

Synthesis of 4-Substituted-3-amino-piperidin-2-ones: Application to the Synthesis of a Conformationally Constrained Tetrapeptide AcSDKP

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General Methods. All reagents obtained from commercial sources were used as received without further purification. THF was distilled from sodium and benzophenone as indicator. CH₂Cl₂ was distilled over P₂O₅ immediately prior to use. Infrared (IR) spectra were obtained using an FTIR spectrophotometer, wavelength (ν) are reported in cm⁻¹. Optical rotations were measured using concentrations (*c*) in g/100 mL in the indicated solvents. ¹H NMR spectra were recorded at 300 MHz and 500 MHz, ¹³C NMR spectra were recorded at 75.5 MHz with chemical shifts reported in ppm (δ) downfield from TMS (internal reference) for ¹H and relative to the center line of the triplets of CDCl₃ at 77.14 ppm for ¹³C, unless indicated otherwise. HRMS spectra were run on waters Micromass LCT with an electrospray source (ZQ) in positive mode ionization (ESI). Flash column chromatography was performed using Kieselgel (230-400 mesh) using indicated solvents (mixture). Analytical thin layer chromatography (TLC) was carried out on plates precoated with 0.25 mm of silica gel containing 60F-254 indicator. Melting points were determined on a B-540 and are uncorrected.

(4*S*,1'*S*)-2,2-Dimethyl-4-(3'-oxo-1'-phenylpropyl)oxazolidine-3-carboxylic acid *tert*-butyl ester (6b): The general procedure 1 was followed using alcohol **5b** (980 mg, 2.77 mmol) to give 857 mg (88%) of **6b** as a yellow oil: ¹H NMR (300 MHz, CDCl₃): δ 9.69-9.64 (m, 1H), 7.37-7.17 (m, 5H), 4.23-3.95 (m, 2H), 3.87 (dd, *J* = 1.4, 9.6 Hz, 1H), 3.75 (dd, *J* = 7.0, 9.6 Hz, 1H), 2.99-2.84 (m, 2H), 1.69-1.42 (m, 15H); ¹³C NMR (75 MHz, CDCl₃): δ 202.2, 201.5, 153.2, 152.6, 140.0, 128.9, 128.6, 128.4, 128.1, 127.2, 95.0, 94.6, 80.7, 63.8, 62.0, 61.8, 42.5, 41.6, 40.9, 40.6, 28.5, 26.6, 26.3, 23.9, 22.4; MS (ESI) *m/z*: 334 [M+H]⁺, 356 [M+Na]⁺, 372 [M+K]⁺.

(4*S*,1'*R*)-2,2-Dimethyl-4-[1'-(2''-oxoethyl)allyl]oxazolidine-3-carboxylic acid *tert*-butyl ester (6c): The general procedure 1 was followed using alcohol **5c** (4.00 g, 14.04 mmol) to give 3.80 g (95%) of **6c** as a yellow oil: ¹H NMR (300 MHz, CDCl₃): δ 9.69 (bs, 1H), 5.83-5.64 (m, 1H), 5.20- 5.07 (m, 2H), 4.14-3.76 (m, 3H), 3.36-3.21 (m, 1H), 2.67-2.38 (m, 2H), 1.65-1.42 (m, 15H); ¹³C NMR (75 MHz, CDCl₃): δ 201.9, 201.6, 153.2, 153.0, 137.4, 117.5, 94.6, 94.2, 80.5, 80.3, 64.4, 59.8, 43.0, 42.7, 40.2, 28.5, 26.6, 26.3, 23.9, 22.4; MS (ESI) *m/z*: 284 [M+H]⁺, 306 [M+Na]⁺, 322 [M+K]⁺.

(4*S*,1'*S*,1''*S*)-4-[3'-(1''-methoxycarbonyl-3''-methylbutylamino)-1'-phenylpropyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (8b): The general procedure 2 was followed using aldehyde **6b** (922 mg, 2.77 mmol) and L-Leu-OMe **7b** (442 mg, 3.05 mmol). Flash column chromatography with heptane/ethyl acetate (4/1) gave 984 mg (77%, two rotamers) of **8b** as a colorless oil: [α]_D¹⁹ (c 1.20, CHCl₃); IR (neat): ν 3026, 3011, 2957, 2872, 1731, 1688, 1454, 1391, 1368, 1247, 1172 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.33-7.14 (m, 5H), 4.14-4.04 (m, 0.5H), 4.02-3.91 (m, 1.5H), 3.79-3.69 (m, 1H), 3.63 (s, 3H), 3.50-3.31 (m, 1H), 3.18-3.06 (m, 1H), 2.65-2.46 (m, 1H), 2.32-2.13 (m, 1H), 1.98-1.87 (m, 2H), 1.70-1.36 (m, 18H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 176.5, 152.6, 152.4, 141.0, 128.7, 128.4, 128.2, 126.5, 94.6, 93.9, 79.8, 64.2, 63.9, 62.5, 62.2,

59.9, 51.4, 46.2, 44.5, 42.7, 28.4, 27.3, 26.7, 26.0, 24.7, 24.2, 22.7, 22.1; MS (ESI) m/z : 463 [M+H]⁺, 485 [M+Na]⁺, 501 [M+K]⁺; Anal.

Calcd for C₂₆H₄₂N₂O₅: C, 67.50; H, 9.15; N, 6.06. Found: C, 67.14; H, 9.28; N, 5.87.

(4*S*,1'*S*,1''*S*)-4-{3'-[benzyloxycarbonyl-(1''-methoxycarbonyl-3''-methylbutyl)amino]-1'-phenylpropyl}-2,2-

dimethylloxazolidine-3-carboxylic acid *tert*-butyl ester (9b): This compound was prepared according to the procedure described for **9a** from amine **8b** (796 mg, 1.72 mmol). Flash column chromatography with heptane/ethyl acetate (7/1) gave 802 mg (78%, two rotamers) of **9b** as an oil: $[\alpha]_D^{25}$ -42 (*c* 0.80, CHCl₃); IR (CHCl₃): ν 3021, 2958, 2874, 1738, 1690, 1454, 1391, 1369, 1251, 1171 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.41-7.03 (m, 10H), 5.29-5.07 (m, 2H), 4.72-4.58 (m, 0.7H), 4.44-4.32 (m, 0.3H), 4.25-3.60 (m, 3H), 3.66, 3.55 (2s, 3H), 3.26-2.92 (m, 3H), 2.03-1.96 (m, 2H), 1.71-1.37 (m, 18H), 0.95-0.76 (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 172.5, 156.7, 155.9, 152.8, 152.4, 140.5, 140.2, 136.5, 128.7, 128.5, 128.3, 128.0, 126.9, 126.7, 94.8, 94.1, 80.1, 67.7, 67.3, 64.2, 64.0, 62.6, 62.4, 57.8, 52.2, 45.9, 45.4, 45.1, 44.7, 38.7, 38.2, 28.6, 27.3, 26.8, 26.6, 26.1, 24.2, 23.1, 23.1, 22.6, 21.8; MS (ESI) m/z : 619 [M+Na]⁺, 635 [M+K]⁺; Anal. Calcd for C₃₄H₄₈N₂O₇: C, 68.43; H, 8.11; N, 4.69. Found: C, 68.51; H, 8.33; N, 4.45.

(2*S*,3*S*,1'*S*)-5-[benzyloxycarbonyl-(1'-methoxycarbonyl-3'-methylbutyl)amino]-2-*tert*-butoxycarbonylamino-3-phenyl

pentanoic acid (10b): The general procedure 3 was followed using **9b** (54 mg, 0.09 mmol). Flash column chromatography with CH₂Cl₂/ethyl acetate (1/1) gave 39 mg (76%, two rotamers) of **10b**: $[\alpha]_D^{25}$ +11 (*c* 1.10, CHCl₃); IR (CHCl₃): ν 3434, 3020, 2958, 2872, 1736, 1702, 1455, 1368, 1226, 1168 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.38-7.01 (m, 10H), 6.24 (bs, 1H), 5.19-5.04 (m, 2H), 4.86-4.66 (m, 1.5H), 4.64-4.51 (m, 0.5H), 4.43-4.34 (m, 1H), 3.66 (s, 1.5H), 3.47 (s, 1.5H), 3.33-3.14 (m, 2H), 3.01-2.86 (m, 1H), 2.19-1.91 (m, 2H), 1.41 (s, 9H), 1.74-1.28 (m, 3H), 0.93-0.75 (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 175.2, 172.6, 172.3, 156.6, 155.9, 138.3,

137.9, 136.5, 136.2, 128.8, 128.6, 128.4, 128.2, 127.7, 80.3, 67.7, 57.6, 52.3, 45.4, 44.7, 43.9, 38.5, 38.1, 31.1, 30.5, 28.3, 24.8, 24.7, 23.1, 21.8, 21.6; MS (ESI) m/z : 593 $[M+Na]^+$; HRMS Calcd for $C_{31}H_{42}N_2O_8$ (M+Na): 593.2839. Found: 593.2828.

(2S,3S,1'S)-5-[Benzyloxycarbonyl-(1'-methoxycarbonyl-3'-methylbutyl)amino]-2-tert-butoxycarbonylamino-pentafluoro-phenyl-3-phenyl pentanoate (11b): This compound was prepared according to the procedure described for **11a** from acid **10b** (155 mg, 0.27 mmol). The flash column chromatography with heptane/ethyl acetate (10/1) gave 111 mg (61%, two rotamers) of **11b**: $[\alpha]_D^{20}$ (c 0.90, $CHCl_3$); IR ($CHCl_3$): ν 3436, 3028, 3021, 2958, 2872, 1788, 1712, 1521, 1497, 1472, 1455, 1369, 1168, 999 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.05 (m, 10H), 5.21-5.07 (m, 2H), 4.98-4.76 (m, 2H), 4.66-4.55 (m, 0.5H), 4.41-4.31 (m, 0.5H), 3.65 (s, 1.5H), 3.55 (s, 1.5H), 3.46-3.16 (m, 2H), 3.04-2.85 (m, 1H), 2.30-2.06 (m, 2H), 1.75-1.45 (m, 3H), 1.43 (s, 9H), 0.95-0.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 167.8, 156.6, 155.4, 137.1, 136.5, 129.1, 128.6, 128.3, 128.2, 128.1, 80.7, 67.7, 67.5, 58.1, 57.6, 52.2, 45.5, 45.0, 43.8, 38.8, 38.2, 31.3, 30.5, 28.3, 24.9, 23.1, 21.8; MS (ESI) m/z : 737 $[M+H]^+$, 759 $[M+Na]^+$, 775 $[M+K]^+$; HRMS Calcd for $C_{37}H_{41}N_2F_5O_8$ (M+Na): 759.2681. Found: 759.2663.

(2S,3'S,4'S)-2-(3'-tert-Butoxycarbonylamino-2'-oxo-4'-phenylpiperidin-1'-yl)-4-methylpentanoic acid methyl ester (12b): This compound was prepared according to the procedure described for **12a** from **11b** (99 mg, 0.134 mmol). Flash column chromatography with heptane/ethyl acetate (1/1) gave 47 mg (86%, two rotamers) of **12b** as colorless oil; $[\alpha]_D^{20}$ (c 0.70, $CHCl_3$); IR ($CHCl_3$): ν 3444, 3021, 2957, 2873, 1736, 1714, 1655, 1504, 1455, 1436, 1392, 1368, 1243, 1168 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5H), 5.24 (t, $J = 7.8$ Hz, 1H), 4.87 (d, $J = 8.3$ Hz, 1H), 4.46-4.32 (m, 1H), 3.74 (s, 3H), 3.55-3.33 (m, 2H), 3.07 (dt, $J = 5.4, 11.2$ Hz, 1H), 2.34-2.20 (m, 1H), 2.19-2.04 (m, 1H), 1.80-1.70 (m, 2H), 1.64-1.45 (m, 1H), 1.28 (s, 9H), 0.97 (d, $J = 7.3$ Hz, 3H), 0.95 (d, $J =$

7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 172.3, 171.0, 156.1, 141.7, 128.6, 127.7, 127.1, 79.8, 54.8, 52.3, 45.2, 42.3, 37.3, 30.2, 28.2, 25.1, 23.4, 21.5; MS (CI) m/z : 419 $[\text{M}+\text{H}]^+$, 441 $[\text{M}+\text{Na}]^+$, 457 $[\text{M}+\text{K}]^+$, 837 $[2\text{M}+\text{H}]^+$, 859 $[2\text{M}+\text{Na}]^+$; HRMS Calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_5$ (M+Na): 441.2365. Found: 441.2372.

(4*S*,1'*S*,1''*S*)-4-(1'-[2''-(5'''-Benzyloxycarbonylamino-1'''-methoxycarbonylpentylamino)ethyl]allyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (13b): The general procedure 2 was followed using L-Lys(Cbz)OCH₃.HCl (**7d**) (460 mg, 1.39 mmol), aldehyde **6c** (300 mg, 1.06 mmol) and triethylamine (0.16 mL, 1.16 mmol). Flash column chromatography with heptane/ethyl acetate (2/1) gave 398 mg (67%, two rotamers) of **13b** as an oil: $[\alpha]_{\text{D}}^{+25}$ (c 1.40, CHCl_3); IR (neat): ν 3351, 3069, 3032, 2977, 2937, 2868, 1731, 1697, 1640, 1530, 1455, 1390, 1365, 1253, 1173, 1089, 917, 848 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.39-7.30 (m, 5H), 5.71-5.53 (m, 1H), 5.38-5.28 (m, 1H), 5.07-4.99 (m, 4H), 3.88-3.76 (m, 3H), 3.70 (s, 3H), 3.16-3.14 (m, 3H), 2.71-2.40 (m, 2H), 2.38-2.24 (m, 1H), 2.09-1.90 (m, 1H), 1.67-1.24 (m, 14H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): δ 175.9, 156.5, 152.6, 152.1, 139.2, 136.8, 128.4, 128.0, 128.0, 117.2, 116.7, 94.1, 93.5, 79.9, 79.6, 66.4, 65.2, 61.4, 60.7, 51.6, 46.3, 45.5, 40.8, 33.0, 30.5, 30.2, 29.7, 28.4, 27.1, 26.3, 24.4, 23.0, 22.8; MS (ESI) m/z : 562 $[\text{M}+\text{H}]^+$, 584 $[\text{M}+\text{Na}]^+$, 600 $[\text{M}+\text{K}]^+$; HRMS Calcd for $\text{C}_{30}\text{H}_{48}\text{N}_3\text{O}_7$ (M+H): 562.3492. Found: 562.3479.

(4*S*,1'*S*,1''*S*)-4-(1'-{2''-[(5'''-Benzyloxycarbonylamino-1'''-methoxycarbonylpentyl)-(9*H*-fluoren-9-ylmethoxycarbonyl)-amino]ethyl}allyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (14b): The general procedure 4 was followed using amine **13b** (3.48 g, 6.20 mmol). Flash column chromatography with heptane/ethyl acetate (4/1) gave 4.52 g (93%, two rotamers) of **14b** as white crystals: Mp 59-61°C; $[\alpha]_{\text{D}}^{+25}$ (c 1.50, CHCl_3); IR (CHCl_3): ν 3423, 3364, 3067, 3037, 2951, 2932, 2871, 1697, 1526,

1477, 1451, 1420, 1390, 1365, 1297, 1252, 1174, 1145, 1103, 1088, 1054, 1031, 1002, 918, 849 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.86-7.65 (m, 2H), 7.64-7.49 (m, 2H), 7.43-7.19 (m, 9H), 5.75-5.25 (m, 1H), 5.19-4.83 (m, 5H), 4.66-4.41 (m, 2H), 4.40-4.26 (m, 1H), 4.25-4.10 (m, 1H), 4.02-3.73 (m, 2H), 3.65 (s, 3H), 3.50 (m, 2H), 3.25-2.83 (m, 3H), 2.45-2.09 (m, 1H), 2.02-0.95 (m, 8H), 1.58, 1.53 (2s, 6H), 1.44, 1.42 (2s, 9H); ^{13}C NMR (75 MHz, CDCl_3): δ 171.8, 171.4, 156.4, 155.8, 152.7, 152.1, 143.9, 141.3, 138.6, 138.5, 136.7, 128.5, 128.1, 127.6, 127.0, 124.8, 124.6, 120.0, 117.8, 117.3, 94.1, 93.6, 80.0, 79.7, 67.0, 66.8, 66.5, 65.3, 60.6, 59.6, 52.2, 47.4, 47.3, 46.0, 45.8, 45.4, 45.1, 40.7, 29.7, 29.4, 29.3, 28.9, 28.4, 27.1, 26.3, 24.4, 23.5, 22.8, 22.7; MS (ESI) m/z : 806 $[\text{M}+\text{Na}]^+$; HRMS Calcd for $\text{C}_{45}\text{H}_{57}\text{N}_3\text{O}_9\text{Na}$ ($\text{M}+\text{Na}$): 806.3993. Found: 806.3986.

(2*S*,3*S*,1''*S*)-3-{2'-[(5''-Benzyloxycarbonylamino-1''-methoxycarbonyl)pentyl]-(9*H*-fluoren-9-ylmethoxycarbonyl)amino}ethyl-2-*tert*-butoxycarbonylaminopent-4-enoic acid (15b**):** The general procedure 3 was followed using **14b** (4.50 g, 5.74 mmol). Flash column chromatography with heptane/ethyl acetate (2/1) gave 2.43 g (81%, two rotamers) of **15b** as white solid: Mp 52-52°C; $[\alpha]_{\text{D}}^{25}$ -12 (c 1.25, CHCl_3); IR (CHCl_3): ν 3441, 3019, 2980, 2953, 1709, 1510, 1478, 1452, 1422, 1393, 1368, 1216, 1159, 1046, 1025, 928, 857 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD): δ 7.84-7.68 (m, 2H), 7.62-7.47 (m, 2H), 7.43-7.19 (m, 9H), 5.76-5.29 (m, 1H), 5.51-4.74 (m, 6H), 4.69-4.43 (m, 2H), 4.32-3.69 (m, 2H), 3.59 (s, 3H), 3.42 (s, 2H), 3.18-2.75 (m, 3H), 2.63-2.22 (m, 1H), 1.99-0.82 (m, 8H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.6, 173.3, 172.9, 158.8, 158.1, 157.8, 145.3, 142.8, 138.5, 137.7, 137.5, 129.6, 129.1, 128.9, 128.3, 125.8, 125.6, 121.2, 119.1, 80.7, 67.9, 67.4, 61.6, 61.3, 61.1, 58.3, 57.8, 52.8, 48.8, 48.3, 47.2, 46.6, 45.3, 41.7, 31.1, 30.8, 30.6, 30.3, 30.0, 29.8, 28.9, 24.7, 24.6; MS (ESI) m/z : 780 $[\text{M}+\text{Na}]^+$; HRMS Calcd for $\text{C}_{42}\text{H}_{51}\text{N}_3\text{O}_{10}\text{Na}$ ($\text{M}+\text{Na}$): 780.3472. Found: 780.3473.

(2*S*,3'*S*,4'*S*)-6-Benzoyloxycarbonylamino-2-(3'-*tert*-butoxycarbonylamino-2'-oxo-4'-vinylpiperidin-1'-yl)-hexanoic acid methyl ester (16b): The general procedure 5 was followed using **15b** (2.10 g, 2.77 mmol). Flash column chromatography with heptane/ethyl acetate (2/1) gave 1.27 g (89%, two rotamers) of **16b**: $[\alpha]_D^{25}$ -13 (*c* 1.30, CHCl₃); IR (CHCl₃): ν 3337, 3068, 3010, 2978, 2952, 2869, 1710, 1651, 1521, 1455, 1437, 1391, 1367, 1326, 1247, 1217, 1170, 1094, 1049, 1023, 919, 866 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.41-7.22 (m, 5H), 5.86-5.70 (m, 1H), 5.61-4.93 (m, 7H), 4.14-3.94 (m, 1H), 3.68 (s, 3H), 3.36-3.03 (m, 4H), 2.55-2.30 (m, 1H), 2.12-1.19 (m, 8H), 1.41 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 171.7, 171.5, 170.5, 169.9, 156.6, 156.2, 155.9, 138.9, 138.7, 136.9, 136.8, 128.5, 128.0, 115.9, 79.4, 66.5, 56.4, 56.1, 56.0, 55.3, 52.2, 43.5, 42.7, 41.8, 40.7, 40.5, 29.3, 28.9, 28.3, 27.8, 27.7, 23.2, 22.8; MS (ESI) *m/z*: 540 [M+Na]⁺; HRMS Calcd for C₂₇H₃₉N₃O₇Na (M+Na): 540.2686. Found: 540.2692.

(4*S*,1'*S*,1''*S*,2''''*S*)-4-(1'-{2''-[5'''-Benzoyloxycarbonylamino-1''''-(2''''-*tert*-butoxycarbonyl-pyrrolidine-1''''-carbonyl)pentylamino]-ethyl}-allyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (18): The general procedure 2 was followed using amine **17** (3.00 g, 6.90 mmol) and aldehyde **6c** (1.96 g, 6.90 mmol). Flash column chromatography with CH₂Cl₂/ethyl acetate (4/1, then 2/1) gave 3.53 g (74%, two rotamers) of **18** as a yellow oil: $[\alpha]_D^{25}$ -28 (*c* 1.00, CHCl₃); IR (neat) ν 3335, 3069, 2977, 2875, 1694, 1643, 1531, 1366, 1253, 1153, 1090, 1055, 915, 848, 807 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.25 (m, 5H), 5.71-5.50 (m, 2H), 5.16-4.93 (m, 4H), 4.45-4.34 (m, 1H), 3.95-3.07 (m, 9H), 2.66-1.25 (m, 15H), 1.60 (s, 3H), 1.55 (s, 3H), 1.45 (s, 9H), 1.40 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.5, 171.4, 156.5, 152.7, 152.1, 139.4, 136.9, 128.1, 127.9, 117.0, 116.6, 94.3, 93.2, 81.3, 79.8, 79.6, 66.3, 65.4, 65.2, 60.8, 59.6, 59.5, 59.3, 46.7, 46.5, 46.4, 45.6, 40.5, 32.8, 32.6, 31.4, 30.8, 30.7, 30.5, 29.8, 29.5, 28.8, 28.4, 27.9,

27.1, 26.4, 26.3, 24.8, 24.9, 24.4, 23.1, 22.9, 22.4; MS (ESI) m/z : 701 [M+H]⁺, 723 [M+Na]⁺; HRMS Calcd for C₃₈H₆₁N₄O₈ (M+H): 701.4489. Found: 701.4479.

(4*S*,1'*S*,1''*S*,2'''*S*)-4-(1'-{2''-[5'''-Benzyloxycarbonylamino-1''-(2''''-*tert*-butoxycarbonyl-pyrrolidine-1''''-carbonyl)-pentyl]-(9*H*-fluoren-9-ylmethoxycarbonyl)-amino]-ethyl)-allyl)-2,2-dimethyl oxazolidine 3-carboxylic acid *tert*-butyl ester (19):

The general procedure 4 was followed using amine **18** (3.18 g, 4.50 mmol). Flash column chromatography with CH₂Cl₂/ethyl acetate (4/1 then 2/1) gave 3.90 g (92%, two rotamers) of **19** as white crystals: Mp 61-62 °C; [α]_D⁻⁶² (*c* 1.20, CHCl₃); IR (CHCl₃): ν 3449, 3021, 2986, 2938, 2878, 1718, 1683, 1654, 1648, 1603, 1560, 1522, 1508, 1477, 1451, 1393, 1367, 1225, 1211, 1208, 1153, 1089, 996, 917, 851 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.79-7.20 (m, 13H), 5.67-3.29 (m, 18H), 1.44 (s, 3H), 1.41 (s, 3H), 1.39 (s, 9H), 1.36 (s, 9H), 3.23-0.95 (m, 15H); ¹³C NMR (75 MHz, CDCl₃): δ 171.2, 169.0, 168.9, 168.1, 156.6, 156.5, 155.0, 152.6, 152.1, 144.0, 143.8, 141.6, 141.4, 141.3, 138.5, 138.4, 136.8, 128.8, 128.4, 128.0, 128.0, 127.9, 127.7, 127.3, 127.1, 127.0, 124.7, 124.7, 124.0, 120.0, 117.7, 117.6, 117.3, 117.0, 94.0, 93.5, 81.2, 79.8, 66.7, 66.4, 65.6, 65.2, 65.0, 60.6, 59.6, 55.7, 47.5, 47.4, 47.3, 46.8, 46.2, 46.0, 45.3, 45.1, 42.1, 41.9, 41.8, 40.8, 29.6, 29.1, 28.9, 28.7, 28.3, 27.0, 26.6, 26.0, 24.7, 24.3, 23.8, 22.6, 22.5, 22.4; MS (ESI) m/z : 945 [M+Na]⁺; HRMS Calcd for C₅₃H₇₀N₄NaO₁₀ (M+Na): 945.4966. Found 945.4963.

(2*S*,2'*S*,3''*S*,2'''*S*)-1-{6'-Benzyloxycarbonylamino-2'-[3''''-(*tert*-butoxycarbonylamino-carboxy-methyl)-pent-4''''-enyl]-(9*H*-fluoren-9-ylmethoxycarbonyl)-amino]-hexanoyl}-pyrrolidine-2-carboxylic acid *tert*-butyl ester (20): The general procedure 3 was followed using **19** (3.40 g, 3.60 mmol). Flash column chromatography with CH₂Cl₂/ethyl acetate (4/1, then 2/1) gave 1.88 g (57%, two rotamers) of **20** as white crystals: Mp 86-88°C; [α]_D⁻⁵¹ (*c* 1.00, CHCl₃); IR (CHCl₃): ν 3449, 3021, 2983, 2938, 2878, 1718, 1686,

1654, 1648, 1618, 1603, 1542, 1508, 1477, 1451, 1393, 1367, 1225, 1211, 1208, 1153, 1089, 996, 917, 851 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 8.56 (bs, 1H), 7.79-7.28 (m, 13H), 5.56-2.43 (m, 20H), 2.42-0.70 (m, 12H), 1.43, 1.42 (2s, 9H), 1.40, 1.38 (2s, 9H); ^{13}C NMR (75 MHz, CDCl_3): δ 173.6, 173.4, 171.3, 171.1, 168.9, 168.0, 156.6, 156.5, 155.7, 155.5, 143.9, 143.8, 143.7, 143.6, 141.6, 141.4, 141.4, 141.2, 136.7, 135.4, 128.4, 128.1, 128.0, 127.7, 127.6, 127.3, 127.1, 127.0, 127.0, 124.7, 124.6, 124.5, 124.1, 123.9, 120.0, 118.9, 118.7, 81.3, 79.7, 79.6, 66.5, 65.9, 59.9, 59.8, 57.3, 56.8, 55.8, 47.6, 47.2, 46.8, 45.8, 44.4, 44.1, 41.4, 40.7, 30.0, 29.6, 29.3, 29.0, 28.9, 28.3, 27.9, 24.7, 22.6, 22.6, 22.5, 22.3; MS (ESI) m/z : 919 $[\text{M}+\text{Na}]^+$; HRMS Calcd for $\text{C}_{50}\text{H}_{64}\text{N}_4\text{NaO}_{11}$ (M+Na): 919.4469. Found 919.4486.

(2S,2'S,3''S,4''S)-1-[6'-Benzyloxycarbonylamino-2'-(3''-tert-butoxycarbonylamino-2''-oxo-4''-vinyl-piperidin-1''-yl)-

hexanoyl]-pyrrolidine-2-carboxylic acid tert-butyl ester (21): The general procedure 5 was followed using acid **20** (1.60 g, 17.80 mmol). Flash column chromatography with heptane/ethyl acetate (4/1, then 2/1) gave 840 mg (71%) of **21** as white crystals: Mp 54-55°C; $[\alpha]_D^{25}$ -96 (c 1.00, CHCl_3); IR (CHCl_3): ν 3445, 3066, 3015, 2929, 2854, 1714, 1644, 1602, 1574, 1538, 1505, 1455, 1393, 1368, 1242, 1156, 1013, 923, 843 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.38-7.25 (m, 5H), 5.81-5.69 (m, 1H), 5.42-5.21 (m, 3H), 5.07-5.03 (m, 4H), 4.35-4.31 (m, 1H), 3.80-3.18 (m, 7H), 2.62-2.50 (m, 1H), 2.47-1.20 (m, 12H), 1.41, 1.42 (2s, 18H); ^{13}C NMR (75 MHz, CDCl_3): δ 171.2, 169.7, 168.9, 156.5, 156.0, 138.9, 136.8, 128.5, 128.1, 128.0, 115.9, 81.2, 79.5, 66.4, 59.8, 56.0, 53.8, 47.1, 42.8, 41.2, 40.6, 29.2, 29.1, 28.3, 27.7, 24.8, 22.7; MS (ESI) m/z 679 $[\text{M}+\text{Na}]^+$; Anal. Calcd for $\text{C}_{35}\text{H}_{52}\text{N}_4\text{O}_8$: C, 64.00; H, 7.98; N, 8.53. Found: C, 64.01; H, 7.86; N, 8.39; HRMS Calcd for $\text{C}_{35}\text{H}_{52}\text{N}_4\text{O}_8\text{Na}$ (M+Na): 679.3683. Found 679.3666.

(2*S*,2'*S*,3''*S*,4''*S*,2'''*S*)-1-(6'-Benzyloxycarbonylamino-2'-{3''-[3'''-*tert*-butoxy-2'''-(9*H*-fluoren-9''''-ylmethoxycarbonylamino)-propionylamino]-2''-oxo-4''-vinyl-piperidin-1''-yl}-hexanoyl)-pyrrolidine-2-carboxylic acid *tert*-butyl ester (28): This compound was prepared according to the procedure described for **23** starting from amine **22** (200 mg, 0.36 mmol) and Fmoc-L-Ser(*Bu*)OH (151 mg, 0.40 mmol). Flash column chromatography with CH₂Cl₂/ethyl acetate (1/1) gave 280 mg (85%) of **28** as white crystals: Mp 67-68°C; [α]_D-47 (*c* 0.50, CHCl₃); IR (neat): ν 2944, 1715, 1633, 1519, 1446, 1363, 1236, 1150, 1104, 1076, 1022, 915, 844 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.75 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.24 Hz, 2H), 7.51-7.14 (m, 10H), 5.86-5.61 (m, 2H), 5.34-4.91 (m, 6H), 4.48-4.01 (m, 6H), 3.91-3.68 (m, 2H), 3.65-3.28 (m, 4H), 3.25-3.01 (m, 2H), 2.64-2.44 (m, 1H), 2.21-1.25 (m, 12H), 1.42 (s, 9H), 1.19 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 171.2, 170.6, 169.2, 168.6, 156.5, 156.0, 143.9, 143.8, 141.3, 138.4, 136.8, 128.4, 128.1, 128.0, 127.7, 127.0, 125.1, 120.0, 116.2, 81.3, 74.2, 67.0, 66.4, 61.7, 59.7, 54.8, 54.2, 53.9, 47.1, 42.9, 41.3, 40.6, 29.3, 29.1, 28.4, 28.1, 27.9, 27.4, 24.8, 22.8; MS (ESI) *m/z* 944 [M+Na]⁺; HRMS Calcd for C₅₂H₆₇N₅O₁₀Na (M+Na): 944.4786. Found 944.4798.

(2*S*,2'*S*,3''*S*,4''*S*,2'''*S*)-1-{2'-[3''-(2'''-Acetylamino-3'''-*tert*-butoxy-propionylamino)-2''-oxo-4''-vinyl-piperidin-1''-yl]-6'-benzyloxycarbonylamino-hexanoyl}-pyrrolidine-2-carboxylic acid *tert*-butyl ester (30): This compound was prepared according to the procedure described for **25** starting from amine **29** (186 mg, 0.27 mmol). Flash column chromatography with heptane/ethyl acetate (1/1), then CH₂Cl₂/MeOH (20/1) gave 169 mg (86%) of **30** as white crystals: Mp 63-64°C; [α]_D-54 (*c* 0.50, CHCl₃); IR (neat): ν 3310, 2972, 1715, 1633, 1521, 1435, 1391, 1364, 1245, 1193, 1150, 1091, 1023, 914, 876, 843 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.41 (d, *J* = 7.7 Hz, 1H), 7.38-7.27 (m, 5H), 6.57 (d, *J* = 5.8 Hz, 1H), 5.80-5.61 (m, 1H), 5.41- 5.29 (m, 1H), 5.24 (t, *J* = 5.2 Hz, 1H), 5.17-4.96

(m, 4H), 4.53-4.39 (m, 1H), 4.37-4.24 (m, 1H), 4.20-4.07 (m, 1H), 3.89-3.68 (m, 2H), 3.65-3.49 (m, 2H), 3.45-3.29 (m, 2H), 3.26-3.12 (m, 2H), 2.61-2.41 (m, 1H), 2.26-1.26 (m, 12H), 2.00 (s, 3H), 1.42 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3): δ 171.2, 170.9, 170.1, 169.2, 168.7, 156.6, 138.4, 136.8, 128.4, 128.1, 128.0, 116.2, 81.3, 74.2, 66.4, 61.2, 59.7, 54.6, 54.0, 52.8, 47.1, 43.0, 41.3, 40.6, 29.3, 29.1, 28.4, 28.2, 27.9, 27.4, 24.8, 23.2, 22.8; MS (ESI) m/z : 764 $[\text{M}+\text{Na}]^+$; HRMS Calcd for $\text{C}_{39}\text{H}_{59}\text{N}_5\text{O}_9\text{Na}$ (M+Na): 764.4210. Found 764.4232.

(3S,4R,2'S,1''S,2'''S)-3-(2'-Acetylamino-3'-tert-butoxy-propionylamino)-1-[5''-benzyloxycarbonylamino-1''-(2'''-tert-butoxycarbonyl-pyrrolidine-1'''-carbonyl)-pentyl]-2-oxo-piperidine-4-carboxylic acid (31): This compound was prepared according to the same procedure as described for **26a** starting from **30** (250 mg, 0.35 mmol). Flash column chromatography with heptane/ethyl acetate (1/1), then CH_2Cl_2 /methanol (20/1) gave 205 mg (75%) of **31** as white solid: Mp 85-86°C; $[\alpha]_{\text{D}}^{-76}$ (*c* 0.50, CHCl_3); IR (CHCl_3) ν 3313, 2929, 1713, 1632, 1530, 1434, 1392, 1365, 1248, 1192, 1151, 1091, 1025, 982, 916, 874, 844 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD): δ 7.42-7.25 (m, 5H), 5.30 (t, $J = 7.4$ Hz, 1H), 5.05 (s, 2H), 4.50 (t, $J = 5.1$ Hz, 1H), 4.33-4.24 (m, 2H), 3.64-3.50 (m, 3H), 3.39-3.34 (m, 2H), 3.14-3.04 (m, 3H), 2.26-2.18 (m, 2H), 1.98-1.10 (m, 10H), 1.98 (s, 3H), 1.44 (s, 9H), 1.17(s, 9H); ^{13}C NMR (75MHz, CD_3OD): δ 175.9, 173.0, 172.2, 170.3, 170.0, 158.9, 138.5, 129.5, 129.0, 128.9, 82.7, 74.7, 67.4, 63.0, 61.6, 55.7, 55.0, 53.8, 48.5, 44.8, 43.1, 41.5, 30.5, 30.2, 29.1, 28.3, 27.8, 27.0, 25.8, 24.0, 22.7; MS (ESI) m/z : 782 $[\text{M}+\text{Na}]^+$; HRMS Calcd for $\text{C}_{38}\text{H}_{57}\text{N}_5\text{O}_{11}\text{Na}$ (M+Na): 782.3952. Found 782.3939.

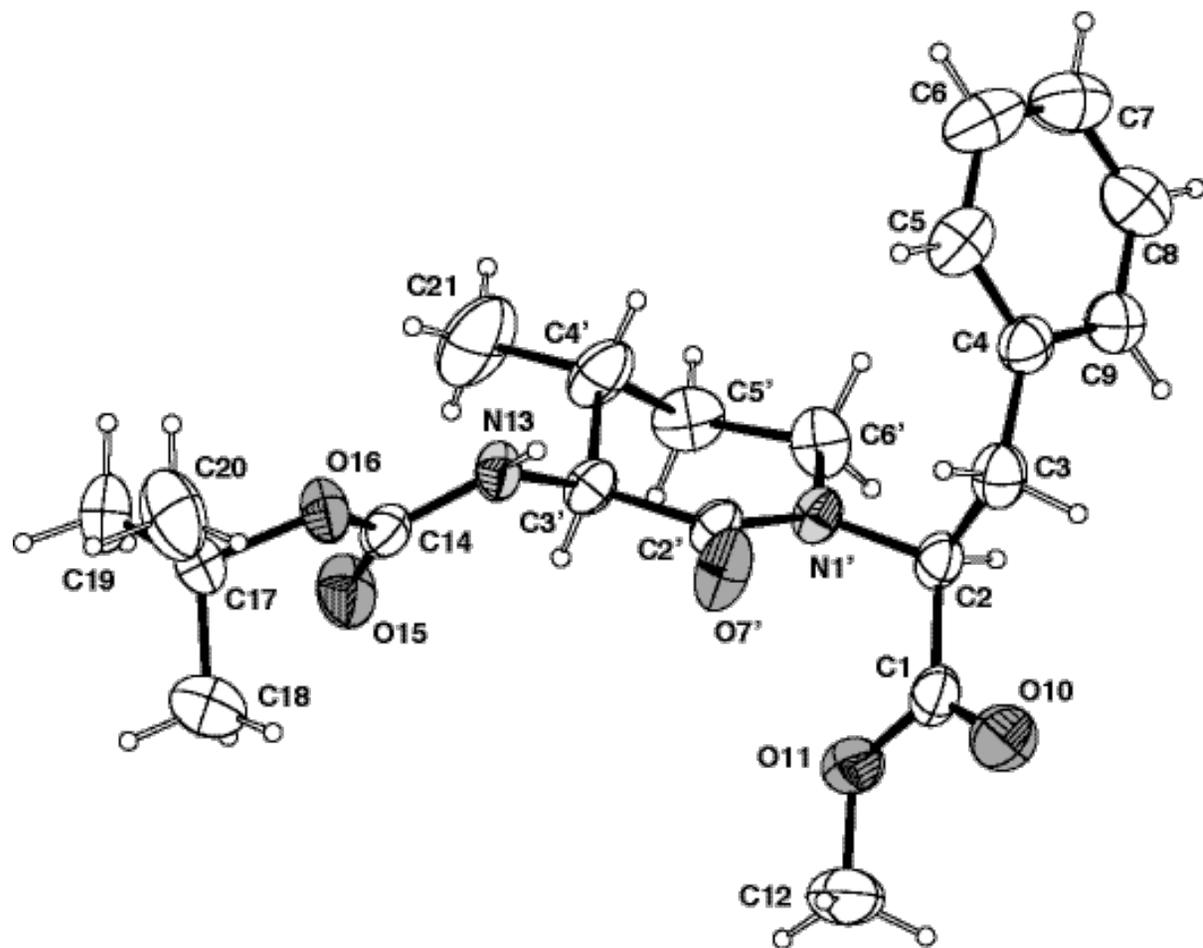


Figure 1. ORTEP drawing of **12a**. Displacement ellipsoids are shown at the 30% probability level.

X-ray structure analysis of (2*S*,3'*S*,4'*R*)-2-(3'-*tert*-butoxycarbonylamino-4'-methyl-2'-oxopiperidin-1'-yl)-3-phenylpropionic acid methyl ester (12a). The molecule appears in Figure 1, with the absolute configuration deduced from the known C3'(S) stereochemistry of the starting material. This study established the whole stereochemistry of the molecule (2*S*, 3'*S*, 4'*R*), showing unambiguously the *trans* position of the hydrogen atoms linked to carbon atoms C3' and C4'. Furthermore, the piperidin-2-one ring was found exhibiting two possible conformations, of respective weight (2/3-1/3), the carbon atoms C5' and C6' being disordered, splitted in positions C5* and C6* as results of a twist motion around the pivot atoms C4' and N1'. The major conformation, shown in the Figure 1, consists in an envelope form, with the atom C4' deviated by +0.751(3) Å from the mean plane of the other five atoms [N1', C2', C3', C5', C6']. The minor one, is quite a boat, with the atoms C3' and C6* deviated by respectively -0.401(3) and -0.767(3) Å from the mean plane of the four other atoms [N1', C2', C4', C5*]. The short distance N13...O7' of 2.681(4) Å could suggests an intramolecular hydrogen bond between the N13-H atoms and the oxygen O7' with the following characteristics: distance HN13...O7' = 2.53 Å, angle N-H-O' = 99.2°. This suggests that no intermolecular hydrogen bonding was found in the packing of the molecule.

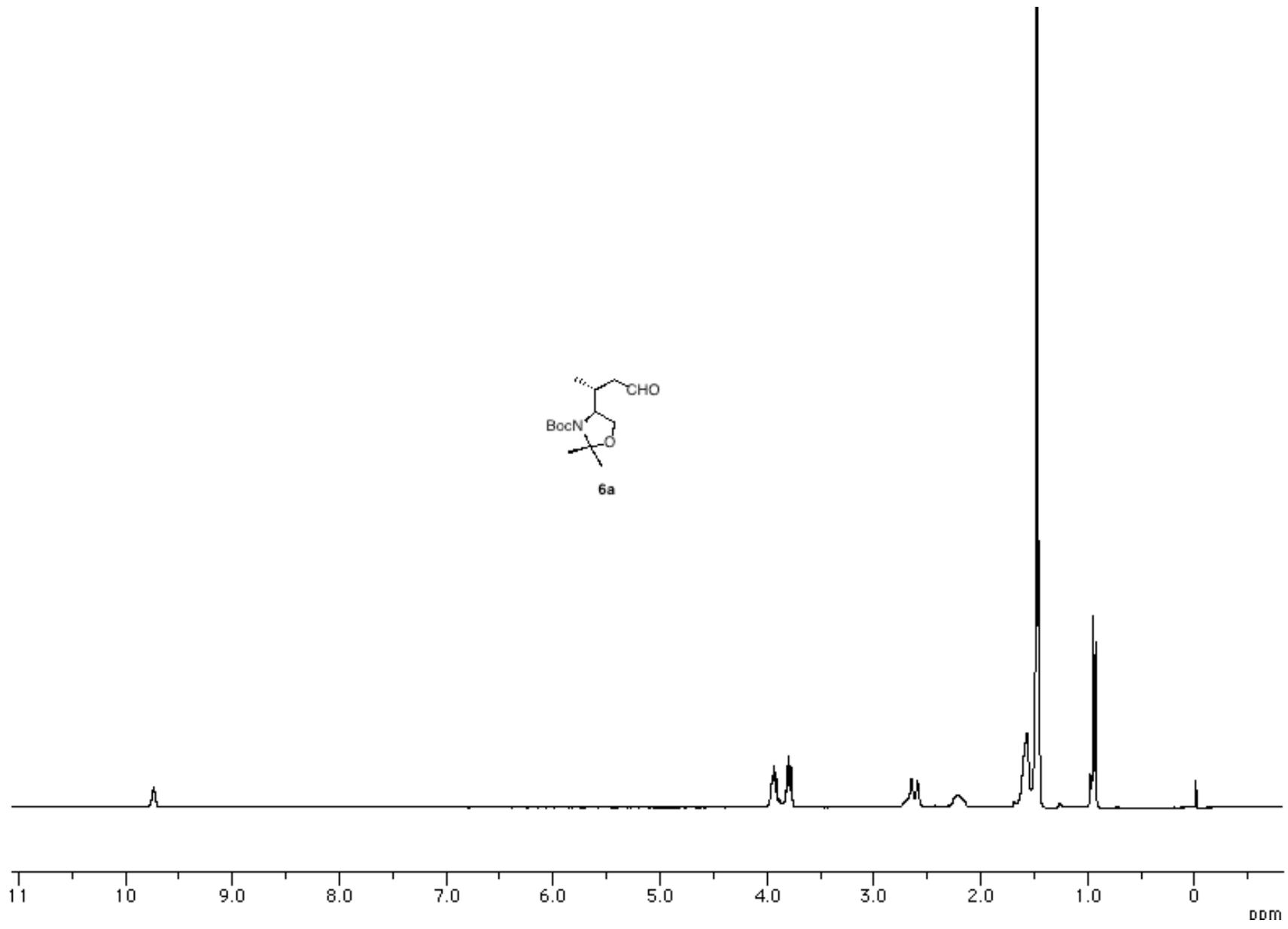
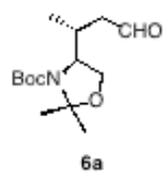
A colorless crystal of 0.40 x 0.50 x 0.50 mm, crystallized from a mixture dichlorometane/heptane was used. This study confirmed the chemical formula: C₂₁H₂₃NO₄. The compound crystallizes in the orthorhombic system, space group P 2₁2₁2₁; Z = 4 (four molecules in the unit cell), MW = 390.47; a = 9.792 (4), b = 10.144 (5), c = 22.818 (14) Å, V = 2266 Å³, d_c = 1.144 gcm⁻³, F(000) = 840, λ (Mo Kα) = 0.71073 Å, μ = 0.080 mm⁻¹. Data were measured with a Nonius Kappa-CCD area-detector diffractometer, using graphite monochromated Mo Kα radiation, in phi scans, up to θ = 30.2°. 10886 data were collected leading to 4289 unique

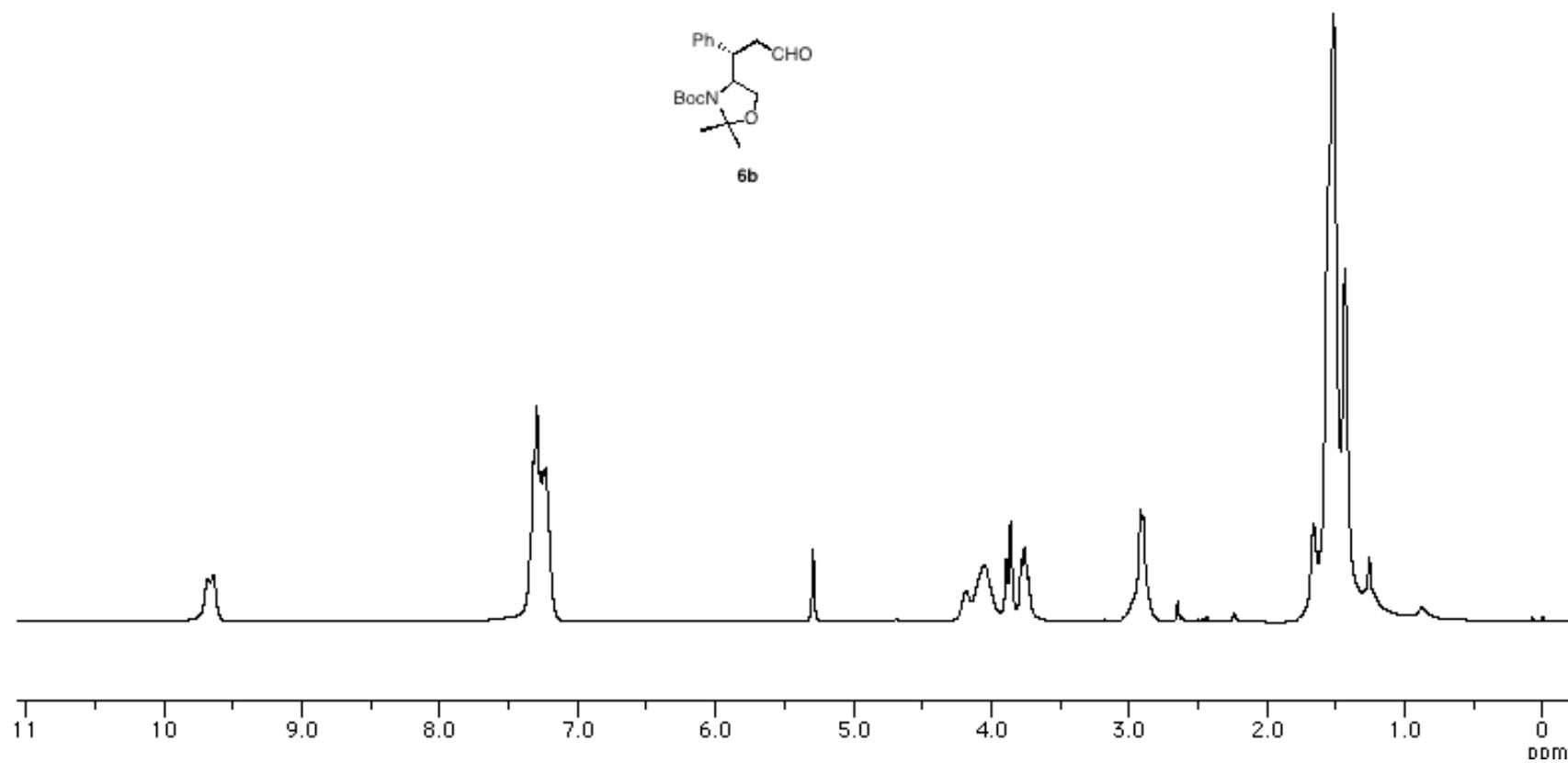
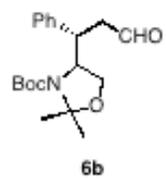
reflections ($R_{int} = 0.039$), of which 3041 were considered as observed, having $I \geq 2 \sigma(I)$.¹ The structure was solved with program *SHELXS86*,² and refined by full-matrix least-squares using unique F^2 with program *SHELXL93*.³ The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions and treated as riding, except the H atom linked to the nitrogen atom N13, kept experimental. These atoms were assigned an isotropic displacement parameter equivalent to 1.2 that one of the bonded atom (1.25 in the methyl groups). Thus, with the observed disorder of atoms C5' and C6', refinement of 203 parameters converged to $R_1(F) = 0.0621$ for the 3041 observed reflections and $wR_2(F^2) = 0.1199$ for all the 4289 data with a goodness-of-fit S factor of 1.042. The residual electron density was found between -0.11 and 0.13 eÅ⁻³. In the crystal packing, only van der Waals contacts were observed.

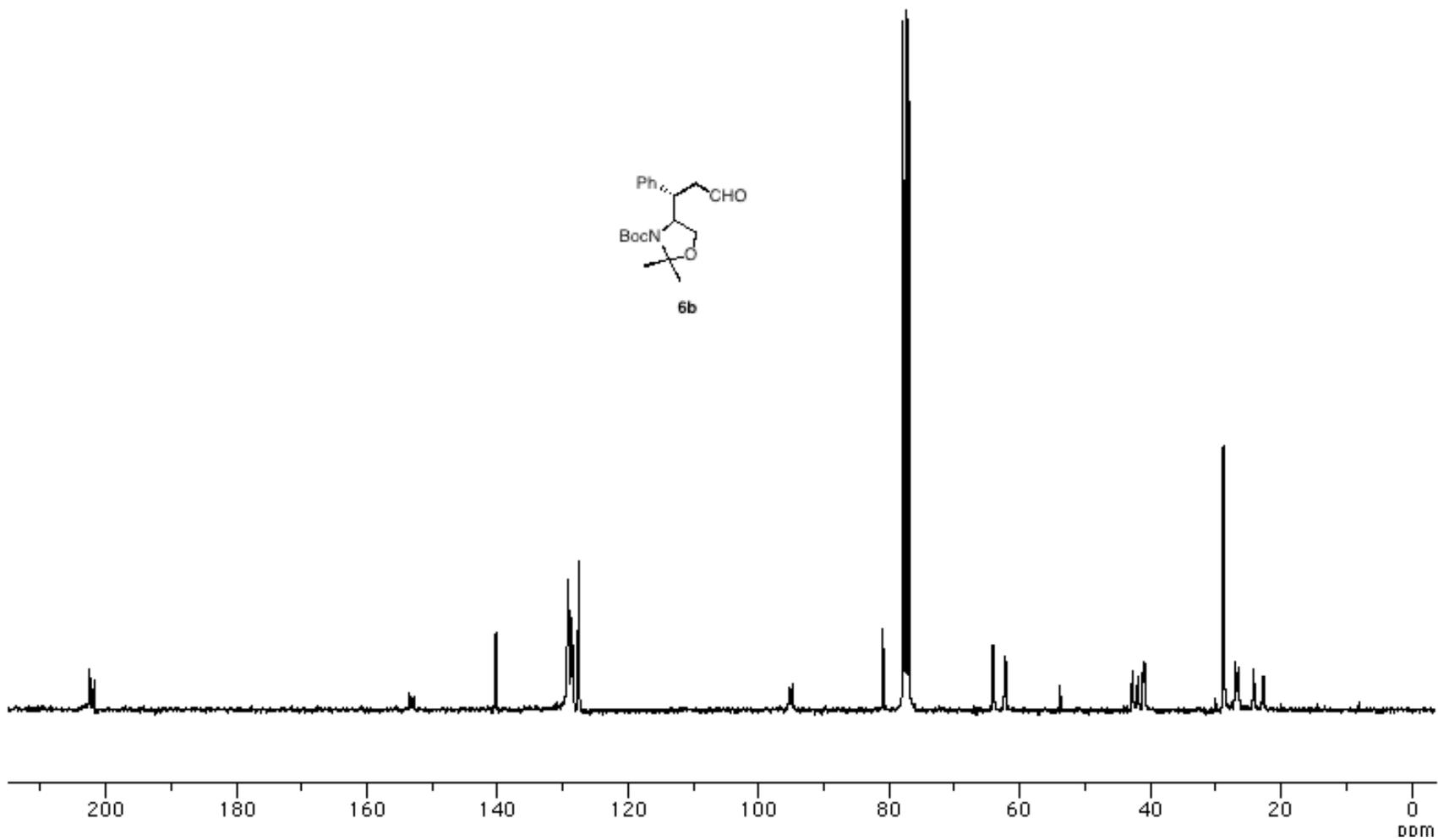
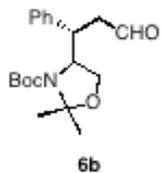
CCDC-267642 contains the Supplementary Crystallographic data for this paper (CIF file). These data can be obtained free of charge at [www.ccdc.cam.ac.uk /conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB 1EZ, UK; fax / (internet.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

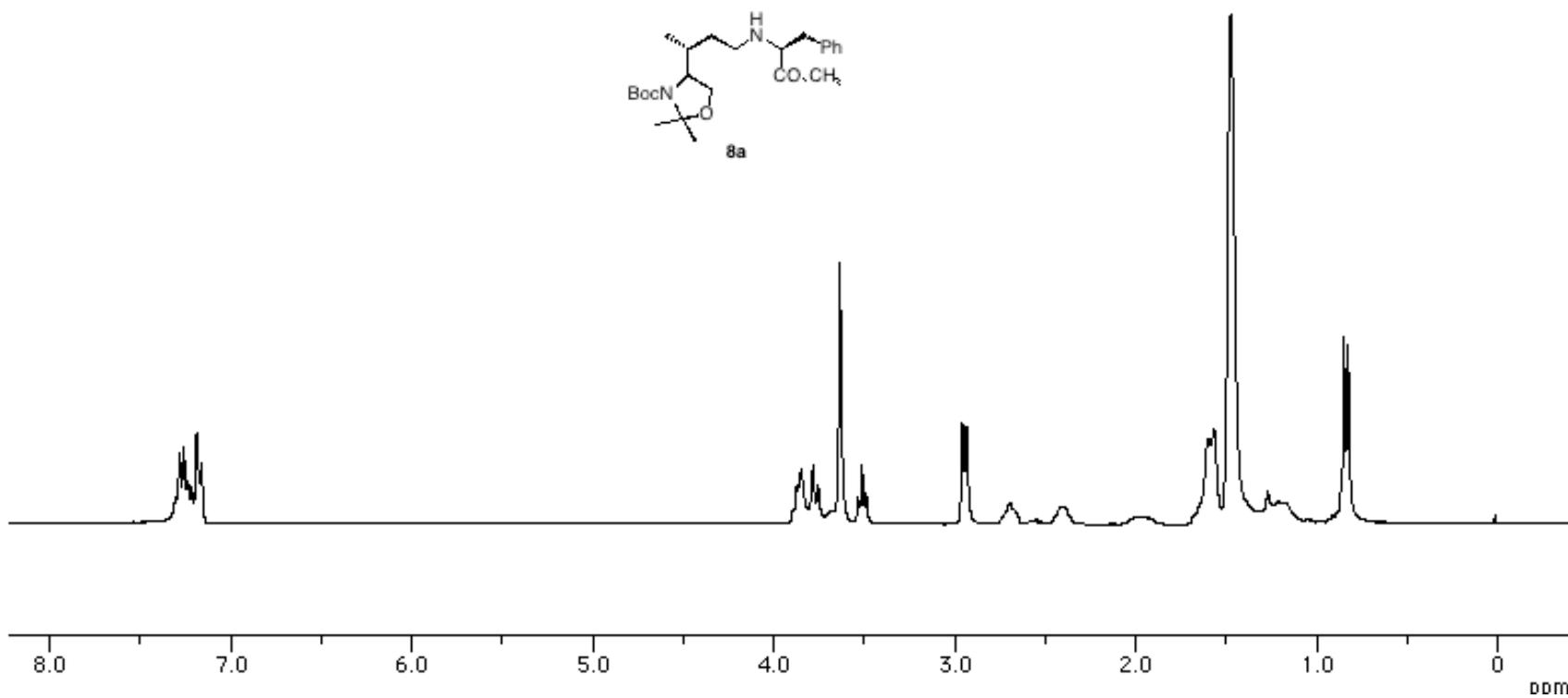
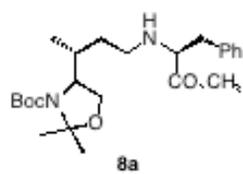
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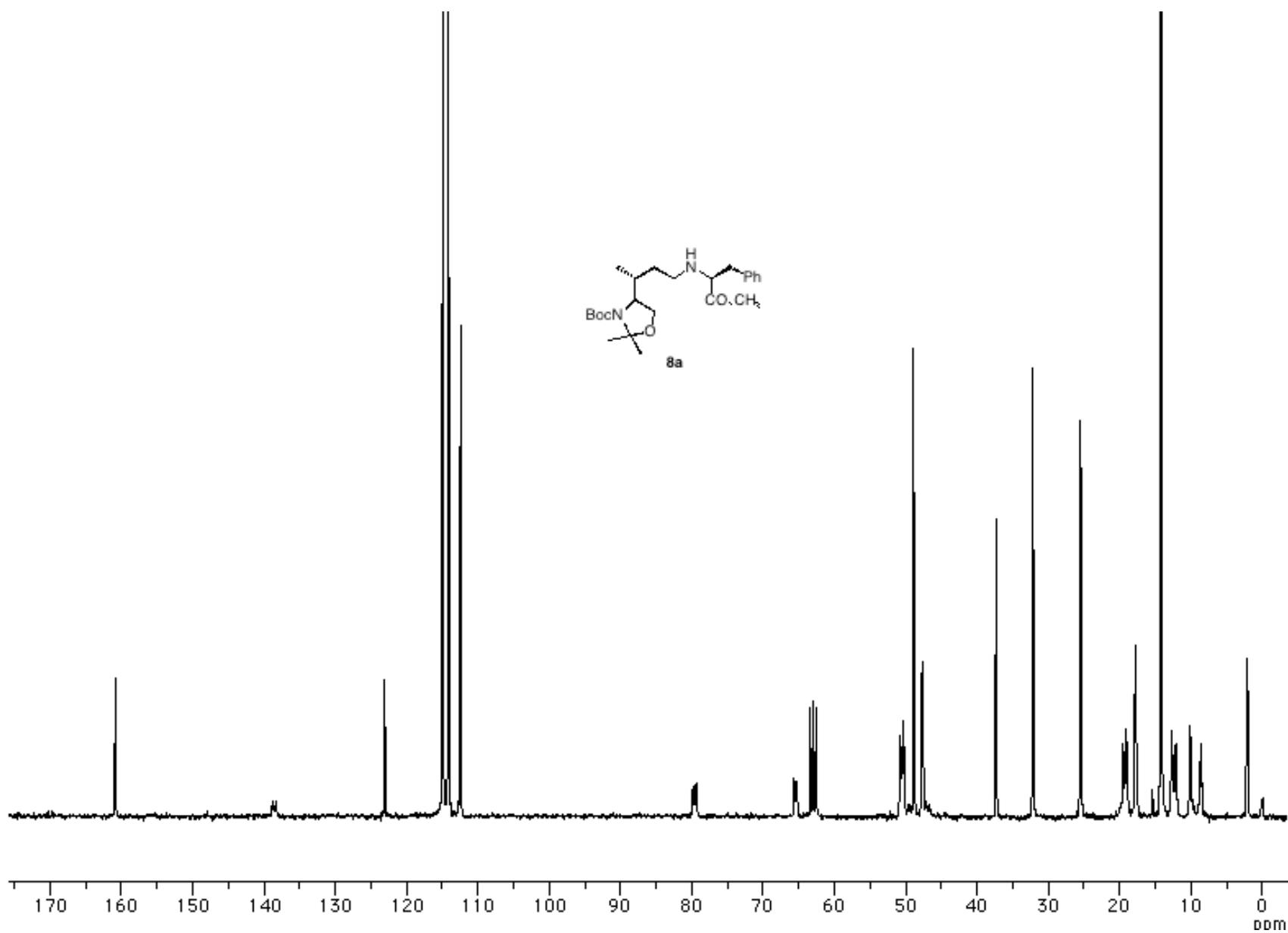
- 1) Enraf-Nonius, *Kappa-CCD Software*, Enraf-Nonius, Delft, The Netherlands, **1997-2000**.
- 2) Sheldrick. G. M. *Acta Cryst.* **1990**, A 46, 467-473.
- 3) Sheldrick. G. M. *SHELXL-93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany, **1993**.

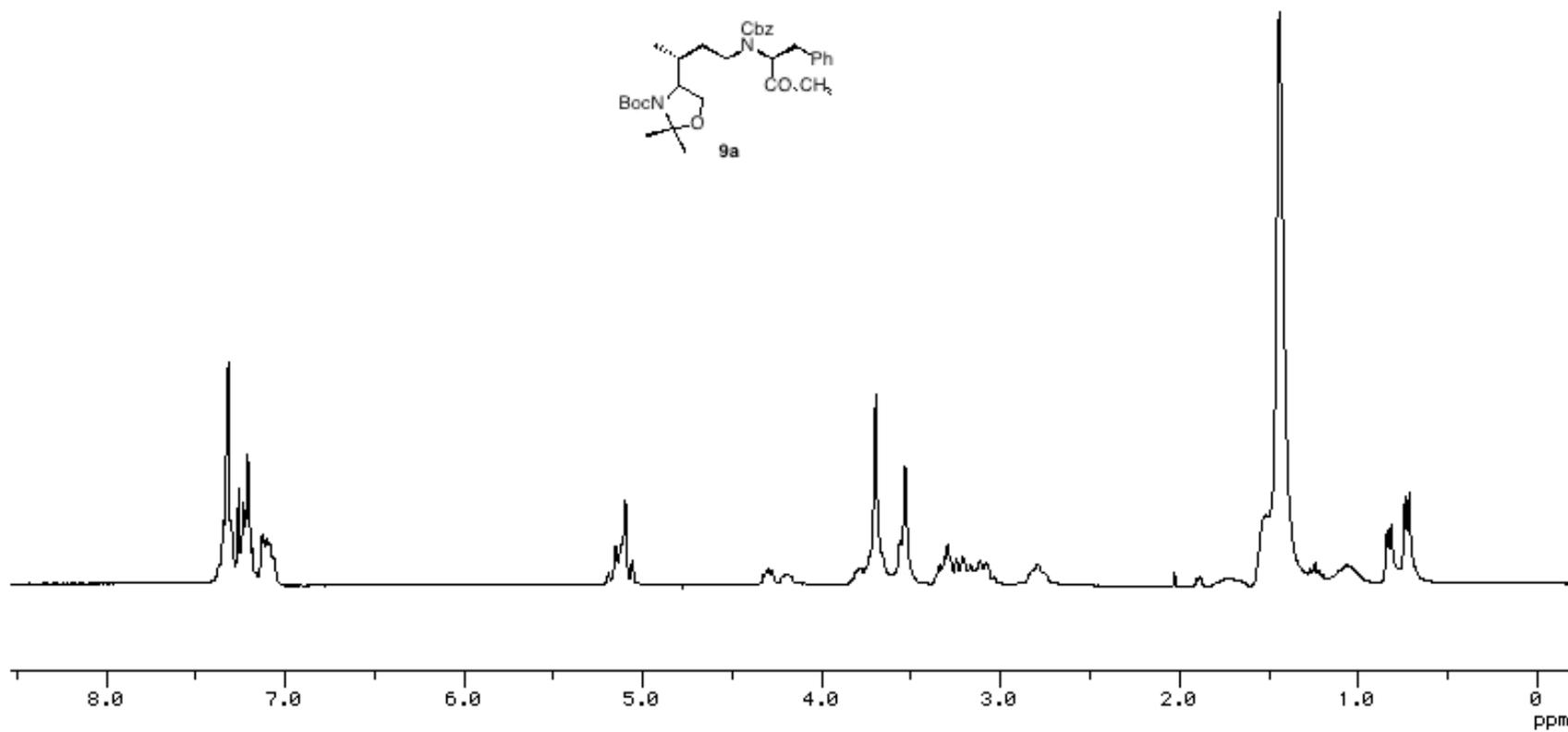
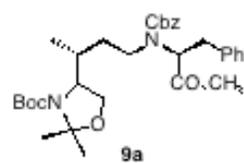


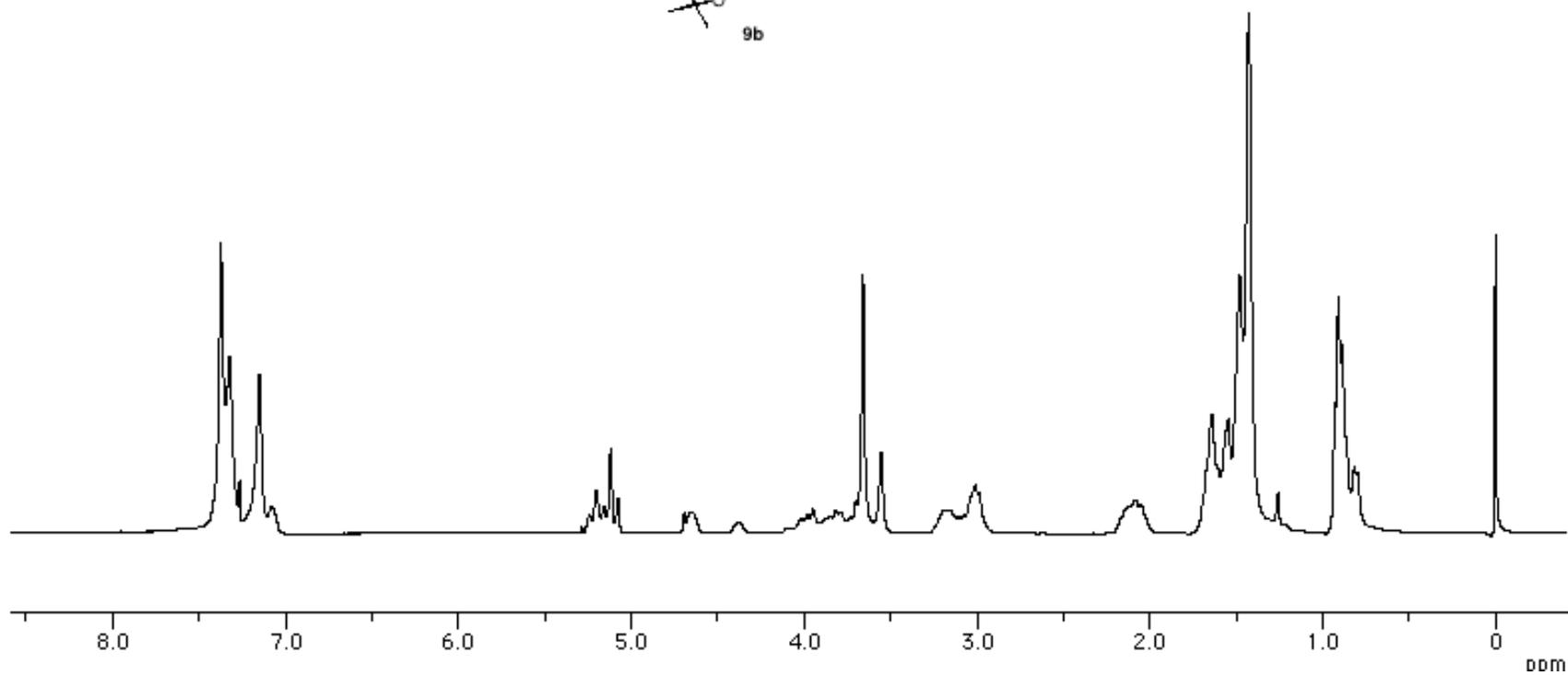
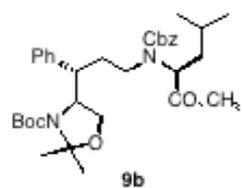


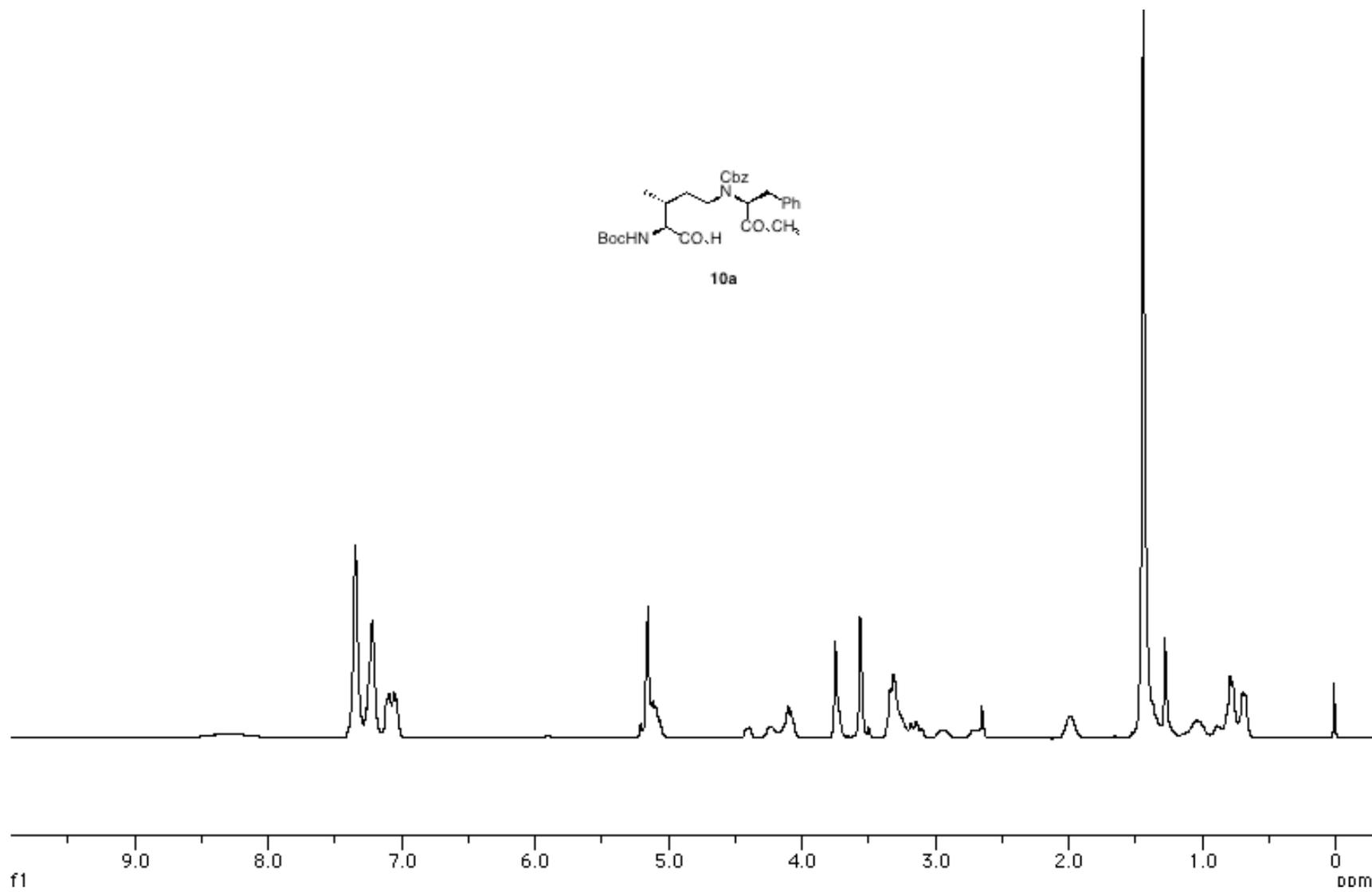
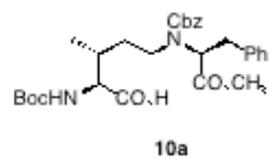


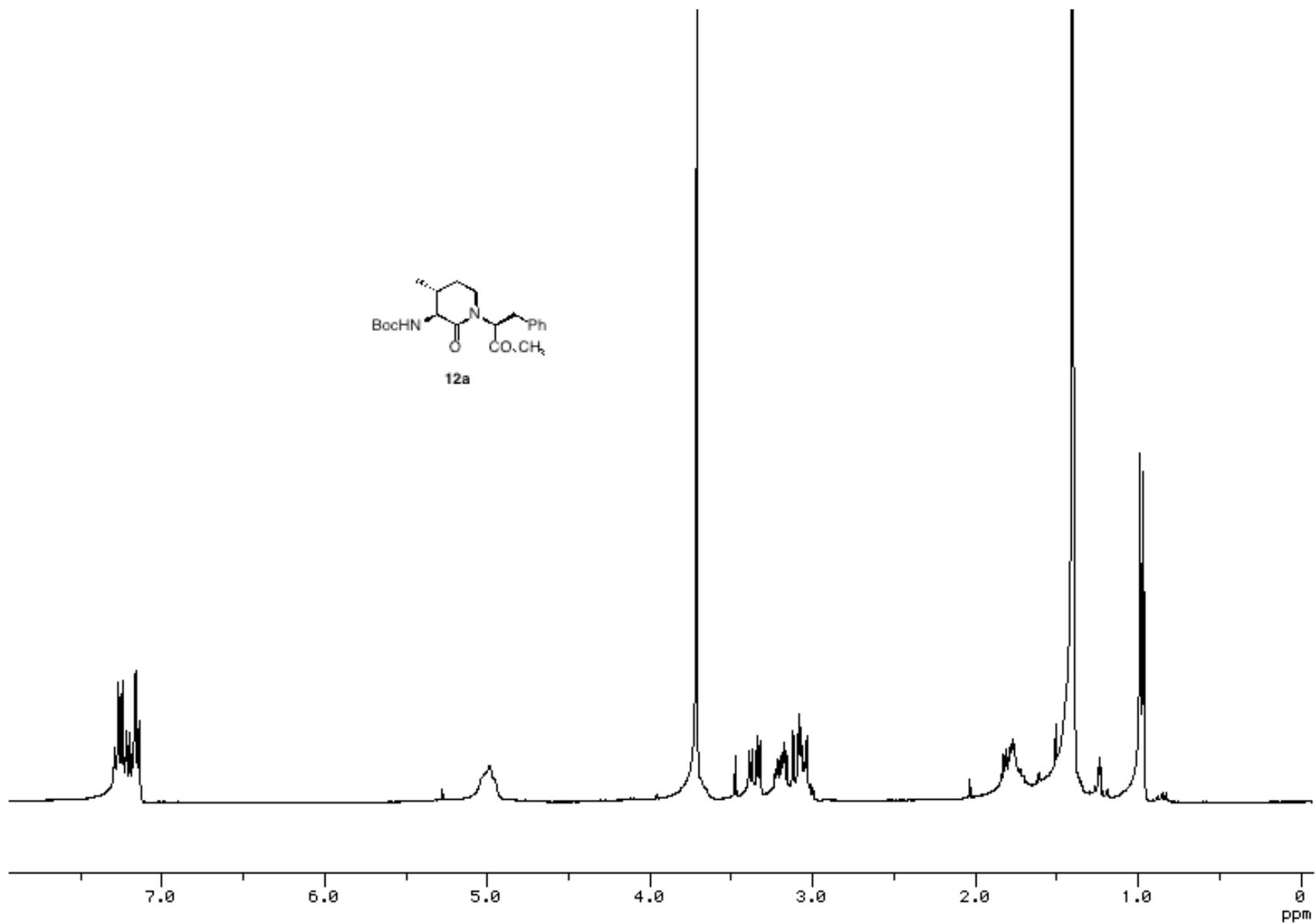
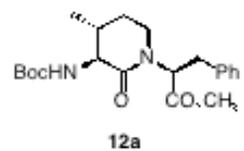


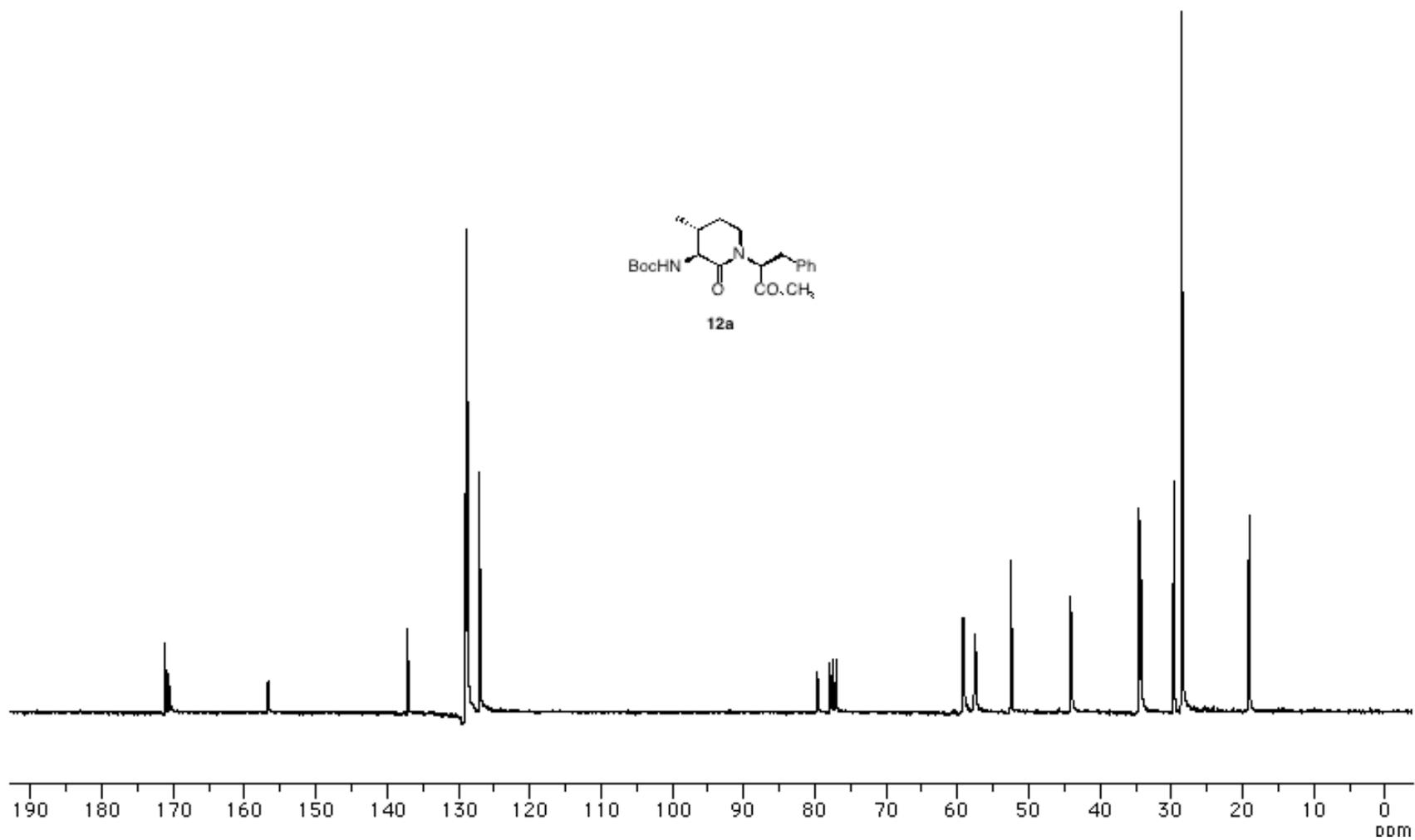


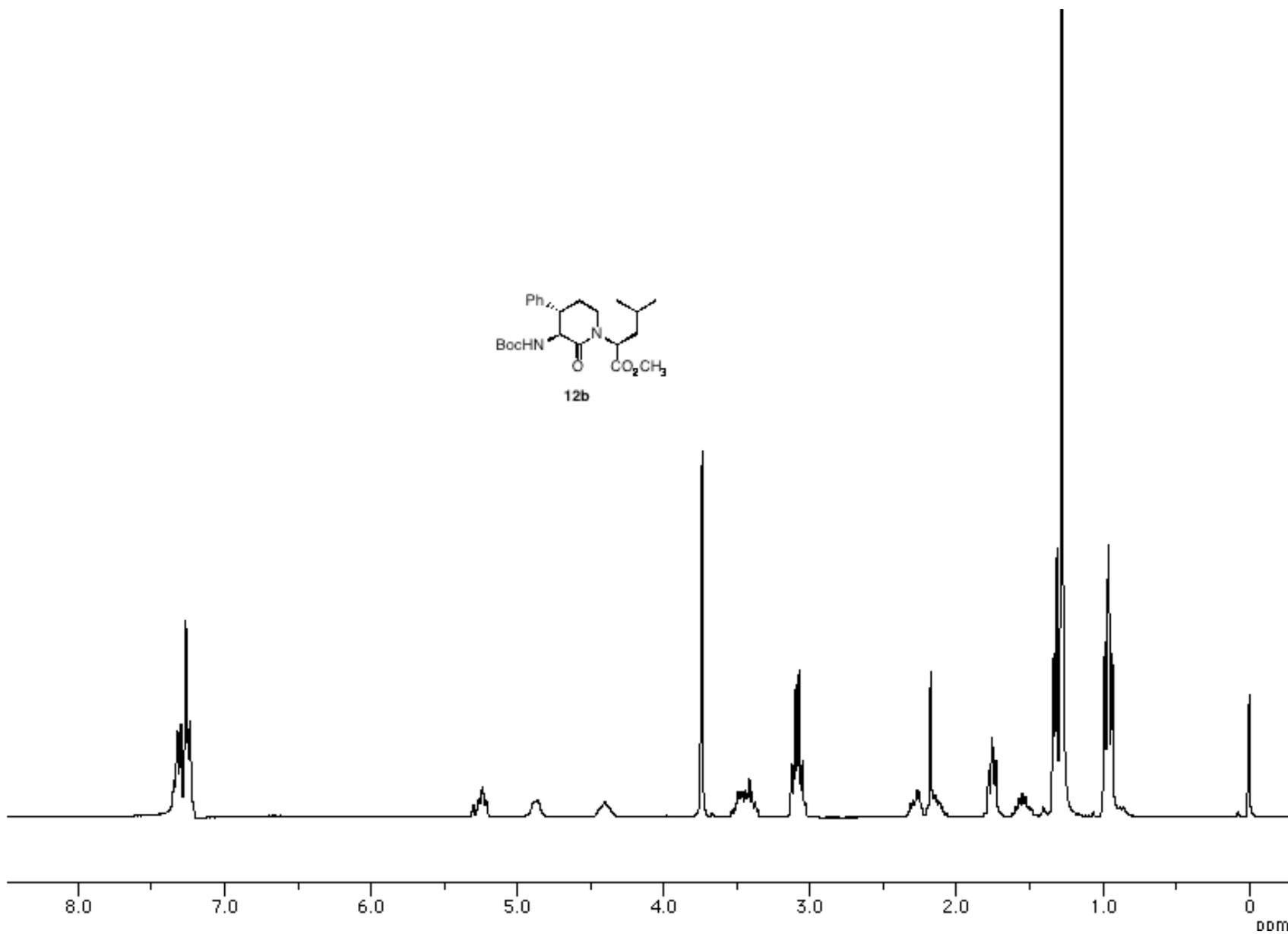
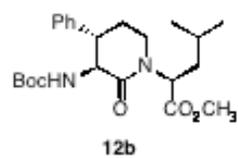


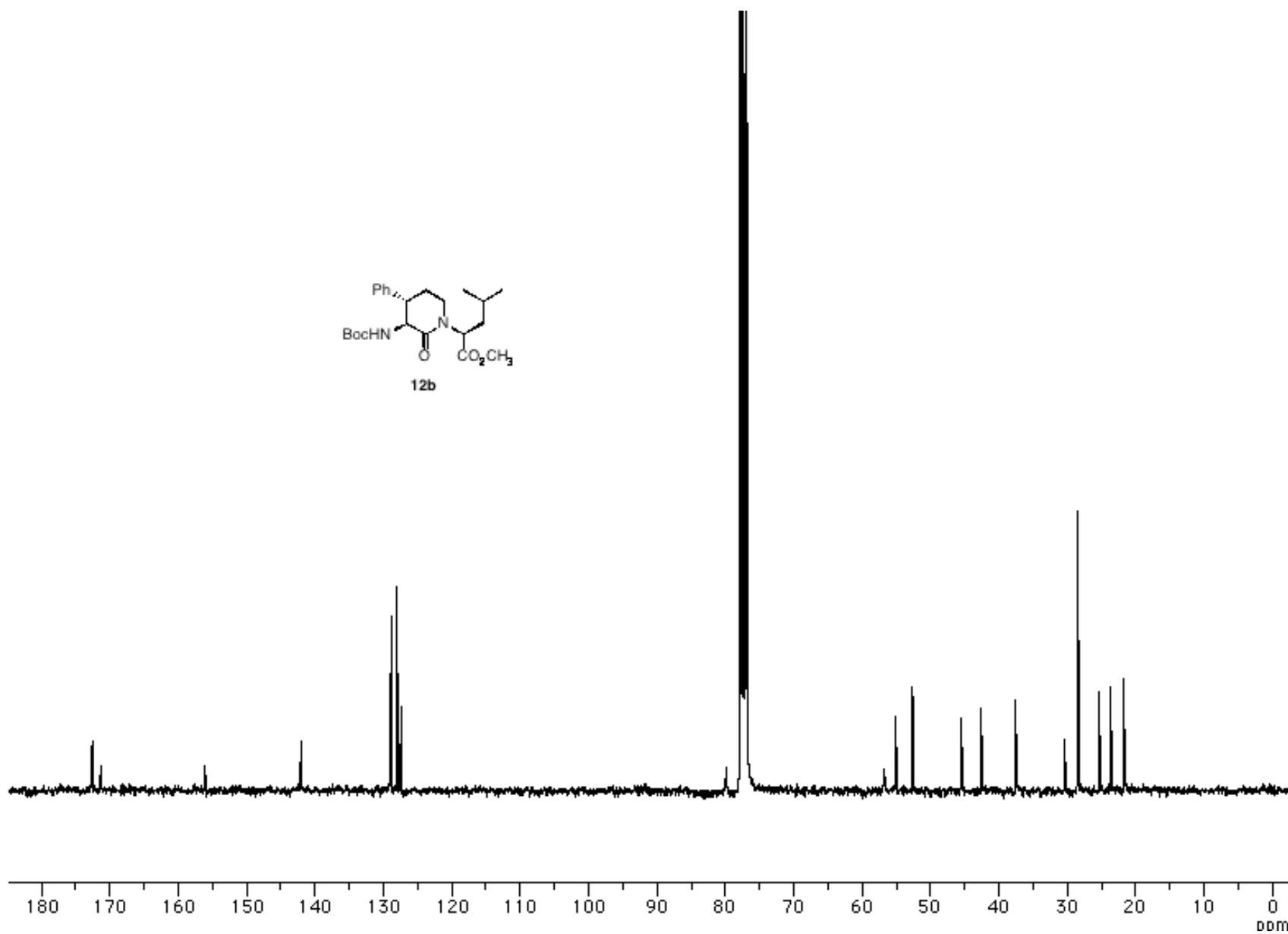
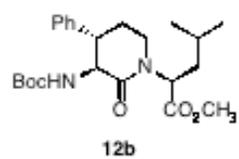


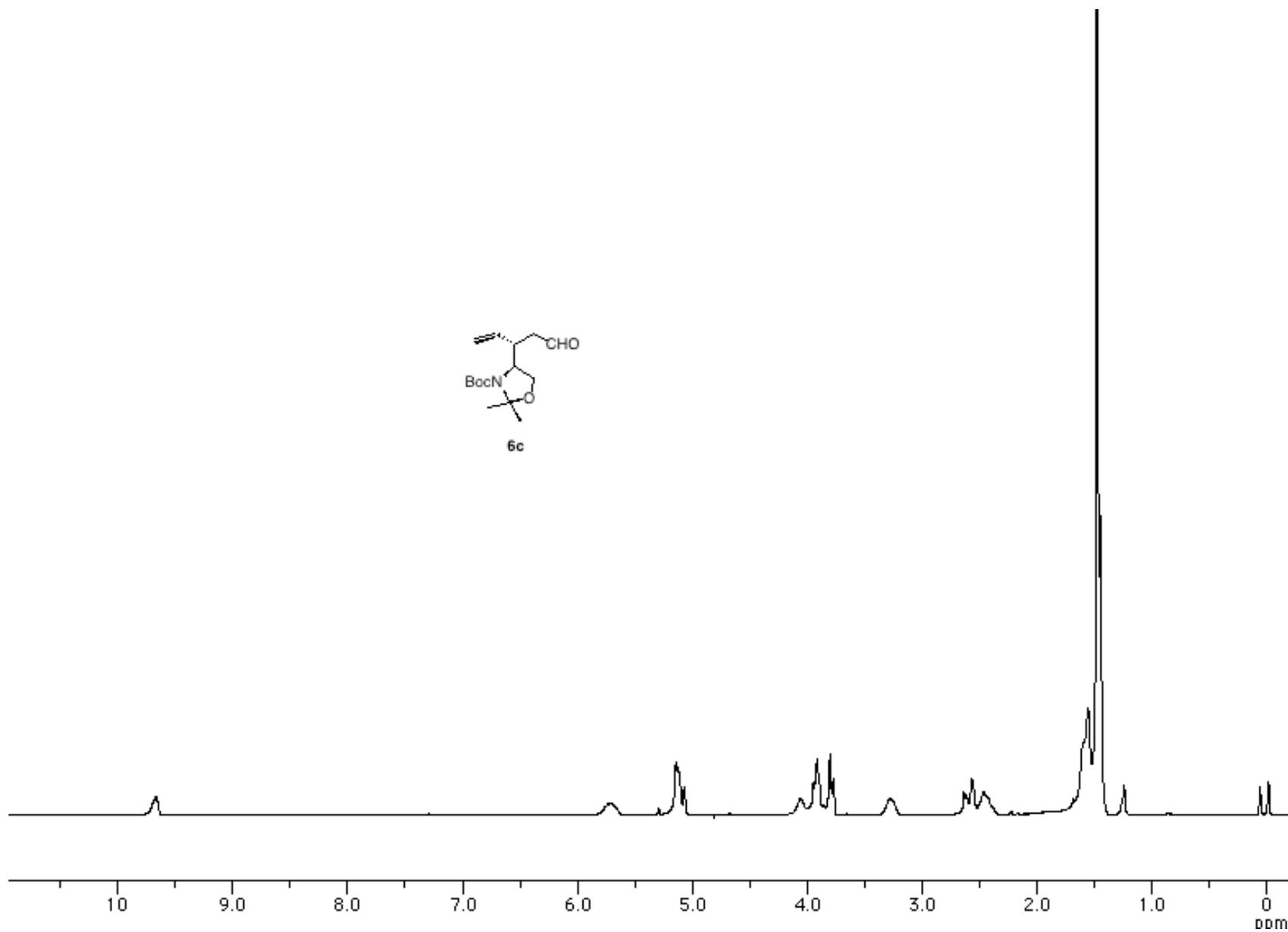
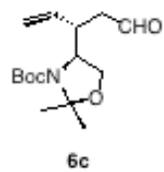


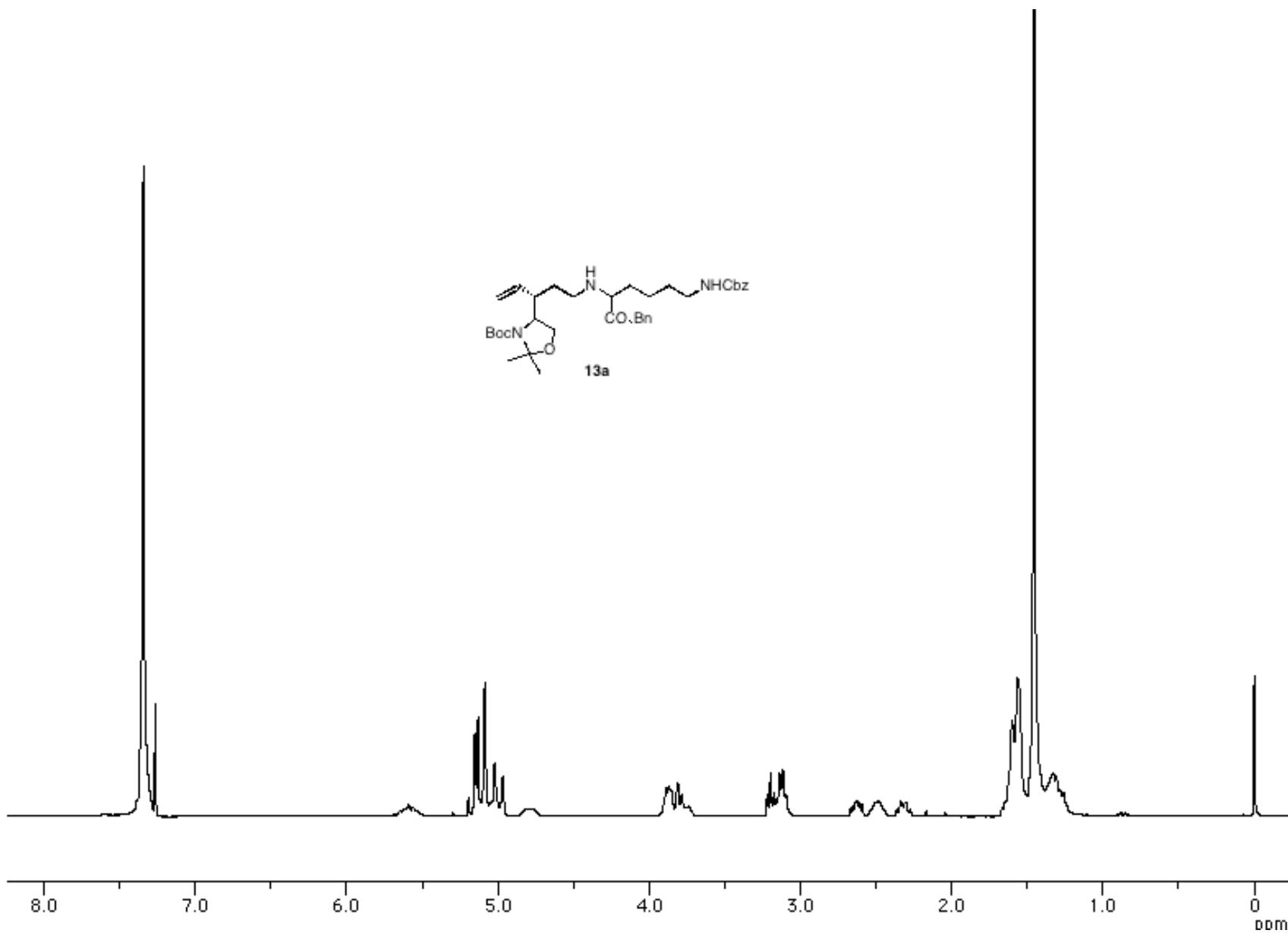


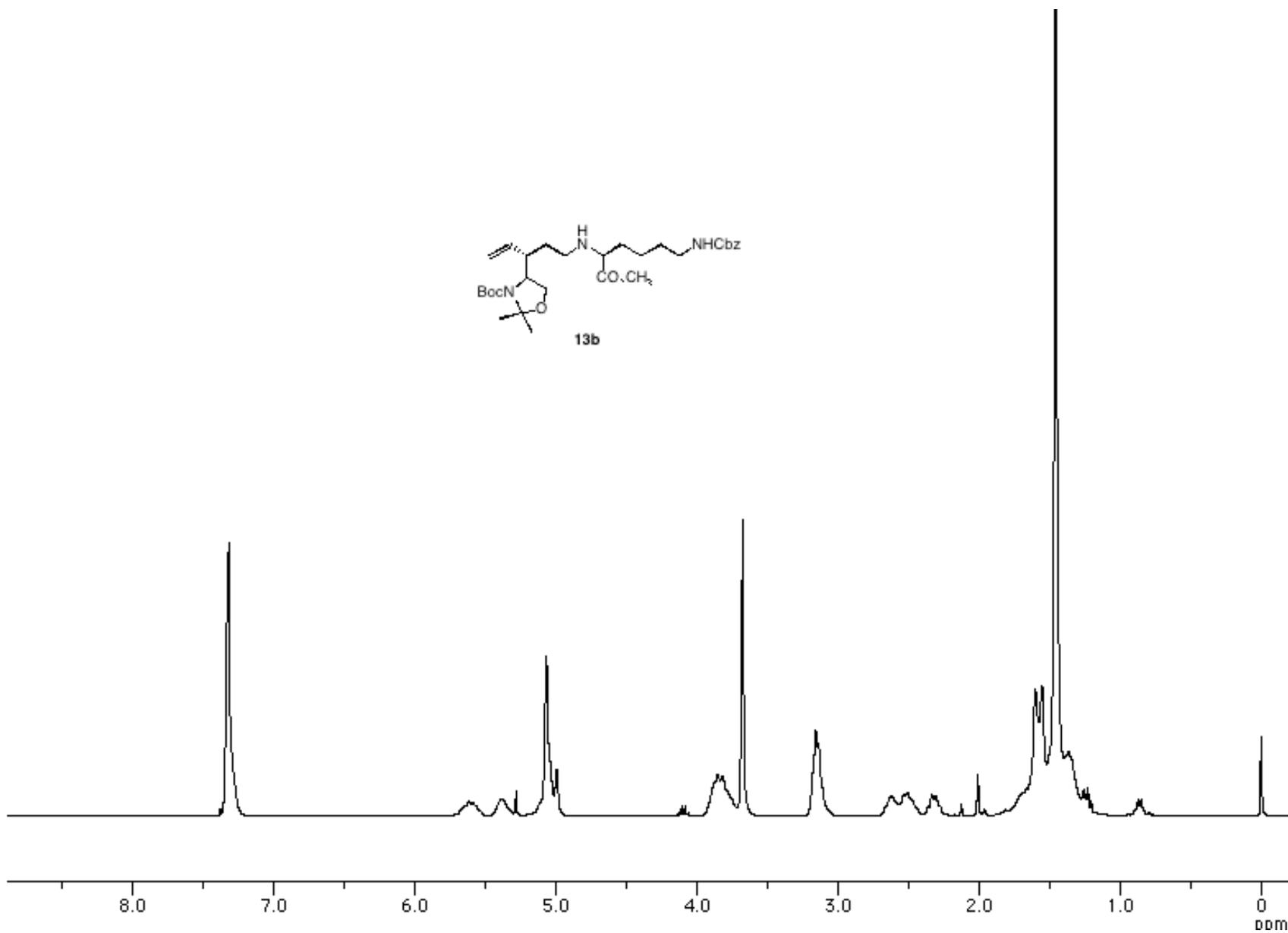
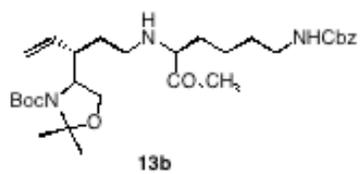


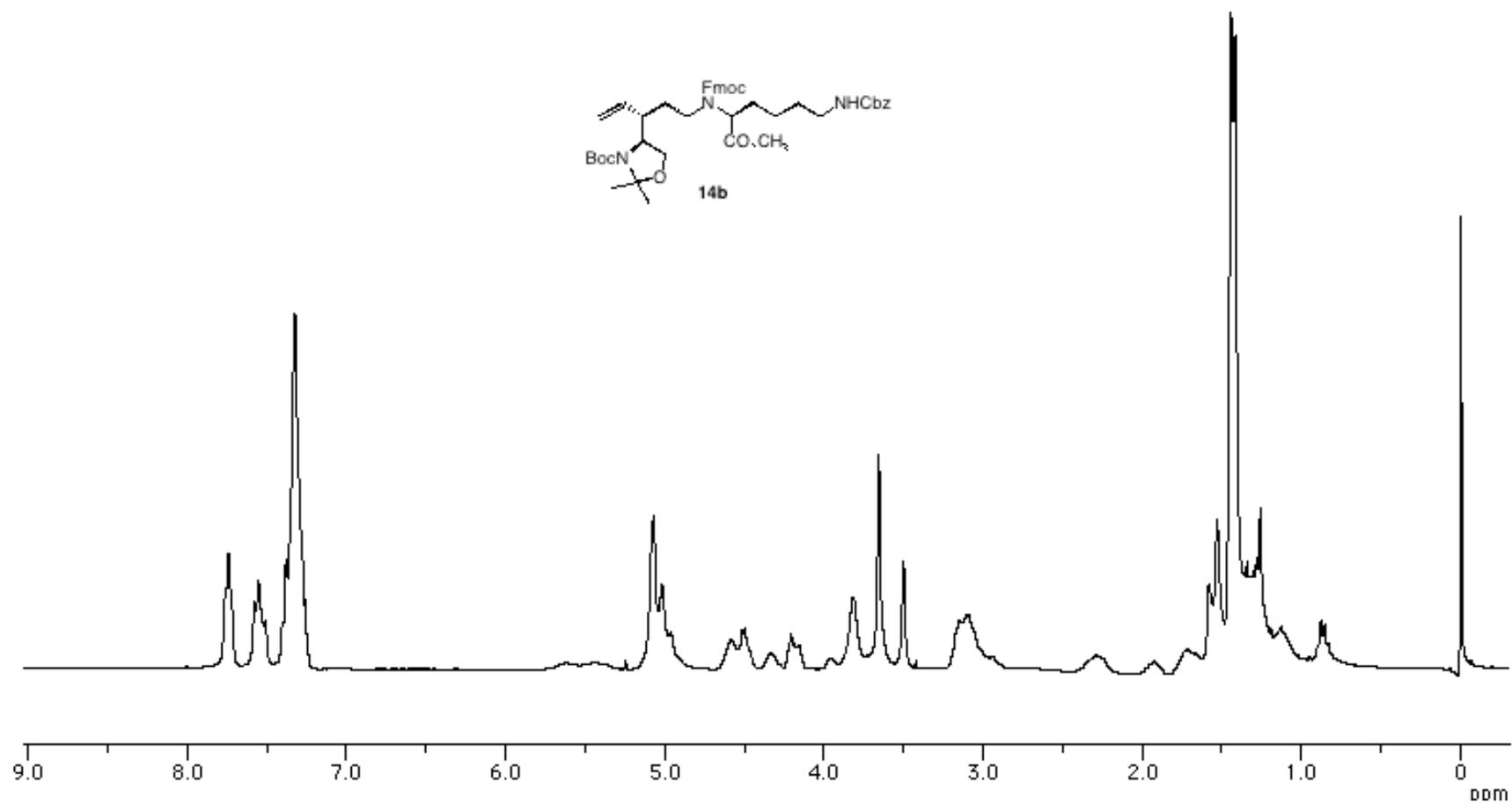


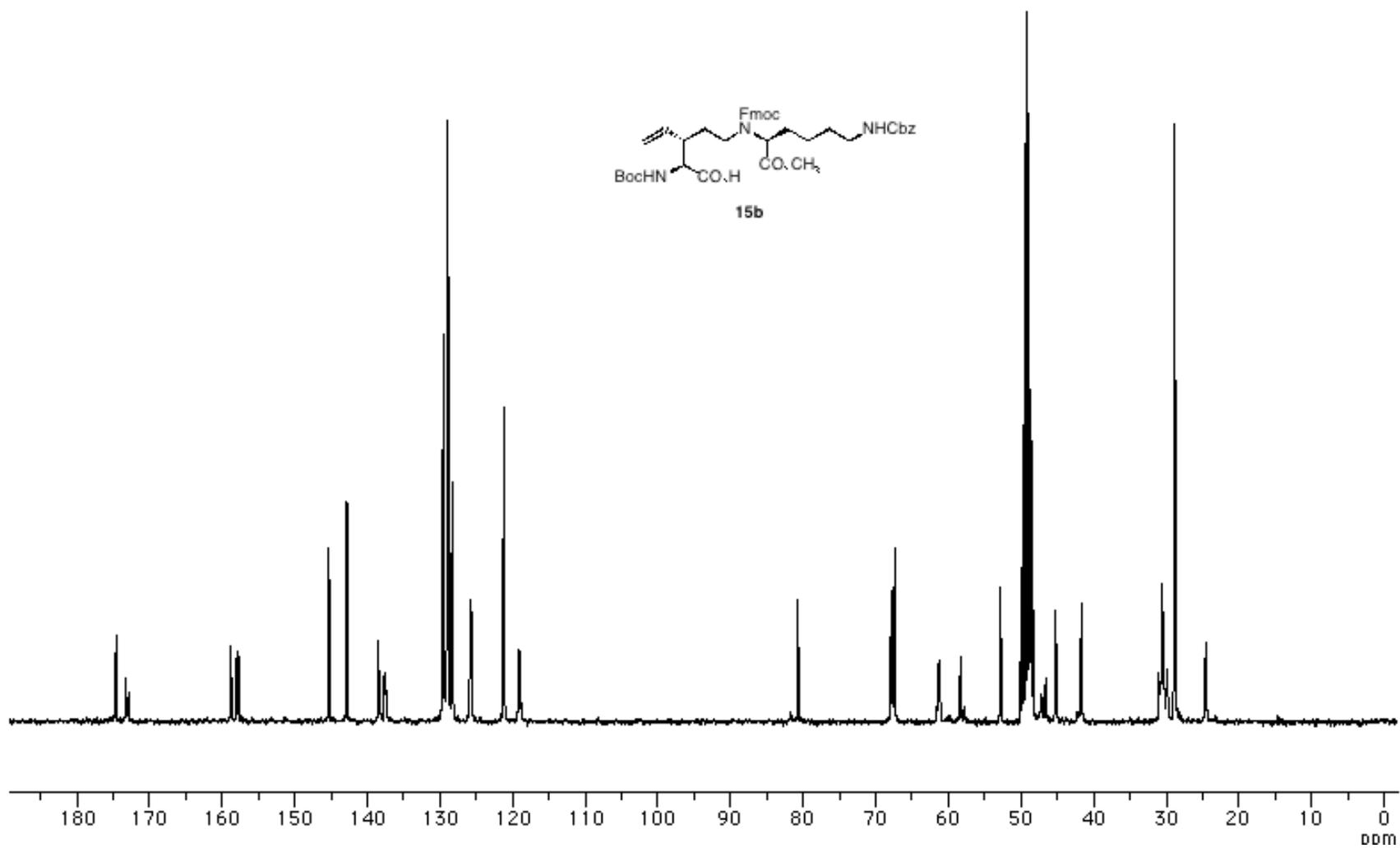
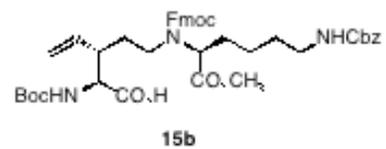


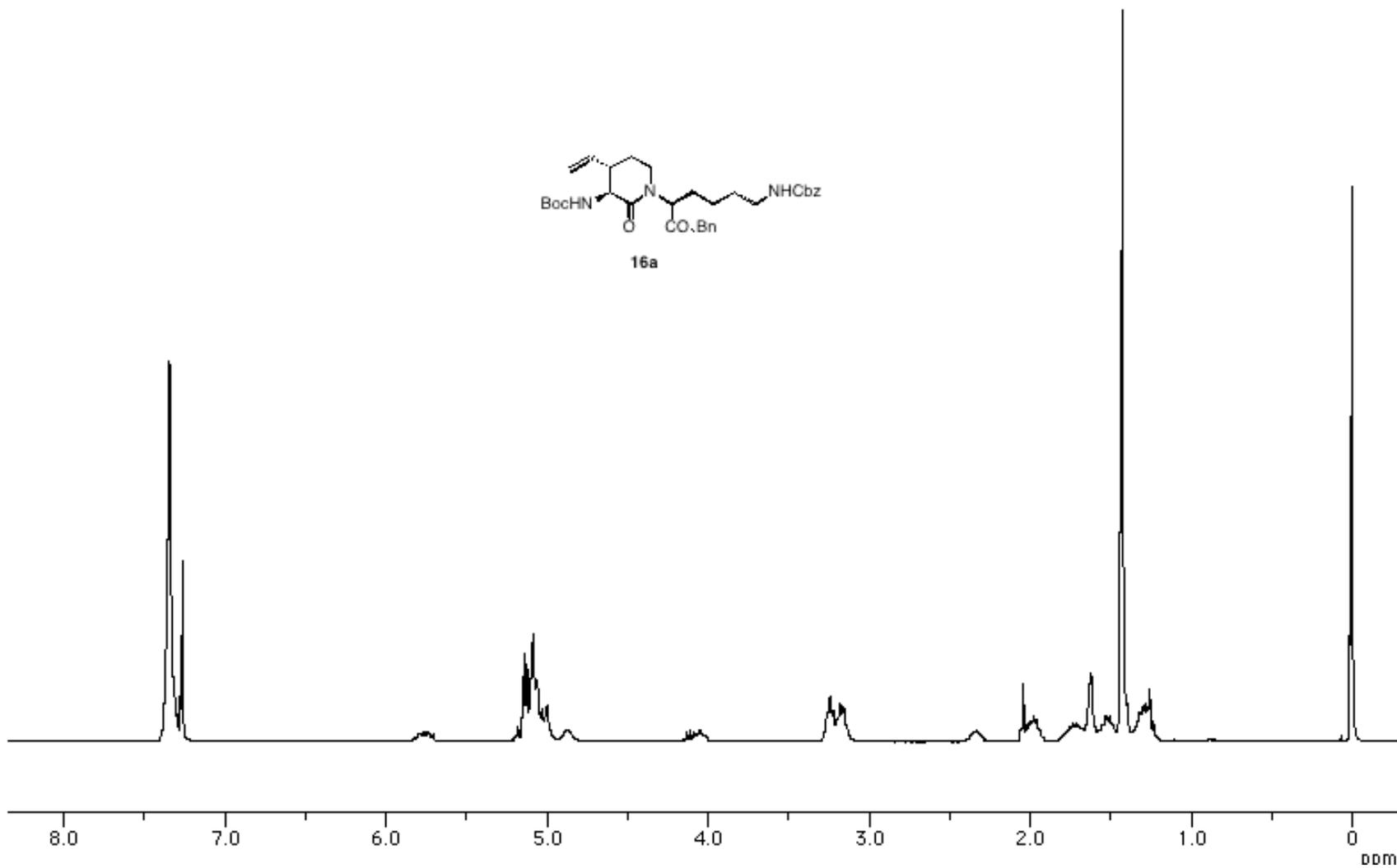
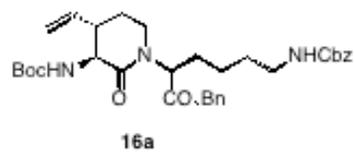


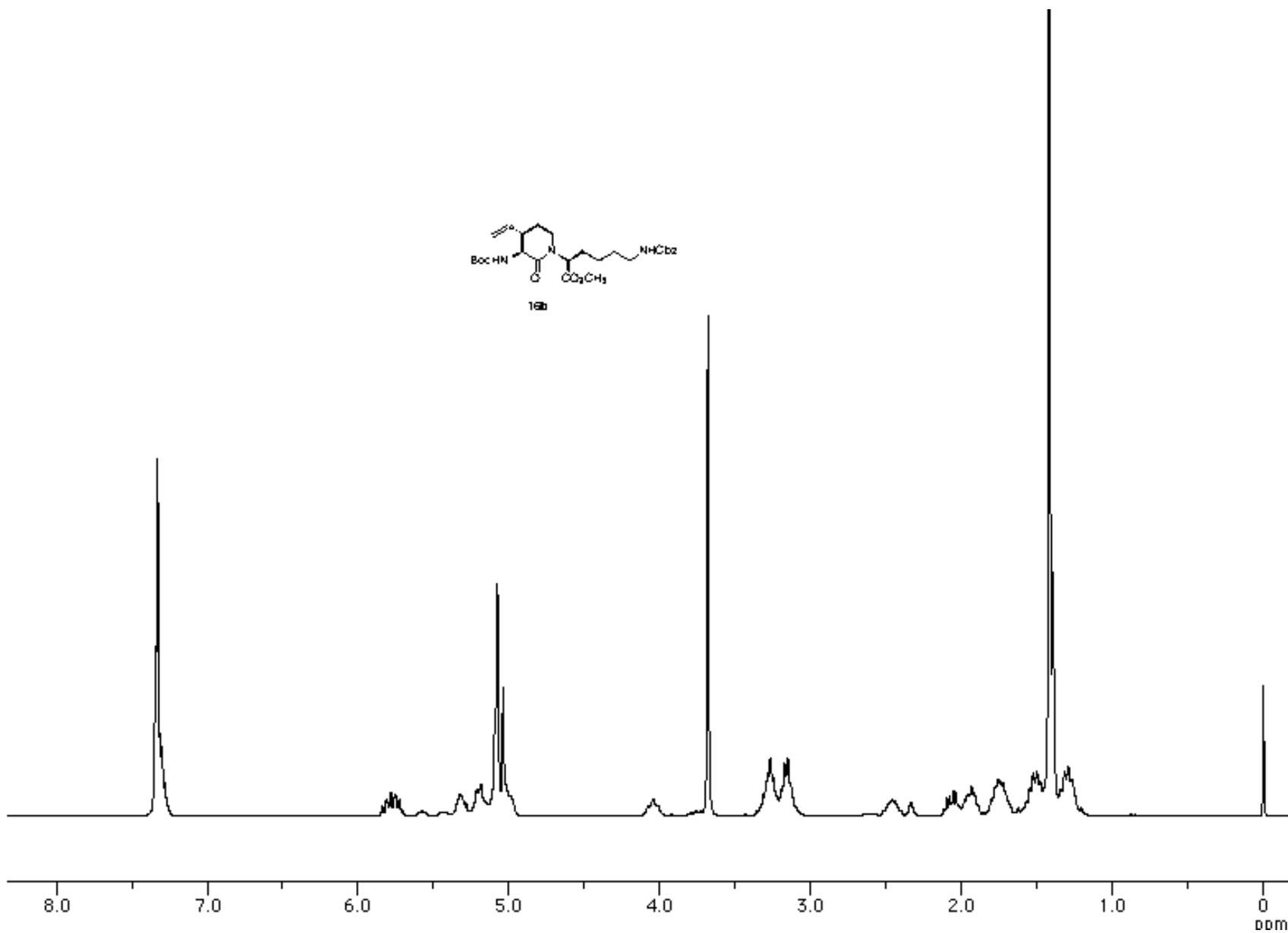
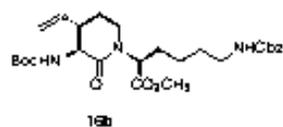


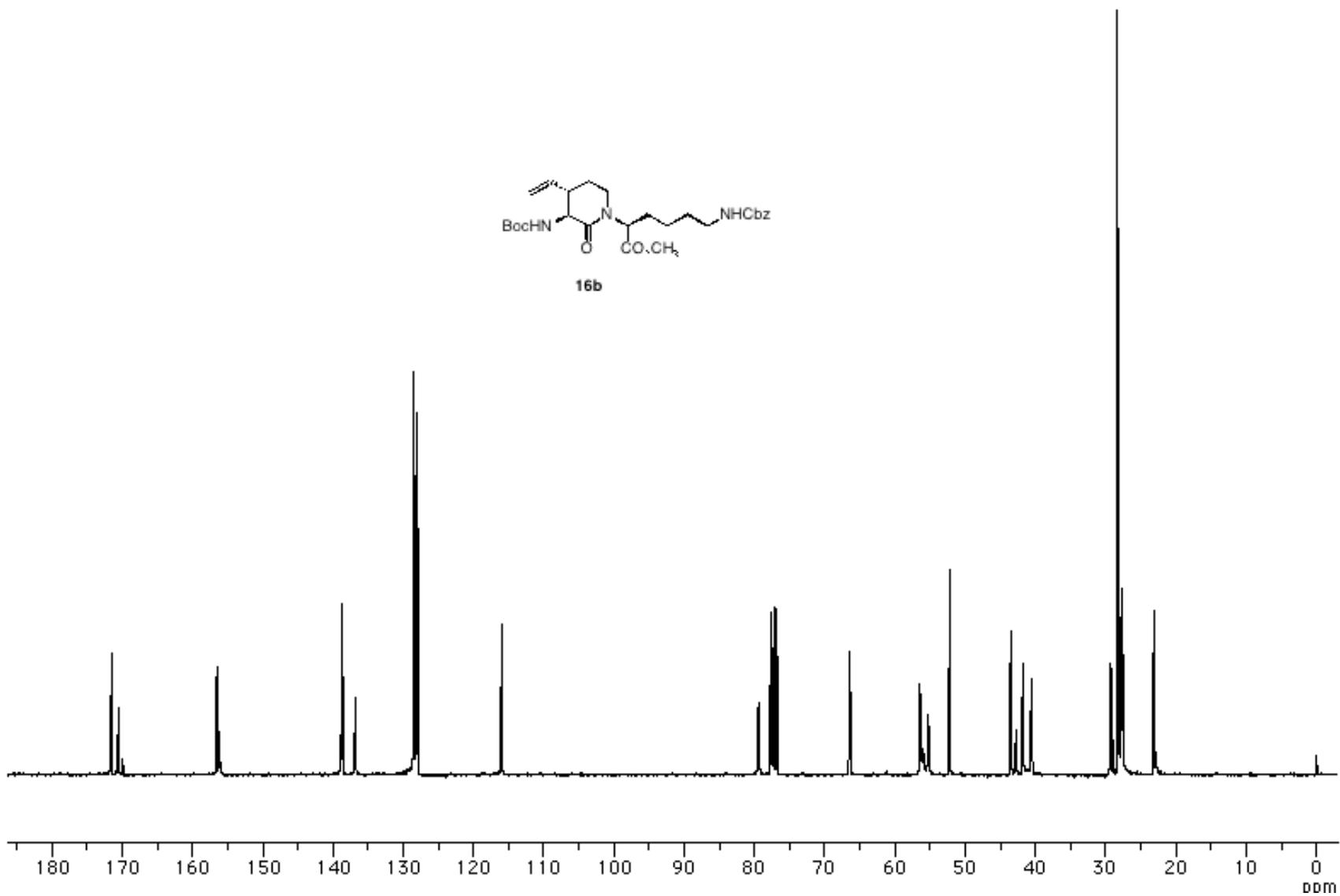
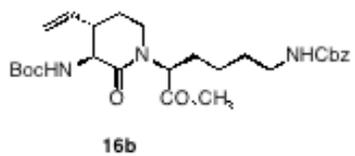


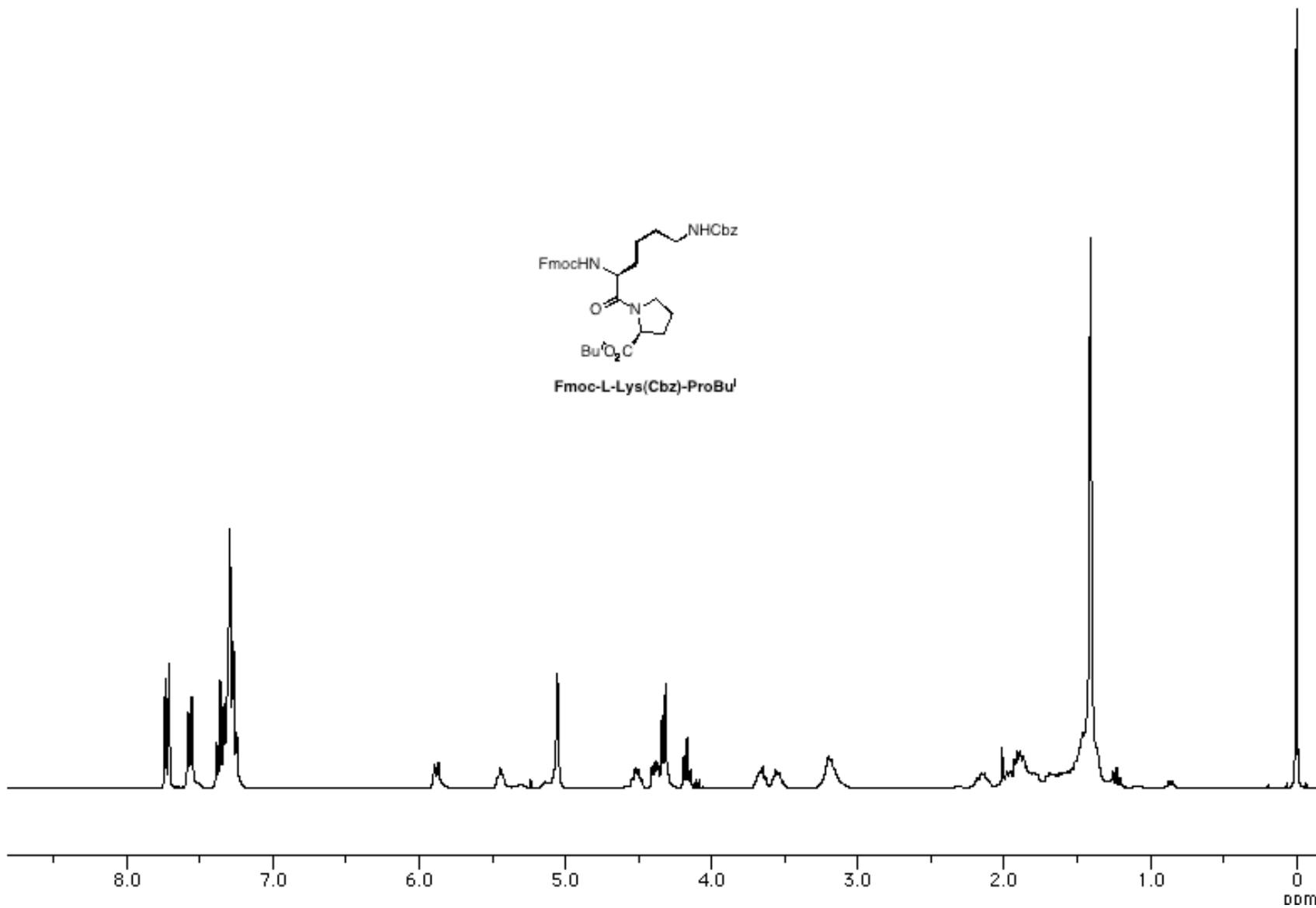


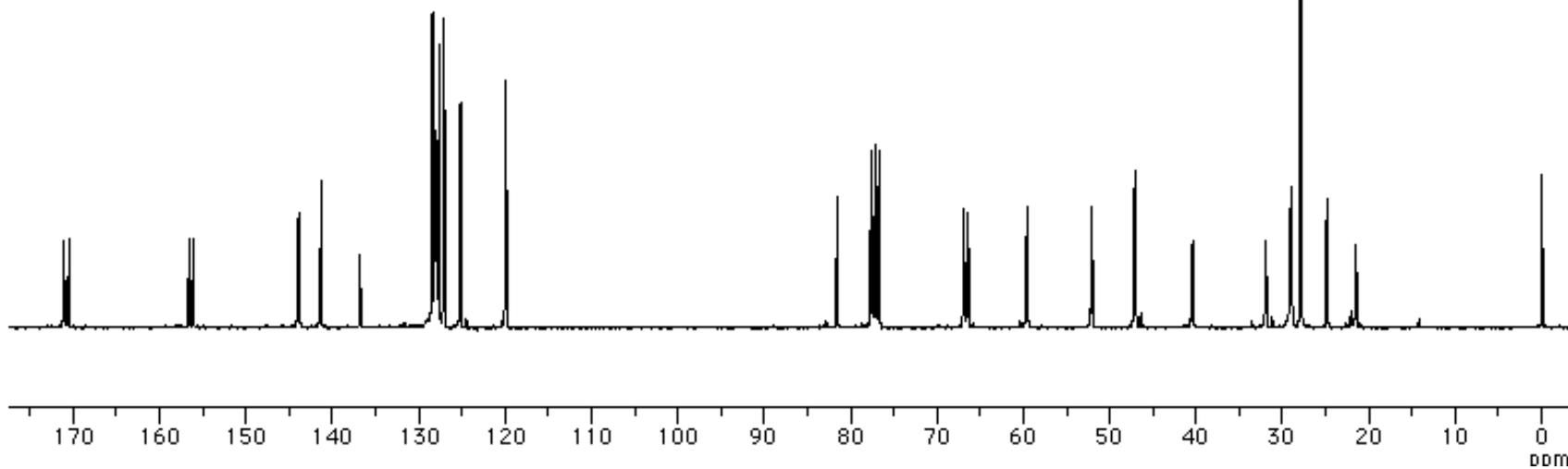
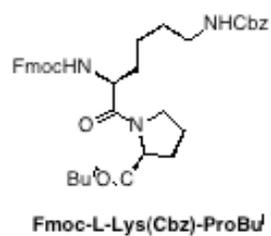


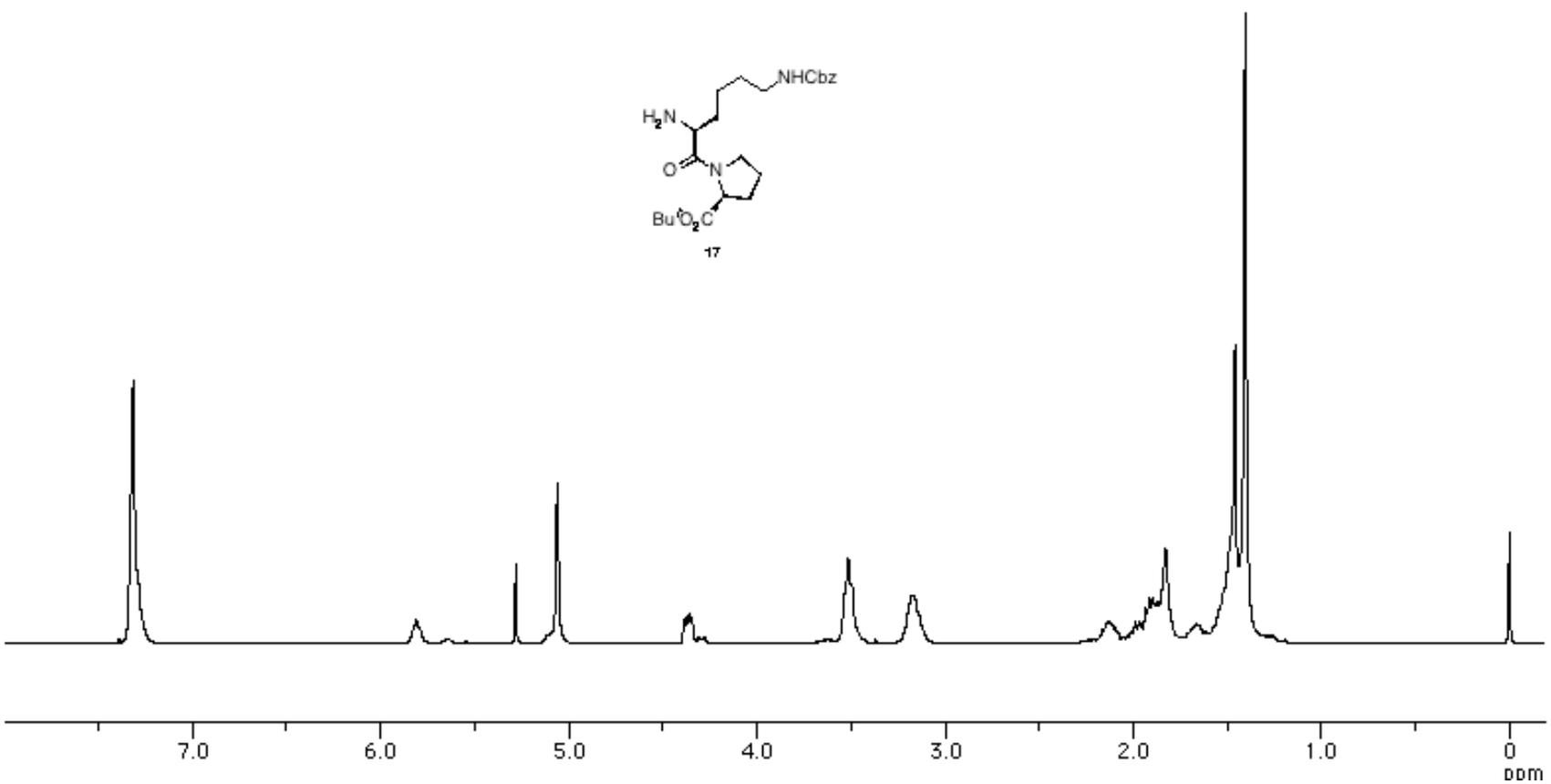
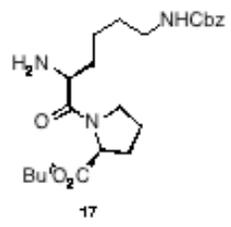


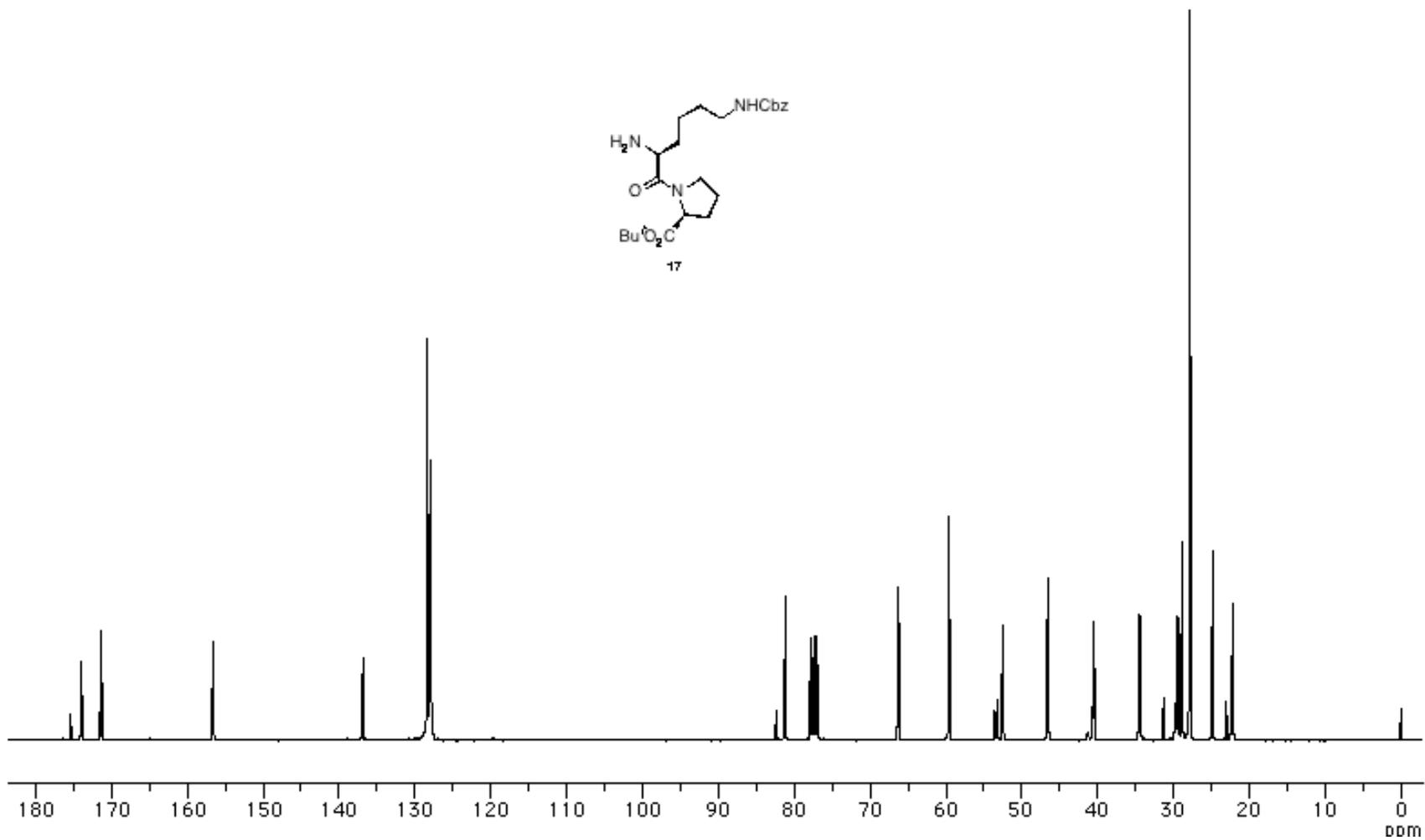
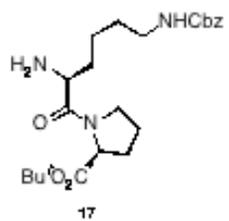


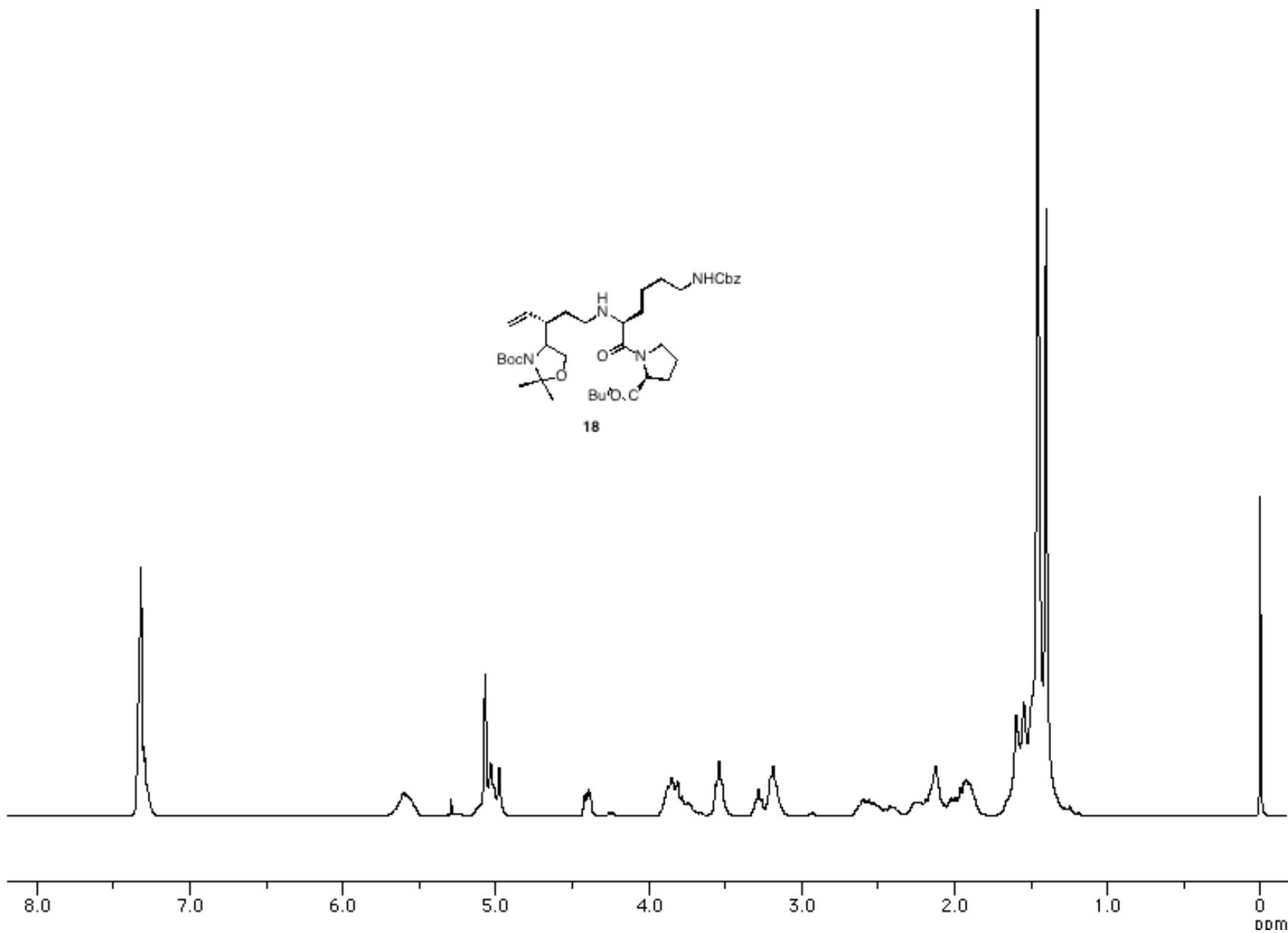
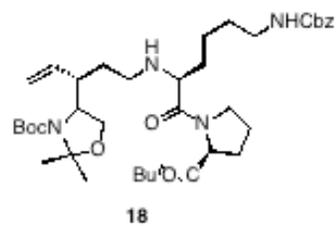


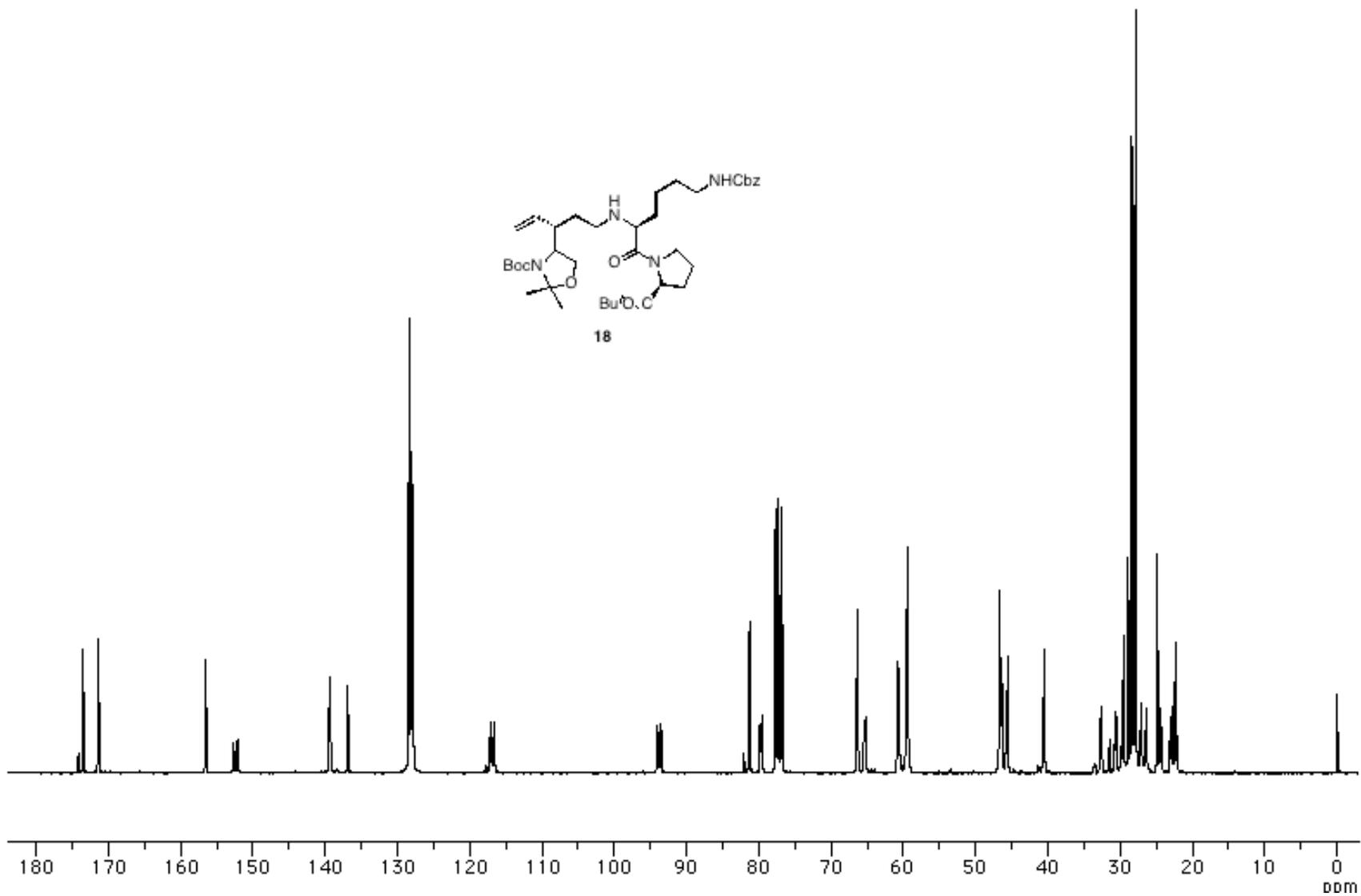
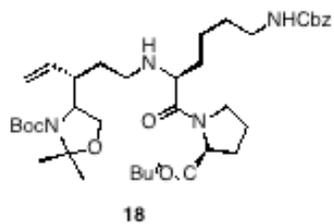


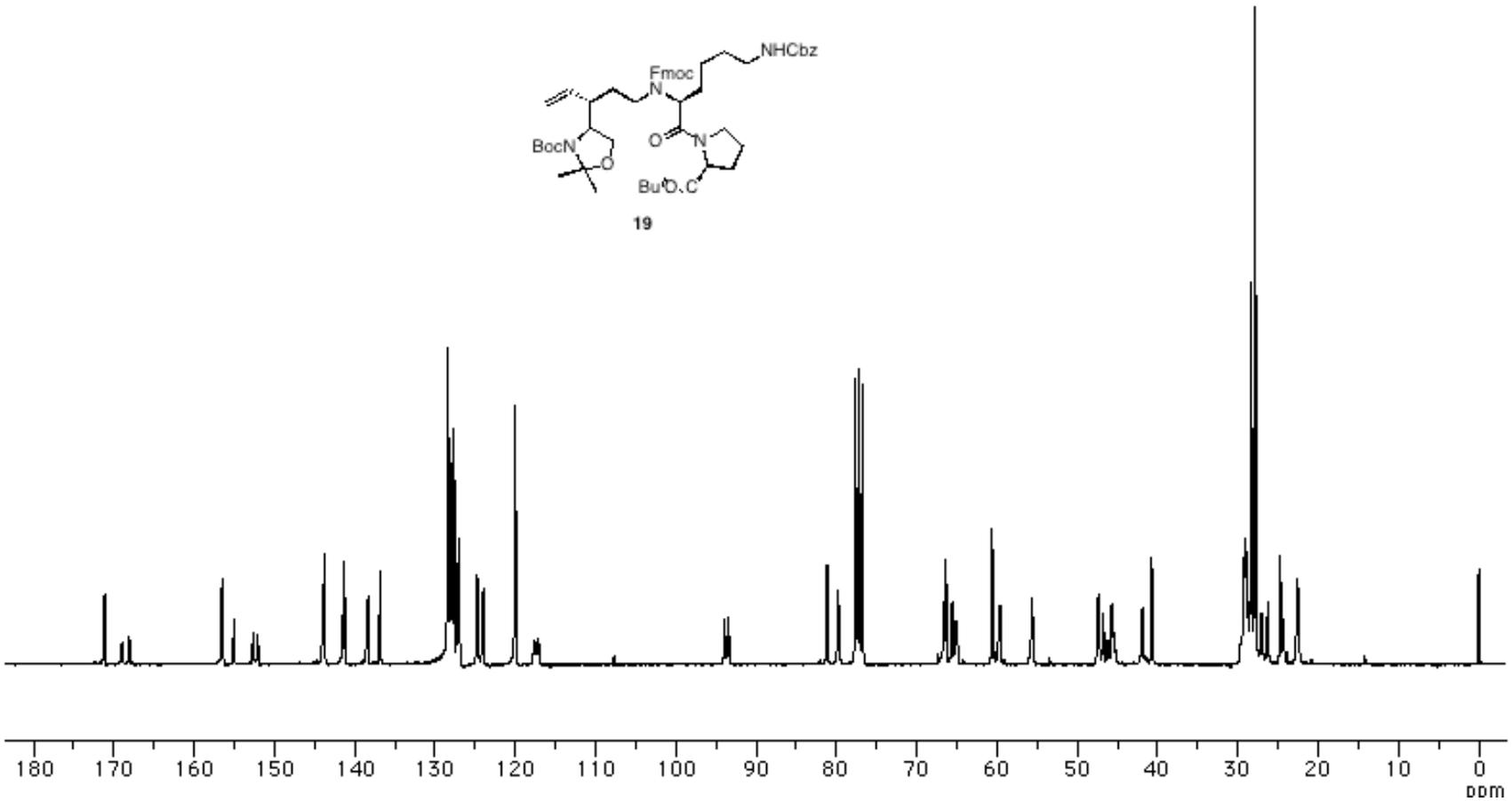
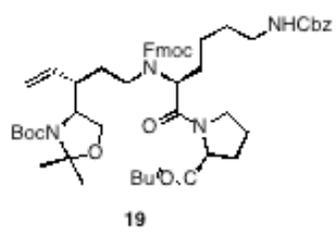


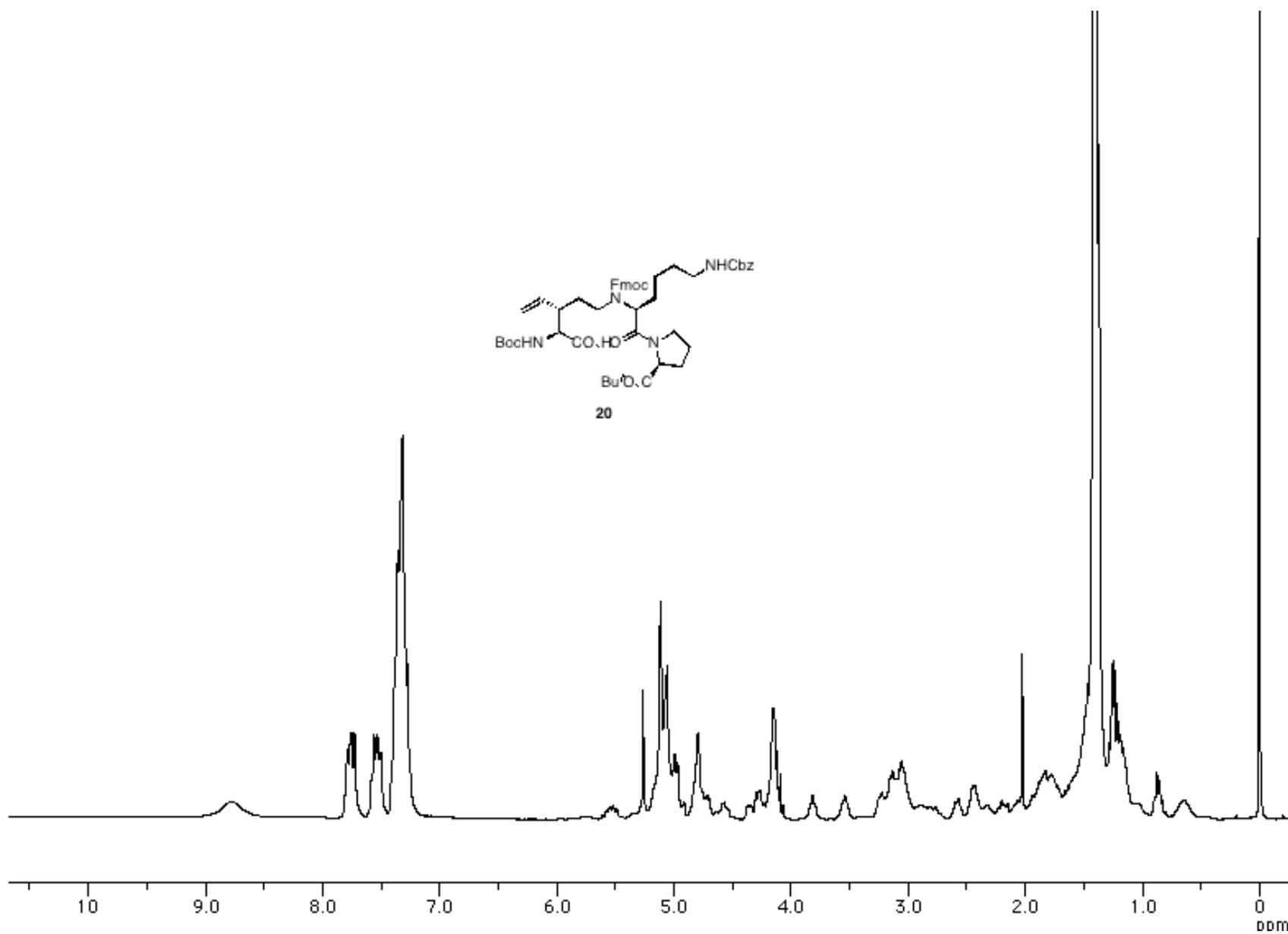
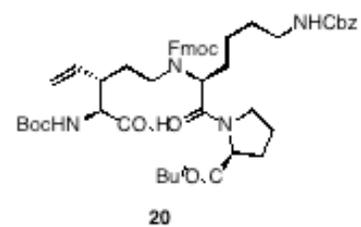


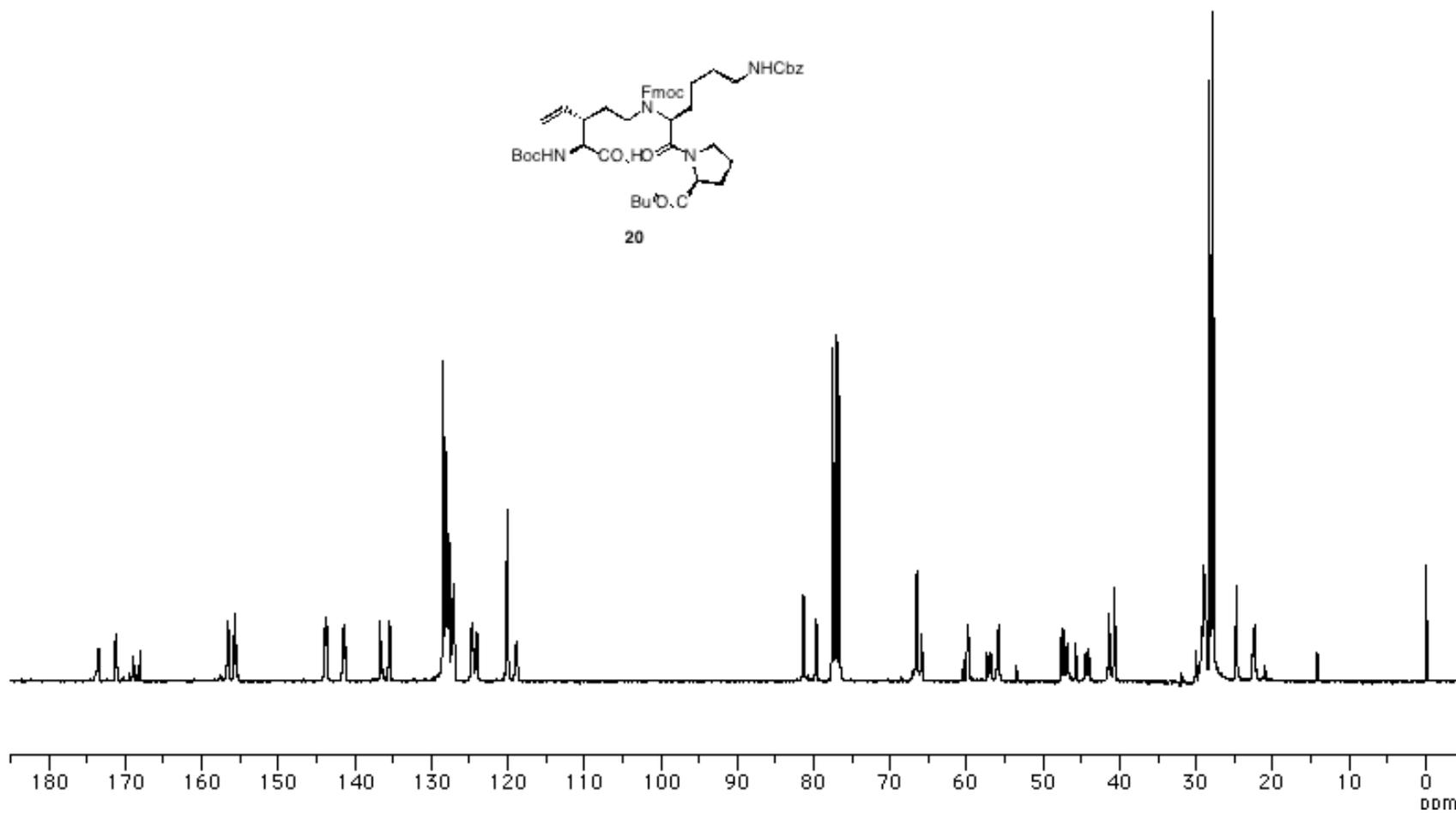
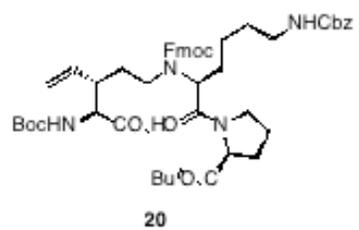


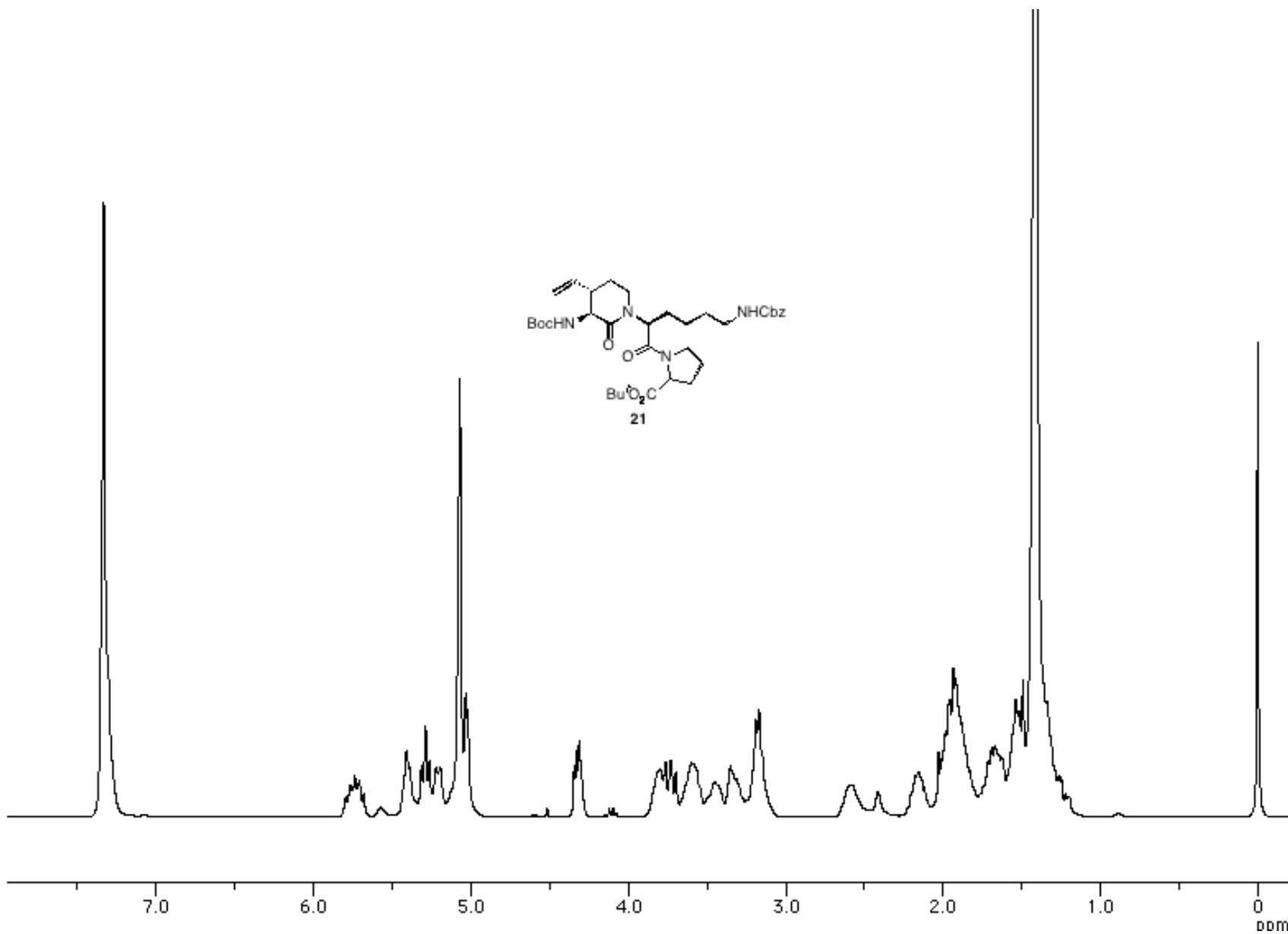


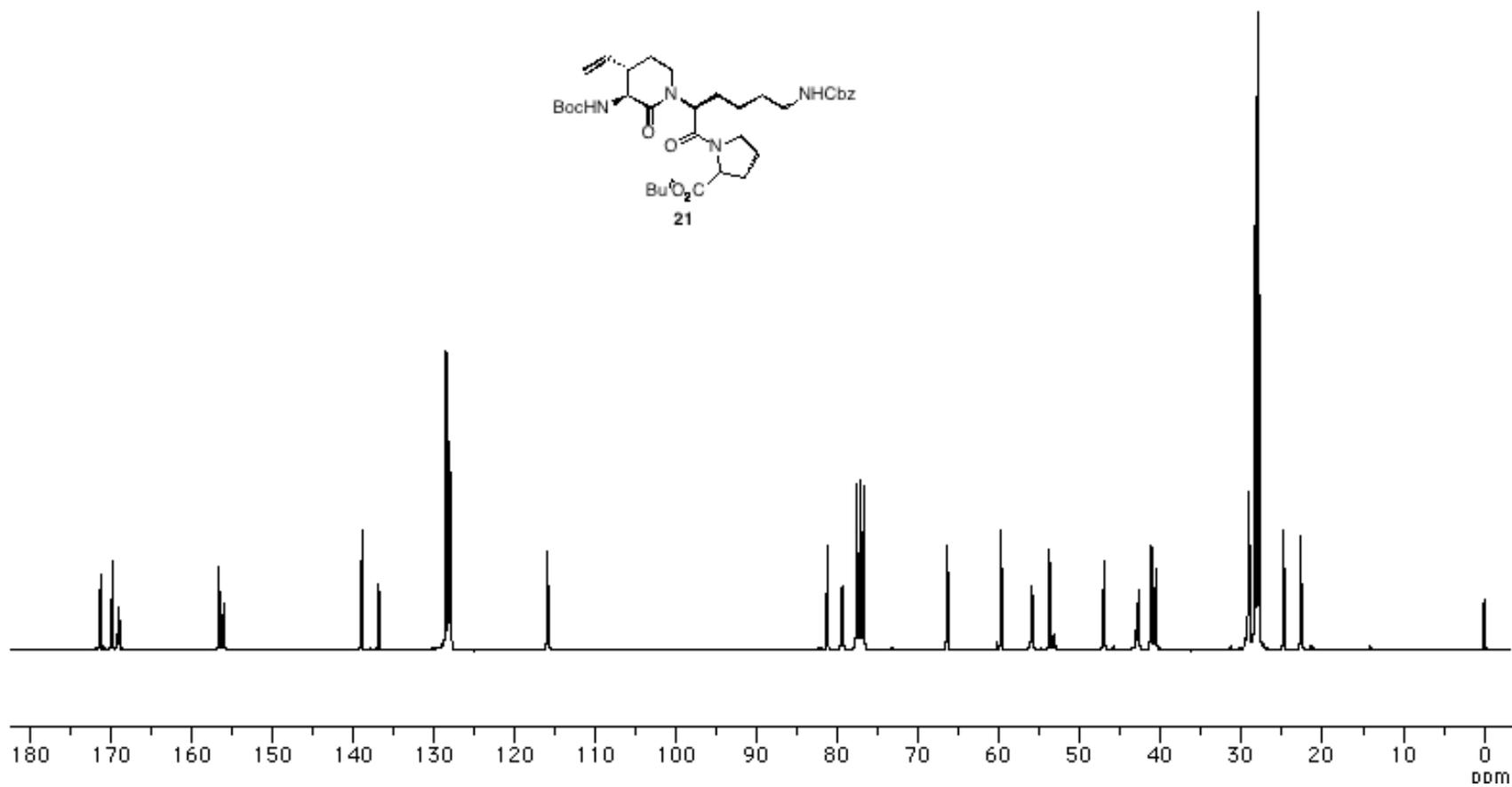
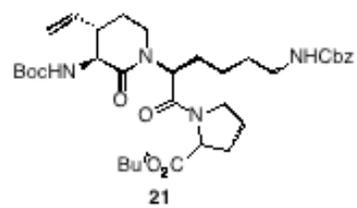


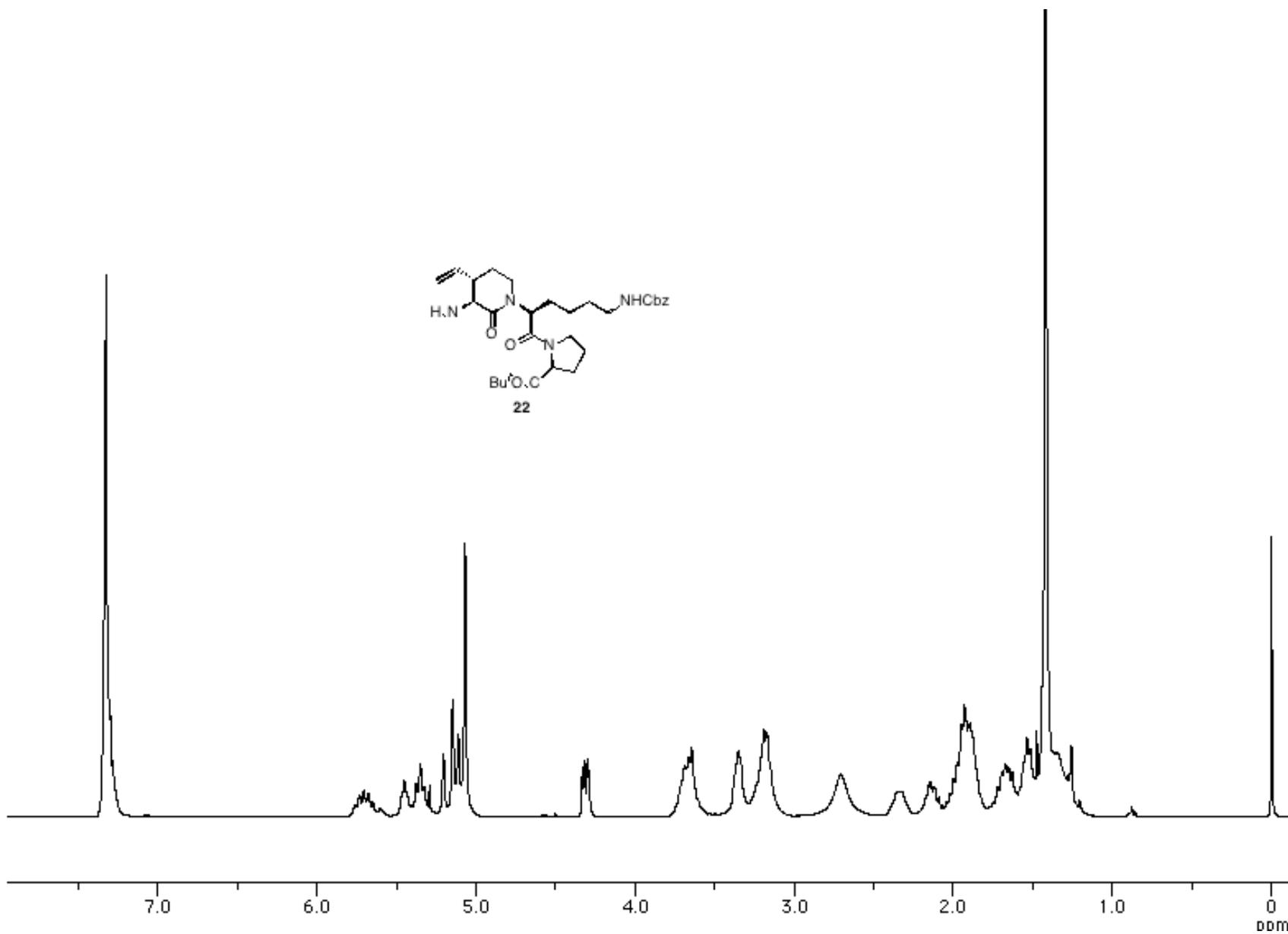


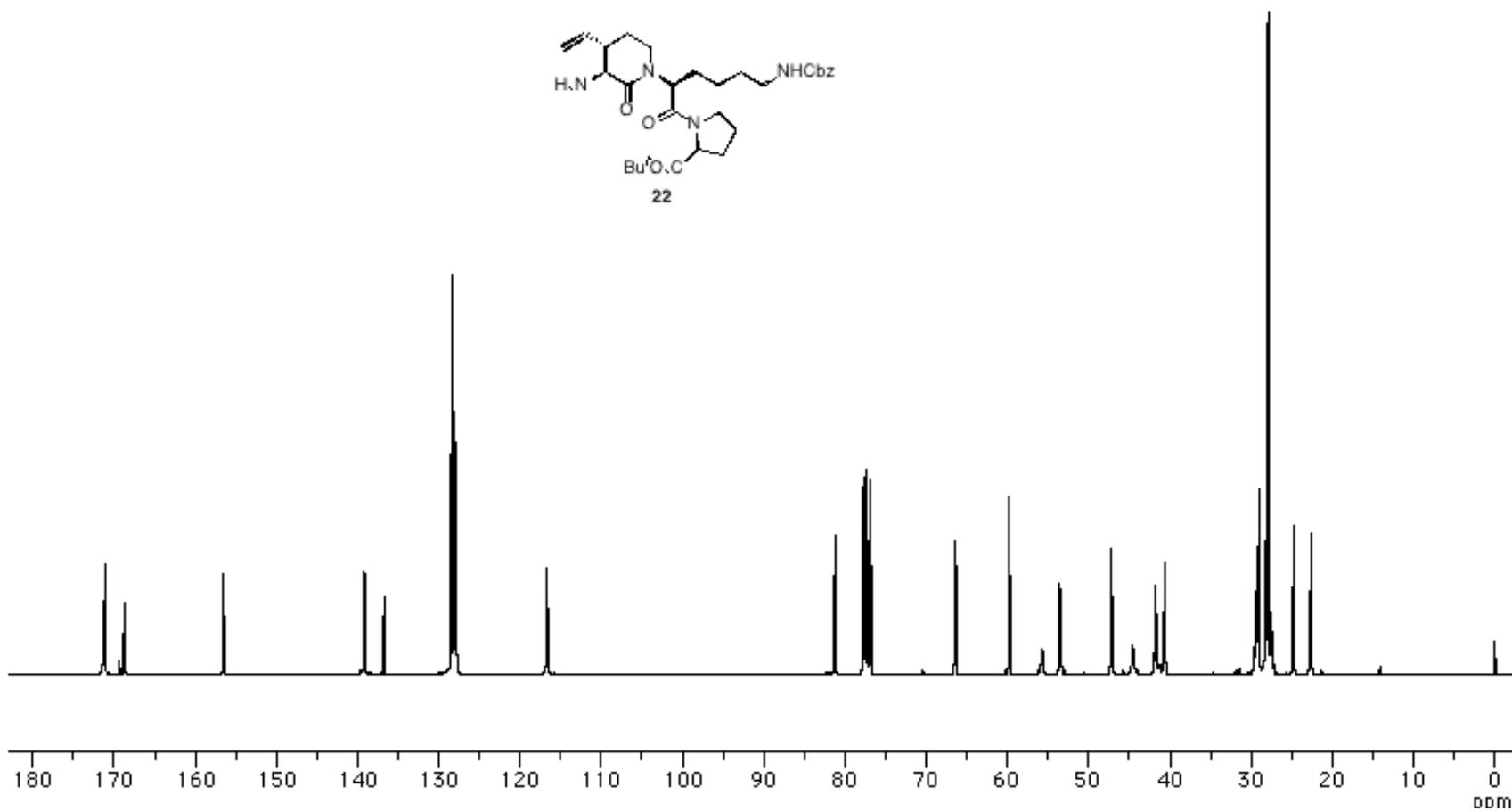
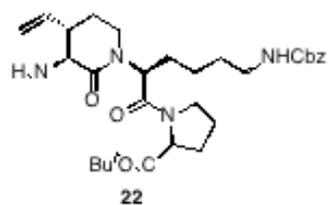


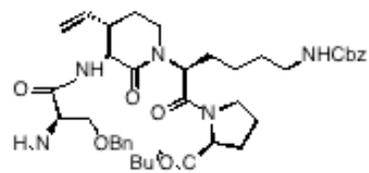




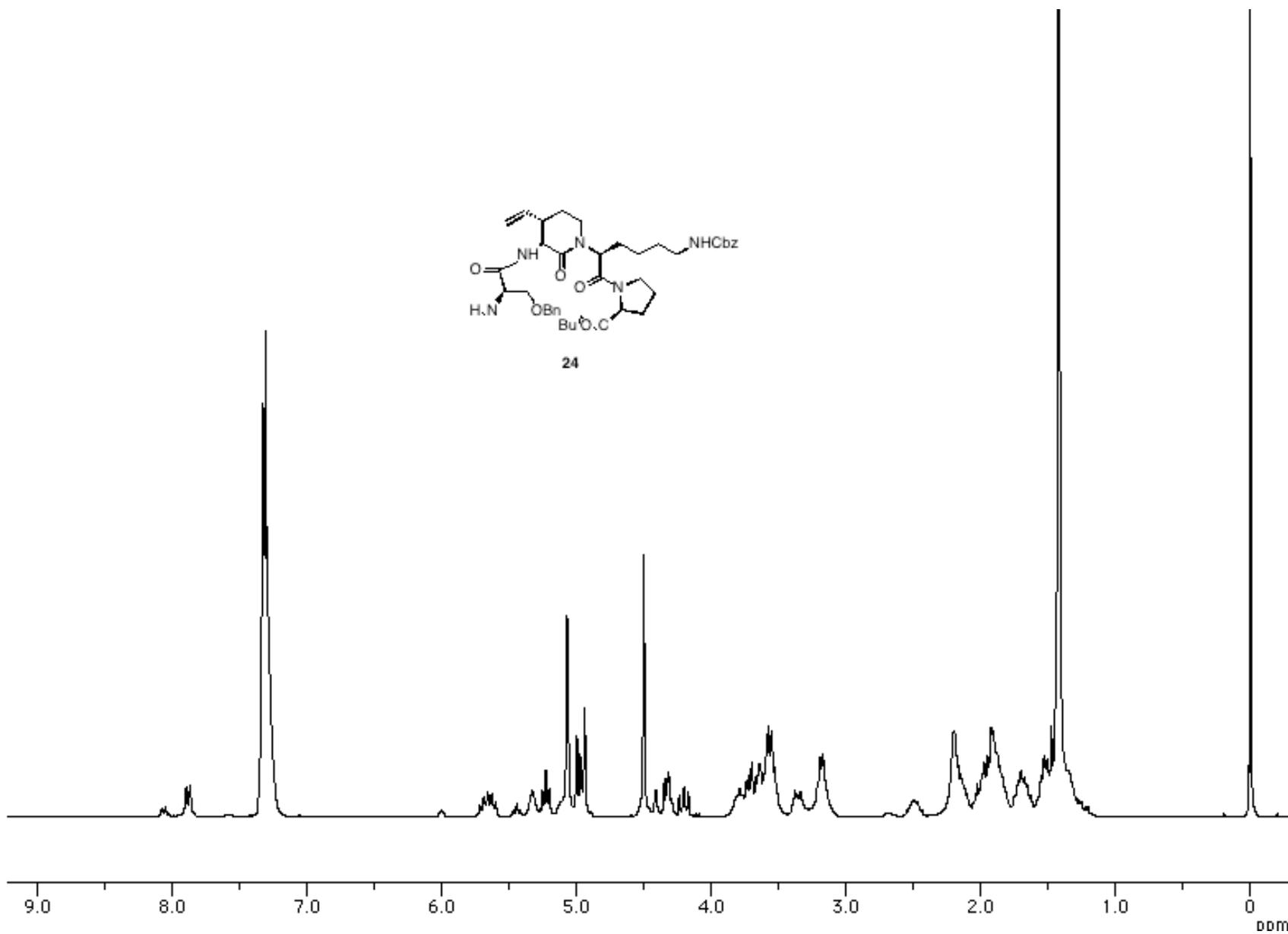


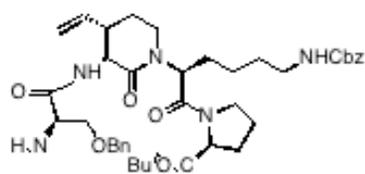






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