Supporting Information

Brief, efficient and highly diastereoselective synthesis of (±)-Pumiliotoxin C based on the generation of an octahydroquinoline precursor *via* a four-component reaction

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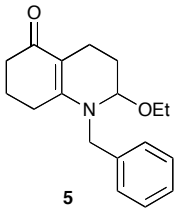
Experimental Section

General experimental information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with Al_2O_3 with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on Al_2O_3 gel (SDS 60 ACC 40-63 μm). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

1-Benzyl-2-ethoxy-1,2,3,4,5,6,7,8-octahydro-1*H*-quinolin-5-one (5)

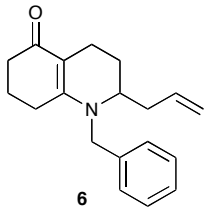


5

To a stirred solution of 1,3-cyclohexanedione **1** (1 mmol), benzylamine **2** and ethanol **4** (5 mmol) in dry dichloromethane (10 mL) was added indium triflate (10 mol %) and stirring was continued for 1 hour at room temperature. Acrolein **3** (1.3 mmol) was then added and stirring was continued at room temperature for 5 h. After completion of the reaction, as judged by TLC, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (5 mL) and dried (anhydrous Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified

by a rapid column chromatography on activated neutral alumina (activity grade IV), eluting with a petroleum ether-ethyl acetate mixture (60:40, V/V), giving compound **5** (270 mg, 95%), as a colourless viscous liquid. IR (neat) 2941.9, 1570.4, 1436.0, 1392.3, 1169.8, 1067.4 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.24 (t, *J* = 5.9 Hz, 3H), 1.52-1.66 (m, 1H), 1.84-1.98 (m, 2H), 2.13-2.19 (m, 2H), 2.24-2.39 (m, 3H), 2.44-2.52 (m, 1H), 2.69 (d, *J* = 12.6 Hz, 1H), 3.38-3.48 (m, 1H), 3.55-3.65 (m, 1H), 4.46 (s, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 4.74 (d, *J* = 14.5 Hz, 1H), 7.17 (d, *J* = 6.3 Hz, 2H), 7.31 (d, *J* = 5.1 Hz, 1H), 7.36-7.41 (m, 2H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 14.4, 15.7, 21.9, 24.7, 26.7, 36.1, 52.7, 62.9, 86.5, 108.3, 126.1 (2C), 127.5, 129.0 (2C), 138.2, 157.9, 194.4. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.68; H, 8.14; N, 4.70.

2-Allyl-1-benzyl-1,2,3,4,5,6,7,8-octahydro-1*H*-quinolin-5-one (6)

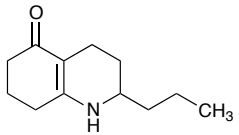


6

To a solution of compound **5** (1 mmol) in dry dichloromethane (10 mL) was added $BF_3.Et_2O$ (2 mmol) and allyltrimethylsilane (1.3 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. After verifying completion of the reaction by TLC, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (5 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude residue was chromatographed on neutral Al_2O_3 (activity grade IV), eluting with a 50:50 petroleum ether-ethyl acetate mixture, to yield 261 mg (93%) of compound **6**, as a white solid, mp 104 °C (EtOAc-hexane). IR (neat) 2941.9, 1552.5, 1439.8, 1393.8, 1192.9, 1168.1, 733.6, 697.9 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.61-1.74 (m, 1H), 1.77-1.99 (m, 3H), 2.16-2.46 (m, 7H), 2.64 (dd, *J* = 4.5 and 13.9 Hz, 1H), 3.32-3.36 (m, 1H), 4.33 (d, *J* = 14.4 Hz, 1H), 4.77 (d, *J* = 14.4 Hz, 1H), 5.07-5.13 (m, 2H), 5.65-5.76 (m, 1H), 7.15 (d, *J* = 5.8 Hz, 2H), 7.31 (d, *J* = 5.9 Hz,

1H), 7.35-7.40 (m, 2H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 22.1, 23.6, 27.2, 36.2, 36.4, 53.5, 57.9, 106.3, 118.5, 126.1 (2C), 127.9, 129.4 (2C), 134.6, 137.9, 159.0, 194.6. Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.87; H, 7.99; N, 5.01.

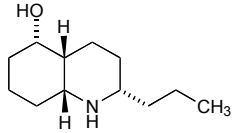
2-Propyl-1,2,3,4,5,6,7,8-octahydro-1*H*-quinolin-5-one (7)



7

To a solution of compound **7** (1 mmol) in glacial acetic acid (6 mL) was added 10% Pd-C (141 mg), and the suspension was stirred under a hydrogen atmosphere (60 psi) at 50 °C for 12 hours. The reaction mixture was filtered through celite and washed with saturated $NaHCO_3$ aqueous solution, dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude residue was purified by column chromatography on neutral Al_2O_3 (activity grade IV), eluting with a 60:40 petroleum ether-ethyl acetate mixture, to give 181 mg (95%) of compound **7** as a white solid, mp 105 °C (EtOAc-hexane). IR (neat) 3249.9, 2934.0, 1574.4, 1519.5, 1403.5, 1287.6, 1189.3, 1131.0 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.96 (t, J = 6.7 Hz, 3H), 1.33-1.54 (m, 5H), 1.87-1.99 (m, 3H), 2.15-2.25 (m, 1H), 2.32(q, J = 7.1 Hz, 4H), 2.53 (dt, J = 4.7 and 16.1 Hz, 1H), 3.24-3.26 (m, 1H), 4.66 (s, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 14.5, 18.6, 19.2, 22.2, 27.1, 29.5, 36.8, 38.0, 51.6, 104.6, 160.2, 194.3. Anal. Calcd. for $C_{12}H_{17}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 75.04; H, 9.10; N, 7.29.

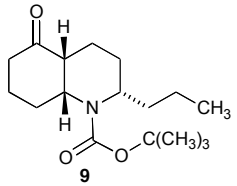
(±)-(2*S,4a*R**,5*S**,8a*R**)-2-Propyldecahydroquinolin-5-ol (8)**



8

To a solution of the compound **7** (1 mmol) in glacial acetic acid (6 mL) was added 5% Pt-C (193 mg) and the suspension was stirred under a hydrogen atmosphere (90 atm) at 50 °C for 24 h. The reaction mixture was filtered through celite and washed with saturated $NaHCO_3$ aqueous solution, dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude residue was purified by column chromatography on neutral Al_2O_3 (activity grade IV), eluting with a 94:6 petroleum ether-ethyl acetate mixture, to give 187 mg (95%) of compound **8** as a white solid, mp 64 °C. IR (neat) 3285.9, 2929.5, 2870.5, 1456.1, 1323.4, 1247.5, 1124.2, 1109.1, 1056.4, 967.5, 782.3 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.83-0.89 (m, 3H), 1.18-1.29 (m, 4H), 1.32-1.45 (m, 3H), 1.55-1.97 (m, 10H), 2.52-2.63 (m, 1H), 2.88 (s, 1H), 3.86 (s, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 14.7, 15.1, 19.2, 29.4, 30.1, 32.9, 34.8, 37.6, 39.8, 57.4, 57.8, 73.6. Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: 72.88; H, 11.50; N, 6.83.

(±)-(2*S,4a*R**,8a*R**)-1-*tert*-Butyloxycarbonyl-2-propyldecahydroquinolin-5-one (9)**

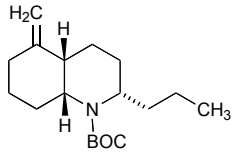


9

To a solution of compound **8** (1 mmol) in dry CH_3CN (6 mL) was sequentially added $(Boc)_2O$ (1.2 mmol) and solid K_2CO_3 (0.3 mmol). The reaction mixture was refluxed under argon for 24 hours, cooled and concentrated to dryness. The crude residue was dissolved in dry

dichloromethene (10 mL), and Dess-Martin periodindane reagent (1.1 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and, after verifying completion of the reaction by TLC, it was concentrated to dryness. The crude residue was purified by column chromatography on neutral Al_2O_3 (activity grade IV), eluting with a 95:5 petroleum ether-ethyl acetate mixture, to yield 270 mg (91%) of compound **9** as a colourless viscous oil. IR (neat) 2957.4, 2868.2, 1709.8, 1688.4, 1407.3, 1367.2, 1322.9, 1173.3, 1140.9 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.97 (t, *J* = 7.0 Hz, 3H), 1.22-1.42 (m, 2H), 1.48 (s, 9H), 1.53-1.64 (m, 4H), 1.67-1.75 (m, 2H), 1.81 (br s, 1H), 1.85 (d, *J* = 2.7 Hz, 1H), 1.93-1.99 (m, 2H), 2.32-2.36 (m, 2H), 2.48-2.57 (m, 1H), 4.11-4.14 (m, 1H) 4.30 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 14.5, 19.8, 20.9, 22.2, 27.1, 27.5, 28.8 (3C), 37.6, 38.4, 49.7, 52.3, 52.9, 79.9, 155.3, 212.9. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.71. Found: C, 68.45; H, 10.38; N, 4.67.

(±)-(2*S,4a*R**,8a*R**)-1-*tert*-Butyloxycarbonyl-5-methylene-2-propyldecahydroquinoline (10)**

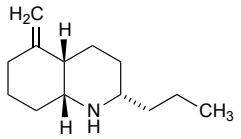


10

To a solution of compound **10** (1 mmol) in dry toluene (6 mL) was added dimethyltitanocene (1.5 mmol) and the reaction mixture was heated at 80 °C for 20 h, cooled and concentrated to dryness. The crude residue was purified by column chromatography on neutral Al_2O_3 (activity grade IV), eluting with a 97:3 petroleum ether-ethyl acetate mixture, to give 266 mg (91%) of compound **10** as a white solid, mp 67 °C. IR (neat) 2935.1, 1688.3, 1403.7, 1365.1, 1314.5, 1174.5, 1146.0, 1084.4 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz, mixture of two rotamers A and B) δ 0.95 (t, *J* = 7.2 Hz, 3H, A & B), 1.24-1.39 (m, 4H, A & B), 1.48 (s, 9H, A & B), 1.52-1.85 (m, 7H, A & B), 1.90-2.16 (m, 3H, A & B), 2.36-2.45 (m, 1H, A & B), 3.93-4.03 (m, 1H, A & B), 4.10-4.15 (m, 1H, A & B), 4.66-4.76 (m, 2H, A & B). ^{13}C-NMR ($CDCl_3$, 62.9 Mhz, mixture of two rotamers

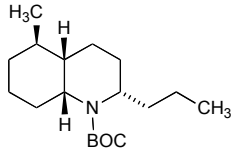
A and B) δ 14.6 (A & B), 21.1(A), 21.6 (B), 21.7 (A), 26.3 (A & B), 27.6 (B), 27.9 (A), 28.0 (B), 28.7 (B), 28.9 (A & B, 3C), 31.3 (A & B), 37.7 (A), 38.2 (A & B), 46.4 (A), 46.4 (B), 49.5 (B), 50.1 (A), 53.3 (A), 54.4 (B), 79.3 (B), 79.5 (A), 109.3 (A & B), 151.9 (A), 152.2 (B), 155.5 (B), 155.7 (A). Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.45; H, 10.31; N, 4.70.

_N_-Deprotection of compound 10. Synthesis of (±)-(2*S,4a*R**,8a*R**)-5-methylene-2-propyldecahydroquinoline**



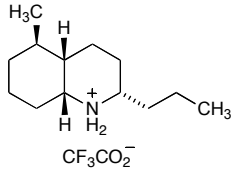
To a solution of compound **10** (1 mmol) in dry dichloromethane (6 ml) was added dropwise trifluroacetic acid (0.75 ml) at 0 °C for 15 min. The reaction mixture was stirred at room temperature for 3 h and concentrated to dryness. The residue was disssolved by dichloromethane (20 ml) and this solution was washed with saturated aqueous $NaHCO_3$ solution (3 x 10 ml), dried over Na_2SO_4 and concentrated to dryness. The crude residue was purified by column chromatography on neutral Al_2O_3 (activity grade IV), eluting with a 97:3 petroleum ether-ethyl acetate mixture, to give the N-deprotection compound as a colourless viscous oil (179 mg, 93%). IR (neat) 2929.2, 2862.5, 1643.0, 1434.2, 1090.4, 888.1, 751.7 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.27-1.46 (m, 7H), 1.51-1.68 (m, 3H), 1.70-1.77 (m, 2H), 1.96-2.09 (m, 1H), 2.15-2.22 (m, 2H), 2.33-2.38 (m, 1H), 2.53-2.58 (m, 1H), 3.00-3.03 (m, 1H) ,4.75 (s, 1H), 4.95 (s, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 14.7, 19.6, 22.6, 27.1, 28.1, 33.5, 36.9, 39.9, 40.5, 57.7, 58.4, 109.5, 147.9. Anal. Calcd for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25. Found: C, 80.48; H, 11.68; N, 7.04.

(±)-(2*S,4a*R**,5*R**,8a*R**)-1-*tert*-Butyloxycarbonyl-5-methylene-2-propyldecahydroquinoline [(±)-*N*-Boc Pumiliotoxin C]**



To a solution of the compound **10** (1 mmol) in dry methanol (5 mL) was added PtO_2 (71 mg). The reaction mixture was stirred under a hydrogen atmosphere (H_2 balloon) at room temperature for 12 h, filtered through Celite and evaporated to dryness. The crude residue was purified by column chromatography on neutral Al_2O_3 (activity grade IV), eluting with a 95:5 petroleum ether-ethyl acetate mixture, to give 280 mg (95%) of [(±)-*N*-Boc pumiliotoxin C as a colourless viscous liquid. IR (neat) 2957.6, 2886.5, 1682.1, 1455.7, 1404.2, 1367.2, 1325.4, 1177.1, 1148.7, 1087.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H), 1.14-1.34 (m, 6H), 1.41 (s, 9H), 1.38-1.51 (m, 5H), 1.55-1.59 (m, 3H), 1.71-1.85 (m, 2H), 3.95 (br s, 1H), 4.17 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.6, 19.7, 20.7, 21.2, 21.7, 27.2, 28.4, 28.9 (4C), 34.9, 38.2, 42.4, 49.6, 50.6, 79.2, 155.8. Anal. Calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C 72.95; H, 10.92; N, 4.66.

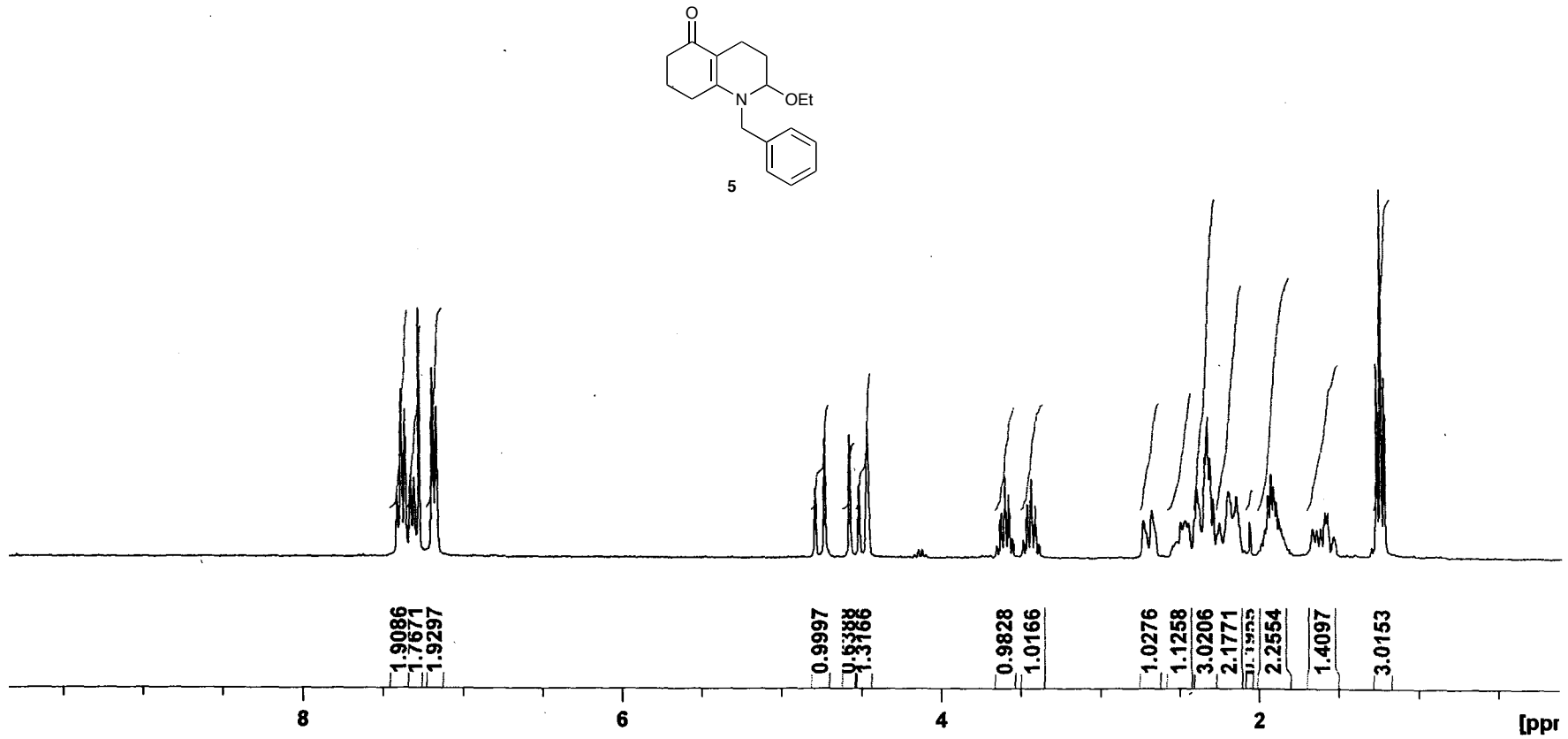
(±)-Pumiliotoxin C (trifluoroacetate salt)

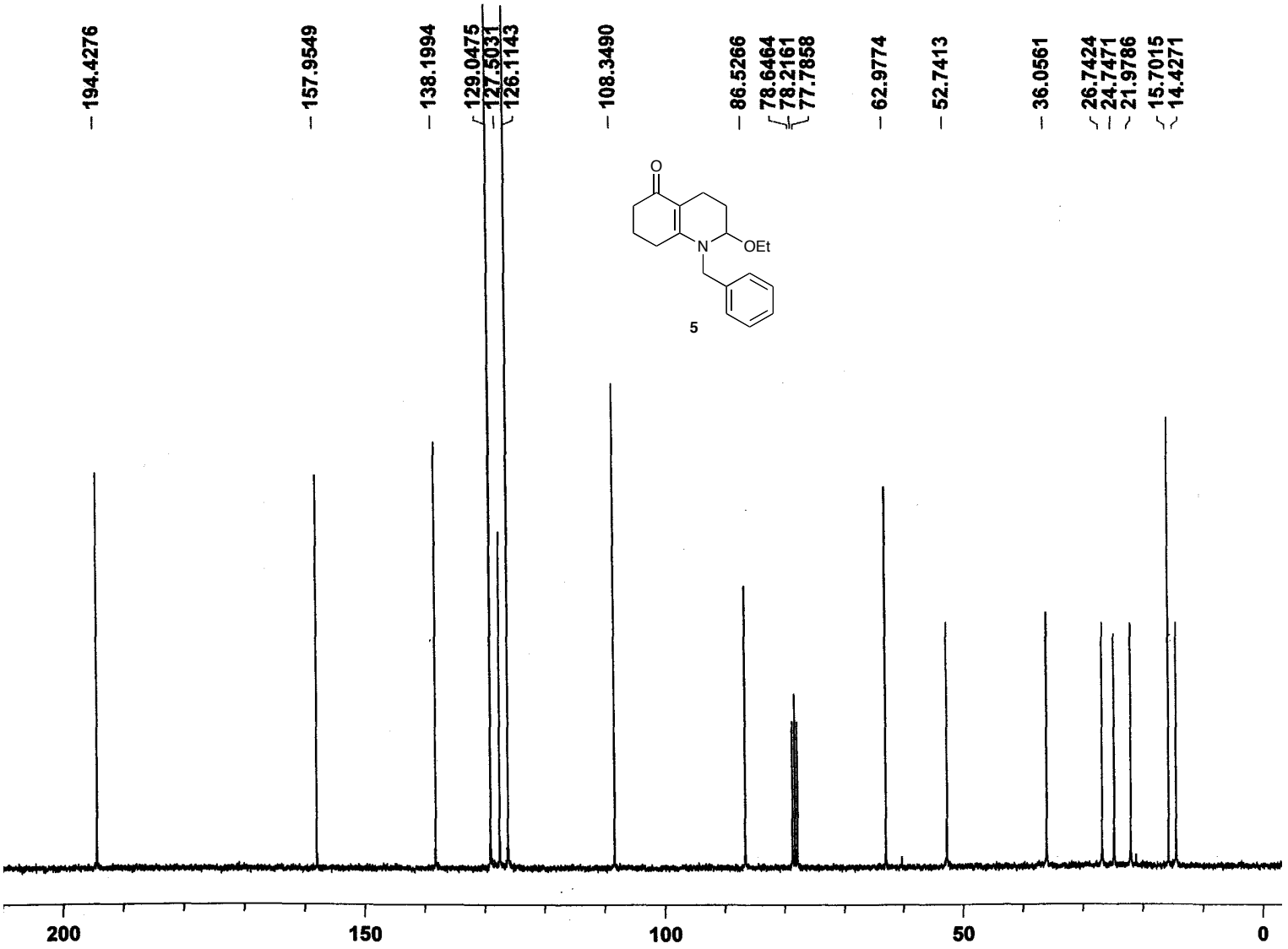


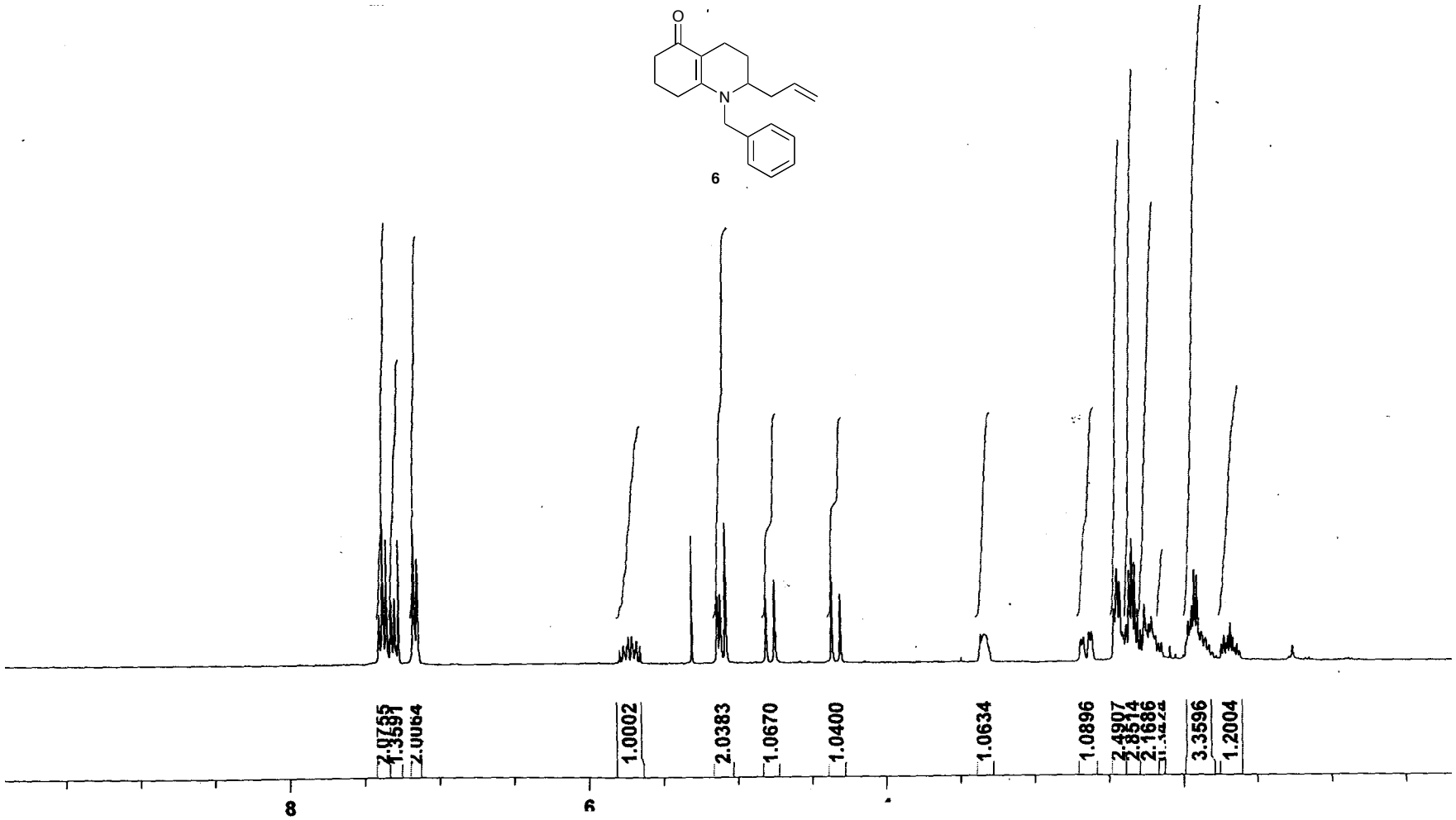
To a solution of the N-Boc derivative (1 mmol) in dry dichloromethane (5 mL) was added trifluroacetic acid (0.07 ml). The reaction mixture was stirred 4 hours at room temperature and the solvent was concentrated to dryness at 50 °C, giving 293 mg (95%) of pure (±)-pumiliotoxin C, as its trifluoroacetate salt. IR (neat) 2960.4, 2875.6, 1673.7, 1453.9, 1202.6, 1135.9, 834.9, 798.8, 721.6 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.85-0.95

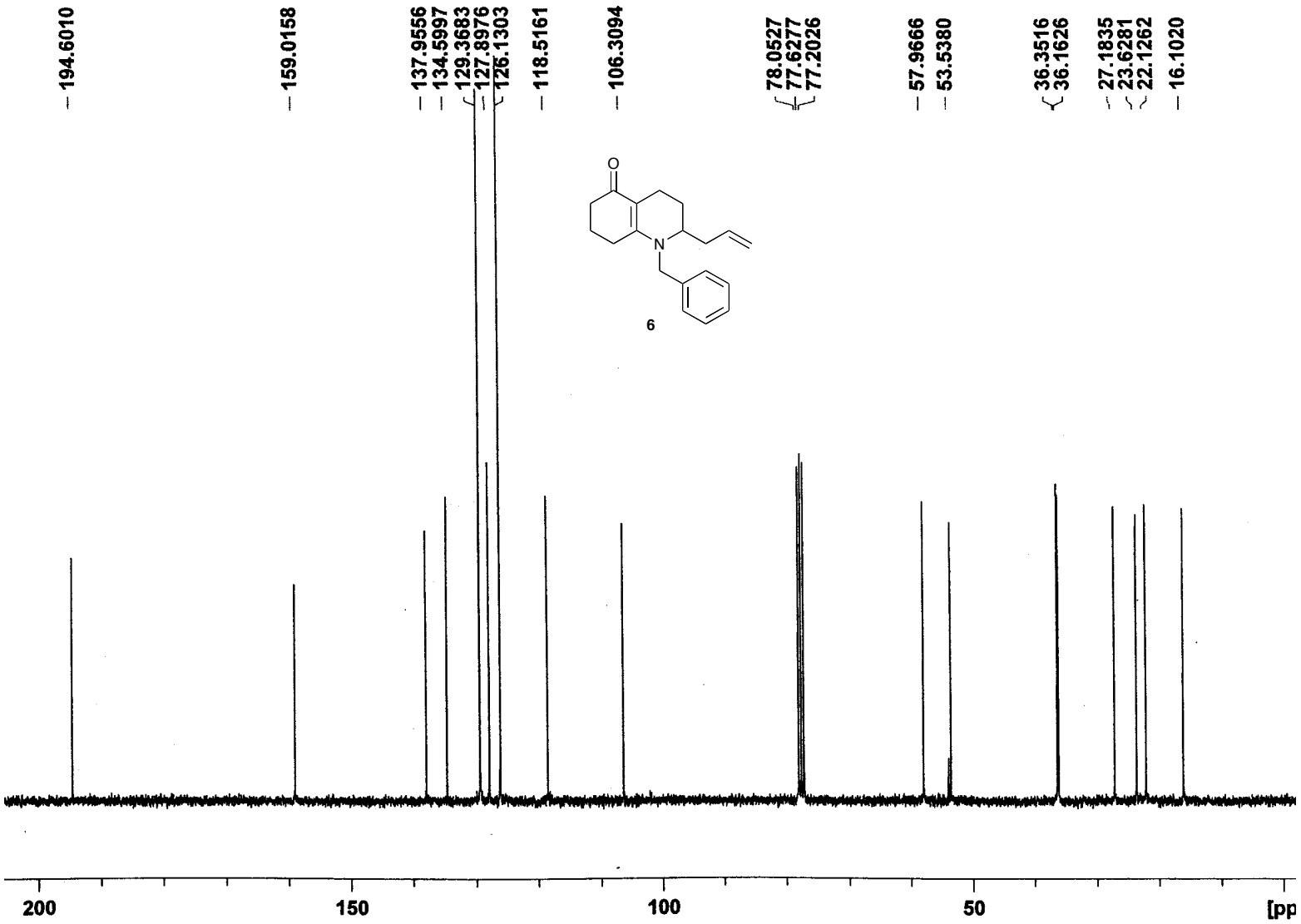
(m, 6H), 1.25-2.11 (m, 16H), 3.04 (s, 1H), 3.38 (d, *J* = 10.1 Hz, 1H), 7.93 (br s, 1H), 9.21 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 13.9, 19.0, 19.9, 20.3, 23.6, 25.4, 27.2, 29.5, 34.9, 35.1, 40.7, 57.5, 59.3, 116.5 (CF_3, *J* = 1160.0 Hz), 161.5 (CO_2, *J* = 145.0 Hz). Anal. Calcd for $C_{15}H_{26}F_3NO_2$: C, 58.24; H, 8.47; N, 4.53. Found: C, 58.06; H, 8.23; N, 4.21.

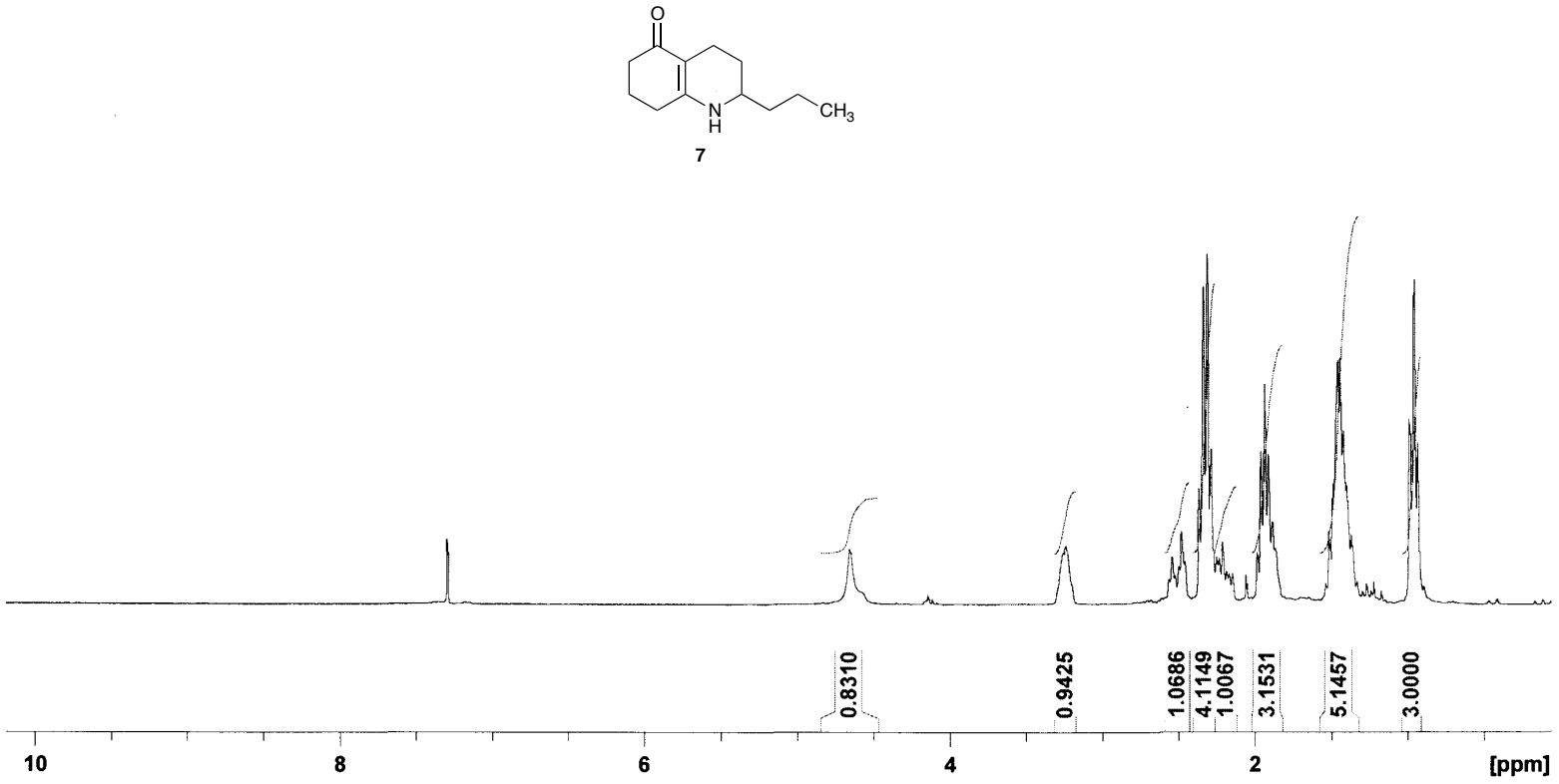
Copies of spectra

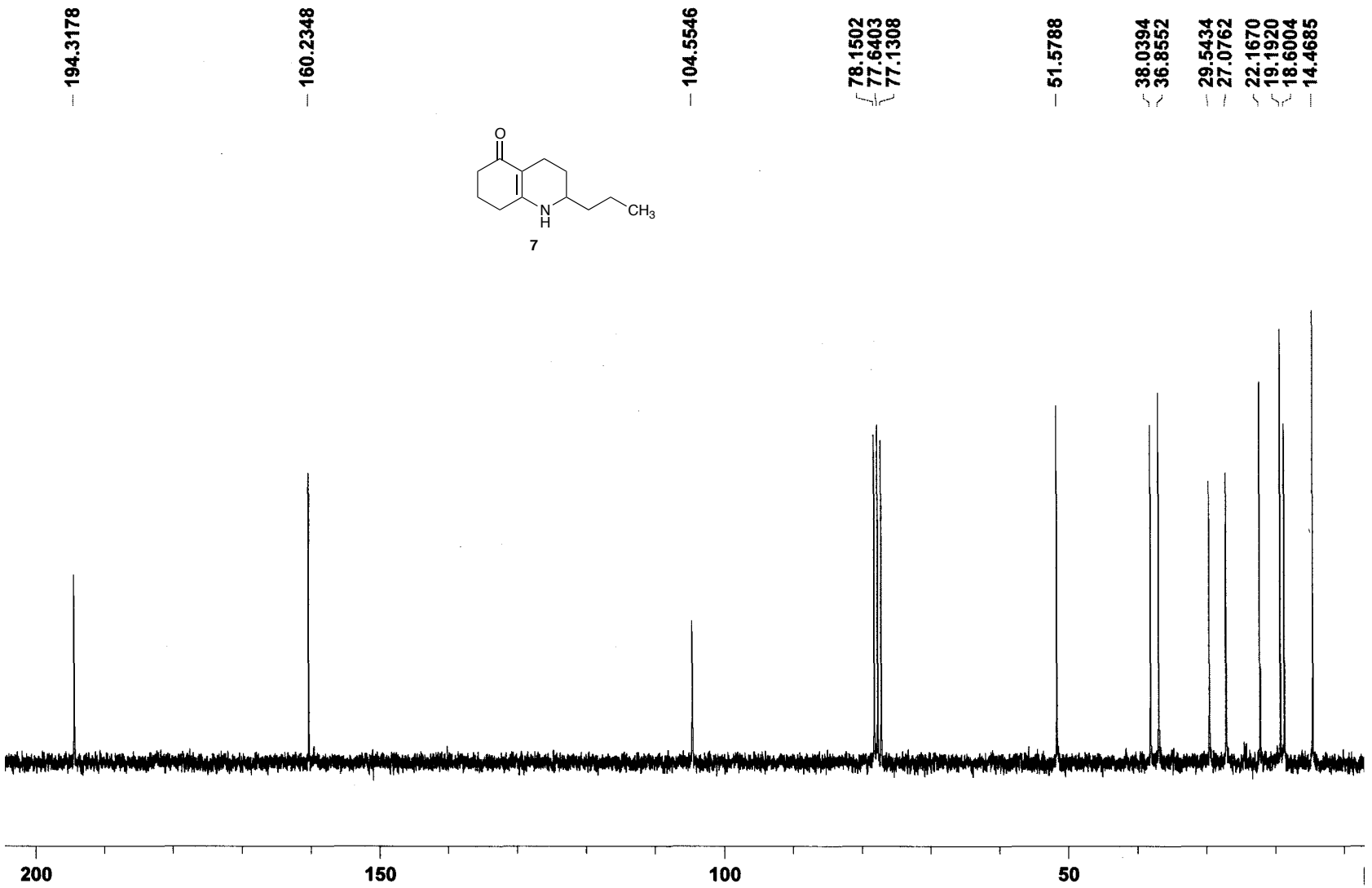


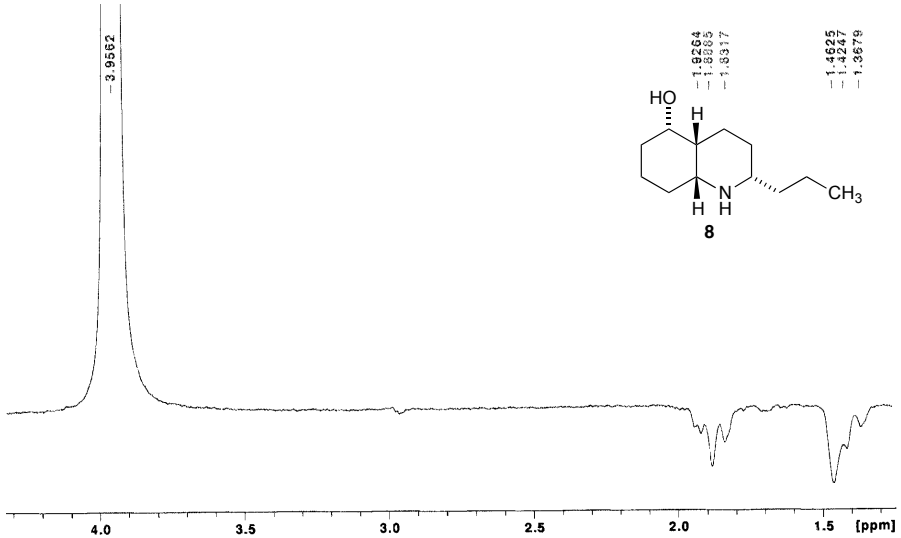




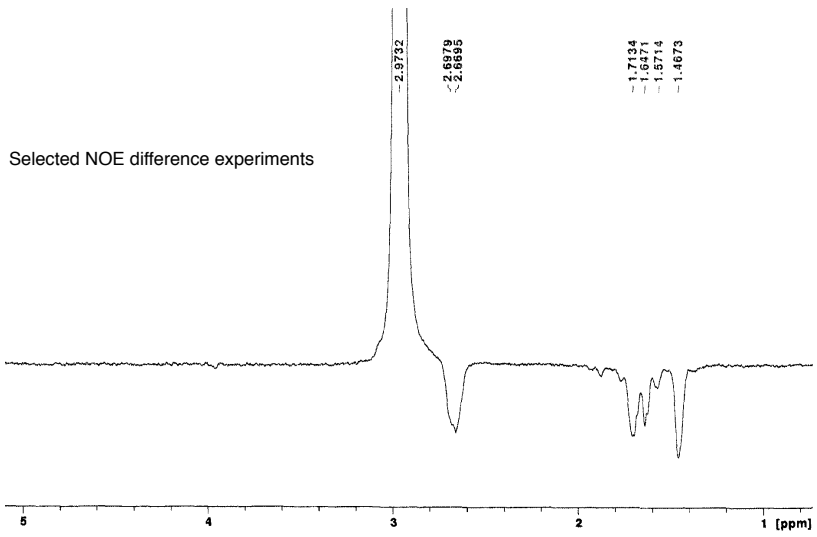


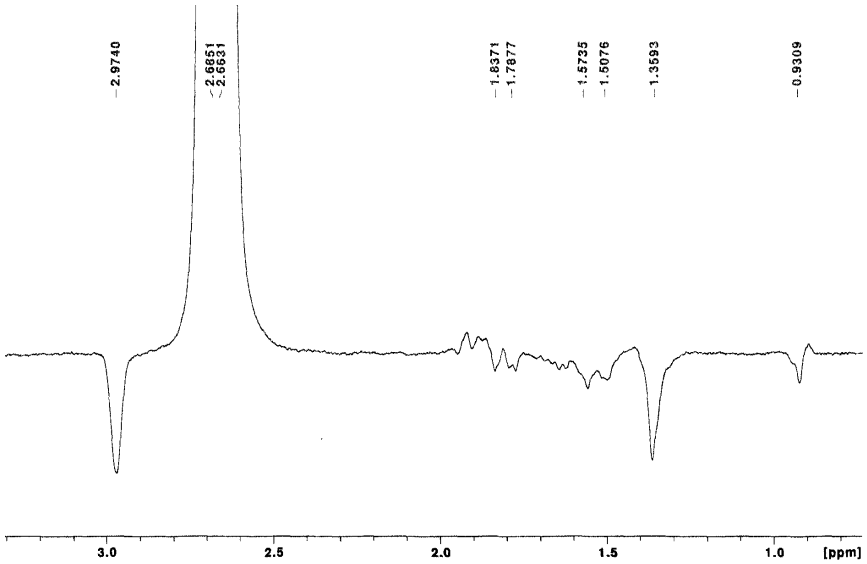


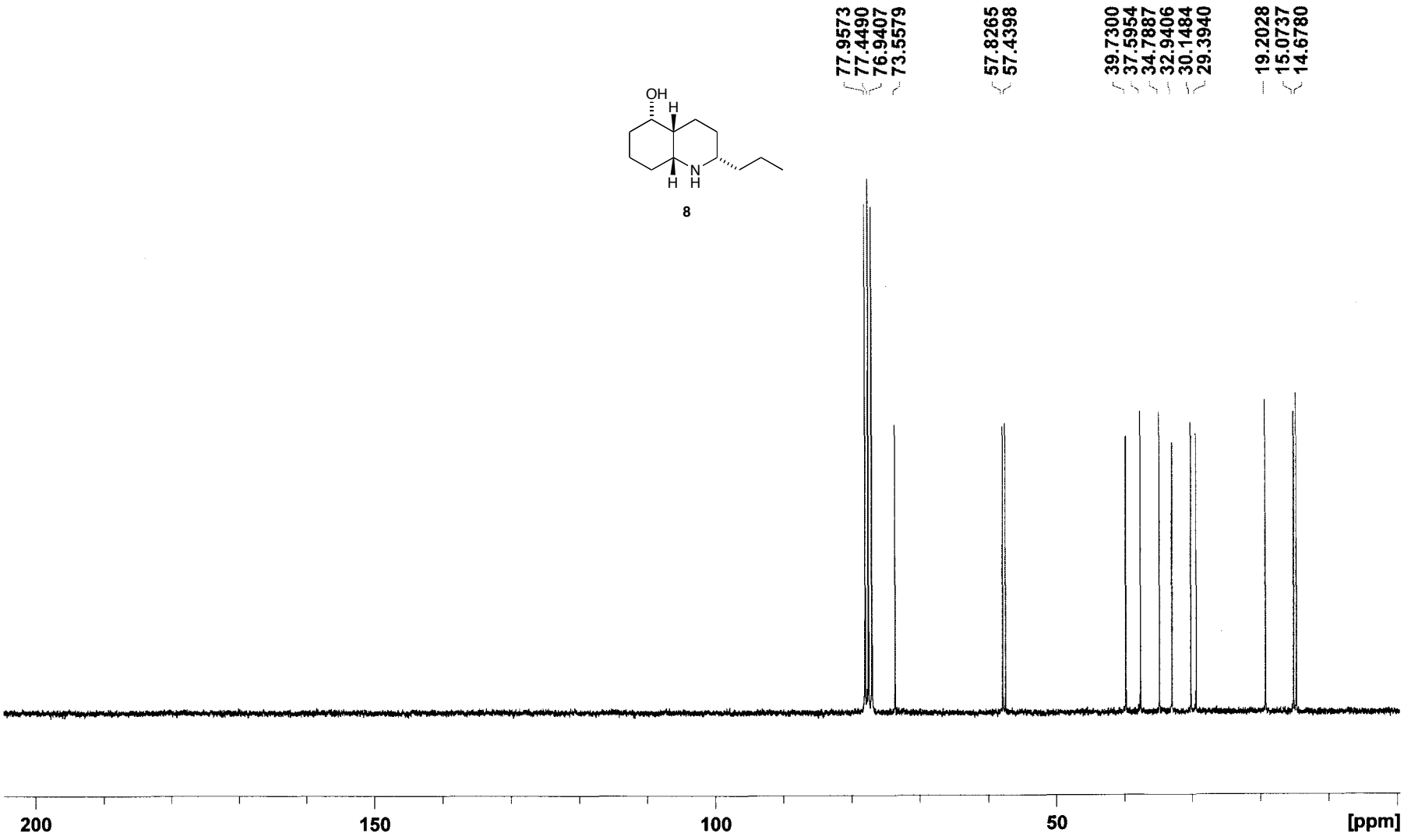


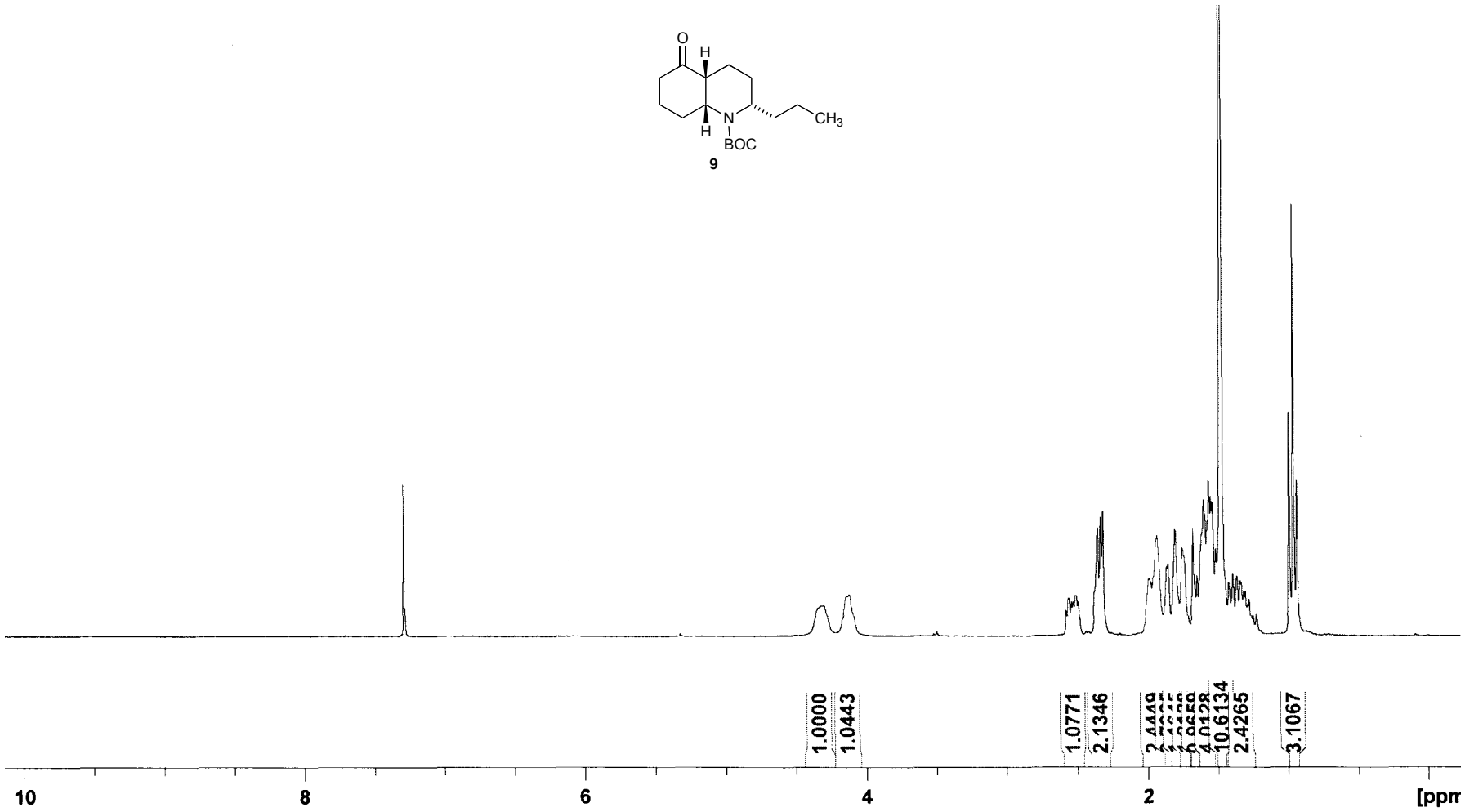


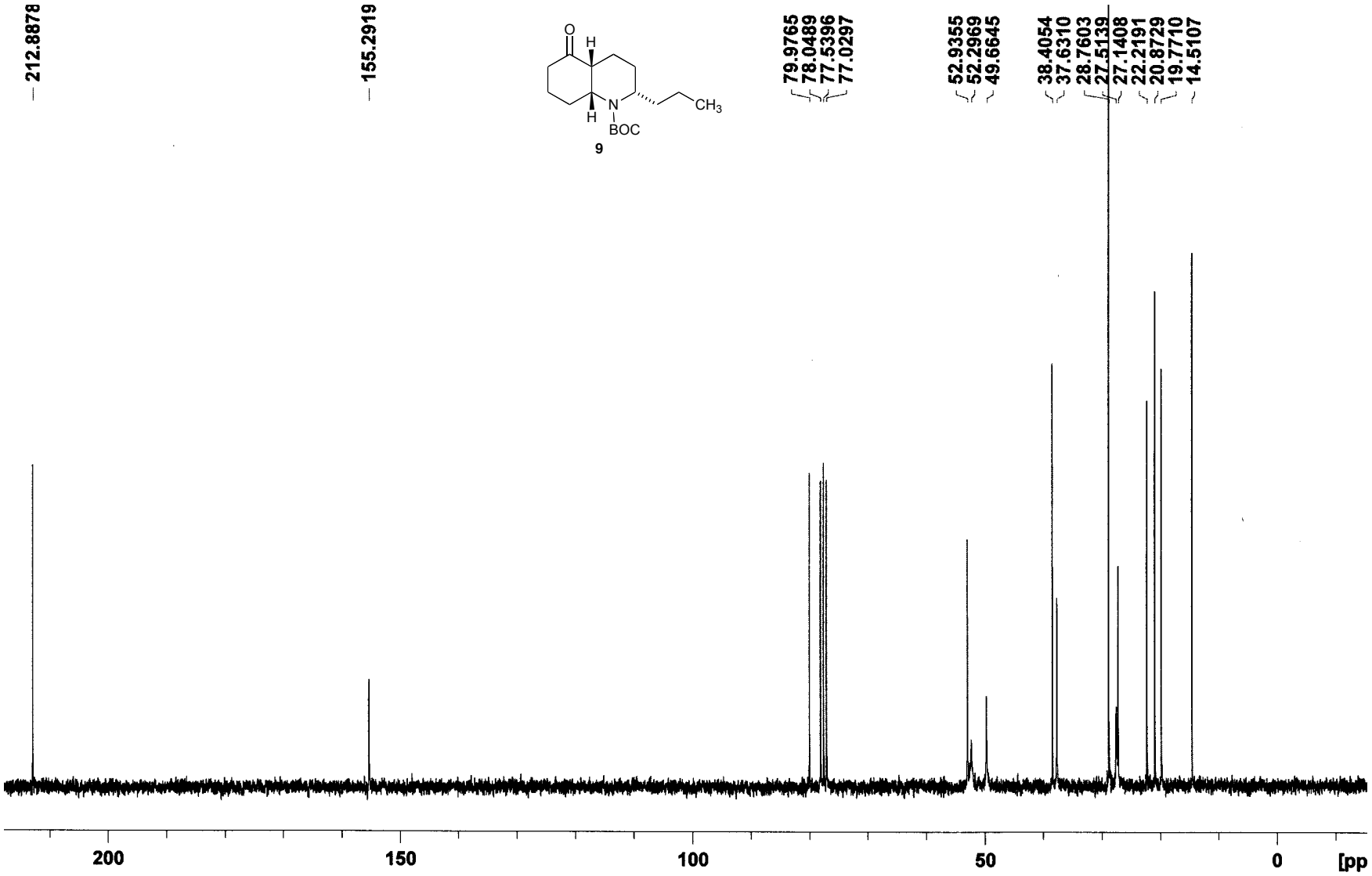
Selected NOE difference experiments

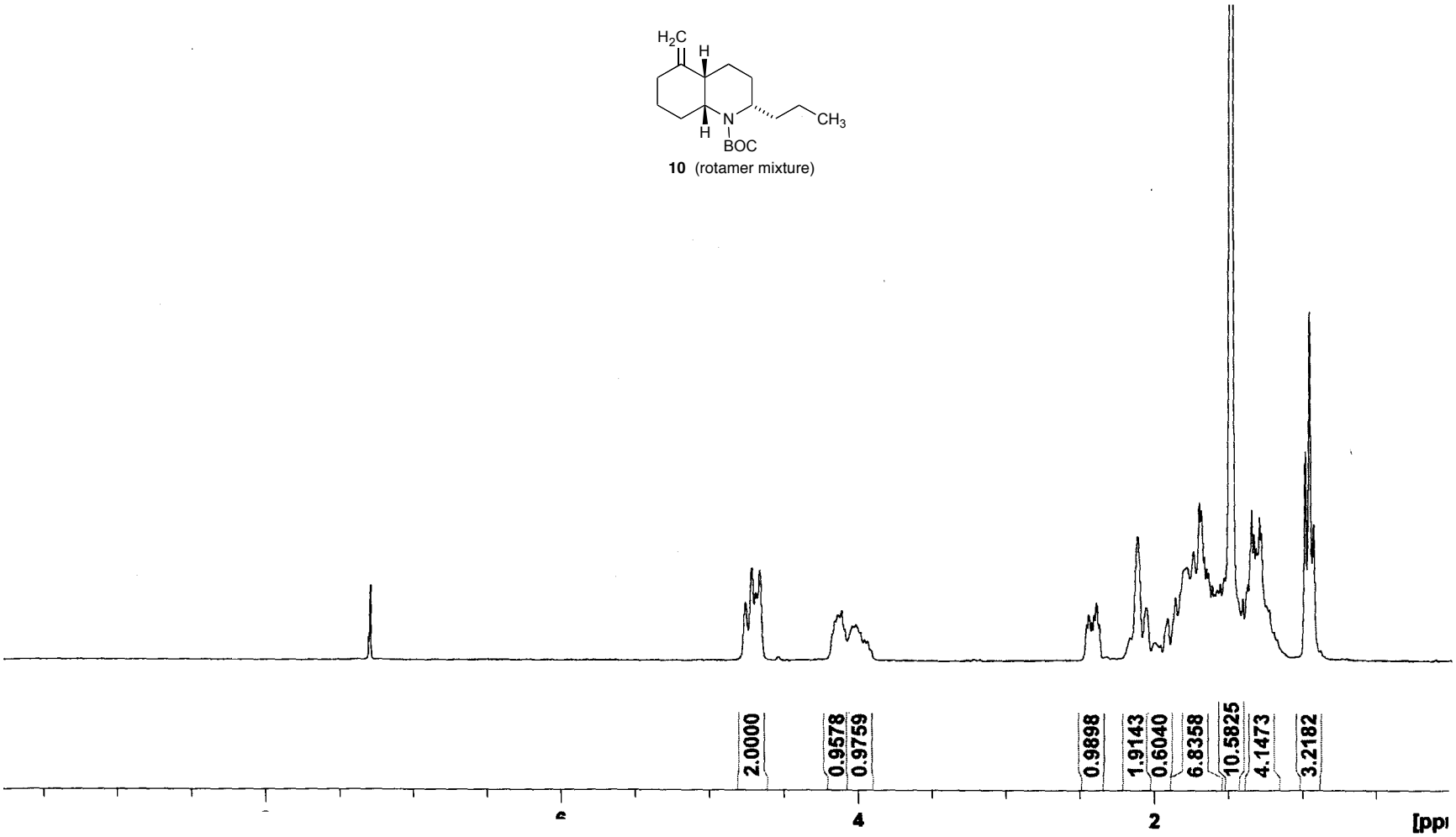




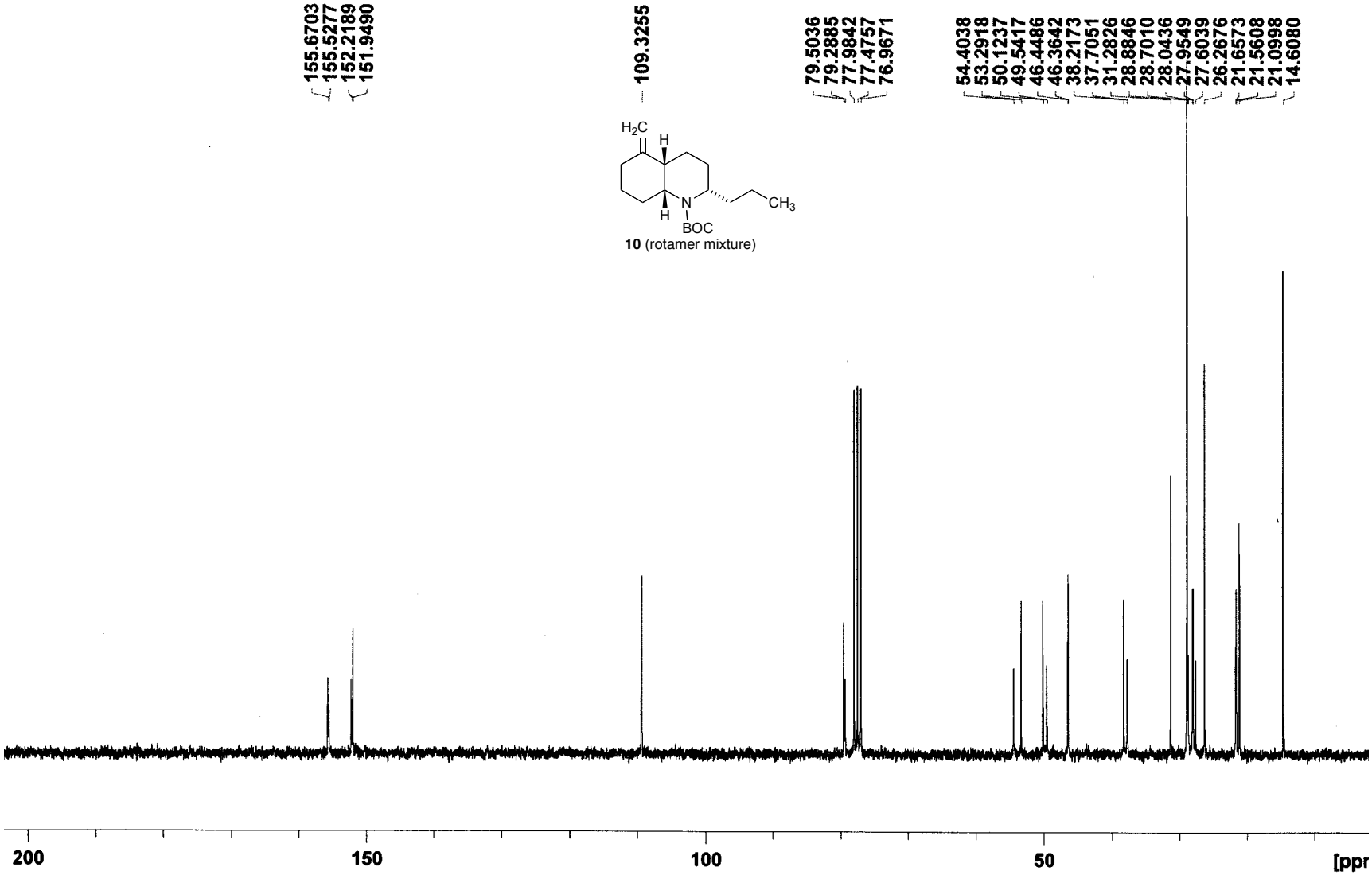




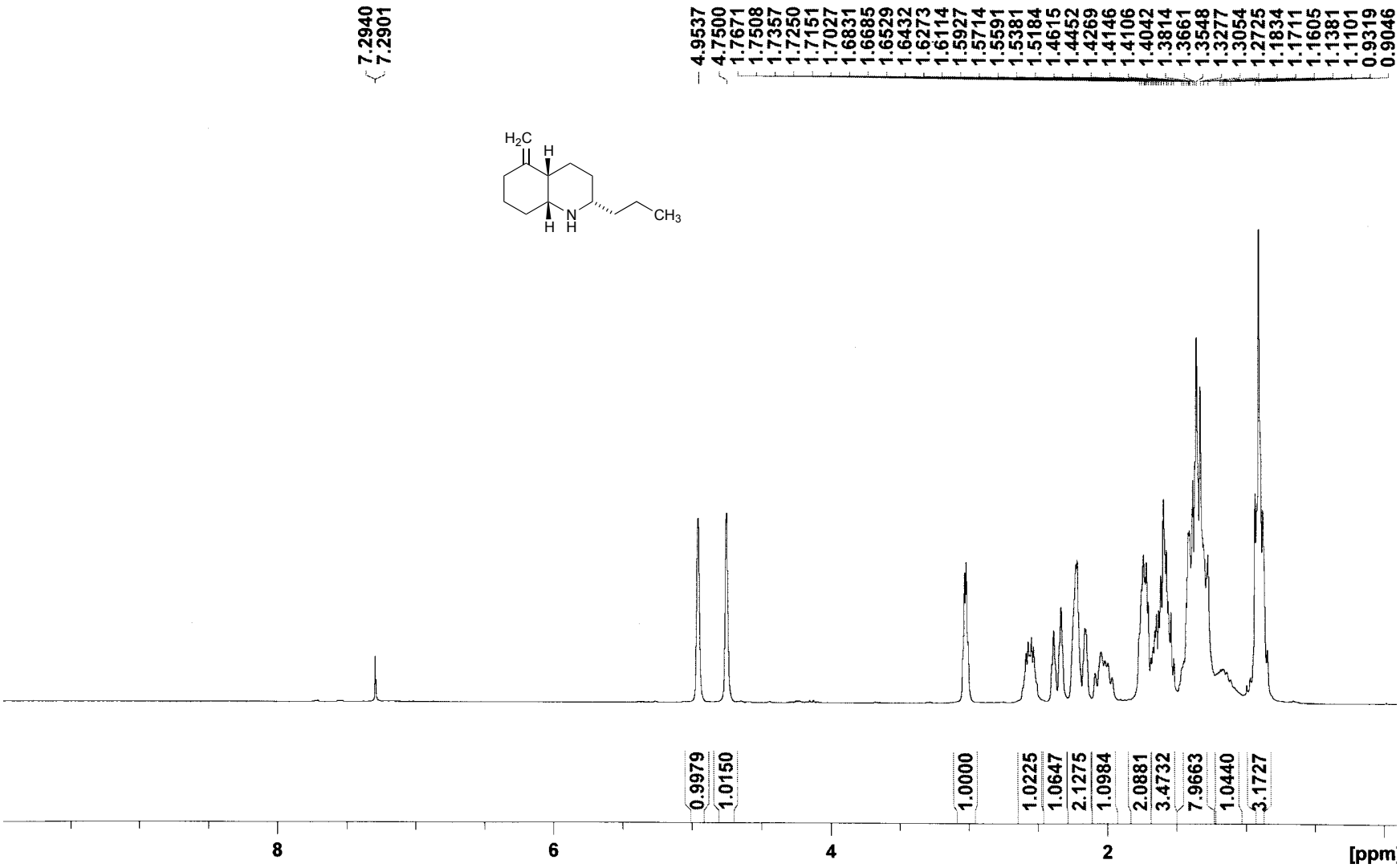


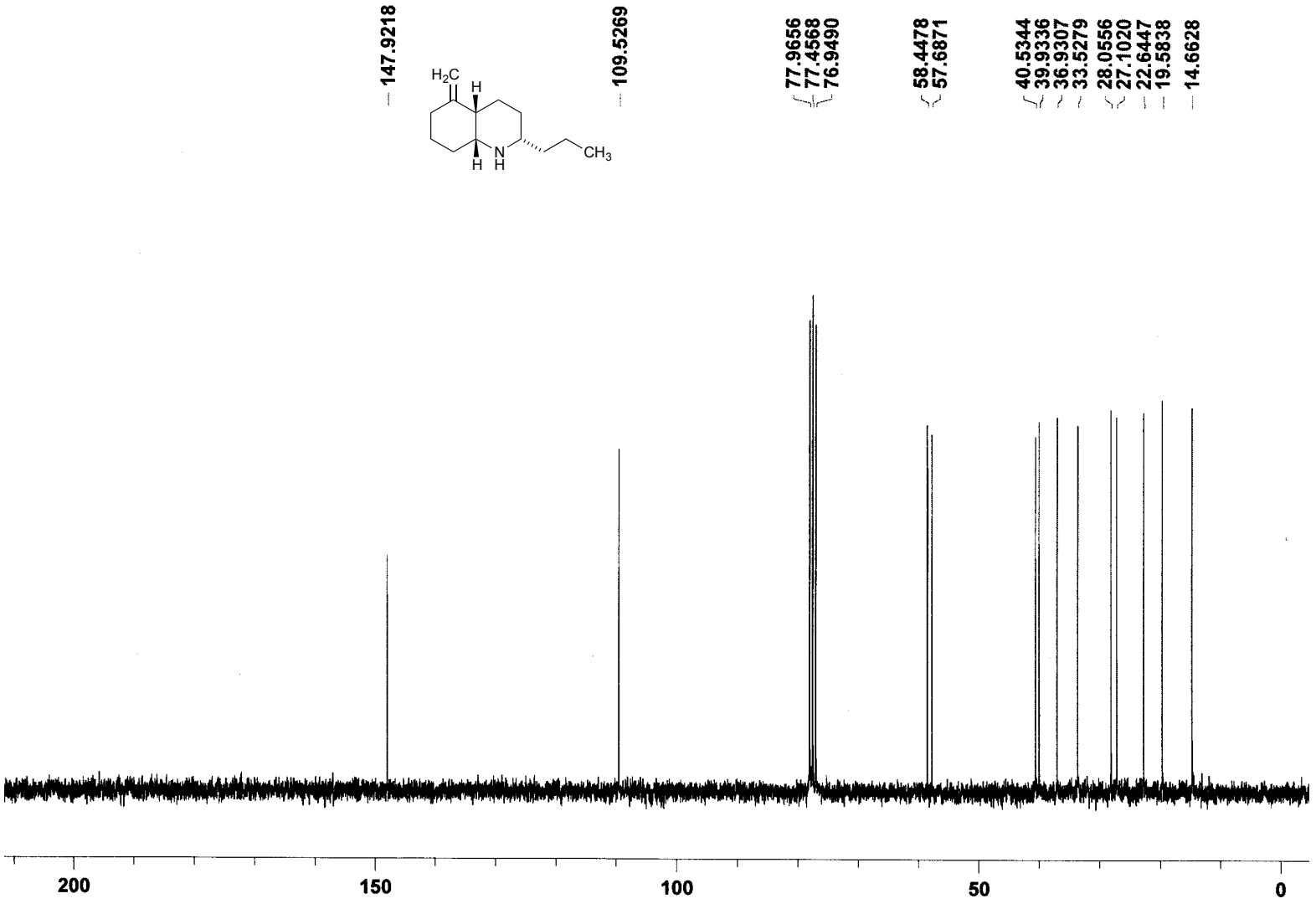


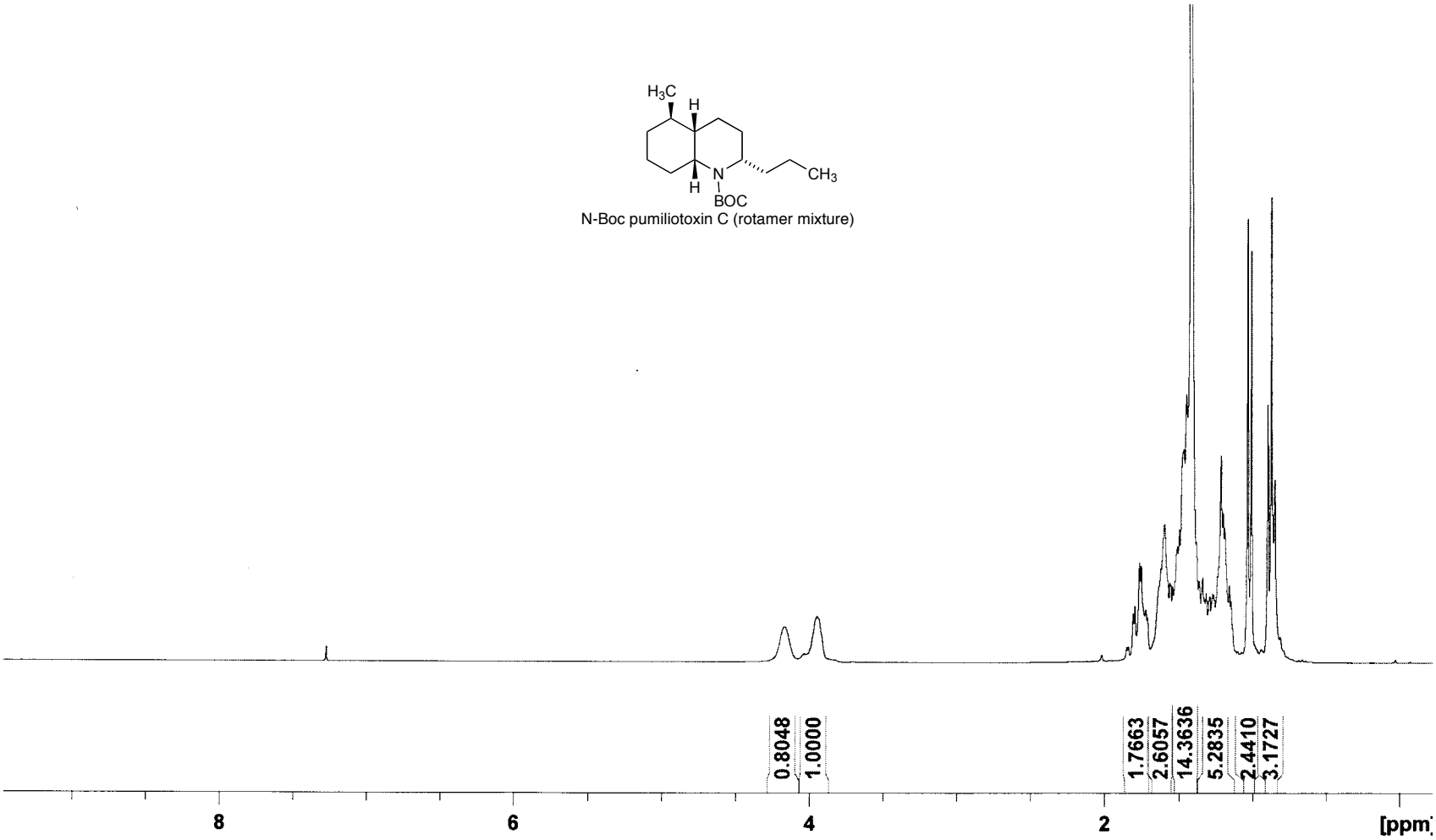
10 (rotamer mixture)



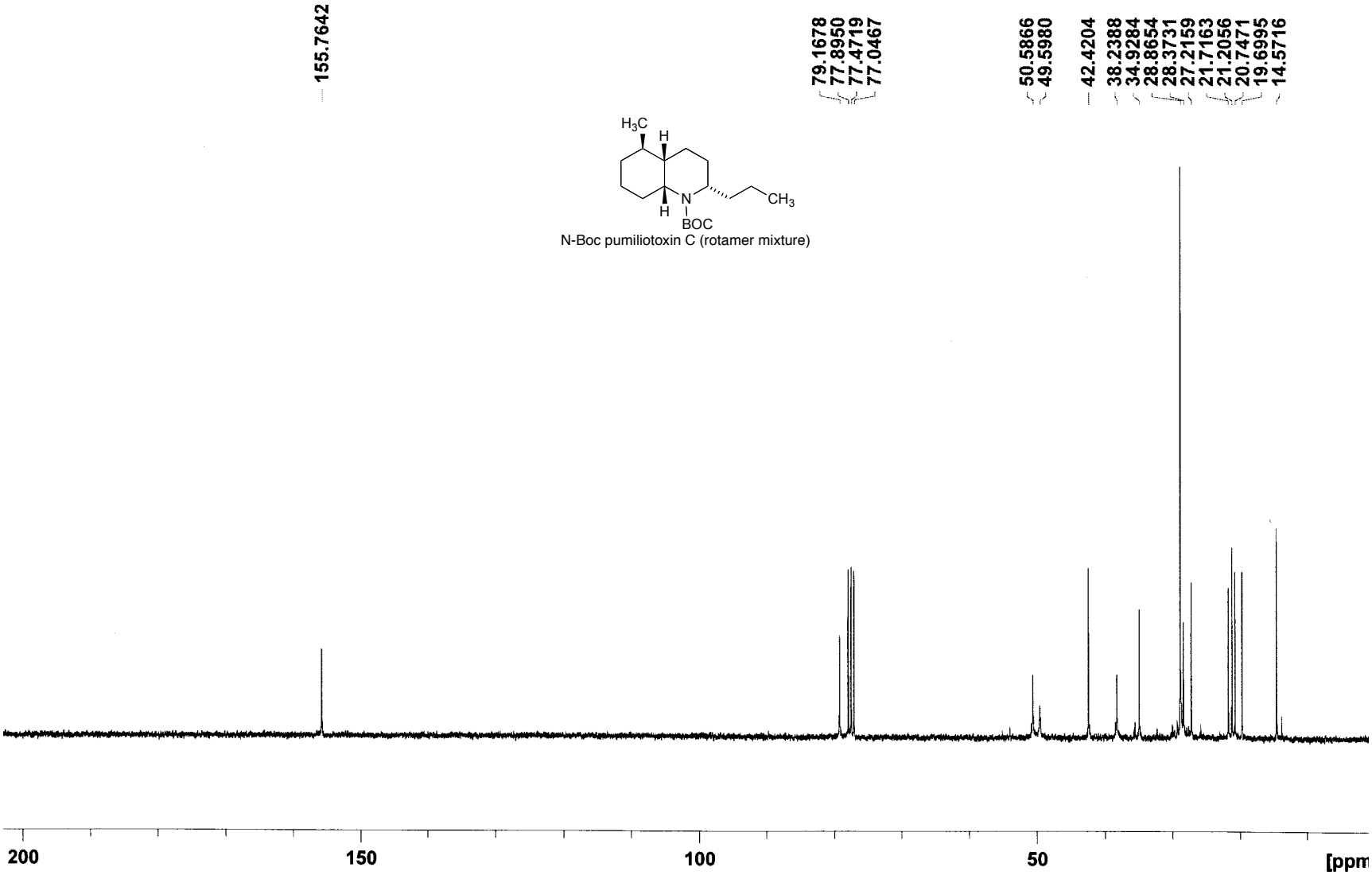
10 (rotamer mixture)



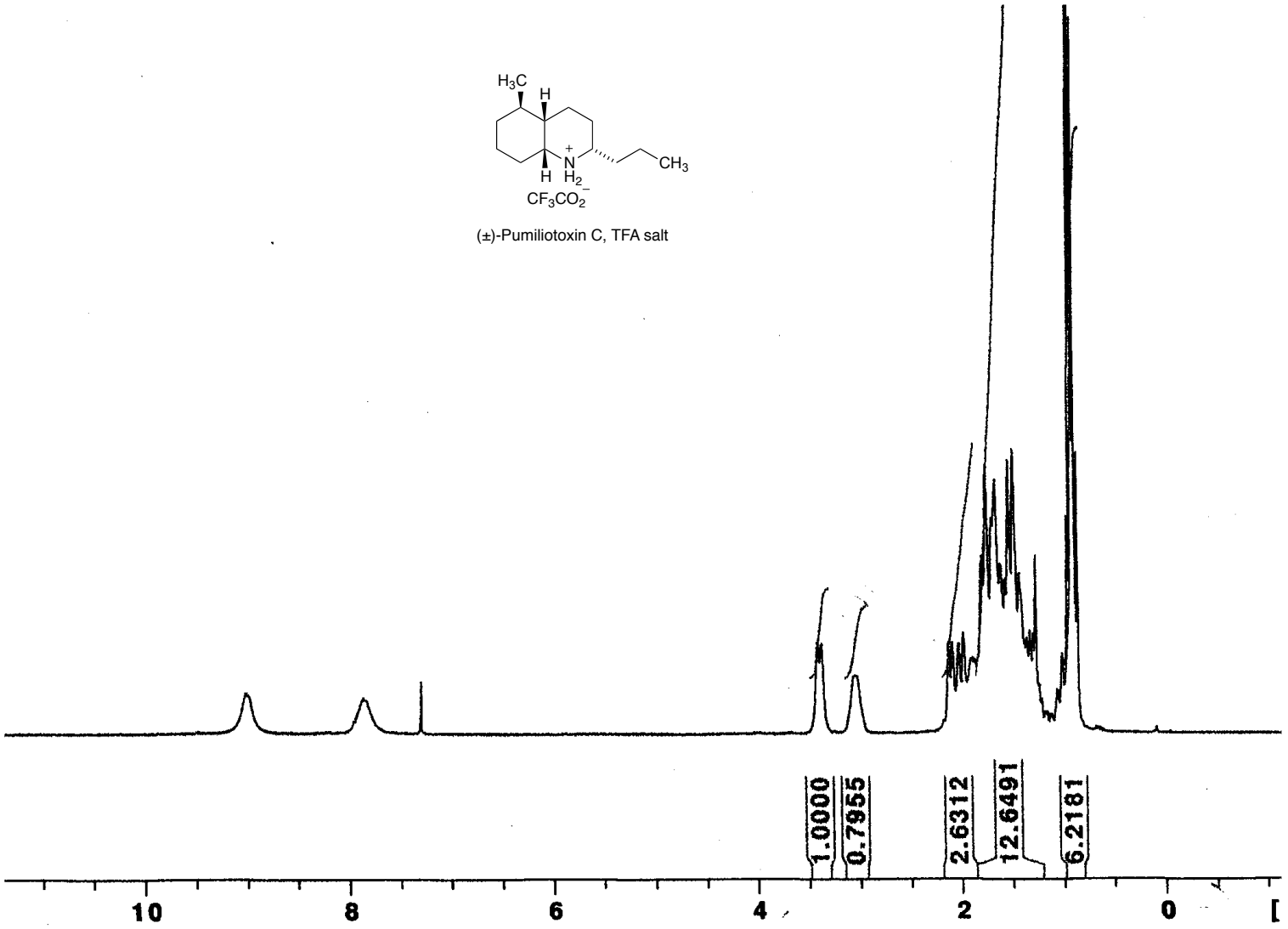


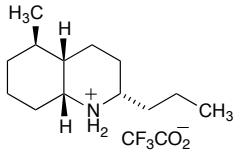


N-Boc pumiliotoxin C (rotamer mixture)

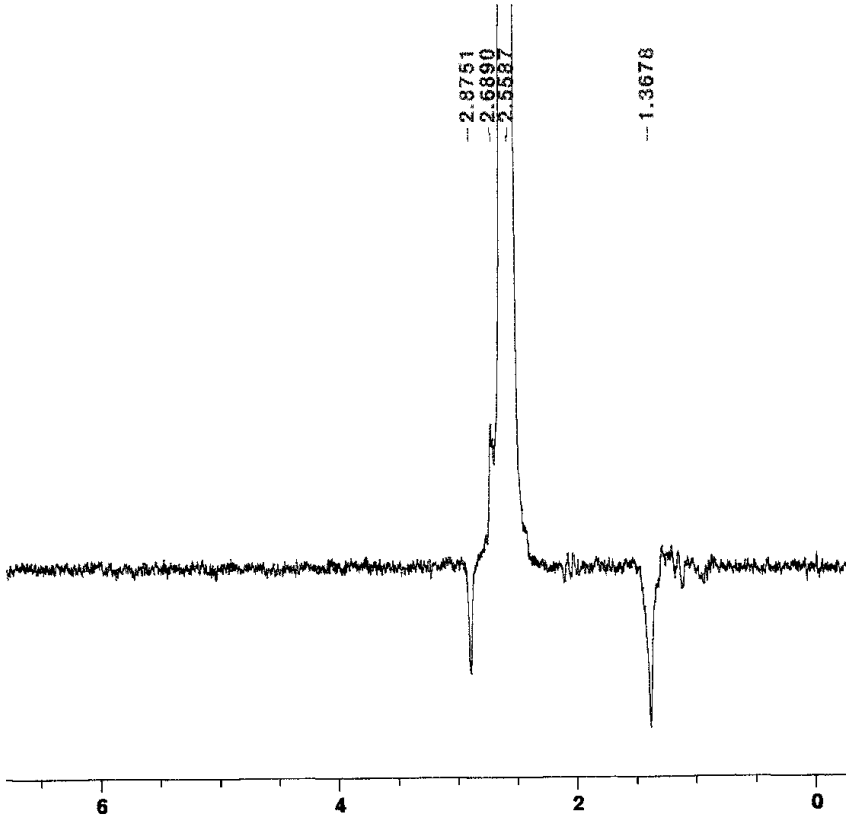


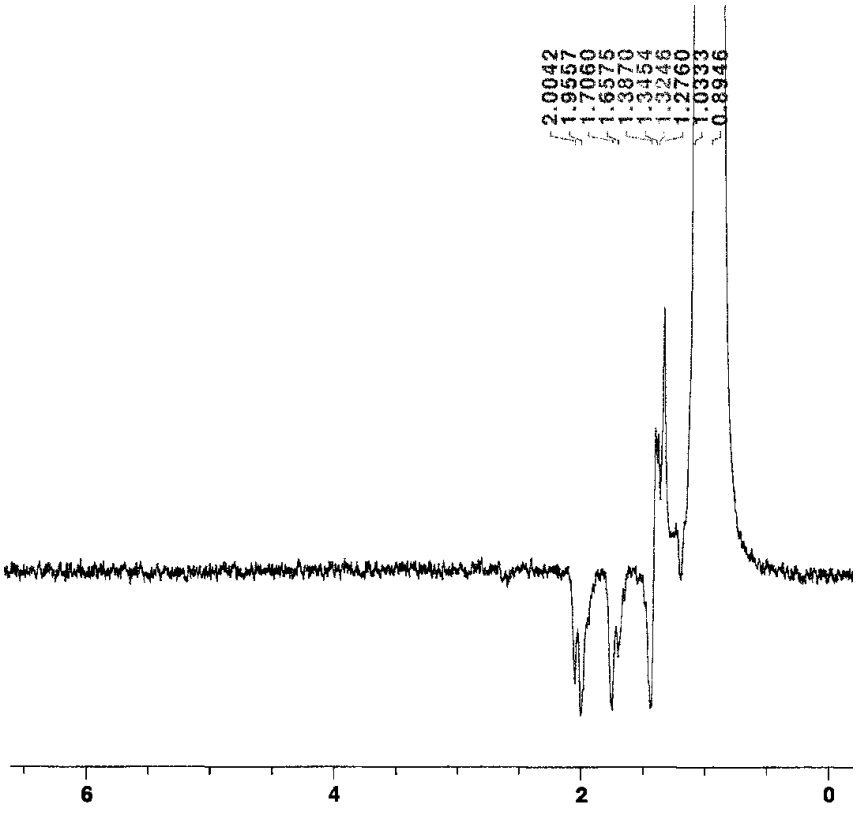
N-Boc pumiliotoxin C (rotamer mixture)

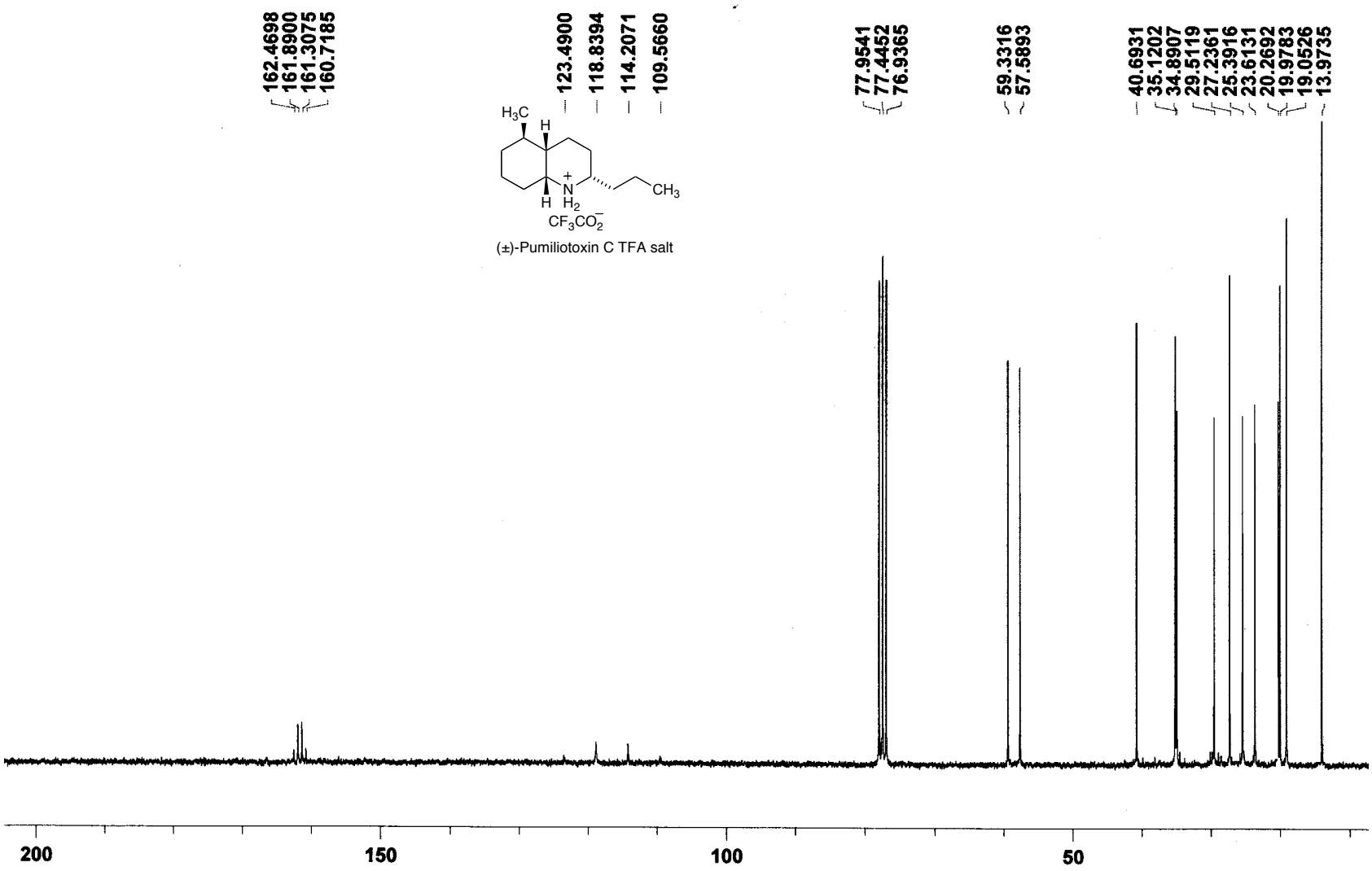




Selected NOE difference experiments







(±)-Pumiliotoxin C TFA salt