Electronic Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

Total Synthesis of Cyclic Heptapeptide Rolloamide B

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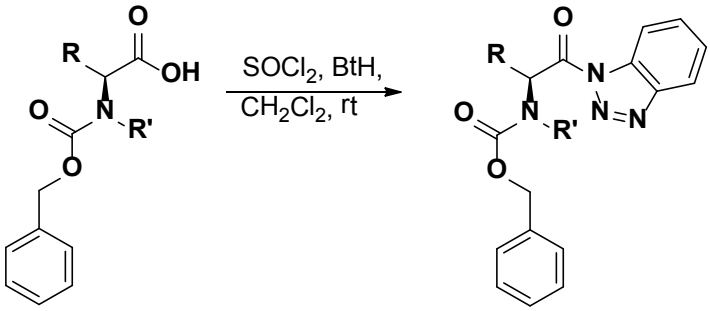
I-Experimental Section

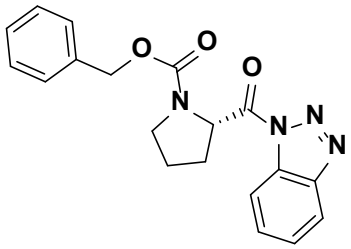
A-General

Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded with TMS for ^{1}H (300 MHz) and ^{13}C (75 MHz) as an internal reference. Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV light. Elemental analyses were performed on a Carlo Erba EA 1108 instrument.

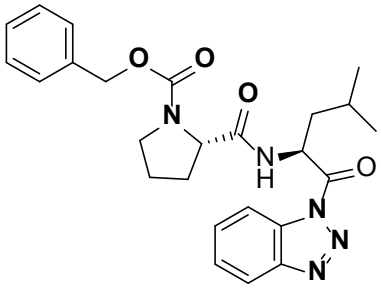
B-General Procedure for the Preparation of *N*-(Z-α-Aminoacyl)benzotriazoles (Method A)



Thionyl chloride (0.6 mL, 8.00 mmol, 1.2 equiv) was added to a solution of 1*H*-benzotriazole (3.17 g, 26.67 mmol, 4 equiv) in methylene chloride to give a clear yellow solution that was stirred for 15 min at room temperature. The amino acid (6.67 mmol, 1 equiv) was then added to give a suspension which was stirred at room temperature for the reported time. The suspension was filtered, the filtrate evaporated, the residue dissolved in EtOAc and the solution was washed with a saturated solution of sodium carbonate. The organic portion was dried over anhyd Na_2SO_4, filtered, and dried to give the corresponding *N*-(Z-α-aminoacyl)benzotriazole.

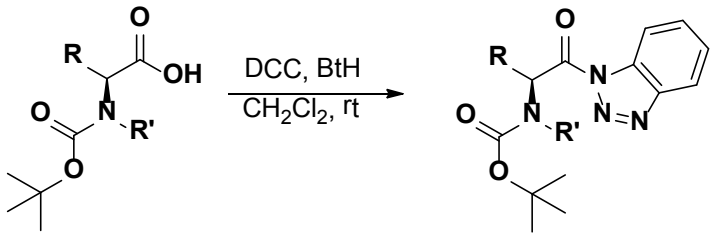


(*S*)-Benzyl 2-(1H-benzo[d][1,2,3]triazole-1-carbonyl)pyrrolidine-1-carboxylate (7a).[1] Stirred for 12 h at room temperature. Yellow oil (77%). ^{1}H NMR ($CDCl_3$): δ 8.23 (d, J = 12 Hz, 1H), 8.11 (d, J = 12.9 Hz, 1H), 7.62 (t, J = 12.6 Hz, 1H), 7.48 (t, J = 11.4 Hz, 1H), 7.40-7.17 (m, 10H), 7.01-6.95 (m, 2H), 5.29-4.91 (m, 3H), 4.51-4.42 (m, 1H), 3.81-3.45 (m, 3H), 2.21-1.93 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 176.2, 175.6, 171.5, 171.0, 155.7, 155.2, 154.8, 154.3, 145.8, 138.4, 136.4, 136.3, 135.7, 131.2, 131.0, 131.7, 130.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.8, 127.8, 127.5, 127.4, 126.5, 126.4, 126.1, 120.2, 120.1, 114.8, 114.3, 114.3, 67.4, 60.0, 59.3, 59.3, 58.9, 47.4, 47.0, 46.6, 31.5, 30.9, 30.7, 29.7, 24.4, 24.3, 23.7, 23.4.

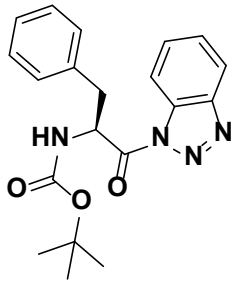


(*S*)-Benzyl 2-(((S)-1-(1H-benzo[d][1,2,3]triazol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (9a). Stirred for 4 h at 0 ^{o}C. Yellow solid (70%); m.p. 74 ^{o}C. Converted to compound **10a** after checking NMR; ^{1}H NMR ($CDCl_3$): δ 8.30-8.21 (m, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.70-7.62 (m, 1H), 7.55-7.48 (m, 1H), 7.40-7.10 (m, 6H), 5.99-5.94 (m, 1H), 5.23-5.13 (m, 2H),4.61-4.30 (m, 1H), 3.68-3.30 (m, 2H), 2.40-1.40 (m, 7H), 1.18-0.70 (m, 6H); ^{13}C NMR ($CDCl_3$): δ rotamers: 175.5, 172.4, 172.0, 146.1, 136.2, 131.3, 130.7, 128.7, 128.3, 128.0, 126.5, 126.4, 126.5, 120.4, 114.6, 67.7, 60.7, 60.6, 52.1, 47.3, 47.2, 41.6, 41.2, 31.3, 29.0, 28.5, 25.6, 25.5, 25.1, 24.8, 23.4, 23.1, 22.0, 21.9, 21.6.

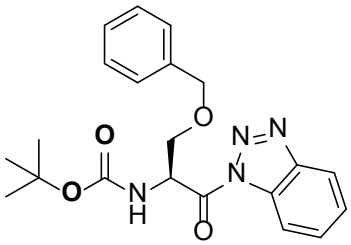
C-General Procedure for the Preparation of *N*-(Boc-α-Aminoacyl)benzotriazoles using DCC (Method B).



Boc-protected amino acid (0.03 mol) was added to a solution of DCC (1 equiv) in methylene chloride under an atmosphere of nitrogen. After 30 minutes, BtH (1 equiv) was added and this was stirred for 12 h. The suspension was filtered on a bed of silica and celite, the filtrate evaporated, and the residue dissolved in EtOAc, then filtered on a bed of silica and celite and washed with a solution of saturated sodium carbonate, then with water and brine. The organic portion was dried over anhyd Na_2SO_4, filtered on a bed of silica, and dried to give the corresponding *N*-(Boc-α-aminoacyl) benzotriazole. ^{1}H NMR and mp of Boc-L-Phe-Bt **14** matched that reported in the literature.[2]

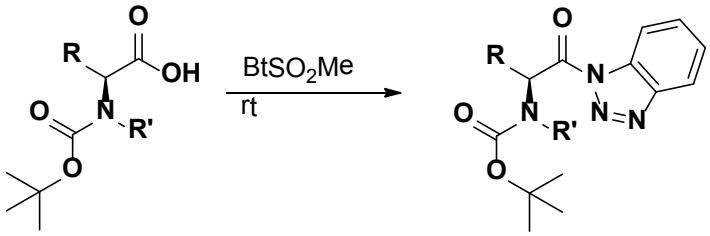


(*S*)-*tert*-Butyl (1-(1H-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (13).[2] White solid (88%). m.p. 114.0-116.0 ^{o}C; ^{1}H NMR and ^{13}C NMR matched that reported in literature.[2]

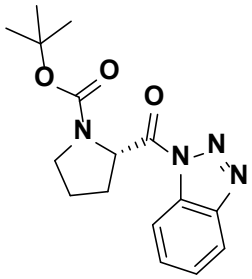


(*S*)-*tert*-Butyl (1-(1H-benzo[d][1,2,3]triazol-1-yl)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate (18b). Colorless oil (75%). Converted to compound **20** after checking NMR; ^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.18-7.05 (m, 5H), 5.85-5.73 (m, 2H), 4.51 (d, J = 12.3 Hz, 1H), 4.40 (d, J = 12.3 Hz, 1H), 4.20 (dd, J = 9.5, 3.2 Hz, 1H), 3.97 (dd, J = 9.9, 3.0 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.6, 155.6, 146.0, 137.1, 131.3, 130.8, 128.4, 127.9, 127.7, 126.6, 120.4, 114.6, 80.6, 73.3, 70.0, 55.3, 28.5; Anal. Calcd for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N 14.13. Found: C, 63.83; H, 6.49; N 13.68.

D-General Procedure for the Preparation of *N*-(Boc-α-Aminoacyl)benzotriazoles using $BtSO_2Me$ (Method C).

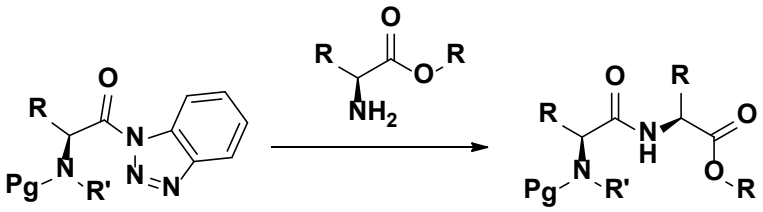


A mixture of Boc-protected amino acid (4.646 mmol), 1-(methylsulfonyl)-1H-benzo[d][1,2,3]triazole (0.9 g, 4.646 mmol) and TEA (0.7 g, 6.969 mmol) in DMF was heated in microwave at 50 °C, 50 W for 1 h. The reaction mixture was poured onto cold Na_2CO_3 solution and extracted with ethyl acetate. The organic layer was extracted twice with water and brine. The organic layer was dried over Na_2SO_4, filtered and filtrate evaporated to give the corresponding *N*-(Boc-α-aminoacyl) benzotriazole.

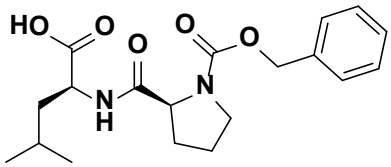


(*S*)-*tert*-Butyl 2-(1H-benzo[d][1,2,3]triazole-1-carbonyl)pyrrolidine-1-carboxylate (7b). Colorless oil (81%). Converted to compound **8b** after checking NMR. ^{1}H NMR ($CDCl_3$): δ 8.34-8.27 (m, 1H), 8.18-8.10 (m, 1H), 7.74-7.62 (m, 1H), 7.59-7.48 (m, 1H), 5.84-5.76 (m, 1H), 3.80-3.63 (m, 2H), 2.65-2.52 (m, 1H), 2.23-2.02 (m, 3H), 1.49 (s, 4H), 1.21 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 172.3, 171.6, 154.5, 153.6, 146.0, 131.4, 131.2, 130.8, 130.5, 126.5, 126.3, 125.5, 120.4, 120.2, 114.7, 114.4, 80.4, 66.0, 59.7, 59.4, 47.2,, 46.9, 31.6, 30.8, 28.6, 28.2, 24.7, 24.1, 15.4, 14.4.

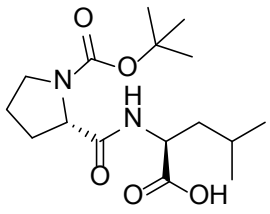
E-General Procedure for the Preparation of Peptides using Benzotriazole Methodology (Method D).



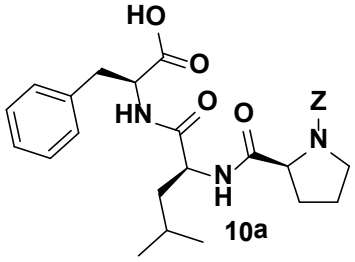
N-(Pg-α-Aminoacyl)benzotriazoles (1.0 mmol) in MeCN (5 mL) was added dropwise to a solution of free amino acid (2 equiv; for AA-OEt, 1 equiv should be used) and Et_3N (or DIPEA, as noted in paper)(2.5-3.5 equiv) in MeCN/H_2O (9:1, 15 mL) at the temperature reported for each reaction and stirred until all the *N*-(Pg-α-aminoacyl)benzotriazoles were consumed. MeCN was evaporated and the residue dissolved in EtOAc (50 mL) and washed with 3N HCl (5 x 50 mL). The organic portion was dried over anhyd. $NaSO_4$, filtered and concentrated to give the desired peptide fragment. No further purification was required in all cases.



(*S*)-2-((*S*)-1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxamido)-4-methylpentanoic acid (8a).[3] Yellow oil (69%). ^{1}H NMR ($CDCl_3$): δ 7.52-7.32 (m, 5H), 5.17 (br s, 2H), 4.53 (br s, 1H), 4.39 (br s, 1H), 3.58-3.38 (m, 2H), 2.00-1.81 (m, 2H), 1.73-1.46 (m. 3H), 0.92-0.88 (m, 6H); ^{13}C NMR ($CDCl_3$): δ rotamers 176.7, 176.3, 175.4, 172.1, 156.5, 156.0, 136.3, 135.8, 129.5, 128.7, 128.6, 128.3, 128.2, 128.0, 127.2, 127.1, 67.2, 66.0, 60.7, 56.3, 54.8, 51.1, 41.1, 38.5, 37.9, 24.9, 22.9, 22.0, 20.9, 15.2, 14.3.

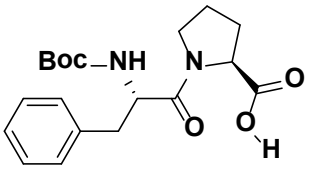


(*S*)-2-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-4-methylpentanoic acid (8b).[4] White sticky solid (73%). ^{1}H NMR ($CDCl_3$): δ 9.45 (br s, 1H), 7.44 (br s, 1H), 6.82 (br s, 1H), 4.59 (br s, 1H), 4.32 (br s, 1H), 3.52-3.33 (m, 2H), 2.32-2.18 (m, 1H), 1.94-1.84 (m, 2H), 1.73-1.57 (m, 4H), 1.45 (s, 9H), 0.93 (s, 6H); ; ^{13}C NMR ($CDCl_3$): δ 176.1, 173.2, 172.6, 156.0, 155.5, 81.5, 80.8, 61.2, 59.8, 59.1, 50.9, 47.2, 41.3, 31.3, 28.5, 28.4, 25.0, 23.8, 23.1, 21.9.

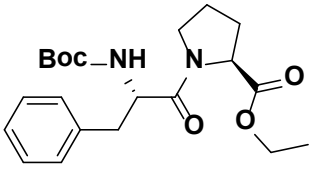


(*S*)-2-((*S*)-2-((*S*)-1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxamido)-4-methylpentanamido)-3-phenylpropanoic acid (10a).[5] Colorless oil (81%). ^{1}H NMR ($CDCl_3$): δ 8.10 (br s, 1H), 7.34-7.14 (m, 10H), 5.30-5.02 (m, 3H), 4.40-4.18 (m, 4H), 2.20-2.17 (m, 2H), 2.00-1.88 (m, 4H), 1.60-1.26 (m, 5H), 0.98-0.82 (m, 6H); ^{13}C NMR ($CDCl_3$):

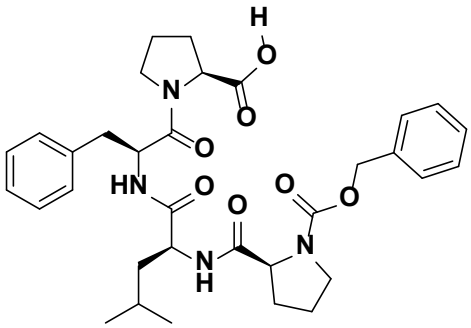
δ 136.4, 129.7, 129.6, 128.8, 128.7, 128.4, 128.1, 127.1, 68.0, 67.8, 67.2, 59.2, 47.2, 46.7, 39.1, 30.8, 30.2, 29.9, 29.2, 25.1, 25.0, 24.5, 24.2, 23.7, 23.2, 23.0, 22.0, 21.9, 14.3.



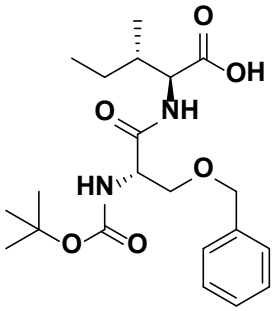
(*S*)-1-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropanoyl)pyrrolidine-2-carboxylic acid (14a).[5] Colorless oil (85%). ^{1}H NMR ($CDCl_3$): δ 9.13 (br s, 1H), 7.42-7.18 (m, 5H), 5.76-5.73 (m, 1H), 4.67-4.64 (m, 1H), 4.55-4.51 (m, 1H), 3.65-3.62 (1H), 3.18-2.90 (m, 3H), 2.15-2.02 (m, 3H), 1.91-1.21 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 176.0, 174.6, 172.1, 155.6, 136.3, 129.8, 128.5, 126.9, 80.0, 59. 3, 53.6, 47.3, 38.9, 28.8, 28.5, 24.9, 22.2, 21.0.



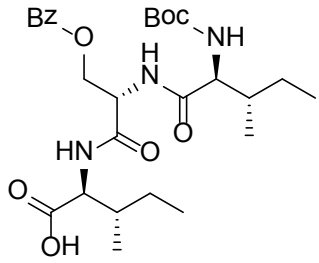
(*S*)-Ethyl 1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (14b). Stirred for 16 h at -40 ^{o}C → rt. Colorless oil (90%). ^{1}H NMR ($CDCl_3$): δ 7.30-7.15 (m, 5H), 5.40-5.37 (m, 1H), 4.22-4.18 (m, 1H), 3.71-3.53 (m, 1H), 2.85-3.2 (m, 2H), 1.80-2.00 (m, 2H), 1.40-1.22 (m, 12 H); ^{13}C NMR ($CDCl_3$): δ rotamers 171.9, 170.9, 155.4, 136.5, 129.8, 129.5, 128.6, 128.4, 127.0, 126.8, 79.7,61.9, 61.3, 59.4, 59.2, 54.0, 53.4,52.3, 47.0,39.1, 30.7, 29.2, 28.4, 25.0,22.3, 20.9, 14.3 Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.60; H, 7.74; N 7.17. Found: C, 64.29; H, 8.04; N 6.95.



(*S*)-1-((*S*)-2-((*S*)-2-((*S*)-1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxamido)-4-methylpentanamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylic acid (16a). Stirred for 18 h at -78 ^{o}C→ rt. Colorless oil (75%). ^{1}H NMR ($CDCl_3$): δ 7.40-7.25 (m, 10H), 5.20-5.14 (m, 2H), 4.30-3.35 (m, 3H), 2.20-2.05 (m, 2H), 2.00-1.80 (m, 4H), 1.80-1.40 (m, 4H), 1.30-1.00 (m, 6H), 0.95-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 176.3, 172.9, 130.1, 129.1, 128.7, 128.5, 126.6, 115.6, 68.1, 50.1, 41.6, 34.3, 30.3, 26.1, 25.4, 23.4, 22.5, 14.7.

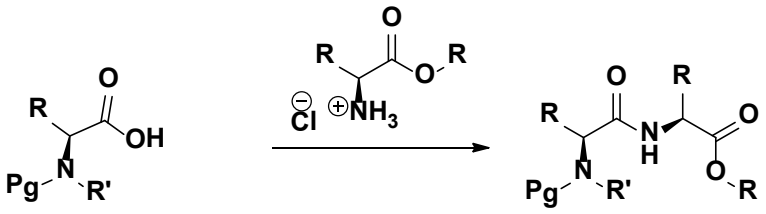


(2*S*,3*S*)-2-((*S*)-3-(Benzyloxy)-2-((tert-butoxycarbonyl)amino)propanamido)-3-methylpentanoic acid (19). Sticky solid/gel (80%). Converted to compound **21** after checking NMR; ^{1}H NMR ($CDCl_3$): δ 11.15 (br s, 1H), 7.34-7.24 (m, 6H), 5.70 (br s, 1H), 4.61 (dd, J = 8.5, 4.4 Hz, 1H), 4.51 (s, 2H), 4.40 (br s, 1H), 3.87 (dd, J = 9.3, 3.9 Hz, 1H), 3.60 (dd, J = 9.3, 6.6 Hz, 1H), 1.97-1.86 (m, 1H), 1.43 (s, 9H), 1.27-1.02 (m, 2H), 0.90-0.82 (m, 6H);); ^{13}C NMR ($CDCl_3$): δ 174.7, 170.9, 155.7, 137.3, 128.4, 127.8, 127.6, 80.4, 73.4, 69.8, 56.7, 53.9, 37.7, 28.2, 24.8, 15.5, 15.4, 11.6.

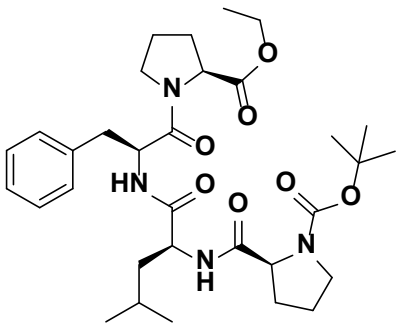


(6*S*,9*S*,12*S*)-9-((Benzoyloxy)methyl)-6,12-di((*S*)-sec-butyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oic acid (5). Required microwave irradiation at 50 W, 50 ^{o}C for 1.5 h. White solid (65%). mp 75.0-77.0 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.39-7.20 (m, 5H), 5.38 (br s, 1H), 4.75-4.68 (m, 1H), 4.57-4.53 (m, 3H), 4.14-4.06 (m, 1H), 3.87-3.82 (m, 1H), 3.61-3.54 (m, 1H), 1.97-1.81 (m, 2H), 1.42 (s, 9H), 1.30-1.04 (m, 4H), 0.93-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 174.4, 172.4, 170.3, 156.2, 137.4, 128.6, 128.0, 80.3, 73.6, 69.6, 59.5, 57.2, 52.6, 37.5, 28.4, 25.1, 24.8, 15.7, 15.6, 11.7, 11.5; Anal. Calcd for $C_{27}H_{43}N_3O_7$: C, 62.17; H, 8.31; N 8.06. Found: C, 62.17; H, 8.61; N 7.83.

F-General Procedure for the Preparation of Peptides (Method E).[6]

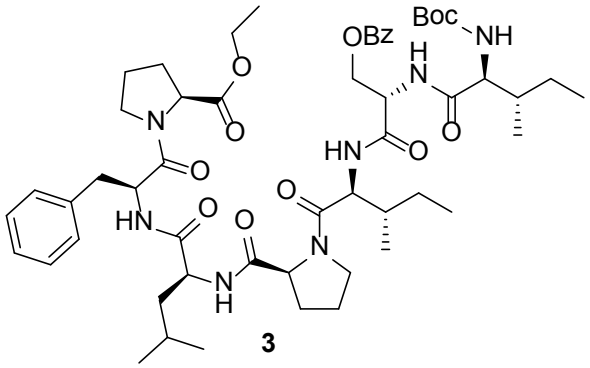


A solution of the amino acid with free carboxyl group (3 mmol) in dry THF (10 mL) under argon was cooled to −15 °C in an ice bath with stirring. N-Methylmorpholine (0.33 g, 3.2 mmol), followed by isobutyl chloroformate (0.45 g, 3.2 mmol) were added. After 4 min, a solution of the amino acid hydrochloride salt (1.5 mmol) and N-methylmorpholine (0.7 g, 1.6 mmol) in DMF (5 mL) was added. The ice bath was removed after 5 min, and the solution was allowed to stir for 12 h at room temperature. The solution was concentrated under vacuum and the residue was dissolved in ethyl acetate (30 mL) and water (5 mL). The organic phase was washed successively with saturated Na_2CO_3 (2 × 15 mL), water (10 mL), 2N HCl (15 mL), and water (10 mL). The solution was dried over $MgSO_4$, filtered, and then concentrated under vacuum. The peptide was recrystallized from ethyl acetate−hexanes to give the desired peptide.



(*S*)-*tert*-Butyl 2-(((*S*)-1-(((*S*)-1-((*S*)-2-(ethoxycarbonyl)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (16b). White solid (83%). mp 81.0-83.0 ^{o}C; ^{1}H NMR (CD_3OD): δ 7.34-7.19 (m, 5H), 4.43-4.36 (m, 2H), 4.21-4.13 (m, 3H), 3.75-3.67

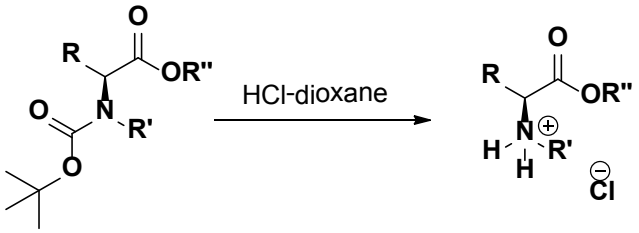
(m, 1H), 3.52-3.34 (m, 3H), 3.12 (dd, J = 14.1, 6.3 Hz, 1H), 2.91 (dd, J = 14.1, 7.5 Hz, 1H), 2.24-2.13 (m, 1H), 2.00-1.79 (m, 6H), 1.76-1.60 (m, 2H), 1.52-1.35 (m, 12H), 1.26 (t, J = 7.2 Hz, 3H), 0.96-0.87 (m, 6H); ^{13}C NMR (CD_3OD): δ 175.5, 175.3, 174.4, 173.4, 172.8, 172.1, 171.9, 156.5, 156.1, 138.1, 137.7, 130.7, 130.6, 129.8, 129.6, 128.3, 127.9, 81.4, 62.3, 61.3, 60.8, 60.7, 54.0, 54.0, 53.1, 48.0, 47.5, 42.4, 38.7, 32.6, 30.2, 28.8, 25.9, 25.9, 24.7, 23.6, 22.2, 14.7; Anal. Calcd for $C_{32}H_{48}N_4O_7$: C, 63.98; H, 8.05; N 9.33. Found: C, 63.68; H, 8.32; N 8.64.



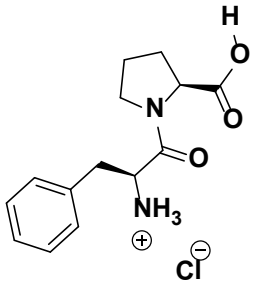
3

(*S*)-Ethyl 1-((*S*)-2-((*S*)-2-((*S*)-1-((6*S*,9*S*,12*S*)-9-((benzoyloxy)methyl)-6,12-di((*S*)-sec-butyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oyl)pyrrolidine-2-carboxamido)-4-methylpentanamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylate (3). White solid (81%). mp 74.0-76.0 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.25-7.09 (m, 10H), 4.85 (br s, 1H), 4.72-4.63 (m, 1H), 4.55-4.32 (m, 4H), 4.22 (br s, 1H), 4.14-4.00 (m, 2H), 3.90-3.72 (m, 3H), 3.70-3.20 (m, 5H), 3.10-2.95 (m, 1H), 2.89-2.79 (m, 1H), 2.16-1.75 (m, 9H), 1.60-1.41 (m, 4H), 1.34 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H), 1.13-1.04 (m, 4H), 0.88-0.70 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 174.3, 173.6, 171.9, 171.7, 170.1, 169.9, 169.6, 155.8, 137.4, 136.2, 129.7, 129.3, 128.6, 128.3, 127.8, 126.8, 79.8, 73.5, 73.4, 73.3, 71.8, 69.8, 69.6, 61.1, 59.1, 59.0, 52.7, 52.0, 47.0, 38.4, 37.5, 29.0, 28.3, 27.9, 26.2, 24.8, 24.7, 23.0, 22.1, 21.7, 19.0, 15.6, 15.5, 14.4, 14.2, 11.8, 11.7, 11.5; Anal. Calcd for $C_{54}H_{83}N_7O_{12}$: C, 63.44; H, 8.18; N 9.15. Found: C, 63.19; H, 8.63; N 9.12.

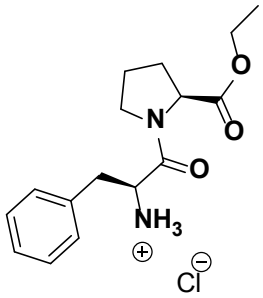
G-General Procedure for the deprotection of Boc- protecting group (Method F). [7]



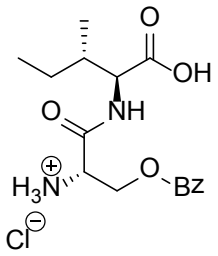
Boc-Protected amino acid (1.0 mmol) was dissolved in HCl-dioxane (4.0 M HCl in dioxane, 15 mL) and stirred for 1 h. Solvent was evaporated, ether was added to the residue and the suspension was stirred for 2h. Filtration (when sticky solid resulted, decantation of ether several times was performed instead) gave the required amino acid/peptide as a hydrochloride salt.



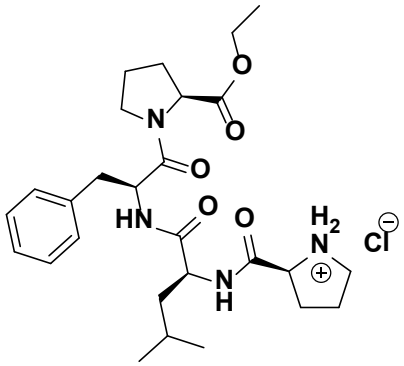
(*S*)-1-((*S*)-2-Carboxypyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-aminium chloride (15a). White solid (95%). m.p. 119 ^{o}C; ^{1}H NMR (CD_3OD): δ mixture of rotamers 7.31-7.13 (m, 5H), 4.42-4.20 (m, 2H), 3.22-3.09 (m, 2H), 3.02-2.85 (m, 2H), 2.22-2.02 (m, 1H), 1.98-1.62 (m, 2H), 1.60-1.40 (m, 1H); ^{13}C NMR (CD_3OD): δ 175.1, 168.9, 135.7, 131.5, 131.0, 130.6, 130.5, 129.3, 68.5, 61.2, 54.8, 48.1, 38.2, 30.5, 26.3. Anal. Calcd for $C_{28}H_{40}Cl_2N_4O_7$: C, 54.63; H, 6.55; N 9.10. Found: C, 54.19; H, 6.68; N 8.76.



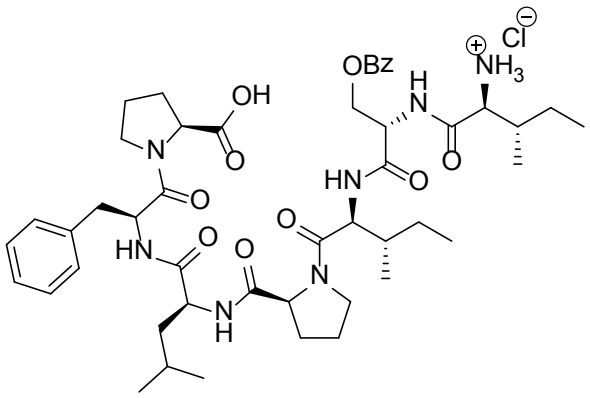
(*S*)-1-((*S*)-2-(ethoxycarbonyl)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-aminium chloride (15b).[8] White hygroscopic solid (97%). ^{1}H NMR ($CDCl_3$): δ mixture of rotamers 7.36-7.10 (m, 5H), 4.42-4.25 (m, 1H), 4.20-4.00 (m, 2H), 3.55 (s, 2H), 3.25-3.00 (m, 2H), 3.05-2.90 (m, 2H), 2.01-2.20 (m, 1H), 1.84-1.72 (m, 3H), 1.22-1.16 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 174.5, 168.4, 135.2, 130.9, 130.6,129.7, 130.1, 130.0, 128.8, 68.1, 64.0, 62.3, 60.8, 54.4, 54.2, 53.0, 48.1, 40.0, 37.8, 31.5, 30.0, 25.9, 23.5, 14.5.



(*S*)-3-(Benzoyloxy)-1-(((1*S*,2*S*)-1-carboxy-2-methylbutyl)amino)-1-oxopropan-2-aminium chloride (20).Gel (95%); ^{1}H NMR (CD_3OD): δ 7.39-7.28 (m, 5H), 4.61 (s, 2H), 4.44 (d, J = 5.3 Hz, 1H), 4.21 (dd, J = 6.6, 3.9 Hz, 1H), 3.92 (dd, J = 10.5, 3.9 Hz, 1H), 3.80 (dd, J = 10.5, 6.6 Hz, 1H), 1.98-1.89 (m, 1H), 1.57-1.44 (m, 1H), 1.34-1.20 (m, 1H), 0.99-0.90 (m, 6H); ^{13}C NMR (CD_3OD): δ 174.1, 168.0, 138.7, 129.6, 129.2, 129.1, 74.7, 69.4, 58.6, 54.6, 38.5, 26.3, 16.2, 12.1; Anal. Calcd for $C_{32}H_{52}Cl_2N_9O_4$: C, 54.31; H, 7.41; N 7.92. Found: C, 54.05; H, 7.28; N 7.88.



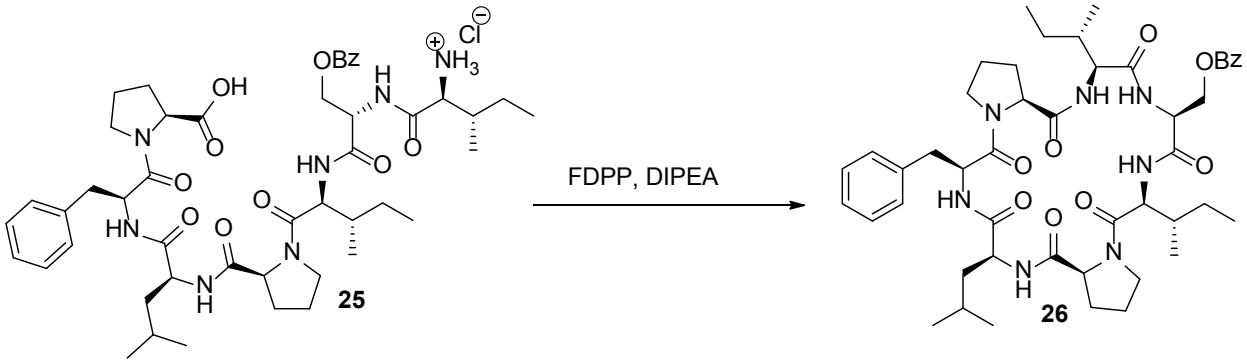
(*S*)-2-(((*S*)-1-(((*S*)-1-((*S*)-2-(Ethoxycarbonyl)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-ium chloride (4b). White solid (87%). m.p. 93.0-95.0 ^{o}C; ^{1}H NMR (CD_3OD): δ 8.38-8.28 (m, 1H), 7.18-7.05 (m, 5H), 4.32-4.22 (m, 2H), 4.17-4.13 (m, 1H), 4.06-3.99 (m, 2H), 3.64-3.55 (m, 1H), 3.31-3.19 (m, 3H), 2.96 (dd, J = 14.1, 5.7 Hz, 1H), 2.80-2.73 (m, 1H), 2.33-2.20 (m, 1H), 2.11-1.76 (m, 7H), 1.57-1.35 (m, 4H), 1.11 (t, J = 7.2 Hz, 3H), 0.81-0.73 (m, 6H); ^{13}C NMR (CD_3OD): δ 173.9, 173.5, 172.0, 169.8, 169.7, 138.1, 137.7, 130.8, 130.6, 129.8, 129.6, 128.4, 127.9, 62.5, 62.4, 61.0, 60.8, 60.7, 53.9, 53.8, 53.7, 48.3, 47.6, 47.5, 41.9, 41.5, 38.6, 32.0, 31.2, 30.2, 26.0, 25.1, 23.5, 22.1, 14.6; Anal. Calcd for $C_{27}H_{43}ClN_4O_6$: C, 58.42; H, 7.81; N 10.09. Found: C, 58.61; H, 7.98; N 9.54.



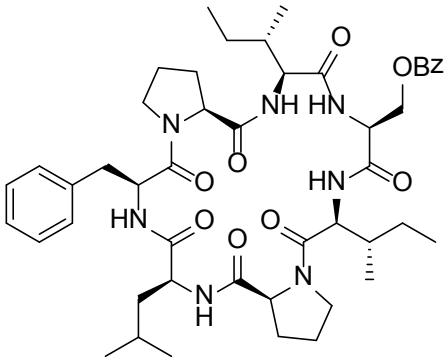
(2*S*,3*S*)-1-(((*S*)-3-(Benzoyloxy)-1-(((2*S*,3*S*)-1-((*S*)-2-(((*S*)-1-(((*S*)-1-((*S*)-2-carboxypyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxopentan-2-aminium chloride (23). White solid (91%).

m.p. 115.0-117.0 °C; ^{1}H NMR ($CDCl_3$): δ 7.36-7.19 (m, 10H), 4.87-4.79 (m, 2H), 4.58-4.54 (m, 2H), 4.46-4.25 (m, 3H), 3.87-3.70 (m, 5H), 3.58-3.36 (m, 3H), 3.16-3.10 (m, 1H), 2.97-2.88 (m, 1H), 2.23-2.14 (m, 1H), 1.98-1.81 (m, 8H), 1.69-1.49 (m, 4H), 1.43-1.22 (m,2H), 1.05 (dd, J = 6.9, 2.8 Hz, 2H), 0.98-0.87 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 175.2, 174.7, 174.3, 174.2, 171.9, 171.5, 169.5, 139.1, 138.1, 130.8, 129.8, 129.5, 129.1, 128.9, 127.8, 74.5, 72.8, 71.5, 71.0, 60.7, 60.6, 59.0, 58.5, 56.0, 54.9, 54.5, 53.8, 53.2, 48.0, 42.0, 42.1, 38.7, 38.5, 38.1, 32.0, 31.0, 30.2, 29.3, 27.4, 26.2, 25.9, 25.5, 24.6, 23.6, 22.3, 19.5, 16.1, 15.2, 12.3, 12.0, 11.8; HRMS (+ESI) m/z for $C_{47}H_{70}N_7O_9$ $[M + H]^+$ calcd. 879.5230, found 879.5057.

H-General Procedure for the Macrocyclization of Linear Heptapeptide (Method G).[9]

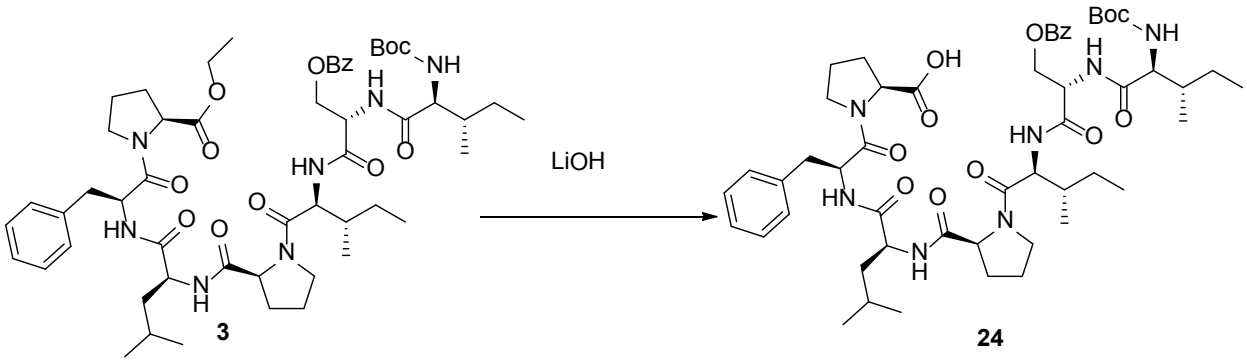


A modified literature procedure[9] was used FDPP (63 mg, 0.164 mmol, 1.5 equiv) was added to a solution of the linear heptapeptide **23** (100 mg, 0.110 mmol) in acetonitrile (20 mL, 0.005 M) under anhydrous conditions. DIPEA (51 mg, 0.394 mmol, 3.6 equiv) was added to this solution. The reaction mixture was then stirred at rt overnight, then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with Na_2CO_3 solution (2x 15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to yield cyclized heptapeptide **24**.



((6*S*,9*S*,12*S*,14a*S*,20*S*,23*S*,25a*S*)-20-benzyl-6,12-di((*S*)-sec-butyl)-23-isobutyl-5,8,11,14,19,22,25-heptaoxotetracosahydro-1H-dipyrrolo[1,2-a:1',2'-j][1,4,7,10,13,16,19]heptaazacyclohenicosin-9-yl)methyl benzoate (24). White solid (74%). m.p. 122-124 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 7.44-7.16 (m, 10H), 4.75-4.63 (m, 1H), 4.56-4.46 (m, 2H), 4.39-4.16 (m, 3H), 3.80-3.63 (m, 6H), 3.59-3.38 (m, 3H), 3.21-3.06 (m, 1H), 3.01-2.84 (m, 1H), 2.30-2.12 (m, 1H), 2.05-1.76 (m, 8H), 1.68-1.55 (m, 2H), 1.53-1.42 (m, 2H), 1.40-1.28 (m, 3H), 1.02-0.81 (m, 19H); ^{13}C NMR ($CDCl_3$): δ 175.2, 175.2, 174.3, 173.7, 172.1, 139.3, 138.3, 130.7, 129.9, 129.8, 129.6, 129.5, 129.0, 128.9, 128.8, 127.9, 74.4, 72.9, 71.1, 61.7, 61.0, 55.8, 53.3, 43.8, 42.2, 41.7, 38.4, 32.8, 31.5, 30.5, 29.4, 26.2, 25.9, 24.7, 23.6, 22.3, 22.0, 19.6, 18.2, 16.2, 13.3, 12.1, 11.9. HRMS *m/z* for $C_{47}H_{65}N_7O_9$ $[M+H]^+$ calcd. 858.5124, found 858.5115.

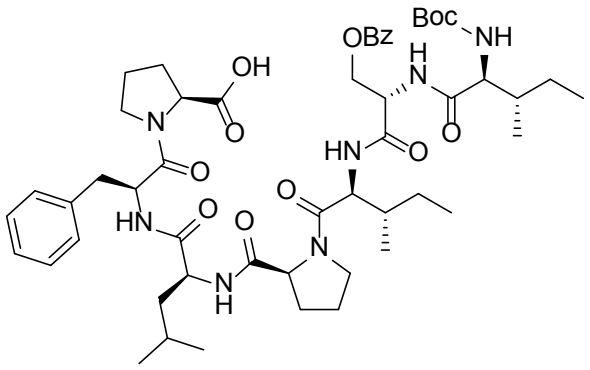
I-General Procedure for Ester Hydrolysis of Linear Heptapeptide (Method H).



3 **24**

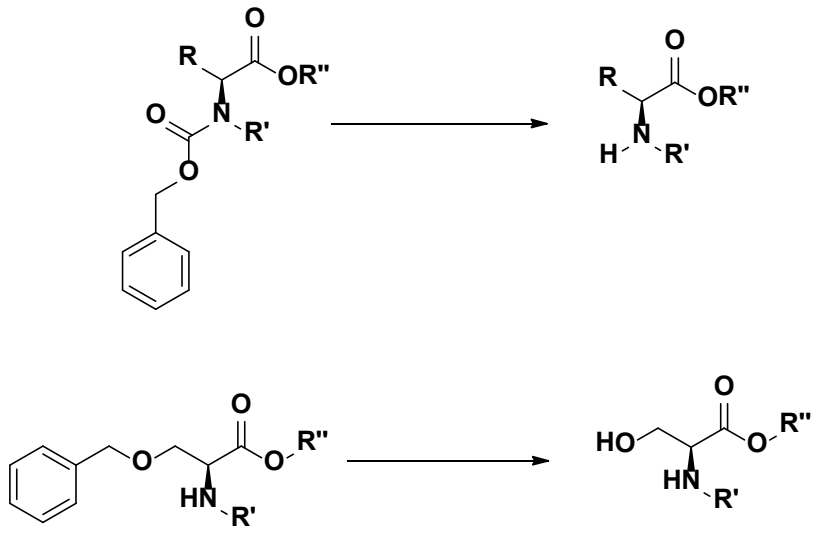
Procedure followed was according to a modified literature method.[10] To a solution of Boc-Heptapeptide ethyl ester **3** (400 mg, 0.398 mmol), in methanol (15 mL), THF (9 mL) was added

LiOH (84 mg, 1.992 mmol) dissolved in water (3 mL). The mixture was allowed to stir at room temperature (25 °C) over 2h. Solvent was evaporated from reaction mixture under reduced pressure, dissolved in water and acidified with 2N HCl, extracted with ethyl acetate. The organic layer was dried over anhyd Na_2SO_4 and concentrated to obtain **22**.

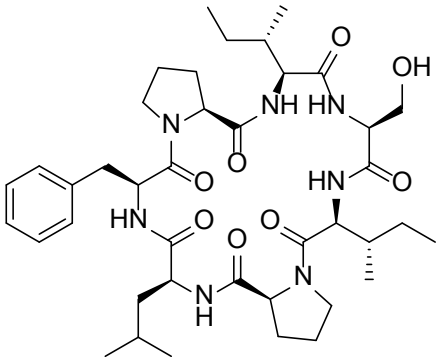


(*S*)-1-((*S*)-2-((*S*)-2-((*S*)-1-((6*S*,9*S*,12*S*)-9-((Benzoyloxy)methyl)-6,12-di((S)-sec-butyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oyl)pyrrolidine-2-carboxamido)-4-methylpentanamido)-3-phenylpropanoyl)pyrrolidine-2-carboxylic acid (22). White solid (75%); m.p. 98-99 °C; ^{1}H NMR ($CDCl_3$): δ 9.72 (br s, 1H), 7.28-7.10 (m, 10H), 4.86 (br s, 1H), 4.67-4.64 (m, 1H), 4.51-4.41 (m, 4H), 4.23 (br s, 1H), 3.80-3.72 (m, 3H), 3.59-3.34 (m, 4H), 3.10-2.98 (m, 2H), 2.85 (dd, J = 13.3, 5.5 Hz, 1H), 2.08-2.01 (m, 1H), 1.93-1.75 (m, 8H), 1.52-1.40 (m, 4H), 1.34 (s, 9H), 1.11-0.92 (m, 4H), 0.87-0.73 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 175.1, 174.6, 174.2, 173.7, 172.3, 170.2, 169.4, 156.5, 156.0, 137.4, 135.9, 129.9, 129.6, 128.5, 127.9, 127.9, 127.0, 80.1, 73.5, 73.4, 71.9, 69.6, 60.5, 59.4, 57.0, 55.8, 52.7, 52.6, 47.4, 41.5, 38.3, 38.0, 37.5, 28.7, 28.4, 28.1, 26.2, 25.0, 24.8, 23.1, 21.9, 21.0, 19.1, 15.7, 15.6, 14.5, 11.9, 11.7, 11.5; ; Anal. Calcd for $C_{52}H_{81}N_7O_{13}$: C, 61.70; H, 8.07; N 9.69. Found: C, 61.57; H, 8.29; N 8.49.

J-General Procedure for the deprotection of the Cbz- and Bz- protecting group (Method I).



The amino acid/peptide (1.0 mmol) was dissolved in anhydrous MeOH (30 mL) and stirred under an atmosphere of hydrogen in the presence of a catalytic amount of Pd/C for 48 h. Filtration through a bed of celite and evaporation afforded the desired amino acid/peptide.



(6*S*,9*S*,12*S*,14a*S*,20*S*,23*S*,25a*S*)-20-Benzyl-6,12-di((*S*)-sec-butyl)-9-(hydroxymethyl)-23-isobutylhexadecahydro-1H-dipyrrolo[1,2-a:1',2'-j][1,4,7,10,13,16,19]heptaazacyclohenicosine-5,8,11,14,19,22,25(25a*H*)-heptaone (1). NMR and optical rotation matched reported.[11]

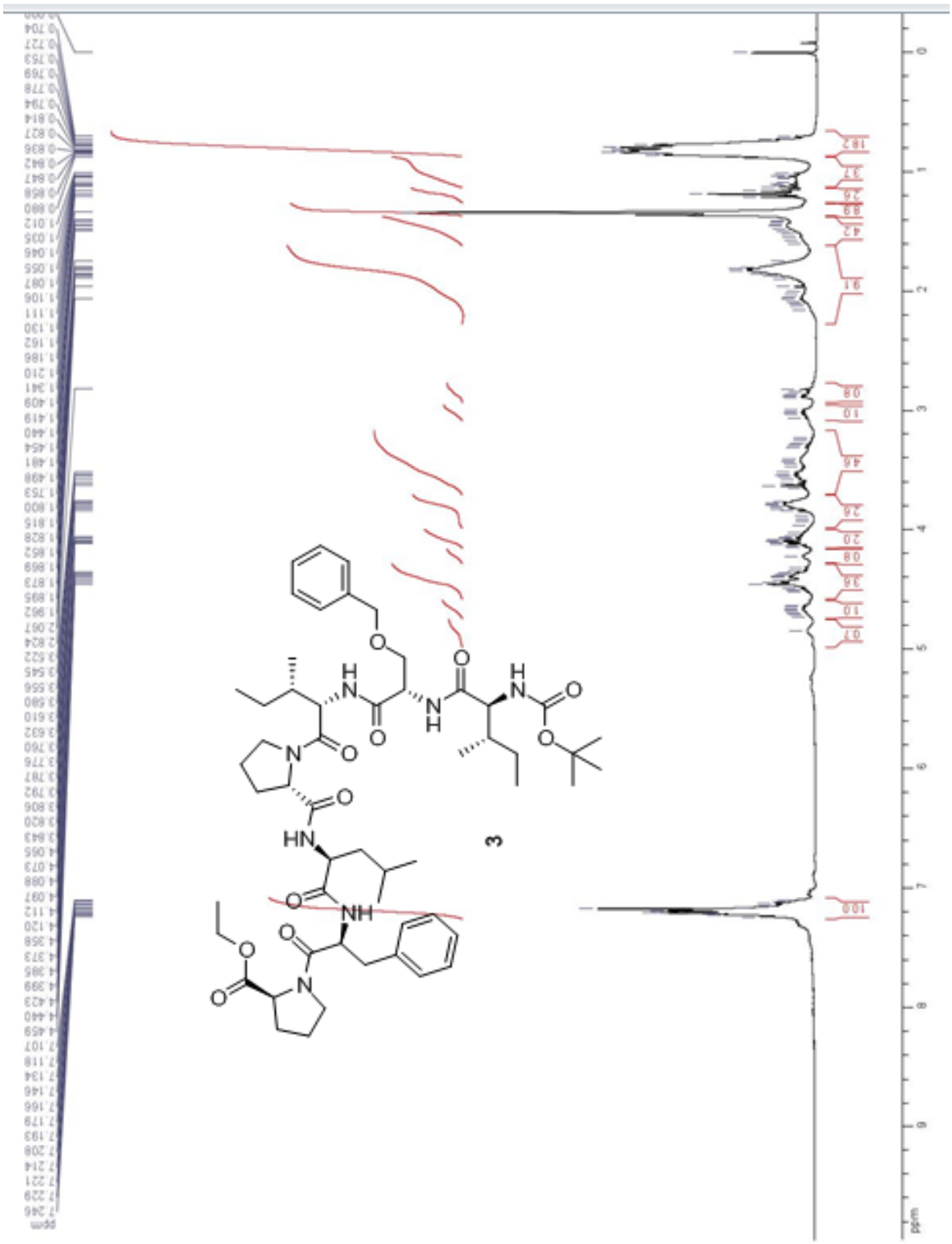
II-References

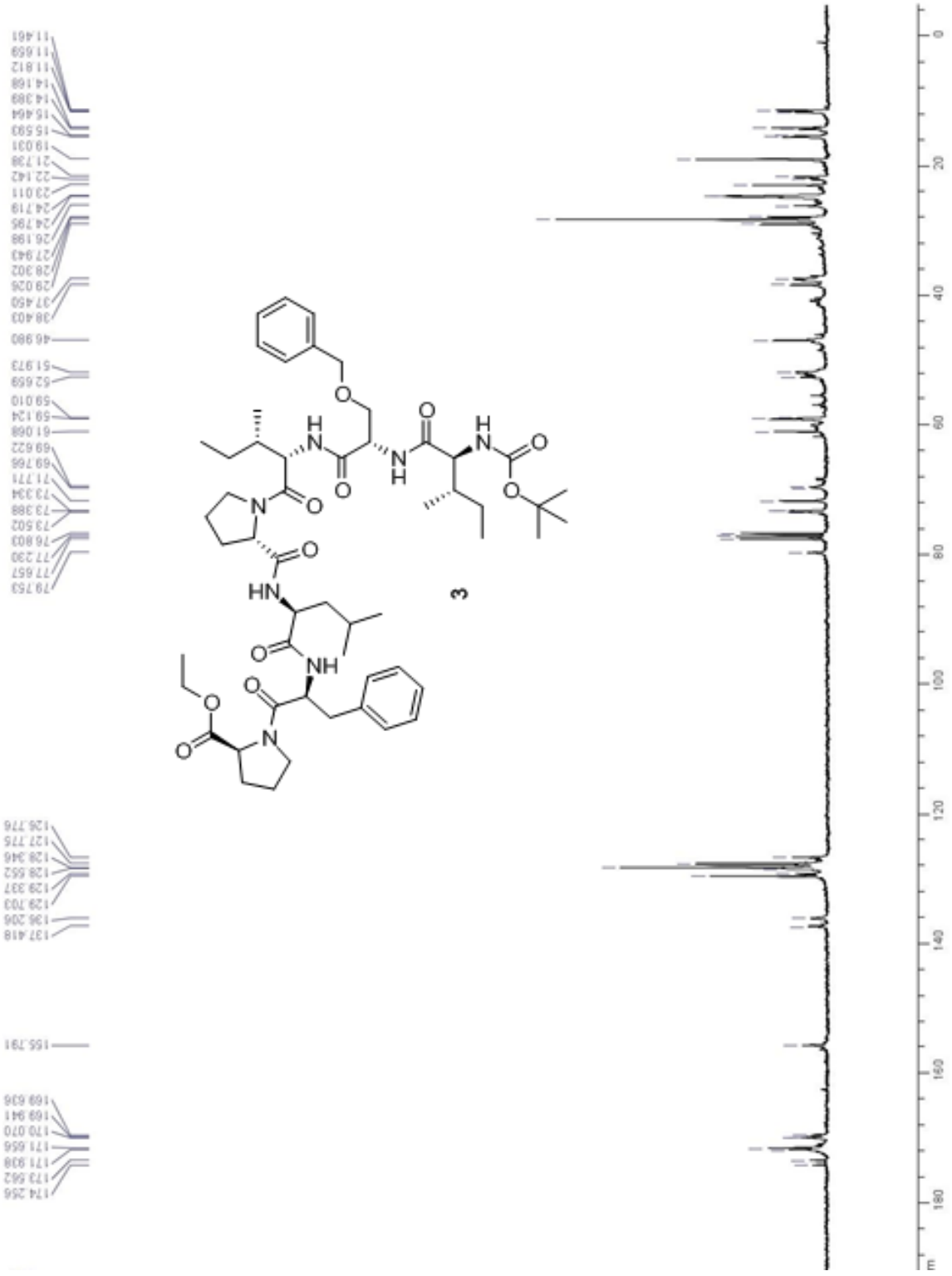
1. A. R. Katritzky, P. Angrish and K. Suzuki, *Synthesis*, 2006, 411-424.
2. A. R. Katritzky, A. A. Shestopalov and K. Suzuki, *Synthesis*, 2004, 1806-1813.
3. W. D. Cash, *Journal of Organic Chemistry*, 1961, 26, 2136-2137.
4. A. A. Mazurov, V. M. Kabanov and S. A. Andronati, *Doklady Akademii Nauk SSSR*, 1989, 306, 364-366.
5. S. Salvadori, M. Marastoni, G. Balboni, P. Borea and R. Tomatis, *European Journal of Medicinal Chemistry*, 1990, 25, 171-177.
6. K. Ha, M. Chahar, J.-C. M. Monbaliu, E. Todadze, F. K. Hansen, A. A. Oliferenko, C. E. Ocampo, D. Leino, A. Lillicotch, C. V. Stevens and A. R. Katritzky, *Journal of Organic Chemistry*, 2012, 77, 2637-2648.
7. M. El Khatib, M. Elagawany, F. Jabeen, E. Todadze, O. Bol'shakov, A. Oliferenko, L. Khelashvili, S. A. El-Feky, A. Asiri and A. R. Katritzky, *Organic & Biomolecular Chemistry*, 2012, 10, 4836-4838.
8. J. I. Harris and T. S. Work, *Biochemical Journal*, 1950, 46, 196-199.
9. D. Skropeta, K. A. Jolliffe and P. Turner, *Journal of Organic Chemistry*, 2004, 69, 8804-8809.
10. *Application: WO*

WO Pat., 2011-IB50290

2011089576, 2011.
11. D. E. Williams, K. Yu, H. W. Behrisch, R. Van Soest and R. J. Andersen, *Journal of Natural Products*, 2009, 72, 1253-1257.

III-^{1}H and ^{13}C NMR spectra for all compounds

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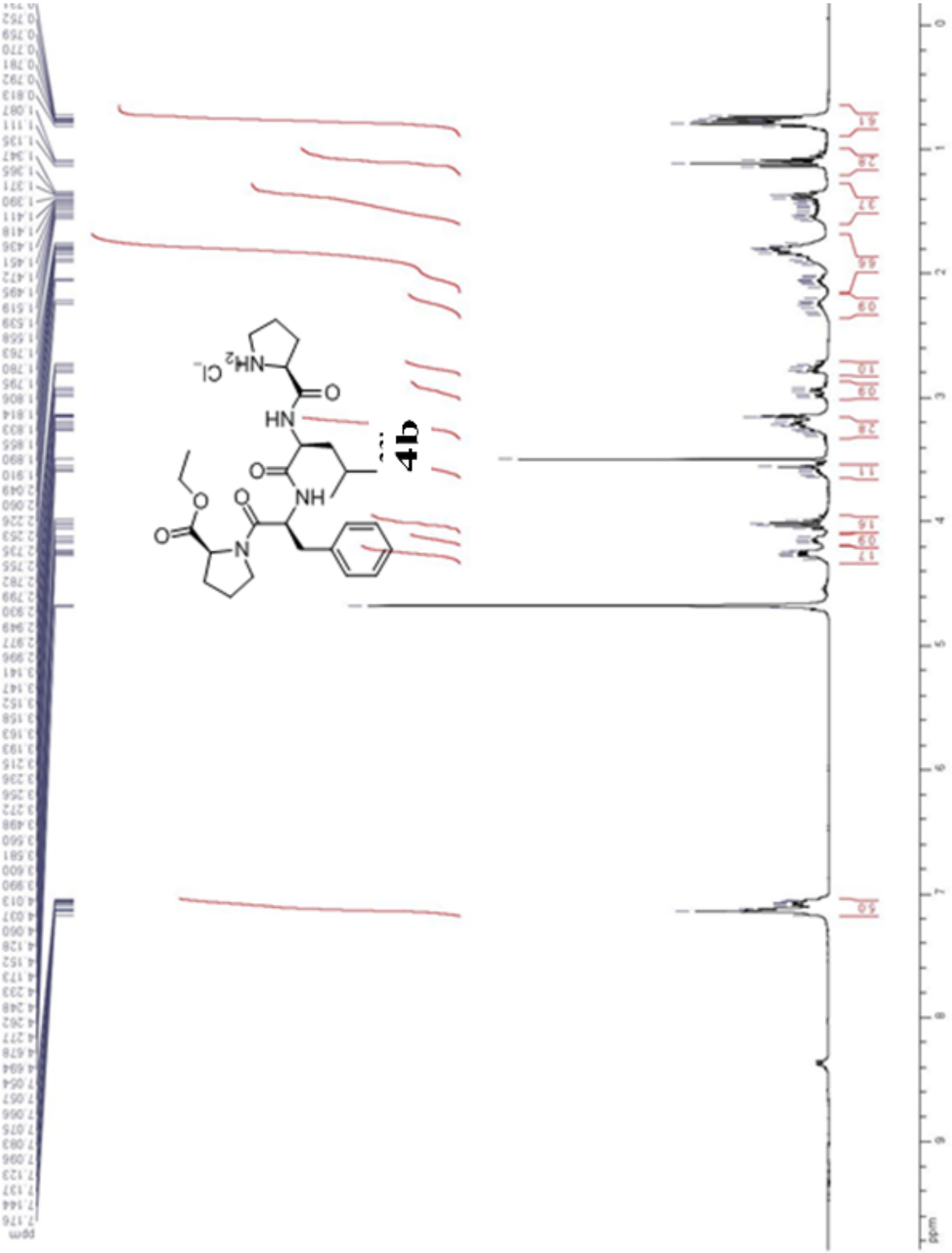
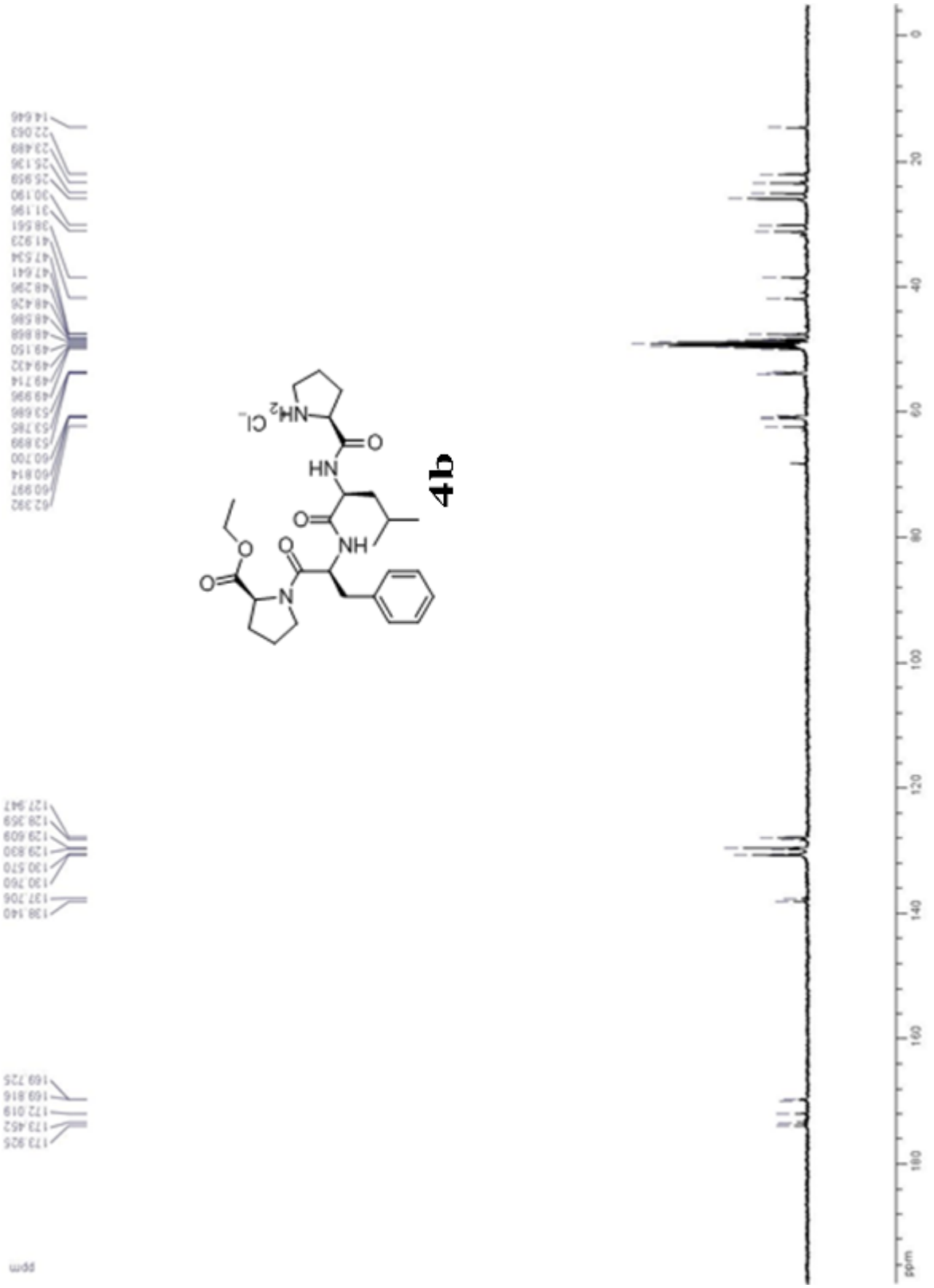

4b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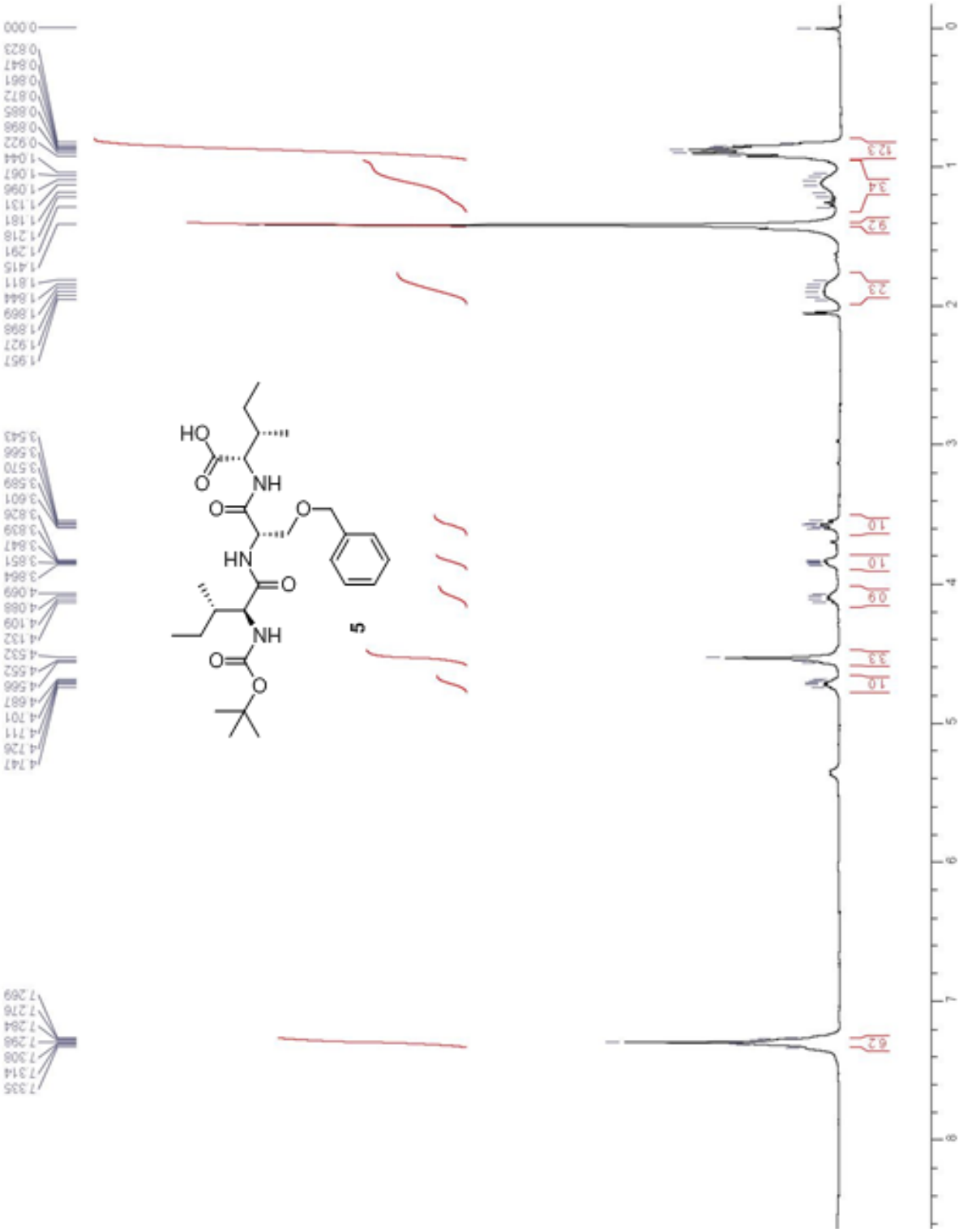
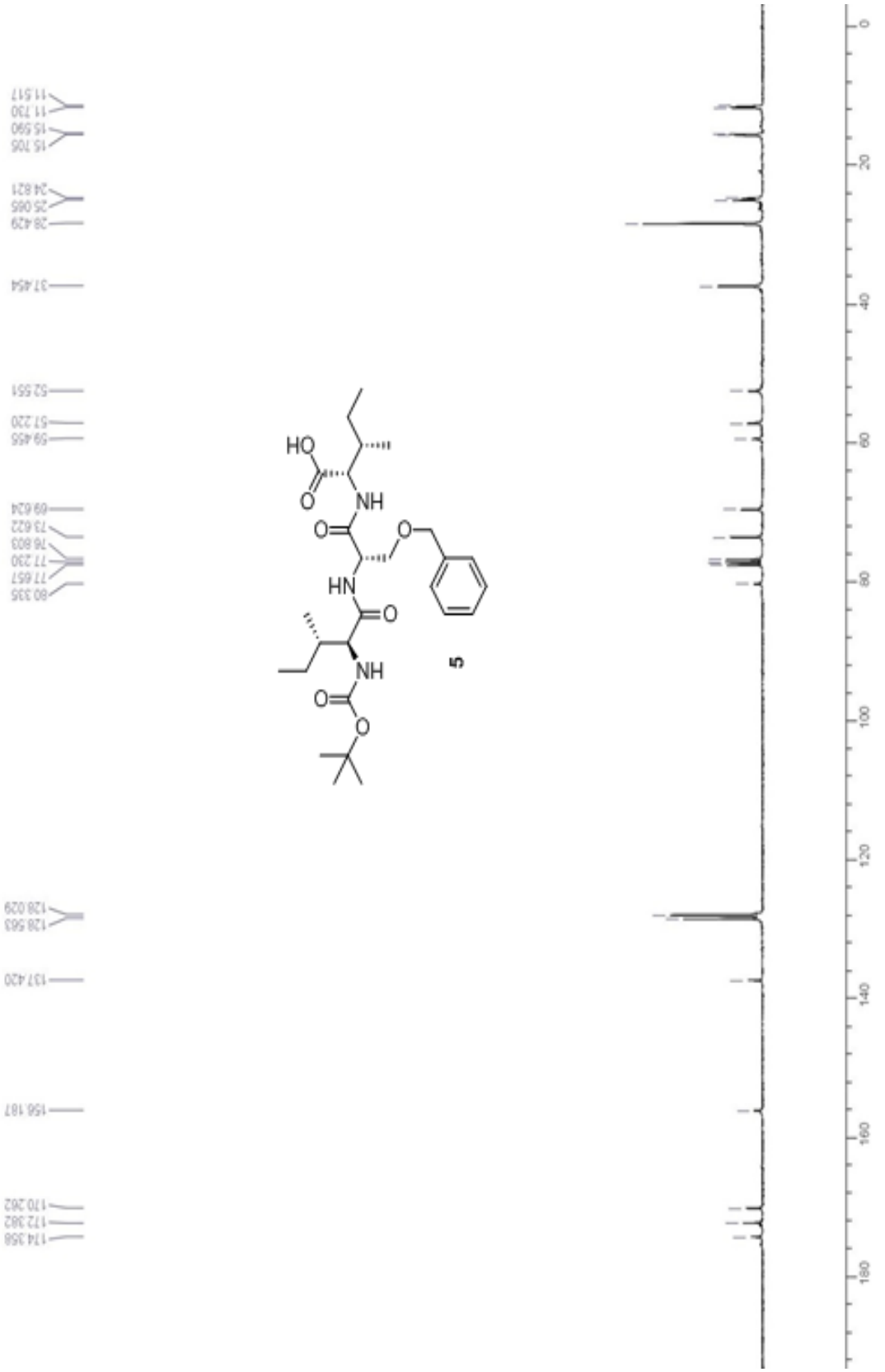
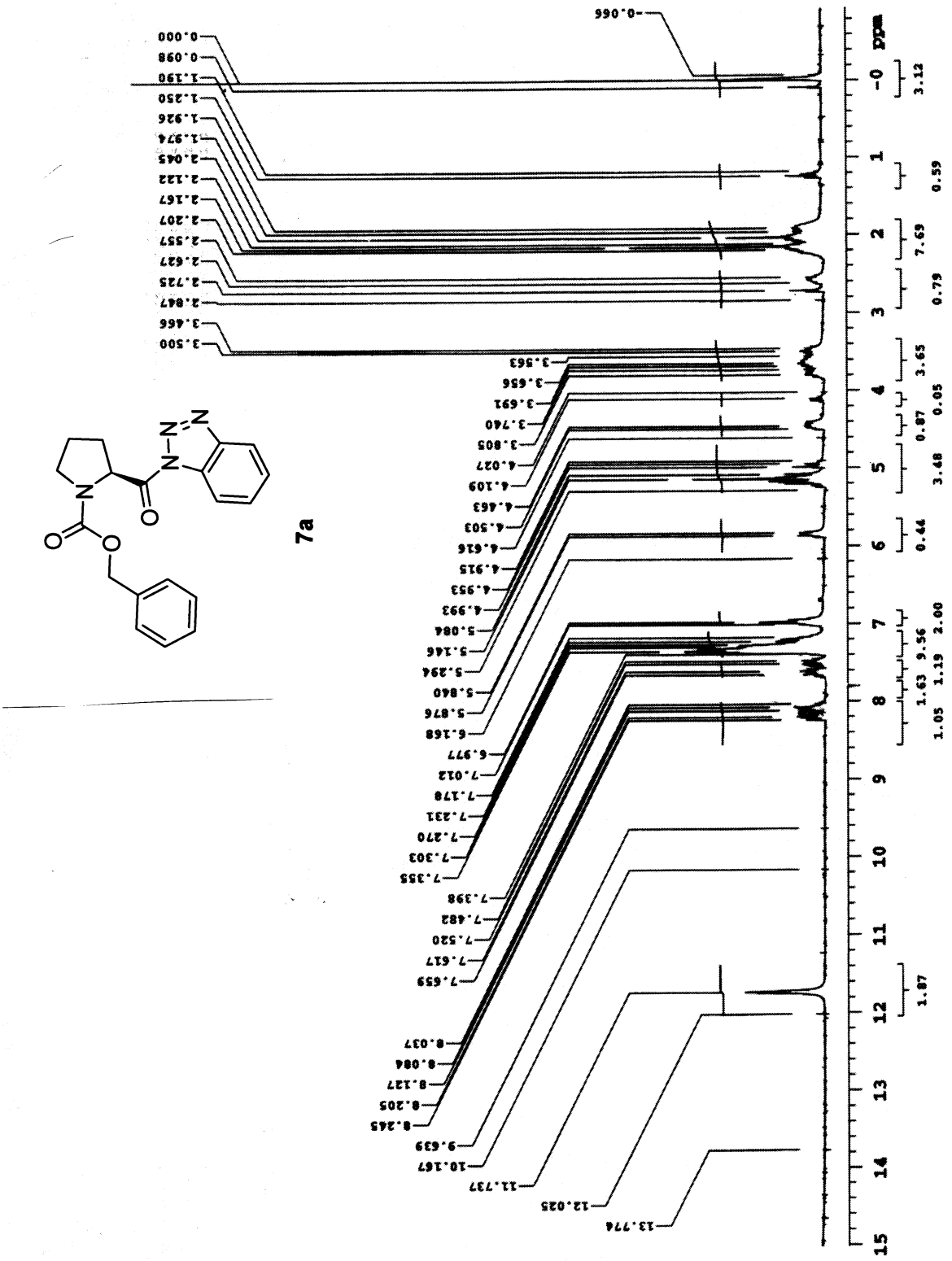
NH2 Cl
HN
O
NH
O
O
O
O
N
ppm


HO
O
NH
O
O
HN
O
NH
O
O
5


HO
O
NH
O
O
HN
O
NH
O
O
5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0.000
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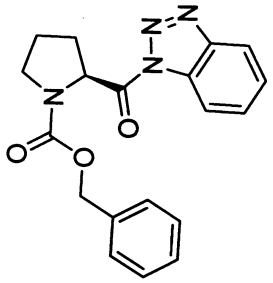
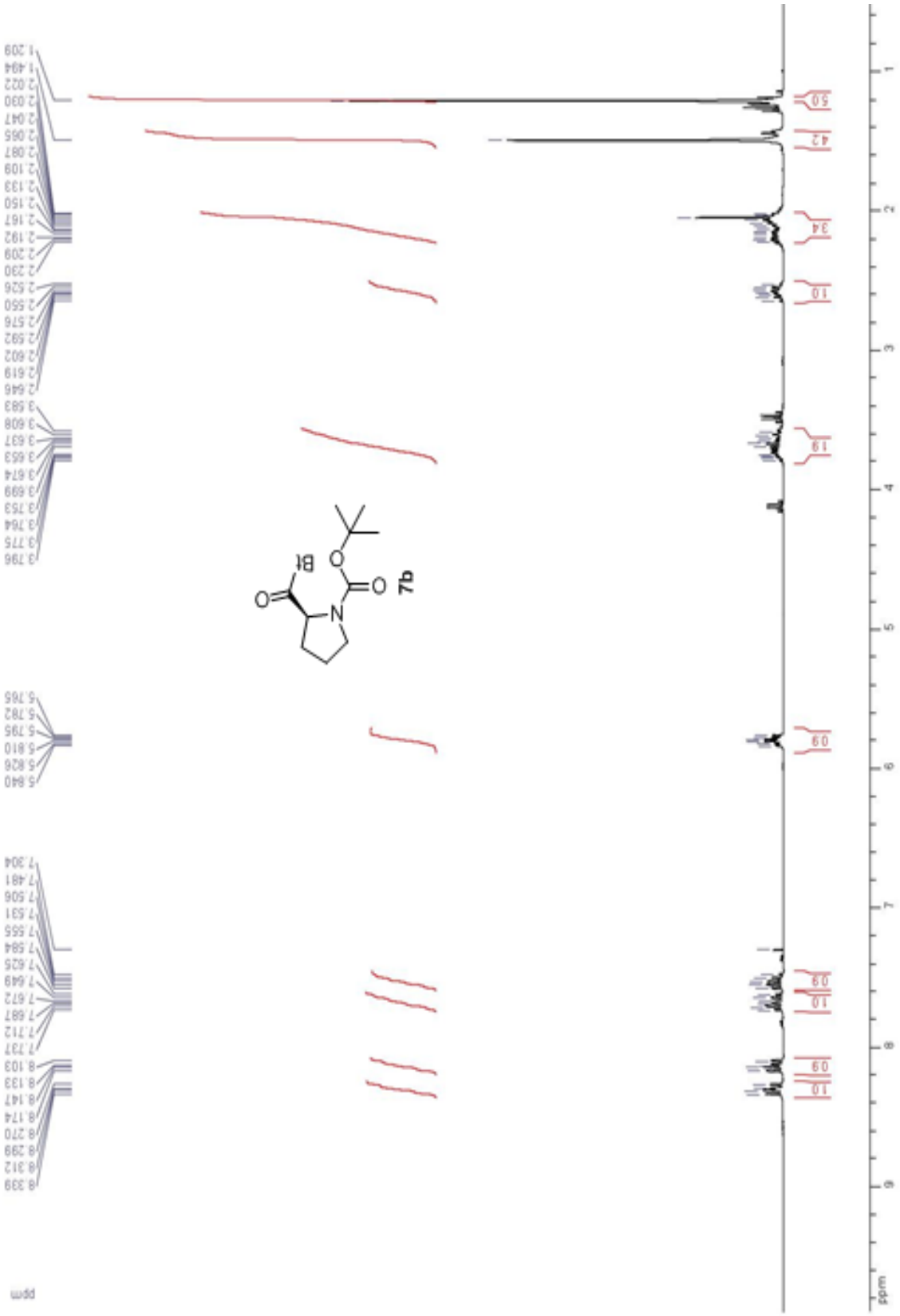
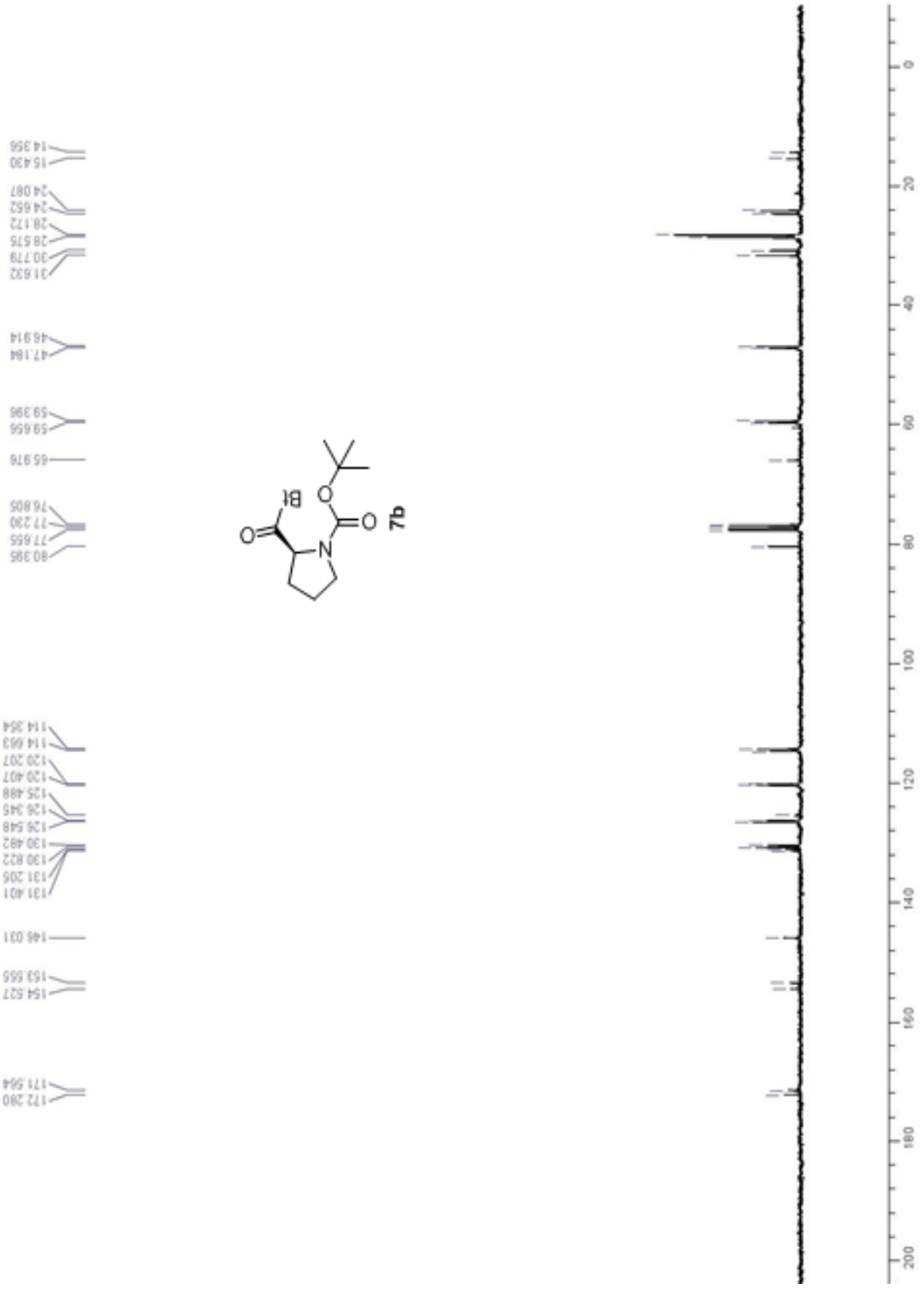
1.250
1.926
1.974
2.045
2.132
2.167
2.207
2.557
2.627
2.725
2.847
3.466
3.500
3.563
3.656
3.691
3.740
3.805
4.027
4.109
4.463
4.503
4.616
4.915
4.953
4.993
5.084
5.146
5.294
5.840
5.876
6.168
6.977
7.013
7.178
7.231
7.270
7.303
7.355
7.398
7.482
7.520
7.617
7.659
8.037
8.084
8.127
8.205
8.245
9.639
10.167
11.737
12.025
13.774
ppm
3.12
0.59
7.69
0.79
3.65
0.05
0.87
3.48
0.44
2.00
9.56
1.19
1.63
1.05
1.87



7a

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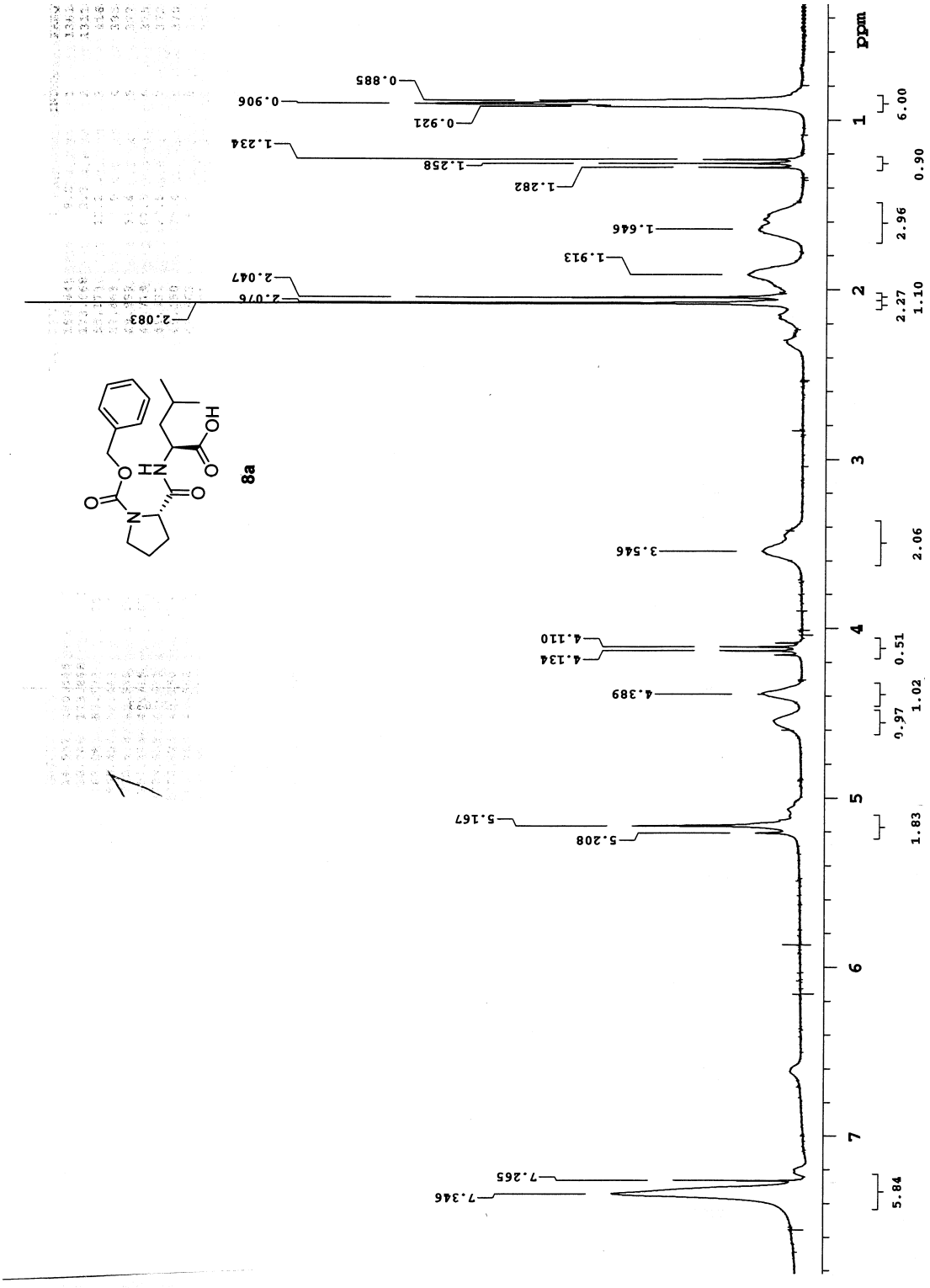
24.087
24.652
28.172
28.575
30.779
31.632
46.914
47.184
59.396
59.656
65.976
76.805
77.230
77.655
80.395
114.354
114.653
120.207
120.407
125.488
126.345
126.548
130.482
130.822
131.206
131.401
146.031
153.555
154.527
171.564
172.280
Bl
O
O
N
O
7b
0
20
40
60
80
100
120
140
160
180
200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0.921
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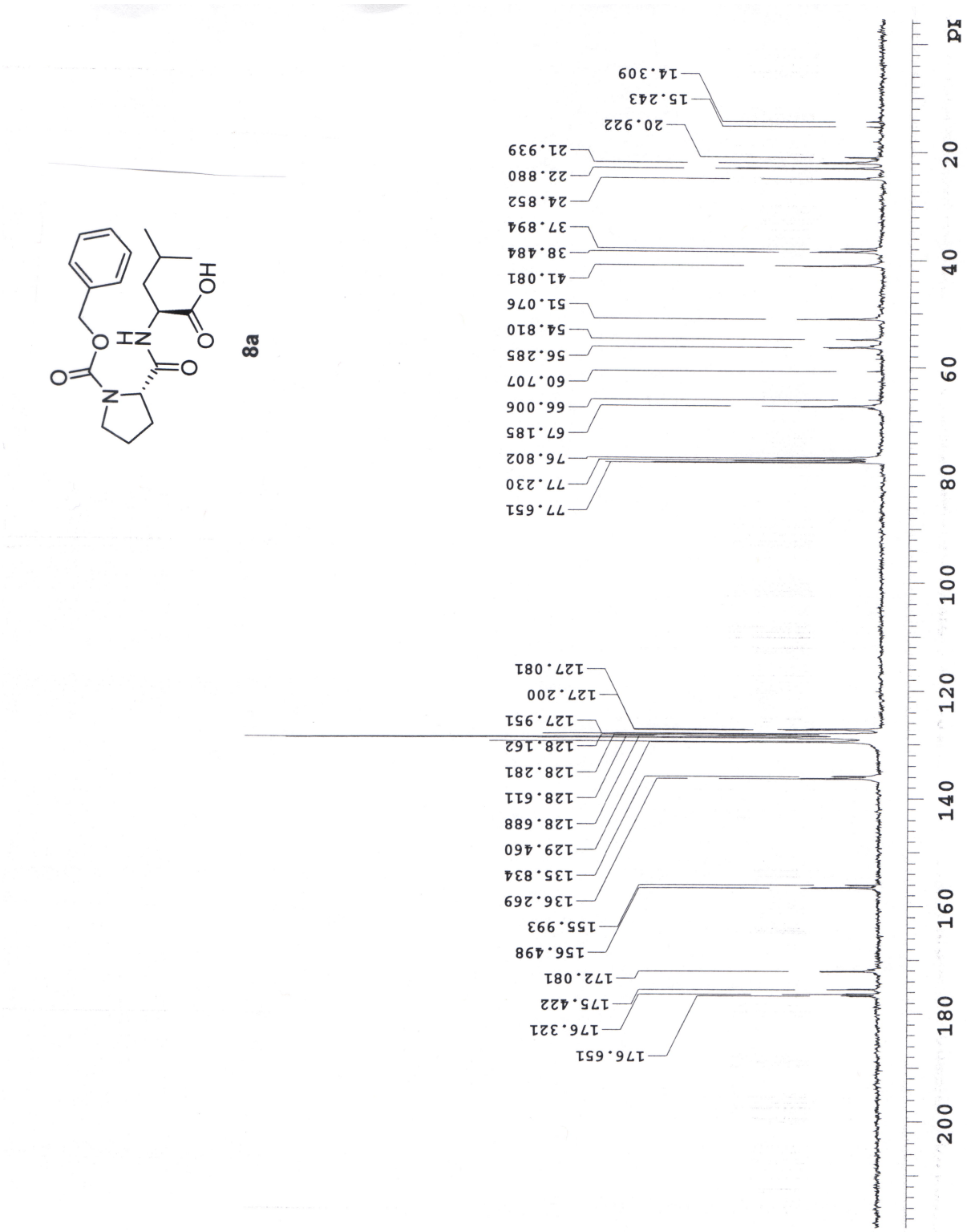
1.258
1.282
1.646
1.913
2.047
2.076
2.083
3.546
4.110
4.134
4.389
5.167
5.208
7.265
7.346
6.00
0.90
2.96
2.27
1.10
2.06
0.51
1.02
0.97
1.83
5.84
8a


8a
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15.243
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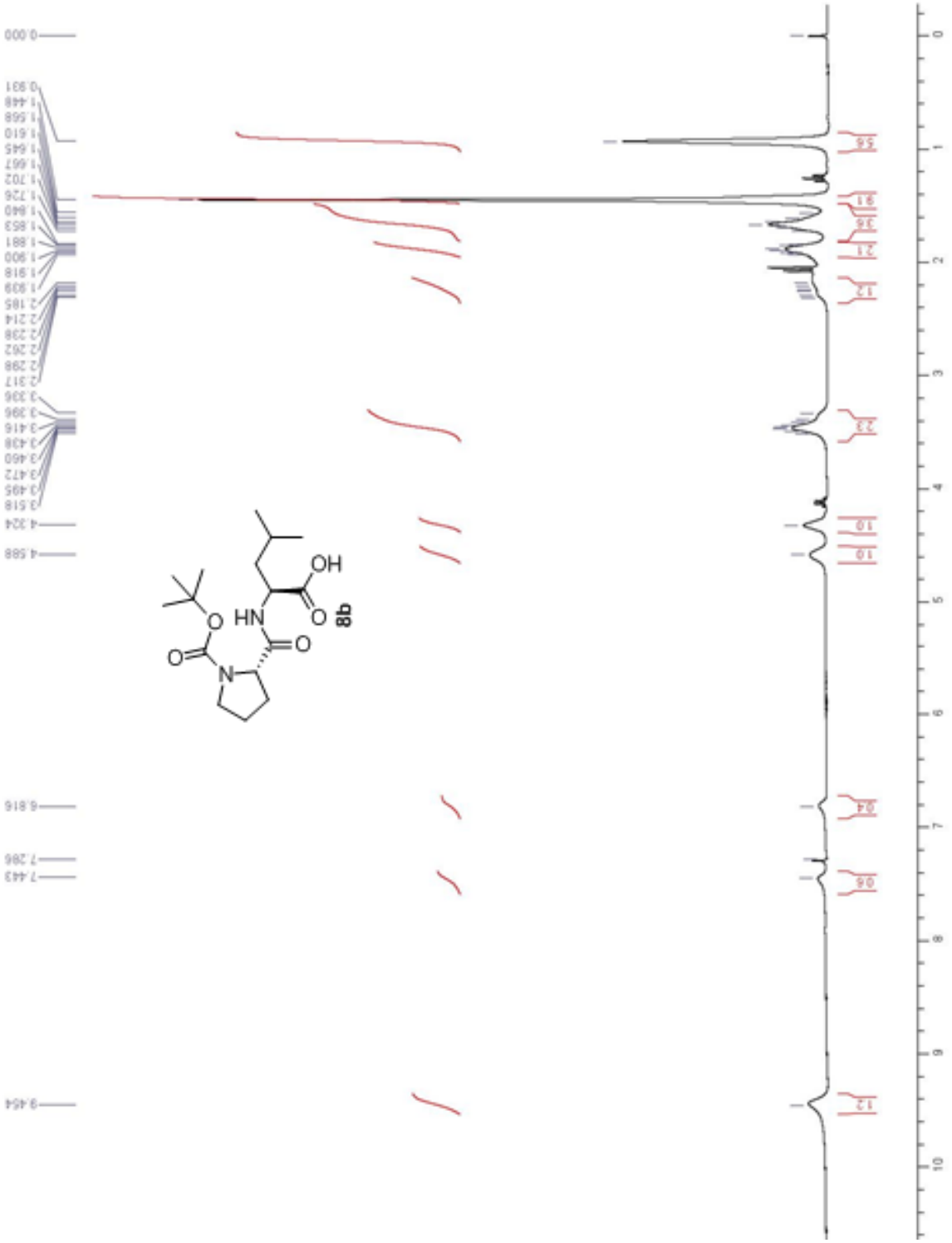
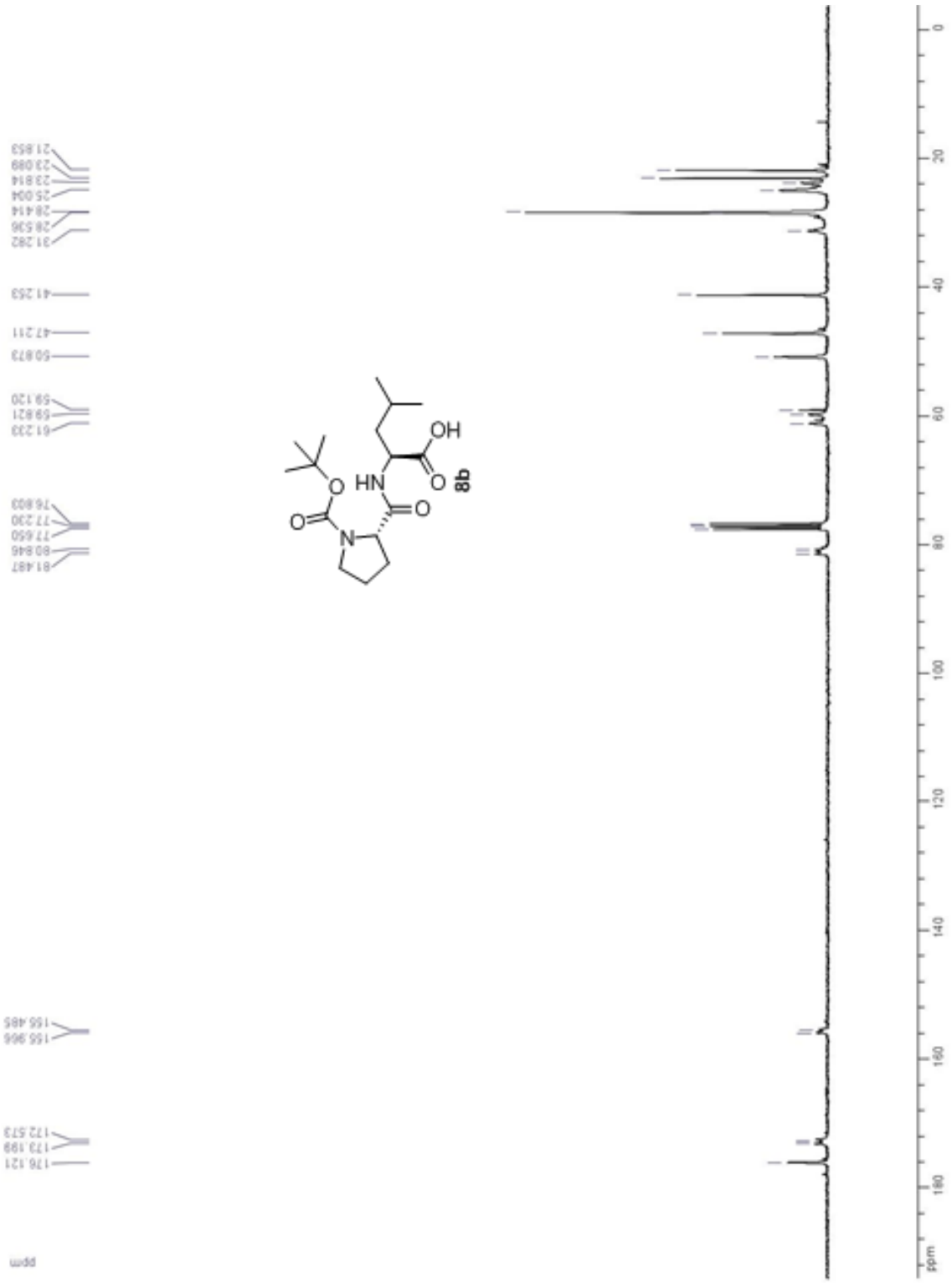
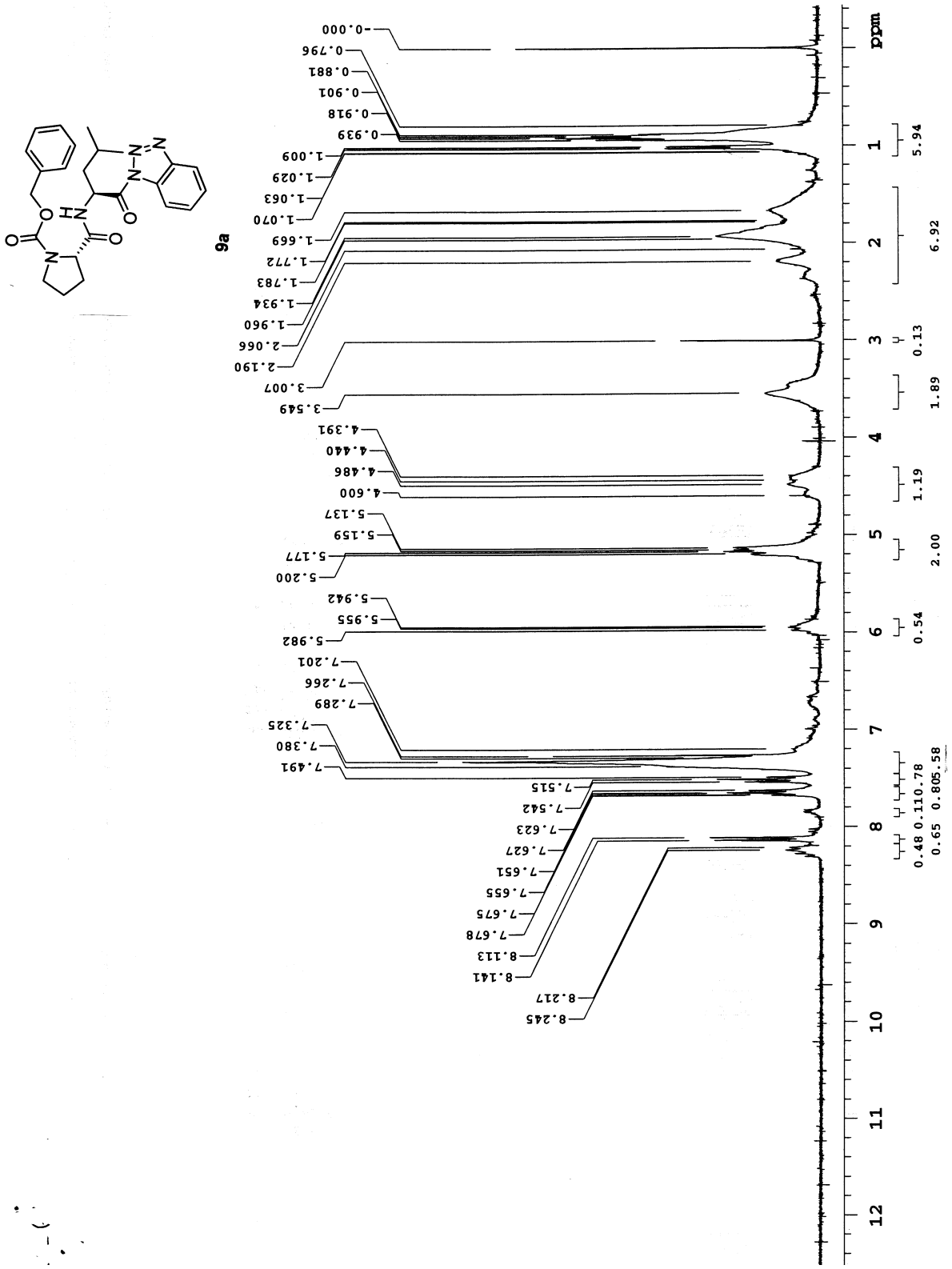
21.939
22.880
24.852
37.894
38.484
41.081
51.076
54.810
56.285
60.707
66.006
67.185
76.802
77.230
77.651
127.081
127.200
127.951
128.162
128.281
128.611
128.688
129.460
135.834
136.269
155.993
156.498
172.081
175.422
176.321
176.651
ppm
20
40
60
80
100
120
140
160
180
200




OH
HN
O
O
O
O
N
8b
ppm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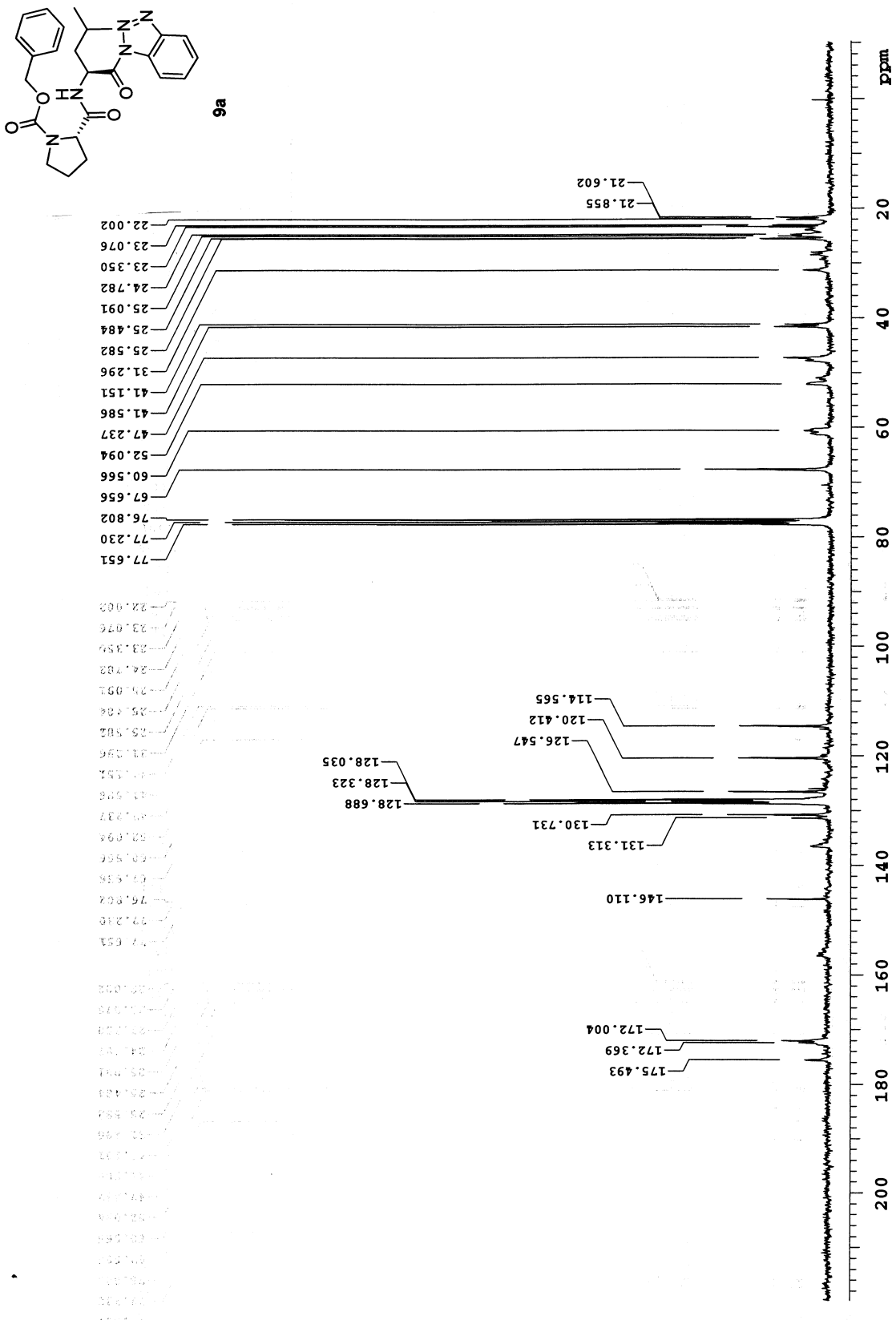
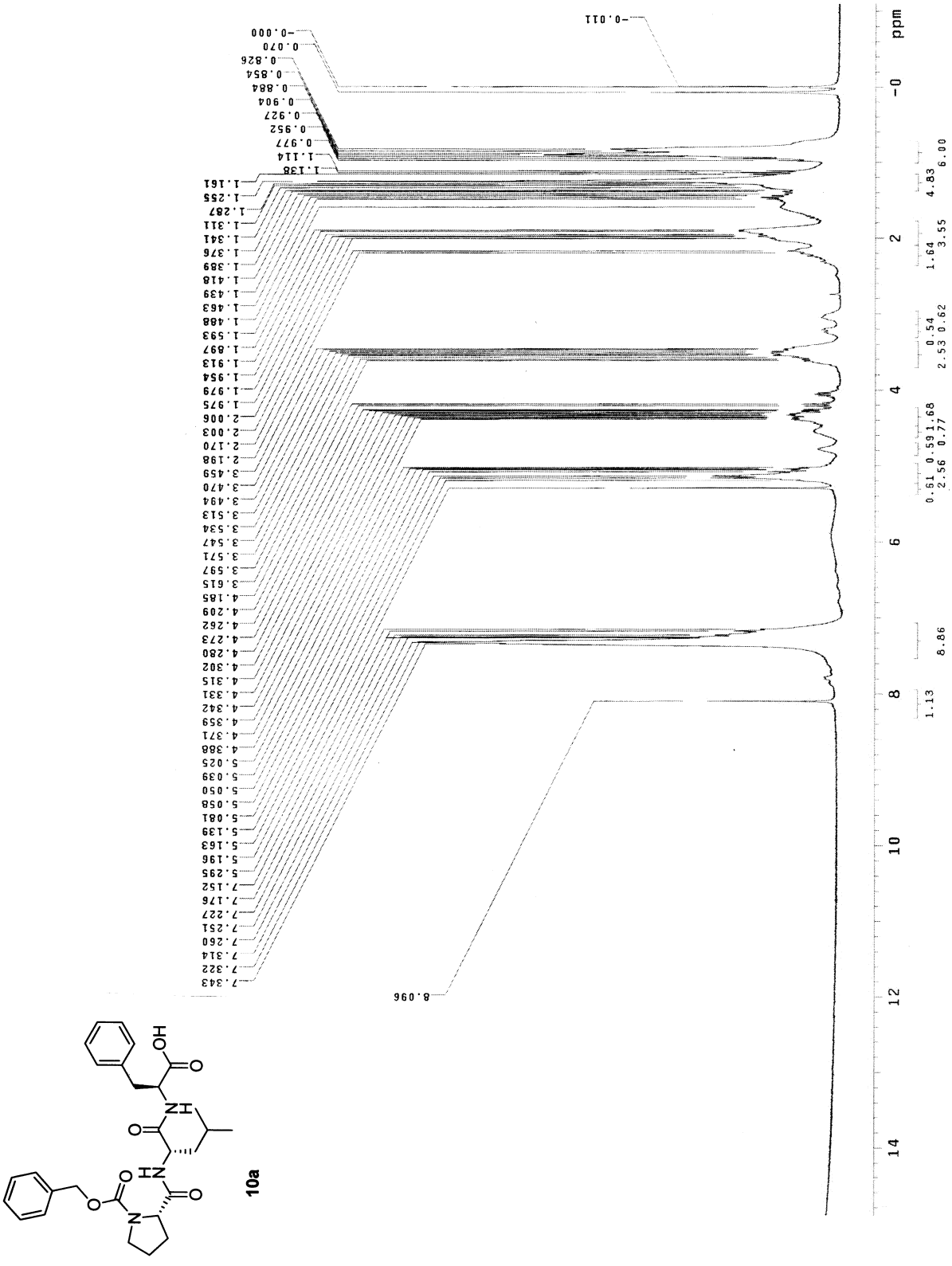
0.881
0.901
0.918
0.939
1.009
1.029
1.063
1.070
1.669
1.772
1.783
1.934
1.960
2.066
2.190
3.007
3.549
4.391
4.440
4.486
4.600
5.137
5.159
5.177
5.200
5.942
5.955
5.982
7.201
7.266
7.289
7.325
7.380
7.491
7.515
7.542
7.623
7.627
7.651
7.655
7.675
7.678
8.113
8.141
8.217
8.245
5.94
6.92
0.13
1.89
1.19
2.00
0.54
0.48 0.11 0.78
0.65 0.80 5.58


9a
21.602
21.855
22.002
23.076
23.350
24.782
25.091
25.484
25.582
31.296
41.151
41.586
47.237
52.094
60.566
67.656
76.802
77.230
77.651
114.565
120.412
126.547
128.035
128.323
128.688
130.731
131.313
146.110
172.004
172.369
175.493
ppm
20
40
60
80
100
120
140
160
180
200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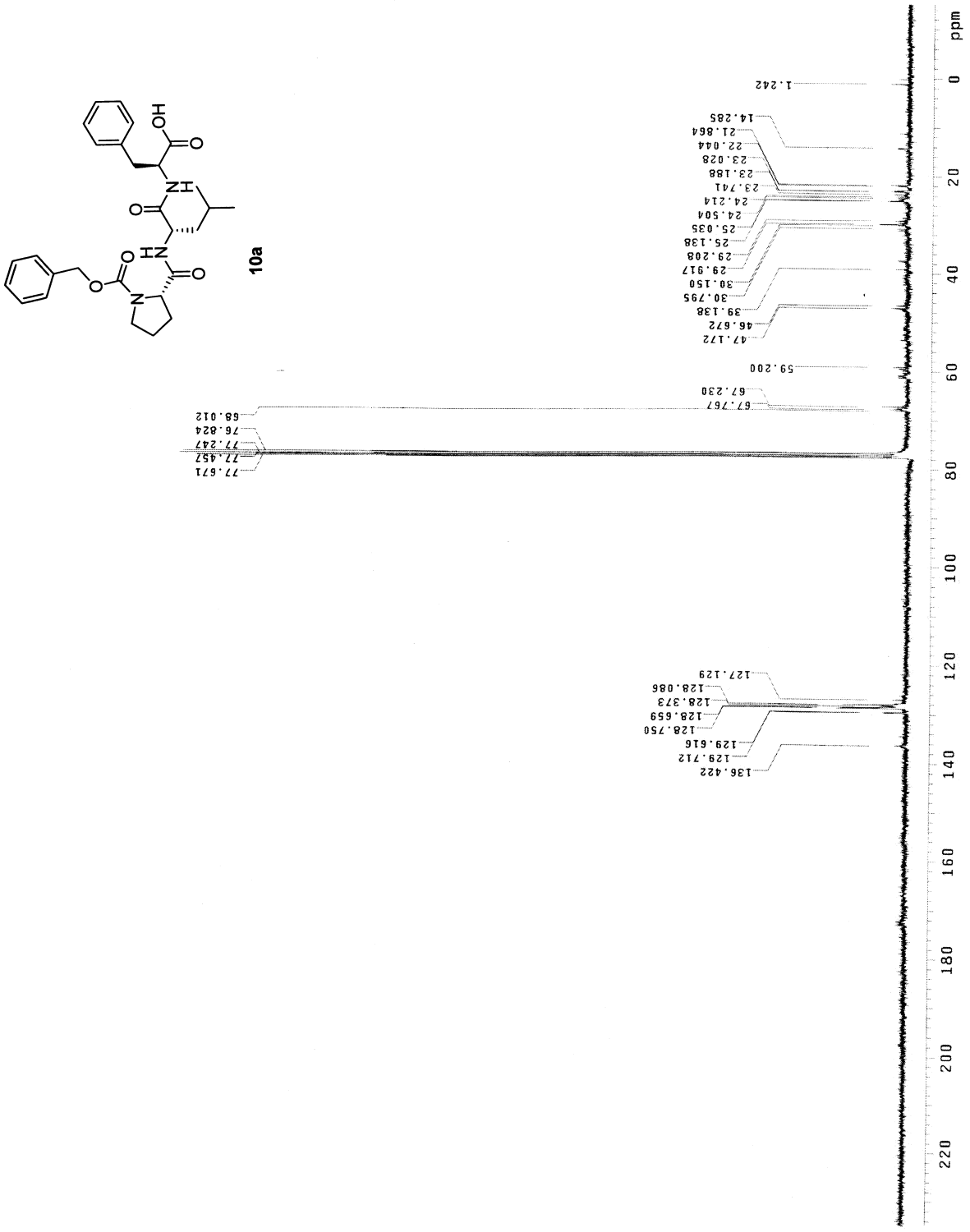
-0.000
0.070
0.826
0.854
0.884
0.904
0.927
0.952
0.977
1.114
1.138
1.161
1.255
1.287
1.311
1.341
1.376
1.389
1.418
1.439
1.463
1.488
1.593
1.697
1.913
1.954
1.979
1.975
2.006
2.003
2.170
2.198
3.459
3.470
3.494
3.513
3.534
3.547
3.571
3.597
3.615
4.185
4.209
4.262
4.273
4.280
4.302
4.315
4.331
4.342
4.359
4.371
4.388
5.025
5.039
5.050
5.058
5.081
5.139
5.163
5.196
5.295
7.152
7.176
7.227
7.251
7.260
7.314
7.322
7.343
8.096
ppm
0 2 4 6 8 10 12 14
0.61 0.59 1.68
2.56 0.77
1.13
8.86
0.54
2.53 0.62
1.64
3.55
4.83
6.00
OH
O
N
O
N
O
O
O
N
10a


10a
1.242
14.285
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22.044
23.028
23.188
23.741
24.214
24.504
25.035
25.138
29.208
29.917
30.150
30.795
39.138
46.672
47.172
59.200
67.230
67.767
68.012
76.824
77.247
77.457
77.671
127.129
128.086
128.373
128.659
128.750
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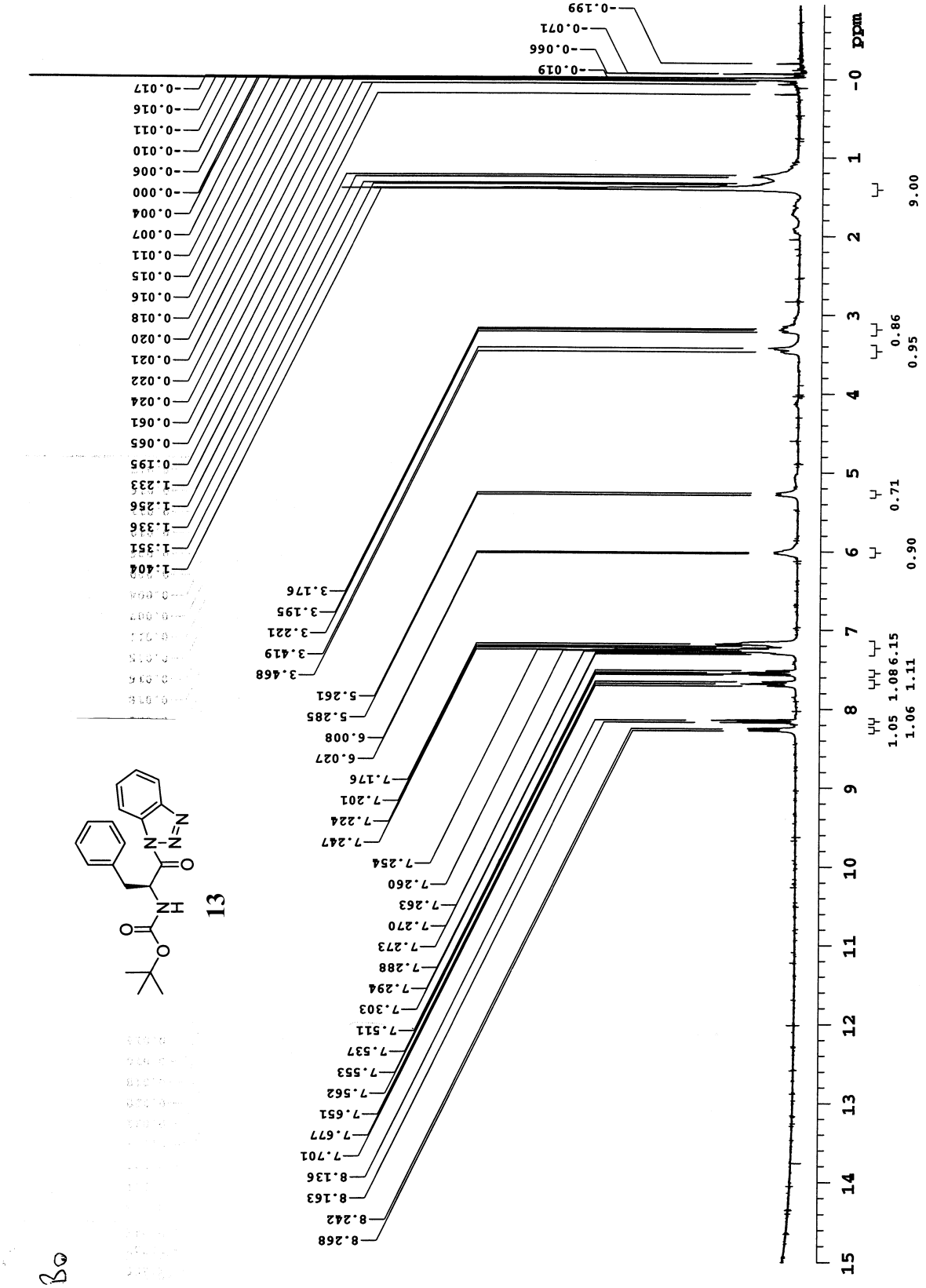
129.712
136.422
ppm
0
20
40
60
80
100
120
140
160
180
200
220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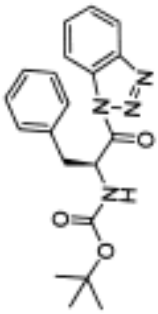
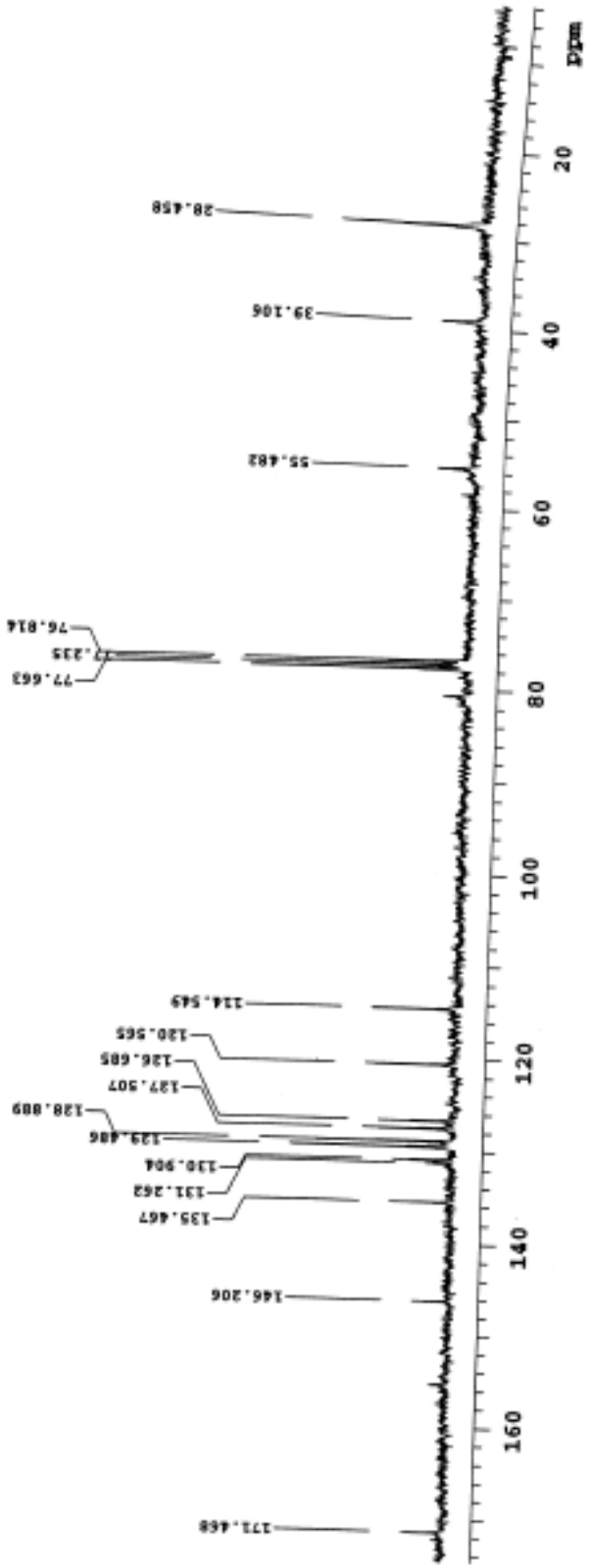
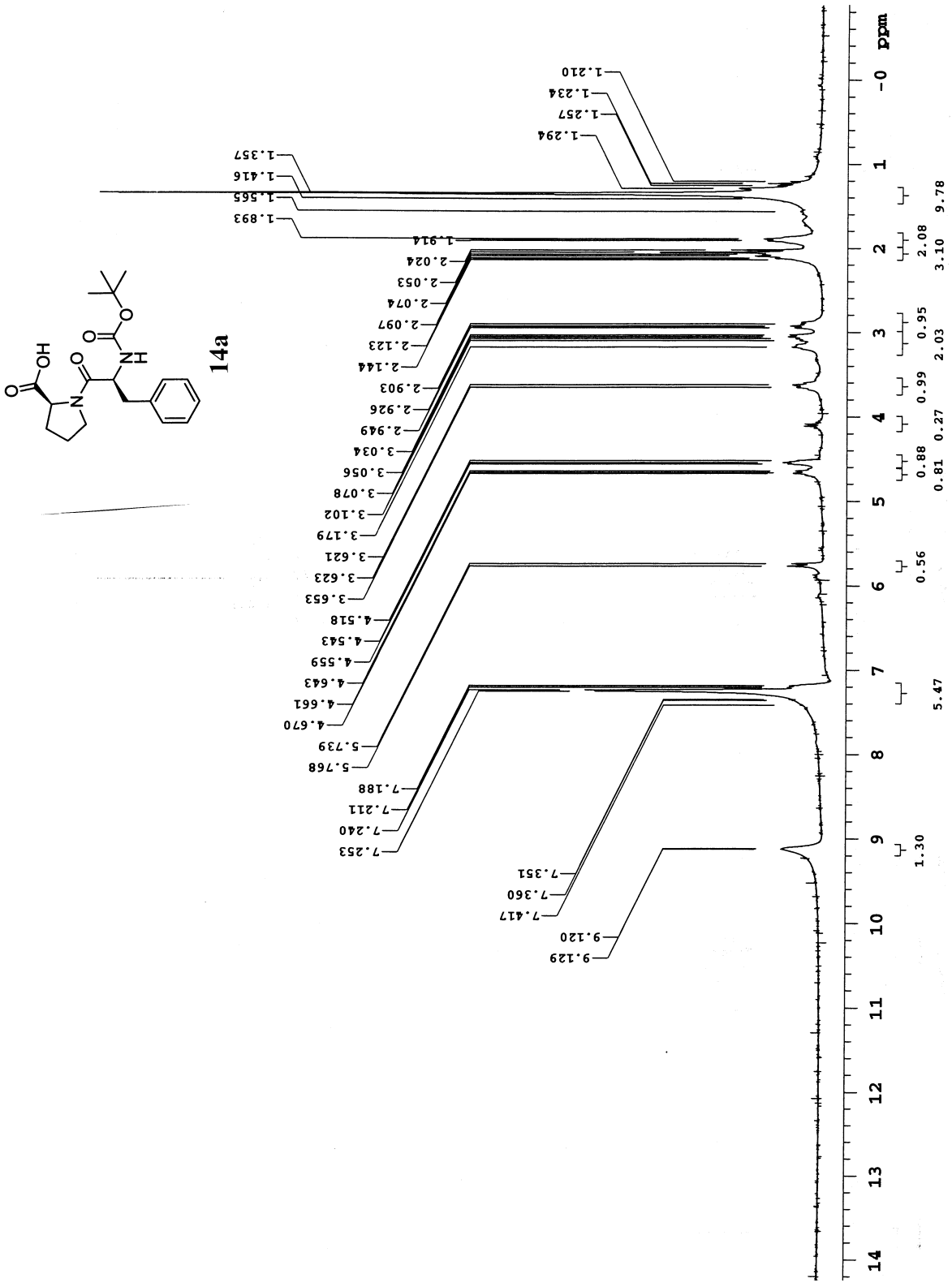
-0.066
-0.019
-0.017
-0.016
-0.011
-0.010
-0.006
-0.000
0.004
0.007
0.011
0.015
0.016
0.018
0.020
0.021
0.022
0.024
0.061
0.065
0.195
1.233
1.256
1.336
1.351
1.404
3.176
3.195
3.221
3.419
3.468
5.261
5.285
6.008
6.027
7.176
7.201
7.224
7.247
7.254
7.260
7.263
7.270
7.273
7.288
7.294
7.303
7.511
7.537
7.553
7.562
7.651
7.677
7.701
8.136
8.163
8.242
8.268
ppm
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
9.00
0.86
0.95
0.71
0.90
1.05 1.08 6.15
1.06 1.11
13



13

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1.257
1.294
1.357
1.416
1.565
1.893
1.914
2.024
2.053
2.074
2.097
2.123
2.144
2.903
2.926
2.949
3.034
3.056
3.078
3.102
3.179
3.621
3.623
3.653
4.518
4.543
4.559
4.643
4.661
4.670
5.739
5.768
7.188
7.211
7.240
7.253
7.351
7.360
7.417
9.120
9.129
ppm
9.78
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2.08
2.03
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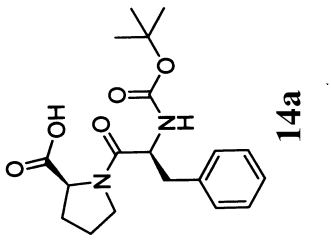
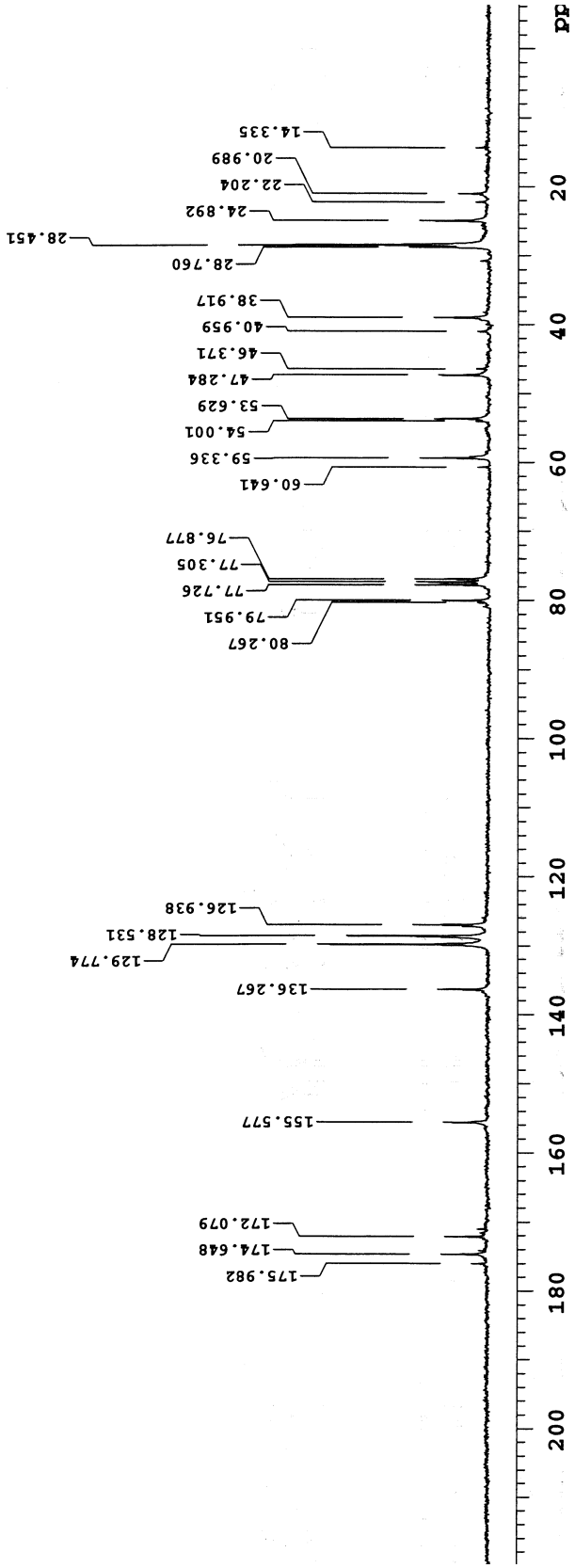
0.99
0.27
0.88
0.81
0.56
5.47
1.30


O
OH
O
N
O
N
H
O

14a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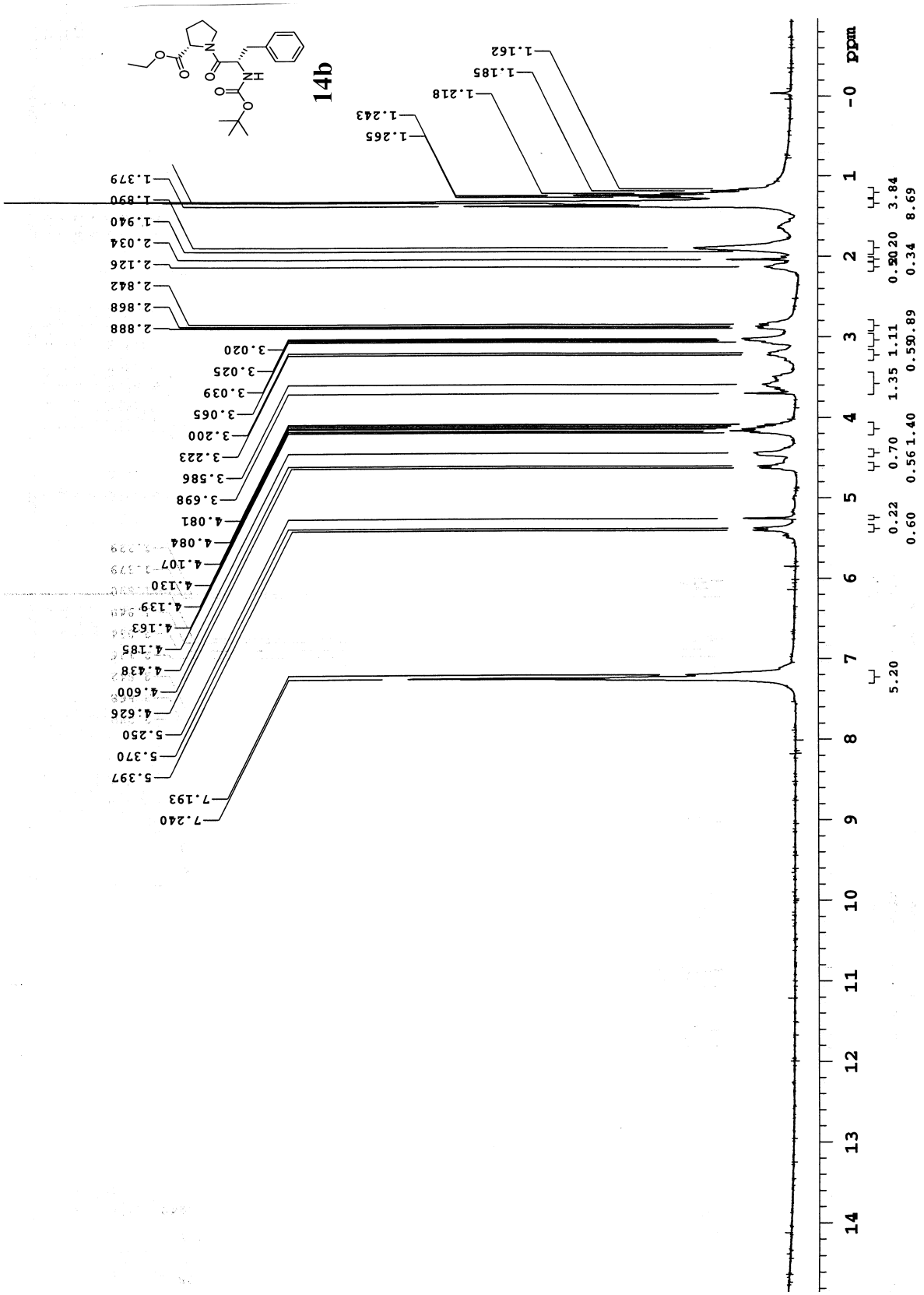
22.204
24.892
28.451
28.760
38.917
40.959
46.371
47.284
53.629
54.001
59.336
60.641
76.877
77.305
77.726
79.951
80.267
126.938
128.531
129.774
136.267
155.577
172.079
174.648
175.982
ppm
20
40
60
80
100
120
140
160
180
200


14b
1.162
1.185
1.218
1.243
1.265
1.379
1.890
1.940
2.034
2.126
2.842
2.868
2.888
3.020
3.025
3.039
3.065
3.200
3.223
3.586
3.698
4.081
4.084
4.107
4.130
4.139
4.163
4.185
4.438
4.600
4.626
5.250
5.370
5.397
7.193
7.240
ppm
0.22
0.60
0.70
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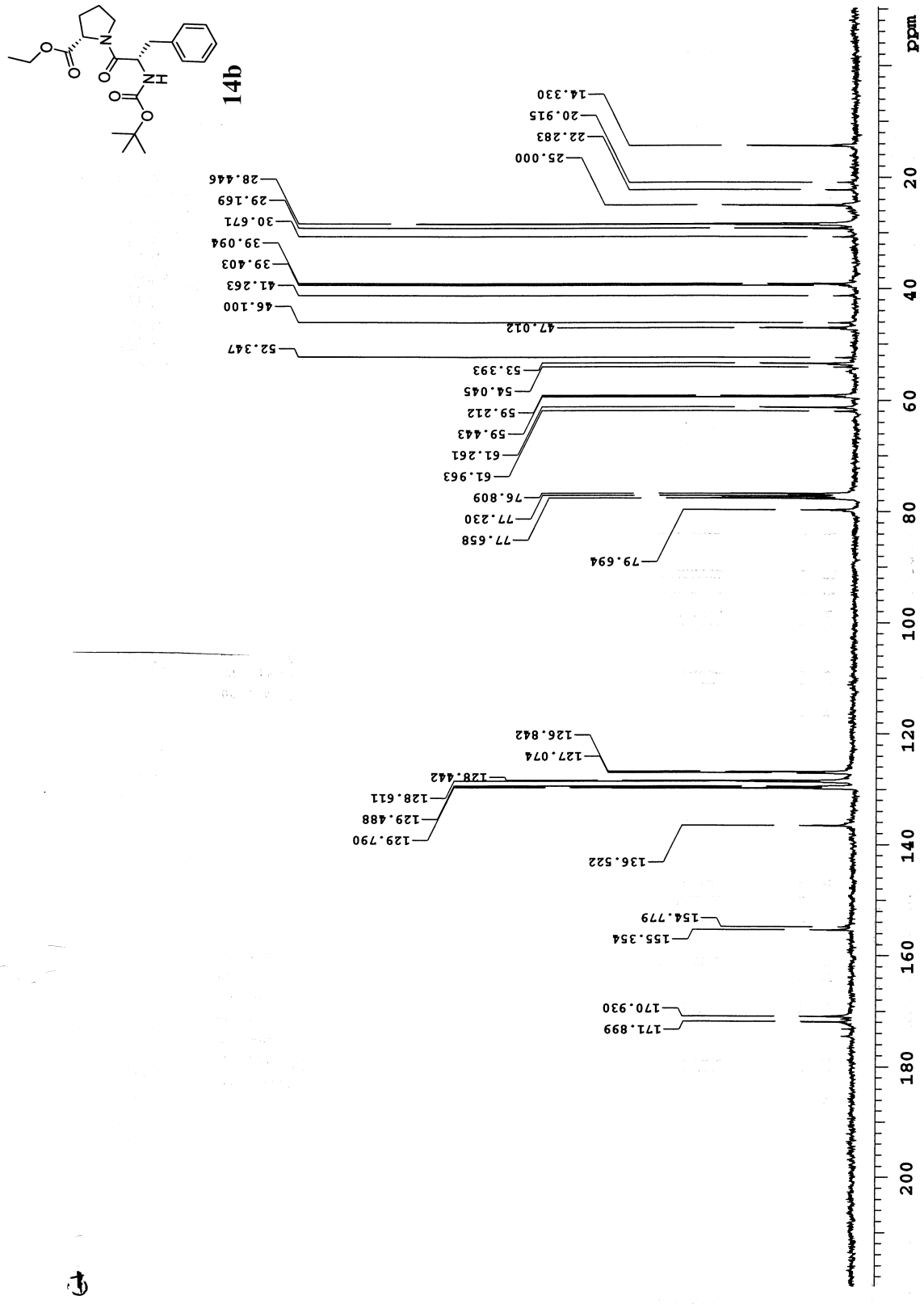
1.40
1.11
0.59
0.89
0.34
3.84
8.69
5.20


14b
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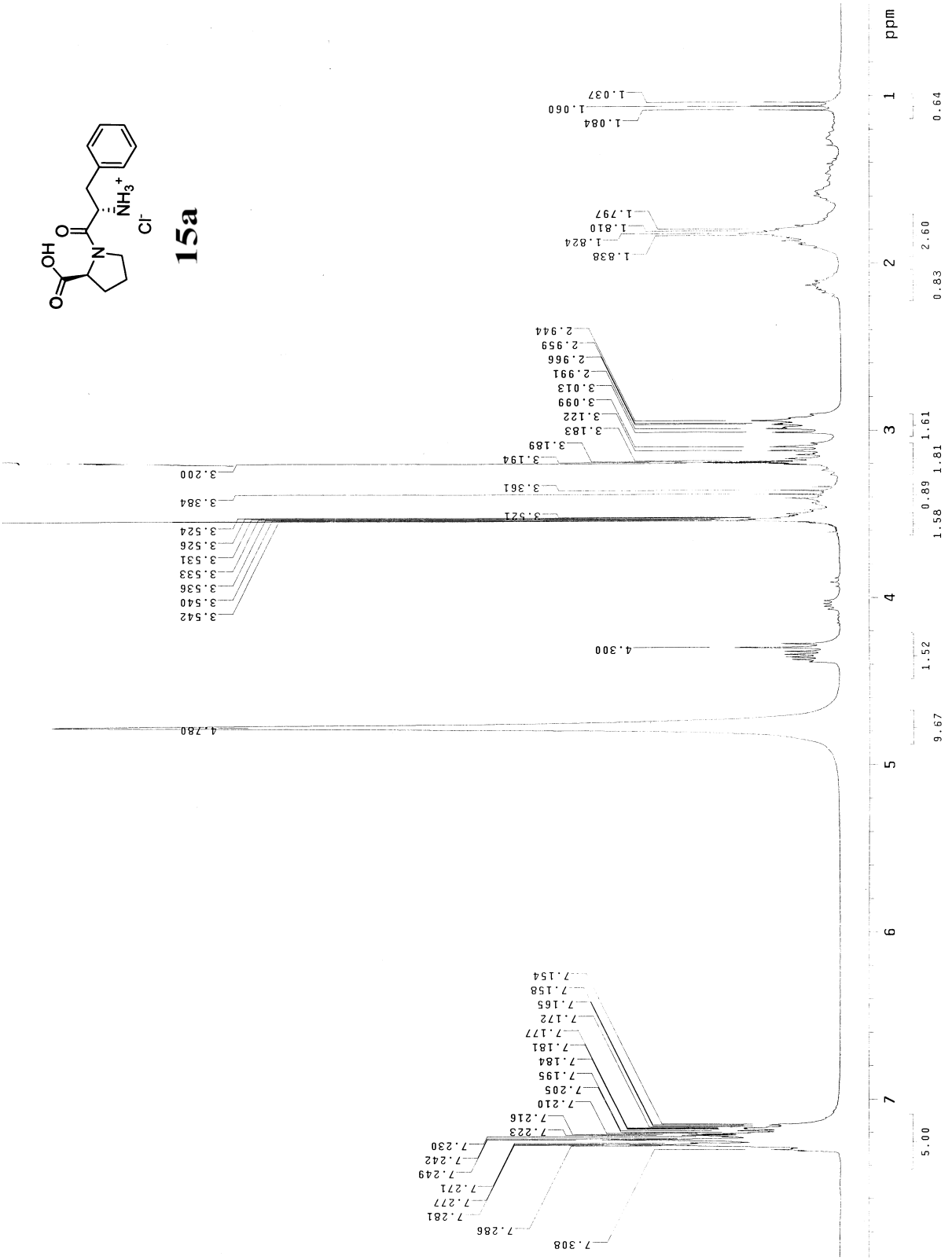
22.283
25.000
28.446
29.169
30.671
39.094
39.403
41.263
46.100
47.012
52.347
53.393
54.045
59.212
59.443
61.261
61.963
76.809
77.230
77.658
79.694
126.842
127.074
128.442
128.611
129.488
129.790
136.522
154.779
155.354
170.930
171.899
ppm
20
40
60
80
100
120
140
160
180
200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Cl-
ppm
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1.060
1.084
1.797
1.810
1.824
1.838
2.944
2.959
2.966
2.991
3.013
3.099
3.122
3.183
3.189
3.194
3.200
3.361
3.384
3.521
3.524
3.526
3.531
3.533
3.536
3.540
3.542
4.300
4.780
7.154
7.158
7.165
7.172
7.177
7.181
7.184
7.195
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7.210
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7.223
7.230
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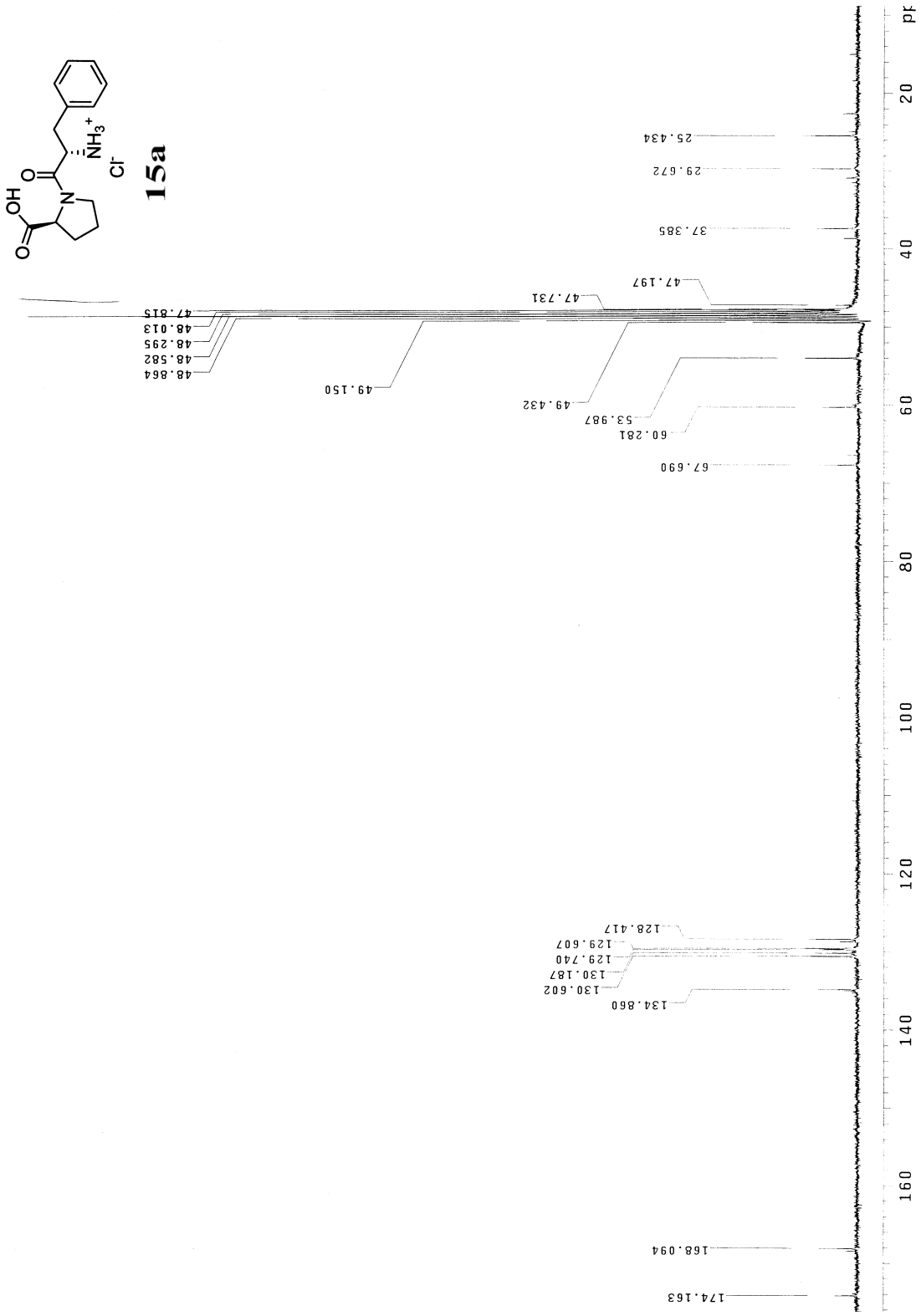
7.281
7.286
7.308


15a
Cl⁻
NH3+
OH
O
N
O
25.434
29.672
37.385
47.197
47.731
47.815
48.013
48.295
48.582
48.864
49.150
49.432
53.987
60.281
67.690
128.417
129.607
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130.187
130.602
134.860
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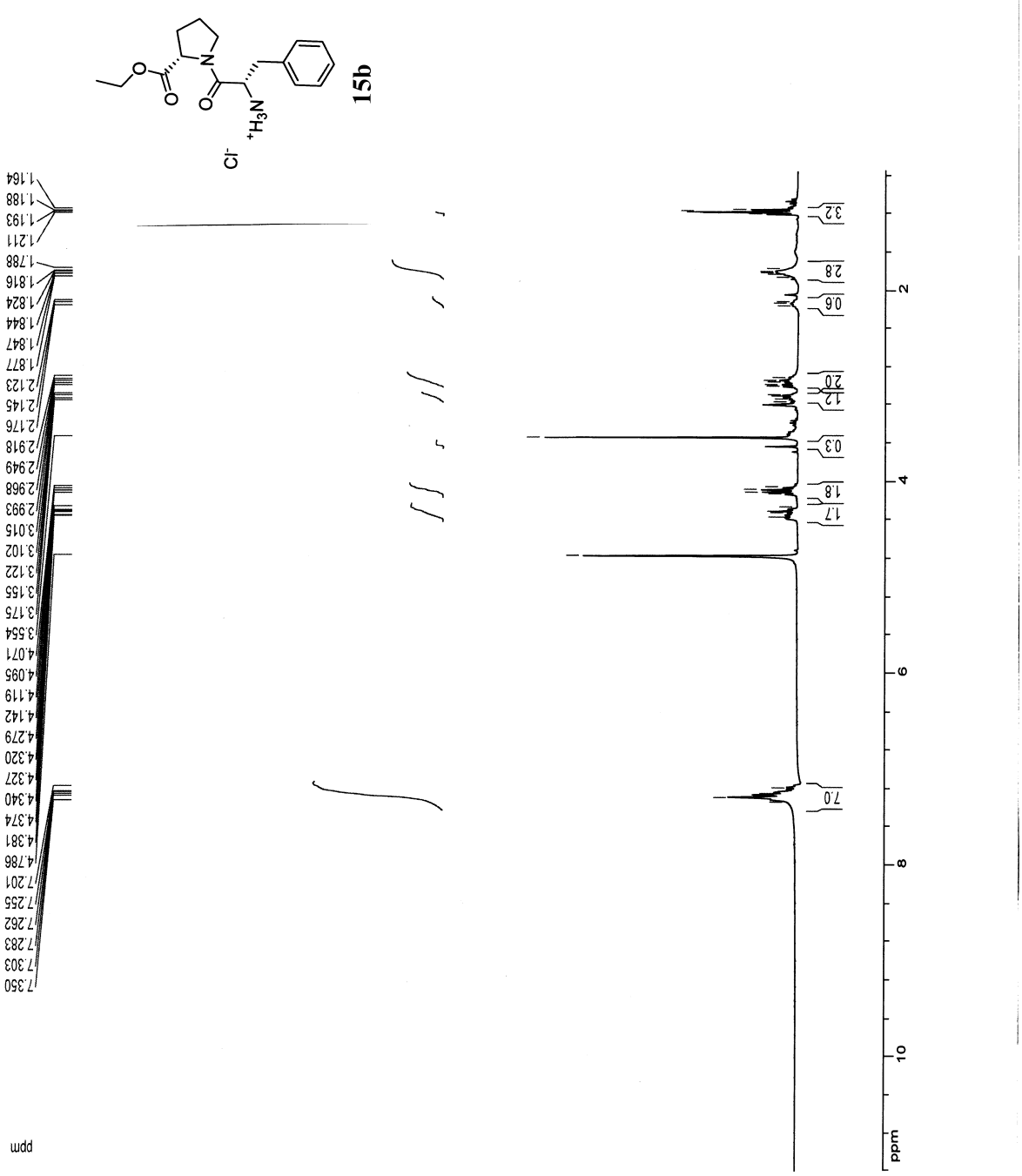
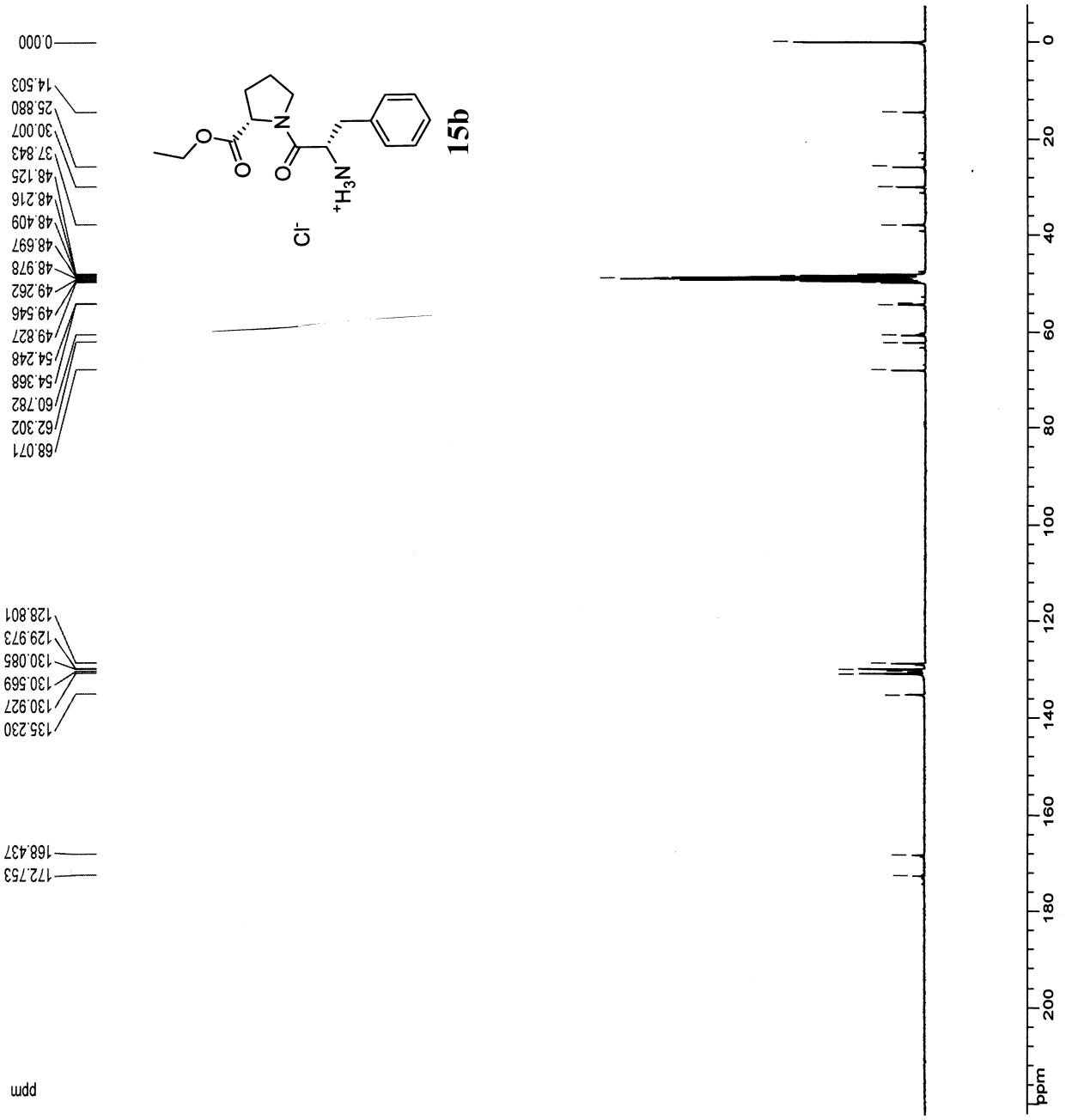
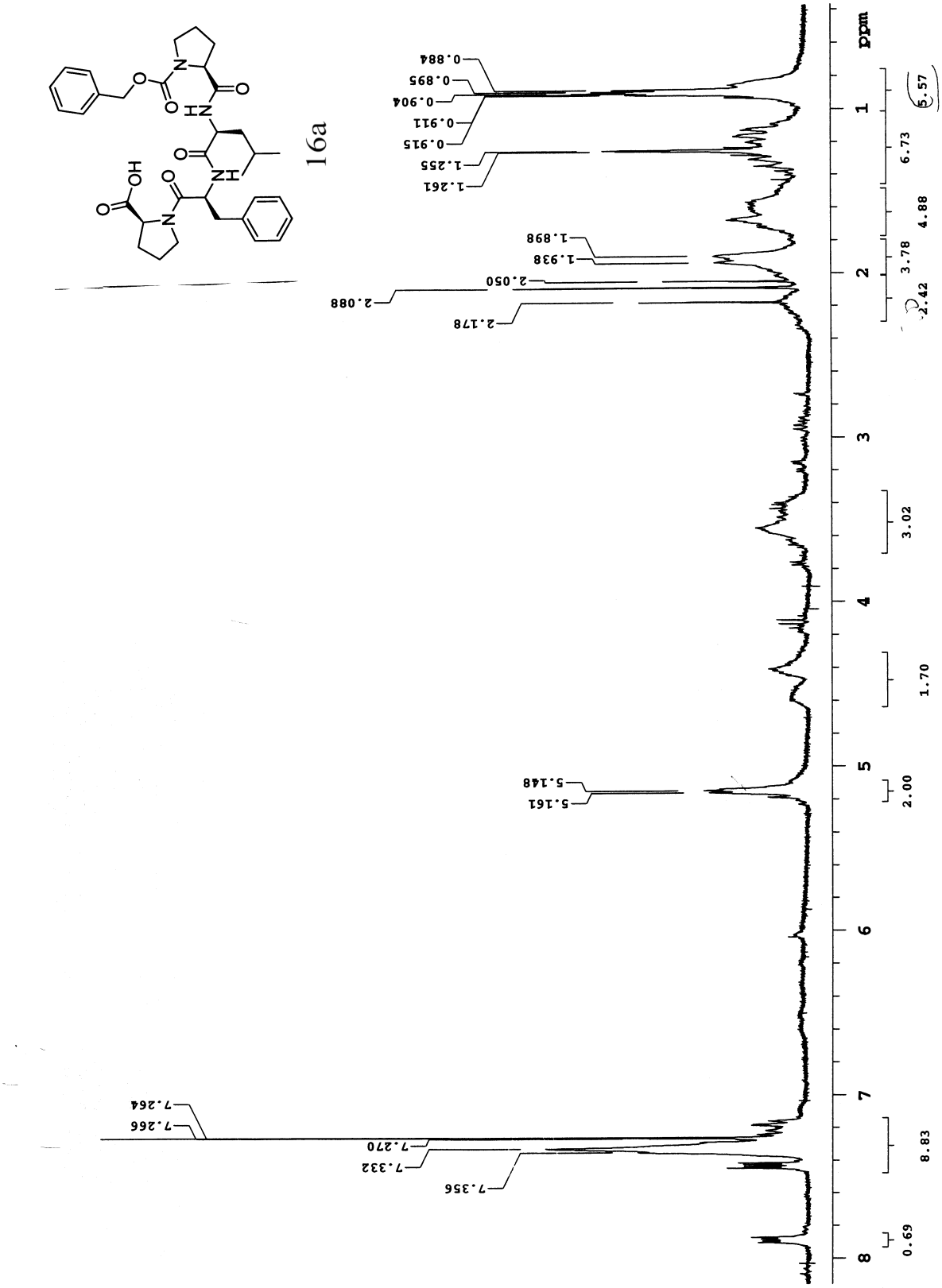
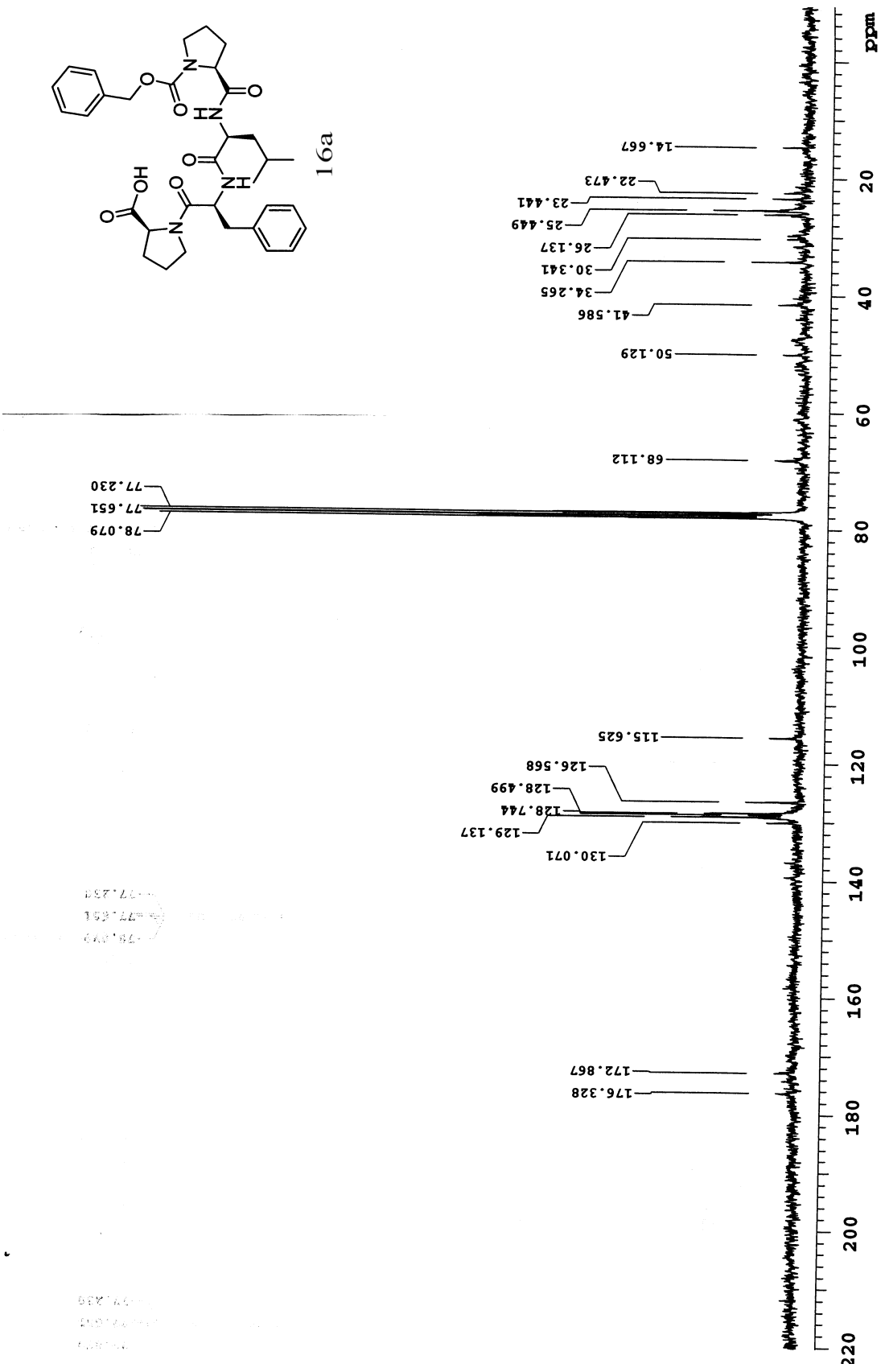
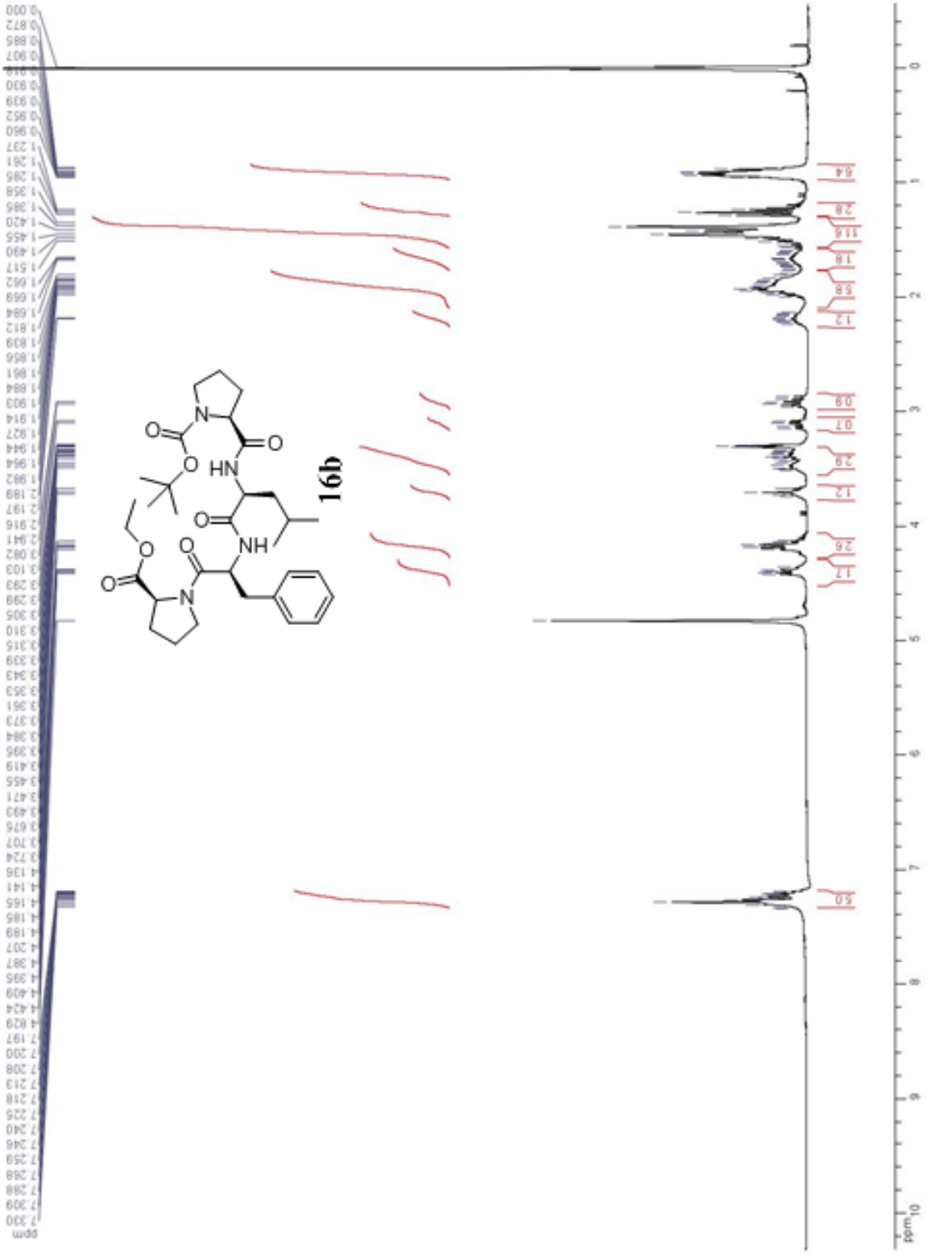
174.163
20
40
60
80
100
120
140
160

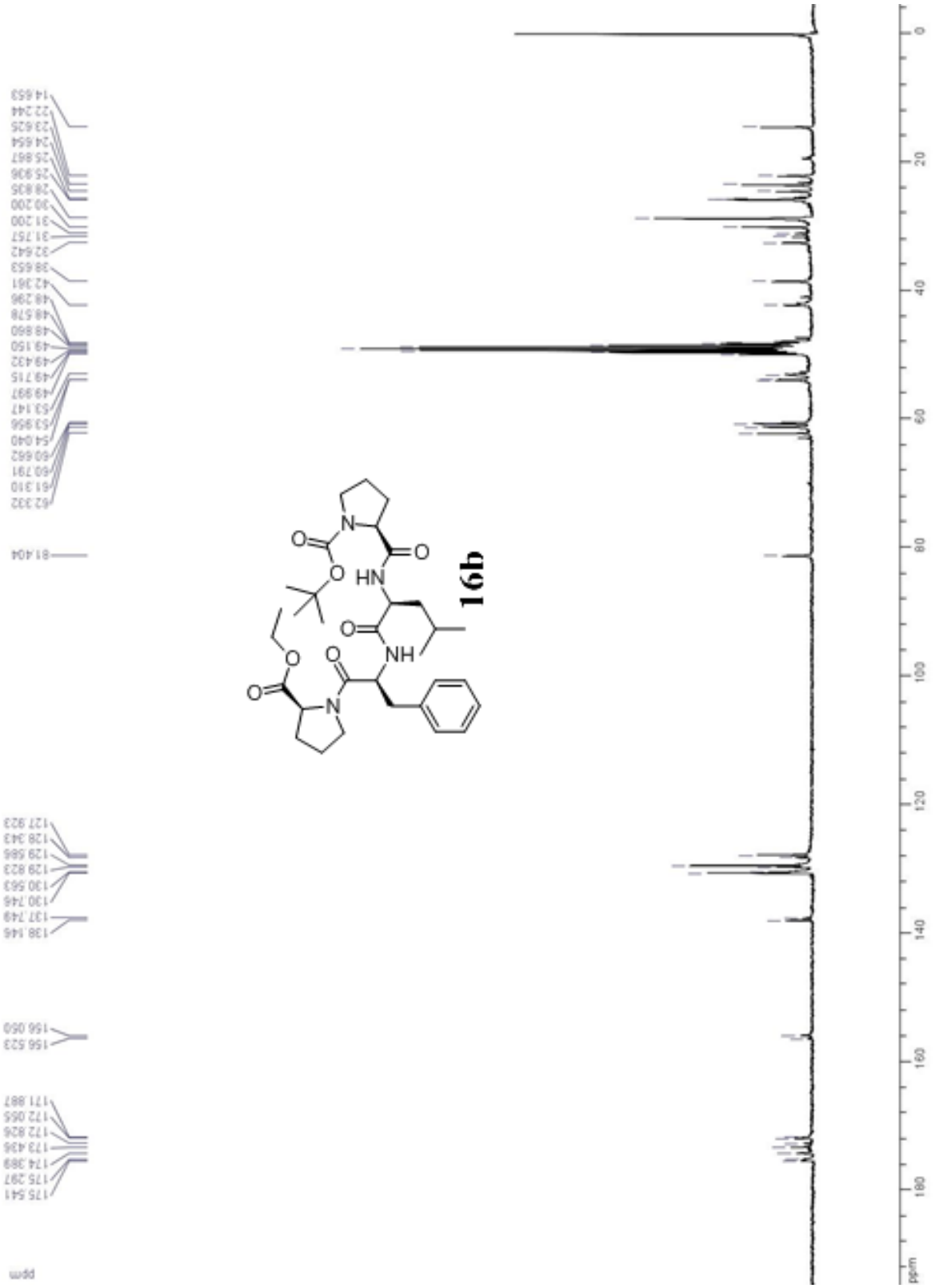

15b
Cl⁻
+H3N
ppm
1.164
1.188
1.193
1.211
1.788
1.816
1.824
1.844
1.847
1.877
2.123
2.145
2.176
2.918
2.949
2.968
2.993
3.015
3.102
3.122
3.155
3.175
3.554
4.071
4.095
4.119
4.142
4.279
4.320
4.327
4.340
4.374
4.381
4.786
7.201
7.255
7.262
7.283
7.303
7.350
3.2
2.8
0.6
2.0
1.2
0.3
1.8
1.7
7.0
2
4
6
8
10
ppm

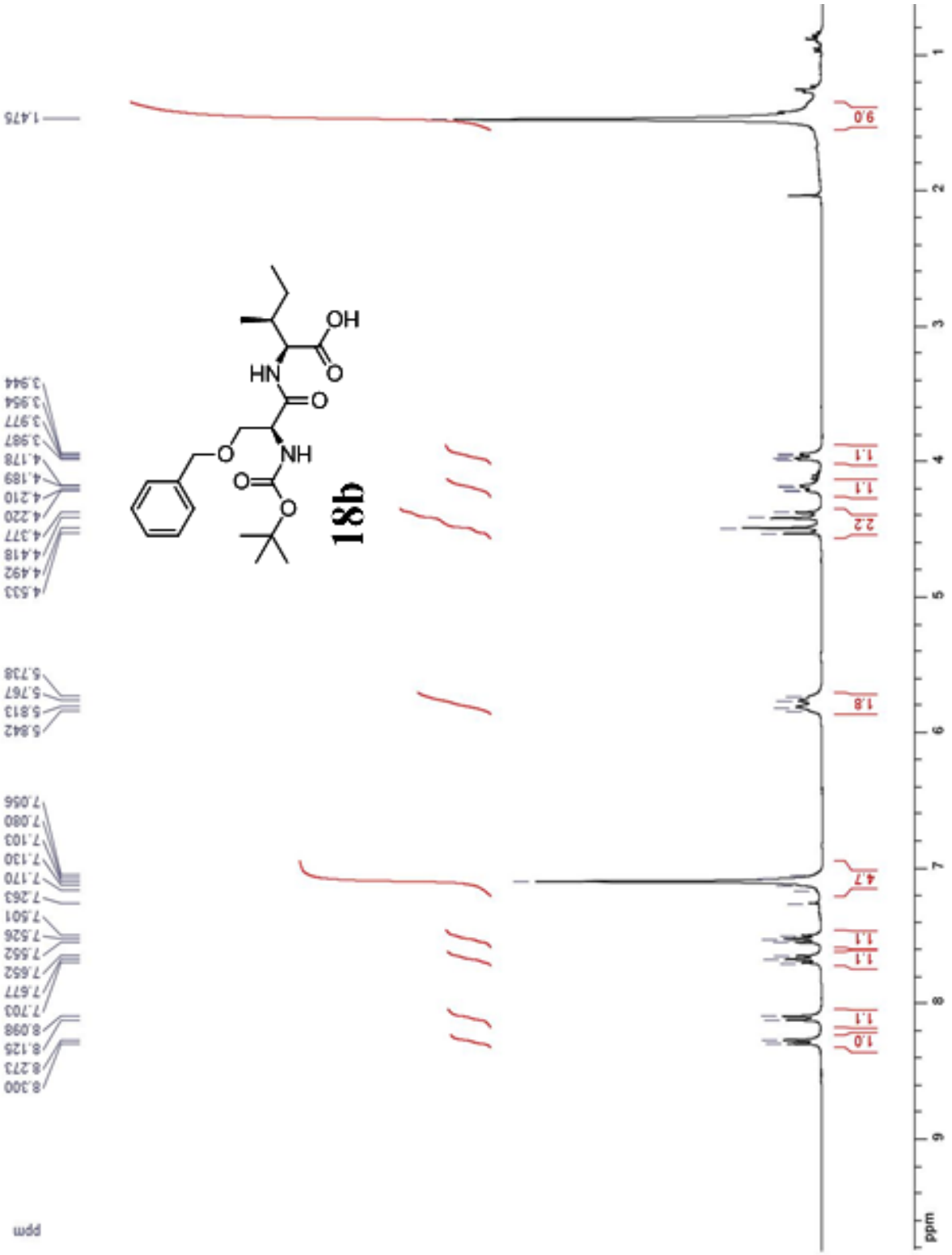

0.000
14.503
25.880
30.007
37.843
48.125
48.216
48.409
48.697
48.978
49.262
49.546
49.827
54.248
54.368
60.782
62.302
68.071
128.801
129.973
130.085
130.569
130.927
135.230
168.437
172.753
ppm
0
20
40
60
80
100
120
140
160
180
200
ppm
15b
Cl-
+H3N

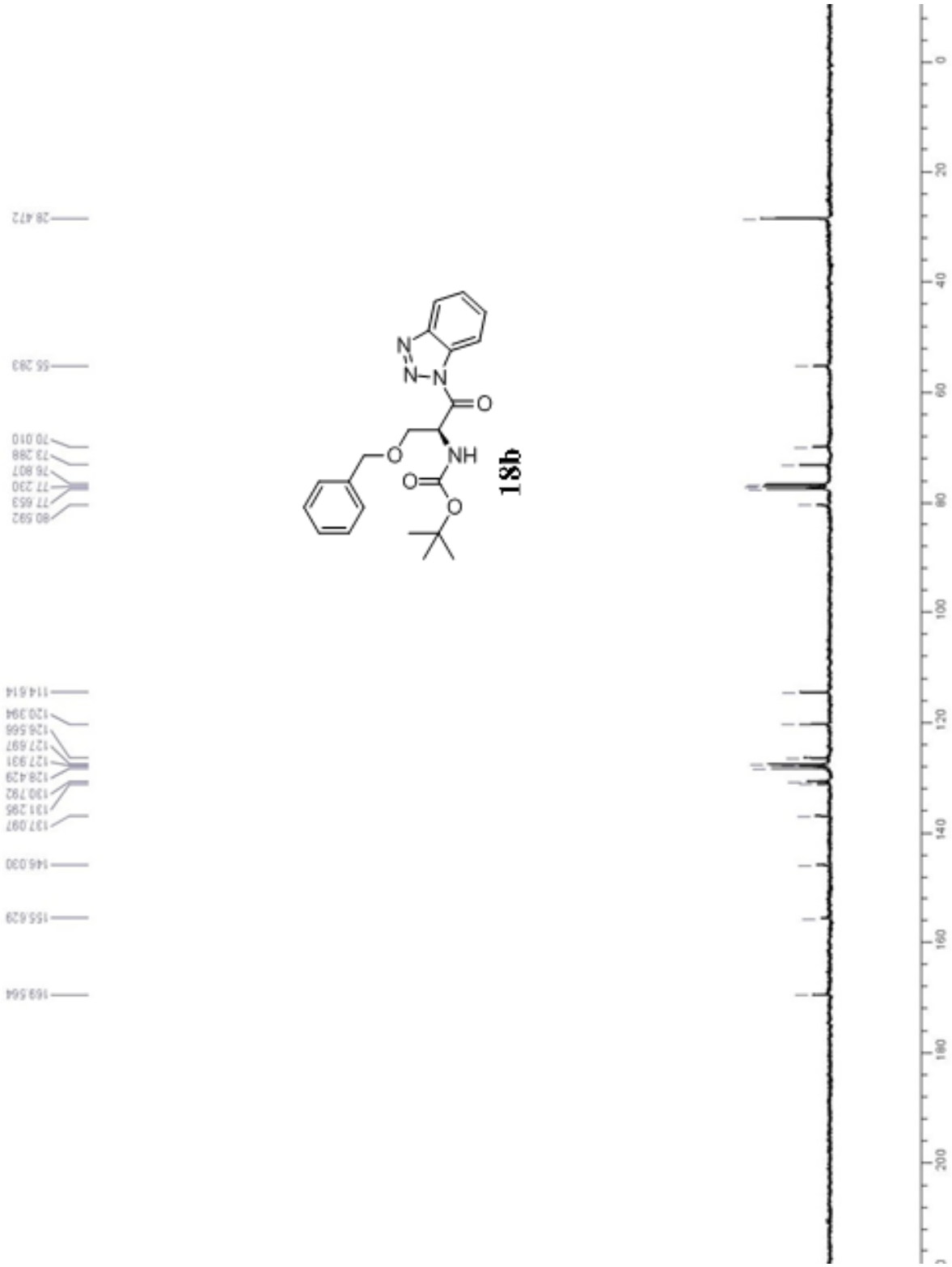

16a
ppm
0.884
0.895
0.904
0.911
0.915
1.255
1.261
1.898
1.938
2.050
2.088
2.178
5.148
5.161
7.264
7.266
7.270
7.332
7.356
0.69
8.83
2.00
1.70
3.02
2.42
3.78
4.88
6.73
5.57

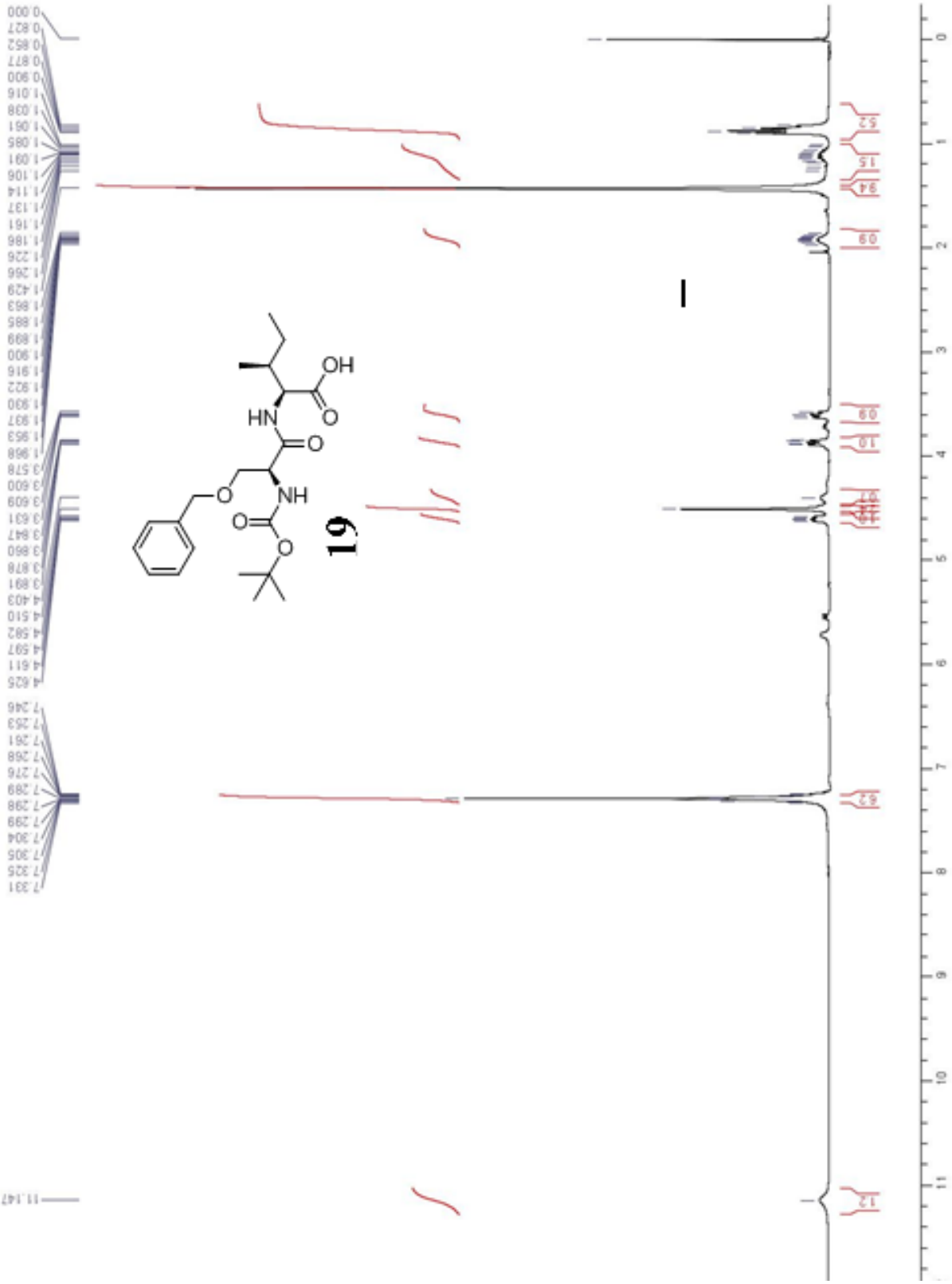

16a
14.667
22.473
23.441
25.449
26.137
30.341
34.265
41.586
50.129
68.112
77.230
77.651
78.079
115.625
126.568
128.499
128.744
129.137
130.071
172.867
176.328
ppm
20
40
60
80
100
120
140
160
180
200
220

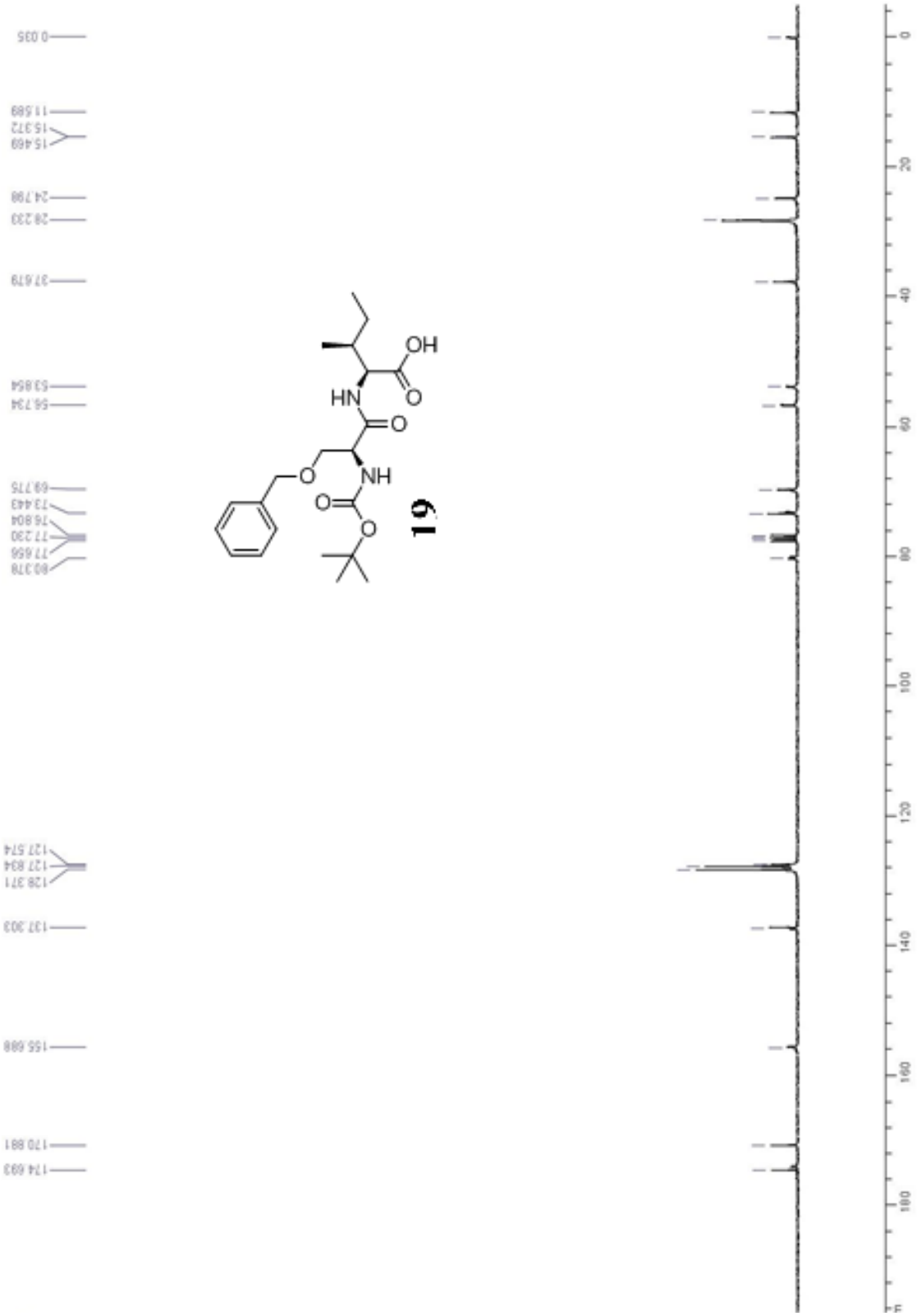

16b
HN
NH
N
O
ppm

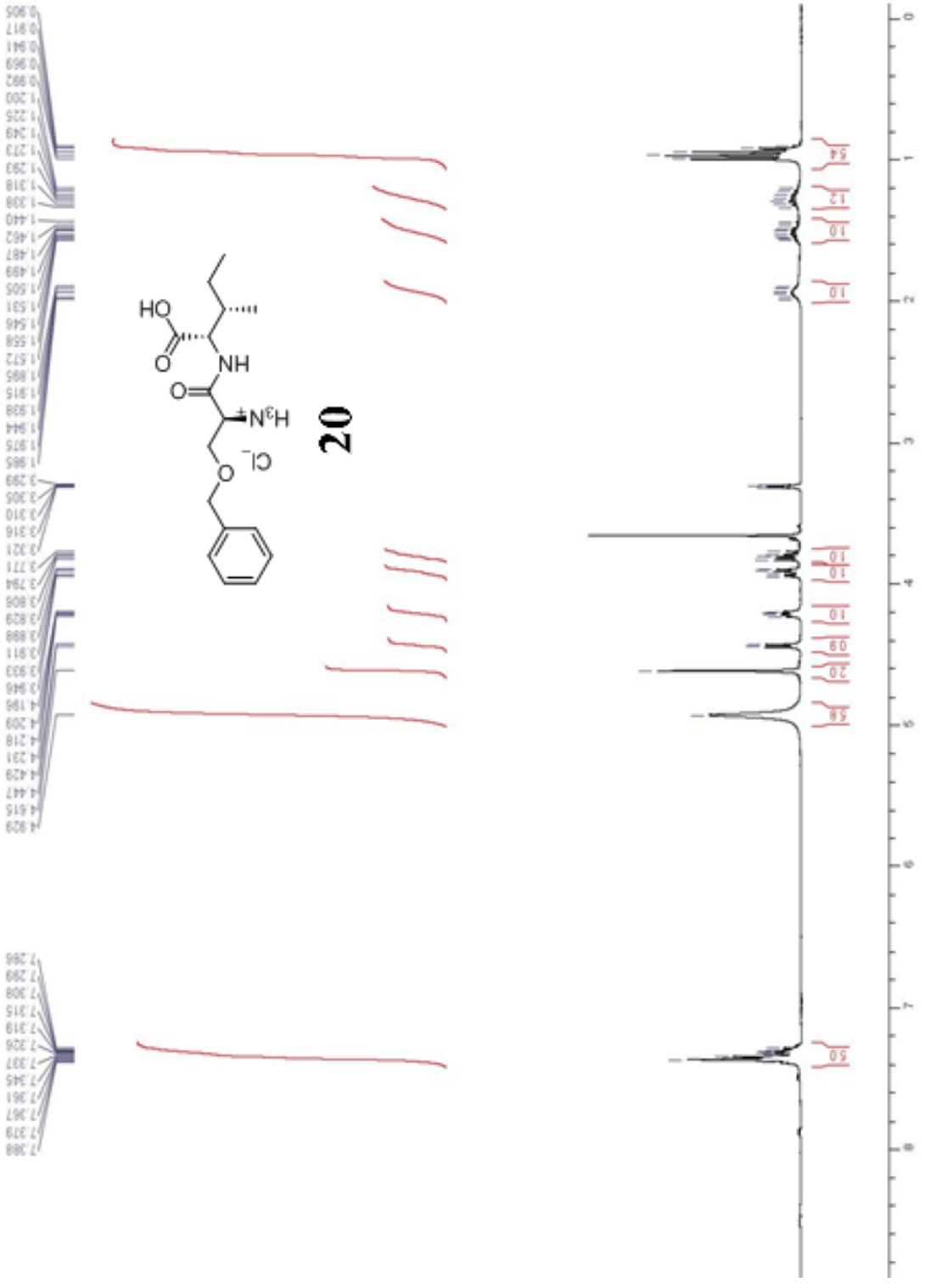

16b
HN
NH
O
N
ppm


OH
HN
O
O
NH
O
O
O
18b
1.475
3.944
3.964
3.977
3.987
4.178
4.189
4.210
4.220
4.377
4.418
4.492
4.533
5.738
5.767
5.813
5.842
7.056
7.080
7.103
7.130
7.170
7.263
7.501
7.526
7.562
7.652
7.677
7.703
8.098
8.125
8.273
8.300
9.0
1.1
1.1
2.2
1.8
4.7
1.1
1.1
1.1
1.0
ppm

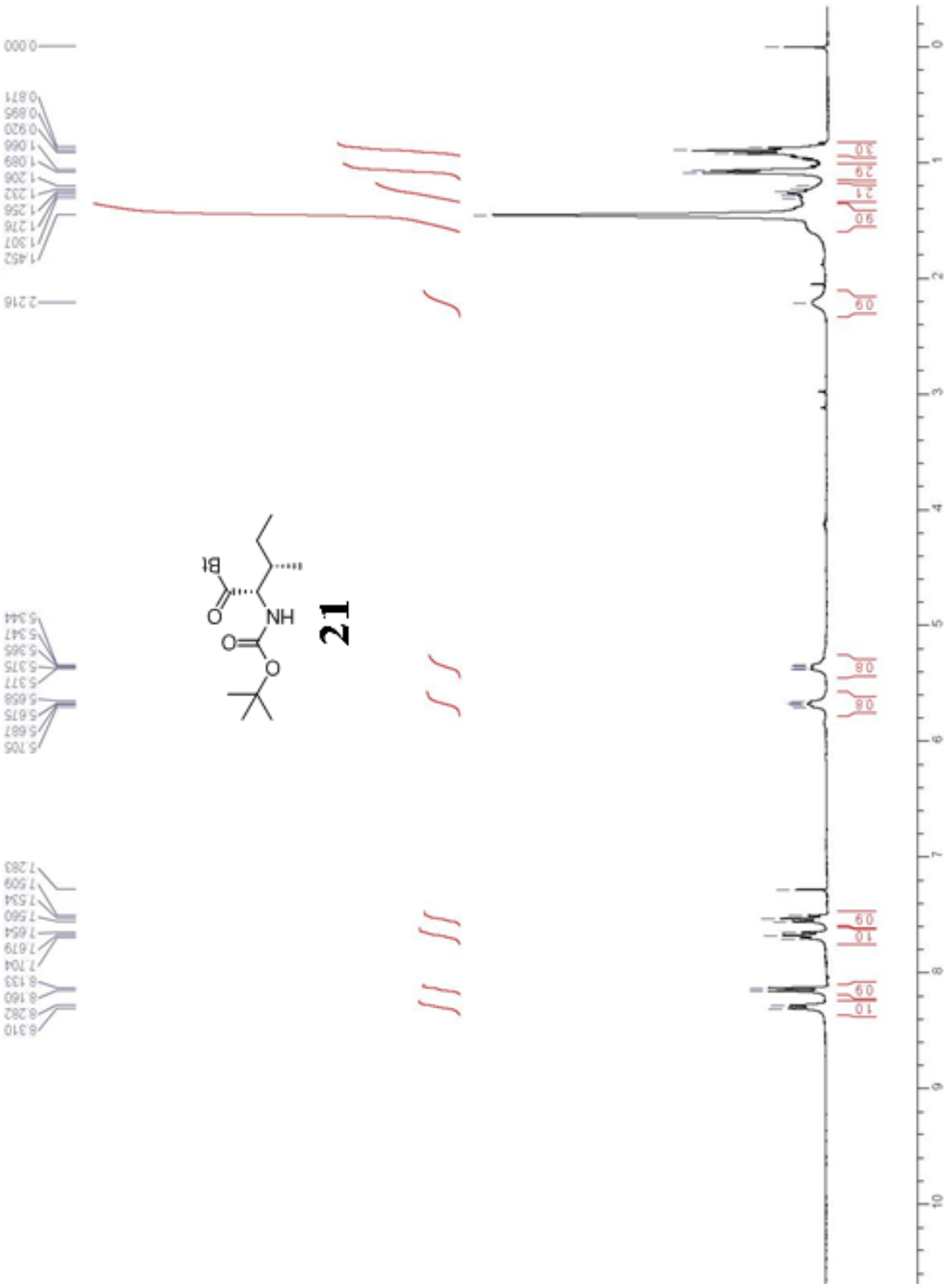

28.472
55.283
70.010
73.288
76.807
77.230
77.653
80.582
114.614
120.394
126.566
127.697
127.931
128.429
130.792
131.295
137.097
146.030
155.629
169.564
18b

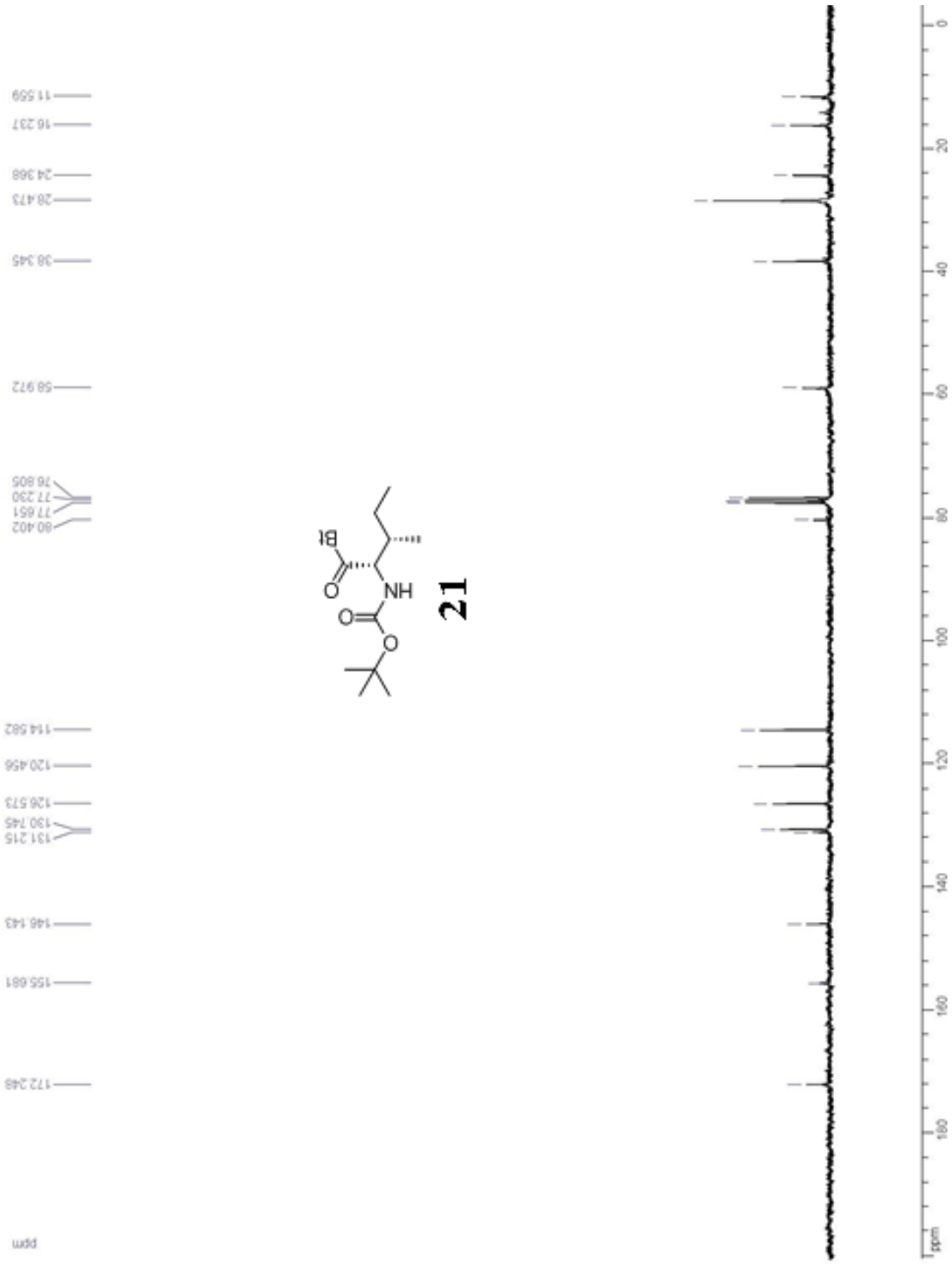

OH
HN
O
O
NH
O
O
O
19
I


OH
HN
O
O
NH
O
O
19

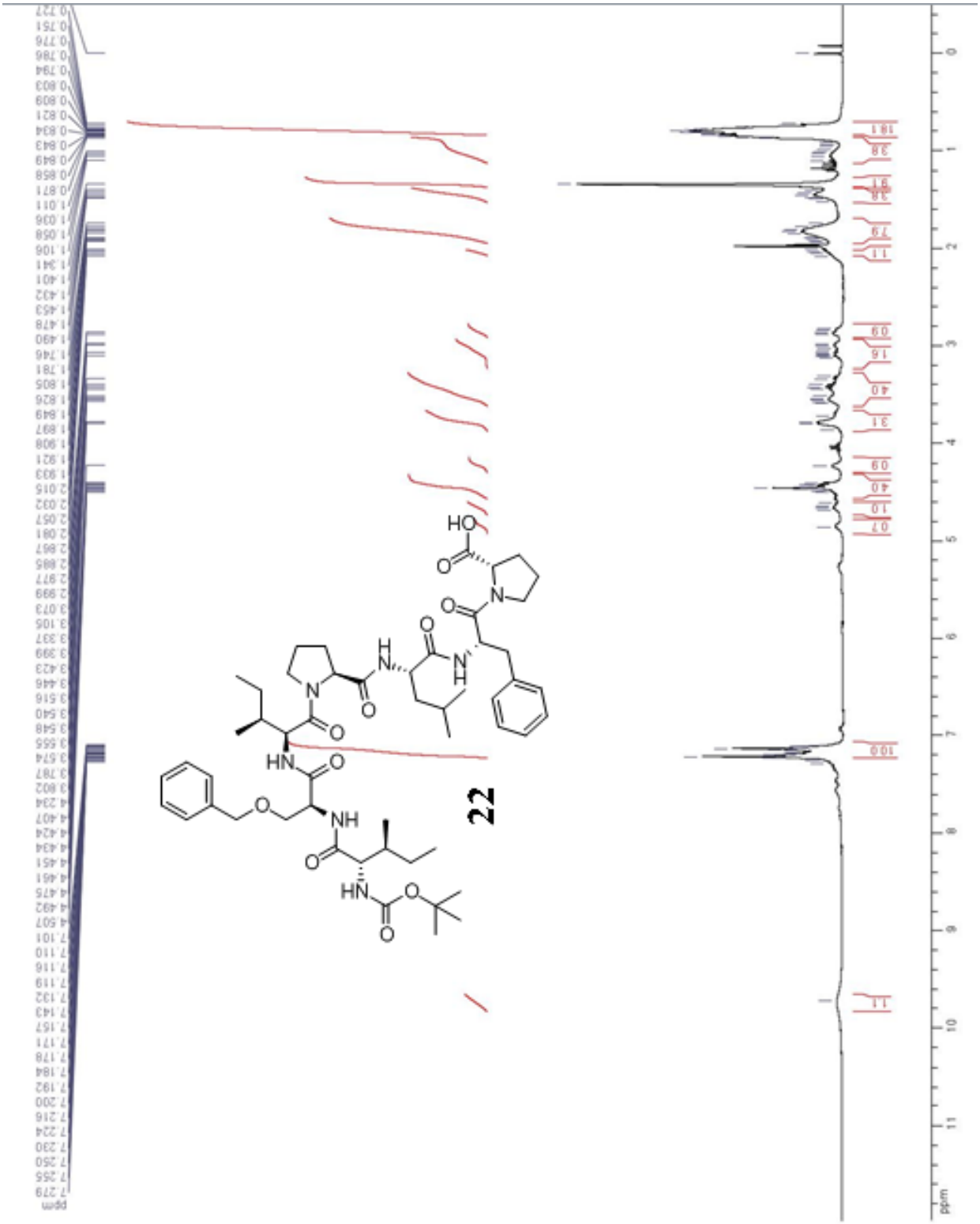

HO
O
NH
O
H_3N^+
Cl^-
O
20

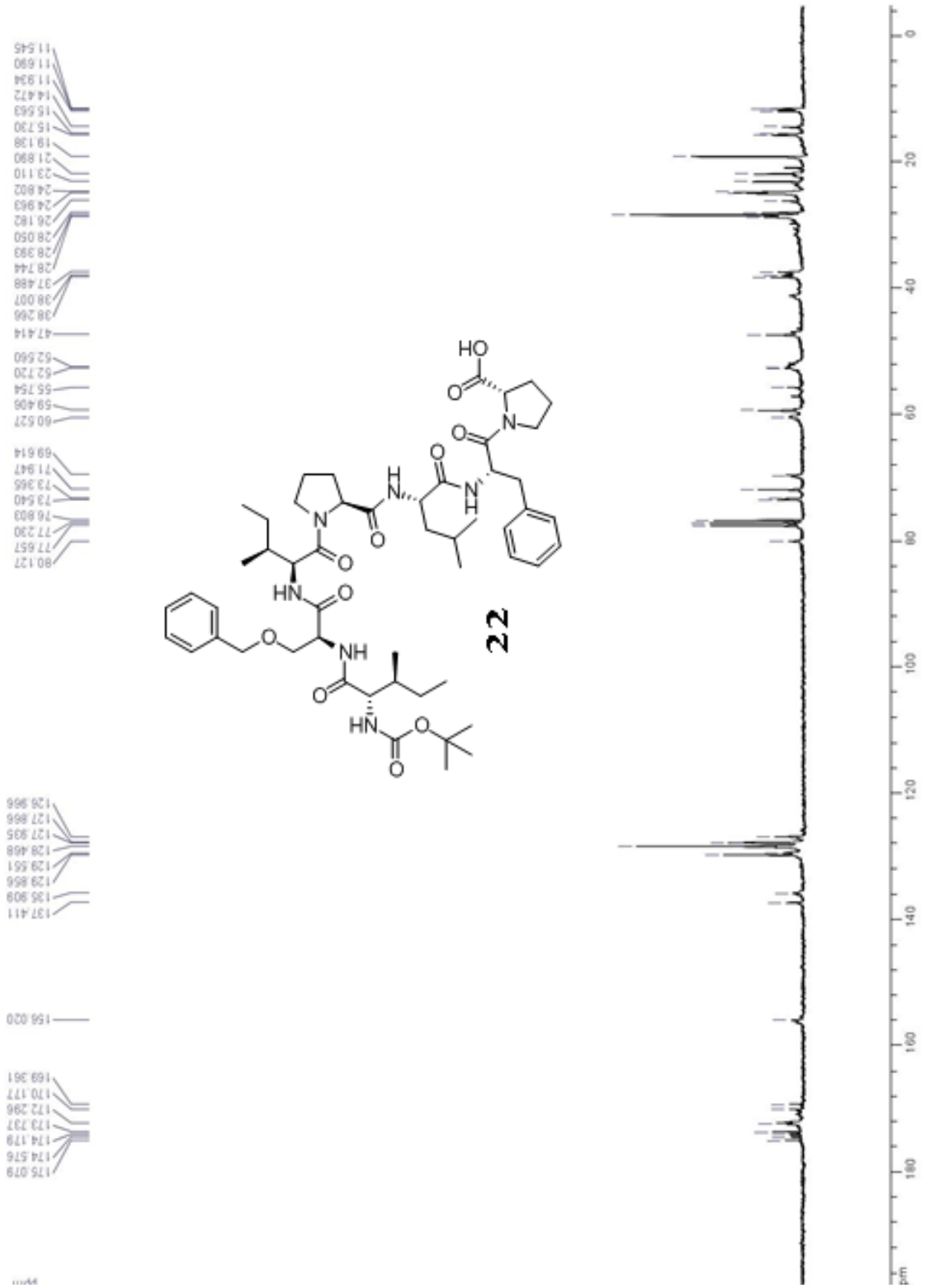

HO
O
NH
O
H3N+
Cl-
O
20

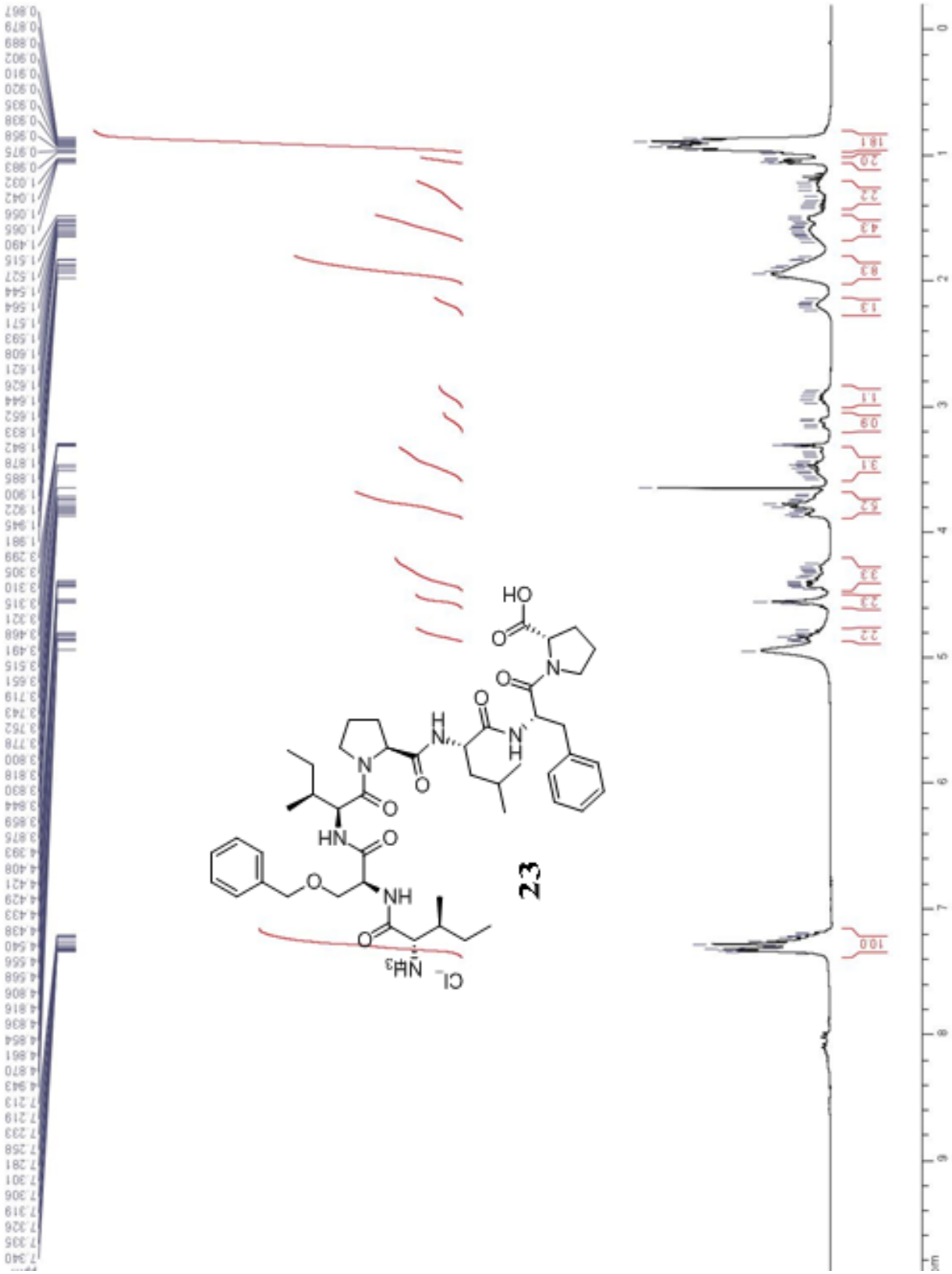

Br
O
NH
O
O
21

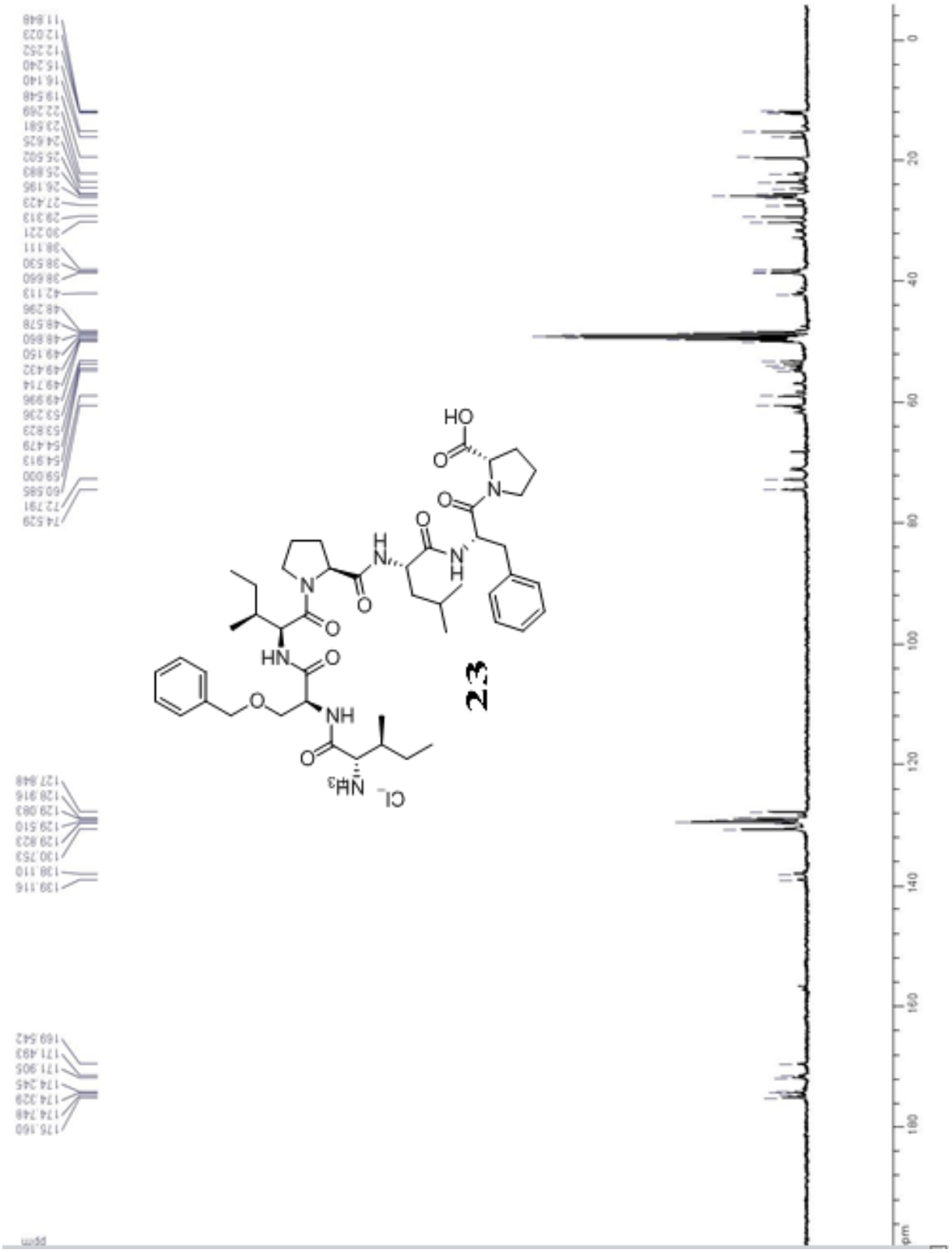

11.559
16.237
24.368
28.473
38.345
58.972
76.805
77.230
77.651
80.402
114.582
120.456
126.573
130.745
131.215
146.143
155.681
172.248
ppm
0
20
40
60
80
100
120
140
160
180
ppm
Br
O
NH
O
O

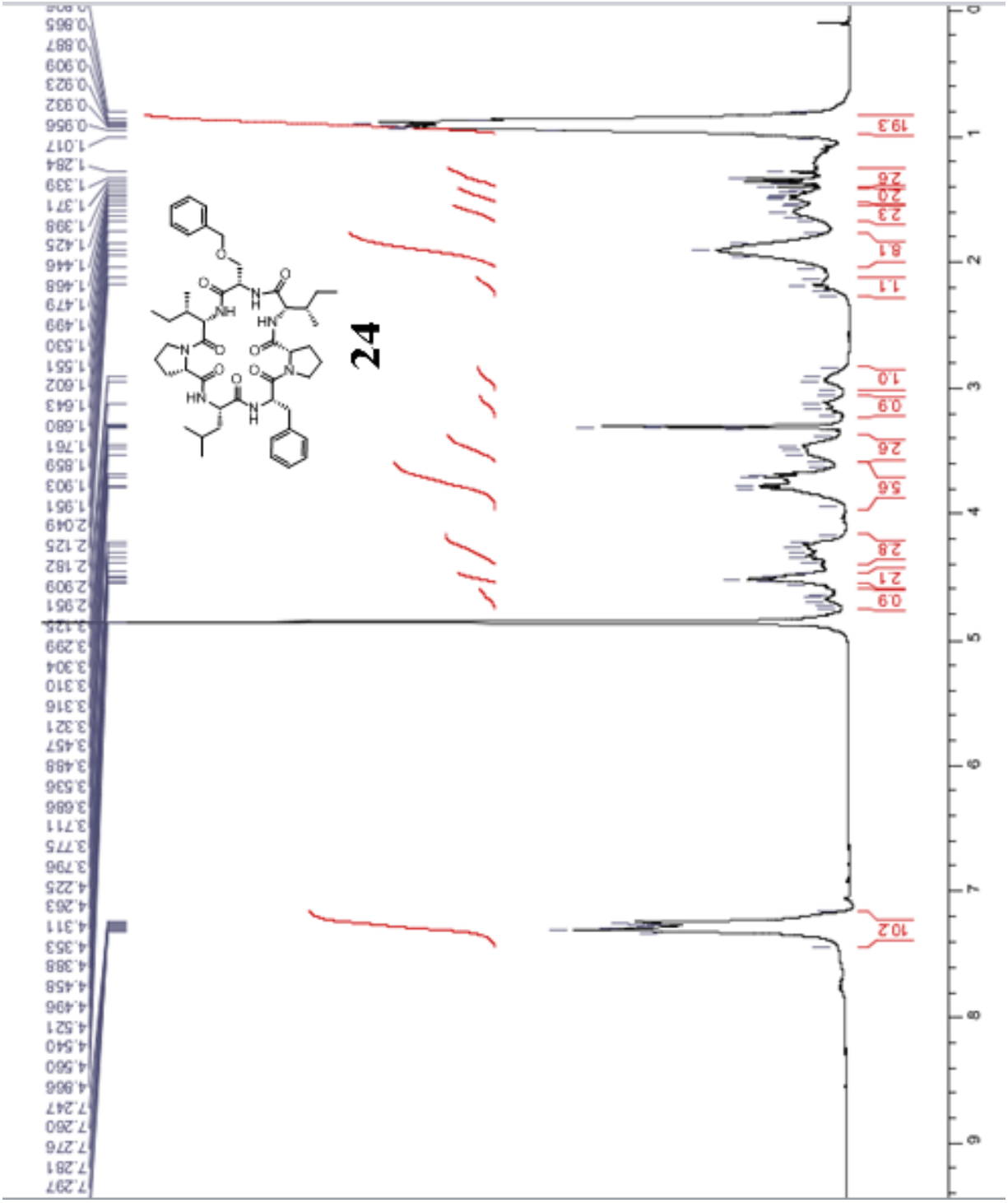
21

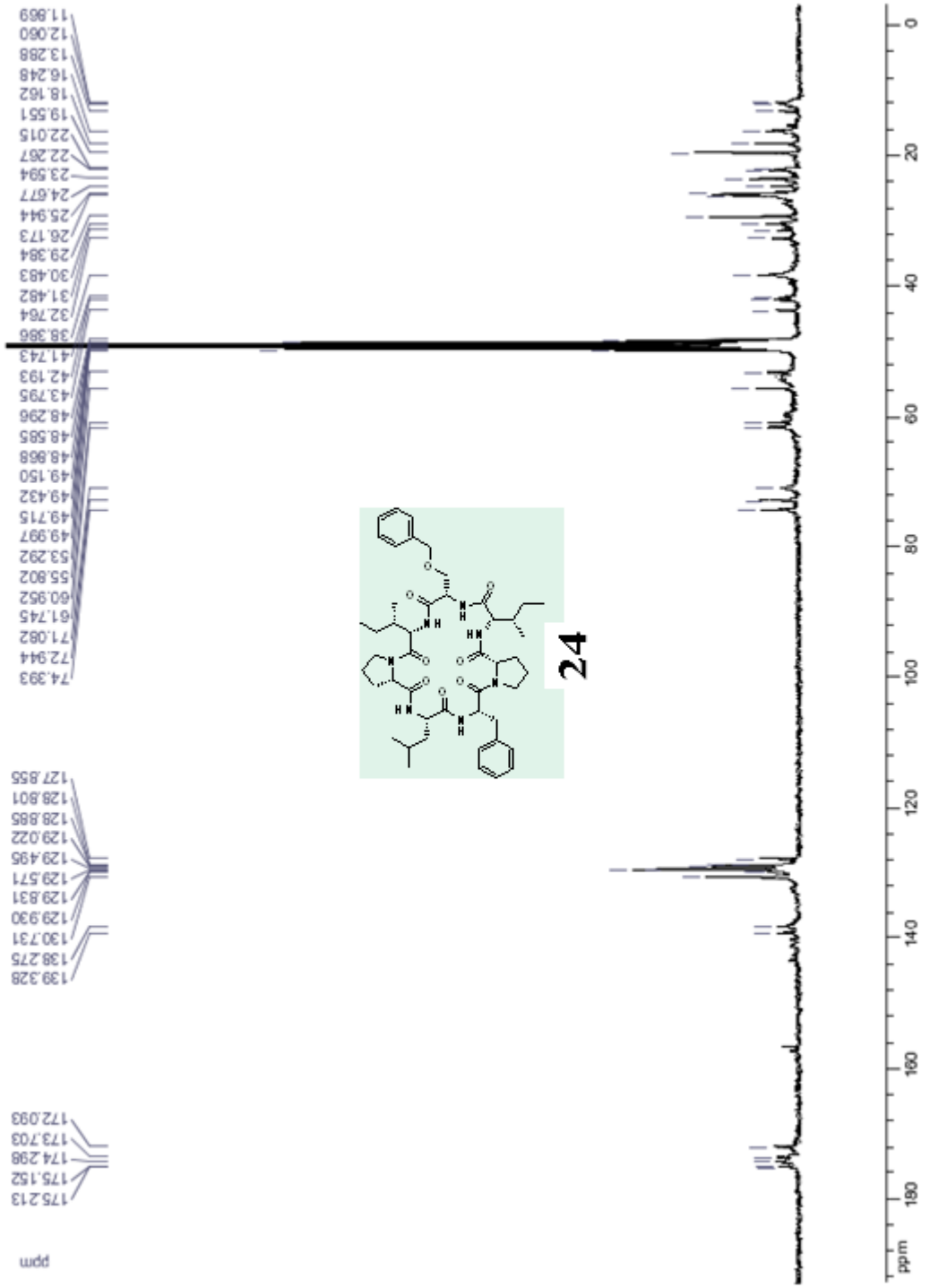

HO
O
N
O
H
N
O
N
O
HN
O
O
NH
O
HN
O
O
22


HO
O
N
O
H
N
N
O
O
HN
O
O
NH
O
HN
O
O
22


HO
O
N
O
N
H
O
N
H
O
O
HN
O
O
NH
O
NH3
Cl
23


HO
O
N
O
N
H
O
N
O
HN
O
O
NH
O
NH3
Cl
23


24


24
ppm