage. Ultimately, we concluded that the inorganic basic additives in the organic solvent may not be effectively quenching the acids due to their low solubility. As expected, using saturated aqueous $NaHCO_3$ as the cosolvent successfully delivered the desired product without detectable TES cleavage. Upon optimization, 100 Psi H_2, THF–Sat. aq. $NaHCO_3$ (V_{THF} : $V_{Sat.\ aq.\ NaHCO_3}$ = 3:1) was used in the reaction to effect rapid transformation. Also, we used aqueous extraction as the workup instead of Celite filtration since H_2O was present in the reaction mixture.

Table 4.3 Investigation of one-pot transformation of Chiral auxilary→Boc.



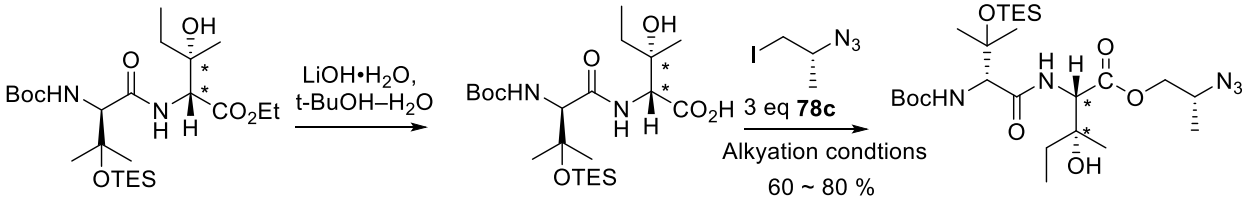
164 **166**

entry	condition	result
1	Boc_2O, MeOH, 60 Psi H_2	Partial TES group cleavage observed
2	Boc_2O, MeOH, $NaHCO_3$, 60 Psi H_2	Partial TES group cleavage observed
3	Boc_2O, MeOH, Na_2CO_3, 60 Psi H_2	Partial TES group cleavage observed
4	Boc_2O, EtOH, 60 Psi H_2; then Boc_2O, NEt_3	Partial TES group cleavage observed
5	Boc_2O, THF, $NaHCO_3$, 60 Psi H_2	Partial TES group cleavage observed
6	Boc_2O, CH_3CN, 60 Psi H_2	Partial TES group cleavage observed
7	**THF–Sat. $NaHCO_3$, 3:1, 100 Psi H_2, 15 h**	**166, > 90% isolated yield, reproducible**

With success in obtaining Boc-protected dipeptide **166**, the LiOH-promoted saponification happened smoothly and delivered the corresponding carboxylic acid **167** (Table 4.4). The alkylation conditions (iodide, DMF, NEt_3, 80 ºC) developed in the model study were sluggish and did not achieve full conversion (entry 1). Additives and different solvents were not effective (Scheme 4.4, entries 2–6). During the process of optimization, we found the reactions with only "partial conversion" observed in MS always led to a low yield (<40%). This correlation made mass spectrometry a convenient tool to monitor the alkylation progress. Other bases, such as

Na_2CO_3, K_2CO_3, did not afford good conversion either (entries 8–9). The Cs_2CO_3–DMF system was most promising, and careful control of loading is crucial. The small scale testing reactions made the strict loading of Cs_2CO_3 difficult, causing variations in the yields (entries 10–15). Especially, extra loading of Cs_2CO_3 could lead to the generation of only retroaldol product. However, the minimum 50% yield is sufficient to move the synthesis forward.

Table 4.4 Synthesis of advanced ester **168** and optimization of the alkylation.

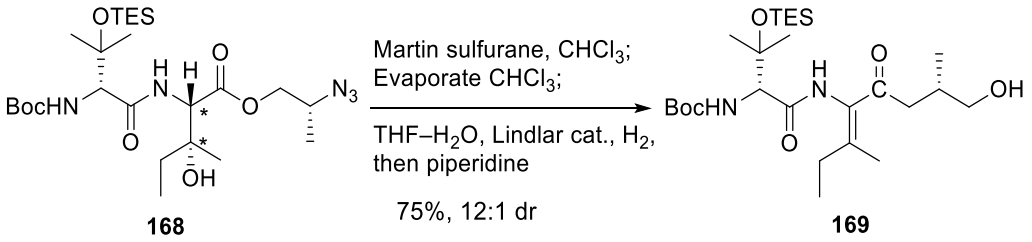


entry	condition	result
1	2.0 eq NEt_3, DMF, 60 °C, 15 h	Partial conversion
2	3.0 eq NEt_3, 4 eq $AgNO_3$, 70°C, 7 h	Partial conversion with retroaldol produt
3	1.0 eq NEt_3, DMA, 70 °C, 15 h	Partial conversion
4	1.0 eq NEt_3, $CH_2Cl)_2$, 70 °C, 20 h	Partial conversion
5	1.0 eq NEt_3, Hexane, 60 °C, 15 h	No reaction
6	1.0 eq NEt_3, DMF, 20 h	Partial conversion
7	1.0 eq NEt_3, DMSO,70 °C, 20 h	Partial conversion
8	2.0 eq Na_2CO_3,50 °C, 15 h	Partial conversion with retroaldol product
9	1.5 eq K_2CO_3, 18-crown-6, DMF, 50 °C, 15 h	All retroaldol product with **167.**
10	1.0 eq $CsCO_3$, DMF, 60 °C, 15 h	87% with minor retroaldol
11	0.5 eq $CsCO_3$, DMF, 75 °C, 15 h	Partial conversion
12	0.75 eq $CsCO_3$, DMF, 75 °C, 15 h	Mostly converted to **168** with minor **167**
13	1.04 eq $CsCO_3$, DMF, 60 °C, 15 h	50%–87%
14	1.1 eq Cs_2CO_3, dioxane, 70 °C, 15 h	Partial conversion
15	1.5 eq $CsCO_3$, DMF, 60 °C, 15 h	58%–88%

4.2.2.4 **Furnishing the tripeptide**

The successful synthesis of the advanced ester **168** set the stage to perform the dehydration–azide reduction–O→N acyl transfer sequence. Upon treatment of alcohol **168** with

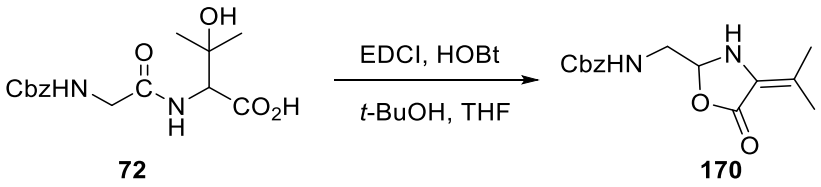
Martin sulfurane, excellent yield and diastereoselectivity were obtained without incident (Scheme 4.9). Considering the possibility that the alkene isomerization was caused by conjugate addition by the basic PMe_3, Lindlar catalyst–H_2 conditions were chosen to reduce the azide and it worked smoothly. Then, one-pot addition of piperidine triggered the O→N acyl transfer with excellent results. For the dehydration step, separation of the alkene product from the diphenyl sulfoxide side product on silica gel was difficult due to the similar polarity on silica gel. Diphenyl sulfoxide was derived from Martin sulfurane. Since there was no apparent conflict between the diphenyl sulfoxide side product and subsequent reaction conditions, we proposed the more convenient one-pot three-step transformation: the solvent of the crude dehydration mixture could be evaporated and H_2–Lindlar catalyst–THF–H_2O would be added to the same vial. Upon completion of azide reduction, base could be added to trigger the O→N acyl transfer chemistry. Gratifyingly, the first attempt of this reaction met with success. The azide was reduced to the corresponding amine smoothly, and addition of piperidine promoted the acyl transfer chemistry (Scheme 4.9). The tripeptide **169** was obtained via a facile chromatographic column separation in 75% yield and 12:1 dr. This set of reactions features the convenient performance of three chemical transformations in one vial without isolation of the reaction intermediates, and the high efficiency of this process was maintained.



Scheme 4.9 One-pot 3-step transformation from ester to amide.

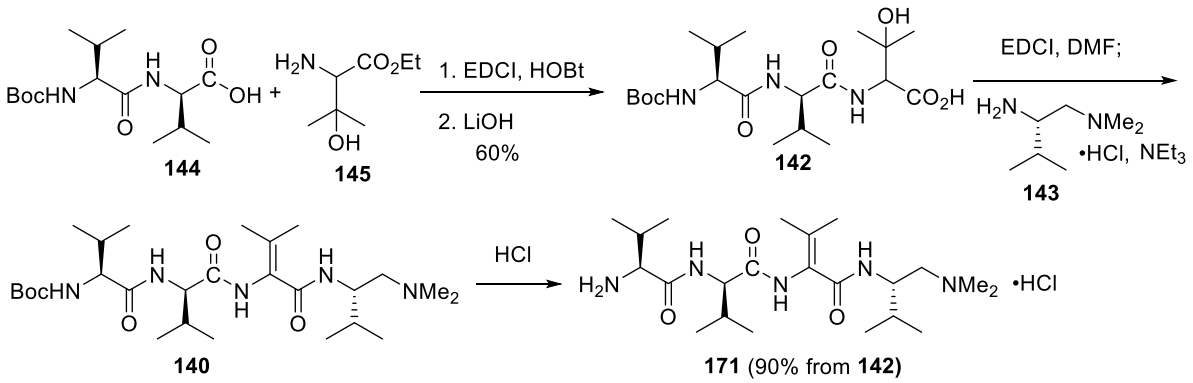
4.2.2.5 **Synthesis of the *C*-terminal tetrapeptide**

During the course of synthesizing activated esters (Chapter 3), EDCI–HOBt conditions were attempted to deliver the *tert*-Butyl ester, and this operation brought the unexpected discovery of the azlactone (oxazalone) **170** formation, possibly via EDCI•HCl promoted double dehydration. Upon further exploration, we found that the azlactone ring opening via attack of amine was widely used to install dehydroamino acids with symmetric alkenes, and dehydrovaline fit this category.[12]



Scheme 4.10 Discovery of azlactone formation promoted by EDCI·HCl.

This result prompted us to take advantage of the facile azlactone formation to synthesize the right-hand tetrapeptide. Due to the symmetric feature of dehydrovaline, alkene isomerization is not a concern in this process. Therefore, the coupling of known dipeptide **144** to amine **145** (derived from an aminohydroxylation adduct) followed by LiOH-promoted hydrolysis delivered tripeptide **142**. Upon treatment with 2 eqiv EDCI at room temperature for 24 h, the azlactone intermediate was delivered (monitored via MS). Then, one-pot addition of the required amine·HCl salt **143** and NEt_3 produced the *N*-Boc protected tetrapeptide in 90% yield within 3 h at room temperature. It is noteworthy that commonly used heating to promote the azlactone ring opening was not required in this process with the presence of extra organic base. Further treatment of **140** with HCl smoothly delivered amine•HCl salt **171** in quantitative yield.

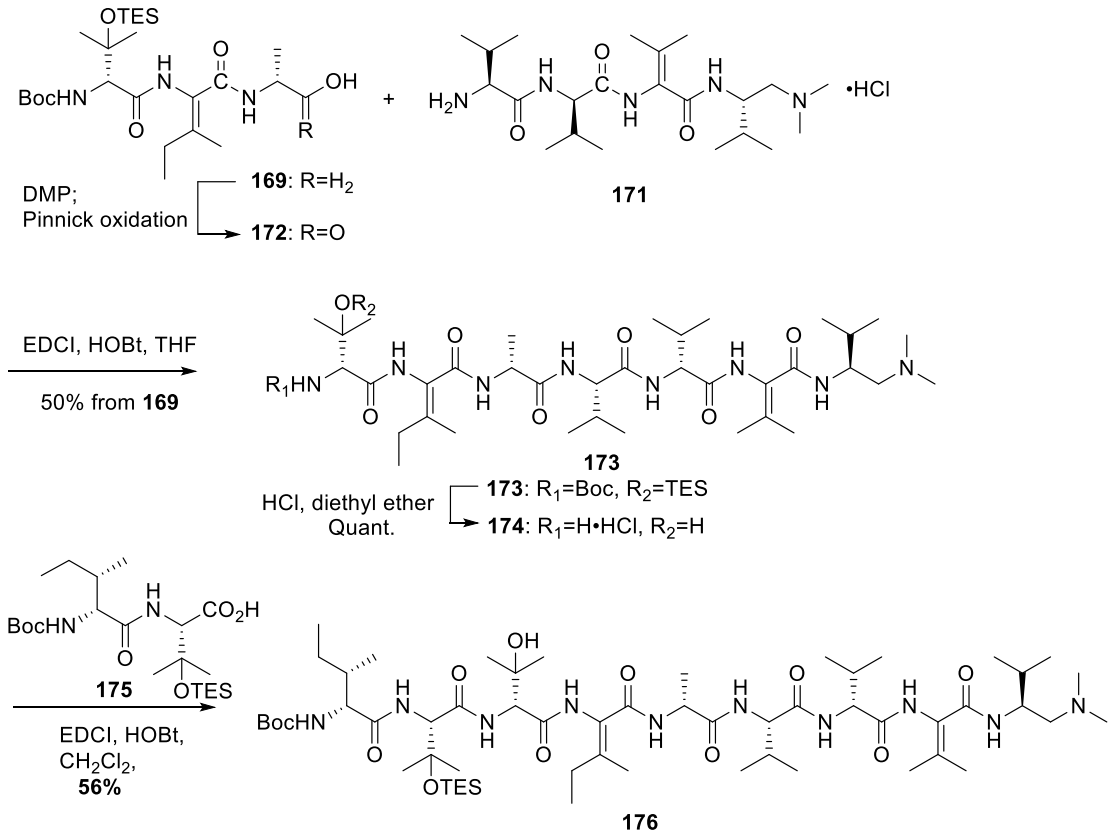


Scheme 4.11 Synthesis of tetrapeptide **171**.

4.2.2.6 **Completion of the nonapeptide**

In our model study, oxidation of the primary alcohol to the carboxylic acid was required for the peptide chain elongation. Among the tested conditions, TPAP-NMO conditions delivered low yields product with poor reproducibility and the TEMPO-bleach mediated one-step condition did not even consume the starting material. Finally, the one-pot two-step oxidation using Dess–Martin periodinane followed by Pinnick conditions delivered the carboxylic acid effectively in our model study. With all the required fragments prepared in the lab, we initiated the coupling reactions to fuse them together. Tripeptide **169** was smoothly oxidized using this DMP–Pinnick oxidation strategy, but the 2-Iodobenzoic acid byproduct interfered with the following coupling reaction with tetrapeptide **171** (Scheme 4.12). The 2-Iodobenzoic acid is derived from Dess–Martin periodinane and is always co-extracted out of the acidic aqueous phase with the acid **172**. To remove this by product from acid **172** and avoid chromatographic operations, we took advantage of the low polarity of the carboxylic acid **172**. Sat. aq. $NaHCO_3$ was added to basify the oxidation reaction mixture, and large volumes of EtOAc were used to extract the sodium salt of the carboxylic acid **172** out of the aqueous media. Pleasantly, we found most of the Iodobenzoic acid stayed in the aqueous media and the minor acid co-extracted could be removed by chromatographic separation after the coupling reaction. Coupling of **172** to **171**

worked smoothly and delivered product **173** in 83% yield from alcohol **169**. Then, HCl-promoted Boc cleavage delivered amine•HCl salt **174** with concomitant cleavage of the TES group. Evaporation of the HCl-ether mixture and coupling to the carboxylic acid **175** delivered the right-hand nonapeptide **176** in 56% yield.[13] It is noteworthy that retroaldol side product was predominantly formed in this coupling reaction when THF or DMF were used as the solvent. Upon investigation, using CH_2Cl_2 as solvent successfully suppressed the retroaldol reaction.

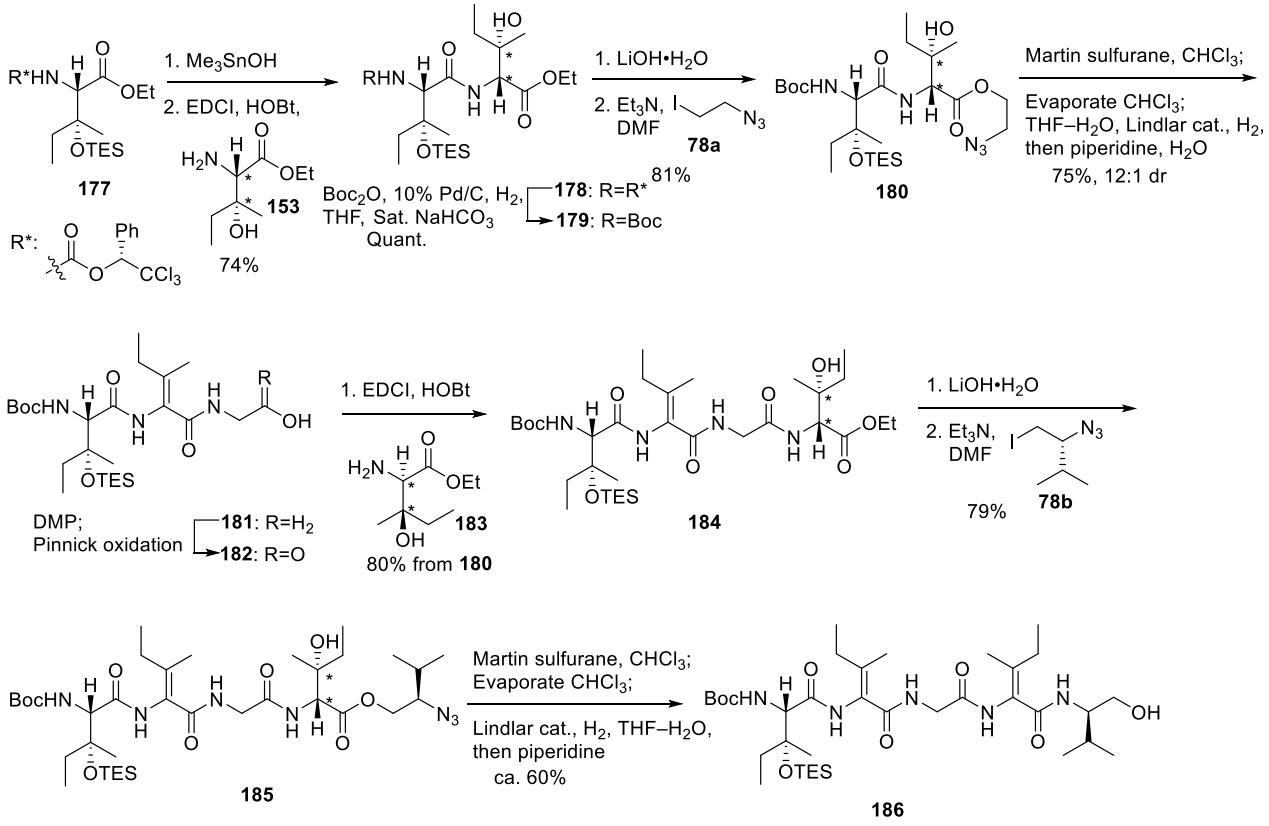


Scheme 4.12 Synthesis of right-hand nonapeptide **176**.

4.3 **Synthesis of left-hand pentapeptide**

With the successful right-hand nonapeptide synthesis, considering the similarity between tripeptide **169** and the left-hand pentapeptide, we initiated our synthesis using the same chemistry. Beginning with the aminohydroxylation of *Z*-enoate, followed by TES protection and

chromatographic separation, carbamate **177** was obtained, and was further submitted to the Me_3SnOH-promoted hydrolysis–coupling sequence (Scheme 4.13).[14] The dipeptide **177** was obtained in 74% yield over two steps, which was quantitatively converted to the Boc-protected dipeptide **178**. The saponification and standard alkylation conditions (developed in our model study) delivered advanced ester **179** without incident, setting the stage for the one-pot three-step peptide construction. The dehydration and azide reduction was evidenced by MS and TLC, and finally piperidine addition promoted the O→N acyl transfer and delivered the tripeptide **180** containing a primary alcohol. Afterwards, Dess-Martin periodiane–Pinnick oxidation converted **180** into carboxylic acid **181**, which was coupled to racemic amine **182** (derived from an aminohydroxylation adduct). The first attempt of the alkylative esterification–*anti* dehydration–azide reduction–O→N acyl transfer sequence was successful and left-hand pentapeptide **186** was obtained efficiently.



Scheme 4.13 Synthesis of left-hand pentapeptide **186**.

4.4 **Synthesis of the revised nonapeptide**

After significant advances in the synthesis of yaku'amide A' **1** (Figure 1.1, Chapter 1) had been achieved in our lab, we were notified that the structure of yaku'amide A was revised. Therefore, no further effort was devoted to this dead end route, such as scaling up the synthesis of heptapeptide and nonapeptide and respective characterizations. Instead, we immediately initiated the synthesis of the nonapeptide with the correct configuration, and this nonapeptide was delivered within three weeks using the same chemistry.[15] In addition, a microscale reaction testing the coupling of right-hand nonapeptide and left-hand pentapeptide was successful, and the formation of respective tetradecapeptide was well-evidenced by MS. This rapid re-synthesis process demonstrates the feasibility and robustness of our route towards the natural product.

4.5 **Conclusion**

Significant progress towards the synthesis of yaku'amide A has been achieved in the lab, such as the left-hand pentapeptide and the right-hand nonapeptide synthesis. In this process, the sequence of Martin sulfurane *anti* dehydration–azide reduction–O→N acyl transfer was able to be performed in one-pot and successfully applied to the synthesis of ΔIle-containing complicated peptide intermediates. With all the advance in this project, we are confident to access yaku'amide A in the near future.

4.6 **References**

(1) Since the structure revision was reported very recently, the beginning retrosynthetic analysis and the investigation of synthetic route were based on the originally proposed structure (yaku'amide A').

(2) The "PG" represents protecting groups. Ideally, all alcohols would be protected with the same group, and all amines would be protected with another group.

(3) Turk, J. A.; Visbal, G. S.; Lipton, M. A. "Asymmetric Synthesis of Four Diastereomers of 3-Hydroxy-2,4,6-trimethylheptanoic Acid: Proof of Configurational Assignment." *J. Org. Chem.* **2003**, *68*, 7841–7844.

(4) Miura, K.; Nakagawa, T.; Hosomi, A. "Metal Chloride-Promoted Aldol Reaction of α-Dimethylsilylesters with Aldehydes, Ketones, and α-Enones." *Synlett* **2005**, 1917–1921.

(5) Kuranaga, T.; Sesoko, Y.; Sakata, K.; Maeda, N.; Hayata, A.; Inoue, M. *J. Am. Chem. Soc.* **2013**, *135*, 5467–5474.

(6)Andrés, J. M.; Manzano, R.; Pedrosa, R. "Novel Bifunctional Chiral Urea and Thiourea Derivatives as Organocatalysts: Enantioselective Nitro-Michael Reaction of Malonates and Diketones." *Chem.Eur. J.* **2008**, *14*, 5116–5119.

(7) Lebel, H.; Trude, C.; Spitz, C. *Chem. Commun*. **2012**, *48*, 7799–7801.

(8) The absolute configurations of those isomers were determined via chemical derivatization to known compounds by J. Jiang and J. M. Cardon.

(9) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.

(10) Normally, MS is not a qualitative method to analyze molecular ratios. However, our observation of this coupling reaction showed that the mass ratio is very good reflection to the real ratio detected in NMR.

(11) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901–6911.

(12) For a recent review covering the application of azlactone ring-opening chemistry in peptide synthesis, see: Jiang, J.; Ma, Z.; Castle, S. L. *Tetrahedron* **2015**, *71*, 5431–5451.

(13) The carboxylic acid **175** was synthesized using the same chemistry for **157** (Scheme 4.4).

(14) The synthesis of (2*S*,3*R*)-OHIle was investigated by J. M. Cardon.

(15) Due to the time limit, characterization of these compounds has not been achieved.

Chapter 5. **EXPERIMENTAL SECTION**

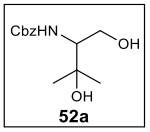
5.1 **General experimental details**

Dimethylformamide, methanol, and tetrahydrofuran were dried by passage through a solvent drying system containing cylinders of activated alumina.[1] 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), methanol (3.34 ppm), or benzene (7.15 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were acquired on a spectrometer operating at 125 MHz with chloroform (77.23 ppm), methanol (49.86 ppm), or benzene (128.62 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

General Procedure for Base-Free Aminohydroxylations. A solution of benzyl 4-chlorobenzoyloxy carbamate[2] (**51a**, 163.2 mg, 0.534 mmol, 1.7 equiv) in CH_3CN (4 mL) at rt was treated with OsO_4 (4 wt % solution in H_2O, 100 μL, 0.0157 mmol, 0.05 equiv), stirred for 10 min, then treated with the alkene (1 equiv) and H_2O (400 μL). A color change from clear to brown typically acccompanied addition of the alkene. The resulting mixture was stirred at either rt, 35 °C, or 45 °C for 20–24 h, then treated with sat aq $K_2S_2O_5$ (400 μL) and stirred for an additional 5 min. It was then diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL).

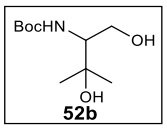
The combined organic layers were washed with sat aq $NaHCO_3$ (2 X 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2) afforded the amino alcohol products.

5.2 **Experimental procedures and spectral date**



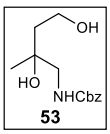
52a

Benzyl 1,3-dihydroxy-3-methylbutan-2-ylcarbamate (52a). Prepared from **51a** (168.1 mg, 0.550 mmol) and prenol (**49**, 32 μL, 27.1 mg, 0.315 mmol) according to the General Procedure with stirring at rt for 23.5 h. Flash chromatography (SiO_2, 1.5 × 8.5 cm, 5–10% MeOH in CH_2Cl_2 gradient elution) afforded **52a** (49.6 mg, 0.196 mmol, 62%) as a colorless oil. Spectral data were in accord with previously reported data.[3]



52b

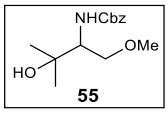
***tert*-Butyl 1,3-dihydroxy-3-methylbutan-2-ylcarbamate (52b).** Prepared from *tert*-butyl 4-chlorobenzoyloxy carbamate[2] (147.1 mg, 0.541 mmol) and prenol (**49**, 32 μL, 27.1 mg, 0.315 mmol) according to the General Procedure with stirring at rt for 24 h. Flash chromatography (SiO_2, 1.5 × 8 cm, 5–10% MeOH in CH_2Cl_2 gradient elution) afforded **52b** (51.6 mg, 0.235 mmol, 75%) as a colorless oil. Spectral data were in accord with previously reported data.[4]



53

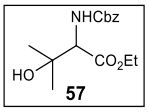
Benzyl (2,4-dihydroxy-2-methylbutyl)carbamate (53). Prepared from **51** (167.9 mg, 0.549 mmol) and isoprenol (**50**, 32 μL, 27.6 mg, 0.321 mmol) according to the General

Procedure with stirring at 35 ºC for 23 h. Flash chromatography (SiO_2, 1.5 × 10 cm, 2–5% MeOH in CH_2Cl_2 gradient elution) afforded **53** (69.1 mg, 0.273 mmol, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.28 (m, 5H), 5.47 (s, 1H), 5.09 (s, 2H), 3.94–3.87 (m, 1H), 3.84–3.78 (m, 1H), 3.73 (br s, 1H), 3.24 (dd, *J* = 13.8, 6.1 Hz, 1H) 3.18 (dd, *J* = 13.8, 6.3 Hz, 1H), 3.11 (br s, 1H), 1.85–1.77 (m, 1H), 1.63–1.56 (m, 1H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 136.4, 128.5 (2C), 128.2, 128.1 (2C), 73.3, 66.9, 59.3, 51.0, 39.4, 24.7; IR (film) ν_{max} 3346, 3066, 2935, 1701, 1535, 1455, 1257, 1144, 1042 cm^{-1}; HRMS (ESI) *m/z* 254.1406 (MH^+, $C_{13}H_{19}NO_4H^+$ requires 254.1387).



55

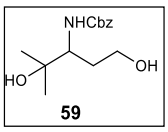
Benzyl (3-hydroxy-1-methoxy-3-methylbutan-2-yl)carbamate (55). Prepared from **51a** (163.5 mg, 0.535 mmol) and **54**[5] (34 μL, 31.6 mg, 0.315 mmol) according to the General Procedure with stirring at 35 ºC for 23.5 h. Flash chromatography (SiO_2, 1.5 × 12 cm, 10–30% EtOAc in hexanes gradient elution) afforded **55** (45.3 mg, 0.169 mmol, 54%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.29 (m, 5H), 5.62 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 3.82 (d, *J* = 7.2 Hz, 1H), 3.60–3.55 (m, 2H), 3.35 (s, 3H), 3.11 (s, 1H), 1.32 (s, 3H), 1.12 (3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 136.5, 128.5 (2C), 128.1, 128.0 (2C), 73.7, 72.8, 66.8, 59.4, 57.0, 27.7, 26.9; IR (film) ν_{max} 3322, 2977, 1701, 1522, 1454, 1216, 1117, 1047 cm^{-1}; HRMS (ESI) *m*/*z* 268.1560 (MH^+, $C_{14}H_{21}NO_4H^+$ requires 268.1543).



57

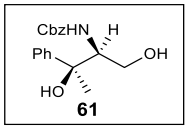
Ethyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-methylbutanoate (57). Prepared from **51a** (492.8 mg, 1.61 mmol) and ethyl 3,3-dimethylacrylate (**56**, 132 μL, 122 mg, 0.951 mmol) according to the General Procedure with 600 μL OsO_4 solution (0.0944 mmol, 0.10 equiv) and stirring at 35 ºC for 10 h. Flash chromatography (SiO_2, 1.5 × 12 cm, 10–50% EtOAc

in hexanes gradient elution) afforded **57** (221.9 mg, 0.751 mmol, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.31 (m, 5H), 5.62 (br s, 1H), 5.13 (s, 2H), 4.31–4.19 (m, 3H), 2.50 (br s, 1H), 1.34–1.26 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 156.5, 136.1, 128.5 (2C), 128.2, 128.1 (2C), 71.9, 67.2, 61.62, 61.56, 26.8, 26.3, 14.1; IR (film) ν_{max} 3406, 2978, 2922, 1720, 1709, 1512, 1501, 1467, 1452, 1211, 1051, 1027 cm^{-1}; HRMS (ESI) *m*/*z* 296.1497 (MH^+, $C_{15}H_{21}NO_5H^+$ requires 296.1492).



59

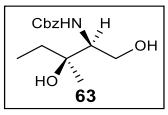
Benzyl (1,4-dihydroxy-4-methylpentan-3-yl)carbamate (59). Prepared from **51a** (168.8 mg, 0.552 mmol) and **58** (37 μL, 31.7 mg, 0.317 mmol) according to the General Procedure with stirring at 35 ºC for 23 h. Flash chromatography (SiO_2, 1.5 × 10 cm, 2–5% MeOH in CH_2Cl_2 gradient elution) afforded **59** (49.5 mg, 0.185 mmol, 58%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.28 (m, 5H), 5.33 (d, *J* = 9.4 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 3.71–3.64 (m, 2H), 3.63–3.56 (m, 1H), 3.38 (br s, 1H), 2.78 (br s, 1H), 1.98–1.89 (m, 1H), 1.57–1.48 (m, 1H), 1.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 136.3, 128.6 (2C), 128.2, 128.0 (2C), 72.2, 67.1, 58.6, 56.1, 32.2, 27.6, 27.0; IR (film) ν_{max} 3330, 2973, 1697, 1535, 1258, 1054 cm^{-1}; HRMS (ESI) *m/z* 268.1561 (MH^+, $C_{14}H_{21}NO_4H^+$ requires 268.1543).



61

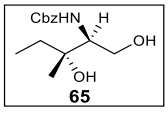
Benzyl ((2*S,3*S**)-1,3-dihydroxy-3-phenylbutan-2-yl)carbamate (61).** Prepared from **51a** (116.4 mg, 0.381 mmol) and **60**[6] (33.2 mg, 0.224 mmol) according to the General Procedure with stirring at 35 ºC for 18 h. Flash chromatography (SiO_2, 1.5 × 11 cm, 2–5% MeOH in CH_2Cl_2 gradient elution) afforded **17** (32.4 mg, 0.103 mmol, 46%) as a colorless

oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50–7.42 (m, 3H), 7.41–7.25 (m, 5H), 7.24–7.17 (m, 2H), 5.44 (d, *J* = 7.6 Hz, 1H), 4.98 (s, 2H), 4.18–4.07 (m, 1H), 4.03–3.91 (m, 2H), 3.37 (br s, 1H), 2.28 (br s, 1H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.4, 145.0, 136.3, 128.5 (2C), 128.3 (2C), 128.0, 127.7 (2C), 127.1, 124.7 (2C), 77.0 (obscured by $CDCl_3$), 66.6, 63.1, 58.9, 28.3; IR (film) ν_{max} 3404, 2977, 1701, 1517, 1447, 1251, 1072, 1048 cm^{-1}; HRMS (ESI) *m/z* 316.1558 (MH^+, $C_{18}H_{21}NO_4H^+$ requires 316.1543.



63

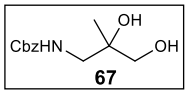
Benzyl ((2*S,3*S**)-1,3-dihydroxy-3-methylpentan-2-yl)carbamate (63)**. Prepared from **51a** (164.2 mg, 0.537 mmol) and **62**[7] (37.5 μL, 27.2 mg, 0.316 mmol) according to the General Procedure with 200 □L OsO_4 solution (0.0315 mmol, 0.10 equiv) and stirring at 35 ºC for 23 h. Flash chromatography (SiO_2, 1.5 × 11 cm, 0.1–2% MeOH in CH_2Cl_2 gradient elution) afforded **63** (46.6 mg, 0.174 mmol, 55%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5H), 5.63 (d, *J* = 8.1 Hz, 1H), 5.12 (s, 2H), 4.06–4.00 (m, 1H), 3.88–3.82 (m, 1H), 3.62–3.57 (m, 1H), 2.63 (br s, 1H), 2.54 (br s, 1H), 1.63–1.55 (m, 1H), 1.54–1.45 (m, 1H), 1.29 (s, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.7, 136.4, 128.5 (2C), 128.1, 128.0 (2C), 75.8, 66.9, 63.6, 56.0, 32.3, 23.9, 8.1; IR (film) ν_{max} 3400, 2970, 1701, 1529, 1455, 1250, 1061, cm^{-1}; HRMS (ESI) *m/z* 268.1557 (MH^+, $C_{14}H_{21}NO_4H^+$ requires 268.1543.



65

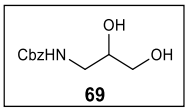
Benzyl ((2*S,3*R**)-1,3-dihydroxy-3-methylpentan-2-yl)carbamate (65)**. Prepared from **51a** (163.7 mg, 0.536 mmol) and **64**[8] (37 μL, 31.3 mg, 0.312 mmol) according to the General Procedure with 200 μL OsO_4 solution (0.0315 mmol, 0.10 equiv) and stirring at 35 ºC for 23 h. Flash chromatography (SiO_2, 1.5 × 11 cm, 0.1–2% MeOH in CH_2Cl_2 gradient elution) afforded **65** (48.9 mg, 0.183 mmol, 59%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz)

 7.40–7.30 (m, 5H), 5.69 (br s, 1H), 5.11 (s, 2H), 4.04–3.98 (m, 1H), 3.83–3.77 (m, 1H), 3.61–3.57 (m, 1H), 2.77–2.55 (m, 2H), 1.77–1.58 (m, 2H), 1.16 (s, 3H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.7, 136.4, 128.5 (2C), 128.2 (2C), 128.0, 76.1, 66.9, 63.1, 56.6, 32.8, 23.4, 8.3; IR (film) ν_{max} 3401, 2971, 1701, 1522, 1455, 1251, 1062 cm^{-1}; HRMS (ESI) *m/z* 268.1543 (MH^+, $C_{14}H_{21}NO_4H^+$ requires 268.1543).



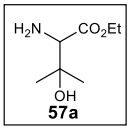
67

Benzyl 2,3-dihydroxy-2-methylpropylcarbamate (67). Prepared from **51a** (163.9 mg, 0.536 mmol) and allylic alcohol **66** (27 μL, 23.0 mg, 0.319 mmol) according to the General Procedure with stirring at rt for 23 h. Flash chromatography (SiO_2, 1.5 × 10 cm, 5–10% MeOH in CH_2Cl_2 gradient elution) afforded **67** (47.7 mg, 0.199 mmol, 62%) as a colorless oil. Spectral data were in accord with previously reported data.[9]



69

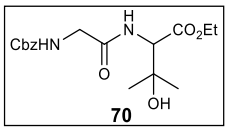
Benzyl 2,3-dihydroxypropylcarbamate (69). Prepared from **51a** (164.5 mg, 0.538 mmol) and allyl alcohol (**68**, 21.5 μL, 18.4 mg, 0.316 mmol) according to the General Procedure with stirring at rt for 23.5 h. Flash chromatography (SiO_2, 1.5 × 9.5 cm, 5–10% MeOH in CH_2Cl_2 gradient elution) afforded **69** (49.6 mg, 0.220 mmol, 70%) as a colorless oil that was a 6.7:1 ratio of regioisomers. Spectral data for both **69** and its *meso* regioisomer were in accord with previously reported data.[10]



57a

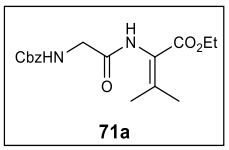
Ethyl 2-amino-3-hydroxy-3-methylbutanoate (57a). A suspension of **57** (280.4 mg, 0.949 mmol) and Pd/C (10 wt %, 42.6 mg) in MeOH (12 mL) was stirred at rt under H_2 (450 psi) for 23 h. The mixture was filtered through Celite, and the Celite pad was washed with MeOH

(125 mL). The filtrate was concentrated *in vacuo* to afford **57a** as a colorless oil, which was used directly in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) □ 4.29–4.16 (m, 2H), 3.14 (s, 1H), 2.75 (br s, 3H), 1.32 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 3H); HRMS (ESI) *m/z* 162.1105 (MH^+, $C_7H_{15}NO_3H^+$ requires 162.1125).



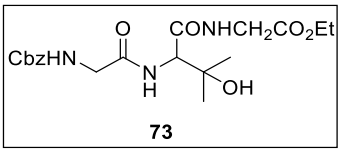
70

Ethyl 2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-hydroxy-3-methylbutanoate (70). A solution of above amine **57a** (0.949 mmol) in THF–DMF (2.5:1, 42.5 mL) at 0 °C under Ar was treated with *N*-Cbz-glycine (370.0 mg, 1.769 mmol), HOBt (298.9 mg, 1.770 mmol), and EDC•HCl (338.5 mg, 1.766 mmol). The resulting mixture was allowed to warm to rt and stir for 24 h. The reaction was quenched with sat aq $NaHCO_3$ (15 mL), and the resulting precipitate was filtered and washed with EtOAc (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography (SiO_2, 2.3 × 17 cm, 1–7% MeOH in CH_2Cl_2 gradient elution) afforded **70** (286.4 mg, 0.812 mmol, 86% over 2 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 5H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.48 (br s, 1H), 5.14 (s, 2H), 4.52 (d, *J* = 8.8 Hz, 1H), 4.30–4.15 (m, 2H), 3.94 (d, *J* = 5.4 Hz, 2H), 2.71 (br s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.28 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 169.2, 156.6, 136.1, 128.6 (2C), 128.3, 128.1 (2C), 71.9, 67.3, 61.7, 59.8, 44.5, 26.7, 26.6, 14.1; IR (film) ν_{max} 3342, 2980, 1731, 1531, 1455, 1374, 1261, 1028 cm^{-1}; HRMS (ESI) *m/z* 353.1716 (MH^+, $C_{17}H_{24}N_2O_6H^+$ requires 353.1707).



71a

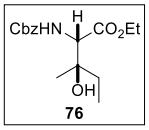
Ethyl 2-(2-(benzyloxycarbonylamino)acetamido)-3-methylbut-2-enoate (71a). A solution of alcohol **70** (20.9 mg, 0.059 mmol) in chloroform (250 μL) was treated with a solution of Martin sulfurane (500 μL, 0.117 mmol, 0.23 M in $CHCl_3$). The resultant mixture was heated to 50 ºC and stirred for 1 h. The reaction mixture was cooled to rt and concentrated *in* vacuo. Flash chromatography (SiO_2, 1.5 × 7 cm, 0–1.6% MeOH in CH_2Cl_2 gradient elution) afforded **71a** (15.9 mg, 0.048 mmol, 80%) as a colorless oil: ^{1}H NMR (13.4:1 mixture of rotomers, data for major rotomer, $CDCl_3$, 500 MHz) δ 7.38–7.32 (m, 5H), 7.15 (br s, 1H), 5.42 (br s, 1H), 5.15 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.96 (d, *J* = 5.7 Hz, 2H), 2.18 (s, 3H), 1.82 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 164.6, 156.7, 146.5, 136.0, 128.6 (2C), 128.3, 128.1 (2C), 120.5, 67.3, 60.9, 44.7, 22.7, 21.4, 14.1; IR (film) ν_{max} 3316, 2923, 2853, 1714, 1514, 1457, 1309, 1237, 1093; HRMS (ESI) *m/z* 335.1592 (MH^+, $C_{17}H_{22}N_2O_5H^+$ requires 335.1601).



73

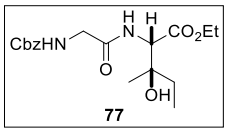
Ethyl (2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-hydroxy-3-methylbutanoyl)glycinate (73). A solution of ester **69** (105 mg, 0.298 mmol) in MeOH–H_2O (1:1, 2 mL) at 0 °C was treated with LiOH•H_2O (90 mg, 2.14 mmol, 7.2 equiv), then stirred at 0 °C for 3 h. The resulting mixture was acidified to pH 3 by the addition of 10% citric acid (5 mL) and dissolved in EtOAc (60 mL), then washed with H2O (30 mL × 2) and brine (30 mL × 2). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid (68 mg, 0.210 mmol, 70%) was used directly without further purification.

The acid was dissolved in CH2Cl2–DMF (2.8 mL–0.2mL) was treated with Ethyl glycine HCl salt (59.9 mg, 0.429 mmol, 2.0 eqiv), HOBt (ca. 14% H_2O content, 58.4 mg, 0.327 mmol, 1.6 equiv), and EDC•HCl (57.4 mg, 0.299 mmol, 1.4 equiv), Na_2CO_3 (24.3 mg, 0.229 mmol, 1.1 eqiv) at 0 °C under Ar. The resulting mixture was stirred at 0 °C to rt under Ar for 11 h. The reaction was treated with H_2O (6 mL), then extracted with EtOAc (5 × 6 mL), and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (7 mL of SiO_2, 1–4% MeOH in CH_2Cl_2 gradient elution) afforded **80** (45 mg, 0.109 mmol, 52%, 36% for two steps) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) of major rotamer: δ 7.42–7.32 (m, 5H), 7.23 (br s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 5. 7 (s, 1H), 5.14 (s, 2H), 4.42 (d, *J* = 8.7 Hz, 1H),.4.21 (q, J = 7.29 Hz, 2H), 4.08–3.87 (m, 2H), 1.35 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 169.8, 169.6, 156.7, 136.1, 128.6 (2C), 128.3, 128.2 (2C), 71.8, 67.3, 61.7, 59.0, 44.5, 41.2, 27.3, 25.5, 14.1; HRMS (ESI) *m/z* 410.2161 (MH^+, $C_{18}H_{28}N_3O_7H^+$ requires 410.1927).



Ethyl (2*S,3*R**)-2-(((Benzyloxy)carbonyl)amino)-3-hydroxy-3-methylpentanoate (76).** A solution of benzyl ((methylsulfonyl)oxy)carbamate[11] (606.1 mg, 2.471 mmol, 1.5 equiv) in CH_3CN (18 mL) at rt was treated with OsO_4 (4 wt % solution in H_2O, 1.0 mL, 0.16 mmol, 0.10 equiv), stirred for 10 min, and then treated with a solution of enoate **75**[12] (234.9 mg, 1.652 mmol) in CH_3CN (9 mL) and H_2O (2.4 mL). The resulting mixture was stirred at 35 °C for 4 d, treated with sat aq $K_2S_2O_5$ (3.6 mL), and stirred for an additional 5 min. It was then diluted with H_2O (15 mL) and extracted with EtOAc (6 × 15 mL). The combined organic layers were washed with sat aq $NaHCO_3$ (2 × 50 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (ca. 80 mL of SiO_2, 0.5–1 % MeOH in

CH_2Cl_2 gradient elution) afforded a mixture of **76** (356.3 mg, 1.152 mmol, 70%) and benzyl carbamate (170.8 mg) as a light yellow oil. This mixture could be used directly in the subsequent hydrogenolysis reaction with no complications. An analytical sample of **76** could be obtained after further chromatography. For **76**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.29 (m, 5H), 5.75 (d, *J* = 8.5 Hz, 1H), 5.10 (s, 2H), 4.30 (d, *J* = 9.0 Hz, 1H), 4.27–4.17 (m, 2H), 2.58 (s, 1H), 1.56 (qd, *J* = 7.5, 1.8 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H), 1.19 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 156.4, 136.1, 128.5 (2C), 128.2 (2C), 128.1, 73.9, 67.2, 61.5, 59.9, 31.3, 23.4, 14.1, 7.9; IR (film) ν_{max} 3434, 2977, 1724, 1516, 1206, 1061 cm^{-1}; HRMS (ESI) *m/z* 310.1632 (MH^+, $C_{16}H_{23}NO_5H^+$ requires 310.1654).

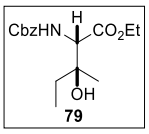


77

Ethyl (2*S,3*R**)-2-(2-(((Benzyloxy)carbonyl)amino)acetamido)-3-hydroxy-3-methylpentanoate (77).** A solution of **76** (356.3 mg contaminated with 170.8 mg of benzyl carbamate, 1.152 mmol) in MeOH (15 mL) was treated with 10% Pd/C (100 mg, 0.28 wt equiv) and stirred at rt under H_2 (500 psi) for 3 d.[13] The mixture was filtered through a pad of Celite (washed with 125 mL of MeOH), and the filtrate was concentrated *in vacuo* to afford the crude amine, which was used without further purification.

A solution of the amine in anhydrous THF–DMF (3:1, 24 mL) at 0 °C under Ar was treated with *N*-Cbz-glycine (473.4 mg, 2.263 mmol), HOBt (ca. 14% H_2O content, 390.1 mg, 2.483 mmol), and EDC•HCl (430.2 mg, 2.244 mmol). The resulting mixture stirred at 0 °C to rt under Ar for 24 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (20 mL) and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (4 × 40 mL), and the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in*

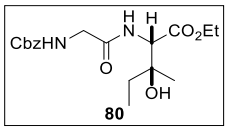
vacuo. Flash chromatography (90 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **77** (332.3 mg, 0.9069 mmol, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.29 (m, 5H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.47 (br s, 1H), 5.14 (s, 2H), 4.56 (d, *J* = 8.8 Hz, 1H), 4.27–4.16 (m, 2H), 3.99–3.88 (m, 2H), 2.60 (br s, 1H), 1.53 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 3H), 0.92 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 169.1, 156.5, 136.1, 128.5 (2C), 128.2 (2C), 128.1, 74.1, 67.2, 61.7, 58.0, 44.4, 31.6, 23.4, 14.1, 7.9; IR (film) ν_{max} 3346, 2977, 1731, 1526, 1261 cm^{-1}; HRMS (ESI) *m/z* 367.1868 (MH^+, $C_{18}H_{26}N_2O_6H^+$ requires 367.1869).



79

Ethyl (2*S,3*S**)-2-(((Benzyloxy)carbonyl)amino)-3-hydroxy-3-methylpentanoate (79).** A solution of benzyl ((methylsulfonyl)oxy)carbamate[2] (820 mg, 3.34 mmol, 1.4 equiv) in CH_3CN (18 mL) at rt was treated with OsO_4 (4 wt % solution in H_2O, 1.5 mL, 0.24 mmol, 0.099 equiv), stirred for 10 min, and then treated with a solution of enoate **78**[14] (340 mg, 2.39 mmol) in CH_3CN (6.0 mL) and H_2O (1.5 mL). The resulting mixture was stirred at 45 °C for 2.5 d, treated with sat aq $K_2S_2O_5$ (7 mL), and stirred for an additional 10 min. It was then diluted with H_2O (35 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with sat aq $NaHCO_3$ (2 × 50 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (100 mL of SiO_2, 1–5% MeOH in CH_2Cl_2 gradient elution) afforded **79** (580 mg, 1.87 mmol, 78%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.30 (m, 5H), 5.62 (d, *J* = 9.3 Hz, 1H), 5.12 (s, 2H), 4.31 (d, *J* = 9.4 Hz, 1H), 4.28–4.18 (m, 2H), 2.39 (br s, 1H), 1.56–1.46 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 156.3, 136.1, 128.5 (2C), 128.2

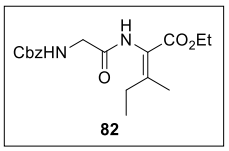
(2C), 128.1, 74.3, 67.2, 61.6, 60.3, 32.5, 22.3, 14.1, 8.0; IR (film) ν_{max} 3363, 2978, 1716, 1519, 1337, 1208, 1058 cm^{-1}; HRMS (ESI) *m/z* 310.1711 (MH^+, $C_{16}H_{23}NO_5H^+$ requires 310.1654).



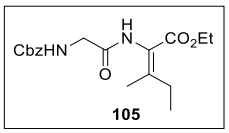
80

Ethyl (2*S,3*S**)-2-(2-(((Benzyloxy)carbonyl)amino)acetamido)-3-hydroxy-3-methylpentanoate (80).** A solution of **79** (353 mg, 1.14 mmol) in MeOH (10 mL) was treated with 10% Pd/C (114.6 mg, 0.32 wt equiv) and stirred at rt under H_2 (550 psi) for 2.5 d. The mixture was filtered through a pad of Celite (washed with 125 mL of MeOH), and the filtrate was concentrated *in vacuo* to afford the crude amine (198 mg, 1.13 mmol), a portion of which was used without further purification.

A solution of the amine (170 mg, 0.970 mmol) in anhydrous DMF (12 mL) at 0 °C under Ar was treated with *N*-Cbz-glycine (401.6 mg, 1.92 mmol, 2.0 equiv), HOBt (ca. 14% H_2O content, 327.5 mg, 2.08 mmol, 2.1 equiv), and EDC•HCl (375.7 mg, 1.96 mmol, 2.0 equiv). The resulting mixture was stirred at 0 °C to rt under Ar for 48 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (12 mL) and diluted with H_2O (12 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (70 mL of SiO_2, 1–5% MeOH in CH_2Cl_2 gradient elution) afforded **80** (220 mg, 0.600 mmol, 62%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 1H), 5.14 (s, 2H), 4.56 (d, *J* = 8.9 Hz, 1H), 4.28–4.16 (m, 2H), 3.98–3.89 (m, 2H), 2.42 (br s, 1H), 1.51 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 169.0, 156.5, 136.0, 128.5 (2C), 128.3, 128.2 (2C), 74.3, 67.3, 61.7, 58.4, 44.5, 32.5, 22.4, 14.1, 8.0; IR (film) ν_{max} 3344, 2979, 1728, 1525, 1212, 1051 cm^{-1}; HRMS (ESI) *m/z* 367.1862 (MH^+, $C_{18}H_{26}N_2O_6H^+$ requires 367.1869).

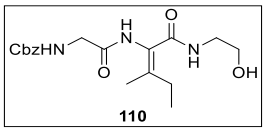


Ethyl (*Z*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-methylpent-2-enoate (82). A solution of alcohol **77** (19.5 mg, 0.0532 mmol) in anhydrous $CHCl_3$ (180 μL) was treated with Martin sulfurane (0.21 M in anhydrous $CHCl_3$, 500 μL, 0.105 mmol, 2.0 equiv). The resulting mixture was stirred at 50 °C under Ar for 1 h, cooled to rt, and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–1.6% MeOH in CH_2Cl_2 gradient elution) afforded **82** (16.2 mg, 0.0465 mmol, 87%, >19:1 dr) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 12:1 mixture of rotamers, data for major rotamer) δ 7.40−7.30 (m, 5H), 7.08 (br s, 1H), 5.38 (br s, 1H), 5.15 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.95 (d, *J* = 5.7 Hz, 2H), 2.20–2.09 (m, 5H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 164.7, 156.7, 151.0, 136.0, 128.6 (2C), 128.3, 128.1 (2C), 120.1, 67.3, 60.9, 44.8, 28.7, 18.6, 14.2, 11.5; IR (film) ν_{max} 3313, 2926, 1718, 1509, 1216 cm^{-1}; HRMS (ESI) *m/z* 349.1777 (MH^+, $C_{18}H_{24}N_2O_5H^+$ requires 349.1763).



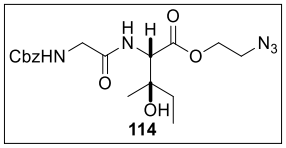
Ethyl (*E*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-methylpent-2-enoate (105). A solution of alcohol **80** (34.6 mg, 0.0.0944 mmol) in anhydrous $CHCl_3$ (0.5 mL) was treated with Martin sulfurane (0.41 M in anhydrous $CHCl_3$, 0.5 mL, 0.21 mmol, 2.2 equiv). The resulting mixture was stirred at 50 °C under Ar for 1 h, cooled to rt, and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 0–2.6 % MeOH in CH_2Cl_2 gradient elution) afforded **105** (24.1 mg, 0.0692 mmol, 73%, >19:1 dr) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 15:1 mixture of rotamers, data for major rotamer) δ 7.40−7.30 (m, 5H), 7.13 (s, 1H), 5.39 (s, 1H), 5.15 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.95 (d, *J* = 5.6 Hz, 2H), 2.53 (q, *J* = 7.5 Hz, 2H),

1.79 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 164.3, 156.7, 150.6, 136.0, 128.6 (2C), 128.3, 128.1 (2C), 120.3, 67.4, 60.9, 44.8, 27.7, 19.9, 14.2, 12.7; IR (film) ν_{max} 3311, 2977, 2934, 1720, 1514, 1266, 1211 cm^{-1}; HRMS (ESI) *m/z* 349.1858 (MH^+, $C_{18}H_{24}N_2O_5H^+$ requires 349.1763).



110

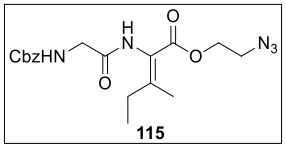
Benzyl (*E*)-(2-((1-((2-hydroxyethyl)amino)-3-methyl-1-oxopent-2-en-2-yl)amino)-2-oxoethyl)carbamate (110). A solution of azide **122a** (3.0 mg, 0.0077 mmol) in THF (210 μL) and H_2O (16 μL) at 0 °C under Ar was treated dropwise with PMe_3 (1 M in THF, 23 μL, 0.023 mmol, 3.0 equiv). The resulting mixture was stirred at 0 °C to rt for 20 h, at which time the starting material had disappeared as evidenced by MS. The mixture was then treated dropwise with morpholine (24 μL, 24 mg, 0.28 mmol), and stirred at rt for 60 h followed by concentration *in vacuo*. The residue was dissolved in EtOAc (5 mL), washed with H_2O (2 × 1 mL) and brine (1 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (2 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **110** (2.7 mg, 0.0074 mmol, 96%, 10:1 dr) as a white film: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (br s, 1H), 7.39−7.31 (m, 5H), 6.59 (br s, 1H), 5.46 (br s, 1H), 5.14 (s, 2H), 3.89 (d, J = 5.7 Hz, 2H), 3.73 (q, J = 5.1 Hz, 2H), 3.43 (q, J = 5.0 Hz, 2H), 3.24 (br s, 1H), 2.41 (q, J = 7.3 Hz, 2H), 1.70 (s, 3H), 1.09 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 166.6, 157.2, 142.4, 135.6, 128.6 (2C), 128.5, 128.2 (2C), 123.7, 67.7, 61.4, 45.1, 42.7, 27.0, 17.5, 12.8; IR (film) ν_{max} 3316, 2919, 1685, 1522, 1248, 1050 cm^{-1}; HRMS (ESI) *m/z* 364.1871 (MH^+, $C_{18}H_{25}N_3O_5H^+$ requires 364.1872).



114

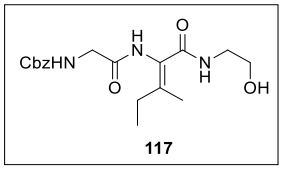
2-Azidoethyl (2*S,3*R**)-2-(2-(((benzyloxy)carbonyl)amino) acetamido)-3-hydroxy-3-methylpentanoate (114).** A solution of ester **15** (541 mg, 1.48 mmol) in *t*-BuOH–H_2O (3:1, 5.3 mL) at 0 °C was treated with LiOH•H_2O (310 mg, 7.39 mmol, 5.0 equiv), then stirred at 0 °C for 2 h. The resulting mixture was acidified to pH 1~2 by the addition of 2 N HCl (4 mL) and extracted with EtOAc (6 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid (490.1 mg, 1.448 mmol, 98%) was used directly without further purification.

A solution of the crude carboxylic acid (36.4 mg, 0.108 mmol) and iodide **22a**[15] (45.3 mg, 0.230 mmol, 2.1 equiv) in anhydrous DMF (1 mL) at rt under Ar was treated with Et_3N (46 µL, 33 mg, 0.33 mmol, 3.1 equiv). The resulting mixture was stirred at 80 °C under Ar for 22 h, then concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with brine (3 × 3 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **114** (37.5 mg, 0.0920 mmol, 86%, 84% from **77**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 5H), 6.73 (d, J = 8.1 Hz, 1H), 5.37 (br s, 1H), 5.14 (s, 2H), 4.58 (d, J = 8.6 Hz, 1H), 4.36–4.26 (m, 2H), 3.96–3.90 (m, 2H), 3.61–3.46 (m, 2H), 2.29 (s, 1H), 1.57–1.49 (m, 2H), 1.25 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.1, 156.5, 136.1, 128.6 (2C), 128.3 (2C), 128.1, 73.9, 67.3, 63.7, 58.2, 49.5, 44.5, 31.6, 23.5, 7.9; IR (film) ν_{max} 3367, 2971, 2106, 1739, 1525, 1270 cm^{-1}; HRMS (ESI) *m/z* 408.1918 (MH^+, $C_{18}H_{25}N_5O_6H^+$ requires 408.1883).



115

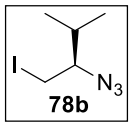
2-Azidoethyl (*Z*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-methylpent-2-enoate (115). A solution of alcohol **114** (23.8 mg, 0.0584 mmol) in anhydrous $CHCl_3$ (250 μL) was treated with Martin sulfurane (0.23 M in anhydrous $CHCl_3$, 500 μL, 0.12 mmol, 2.0 equiv) dropwise at 0 °C. The resulting mixture was stirred at 0 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 0–1.5% MeOH in CH_2Cl_2 gradient elution) afforded **115** (19.4 mg, 0.0498 mmol, 85%, >19:1 dr) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.30 (m, 5H), 7.16 (br s, 1H), 5.40 (br s, 1H), 5.15 (s, 2H), 4.29 (t, *J* = 5.0 Hz, 2H), 3.95 (d, *J* = 5.9 Hz, 2H), 3.47 (t, *J* = 4.5 Hz, 2H), 2.22–2.09 (m, 5H), 1.03 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 163.9, 156.8, 153.0, 136.0, 128.6 (2C), 128.4, 128.2 (2C), 119.5, 67.4, 63.4, 49.8, 44.8, 28.7, 18.7, 11.4; IR (film) ν_{max} 3316, 2938, 2108, 1719, 1509, 1259 cm^{-1}; HRMS (ESI) *m/z* 390.1674 (MH^+, $C_{18}H_{23}N_5O_5H^+$ requires 390.1777).



117

Benzyl (*Z*)-(2-((1-((2-hydroxyethyl)amino)-3-methyl-1-oxopent-2-en-2-yl)amino)-2-oxoethyl)carbamate (117). A solution of azide **115** (9.4 mg, 0.0241 mmol) in THF (650 μL) and H_2O (50 μL) at 0 °C under Ar was treated dropwise with PMe_3 (1 M in THF, 72 μL, 0.072 mmol, 3.0 equiv). The resulting mixture was stirred at 0 °C to rt for 21 h, at which time the starting material had disappeared as evidenced by MS. The mixture was then cooled to 0 °C, treated dropwise with morpholine (98 μL, 99 mg, 1.1 mmol), and stirred at 0 °C to rt for 72 h followed by concentration *in vacuo*. The residue was dissolved in EtOAc (10 mL), washed with H_2O (2 × 2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash

chromatography (2 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **117** (7.9 mg, 0.0217 mmol, 90%, 16:1 dr) as a white film: ^{1}H NMR ($CDCl_3$, 500 MHz, 20:1 mixture of rotamers, data for major rotamer) δ 7.74 (br s, 1H), 7.40−7.30 (m, 5H), 6.64 (br s, 1H), 5.48 (br s, 1H), 5.14 (s, 2H), 3.89 (d, *J* = 5.6 Hz, 2H), 3.73 (q, *J* = 4.8 Hz, 2H), 3.44 (q, *J* = 5.1 Hz, 2H), 3.22 (br s, 1H), 2.06 (q, *J* = 7.1 Hz, 2H), 2.02 (s, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 167.2, 157.2, 142.7, 135.8, 128.6 (2C), 128.4, 128.2 (2C), 123.3, 67.6, 61.4, 44.9, 42.6, 27.0, 17.9, 11.5; IR (film) ν_{max} 3286, 2925, 1655, 1526, 1236, 1050 cm^{-1}; HRMS (ESI) *m/z* 364.1923 (MH^+, $C_{18}H_{25}N_3O_5H^+$ requires 364.1872).

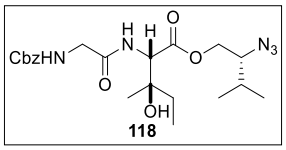


78b

(*R*)-2-azido-1-iodo-3-methylbutane (78b). A solution of (*R*)-(–)-2-amino-3-methyl-1-butanol (321 μL, 299 mg, 2.88 mmol), K_2CO_3 (398 mg, 2.88 mmol), and $CuSO_4$•$5H_2O$ (7.8 mg, 0.031 mmol) in H_2O (9.3 mL) and MeOH (18.6 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,[16] ca. 0.42 M, 13.7 mL, ca. 5.8 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.

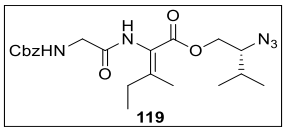
A solution of PPh_3 (937 mg, 3.57 mmol) in anhydrous CH_2Cl_2 (30 mL) at rt under Ar was treated with imidazole (525 mg, 7.71 mmol) followed by I_2 (1.44 g, 5.67 mmol), stirred for 5 min, then treated dropwise with the crude azido alcohol. The resulting mixture was refluxed for 48 h, cooled to rt, and 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 **78b** (459 mg, 1.92 mmol, 67% over 2 steps) as a colorless oil: $[\alpha]^{25}_D$ –5.0 (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.43–3.24 (m, 3H), 2.08–1.92 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 69.4, 32.9, 19.5, 17.3, 6.9; IR (film) ν_{max} 2965, 2110, 1270 cm^{-1}.



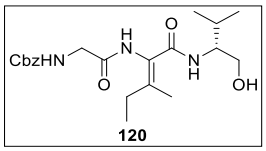
118

(*R*)-2-azido-3-methylbutyl (2*S,3*R**)-2-(2-(((benzyloxy)carbonyl) amino)acetamido)-3-hydroxy-3-methylpentanoate (118).** A solution of the acid derived from hydrolysis of ester **77** (prepared as described for azidoethyl ester **114a**, 33.5 mg, 0.0990 mmol) and iodide **78b** (48 mg, 0.20 mmol, 2.0 equiv) in anhydrous DMF (950 μL) at rt under Ar was treated with Et_3N (40 μL, 29 mg, 0.29 mmol, 2.9 equiv). The resulting mixture was stirred at 75 °C under Ar for 24 h, then concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with brine (3 × 3 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **118** (32.9 mg, 0.0732 mmol, 74%, 72% from **15**) as a yellow oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.29 (m, 5H), 6.82 and 6.80 (2d, *J* = 9.5 Hz, 1H), 5.44 (s, 1H), 5.13 (s, 2H), 4.60 and 4.58 (2d, *J* = 8.8 Hz, 1H), 4.40–4.28 (m, 1H), 4.20–4.08 (m, 1H), 3.97–3.85 (m, 2H), 3.50–3.44 and 3.44–3.36 (2m, 1H), 2.60–2.17 (br s, 1H), 1.92–1.78 (m, 1H), 1.61–1.44 (m, 2H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.02–0.95 (m, 6H), 0.92 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1 and 170.8, 169.1, 156.5, 136.1, 128.6 (2C), 128.3 (2C), 128.1, 74.0, 67.3, 66.6, 66.2, 58.4 and 58.3, 44.5, 31.7, 30.1 and 29.9, 23.5 and 23.3, 19.4, 18.2 and 18.1, 8.0 and 7.9; IR (film) ν_{max} 3341, 2969, 2101, 1733, 1522, 1270 cm^{-1}; HRMS (ESI) *m/z* 450.2359 (MH^+, $C_{21}H_{31}N_5O_6H^+$ requires 450.2353).



119

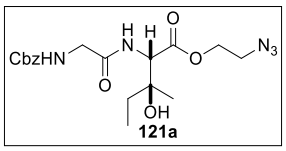
(*R*)-2-azido-3-methylbutyl (*Z*)-2-(2-(((benzyloxy)carbonyl)amino) acetamido)-3-methylpent-2-enoate (119). A solution of alcohol **118** (23.5 mg, 0.0523 mmol) in anhydrous $CHCl_3$ (220 μL) was treated with Martin sulfurane (0.24 M in anhydrous $CHCl_3$, 440 μL, 0.11 mmol, 2.0 equiv) dropwise at –20 °C. The resulting mixture was stirred at –20 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 0–1.5% MeOH in CH_2Cl_2 gradient elution) afforded **119** (18.7 mg, 0.0433 mmol, 83%, >19:1 dr) as a colorless oil: $[\alpha]^{25}_D$ +2.1 (*c* 0.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.30 (m, 5H), 7.14 (br s, 1H), 5.40 (br s, 1H), 5.15 (s, 2H), 4.44–4.37 (m, 1H), 4.11–4.02 (m, 1H), 4.00–3.91 (m, 2H), 3.46–3.39 (m, 1H), 2.22–2.12 (m, 5H), 1.86–1.76 (m, 1H), 1.07–0.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 164.0, 156.7, 153.5, 136.0, 128.6 (2C), 128.3, 128.2 (2C), 119.4, 67.4, 67.1, 66.1, 44.8, 29.9, 28.8, 19.4, 18.7, 18.2, 11.4; IR (film) ν_{max} 3313, 2967, 2100, 1721, 1509, 1212 cm^{-1}; HRMS (ESI) *m/z* 432.2118 (MH^+, $C_{21}H_{29}N_5O_5H^+$ requires 432.2247).



120

Benzyl (*R*,*Z*)-(2-((1-((1-hydroxy-3-methylbutan-2-yl)amino)-3-methyl-1-oxopent-2-en-2-yl)amino)-2-oxoethyl)carbamate (120). A solution of azide **119** (8.7 mg, 0.020 mmol) in THF (550 μL) and H_2O (90 μL) at 0 °C under Ar was treated dropwise with PMe_3 (1 M in THF, 61 μL, 0.061 mmol, 3.0 equiv). The resulting mixture was stirred at 0 °C to rt for 22 h, at which time the starting material had disappeared as evidenced by MS. The mixture was treated dropwise with piperidine (92 μL, 79 mg, 0.93 mmol), and stirred at rt for 24 h followed by concentration *in vacuo*. The residue was dissolved in EtOAc (10 mL), washed with H_2O (2 × 2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash

chromatography (3 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **120** (5.5 mg, 0.014 mmol, 67%, 10:1 dr) as a white film: $[\alpha]^{25}_D$ +27 (*c* 0.033, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (br s, 1H), 7.41−7.31 (m, 5H), 6.23 (br s, 1H), 5.43 (br s, 1H), 5.18–5.09 (m, 2H), 3.95–3.84 (m, 2H), 3.77 (br s, 2H), 3.63–3.56 (m, 1H), 3.15 (br s, 1H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.97 (s, 3H), 1.92–1.83 (m, 1H), 1.03–0.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2, 167.3, 157.1, 139.8, 135.9, 128.6 (2C), 128.4, 128.1 (2C), 124.3, 67.5, 63.2, 57.8, 44.8, 29.0, 26.5, 19.7, 19.1, 17.8, 11.6; IR (film) ν_{max} 3289, 2924, 2360, 1654, 1522, 1255, 1147 cm^{-1}; HRMS (ESI) *m/z* 406.2322 (MH^+, $C_{21}H_{31}N_3O_5H^+$ requires 406.2342).

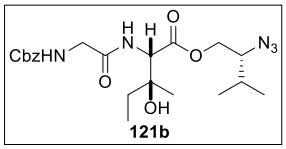


121a

2-Azidoethyl (2*S,3*S**)-2-(2-(((benzyloxy)carbonyl)amino) acetamido)-3-hydroxy-3-methylpentanoate (121a).** A solution of ester **80** (163.4 mg, 0.446 mmol) in *t*-BuOH–H_2O (3:1, 1.6 mL) at 0 °C was treated with LiOH•H_2O (93.1 mg, 2.22 mmol, 5.0 equiv), then stirred at 0 °C for 2 h. The resulting mixture was acidified to pH 1~2 by the addition of 2 N HCl (2 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 (152.2 mg, 150.9 mg theoretical yield, quant.) was used directly without further purification.

A solution of the crude carboxylic acid (38.3 mg, 0.113 mmol) and iodide **78a** (47.7 mg, 0.242 mmol, 2.1 equiv) in anhydrous DMF (1.1 mL) at rt under Ar was treated with Et_3N (49 µL, 36 mg, 0.35 mmol, 3.1 equiv). The resulting mixture was stirred at 80 °C under Ar for 48 h, then concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with brine (3 × 3 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (3 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **121a** (43.6 mg, 0.107 mmol,

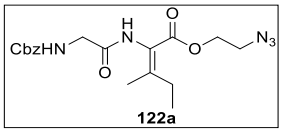
95% from **80**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5H), 6.92 (d, *J* = 8.2 Hz, 1H), 5.51 (s, 1H), 5.13 (s, 2H), 4.60 (d, *J* = 8.9 Hz, 1H), 4.34–4.24 (m, 2H), 3.97–3.89 (m, 2H), 3.56–3.46 (m, 2H), 2.50 (br s, 1H), 1.55 (q, *J* = 7.2 Hz, 2H), 1.16 (s, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.2, 156.6, 136.1, 128.6 (2C), 128.3 (2C), 128.1, 74.3, 67.3, 63.7, 58.7, 49.5, 44.5, 32.4, 22.7, 8.0; IR (film) ν_{max} 3353, 2925, 2106, 1728, 1522, 1259, 1050 cm^{-1}; HRMS (ESI) *m/z* 408.1836 (MH^+, $C_{18}H_{25}N_5O_6H^+$ requires 408.1883).



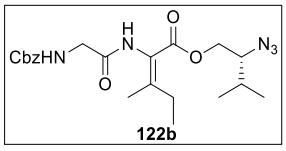
121b

(*R*)-2-Azido-3-methylbutyl (2*S,3*S**)-2-(2-(((benzyloxy)carbonyl) amino)acetamido)-3-hydroxy-3-methylpentanoate (121b).** A solution of the acid derived from hydrolysis of ester **80** (prepared as described for azidoethyl ester **121a**, 30.7 mg, 0.0907 mmol) and iodide **78b** (44 mg, 0.184 mmol, 2.0 equiv) in anhydrous DMF (870 μL) at rt under Ar was treated with Et_3N (38 μL, 28 mg, 0.27 mmol, 3.0 equiv). The resulting mixture was stirred at 80 °C under Ar for 24 h, then the reaction mixture was dissolved in EtOAc (20 mL) and washed with brine (3 × 3 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 **121b** (34.8 mg, 0.0774 mmol, 85% from **80**) as a yellow oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.29 (m, 5H), 6.85 and 6.83 (2d, *J* = 10.6 Hz, 1H), 5.44 (s, 1H), 5.13 (s, 2H), 4.62 and 4.61 (2d, *J* = 9.6 Hz, 1H), 4.39–4.27 (m, 1H), 4.19–4.08 (m, 1H), 3.98–3.88 (m, 2H), 3.48–3.43 and 3.43–3.37 (2m, 1H), 2.44 and 2.40 (2s, 1H), 1.92–1.79 (m, 1H), 1.62–1.50 (m, 2H), 1.17 (s, 3H), 1.03–0.95 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0 and 170.7, 169.1 and 169.0, 156.6, 136.1, 128.6 (2C), 128.3 (2C), 128.2, 74.3, 67.3, 66.7 and 66.6, 66.4 and 66.1, 58.7, 44.5, 32.4, 30.2 and 30.0, 22.7 and 22.6, 19.4, 18.1, 8.0; IR (film)

ν_{max} 3344, 2968, 2101, 1735, 1522, 1262 cm^{-1}; HRMS (ESI) *m/z* 450.2345 (MH^+, $C_{21}H_{31}N_5O_6H^+$ requires 450.2353).

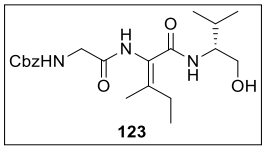


2-Azidoethyl (*E*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-methylpent-2-enoate (122a). A solution of alcohol **121a** (19.3 mg, 0.0474 mmol) in anhydrous $CHCl_3$ (210 μL) was treated with Martin sulfurane (0.24 M in anhydrous $CHCl_3$, 400 μL, 0.096 mmol, 2.0 equiv) dropwise at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h and concentrated *in vacuo*. Flash chromatography (3 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **122a** (13.8 mg, 0.0354 mmol, 75%, >19:1 dr) as a light yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.30 (m, 5H), 7.16 (s, 1H), 5.38 (s, 1H), 5.15 (s, 2H), 4.30 (t, *J* = 5.0 Hz, 2H), 3.95 (d, *J* = 5.9 Hz, 2H), 3.47 (t, *J* = 4.6 Hz, 2H), 2.55 (q, *J* = 7.5 Hz, 2H), 1.81 (s, 3H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 163.5, 156.7, 152.6, 136.0, 128.6 (2C), 128.4, 128.2 (2C), 119.7, 67.4, 63.4, 49.8, 44.8, 27.7, 19.8, 12.6; IR (film) ν_{max} 3313, 2936, 2107, 1722, 1515, 1264 cm^{-1}; HRMS (ESI) *m/z* 390.1776 (MH^+, $C_{18}H_{23}N_5O_5H^+$ requires 390.1777).



(*R*)-2-azido-3-methylbutyl (*E*)-2-(2-(((benzyloxy)carbonyl)amino) acetamido)-3-methylpent-2-enoate (122b). A solution of alcohol **121b** (24.5 mg, 0.0545 mmol) in anhydrous $CHCl_3$ (240 μL) was treated with Martin sulfurane (0.24 M in anhydrous $CHCl_3$, 460 μL, 0.11 mmol, 2.0 equiv) dropwise at –20 °C. The resulting mixture was stirred at –20 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–1.5% MeOH in CH_2Cl_2 gradient elution) afforded **122b** (19.7 mg, 0.0457 mmol,

84%, >19:1 dr) as a colorless oil: $[\alpha]^{25}_D$ +3.7 (*c* 0.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.30 (m, 5H), 7.17 (br s, 1H), 5.40 (br s, 1H), 5.15 (s, 2H), 4.44–4.37 (m, 1H), 4.12–4.01 (m, 1H), 4.00–3.89 (m, 2H), 3.47–3.40 (m, 1H), 2.57 (qd, *J* = 7.5, 1.9 Hz, 2H), 1.88–1.72 (m, 4H), 1.12 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 163.6, 156.7, 153.1, 136.0, 128.6 (2C), 128.3, 128.2 (2C), 119.6, 67.4, 67.0, 66.1, 44.8, 29.9, 27.7, 19.9, 19.4, 18.2, 12.6; IR (film) ν_{max} 3321, 2966, 2101, 1725, 1514, 1264 cm^{-1}; HRMS (ESI) *m/z* 432.2261 (MH^+, $C_{21}H_{29}N_5O_5H^+$ requires 432.2247).



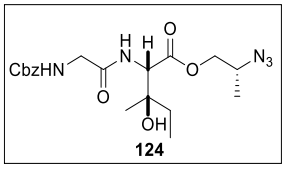
123

Benzyl (*R*,*E*)-(2-((1-((1-hydroxy-3-methylbutan-2-yl)amino)-3-methyl-1-oxopent-2-en-2-yl)amino)-2-oxoethyl)carbamate (123). A solution of azide **122b** (6.1 mg, 0.014 mmol) in DMF (400 μL) and H_2O (31 μL) at 0 °C under Ar was treated dropwise with PMe_3 (1 M in THF, 43 μL, 0.043 mmol, 3.0 equiv). The resulting mixture was stirred at 0 °C to rt for 24 h, at which time the starting material had disappeared as evidenced by MS. The mixture was then treated dropwise with morpholine (173 μL, 174 mg, 2.0 mmol) and stirred at rt for 80 h followed by concentration *in vacuo*. The residue was dissolved in EtOAc (10 mL), washed with H_2O (2 × 2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (3 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **123** (5.4 mg, 0.013 mmol, 94%, 13:1 dr) as a white film: $[\alpha]^{25}_D$ +38 (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.31 (m, 6H), 6.15 (d, *J* = 5.0 Hz, 1H), 5.39 (br s, 1H), 5.19–5.09 (m, 2H), 3.97–3.85 (m, 2H), 3.84–3.76 (m, 2H), 3.65–3.57 (m, 1H), 3.16 (br s, 1H), 2.36 (q, *J* = 7.5 Hz, 2H), 1.94–1.84 (m, 1H), 1.69 (s, 3H), 1.09 (t, *J* = 7.5 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 166.8, 157.1, 139.0, 135.8, 128.6 (2C), 128.4, 128.2 (2C), 124.8, 67.6, 63.2, 57.8, 44.9, 29.0, 27.0, 19.7, 19.0, 16.8, 12.9; IR (film) ν_{max} 3284,

2923, 2360, 1653, 1522, 1232, 1048 cm^{-1}; HRMS (ESI) *m/z* 406.2338 (MH^+, $C_{21}H_{31}N_3O_5H^+$ requires 406.2342).

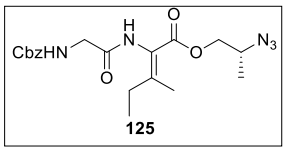
(*R*)-2-azido-1-iodopropane (78c). A solution of (*R*)-(–)-2-amino-1-propanol (222 µL, 214 mg, 2.85 mmol), K_2CO_3 (386.7 mg, 2.80 mmol), and $CuSO_4•5H_2O$ (7.7 mg, 0.031 mmol) in H_2O (9 mL) and MeOH (18 mL) at rt under Ar was treated with a solution of TfN_3 in CH_2Cl_2 (prepared according to the procedure of Lundquist and Pelletier, 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 **78c** (449 mg, 2.13 mmol, 74% over 2 steps) as a light yellow oil: $[a]^{25}_D$ −29 (*c* 0.90, $CHCl_3$); ^1H 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) n_{max} 2922, 2851, 2105, 1261 cm^{-1}.



124

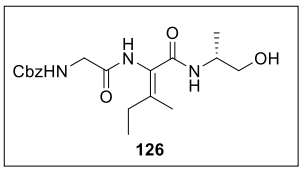
(*R*)-2-Azidopropyl (2*S,3*R**)-2-(2-(((benzyloxy)carbonyl)amino) acetamido)-3-hydroxy-3-methylpentanoate (124).** A solution of the acid derived from hydrolysis of ester **77** (prepared as described for azidoethyl ester **114a**, 6.3 mg, 0.019 mmol) and iodide **78c** (10.5 mg, 0.0498 mmol) in anhydrous DMF (0.13 mL) at rt under Ar was treated with Et_3N (10 μL, 7.3 mg, 0.072 mmol). The resulting mixture was stirred at 80 °C under Ar for 24 h, then treated with additional iodide **78c** (6.0 mg, 0.028 mmol) and Et_3N (6.0 μL, 4.4 mg, 0.043 mmol) and stirred at 80 °C for 24 h. It was then concentrated *in vacuo* and purified by flash chromatography (1.5 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) to afford **124** (6.2 mg, 0.015 mmol, 79%, 77% from **77**) as a light yellow oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.30 (m, 5H), 6.73 (s, 1H), 5.36 (s, 1H), 5.14 (s, 2H), 4.60–4.57 (m, 1H), 4.21–4.16 (m, 1H), 4.11–4.04 (m, 1H), 3.97–3.88 (m, 2H), 3.81–3.74 (m, 1H), 2.32 (s, 1H), 1.54 (q, *J* = 7.3 Hz, 2H), 1.30–1.22 (m, 6H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8 and 170.7, 169.1, 156.5, 136.1, 128.6 (2C), 128.3 (2C), 128.1, 73.9, 68.1 and 67.9, 67.3, 58.3 and 58.2, 55.7 and 55.6, 44.5, 31.6, 23.5, 16.0 and 15.9, 7.9; IR (film) n_{max} 3345, 2920, 2121, 1730, 1671, 1523, 1259, 1156, 1051 cm^{-1}; HRMS (ESI) *m/z* 422.2104 (MH^+, $C_{19}H_{27}N_5O_6H^+$ requires 422.2040).



125

(*R*)-2-azidopropyl (*Z*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-methylpent-2-enoate (125). A solution of alcohol **124** (6.0 mg, 0.0142 mmol) in anhydrous $CHCl_3$ (70 μL) was treated with Martin sulfurane (0.21 M in anhydrous $CHCl_3$, 140 μL, 0.029 mmol, 2.0 equiv) dropwise at rt under Ar. The resulting mixture was stirred at 50 °C for 1 h and

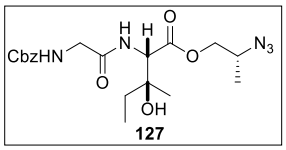
concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–2.5% MeOH in CH_2Cl_2 gradient elution) afforded **125** (5.1 mg, 0.013 mmol, 89%, >19:1 dr) as a light yellow oil: $[a]^{25}_D$ −36 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.30 (m, 5H), 7.16 (s, 1H), 5.42 (s, 1H), 5.15 (s, 2H), 4.23 (dd, *J* = 11.6, 3.5 Hz, 1H), 4.01 (dd, *J* = 11.4, 7.6 Hz, 1H), 3.96 (d, *J* = 5.9 Hz, 2H), 3.78−3.70 (m, 1H), 2.19−2.14 (m, 5H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 163.9, 156.7, 153.2, 136.0, 128.6 (2C), 128.4, 128.2 (2C), 119.5, 67.7, 67.4, 56.1, 44.8, 28.7, 18.7, 16.0, 11.5; IR (film) n_{max} 3316, 2937, 2119, 1722, 1515, 1260 cm^{-1}; HRMS (ESI) *m/z* 404.1960 (MH^+, $C_{19}H_{25}N_5O_5H^+$ requires 404.1934).



126

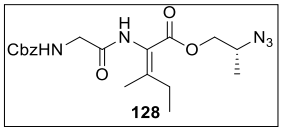
Benzyl (R,Z)-(2-((1-((1-hydroxypropan-2-yl)amino)-3-methyl-1-oxopent-2-en-2-yl)amino)-2-oxoethyl)carbamate (126). A solution of azide **125** (6.8 mg, 0.017 mmol) in THF (460 μL) and H_2O (76 μL) at 0 °C under Ar was treated dropwise with PMe_3 (1 M in THF, 51 μL, 0.051 mmol, 3.0 equiv). The resulting mixture was stirred at 0 °C to rt for 62 h, at which time the starting material had disappeared as evidenced by MS. The mixture was then treated dropwise with piperidine (76 μL, 66 mg, 0.77 mmol) and stirred at rt for 30 h followed by concentration *in vacuo* after adding 0.4 mL DMF. The residue was dissolved in EtOAc (10 mL), washed with H_2O (2 × 2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (3 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **126** (5.5 mg, 0.015 mmol, 86%, 6:1 dr) as a white film: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (s, 1H), 7.40−7.30 (m, 5H), 6.27 (br s, 1H), 5.47 (br s, 1H), 5.13 (s, 2H), 4.11 (br s, 1H), 3.93–3.83 (m, 2H), 3.78–3.72 (m, 1H), 3.48–3.41 (m, 1H), 3.21 (br s, 1H), 2.05 (q, *J* = 7.5 Hz, 2H), 1.99 (s,

3H), 1.18 (d, J = 7.0 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H); HRMS (ESI) *m/z* 378.2020 (MH^+, $C_{19}H_{27}N_3O_5H^+$ requires 378.2029).



127

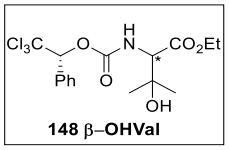
(*R*)-2-Azidopropyl (2*S,3*S**)-2-(2-(((benzyloxy)carbonyl)amino) acetamido)-3-hydroxy-3-methylpentanoate (127).** A solution of the acid derived from hydrolysis of ester **80** (prepared as described for azidoethyl ester **121a**, 25.0 mg, 0.0739 mmol) and iodide **78c** (93.8 mg, 0.445 mmol, 6.0 equiv) in anhydrous DMF (750 mL) at rt under Ar was treated with Et_3N (83 μL, 60 mg, 0.60 mmol, 8.1 equiv). The resulting mixture was stirred at 75 °C under Ar for 72 h, then concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with brine (2 × 2 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–3% MeOH in CH_2Cl_2 gradient elution) afforded **127** (17.1 mg, 0.0406 mmol, 55% from **80**) as a light yellow oil that was a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5H), 6.78 (s, 1H), 5.38 (s, 1H), 5.14 (s, 2H), 4.62–4.58 (m, 1H), 4.22–4.14 (m, 1H), 4.10–4.04 (m, 1H), 3.98–3.88 (m, 2H), 3.81–3.74 (m, 1H), 2.31 (br s, 1H), 1.55 (q, J = 6.9 Hz, 2H), 1.28 (t, J = 7.4 Hz, 3H), 1.16 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8 and 170.7, 169.0, 156.5, 136.0, 128.6 (2C), 128.3 (2C), 128.2, 74.3, 68.0 and 67.8, 67.3, 58.7, 55.7 and 55.6, 44.5, 32.5, 22.6, 16.0 and 15.9, 8.0; IR (film) n_{max} 3341, 2977, 2121, 1731, 1673, 1524, 1261, 1051 cm^{-1}; HRMS (ESI) *m/z* 422.2025 (MH^+, $C_{19}H_{27}N_5O_6H^+$ requires 422.2040).



128

(*R*)-2-azidopropyl (*E*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-methylpent-2-enoate (128). A solution of alcohol **127** (10.1 mg, 0.0240 mmol) in anhydrous

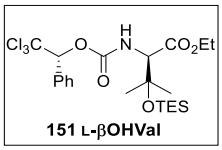
$CHCl_3$ (150 μL) was treated with Martin sulfurane (0.32 M in anhydrous $CHCl_3$, 150 μL, 0.051 mmol, 2.1 equiv) dropwise at rt under Ar. The resulting mixture was stirred at 50 °C for 1 h and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–2.5% MeOH in CH_2Cl_2 gradient elution) afforded **128** (8.1 mg, 0.020 mmol, 84%, >19:1 dr) as a light yellow oil: $[\alpha]^{25}_D$ −30 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.30 (m, 5H), 7.15 (s, 1H), 5.39 (s, 1H), 5.16 (s, 2H), 4.24 (dd, *J* = 11.6, 3.5 Hz, 1H), 4.01 (dd, *J* = 11.5, 7.8 Hz, 1H), 3.95 (d, *J* = 5.9 Hz, 2H), 3.97–3.93 (m, 2H), 3.81–3.71 (m, 1H), 2.56 (q, *J* = 7.5 Hz, 2H), 1.82 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 163.5, 156.7, 152.9, 136.0, 128.6 (2C), 128.4, 128.2 (2C), 119.7, 67.7, 67.4, 56.1, 44.8, 27.7, 19.8, 16.0, 12.7; IR (film) ν_{max} 3314, 2920, 2850, 2120, 1723, 1514, 1264, 1207 cm^{-1}; HRMS (ESI) *m/z* 404.1949 (MH^+, $C_{19}H_{25}N_5O_5H^+$ requires 404.1934).



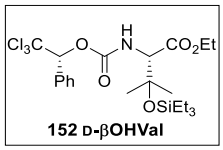
148 β–OHVal

Ethyl (R*)-3-hydroxy-3-methyl-2-((((R)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)butanoate (148). A solution of (*R*)-2,2,2-trichloro-1-phenylethyl ((methylsulfonyl)oxy)carbamate **147** (740 mg, 2.04 mmol, 1.2 equiv) in CH_3CN (10 mL) at rt was treated with OsO_4 (4 wt % solution in H_2O, 0.6 mL, 0.094 mmol, 0.075 equiv), stirred at rt for 20 min, then treated with the Ethyl 3-methylbut-2-enoate **54** (159 mg, 1.24 mmol, 1 equiv) and H_2O (0.68 ml). The resulting mixture was stirred at 40 °C for 48 h, then worked up following standard procedure. Flash chromatography (30 mL SiO_2, 0–1% MeOH in CH_2Cl_2 gradient elution) afforded **151**(348.1 mg, 0.843 mmol, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, consisted of 2 diastereomers) δ 7.62 (d, *J* = 6.5 Hz, 2H), 7.46–7.35 (m, 3H), 6.33 (s, 0.5H), 6.27 (s, 0.5H), 6.02–5.93 (m, 1H), 4.43–4.11 (m, 3H), 2.59–2.47 (m, 1H), 1.45–1.16 (m, 6H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 171.2, 154.3,154.2, 133.1, 133.0, 129.7

(2C), 129.6, 127.9 (2C), 99.7, 99.4, 83.7, 83.5, 72.1, 71.7, 61.8 (2C), 61.6, 61.5, 27.0, 26.3, 26.2, 14.1, 14.0; HRMS (ESI) *m/z* 412.0503 (MH^+, $C_{16}H_{20}Cl_3NO_5H^+$ requires 412.0485).



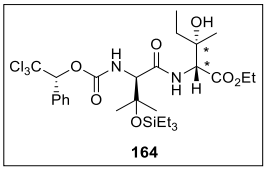
151 L-βOHVal



152 D-βOHVal

Ethyl (R)-3-methyl-2-((((R)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)-3-((triethylsilyl)oxy)butanoate (151) and **Ethyl (S)-3-((ethyl-l2-silyl)oxy)-3-methyl-2-((((R)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)butanoate (152)**. A solution of 1:1 diastereomeric **148** (120 mg, 0.291 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 0 ^oC was treated with 2, 6-lutidine (0.1 ml, 0.882 mmol, 3.0 equiv) followed by TES-OTf (0.13 ml, 0.577 mmol, 2.0 equiv). The resulting mixture was stirred at 0 °C for 2 h, then treated with H_2O and and extracted with CH_2Cl_2 (3 times), dried (Na_2SO_4), and concentrated *in vacuo*. Simple column sepration (5 mL SiO_2 at 50% hexane–CH_2Cl_2) delivered the desired product (160 mg, quant.). For convenience, the crude material is normally sujected to flash chromatography (SiO_2) to separate the diastereomers. 1 g of the crude 1:1 mixture after 3 chromatographic separation (40 mL of SiO_2, 10%–50% CH_2Cl_2 in hexane gradient elution) can afford 100 mg **151** and 100 mg **152** each with dr>10:1 as colorless oils. For **151**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.44–7.36 (m, 3H), 6.32 (s, 1H), 5.85 (d, *J* = 9.5 Hz, 1H), 4.19–4.09 (m, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 9H), 0.62 (1, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 153.9, 133.2, 129.7, 129.6 (3C), 127.9, 99.8, 83.3, 75.0, 63.1, 27.7, 27.6, 14.0, 7.0, 6.9, 6.5. For **152**: ^1H NMR ($CDCl_3$, 500 MHz, major rotamor) δ 7.62 (d, *J* = 6.5 Hz, 2), , 7.44–7.35 (m, 3H), 6.27 (s, 1H), 5.83 (d, *J* = 9.0 Hz, 1H), 4.27–4.17 (m, 2H), 4.11 (d, *J* = 9,5Hz, 1H), 1.35 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.21 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.8, 154.0,

133.4, 129.7, 129.6 (2C), 127.8 (2C), 99.5, 83.5, 83.4, 74.6, 63.3, 61.2, 28.0, 27.7, 14.1, 6.9, 6.3; HRMS (ESI) *m/z* 526.1386 (MH^+, $C_{22}H_{34}Cl_3NO_5SiH^+$ requires 526.1350).

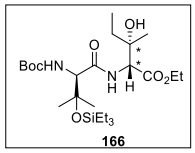


164

Ethyl (2R*,3S*) -3-hydroxy-3-methyl-2-((R)-3-methyl-2-((((R)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)-3-((triethylsilyl)oxy)butanamido)pentanoate (164).A suspension of **151** (106.3 mg, 0.202 mmol) and Me_3SnOH (80.0 mg, 0.444 mmol, 2.2 equiv) in hexane (8 mL, pretreated with Na_2SO_4 for 6 h) was flushed with Ar and stirred at 60 °C for 48 h. The solvent was evaporated, and 10 mL diethyl ether was added. The mixture was filtered through Celite, and the Celite pad was washed with diethyl ether (60 mL). The filtrate was concentrated *in vacuo* to afford **163** as a colorless oil, which was used directly in the next step without further purification.

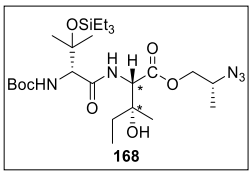
A solution of the acid in anhydrous CH_2Cl_2 (4 mL) at 0 °C under Ar was treated with amine **153** (49.6 mg, 0.283 mmol, 1.4 equiv), HOBt (ca. 20% H_2O content, 51.0 mg, 0.310 mmol, 1.54 equiv), and EDC•HCl (58.0 mg, 0.303 mmol, 1.5 equiv). The resulting mixture stirred at 0 °C under Ar for 3 h. The reaction was quenched by the addition of sat. aq, $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL), 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 **77** (111.0 mg, 0.170 mmol, 84%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz, consisted of two diastereomers) δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.44–7.34 (m, 3H), 6.32 (s, 1H), 6.11 (d, *J* = 8.0 Hz, 0.5H), 6.05 (d, *J* = 7.5 Hz, 0.5H), 4.55 (d, *J* = 8.5 Hz, 0.5H), 4.41 (d, *J* =8.5 Hz, 0.5H), 4.27–4.13 (m, 3H),2.55 (s, 0.5 H), 2.50 (s, 0.5 H), 1.58–1.45 (m, 2H), 1.44–1.39 (m, 3H), 1.34–1.24 (m, 6H), 1.21–1.17 (m, 3H), 1.03–0.97 (m, 9H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.76–0.66 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 171.1, 170.0, 169.6, 154.7, 154.5, 133.1, 129.7 (3C),

129.6, 127.9, 99.8, 99.7, 83.4, 76.1, 74.1, 73.4, 63.7, 62.8, 61.6, 61.5, 58.5, 58.4, 31.6, 31.3, 27.5, 27.3, 26.0, 25.0, 23.7, 23.3, 14.2, 14.1, 7.9, 7.7, 6.8, 6.5. IR (film) ν_{max} 3358, 2957, 2877, 2359, 1736, 1665, 1508, 1372, 1203, 1057 cm^{-1}; HRMS (ESI) *m/z* 655.2134 (MH^+, $C_{18}H_{26}N_2O_6H^+$ requires 655.2140).



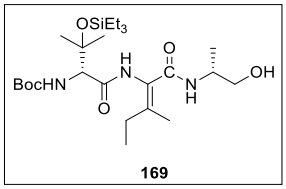
166

Ethyl (2R*,3S*)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanamido)-3-hydroxy-3-methylpentanoate (166). A suspension of **164** (53.0 mg, 0.081 mmol) in THF/Sat. aq $NaHCO_3$ 3:1 solution (4 mL) was treated with 10% Pd/C (9.6 mg, 0.18 wt eqiv) and Boc_2O (18.5 mg, 0.085 mmol, 1.05 equiv.) sequentially at rt under Ar, and stirred at rt under H_2 (100 psi) for 15 h. H_2O (2 mL) were added and extracted with EtOAc (5 × 3 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (3.5 mL of SiO_2, 0–1% MeOH in CH_2Cl_2 gradient elution) afforded **166** (37.3 mg, 0.074 mmol, 92%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) 7.14 (s, 1H), 5.45 (br s, 1H), 4.62 (d, *J* = 8.5 Hz, 1H), , 4.30–4.17 (m, 2H), 4.04 (br s, 1H), 2.75 (s, 1H), 2.65 (s, 0.3H), 1.57 (q, *J* = 7.5 Hz, 2H), 1.45 (s, 9H), 1.39–1.25 (m, 9H), 1.18 (s, 3H), 1.03–0.89 (m, 12H), 0.73–0.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 170.9, 170.5, 156.1, 80.0, 75.5, 74.2, 73.7, 63.7, 61.5, 58.5, 58.2, 31.5, 31.4, 28.3, 27.6, 27.2, 26.7, 23.6, 14.2, 14.1, 7.9, 7.0, 6.5. IR (film) ν_{max} 3406, 2977, 2360, 1734, 1507, 1162, 1028 cm^{-1}; HRMS (ESI) *m/z* 505.3335 (MH^+, $C_{18}H_{26}N_2O_6H^+$ requires 505.3309).



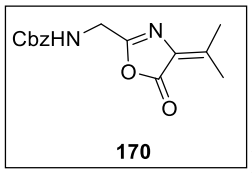
(R)-2-azidopropyl (2S,3R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanamido)-3-hydroxy-3-methylpentanoate (168). A solution of ester **166** (17 mg, 0.0337 mmol) in *t*-BuOH–H_2O (3:1, 1.3 mL) at 0 °C was treated with LiOH•H_2O (8.5 mg, 0.202 mmol, 6.0 equiv), then stirred at rt for 3 h. The resulting mixture was acidified to pH 4~5 by the addition of 2 N HCl and diluted with H_2O (2 mL), and then the aqueous mixture was extracted with EtOAc (2 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid (15.1 mg, 0.0316 mmol, 94%) was used directly without further purification.

A solution of the crude carboxylic acid (9.1 mg, 0.0191 mmol) and iodide **78c** (12.0 mg, 0.230 mmol, 2.1 equiv) in anhydrous DMF (0.5 mL) at rt under Ar was treated with Cs_2CO_3 (6.5 mg, 0.020 mmol, 1.04 equiv). The resulting mixture was stirred at 80 °C under Ar for 15 h, and dissolved in EtOAc (4 mL) and washed with H_2O (3 × 0.5 mL) and brine (1 × 1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (1 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **168** (8.5 mg, 0.0152 mmol, 80%, 75% for 2 steps from **166**) as a colorless oil. HRMS (ESI) *m/z* 560.3502 (MH^+, $C_{25}H_{49}N_5O_7SiH^+$ requires 560.3480).

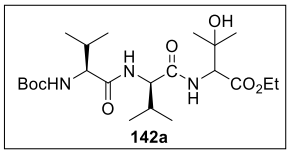


Tert-butyl ((6R,12R,Z)-9-(butan-2-ylidene)-3,3-diethyl-13-hydroxy-5,5,12-trimethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-6-yl)carbamate (169). **6182** A solution of alcohol **168** (10.6 mg, 0.0189 mmol) in anhydrous $CHCl_3$ (100 μL) was treated with

Martin sulfurane (25.4 mg in anhydrous 400 μL $CHCl_3$, 0.0378 mmol, 2.0 equiv) dropwise at 0 °C. The resulting mixture was stirred at 0 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. This oil mixture was treated with DMF (550 μL), H_2O (90 μL) and lindlar catalyst (100 mg) sequentially at rt. Then, the resulting suspension was stirred at rt under H_2 (1 atm) for 15 h (azide reduction can be evidenced by MS), then peperidine (90 μL) was added under Ar, and stirred at rt for 24 h. The mixture was treated with sat. aq $NaHCO_3$ 2 mL, and extracted with EtOAc (5 × 2 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–4% MeOH in CH_2Cl_2 gradient elution) afforded **169** (8.3 mg, 0.0161 mmol, 75%, 12:1 dr) as a white film: $[\alpha]^{25}_D$ +7.2 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (s, 1H), 6.48 (br s, 1H), 5.49 (br s, 1H), 4.13 (d, *J* = 4.0 Hz, 1H), 3.93 (d, *J* = 5.0 Hz, 1H), 3.87–3.74 (m, 1H), 3.55–3.41 (m, 1H), 3.26 (br s, 1H), 2.18–2.08 (m, 2H), 2.04 (s, 3H), 1.46 (s, 9H), 1.36 (d, *J* = 9.0 Hz, 6H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 8.0 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.66 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 165.6, 156.8, 141.6, 123.7, 80.8, 74.8, 66.2, 64.9, 48.0, 28.3, 27.4, 27.1, 17.8, 16.6, 11.7, 7.0, 6.3. IR (film) ν_{max} 3348, 2924, 2283, 1665, 1461, 1367, 1169, 1051 cm^{-1}; HRMS (ESI) *m/z* 516.3424 (MH^+, $C_{25}H_{49}N_3O_6SiH^+$ requires 516.3469).

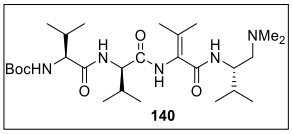


Benzyl ((5-oxo-4-(propan-2-ylidene)oxazolidin-2-yl)methyl)carbamate (**170**) or azlactone characterization: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42−7.29 (m, 5H), 5.35 (br s, 1H), 5.14 (s, 2H), 4.30 (d, *J* = 5.3 Hz, 2H), 2.34 (s, 3H), 2.23 (s, 3H); HRMS (ESI) *m/z* 289.0204 (MH^+, $C_{15}H_{18}N_2O_4H^+$ requires 289.1188).



142a

Ethyl (6S,9R)-12-(2-hydroxypropan-2-yl)-6,9-diisopropyl-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (142a). A solution of the acid Boc-Val-Val-OH (27 mg, 0.085 mmol)in anhydrous DMF–CH_2Cl_2 (3mL 5:1) at 0 °C under Ar was treated with amine **57a** (20 mg, 0.124 mmol), HOBt (ca. 20% H_2O content, 23 mg, 0.136 mmol), and EDC•HCl (21 mg, 0.110 mmol). The resulting mixture stirred at 0 °C under Ar for 3 h. The reaction was quenched by the addition of sat aq $NaHCO_3$ (3 mL) and H_2O (2 mL), and CH_2Cl_2 was vacuumed off. It was extracted with EtOAc (10 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–50% EtOAc in CH_2Cl_2 gradient elution) afforded **142a** (30.4 mg, 0.066 mmol, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, 2 diastereomers) δ 7.12–6.95 (m, 1H), 6.77 (d, *J* = 7.0 Hz, 0.5H), 6.68 (d, *J* = 8.0 Hz, 0.5H), 5.20 (t, *J* = 7.0 Hz, 1H), 4.51 (q, *J* =5.5 Hz, 1H), 4.45–4.40 (m, 1H), 4.30–4.17 (m, 2H), 4.01 (br s, 1H), 3.10 (s, 1H), 2.33–2.08 (m, 2H), 1.87 (s, 0.5H), 1.44 (s, 9H), 1.35–1.21 (m, 9H), 1.03–0.87 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 171.8, 171.2, 171.0, 155.8, 155.7, 80.0, 71.8, 61.6, 60.0, 58.4, 58.3, 30.8, 28.3, 26.9, 26.8, 26.7, 19.4 (2C), 19.1, 18.2, 17.7, 17.5, 14.1.; IR (film) ν_{max} 3361, 3275, 2973, 2361, 1733, 1641, 1532, 1368, 1168 cm^{-1}; HRMS (ESI) *m/z* 460.3038 (MH^+, $C_{18}H_{26}N_2O_6H^+$ requires 460.3023).

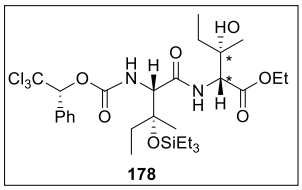


140

Tert-butyl ((4S,10R,13S)-4,10-diisopropyl-2,14-dimethyl-6,9,12-trioxo-7-(propan-2-ylidene)-2,5,8,11-tetraazapentadecan-143-yl)carbamate (140). A solution of ester **142a** (40 mg, 0.087 mmol) in *t*-BuOH–H_2O (2:1, 3.0 mL) at 0 °C was treated with LiOH•H_2O (20 mg, 0.476 mmol, 5.5 equiv), then stirred at 0 °C for 3 h. The resulting mixture

was acidified to pH 4~5 by the addition of 2 N HCl and diluted with H_2O 3 mL, extracted with EtOAc (8 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid was used directly without further purification.

A solution of the acid **142** in anhydrous DMF (0.6 mL) at rt under Ar was treated EDCI•HCl (34 mg, 0.177 mmol, 2 equiv) and stirred for 15 h. The disappearance of start material was evidenced by MS. Amine **143** HCl salt (24 mg, 0.144 mmol, 1.7 equiv) was added followed by DMF (1.4 mL, to rinse the amine·HCl off vial) and NEt3 (50 μL), and the resulting mixture was stirred at rt for 3 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ (2 mL) and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (8 × 4 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (8 mL of SiO_2, 0–3% MeOH in EtOAc with 1% NEt3 gradient elution) afforded peptide **140** (45.1 mg, 0.0859 mmol, 97%) as a white film: $[\alpha]^{25}_D$ +8.8 (*c* 0.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (br s, 1H), 6.96 (br s, 1H), 6.61 (br s, 1H), 6.05 (br s, 1H), 4.31–4.21 (m, 1H), 4.09–3.98 (m, 1H), 3.75–3.63 (m, 1H), 2.66 (br s, 2H), 2.46–2.32 (m, 1H), 2.13 (s, 6H), 2.17 (s, 3H), 2.15–2.02 (m, 1H), 1.96–1.85 (m, 1H), 1.75 (s, 3H), 1.43 (s, 9H), 1.10–0.82 (m, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 170.3, 165.4, 156.8, 141.7, 123.7, 80.3, 61.5, 59.8, 59.5, 51.2, 45.3, 30.9, 29.7, 28.1, 21.7, 20.8, 19.8, 19.5, 19.1, 18.5, 17.9; IR (film) ν_{max} 3266, 2964, 2764, 2360, 1717, 1642, 1541, 1390, 1174 cm^{-1}; HRMS (ESI) *m/z* 526.3980 (MH^+, $C_{27}H_{52}N_5O_5H^+$ requires 526. 3968).

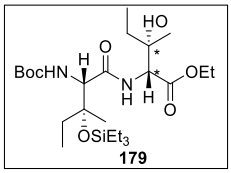


178

Ethyl (2R*,3S*)-3-hydroxy-3-methyl-2-((2S,3R)-3-methyl-2-((((R)-2,2,2-trichloro-1-phenylethoxy)carbonyl)amino)-3-((triethylsilyl)oxy)pentanamido)pentanoate (178). A suspension of **177** (109 mg, 0.2022 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 flushed with Ar and stirred at 60 °C for 72 h. The solvent was evaporated, and 10 mL diethyl ether was added. The mixture was filtered through Celite, and the Celite pad was washed with diethyl ether (60 mL). The filtrate was concentrated *in vacuo* to afford the respective carboxylic acid (125.8 mg crude weight) as a colorless oil, which was used directly in the next step without further purification.

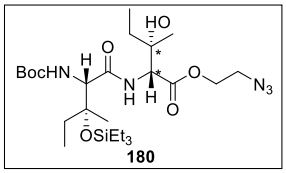
A solution of the acid (97 mg was used out of 125.8 mg, assuming 0.155 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C under Ar was treated with amine **153** (30 mg, 0.171 mmol, 1.1 equiv), HOBt (ca. 20% H_2O content, 39.2 mg, 0.232 mmol, 1.5 equiv), and EDC•HCl (44.6 mg, 0.233 mmol, 1.5 equiv). The resulting mixture stirred at 0 °C under Ar for 3 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ (4 mL) and the aqueous layer was extracted with CH_2Cl_2 (6 × 4 mL), 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 **178** (77.3 mg, 0.115 mmol, 74% from ester **177**, 2 step) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, consisted of two diastereomers) δ 7.62 (d, J = 7.6 Hz, 2H), 7.46–7.36 (m, 3H), 6.28 (d, J = 4.6 Hz, 1H), 6.08–5.96 (m, 1H), 4.32 (d, J = 2.2 Hz, 0.5H), 4.30 (d, J = 2.2 Hz, 0.5H), 4.28–4.16 (m, 3H), 2.80–2.42 (m, 1H), 1.64–1.47 (m, 4H), 1.40–1.19 (m, 9H), 1.18 (s, 3H), 1.06–0.90 (m, 12H), 0.78–0.61 (m, 6H); HRMS (ESI) HRMS (ESI) *m/z* 669.2293 (MH^+, $C_{30}H_{48}N_2O_7SiH^+$ requires 669.2296).



179

Ethyl (2R*,3S*)-2-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)pentanamido)-3-hydroxy-3-methylpentanoate (179). A suspension of carbamate **178** (84.9 mg, 0.127 mmol) in THF/Sat. aq $NaHCO_3$ 2:1 solution (2.3 mL) was treated with 10% Pd/C (10 mg, 0.12 wt equiv) and Boc_2O (29 mg, 0.133 mmol, 1.05 equiv) sequentially

at rt under Ar, and stirred at rt under H_2 (100 psi) for 15 h. H_2O (1 mL) and Sat. aq $NaHCO_3$ solution (1ml) were added 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 **178** (71 mg, 0.127 mmol, quant.) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (br s, 1H), 6.15 (br s, 1H), 4.62, 4.55 (d, *J* = 8.6 Hz, 1H), 4.38–4.15 (m, 3H), 4.05 (d, *J* = 6.9 Hz, 0.5 H), 3.19 (d, *J* = 7.0 Hz, 0.5H), 1.65–1.50 (m, 4H), 1.47 (s, 9H), 1.40–1.15 (m, 9H), 1.07–0.83 (m, 15H), 0.79–0.61 (m, 6H); HRMS (ESI) *m/z* 519.3458 (MH^+, $C_{18}H_{26}N_2O_6H^+$ requires 519.3466).

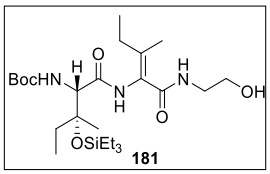


180

2-azidoethyl (2R*,3S*)-2-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)pentanamido)-3-hydroxy-3-methylpentanoate (180). A solution of ester **179** (21.2 mg, 0.041 mmol) in *t*-BuOH–H_2O (2:1, 0.9 mL) at 0 °C was treated with LiOH•H_2O (10 mg, 0.238 mmol, 5.8 equiv), then stirred at rt for 3 h. The resulting mixture was added water (1 mL) and extracted with EtOAc (1.5 mL × 5). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude carboxylic acid was used directly without further purification.

A solution of the crude carboxylic acid and iodide **78b** (14.4 mg, 0.0731 mmol, 1.8 equiv) in anhydrous DMF (0.51 mL) at rt under Ar was treated with triethylamine (15.2 μL, 0.109 mmol, 3.23 equiv). The resulting mixture was stirred at 80 °C under Ar for 15 h, and was added H_2O (2 mL) and extracted with EtOAc (5 × 2 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (2 mL of SiO_2, 0–2% MeOH in CH_2Cl_2 gradient elution) afforded **180** (17.8 mg, 0.0318 mmol, 78% from ester **179** for 2 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, consisted of two diastereomers) δ 7.09 (br s, 1H), 5.46–5.28 (m,

1H), 4.53 (d, *J* = 8.3, 0.5H), 4.39–4.35 (m, 1H), 4.35–4.25 (m, 2H), 4.16 (d, *J* = 1.4 Hz, 0.5H), 3.61–3.48 (m, 2H), 1.67–1.49 (m, 4H), 1.45 (s, 9H), 3.8–3.6 (m, 6H), 1.12–0.85 (m, 15H), 0.74–0.61 (m, 6H). 560.3494 (MH^+, $C_{25}H_{49}N_5O_7SiH^+$ requires 560.3480).



181

2tert-butyl ((5R,6S,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 (181). A solution of alcohol **180** (15.4 mg, 0.0275 mmol) in anhydrous $CHCl_3$ (100 μL) was treated with Martin sulfurane (37.0 mg in anhydrous 400 μL $CHCl_3$, 0.055 mmol, 2.0 equiv) dropwise at 0 °C. The resulting mixture was stirred at 0 °C under Ar for 1 h, warmed to rt, and concentrated *in vacuo*. This oil mixture was treated with THF (550 μL), H_2O (50 μL) and lindlar catalyst (130 mg) sequentially at rt. Then, the resulting suspension was stirred at rt under H_2 (1 atm) for 15 h (azide reduction can be evidenced by MS), then peperidine (50 μL) was added under Ar, and stirred at rt for 24 h. The mixture was treated with sat. NH_4Cl 0.5 mL and H_2O 1.5 mL, and the mixture was extracted with EtOAc (7 × 2 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 0–4% MeOH in CH_2Cl_2 gradient elution) afforded **169** (10.6 mg, 0.0205 mmol, 75%, 12:1 dr) as a white film: $[\alpha]^{25}_D$ -4.1 (*c* 0.35, $CHCl_3$); δ ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (s, 1H), 6.85 (s, 1H), 5.39 (s, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 3.73 (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, 4H), 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, 75.7, 77.7, 61.8, 42.8, 33.2, 28.3, 27.2, 24.4, 17.8, 11.7, 8.9, 7.1, 7.0, 6.7, 6.5; 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).

5.3 **References**

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(9) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900-9901.

(10) (a) Data for **21**: Schmidt, U.; Meyer, R.; Leitenberger, V.; Stäbler, F.; Lieberknecht, A. *Synthesis* **1991**, 409-423. (b) Data for *meso* isomer: Wharton, T.; Wilson, L. J. *Bioorg. Med. Chem.* **2002**, *10*, 3545-3554.

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(12) **75** could be prepared via the procedure employed by Inoue and co-workers (*J. Am. Chem. Soc.* **2013**, *135*, 5467-5474.) for synthesis of the analogous vinyl iodide (listed as compound **33** in their paper), using MeOH or H_2O trapping instead of I2 trapping.

(13) A hydrogenation conducted on smaller scale (141 mg of **76**) at 750 psi H2 was complete within 24 h.

(14) Shangguan, N.; Joullié, M. *Tetrahedron Lett.* **2009**, *50*, 6748-6750.

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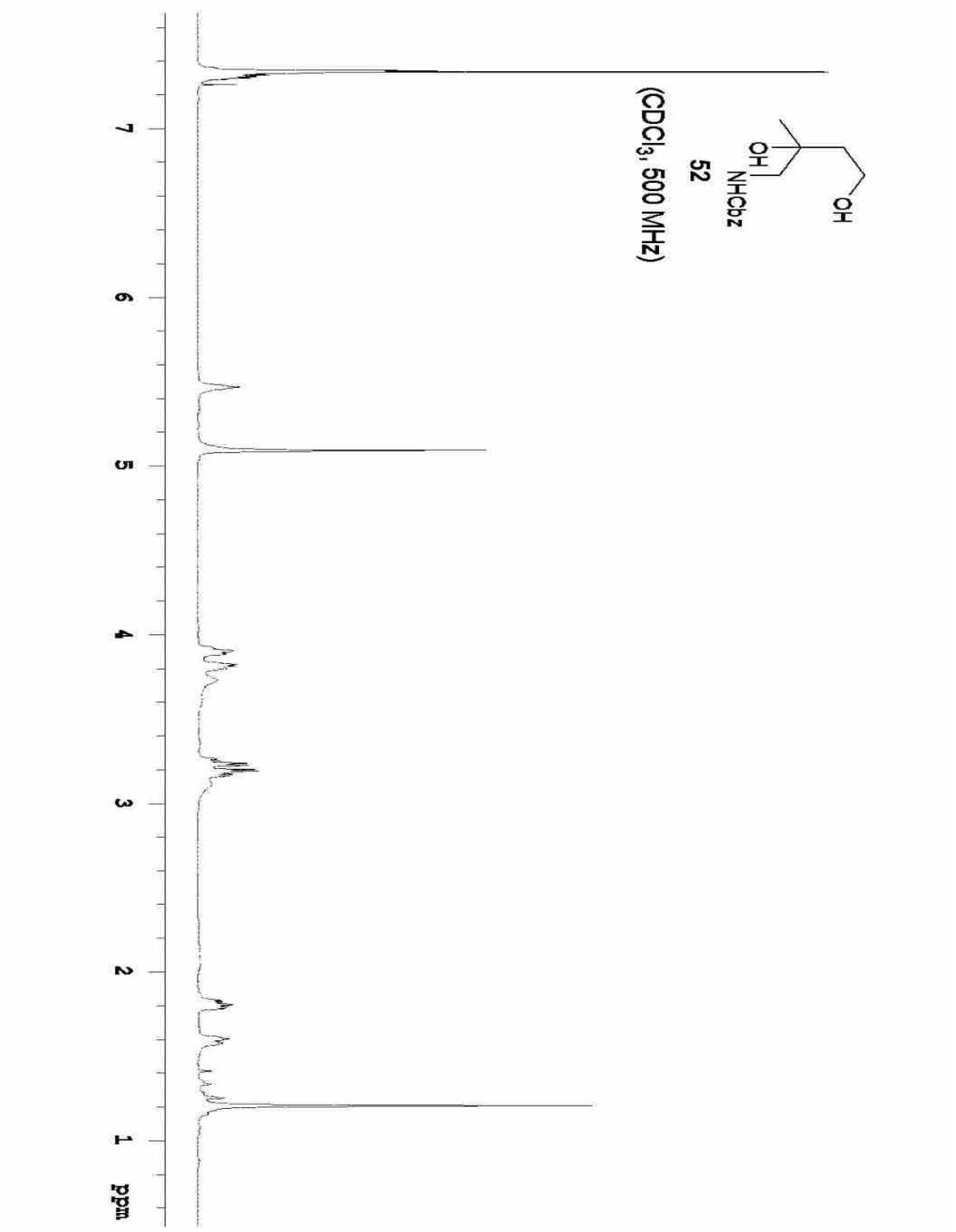
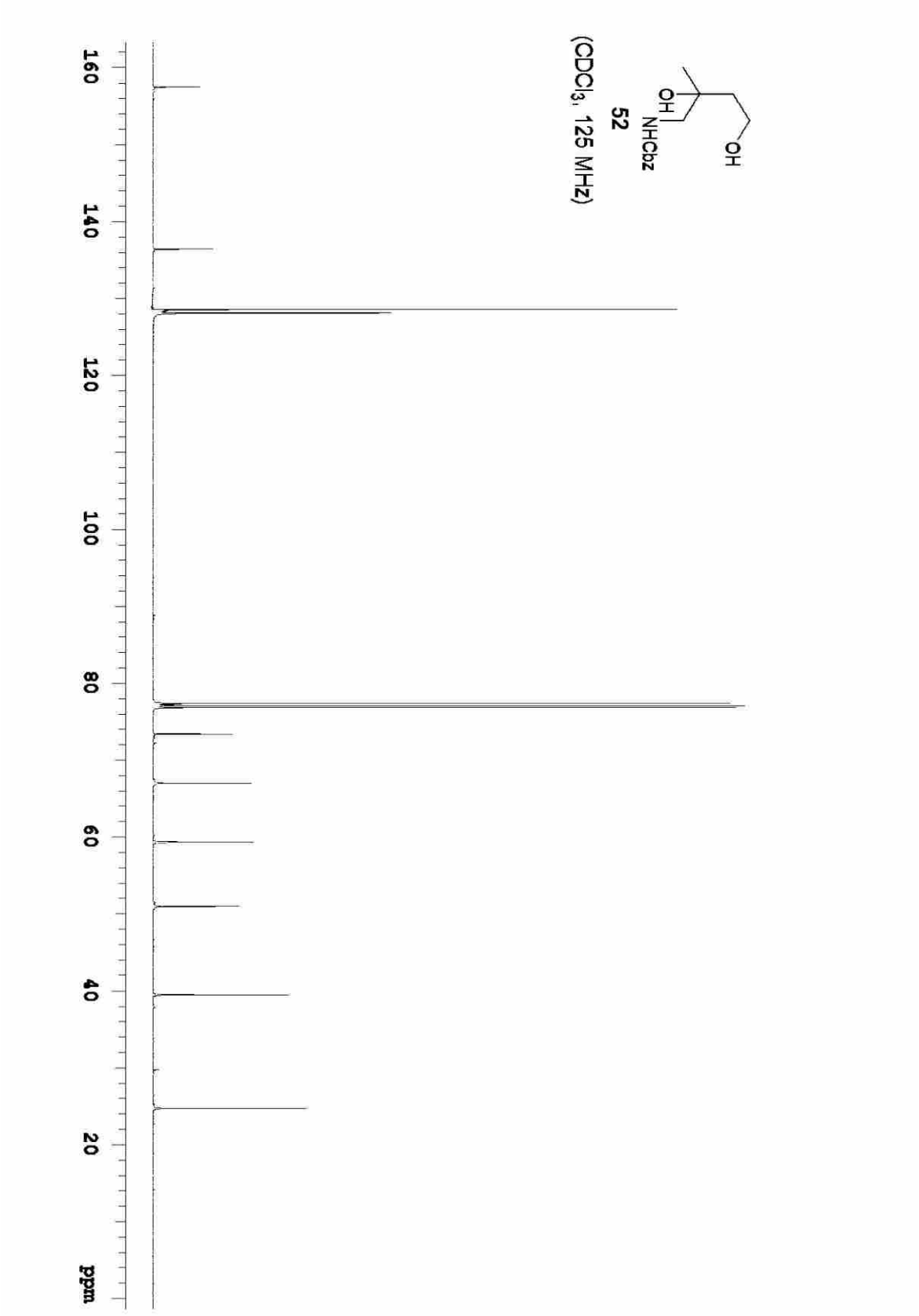
5.4 **Spectra**

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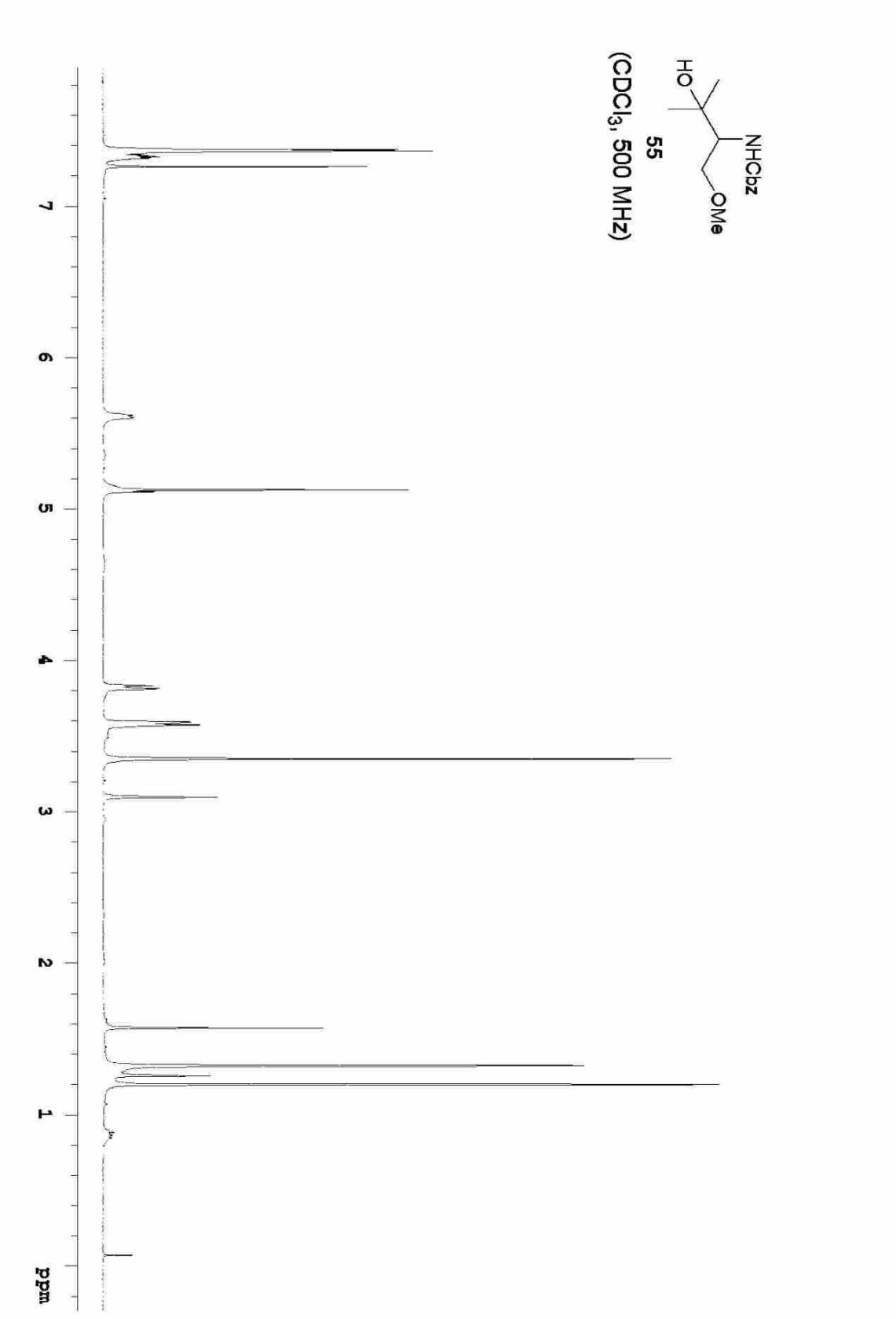
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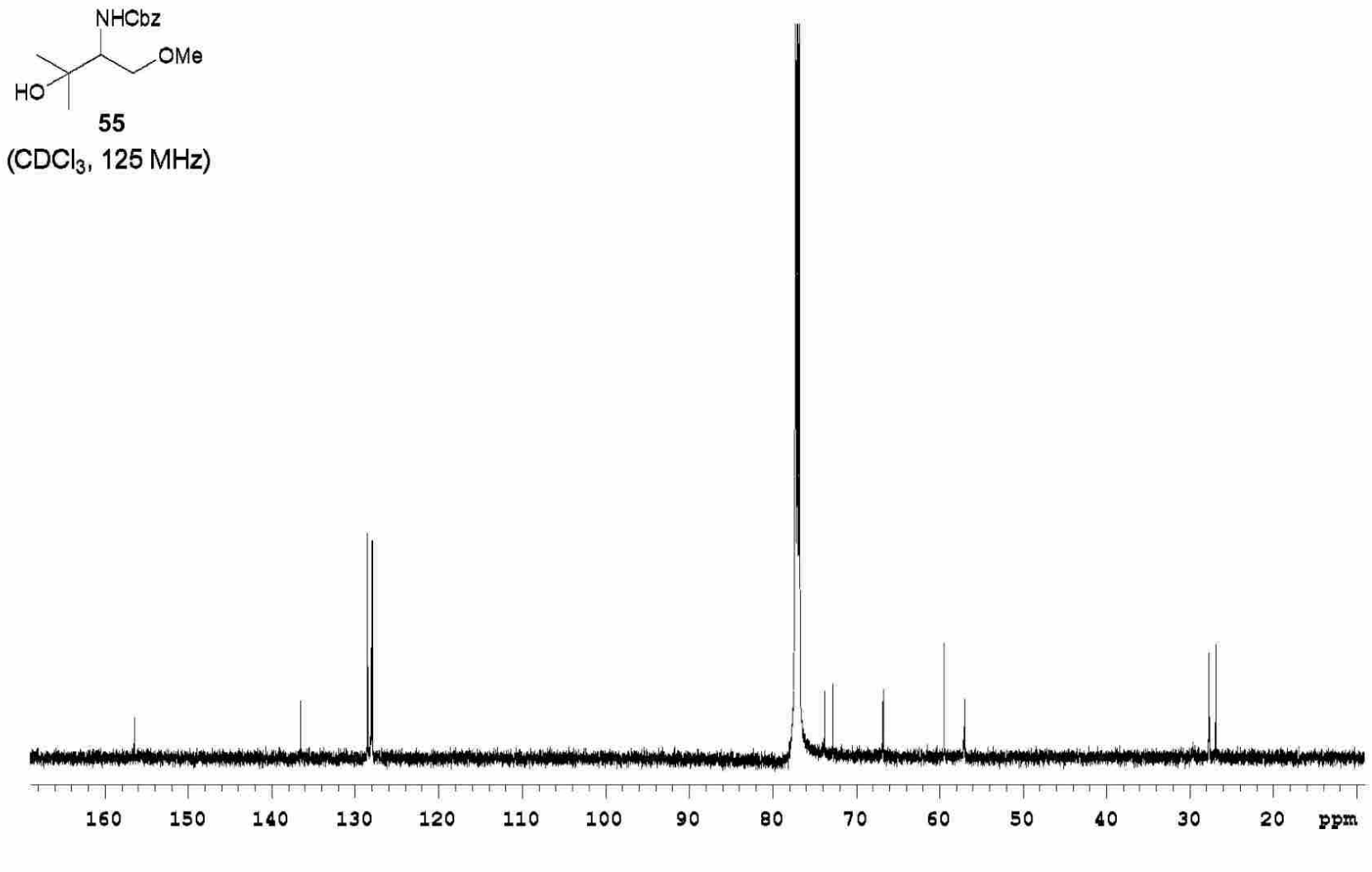
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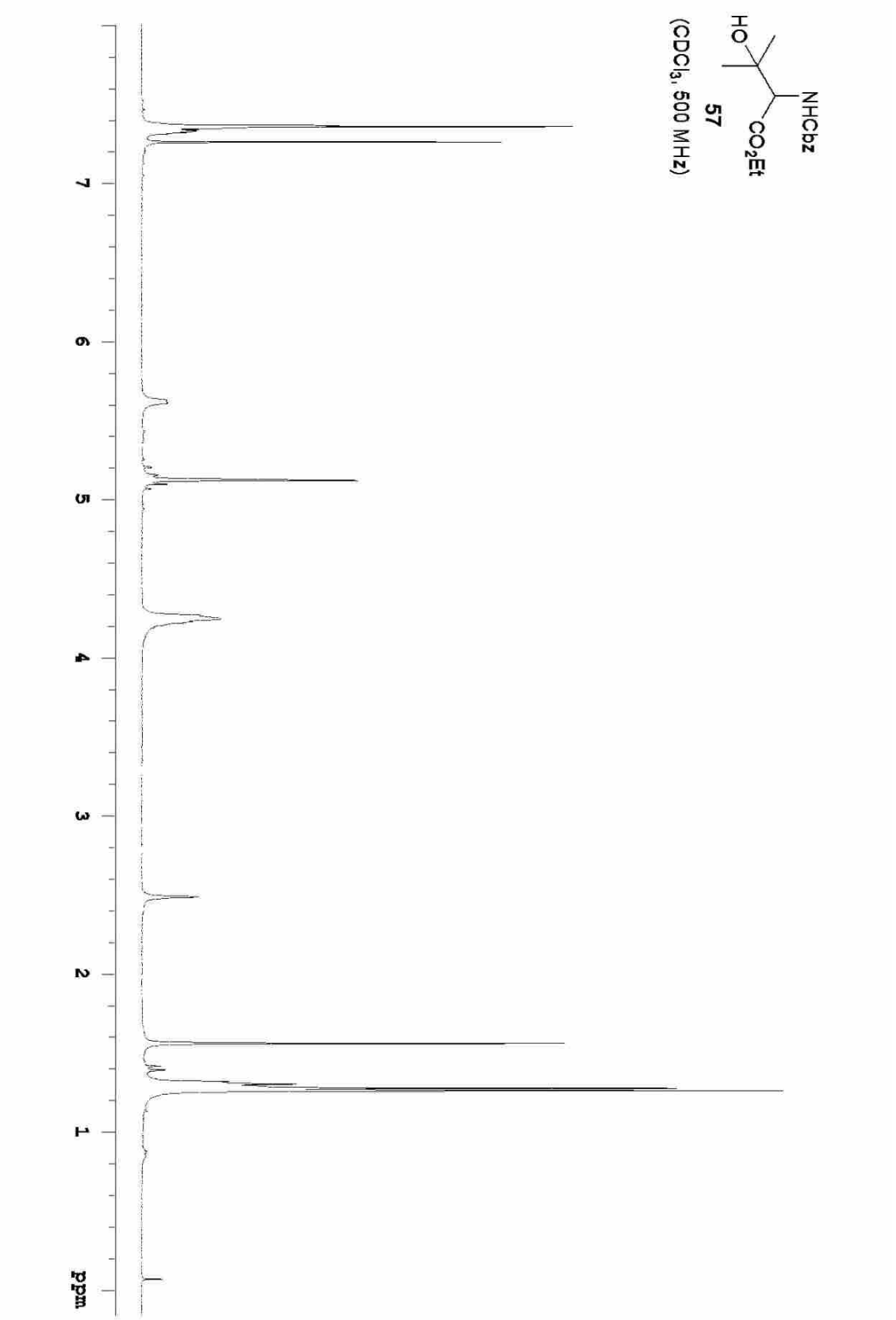
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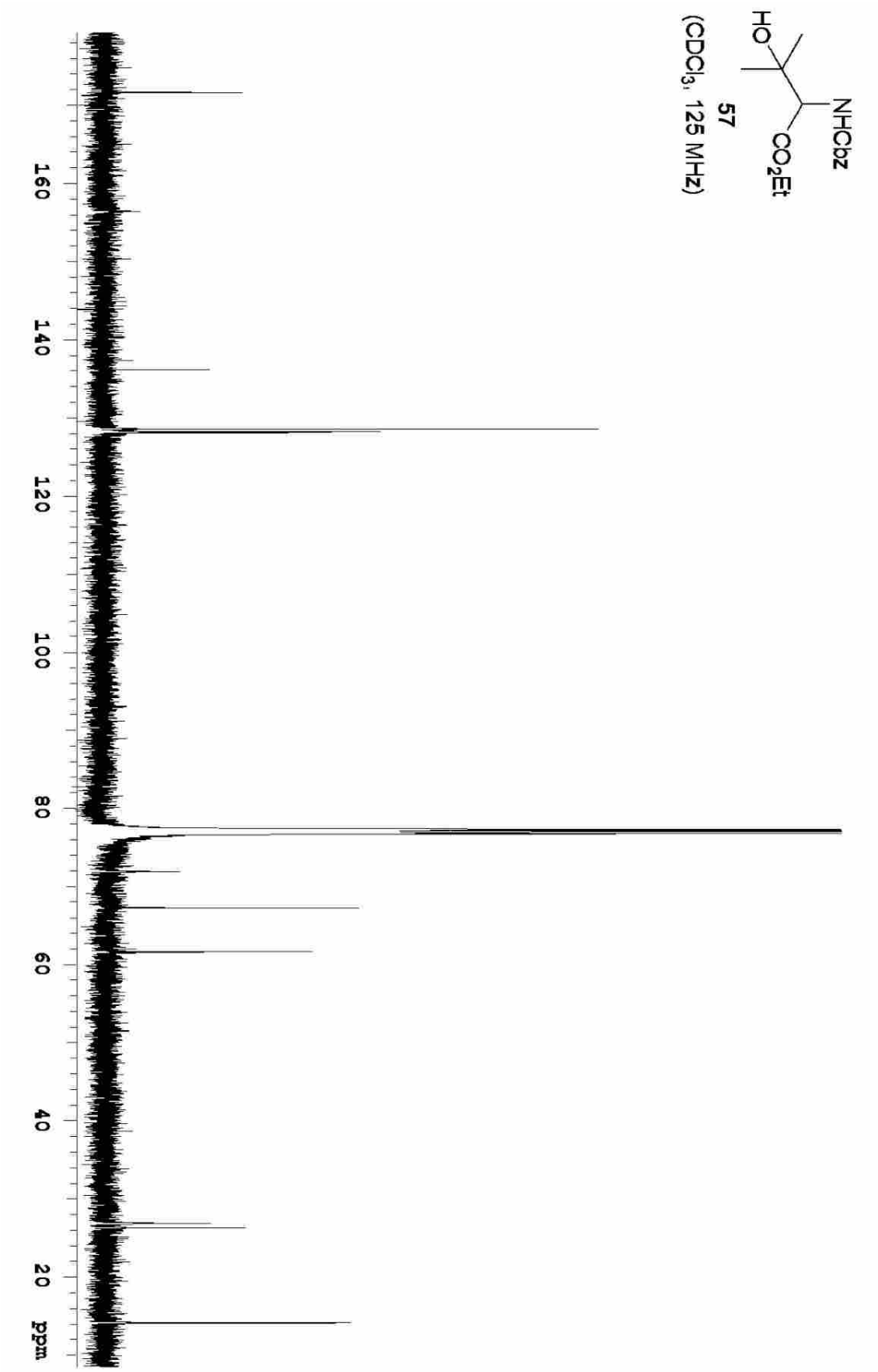
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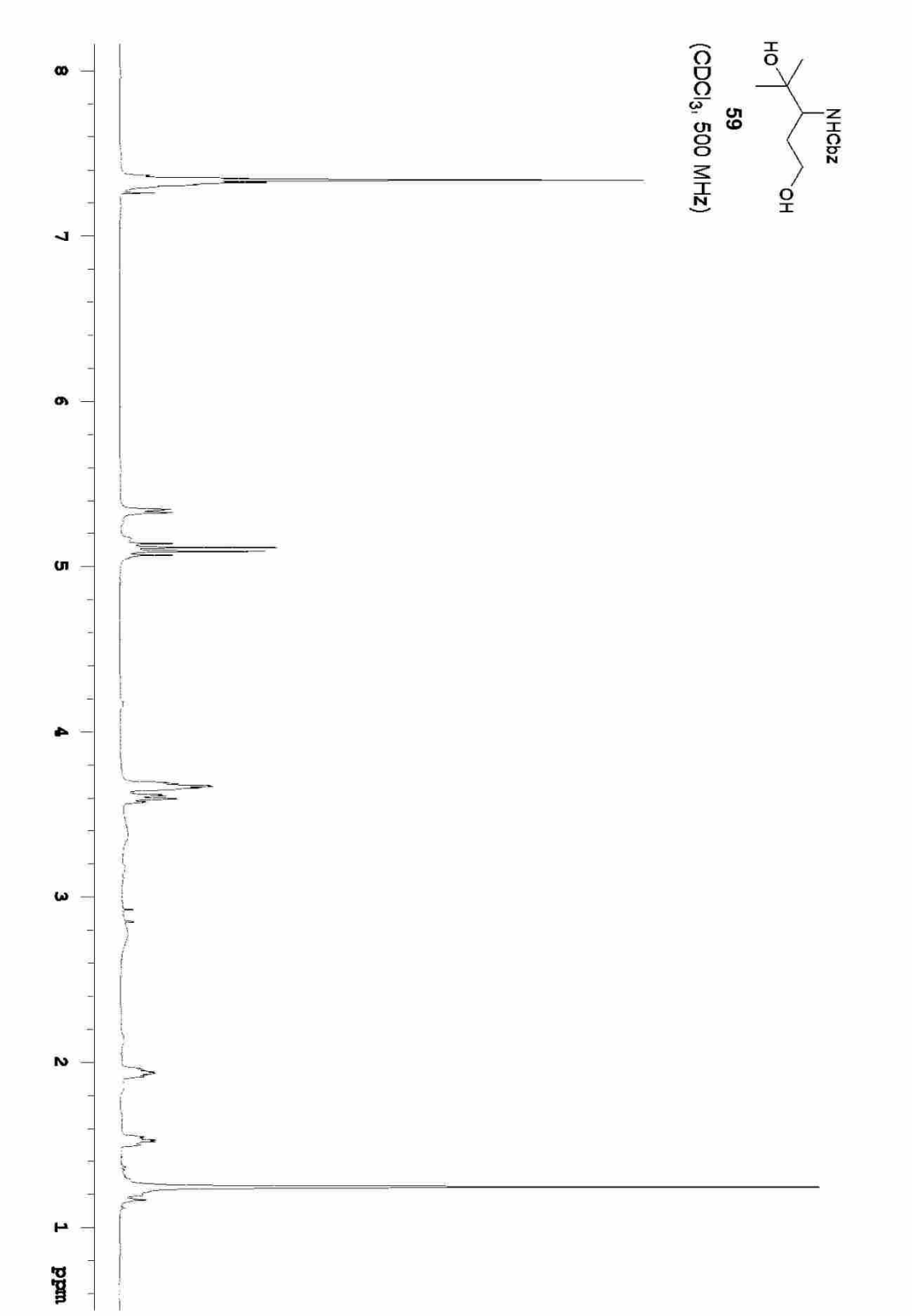
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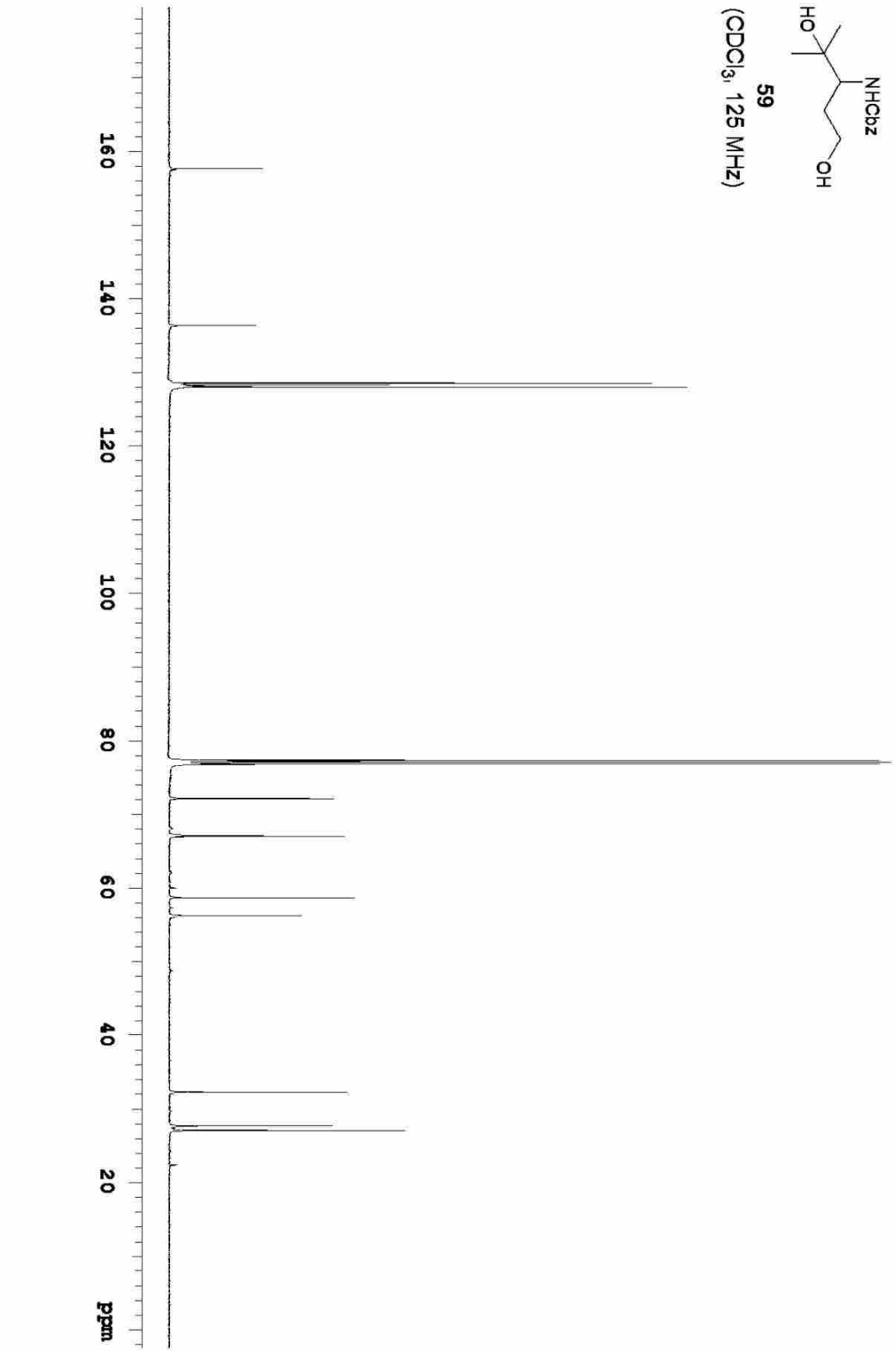
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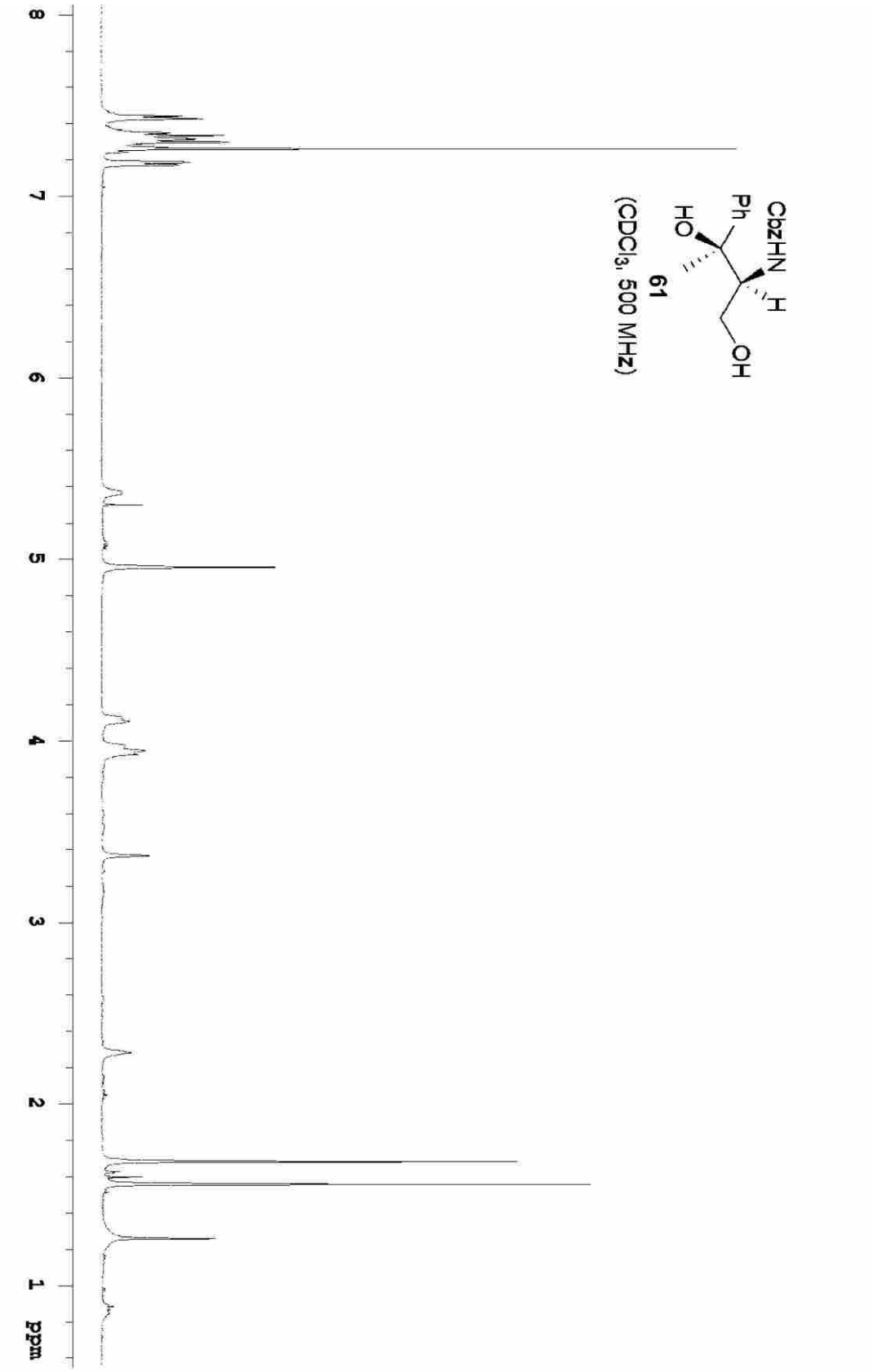
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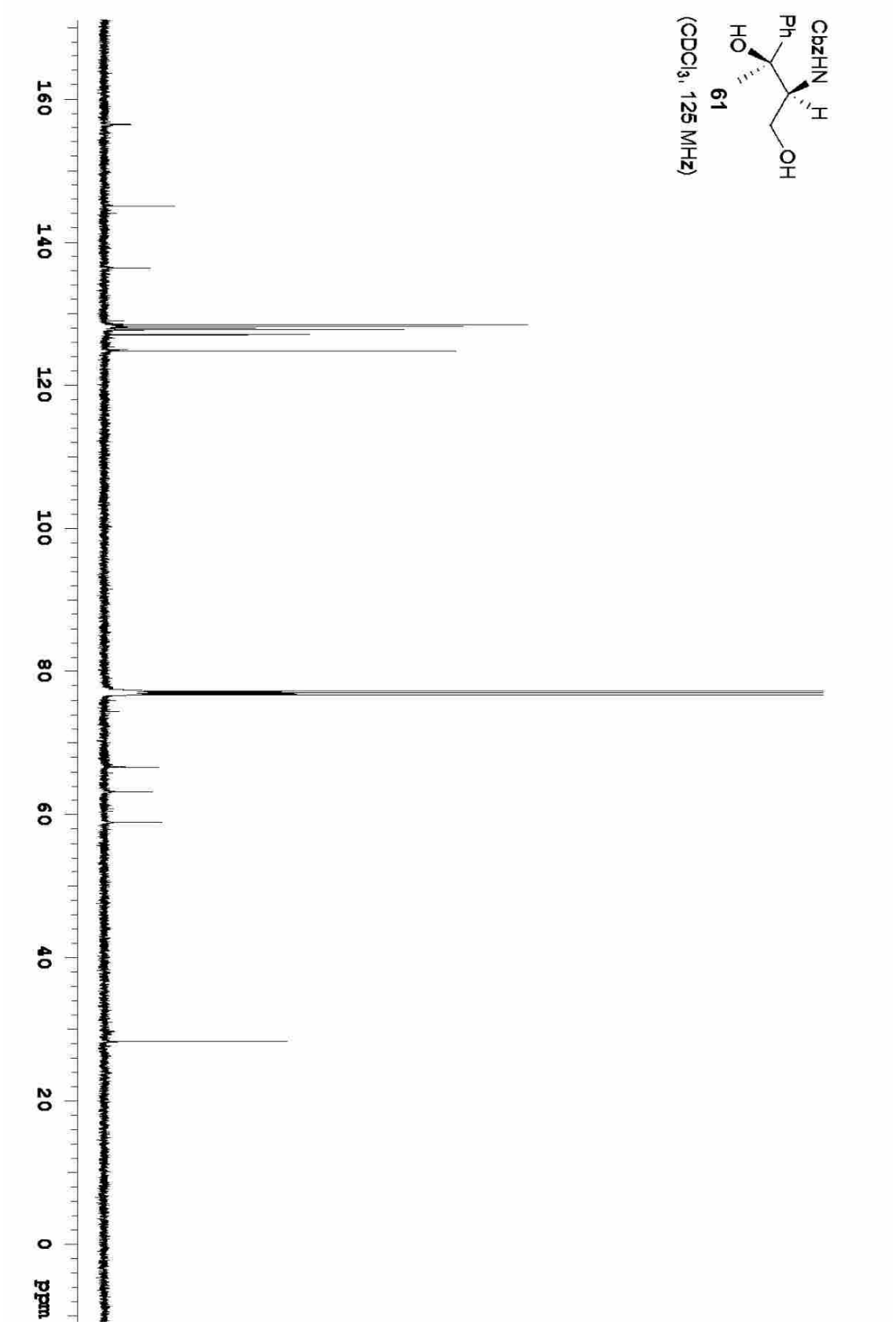
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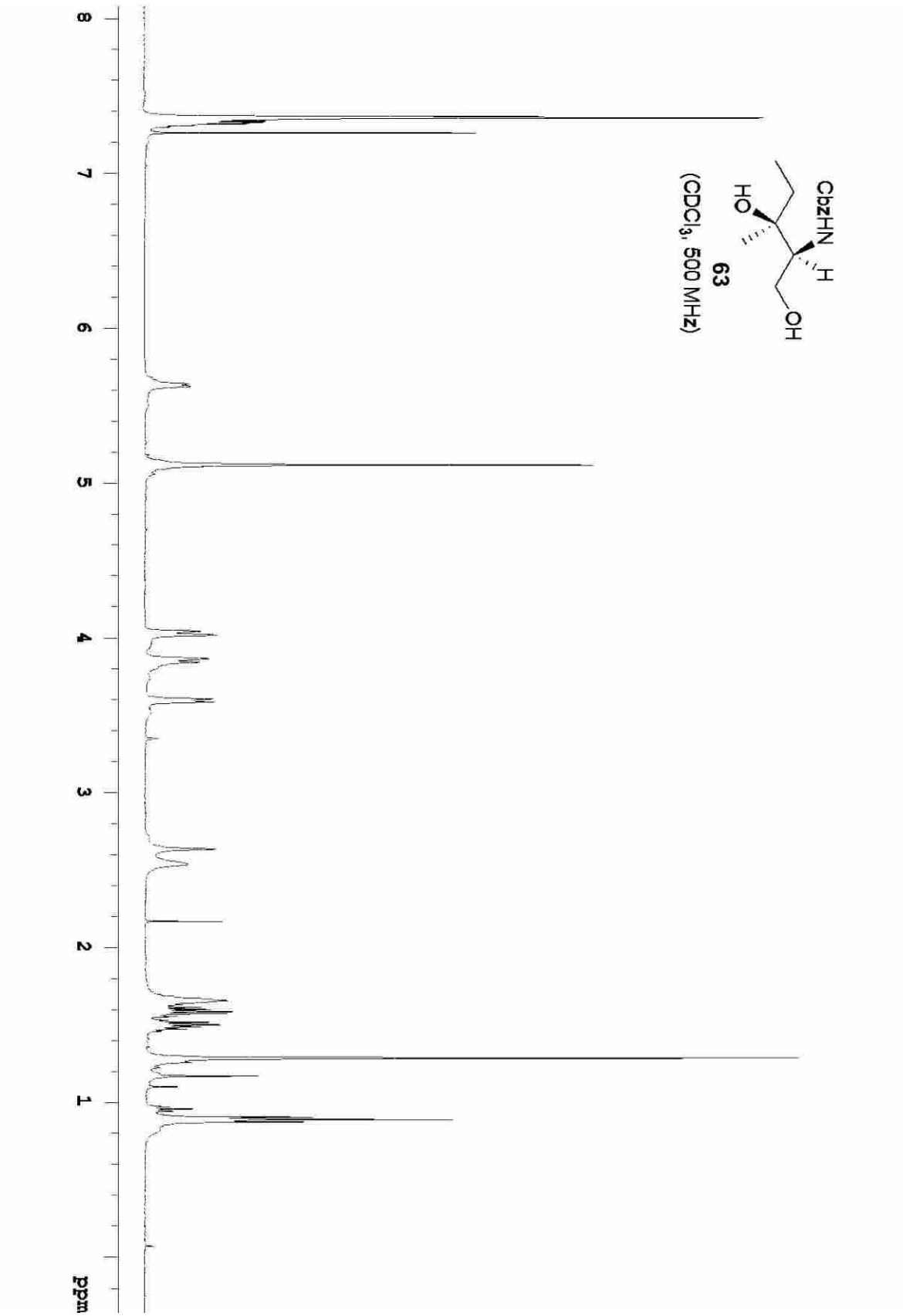
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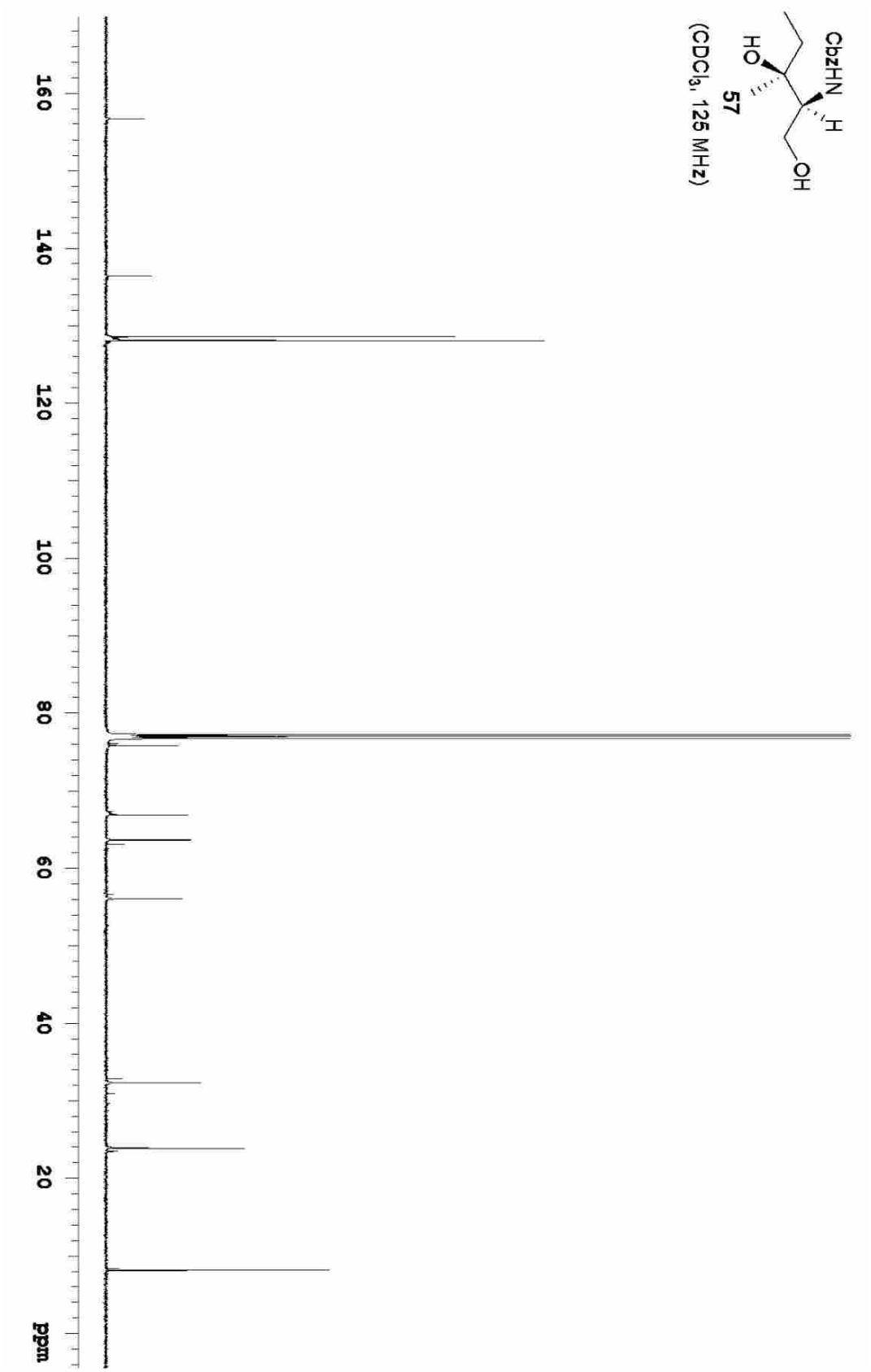
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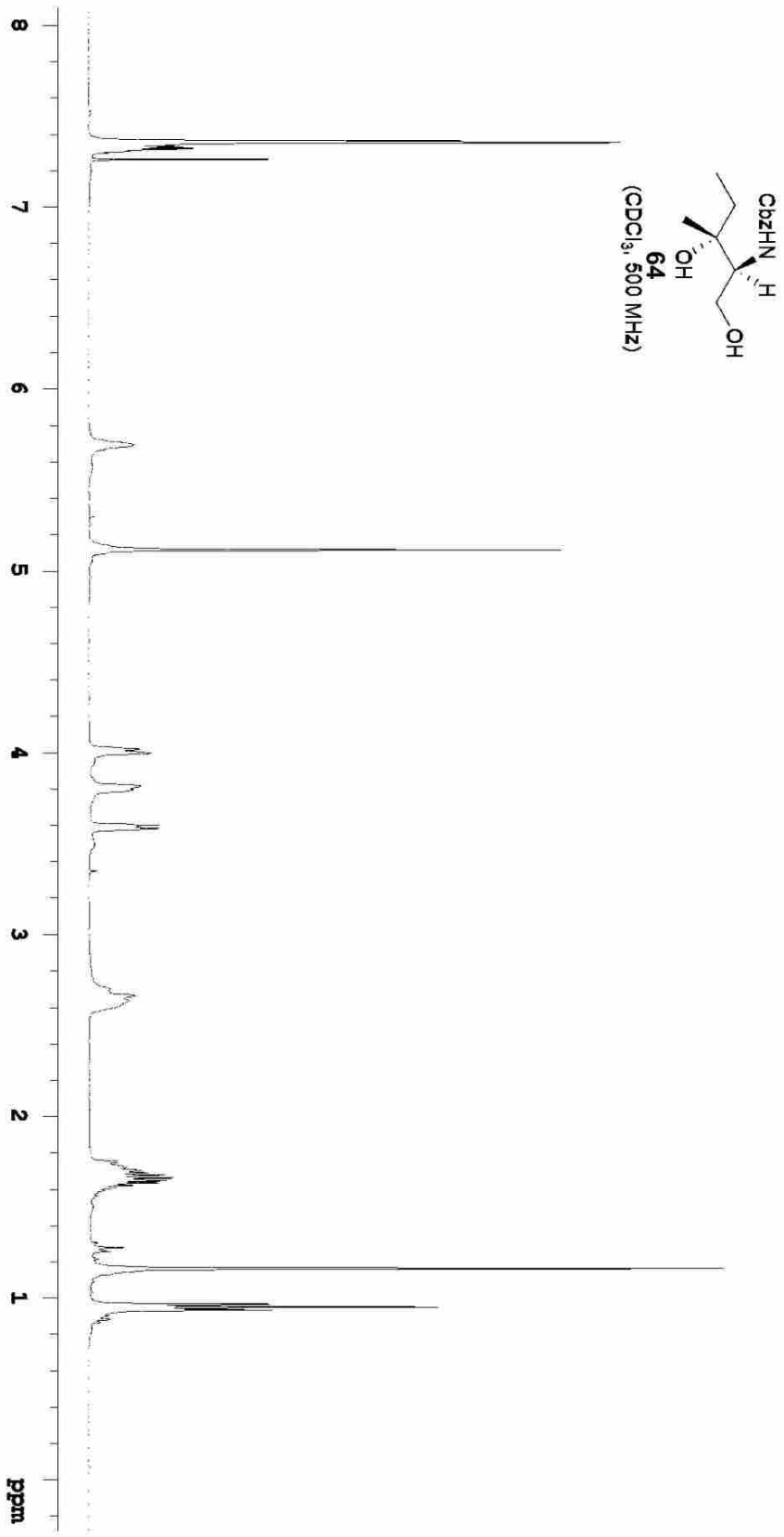
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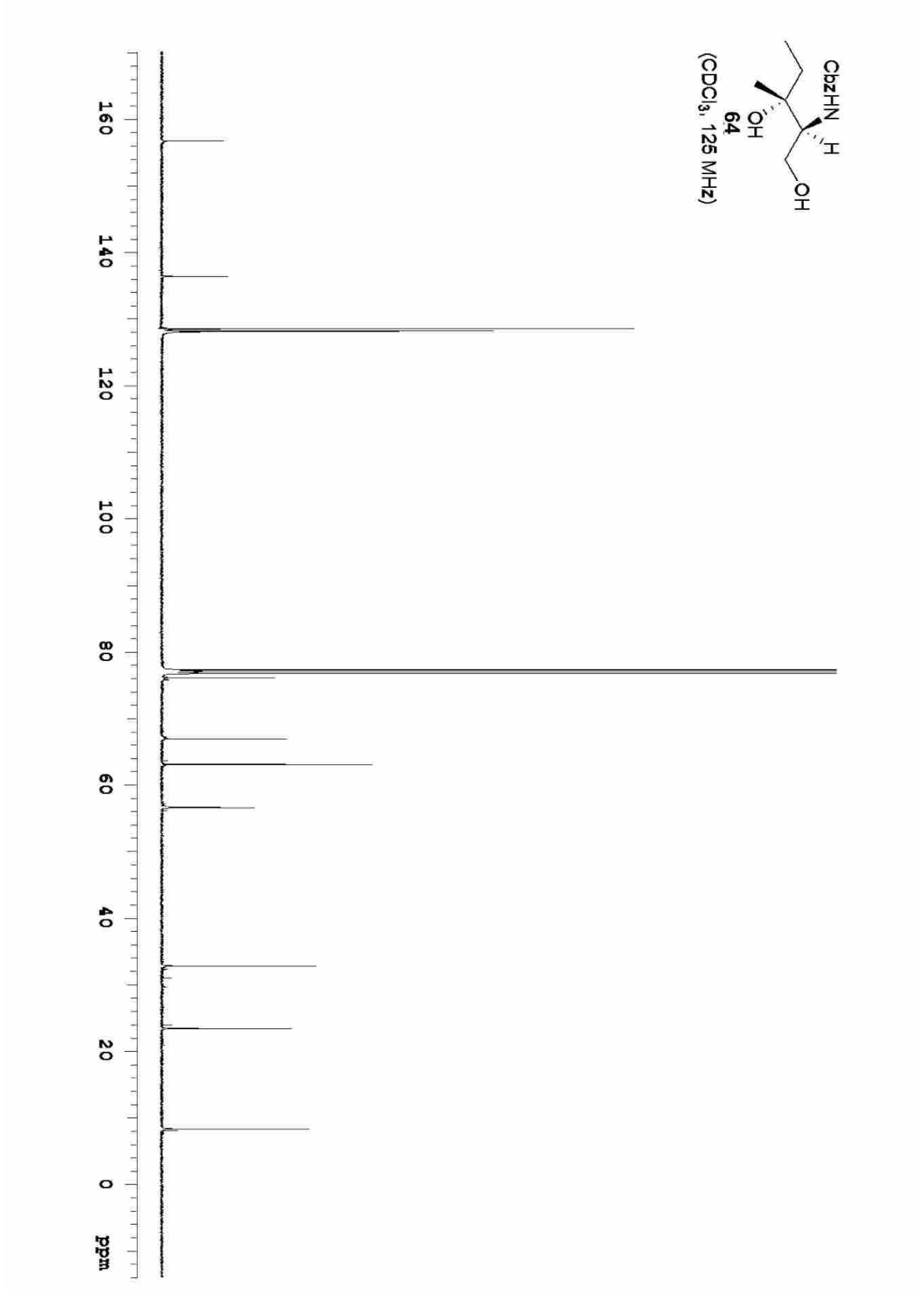
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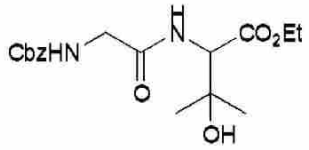

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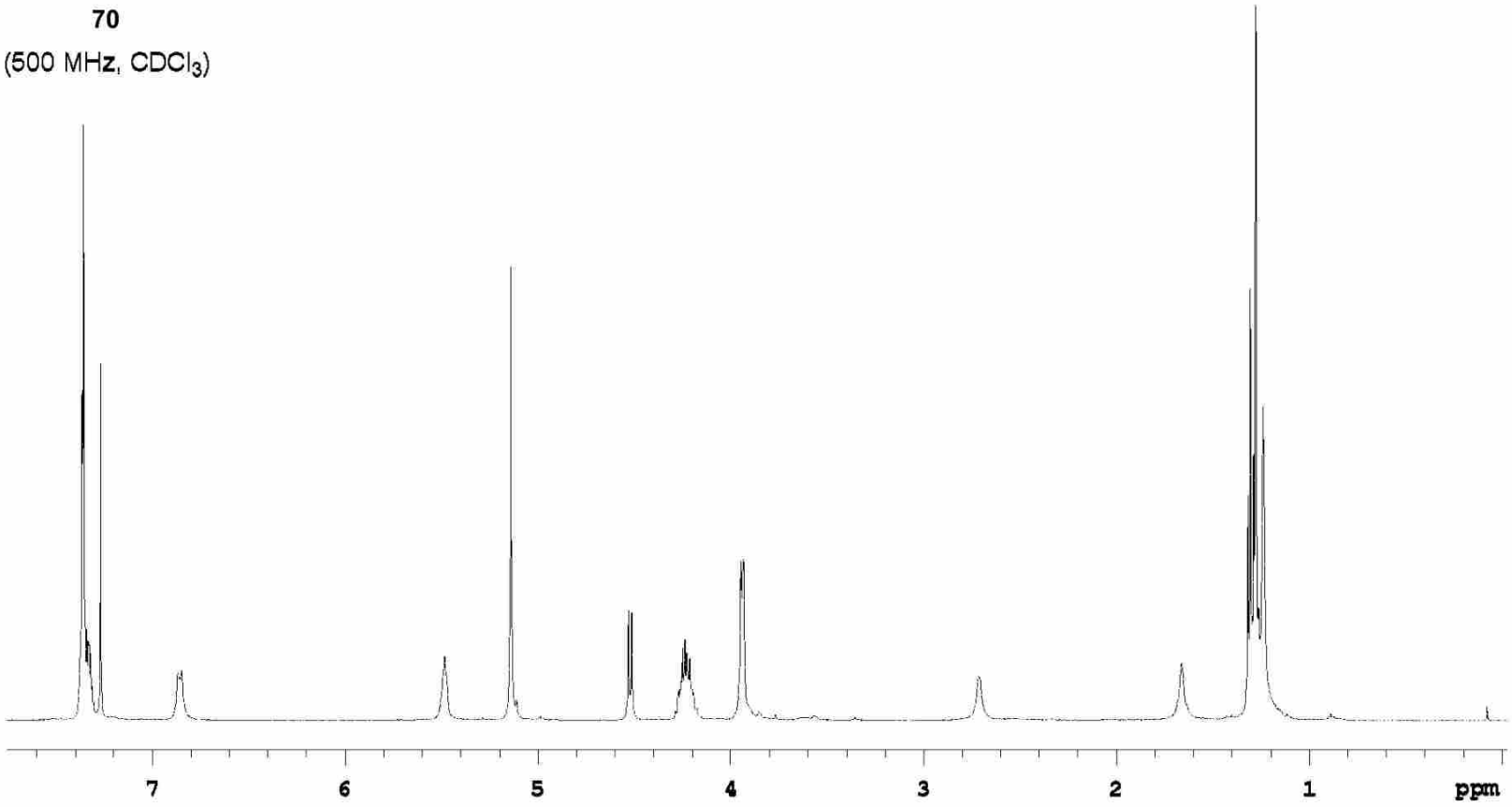

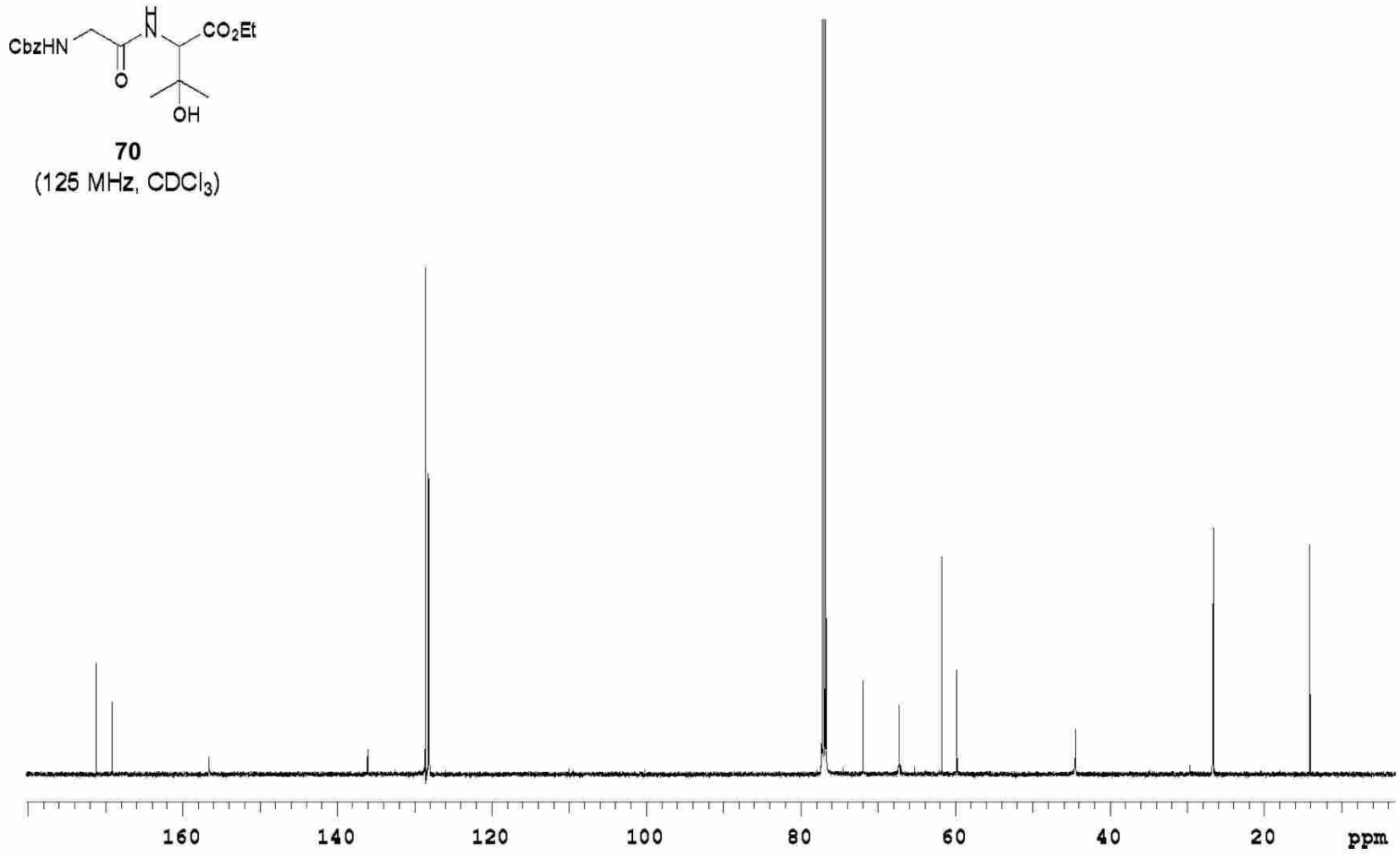
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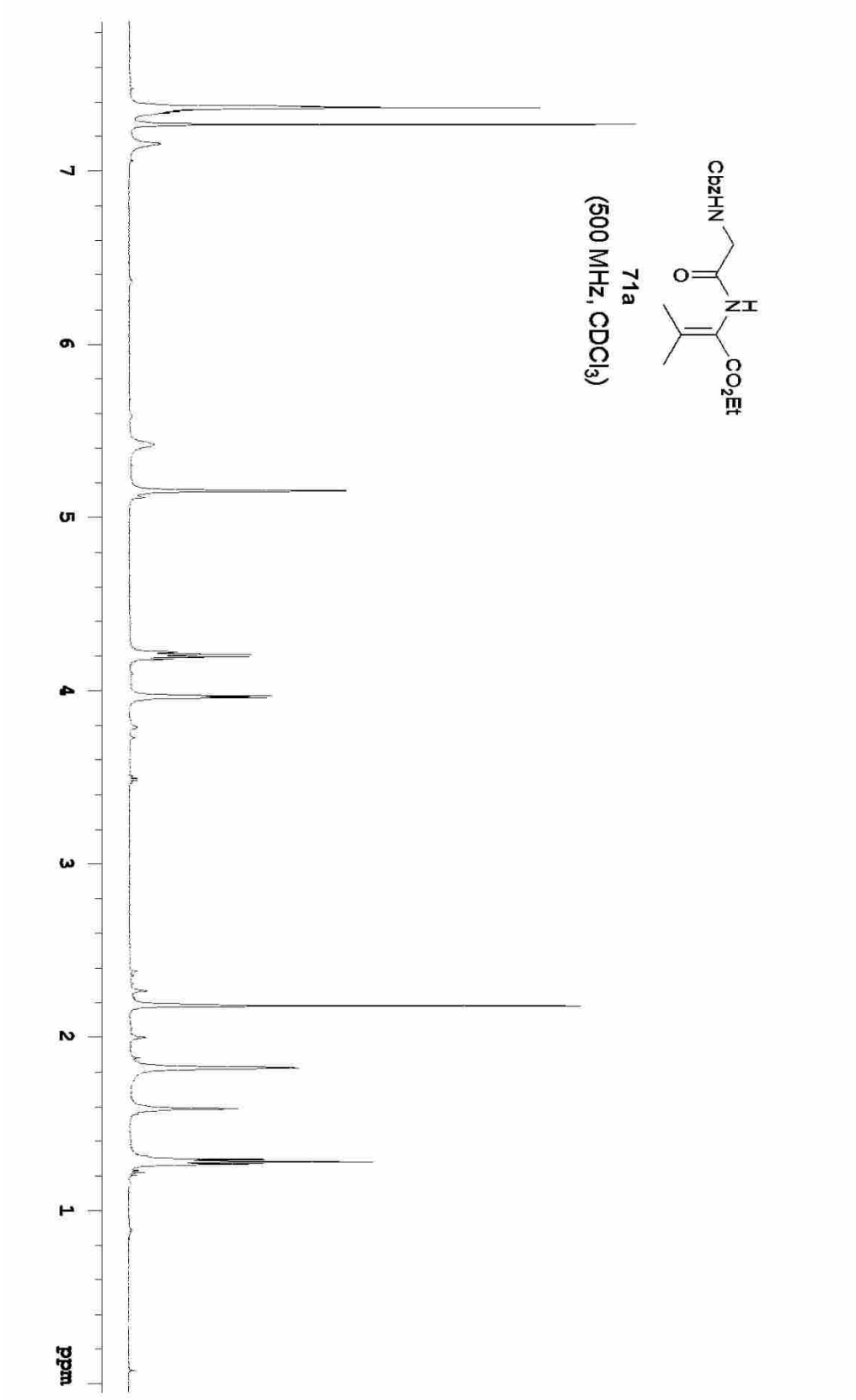
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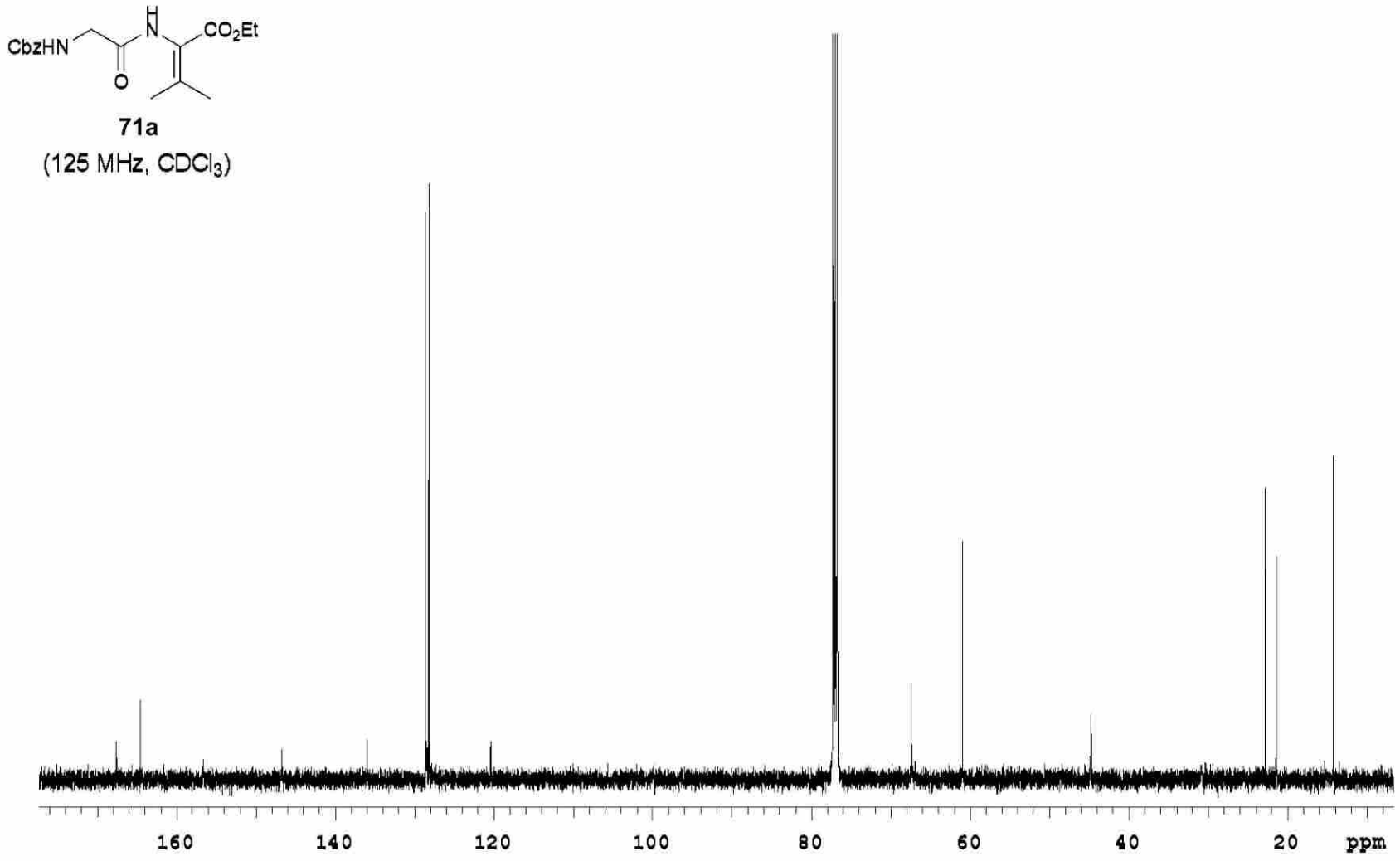
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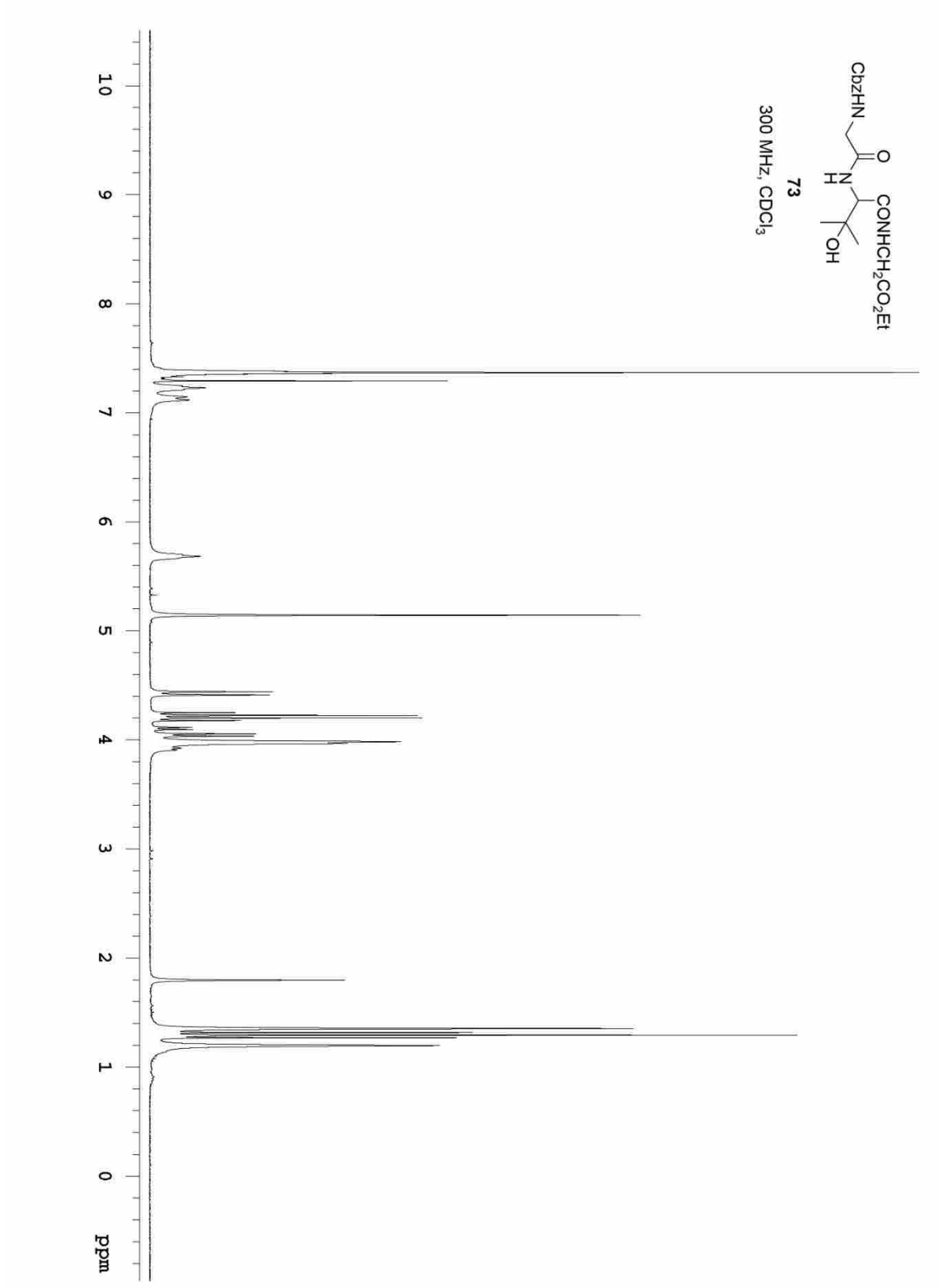
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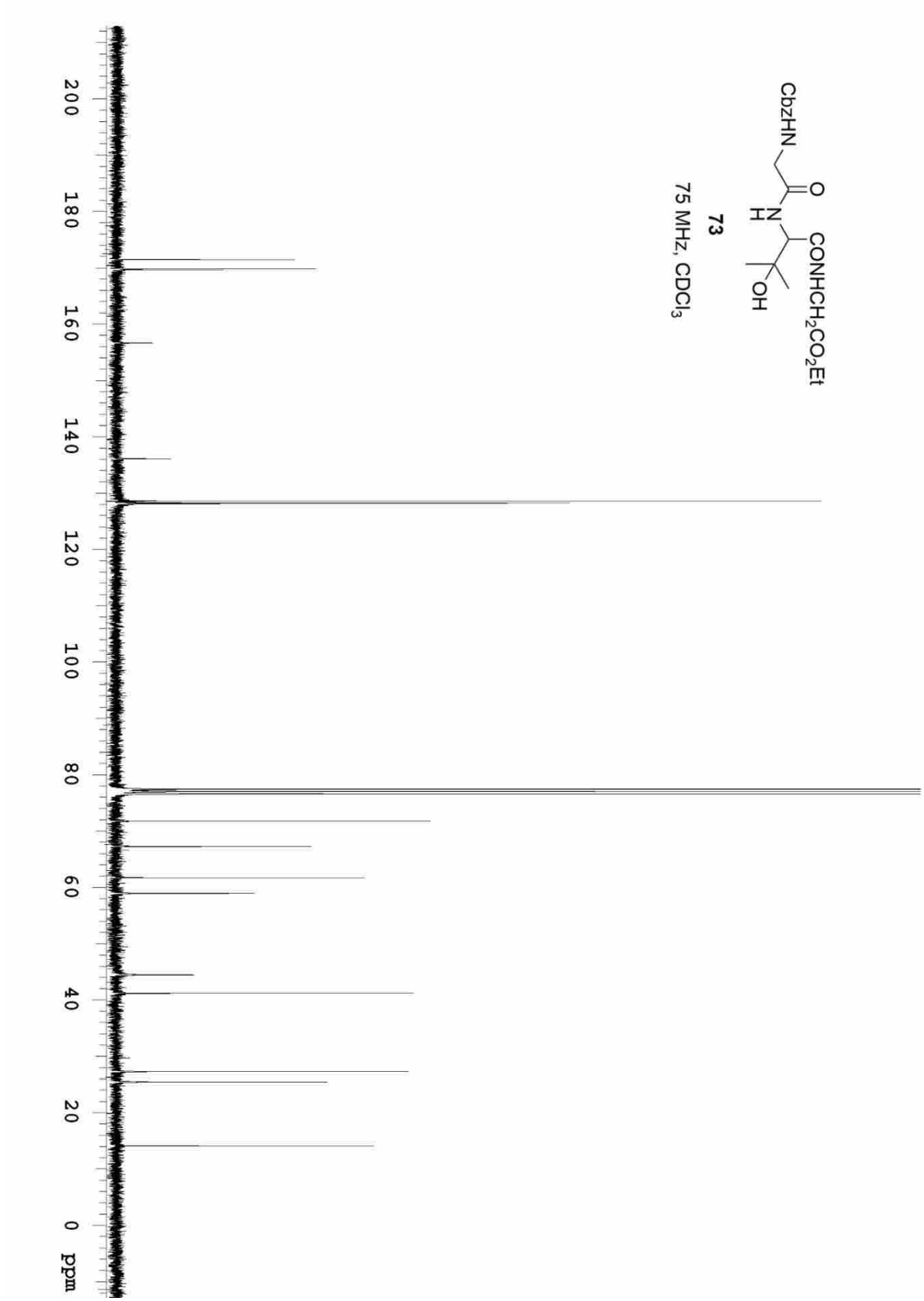
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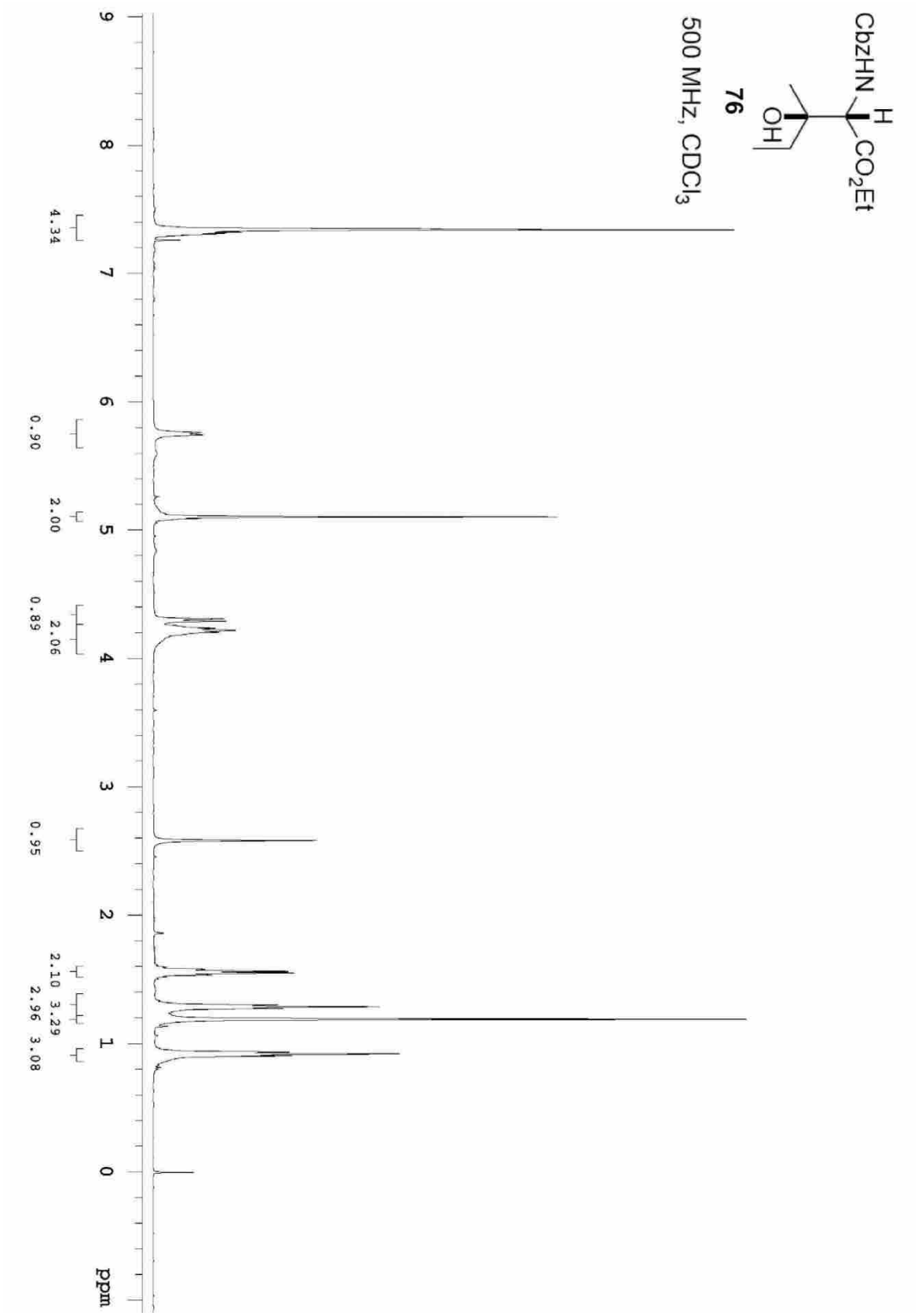
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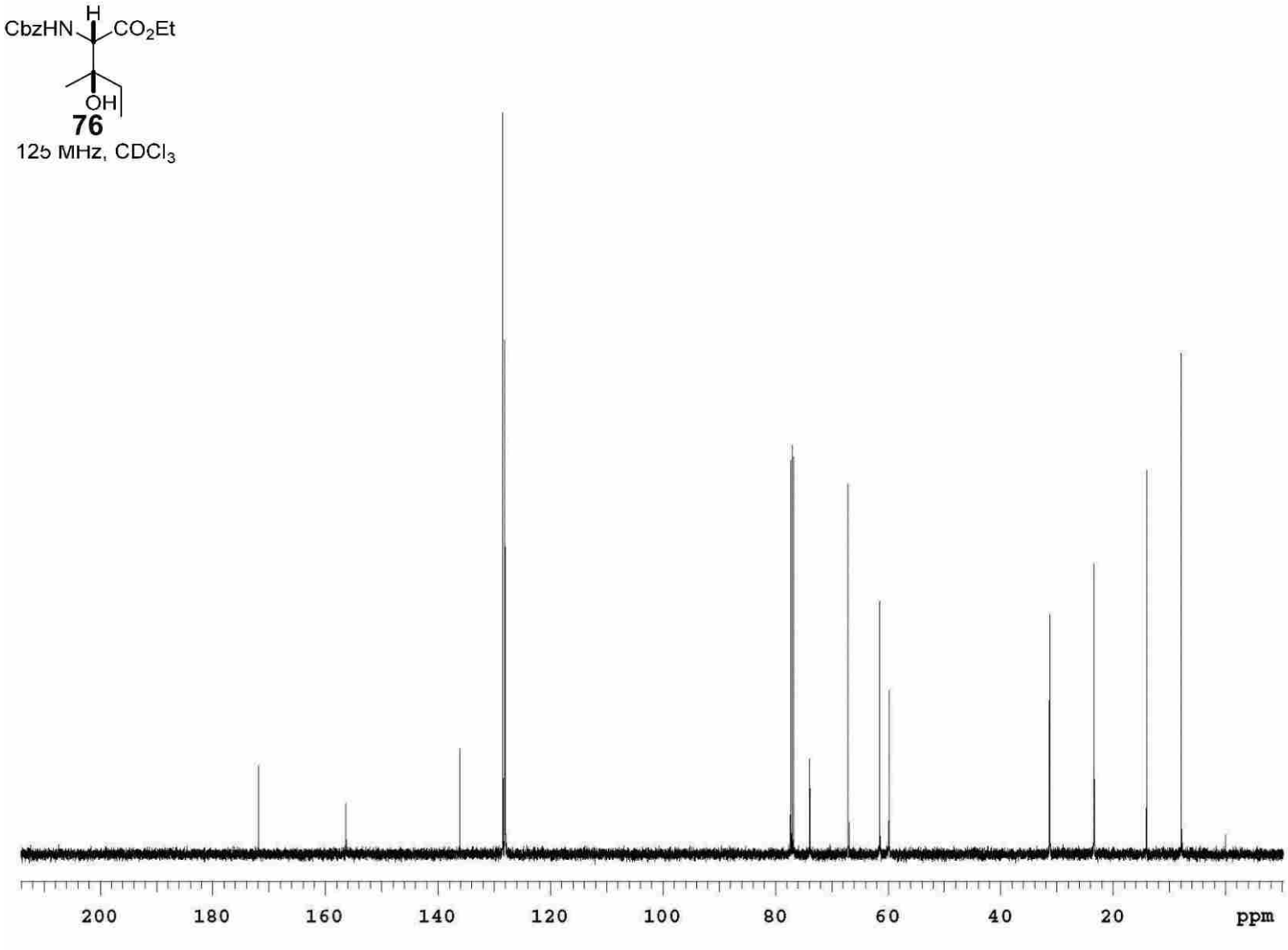
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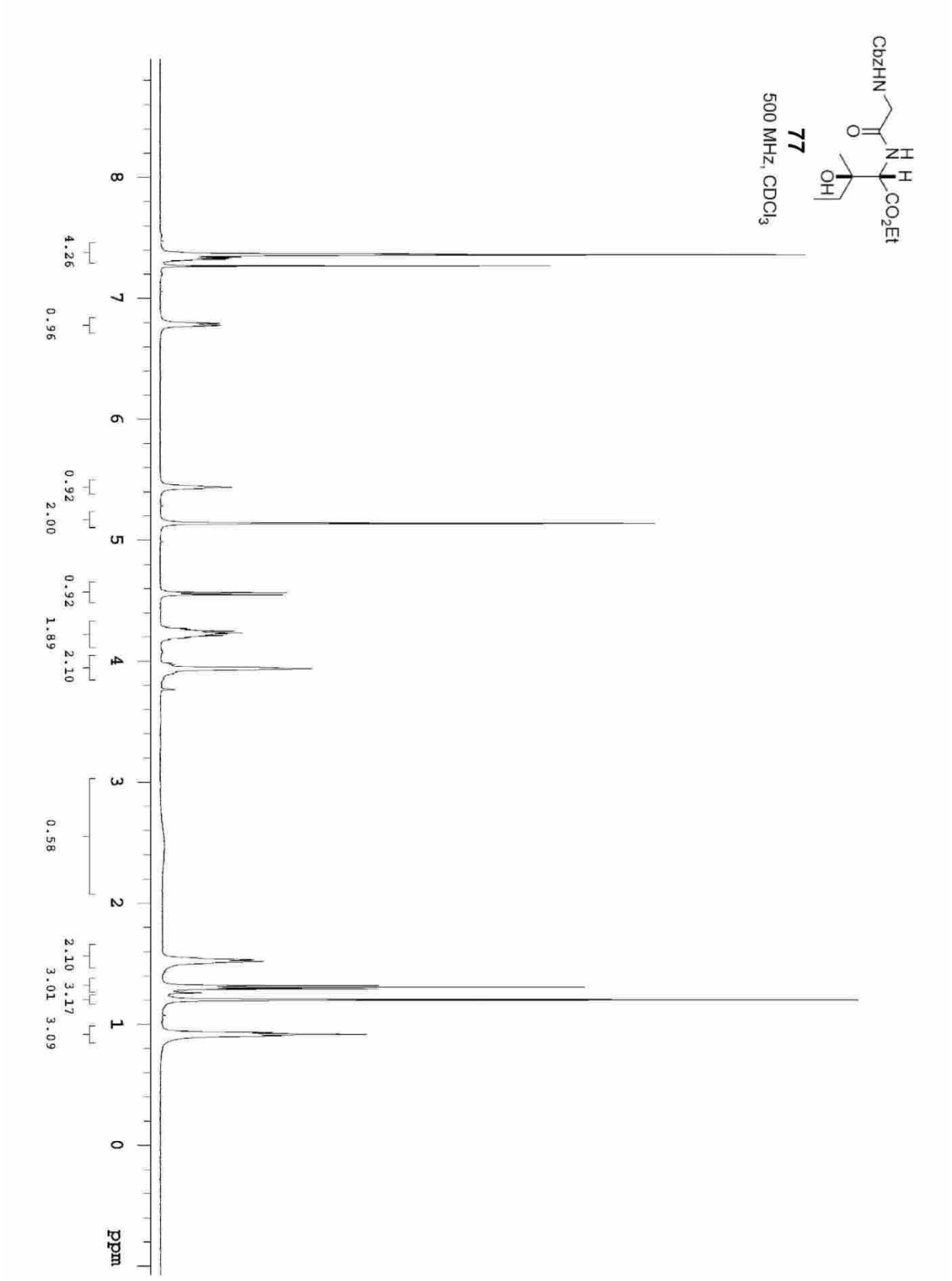
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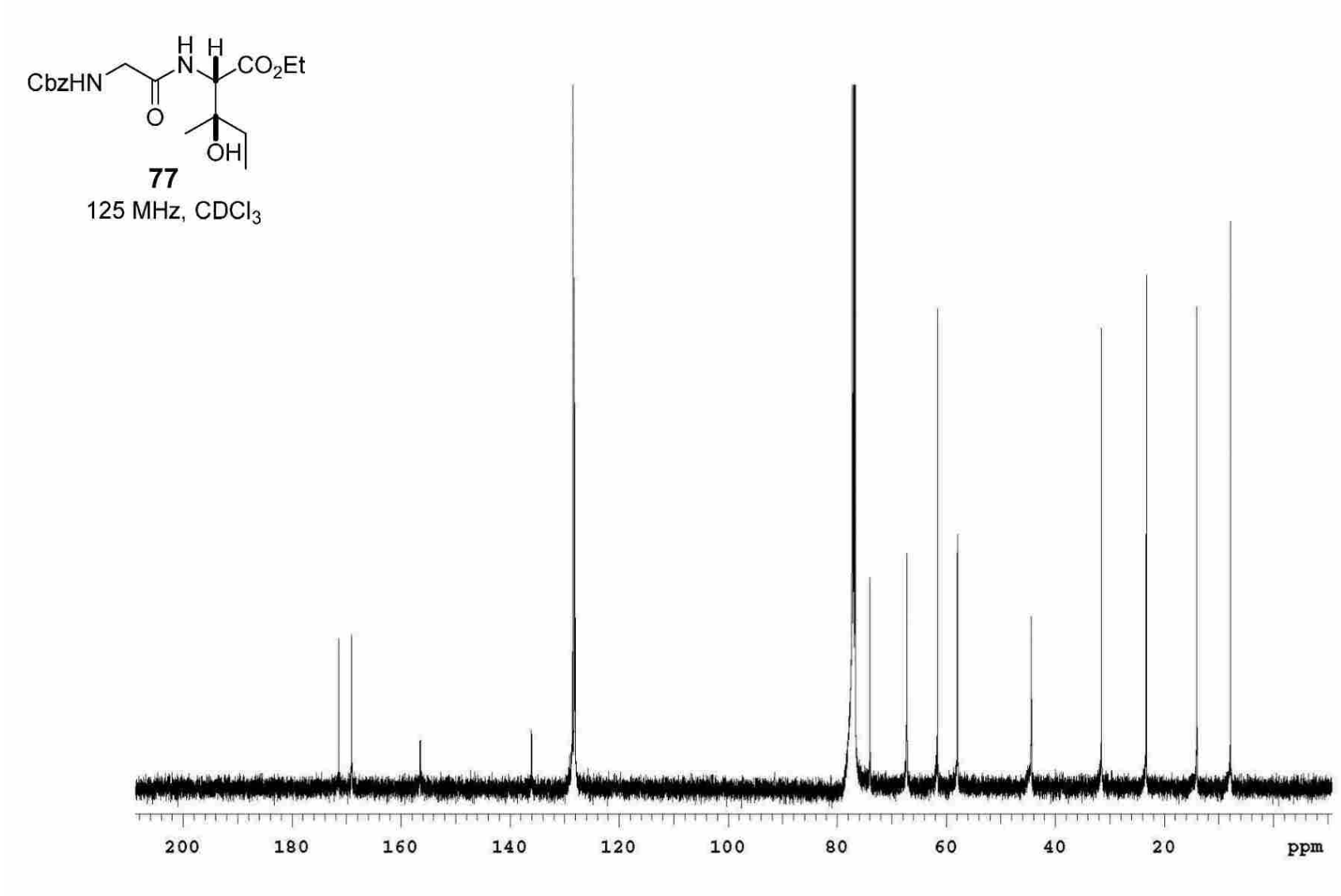
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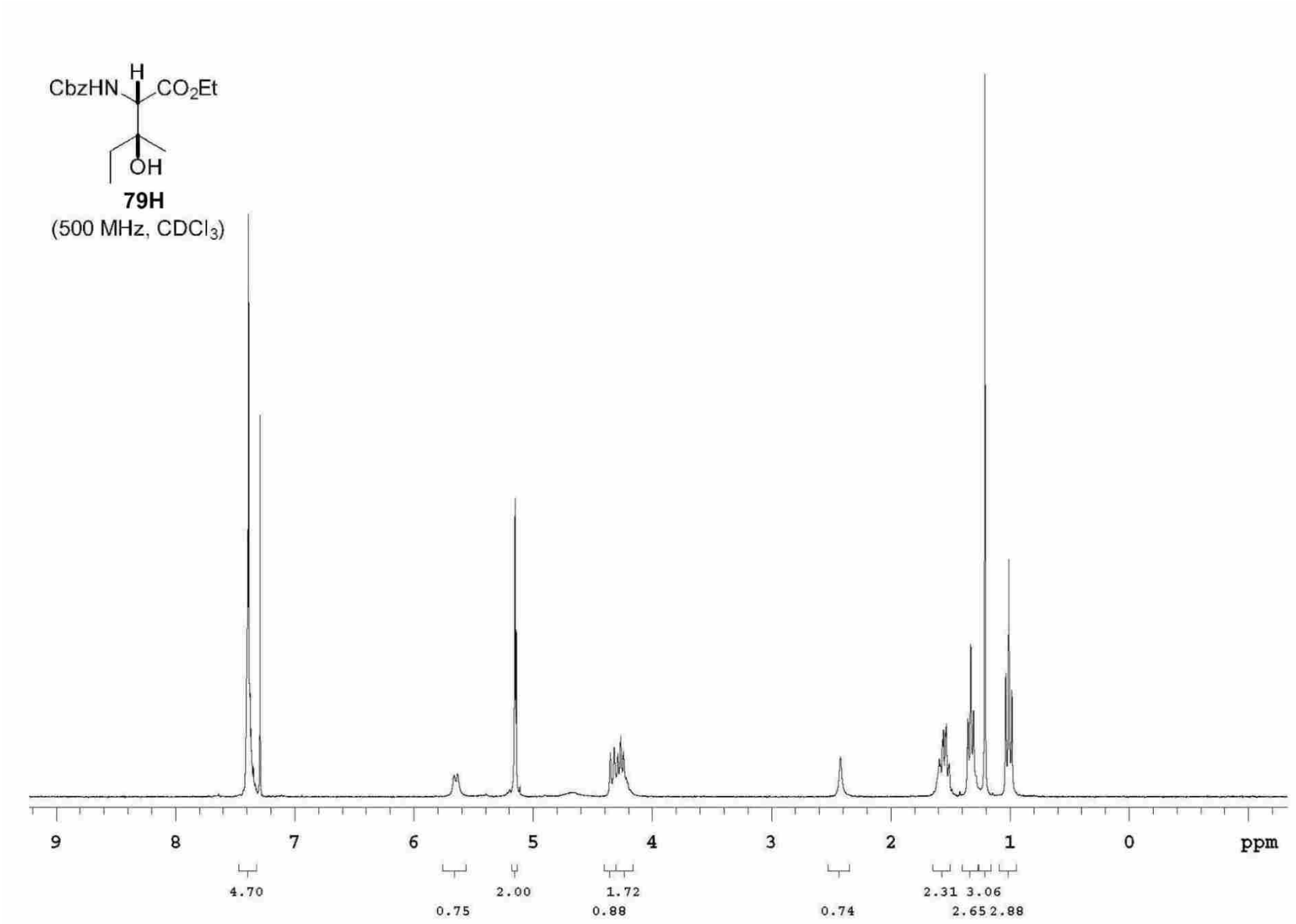
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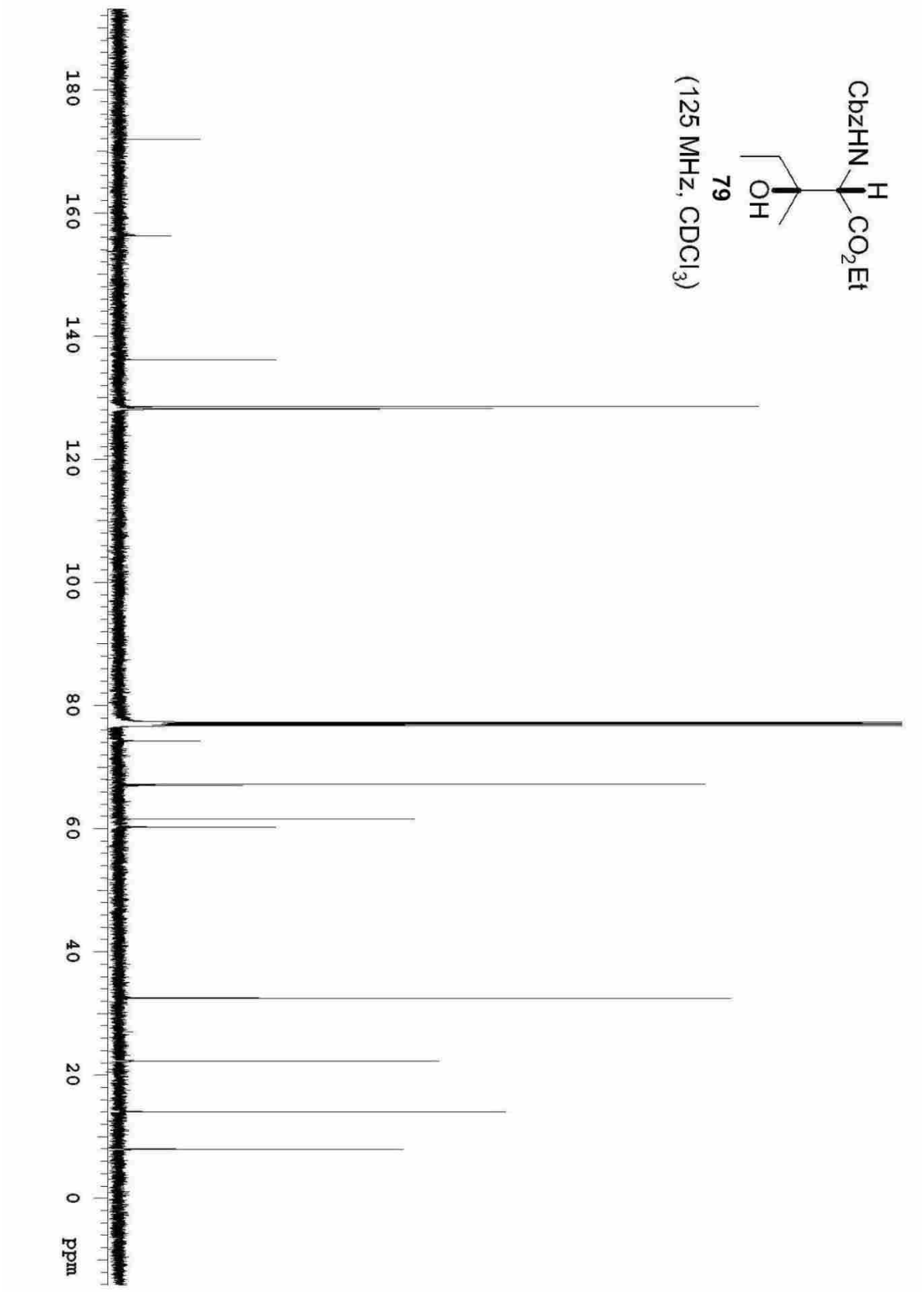
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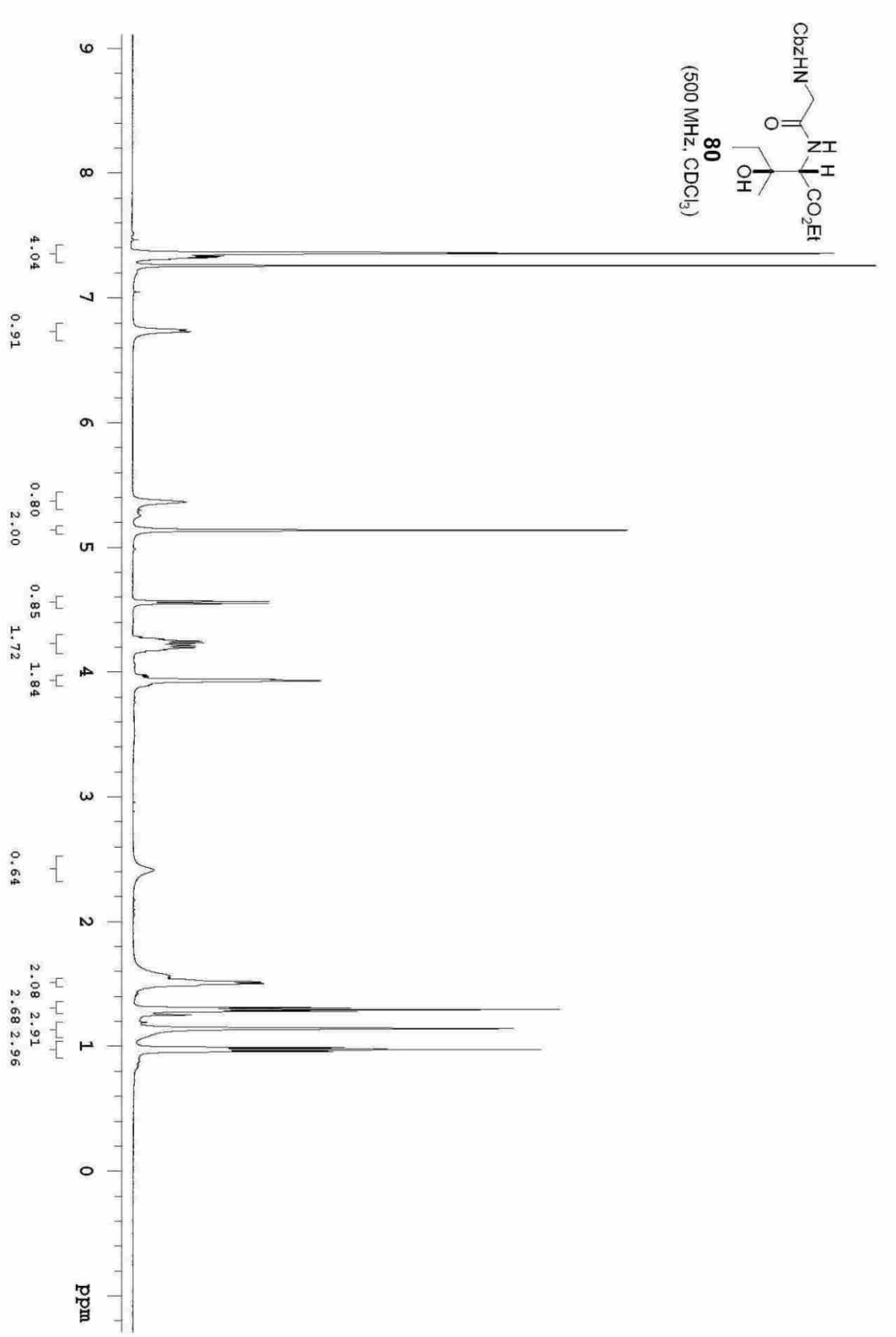
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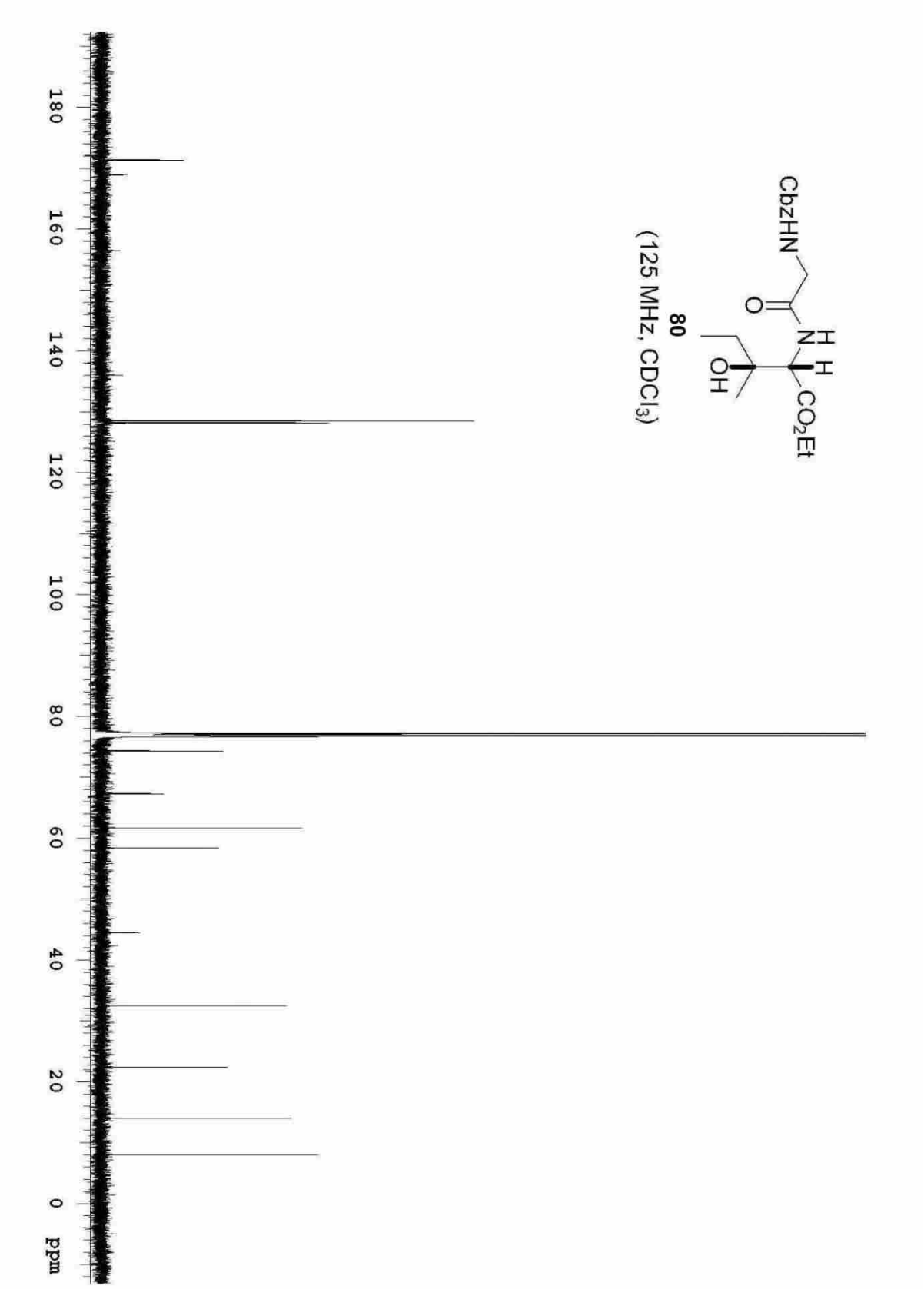
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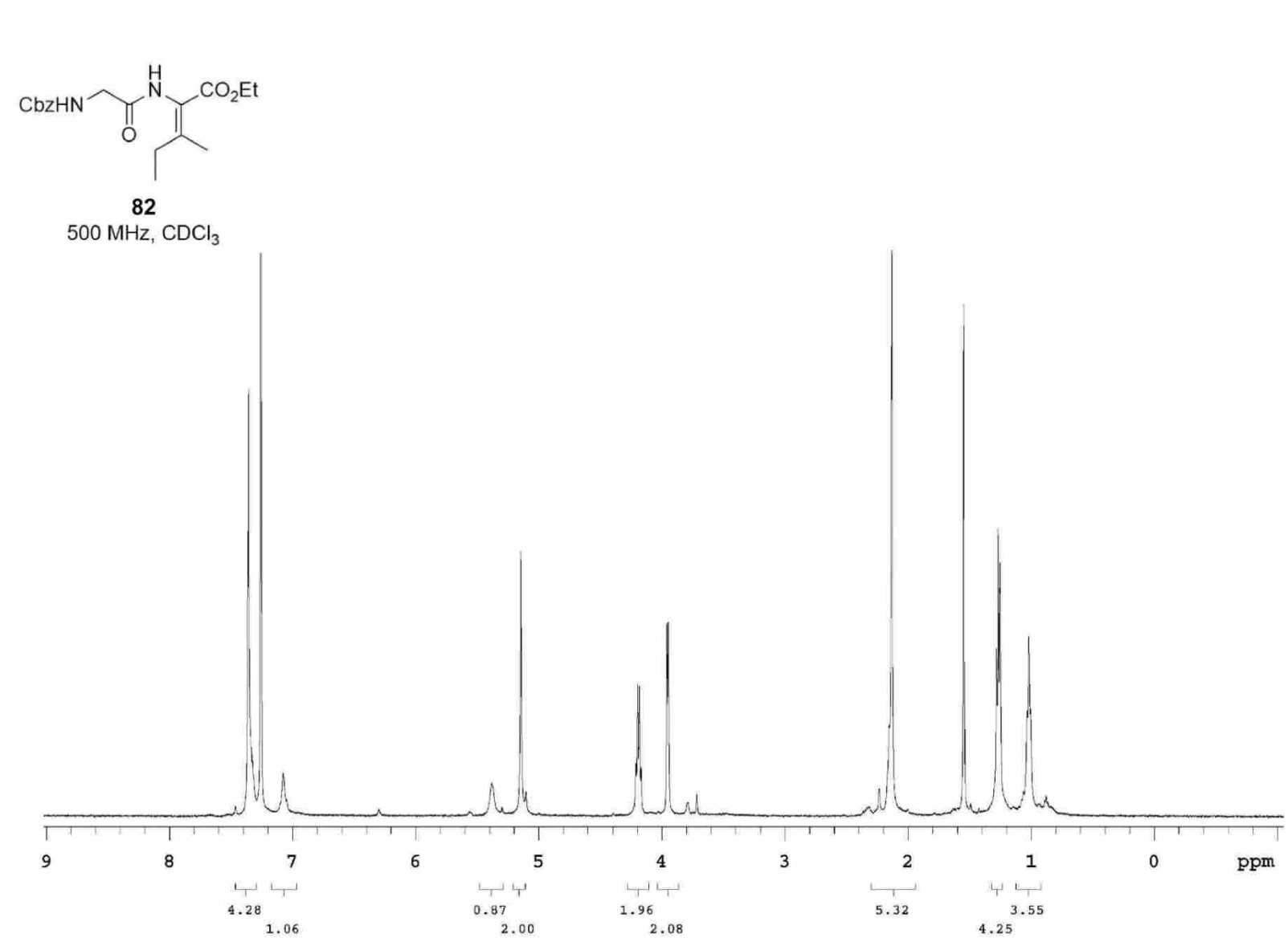
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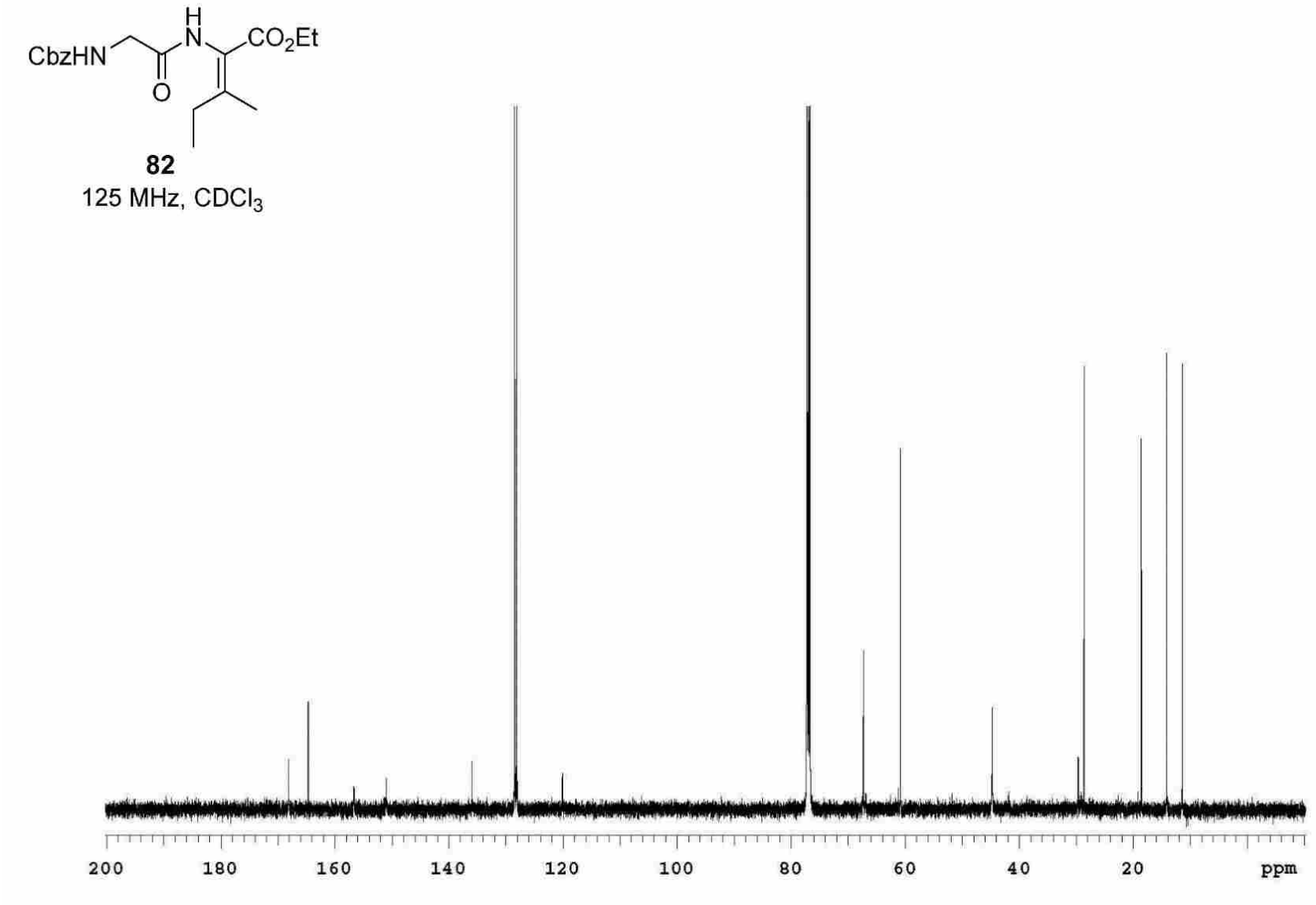
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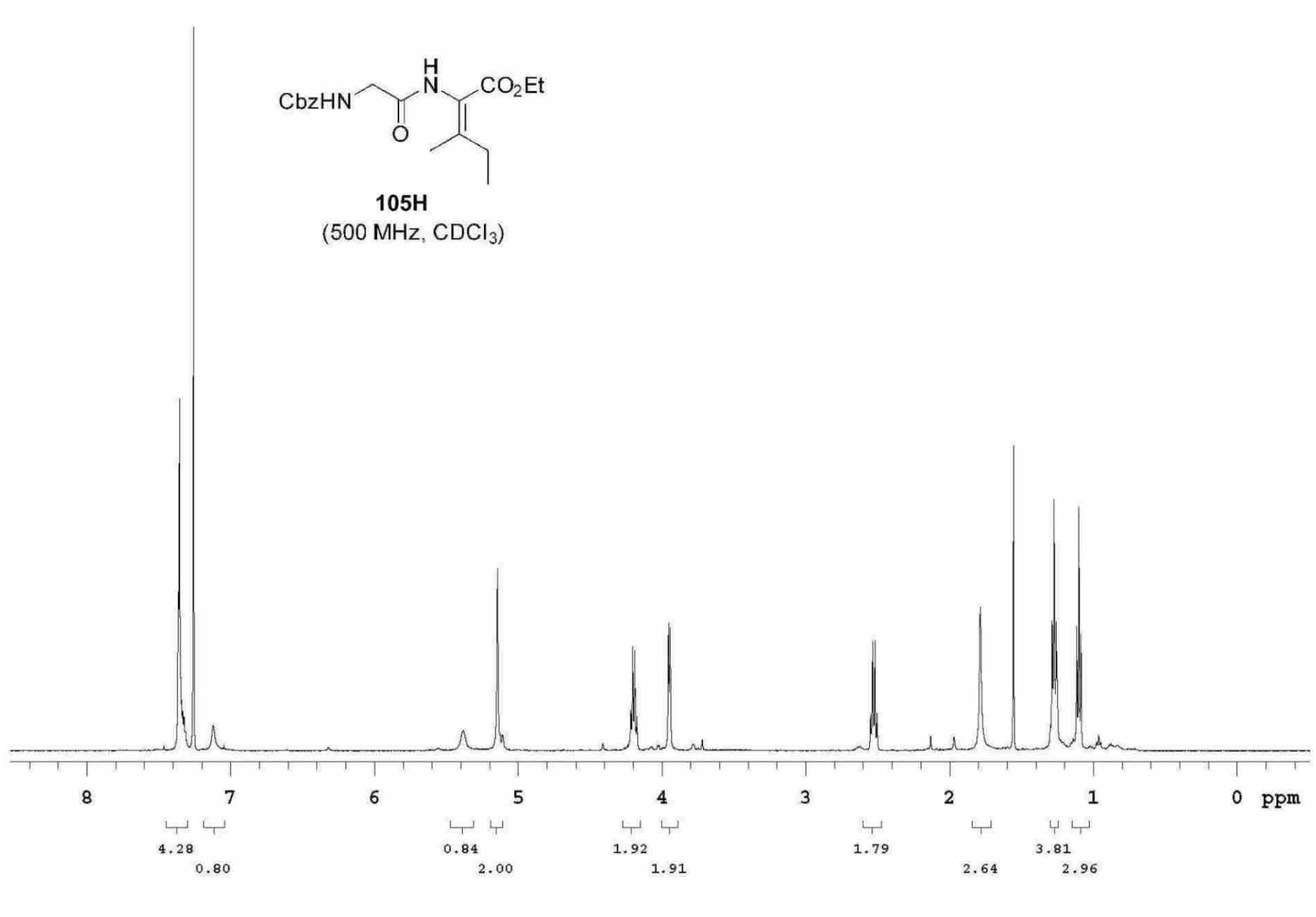
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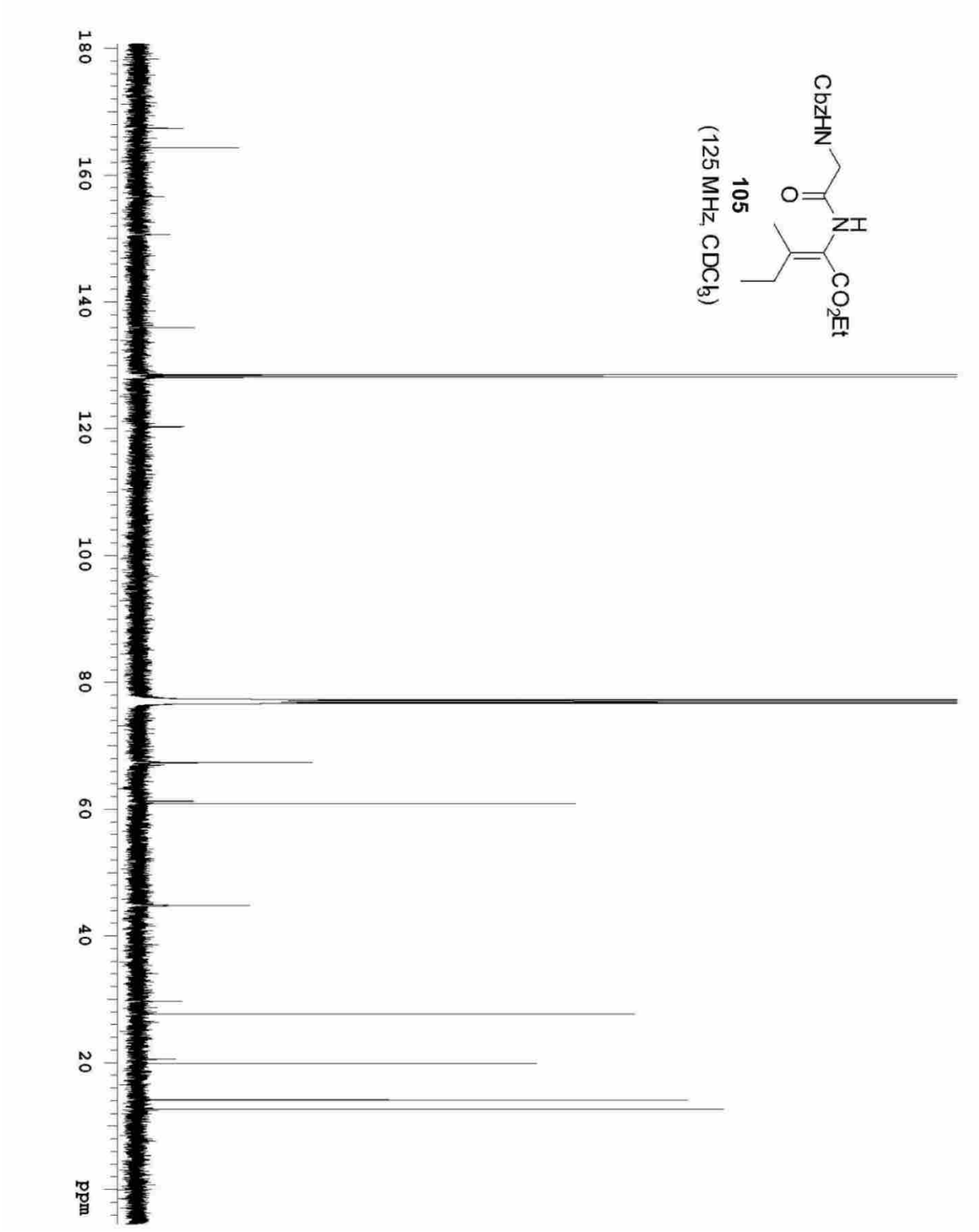
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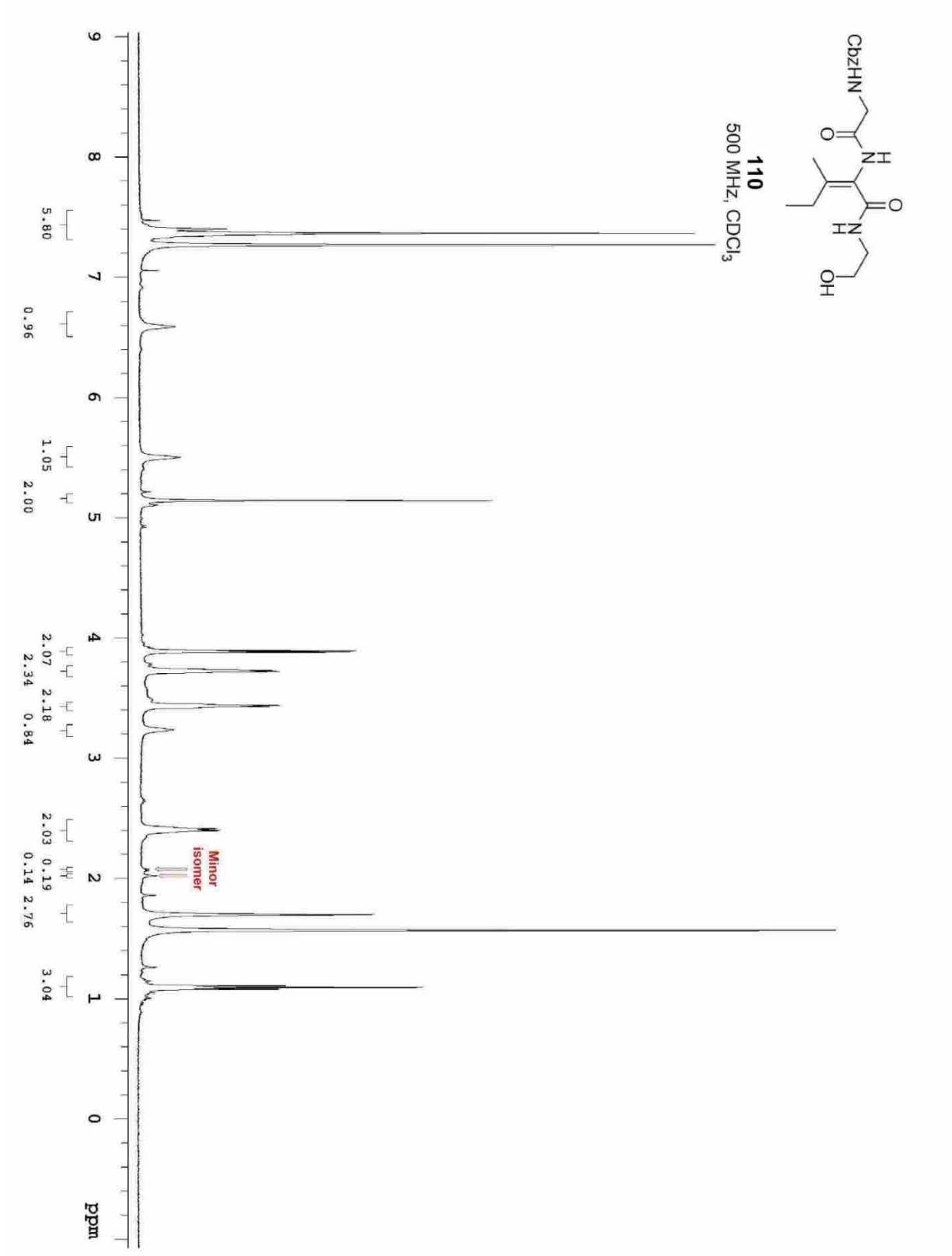
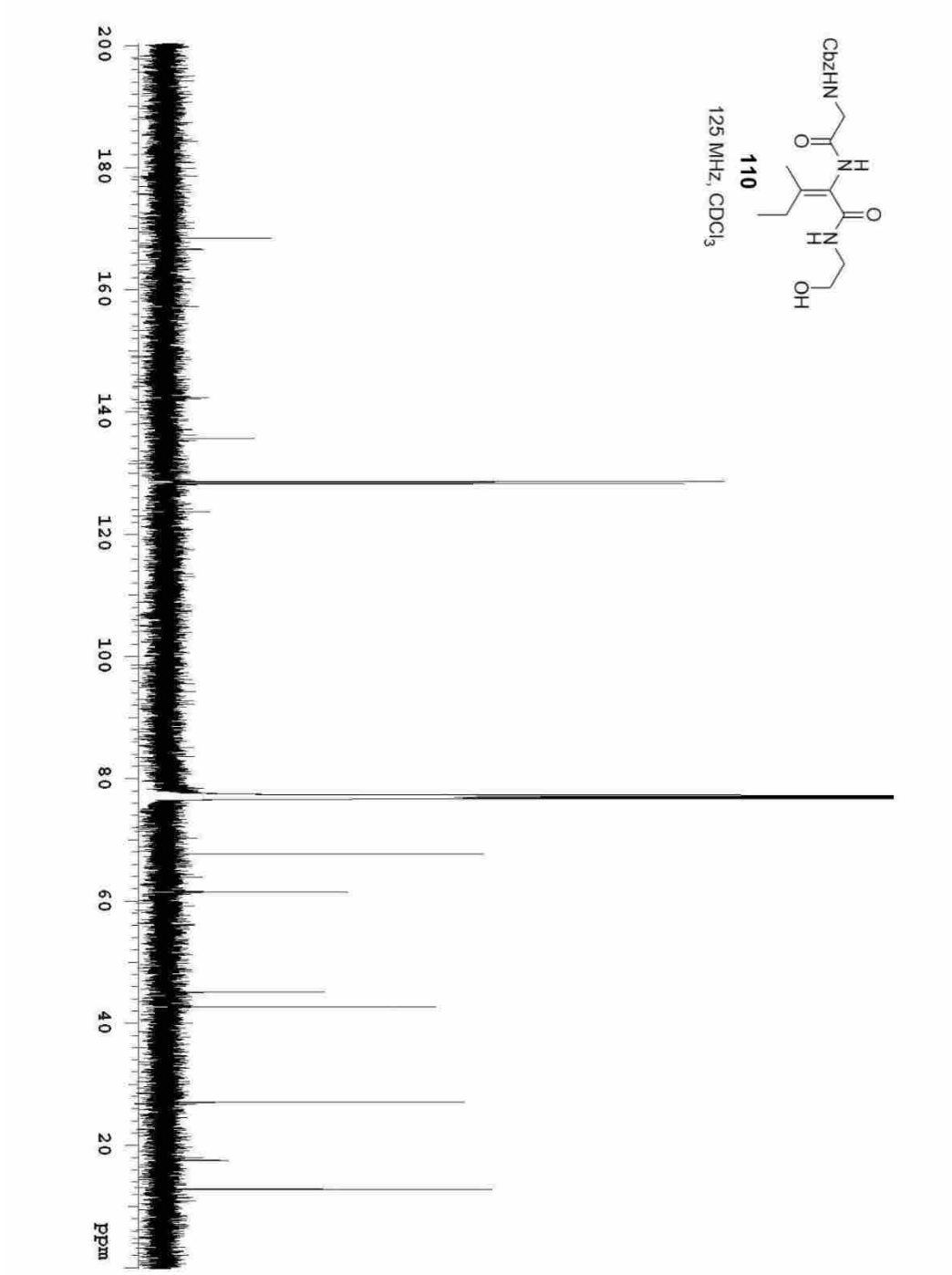
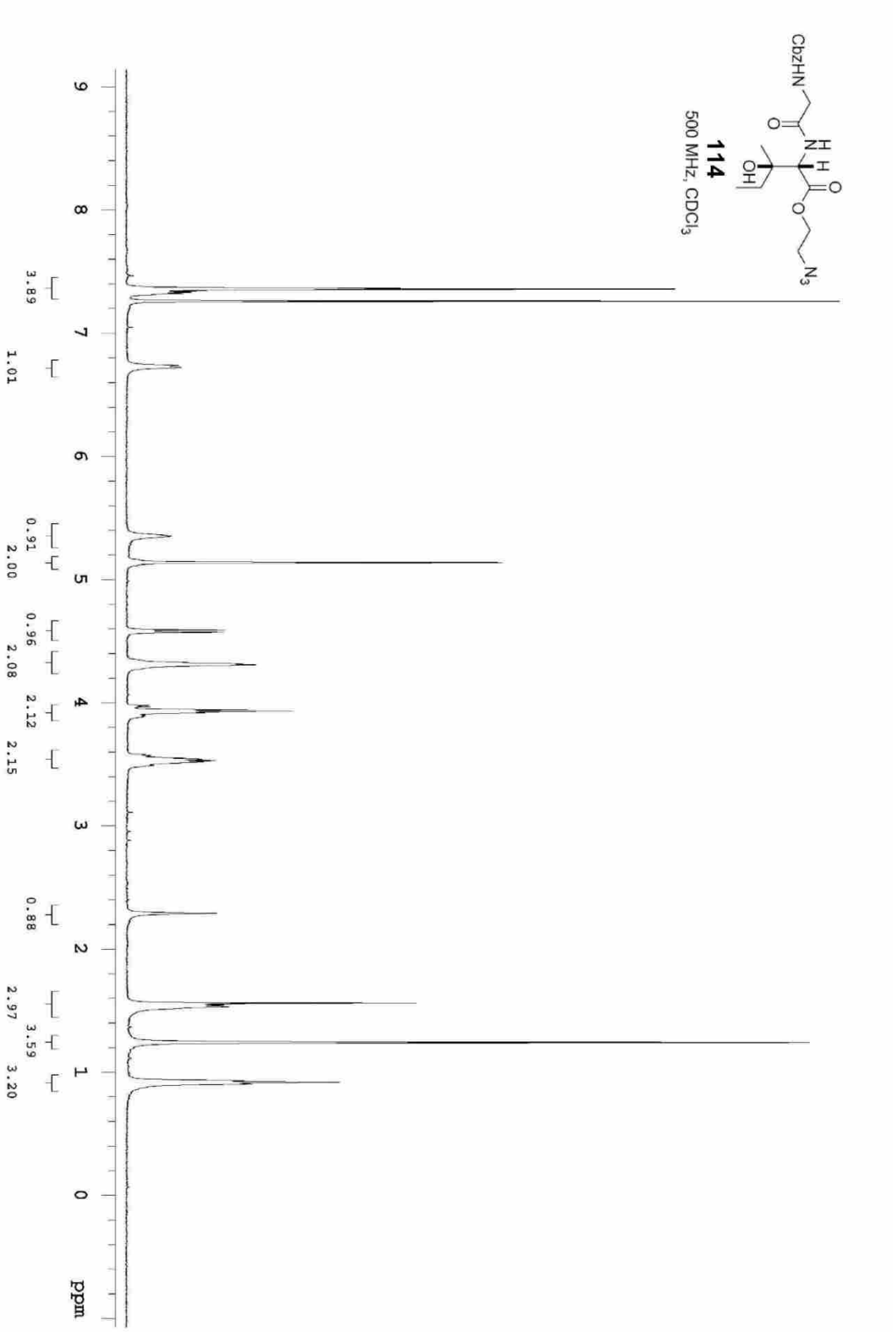
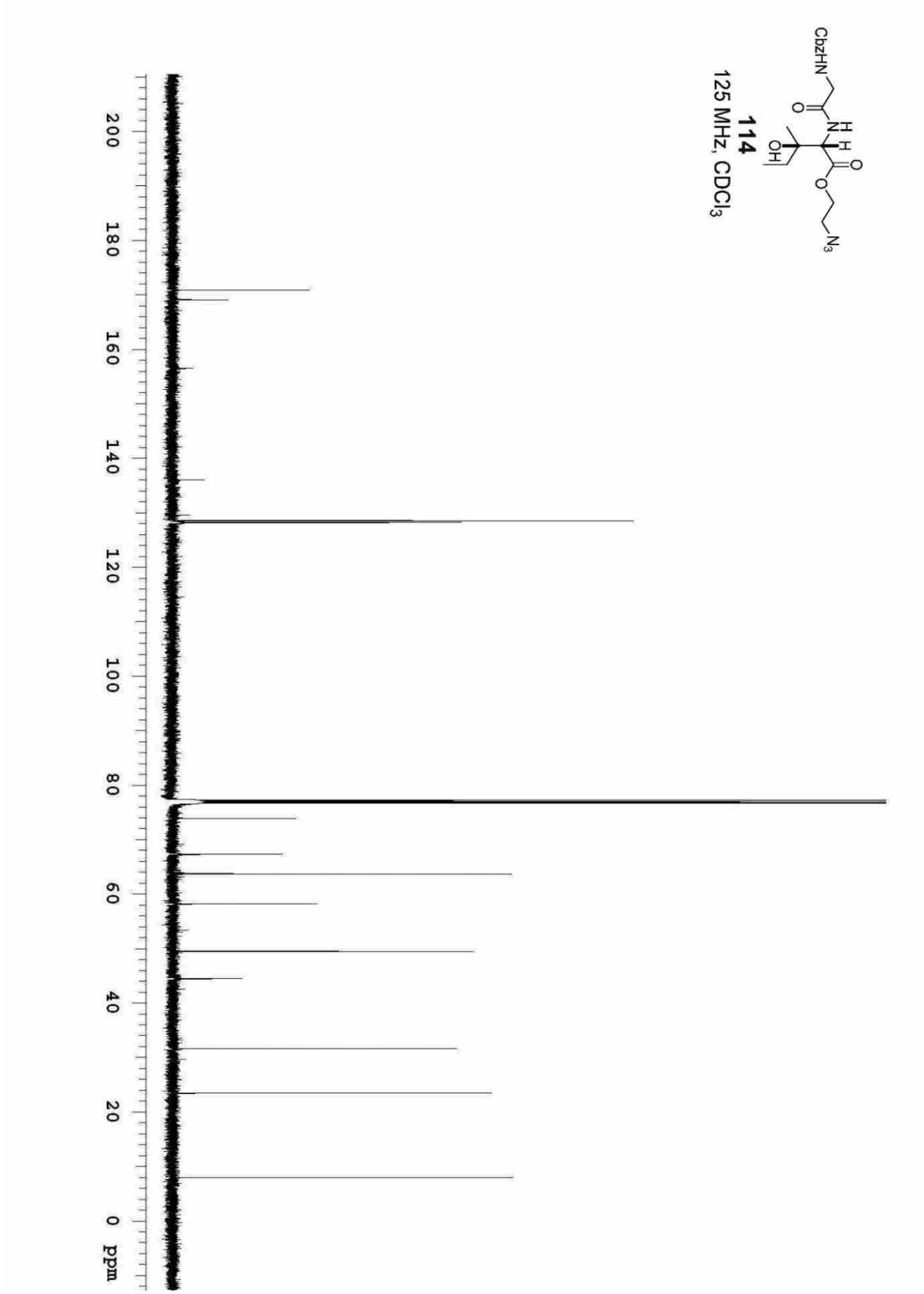
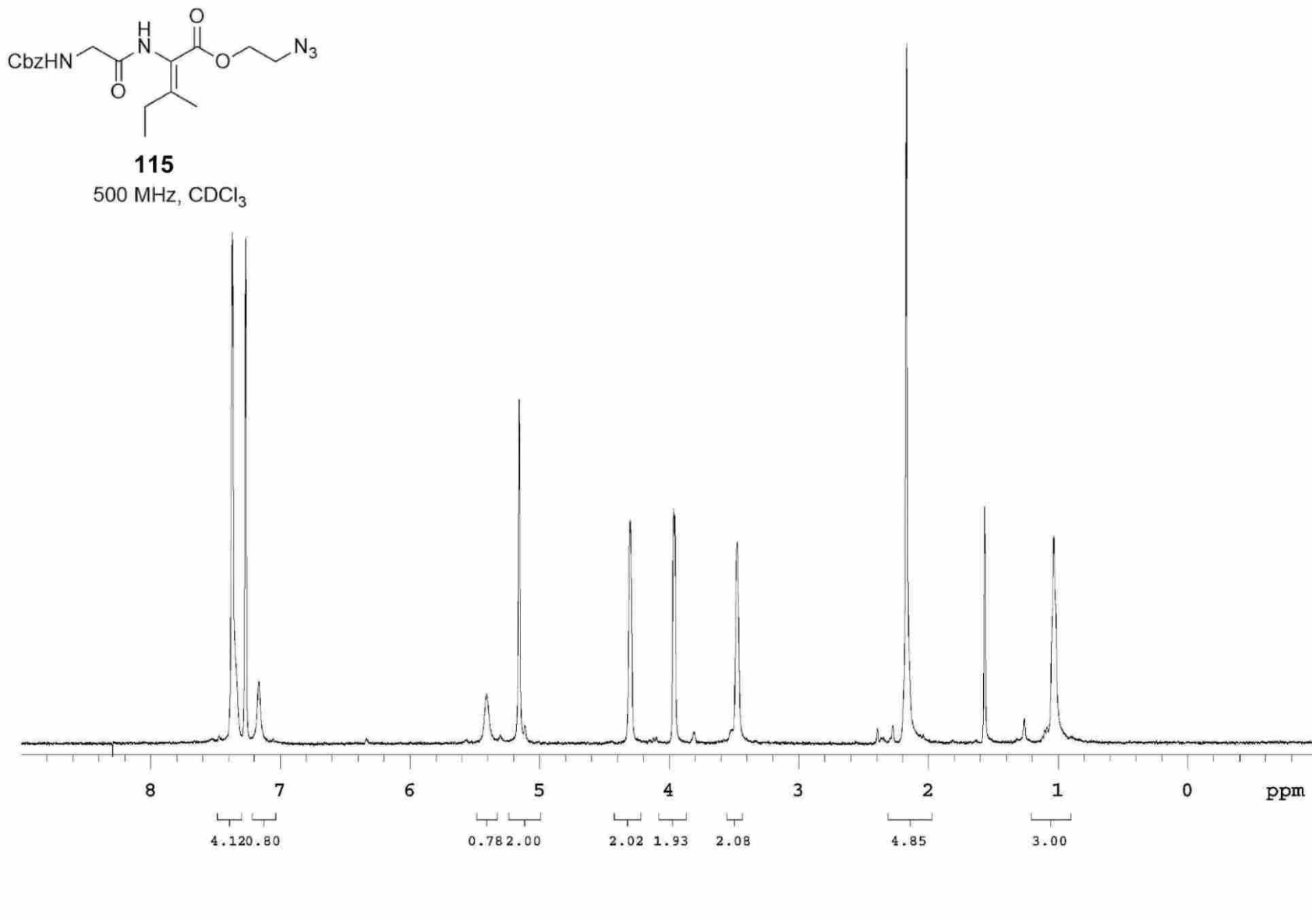
100
80
60
40
20
ppm

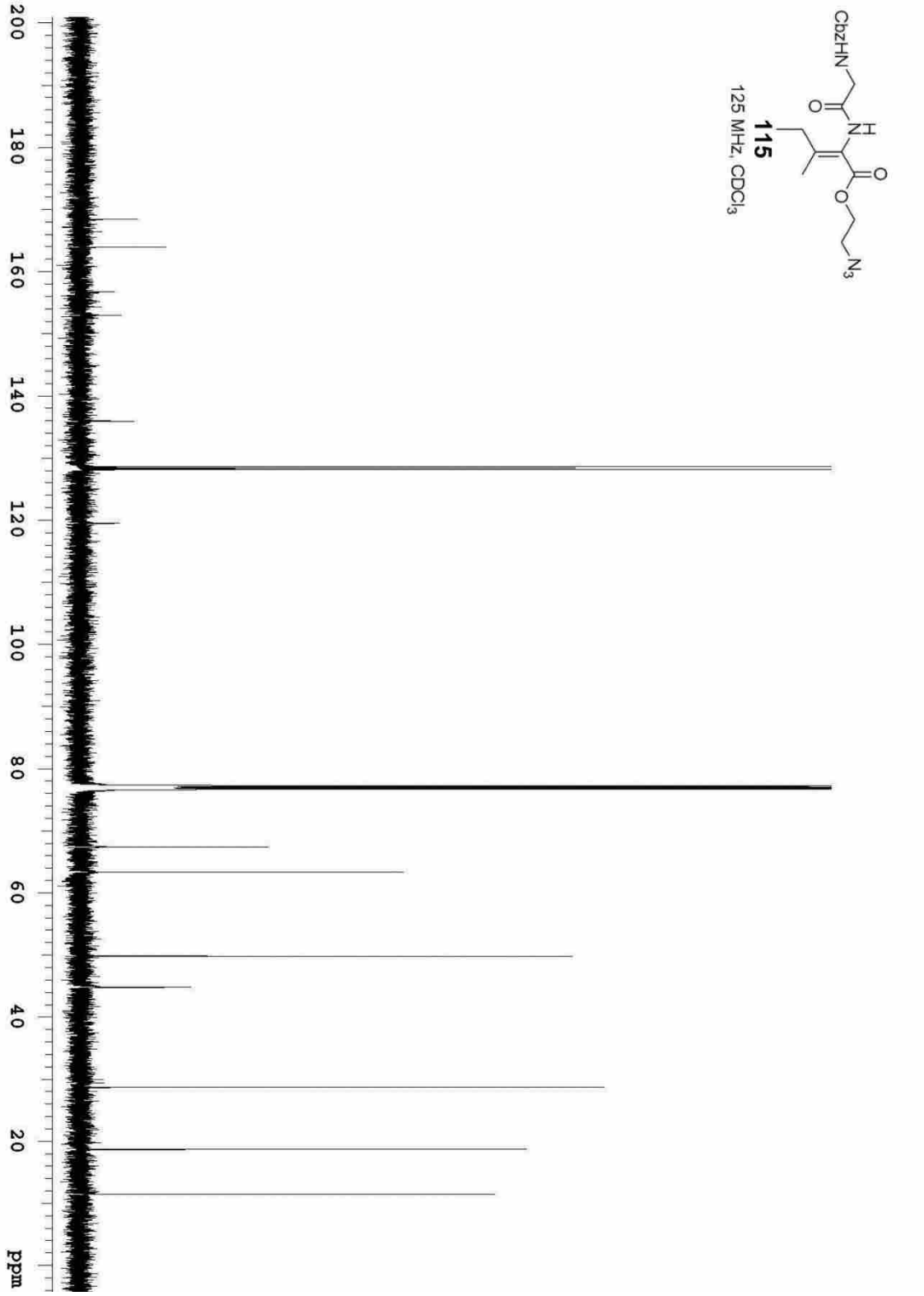

CbzHN
O
H
N
O
H
N
OH
110
500 MHz, CDCl3
Minor
isomer
9
8
7
6
5
4
3
2
1
0
ppm
5.80
0.96
1.05
2.00
2.07
2.18
2.34
0.84
2.03
0.19
0.14
2.76
3.04

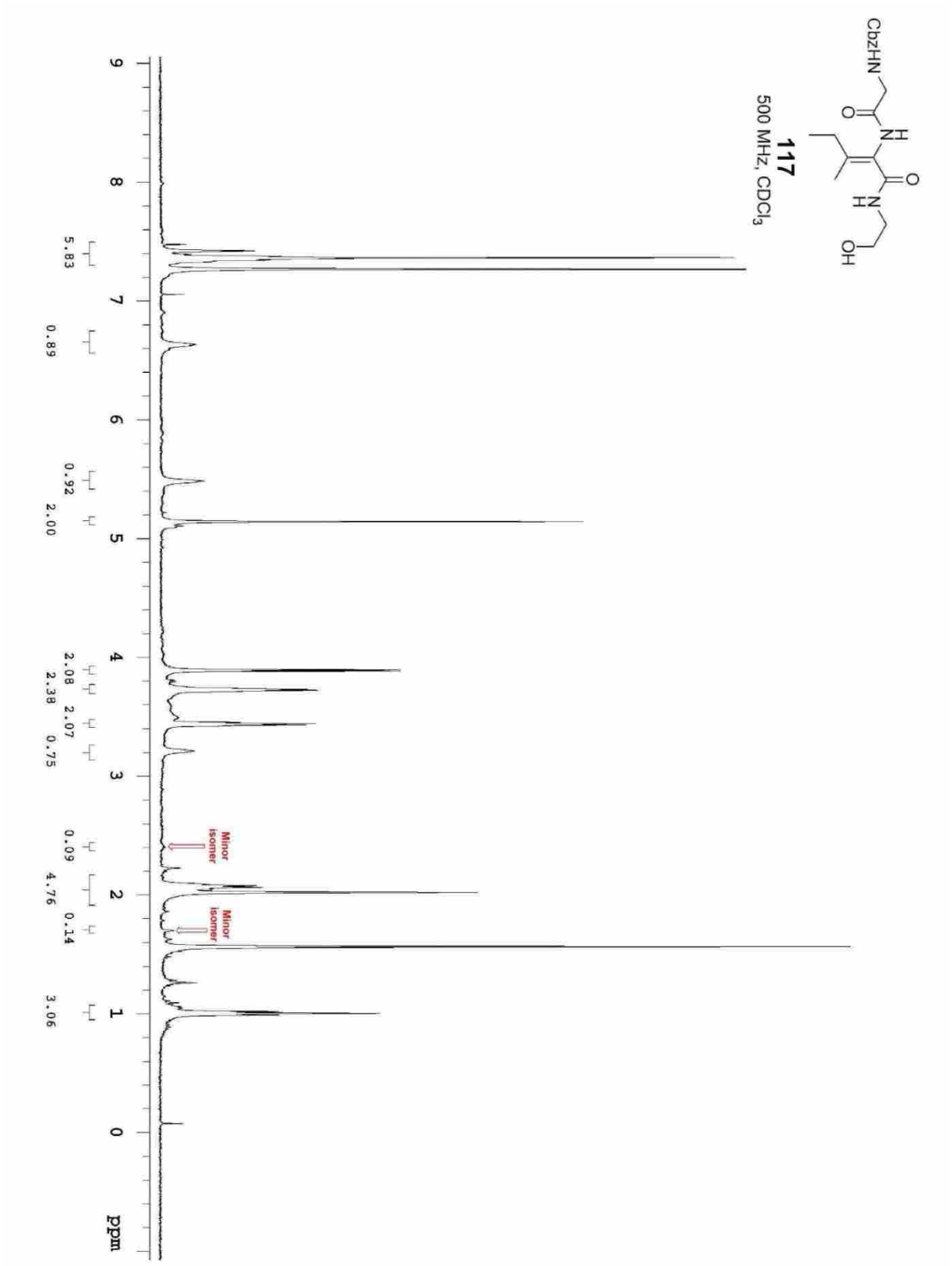

CbzHN
O
H
N
O
H
N
OH
110
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

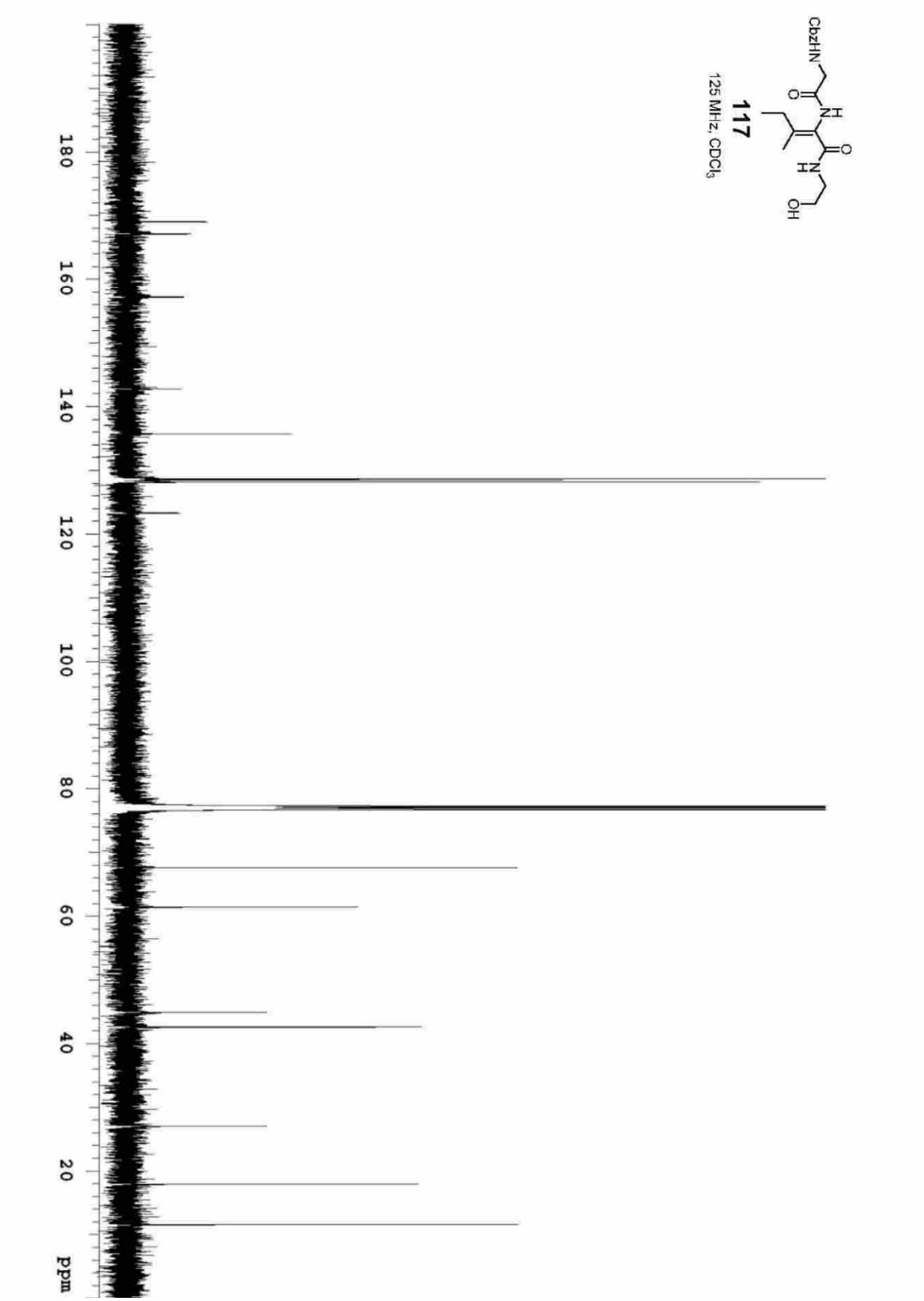

CbzHN
O
H N
O
H
O
OH
O
N3
114
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
0
ppm
3.89
1.01
0.91
2.00
0.96
2.08
2.12
2.15
0.88
2.97
3.59
3.20

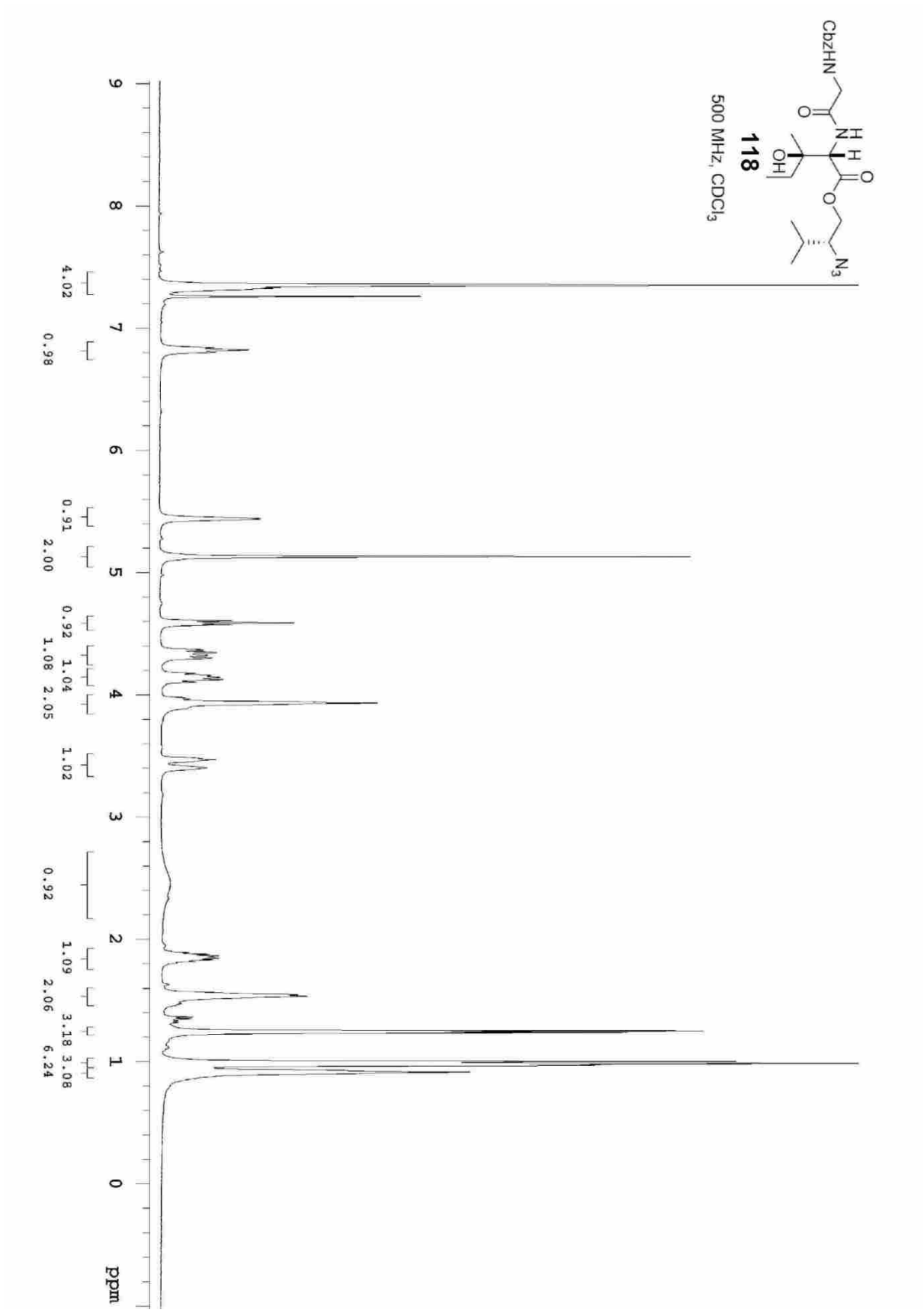

CbzHN
OH
N3
114
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm

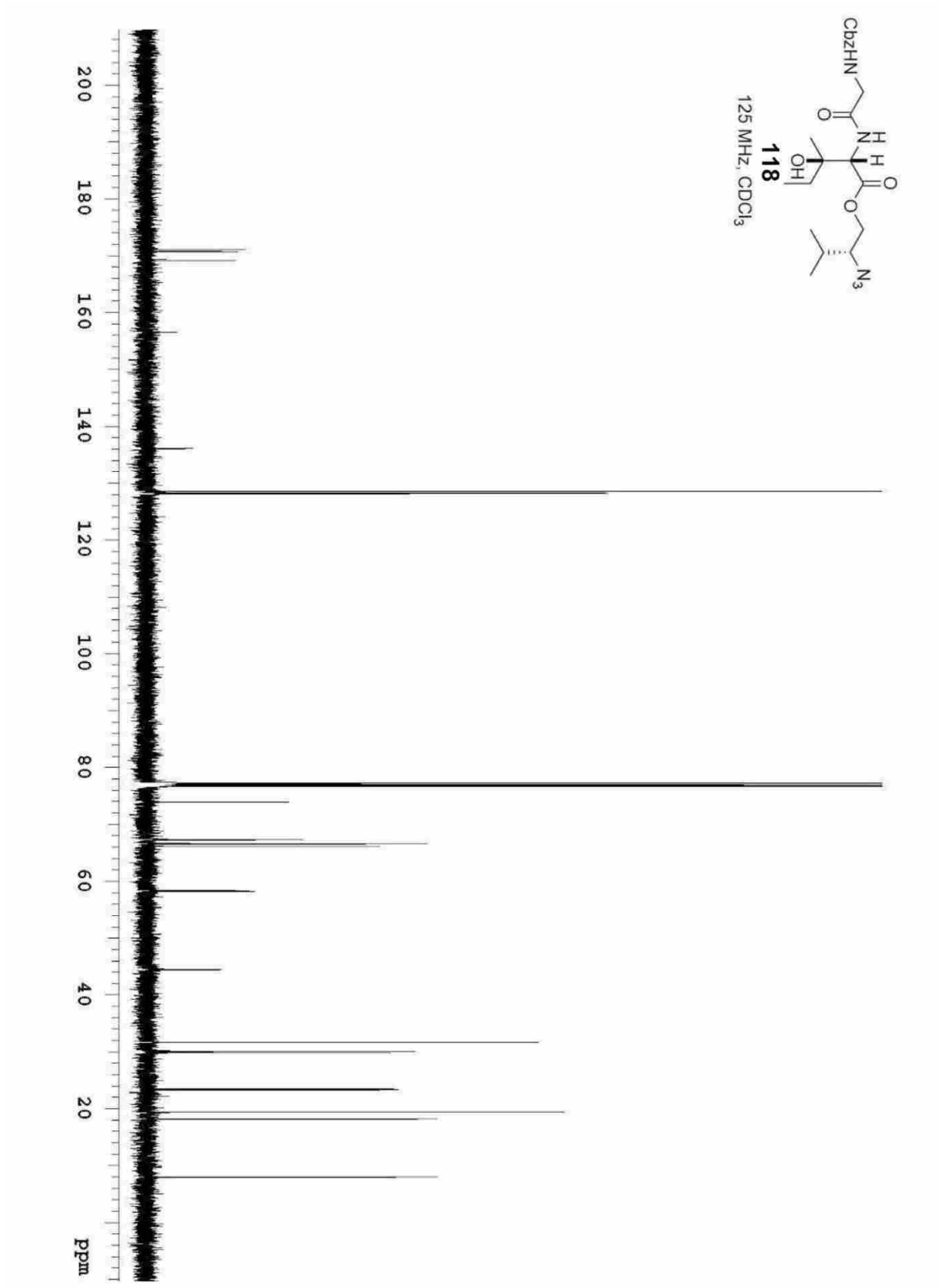

CbzHN
H
N
O
O
O
O
N3
115
500 MHz, CDCl3
8
7
6
5
4
3
2
1
0
ppm
4.12
0.80
0.78
2.00
2.02
1.93
2.08
4.85
3.00

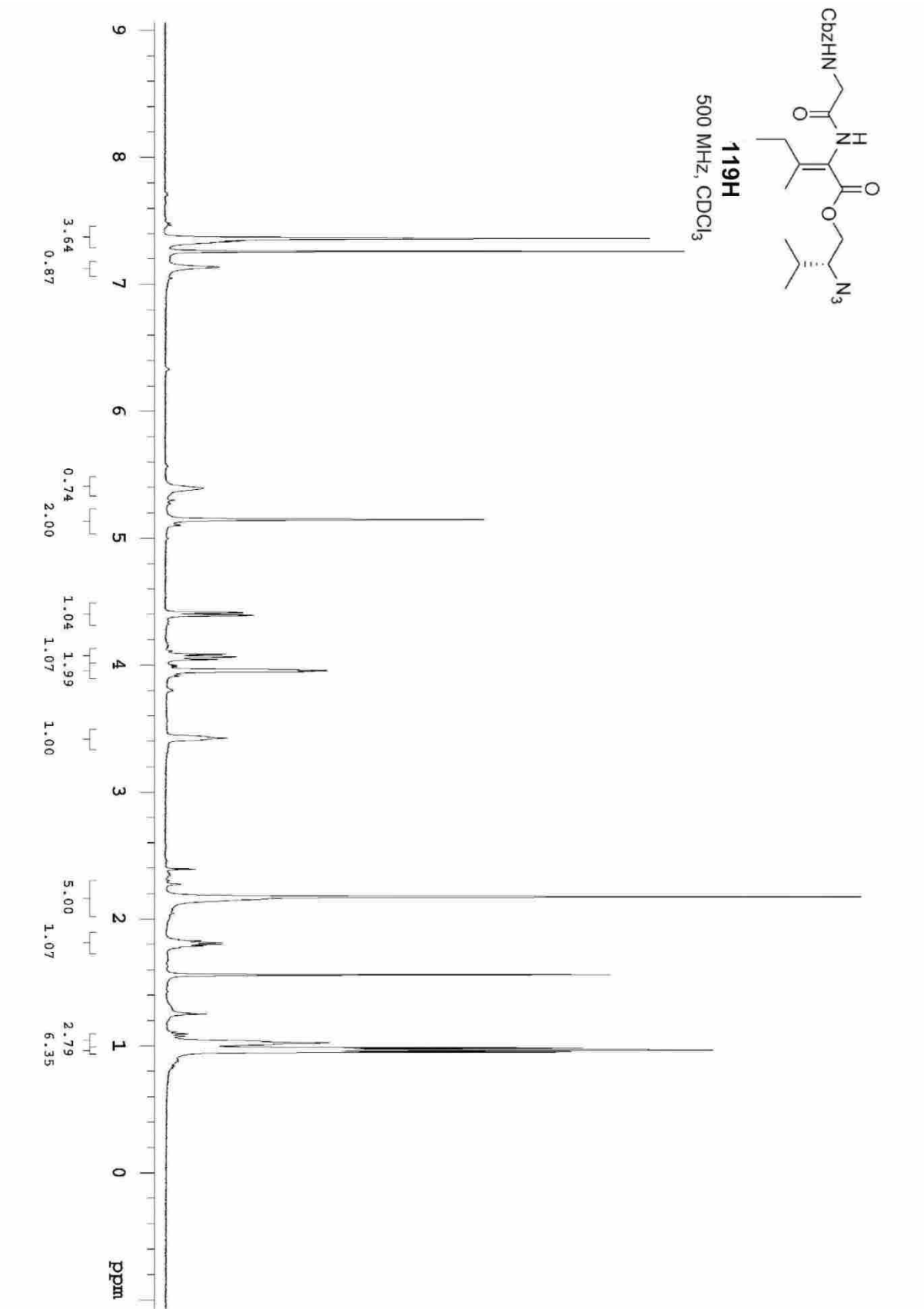

CbzHN
N
H
O
O
O
O
N3
115
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

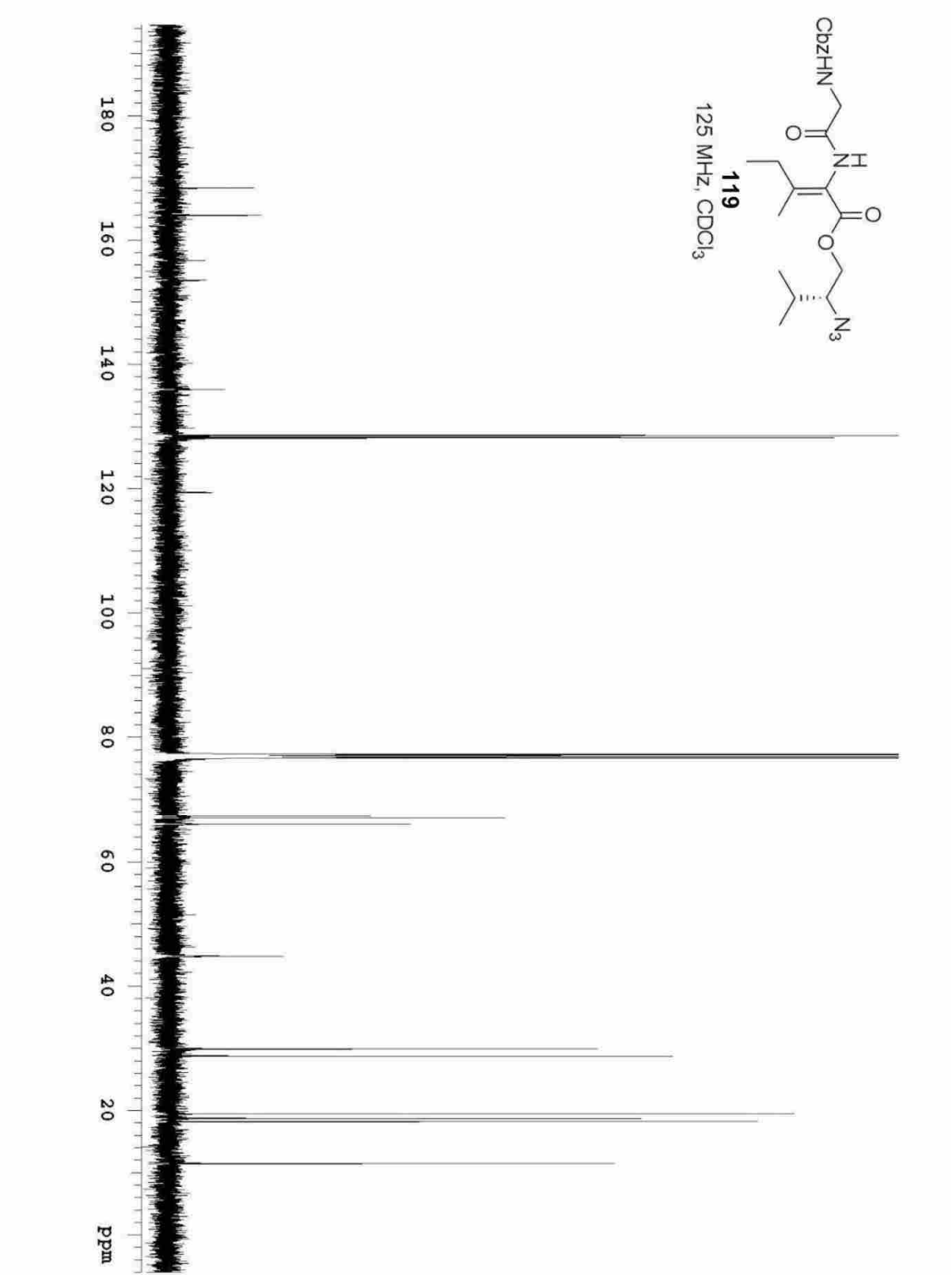

CbzHN
O
H
N
O
H
N
OH
117
500 MHz, CDCl3
Minor isomer
Minor isomer
5.83
0.89
0.92
2.00
2.08
2.38
2.07
0.75
0.09
4.76
0.14
3.06
9
8
7
6
5
4
3
2
1
0
ppm

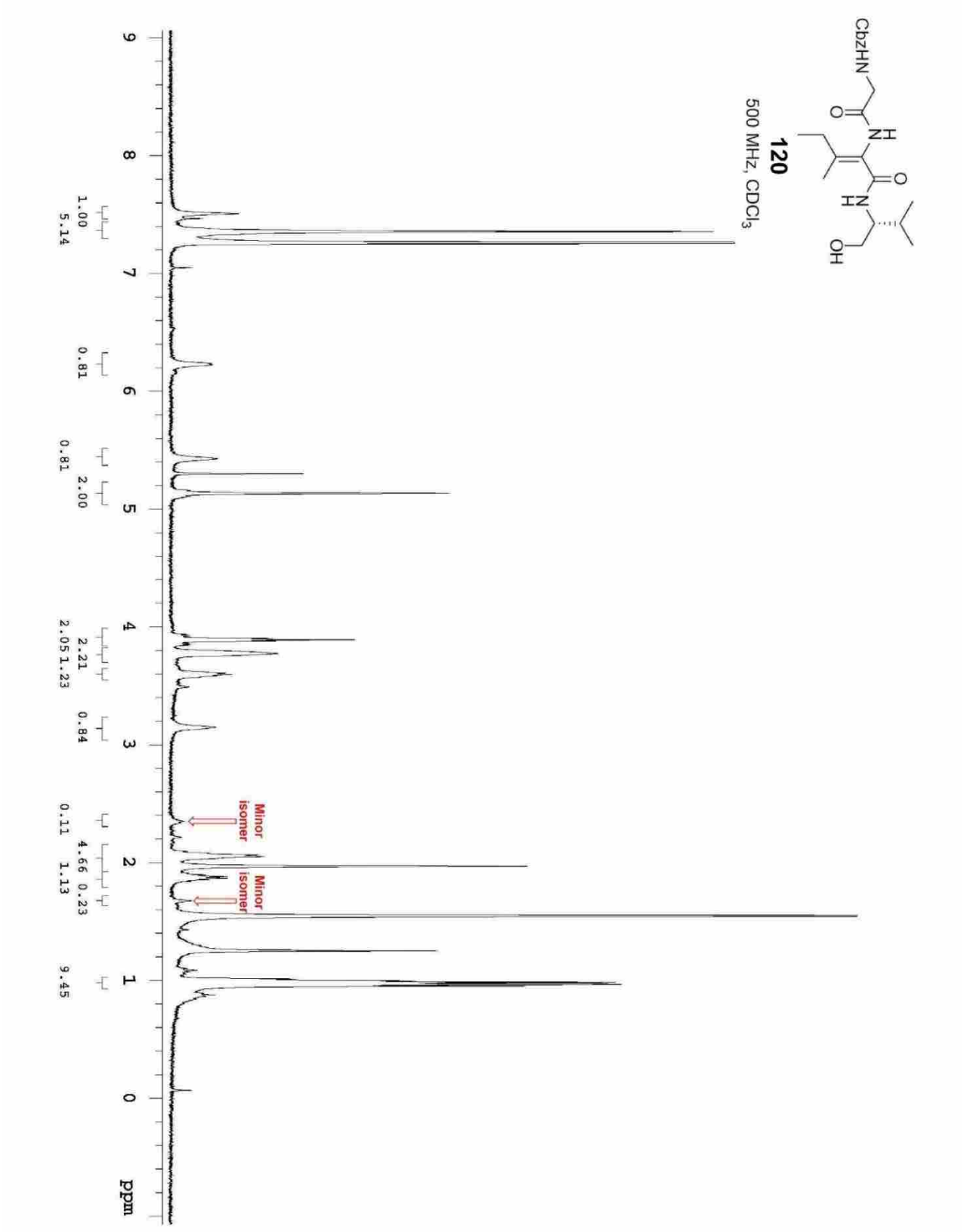

CbzHN
O
H
N
O
H
N
OH
117
125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

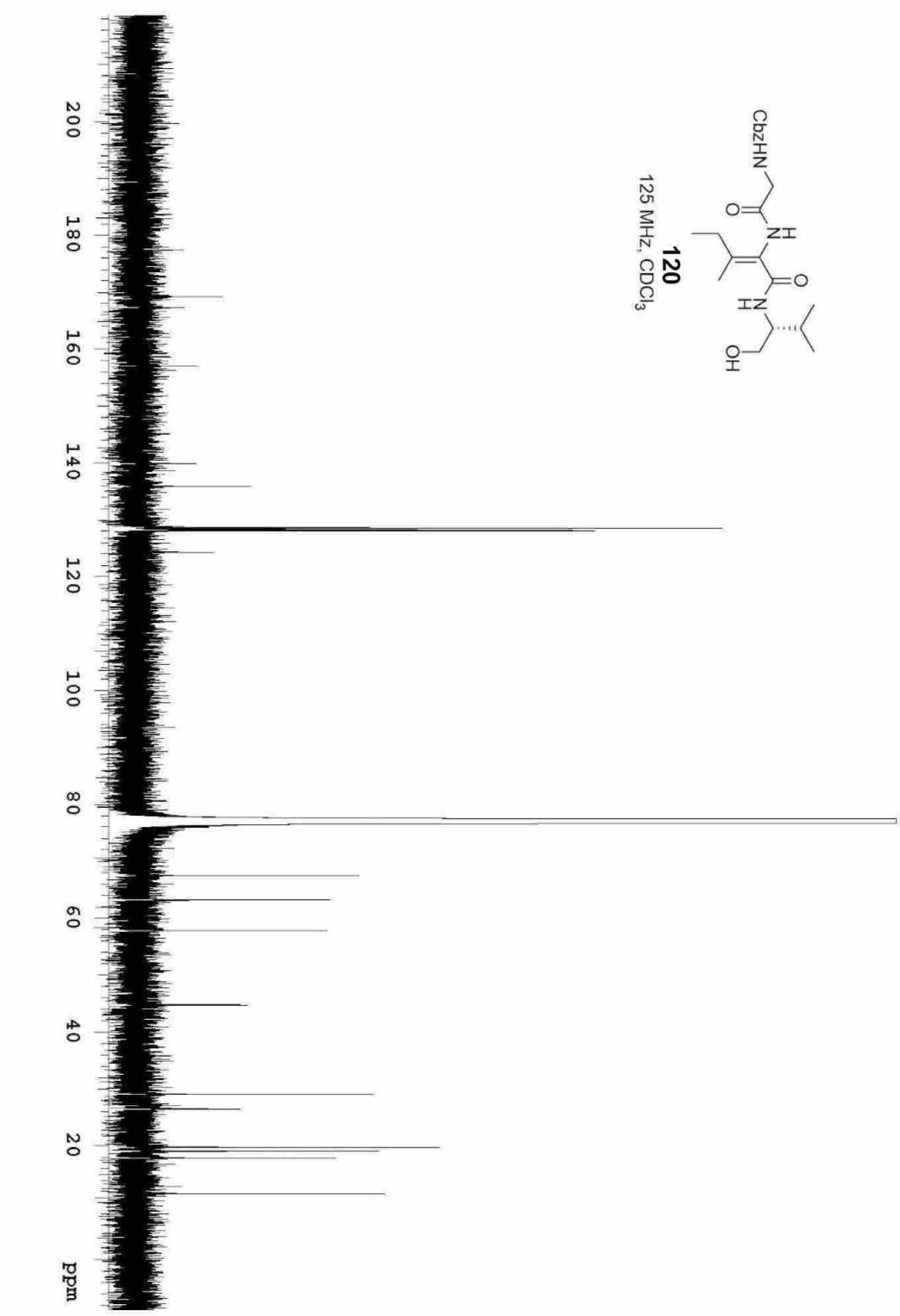

CbzHN
N
H
H
O
O
OH
O
N3
118
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
0
ppm
4.02
0.98
0.91
2.00
0.92
1.04
1.08
2.05
1.02
0.92
1.09
2.06
3.18
3.08
6.24

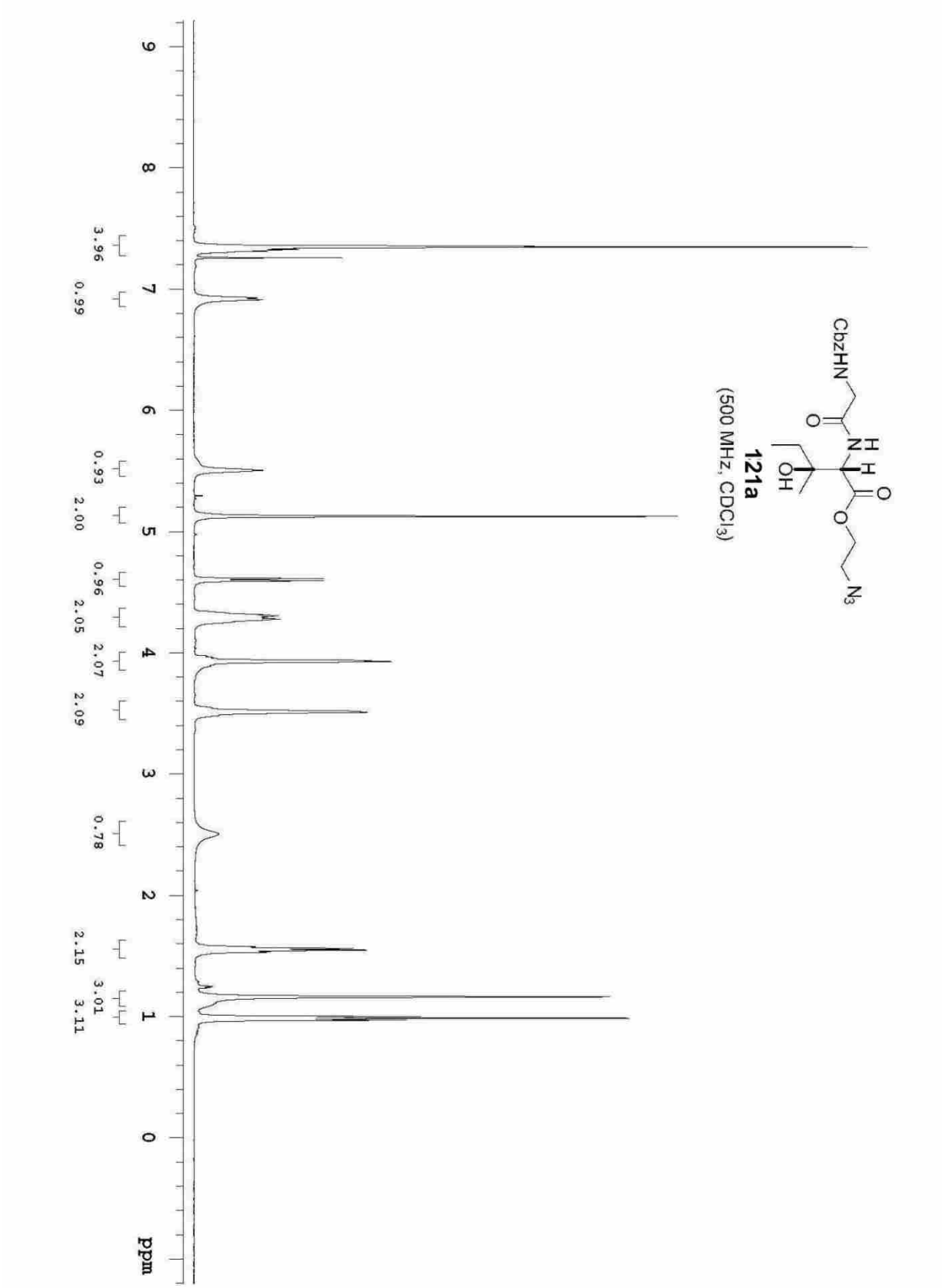

CbzHN
N
H
H
O
O
OH
O
N3
118
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

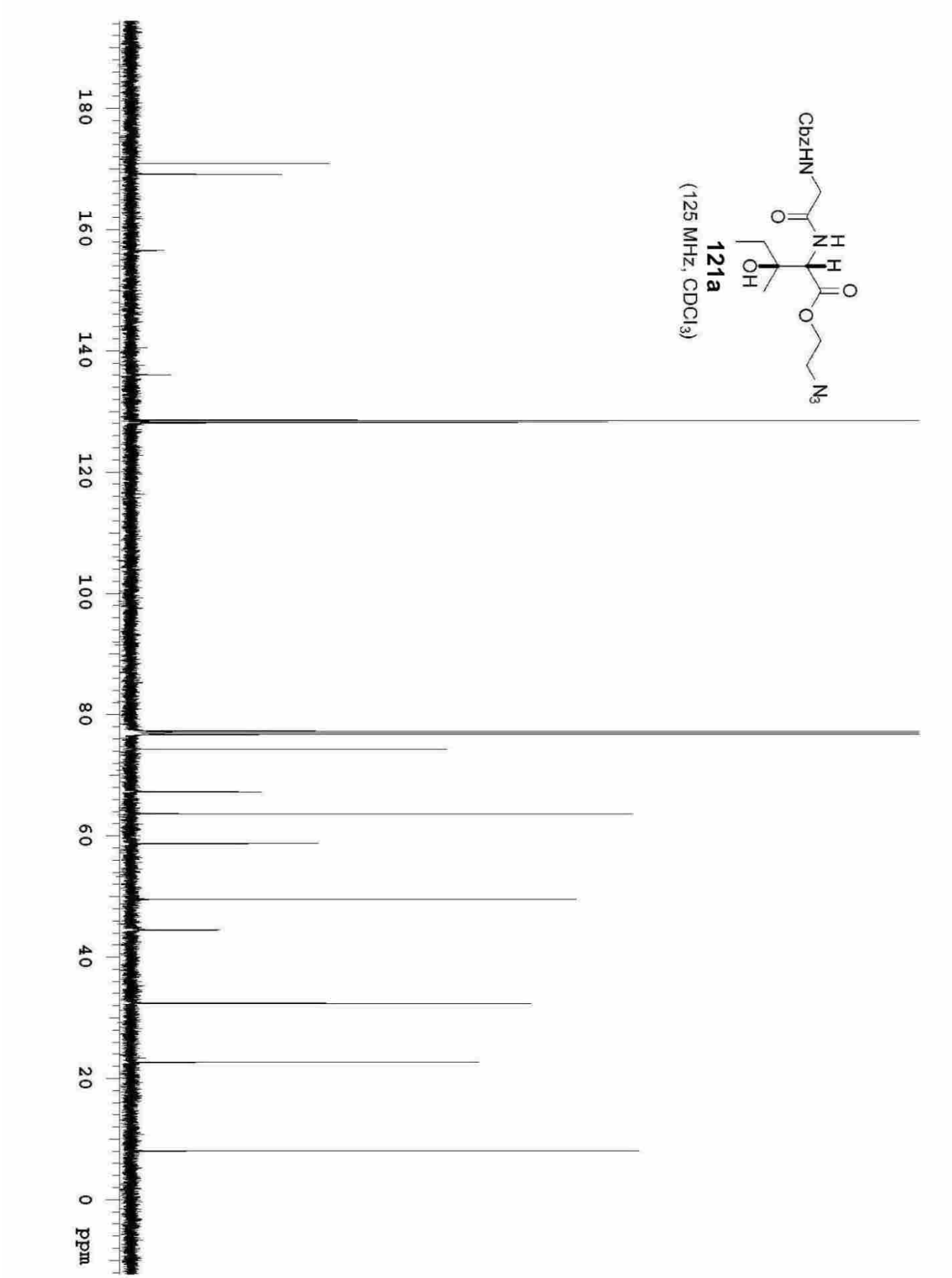

CbzHN
O
N
H
O
O
O
N3
119H
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
0
ppm
3.64
0.87
0.74
2.00
1.04
1.99
1.07
1.00
5.00
1.07
2.79
6.35

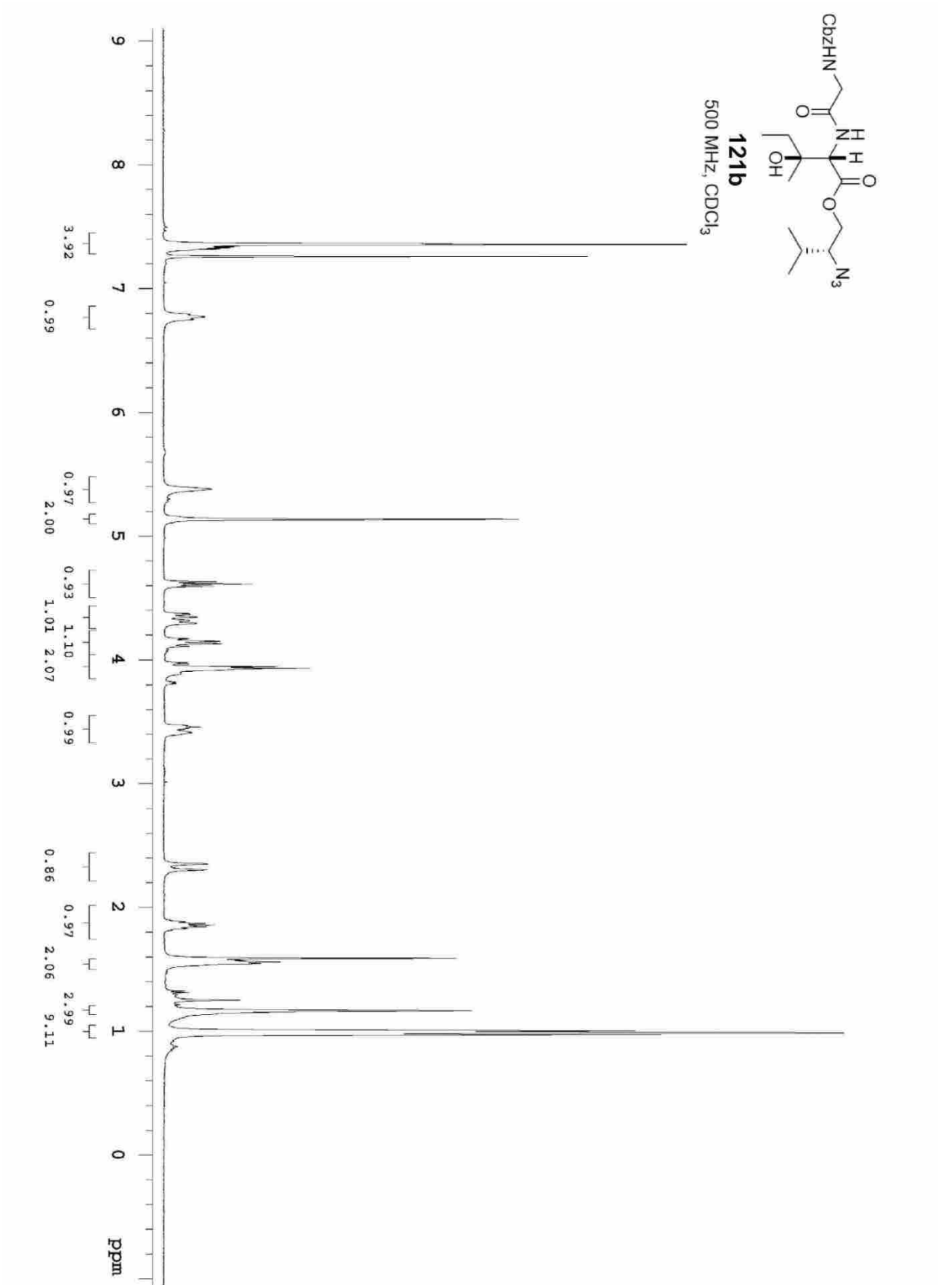

CbzHN
H
N
O
O
O
O
N3
119
125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

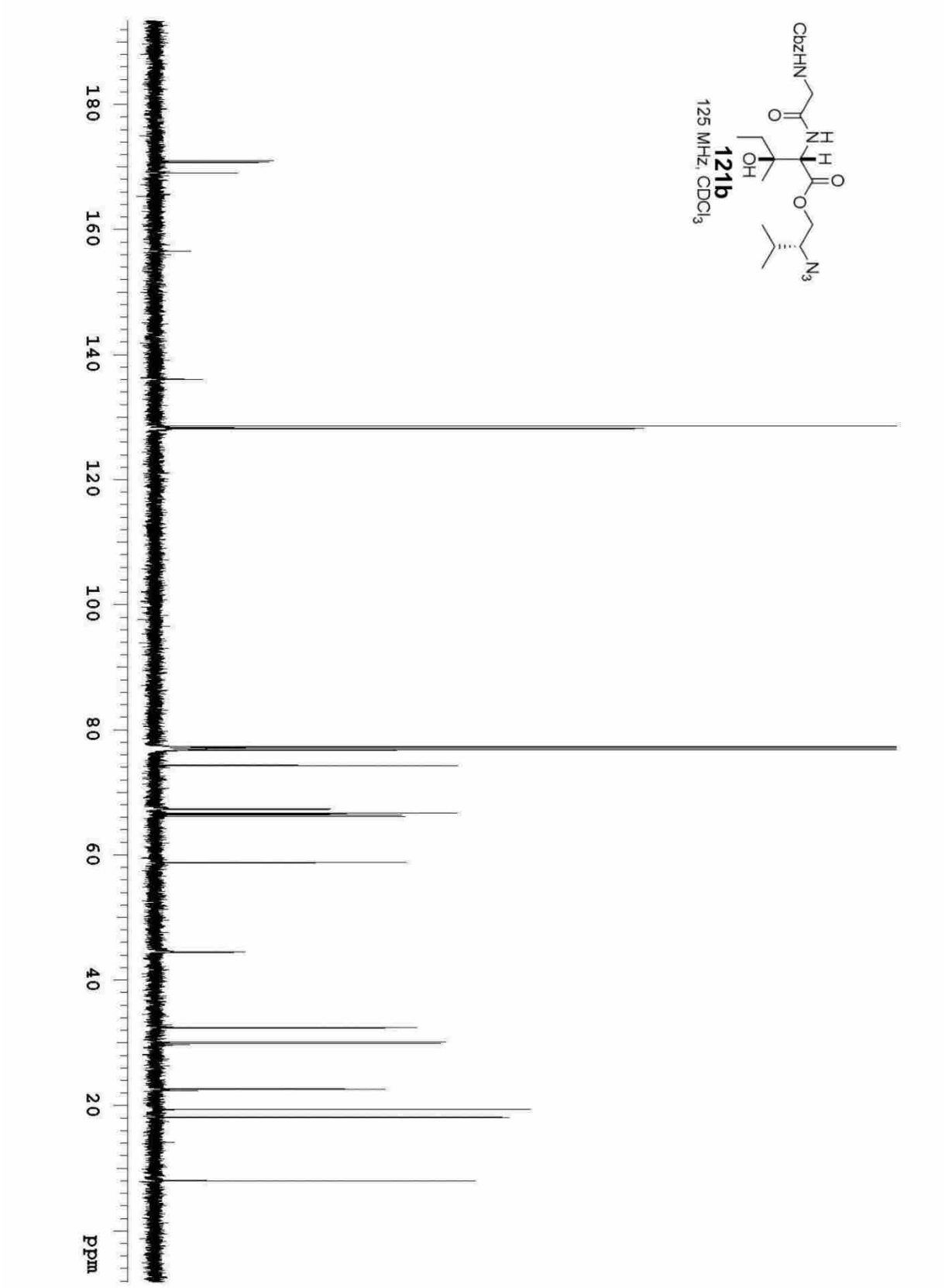

CbzHN
O
H
N
O
H
N
OH
120
500 MHz, CDCl3
Minor isomer
Minor isomer
9 8 7 6 5 4 3 2 1 0 ppm
1.00 0.81 0.81 2.00 2.05 1.23 2.21 0.84 0.11 4.66 0.23 1.13 9.45
5.14

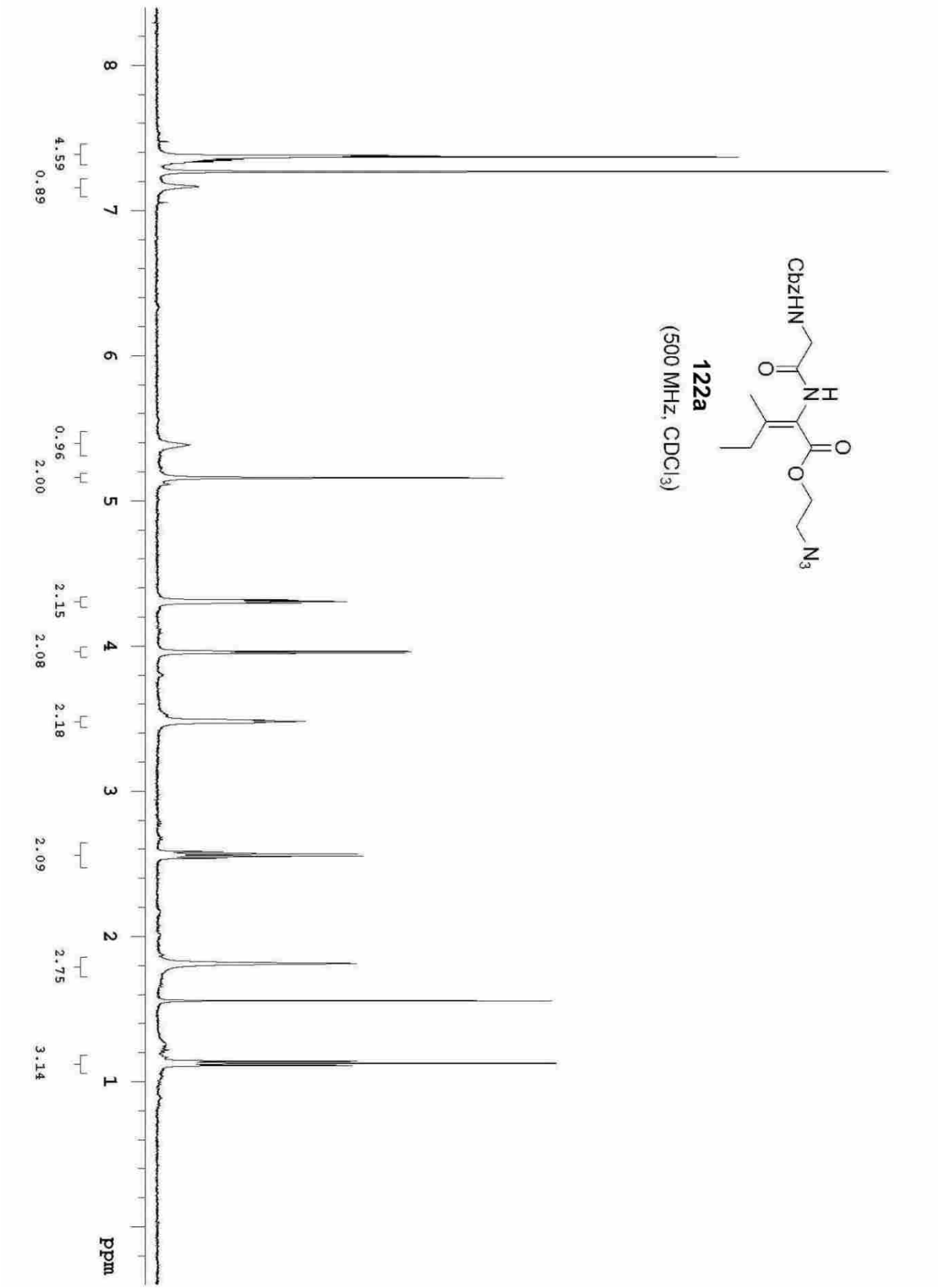

CbzHN
O
H
N
O
H
N
OH
120
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

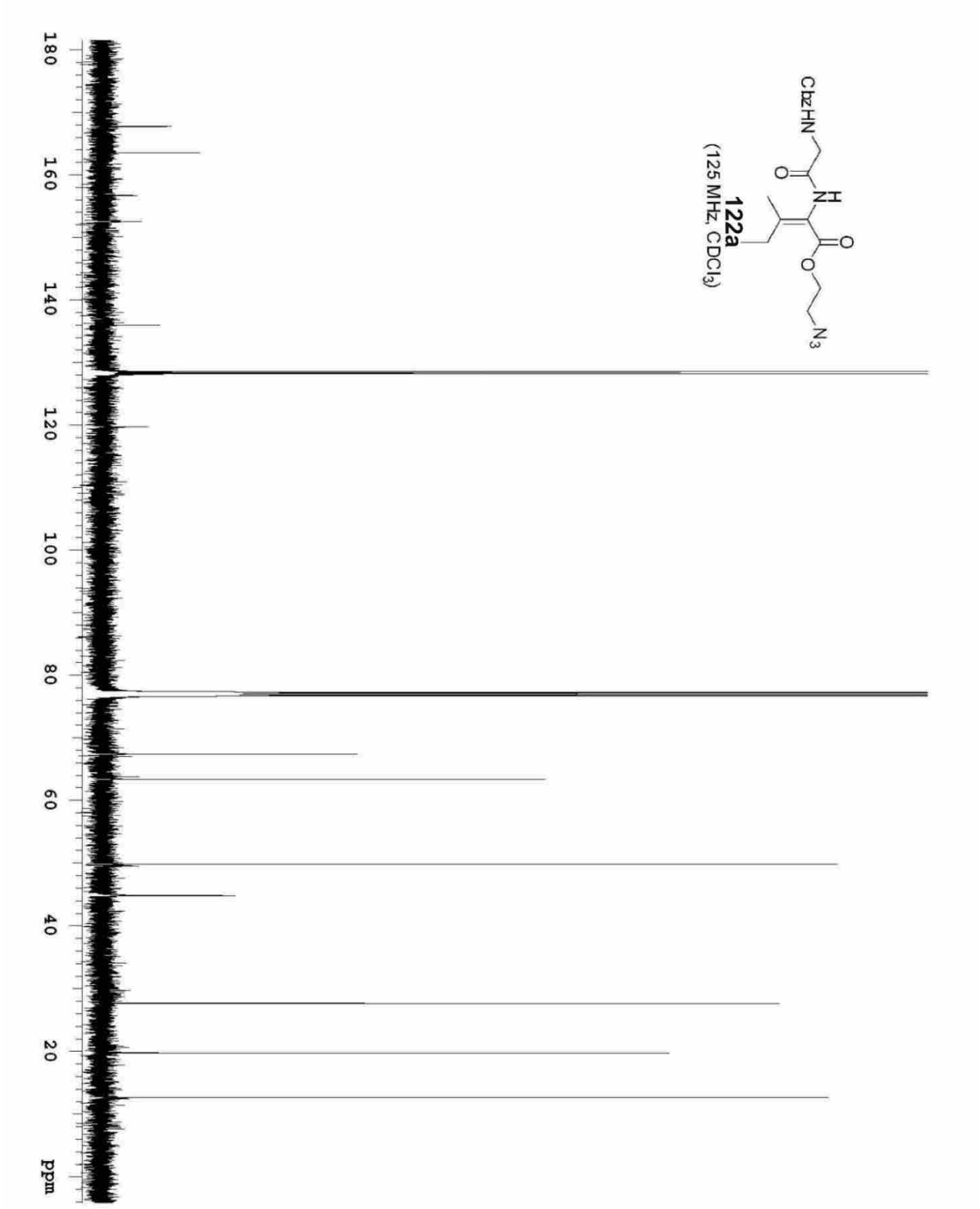

CbzHN
N
H
O
H
N
O
OH
O
N3
121a
(500 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
3.96
0.99
0.93
2.00
0.96
2.05
2.07
2.09
0.78
2.15
3.01
3.11

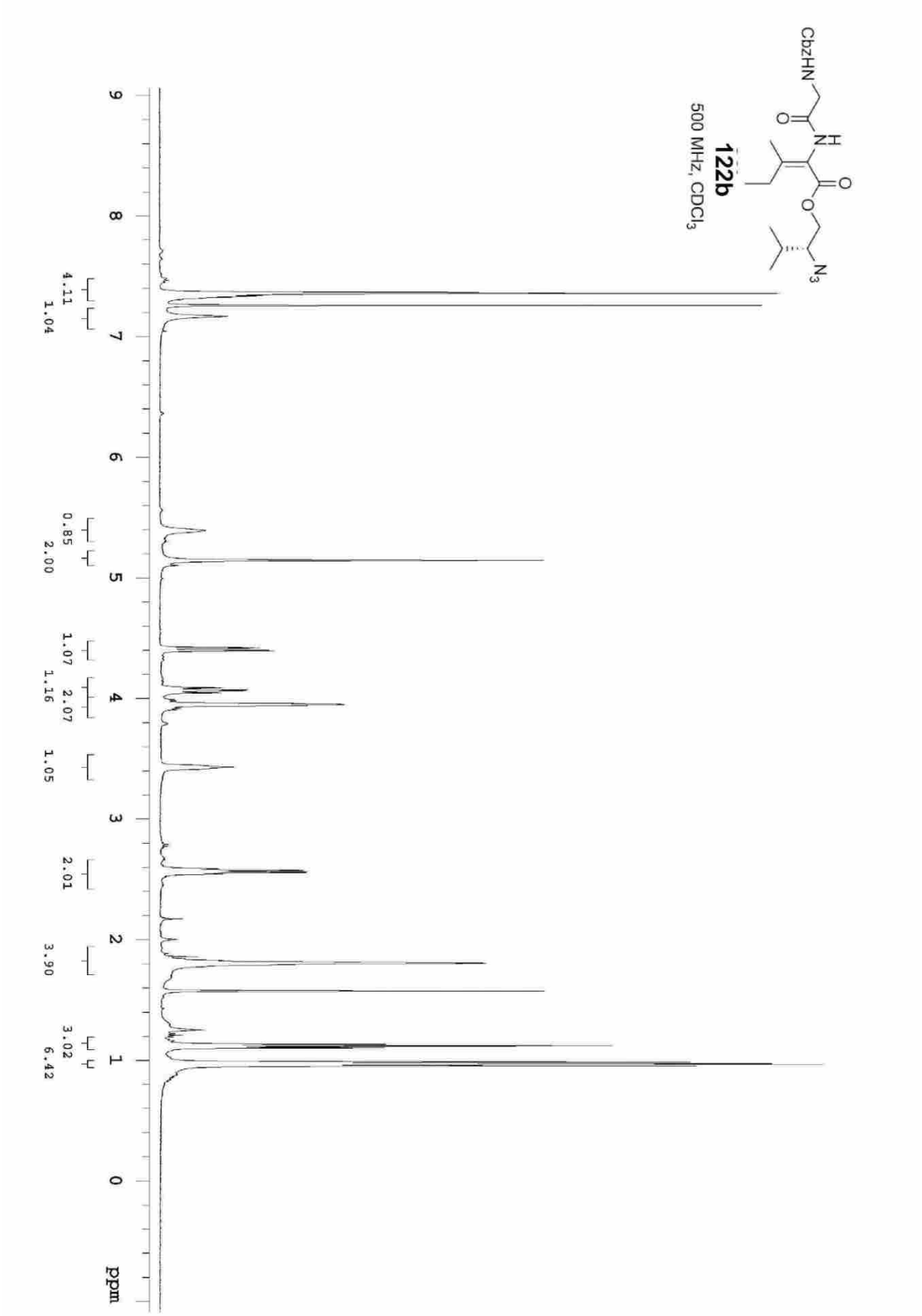

CbzHN
O
N
H
H
O
OH
O
O
N3
121a
(125 MHz, CDCl3)
180
160
140
120
100
80
60
40
20
0 ppm

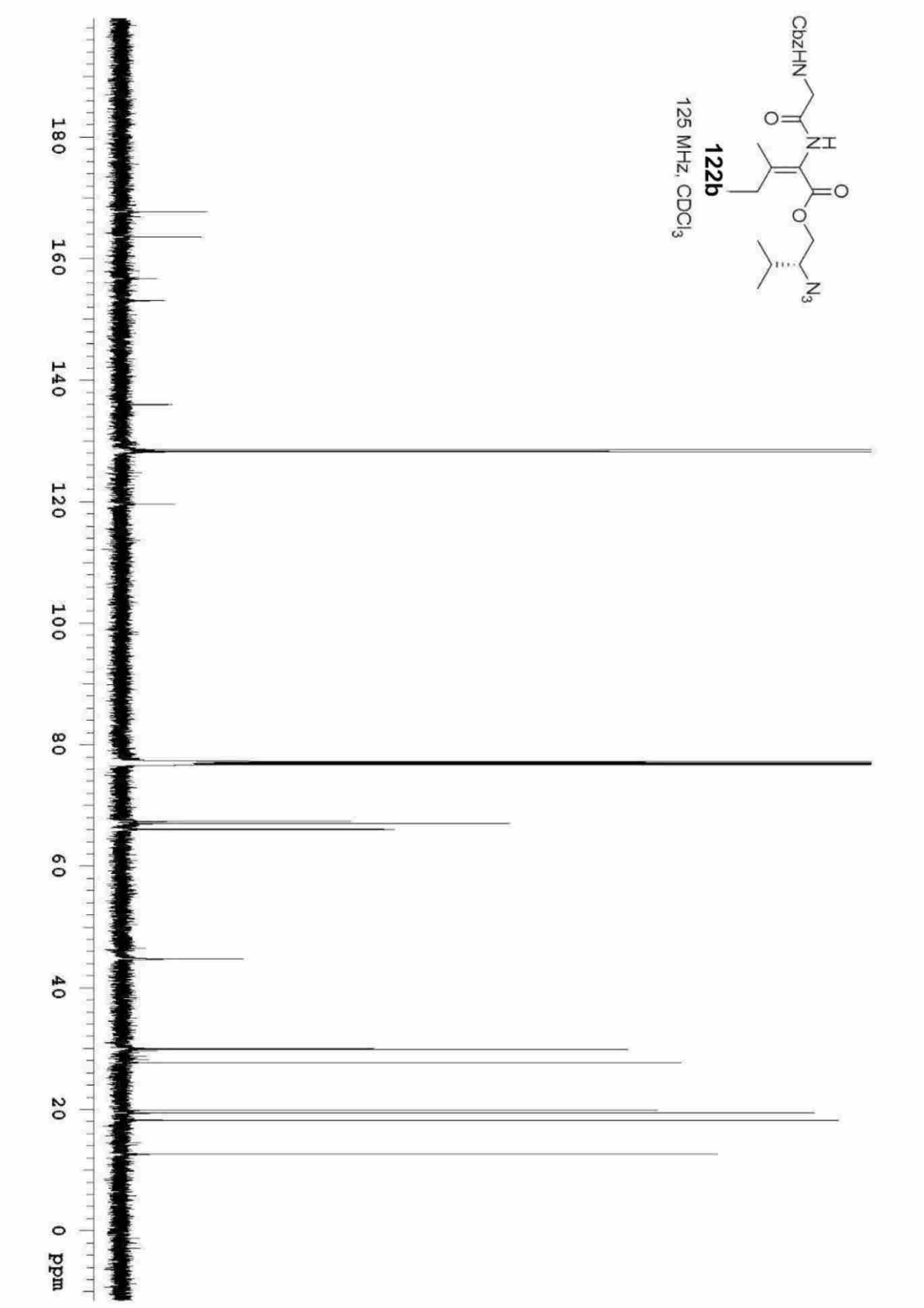

CbzHN
O
H
N
H
O
OH
O
O
N3
121b
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
0
ppm
3.92
0.99
0.97
2.00
0.93
1.10
1.01
2.07
0.99
0.86
0.97
2.06
2.99
9.11

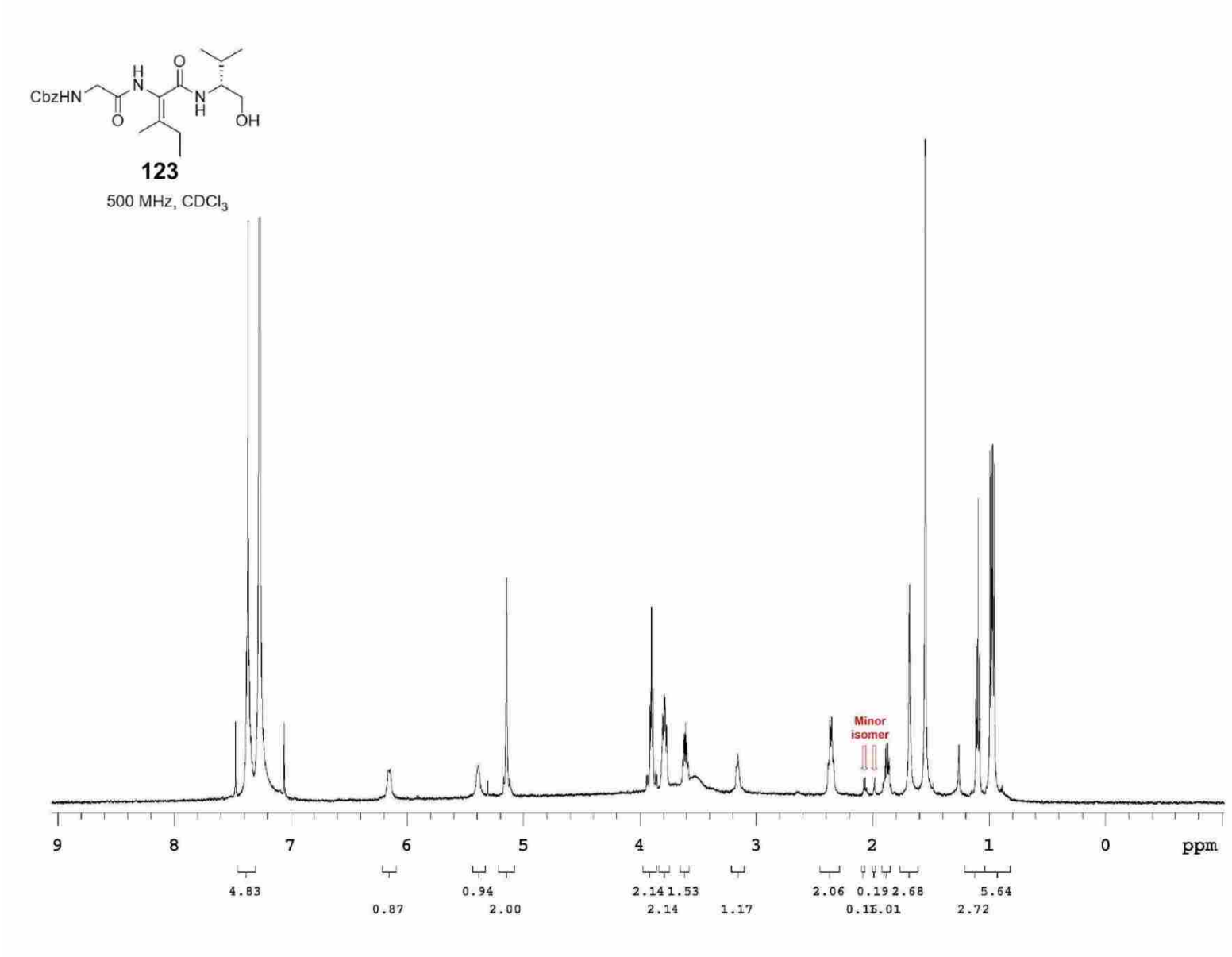

CbzHN
O
N
H
H
O
OH
O
O
N3
121b
125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

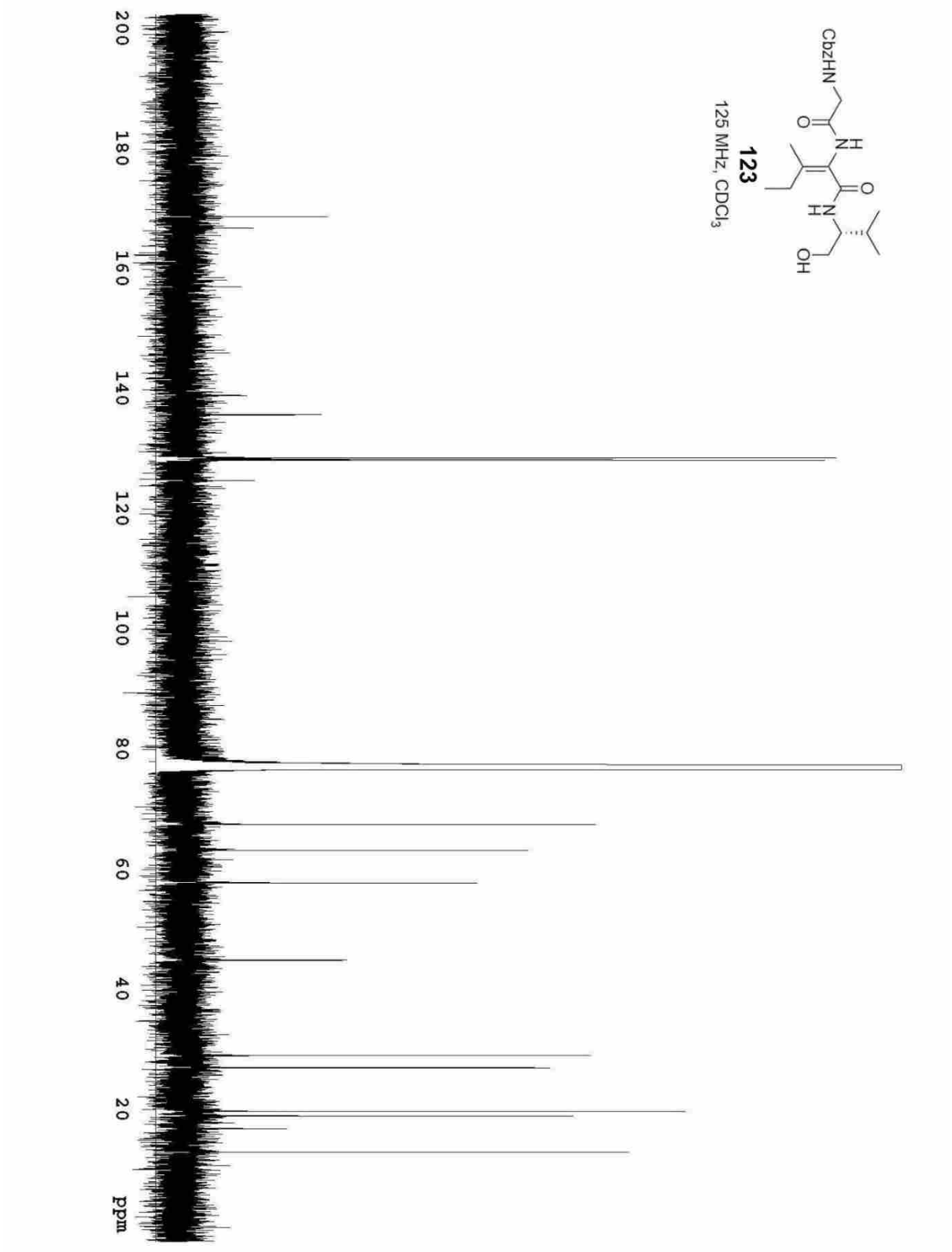

CbzHN
N
H
O
O
O
O
N3
122a
(500 MHz, CDCl3)
8
7
6
5
4
3
2
1
ppm
4.59
0.89
0.96
2.00
2.15
2.08
2.18
2.09
2.75
3.14

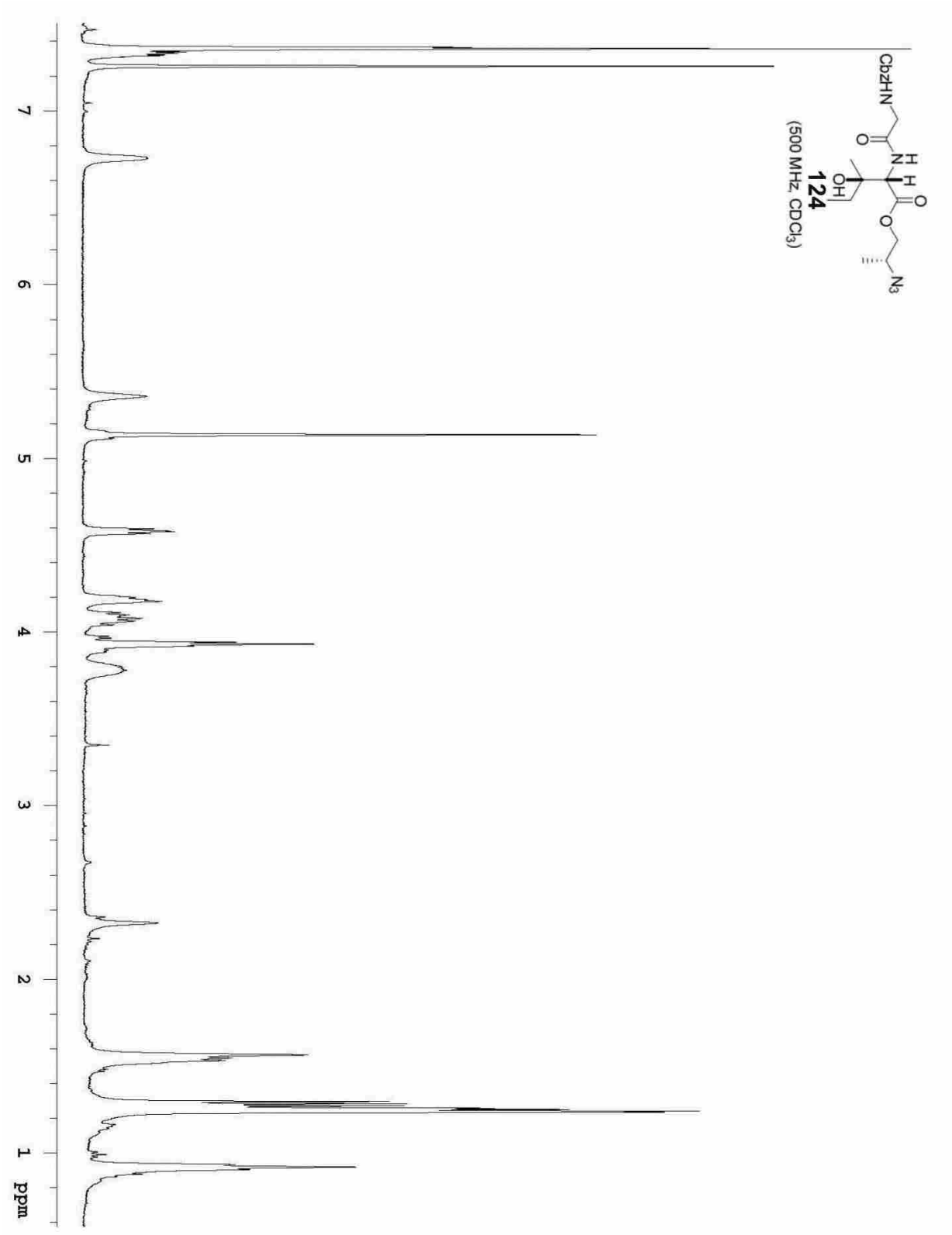

CbzHN
O
H
N
O
O
O
N3
122a
(125 MHz, CDCl3)
180
160
140
120
100
80
60
40
20
ppm

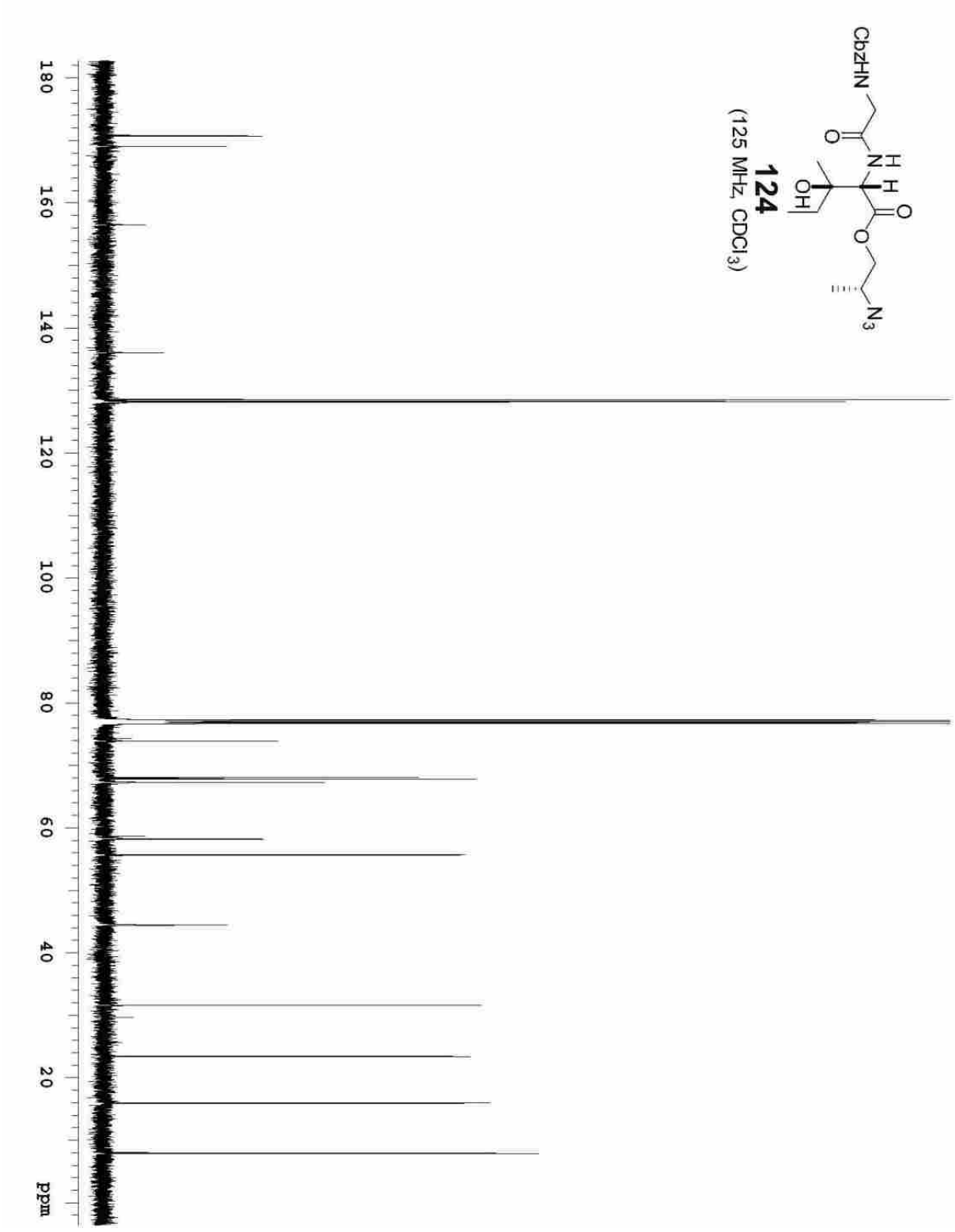

CbzHN
H
N
O
O
O
O
N3
122b
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
0
ppm
4.11
1.04
0.85
2.00
1.07
2.07
1.16
1.05
2.01
3.90
3.02
6.42

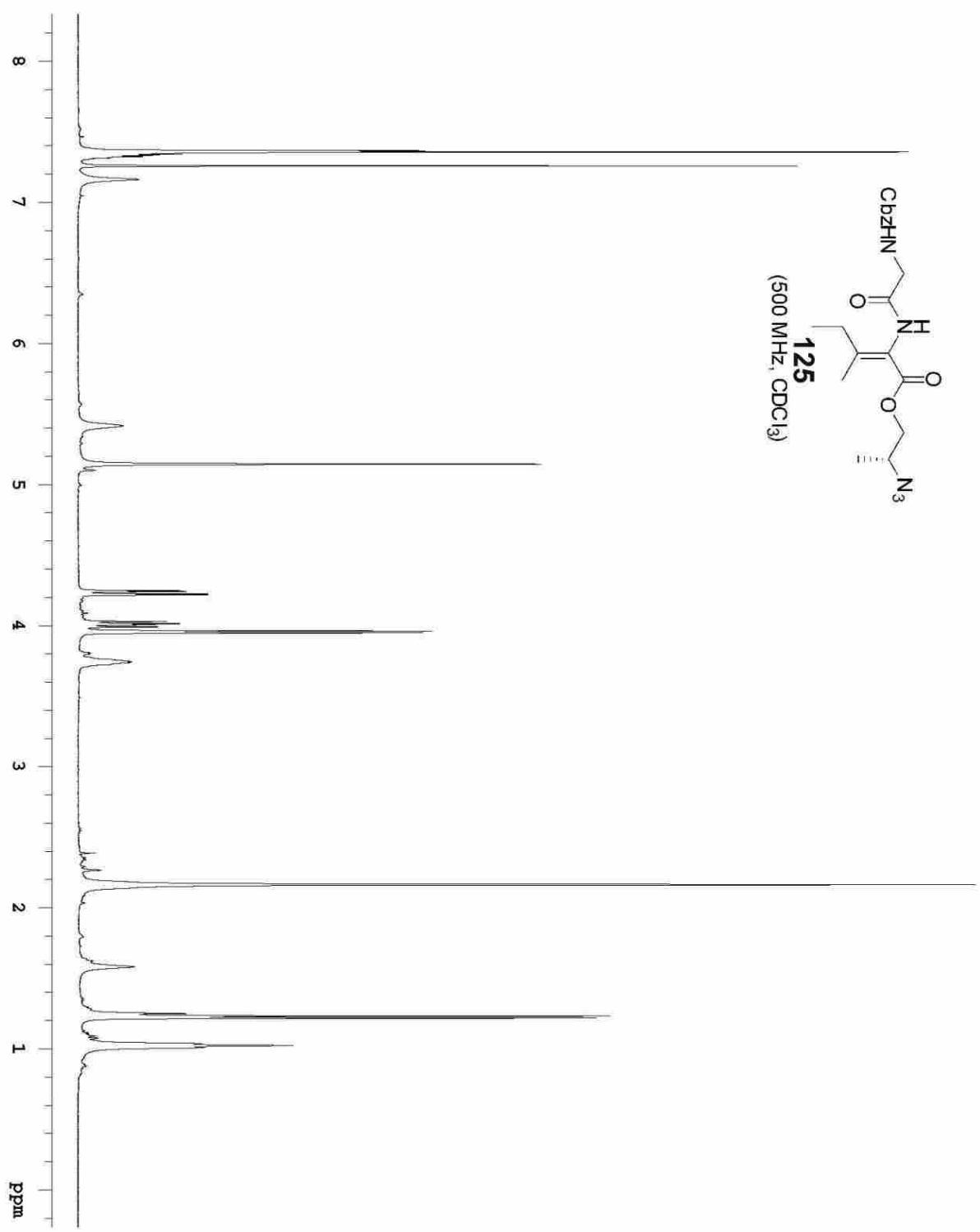

CbzHN
O
H
N
O
O
O
N3
122b
125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
0 ppm

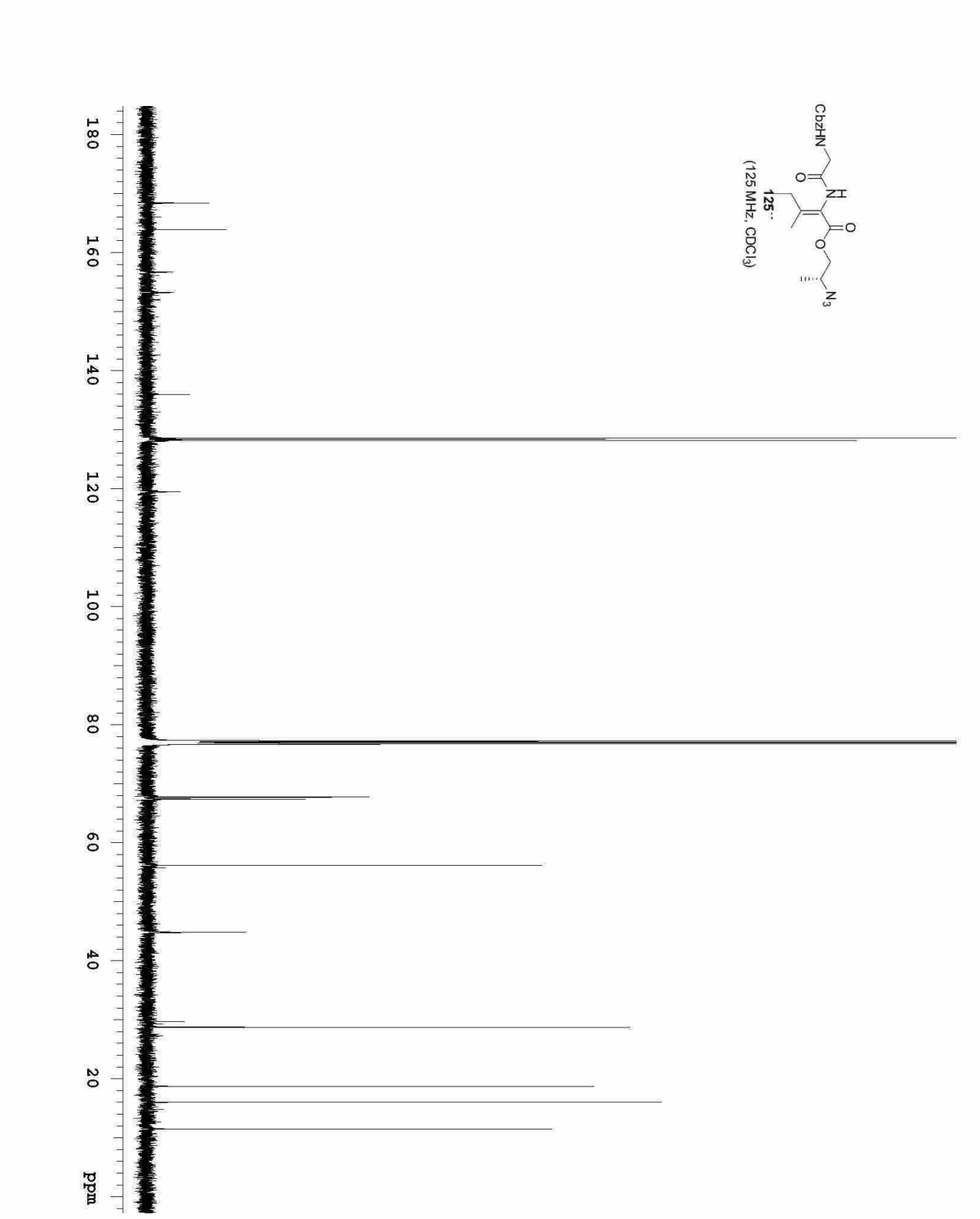

CbzHN
H
N
O
O
N
H
OH
123
500 MHz, CDCl3
Minor
isomer
9
8
7
6
5
4
3
2
1
0
ppm
4.83
0.87
0.94
2.00
2.14
2.14
1.53
1.17
2.06
0.19
2.68
0.15
5.01
5.64
2.72

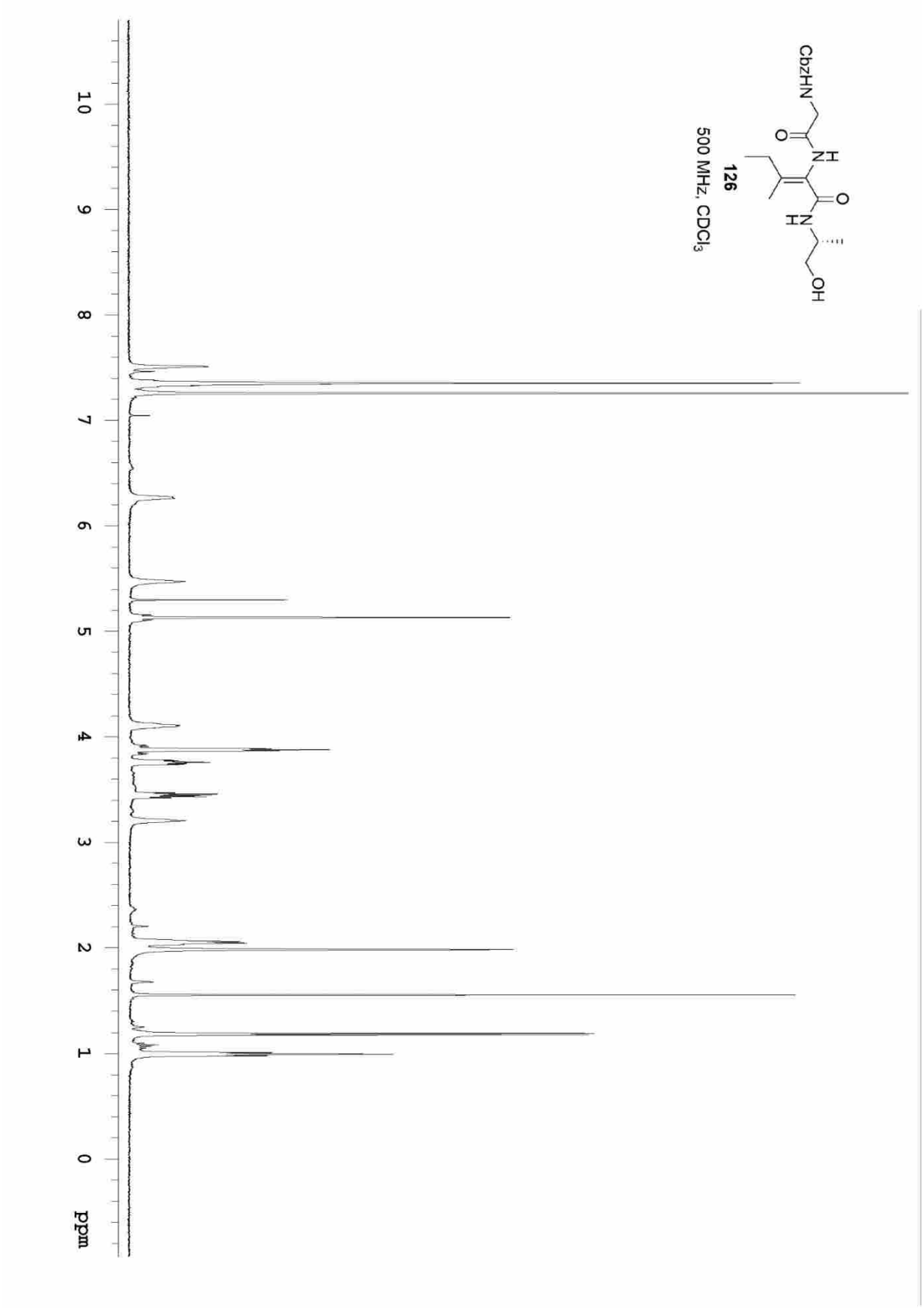

CbzHN
O
H
N
O
H
N
O
OH
123
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

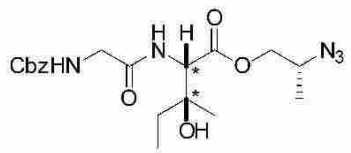

CbzHN
O
N
H
H
O
OH
O
N3
124
(500 MHz, CDCl3)
7
6
5
4
3
2
1
ppm


CbzHN
O
N
H
H
O
OH
O
O
N3
124
(125 MHz, CDCl3)
180
160
140
120
100
80
60
40
20
ppm


CbzHN
H
N
O
O
O
O
N3
125
(500 MHz, CDCl3)
8
7
6
5
4
3
2
1
ppm

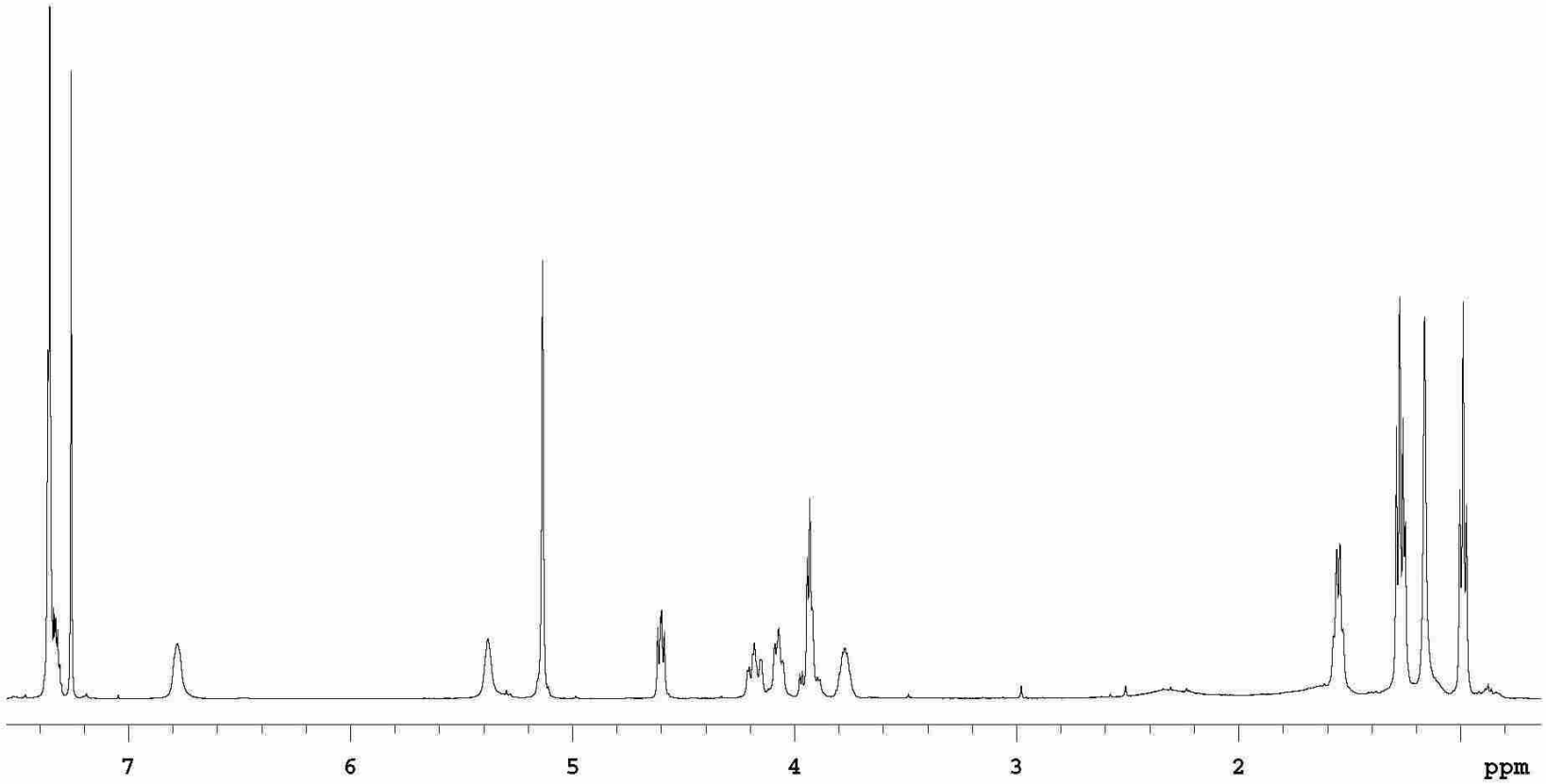

CbzHN
O
H
N
O
O
O
N3
125
(125 MHz, CDCl3)
180
160
140
120
100
80
60
40
20
ppm

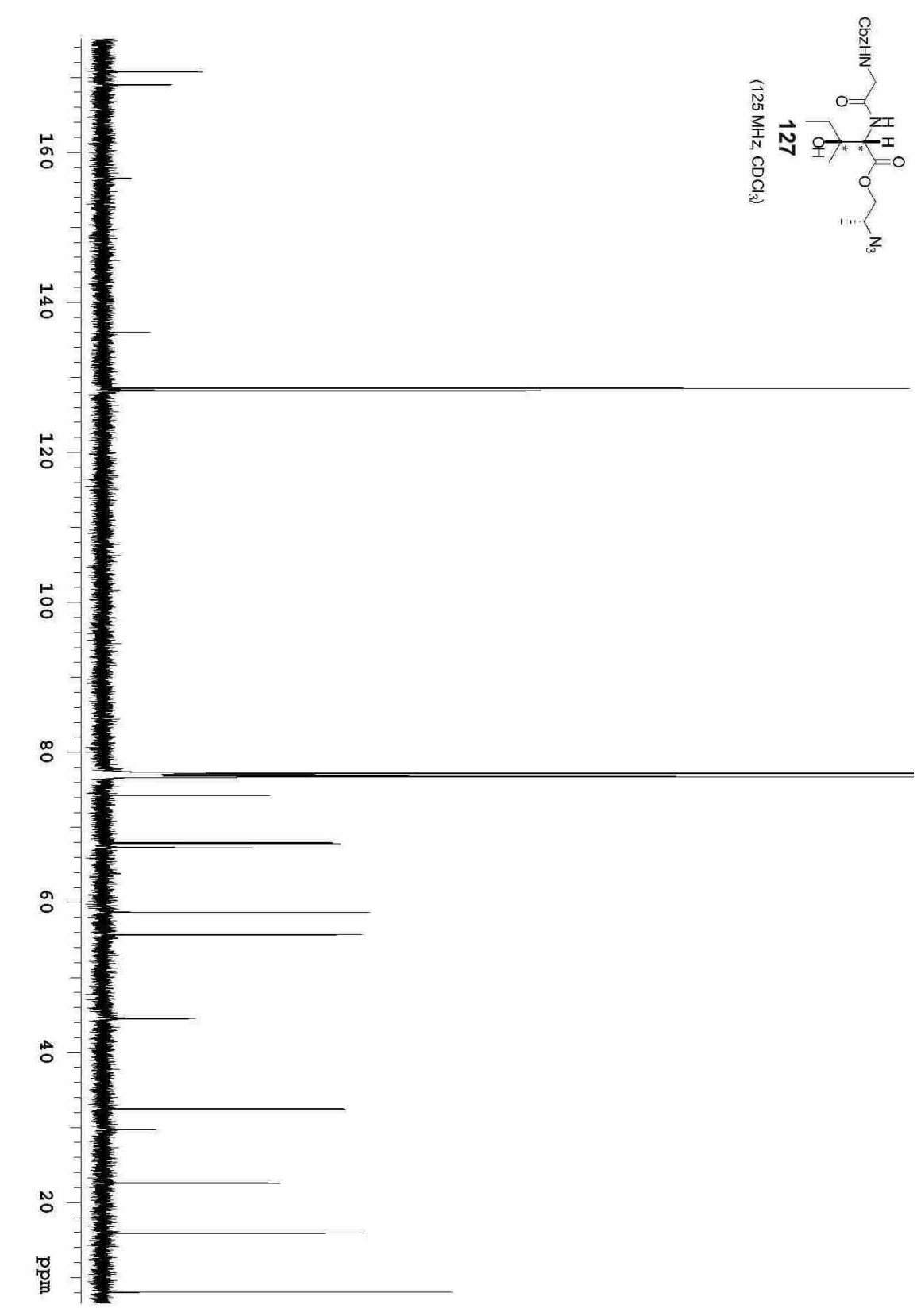

CbzHN
O
H
N
O
H
N
OH
126
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm

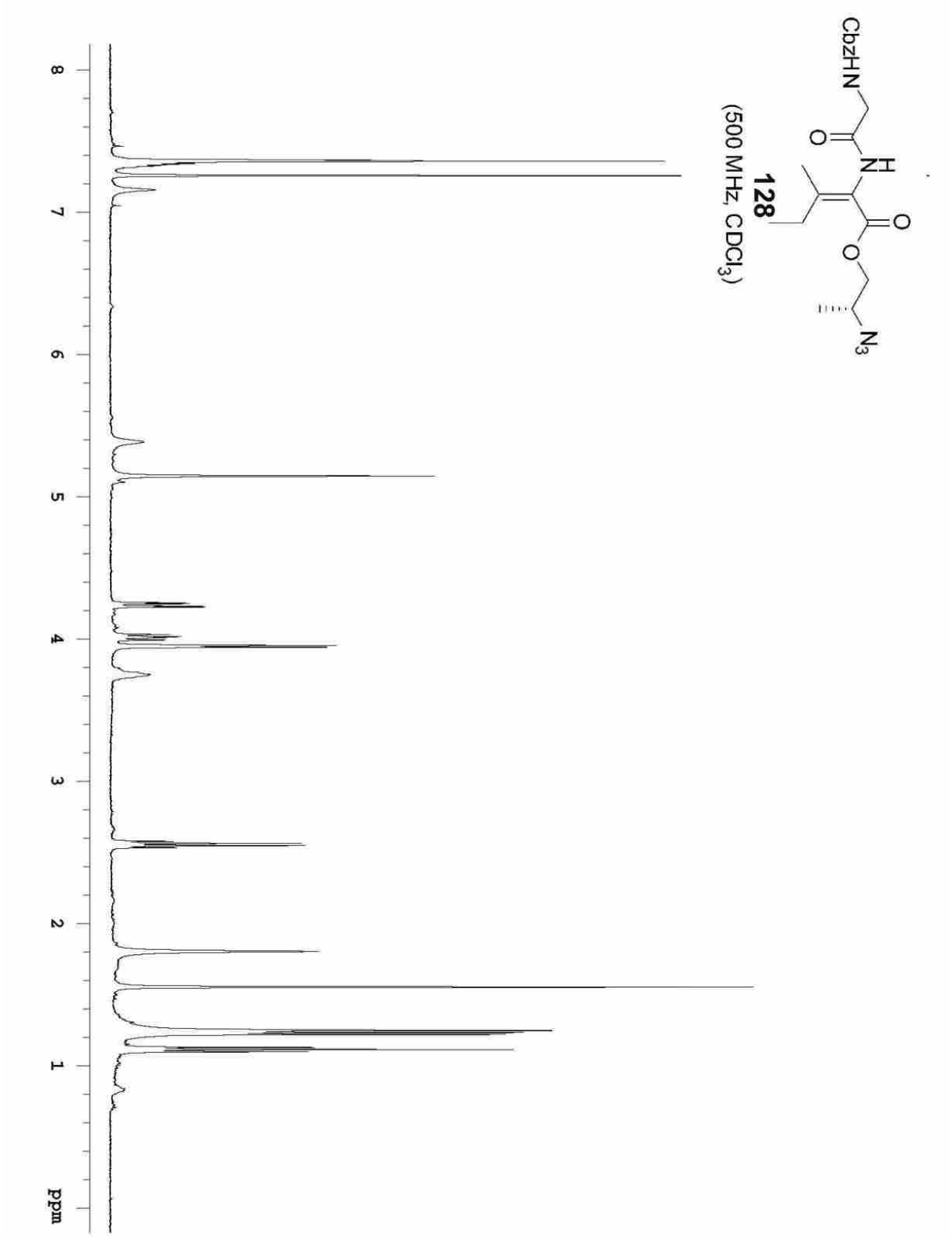


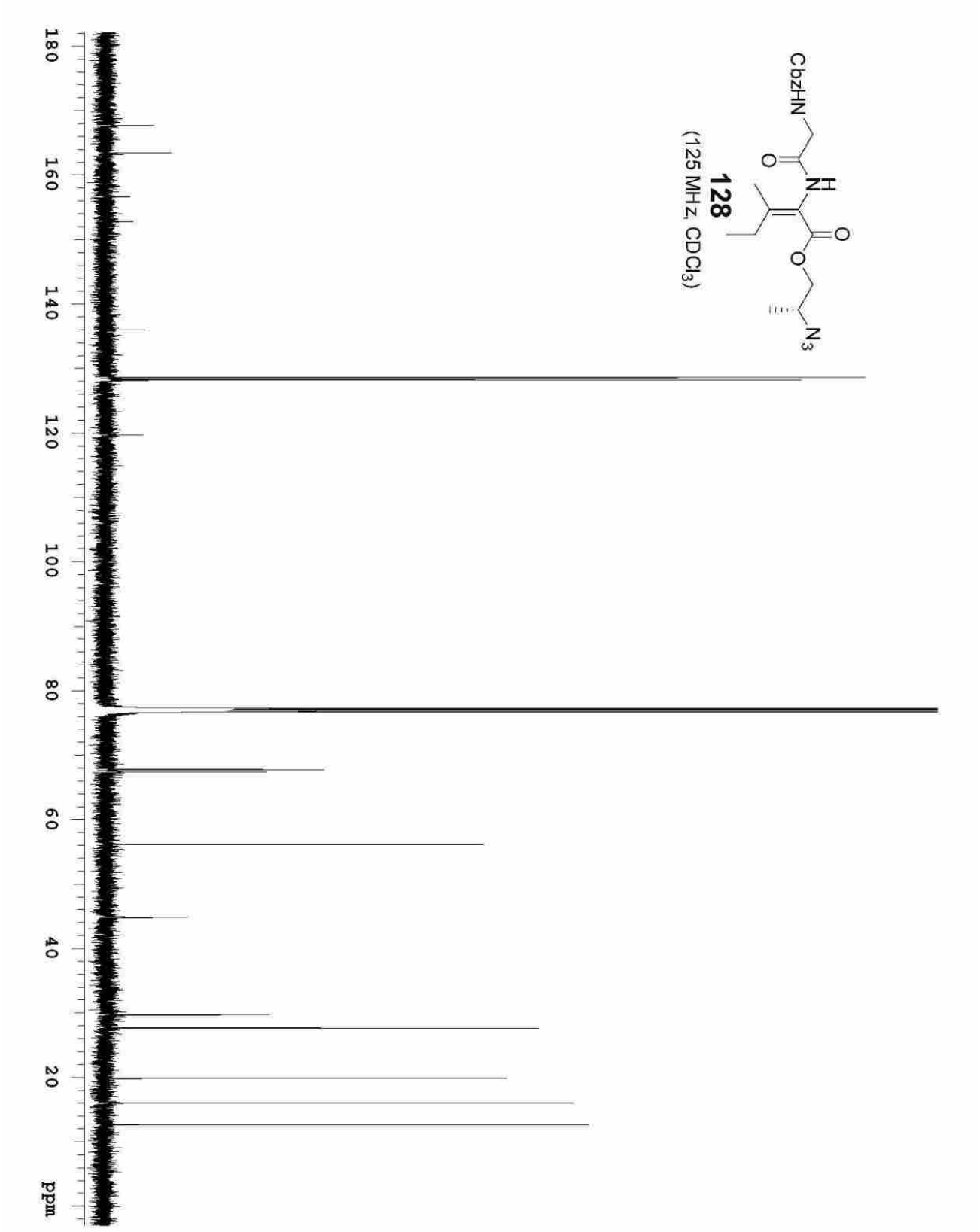
127

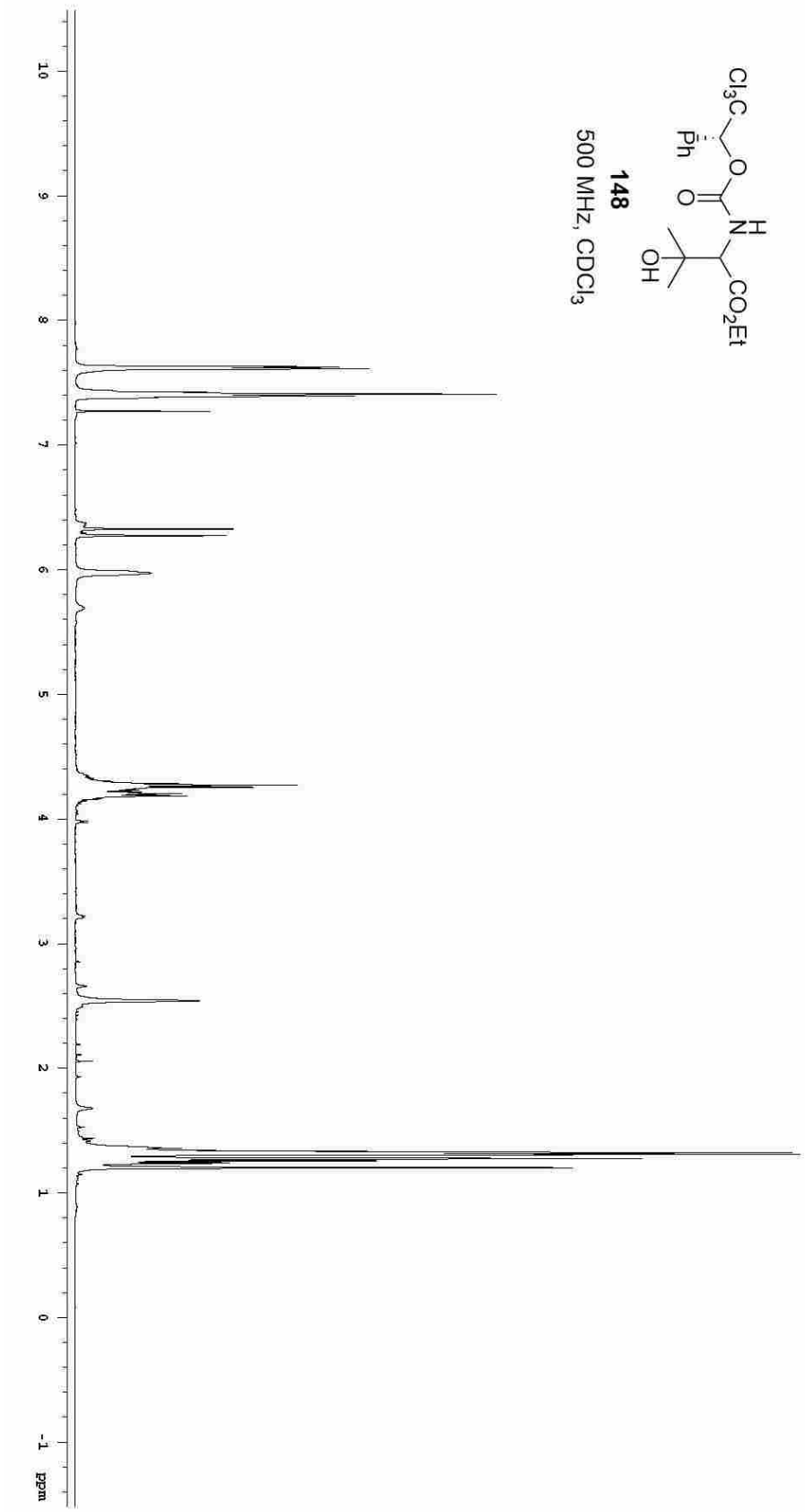
(500 MHz, $CDCl_3$)

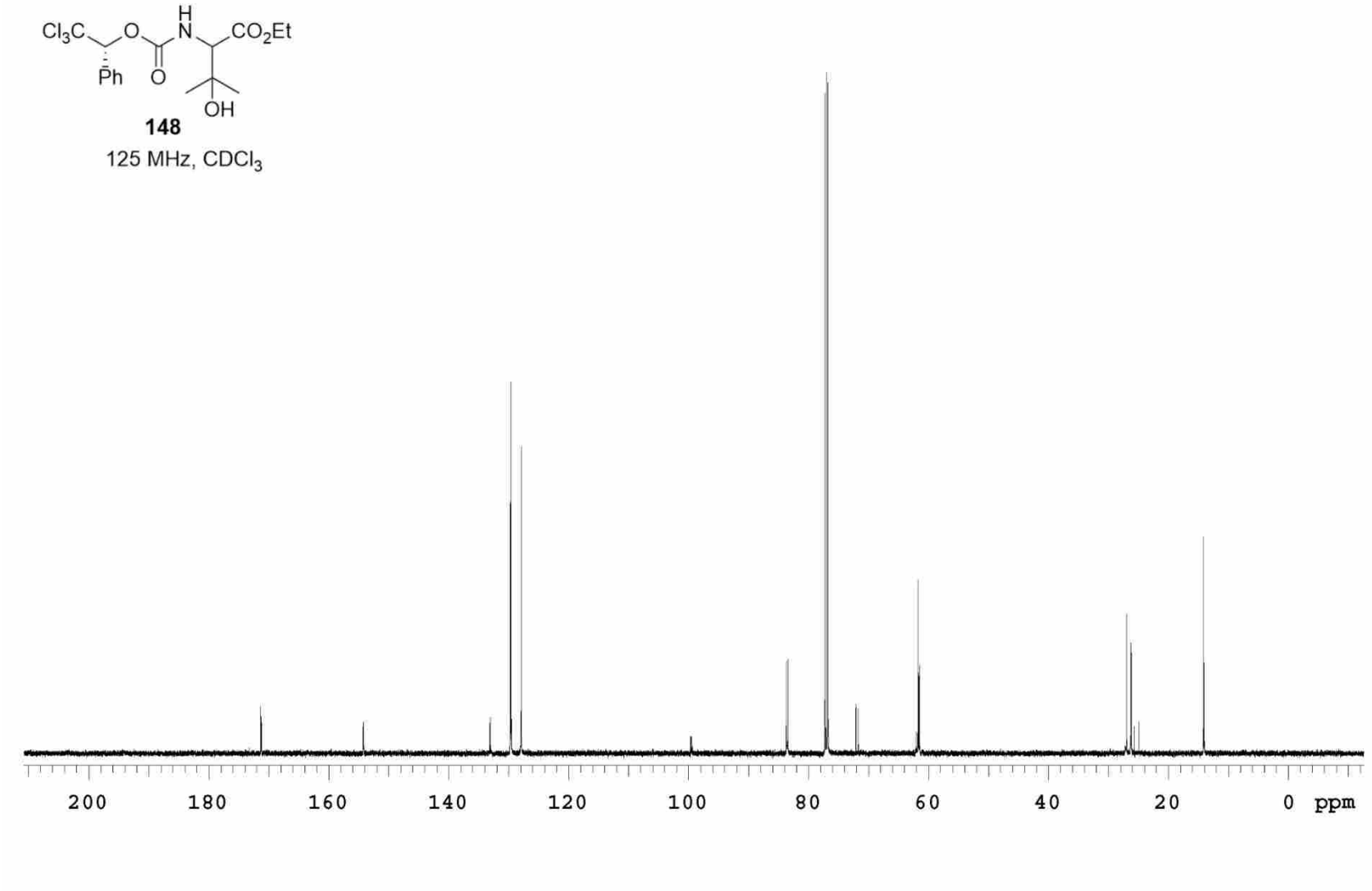


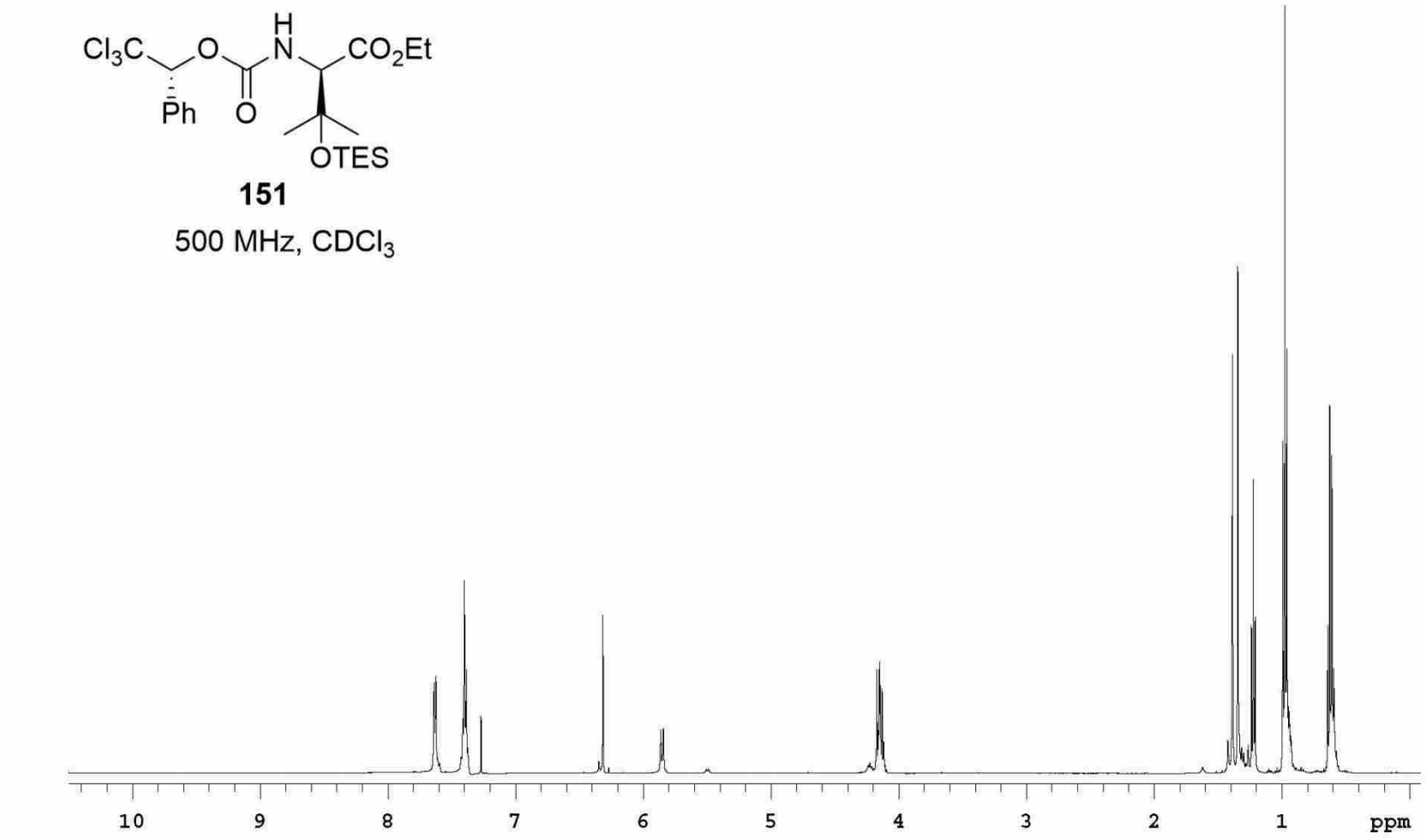

CbzHN
O
N
H
H
O
O
OH
N3
127
(125 MHz, CDCl3)
160
140
120
100
80
60
40
20
ppm

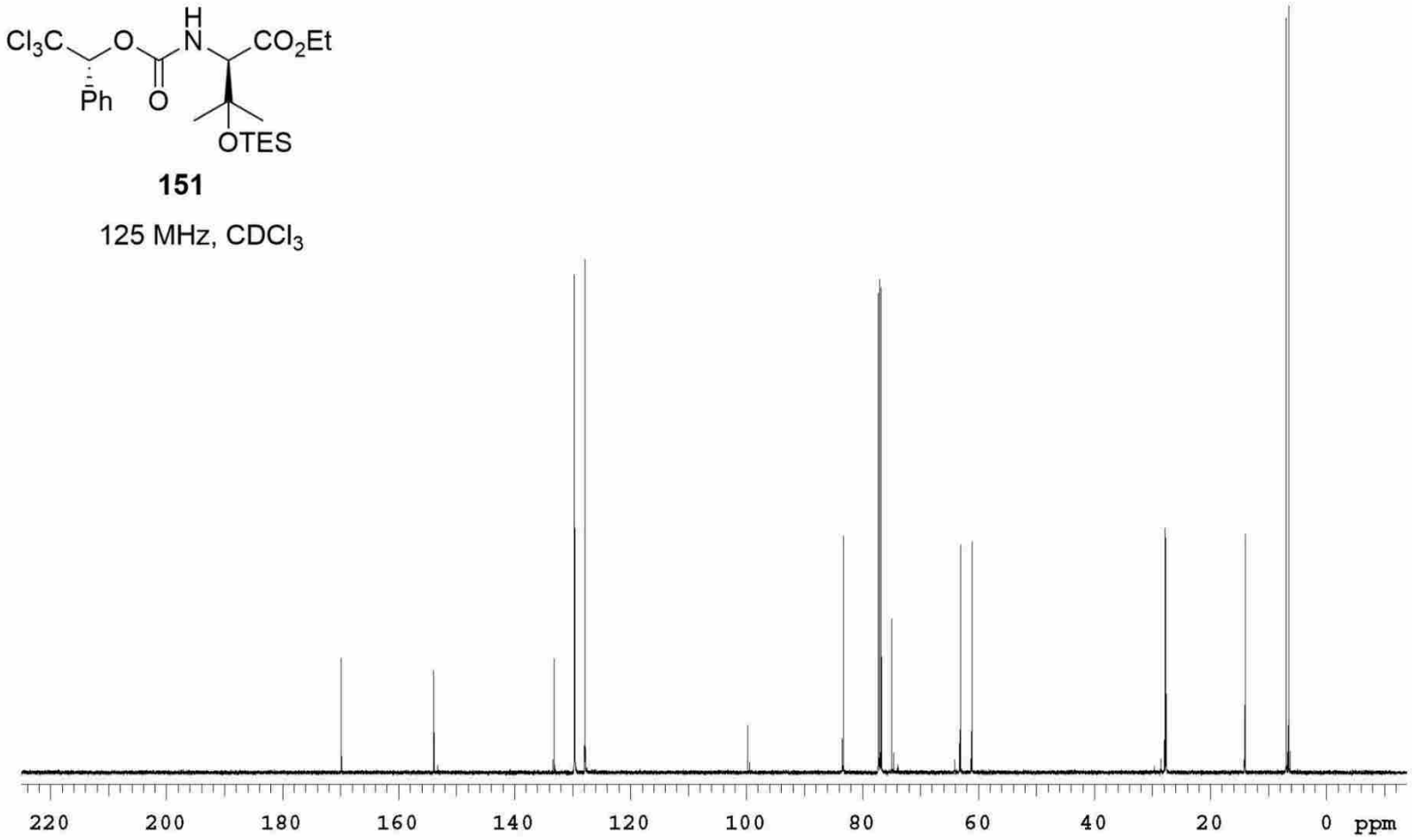

CbzHN
O
H
N
O
O
O
N3
128
(500 MHz, CDCl3)
8
7
6
5
4
3
2
1
ppm

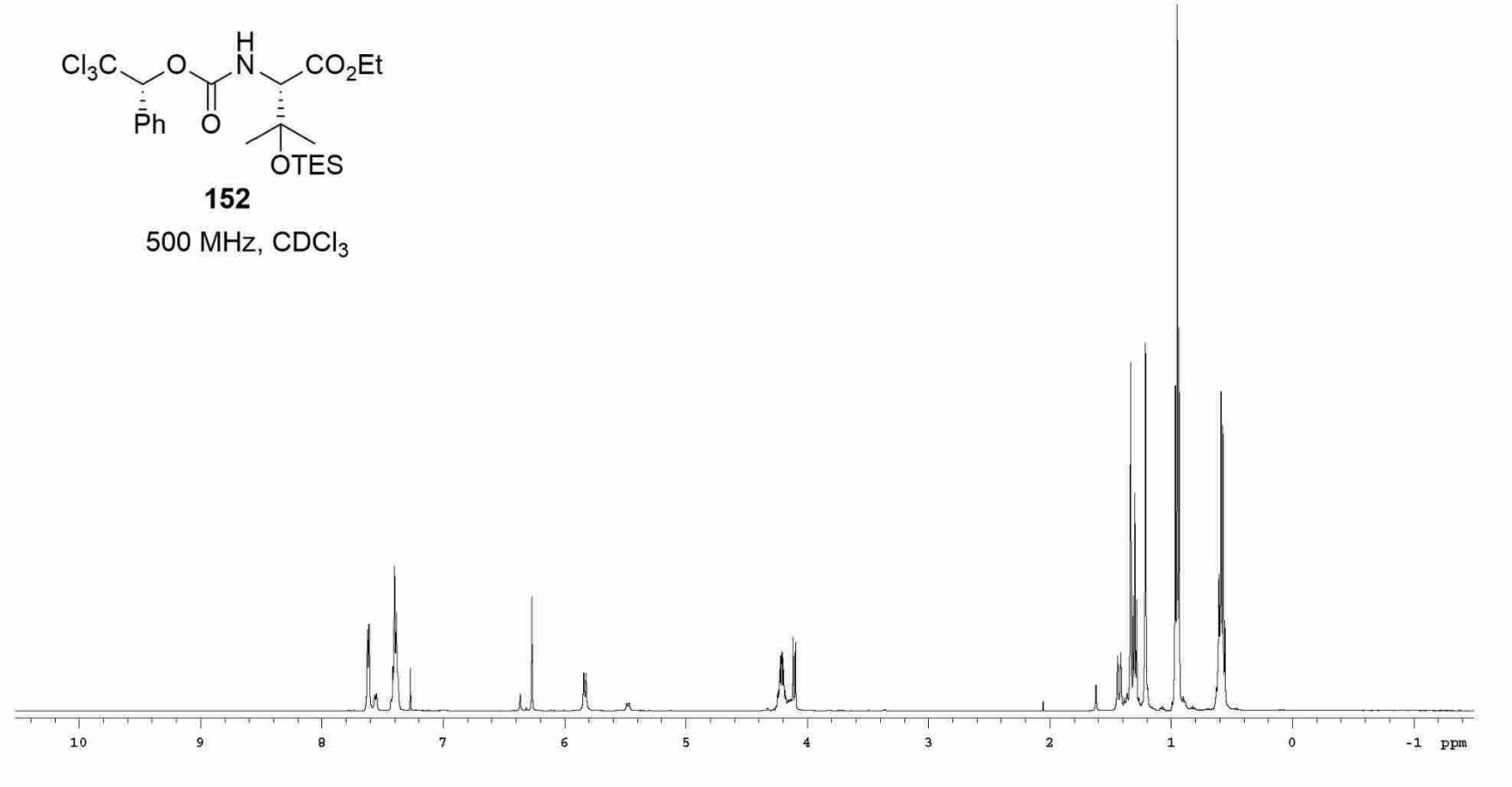

CbzHN
O
H
N
O
O
O
N3
128
(125 MHz, CDCl3)
180
160
140
120
100
80
60
40
20
ppm

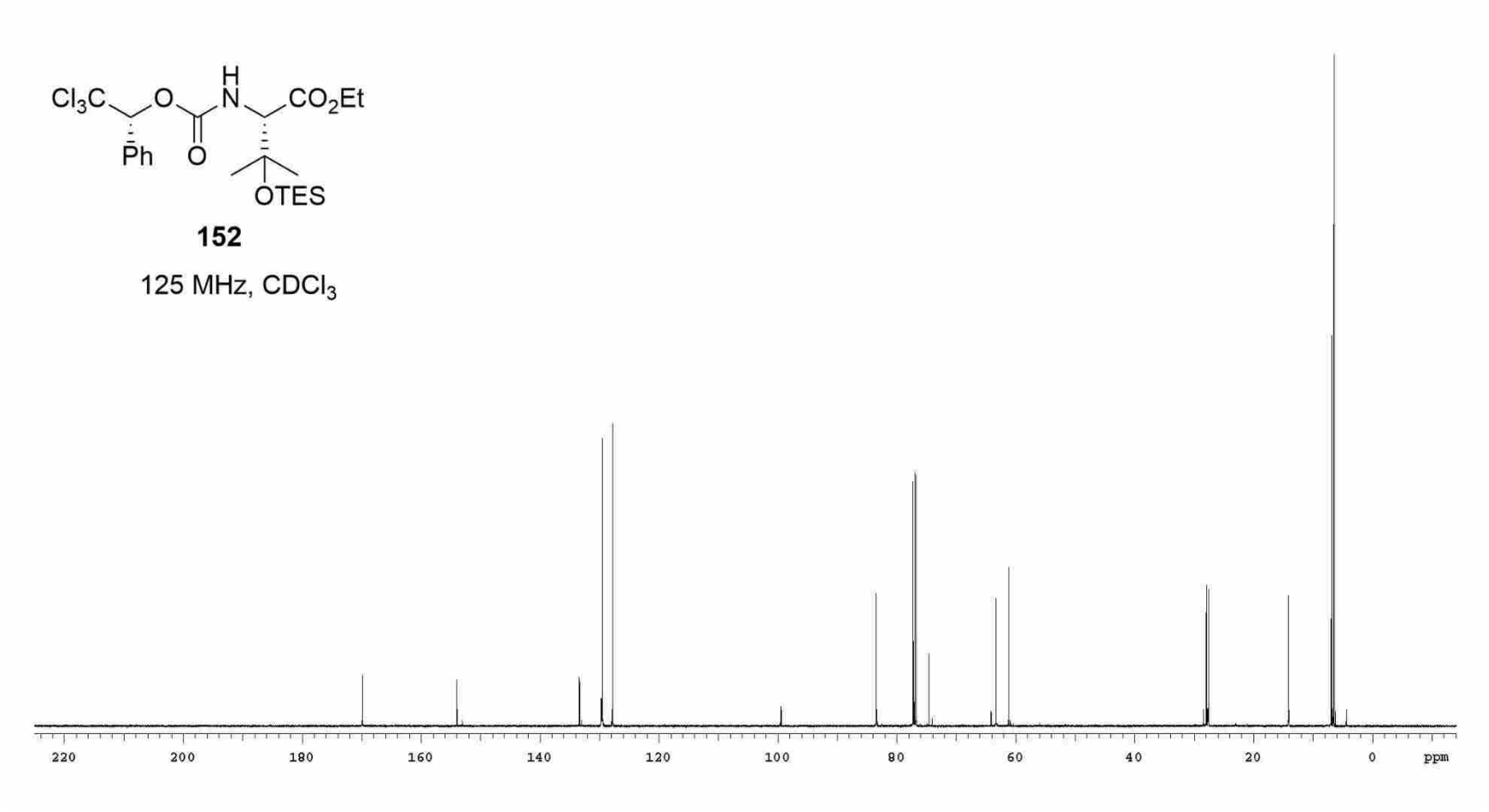

Cl3C
O
Ph
O
H
N
CO2Et
OH
148
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

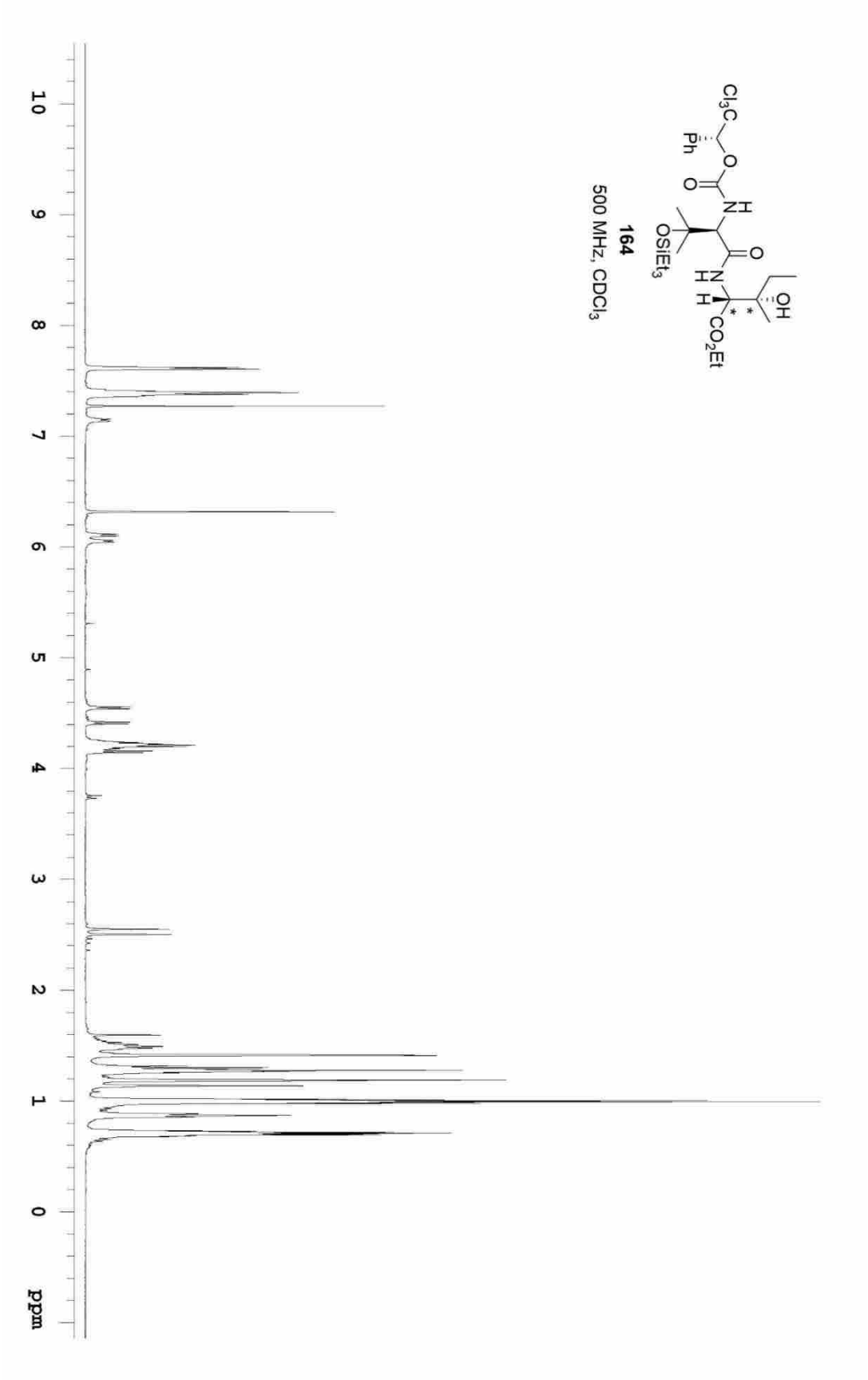

Cl3C
O
H
N
CO2Et
Ph
O
OH
148
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm

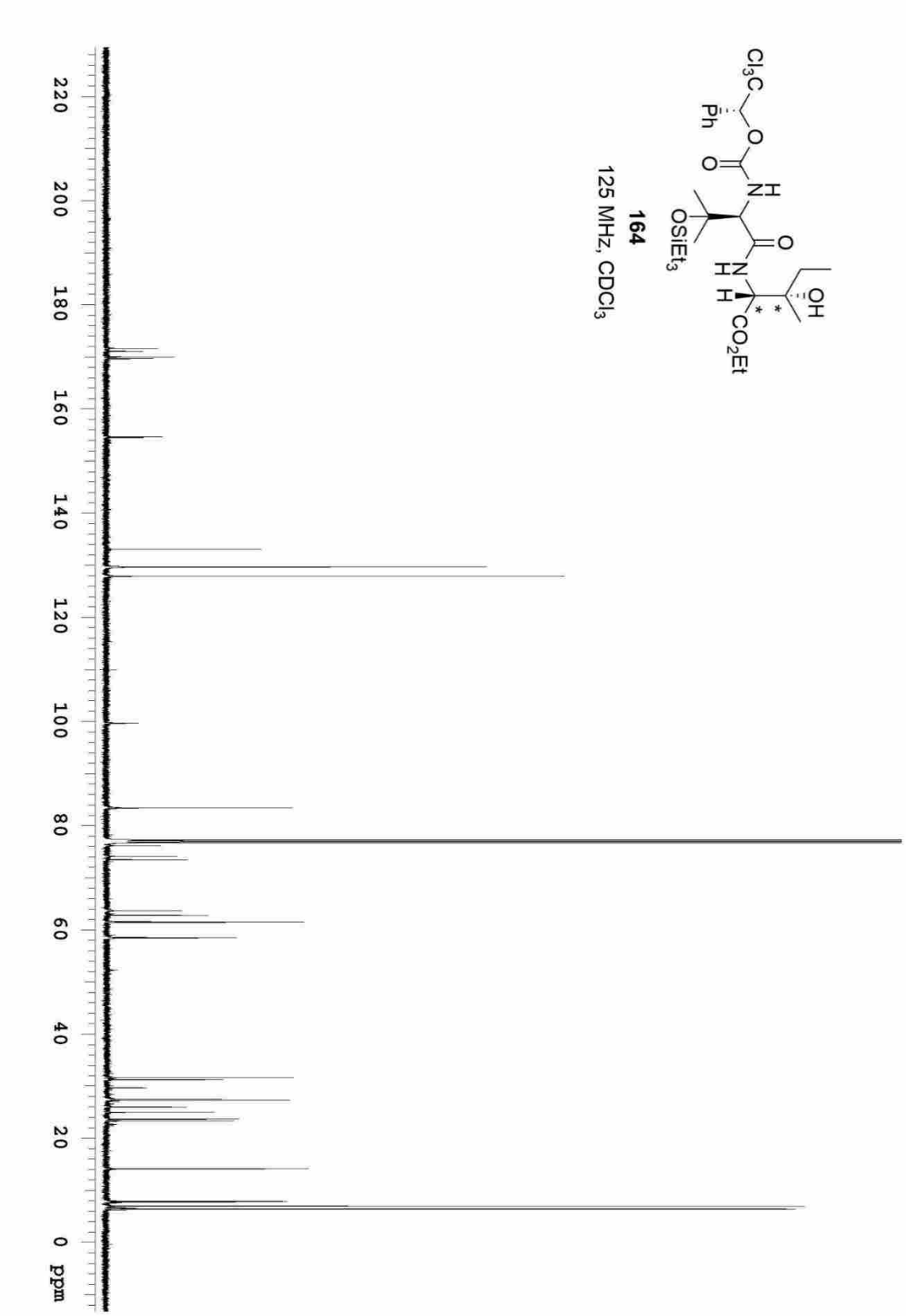

Cl3C
O
H
N
CO2Et
Ph
O
OTES
151
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
ppm

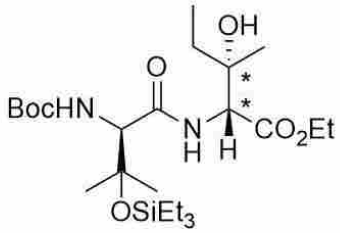

Cl3C
O
H
N
CO2Et
Ph
O
OTES
151
125 MHz, CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Cl3C
O
H
N
CO2Et
Ph
O
OTES
152
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


Cl3C
O
H
N
CO2Et
Ph
O
OTES
152
125 MHz, CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

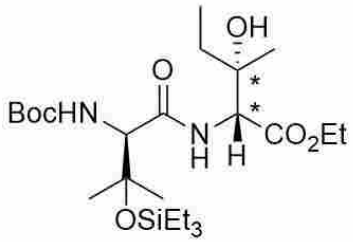

Cl3C
Ph
O
H
N
O
OSiEt3
N
H
H
CO2Et
OH
164
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm


Cl3C
Ph
O
H
N
O
OSiEt3
O
H
N
H
CO2Et
OH
164
125 MHz, CDCl3
220
200
180
160
140
120
100
80
60
40
20
0 ppm



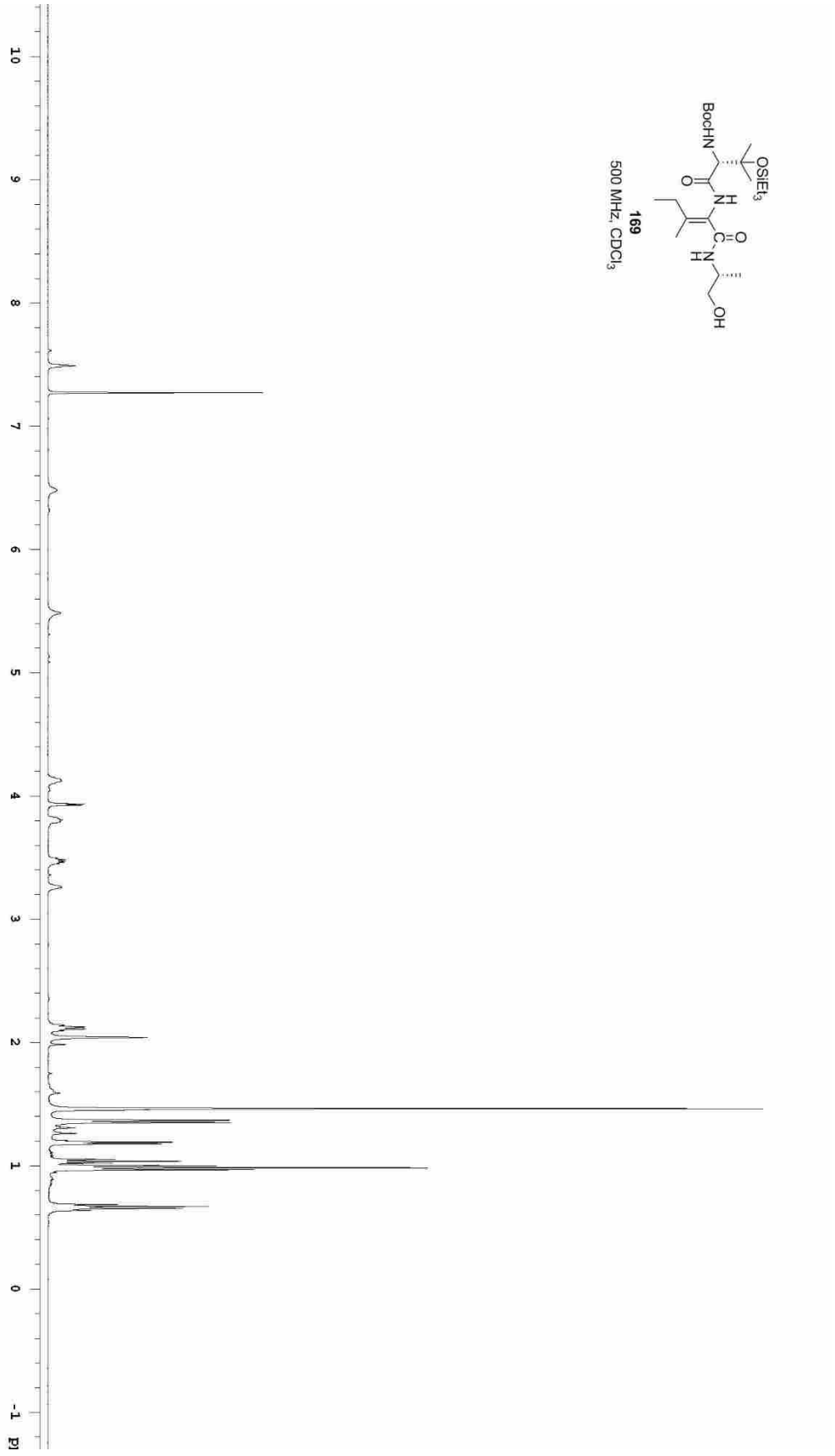
166

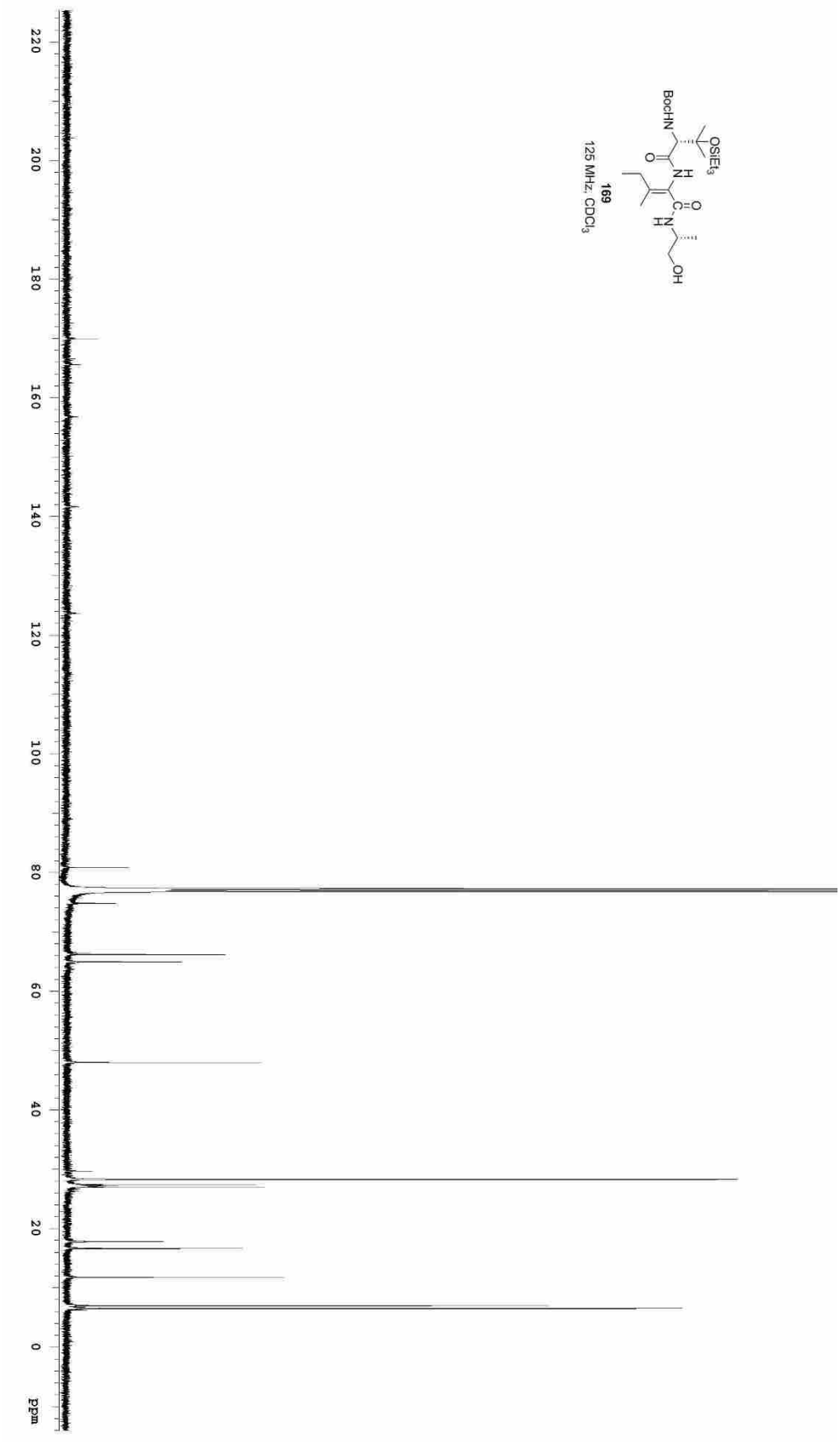
500 MHz, $CDCl_3$

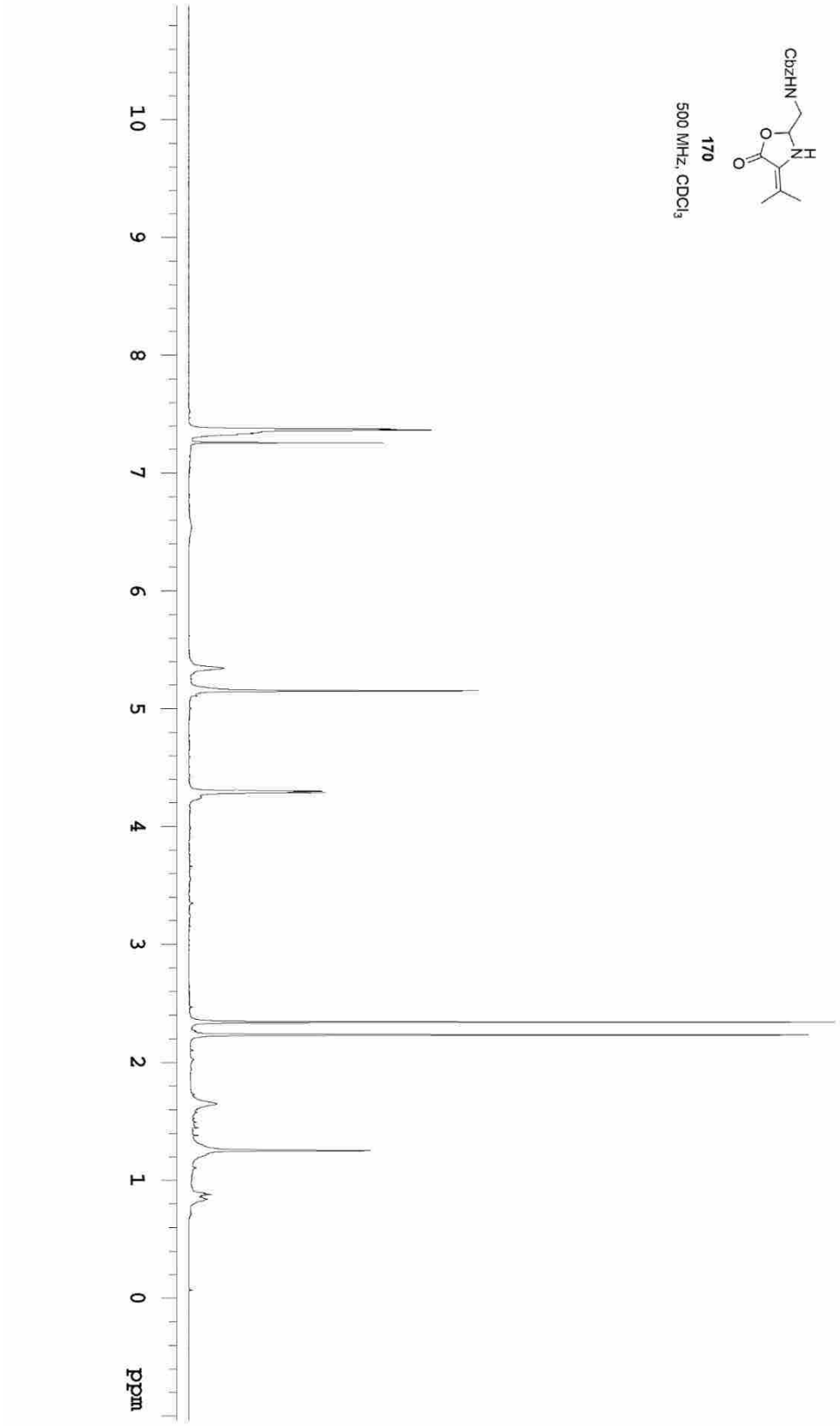


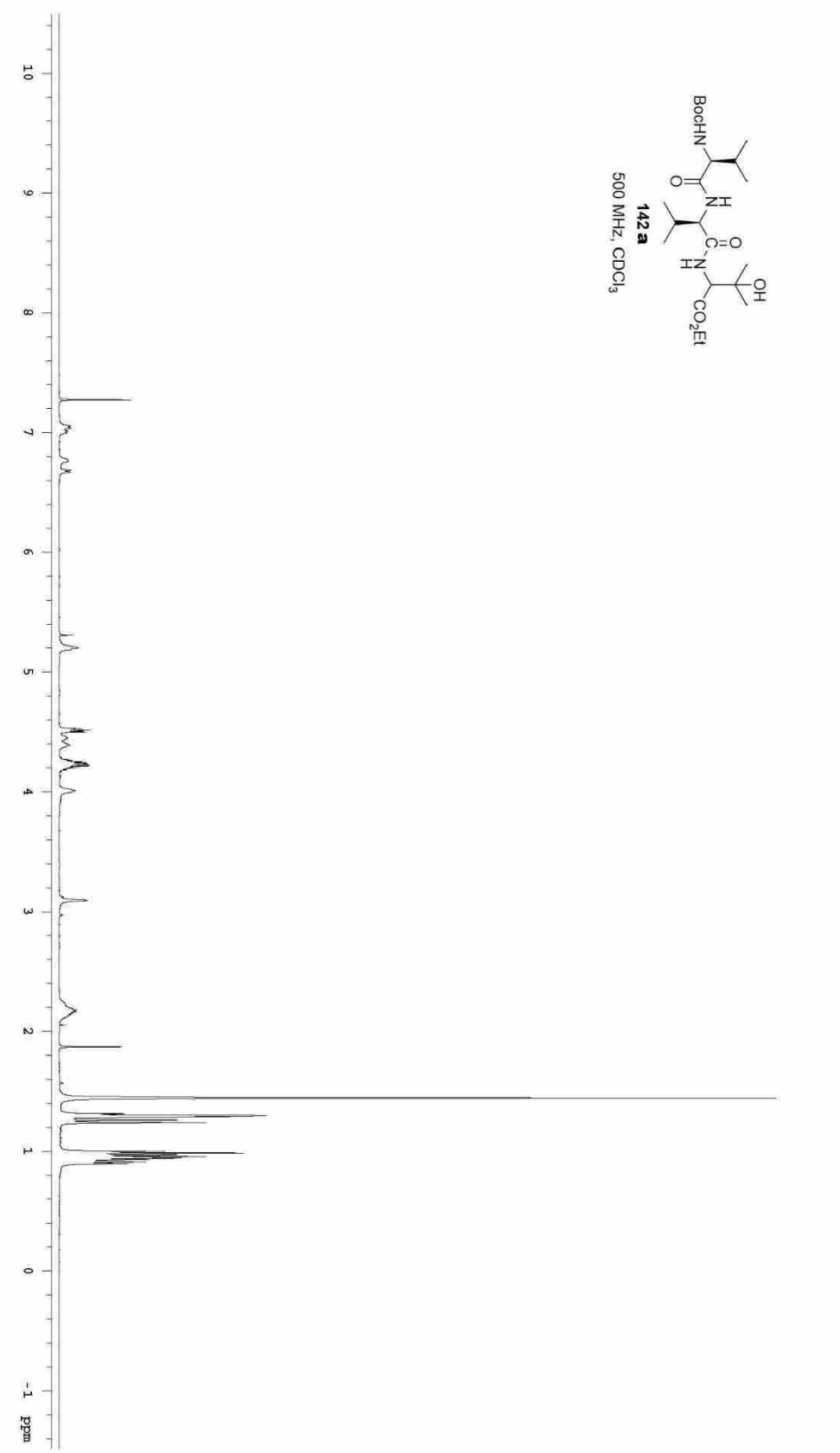
166

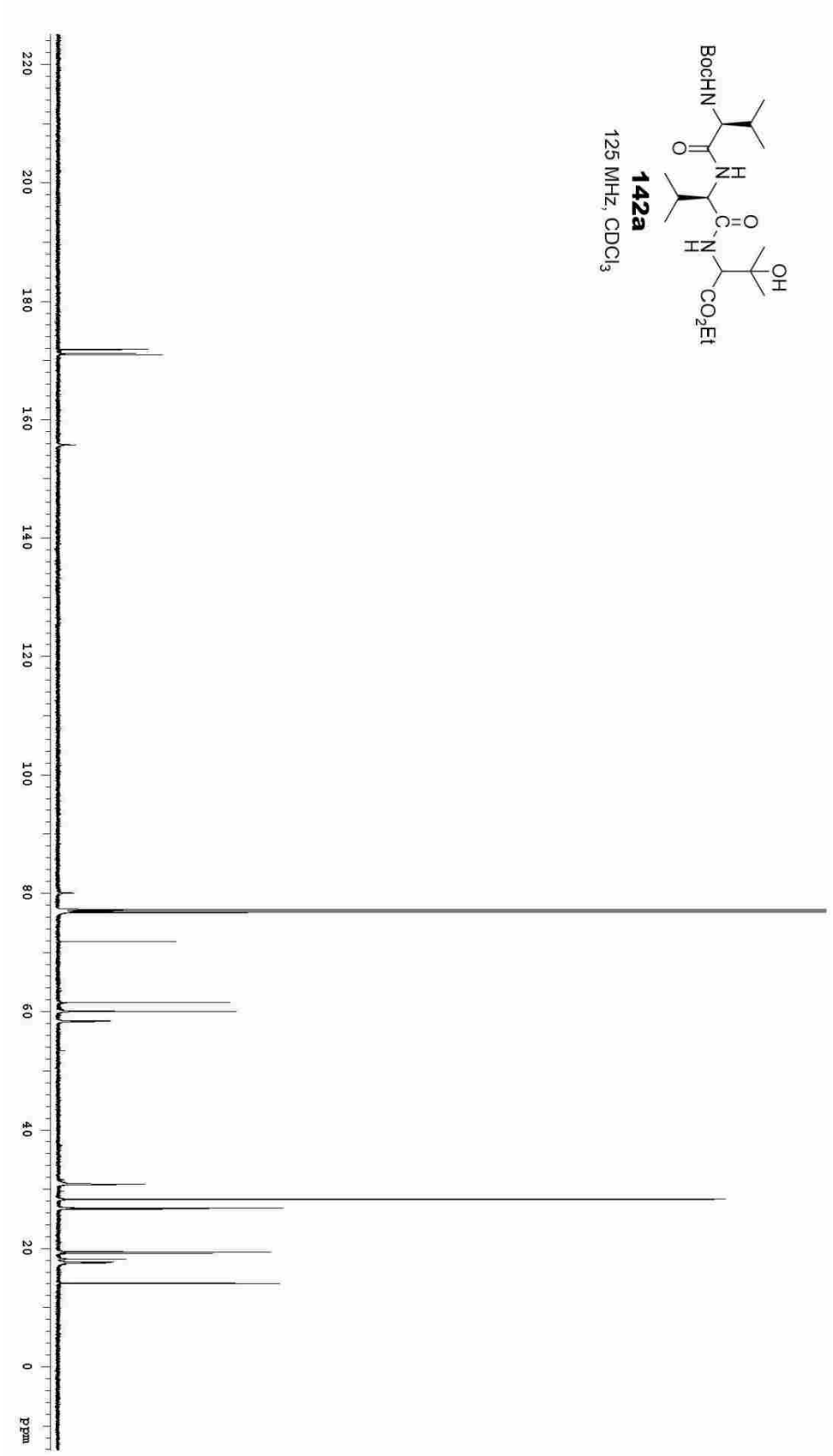
125 MHz, $CDCl_3$

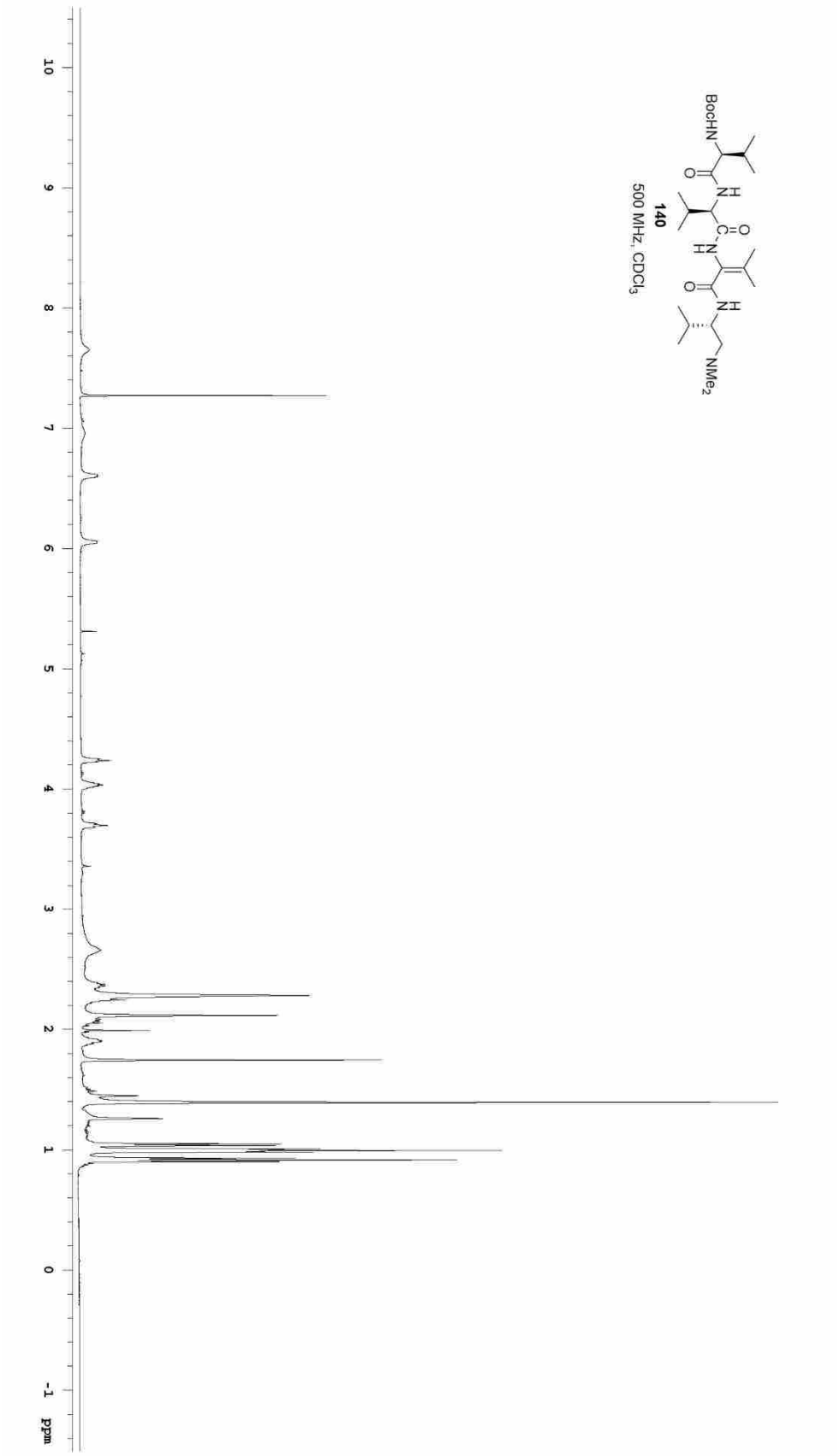

BocHN
OSiEt3
169
500 MHz, CDCl3
OH
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

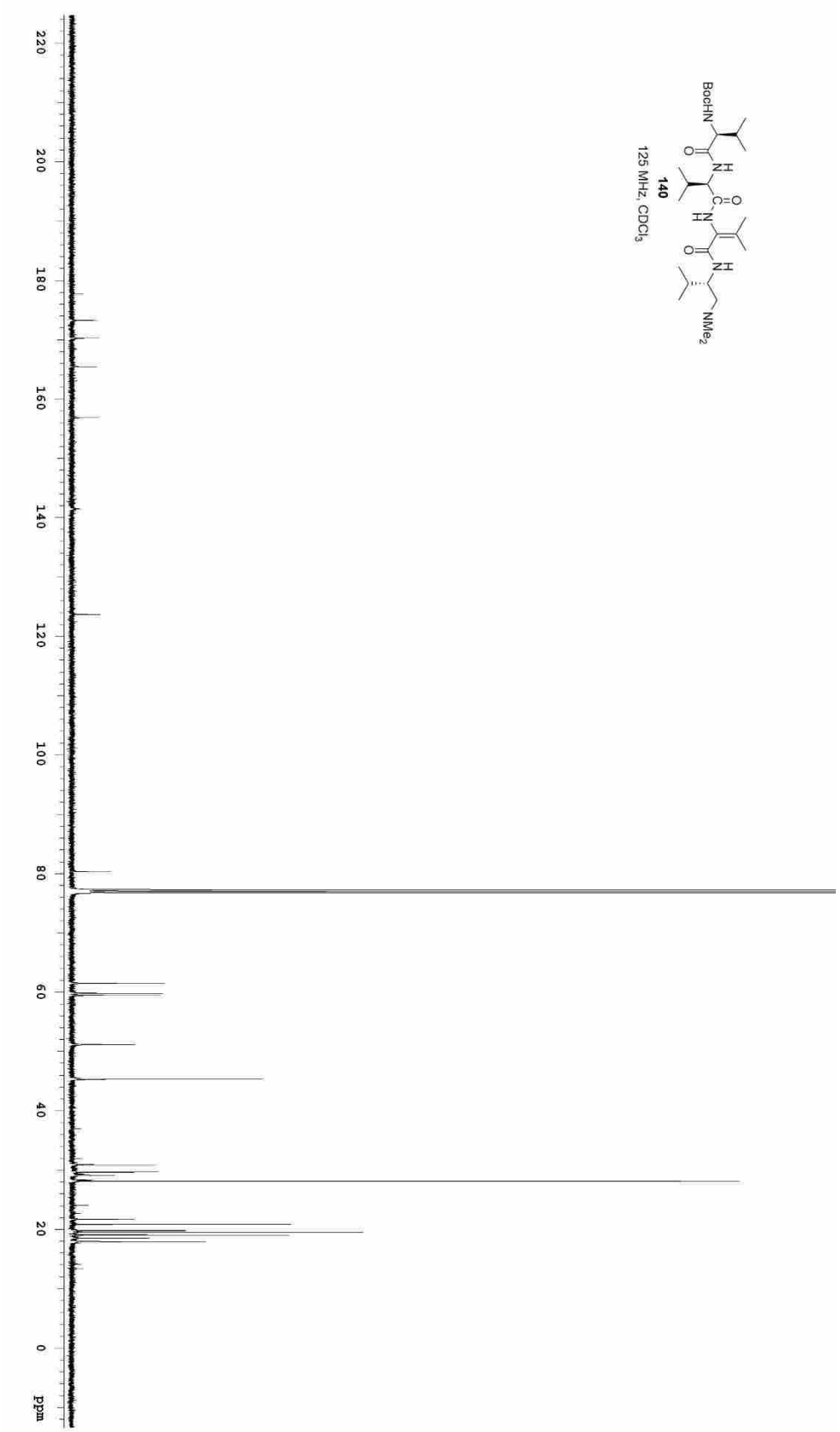

169
125 MHz; $CDCl_3$
BocHN
OSiEt$_3$
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

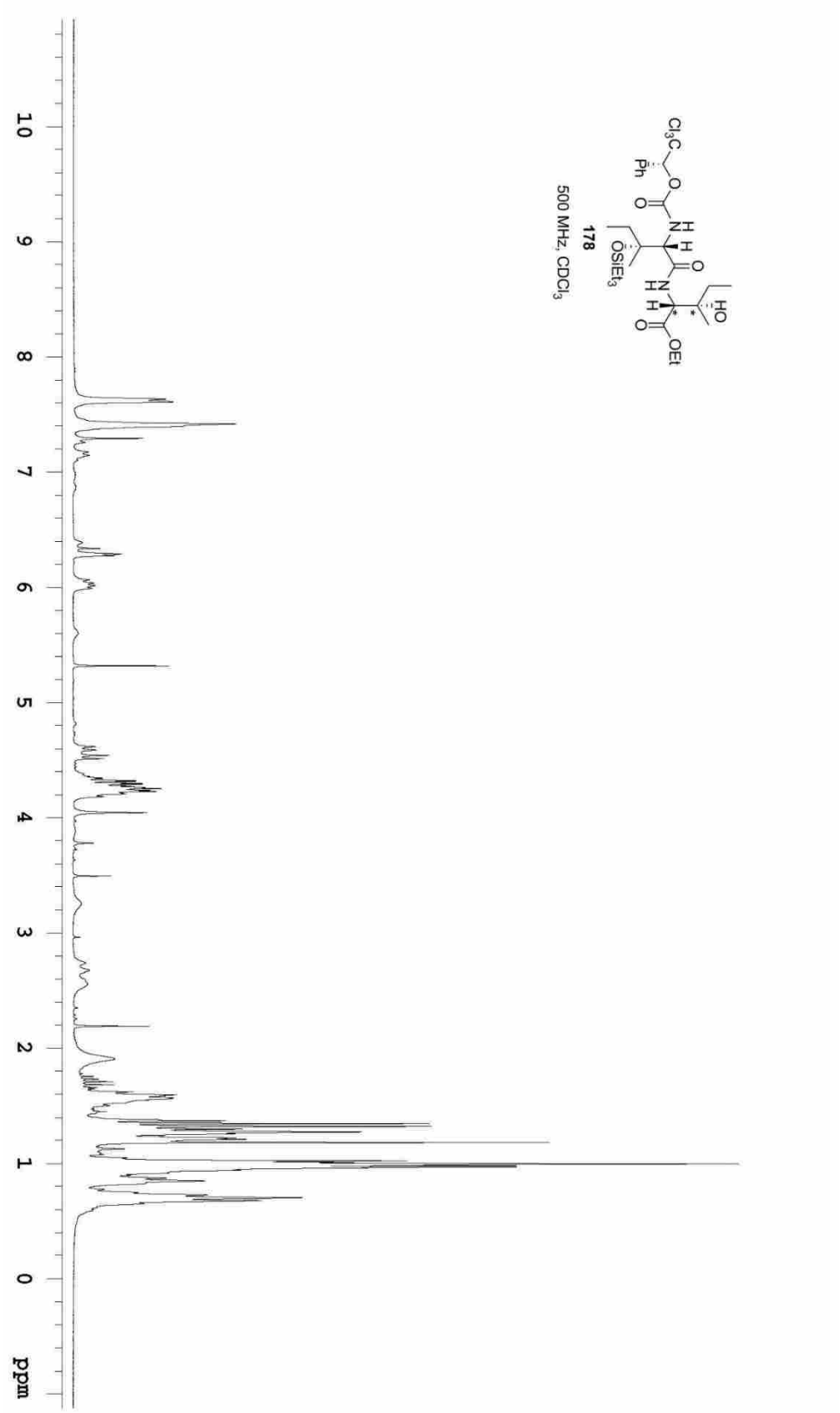

CbzHN
O
O
H
N
O
170
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm

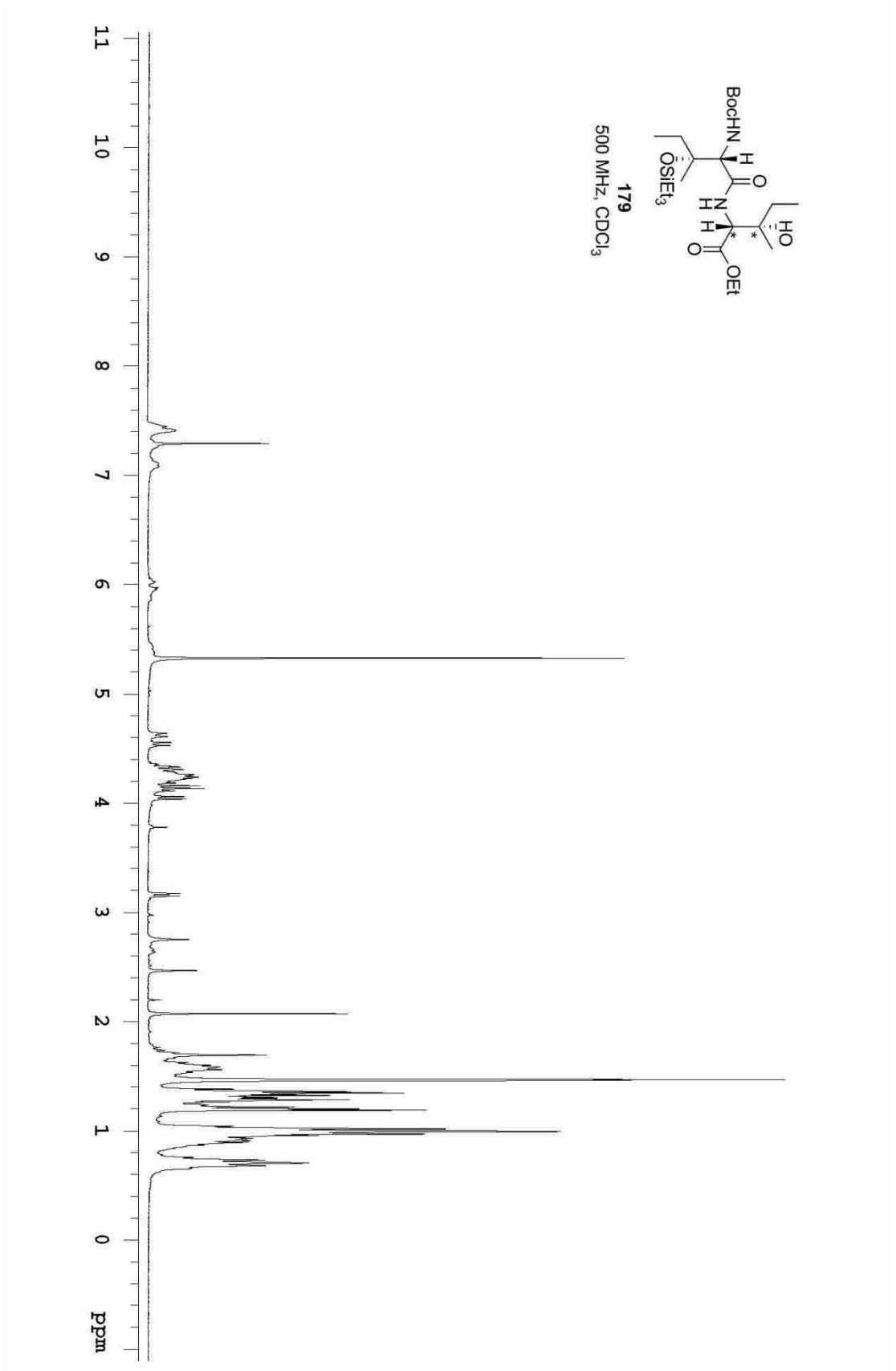

BocHN
O
H
N
O
C
N
H
OH
CO2Et
142 a
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

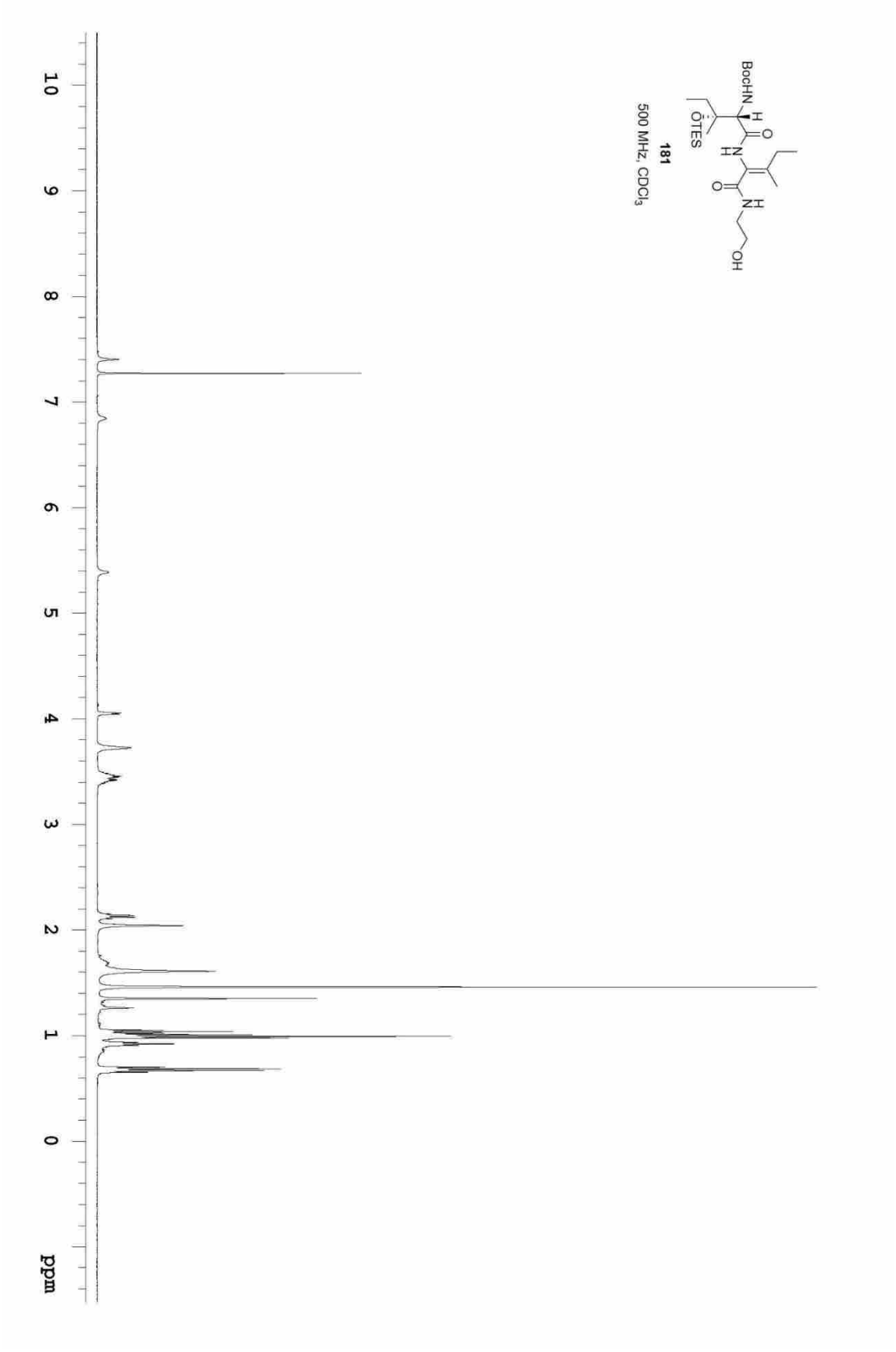

BocHN
H
N
O
O
C
N
H
OH
CO2Et
142a
125 MHz, CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

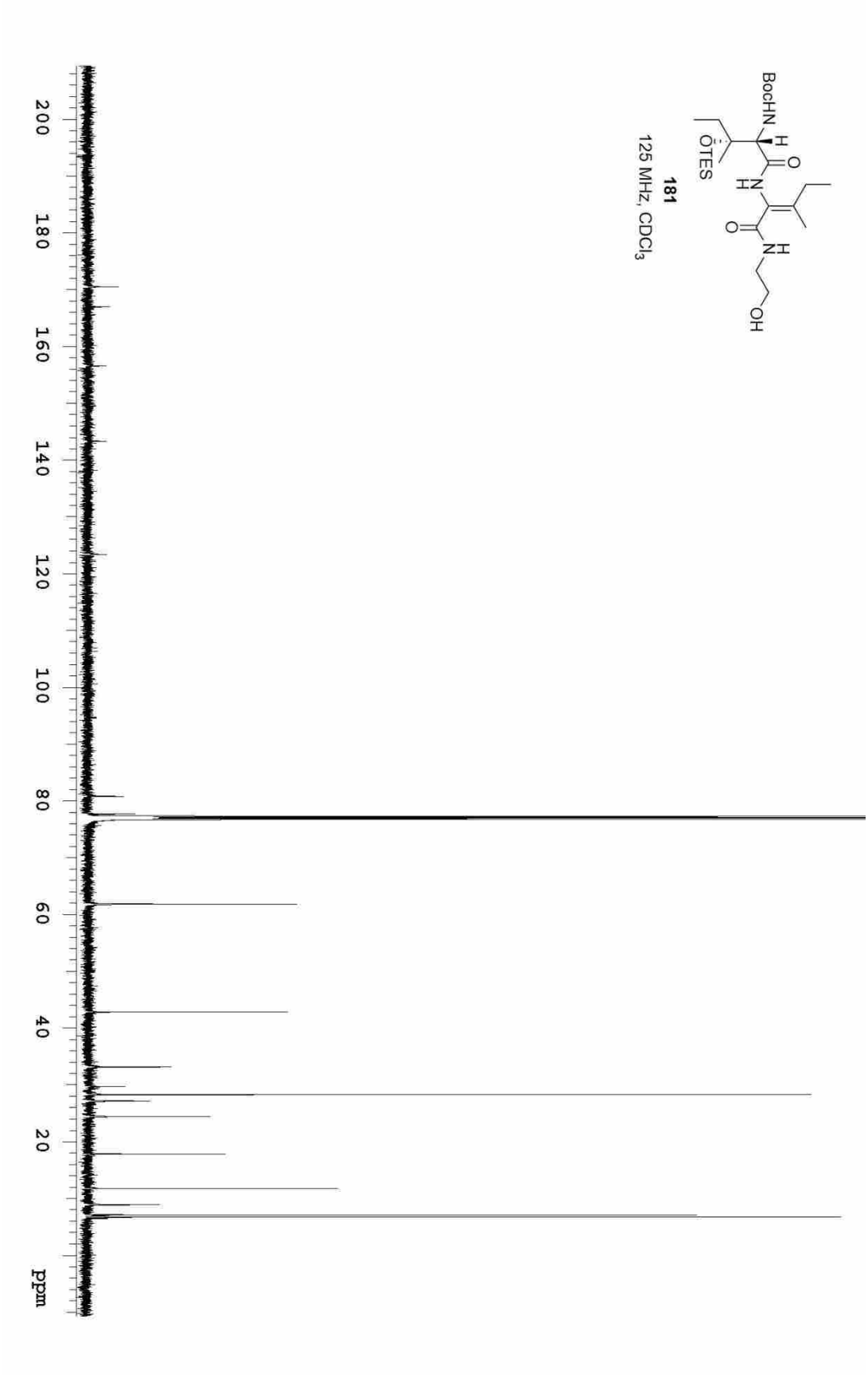

BocHN
NMe2
140
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


BocHN
NMe2
140
125 MHz, CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Cl3C
Ph
O
O
H
N
H
O
OSiEt3
N
H
O
HO
OEt
178
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm


BocHN
OSiEt3
HO
OEt
179
500 MHz, CDCl3
11
10
9
8
7
6
5
4
3
2
1
0
ppm


BocHN
OTES
OH
181
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm


BocHN
H
O
N
H
O
N
H
OH
ÖTES
181
125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
ppm