Diastereoselective Control of Intramolecular Aza-Michael Reactions Using Achiral Catalysts

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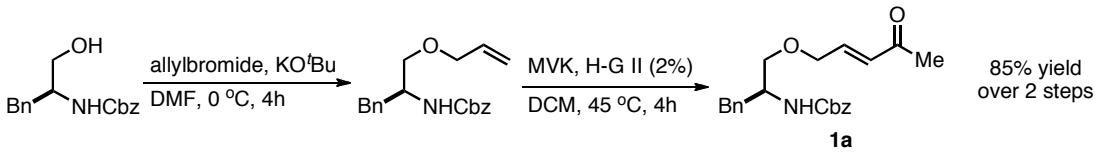
Material and Methods.

Except as otherwise noted, all reactions were carried out under Argon protection. All reaction solvents were dispensed from a solvent purification system wherein solvents are passed through a packed activated alumina column. NMR spectra were recorded at 500 MHz and 600MHz using Varian I-500 instrument. Chemical shifts for proton NMR spectra are reported in parts per million downfield from tetramethylsilane and were referenced to residual protonated solvent ($CHCl_3$: d 7.26, C_6H_6: d 7.15, CH_2Cl_2: D 5.32). Chemical shifts for carbon NMR spectra are reported in parts per million downfield from tetramethylsilane and referenced to protonated solvent ($CHCl_3$: d 77.0, C_6H_6: d 128.0, CH_2Cl_2: d 54.0). Data are represented as follows: chemical shift (multiplicity [bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constant *J* in Hertz, integration). High-resolution mass spectra were obtained through the Harvard University mass spectrometry facility. Infrared spectra were obtained with a Nicolet IR100 FTIR from Thermo Scientific. Optical rotations were obtained using digital polarimeter Autopol IV (Rudolph research Analytical) with a 1 mL cell and a 1 dm path length. Microwave heating was performed using Explorer®-48 positions, CEM. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed either with the indicated solvent on E. Merck silica gel 60 (230-400 mesh) or using a CombiFlash companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica gel columns (Biotage, Inc.). HPLC purification was performed on a Waters mass-directed autopurification system. The system consisted of 2767 injection/collection sample manager, a 2525 binary gradient high pressure LC pump, two 515 pumps to deliver makeup and dilution flow, a column fluidic organizer (CFO), a 2996 photodiode array detector, and a ZQ quadropole MS equipped with an electrospray interface. All of the instrumentation was controlled by MassLynx and FractionLynx software versions 4.1. All reagents were obtained from commercial sources and used without further purification.

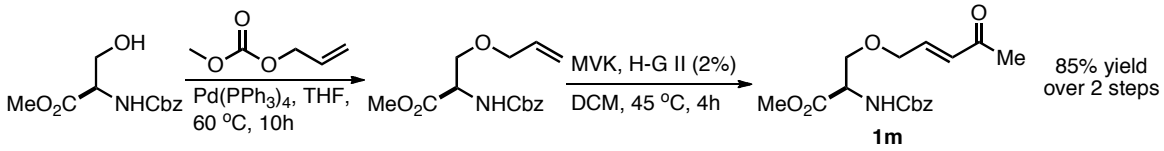
Experimental Procedures.

A. General procedure for preparation of substrate 1 (**1a** as representative example)



Into an oven dried round bottom flask equipped with a magnetic stir bar was added Z-L-phenylalaninol (570 mg, 2.0 mmol) in dry DMF (20 mL, 0.1 M) followed by allylbromide (960 mg, 8.0 mmol, 4.0 equiv.). The solution was cooled to 0 °C and stirred for an additional 15 minutes then KO*t*Bu (246 mg, 1.1 equiv.) was added portion-wise through the septum over 10 minutes. The reaction was then warmed up to room temperature over 2 hours. Once the TLC indicated the disappearance of the starting material(~ 2 hours), the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.) and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 5:95) was then applied to give the allyl ether intermediate 600 mg, yield 92%.

The allyl ether (600 mg, 1.85 mmol) was then dissolved in dichloromethane (26 ml, 0.07 M). MVK (647 mg, 9.25 mmol, 5.0 equiv.) under argon protection. Next, Hoveyda-Grubbs II catalyst (34 mg, 0.055 mmol, 0.02 equiv.) was added to the reaction mixture. The reaction mixture was then warmed up to 45 °C and kept stirring for 4 hours, until the TLC indicated the consumption of the starting material. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 20:80) was then applied to give the intramolecular aza-Michael precursor **1a** 624 mg, yield 93%. All other substrates in Table 1, except **1m**, were prepared from corresponding amino alcohols and vinyl ketones, following the same procedure, 79%~90% yields were received.



Z-L-serine (506 mg, 2.0 mmol) was dissolved in dry THF (20 mL, 0.1 M) and mix with methyl allyl carbonate (300 mg, 2.6 mmol, 1.3 equiv.) and palladium catalyst (115 mg, 0.1 mmol, 0.05 equiv.). The solution was kept under argon protection and heated to 60 °C for 10 hours. Once TLC indicated the completion of the reaction, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.) and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 10:90) was then applied to give the allyl ether intermediate 540 mg, yield 92%.

The allyl ether (540 mg, 1.85 mmol) was dissolved in dichloromethane (26 ml, 0.07 M) and methyl vinyl ketone (647 mg, 9.25 mmol, 5.0 equiv.) was added under argon atmosphere. Next, Hoveyda-Grubbs II catalyst (34 mg, 0.055 mmol, 0.02 equiv.) was added to the reaction mixture. The reaction mixture was then heated to 45 °C and kept stirred for an additional 4 hours until the TLC indicated the completion of reaction. The solvent was

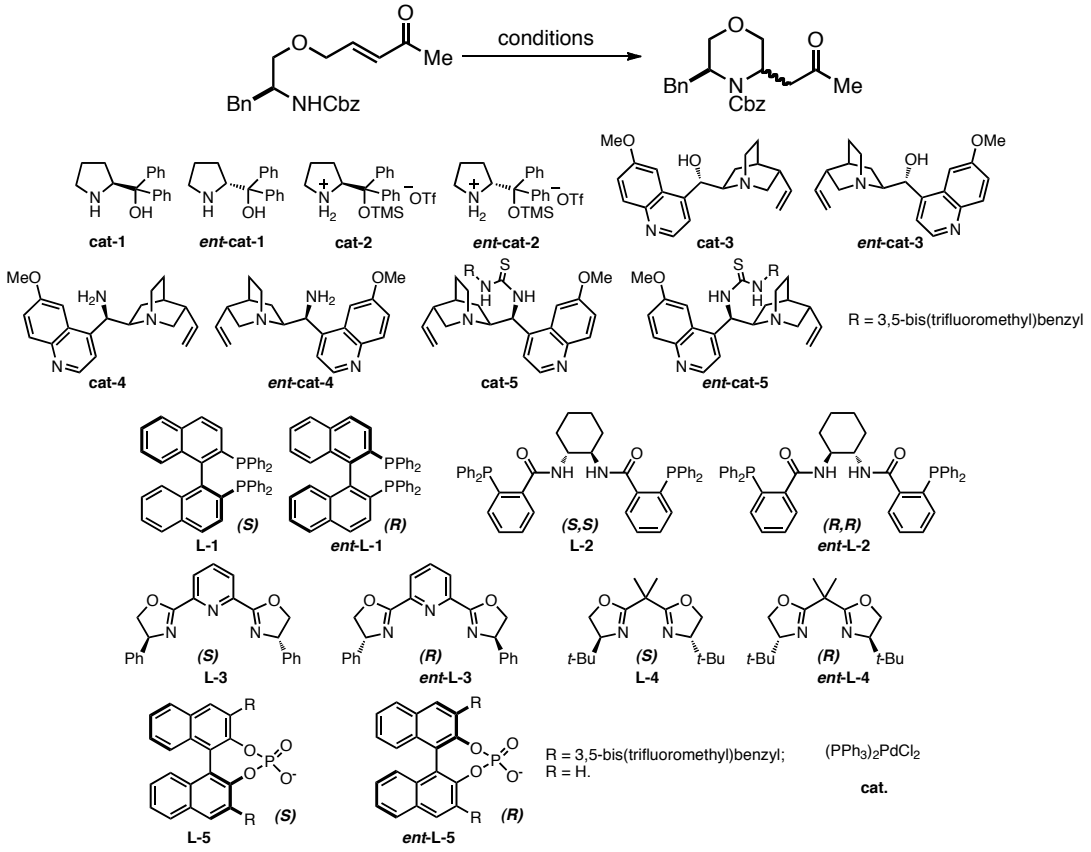
removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 20:80) was then applied to give 554 mg, (90% yield) of the intramolecular aza-Michael precursor **1m**.

B. General procedure for intramolecular aza-Michael reaction

Pd (II) catalysis of intramolecular aza-Michael reaction of **1a**: To an oven dried flask at room temperature, **1a** (73 mg, 0.02 mmol) was dissolved in dry dichloromethane (0.1 M) under argon atmosphere. Next, $(MeCN)_2PdCl_2$ (5.0 mg, 0.1 equiv.) was added and stirring was continued for an additional 4 hours. The reaction mixture was then filtered using diethyl ether through a pad of silica to remove the catalyst. The resulting filtrate was condensed by vacuum and applied to flash silica gel chromatography (Ethyl Acetate/ Hexane 15:85) to give 65 mg, (89% yield) of the intramolecular aza-Michael product **2a-*cis***. The ratio of diastereomers (*cis*/*trans*) was 93:7, based on the NMR integration.

Brønsted acid catalysis of intramolecular aza-Michael reaction of **1a**: To an oven dried flask equipped with magnetic stir bar was dissolved **1a** (73 mg, 0.02 mmol) in dry dichloromethane (0.1 M) under argon atmosphere. The solution was kept at low the temperature (-20 ^{o}C) for 10 minutes before 10 µl of TfOH solution (DCM, 0.2 M, 0.1 equiv.) was added . The reaction mixture was stirred for 5 hours until TLC indicated the complete consumption of the starting material and 10 µl of triethylamine (0.1 equiv.) was added in the reaction mixture before warming up to room temperature. The reaction mixture was then filtered through a pad of celite using diethyl ether to remove the catalyst. The resulting filtrate was condensed *in vacuo* to provide the crude residue. Purification using flash silica gel chromatography (Ethyl Acetate/ Hexane 15:85) provided 68 mg (93% yield) of the intramolecular aza-Michael product **2a-*trans***. The ratio of diastereomers (*cis*/*trans*) was 9:91, based on the NMR integration.

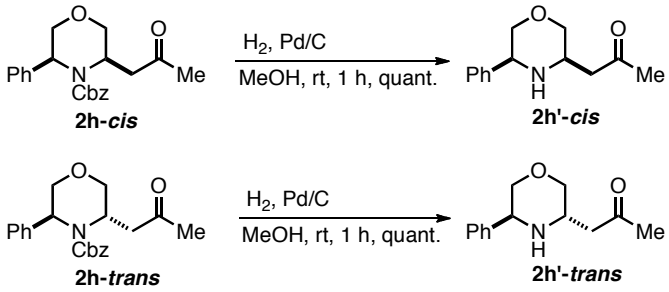
C. Condition screening for diastereoselective intramolecular aza-Michael reaction[a]



entry	sol.	cat. (0.2 eq.)	co-cat. (0.2 eq.)	temp (°C)	time (h)	conv. (%)[b]	yield (%)[c]	*d.r.* (*cis*/*trans*)[d]
1	DMF	BF_3•Et_2O	--	rt	2 (8)	57 (74)	--	--
2	$CHCl_3$	BF_3•Et_2O	--	rt	8	60	--	--
3	$CHCl_3$	**cat-1**	$PhCO_2H$	rt	12	--	--	--
4	DMF	**cat-1**	$PhCO_2H$	rt	8	12	--	--
5	MeOH	**cat-1**	$PhCO_2H$	rt	8	84[e]	--	--
6	$CHCl_3$	***ent*-cat-1**	$PhCO_2H$	rt	12	--	--	--
7	others[f]	**cat-1**	$PhCO_2H$	rt	12	--	--	--
8	DMF	others[g]	--	rt	12	<15	--	--
9	THF	KO^{t}Bu (1.0 eq.)		-78	8	93	54	2:1
10	CH_2Cl_2	**$(MeCN)_2PdCl_2$** (0.1)	--	rt	4	>95	**89**[i]	**93:7**
11	CH_2Cl_2	$(MeCN)_2PdCl_2$	L-1[h]	rt	12	--	--	--
12	CH_2Cl_2	$(MeCN)_2PdCl_2$	*ent*-L-1[h]	rt	12	--	--	--
13	CH_2Cl_2	**cat.**	AgOTf	rt	12	--	--	--
14	CH_2Cl_2	$(MeCN)_2PdCl_2$	L-3[h]	rt	12	13	--	--
15	CH_2Cl_2	$(MeCN)_2PdCl_2$	*ent*-L-3[h]	rt	12	16	--	--
16	CH_2Cl_2	$(MeCN)_2PdCl_2$	others[h]	rt	12	--	--	--
17	CH_2Cl_2	TfOH (0.1)	--	rt	0.5	>95	93	15:85
18	CH_2Cl_2	**TfOH (0.1)**	--	-20	5	>95	**92**[i]	**9:91**

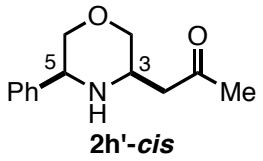
[a] Compound **1a** (73 mg, 0.02 mmol) was dissolved in solvents (0.1 M) under argon atmosphere. The reactions were monitored by TLC; [b] based on the consumption of **1a**; [c] NMR yields with 1,3,5-trimethoxybenzene as internal standard; [d] Determined by NMR; [e] New product was detected, instead of the aza-Michael adduct. [f] other solvents include EtOAc, THF, Toluene, MeCN, *i*PrOH. [g] other catalysts included **cat-2** to **cat 5**, with their enantiomers. [h] AgOTf (0.2equiv.) was applied to activate the Pd (II) species. [i] isolated yield.

D. Cbz removal and relative stereochemistry studies of morpholines 2h'

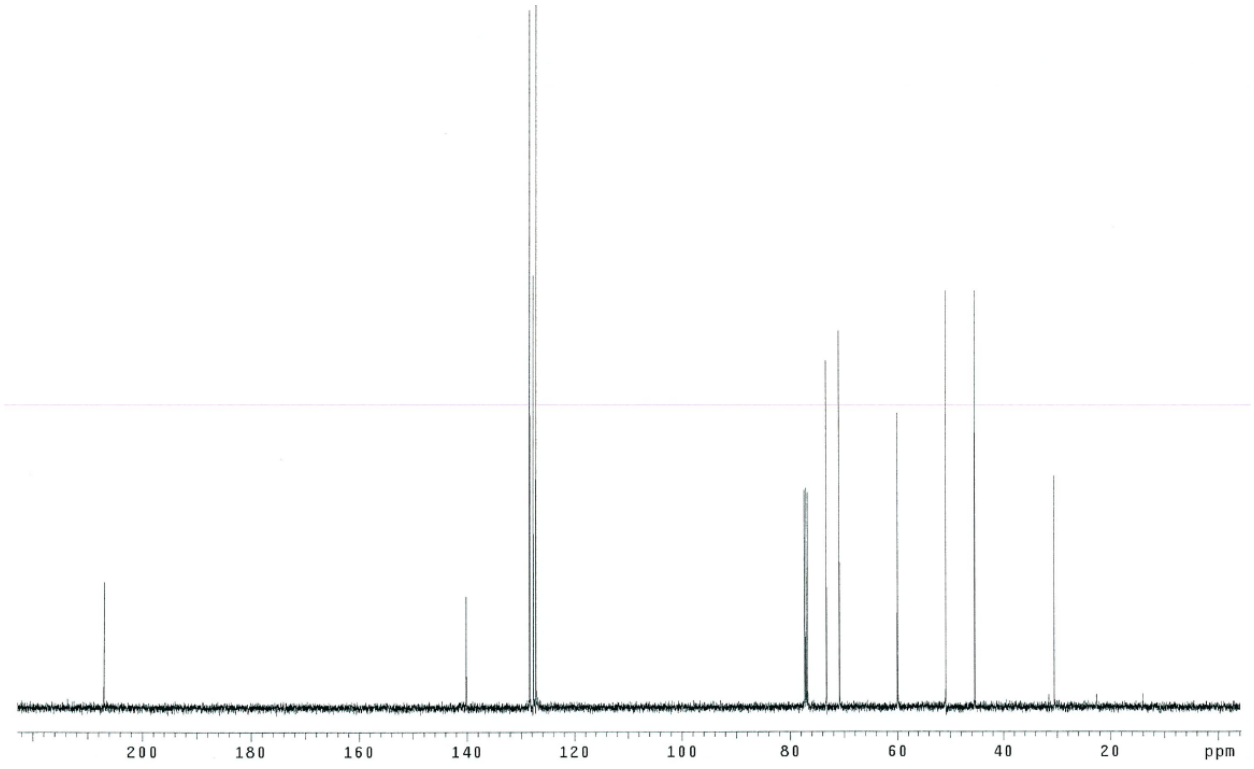


The relative stereochemistry could not be identified for the Cbz-protected morpholines **2**. NMR studies were carried out for both isomers and no NOE was observed. In order to clarify the relative stereochemistry of the aza-Michael reaction, both purified diastereomers (**2h-*cis*** and **2h-*trans***) were subjected to hydrogenation using palladium (on carbon) (0.2 eq.) under hydrogen atmosphere at room temperature. The Cbz protecting group was completely removed aver 1 hr and quantitative yields were obtained for both isomers without epimerization on C-6 position. NOE studies were subsequently performed on the N-H compounds to identify the *cis* and *trans* relationships, as shown below.

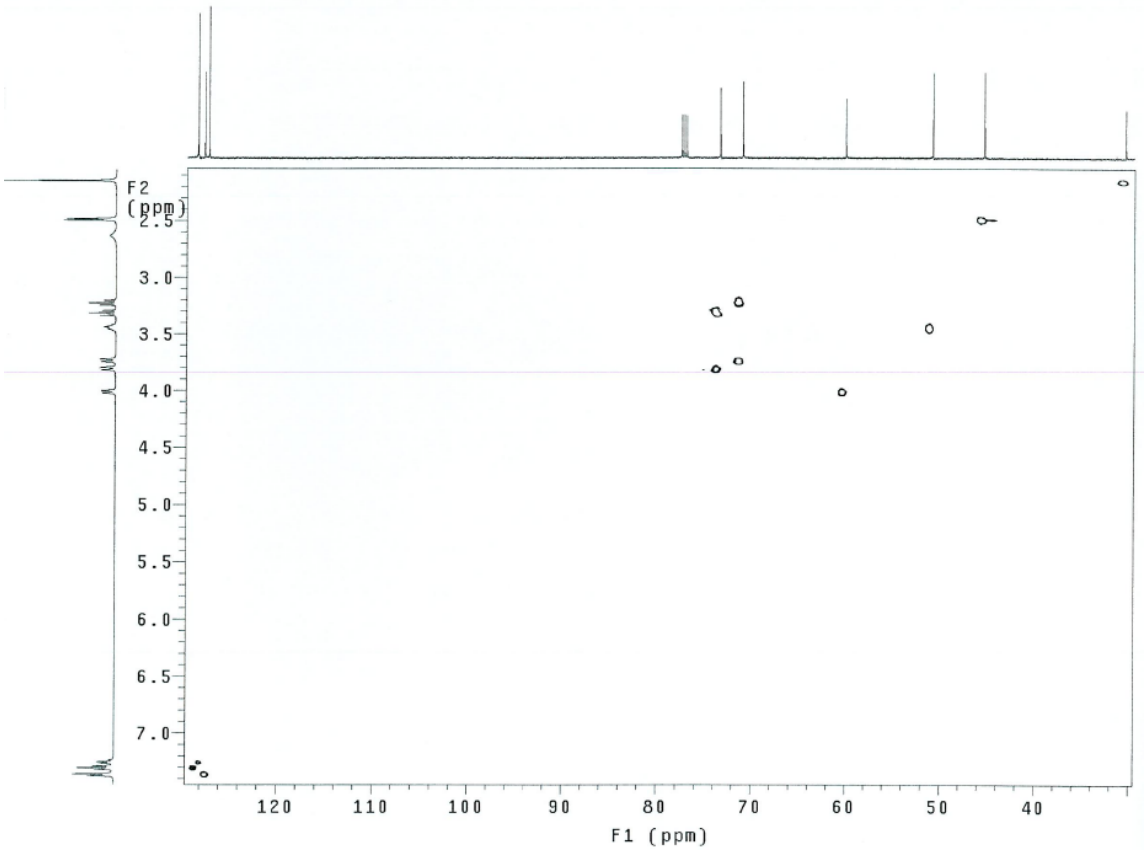
2h'-*cis* ^{1}HNMR



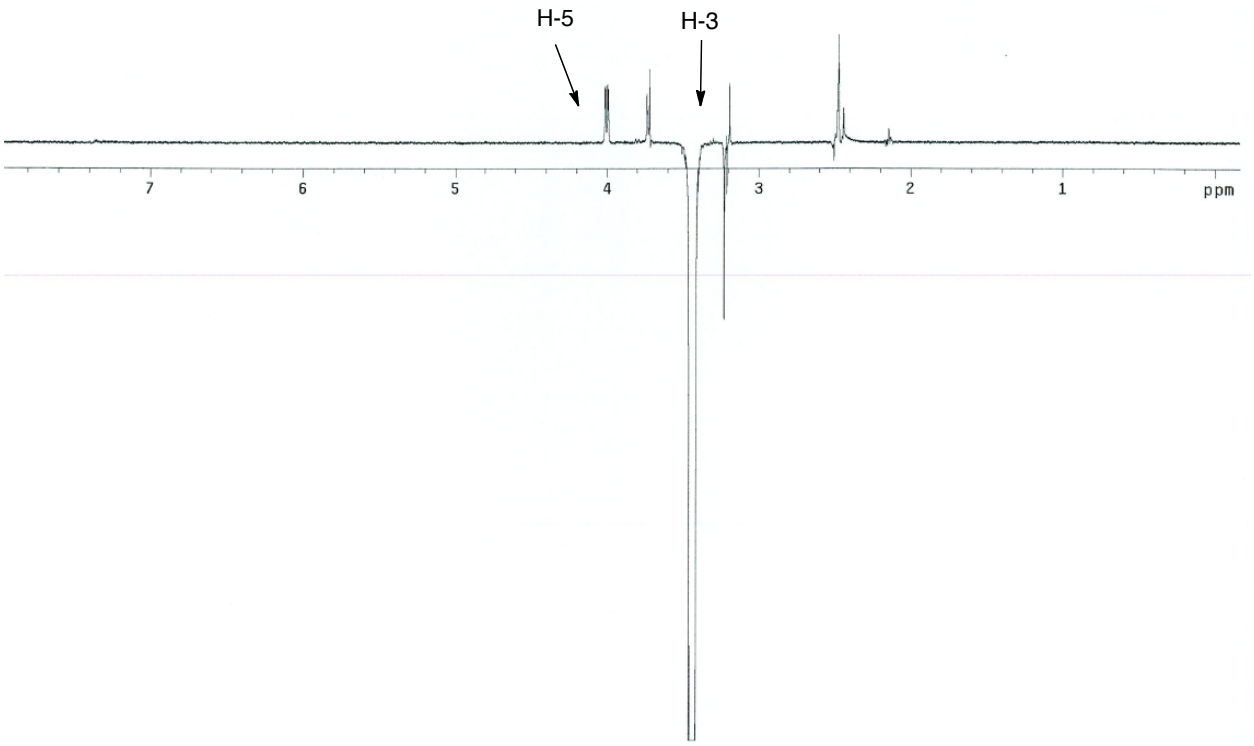
2h'-*cis* ^{13}CNMR



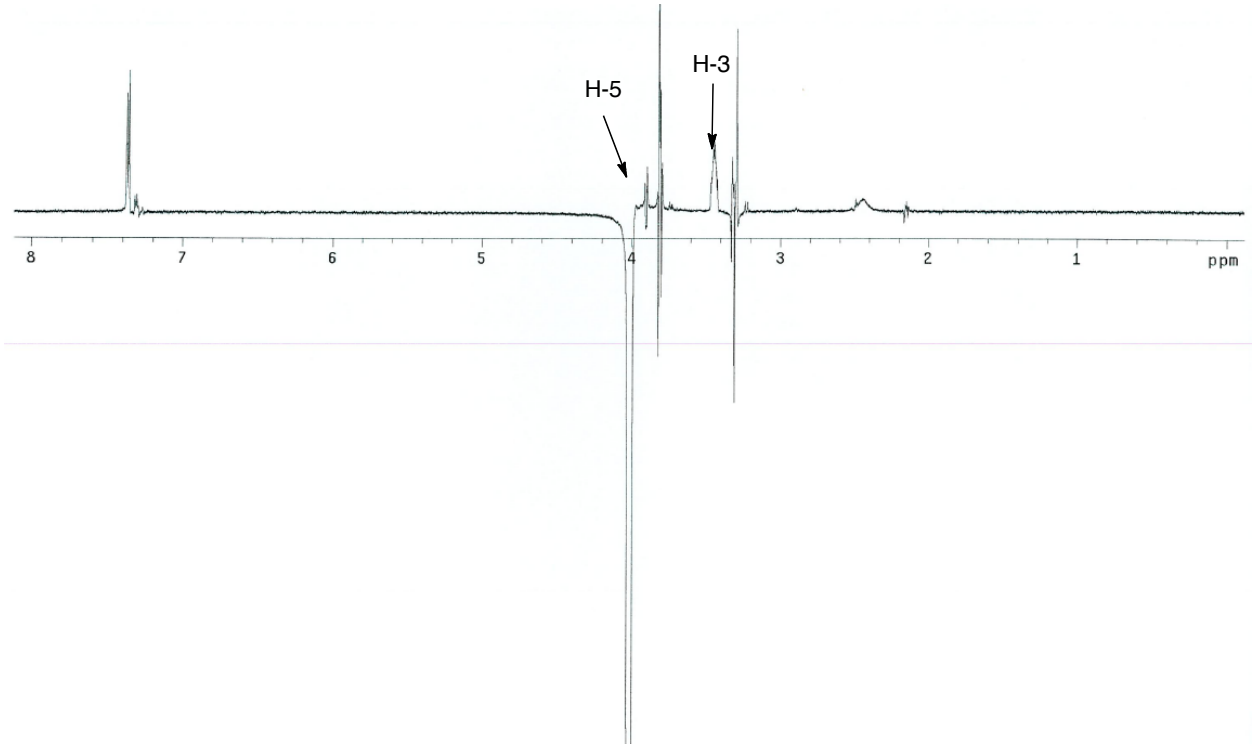
HSQC



1D-NOE 3.41 (H-3)

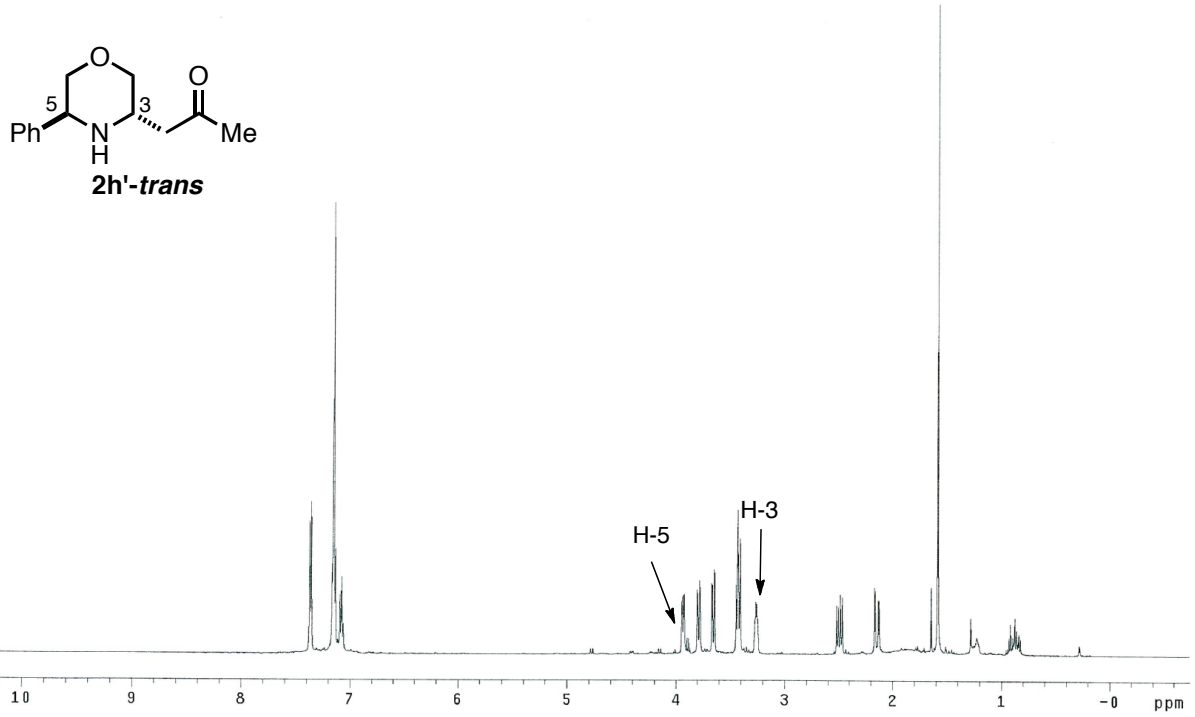


1D-NOE 4.05 (H-5)

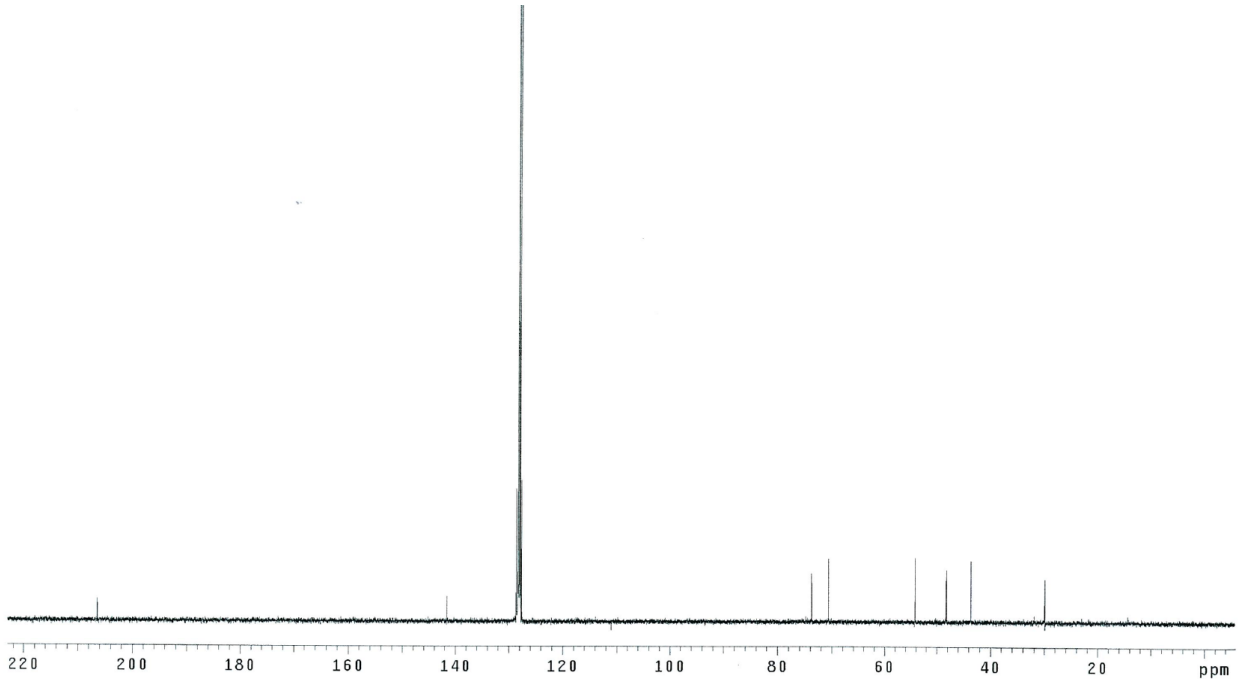


2h'-*trans*

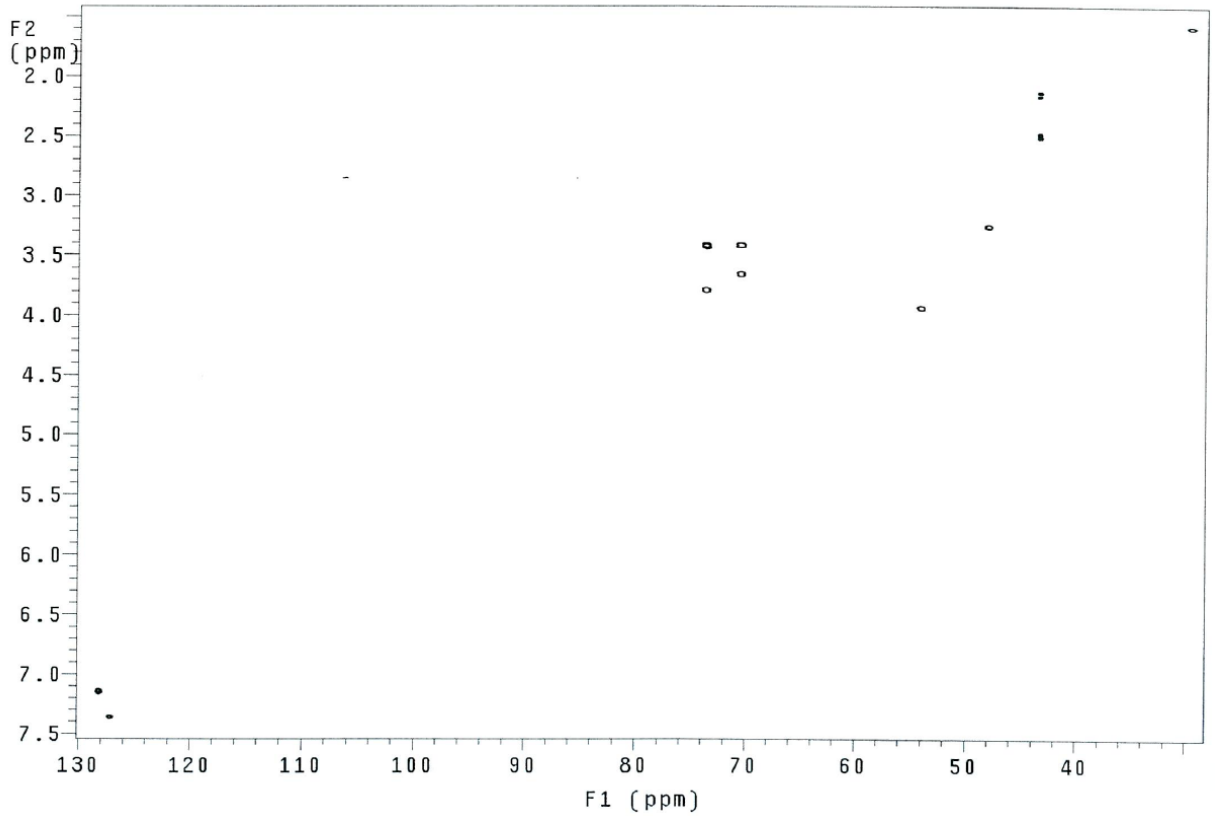
^{1}H-NMR



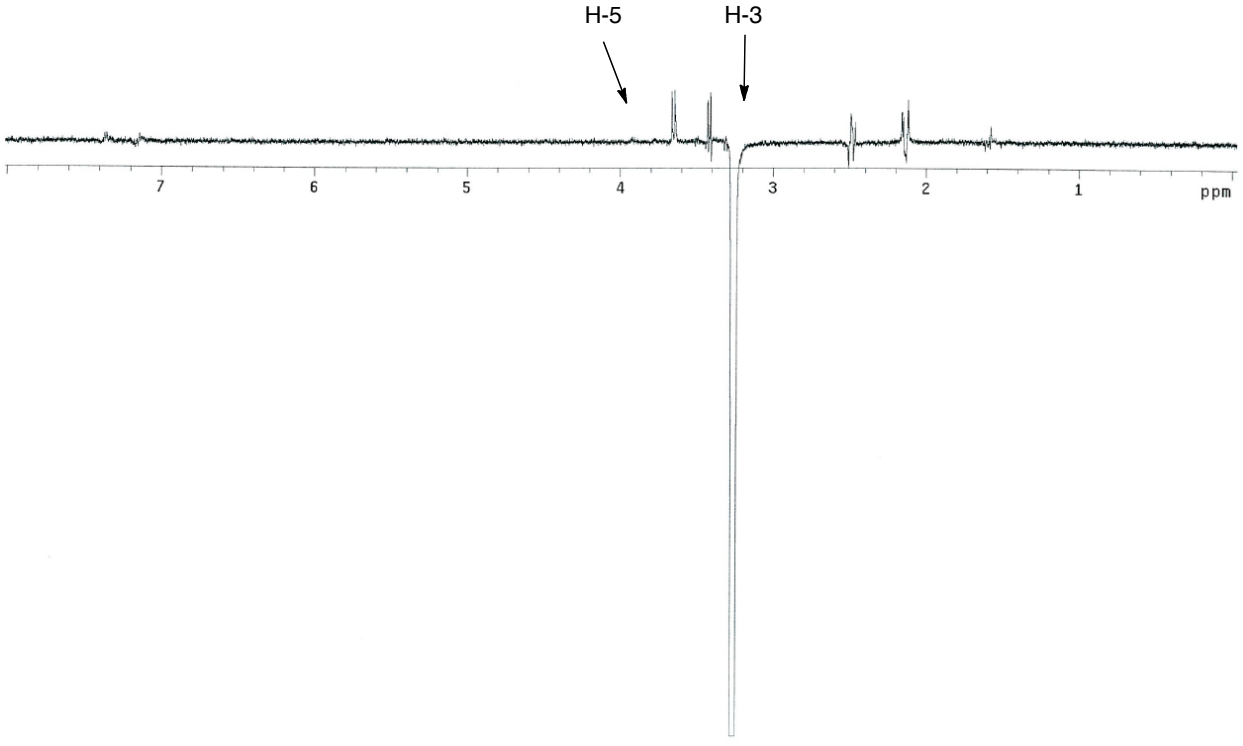
^{13}C-NMR



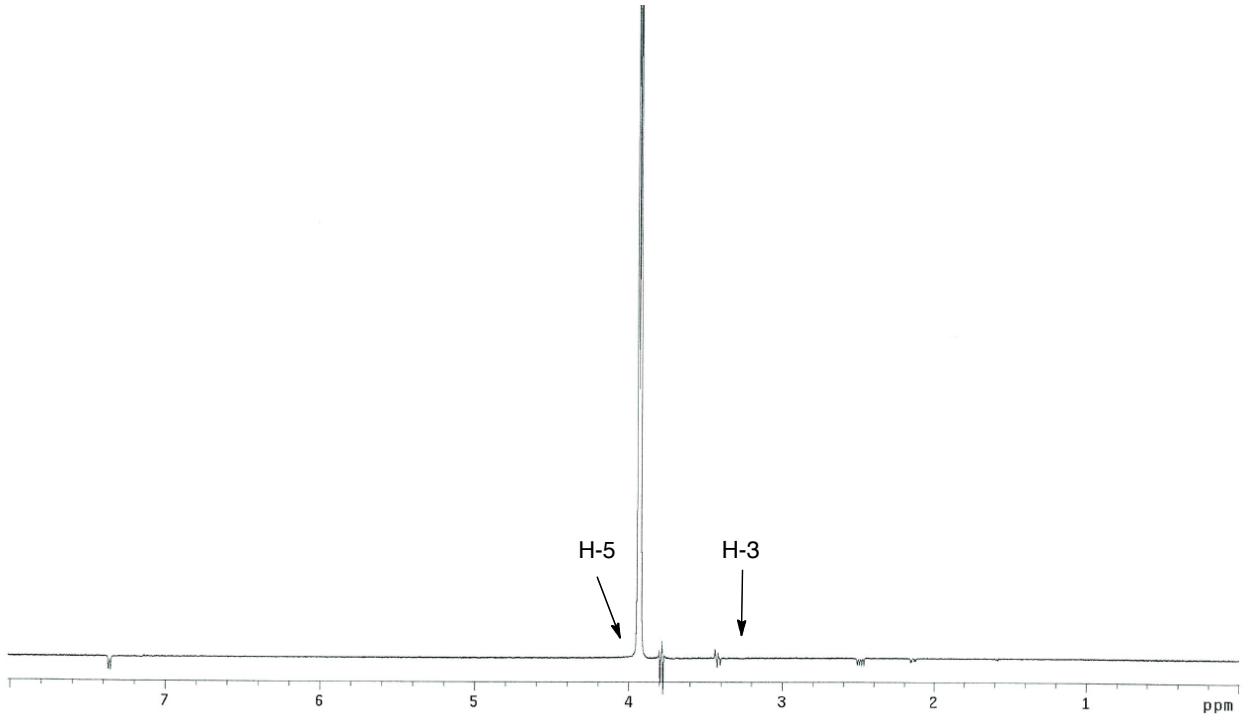
HSQC



NOE-3.2 (H-3)

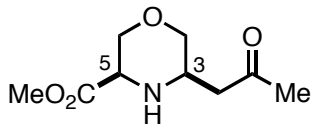


NOE-3.9 (H-5)



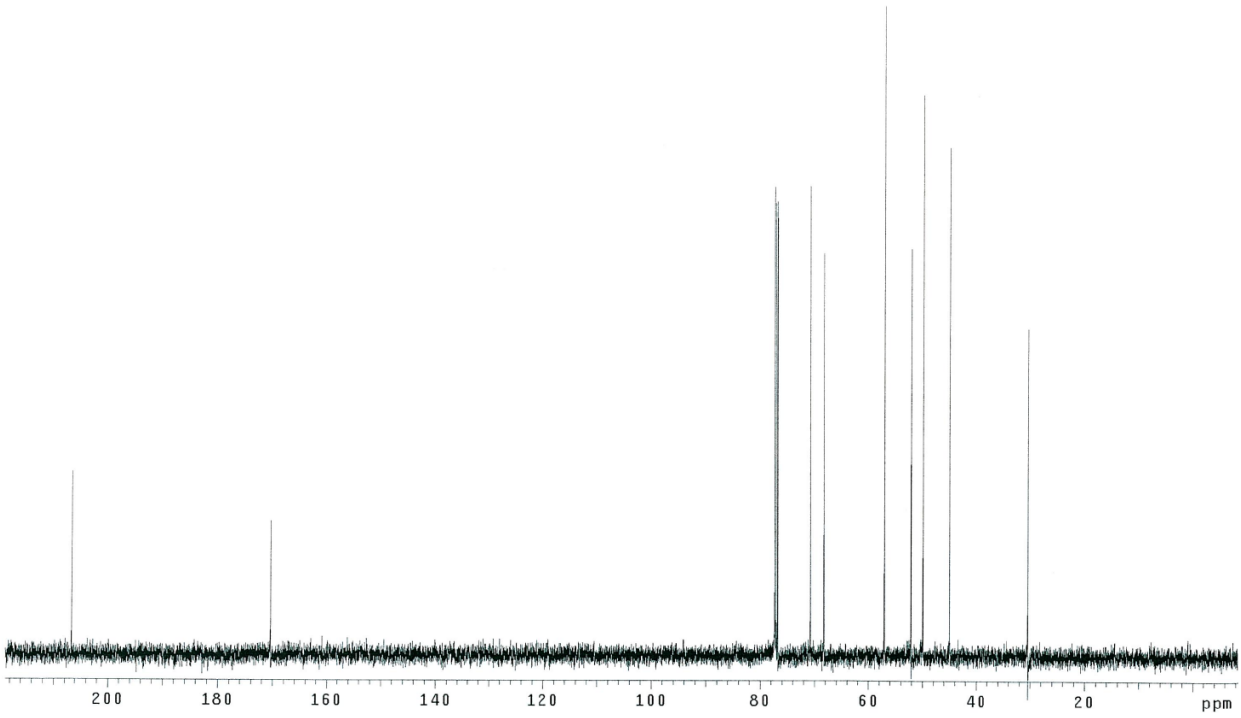
2m'-*cis*

^{1}H-NMR

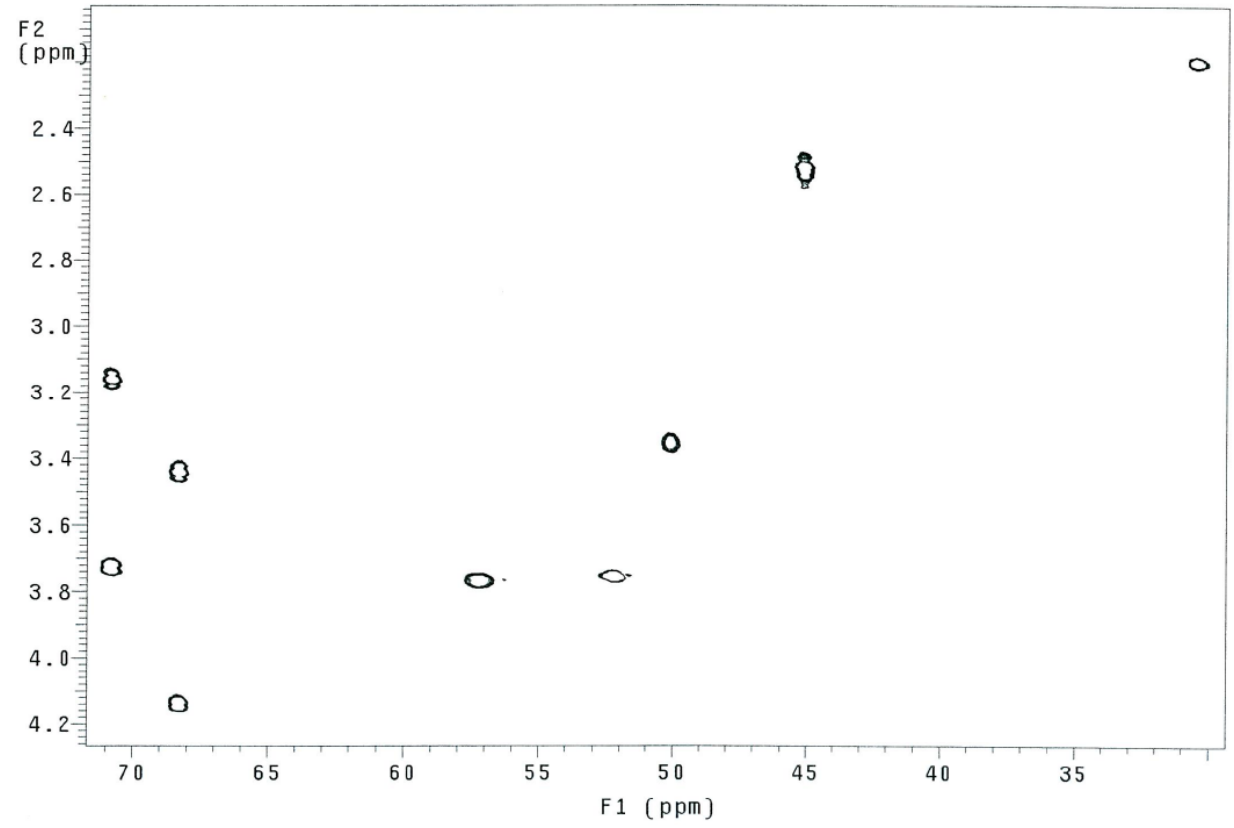


2m'-*cis*

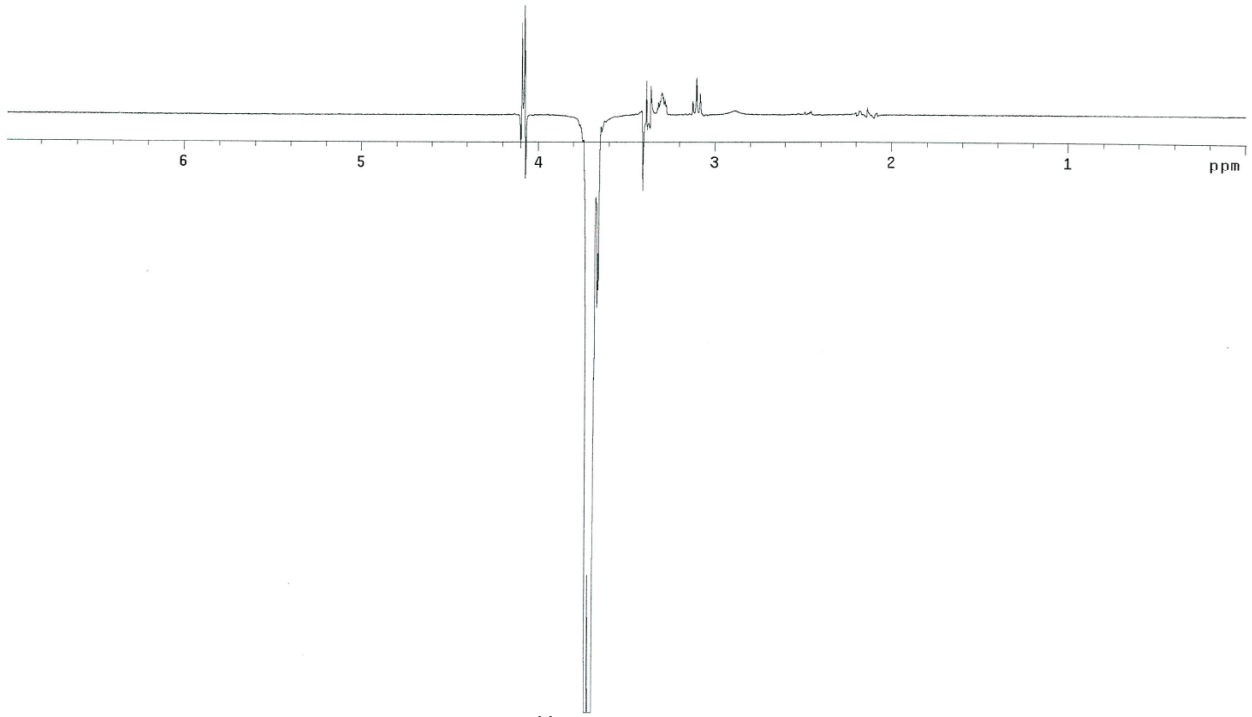
^{13}C-NMR


200
180
160
140
120
100
80
60
40
20
ppm

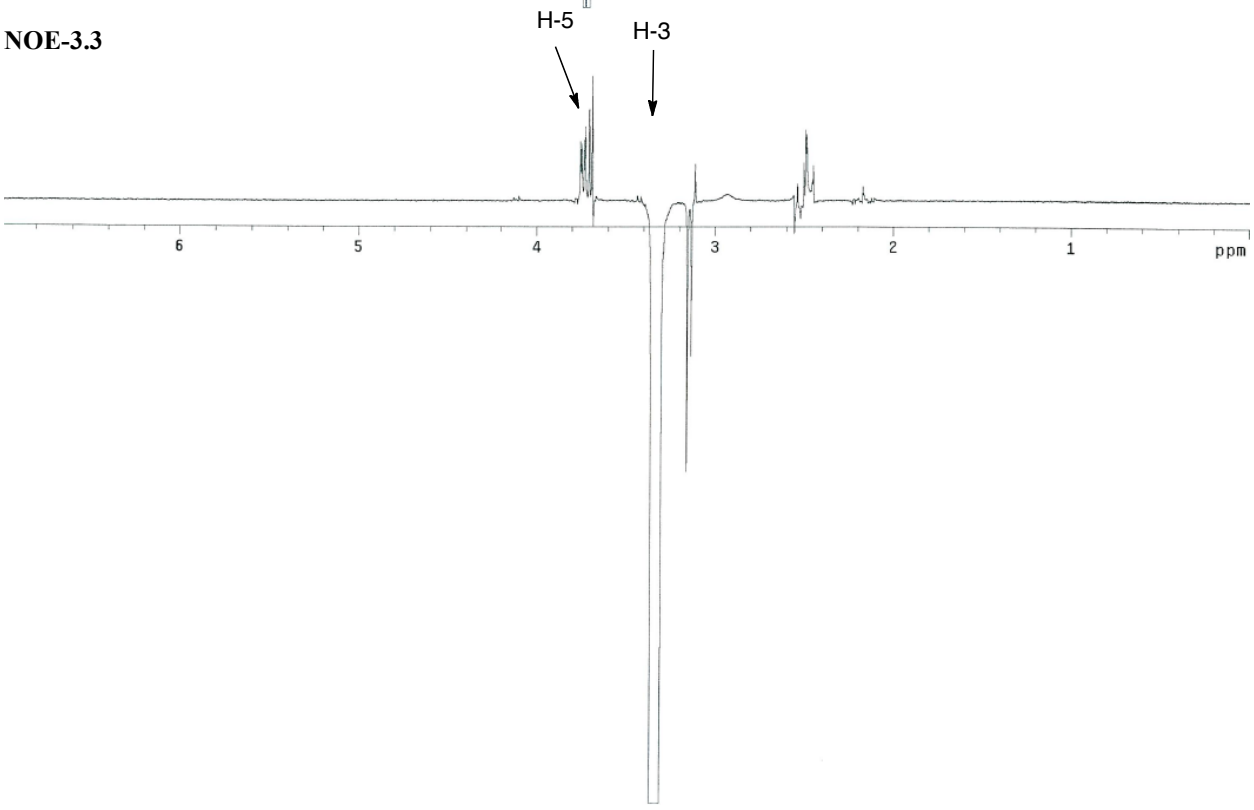
HSQC


F2
(ppm)
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
70
65
60
55
50
45
40
35
F1 (ppm)

NOE-3.7



NOE-3.3

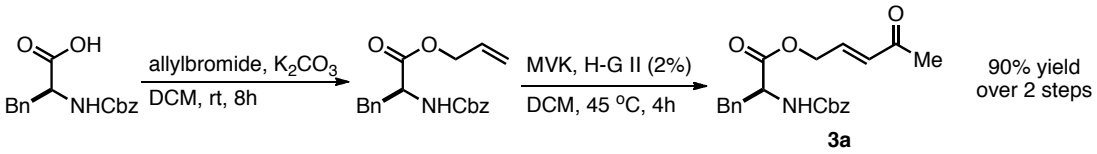


2m'-*trans*

The ^{1}H-NMR signals of H-3 and H-5 in *trans* isomer overlaps with each other in all the NMR solvents available, no NOE experiment was performed.

E. Preparation of the other intramolecular aza-Michael reaction substrates 3

1. 3a



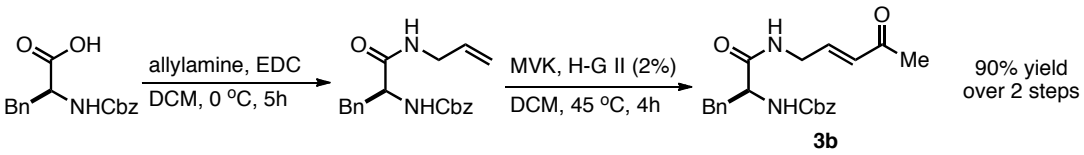
3a

To an oven dried round bottom flask equipped with magnetic stir bar was added Z-L-phenylalanine (600 mg, 2.0 mmol) in dry DMF (20 ml, 0.1 M) followed by allylbromide (480 mg, 4.0 mmol, 2.0 equiv.) at room temperature. Next, solid K_2CO_3 (339 mg, 1.5 equiv.) was added in one portion through the septum. The reaction was stirred for 8 hours at room temperature. Once the TLC indicated consumption of the starting material, the mixture was diluted with EtOAc (100 mL) and the organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.), brine, and dried over anhydrous Na_2SO_4. The solvent removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 5:95) provided 665 mg, (95% yield) of the allyl ester intermediate.

The allyl ester (665 mg, 1.96 mmol) was dissolved in dichloromethane (28 ml, 0.07 M) and methyl vinyl ketone (549 mg, 7.84 mmol, 4.0 equiv.) was added under argon atmosphere. Next, Hoveyda-Grubbs II catalyst (34 mg, 0.055 mmol, 0.02 equiv.) was added and the reaction mixture was warmed up to 45 °C. Stirring was continued for 4 hours, until the TLC indicated consumption of the starting material. The solvent was removed under reduced pressure to give a residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 25:75) was then applied to give 707 mg, (93% yield) of the intramolecular aza-Michael precursor **3a**

Other substrates in Table 1 were all prepared from the corresponding amino alcohols and vinyl ketones, following the same procedure, 79%~90% yields were received.

2. 3b



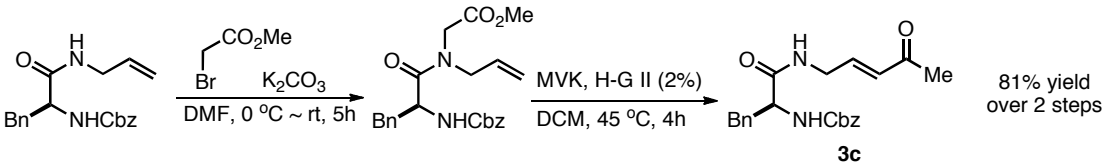
3b

To an oven dried round bottom flask equipped with magnetic stir bar was added Z-L-phenylalanine (600 mg, 2.0 mmol) and allylamine (150 mg, 2.6 mmol, 1.3 equiv.) in dry DCM (20 ml, 0.1 M). The reaction mixture was cooled by ice bath under argon atmosphere. Next, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (310 mg, 2.2 mmol, 1.1 equiv.) was added dropwise over 5 minutes. The reaction was stirred for 5 hours at 0 °C. Once TLC indicated consumption of the starting material, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.), brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 30:70) provided 642 mg, (95% yield) of allyl amide intermediate

The allyl amide (642 mg, 1.9 mmol) was then dissolved in dichloromethane (28 mL, 0.07 M). Next methyl vinyl ketone (532 mg, 7.6 mmol, 4.0 equiv.) was added under an argon atmosphere. Hoveyda-Grubbs II catalyst (34 mg, 0.055 mmol, 0.02 equiv.) was added and the reaction mixture was then warmed up to 45 °C while

stirring was continue for 6 hours, when the TLC indicated complete consumption of the starting material. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 25:75) provided 684 mg, (95% yield) of the intramolecular aza-Michael precursor **3b**.

3. 3c

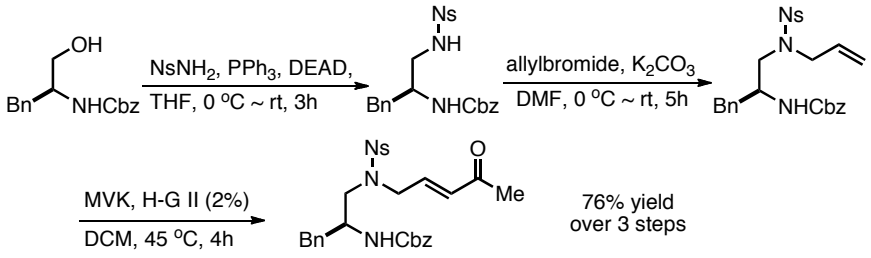


3c

To an oven dried round bottom flask equipped with magnetic stir bar, the allyl amide (642 mg, 1.9 mmol) and methyl 2-bromoacetate (315 mg, 2.1 mmol, 1.1 equiv.) were dissolved in dry DMF (20 ml, 0.1 M). The reaction mixture was cooled by ice bath under an argon atmosphere. Next, K_2CO_3 (303 mg, 2.1 mmol, 1.1 equiv.) was added to the mixture in one portion. The reaction was stirred for 1 hour at 0 ^oC, then warmed to room temperature and stirred for an additional 4 hours. Once TLC indicated consumption of the starting material, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.), brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 30:70) provided 701 mg, (90% yield) of the allyl dipeptide intermediate.

The allyl dipeptide (701 mg, 1.7 mmol) was then dissolved in dichloromethane (28 mL, 0.07 M) and methyl vinyl ketone (476 mg, 6.8 mmol, 4.0 equiv.) was added in under argon. Hoveyda-Grubbs II catalyst (30 mg, 0.050 mmol, 0.02 equiv.) was then added and the reaction mixture was warmed up to 45 ^oC and kept stirring for 6 hours, when the TLC indicated the consumption of the starting material. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 25:75) was then applied to give 616 mg, (90% yield) of the intramolecular aza-Michael precursor **3c**

4. 3d



3d

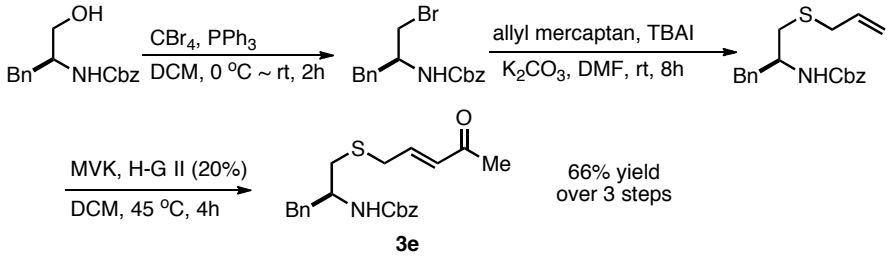
To an oven dried round bottom flask equipped with magnetic stir bar was added Z-L-phenylalaninol (570 mg, 2.0 mmol), nosylamine (485 mg, 2.4 mmol, 1.2 equiv.), with and PPh_3 (786 mg, 3.0 mmol, 1.5 equiv.) in dry THF (20 ml, 0.1 M). The reaction mixture was then cooled to 0 ^oC by ice bath under argon and diethyl azodicarboxylate (DEAD) (522 mg, 3.0 mmol, 1.5 equiv.) was added in the reaction mixture drop-wise over 5 minutes. The reaction was stirred for 2 hours at 0 ^oC, and then warm up to room temperature over another hour. Once TLC indicated the consumption of the starting material, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.) and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel

chromatography (Ethyl Acetate/Hexane 50:50) was applied to give the 797 mg, (85% yield) of the Nosyl amine intermediate.

The nosyl amine (797 mg, 1.7 mmol) and allylbromide (408 mg, 3.4 mmol, 2.0 equiv.) were then dissolved in dry DMF (20 mL, 0.1 M) and cooled 0 ^{o}C. Next, K_2CO_3 (351 mg, 1.5 equiv.) was added in one portion. The reaction was stirred for 4 hours and gradually warmed up to room tempeature. Once TLC indicated the consumption of the starting materials, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.) and brine and dried over anhydrous Na_2SO_4. The solvent was put under reduced pressure to the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 30:70) was applied to give 796 mg, (92% yield) of the allyl nosyl amine intermediate.

The allyl amide (796 mg, 1.56 mmol) was then dissolved in dichloromethane (22 ml, 0.07 M). Next methyl vinyl ketone (437 mg, 6.24 mmol, 4.0 equiv.) was added in under argon. Hoveyda-Grubbs II catalyst (34 mg, 0.055 mmol, 0.03 equiv.) was added and the reaction mixture was then warmed up to 45 ^{o}C and kept stirring for 5 hours when the TLC indicated the consumption of the starting material. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 35:65) was then applied to give 799 mg, yield (93% yield) of the intramolecular aza-Michael precursor **3d**.

5. 3e



3e

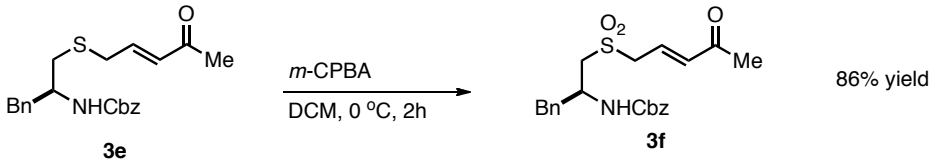
To an oven dried round bottom flask equipped with magnetic stir bar was dissolved Z-L-phenylalaninol (570 mg, 2.0 mmol) and PPh_3 (655 mg, 2.5 mmol, 1.3 equiv.) in dry DCM (20 ml, 0.1 M). The reaction mixture was cooled to 0 ^{o}C by ice bath for 30 minutes before CBr_4 (850 mg, 2.6 mmol, 1.3 equiv.) was added. The reaction was stirred for 1 hour at 0 ^{o}C, and then warmed to room temperature over an additional hour. Once TLC indicated the consumption of the starting materials, the solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 10:90) was applied to give 666 mg, (96% yield) the bromide intermediate.

The bromide (666 mg, 1.92 mmol) was then dissolved in DMF (10 ml, 0.2 M) and allyl mercaptan (156 mg, 2.1 mmol, 1.1 equiv.) was added. The mixture was cooled to 0 ^{o}C and K_2CO_3 (397 mg, 2.25 mmol, 1.5 equiv.) was added in one portion. The reaction was stirred for 8 hours at room temperature. Once TLC indicated the consumption of the starting materials, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.) and brine and dried over anhydrous Na_2SO_4. The solvent was put under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 30:70) was applied to give 602 mg, (92% yield) of the allyl thioether intermediate

The allyl thioether intermediate (602 mg, 1.77 mmol) and methyl vinyl ketone (620 mg, 8.85 mmol, 5.0 equiv.) were dissolved in DCM (17 ml, 0.1 M) under argon. Hoveyda-Grubbs II catalyst (219 mg, 0.35 mmol, 0.2 equiv.) was added to the mixture in two portions over 2 hours and the reaction mixture was warmed up to 45 ^{o}C

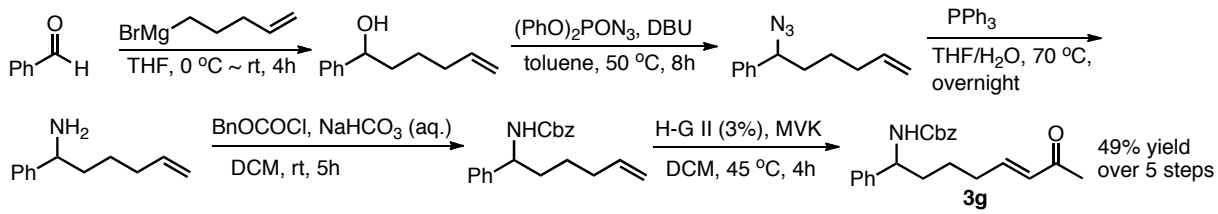
and stirred an additional 8 hours. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 20:80) was then applied to give 508 mg (75% yield) of the intramolecular aza-Michael precursor **3e**.

6. 3f



To an oven dried round bottom flask, was added thioether **3e** (300mg, 0.78 mmol) in DCM (16 mL, 0.05 M) and the temperature was cooled to 0 ^{o}C. Next, *m*-CPBA (268 mg, 1.56 mmol, 2.0 equiv.) was added to the mixture in 3 portions over 30 minutes. The reaction was kept at 0 ^{o}C by ice bath for 2 hours until TLC indicated the disappearance of the starting material. Saturated NaS_2O_3 solution (10 mL) was added to quench the reaction and 100 mL of DCM was added, after which the reaction mixture was warmed to room temperature. The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.) and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 30:70) was applied to give 288 mg, (89% yield) of the sulfone substrate **3f**.

7. 3g



The Grignard reagent in THF solution (6 mmol, 0.5 M, 12 mL) was prepared according to the literature from 5-bromopent-1-ene and Magnesium. At 0 ^{o}C, the Grignard was added in to benzylaldehyde THF solution (5 mmol, 0.5 M 10 ml), under argon atmosphere. The reaction mixture was gradually warmed to room temperature and stirred for an additional 4 hours. Next, HCl aqueous solution (5 mL, 1.0 M) was added slowly to quench the reaction. The mixture was diluted with EtOAc (200 mL) and washed by saturated $NaHCO_3$ (aq.) and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 20:80) afforded 836 mg, 95%. of the alcohol.

The alcohol (863 mg, 4.75 mmol) was dissolved in toluene (0.2 M) at room temperature and DBU (1083 mg, 7.13 mmol, 1.5 equiv.) was added under argon. Next, $(PhO)_2P(O)N_3$ (1960 mg, 7.13 mmol, 1.5 equiv.) was added in the solution. The reaction mixture was warmed up to 50 ^{o}C and kept stirring for 8 hours, until the complete consumption of the alcohol. Two layers were formed and the top layer was directly applied to flash silica gel chromatography (Et_2O/pentane 5:95) to provide 763 mg (80% yield) of the azide.

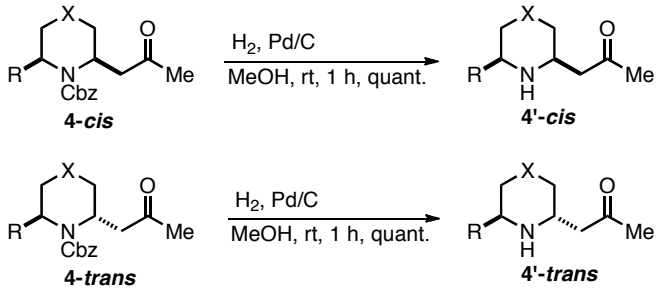
The azide (763 mg, 3.8 mmol) was then dissolved with THF (19 mL, 0.2 M) and PPh_3 (1493 mg, 5.7 mmol, 1.5 equiv.) was added at room temperature. Next, 5 mL of water was added and the temperature was raised to 70 ^{o}C and stirred overnight. The reaction was cooled to room temperature and dried over Na_2SO_4 directly. The organic solvent was then removed under reduced pressure and the residue was redissolved in DCM (40 mL, 0.1 M).

Next, 20 mL of saturated $NaHCO_3$ (aq.) was added, followed by BnOCOCl (969 mg, 5.7 mmol, 1.5 equiv.) and the reaction was kept stirring for 5 hours at room temperature. The mixture was diluted with EtOAc (150 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq.), brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/Hexane 15:85) was applied to give 821 mg (70% yield) of the Cbz alkene.

The Cbz alkene (821 mg, 2.66 mmol) was then dissolved in dichloromethane (38 ml, 0.07 M) and methyl vinyl ketone (745 mg, 10.64 mmol, 4.0 equiv.) was added in under argon. Hoveyda-Grubbs II catalyst (50 mg, 0.081 mmol, 0.03 equiv.) was added the reaction mixture was then warmed up 45 ^{o}C and kept stirring for 5 hours, until the TLC indicated consumption of the starting material. The solvent was removed under reduced pressure to give the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 35:65) provided 868 mg, (92% yield) of the intramolecular aza-Michael precursor **3d.**

Substrates **3h**, **3i** and **3j** were prepared via the same procedure as **3g**.

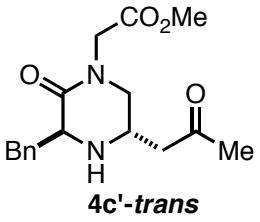
F. Cbz removal and relative stereochemistry of N-containing heterocycles 4



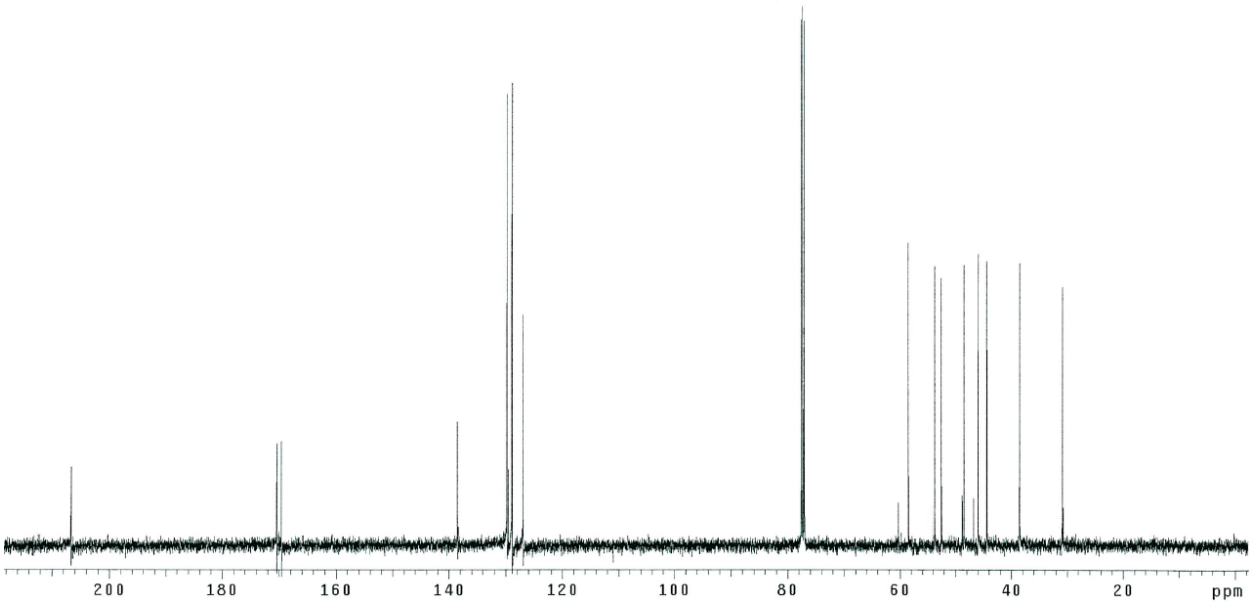
The relative stereochemistry could not be identified for the N-Cbz-protected heterocycles **4**. NMR studies were carried out for both *cis* and *trans* isomers. No NOE was observed in both cases. In order to elucidate the relative stereochemistry of the aza-Michael reaction, both purified diastereomers were separately subjected to Pd/C (0.2 eq.) hydrogenation. At room temperature, the Cbz protecting group was removed under hydrogen atmosphere (1.0 atm) after 1 hour. Quantitative yields were obtained for both isomers without epimerization on C-6 position. NOE studies were then performed to identify confirm the relative stereochemistry, as shown below.

1. 4c

4c'-trans (^{1}HNMR)



^{13}CNMR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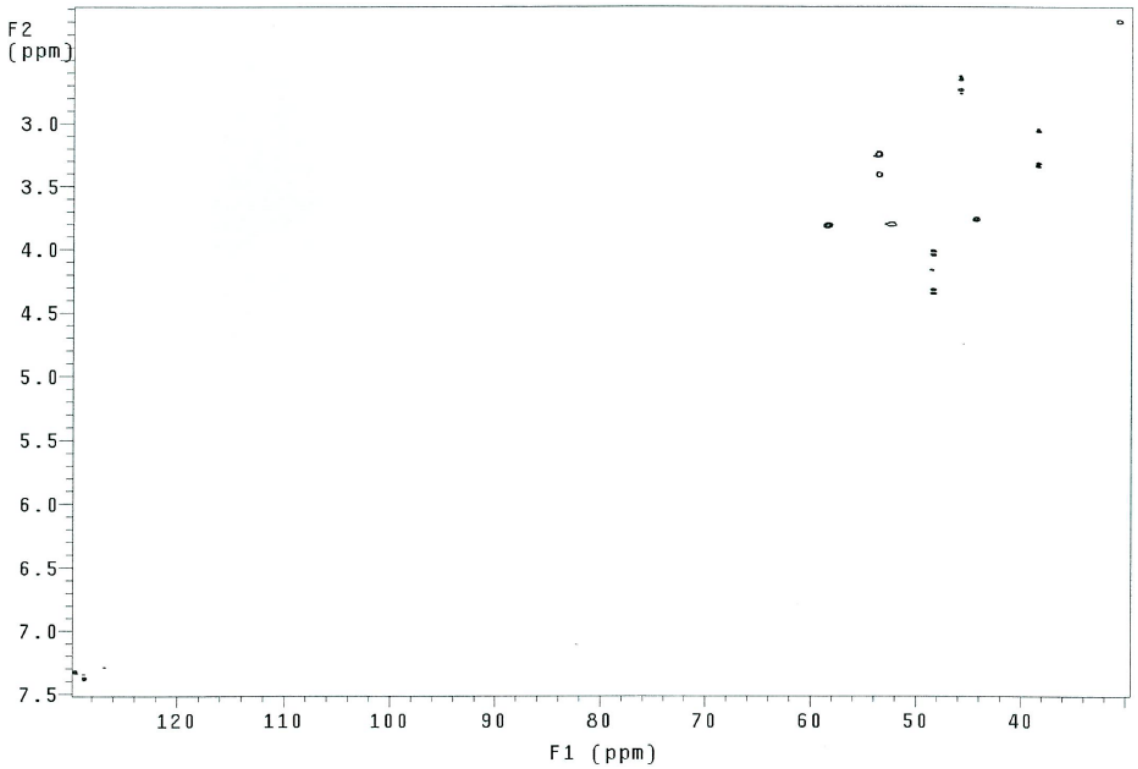
80
60
40
20
ppm

HSQC


F2
(ppm)
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3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
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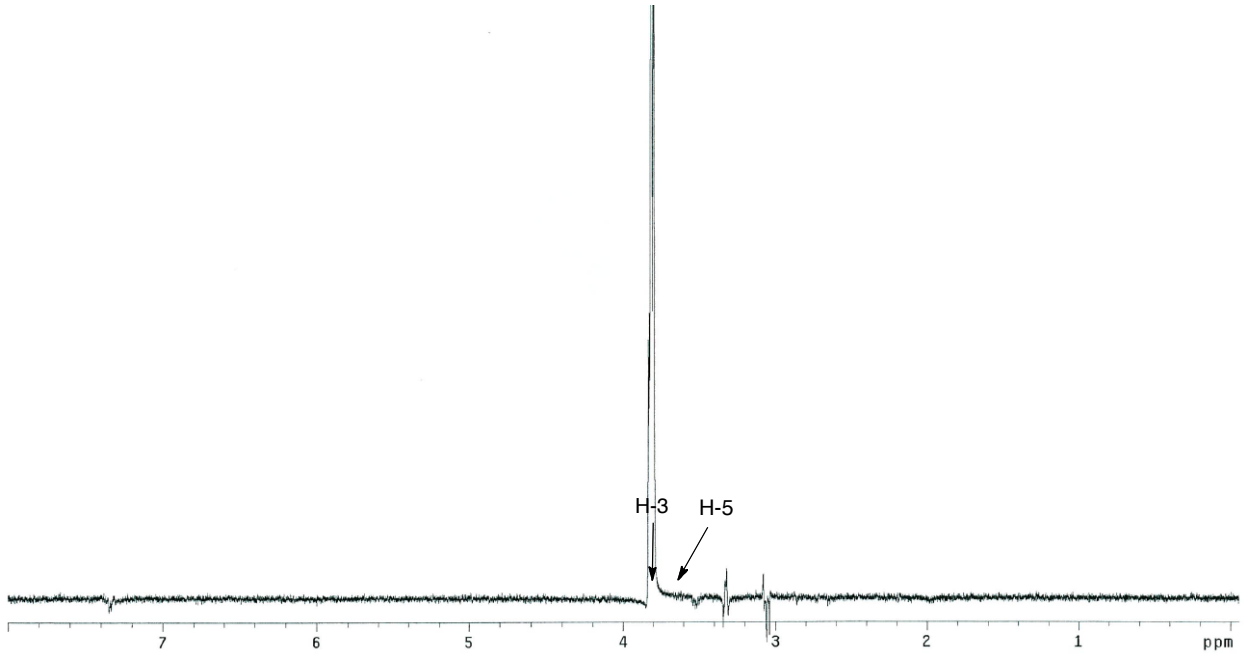
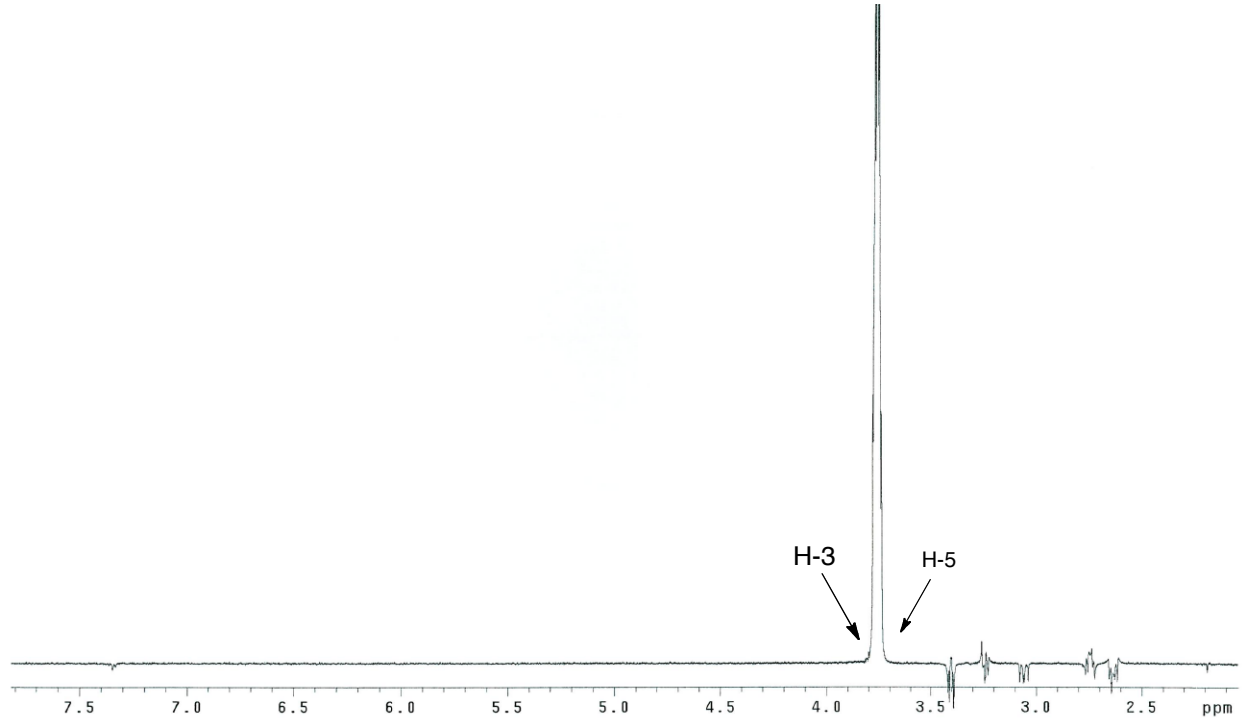
60
50
40
F1 (ppm)

1DNOE-3.71

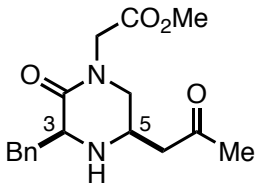


1DNOE-3.75

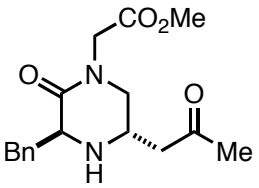


4c'-*cis* + 4c'-*trans*

^{1}HNMR

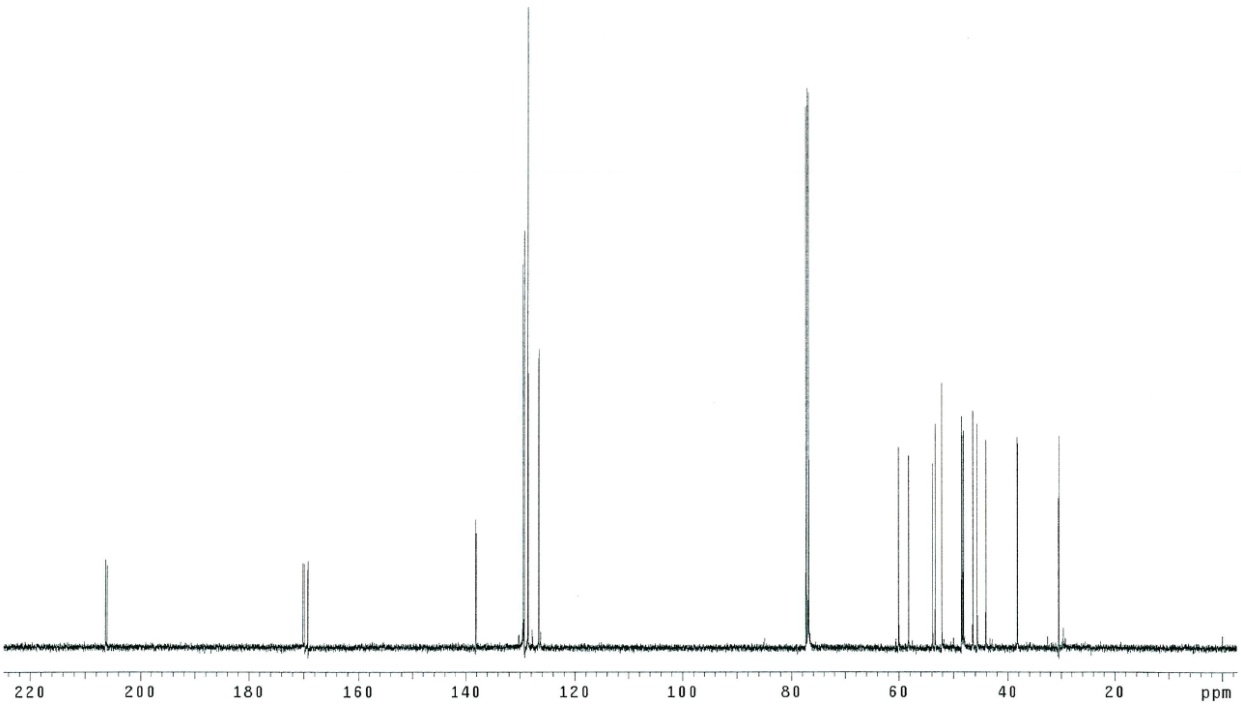


4c'-*cis*



4c'-*trans*

^{13}CNMR



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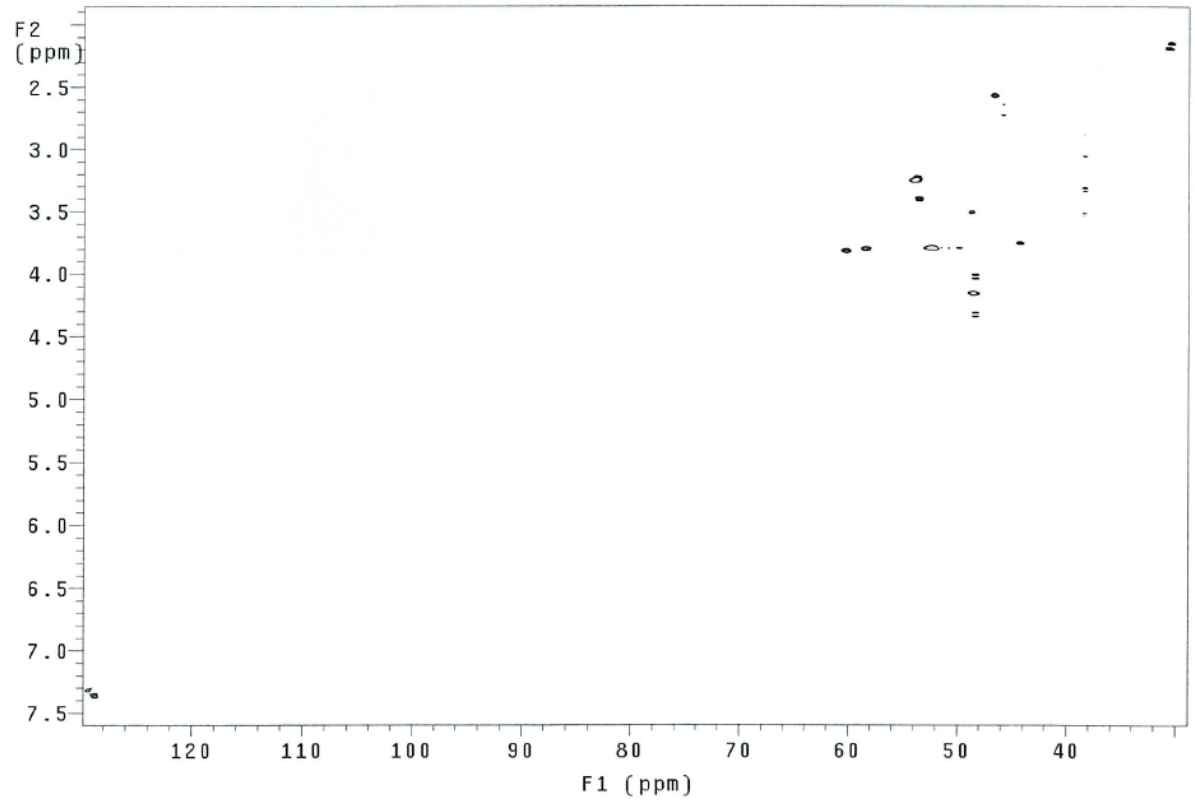
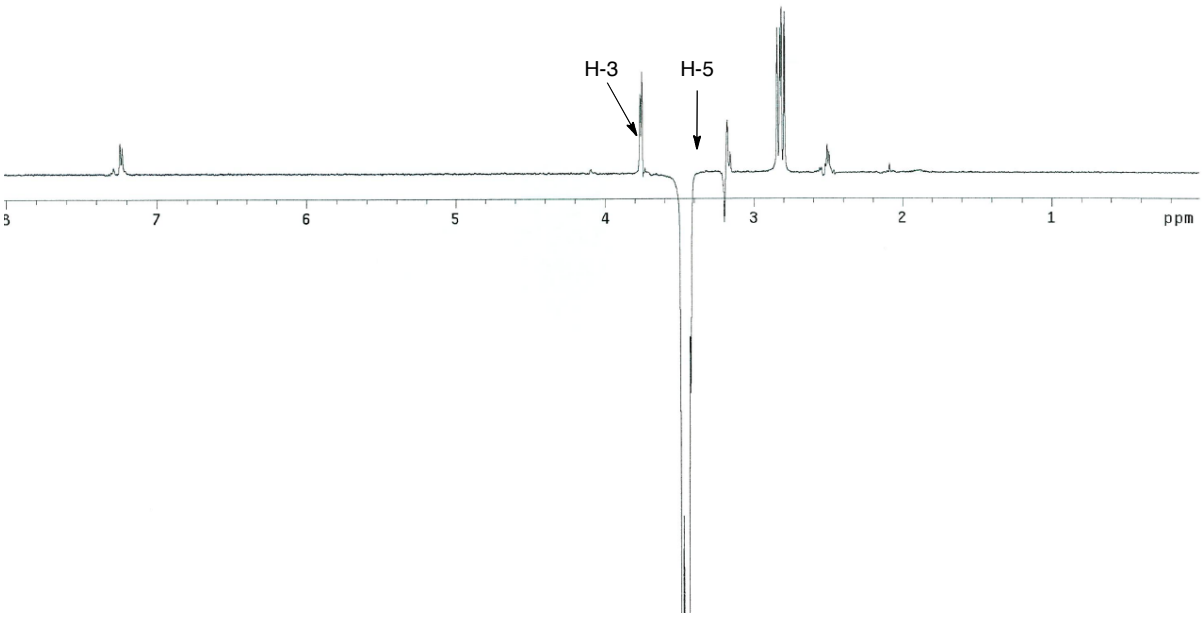
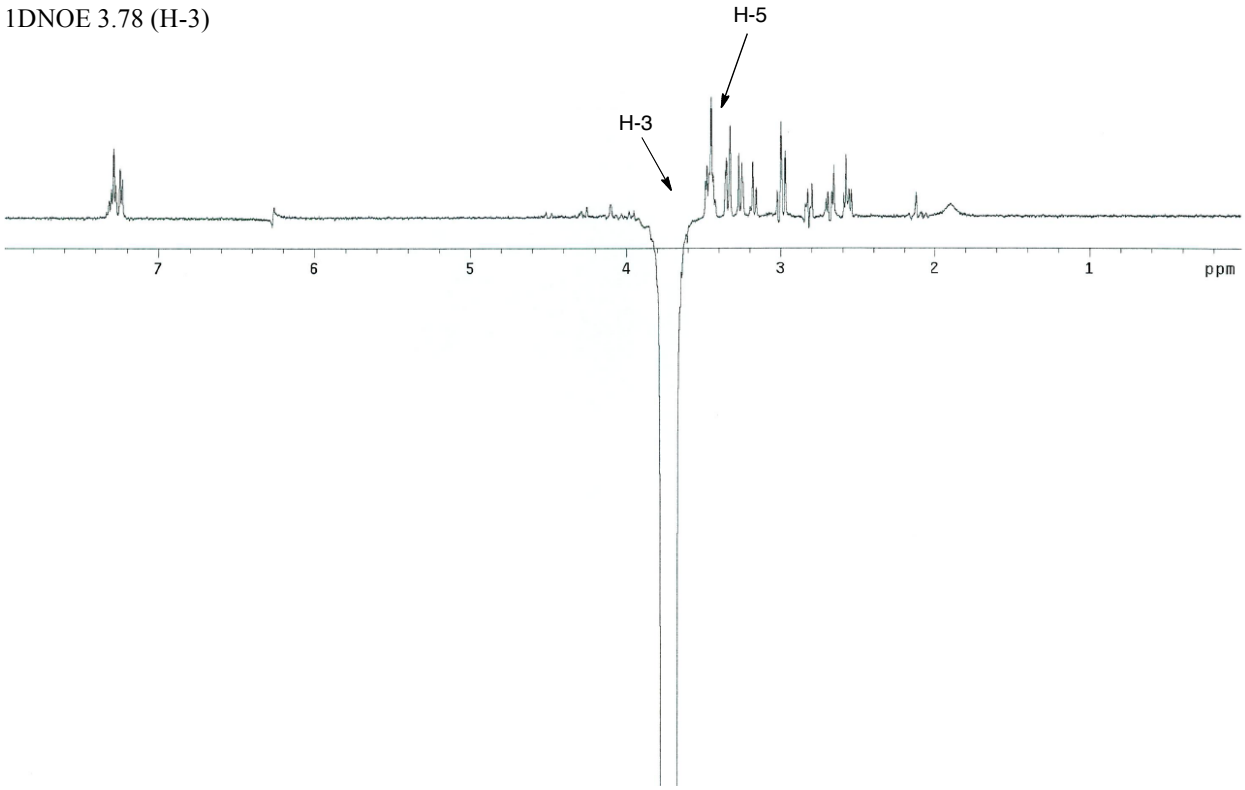


1DNOE 3.42 (H-5)

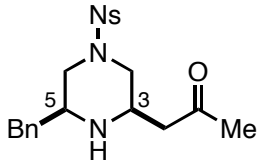


1DNOE 3.78 (H-3)



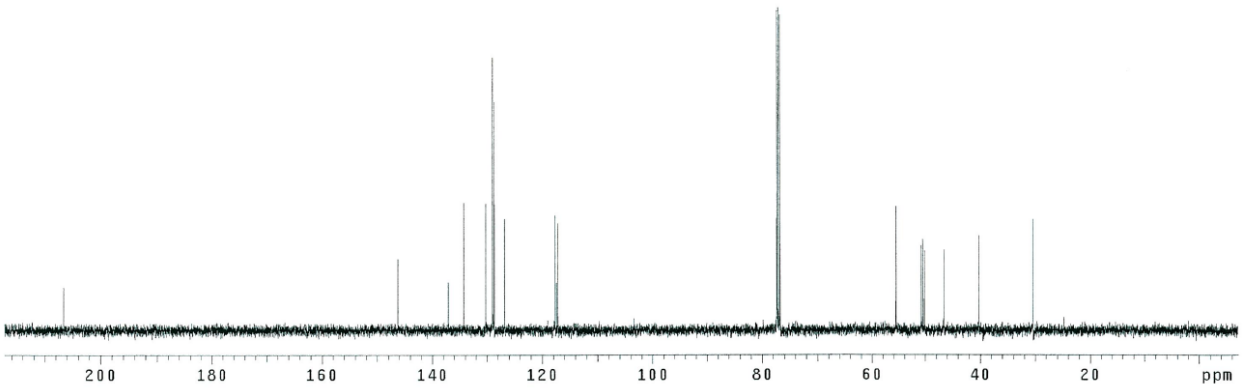
2. 4d

4d'-cis (^{1}HNMR)



4d'-*cis*

^{13}CNMR


200
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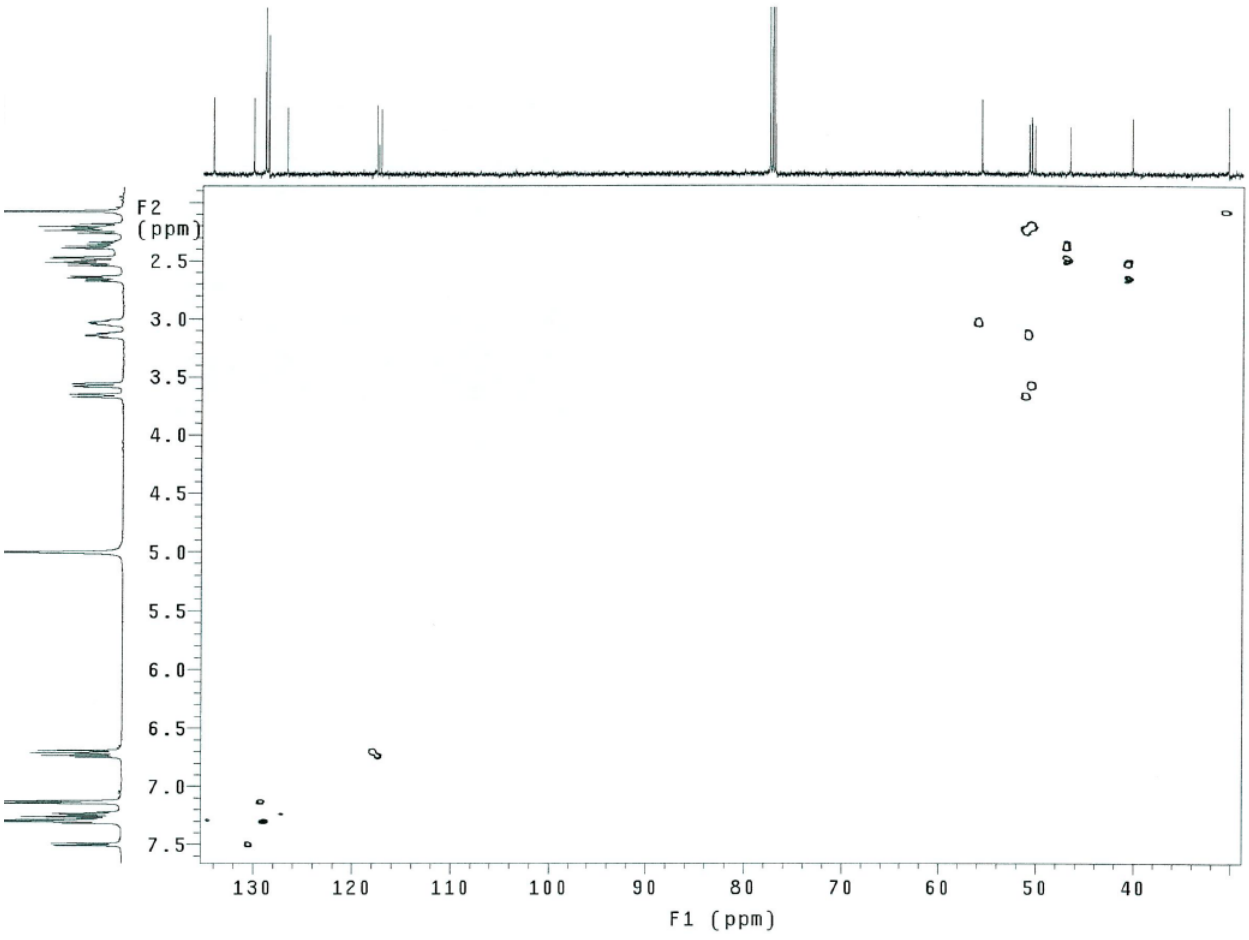
160
140
120
100
80
60
40
20
ppm

HSQC


F2
(ppm)
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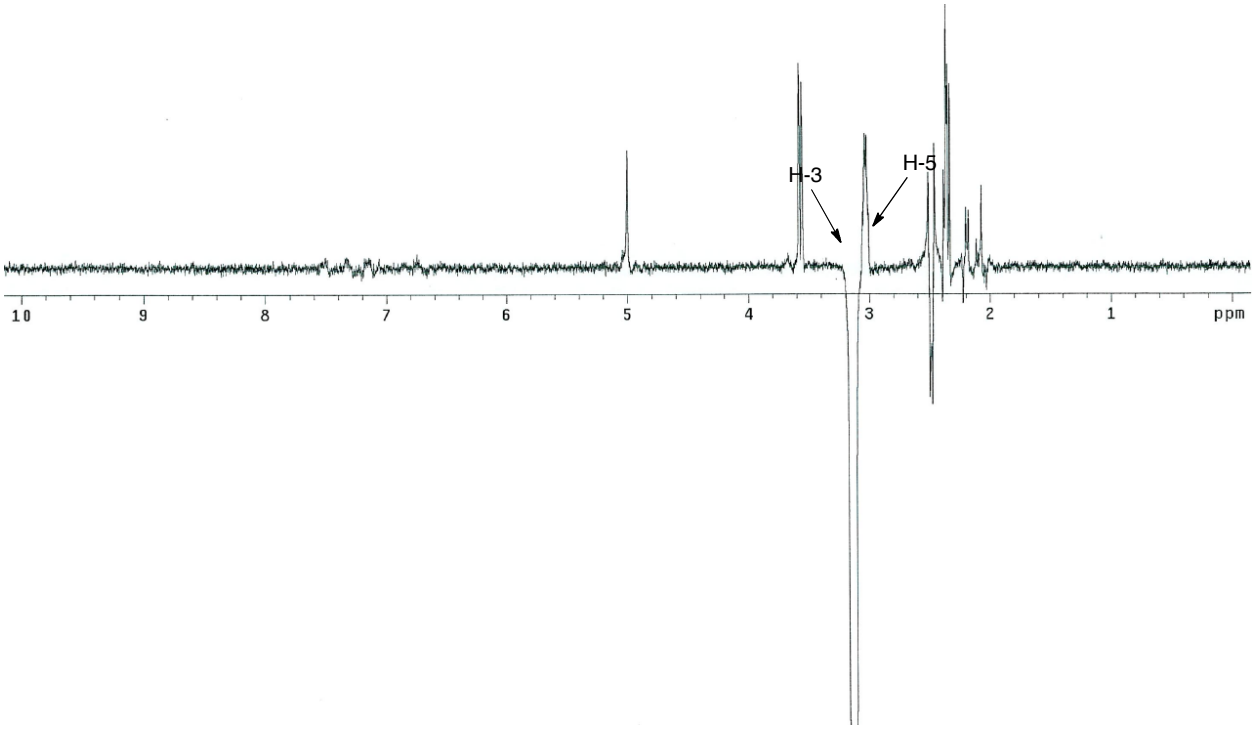
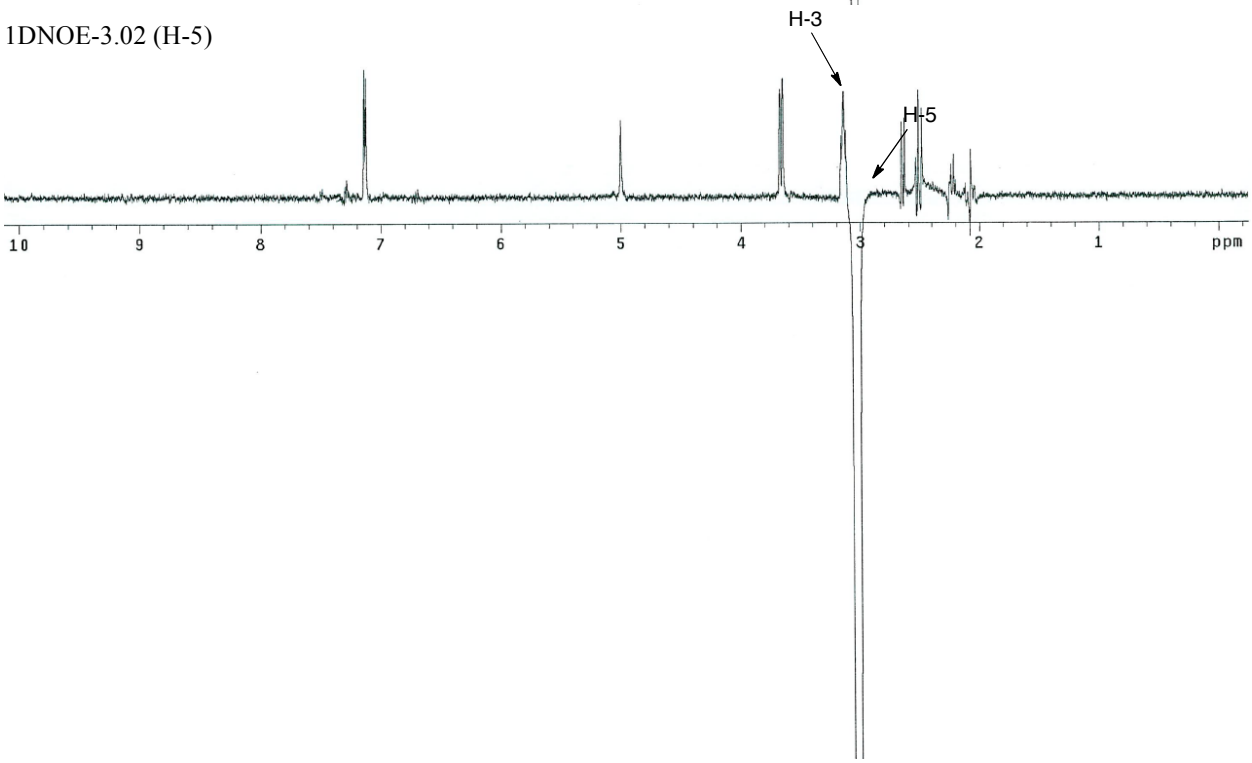
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
130
120
110
100
90
80
70
60
50
40
F1 (ppm)

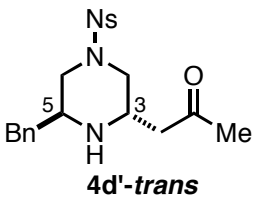
1DNOE-3.17 (H-3)



1DNOE-3.02 (H-5)

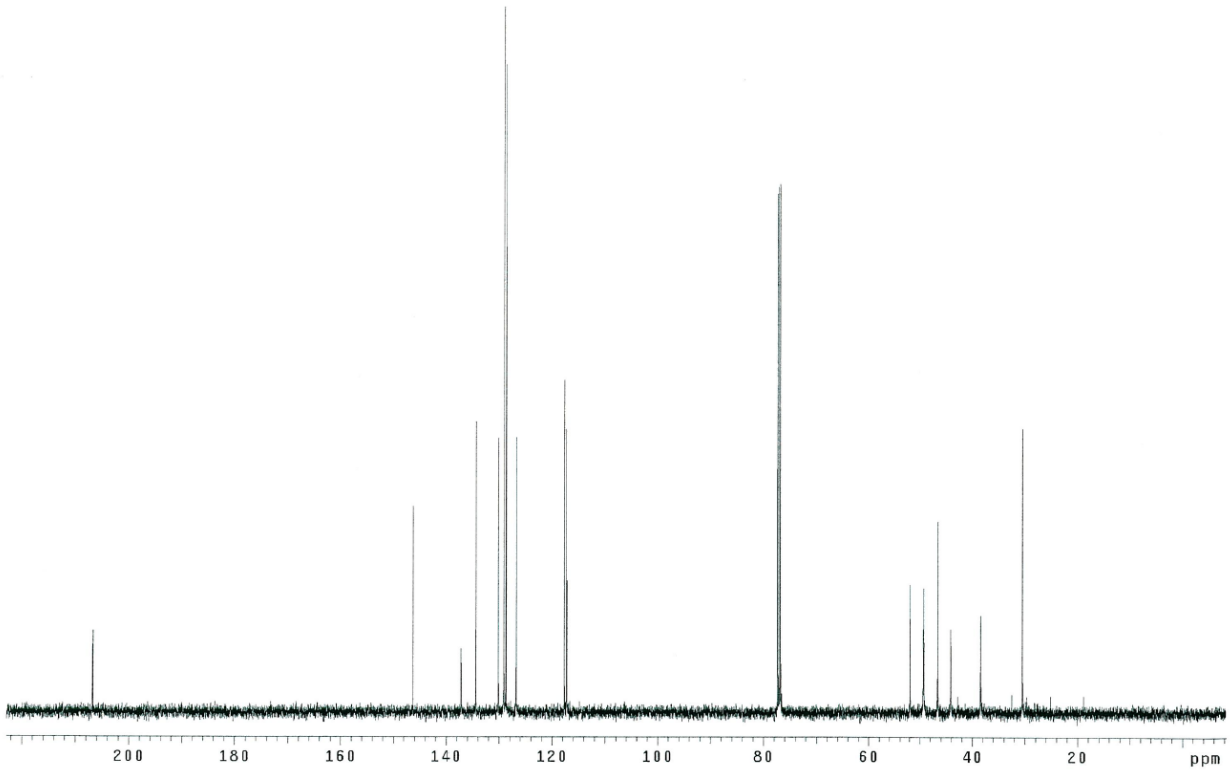


4d'-*trans* (^{1}HNMR)

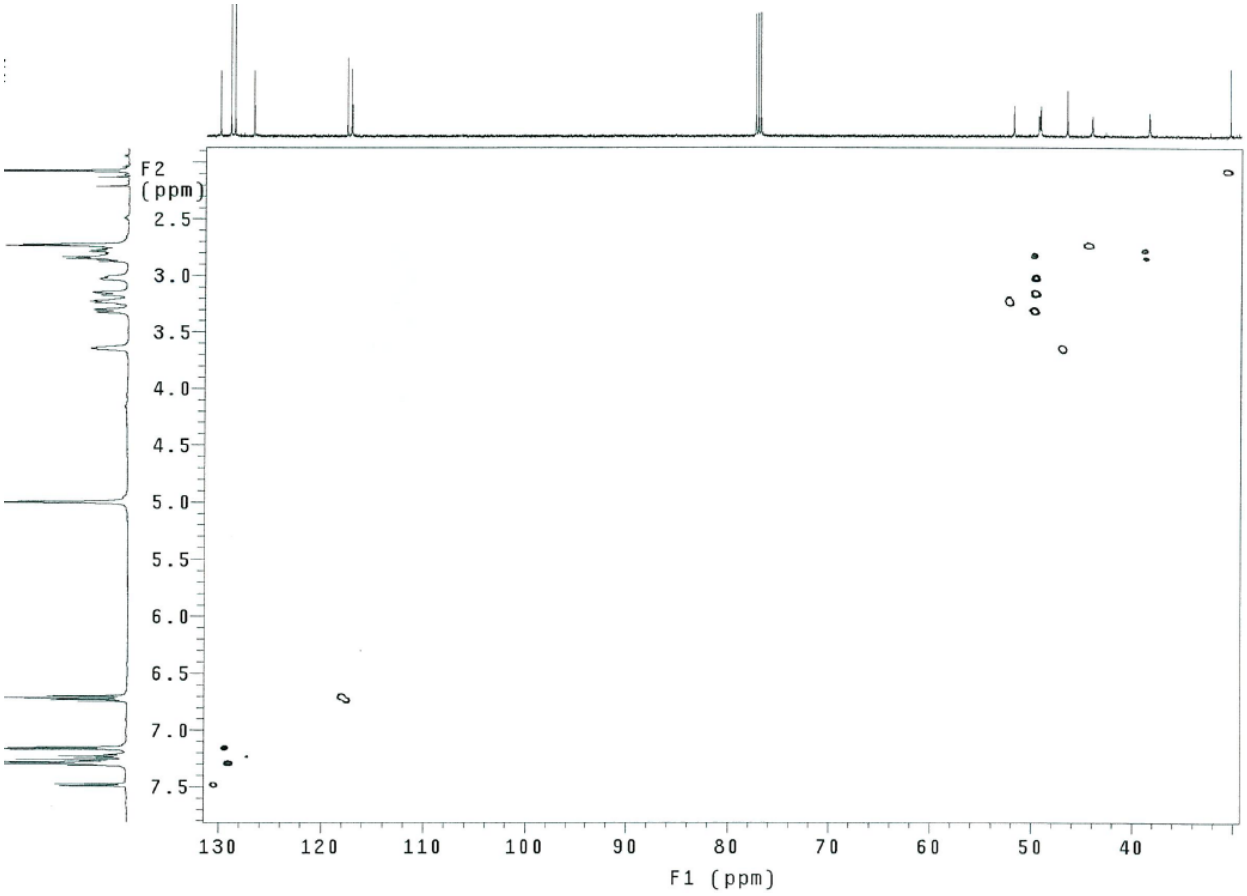


4d'-*trans*

^{13}CNMR



HSQC



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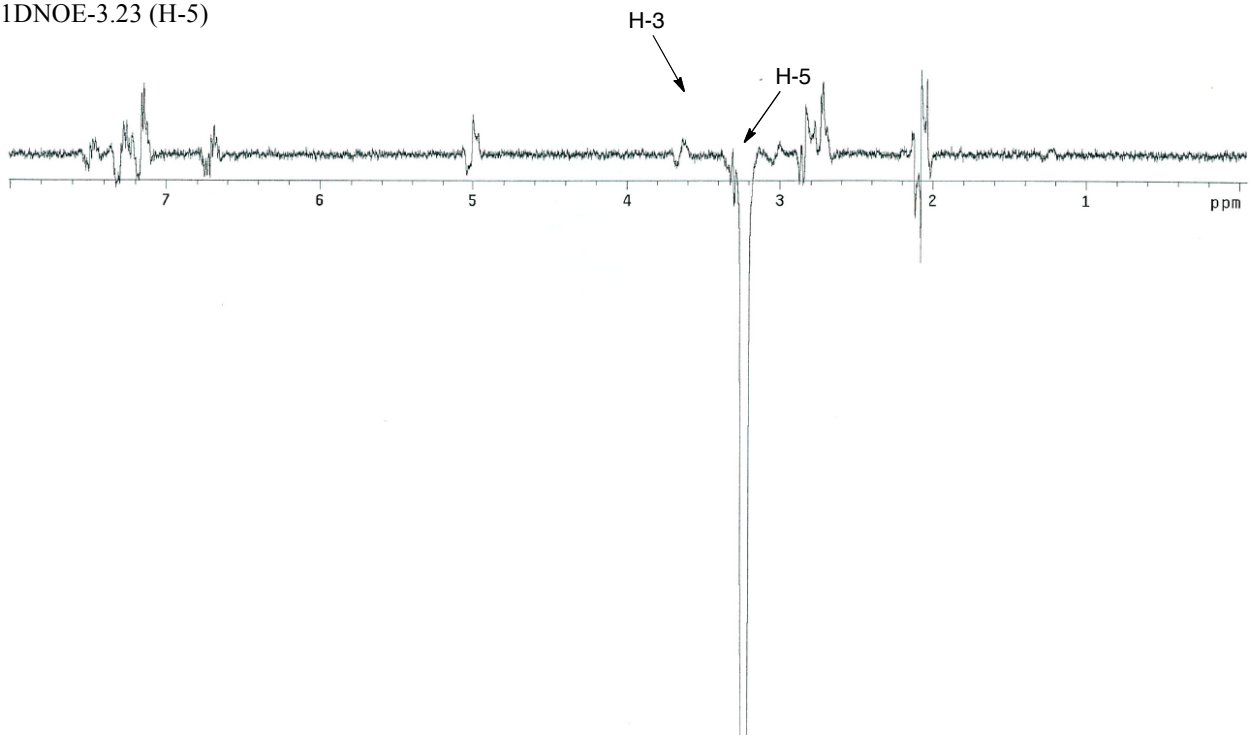
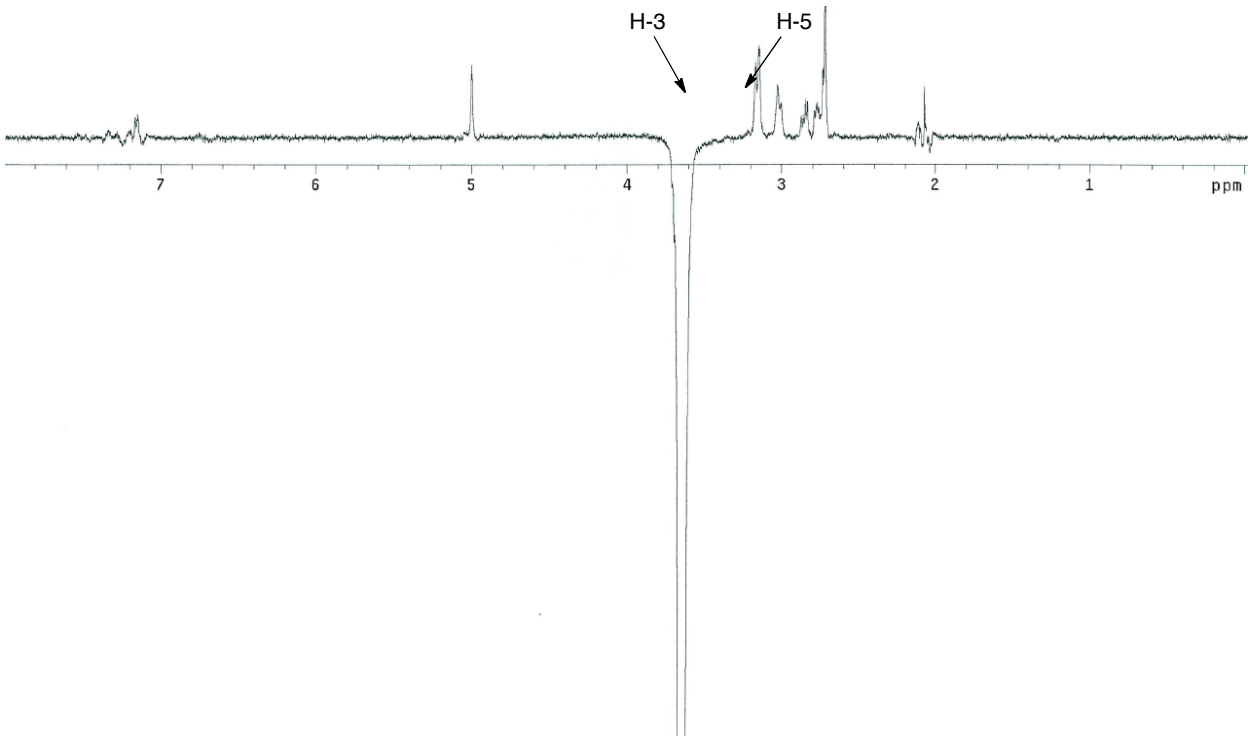


1DNOE-3.63 (H-3)

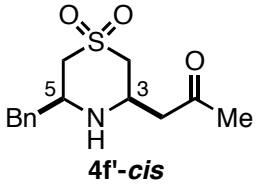


3. 4e

Hydrogenation was not successful for sulfide **4e**. It was then oxidized to sulfone **4f** to carry out the stereochemistry studies as shown below.

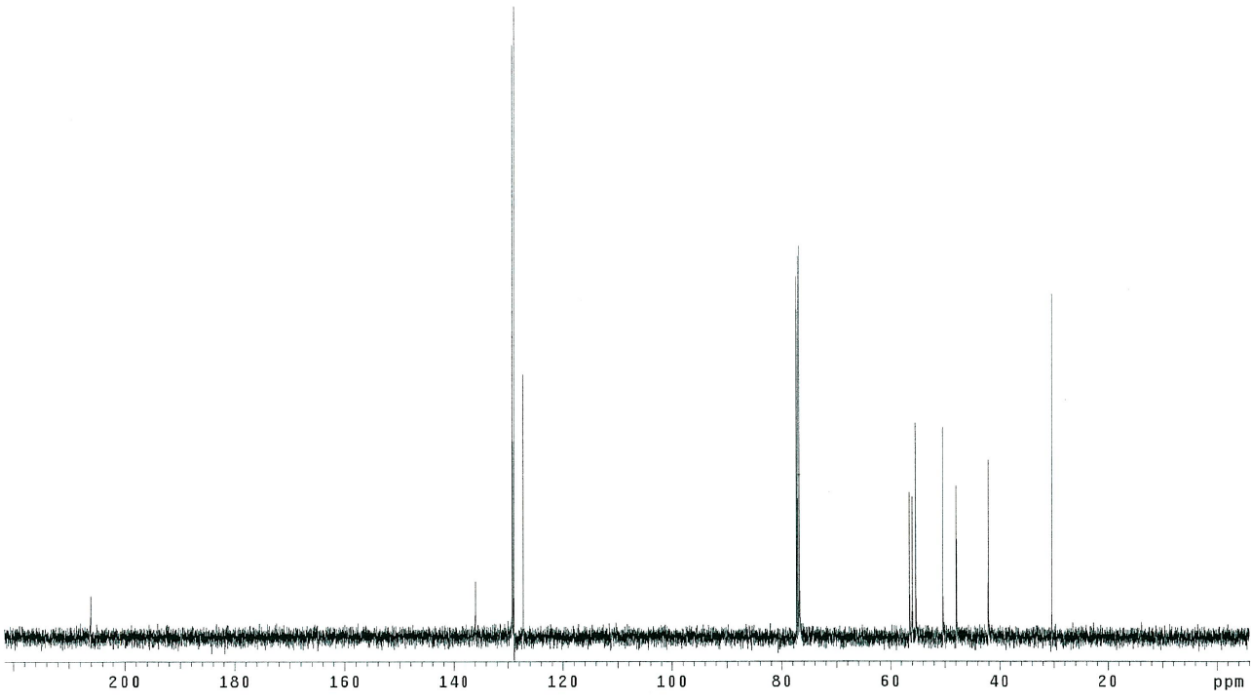
4. 4f

4f'-*cis* (^{1}HNMR)

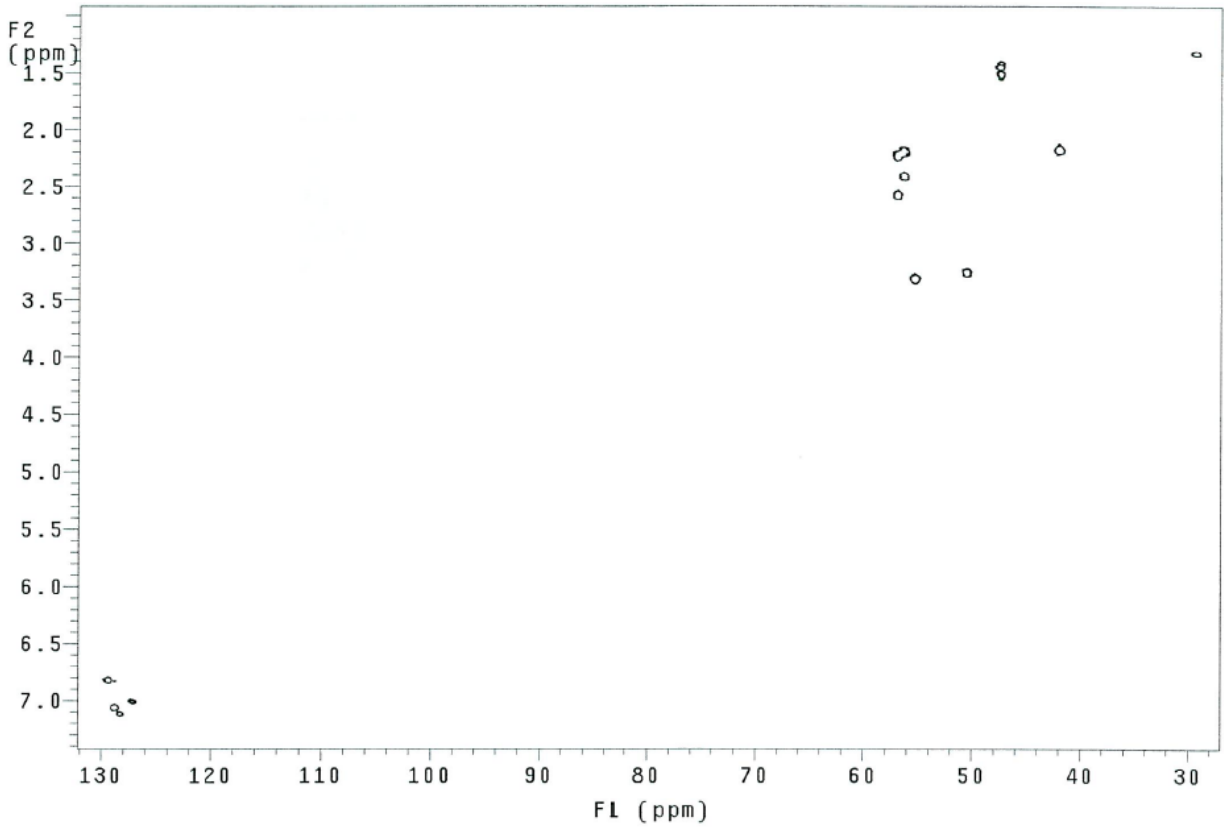


4f'-*cis*

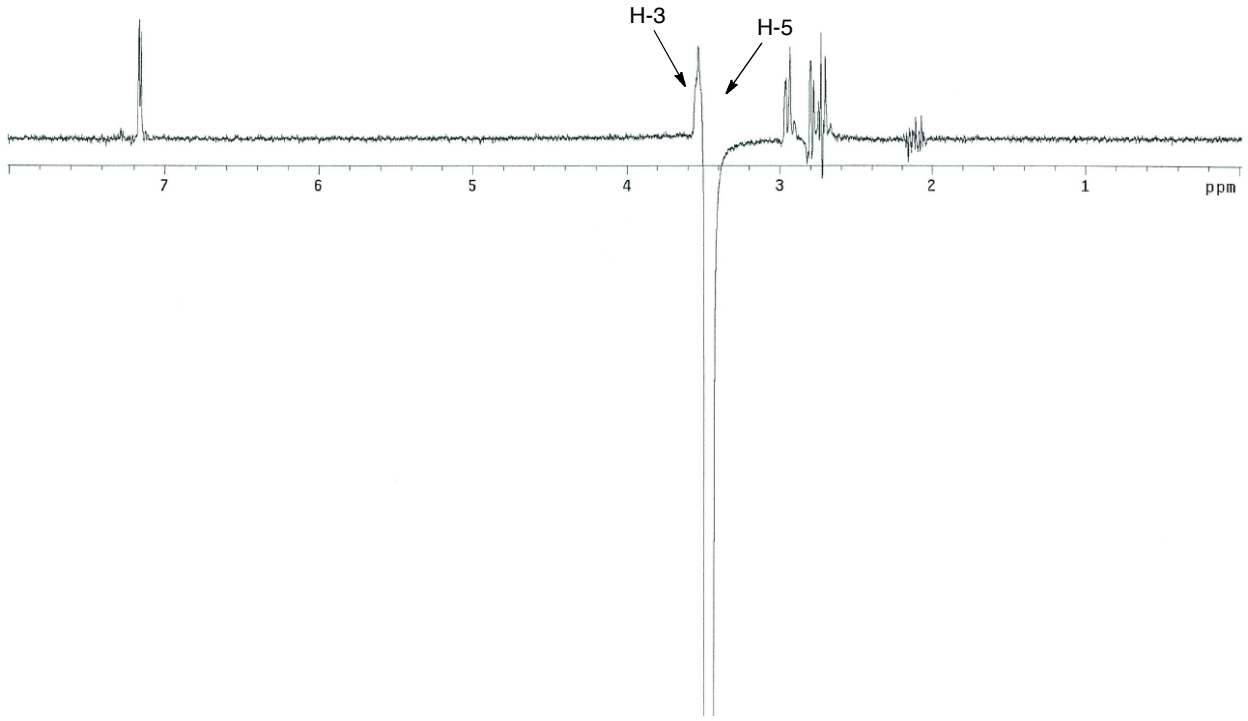
4f'-*cis* (^{13}CNMR)



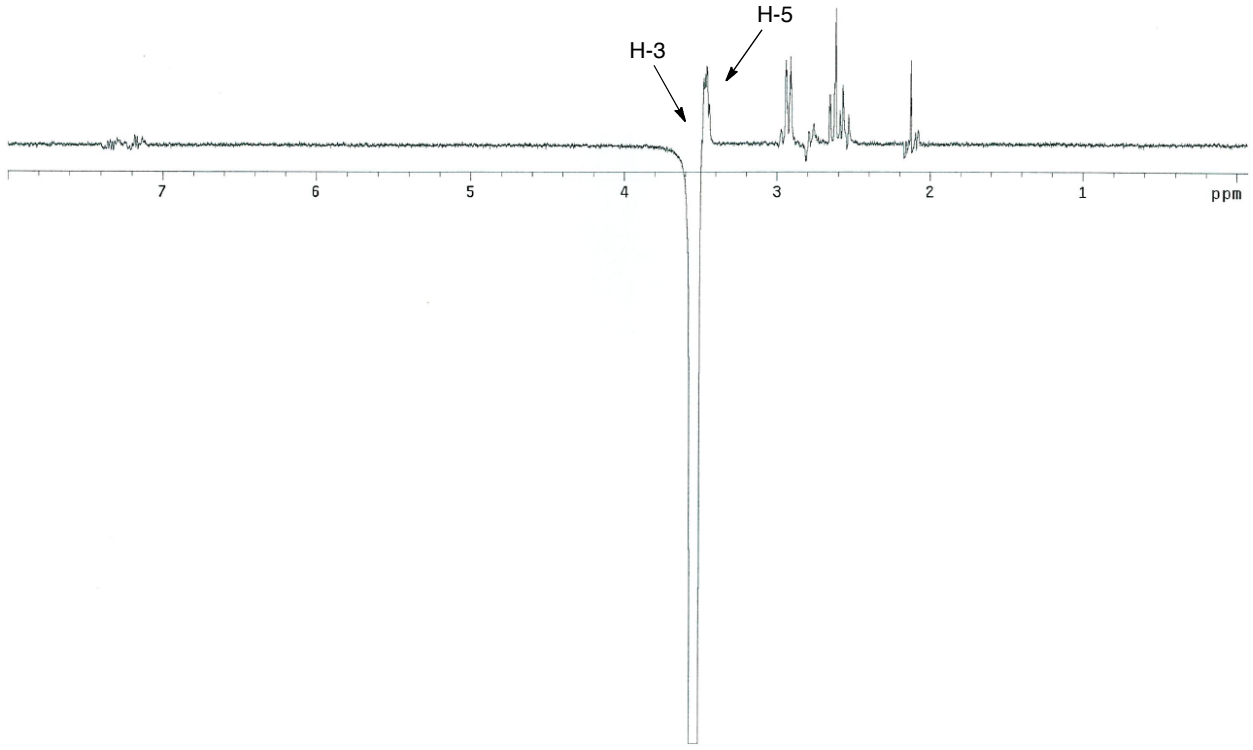
HSQC



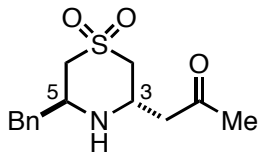
1DNOE-3.43 (H-5)



1DNOE-3.52 (H-3)

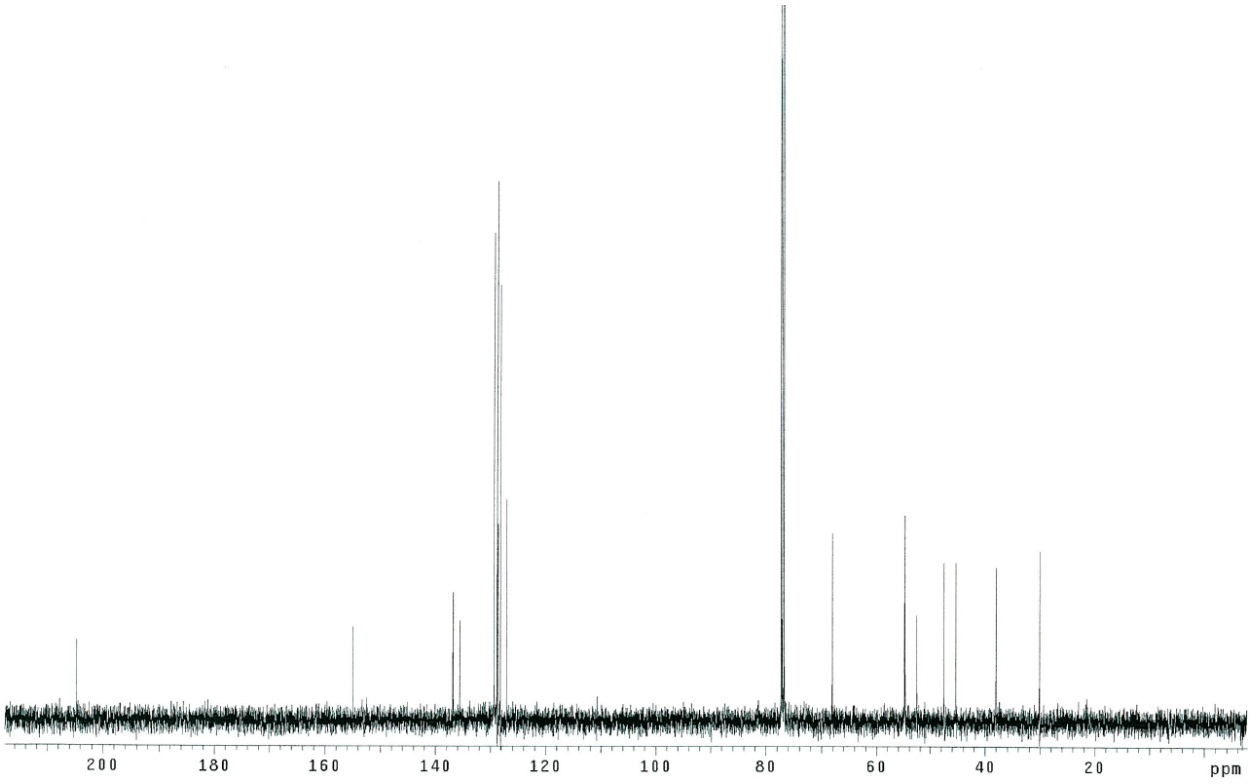


4f'-trans (^{1}HNMR)

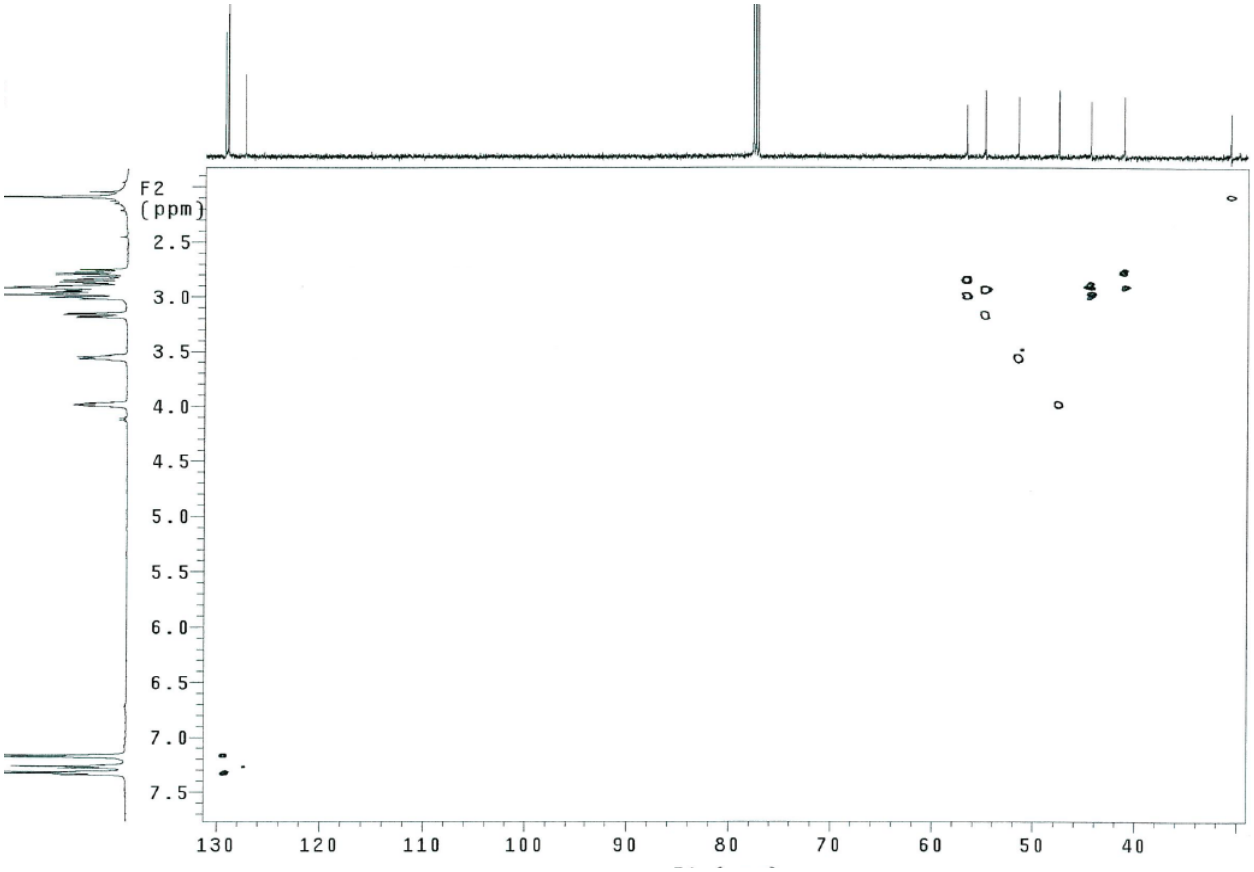


4f'-*trans*

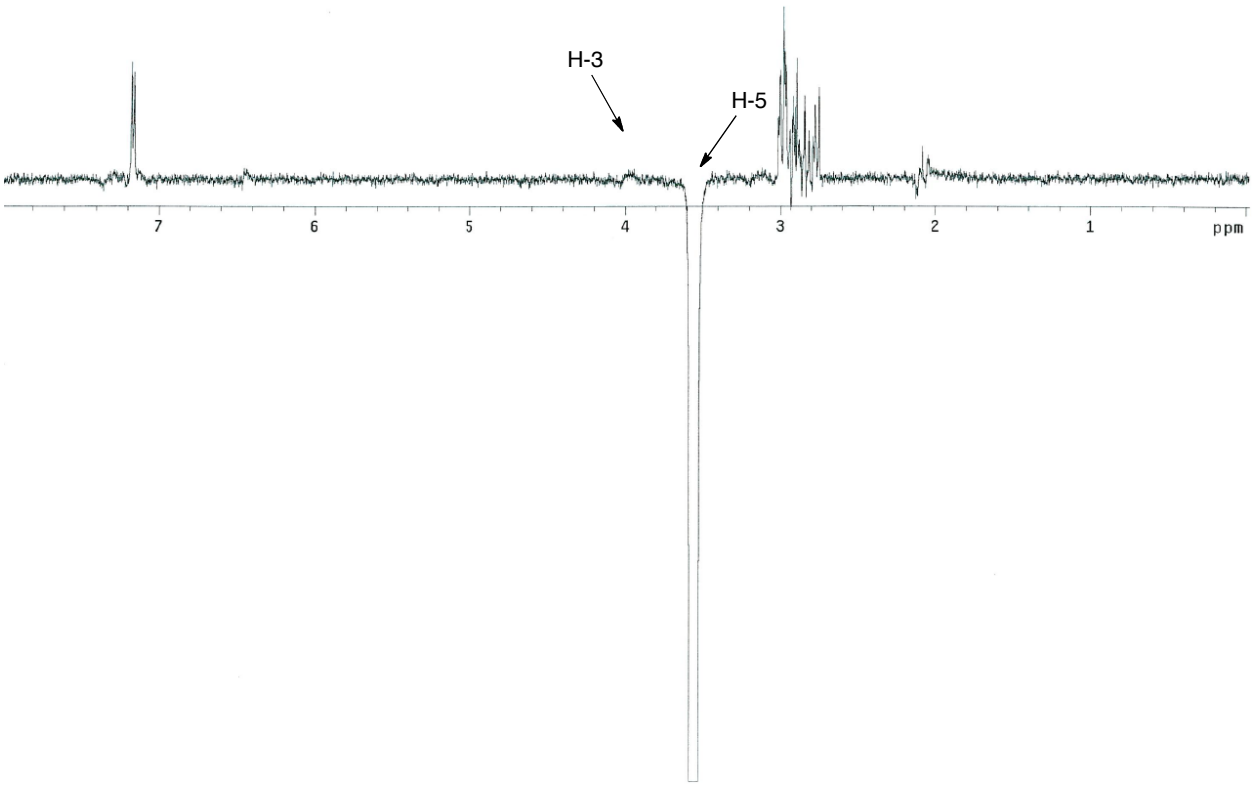
^{13}CNMR



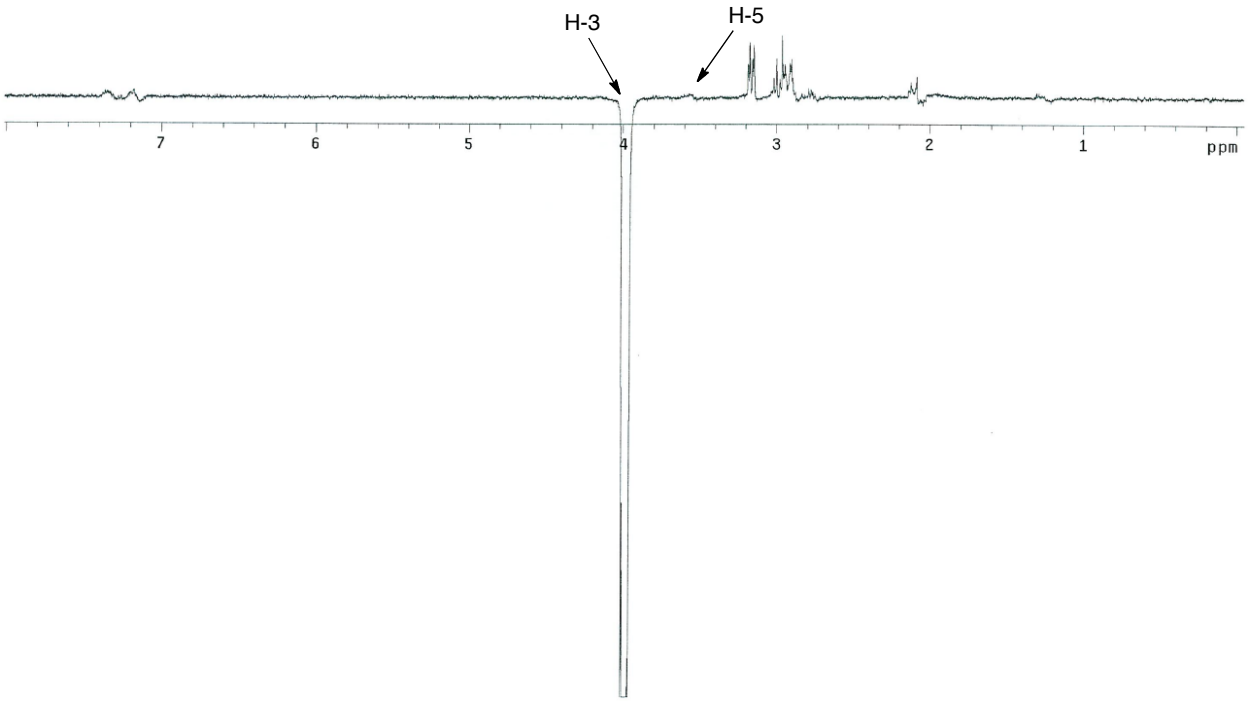
HSQC



1DNOE-3.57 (H-5)

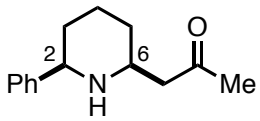


1DNOE-3.97 (H-3)



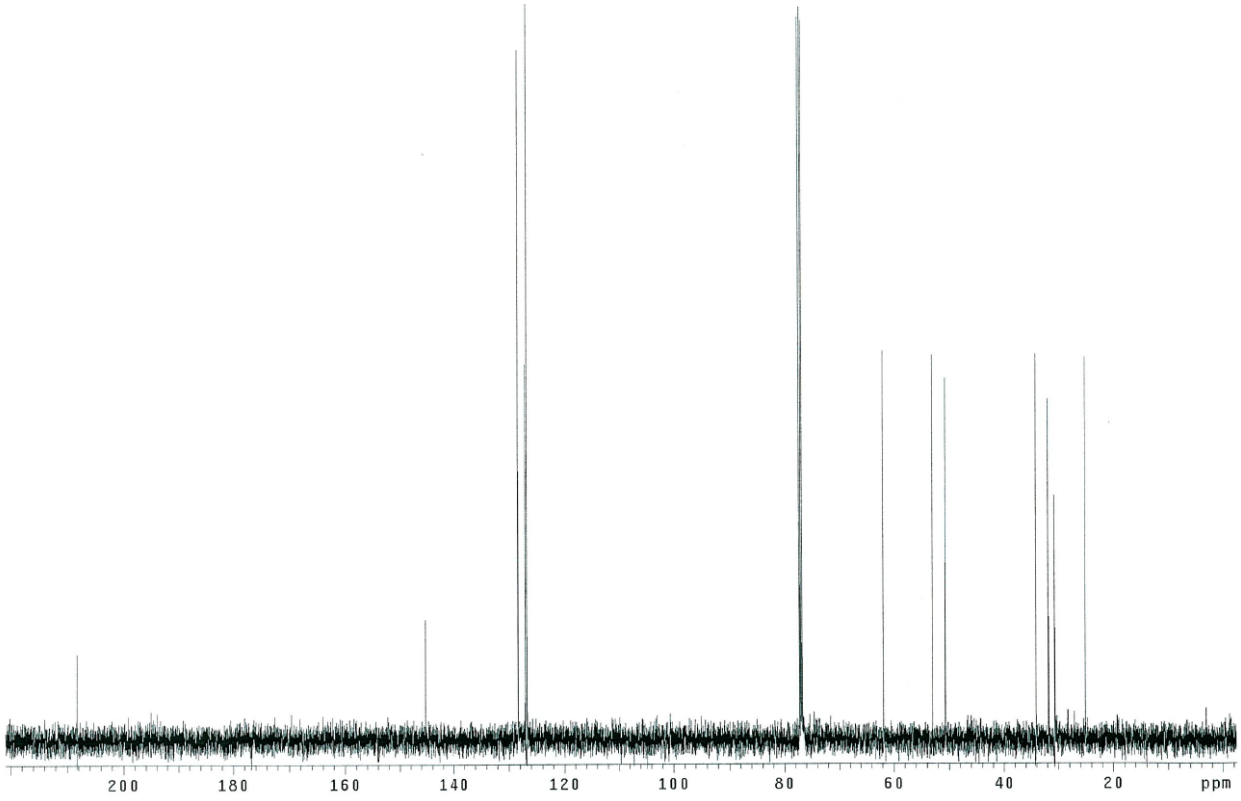
5. 4g

4g'-*cis* (^{1}HNMR)

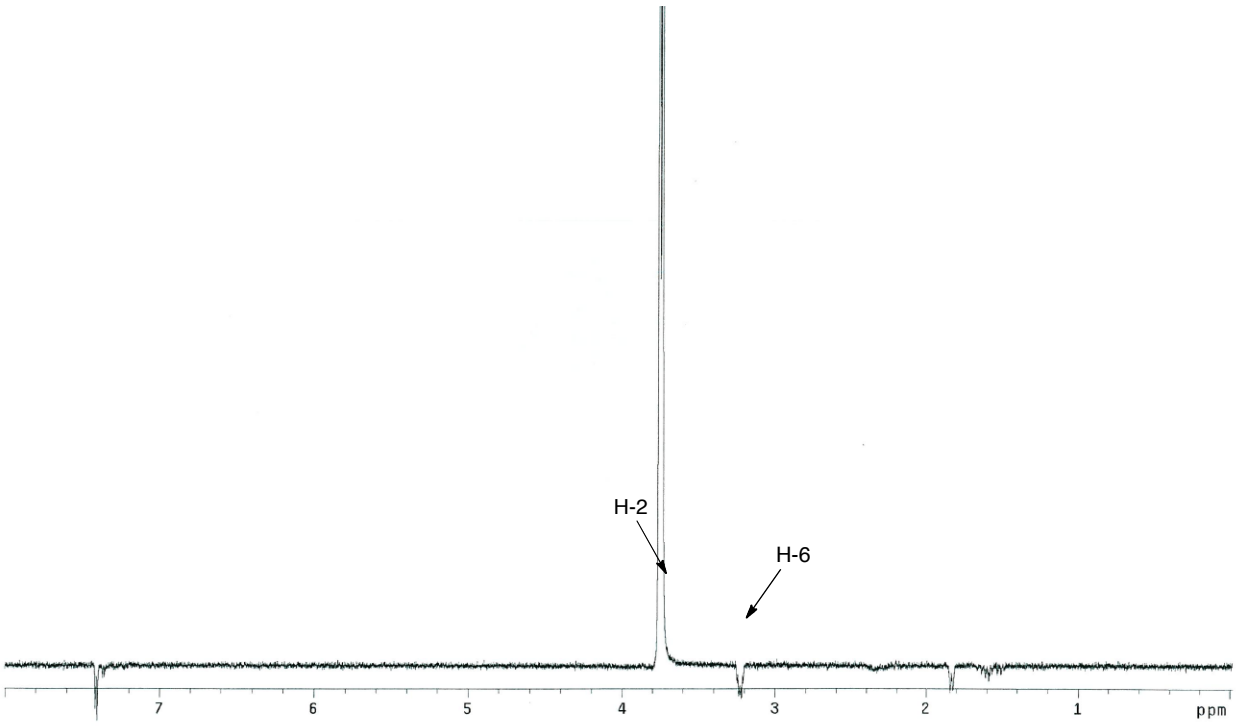


4g'-*cis*

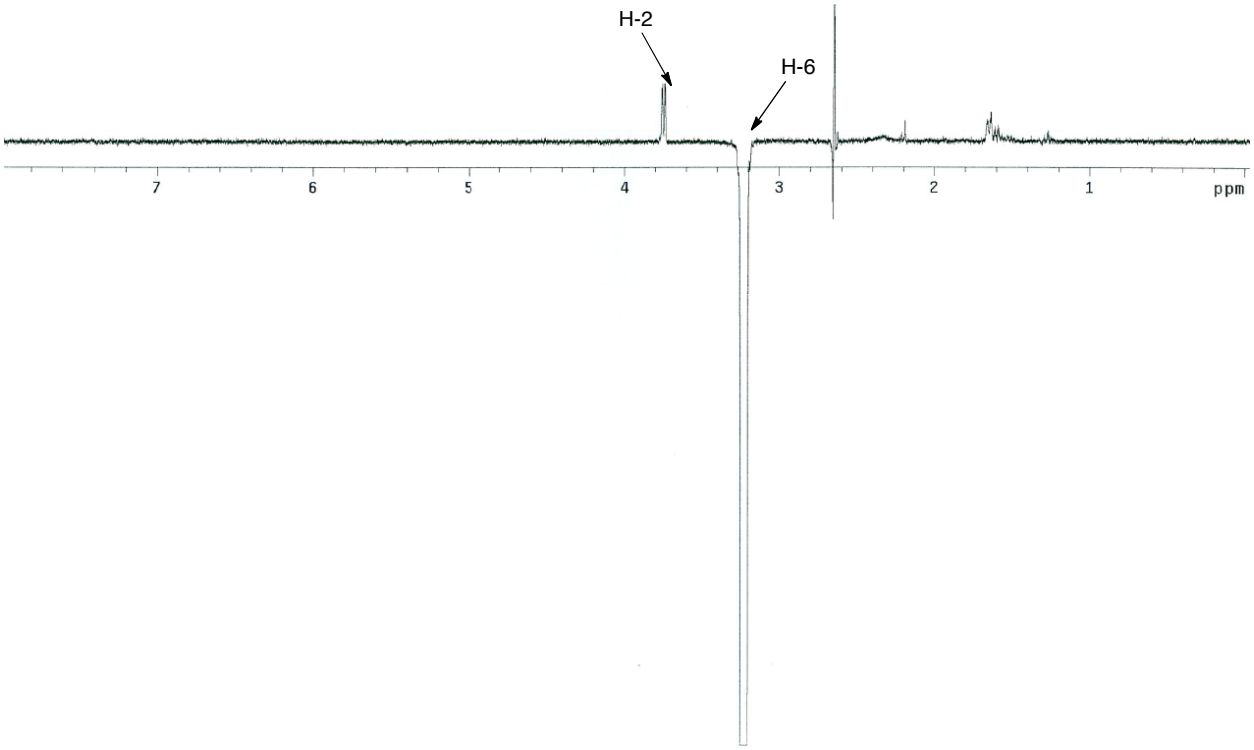
^{13}CNMR



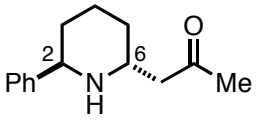
1DNOE-3.87 (H-2)



1DNOE-3.22 (H-6)

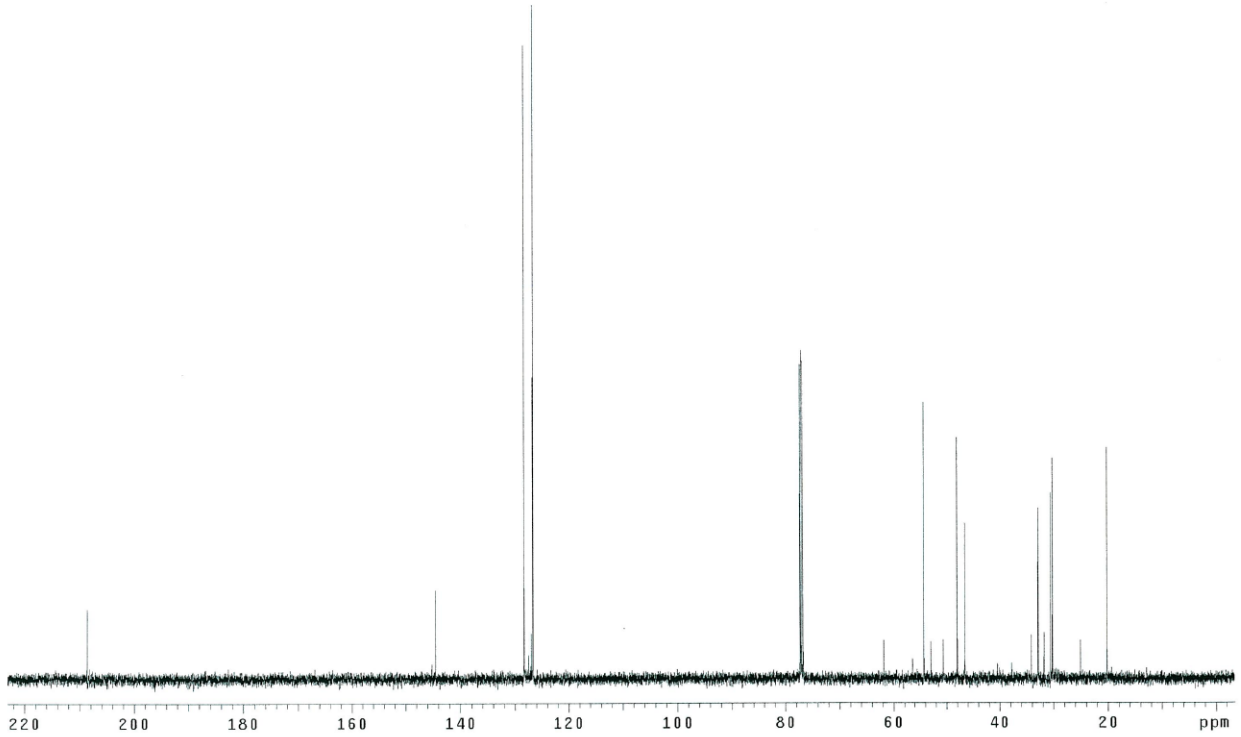


4g'-*trans* (^{1}HNMR)

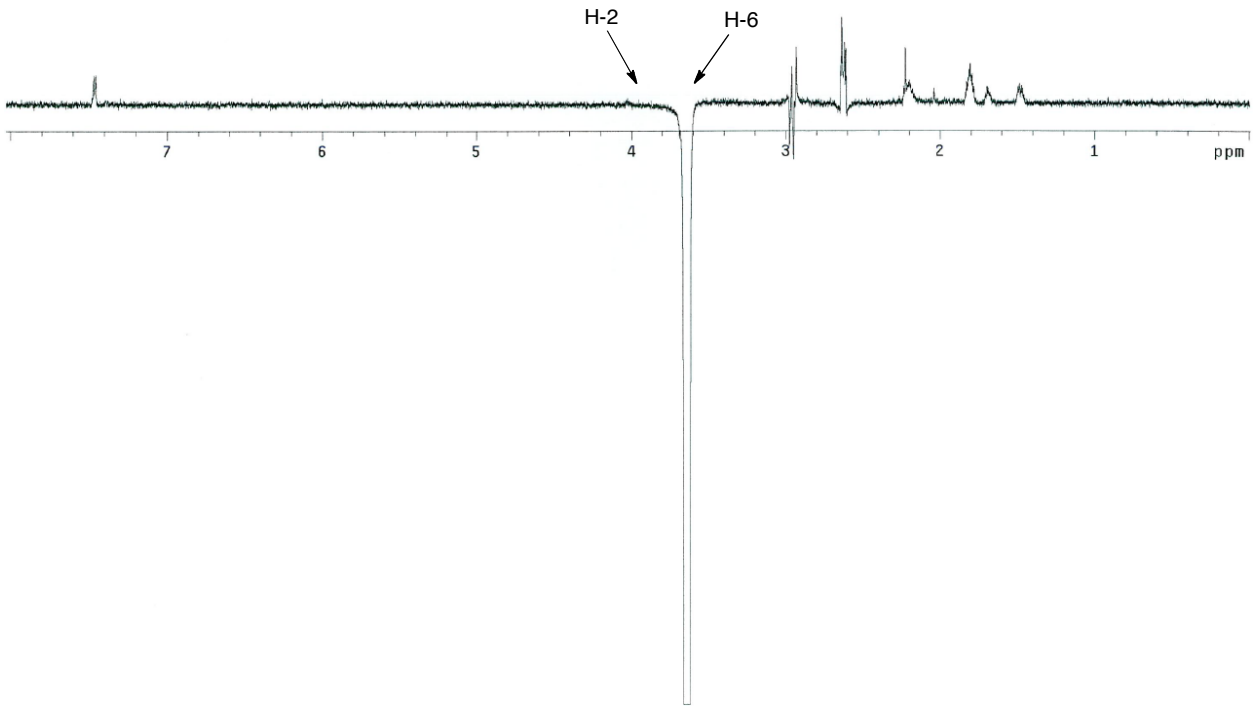


4g'-*trans*

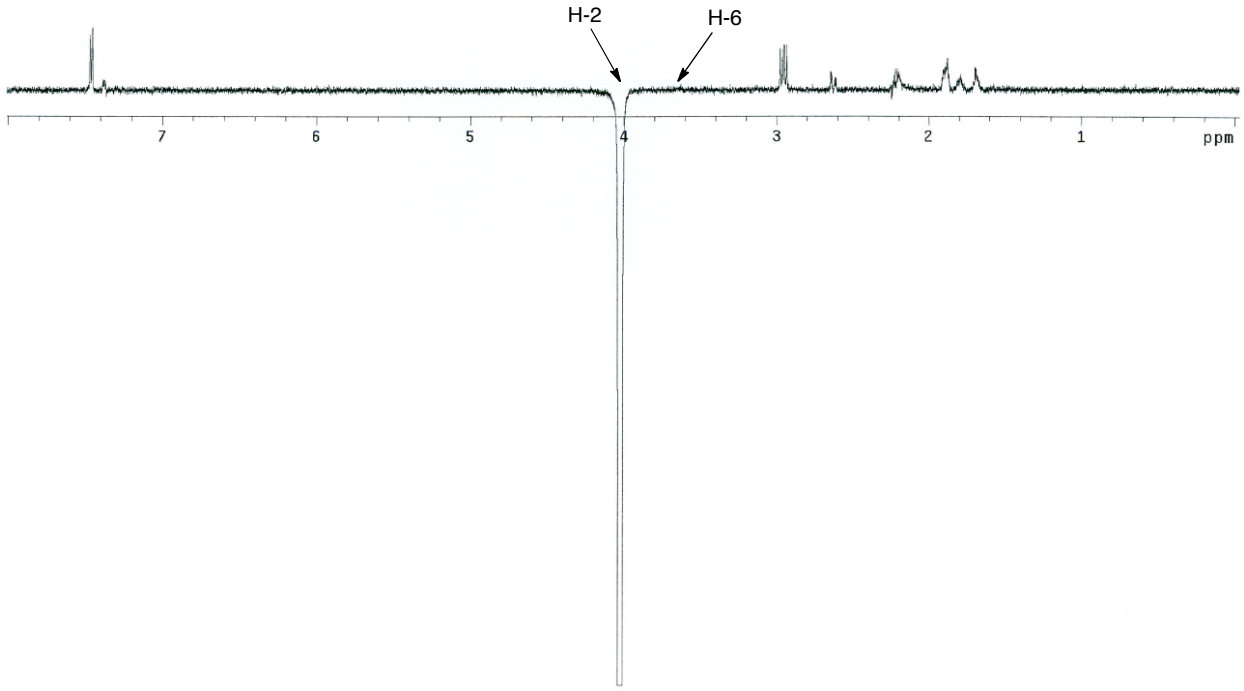
^{13}CNMR



1DNOE-3.62 (H-6)



1DNOE-4.05 (H-2)

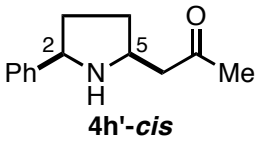


6. 4h

For **4h**, Et_3N (1.0 equiv.) was added in before the hydrogenation, in order to prevent the oligomerization of the product.

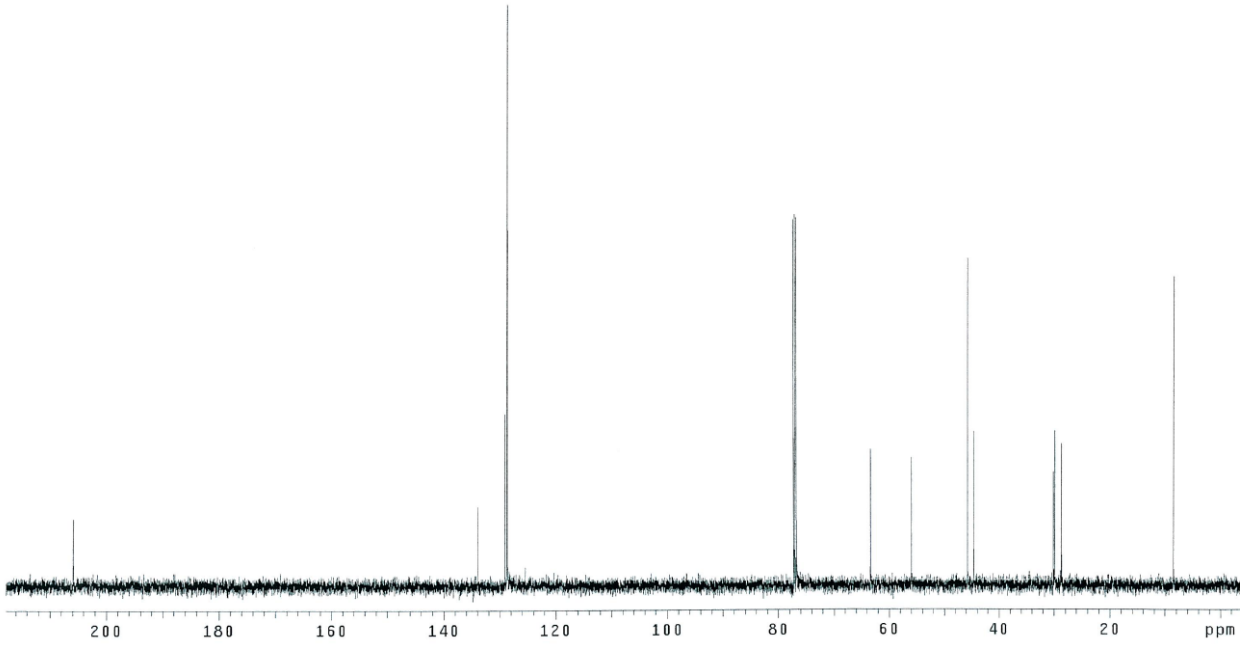
4h'-cis

^{1}HNMR

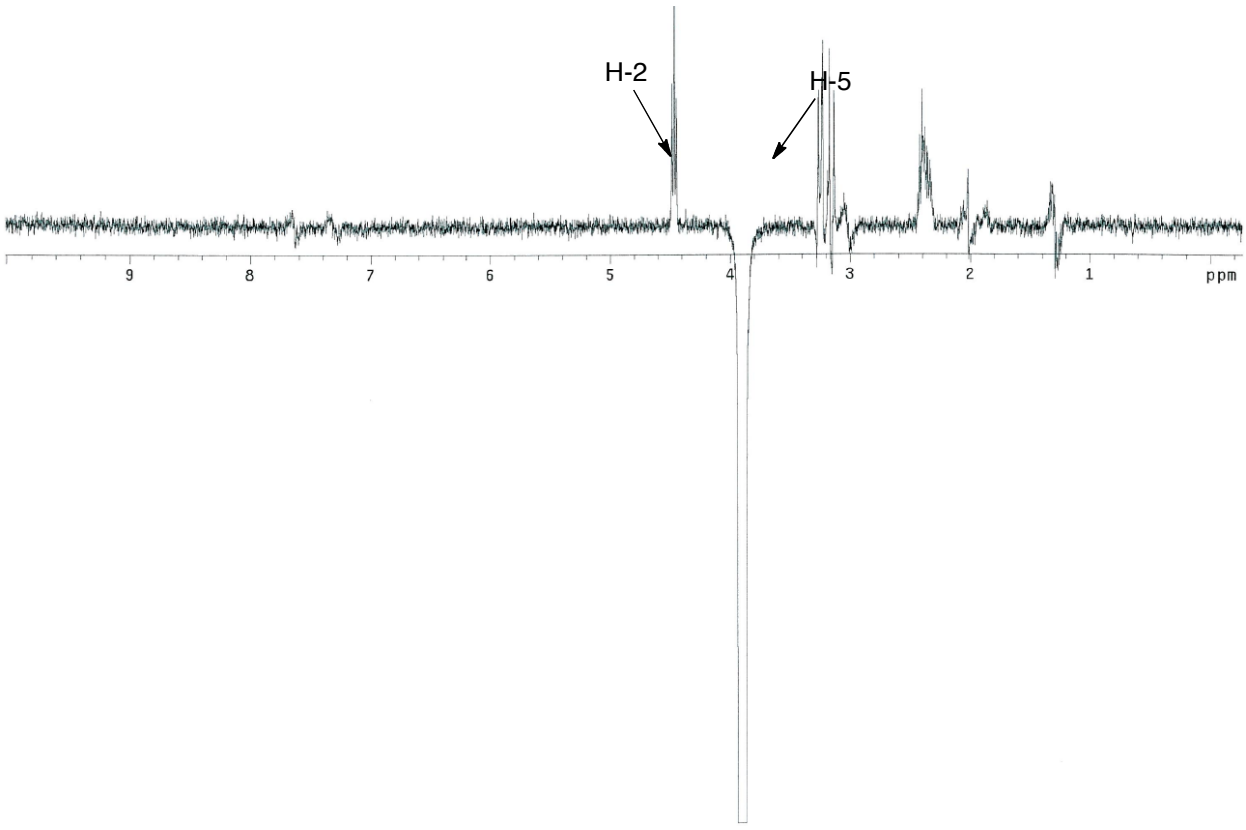


4h'-*cis*

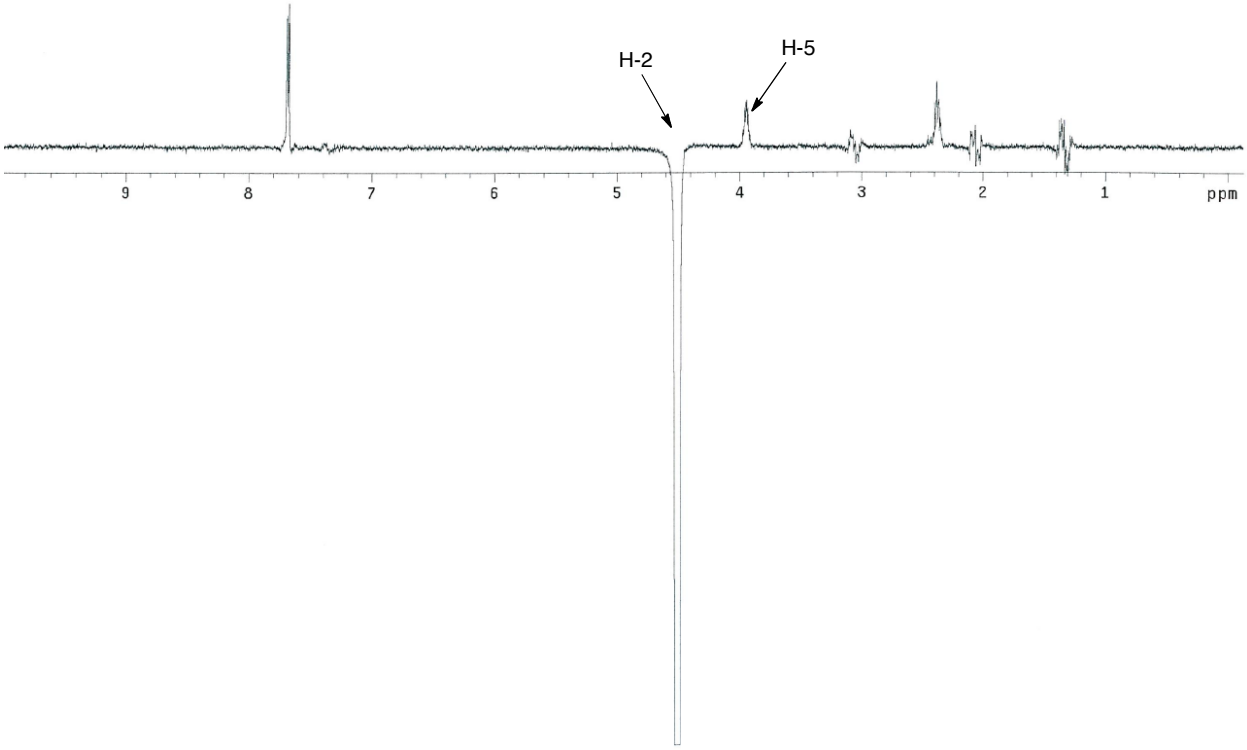
^{13}CNMR



1DNOE-3.91 (H-5)

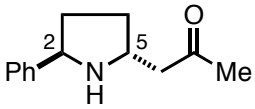


1DNOE-4.43 (H-2)



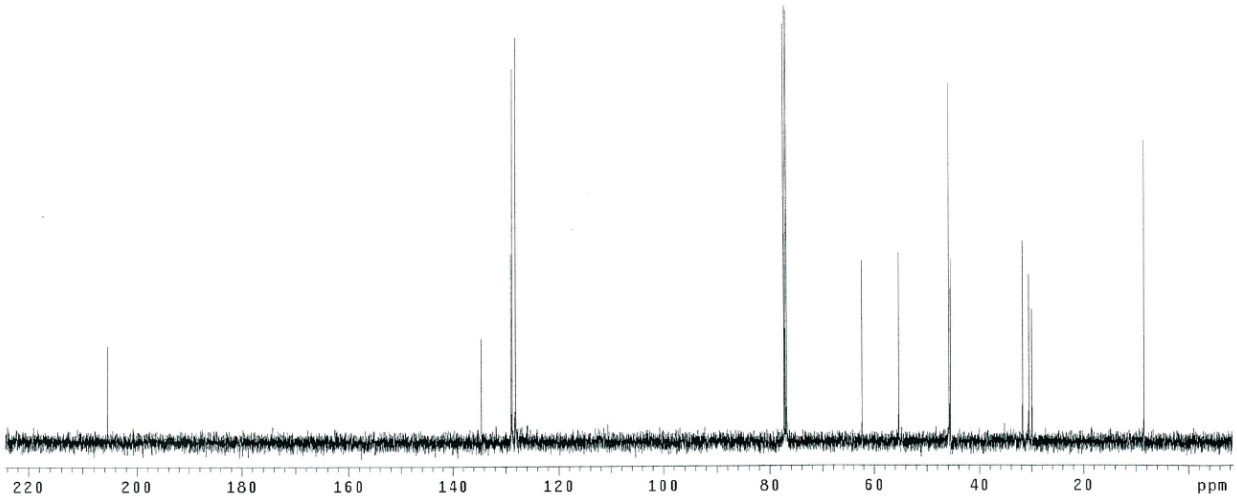
4h'-trans

^{1}HNMR

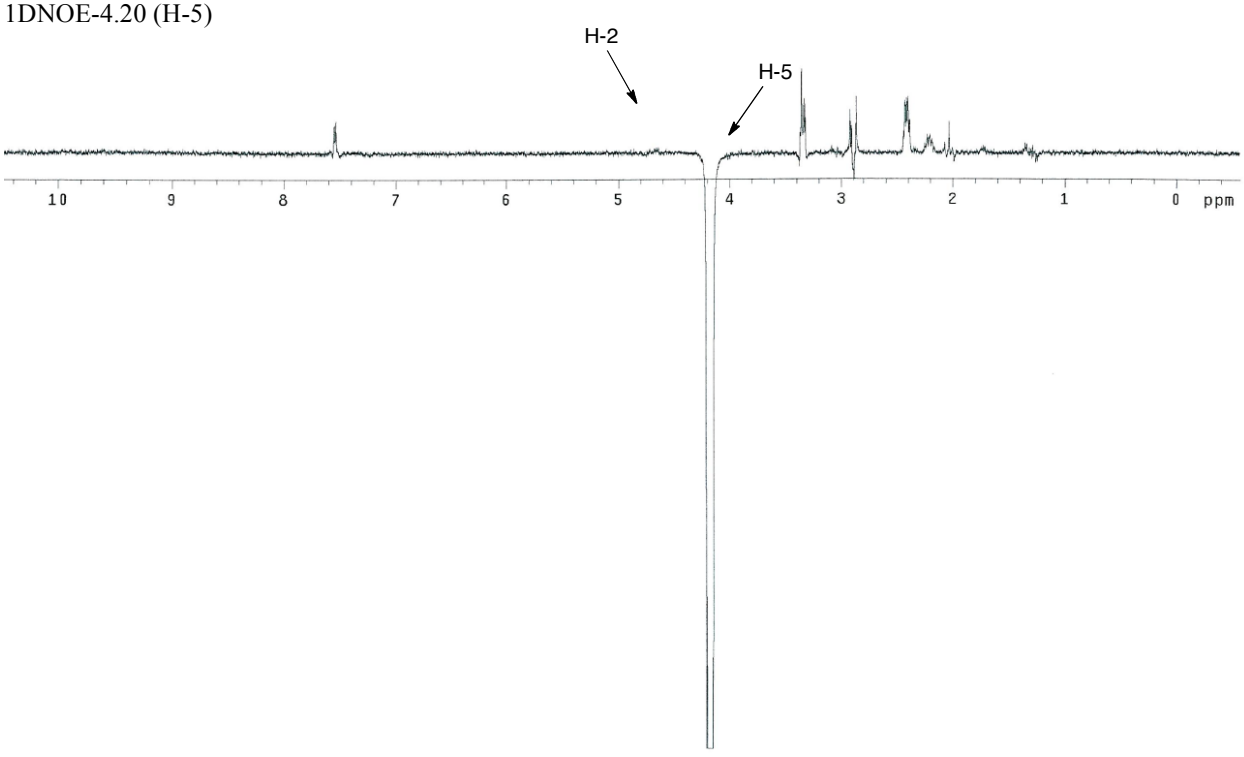


4h'-*trans*

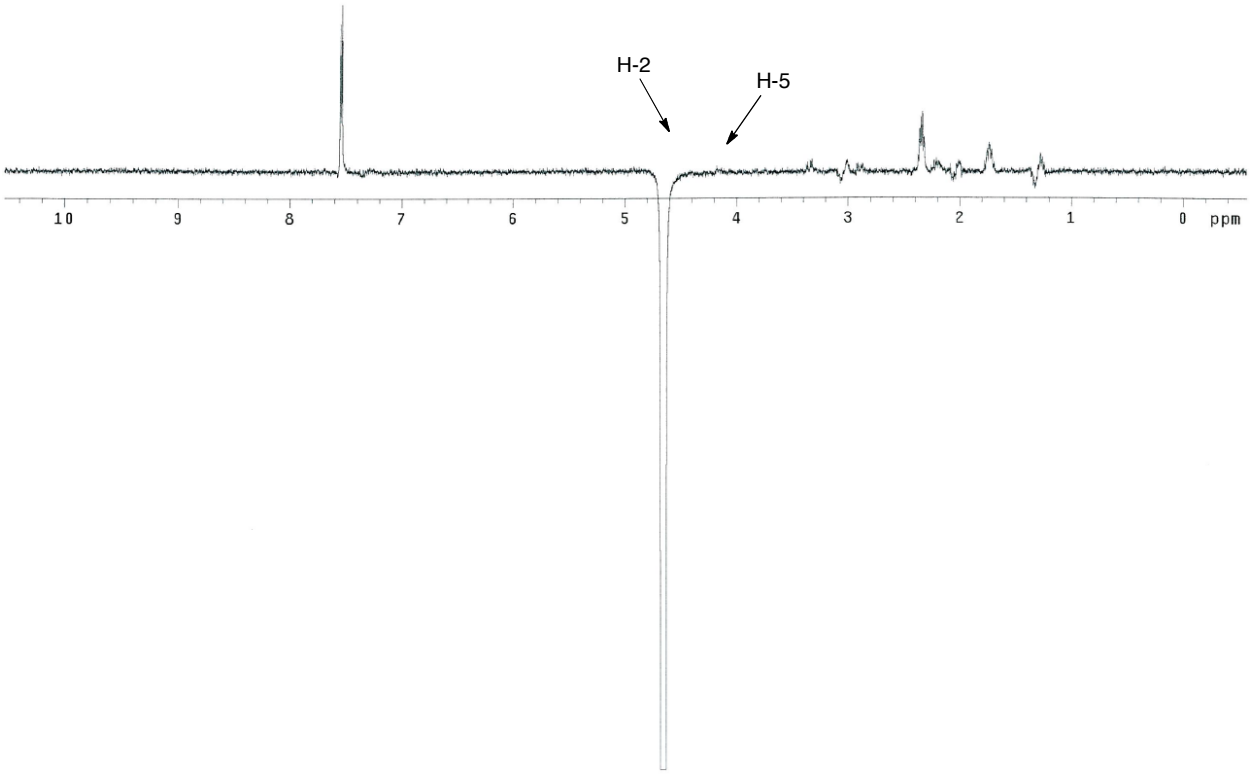
^{13}CNMR



1DNOE-4.20 (H-5)



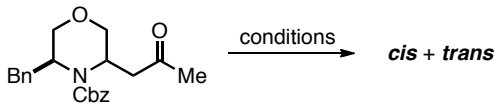
1DNOE-4.81 (H-2)



G. Mechanistic probing of the intramolecular aza-Michael reaction

In order to probe the reaction mechanism, several experiments were carried out. When **2a-*cis*** was resubjected to both Pd (II) and TfOH conditions, it remained stable. Treatment of the strong Lewis acid BF_3 only lead to the decomposition without forming any *trans* isomer. On the other hand, **2a-*trans*** could be slowly transformed into *cis* isomer under both TfOH and BF_3 conditions, although severe decomposition was detected in both cases. Finally, the Pd (II) complex did not transform the *trans* isomer into *cis* configuration. Although it has been extensively studied and discussed in the literature, the mechanism involving Pd(II) catalysis is still not clear to account for the reactivity and stereoselectivity. Further mechanistic investigations concerning both pathways are ongoing in our laboratories and will be reported in due course.

Table 2. Probing the reaction mechanism[a]

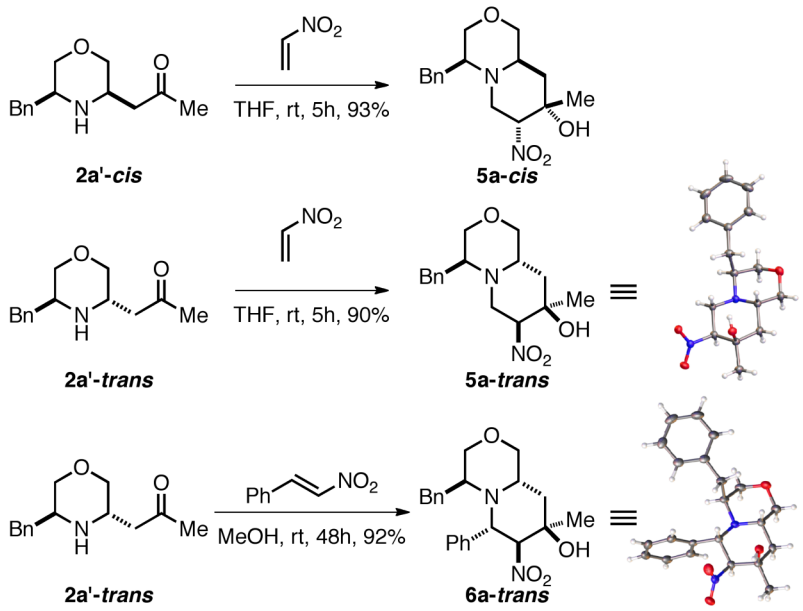


2a-*cis* or 2a-*trans*

	cat. (0.2 eq.)	Time (h)	yield[b] (%)	*d.r.*[c] (*cis*:*trans*)
2a-*cis*	TfOH	12	93	*cis* only
	$Pd(MeCN)_2Cl_2$	12	85	*cis* only
	$BF_3•Et_2O$	12	55	*cis* only
2a-*trans*	TfOH	12	86	1:9
	$Pd(MeCN)_2Cl_2$	12	81	*trans* only
	$BF_3•Et_2O$	12	29	1:6

[a] the reactions were conducted in DCM at room temperature with the 0.1M concentration of **2a**; [b] NMR yield; [c] determined by crude NMR.

H. Syntheses of more complex hetero bicyclic molecules



The nitro alkenes were prepared according to literature procedures. (D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, R. Iyengar, *J. Org. Chem.* **1980**, *45*, 1185-1189. G. Demicheli, R. Maggi, A. Mazzacani, P. Righi, G. Sartoria, F. Bigia, *Tetrahedron Lett.* **2001**, *42*, 2401-2403.)

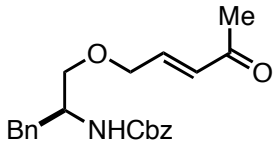
Syntheses of **5a-*cis*** and **5a-*trans***.

Morpholine **2a'-*cis*** (200 mg, 0.87 mmol) was dissolved in THF (9 mL, 0.1 M). Nitroethene (76 mg, 1.0 mmol, 1.2 equiv.) was then added to the solution and the reaction mixture was stirred for 5 hours at room temperature. Once TLC indicated consumption of the starting material the solvent was removed under reduced pressure to provide the crude residue. Flash silica gel chromatography (Ethyl Acetate/ Hexane 20:80) afforded 247 mg (93% yield) of the product **5a-*cis*** (*d.r.* 91:9). **5a-*trans*** was synthesized through the same procedure, in 90% yield with *d.r.* > 95:5.

Syntheses of **6a-*trans*.**

Morpholine **2a'-*trans*** (200 mg, 0.87 mmol) was dissolved in MeOH (9 mL, 0.1 M) at room temperature and β-nitro styrene (155 mg, 1.0 mmol, 1.2 equiv.) was added and the reaction mixture was stirred for 2 days. Once TLC indicated consumption of the starting material the solvent was removed under reduced pressure. Flash silica gel chromatography (Ethyl Acetate/ Hexane 20:80) provided 305 mg (92% yield) of the product **6a-*trans***. When **2a'-*cis*** was applied to the same condition, no reaction occurred over a week. Additional base promoted the decomposition of nitro alkene, without any desired product formation.

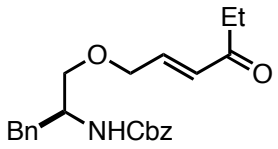
Compounds Characterization



1a

(S, E)-benzyl (1-((4-oxopent-2-en-1-yl)oxy)-3-phenylpropan-2-yl)carbamate (1a).

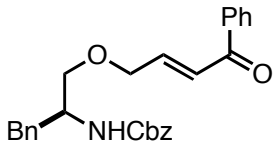
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 85% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.19 (m, 10 H), 6.75 (dt, J = 16.0 Hz, J = 4.5 Hz 1 H), 6.29 (d, J = 11.0, 1 H), 5.09 (s, 2 H), 4.17-4.08 (m, 2 H), 4.05 (bs, 1 H), 3.44-3.38 (m, 2 H), 2.93-2.86 (m 2 H), 2.27 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.0, 155.8, 142.5, 137.6, 136.4, 130.3, 129.3, 128.5, 128.1, 128.1, 126.5, 70.8, 69.8, 66.7, 52.0, 37.7, 27.3; HRMS Calculated for $[C_{22}H_{25}NO_4+H]^+$: 368.18564, Found: 368.18537.



1b

(S,E)-benzyl (1-((4-oxohex-2-en-1-yl)oxy)-3-phenylpropan-2-yl)carbamate (1b).

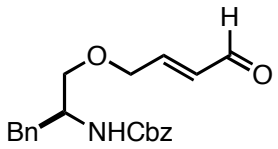
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 88% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.19 (m, 10 H), 6.77 (dt, J = 16.0 Hz, J = 5.0 Hz, 1 H), 6.31 (d, J = 16.0 Hz, 1 H), 5.10 (bs, 1 H), 5.08 (s, 2 H), 4.16-4.06 (m, 2 H), 4.05 (bs, 1 H), 3.43-3.37 (m, 2 H), 2.57 (q, J = 7.5 Hz, 2 H), 1.10 (t, J = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.4, 155.7, 141.2, 137.2, 136.4, 129.3, 129.1, 128.5, 128.1, 128.0, 126.5, 70.7, 69.8, 66.6, 51.9, 37.7, 33.7, 7.9; HRMS Calculated for $[C_{23}H_{27}NO_4+H]^+$: 382.20128, Found: 382.19960.



1c

(S,E)-benzyl (1-((4-oxo-4-phenylbut-2-en-1-yl)oxy)-3-phenylpropan-2-yl)carbamate (1c).

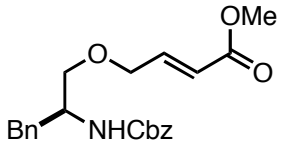
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 78% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (d, J = 13.0 Hz, 2 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 2 H), 7.36-7.21 (m, 10 H), 7.13 (d, J = 15.0 Hz, 1 H), 7.02 (dt, J = 15.0 Hz, J = 2.5 Hz, 1 H), 5.12-5.06 (m, 2 H), 4.27-4.17 (m, 2 H), 4.09 (bs, 1 H), 3.50-3.44 (m, 2 H), 2.96-2.90 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.2, 155.8, 143.9, 137.6, 137.5, 136.4, 132.8, 129.3, 128.6, 128.5, 128.4, 128.1, 128.0, 126.5, 125.0, 70.9, 70.2, 66.7, 66.7, 52.4, 37.8; HRMS Calculated for $[C_{27}H_{27}NO_4+H]^+$: 430.20128, Found: 430.20165.



1d

(S,E)-benzyl (1-((4-oxobut-2-en-1-yl)oxy)-3-phenylpropan-2-yl)carbamate (1d).

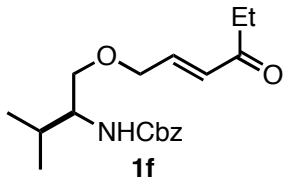
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 75% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.57 (d, J = 8.0 Hz, 1 H), 7.37-7.18 (m, 10 H), 6.79 (dt, J = 16.0 Hz, J = 6.0 Hz, 1 H), 6.34 (dd, J = 16.0 Hz, J = 8.0 Hz, 1 H), 5.08 (s, 2 H), 4.26-4.17 (m, 2 H), 4.06 (bs, 1 H), 3.45-3.40 (m, 2 H), 2.95-2.85 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.0, 155.7, 152.4, 137.5, 136.4, 131.7, 129.2, 128.5, 128.4, 128.1, 128.0, 126.6, 70.9, 69.6, 66.7, 51.9, 37.6; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16973.



1e

(S,E)-methyl 4-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropoxy)but-2-enoate (1e)

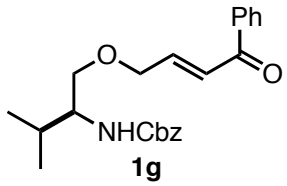
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 89% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.18 (m, 10 H), 6.94 (dt, J = 16.5 Hz, J = 4.0 Hz, 1 H), 6.06 (d, J = 16.5 Hz, 1 H), 5.12 (bs, 1 H), 5.10-5.07 (m, 2 H), 4.13-4.00 (m, 3 H), 3.74 (s, 3 H), 3.43-3.36 (m, 2 H), 2.94-2.85 (m 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 155.7, 144.0, 137.6, 136.4, 129.2, 128.4, 128.3, 128.0, 127.9, 126.4, 120.8, 77.2, 70.7, 69.5, 66.6, 52.0, 51.5, 37.6; HRMS Calculated for $[C_{22}H_{25}NO_5+H]^+$: 385.96277, Found: 328.96299.



1f

(S,E)-benzyl (3-methyl-1-((4-oxopent-2-en-1-yl)oxy)butan-2-yl)carbamate (1f).

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 86% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.30 (m, 5 H), 6.76 (dt, J = 16.0 Hz, J = 4.0 Hz, 1 H), 6.30 (d, J = 11.0 Hz, 1 H), 5.10 (s, 2 H), 5.02 (d, J = 8.5 Hz, 1 H), 4.16-4.08 (m, 2 H), 3.60 (bs, 1 H), 3.59-3.56 (m, 1 H), 2.58-2.53 (m, 2 H), 1.92-1.87 (m, 1 H), 1.09 (t, J = 7.5 Hz, 3 H), 0.96-0.93 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.5, 156.2, 141.3, 136.5, 128.9, 128.4, 128.0, 127.9, 71.0, 69.8, 66.5, 56.0, 33.6, 29.4, 19.4, 18.5, 7.8; HRMS Calculated for $[C_{19}H_{27}NO_4+H]^+$: 334.20128, Found: 334.20162.

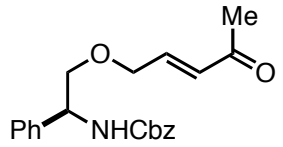


1g

(S,E)-benzyl (3-methyl-1-((4-oxo-4-phenylbut-2-en-1-yl)oxy)butan-2-yl)carbamate (1g)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 86% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (d, J = 7.5 Hz, 1 H), 7.55 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.34-7.28 (m, 5 H), 7.11 (d, J = 16.5 Hz, 1 H), 7.01 (dt, J = 16.5 Hz, J = 3.5 Hz, 1 H), 5.14-5.07 (m, 2 H), 5.00 (d, J = 7.5 Hz, 1 H), 4.27-4.18 (m, 2 H), 3.66 (bs, 1 H), 3.63-3.53 (m, 2 H), 1.96-1.92 (m, 1 H), 0.99-0.95 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.2, 156.3, 144.1, 137.5, 136.5, 132.8, 128.5, 128.4, 128.3, 128.0,

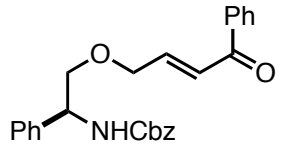
127.9, 124.8, 71.3, 70.2, 66.6, 56.1, 29.5, 19.5, 18.6; HRMS Calculated for $[C_{23}H_{27}NO_4+H]^+$: 382.20129, Found: 382.20106.



1h

(S,E)-benzyl (2-((4-oxopent-2-en-1-yl)oxy)-1-phenylethyl)carbamate (1h).

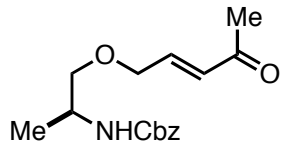
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 89% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39-7.29 (m, 5 H), 6.69 (dt, J = 16.0 Hz, J = 4.5 Hz, 1 H), 6.19 (d, J = 11.0 Hz, 1 H), 5.57 (bs, 1 H), 5.15-5.08 (m, 2 H), 4.96 (bs, 1 H), 4.21-4.09 (m, 2 H), 3.80-3.71 (m, 2 H), 2.24 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 155.8, 142.1, 136.3, 130.2, 128.5, 128.4, 128.1, 127.9, 1.7.6, 126.6, 73.6, 69.8, 66.8, 54.6, 27.3; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16983.



1i

(S,E)-benzyl (2-((4-oxo-4-phenylbut-2-en-1-yl)oxy)-1-phenylethyl)carbamate (1i)

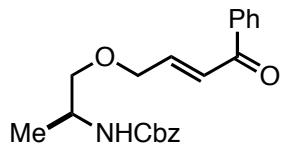
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 80% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.86 (d, J = 7.5 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.38-7.28 (m, 5 H), 7.03-6.99 (m, 1 H), 6.98-6.38 (m, 1 H), 5.58, (bs, 1 H), 5.13-5.06 (m, 2 H), 4.98 (bs, 1 H), 4.31-4.16 (m, 1 H), 3.83-3.79 (m, 1 H), 3.76 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.9, 155.8, 143.6, 137.4, 136.3, 132.9, 128.6, 128.5, 128.4, 128.1, 127.7, 126.7, 124.7, 73.7, 70.1, 66.9, 54.8; HRMS Calculated for $[C_{26}H_{25}NO_4+H]^+$: 416.18564, Found: 416.18501.



1j

(S,E)-benzyl (1-((4-oxopent-2-en-1-yl)oxy)propan-2-yl)carbamate (1j)

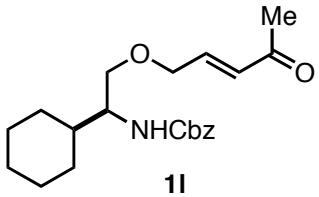
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 81% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.30 (m, 5 H), 6.74 (dd, J = 16.0 Hz, J = 4.5 Hz, 1 H), 6.28 (d, J = 16.0 Hz, 1 H), 5.10 (bs, 2 H), 5.01-5.99 (m, 1 H), 4.19-4.12 (m, 2 H), 3.97-3.93 (m, 1 H), 3.49-3.43 (m, 1 H), 2.26 (s, 3 H), 1.22 (d, 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.1, 155.7, 142.7, 136.4, 130.1, 128.5, 128.4, 128.0, 73.9, 70.9, 69.7, 66.6, 46.6, 27.2, 17.8; HRMS Calculated for $[C_{16}H_{21}NO_4+Na]^+$: 314.13628, Found: 314.13359.



1k

(S,E)-benzyl (1-((4-oxo-4-phenylbut-2-en-1-yl)oxy)propan-2-yl)carbamate (1k)

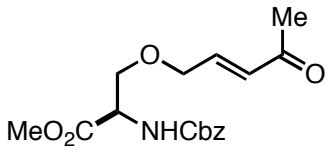
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 76% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.95 (d, J = 6.5 Hz, 2 H), 7.56 (t, J = 6.5 Hz, 1 H), 7.46 (t, J = 6.5 Hz, 2 H), 7.35-7.29 (m, 5 H), 7.13 9d, J = 15.5 Hz, 1 H), 7.01 (dt, J = 15.5 Hz, J = 4.0 Hz, 1 H), 5.14-5.07 (m, 2 H), 4.97 (bs, 1 H), 4.29-4.21 (m, 2 H), 3.98 (bs, 1 H), 3.53-3.48 (m, 2 H), 1.25 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.2, 155.8, 144.0, 137.6, 136.5, 132.9, 128.6, 128.5, 128.4, 128.1, 124.9, 74.1, 70.2, 66.6, 46.7, 17.9; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16983.



1l

(S,E)-benzyl (1-cyclohexyl-2-((4-oxopent-2-en-1-yl)oxy)ethyl)carbamate (1l)

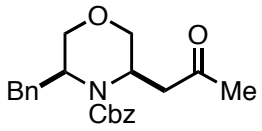
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 76% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.29 (m, 5 H), 6.74 (dt, J = 16.0 Hz, J = 4.0 Hz, 1 H), 6.26 (d, J = 16.0 Hz, 1 H), 5.13-5.07 (m, 2 H), 4.93 (d, J = 9.0 Hz, 1 H), 4.17-4.10 (m, 2 H), 3.61-3.47 (m, 3 H), 2.26 (s, 3 H), 1.81-1.64 (m, 6 H), 1.56-1.53 (m 1 H), 1.28-0.96 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.8, 156.3, 142.8, 136.5, 130.2, 128.5, 128.0, 70.8, 69.7, 66.7, 55.4, 39.1, 29.8, 29.1, 27.2, 26.2, 26.1, 26.0; HRMS Calculated for $[C_{21}H_{29}NO_4+H]^+$: 360.21693, Found: 360.21682.



1m

(R,E)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((4-oxopent-2-en-1-yl)oxy)propanoate (1m)

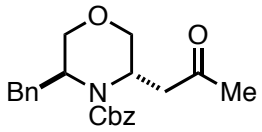
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 79% over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.29 (m, 5 H), 6.68 (dt, J = 16.0 Hz, J = 4.0 Hz, 1 H), 6.20 (dt, J = 16.0 Hz, J = 1.5 Hz, 1 H), 5.79 (d, J = 8.5 Hz, 1 H), 5.12 (s, 2 H), 4.55-4.52 (m, 1 H), 4.18-4.09 (m, 2 H), 3.92 (dd, J = 9.0 Hz, J = 3.5 Hz, 1 H), 3.76 (s, 3 H), 3.73 (dd, J = 9.0 Hz, J = 3.5 Hz, 1 H) 2.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.7, 170.3, 155.7, 141.8, 135.9, 130.1, 128.3, 128.0, 127.8, 77.2, 70.5, 69.7, 66.8, 54.8, 52.4, 27.0; HRMS Calculated for $[C_{17}H_{21}NO_6+H]^+$: 336.14417, Found: 336.14435.



2a-*cis*

(3S,5R)-benzyl 3-benzyl-5-(2-oxopropyl)morpholine-4-carboxylate (2a-*cis*)

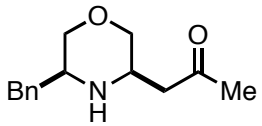
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-7.08 (m, 10 H), 5.20 (s, 2 H), 4.41 (dd, *J* = 8 Hz, *J* = 1.5 Hz, 1 H), 3.95 (bs, 1 H), 3.85 (bs, 1 H), 3.72 (d, *J* = 11 Hz, 1 H), 3.58 (d, *J* = 11 Hz, 1 H), 3.31 (dd, *J* = 12 Hz, *J* = 2.5 Hz, 1 H), 3.20-3.15 (m, 1 H), 3.00-2.96 (m, 1 H), 2.82 (bs, 1 H), 2.65 (bs, 1 H), 2.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 155.9, 138.4, 136.3, 129.4, 128.6, 128.5, 128.3, 126.5, 69.3, 67.5, 66.7, 52.8, 46.1, 39.3, 30.3; IR (neat, cm^{-1}): 3029, 2974, 2936, 2865, 1693, 1381, 1325, 1279, 1110, 1073, 1034, 740, 702; HRMS Calculated for $[C_{22}H_{25}NO_4+H]^+$: 368.18564, Found: 368.18537; $[\alpha]_D^{26}$ = -68.3° (c = 1.0 $CHCl_3$).



2a-*trans*

(3S,5R)-benzyl 3-benzyl-5-(2-oxopropyl)morpholine-4-carboxylate (2a-*trans*)

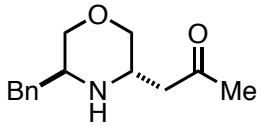
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.31 (m, 4 H), 7.25-7.13 (m, 6 H), 5.02 (s, 2 H), 4.36-4.32 (m, 1 H), 4.02 (t, *J* = 6.5 Hz, 1 H), 3.92 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1 H), 3.67 (d, *J* = 11.0 Hz, 1 H), 3.57 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1 H), 3.52 (dd, *J* = 10.0 Hz, J = 8.0 Hz, 1 H), 3.11 (d, J = 15.0 Hz, 1 H), 3.01 (D, J = 7.0 Hz, 1 H), 2.42 (d, *J* = 15.0 Hz, 1 H), 2.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.5, 155.4, 138.2, 136.1, 129.5, 128.5, 128.4, 1.8.3, 128.2, 126.4, 69.3, 67.2, 65.9, 55.0, 47.5, 44.9, 37.3, 30.1; IR (neat, cm^{-1}): 3029, 2974, 2938, 2865, 1702, 1381, 1325, 1279, 1110, 1073, 1034, 740, 702; HRMS Calculated for $[C_{22}H_{25}NO_4+H]^+$: 368.18564, Found: 368.18537. $[\alpha]_D^{26}$ = -36.9° (c = 1.0 $CHCl_3$).



2a'-*cis*

1-((3R,5S)-5-benzylmorpholin-3-yl)propan-2-one (2a'-*cis*)

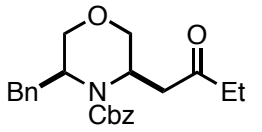
Colorless oil (yield: 99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31 (t, *J* = 7.5 Hz, 2 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.5 Hz, 2 H), 3.78 (dd, *J* = 11.5 Hz, *J* = 2.5 Hz, 1 H), 3.70 (dd, *J* = 11.5 Hz, *J* = 2.5 Hz, 1 H), 3.28-3.14 (m, 5 H), 2.65-2.54 (m, 2 H), 2.44 (d, *J* = 6.0 Hz, 2 H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.8, 137.2, 128.9, 128.6, 126.6, 71.7, 70.8, 56.0, 50.9, 45.0, 38.6, 30.4; IR (neat, cm^{-1}): 3327, 3061, 3027, 2959, 2886, 2841, 1715, 1451, 1364, 1338, 1312, 1170, 1105, 757, 703; HRMS Calculated for $[C_{14}H_{19}NO_2+H]^+$: 234.14886, Found: 234.14840. $[\alpha]_D^{26}$ = 73.9° (c = 1.0 $CHCl_3$).



2a'-*trans*

1-((3S,5S)-5-benzylmorpholin-3-yl)propan-2-one (2a'-*trans*)

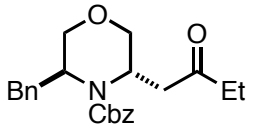
Colorless oil (yield: 98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32 (t, J = 7.5 Hz, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.20 (d, J = 7.5 Hz, 2 H), 3.74 (d, J = 11.0 Hz, 2 H), 3.53-3.48 (m, 1 H), 3.45 (dd, J = 11.0 Hz, J = 6.0 Hz, 1 H), 3.41 (dd, J = 11.0 Hz, J = 6.0 Hz, 1 H), 3.11-3.09 (m, 1 H), 2.82-2.73 (m, 2 H), 2.66-2.58 (m, 2 H), 2.20 (bs, 1 H), 2.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.4, 138.3, 129.1, 128.6, 126.4, 71.2, 71.0, 51.9, 46.4, 44.7, 38.1, 30.6; IR (neat, cm^{-1}): 3324, 3063, 3026, 2958, 2918, 2850, 1709, 1455, 1405, 1364, 1263, 1164, 1102, 757, 702; HRMS Calculated for $[C_{14}H_{19}NO_2+H]^+$: 234.14886, Found: 234.14846. $[\alpha]_D^{26}$ = 24.2° (c = 1.0 $CHCl_3$).



2b-*cis*

(3S,5R)-benzyl 3-benzyl-5-(2-oxobutyl)morpholine-4-carboxylate (2b-*cis*)

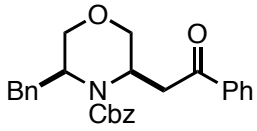
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-7.09 (m, 10 H), 5.20 (s, 2 H), 4.41 (d, J = 10.0 Hz, 1 H), 3.95 (bs, 1 H), 3.86 (bs, 1 H), 3.58 (d, J = 12.0 Hz, 1 H), 3.58 (d, J = 11.0 Hz, 1 H), 3.31 (dd, J = 11.0 Hz, J = 3.0 Hz, 1 H), 3.17-3.12 (m, 1 H), 2.99 (t, J = 12.0 Hz, 1 H), 2.82 (d, J = 10.0 Hz, 1 H), 2.61 (bs, 1 H), 2.44 (bs, 2 H), 1.05 (t, J = 10.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.0, 155.1, 138.5, 136.3, 129.4, 128.6, 128.2, 126.5, 69.4, 67.5, 66.7, 52.9, 46.3, 44.8, 39.1, 36.2, 7.6. 0 IR (neat, cm^{-1}): 3029, 2973, 2937, 2863, 1693, 1381, 1326, 1278, 1109, 1077, 1033, 744, 700; HRMS Calculated for $[C_{23}H_{27}NO_4+H]^+$: 382.20128, Found: 382.19960. $[\alpha]_D^{26}$ = 69.6° (c = 1.0 $CHCl_3$).



2b-*trans*

(3S,5S)-benzyl 3-benzyl-5-(2-oxobutyl)morpholine-4-carboxylate (2b-*trans*)

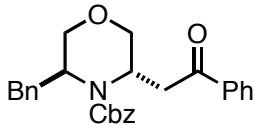
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.32 (m, 4 H), 7.25-7.13 (m, 6 H), 5.07-5.02 (m, 2 H), 4.38-4.34 (m, 1 H), 4.02-4.00 (m, 1 H), 3.93 (dd, J = 11.0 Hz, J = 3.0 Hz, 1 H), 3.66 (d, J = 11.0 Hz, 1 H), 3.56 (dd, J = 12.0 Hz, J = 3.0 Hz, 1 H), 3.55-3.52 (m, 1 H), 3.08 (bs, 1 H), 3.01 (d, J = 9.0 Hz, 2 H), 2.46 (bs, 1 H), 2.42- 2.36 (m, 2 H), 1.05 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.8, 155.4, 138.2, 136.2, 129.5, 128.5, 128.4, 128.2, 128.1, 126.4, 69.1, 67.2, 65.7, 55.6, 47.7, 43.8, 37.5, 35.9, 31.5, 7.6; IR (neat, cm^{-1}): 3029, 2773, 2937, 1704, 1497, 1455, 1412, 1356, 1313, 1273, 1216, 1122, 1068, 747, 700; HRMS Calculated for $[C_{23}H_{27}NO_4+H]^+$: 382.20128, Found: 382.19960. $[\alpha]_D^{26}$ = 33.3° (c = 1.0 $CHCl_3$).



2c-*cis*

(3S,5R)-benzyl 3-benzyl-5-(2-oxo-2-phenylethyl)morpholine-4-carboxylate (2c-*cis*)

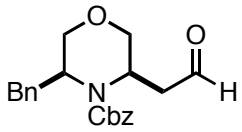
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.98 (bs, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.38-7.20 (m, 10 H), 5.20 (m, 2 H), 4.64 (d, *J* =11.0 Hz, 1 H), 4.01-3.98 (m, 2 H), 3.78 (d, *J* = 7.0 Hz, 1 H), 3.77-3.63 (m, 2 H), 3.36 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1 H), 3.16 (bs, 1 H), 3.11 (t, *J* = 12.0 Hz, 2 H), 2.93 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8, 155.2, 138.5, 136.6, 136.3, 133.3, 129.5, 128.7, 128.6, 128.5, 128.0, 126.6, 69.3, 67.6, 66.9, 52.99, 466.8, 41.4, 39.5; IR (neat, cm^{-1}): 3062, 3032, 2927, 2861, 1690, 1598, 1581, 1497, 1450, 1412, 1283, 1217, 1179, 1134, 1097, 1064, 1026, 1004, 898, 760, 698, 581; HRMS Calculated for $[C_{27}H_{27}NO_4+H]^+$: 430.20128, Found: 430.20165. $[\alpha]_D^{26}$ = 52.9° (c = 1.0 $CHCl_3$).



2c-*trans*

(3S,5S)-benzyl 3-benzyl-5-(2-oxo-2-phenylethyl)morpholine-4-carboxylate (2c-*trans*)

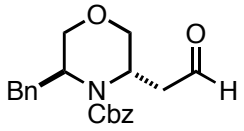
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 7.5 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.32-7.16 (m, 10 H), 5.07-5.00 (m, 2 H), 4.60-4.59 (m, 1 H), 4.08-4.06 (m, 1 H), 3.71-3.67 (m, 2 H), 3.11-3.01 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.0, 155.5, 138.2, 136.8, 136.1, 133.0, 129.5, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 126.5, 68.4, 67.3, 65.4, 55.1, 48.3, 40.8, 38.0. IR (neat, cm^{-1}): 3062, 3031, 2961, 2926, 2860, 1691, 1597, 1495, 1450, 1407, 1366, 1283, 1217, 1116, 1054, 1002, 757, 698; HRMS Calculated for $[C_{27}H_{27}NO_4+H]^+$: 430.20128, Found: 430.20165. $[\alpha]_D^{26}$ = 74.3° (c = 1.0 $CHCl_3$).



2d-*cis*

(3S,5R)-benzyl 3-benzyl-5-(2-oxoethyl)morpholine-4-carboxylate (2d-*cis*)

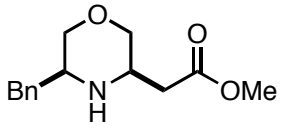
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.79 (s, 1 H), 7.40-7.18 (m, 10 H), 5.24-5.16 (m, 2 H), 4.54-4.51 (m, 1 H), 3.97 (bs, 1 H), 3.84 (d, *J* = 11.0 Hz, 1 H), 3.74 (d, *J* = 11.5 Hz, 1 H), 3.62 (dd, *J* = 11.5 Hz, *J* = 2.5 Hz, 1 H), 3.35-3.31 (m, 1 H), 3.16-3.11 (m, 1 H), 3.00 (t, *J* = 12.5 Hz, 1 H), 2.83-2.79 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.7, 155.1, 140.9, 138.3, 136.1, 129.4, 128.7, 128.6, 128.5, 128.4, 128.3, 126.6, 126.5, 69.6, 67.7, 67.5, 66.8, 55.0, 52.8, 47.5, 45.1, 39.5; IR (neat, cm^{-1}): 3063, 3028, 2960, 2857, 1696, 1494, 1454, 1410, 1277, 1107, 1072, 746, 700; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16983. $[\alpha]_D^{26}$ = -56.9° (c = 1.0 $CHCl_3$).



2d-*trans*

(3S,5S)-benzyl 3-benzyl-5-(2-oxoethyl)morpholine-4-carboxylate (2d-*trans*)

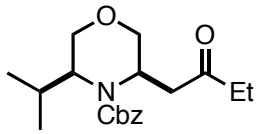
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.75 (s, 1 H), 7.39-7.32 (m, 5 H), 7.26-7.17 (m, 3 H), 7.12-7.10 (m, 2 H), 5.06-4.98 (m, 2 H), 4.34-4.29 (m, 1 H), 4.08-4.04 (m, 1 H), 4.93 (dt, J = 12 Hz, J = 3.5 Hz, 1 H), 3.69 (d, J = 12 Hz, 1 H), 3.55 (dd, J = 11.5 Hz, J = 3.5 Hz, 1 H), 3.49-3.44 (m, 1 H), 3.05-2.95 (m, 3 H), 2.39 (d, J = 6.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.1, 155.8, 137.9, 135.9, 129.4, 128.6, 128.5, 128.4, 128.3, 126.5, 70.0, 67.5, 66.2, 55.0, 46.7, 44.8, 36.9; IR (neat, cm^{-1}): 3063, 3028, 2960, 2858, 1696, 1496, 1454, 1412, 1313, 1274, 1218, 1311, 1059, 748, 700; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16969. $[\alpha]_D^{26}$ = -52.1° (c = 1.0 $CHCl_3$).



2e'-*cis*

methyl 2-((3R,5S)-5-benzylmorpholin-3-yl)acetate (2e'-*cis*)

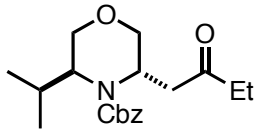
Filter after hydrogenation and no flash chromatography was applied, colorless oil (yield: 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31-7.19 (m, 5 H), 3.70 (s, 3 H), 3.49-3.40 (m, 3 H), 3.28-3.22 (m, 2 H), 2.78 (dd, J = 13.5 Hz, J = 5.5 Hz, 1 H), 2.60 (dd, J = 13.5 Hz, J = 7.5 Hz, 1 H), 2.47 (bs, 1 H), 2.42 (t, J = 7.5 Hz, 2 H), 1.94-1.86 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9, 138.6, 129.2, 129.1, 128.5, 128.4, 126.3, 74.7, 70.0, 52.4, 51.5, 40.3, 30.5, 25.0; IR (neat, cm^{-1}): 3327, 3061, 3027, 2959, 2886, 2841, 1693, 1455, 1362, 1336, 1310, 1172, 1104, 757, 702; HRMS Calculated for $[C_{14}H_{19}NO_3+H]^+$: 250.14377, Found: 250.14396. $[\alpha]_D^{26}$ = 57.9° (c = 1.0 $CHCl_3$).



2f-*cis*

(3S,5R)-benzyl 3-isopropyl-5-(2-oxobutyl)morpholine-4-carboxylate (2f-*cis*)

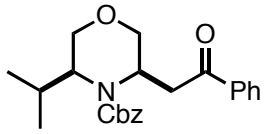
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.30 (m, 5 H), 5.17-5.09 (m, 2 H), 4.55-4.53 (m, 1 H), 4.02 (d, J = 12.0 Hz, 1 H), 3.78-3.75 (m, 1 H), 3.58-3.56 (m, 2 H), 3.41 (dd, J = 12.0 Hz, J = 3.0 Hz, 1 H), 3.09 (dd, J = 17.0 Hz, J = 11.0 Hz, 1 H), 2.66 (d, J = 17.0 Hz, 1 H), 2.42-2.36 (m, 2 H), 2.15-2.08 (m, 1 H), 1.04 (t, J = 7.5 Hz, 3 H), 0.98-0.88 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.0, 155.8, 128.5, 128.0, 69.7, 67.7, 67.3, 56.8, 46.5, 44.0, 36.3, 29.8, 20.6, 19.9, 7.6; IR (neat, cm^{-1}): 2967, 2935, 2867, 1697, 1451, 1414, 1369, 1289, 1118, 1063; HRMS Calculated for $[C_{19}H_{27}NO_4+H]^+$: 334.20128, Found: 334.20162. $[\alpha]_D^{26}$ = -7.3° (c = 1.0 $CHCl_3$).



2f-*trans*

(3S,5S)-benzyl 3-isopropyl-5-(2-oxobutyl)morpholine-4-carboxylate (2f-*trans*)

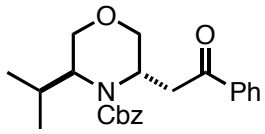
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.29 (m, 5 H), 5.08-4.99 (m, 2 H), 4.17-4.12 (m, 1 H), 3.90 (dd, *J* = 12.0 Hz, *J* = 1.5 Hz, 1 H), 3.71-7.66 (m, 2 H), 3.58 (dd, *J* = 11.5 Hz, *J* = 3.0 Hz, 1 H), 3.44-3.40 (m, 1 H), 3.29-3.24 (m, 1 H), 2.41-2.35 (m, 2 H), 2.29 (d, *J* = 17.0 Hz, 1 H), 1.03 (t, *J* = 7.5 Hz, 3 H), 0.99-0.96 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.5, 155.3, 136.5, 128.5, 128.0, 127.8, 70.3, 66.8, 59.6, 48.3, 42.5, 35.6, 26.7, 20.3, 18.7, 7.5. IR (neat, cm^{-1}): 2967, 2935, 2867, 1698, 1453, 1413, 1369, 1289, 1117, 1064; HRMS Calculated for $[C_{19}H_{27}NO_4+H]^+$: 334.20128, Found: 334.20162. $[\alpha]_D^{26}$ = -3.4° (c = 1.0 $CHCl_3$).



2g-*cis*

(3S,5R)-benzyl 3-isopropyl-5-(2-oxo-2-phenylethyl)morpholine-4-carboxylate (2g-*cis*)

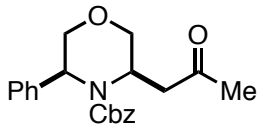
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 7.5 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.36-7.31 (m, 5 H), 5.19-5.13 (m, 2 H), 4.76-4.73 (m, 1 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 3.86 (d, *J* = 10.0 Hz, 1 H), 3.68-3.61 (m, 3 H), 3.47 (dd, *J* = 12.0 Hz, *J* = 3.5 Hz, 1 H) 3.24 (d, *J* = 14.0 Hz, 1 H), 2.28-2.21 (m, 1 H), 1.03-0.99 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 155.9, 136.7, 133.3, 128.7, 128.5, 128.1, 128.0, 69.5, 67.8, 67.4, 56.5, 47.1, 40.5, 30.0, 20.7, 19.9; IR (neat, cm^{-1}): 3062, 3031, 2961, 2926, 2860, 1691, 1597, 1453, 1413, 1283, 1217, 1116, 1054, 1002, 757, 698; HRMS Calculated for $[C_{23}H_{27}NO_4+H]^+$: 382.20129, Found: 382.20101. $[\alpha]_D^{26}$ = -31.8° (c = 1.0 $CHCl_3$).



2g-*trans*

(3S,5S)-benzyl 3-isopropyl-5-(2-oxo-2-phenylethyl)morpholine-4-carboxylate (2g-*trans*)

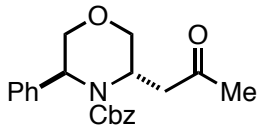
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 7.5 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.29-7.22 (m, 5 H), 5.04-4.93 (m, 2 H), 4.39-4.35 (m, 1 H), 3.94 (dd, *J* = 11.0 Hz, *J* = 1.5 Hz, 1 H), 3.83 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1 H), 3.74 (d, *J* = 10.5 Hz, 1 H), 3.67 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1 H), 3.55 (dd, *J* = 11.0 Hz, *J* = 8.5 Hz, 1 H), 2.86 (dd, *J* = 17.5 Hz, *J* = 5.0 Hz, 1 H), 2.45-2.38 (m, 1 H), 1.04-0.99 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.6, 155.6, 136.8, 1364, 132.9, 128.5, 128.4, 128.0, 127.9, 127.8, 69.7, 66.9, 66.7, 59.7, 48.9, 39.5, 27.3, 20.3, 18.8; IR (neat, cm^{-1}): 3061, 3031, 2963, 2925, 2861, 1689, 1596, 1452, 1413, 1285, 1218, 1115, 1056, 1004, 757, 698; HRMS Calculated for $[C_{23}H_{27}NO_4+H]^+$: 382.20129, Found: 382.20106. $[\alpha]_D^{26}$ = 35.2° (c = 1.0 $CHCl_3$).



2h-*cis*

(3R,5S)-benzyl 3-(2-oxopropyl)-5-phenylmorpholine-4-carboxylate (2h-*cis*)

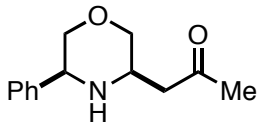
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.57 (d, J = 7.0 Hz, 2 H) 7.38-7.28 (m, 8 H), 5.27-5.20 (m, 2 H), 4.57-4.55 (m, 2 H), 3.83-3.78 (m, 2 H), 3.70 (dd, J = 12.0 Hz, J = 2.5 Hz, 1 H), 2.56 (dd, J = 17.5 Hz, J = 10.0 Hz, 1 H), 2.16 (dd, J = 18.0 Hz, J = 2.5 Hz, 1 H), 1.82 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 155.6, 141.1, 136.3, 128.5, 128.4, 128.1, 127.9, 127.8, 127.4, 69.6, 68.3, 67.6, 51.1, 46.7, 45.2, 30.0; IR (neat, cm^{-1}): 3062, 3032, 2966, 2862, 1693, 1497, 1453, 1413, 1381, 1356, 1324, 1283, 1193, 1159, 1135, 1102, 1065, 1029, 935, 911, 740, 700, 572, 546; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16979. $[\alpha]_D^{26}$ = 43.6° (c = 1.0 $CHCl_3$).



2h-*trans*

(3S,5S)-benzyl 3-(2-oxopropyl)-5-phenylmorpholine-4-carboxylate (2h-*trans*)

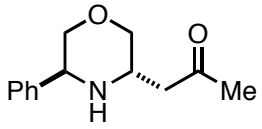
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.22 (m, 8 H), 7.04 (bs, 2 H), 5.05-4.87 (m, 2 H), 4.60 (dd, J = 8.5 Hz, J = 4.5 Hz, 1 H), 4.50-4.46 (m, 1 H), 3.88 (dd, J = 12.0 Hz, J = 4.5 Hz, 1 H), 3.84-3.77 (m, 2 H), 3.58 (dd, J = 12.0 Hz, J = 7.5 Hz, 1 H), 3.04 (dd, J = 17.0 Hz, J = 9.0 Hz, 1 H), 2.59 (d, J = 17.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.0, 156.4, 140.4, 135.9, 128.8, 128.4, 128.3, 128.1, 128.0, 127.1, 126.1, 77.2, 72.0, 68.6, 67.1, 56.0, 48.9, 43.5, 30.1; IR (neat, cm^{-1}): 3062, 3031, 2963, 2862, 1710, 1495, 1453, 1280, 1159, 1116, 1080, 1056, 1028, 974, 943, 912, 757, 699, 549, 529.1; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16989. $[\alpha]_D^{26}$ = 34.6° (c = 1.0 $CHCl_3$).



2h'-*cis*

1-((3R,5S)-5-phenylmorpholin-3-yl)propan-2-one (2h'-*cis*)

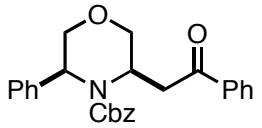
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37 (d, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.25 (t, J = 7.5 Hz, 1 H), 4.01 (dd, J = 10.0 Hz, J = 2.5 Hz, 1 H), 3.81 (dd, J = 11.0 Hz, J = 3.0 Hz, 1 H), 3.73 (dd, J = 11.0 Hz, J = 3.0 Hz, 1 H), 3.48-3.41 (m, 1 H), 3.31 (t, J = 10.5 Hz, 1 H), 3.22 (t, J = 10.5 Hz, 1 H), 2.63 (bs, 1 H), 2.49 (d, J = 8.0 Hz, 2 H), 2.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.0, 140.1, 128.3, 127.6, 127.2, 73.2, 60.0, 50.8, 45.4, 30.5; IR (neat, cm^{-1}): 3326, 3061, 3029, 2958, 2886, 2848, 1713, 1453, 1364, 1338, 1312, 1170, 1106, 757, 702; HRMS Calculated for $[C_{13}H_{17}NO_2+H]^+$: 220.13321, Found: 220.13304. $[\alpha]_D^{26}$ = 60.4° (c = 1.0 $CHCl_3$).



2h'-*trans*

1-((3S,5S)-5-phenylmorpholin-3-yl)propan-2-one (2h'-*trans*)

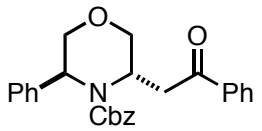
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, C_6D_6) δ = 7.36 (d, J = 7.5 Hz, 2 H), 7.15 (t, J = 7.5 Hz, 2 H), 7.07 (t, J = 7.5 Hz, 2 H), 3.93 (dd, J = 8.5 Hz, J = 3.5 Hz, 1 H), 3.79 (dd, J = 11.0 Hz, J = 3.5 Hz, 1 H), 3.65 (dd, J = 11.0 Hz, J = 3.5 Hz, 1 H), 3.44-3.40 (m, 2 H), 3.28-3.23 (m, 1 H), 2.49 (dd, J = 17.0 Hz, J = 8.0 Hz, 1H), 2.14 (dd, J = 17.0 Hz, J = 5.0 Hz, 1 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6): δ = 206.5, 141.6, 128.6, 128.1, 127.5, 73.7, 70.6, 54.2, 48.2, 43.6, 29.9; IR (neat, cm^{-1}): 3322, 3060, 3028, 2959, 2916, 2852, 1709, 1454, 1405, 1364, 1262, 1163, 1104, 757, 701; HRMS Calculated for $[C_{13}H_{17}NO_2+H]^+$: 220.13321, Found: 220.13304. $[\alpha]_D^{26}$ = 21.8° (c = 1.0 $CHCl_3$).



2i-*cis*

(3R,5S)-benzyl 3-(2-oxo-2-phenylethyl)-5-phenylmorpholine-4-carboxylate (2i- *cis*)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.38-7.30 (m, 7 H), 5.32-5.20 (m, 2 H), 4.80-4.78 (m, 1 H), 4.63 (d, J = 11.5 Hz, 1 H), 3.91 (d, J = 11.5 Hz, 1 H), 3.86 (dd, J = 11.5 Hz, J = 3.5 Hz, 1 H), 3.78 (dd, J = 11.5 Hz, J = 2.0 Hz, 1 H), 3.15 (dd, J = 17.5 Hz, J = 11.0 Hz, 1 H), 2.56 (d, J = 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.6, 155.6, 141.4, 136.4, 136.3, 133.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.5, 126.1, 69.6, 68.2, 67.7, 51.2, 47.5, 40.6; IR (neat, cm^{-1}): 3062, 3032, 2927, 2861, 1690, 1598, 1581, 1497, 1450, 1412, 1283, 1217, 1179, 1134, 1097, 1064, 1026, 1004, 898, 760, 698, 581; HRMS Calculated for $[C_{26}H_{25}NO_4+H]^+$: 416.18564, Found: 416.18501. $[\alpha]_D^{26}$ = 51.6° (c = 1.0 $CHCl_3$).

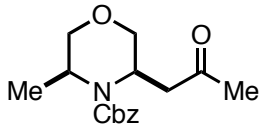


2i-*trans*

(3S,5S)-benzyl 3-(2-oxo-2-phenylethyl)-5-phenylmorpholine-4-carboxylate (2i-*trans*)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.36-7.25 (m, 6 H), 7.16-7.12 (m, 2 H), 7.00 (bs, 2 H), 5.03-4.88 (m, 2 H), 4.74 (dd, J = 10.0 Hz, J = 2.5 Hz, 1 H), 4.68 (dd, J = 9.0 Hz, J = 5.0 Hz), 3.96-3.84 (m, 3 H), 3.65 (dd, J = 12.0 Hz, J = 9.0 Hz, 1 H), (dd, J = 12.0 Hz, J = 9.0 Hz, 1 H), 3.15-3.08 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.7, 156.6, 140.6, 136.7, 135.8, 133.2, 133.0, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 127.2, 126.1, 72.4, 67.7, 67.3, 56.2, 49.7, 38.9; IR (neat, cm^{-1}): 3062, 3031, 2961, 2926, 2860, 1691, 1597, 1495, 1450, 1407, 1366, 1283, 1217, 1116,

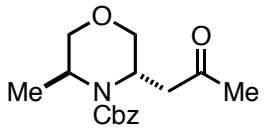
1054, 1002, 757, 698; HRMS Calculated for $[C_{26}H_{25}NO_4+H]^+$: 416.18564, Found: 416.18501. $[\alpha]_D^{26}$ = 71.7° (c = 1.0 $CHCl_3$).



2j-*cis*

(3S,5R)-benzyl 3-methyl-5-(2-oxopropyl)morpholine-4-carboxylate (2j-*cis*)

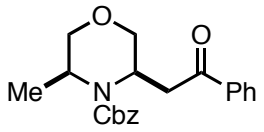
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.30 (m, 5 H), 5.19-5.14 (m, 2 H), 4.36 (dt, *J* = 10.5 Hz, *J* = 3.0 Hz, 1 H), 4.06-4.01 (m, 1 H), 3.79 (d, *J* = 11.5 Hz, 1 H), 3.68 (d, *J* = 11.5 Hz, 1 H), 3.59-3.53 (m 2 H), 3.12 (dd, *J* = 17.5 Hz, *J* = 10.5 Hz, 1 H), 2.56 (d, *J* = 16.0 Hz, 1 H), 2.12 (s, 3 H), 1.29 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.4, 155.0, 136.5, 128.5, 128.1, 127.8, 71.1, 69.2, 67.2, 48.2, 46.1, 30.2, 19.4; IR (neat, cm^{-1}): 3062, 2972, 2861, 1701, 1596, 1597, 1449, 1410, 1291, 1219, 1140, 1090, 1025, 747, 694; HRMS Calculated for $[C_{16}H_{21}NO_4+Na]^+$: 314.13628, Found: 314.13359. $[\alpha]_D^{26}$ = 19.5° (c = 1.0 $CHCl_3$).



2j-*trans*

(3S,5S)-benzyl 3-methyl-5-(2-oxopropyl)morpholine-4-carboxylate (2j-*trans*)

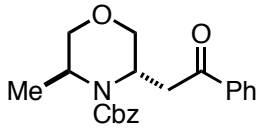
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.32 (m, 5 H), 5.17-5.04 (m, 2 H), 4.32-4.29 (m, 1 H), 3.89-3.86 (m, 1 H), 3.77 (td, *J* = 11.0 Hz, *J* = 3.0 Hz, 2 H), 3.58 (dd, *J* = 11.5 Hz, *J* = 5.0 Hz, 1 H), 3.47 (dd, *J* = 11.5 Hz, *J* = 5.0 Hz, 1 H), 2.81 (d, *J* = 15.5 Hz, 1H), 2.66 (dd, *J* = 16.5 Hz, *J* = 6.5 Hz, 1 H), 2.10 (s, 3 H), 1.34 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.7, 155.9, 136.4, 128.5, 128.1, 128.0, 127.8, 70.8, 68.8, 67.0, 48.2, 47.9, 44.4, 30.2, 17.7. IR (neat, cm^{-1}): 3032, 2968, 2930, 1703, 1597, 1449, 1410, 1362, 1279, 1250, 1216, 1180, 1149, 1114, 1001, 754, 694; HRMS Calculated for $[C_{16}H_{21}NO_4+Na]^+$: 314.13628, Found: 314.13359. $[\alpha]_D^{26}$ = -12.6° (c = 1.0 $CHCl_3$).



2k-*cis*

(3S,5R)-benzyl 3-methyl-5-(2-oxo-2-phenylethyl)morpholine-4-carboxylate (2k-*cis*)

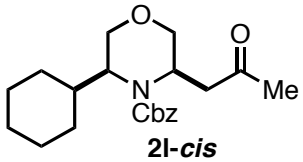
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.46 t, *J* = 7.5 Hz, 2 H), 7.33 (bs, 5 H), 5.18 (bd, 2 H), 4.61 (d, *J* = 11.0 Hz, 1 H), 4.15-4.11 (m, 1 H), 3.93 (d, *J* = 11.0 Hz, 1 H), 3.77-3.62 (m, 4 H), 3.16 (d, *J* = 16.5 Hz, 1 H), 1.41 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 155.1, 136.6, 136.5, 133.3, 128.6, 128.5, 128.4, 128.0, 127.8, 71.1, 69.2, 67.2, 46.8, 46.2, 41.5, 19.6; IR (neat, cm^{-1}): 3062, 2972, 2861, 1690, 1590, 1597, 1449, 1410, 1291, 1219, 1140, 1090, 1025, 747, 694; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16971. $[\alpha]_D^{26}$ = -22.5° (c = 1.0 $CHCl_3$).



2k-*trans*

(3S,5S)-benzyl 3-methyl-5-(2-oxo-2-phenylethyl)morpholine-4-carboxylate (2k-*trans*)

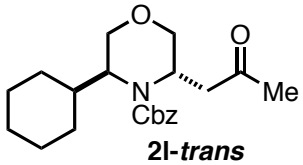
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91 (d, J = 7.0 Hz, 2 H), 7.55 (t, J = 7.0 Hz, 7.43 (t, J = 8.0 Hz, 2 H), 7.26 (bs, 5 H), 5.13-5.01 (m, 2 H), 4.58-4.54 (m, 1 H), 3.93-3.85 (m, 2 H), 3.74 (dd, J = 12.0 Hz, J = 4.0 Hz, 1 H), 3.48 (dd, J = 11.5 Hz, J = 4.5 Hz, 1 H), 3.34-3.27 (m, 2 H), 1.39 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5, 156.0, 136.7, 136.3, 133.1, 128.6, 128.5, 128.1, 128.0, 70.9, 68.3, 67.0, 48.8, 48.2, 39.8, 18.1; IR (neat, cm^{-1}): 3032, 2968, 2930, 1692, 1597, 1449, 1410, 1362, 1279, 1250, 1216, 1180, 1149, 1114, 1001, 754, 694; HRMS Calculated for $[C_{21}H_{23}NO_4+H]^+$: 354.16999, Found: 354.16970. $[\alpha]_D^{26}$ = -44.2° (c = 1.0 $CHCl_3$).



2l-*cis*

(3S,5R)-benzyl 3-cyclohexyl-5-(2-oxopropyl)morpholine-4-carboxylate

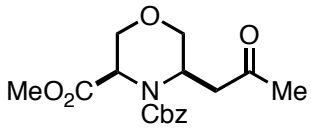
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.31 (m, 5 H), 5.17-5.01 (m, 2 H), 4.52 (dt, J = 9.0 Hz, J = 2.5 Hz, 1 H), 4.07 (d, J = 12.0 Hz, 3.75-3.56 (m, 3 H), 3.38 (dd, J = 12.0 Hz, J = 5.0 Hz, 1 H), 3.12-3.06 (m, 1 H), 2.71-2.68 (m, 1 H), 2.15 (s, 3 H), 1.86-1.57 (m, 7 H), 1.30-0.84 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.3, 186.7, 155.8, 136.5, 128.5, 128.0, 69.7, 67.3, 67.1, 55.6, 46.4, 45.2, 39.3, 30.9, 30.3, 30.0, 26.3, 26.2, 26.0; IR (neat, cm^{-1}): 2929, 2852, 1694, 1450, 1414, 1355, 1286, 1134, 1102, 1080, 766, 698; HRMS Calculated for $[C_{21}H_{29}NO_4+H]^+$: 360.21693, Found: 360.21682. $[\alpha]_D^{26}$ = -34.2° (c = 1.0 $CHCl_3$).



2l-*trans*

(3S,5S)-benzyl 3-cyclohexyl-5-(2-oxopropyl)morpholine-4-carboxylate

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.27, (m, 5 H), 5.08-5.02 (m, 2 H), 4.13-4.07 (m, 1 H), 3.93 (dd, J = 11.5 Hz, J = 1.0 Hz, 1 H), 3.74-3.69 (m, 2 H), 3.55 (dd, J = 11.5 J = 3.0 Hz, 1 H), 3.41 (dd, J = 11.0 Hz, J = 5.5 Hz, 1 H), 3.27-3.25 (m, 1 H), 2.31-2.28 (m, 1 H), 2.14 (bs, 3 H), 2.03-1.95 (m, 1 H), 1.87-1.64 (m, 5 H), 1.30-1.19 (m, 2 H), 1.14-1.05 (m, 1 H), 0.94-0.85 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.8, 155.4, 136.5, 128.5, 128.0, 127.9, 70.2, 66.8, 66.4, 58.4, 48.4, 43.7, 42.7, 36.2, 36.2, 30.7, 29.9, 28.4, 26.3, 26.1, 26.0; IR (neat, cm^{-1}): 2926, 2851, 1720, 1697, 1448, 1425, 1358, 1289, 1265, 1244, 1129, 1110, 1049, 756, 698; HRMS Calculated for $[C_{21}H_{29}NO_4+H]^+$: 360.21693, Found: 360.21682. $[\alpha]_D^{26}$ = -40.1° (c = 1.0 $CHCl_3$).

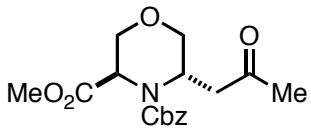


2m-*cis*

(3R,5R)-4-benzyl 3-methyl 5-(2-oxopropyl)morpholine-3,4-dicarboxylate (2m-*cis*)

Due to the rotamer issue, major isomer was reported. Minor isomer signals are in parentheses. See Cbz-removal product **2m'-*cis*** *for detailed information.*

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35-7.27 (m, 5 H), 5.26-5.11 (m, 2 H), 4.56-4.40 (m, 3 H), 3.90-3.73 (m, 1 H), 3.78 (s, 3 H), 3.06-2.81 (m, 2H), 2.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.1, 117.7, 155.7, 136.1, 128.5, 128.1, 127.7, 69.5, 69.2, 67.5, 66.9, 53.1, 52.7, 52.5, 46.4, 46.1, 44.2, 43.1, 30.3; IR (neat, cm^{-1}): 3032, 2968, 2930, 1751, 1703, 1411, 1285, 1225, 1111, 1071, 1149, 1114, 1001, 754, 694; HRMS Calculated for $[C_{17}H_{21}NO_6+H]^+$: 336.14417, Found: 336.14432. $[\alpha]_D^{26}$ = 42.3° (c = 1.0 $CHCl_3$).

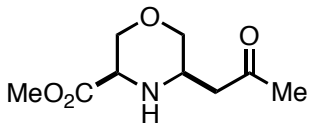


2m-*trans*

(3R,5S)-4-benzyl 3-methyl 5-(2-oxopropyl)morpholine-3,4-dicarboxylate (2m-*trans*)

Due to the rotamers, major isomer was reported. Minor isomer signals are in parentheses. See Cbz-removal product **2m'-*trans*** *for detailed information.*

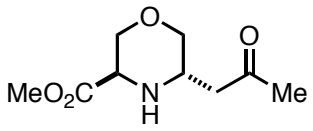
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.26 (m, 5 H), 5.22 (bs, 1 H), 5.03 (d, J = 12.0 Hz, 1 H), 4.35-3.57 (m, 1 1H), 2.96 (bs, 1 H), 2.68-2.38 (m, 1 H), 2.17 (2.00) (bs, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.6, 170.5, 156.2, 135.8, 128.5, 128.3, 128.2, 69.1, 67.6, 55.4, 54.6, 52.5, 48.1, 43.9, 30.2; IR (neat, cm^{-1}): 3031, 2969, 2930, 1750, 1702, 1413, 1285, 1224, 1113, 1070, 1148, 1114, 1001, 755, 696; HRMS Calculated for $[C_{17}H_{21}NO_6+H]^+$: 336.14417, Found: 336.14435. $[\alpha]_D^{26}$ = 32.6° (c = 1.0 $CHCl_3$).



2m'-*cis*

(3R,5R)-methyl 5-(2-oxopropyl)morpholine-3-carboxylate (2m'-*cis*)

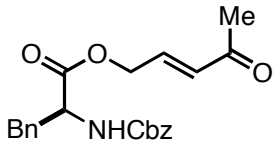
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.11 (dd, J = 11.0 Hz, J = 3.0 Hz, 1 H), 3.75-3.72 (m, 1 H), 3.73 (s, 3 H), 3.70 (dd, J = 11.0 Hz, J = 2.5 Hz, 1 H), 3.41 (t, J = 11.0 Hz, 1 H), 3.36-3.30 (m, 1 H), 3.13 (t, J = 11.0 Hz, 1 H), 2.93 (bs, 1 H), 2.55-2.44 (m, 2 H), 2.17 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.6, 170.3, 70.7, 68.2, 57.1, 52.1, 49.9, 44.9, 30.4; IR (neat, cm^{-1}): 3329, 2956, 2855, 1740, 1712, 1438, 1372, 1285, 1216, 1170, 1107, 939; HRMS Calculated for $[C_{17}H_{21}NO_6+H]^+$: 336.14417, Found: 336.14439. $[\alpha]_D^{26}$ = 64.8° (c = 1.0 $CHCl_3$).



2m'-*trans*

(3R,5S)-methyl 5-(2-oxopropyl)morpholine-3-carboxylate (2m'-*trans*)

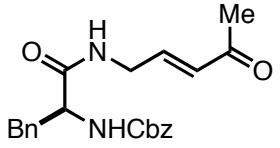
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.22 (dd, J = 12.0 Hz, J = 2.5 Hz, 1 H), 3.93 (bs, 1 H), 3.84-3.80 (m, 1 H), 3.80 (s, 3 H), 3.74 (dd, J = 11.5 Hz, J = 4.0 Hz, 1 H), 3.62-3.57 (m, 2 H), 3.29 (dd, J = 11.0 Hz, J = 9.0 Hz, 1 H), 2.55-2.52 (m, 2 H), 2.18 9s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.6, 172.1, 70.8, 67.3, 55.1, 52.3, 46.9, 44.9, 30.4; IR (neat, cm^{-1}): 3328, 2957, 2856, 1740, 1711, 1437, 1372, 1285, 1215, 1170, 1108, 939; HRMS Calculated for $[C_{17}H_{21}NO_6+H]^+$: 336.14417, Found: 336.14439. $[\alpha]_D^{26}$ = 16.3° (c = 1.0 $CHCl_3$).



3a

(S,E)-4-oxopent-2-en-1-yl 2-(((benzyloxy)carbonyl)amino)-3-phenylpropanoate (3a)

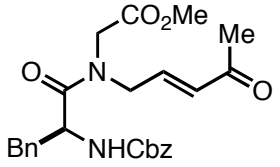
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.24 (m, 8 H), 7.11 (d, J = 7.5 Hz, 2 H), 6.64 (dt, J = 16.0 Hz, J = 4.5 Hz, 1 H), 6.16 (d, J = 16.0 Hz, 1 H), 5.28-5.26 (m, 1 H), 5.14-5.07 (m, 2 H), 4.80-4.68 (m, 3 H), 3.14-3.09 (m, 2 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4, 171.1, 155.6, 138.5, 136.1, 135.4, 131.3, 129.1, 128.7, 128.5, 128.2, 128.1, 127.2, 67.0, 63.5, 54.9, 38.2, 27.5; HRMS Calculated for $[C_{22}H_{23}NO_5+H]^+$: 382.16490, Found: 382.16465.



3b

(S,E)-benzyl (1-oxo-1-((4-oxopent-2-en-1-yl)amino)-3-phenylpropan-2-yl)carbamate (3b)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35-7.16 (m, 10 H), 6.53 (dt, J = 16.0 Hz, J = 5.0 Hz, 1 H), 6.38 (bs, 1 H), 5.95 (d, J = 16.0 Hz, 1 H), 5.55-5.52 (m, 1 H), 50.7-5.01 (m, 2 H), 4.5-4.4 (m, 1 H), 3.94-3.87 (m, 1 H), 3.12-3.03 (m, 2 H), 2.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8, 171.1, 156.0, 142.1, 136.2, 135.9, 130.7, 129.2, 128.7, 128.5, 128.2, 127.1, 67.1, 56.4, 40.1, 38.5, 27.3; HRMS Calculated for $[C_{22}H_{24}N_2O_4+H]^+$: 381.18089, Found: 381.18063.

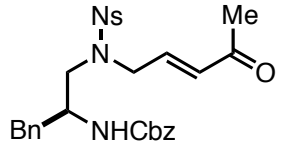


3c

(S,E)-methyl 2-(2-(((benzyloxy)carbonyl)amino)-N-(4-oxopent-2-en-1-yl)-3-phenylpropanamido)acetate (3c)

Due to the rotamers , major isomer was reported. Minor isomer signals are in parentheses.

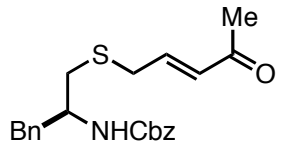
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.17 (m, 10H), 6.71-6.57 (m, 1 H), 6.035 (t, J = 16.5 Hz, 1 H), 5.64 (d, J = 9.0 Hz, 1 H), 5.12-5.00 (m, 2H), 4.89-4.85 (4.66-4.61) (m, 1 H), 4.15-4.06 (m, 1 H), 3.86 (3.78) (d, J = 17.0 Hz (J = 18.5 Hz), 1 H), 2.72 (2.71), (s, 3 H), 3.60-3.54 (3.31-3.24), (m, 1 H), 3.41-3.27 (m, 1 H), 3.13-3.29 (m, 2 H), 2.42-2.35 (m, 1 H), 2.21(2.22) (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.5(198.2), 172.4(172.6), 169.3(169.6), 155.1, 142.4(144.1), 136.5(1.6.2), 133.6(133.0), 129.8(129.6), 128.9(128.8), 128.7(128.4), 128.2(128.1), 127.4(127.3), 67.2(67.1), 52.5(52.9), 52.3(52.4), 40.0(39.7), 31.7(30.7), 27.3(27.1); HRMS Calculated for $[C_{25}H_{28}N_2O_6+H]^+$: 453.20202, Found: 453.20103.



3d

(S,E)-benzyl (1-(2-nitro-N-(4-oxopent-2-en-1-yl)phenylsulfonamido)-3-phenylpropan-2-yl)carbamate (3d)

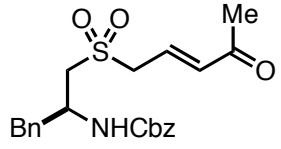
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.92-7.89 (m, 1 H), 7.62-7.52 (m, 3 H), 7.35-7.12 (m, 10 H), 6.46 (dt, *J* = 16.0 Hz, *J* = 4.0 Hz, 1 H), 6.02 (d, *J* = 16.0 Hz, 1 H), 5.04-4.93 (m, 3 H), 4.17-4.03 (m, 3 H), 3.57 (dd, *J* = 14.5 Hz, *J* = 10.5 Hz, 1 H), 3.19 (dd, *J* = 15.0 Hz, *J* = 4.0 Hz, 1 H), 2.84 (dd, *J* = 14.0, *J* = 7.0 Hz, 1 H), 2.73 (dd, *J* = 14.0 Hz, *J* = 7.0 Hz, 1 H), 2.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4, 156.0, 147.6, 140.0, 136.7, 136.3, 133.8, 133.2, 133.0, 131.8, 130.8, 129.0, 128.6, 128.4, 128.0, 127.8, 126.8, 124.3, 77.2, 66.6, 50.4, 49.8, 48.4, 39.1, 27.1; HRMS Calculated for $[C_{28}H_{29}N_3O_7S+H]^+$: 552.17990, Found: 552.17883.



3e

(S,E)-benzyl (1-((4-oxopent-2-en-1-yl)thio)-3-phenylpropan-2-yl)carbamate (3e)

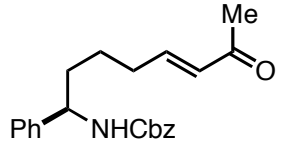
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.15 (m, 10 H), 6.66-6.59 (m, 1 H), 5.98 (d, *J* = 16.0 Hz, 1 H), 5.07 (s, 2 H), 4.90 (d, *J* = 6.5 Hz, 1 H), 4.06-4.03 (m, 1 H), 3.22 (d, *J* = 7.0 Hz, 2 H), 2.90-2.83 (m, 2 H), 2.57-2.50 (m, 2 H), 2.20 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 155.7, 141.8, 137.0, 136.3, 132.2, 129.2, 128.6, 128.5, 128.1, 127.9, 126.7, 66.7, 51.4, 39.6, 34.9, 33.4, 27.1; HRMS Calculated for $[C_{22}H_{25}NO_3S+H]^+$: 384.16280, Found: 384.16240.



3f

(S,E)-benzyl (1-((4-oxopent-2-en-1-yl)sulfonyl)-3-phenylpropan-2-yl)carbamate (3f)

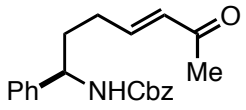
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34-7.23 (m, 8 H), 7.17 (d, *J* = 6.5 Hz, 2 H), 6.67-6.60 (m, 1 H), 6.23 (d, *J* = 16.0 Hz, 1 H), 5.26 (d, *J* = 7.0 Hz, 1 H), 5.11-5.05 (m, 2 H), 4.31-4.29 (m, 1 H), 3.85 (d, *J* = 6.0 Hz, 2 H), 3.38-3.34 (m, 1 H), 3.13-3.02 (m, 3 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.8, 155.6, 138.1, 136.2, 136.0, 131.0, 129.2, 128.9, 128.6, 128.3, 128.1, 127.2, 66.9, 57.1, 54.6, 48.7, 39.9, 27.3; HRMS Calculated for $[C_{22}H_{25}NO_5S+H]^+$: 416.15263, Found: 416.15299.



3g

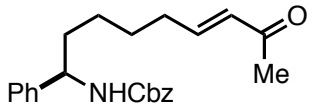
E-benzyl (7-oxo-1-phenyloct-5-en-1-yl)carbamate (3g)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34-7.24 (m, 10 H), 6.74-6.67 (m, 1 H), 6.02 (d, J = 16.0 Hz, 1 H), 5.22 (d, J = 8.5 Hz, 1 H), 5.11-5.01 (m, 2 H), 4.70-4.67 (m, 1 H), 2.29-2.15 (m, 2 H), 2.20 (s, 3 H), 1.86-1.72 (m, 2 H), 1.56-1.37 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.5, 155.6, 147.4, 142.0, 136.3, 131.5, 128.6, 128.4, 128.0, 127.4, 126.2, 66.7, 55.1, 36.0, 31.9, 26.8, 24.6; HRMS Calculated for $[C_{22}H_{25}NO_3+H]^+$: 352.19072, Found: 352.19179.



3h

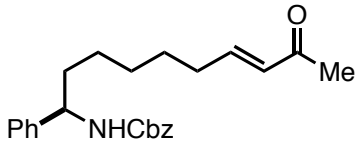
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 53%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.36-7.26 (m, 10 H), 6.76-6.67 (m, 1 H), 6.01 (d, J = 16.0 Hz, 1 H), 5.36-5.30 (m, 1 H), 5.10-5.01 (m, 2 H), 4.69-4.66 (m, 1 H), 2.30-2.15 (m, 4 H), ^{13}H NMR (125 MHz, CD_2Cl_2) δ = 198.4, 155.9, 146.9, 137.1, 132.0, 129.0, 128.8, 128.3, 128.2, 127.9, 126.7, 66.9, 55.4, 35.3, 29.5, 26.9; HRMS Calculated for $[C_{21}H_{23}NO_3+H]^+$: 338.17507, Found: 338.17596.



3i

(R,E)-benzyl (8-oxo-1-phenylnon-6-en-1-yl)carbamate (3i)

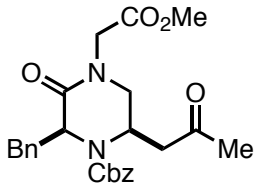
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31-7.23 (m, 10 H), 6.74-6.68 (m, 1 H), 6.01 (d, J = 16.0 Hz, 1 H), 5.31 (d, J = 8.5 Hz, 1 H), 5.09-5.01 (m, 2 H), 4.68-4.66 (m, 1 H), 2.19 (s, 3 H), 2.18-2.14 (m, 2 H), 1.80-1.73 (m, 2 H), 1.47-1.25 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.5, 155.6, 147.8, 142.3, 136.3, 131.2, 128.5, 128.3, 127.9, 127.2, 126.2, 77.2, 66.5, 55.1, 36.2, 32.0, 27.5, 26.7, 25.6; HRMS Calculated for $[C_{23}H_{27}NO_3+H]^+$: 366.20637, Found: 366.20620.



3j

(R,E)-benzyl (9-oxo-1-phenyldec-7-en-1-yl)carbamate (3j)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32-7.24 (m, 10 H), 6.75 (dt, J = 16.0 Hz, J = 7.0 Hz, 1 H), 6.02 (d, J = 16.0 Hz, 1 H), 5.11-5.02 (m, 3 H), 4.68-4.66 (m, 1 H), 2.20 (s, 3 H), 2.17, (q, J = 7.0 Hz, 2 H), 1.75 (bs, 2 H), 1.44-1.22 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.6, 155.6, 148.4, 136.4, 131.3, 128.6, 128.4, 128.0, 127.3, 126.3, 66.7, 55.3, 36.4, 32.2, 28.8, 27.8, 26.8, 25.8; HRMS Calculated for $[C_{24}H_{29}NO_3+H]^+$: 380.22202, Found: 380.22230.

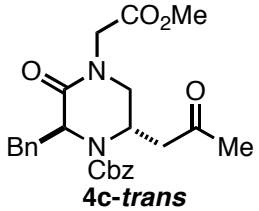


4c-*cis*

Due to the rotamers, major isomer was reported. Minor isomer signals are in parentheses. See Cbz-removal product **4c'-*cis*** *for detailed information.*

(2S,6R)-benzyl 2-benzyl-4-(2-methoxy-2-oxoethyl)-3-oxo-6-(2-oxopropyl)piperazine-1-carboxylate (4c-*cis*)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.32 (m, 4 H), 7.26 (bs, 4 H), 7.11 (bs, 2 H), 5.09(4.99) (bs, 2 H), 4.78 (t, J = 5.0 Hz, 1 H), 4.69-4.50 (m, 2H), 3.71 (s, 3 H), 3.35-3.23 (m, 2 H), 3.15-3.05 (m, 2 H), 2.75-2.64 (m, 1 H), 1.98 (1387) (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.4, 169.0 (168.1), 153.9, 136.0, 129.9, 128.7, 128.7, 128.5, 128.3, 128.1, 127.1, 126.8, 67.8(67.4), 58.8, 52.1(52.3), 46.9(47.0), 44.5(43.6), 40.3(39.0), 29.8; IR (neat, cm^{-1}): 3029, 2973, 2937, 2863, 1747, 1711, 1643, 1494, 1452, 1404, 1381, 1364, 1326, 1211, 702; HRMS Calculated for $[C_{25}H_{28}N_2O_6+H]^+$: 453.20202, Found: 453.20103.

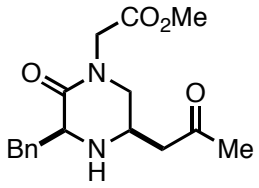


4c-*trans*

Due to the rotamers, major isomer was reported. Minor isomer signals are in parentheses. See Cbz-removal product **4c'-*cis*** *for detailed information.*

(2S,6S)-benzyl 2-benzyl-4-(2-methoxy-2-oxoethyl)-3-oxo-6-(2-oxopropyl)piperazine-1-carboxylate (4c-*trans*)

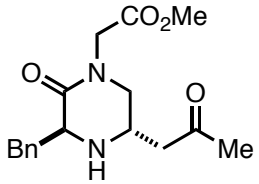
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39-7.32 (m, 4 H), 7.24-7.18 (m, 4 H), 6.95 (d, J = 7.5 Hz, 2 H), 5.24-5.20 (m, 2 H), 4.61-4.59 (m, 1 H), 4.30 (d, J = 5.5 Hz, 1 H), 3.66 (s, 3 H), 3.35-3.22 (m, 2 H), 3.15-3.05 (m, 2 H), 2.75 (2.95) (d, J = 14.0 Hz (J = 12.5 Hz), 1 H), 2.11 (2.04) (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.4, 169.0 (168.1), 153.9, 136.0, 129.9, 128.7, 128.7, 128.5, 128.3, 128.1, 127.1, 126.8, 67.8(67.4), 58.8, 52.1(52.3), 46.6(47.2), 44.3(43.2), 39.7(38.0), 29.9; IR (neat, cm^{-1}): 3029, 2973, 2937, 2863, 1747, 1711, 1643, 1494, 1452, 1404, 1381, 1364, 1326, 1211, 702; HRMS Calculated for $[C_{25}H_{28}N_2O_6+H]^+$: 453.20202, Found: 453.20103. $[\alpha]_D^{26}$ = -51.2° (c = 1.0 $CHCl_3$).



4c'-*cis*

methyl 2-((3S,5R)-3-benzyl-2-oxo-5-(2-oxopropyl)piperazin-1-yl)acetate (4c'-*cis*)

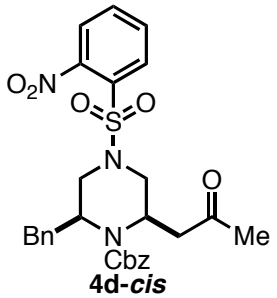
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34-7.23 (m, 10 H), 4.28 (d, J = 17.0 Hz, 1 H), 3.97 (d, J = 17.0 Hz, 1 H), 3.77-3.74 (m, 1 H), 3.75 (s, 3 H), 3.73-3.69 (m, 1 H), 3.35 (dd, J = 11.0 Hz, J = 4.0 Hz, 1H), 3.27 (dd, J = 13.5 Hz, J = 3.5 Hz, 1 H), 3.22-3.17 (m, 1 H), 3.01 9dd, J = 11.0 Hz, J = 10.0 Hz, 1 H), 2.69 (dd, J = 17.5 Hz, J = 6.0 Hz, 1 H), 2.58 (dd, J = 17.5 Hz, J = 7.0 Hz, 1 H), 2.14 (s, 3 H), 1.88 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.7, 170.4, 169.5, 138.5, 129.7, 128.8, 126.9, 58.5, 53.6, 52.5, 48.5, 46.7 45.9, 44.3, 38.5, 30.8; IR (neat, cm^{-1}): 3315, 2925, 1749, 1710, 1646, 1494, 1452, 1404, 1364, 1211, 702; HRMS Calculated for $[C_{17}H_{22}N_2O_4+H]^+$: 319.16524, Found: 319.16501.



4c'-*trans*

methyl 2-((3S,5S)-3-benzyl-2-oxo-5-(2-oxopropyl)piperazin-1-yl)acetate (4c'-*trans*)

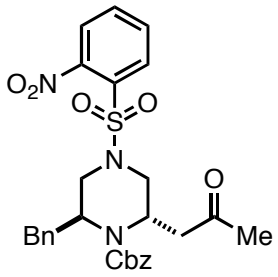
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33-7.21 (m, 10 H), 4.10 (d, J = 3.5 Hz, 2 H), 3.78-3.75 (m, 1 H), 3.73 (s, 3 H), 3.71-3.68 (m, 1 H), 3.46-3.44 (m, 1 H), 3.21-3.17 (m, 2 H), 2.82 (dd, J = 14.0 Hz, J = 9.5 Hz, 1 H), 2.51 (t, J = 10.5 Hz, 2 H), 2.09 (s, 3 H), 1.90 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.0, 169.9, 169.2, 138.1, 129.5, 129,2, 128.6, 126.6, 60.0, 53.3, 48.5, 48.1 46.5, 38.1, 30.2; IR (neat, cm^{-1}): 3316, 2926, 1747, 1711, 1643, 1494, 1455, 1405, 1363, 1210, 702; HRMS Calculated for $[C_{17}H_{22}N_2O_4+H]^+$: 319.16524, Found: 319.16501.



4d-*cis*

(2S,6R)-benzyl 2-benzyl-4-((2-nitrophenyl)sulfonyl)-6-(2-oxopropyl)piperazine-1-carboxylate (4d-*cis*)

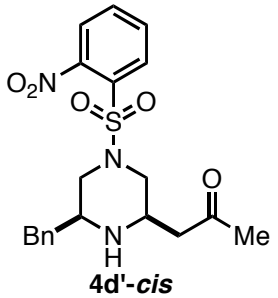
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.89 (d, J = 7.5 Hz, 1 H), 7.72-7.62 (m, 3 H), 7.48-7.05 (m, 10 H), 5.2 (bs, 2 H), 4.72 (d, J = 11.0 Hz, 1 H), 4.26-4.14 (m, 1 H), 3.83 (bs, 1 H), 3.76 (d, J = 13.0 Hz, 1 H), 3.29 (bs, 1 H), 3.03 (t, J = 11.5 Hz, 1 H), 2.91 (dd, J = 12.5 Hz, J = 2.5 Hz, 1 H), 2.74 (dd, J = 12.5 Hz, J = 3.0 Hz, 1 H), 2.70-2.64 (m, 1 H), 2.53-2.48 (m, 1 H), 2.20 (bs, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.1, 154.9, 148.3, 137.9, 133.9, 131.7, 131.2, 131.0, 129.6, 128.7, 127.8, 126.7, 124.3, 68.5, 53.9, 48.2, 46.6, 46.2, 45.0, 39.9, 30.5; IR (neat, cm^{-1}): 3027, 2921, 2853, 1712, 1619, 1565, 1497, 1485, 1453, 1411, 1323, 936, 840, 753, 699, 653, 594; HRMS Calculated for $[C_{28}H_{29}N_3O_7S+H]^+$: 552.17990, Found: 552.17883. $[\alpha]_D^{26}$ = -96.2° (c = 1.0 $CHCl_3$).



4d-*trans*

(2S,6S)-benzyl 2-benzyl-4-((2-nitrophenyl)sulfonyl)-6-(2-oxopropyl)piperazine-1-carboxylate (4d-*trans*)

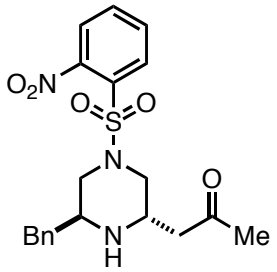
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 (d, J = 7.5 Hz, 1 H), 7.75 (t, J = 7.5 Hz, 1 H), 7.69 (t, J = 7.5 Hz, 2 H), 7.39-7.33 (m, 4 H), 7.17-7.11 (m, 3 H), 6.97 (d, J = 11.0 Hz, 2 H), 5.19-5.08 (m, 2 H), 4.55 (dd, J = 9.0 Hz, J = 3.0 Hz, 1 H), 4.17-4.15 (m, 1 H), 3.77-3.67 (m, 2 H), 3.54 (d, J = 13.0 Hz, 1 H), 3.30 (dd, J = 13.0 Hz, J = 3.0 Hz, 1 H), 3.04 (d, J = 12.0 Hz, 1 H), 2.83-2.71 (m, 2 H), 2.61 (dd, J = 17.5 Hz, J = 10.0 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.2, 154.5, 147.8, 137.3, 135.9, 133.9, 131.8, 131.7, 131.5, 129.2, 128.6, 128.5, 128.4, 128.2, 126.7, 124.3, 67.7, 54.8, 48.2, 46.2, 45.8, 43.6, 40.1, 30.1; IR (neat, cm^{-1}): 3027, 2920, 2854, 1710, 1619, 1565, 1497, 1484, 1453, 1412, 1323, 936, 840, 753, 699, 653, 594; HRMS Calculated for $[C_{28}H_{29}N_3O_7S+H]^+$: 552.17990, Found: 552.17883. $[\alpha]_D^{26}$ = -94.2° (c = 1.0 $CHCl_3$).



4d'-*cis*

1-((2R,6S)-6-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)propan-2-one (4d'-*cis*)

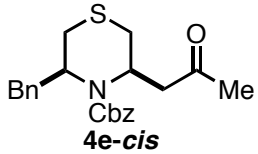
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H), 7.39-7.14 (m, 4 H), 7.13 (d, J = 7.5 Hz, 2 H), 6.75-6.70 (m, 2 H), 3.66 (dd, J = 11.0 Hz, J = 2.0 Hz, 1 H), 3.59-3.55 (m, 1 H), 3.17-3.11 (m, 1 H), 3.06-3.00 (m, 1 H), 2.65 (dd, J = 13.5 Hz, J = 6.0 Hz, 1 H), 2.54-2.46 (m, 3 H), 2.36 (dd, J = 17.5 Hz, J = 9.0 Hz, 1 H), 2.62-2.18 (m, 2 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.6, 146.2, 137.0, 134.2, 130.2, 128.9, 128.6, 126.8, 117.6, 117.4, 117.1, 55.5, 50.7, 50.5, 50.1, 46.6, 40.2, 30.4; IR (neat, cm^{-1}): 3477, 3378, 3027, 2919, 2851, 1711, 1618, 1483, 1452, 1323, 1151, 1009, 752, 701, 596; HRMS Calculated for $[C_{20}H_{23}N_3O_5S+H]^+$: 418.14312, Found: 418.14339. $[\alpha]_D^{26}$ = 39.5° (c = 1.0 $CHCl_3$).



4d'-*trans*

1-((2S,6S)-6-benzyl-4-((2-nitrophenyl)sulfonyl)piperazin-2-yl)propan-2-one (4d'-*trans*)

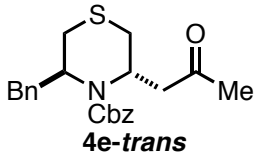
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.49 (dd, J = 7.5 Hz, J = 2.0 Hz, 1 H), 7.32-7.22 (m, 4 H), 7.16 (d, J = 7.5 Hz, 2 H), 6.75-6.70 (m, 2 H), 3.66-3.63 (m, 1 H), 3.31 (d, J = 11.0 Hz, 1 H), 3.25-3.21 (m, 1 H), 3.16 (d, J = 10.5 Hz, 1 H), 2.88-2.72 (m, 5 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.7, 146.2, 137.1, 134.4, 130.1, 129.1, 128.7, 126.8, 117.6, 117.2, 117.1, 77.2, 51.8, 49.4, 49.2, 46.6, 44.1, 38.4, 30.5; IR (neat, cm^{-1}): 3473, 3377, 3027, 2920, 2854, 1710, 1619, 1565, 1484, 1453, 1323, 1522, 936, 840, 753, 699, 653, 594; HRMS Calculated for $[C_{20}H_{23}N_3O_5S+H]^+$: 418.14312, Found: 418.14339. $[\alpha]_D^{26}$ = 10.2° (c = 1.0 $CHCl_3$).



4e-*cis*

(3S,5R)-benzyl 3-benzyl-5-(2-oxopropyl)thiomorpholine-4-carboxylate (4e-*cis*)

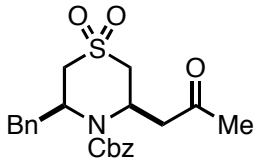
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45-7.02 (m, 10 H), 5.21 (bs, 2 H), 4.89 (d, J = 10.0 Hz, 1 H), 4.50 (m, 1 H), 3.41 (bs, 1 H), 3.26-3.20 (m, 1 H), 2.90 (dd, J = 14.0 Hz, J = 2.0 Hz, 1 H), 2.78-2.55 (m, 3 H), 2.61 (dd, J = 14.0 Hz, J = 2.5 Hz, 1 H), 2.37 (bs, 1 H), 2.15 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.2, 162.5, 155.5, 138.6, 136.2, 129.3, 128.6, 128.3, 126.6, 67.9, 52.3, 47.0, 45.5, 39.8, 32.0, 30.4, 29.5; IR (neat, cm^{-1}): 3062, 3028, 2908, 1692, 1496, 1454, 1406, 1354, 1325, 1300, 1275, 1255, 1223, 1167, 1103, 1073, 1042, 1012, 746, 700; HRMS Calculated for $[C_{22}H_{25}NO_3S+H]^+$: 384.16280, Found: 384.16240. $[\alpha]_D^{26}$ = -23.2° (c = 1.0 $CHCl_3$).



4e-*trans*

(3S,5S)-benzyl 3-benzyl-5-(2-oxopropyl)thiomorpholine-4-carboxylate (4e-*trans*)

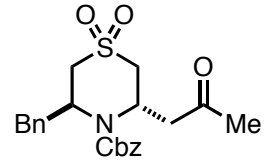
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40-7.20 (m, 10 H), 5.22-5.10 (m, 2 H), 4.74-4.71 (m, 1 H), 4.33-4.29 (m, 1 H), 3.18-3.11 (m, 2 H), 3.09-2.76 (m, 2 H), 2.86-2.82 (m, 1 H), 2.77 (dd, J = 13.0 Hz, J = 4.0 Hz, 2 H), 2.51 (dd, J = 13.5 Hz, J = 3.5 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.1, 155.3, 138.6, 136.1, 129.5, 128.8, 128.6, 128.3, 128.1, 126.7, 67.3, 54.5, 47.8, 47.0, 39.7, 30.4, 28.1, 26.0; IR (neat, cm^{-1}): 3062, 3027, 2929, 1692, 1496, 1454, 1406, 1354, 1324, 1300, 1275, 1255, 1223, 1167, 1103, 1073, 1042, 1012, 746, 700; HRMS Calculated for $[C_{22}H_{25}NO_3S+H]^+$: 384.16280, Found: 384.16240. $[\alpha]_D^{26}$ = -43.2° (c = 1.0 $CHCl_3$).



4f-*cis*

(3S,5R)-benzyl 3-benzyl-5-(2-oxopropyl)thiomorpholine-4-carboxylate 1,1-dioxide (4f-*cis*)

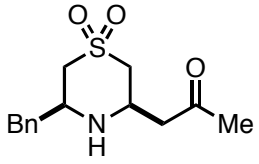
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39-7.22 (M, 10 H), 5.40-5.38 (m, 1 H), 5.24-5.18 (m, 2 H), 4.93 (bs, 1 H), 3.84 (dd, J = 18.0 Hz, J = 11.0 Hz), 3.56 (t, J = 12.5 Hz, 1 H), 3.24 (bs, 2 H), 2.98-2.86 (m, 3 H), 2.71 (d, J = 16.5 Hz, 1 H), 2.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.6, 154.7, 137.0, 135.5, 129.6, 128.9, 128.6, 128.5, 128.2, 127.0, 77.2, 68.5, 55.4, 50.8, 48.3, 48.9, 45.3, 38.3, 30.2; IR (neat, cm^{-1}): 3062, 3027, 2929, 1699, 1496, 1454, 1406, 1354, 1300, 1275, 1255, 1238, 1223, 1167, 1119, 1103, 1073, 1042, 1012, 893, 746, 700; HRMS Calculated for $[C_{22}H_{25}NO_5S+H]^+$: 416.15263, Found: 416.15299. $[\alpha]_D^{26}$ = -8.2° (c = 1.0 $CHCl_3$).



4f-*trans*

(3S,5S)-benzyl 3-benzyl-5-(2-oxopropyl)thiomorpholine-4-carboxylate 1,1-dioxide (4f-*trans*)

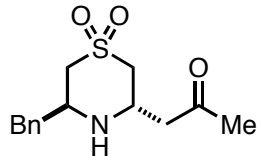
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40-7.20 (m, 10 H), 5.19-5.12 (m, 2 H), 4.82-4.76 (m, 1 H), 4.57-4.52 (m, 1 H), 3.34 (dd, J = 14.5 Hz, J = 7.0 Hz, 1 H), 3.28-3.01 (m, 7 H), 2.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.8, 154.9, 136.8, 135.5, 129.3, 128.8, 128.7, 128.6, 128.2, 127.0, 68.0, 54.8, 54.7, 52.6, 47.5, 45.3, 38.0, 30.1; IR (neat, cm^{-1}): 3062, 3027, 2929, 1698, 1497, 1454, 1405, 1354, 1300, 1274, 1255, 1238, 1225, 1167, 1119, 1103, 1073, 1042, 1012, 893, 746, 700; HRMS Calculated for $[C_{22}H_{25}NO_5S+H]^+$: 416.15263, Found: 416.15299. $[\alpha]_D^{26}$ = -17.2° (c = 1.0 $CHCl_3$).



4f'-*cis*

1-((3R,5S)-5-benzyl-1,1-dioxidothiomorpholin-3-yl)propan-2-one (4f'-*cis*)

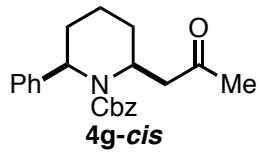
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34 (t, J = 7.5 Hz, 2 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.17 (d, J = 7.5 Hz, 2 H), 3.57-3.51 (m, 1 H), 3.50-3.44 (m, 1 H), 2.98-2.90 (m, 2 H), 2.83-2.67 (m, 4 H), 2.63 (dd, J = 17.5 Hz, J = 4.0 Hz, 1 H), 2.56 (dd, J = 17.5 Hz, J = 3.5 Hz, 1 H), 2.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.0, 135.9, 129.1, 128.8, 127.2, 56.5, 55.9, 55.3, 50.3, 47.8, 42.0, 30.4; IR (neat, cm^{-1}): 3581, 3317, 3027, 2923, 2854, 1712, 1494, 1455, 1360, 1294, 1259, 1238, 1119, 1030, 893, 755, 735, 702; HRMS Calculated for $[C_{14}H_{19}NO_3S+H]^+$: 282.11585, Found: 282.11569. $[\alpha]_D^{26}$ = 66.7° (c = 1.0 $CHCl_3$).



4f'-*trans*

1-((3S,5S)-5-benzyl-1,1-dioxidothiomorpholin-3-yl)propan-2-one (4f'-*trans*)

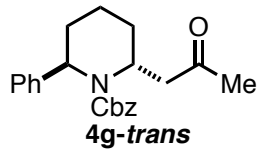
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 (t, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.17 (d, J = 7.5 Hz, 2 H), 4.01-3.95 (m, 1 H), 3.59-3.53 (m, 1 H), 3.17 (dd, J = 11.0 Hz, J = 5.0 Hz, 1 H), 3.02-2.75 (m, 7 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.1, 136.8, 129.4, 129.1, 127.5, 56.6, 54.8, 51.5, 47.5, 44.4, 41.1, 30.7. IR (neat, cm^{-1}): 3581, 3329, 3027, 2921, 2854, 1710, 1494, 1455, 1359, 1293, 1259, 1227, 1119, 1030, 893, 755, 735, 703; HRMS Calculated for $[C_{14}H_{19}NO_3S+H]^+$: 282.11585, Found: 282.11569. $[\alpha]_D^{26}$ = 96.1° (c = 1.0 $CHCl_3$).



4g-*cis*

(2S,6R)-benzyl 2-(2-oxopropyl)-6-phenylpiperidine-1-carboxylate (4g-*cis*)

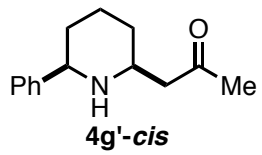
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.22 (m, 10H), 5.56 (d, J = 3.5 Hz, 1 H), 5.23-5.21 (m, 2 H), 4.93-4.88 (m, 1 H), 2.42 (dd, J = 13.5 Hz, J = 2.0 Hz, 1 H), 2.36 (dd, J = 16.5 Hz, J = 5.0 Hz, 1 H), 1.90-1.82 (m, 1 H), 1.85 (s, 3 H), 1.81-1.72 (m, 2 H), 1.63-1.53 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.4, 156.4, 141.9, 136.7, 128.4, 128.3, 128.3, 128.0, 127.9, 127.7, 126.7, 127.0, 126.4, 125.8, 67.5, 51.4, 47.2, 46.9, 29.8, 28.2, 26.3, 15.0; IR (neat, cm^{-1}): 3029, 2974, 2936, 2865, 1693, 1381, 1325, 1279, 1110, 1073, 1034, 740, 702; HRMS Calculated for $[C_{22}H_{25}NO_3+H]^+$: 352.19072, Found: 352.19093.



4g-*trans*

(2R,6R)-benzyl 2-(2-oxopropyl)-6-phenylpiperidine-1-carboxylate (3g-*trans*)

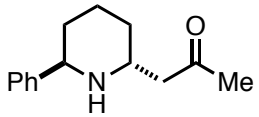
Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33-7.17 (m, 10 H), 5.26 (t, J = 4.0 Hz, 1 H), 5.12-5.04 (m, 2 H), 4.34-4.31 (m, 1 H), 3.12-3.09 (m, 1 H), 2.64 (dd, J = 16.0 Hz, J = 8.0 Hz, 1 H), 2.26-2.20 (m, 1 H), 2.12 (s, 3 H), 2.07-1.99 (m, 1 H), 1.76-1.67 (m, 1 H), 1.64-1.48 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.5, 155.9, 141.7, 136.5, 128.3, 128.2, 127.8, 127.6, 126.3, 125.8, 66.8, 55.0, 48.5, 48.3, 29.9, 27.1, 25.8, 15.1; IR (neat, cm^{-1}): 3029, 2974, 2938, 2865, 1702, 1381, 1325, 1279, 1110, 1073, 1034, 740, 702; HRMS Calculated for $[C_{22}H_{25}NO_3+H]^+$: 352.19072, Found: 352.19093.



4g'-*cis*

1-((2S,6R)-6-phenylpiperidin-2-yl)propan-2-one (4g'-*cis*)

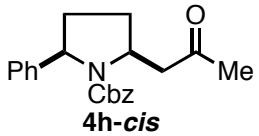
Colorless oil (yield: 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (d, J = 7.5 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.22 (t, J = 7.5 Hz, 1 H), 3.68 (dd, J = 11.0 Hz, J = 2.0 Hz, 1 H), 3.19-3.14 (m, 1 H), 2.59 (d, J = 6.0 Hz, 2 H), 2.25 (bs, 1 H), 2.13 (s, 3 H), 1.89-1.86 (m, 1 H), 1.79-1.75 (m, 1 H), 1.61-1.41 (m, 3 H), 1.26-1.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.3, 145.2, 128.3, 127.0, 126.7, 61.8, 52.9, 50.6, 34.0, 31.8, 30.7, 25.0; IR (neat, cm^{-1}): 3405, 2949, 2600, 2495, 1710, 1479, 1465, 1442, 1365, 1172, 1034, 930, 748, 699; HRMS Calculated for $[C_{14}H_{19}NO+H]^+$: 218.15394, Found: 218.15389.



4g'-*trans*

1-((2R,6R)-6-phenylpiperidin-2-yl)propan-2-one (4g'-*trans*)

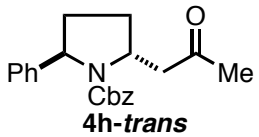
Colorless oil (yield: 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41-7.20 (m, 5 H), 3.96 (dd, J = 8.5 Hz, J = 3.0 Hz, 1 H), 3.60-3.55 (m, 1 H), 2.89 (dd, J = 17.0 Hz, J = 9.5 Hz, 1 H), 2.60-2.54 (m, 1 H), 2.21-2.12 (m, 1 H), 2.17 (s, 3 H), 1.86-1.80 (m, 1 H), 1.79-1.70 (m, 2 H), 1.62-1.60 (m, 2 H), 1.45-1.39 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.6, 144.5, 128.3, 128.2, 126.7, 61.8, 54.2, 52.9, 50.6, 47.9, 46.6, 34.1, 32.8, 31.8, 30.6, 30.2, 25.0, 20.2; IR (neat, cm^{-1}): 3405, 2939, 2601, 2495, 2284, 1854, 1818, 1714, 1677, 1641, 1587, 1494, 1479, 1381, 1357, 1174, 1035, 698; HRMS Calculated for $[C_{14}H_{19}NO+H]^+$: 218.15394, Found: 218.15389.



4h-*cis*

(2S,5R)-benzyl 2-(2-oxopropyl)-5-phenylpyrrolidine-1-carboxylate (4h-*cis*)

Due to the rotamers, major isomer was reported. Minor isomer signals are in parentheses. Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 96%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.35-7.20 (m, 9 H), 6.91 (bs, 1 H), 5.01-4.96 (m, 2 H), 4.93-4.84 (m, 2 H), 4.39 (bs, 1 H), 3.37 (d, J = 13.0 Hz, 1 H), 2.64 (dd, J = 16.5 Hz, J = 10.0 Hz, 1 H), 2.34-2.27 (m, 1 H), 2.21-2.05 (m, 4 H), 1.90-1.84 (m, 1 H), 1.64-1.60 (m, 2 H); ^{13}H NMR (125 MHz, CD_2Cl_2) δ = 207.0, 155.5, 144.4, 137.3, 128.7, 127.9, 127.4, 127.1, 125.9, 66.8, 62.9, 56.2, 49.7, 49.0, 34.8, 30.5. IR (neat, cm^{-1}): 3029, 2974, 2936, 2865, 1701, 1381, 1325, 1279, 1110, 1073, 1034, 740, 702; HRMS Calculated for $[C_{21}H_{23}NO_3+H]^+$: 338.17507, Found: 338.17596.



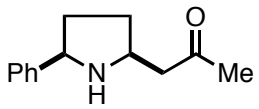
4h-*trans*

(2S,5S)-benzyl 2-(2-oxopropyl)-5-phenylpyrrolidine-1-carboxylate (4h-*trans*)

Due to the rotamers, major isomer was reported. Minor isomer signals are in parentheses.

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 96%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.37-7.11 (m, 10 H), 6.83-6.80 (m, 1 H), 5.15-5.07 (m, 2 H), 5.00-4.96 (m, 2 H), 4.66 (4.75) (d, J = 13.0 Hz (J = 13.0 Hz), 1 H), 4.55-4.50 (m, 1 H), 3.27 (3.01), (dd, J = 17.0 Hz, J = 3.0 Hz (J = 17.0 Hz, J = 2.5 Hz), 1 H), 2.56-2.48 (m, 1 H), 2.41-2.29 (m, 1 H), 2.20-2.12 (m, 2 H), 2.16 (2.05) (s, 3 H), 1.77-1.73 (1.73-

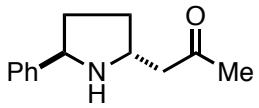
1.69) (m, 1 H), 1.64-1.58 (m, 1H); ^{13}H NMR (125 MHz, CD_2Cl_2) δ = 207.4 (207.0), 154.5 (154.1), 144.8 (144.0), 137.2 (137.3), 128.8 (128.7), 128.6 (128.6), 128.4 (128.3), 127.7 (127.3), 127.0, 125.6, 67.1 (66.6), 61.8 (61.8), 55.2 (54.5), 47.1 (48.3), 32.9 (31.9), 30.6 (30.5), 27.6 (28.5); IR (neat, cm^{-1}): 3029, 2974, 2936, 2865, 1703, 1381, 1325, 1279, 1110, 1073, 1034, 740, 702; HRMS Calculated for $[C_{21}H_{23}NO_3+H]^+$: 338.17507, Found: 338.17596.



4h'-*cis*

1-((2S,5R)-5-phenylpyrrolidin-2-yl)propan-2-one (4h'-*cis*)

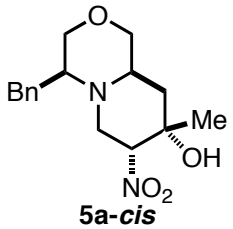
Colorless oil (yield: 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.41 (bs, 1 H), 7.68 (d, J = 7.5 Hz, 2 H), 7.38-7.30 (m, 3 H), 4.50 (t, J = 9.0 Hz, 1 H), 3.97-3.91 (m, 1 H), 3.29 (dd, J = 17.5 Hz, J = 5.0 Hz, 1 H), 3.20 (dd, J = 18.5 Hz, J = 8.0 Hz, 1 H), 2.48-2.24 (m, 3 H), 2.06 (s, 3 H), 1.95-1.87 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.9, 134.0, 129.1, 128.7, 63.3, 55.9, 44.6, 30.1, 30.0, 28.7. IR (neat, cm^{-1}): 3406, 2946, 2602, 2496, 1711, 1479, 1465, 1443, 1367, 1172, 1035, 931, 747, 699; HRMS Calculated for $[C_{13}H_{17}NO+Na]^+$: 226.12024, Found: 226.12016.



4h'-*trans*

1-((2R,5R)-5-phenylpyrrolidin-2-yl)propan-2-one (4h'-*trans*)

Colorless oil (yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.40 (bs, 1 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.38-7.30 (m, 3 H), 4.69 (dd, J = 11.0 Hz, J = 6.0 Hz, 1 H), 4.24-4.18 (m, 1 H), 3.38 (dd, J = 18.5 Hz, J = 6.5 Hz, 1 H), 2.93 (dd, J = 18.5 Hz, J = 6.5 Hz, 1 H), 2.48-2.35 (m, 2 H), 2.28-2.20 (m, 1 H), 2.07 (s, 3 H), 1.81-1.74 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.5, 134.6, 129.0, 128.8, 128.1, 62.3, 55.3, 45.5, 31.7, 30.5, 29.9; IR (neat, cm^{-1}): 3405, 2939, 2601, 2495, 2284, 1854, 1818, 1710, 1677, 1641, 1587, 1494, 1479, 1381, 1357, 1174, 1035, 698; HRMS Calculated for $[C_{13}H_{17}NO+Na]^+$: 226.12024, Found: 226.12016.

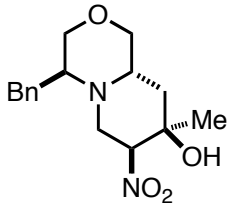


5a-*cis*

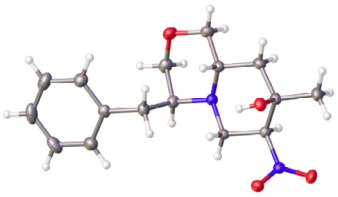
(4S,7R,8S,9aR)-4-benzyl-8-methyl-7-nitrooctahydropyrido[2,1-c][1,4]oxazin-8-ol (5a-*cis*)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 93%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.29 (t, J = 7.5 Hz, 2 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.12 (d, J = 7.5 Hz, 2 H), 4.60 (dd, J = 11.5 Hz, J = 3.5 Hz, 1 H), 4.51 (t, J = 5.0 Hz, 1 H), 4.12 (t, J = 5.0 Hz, 1 H), 3.64 (dd, J = 11.0 Hz, J = 3.0 Hz, 1 H), 3.61 (m, 3 H), 3.23-3.12 (m, 2 H), 3.08 (dd, J = 13.5 Hz, J = 4.5 Hz, 1 H), 3.00 (d, J = 1.5 Hz, 1 H), 2.89 (t, J = 11.0 Hz, 1 H), 2.78-2.73 (m, 1 H), 2.71-2.65 (m, 1 H), 2.34 (dd, J = 15.0 Hz, J = 9.0 Hz, 1 H), 1.64 (dd, J = 13.5 Hz, J = 2.0 Hz, 1 H), 1.37 (s, 3 H), 1.24 (t, J = 11.5 Hz, 1 H); ^{13}H NMR (125 MHz, CD_2Cl_2) δ = 137.5, 128.9, 128.5, 126.5, 89.4, 71.1, 68.3, 61.3, 58.5, 55.0, 48.5, 39.5, 35.8, 26.9; IR (neat, cm^{-1}): 3399,

3027, 2923, 2862, 1552, 1496, 1457, 1421, 1371, 1299, 1276, 1245, 1179, 1127, 1076, 1014, 928, 894, 738, 702, 606; HRMS Calculated for $[C_{16}H_{22}N_2O_4+H]^+$: 307.16523, Found: 307.16596. $[\alpha]_D^{26}$ = 157.0° (c = 1.0 $CHCl_3$).

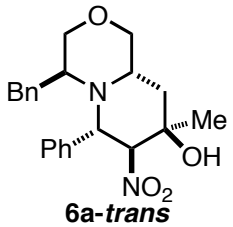


5a-*trans*

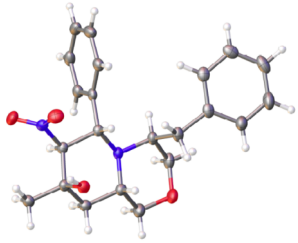


(4S,7S,8R,9aS)-4-benzyl-8-methyl-7-nitrooctahydropyrido[2,1-c][1,4]oxazin-8-ol (5a-*trans*)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.31-7.16 (m, 5 H), 4.65 (dd, *J* = 11.0 Hz, *J* = 3.5 Hz, 1 H), 3.80 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1 H), 3.64-3.59 (m, 2 H), 3.39 (d, *J* = 11.5 Hz, 1 H), 3.24-3.20 (m, 1 H), 3.09 (t, *J* = 10.5 Hz, 1 H), 3.05-3.00 (m, 3 H), 2.95-2.92 (m, 1 H), 2.78 (d, *J* = 10.5 Hz, 1 H), 1.69 (dd, *J* = 13.5 Hz, J = 2.5 Hz, 1 H), 1.36 (s, 3 H), 1.15 (t, *J* = 11.5 Hz, 1 H); ^{13}H NMR (125 MHz, CD_2Cl_2) δ = 139.4, 129.4, 128.6, 126.1, 89.5, 71.9, 68.7, 68.0, 60.8, 49.9, 47.9, 39.9, 28.7, 27.0; IR (neat, cm^{-1}): 3399, 3027, 2923, 2862, 1552, 1496, 1457, 1421, 1371, 1299, 1276, 1245, 1179, 1127, 1076, 1014, 928, 894, 738, 702, 606; HRMS Calculated for $[C_{16}H_{22}N_2O_4+H]^+$: 307.16523, Found: 307.16596. $[\alpha]_D^{26}$ = 36.9° (c = 1.0 $CHCl_3$).



6a-*trans*



(4S,6S,7S,8R,9aS)-4-benzyl-8-methyl-7-nitro-6-phenyloctahydropyrido[2,1-c][1,4]oxazin-8-ol (6a-*trans*)

Purified by flash chromatography (EtOAc/Hexane) as colorless oil (yield: 90%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.58 (d, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 7.32-7.30 (m, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 7.11-7.05 (m, 3 H), 6.68 (d, *J* = 7.5 Hz, 2 H), 4.63 (d, *J* = 10.0 Hz, 1 H), 4.56 (d, *J* = 10.0 Hz, 1 H), 3.84 (dd, *J* = 11.0 Hz, *J* = 2.5 Hz, 1 H), 3.55-3.45 (m, 2 H), 3.29 (t, *J* = 11.0 Hz, 1 H), 3.23-3.16 (m, 2 H), 3.05 (t, *J* = 11.0 Hz, 1 H), 2.85 (d, *J* = 12.0 Hz, 1 H), 2.52 (d, *J* = 11.5 Hz, 1 H), 1.81 (dd, *J* = 13.5 Hz, *J* = 2.5 Hz, 1 H), 1.31 (s, 3 H), 1.28 (t, *J* = 8.5 Hz, 1 H); ^{13}H NMR (125 MHz, CD_2Cl_2) δ = 139.4, 135.4, 130.5, 129.4, 129.2, 128.6, 128.3, 128.0, 127.2, 125.9, 97.8, 72.1, 68.6, 67.9, 32.1, 56.5, 48.1, 39.4, 27.2, 27.1. IR (neat, cm^{-1}): 3397, 3025, 2922, 2860, 1553, 1499, 1454, 1420, 1370, 1286, 1272, 1246, 1178, 1127, 1075, 1013, 928, 893, 736, 701, 606; HRMS Calculated for $[C_{22}H_{26}N_2O_4+H]^+$: 383.19654, Found: 383.19676. $[\alpha]_D^{26}$ = 52.6° (c = 1.0 $CHCl_3$).

IV. ORTEP Drawing of the crystal structures

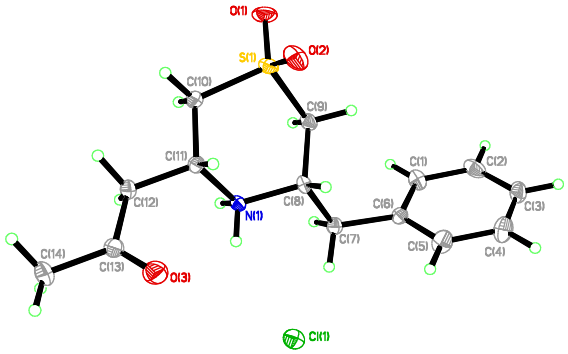


Figure 1. Perspective view of the molecular structure of **4f'-*trans*** (ammonium chloride salt) with the atom labeling scheme. The thermal ellipsoids are scaled to enclose 50% probability. **CCDC: 823511**.

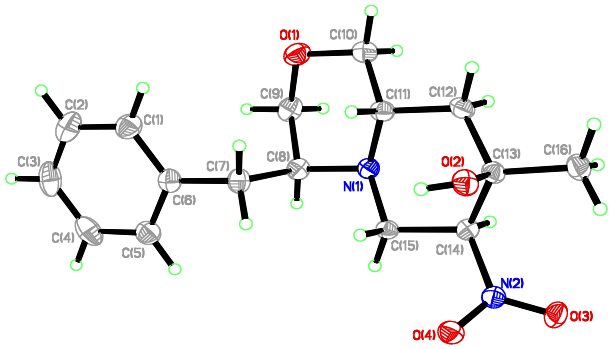


Figure 2. Perspective view of the molecular structure of **5a-*trans*** with the atom labeling scheme. The thermal ellipsoids are scaled to enclose 50% probability. **CCDC: 823510**.

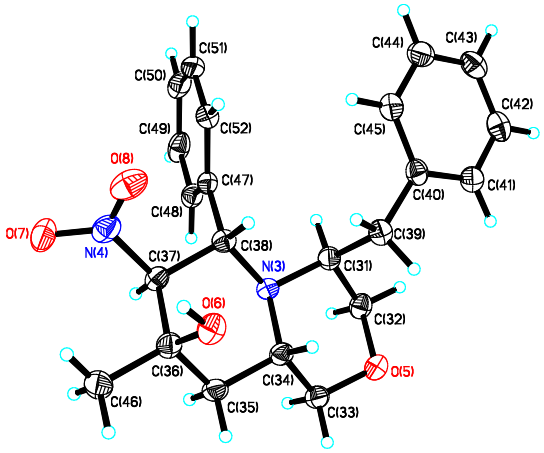
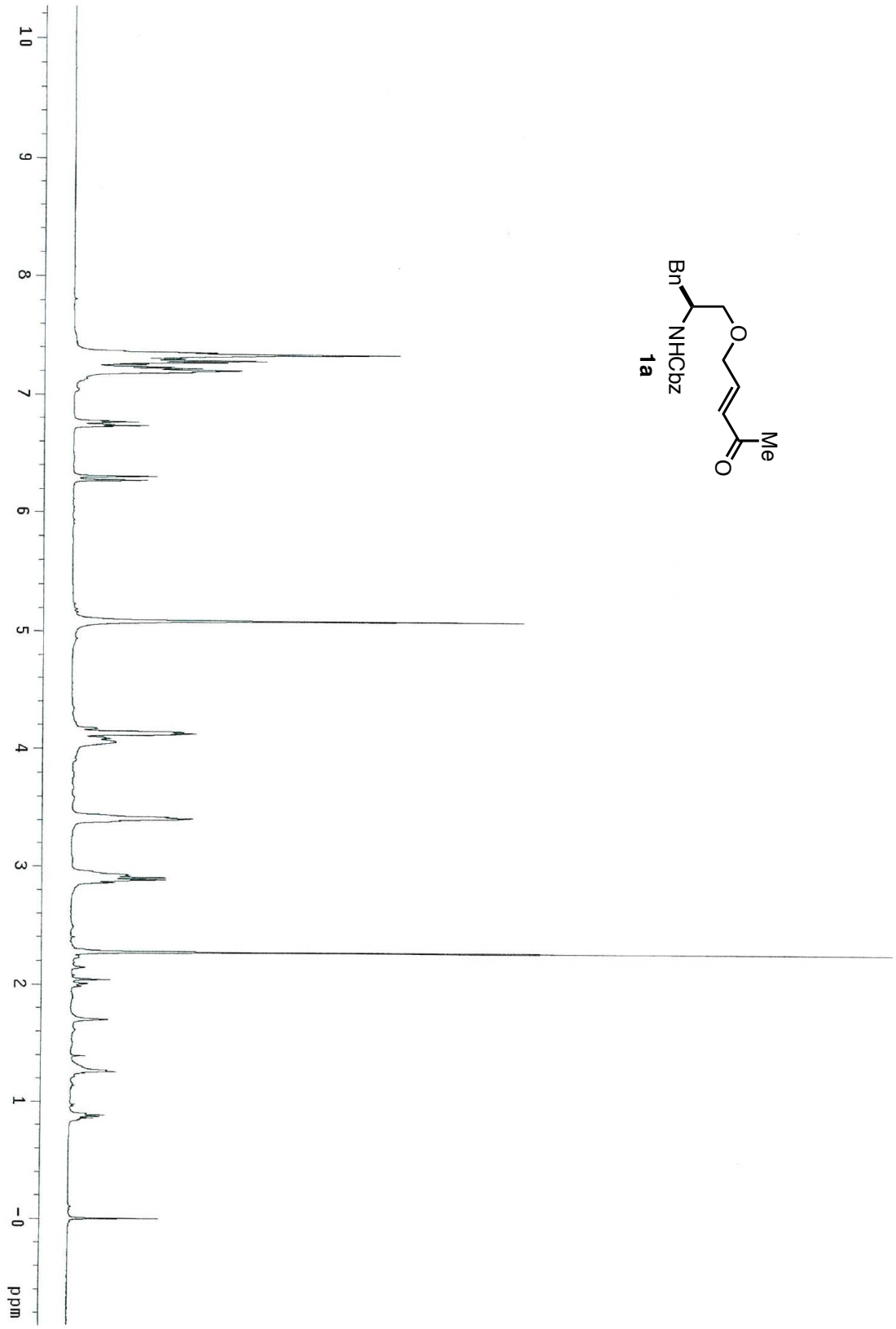
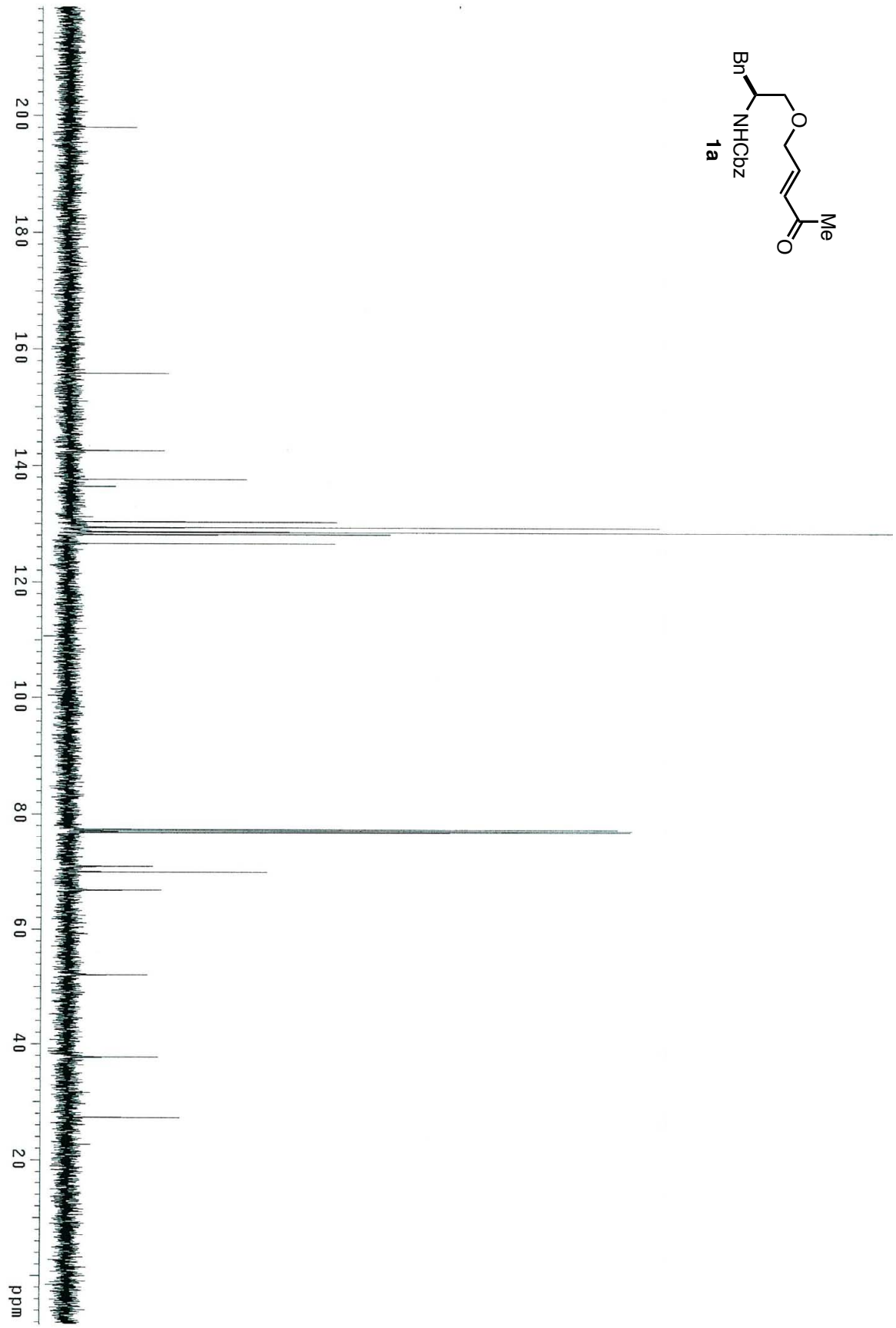


Figure 3. Perspective view of the molecular structure of **6a-*trans*** with the atom labeling scheme. The thermal ellipsoids are scaled to enclose 50% probability. **CCDC: 823509**.

V. **NMR** spectra

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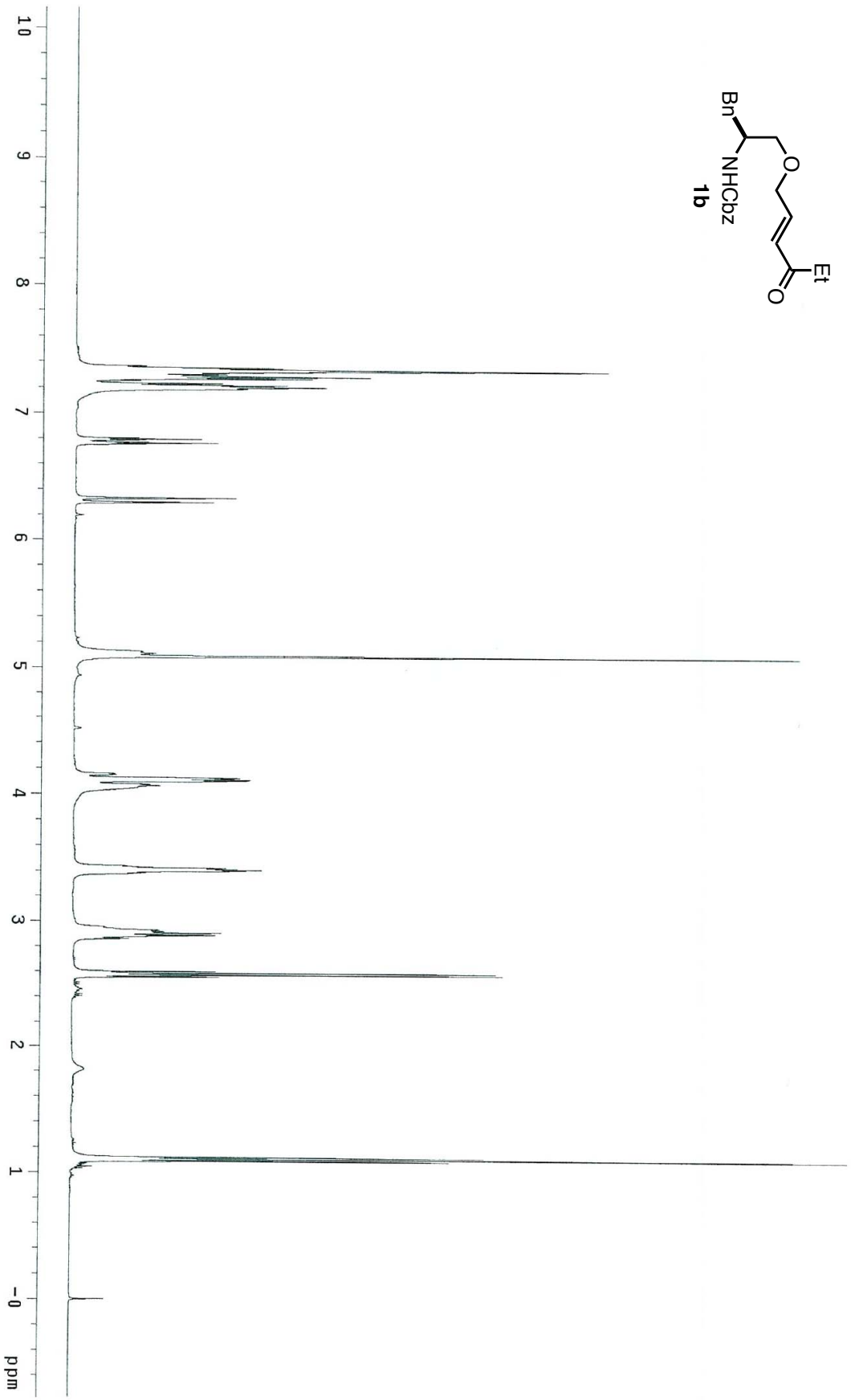
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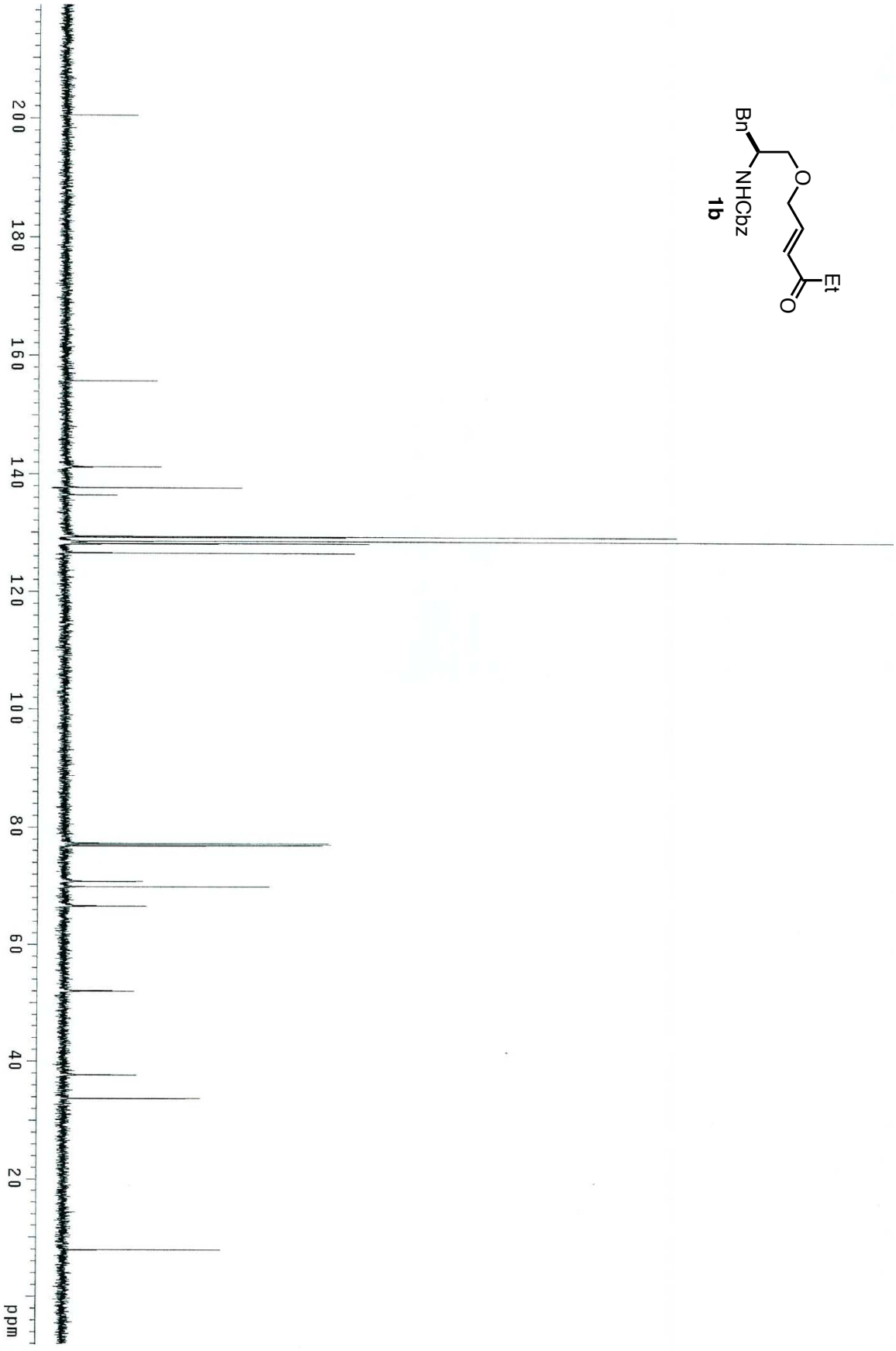
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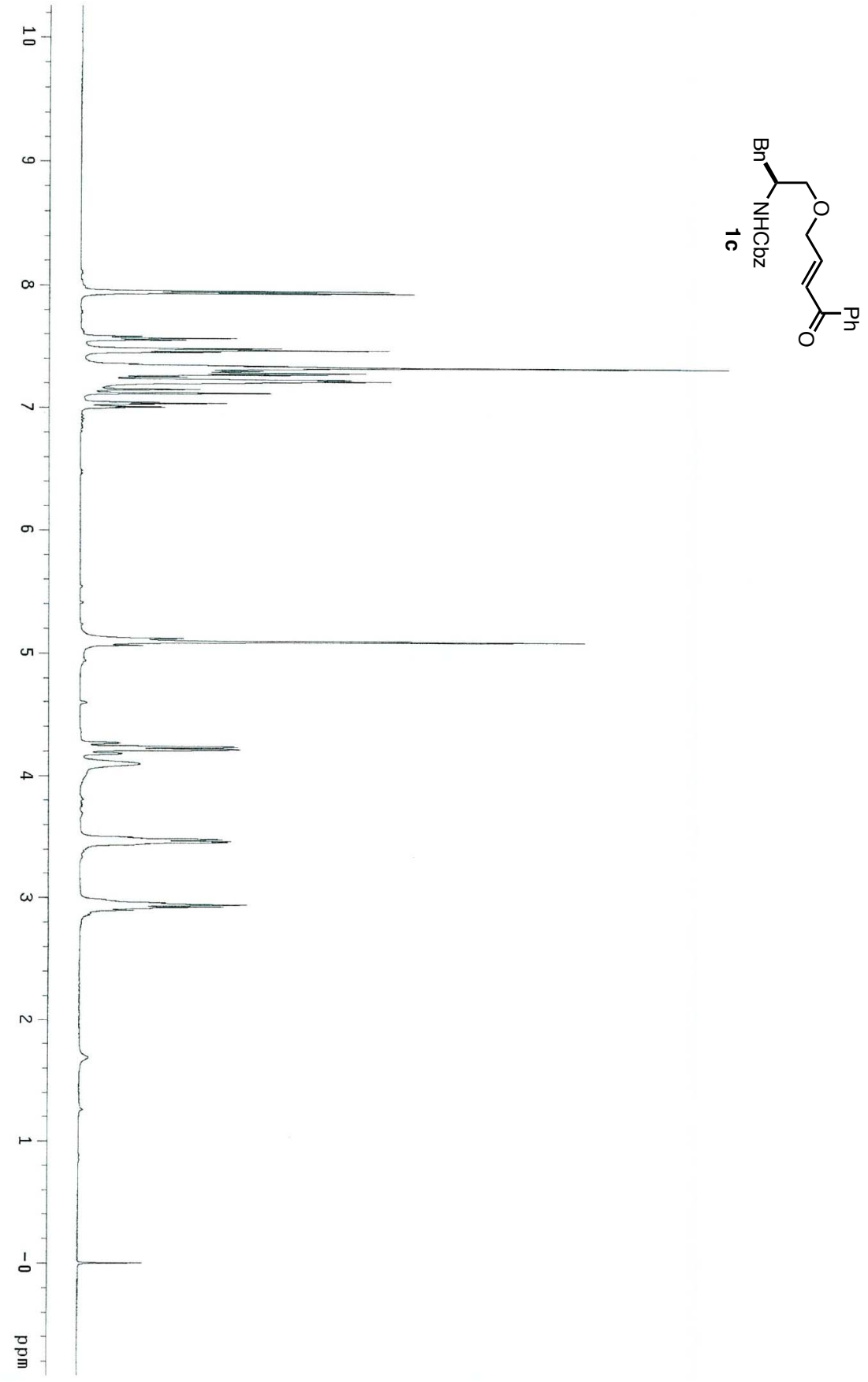
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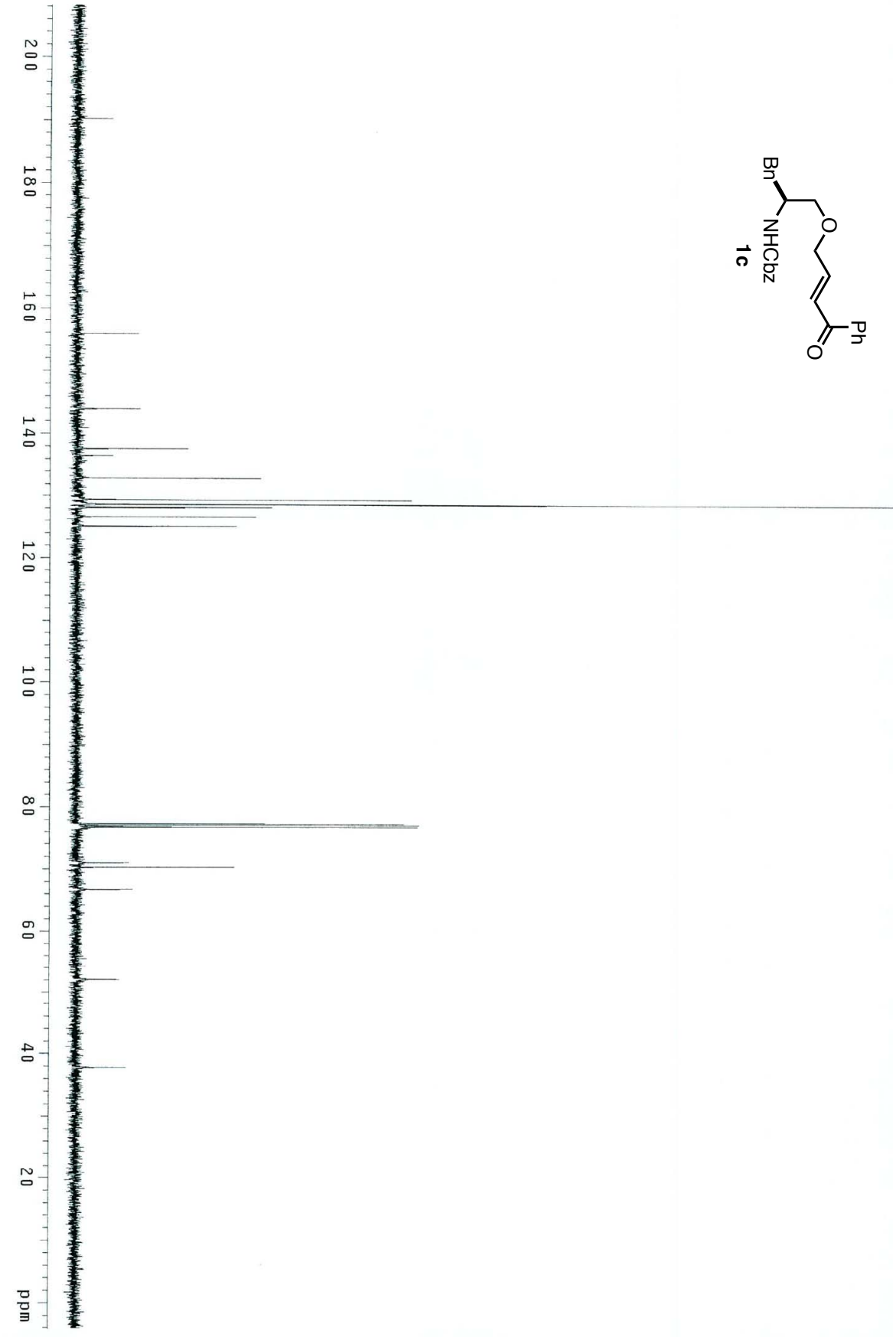
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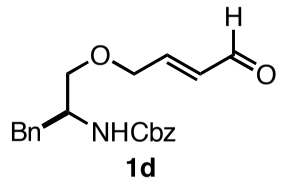

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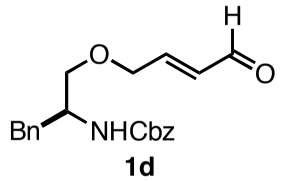

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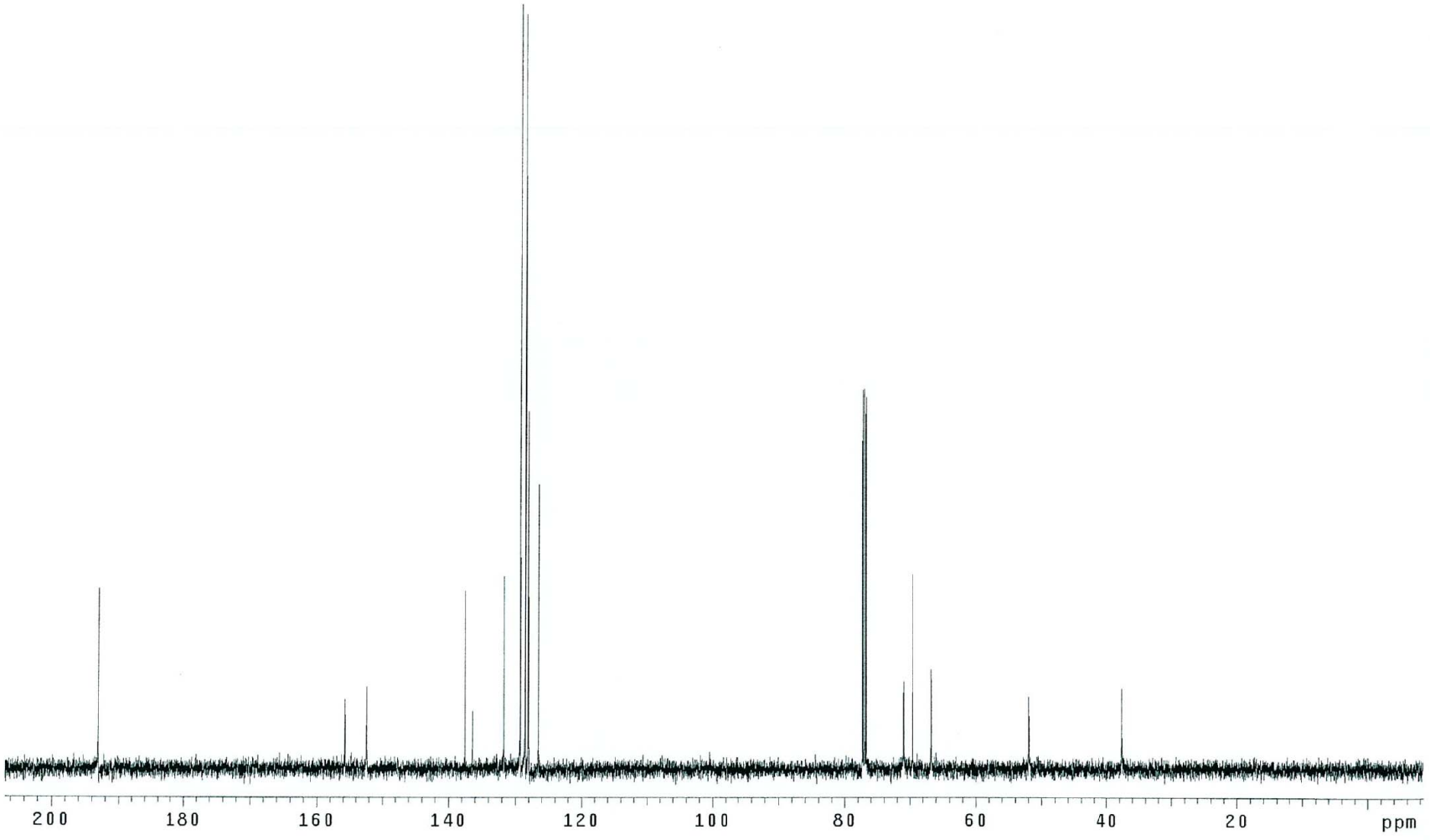

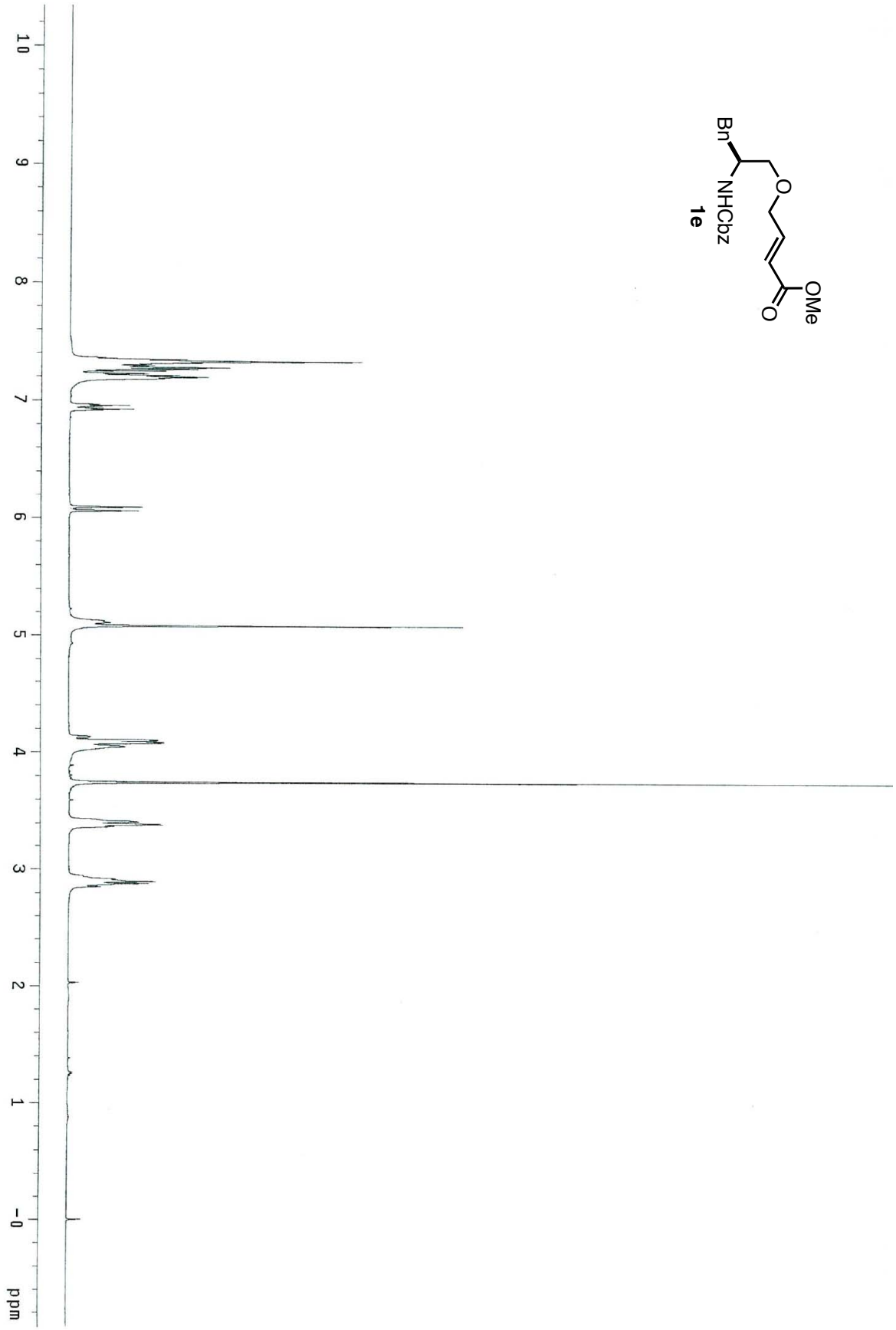
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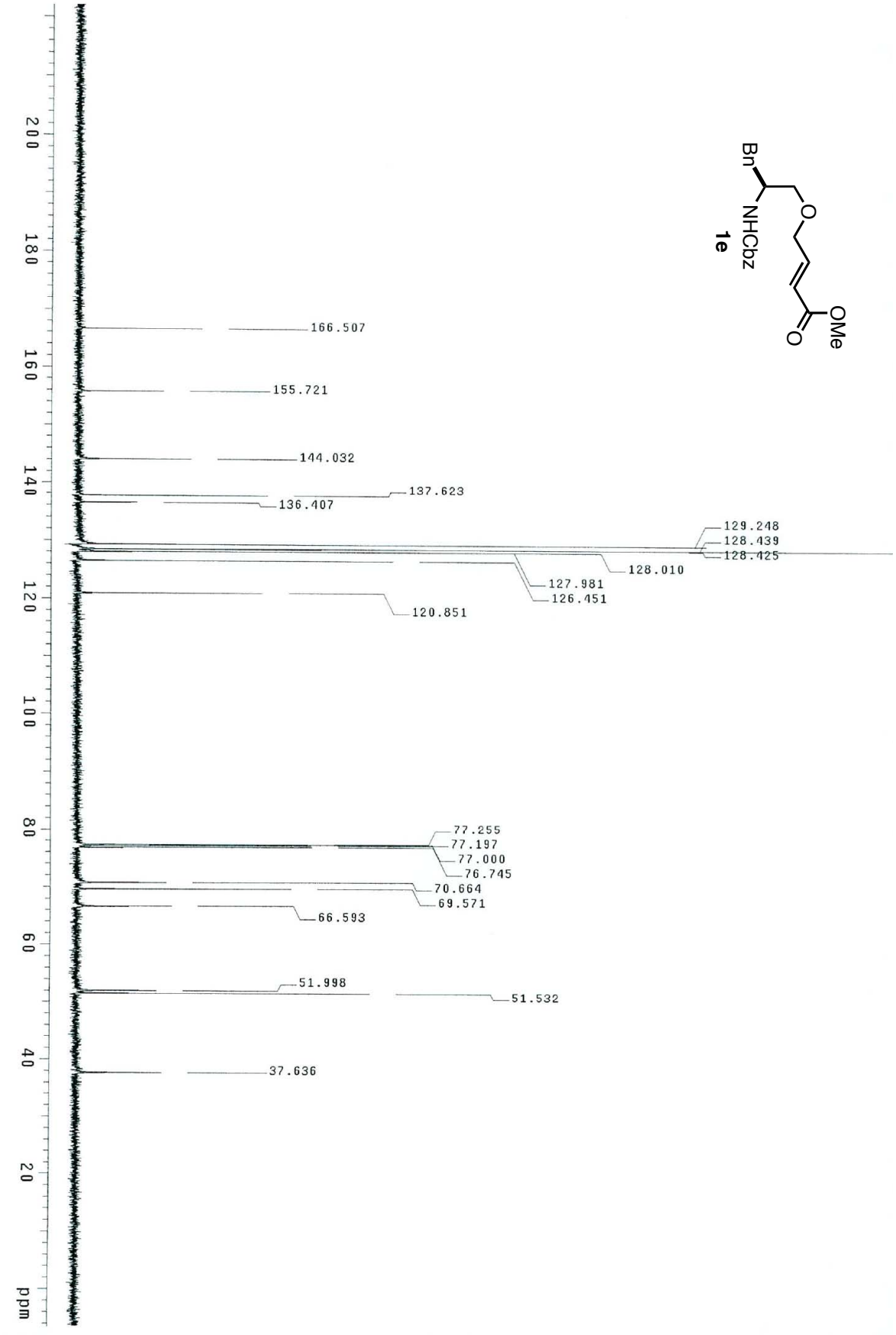
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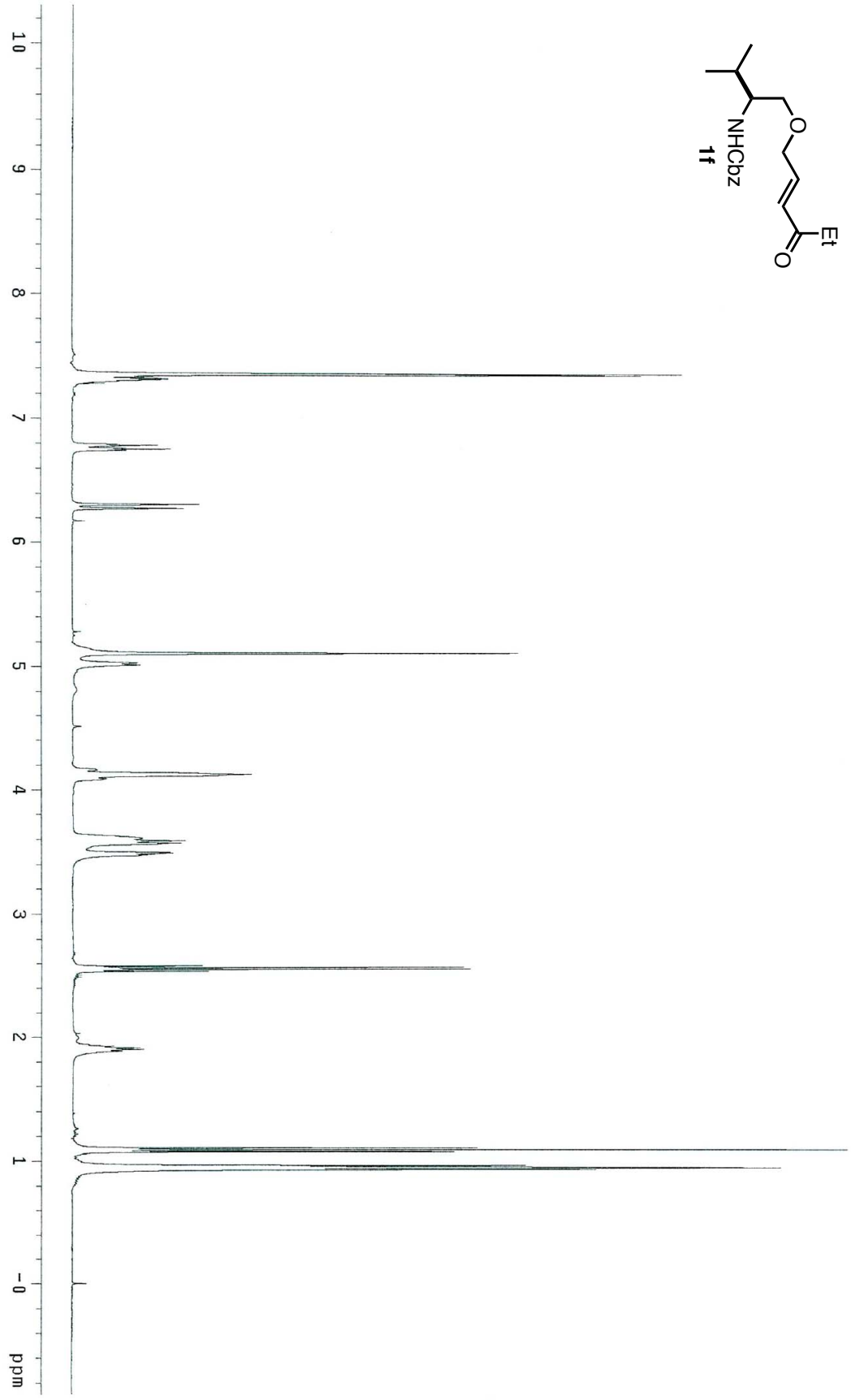
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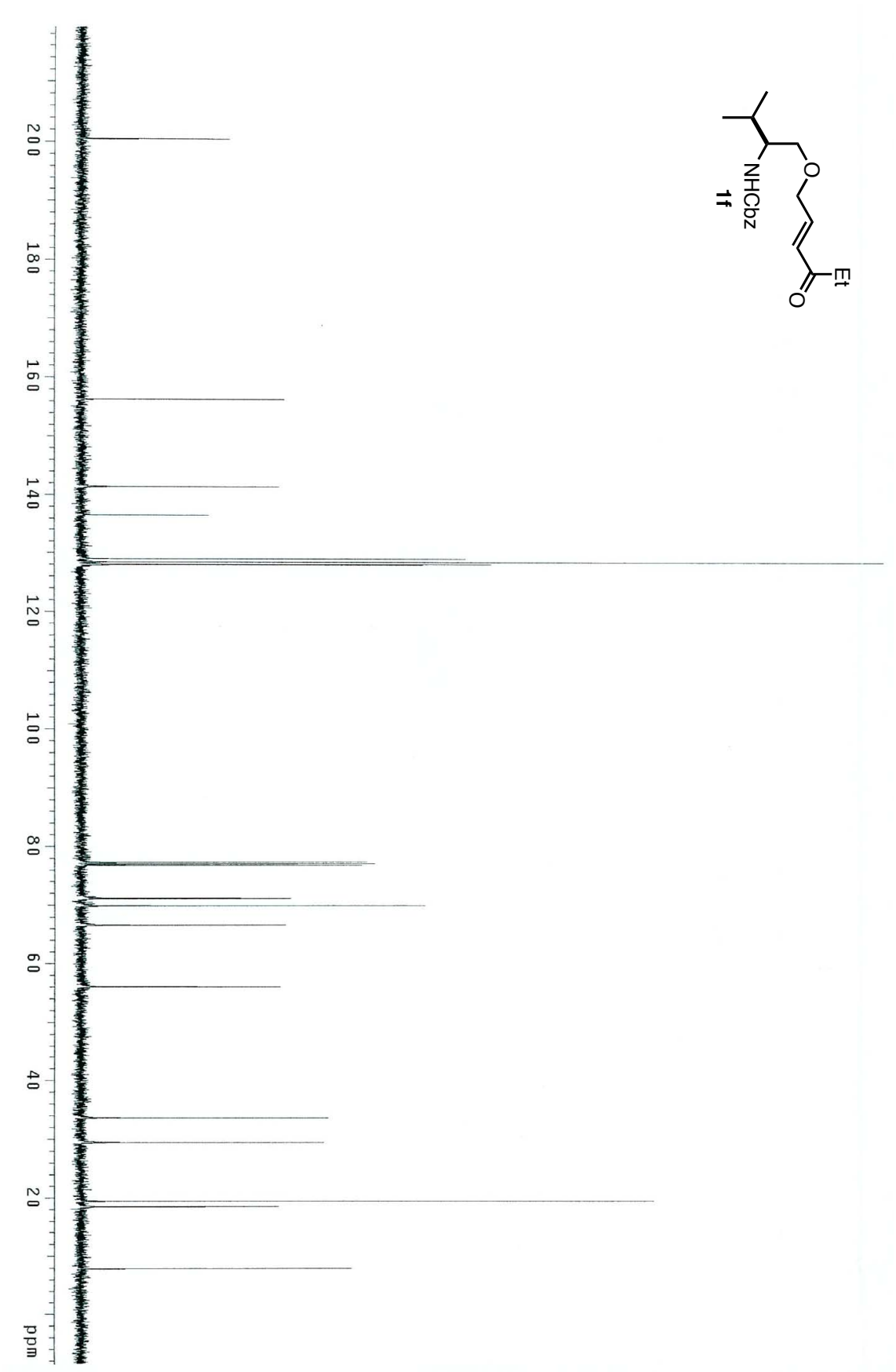
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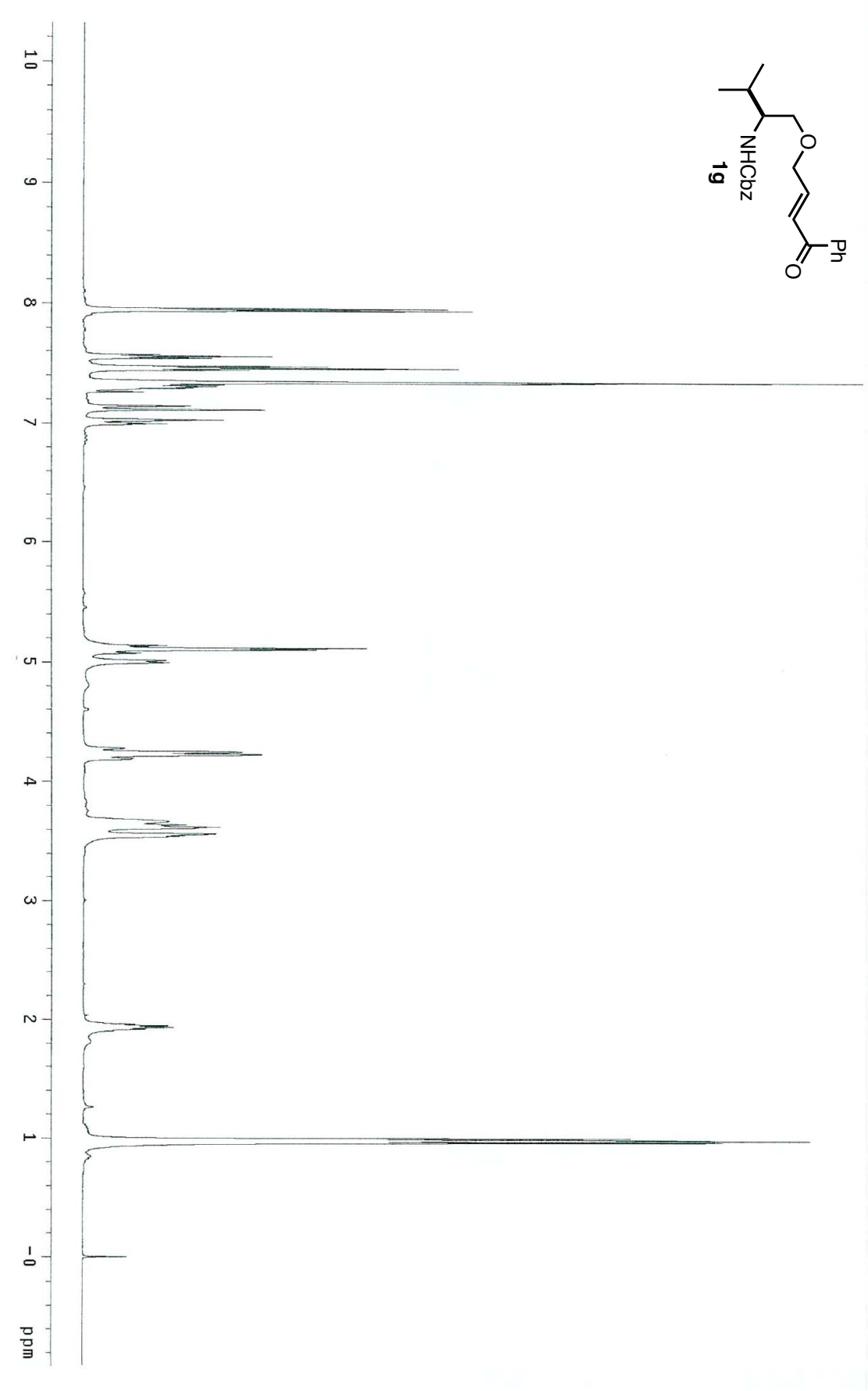
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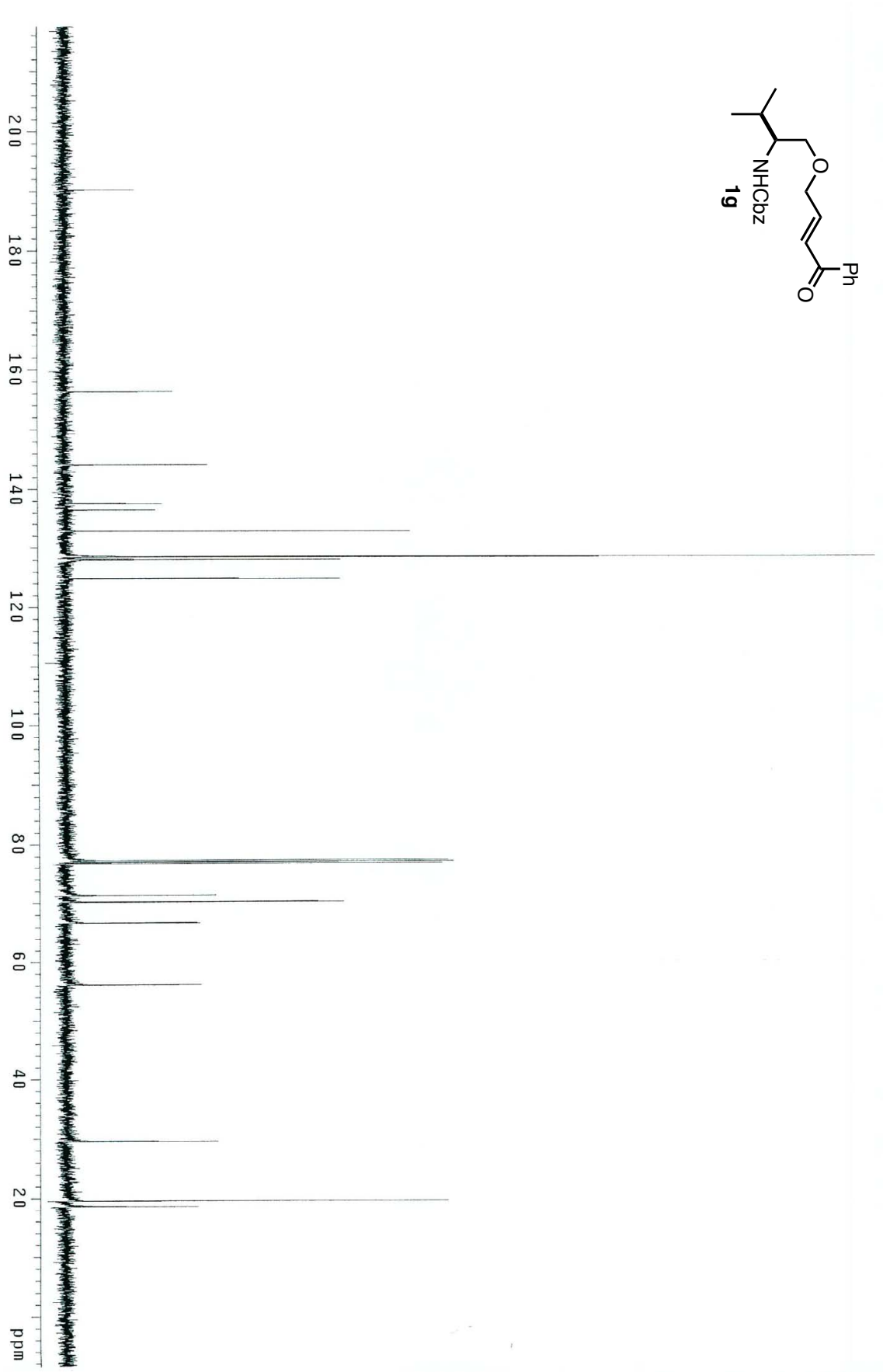
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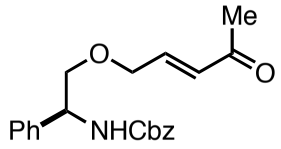

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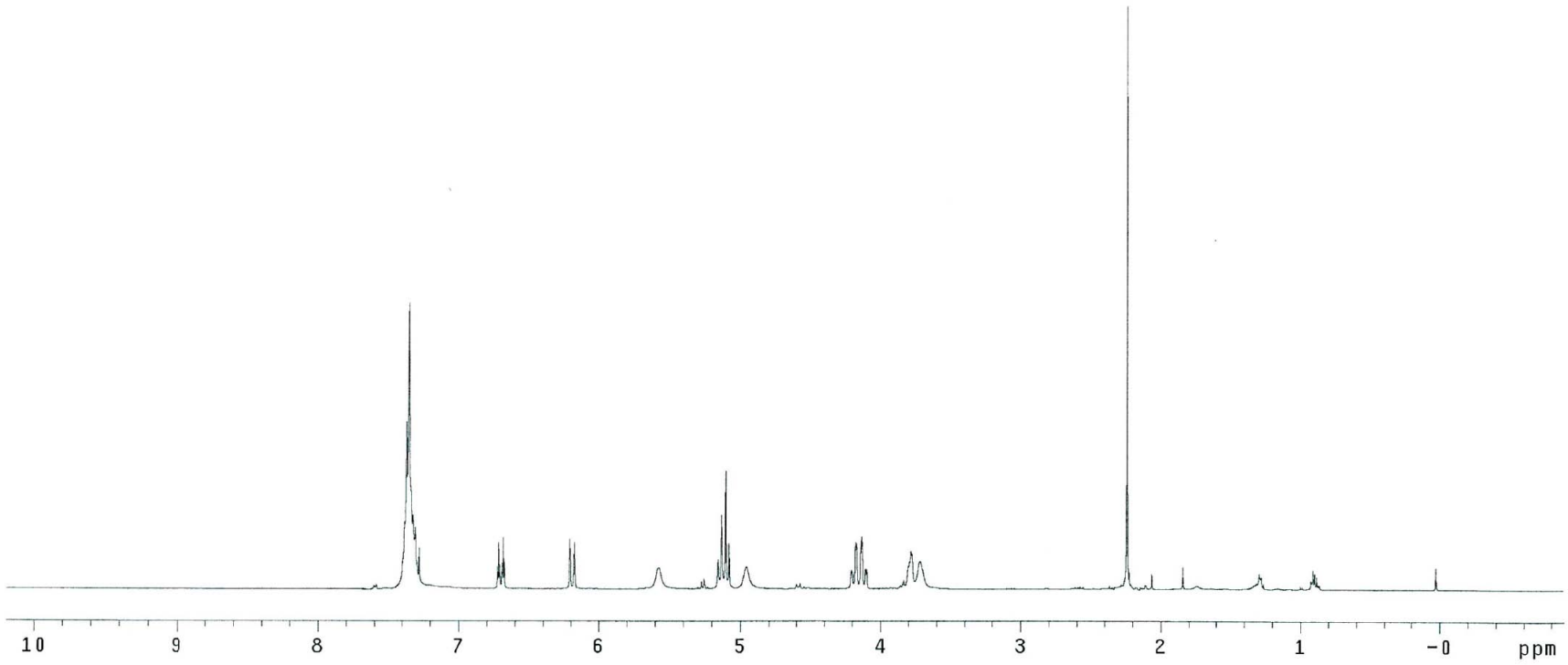

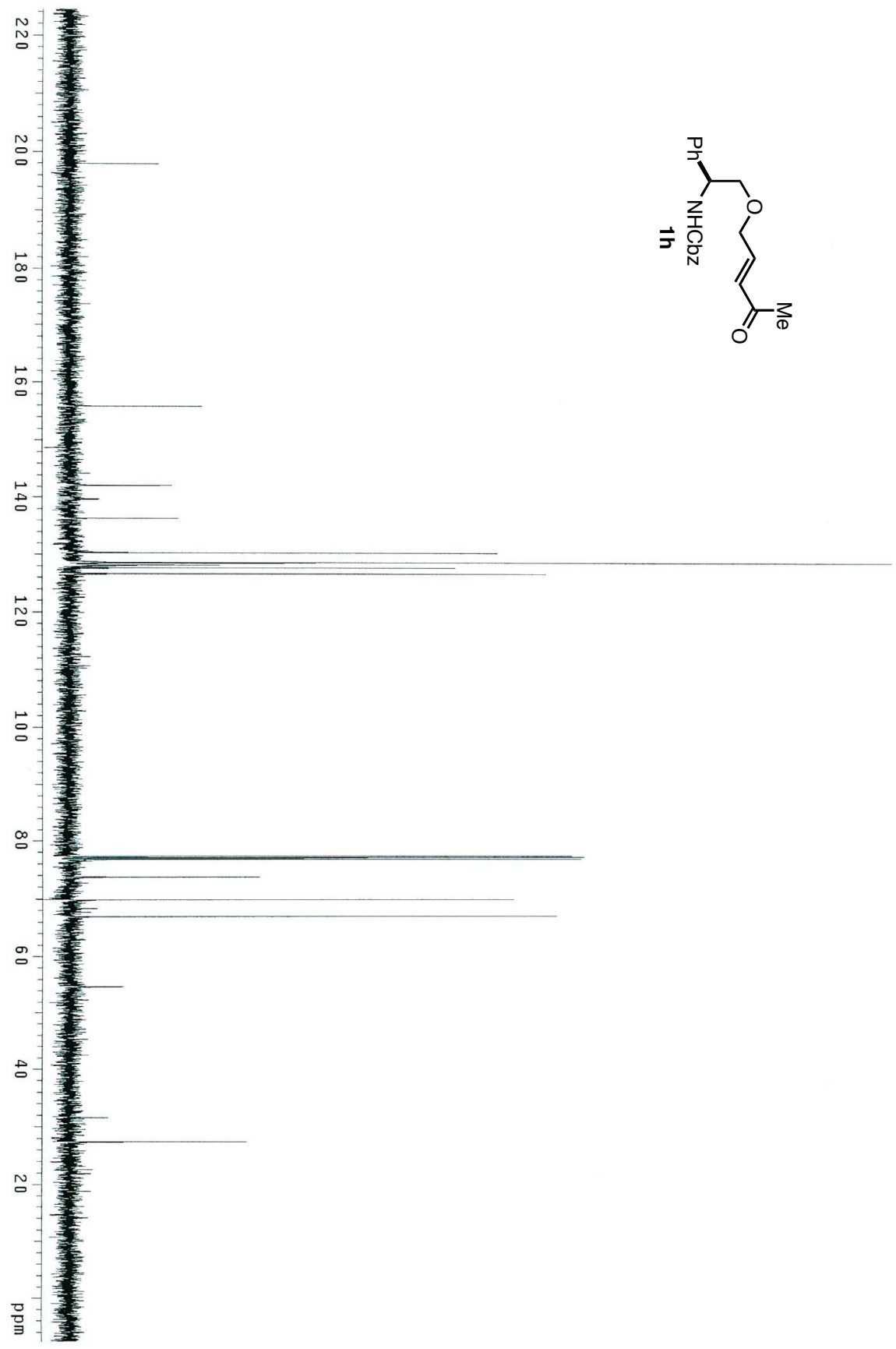
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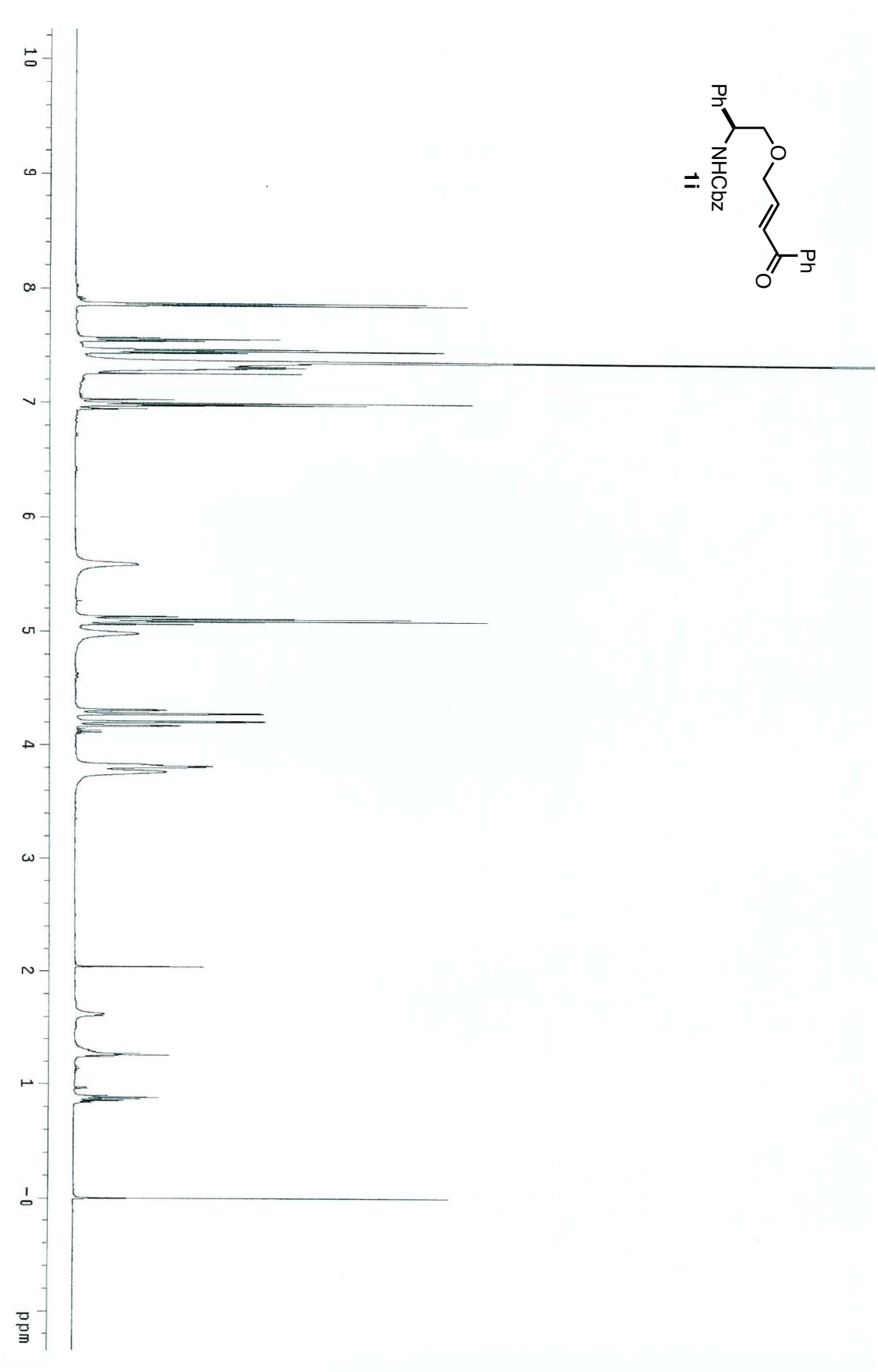
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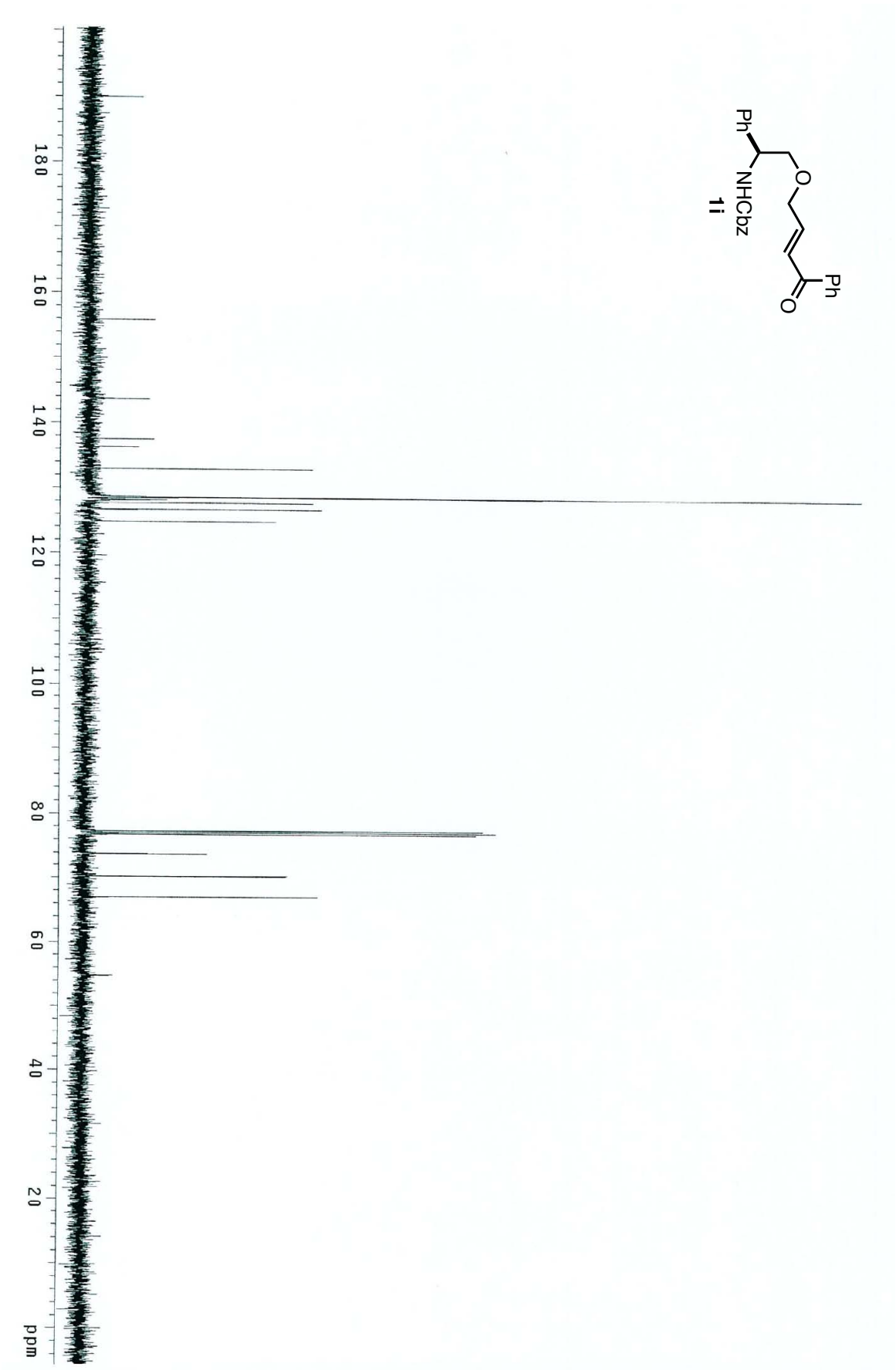
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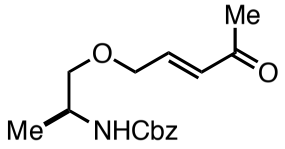

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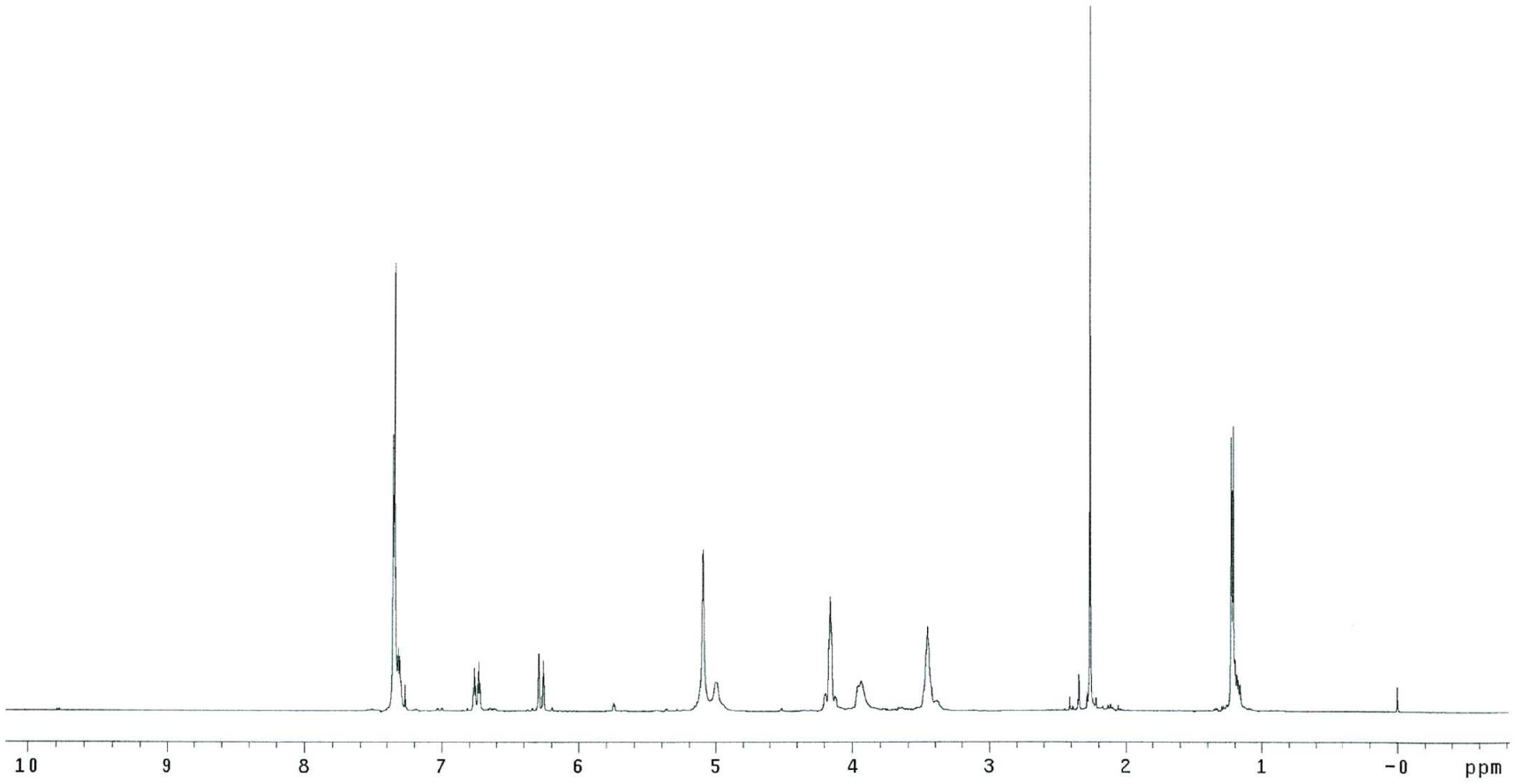

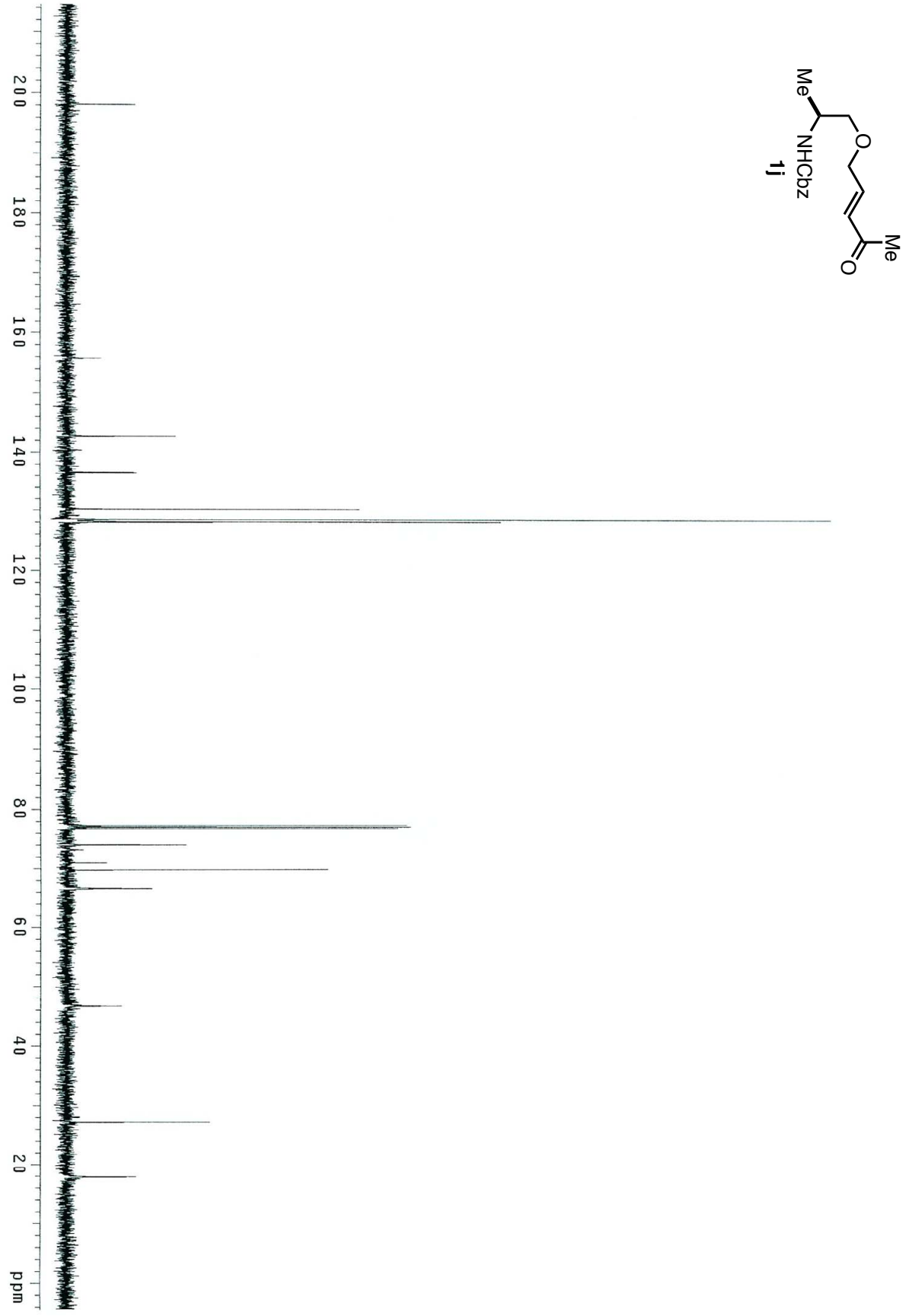
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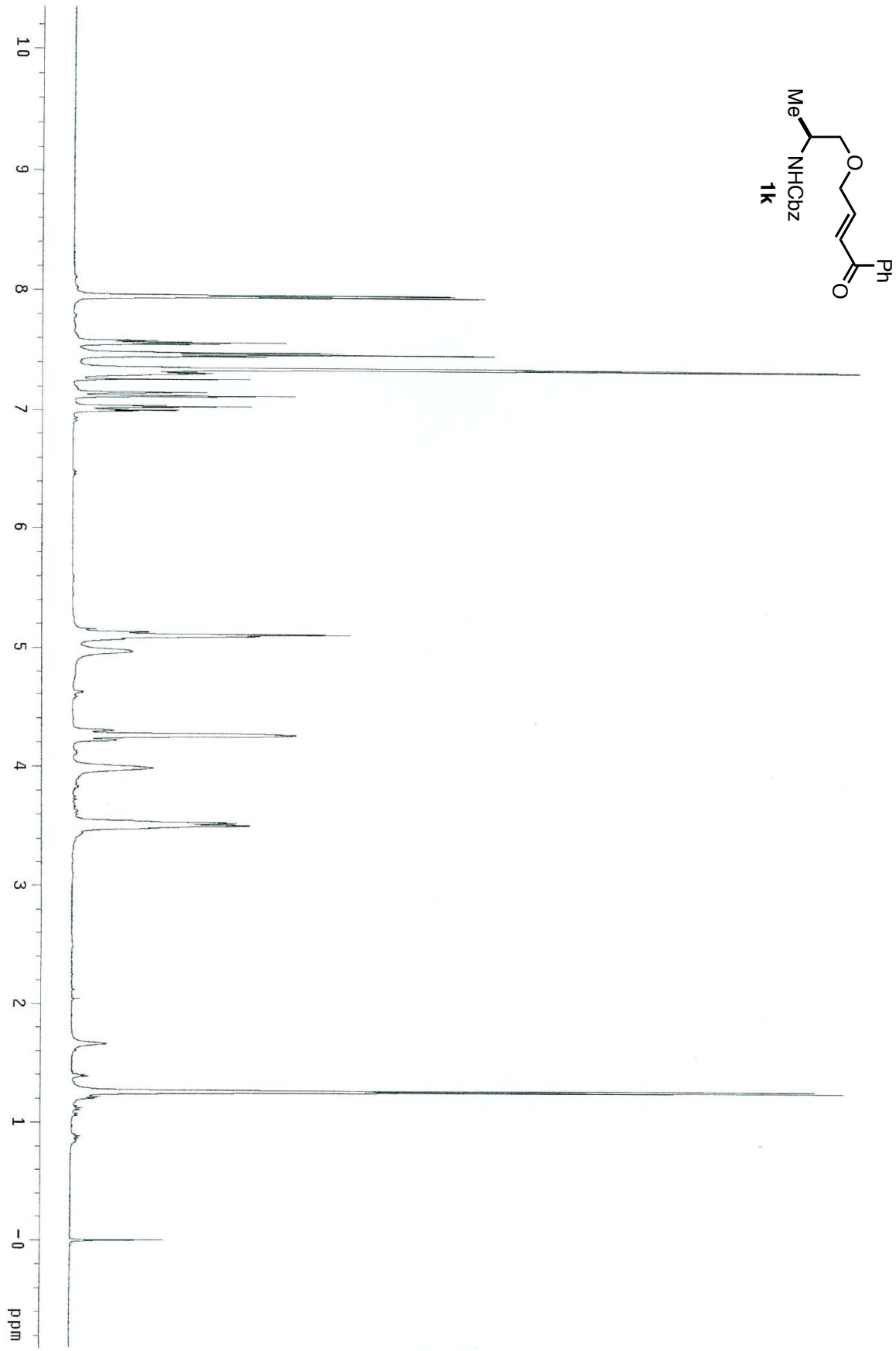
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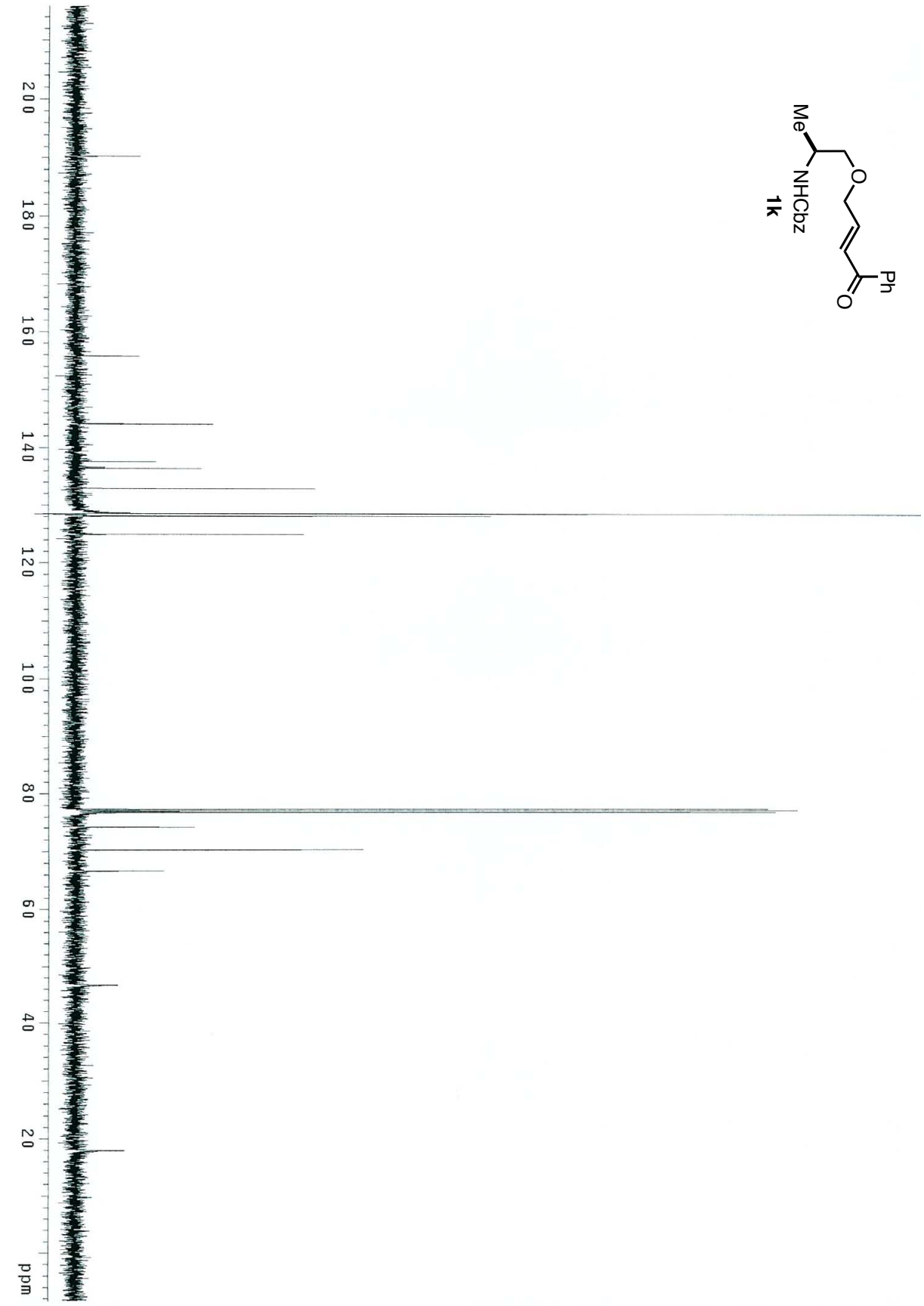
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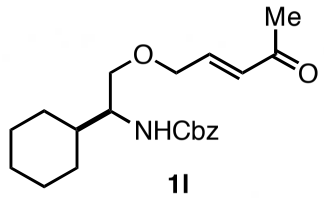

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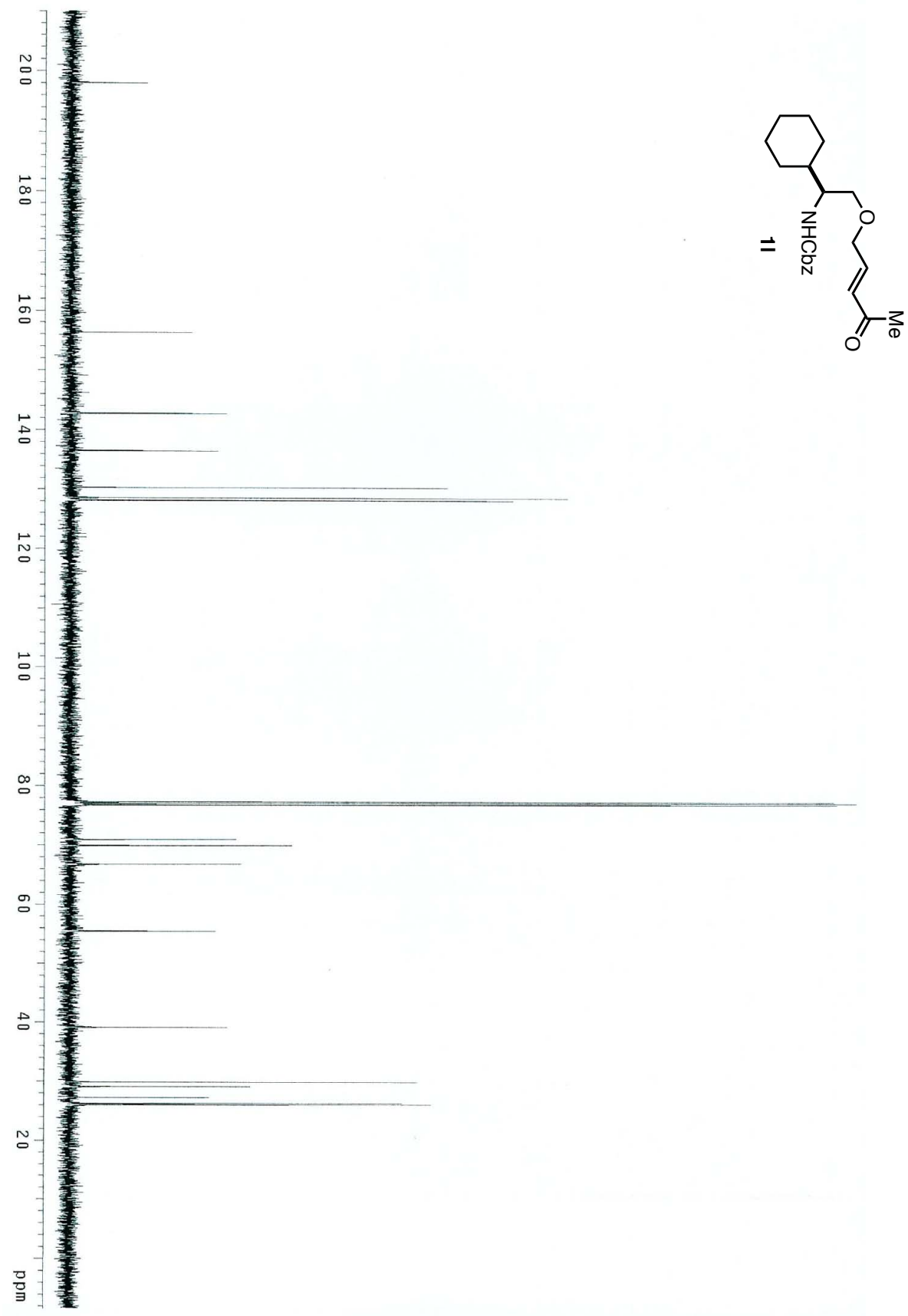
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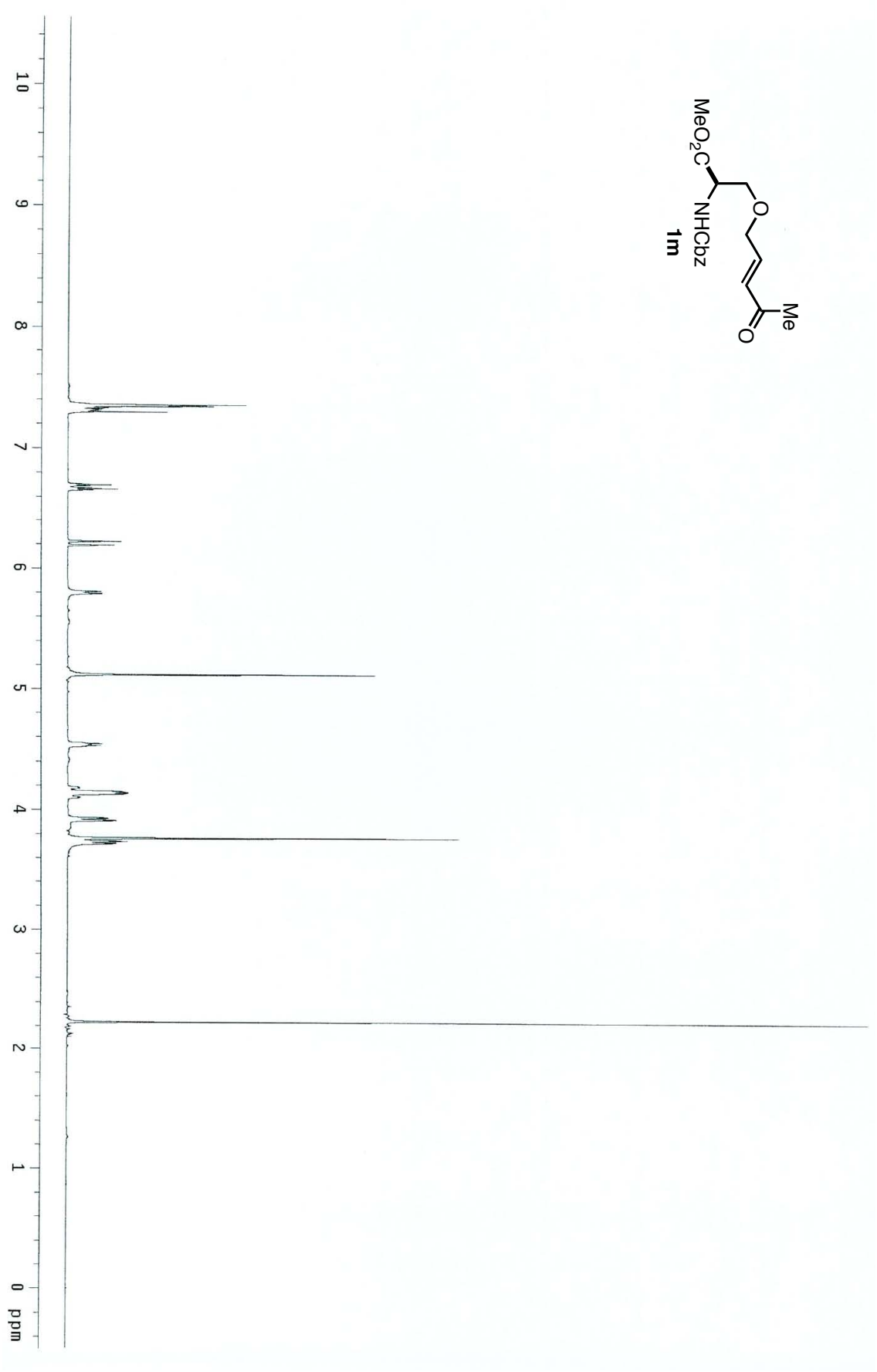
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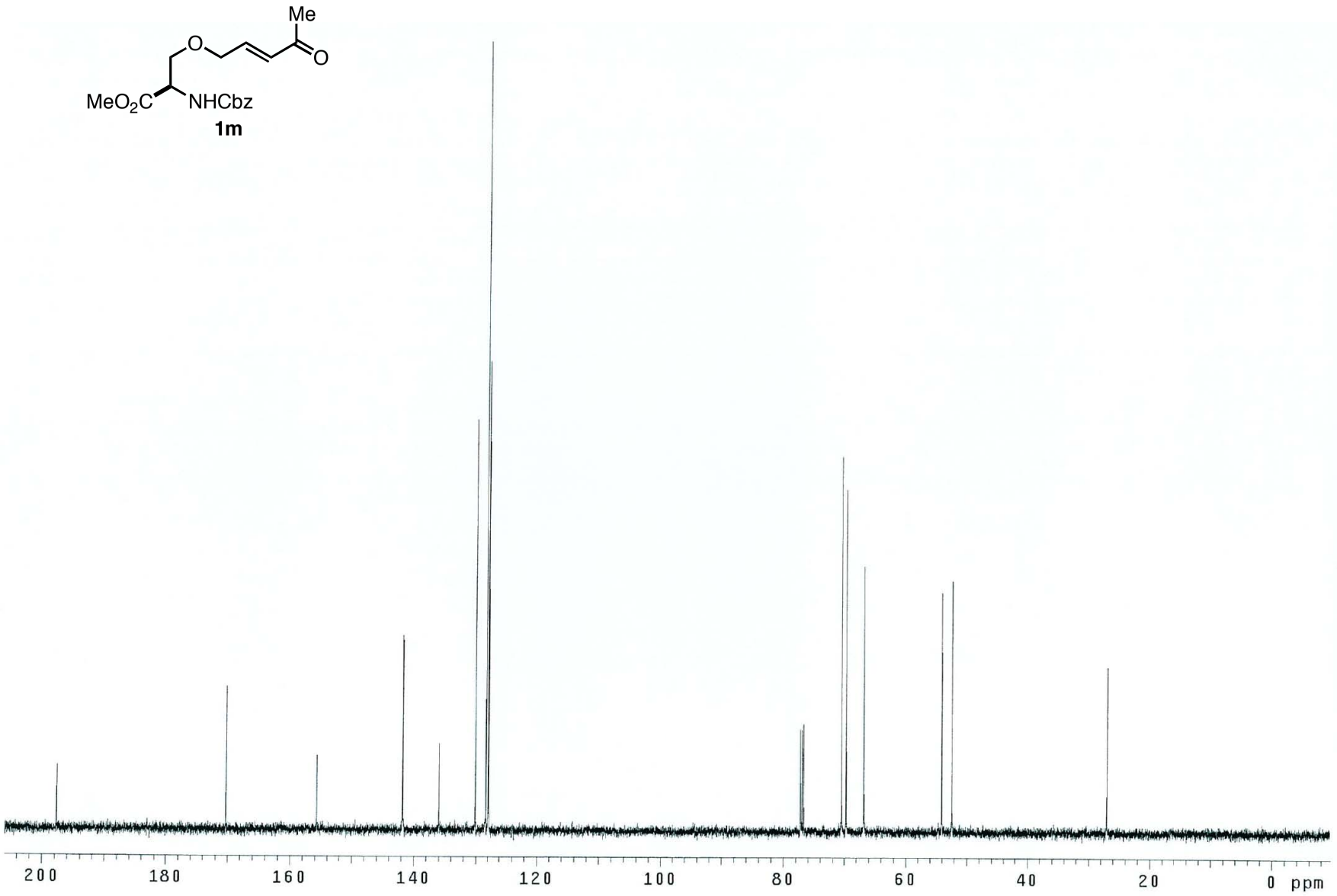
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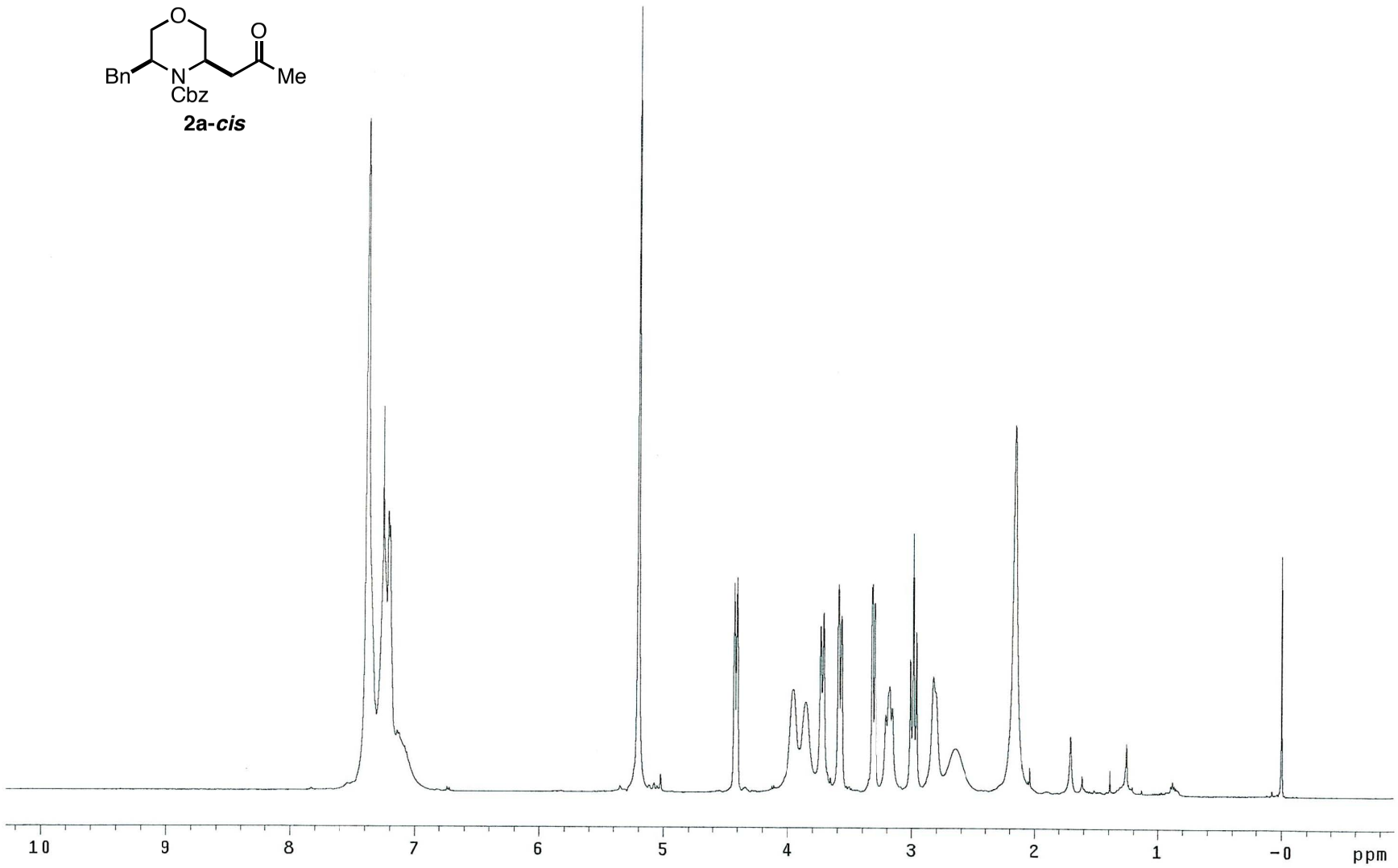
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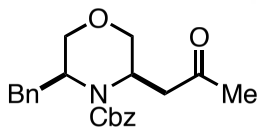

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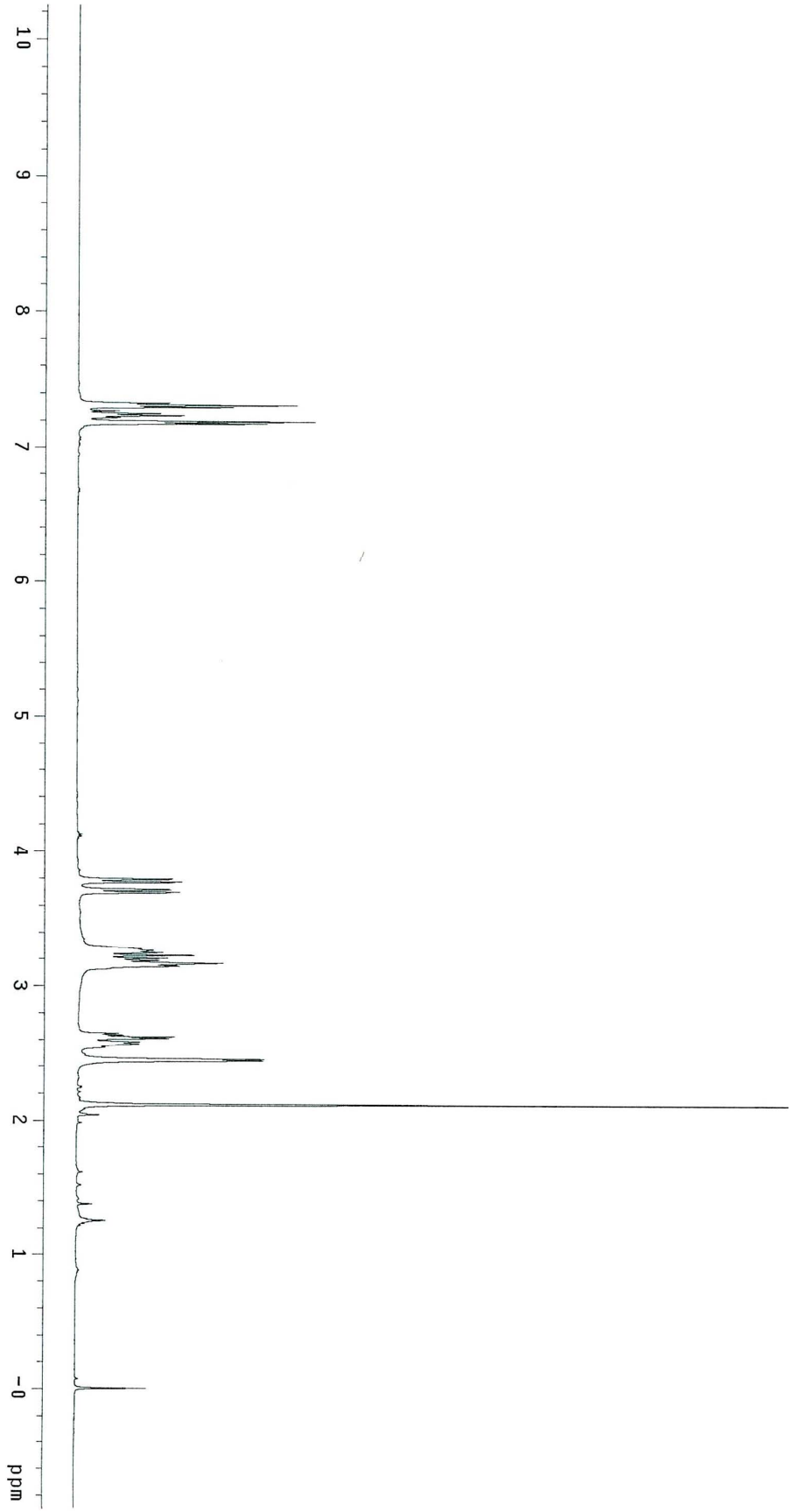

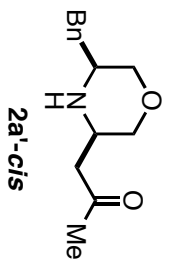

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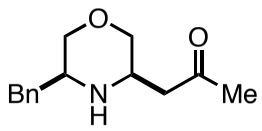

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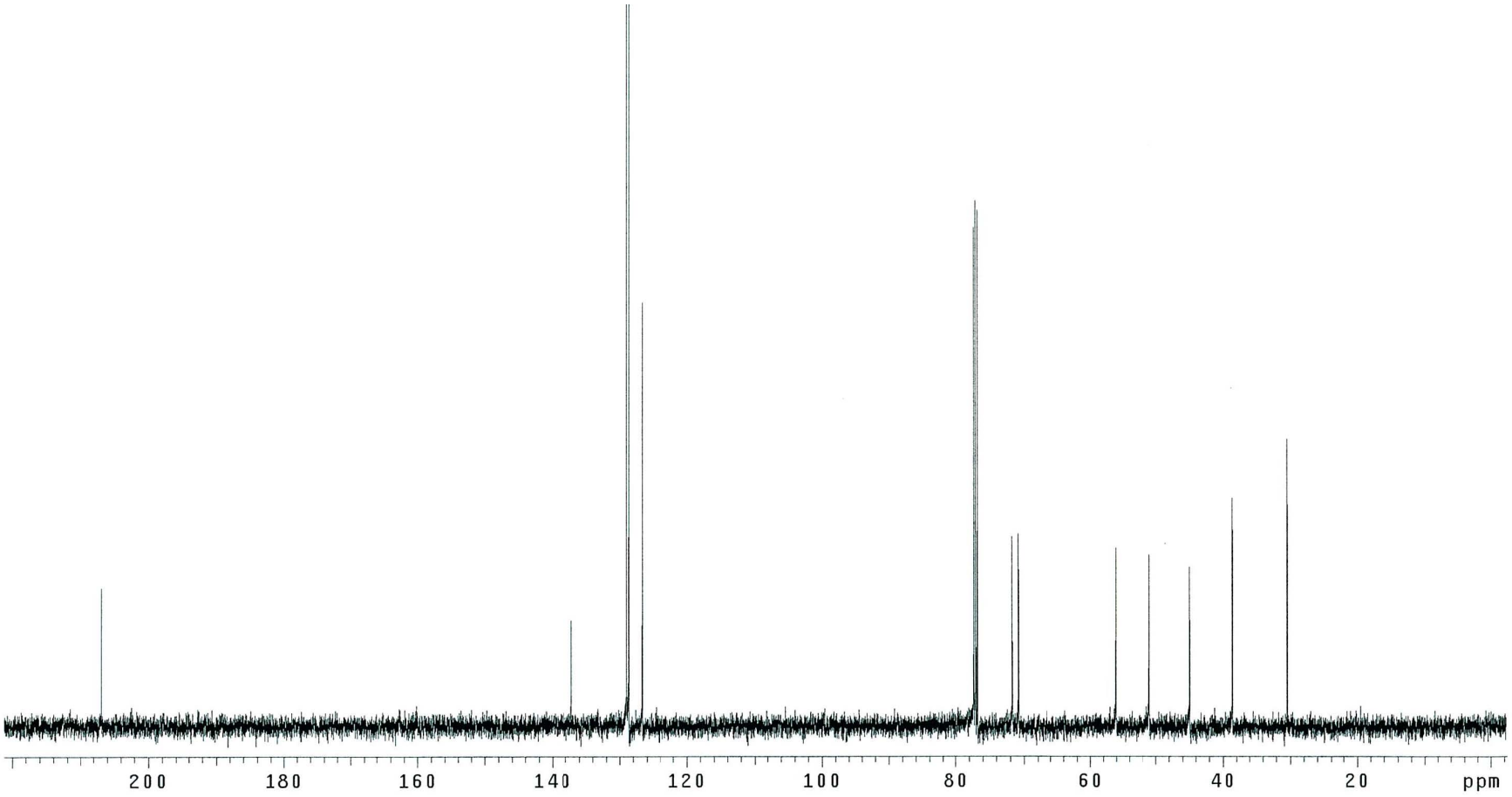

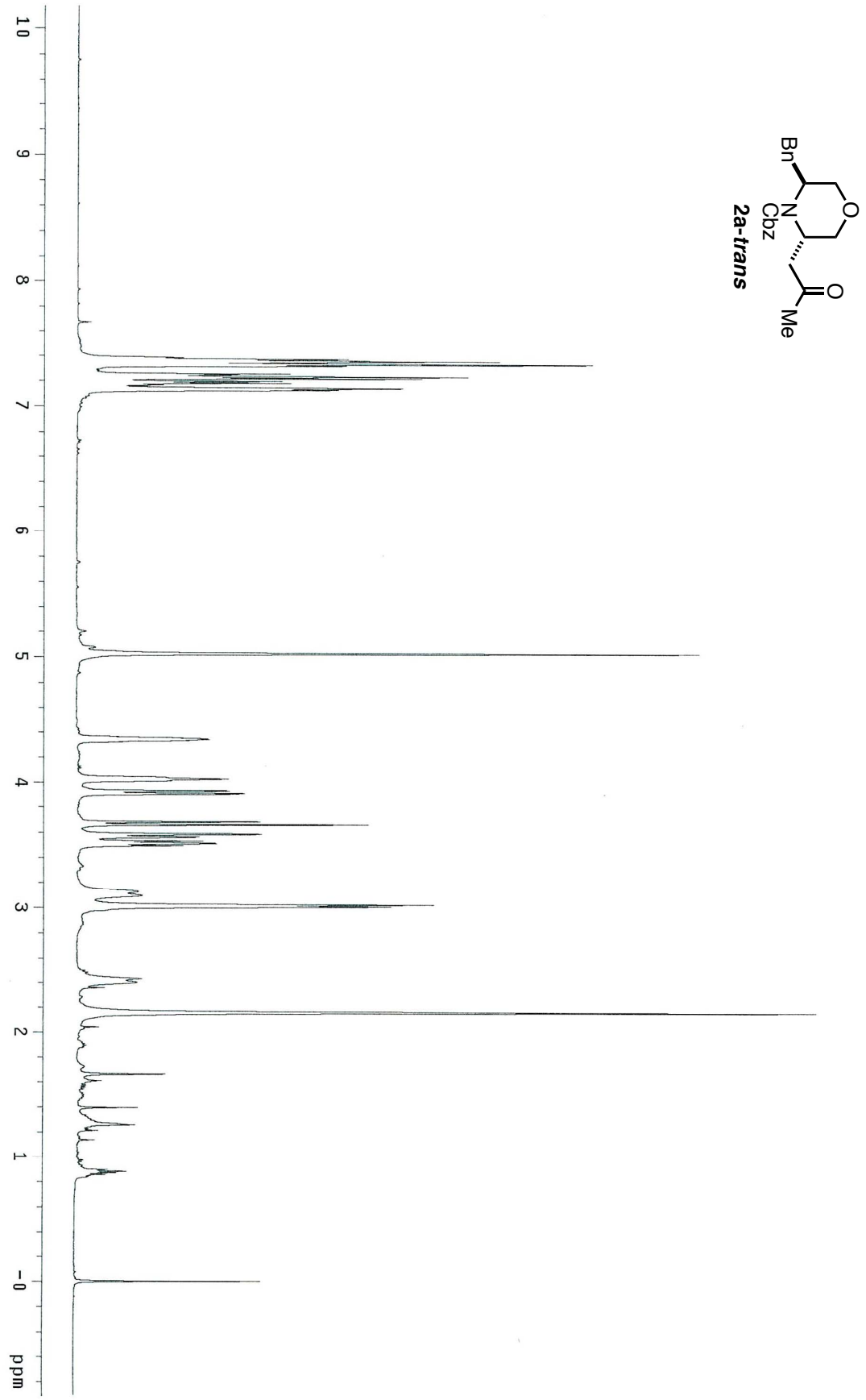
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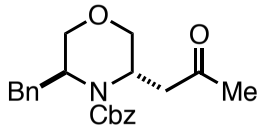
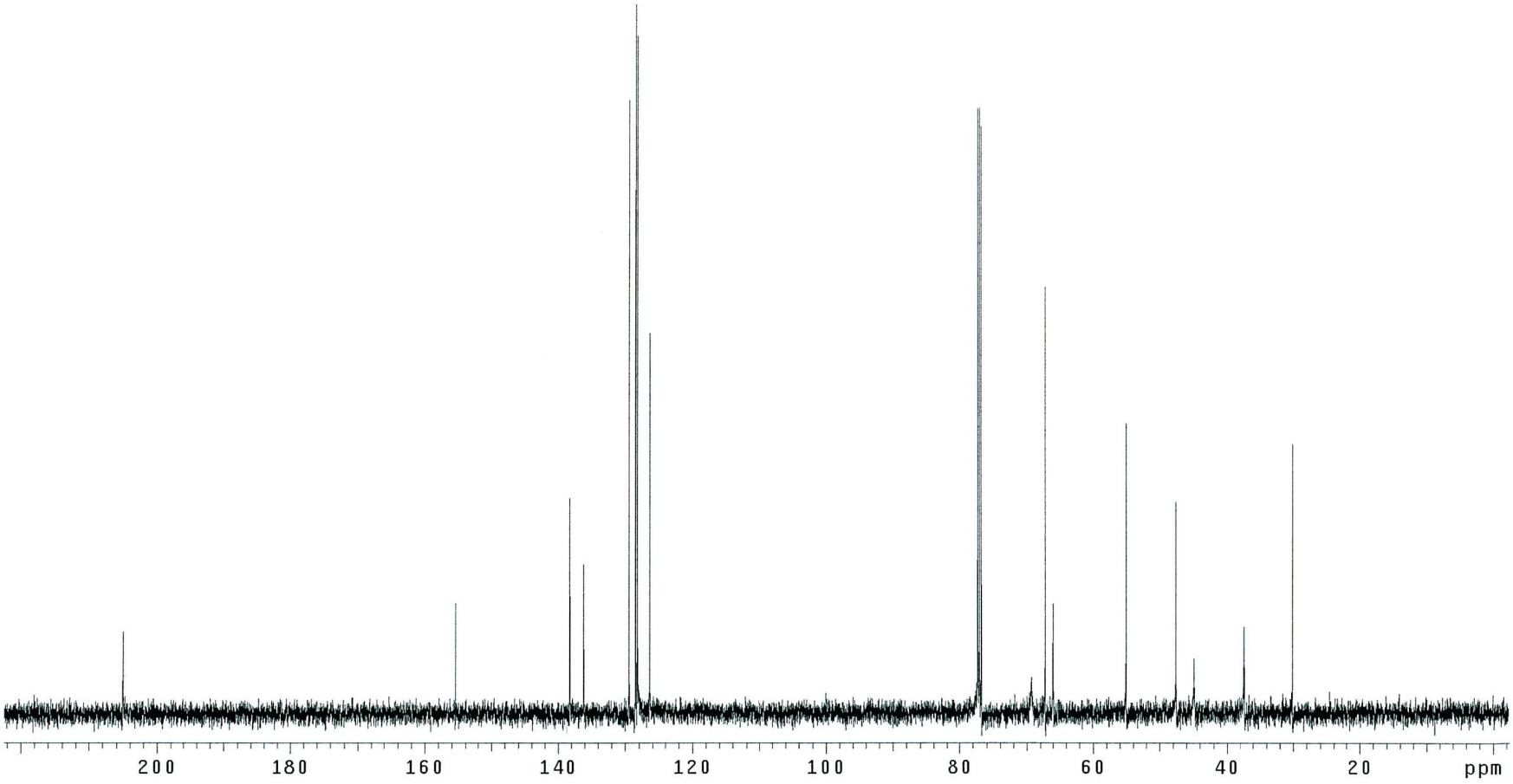
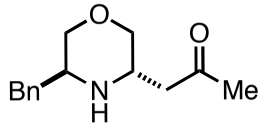


2a-*trans*





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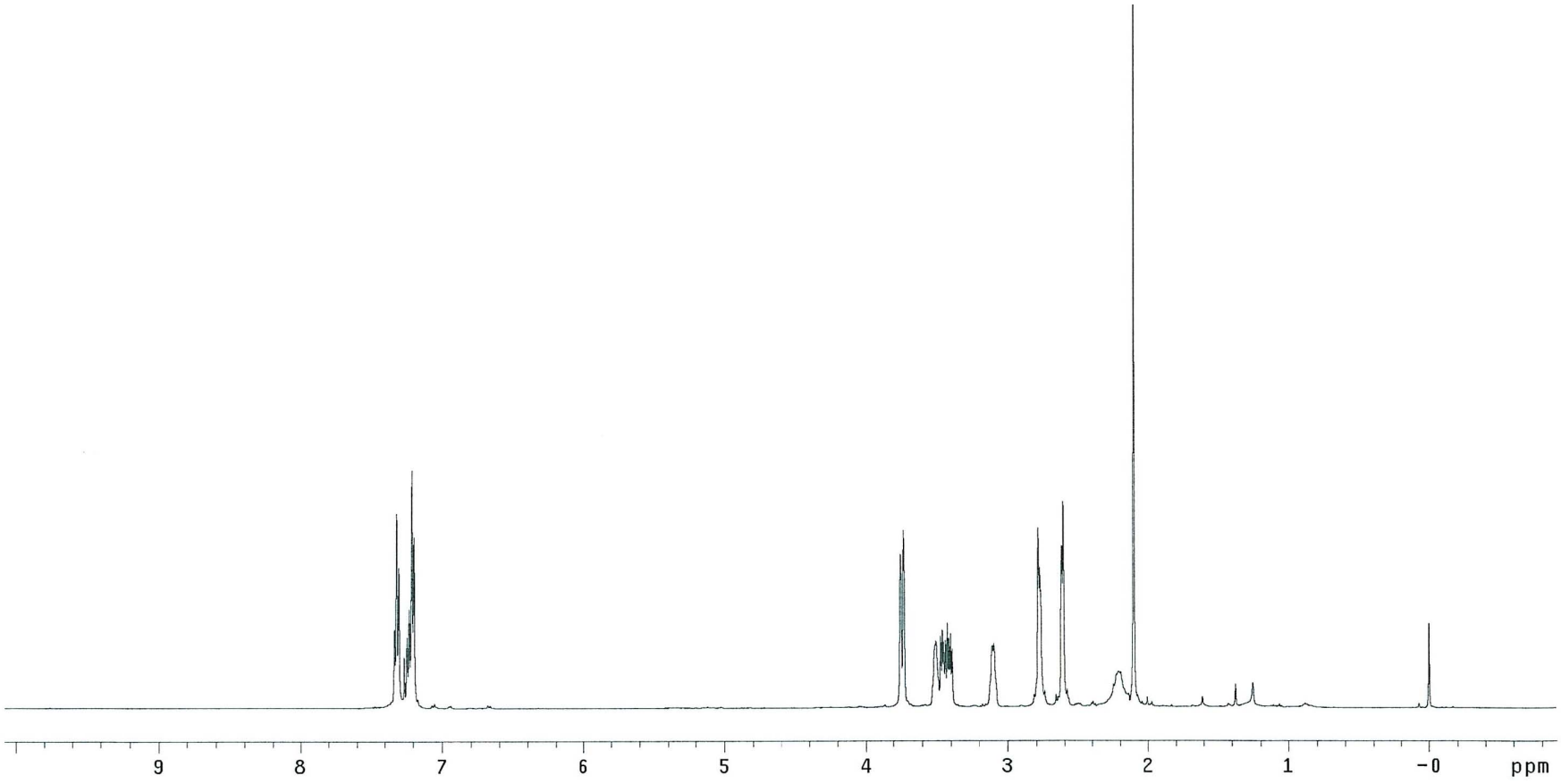

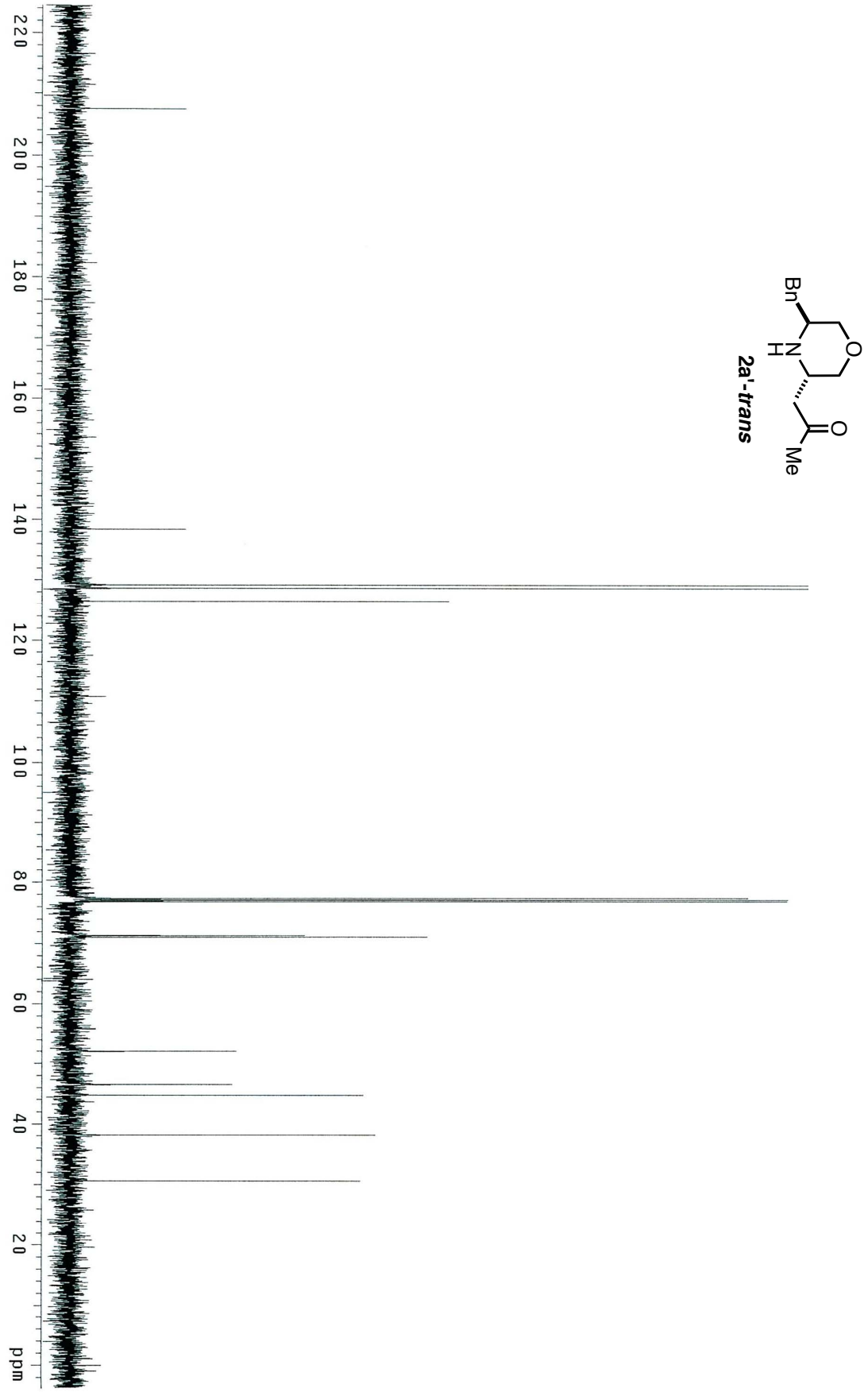
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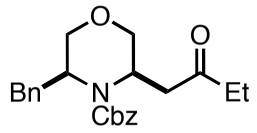
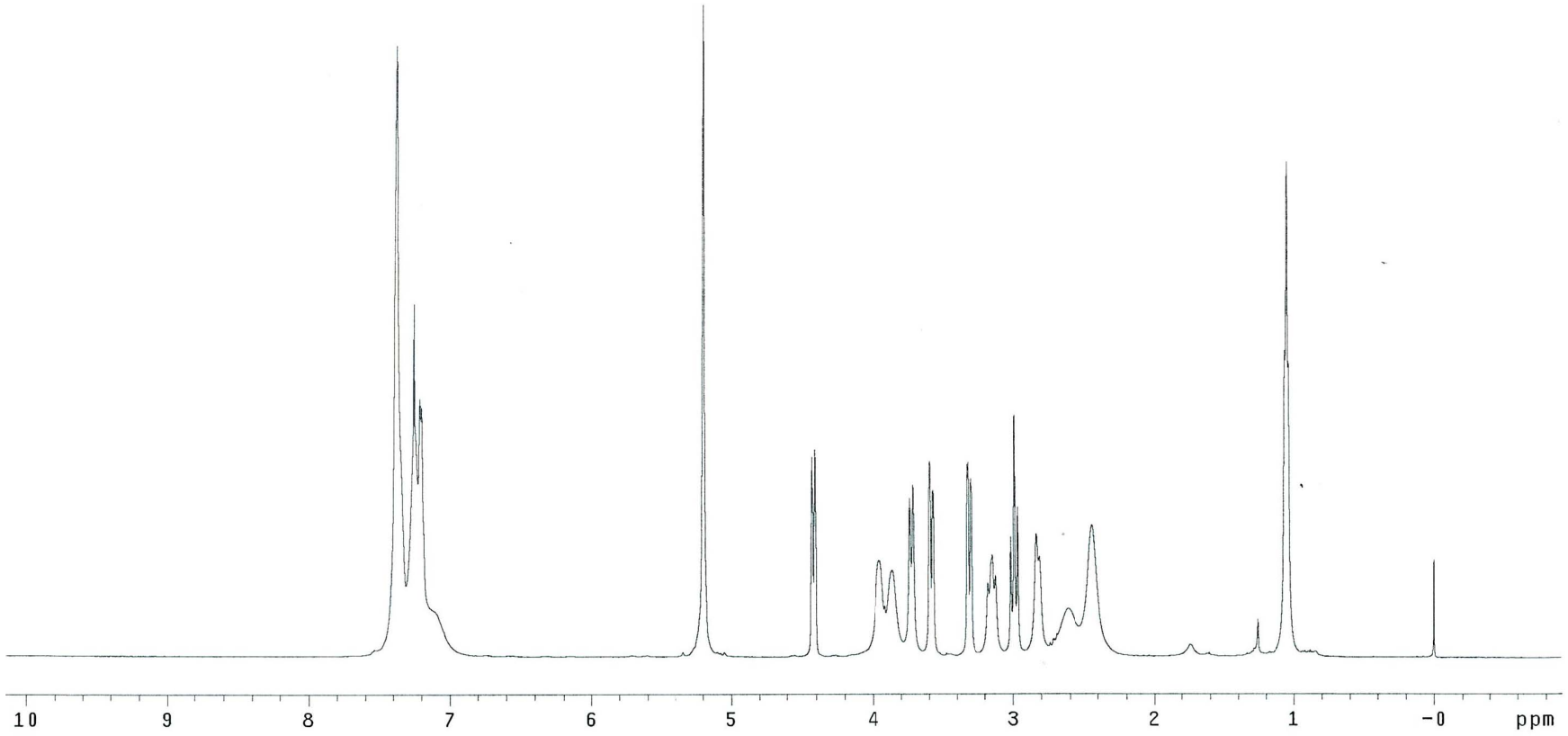
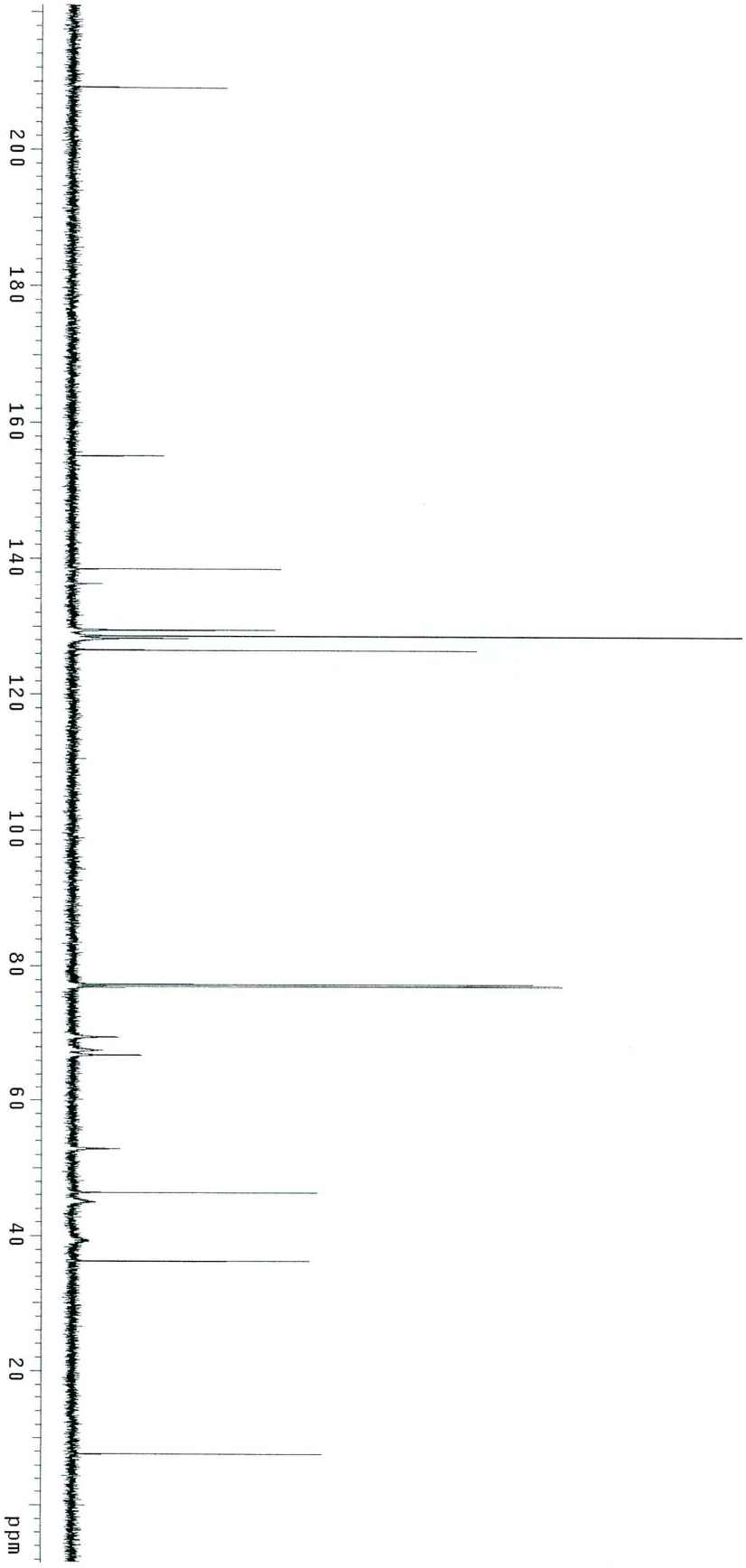


2b-*cis*

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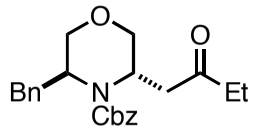

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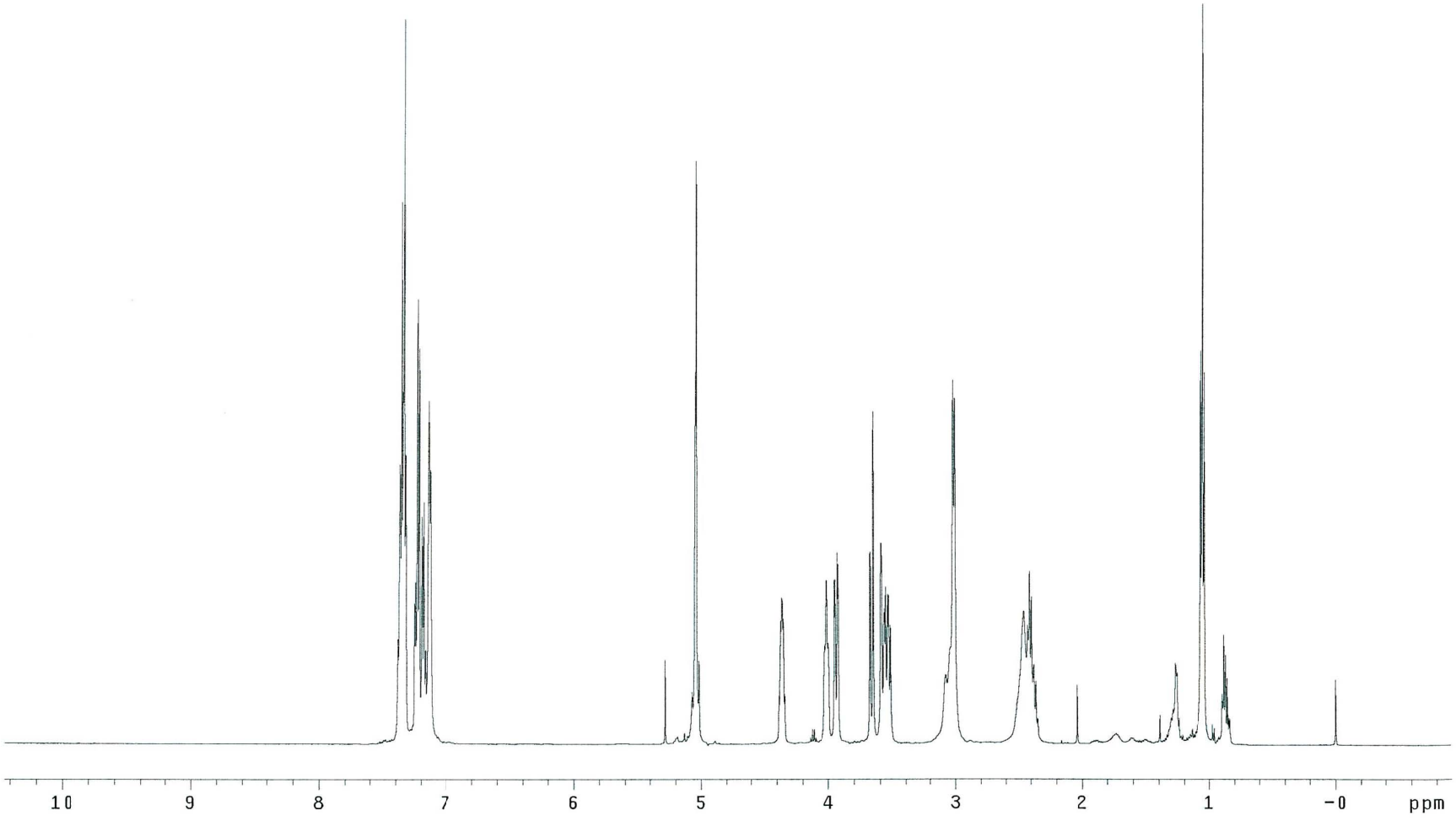
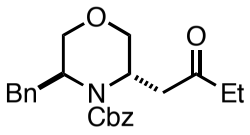
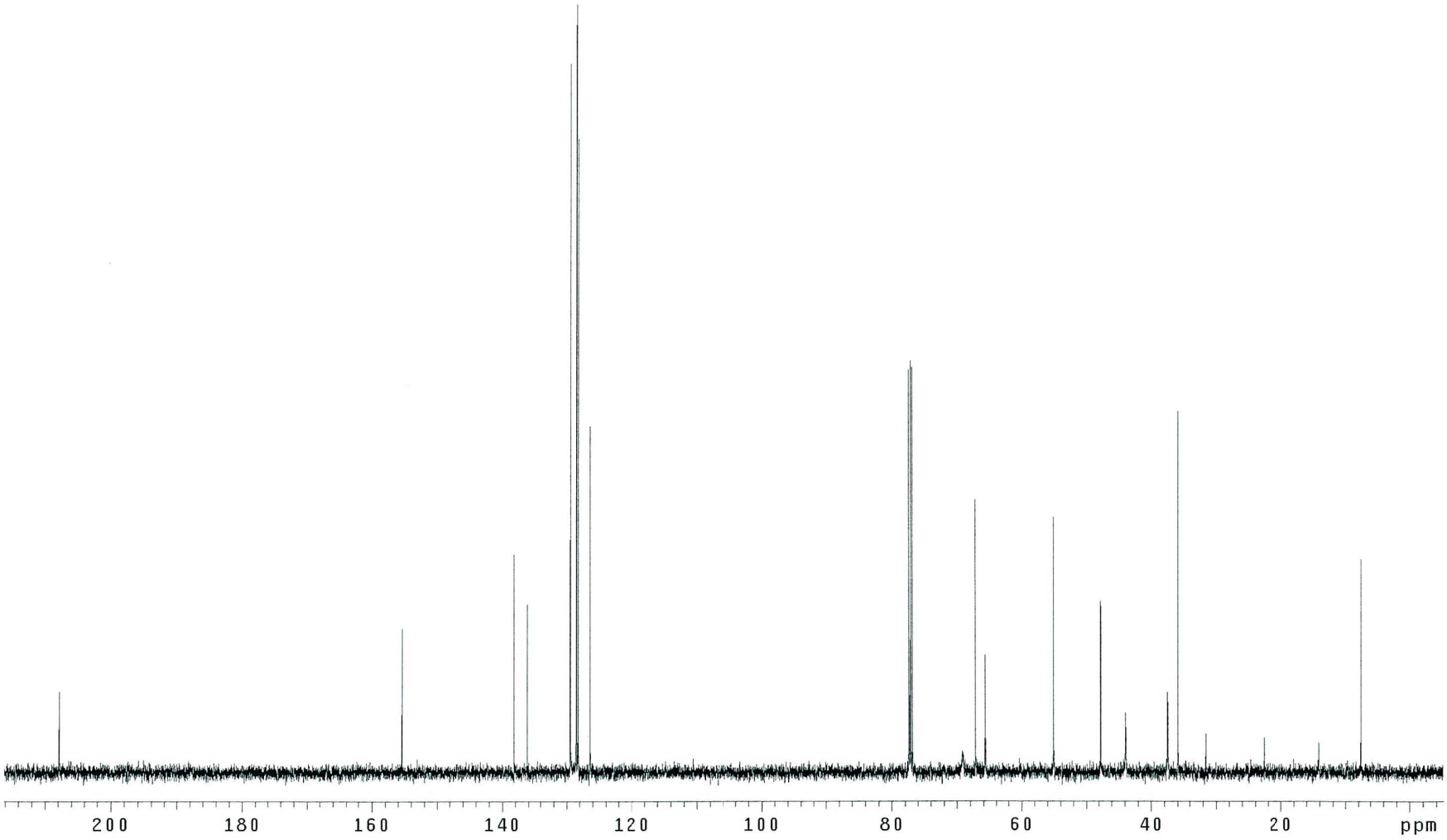
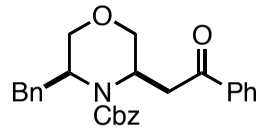




2b-*trans*





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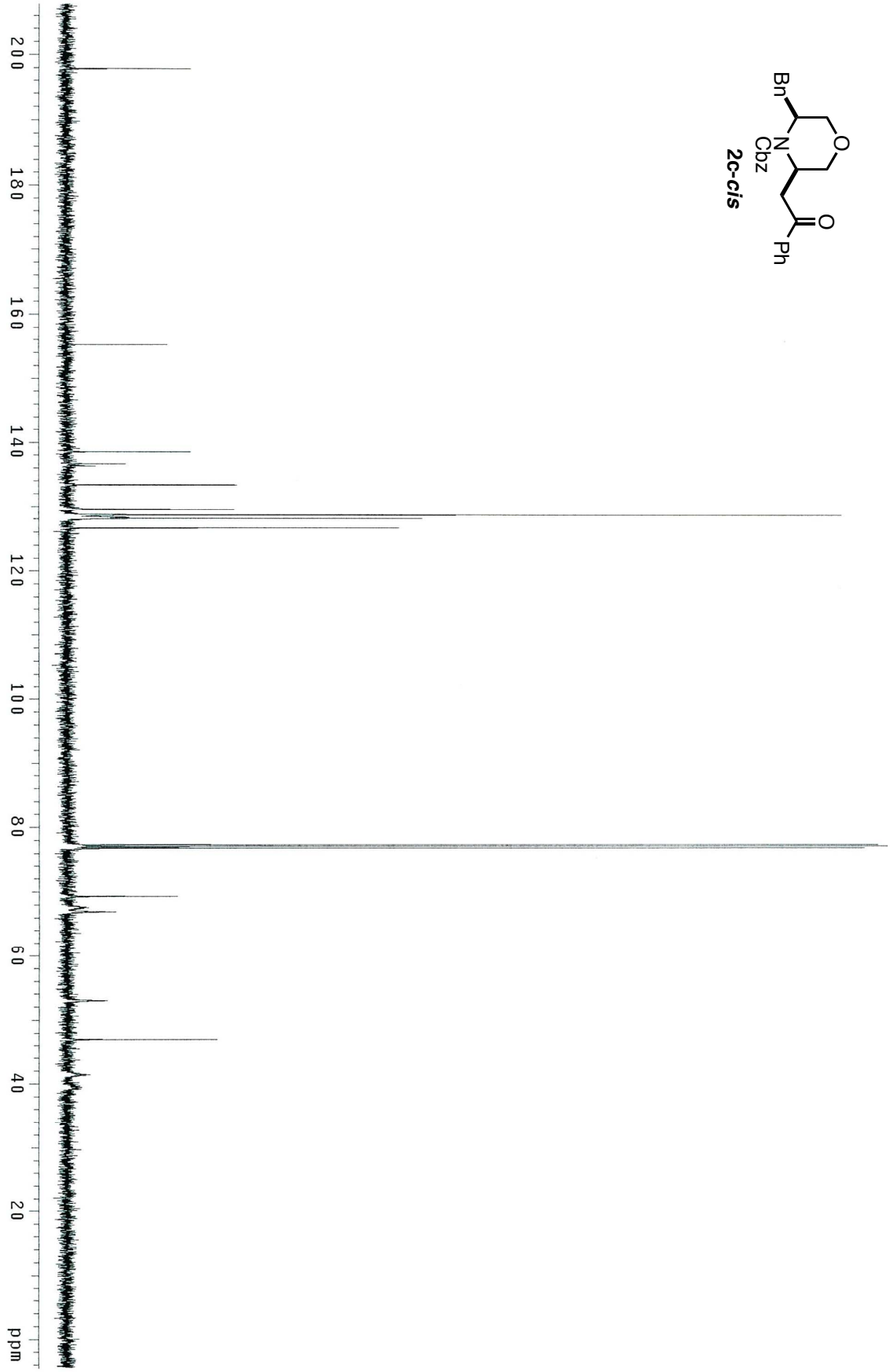
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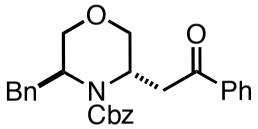

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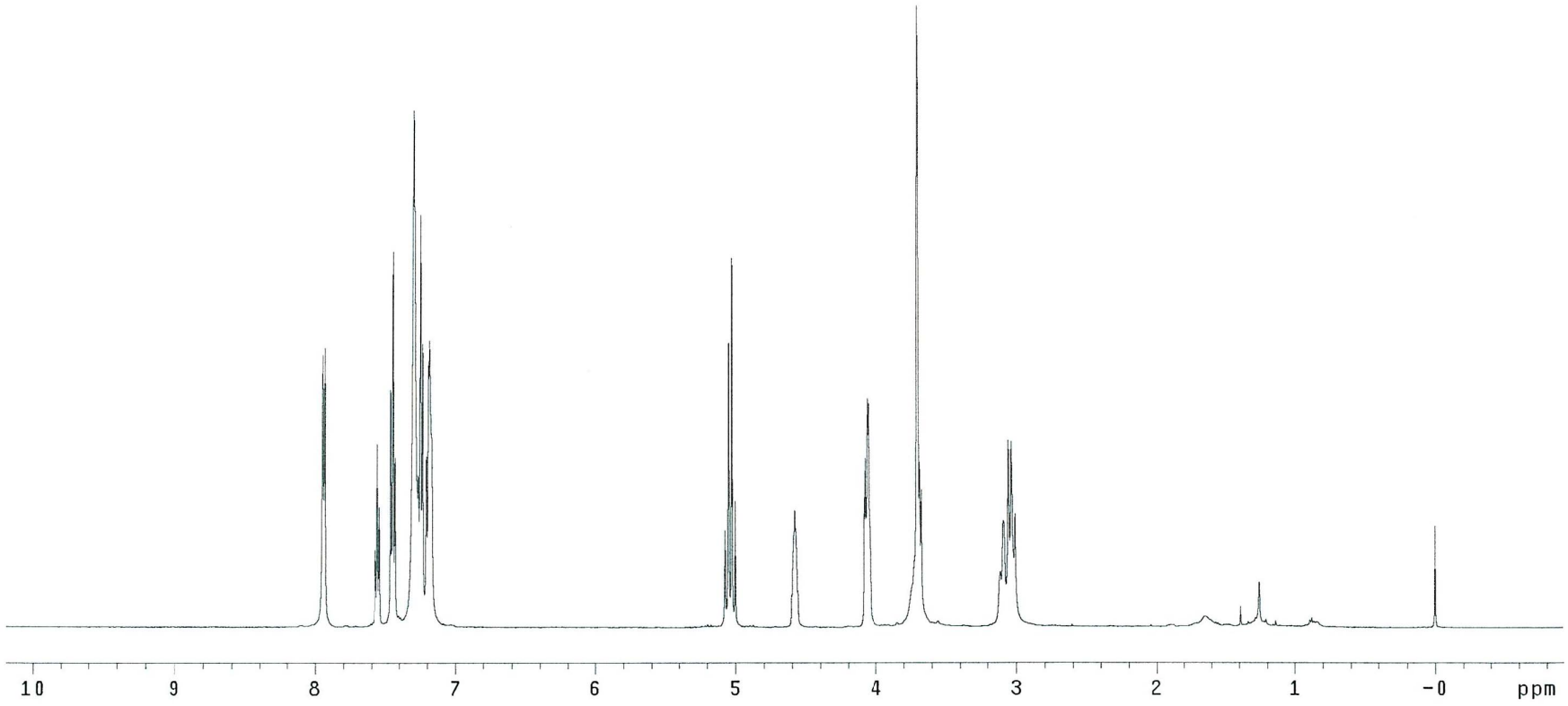

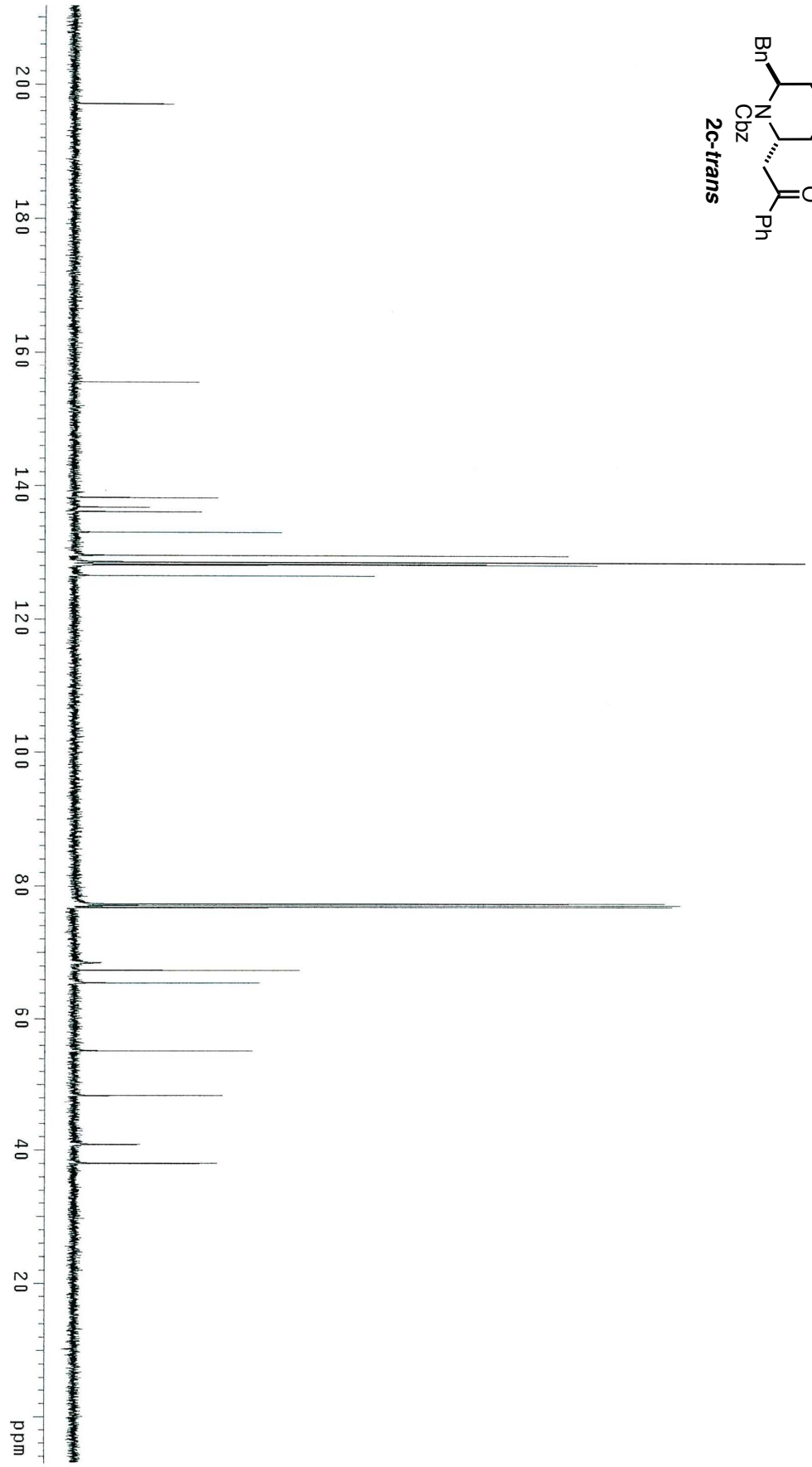
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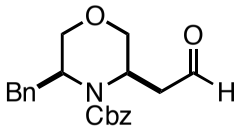

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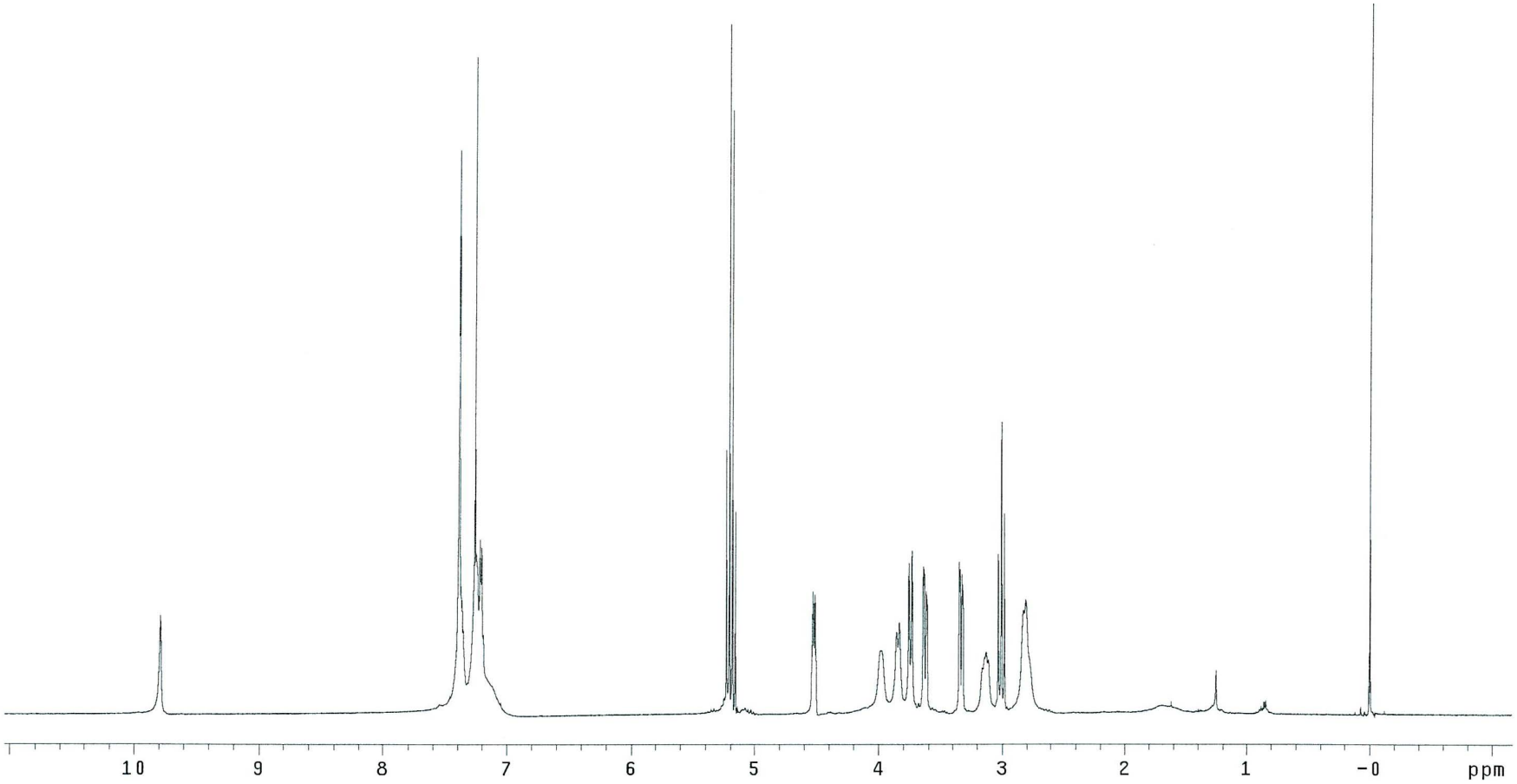

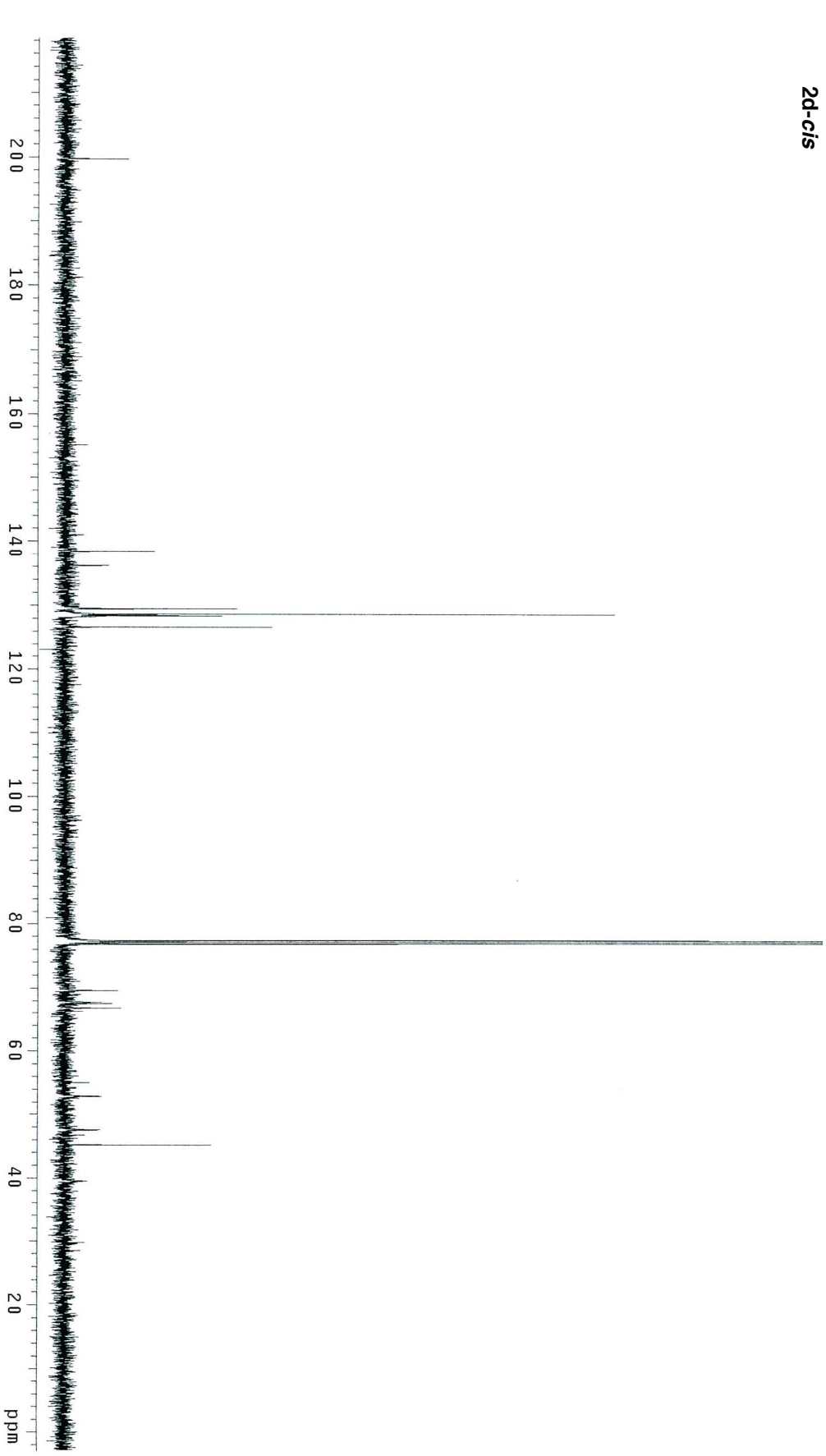
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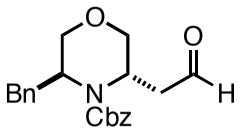

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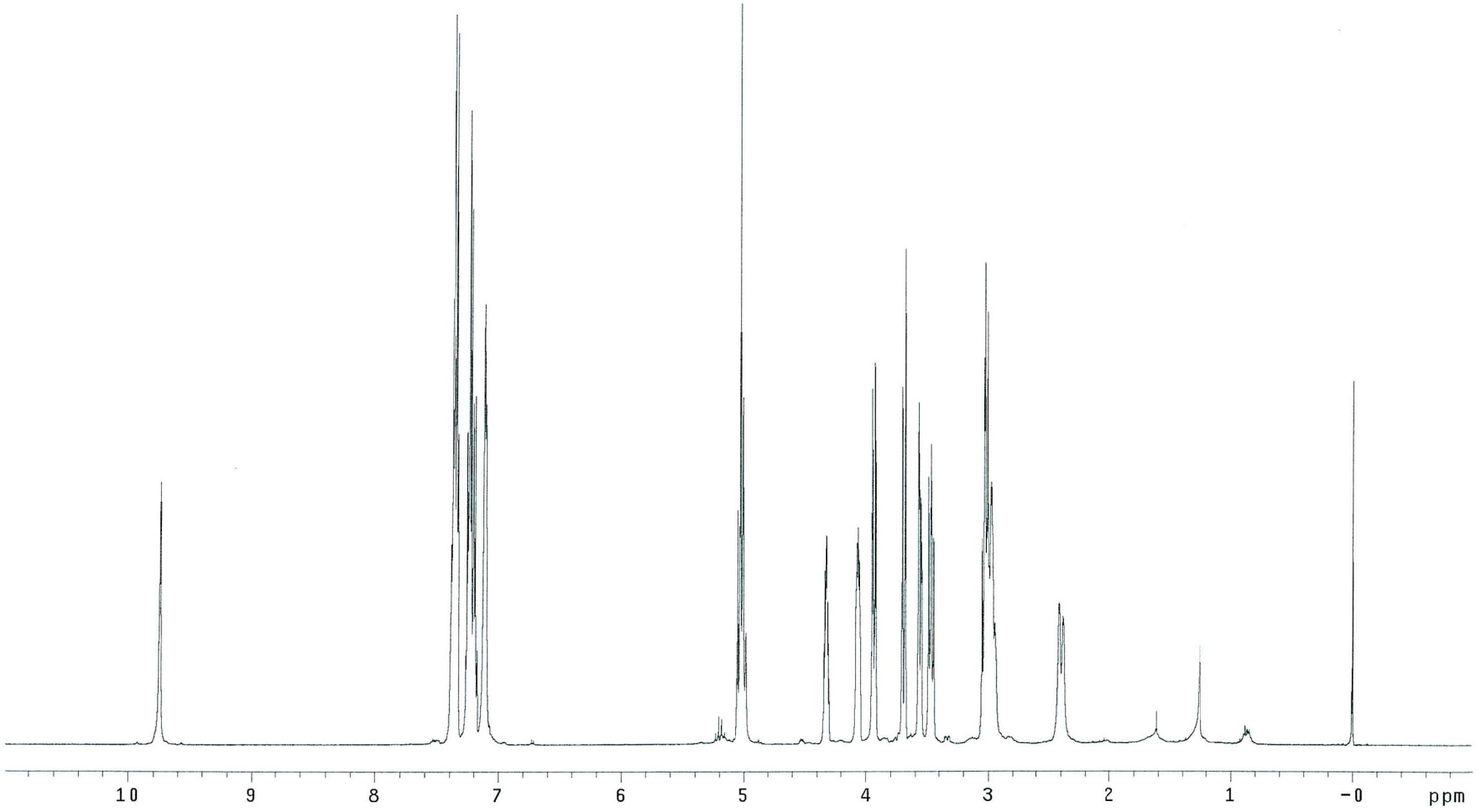

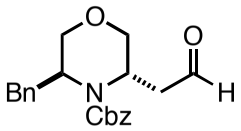

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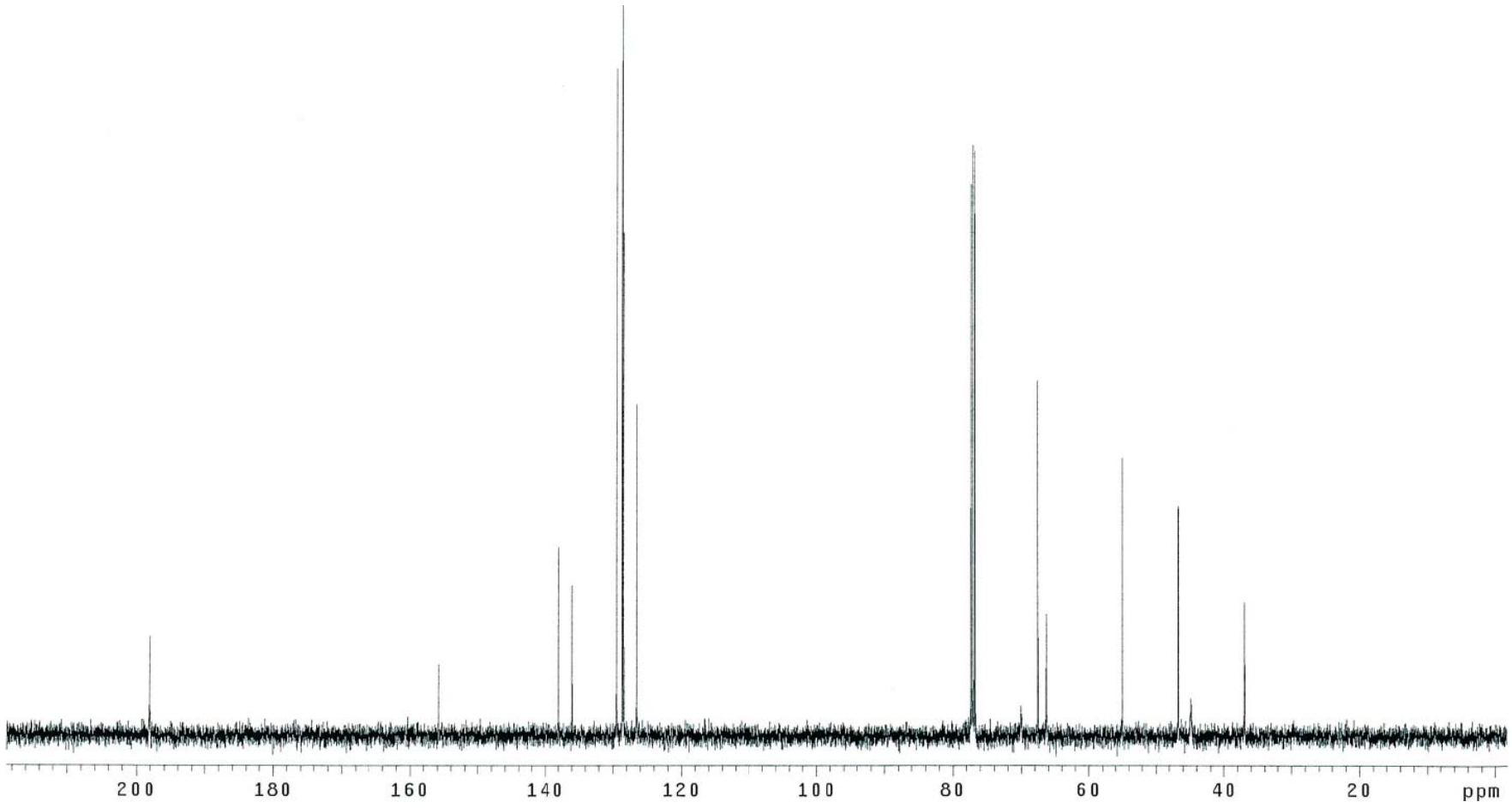

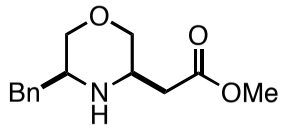

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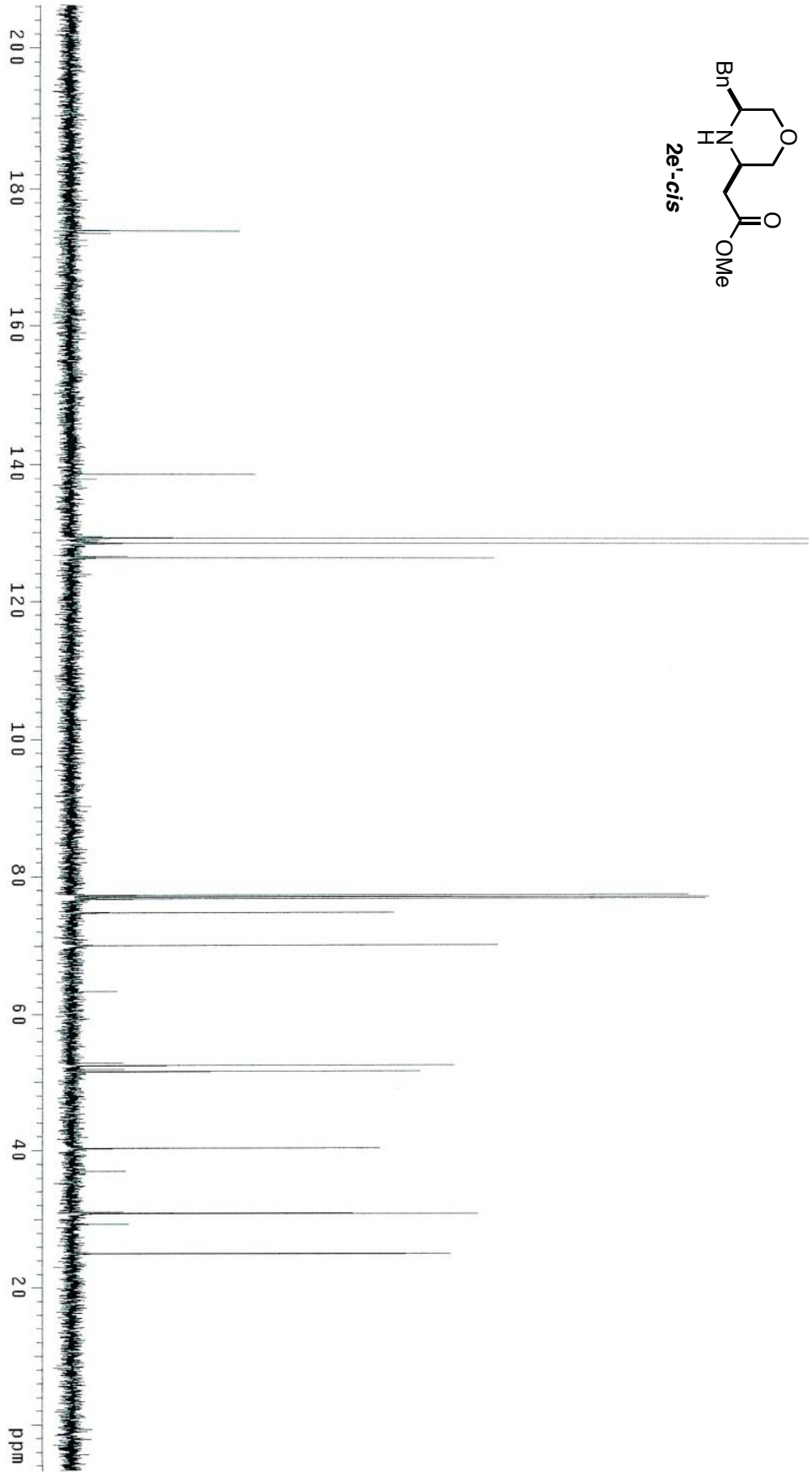
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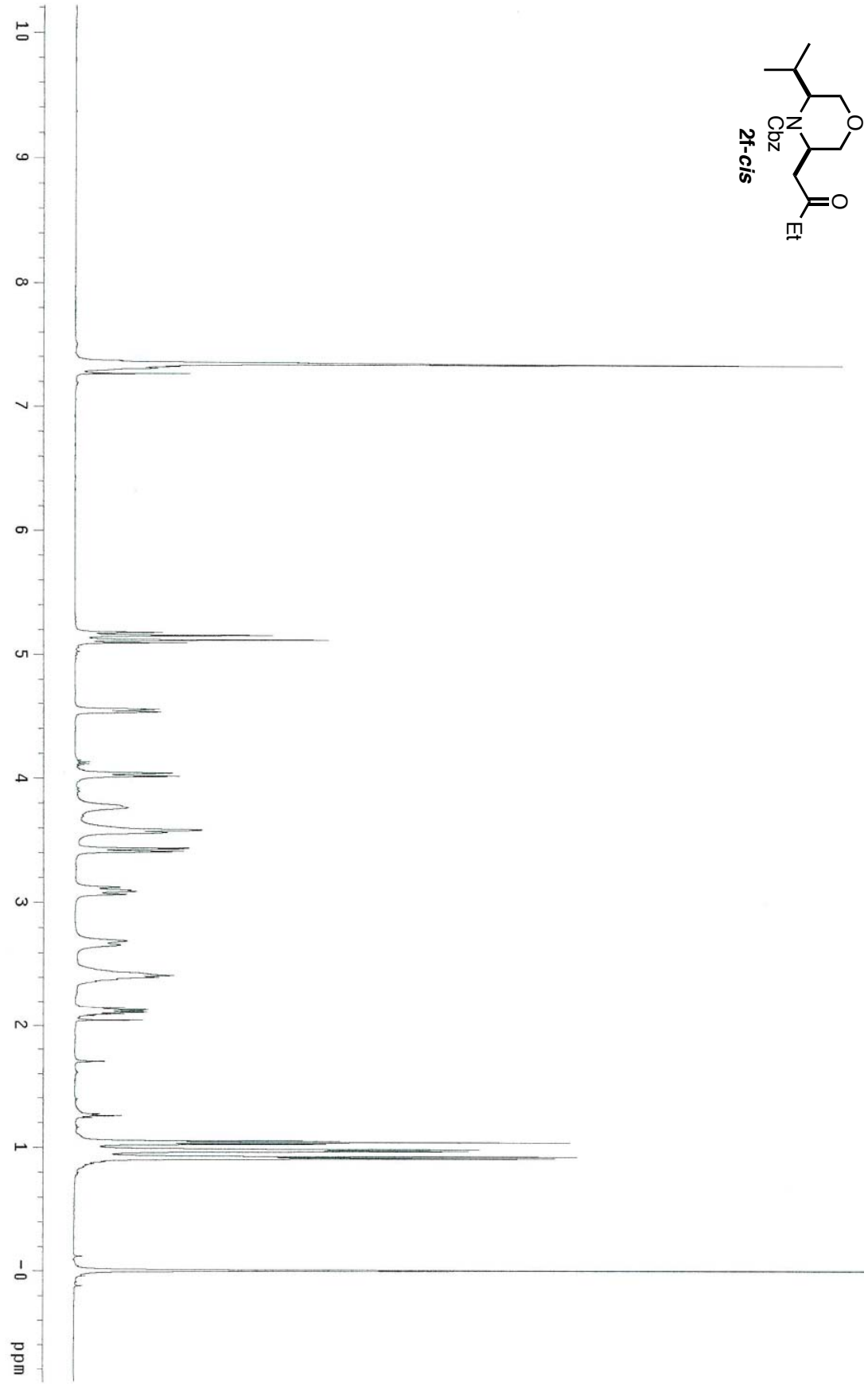
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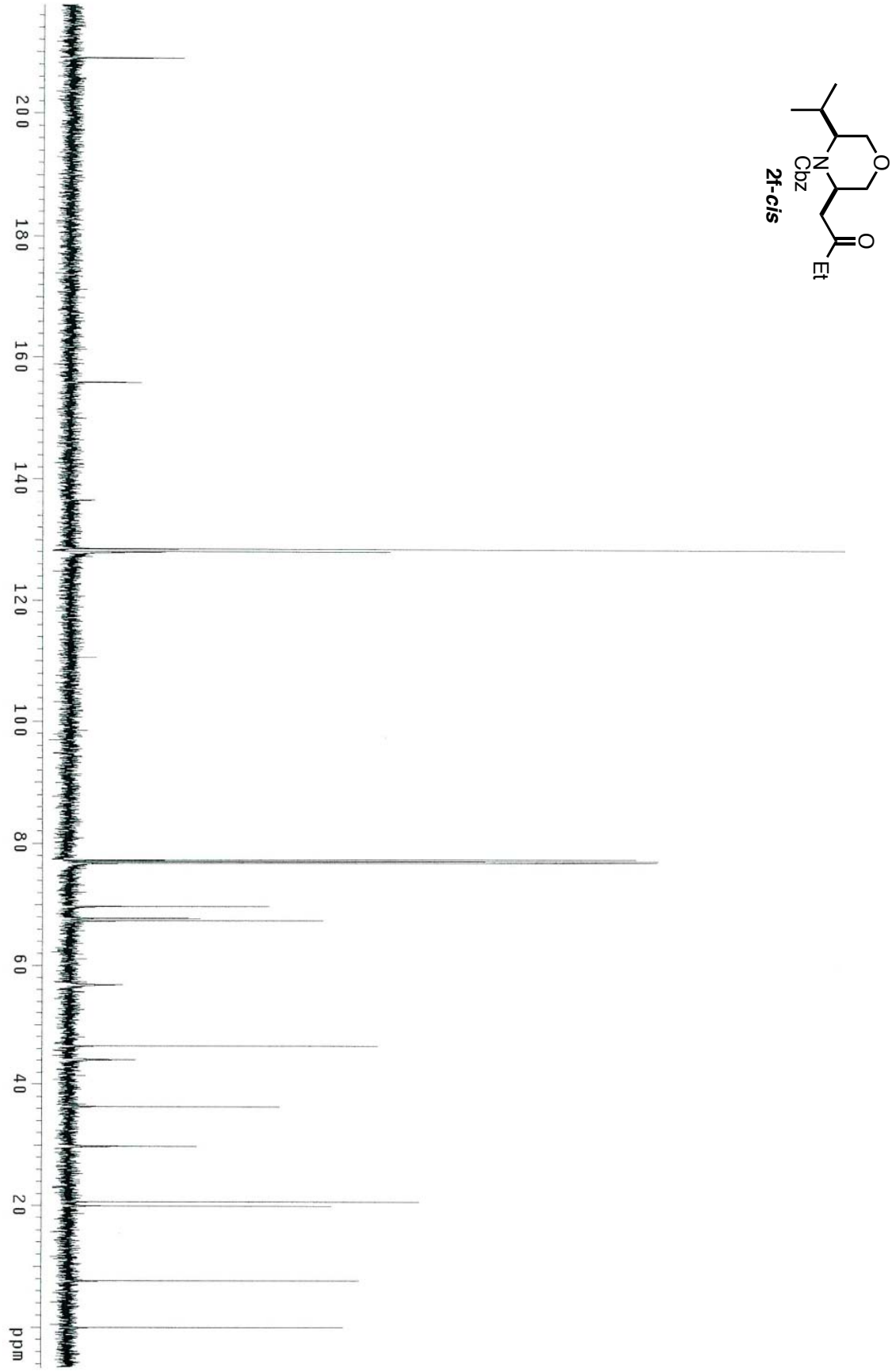
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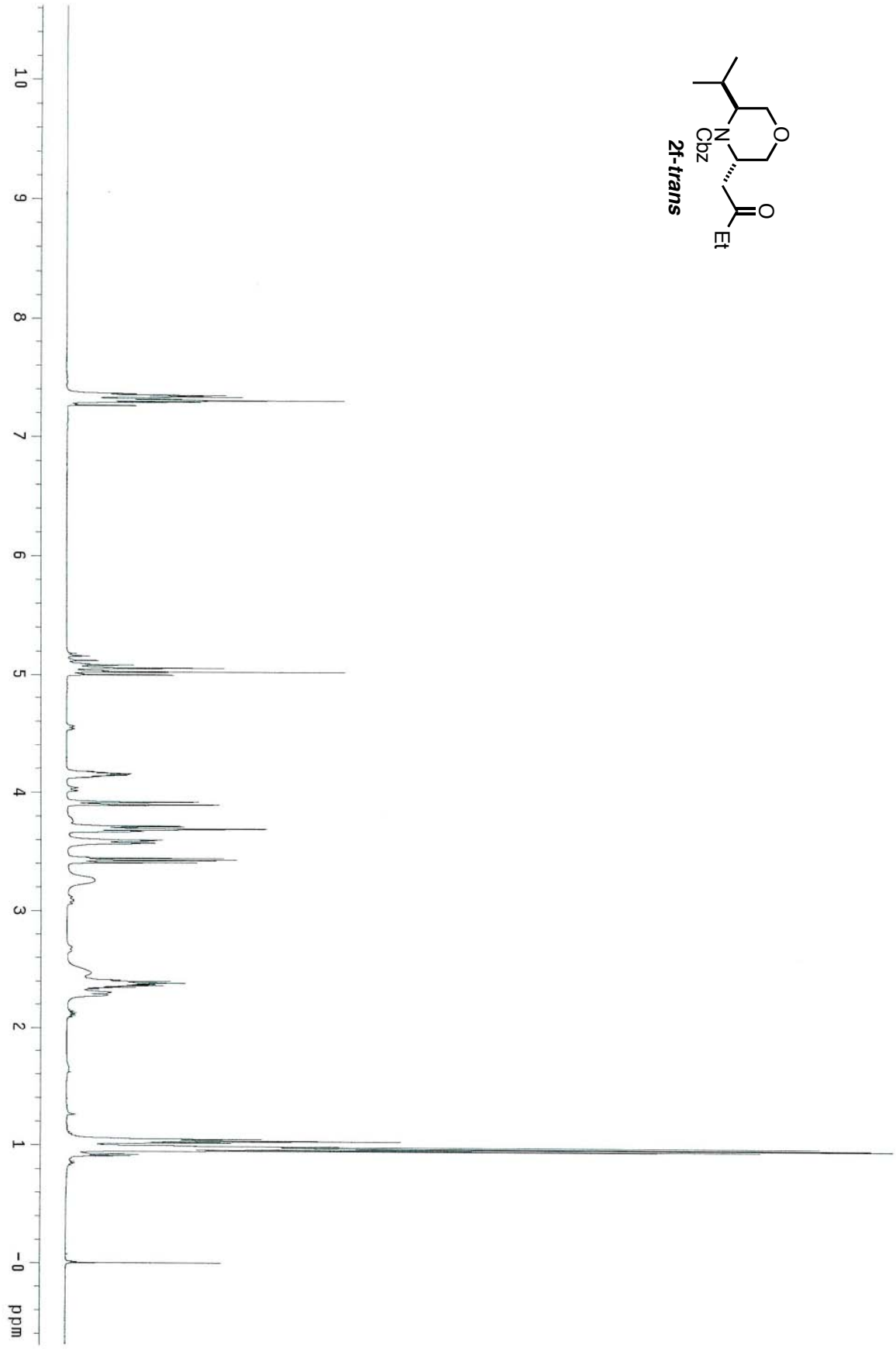
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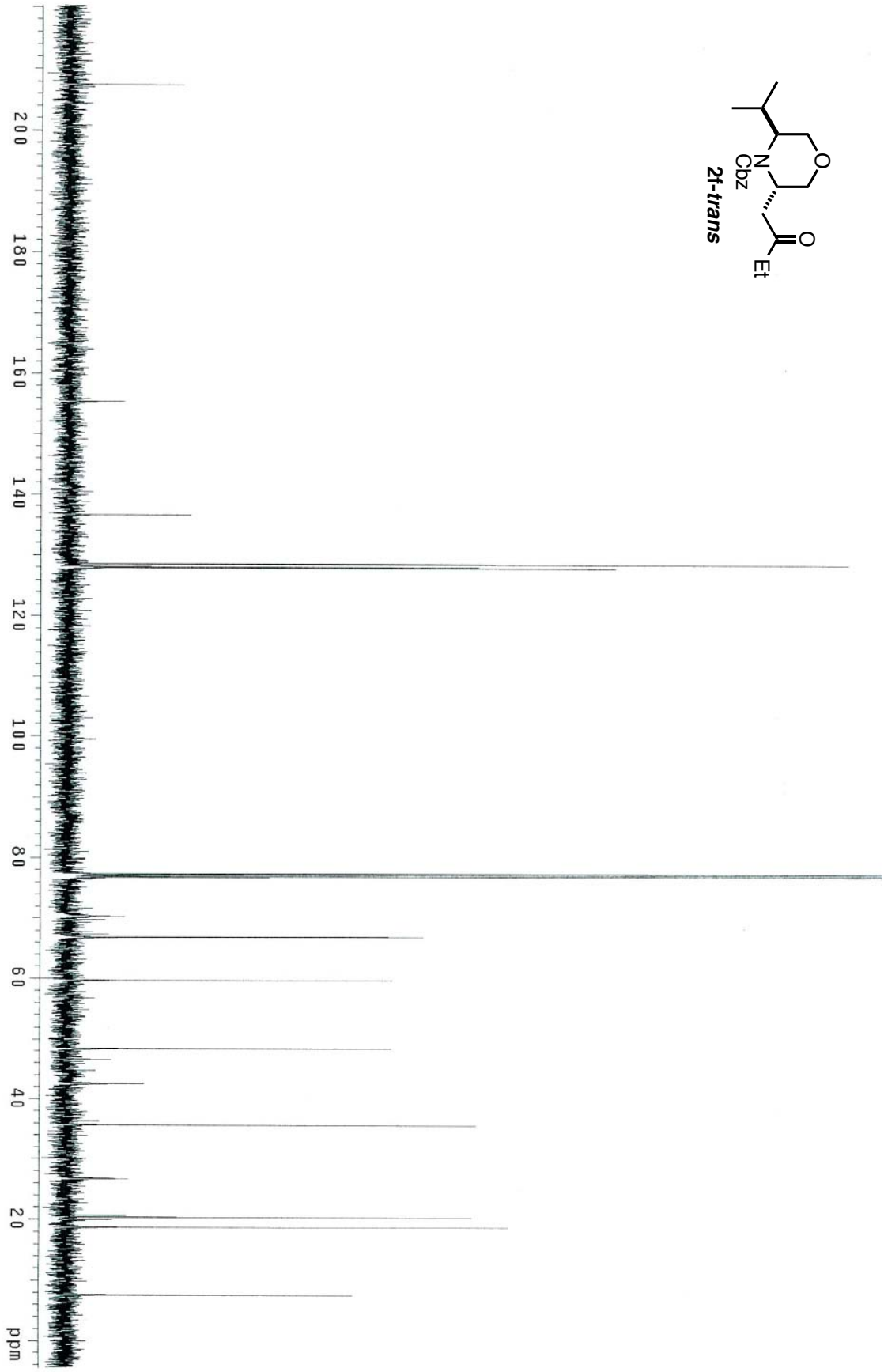
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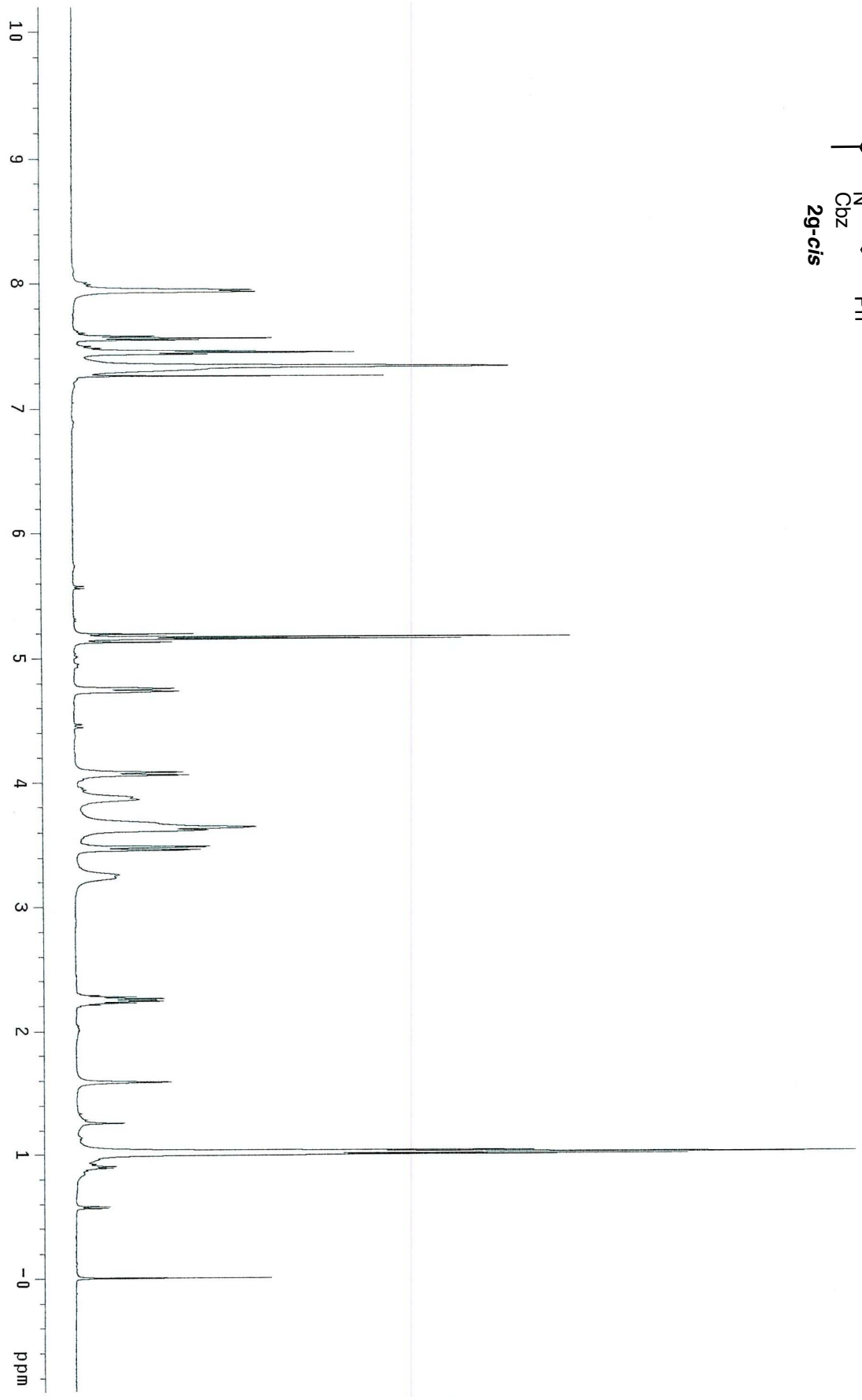

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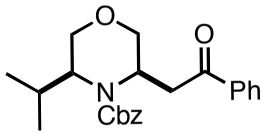

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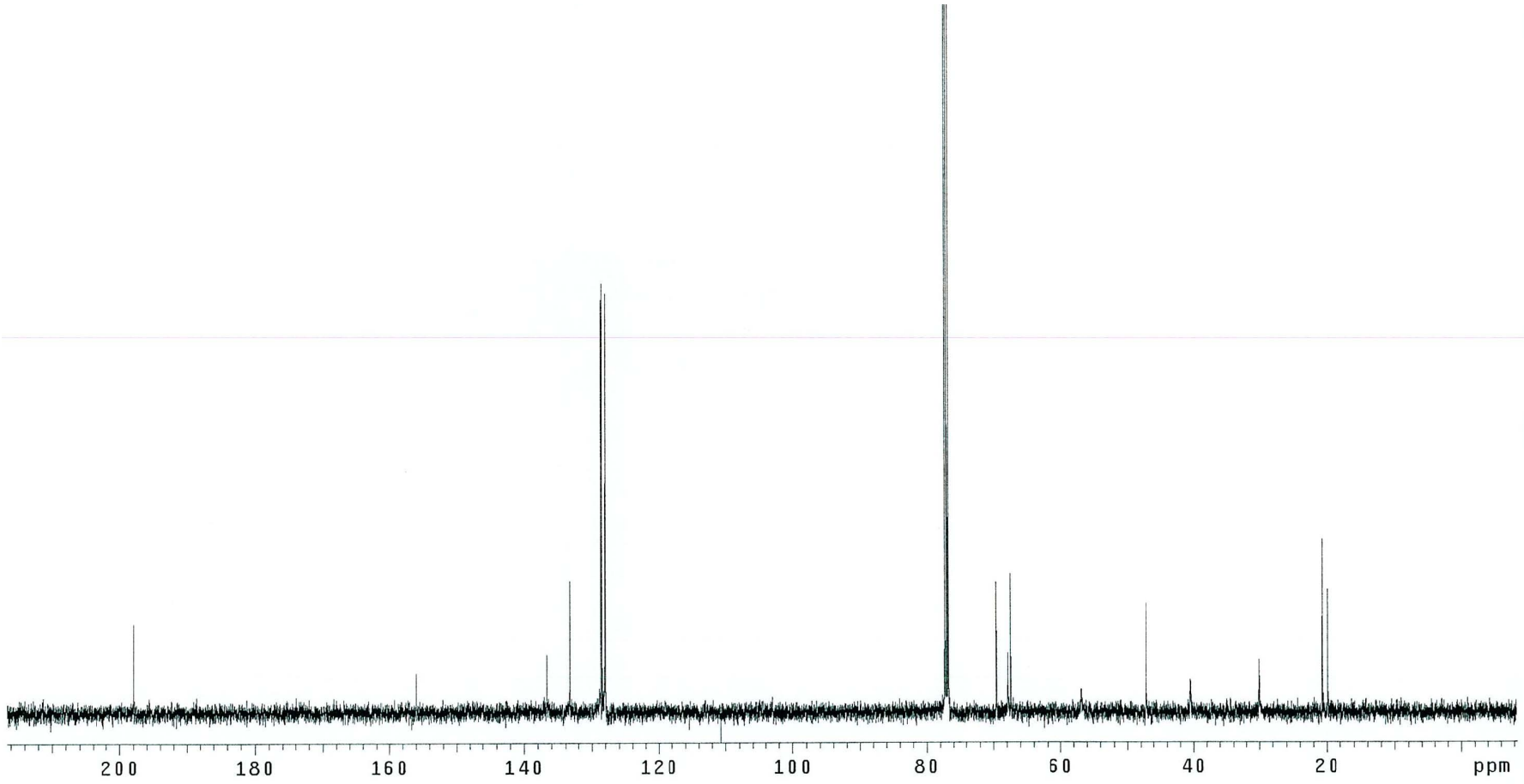

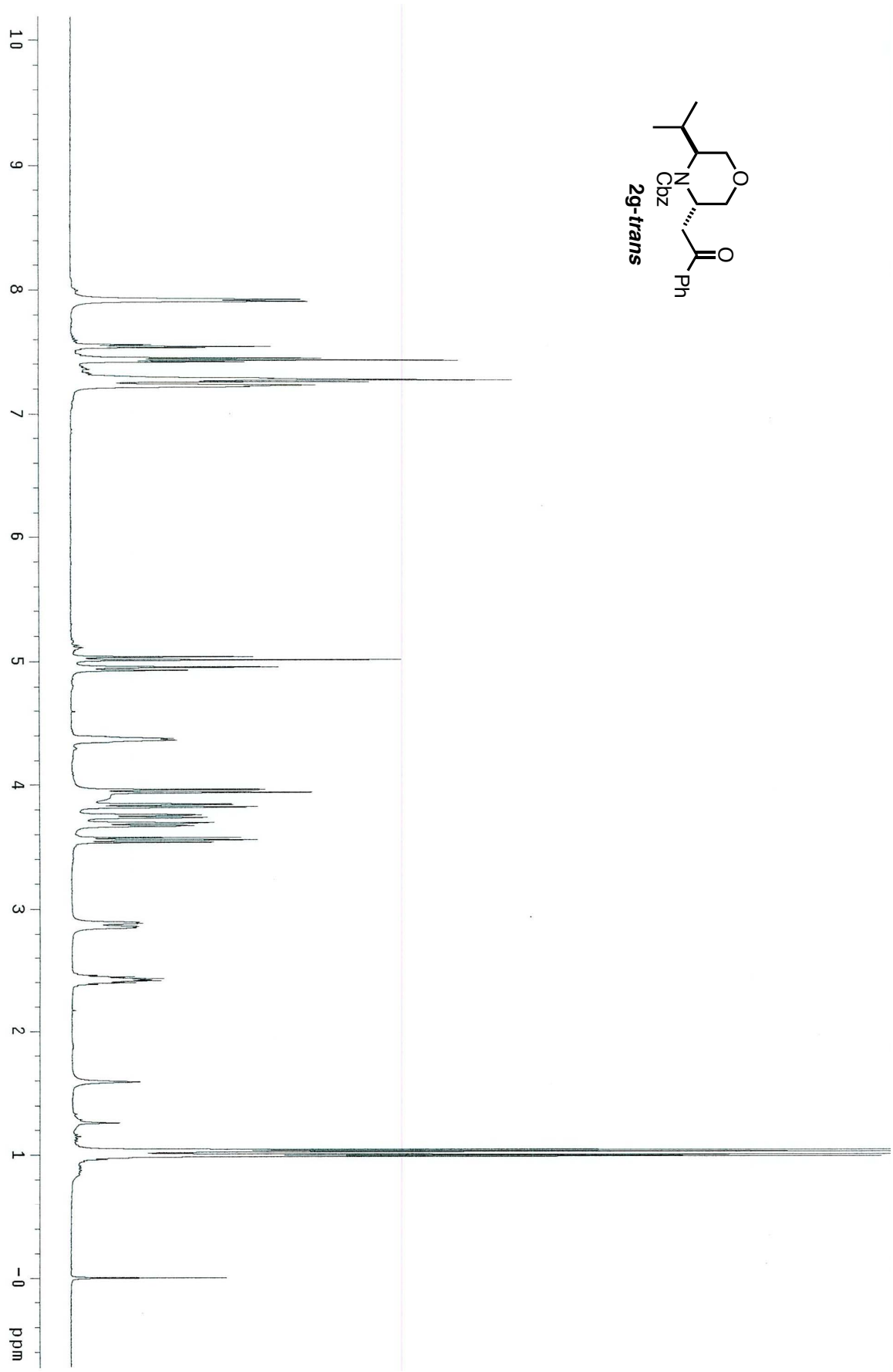
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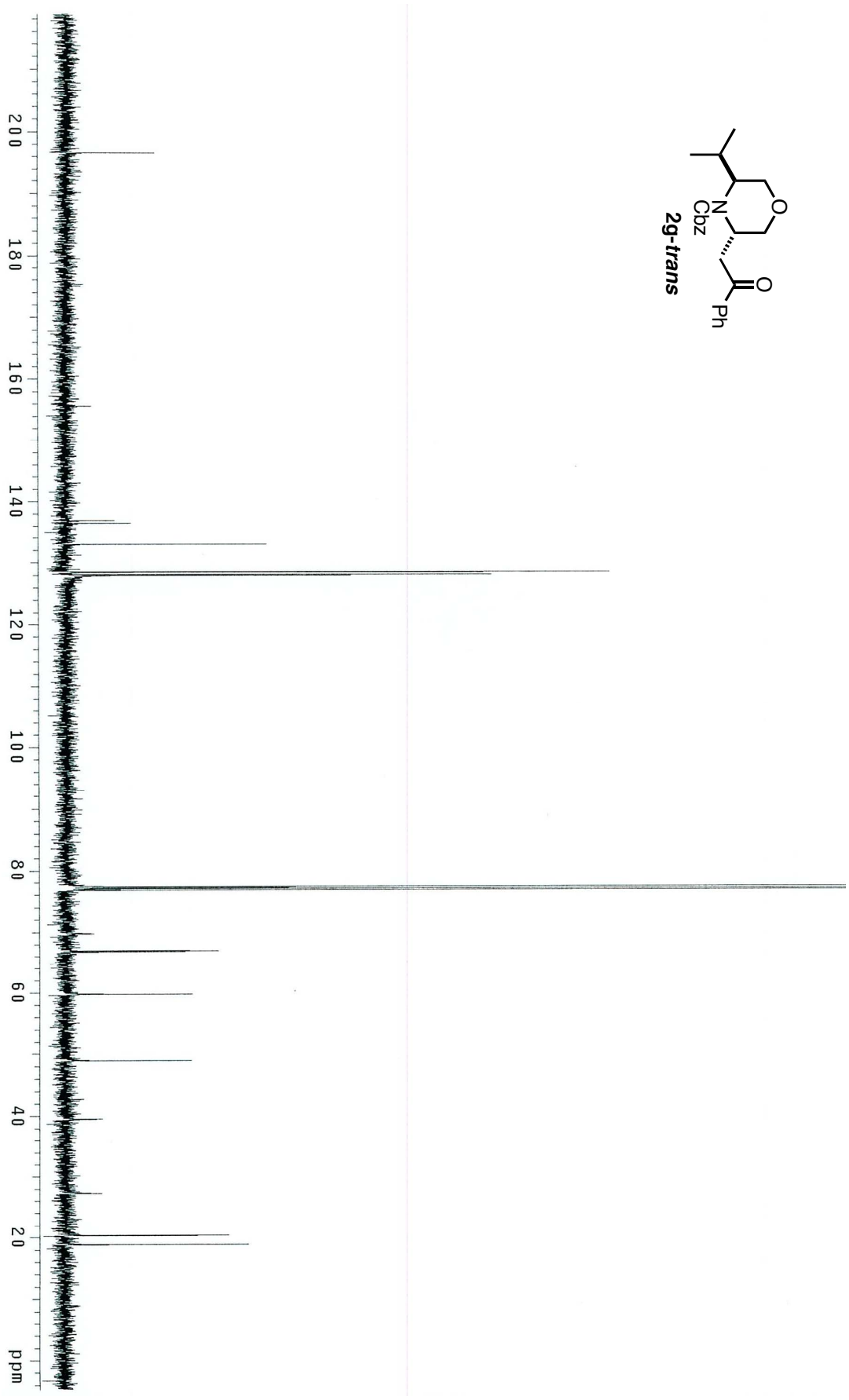
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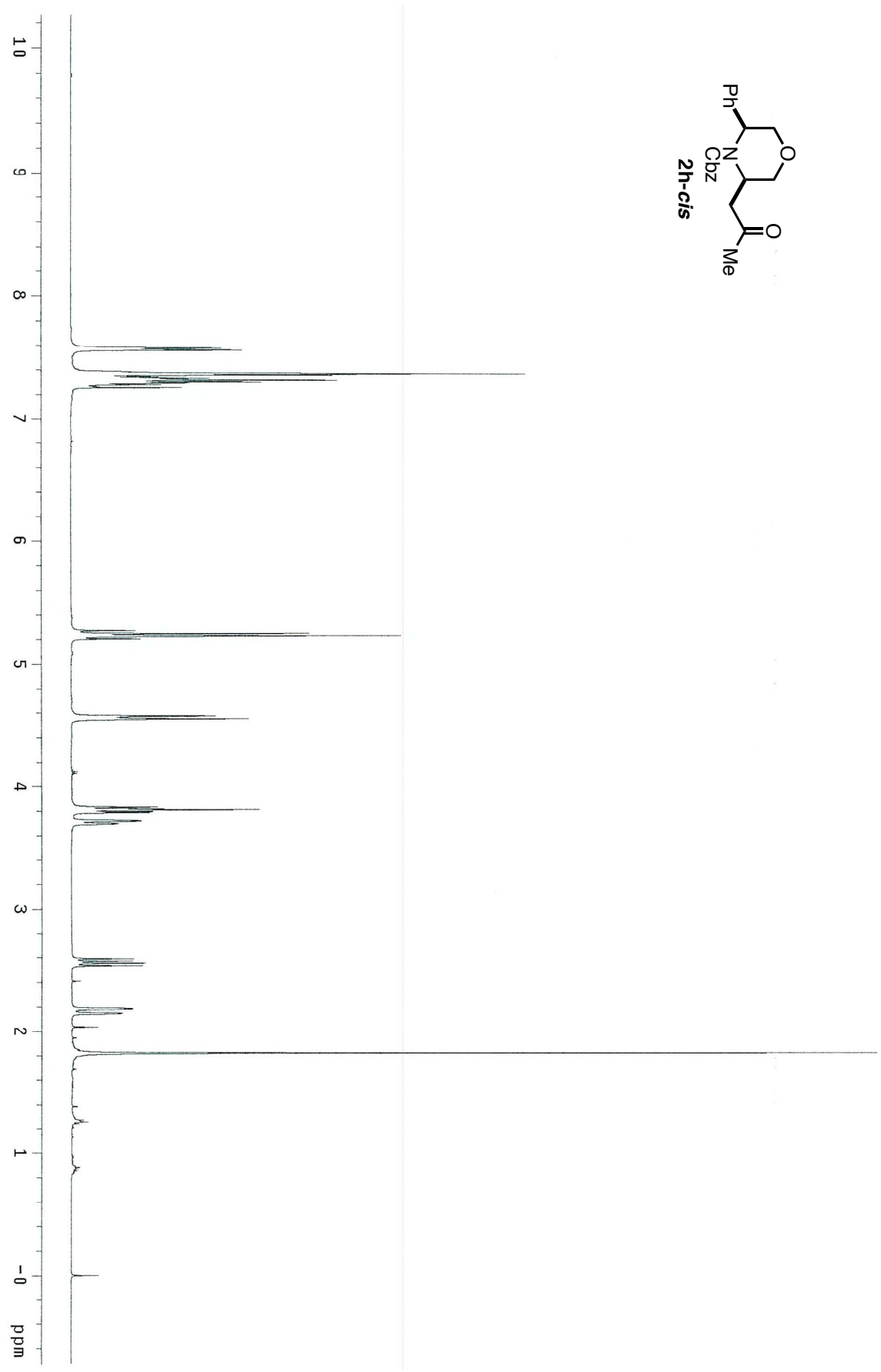
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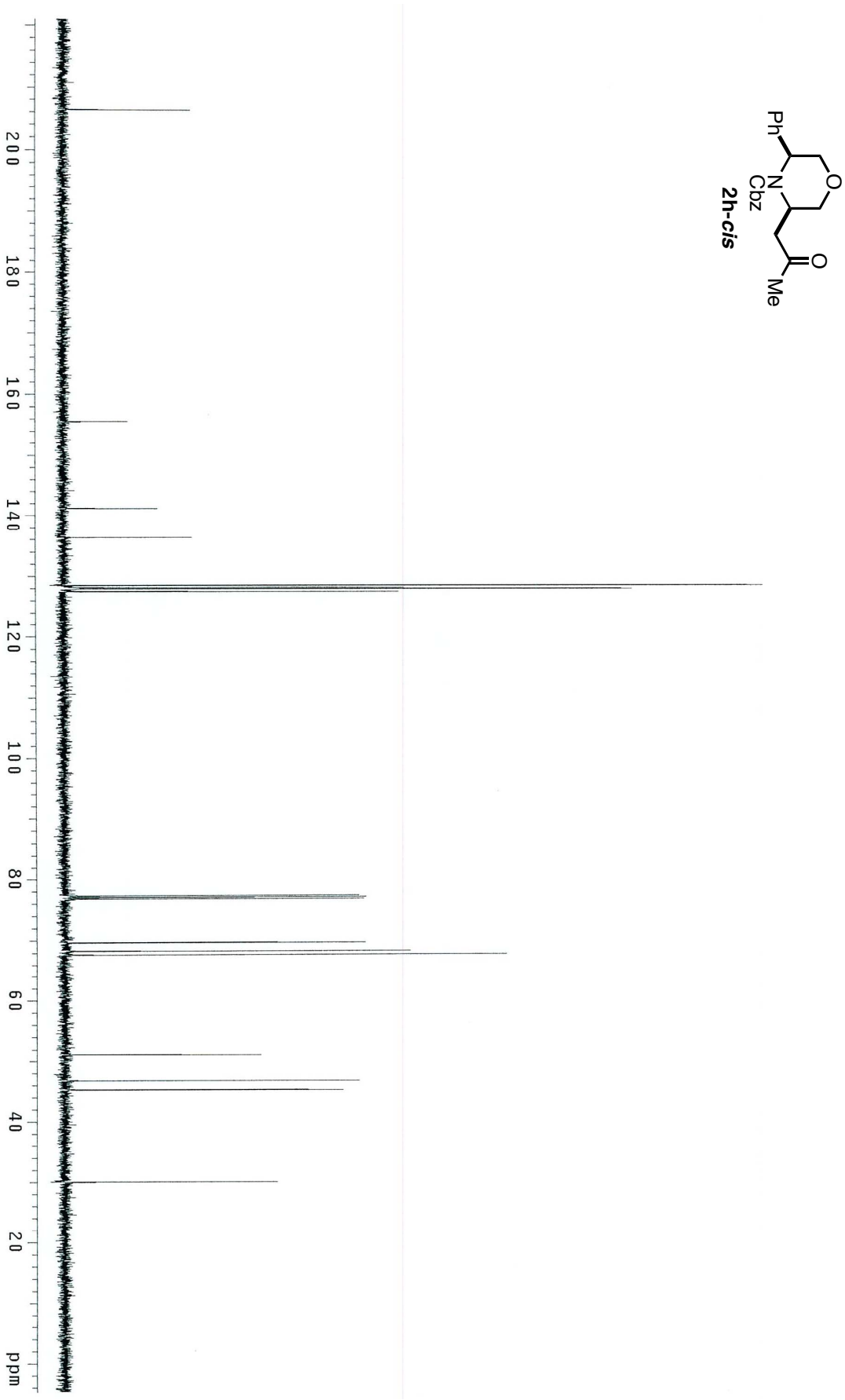
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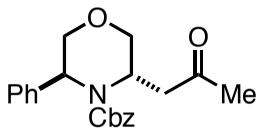

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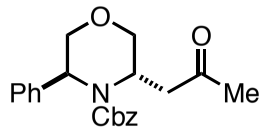

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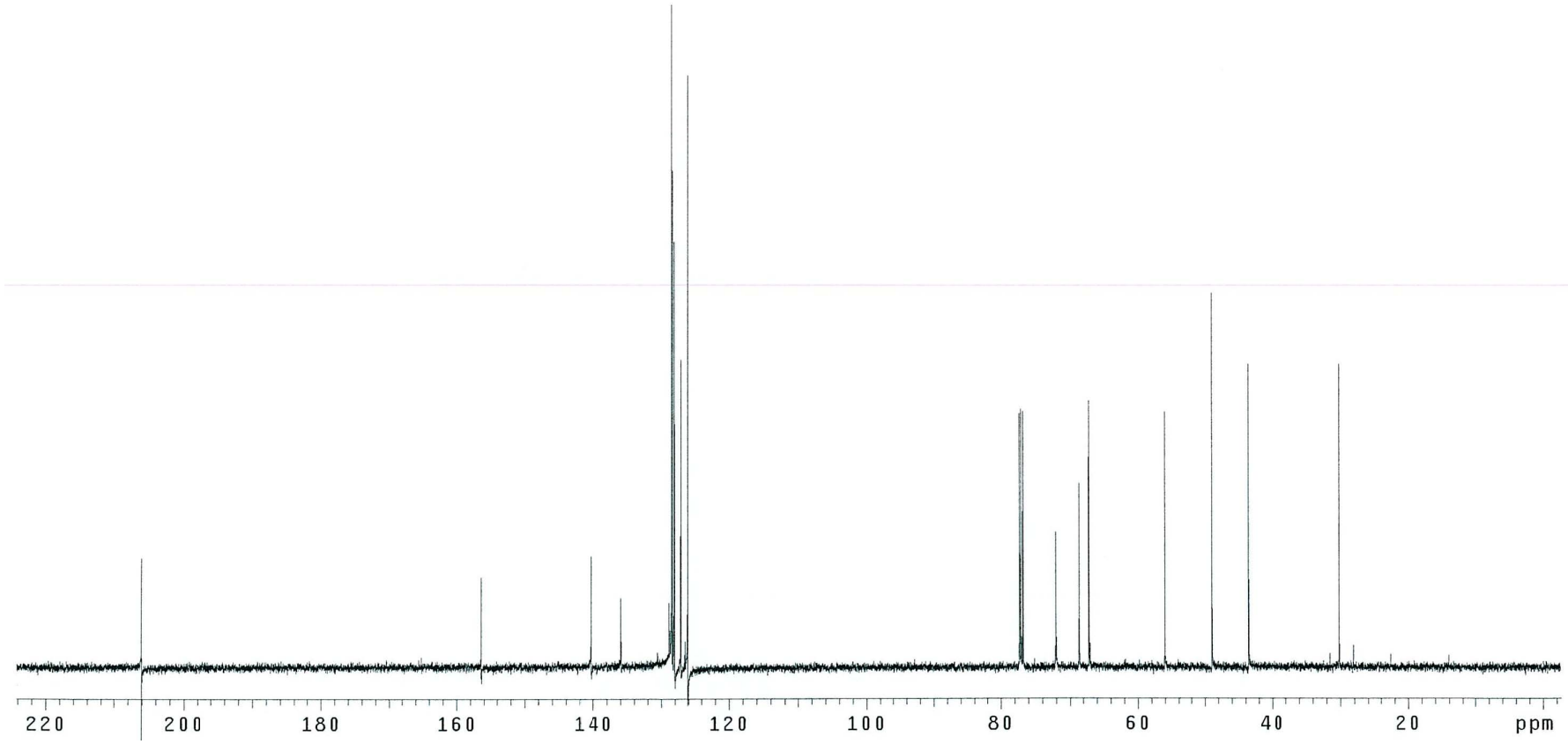

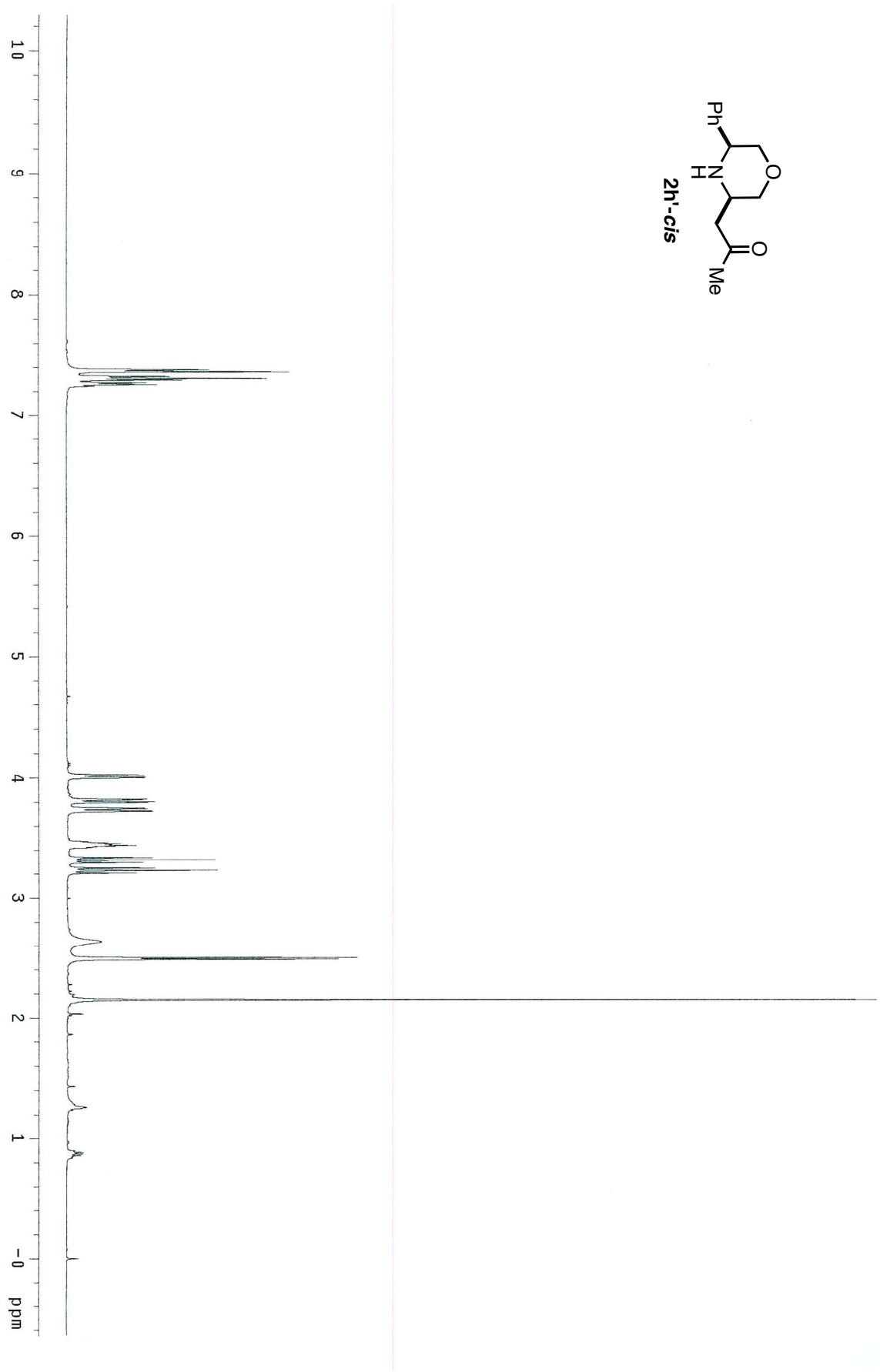
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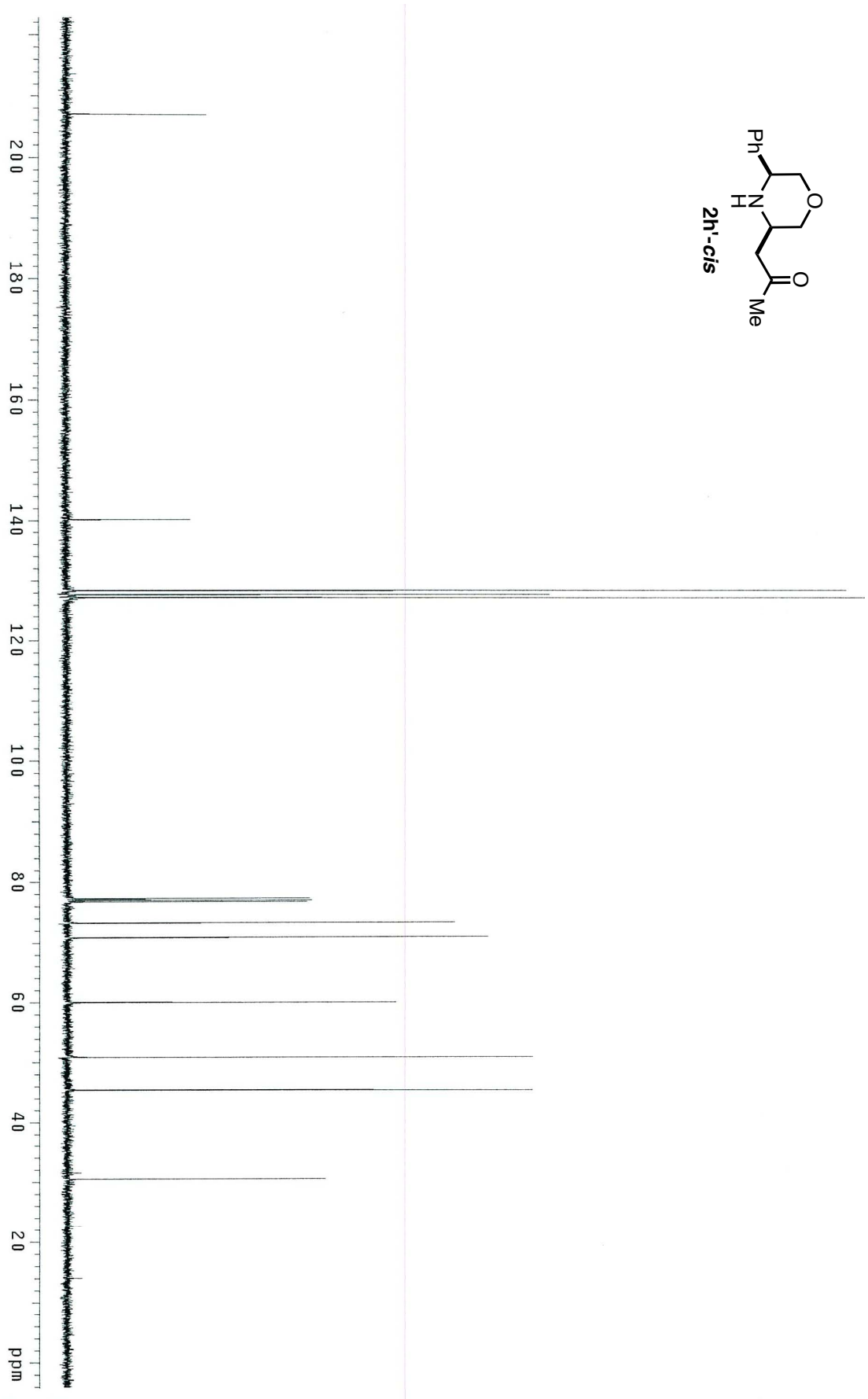
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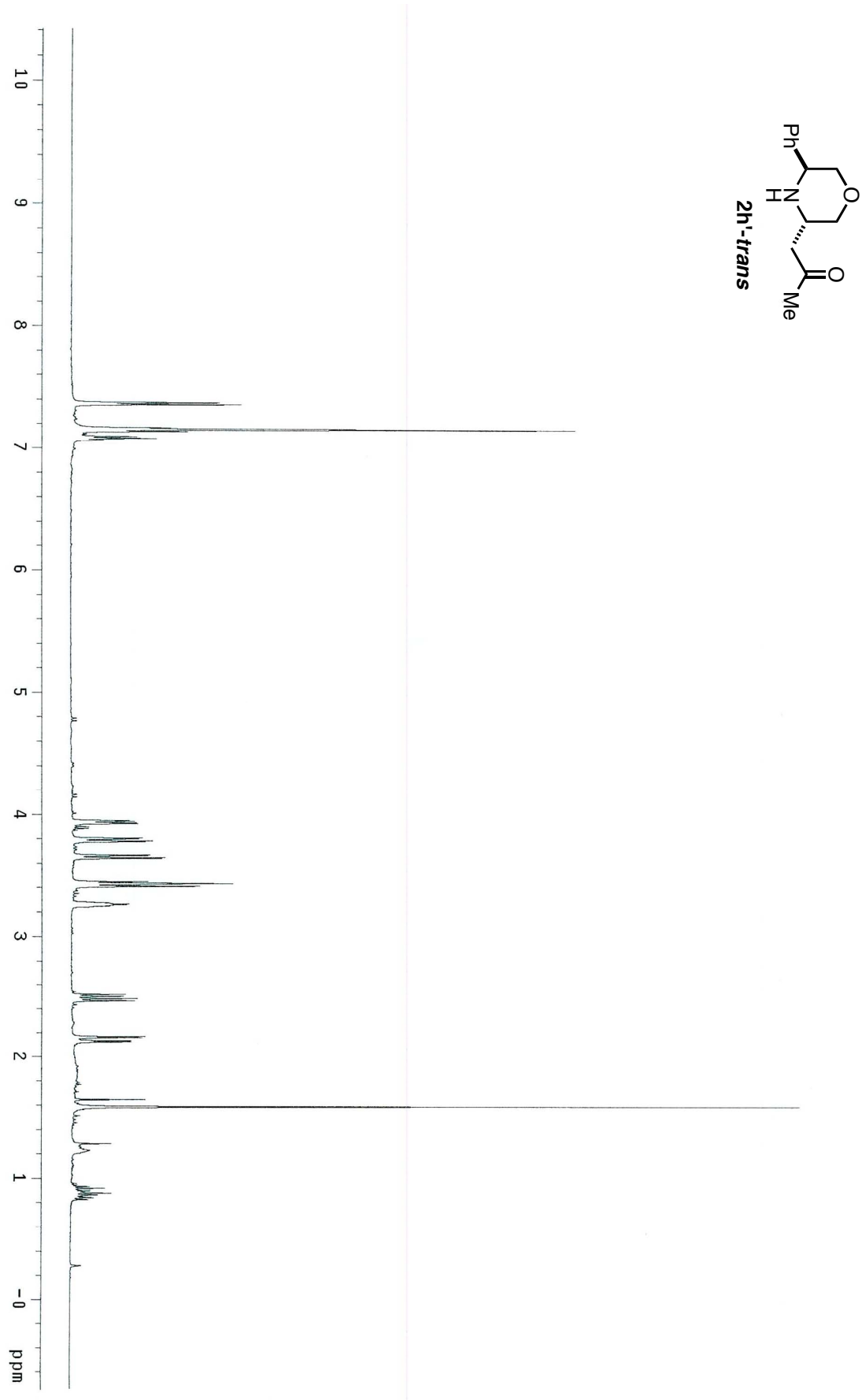
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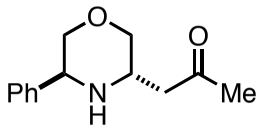

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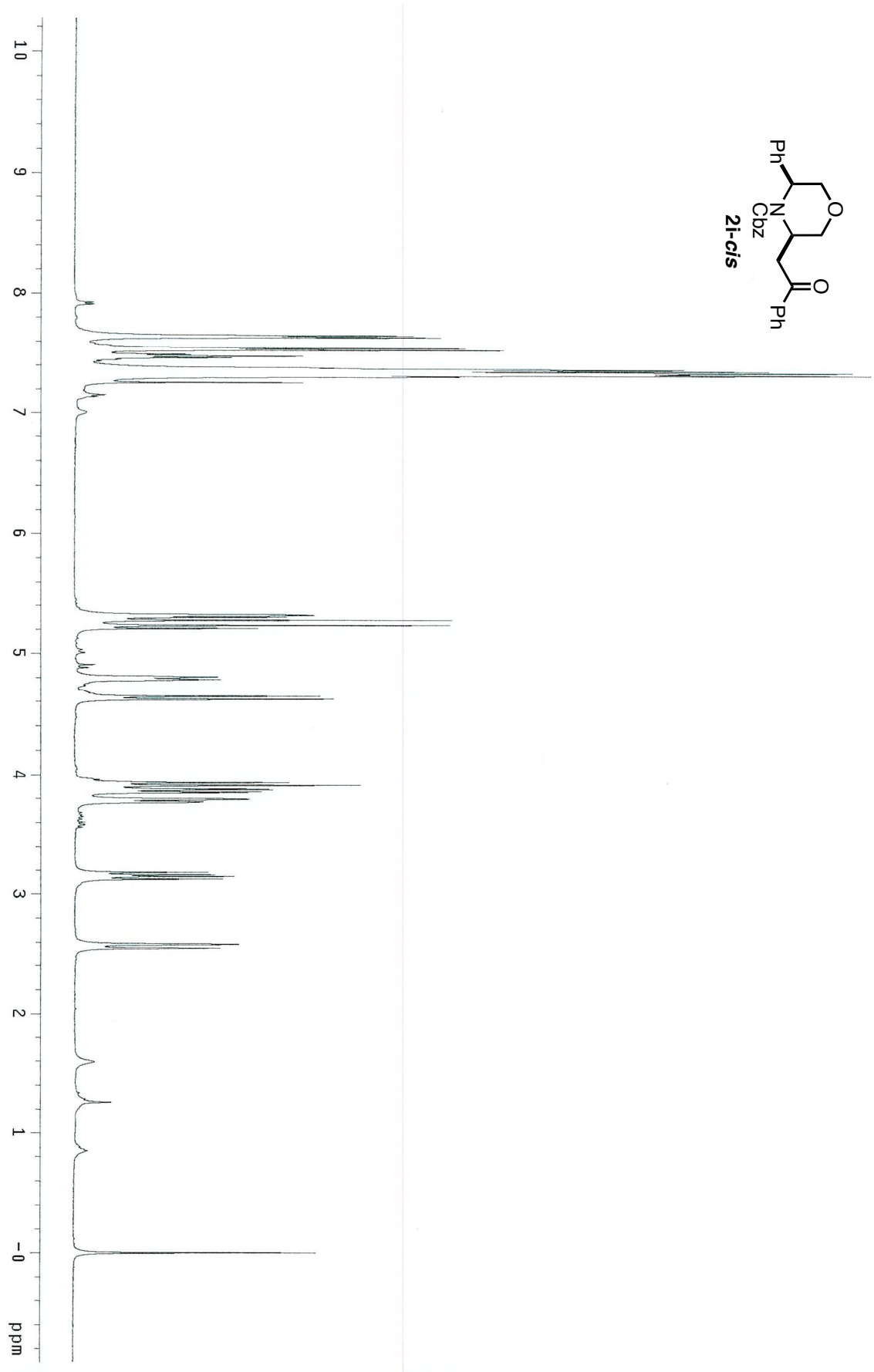
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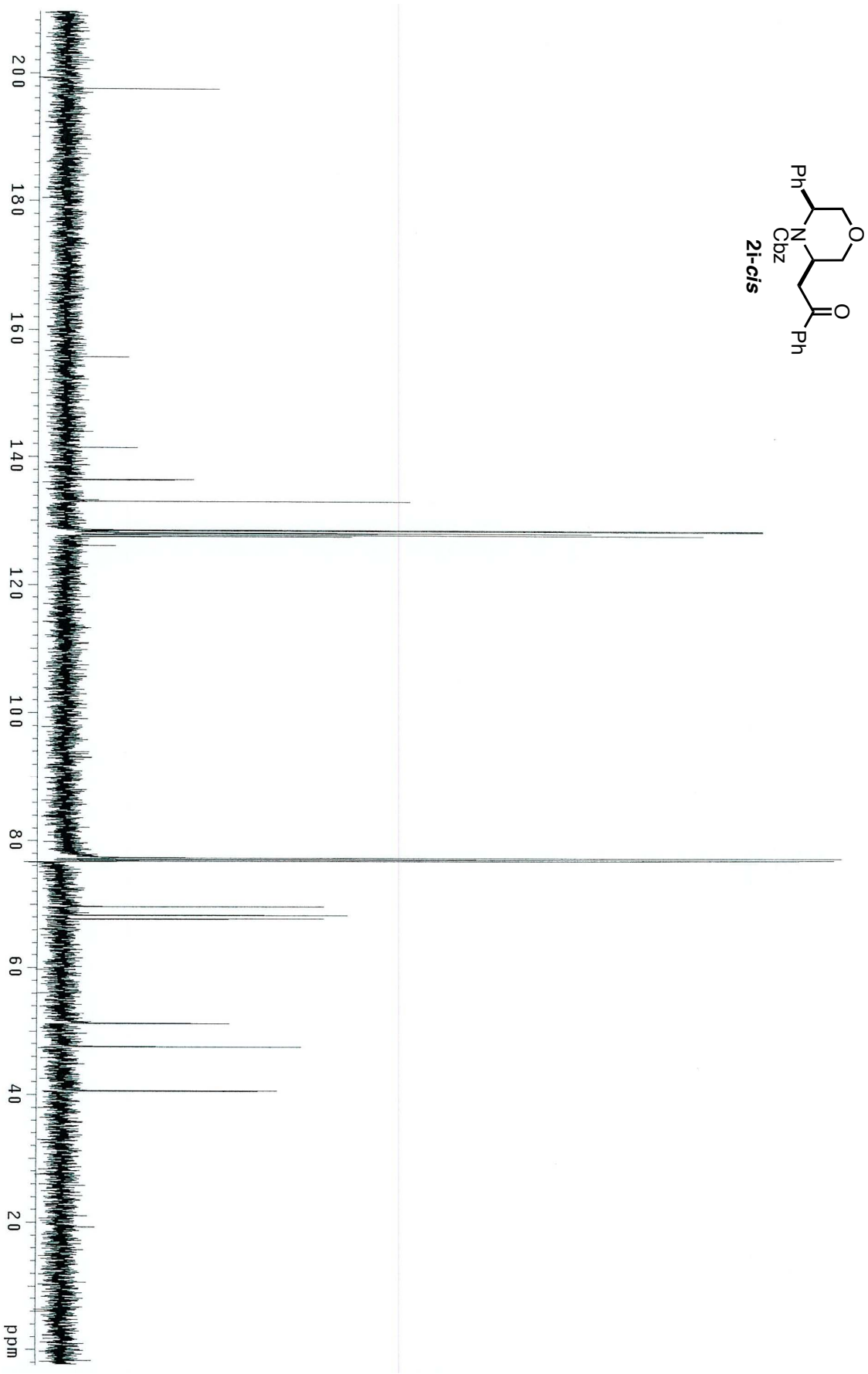
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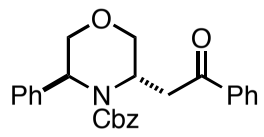

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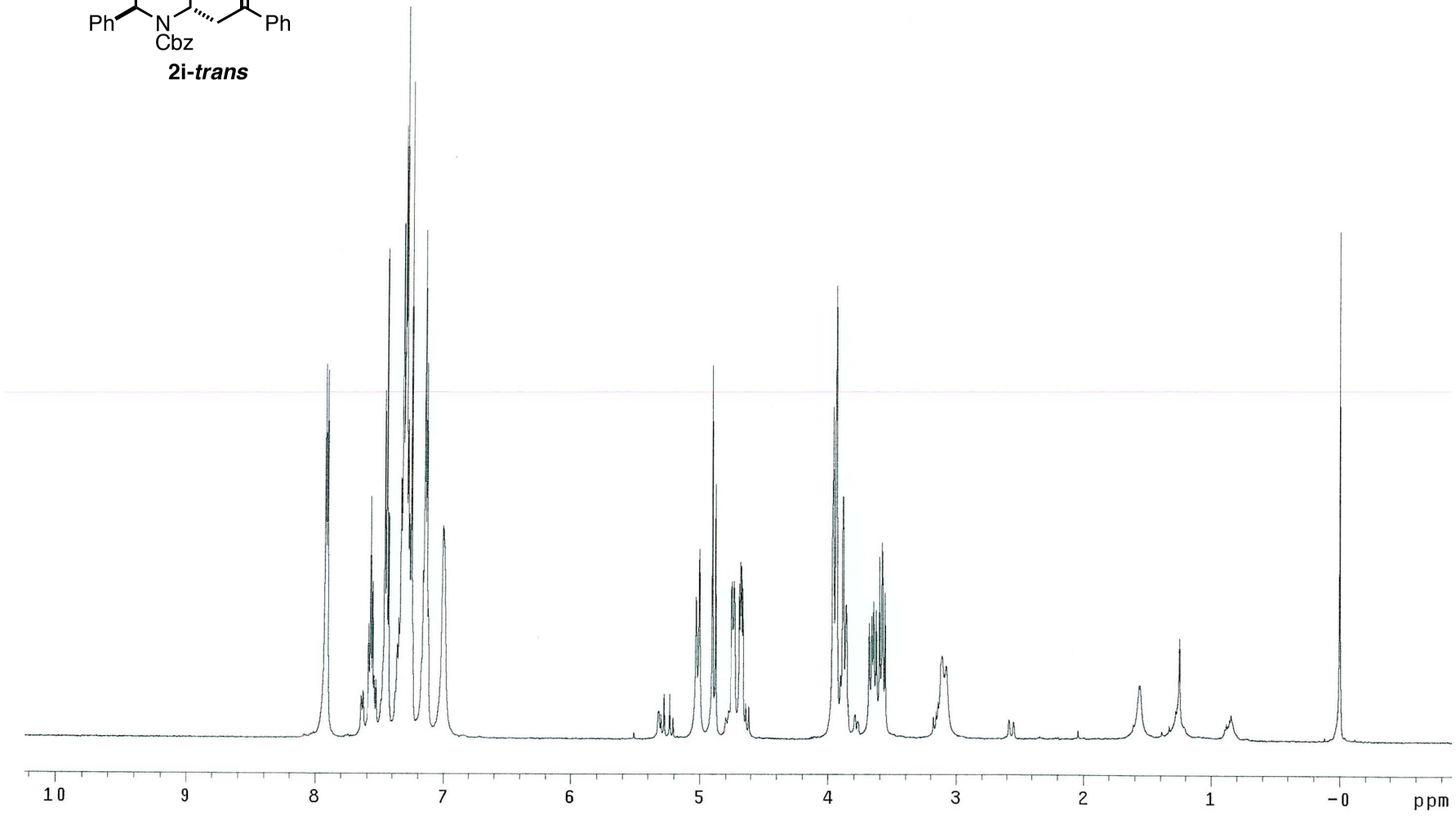

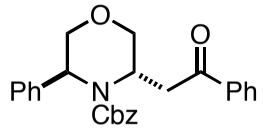

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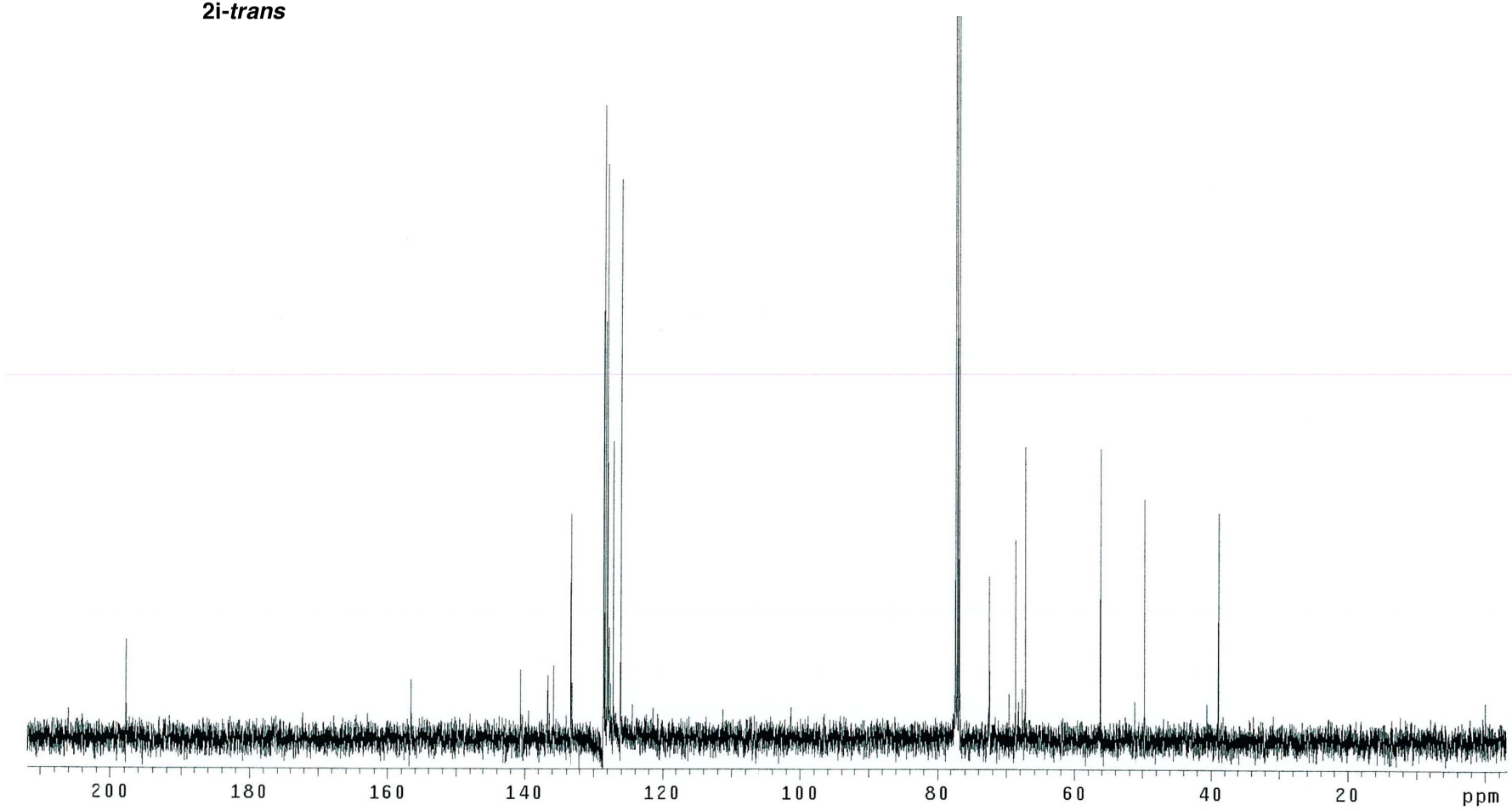

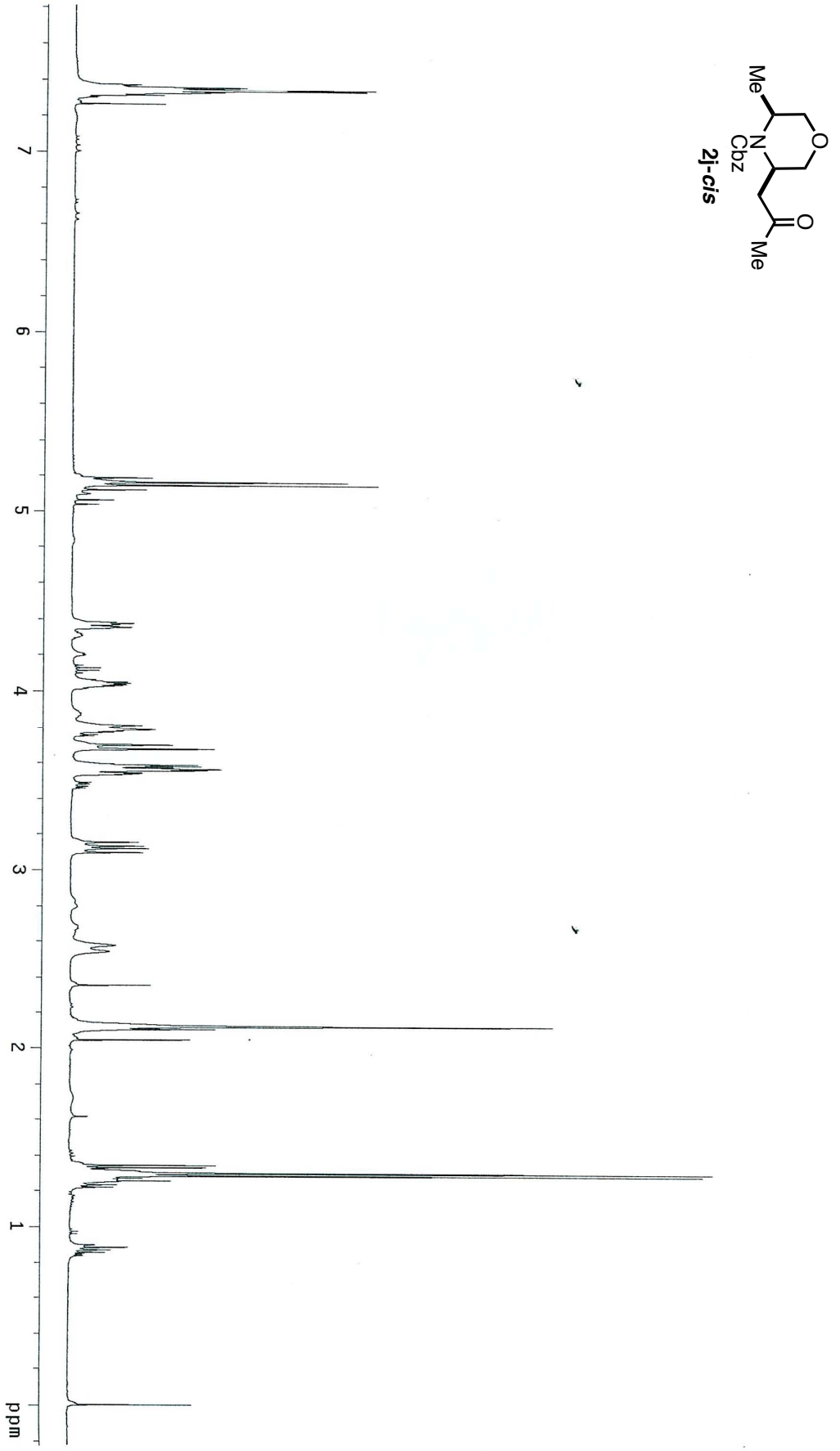
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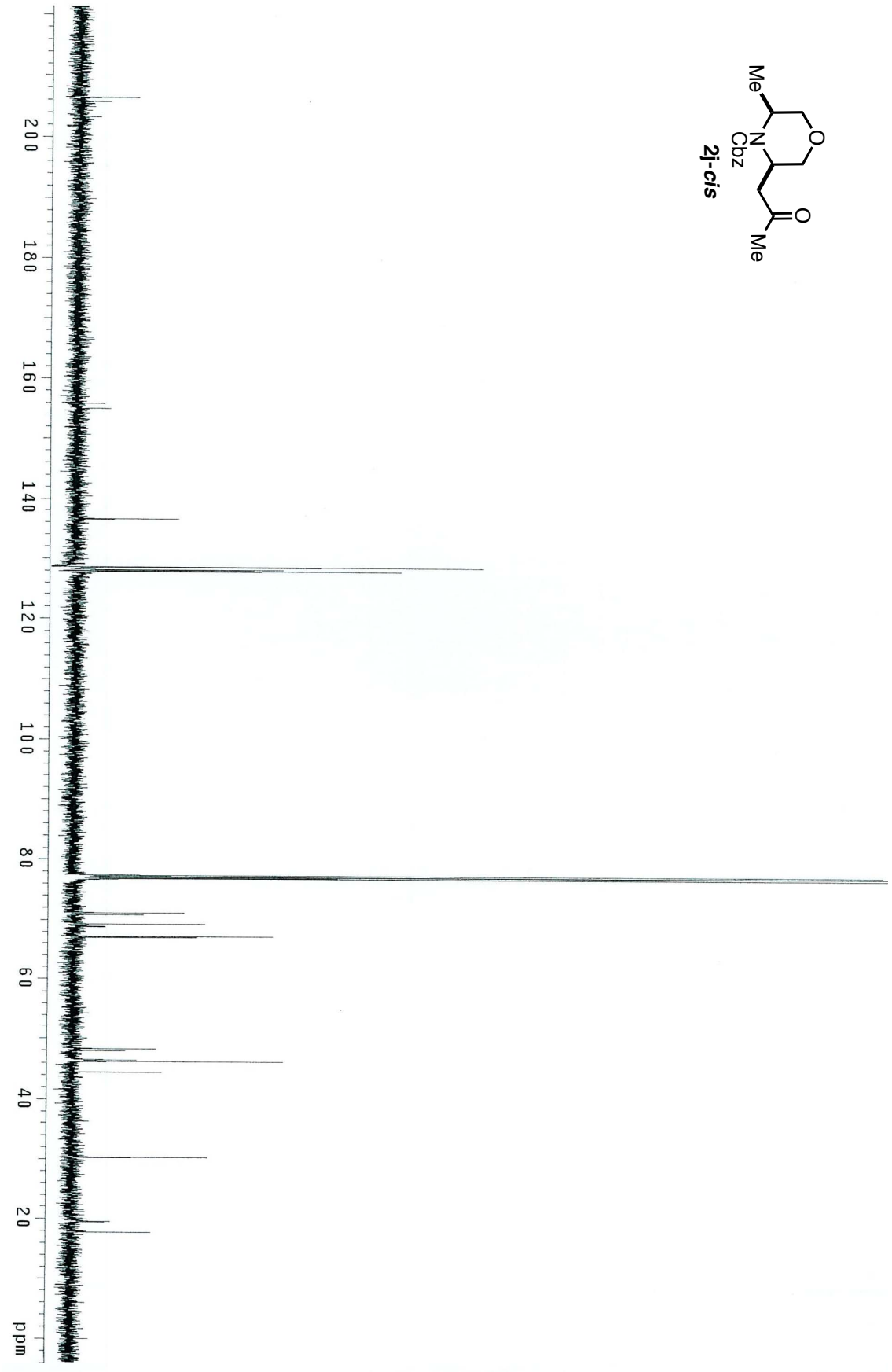
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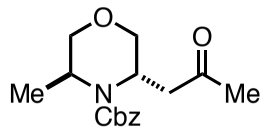

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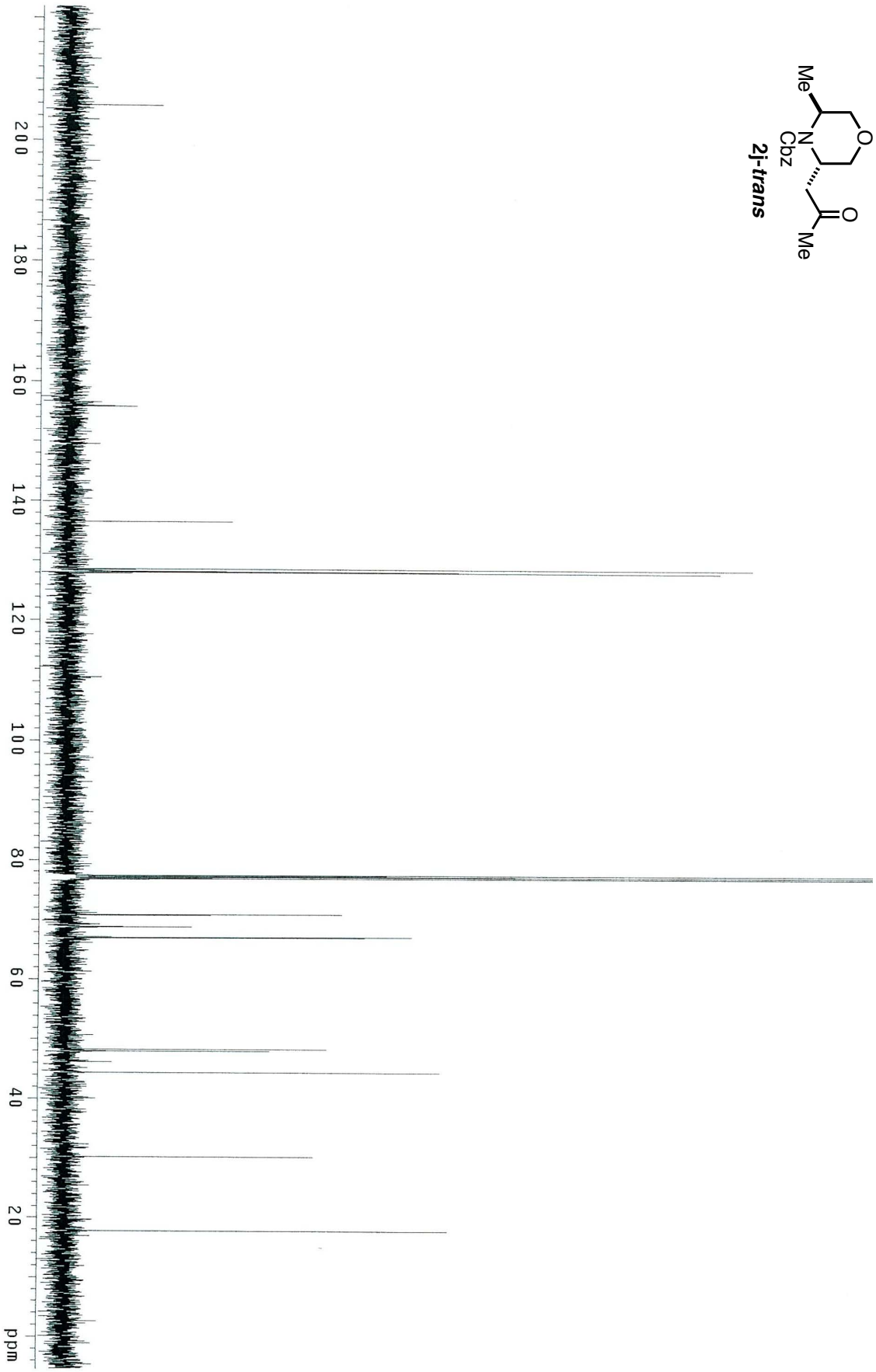
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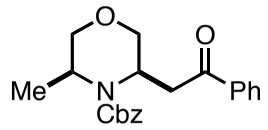

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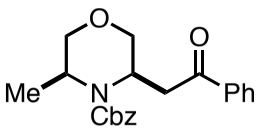

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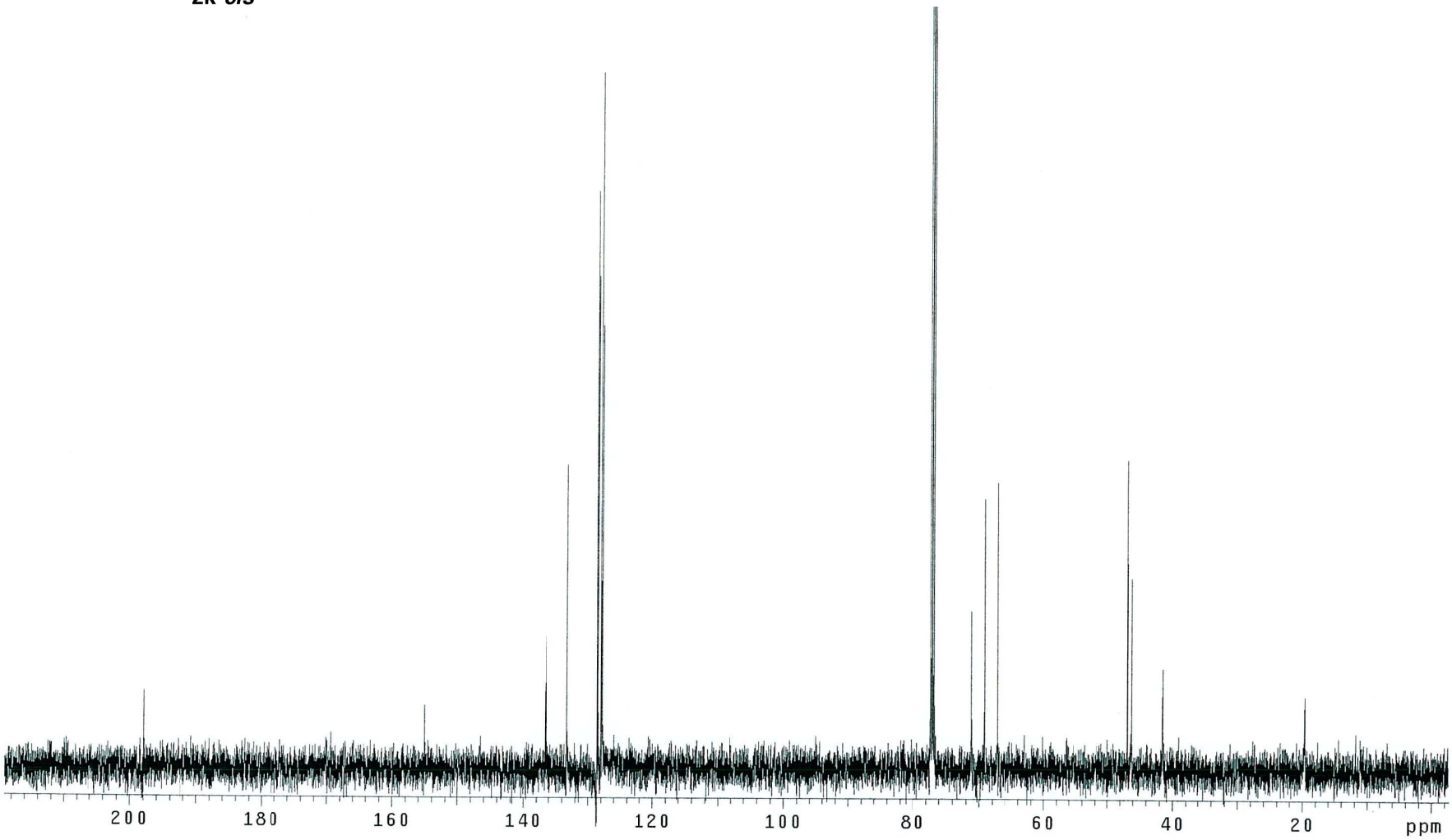

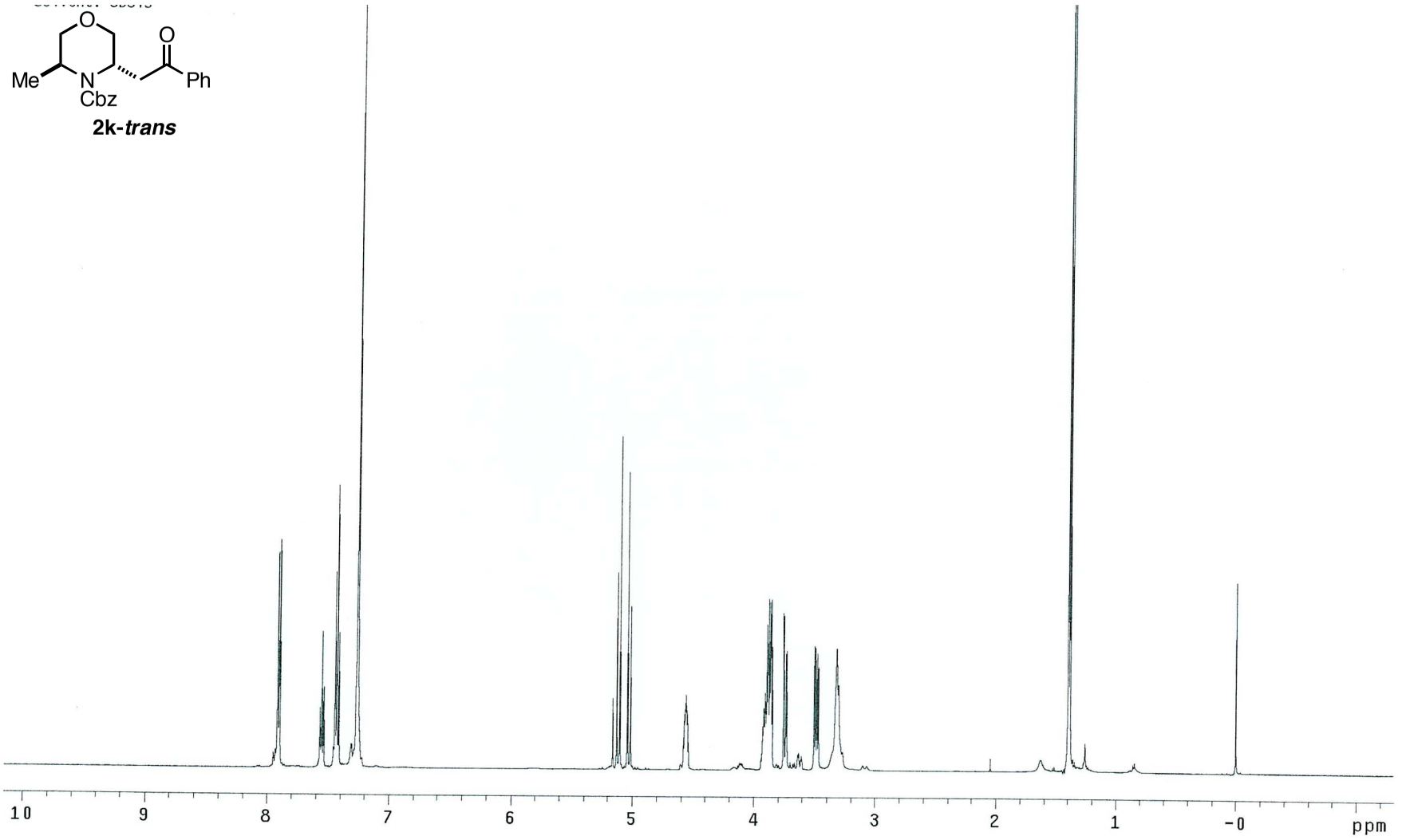
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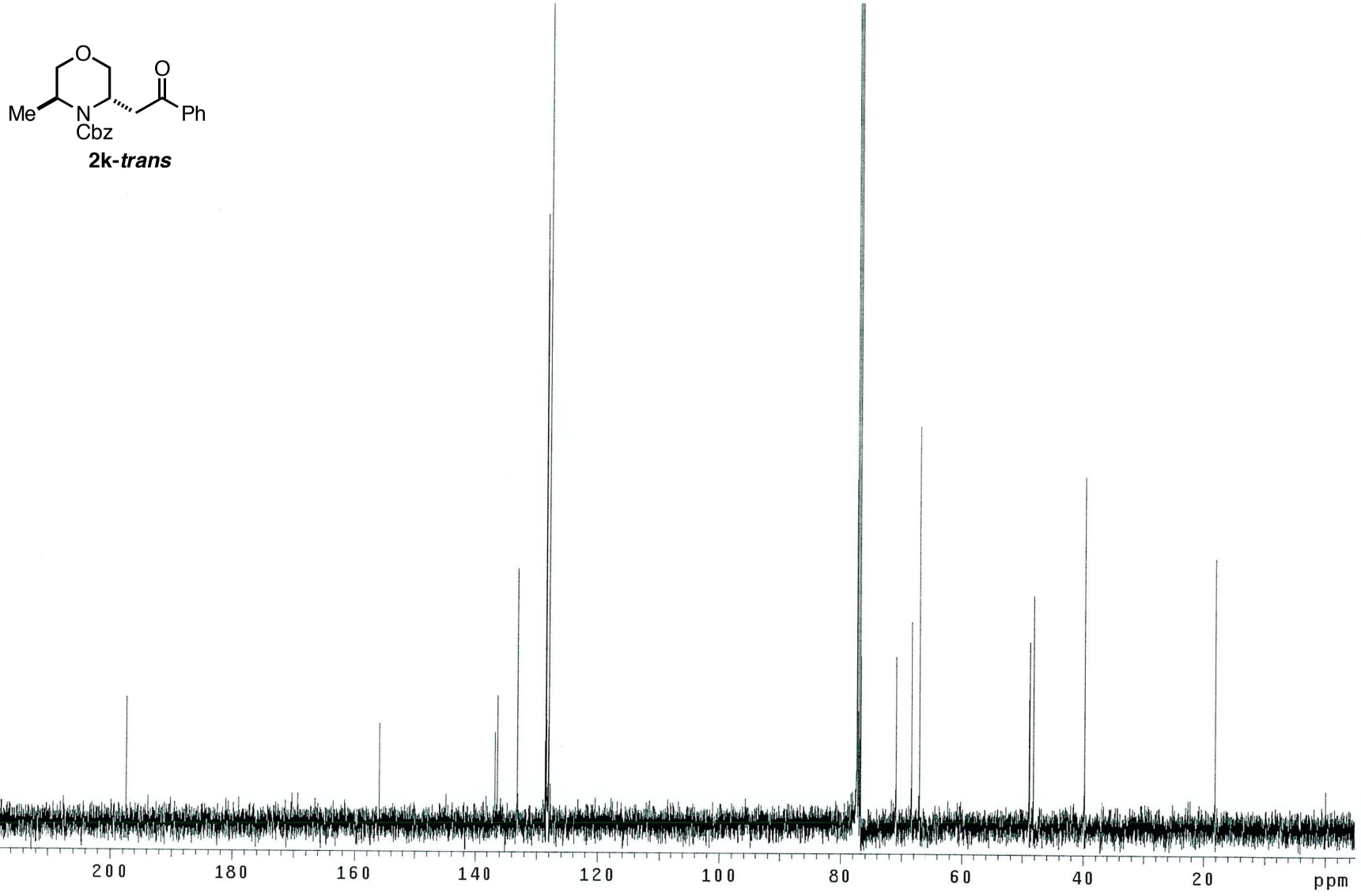
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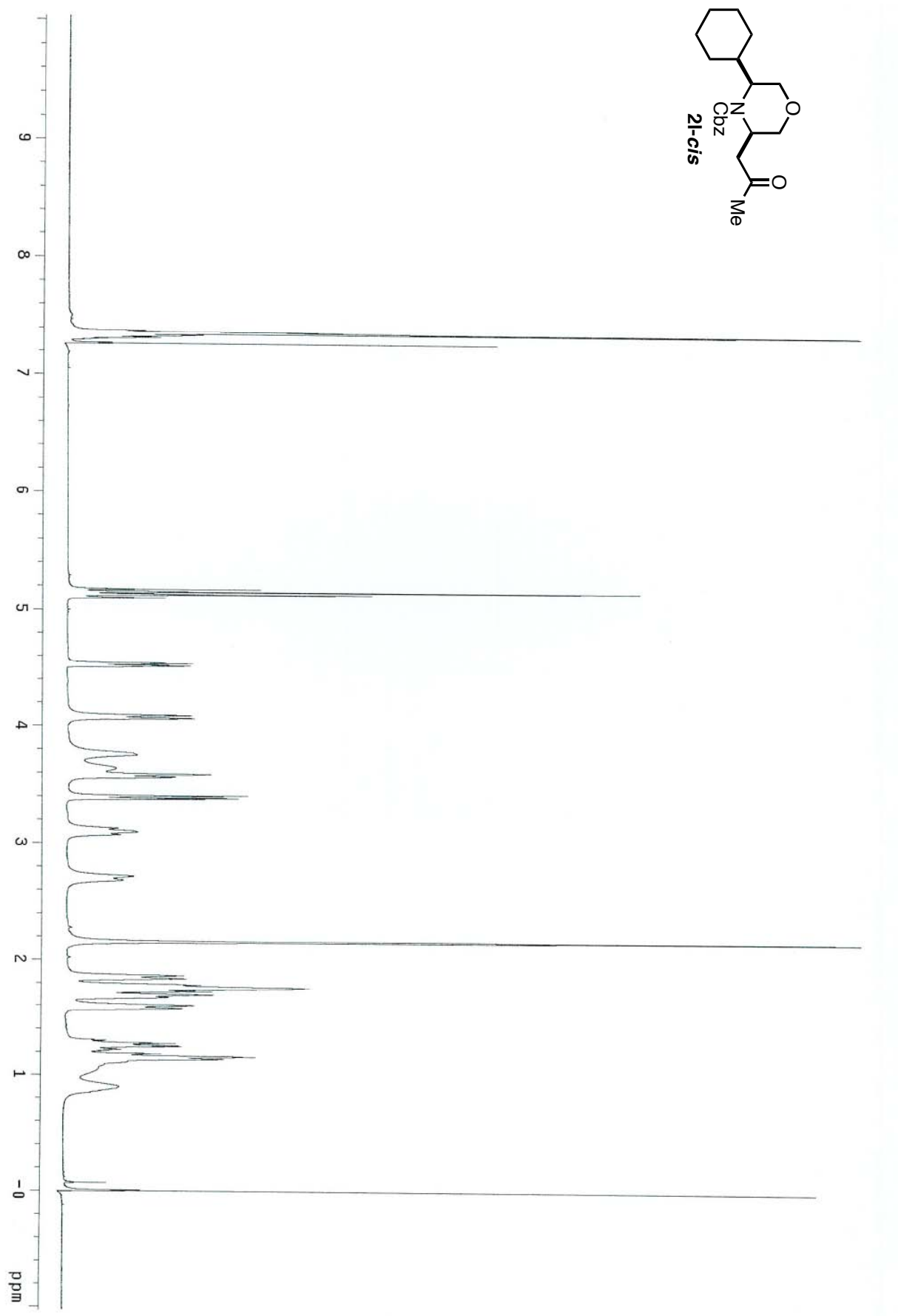
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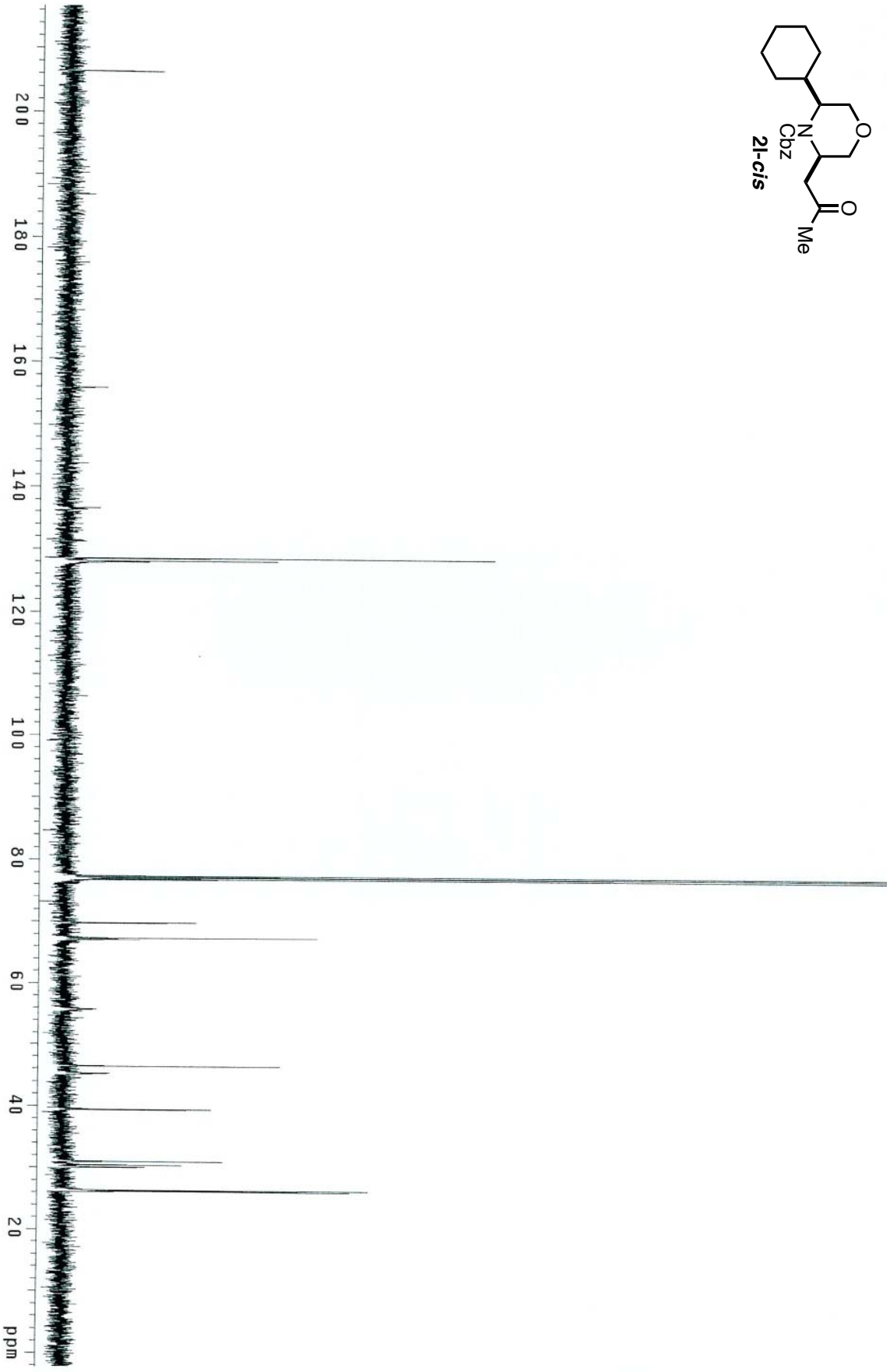
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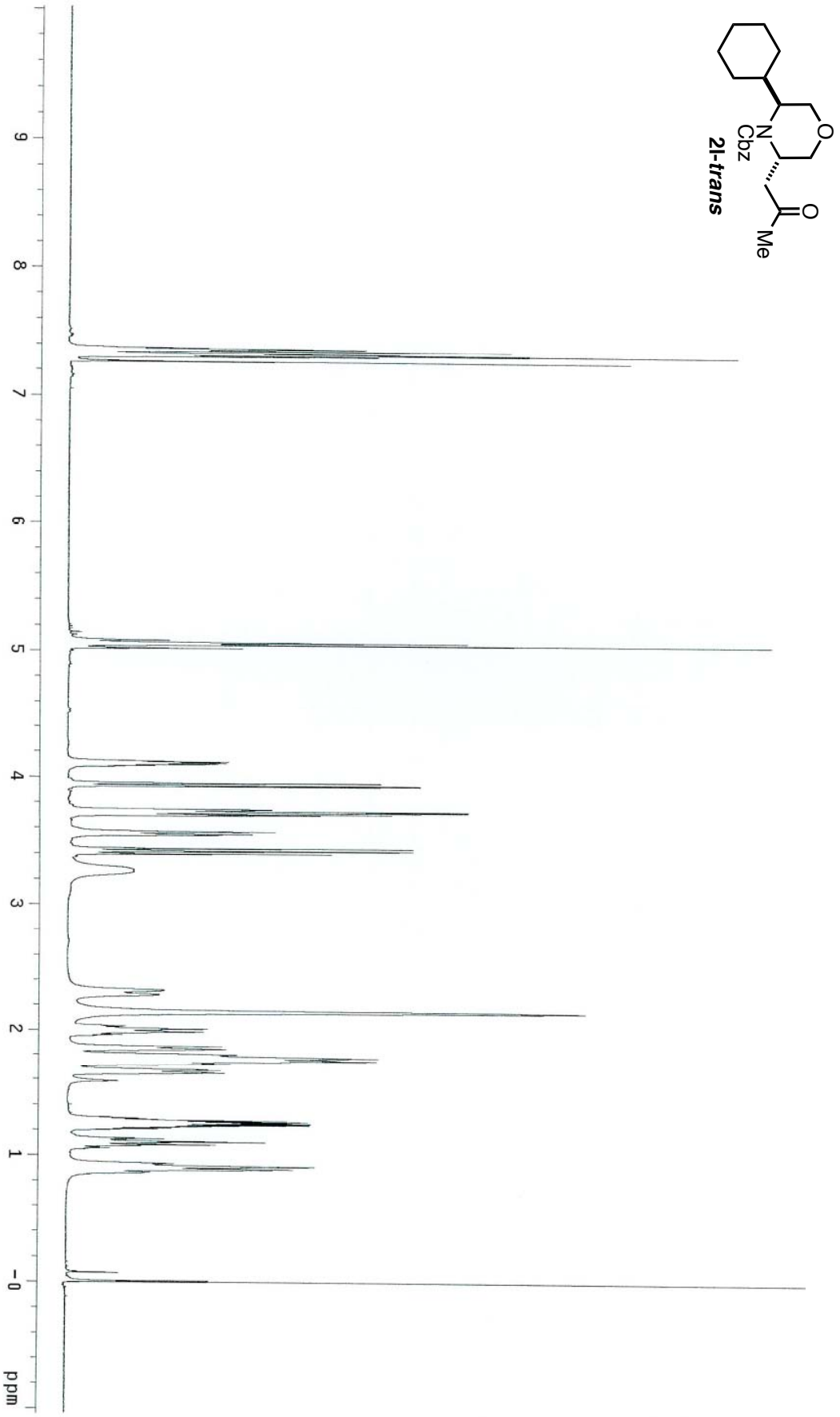
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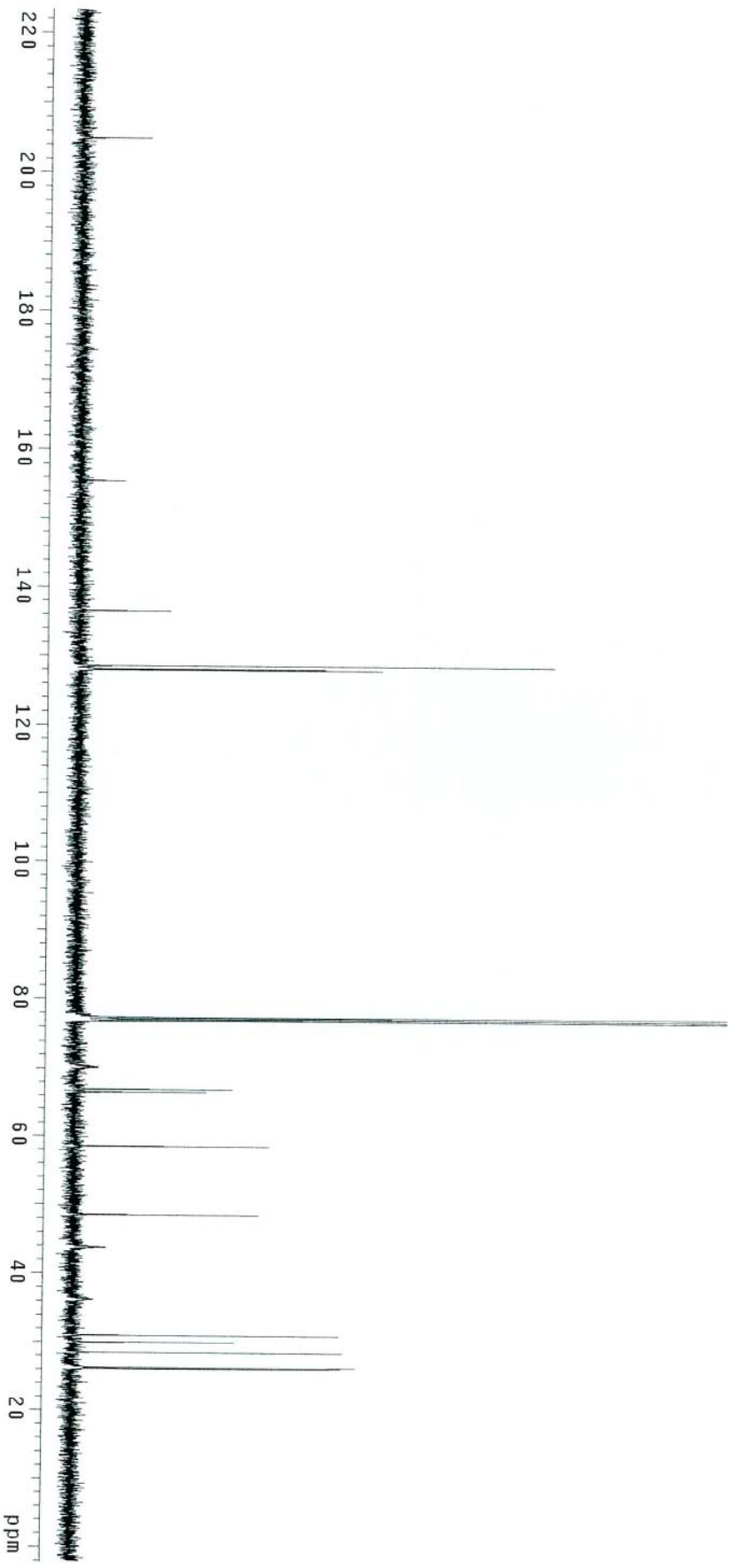
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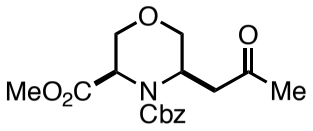
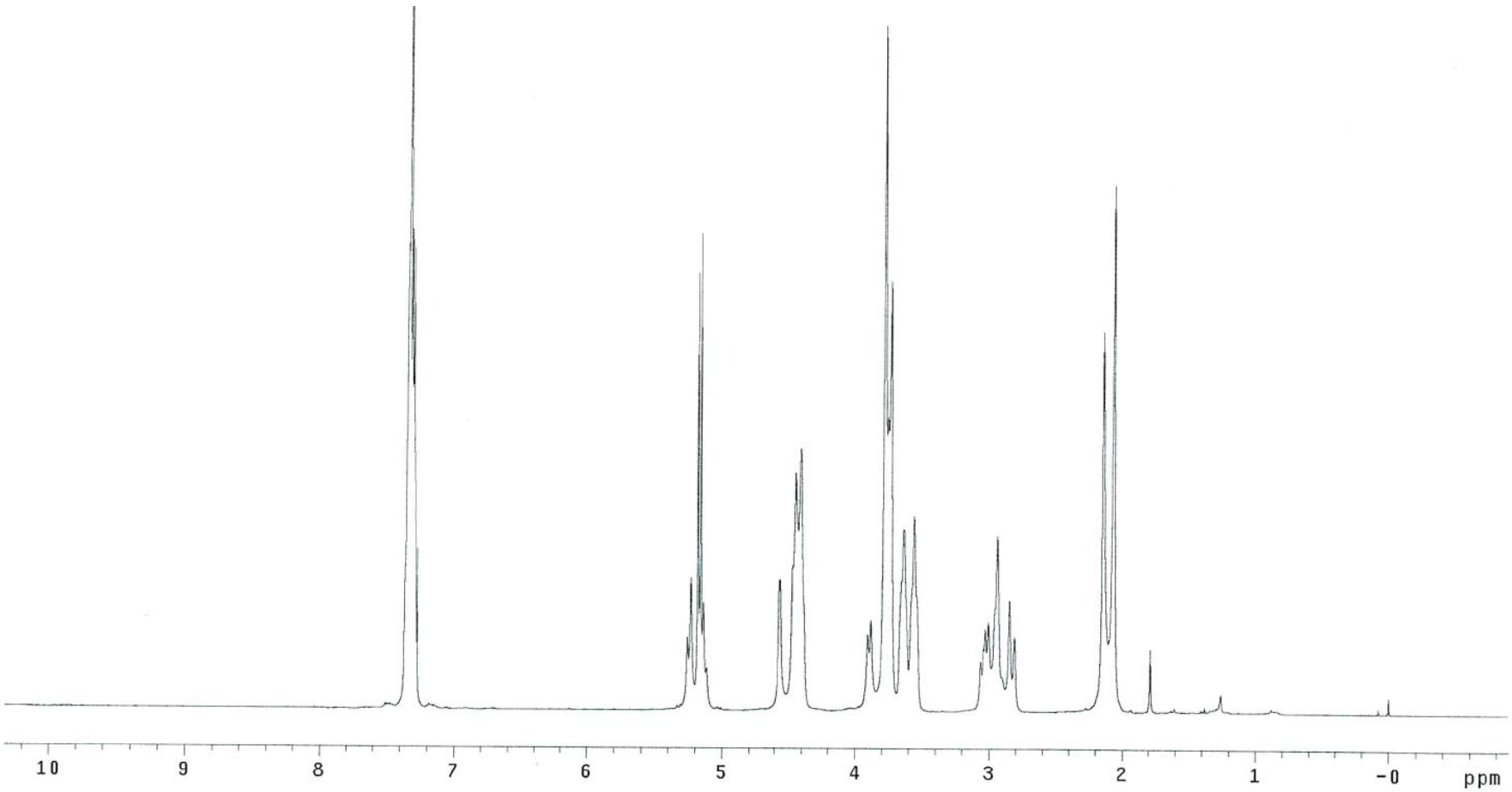
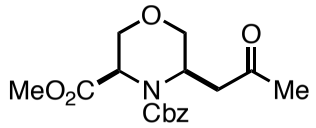
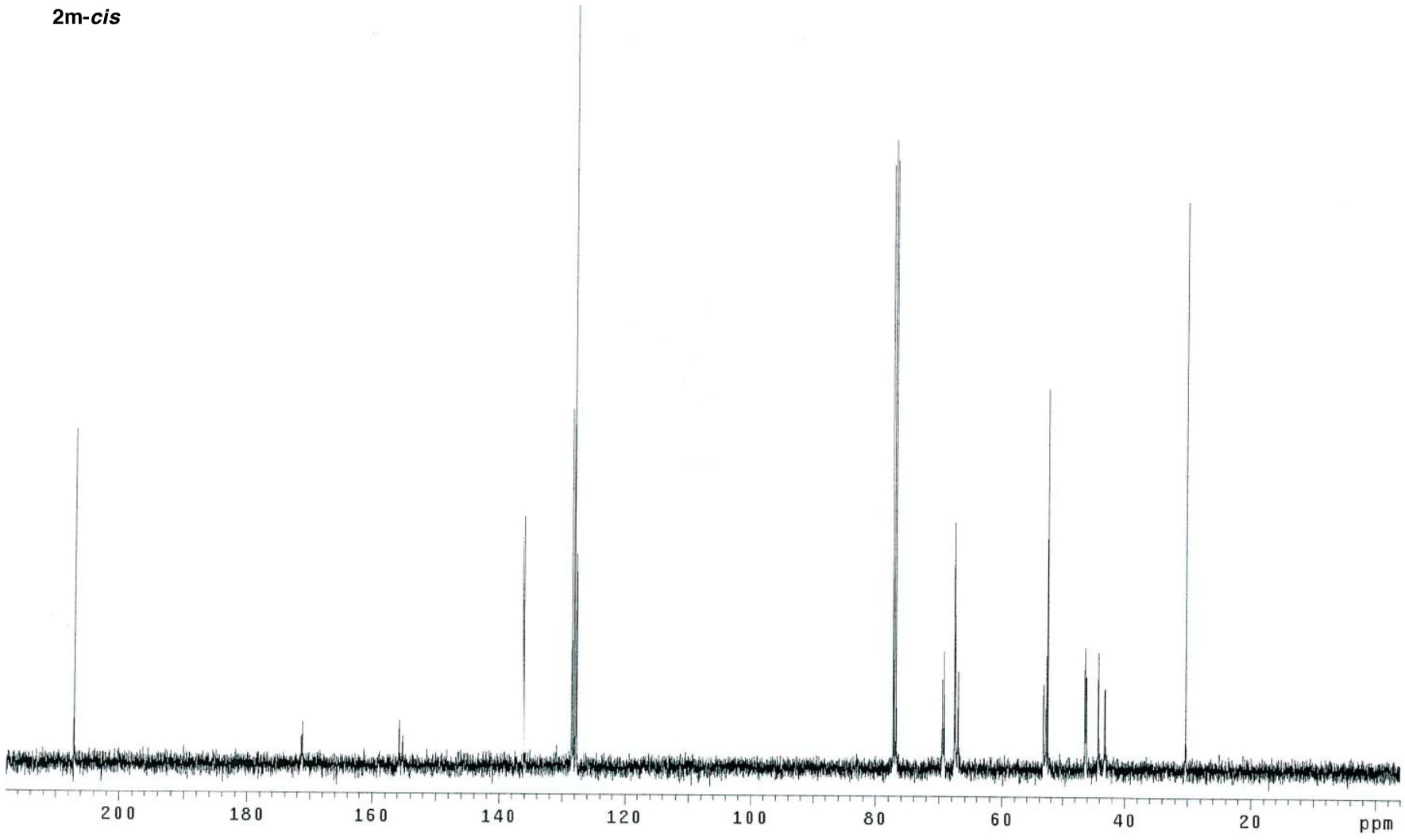


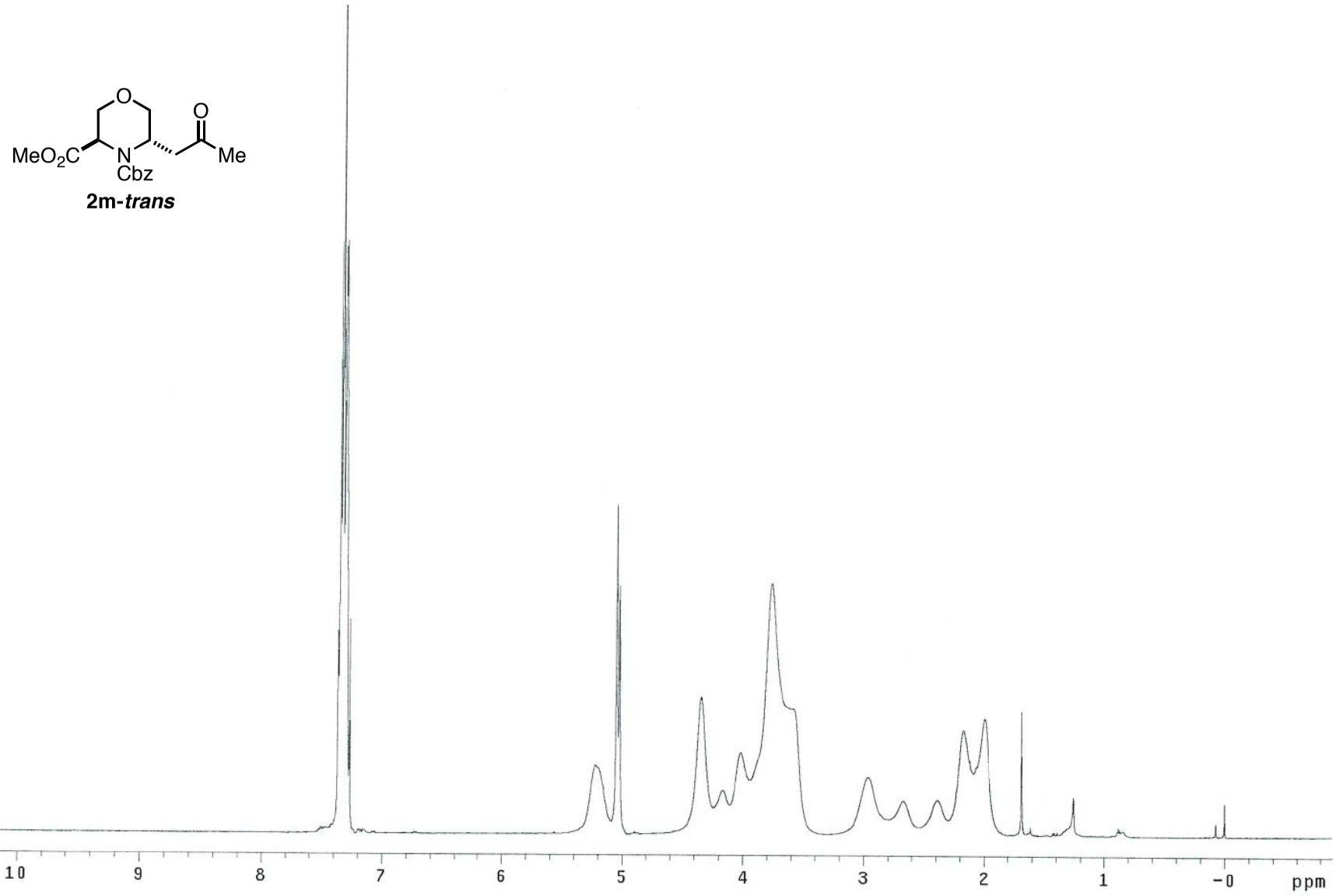
2m-*cis*





2m-*cis*

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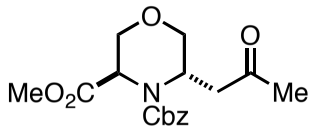

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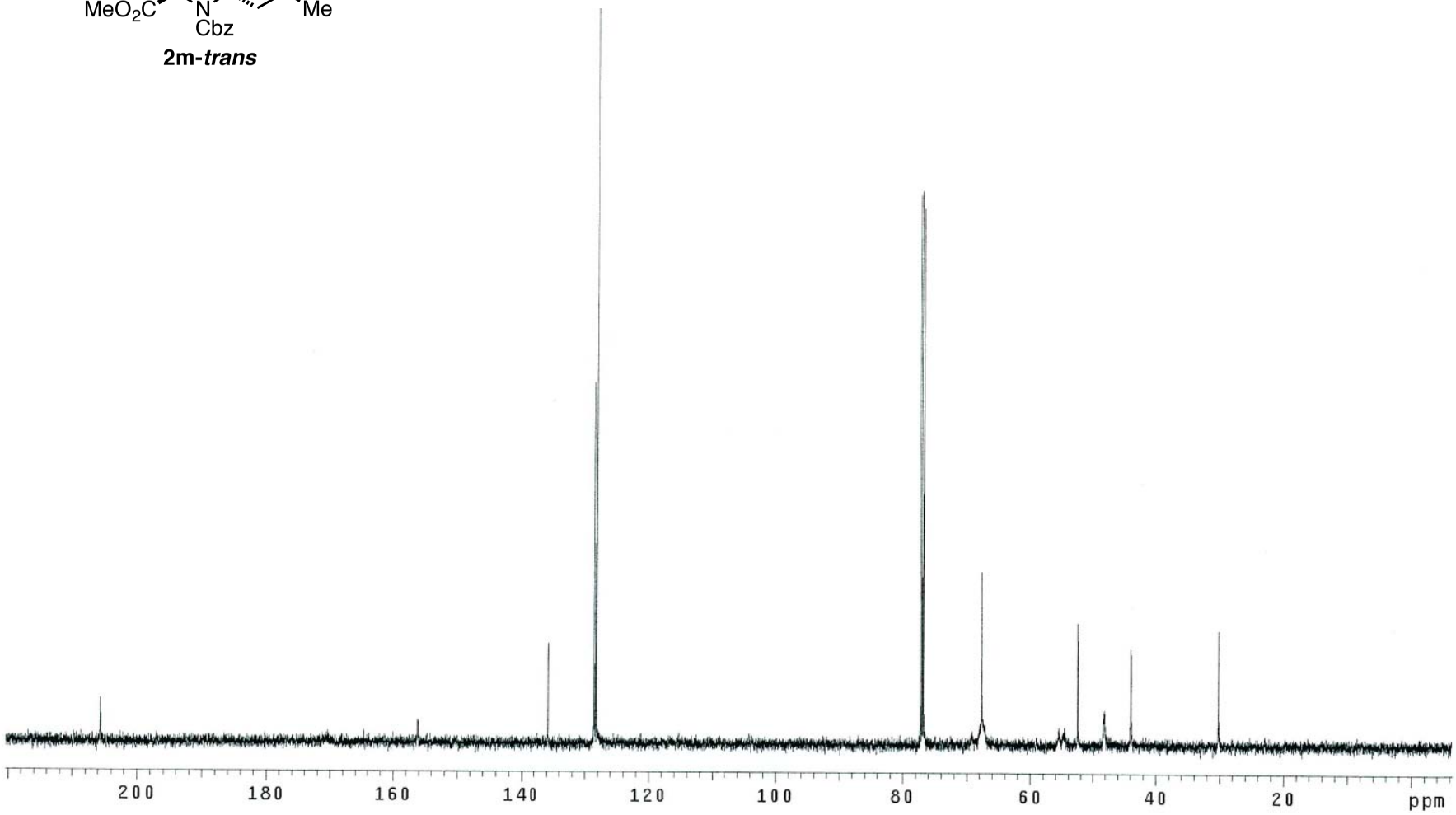

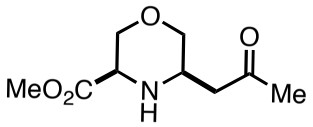

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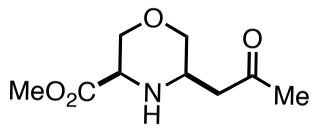

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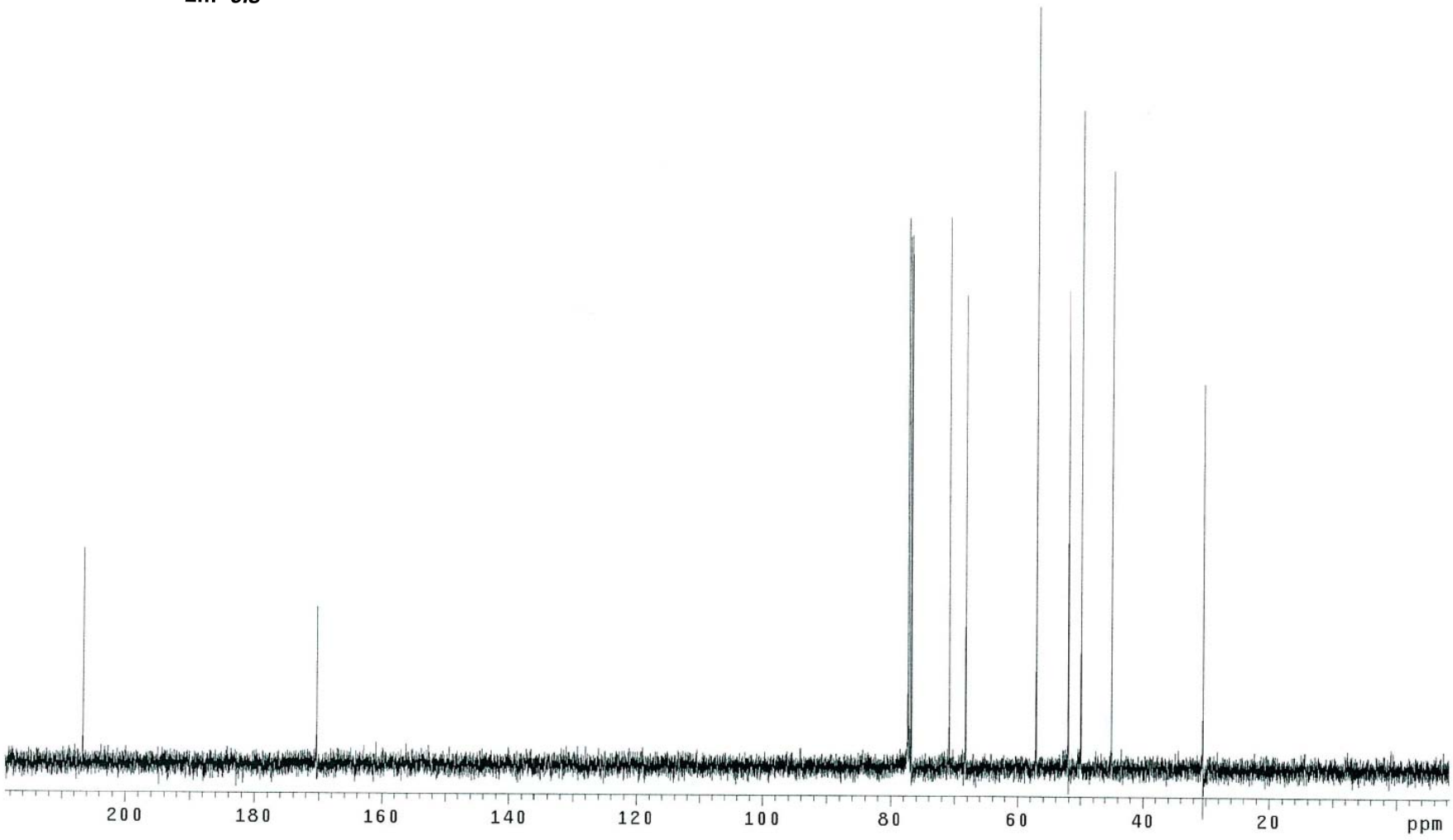

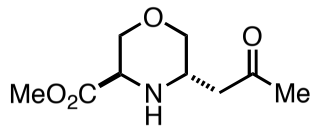

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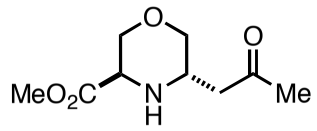

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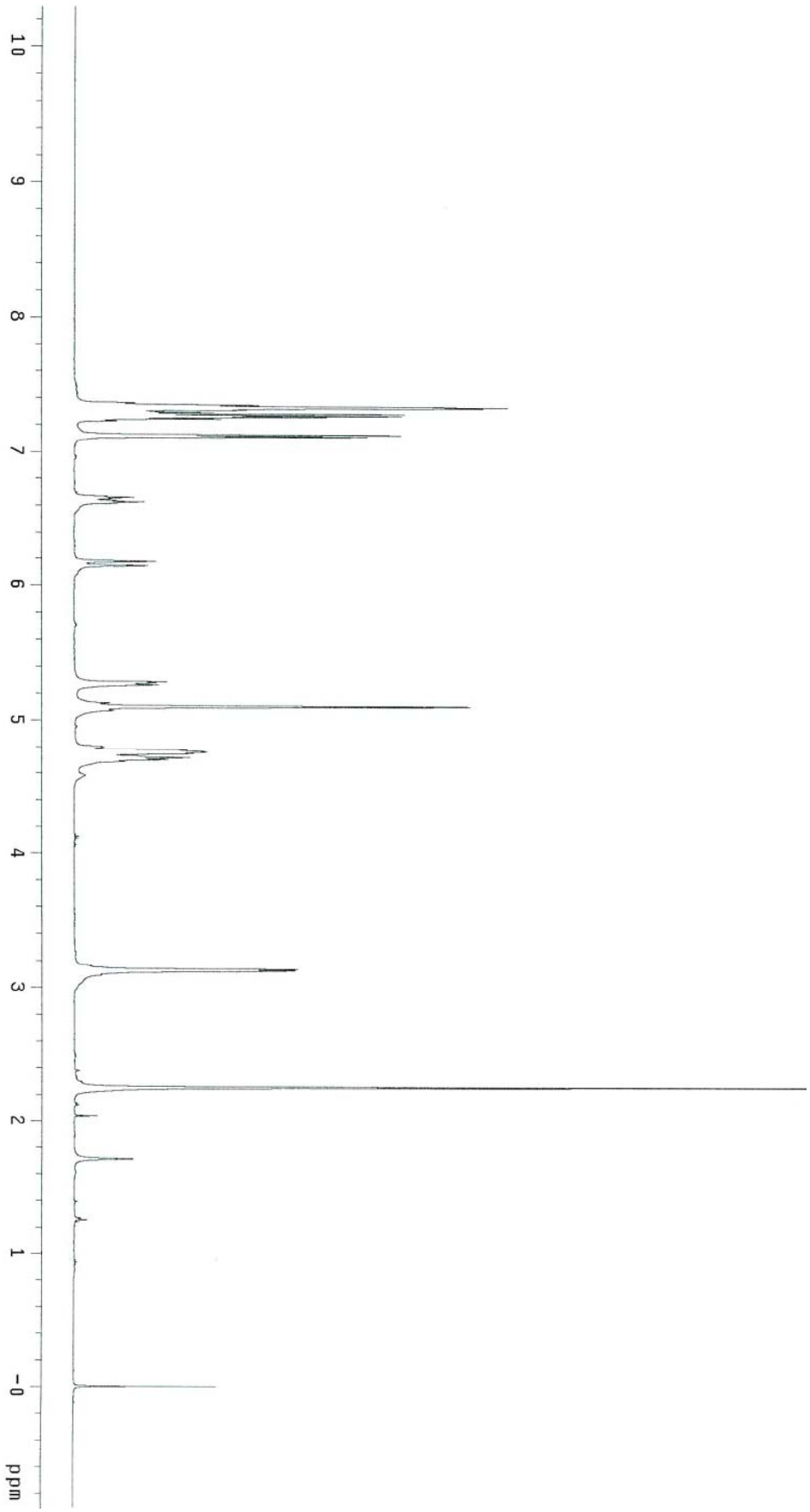
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-0
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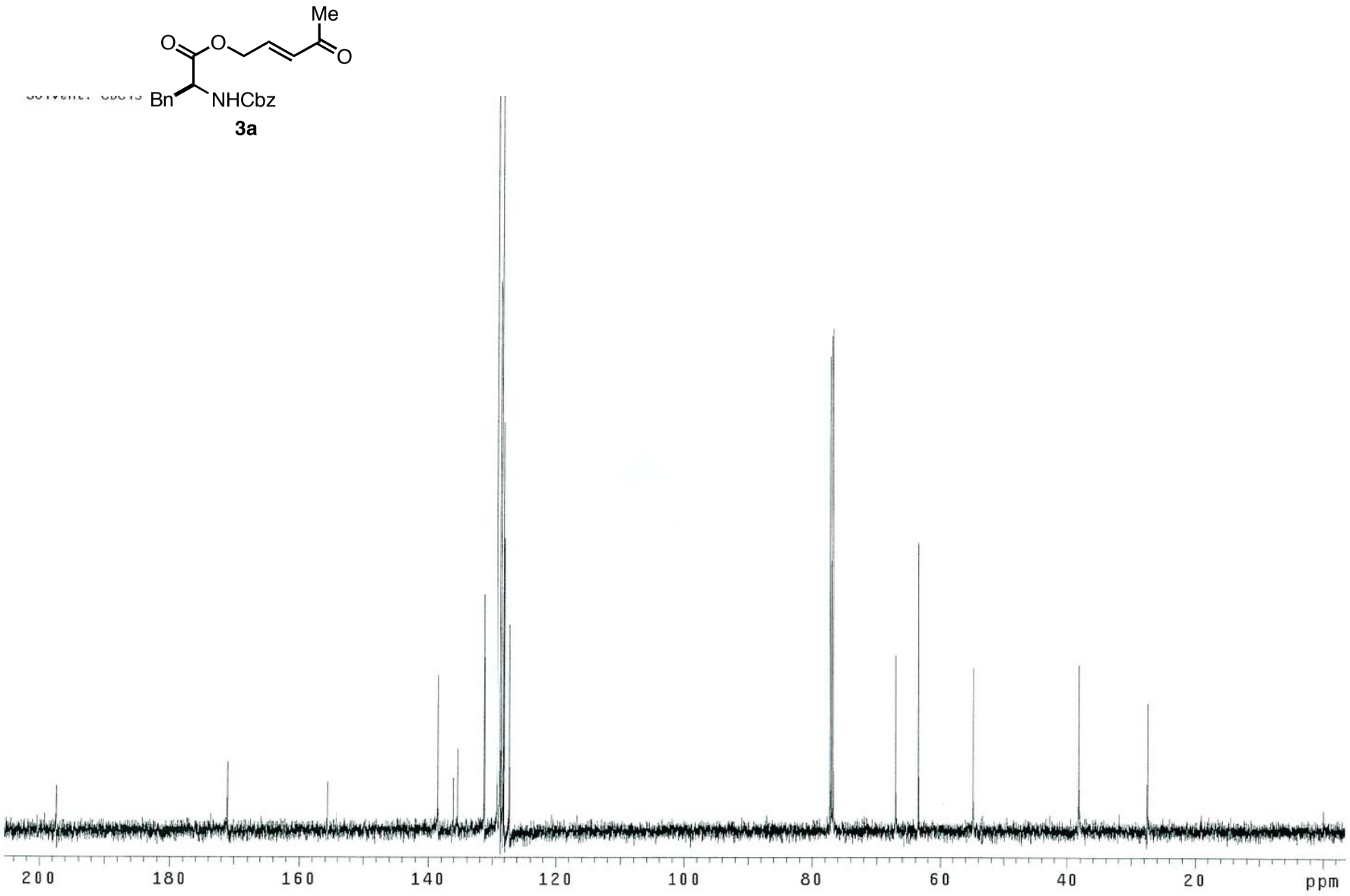
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Bn
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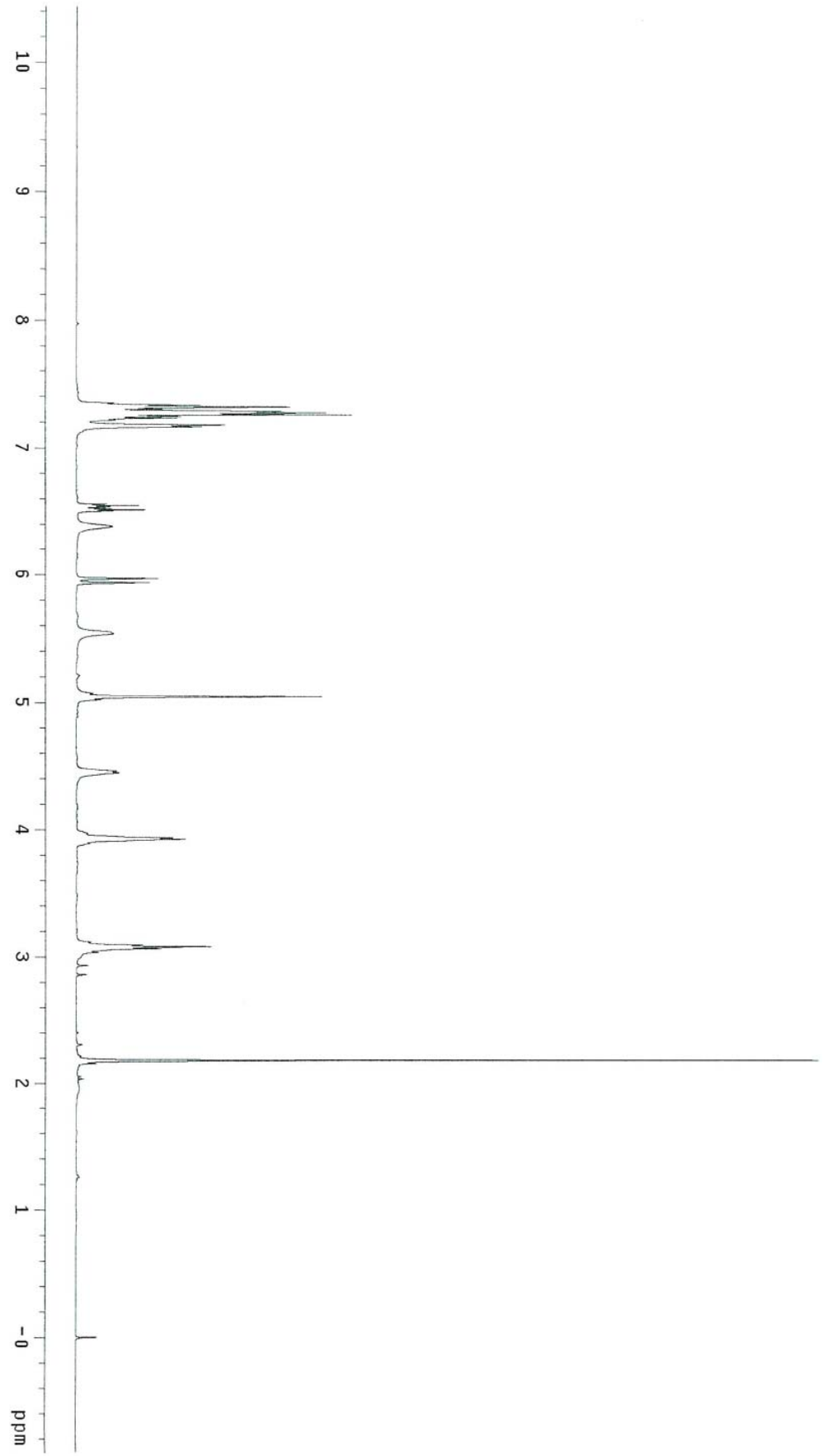
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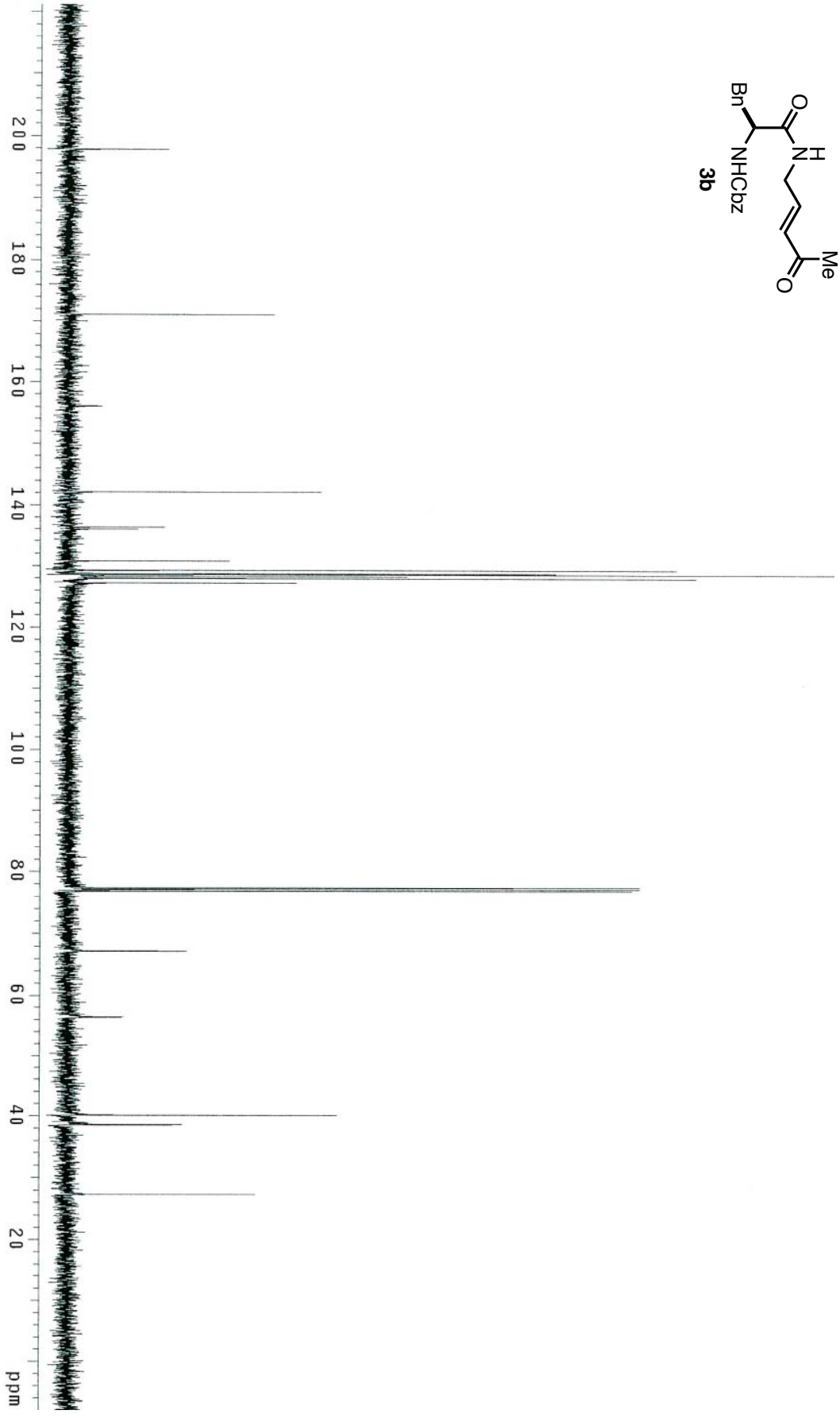
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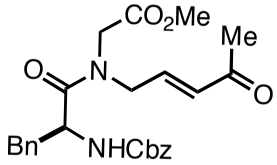
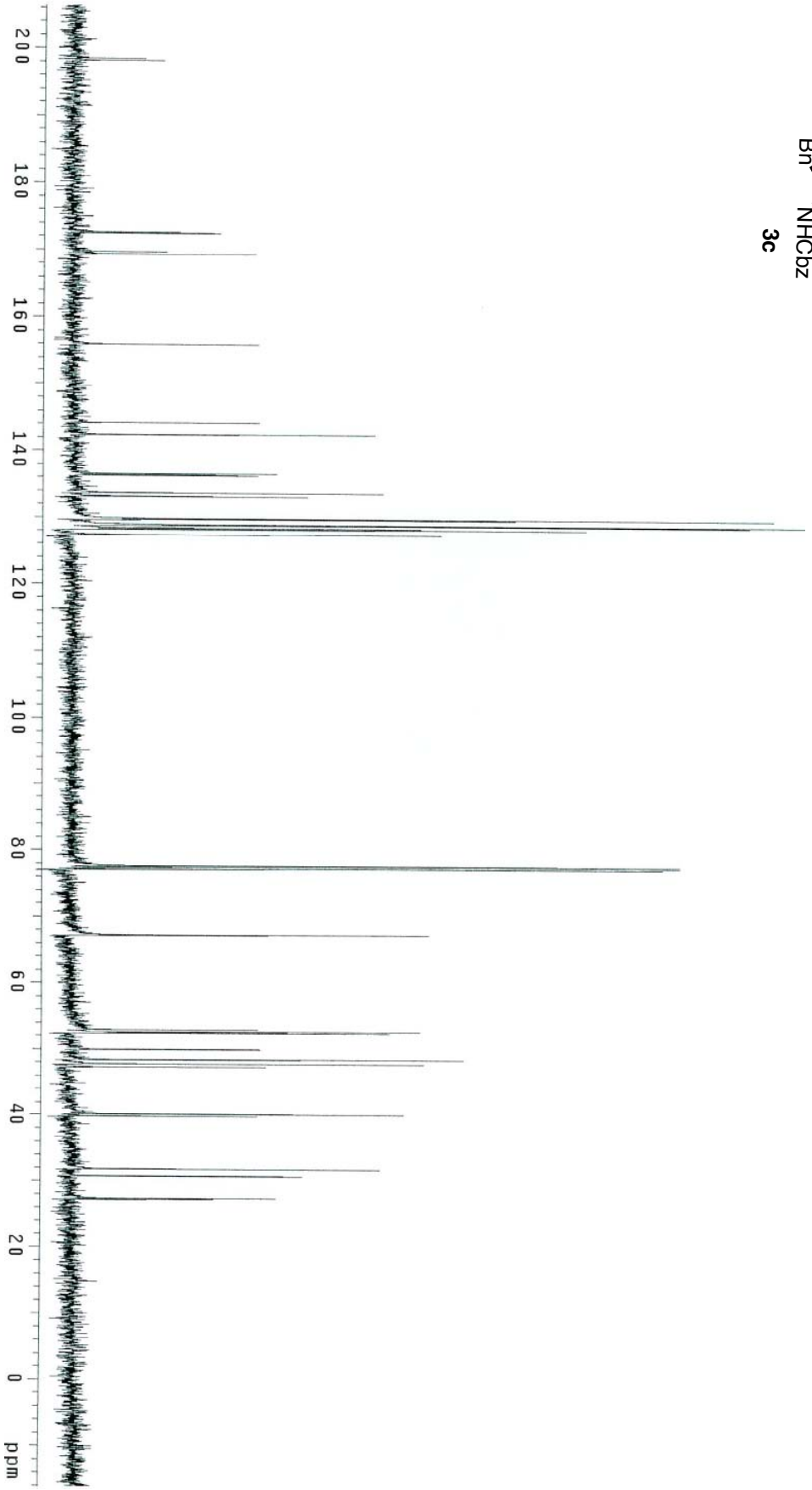
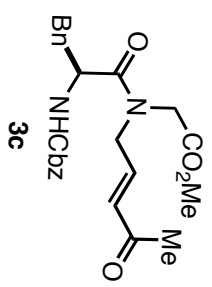


3c





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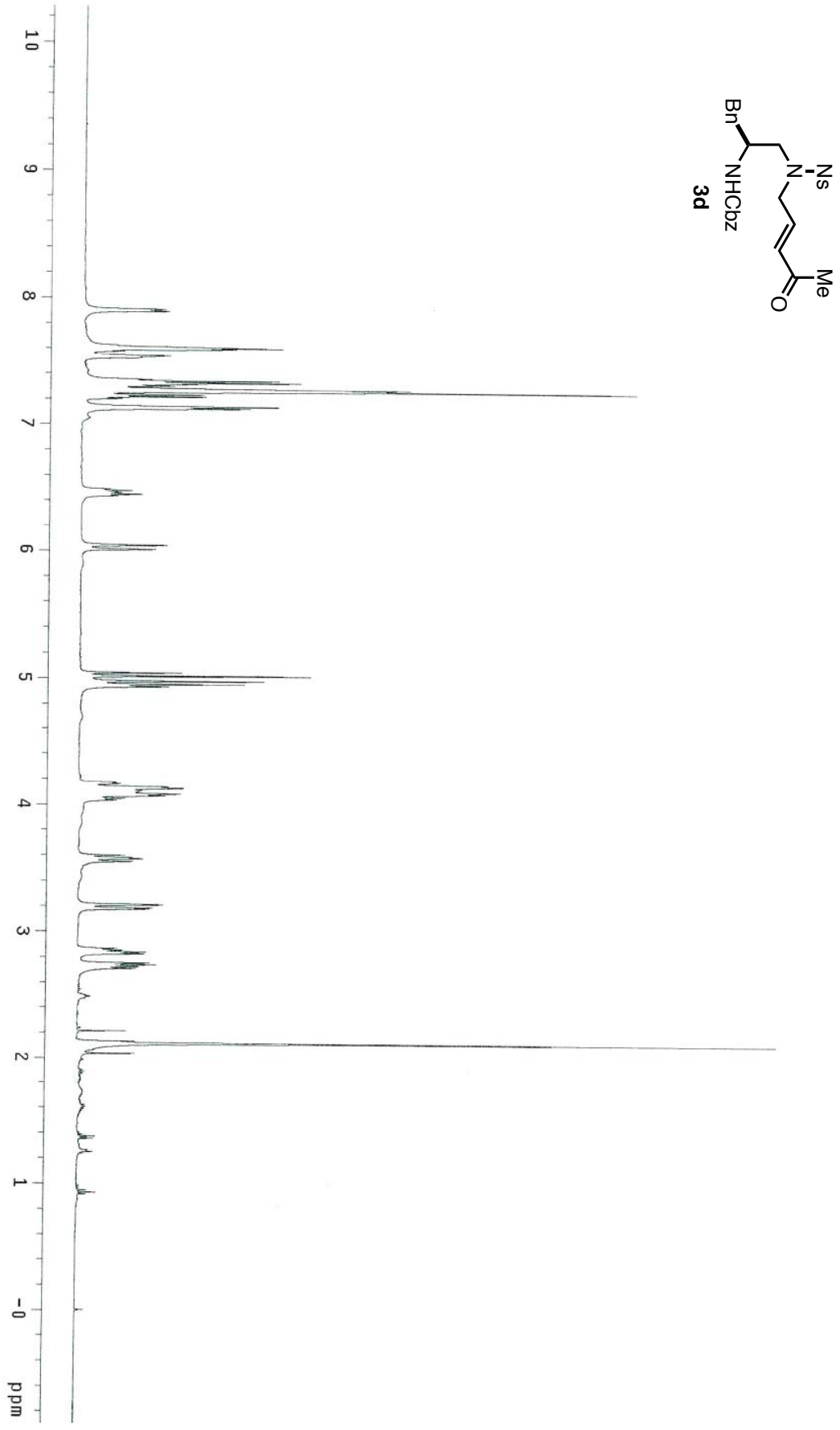
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Ns
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9
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5
4
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2
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-0
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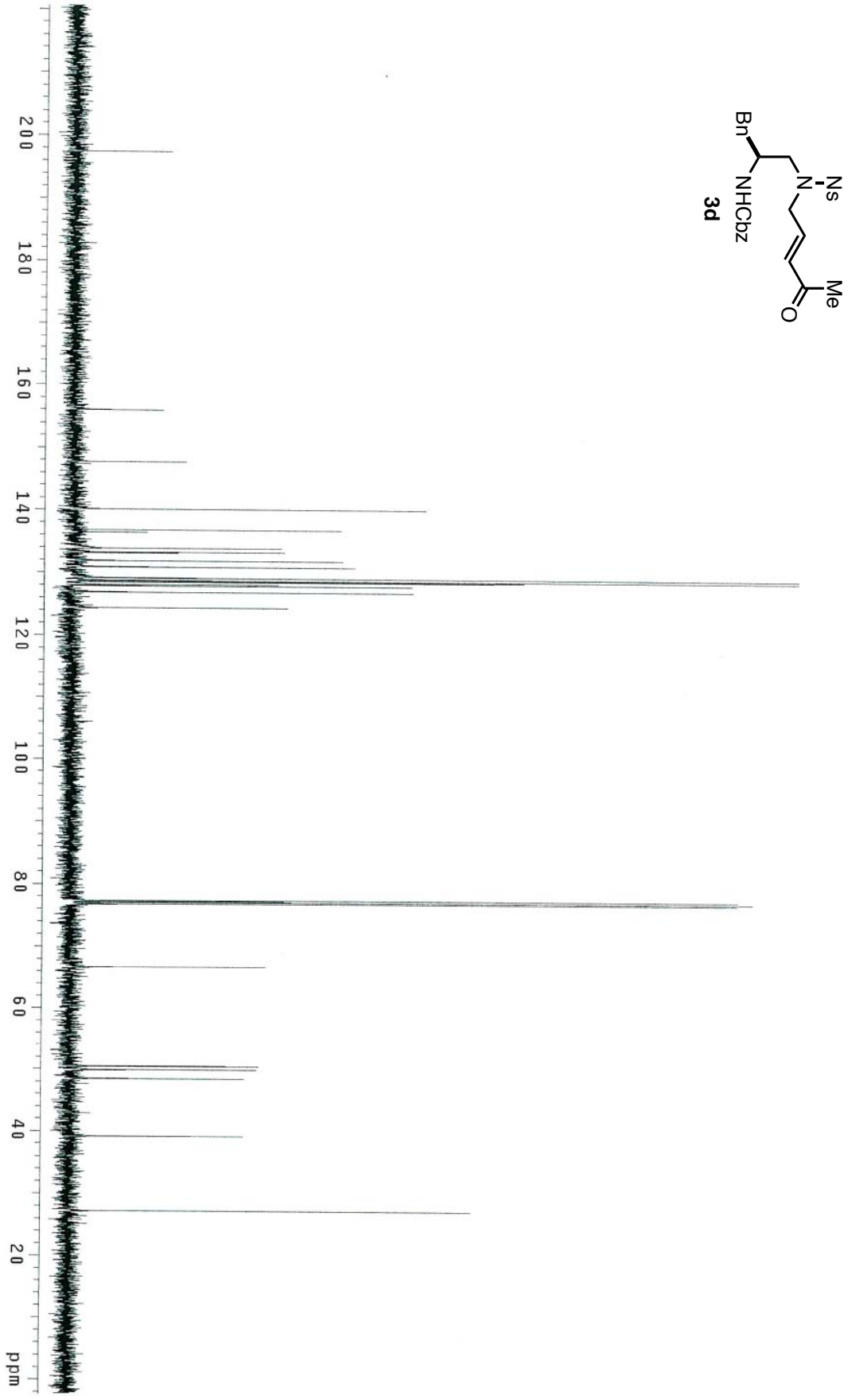
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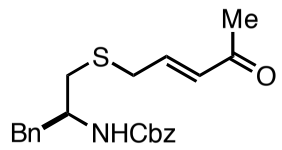

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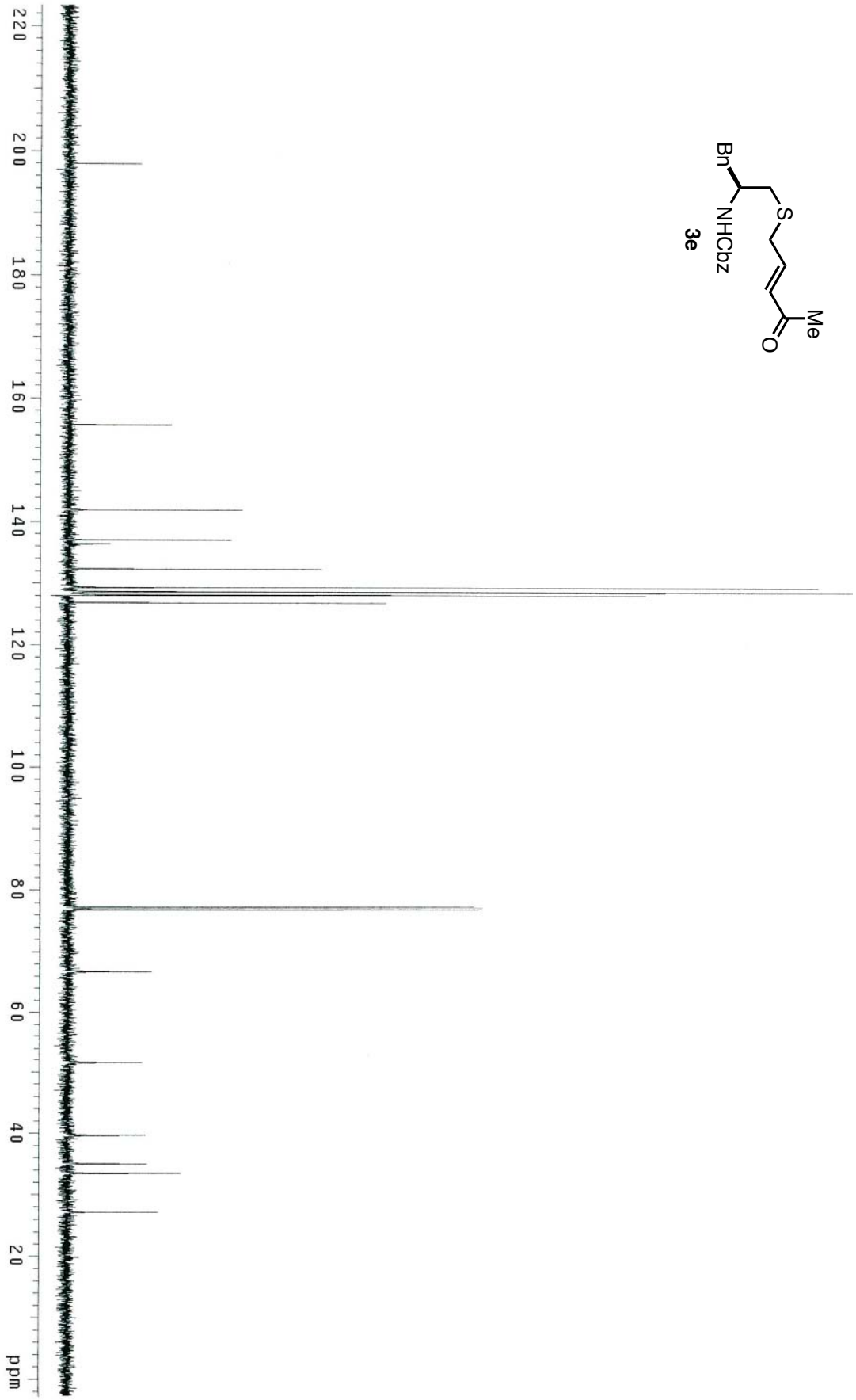
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60
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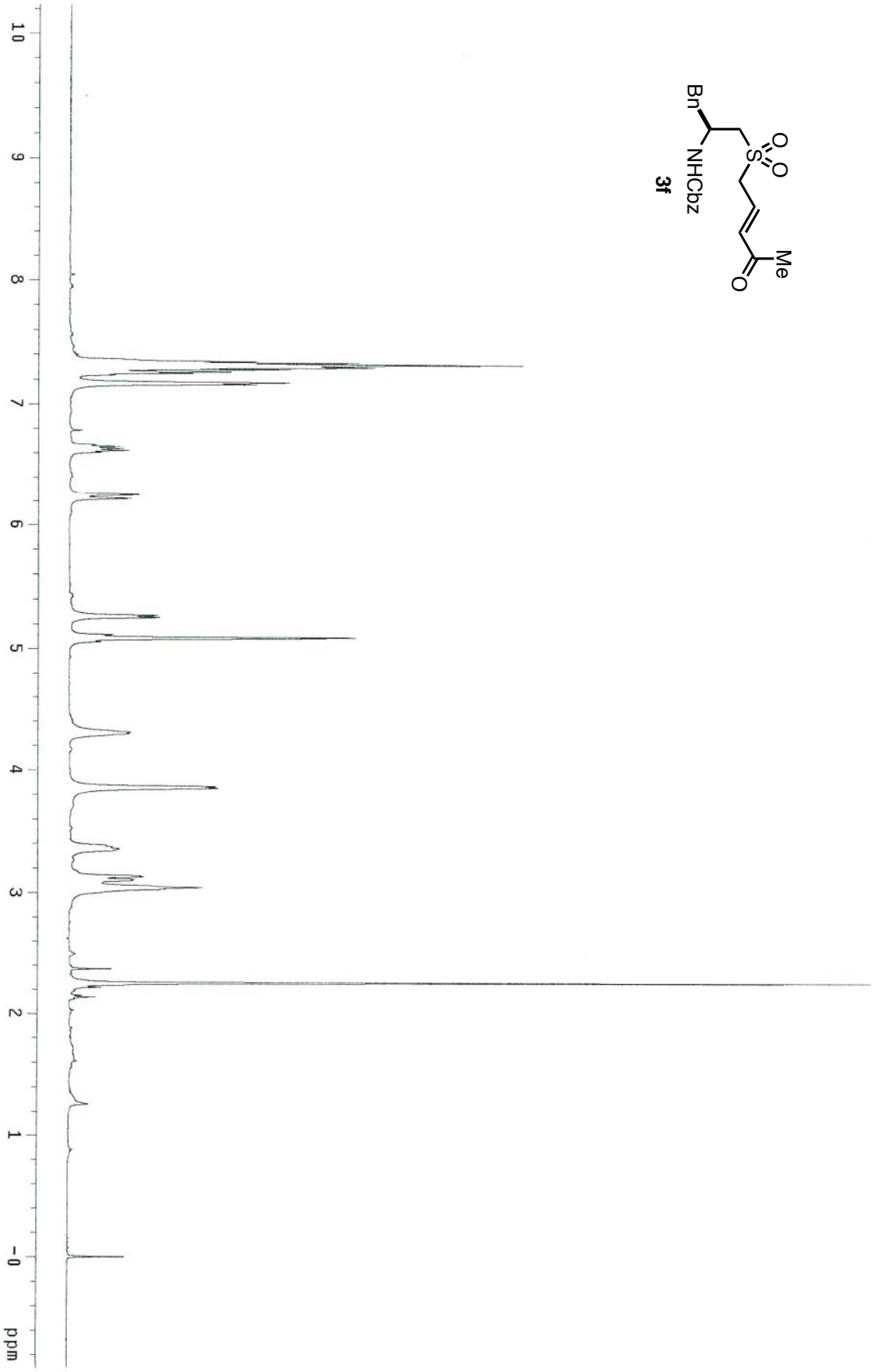
ppm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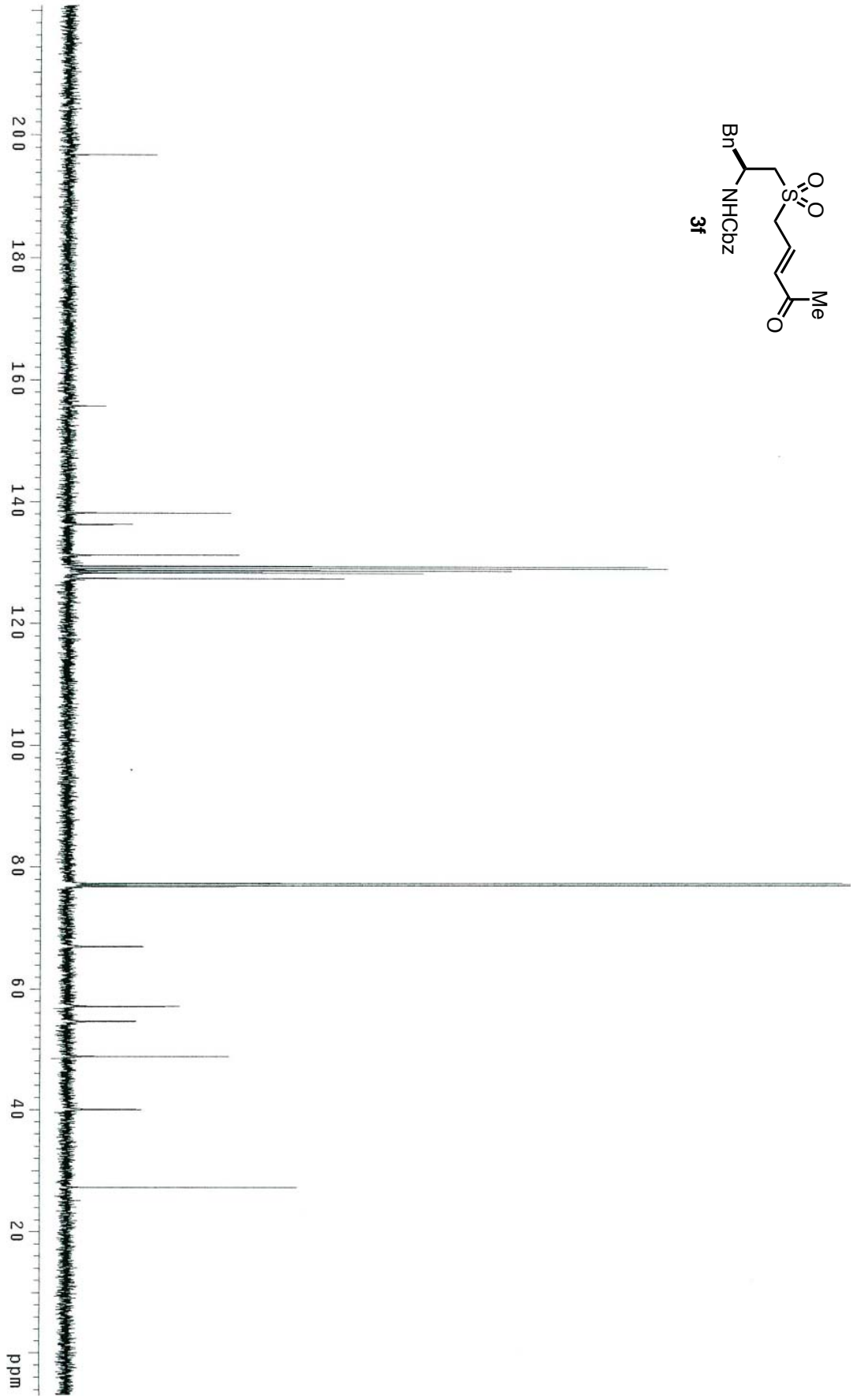
ppm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O
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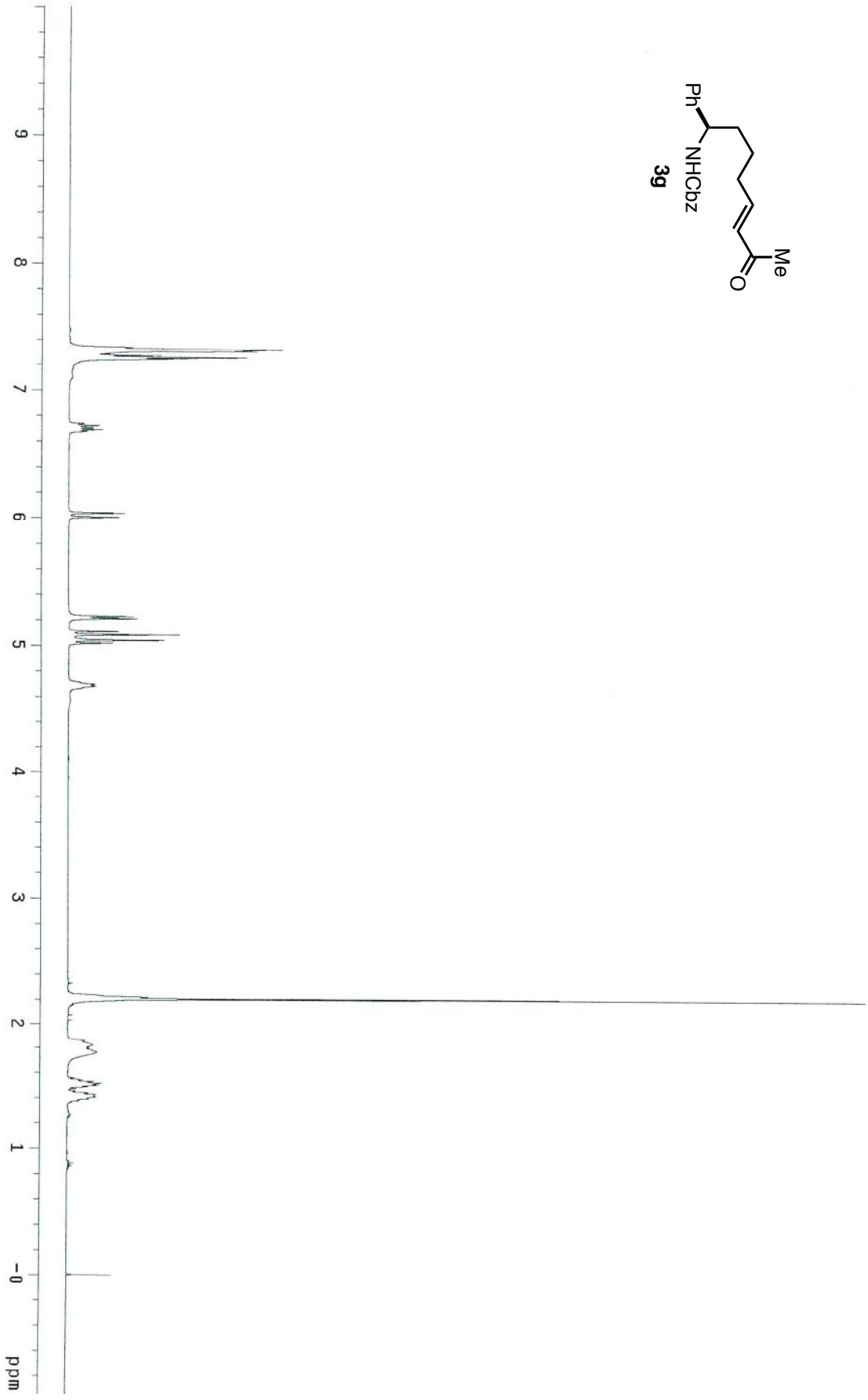
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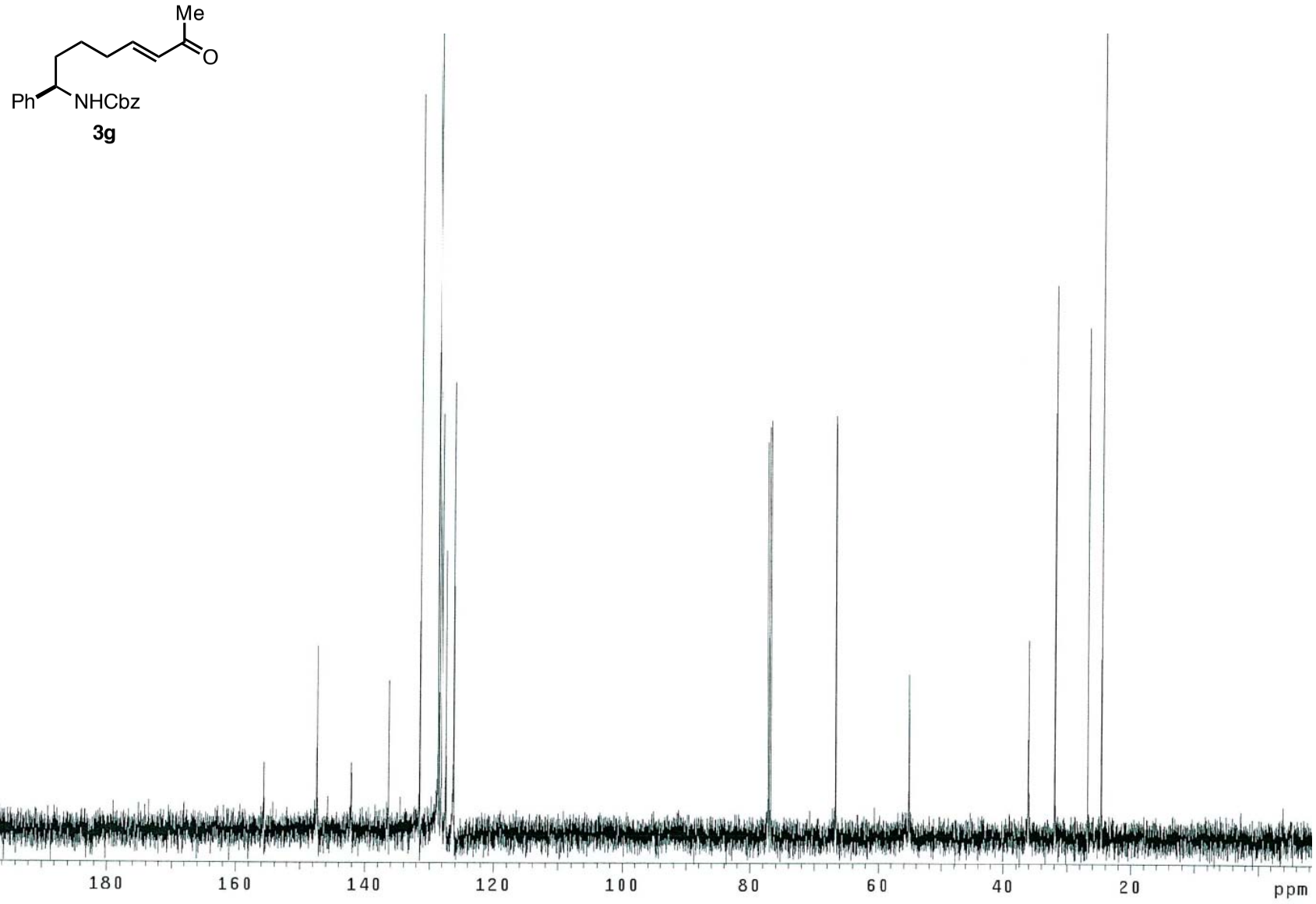
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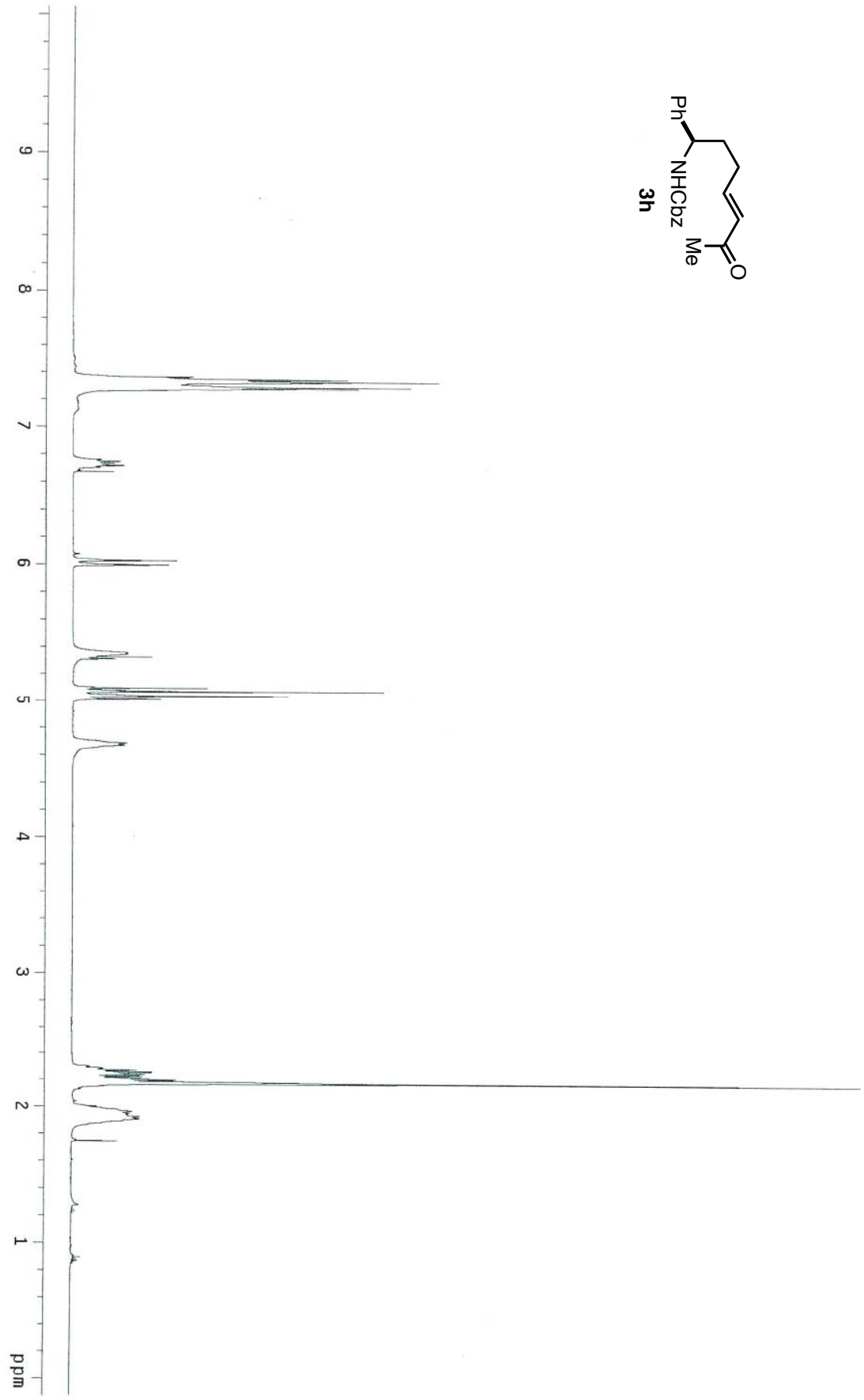
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2
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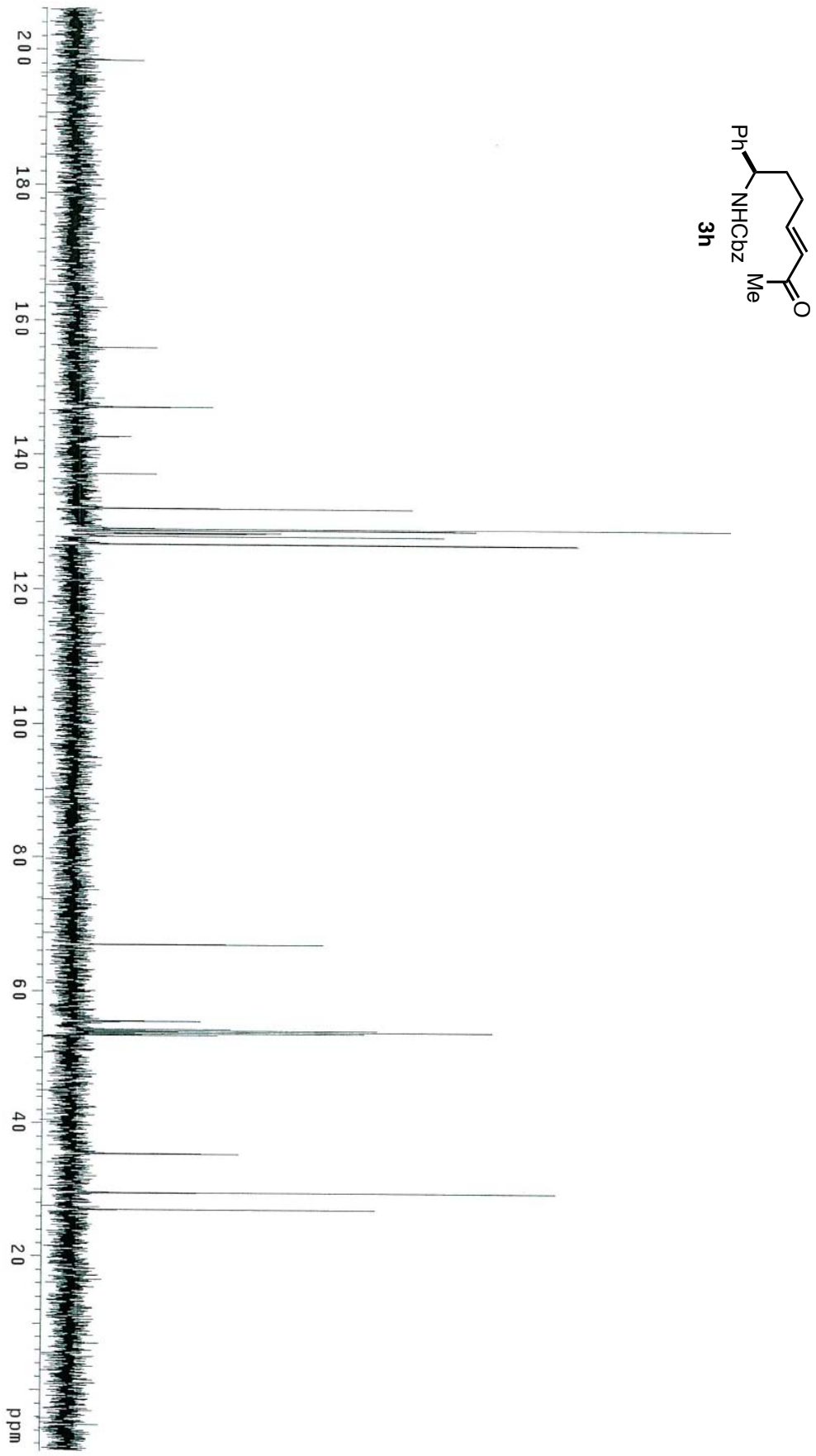
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Me
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3h
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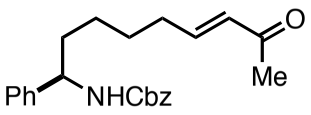

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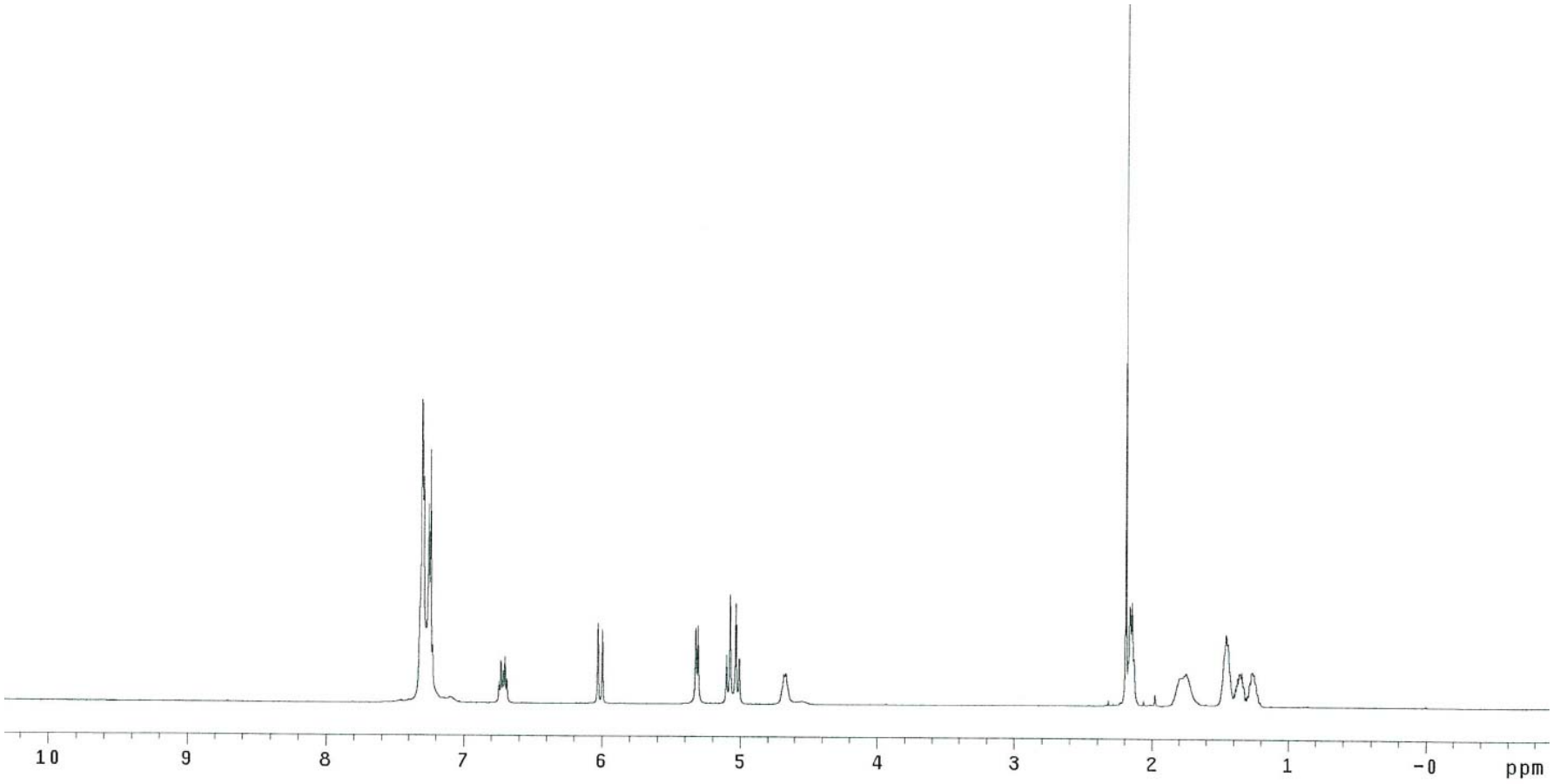

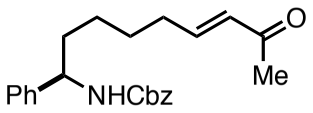

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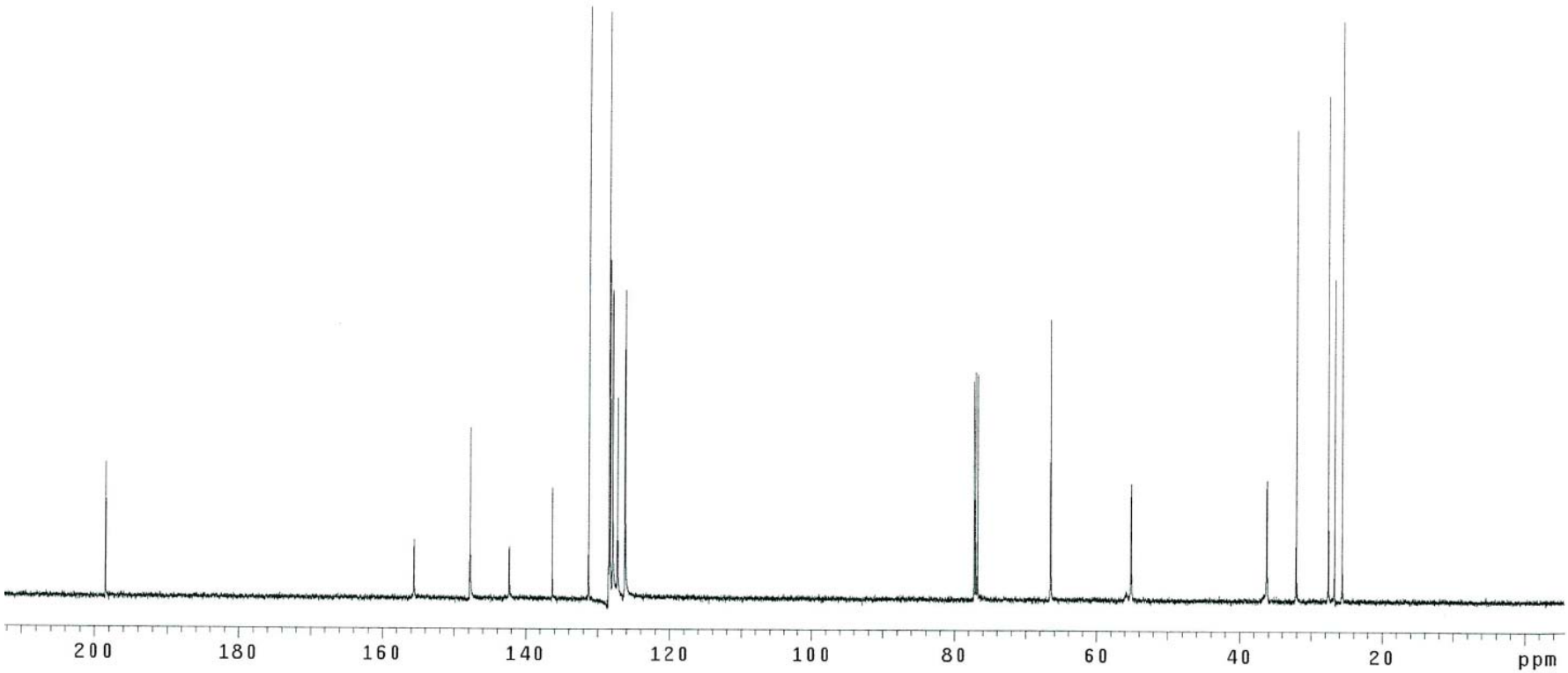

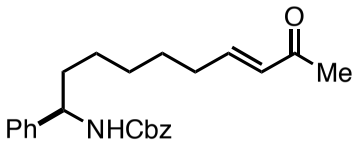

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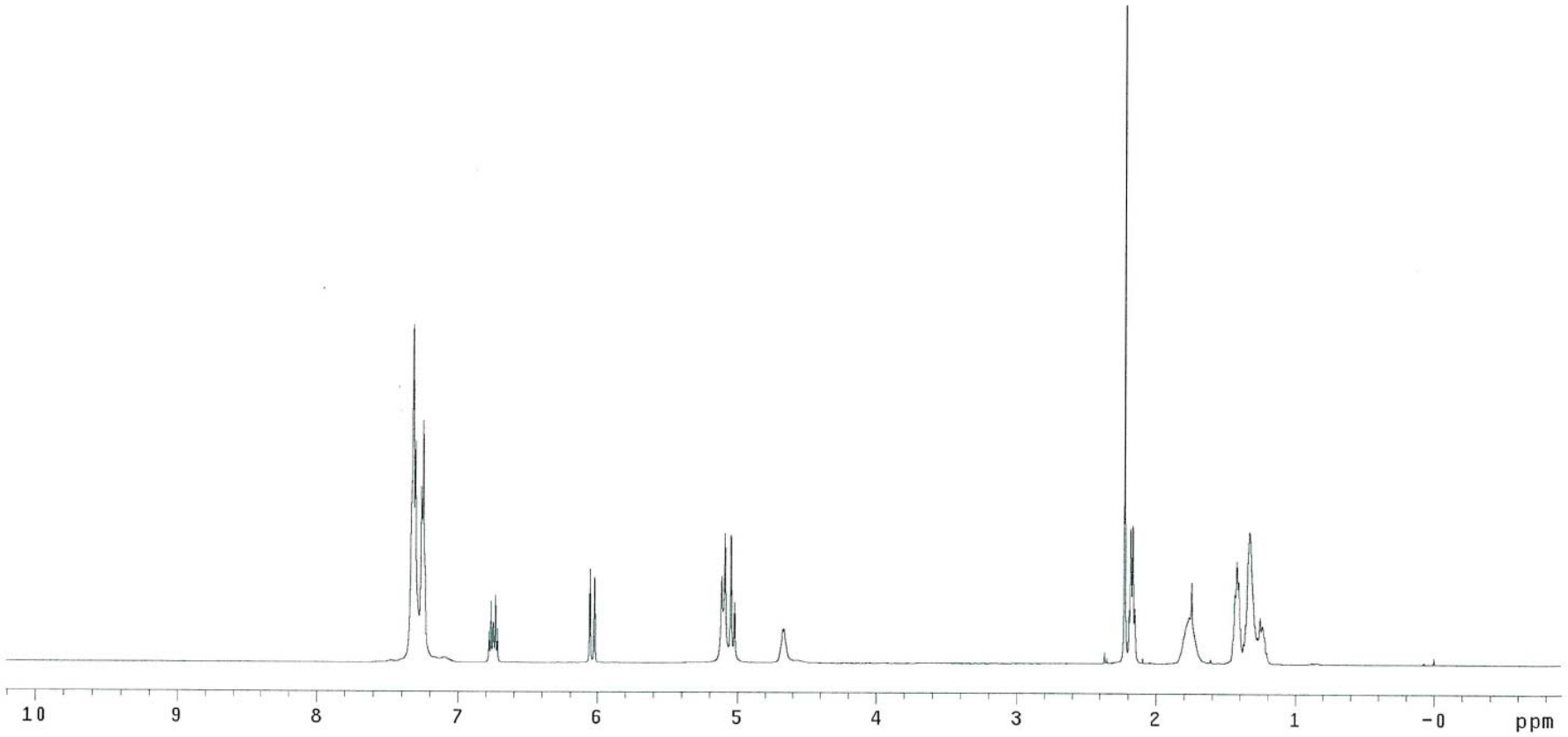

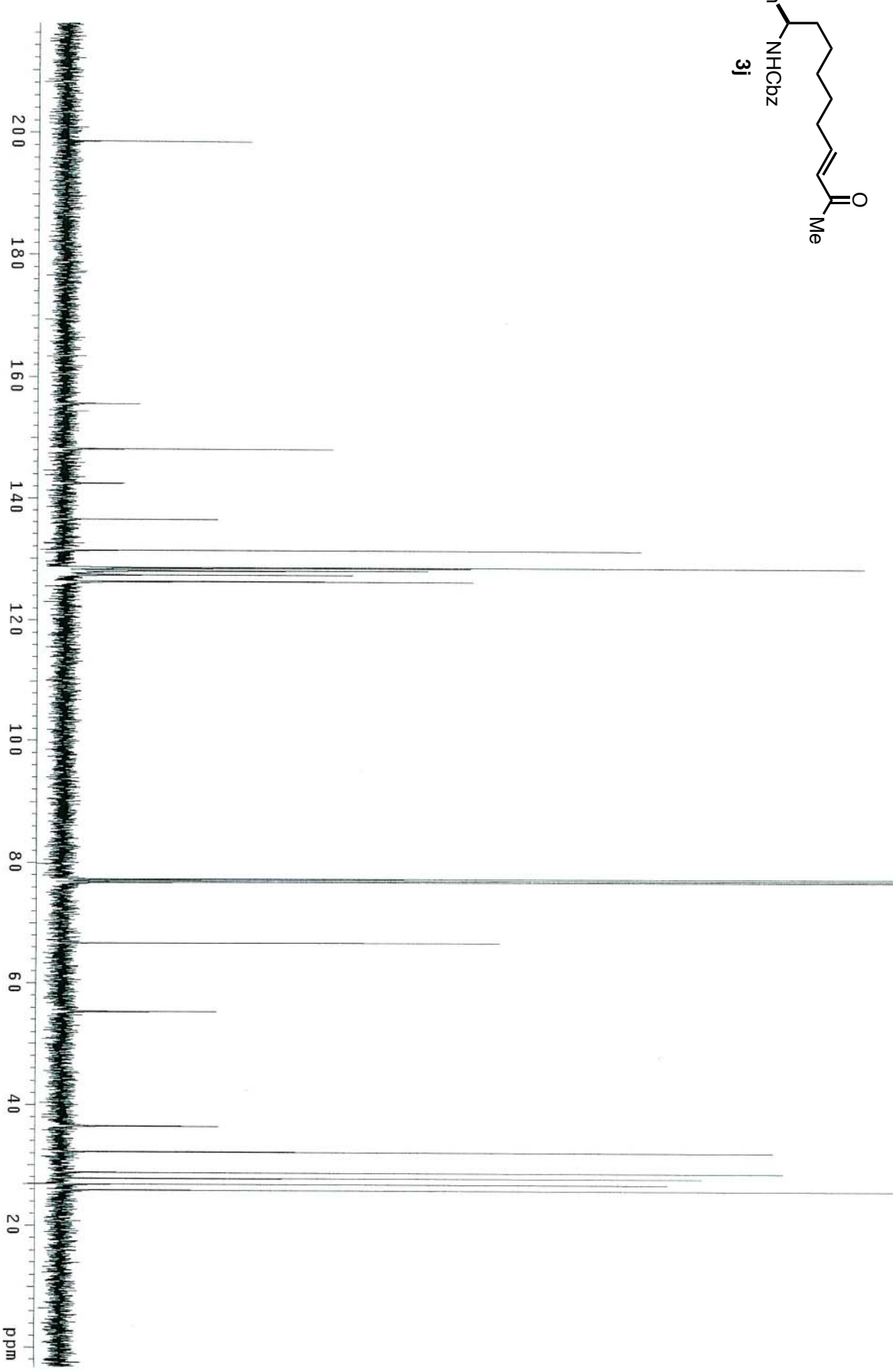
Ph
NHCbz
3j
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Me
200
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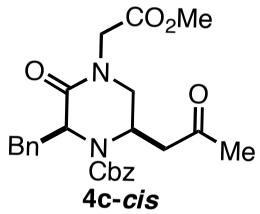
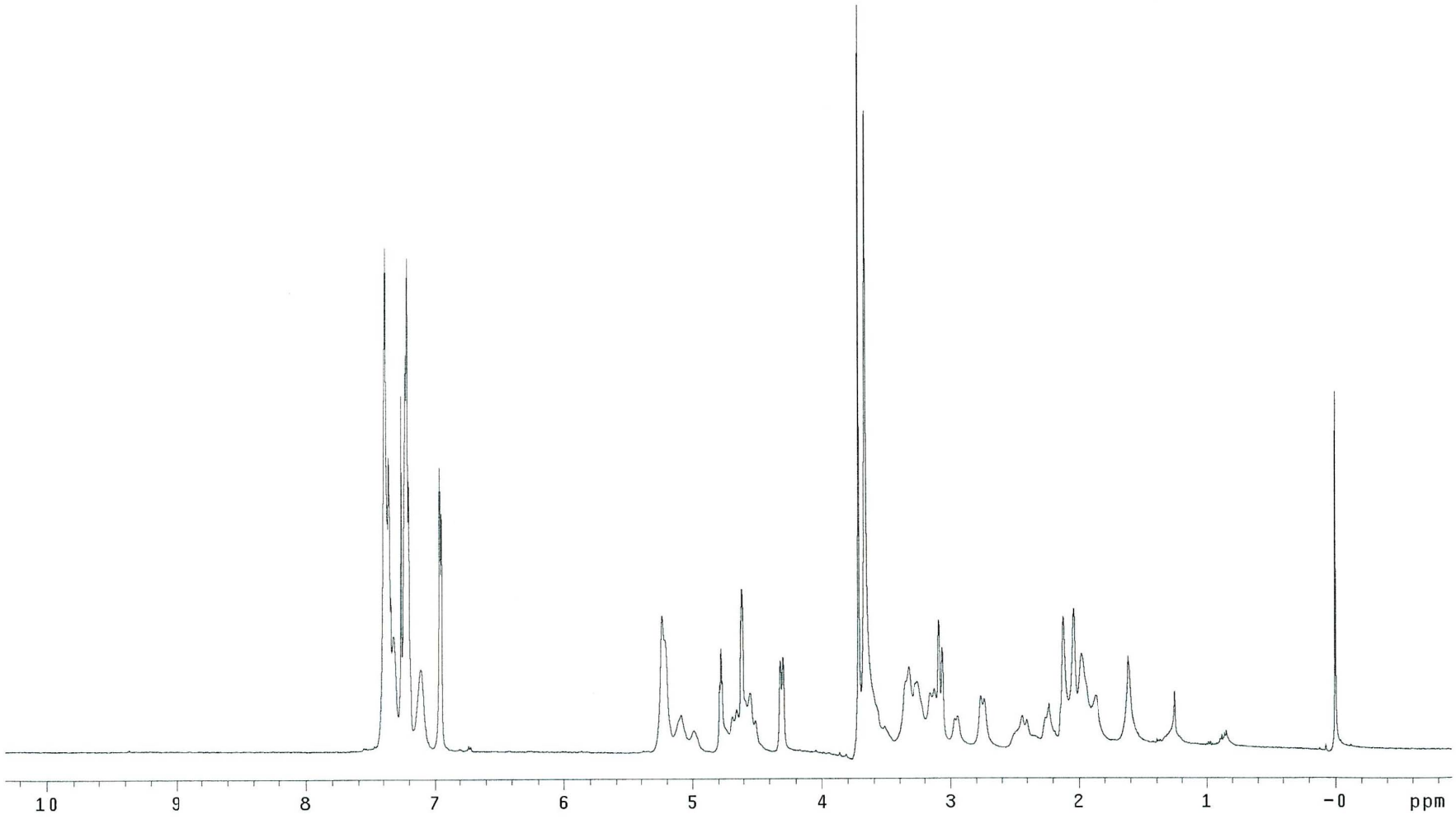
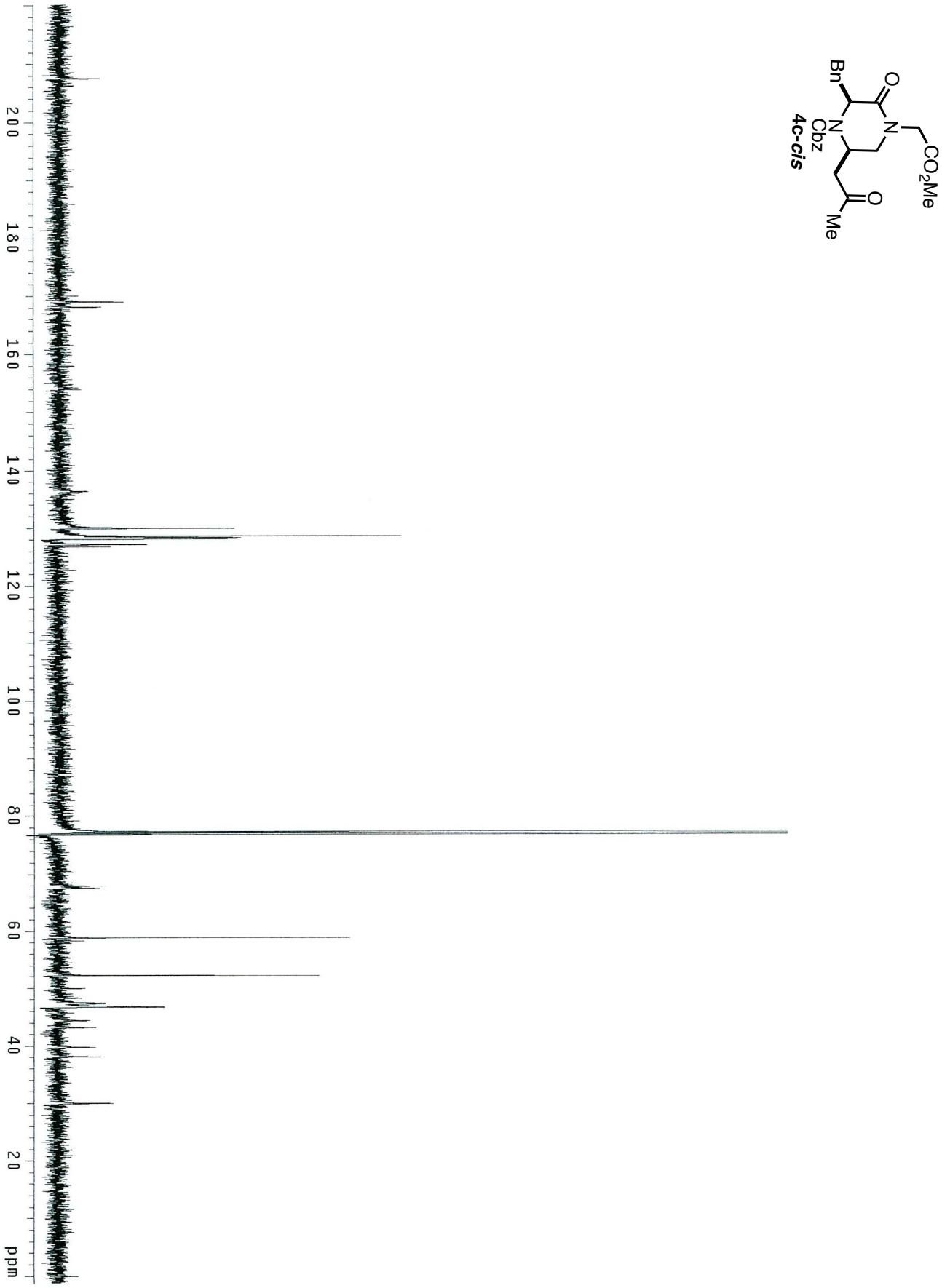
140
120
100
80
60
40
20
ppm



4c-*cis*




Bn
N
Cbz
4c-cis
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N
CO2Me
O
Me
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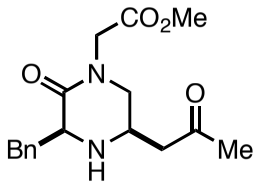
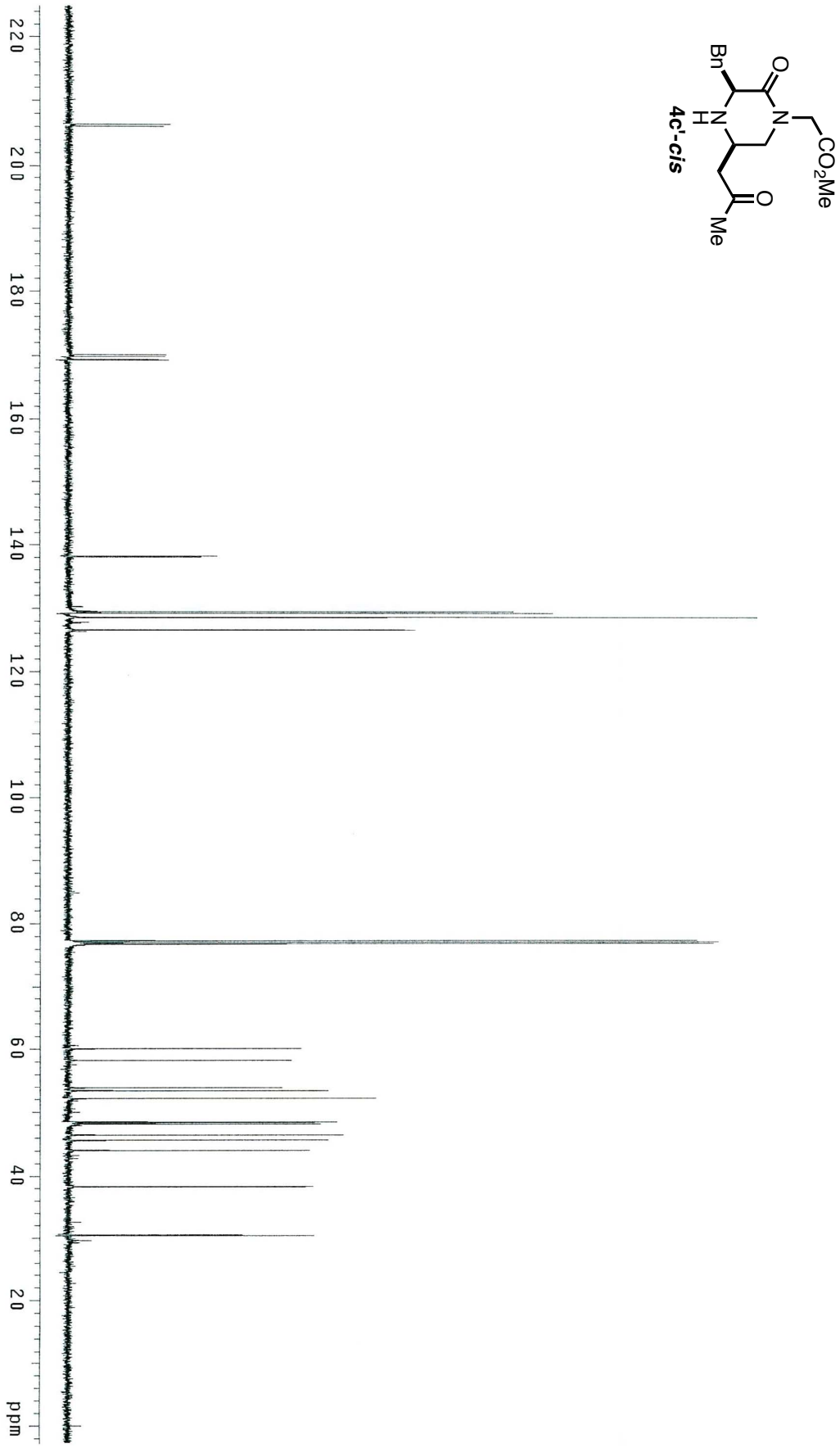
160
140
120
100
80
60
40
20
ppm

Solvent: CDCl3



4c'-*cis*


Bn
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CO2Me
O
Me
4c'-cis
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200
180
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140
120
100
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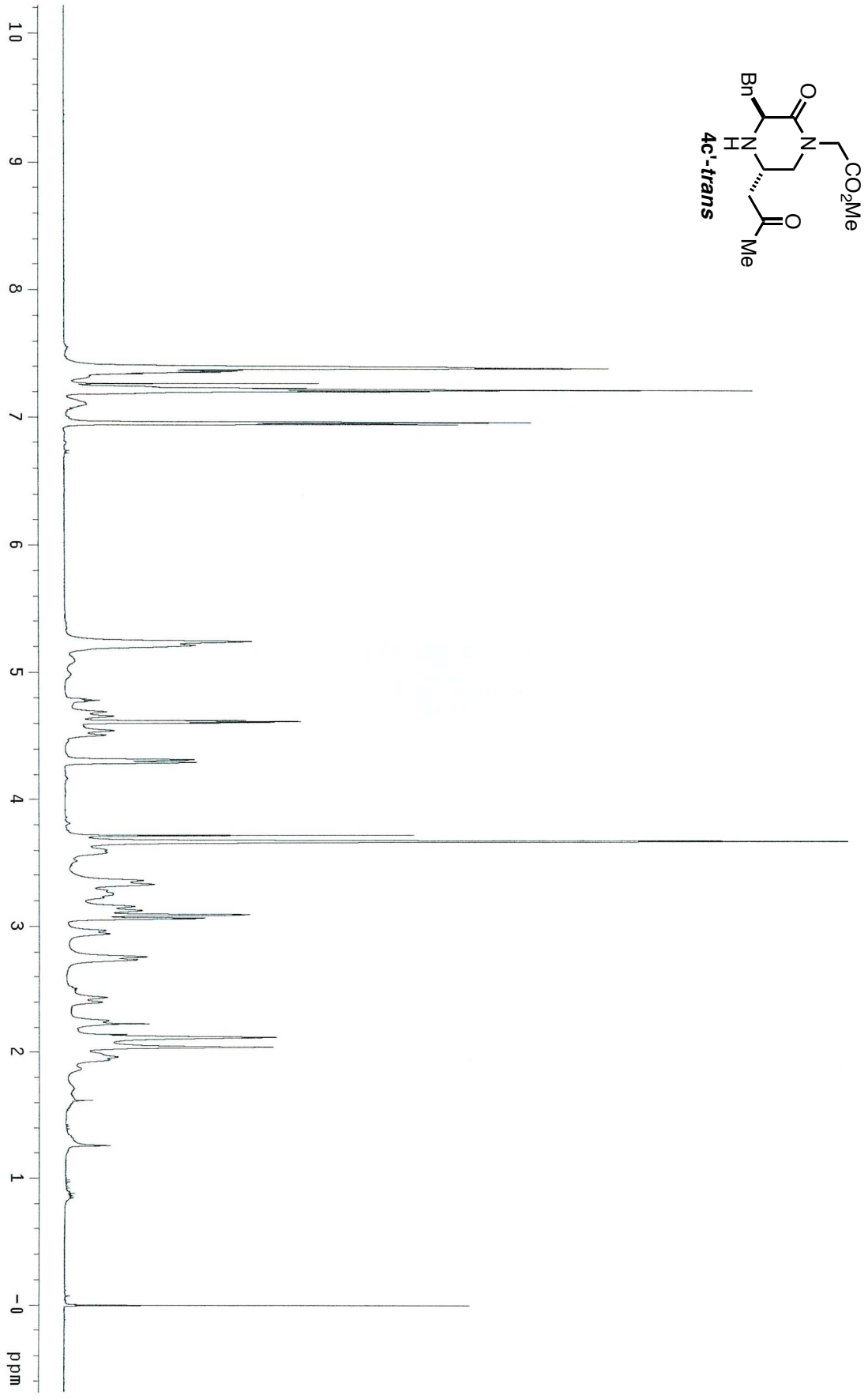
60
40
20
ppm


Bn
O
N
CO2Me
H
N
O
Me
4c'-trans
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8
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6
5
4
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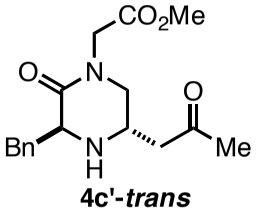
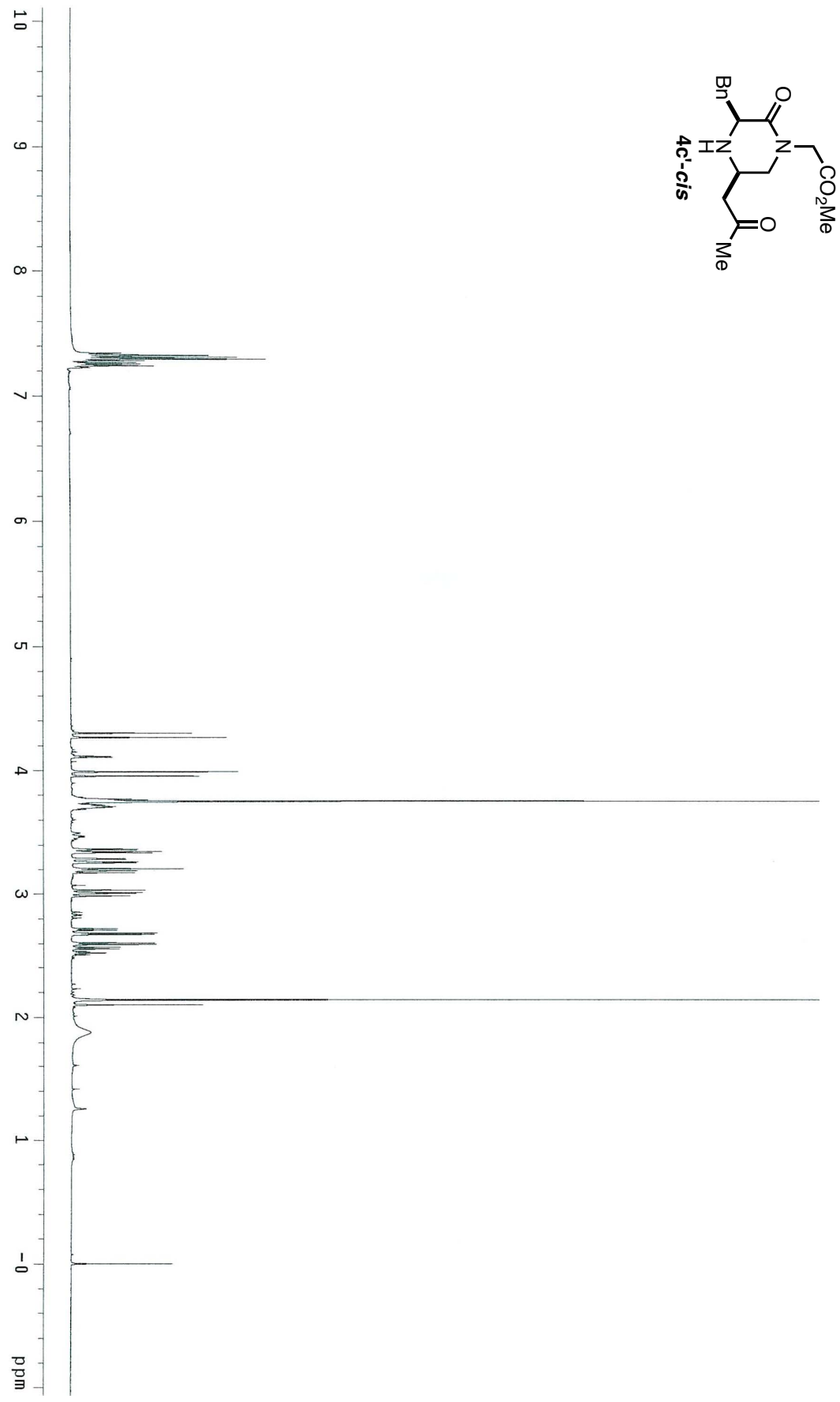
2
1
-0
ppm



4c'-*trans*


Bn
O
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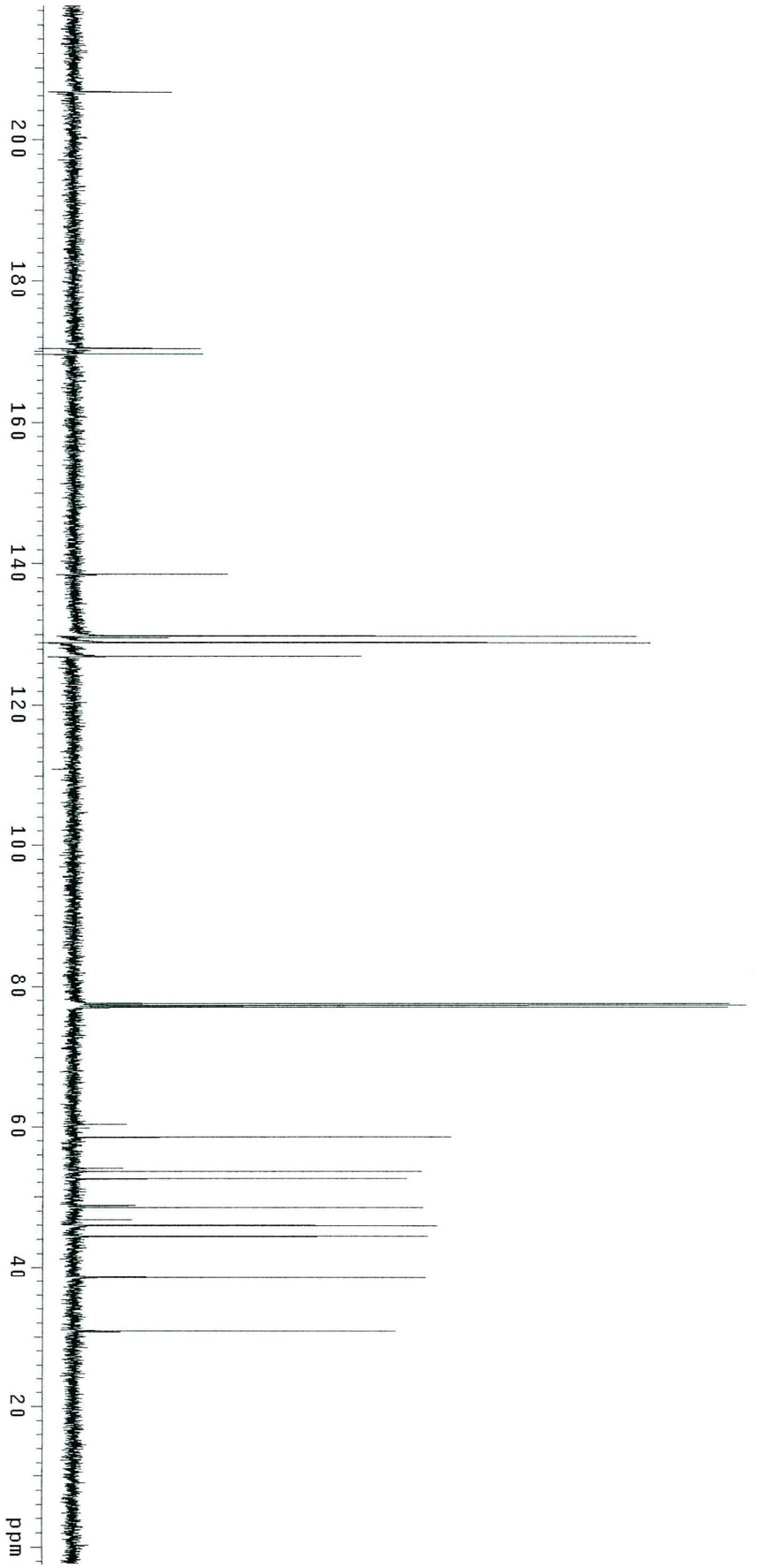
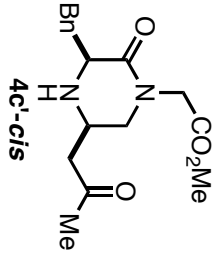
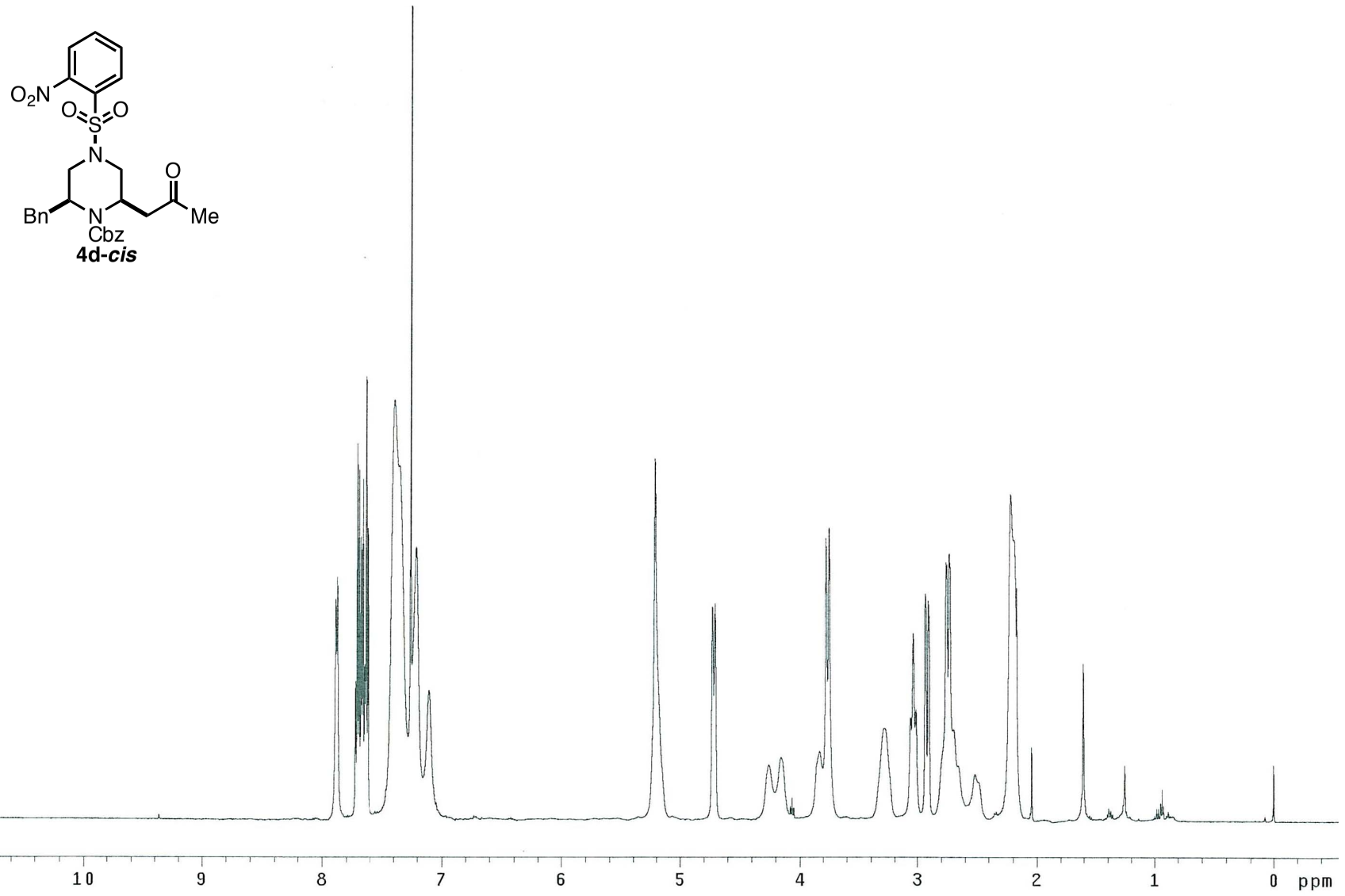
CO2Me
N
H
4c'-cis
O
Me
10
9
8
7
6
5
4
3
2
1
0
ppm





4c'-*cis*


O2N
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S
O
N
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Bn
N
Cbz
Me
4d-cis
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5
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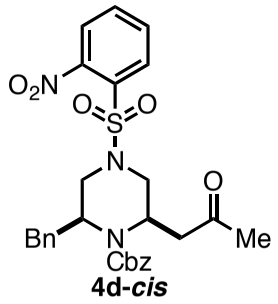
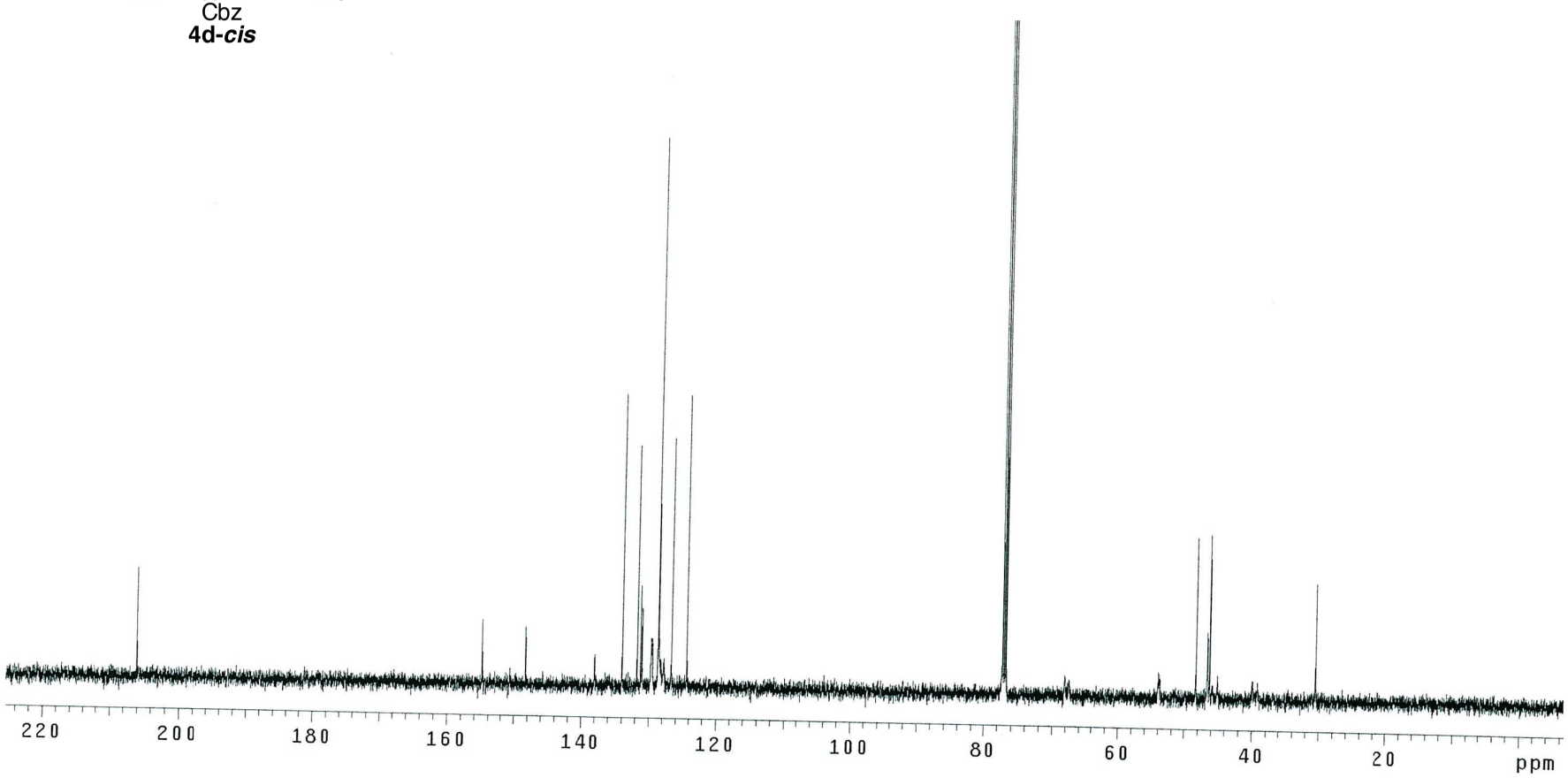
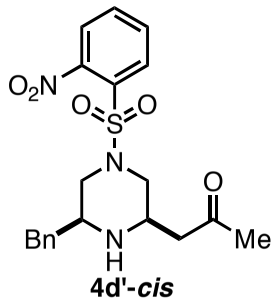
2
1
0
ppm

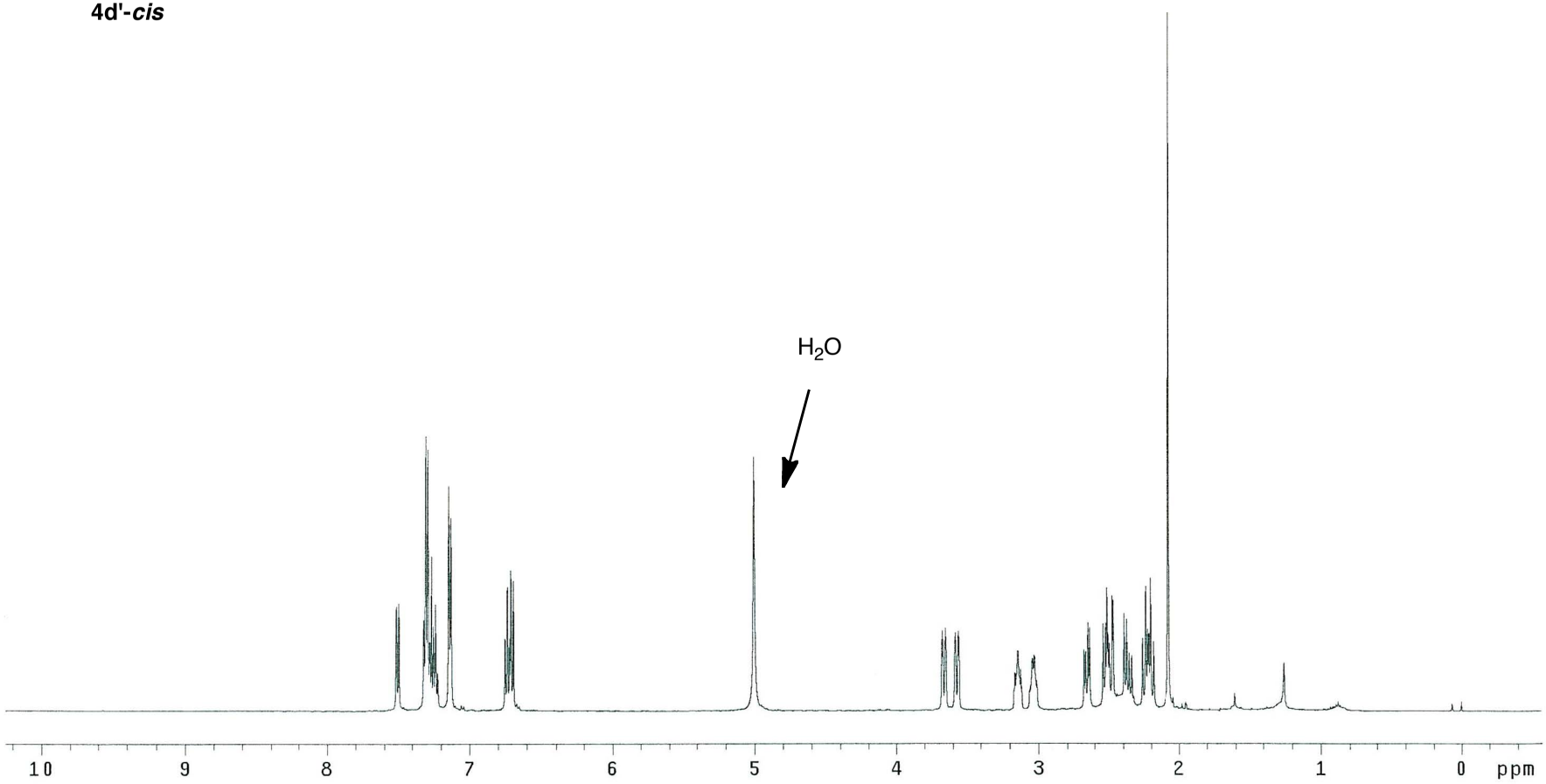


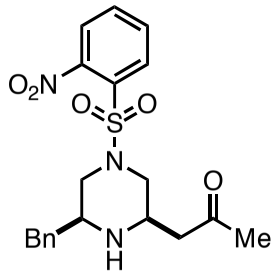
4d-*cis*





4d'-*cis*





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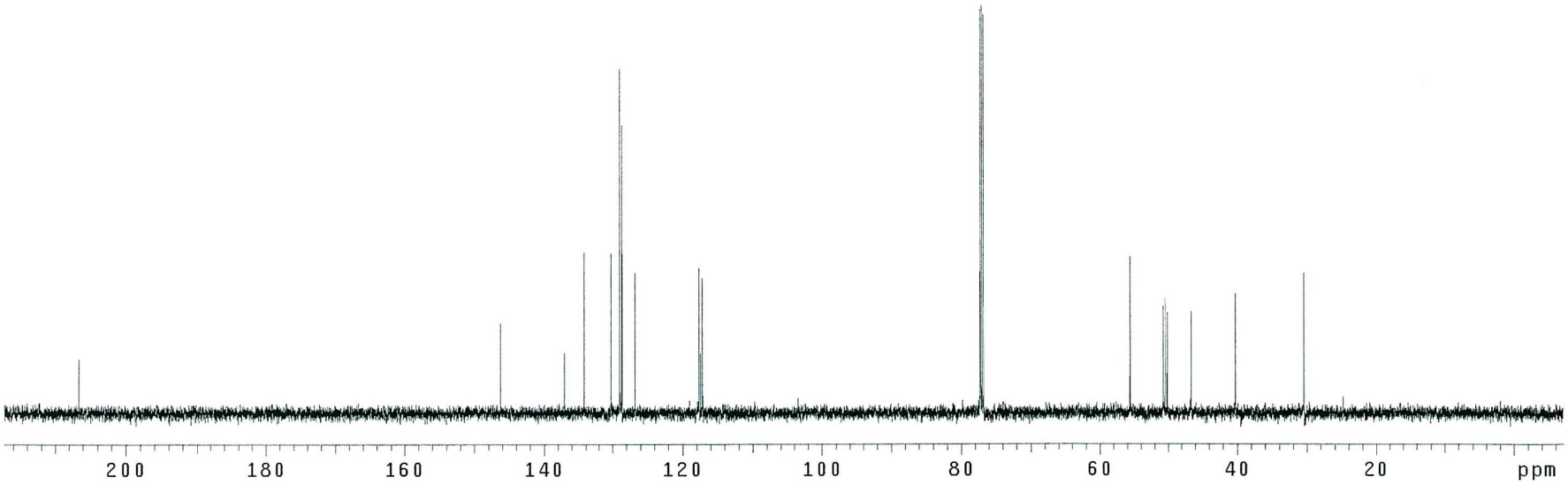

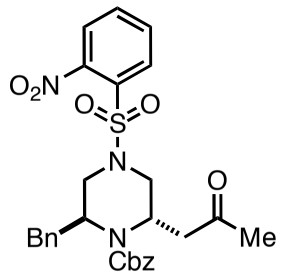

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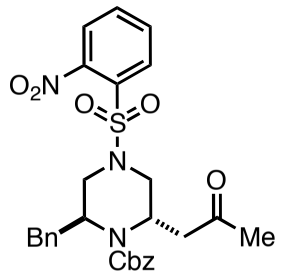

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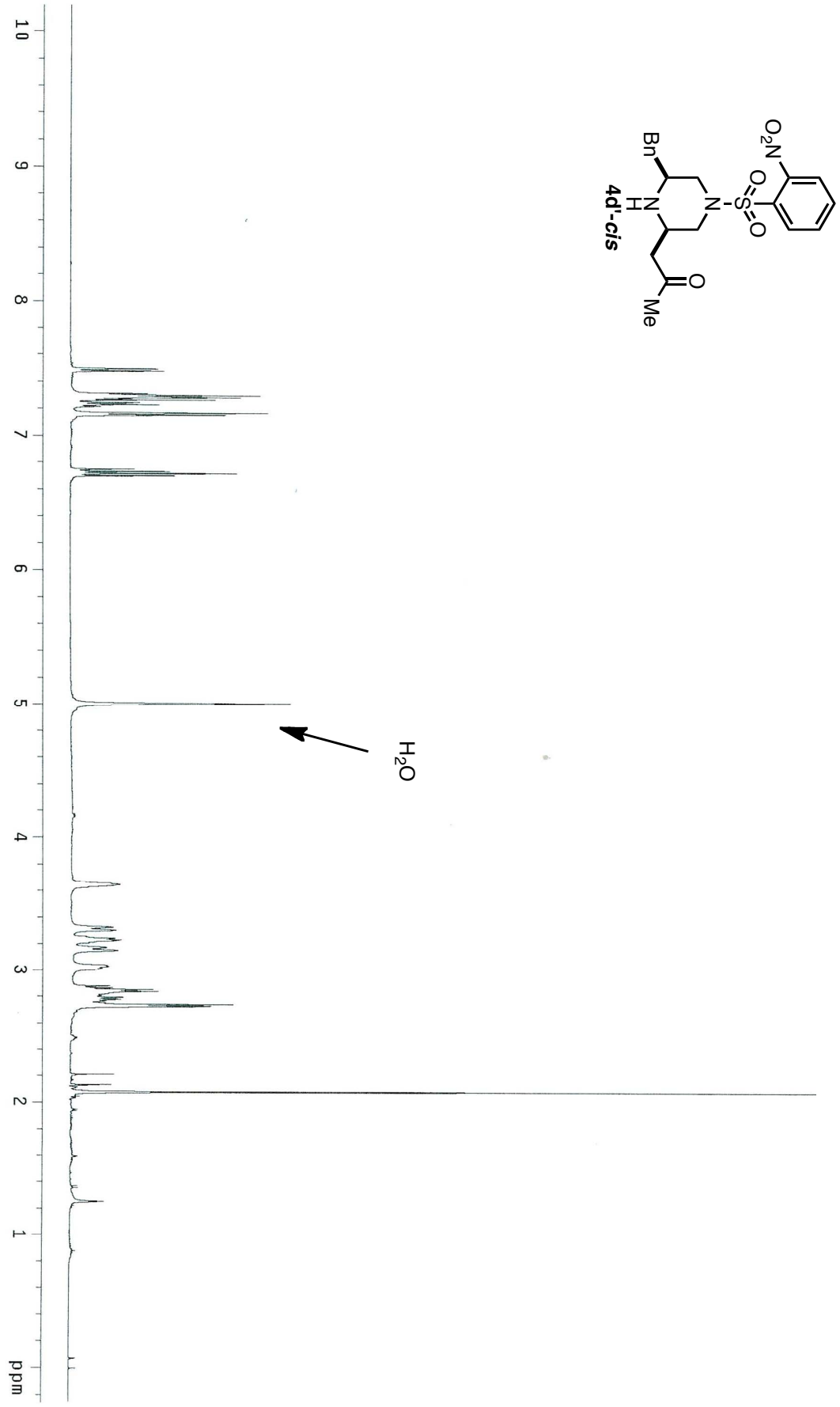
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1
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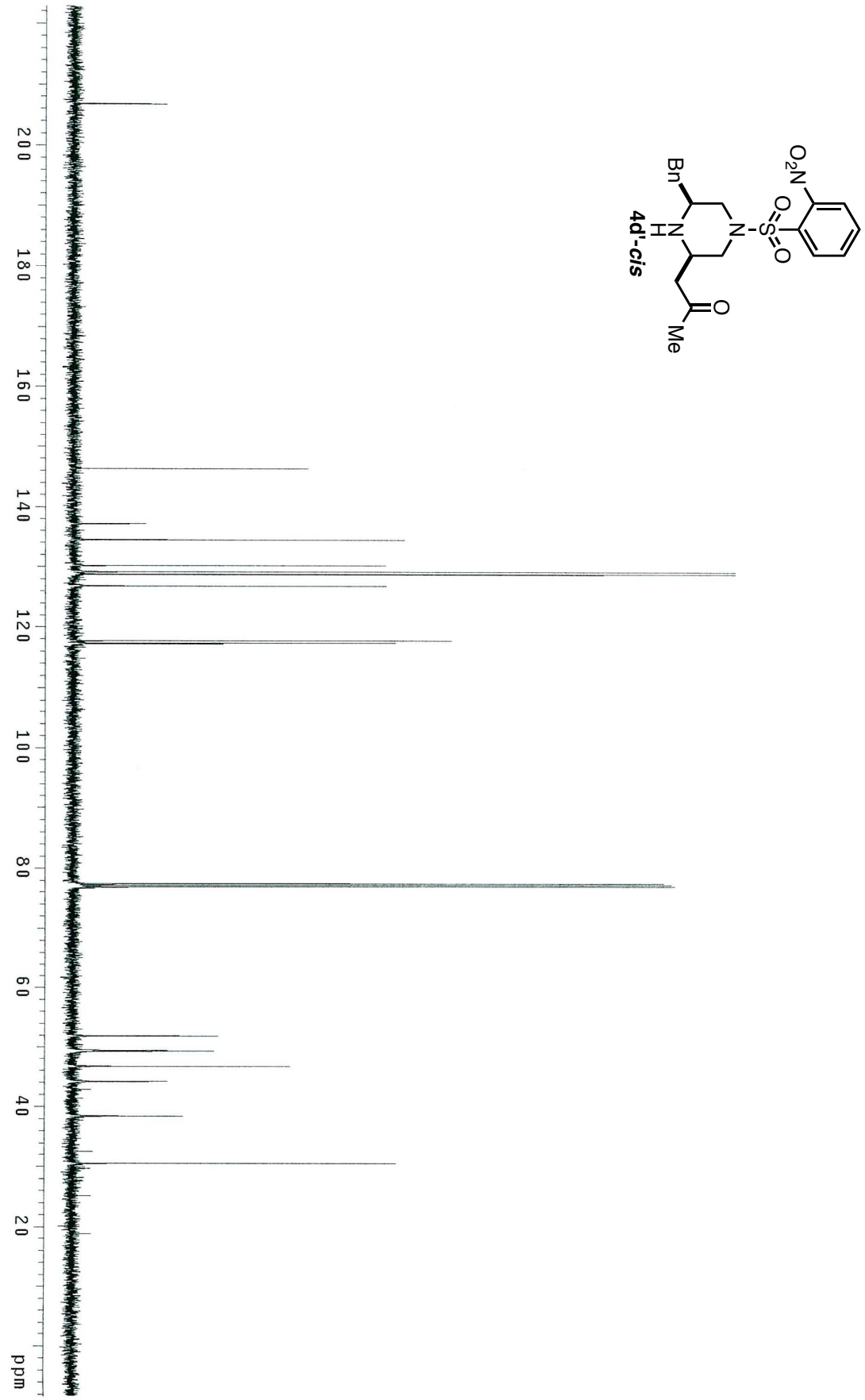
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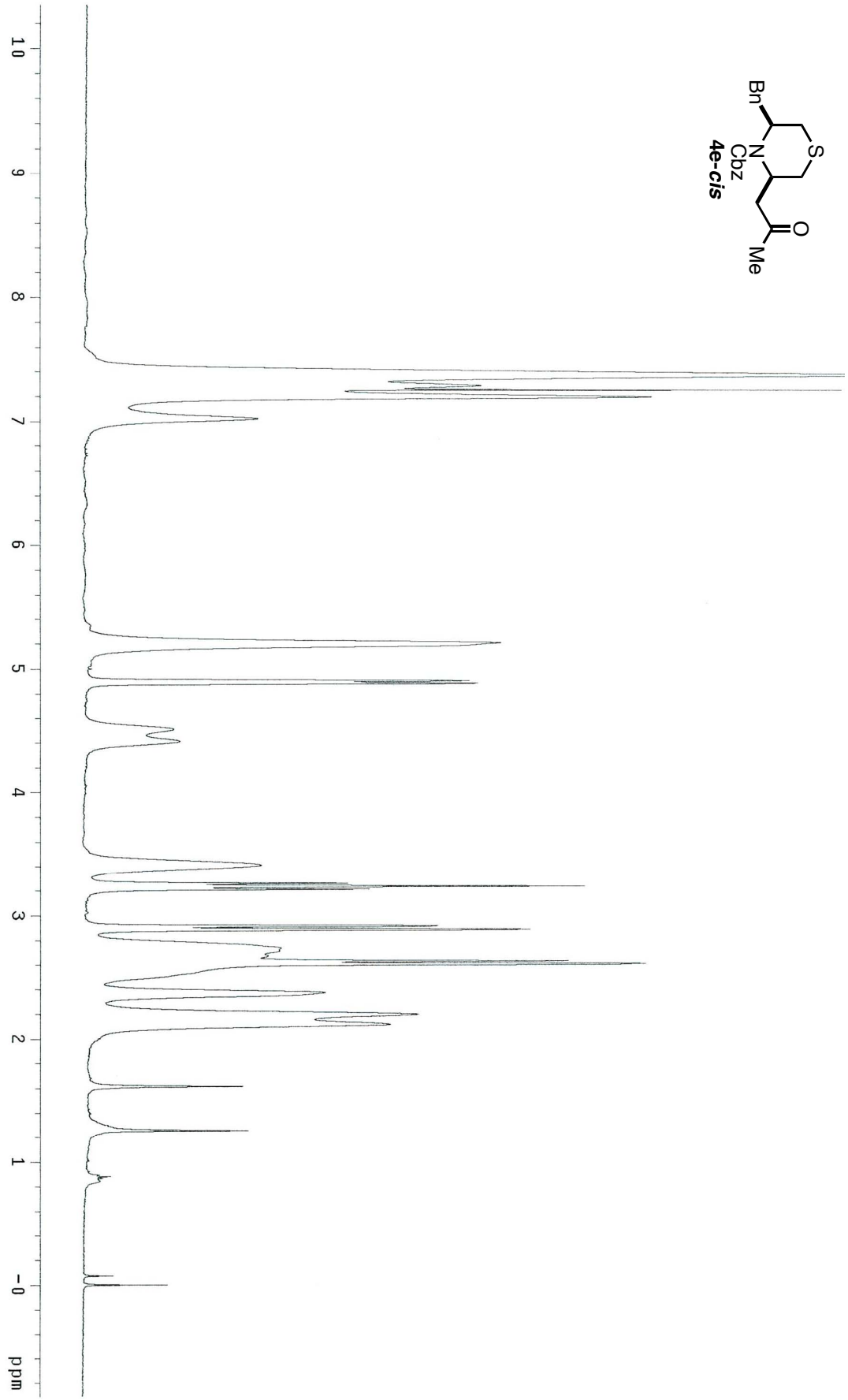
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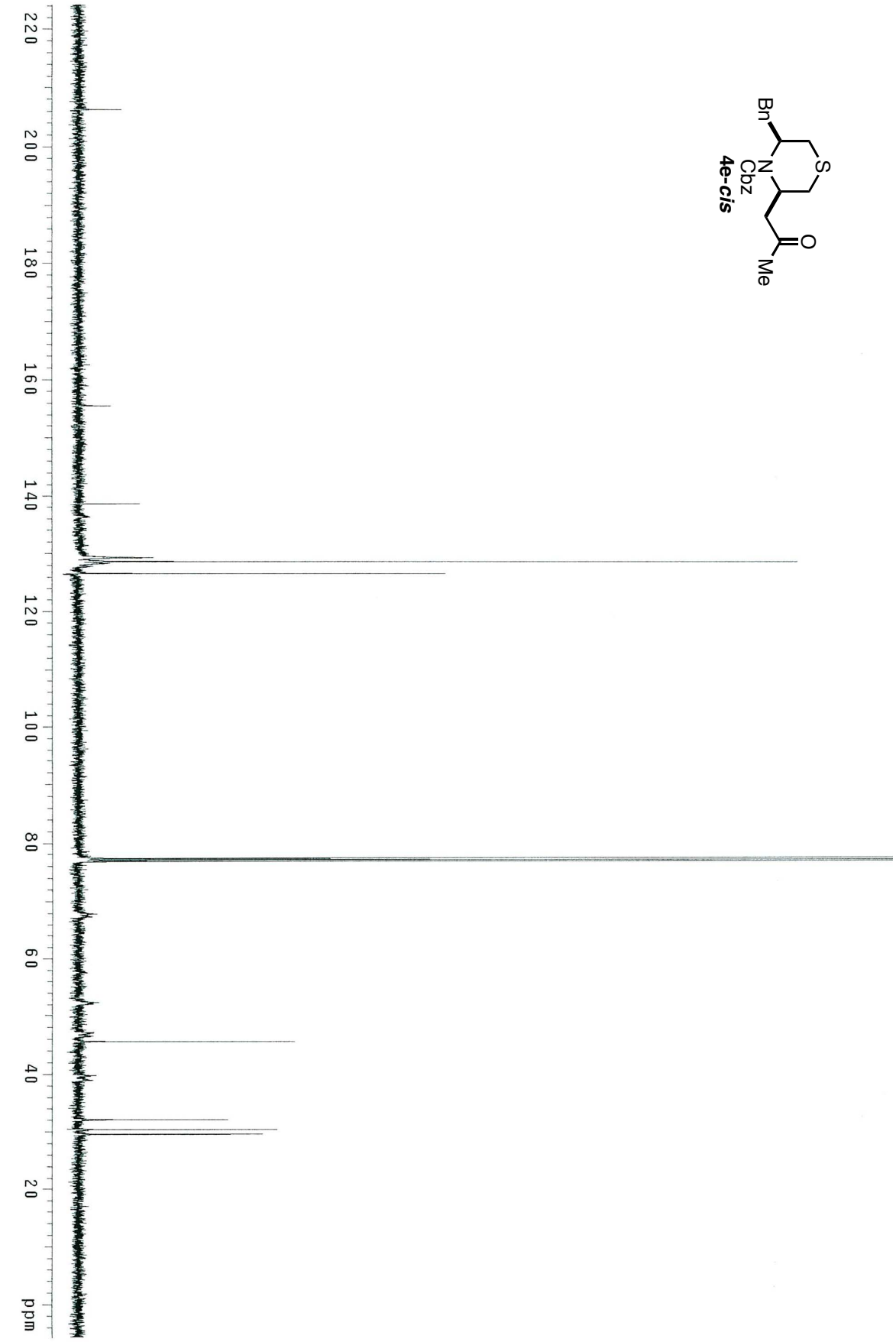
ppm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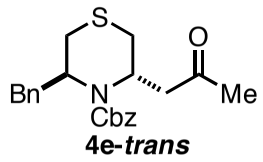

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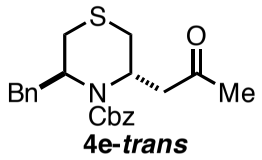

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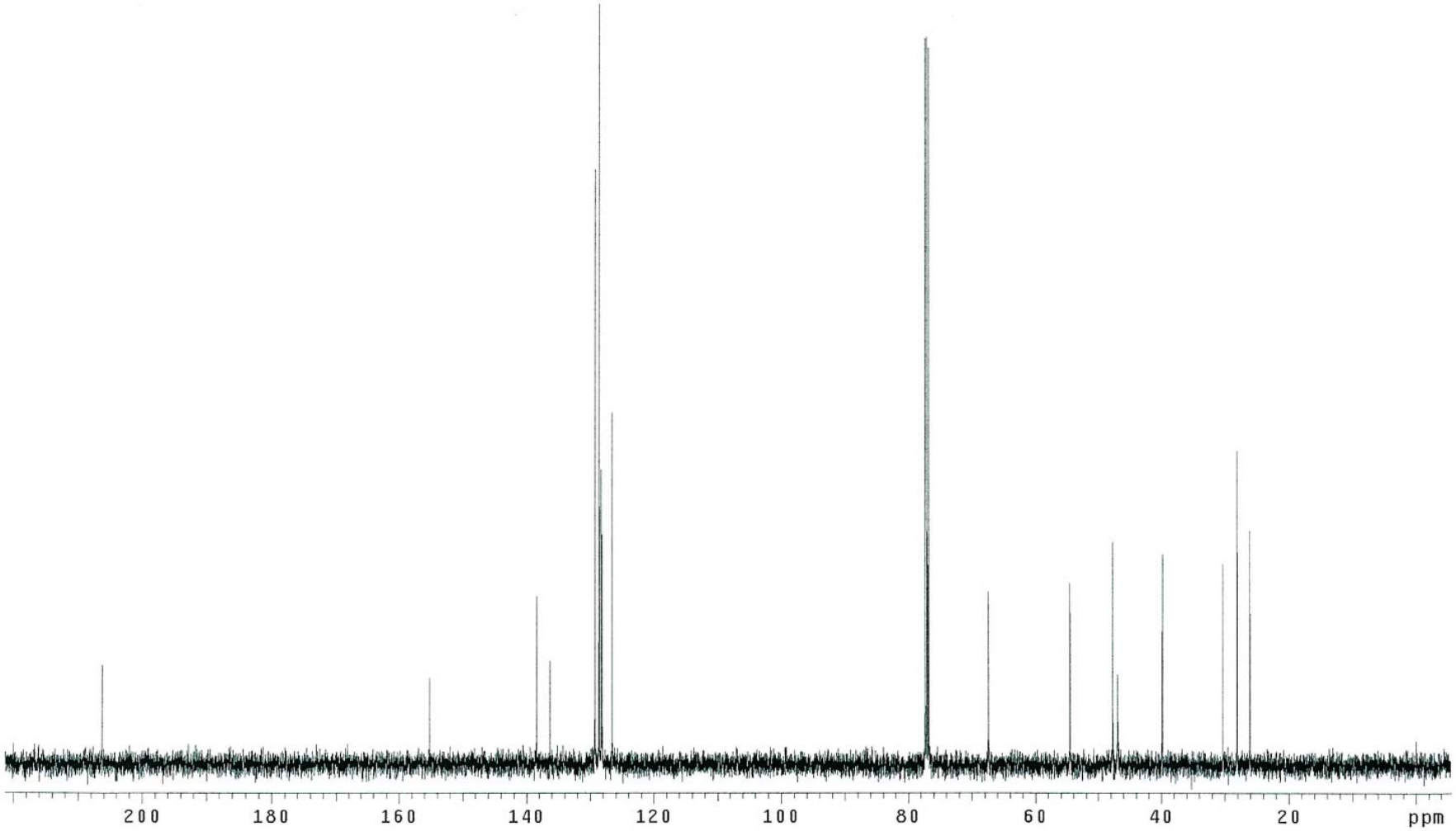

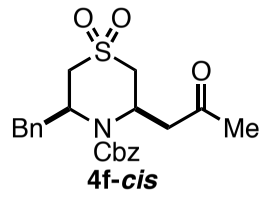

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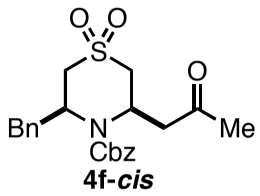
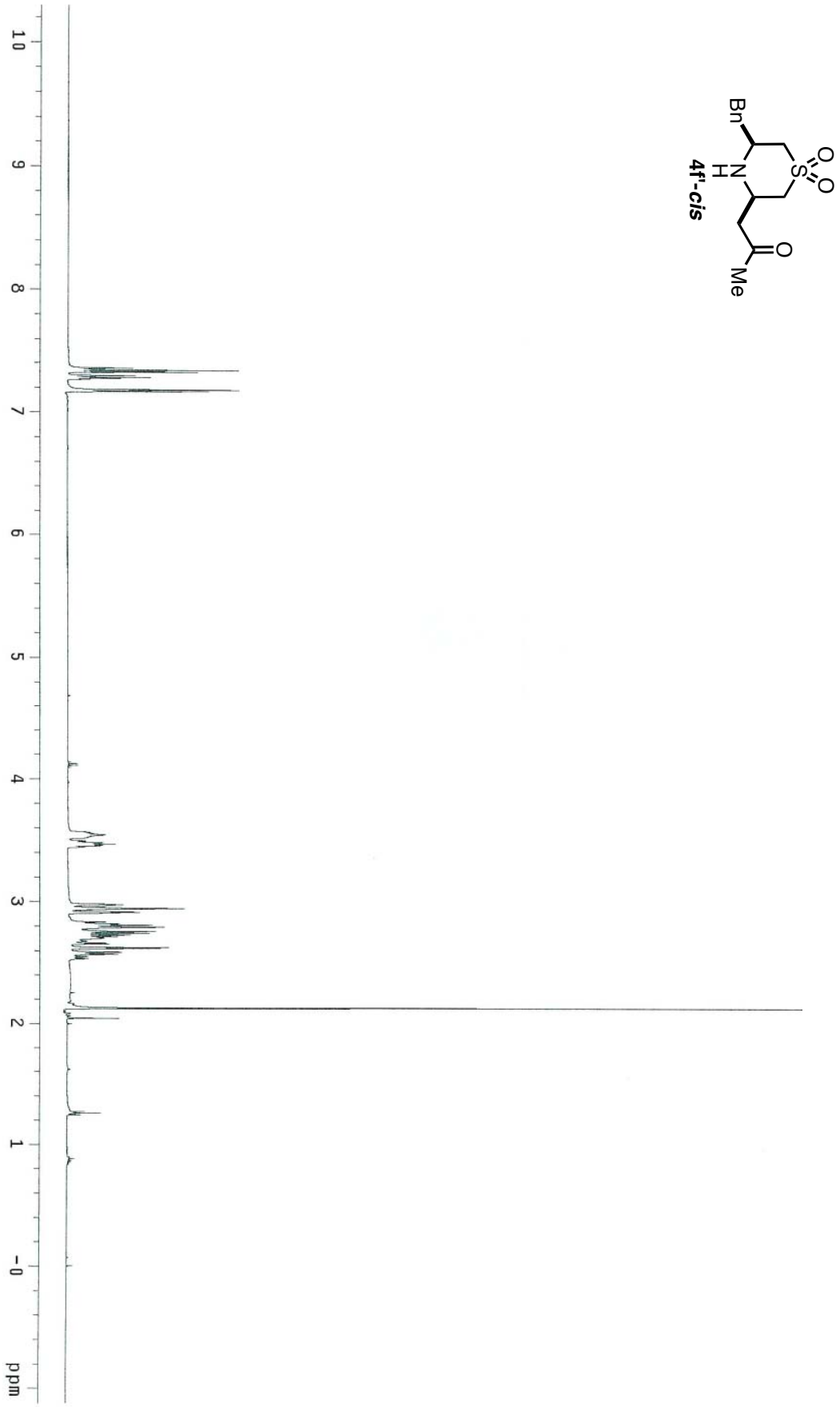


4f-*cis*


Bn
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O
O
Me
4f'-cis
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2
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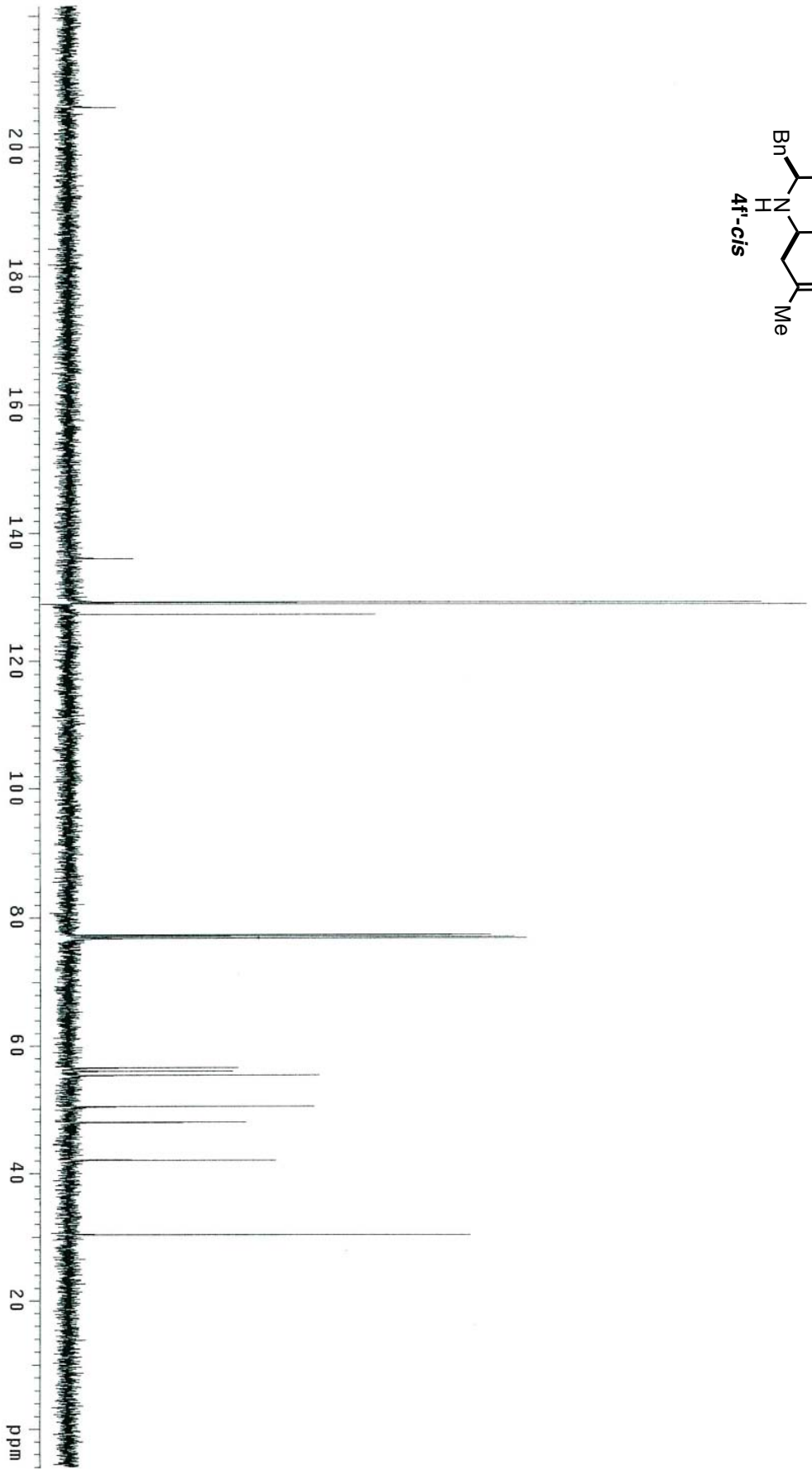
0
ppm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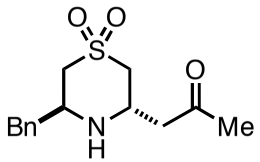

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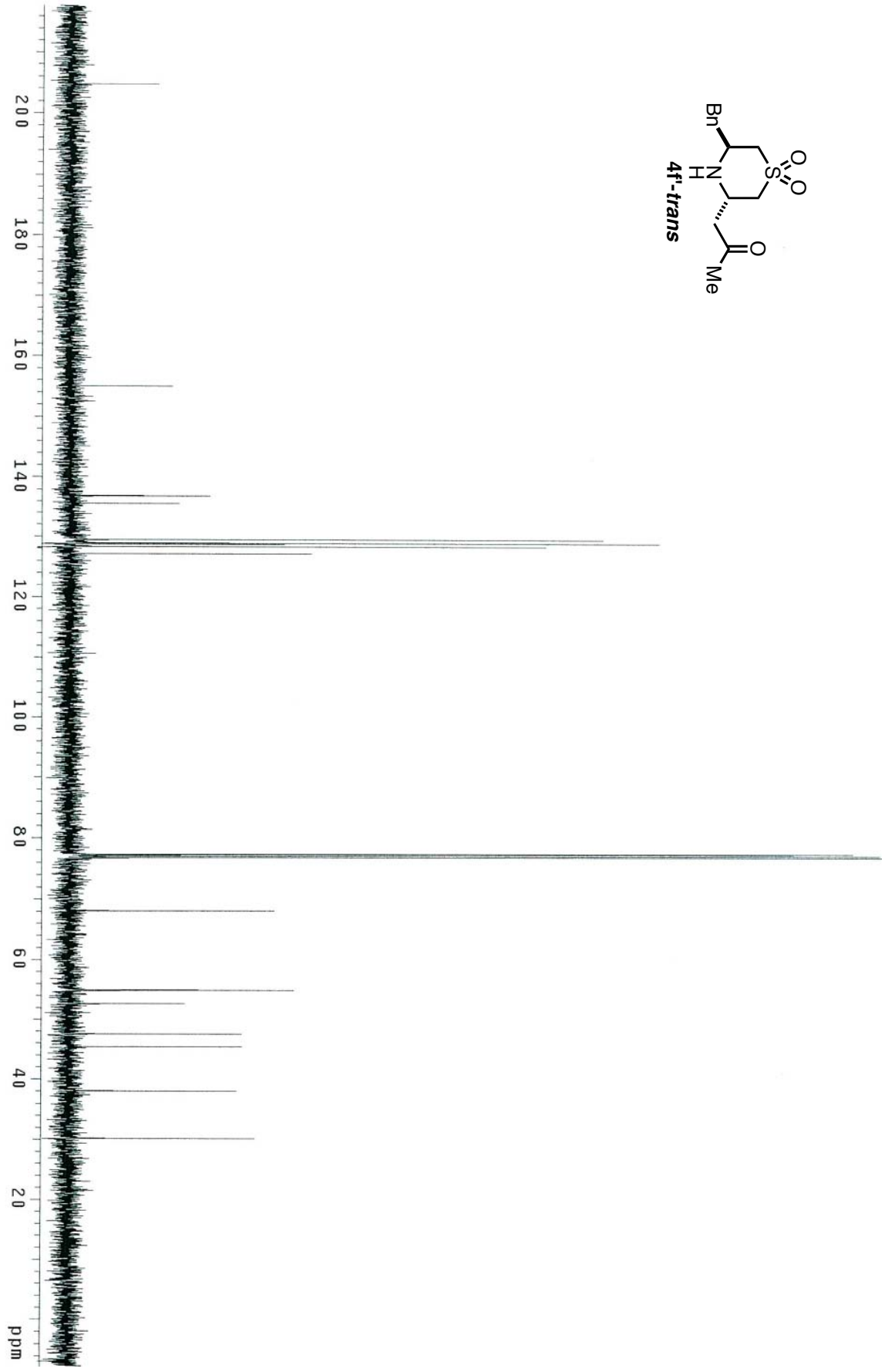
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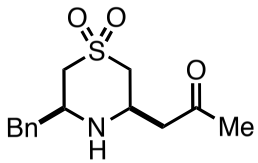

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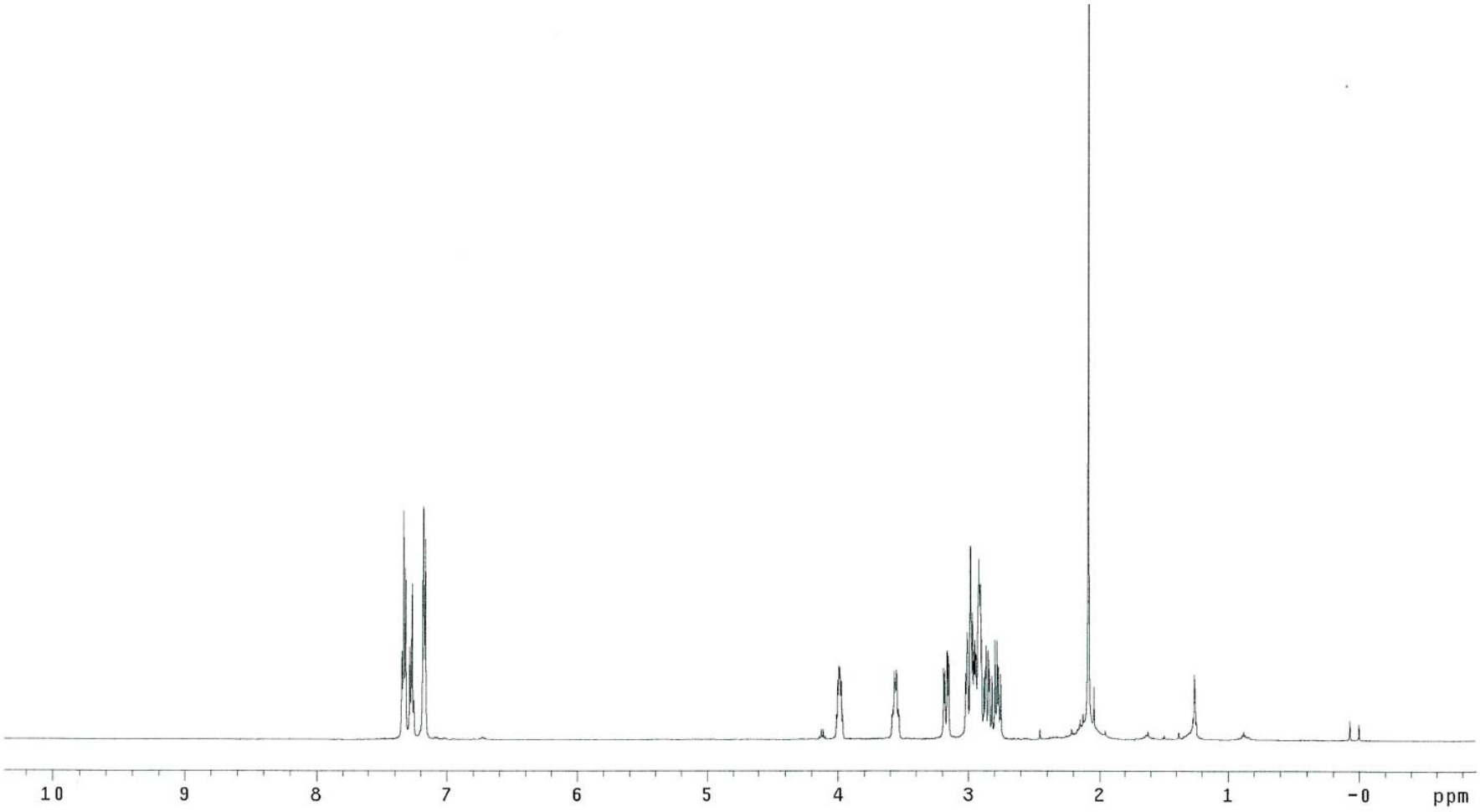

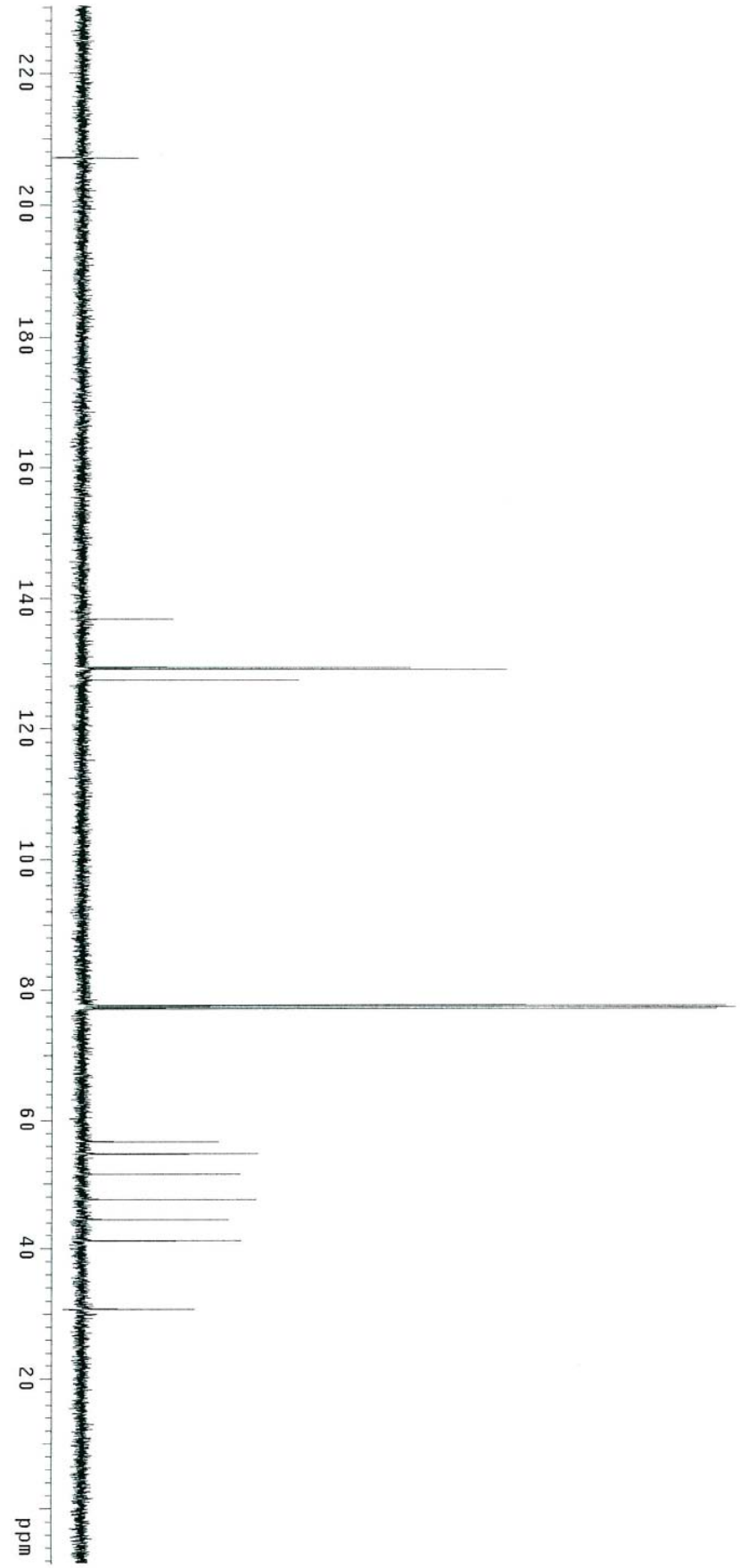

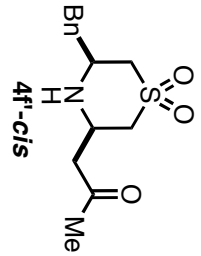

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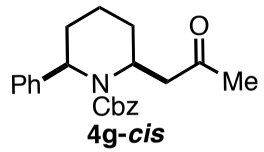
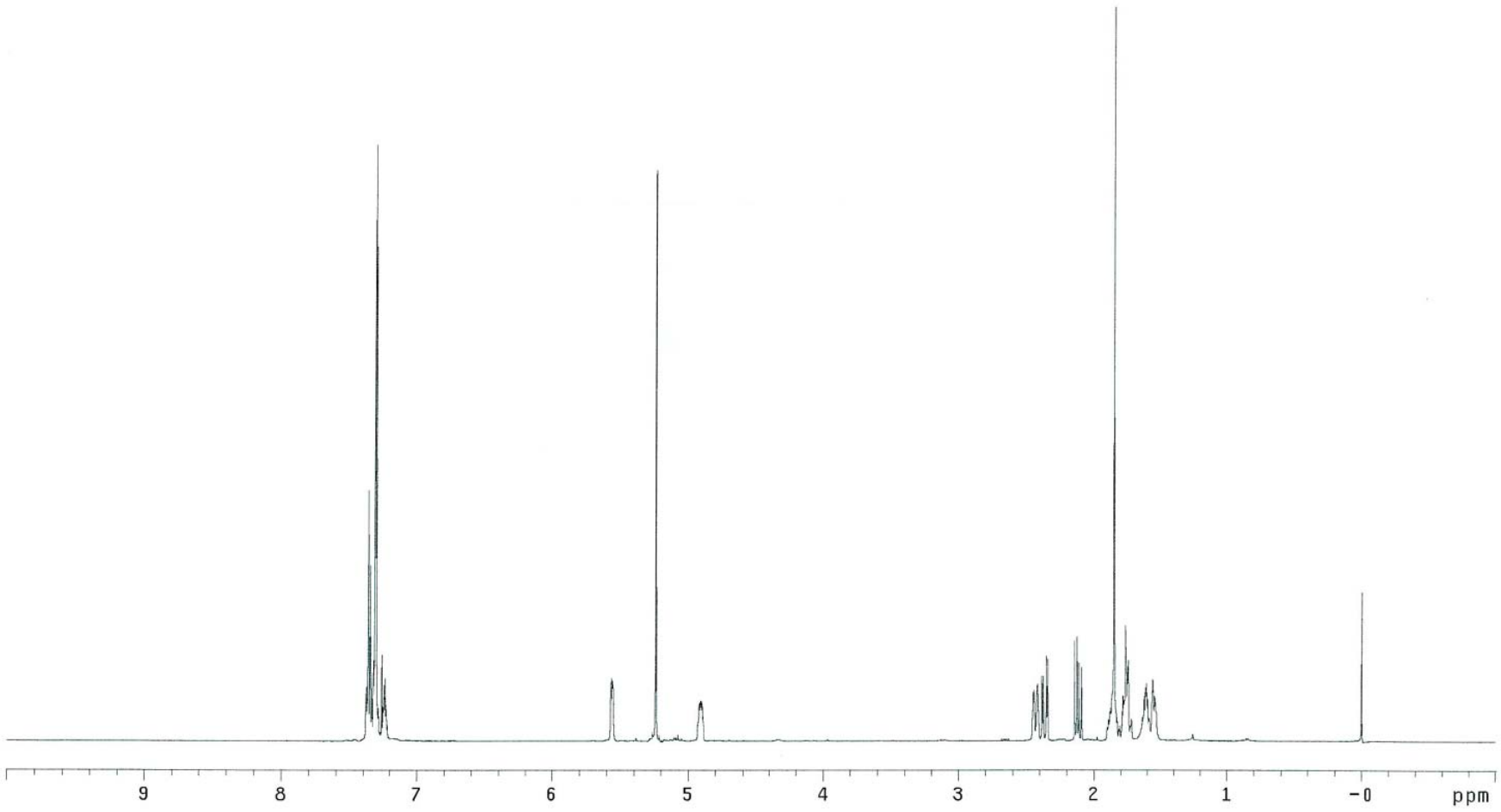
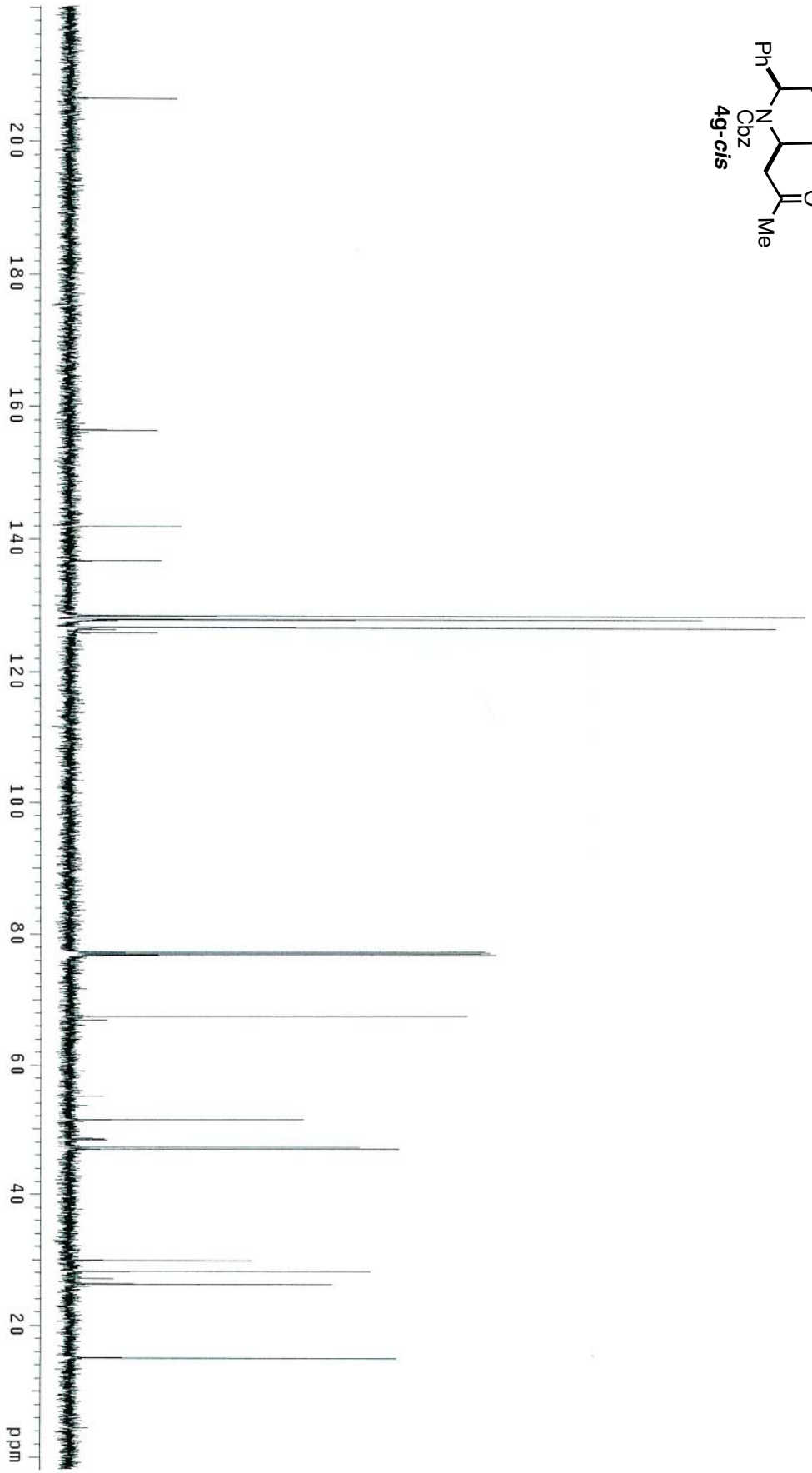


4g-*cis*

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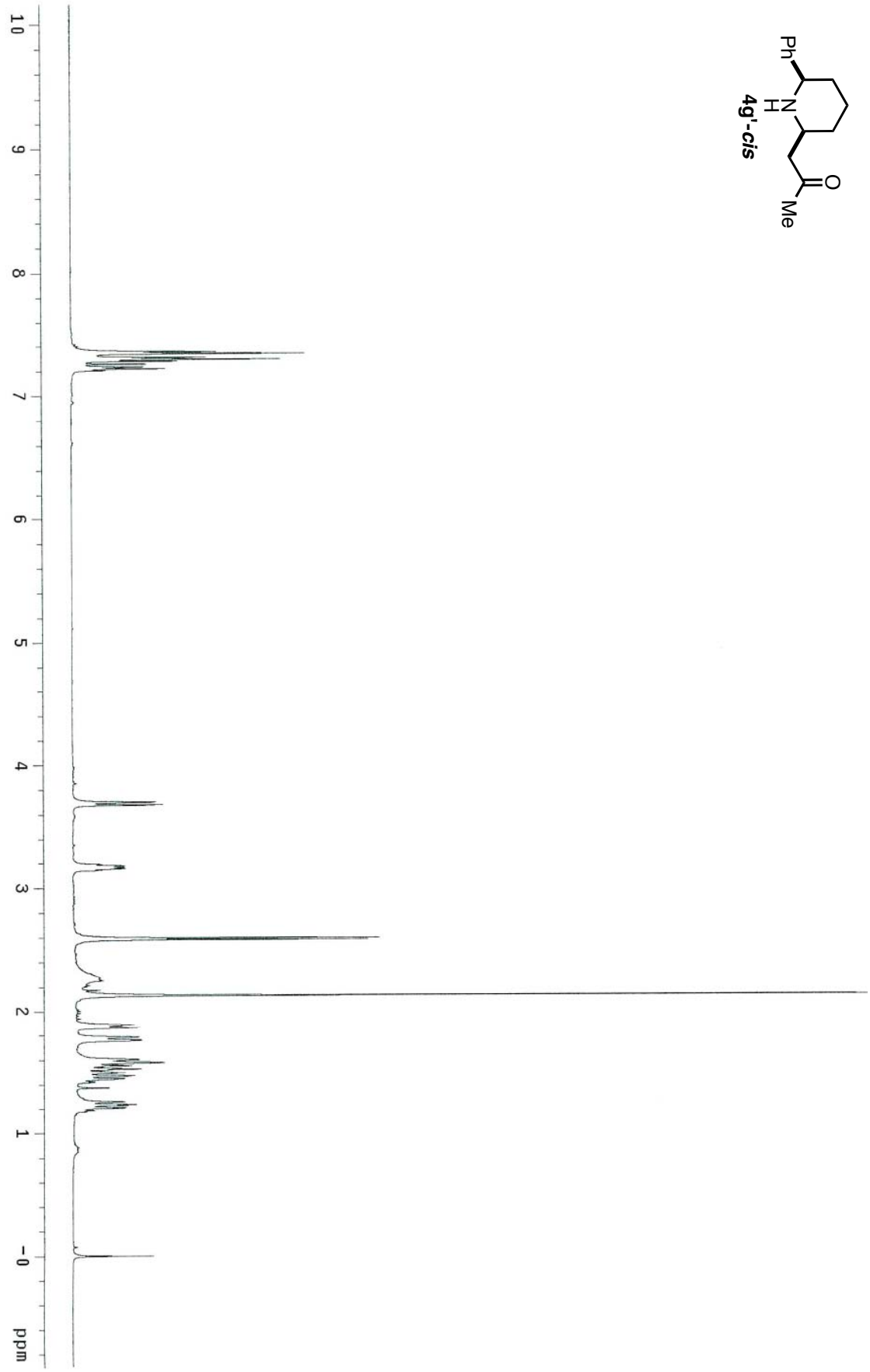
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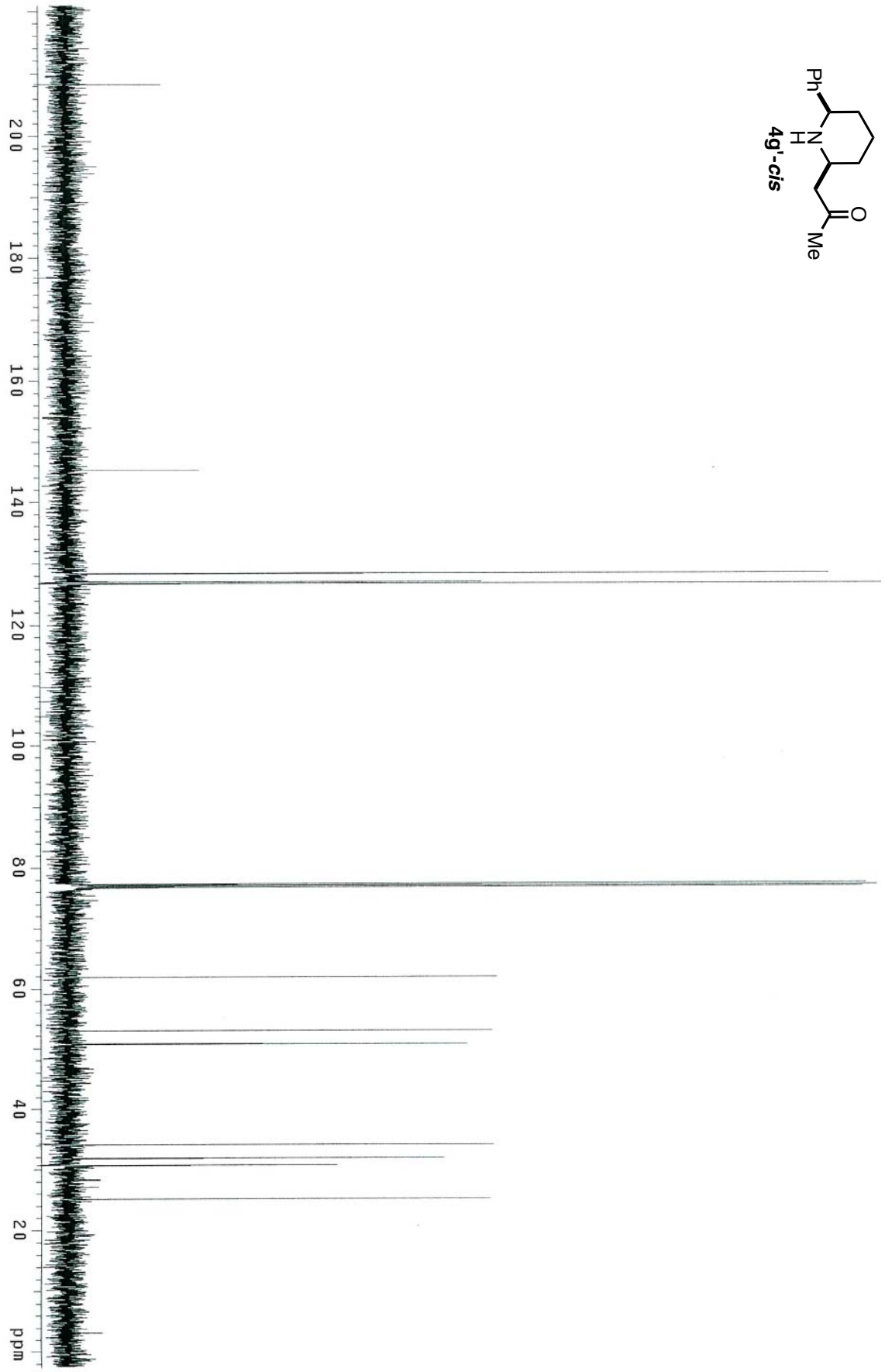
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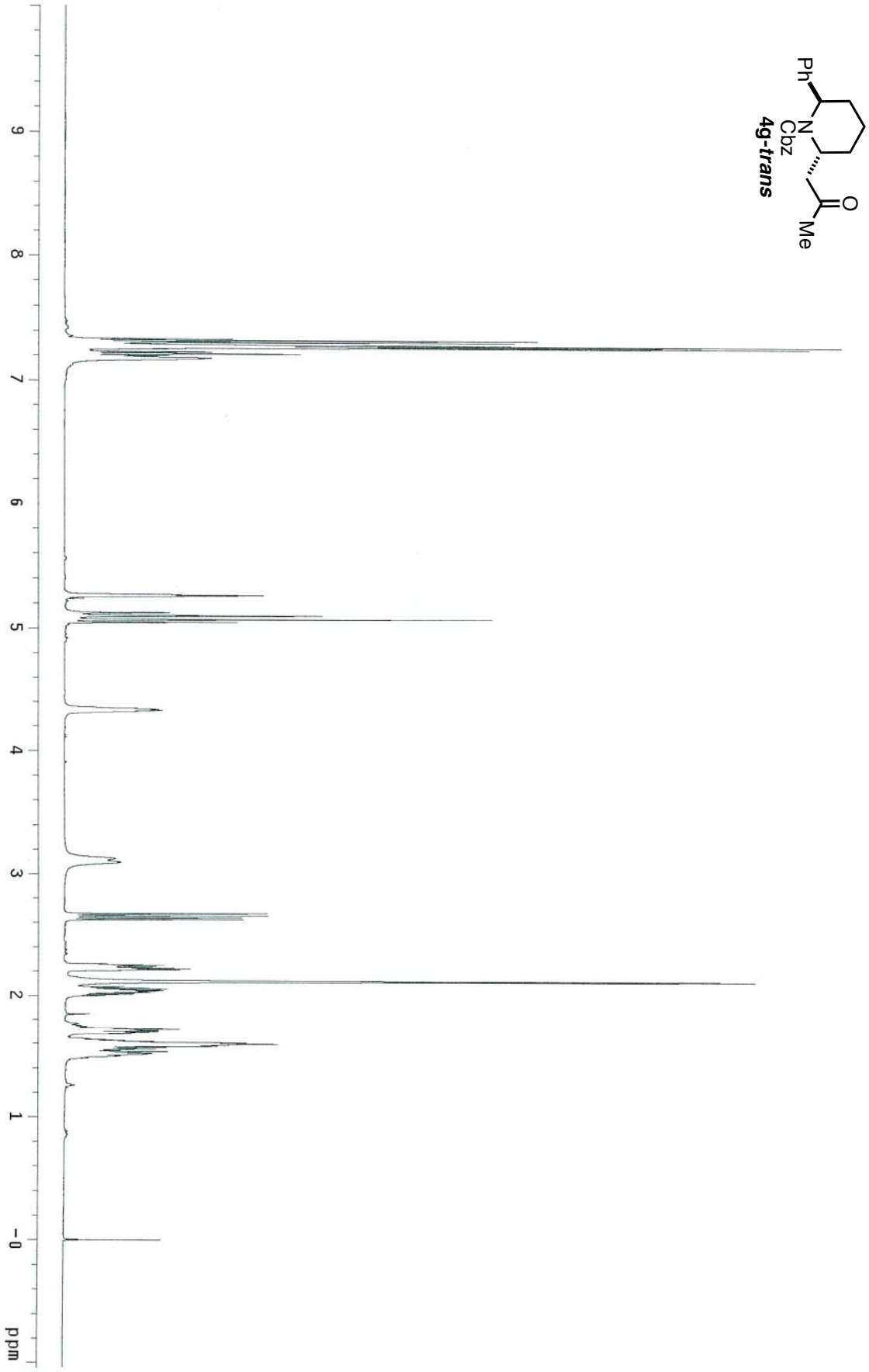
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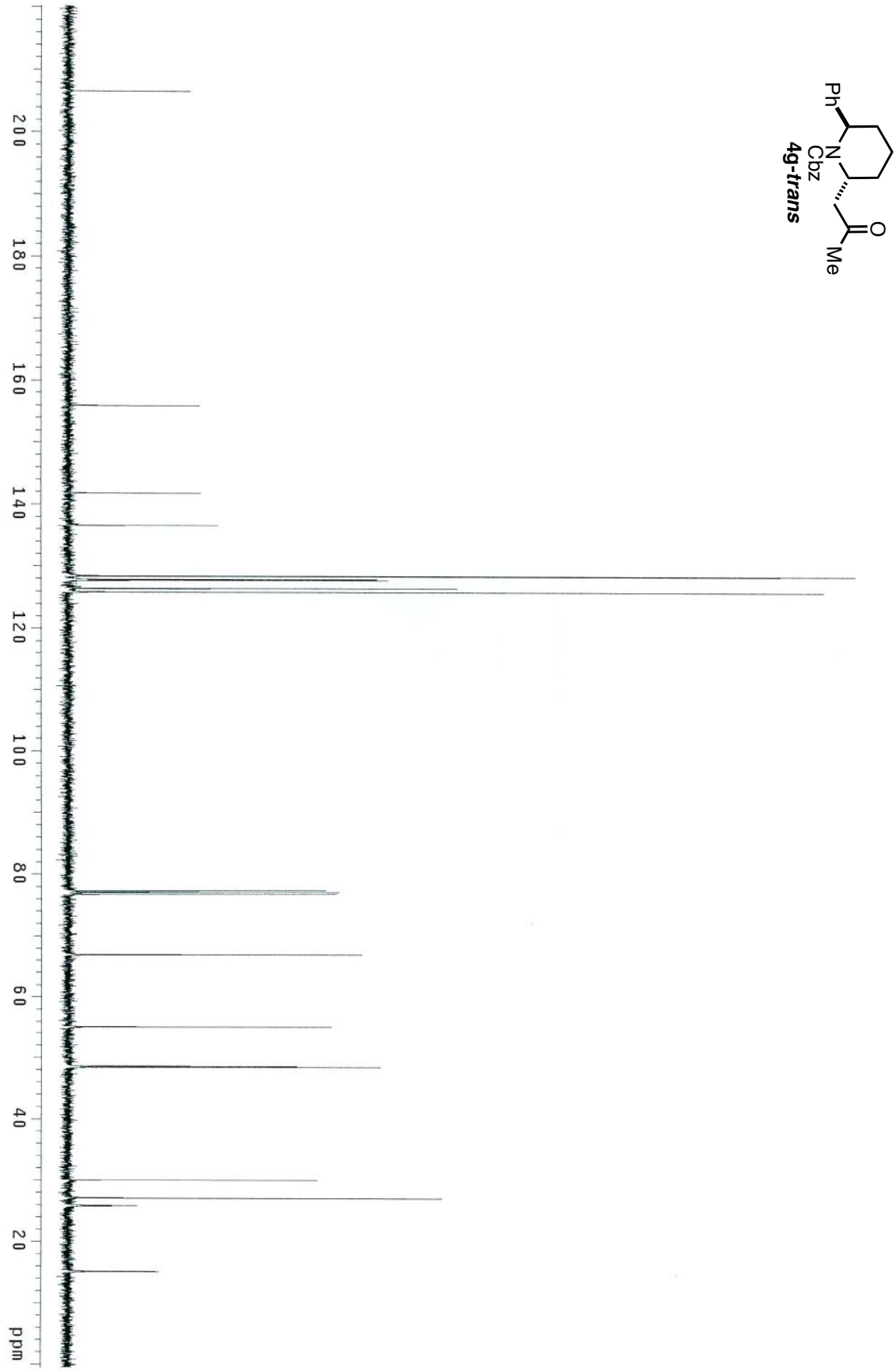
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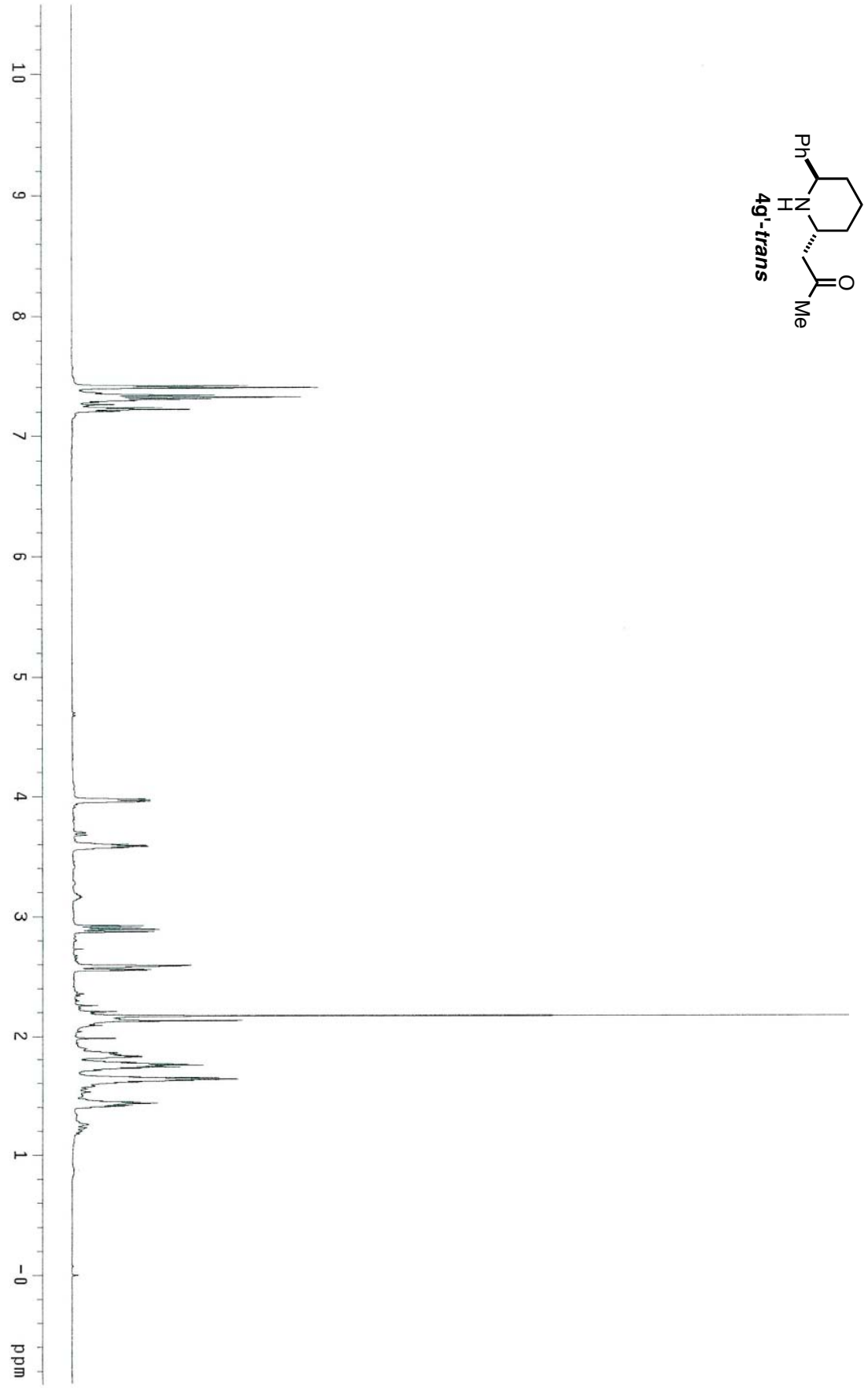
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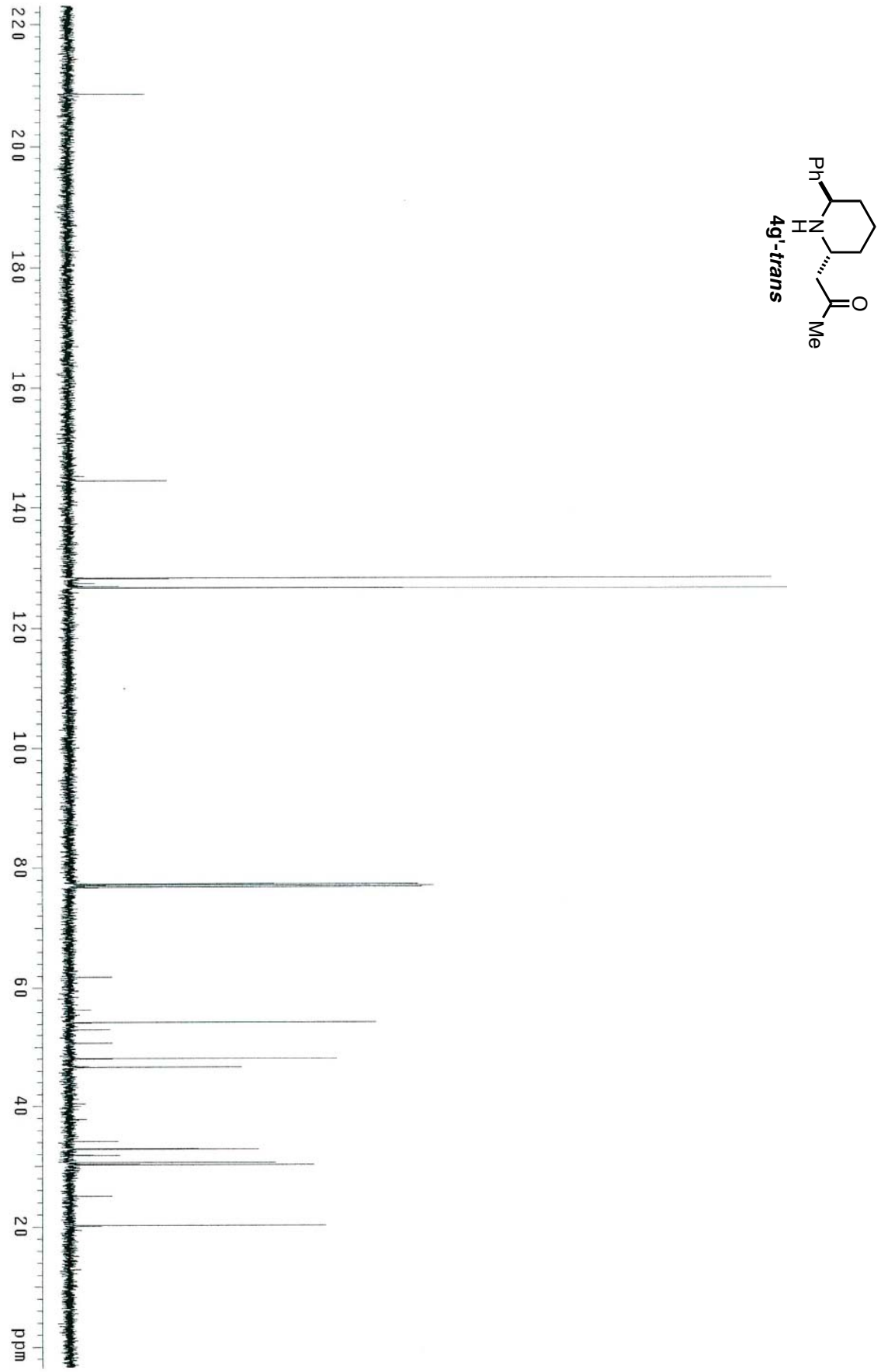
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Me
4g'-trans
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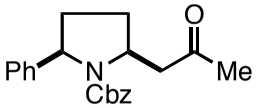
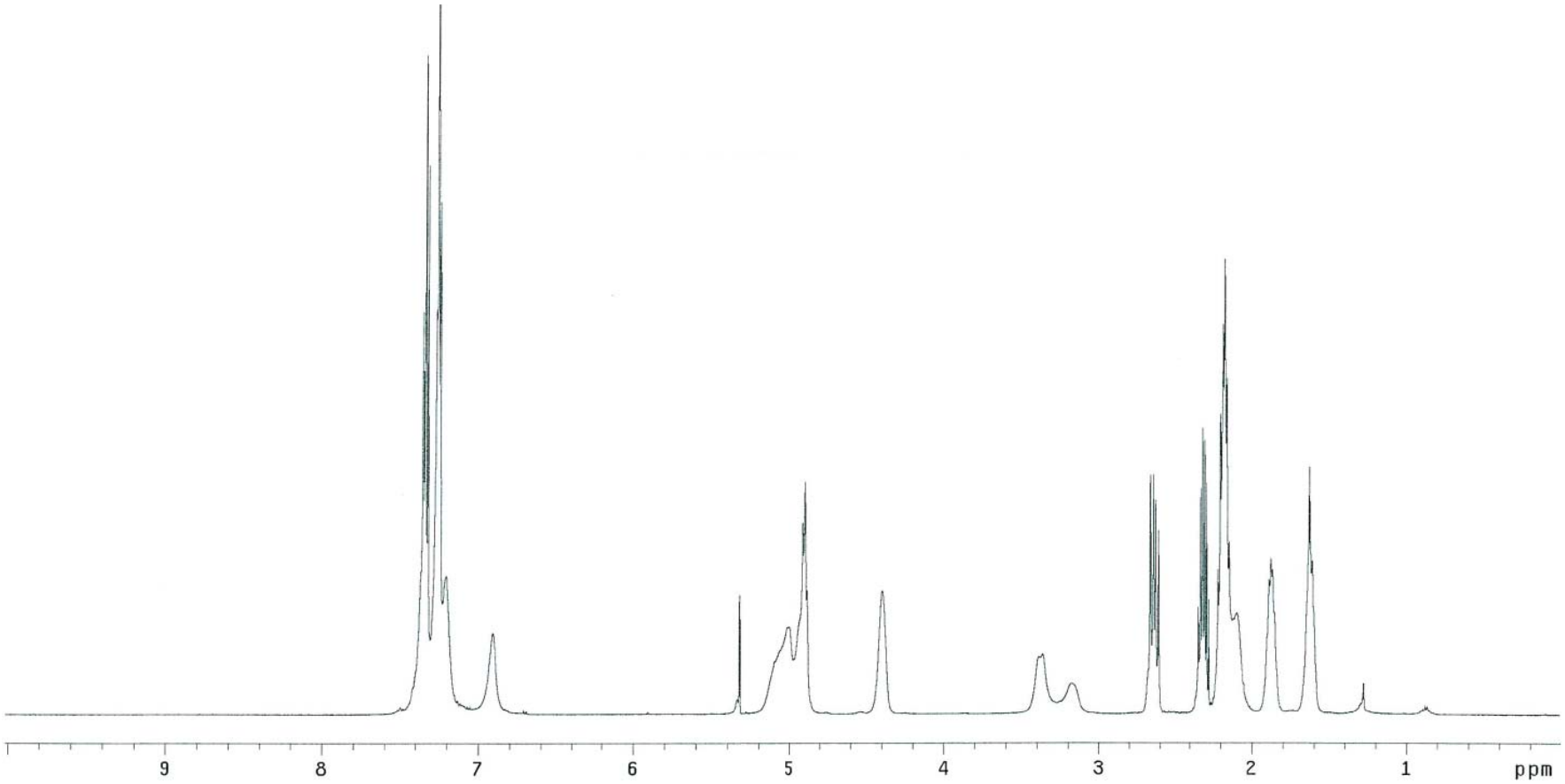
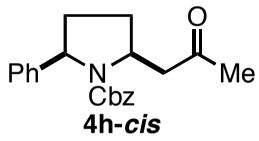
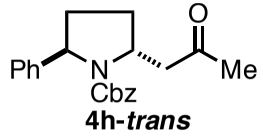


4h-*cis*





4h-*cis*



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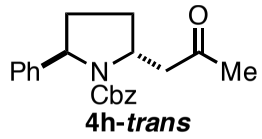

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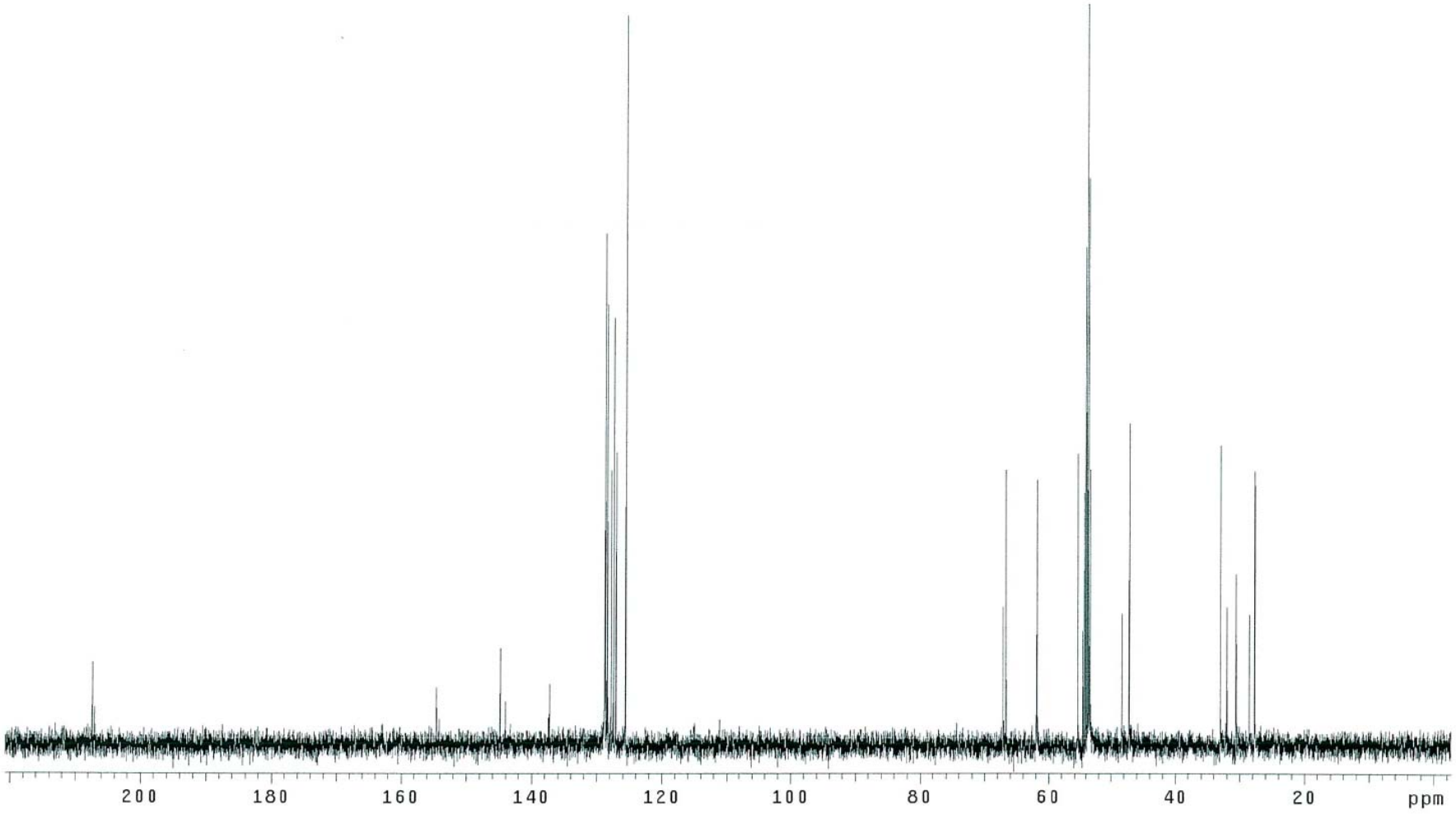
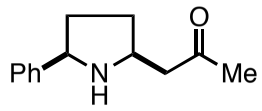
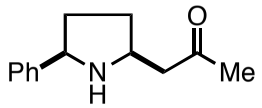
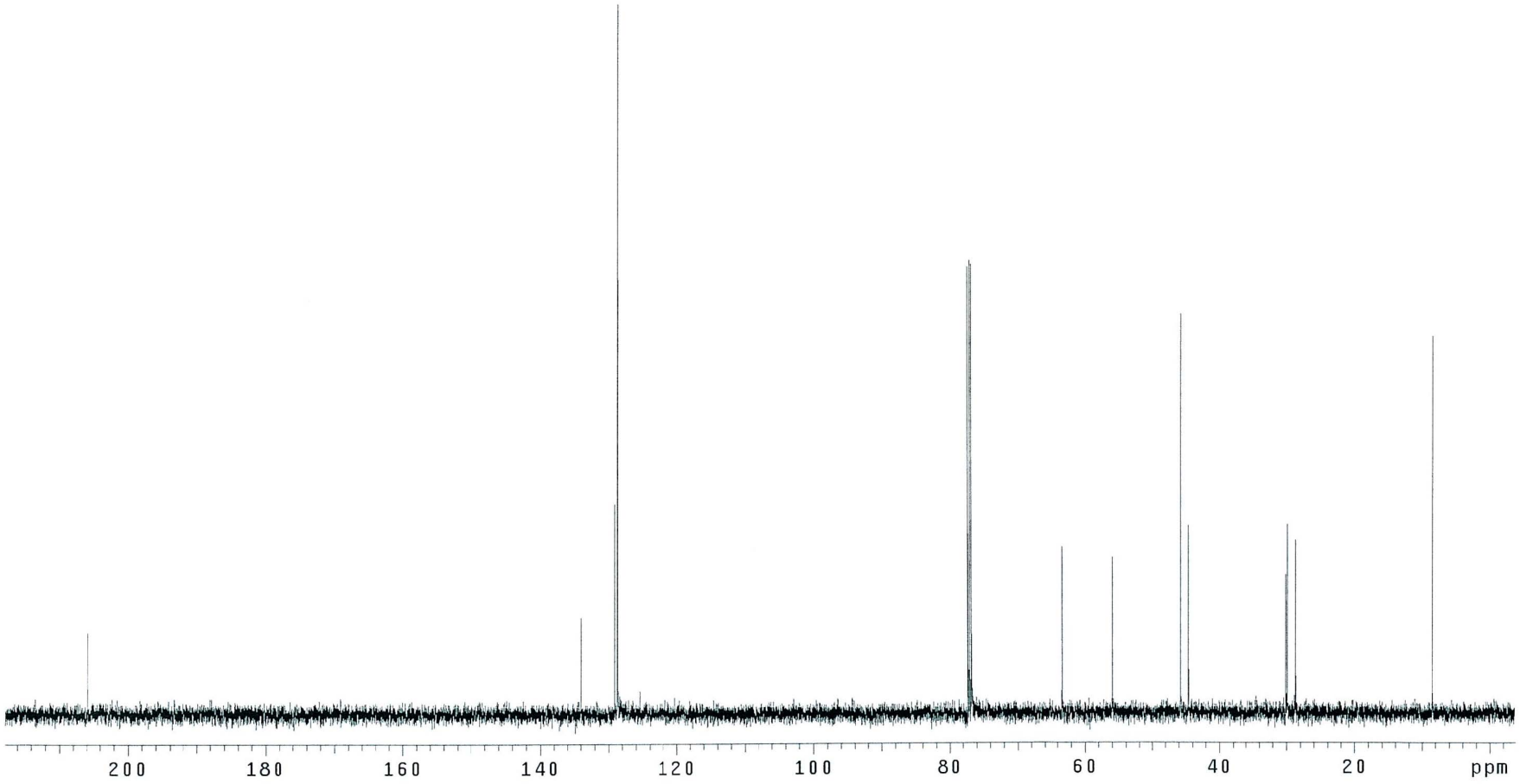


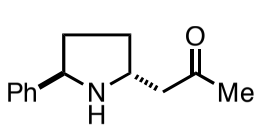


4h'-*cis*



4h'-*cis*





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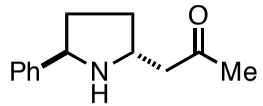
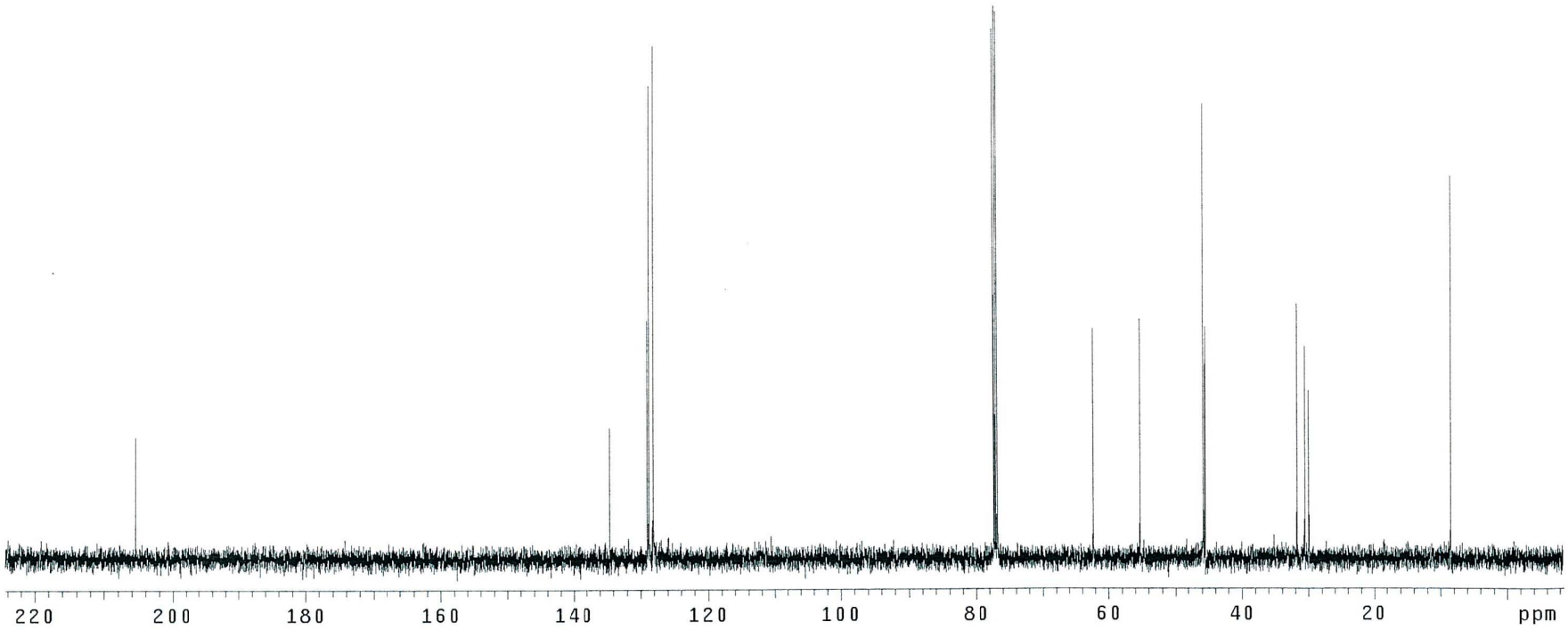
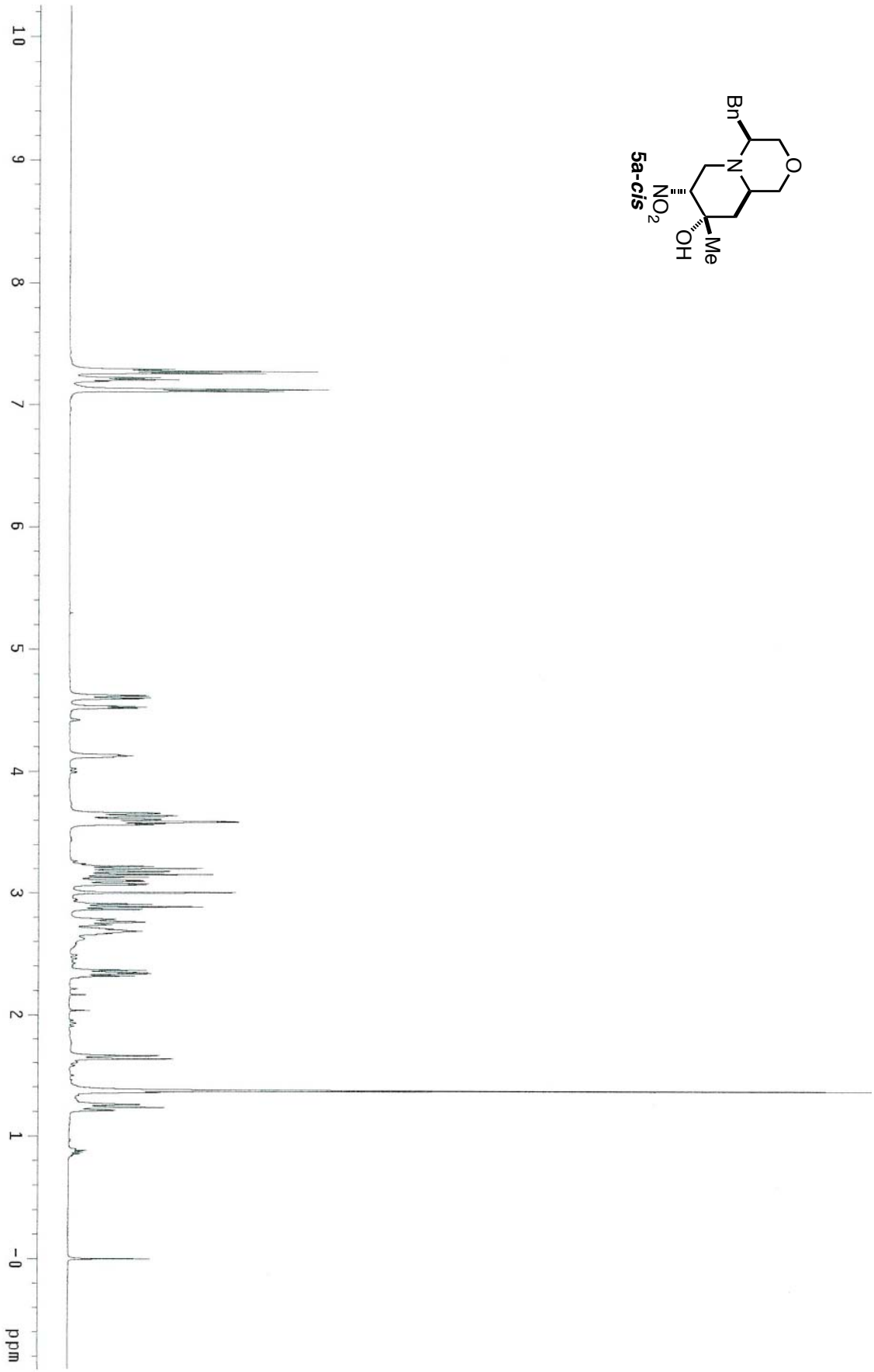


4h'-*trans*

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OH
Me
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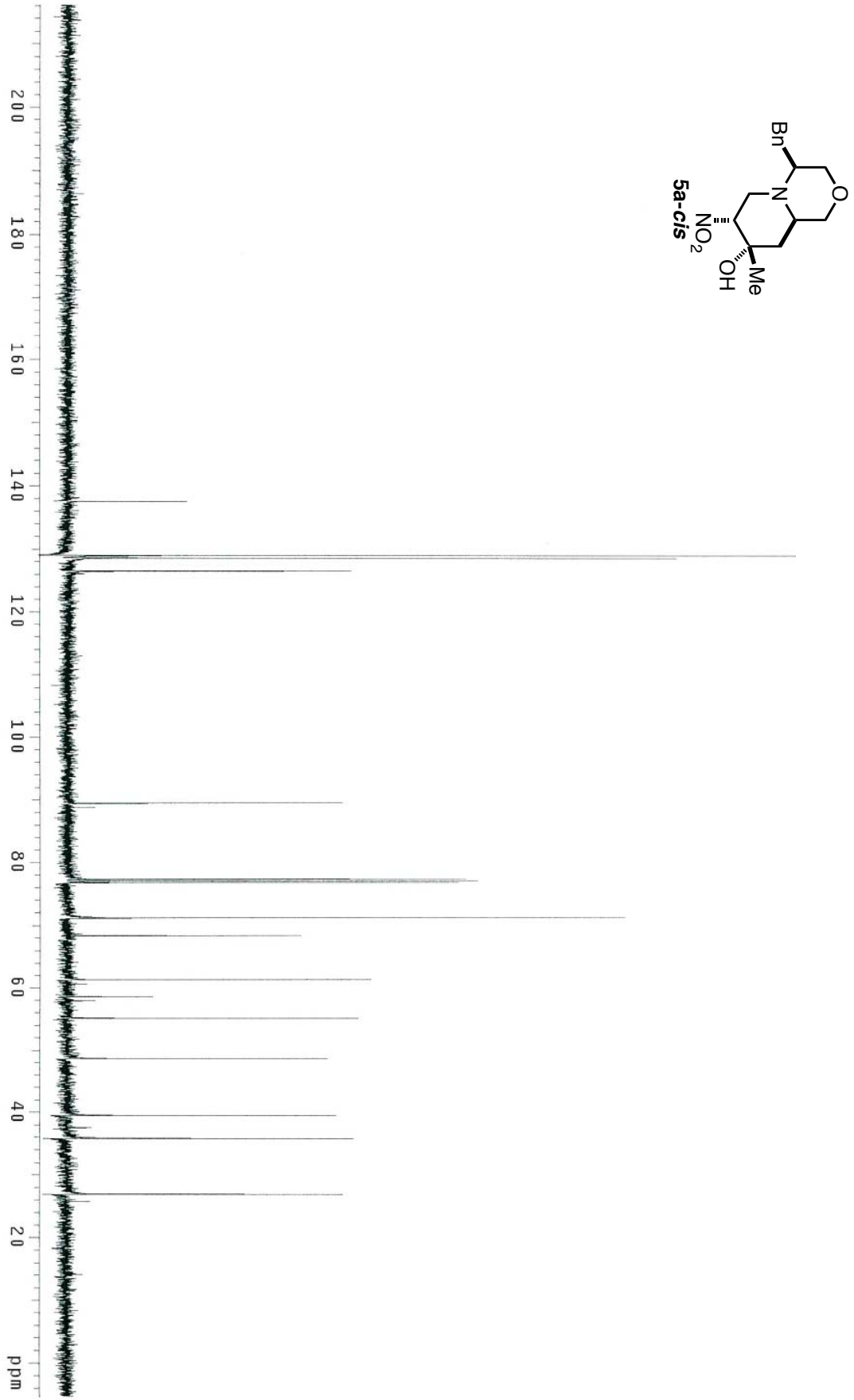
-0
ppm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NO2
OH
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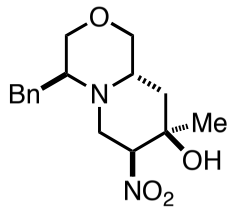
ppm



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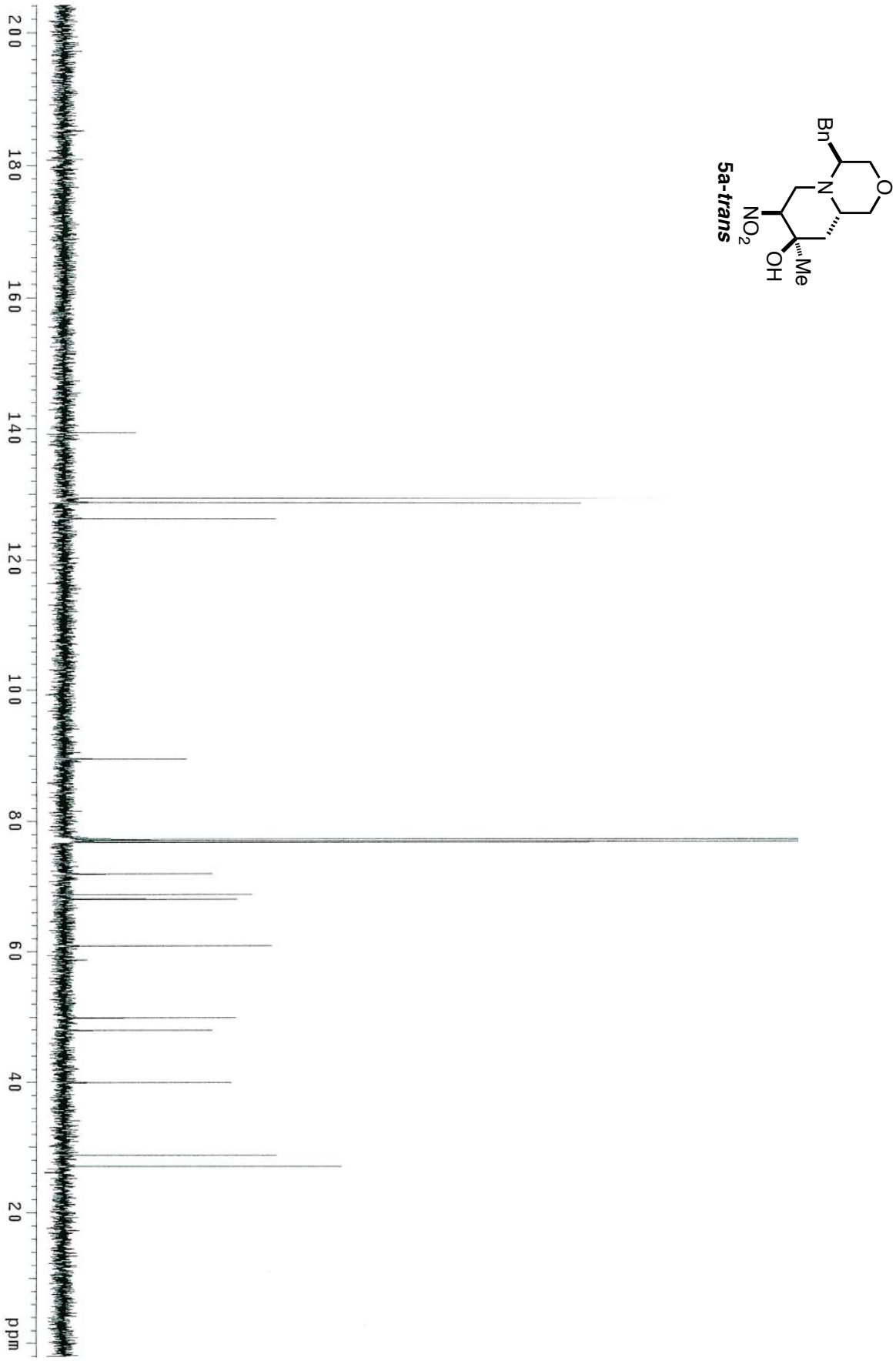
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OH
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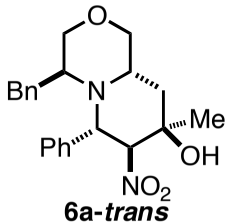
ppm



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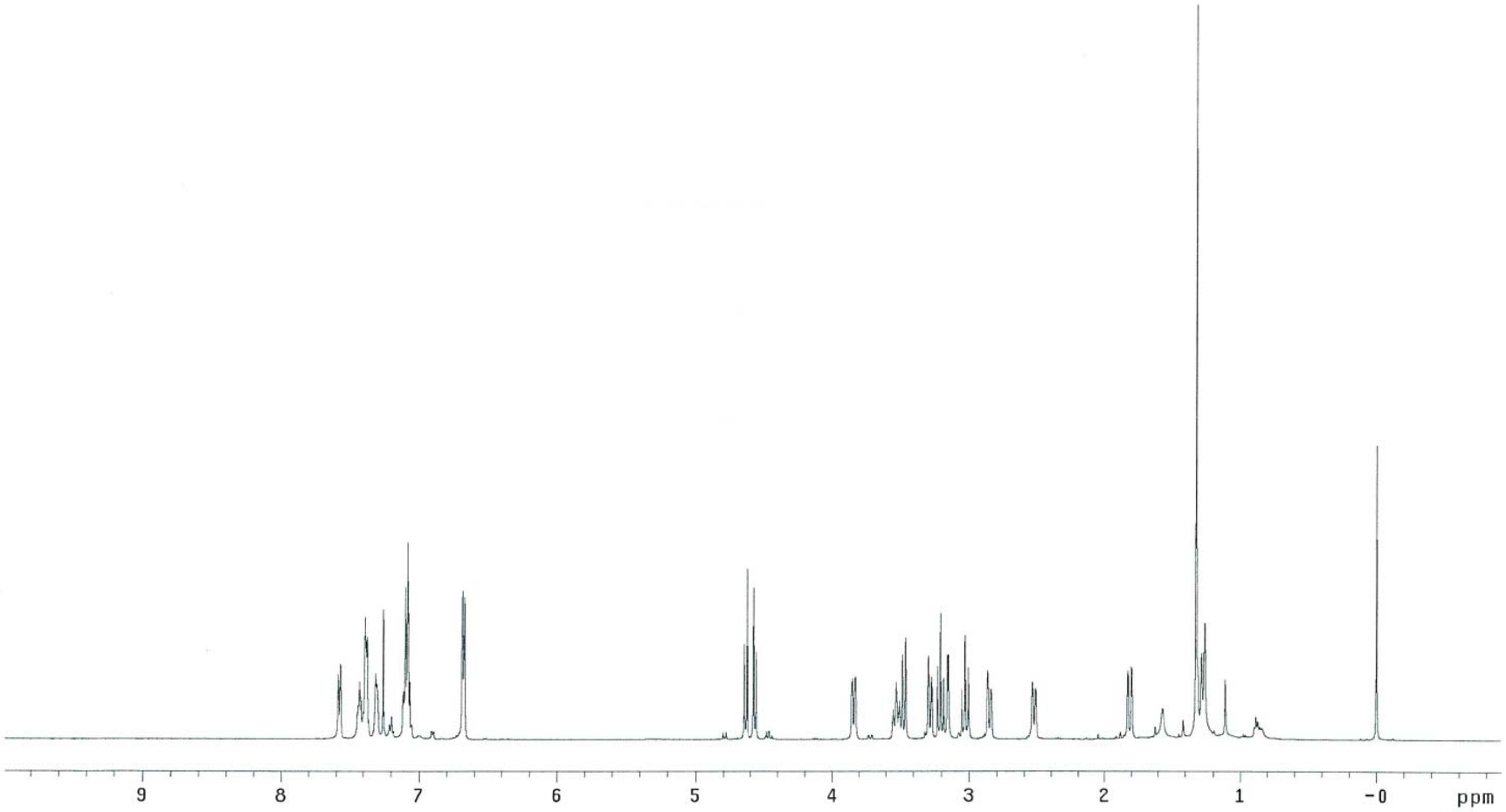

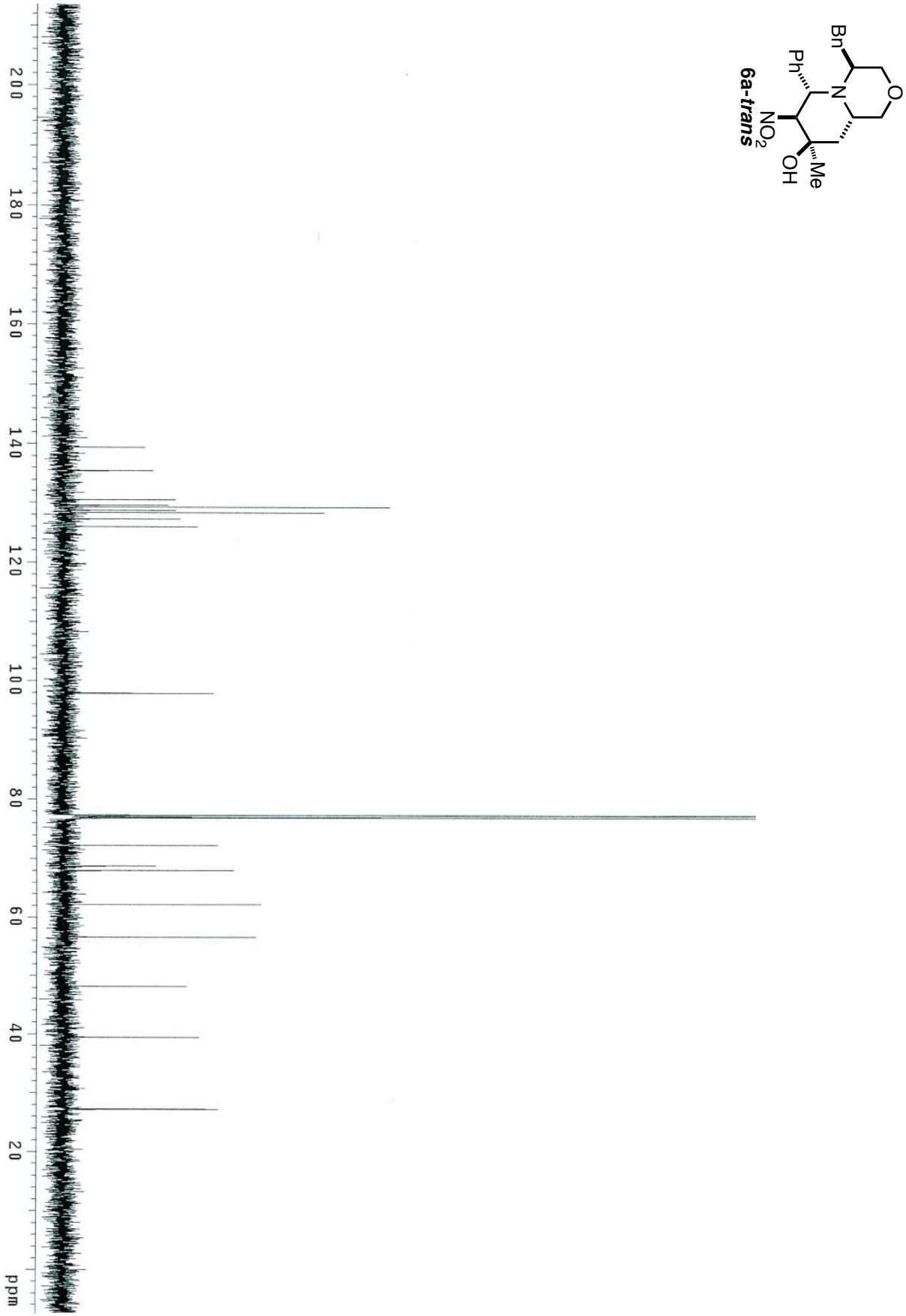
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NO2
OH
Me
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ppm