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SUPPORTING INFORMATION

Directed Functionalization of 1,2-Dihydropyridines: Stereoselective Synthesis of 2,6-Disubstituted Piperidines

Guillaume Pelletier, Léa Constantineau-Forget, and André B. Charette*

Department of Chemistry, Faculty of Arts and Sciences, Université de Montréal, P.O. Box 6128, Station Downtown, Québec, Canada H3C 3J7. E-Mail: andre.charette@umontreal.ca

Experimental procedures, characterization data, ^{1}H, ^{13}C, and ^{19}F for new compounds

Table of Contents

General Information

Unless otherwise stated, reactions were run under an argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[1] All glassware was flame-dried prior to use. THF and Et_2O were obtained by filtration through drying columns on a filtration system. MeOH was distilled over prior to its use. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Silicycle Glass Backed TLC Extra Hard Layer, 60 Å). Visualization of the developed chromatogram was performed by UV, aqueous potassium permanganate ($KMnO_4$), ceric ammonium molybdate (CAM), or ninhydrin. Flash column chromatography were performed on an automatic purification system (Teledyne Isco Combiflash® Companion or Sq16x) or on a glass chromatography column support. Prepacked normal phase silica gel column was used for separation of products using Teledyne Isco Redi*Sep*® Rf High Performance Gold (Silica gel, Diol, Amine) or Grace Reveleris® High Performance. Melting points were obtained on a Büchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on an Avance AV700 MHz, Avance AV500 MHz, Avance AV400 MHz, Avance AV 300 MHZ, or Avance DRX400 MHz (^{1}H, ^{13}C, ^{19}F, DEPT 135, COSY, HMQC/HSQC) spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet, br = broad and app = apparent), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ = 77.23 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Bruker Alpha Vertex Series ATR (neat) and are reported in reciprocal centimeters (cm^{-1}). Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm. Data are reported as follows: $[\alpha]^{\lambda}$ temp, concentration (*c* in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

Reagents

Reagents: Unless otherwise stated, commercial reagents were used without purification. Trifluoromethanesulfonic (triflic) anhydride was distilled over phosphorus pentoxide and was stored for no more than five days before redistilling. Pyridine was distilled over sodium and kept under argon before use. All catalysts, ligands, and zinc salts were kept under argon in a glovebox before use. *n*-Butyl lithium, *sec*-butyl lithium, MeMgBr, EtMgBr, $Ph(CH_2)_2MgCl$ and 4-(F)PhMgBr were titrated using standard techniques prior to their use (*see next section*). *n*-Butyllithium in hexanes (originally sold as a 2.5 M solution) was purchased from FMC Lithium. *Sec*-Butyllithium in cyclohexane (originally sold as a 1.37 M

1. Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd Edition; Wiley: New York, 1986.

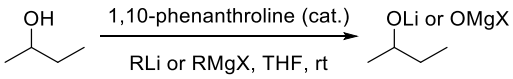
solution) was purchased from Strem Chemicals. Anhydrous zinc bromide was purchased from Alfa Aesar (98%) and was stored in a glovebox before use. Eschenmoser's salt was kept in a dry glovebox before use. The dihydropyridines **1a** and **1b** were prepared according to literature procedures.[2] The chiral amide used in the synthesis of dihydropyridines **1a**-**1d** was prepared according to literature procedures.[2] $Ph(CH_2)_2MgCl$ was made according to literature procedures with $Ph(CH_2)_2Cl$, I_2 (cat.) and Mg turnings in Et_2O.[3] The following reagents were purchased from commercial sources and used as received:

Zinc bromide (Alfa Aesar, 98%), palladium acetate (StremChem, 98%), PPh_3 (StremChem, 99%), 4-bromoanisole (Alfa Aesar, 99%), 3-bromotoluene (Aldrich, 98%), ethyl 4-bromobenzoate (Aldrich, 98%), 1-bromo-4-fluorobenzene (Oakwood Product, 99%), 4-bromobenzotrifluoride (Oakwood Products, 99%), 1-bromonaphthalene (Aldrich, 97%), 1-bromo-4-nitrobenzene (Aldrich, 99%), 4-bromobenzonitrile (Aldrich, 99%), 2-bromothiophene (Aldrich, 98%), ethyl *trans*-4-bromocinnamate (Alfa Aesar, 98%), *cis*-1-bromo-1-propene (Alfa Aesar, 98%), methyl iodide (Aldrich, 99%), 1-iodoundecane (Aldrich, 98%), 1-chloro-3-iodopropane (Aldrich, 99%), NFSI (Aldrich, 97%), NIS (Aldrich, 99%), NCS (Aldrich, 98%+), D_2O (Cambridge Isotopes, 99%), bromotrimethylsilane (Alfa Aesar, 97%), Eschenmoser's salt (Aldrich, 98%), diphenyl disulfide (Alfa Aesar, 99%), Palladium on carbon, 10%wt dry (Aldrich), 4-(F)PhMgBr (Aldrich, 2.0 M in Et_2O).

N,*N*-dimethylcarbamoyl chloride (Aldrich, 98%) and allyl bromide (Aldrich, 99%) were distilled prior to their use.

Titration procedures

Titration of lithium and magnesium reagents[4]



To an argon-flushed and flame-dried 10 mL round-bottom flask equipped with a teflon septum and a stirbar was added catalytic amount of 1,10-phenanthroline (2 to 5 mg). Then, it was solubilized with 1.0 mL of THF and stirred a room temperature. An accurately syringed volume of lithium or magnesium reagent was added to the 1,10-phenanthroline solution using a gas tight syringe (normally between 0.5 mL to 1.0 mL). A light purple color forms within a 5 minute range indicating the complexation of the 1,10-phenanthroline to the lithium/magnesium species. Then, a solution of anhydrous 2-butanol (1.0 M in anhydrous toluene) was slowly added dropwise *via* a gas tight syringe until the end point is reached indicated by a change in color to a yellow or translucid solution. The molarity of the lithium or magnesium reagent was averaged from a duplicate of the procedure.

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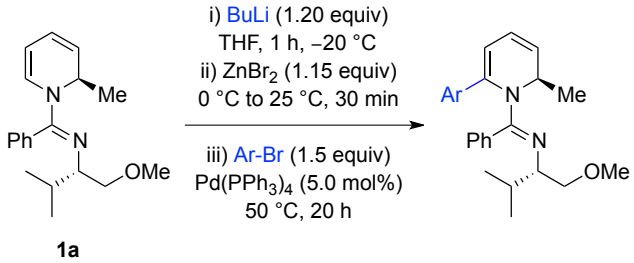
2 A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel *J. Am. Chem. Soc.* 2001, **123**, 11829.
3. Olah, G. A.; Arvanaghi, M. *Org. Synth.* 1986, **64**, 114.
4. The titration procedure for Grignard and organolithium reagents was reported previously: S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* 1967, **9**, 165-168.

Reaction optimization-

*Optimization of the Negishi cross-coupling with **1a**: Initial trials and variation of the base*



1a

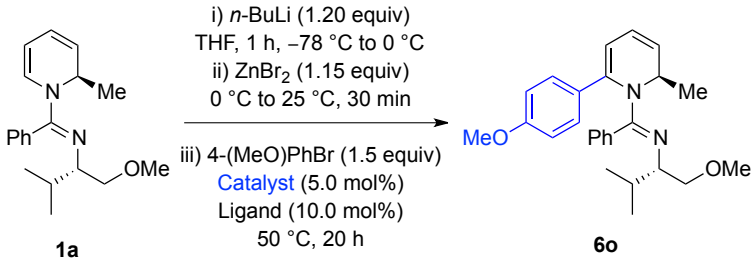
To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[5] **1a** (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, (0.25 M)). The reaction flask was then cooled to –20 °C using a *i*-PrOH:H_2O (1:1) cooling bath and *n*-BuLi or *sec*-BuLi (1.2 mmol, 1.0 equiv) was added dropwise to the reaction. The reaction was stirred at –20 °C for 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. Then, the flask was opened and anhydrous $ZnBr_2$ (255.1 mg, 1.15 mmol, 1.15 equiv) was added rapidly to the reaction at –20 °C and the vial was recapped rapidly. The reaction was slowly heated to 25 °C over the course of 30 min. The reaction returned gradually to a yellow solution and disappearing of the zinc precipitate was usually observed over the course of the reaction. Then, the cap was opened and $Pd(PPh_3)_4$ (57.5 mg, 0.05 mmol, 0.05 equiv) was rapidly added and the vial was recapped. The arylbromide (1.5 mmol, 1.5 equiv) was added via syringe and the reaction was slowly heated to 50 °C using an oil bath and the reaction was stirred for 20 hours at 50 °C. The reaction was cooled to rt and decapped. A (1.0 M) solution of mesitylene in DCM was added to the reaction (120.2 mg, 1.0 mL of solution, 1.0 mmol, 1.0 equiv) and the reaction was quenched by addition of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$) was added to the vial (2.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The conversion and yield for the 2,6-disubstituted dihydropyridine **6** was determined by ^1H NMR by comparing signals obtained from pure samples with mesitylene as the internal standard.

5. The 2-substituted dihydropyridine **1a** can easily discolor and decompose *via* oxidation if not stored properly under argon in a freezer. The dihydropyridine **1a** was periodically repurified by flash chromatography if partially decomposed prior to its use.

entry	base	Ar-Br	temp. (°C)	yield (%)
1	*sec*-BuLi	4-MeOPhBr	–20	51[a] (**6o**)
2	*sec*-BuLi	3-MePhBr	–20	67[a] (**6p**)
3	*sec*-BuLi	4-(EtO_2C)PhBr	–20	75[a] (**6q**)
4	*n*-BuLi	4-MeOPhBr	–20	30[b] (**6o**)
5	*n*-BuLi	4-MeOPhBr	–10	36[b] (**6o**)
6	*n*-BuLi	4-MeOPhBr	0	40[b] (**6o**)
7	*n*-BuLi	4-MeOPhBr	25	21[b] (**6o**)
8	*n*-BuLi	4-MeOPhBr	reflux (65)	0[b] (**6o**)

[a] Isolated yield [b] Yield determined by ^{1}H NMR versus mesitylene as the internal standard

*Optimization of the Negishi cross-coupling with **1a**: Variation of the catalyst's nature*



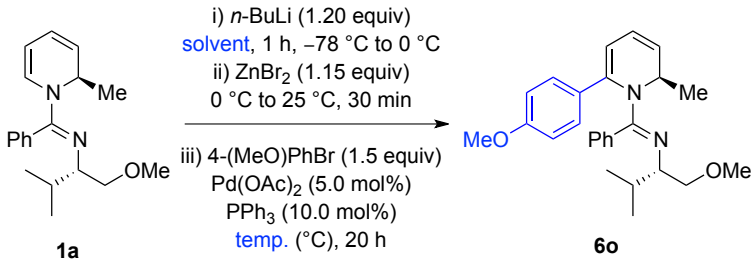
To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[5] **1a** (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, (0.25 M)). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and *n*-BuLi (1.2 mmol, 1.0 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C for 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. Then, the flask was opened and anhydrous $ZnBr_2$ (255.1 mg, 1.15 mmol, 1.15 equiv) was added rapidly to the reaction at 0 °C and the vial was recapped rapidly. The reaction was slowly heated to 25 °C over the course of 30 min. The reaction returned gradually to a yellow solution and disappearing of the zinc precipitate was usually observed over the course of the reaction. Then, the cap was opened and the catalyst (0.05 mmol, 0.05 equiv) and the ligand (0.10 mmol, 0.10 equiv) were rapidly added and the vial was recapped. 4-Bromoanisole (280.5 mg, 188µL 1.5 mmol, 1.5 equiv) was added via syringe and the reaction was slowly heated to 50 °C using an oil bath and the reaction was stirred for 20 hours at 50 °C. The reaction was cooled to rt and decapped. A (1.0 M) solution of mesitylene in DCM was added to the reaction (120.2 mg, 1.0 mL of solution, 1.0 mmol, 1.0 equiv) and the reaction was quenched by addition of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$)

was added to the vial (2.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The conversion and yield for the 2,6-disubstituted dihydropyridine **6o** was determined by ^{1}H NMR by comparing signals obtained from pure samples with mesitylene as the internal standard.

entry	catalyst	Ligand	conversion (%)[a]	yield **6o** (%)[a]
1	$Pd(PPh_3)_4$	–	52	40
2	$Pd(OAc)_2$	–	33	0
3	$Pd(dba)_2$	–	25	0
4	$Pd(P(t\text{-}Bu)_3)_2$	–	38	0
5	$PdCl_2(dppf)\bullet CH_2Cl_2$	–	22	0
6	$Pd_2(dba)_3$	–	19	0
7	$Ni(PPh_3)_4$	–	37	0
8	$PdCl_2(allyl)$	–	80	0
9	$Pd(OAc)_2(PPh_3)_2$	–	55	45
10	$Pd(dba)_2$	PPh_3	43	42
11	$Pd_2(dba)_3$	PPh_3	71	33
12	$Pd(OAc)_2$	PPh_3	58	50
13	$PdBr_2$	PPh_3	46	0

[a] Yield and conversion were determined by ^{1}H NMR versus mesitylene as the internal standard

*Optimization of the Negishi cross-coupling with **1a**: Variation of the solvent and temperature*



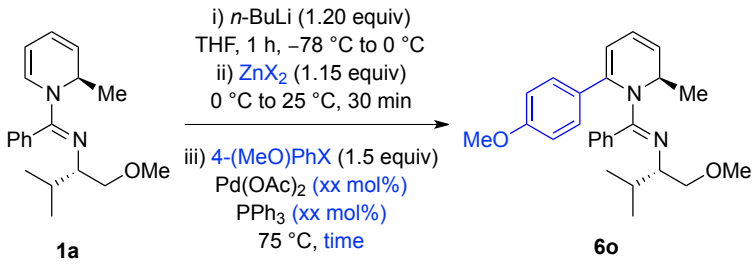
To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[5] **1a** (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous solvent (4.0 mL, (0.25 M)). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and *n*-BuLi (1.2 mmol, 1.0 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C for 1 hour. The reaction turned gradually from a yellow solution to a

red/brown solution over the course of the reaction. Then, the flask was opened and anhydrous $ZnBr_2$ (255.1 mg, 1.15 mmol, 1.15 equiv) was added rapidly to the reaction at 0 °C and the vial was recapped rapidly. The reaction was slowly heated to 25 °C over the course of 30 min. The reaction returned gradually to a yellow solution and disappearing of the zinc precipitate was usually observed over the course of the reaction. Then, the cap was opened and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.05 equiv) as well as PPh_3 (26.2 mg, 0.10 mmol, 0.10 equiv) were rapidly added and the vial was recapped. 4-Bromoanisole (280.5 mg, 188µL, 1.5 mmol, 1.5 equiv) was added via syringe and the reaction was slowly heated at the indicated temperature using an oil bath and the reaction was stirred for 20 hours. The reaction was cooled to rt and decapped. A (1.0 M) solution of mesitylene in DCM was added to the reaction (120.2 mg, 1.0 mL of solution, 1.0 mmol, 1.0 equiv) and the reaction was quenched by addition of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$) was added to the vial (2.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The conversion and yield for the 2,6-disubstituted dihydropyridine **6o** was determined by ^1H NMR by comparing signals obtained from pure samples with mesitylene as the internal standard.

entry	solvent	temp. (°C)	conversion (%)[a]	yield **6o** (%)[a]
1	CH_2Cl_2	50	0	0
2	Benzene	50	0	0
3	toluene	50	0	0
4	MeCN	50	0	0
5	Et_2O	50	30	18
6	THF	50	58	50
7	THF	60	66	60
8	THF	60	53	28[b]
9	THF	75	81	70

[a] Yield and conversion were determined by ^1H NMR versus mesitylene as the internal standard [b] TBAB (1.0 equiv) was added during the Negishi cross-coupling.

*Optimization of the Negishi cross-coupling with **1a**: Variation of the catalyst amount, zinc source, aryl halide source and time of reaction*

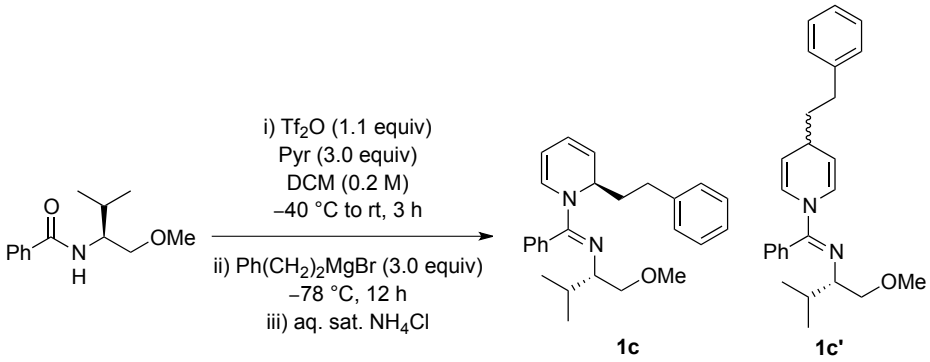


To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[5] **1a** (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, (0.25 M)). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and *n*-BuLi (1.2 mmol, 1.0 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C for 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. Then, the flask was opened and anhydrous Zinc source (1.15 mmol, 1.15 equiv) was added rapidly to the reaction at 0 °C and the vial was recapped rapidly. The reaction was slowly heated to 25 °C over the course of 30 min. The reaction returned gradually to a yellow solution and disappearing of the zinc precipitate was usually observed over the course of the reaction. Then, the cap was opened and $Pd(OAc)_2$ (x.xx mmol, x.xx equiv) as well as PPh_3 (x.xx mmol, x.xx equiv) were rapidly added and the vial was recapped. 4-Haloanisole (1.5 mmol, 1.5 equiv) was added via syringe and the reaction was slowly heated at 75 °C using an oil bath and the reaction was stirred for the indicated amount of time. The reaction was cooled to rt and decapped. A (1.0 M) solution of mesitylene in DCM was added to the reaction (120.2 mg, 1.0 mL of solution, 1.0 mmol, 1.0 equiv) and the reaction was quenched by addition of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$) was added to the vial (2.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The conversion and yield for the 2,6-disubstituted dihydropyridine **6o** was determined by ^1H NMR by comparing signals obtained from pure samples with mesitylene as the internal standard.

entry	$Pd(OAc)_2/PPh_3$ (mol%)	ZnX_2	4-MeOPhX	time (h)	yield **6o** (%)[a]
1	5.0/10.0	$ZnBr_2$	4-MeOPhBr	20	70
2	10.0/20.0	$ZnBr_2$	4-MeOPhBr	20	73
3	**2.5/5.0**	**$ZnBr_2$**	**4-MeOPhBr**	**20**	**68**
4	2.5/5.0	$ZnCl_2$	4-MeOPhBr	20	51
5	2.5/5.0	ZnI_2	4-MeOPhBr	20	18
6	2.5/5.0	$Zn(OAc)_2$	4-MeOPhBr	20	35
7	2.5/5.0	$ZnBr_2$	4-MeOPhCl	20	35
8	2.5/5.0	$ZnBr_2$	4-MeOPhI	20	18
9	2.5/5.0	$ZnBr_2$	4-MeOPhBr	4	65
10	2.5/5.0	$ZnBr_2$	4-MeOPhBr	2.5	49

[a] Yield and conversion were determined by ^1H NMR versus mesitylene as the internal standard

Dihydropyridine synthesis (1c-1d)

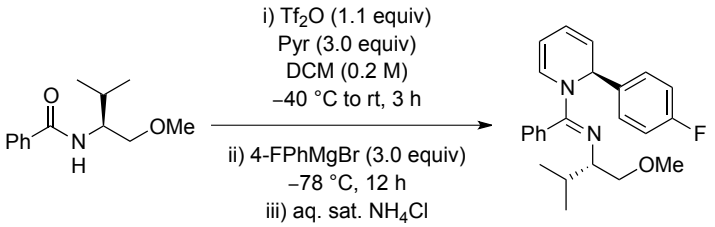


***N*-[(*R*)-2-Phenethyl-2*H*-pyridin-1-yl]-*N*-[(*S*)-2-(1-methoxy-3-methylbutyl)]-benzamidine (1c).** (*S*)-*N*-[2-(1-methoxy-3-methylbutyl)]-benzamide (885 mg, 4.0 mmol) was added to a 50 mL round-bottomed flask, previously dried and flushed with nitrogen. Dichloromethane (20.0 mL, 0.2 M) and pyridine (0.949 g, 0.967 mL, 12.0 mmol, 3.0 equiv) were then added and the resulting solution was cooled to –40 °C. Triflic anhydride (1.241 g, 0.730 mL, 4.4 mmol, 1.1 mmol) was then slowly added along the side of the flask. The reaction was left to warm up to 0 °C over two hours, during which a pale yellow color appeared. The reaction was then stirred for one hour at room temperature to ensure complete formation of the pyridinium intermediate. The solution containing the pyridinium intermediate was cooled to –78 °C and phenethylmagnesium chloride[3] (8.0 mL of a 1.50 M solution in ether, 12.0 mmol, 3.0 equiv) was added dropwise to the solution while maintaining the internal temperature below –75 °C with an internal monitor. The reaction was stirred at –78 °C until TLC analysis showed complete consumption of the starting material (~7 hrs/over-night). Temperature was maintained with a cryostat cooling apparatus over reaction time. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and left to warm to room temperature. The mixture was then transferred to an extraction funnel and the aqueous phase was extracted twice with EtOAc. The organic phases were then combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Analysis of the crude mixture by ^{1}H NMR showed a ratio of 83% of **1c** along with 17% of 1,4-adduct **1c'** and >95:5 d.r for **1c**. Flash chromatography of the oily residue with a gradient of 100% Hexanes to 30% EtOAc/Hexanes with a Isco 120g silica gel column resulted in a yellow oil consisting of pure 1,2-adduct **1c** (670 mg, 43 % Yield) along with 1,4-adduct (150 mg, 10% Yield).

For 1,2-adduct **1c** (major) $\mathbf{R_f}$ **=** 0.7 (20% EtOAc/hexanes); $\mathbf{[\alpha]_D^{25}}$ = –648.5 (*c* = 0.60, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46-7.37 (m, 3H), 7.32-7.25 (m, 5H), 7.22-7.17 (m, 1H), 7.14-7.08 (m, 1H), 6.00-5.89 (br m, 1H), 5.97 (dd, *J* = 6.0, 7.0 Hz, 1H), 5.60-5.55 (m, 1H), 5.53-5.39 (br m, 1H), 4.86 (app t, *J* = 5.0 Hz, 1H), 3.48 (dd, *J* = 4.0, 7.0 Hz, 1H), 3.33 (dd, *J* = 5.5, 7.0 Hz, 1H), 3.28 (s, 3H), 3.01-2.97 (m, 1H), 2.82-2.97 (m, 2H), 2.18-2.09 (m, 1H), 1.98-1.90 (m, 1H), 1.71-1.63 (m, 1H), 0.83 (d, *J* = 5.0 Hz, 3H), 0.72 (d, *J* = 5.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.0, 142.8, 133.1, 129.5, 129.0, 128.9, 128.5, 128.4, 128.2, 125.5, 122.3, 119.8, 100.9, 76.0, 63.4, 59.0, 51.6, 34.5, 30.8 (2), 20.0, 17.6; **FTIR**

(neat) (cm^{-1}) 3026, 2956, 2925, 1626, 1599, 1562, 1389, 1333, 1264; **HRMS** (ESI) calcd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587, found 389.2587.

For 1,4-adduct **1c'** (minor): $\mathbf{R_f}$ **=** 0.90 (20% EtOAc/hexanes); $\mathbf{[\alpha]_D^{25}}$ = –96.9 (*c* 0.425, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.39 (m, 3H), 7.31-7.17 (m, 7H), 6.83-6.53 (br m, 2H), 4.72-4.61 (br m, 2H), 3.44 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.34 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.28 (s, 3H), 3.15-3.09 (m, 1H), 3.03-2.98 (m, 1H), 2.70-2.66 (m, 2H), 1.76-1.70 (m, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 149.7, 142.8, 132.4, 128.8, 128.6, 128.5, 128.3, 125.6, 125.3, 106.6, 75.8, 63.6, 59.0, 40.9, 33.2, 32.1, 31.0, 19.9, 17.9; **FTIR** (neat) (cm^{-1}) 2957, 2925, 2889, 1681, 1638, 1613, 1580, 1561, 1520, 1493, 1453, 1417, 1372; **HRMS** (ESI) calcd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587, found 389.2588.

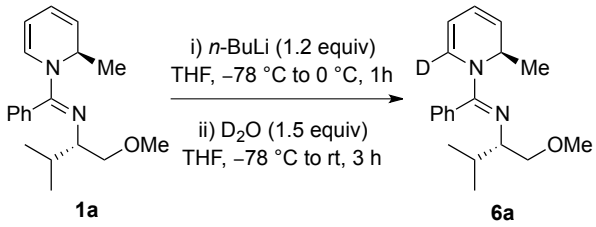


1d

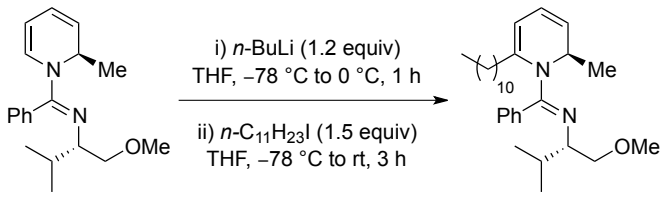
***N*-[(*R*)-2-(4-Fluorophenyl)-2*H*-pyridin-1-yl]-*N*-[(*S*)-2-(1-methoxy-3-methylbutyl)]-benzamidine (1d).** (*S*)-*N*-[2-(1-methoxy-3-methylbutyl)]-benzamide (1.327 g, 6.0 mmol, 1.0 equiv) was added to a 125 mL round-bottomed flask, previously dried and flushed with nitrogen. Dichloromethane (30.0 mL, 0.2 M) and pyridine (1.423 g, 1.45 mL, 18.0 mmol, 3.0 equiv) were then added and the resulting solution was cooled to –40 °C. Triflic anhydride (1.862 g, 1.095 mL, 6.6 mmol, 1.1 mmol) was then slowly added along the side of the flask. The reaction was left to warm up to 0 °C over two hours, during which a pale yellow color appeared. The reaction was then stirred for one hour at room temperature to ensure complete formation of the pyridinium intermediate. The solution containing the pyridinium intermediate was cooled to –78 °C and 4-fluorophenylmagnesium bromide (16.82 mL of a 1.07 M solution in ether, 18.0 mmol, 3.0 equiv) was added dropwise to the solution while maintaining the internal temperature below –75 °C with an internal monitor. The reaction was stirred at –78 °C until TLC analysis showed complete consumption of the starting material (~7 hrs/over night). Temperature was maintained with a cryostat cooling apparatus over reaction time. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and left to warm to room temperature. The mixture was then transferred to an extraction funnel and the aqueous phase was extracted twice with EtOAc. The organic phases were then combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Analysis of the crude mixture by ^{1}H NMR showed a ratio of 89% of **1d** along with 11% of 1,4-adduct and >95:5 d.r. for **1d**. Flash chromatography of the oily residue with a gradient of 100% Hexanes to 30% EtOAc/Hexanes with a Isco 120g silica gel column resulted in a yellow oil consisting of pure 1,2-adduct **1d** (1.771 g, 78% Yield). $\mathbf{R_f}$ = 0.7 (10% EtOAc/hexanes); $\mathbf{[\alpha]_D^{20}}$ = –721.4 (*c* = 0.78, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 5.5, 9.0 Hz, 2H), 7.43-7.37 (m, 3H), 7.12 (br s, 2H), 6.98 (app t, *J* = 7.5 Hz, 2H), 6.47

(br d, J = 5.5 Hz, 1H), 6.04-5.99 (m, 2H), 5.61 (dd, J = 6.0 Hz, 1H), 4.90-4.86 (m, 1H), 3.33 (dd, J = 4.5, 9.0 Hz, 1H), 3.07 (s, 3H), 3.03 (dd, J = 7.5, 9.0 Hz, 1H), 2.96-2.91 (m, 1H), 1.73-1.62 (m, 1H), 0.88 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.5 (d, J = 260.0 Hz, $J_{C\text{-}F}$), 156.8, 139.6 (d, J = 3.0 Hz, $J_{C\text{-}F}$), 132.7, 129.2 (d, J = 44.5 Hz, $J_{C\text{-}F}$), 128.8, 128.7, 128.6, 128.5, 121.5, 120.4, 114.5 (d, J = 21 Hz, $J_{C\text{-}F}$), 100.2, 75.6, 63.6, 58.7, 54.7, 30.5, 20.0, 12.6; **^{19}F NMR** (288 MHz, $CDCl_3$): δ –117.0; **FTIR** (neat) (cm^{-1}) 2957, 2923, 2881, 1627, 1599, 1570, 1507, 1467, 1445; **HRMS** (ESI) calcd for $C_{24}H_{28}N_2OF$ $[M+H]^+$: 379.2186, found 379.2179.

Directed lithiation/electrophilic quench (6a-6n)

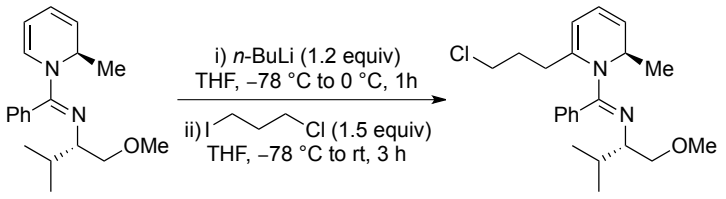


***N*-[(*R*)-2-methyl-2*H*-pyridin-1-yl]-*N*-[(*S*)-2-(1-methoxy-3-methylbutyl)]-benzamidine-6-deuteride (6a):** To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added D_2O (30.0 mg, 30 µL, 1.5 mmol, 1.5 equiv). D_2O was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6a**) was recuperated as a yellow oil (288 mg, 96% Yield, >95% D incorporation). $\mathbf{R_f}$: 0.80 (30% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –495.3 (*c* = 0.75, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46-7.36 (m, 3H), 7.33-7.27 (m, 1H), 7.17-7.09 (m, 1H), 5.88 (dd, *J* = 5.0, 9.0 Hz, 1H), 5.48 (ddd, *J* = 1.0, 5.5, 9.0 Hz, 1H), 5.43-5.32 (br m, 1H), 4.85 (d, *J* = 5.0 Hz, 1H), 3.50 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.35 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.31 (s, 3H), 3.00-2.95 (m, 1H), 1.72-1.64 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 156.8, 133.2, 129.0, 128.5, 128.4, 121.7, 121.2, 100.4, 76.0, 63.6, 59.0, 48.2, 30.8, 20.0, 17.8, 17.7; **FTIR** (cm^{-1}) (neat): 2959, 2923, 2886, 1625, 1555, 1410, 1386; **HRMS** (ESI, Pos): calcd for $C_{19}H_{26}N_2OD$ $[M+H]^+$: 300.2185 *m/z*, found: 300.2185 *m/z*.



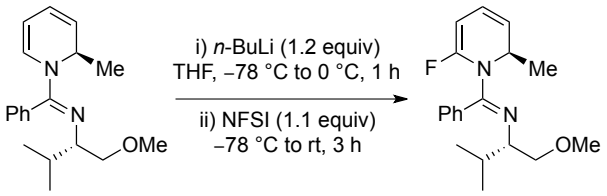
1a **6b**

(*S*,*E*)-1-Methoxy-3-methyl-*N*-(((*R*)-2-methyl-6-undecylpyridin-1(2*H*)-yl)(phenyl)methylene)butan-2-amine (6b): To a flame-dried 5 mL microwave glass reactor (Biotage ® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added 1-iodoundecane (424 mg, 350 µL, 1.5 mmol, 1.5 equiv). The iodide was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 80% EtOAc in hexanes over a 40 g Isco Gold column using 45 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6b**) was recuperated as a translucid oil (323 mg, 72% Yield). $\mathbf{R_f}$: 0.90 (10% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –309.5 (*c* = 0.79, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.42-7.25 (m, 5H), 5.91 (dd, *J* = 4.5, 9.0 Hz, 1H), 5.55 (dd, *J* = 5.5, 9.0 Hz, 1H), 5.33 (d, *J* = 4.5 Hz, 1H), 4.83-4.76 (m, 1H), 3.64 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.49 (app t, *J* = 7.5 Hz, 1H), 3.41 (s, 3H), 3.31-3.25 (m, 1H), 1.88-1.79 (m, 1H), 1.78-1.71 (m, 1H), 1.70-1.61 (m, 1H), 1.48-1.39 (m, 1H), 1.36-1.10 (m, 17H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.91 (t, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 158.7, 140.5, 133.9, 128.9, 128.3, 127.7, 122.3, 121.3, 108.2, 75.9, 63.4, 58.9, 50.3, 34.6, 31.6, 31.1, 29.3, 29.2 (2), 29.1, 29.0, 28.9, 27.3, 22.3, 19.5, 17.1, 17.0, 13.8; **FTIR** (cm^{-1}) (neat): 2956, 2922, 2853, 1616, 1598, 1597, 1446, 1409, 1383, 1227; **HRMS** (ESI, Pos): calcd for $C_{30}H_{49}N_2O$ $[M+H]^+$: 453.3839 *m/z*, found: 453.3849 *m/z*.

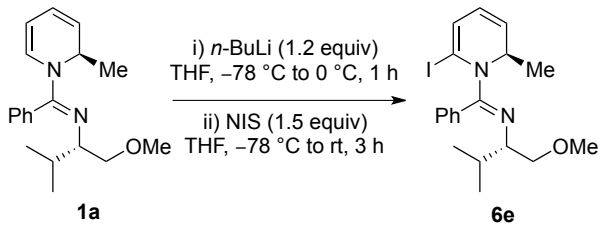


1a **6c**

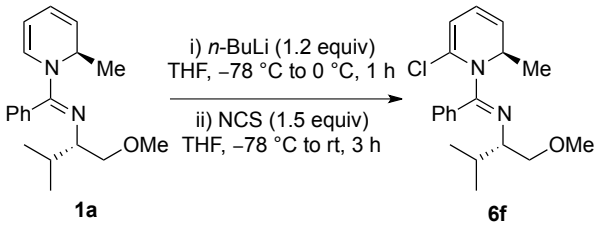
(*S*,*E*)-*N*-(((*R*)-6-(3-Chloropropyl)-2-methylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6c): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added 1-chloro-3-iodopropane (306.7 mg, 161 µL, 1.5 mmol, 1.5 equiv). The iodide was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 80% EtOAc in hexanes over a 40 g Isco Gold column using 45 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6c**) was recuperated as a translucid oil (278 mg, 75% Yield). $\mathbf{R_f}$: 0.80 (20% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –666.7 (*c* = 0.75, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.30 (m, 5H), 5.92 (dd, *J* = 5.0, 9.0 Hz, 1H), 5.57 (dd, *J* = 6.0, 9.0 Hz, 1H), 5.39 (d, *J* = 5.0 Hz, 1H), 4.79-4.72 (m, 1H), 3.63 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.50-3.41 (m, 3H), 3.40 (s, 3H), 3.27 (dt, *J* = 5.0, 8.0 Hz, 1H), 2.04-1.85 (m, 3H), 1.82-1.74 (m, 1H), 1.70-1.61 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.64 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 158.7, 138.5, 133.6, 128.8, 128.5, 127.9, 122.9, 121.2, 109.2, 75.7, 63.5, 58.9, 50.4, 44.0, 31.7, 31.1, 30.4, 19.5, 17.3, 17.2; **FTIR** (cm^{-1}) (neat): 2958, 2923, 2872, 1615, 1597, 1567, 1445, 1409, 1313; **HRMS** (ESI, Pos): calcd for $C_{22}H_{32}N_2OCl$ $[M+H]^+$: 375.2203 *m/z*, found: 375.2207 *m/z*.



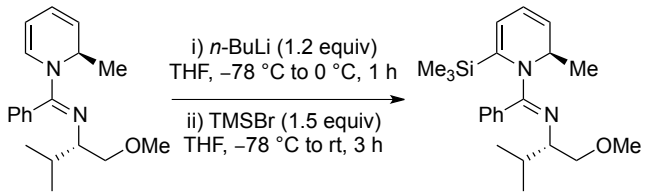
(*S*,*E*)-*N*-(((*R*)-6-fluoro-2-methylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6d): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. Solid *N*-fluorobenzenesulfonimine (NFSI) (346.8 mg, 1.1 mmol, 1.1 equiv) was transferred to the reaction rapidly. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 30% EtOAc in hexanes over a 40 g Grace Reveleris column using 45 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6d**) was recuperated as a translucid oil (163.0 mg, 52% Yield). $\mathbf{R_f}$: 0.75 (20% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –437.2 (*c* = 1.18, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.37 (m, 3H), 7.34-7.25 (br m, 2H), 5.92 (dt, *J* = 5.5, 11.5 Hz, 1H), 5.46 (dd, *J* = 6.0, 12.0 Hz, 1H), 5.17-5.08 (m, 1H), 4.93 (dd, *J* = 4.0, 5.5 Hz, 1H), 3.60 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.51 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.40 (s, 3H), 3.24 (dt, *J* = 5.0, 7.5 Hz, 1H), 1.72-1.64 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.64 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 155.8 (d, *J* = 2.5 Hz, $J_{C\text{-}F}$), 151.2 (d, *J* = 267.0 Hz, $J_{C\text{-}F}$), 132.8 (d, *J* = 3.0 Hz, $J_{C\text{-}F}$), 128.5, 127.7, 126.9, 120.5 (d, *J* = 5.0 Hz, $J_{C\text{-}F}$), 120.2 (d, *J* = 4.0 Hz, $J_{C\text{-}F}$), 85.3 (d, *J* = 25.0 Hz, $J_{C\text{-}F}$), 75.6, 63.1, 58.9, 52.3 (d, *J* = 1.5 Hz, $J_{C\text{-}F}$), 30.9, 19.6, 17.6, 17.2; **^{19}F NMR** ($CDCl_3$, 376 MHz): δ –89.5 **FTIR** (cm^{-1}) (neat): 2961, 2929, 2874, 1677, 1630, 1386, 1259, 1198, 1113; **HRMS** (ESI, Pos): calcd for $C_{19}H_{26}N_2OF$ $[M+H]^+$: 317.2024 *m/z*, found: 317.2021 *m/z*. **Note:** *The product is unstable on the bench and decomposes within a couple of hours in solution.*



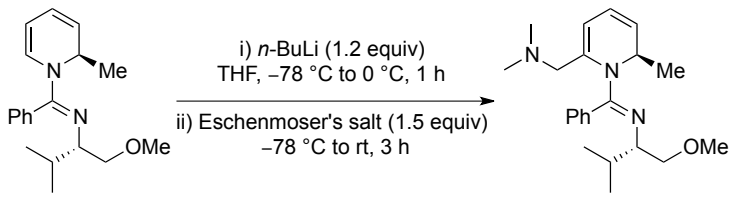
(*S*,*E*)-*N*-(((*R*)-6-iodo-2-methylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6e): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added NIS (338 mg, 1.5 mmol, 1.5 equiv). NIS was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6e**) was recuperated as an orange oil (312 mg, 74% Yield). $\mathbf{R_f}$: 0.70 (10% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –468.0 (*c* = 0.48, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.30 (m, 5H), 6.28 (d, *J* = 3.0 Hz, 1H), 5.79-5.67 (m, 1H), 4.46 (app br qn, *J* = 6.0 Hz, 1H), 3.63 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.52 (app t, *J* = 8.0 Hz, 1H), 3.39 (s, 3H), 3.35-3.27 (m, 1H), 1.80-1.68 (m, 1H), 1.11 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 158.3, 133.0, 129.4, 128.7, 127.7, 125.8, 125.4, 122.4, 90.3, 75.4, 64.7, 58.9, 51.4, 31.2, 19.3, 17.6, 15.8; **FTIR** (cm^{-1}) (neat): 2964, 2872, 1638, 1591, 1531, 1448, 1367, 1268, 695; **HRMS** (ESI, Pos): calcd for $C_{19}H_{26}N_2OI$ $[M+H]^+$: 425.1090 *m/z*, found: 425.1091 *m/z*. **Note:** *The product is unstable on the bench and decomposes within a couple of hours in solution.*



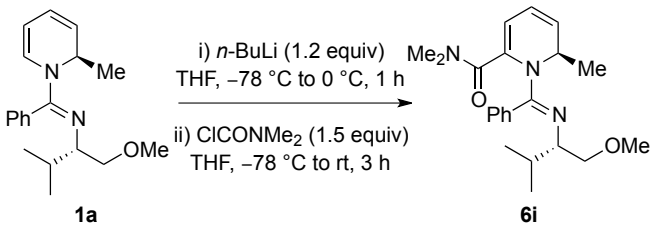
(*S*,*E*)-*N*-(((*R*)-6-chloro-2-methylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6f): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added NCS (200.0 mg, 1.5 mmol, 1.5 equiv). NCS was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6f**) was recuperated as a yellow oil (210 mg, 64% Yield). $\mathbf{R_f}$: 0.70 (10% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –456.2 (*c* = 0.72, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.30 (m, 5H), 5.93 (dd, *J* = 5.0, 9.0 Hz, 1H), 5.70 (d, *J* = 5.0 Hz, 1H), 5.63 (dd, *J* = 5.5, 9.0 Hz, 1H), 4.75 (app qn, *J* = 7.0 Hz, 1H), 3.63 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.54 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.40 (s, 3H), 3.33-3.29 (m, 1H), 1.76-1.64 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 158.0, 133.2, 129.7, 129.4, 128.9, 128.1, 124.3, 121.8, 111.2, 76.0, 64.3, 59.2, 52.5, 31.6, 19.9, 17.5, 17.4; **FTIR** (cm^{-1}) (neat): 2959, 2890, 1625, 1600, 1554, 1491, 1446, 1380; **HRMS** (ESI, Pos): calcd for $C_{19}H_{26}N_2OCl$ $[M+H]^+$: 333.1734 *m/z*, found: 333.1734 *m/z*. **Note:** *The product is unstable on the bench and decomposes within a couple of hours in solution.*



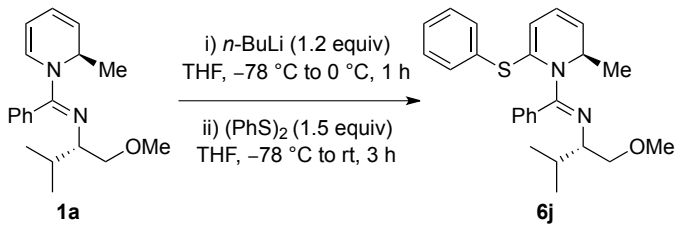
(*S*,*E*)-1-Methoxy-3-methyl-*N*-(((*R*)-2-methyl-6(trimethylsilyl)pyridin-1(2*H*)-yl)(phenyl) methylene)butan-2-amine (6g): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added TMSBr (229.6 mg, 200 µL, 1.5 mmol, 1.5 equiv). TMSBr was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6g**) was recuperated as a yellow oil (260.9 mg, 71% Yield). $\mathbf{R_f}$: 0.60 (30% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –940.7 (*c* = 0.533, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.43-7.26 (m, 5H), 5.97 (dd, *J* = 4.0, 7.0 Hz, 1H), 5.85 (dd, *J* = 0.5, 3.5 Hz, 1H), 5.69 (dd, *J* = 4.0, 6.5 Hz, 1H), 4.84-4.74 (br m, 1H), 3.65 (dd, *J* = 4.0, 7.5 Hz, 1H), 3.45 (dd, *J* = 5.5, 7.5 Hz, 1H), 3.37 (s, 3H), 3.20-3.16 (m, 1H), 1.68-1.60 (m, 1H), 1.01 (d, *J* = 5.5 Hz, 3H), 0.75 (d, *J* = 5.5 Hz, 3H), 0.64 (d, *J* = 5.5 Hz, 3H), -0.10 (s, 9H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 160.2, 144.0, 133.6, 130.8, 129.1, 128.3, 126.2, 121.4, 121.3, 76.5, 64.6, 59.5, 49.9, 31.9, 19.7, 19.0, 16.6, 0.0; **FTIR** (cm^{-1}) (neat): 2957, 2921, 2892, 1611, 1596, 1523, 1491, 1467, 1382; **HRMS** (ESI, Pos): calcd for $C_{22}H_{35}N_2OSi$ $[M+H]^+$: 371.2513 *m/z*, found: 371.2519 *m/z*.



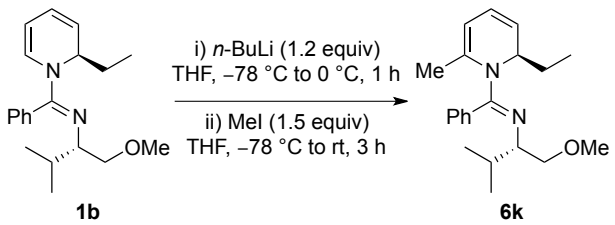
(*S*,*E*)-*N*-(((*R*)-6-((dimethylamino)methyl)-2-methylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6h): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. Then, solid dimethylmethyleneammonium iodide (Eschenmoser's salt) (277.5 mg, 1.5 mmol, 1.5 equiv) was transferred directly to the reaction at –78 °C. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium carbonate (Na_2CO_3) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 30% Hexanes to 100% EtOAc in hexanes over a 30 g ***Isco Amino Gold column*** using 45 mL/min flow, and injecting the crude on a celite precolumn pad. The column was pre-equilibrated with 30% EtOAc in hexanes. The fractions containing pure product were combined and concentrated. The product (**6h**) was recuperated as a translucid oil (283.6 mg, 80% Yield). $\mathbf{R_f}$: 0.20 (10% MeOH in EtOAc, silica gel); $\mathbf{[\alpha]_D^{25}}$: –473.5 (*c* = 0.958, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.45-7.22 (m, 5H), 5.95 (br dd, *J* = 5.5, 9.0 Hz, 1H), 5.62-5.55 (br m, 1H), 5.51-5.45 (br m, 1H), 4.87-4.78 (br m, 1H), 3.70-3.63 (br m, 1H), 3.48 (dd, *J* = 7.0, 10 Hz, 1H), 3.42 (s, 3H), 3.31-3.24 (br m, 1H), 2.60-2.40 (m, 2H), 2.07 (s, 6H), 1.72-1.60 (br m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 159.3, 138.1, 134.2, 129.6, 128.5, 127.9, 123.2, 121.5, 108.9, 76.1, 63.9, 62.9, 59.3, 51.5, 44.9, 31.4, 19.9, 18.4, 17.5; **FTIR** (cm^{-1}) (neat): 2959, 2872, 2913, 2767, 1618, 1567, 1490, 1446, ; **HRMS** (ESI, Pos): calcd for $C_{22}H_{34}N_3O$ $[M+H]^+$: 356.2702 *m/z*, found: 356.2705 *m/z*.



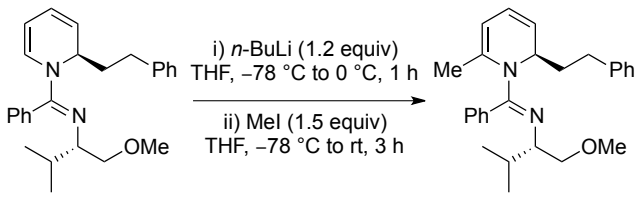
(*R*)-1-((*E*)-1-(((*S*)-1-Methoxy-3-methylbutan-2-yl)imino)(phenyl)methyl)-*N*,*N*-6-trimethyl-1,6-dihydropyridine-2-carboxamide (6i): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethan imine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added distilled *N*,*N*-dimethylcarbamoyl chloride (161.3 mg, 140 µL, 1.5 mmol, 1.5 equiv). The chloride was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6i**) was recuperated as a yellow oil (297 mg, 81% Yield). $\mathbf{R_f}$: 0.10 (30% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –685.1 (*c* = 0.458, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46-7.23 (m, 5H), 5.98 (dd, *J* = 5.0, 9.0 Hz, 1H), 5.70-5.58 (m, 1H), 5.56 (d, *J* = 5.0 Hz, 1H), 5.20-3.73 (very br m, 1H), 3.58-3.45 (m, 1H), 3.39-3.32 (m, 1H), 3.33 (s, 3H), 3.11-2.88 (m, 4H), 2.87-2.53 (br s, 3H), 1.62-1.48 (m, 1H), 1.07 (br d, *J* = 4.5 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.7, 157.9, 133.0, 132.7, 128.9 (br), 128.3, 127.6 (br), 125.8, 120.5, 110.6, 75.8, 63.9, 58.7, 49.1 and 39.0 (rotamers), 34.8, 30.8, 19.4, 17.4, 17.3; **FTIR** (cm^{-1}) (neat): 2955, 2922, 2872, 2824, 1641, 1623, 1560, 1491, 1445, 1387; **HRMS** (ESI, Pos): calcd for $C_{22}H_{32}N_3O_2$ $[M+H]^+$: 370.2495 *m/z*, found: 370.2497 *m/z*.



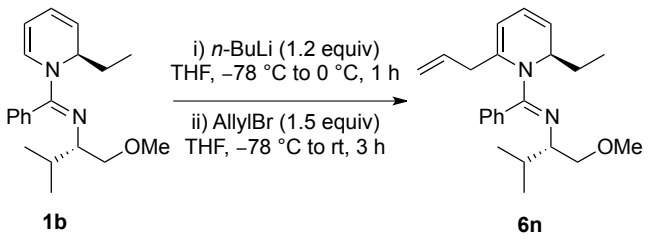
(*S*,*E*)-1-Methoxy-3-methyl-*N*-(((*R*)-2-methyl-6-(phenylthio)pyridin-1(2*H*)-yl)(phenyl) methylene)butan-2-amine (6j): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-methylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1a**) (298.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added diphenyl disulfide (327.5 mg, 1.5 mmol, 1.5 equiv). The disulfide was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 80% EtOAc in hexanes over a 40 g Isco Gold column using 45 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6j**) was recuperated as a red oil (347 mg, 86% Yield). $\mathbf{R_f}$: 0.75 (20% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –353.0 (*c* = 0.475, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43-7.21 (m, 10H), 5.97 (dd, *J* = 5.0, 9.0 Hz, 1H), 5.81 (d, *J* = 5.0 Hz, 1H), 5.62 (dd, *J* = 6.5, 9.0 Hz, 1H), 4.69 (app qn, *J* = 8.5 Hz, 1H), 3.59 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.41 (dd, *J* = 7.0, 9.5 Hz, 1H), 3.33 (s, 3H), 3.28 (dt, *J* = 5.0, 7.0 Hz, 1H), 1.73-1.64 (m, 1H), 1.82-1.74 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.2, 135.2, 133.8, 132.0, 131.5, 129.4, 128.7, 128.6, 127.9, 127.2, 124.3, 122.1, 116.5, 76.0, 64.3, 59.2, 52.0, 31.5, 19.9, 18.1, 17.8; **FTIR** (cm^{-1}) (neat): 3059, 2959, 2923, 2890, 1624, 1533, 1475, 1445; **HRMS** (ESI, Pos): calcd for $C_{25}H_{31}N_2S$ $[M+H]^+$: 407.2152 *m/z*, found: 407.2162 *m/z*.



(*S*,*E*)-*N*-(((*R*)-2-ethyl-6-methylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6k): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-ethylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1b**) (312.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added iodomethane (212.9 mg, 94 µL, 1.5 mmol, 1.5 equiv). The iodide was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6k**) was recuperated as a yellow oil (278.2 mg, 86% Yield). $\mathbf{R_f}$: 0.60 (30% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –880 (*c* = 0.55, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.40-7.34 (m, 3H), 7.31-7.24 (br m, 2H), 5.94 (dd, *J* = 4.0, 7.0 Hz, 1H), 5.60 (dd, *J* = 4.5, 7.0 Hz, 1H), 5.27 (d, *J* = 4.0 Hz, 1H), 4.73 (q, *J* = 5.5 Hz, 1H), 3.62 (dd, *J* = 4.0, 7.0 Hz, 1H), 3.48 (dd, *J* = 5.5, 7.0 Hz, 1H), 3.40 (s, 3H), 3.25 (dt, *J* = 4.0, 5.5 Hz, 1H), 1.71-1.62 (m, 1H), 1.58-1.47 (m, 2H), 1.49 (s, 3H), 0.87 (t, *J* = 5.5 Hz, 3H), 0.83 (d, *J* = 5.0 Hz, 3H), 0.62 (d, *J* = 5.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.2, 137.1, 134.5, 129.4, 128.5, 128.1, 122.3, 121.1, 109.1, 76.2, 63.5, 59.2, 55.9, 31.4, 25.2, 22.5, 20.0, 17.2, 9.7; **FTIR** (cm^{-1}) (neat): 2959, 2926, 2889, 2872, 2822, 2808, 1617, 1568, 1458, 1446, 1383; **HRMS** (ESI, Pos): calcd for $C_{21}H_{31}N_2O$ $[M+H]^+$: 327.2430 *m/z*, found: 327.2436 *m/z*.



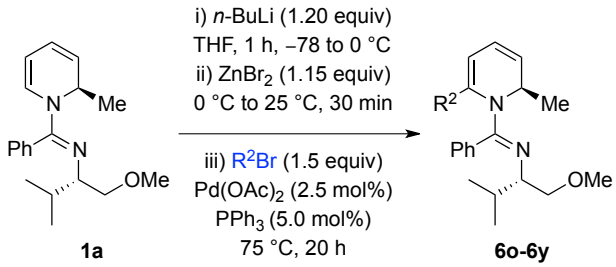
(*S*,*E*)-1-Methoxy-3-methyl-*N*-(((*R*)-6-methyl-2-phenethylpyridin-1(2*H*)-yl)(phenyl) methylene)butan-2-amine (6l): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added *N*-[(*R*)-2-phenethyl-2*H*-pyridin-1-yl]-*N*-[(*S*)-2-(1-methoxy-3-methylbutyl)]-benzamidine (**1c**) (388.3 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added iodomethane (212.9 mg, 94 µL, 1.5 mmol, 1.5 equiv). The iodide was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6l**) was recuperated as a yellow oil (324 mg, 81% Yield). **R_f**: 0.80 (30% EtOAc in Hexanes); **$[\alpha]_D^{25}$**: –567 (*c* = 0.667, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.37-7.35 (m, 3H), 7.28-7.15 (m, 7H), 5.95 (dd, *J* = 5.0, 7.0 Hz, 1H), 5.65-5.58 (m, 1H), 5.27 (dt, *J* = 1.0, 5.0 Hz, 1H), 4.98 (app q, *J* = 6.5 Hz, 1H), 3.62 (dd, *J* = 4.0, 9.5 Hz, 1H), 3.49 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.40 (s, 3H), 3.27-3.25 (m, 1H), 2.67 (dt, *J* = 6.5, 9.0 Hz, 2H), 1.84 (app q, *J* = 7.0 Hz, 2H), 1.71-1.59 (m, 1H), 1.40 (s, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.60 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.0, 143.1, 137.0, 134.4, 129.4, 128.6, 128.4, 128.2, 128.1, 125.4, 122.5, 120.9, 109.1, 76.4, 63.5, 59.2, 54.3, 33.6, 31.6, 31.5, 22.5, 20.0, 17.4; **FTIR** (cm^{-1}) (neat): 2955, 2923, 2889, 1617, 1598, 1568, 1366; **HRMS** (ESI, Pos): calcd for $C_{25}H_{35}N_2O$ $[M+H]^+$: 403.2744 *m/z*, found: 403.2752 *m/z*.



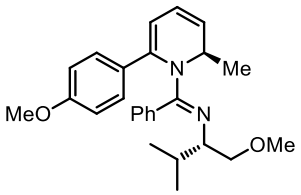
(*S*,*E*)-*N*-(((*R*)-6-allyl-2-ethylpyridin-1(2*H*)-yl)(phenyl)methylene)-1-methoxy-3-methylbutan-2-amine (6n): To a flame-dried 5 mL microwave glass reactor (Biotage® 2-5 mL vials) equipped with a magnetic stir bar was added (*E*)-*N*-[(2*S*)-1-methoxy-3-methylbutan-2-yl]-1-[(2*R*)-2-ethylpyridin-1(2*H*)-yl]-1-phenylmethanimine[2] (**1b**) (312.2 mg, 1.0 mmol, 1.0 equiv) and the vial was capped with a 14 mm rubber septum. Then, the vial was purged with argon (10 min) and the dihydropyridine was diluted with anhydrous THF (4.0 mL, 0.25 M). The reaction flask was then cooled to –78 °C using an acetone/dry ice cooling bath and a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise to the reaction. The reaction was stirred from –78 °C to 0 °C over the course of 1 hour. The reaction turned gradually from a yellow solution to a red/brown solution over the course of the reaction. The reaction was then cooled again to –78 °C. In a separate 10 mL flame-dried round bottom flask equipped with a magnetic stirbar was added distilled allylbromide (181.2 mg, 130 µL, 1.5 mmol, 1.5 equiv). The bromide was diluted with anhydrous THF (1.0 mL, 1.0 M) and the solution was transferred to the reaction dropwise at –78 °C. The flask was rinsed with anhydrous THF (0.5 mL, 2.0 M) and the solvent was transferred to the reaction. The reaction was slowly heated to room temperature over the course of 3 hours. The reaction was then quenched by addition of a saturated solution of sodium bicarbonate ($NaHCO_3$) (1.0 mL). The biphasic solution was transferred to a 30 mL extraction funnel and DCM was added (~15 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried over Na_2SO_4, filtered over a sintered funnel, and evaporated to dryness. The oily residue was then directly flashed using a gradient of 100% Hexanes to 70% EtOAc in hexanes over a 24 g Isco Gold column using 35 mL/min flow, and injecting the crude on a silica gel precolumn pad. The column was pre-equilibrated with 100% Hexanes. The fractions containing pure product were combined and concentrated. The product (**6n**) was recuperated as a clear oil (301 mg, 85% Yield). $\mathbf{R_f}$: 0.70 (30% EtOAc in Hexanes); $\mathbf{[\alpha]_D^{25}}$: –712.1 (*c* = 0.87, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.41-7.34 (m, 3H), 7.32-7.24 (br m, 2H), 5.97 (dd, *J* = 4.0, 7.0 Hz, 1H), 5.67-5.57 (m, 2H), 5.39 (d, *J* = 4.0 Hz, 1H), 4.98-4.88 (m, 2H), 4.60 (q, *J* = 5.0 Hz, 1H), 3.63 (dd, *J* = 4.0, 7.0 Hz, 1H), 3.45 (dd, *J* = 5.5, 7.0 Hz, 1H), 3.39 (s, 3H), 3.27-3.22 (m, 1H), 2.69-2.52 (m, 2H), 1.70-1.62 (m, 1H), 1.47 (qn, *J* = 5.5 Hz, 2H), 0.85 (t, *J* = 5.5 Hz, 3H), 0.82 (d, *J* = 5.0 Hz, 3H), 0.63 (d, *J* = 5.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.4, 139.6, 135.8, 134.1, 129.3, 128.6, 128.1, 122.2, 122.1, 116.0, 110.1, 76.2, 63.7, 59.2, 56.0, 39.7, 31.4, 25.0, 20.0, 17.3, 9.8; **FTIR** (cm^{-1}) (neat): 2967, 1613, 1598, 1549, 1452; **HRMS** (ESI, Pos): calcd for $C_{23}H_{33}N_2O$ $[M+H]^+$: 353.2593 *m/z*, found: 353.2599 *m/z*.

Directed lithiation/Negishi cross-coupling (6o-6y)

General procedure for the lithiation/Negishi sequence on dihydropyridine 1a



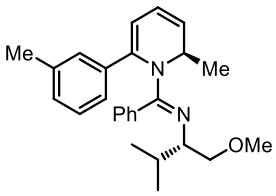
To a 2 mL oven-dried sealed tube (Biotage® 5 mL) equipped with a magnetic stirring bar, a rubber septum, and argon intlet was placed (2*S*)-1-methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2-methylpyridin-1(2*H*)-yl](phenyl)methylene]butan-2-amine **1a** (298.4 mg, 1.0 mmol, 1.0 equiv). The dihydropyridine was dissolved in 4 mL of anhydrous THF and was stirred 10 minutes at –78 °C in a dry ice and acetone bath. Then, a solution of *n*-BuLi in hexanes (1.2 mmol, 1.2 equiv) was added dropwise and was stirred 5 minutes at –78 °C. The flask was then warmed at 0 °C over the course of 1 hour in an ice and water bath. The sealed tube was rapidly opened under a positive pressure of argon stream and anhydrous $ZnBr_2$ (255 mg, 1.15 mmol, 1.15 equiv) (weighted in a 2 mL scintillation vial, sealed with a plastic cap) was added quickly and tube was resealed. The tube was warmed to room temperature and stirred for 30 minutes. The sealed tube was opened again, and the aryl or vinyl bromide (1.5 mmol, 1.5 equiv), the $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 2.5 mol%) and the PPh_3 (13.1 mg, 0.05 mmol, 5.0 mol%) (weighted in a 2 mL scintillation vial, sealed with a plastic cap) were rapidly added under a positive pressure of argon stream and the tube was crimped with a Biotage microwave Teflon cap. The tube was heated at 75 °C with an oil bath and was stirred 20 hours at 75 °C. The reaction was cooled to room temperature, decapped and it was diluted with a solution of $NaHCO_3$ (sat.) and DCM. The biphasic mixture was transferred into a 60 mL separation funnel and the layers were separated. The water layer was extracted with dichloromethane (4 x 10 mL) and the organic layers were combined and dried over Na_2SO_4, filtered and concentrated.



6o

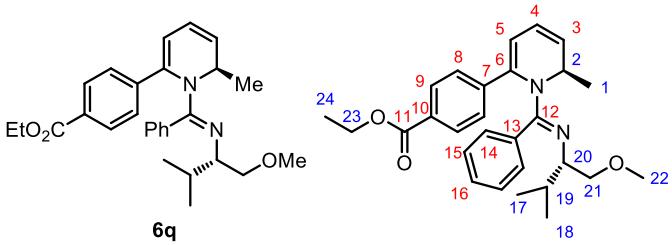
(2*S*)-1-methoxy-*N*-{[(2*R*)-6-(4-methoxyphenyl)-2-methylpyridin-1(2*H*)-yl](phenyl) methyl}-3-methylbutan-2-amine (6o): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine **6o** was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6o**) was isolated as a yellow oil (275.0 mg, 68% Yield). $\mathbf{R_f}$: 0.45 (30% EtOAc/Hexanes); $\mathbf{[\alpha]_D^{25}}$ = –531 (*c* = 1.21, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.09-6.90 (br m, 7H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.10 (dd, *J* = 6.0, 9.5

Hz, 1H), 5.75 (dd, *J* = 6.0, 9.0 Hz, 1H), 5.53 (d, *J* = 5.5 Hz, 1H), 5.28-5.15 (m, 1H), 3.77 (s, 3H), 3.61 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.48-3.43 (m, 1H), 3.42 (s, 3H), 3.16-3.11 (m, 1H), 1.65-1.55 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H), 0.54 (d, *J*= 6.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 160.2, 158.8, 139.5, 134.3, 133.6, 127.6, 127.4 (2), 127.0, 124.1, 122.2, 113.3, 108.3, 76.1, 63.7, 59.2, 55.3, 50.9, 31.2, 19.9, 17.6, 17.3; **FTIR** (neat) 2957, 1614, 1557, 1507, 1445, 1383, 1316, 1244 cm^{-1}; **HRMS** (ESI) Calcd for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2542, Found: 405.2548.



6p

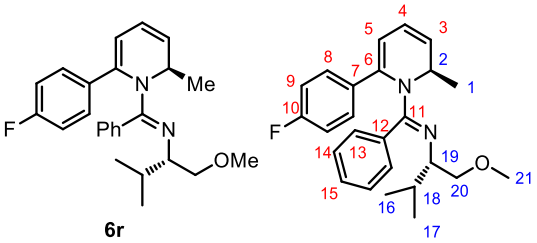
(2*S*)-1-Methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2-methyl-6-(3-methylphenyl)pyridine-1(2*H*)-yl](phenyl)methylene]butan-2-amine (6p): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6p**) was isolated as a yellow oil (272.7 mg, 68% Yield). **R_f**: 0.70 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –871 (*c* = 0.96, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.37-6.59 (m, 9H), 6.11 (dd, *J* = 5.5, 9.5 Hz, 1H), 5.76 (dd, *J* = 5.5, 9.0 Hz, 1H), 5.58 (d, *J* = 5.0 Hz, 1H), 5.26-5.16 (m, 1H), 3.60 (dd, *J* = 5.5, 10 Hz, 1H), 3.45 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.42 (s, 3H), 3.16-3.12 (m, 1H), 2.20 (s, 3H), 1.62-1.54 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H), 0.52 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 160.0, 140.6, 140.0, 137.2, 134.2, 130.3, 128.1, 127.6 (2), 127.4, 127.1, 124.5, 123.3, 122.1, 109.2, 76.2, 63.7, 59.3, 50.7, 31.2, 21.2, 19.8, 17.6, 17.3; **FTIR** (cm^{-1}) (neat): 2957, 2922, 2871, 1613, 1597, 1445, 1383; **HRMS** (ESI, Pos): calcd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2593 *m/z*, found: 389.2600 *m/z*.



6q

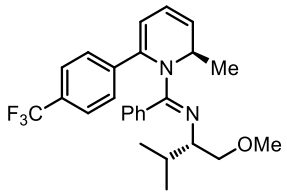
Ethyl 4-{(6*R*)-1-[(*E*)-{[(1*S*)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl) methyl]-6-methyl-1,6-dihydropyridin-2-yl}benzoate (6q): Following general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6q**) was isolated as a yellow oil (312.4 mg, 70% Yield). **R_f**: 0.60 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –602 (*c* = 2.31, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.77 (d, *J* = 7.5 Hz, 2H, C_8-*H*), 7.11-7.08 (br m, 7H, $C_{9\text{-}14\text{-}15\text{-}16}$-*H*), 6.12 (dd, *J* = 5.0, 9.5 Hz, 1H, C_4-*H*), 5.80 (dd, *J* = 3.5, 9.5 Hz, 1H, C_3-*H*), 5.69 (d, *J* = 5.0 Hz, 1H, C_5-*H*), 5.32-5.12 (m, 1H, C_2-*H*), 4.37 (q, *J* = 7.0 Hz, 2H, C_{23}-H), 3.59 (dd, *J* = 7.0, 10.0 Hz, 1H, C_{21}-*H*), 3.44 (dd, *J* = 7.5, 10.0 Hz, 1H, C_{21}-*H*), 3.41 (s, 3H, C_{22}-*H*), 3.14-3.10 (m, 1H, C_{20}-*H*), 1.60-1.52 (m, 1H, C_{19}-*H*), 1.40 (t, *J* = 7.0 Hz, 3H, C_{24}-H) 1.24 (d, *J* =

6.5 Hz, 3H, C_1-*H*), 0.67 (d, *J* = 7.0 Hz, 3H, C_{17}-*H*), 0.51 (d, *J* = 6.5 Hz, 3H, C_{18}-*H*); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 167.0 (C_{11}), 160.2 (C_{12}), 145.4 (C_{13}), 139.4 (C_7), 134.2 (C_{10}), 129.5 (C_8), 128.9 (C_{14}), 128.7 (2) ($C_{15\text{-}16}$), 128.4 (C_6), 126.3 (C_9), 126.2 (C_3), 122.3 (C_4), 111.5 (C_5), 76.4 (C_{21}), 64.2 (C_{20}), 61.2 (C_{23}), 59.6 (C_{22}), 51.1 (C_2), 31.6 (C_{19}), 20.2 (C_{18}), 18.1 (C_1), 17.7 (C_{17}), 14.7 (C_{24}); **FTIR** (cm^{-1}) (neat): 3039, 2958, 2923, 2872, 1714, 1618, 1265, 1100, 772, 714, 700; **HRMS** (ESI, Pos): calcd for $C_{28}H_{34}N_2O_3$ $[M+H]^+$: 447.2642 *m/z*, found: 447.2651 *m/z*.



6r

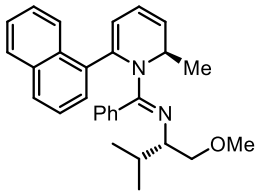
(2*S*)-*N*-[(1*E*)-[(2*R*)-6-(4-fluorophenyl)-2-methylpyridin-1(2*H*)-yl]-1-methoxy-3-methyl butan-2-amine (6r): Following general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 35% AcOEt/Hexanes) and the product (**6r**) was isolated as a yellow oil (258.0 mg, 66% Yield). **R_f**: 0.60 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –674.0 (*c* = 1.87, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.27-6.66 (br m, 9H, $C_{8\text{-}9\text{-}13\text{-}14\text{-}15}$-*H*), 6.11 (dd, *J* = 5.0, 9.0 Hz, 1H, C_4-*H*), 5.77 (dd, *J* = 5.5, 9.0 Hz, 1H, C_3-*H*), 5.55 (d, *J* = 5.0 Hz, 1H, C_5-*H*), 5.26-5.20 (m, 1H, C_2-*H*), 3.59 (dd, *J* = 5.0, 9.5 Hz, 1H, C_{20}-*H*), 3.46 (dd, *J* = 7.5, 9.5 Hz, 1H, C_{20}-H), 3.41 (s, 3H, C_{21}-*H*), 3.16-3.11 (m, 1H, C_{19}-*H*), 1.62-1.54 (m, 1H, C_{18}-*H*), 1.24 (d, *J* = 3.0 Hz, 3H, C_1-*H*), 0.70 (d, *J* = 7.0 Hz, 3H, C_{16}-*H*), 0.53 (d, *J* = 7.0 Hz, 3H, C_{17}-H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 161.6 (d, *J* = 245.0 Hz, $J_{C\text{-}F}$) (C_{10}), 159.5 (C_{11}), 138.5 (C_{12}), 136.4 (d, *J* = 4.0 Hz, $J_{C\text{-}F}$) (C_7), 133.8 (C_6), 129.9 (C_{15}), 127.5 (C_{14}), 127.4 (d, *J* = 12.0 Hz, $J_{C\text{-}F}$) (C_8), 127.4 (C_{13}), 124.4 (C_3), 121.6 (C_4), 114.2 (d, *J* = 21.0 Hz, $J_{C\text{-}F}$) (C_9), 108.9 (C_5), 75.7 (C_{20}), 63.4 (C_{21}), 58.8 (C_{19}), 50.5 (C_2), 30.9 (C_{18}), 19.5 (C_{17}), 17.2 (C_1), 17.0 (C_{16}); **^{19}F NMR** ($CHCl_3$, 375.5 MHz): δ –115.9 (F); **FTIR** (cm^{-1}) (neat): 3040, 2961, 2890, 1619, 1505, 1315, 1267, 701; **HRMS** (ESI, Pos): calcd for $C_{25}H_{30}FN_2O$ $[M+H]^+$: 393.2338 *m/z*, found: 393.2347 *m/z*.



6s

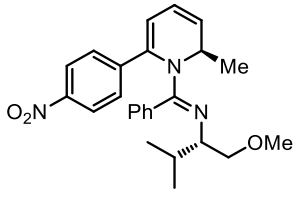
(2*S*)-1-methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2methyl-6-[4-(trifluoromethyl)phenyl] pyridine-1(2*H*)-yl](phenyl)methylene]butan-2-amine (6s): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6s**) was isolated as a yellow oil (290.0 mg, 66% Yield). **R_f**: 0.70 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –676.4 (*c* = 2.35, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.35 (d, *J* = 4.5 Hz, 2H), 7.16-6.61 (br m, 7H), 6.13 (dd, *J* = 6.0, 9.5 Hz, 1H), 5.82 (dd, *J* = 6.0, 9.0 Hz, 1H), 5.69 (d, *J* = 5.0 Hz, 1H), 5.25-5.11

(m, 1H), 3.58 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.45 (dd, *J* = 7.5, 9.0 Hz, 1H), 3.41 (s, 1H), 3.15-3.11 (m, 1H), 1.59-1.51 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 7.0 Hz, 3H), 0.51 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 159.2, 143.7, 138.2, 133.5, 128.3 (q, *J* = 32.0 Hz, $J_{C\text{-}F}$), 127.7, 127.5, 125.9 (2), 125.5, 124.3 (q, *J* = 3.4 Hz, $J_{C\text{-}F}$), 123.8 (q, *J* = 270 Hz, $J_{C\text{-}F}$), 121.5, 110.7, 75.6, 63.5, 58.8, 50.2, 30.8, 19.4, 17.3, 16.9; **^{19}F NMR** ($CHCl_3$, 97.07 MHz): δ –62.9 (CF_3); **FTIR** (cm^{-1}) (neat): 2961, 2890, 2245, 1617, 1599, 1557, 1324, 1126, 908, 733; **HRMS** (ESI, Pos): calcd for $C_{26}H_{30}F_3N_2O$ $[M+H]^+$: 443.2305 *m/z*, found: 443.2318 *m/z*.



6t

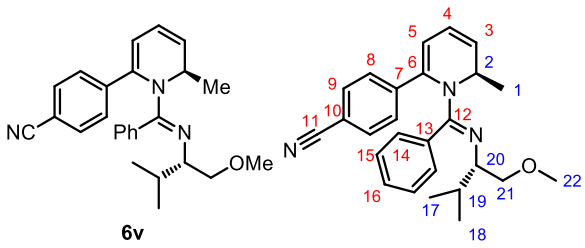
(2*S*)-1-methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2-methyl-6-(1-naphthyl)pyridine-1(2*H*)-yl] (phenyl)methylene]butan-2-amine (6t): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 15% AcOEt/Hexanes) and the product (**6t**) was isolated as a yellow oil (324.0 mg, 76% Yield). **R_f**: 0.40 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –337.4 (*c* = 2.2, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 300 MHz): δ 8.14 (br d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38-6.38 (br m, 9H), 6.19 (dd, *J* = 5.5, 9.5 Hz, 1H), 5.79 (dd, *J* = 6.5, 9.5 Hz, 1H), 5.60 (d, *J* = 5.5 Hz, 1H), 5.40-5.31 (m, 1H), 3.51 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.33-3.27 (m, 4H), 2.98-2.92 (m, 1H), 1.58-1.50 (m, 1H), 1.46 (d, *J* = 6.5 Hz, 3H), 0.67 (d, *J* = 6.0 Hz, 3H), 0.49 (d, *J* = 8.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 159.7, 137.7, 134.3, 133.5, 130.8, 128.8 (2), 127.6, 127.5, 127.2, 126.1, 125.2, 125.0, 124.9, 123.7, 122.0, 111.2, 75.9, 63.5, 59.2, 51.6, 31.0, 19.9, 17.8, 17.2 *Note: Two of the "Ph" carbons of the amidine are too broad to be identified/assigned properly at 25ºC in $CDCl_3$*; **FTIR** (cm^{-1}) (neat): 2958, 2923, 1617, 1555, 1445, 1383; **HRMS** (ESI, Pos): calcd for $C_{29}H_{33}N_2O$ $[M+H]^+$: 425.2593 *m/z*, found: 425.2598 *m/z*.



6u

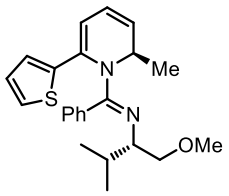
(2*S*)-1-methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2-methyl-6-(4-nitrophenyl)pyridin-1(2*H*)-yl] (phenyl)methylene]butan-2-amine (6u): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6u**) was isolated as a yellow oil (215.0 mg, 51% Yield). **R_f**: 0.65 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –663.0 (*c* = 0.27, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.96 (d, *J* = 9.0 Hz, 2H), 7.28-6.92 (br m, 7H), 6.14 (dd, *J* = 5.5, 9.5 Hz, 1H), 5.85-5.84 (m, 1H), 5.76 (d, *J* = 5.0 Hz, 1H), 5.18 (br m, 1H), 3.55 (dd, *J* = 4.5, 9.5

Hz, 1H), 3.45 (dd, *J* = 8.0, 9.5 Hz, 1H), 3.40 (s, 3H), 3.14-3.10 (m, 1H), 1.57-1.49 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.64 (d, *J* = 7.0 Hz, 3H), 0.50 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 160.2, 147.8, 147.1, 138.8, 134.3, 131.3, 129.2, 128.5, 127.8, 127.3, 124.1, 122.6, 113.3, 76.8, 64.8, 60.0, 51.5, 32.1, 20.6, 18.7, 18.2. **FTIR** (cm^{-1}) (neat): 2962, 2253, 1620, 1598, 1556, 1515, 1384, 1343; **HRMS** (ESI, Pos): calcd for $C_{25}H_{30}N_3O_3$ $[M+H]^+$: 420.2282 *m/z*, found: 420.2289 *m/z*.



6v

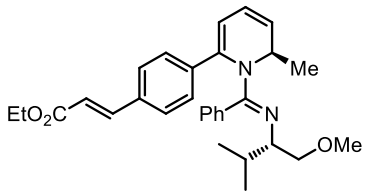
4-{(6*R*)-1-[(*E*)-{[(1*S*)-1-(methoxymethyl)-2-methylpropyl]imino}(phenyl)methyl]-6-methyl-1,6-dihydropyridin-2-yl}benzonitrile (6v) : Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 20% AcOEt/Hexanes) and the product (**6v**) was isolated as a yellow oil (306.7 mg, 77% Yield). **R_f**: 0.60 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –652.3 (*c* = 3.00, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 300 MHz): δ 7.36 (d, *J* = 8.5 Hz, 2H, C_8-*H*), 7.14-6.74 (br m, 5H, $C_{14\text{-}16}$-*H*), 7.11-7.05 (m, 2H, C_9-*H*), 6.11 (dd, *J* = 5.0, 9.0 Hz, 1H, C_4-*H*), 5.80 (dd, *J* = 6.5, 9.5 Hz, 1H, C_3-*H*), 5.69 (d, *J* = 5.0 Hz, 1H, C_5-*H*), 5.19-5.09 (m, 1H, C_2-*H*), 3.54 (dd, *J* = 5.0, 10.0 Hz, 1H, C_{21}-*H*), 3.43 (dd, *J* = 8.0, 8.5 Hz, 1H, C_{21}-*H*), 3.38 (s, 3H, C_{22}-*H*), 3.10 (ddd, *J* = 5.0, 8.0, 10.0 Hz, 1H, C_{20}-*H*), 1.57-1.46 (m, 1H, C_{19}-*H*), 1.21 (d, *J* = 6.5 Hz, 3H, C_1-*H*), 0.62 (d, *J* = 7.0 Hz, 3H, C_{17}-*H*), 0.48 (d, *J* = 7.0 Hz, 3H, C_{18}-*H*); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 159.8 (C_{12}), 145.5 (C_{13}), 138.6 (C_7), 134.0 (C_{10}), 132.1 (C_8), 131.0 (C_{16}), 128.6 (C_{14}), 127.0 (C_3), 126.9 (C_9), 123.0 (C_{15}), 122.2 (C_4), 119.6 (C_6), 112.3 (C_5), 110.3 (C_{11}), 76.4 (C_{21}), 64.3 (C_{20}), 59.6 (C_{22}), 51.0 (C_2), 31.7 (C_{19}), 20.2 (C_{18}), 18.2 (C_1), 17.8 (C_{17}); **FTIR** (cm^{-1}) (neat): 3040, 2960, 2922, 2890, 2225, 1619, 1604, 1315, 1268, 1112, 702; **HRMS** (ESI, Pos): calcd for $C_{26}H_{30}N_3O$ $[M+H]^+$: 400.2383 *m/z*, found: 400.2391 *m/z*.



6w

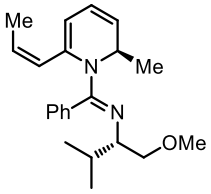
(2*S*)-1-methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2-methyl-6-(2-thienyl)pyridin-1(2*H*)-yl](phenyl)methylene]butan-2-amine (6w): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6w**) was isolated as a yellow oil (209.9 mg, 55% Yield); **R_f**: 0.80 (30% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –574 (*c* = 0.316, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.23-6.94 (br m, 6H), 6.84-6.77 (m, 2H), 6.13-6.08 (dd, *J* = 5.5, 9.0 Hz, 1H), 5.77-5.72 (m, 2H), 5.10-5.00 (m, 1H), 3.60 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.47 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.41 (s, 3H), 3.19-3.15 (m, 1H), 1.62-1.54 (m, 1H), 1.20 (d, *J* = 7.0 Hz,

3H), 0.69 (d, *J* = 7.0 Hz, 3H), 0.52 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 160.1, 144.6, 133.8, 133.6, 128.6, 127.8, 127.4, 126.8, 125.4, 124.5, 124.2, 122.1, 109.7, 76.0, 63.9, 59.3, 51.0, 31.2, 19.8, 17.8, 17.3; **FTIR** (cm^{-1}) (neat): 2958, 2923, 2892, 2873, 1620, 1555, 1445; **HRMS** (ESI, Pos): calcd for $C_{23}H_{29}N_2OS$ $[M+H]^+$: 381.2001 *m/z*, found: 381.2000 *m/z*.



6x

(*E*)-Ethyl-3-(4-((*R*)-1-((*E*)-(((*S*)-1-methoxy-3-methylbutan-2-yl)imino)(phenyl)methyl)-6-methyl-1,6-dihydropyridin-2-yl)phenyl)acrylate (6x): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 30% AcOEt/Hexanes) and the product (**6x**) was isolated as a yellow oil (328 mg, 70% Yield); **R_f**: 0.30 (20% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –531 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.60 (d, *J* = 16.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.35-6.65 (br m, 5H), 7.12-7.01 (m, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.12 (dd, *J* = 5.0, 8.5 Hz, 1H), 5.79 (dd, *J* = 3.0, 8.5 Hz, 1H), 5.67 (d, *J* = 5.0 Hz, 1H), 5.20 (br s, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.58 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.45 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.41 (s, 3H), 3.14-3.10 (m, 1H), 1.60-1.51 (m, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 6.5 Hz, 3H), 0.50 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.8, 159.4, 143.9 (2), 142.2, 138.8, 133.5, 132.5, 130.1 (br), 127.5, 127.3, 127.2 (br), 126.1, 125.2, 121.6, 117.1, 75.7, 63.4, 60.1, 58.8, 50.3, 30.8, 19.4, 17.3, 16.9, 14.0; **FTIR** (cm^{-1}) (neat): 2960, 2924, 2891, 1713, 1632, 1601, 1562, 1366, 1311, 1267; **HRMS** (ESI, Pos): calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804 *m/z*, found: 473.2811 *m/z*.

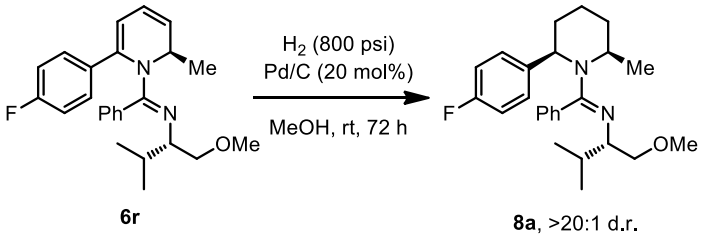


6y

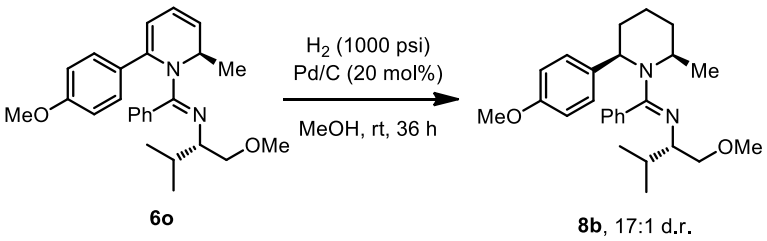
(2*S*)-1-methoxy-3-methyl-*N*-[(1*E*)-[(2*R*)-2-methyl-6-[(1*Z*)-prop-1-en-1-yl]pyridin-1(2*H*)-yl](phenyl)methylene]butan-2-amine (6y): Following the general Negishi procedure, the crude 2,6-disubstituted dihydropyridine was purified by chromatography on silica gel (100% Hexanes to 10% AcOEt/Hexanes) and the product (**6y**) was isolated as a yellow oil (259.0 mg g, 77% Yield). **R_f**: 0.20 (15% EtOAc/Hexanes); **$[\alpha]_D^{25}$**: –286.0 (*c* = 1.51, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 300 MHz): δ 7.27-7.10 (br m, 5H), 6.02 (dd, *J* = 5.0, 9.5 Hz, 1H), 5.65 (dd, *J* = 6.0, 9.0 Hz, 1H), 5.32-5.22 (m, 3H), 5.05-4.94 (m, 1H), 3.63 (dd, *J* = 5.0, 10.5 Hz, 1H), 3.52 (dd, *J* = 7.0, 9.0 Hz, 1H), 3.41 (s, 3H), 3.31-3.33 (m, 1H), 1.70-1.61 (m, 1H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.60 (d, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 160.2, 136.6, 135.3, 130.5, 129.8, 129.1, 128.5, 127.3, 124.8,

122.4, 110.5, 77.2, 64.2, 60.0, 51.8, 32.4, 20.8, 18.2, 18.1, 15.8; **FTIR** (cm^{-1}) (neat): 2958, 2922, 2871, 1616, 1598, 1564, 1414, 1384; **HRMS** (ESI, Pos): calcd for $C_{22}H_{31}N_2O$ $[M+H]^+$: 339.2436 *m/z*, found: 339.2441 *m/z.*

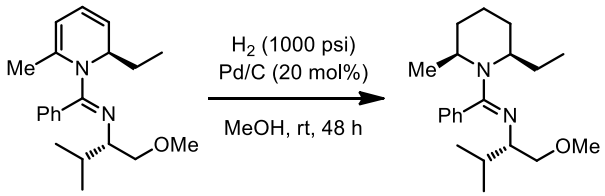
Diastereoselective hydrogenation of 2,6-disubstituted dihydropyridines (8a-8d)



(2*R*)-*N*-[(1*E*)-[(6*R*)-2-(4-Fluorophenyl)-6-methylpiperidin-1-yl](phenyl)methylene]-1-methoxy-3-methylbutan-2-amine (8a): To a 25 mL round bottom flask was added the freshly purified dihydropyridine **6r** (100.0 mg, 0.254 mmol, 1.0 equiv). It was dissolved in anhydrous MeOH (1.0 mL, 0.25 M) and anhydrous Pd/C 10%wt was added to the solution (55 mg, 0.05 mmol, 0.2 equiv). ***Caution:** *Dry palladium black is pyrophoric and should always be wet with the appropriate solvent prior to its transfer to the flask or autoclave.** The black suspension was stirred for 2 minutes at rt then the flask was transferred to a metal autoclave. The flask was capped with a septa pierced with a needle. The autoclave was sealed and pressurized at 800 psi of hydrogen (with 2 purges). The hydrogenation was stirred at rt for 72 hours (conversion monitored by LCMS). The hydrogen pressure was slowly lowered to ambient pressure and the autoclave was opened to air. The black suspension was then filtered on a Celite® plug and the cake was washed with MeOH thoroughly (~50 mL). The solvent was evaporated to dryness under vacuum and the crude mixture was analyzed by ^{1}H NMR showing a ratio of >20:1 of diastereoisomers. The crude mixture was then flashed on silica gel using a gradient of 80% EtOAc in hexanes to 10% MeOH in EtOAc and the piperidine **8a** was recuperated as a translucid oil (59 mg, 57% Yield). $\mathbf{R_f}$ = 0.40 (15% MeOH/EtOAc); $\mathbf{[\alpha]_D^{25}}$: +26.1 (*c* = 1.28, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.49-7.44 (m, 2H), 7.42-7.32 (m, 3H), 7.27-7.23 (m, 2H), 7.01 (app t, *J* = 7.5 Hz, 2H), 5.75 (br s, 1H), 3.95-3.88 (m, 1H), 3.44 (dd, *J* = 5.5, 9.5 Hz, 1H), 3.31 (s, 1H), 3.23 (dd, *J* = 7.5, 9.5 Hz, 1H), 2.89-2.85 (m, 1H), 2.41-2.32 (m, 1H), 1.90-1.79 (m, 2H), 1.72-1.59 (m, 3H), 1.42-1.34 (m, 1H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.9, 160.8 (d, *J* = 241.5 Hz, $J_{C\text{-}F}$), 140.1 (d, *J* = 3.0 Hz, $J_{C\text{-}F}$), 135.1, 128.1 (d, *J* = 7.5 Hz, $J_{C\text{-}F}$), 127.8, 127.5 (2), 114.0 (d, *J* = 21.0 Hz, $J_{C\text{-}F}$), 76.1, 62.6, 58.6, 49.5, 48.1, 30.4 (2), 26.3, 20.3, 19.8, 17.1, 15.4; **^{19}F NMR** (375.5 MHz, $CDCl_3$) δ –118.7; **FTIR** (cm^{-1}) (neat): 2933, 2870, 1609, 1593, 1508, 1408, 1341; **HRMS** (ESI, Pos): calcd for $C_{25}H_{34}N_2OF$ $[M+H]^+$: 397.2650 *m/z*, found: 397.2657 *m/z*.



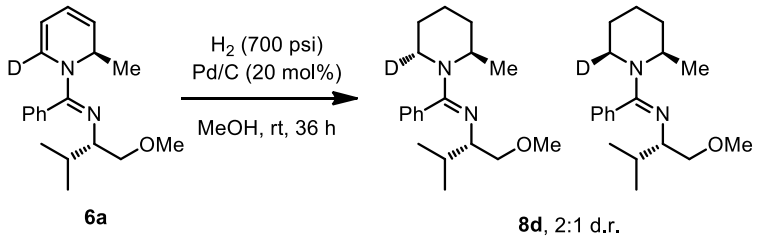
(2*R*)-*N*-[(1*E*)-[(6*R*)-2-(4-Methoxyphenyl)-6-methylpiperidin-1-yl](phenyl)methylene]-1-methoxy-3-methylbutan-2-amine (8b): To a 300 mL stainless steel autoclave was added the freshly purified dihydropyridine **6o** (270.0 mg, 0.668 mmol, 1.0 equiv). It was dissolved in anhydrous MeOH (15.0 mL, 0.05 M) and anhydrous Pd/C 10%wt was added to the solution (142 mg, 0.134 mmol, 0.2 equiv). ***Caution:** *Dry palladium black is pyrophoric and should always be wet with the appropriate solvent prior to its transfer to the flask or autoclave*.* The black suspension was stirred for 2 minutes at rt. The autoclave was sealed and pressurized at 1000 psi of hydrogen (with 2 purges). The hydrogenation was stirred at rt for 36 hours. The hydrogen pressure was slowly lowered to ambient pressure and the autoclave was opened to air (conversion monitored by LCMS). The black suspension was then filtered on a Celite® plug and the cake was washed with MeOH thoroughly (~50 mL). The solvent was evaporated to dryness under vacuum and the crude mixture was analyzed by ^{1}H NMR showing a ratio of 17:1 of diastereoisomers. The crude mixture was then flashed on silica gel using a gradient of 100% Hexanes to 60% EtOAc in Hexanes using a **Isco Gold DIOL 30 g** column pre-equilibrated with 100% Hexanes. The flow rate was set at 40 mL/min and the crude mixture was injected on a prepacked Celite ® precolumn. The piperidine **8b** was recuperated as a translucid oil (170 mg, 62% Yield, 17:1 d.r.). $\mathbf{R_f}$ = 0.70 (50% EtOAc in Hexanes with Gold DIOL coated TLC plates); $\mathbf{[\alpha]_D^{25}}$: +41.2 (*c* = 0.958, $CHCl_3$); For major diastereoisomer: **^{1}H NMR** ($CDCl_3$, 700 MHz): δ 7.48-7.31 (m, 5H), 7.31-7.26 (m, 2H). 6.88 (d, *J* = 9.0 Hz, 2H), 5.75-5.63 (m, 1H), 4.00 (br app qn, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.47 (dd, *J* = 5.5, 8.0 Hz, 1H), 3.33 (s, 3H), 3.27 (dd, *J* = 7.0 Hz, 8.0 Hz, 1H), 2.94-2.86 (m, 1H), 2.43-2.34 (m, 1H), 1.97-1.77 (m, 2H), 1.76-1.56 (m, 3H), 1.44-1.35 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H, 0.75 (d, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 175 MHz): δ 161.4, 157.7, 136.8, 135.7, 128.2, 128.1, 128.0, 127.8, 113.1, 76.5, 63.0, 59.0, 55.2, 49.8, 48.4, 31.1, 30.8, 26.6, 20.4, 20.3, 17.4, 15.9; **FTIR** (cm^{-1}) (neat): 2931, 2867, 1608, 1591, 1509, 1282; **HRMS** (ESI, Pos): calcd for $C_{26}H_{37}N_2O_2$ $[M+H]^+$: 409.2855 *m/z*, found: 409.2855 *m/z*.



6k **8c**, >20:1 d.r.

(2*R*)-*N*-[(1*E*)-[(6*R*)-2-Ethyl-6-methylpiperidin-1-yl](phenyl)methylene]-1-methoxy-3-methylbutan-2-amine (8c): To a 20 mL vial with a plastic screwcap pierced with a needle was added the freshly purified dihydropyridine **6k** (170.0 mg, 0.52 mmol, 1.0 equiv). It was dissolved in anhydrous MeOH (10.0 mL, 0.05 M) and anhydrous Pd/C 10% wt was added to the solution (115 mg, 0.104 mmol, 0.2 equiv). ***Caution:** *Dry palladium black is pyrophoric and should always be wet with the appropriate solvent prior to its transfer to the flask or autoclave*.* The black suspension was stirred for 2 minutes at rt. The vial was transferred to an autoclave and it was sealed and pressurized at 1000 psi of hydrogen (with 2 purges). The hydrogenation was stirred at rt for 48 hours (conversion monitored by

LCMS). The hydrogen pressure was slowly lowered to ambient pressure and the autoclave was opened to air. The black suspension was then filtered on a Celite® plug and the cake was washed with MeOH thoroughly (~50 mL). The solvent was evaporated to dryness under vacuum and the crude mixture was analyzed by ^{1}H NMR showing a ratio of >20:1 of diastereoisomers. The crude mixture was then flashed on silica gel using a gradient of 100% Hexanes to 60% EtOAc in Hexanes using a **Isco Gold DIOL 30 g** column pre-equilibrated with 100% Hexanes. The flow rate was set at 40 mL/min and the crude mixture was injected on a prepacked Celite ® precolumn. The piperidine **8c** was recuperated as a translucid oil (118 mg, 70% Yield). $\mathbf{R_f}$ = 0.70 (30% EtOAc in Hexanes with Gold DIOL coated TLC plates); $\mathbf{[\alpha]_D^{25}}$: −17.1 (*c* = 0.760, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.30 (m, 3H), 7.14 (d, *J* = 5.5 Hz, 2H), 4.17 (very br s, 1H), 3.62 (very br s, 1H), 3.36 (dd, *J* = 5.0, 7.5 Hz, 1H), 3.20 (s, 3H), 3.12 (dd, *J* = 5.0, 8.0 Hz, 1H), 2.85-2.81 (m, 1H), 1.80-1.68 (m, 2H), 1.67-1.55 (m, 4H), 1.51-1.43 (m, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.71 (br t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.6, 135.8, 128.1, 128.0, 127.5, 76.3, 62.3, 58.8, 53.3, 46.3, 30.8, 30.5, 27.4, 27.0, 20.3, 19.8, 17.2, 15.2, 12.3; **FTIR** (cm^{-1}) (neat): 2957, 2930, 2870, 1608, 1593, 1491, 1344, 1275, 1156; **HRMS** (ESI, Pos): calcd for $C_{21}H_{35}N_2O$ $[M+H]^+$: 331.2744 *m/z*, found: 331.2751 *m/z*.

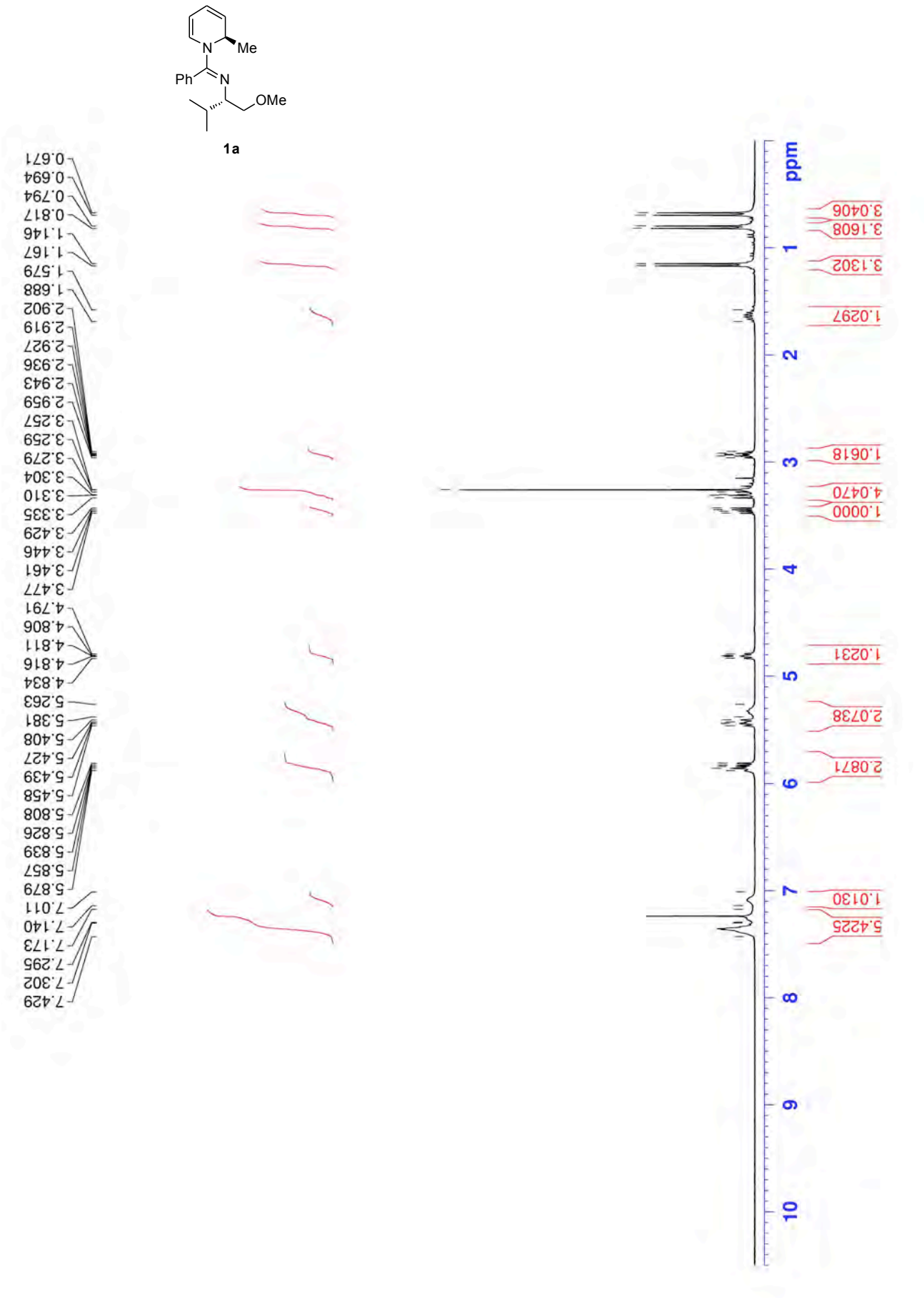


(2*S*)-*N*-[(1*E*)-[(6*R*)-2-(Deutero)-6-methylpiperidin-1-yl](phenyl)methylene]-1-methoxy-3-methylbutan-2-amine (8d): To a 20 mL vial with a plastic screwcap pierced with a needle was added the freshly purified dihydropyridine **6a** (250.0 mg, 0.836 mmol, 1.0 equiv). It was dissolved in anhydrous MeOH (10.0 mL, 0.083 M) and anhydrous Pd/C 10%wt was added to the solution (178 mg, 0.167 mmol, 0.2 equiv). ***Caution:** *Dry palladium black is pyrophoric and should always be wet with the appropriate solvent prior to its transfer to the flask or autoclave.** The black suspension was stirred for 2 minutes at rt. The vial was transferred to an autoclave and it was sealed and pressurized at 700 psi of hydrogen. The hydrogenation was stirred at rt for 36 hours (conversion monitored by LCMS). The hydrogen pressure was slowly lowered to ambient pressure and the autoclave was opened to air. The black suspension was then filtered on a Celite® plug and the cake was washed with MeOH thoroughly (~50 mL). The solvent was evaporated to dryness under vacuum and the crude mixture was analyzed by ^{1}H NMR showing a ratio of 2:1 of diastereoisomers favoring the *trans* isomer (see attached nOe analysis). The crude mixture was then flashed on silica gel using a gradient of 100% Hexanes to 60% EtOAc in Hexanes using a **Isco Gold DIOL 30 g** column pre-equilibrated with 100% Hexanes. The flow rate was set at 40 mL/min and the crude mixture was injected on a prepacked Celite ® precolumn. The piperidine **8d** was recuperated as a yellow oil (182 mg, 73% Yield for

combined diastereoisomers, 2:1 d.r.). **R_f** = 0.50 (10% MeOH/EtOAc over silica gel TLC); **$[\alpha]_D^{25}$**: –74.7 (*c* = 1.159, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.42-7.31 (m, 3H), 7.22-7.13 (m, 2H), 4.10 (br s, 1H), 3.61 (br s, 1H, minor diastereoisomer), 3.39 (dd, *J* = 5.5, 7.5 Hz, 1H), 3.23 (s, 3H), 2.90-2.83 (m, 1H), 2.88 (d, *J* = 12.0 Hz, 1H, major diastereoisomer), 1.75-1.50 (m, 5H), 1.48-1.37 (m, 2H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): For major diastereoisomer δ 160.9, 135.7, 128.2, 128.1, 127.7, 76.4, 62.9, 58.8, 47.0, 40.0 (br t, *J* = 16.5 Hz, *C*□D), 30.7, 30.4, 25.8, 20.1, 19.5, 18.1, 14.6; **FTIR** (cm^{-1}) (neat): 2929, 2868, 1610, 1594, 1401, 1354, 1300, 1244, 1112; **HRMS** (ESI, Pos): calcd for $C_{19}H_{30}DN_2O$ $[M+H]^+$: 304.2494 *m/z*, found: 304.2494 *m/z*.

Copy of spectra for all synthesized compounds (^{1}H, ^{13}C, ^{19}F)

Attached selective nOe spectra for **8a**-**8d**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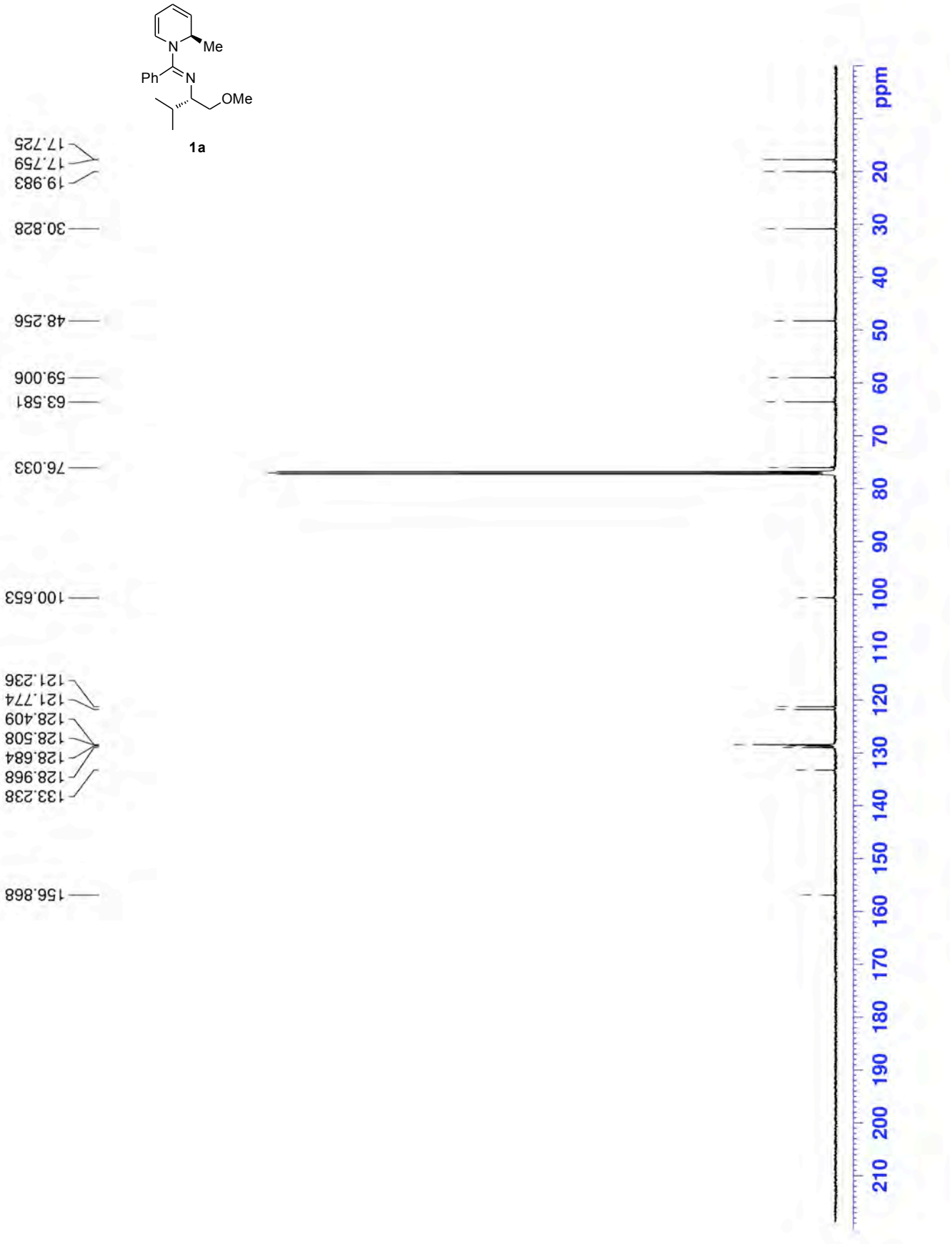
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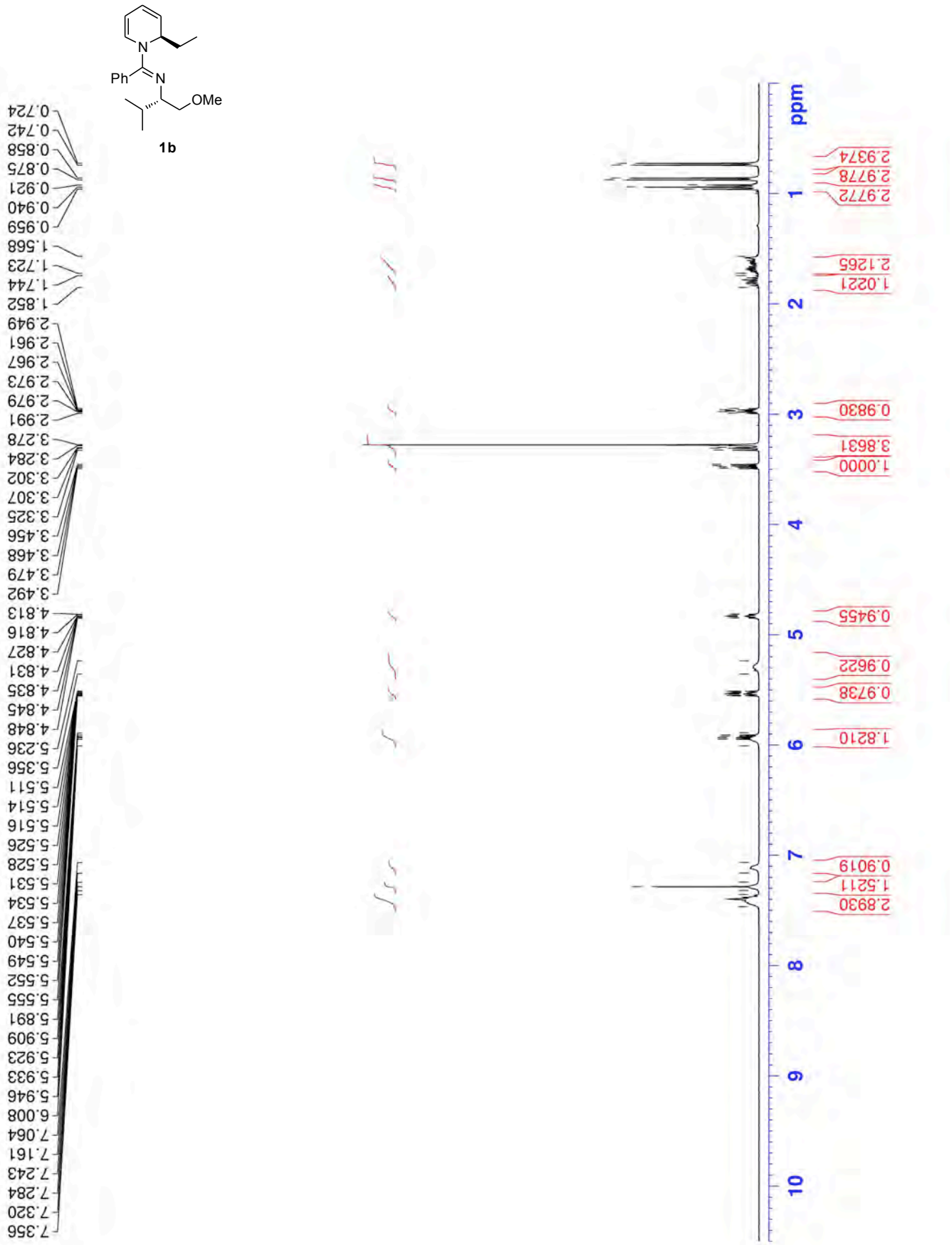
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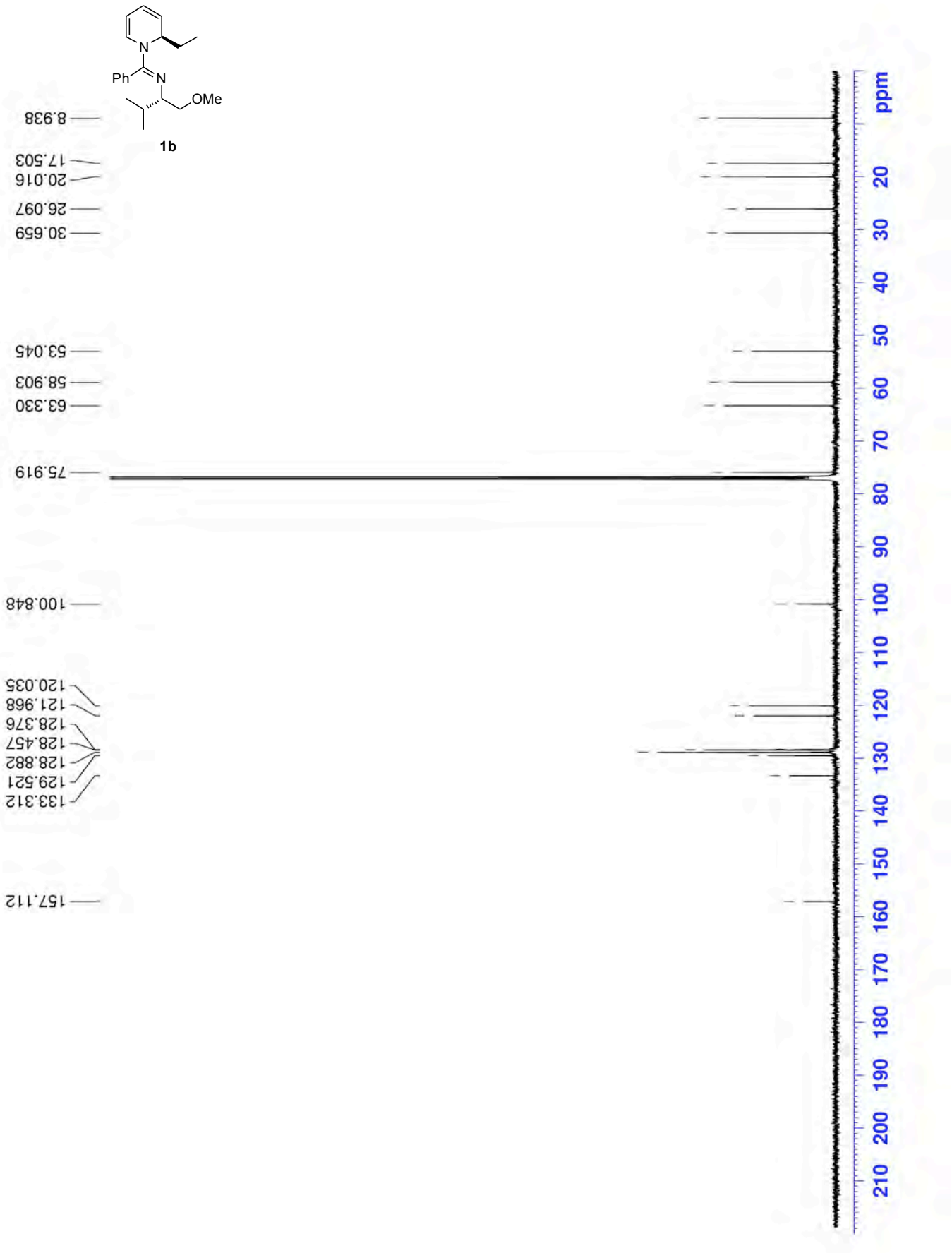
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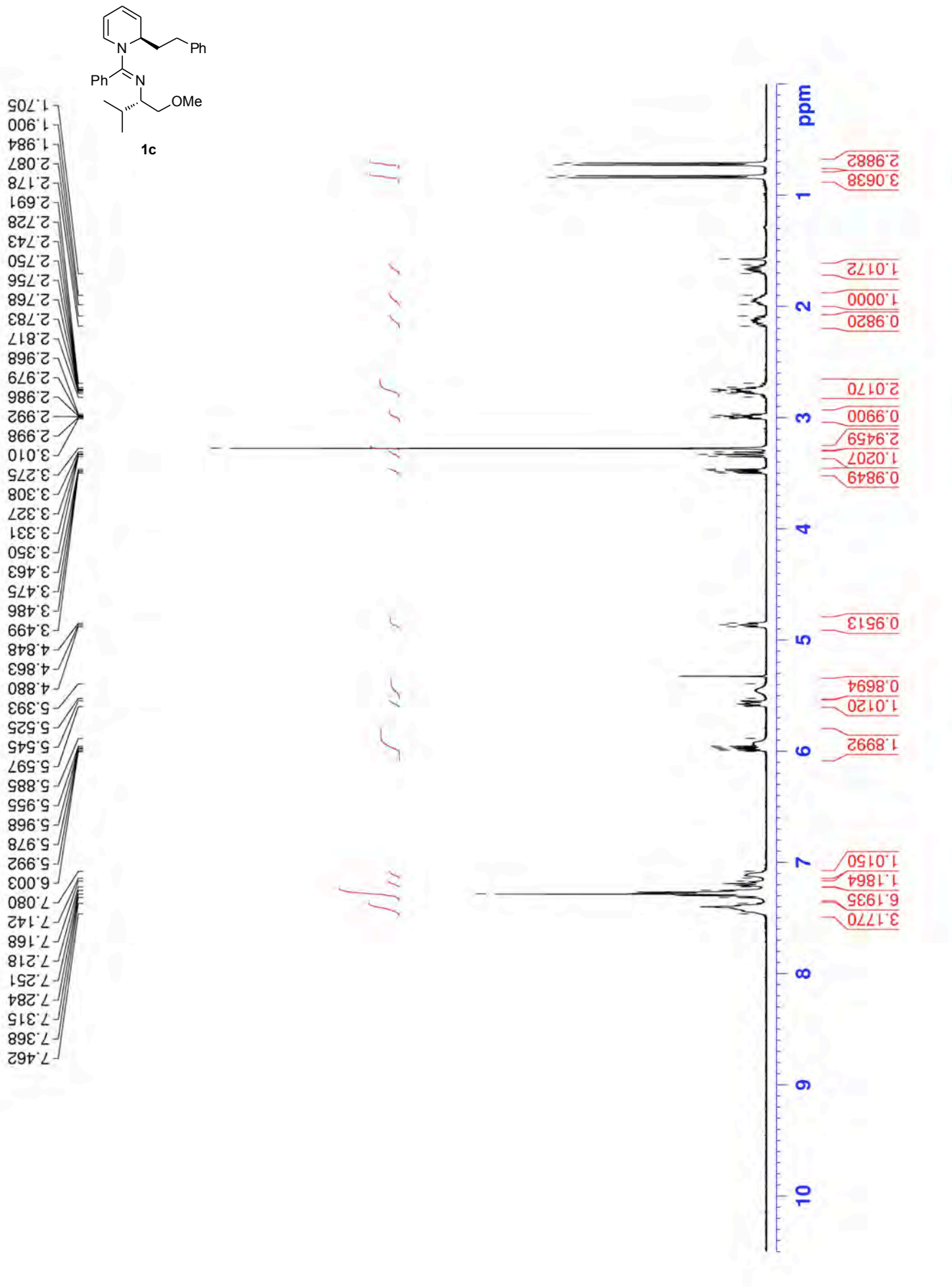
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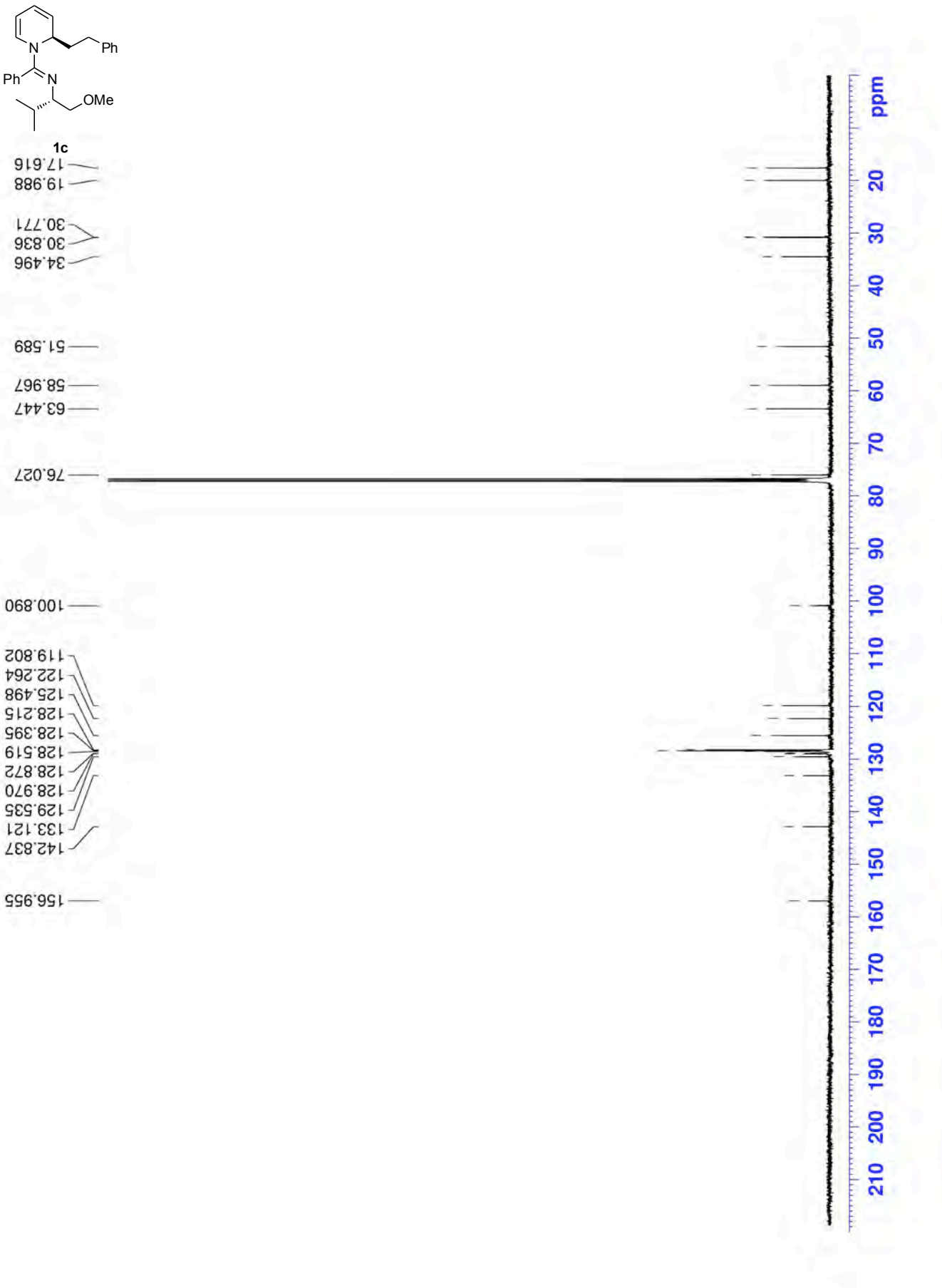
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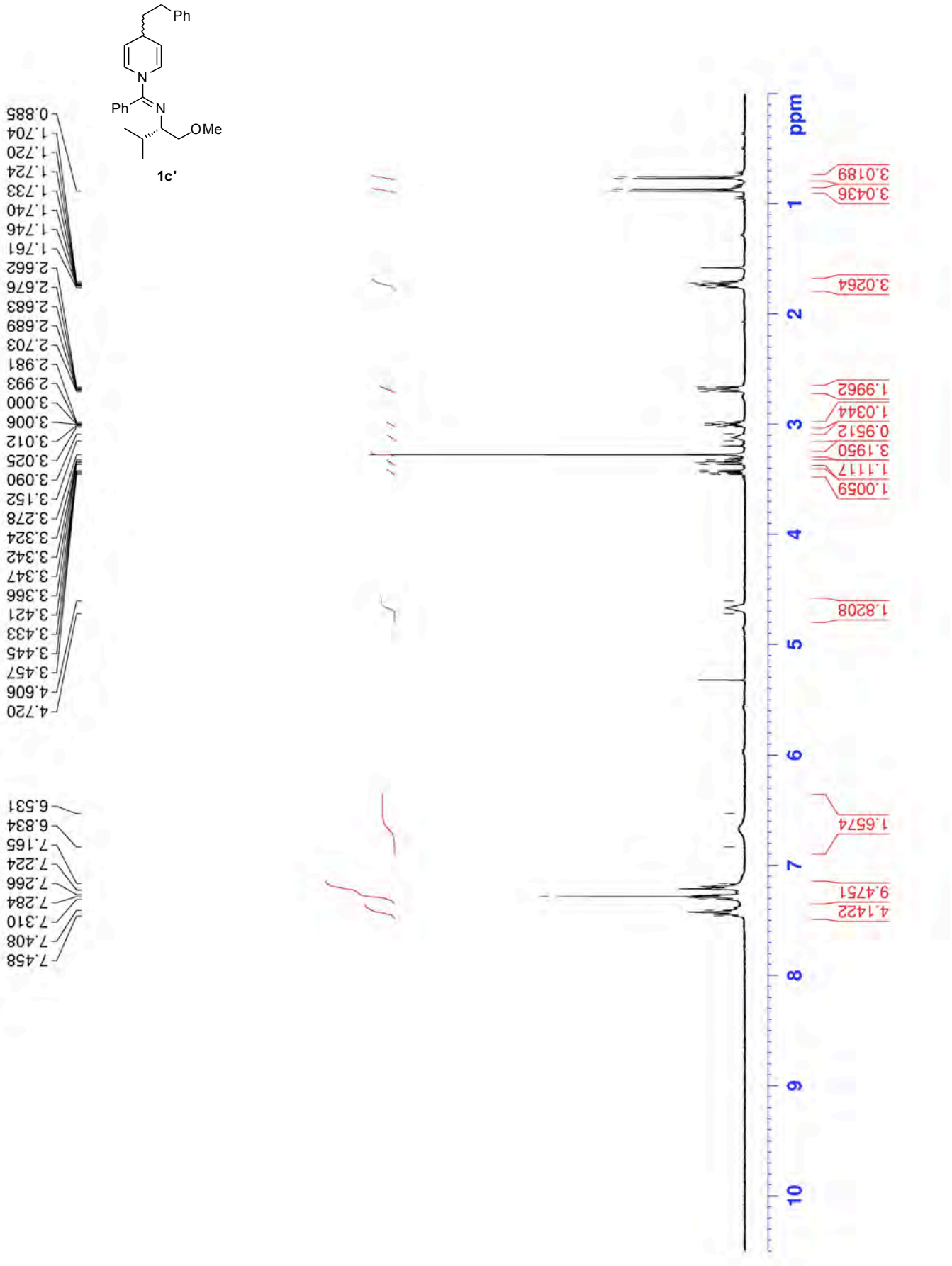
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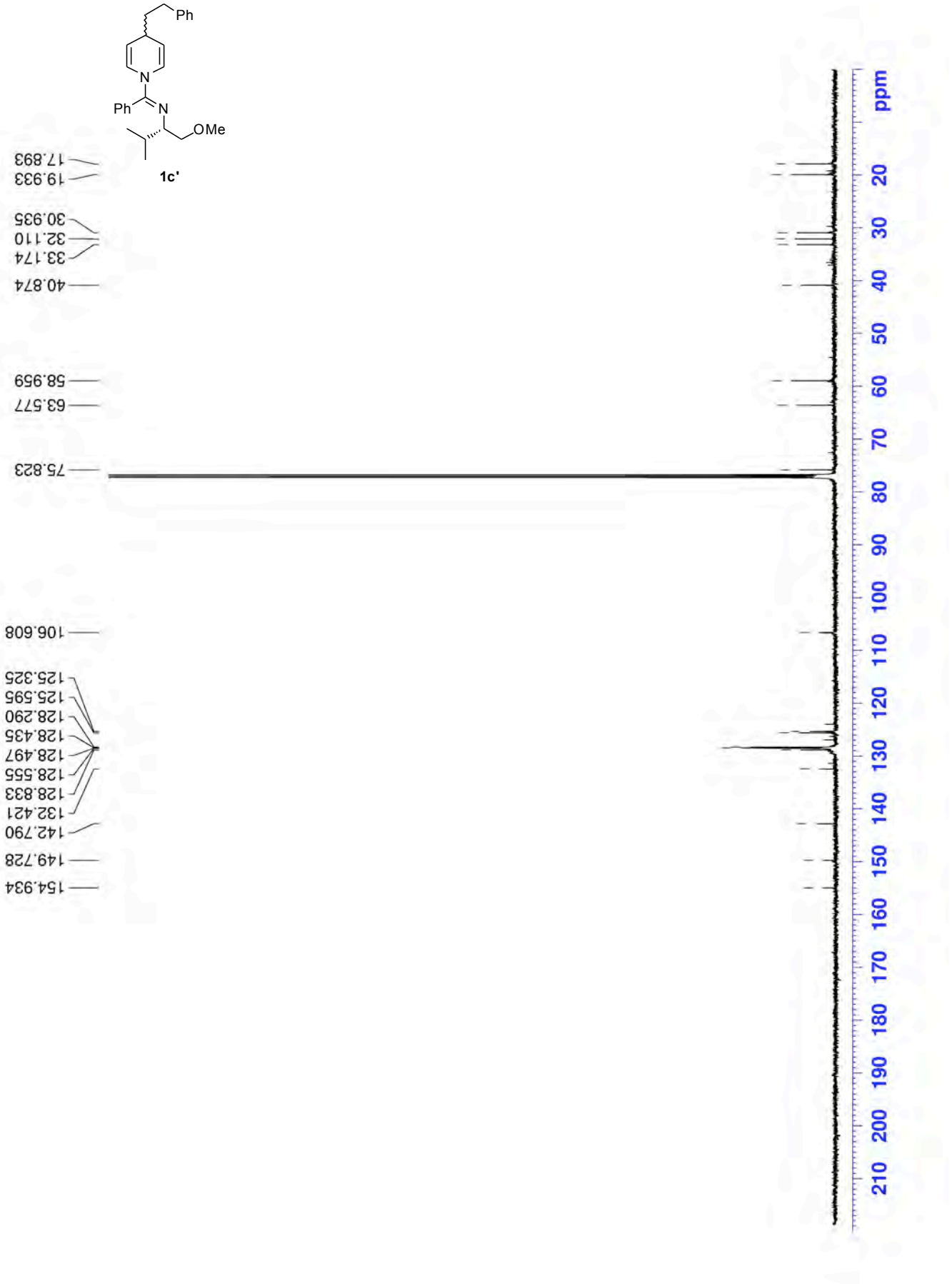
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Ph
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OMe
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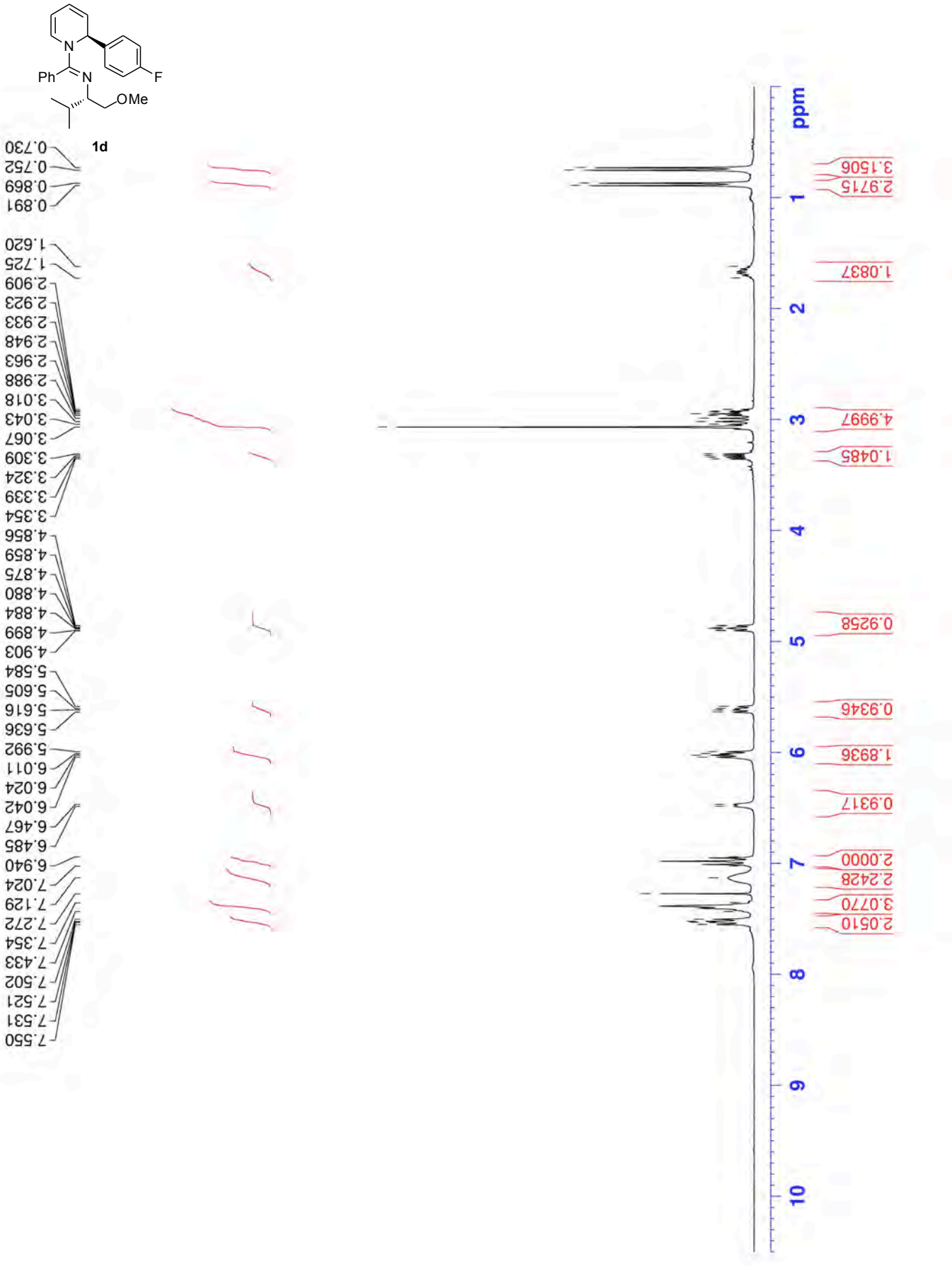
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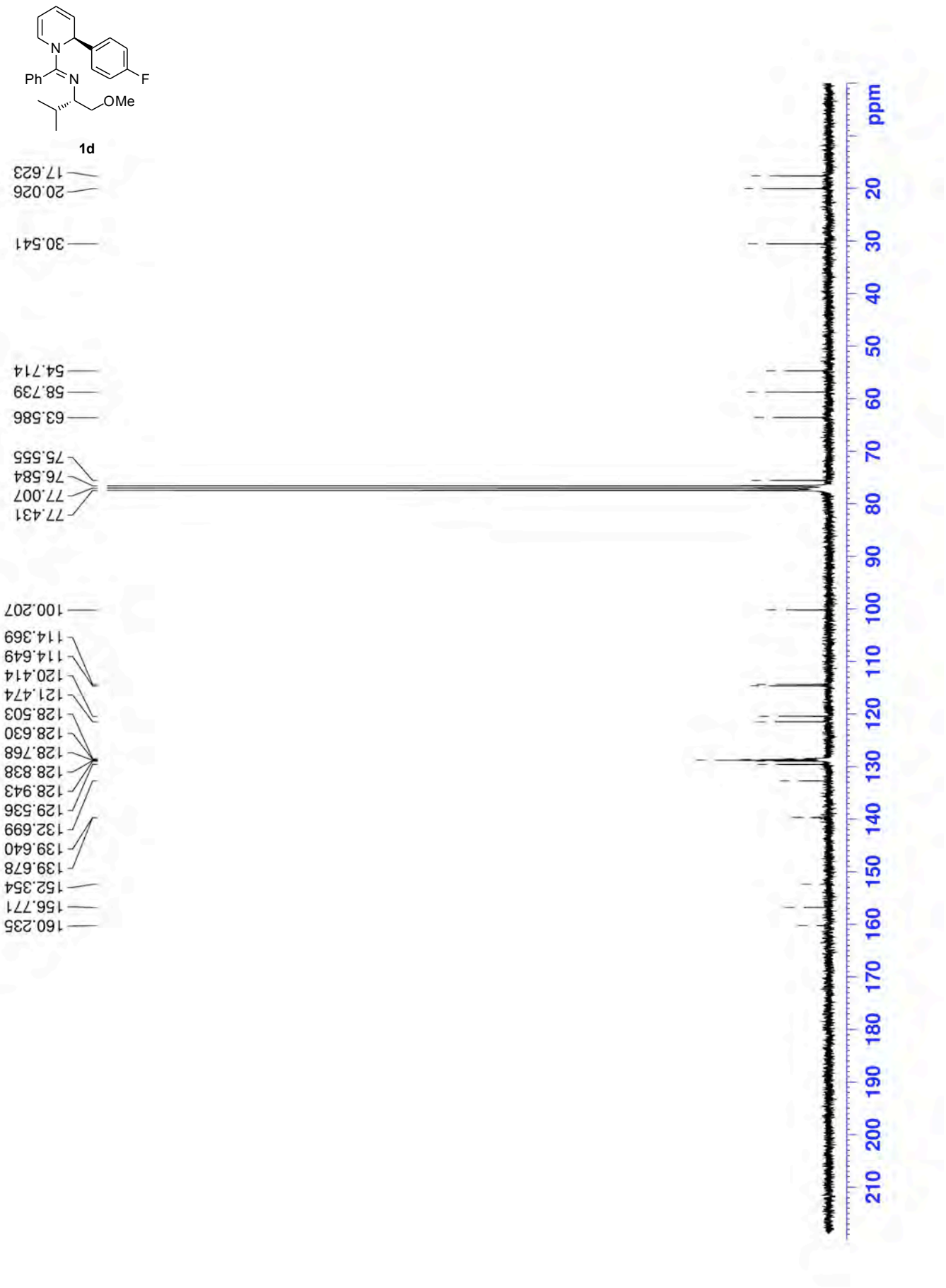
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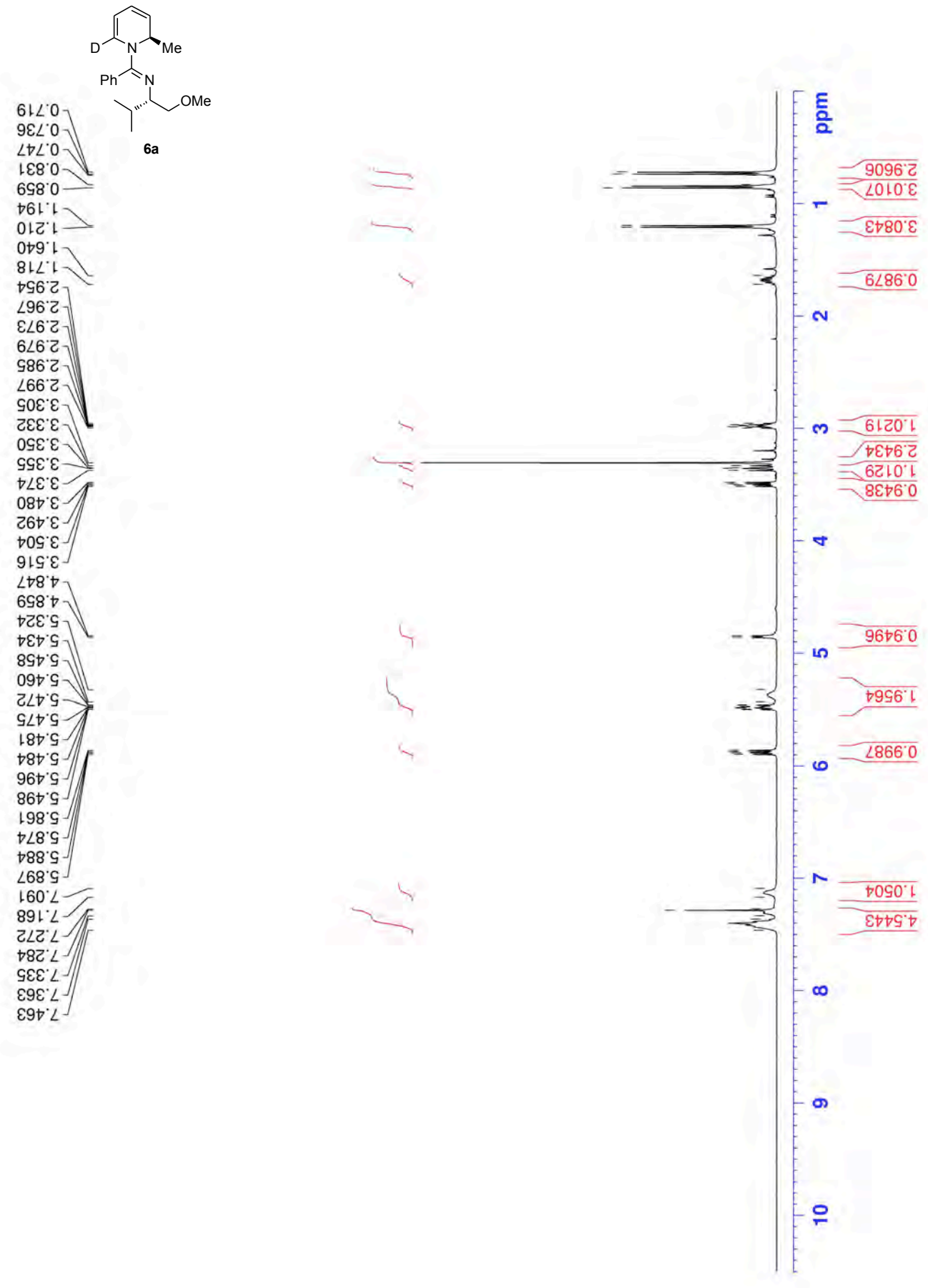
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3.374
3.480
3.492
3.504
3.516
4.847
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5.324
5.434
5.458
5.460
5.472
5.475
5.481
5.484
5.496
5.498
5.861
5.874
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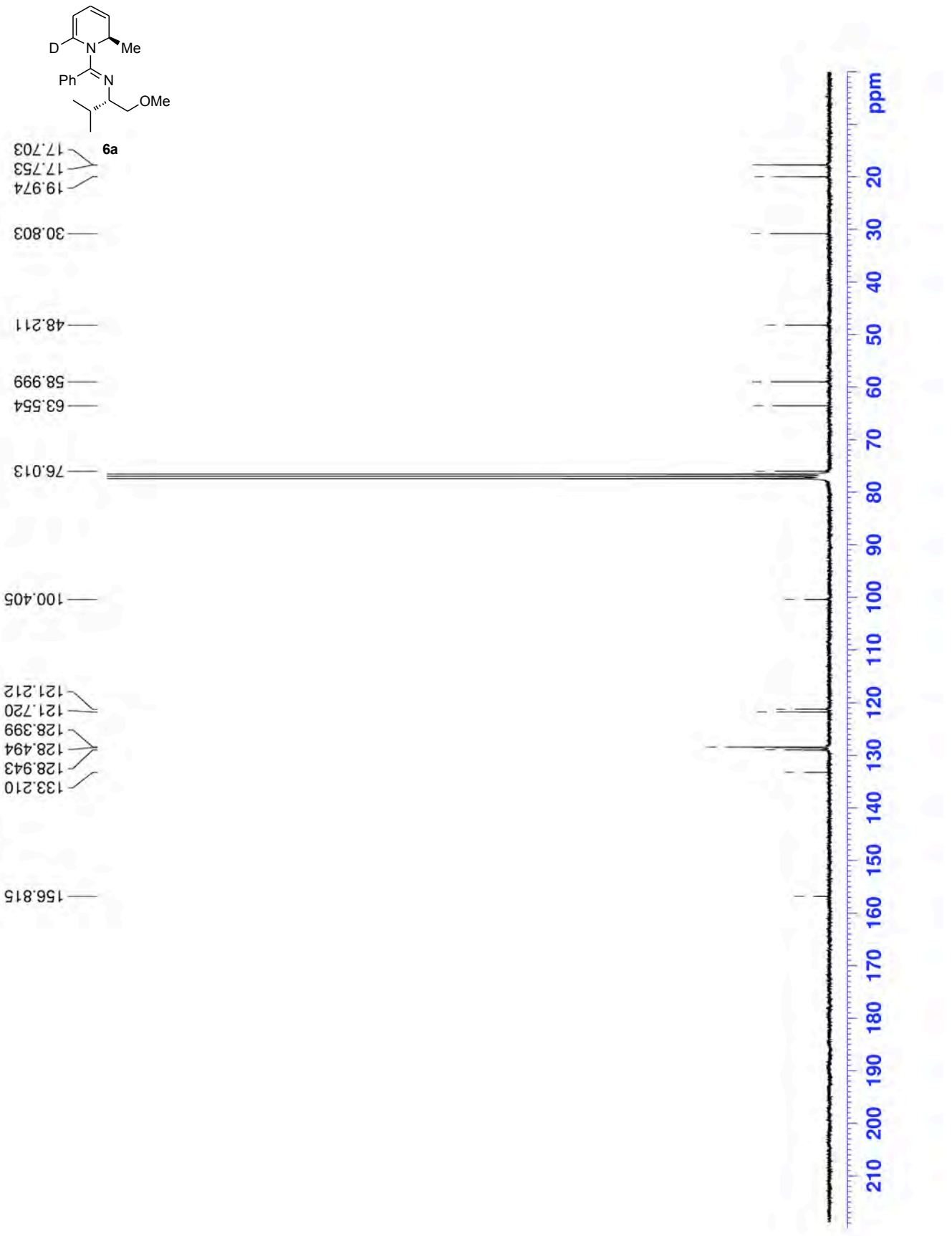
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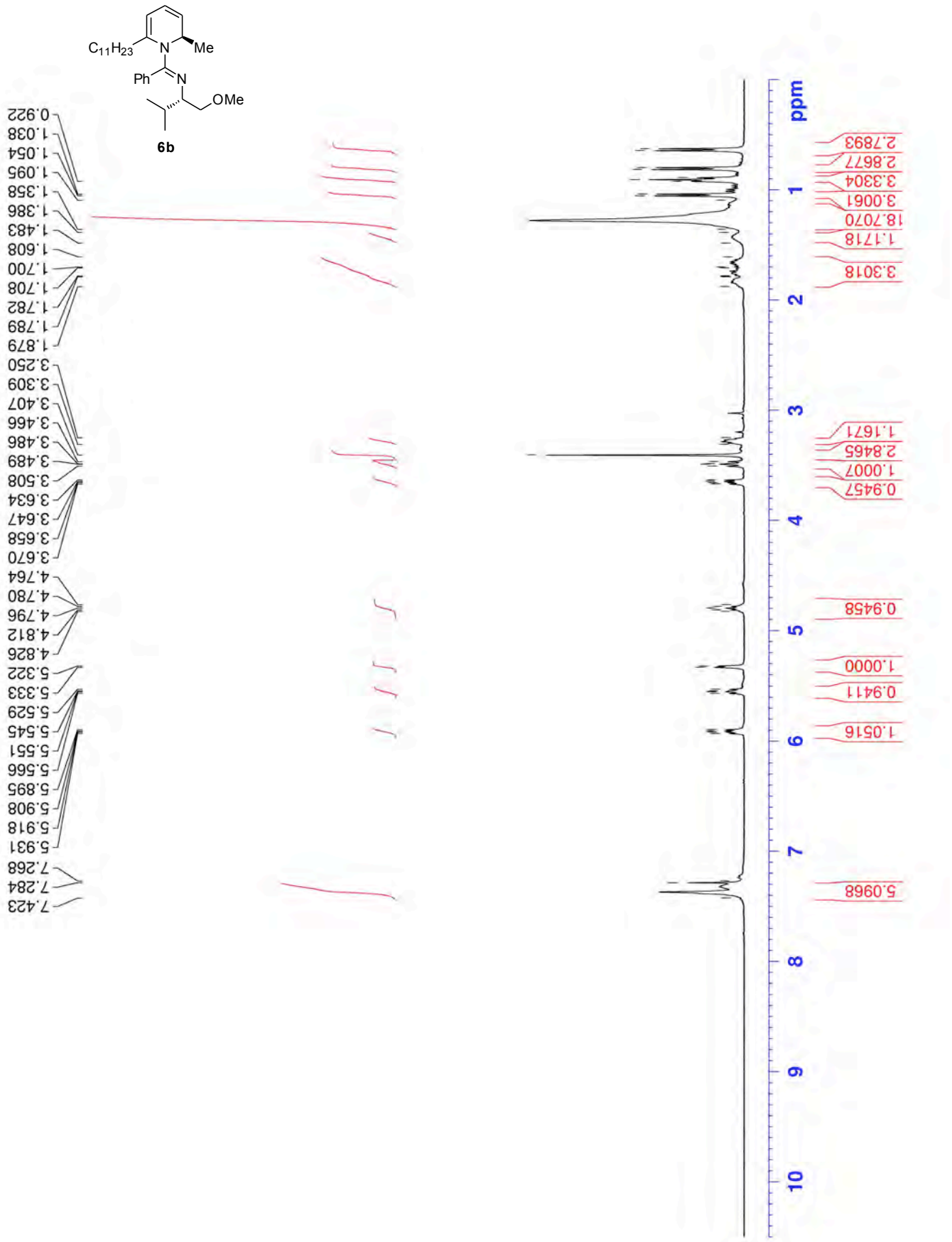
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Me
Ph
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OMe
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1.608
1.700
1.708
1.782
1.789
1.879
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3.309
3.407
3.466
3.486
3.489
3.508
3.634
3.647
3.658
3.670
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4.780
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4.812
4.826
5.322
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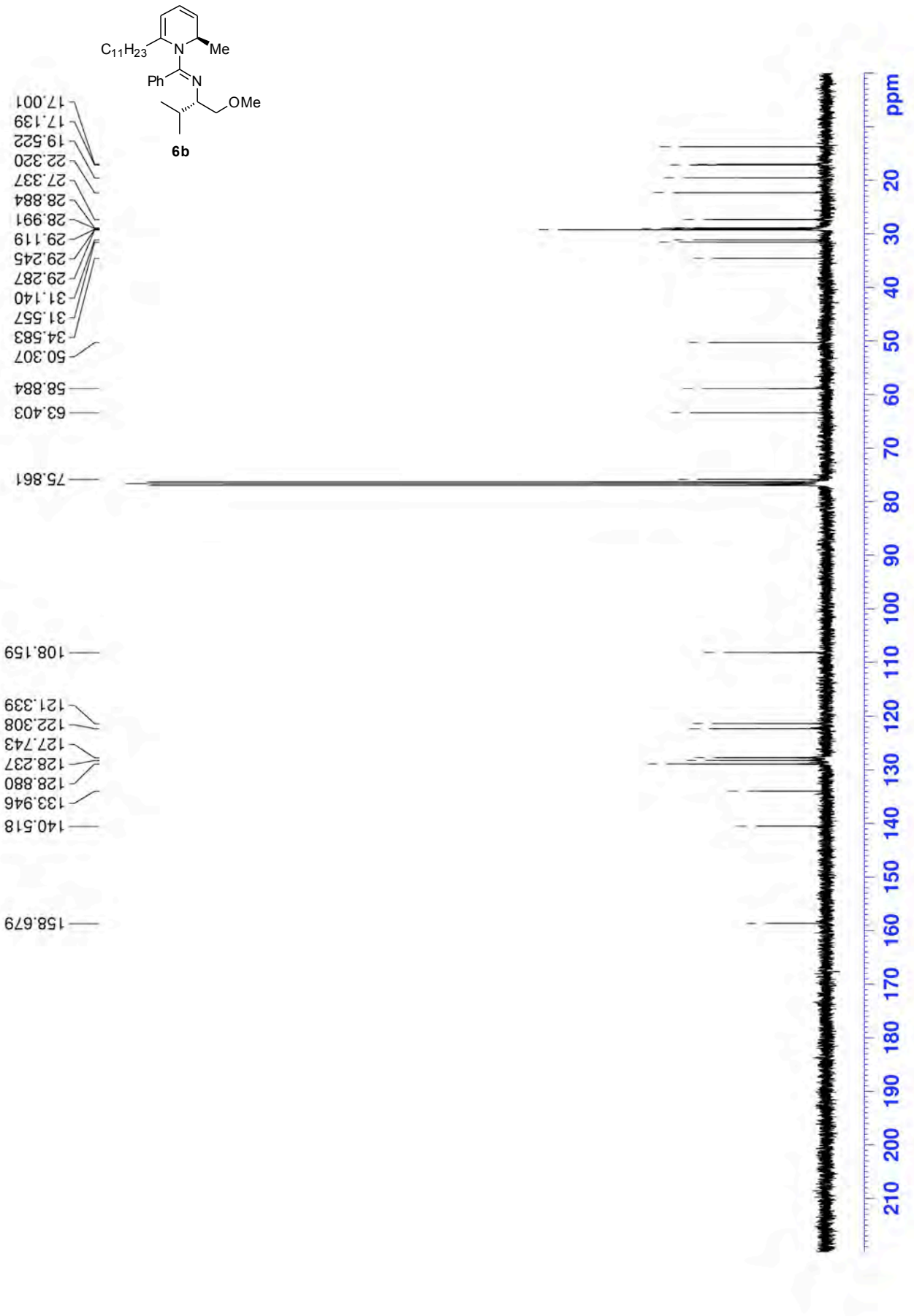
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29.287
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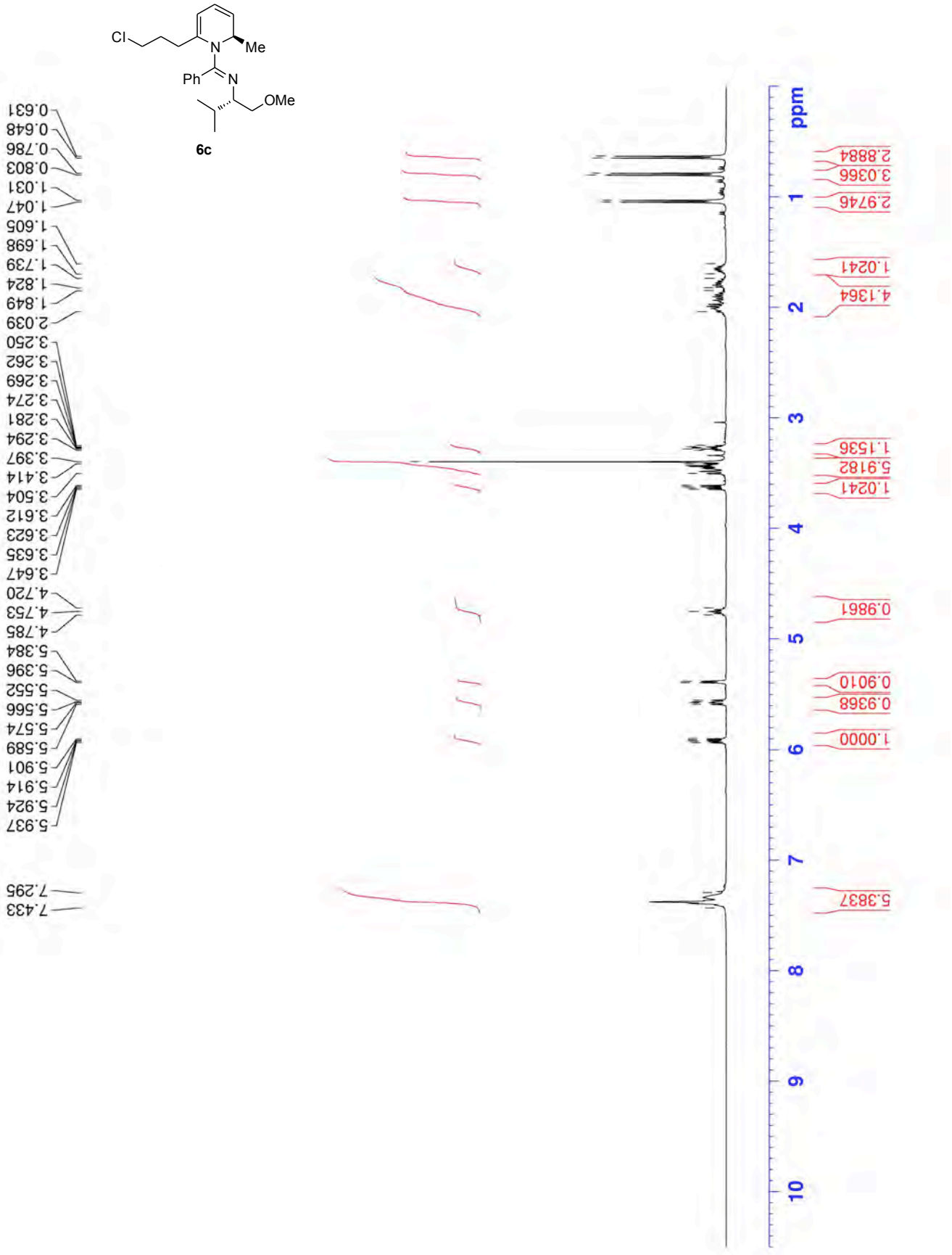
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3.274
3.281
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3.397
3.414
3.504
3.612
3.623
3.635
3.647
4.720
4.753
4.785
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5.396
5.552
5.566
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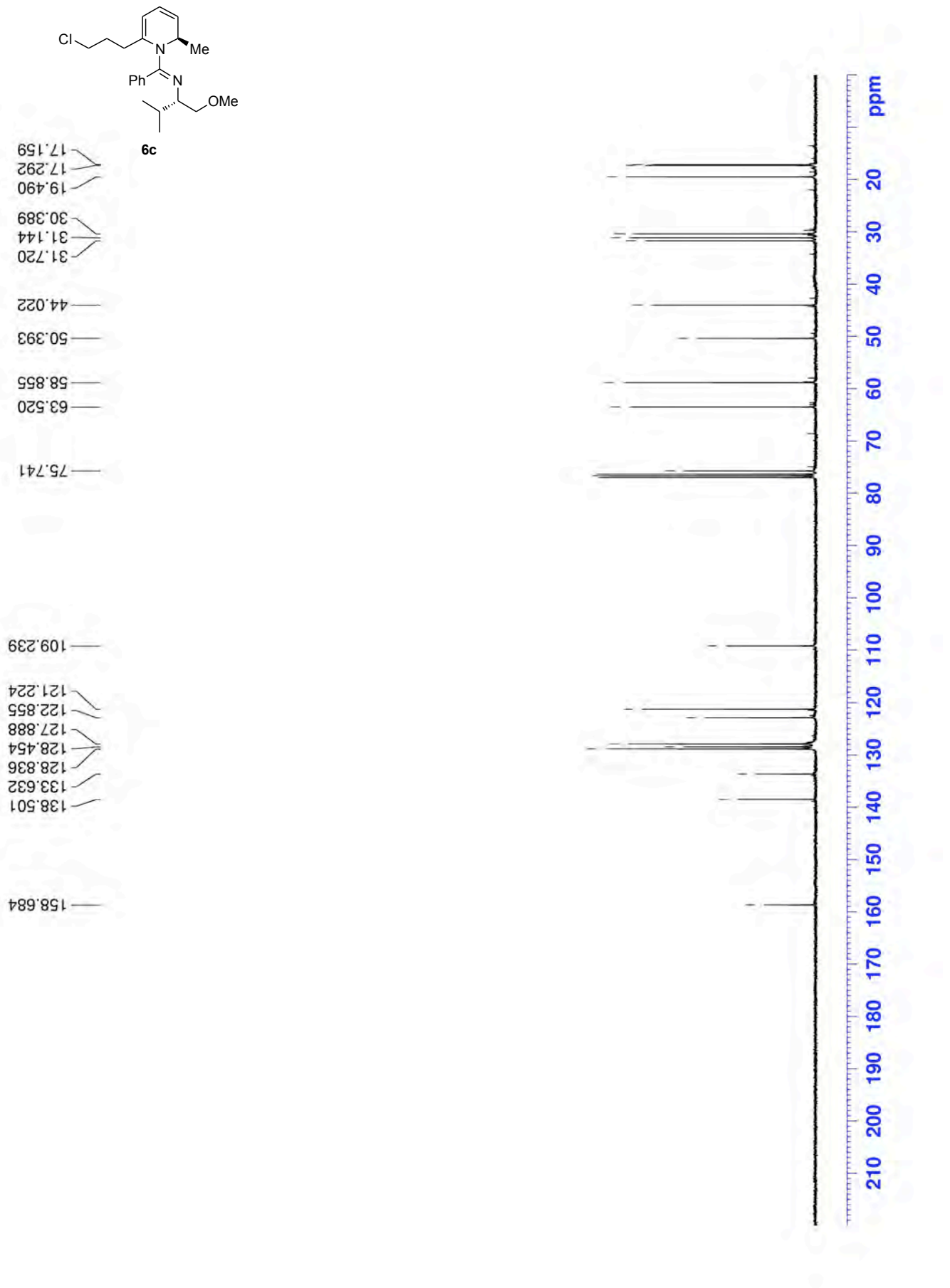
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Ph
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OMe
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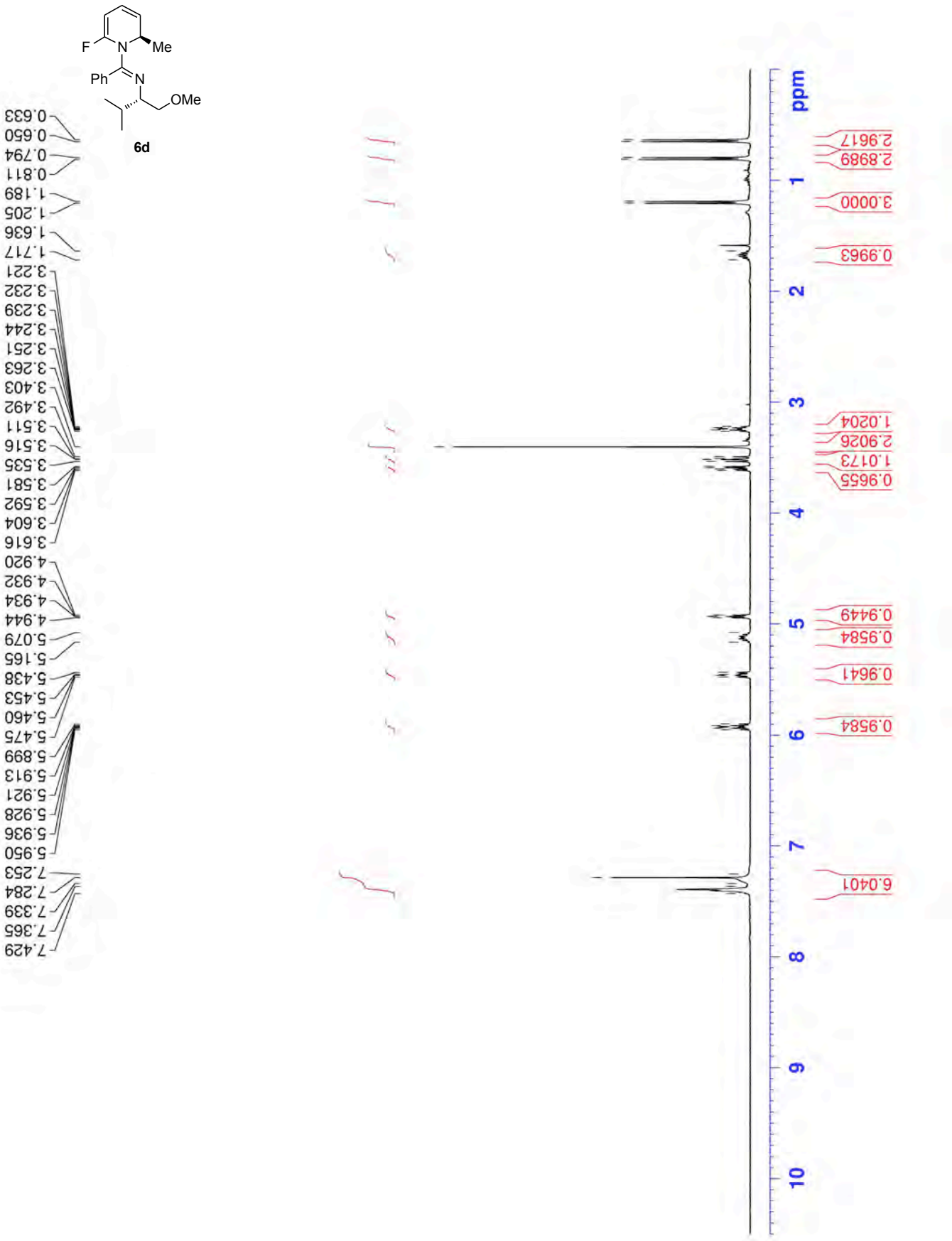
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Me
Ph
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OMe
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3.581
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5.936
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ppm
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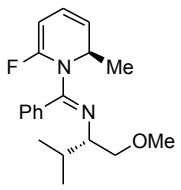
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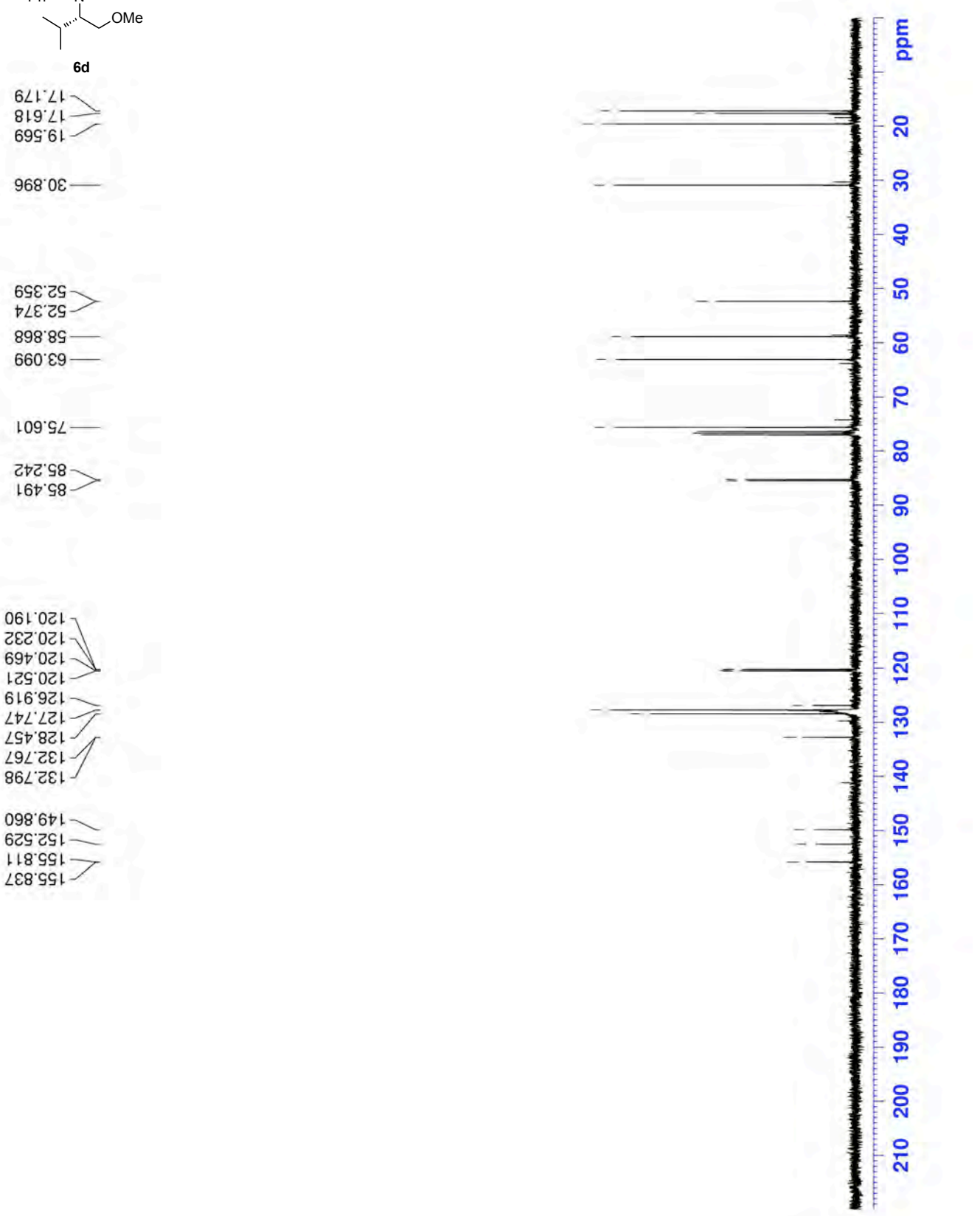
Ph
N
OMe

6d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120.521
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132.798
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152.529
155.811
155.837
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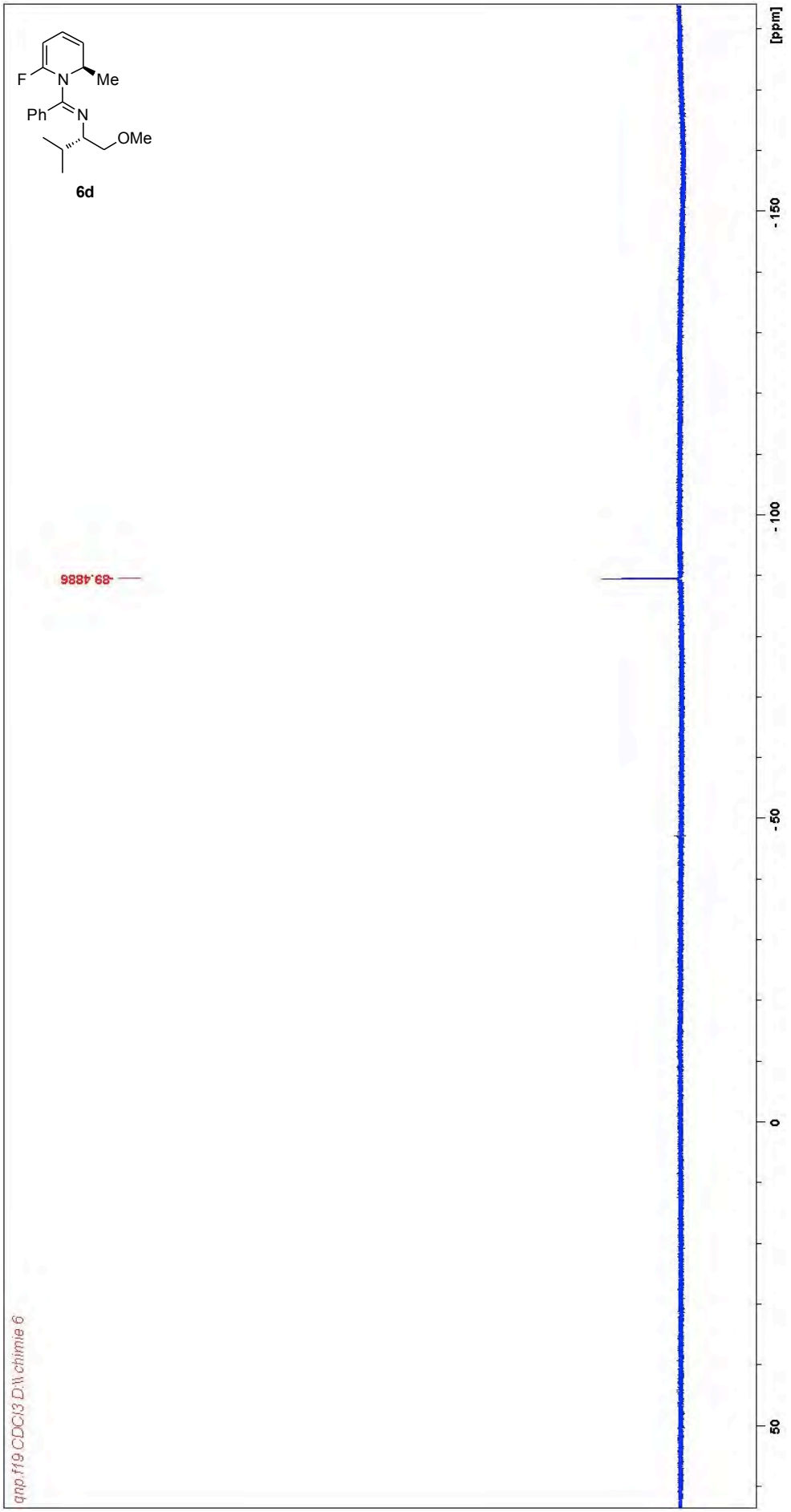
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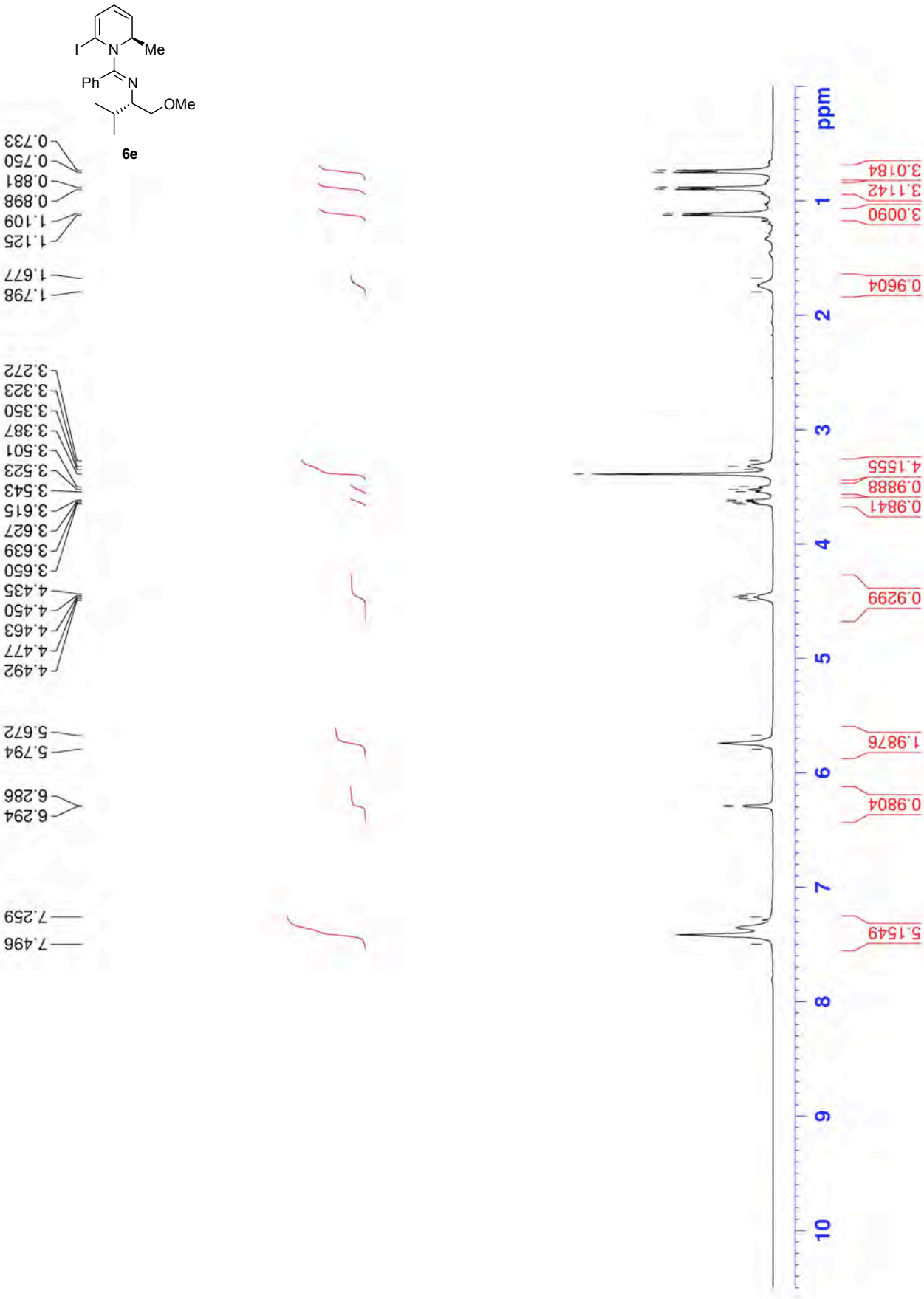
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3.543
3.615
3.627
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7.496
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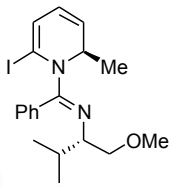
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Me
Ph
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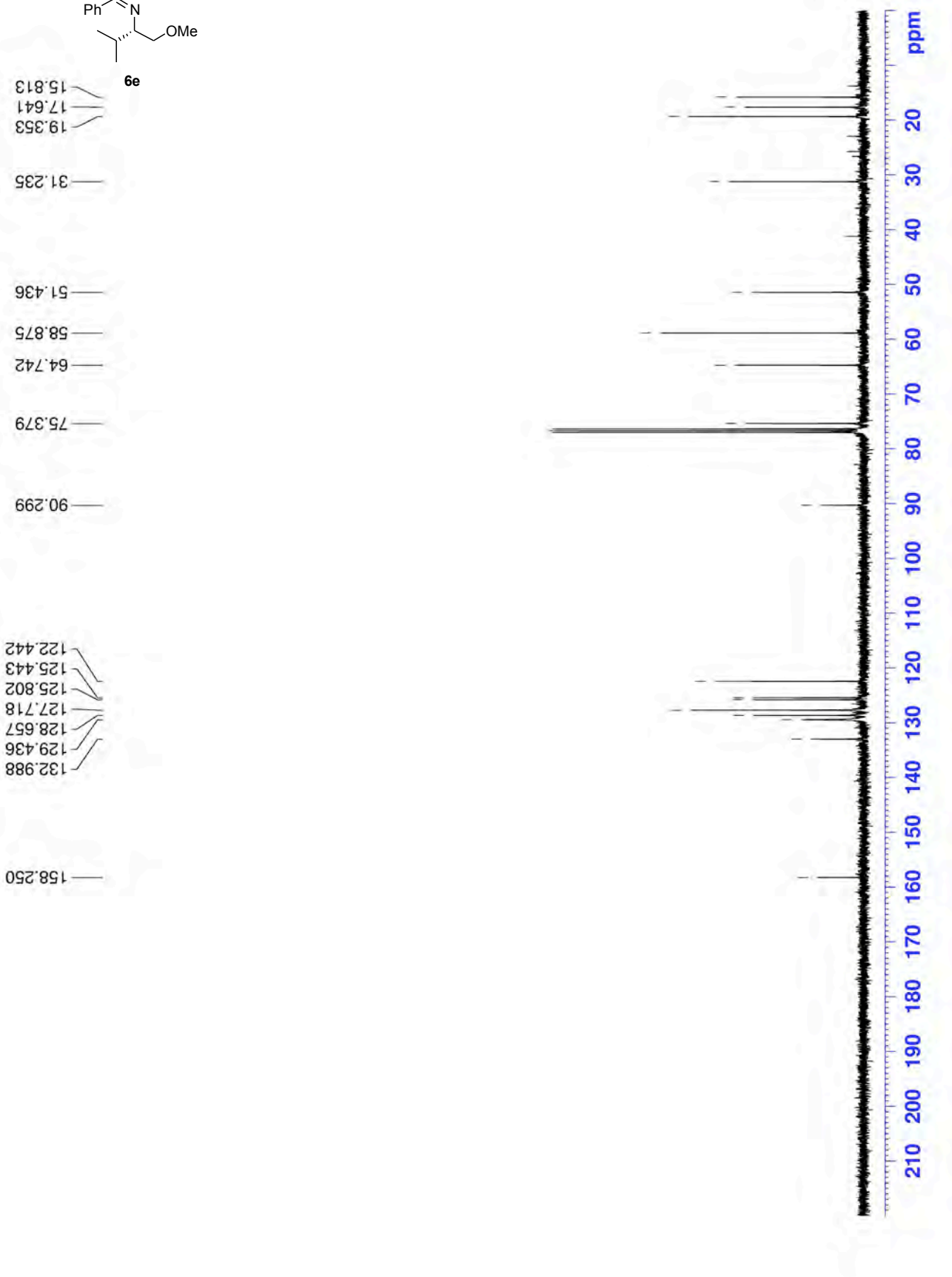
OMe

6e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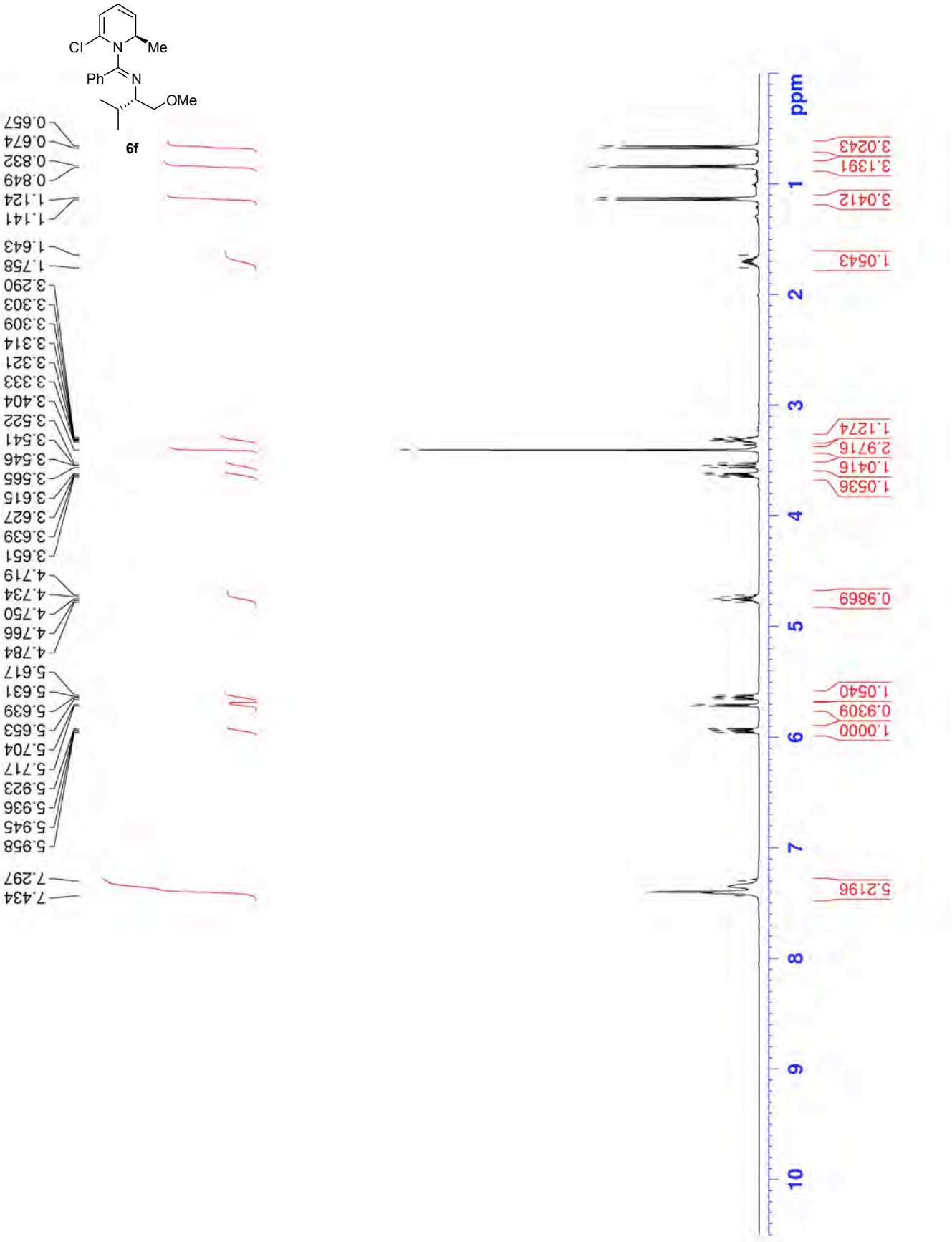
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3.541
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4.734
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5.717
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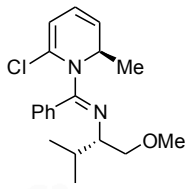
Cl
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Ph
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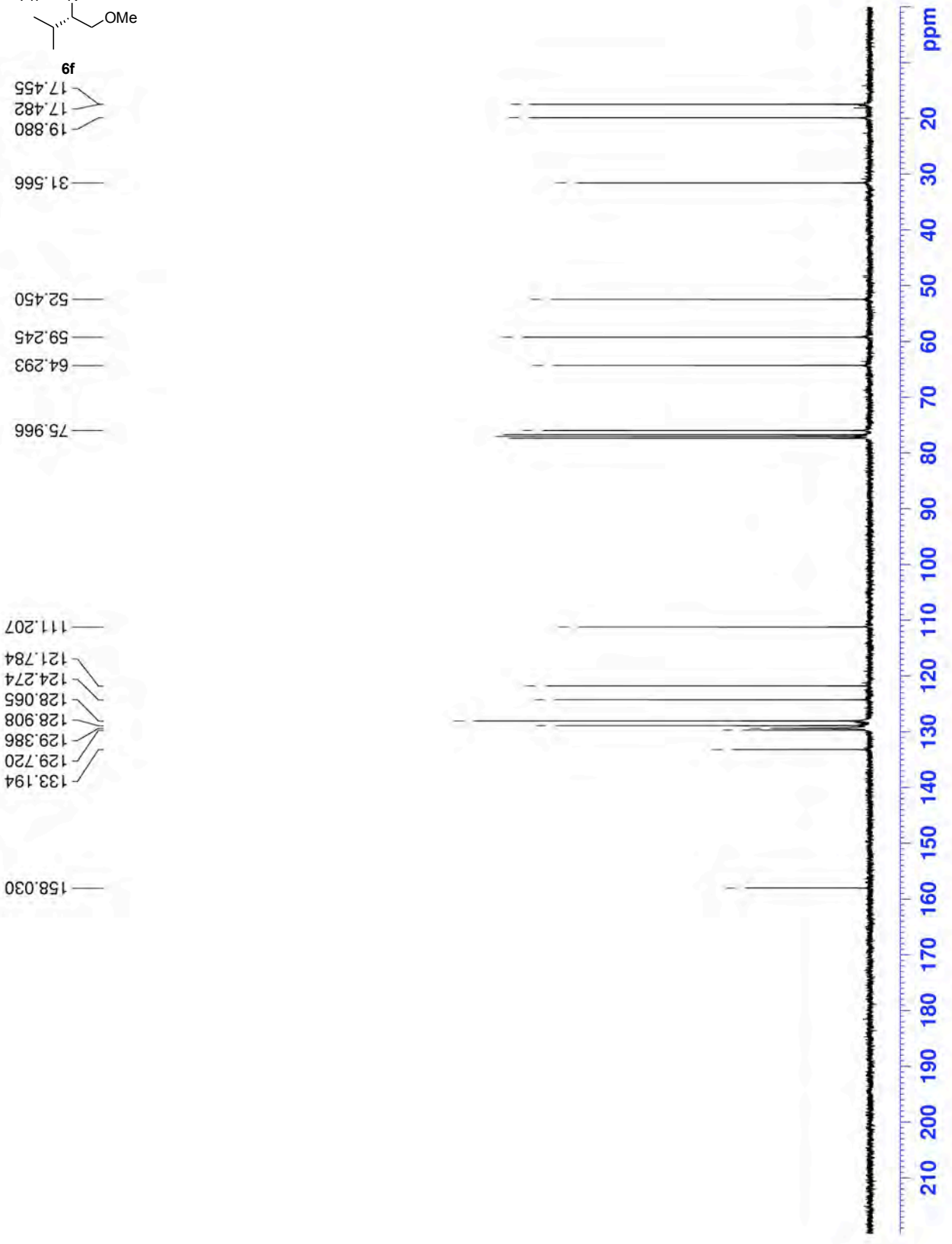
OMe

6f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133.194
158.030
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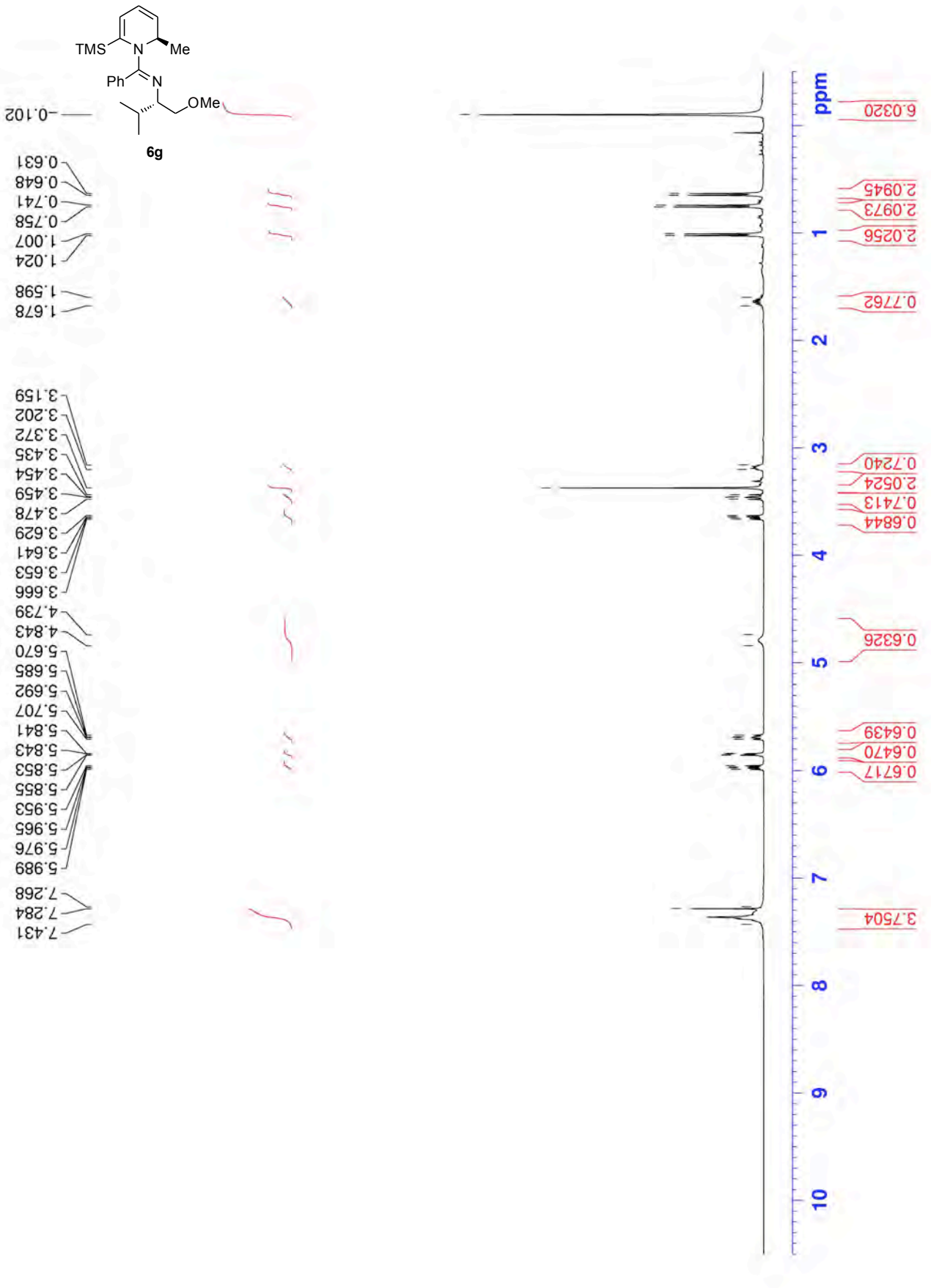
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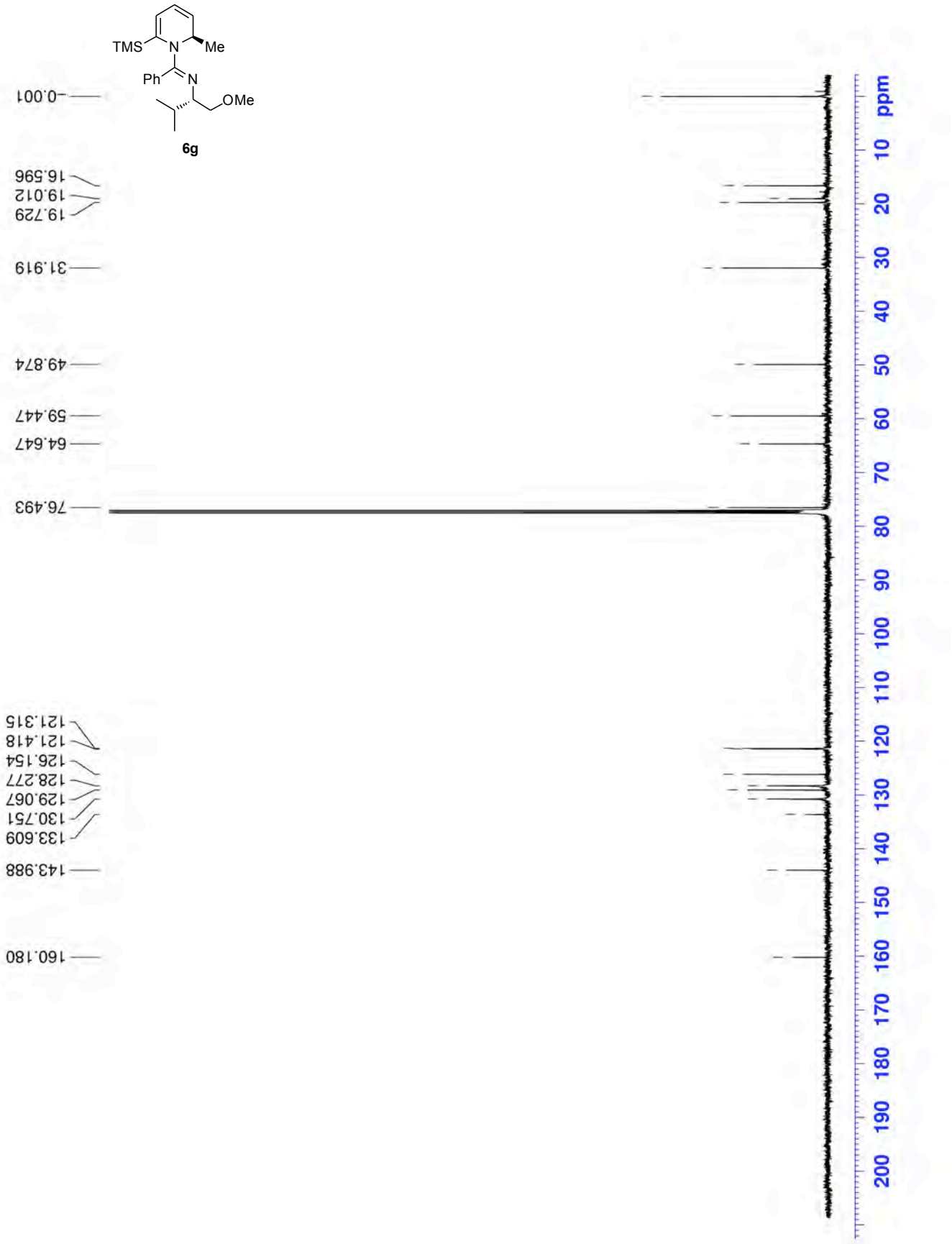
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OMe
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64.647
76.493
121.315
121.418
126.154
128.277
129.067
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143.988
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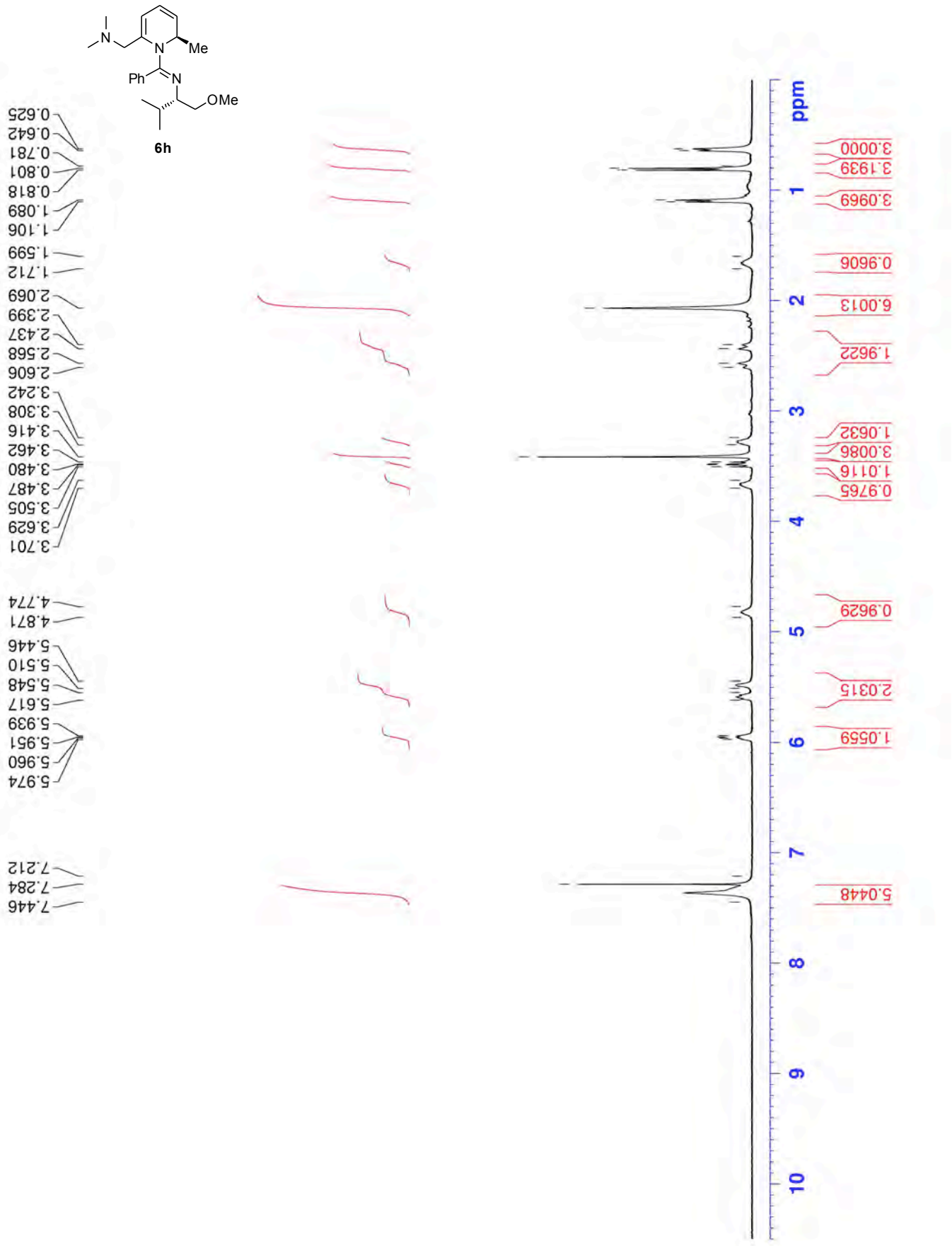
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ppm
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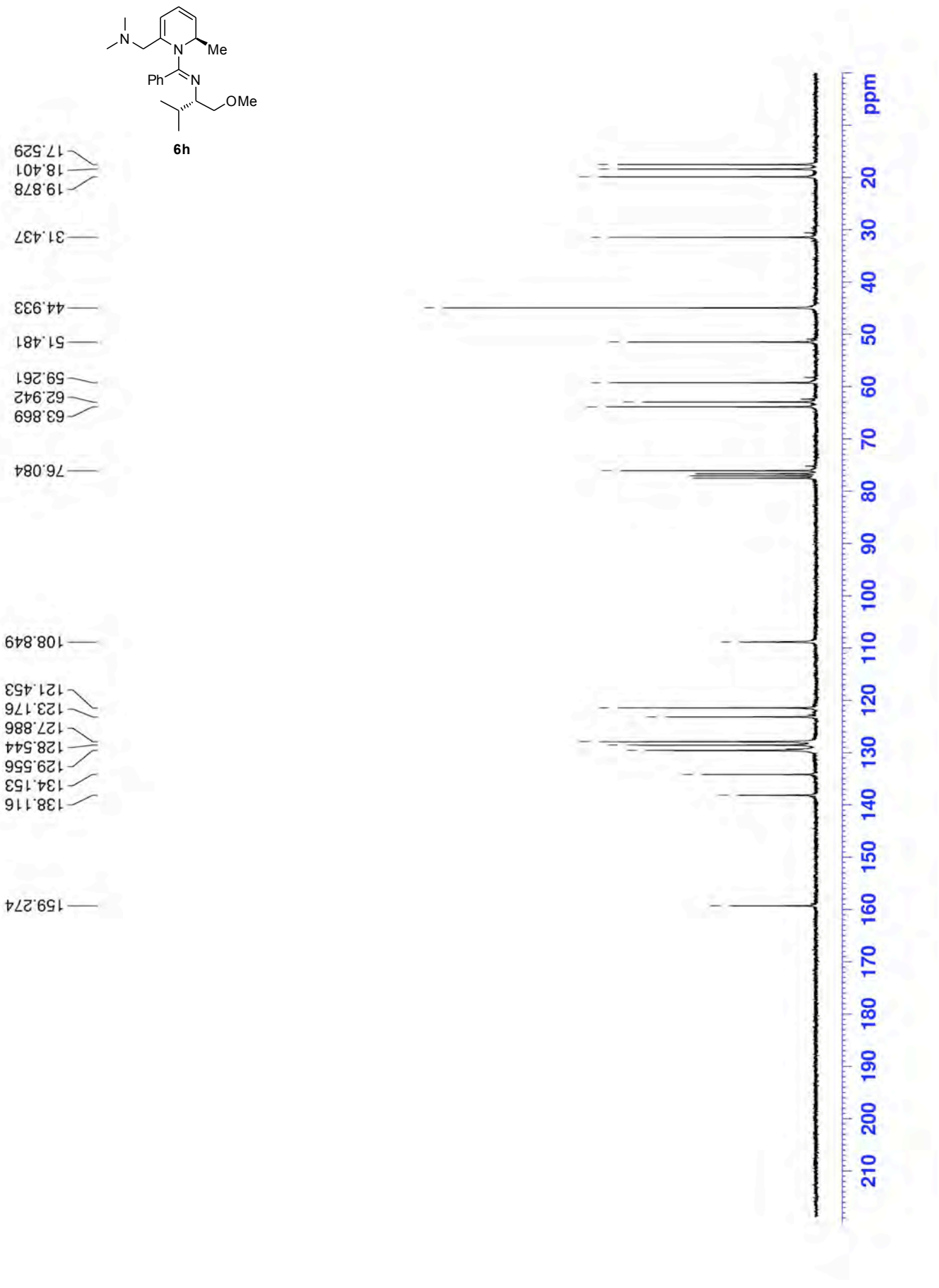
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OMe
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ppm
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80
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100
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190
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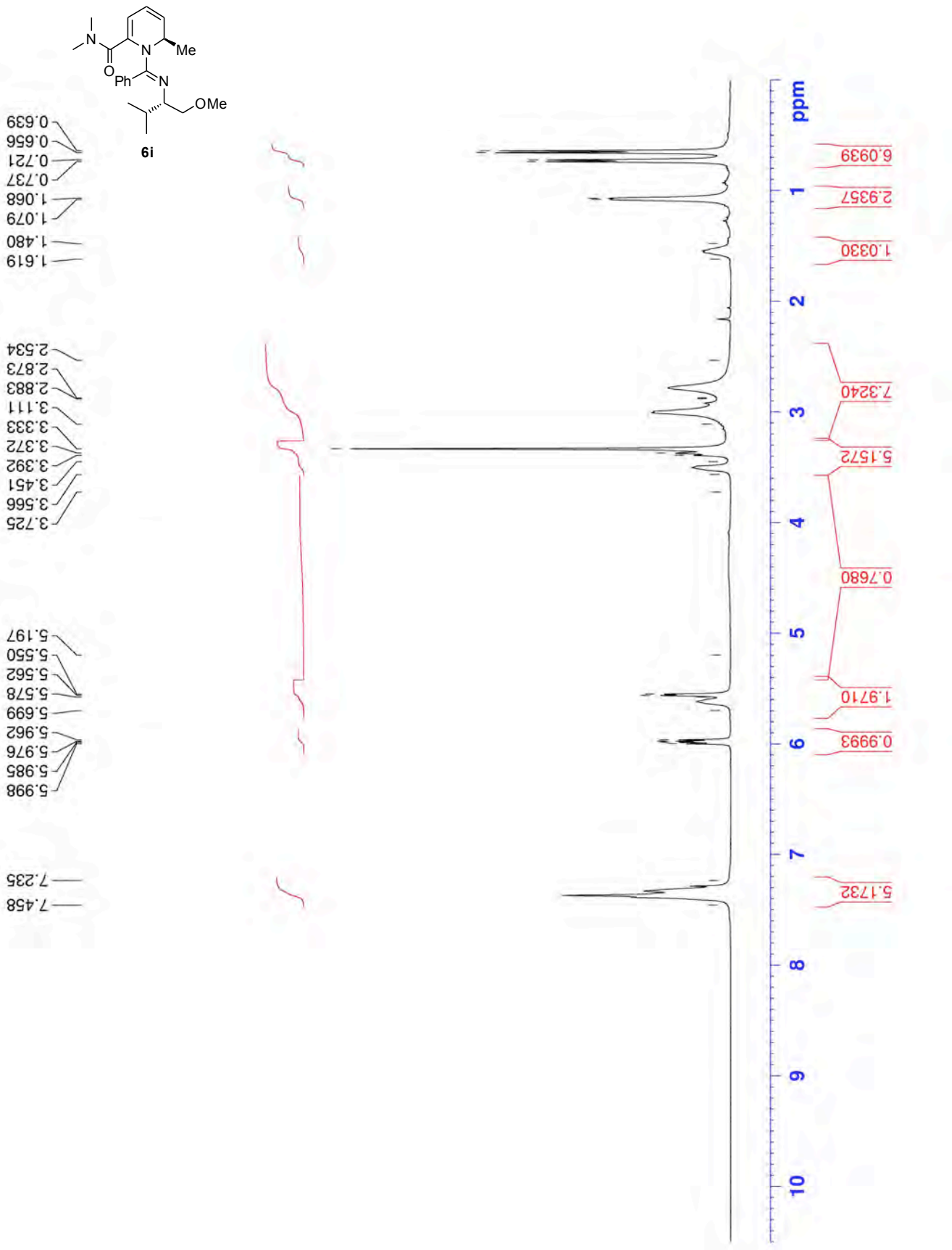
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1.619
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2.883
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3.333
3.372
3.392
3.451
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5.562
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5.998
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7.458
ppm
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7
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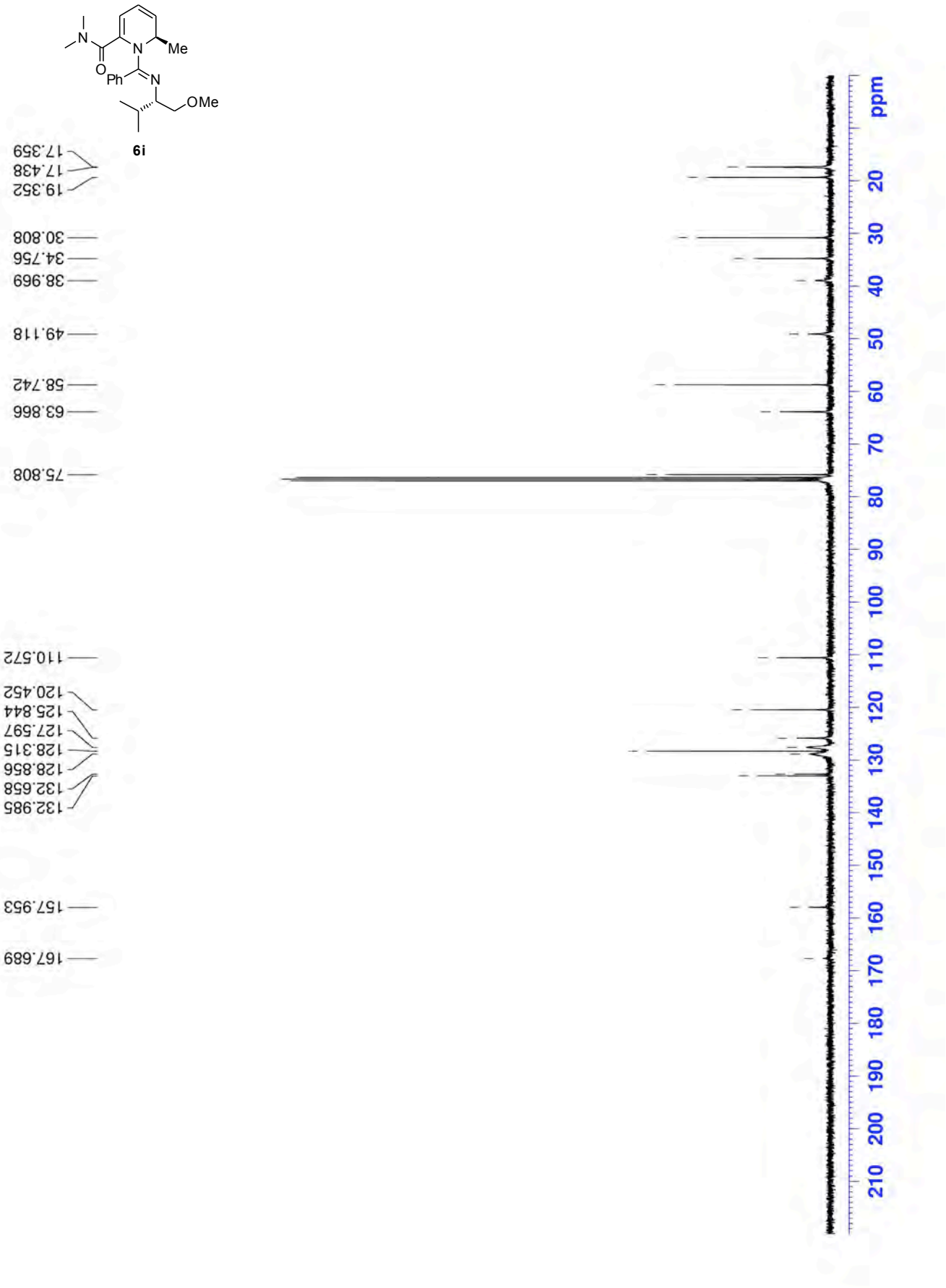
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128.856
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132.985
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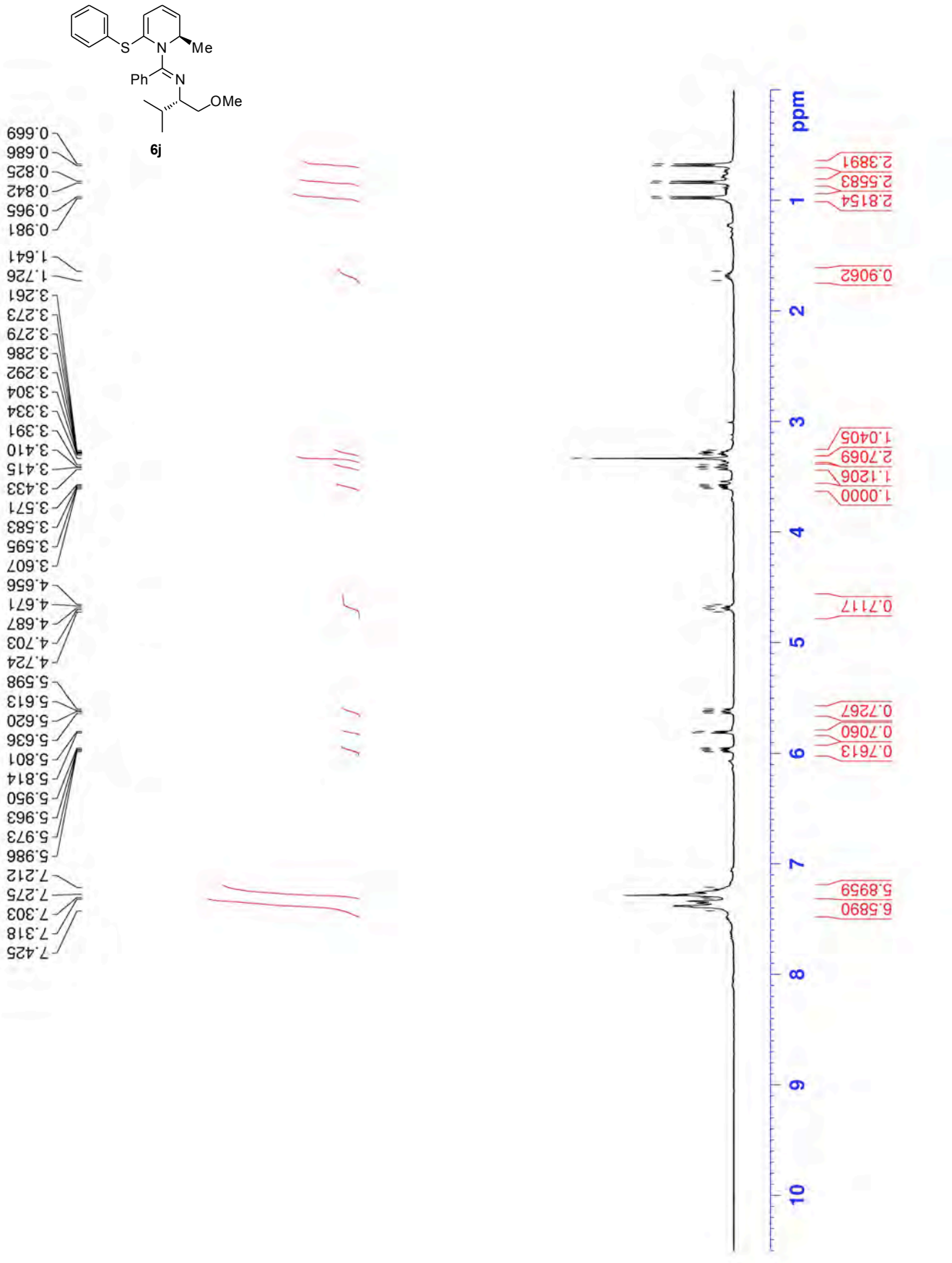
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3.415
3.433
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3.595
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4.703
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5.613
5.620
5.636
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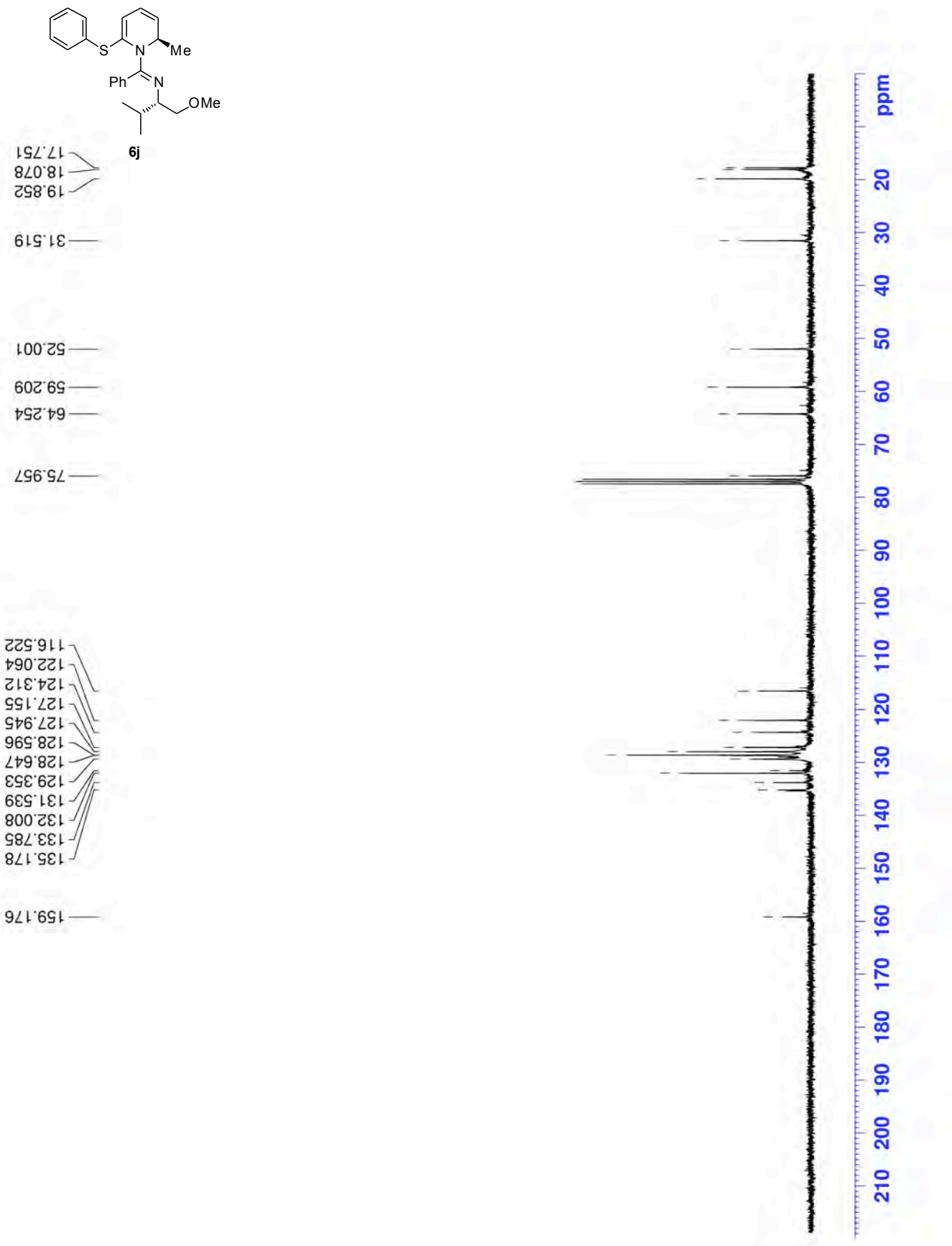
6.5890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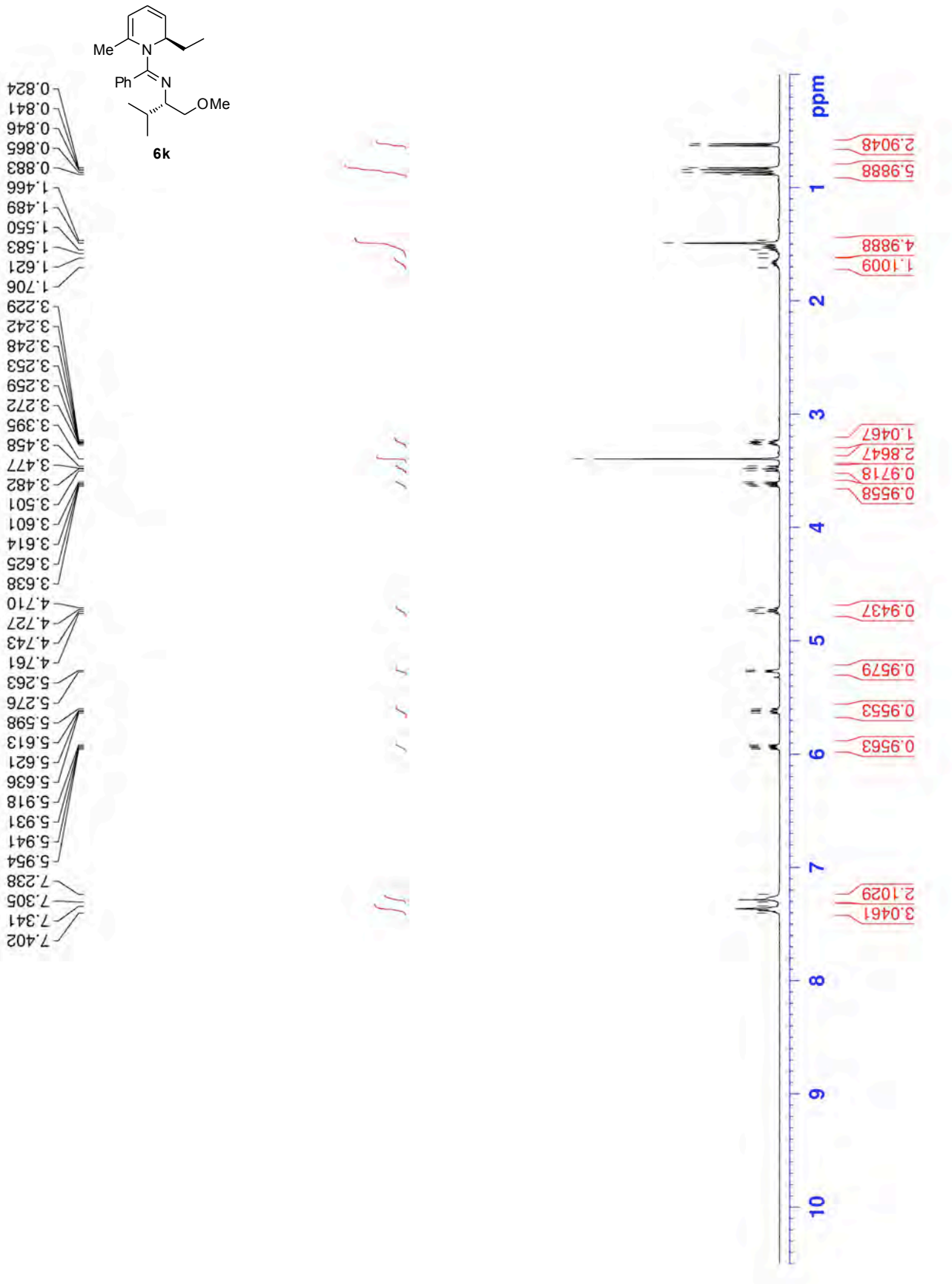
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3.272
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3.601
3.614
3.625
3.638
4.710
4.727
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5.276
5.598
5.613
5.621
5.636
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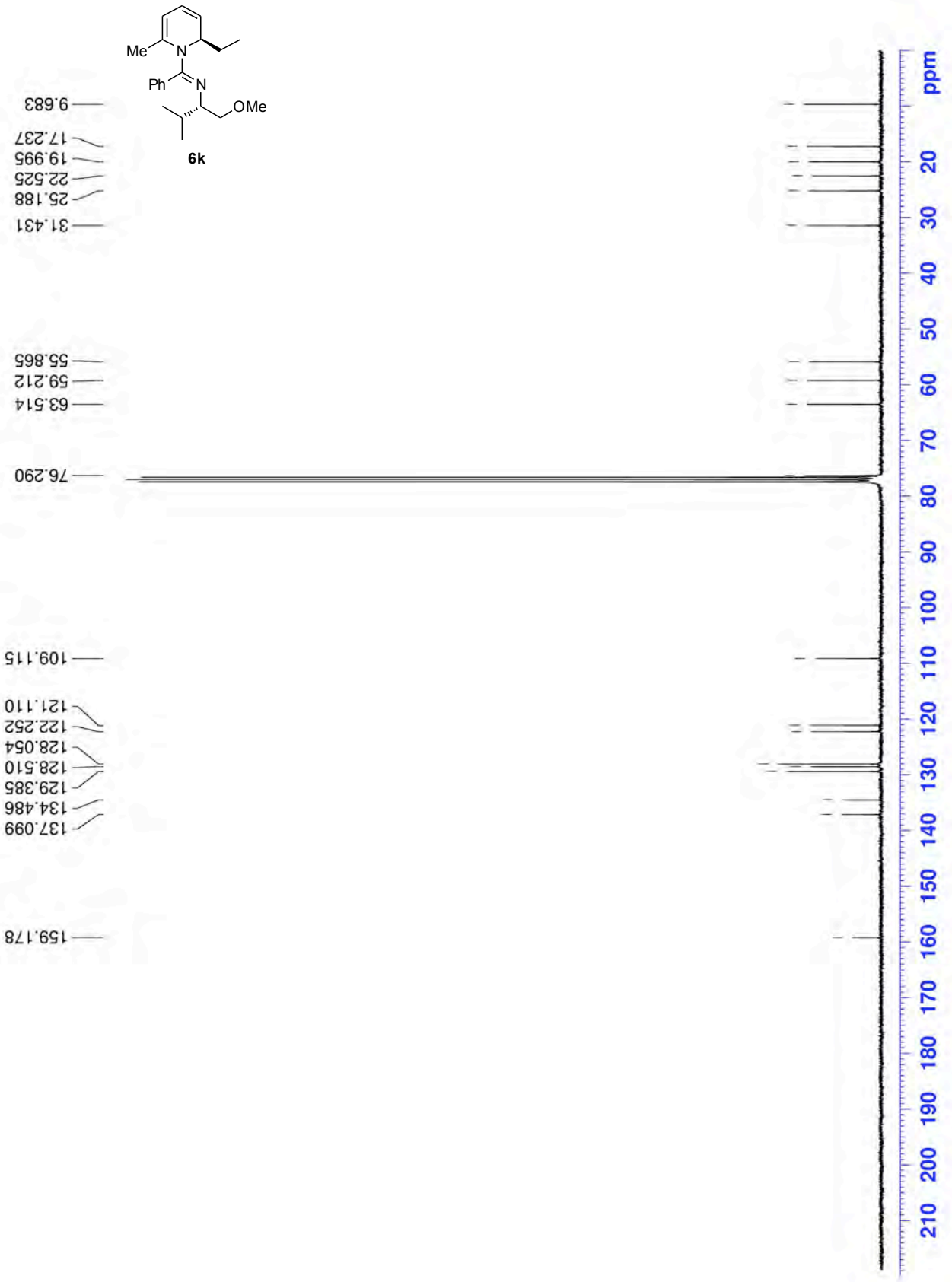
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OMe
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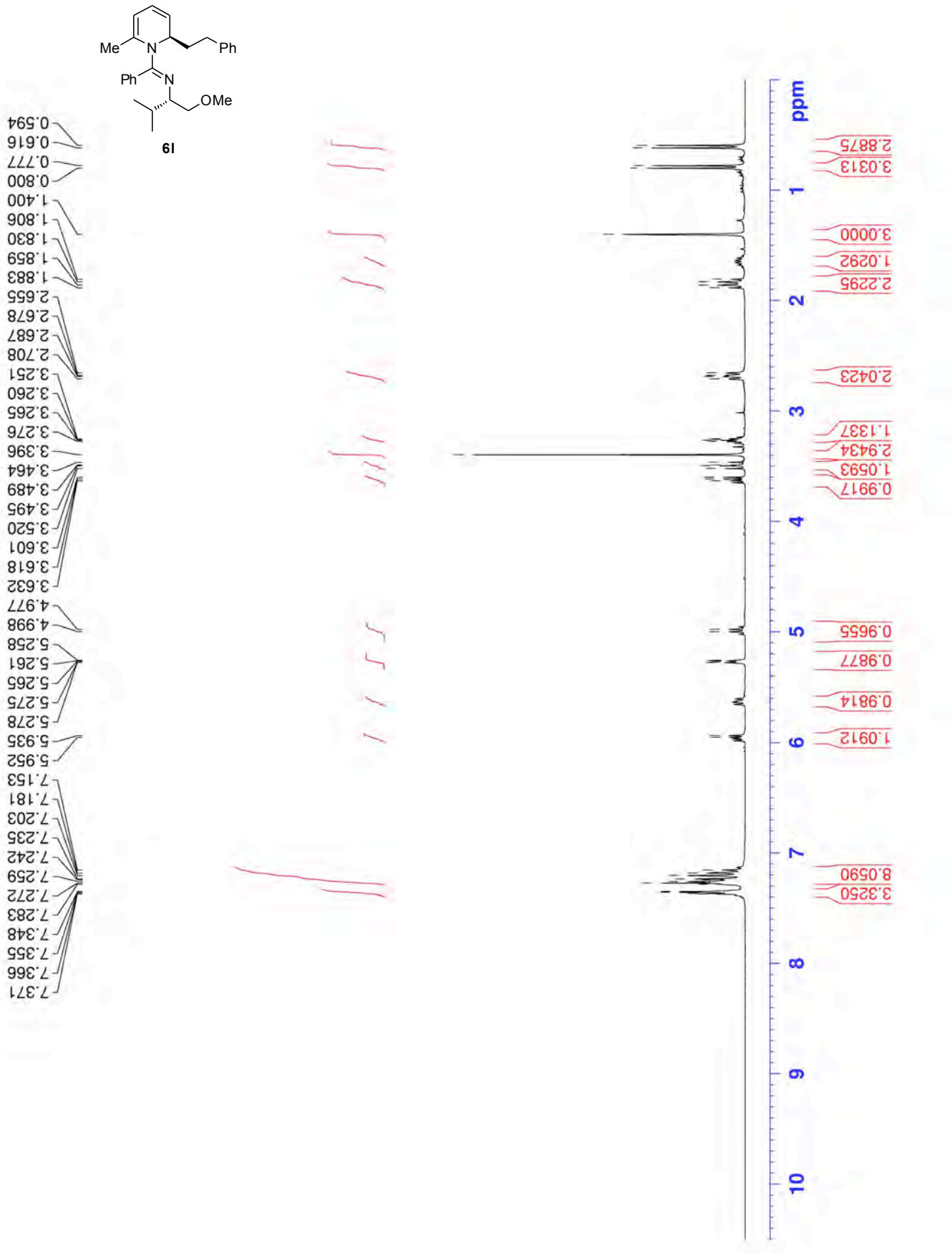
159.178
ppm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Ph
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2.678
2.687
2.708
3.251
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3.265
3.276
3.396
3.464
3.489
3.495
3.520
3.601
3.618
3.632
4.977
4.998
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5.261
5.265
5.275
5.278
5.935
5.952
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7.203
7.235
7.242
7.259
7.272
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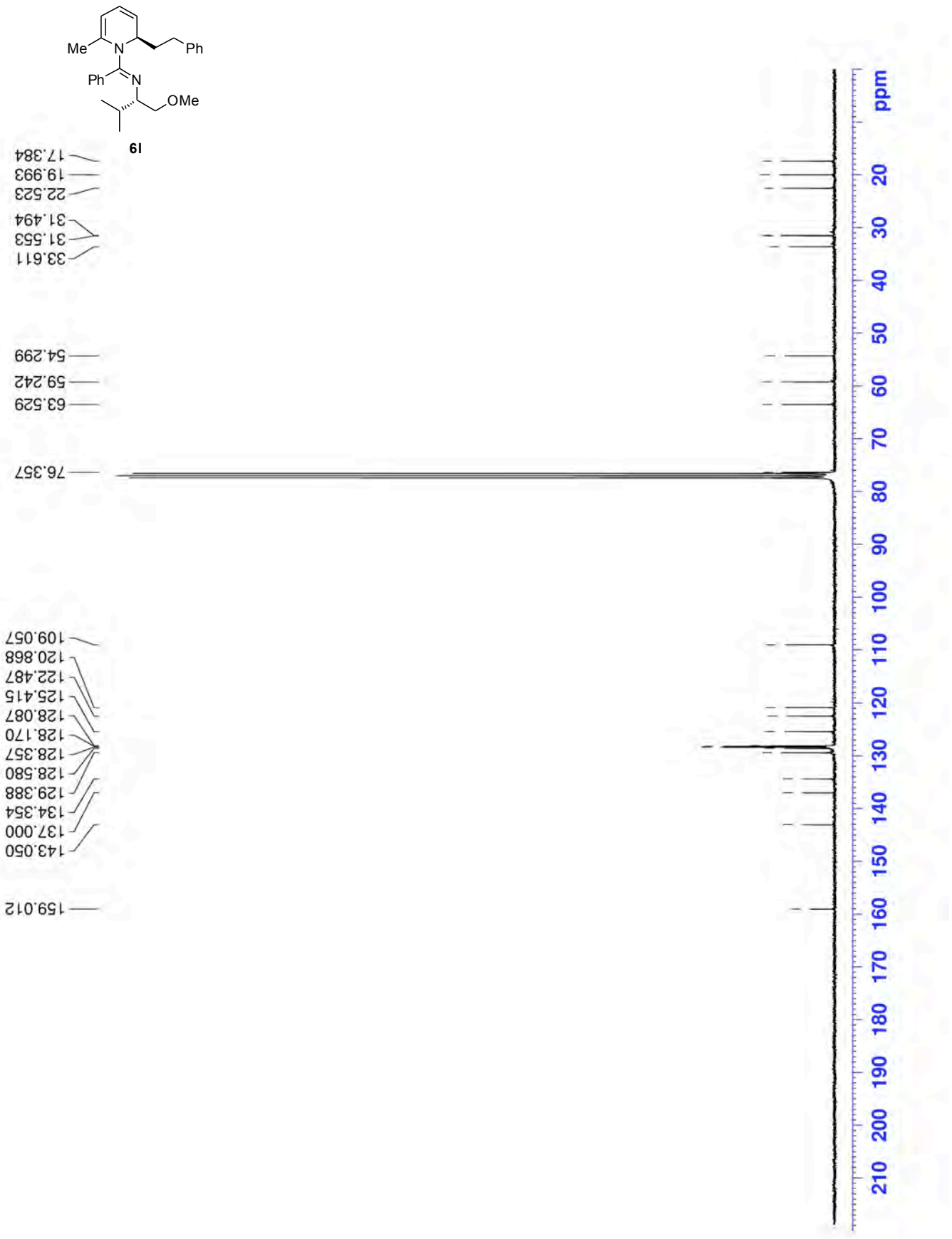
3.3250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Ph
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120.868
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125.415
128.087
128.170
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129.388
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137.000
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159.012
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200
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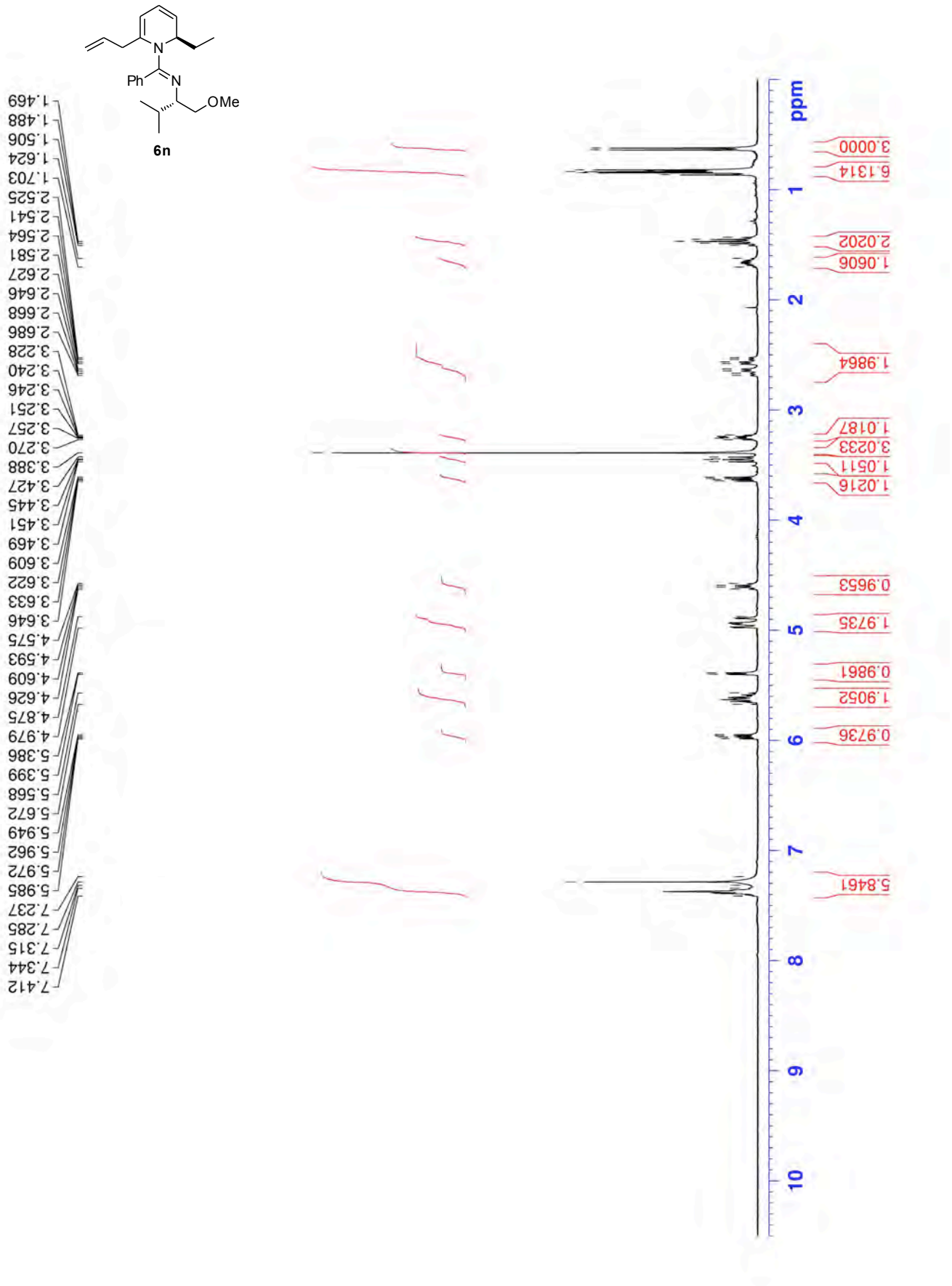
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3.228
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3.246
3.251
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3.445
3.451
3.469
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3.622
3.633
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4.875
4.979
5.386
5.399
5.568
5.672
5.949
5.962
5.972
5.985
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7.315
7.344
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ppm
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6.1314
2.0202
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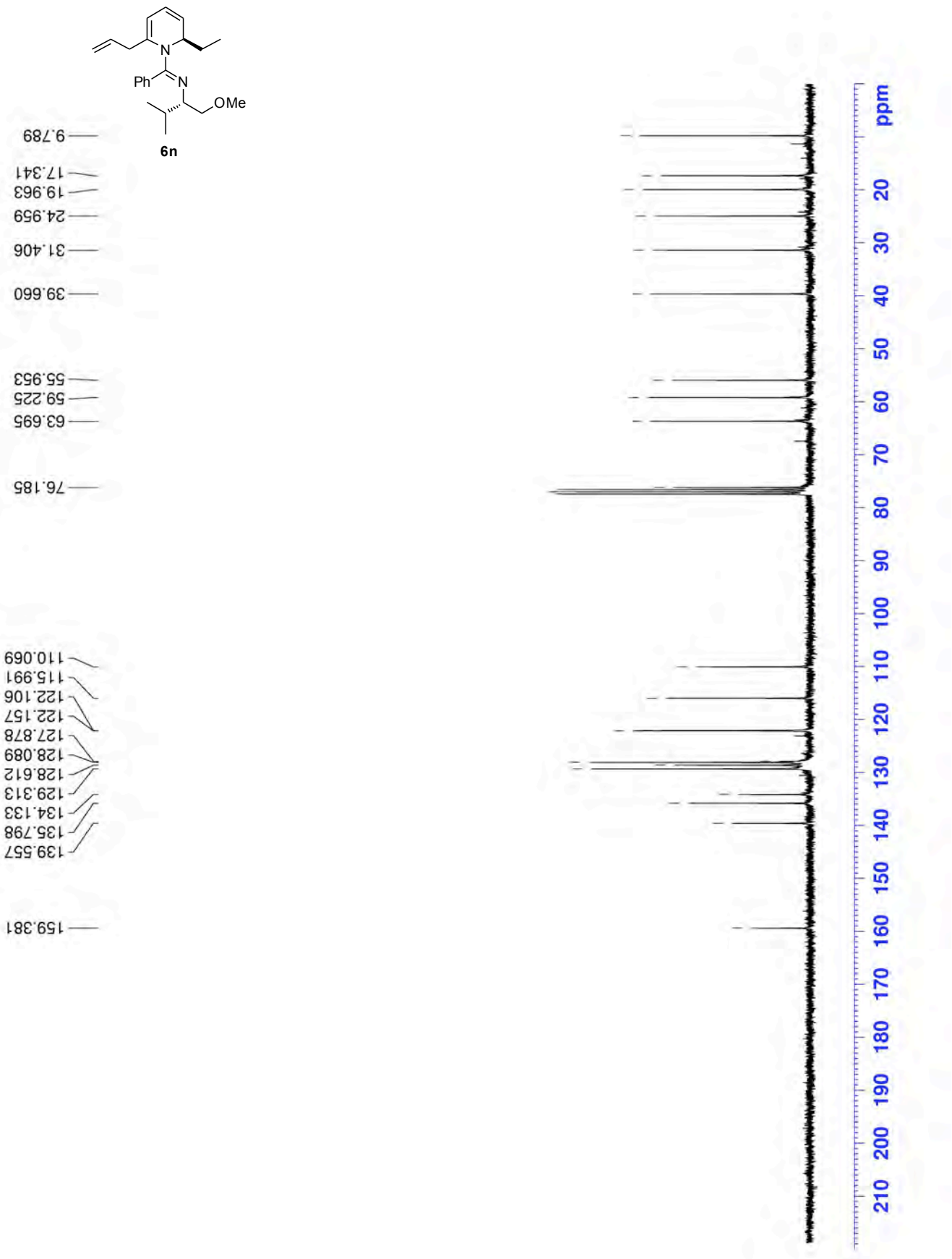
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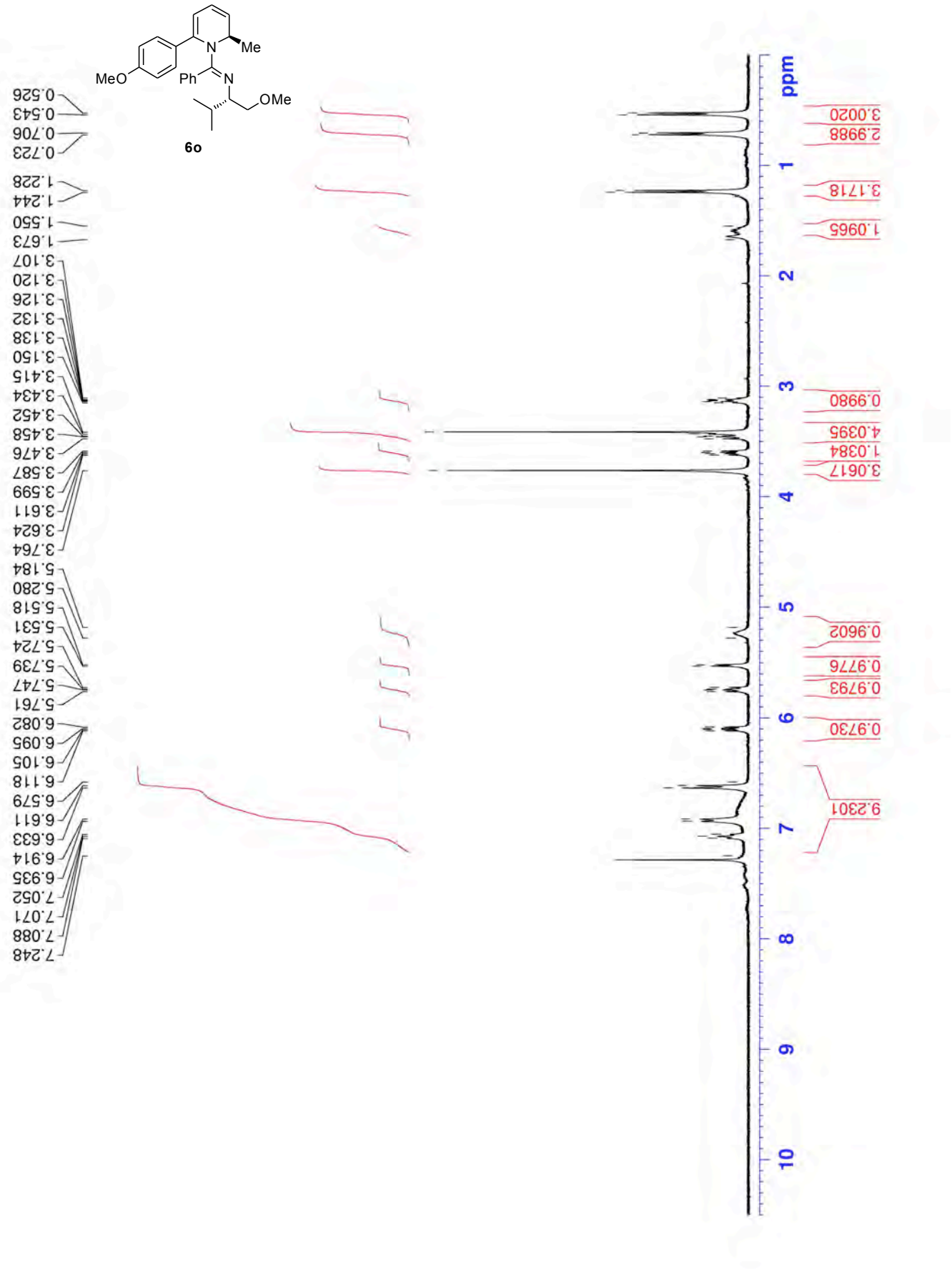
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3.126
3.132
3.138
3.150
3.415
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3.452
3.458
3.476
3.587
3.599
3.611
3.624
3.764
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5.531
5.724
5.739
5.747
5.761
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6.611
6.633
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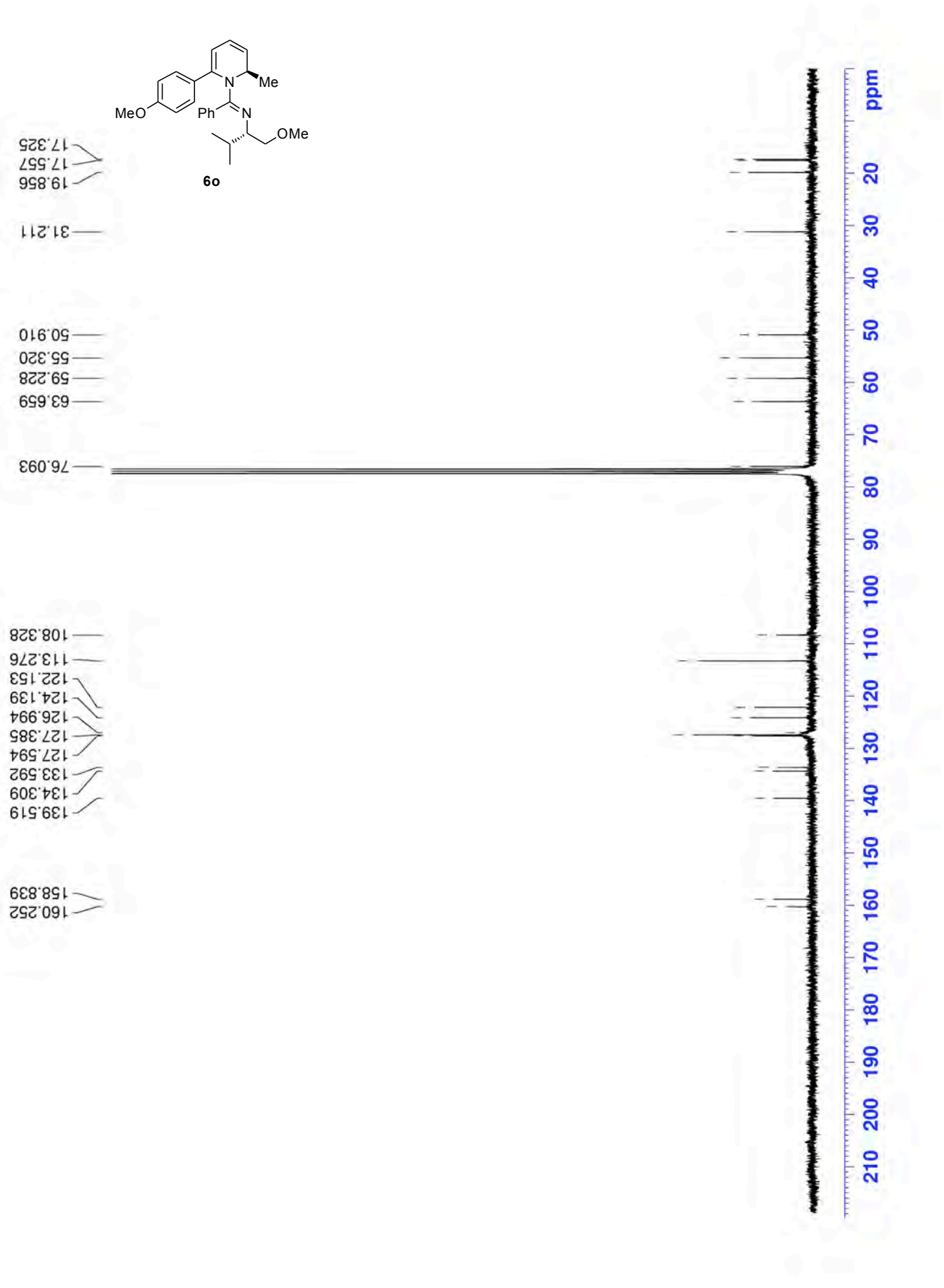
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OMe
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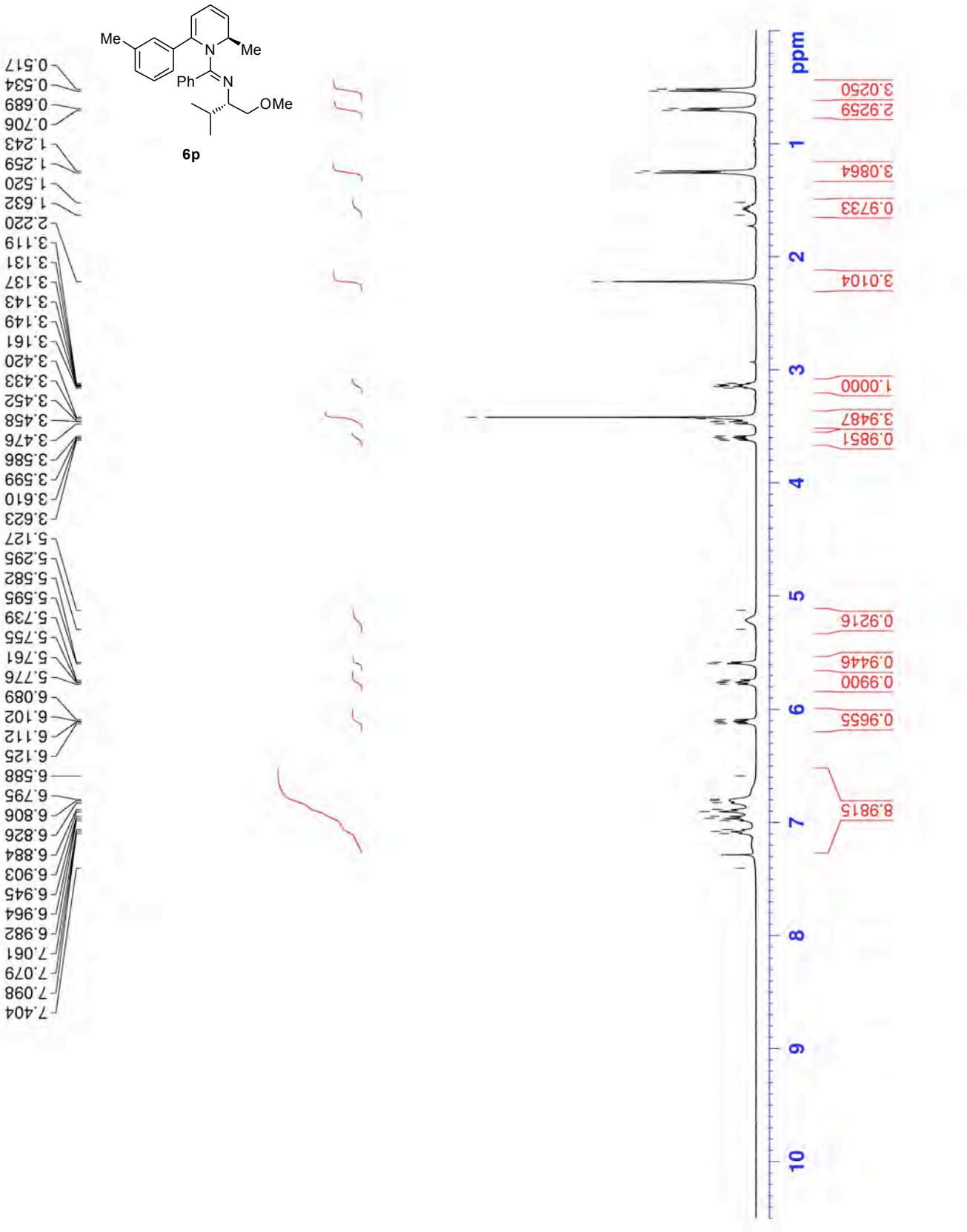
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3.137
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3.599
3.610
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5.582
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6.112
6.125
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6.795
6.806
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6.945
6.964
6.982
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7.404
ppm
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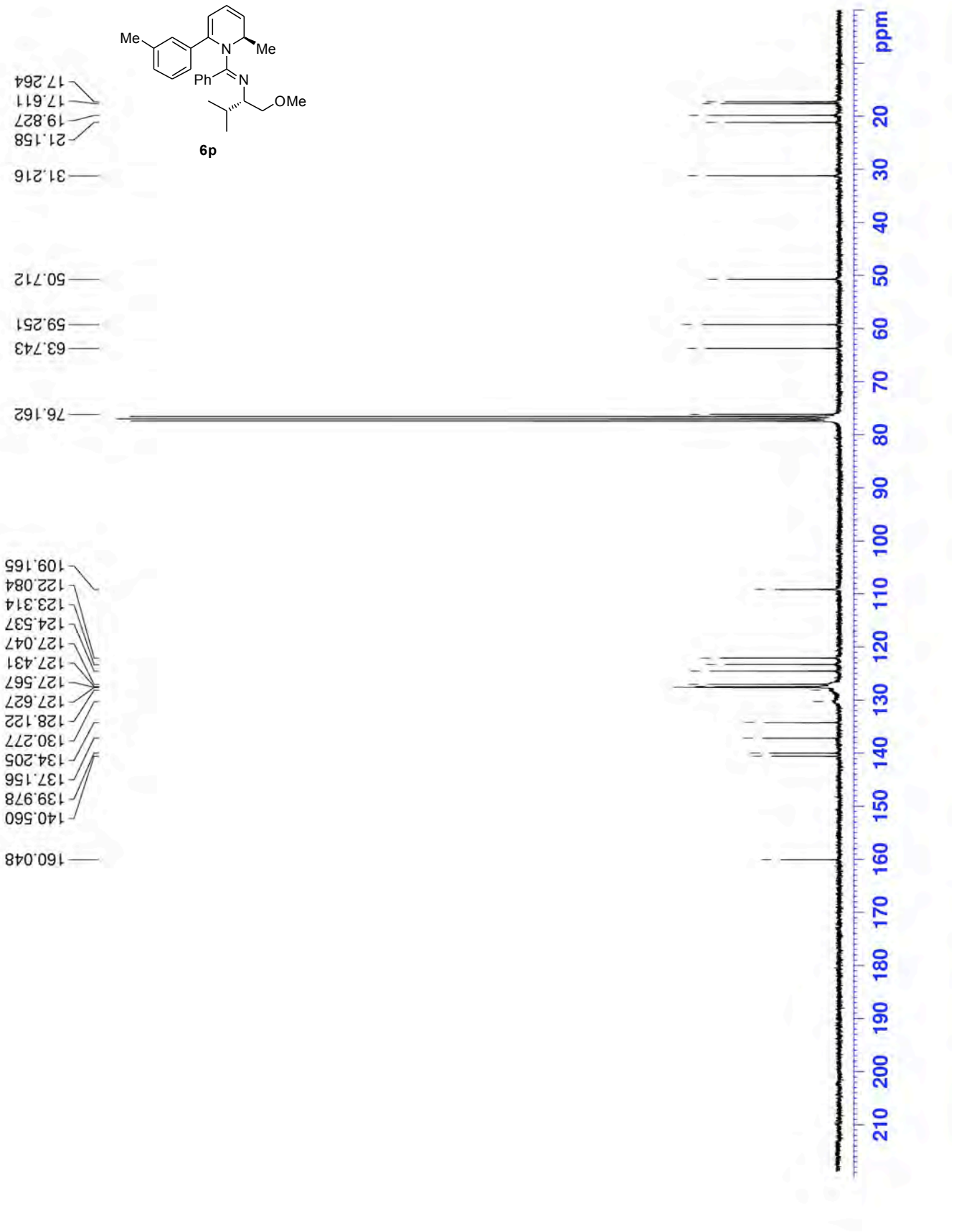
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Ph
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OMe
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127.047
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127.567
127.627
128.122
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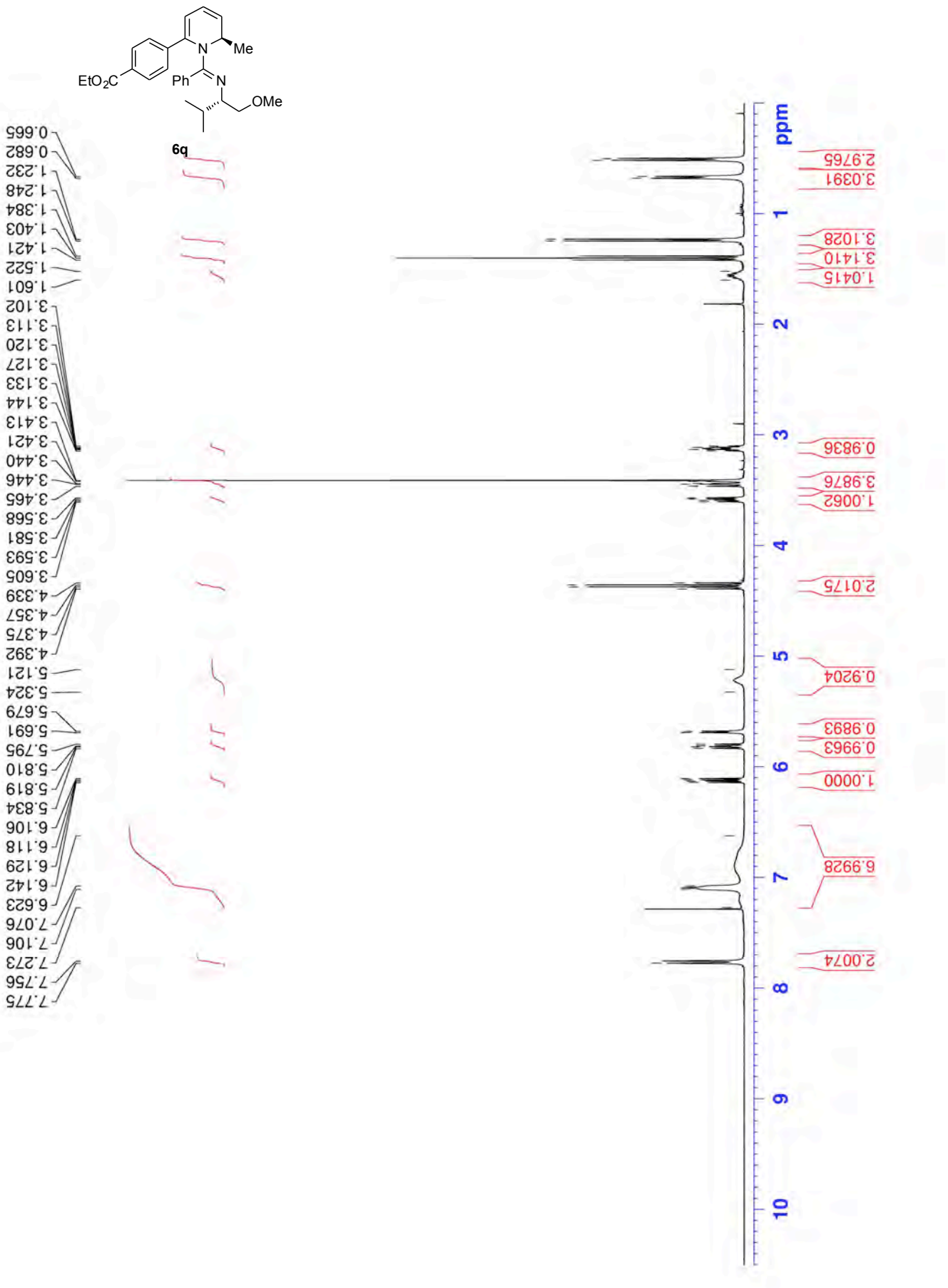
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3.127
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3.421
3.440
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3.465
3.568
3.581
3.593
3.605
4.339
4.357
4.375
4.392
5.121
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5.679
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5.795
5.810
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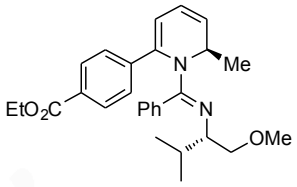
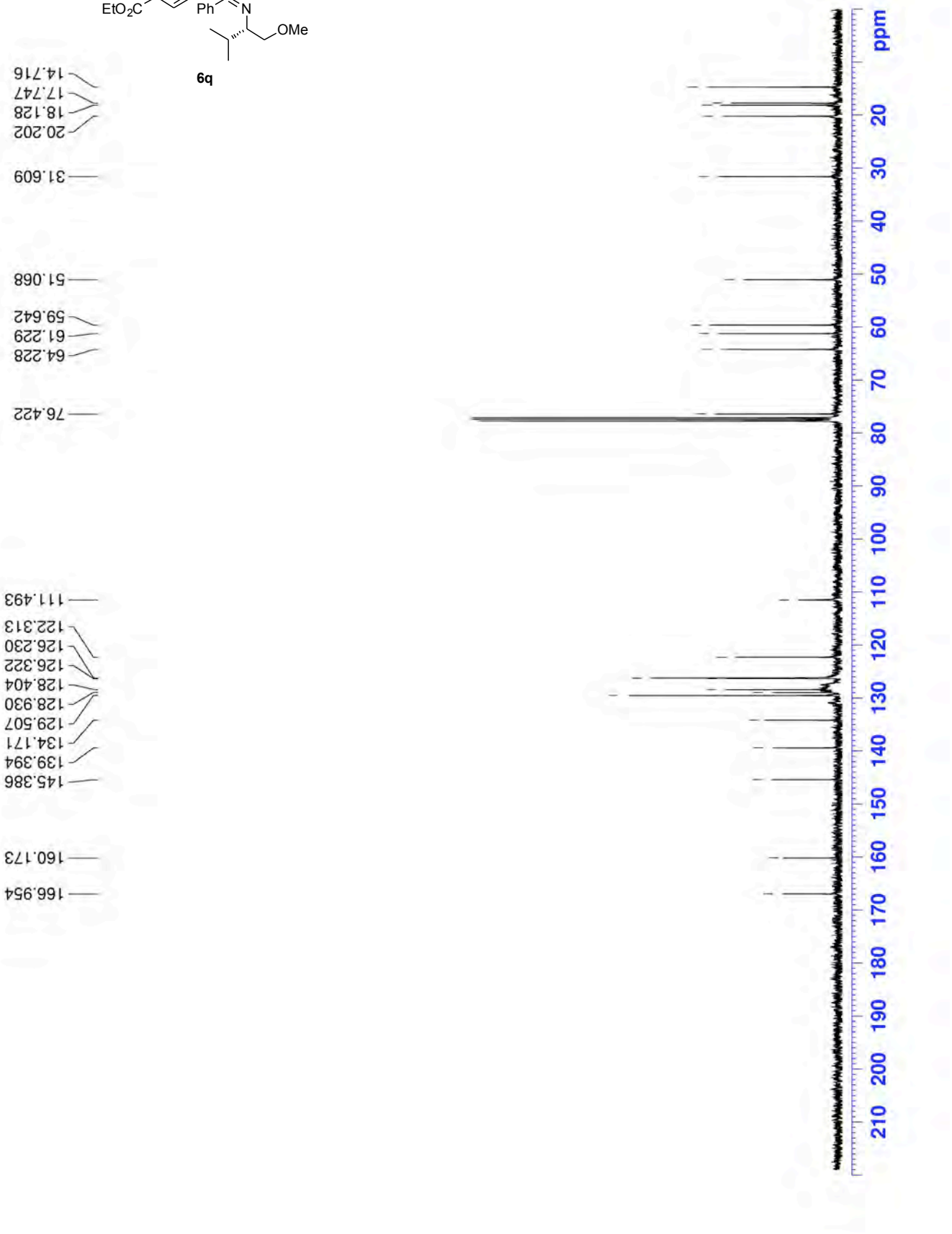

EtO2C
N
Me
Ph
N
OMe

6q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126.322
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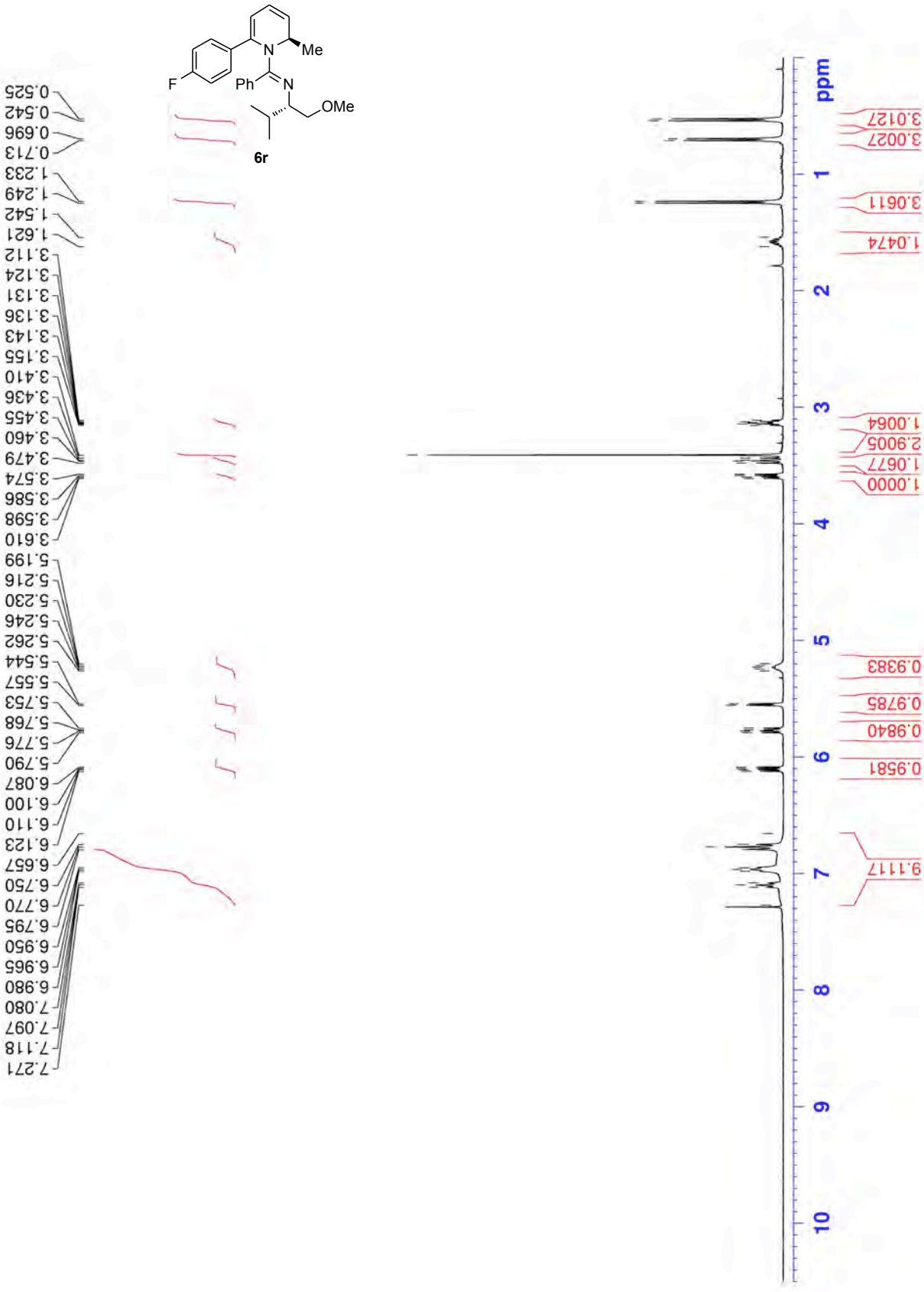
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OMe
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3.136
3.143
3.155
3.410
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5.230
5.246
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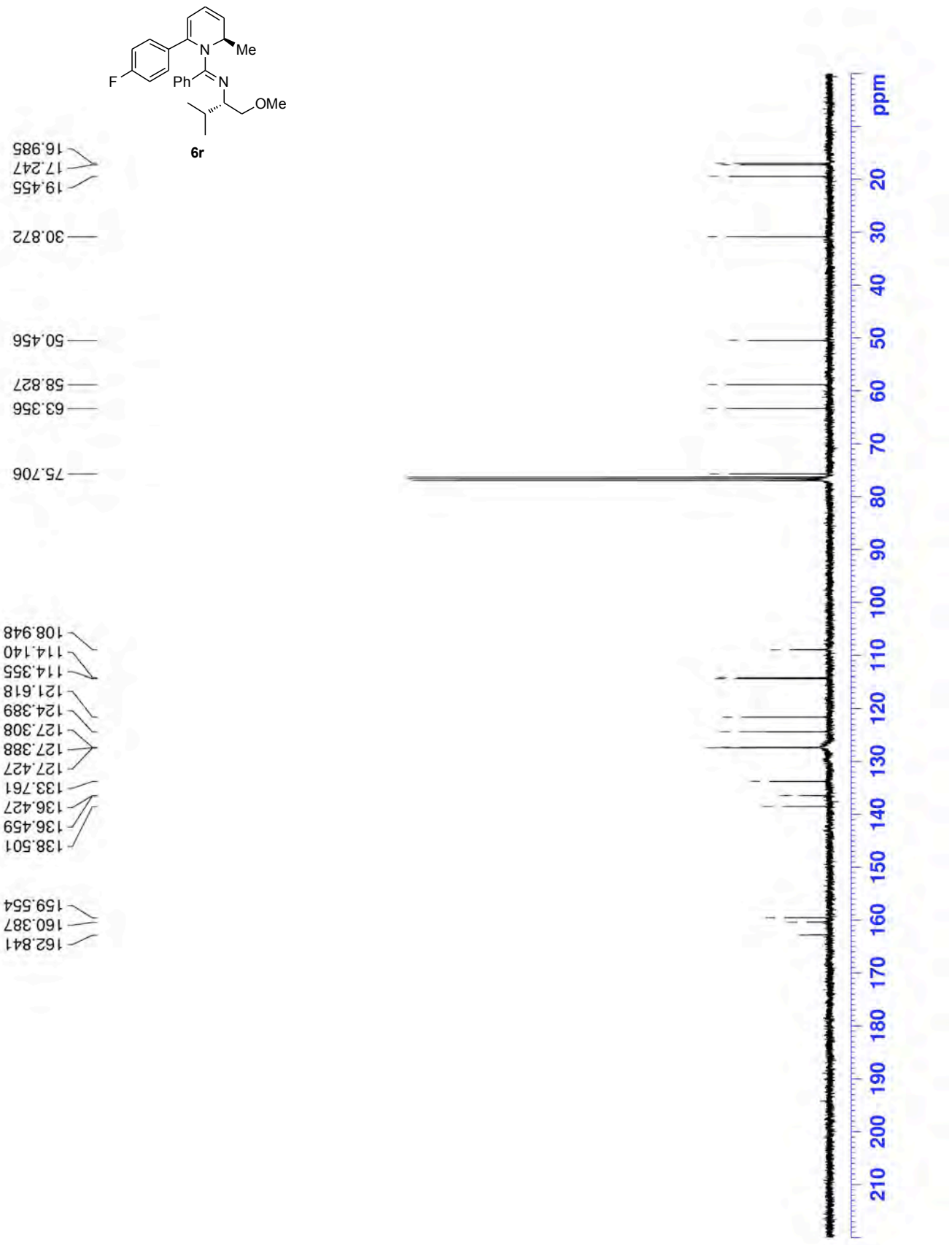
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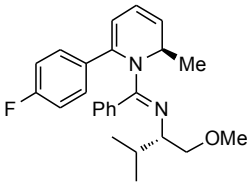
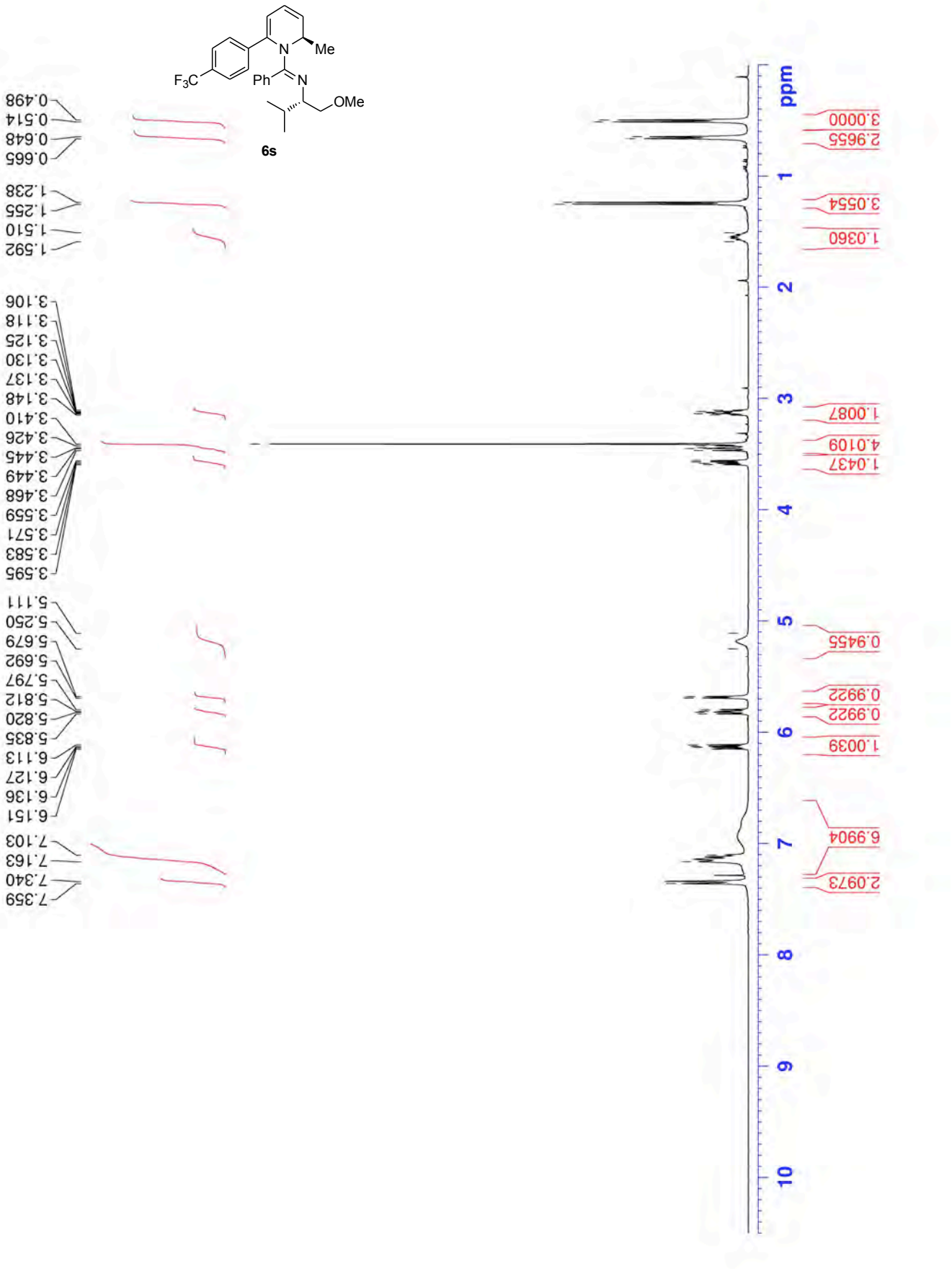


6r


F3C
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OMe
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1.592
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3.571
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5.250
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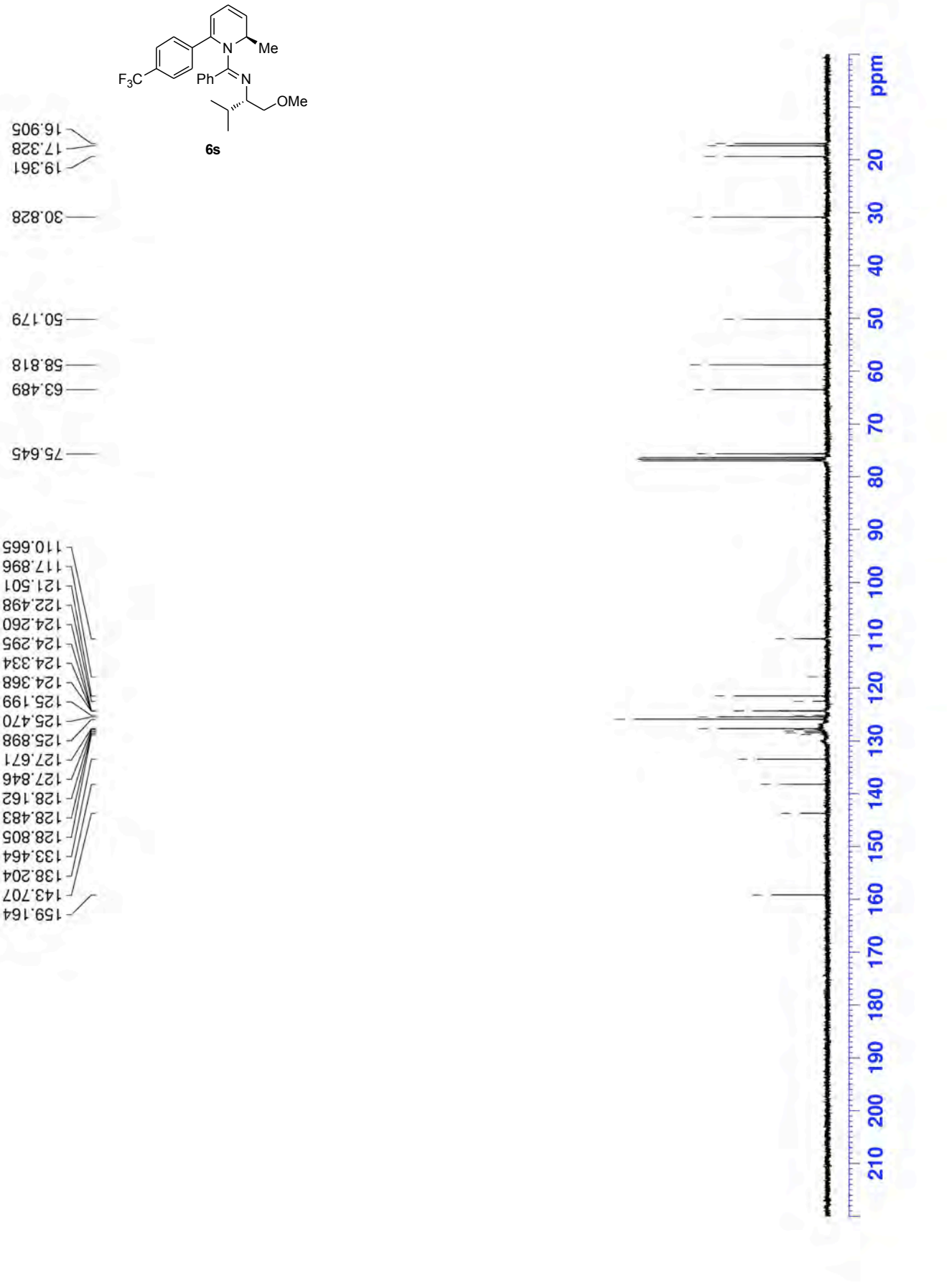
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16.905
17.328
19.361
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50.179
58.818
63.489
75.645
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117.896
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124.260
124.295
124.334
124.368
125.199
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127.846
128.162
128.483
128.805
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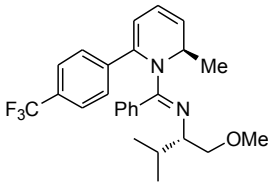
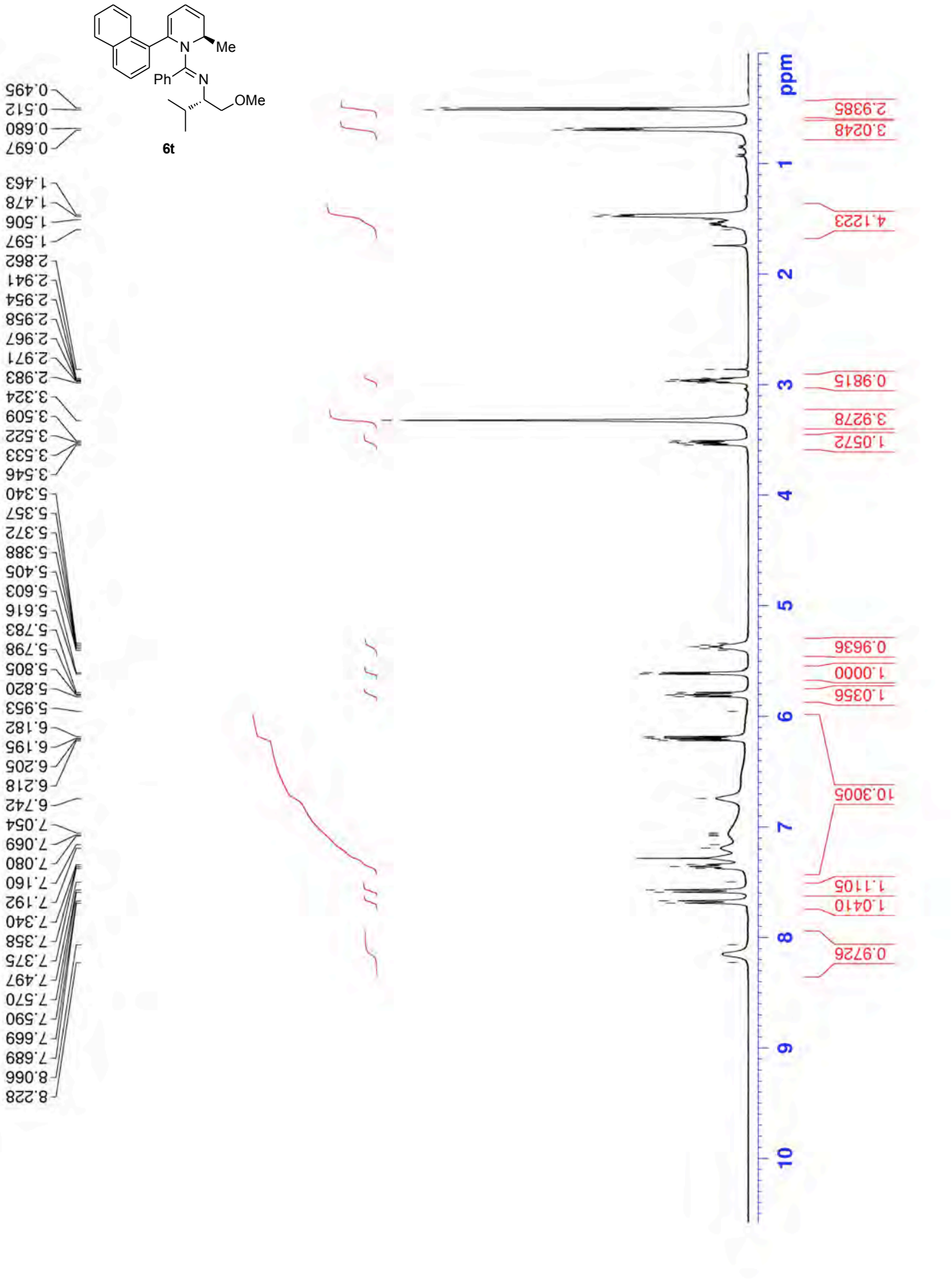


6s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3.533
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5.388
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6.218
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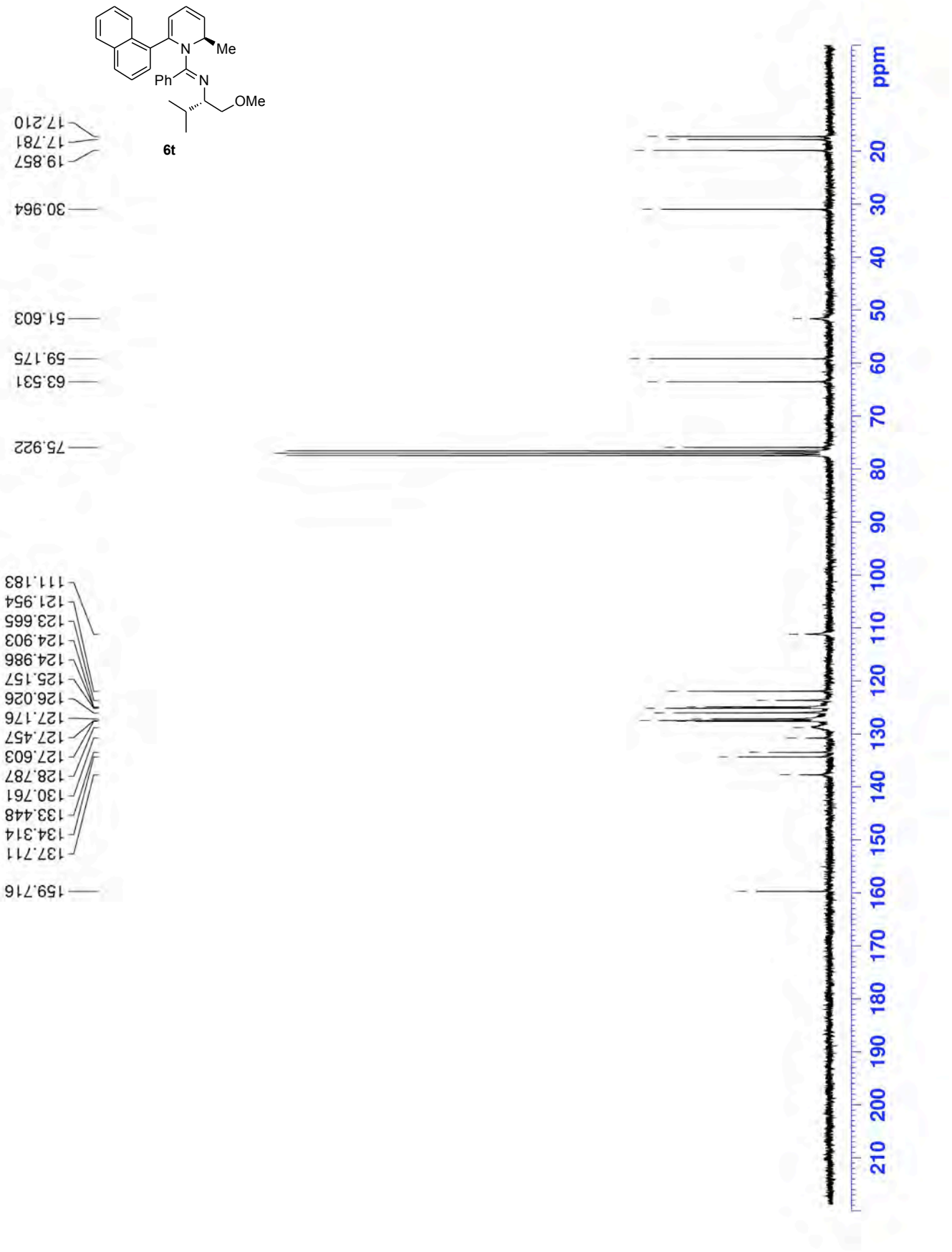
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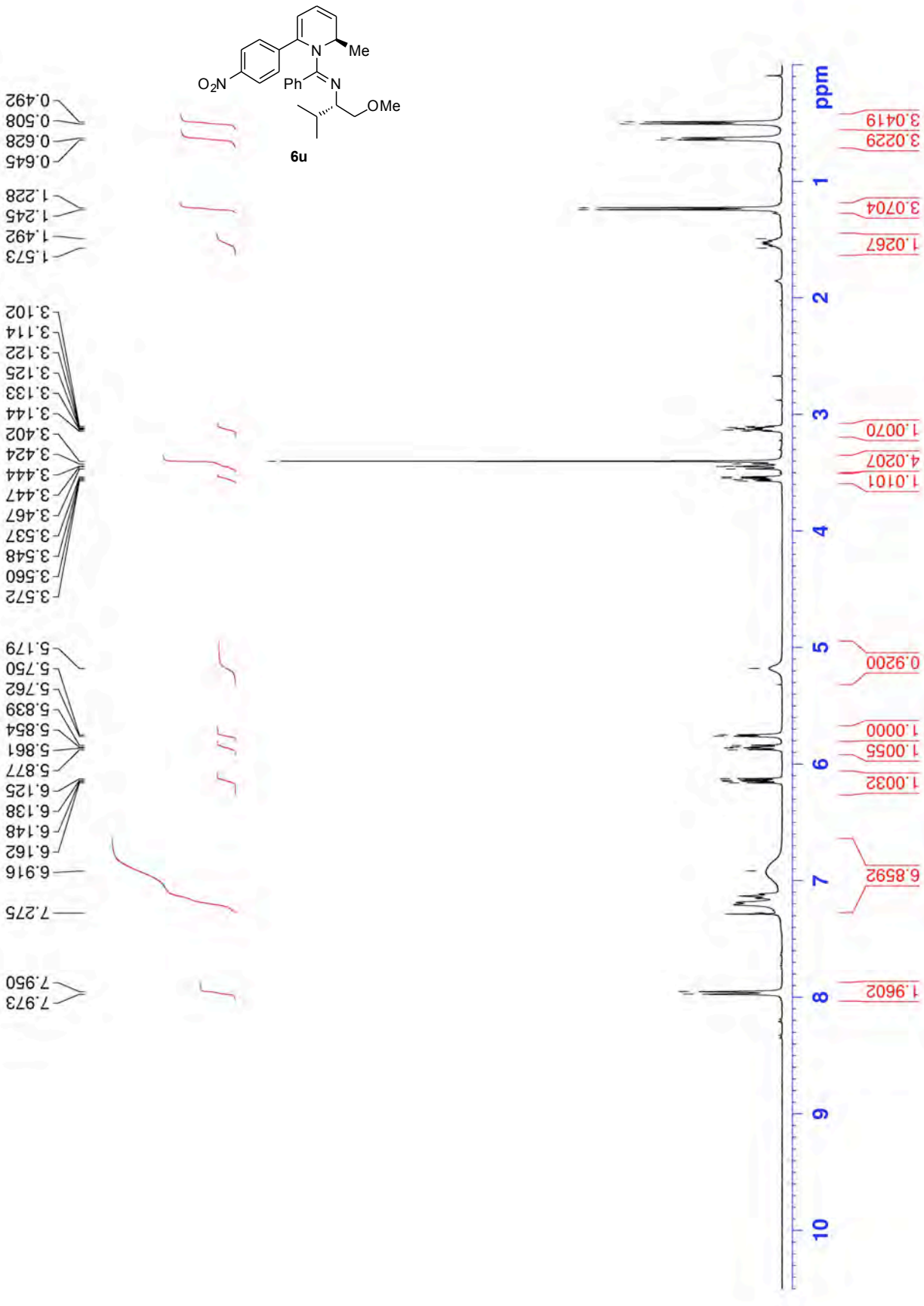
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Me
OMe
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3.122
3.125
3.133
3.144
3.402
3.424
3.444
3.447
3.467
3.537
3.548
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3.572
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5.750
5.762
5.839
5.854
5.861
5.877
6.125
6.138
6.148
6.162
6.916
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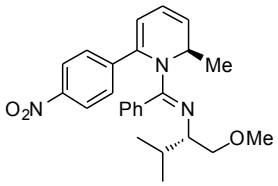
N
Me
O_2N
Ph
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OMe

6u

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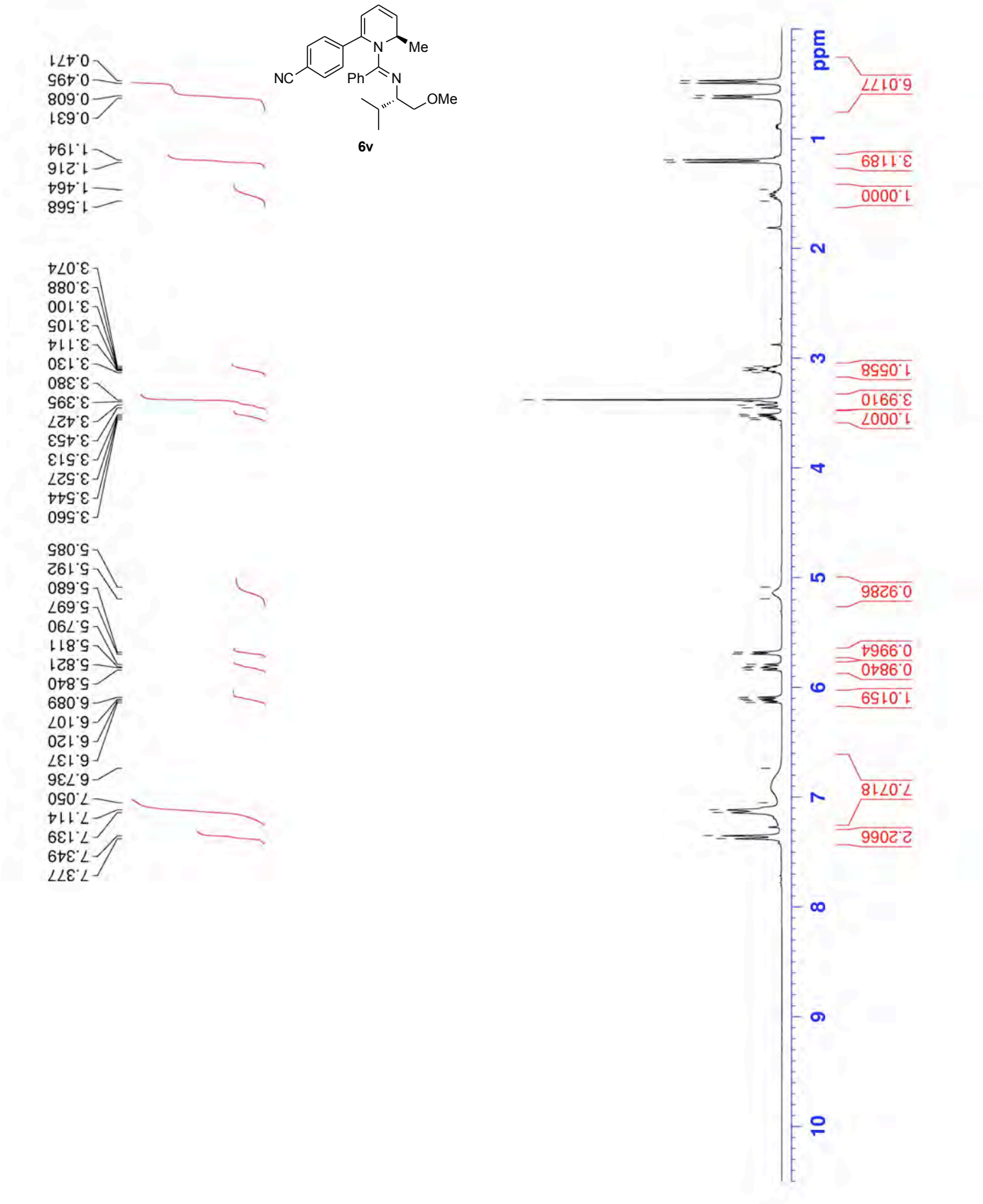
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3.527
3.544
3.560
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5.680
5.697
5.790
5.811
5.821
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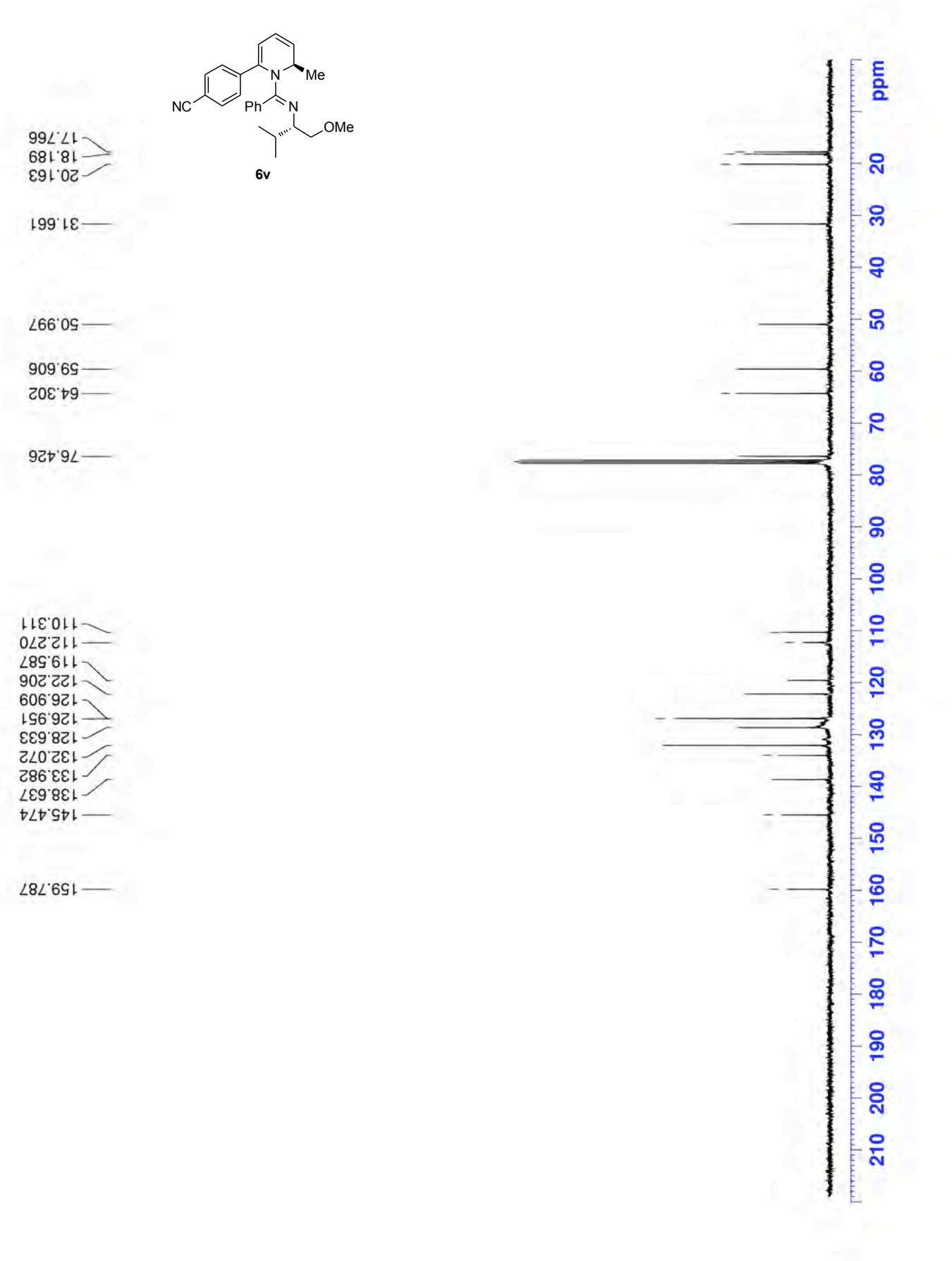
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OMe
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126.909
126.951
128.633
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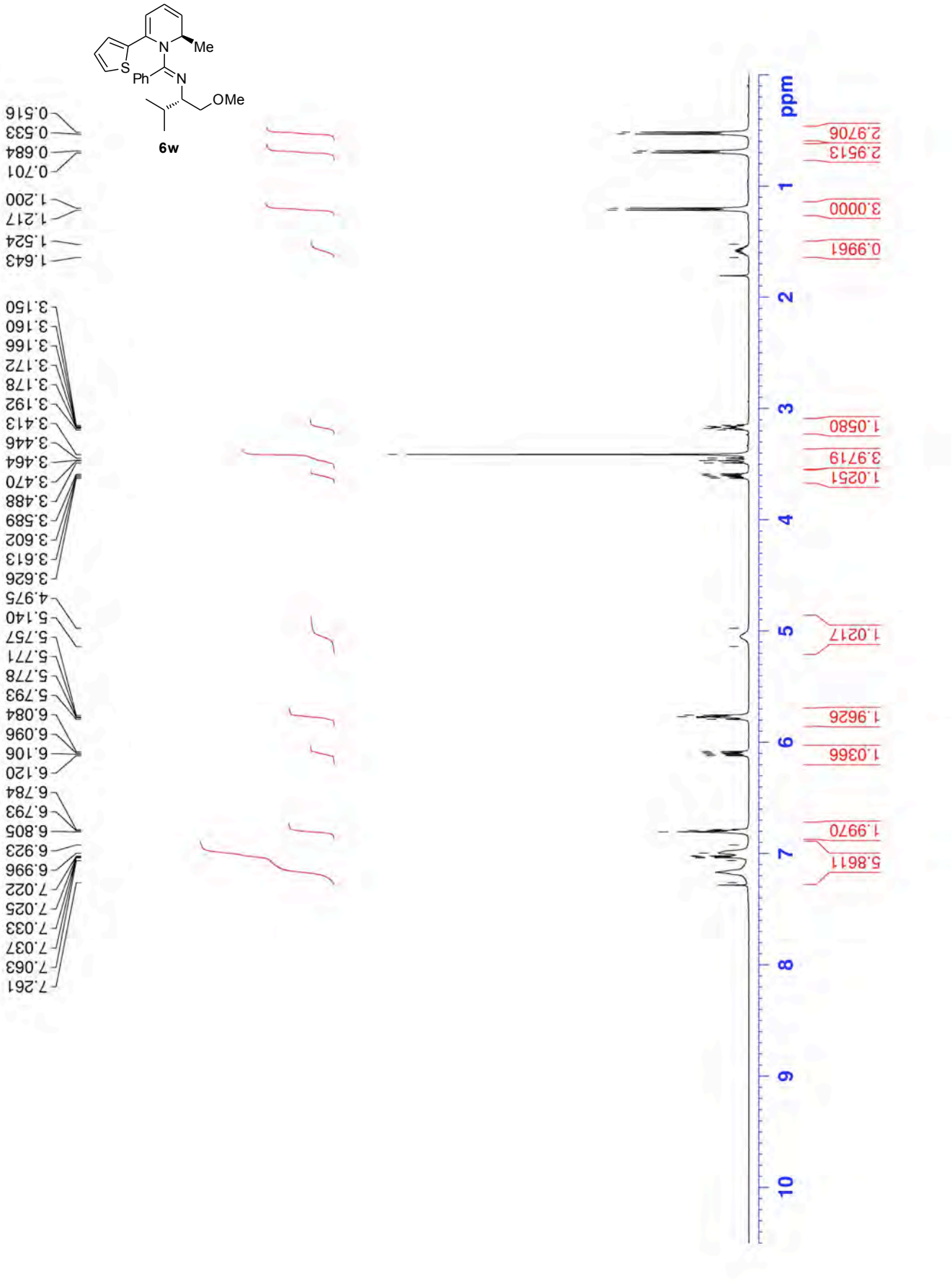
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Ph
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3.172
3.178
3.192
3.413
3.446
3.464
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3.602
3.613
3.626
4.975
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5.757
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5.778
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6.096
6.106
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6.793
6.805
6.923
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7.037
7.063
7.261
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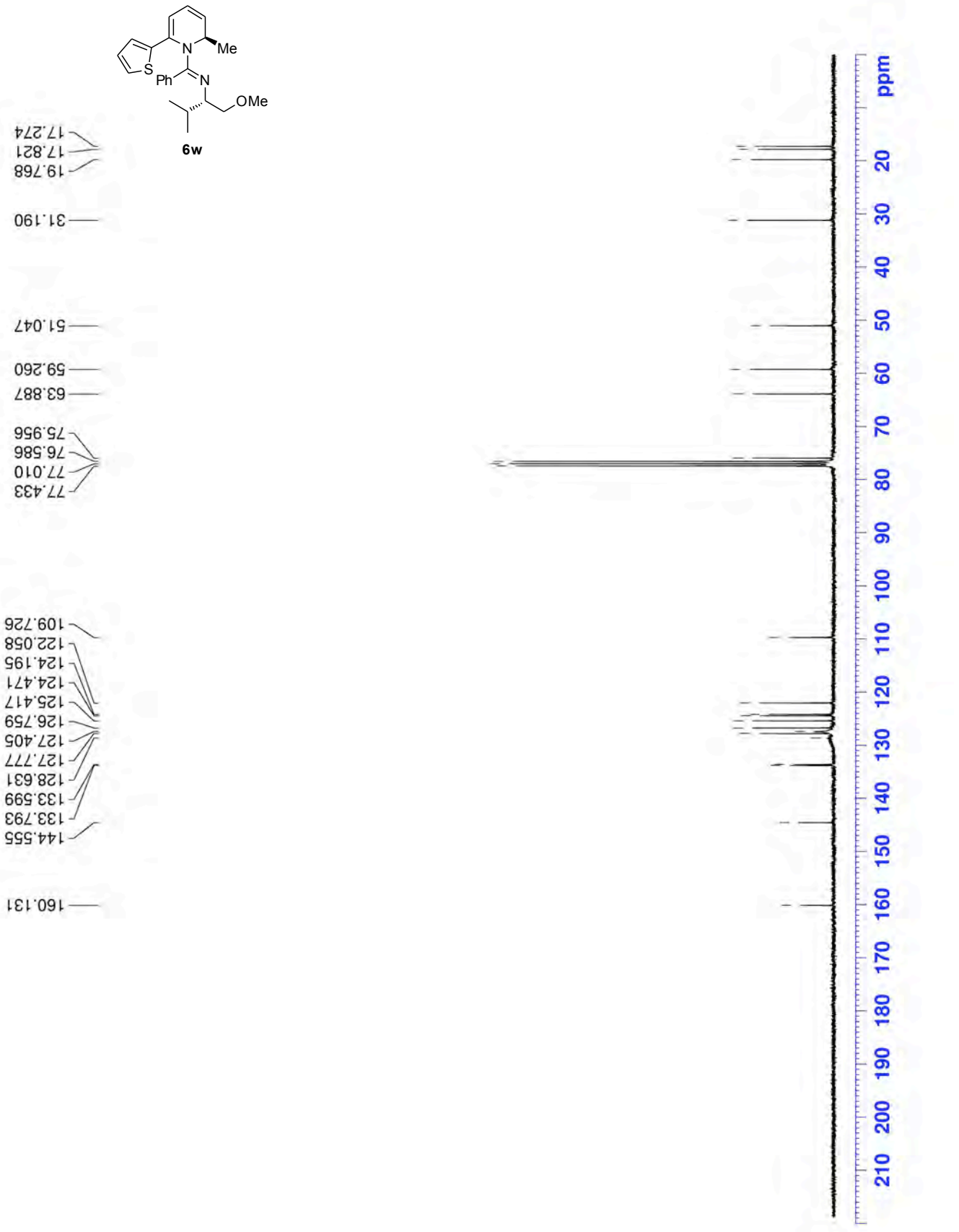
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Ph
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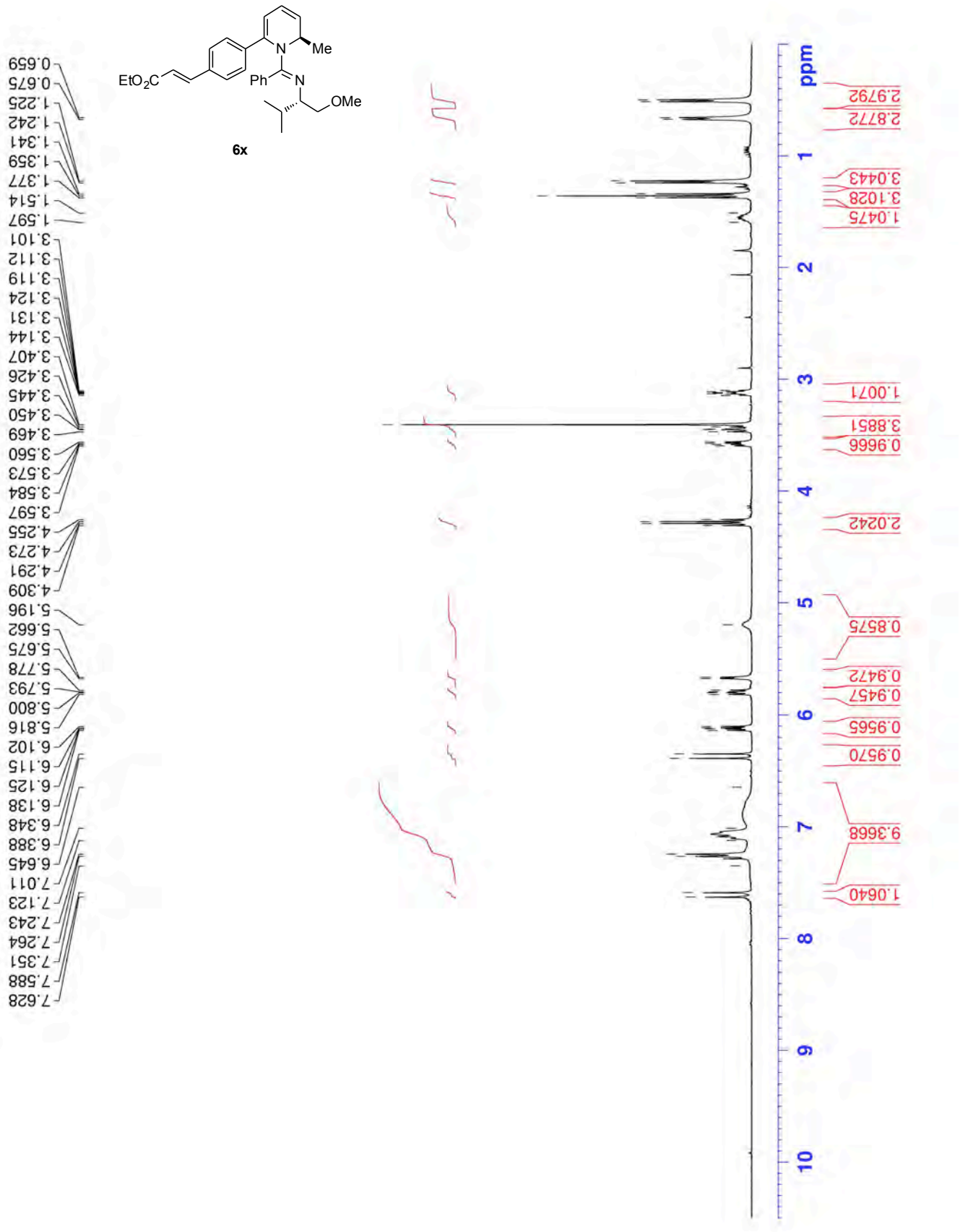
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OMe
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5.778
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6.115
6.125
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6.348
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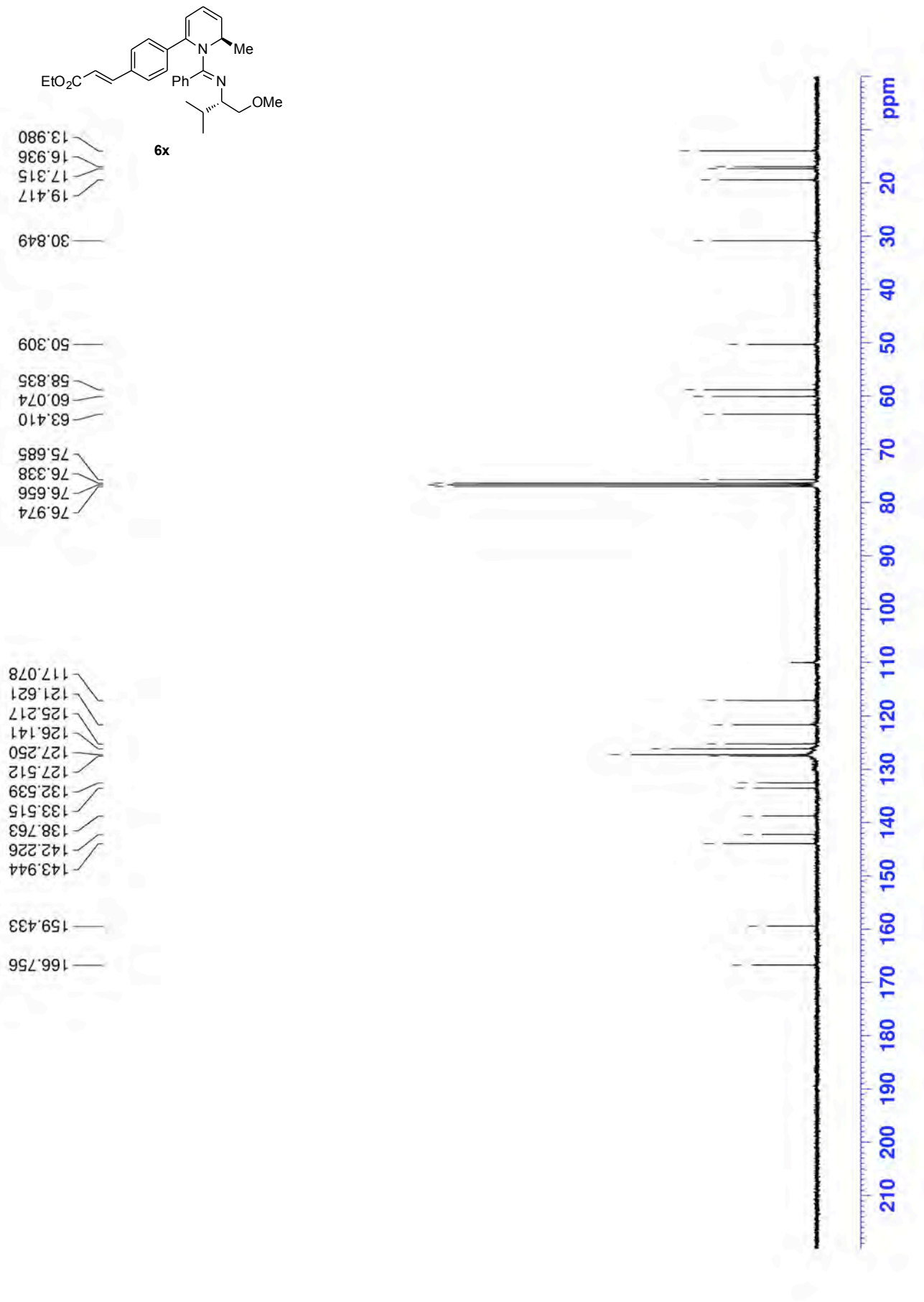
EtO2C
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OMe
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76.656
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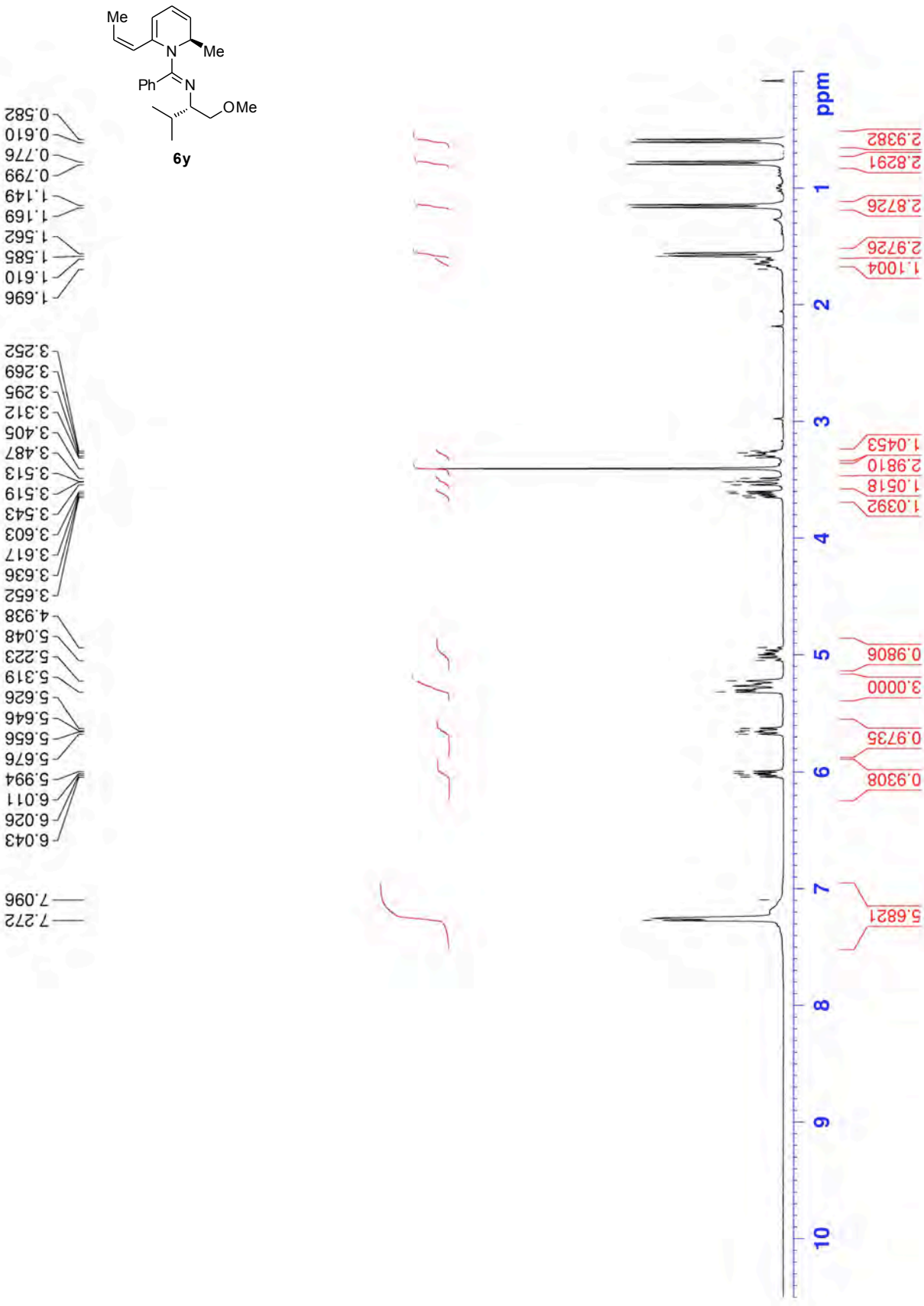
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3.312
3.405
3.487
3.513
3.519
3.543
3.603
3.617
3.636
3.652
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5.048
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5.319
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5.646
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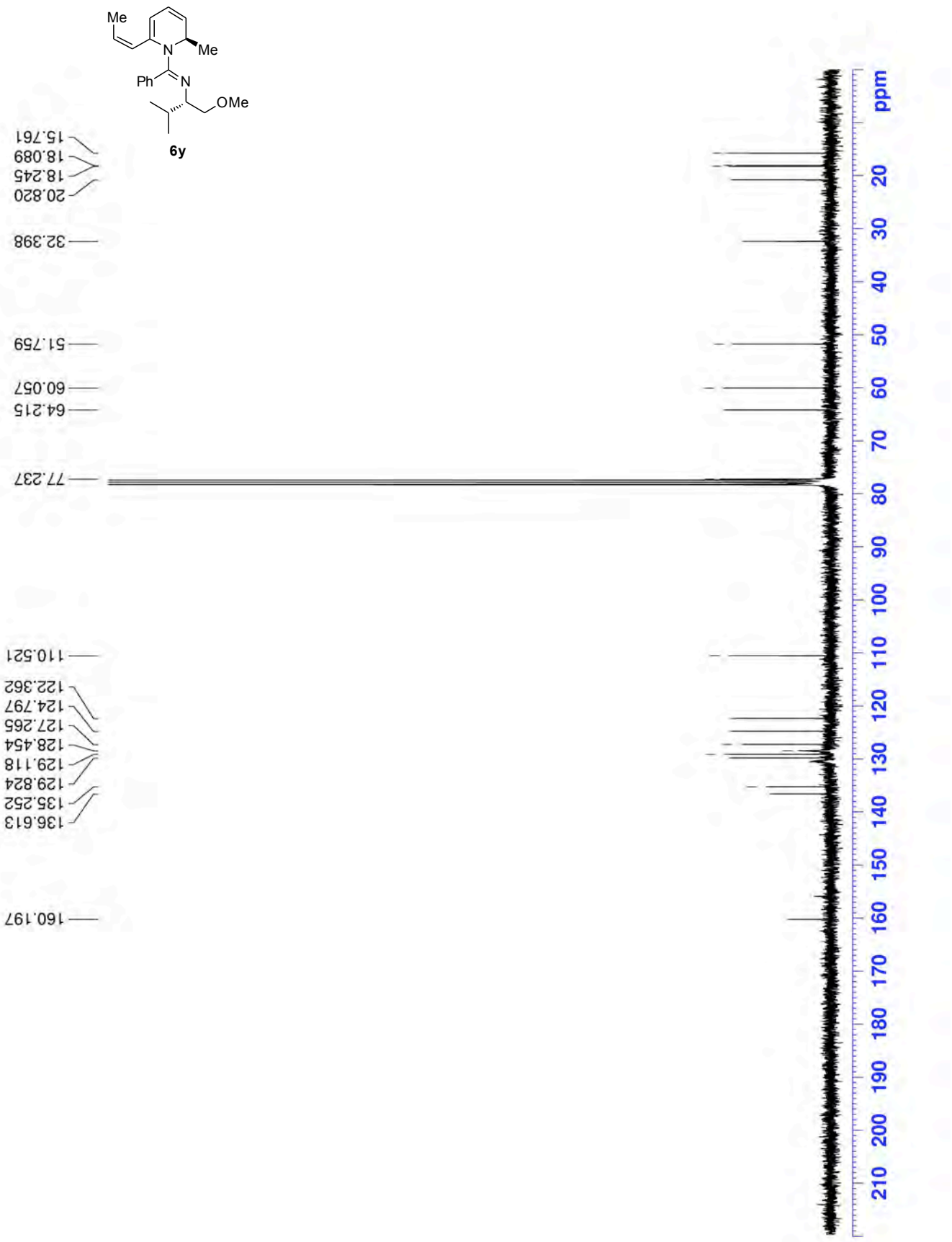
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OMe
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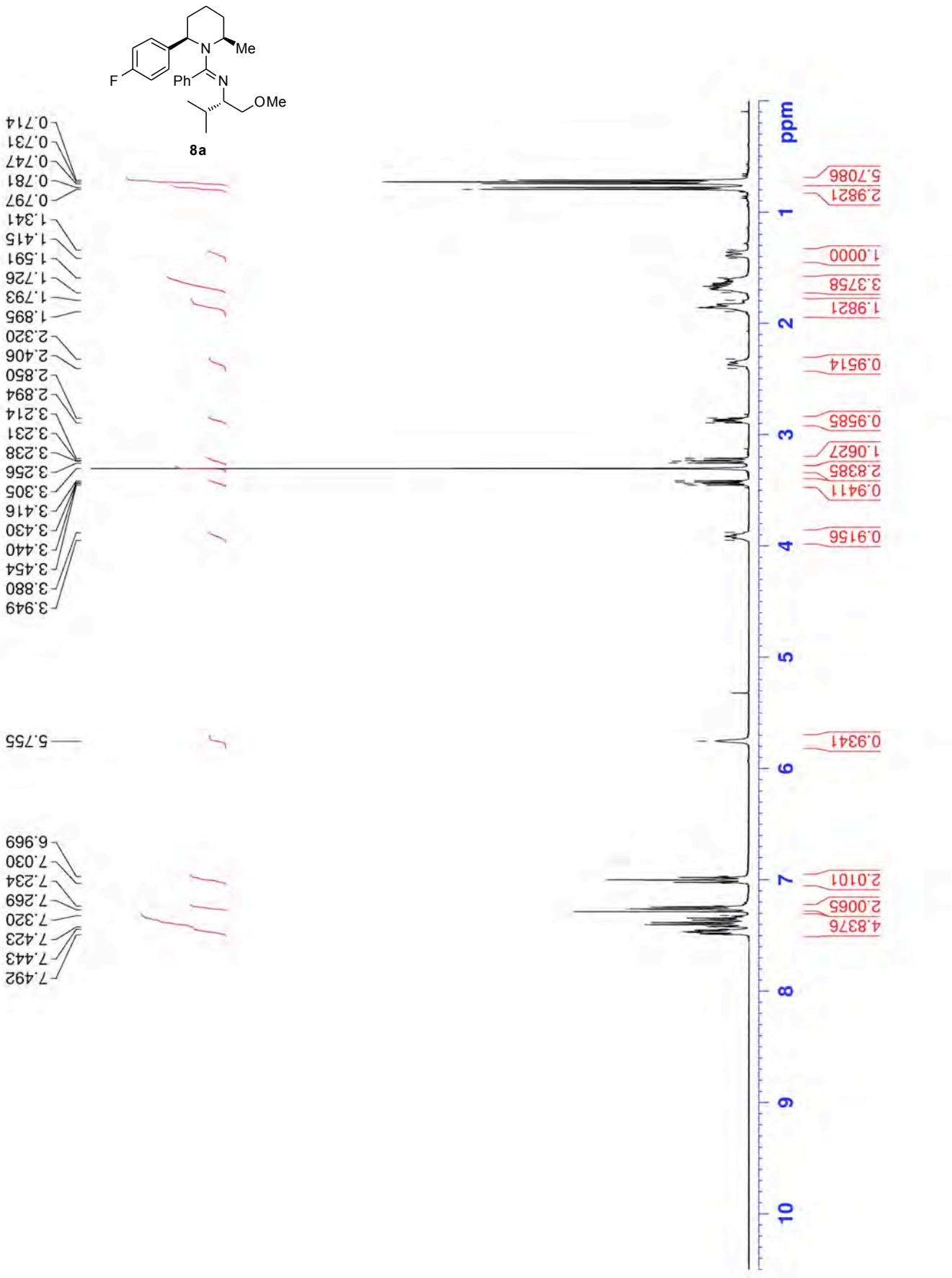
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3.238
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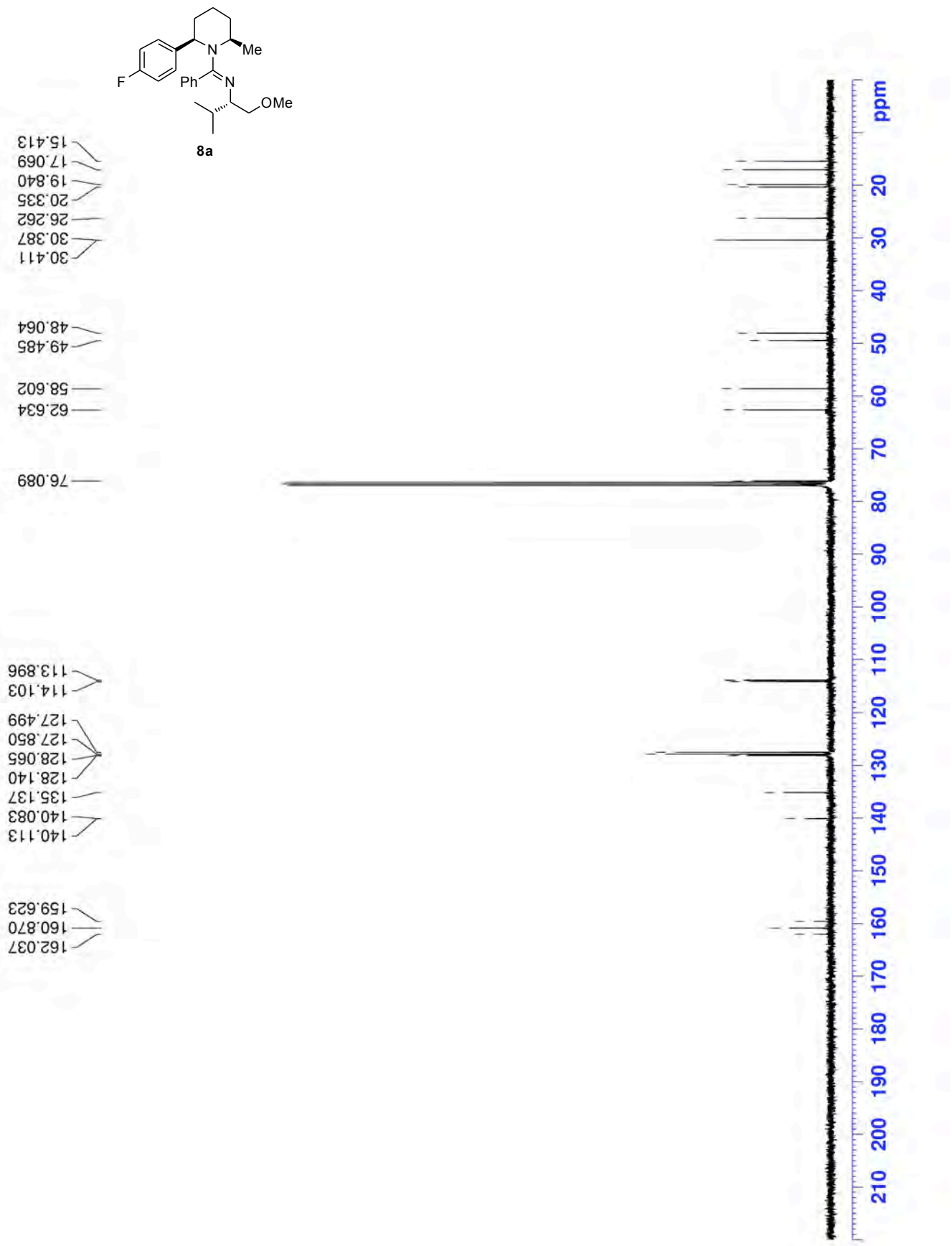
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128.065
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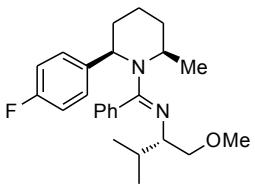

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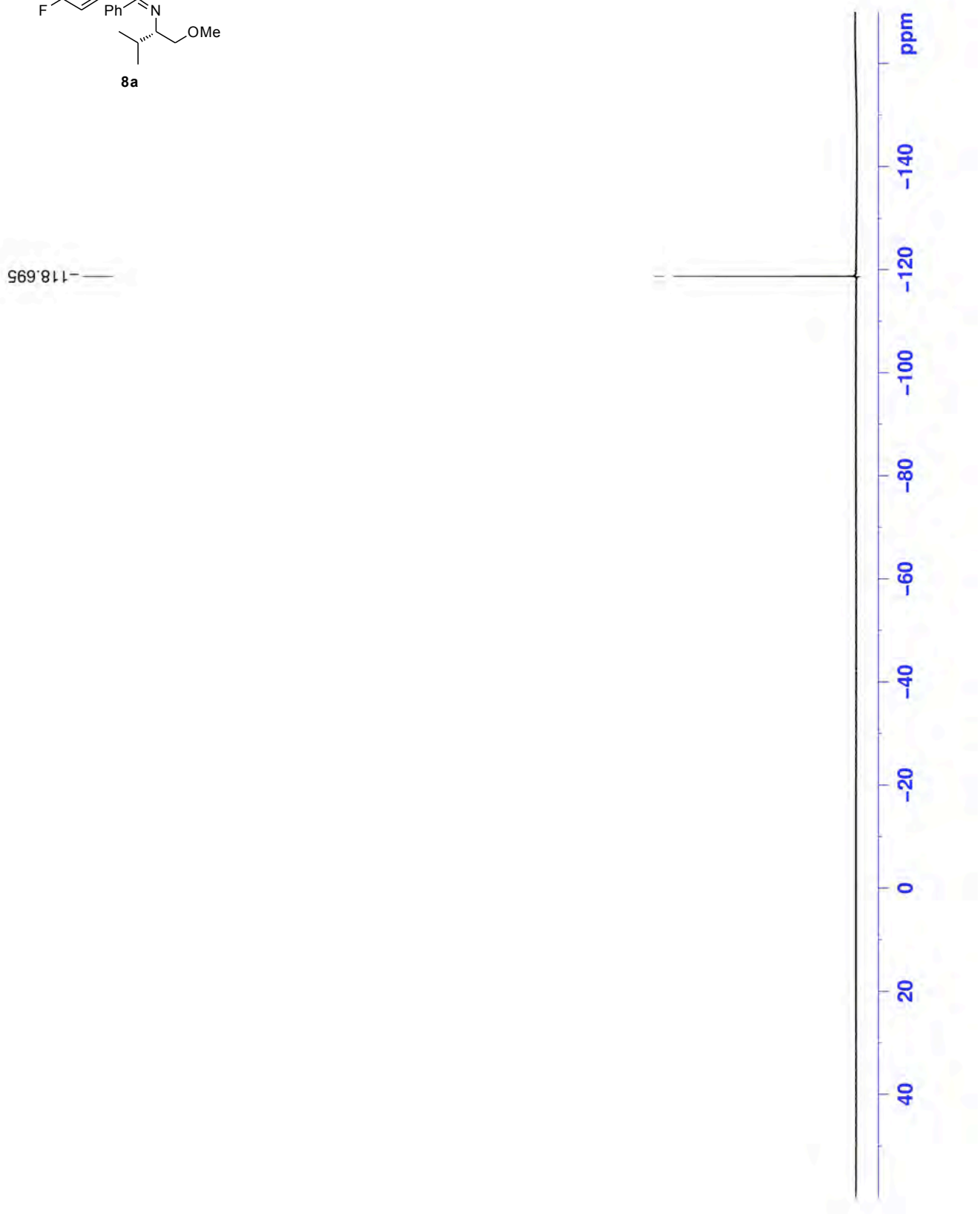

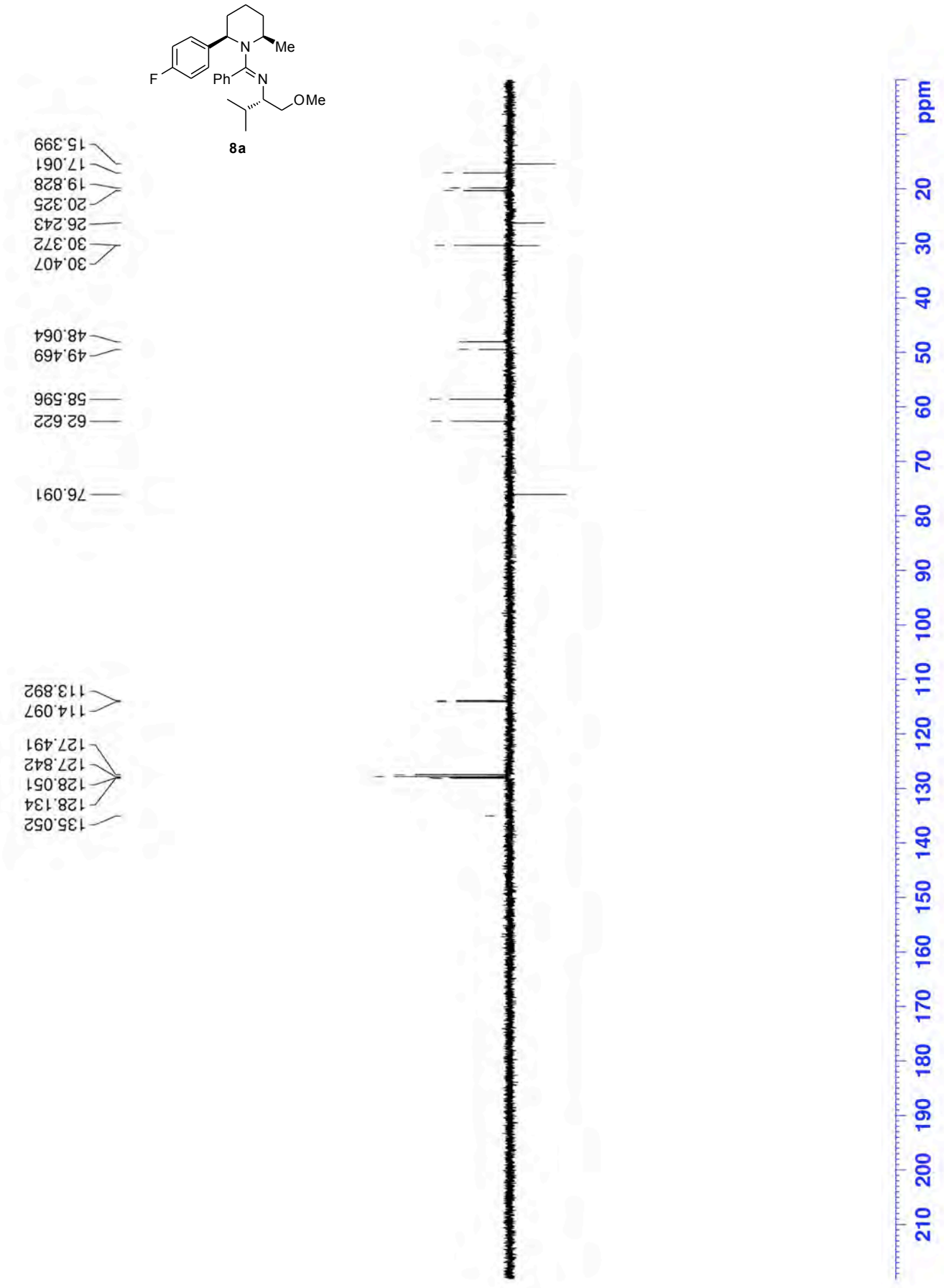
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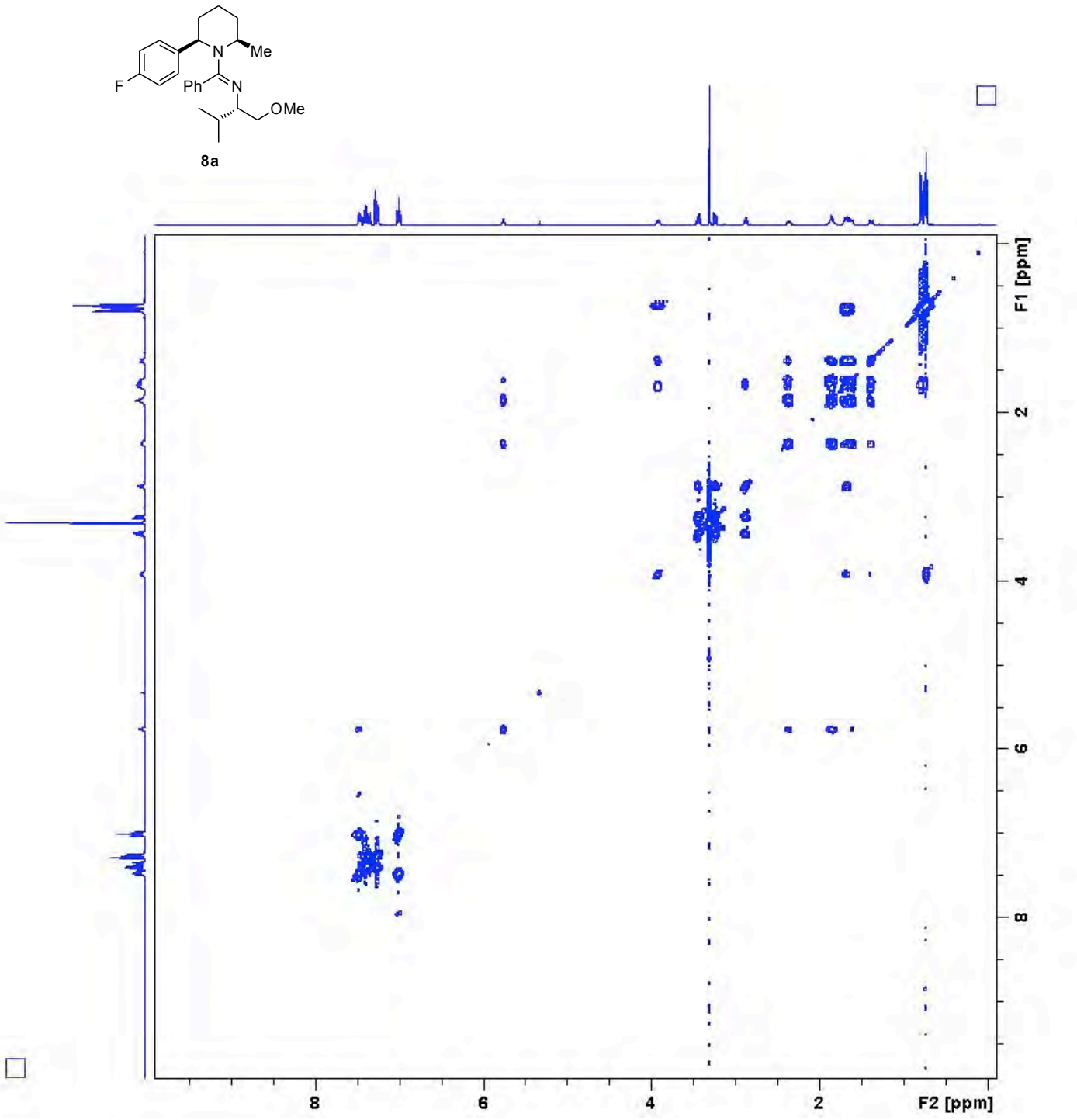
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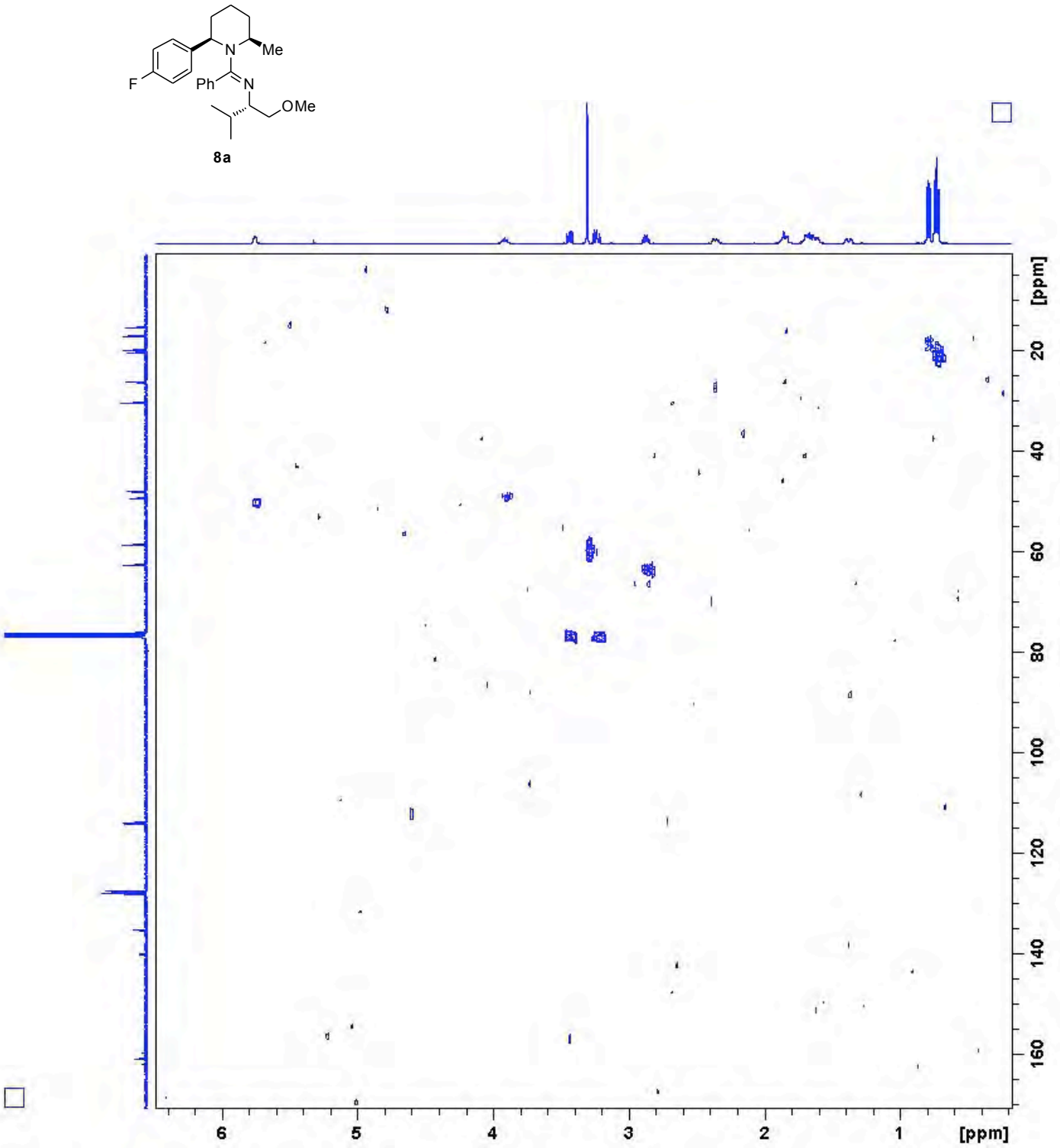
F2 [ppm]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Ph
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OMe
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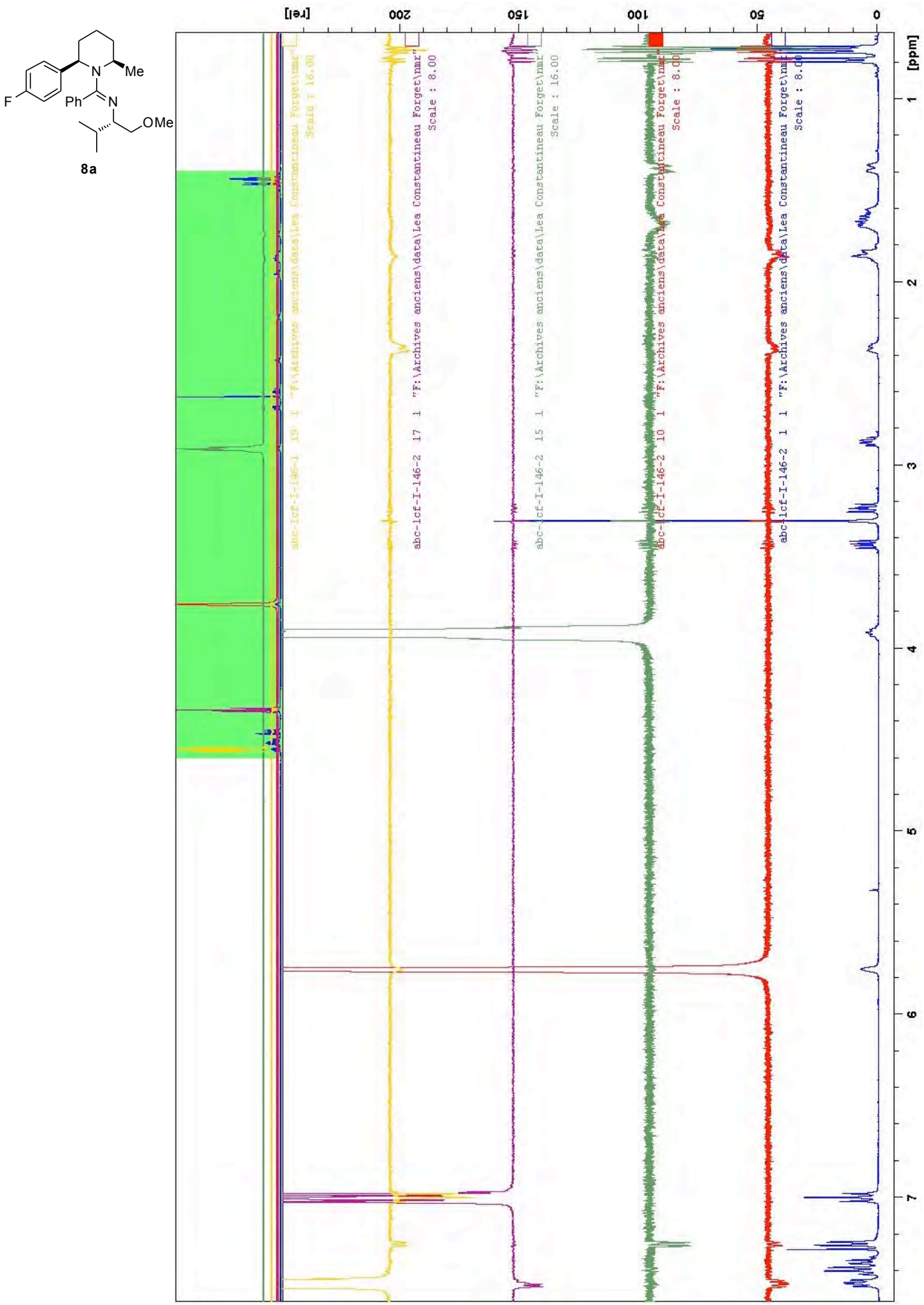
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6
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Scale : 8.00
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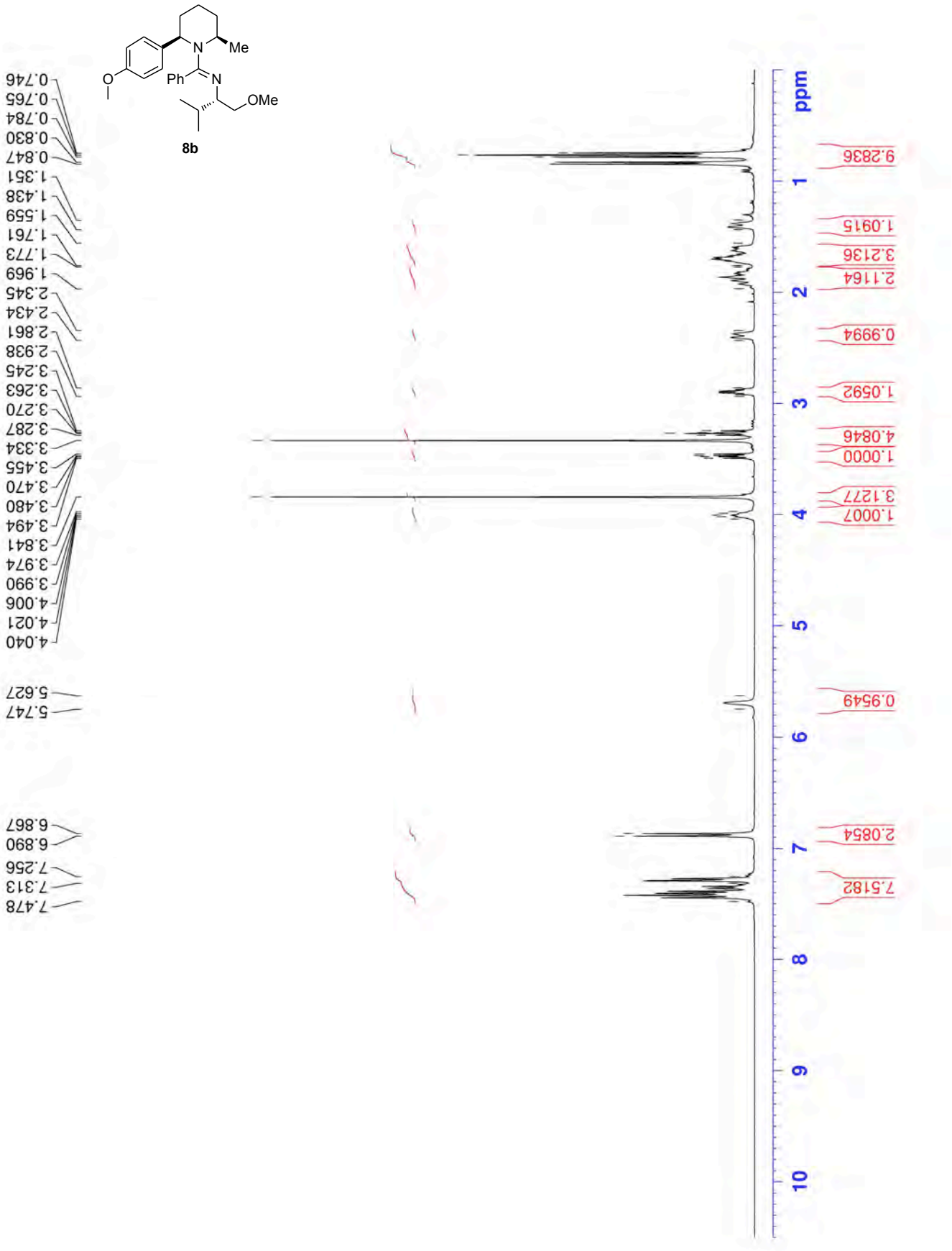
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2.434
2.861
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3.245
3.263
3.270
3.287
3.334
3.455
3.470
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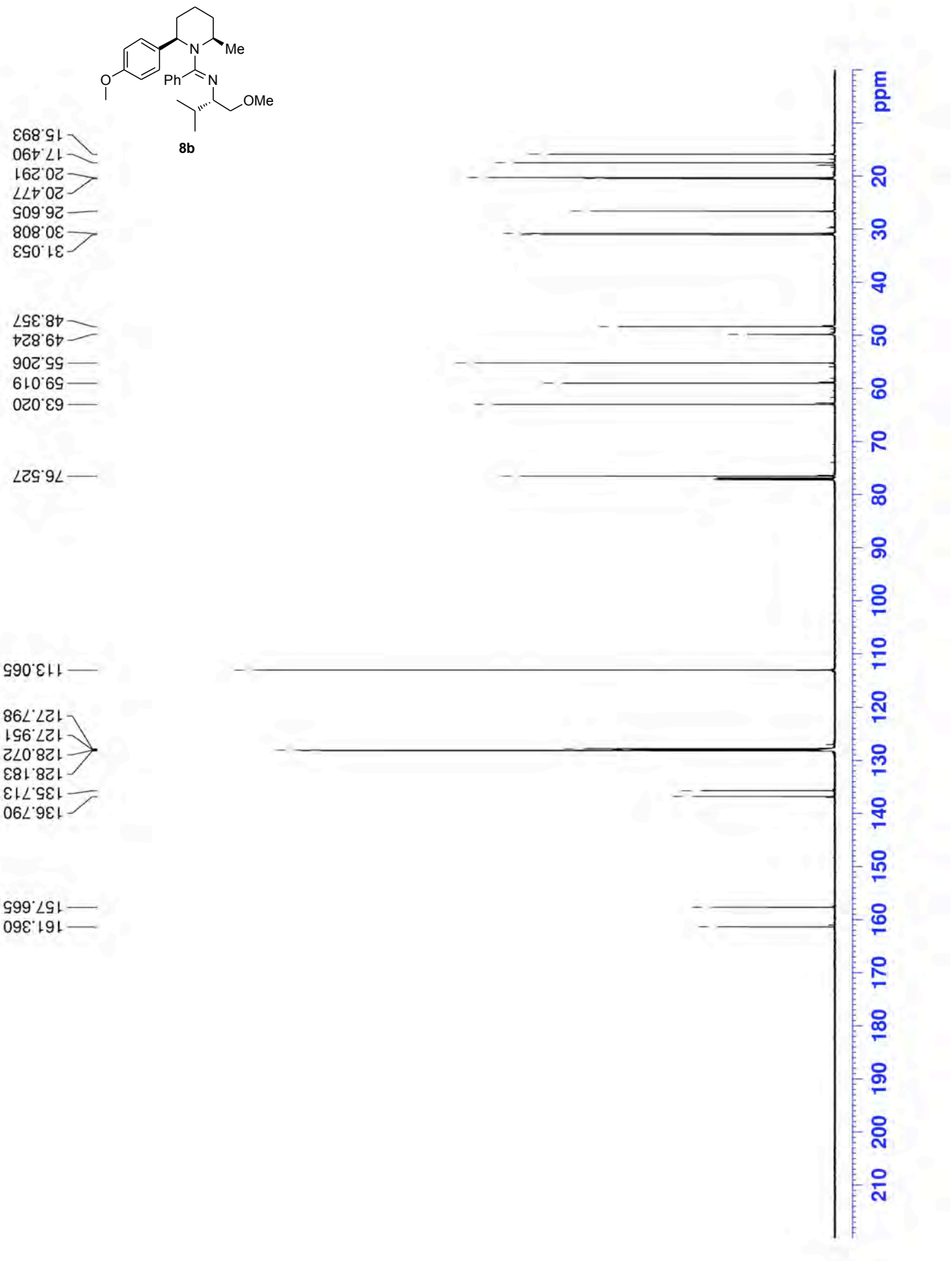
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127.798
127.951
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128.183
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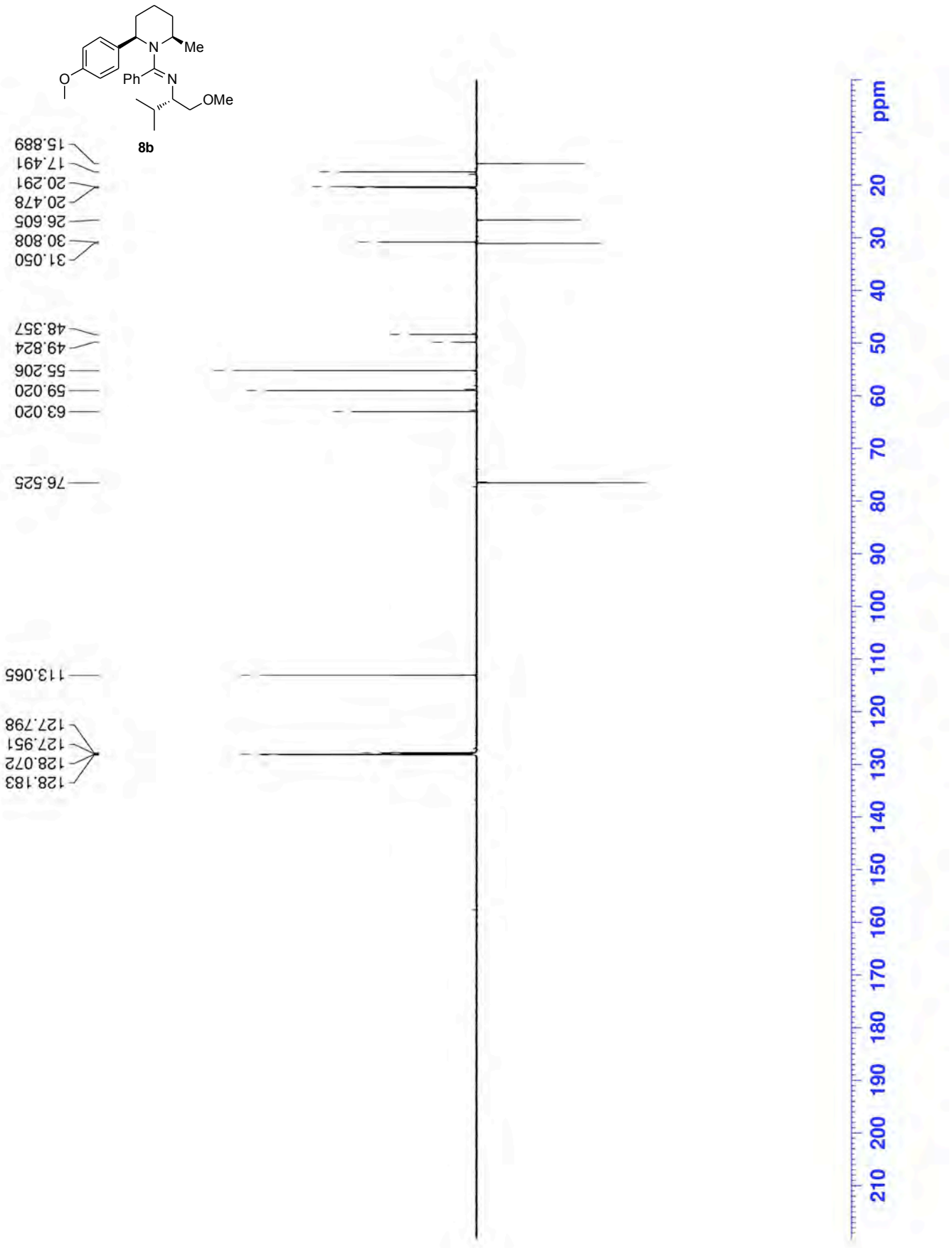
Me
N
Ph
N
O
OMe
8b
15.889
17.491
20.291
20.478
26.605
30.808
31.050
48.357
49.824
55.206
59.020
63.020
76.525
113.065
127.798
127.951
128.072
128.183
ppm
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40
50
60
70
80
90
100
110
120
130
140
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180
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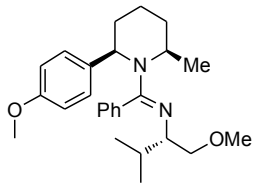
200
210



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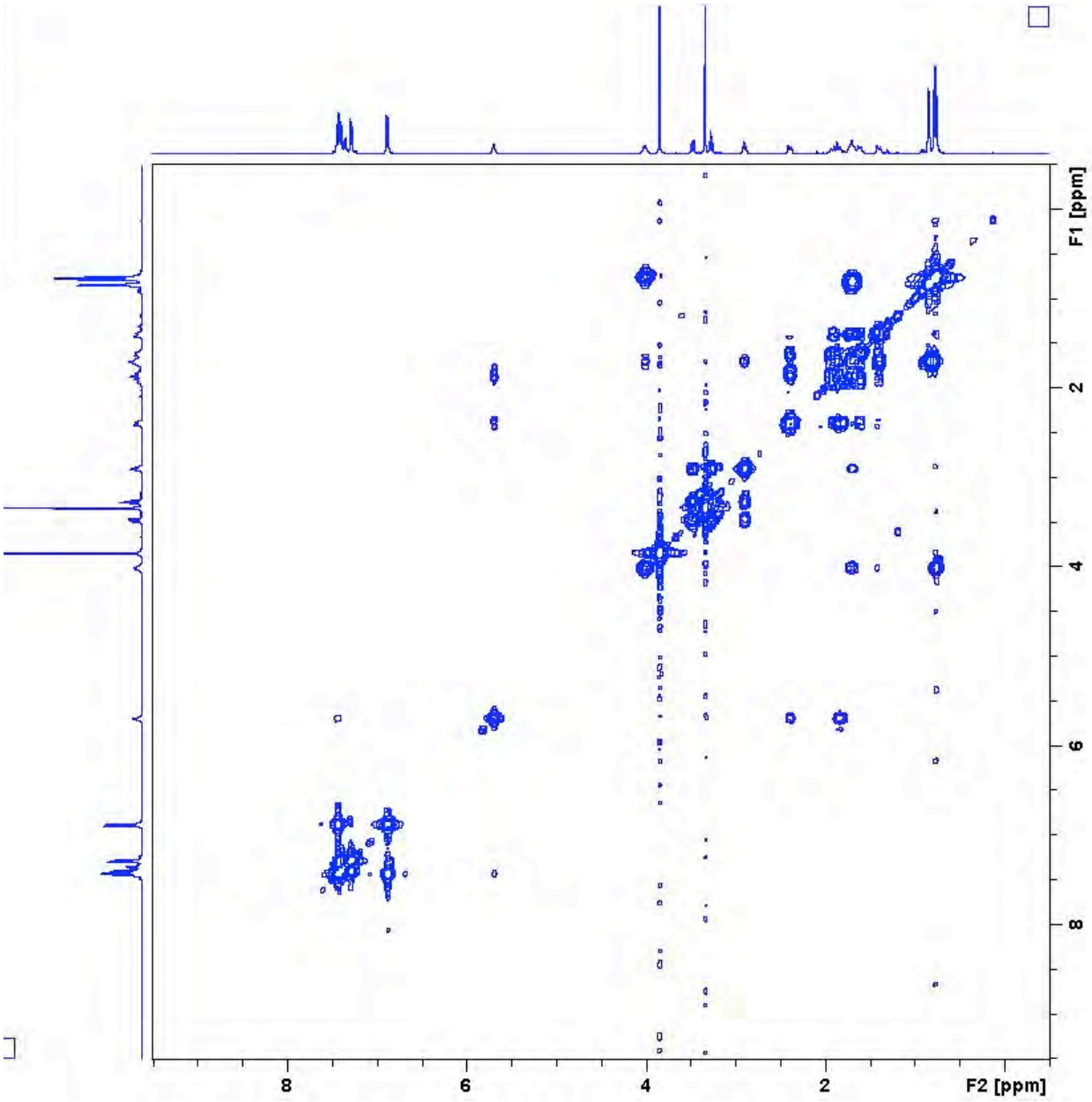

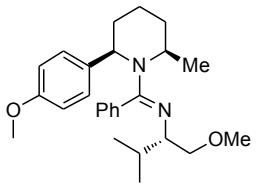

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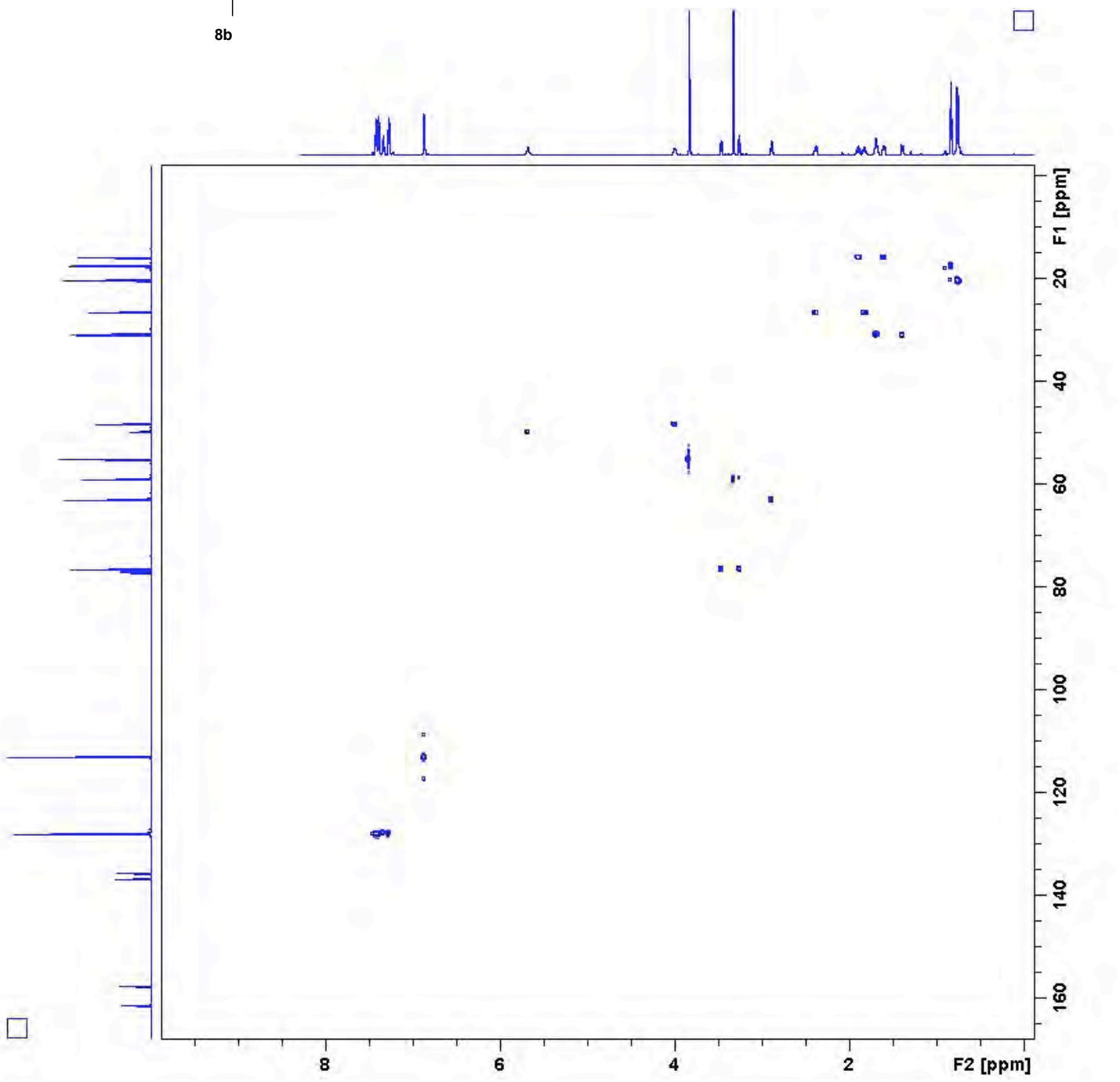

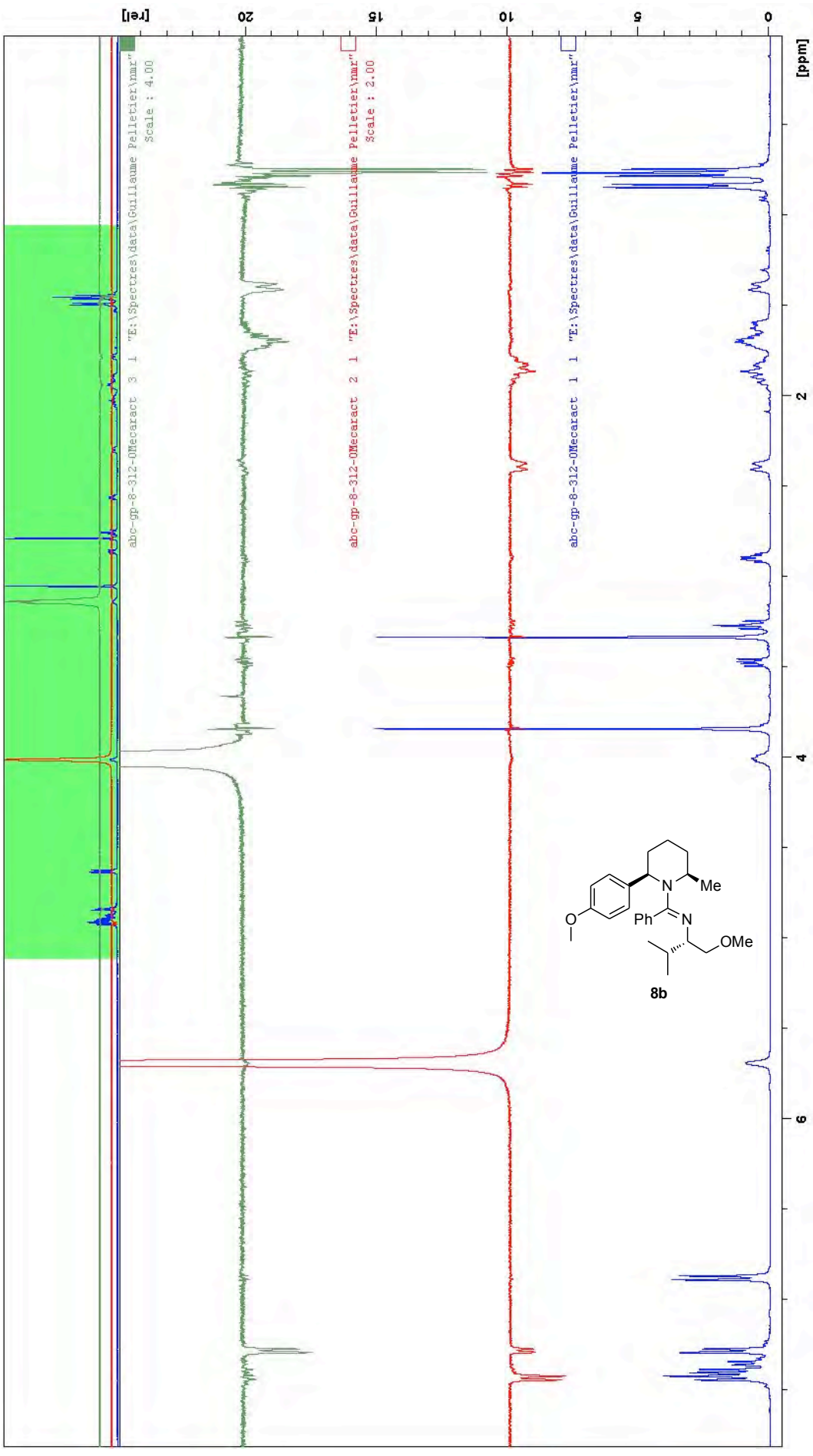
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20
15
10
5
0
[ppm]
2
4
6
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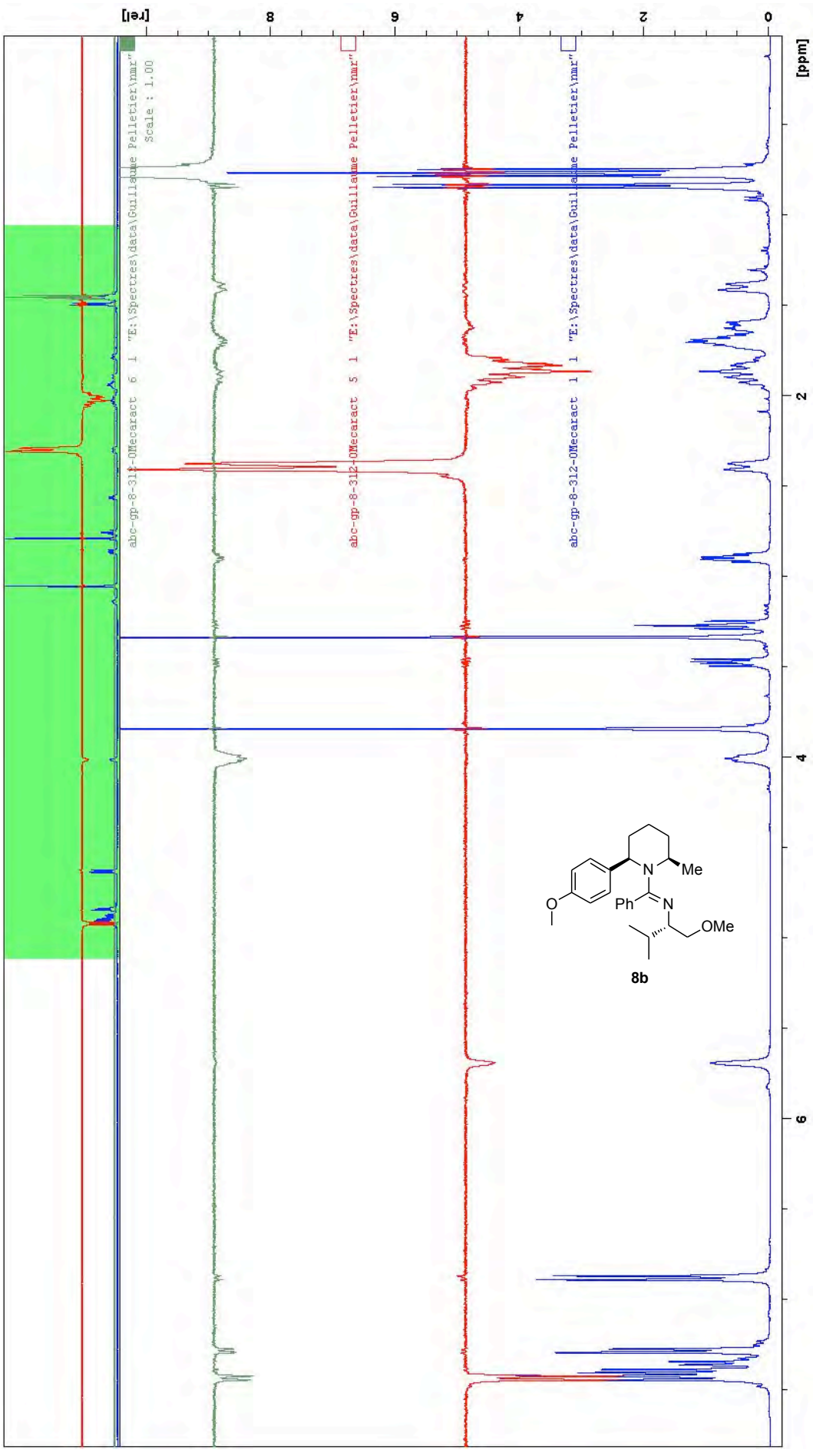
Scale : 4.00
abc-gp-8-312-OMecaract 2 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
Scale : 2.00
abc-gp-8-312-OMecaract 1 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
N
Me
Ph
N
O
OMe

8b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4
2
0
[ppm]
2
4
6
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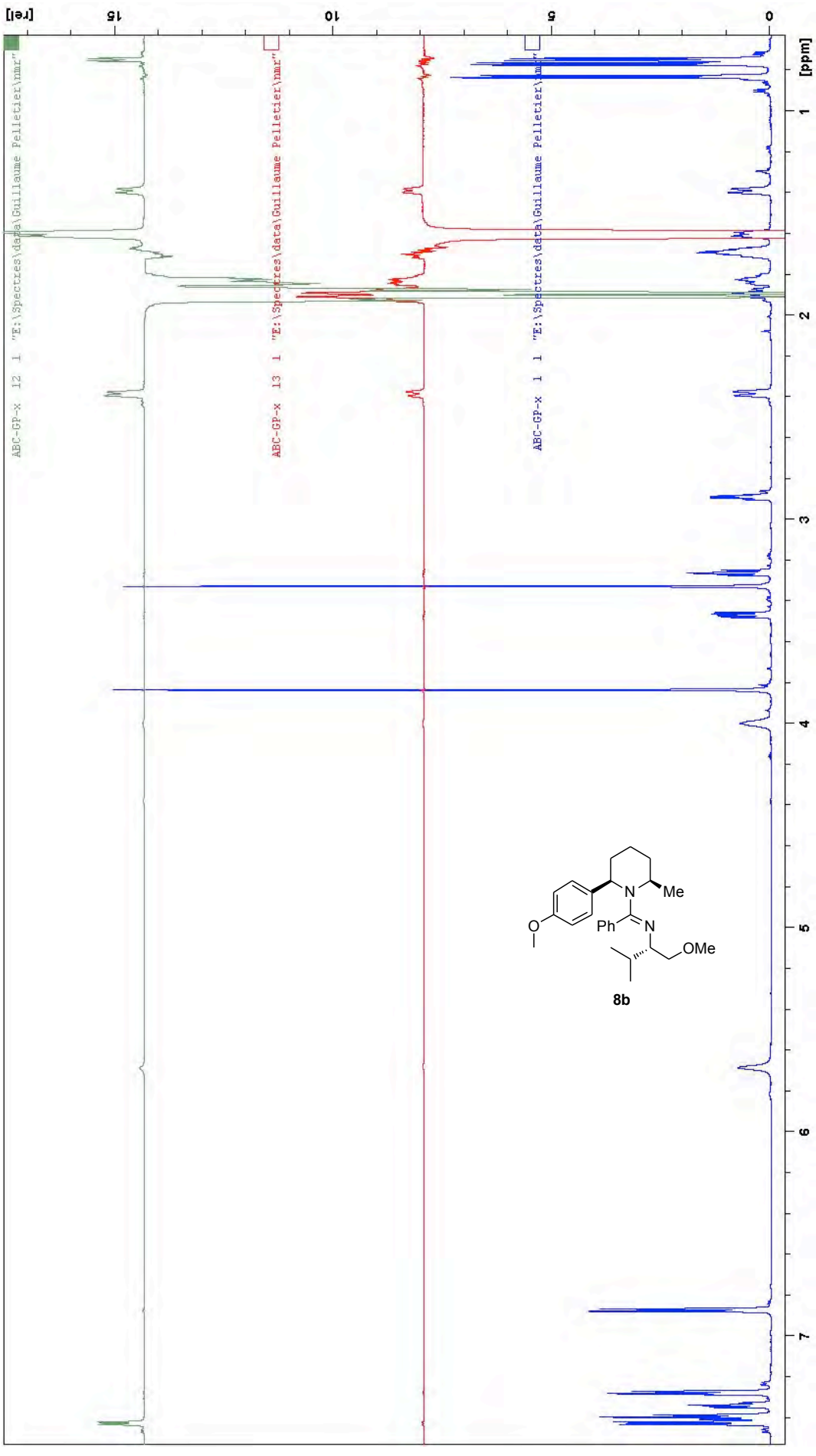
Scale : 1.00
abc-gp-8-312-OMecaract 5 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
abc-gp-8-312-OMecaract 1 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
N
Me
Ph
N
OMe
O
8b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[ppm]
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3
4
5
6
7
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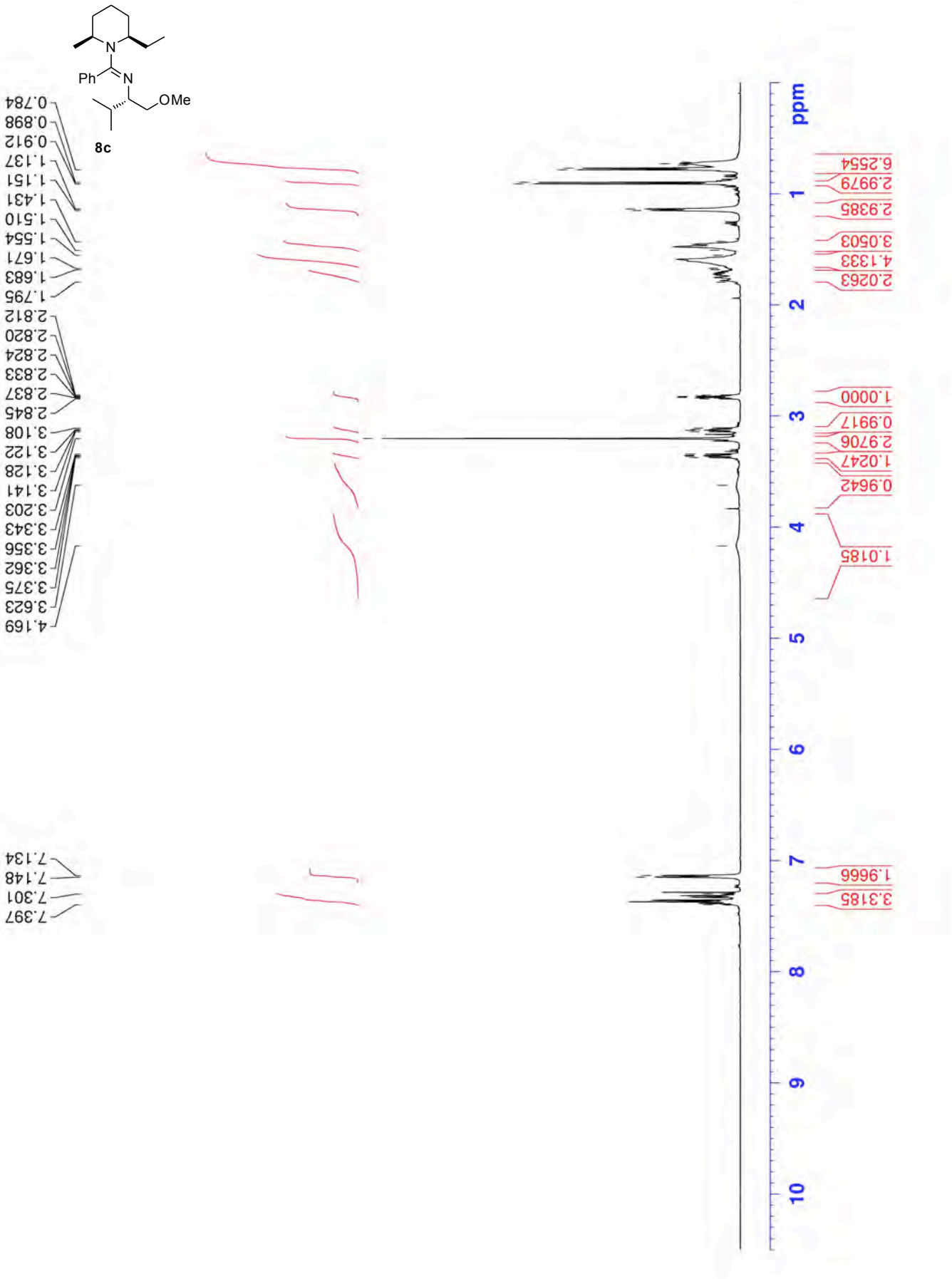
ABC-GP-x 13 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
ABC-GP-x 1 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
N
Me
Ph
N
O
OMe

8b


N
Ph
N
OMe
8c
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0.898
0.912
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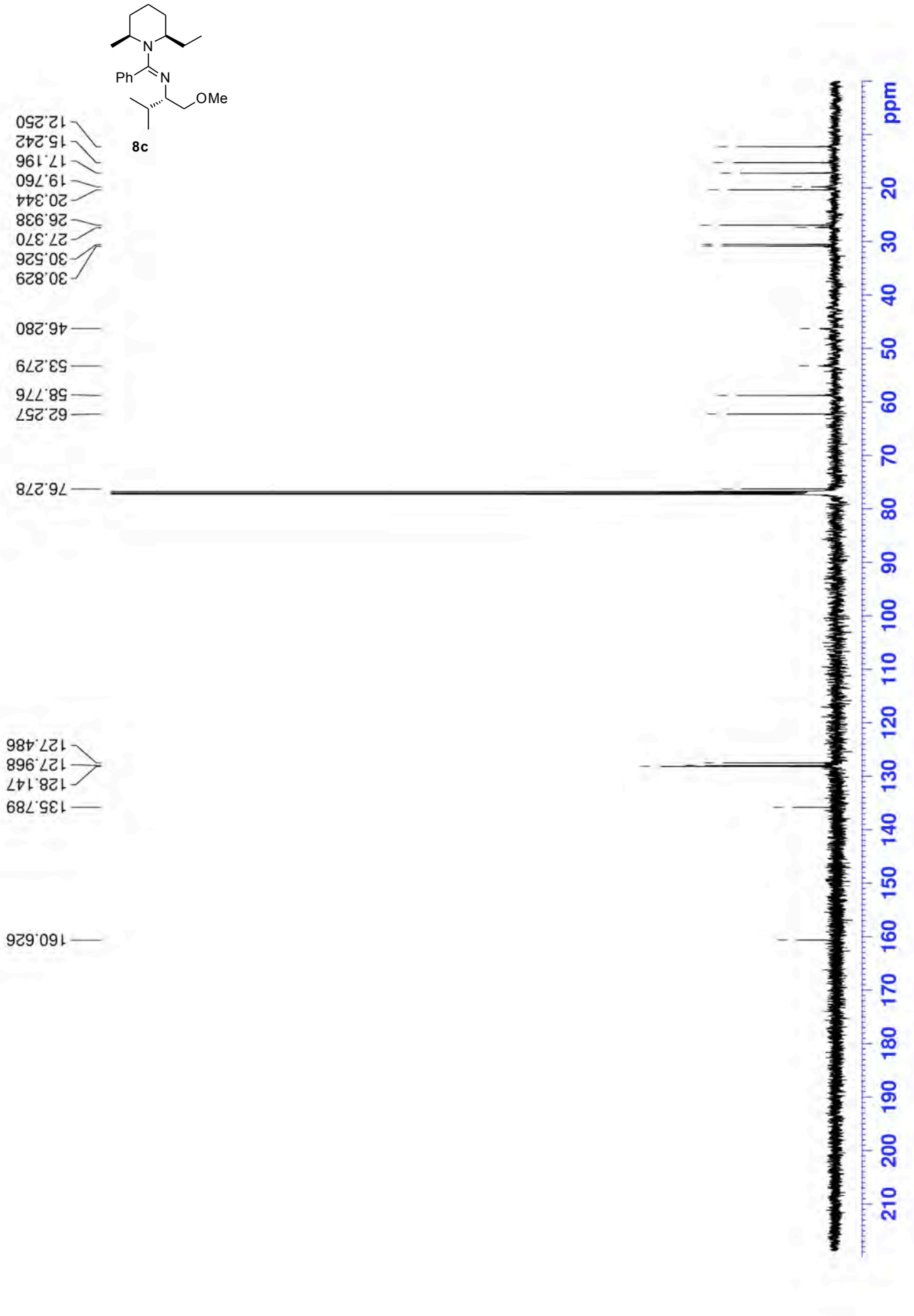
1.151
1.431
1.510
1.554
1.671
1.683
1.795
2.812
2.820
2.824
2.833
2.837
2.845
3.108
3.122
3.128
3.141
3.203
3.343
3.356
3.362
3.375
3.623
4.169
7.134
7.148
7.301
7.397
ppm
1
2
3
4
5
6
7
8
9
10
6.2554
2.9979
2.9385
3.0503
4.1333
2.0263
1.0000
0.9917
2.9706
1.0247
0.9642
1.0185
1.9666
3.3185


Ph
N
N
OMe
8c
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15.242
17.196
19.760
20.344
26.938
27.370
30.526
30.829
46.280
53.279
58.776
62.257
76.278
127.486
127.968
128.147
135.789
160.626
ppm
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60
70
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90
100
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120
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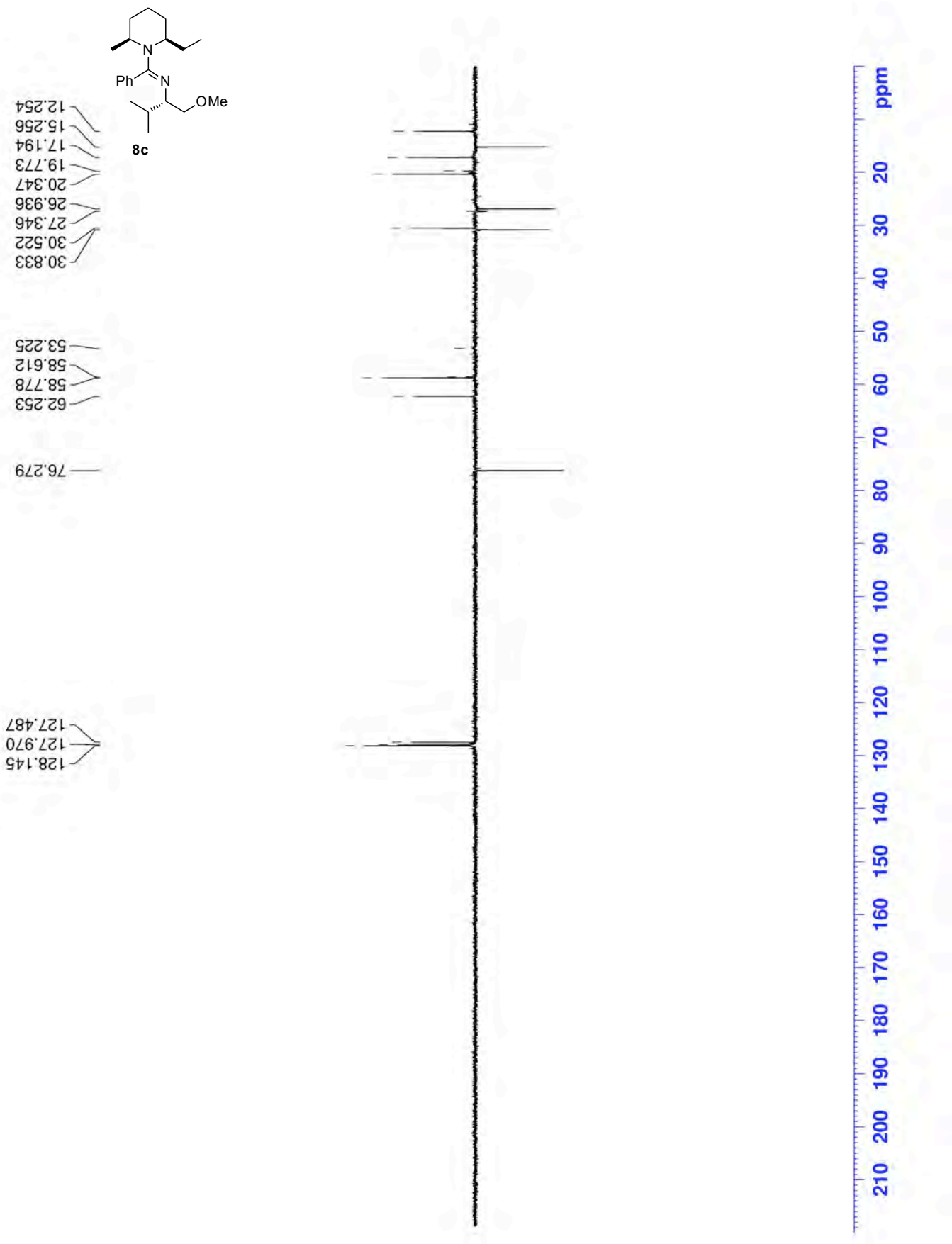
180
190
200
210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Ph
N
OMe
8c
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17.194
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20.347
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27.346
30.522
30.833
53.225
58.612
58.778
62.253
76.279
127.487
127.970
128.145
ppm
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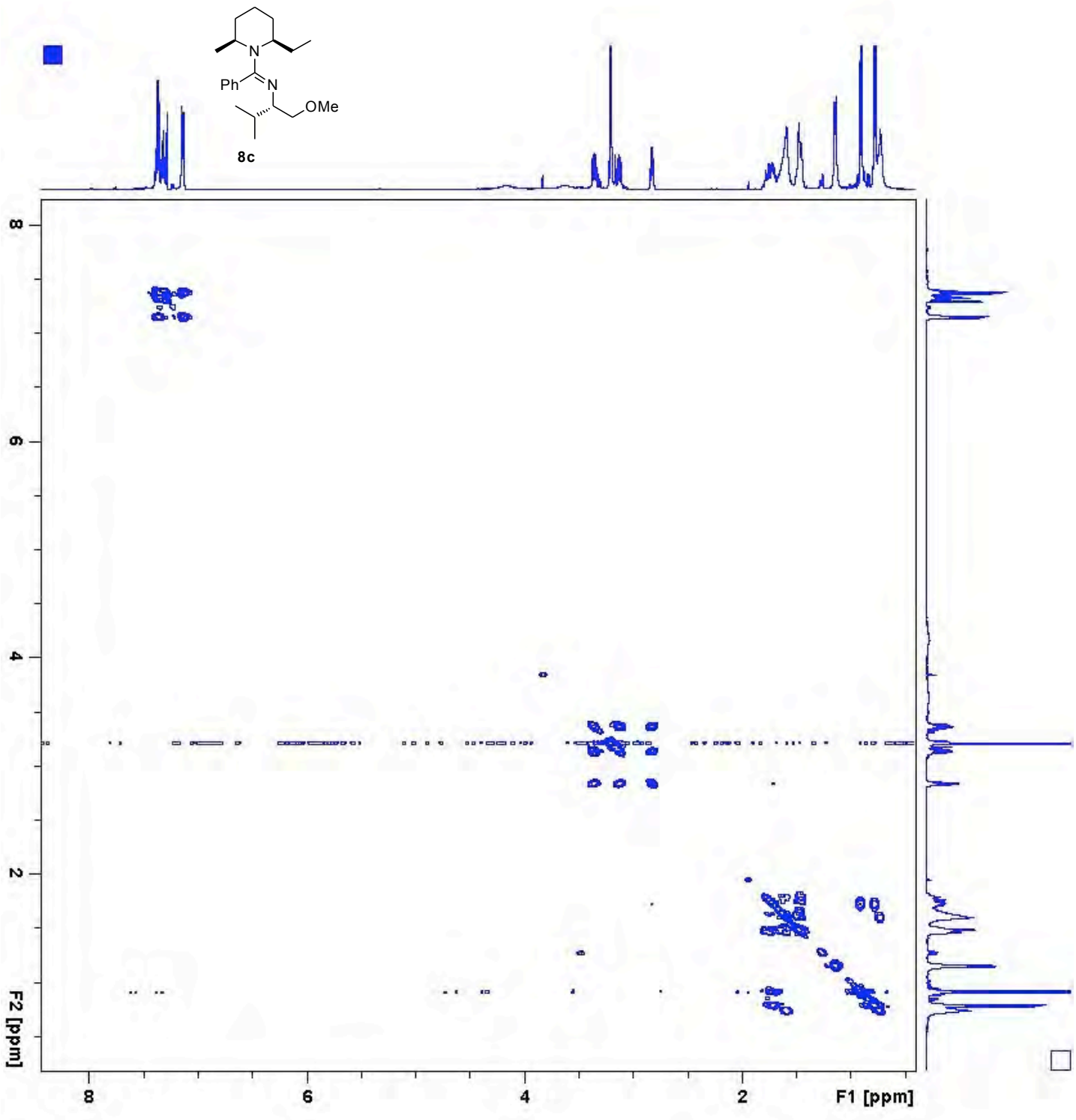
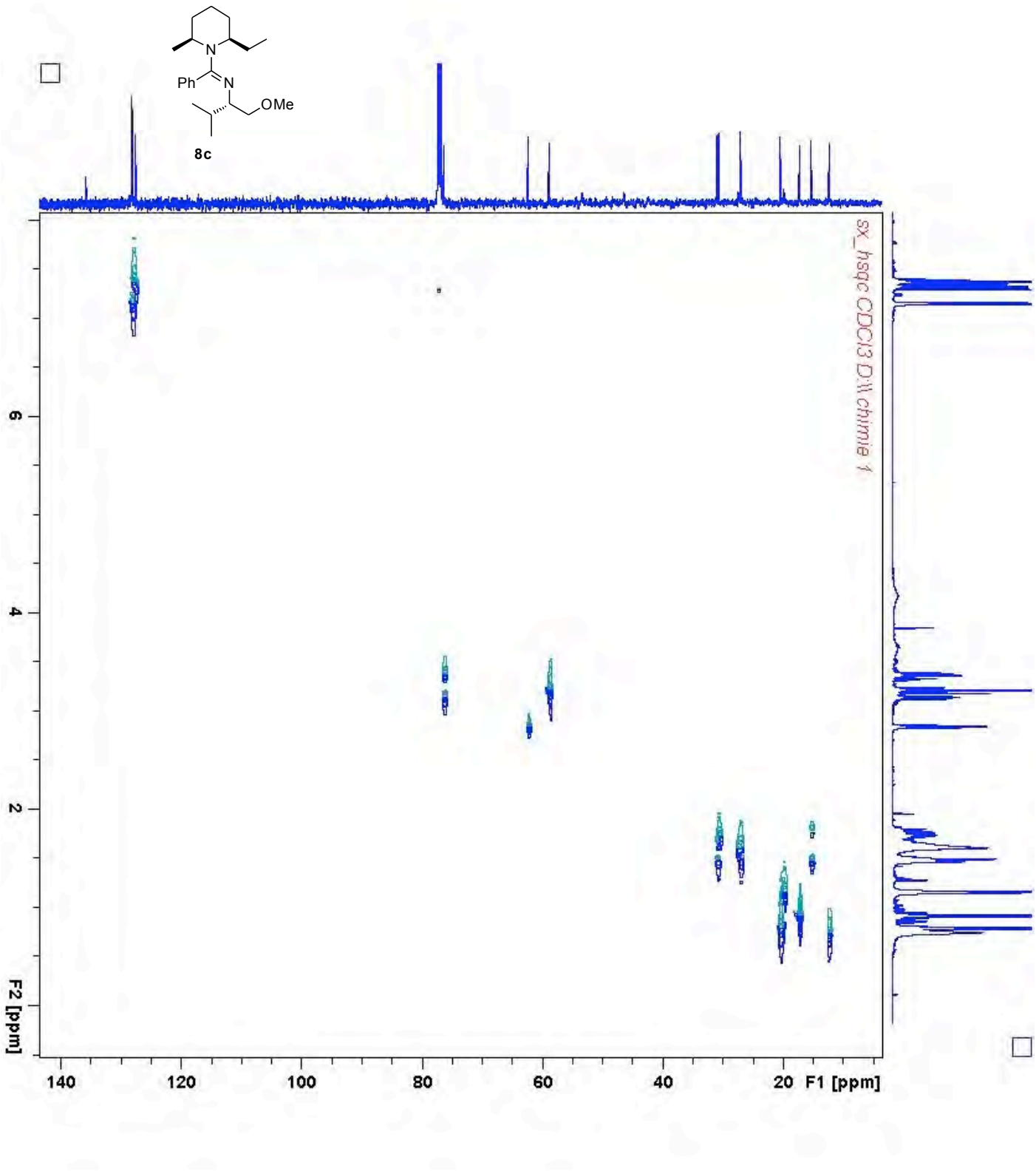
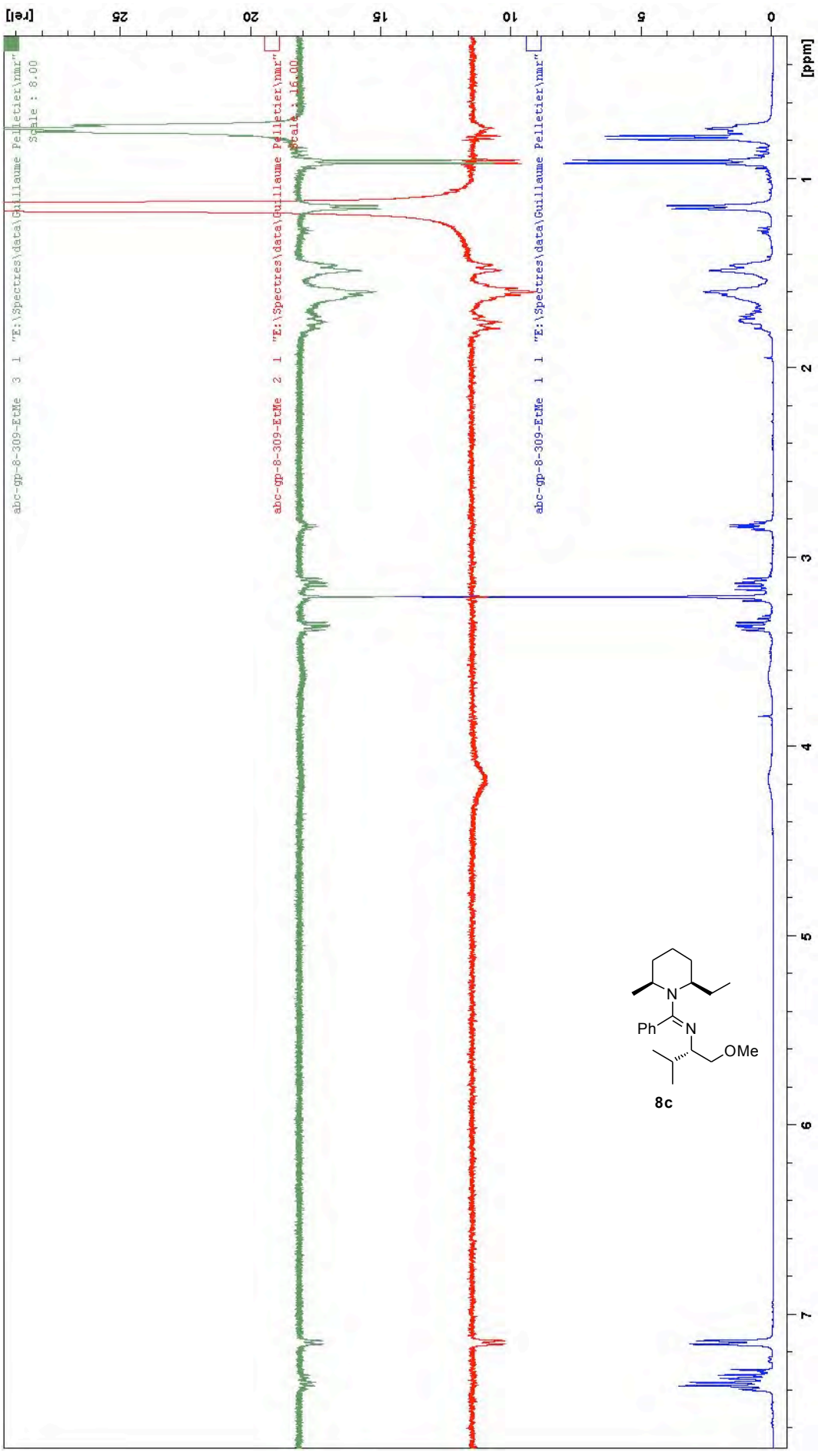
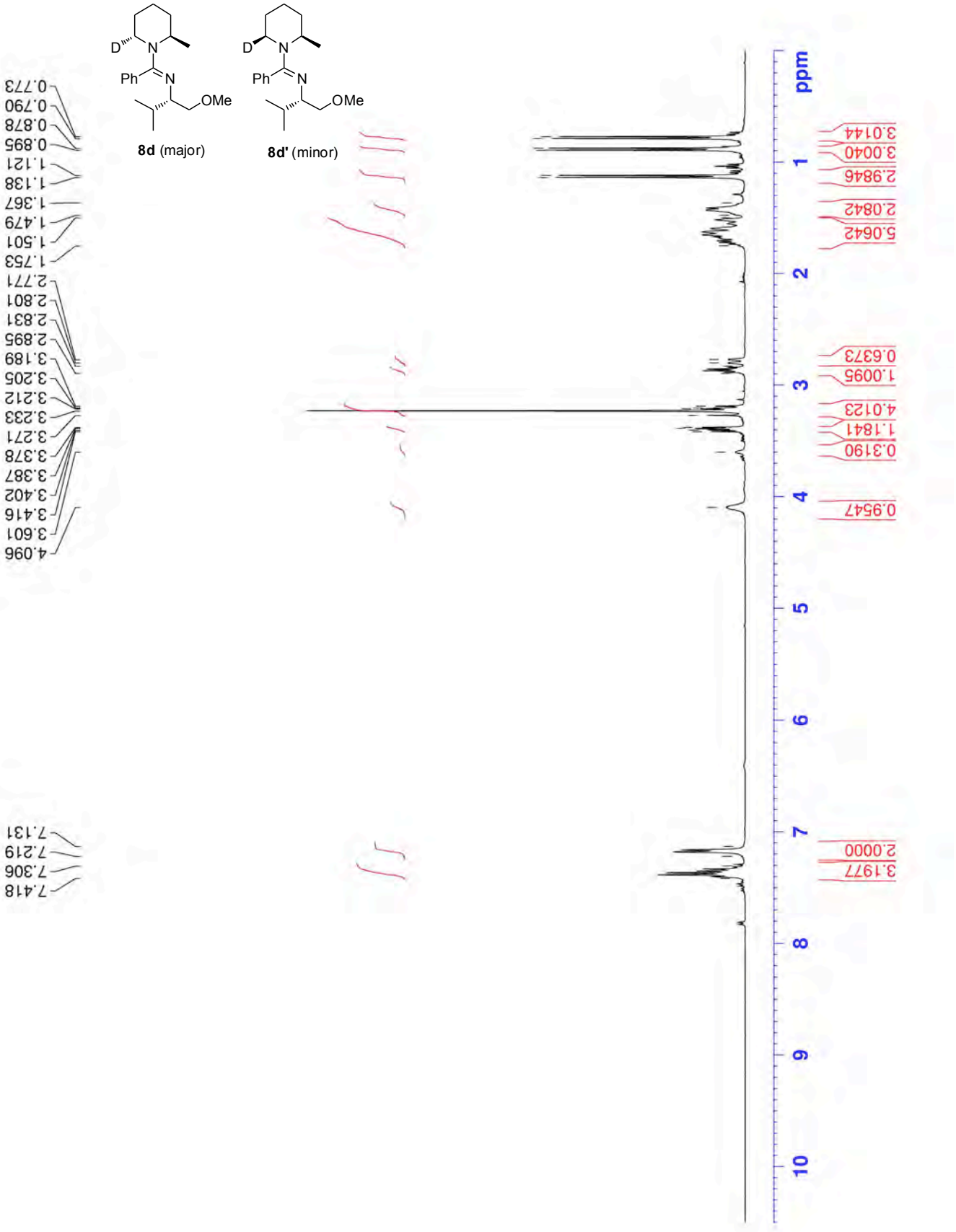
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


Ph
N
N
OMe
8c
F2 [ppm]
F1 [ppm]
8
6
4
2


Ph
N
N
OMe
8c
sx_hsqc CDCl3 D:\chimie 1
F2 [ppm]
F1 [ppm]
140
120
100
80
60
40
20
2
4
6


[rel]
25
20
15
10
5
0
[ppm]
1
2
3
4
5
6
7
abc-gp-8-309-EtMe 3 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
Scale : 8.00
abc-gp-8-309-EtMe 2 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
Scale : 16.00
abc-gp-8-309-EtMe 1 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
N
Ph
N
OMe
8c


D
N
Ph
N
OMe
8d (major)
8d' (minor)
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0.790
0.878
0.895
1.121
1.138
1.367
1.479
1.501
1.753
2.771
2.801
2.831
2.895
3.189
3.205
3.212
3.233
3.271
3.378
3.387
3.402
3.416
3.601
4.096
7.131
7.219
7.306
7.418
ppm
3.0144
3.0040
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2.0842
5.0642
0.6373
1.0095
4.0123
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0.3190
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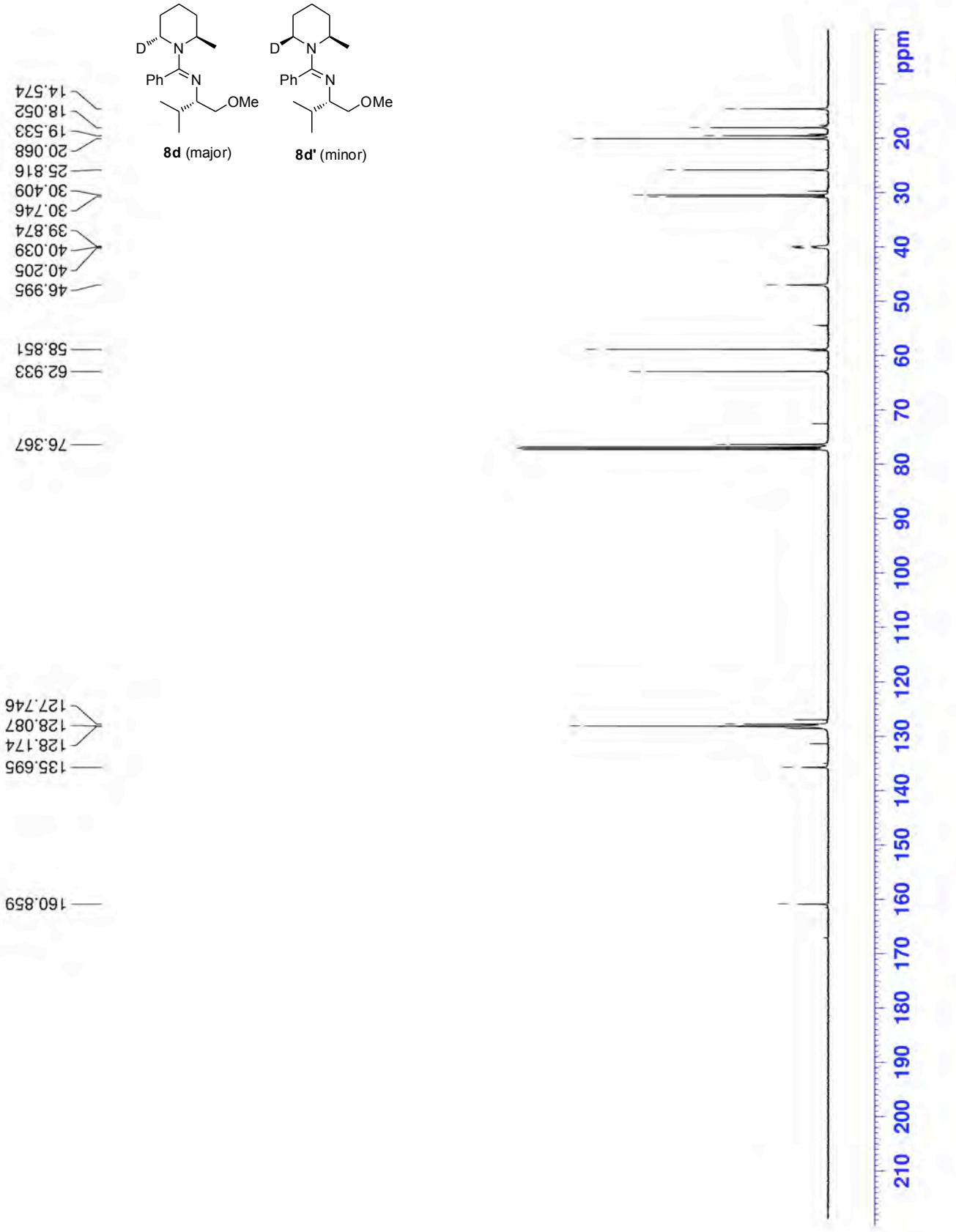
2.0000
3.1977


D
N
Ph
N
OMe
8d (major)
8d' (minor)
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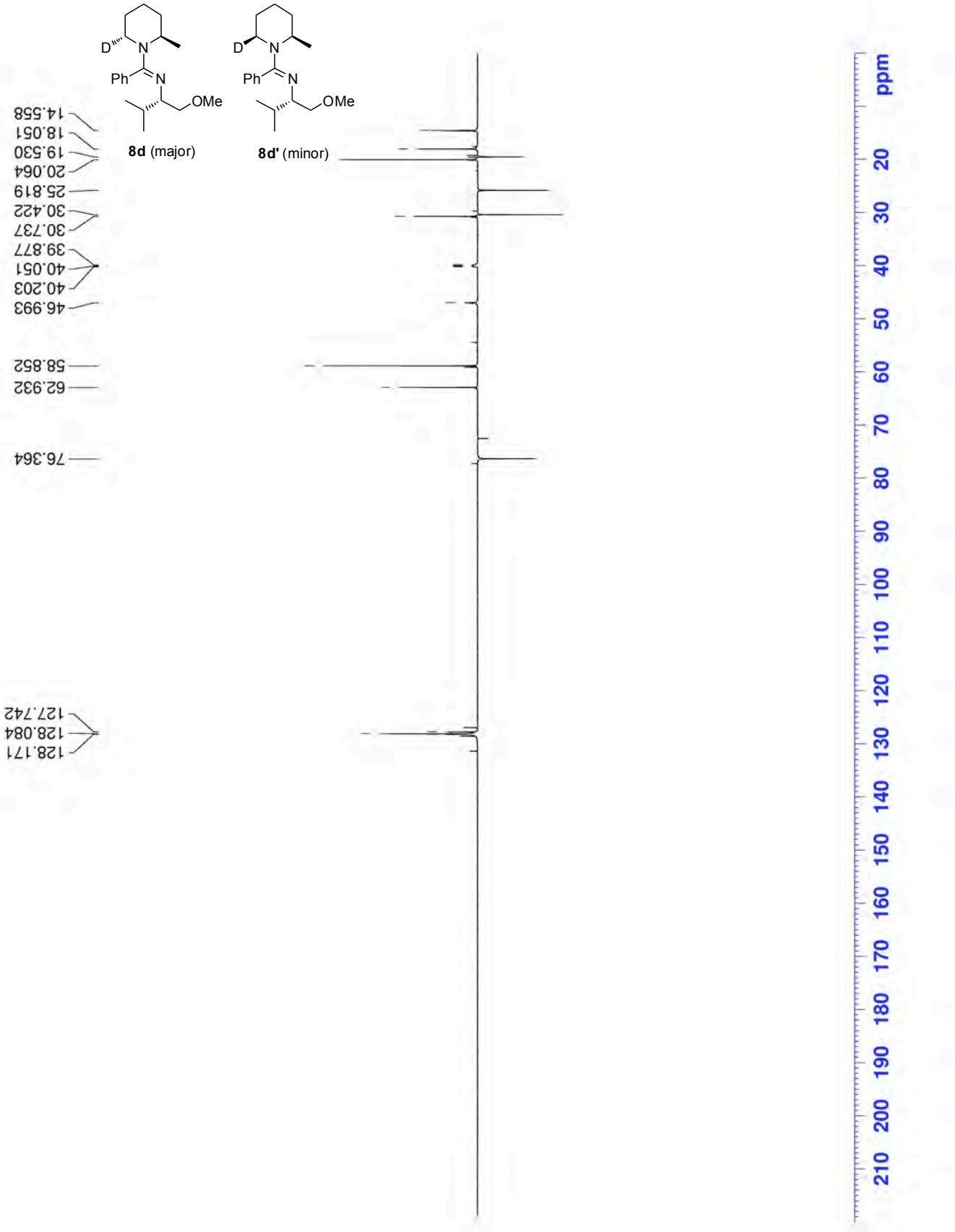
18.052
19.533
20.068
25.816
30.409
30.746
39.874
40.039
40.205
46.995
58.851
62.933
76.367
127.746
128.087
128.174
135.695
160.859
ppm


D
N
Ph
N
OMe
8d (major)
8d' (minor)
14.558
18.051
19.530
20.064
25.819
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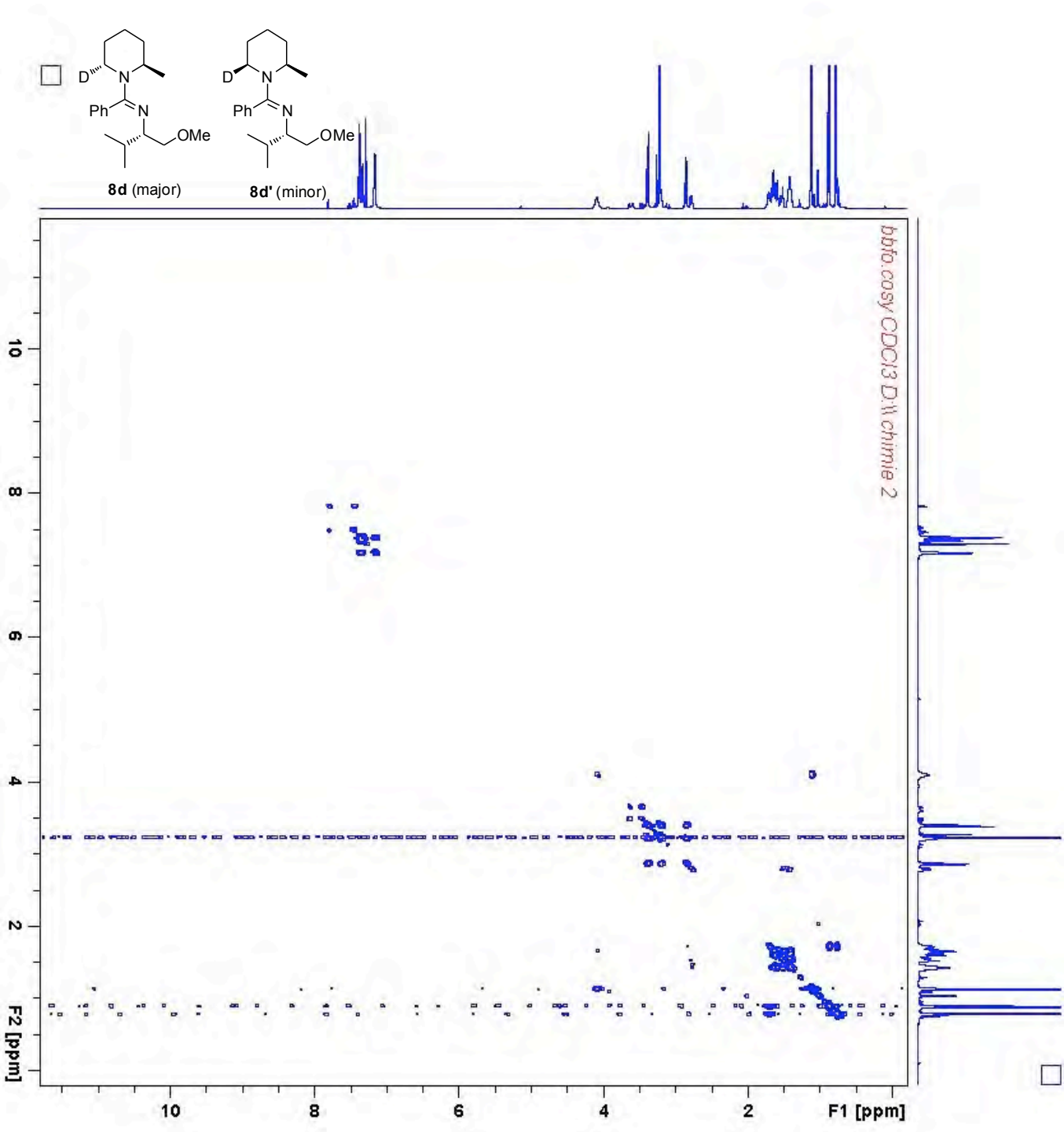
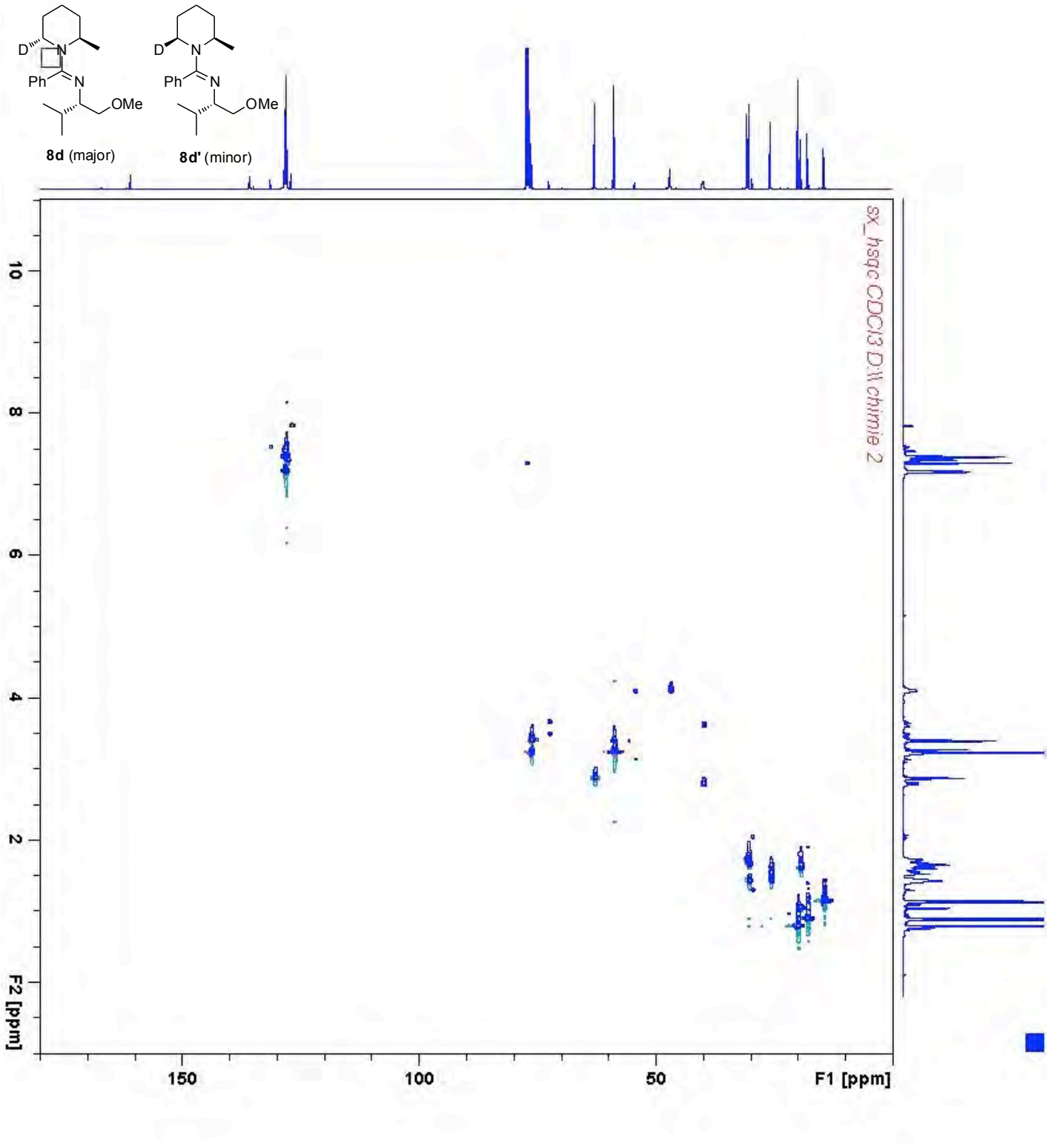
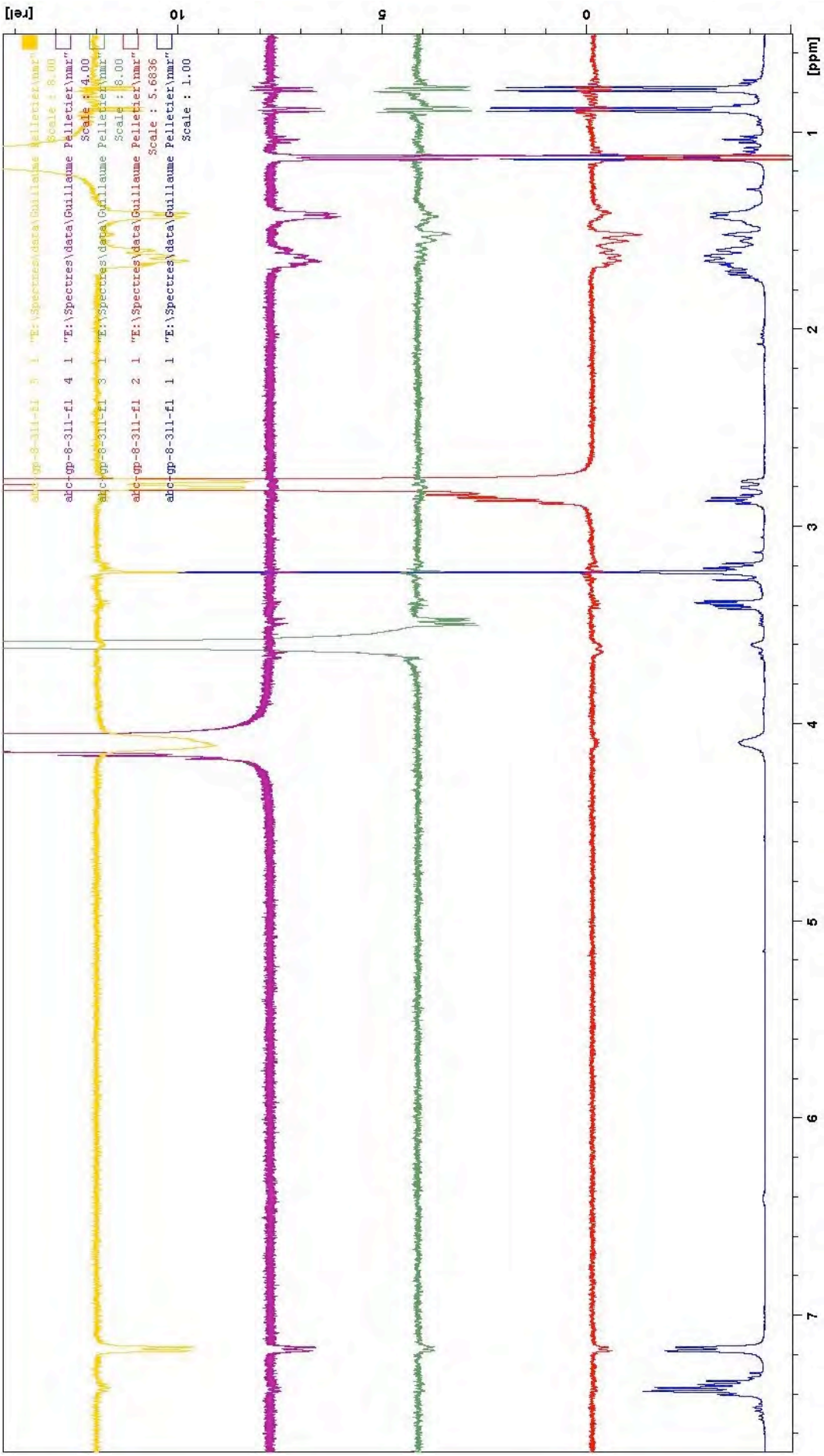
62.932
76.364
127.742
128.084
128.171
ppm


D
N
Ph
N
OMe
8d (major)
8d' (minor)
bbfo.cosy CDCl3 D:\\ chimie 2
F2 [ppm]
F1 [ppm]
10
8
6
4
2


D
N
Ph
N
OMe
8d (major)
8d' (minor)
sx_hsqc CDCl3 D:\\ chimie 2
F2 [ppm]
F1 [ppm]
10
8
6
4
2
150
100
50


[rel]
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0
[ppm]
1
2
3
4
5
6
7
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Scale : 4.00
abc-gp-8-311-f1 3 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
Scale : 8.00
abc-gp-8-311-f1 2 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
Scale : 5.6836
abc-gp-8-311-f1 1 1 "E:\Spectres\data\Guillaume Pelletier\nmr"
Scale : 1.00