Supporting Information

for

A New Oxyma Derivative for Non-racemizable Amide-forming Reactions in Water

Qinghui Wang, Yong Wang, and Michio Kurosu*

Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, 881 Madison, Memphis, TN 38163-0001, United States

mkurosu@uthsc.edu

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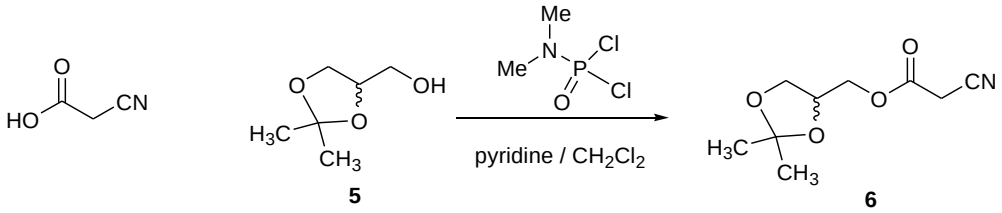
General

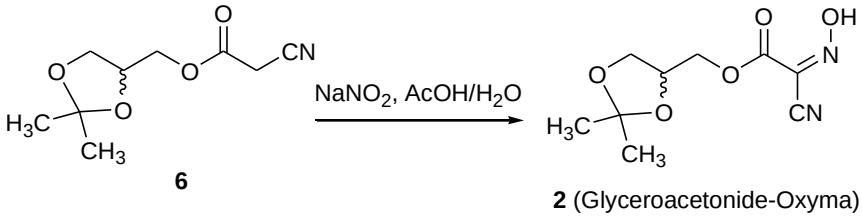
All reactions were carried out using oven-dried glassware, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques. Commercially available reagents were used as received without further purification. Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (EMD, Silica Gel $60F_{254}$) visualizing at 254 nm or being stained with Ninhydrin and heated at 120 degree. Infrared spectra were recorded as solutions in $CDCl_3$ using CaF_2 cells or as solids in Nujol using KBr cells, on a Perkin-Elmer FT 1600. ^{1}HNMR spectral data were obtained using 400, and 500 MHz instruments. ^{13}CNMR spectral data were obtained using a 100, 125 MHz spectrometer. For all NMR spectra, δ values are given in ppm and *J* values in Hz. HPLC data were obtained on a Shimadzu prominence HPLC using Phenomenex Kinetex 2.6 µ C18 column (100 * 4.6 mm) and monitoring at 254, 280 nm. Z in the name of compounds refers to Cbz.

Experimental Procedures



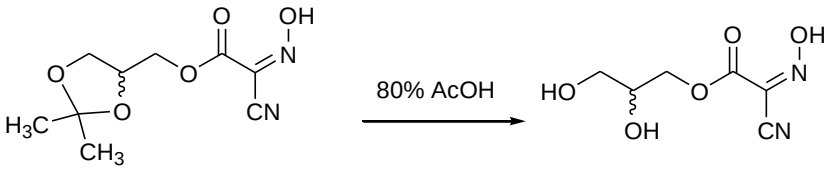
Cyano-acetic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (6)

To a solution of cyanoacetic acid (0.6 g, 7.05 mmol) in anhydrous CH_2Cl_2 (80 ml) at 0 ^oC was added sequentially pyridine (1.71 ml, 21.15 mmol), N,N-dimethyl phosphoramidichloridate (1.68 ml, 14.10 mmol), and compound **5** (0.87 ml, 7.05 mmol). The resulting solution was stirred at room temperature under a N_2 atmosphere for 24 hours, and then the solution was poured into ice-cold 1 N HCl (100 ml) and extracted with CH_2Cl_2 four times. The combined organic layers were washed with brine and then dried over Na_2SO_4. Solvent was removed *in vacuo*. The resulting crude product was purified by column chromatography on silica gel (hexanes : ethyl acetate = 10: 1 to 5:1) to provide **6** as a colorless oil (1.26 g, 95% yield). TLC (Hexane:EtOAc=3:1): R_f = 0.35; IR ($CDCl_3$) υ_{max} = 2987, 2936, 1750, 1187, 1053, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.38-4.51 (m, 3H), 4.14-4.20 (m, 1H), 3.88-3.91 (m, 1H), 1.49 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.3, 126.3, 110.6, 107.4, 73.1, 66.8, 65.9, 26.5, 25.2; HRMS (ESI) Calcd. for $C_9H_{14}NO_4$ $[M+H]^+$: 200.0923, found: 200.0926.



Cyano-hydroxyimino-acetic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (2)

To a suspension of **6** (10.0 g, 53.2 mmol) and sodium nitrite (4.41g, 63.85 mmol) in water (8 mL), acetic acid (7 g, 116.6 mmol) was added at 0-5°C over a period of 10 minutes. Temperature was slowly raised to 23-27°C and the reaction mixture was stirred for one hour at that temperature. After the complete consumption of **6** (monitored by TLC), the reaction mixture was extracted with ethyl acetate (5 × 15 mL). The combined organic layers were successively neutralized with saturated sodium bicarbonate to pH = 7.0 and then washed with brine, dried over Na_2SO_4 and filtered through celite. Solvent was removed with evaperator *in vacu* to provide **2** as yellow oil (11.52 g, 95%). TLC (Hexane:EtOAc=3:1): R_f = 0.25; IR ($CDCl_3$) υ_{max} = 2989, 1736, 1053, 839, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.20-4.25 (m, 1H), 4.13-4.17 (m, 1H), 4.05-4.09 (m, 1H), 3.95-3.99 (m, 1H), 3.63-3.66 (m, 1H), 3.48 (s, 2H), 1.30 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.2, 113.2, 109.9, 73.0, 66.5, 65.8, 26.5, 25.2, 24.5; HRMS (ESI) Calcd. for $C_9H_{13}N_2O_5$ $[M+H]^+$: 229.0824, found: 229.0822.



2 (Glyceroacetonide-Oxyma) **3** (Glycero-Oxyma)

Cyano-hydroxyimino-acetic acid 2,3-dihydroxy-propyl ester (3)

AcOH (80%, 2ml) was added to compound **2** (114 mg, 0.5 mmol) in a round bottom flask. The resulting solution was stirred for 30 minutes. All volatiles were removed *in vacuo*, the crude product was portioned between H_2O (2 ml) and EtOAc (5 ml). Wash the aqueous layer with EtOAc (5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4. Concentration of the dry solution gave **3** as yellow oil (92 mg, 97%). TLC ($CHCl_3$:MeOH=1:2): R_f = 0.5; IR ($CHCl_3$) υ_{max} = 3343, 1734, 1305, 1063, 763 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.38-4.51 (m, 3H), 4.14-4.20 (m, 1H), 3.88-3.91 (m, 1H), 1.49 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 158.9, 125.8, 110.0, 107.8, 69.4, 67.2, 62.4; HRMS (ESI) Calcd. for $C_6H_8N_2O_5$ $[M+H]^+$: 189.0511, found: 189.0516.

Method A

To a stirred solution of N-protected α-amino acid (1.5 eq) and C-protected α-amino acid (1.0 eq) in H_2O (0.2 M) were added sequentially **2** (1.2 eq), EDCI (1.2 eq), and $NaHCO_3$ (3.0 eq) at rt. After the times indicated in **Table 2**, 1 N HCl (2.0 ml for 0.1 mmol C-protected α-amino acid) was added. The solution was extracted with EtOAc (2 × 5 ml for 0.1 mmol C-protected α-amino acid). The combined organic layers were washed with sat. $NaHCO_3$ (2 × 5 ml), H_2O (3 ml), and finally brine (3 ml), and then dried over Na_2SO_4. Concentration of the dry solution gave crude product with high purity.

Method B

To a stirred solution of N-protected α-amino acid (1.5 eq) and C-protected α-amino acid (1.0 eq) in DMF/H_2O (1:2, 0.2 M) were added sequentially **2** (1.2 eq), EDCI (1.2 eq), and $NaHCO_3$ (3.0 eq) at room temperature. After the times indicated in **Table 2**, 1 N HCl (2.0 ml for 0.1 mmol C-protected α-amino acid) was added. The solution was extracted with EtOAc (2 × 5 ml for 0.1 mmol C-protected α-amino acid). The combined organic layers were washed with sat. $NaHCO_3$ (2 × 5 ml), H_2O (3 ml), and finally brine (3 ml), and then dried over Na_2SO_4. Concentration of the dry solution gave crude product with high purity.

Method C

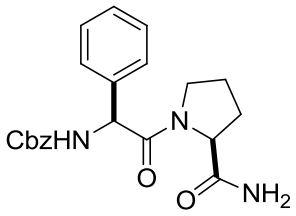
To a stirred solution of N-protected α-amino acid (1.5 eq) and C-protected α-amino acid (1.0 eq) in H_2O (0.2 M) were added sequentially Octyltrimethyl ammonium bromide (2 eq), **2** (1.2 eq), EDCI (1.2 eq), and $NaHCO_3$ (3.0 eq) at room temperature. After the times indicated in **Table 2**, 1 N HCl (2.0 ml for 0.1 mmol C-protected α-amino acid) was added. The solution was extracted with EtOAc (2 × 5 ml for 0.1 mmol C-protected α-amino acid). The combined organic layers were washed with sat. $NaHCO_3$ (2 × 5 ml), H_2O (3 ml), and finally brine (3 ml), and then dried over Na_2SO_4. Concentration of the dry solution gave crude product with high purity.

Syntheses of di- and tri-peptides using EDCI, glyceroacetonide-Oxyme **2**, and $NaHCO_3$ in water-based solvent system.[a]

entry	*N*-protected α-amino acid	*C*-protected α-amino acid	conditions[b]	time (h)	product	yield (%)	*de* (%)
1	Z-L-Tyr-OH	HCl•H-L-Ala-OMe	A	2	Z-L-Tyr-L-Ala-OMe	93	>99
2	Boc-L-Tyr-OH	HCl•H-L-Ala-OMe	A	2	Boc-L-Tyr-L-Ala-OMe	95	>99
3	Boc-L-Val-OH	HCl•H-L-Pro-NH_2	A	2	Boc-L-Val-L-Pro-NH_2	94	>92
4	Fmoc-L-Tyr-OH	HCl•H-L-Ala-OMe	A	2	Fmoc-L-Val-L-Pro-NH_2	95	>99
5	Fmoc-L-Val-OH	HCl•H-L-Pro-NH_2	A	2	Fmoc-L-Val-L-Pro-NH_2	94	>99
6	Fmoc-L-Val-OH	HCl•H-L-Pro-NH_2	A	12	Fmoc-L-Val-L-Pro-NH_2	98	>99
7	Boc-L-Lys($COCF_3$)-OH	HCl•H-L-Pro-NH_2	A	2	Boc-L-Lys($COCF_3$)-L-Pro-NH_2	93	>92
8	Boc-L-Lys($COCF_3$)-OH	HCl•H-L-Ala-NH_2	A	2	Boc-L-Lys($COCF_3$)-L-Ala-OMe	92	>92
9	Boc-L-Val-OH	HCl•H-Gly-OMe	A	2	Boc-L-Val-Gly-OMe	95	>92
10	Z-L-Phg-OH	HCl•H-L-Phe-OMe	A	4	Z-L-Phg-L-Phe-OMe	92	>92
11	Z-L-Phg-OH	HCl•H-L-Phe-O^{t}Bu	A	12	Z-L-Phg-L-Phe-O^{t}Bu	40	>99
12	Z-L-Phg-OH	HCl•H-L-Phe-O^{t}Bu	B	4	Z-L-Phg-L-Phe-O^{t}Bu	90	>99
13	Z-L-Phg-OH	HCl•H-L-Val-O^{t}Bu	C	4	Z-L-Phg-L-Val-O^{t}Bu	90	>99
14	Boc-L-Thr-OH	HCl•H-L-Ala-OMe	A	2	Boc-L-Thr-L-Ala-OMe	92	>92
15	Boc-L-Tyr-OH	HCl•*N*-Me-Gly-OMe[f]	A	2	Boc-L-Tyr-*N*-Me-L-Ala-OMe	90	98
16	Boc-L-Tyr-OH	HCl•*N*-Me-L-Ala-OMe	A	2	Boc-L-Tyr-*N*-Me-L-Ala-OMe	70	>99
17	Boc-L-Tyr-OH	HCl•*N*-Me-L-Ala-OMe	A	6	Boc-L-Tyr-*N*-Me-L-Ala-OMe	92	>99
18	Boc-L-Tyr-OH	HCl•H-L-Pro-OMe	A	2	Boc-L-Tyr-L-Pro-OMe	95	>99
19	Ac-L-Ala-OH[d]	HCl•H-L-Ala-OMe	A	2	Ac-L-Ala-L-Ala-OMe	95	>92
20	Ac-L-Phe-OH[d]	HCl•H-L-Ala-OMe	A	2	Ac-L-Phe-L-Ala-OMe	93	98
21	Ac-L-Tyr-OH[d]	HCl•H-L-Ala-OMe	A	2	Ac-L-Tyr-L-Ala-OMe	93	>99
22	Boc-L-Ala-D-(4-OH)Phg-OH[e]	HCl•H-D-Ala-OMe	A	2	Boc-L-Ala-D-(4-OH)Phg-L-Ala-OMe	95	>92
23	Boc-L-Ala-L-Phe-OH	HCl•H-D-Val-OMe	A	2	Boc-L-Ala-L-Phe-D-Val-OMe	95	>99
24	Boc-L-Ala-L-Phe-OH	HCl•H-D-Ala-OMe	A	2	Boc-L-Ala-L-Phe-D-Ala-OMe	95	>99
25	Boc-L-Ala-L-Phe-OH	HCl•H-Gly-OMe	A	2	Boc-L-Ala-L-Phe-Gly-OMe	95	>99

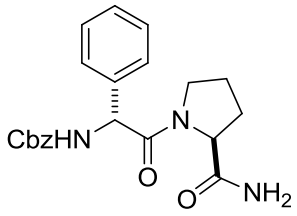
[a] *N*-protected α-amino acid (1.5 equiv), *C*-protected α-amino acid (1.0 eqiv), **2** (1.2 equiv), EDCI (1.2 equiv), $NaHCO_3$ (3 equiv).; [b] A: in H_2O (0.2 M), B: H_2O : DMF = 2 : 1 (0.2 M); C: Octyltrimethylammonium bromide (2 equiv.) in water (0.2 M). [b] *de* was determined via ^{1}H-NMR analyses; [d] 3 equv. of acetylated α-amino acid was used; [e] (4-OH)Phg = 4-hydroxyphenylglycine.; [f] *N*-Methylglycine methyl ester hydrochloride (Sar-OMe).

Z-L-Phg-L-Pro-NH_2



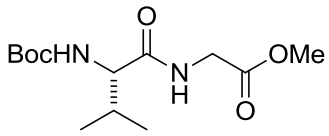
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (EtOAc): R_f = 0.3; $[\alpha]^{22}_D$ = - 43.6 (*c* =1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max}= 3398, 3319, 2955, 2879, 1683, 1643, 1441, 1242, 732, 699 cm^{-1};^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.42 (m, 10H), 6.58 (br s, 1H), 6.19 (d, *J* = 7.0 Hz, 1H), 5.49 (d, *J* = 8.0 Hz, 1H), 5.43 (br s, 1H), 5.09 (q, *J* = 12.5 Hz, 2H), 4.60 (d, *J* = 7.5 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 1H), 3.21-3.24 (m, 1H), 2.31-2.34 (m, 1H), 1.87-1.97 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 169.3, 155.6, 136.6, 136.3, 129.5, 129.3, 128.8, 128.5, 128.1, 128.1, 128.0, 127.8, 67.0, 59.9, 56.9, 47.0, 27.1, 24.8; HRMS (ESI) Calcd. for $C_{21}H_{24}N_3O_4$ $[M+H]^+$: 382.1767, found: 382.1769.

Z-D-Phg-L-Pro-NH_2



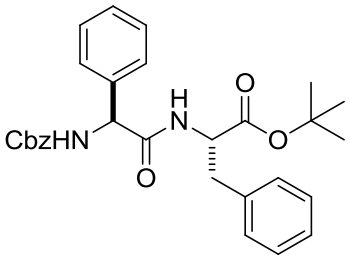
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (EtOAc): R_f = 0.3; $[\alpha]^{22}_D$ = + 43.6 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3316, 2956, 1677, 1647, 1497, 1434, 1056, 699cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.44 (m, 10H), 6.85 (br s, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 5.44 (d, *J* = 6.8 Hz, 1H), 5.34 (br s, 1H), 5.10 (q, *J* = 12.0 Hz, 2H), 4.60 (d, *J* = 6.4 Hz, 1H), 3.79 (m, 1H), 3.21 (q, 1H), 2.36 (q, 1H), 2.02-2.10 (m, 1H), 1.81-1.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 169.8, 155.9, 136.1, 135.4, 129.3, 129.0, 128.5, 128.2, 128.1, 128.0, 67.1, 60.3, 57.6, 46.9, 29.7, 27.9, 24.5; HRMS (ESI) Calcd. for $C_{21}H_{24}N_3O_4$ $[M+H]^+$: 382.1767, found: 382.1768.

Boc-L-Val-L-Gly-OMe



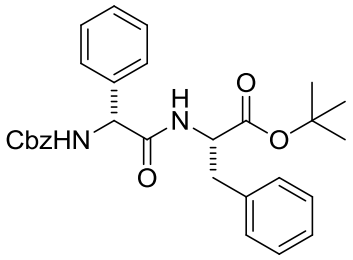
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane : EtOAc = 1 : 1): R_f = 0.3; $[\alpha]^{22}_D$ = + 216.3 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3318, 2967, 1750, 1687, 1657, 1523, 1210, 1167, 907, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.61 (br s, 1H), 5.09 (d, *J* = 7.6 Hz , 1H), 4.05 (q, *J* = 5.2 Hz, 2H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 2.18 (m, 1H), 1.44 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 170.1, 155.9, 80.0, 59.8, 52.4, 41.1, 30.8, 28.3, 19.2, 17.6; HRMS (ESI) Calcd. for $C_{13}H_{25}N_2O_5$ $[M+H]^+$: 289.1763, found: 289.1762.

Z-L-Phg-L-Phe-O^{t}Bu



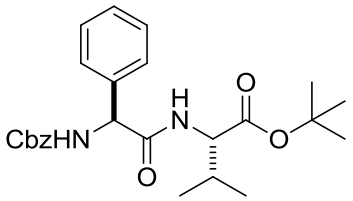
Reaction conducted according to **Method A/B** afforded product as an amorphous solid. TLC (Hexane : EtOAc = 1 : 2): R_f = 0.7; $[\alpha]^{22}_D$ = - 38.3 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3328, 2979, 2936, 1727, 1697, 1653, 1513, 1497, 1367, 1238, 1154, 907, 731, 698 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.28 (m, 13H), 7.12 (d, *J* = 6.4 Hz, 2H), 6.14 (d, *J* = 6.8 Hz, 1H), 6.05 (br s, 1H), 5.17 (d, *J* = 5.2 Hz, 1H), 5.09 (q, *J* = 12.4 Hz, 1H), 4.67 (q, *J* = 6.0 Hz, 2H), 3.04-3.14 (m, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 169.0, 155.6, 137.6, 136.2, 135.8, 129.5, 129.1, 128.6, 128.5, 128.5, 128.2, 127.2, 127.1, 82.6, 67.1, 59.0, 54.0, 37.8, 28.0, 27.9; HRMS (ESI) Calcd. for $C_{29}H_{33}N_2O_5$ $[M+H]^+$: 489.2389, found: 489.2387.

Z-D-Phg-L-Phe-O^{t}Bu



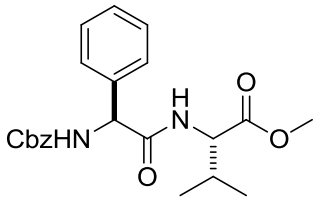
Reaction conducted according to **Method A/B** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:2): R_f = 0.7; $[\alpha]^{22}_D$ = + 38.3 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3352, 3031, 2978, 1726, 1698, 1654, 1515, 1240, 1160, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.39 (m, 10H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 2H), 6.69 (d, *J* = 4.4 Hz, 2H), 6.20 (br s, 1H), 6.09 (d, *J* = 4.0 Hz, 1H), 5.19 (s, 1H), 5.07 (q, *J* = 7.5 Hz, 2H), 4.77 (q, *J* = 5.5 Hz, 1H), 2.95 (s, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 168.7, 155.5, 138.1, 136.2, 135.3, 129.4, 129.2, 128.6, 128.5, 128.3, 128.1, 127.3, 126.8, 82.8, 67.0, 66.9, 58.9, 53.4, 37.6, 28.0; HRMS (ESI) Calcd. for $C_{29}H_{33}N_2O_5$ $[M+H]^+$: 489.2389, found: 489.2388.

Z-L-Phg-L-Val-O^{t}Bu



Reaction conducted according to **Method C** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:2): R_f = 0.8; $[\alpha]^{22}_D$ = + 165.3 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3316, 2968, 2934, 2876, 1727, 1661, 1531, 1498, 1238, 1154, 1141, 732, 697 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.41 (m, 10H), 6.12 (d, *J* = 7.6 Hz, 2H), 5.26 (d, *J* = 7.2 Hz, 1H), 5.11 (q, *J* = 12.4 Hz, 2H), 4.37 (q, *J* = 3.6 Hz, 1H), 2.12-2.16 (m, 1H), 1.37 (s, 9H), 0.94 (d, *J* = 7.2 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 169.4, 155.6, 137.8, 136.2, 129.1, 128.6, 128.5, 128.1, 127.3, 67.1, 59.0, 58.0, 31.5, 27.9, 18.8, 17.8; HRMS (ESI) Calcd. for $C_{29}H_{33}N_2O_5$ $[M+H]^+$: 489.2389, found: 489.2388.

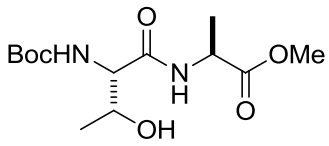
Z-L-Phg-L-Val-OMe



Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:2): R_f = 0.6; $[\alpha]^{22}_D$ = + 28.7 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3317, 2964, 1739, 1707, 1662, 1529, 1238, 1212, 697 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.37 (m, 10H), 6.13 (d, *J* = 8.4 Hz, 1H), 6.05 (br s, 2H), 5.24 (br s, 1H), 5.08 (q, *J* = 12.4 Hz, 2H), 4.48 (q, *J* = 4.8 Hz, 1H), 3.62 (s, 3H), 2.12-2.16 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7,

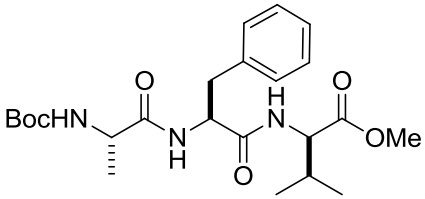
169.7, 155.7, 137.5, 136.2, 129.1, 128.7, 128.5, 128.2, 128.1, 127.3, 67.1, 59.0, 57.5, 52.2, 31.3, 18.9, 17.7; HRMS (ESI) Calcd. for $C_{22}H_{27}N_2O_5$ $[M+H]^+$: 399.1920, found: 399.1924.

Boc-L-Thr-L-Ala-OMe



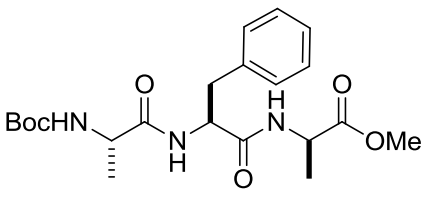
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:5): R_f = 0.3; $[\alpha]^{22}_D$ = + 8.6 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3316, 2979, 2936, 1743, 1658, 1515, 1367, 1162, 1057 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (d, *J* = 6.8 Hz, 1H), 5.53 (d, *J* = 8.0 Hz, 1H), 4.51-4.58 (m, 1H), 4.31 (q, *J* = 1.6 Hz, 1H), 4.10 (q, *J* = 1.2 Hz, 1H), 3.73 (s, 3H), 3.42 (br s, 1H), 1.44 (s, 9H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 171.1, 156.4, 80.4, 67.0, 57.9, 52.6, 48.1, 28.5, 28.3, 28.1, 18.0, 18.0; HRMS (ESI) Calcd. for $C_{13}H_{25}N_2O_6$ $[M+H]^+$: 305.1712, found: 305.1716.

Boc-L-Ala-L-Phe-D-Val-OMe



To a stirred solution of Boc-L-Ala-L-Phe-OBn (85.2 mg, 0.2 mmol) in MeOH (1.0 ml) was added 10% Pd/C, then a H_2 balloon was charged. The suspension was stirred for 2 hours, then filtered on celite and eluted with MeOH. The filtrate was concentrated to afford the acid, Boc-L-Ala-L-Phe-OH, as a colorless solid. Without further purification, the acid reacted with D-Val-OMe hydrochloride (50.2mg, 0.3 mmol)) to provide the title compound (85.3 mg) as an amorphous solid according to **Method A**: TLC (Hexane:EtOAc=1:2): R_f = 0.4; $[\alpha]^{22}_D$ = + 2.6 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3288, 2967, 2929, 1743, 1717, 1646, 1547, 1168, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.30 (m, 5H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.38 (br s, 1H), 4.93 (br s, 1H), 4.66 (q, *J* = 7.2 Hz, 1H), 4.43 (q, *J* = 4.8 Hz, 1H), 4.12 (t, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 3.10 (d, *J* = 6.8 Hz, 1H), 2.06-2.16 (m, 1H), 1.43 (s, 9H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 171.7, 170.5, 136.4, 129.3, 128.7, 127.1, 80.3, 57.4, 54.4, 52.1, 50.3, 37.7, 31.1, 29.7, 28.3, 18.9, 18.2, 17.8; HRMS (ESI) Calcd. for $C_{23}H_{36}N_3O_6$ $[M+H]^+$: 450.2604, found: 450.2601.

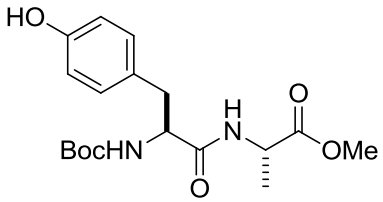
Boc-L-Ala-L-Phe-D-Ala-OMe



To a stirred solution of Boc-L-Ala-L-Phe-OBn (85.0 mg, 0.2 mmol) in MeOH (1.0 ml) was added 10% Pd/C under N_2, then a H_2 balloon was charged. The suspension was stirred for 2 hours, then filtered on celite pad

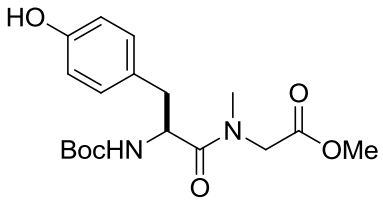
and washed with MeOH. The filtrate was concentrated to afford the acid, Boc-L-Ala-L-Phe-OH, as a colorless solid. Without further purification, the acid reacted with D-Ala-OMe hydrochloride (41.7 mg, 0.3 mmol)) according to **Method A** to provide the title compound (79.9 mg, 95%) as an amorphous solid. TLC (hexanes:EtOAc=1:2): Rf = 0.3; $[\alpha]^{22}_{D}$ = + 7.2 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3285, 2980, 2932, 1747, 1716, 1697, 1645, 550, 1164, 733, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.29 (m, 5H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.59 (br s, 1H), 4.99 (br s, 1H), 4.69 (q, *J* = 6.8 Hz, 1H), 4.50 (q, *J* = 7.2 Hz, 1H), 4.08 (m, 1H), 3.73 (s, 3H), 3.09-3.18 (m, 1H), 1.44 (s, 9H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 172.6, 170.1, 136.4, 129.4, 128.7, 127.1, 80.3, 54.1, 52.4, 48.2, 37.8, 28.3, 18.0; HRMS (ESI) Calcd. for $C_{21}H_{32}N_3O_6$ $[M+H]^+$: 422.2291, found: 422.2294.

Boc-L-Tyr-L-Ala-OMe



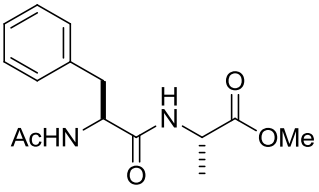
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:3): R_f = 0.3; $[\alpha]^{22}_{D}$ = + 0.9 (*c* = 1.00, $CHCl_3$); IR (thin film) υ_{max} = cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.04 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 7.2 Hz, 1H), 6.13 (br s, 1H), 5.08 (br s, 1H), 4.51 (m, 1H), 4.30 (br s, 1H), 3.72 (s, 3H), 2.94-3.04 (m, 2H), 1.43 (s, 9H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 171.2, 155.7, 155.3, 130.7, 128.2, 115.8, 80.6, 56.0, 52.7, 48.4, 37.8, 28.5, 18.6; HRMS (ESI) Calcd. for $C_{18}H_{27}N_2O_6$ $[M+H]^+$: 367.1869, found: 367.1874.

Boc-L-Tyr-L-Sar-OMe



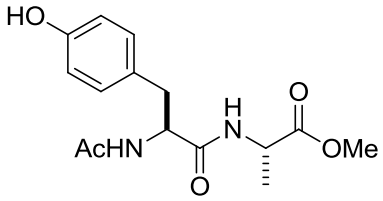
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:3): R_f = 0.3; $[\alpha]^{22}_{D}$ = +12.0 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3322, 2980, 1750, 1703, 1644, 1517, 1367, 1218, 1168, 828 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.02 (br s, 1H), 5.35 (d, *J* = 8.4 Hz, 2H), 4.85 (q, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 2.85-3.00 (m, 1H), 2.92 (s, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 169.5, 155.4, 155.2, 130.9, 130.7, 127.9, 115.5, 115.5, 80.1, 52.7, 52.4, 49.8, 39.1, 38.8, 36.5, 28.5; HRMS (ESI) Calcd. for $C_{18}H_{27}N_2O_6$ $[M+H]^+$: 367.4166, found: 367.4169.

Ac-L-Phe-L-Ala-OMe



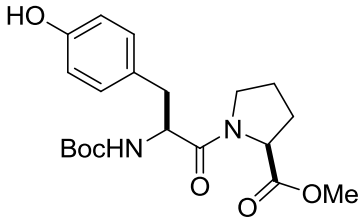
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:3): R_f = 0.3; $[\alpha]^{22}_D$ = + 22.0 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3260, 3073, 2955, 1760, 1729, 1674, 1641, 1559, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.32 (m, 5H), 6.45 (d, *J* = 6.8 Hz, 1H), 6.29 (d, *J* = 7.6 Hz, 1H), 4.70 (q, *J* = 7.2 Hz, 1H), 4.44-4.49 (m, 1H), 3.70 (s, 3H), 2.98-3.11 (m, 2H), 1.98 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 172.7, 170.5, 170.3, 170.0, 136.6, 136.4, 129.3, 129.3, 128.7, 128.6, 127.0, 54.4, 54.3, 52.5, 48.2, 47.9, 38.7, 38.5, 23.2, 18.2, 17.9; HRMS (ESI) Calcd. for $C_{15}H_{21}N_2O_4$ $[M+H]^+$: 293.1501, found: 293.1504.

Ac-L-Tyr-L-Ala-OMe



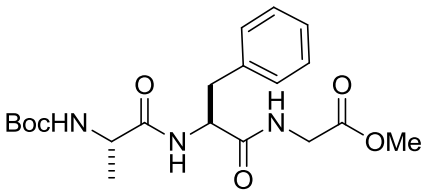
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:4): R_f = 0.3; $[\alpha]^{22}_D$ = + 45.3 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3288, 3018, 2954, 2851, 1740, 1641, 1516, 1451, 1223, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (dd, *J* = 1.2, 7.6 Hz, 2H), 6.67 (dd, *J* = 1.2, 7.6 Hz, 2H), 4.47-4.50 (m, 1H), 4.32-4.40 (m, 1H), 3.65 (s, 3H), 2.90 (dd, *J* = 6.0, 13.6 Hz, 1H), 2.80 (dd, *J* = 6.0, 13.6 Hz, 1H), 1.87 (s, 3H), 1.30 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$-MeOD = 10:1, 100 MHz) δ 174.4, 172.7, 172.4, 157.0, 131.7, 128.6, 116.7, 55.8, 55.7, 53.8, 49.5, 49.3, 39.0, 38.8, 24.0, 24.0, 18.9, 18.7; HRMS (ESI) Calcd. for $C_{15}H_{21}N_2O_5$ $[M+H]^+$: 309.1450, found: 309.1452.

Boc-L-Tyr-L-Pro-OMe



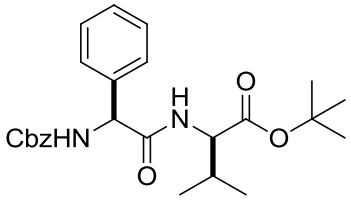
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:4): R_f = 0.35; $[\alpha]^{22}_D$ = + 65.3 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3318, 2978, 2933, 2884, 1744, 1696, 1637, 1516, 1448, 1367, 1169, 732 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.46 (s, 1H), 5.29 (d, *J* = 8.8 Hz, 1H), 4.63 (q, *J* = 6.4 Hz, 1H), 4.52 (dd, *J* = 4.0, 8.0 Hz, 1H), 3.74 (s, 3H), 3.28-3.36 (m, 1H), 3.02 (dd, *J* = 6.4, 13.6 Hz, 1H), 2.90 (dd, *J* = 6.4, 13.6 Hz, 3H), 2.15-2.21 (m, 1H), 1.91-1.99 (m, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4, 170.9, 155.4, 155.2, 130.8, 127.4, 115.4, 79.9, 59.0, 53.3, 52.3, 46.9, 38.0, 29.0, 28.3, 24.9; HRMS (ESI) Calcd. for $C_{20}H_{29}N_2O_6$ $[M+H]^+$: 393.2025, found: 393.2022.

Boc-L-Ala-L-Phe-Gly-OMe



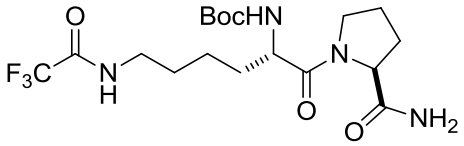
To a stirred solution of Boc-L-Ala-L-Phe-OBn (85.3 mg, 0.2 mmol) in MeOH (1.0 ml) was added 10% Pd/C, then a H_2 balloon was charged. The suspension was stirred for 2 hours, then filtered on celite and eluted with MeOH. The filtrate was concentrated to afford the acid, Boc-L-Ala-L-Phe-OH, as a colorless solid. Without further purification, the acid reacted with D-Gly-OMe hydrochloride (37.5 mg, 0.3 mmol) to provide the title compound according to **Method A** to afford product (77.6 mg) as an amorphous solid. TLC (Hexane:EtOAc=1:2): R_f = 0.25; $[\alpha]^{22}_D$ = (*c* =, $CHCl_3$); IR (thin film) υ_{max} = cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.29 (m, 5H), 6.98 (br s, 1H), 6.70 (d, 1H), 4.99 (br s, *J* = 8.4 Hz, 1H), 5.08 (d, *J* = 6.4 Hz, 1H), 4.77 (q, *J* = 7.2 Hz, 1H), 4.01-4.13 (m, 2H), 3.90 (d, *J* = 5.2 Hz, 1H), 3.74 (s, 3H), 3.09-3.22 (m, 2H), 1.43 (s, 9H), 1.25 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 171.1, 169.9, 155.7, 136.5, 129.4, 129.3, 128.7, 128.6, 127.0, 80.4, 54.0, 52.3, 50.6, 41.2, 37.5, 28.3, 17.9; HRMS (ESI) Calcd. for $C_{20}H_{30}N_3O_6$ $[M+H]^+$: 408.2134, found: 408.2130.

Z-D-Phg-L-Val-O^{t}Bu



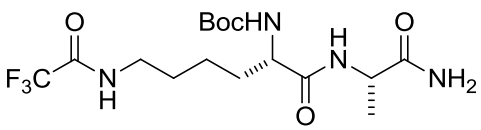
Reaction conducted according to **Method C** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:2): R_f = 0.8; $[\alpha]^{22}_D$ = -165.3 (*c* =1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3325, 2967, 2934, 2875, 1725, 1659,1497,1228, 1152, 1138,1053, 909, 728, 695 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.39 (m, 10H), 6.20 (br s, 2H), 6.11 (d, *J* = 8.4 Hz, 1H), 5.25 (d, *J* = 4.4 Hz, 1H), 5.10 (q, *J* = 12.4 Hz, 2H), 4.44 (dd, *J* = 4.4, 8.8 Hz, 1H), 2.03-2.07 (m, 1H), 1.48 (s, 9H), 0.70 (d, *J* = 6.8 Hz, 1H), 0.66 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 169.3, 155.5, 138.5, 136.2, 129.1, 128.6, 128.5, 128.1, 127.2, 82.4, 67.0, 59.1, 57.4, 31.5, 28.0, 18.6, 17.1; HRMS (ESI) Calcd. for $C_{29}H_{33}N_2O_5$ $[M+H]^+$: 489.2389, found: 489.2392.

Boc-L-Lys-L-Pro-NH$_2$



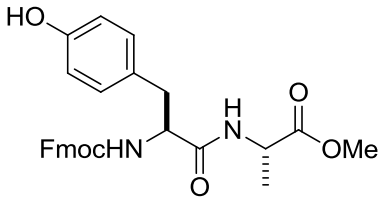
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:5): R_f = 0.3; $[\alpha]^{22}_D$ = + 5.0 (*c* = 1.00, $CHCl_3$); IR ($CHCl_3$) υ_{max} = 3302, 2978, 1687, 1641, 1447, 1161 cm^{-1};^1H NMR (CD_3OD, 500 MHz) δ 4.44 (d, *J* = 4.5 Hz, 1H), 4.33 (s, 1H), 3.83 (s, 1H), 3.67 (s, 1H), 2.23 (d, *J* = 5.0 Hz, 1H), 2.09 (t, *J* = 6.0 Hz, 1H), 1.95-2.00 (m, 3H), 1.79 (s, 1H), 1.57-1.64 (m, 4H), 1.43-1.45 (m, 14H); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.6, 172.2, 157.4, 156.6, 117.3, 115.0, 79.2, 59.9, 52.2, 39.1, 30.6, 29.3, 28.1, 27.3, 24.6, 22.5; HRMS (ESI) Calcd. for $C_{18}H_{30}N_4O_5$ $[M+H]^+$: 439.2168, found: 439.2169.

Boc-L-Lys-L-Ala-NH$_2$



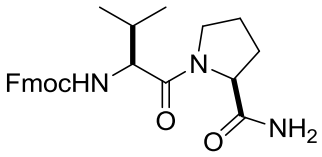
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:5): R_f = 0.3; $[\alpha]^{22}_D$ = + 13.3 (*c* = 1.00, $CHCl_3$); IR ($CHCl_3$) υ_{max} = 3308, 2981, 1744, 1659, 1517, 1227, 1163 cm^{-1};^{1}H NMR (CD_3OD, 500 MHz) δ 4.37 (s, 1H), 4.00 (s, 1H), 1.79 (s, 1H), 1.60 (s, 3H), 1.46 (s, 12H), 1.38 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.0, 173.5, 157.7, 156.7, 117.3, 79.4, 54.8, 48.5, 39.1, 31.2, 28.1, 27.3, 22.7, 16.9; HRMS (ESI) Calcd. for $C_{16}H_{28}F_3N_4O_5$ $[M+H]^+$: 413.2012, found: 413.2014.

Fmoc-L-Tyr-L-Ala-OMe



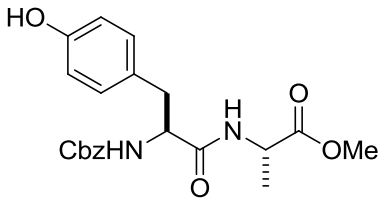
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:2): R_f = 0.6; $[\alpha]^{22}_D$ = +13.7 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3301, 3065, 2925, 2851, 1703, 1660, 1516, 1450, 1227, 759, 740 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 6.0 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.30-7.33 (m, 2H), 7.05 (d, *J* = 6.8 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.24 (s, 1H), 5.34 (d, *J* = 5.6 Hz, 1H), 5.06 (d, *J* = 2.0 Hz, 1H), 4.42-4.52 (m, 2H), 4.33-4.38 (m, 1H), 4.20 (t, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 3.06 (dd, *J* = 8.4 Hz, 1H), 2.95 (dd, *J* = 8.4 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ172.8, 170.3, 154.8, 143.8, 143.7, 141.3, 130.6, 128.2, 127.8, 127.1, 125.0, 120.0, 115.6, 67.1, 56.2, 52.6, 48.2, 47.1, 37.8, 29.7, 18.4; HRMS (ESI) Calcd. for $C_{28}H_{29}N_2O_6$ $[M+H]^+$: 489.2025, found: 489.2023.

Fmoc-L-Val-L-Pro-NH_2



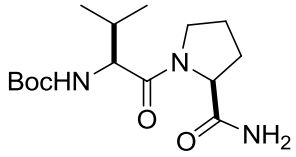
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:1): R_f = 0.6; $[\alpha]^{22}_D$ = + 18.4(*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3320, 2962, 1707, 1646, 1498, 1447, 1238, 1054, 908, 738, 699 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.30-7.34 (m, 2H), 5.24 (d, *J* = 8.8 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 2H), 4.36 (dd, *J* = 4.8, 9.2 Hz, 1H), 4.24 (t, *J* = 6.8 Hz, 1H), 2.22-2.29 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 143.9, 141.6, 128.0, 127.3, 125.3, 120.2, 67.4, 58.9, 47.4, 31.2, 19.2, 17.7; HRMS (ESI) Calcd. for $C_{25}H_{30}N_3O_4$ $[M+H]^+$: 436.2236, found: 436.2233.

Z-L-Tyr-L-Ala-OMe



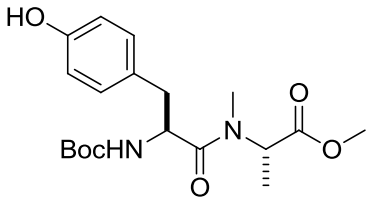
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:5): R_f = 0.3; $[\alpha]^{22}_D$ = + 90.9 (*c* = 1.00, $CHCl_3$); IR ($CHCl_3$) υ_{max} = 3320, 3030, 2953, 1697, 1654, 1516,1450, 1216, 753cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.26-7.35 (m, 5H), 7.06-7.10 (m, 2H), 6.69-6.73 (m, 2H), 5.04 (q, *J* = 12.8 Hz, 2H), 4.43 (q, *J* = 7.2 Hz, 1H), 4.436 (dd, *J* = 5.6, 9.2 Hz, 1H), 3.71 (s, 3H), 3.05 (dd, *J* = 5.6, 14.0 Hz, 1H), 2.77 (dd, *J* = 9.2, 14.0 Hz, 1H), 1.39 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.4, 174.1, 158.2, 157.3, 138.2, 131.4, 129.5, 129.1, 128.9, 128.6, 116.2, 67.5, 57.8, 52.8, 38.5, 17.5; HRMS (ESI) Calcd. for $C_{21}H_{25}N_2O_6$ $[M+H]^+$: 401.1712, found: 401.1717.

Boc-L-Val-L-Pro-NH$_2$



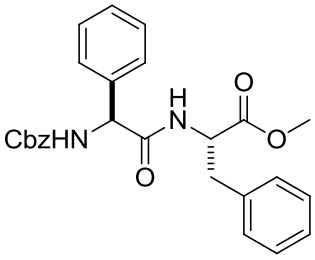
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:3): R_f = 0.3; $[\alpha]^{22}_D$ = + 35.5 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3320, 3030, 2953, 1697, 1654, 1516,1450, 1216, 753cm^{-1}; ^{1}H NMR (MeOD, 500 MHz) δ 6.85 (br s, 1H), 5.48 (br s, 1H), 5.22 (d, *J* = 8.5 Hz, 1H), 4.62 (d, *J* = 8.5 Hz, 1H), 4.29 (t, *J* = 7.0 Hz, 1H), 3.75 (q, *J* = 7.5 Hz, 1H), 3.61 (m, 1H), 2.37-2.40 (q, *J* = 6.0 Hz, 1H), 2.10-2.14 (m, 1H), 1.97-2.04 (m, 2H), 1.88-1.95 (m, 1H), 1.44 (s, 9H), 0.99 (d, *J* = 7.0 Hz, 1H), 0.93 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 172.7, 155.8, 79.7, 59.3, 56.9, 47.6, 31.5, 28.3, 28.3, 26.8, 25.1, 19.4, 17.5; HRMS (ESI) Calcd. for $C_{15}H_{28}N_3O_4$ $[M+H]^+$: 314.2080, found: 314.2078.

Boc-L-Tyr-N-Me-L-Ala-OMe



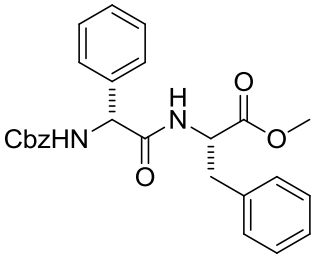
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:3): R_f = 0.4; $[\alpha]^{22}_D$ = - 10.9 (*c* = 1.00, $CHCl_3$); IR (thin film) υ_{max} = 3311, 2979, 1742, 1637, 1516, 1248, 1170, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.52 (s, 1H), 5.33 (d, *J* = 8.8 Hz, 1H), 5.15 (q, *J* = 7.2 Hz, 1H), 4.78-4.83 (m, 1H), 3.72 (s, 3H), 3.00 (dd, *J* = 6.8, 7.2 Hz, 1H), 2.85 (s, 3H), 1.41 (s, 9H), 1.41 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 171.9, 155.2, 154.8, 130.8, 130.6, 127.9, 115.4, 115.3, 79.8, 52.6, 52.3, 51.8, 38.3, 31.4, 28.3, 14.2; HRMS (ESI) Calcd. for $C_{19}H_{29}N_2O_6$ $[M+H]^+$: 381.2025, found: 381.2022.

Z-L-Phg-L-Phe-OMe



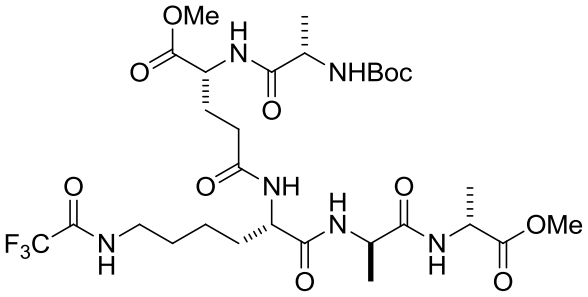
Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane:EtOAc=1:3): R_f = 0.3; $[\alpha]^{22}_D$ = - 35.5 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3320, 3030, 2953, 1697, 1654, 1516,1450, 1216, 753cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.-25-7.35 (m, 13H), 7.05 (d, *J* = 6.4 Hz, 2H), 6.08 (d, *J* = 7.6 Hz, 1H), 5.99 (br s, 1H), 5.15 (d, *J* = 13.6 Hz, 1H), 5.09 (q, *J* = 12.4 Hz, 2H), 4.80 (q, *J* = 5.6 Hz, 1H), 3.65 (s, 3H; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 169.3, 155.6, 137.4, 136.1, 135.4, 129.2, 129.1, 128.7, 128.5, 128.2, 128.1, 127.7, 127.3, 67.1, 59.0, 53.5, 52.4, 37.6; HRMS (ESI) Calcd. for $C_{26}H_{27}N_2O_5$ $[M+H]^+$: 447.1920, found: 447.1977.

Z-D-Phg-L-Phe-OMe



Reaction conducted according to **Method A** afforded product as an amorphous solid. TLC (Hexane : EtOAc = 1 : 3): R_f = 0.3; $[\alpha]^{22}_D$ = + 35.5 (*c* = 1.00, $CHCl_3$); IR ($CDCl_3$) υ_{max} = 3320, 3030, 2953, 1697, 1654, 1516,1450, 1216, 753cm^{-1}; ^{1}H NMR (MeOD, 400 MHz) δ 7.27-7.36 (m, 12H), (m, 2H), 7.07 (d, *J* = 6.4 Hz, 2H), 6.10 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 5.17 (d, *J* = 14.0 Hz, 1H), 5.09 (q, *J* = 12.4 Hz, 1H), 4.82 (q, *J* = 5.6 Hz, 1H), 3.67 (s, 3H), 3.19 (dd, *J* = 5.6, 14.0 Hz, 1H), 3.08 (dd, *J* = 6.0, 14.0 Hz, 1H); ^{13}C NMR (MeOD, 100 MHz) δ 171.2, 169.3, 137.4, 136.2, 135.4, 129.2, 129.1, 128.7, 128.5, 128.2, 128.1, 127.7, 127.3, 67.1, 59.0, 53.5, 52.4, 37.6; HRMS (ESI) Calcd. for $C_{26}H_{27}N_2O_5$ $[M+H]^+$: 447.1920, found: 447.1978.

Boc-L-Ala-D-Glu(OMe)-L-Lys(OTf)-D-Ala-D-Ala-OMe

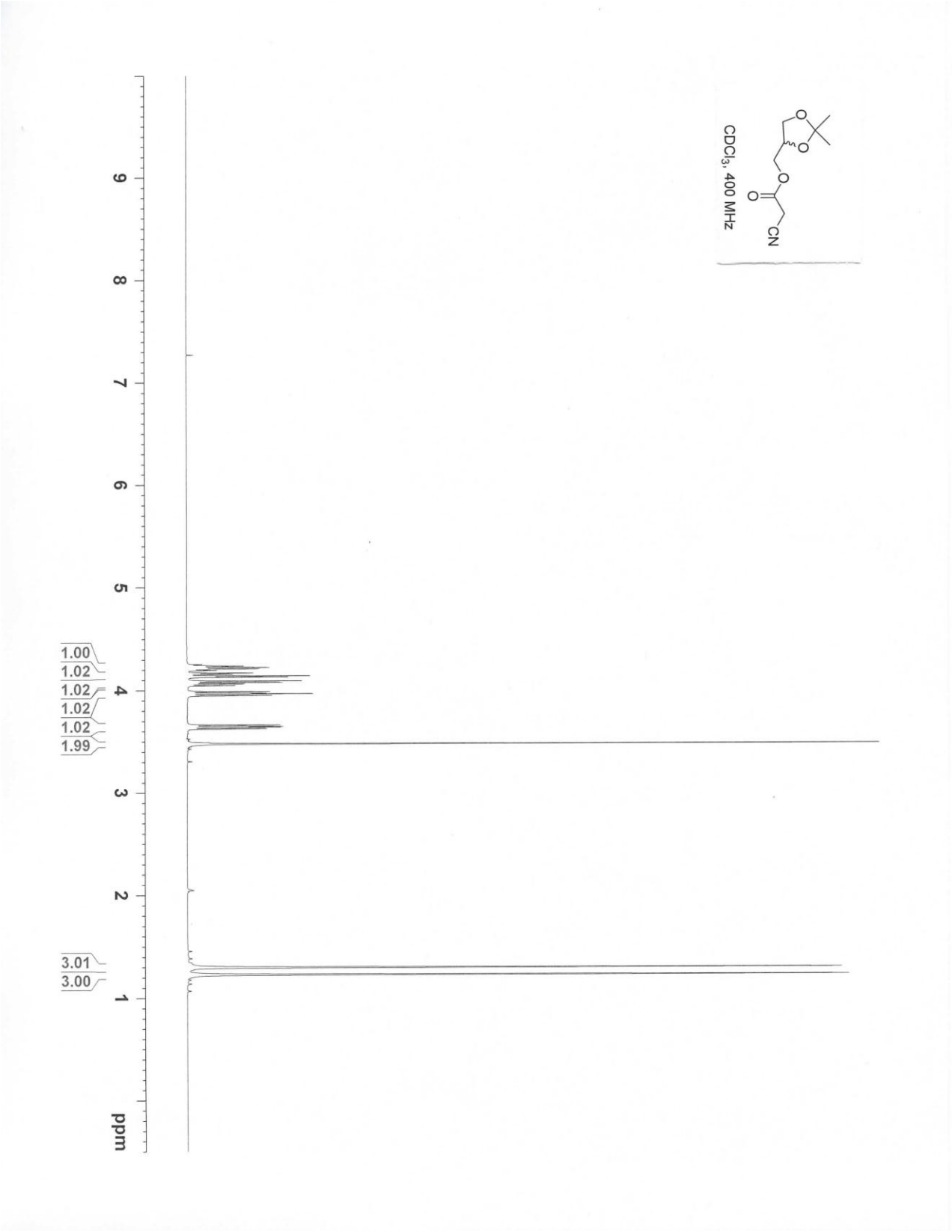


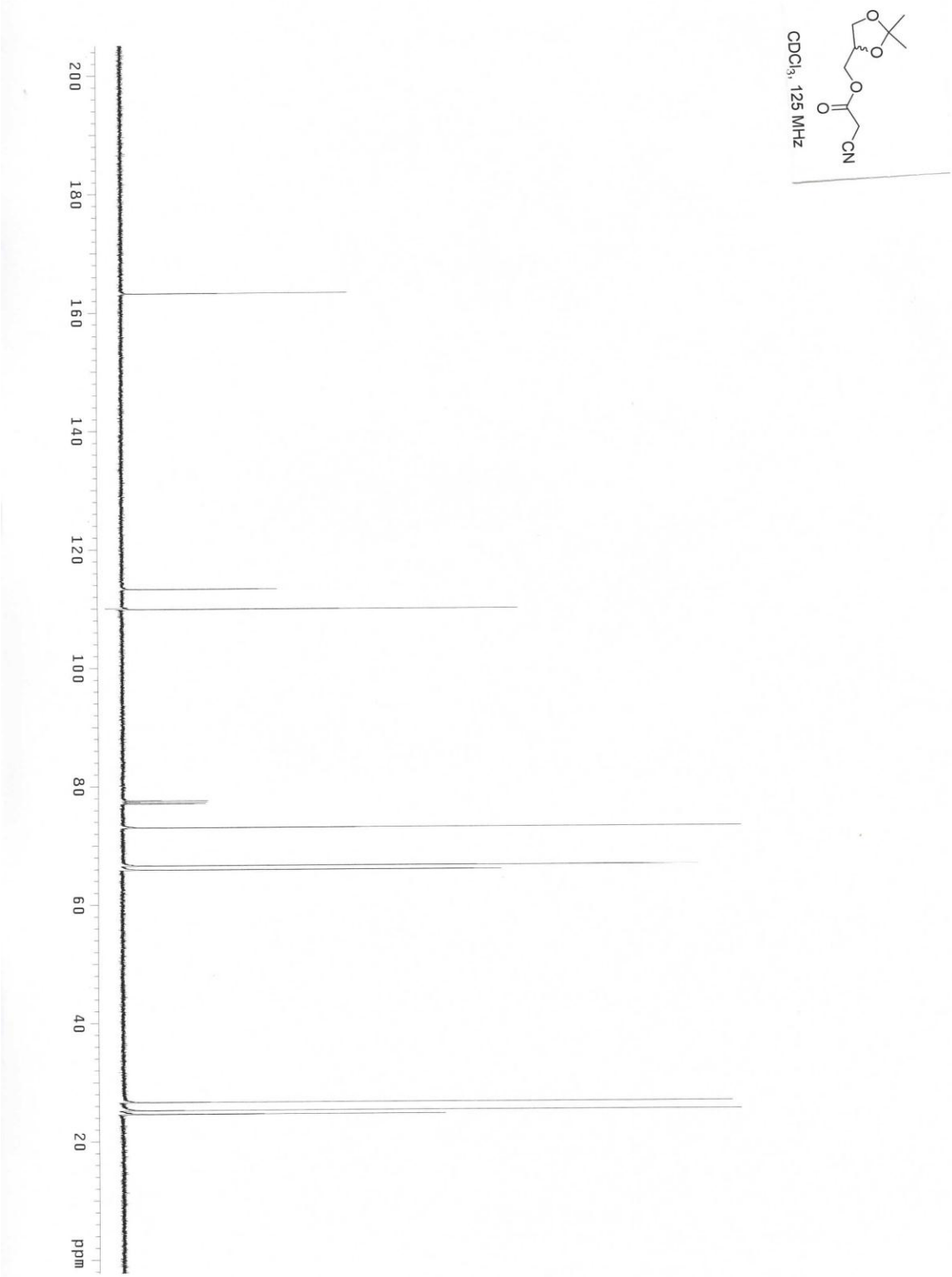
Reaction of Boc-D-Ala-OMe (567.6 mg, 3.0 mmol) and D-Ala-OMe hydrochloride (278.1 mg, 2.0 mmol) was conducted according to **Method A** to afford dipeptide Boc-D-Ala-D-Ala-OMe (521.2 mg, 95%), which was treated with 10.0 ml of 4N HCl/dioxane under Ar atm. After stirring for 15 minutes, the volatiles were removed under *vacuo*. Residual HCl was removed by repeating three times of adding 10.0 ml of diethylether and removing it under *vacuo*. The hydrochloride salt was dried under vacuum for 1h and directly used for the next reaction that was conducted according to **Method A.** Repeating the same deprotection and coupling procedures finally afforded Boc-L-Ala-D-Glu(OMe)-L-Lys(OTf)-D-Ala-D-Ala-OMe (1150.2 mg) as an amorphous solid. TLC (Choloform : MeOH = 4 : 1) R_f = 0.35; $[\alpha]^{22}_D$ = + 53.7 (*c* = 1.00, $CHCl_3$); IR (DMSO-D_6) υ_{max} = 3320, 3030, 2953, 1697, 1654, 1516,1450, 1216, 753cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.40 (t, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 9.2 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.16-4.31 (m, 4H), 3.96-4.03 (m, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 3.14 (q, *J* = 6.0 Hz, 2H), 2.13-2.18 (m, 1H), 1.73-1.83 (m, 1H), 1.54-1.62 (m, 1H),

1.48-1.58 (m, 4H), 1.46 (s, 9H), 1.16-1.37 (m, 12H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.9, 172.8,172.1, 172.0, 171.5, 171.4, 156.3, 155.9, 154.9, 117.4, 114.5, 78.0, 52.7, 51.8, 51.4, 49.5, 47.5, 47.5, 31.3, 31.1, 28.1, 27.9, 27.0, 22.5, 18.4, 17.9, 16.7; HRMS (ESI) Calcd. for $C_{29}H_{48}F_3N_6O_{11}$ $[M+H]^+$: 713.3333, found: 713.3331.

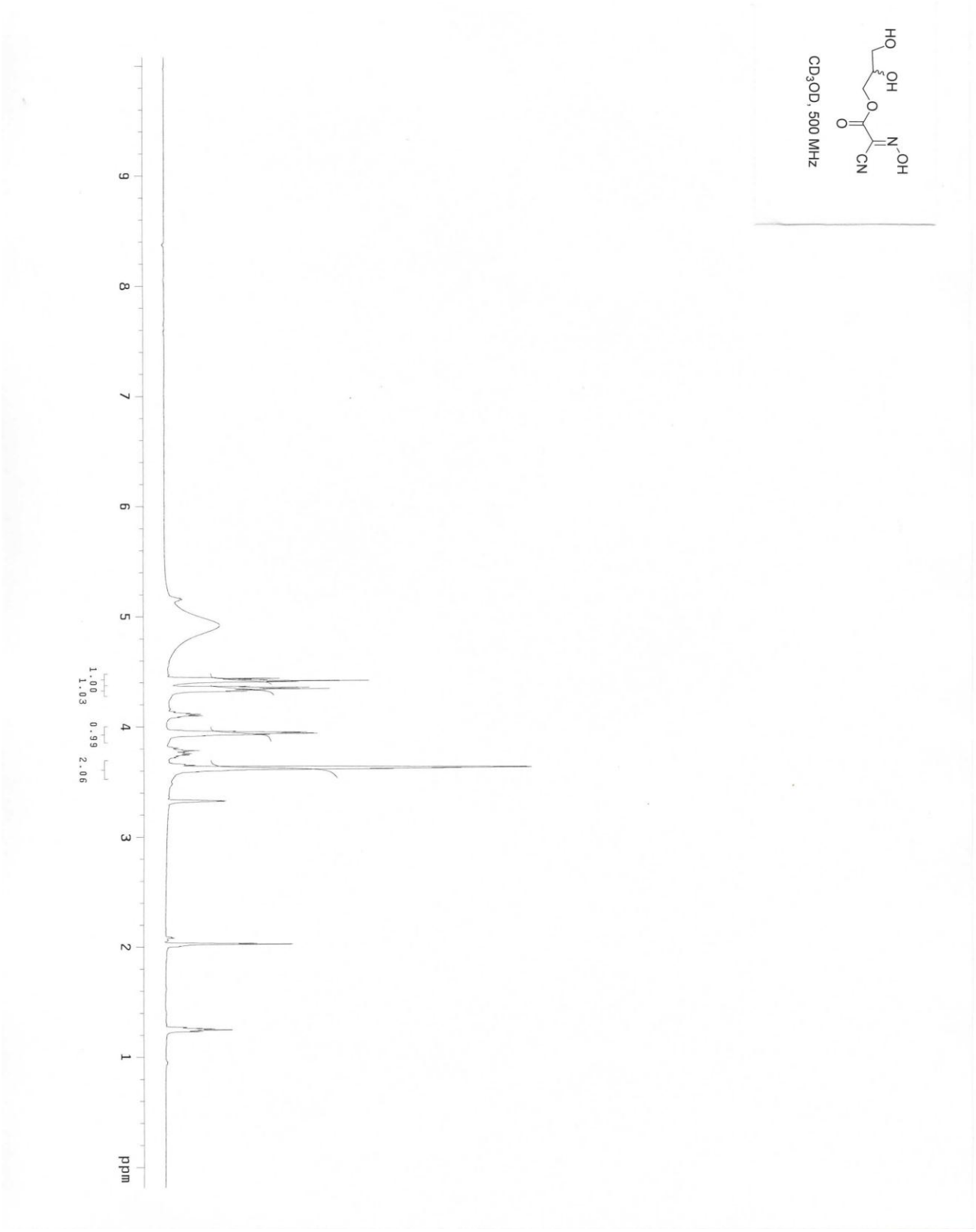
NMR spectra

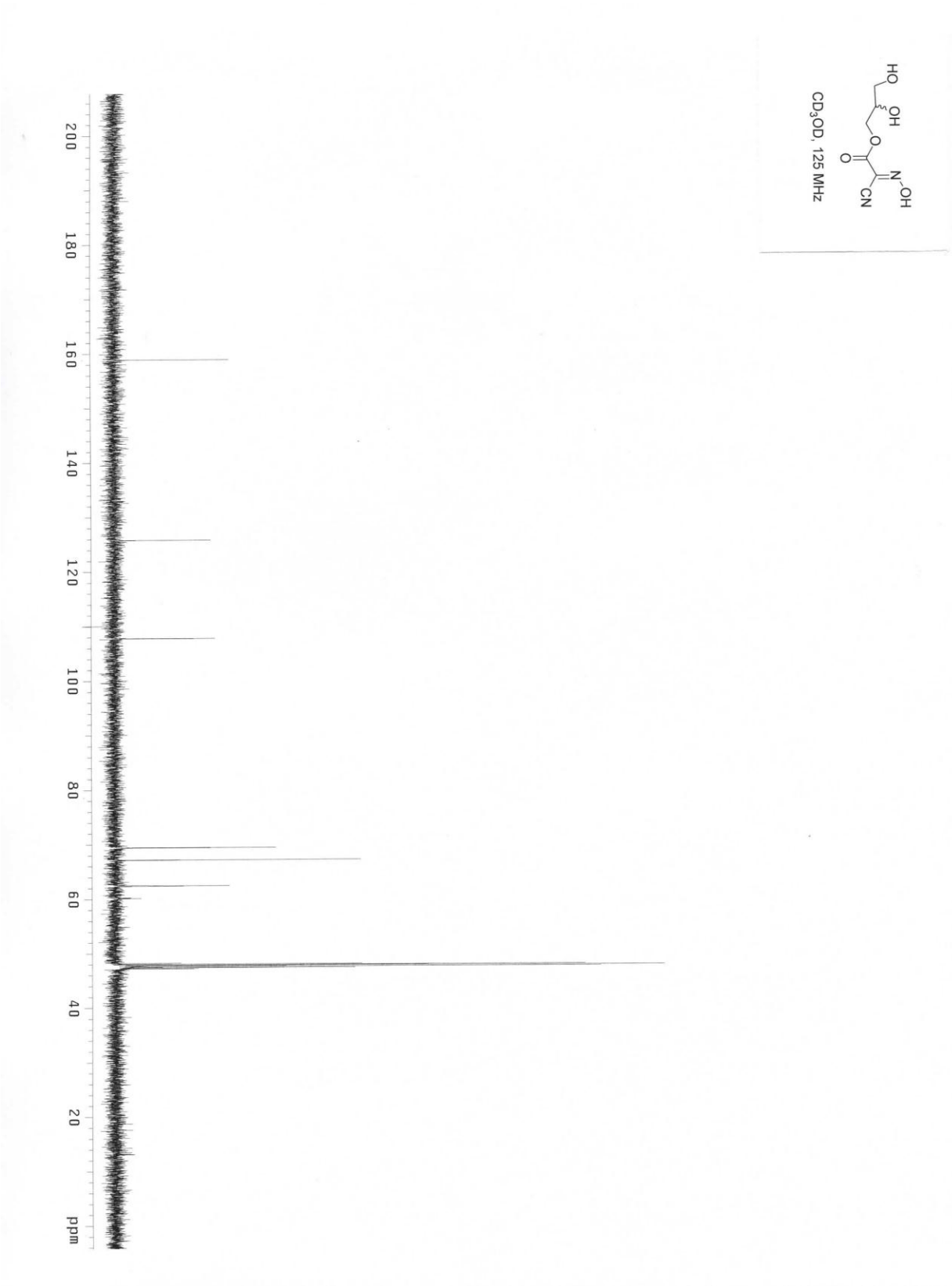
Cyano-acetic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (**6**)



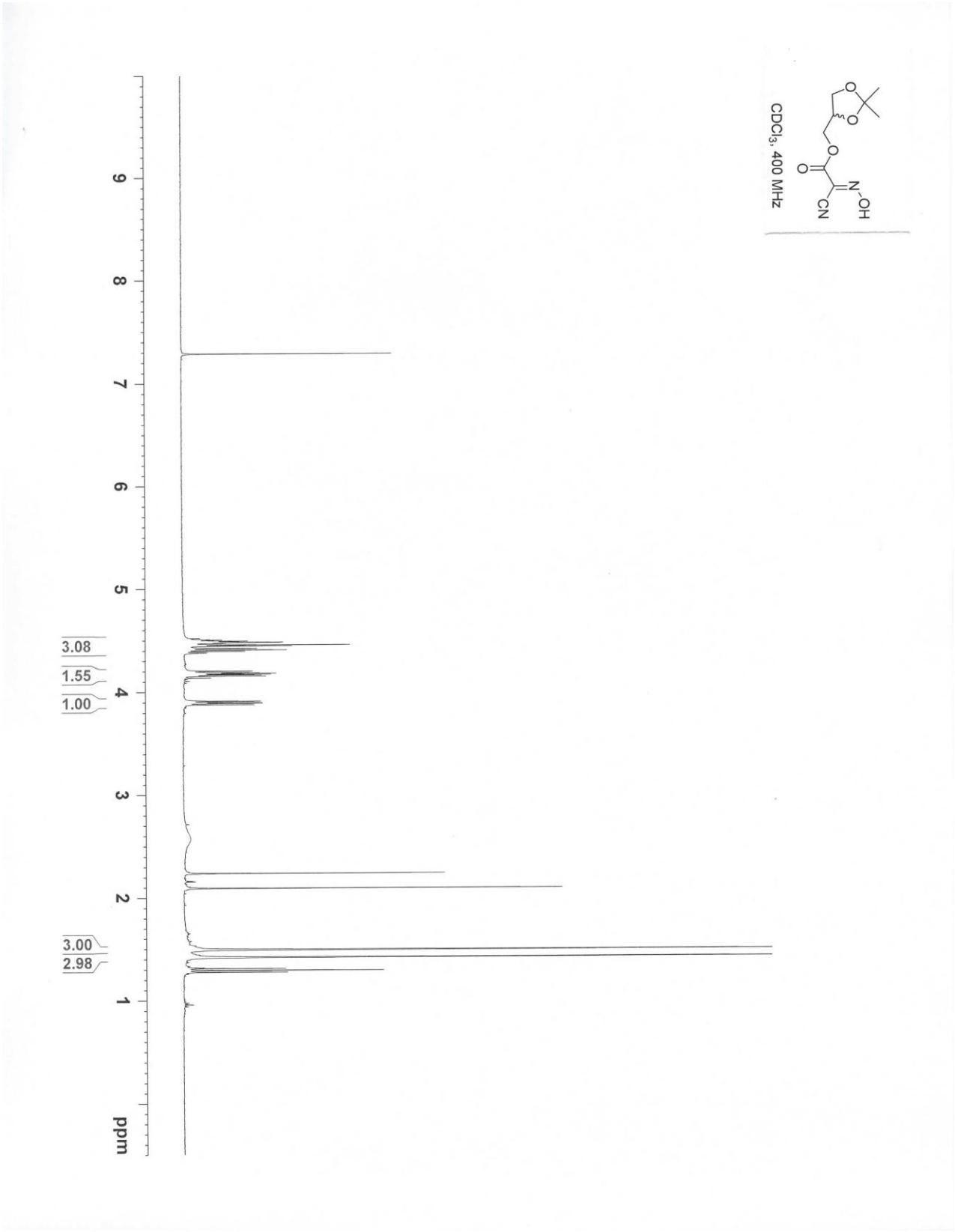

CDCl3, 125 MHz
CN
200
180
160
140
120
100
80
60
40
20
ppm

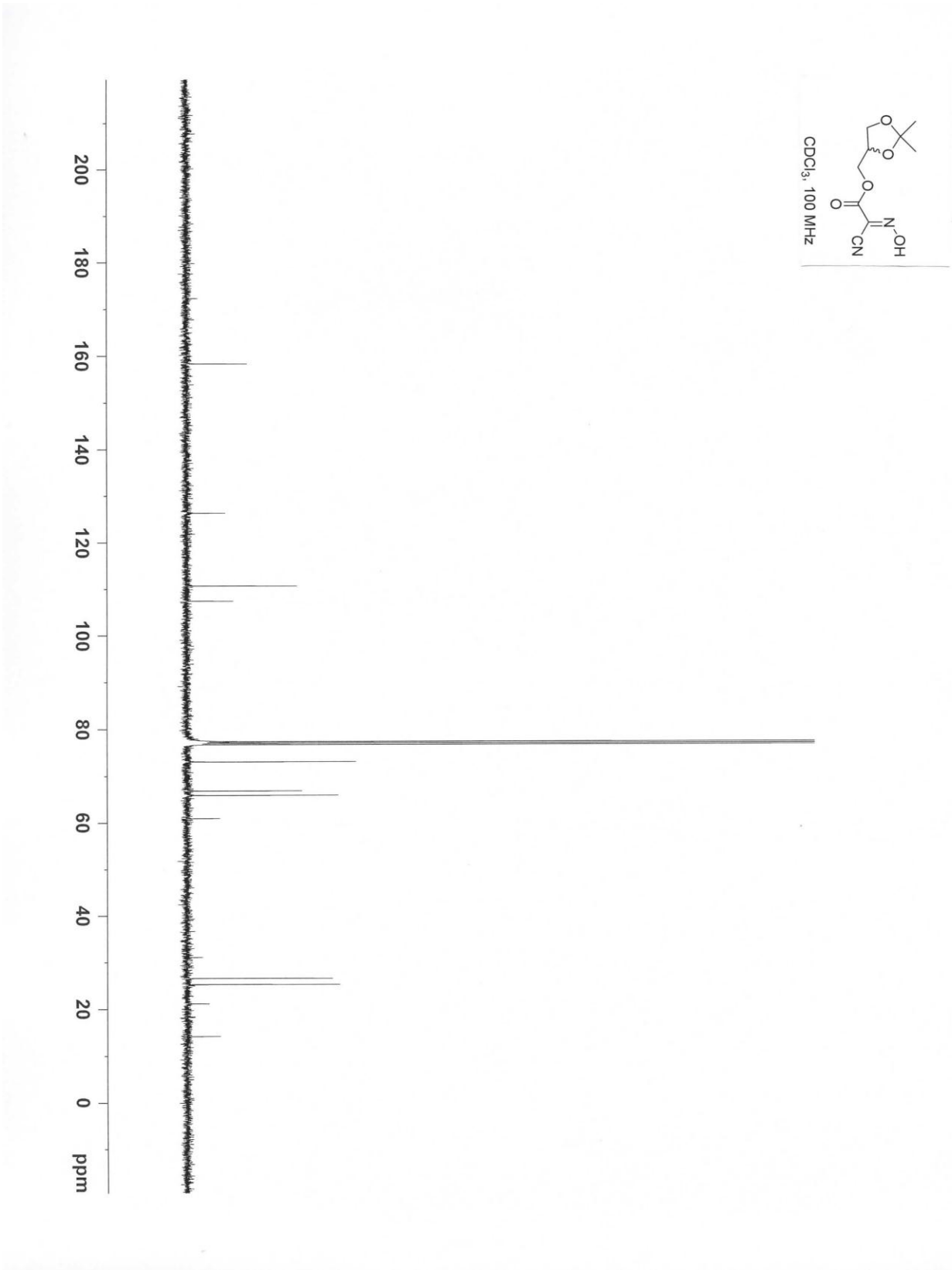
Cyano-hydroxyimino-acetic acid 2,3-dihydroxy-propyl ester (**3**)



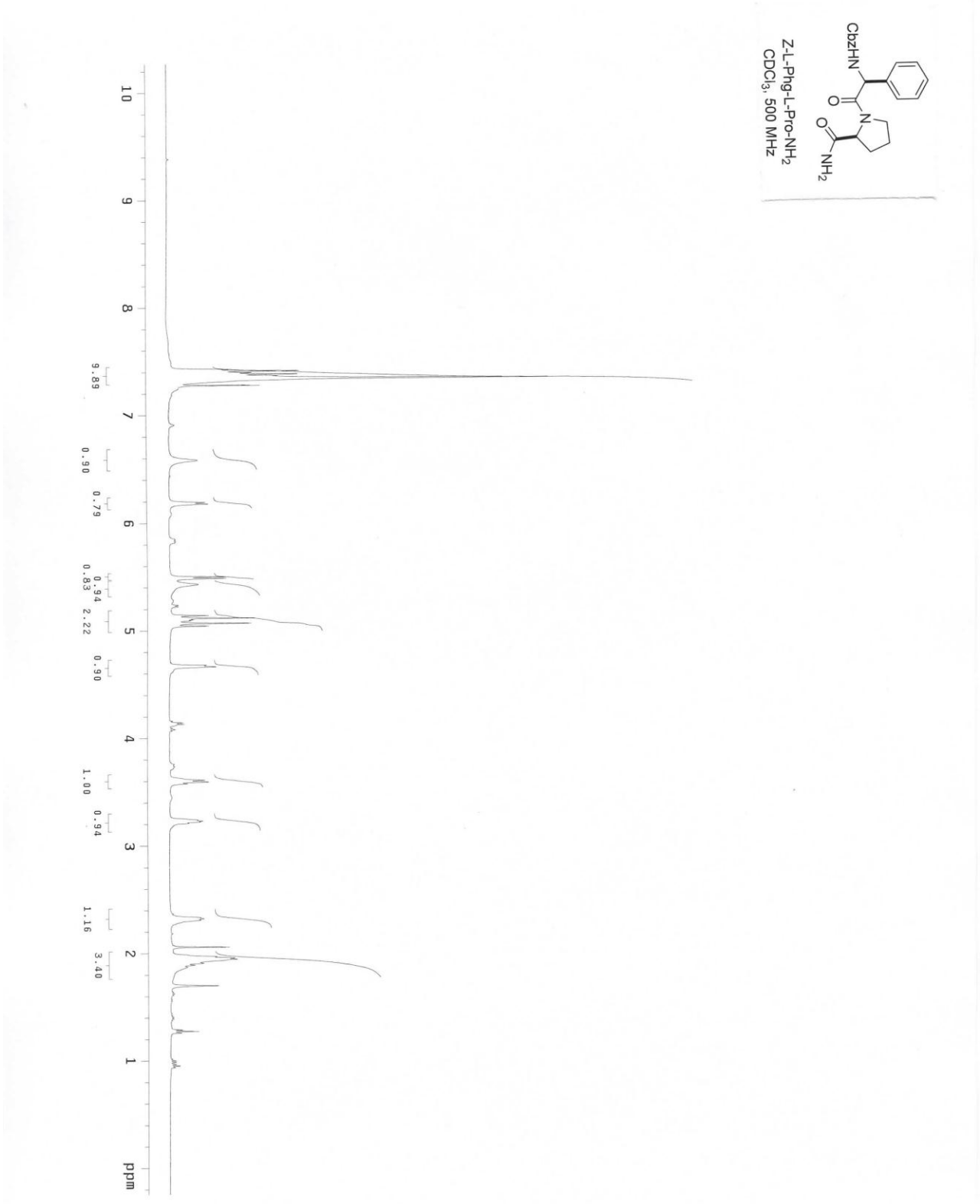

HO
OH
O
O
N
OH
CN
CD3OD, 125 MHz
200
180
160
140
120
100
80
60
40
20
ppm

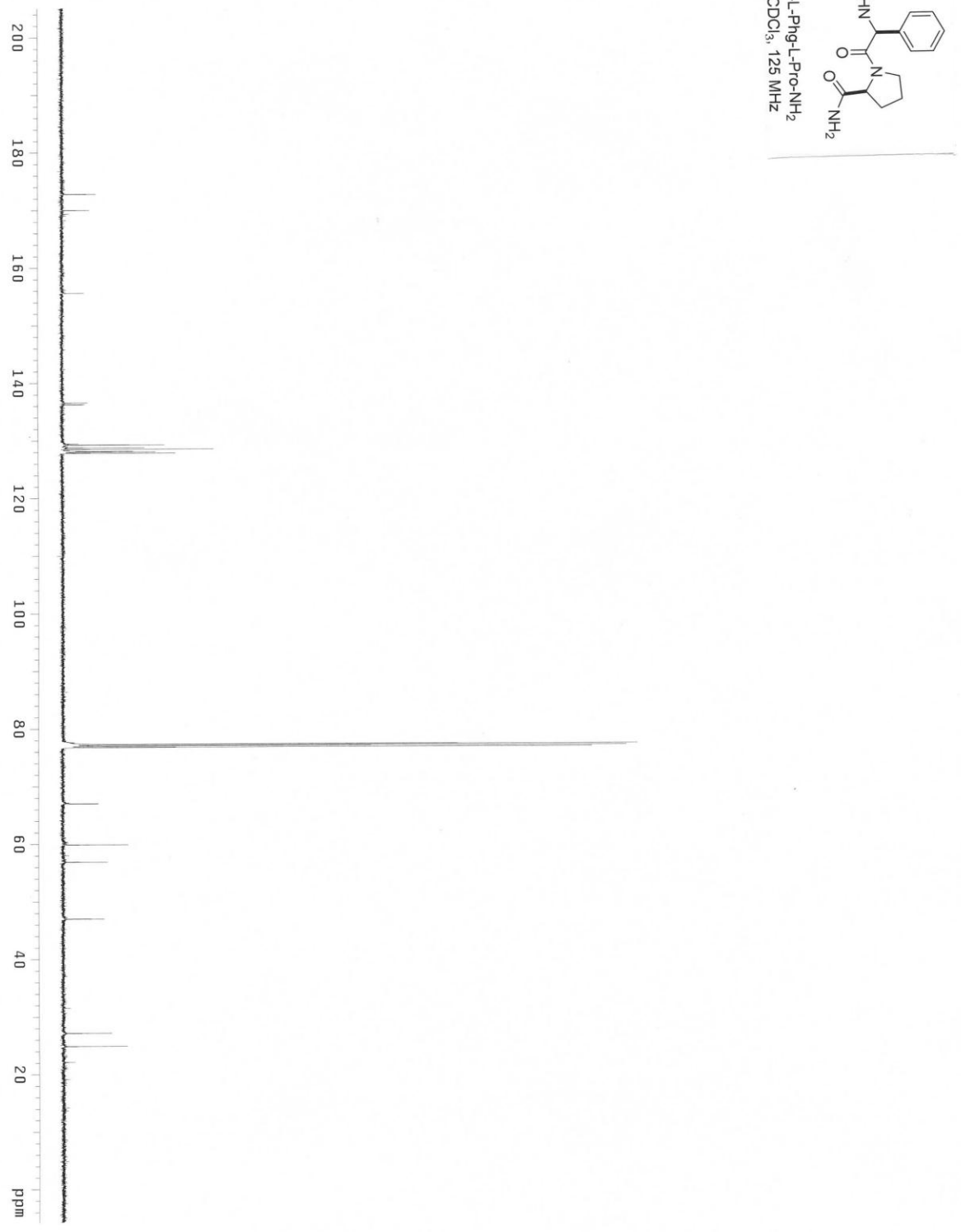
Cyano-hydroxyimino-acetic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (**2**)



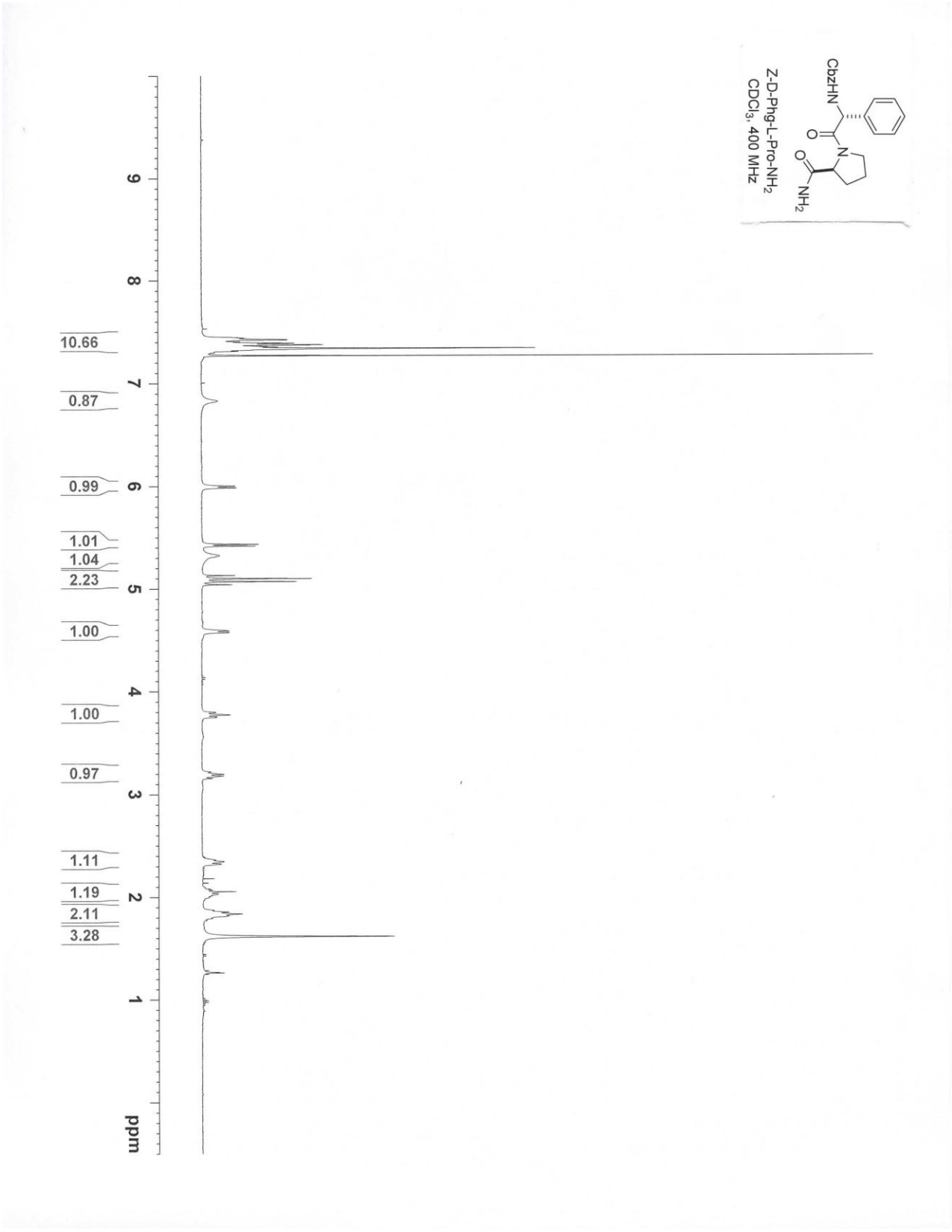

CDCl3, 100 MHz
O
O
O
O
N
OH
CN
200
180
160
140
120
100
80
60
40
20
0
ppm

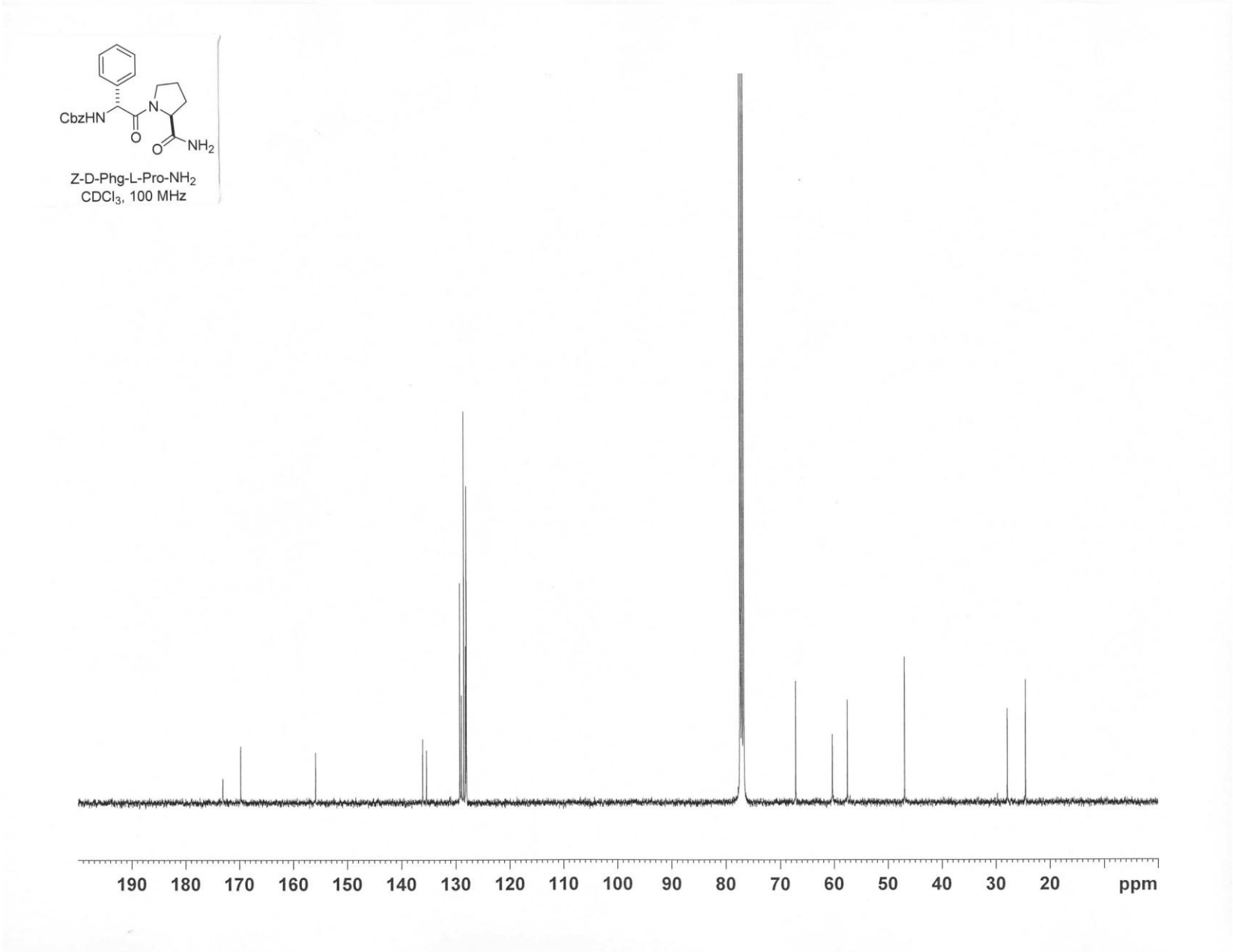
Z-L-Phg-L-Pro-NH_2



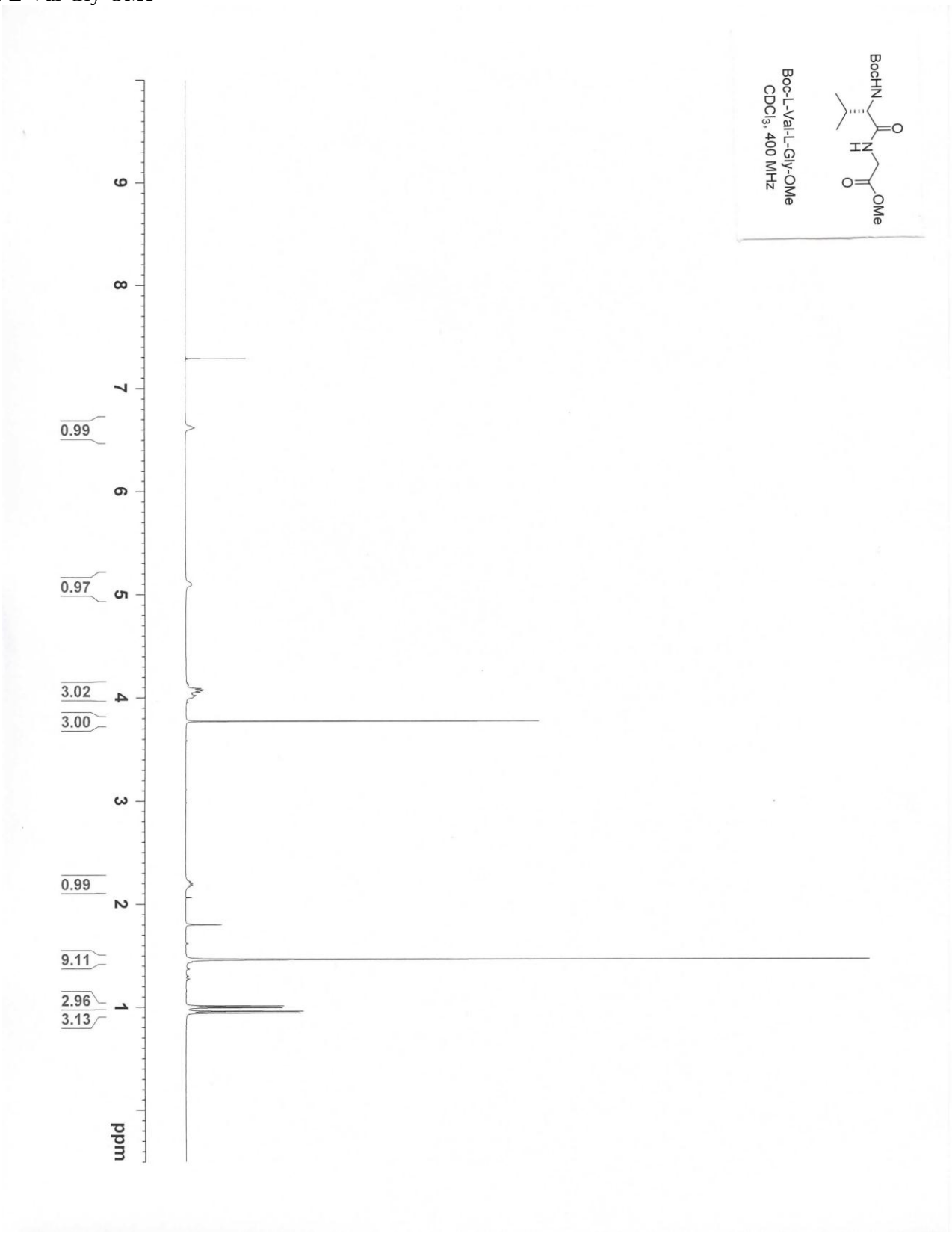

CbzHN
O
N
O
NH2
Z-L-Phg-L-Pro-NH2
CDCl3, 125 MHz
200
180
160
140
120
100
80
60
40
20
ppm

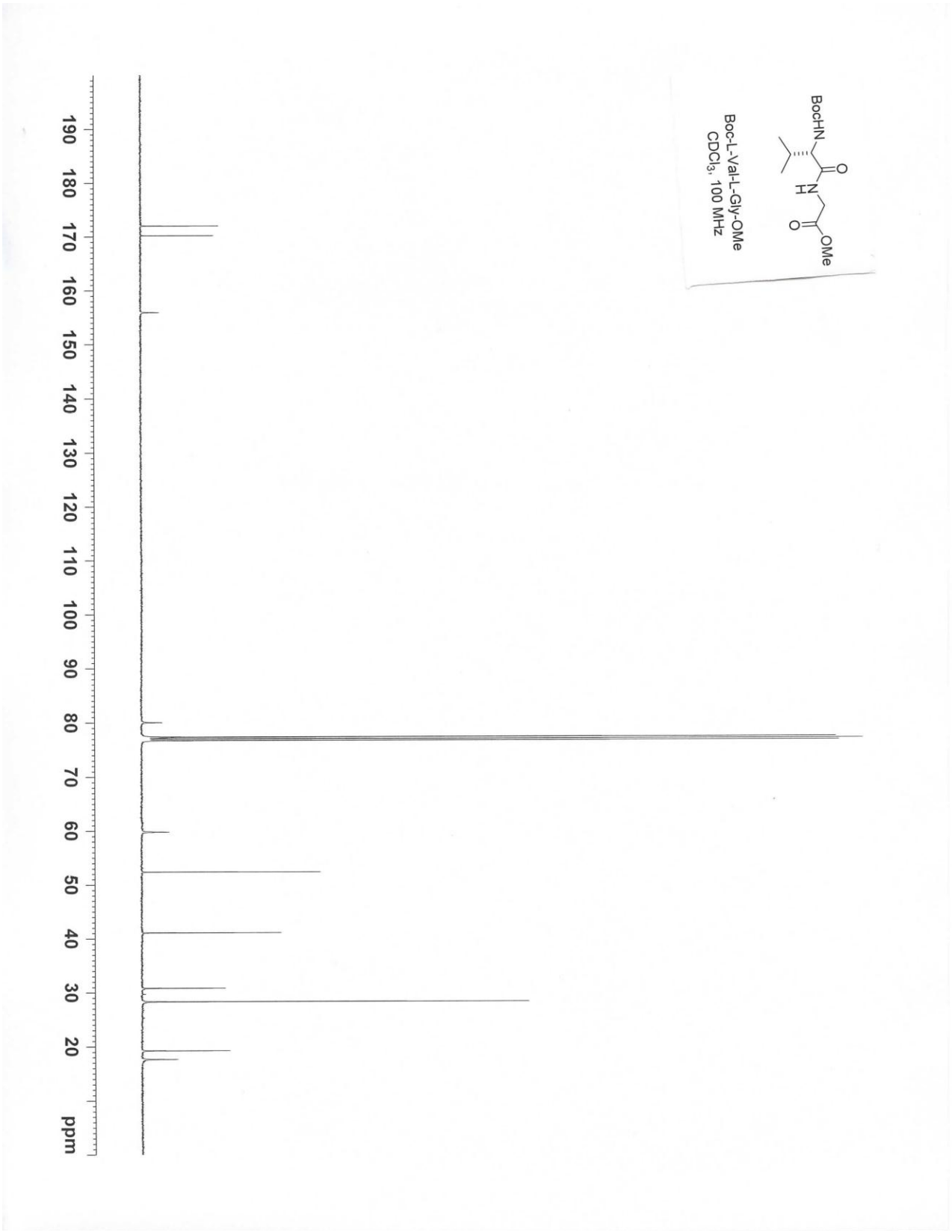
Z-D-Phg-L-Pro-NH_2



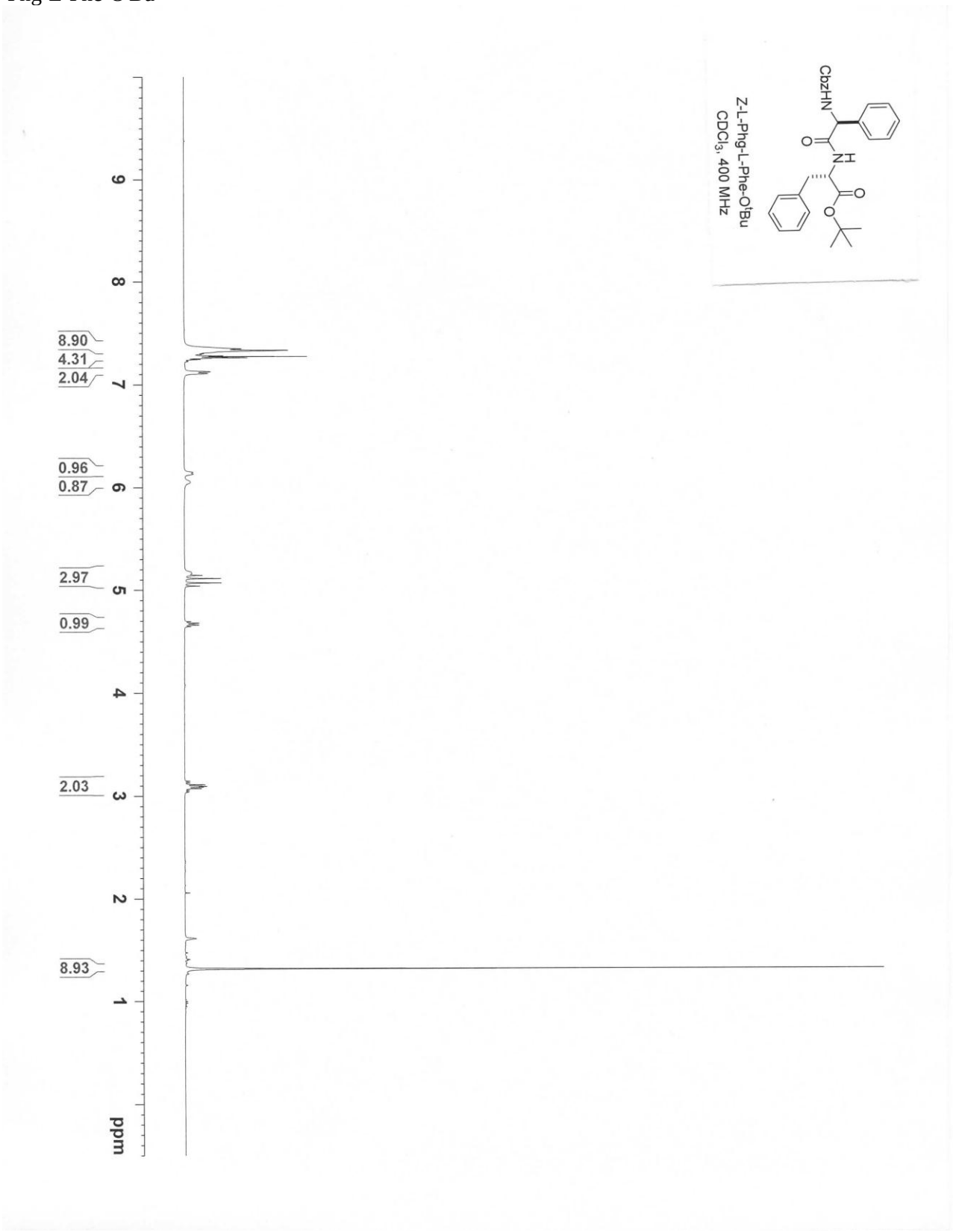

CbzHN
O
N
O
NH2
Z-D-Phg-L-Pro-NH2
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

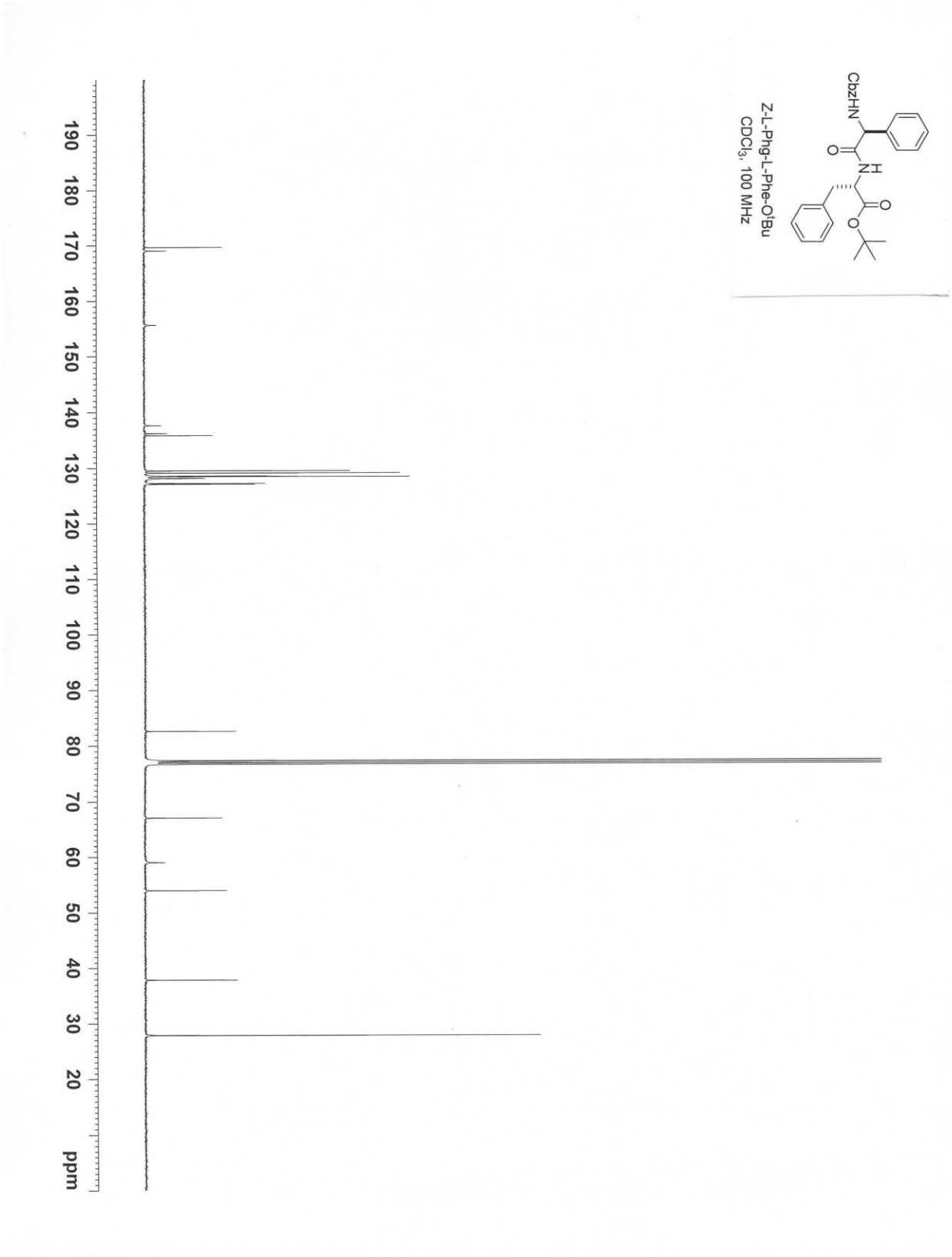
Boc-L-Val-Gly-OMe



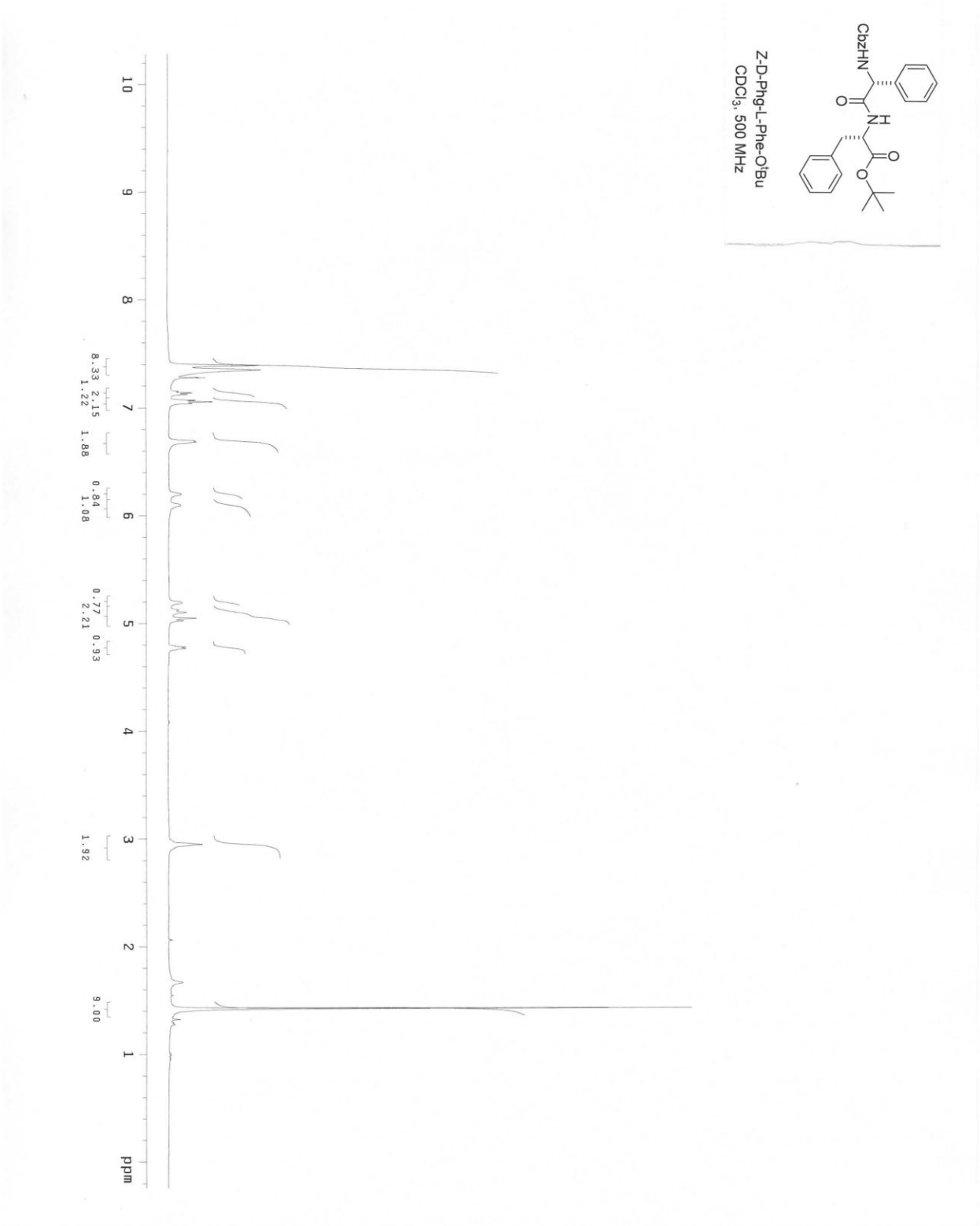

BocHN
O
N
H
O
OMe
Boc-L-Val-L-Gly-OMe
CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

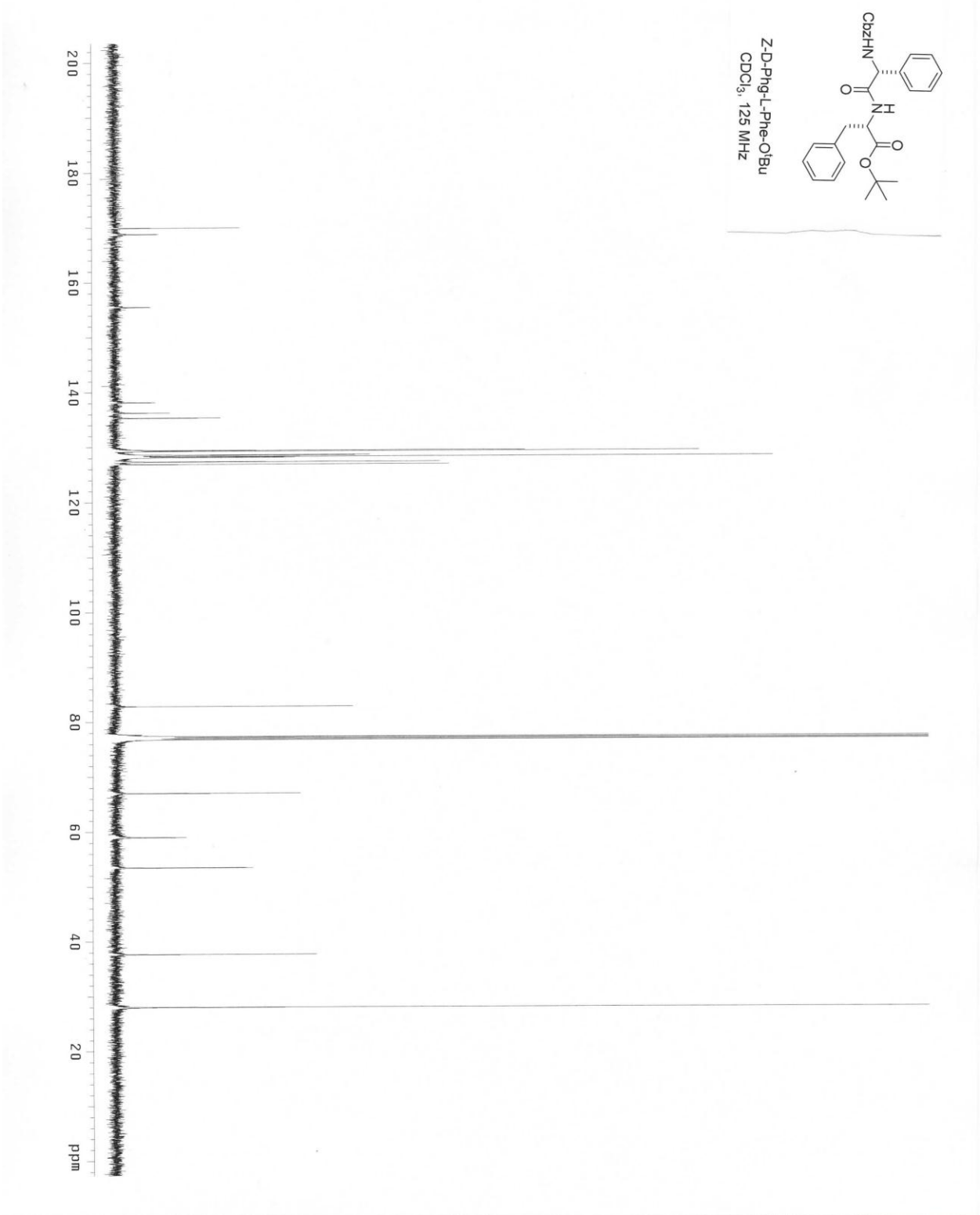
Z-L-Phg-L-Phe-O^{t}Bu



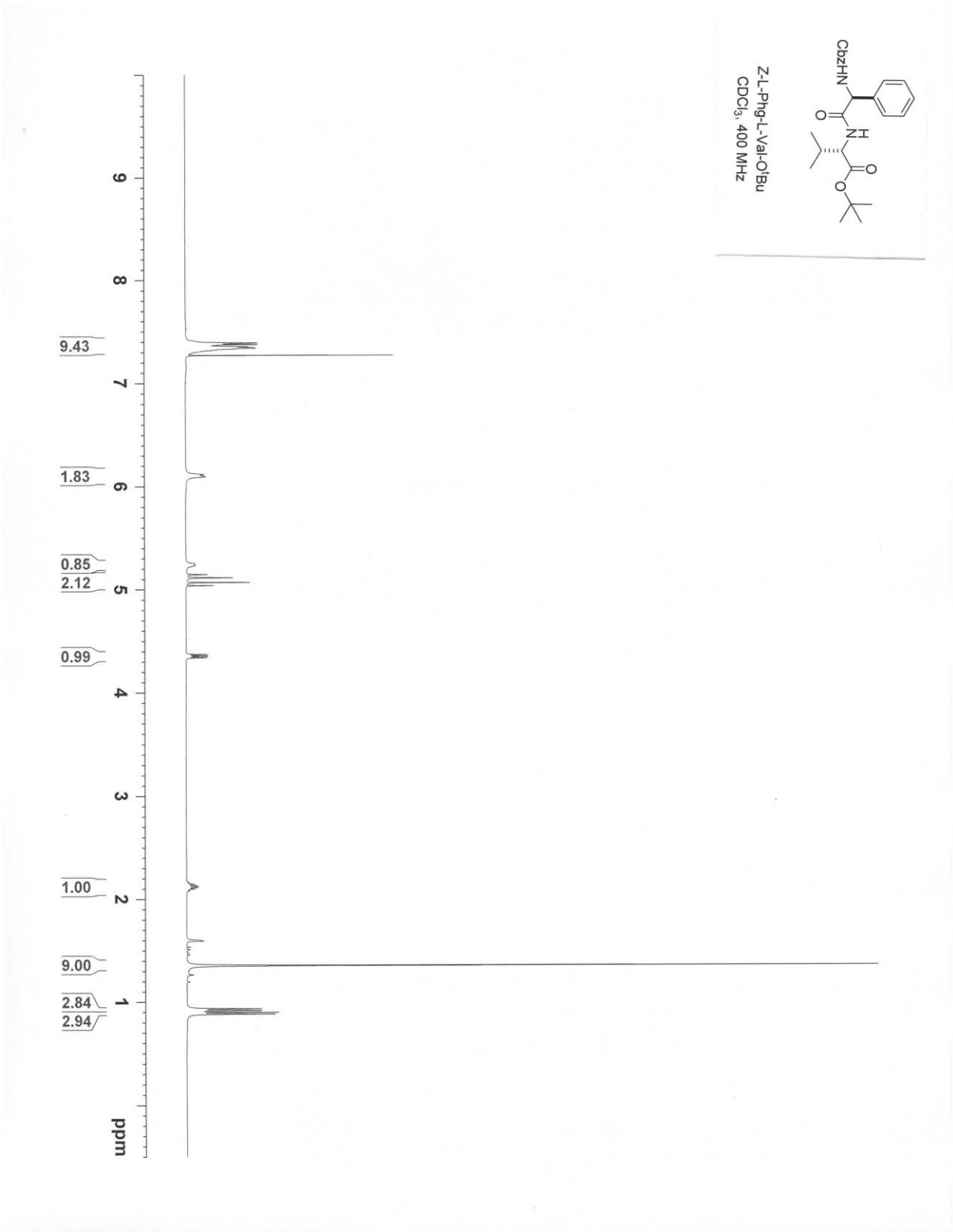

CbzHN
H
N
O
O
O
O
Z-L-Phg-L-Phe-O'Bu
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

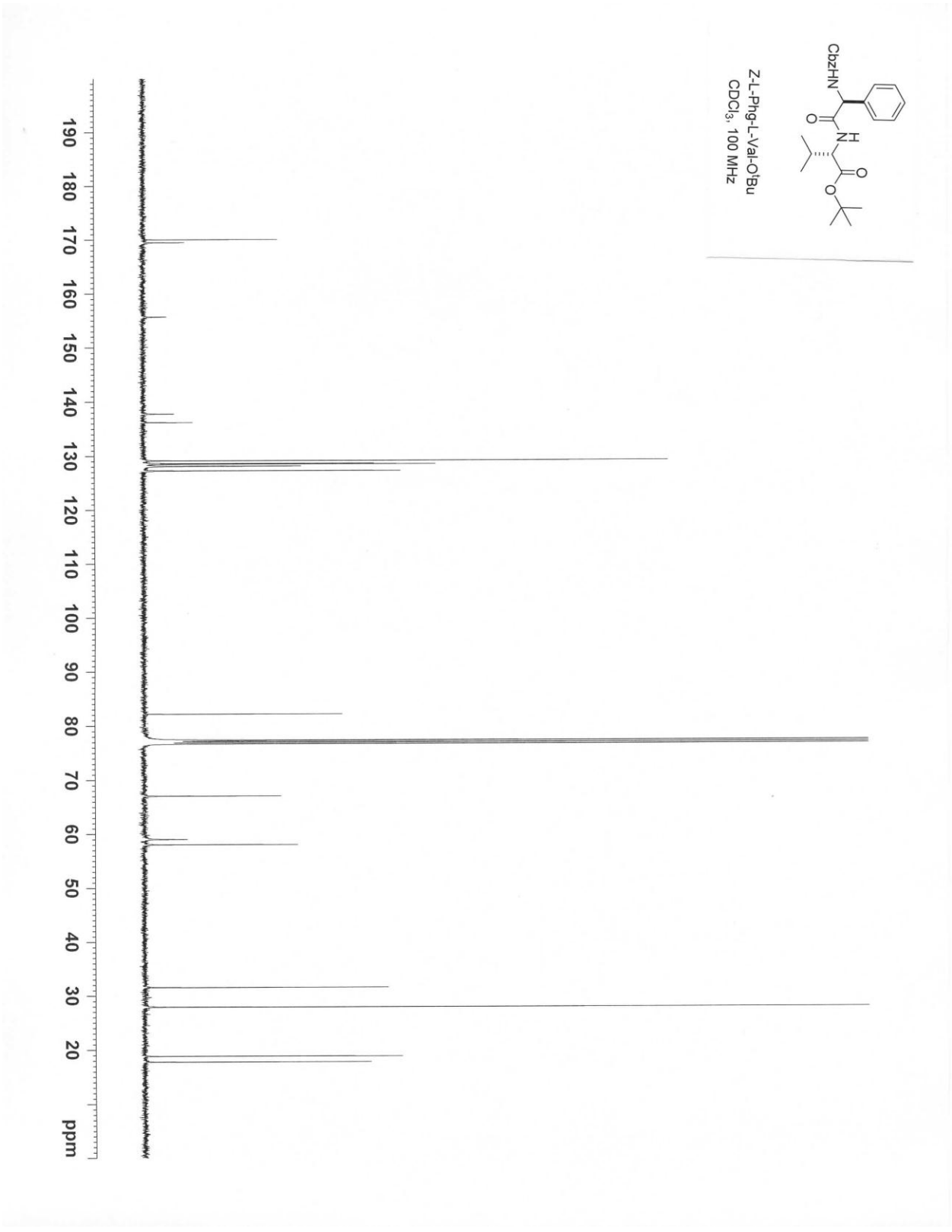
Z-D-Phg-L-Phe-O^{t}Bu



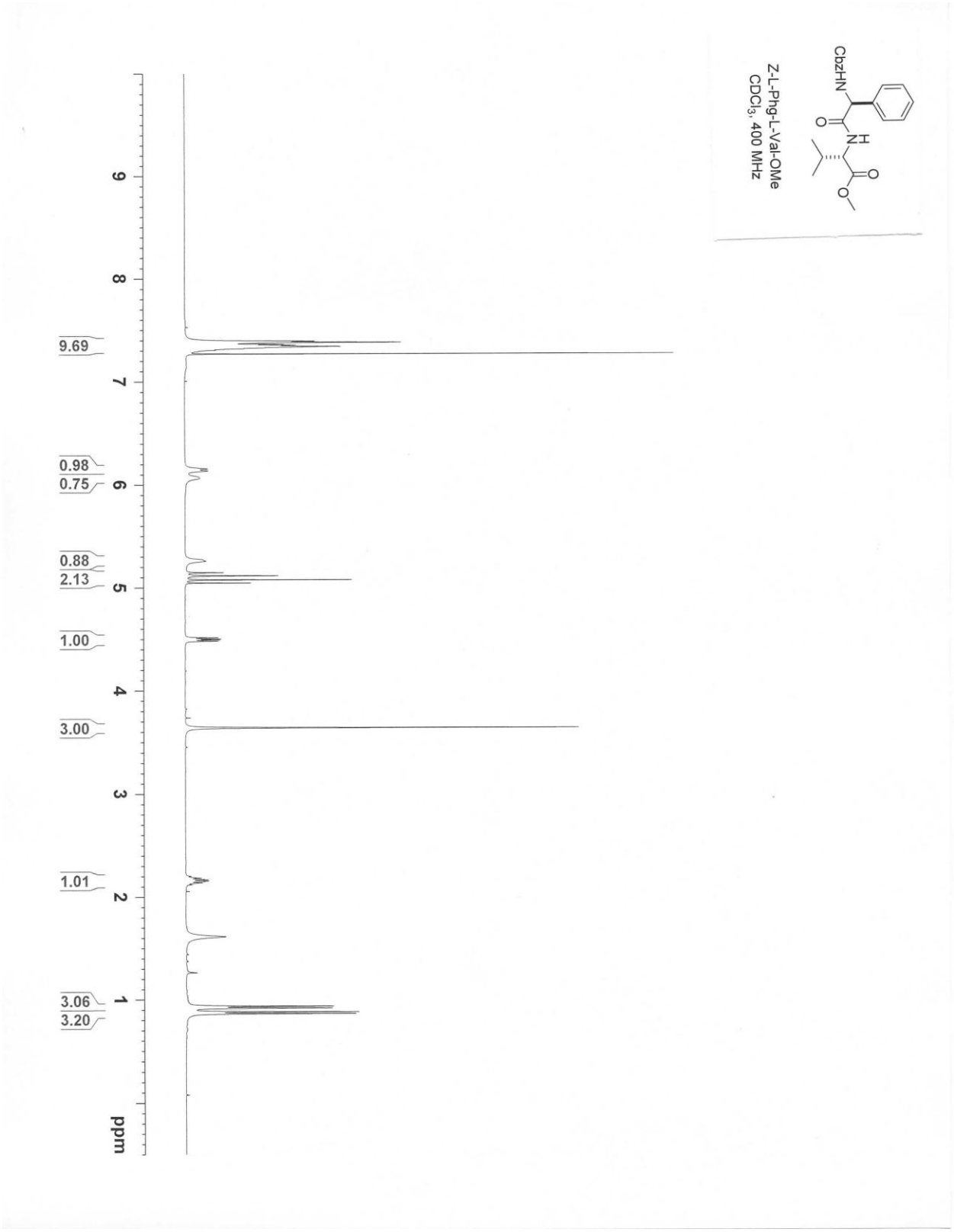

Z-D-Phg-L-Phe-O'Bu
CDCl3, 125 MHz
CbzHN
O
H
N
O
O
200
180
160
140
120
100
80
60
40
20
ppm

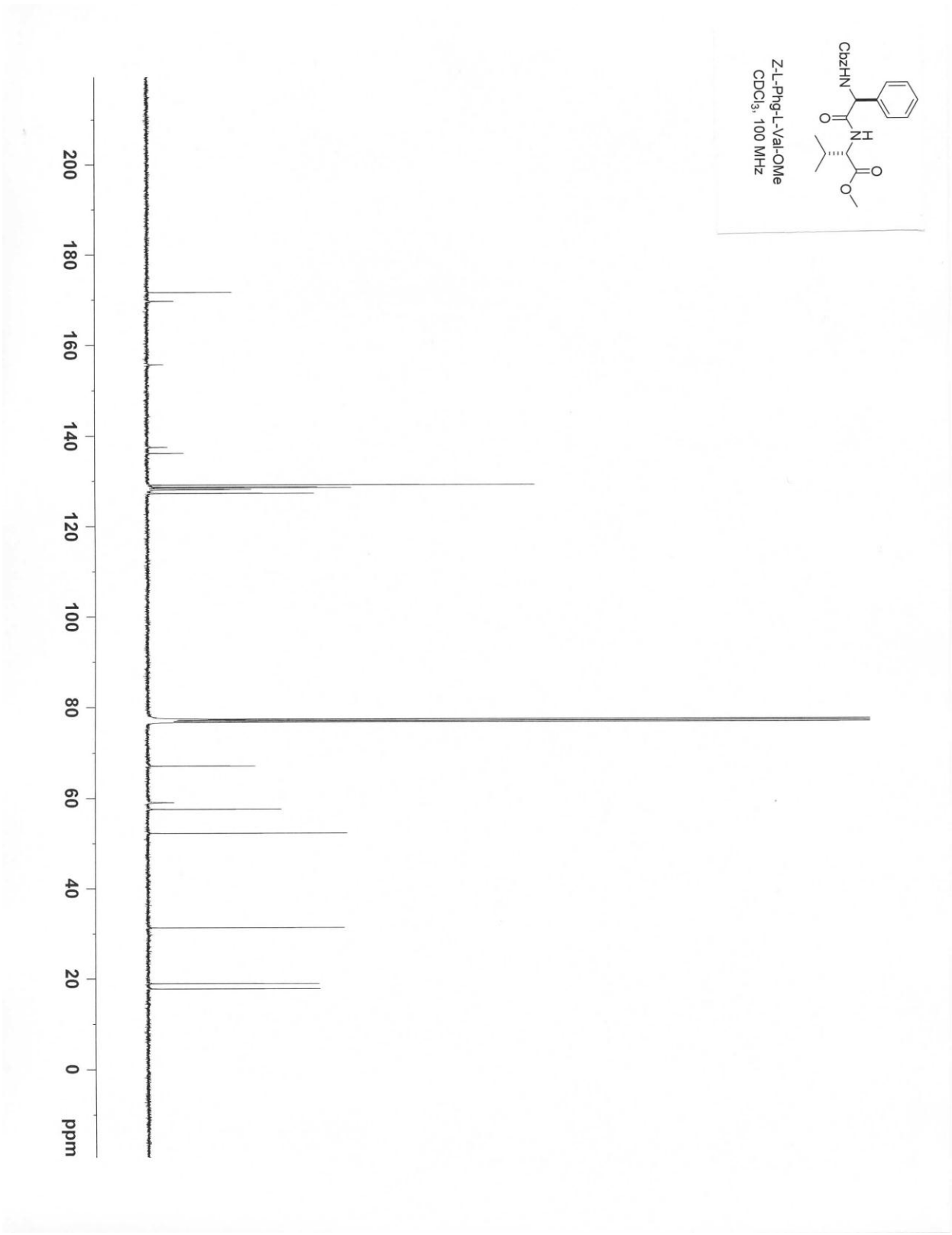
Z-L-Phg-L-Val-O^{t}Bu



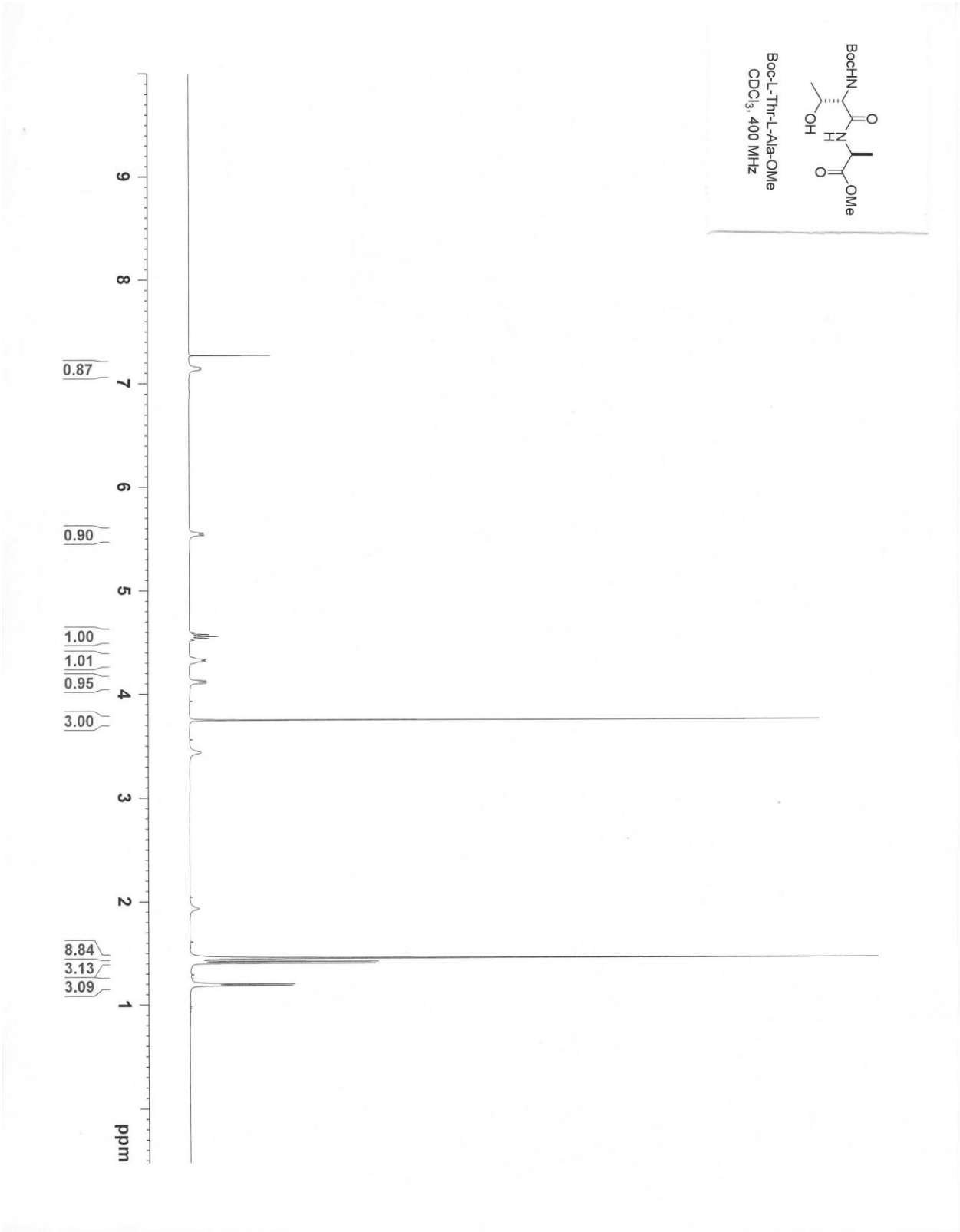

CbzHN
O
H
N
O
O
O
Z-L-Phg-L-Val-O'Bu
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

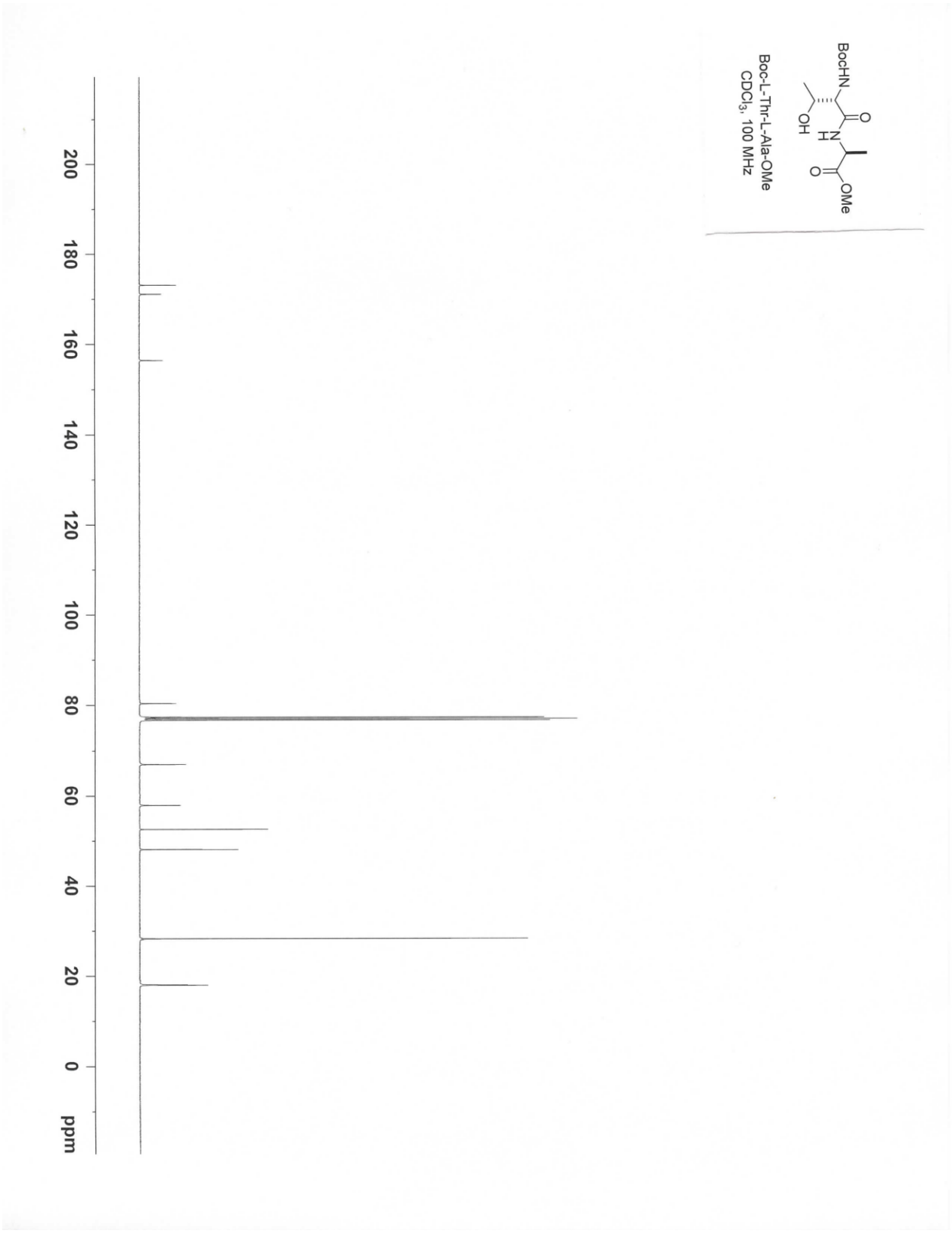
Z-L-Phg-L-Val-OMe



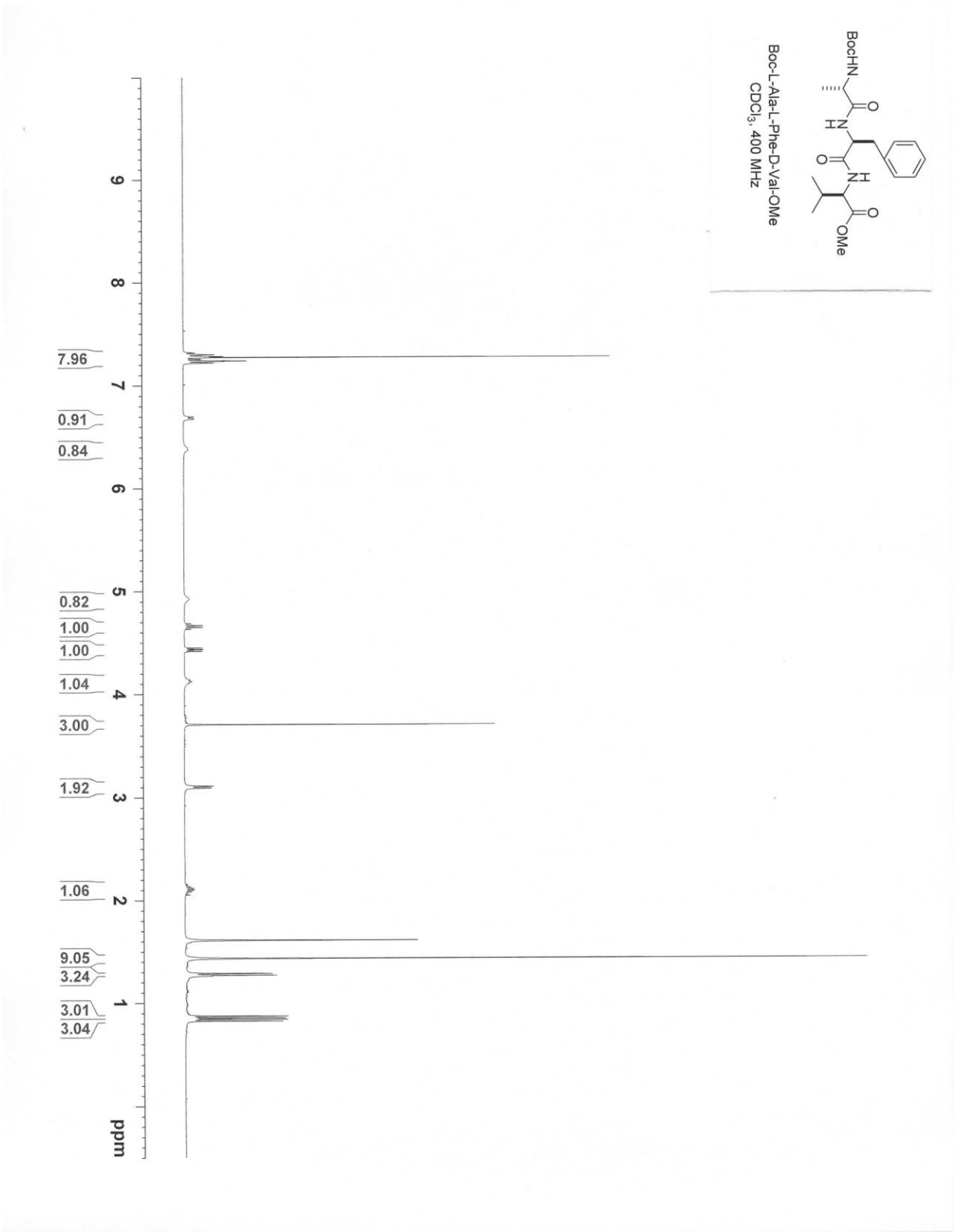

CbzHN
H
N
O
O
O
Z-L-Phg-L-Val-OMe
CDCl3, 100 MHz
200
180
160
140
120
100
80
60
40
20
0
ppm

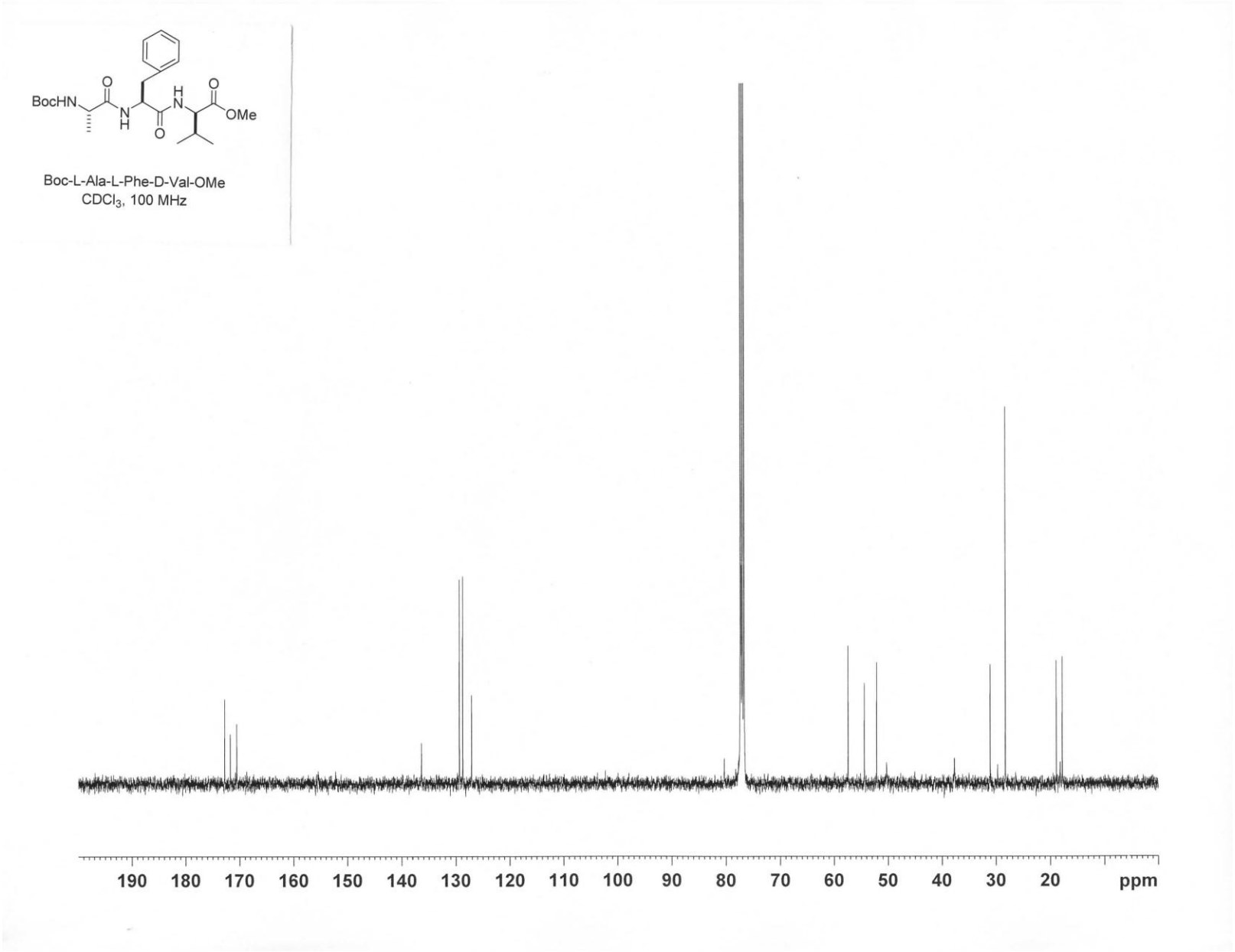
Boc-L-Thr-L-Ala-OMe



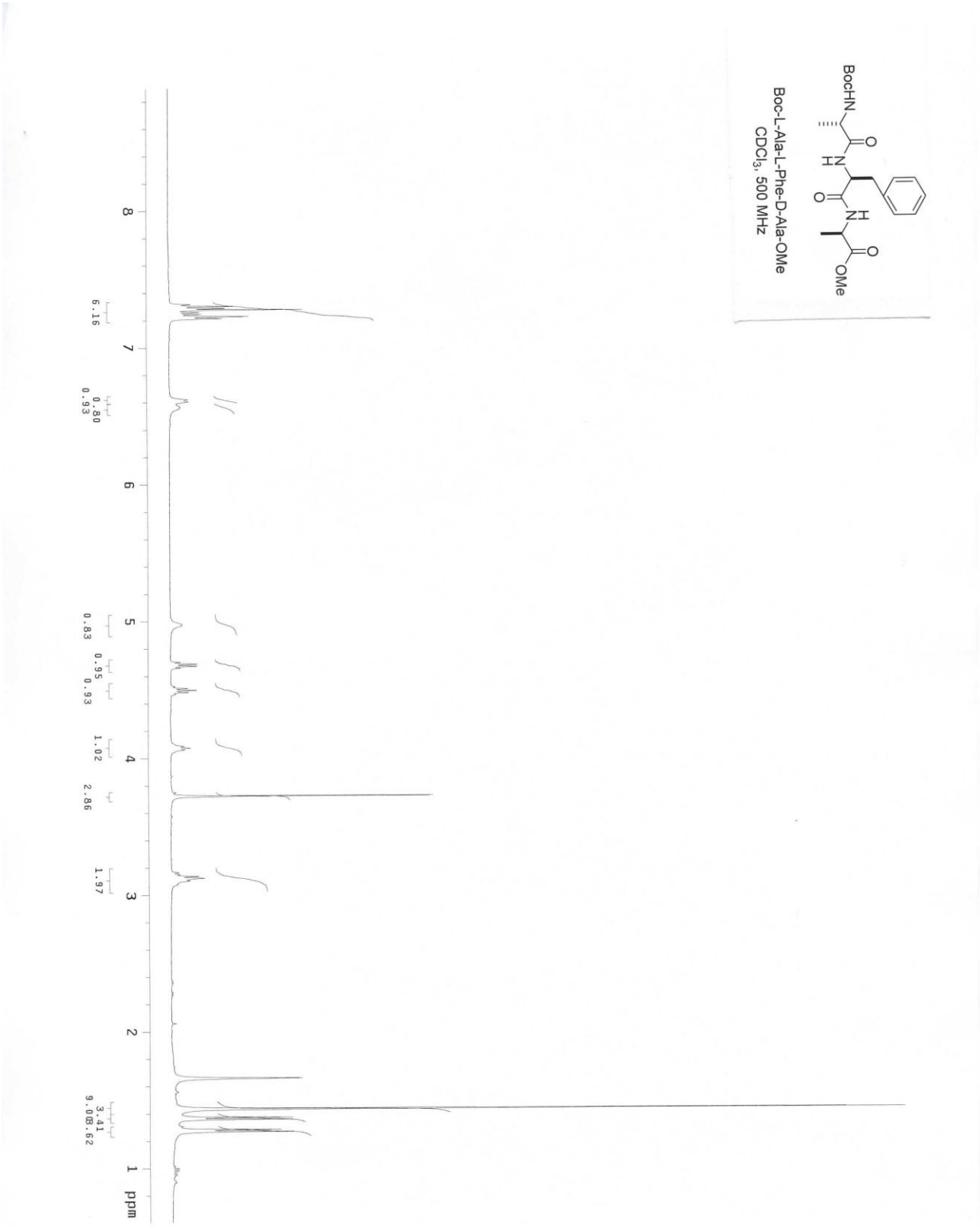

BocHN
OH
N
H
OMe
Boc-L-Thr-L-Ala-OMe
CDCl3, 100 MHz
200
180
160
140
120
100
80
60
40
20
0
ppm

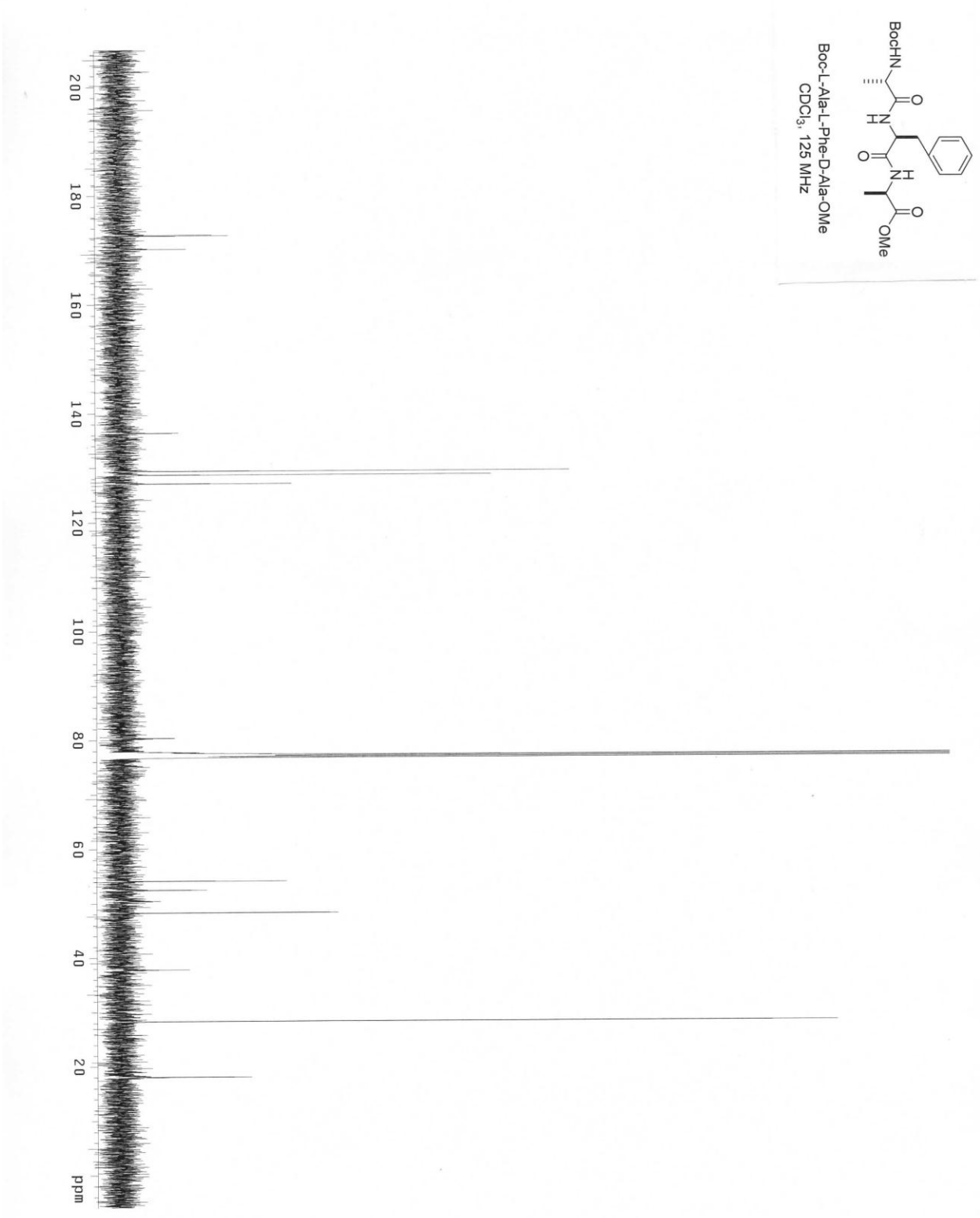
Boc-L-Ala-L-Phe-D-Val-OMe



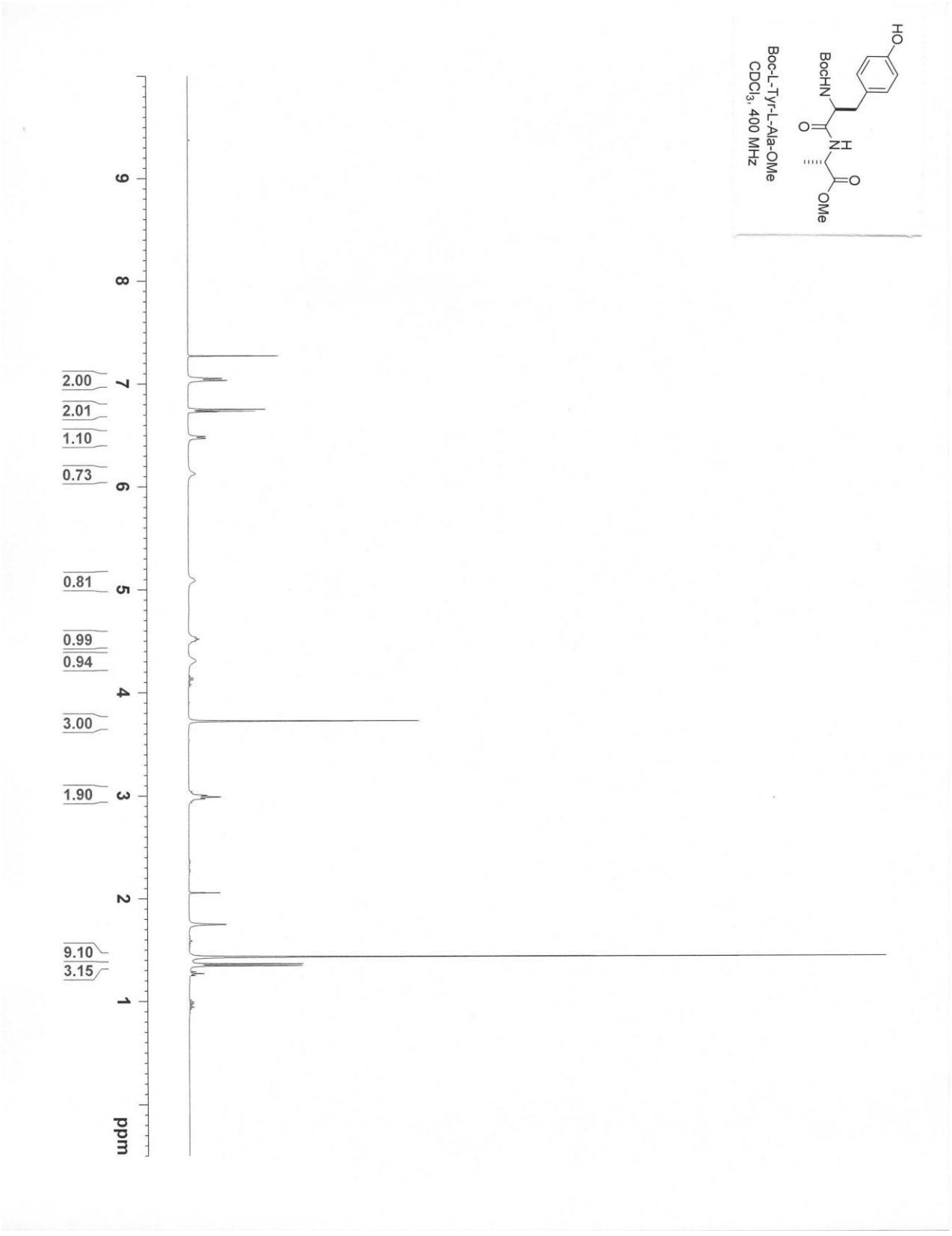

BocHN
O
N
H
O
H
N
O
OMe
Boc-L-Ala-L-Phe-D-Val-OMe
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

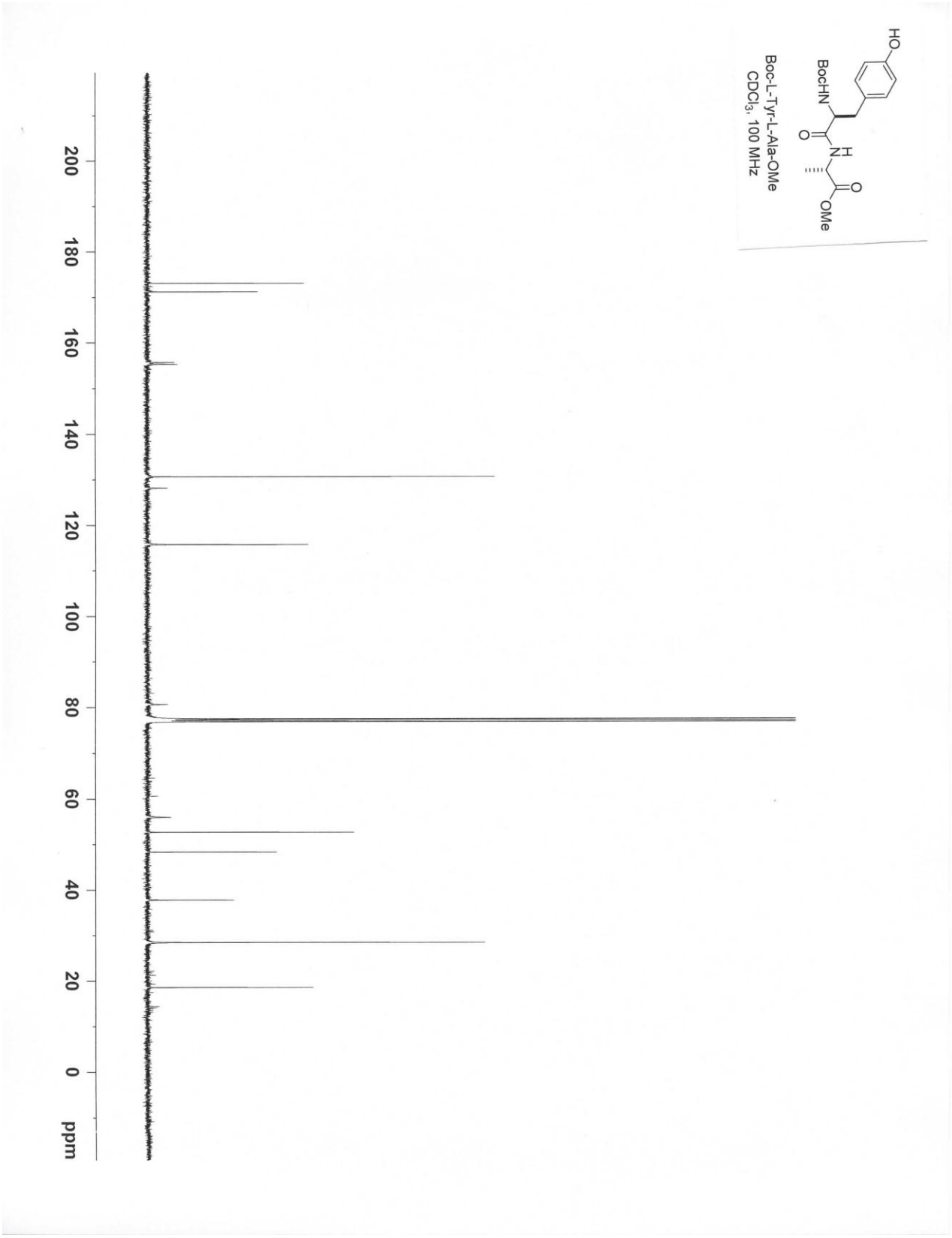
Boc-L-Ala-L-Phe-D-Ala-OMe



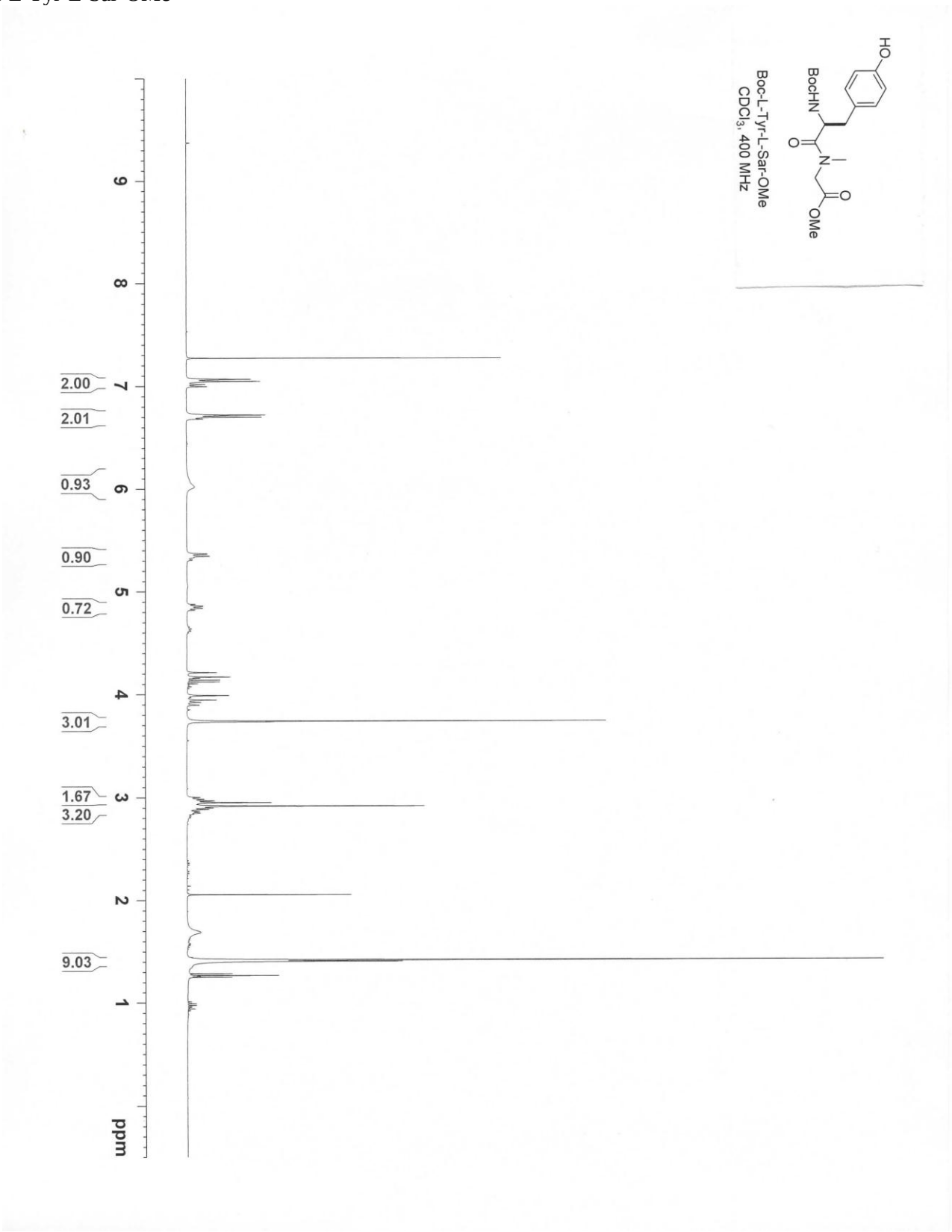

BocHN
O
N
H
O
H
N
O
OMe
Boc-L-Ala-L-Phe-D-Ala-OMe
CDCl3, 125 MHz
200
180
160
140
120
100
80
60
40
20
ppm

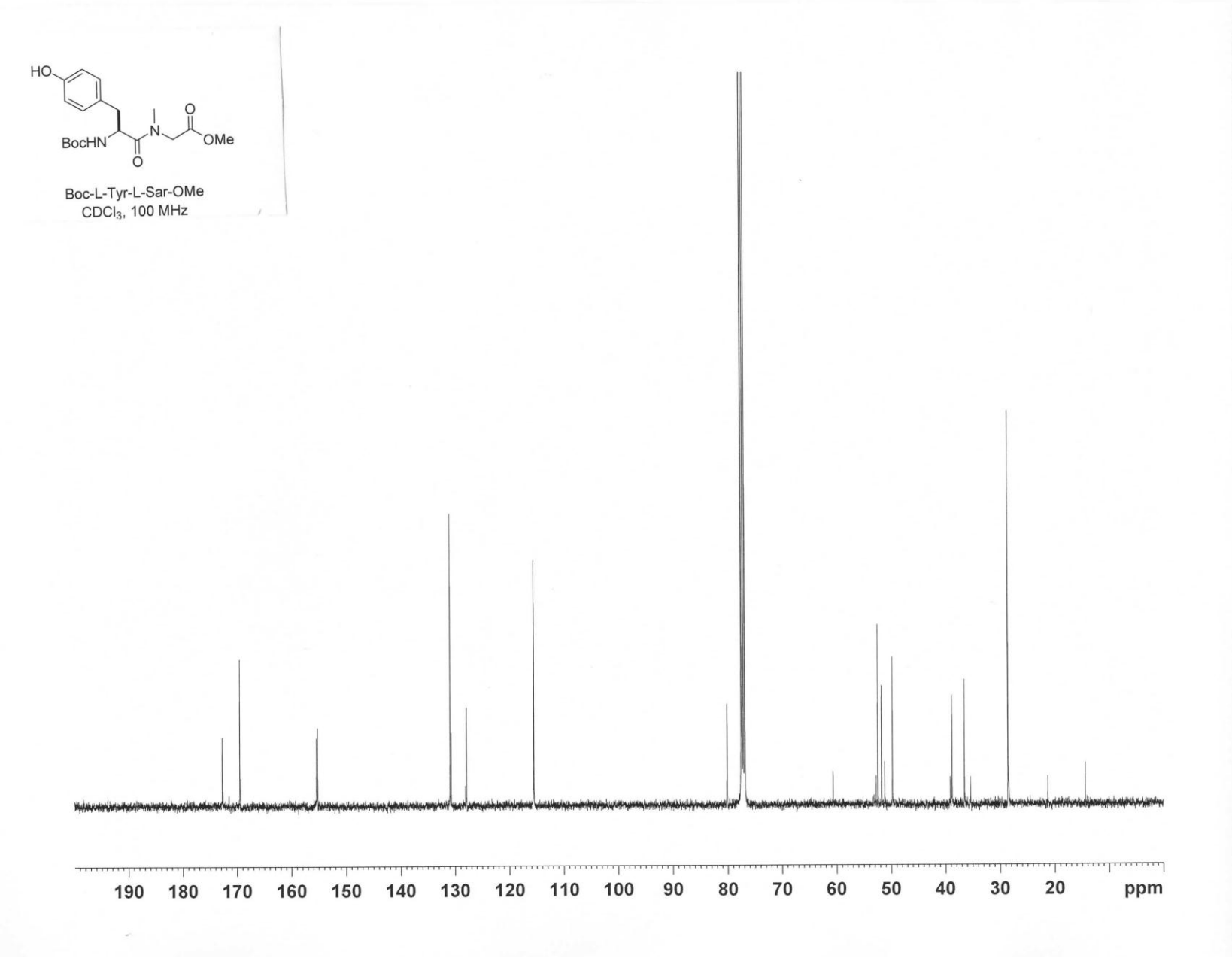
Boc-L-Tyr-L-Ala-OMe



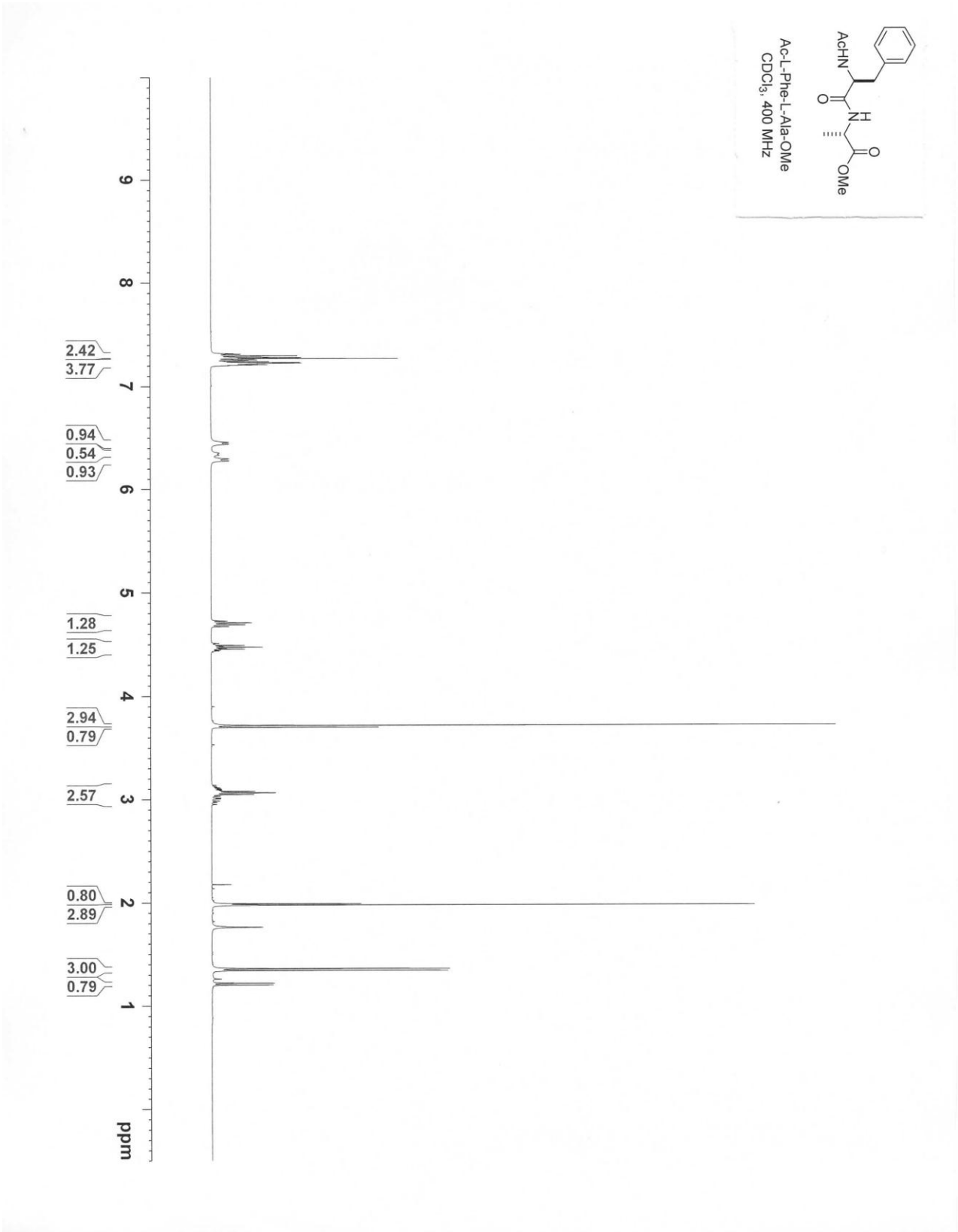

HO
BocHN
O
H
N
O
OMe
Boc-L-Tyr-L-Ala-OMe
CDCl3, 100 MHz
200
180
160
140
120
100
80
60
40
20
0
ppm

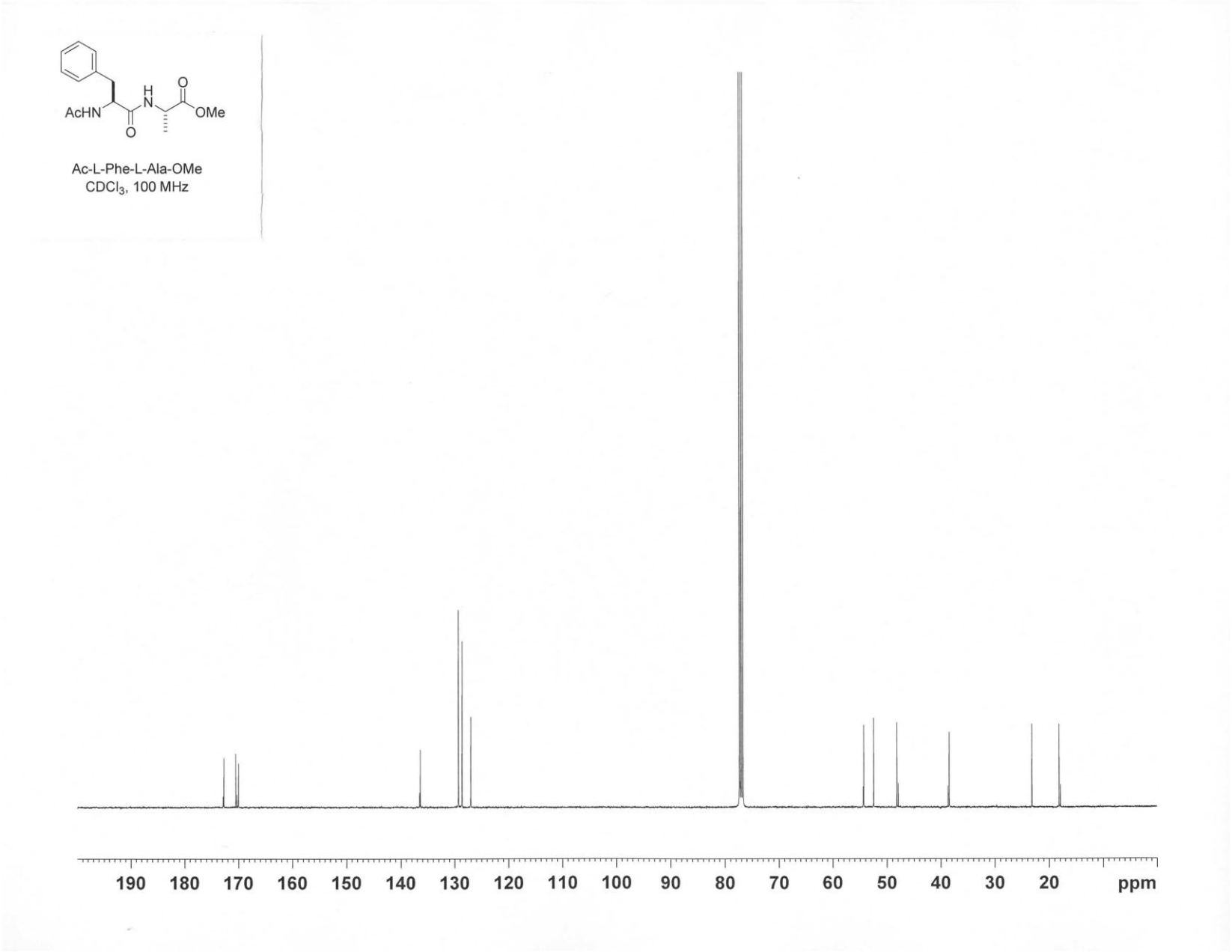
Boc-L-Tyr-L-Sar-OMe



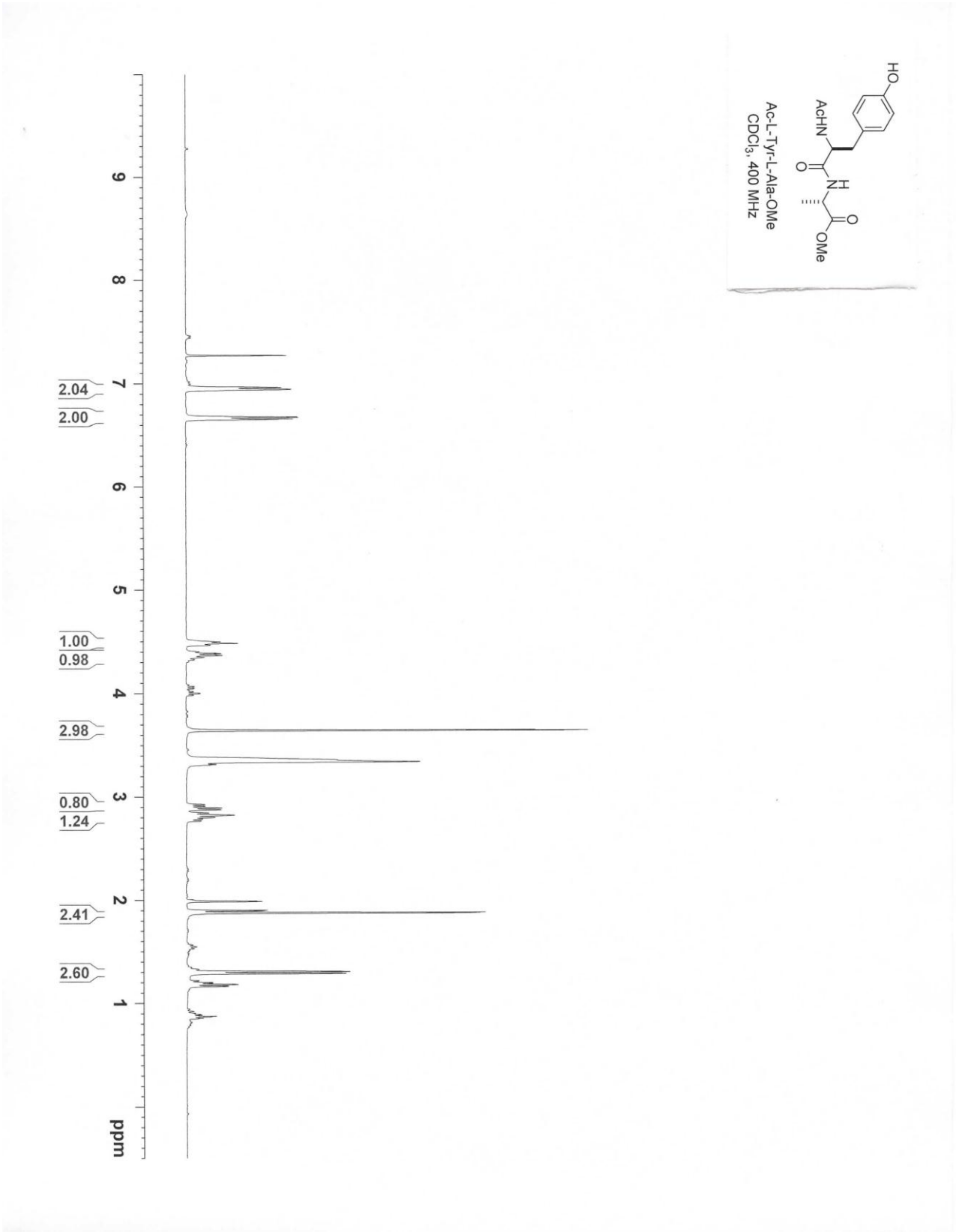

HO
BocHN
N
O
OMe
O
Boc-L-Tyr-L-Sar-OMe
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

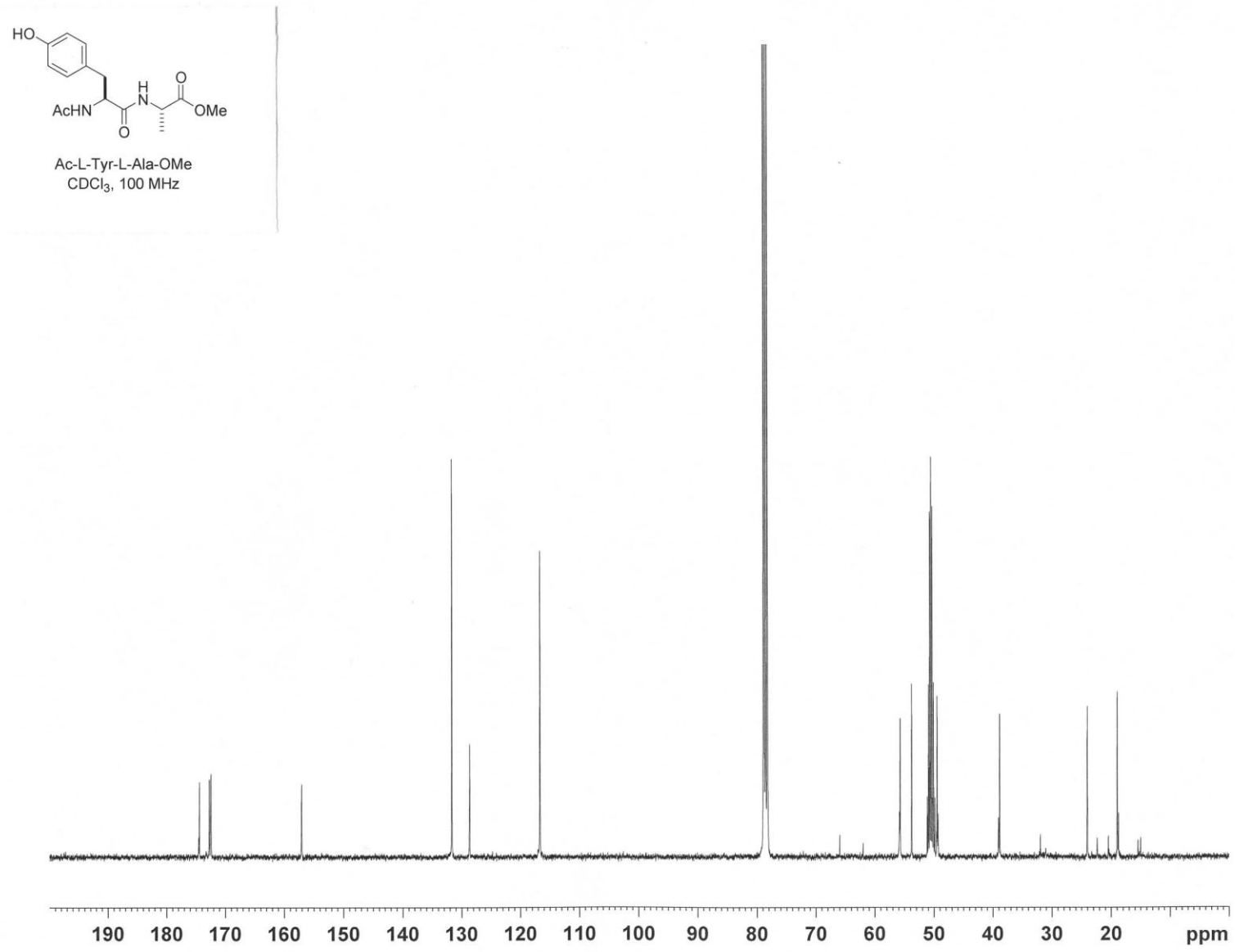
Ac-L-Phe-L-Ala-OMe



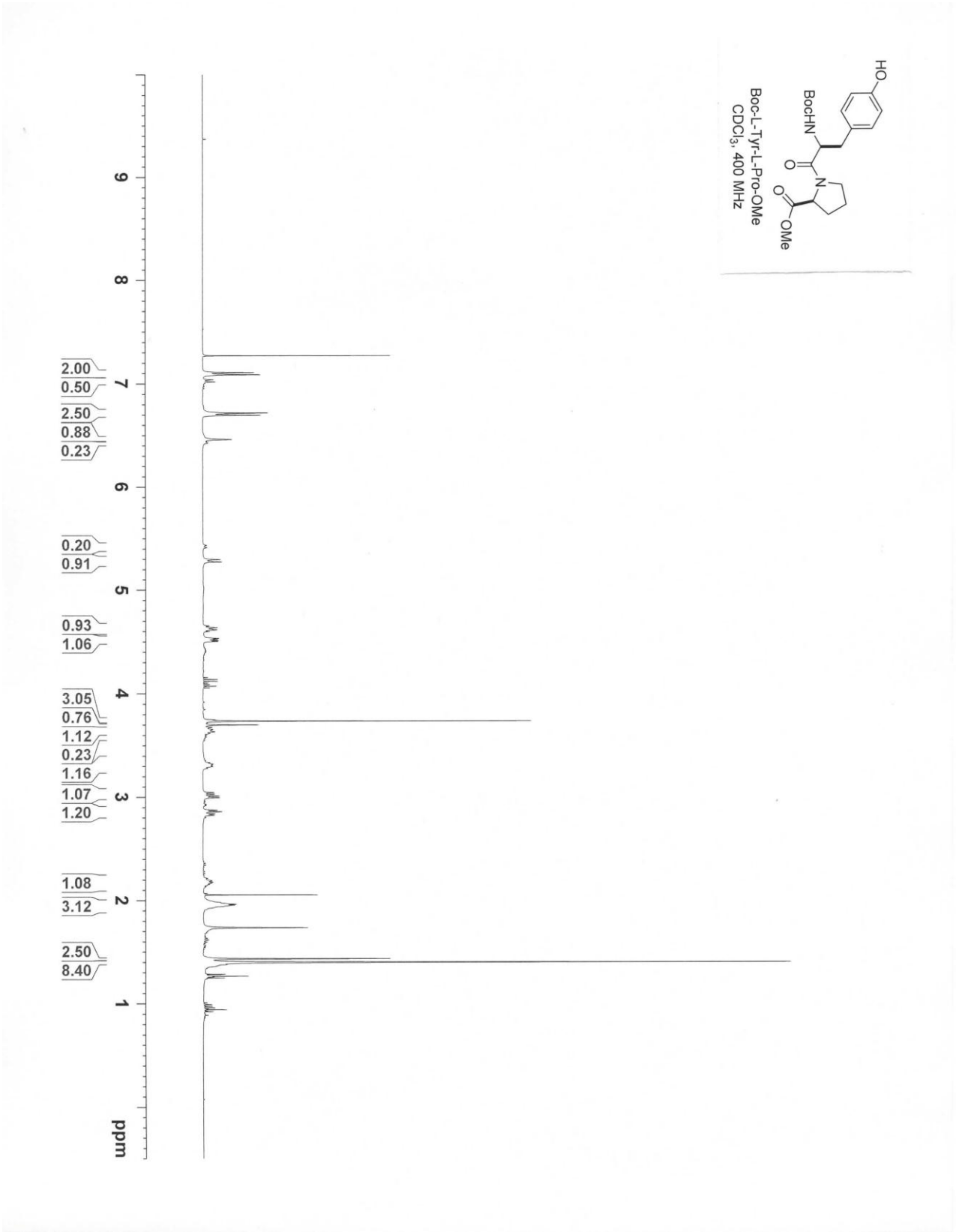

AcHN
H
N
O
O
OMe
O
Ac-L-Phe-L-Ala-OMe
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

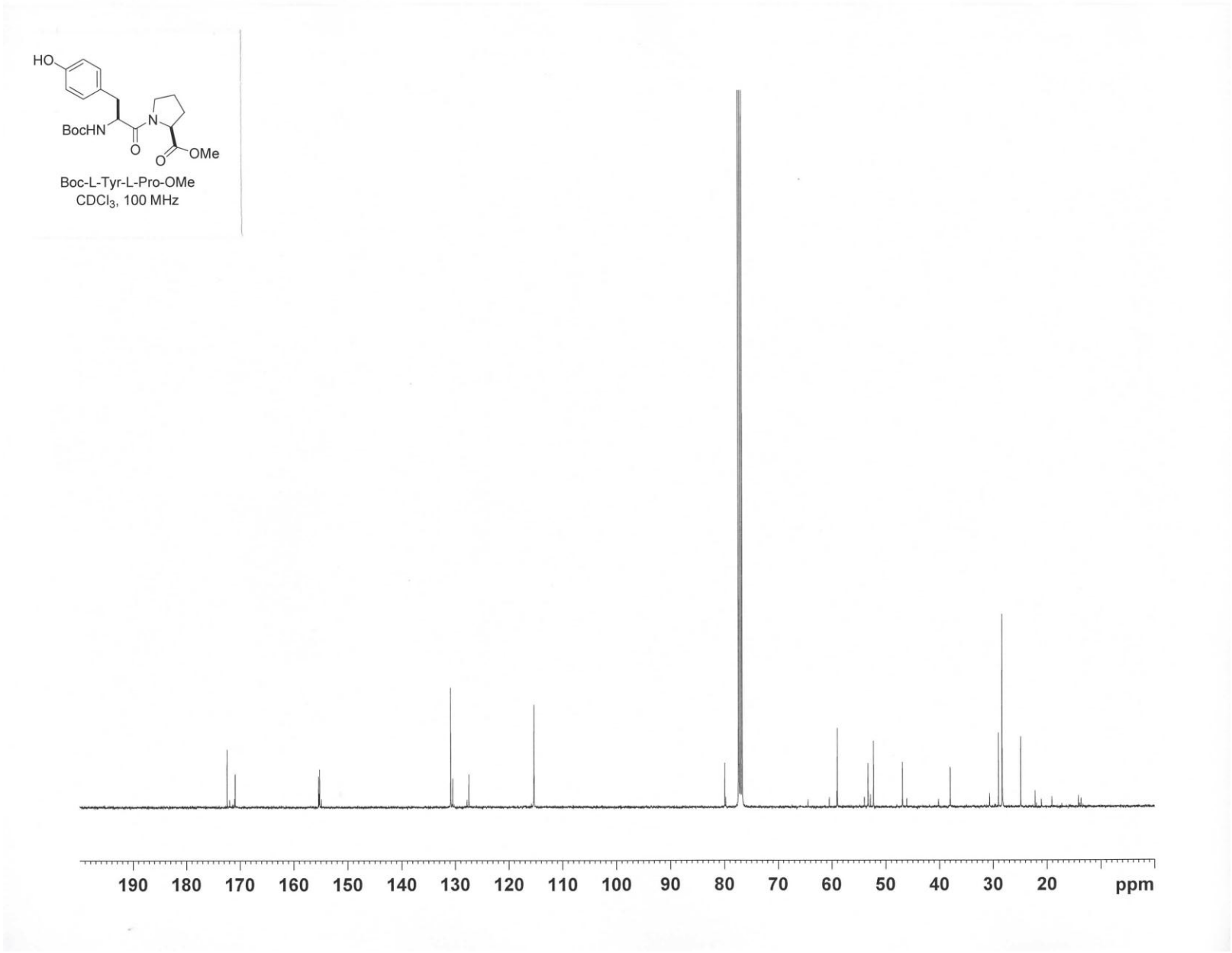
Ac-L-Tyr-L-Ala-OMe



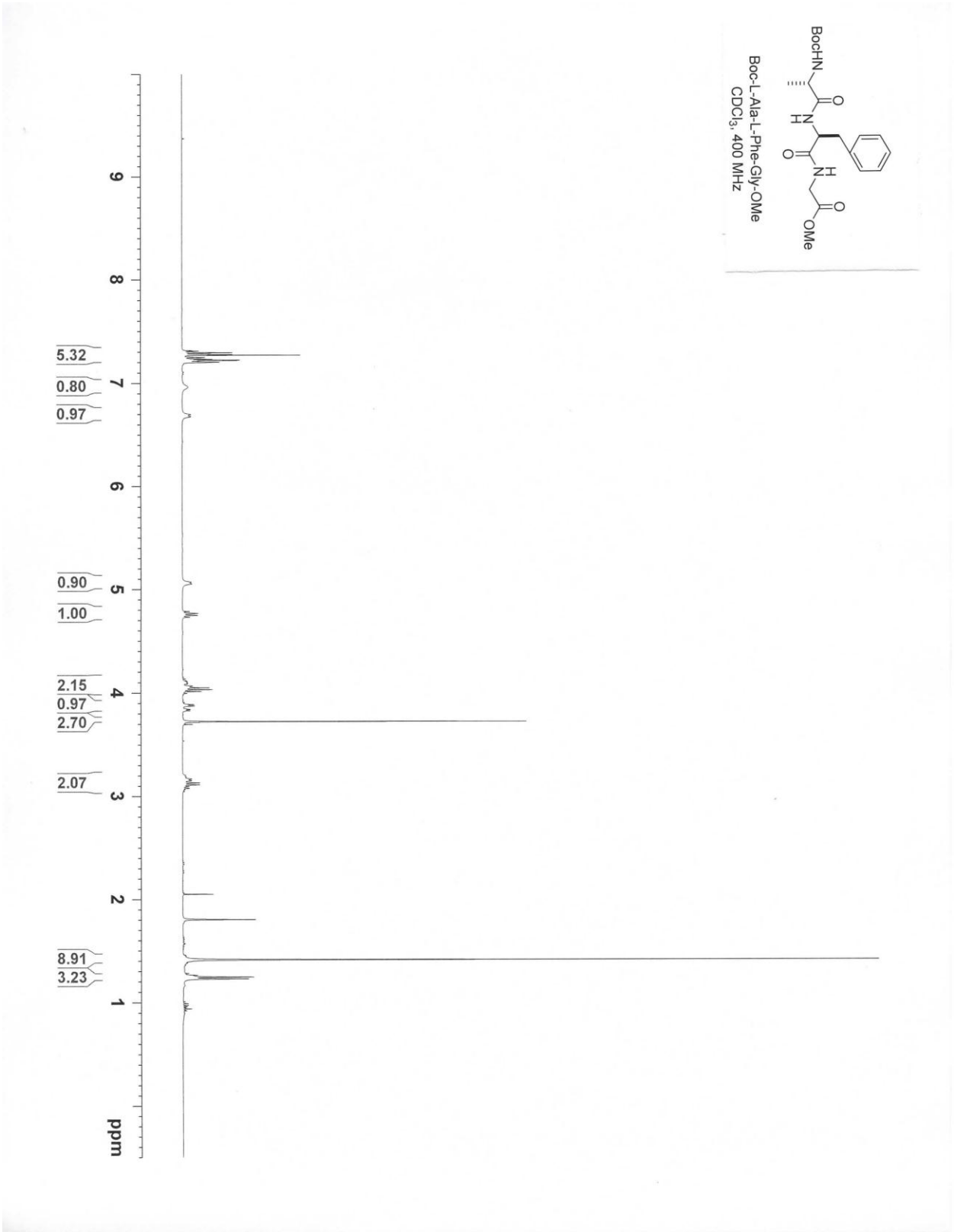

HO
AcHN
H
N
O
O
OMe
O
Ac-L-Tyr-L-Ala-OMe
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

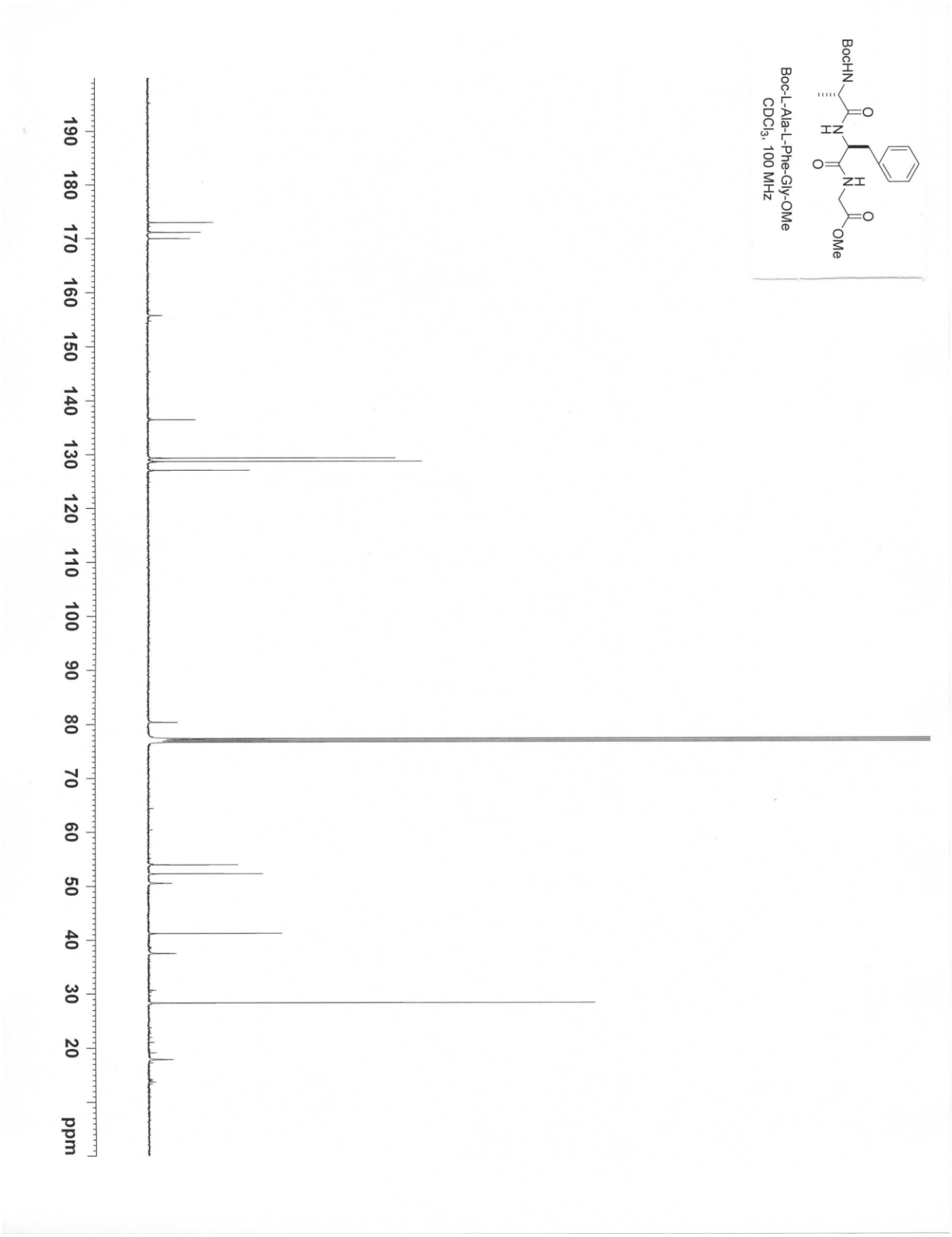
Boc-L-Tyr-L-Pro-OMe



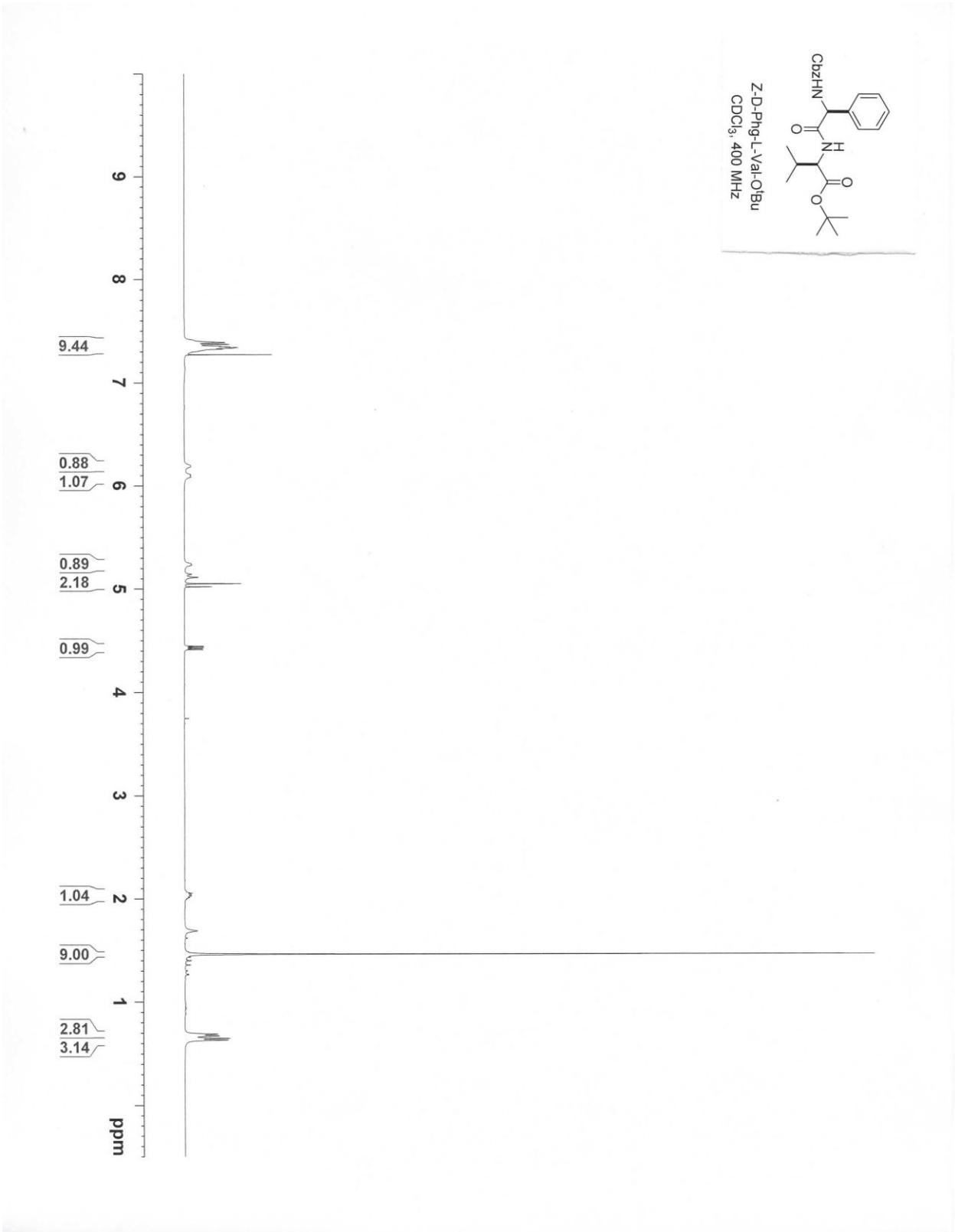

HO
BocHN
O
N
O
OMe
Boc-L-Tyr-L-Pro-OMe
CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

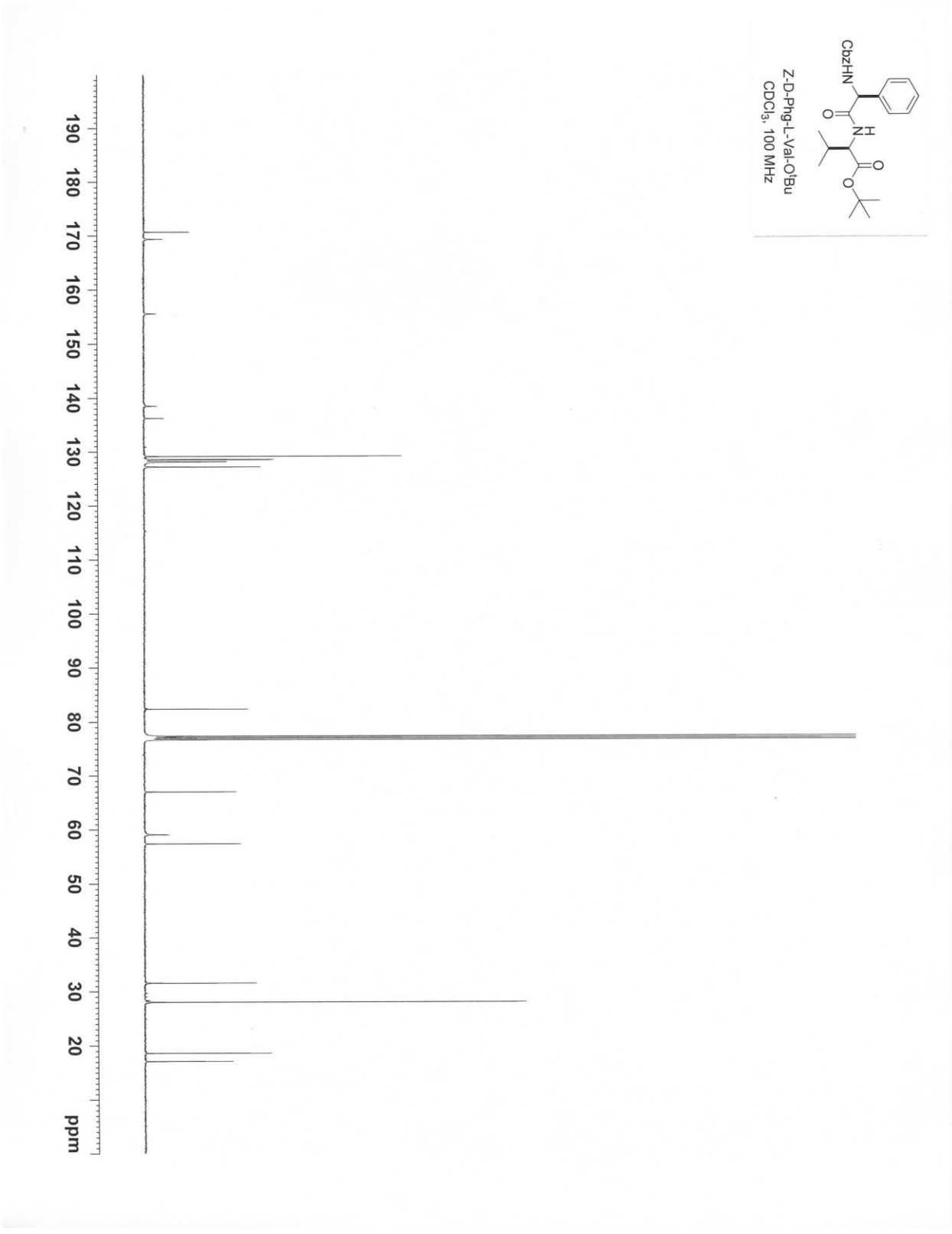
Boc-L-Ala-L-Phe-Gly-OMe



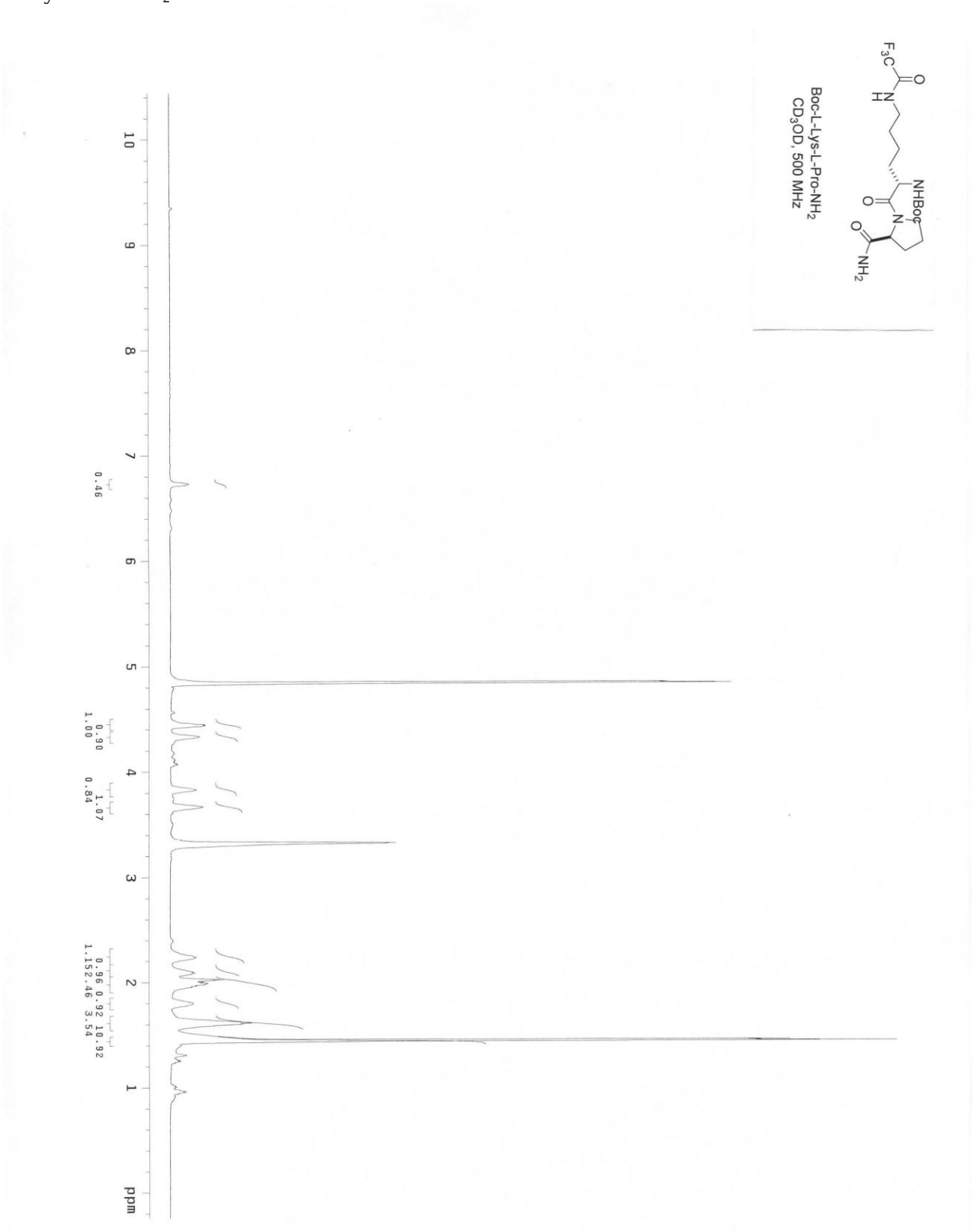

BocHN
O
N
H
O
H
N
O
O
OMe
Boc-L-Ala-L-Phe-Gly-OMe
CDCl3, 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

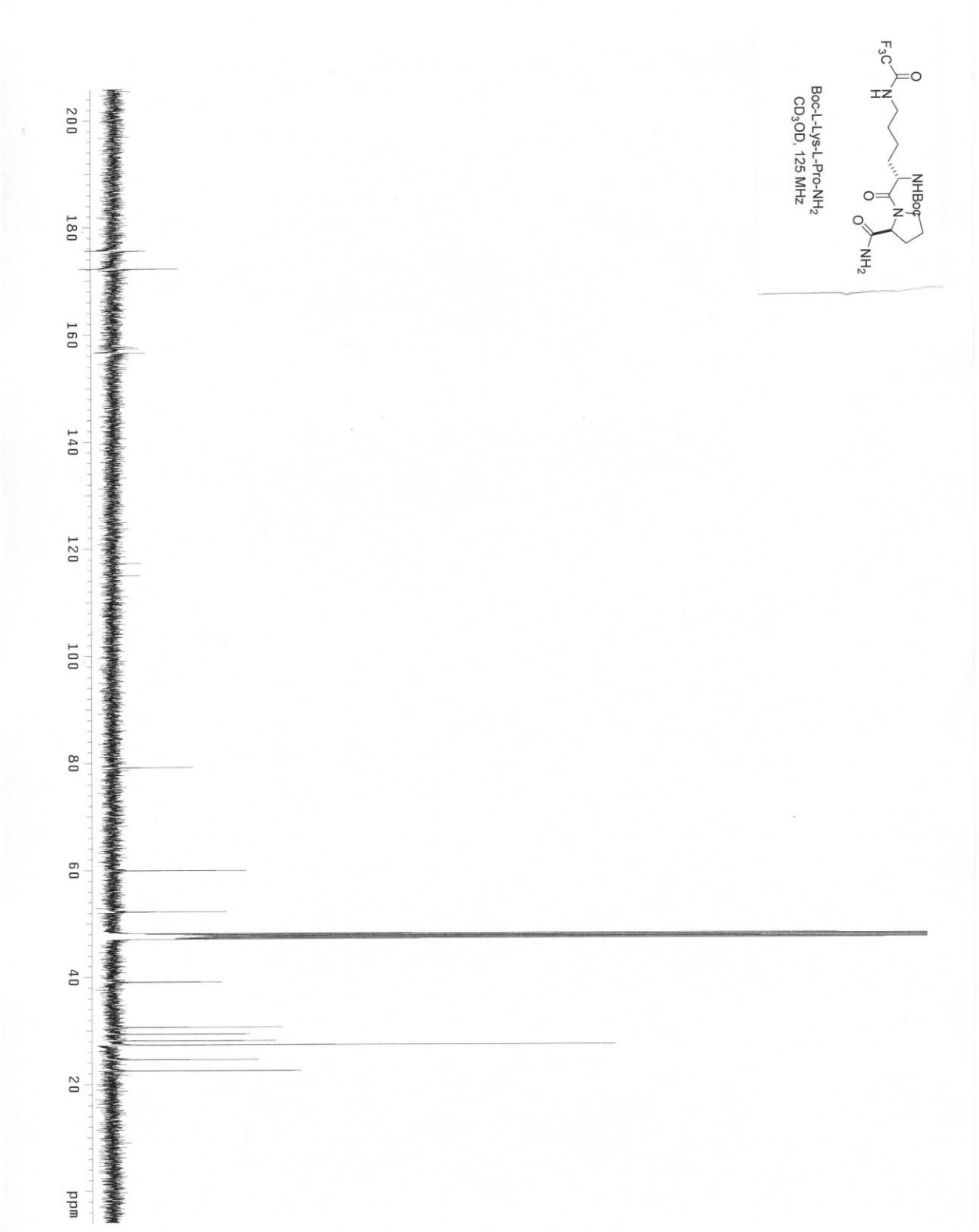
Z-D-Phg-L-Val-O^{t}Bu



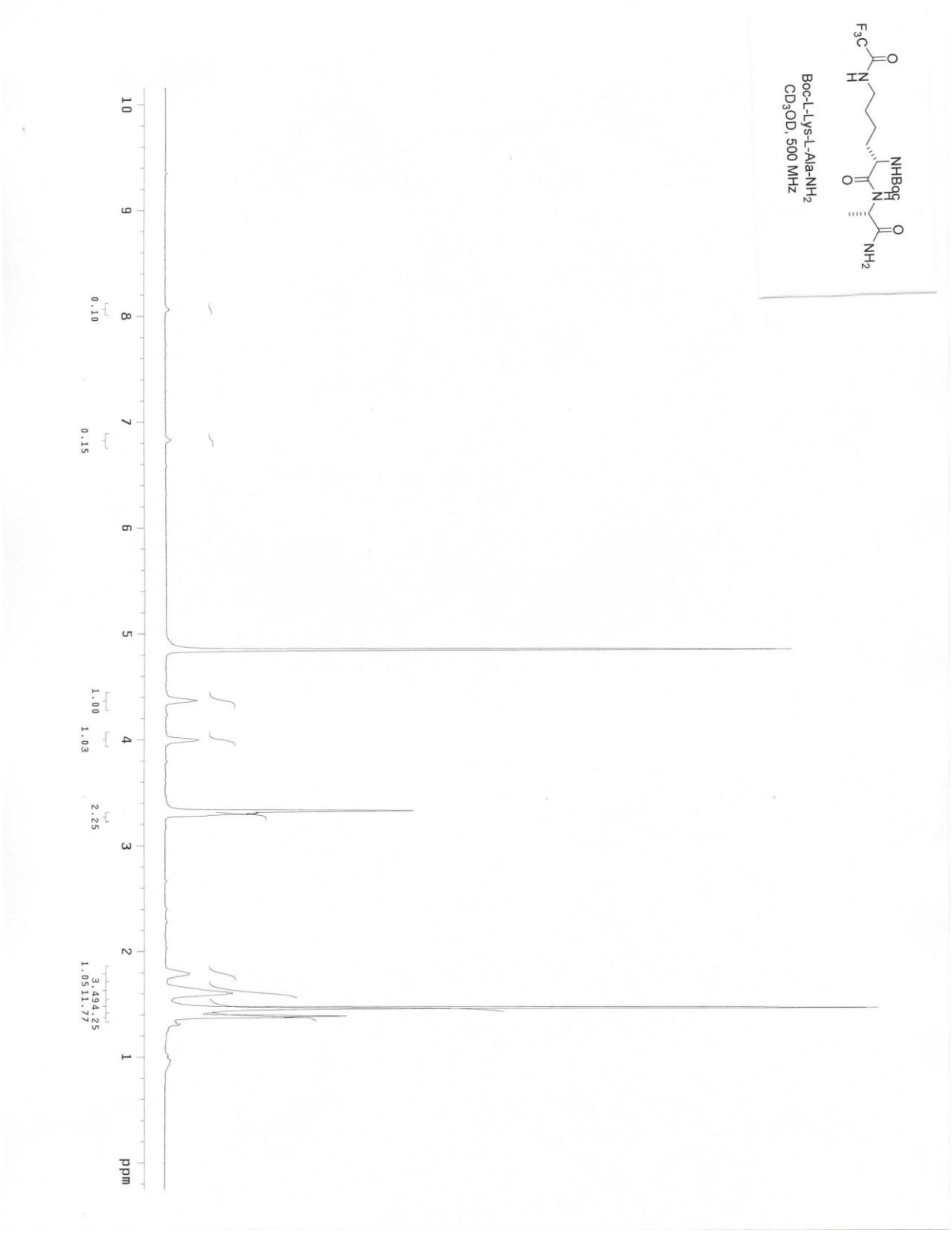

CbzHN
H
N
O
O
O
Z-D-Phg-L-Val-O^{t}Bu
$CDCl_3$, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

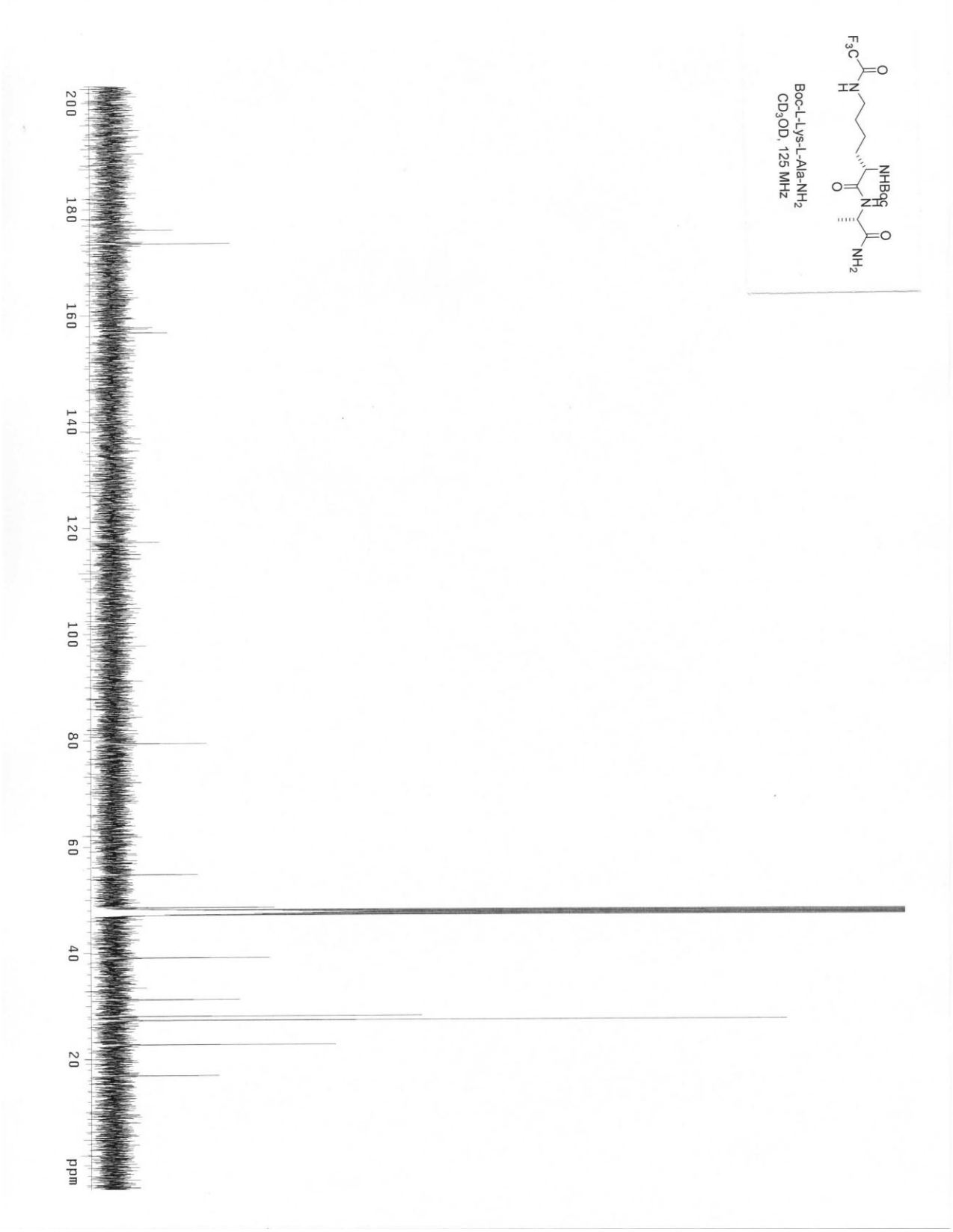
Boc-L-Lys-L-Pro-NH_2



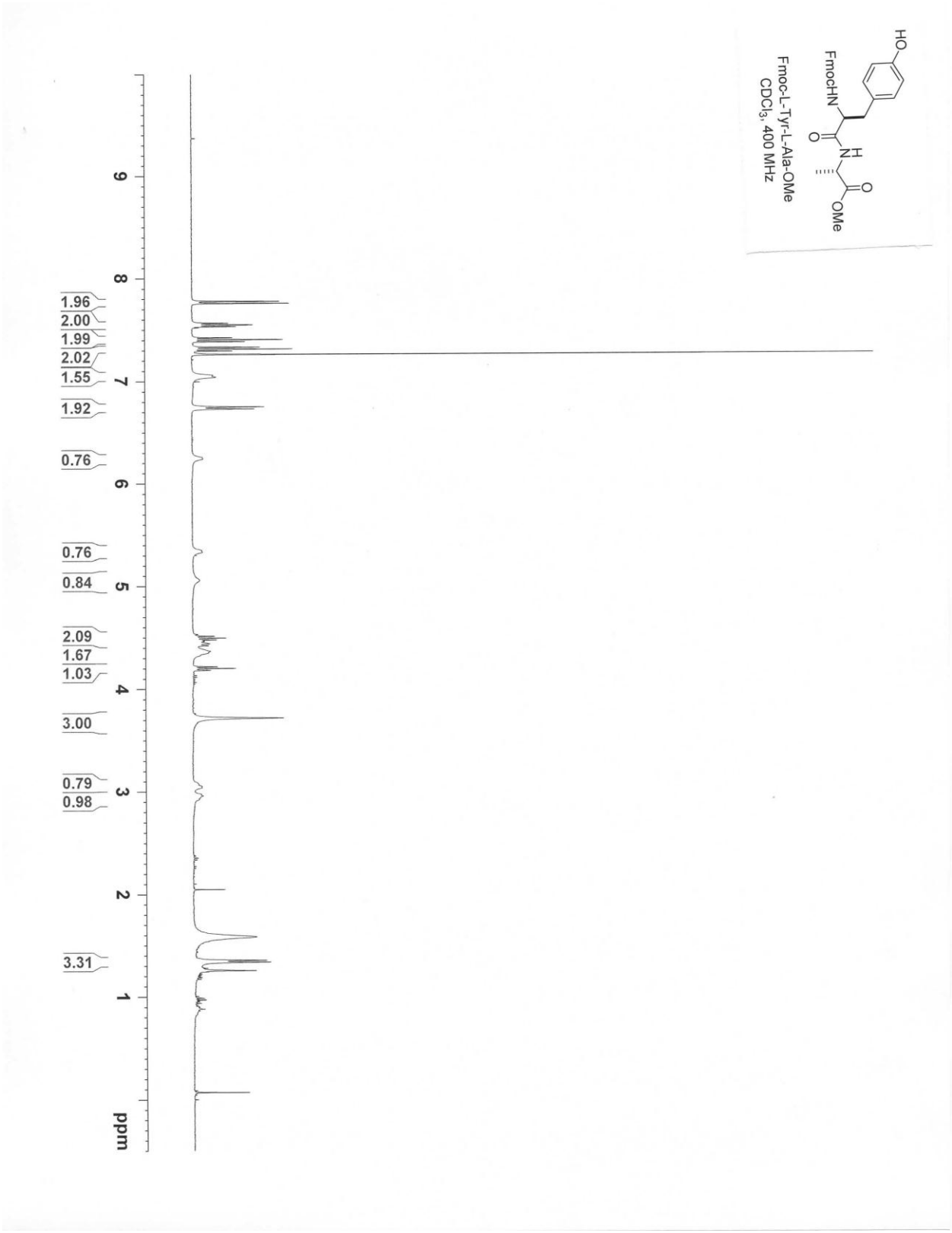

Boc-L-Lys-L-Pro-NH2
CD3OD, 125 MHz
F3C
NHBoc
NH2
200
180
160
140
120
100
80
60
40
20
ppm

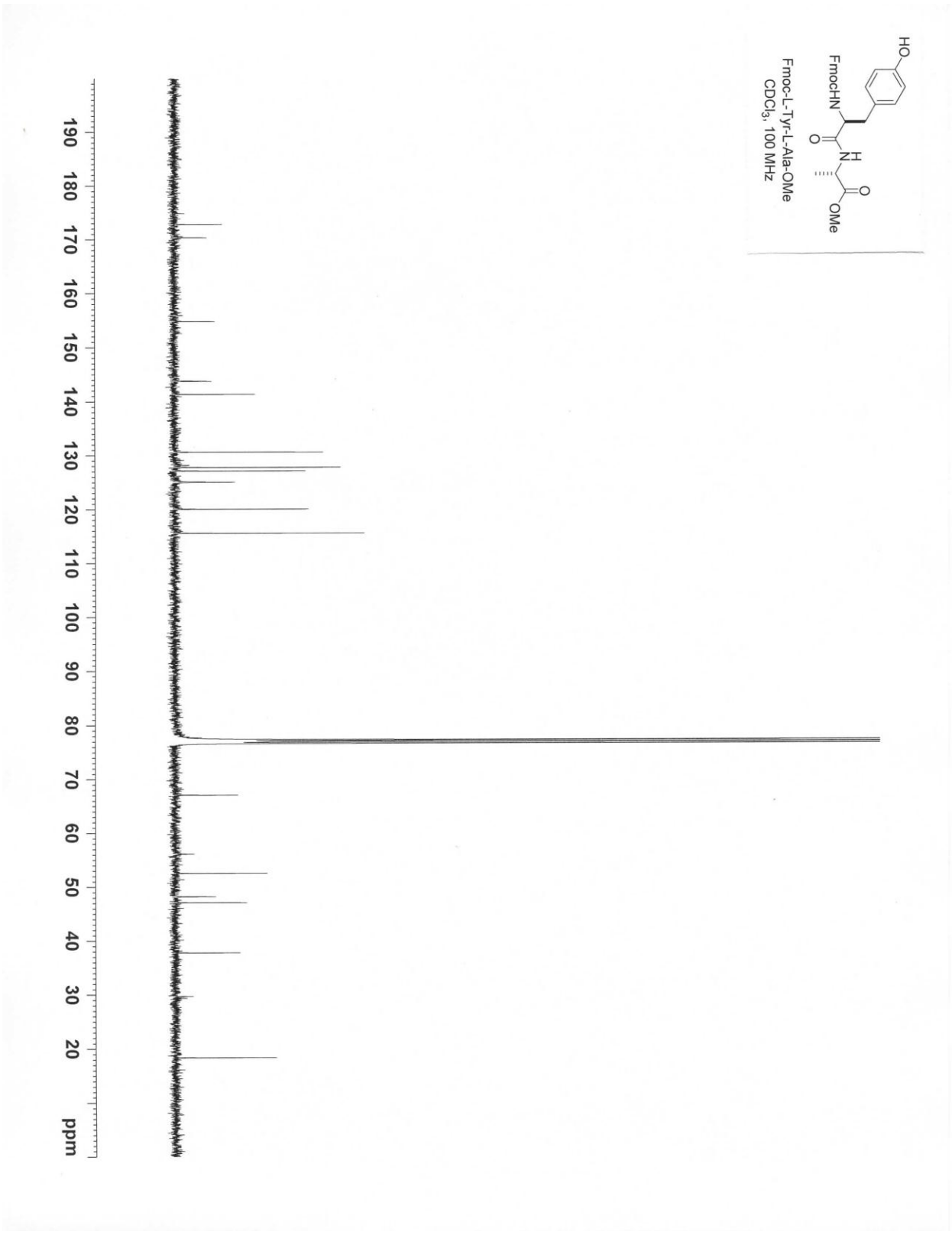
Boc-L-Lys-L-Ala-NH_2



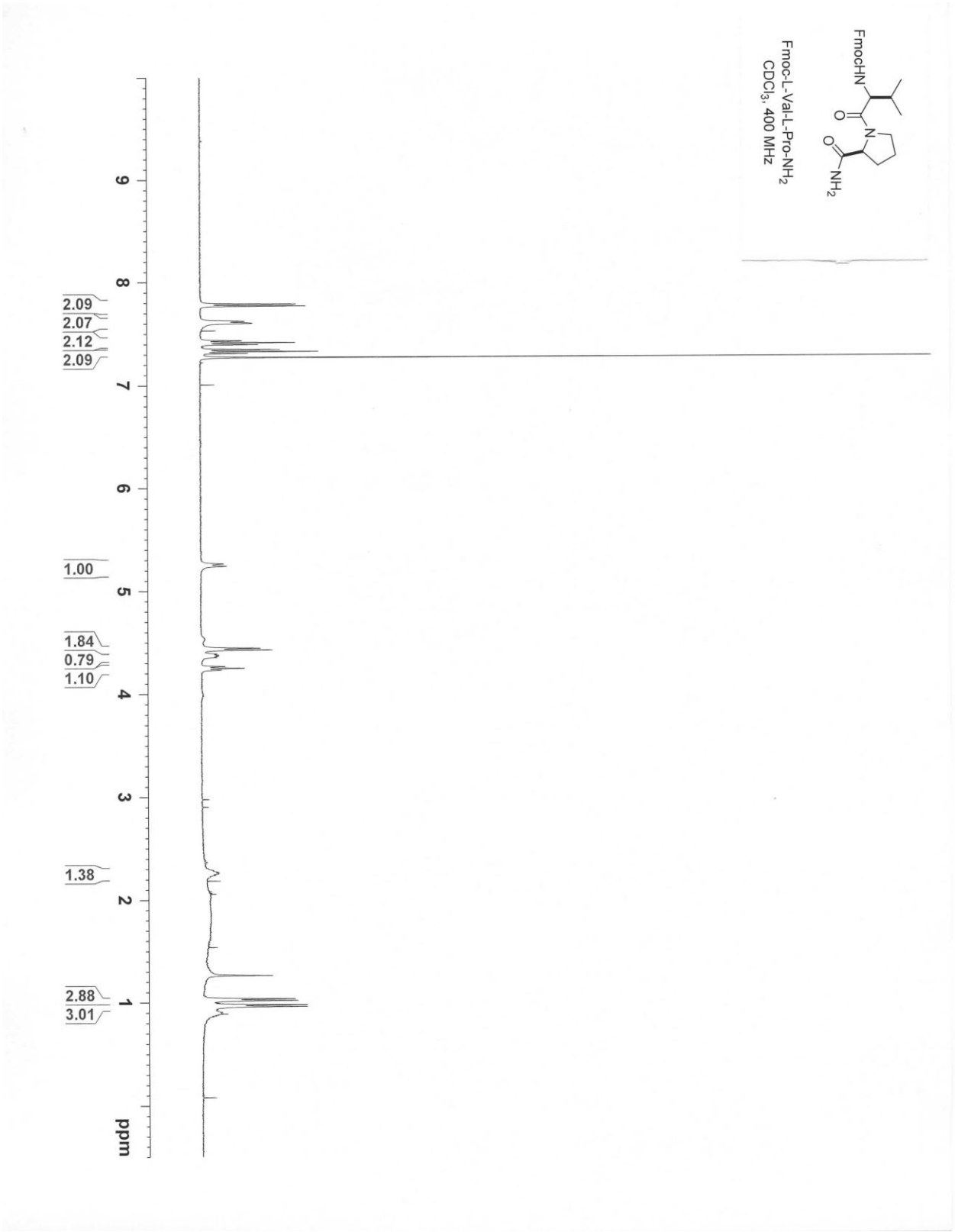

Boc-L-Lys-L-Ala-NH2
CD3OD, 125 MHz
NHBoc
NH2
200
180
160
140
120
100
80
60
40
20
ppm

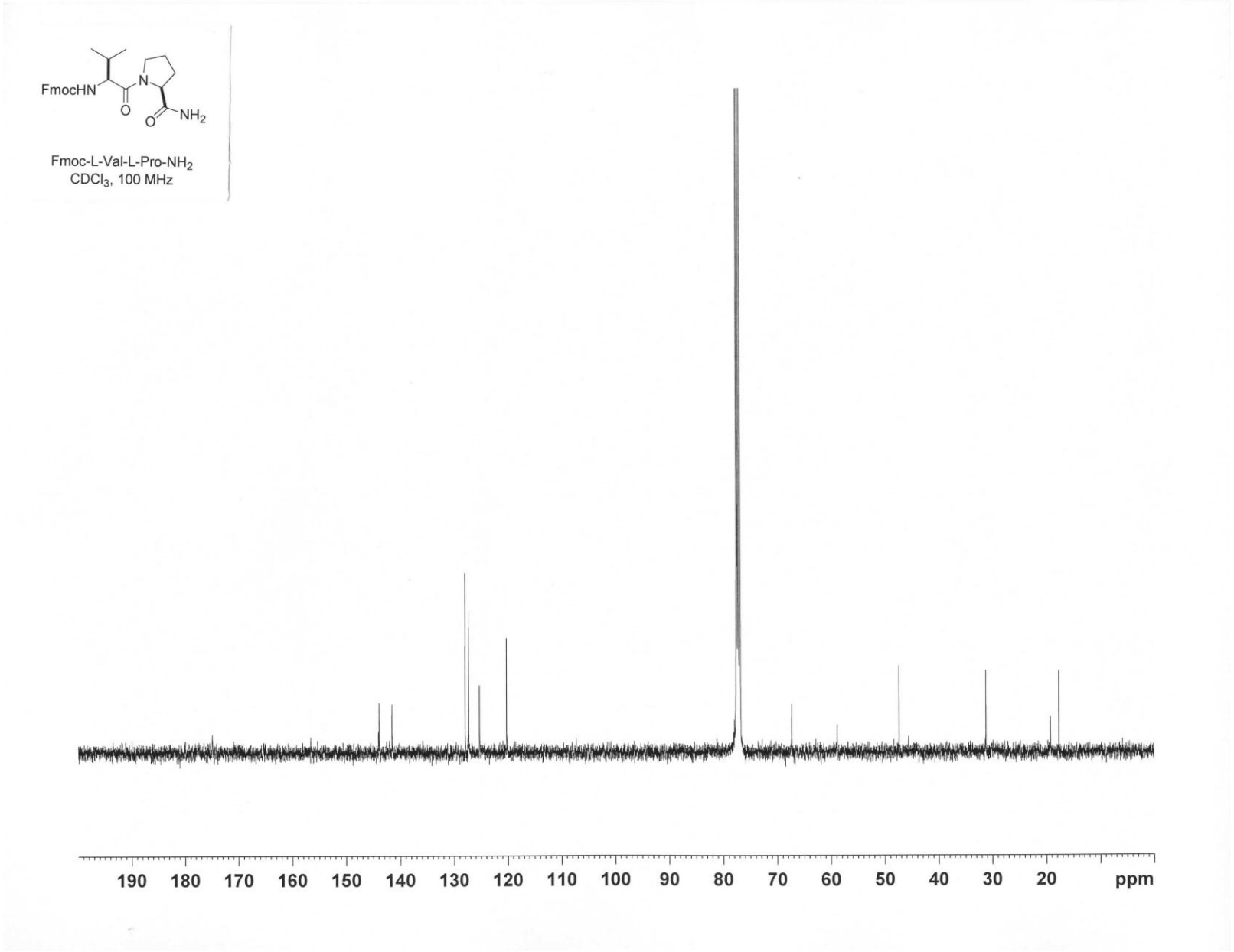
Fmoc-L-Tyr-L-Ala-OMe



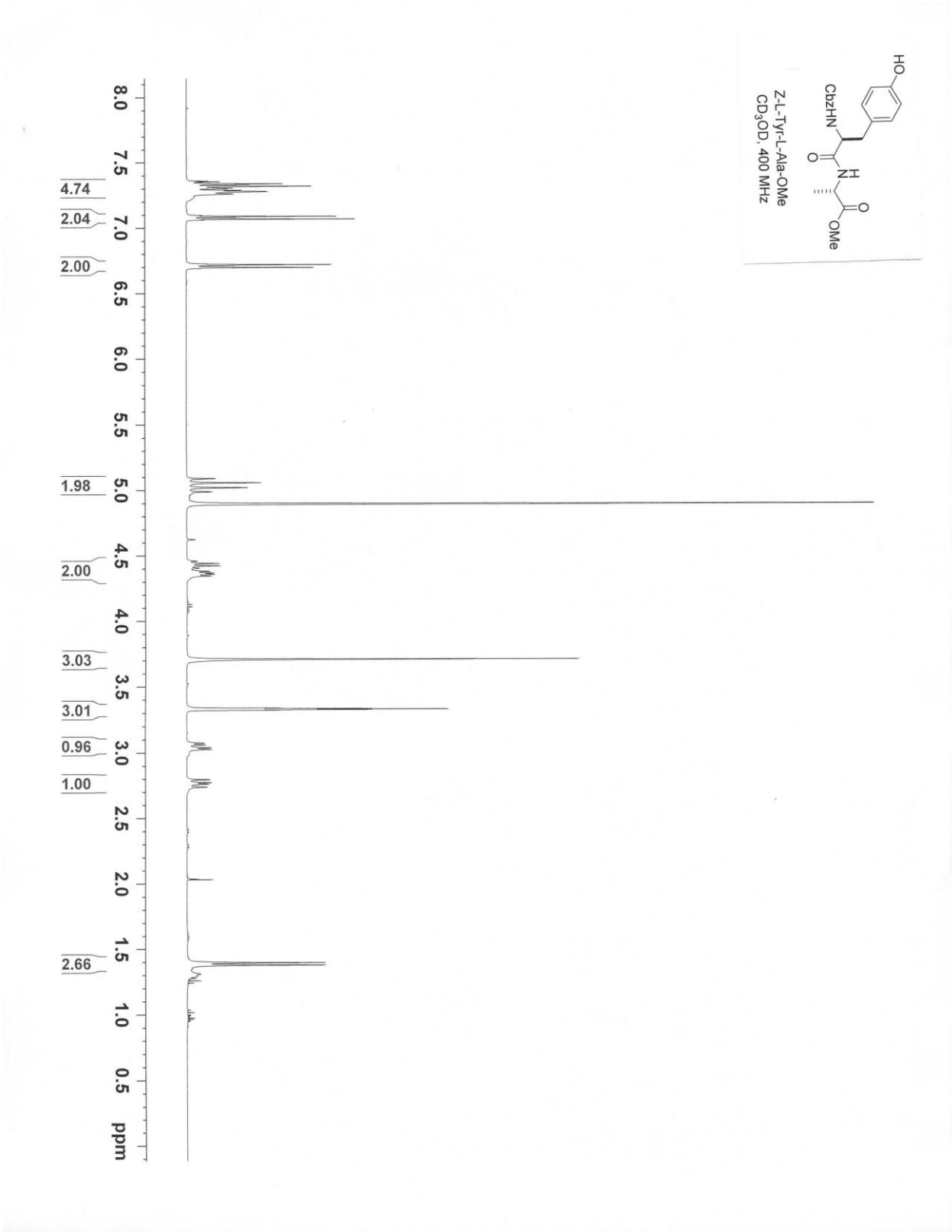

HO
FmocHN
H
N
O
O
OMe
Fmoc-L-Tyr-L-Ala-OMe
CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

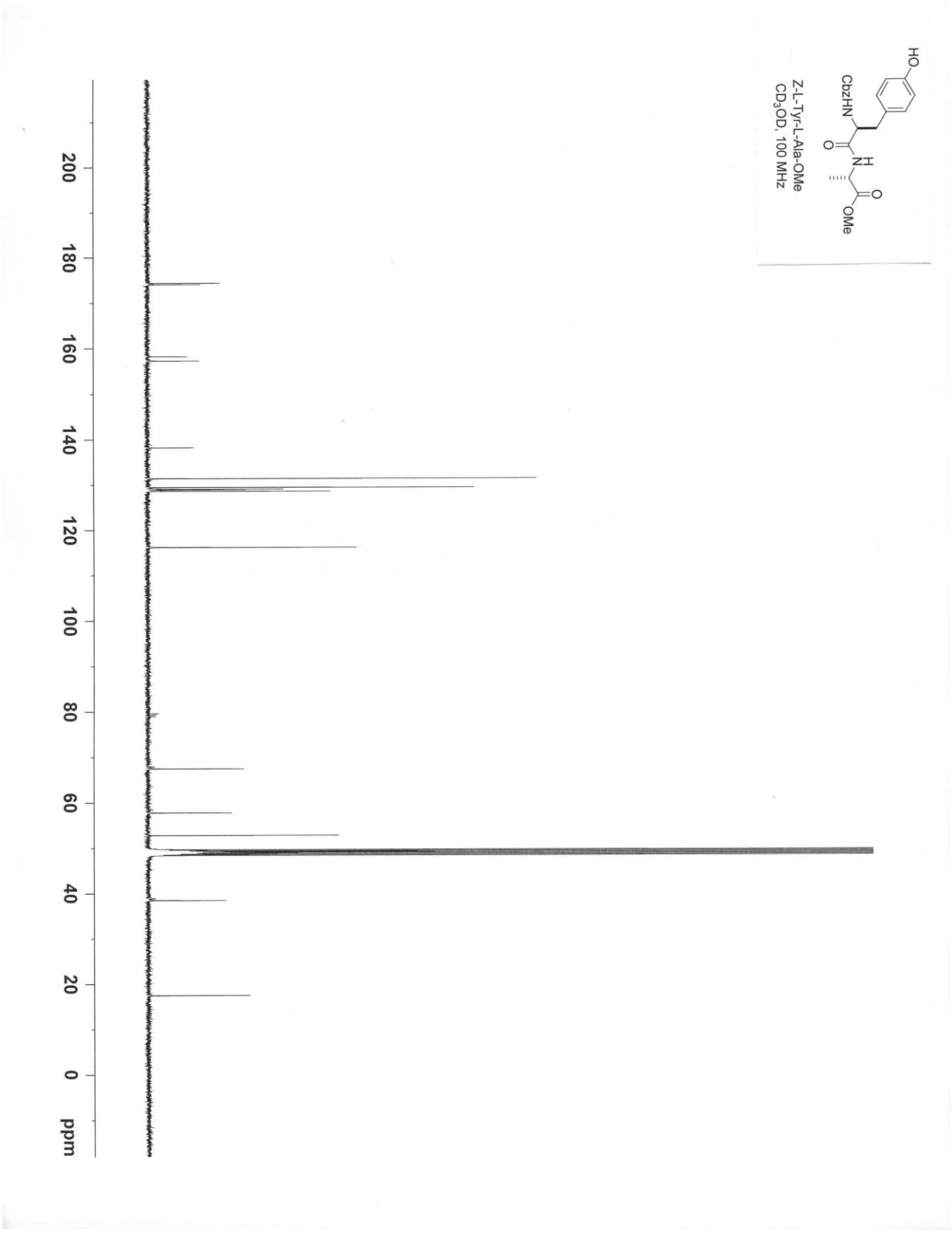
Fmoc-L-Val-L-Pro-NH_2



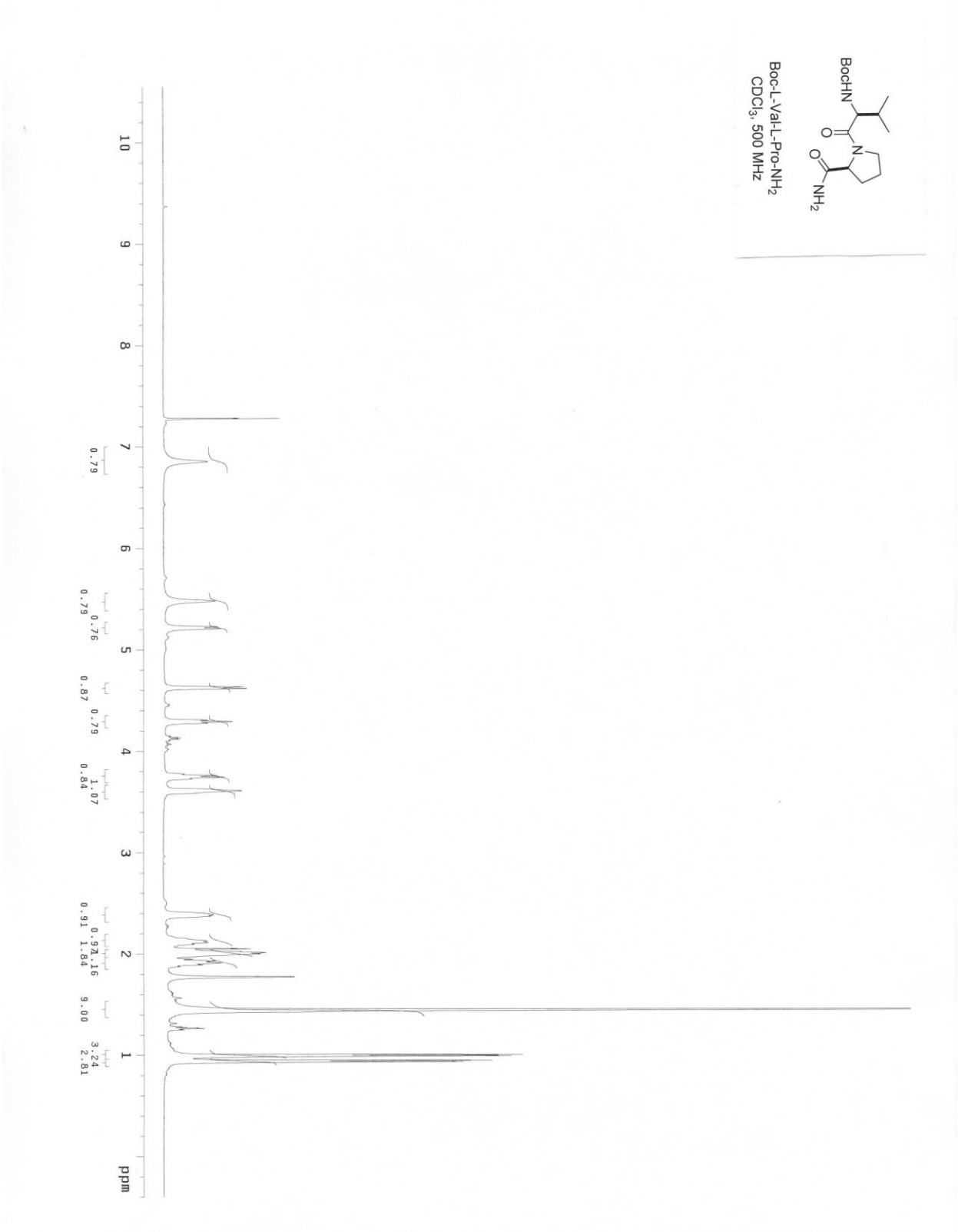

FmocHN
N
O
O
NH2
Fmoc-L-Val-L-Pro-NH2
CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

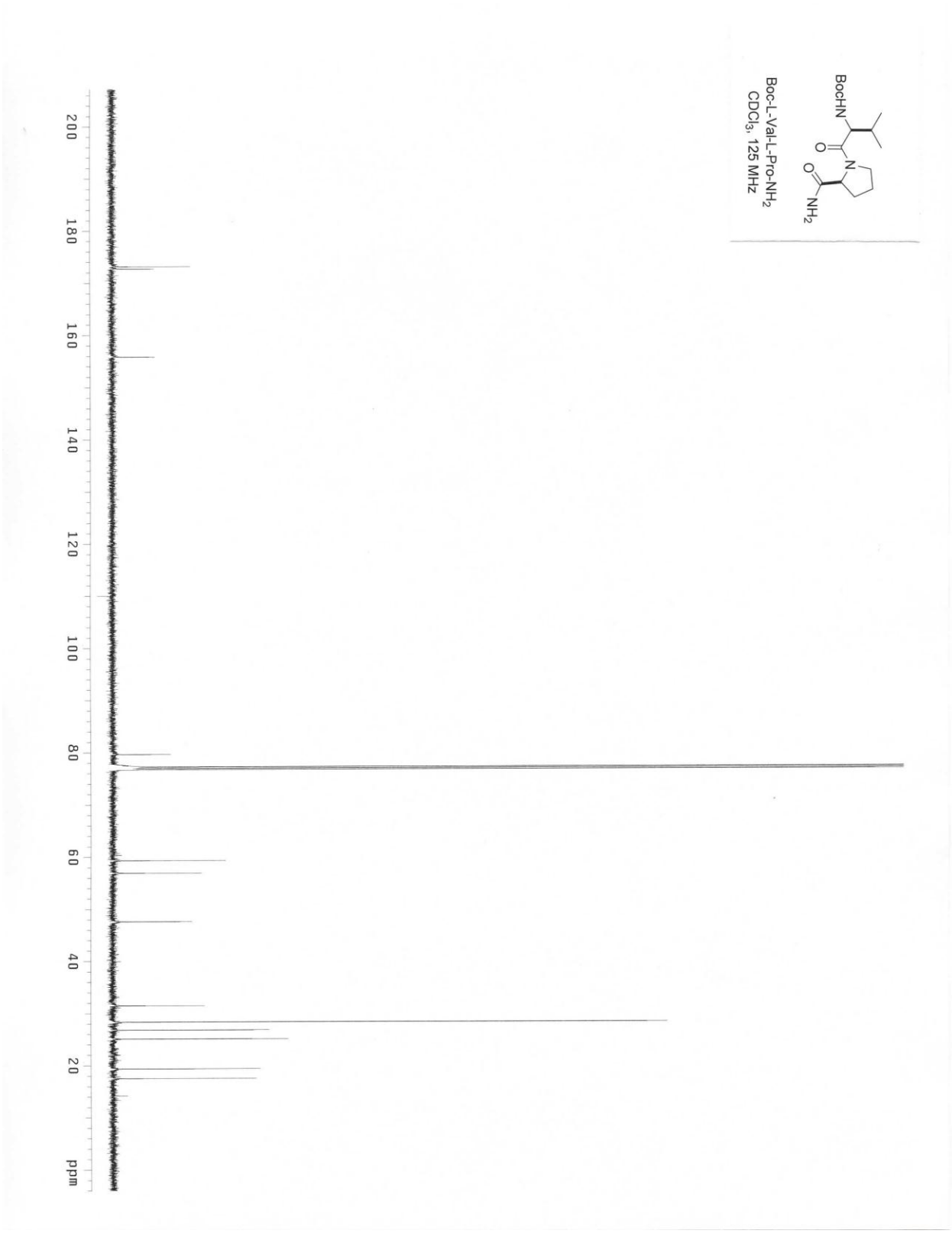
Z-L-Tyr-L-Ala-OMe



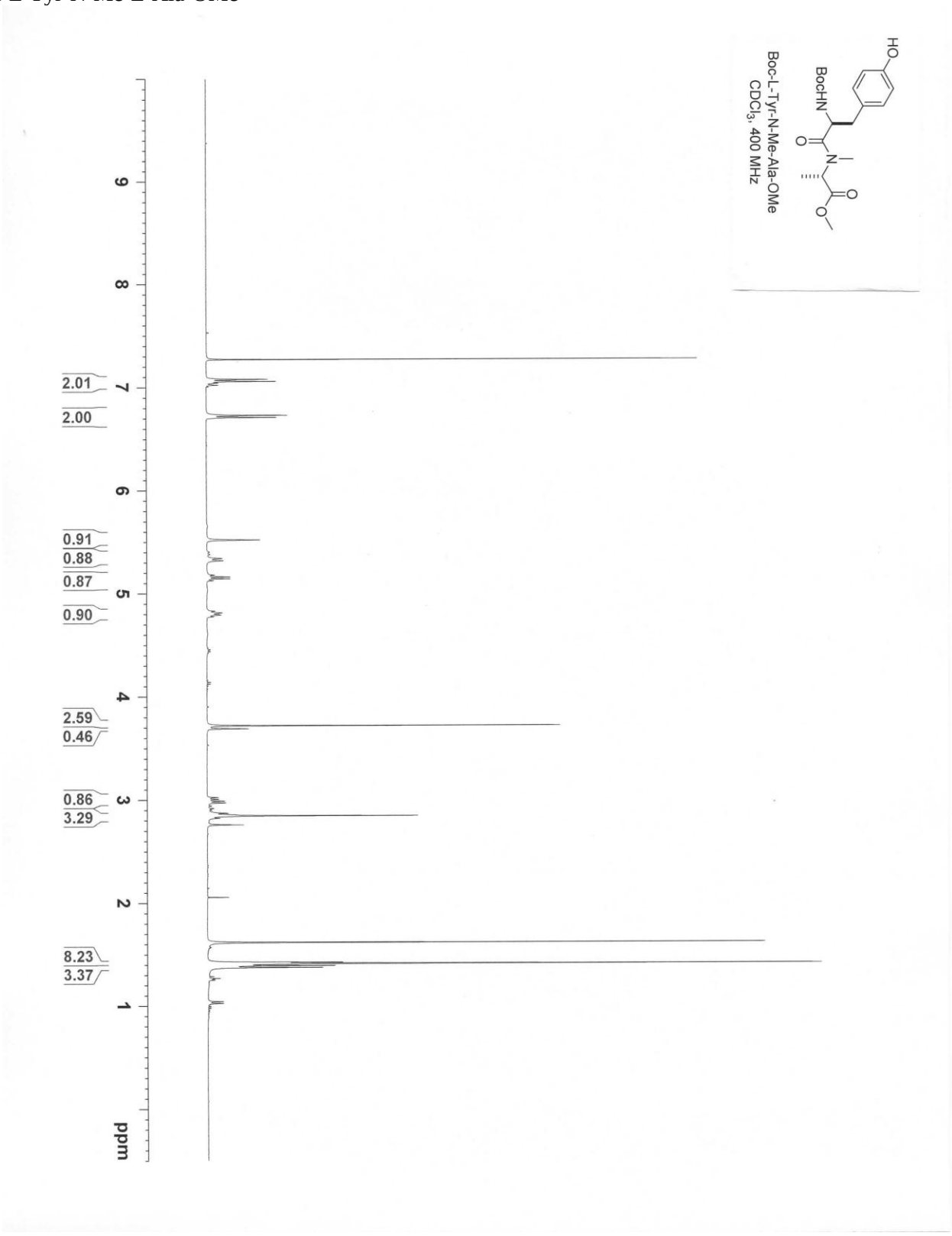

HO
CbzHN
H
N
O
O
OMe
Z-L-Tyr-L-Ala-OMe
CD3OD, 100 MHz
200
180
160
140
120
100
80
60
40
20
0
ppm

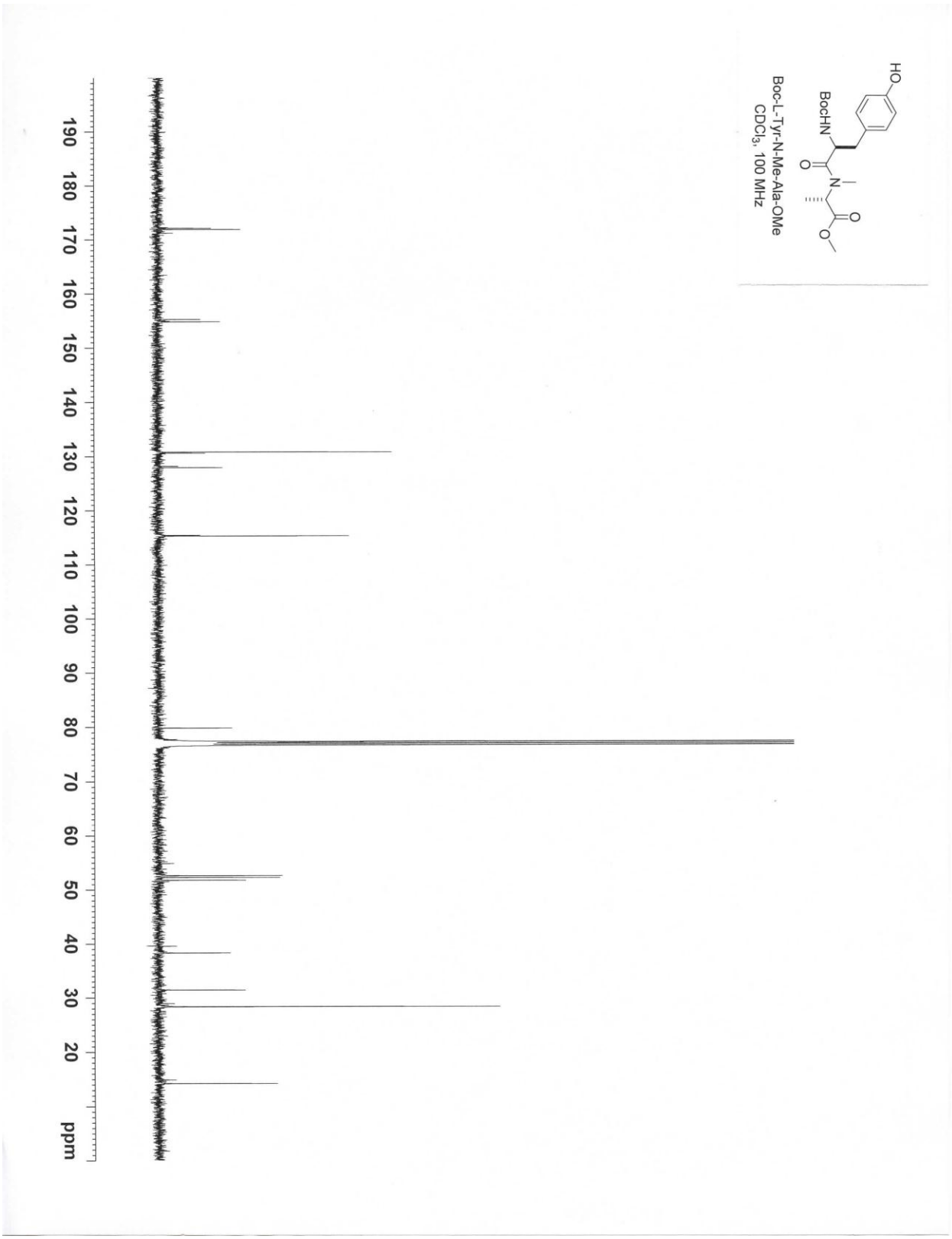
Boc-L-Val-L-Pro-NH_2



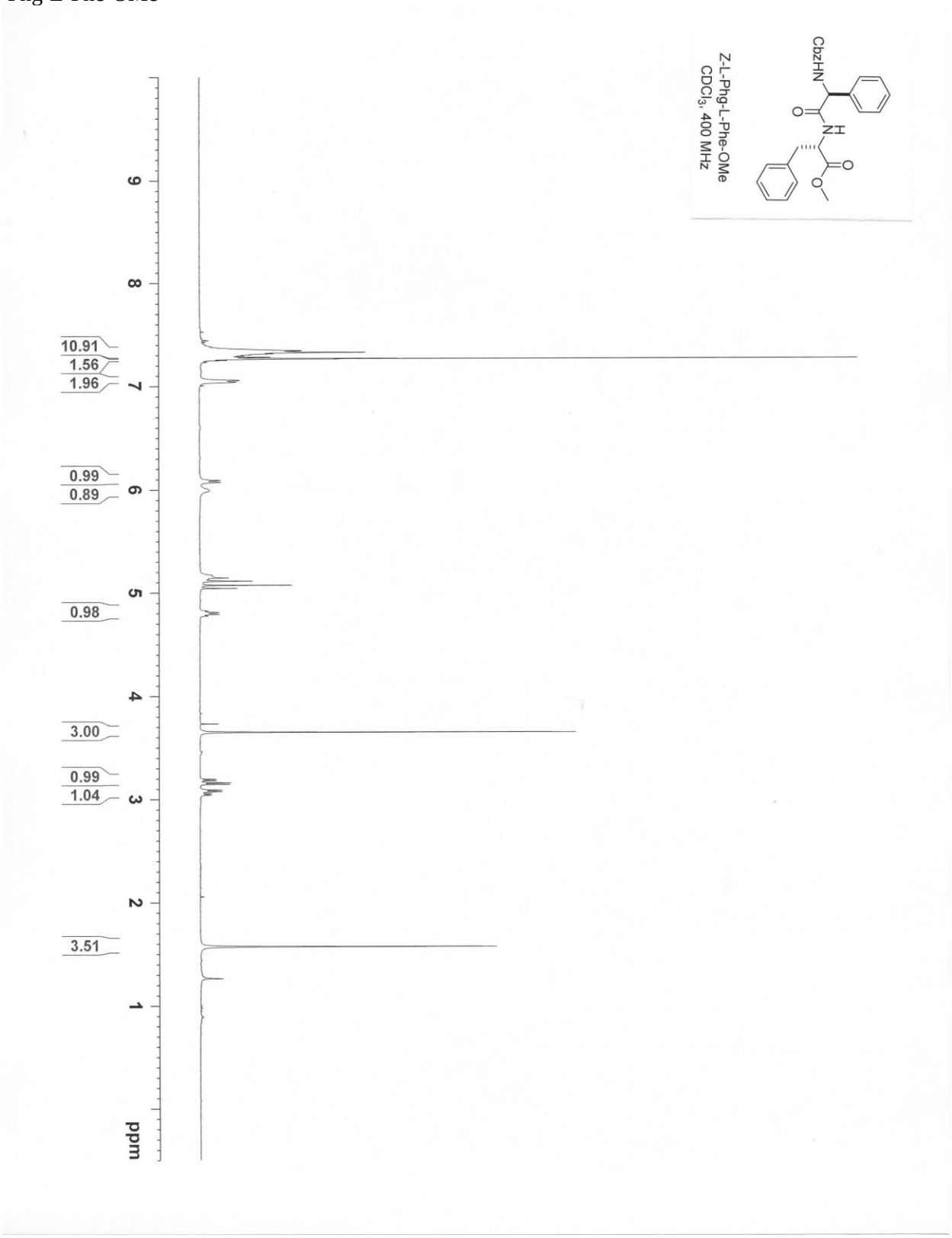

BocHN
O
N
O
NH2
Boc-L-Val-L-Pro-NH2
CDCl3, 125 MHz
200
180
160
140
120
100
80
60
40
20
ppm

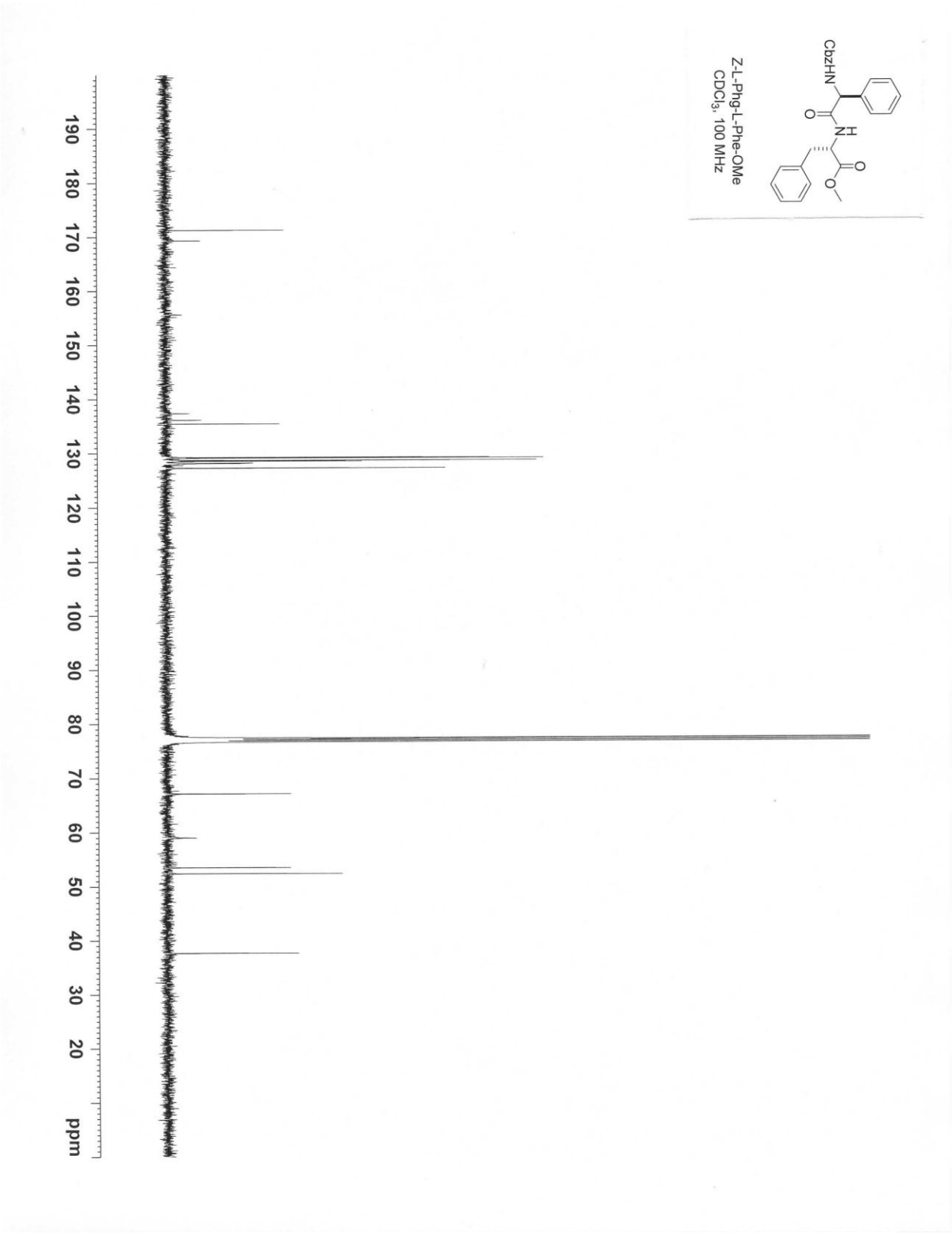
Boc-L-Tyr-N-Me-L-Ala-OMe



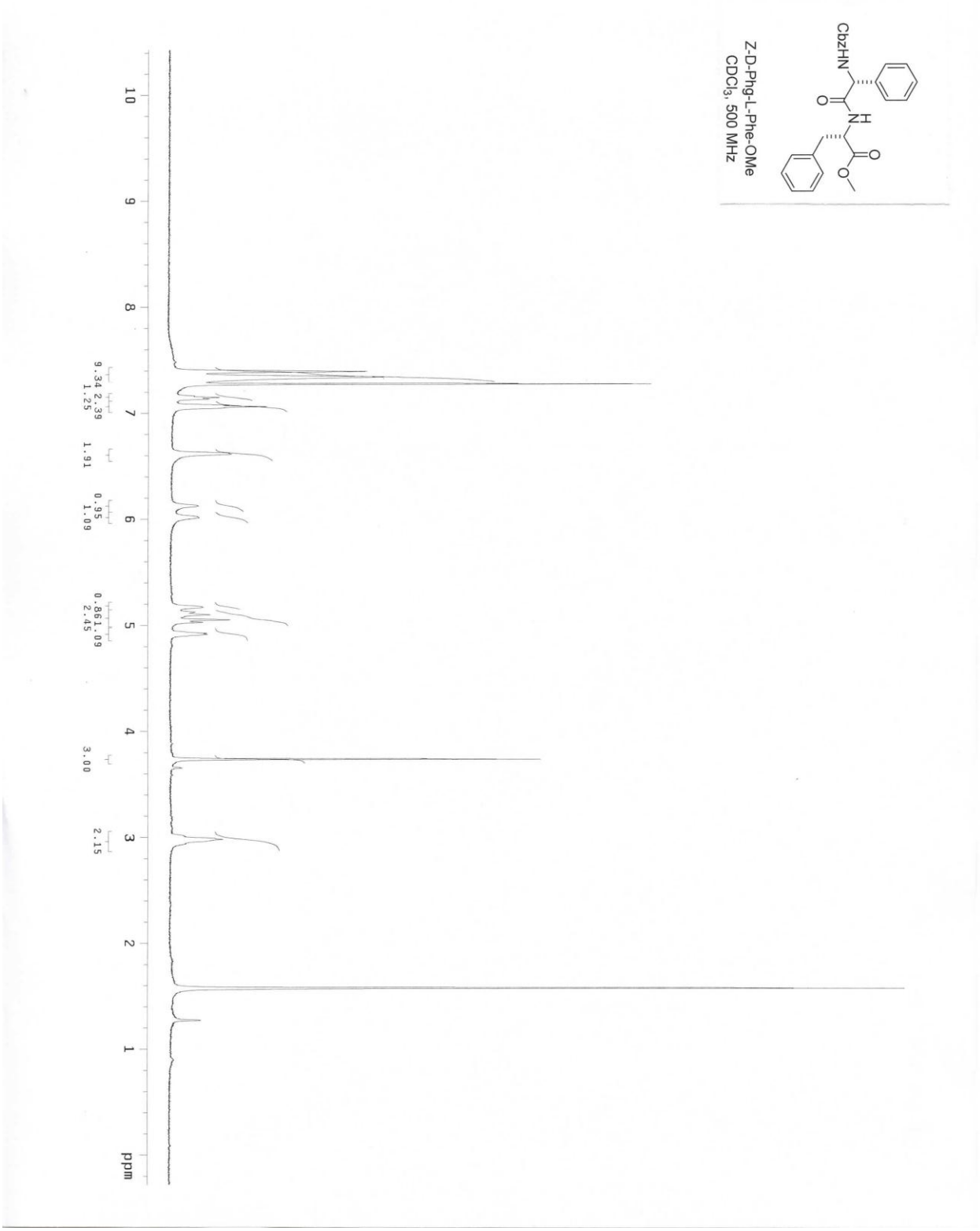

HO
BocHN
N
O
O
O
Boc-L-Tyr-N-Me-Ala-OMe
CDCl3, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

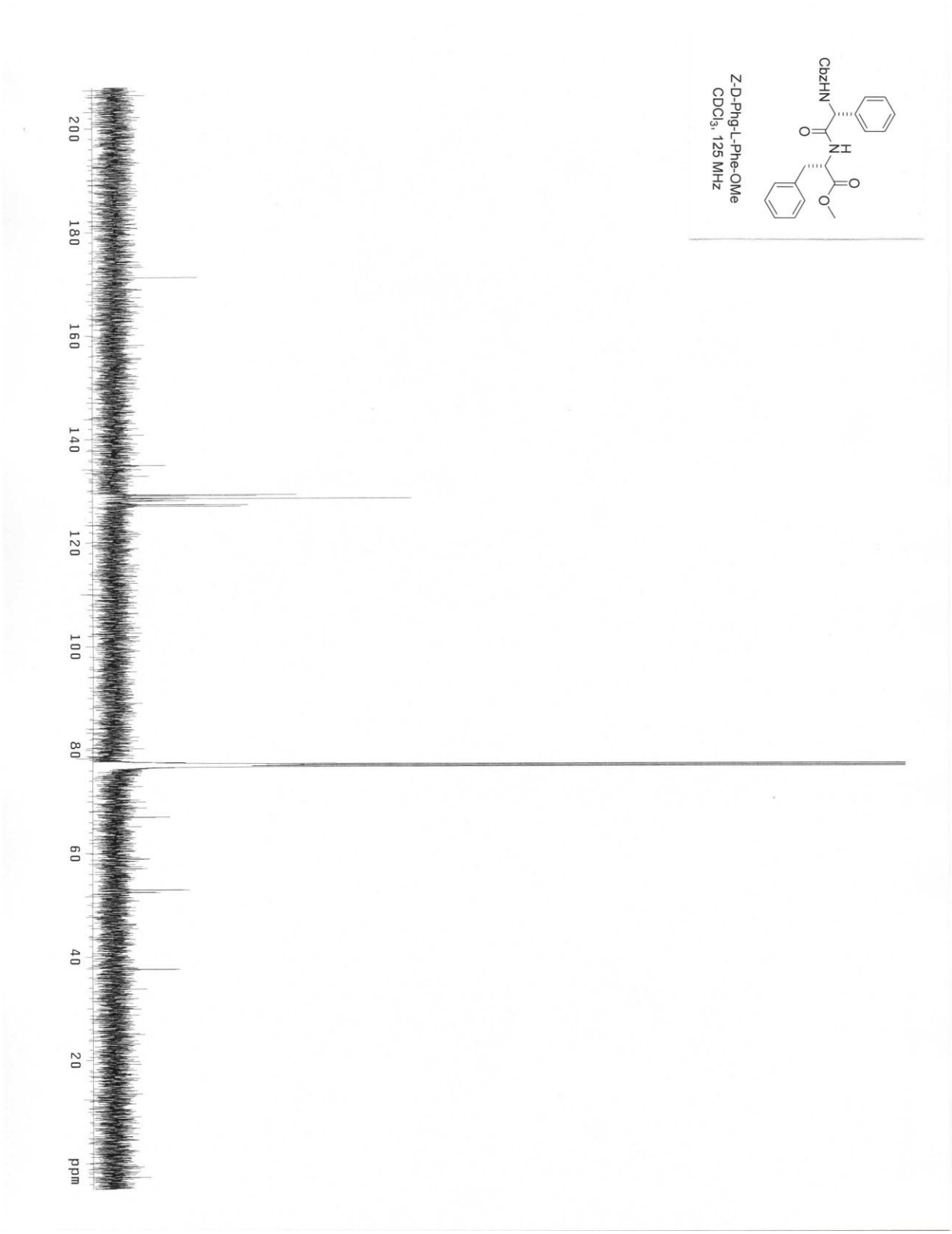
Z-L-Phg-L-Phe-OMe



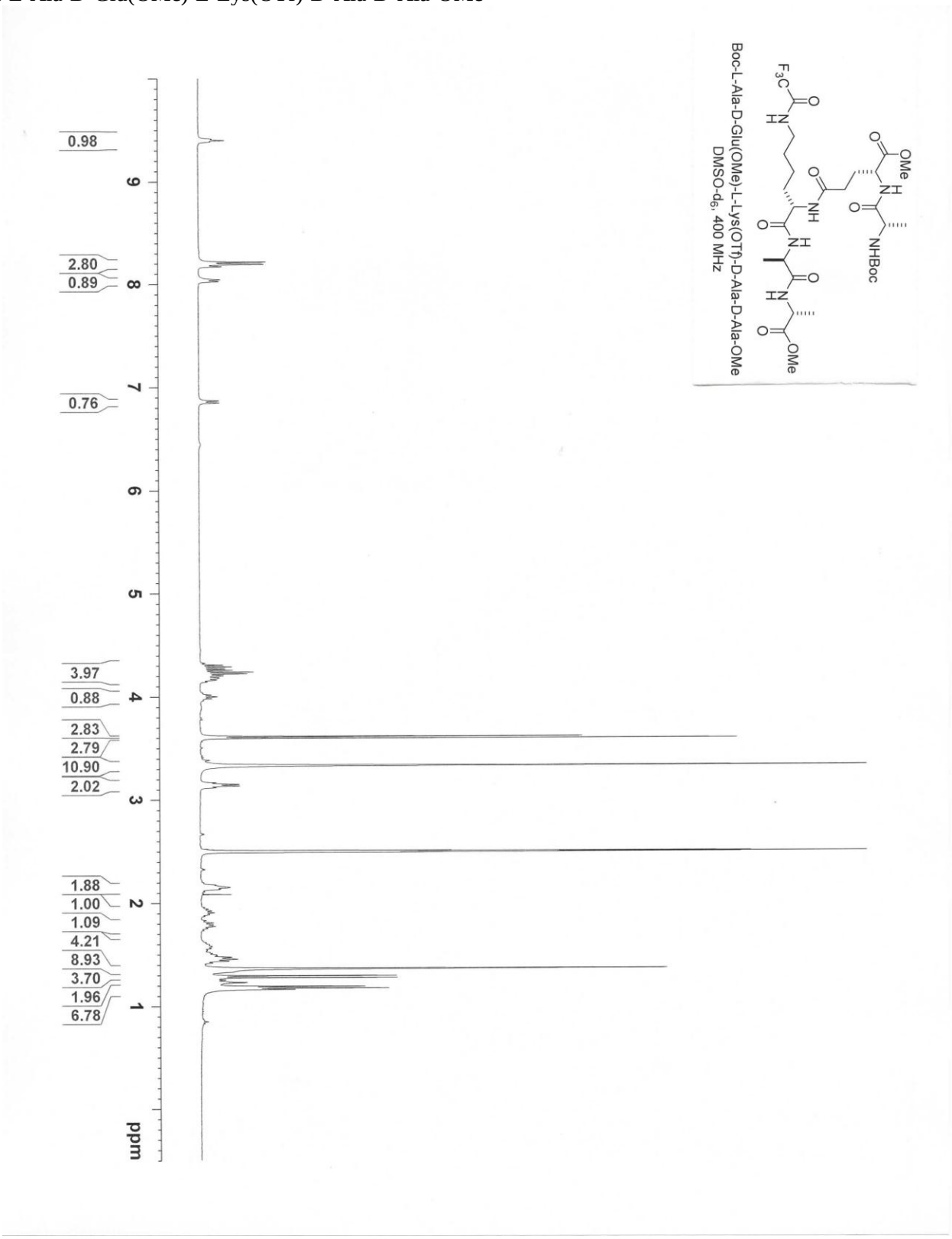

Z-L-Phg-L-Phe-OMe
CDCl3, 100 MHz
CbzHN
O
H
N
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

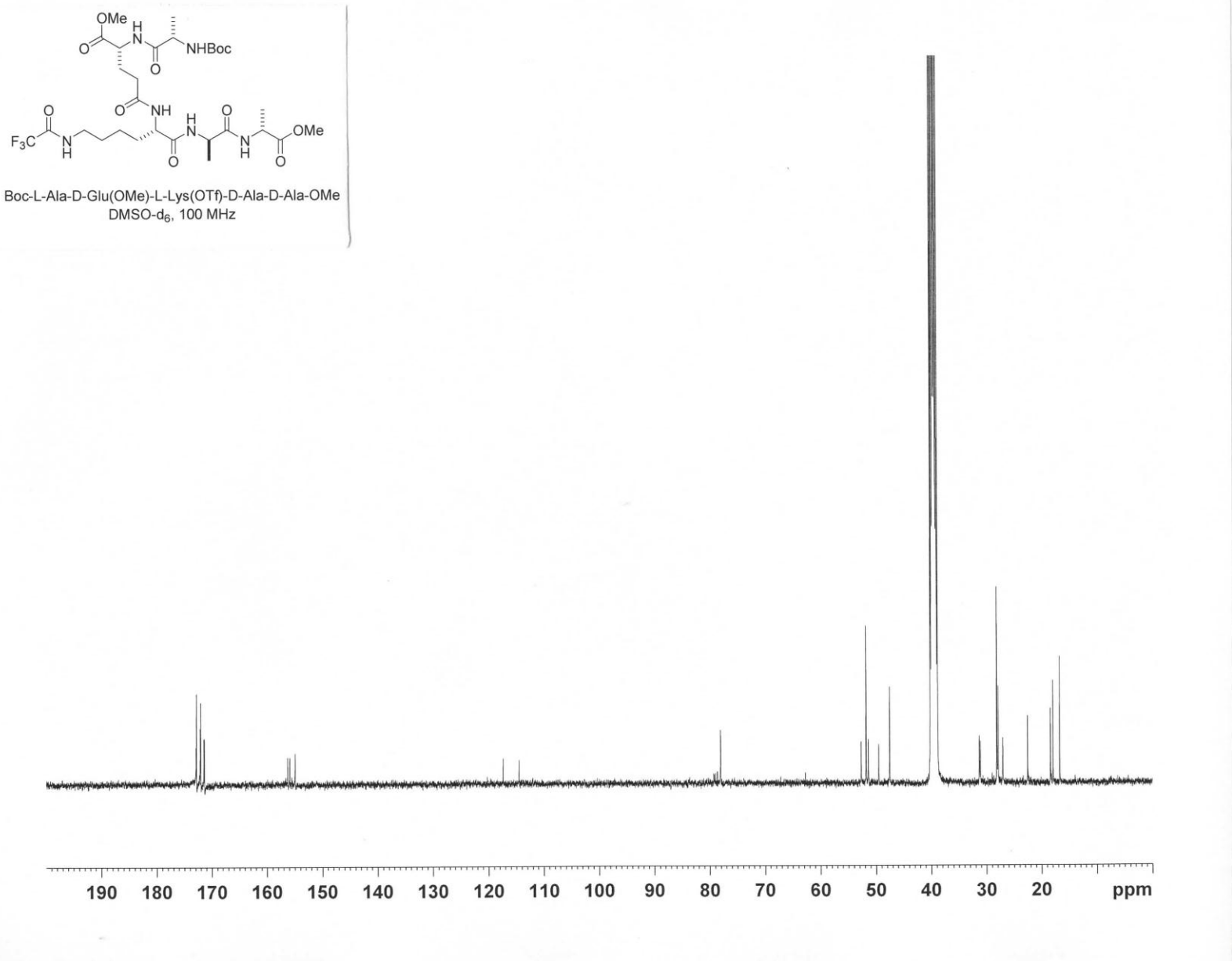
Z-D-Phg-L-Phe-OMe




Z-D-Phg-L-Phe-OMe
CDCl3, 125 MHz
CbzHN
O
N
H
O
O
200
180
160
140
120
100
80
60
40
20
ppm

Boc-L-Ala-D-Glu(OMe)-L-Lys(OTf)-D-Ala-D-Ala-OMe

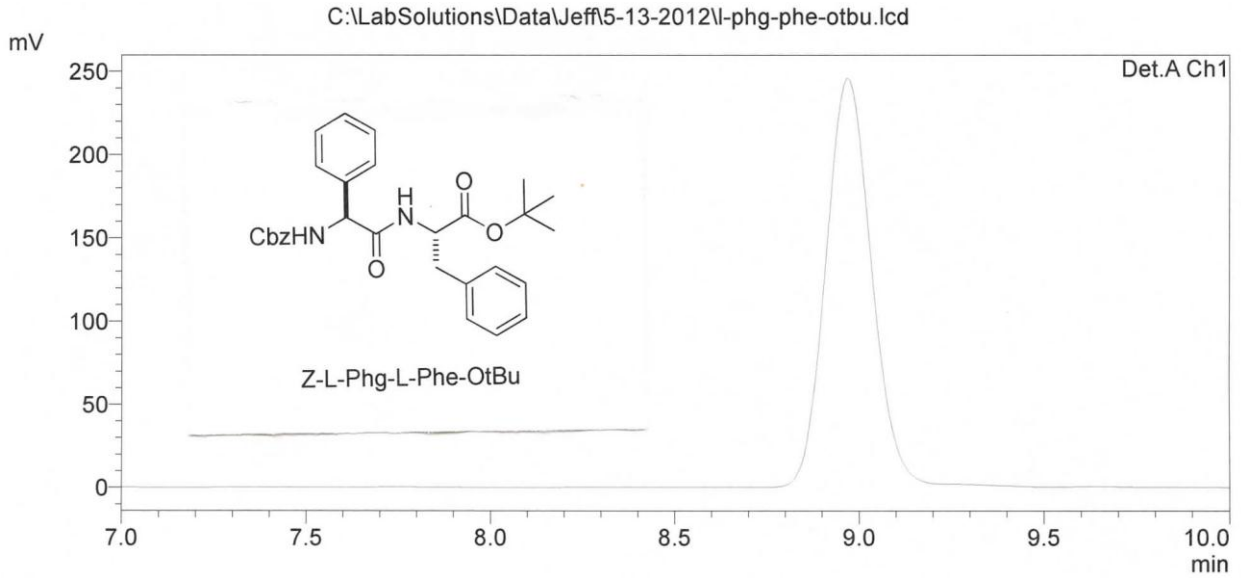



OMe
NHBoc
NH
OMe
F3C
Boc-L-Ala-D-Glu(OMe)-L-Lys(OTf)-D-Ala-D-Ala-OMe
DMSO-d6, 100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Racemic analysis *via* HPLC

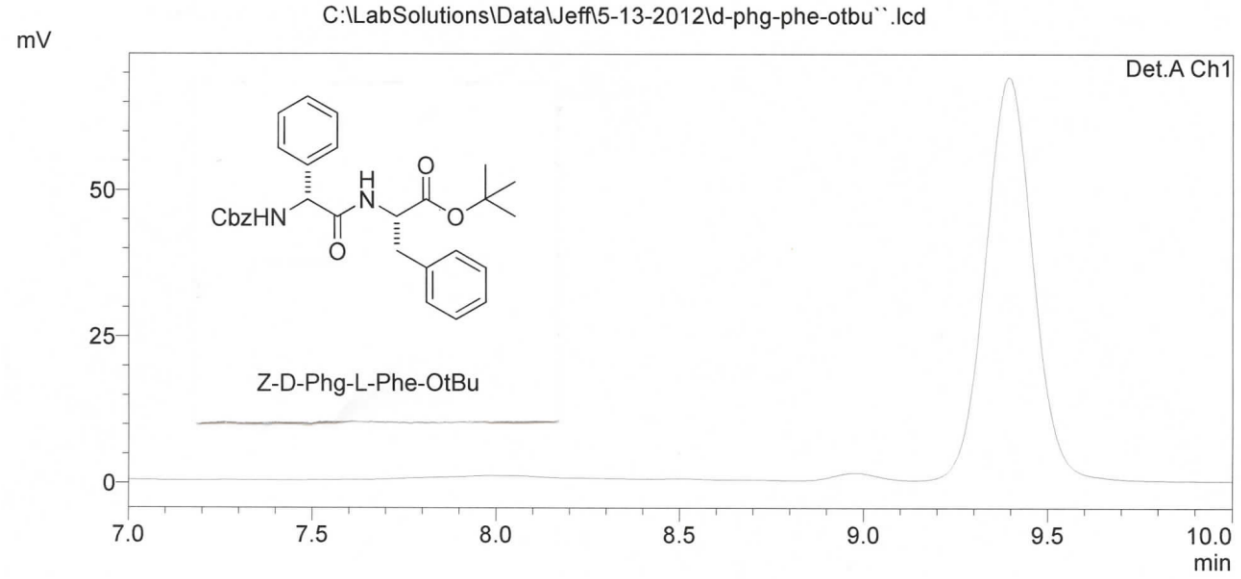
Z-L-Phg-L-Phe-O^{t}Bu

Chromatography condition: 60-70% acetonitrile in 0.05% formic acid in 12 min, 0.5 ml/min, 254 nm
Result: t_R = 8.98 min, *de* > 99.8%



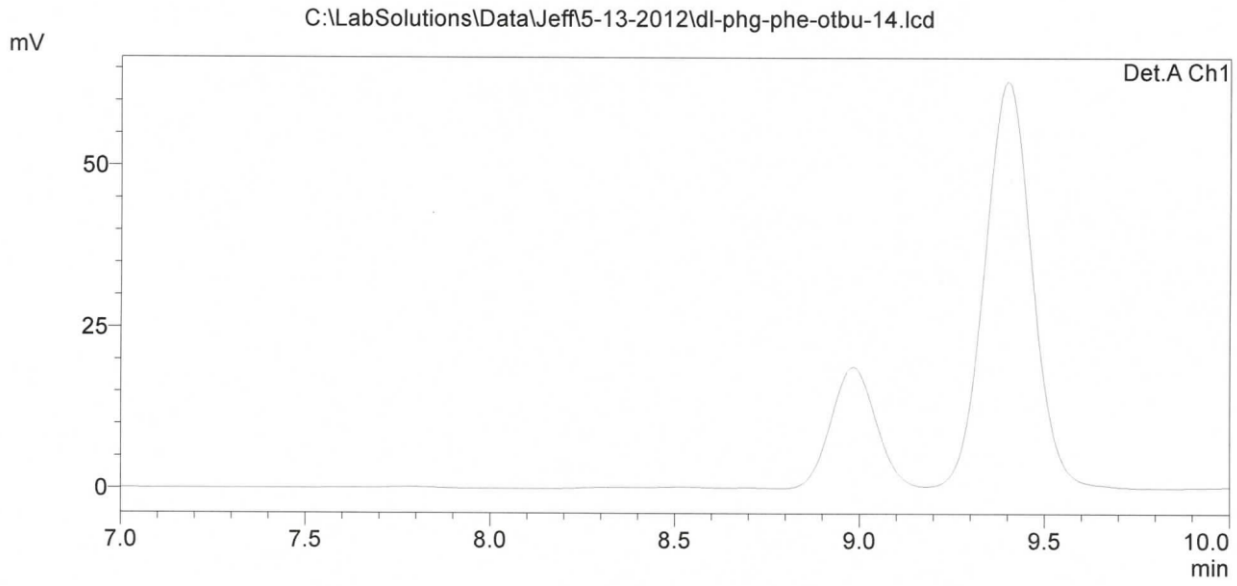
Z-D-Phg-L-Phe-O^{t}Bu

Chromatography condition: 60-70% acetonitrile in 0.05% formic acid in 12 min, 0.5 ml/min, 254 nm
Result: t_R = 9.40 min, *de* = 95.9%



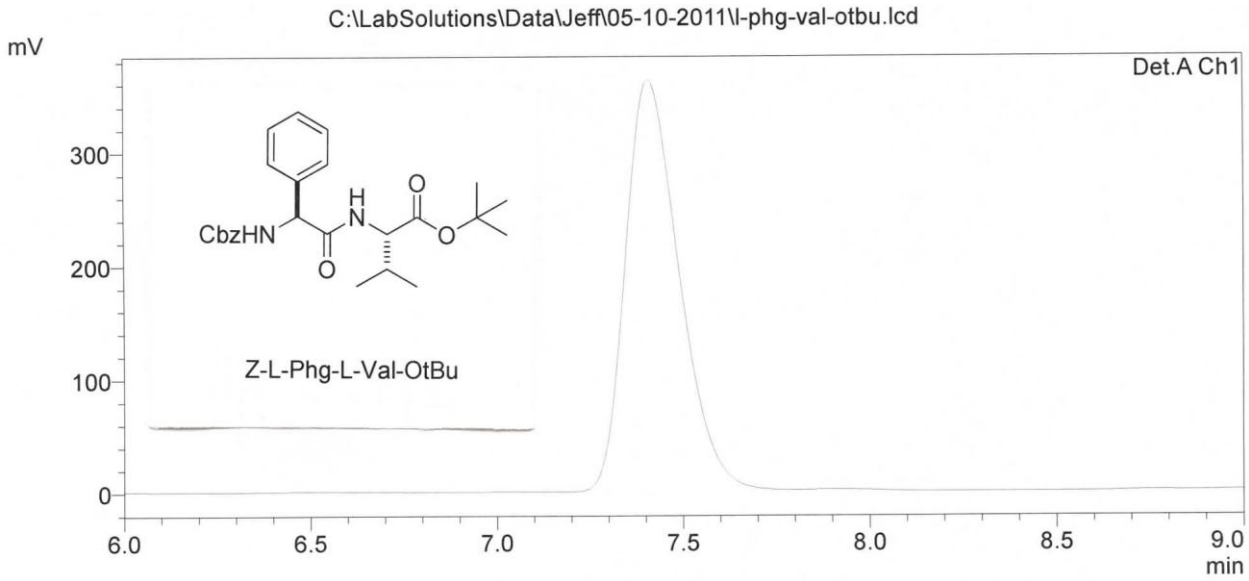
Z-L-Phg-L-Phe-O^{t}Bu + Z-D-Phg-L-Phe-O^{t}Bu

Chromatography condition: 60-70% acetonitrile in 0.05% formic acid in 12 min, 0.5 ml/min, 254 nm



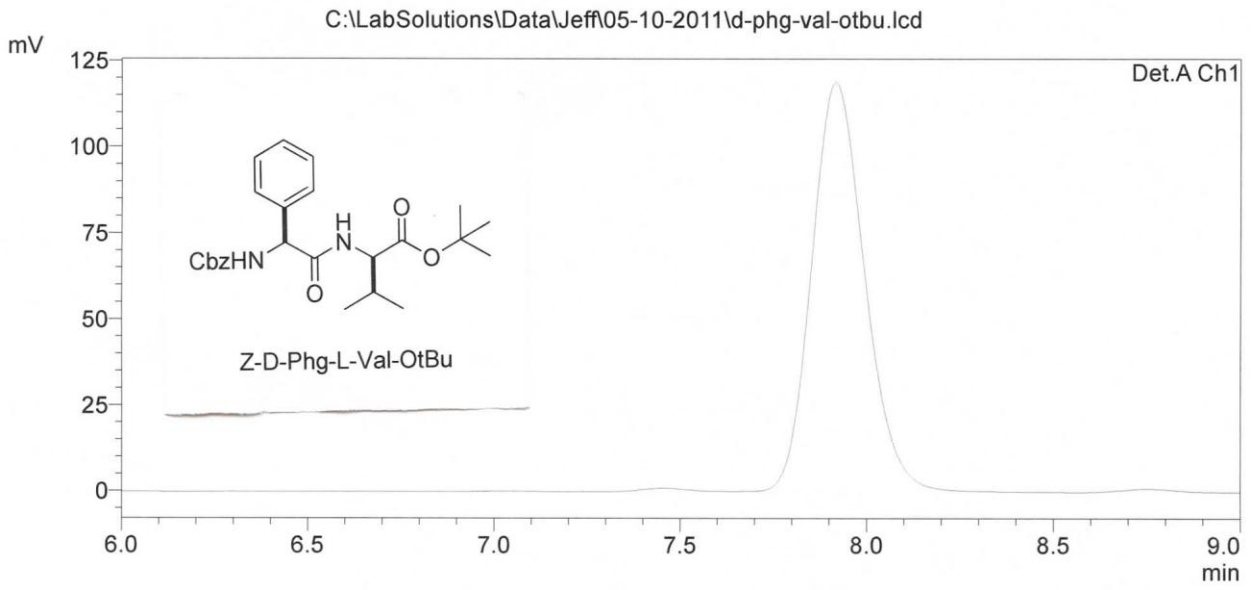
Z-L-Phg-L-Val-O^{t}Bu

Chromatography condition: 60-70% acetonitrile in 0.05% formic acid in 12 min, 0.5 ml/min, 254 nm
Result: t_R = 7.42 min, *de* > 99.8%



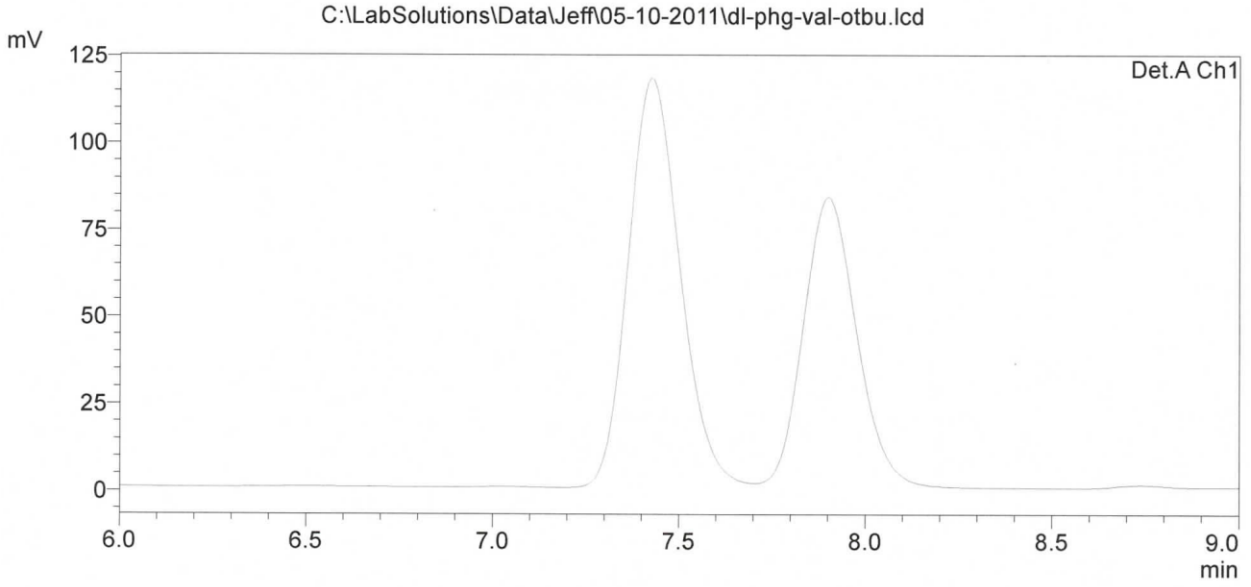
Z-D-Phg-L-Val-O^{t}Bu

Chromatography condition: 60-70% acetonitrile in 0.05% formic acid in 12 min, 0.5 ml/min, 254 nm
Result: t_R = 7.90 min, *de* = 96.3%



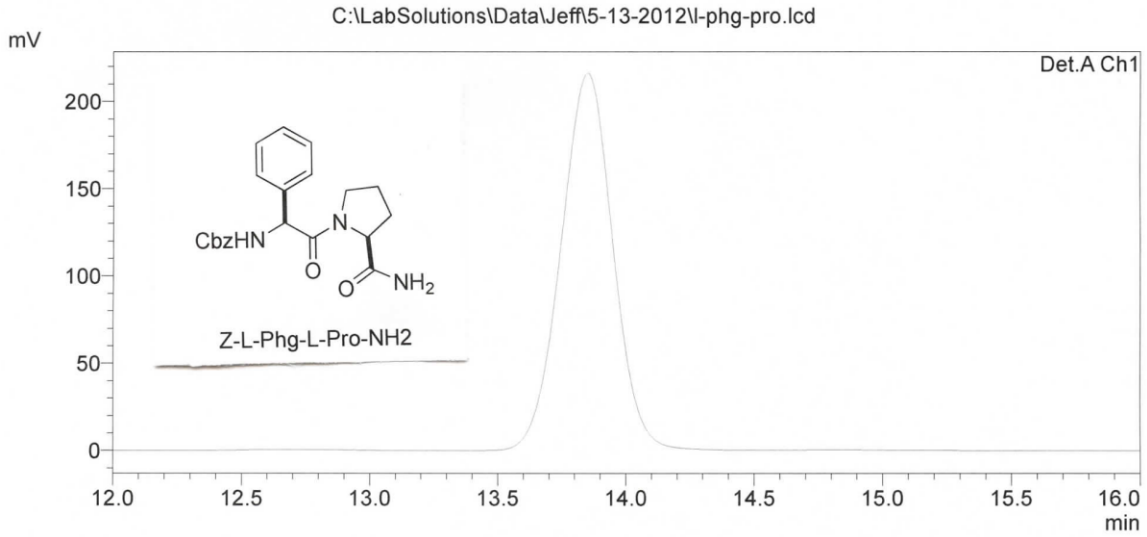
Z-L-Phg-L-Val-O^{t}Bu + Z-D-Phg-L-Val-O^{t}Bu

Chromatography condition: 60-70% acetonitrile in 0.05% formic acid in 12 min, 0.5 ml/min, 254 nm



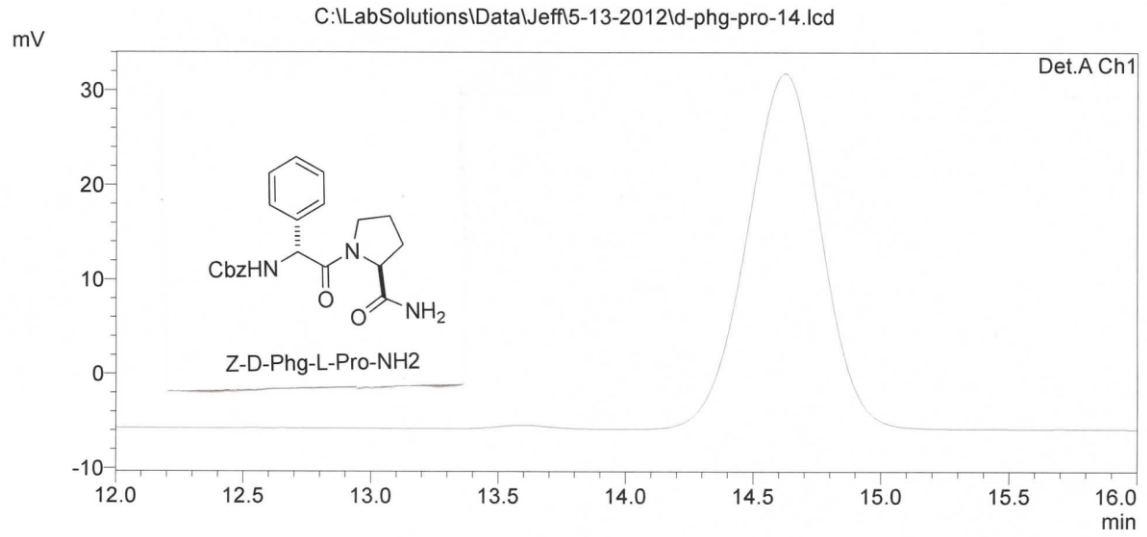
Z-L-Phg-L-Pro-NH_2

Chromatography condition: 30-42% acetonitrile in 0.05% formic acid in 20 min, 0.3 ml/min, 254 nm
Result: t_R = 13.85 min, *de* > 99.8%



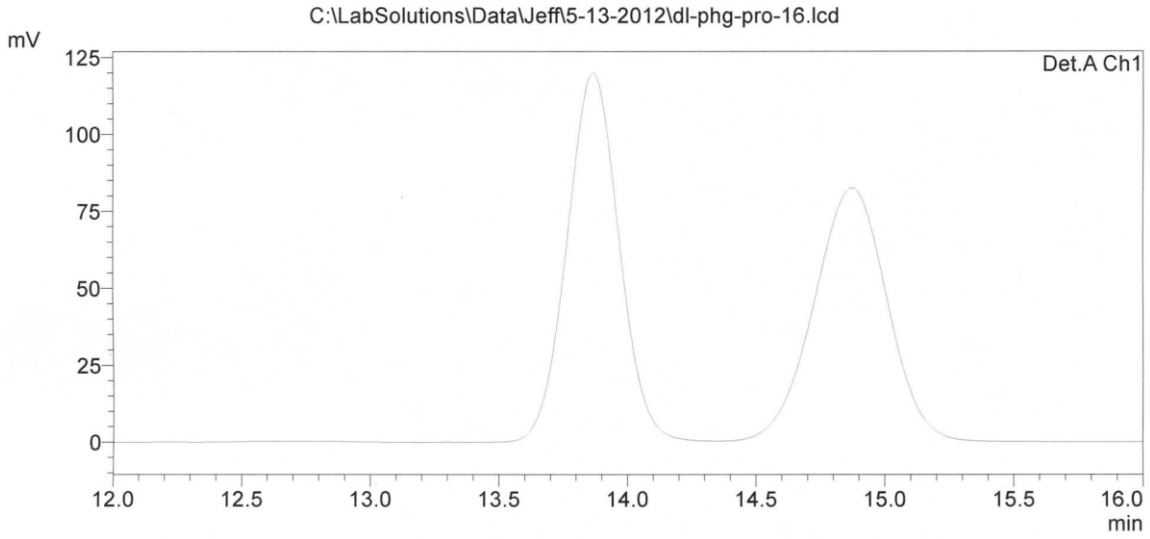
Z-D-Phg-L-Pro-NH_2

Chromatography condition: 30-42% acetonitrile in 0.05% formic acid in 20 min, 0.3 ml/min, 254 nm
Result: t_R = 14.62 min, *de* = 97.9%



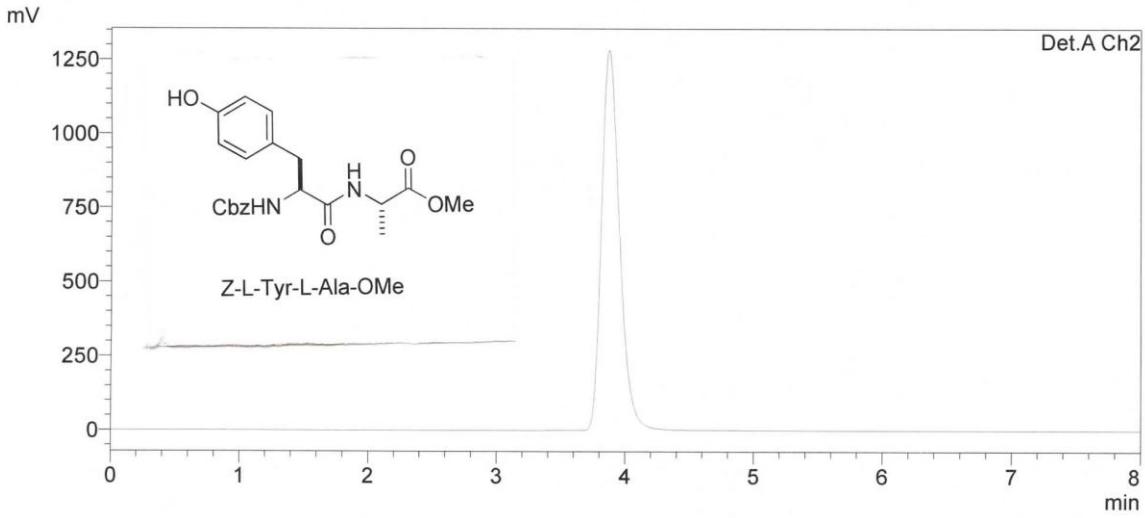
Z-L-Phg-L-Pro-NH_2 + Z-D-Phg-L-Pro-NH_2

Chromatography condition: 30-42% acetonitrile in 0.05% formic acid in 20 min, 0.3 ml/min, 254 nm



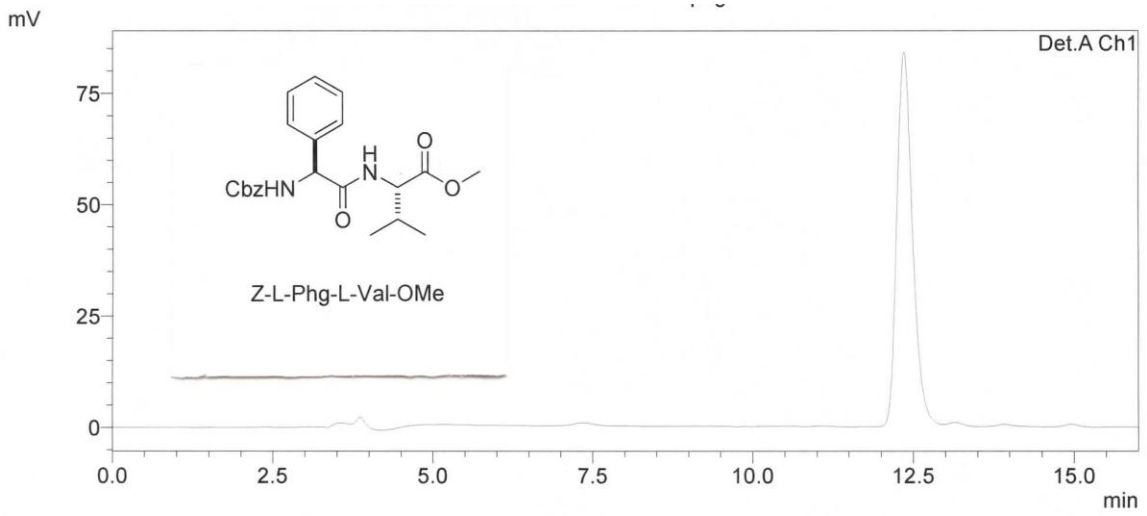
Z-L-Tyr-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 280 nm
Result: t_R = 3.87 min, *de* > 99.8%



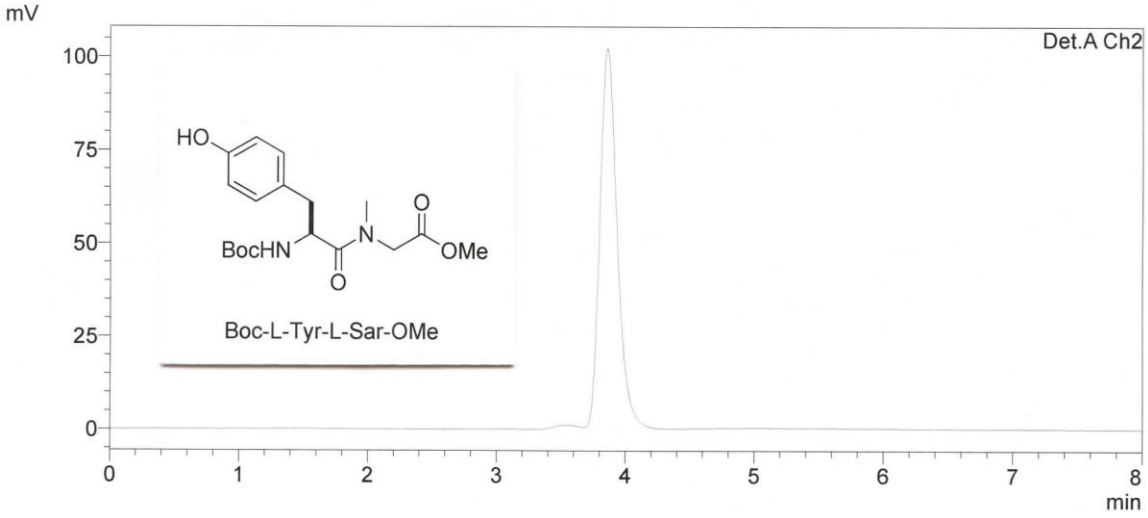
Z-L-Phg-L-Val-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 12.36 min, *de* = 98.4%



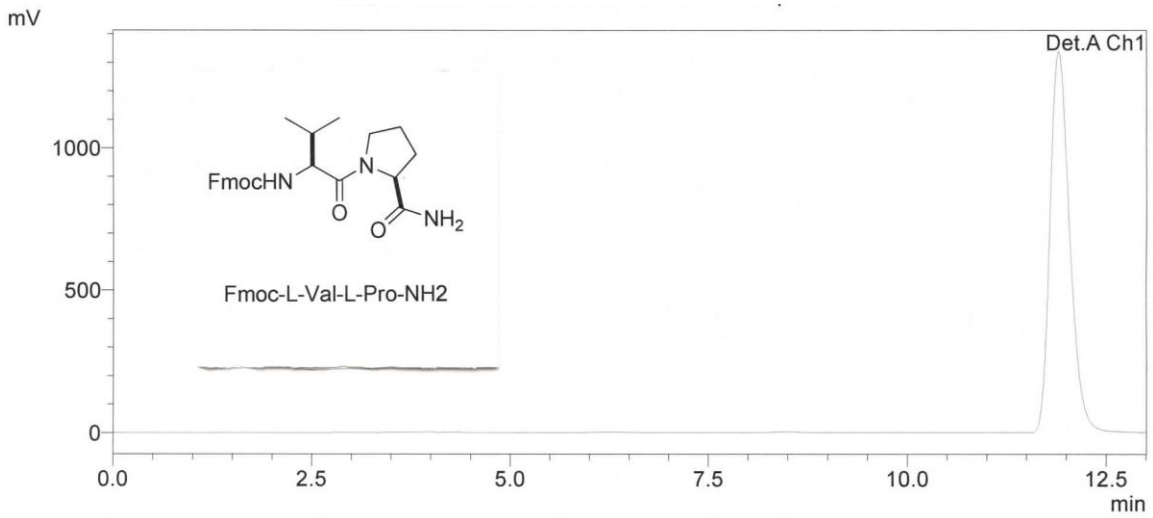
Boc-L-Tyr-Sar-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 280 nm
Result: t_R = 3.85 min, *de* = 97.8%



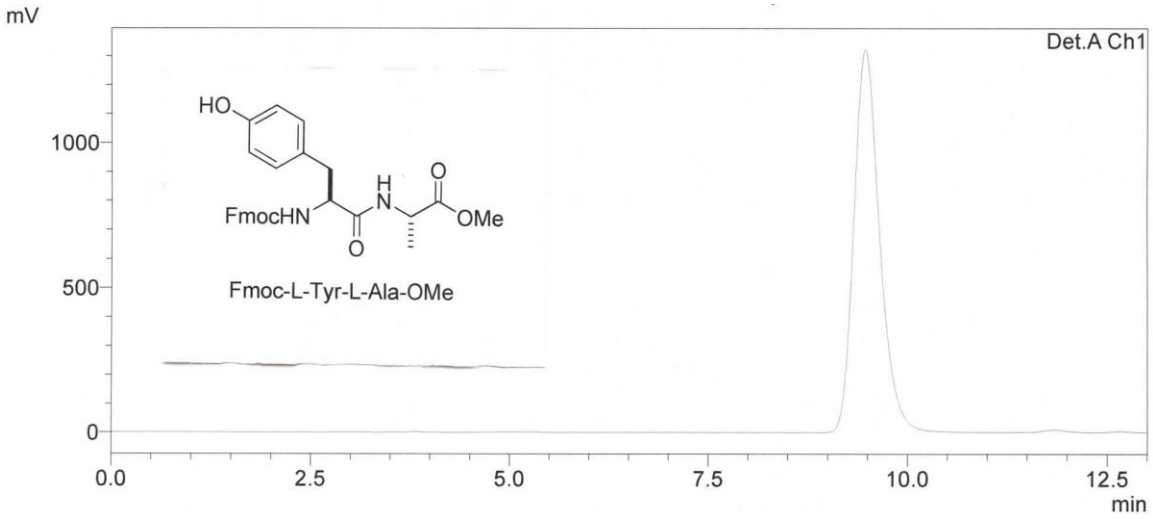
Fmoc-L-Val-L-Pro-NH_2

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 11.90 min, *de* > 99.8%



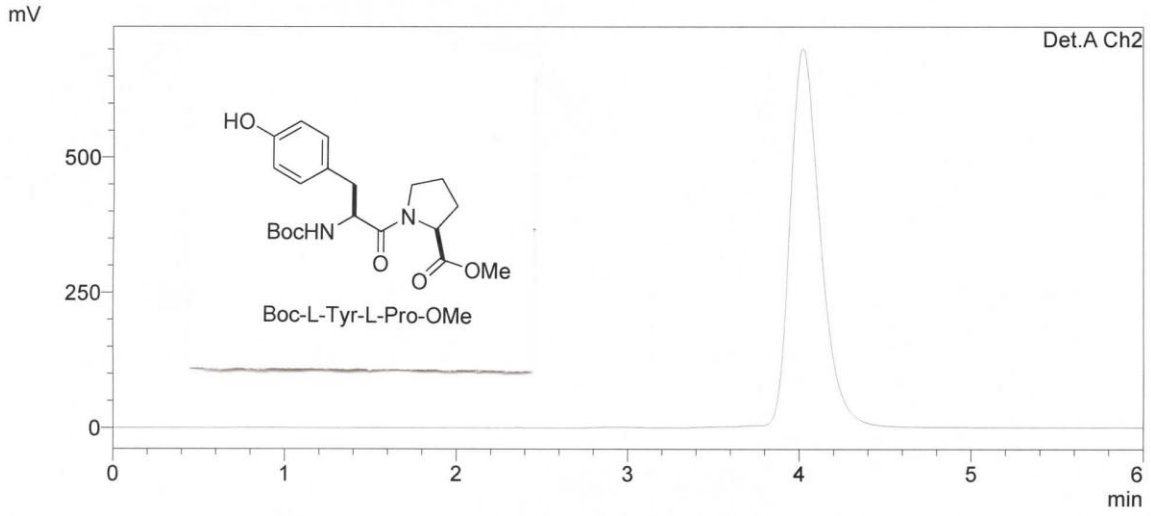
Fmoc-L-Tyr-L-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 9.47 min, *de* = 98.6%



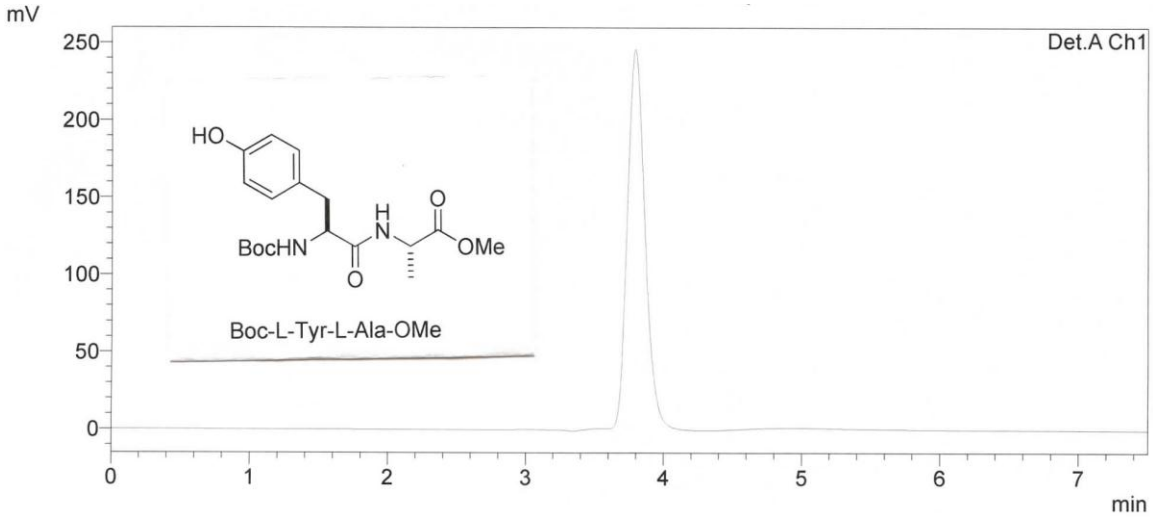
Boc-L-Tyr-L-Pro-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 280 nm
Result: t_R = 4.02 min, *de* > 99.8%



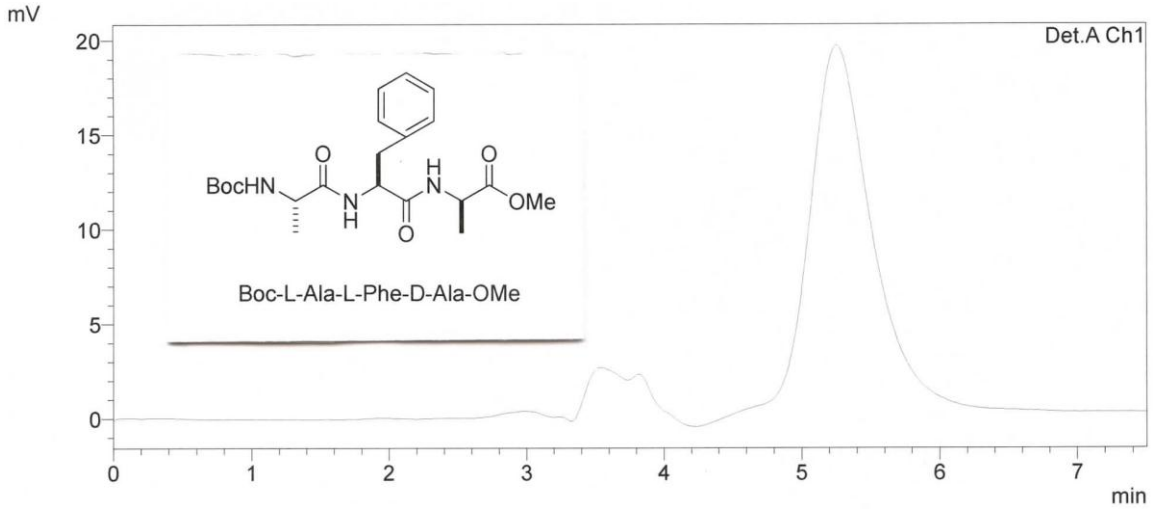
Boc-L-Tyr-L-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 3.79 min, *de* = 98.7%



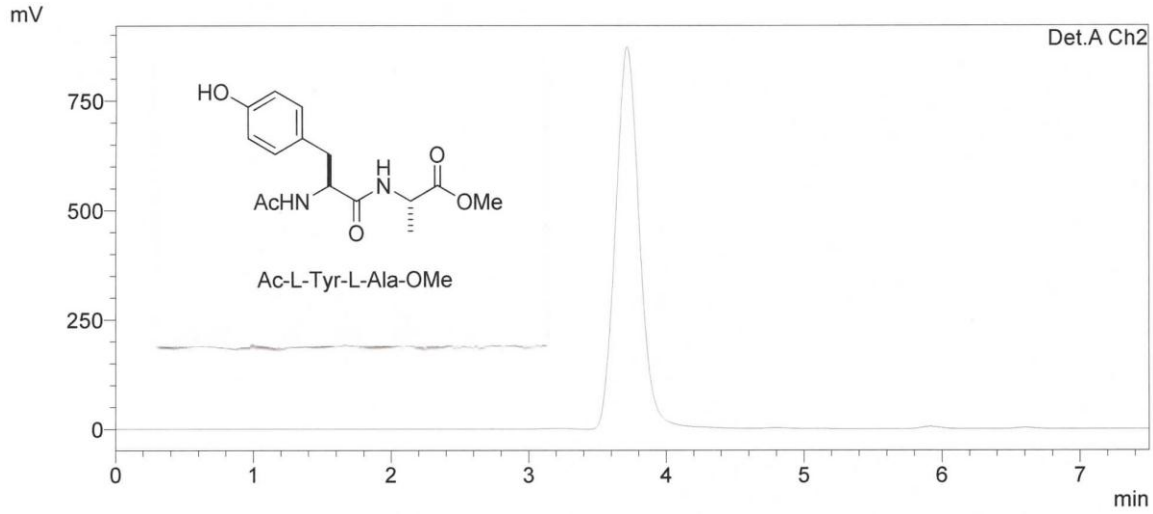
Boc-L-Ala-L-Phe-D-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 5.26 min, *de* > 99.8%



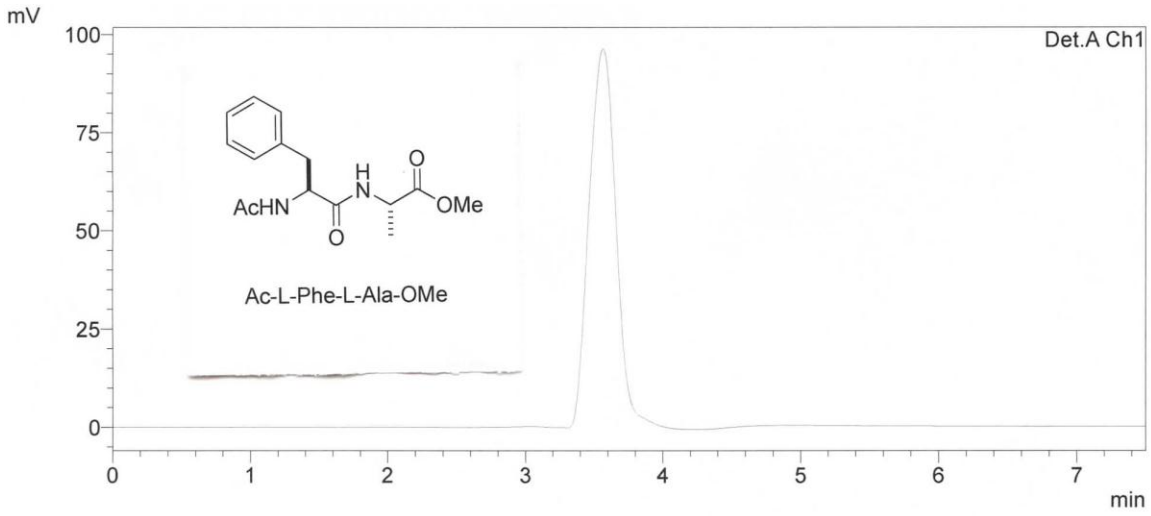
Ac-L-Tyr-L-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 280 nm
Result: t_R = 3.71 min, *de* > 99.8%



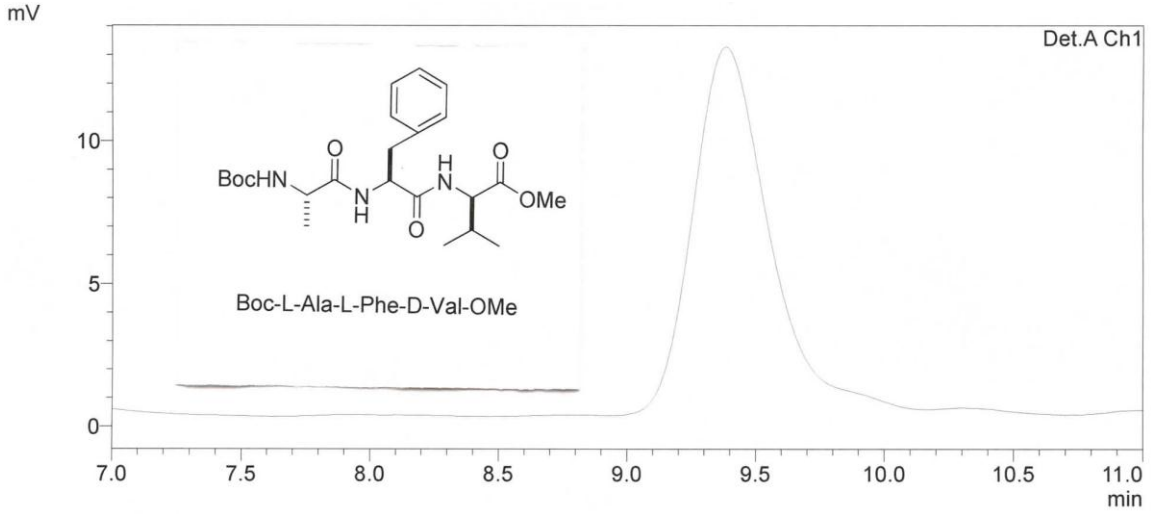
Ac-L-Phe-L-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 3.56 min, *de* = 97.9%



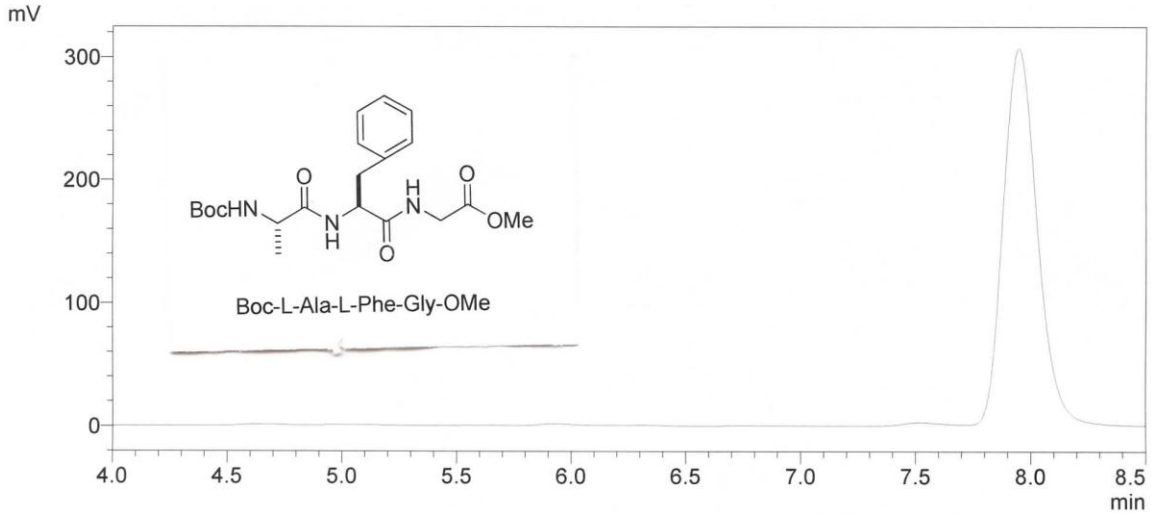
Boc-L-Ala-L-Phe-D-Val-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 9.38 min, *de* > 99.8%



Boc-L-Ala-L-Phe-Gly-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 254 nm
Result: t_R = 9.38 min, *de* = 96.8%



Boc-L-Tyr-N-Me-L-Ala-OMe

Chromatography condition: 40-70% acetonitrile in 0.05% formic acid in 15 min, 0.3 ml/min, 280 nm
Result: t_R = 7.96 min, *de* > 99.8%