Supporting Information

Expedient Preparation of Nazlinine and a Small Library of Indole Alkaloids Using Flow Electrochemistry as an Enabling Technology

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Content

General

^{1}H-NMR spectra were recorded on either Bruker Avance DPX-400, Bruker Avance DPX-500 or Bruker Avance DPX-600 spectrometer, as specified, with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm, d_4-methanol = 3.31 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on the same spectrometer, as specified, with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.00 ppm, d_4-methanol = 49.05 ppm). All ^{13}C resonances are reported to the nearest 0.01 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. The multiplicity of ^{1}H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, q = quadruplet, sext = sextet, m = multiplet, br = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Unless stated otherwise, reagents were obtained from commercial sources and used without purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. High resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight with positive ESI, or a Bruker BioApex 47e FTICR spectrometer using (positive or negative) ESI or EI at 70 eV to within a tolerance of 5 ppm of the theoretically calculated value. Biotage Initiator Microwave Synthesiser was used to perform reactions under microwave conditions. The flow apparatus is the Asia Flux Module commercialized by Syrris. Two Asia Syringe Pumps, equipped with Asia Blue Syringes (500µl/1 ml). The microfluidic electrolytic cell was supplied by Syrris Ltd. The anode was made of carbon filled with polivinylidene fluoride (PVDF), the cathode of stainless steel and the spacer of perfluoroelastomer (FFKM, TRPlast 330B, 500 µm thickness). The cell parameters are: channel depth 200 µm, channel width 1.5 mm, channel length 600 mm, surface area of the channel 900 mm^2, the channel volume 180 µl, current density 48.89 mA cm^{-2}. All the modules were connected by PTFE tubing and end fittings.[1] Unless stated otherwise all chemicals were obtained from commercial sources, and were used without further purification. Compounds **10c**,[2] **10d**,[3] **10e**,[3] **10f**,[4] **10g**,[5] **10h**,[6] **10i**[7] were synthetized using the reported procedures.

General procedure for the anodic oxidation of 10 in the microfluidic electrochemical cell. 0.1 M solution of the *N*-protected amine **10** in methanol containing 20 mol% of $Et_4N^+BF_4^-$ was pumped through the Syrris microfluidic electrolytic cell (flow rate 120 μl min^{-1}). The current (*I*) was set constant (galvanostatic mode) at 44 mA (2.3 F mol^{-1}). The solution was collected and evaporated *in vacuo*. The residue was dissolved in chloroform (10 ml per 1 g of the product) and filtered to remove $Et_4N^+BF_4^-$. The product obtained after solvent evaporation *in vacuo* was sufficiently pure to be used in the following step or could be purified by flash column chromatography (SiO_2) to attain the analytically pure material **11**.

***tert*-Butyl-2-methoxypyrrolidine-1-carboxylate 11a.**[3] Colorless oil, 92%. ^{1}H NMR (500 MHz, CD_3OD, mixture of rotamers) δ 1.45 (s, 9H Major + 9H Minor), 1.58 – 2.11 (m, 4H Major + 4 H Minor)), 3.25 – 3.45 (m overlapping the solvent signal at 3.31 ppm and the s at 3.32 ppm, 2H Major + 2H Minor), 5.05 – 5.15 (m, 1H Major + 1H Minor). ^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers) δ 22.6, 23.5, 28.6, 28.8, 32.5, 33.3, 46.5, 47.1, 55.8, 56.0, 81.2, 81.6, 90.0, 90.2, 156.2, 156.8. IR (Neat, cm^{-1}) 2976, 2935, 1698, 1380, 1365, 1161, 1080, 931, 916, 878, 773. HRMS *m/z* calculated for $C_{10}H_{19}NNaO_3$ $[M + Na]^+$ 224.1257, found 224.1247.

***tert*-Butyl-2-methoxypiperidine-1-carboxylate 11b.** Colorless oil, 98%. ^{1}H NMR (600 MHz, CD_3OD, mixture of rotamers) δ 1.36 – 1.58 (m overlapping s at 1.47 ppm, 3H Major + 3H Minor), 1.47 (s, 9H Major + 9H Minor), 1.59 – 1.68 (m, 1H Major + 1H Minor), 1.71 – 1.79 (m, 1H Major + 1H Minor), 1.82 – 1.84 (m, 1H Major + 1H Minor), 2.82 – 2.97 (m, 1H Major + 1H Minor), 3.21 (s, 3H Major + 3H Minor), 3.79 – 3.91 (m, 1H Major + 1H Minor), 5.23 (m, 1H Major + 1H Minor). ^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers) δ 19.5, 26.2, 28.7, 31.2, 39.1, 40.4, 49.7, 49.9, 54.8, 81.4, 81.5, 82.6, 83.7, 156.6, 156.9. IR (Neat, cm^{-1}) 2939, 1697, 1409, 1160, 1082, 1034, 951, 869. HRMS *m/z* calculated for $C_{11}H_{21}NNaO_3$ $[M + Na]^+$ 238.1414, found 238.1403.

***tert*-Butyl-2-methoxyazapane-1-carboxylate 11c.** Colorless oil, 94%. ^{1}H NMR (400 MHz, CD_3OD, mixture of rotamers) δ 1.08 – 1.18 (m, 1H Major + 1H Minor), 1.29 – 1.40 (m, 1H Major + 1H Minor), 1.44 – 1.69 (m overlapping s at 1.49 ppm, 4H Major + 4H Minor), 1.49 (s, 9H Major + 9H Minor), 1.79 – 1.82 (m, 1H Major + 1H Minor), 2.18 – 2.27 (m, 1H Major + 1H Minor), 2.89 – 2.97 (m, 1H Major + 1H Minor), 3.20 (s, 3H Major), 3.23 (s, 3H Minor), 3.55 – 3.63 (m, 1H Major + 1H Minor), 5.20 – 5.24 (m, 1H Minor), 5.27 – 5.30 (m, 1H Major). ^{13}C NMR (100 MHz, CD_3OD, mixture of rotamers) δ 23.6, 23.8, 28.7, 28.7[5], 28.8,

29.3, 30.9[8], 31.0, 35.5, 35.8, 41.3, 41.8, 55.2, 55.3, 81.3, 81.7, 86.7, 87.7, 157.1, 158.1. IR (Neat, cm^{-1}) 2930, 2857, 1694, 1411, 1153, 1086, 1068, 936. HRMS *m/z* calculated for $C_{12}H_{24}NO_3$ $[M + H]^+$ 230.1751, found 230.1743.

Benzyl-2-methoxypyrrolidine-1-carboxylate 11d.[3] Colorless oil, 89%. ^1H NMR (500 MHz, CD_3OD, mixture of rotamers) δ 1.73 – 2.08 (m, 4 H Major + Minor), 3.24 (s, 3H Minor), 3.33 – 3.50 (m, 2H Major + Minor), 3.33 (s overlapping solvent signal at 3.31 ppm, 3H Major), 5.10 – 5.20 (m, 3 H Major + 3H Minor), 7.29 – 7.39 (m, 5H Major + 5H Minor). ^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers) 22.6, 23.6, 32.6, 33.2, 46.9, 47.0, 55.9, 56.1, 68.1, 68.4, 90.1, 90.6, 128.9, 129.2, 129.6, 137.9, 138.1, 156.7, 157.4. IR (Neat, cm^{-1}) 2945, 2893, 1704, 1404, 1358, 1082, 698. HRMS *m/z* calculated for $C_{13}H_{18}NO_3$ $[M + H]^+$ 236.1281, found 236.1280.

Benzyl-2-methoxypiperidine-1-carboxylate 11e.[3] Colorless oil, 90%. ^1H NMR (600 MHz, CD_3OD, mixture of rotamers) δ 1.40 - 1.48 (m, 1H Major + 1H Minor), 1.52 - 1.56 (m, 2H Major + 2H Minor), 1.59 - 1.68 (m, 1H Major + 1H Minor), 1.72 - 1.80 (m, 1H Major + 1H Minor), 1.82 - 1.88 (m, 1H Major + 1H Minor), 2.91 - 3.03 (m, 1H Major + 1H Minor), 3.14 (br s, 3H Major), 3.20 (br s, 3H Minor), 3.92 - 3.95 (m, 1H Major + 1H Minor), 5.09 - 5.20 (m, 2H Major + 2H Minor), 5.35 (br s, 1H Major + 1H Minor), 7.24 - 7.32 (m, 1H Major + 1H Minor), 7.34 – 7.38 (m, 4H Major + 4H Minor). ^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers) 19.4, 26.1, 26.2, 31.1, 31.2, 39.9, 40.2, 54.9, 55.0, 68.3, 68.4, 83.4, 83.6, 128.9, 129.2, 129.4, 138.0, 138.0[5], 157.1, 157.4. IR (Neat, cm^{-1}) 2942, 1698, 1417, 1337, 1263, 1168, 1081, 1067, 1035, 952, 697. HR-MS *m/z* calculated for $C_{14}H_{20}NO_3$ $[M + H]^+$ 250.1443, found 250.1443.

Benzyl-2-methoxyazapane-1-carboxylate 11f.[8] Colorless oil, 92%. ^1H NMR (400 MHz, CD_3OD, mixture of rotamers) δ 1.08 – 1.17 (m, 1H Major + 1H Minor), 1.28 – 1.41 (m, 1H Major + 1H Minor), 1.46 – 1.69 (m, 4H Major + 4H Minor), 1.76 – 1.80 (m, 1H Major + 1H Minor), 2.18 – 2.28 (m, 1H Major + 1H Minor), 2.96 – 3.03 (m, 1H Major + 1H Minor), 3.14 (s, 3H Minor), 3.20 (s, 3H Major), 3.65 – 3.68 (m, 1H Major + 1H Minor), 5.14 (d, J = 12.2 Hz, 1H Minor), 5.15 (d, J = 12.4 Hz, 1H Major), 5.20 (d, J = 12.4 Hz, 1H Major), 5.21 (d, J = 12.2 Hz, 1H Minor), 5.27 – 5.36 (m, 1H Major + 1H Minor), 7.29 – 7.40 (m, 5H Major + 5H Minor). ^{13}C NMR (100 MHz, CD_3OD, mixture of rotamers) 23.6, 23.7, 28.7, 29.4, 30.9, 31.0, 35.4, 35.7, 41.7, 42.0, 55.3, 55.4, 68.4, 68.5, 87.5, 87.6, 128.9, 129.2, 129.3, 129.6, 138.0,

138.1, 157.7, 158.9. IR (Neat, cm^{-1}) 2930, 2856, 1698, 1417, 1336, 1171, 1071, 938, 698. HR-MS *m/z* calculated for $C_{15}H_{20}NO_3$ $[M - H]^+$ 262.1438, found 262.1430.

Benzyl-2-methoxymorpholine-1-carboxylate 11g. Colorless oil, 90%. ^1H NMR (500 MHz, CD_3OD, mixture of rotamers) δ 3.11 – 3.30 (m, 4H Major + 4H Minor), 3.40 – 3.52 (m, 2H Major + 2H Minor), 3.71 – 3.90 (m, 3H Major + 3H Minor), 5.10 – 5.30 (m, 3H Major + 3H minor), 7.25 – 7.45 (m, 5H Major + 5H Minor). ^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers) δ 40.1, 40.8, 55.4, 55.5, 67.2, 67.4, 68.7, 68.8, 69.9, 70.1, 81.7, 82.2, 128.9, 129.1, 129.2, 129.4, 129.5, 129.6, 137.7, 137.8, 156.9, 157.2. IR (Neat, cm^{-1}) 2936, 1705, 1417, 1303, 1227, 1078, 875, 750, 699. HRMS *m/z* calculated for $C_{13}H_{16}NO_4$ $[M - H]^+$ 250.1074, found 250.1067.

Methyl-2-methoxyazapane-1-carboxylate 11h. Colorless oil, 90%. ^1H NMR (400 MHz, CD_3OD, mixture of rotamers) δ 1.13 – 1.25 (m, 1H Major + 1H Minor), 1.35 – 1.49 (m, 1H Major + 1H Minor), 1.51 – 1.82 (m, 5H Major + 5H Minor), 2.21 (s, 3H Minor), 2.22 (s, 3H Major), 2.19 – 2.37 (m overlapping s at 2.21 ppm and s at 2.22 ppm, 1H Major + 1H Minor), 2.95 (ddd, J = 13.8, 11.3, 2.7 Hz, 1H Minor), 3.21 (s, 3H Major), 3.27 (s, 3H Minor), 3.25 – 3.44 (m overlapping solvent signal at 3.31 ppm, 1H Major), 3.56 – 3.60 (m, 1H Major), 3.90 – 3.93 (m, 1H Minor), 5.08 (t, J = 7.3 Hz, 1H Minor), 5.71 (t, J = 7.5 Hz, 1H Major). ^{13}C NMR (125 MHz, CD_3OD, mixture of rotamers) δ 21.6, 21.8, 23.3, 23.7, 28.1, 29.8, 30.5, 30.8, 35.1, 35.6, 40.7, 42.9, 54.8, 55.7, 84.2, 89.4, 173.5, 175.1. IR (Neat, cm^{-1}) 2930, 2856, 1643, 1412, 1078, 1060, 932. HRMS *m/z* calculated for $C_9H_{18}NO_2$ $[M + H]^+$ 172.1332, found 172.1326.

2-(trimethylsilyl)ethyl 2-methoxyazepane-1-carboxylate 11i.[9] Colorless oil, 92%. ^1H NMR (600 MHz, CD_3OD, mixture of rotamers) δ 0.07 (s, 9H Minor), 0.07^3 (s, 9H Major), 1.03 – 1.06 (m, 2H Major + 2H Minor), 1.11 – 1.19 (m, 1H Major + 1H Minor), 1.31 – 1.40 (m, 1H Major + 1H Minor), 1.48 – 1.59 (m, 2H Major + 2H Minor), 1.62 – 1.69 (m, 2H Major + 2H Minor), 1.80 – 1.82 (m, 1H Major + 1H Minor), 2.20 – 2.27 (m, 1H Major + 1H Minor), 2.96 – 3.01 (m, 1H Major + 1H Minor), 3.22 (s, 3H Major), 3.22^5 (s, 3H Minor), 3.62 – 3.68 (m, 1H Major + 1H Minor), 4.20 – 4.28 (m, 2H Major + 2H Minor), 5.31 – 5.34 (m, 1H Major + 1H Minor). ^{13}C NMR (150 MHz, CD_3OD, mixture of rotamers) δ -1.4, -1.4^1, 18.7, 18.8, 23.6, 23.7, 28.8, 29.5, 30.9, 31.0, 35.5, 35.7, 41.6, 41.8, 55.3, 55.4, 65.0, 65.0^2, 87.3, 87.4, 158.2, 159.2. IR (Neat, cm^{-1}) 2931, 2857, 1698, 1417, 1249, 1171, 1085, 1072, 939, 860, 836. HRMS *m/z* calculated for $C_{13}H_{27}NNaO_2Si$ $[M + Na]^+$ 296.1658, found 296.1667.

General procedure for the Pictet-Spengler cyclisation reaction under microwave conditions. Tryptamine **12** (1.0 mmol), α-methoxy-*N*-protected amine **11** (2.0 mmol, unless stated otherwise), camphorsulfonic acid (6 mmol, unless stated otherwise) and distilled water (8 mL) were sealed in a tube and heated at 130 °C for 30 minutes under microwave irradiation. The reaction mixture was diluted with dichloromethane (30 mL), mixed with 10% aqueous NaOH (30 mL) and stirred overnight. The organic phase was separated; the aqueous phase was extracted with dichloromethane (2 × 20 mL) and ethyl acetate (1 × 20 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*. The product **1** was purified by using KP-NH silica (10 g × 0.5 mmol) and IsoleraTM Spektra Systems from Biotage. The following gradient elution was used: 1CV – AcOEt 100%; 12CV – AcOEt / MeOH 0-50%; 2CV – AcOEt / MeOH 50-50%). Spectroscopic data for **1b** are in agreement with literature.[10]

4-(1,2,3,4-Tetrahydroisoquinolin-1-yl)propanamine 1a. Yellow oil, 87%. ^{1}H NMR (600 MHz, CD_3OD) δ 1.57 - 1.68 (m, 2H), 1.74 (dddd, *J* = 13.7, 10.2, 8.5, 5.1 Hz, 1H), 2.01 (dddd, *J* = 13.7, 10.0, 6.2, 3.7 Hz, 1H), 2.66 - 2.74 (m, 3H), 2.77 (dddd, *J* = 14.6, 9.2, 5.3, 2.0 Hz, 1H), 2.95 (ddd, *J* = 12.5, 9.2, 4.8 Hz, 1H), 3.29 – 3.32 (m overlapping to solvent signal, 1H), 4.03 - 4.05 (m, 1H), 6.96 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, 1H), 7.04 (ddd, *J* = 7.5, 7.1, 1.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 23.0, 29.6, 32.8, 42.5, 43.6, 53.7, 108.9, 111.8, 118.6, 119.7, 122.0, 128.7, 136.7, 137.8. FT-IR (Neat, cm^{-1}) 3171, 3051, 2932, 2849, 1592, 1453, 1264, 1118, 729. HRMS *m/z* calculated for $C_{14}H_{20}N_3$ $[M + H]^+$ 230.1657, found 230.1653.

4-(1,2,3,4-Tetrahydroisoquinolin-1-yl)butanamine 1b. Synthesized using *tert*-Butyl-2-methoxypiperidine-1-carboxylate **11b** (1.075 g, 5.0 mmol) and camphorsulfonic acid (2.8 g, 12 mmol) Yellow oil, 60%. ^{1}H NMR (600 MHz, CD_3OD) δ 1.46 - 1.62 (m, 5H), 1.69 - 1.76 (m, 1H), 1.98 - 2.04 (m, 1 H), 2.67 - 2.72 (m, 3H), 2.78 (dddd, *J* = 14.7, 9.2, 5.2, 2.0 Hz, 1H), 2.94 (ddd, *J* = 12.5, 9.3, 4.8 Hz, 1H), 3.29 – 2.33 (m overlapping to solvent signal, 1H), 4.02 - 4.06 (m, 1H), 6.96 (ddd, *J* = 7.9, 6.9, 0.9 Hz, 1H, 1H), 7.03 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 23.0, 24.0, 33.5, 35.3, 42.3, 43.7, 54.0, 108.7, 111.8, 118.5, 119.6, 121.9, 128.7, 136.9, 137.8. FT-IR (Neat, cm^{-1}) 3230, 3048, 2929, 2857, 1617, 1453, 1318, 1302, 1266, 739, 701. HRMS *m/z* calculated for $C_{15}H_{22}N_3$ $[M + H]^+$ 244.1814, found 244.1820.

4-(1,2,3,4-Tetrahydroisoquinolin-1-yl)pentanamine 1c. Yellow oil, 79%. ^{1}H NMR (600 MHz, CD_3OD) δ 1.36 - 1.56 (m, 7H), 1.68 - 1.74 (m, 1H), 1.98 - 2.04 (m, 1H), 2.65 - 2.71 (m, 3H), 2.77 (dddd, *J* = 14.7, 9.2, 5.2, 1.9 Hz, 1H), 2.93 (ddd, *J* = 12.5, 9.3, 4.8 Hz, 1H), 3.29 – 3.32 (m overlapping signal solvent, 1H), 4.02 - 4.04 (m, 1H), 6.96 (ddd, *J* = 7.8, 7.0, 0.8 Hz, 1H, 1H), 7.03 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 23.0, 26.5, 28.1, 33.2, 35.4, 42.3, 43.7, 54.0, 108.7, 111.8, 118.5, 119.6, 121.9, 128.7, 137.0, 137.8. FT-IR (Neat, cm^{-1}) 3186, 3048, 2929, 2853, 1647, 1453, 1316, 1302, 1264, 735, 699. HRMS *m/z* calculated for $C_{16}H_{24}N_3$ $[M + H]^+$ 258.1970, found 258.1975.

(7-Fluoro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)propanamine 1d. Yellow oil, 77%. ^{1}H NMR (600 MHz, CD_3OD) δ 1.58 - 1.69 (m, 2H), 1.74 (dddd, *J* = 13.7, 10.2, 8.5, 5.1 Hz, 1H), 2.00 (dddd, *J* = 13.7, 9.9, 6.2, 3.7 Hz, 1H), 2.66 – 2.79 (m, 4H), 2.95 (ddd, *J* = 12.5, 9.2, 4.8 Hz, 1H), 3.29 – 3.33 (m overlapping to solvent signal, 1H), 4.02 - 4.06 (m, 1H), 6.74 (ddd, *J* = 9.8, 8.6, 2.3 Hz, 1H), 6.97 (dd, *J* = 10.0, 2.2 Hz, 1H), 7.32 (dd, *J* = 8.6, 5.3 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 22.9, 29.5, 32.7, 42.5, 43.5, 53.7, 98.0 (d, *J* = 25.9 Hz), 107.8 (d, *J* = 24.5 Hz), 109.0, 119.2 (d, *J* = 10.2 Hz), 125.4, 137.2 (d, *J* = 3.5 Hz), 137.7 (d, *J* = 12.5 Hz), 160.9 (d, *J* = 234.5 Hz). ^{19}F NMR (376 MHz, CD_3OD) δ -125.0 (s). FT-IR (Neat, cm^{-1}) 3190, 3055, 2932, 2849, 1623, 1469, 1440, 1264, 1132, 931, 834, 799, 733, 701. HRMS *m/z* calculated for $C_{14}H_{19}FN_3$ $[M + H]^+$ 248.1563, found 248.1550.

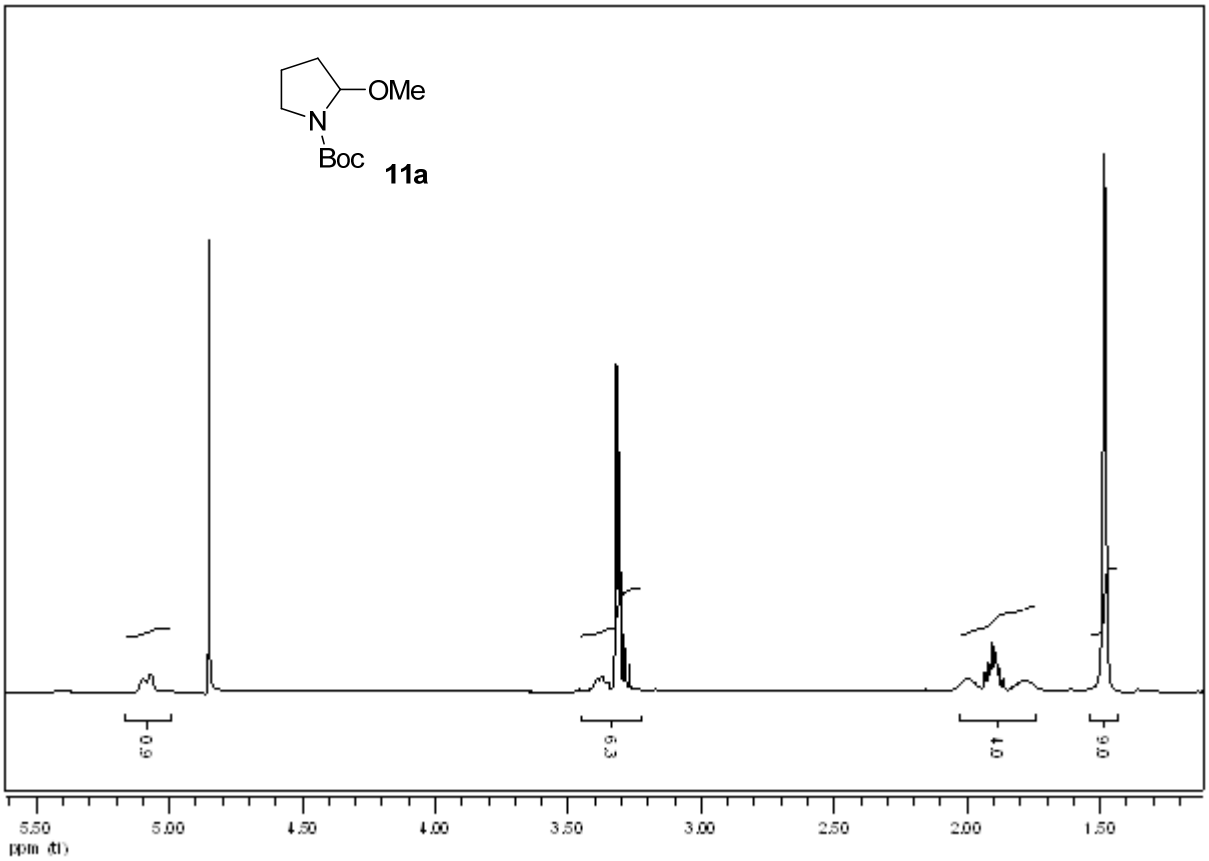
(7-Fluoro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)pentanamine 1e. Yellow oil, 61%. ^{1}H NMR (400 MHz, CD_3OD) δ 1.37 - 1.59 (m, 7H), 1.66 – 1.75 (m, 1H), 1.95 – 2.03 (m, 1H), 2.27 – 2.80 (m, 4H), 2.90 – 2.97 (m, 1H), 3.28 – 3.35 (m overlapping to solvent signal, 1H), 4.01 - 4.02 (m, 1H), 6.74 (ddd, *J* = 9.9, 8.8, 2.3 Hz, 1H), 6.97 (dd, *J* = 10.0, 2.2 Hz, 1H), 7.31 (dd, *J* = 8.6, 5.3 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 22.9, 26.5, 28.1, 32.9, 35.4, 42.2, 43.6, 53.9, 98.0 (d, *J* = 26.0 Hz), 107.7 (d, *J* = 24.5 Hz), 108.8, 119.2 (d, *J* = 10.2 Hz), 125.4, 137.5 (d, *J* = 3.1 Hz), 137.7 (d, *J* = 12.4 Hz), 160.9 (d, *J* = 234.0 Hz). ^{19}F NMR (376 MHz, CD_3OD) δ -125.1 (s). FT-IR (Neat, cm^{-1}) 3179, 3059, 2925, 2853, 1625, 1572, 1552, 1473, 1346, 1134, 799. HRMS *m/z* calculated for $C_{16}H_{23}FN_3$ $[M + H]^+$ 276.1876, found 276.1864.

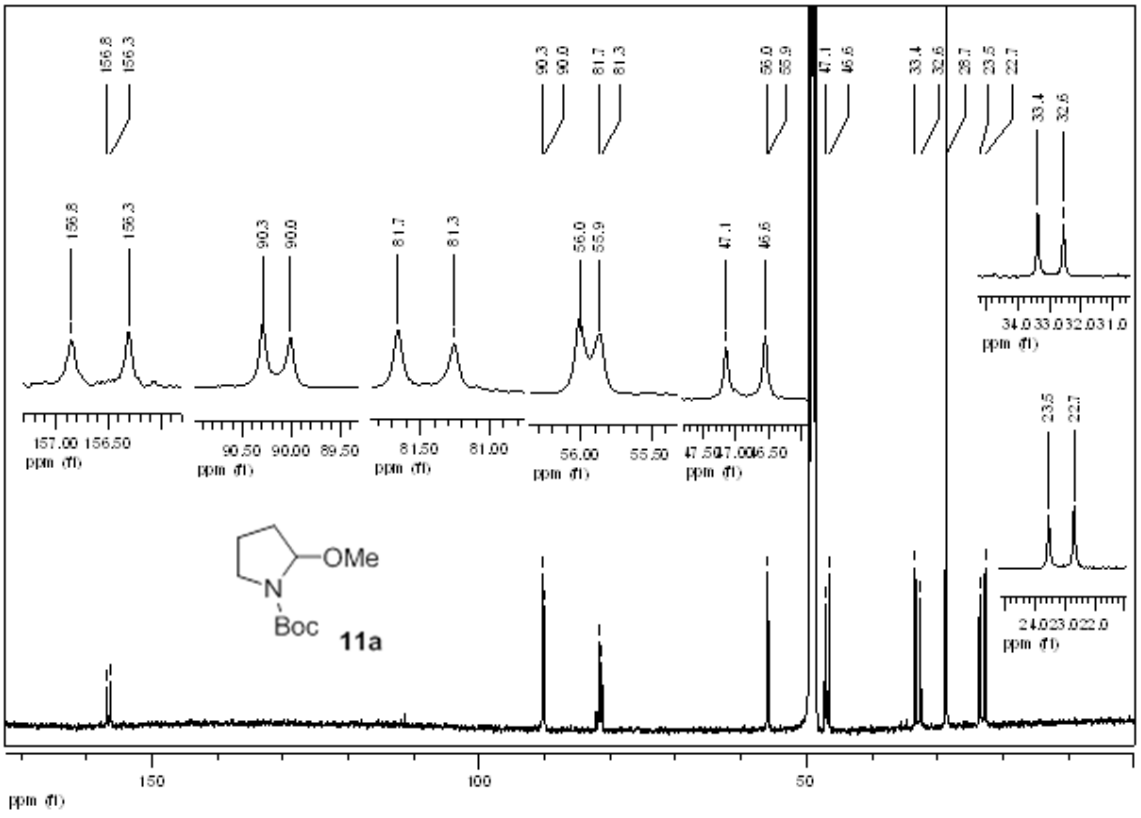
(8-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)propanamine 1f. Yellow oil, 61%. ^{1}H NMR (600 MHz, CD_3OD) δ 1.58 - 1.70 (m, 2H), 1.74 – 1.80 (m, 1H), 2.06 – 2.12 (m, 1H), 2.46 (s, 3H), 2.66 – 2.77 (m, 4H), 2.93 (ddd, *J* = 12.6, 8.7, 4.8 Hz, 1H), 3.28 (td, *J* =

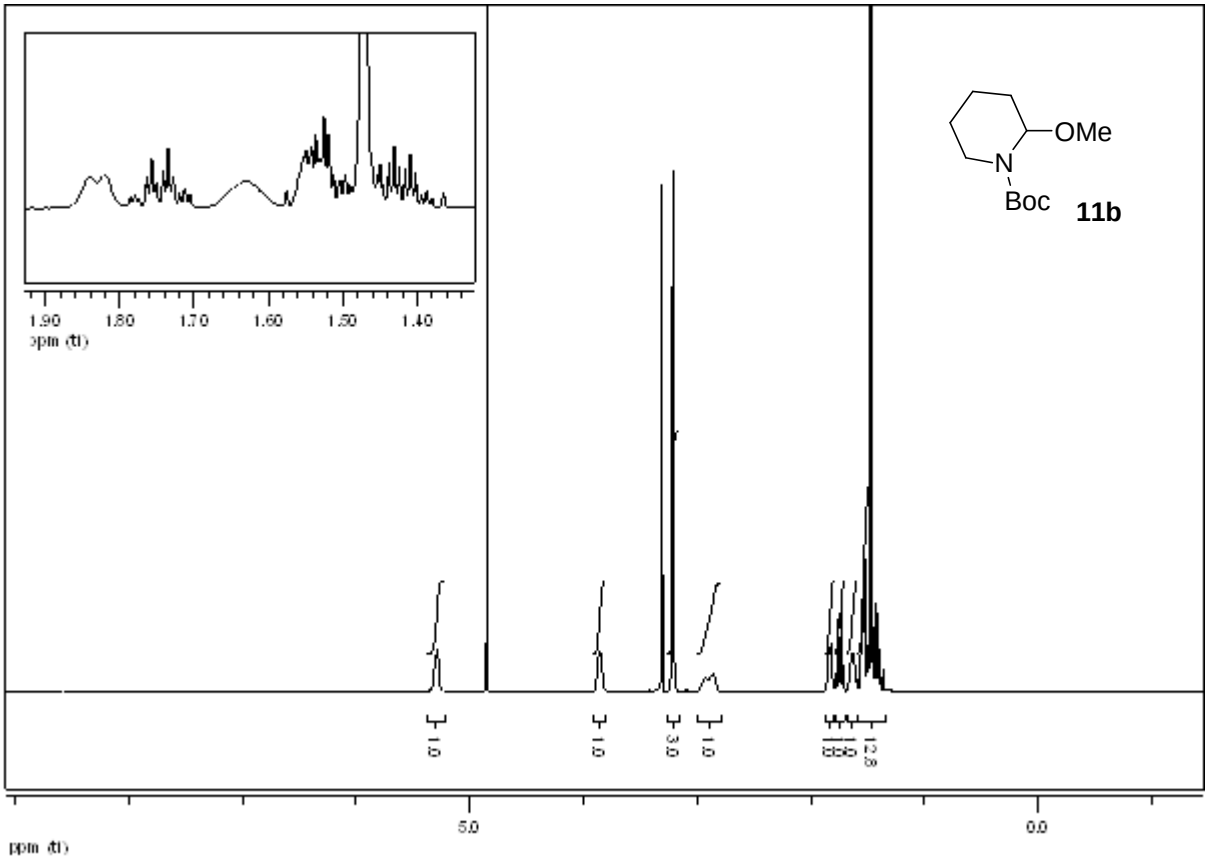
12.4, 4.7 Hz, 1H), 4.05 - 4.07 (m, 1H), 6.84 (d, *J* = 7.1 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 17.1, 23.1, 29.4, 32.7, 42.3, 43.2, 53.6, 109.4, 116.3, 119.9, 121.4, 122.8, 128.3, 136.6, 137.1. FT-IR (Neat, cm^{-1}) 3222, 2922, 2913, 1576, 1451, 1393, 1074, 1058, 779, 743. HRMS *m/z* calculated for $C_{15}H_{22}N_3$ $[M + H]^+$ 244.1814, found 244.1812.

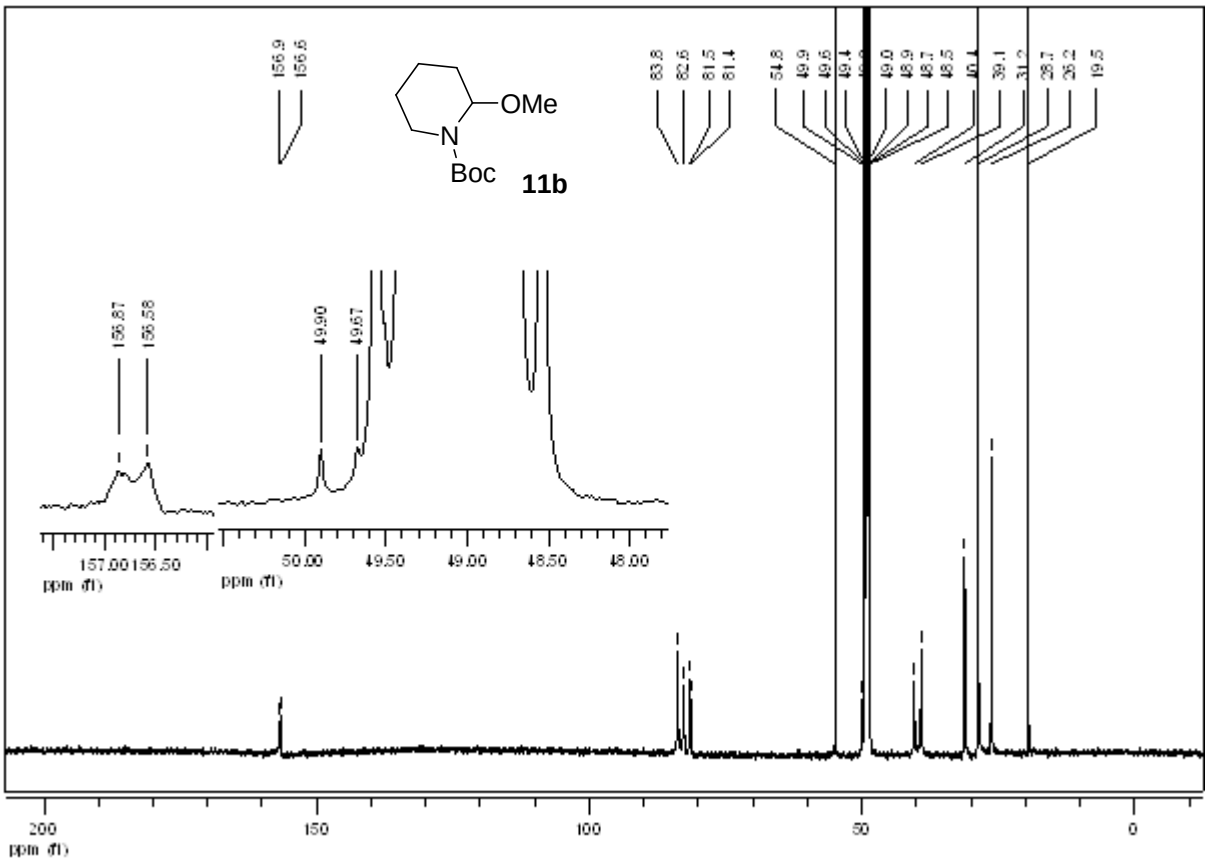
(6-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)propanamine 1g. Yellow oil, 44%. ^{1}H NMR (600 MHz, CD_3OD) δ 1.58 - 1.69 (m, 2H), 1.72 – 1.78 (m, 1H), 2.01 (dddd, *J* = 13.6, 9.9, 6.3, 3.6 Hz, 1H), 2.64 – 2.76 (m, 4H), 2.94 (ddd, *J* = 12.6, 9.2, 4.8 Hz, 1H), 3.29 – 3.32 (m overlapping to solvent signal, 1H), 4.03 - 4.05 (m, 1H), 7.12 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 22.8, 29.4, 32.7, 42.4, 43.4, 53.7, 108.8, 112.8, 113.4, 121.2, 124.6, 130.5, 136.4, 138.5. FT-IR (Neat, cm^{-1}) 3214, 2929, 2845, 1568, 1437, 1308, 1116, 1045, 971, 795. HRMS *m/z* calculated for $C_{14}H_{19}BrN_3$ $[M + H]^+$ 308.0762, found 308.0762.

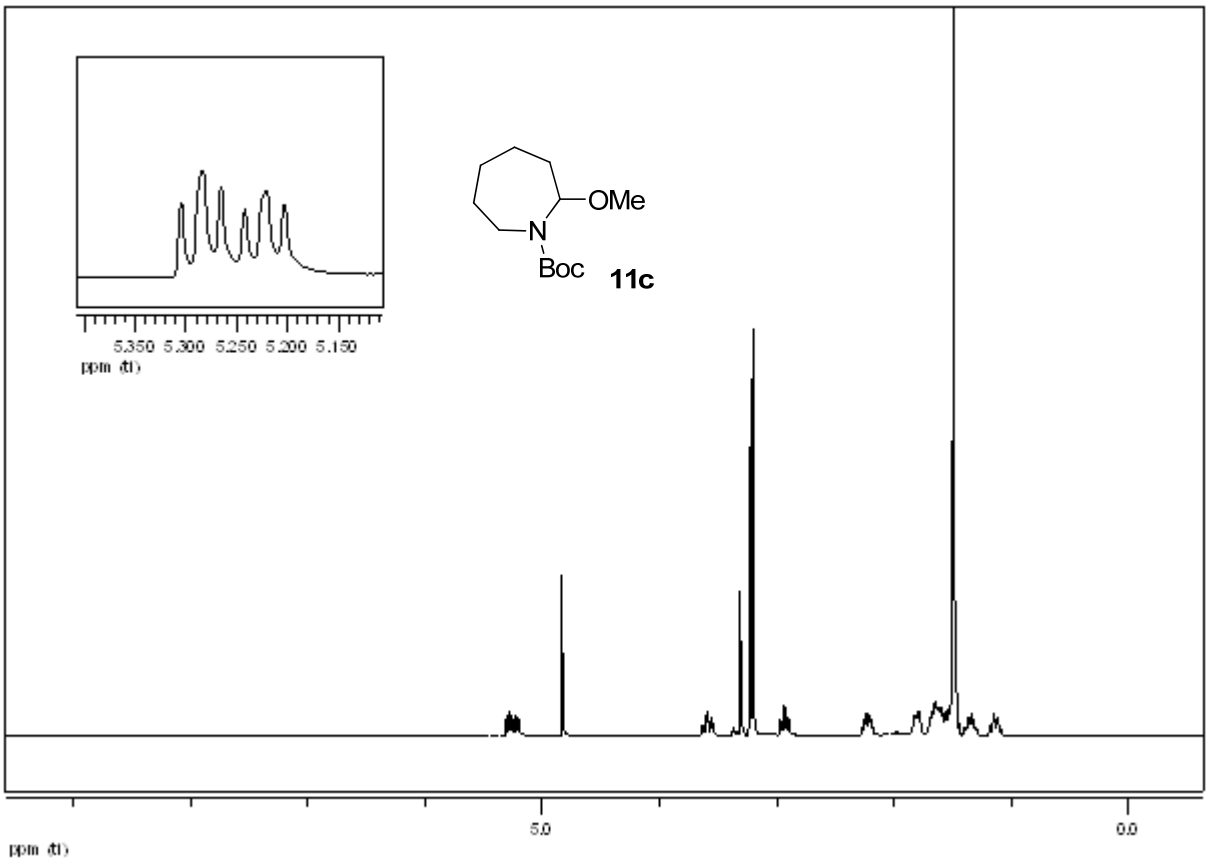
Copies of ^{1}H-NMR, ^{13}C-NMR for compounds 11a – 11i.

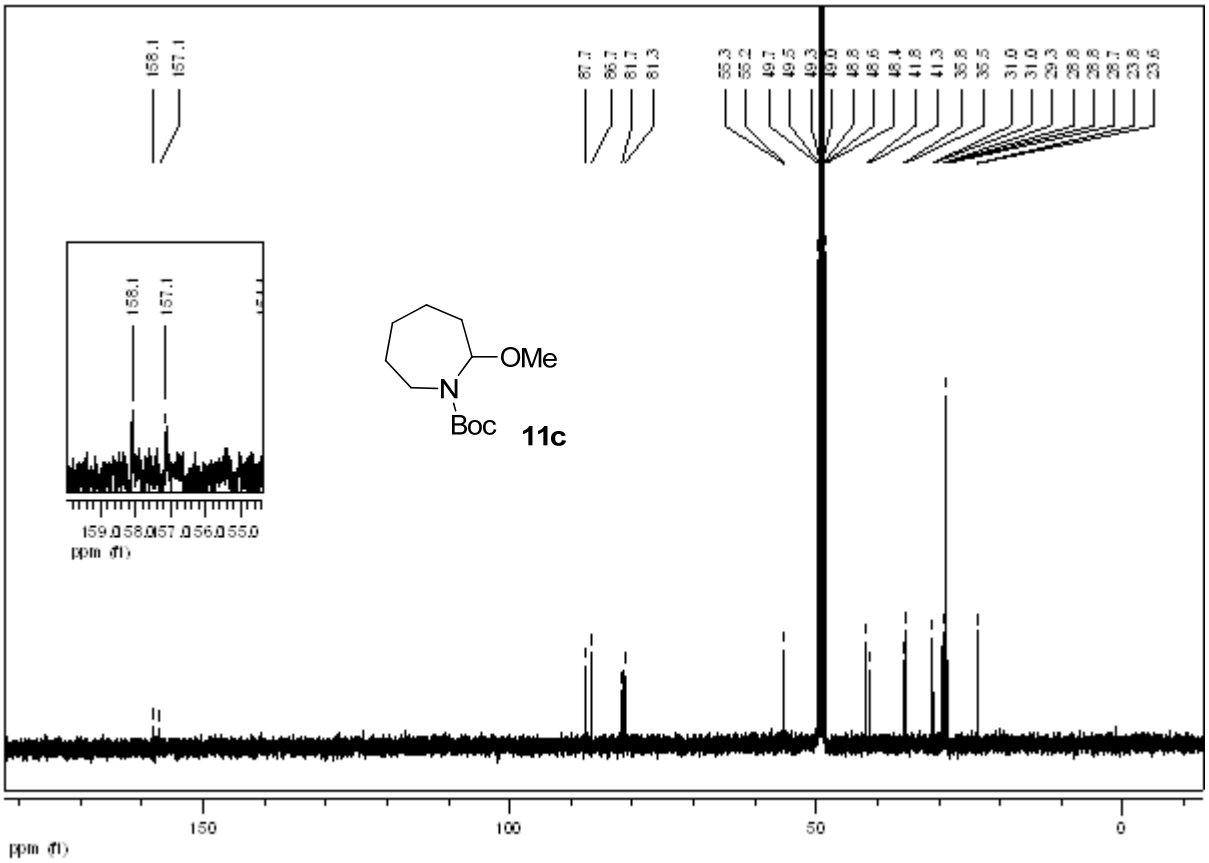


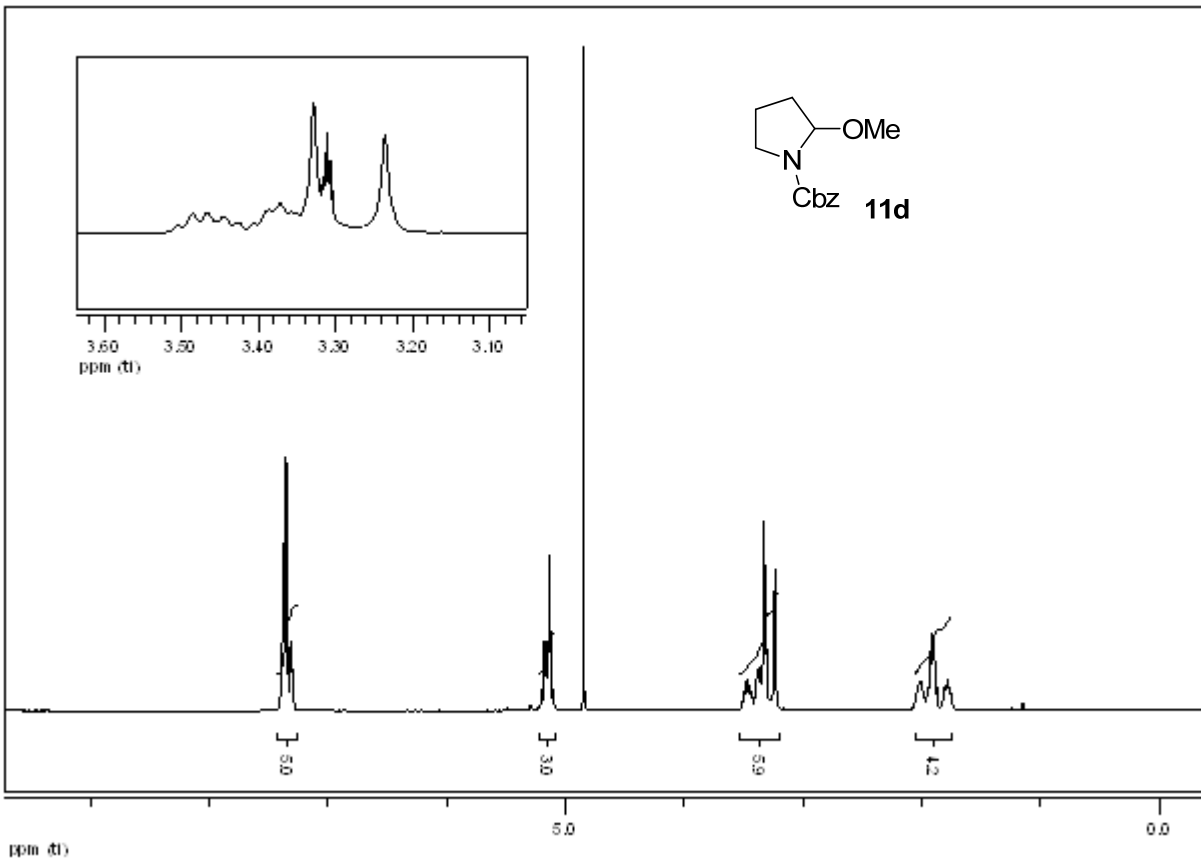


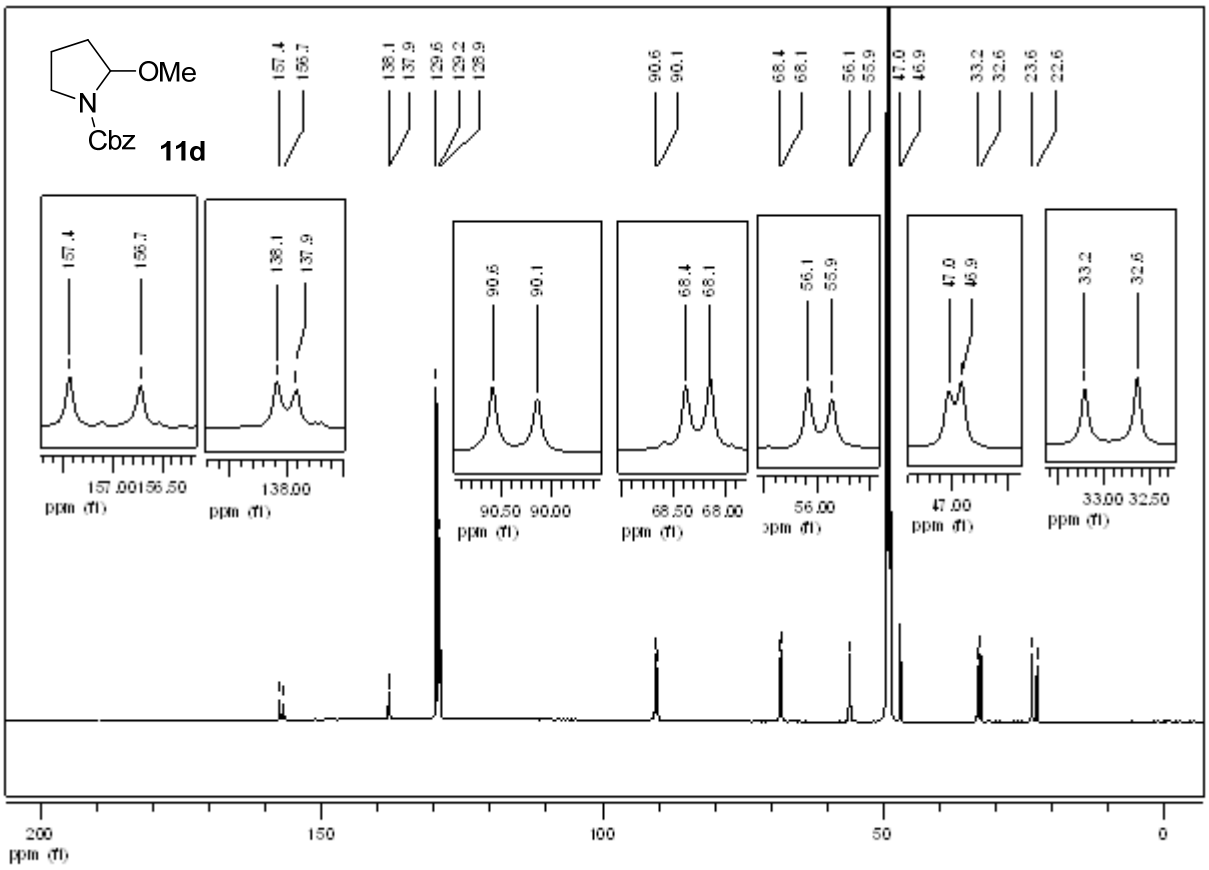

OMe
N
Boc
11b
1.90
1.80
1.70
1.60
1.50
1.40
ppm (f1)
1.0
1.0
3.0
1.0
1.8
1.9
2.0
1.8
5.0
0.0
ppm (f1)

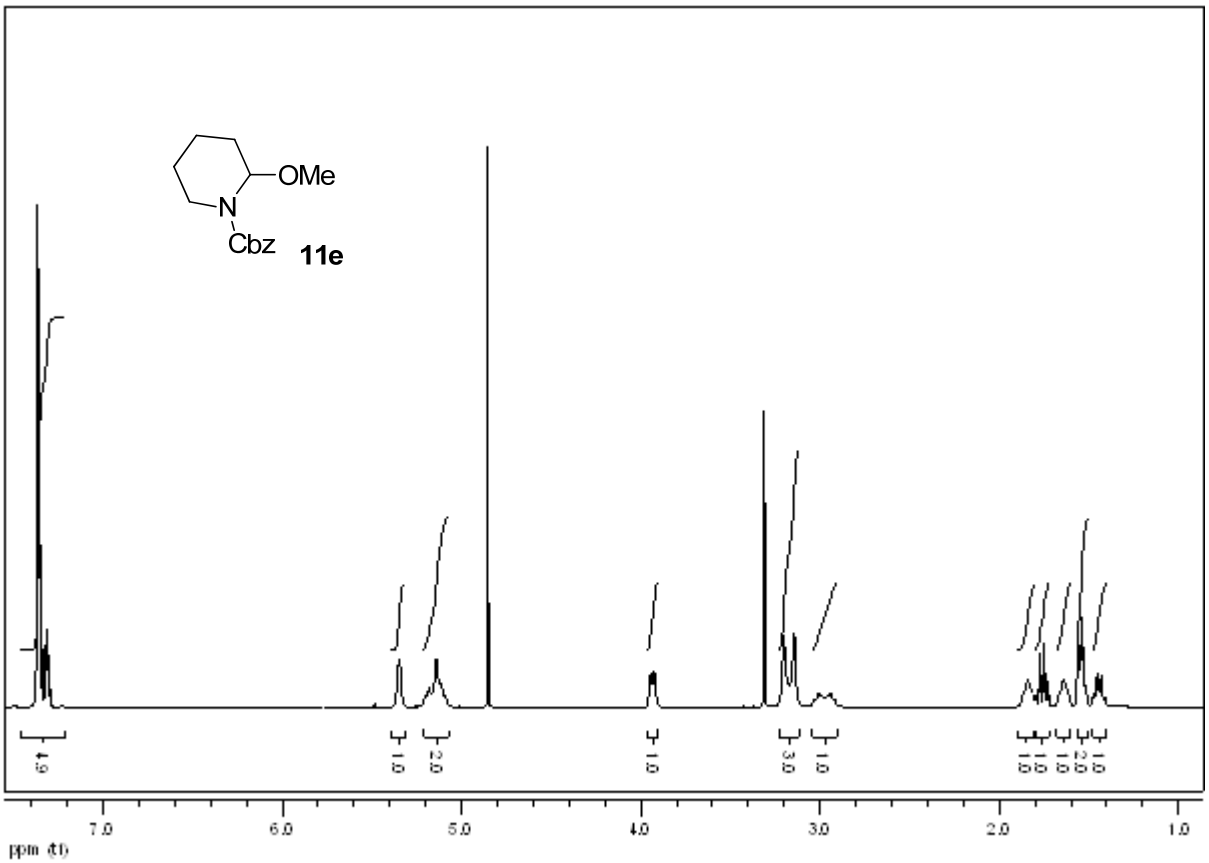

156.9
156.6
OMe
N
Boc
11b
83.8
82.6
81.5
81.4
54.8
49.9
49.6
49.4
49.0
48.9
48.7
48.5
40.1
39.1
31.2
28.7
28.2
19.5
156.87
156.58
49.90
49.67
157.00
156.50
ppm (f1)
50.00
49.50
49.00
48.50
48.00
ppm (f1)
200
150
100
50
0
ppm (f1)

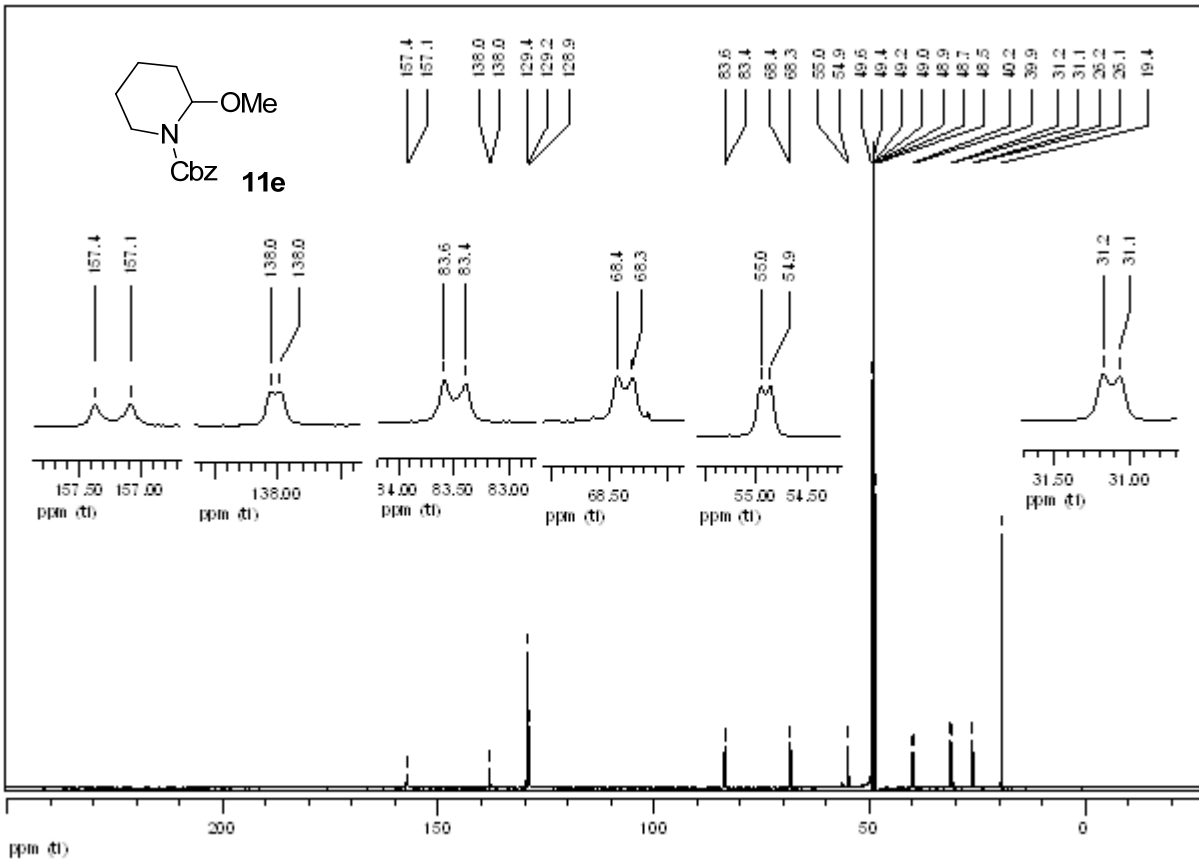

OMe
N
Boc
11c
5.350 5.300 5.250 5.200 5.150
ppm (t1)
5.0
0.0
ppm (t1)

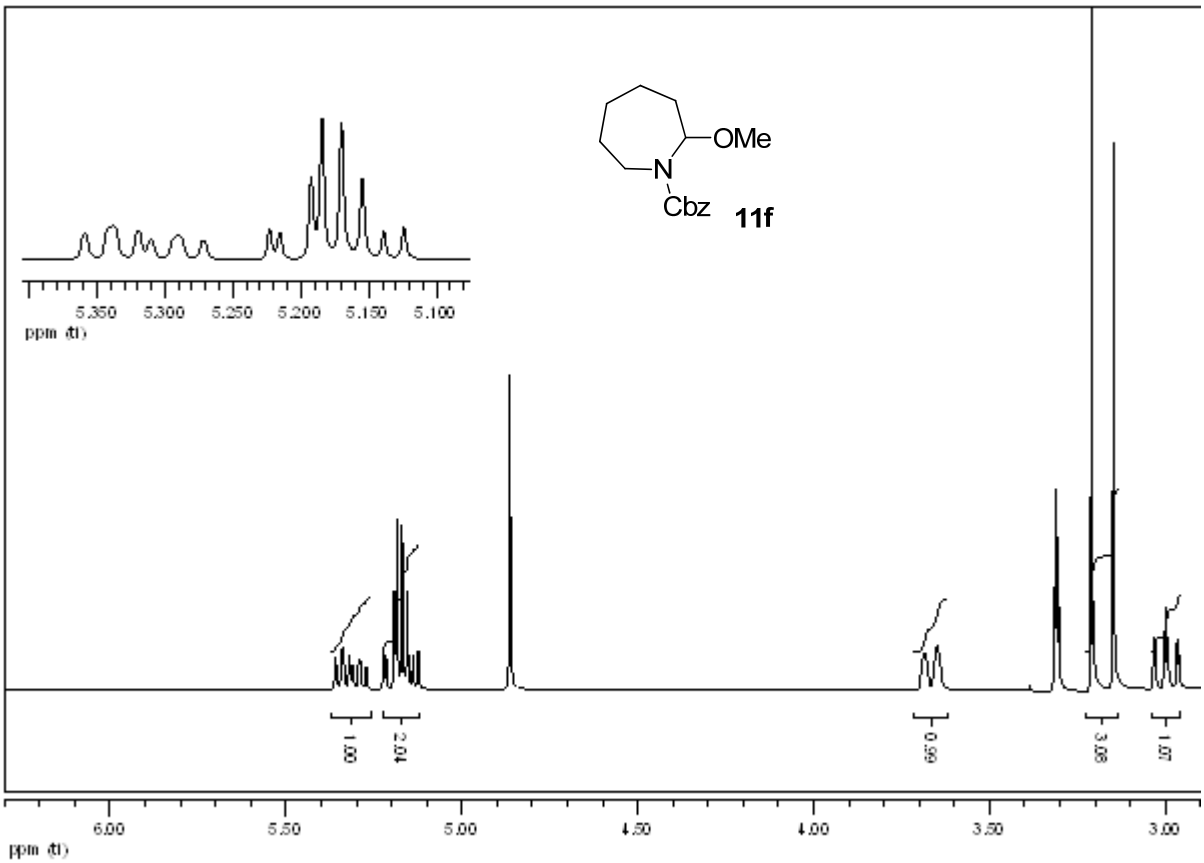

158.1
157.1
87.7
86.7
81.7
81.3
55.3
55.2
49.7
49.5
49.3
48.8
48.6
48.4
41.8
41.3
35.8
35.5
31.0
30.9
29.3
28.8
28.8
28.7
23.8
23.6
OMe
N
Boc
11c
159.0 158.0 157.0 156.0 155.0
ppm (t1)
150
100
50
0
ppm (t1)

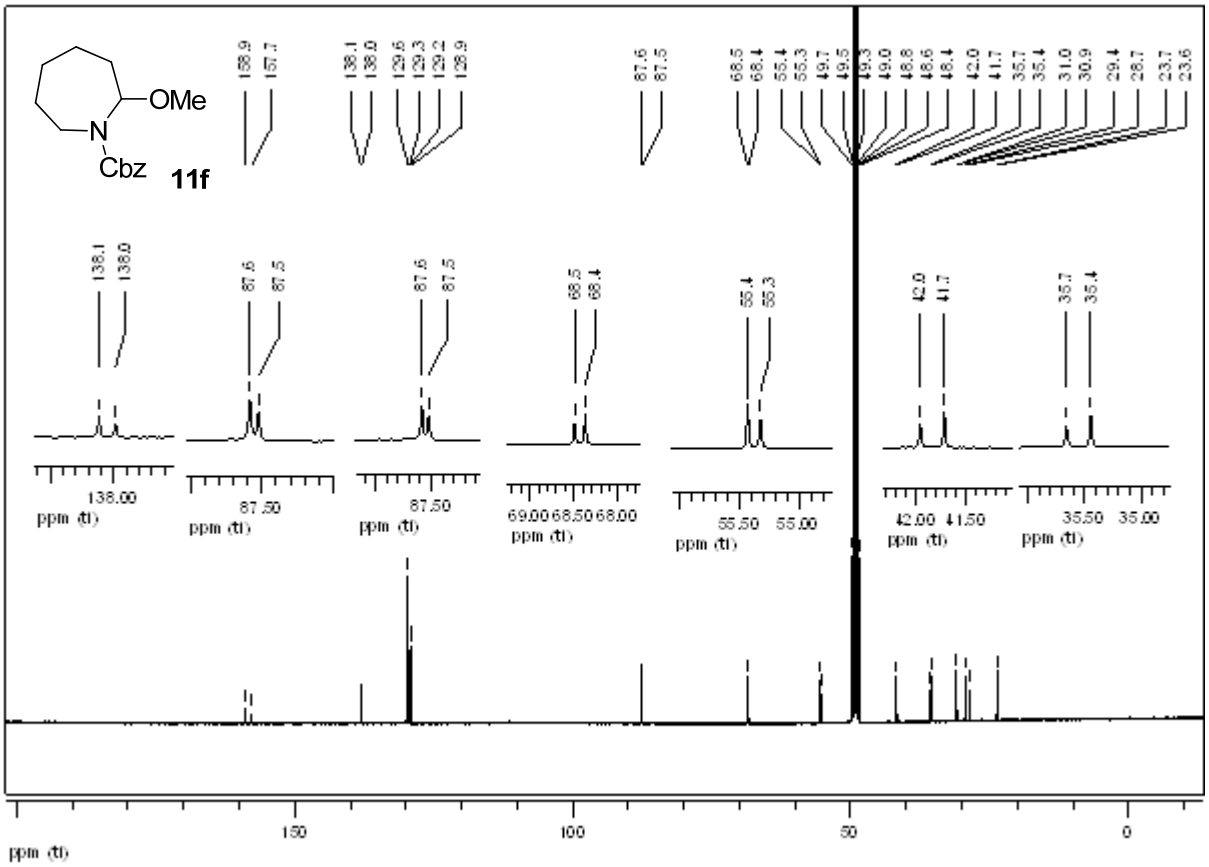

OMe
N
Cbz
11d
3.60
3.50
3.40
3.30
3.20
3.10
ppm (f1)
3.0
3.0
5.9
4.2
5.0
0.0
ppm (f1)

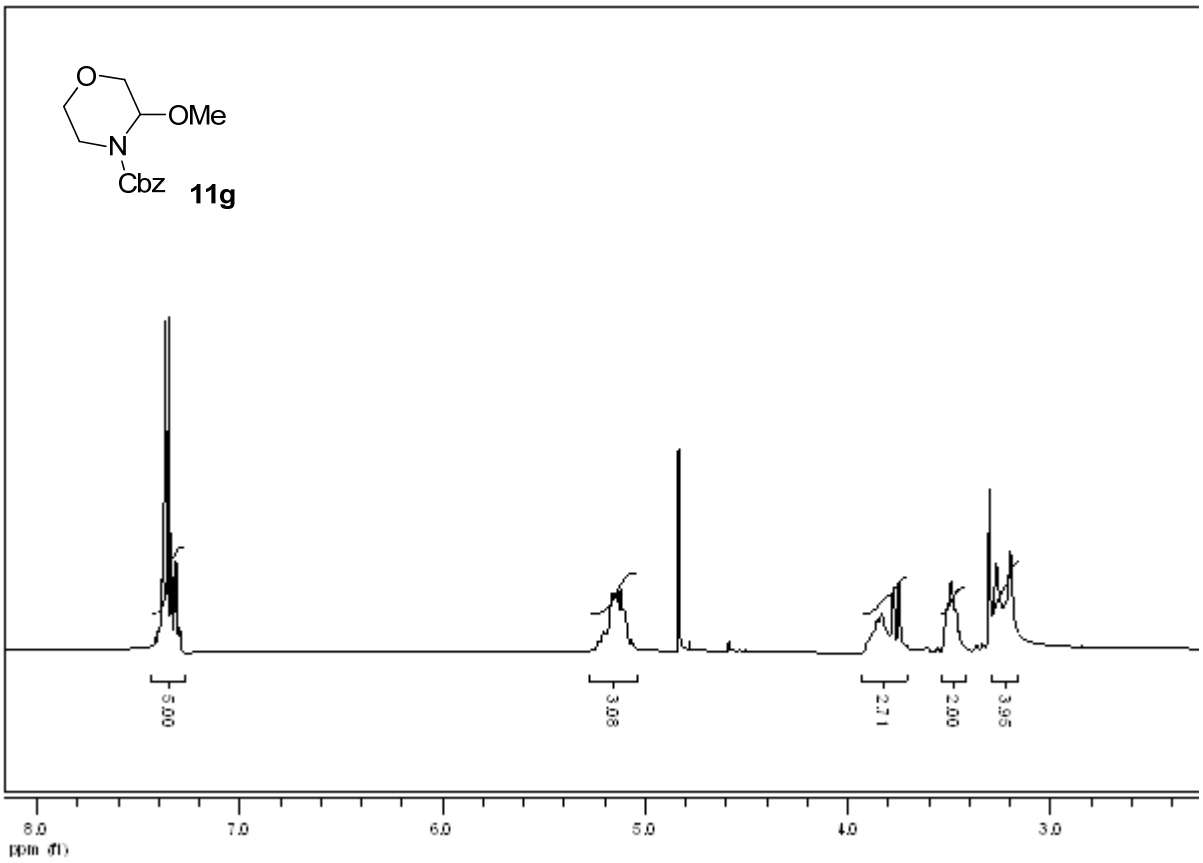

OMe
N
Cbz
11d
157.4
156.7
138.1
137.9
129.6
129.2
128.9
90.6
90.1
68.4
68.1
56.1
55.9
47.0
46.9
33.2
32.6
23.6
22.6
157.00 156.50
ppm (f1)
138.00
ppm (f1)
90.50 90.00
ppm (f1)
68.50 68.00
ppm (f1)
56.00
ppm (f1)
47.00
ppm (f1)
33.00 32.50
ppm (f1)
200
150
100
50
0
ppm (f1)

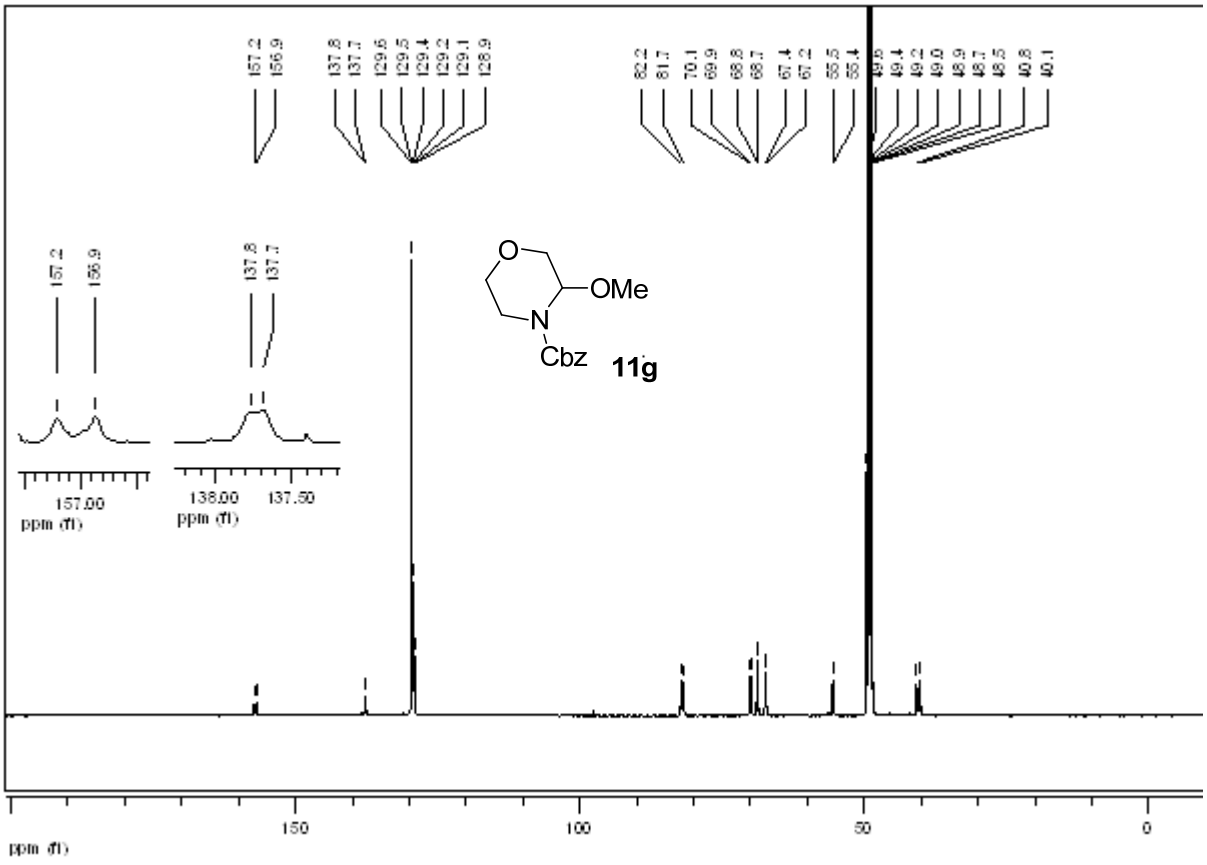

OMe
N
Cbz
11e
ppm (t1)

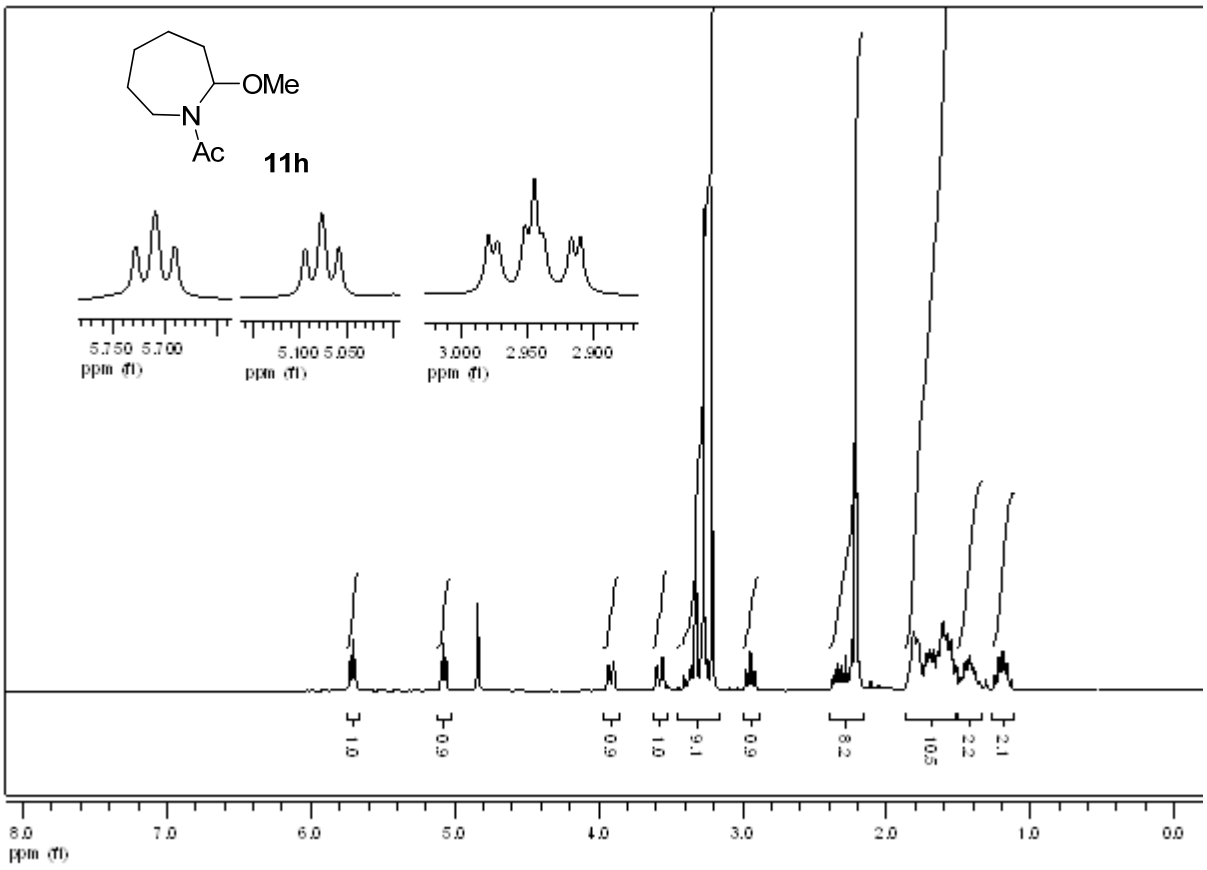

OMe
N
Cbz
11e
ppm (t1)

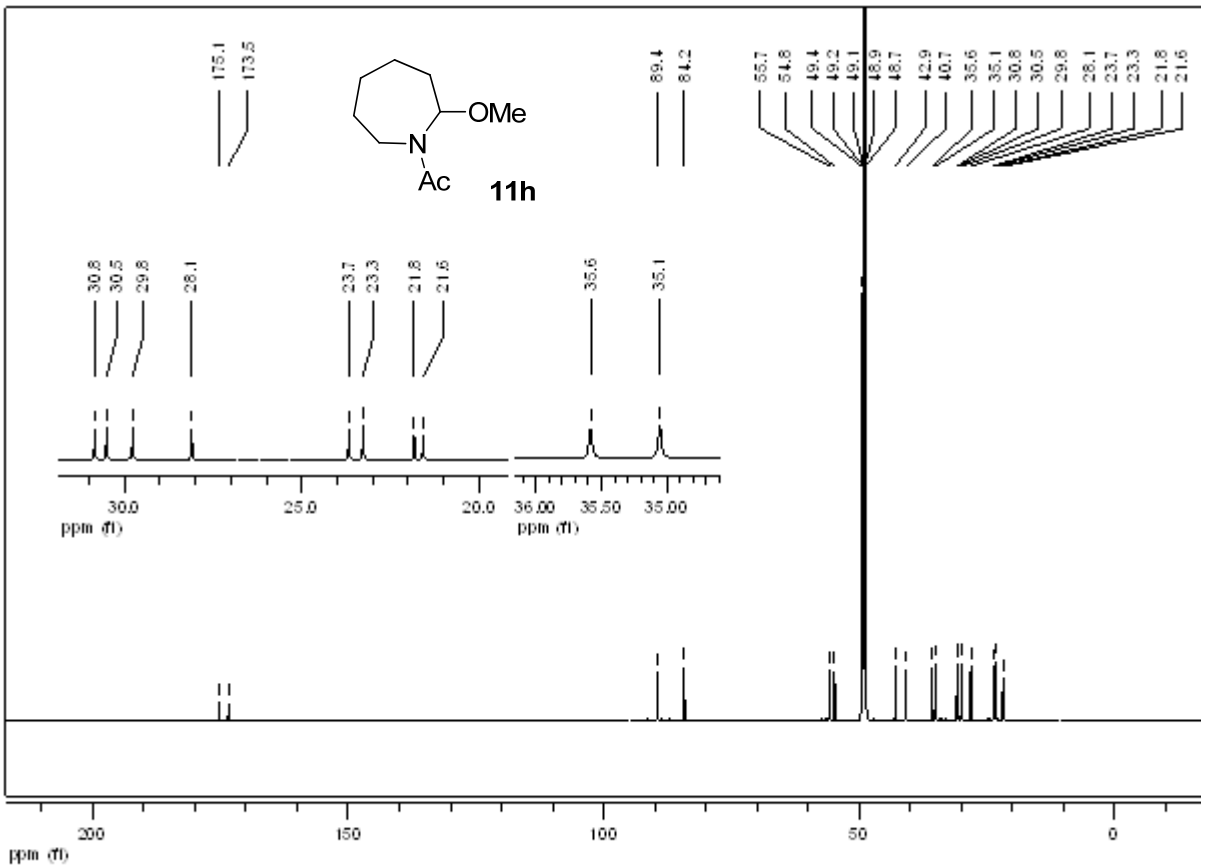

OMe
N
Cbz
11f
5.350 5.300 5.250 5.200 5.150 5.100
ppm (t)
1.00
2.04
0.99
3.08
1.07
6.00 5.50 5.00 4.50 4.00 3.50 3.00
ppm (t)

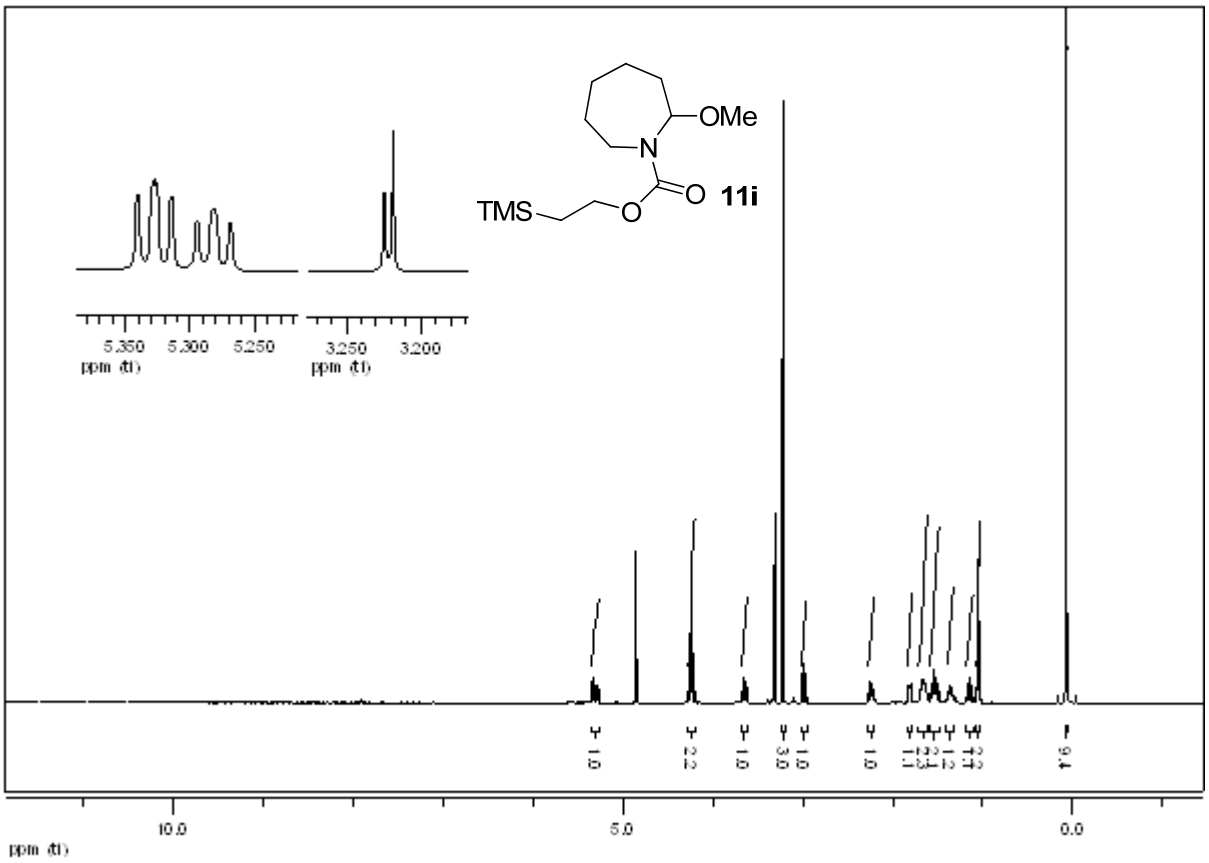

OMe
N
Cbz
11f
138.9 157.7 138.1 138.0 129.6 129.3 129.2 128.9 87.6 87.5 68.5 68.4 55.4 55.3 49.7 49.5 49.3 49.0 48.8 48.6 48.4 42.0 41.7 35.7 35.4 31.0 30.9 29.4 28.7 23.7 23.6
138.00
87.50
87.50
69.00 68.50 68.00
55.50 55.00
42.00 41.50
35.50 35.00
ppm (t)
150 100 50 0
ppm (t)

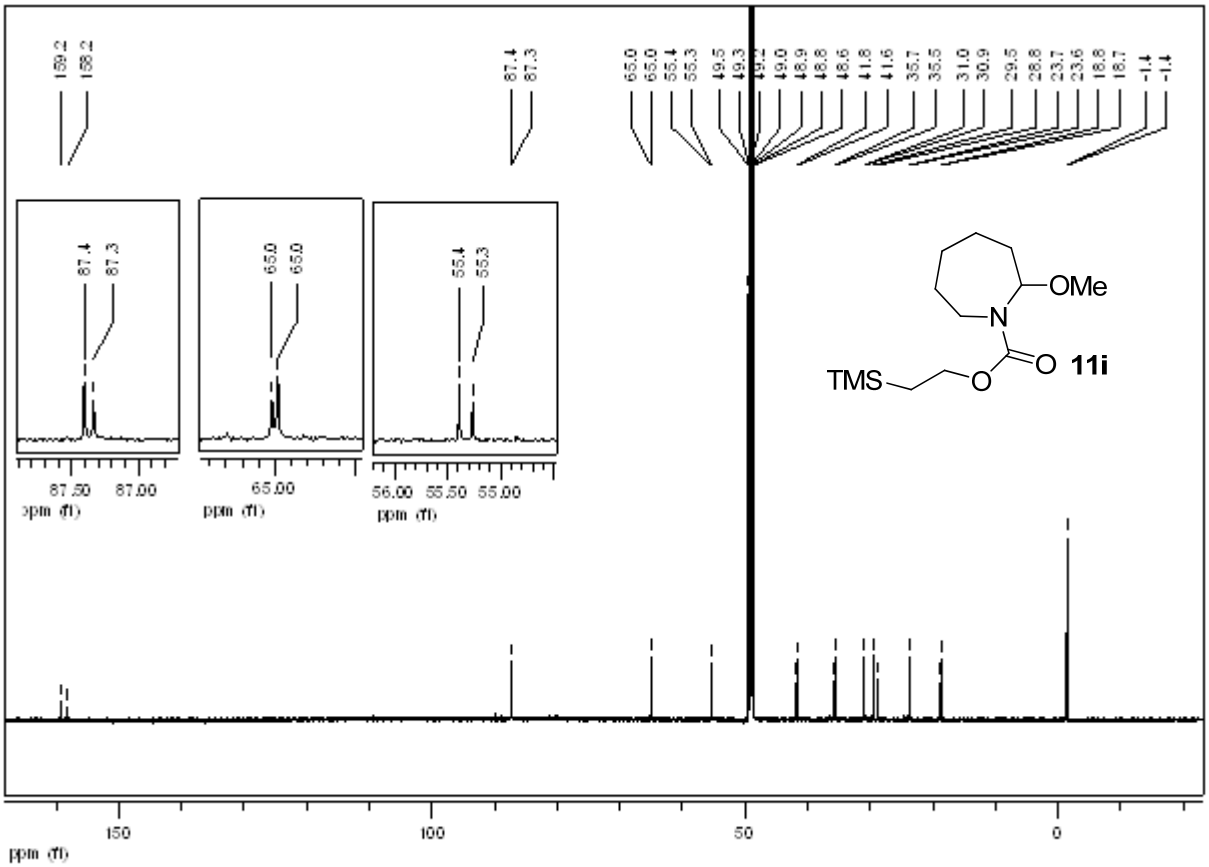

O
OMe
N
Cbz
11g
3.00
3.08
2.71
2.00
3.95
8.0
7.0
6.0
5.0
4.0
3.0
ppm (f1)

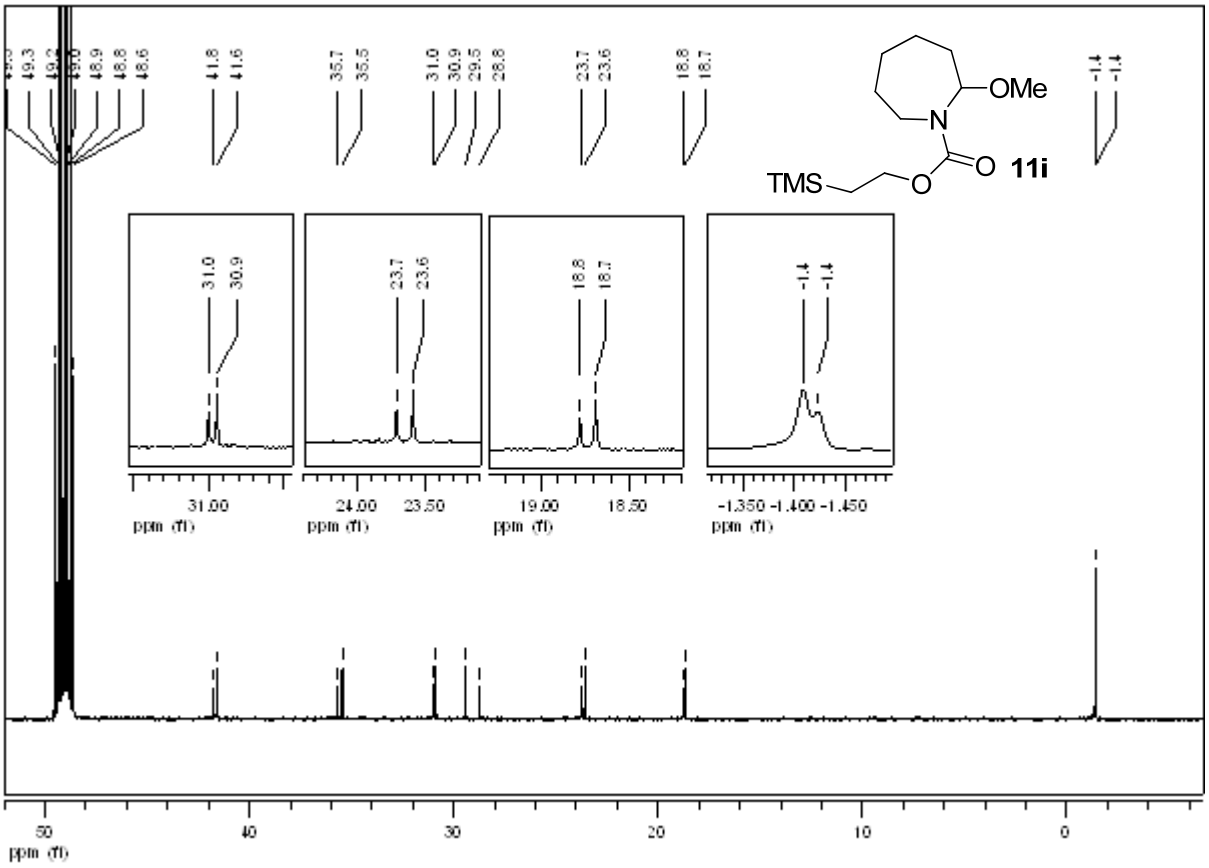

157.2
156.9
137.8
137.7
129.6
129.5
129.4
129.2
129.1
128.9
82.2
81.7
70.1
69.9
68.8
68.7
67.4
67.2
55.5
55.4
49.6
49.4
49.2
49.0
48.9
48.7
48.5
48.3
48.1
O
OMe
N
Cbz
11g
157.00
ppm (f1)
138.00
137.50
ppm (f1)
150
100
50
0
ppm (f1)


OMe
N
Ac
11h
5.750 5.700
5.100 5.050
3.000 2.950 2.900
ppm (f1)
1.0
0.9
0.9
1.0
9.1
6.0
8.2
10.5
2.2
2.1
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

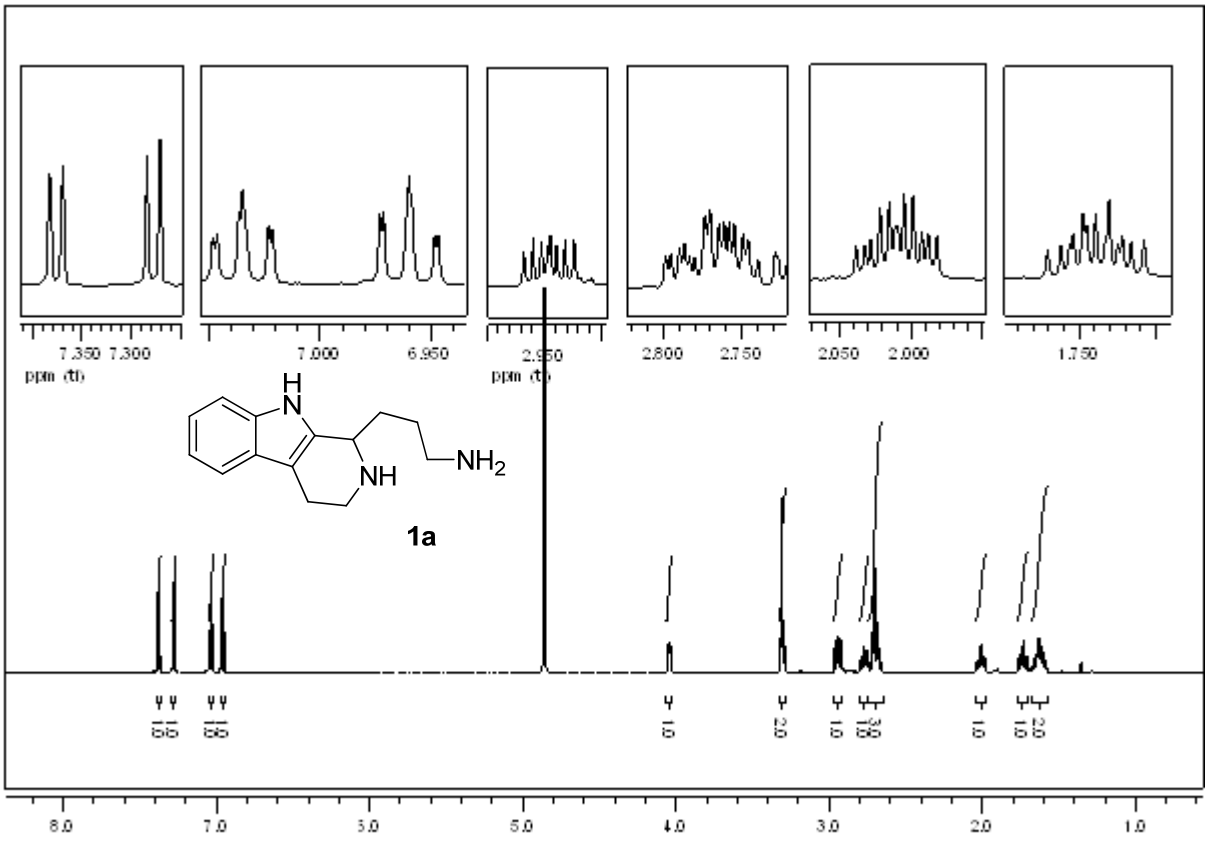

175.1
173.5
89.4
84.2
55.7
54.8
49.4
49.2
49.1
48.9
48.7
42.9
40.7
35.6
35.1
30.8
30.5
29.8
28.1
23.7
23.3
21.8
21.6
OMe
N
Ac
11h
30.0
25.0
20.0
36.00 35.50 35.00
ppm (f1)
200
150
100
50
0

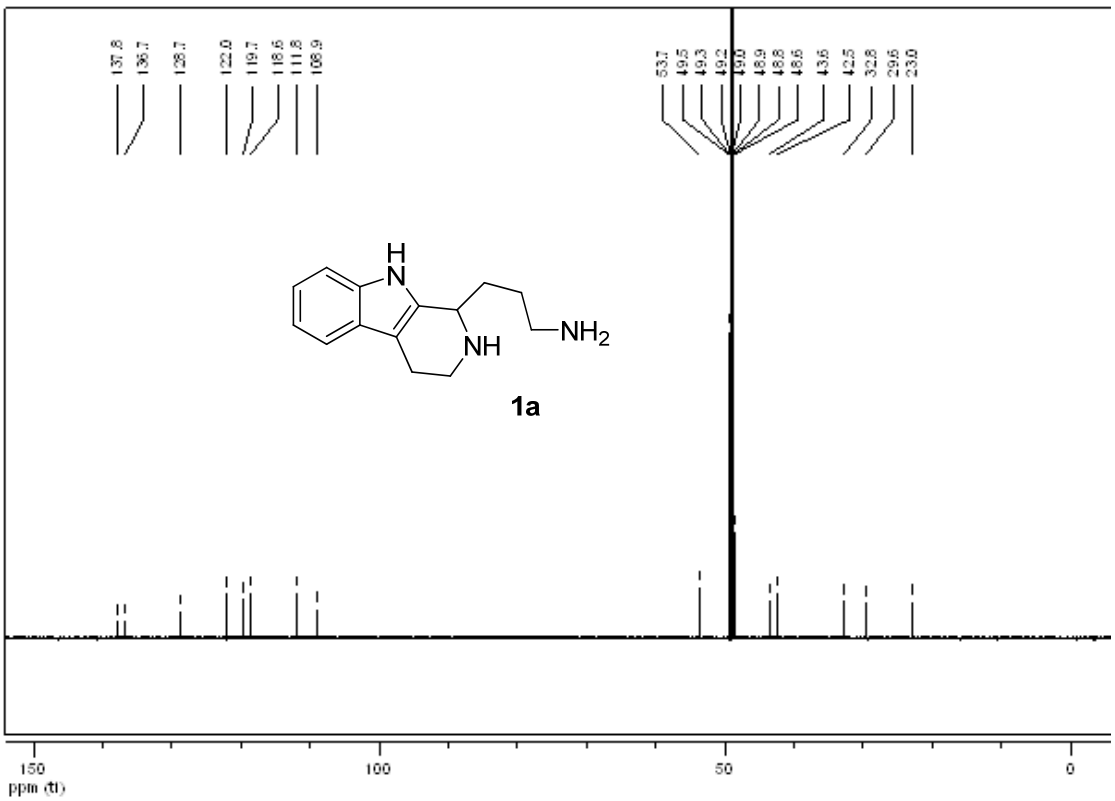

OMe
N
O
O
TMS
11i
5.350 5.300 5.250
ppm (t)
3.250 3.200
ppm (t)
10.0
5.0
0.0
ppm (t)

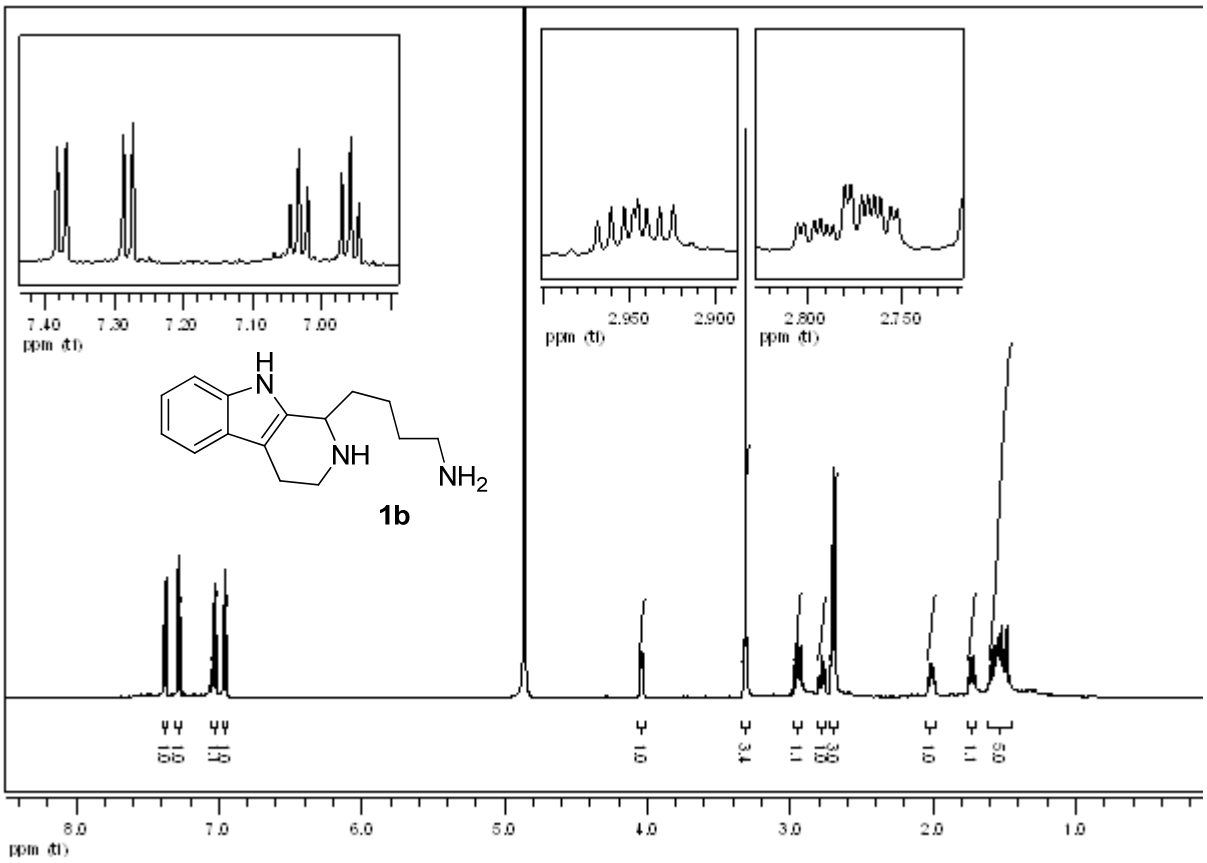

159.2
158.2
87.4
87.3
65.0
65.0
55.4
55.3
49.5
49.3
49.2
49.0
48.9
48.8
48.6
41.8
41.6
35.7
35.5
31.0
30.9
29.5
28.8
23.7
23.6
18.8
18.7
-1.4
-1.4
87.50 87.00
ppm (t)
65.00
ppm (t)
56.00 55.50 55.00
ppm (t)
OMe
N
O
O
TMS
11i
150
100
50
0
ppm (t)

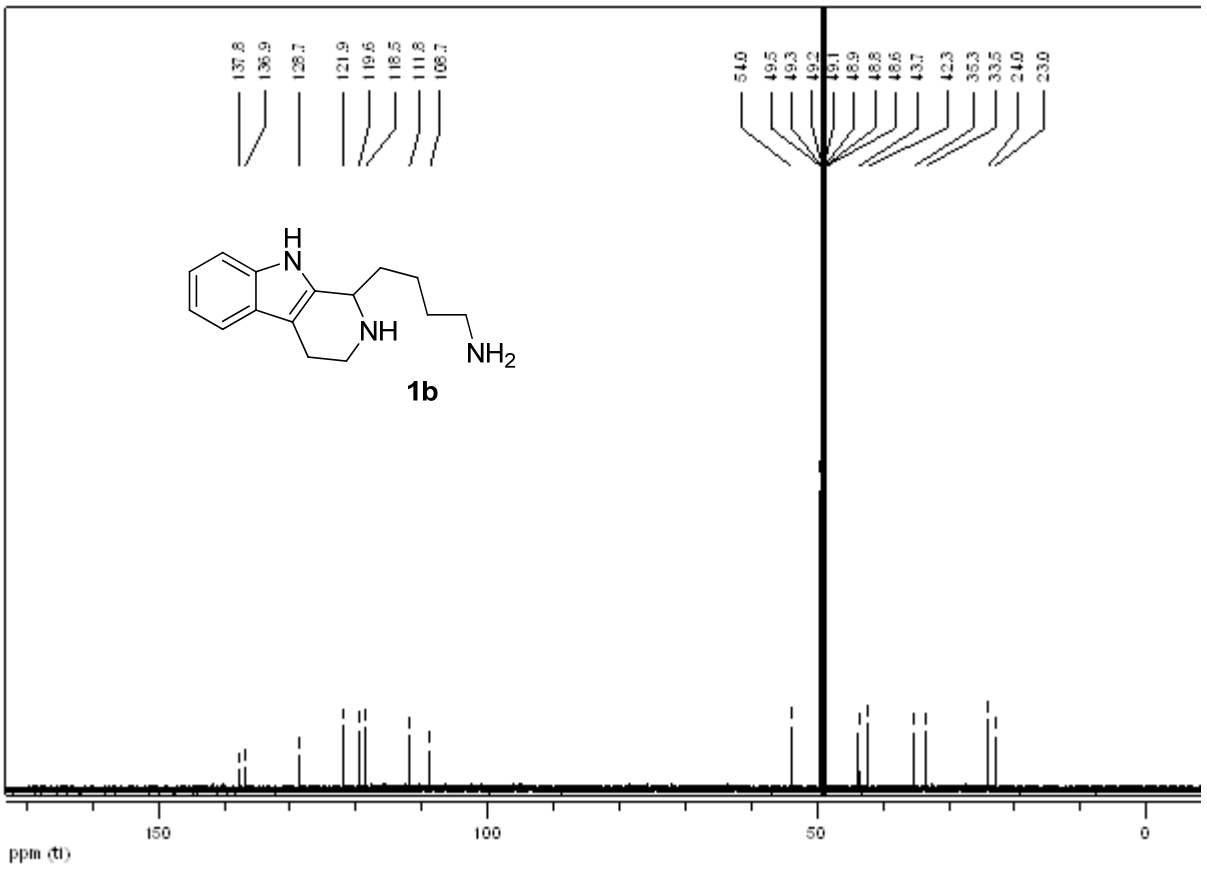

OMe
N
O
TMS
O
11i
50
40
30
20
10
0
ppm (f1)

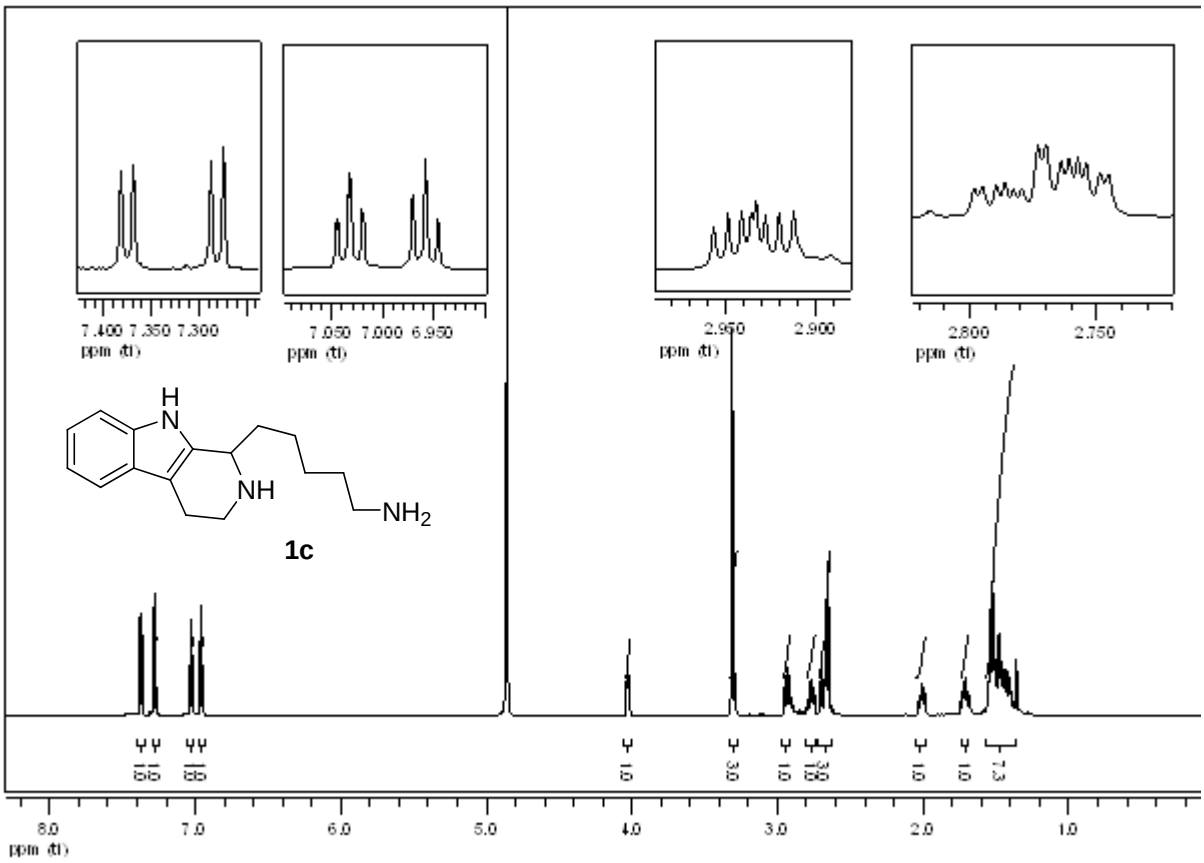
Copies of ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR for compounds 1a – 1g.

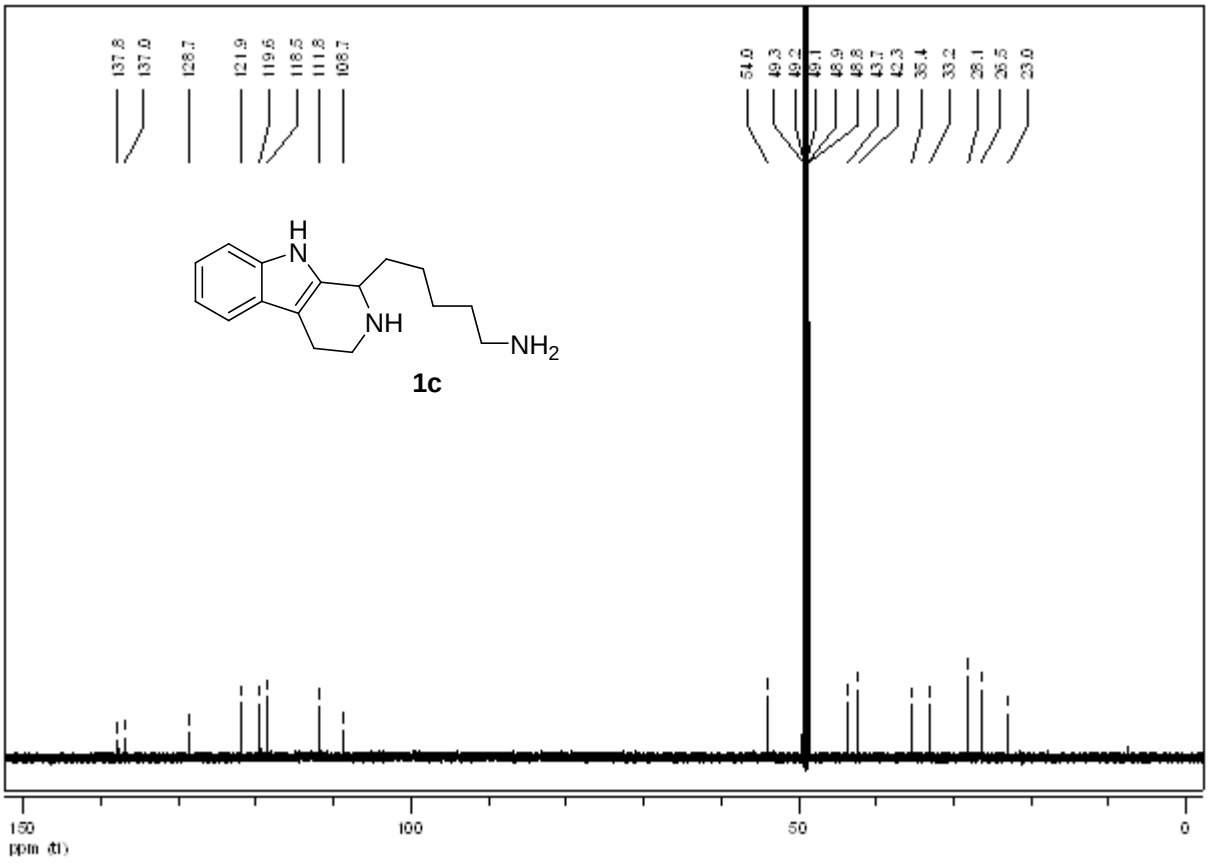


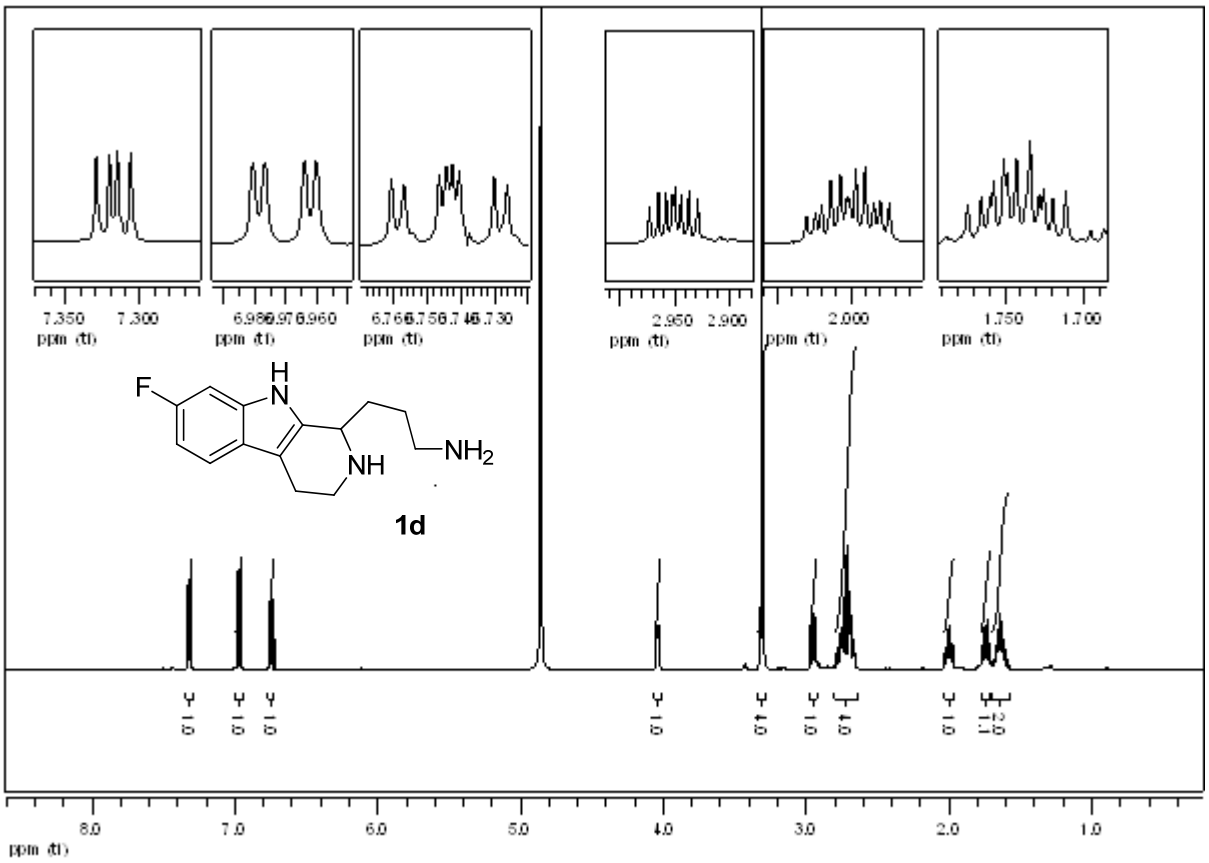


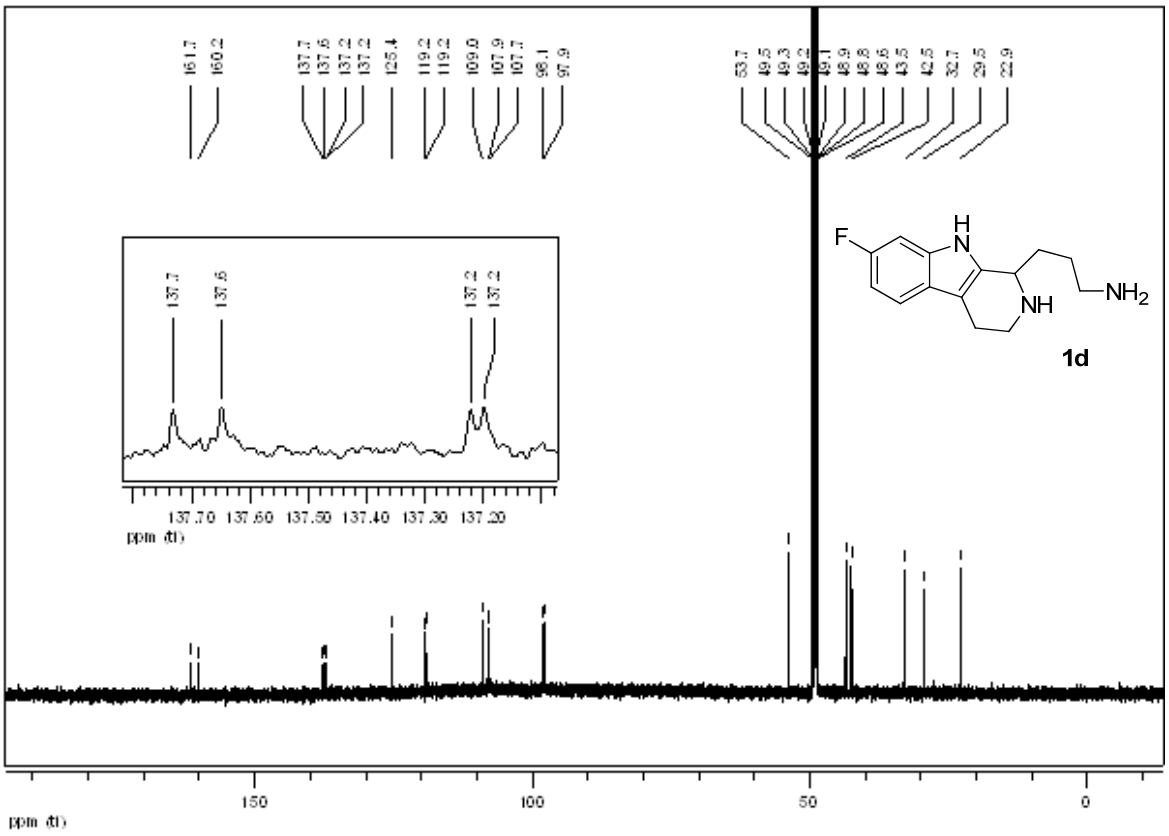

7.40
7.30
7.20
7.10
7.00
ppm (t1)
2.950
2.900
ppm (t1)
2.800
2.750
ppm (t1)
H
N
NH
NH2
1b
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

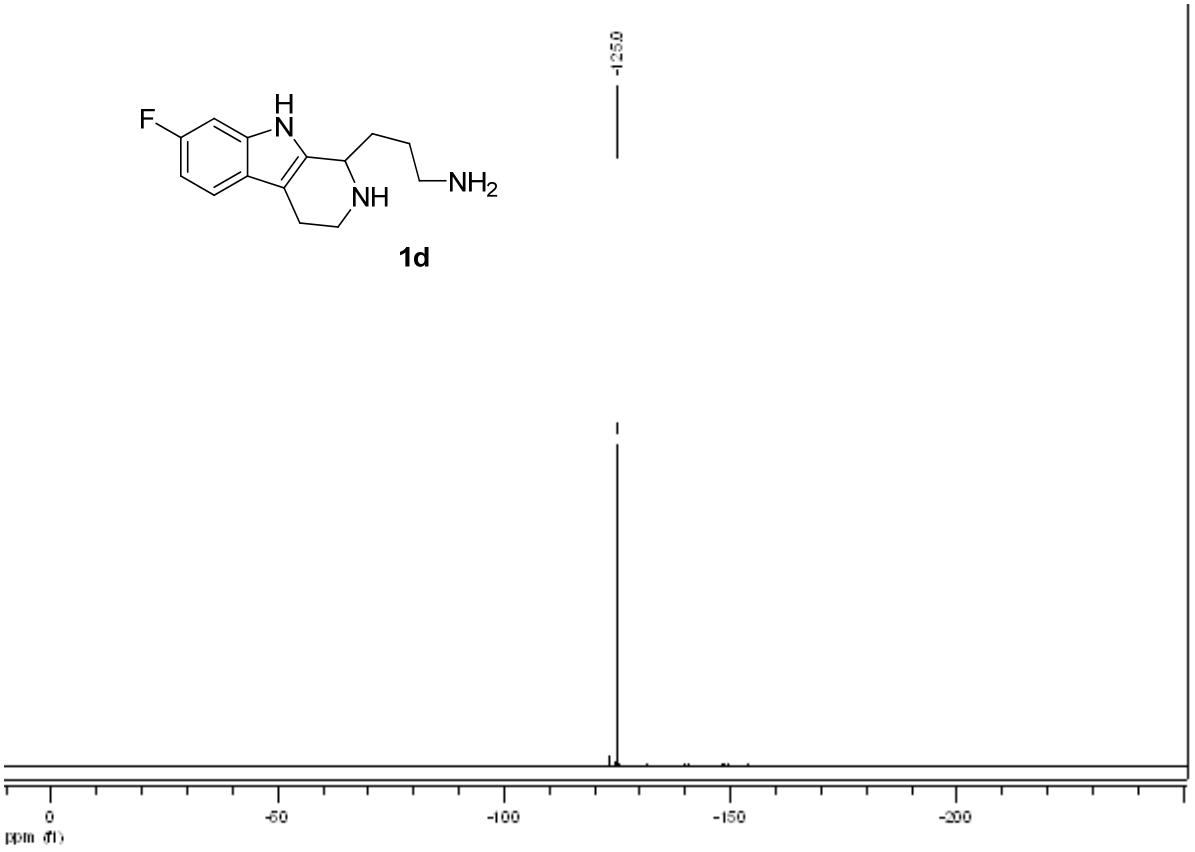

137.8
136.9
128.7
121.9
119.6
118.5
111.8
108.7
54.0
49.5
49.3
49.2
49.1
48.9
48.8
48.6
43.7
42.3
35.3
33.5
24.0
23.0
H
N
NH
NH2
1b
150
100
50
0
ppm (t1)


7.400 7.350 7.300
ppm (t1)
7.050 7.000 6.950
ppm (t1)
2.950 2.900
ppm (t1)
2.800 2.750
ppm (t1)
H
N
NH
NH2
1c
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

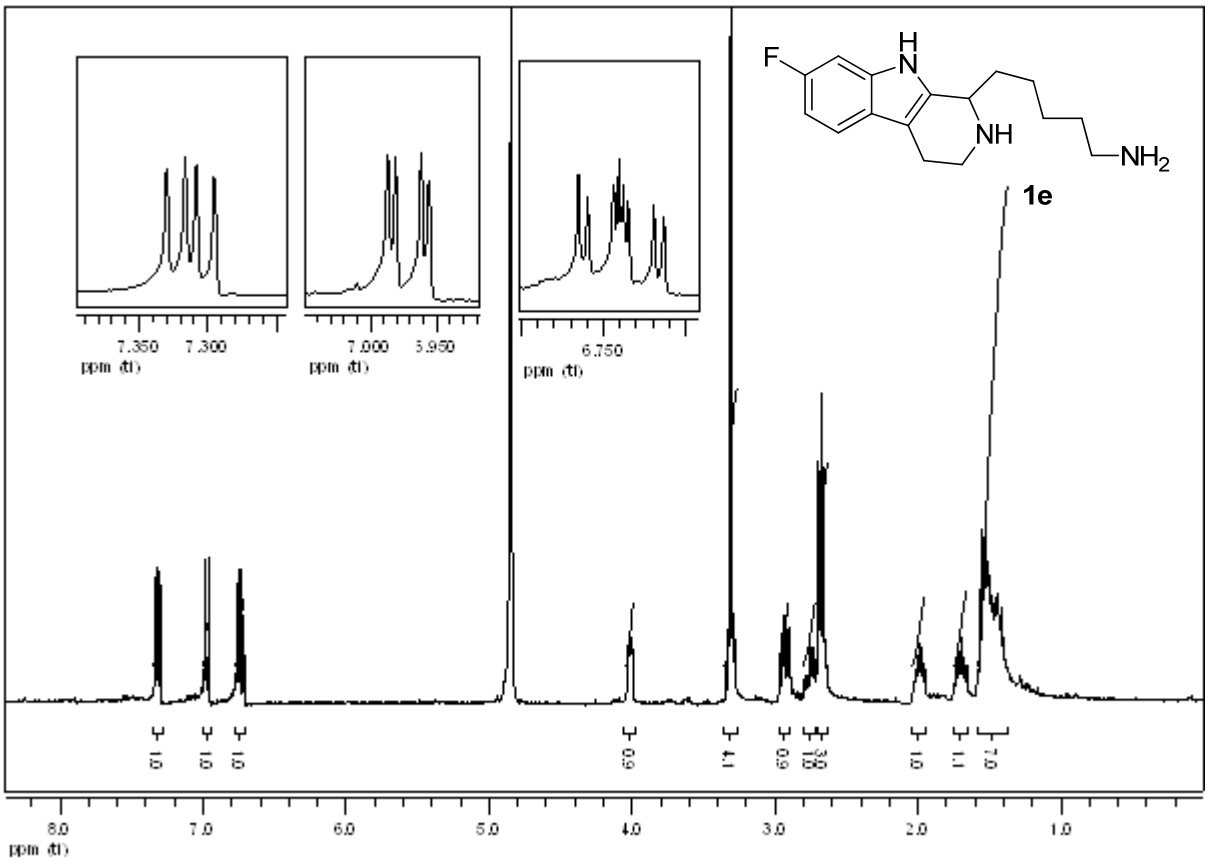

137.8
137.0
128.7
121.9
119.6
118.5
111.8
108.7
54.0
49.3
49.2
49.1
48.9
48.8
43.7
42.3
35.4
33.2
28.1
26.5
23.0
H
N
NH
NH2
1c
150
100
50
0
ppm (t1)

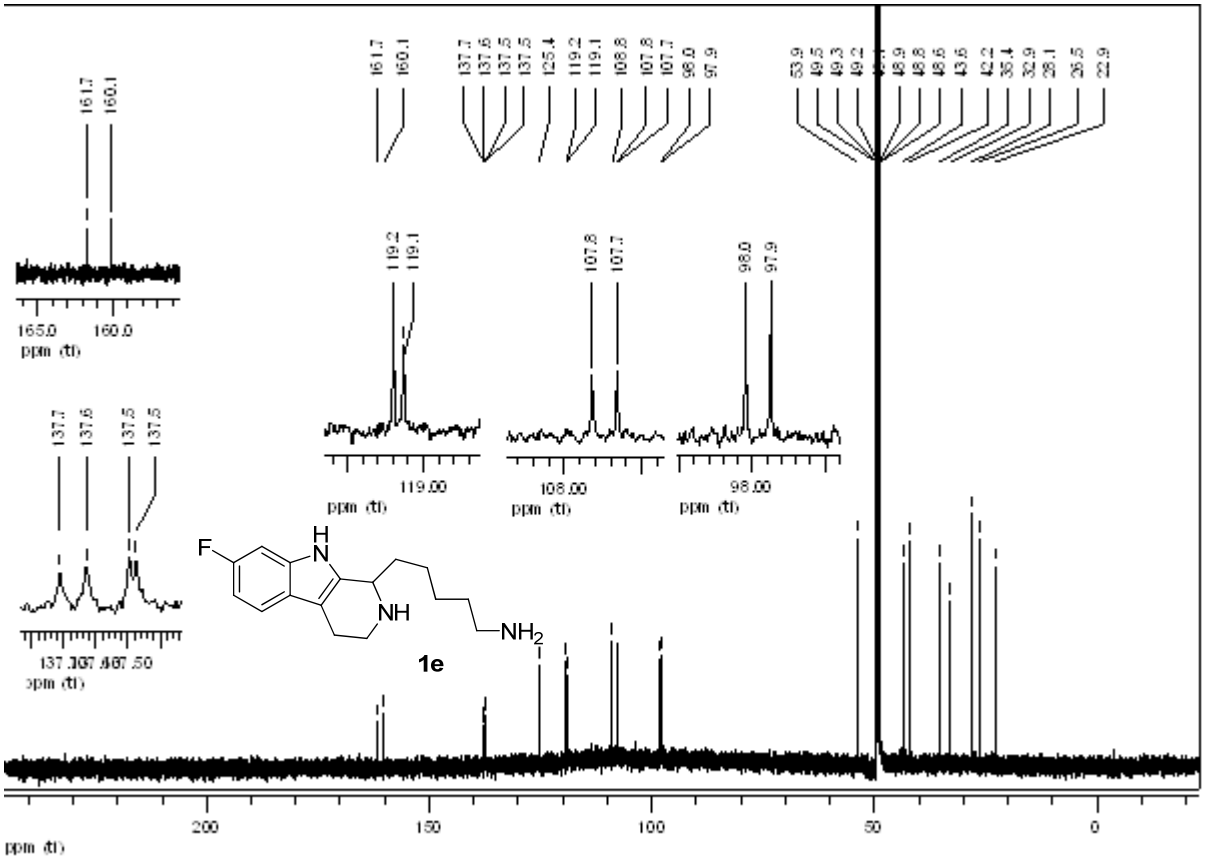

F
H
N
NH
NH2
1d
ppm (t1)

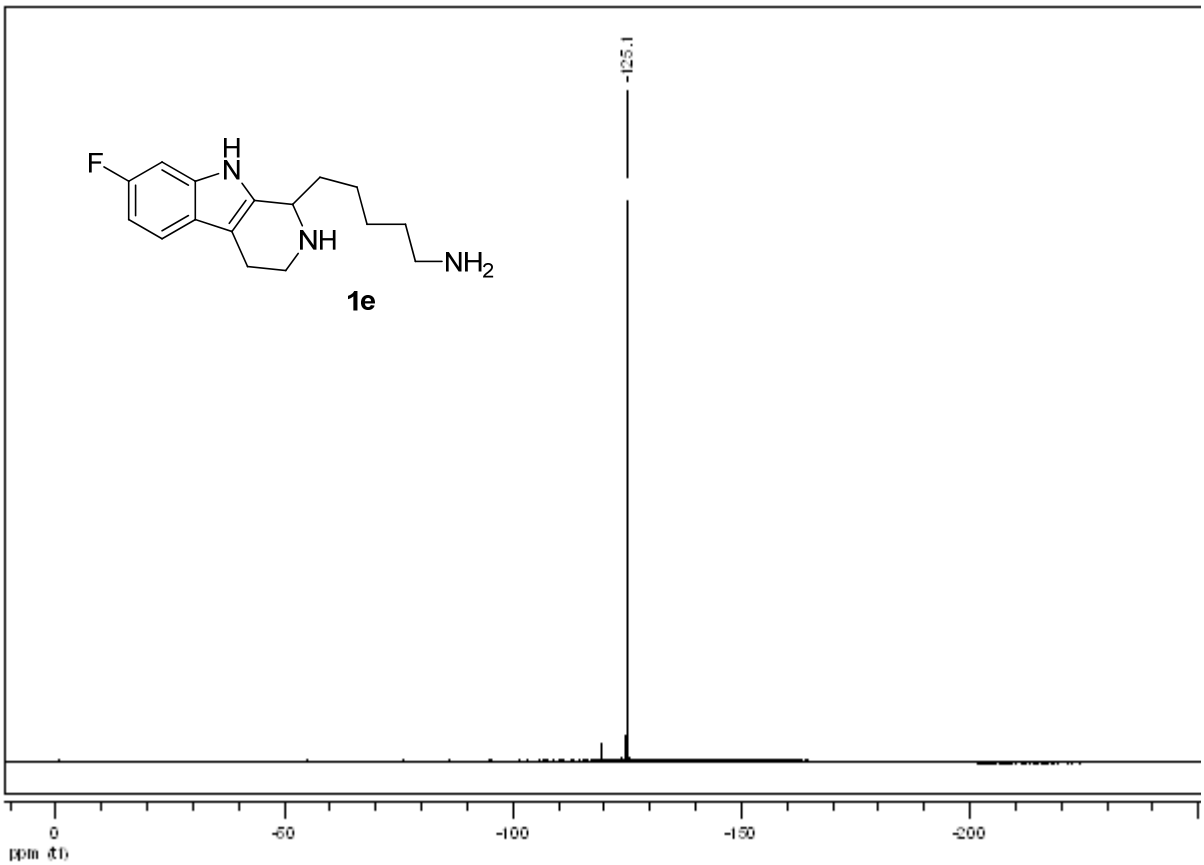

F
H
N
NH
NH2
1d
ppm (t1)

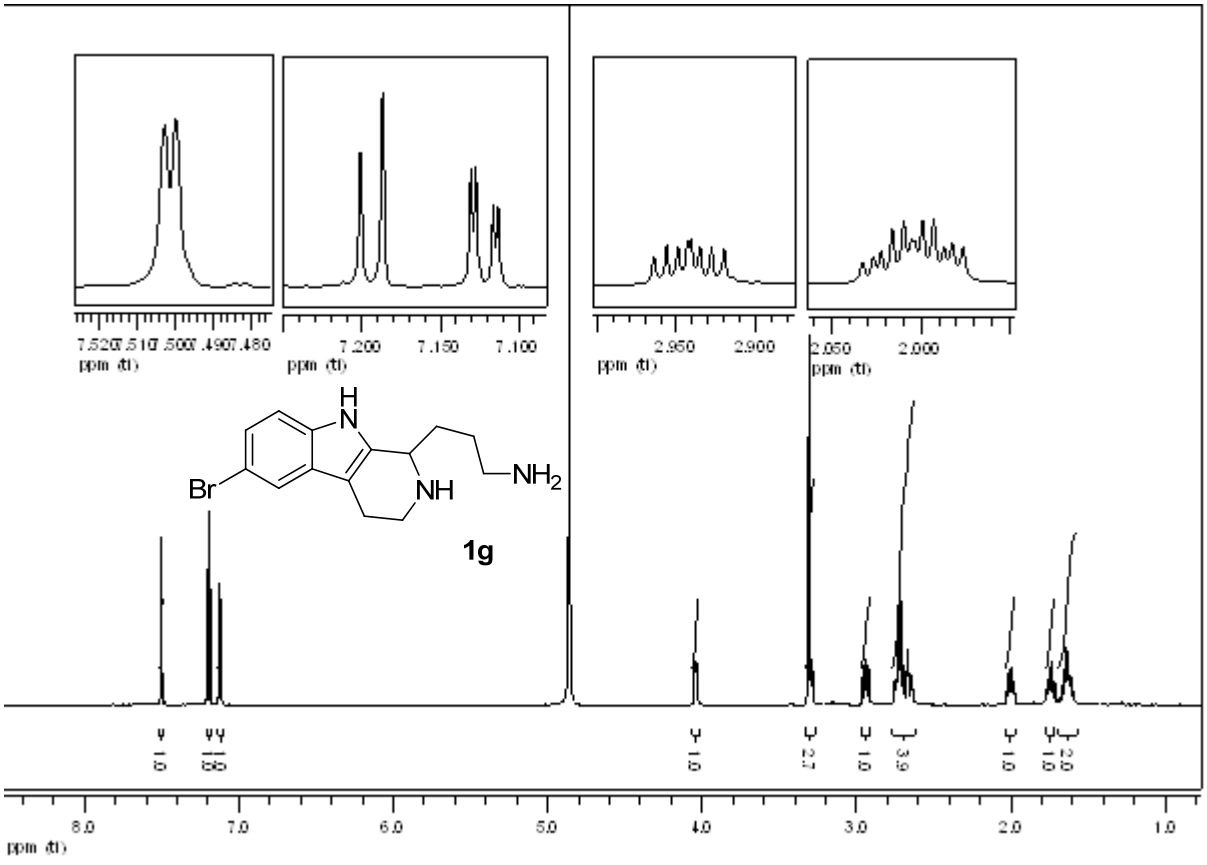


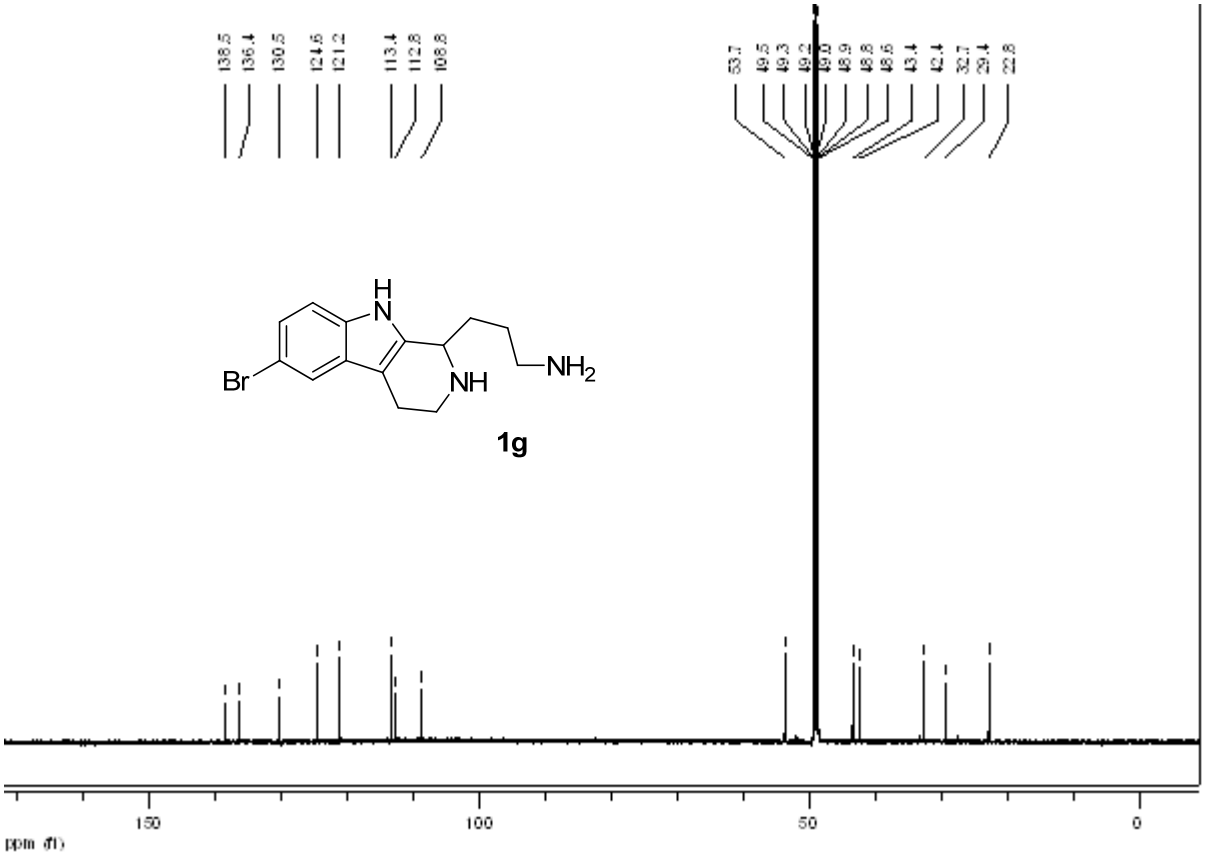
1d


F
H
N
NH
NH2
1e
7.350
7.300
7.000
6.950
6.750
ppm (t)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t)

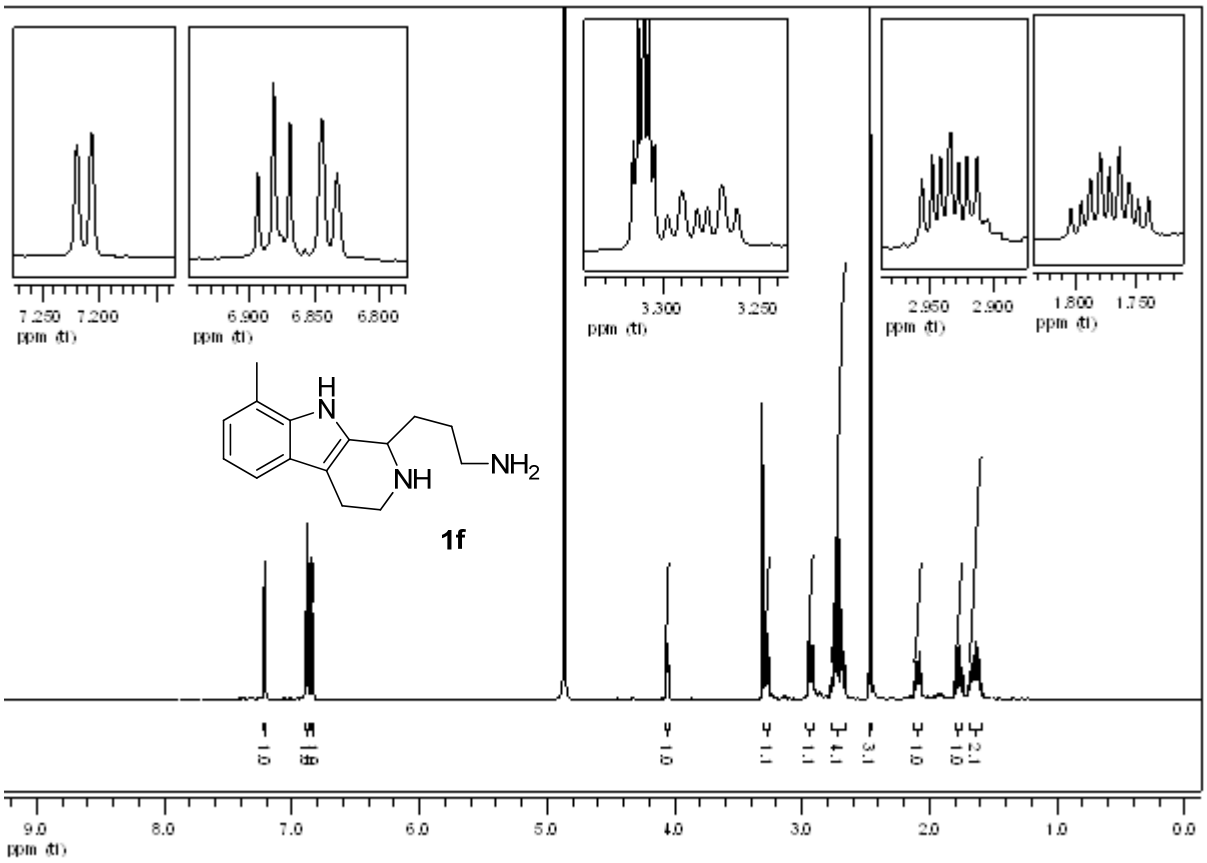

161.7
160.1
137.7
137.6
137.5
137.5
125.4
119.2
119.1
108.8
107.8
107.7
98.0
97.9
53.9
49.5
49.3
49.2
48.9
48.8
48.6
43.6
42.2
35.4
32.9
29.1
26.5
22.9
165.0
160.0
ppm (t)
119.00
108.00
98.00
ppm (t)
F
H
N
NH
NH2
1e
200
150
100
50
0
ppm (t)


-125.1
F
H
N
NH
NH2
1e
0
-50
-100
-150
-200
ppm (t1)


7.200
7.150
7.100
ppm (t1)
2.950
2.900
2.050
2.000
ppm (t1)
H
N
Br
NH
NH2
1g
1.0
1.68
1.0
2.27
1.16
3.39
1.16
1.16
2.20
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


138.5
136.4
130.5
124.6
121.2
113.4
112.8
108.8
53.7
49.5
49.3
49.2
49.0
48.9
48.8
48.6
43.4
42.4
32.7
29.4
22.8
H
N
Br
NH
NH2
150
100
50
0
ppm (f1)

1g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ppm (t1)
6.900 6.850 6.800
ppm (t1)
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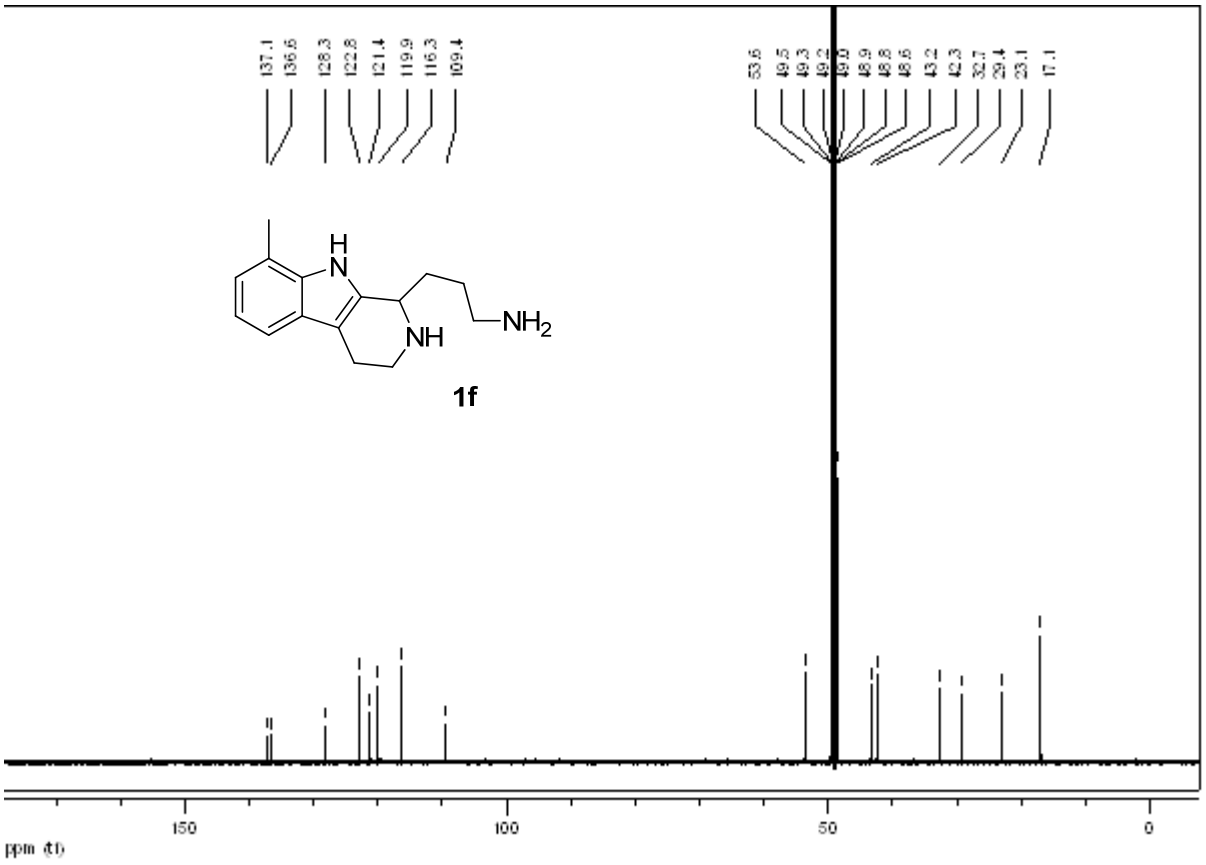
ppm (t1)
2.950 2.900
ppm (t1)
1.800 1.750
ppm (t1)
H
N
NH
NH2
1f
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (t1)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136.6
128.3
122.8
121.4
119.9
116.3
109.4
53.6
49.5
49.3
49.2
49.0
48.9
48.8
48.6
43.2
42.3
32.7
29.4
23.1
17.1
H
N
NH
NH2
1f
150 100 50 0
ppm (t1)

Computational data.

Geometries of all structures (minima and saddle points) were optimized at the ωB97xd/cc-PVDZ levels using the SMD solvation model; subsequent vibrational frequency calculations were performed at the same level for all calculated structures. All transition states thus found possess exactly one negative Hessian eigenvalue, while all other stationary points were confirmed to be genuine minima on the potential energy surface (PES). Intrinsic reaction coordinate (IRC) analysis was performed to unambiguously assign located transition states for all the potential reaction pathways. Electronic energies were obtained by performing single point calculations at the ωB97xd/cc-pVTZ level (unless stated otherwise) in solvent. Enthalpies are reported as sums of ΔE, zero point vibrational energy (ZPVE) corrections, and thermal corrections at 298 K; Gibbs energies were obtained as $\Delta G = \Delta H - T\Delta S$ at 298 K. Corrections for enthalpies and entropies were obtained from frequency analysis.

The Boc group deprotection step was found to be very quick, as it completes within 5 minutes at 50 ^{o}C in either water or methanol as a solvent. Consequently, a protonated α-methoxyamine **13**, a cyclic imine **16** and a linear aminoaldehyde **17** could potentially be formed from the carbamate **11** under acidic conditions, and stay in equilibrium. All of these intermediates might lead, through three different reaction pathways, to the final product **1** (Scheme 1).

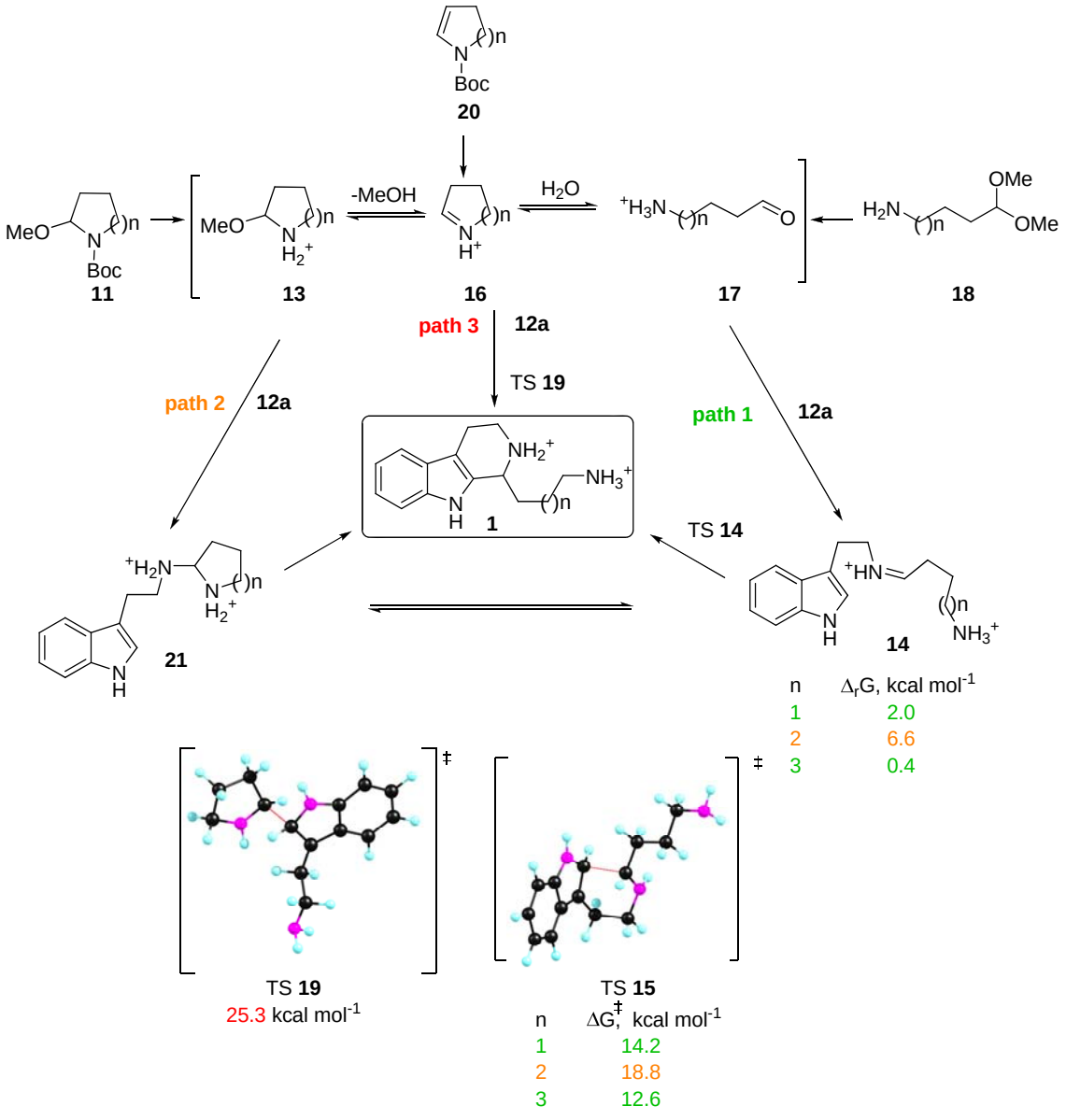
The formation of the iminium **14** (Path 1; Scheme 1) was considered and, to check that, the acetal **18**, which is the closest analogue of **17**, was reacted with the tryptamine **12a** under the optimised conditions (Entry 6, Table 3). The compounds **18** and **11a** exhibited very similar reactivity (93% conversion; compare with 90% for **11a**, Entry 6, Table 3), what is consistent with the iminium **14** as a plausible reactive intermediate. Moreover, the 6-*endo*-*trig* cyclization step towards **1** was characterized as a feasible elementary reaction with a single transition state **TS 15,** which is relatively low in energy ($\Delta G^{\neq}$ = 14.2 – 18.8 kcal mol^{-1} for **TS 15a** – **c**, Scheme 1).

Alternatively, the C-C bond formation between the iminium **16** and tryptamine **12a** could happen first in an intermolecular reaction (Path 2; Scheme 1). Although the corresponding transition state **TS19** was located, its energy was found to be significantly higher than of **TS15** (25.3 *vs* 14.2 kcal mol^{-1}). Also, the *N*-Boc protected enamine **20**, a close analogue of **16**, appeared to be less reactive than *N*-Boc-2-methoxypyrrolidine **11a.** In particular, a lower conversion into the product **1a** (76% *vs* 90%) was observed when the enamine **20a** was used instead of **11a** under the same reaction conditions (compare with the entry 6, Table 3).

At last, an intermediate **21** might be formed directly from α-methoxyamine **13** and tryptamine **12a**, but no evidence was found in support of its participation (Path 2; Scheme 1). In particular, no transition state could be found for the intramolecular cyclization, transforming the intermediate **21** into the product **1** in a single elementary reaction. On the other hand, cyclic **21** and linear **14** intermediates can be in equilibrium producing the product **1** through the transition state **TS15** (Scheme 1).

Based on this information, we can propose that the reaction pathway 1 is the most likely to be operational.

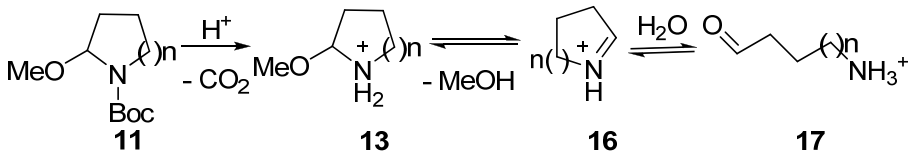
Scheme 1. Pictet-Spengler reaction of *N*-Boc protected cyclic α-methoxyamines with tryptamines.[a]



[a]Computed (at ωB97XD/PVTZ// ωB97XD/PVDZ level using SMD solvation (water as a solvent) model during geometry optimization) reaction Gibbs free energies are listed; Energy of **13** is set as a reference for every entry.

Importantly, different reactivities of the *N*-Boc protected homologues **11** could be explained and used as a confirmation of our mechanistic hypothesis. It was found that the formation of the cyclic iminium **16** and the subsequent ring opening reaction towards the linear aminoaldehyde **17** is thermodynamically disfavored for *N*-Boc-2-methoxypiperidine **11b**, with respect either to *N*-Boc-2-methoxypyrrolidine **11a** and *N*-Boc-2-methoxyazapane **11c** (compare entries 1, 2 and 3, Table 5). The higher thermodynamic stability of the **13b** towards ring opening, compared to its analogues **13a** and **13c**, translates into the higher energy of the corresponding linear intermediate **14b** (compare Gibbs free energies for n = 1 – 3, **9**; Scheme 1) as well as the transition state **TS 15b** (compare Gibbs free energies for n = 1 – 3, **TS 15**; Scheme 1). This is in agreement with the lower reactivity of **11b**, which requires longer reaction time and higher temperature to form the corresponding product **1b** (compare entry 12 with entries 6 and 13; Table 3), and, therefore, is in support to the proposed mechanism.

Table 5. Possible equilibria involving cyclic α-methoxyamines in aqueous media.[a]



11 **13** **16** **17**

n	**2**	Δ_rG (**16**), kcal mol^{-1}	Δ_rG (**17**), kcal mol^{-1}
1	**11a**	-3.5	2.9
2	**11b**	-2.7	6.4
3	**11c**	-0.7	0.0

[a]Computed (at ωB97XD/PVTZ// ωB97XD/PVDZ level using SMD solvation (water as a solvent) model during geometry optimisation) reaction Gibbs free energies are listed;[11] Energy of **13** is set as a reference for every entry.

Cartesian coordinates and electronic energies [ωB97xd/cc-pVTZ SCRF = (smd, solvent = water); Hartree] of the computed systems.

3a

0 1

C	-1.501080000	0.854187000	-0.008462000
C	-0.647924000	-0.279334000	0.008422000
C	-1.218575000	-1.565444000	0.016800000
C	-2.601092000	-1.687434000	0.007444000
C	-3.432003000	-0.545314000	-0.010613000
C	-2.897521000	0.735667000	-0.018897000
C	0.618992000	1.575749000	0.001793000
C	0.711008000	0.205857000	0.013623000
H	-0.581123000	-2.452691000	0.030508000
H	-3.058322000	-2.678764000	0.014493000
H	-4.516346000	-0.673304000	-0.018197000
H	-3.537131000	1.620270000	-0.032584000
H	1.403456000	2.328027000	0.000355000
N	-0.702180000	1.968506000	-0.012028000
H	-1.025507000	2.926384000	-0.024232000
C	1.948241000	-0.642262000	0.027736000
H	1.934353000	-1.312184000	0.905012000
H	1.942497000	-1.309230000	-0.853918000
C	3.246499000	0.151357000	0.035260000
H	3.246342000	0.852236000	-0.822170000
H	3.287458000	0.772277000	0.944916000
N	4.398756000	-0.751532000	0.045060000
H	4.423410000	-1.229505000	-0.858978000
H	5.245611000	-0.180510000	0.044938000

E(RωB97XD) = -497.812263017

5a

1 1

C	-1.646823000	0.907901000	-0.370325000
C	0.360496000	-0.298016000	0.370654000
C	-0.750721000	-1.264604000	-0.023367000
C	-2.048609000	-0.472511000	0.120709000
H	-2.298727000	1.728998000	-0.055993000
H	-1.521603000	0.930227000	-1.459613000
H	0.661008000	-0.381135000	1.424825000
H	-0.587518000	-1.543666000	-1.074905000
H	-0.716373000	-2.171179000	0.591734000
H	-2.871846000	-0.888027000	-0.472220000
H	-2.366650000	-0.421491000	1.173253000
N	-0.291656000	1.093074000	0.236343000
O	1.442597000	-0.402686000	-0.482791000
C	2.647799000	0.159249000	0.033242000
H	3.417965000	0.004276000	-0.731501000
H	2.540748000	1.240403000	0.221791000
H	2.943990000	-0.347018000	0.966210000
H	-0.379593000	1.517957000	1.165534000
H	0.306564000	1.708506000	-0.326669000

E(RωB97XD) = -327.606600387

5b

1 1

C	1.341579000	1.358091000	0.226954000

C	2.285526000	0.230923000	-0.149664000
C	1.747249000	-1.119929000	0.318049000
C	0.332966000	-1.357333000	-0.210870000
C	-0.606035000	-0.234154000	0.177745000
H	2.408491000	-1.929235000	-0.021404000
H	2.424200000	0.226020000	-1.243671000
H	3.264731000	0.441651000	0.302504000
H	1.230231000	1.451718000	1.315757000
H	1.654800000	2.325512000	-0.181320000
H	0.337215000	-1.436490000	-1.311058000
H	-0.090670000	-2.289183000	0.187709000
H	1.735556000	-1.149975000	1.420253000
N	-0.024983000	1.078034000	-0.313871000
H	-0.683300000	-0.124099000	1.271818000
O	-1.845976000	-0.420457000	-0.414252000
C	-2.933859000	0.189053000	0.277666000
H	-3.839530000	-0.054380000	-0.290479000
H	-3.022397000	-0.217193000	1.298337000
H	-2.829215000	1.285544000	0.328415000
H	0.004590000	1.040368000	-1.341480000
H	-0.656566000	1.847264000	-0.063550000

E(RωB97XD) = -366.930622985

5c

1 1

C	-0.792614000	-0.239099000	0.040314000
C	0.909933000	1.700527000	0.090587000

C	0.073689000	-1.299593000	-0.621637000
C	2.129835000	0.833022000	-0.172831000
C	1.384197000	-1.636912000	0.097862000
C	2.175427000	-0.449039000	0.662865000
H	0.762375000	1.854430000	1.168091000
H	2.217786000	0.617446000	-1.250827000
H	0.266602000	-0.987014000	-1.660677000
H	2.011029000	-2.189321000	-0.618886000
H	1.013705000	2.681846000	-0.387655000
H	-0.546814000	-2.203712000	-0.682554000
H	2.992139000	1.464724000	0.088070000
H	1.171898000	-2.336172000	0.921497000
H	3.222941000	-0.761066000	0.787120000
H	1.811197000	-0.207278000	1.675750000
N	-0.372762000	1.140998000	-0.434676000
H	-1.121742000	1.800522000	-0.192027000
H	-0.691884000	-0.223756000	1.138142000
O	-2.116072000	-0.417838000	-0.351056000
C	-3.079554000	0.099405000	0.562342000
H	-4.064218000	-0.102041000	0.124517000
H	-2.997970000	-0.403545000	1.539469000
H	-2.973846000	1.188102000	0.706265000
H	-0.340758000	1.112684000	-1.462130000

E(RωB97XD) = -406.236503126

6a

1 1

C	-0.017719000	1.218553000	0.038912000
C	0.841981000	-0.922089000	-0.094425000
C	-0.672163000	-1.054313000	0.118753000
C	-1.222987000	0.370634000	-0.087098000
H	0.017883000	2.307088000	0.098752000
H	1.173490000	-1.216167000	-1.099326000
H	1.449980000	-1.452182000	0.646480000
H	-1.114282000	-1.776679000	-0.575755000
H	-0.878062000	-1.387537000	1.144180000
H	-1.635232000	0.541983000	-1.096672000
H	-1.995649000	0.676621000	0.630397000
N	1.059724000	0.526369000	0.043989000
H	1.989130000	0.945589000	0.087172000

E(RωB97XD) = -211.848815417

6b

1 1

C	1.378937000	-0.452688000	-0.146830000
C	0.255600000	-1.350526000	0.339222000
C	-1.071104000	-0.932790000	-0.290026000
C	-1.388825000	0.514911000	0.074344000
C	-0.205463000	1.396938000	0.064694000
H	0.506906000	-2.388601000	0.083903000
H	1.626297000	-0.639970000	-1.201701000
H	2.294962000	-0.576754000	0.441882000
H	-1.003807000	-1.028006000	-1.385341000
H	-1.886884000	-1.585388000	0.046651000

H	-2.139494000	0.971409000	-0.589240000
H	-1.809253000	0.608340000	1.093042000
H	-0.328810000	2.478211000	0.162569000
H	0.186167000	-1.285398000	1.437243000
N	0.997741000	0.963340000	-0.041512000
H	1.754863000	1.647711000	-0.046850000

E(RωB97XD) = -251.171581921

6c

1 1

C	-0.216876000	1.551499000	-0.138802000
C	-1.593921000	-0.527537000	0.106646000
C	1.032926000	1.088570000	0.513897000
C	-0.403083000	-1.408441000	0.465010000
C	1.713280000	-0.111863000	-0.171426000
C	0.765089000	-1.271311000	-0.513384000
H	-2.113151000	-0.940399000	-0.769093000
H	-0.074021000	-1.223192000	1.498274000
H	0.773127000	0.832500000	1.553638000
H	2.494124000	-0.455131000	0.522990000
H	-0.276557000	2.567980000	-0.536898000
H	-2.327208000	-0.479075000	0.923882000
H	1.724618000	1.937904000	0.554784000
H	-0.793461000	-2.436219000	0.447936000
H	2.225398000	0.232344000	-1.081585000
H	1.345891000	-2.204634000	-0.532422000
H	0.361654000	-1.142633000	-1.531786000

N	-1.292969000	0.863503000	-0.270889000
H	-2.074123000	1.340541000	-0.725142000

E(RωB97XD) = -290.475711185

7a

1 1

C	1.656614000	0.530514000	0.034450000
H	1.759198000	1.073801000	0.981618000
H	1.661140000	1.255041000	-0.788795000
C	0.408750000	-0.330732000	0.017647000
H	0.370838000	-0.904113000	-0.922728000
H	0.453161000	-1.055947000	0.846714000
C	-0.844650000	0.534401000	0.150133000
H	-0.946591000	1.244565000	-0.683209000
H	-0.788455000	1.115472000	1.089322000
N	2.876873000	-0.307687000	-0.119303000
H	3.729868000	0.260912000	-0.079053000
H	2.938002000	-1.015608000	0.621803000
C	-2.093090000	-0.288710000	0.253949000
O	-3.114262000	-0.068841000	-0.365725000
H	-2.043005000	-1.137698000	0.976285000
H	2.876080000	-0.804726000	-1.018104000

E(RωB97XD) = -288.304014009

7b

1 1

C	1.065084000	-0.368741000	0.054777000

H	1.075237000	-1.124323000	-0.748289000
H	1.156674000	-0.908612000	1.012260000
C	-0.250198000	0.402702000	0.023881000
H	-0.261382000	1.143380000	0.840883000
H	-0.326126000	0.967547000	-0.920011000
C	-1.457099000	-0.527682000	0.160389000
H	-1.369032000	-1.096211000	1.104928000
H	-1.517035000	-1.249672000	-0.667334000
C	-2.747766000	0.225767000	0.253886000
O	-3.745569000	-0.026959000	-0.392618000
H	-2.754058000	1.062435000	0.992759000
C	2.254799000	0.557086000	-0.113772000
H	2.294213000	1.316327000	0.676882000
H	2.244413000	1.062416000	-1.087079000
N	3.528365000	-0.210371000	-0.039449000
H	4.344232000	0.396481000	-0.172781000
H	3.627471000	-0.675790000	0.870330000
H	3.562475000	-0.940504000	-0.760424000

E(RωB97XD) = -327.620672864

7c

1 1

C	-0.409425000	0.504211000	0.039322000
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H	-0.451924000	1.177005000	0.913344000
C	0.869707000	-0.324560000	0.105871000
H	0.864284000	-0.934450000	1.025642000

H	0.900305000	-1.030528000	-0.741107000
C	2.124956000	0.551669000	0.081809000
H	2.080411000	1.270796000	0.920513000
H	2.207185000	1.122077000	-0.855438000
C	3.374971000	-0.247423000	0.279393000
O	4.348715000	-0.203809000	-0.447315000
H	3.372691000	-0.917215000	1.172612000
C	-1.666754000	-0.359136000	-0.003468000
H	-1.684192000	-1.043866000	0.861231000
H	-1.659553000	-0.983215000	-0.913255000
C	-2.920208000	0.494162000	0.010005000
H	-2.941861000	1.199521000	-0.829864000
H	-3.014661000	1.060449000	0.944617000
N	-4.140883000	-0.351163000	-0.105549000
H	-4.996444000	0.212381000	-0.054654000
H	-4.155806000	-0.861230000	-0.996725000
H	-4.181112000	-1.049071000	0.646251000

E(RωB97XD) = -366.936577944

9a

1 1

C	-3.994105000	0.308987000	-0.317692000
C	-2.808678000	-0.346803000	0.099902000
C	-2.864478000	-1.707476000	0.453808000
C	-4.082483000	-2.368135000	0.382426000
C	-5.251886000	-1.696539000	-0.037779000
C	-5.226068000	-0.354974000	-0.392115000

C	-2.321451000	1.797173000	-0.377035000
C	-1.746256000	0.626981000	0.053012000
H	-1.963021000	-2.232231000	0.777909000
H	-4.143032000	-3.424237000	0.652439000
H	-6.195355000	-2.243919000	-0.084173000
H	-6.128198000	0.166463000	-0.716541000
H	-1.876257000	2.774059000	-0.548816000
N	-3.667084000	1.611040000	-0.599723000
H	-4.307749000	2.322289000	-0.926150000
C	-0.313336000	0.362986000	0.403348000
H	-0.248291000	-0.050991000	1.423756000
H	0.106922000	-0.403647000	-0.269142000
C	0.552122000	1.612915000	0.316346000
H	0.589457000	2.010978000	-0.705280000
H	0.181626000	2.398157000	0.988269000
N	1.922954000	1.309911000	0.724626000
H	2.064251000	1.094128000	1.715622000
C	2.930171000	1.224325000	-0.062468000
H	2.746877000	1.434044000	-1.121895000
C	4.284315000	0.841533000	0.379636000
H	4.312352000	0.711225000	1.471118000
H	4.952281000	1.677111000	0.109336000
C	4.741221000	-0.431184000	-0.348816000
H	4.059487000	-1.261103000	-0.104780000
H	4.681751000	-0.269701000	-1.438488000
C	6.164041000	-0.815334000	0.029665000
H	6.217741000	-0.977669000	1.117972000

H	6.834269000	0.037372000	-0.195167000
N	6.547309000	-2.057077000	-0.641927000
H	6.604850000	-1.860845000	-1.644126000
H	7.509002000	-2.275323000	-0.376133000

E(RωB97XD) = -709.672020000

9b

1 1

C	-4.555631000	0.200561000	-0.350867000
C	-3.355852000	-0.413830000	0.088682000
C	-3.376765000	-1.768767000	0.467151000
C	-4.575348000	-2.464474000	0.398743000
C	-5.759618000	-1.833404000	-0.042086000
C	-5.768051000	-0.498600000	-0.421771000
C	-2.925470000	1.734444000	-0.421111000
C	-2.321208000	0.588835000	0.034643000
H	-2.464139000	-2.261892000	0.809060000
H	-4.608584000	-3.516397000	0.689112000
H	-6.687608000	-2.407084000	-0.083997000
H	-6.681440000	-0.008218000	-0.762652000
H	-2.506151000	2.720643000	-0.604620000
N	-4.262789000	1.506226000	-0.653264000
H	-4.920066000	2.193796000	-0.996732000
C	-0.885477000	0.377747000	0.410408000
H	-0.822261000	-0.000361000	1.444814000
H	-0.433084000	-0.396927000	-0.230950000
C	-0.062573000	1.652896000	0.292875000

H	-0.017616000	2.013066000	-0.742387000
H	-0.479612000	2.448692000	0.924025000
N	1.310405000	1.426752000	0.742648000
H	1.436670000	1.231685000	1.739992000
C	2.345704000	1.410511000	-0.012004000
H	2.180110000	1.601302000	-1.077987000
C	3.712915000	1.150300000	0.475960000
H	3.712290000	0.996978000	1.564659000
H	4.293083000	2.063257000	0.253772000
C	4.345807000	-0.039227000	-0.260473000
H	3.773019000	-0.951863000	-0.026830000
H	4.264019000	0.121079000	-1.348258000
C	5.808638000	-0.225663000	0.126445000
H	5.896591000	-0.357078000	1.218197000
H	6.368437000	0.692500000	-0.127319000
C	6.453706000	-1.412596000	-0.573506000
H	5.931967000	-2.336906000	-0.276055000
H	6.303062000	-1.307964000	-1.666368000
N	7.861672000	-1.536691000	-0.190161000
H	8.255263000	-2.334064000	-0.692633000
H	8.356357000	-0.730652000	-0.579940000

E(RωB97XD) = -748.987693458

9c

1 1

C	-5.070972000	0.030867000	0.371523000
C	-3.839188000	-0.502166000	-0.085848000

C	-3.785532000	-1.842740000	-0.509071000
C	-4.944471000	-2.604720000	-0.467676000
C	-6.162054000	-2.054043000	-0.010056000
C	-6.243599000	-0.735400000	0.414633000
C	-3.527752000	1.649170000	0.492174000
C	-2.861638000	0.553973000	0.000626000
H	-2.847221000	-2.273631000	-0.865499000
H	-4.919837000	-3.646262000	-0.794159000
H	-7.057507000	-2.678621000	0.009573000
H	-7.182495000	-0.306645000	0.769255000
H	-3.163577000	2.650683000	0.707133000
N	-4.850149000	1.340307000	0.716078000
H	-5.544064000	1.981191000	1.077189000
C	-1.417713000	0.437176000	-0.384643000
H	-0.919928000	-0.329811000	0.231557000
H	-1.338430000	0.094233000	-1.430196000
C	-0.669029000	1.753886000	-0.233464000
H	-1.138962000	2.543172000	-0.835585000
H	-0.632698000	2.084548000	0.811796000
N	0.708908000	1.621944000	-0.703521000
H	0.831708000	1.412003000	-1.698435000
C	1.758010000	1.717658000	0.026174000
H	1.601667000	1.925562000	1.090136000
C	3.127909000	1.554532000	-0.495487000
H	3.640031000	2.517698000	-0.326052000
H	3.104361000	1.362165000	-1.577796000
C	3.879856000	0.443290000	0.252078000

H	3.888131000	0.667982000	1.331389000
H	3.337171000	-0.507914000	0.126094000
C	5.308972000	0.293295000	-0.260513000
H	5.839609000	1.254062000	-0.140381000
H	5.283838000	0.085041000	-1.344434000
C	6.081139000	-0.811419000	0.453302000
H	6.131685000	-0.598102000	1.535025000
H	5.535490000	-1.766744000	0.346658000
C	7.493231000	-0.987739000	-0.085423000
H	8.049501000	-0.044263000	0.041349000
H	7.437190000	-1.170393000	-1.177178000
N	8.204119000	-2.041273000	0.642474000
H	7.733987000	-2.926592000	0.438194000
H	9.127200000	-2.149938000	0.219177000

E(RωB97XD) = -788.303397416

10a

1 1

C	1.831834000	-1.095191000	-0.593020000
C	2.240104000	0.180336000	-0.119260000
C	3.334001000	0.285683000	0.769757000
C	3.984862000	-0.868667000	1.147702000
C	3.565405000	-2.135100000	0.660115000
C	2.495627000	-2.273156000	-0.201687000
C	0.372064000	0.409533000	-1.397069000
C	1.352532000	1.137992000	-0.679148000
H	3.650771000	1.262540000	1.138955000

H	4.834505000	-0.818777000	1.830032000
H	4.106550000	-3.027390000	0.980624000
H	2.174149000	-3.248100000	-0.568925000
H	-0.237497000	0.790664000	-2.214408000
N	0.757094000	-0.928572000	-1.410246000
H	0.231772000	-1.675805000	-1.847792000
C	1.193318000	2.553479000	-0.312631000
H	2.114729000	2.972461000	0.112026000
H	0.874626000	3.164040000	-1.167508000
C	0.073434000	2.622221000	0.785141000
H	0.440655000	2.133105000	1.697632000
H	-0.165090000	3.667288000	1.008981000
N	-1.100893000	1.943412000	0.317003000
H	-1.690609000	2.480590000	-0.317563000
C	-1.006571000	0.626755000	0.024828000
H	-0.471264000	0.034469000	0.777216000
C	-2.218742000	-0.030687000	-0.579019000
H	-1.915226000	-0.972031000	-1.058171000
H	-2.636287000	0.623395000	-1.361367000
C	-3.271969000	-0.332426000	0.490757000
H	-2.825539000	-0.949215000	1.288040000
H	-3.604056000	0.608986000	0.959822000
C	-4.475360000	-1.057749000	-0.093857000
H	-4.140872000	-2.008153000	-0.540683000
H	-4.888365000	-0.450912000	-0.923710000
N	-5.454252000	-1.360681000	0.950926000
H	-5.843207000	-0.472294000	1.276172000

H -6.246621000 -1.832105000 0.511190000

E(RωB97XD) = -709.657326297

11

1 1

C -1.796358000 -0.948694000 0.551828000

C -1.596929000 0.292917000 -0.119918000

C -2.673122000 0.897962000 -0.820446000

C -3.885674000 0.253068000 -0.835962000

C -4.060837000 -0.995344000 -0.169511000

C -3.041737000 -1.612001000 0.520975000

C 0.374660000 -0.405430000 0.783210000

C -0.254891000 0.665975000 0.087056000

H -2.529806000 1.852156000 -1.329927000

H -4.732989000 0.691379000 -1.364665000

H -5.040115000 -1.475970000 -0.209901000

H -3.182714000 -2.566092000 1.029122000

H 1.203517000 -0.249451000 1.474508000

N -0.645140000 -1.296161000 1.167715000

H -0.482737000 -2.193064000 1.610911000

C 0.426001000 1.911201000 -0.342683000

H 1.396966000 1.657558000 -0.800646000

H -0.181125000 2.429333000 -1.100463000

C 0.699439000 2.858166000 0.830408000

H -0.259620000 3.088618000 1.331589000

H 1.329030000 2.340039000 1.570242000

N 1.415819000 4.039527000 0.354824000

H	0.774654000	4.573098000	-0.237292000
H	1.578674000	4.649766000	1.157494000
C	1.289148000	-1.333973000	-0.599756000
C	2.114242000	-2.359117000	0.161370000
H	0.392815000	-1.654684000	-1.140773000
C	3.549741000	-0.650621000	-0.776982000
C	3.429020000	-1.611037000	0.414746000
H	2.263005000	-3.211125000	-0.521077000
H	1.638171000	-2.737318000	1.073228000
H	4.230910000	-1.033406000	-1.552582000
H	3.899205000	0.349233000	-0.481803000
H	4.288292000	-2.288135000	0.490715000
H	3.363518000	-1.043517000	1.354594000
N	2.187217000	-0.603729000	-1.301307000
H	1.908863000	0.065694000	-2.007903000

E(RωB97XD) = -709.643395375

MeOH

0 1

C	0.661029000	-0.018602000	0.000000000
H	1.095747000	0.991571000	-0.000002000
H	1.028042000	-0.550857000	-0.895945000
H	1.028042000	-0.550853000	0.895947000
O	-0.749471000	0.123646000	0.000000000
H	-1.122238000	-0.767418000	0.000000000

E(RωB97XD) = -115.737567398

H_2O

0 1

O	0.000000000	0.000000000	0.121312000
H	0.000000000	0.751928000	-0.485246000
H	0.000000000	-0.751928000	-0.485246000

E(RωB97XD) = -76.4464702684

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