Total Synthesis of Lys^3 tamandarin M. A potential affinity ligand

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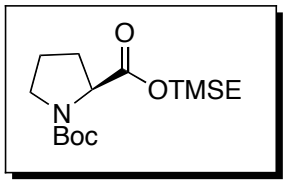
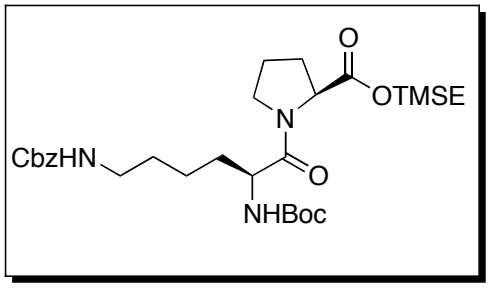
Table of Contents

General Methods. All reactions were performed under an argon atmosphere. Tetrahydrofuran was distilled over sodium-benzophenone, dichloromethane was distilled over calcium hydride, DMF in Acroseal bottles were used without further purification prior to use. Flash chromatography was carried out on Merck silica gel 60 (240-400 mesh) using the solvent conditions listed under individual experiments. Analytical thin-layer chromatography was performed on Merck silica gel (60F-254) plates (0.25 mm). Visualization was effected with ultraviolet light or cerium ammonium molybdate (CAM). Proton magnetic resonance spectra (^{1}H NMR) and Carbon magnetic resonance spectra (^{13}C NMR) were performed on a Bruker DRX-500 operating at 500 and 125 MHz respectively. Infrared spectra (IR) were obtained on a Perkin-Elmer 281-B spectrometer. High resolution mass spectra (HRMS) were obtained on a Micromass Autospec or a Waters LCTOF-Xe premier. Optical rotations were measured on a Jasco P-1010 polarimeter.

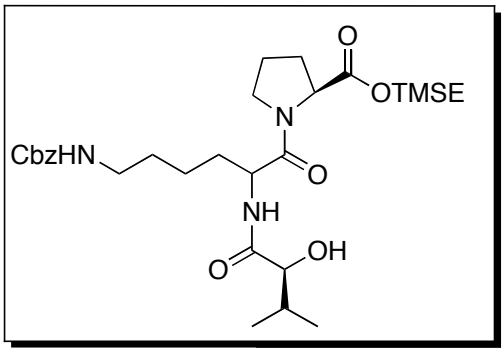


***N*-Boc-Proline-(2-trimethylsilylethyl)ester.** *N*-Boc-Proline (1.00 g, 4.60 mmol) was dissolved in anhydrous dichloromethane (23 mL) and cooled to 0^o C. To this was added EDCI (0.89 g, 4.60 mmol), DMAP (0.051g, 0.42 mmol) and 2-(trimethylsilyl) ethanol (0.61 mL, 4.2 mmol) was added dropwise to the reaction mixture via syringe. The reaction was allowed to warm to room temperature and stir overnight. The solvent was evaporated and the residue was redissolved in ethyl acetate (50 mL) . This solution was washed with 10% HCl (25 mL), saturated sodium bicarbonate (25 mL), brine (25 mL), and dried over $MgSO_4$. The solvent was evaporated to yield the product (1.32g, 90%) as an oil. R_f 0.68 (30% acetone/hexanes); ^{1}H NMR: (500 MHz, $CDCl_3$) δ 0.04 (m, 9H), 0.99 (m, 2H), 1.44 (m, 9H), 1.89 (m, 3H), 2.20 (m, 1H), 3.46 (m, 2H), 4.25 (m, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ -1.6, 17.3, 23.5, 24.2, 28.3, 29.8, 30.8, 46.4, 58.9, 63.1, 79.6, 153.8, 173.3; Infrared (cm^{-1}): 2954, 1745, 1703, 1454, 1396, 1250, 1163, 1121; HRMS (ES) *m/z*; calcd for $C_{15}H_{29}NO_4SiNa$ $(M+Na)^+$: 338.1764, found: 338.1765; $[\alpha]_D^{28}$-44.3 (c 1.0, $CHCl_3$).

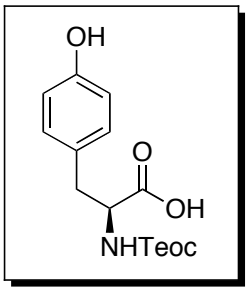


N^{α}–Boc-N^{ε}-Cbz-lysylproline-2-(trimethylsilylester) (15)
N-Boc-Proline-(2-trimethylsilylethyl)ester (2.55 g, 8.1 mmol) was dissolved in 4.0M HCl in dioxane (10 mL). After 1.5 h the starting material had been consumed. The solvent was evaporated and the material was redissolved in dichloromethane and evaporated again to recover the salt (2.03 g, quant). The salt was dissolved in DMF (15 mL) and cooled to 0^o C. To this was added N^{α}-Boc-N^{ε}–Cbz-Lysine (2.80 g, 7.4 mmol), DEPC (1.80 mL, 11.80 mmol) and triethylamine (2.56 mL, 18.5 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with ethyl acetate (30 mL) and washed with 10% HCl (20 mL), water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered, and

evaporated to yield the crude product. Purification by column chromatography (30% acetone/hexanes) yielded the product (2.66g, 62%) as a clear oil.
R_f 0.39 (30% acetone/hexanes); ^{1}H NMR: (500 MHz, $CDCl_3$) δ 0.27 (s, 9H), 0.96 (t, *J*=8.17 Hz, 2H), 1.41 (m, 12H), 1.61 (m, 3H), 1.76 (m, 1H), 1.97 (m, 3H), 2.2 (m, 1H), 3.21 (m, 2H), 3.59 (m, 1H), 3.71 (m, 1H) 4.18 (t, *J*=9.3 Hz, 2H) 4.44 (m, 1H), 4.49 (m, 1H), 5.11 (m, 1H), 5.31 (d, *J*=6.33 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR: (125 MHz, $CDCl_3$): δ -1.6, 17.2, 21.8, 24.8, 28.3, 28.8, 29.1, 32.3, 40.6, 46.9, 51.4, 58.9, 63.5, 66.4, 79.5, 127.9, 128.4, 136.7, 155.6, 156.4, 171.0, 172.0; Infrared (cm^{-1}) 3330, 2951, 1714, 1652, 1515, 1456, 1456, 1249, 1170; HRMS (ES) *m/z* calcd for $C_{30}H_{49}N_3O_6SiNa$ $(M+Na)^+$: 600.3081 found: 600.3088; $[\alpha]_D^{28}$-31.4 (c 1.04, $CHCl_3$).

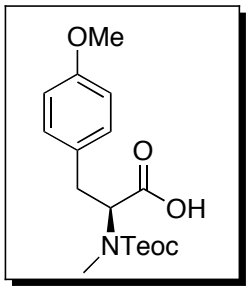


Alcohol 10. N^{α}-Boc-N^{ε}–Cbz-Lysylproline-(2-trimethylsilylethyl)ester (2.66 g, 4.60 mmol) was dissolved in 4.0 M HCl/dioxane (15 mL). This solution was allowed to stir at room temperature for 2 h. After this time the reaction appeared to be complete by TLC. The solvent was evaporated under reduced pressure to yield the HCl salt as a white foam (2.36 g, quantitative). The salt was dissolved in anhydrous dichloromethane (27 mL) and cooled to 0^o C. To this solution was added *N*-methylmorpholine (1.26 mL, 11.50 mmol), BOP (2.26 g, 5.10 mmol) and 2*S*-hydroxyisovaleric acid (0.60 g, 5.10 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with ethyl acetate (20 mL) and washed with 10% HCl (15 mL), saturated sodium bicarbonate (15 mL), brine (15 mL), and dried over $MgSO_4$. The crude product was purified by column chromatography (20→25% acetone/hexanes) to yield the product (1.46 g, 55%) as a clear oil. R_f 0.18 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.85 (d, *J*= 6.76 Hz, 3H), 0.98 (m, 5H), 1.36-1.78 (m, 8H), 1.80-2.27 (m, 6H), 2.58 (m, 1H), 3.21 (d, *J*= 6.08 Hz, 2H), 3.62 (m, 1H), 3.76 (m, 1H), 4.19 (t, *J*= 8.71 Hz, 2H), 4.48 (dd, *J*= 9.58, 4.67 Hz, 1H), 4.78 (m, 1H), 5.10 (m, 2H), 7.35 (m, 5H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ -1.6, 15.5, 17.2, 19.1, 22.0, 24.8, 28.8, 29.1, 29.6, 31.6, 40.5, 47.1, 49.8, 59.0, 59.3, 63.5, 64.5, 66.3, 75.9, 127.8, 127.9, 128.3, 136.7, 156.4, 171.1, 171.8, 173.7; Infrared (cm^{-1}) 3376, 2956, 1719, 1654, 1552, 1458, 1250; HRMS (ES) *m/z* calcd for $C_{29}H_{47}N_3O_7SiNa$ $(M+H)^+$: 578.3263 found: 578.3284; $[\alpha]_D^{27}$ -44.5 (c 1.06, $CHCl_3$).

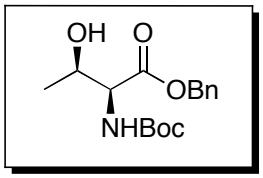


***N*-Teoc-L-Tyrosine**. L-Tyrosine (6.18 g, 34.11 mmol) and sodium bicarbonate (10.03 g, 119 mmol) were suspended in deionized water (170 mL). Teoc-Cl (6.78 g, 37.5 mmol) was dissolved in THF (170 mL) and added dropwise to the reaction mixture. The reaction was allowed to stir overnight. THF was evaporated and the remaining aqueous layer was extracted with diethyl ether (50 mL x

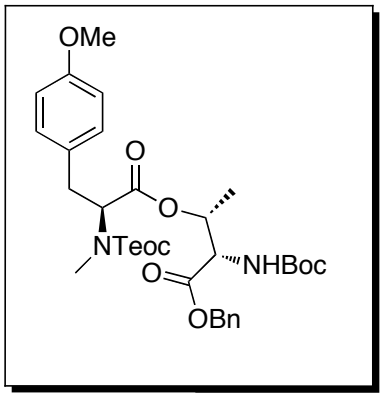
2). The combined organic phase was extracted with 1M NaOH (2 x 20 mL). The combined aqueous layers were cooled to 0° C and acidified to pH 4 with 50% HCl. The acidified aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic extracts were washed with acidified brine and dried over $MgSO_4$. The solvent was evaporated to yield the product as a white foam (2.07g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.97 (m, 2H), 3.08 (m, 3H), 4.16 (m, 2H), 4.62 (s, 1H), 5.04 (s, 1H), 6.75 (d, *J*=7.41 Hz, 2H), 7.03 (d, *J*=7.41, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.6, 17.6, 37.1, 54.6, 63.9, 115,7, 130.5, 154.9, 175.4; HRMS (ES) *m/z* calcd for $C_{15}H_{23}NO_5SiNa$ $(M+Na)^+$: 348.1244, found: 348.1237; $[\alpha]_D^{30}$ +42.7 (c 1.05, $CHCl_3$).



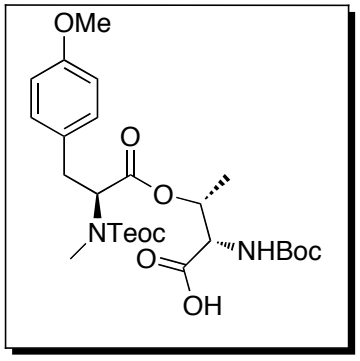
***N,O*-Dimethyl-*N*-(2-trimethylsilylethoxycarbonyl)tyrosine** (**18**). *N*-Teoc-L-Tyrosine (1g, 3.1 mmol) was dissolved in anhydrous THF (31 mL). To this solution was added dimethyl sulfate (1.9 mL, 20.2 mmol), potassium hydroxide (1.74g, 31 mmol), and tetrabutylammonium bisulfate (0.10g, 10% wt). After 2 h the reaction flask was cooled to 0 °C. Deionized water (31 mL) was added dropwise. After 3 h the solvent was evaporated and the remaining aqueous mixture was extracted with diethyl ether (2 x 20 mL). The combined diethyl ether extracts were washed with saturated sodium bicarbonate (2 x 25 mL). The combined aqueous layers were acidified to pH 4 with solid citric acid. The acidified aqueous layer was extracted with ethyl acetate (3 x 50 mL), dried over $MgSO_4$, filtered and the solvent evaporated to yield the crude product as a yellow oil. Purification by flash chromatography (5% MeOH/$CHCl_3$) yielded the pure product (0.72g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.92 (m, 2H), 2.80 (m, 3H), 3.00 (m, 1H), 3.28 (m, 1H), 3.78 (s, 3H), 4.11 (m, 2H), 4.84 (m, 1H), 6.82 (d, *J*=8.46 Hz, 2H), 7.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.3, 17.9, 32.5, 34.1, 34.5, 55.6, 60.7, 61.2, 63.9, 64.6, 114.3, 129.2, 130.1, 130.6, 157.6, 158.7, 159.0, 175.8; Infrared (cm^{-1}) 2954, 1701, 1654, 1514, 1249, 1179, 1037; HRMS (ES) *m/z* calcd for $C_{17}H_{27}NO_5SiNa$ $(M+Na)^+$: 376.1557, found: 376.1562; $[\alpha]_D^{28}$ -1.4 (c 0.54, $CHCl_3$).



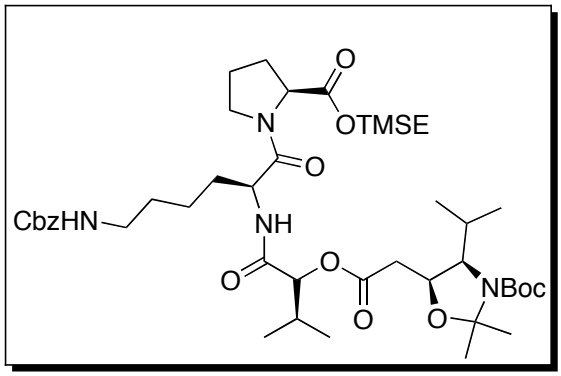
***N*-Boc-L-Threonine benzylester**. *N*-Boc-L-Threonine (5.0 g, 22.8 mmol) was dissolved in anhydrous DMF (75 mL) and cooled to 0 °C. To this solution was added benzyl bromide (5.42 mL, 45.6 mmol) and sodium carbonate (7.28 g, 68.4 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with ethyl acetate (150 mL) and was washed with water (2 x 50 mL), 10 % HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated to yield the crude product. The crude product was purified by flash chromatography (15% acetone/hexanes) to yield the pure product (6.22 g, 88 %) as a clear oil. R_f 0.34 (30% Acetone/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, *J*= 2.17 Hz, 3H), 1.44 (s, 9H), 2.04 (s, 1H), 4.31 (s, 1H), 5.20 (q, *J*= 5.38 Hz, 2H), 5.33 9 (s, 1H), 7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 28.2, 58.7, 67.1, 68.1, 128.1, 128.4, 128.5, 135.3, 156.0, 171.3; Infrared (cm^{-1}): 3378, 2974, 2930, 1716, 1514, 1163; HRMS (ES) *m/z* calcd for $C_{16}H_{23}NO_5Na$ $(M + Na)^+$: 332.1474, found: 332.1485; $[\alpha]_D^{26}$ -18.9 (c 0.5, MeOH).



***N,O*-Me$_2$-*N*-Teoc-Tyrosine-*O*-(*N*-Boc)-Threonine-benzyl ester**. *N,O*-dimethyl-*N*-Teoc-tyrosine (0.50 g, 1.4 mmol) and *N*-Boc-threonine benzyl ester (0.40 g, 1.3 mmol) were dissolved in anhydrous dichloromethane (7 mL). To this solution was added DMAP (15 mg, 0.13 mmol) and EDCI (0.30 g, 1.5 mmol). The reaction was allowed to warm slowly to room temperature. After 3 h the reaction mixture was diluted with dichloromethane (25 mL). This solution was then washed with 10% HCl (20 mL), saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over $MgSO_4$, and the solvent evaporated to yield crude product. Purified by flash chromatography (15% acetone/hexanes) yielded the product (0.44g, 50%) as a clear oil. R_f 0.42 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ (s, 9H), 2.67 (m, 3H), 2.86 (m, 1H), 3.13 (m, 1H), 3.76 (s, 3H), 4.08 (m, 2H), 4.46 (m, 1H), 4.73 (m, 1H), 5.14 (m, 3H), 5.46 (m, 1H), 6.81 (d, *J*= 8.5 Hz, 2H), 7.06 (m, 2H), 7.35 (m, 5H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ -1.4, 17.0, 17.7, 28.0, 31.6, 33.7, 55.1, 57.3, 60.3, 64.1, 67.6, 71.6, 82.4, 114.1, 128.4, 128.6, 128.9, 155.9, 156.8, 158.4, 169.8, 170.0; HRMS (ES) *m/z* calcd for $C_{33}H_{48}N_2O_9Na$ $(M + Na)^+$: 667.3027, found: 667.3038; $[\alpha]_D^{28}$-13.4 (c 1.0, $CHCl_3$).

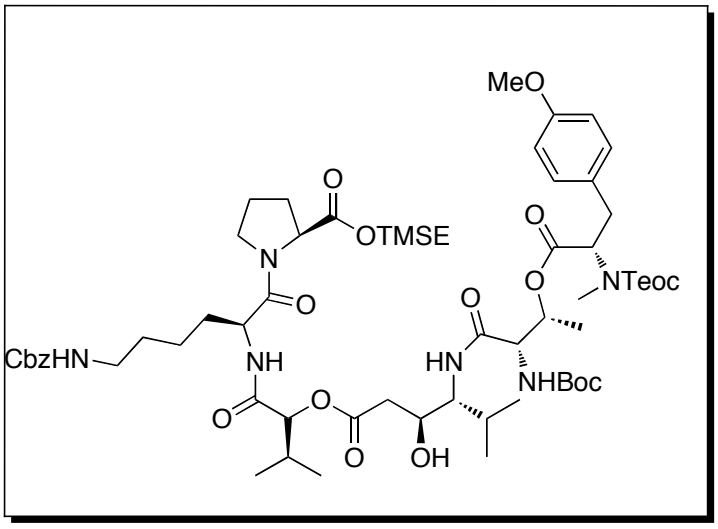


***N,O*-Me$_2$-*N*-Teoc-Tyrosine-*O*-(*N*-Boc)-Threonine** (**12**). The corresponding benzyl ester (0.38 g, 0.59 mmol) was dissolved in anhydrous methanol (4 mL). To this solution was added 10% Pd/C (38 mg, 10% wt). The reaction vessel was evacuated and purged with hydrogen (3x). The reaction was allowed to stir for 24 h at which time it was diluted with MeOH (25 mL) and filtered through a pad of Celite. Evaporation of the solvent led to the product (0.33 g, quantitative) that was used without further purification.

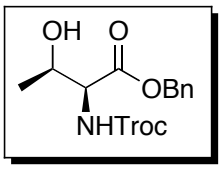


Oxazolidine 19. Oxazolidine acid **11** (0.178 g, 0.56 mmol) was dissolved in tetrahydrofuran (6 mL). To this solution was added alcohol **10** (0.310 g, 0.56 mmol), EDCI (0.123 g, 0.64 mmol), and DMAP (0.65 g, 0.53 mmol). The reaction was allowed to stir for 18 h. The reaction mixture was diluted with dichloromethane (20 mL), washed with 10% HCl (10 mL), saturated sodium bicarbonate (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated. Flash chromatography (10→20% acetone/hexanes) yielded the product (0.338 g, 73%) as a white foam. R_f 0.52 (50% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.85-0.92 (m, 14H), 1.39 (s, 9H), 1.46 (s, 6H), 1.50 (s,

2H), 1.62 (m, 2H), 1.74-1.99 (m, 5H), 2.08-2.32 (m, 2H), 2.70 (d, *J*= 6.05 Hz, 2H), 3.11 (s, 2H), 3.46-3.61 (m, 2H), 3.70 (s, 1H), 3.83 (s, 1H), 4.10 (dd, *J*= 8.95, 6.69 Hz, 2H), 4.37 (dd, *J*= 8.57, 4.87 Hz, 2H), 4.68 (q, *J*= 7.30 Hz, 1H), 4.98 (m, 3H), 5.27 (m, 1H), 6.89 (d, *J*= 7.60 Hz, 1H), 7.23 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.6, 16.9, 17.1, 18.6, 21.5, 21.8, 22.4, 24.8, 26.0, 26.6, 28.3, 28.8, 28.9, 30.5, 31.8, 34.7, 40.4, 46.9, 50.0, 58.8, 63.2, 63.5, 66.2, 73.0, 78.3, 79.5, 92.5, 127.8, 128.0, 128.3, 136.7, 153.2, 156.4, 168.7, 169.6, 169.8, 171.8; IR (cm^{-1}) 3380, 2961, 1737, 1724, 1690, 1651, 1383, 1248, 1173; HRMS (ES) *m/z* calcd for $C_{44}H_{72}N_4O_{11}SiNa$ $(M + Na)^+$: 883.4865, found: 883.4847; $[\alpha]_D^{21}$ -25.7 (c 1.04, CH_2Cl_2).

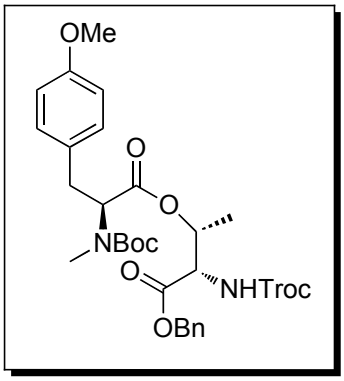


Linear precursor (9). Oxazoline **19** (0.40 g, 0.46 mmol) was dissolved in 4.0 M HCl in dioxane. After 1.5 h the solvent was removed under reduced pressure to yield the HCl salt as a white foam (0.35 g, quantitative). This salt was dissolved in DMF (4 mL) and cooled to 0 °C. To this solution was added acid **12** (0.35 g, 0.43 mmol), DIPEA (0.32 mL, 1.80 mmol) and HATU (0.18g, 0.46 mmoL). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with EtOAc, washed with 10% HCl, saturated sodium bicarbonate, brine, dried over Na_2SO_4, filtered, and evaporated to yield the product (0.38 g, 70%) as a white solid. R_f 0.59 (1:2 Hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 18H), 0.84 (m, 2H), 0.94 (m, 14H), 1.14-1.27 (m, 4H), 1.44 (s, 9H), 1.61 (s, 6H), 1.78 (m, 1H), 2.00 (m, 4H), 2.22 (m, 2H), 2.57 (m, 1H), 2.70 (m, 1H), 2.79 (s, 3H), 2.94 (m, 1H), 3.18 (m, 3H), 3.60 (m, 1H), 3.76 (s, 3H), 3.94-4.24 (m, 6H), 4.28 (m, 1H), 4.43 (m, 1H), 4.76 (m, 2H), 4.97 (m, 1H), 5.08 (s, 2H), 5.14 (m, 1H), 5.21 (m, 1H), 5.29 (m, 1H), 5.48 (m, 1H), 6.80 (d, *J*= 8.30 Hz, 2H), 7.09 (d, *J*= 8.15 Hz, 2H), 7.34 (m, 5H), 7.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.20, 13.4, 14.4, 15.8, 17.1, 17.2, 17.6, 19.0, 19.4, 20.5, 22.2, 25.1, 25.2, 28.1, 28.4, 28.5, 29.2, 29.8, 29.9, 30.6, 31.2, 31.6, 31.8, 32.1, 32.2, 39.4, 40.8, 47.4, 50.3, 50.5, 54.4, 59.2, 59.3, 64.0, 66.7, 69.3, 76.4, 78.2, 81.1, 114.2, 128.2, 1305, 137.0, 156.9, 166.3, 169.8, 170.9, 171.1, 172.0, 172.2, 173.6; IR (cm^{-1}) 3334, 2958, 1737, 1721, 1639, 1514, 1249, 1175; HRMS (ES) *m/z* calcd for $C_{62}H_{100}N_6O_{17}Si_2Na$ $(M + Na)^+$: 1279.6582, found: 1279.6608; $[\alpha]_D^{23.8}$ -28.14 (c 0.3, $CHCl_3$).

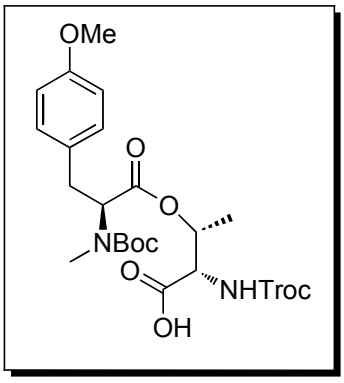


***N*-Troc-Thr-OBn**. Boc-Thr-OBn (3.67 g, 12.2 mmol) was dissolved in 4.0 M HCl in dioxane (15 mL). This solution was allowed to stir at room temperature for 4 h. The solvent was evaporated to yield the HCl salt in quantitative yield. The salt was added in portions to a

biphasic mixture of 10% $NaHCO_3$ (7 mL), diethyl ether (7 mL) and $NaHCO_3$ (1.02 g, 12.2 mmol) cooled to 0 °C. Troc-Cl (1.64 mL, 12.2 mmol) in diethyl ether (5 mL) was added to the reaction mixture over 1.5 h. The reaction was allowed to warm to room temperature and stir overnight. 10 % $NaHCO_3$ (15 mL) was added to this solution and the mixture stirred for an additional 2 h. Diethyl ether (40 mL) was then added. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield the product (3.92 g, 84 %) as a yellow oil. R_f 0.42 (30% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, *J*= 6.25 Hz, 3H), 2.30 (m, 1H), 4.37 (m, 2H) 4.69 (d, *J*= 11.99 Hz, 1H), 4.79 (d, *J*=12.04 Hz, 1H), 5.19 (m, 2H), 5.97 (d, *J*= 8.95 Hz, 1H), 7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 25.5, 59.4, 67.5, 67.8, 74.7, 95.3, 128.2, 128.5, 128.6, 130.0, 155.0, 170.5; IR (cm^{-1}): 3310, 2977, 1716, 1508, 1456, 1395, 1262, 1204; HRMS (ES) *m/z* calcd for $C_{14}H_{16}Cl_3NO_5Na$ $(M + Na)^+$: 405.9992 found: 405.9992; $[\alpha]_D^{24}$ -17.6 (c 1.04, MeOH).

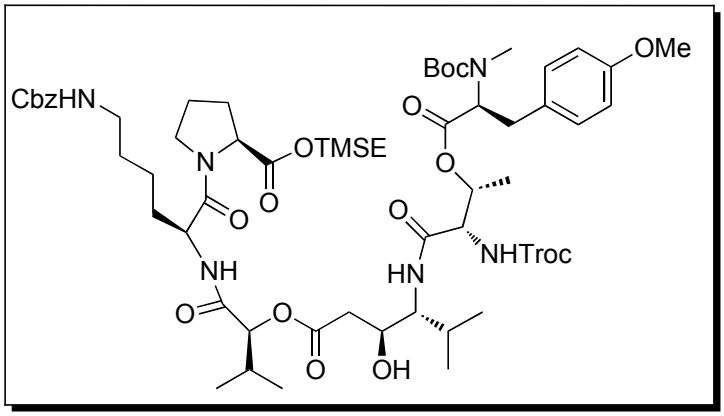


***N,O*-Me$_2$-Boc-Tyr-*O*-(*N*-Troc)-Thr-OBn**. *N,O*-Me_2-Boc Tyr (1.85 g, 6 mmol) was dissolved in anhydrous THF (24 mL) and cooled to 0 °C. To this solution was added Troc-Thr-OBn (1.54 g, 4 mmol), EDCI (1.23 g, 6.4 mmol) and DMAP (0.73g, .6 mmol). The reaction mixture was allowed to warm to room temperature and stir overnight. It was diluted with EtOAc (50 mL) and washed with 10% $KHSO_4$ (25 mL), saturated $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated to yield the crude product. The crude product was purified by column chromatography (10→15% EtOAc/Hexanes) to yield the product (2.16g, 80%) as a clear oil. R_f 0.55 (30% EtOAc, Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07–1.28 (m, 12H), 2.61 (s, 3H), 2.87 (m, 1H), 3.11 (m, 1H), 3.77 (s, 3H), 4.51 (m, 1H), 4.74 (m, 3H), 5.13 (m, 2H), 5.21 (m, 1H), 5.79 (s, 1H), 6.82 (m, 2H), 7.06 (m, 2H), 7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 22.6, 25.2, 28.2, 31.3, 33.9, 34.6, 55.2, 57.7, 60.3, 67.8, 71.0, 74.7, 80.2, 95.2, 113.9, 127.6, 128.5, 128.6, 129.7, 130.2, 134.9, 154.9, 158.7, 168.9, 170.2; IR (cm^{-1}): 3421, 3319, 2975, 2934, 1732, 1716, 1702, 1514, 1249, 1162; HRMS (ES) *m/z* calcd for $C_{30}H_{37}Cl_3N_2O_7Na$ $(M + Na)^+$: 697.1464, found: 697.1462; $[\alpha]_D^{25}$ -14.8 (c = 0.65, MeOH).

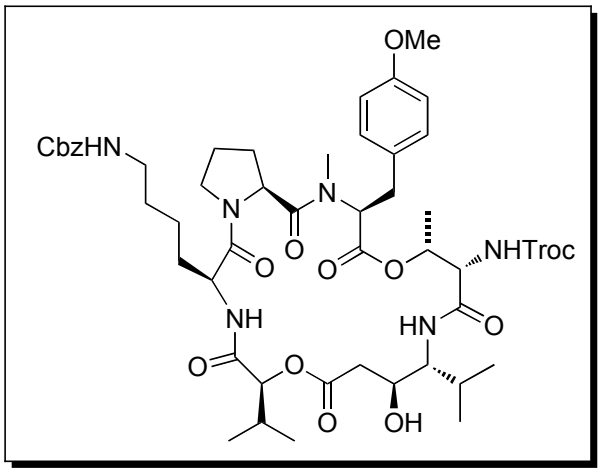


***N,O*-Me$_2$-Boc-Tyr-Troc-Thr-OH (22)**. *N,O*-Me_2-Boc-Tyr-Troc-Thr-OBn (3.27 g, 4.84 mmol) was dissolved in THF (130 mL). To this solution was added 10% Pd/C (0.32 g, 10% wt). The reaction vessel was evacuated and purged with hydrogen. The reaction was allowed to stir overnight then filtered through a pad of Celite and the residue rinsed thoroughly with THF.

The solvent was evaporated to yield the product as a white solid (1.78 g, 63%) which was used without further purification.

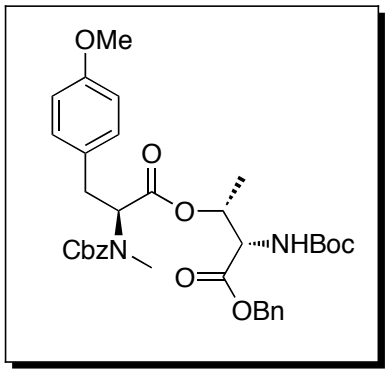


Protected linear precursor 20. oxazolidine **19** (69 mg, 0.080 mmol) was dissolved in 4.0 M HCl in dioxane (2 mL) and was allowed to stir to 2 h at which time the solvent was removed and dried under reduced pressure to yield the HCl salt (61 mg, quantitative) as a white solid. This HCl salt (61 mg, 0.080 mmol was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C. Acid **22** (56 mg, 0.096 mmol), DIPEA (56 μL, 0.12 mmol), and HATU (46 mg, 0.096 mmol) were added and the reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with ethyl acetate (25 mL), washed with 10% HCl (15 mL), saturated $NaHCO_3$ (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to yield the crude product as a brown oil. Purification by column chromatography (20→25→35% acetone/hexanes) yielded the product (63 mg, 61%) as an off white foam. R_f 0.57 (60% acetone/hexanes) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.93 (m, 14H), 1.03 (m, 2H), 1.39 (m, 12H), 1.60 (m, 6H), 1.71 (m, 1H), 1.96 (m, 4H), 2.21 (m, 2H), 2.52 (m, 1H), 2.63 (m, 1H), 2.81 (m, 3H), 2.85-2.99 (m, 2H), 3.16 (m, 2H), 3.59 (m, 2H), 3.71 (m, 1H), 3.74 (s, 3H), 3.82-4.00 (m, 2H), 4.06-4.25 (m, 3H), 4.29 (s, 1H), 4.41 (m, 2H), 4.63 (m, 3H), 4.95-5.16 (m, 3H), 5.23 (m, 1H), 6.79 (m, 2H), 7.06 (m, 2H), 7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.5, 11.5, 15.9, 17.2, 18.8, 20.5, 20.8, 22.2, 24.8, 25.3, 27.9, 28.4, 29.0, 29.1, 30.4, 30.7, 31.6, 34.2, 34.7, 36.5, 36.9, 38.9, 40.6, 46.2, 47.2, 50.1, 55.3, 59.1, 63.7, 66.5, 68.9, 74.8, 78.2, 80.6, 95.4, 114.1, 128.0, 128.1, 128.5, 129.9, 136.9, 154.6, 156.6, 158.5, 169.3, 169.6, 170.6, 170.9, 171.2, 171.5, 171.7; IR (cm^{-1}) 3326, 2953, 1736, 1714, 1699, 1636, 1514, 1455, 1248; HRMS (ES) *m/z* calcd for $C_{59}H_{89}Cl_3N_6O_{17}SiNa$ $(M + Na)^+$: 1309.5016, found: 1309.4969; $[\alpha]_D^{25}$ -20.7 (c 0.5, CH_2Cl_2).

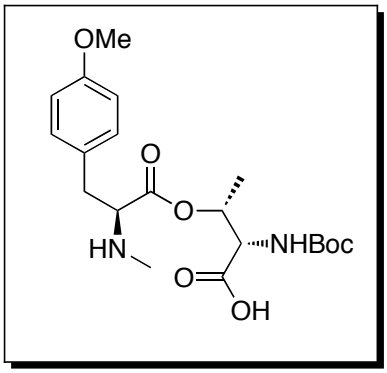


Macrocycle 24. Linear precursor (164 mg, 0.151 mmol) was dissolved in anhydrous dichloromethane (8 mL) and to this solution was added trifluoroacetic acid (2 mL). The reaction was allowed to stir for 7 h at which time ^{1}H NMR revealed removal of both the desired protecting groups. The solvent was evaporated to yield the TFA salt as a brown oil. This salt was dissolved in anhydrous dichloromethane (410 mL) and cooled to -10 °C. To this was added

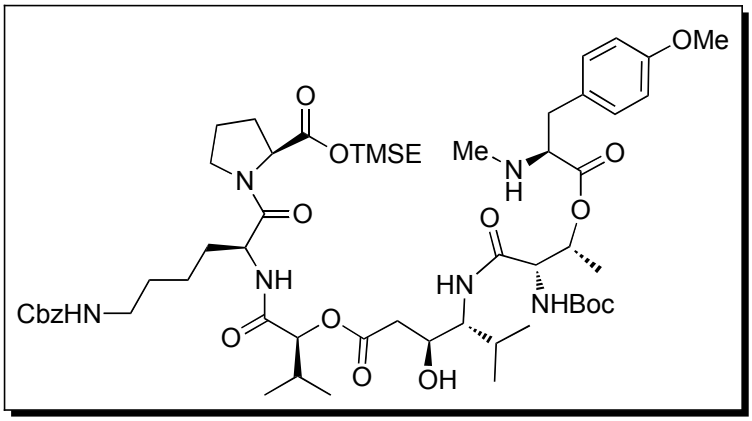
BOP-Cl (39 mg, 0.153 mmol) and triethylamine (53 μL, 0.460 mmol). The reaction was allowed to warm to room temperature and stir overnight. The following day, additional portions of BOP-Cl (39 mg, 0.153 mmol) and triethylamine (53 μL, 0.460 mmol) were added and the reaction was allowed to stir for an additional 5 days. The solvent was evaporated and the remaining residue was dissolved in dichloromethane (50 mL) and washed with 10% $KHSO_4$ (20 mL), 5% $NaHCO_3$ (20 mL), brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to yield the crude product, which was purified by column chromatography (15→40% EtOAc/CH_2Cl_2) to yield the product (36 mg, 27%) as a white solid. R_f 0.27 (50% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-1.01 (m, 12H), 1.15-1.28 (m, 2H), 1.33-1.48 (m, 4H), 1.70-1.81 (m, 2H), 1.92-2.03 (m, 2H), 2.04-2.13 (m, 2H), 21.5-2.26 (m, 2H), 2.40 (dd, *J*= 16.73, 8.80 Hz, 1H), 2.56 (s, 3H), 2.79-2.86 (m, 1H), 3.01 (d, *J*= 3.11 Hz, 1H), 3.10-3.21 (m, 3H), 3.32 (dd, *J*= 14.18, 3.93 Hz, 1H), 3.55-3.67 (m, 3H), 3.77 (s, 3H), 3.89 (m, 1H) 4.39 (dd, *J*= 9.28, 2.88 Hz, 1H), 4.54 (m, 1H), 4.61-4.73 (m, 2H), 4.78 (t, *J*= 9.53 Hz, 1H), 5.00-5.08 (m, 3H), 5.11 (dd, *J*= 6.43, 3.03 Hz, 1H), 5.19 (s, 1H), 5.54 (d, *J*= 9.25 Hz, 1H), 6.81 (d, *J*= 8.25 Hz, 2H), 7.04 (d, *J*=8.20 Hz, 2H), 7.31 (m, 5H), 7.63 (d, *J*= 9.30 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 15.2, 16.8, 17.2, 18.8, 20.2, 24.8, 27.0, 28.0, 29.7, 30.1, 31.3, 33.9, 38.8, 39.7, 47.2, 48.6, 55.3, 56.8, 57.5, 57.7, 60.4, 65.9, 69.1, 70.7, 74.6, 78.7, 95.3, 114.1, 128.0, 128.1, 128.4, 129.7, 130.3, 136.8, 154.5, 156.6, 158.7, 168.4, 169.3, 169.8, 170.5, 173.4; IR (neat): 3341, 2930, 1726, 1655, 1631, 1535, 1458, 1246; HRMS (ES) *m/z* calcd for $C_{49}H_{67}Cl_3N_6O_{14}$ $(M + Na)^+$: 1091.3679: found: 1091.3694; $[\alpha]_D^{21}$ -56.1 (c 0.72, CH_2Cl_2).



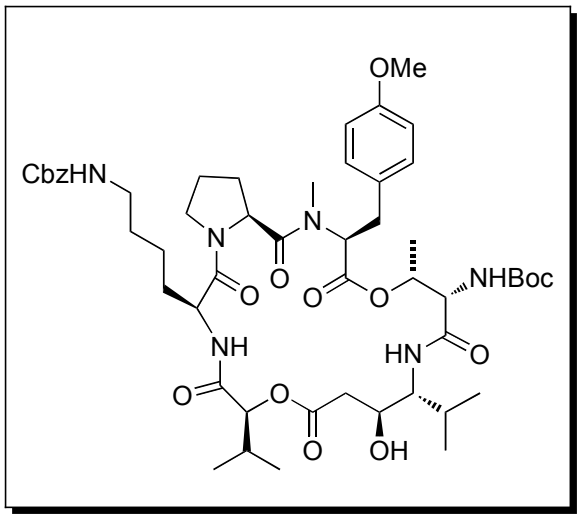
***N,O*-Me$_2$-Cbz-Tyr-Boc-Thr-OBn**. Tyrosine derivative **26** (1.00 g, 3.23 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. To this solution was added alcohol **21** (1.33 g, 3.89 mmol), EDCI (0.75 g, 3.89 mmol), and DMAP (0.039 g, 0.32 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with EtOAc (50 mL), washed with 10% HCl (15 mL), saturated sodium bicarbonate (15 mL), brine (15 mL), dried over Na_2SO_4, filtered and concentrated to yield the crude product. Purification by flash chromatography (10→25% EtOAc/hexanes) yielded the pure product (1.45 g, 71%) as a clear oil. R_f 0.50 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, *J*= 6.40 Hz, 3H), 1.47 (s, 9H), 2.66-2.72 (m, 3H), 2.78-2.98 (m, 1H), 3.06-3.22 (m, 1H), 3.77 (s, 3H), 4.50 (t, *J*= 9.25 Hz, 1H), 4.73 (dd, *J*= 10.23, 5.73 Hz, 1H), 5.05 (d, *J*= 3.55 Hz, 1H), 5.07-5.23 (m, 3H), 5.33 (d, *J*= 9.60 Hz, 1H), 5.47 (dd, *J*= 13.35, 6.45 Hz, 1H), 6.79 (m, 2H), 6.96-7.10 (m, 2H), 7.20-7.41 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.5, 16.8, 28.1, 31.9, 33.7, 54.9, 56.9, 60.1, 60.6, 67.1, 67.4, 71.5, 80.0, 113.9, 127.5, 127.8, 128.3, 128.5, 128.6, 129.6, 130.1, 136.5, 155.7, 156.4, 158.2, 169.6, 169.7; IR (cm^{-1}); HRMS (ES) *m/z* calcd for $C_{35}H_{42}N_2O_9Na$ $(M + Na)^+$: 657.2788, found: 657.2766; $[\alpha]_D^{17}$ -22.3 (c 1.40, $CHCl_3$).



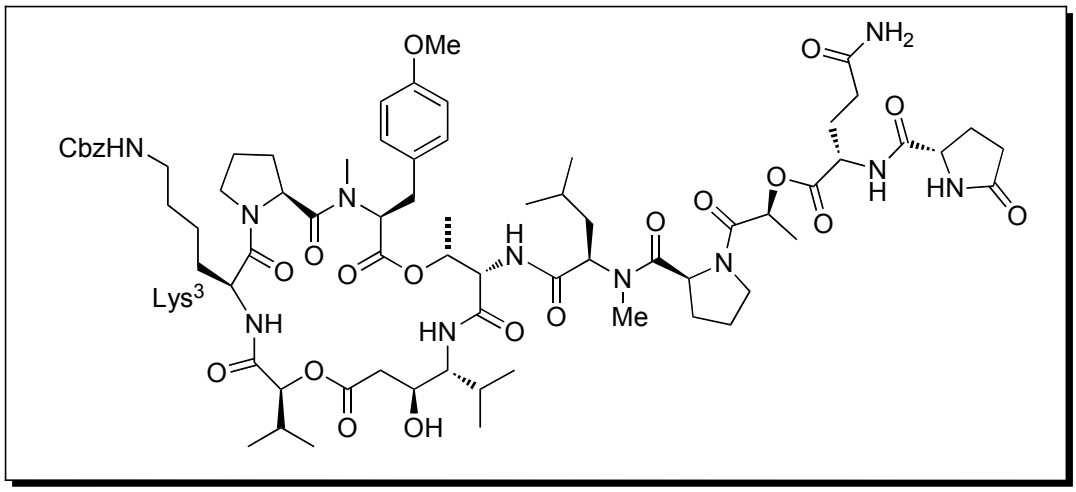
***N,O*-Me$_2$Tyr-Boc-Thr-OH (27)**. *N*,O-Me$_2$-Cbz-Tyr-Boc-Thr-OBn (213 mg, 0.34 mmol) was dissolved in MeOH (10 mL). To this was added 10% Pd/C (21 mg, 10% wt.) and the reaction flask was evacuated and purged with hydrogen. The reaction was allowed to stir for 12 h at which time the mixture was filtered through a pad of celite and rinsed thoroughly with MeOH. The solvent was evaporated to yield the product (137 mg, quantitative) as a white solid which was used without further purification.



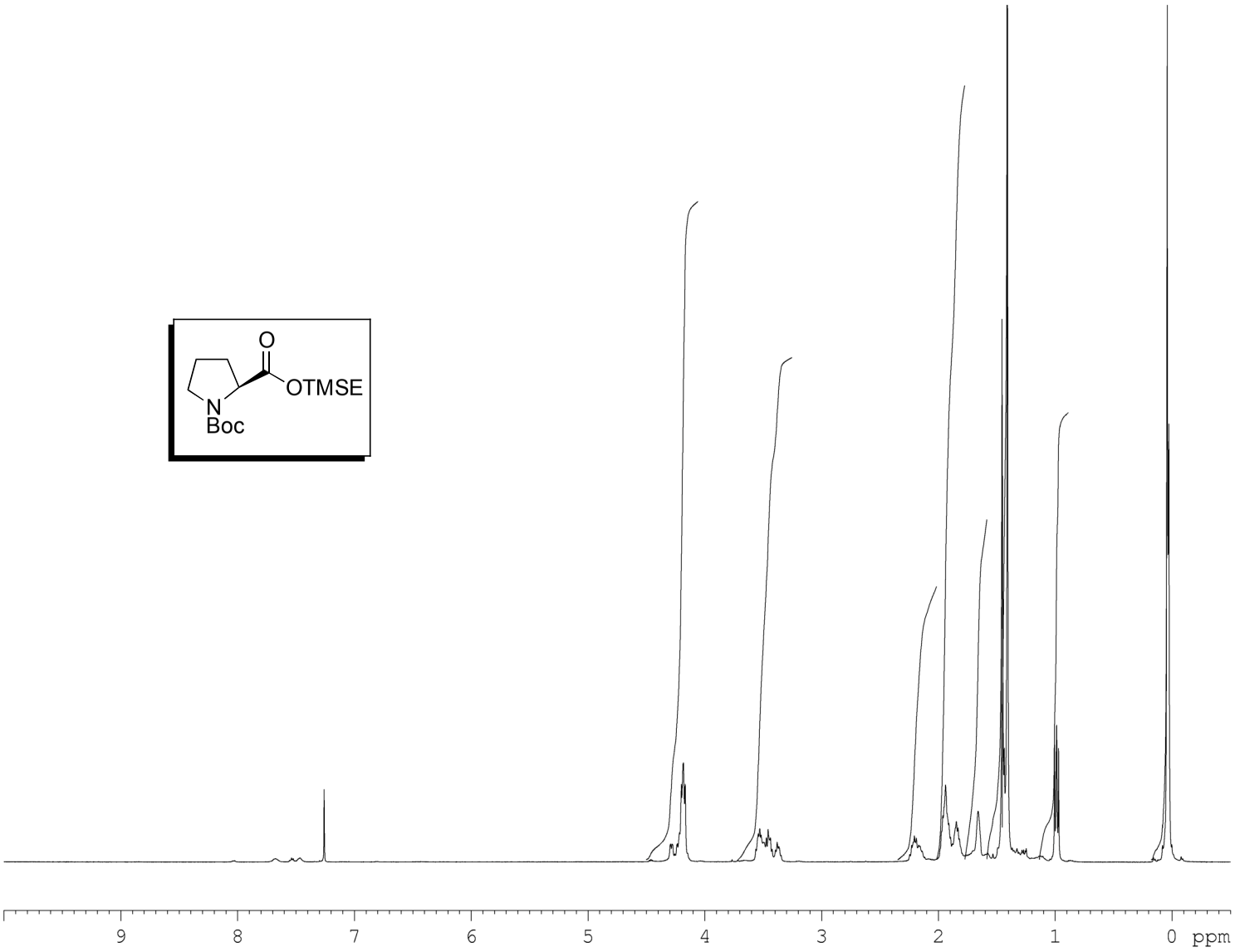
Linear precursor. The HCl salt **23** (83 mg, 0.110 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. To solution this was added acid **27** (45 mg, 0.110 mmol), EDCI (22 mg, 0.115 mmol), HOBt (16 mg, 0.0115 mmol) and NMM (25 μL, 0.230 mmol). The reaction was allowed to warm to room temperature and stir for 48 h. The reaction was diluted with EtOAc (30 mL), washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (15→40 Acetone/Hexanes) yielded the product (44 mg, 38%) as a white solid. R_f 0.23 (50% Acetone/Hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 9H), 0.8-0.99 (m, 16H), 1.07 (d, *J*= 5.45 Hz, 3H), 1.25 (m, 2H), 1.43 (s, 9H), 1.51-1.89 (m, 7H), 1.90-2.06 (m, 4H), 2.16 (m, 2H), 2.22 (m, 1H), 2.32 (s, 3H), 2.50 (m, 1H), 2.66 (m, 1H), 2.75-2.94 (m, 2H), 3.17 (m, 2H), 3.36 (m, 1H), 3.60 (m, 1H), 3.76 (s, 3H), 3.77 (s, 1H), 4.04-4.30 (m, 3H), 4.40 (m, 1H), 4.78 (m, 1H), 4.95 (m, 1H), 5.08 (m, 3H), 5.23-5.50 (m, 2H), 6.82 (m, 2H), 7.09 (m, 2H) 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.61, 11.4, 14.0, 15.3, 16.6, 17.3, 18.7, 20.2, 22.1, 22.5, 24.7, 25.2, 28.1, 28.2, 29.2, 29.9, 30.3, 31.5, 33.5, 34.4, 34.6, 38.4, 40.5, 47.2, 49.5, 49.9, 55.1, 57.8, 58.7, 59.1, 63.5, 64.5, 66.4, 78.5, 80.3, 113.8, 114.2, 127.9, 128.4, 130.1, 130.4, 136.7, 156.3, 158.4, 165.6, 169.4, 171.1, 171.3, 171.1; IR (cm^{-1}) 3442, 3340, 3028, 2977, 1742, 1713, 1514, 1248, 1165; HRMS (ES) *m/z* calcd for $C_{56}H_{89}N_6O_{15}Si$ $(M + H)^+$: 1113.6155, found: 1113.6145;
$[\alpha]_D^{20}$ -45.5 (c 1.71, CH_2Cl_2)



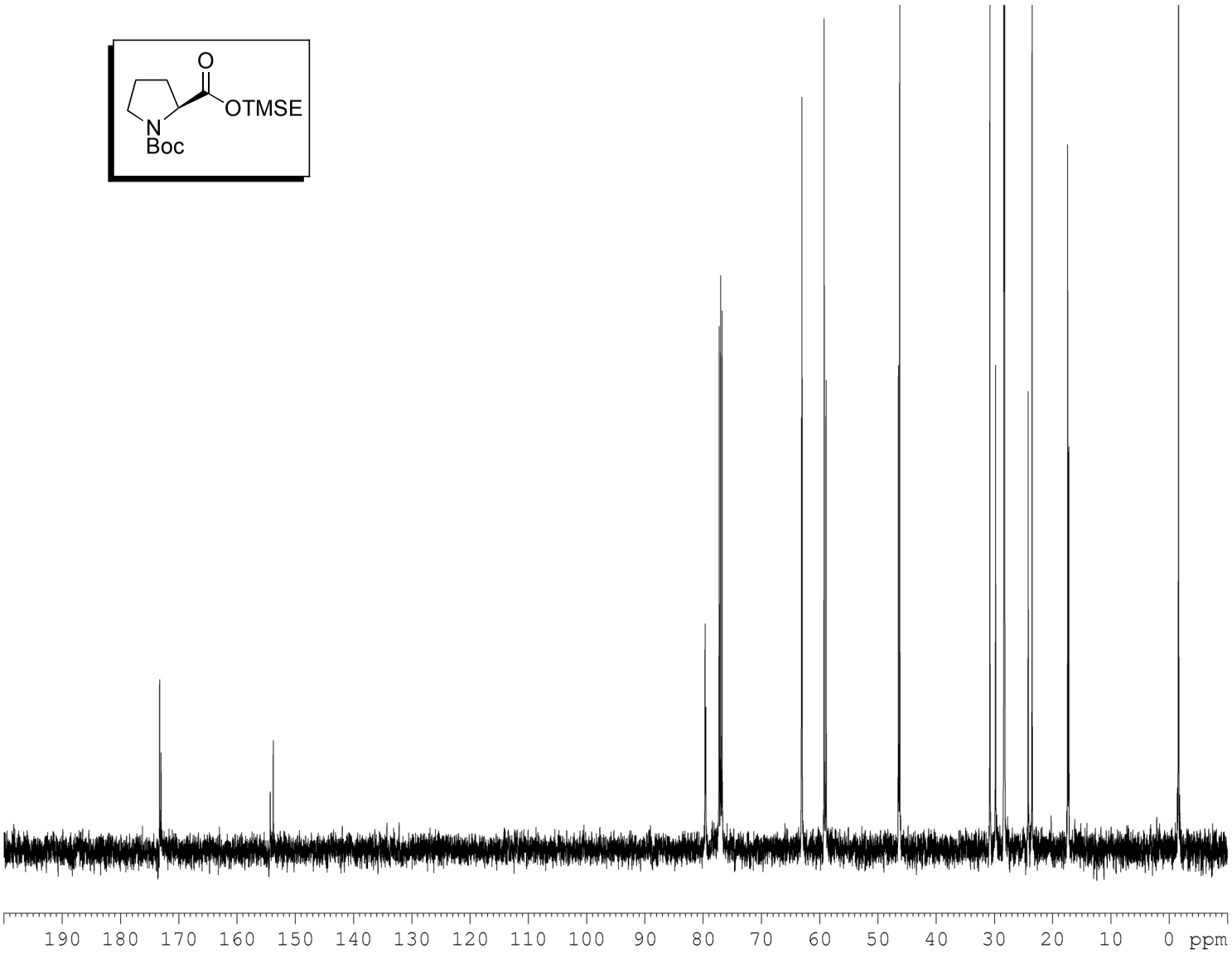
Macrocycle 7. The previous linear Precursor (40 mg, 0.36 mmol) was dissolved in THF (0.8 mL) and MeCN (0.2 mL) and cooled to 0 ºC. To this was added TASF (32 mg, 0.116 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction mixture was diluted with EtOAc (25 mL) and washed with 10% HCl (2 x 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to yield the crude product (29 mg, 81) as a white foam, which was used without any further purification. The crude product was dissolved in CH_2Cl_2 (20 mL) and loaded in to a syringe. In a separated flask BOP-Cl (29 mg, 0.114 mmol) and NMM (31 μL, 0.285 mmol) were added sequentially to CH_2Cl_2 (20 mL) and this mixture was cooled to -20 ºC. The crude product solution was added to this flask over 5 h using a syringe pump while the reaction mixture was kept at -20 ºC. After the addition was complete the reaction was allowed to warm to room temperature and stir for 48 h. The reaction mixture was washed with 10% HCl (20 mL), 5% $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to yield the crude product. Purification by flash chromatography (20→50% EtOAc/CH_2Cl_2) yielded the product (10 mg, 35%) as an oil. R_f 0.40 (60% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.74-1.01 (m, 12H), 1.24 (m, 7H), 1.40 (s, 9H), 1.50-1.69 (m, 6H), 1.73 (m, 2H), 2.01 (m, 2H), 2.08 (m, 2H), 2.18 (m, 1H), 2.45 (dd, *J*= 16.8, 6.9Hz, 1H), 2.52-2.74(m, 3H), 2.78-2.94 (m, 1H), 3.04-3.20 (m, 3H), 3.31 (dd, *J*= 14.1 Hz, 3.79 Hz, 1H), 3.55 (m, 1H), 3.60-3.69 (m, 1H), 3.71-3.78 (m, 3H), 3.80-3.86 (m, 1H), 3.92 (s, 1H), 4.28 (m, 1H), 4.55 (t, *J*= 4.20 Hz, 1H), 4.79 (m, 1H), 4.95-5.15 (m, 3H), 6.81 (m, 2H), 7.01 (m, 2H), 7.33 (m, 5H), 7.52 (d, *J*= 9.65 Hz, 1H), 7.85 (d, *J*= 8.70 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.53, 14.1, 15.1, 17.7, 18.5, 20.1, 22.7, 24.8, 27.3, 27.9, 29.6, 30.1, 30.5, 33.8, 38.1, 38.6, 38.9, 40.7, 45.7, 46.9, 49.5, 52.8, 55.1, 55.9, 57.2, 59.4, 60.3, 64.3, 65.7, 66.4, 68.8, 71.2, 78.8, 80.1, 113.9, 114.2, 127.9, 128.0, 129.7, 130.2, 136.7, 155.5, 156.3, 158.5, 168.6, 169.7, 170.0, 170.5, 171.2, 173.0; IR (cm^{-1}) 3437, 3339, 2961, 2925, 1731, 1700, 1713, 1667, 1651, 1635, 1537, 1512, 1452, 1246, 1168, 1021; ; HRMS (ES) *m/z* calcd for $C_{51}H_{75}N_6O_{14}$ $(M + H)^+$: 995.5341, found: 995.5370; $[\alpha]_D^{19}$ -50.2 (c 1.20, CH_2Cl_2).



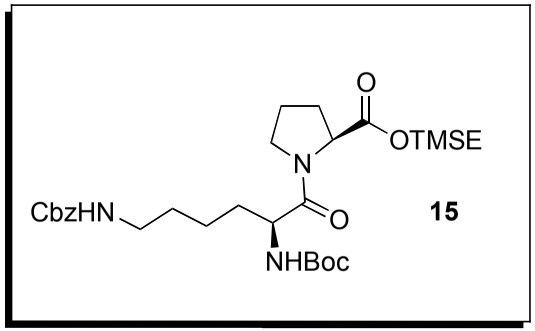
Lys^3 Tamandarin M (6). Macrocycle **7** (12 mg, 0.0121 mmol) was dissolved in EtOAc (3 mL) and the solution was cooled to -20 ºC. HCl gas was bubbled into the solution for 5 min. The reaction mixture is allowed to stir at -20 ºC for 1 h and then stirred at 0 ºC for an additional 30 min. At this time the ice bath is removed and argon is bubbled through the solution for 30 minutes. The solvent was evaporated to yield the macrocyclic salt (11 mg, 99%) as an off-white solid, which was used without further purification. The salt was dissolved in CH_2Cl_2 (1 mL) and to this solution was added acid **8** (10 mg, 0.0181 mmol), BOP (8 mg, 0.0181 mmol) and NMM (5μL, 0.0484 mmol). The reaction was stirred for 24 h. The reaction was diluted with EtOAc (15 mL), washed with 10% HCl (5 mL), 5% $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated to yield the crude product. Purification by flash chromatography (1→10% MeOH/CH_2Cl_2) yielded the product (8 mg, 47%) as a white solid. R_f 0.24 (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70-1.06 (m, 14H), 1.12-1.44 (m, 16H), 1.48-1.63 (m, 3H), 1.65-1.92 (m, 11H), 1.95-2.34 (m, 10H), 2.38-2.67 (m, 5H), 3.00 (s, 3H), 3.07 (m, 3H), 3.15 (m, 1H), 3.31 (m, 1H), 3.42-3.68 (m, 4H), 3.77 (s, 1H), 3.86 (t, *J*= 9.19 Hz, 1H), 4.13 (m, 2H), 4.52 (m, 3H), 4.70 (t, *J*= 6.89 Hz, 1H), 4.78 (t, *J*= 8.68 Hz, 1H), 4.95-5.12 (m, 3H), 5.21 (m, 1H), 5.35 (m, 1H), 5.53 (s, 1H), 6.23 (s, 1H), 6.82 (d, *J*= 8.14 Hz, 2H), 6.90 (d, *J*= 7.79 Hz, 1H), 7.04 (d, *J*= 8.19 Hz, 2H), 7.32 (m, 5H), 7.62 (d, *J*= 9.24 Hz, 1H), 7.73 (d, *J*= 9.84 Hz, 1H), 7.81 (m, 1H), 8.36 (d, *J*= 6.40 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 15.7, 15.9, 16.6, 17.8, 18.8, 20.1, 21.7, 22.7, 23.2, 25.6, 25.0, 25.2, 25.5, 25.8, 27.3, 28.0, 28.4, 28.9, 29.4, 29.7, 30.1, 30.4, 30.9, 31.2, 31.8, 32.0, 32.8, 33.8, 36.1, 38.7, 39.3, 40.8, 47.1, 49.5, 52.1, 54.1, 55.3, 55.9, 56.8, 57.1, 57.3, 58.2, 65.3, 66.6, 68.7, 69.5, 70.8, 79.3, 114.1, 128.1, 128.2, 128.5, 129.7, 130.0, 130.5, 136.7, 156.5, 158.6, 168.8, 169.5, 169.9, 170.3, 170.4, 170.9, 171.3, 173.3, 173.4, 173.6, 176.9; IR (cm^{-1}) 3437, 3344, 2956, 2930, 1659, 1651, 1633, 1535, 1455, 1246, 1091; HRMS (ES) *m/z* calcd for $C_{71}H_{103}N_{11}O_{20}$: 1452.7279, found: 1452.7245; $[\alpha]_D^{22}$ -24.9 (c 0.7, CH_2Cl_2).



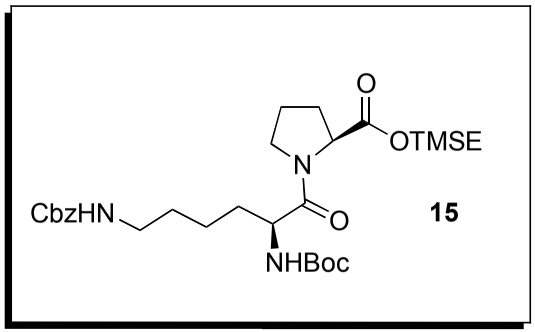
^{1}H NMR ($CDCl_3$, 500 MHz)



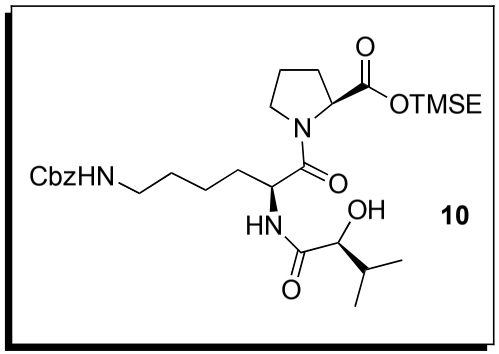
^{13}C NMR ($CDCl_3$, 125 MHz)



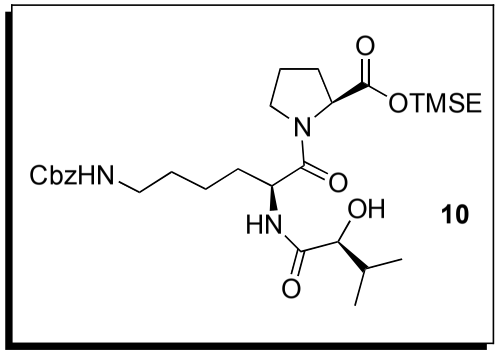
^{1}H NMR of **15** ($CDCl_3$, 500 MHz)

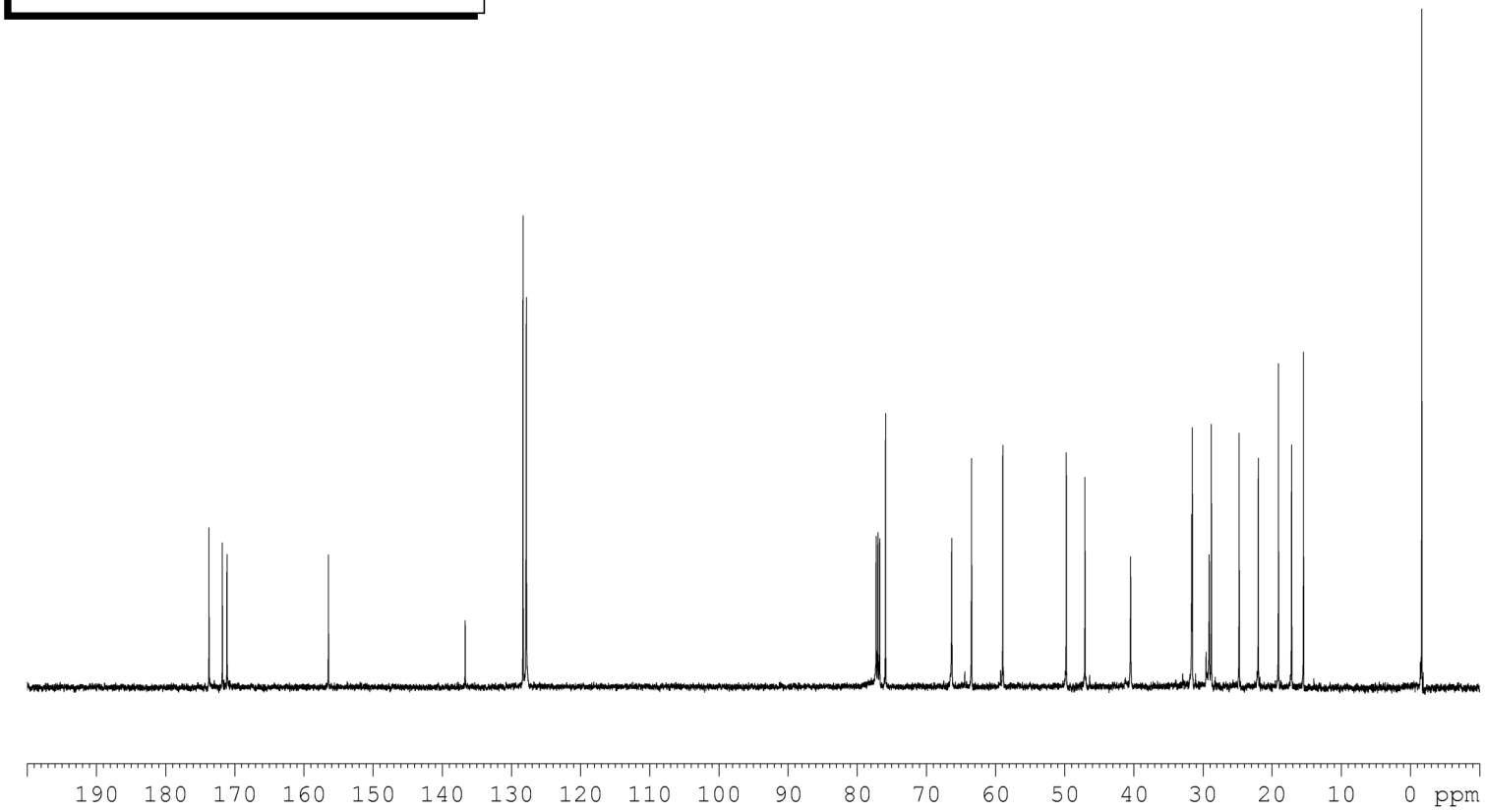


^{13}C NMR of **15** ($CDCl_3$, 125 MHz)

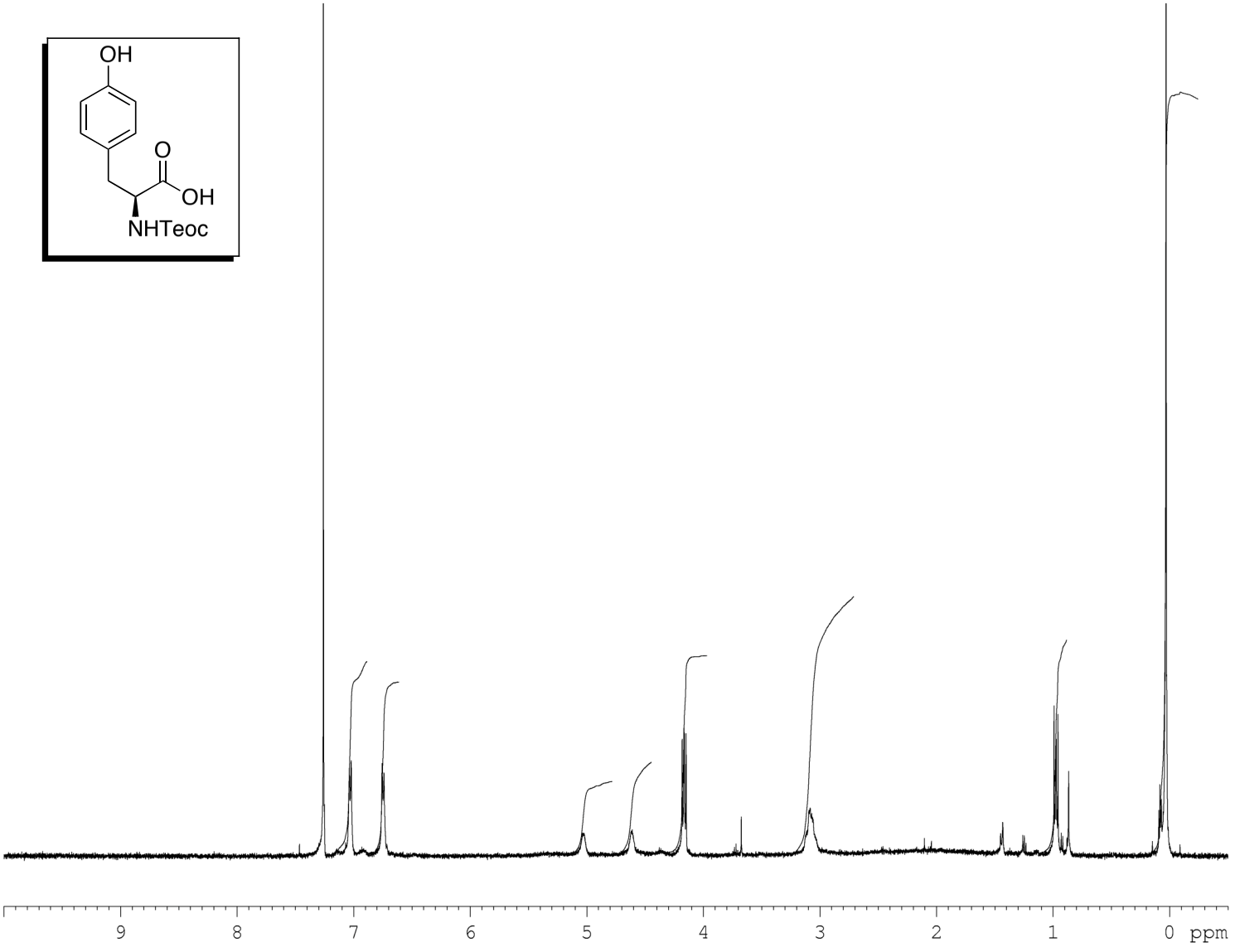


^{1}H NMR of **10** ($CDCl_3$, 500 MHz)

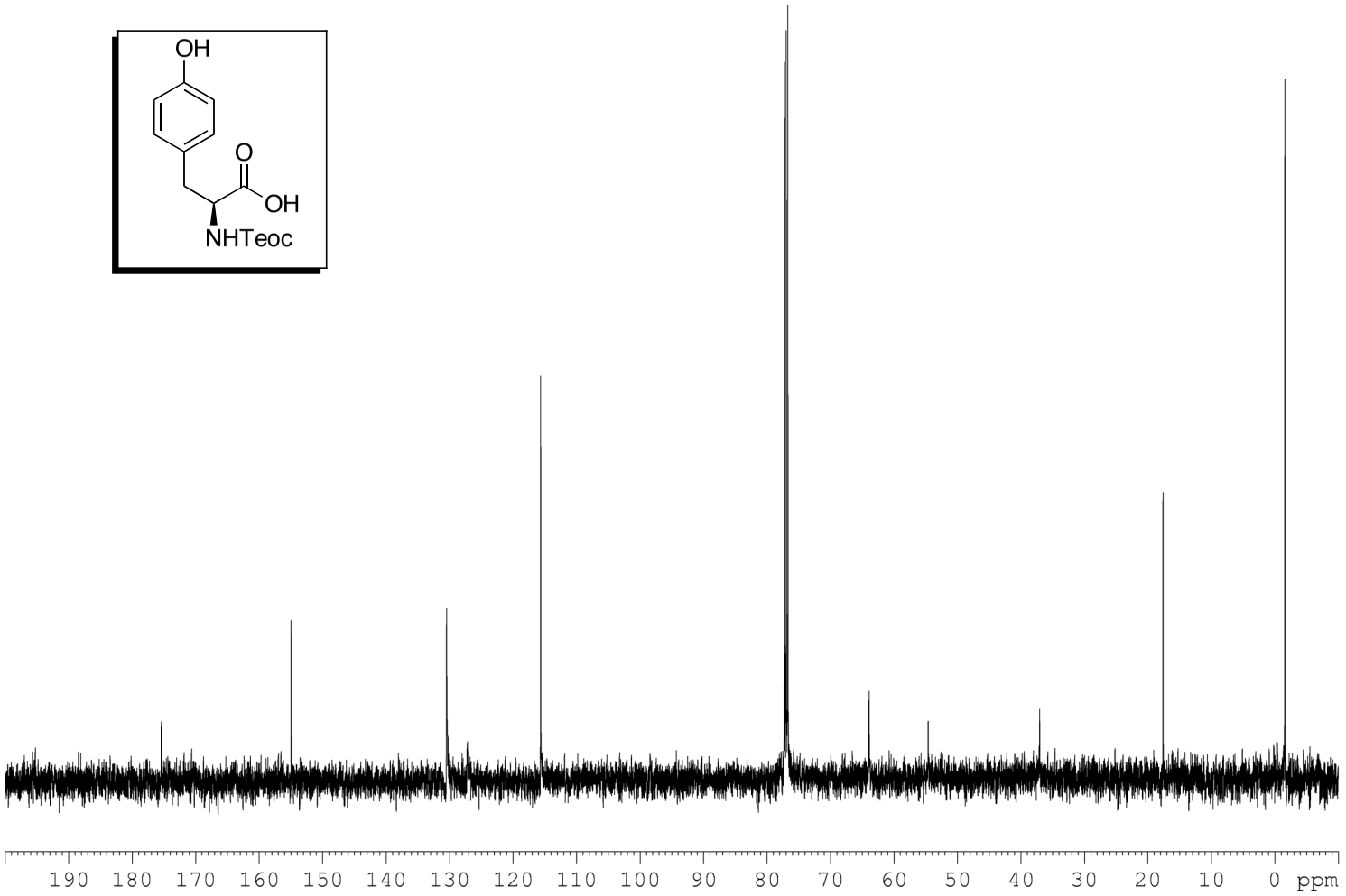




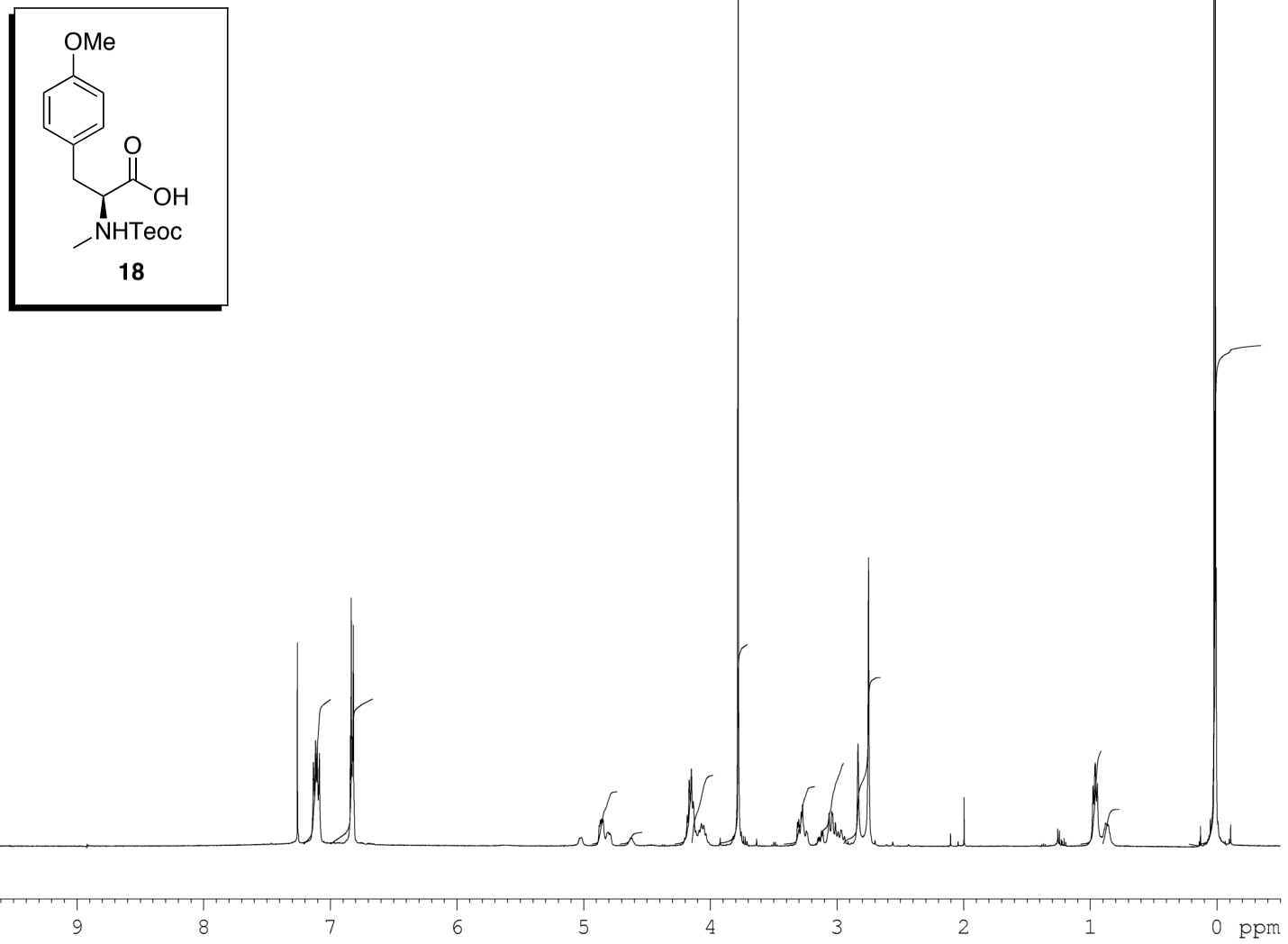
^{13}C NMR of **10** ($CDCl_3$, 125 MHz)



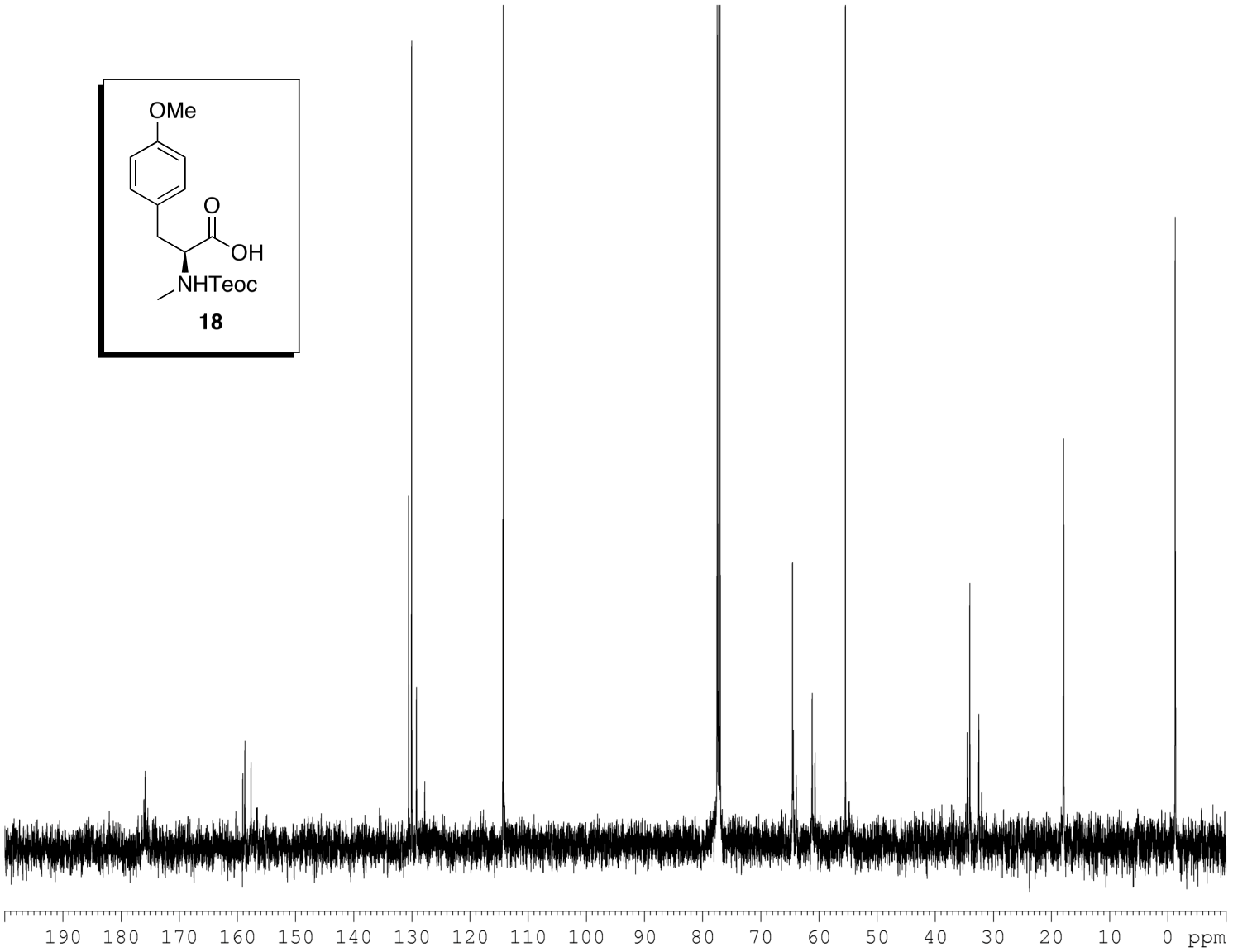
^{1}H NMR ($CDCl_3$, 500 MHz)



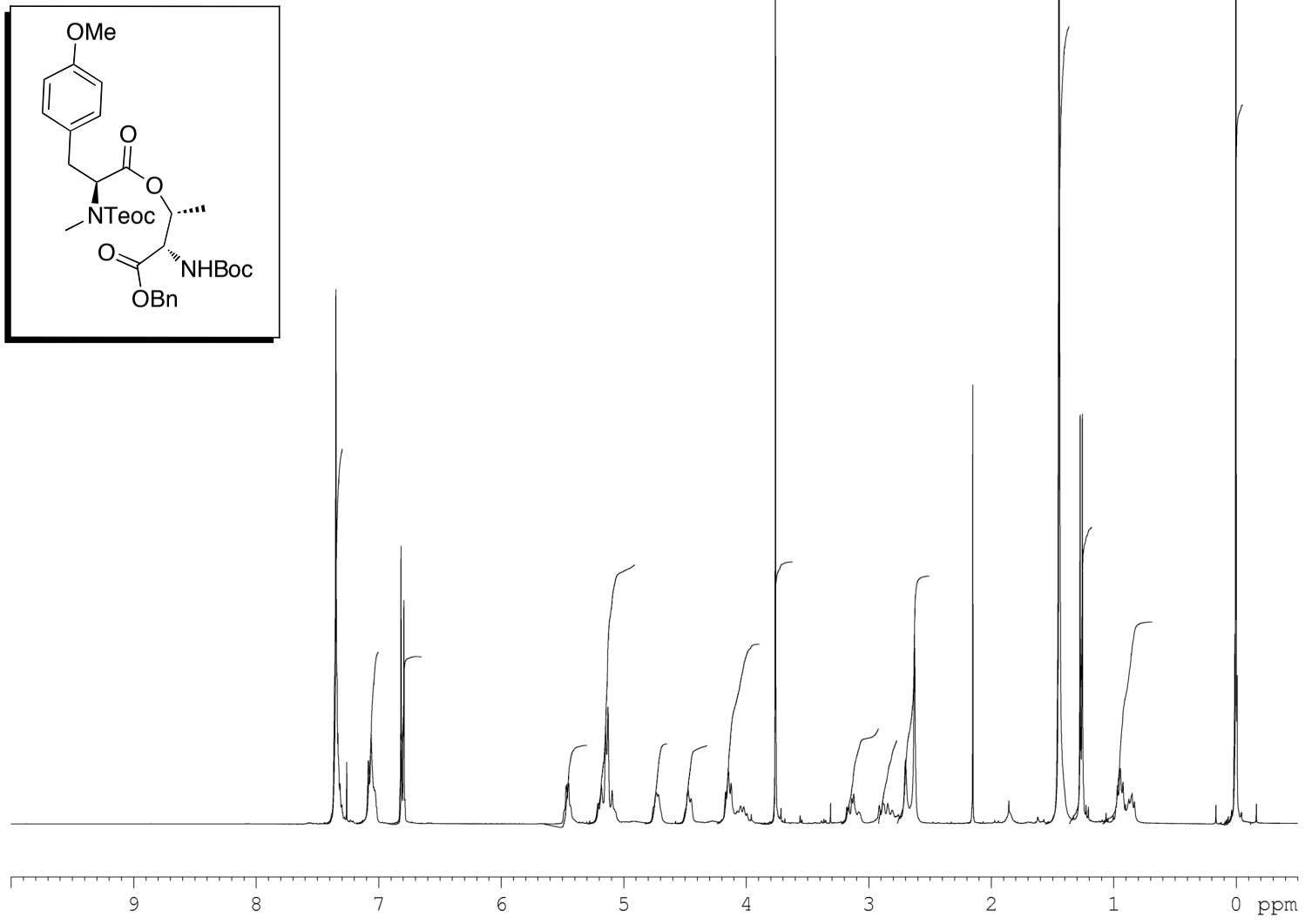
^{13}C NMR ($CDCl_3$, 125 MHz)



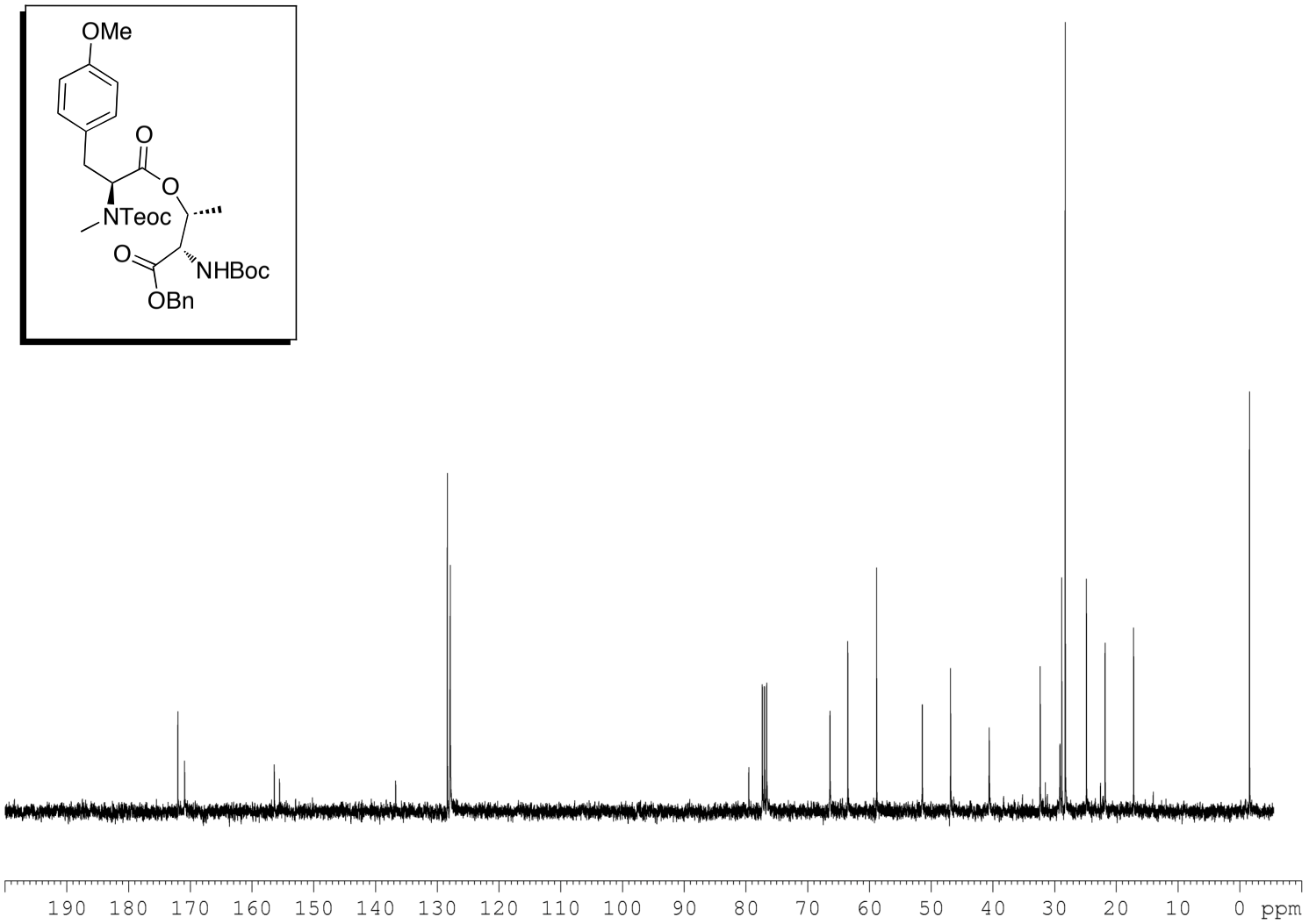
^{1}H NMR of **18** ($CDCl_3$, 500 MHz)



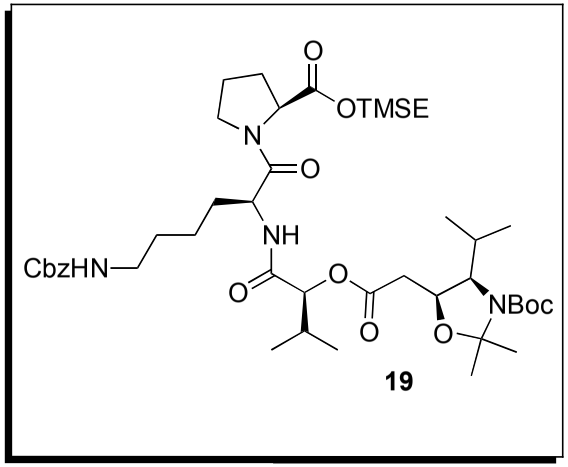
^{13}C NMR of **18** ($CDCl_3$, 125 MHz)



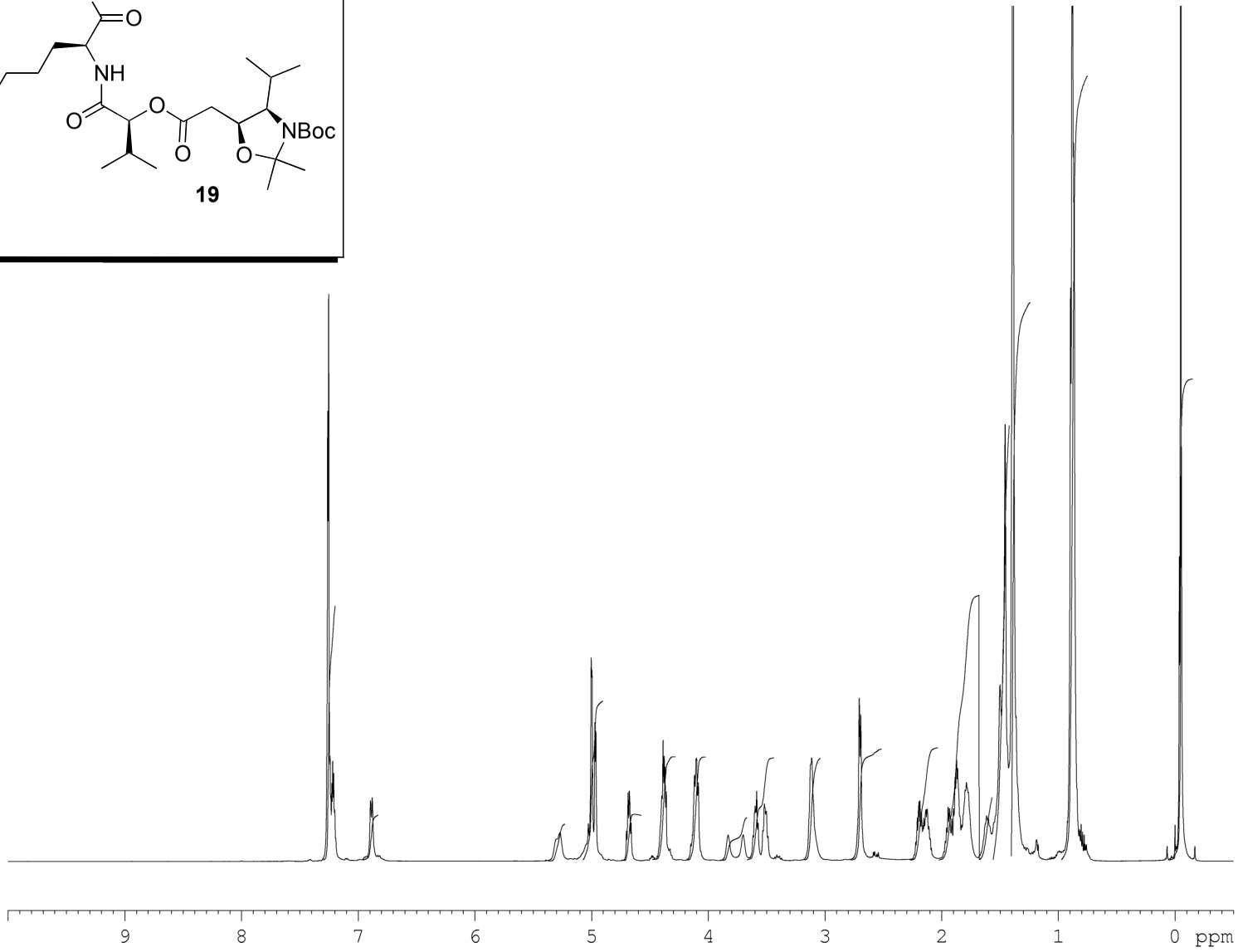
^{1}H NMR ($CDCl_3$, 500 MHz)



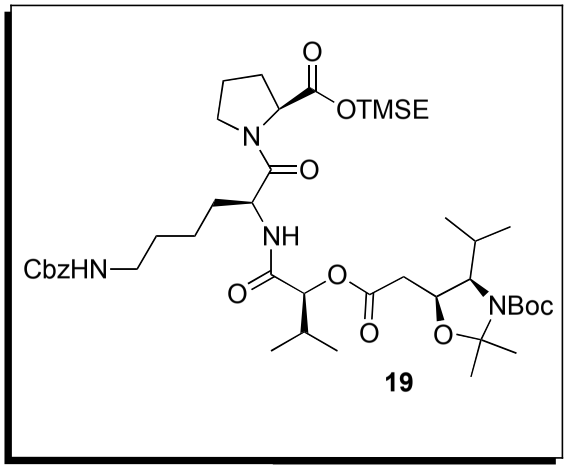
^{13}C NMR ($CDCl_3$, 125 MHz)



19

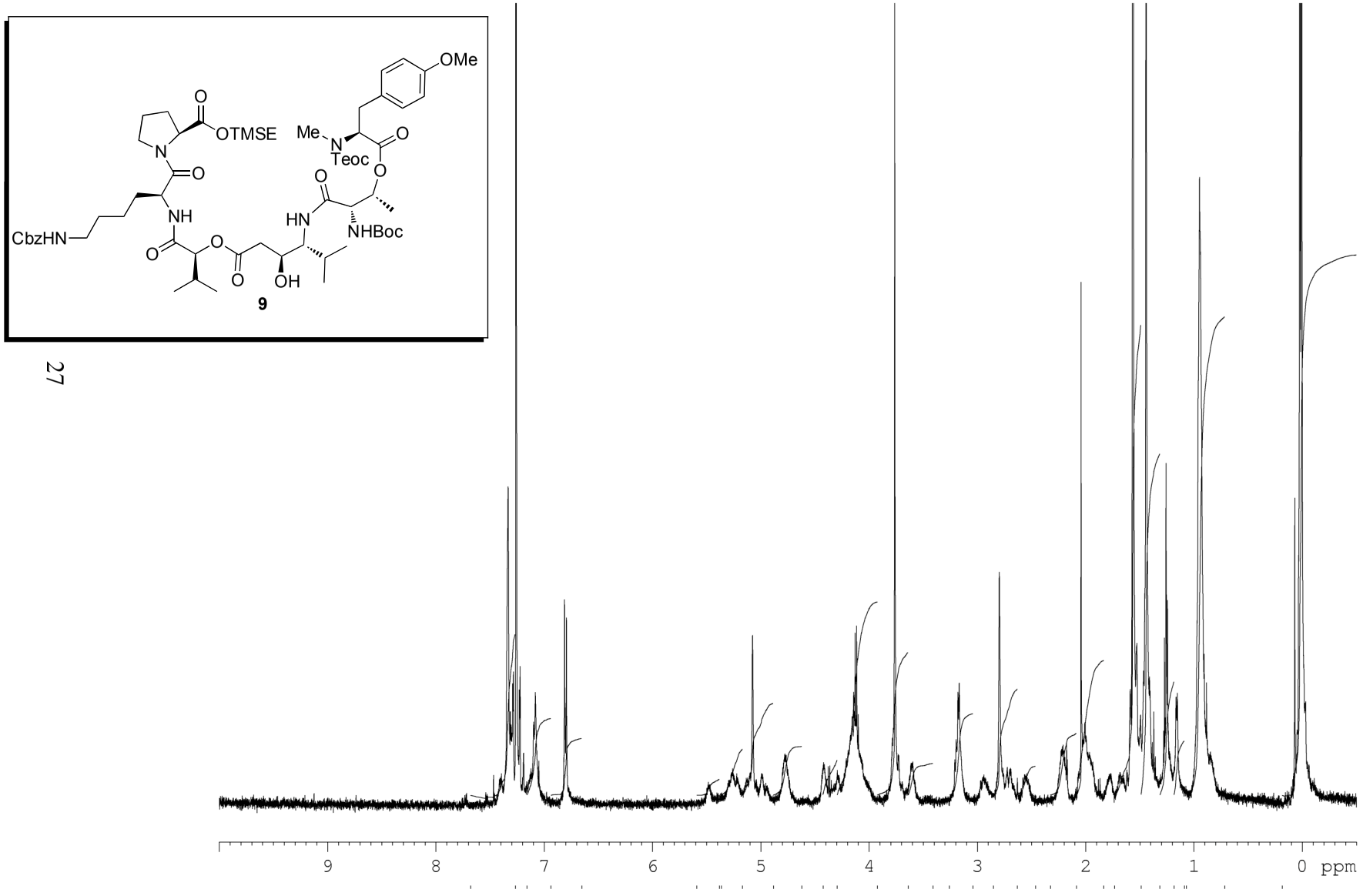


^{1}H NMR of **19** ($CDCl_3$, 500 MHz)

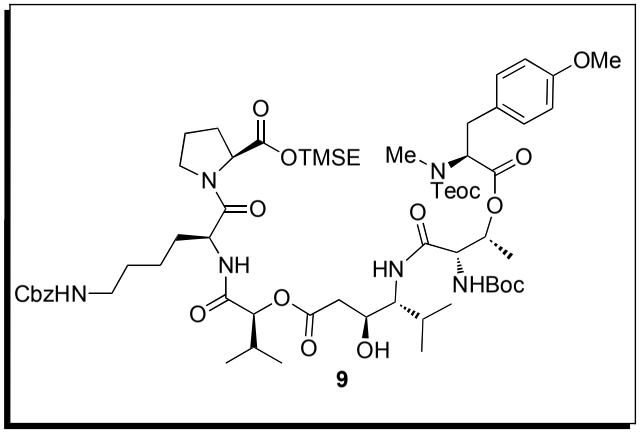


19

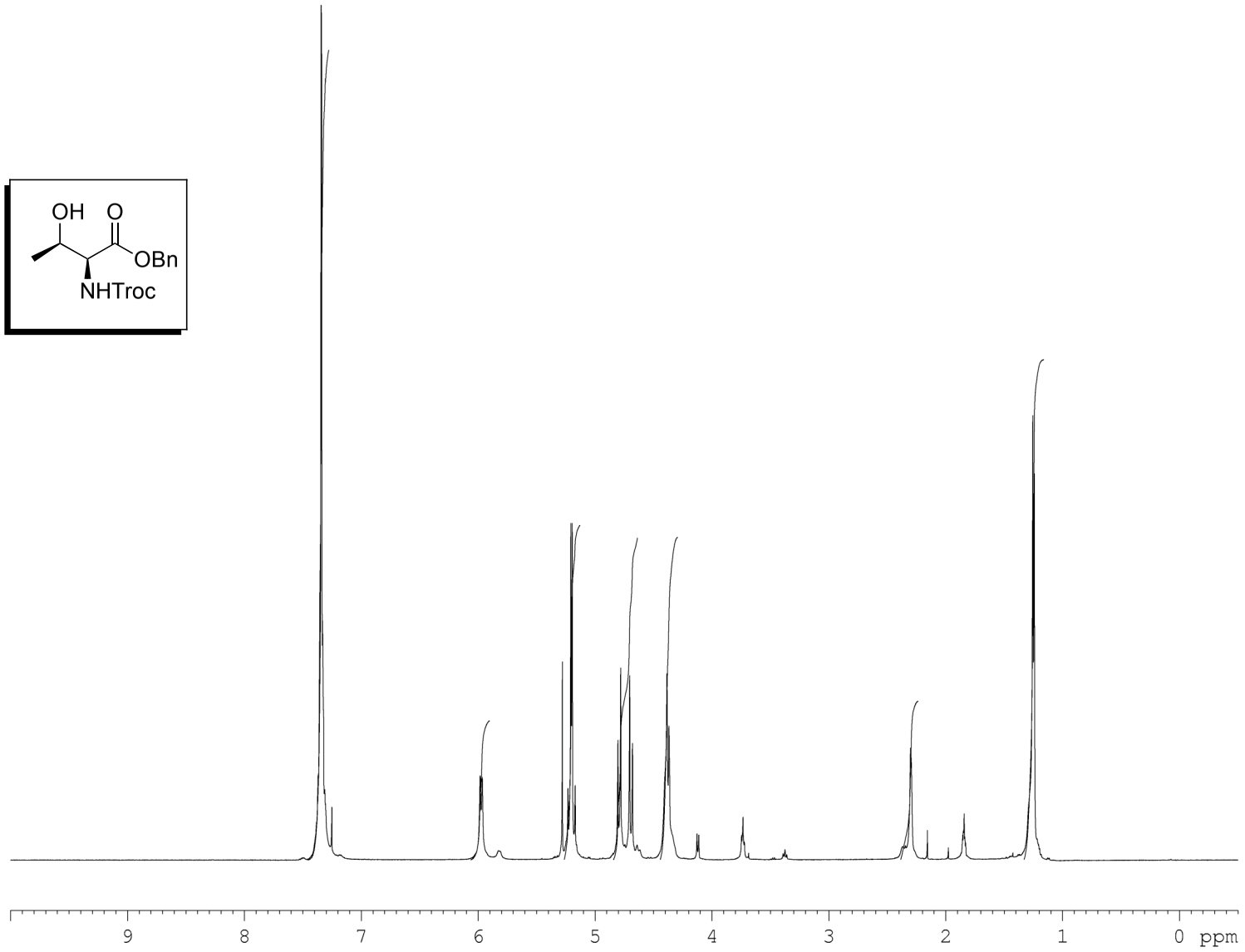
^{13}C NMR of **19** ($CDCl_3$, 125 MHz)



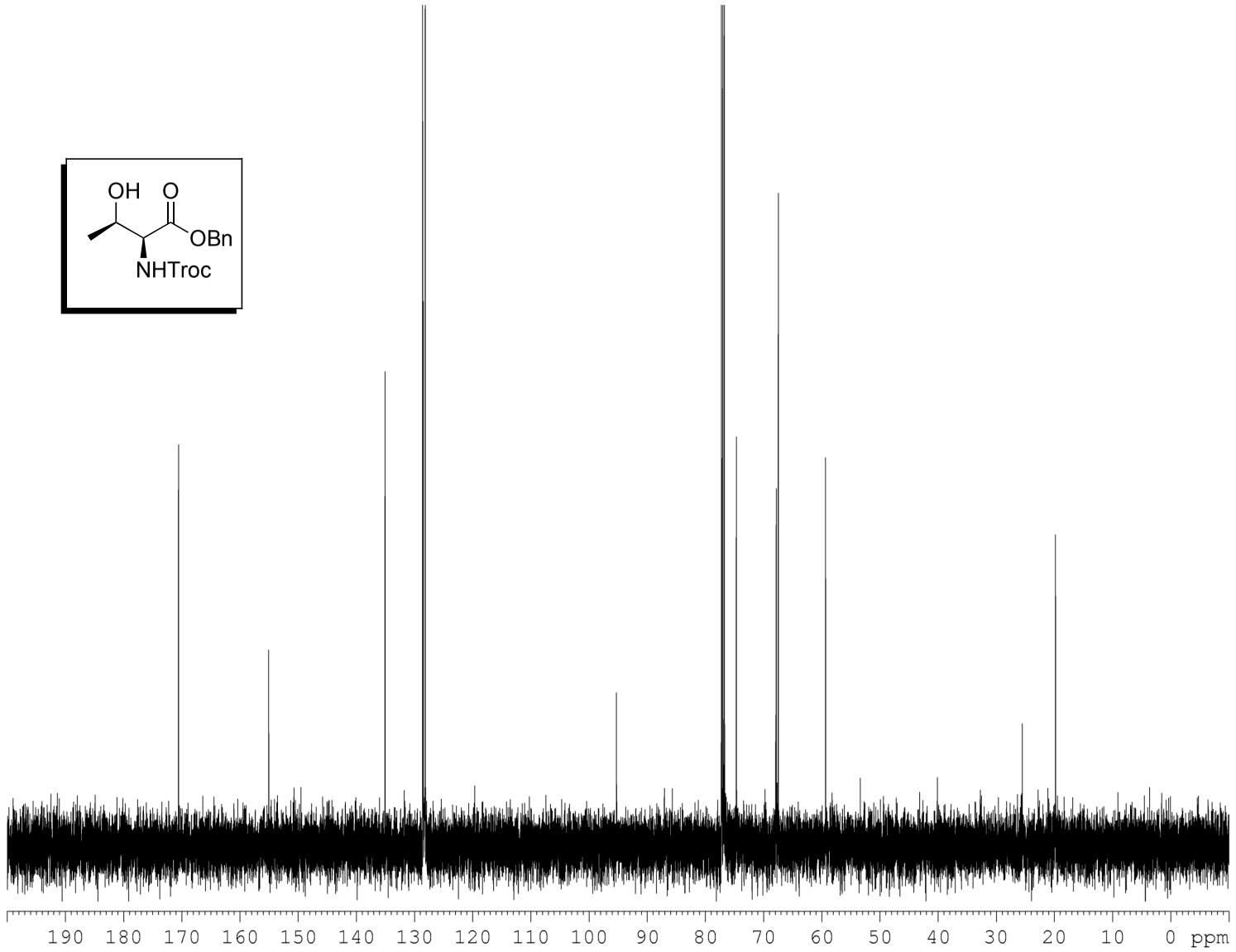
^{1}H NMR of **9** ($CDCl_3$, 500MHz)



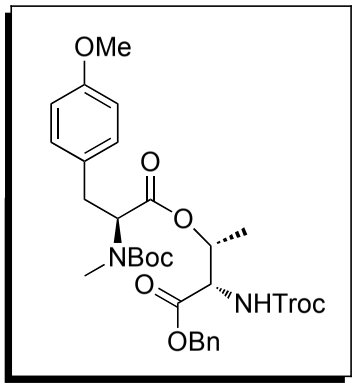
^{13}C NMR of **9** ($CDCl_3$, 125MHz)



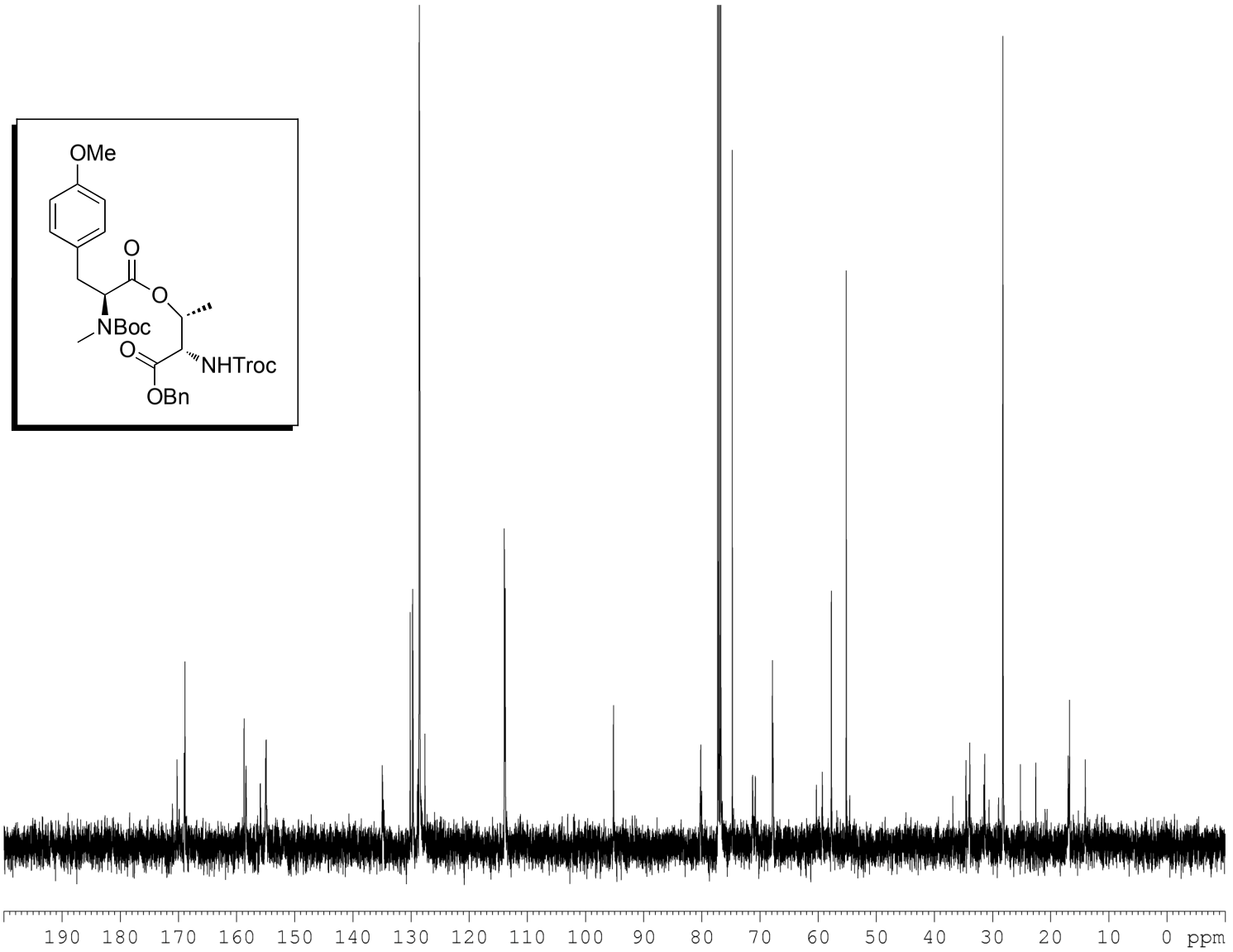
^{1}H NMR (CDCl$_3$, 500MHz)



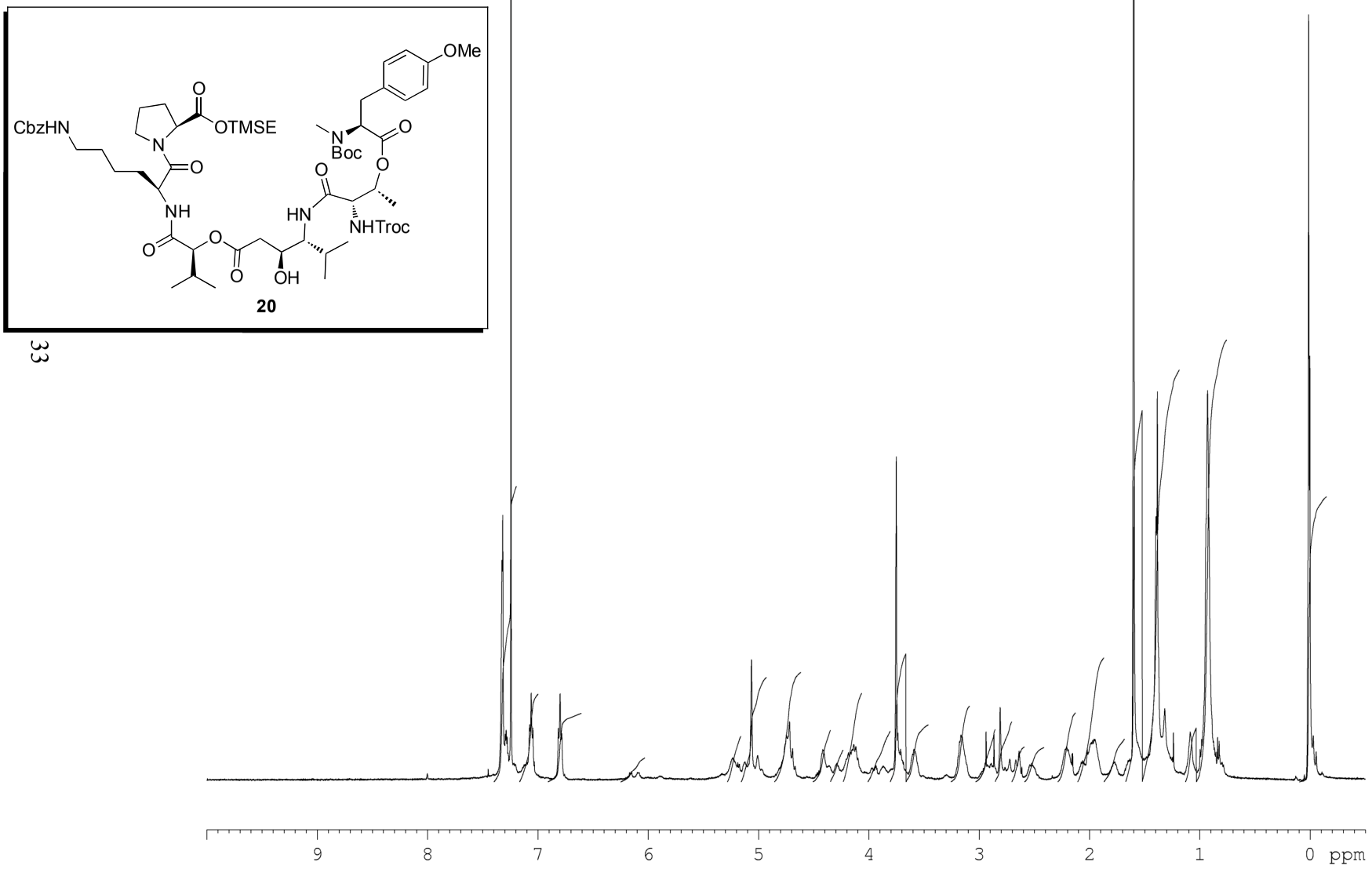
^{13}C NMR ($CDCl_3$, 125MHz)



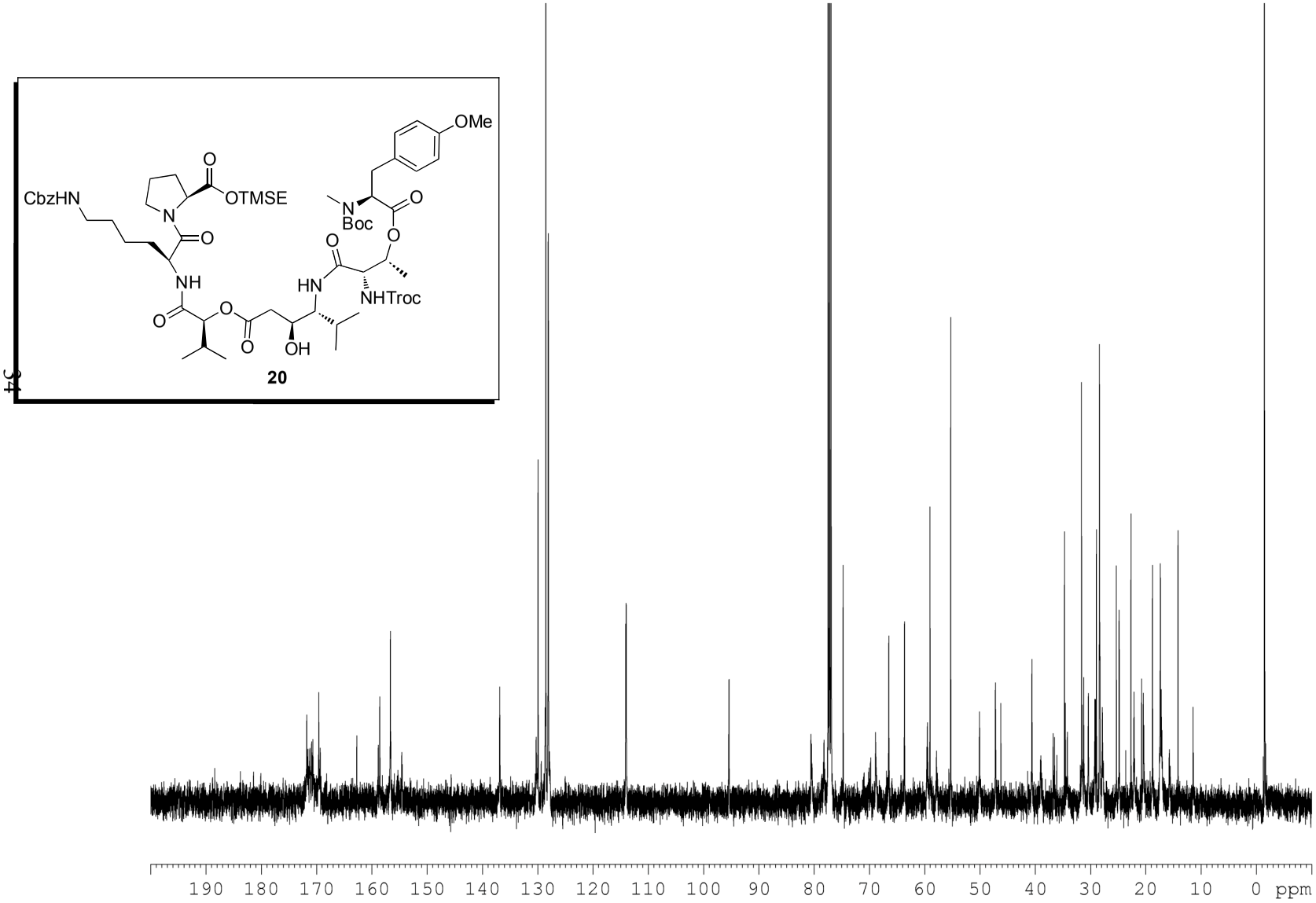
^{1}H NMR (CDCl$_3$, 500MHz)



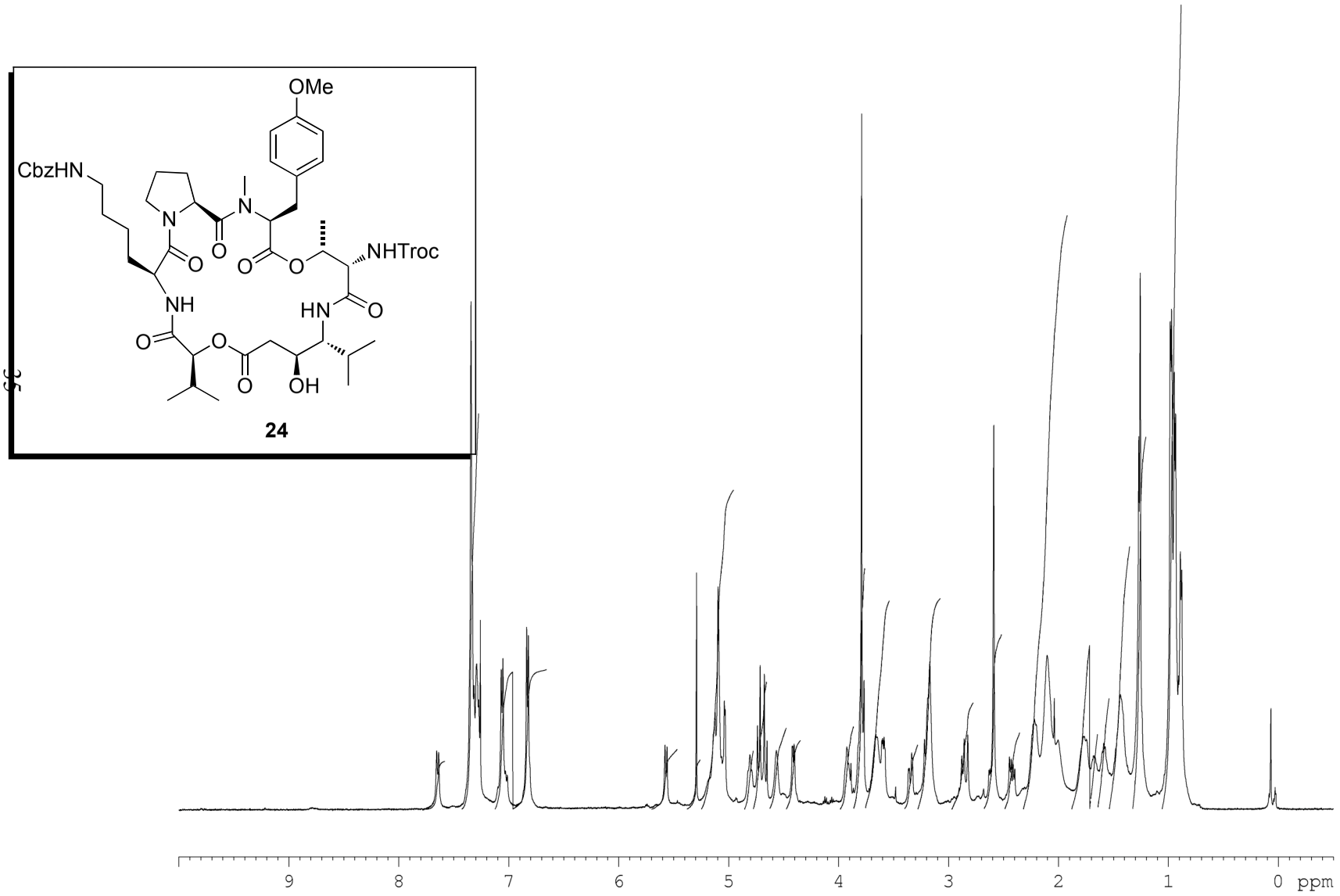
^{13}C NMR ($CDCl_3$, 125MHz)



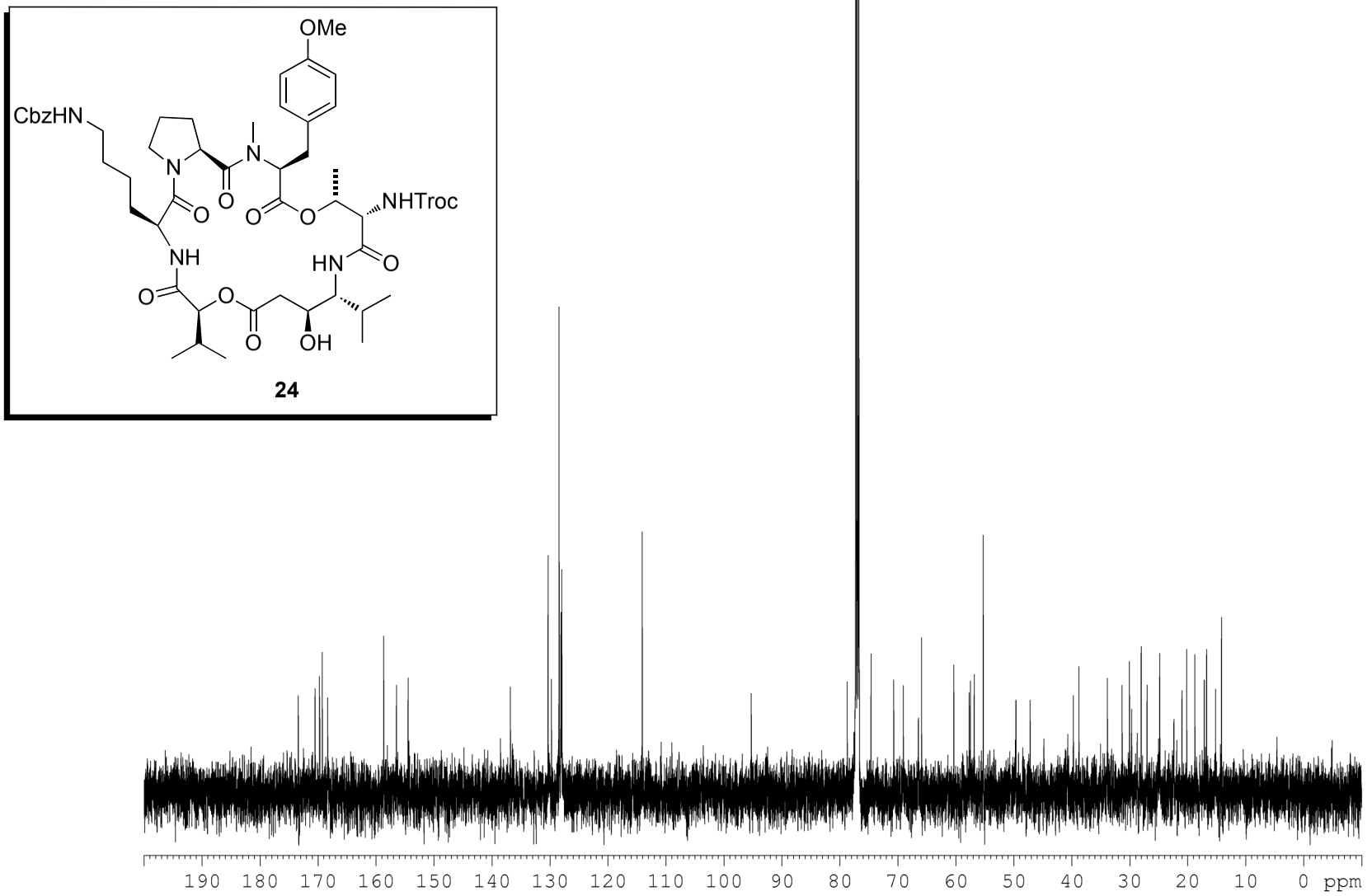
^{1}H NMR of **20**($CDCl_3$, 500MHz)



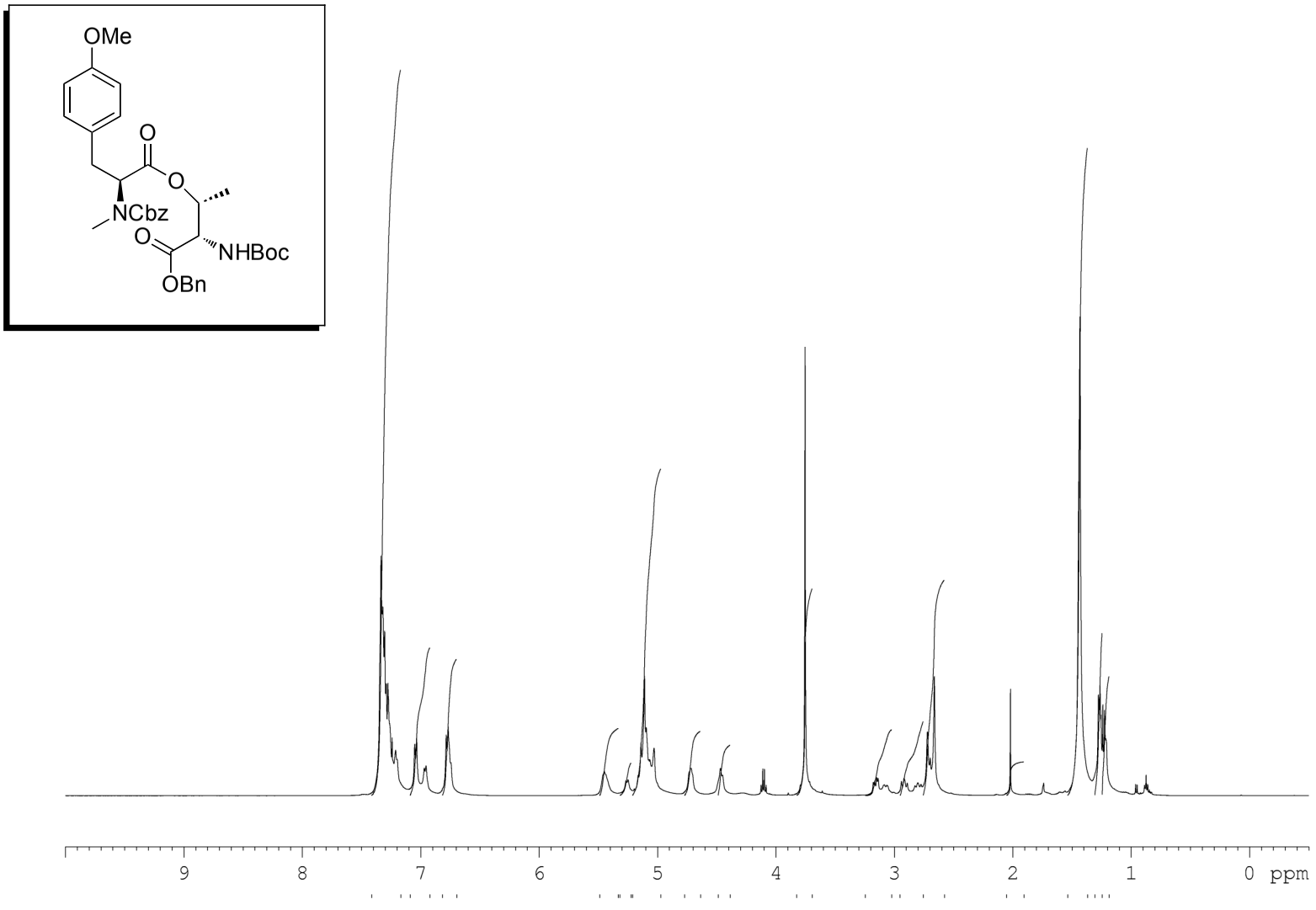
^{13}C NMR of **20** ($CDCl_3$, 125MHz)



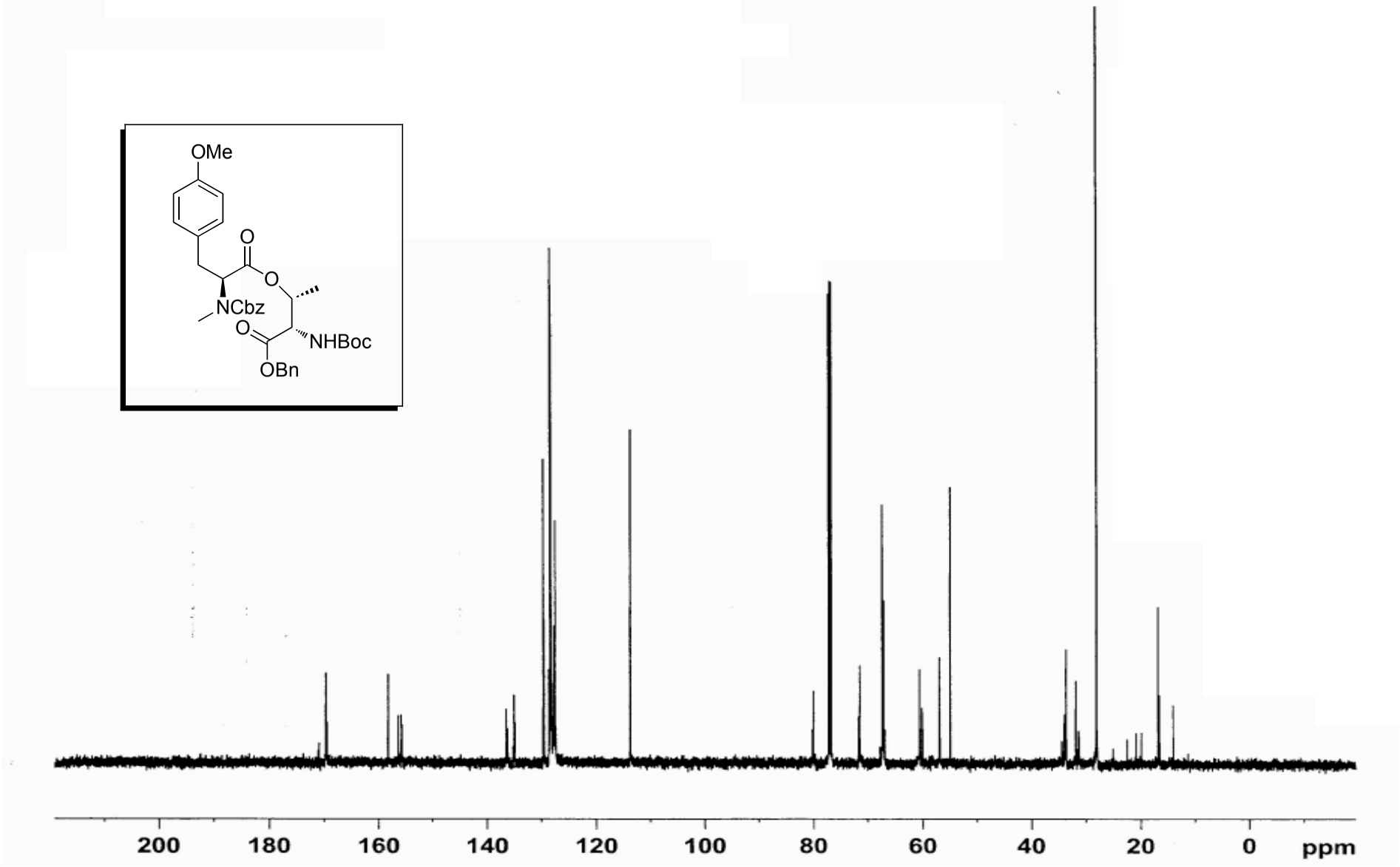
^{1}H NMR of **24** ($CDCl_3$, 500MHz)



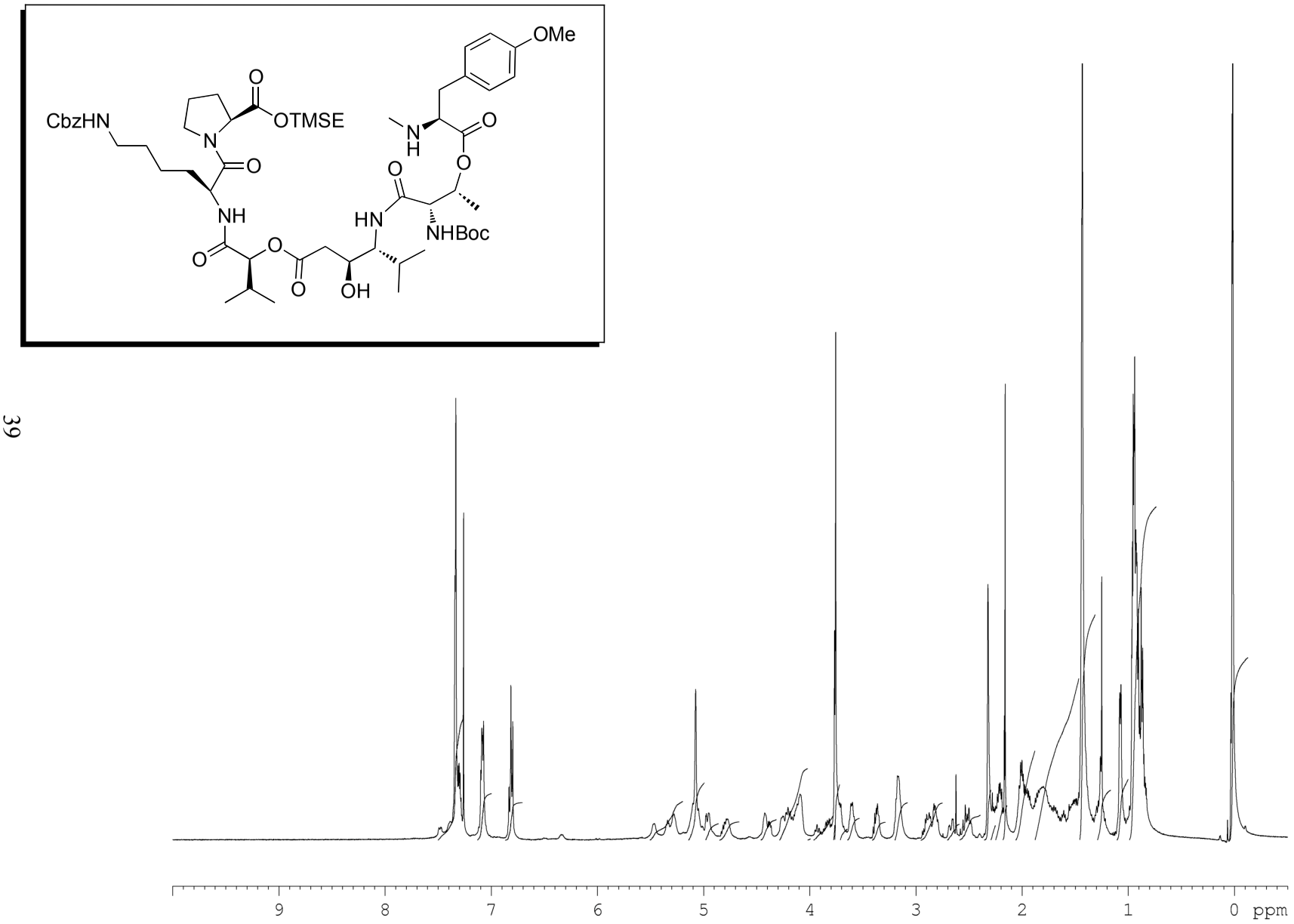
^{13}C NMR of **24** ($CDCl_3$, 125 MHz)



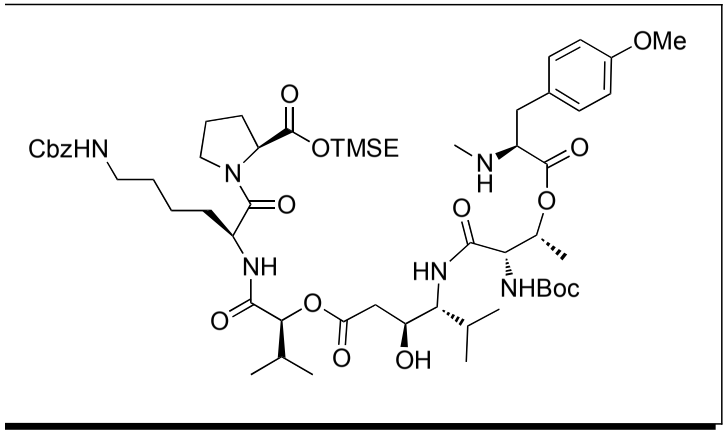
^{1}H NMR ($CDCl_3$, 500 MHz)



^{13}C NMR ($CDCl_3$, 125 MHz)

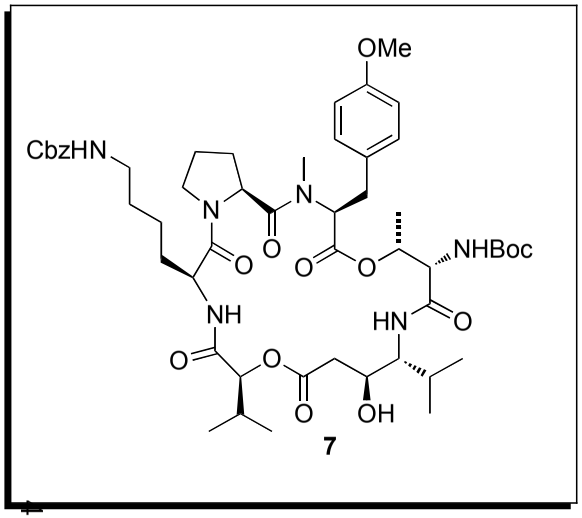


^{1}H NMR of **linear precursor** ($CDCl_3$, 500 MHz)

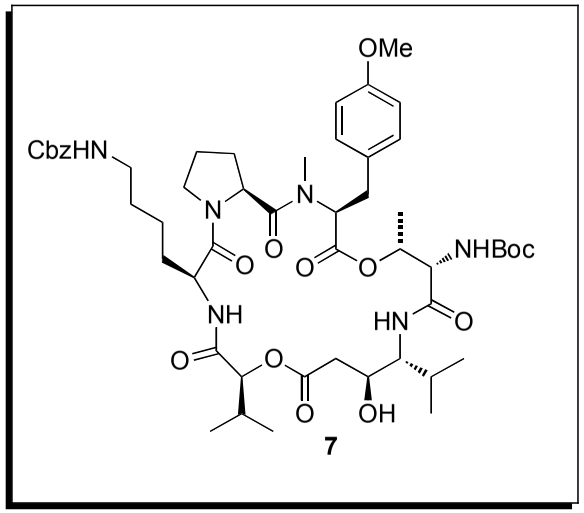


40

^{13}C NMR of **linear precursor** ($CDCl_3$, 125 MHz)

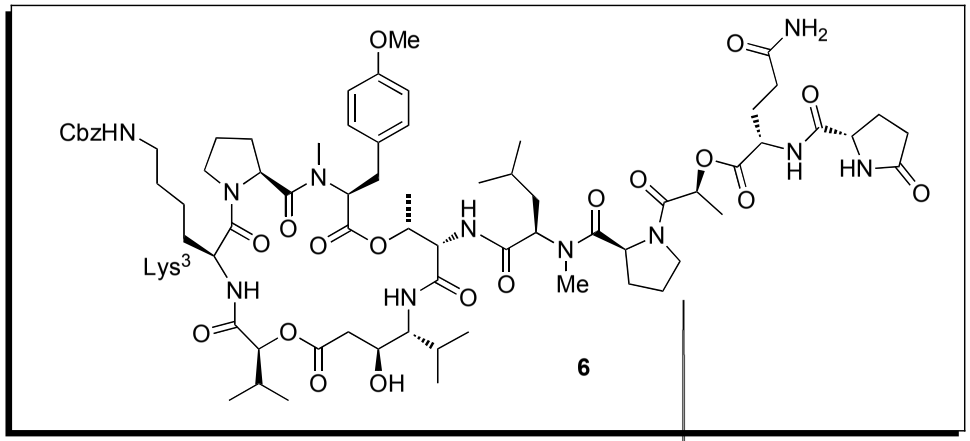


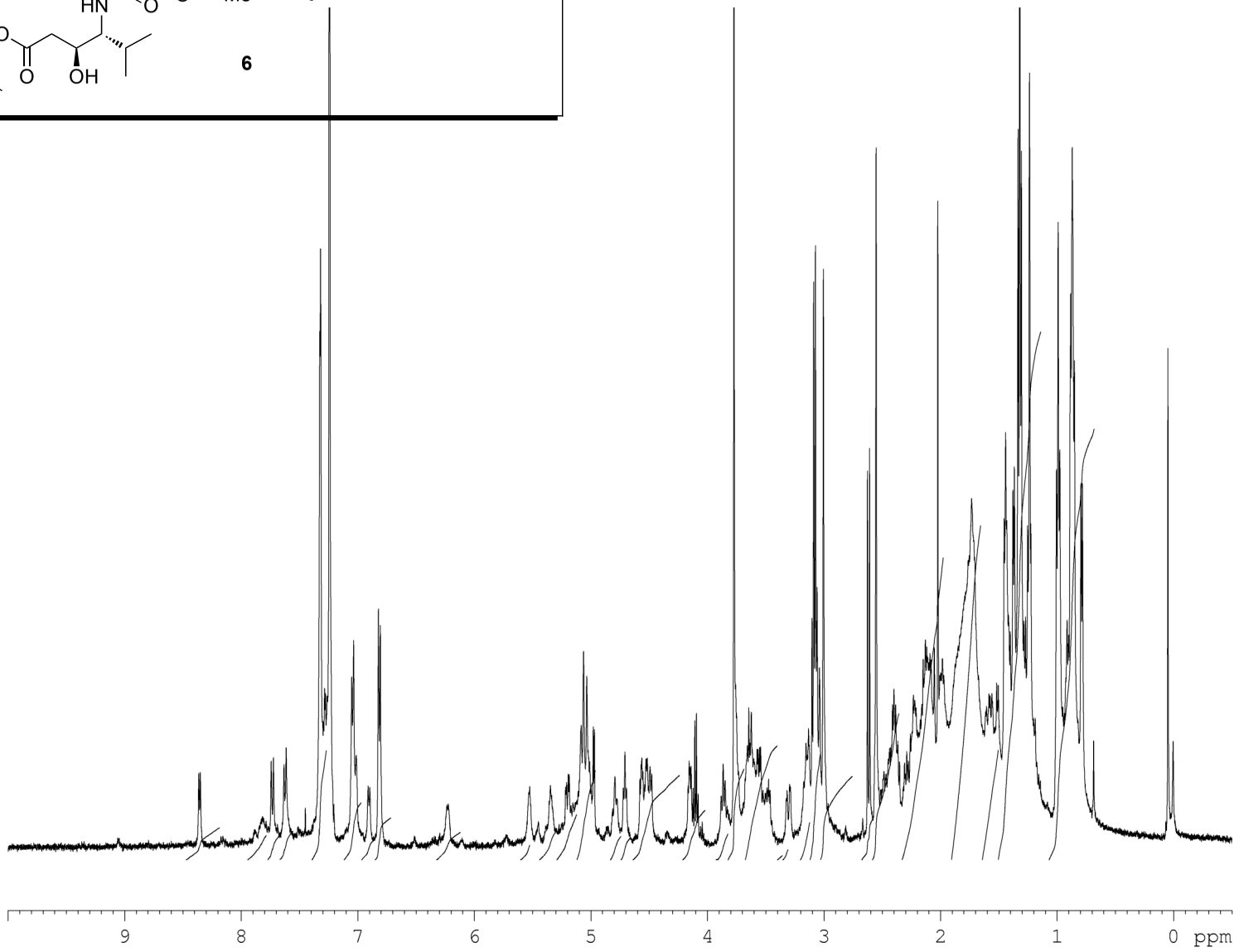
^{1}H NMR of **6** ($CDCl_3$, 500 MHz)



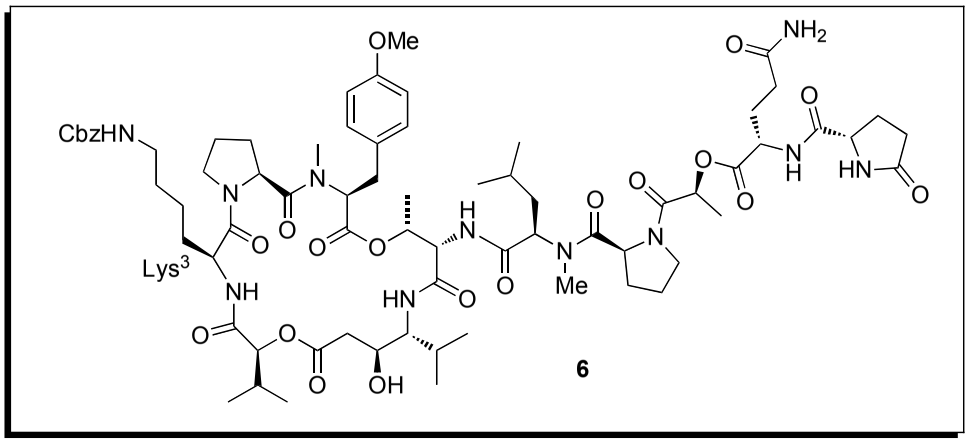
7

^{13}C NMR of **7** ($CDCl_3$, 125 MHz)





^{1}H NMR of **6** ($CDCl_3$, 500 MHz)



^{13}C NMR of **6** ($CDCl_3$, 125 MHz)