Electronic Supplementary Material (ESI) for ChemComm.

C-F bond substitution via aziridinium ion intermediates

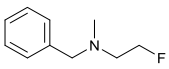
Annika Maria Träff, Mario Janjetovic, and Göran Hilmersson

General methods

Dichloromethane (CH_2Cl_2) was distilled from CaH_2 and stored over molecular sieves (3 Å). $La[N(SiMe_3)_2]_3$ ≥98% (99.9%-La) was purchased from Strem Chemicals Inc. and stored in a glove box. All other solvents and reagents were used as purchased without further purifications. Silica column chromatography was performed with chromatographic silica media for separation and purification applications (35-70 micron). ^{1}H NMR and ^{13}C NMR were recorded with Varian 400, Varian 500 or Bruker 800. ^{19}F NMR was recorded with Varian 500. The chemical shifts are reported in ppm relative to the residual peak from the solvent $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.16) or CD_2Cl_2 (^{1}H NMR δ 5.32). For ^{19}F NMR, the peaks are reported in ppm, using hexafluorobenzene in $CDCl_3$ as internal reference (^{19}F NMR δ −162.2).[1] The conversion of the substitution reactions were measured by GC-FID with *n*-dodecane as internal standard, standardized by calibrating against authentic samples of pure starting material, or analyzed by ^{1}H and ^{19}F NMR. GC-FID was performed on a GC Varian 3900 with an auto sampler equipped with an EQUITYTM-5 column (30 m * 0.25 mm * 0.25 µm), and with hydrogen as carrier gas. GC-FID method: 80 °C, 2 min; 20 °C·min^{-1} to 300 °C, 2 min; injector temperature 300 °C, Rt (*n*-dodecane) = 5.6 min.

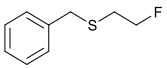
Synthetic procedures

Synthesis of *N*-benzyl-*N*-methyl-2-fluoroethylamine (1a)



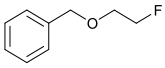
To K_2CO_3 (2.8 g, 20 mmol) was added MeCN (22 mL), BnMeNH (1.0 mL, 8 mmol), and 1-bromo-2-fluoroethane (0.88 mL, 12 mmol). The reaction was heated to 60 °C and stirred overnight (~18-20 h). The reaction was quenched by adding ~100 mL of H_2O. The crude was extracted with Et_2O 3x100 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by silica gel flash chromatography, gradient eluent 20:1 to 5:2 pentane:Et_2O. The product was collected as a clear colorless oil (1.06 g, 6.4 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 4.56 (dt, *J* = 47.6, 5.1 Hz, 2H), 3.59 (s, 2H), 2.73 (dt, *J* = 26.9, 5.1 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.81, 129.15, 128.42, 127.24, 82.64 (d, *J* = 167.3 Hz), 62.76 (d, *J* = 0.9 Hz), 56.84 (d, *J* = 20.2 Hz), 42.90 (d, *J* = 1.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -218.82. HRMS calculated for $C_{10}H_{14}FN$ $(M+H)^+$: 168.1182, found: 168.1181.

Synthesis of Benzyl(2-fluoroethyl)sulfane (3)



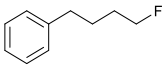
To a solution of benzyl mercaptan (0.35 mL, 3.0 mmol), K_2CO_3 (0.55 g, 4.0 mmol), and DMF (7 mL) was added 1-bromo-2-fluoroethane (0.33 mL, 4.5 mmol). The reaction mixture was allowed to stir at room temperature for 17 h. The content was portioned between H_2O and Et_2O. The water phase was extracted one more time with Et_2O. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel flash chromatography using 2% Et_2O in pentane as eluent, yielding a colorless oil (0.40 g, 2.4 mmol, 80%). NMR was in agreement with that previously reported.[2]

Synthesis of 2-fluoroethyl benzyl ether (5a)



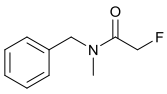
To a solution of benzyl alcohol (0.31 mL, 3.0 mmol) in dry DMF (1 mL) was added NaH (60% dispersion in mineral oil, 0.13 g, 3.3 mmol) at 0 °C. 1-bromo-2-fluoroethane (0.26 mL, 3.5 mmol) was then added drop-wise at 0 °C. The reaction mixture was then stirred for 1 h and allowed to reach room temperature where it stirred for 3 h. The content was quenched by adding water and extracted twice with Et_2O. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel flash chromatography using 3% EtOAc in pentane as eluent, yielding a colorless oil (0.40 g, 2.37 mmol, 79%). NMR was in agreement with that previously reported.[3]

Synthesis of (4-fluorobutyl)benzene (7)



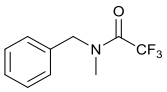
To phenylbutanol (0.15 mL, 1.0 mmol), and TEA*3HF (0.16 mL, 1.0 mmol) in dry CH_2Cl_2 (3 mL) was added Xtalfluor-E (0.34 g, 1.5 mmol) at -78 ˚C. The reaction mixture was stirred at -78 ˚C for 30 min. and was then allowed to reach room temperature and stirred for 18 h. The content was quenched by adding sat. NaHCO3, and was stirred for 30 min. and then extracted with CH_2Cl_2 (3x25 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel flash chromatography using pentane/ CH_2Cl_2 (9:1) as eluent, yielding a colorless oil (0.063 g, 0.41 mmol, 41%). NMR was in agreement with that previously reported.[4]

Synthesis of *N*-benzyl-2-fluoro-*N*-methylacetamide (9)



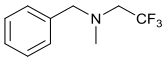
N-benzyl-2-fluoro-N-methylacetamide was synthesized following a literature procedure for amidation of esters.[5] To $La(OTf)_3$ (0.088 g, 0.15 mmol) was added ethyl fluoroacetate (0.29 mL, 3 mmol) and BnMeNH (0.46 mL, 3.6 mmol). The reaction mixture was stirred at 50 °C and followed until completion by GC. The mixture was diluted by CH_2Cl_2 and applied on silica gel flash chromatography using pentane/EtOAc (3:1) as eluent, yielding a colorless oil (0.26 g, 1.43 mmol, 48%), which consist as mixtures of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 5H), 5.03 (d, *J* = 47.1 Hz, 2H), 4.61 (s, 1H), 4.47 (s, 1H), 2.96 (s, 1H), 2.87 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.18 (d, *J* = 18.0 Hz), 166.92 (d, *J* = 18.5 Hz), 136.46, 135.74, 129.14, 128.81, 128.32, 128.06, 127.78, 126.69, 80.01(d, *J* = 179.7 Hz), 79.75 (d, *J* = 179.2 Hz), 52.28 (d, *J* = 4.6 Hz), 51.14, 33.94, 33.31 (d, *J* = 4.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -219.77, -220.96. HRMS calculated for $C_{10}H_{12}FNO$ $(M+H)^+$: 182.0975, found: 182.0976.

Synthesis of *N*-benzyl-2,2,2-trifluoro-*N*-methylacetamide



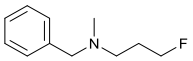
N-benzyl-2,2,2,-trifluoro-N-methylacetamide was prepared according to literature procedure and NMR was in agreement with that previously reported.[6]

Synthesis of *N*-benzyl-2,2,2-trifluoro-*N*-methylethan-1-amine (1k)



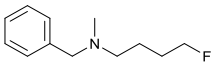
N-benzyl-2,2,2-trifluoro-*N*-methylacetamide (0.70 g, 3.2 mmol) was dissolved in dry THF. The content was cooled to 0 °C and borane dimethyl sulfide complex (3.5 mL, 7.1 mmol, 2.0 M in THF) was added dropwise. The reaction mixture was allowed to reach room temperature and was then refluxed for 2 h. After cooling to room temperature the mixture was cooled to 0 °C and carefully quenched by adding methanol followed by water. The crude was extracted with Et_2O (3x30 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel flash chromatography using pentane/EtOAc (95:5) as eluent, yielding a colorless oil (0.54 g, 2.66 mmol, 83%). NMR was in agreement with that previously reported.[7]

Synthesis of *N*-benzyl-3-fluoro-*N*-methylpropan-1-amine (1b)



To K_2CO_3 (1.0 g, 7.5 mmol) was added MeCN (8.2 mL), BnMeNH (0.39 mL, 3 mmol), and 1-bromo-3-fluoropropane (0.29 mL, 3.1 mmol). The reaction was heated to 60 °C and stirred overnight (~18-20 h). The reaction was quenched by adding ~35 mL of H_2O. The crude was extracted with Et_2O 3x35 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography using pentane:Et_2O (4:1) as eluent. The product was collected as a clear colorless oil (0.46 g, 2.54 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 5H), 4.52 (dt, *J* = 47.3, 6.1 Hz, 2H), 3.50 (s, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 2.20 (s, 3H), 1.99 – 1.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.22, 129.05, 128.36, 127.10, 82.83 (d, *J* = 163.8 Hz), 62.56, 53.34 (d, *J* = 5.7 Hz), 42.27, 28.64 (d, *J* = 19.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -215.51. HRMS calculated for $C_{11}H_{16}FN$ $(M+H)^+$: 182.1339, found: 182.1338.

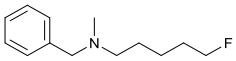
Synthesis of *N*-benzyl-4-fluoro-*N*-methylbutan-1-amine (1c)



To K_2CO_3 (2.8 g, 20 mmol) was added MeCN (22 mL), BnMeNH (1.0 mL, 8 mmol), and 1-bromo-4-fluorobutane (1.3 mL, 12 mmol). The reaction was heated to 60 °C and stirred overnight (~18-20 h). The reaction was quenched by adding ~100 mL of H_2O. The crude was extracted with Et_2O 3x100 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography, gradient eluent 4:1 to 1:1 pentane:Et_2O. The product was collected as a clear colorless oil (0.646 g, 3.3 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 4.47 (dt, *J* = 47.3, 6.0 Hz, 2H), 3.51 (s, 2H), 2.46 – 2.40 (m, 2H),

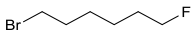
2.22 (s, 3H), 1.84 – 1.60 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 129.1, 128.3, 127.0, 84.2 (d, *J* = 164.3 Hz), 62.5, 56.9, 42.3, 28.4 (d, *J* = 19.7 Hz), 23.2 (d, *J* = 5.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -213.69. HRMS calculated for $C_{12}H_{18}FN$ $(M+H)^+$: 196.1495, found: 196.1495.

Synthesis of *N*-benzyl-5-fluoro-*N*-methylpentan-1-amine (1d)



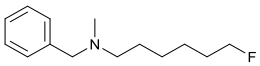
To K_2CO_3 (2.8 g, 20 mmol) was added MeCN (22 mL), N-benzylmethylamine (1.0 mL, 8 mmol), and 1-bromo-5-fluoropentane (1.5 mL, 12 mmol). The reaction was heated to 60 °C and stirred for ~48 h. The reaction was quenched by adding 100 mL of H_2O. The crude was extracted with Et_2O 3x75 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography, gradient eluent 16:1 to 1:1 pentane:Et_2O. The product was collected as a clear colorless oil (1.27 g, 6.1 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 5H), 4.46 (dt, *J* = 47.4, 6.1 Hz, 2H), 3.50 (s, 2H), 2.40 (dd, *J* = 8.0, 6.6 Hz, 2H), 2.21 (s, 3H), 1.81 – 1.41 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 129.1, 128.3, 127.0, 84.2 (d, *J* = 164.3 Hz), 62.5, 57.4, 42.4, 30.4 (d, *J* = 19.4 Hz), 27.2, 23.2 (d, *J* = 5.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -213.80. HRMS calculated for $C_{13}H_{20}FN$ $(M+H)^+$: 210.1652, found: 210.1650.

Synthesis of 1-bromo-6-fluorohexane



To 6-bromo-1-hexanol (0.39 mL, 3.0 mmol) in dry CH_2Cl_2 (7 mL), was added Deoxo-Fluor (50% in THF, 1.5 mL, 3.6 mmol) dropwise at -78 °C. The reaction mixture was stirred for 30 min. and was then allowed to reach room temperature and was stirred for 18 h. The mixture was quenched by carefully adding sat. $NaHCO_3$. The content was stirred for 30 min. and then extracted with CH_2Cl_2 (2x30 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel chromatography using pentane/ CH_2Cl_2 (9:1) as eluent. The product was collected as a clear colorless oil (0.25 g, 1.36 mmol, 45%). NMR was in agreement with that previously reported.[8]

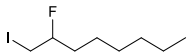
Synthesis of *N*-benzyl-6-fluoro-*N*-methylhexan-1-amine (1e)



To K_2CO_3 (0.52 g, 3.75 mmol) was added MeCN (4 mL), *N*-benzylmethylamine (0.19 mL, 1.5 mmol), and 1-bromo-6-fluorohexane (0.25 g, 1.36 mmol). The reaction was heated to 60 °C and stirred for ~18 h. The reaction was quenched by adding 20 mL of H_2O. The crude was extracted with Et_2O 3x20 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography, gradient eluent pentane:Et_2O (2:1). The product was collected as a clear colorless oil (0.24 g, 1.07 mmol, 79%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 4.43 (dt, *J* = 47.3, 6.1 Hz, 2H), 3.47 (s, 2H), 2.39 – 2.33 (m, 2H), 2.18 (s, 3H), 1.76 – 1.62 (m, 2H), 1.58 – 1.48 (m, 2H), 1.45 – 1.32 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.43, 129.16, 128.30, 126.99, 84.33 (d, *J* = 164.0 Hz), 62.53, 57.50, 42.42, 30.55 (d, *J* = 19.4 Hz), 27.47, 27.19, 25.27 (d,

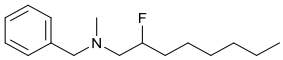
J = 5.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -213.73. HRMS calculated for $C_{14}H_{22}FN$ $(M+H)^+$: 224.1808, found: 224.1806.

Synthesis of 2-fluoro-1-iodooctane



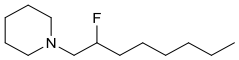
To 1-octene (0.31 mL, 2.0 mmol), and TEA*3HF (0.49 mL, 3.0 mmol) in dry CH_2Cl_2 (2 mL) was added N-iodo succinimide (0.49 g, 2.2 mmol) at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 15 min. and was then allowed to reach room temperature and stirred for 6 h. The content was quenched by adding water and neutralized with 25% aq. NH_3. The crude was extracted with CH_2Cl_2 (3x25 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel flash chromatography using pentane as eluent, yielding a colorless oil (0.33g, 1.28 mmol, 64%). NMR was in agreement with that previously reported.[9]

Synthesis of *N*-benzyl-2-fluoro-*N*-methyloctan-1-amine (1f)



To 2-fluoro-1-iodooctane (0.33 g, 1.28 mmol), and K_2CO_3 (0.42 g, 3.03 mmol) in MeCN (7.5 mL) was added *N*-benzylmethylamine (0.196 mL, 1.52 mmol). The reaction mixture was allowed to stir at 60 °C until full conversion of 2-fluoro-1-iodooctane was reached indicated by GC-FID, 72 h. The content was portioned between 30 mL H_2O and 30 mL Et_2O. The water phase was extracted with Et_2O 3 x 30 mL. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel flash chromatography, gradient eluent 24:1 to 3:1 penatne: Et_2O, yielding a colorless oil (0.193 g, 0.76 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 4.76 – 4.53 (m, 1H), 3.57 (s, 2H), 2.64 (ddd, *J* = 19.0, 13.8, 7.1 Hz, 1H), 2.51 (ddd, *J* = 28.5, 13.8, 3.3 Hz, 1H), 2.30 (s, 3H), 1.72 – 1.20 (m, 10H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 129.0, 128.2, 127.0, 93.0 (d, *J* = 169.0 Hz, F-CH-), 62.8 (d, *J* = 1.4 Hz, Ph-CH_2-N), 60.9 (d, *J* = 21.4 Hz, N-CH_2-CHF), 43.1 (d, *J* = 1.6 Hz, CH_3-N), 33.4 (d, *J* = 20.6 Hz, FCH-CH_2-CH_2-), 31.7, 29.1, 24.9 (d, *J* = 4.6 Hz, FCH-CH_2-CH_2-), 22.6, 14.0 (-CH_2-CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ -176.79. HRMS calculated for $C_{16}H_{26}FN$ $(M+H)^+$: 252.2121, found: 252.2118.

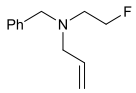
Synthesis of 1-(2-fluorooctyl)piperidine (1g)



To 2-fluoro-1-iodooctane (0.33 g, 1.28 mmol), and K_2CO_3 (0.42 g, 3.03 mmol) in MeCN (7.5 mL) was added piperidine (1.52 mmol, 0.15 mL). The reaction mixture was allowed to stir at room temperature for 18 h (or until full conversion of 2-fluoro-1-iodooctane was reached indicated by GC-FID). The content was portioned between H_2O and Et_2O. The water phase was extracted one more time with Et_2O. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel flash chromatography using pentane:Et_2O (2:1) as eluent, yielding a colorless oil (0.15g, 0.71 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 – 4.56 (m, 1H), 2.63 – 2.31 (m, 6H), 1.66 – 1.22 (m, 16H), 0.94 – 0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 92.67 (d, *J* = 168.9

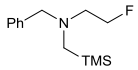
Hz), 63.65 (d, *J* = 21.0 Hz), 55.29 (d, *J* = 1.2 Hz), 33.96 (d, *J* = 20.9 Hz), 31.85, 29.26, 26.11, 25.11 (d, *J* = 4.5 Hz), 24.34, 22.71, 14.20. ^{19}F NMR (376 MHz, $CDCl_3$) δ -175.22. HRMS calculated for $C_{13}H_{26}FN$ $(M+H)^+$: 216.2121, found: 216.2118.

Synthesis of *N*-benzyl-*N*-(2-fluoroethyl)prop-2-en-1-amine (1h)



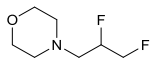
To K_2CO_3 (2.3 g, 17 mmol) was added MeCN (20 mL), *N*-benzyl-*N*-allyl-amine (1.0 g, 6.8 mmol), and 1-bromo-2-fluoroethane (0.76 mL, 10.2 mmol). The reaction was heated to 60 °C and stirred for ~72 h, or until completion of amine. The reaction was quenched by adding 100 mL of H_2O. The crude was extracted with Et_2O 3x75 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by silica gel flash chromatography, gradient eluent 20:1 to 5:2 pentane:Et_2O. The product was collected as a clear colorless oil (1.01 g, 5.2 mmol, 77%). NMR was in agreement with that previously reported.[10]

Synthesis of *N*-benzyl-2-fluoro-*N*-((trimethylsilyl)methyl)ethan-1-amine (1i)



To K_2CO_3 (2.8 g, 20 mmol) was added MeCN (22 mL), *N*-[(trimethylsilyl)methyl]benzylamine (1.8 mL, 8 mmol), and 1-bromo-2-fluoroethane (0.88 mL, 12 mmol). The reaction was heated to 60 °C and stirred for ~72 h, or until completion of amine. The reaction was quenched by adding 100 mL of H_2O. The crude was extracted with Et_2O 3x75 mL. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by silica gel flash chromatography, gradient eluent 100:0 to 94:6 pentane:Et_2O. The product was collected as a clear colorless oil (1.32 g, 5.5 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 5H, Ph), 4.48 (dtd, *J* = 47.6, 5.3, 1.2 Hz, 2H,-C$\underline{H}_2$F), 3.59 (s, 2H, Ph-C$\underline{H}_2$-N), 2.70 (dtd, *J* = 25.2, 5.3, 1.4 Hz, 2H, N-C$\underline{H}_2$-CH_2F), 2.08 (d, *J* = 1.5 Hz, 2H, N-C$\underline{H}_2$-TMS), 0.07 (d, *J* = 1.6 Hz, 9H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 (Ph), 128.8 (Ph), 128.3 (Ph), 127.0 (Ph), 82.9 (d, *J* = 167.5 Hz, -$\underline{C}H_2$F), 62.8, 56.8 (d, *J* = 20.2 Hz, N-$\underline{C}H_2$-CH_2F), 46.9, -1.3 (TMS). ^{19}F NMR (376 MHz, $CDCl_3$) δ -215.40. HRMS calculated for $C_{13}H_{22}FNSi$ $(M+H)^+$: 240.1578, found: 240.1575.

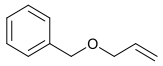
Synthesis of 4-(2,3-difluoropropyl)morpholine (1j)



To 3-morpholino-1,2-propanediol (0.7 mL, 5.0 mmol) in dry CH_2Cl_2 (5 mL), was added Deoxo-Fluor (50% in THF, 4.4 mL, 10.4 mmol) dropwise at 0 °C. The reaction mixture was stirred for 30 min. and was then allowed to reach room temperature and was stirred for 24 h. The mixture was quenched by carefully adding sat. $NaHCO_3$. The content was stirred for 30 min. and then extracted with CH_2Cl_2 (2x30 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel chromatography using Et_2O as eluent. The product was collected as a clear colorless oil (0.11 g, 0.66 mmol, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

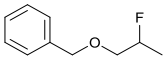
4.95 – 4.43 (m, 3H), 3.70 (td, 4H), 2.76 – 2.58 (m, 2H), 2.54 (td, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 90.11 (dd, *J* = 174.5, 19.5 Hz), 83.19 (dd, *J* = 173.0, 23.1 Hz), 67.03, 58.10 (dd, *J* = 22.2, 7.1 Hz), 54.37 (d, *J* = 1.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -186.28, -228.14. HRMS calculated for $C_7H_{13}F_2NO$ $(M+H)^+$: 166.1037, found: 166.1039.

Synthesis of ((allyloxy)methyl)benzene



((allyloxy)methyl)benzene was prepared according to literature procedure and NMR was in agreement with that previously reported.[11]

Synthesis of 2-fluorooctyl benzyl ether (5b)

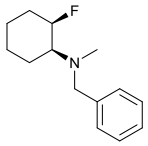


2-fluorooctyl benzyl ether was synthesized following a general literature procedure for hydrofluorination of unactivated alkenes.[12] $Fe_2(ox)_3$ (1.31 g, 2.7 mmol) was stirred in degassed water (55 mL) for 1.5 h. The content was cooled to 0 °C and selectfluor (0.96 g, 2.7 mmol) and acetonitrile (27 mL) was added. A solution of benzyl allyl ether (0.20 g, 1.35 mmol, in 27 mL acetonitrile) was added. $NaBH_4$ (0.33 g, 8.7 mmol) was added in two portions over a period of 2 min. The reaction mixture was stirred for 30 min. and was then allowed to reach room temperature. The mixture was quenched by adding 28-30% NH_4OH (20 mL) and extracted with 10% MeOH in CH_2Cl_2 (2x75 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel chromatography using 3% EtOAc in pentane as eluent, yielding a colorless oil (0.065 g, 0.38 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.07 (m, 5H), 4.96 – 4.71 (m, 1H), 4.60 (dd, *J* = 2.0, 0.7 Hz, 2H), 3.64 – 3.46 (m, 2H), 1.34 (dd, *J* = 23.8, 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.10, 128.57, 127.87, 127.84, 89.70 (d, *J* = 168.2 Hz), 73.58, 73.26 (d, *J* = 22.0 Hz), 17.58 (d, *J* = 22.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -175.08.

Synthesis of 2-fluorocyclohexan-1-one

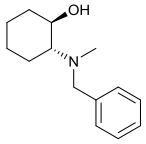
2-fluorocyclohexan-1-one was prepared according to literature procedure and NMR was in agreement with that previously reported.[13]

Synthesis of (1*S*,2*R*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*syn*-1l)



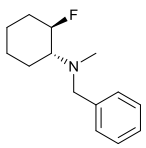
(1*S*,2*R*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine was synthesized following a general literature procedure for formation of hindered tertiary amines.[14] To 2-fluorocyclohexan-1-one (0.4 g, 3.4 mmol) was added dry CH_2Cl_2 (18 mL), *N*-benzylmethylamine (0.53 mL, 4.1 mmol), and TMEDA (0.52 mL, 3.4 mmol). The content was stirred for 30 min. and trichlorosilane (0.69 mL, 6.9 mmol) was then added dropwise. The reaction mixture was allowed to stir at room temperature for 72h. The reaction was quenched by carefully adding sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3x30 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel flash chromatography using 2% EtOAc in pentane as eluent. The product was collected as a clear colorless oil (0.09 g, 0.4 mmol, 12 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 5H), 5.10 (ddt, *J* = 50.0, 4.1, 1.7 Hz, 1H), 3.75 – 3.64 (m, 2H), 2.57 – 2.40 (m, 1H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.12 – 1.19 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.40 , 128.84 , 128.34 , 126.87 , 91.53 (d, *J* = 173.6 Hz), 63.91 (d, *J* = 17.7 Hz), 58.70 (d, *J* = 3.1 Hz), 39.18 (d, *J* = 3.4 Hz), 31.57 (d, *J* = 21.6 Hz), 25.63 , 23.20 (d, *J* = 1.8 Hz), 20.21 (d, *J* = 1.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -191.98. HRMS calculated for $C_{14}H_{20}FN$ $(M+H)^+$: 222.1652, found: 222.1652.

Synthesis of (1*S*,2*S*)-2-(benzyl(methyl)amino)cyclohexan-1-ol



(1*S*,2*S*)-2-(benzyl(methyl)amino)cyclohexan-1-ol was synthesized following a general literature procedure for ring opening of epoxides with amines.[15] To $Yb(OTf)_3$ (0.31 g, 0.5 mmol) was added dry THF (5 mL), cyclohexene oxide (0.5 mL, 5 mmol), and N-benzylmethylamine (1.3 mL, 10 mmol). The reaction mixture was refluxed for 15 h. The reaction was quenched by adding water and extracted with Et_2O (3x30 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel flash chromatography using pentane/EtOAc (10:1). The product was collected as a clear colorless oil (0.53 g, 2.4 mmol, 48%). NMR was in agreement with that previously reported.[16]

Synthesis of (1*S*,2*S*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*anti*-1l)



(1*S*,2*S*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine was synthesized following a general literature procedure for ring opening of cyclohexyl-substituted β-haloamines and aziridinium ions.[17] To (1*S*,2*S*)-2-

(benzyl(methyl)amino)cyclohexan-1-ol (0.53 g, 2.4 mmol) in dry CH_2Cl_2 (14 mL), was added Deoxo-Fluor (50% in THF, 1 mL, 2.39 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and was then quenched by carefully adding 10% Na_2CO_3. The crude was extracted with CH_2Cl_2 (3x30 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel chromatography using 2% EtOAc in pentane as eluent. The product was collected as a clear colorless oil (0.29 g, 1.31 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 5H), 4.60 (dtd, *J* = 50.5, 10.1, 4.8 Hz, 1H), 3.83 – 3.65 (m, 2H), 2.73 – 2.62 (m, 1H), 2.32 (s, 3H), 2.21 – 1.14 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.49, 128.78, 128.32, 126.85, 92.71 (d, *J* = 177.1 Hz), 65.99 (d, *J* = 15.2 Hz), 59.17 (d, *J* = 1.6 Hz), 37.58, 32.66 (d, *J* = 17.7 Hz), 27.11 (d, *J* = 8.7 Hz), 25.01 (d, *J* = 2.1 Hz), 24.10 (d, *J* = 11.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -170.23. HRMS calculated for $C_{14}H_{20}FN$ $(M+H)^+$: 222.1652, found: 222.1653.

Lewis acid screening

To the Lewis acid (0.044 mmol) was added CH_2Cl_2 (0.25 mL), BnMeNH (8.0 µL, 0.060 mmol), and *N*-benzyl-*N*-methyl-2-fluoroethylamine **1a** (40 µL, 1.0 M in CH_2Cl_2, 0.040 mmol). *n*-Dodecane (9.1 µL, 0.040 mmol) was added to the reaction as internal standard. The reaction was quenched after 5 min by adding 10% K_2CO_3/tartrate (aq) and extracted with Et_2O. The crude was analyzed by GC-FID.

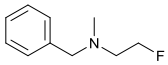
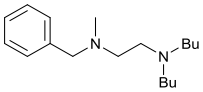
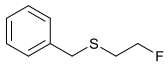
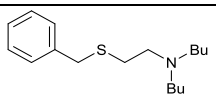
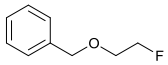
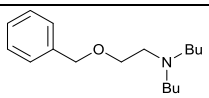
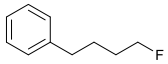
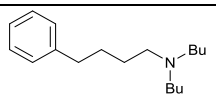
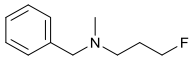
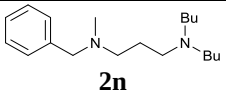
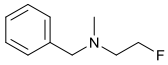
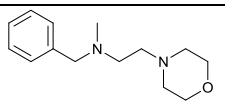
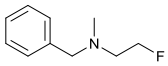
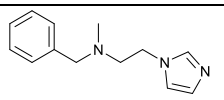
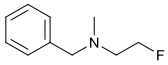
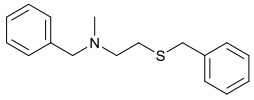
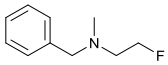
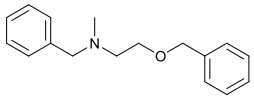
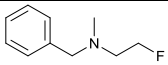
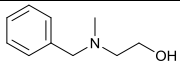
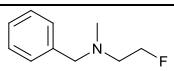
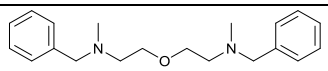
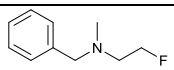
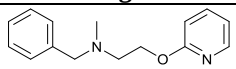
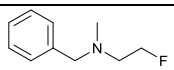
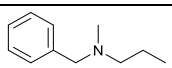
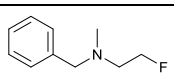
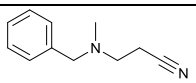
Entry	Lewis acid	Yield (%)	comment
1[a]	$SmCl_3$	8	
2	$SmBr_3$	74	
3[a]	YbF_3	9	
4	YbI_3	66	100% conv of **1a**. Formation of iodo-product
5[a]	$Yb(OTf)_3$	15	
6[a]	$La(OTf)_3$	9	
7[a]	$Sm(OTf)_3$	10	
8[a]	SmF_3	7	
9[a]	LiI	8	
10	AlI_3	16	100% conv of **1a**. Formation of iodo-product
11[a]	KI	8	
12[a]	KBr	8	
13[a]	$MgCl_2$	11	
14	-	11	
15	$AlCl_3$	26	
16[a]	TMS-HMDS	~10	

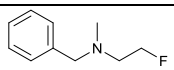
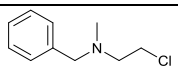
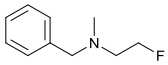
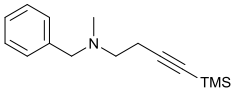
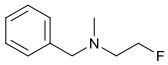
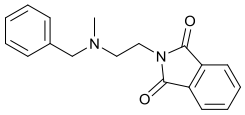
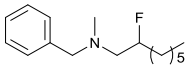
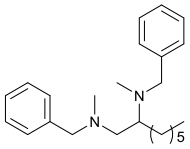
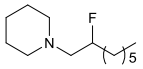
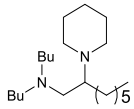
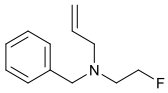
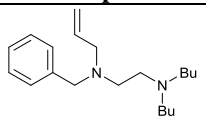
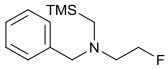
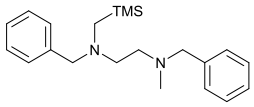
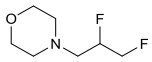
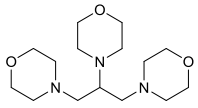
[a] The corresponding Lewis acids gave ~10% yield due to work-up (see Entry 14). Prolonged reaction times resulted in the same outcome and only ~10% yield was obtained. Thus, showing no effect of the corresponding Lewis acid in the C-F bond activation.

General method for C-F bond substitution

The reaction was run under dry and inert conditions. To $La[N(SiMe_3)_2]_3$ (124 mg, 0.20 mmol, stored and weighed in the glove box) was added CH_2Cl_2 (1.25 mL) followed by the substrate (200 µL, 0.20 mmol, 1.0 M in CH_2Cl_2) and the nucleophile [dibutylamine (37 µL, 0.22 mmol)]. The reaction was stirred at room temperature to completion after which it was quenched by adding it directly to silica gel column and purified by flash column chromatography.

Table S1: Reaction conditions for substitution of β-heteroatom-fluorines

Entry	Substrate	*t* (min)	Product	m (mg)	yield (%)	eluent
1[a]	 **1a**	1	 **2a**	41.1	93	1:4 Pentane:Et_2O
2[a]	 **3**	1	 **4**	39	87	4:1 – 0:1 Pentane: Et_2O
3[a,b]	 **5a**	60	 **6**	37.5	89	4:1 – 0:1 Pentane: Et_2O
4[a,b]	 **7**	60	 **8**	39	93	1:1 Pentane:Et_2O
5[g]	 **1b**	180	 **2n**	52.2	90	1:1 – 1:3 Pentane:Et_2O
6[c]	 **1a**	1	 **2b**	43.5	93	95:5 CH_2Cl_2:MeOH
7[d]	 **1a**	60	 **2c**	34.9	81	90:10 CH_2Cl_2:MeOH
8	 **1a**	5	 **2d**	52.2	96	2:1 Pentane:Et_2O
9[e]	 **1a**	5	 **2e**	37	72	1:2 Pentane:Et_2O
10	 **1a**	60	 **2f**[18]	23.4	70	90:10 CH_2Cl_2:MeOH
11[f]	 **1a**	1	 **2g**	38.1	61	90:10 CH_2Cl_2:MeOH
12[d]	 **1a**	60	 **2h**	33.2	69	95:5 CH_2Cl_2:MeOH
13	 **1a**	60	 **2i**[19]	28.4	87	2:1 Pentane:Et_2O
14	 **1a**	5	 **2j**[20]	31	89	7:3 Pentane/EtOAc

15[e]	 **1a**	1	 **2k**[21]	28.7	78	2:1 Pentane:Et_2O
16[e]	 **1a**	5	 **2l**	34.8	71	2:1 Pentane:Et_2O
17[d]	 **1a**	120	 **2m**	46.2	78	2:1 Pentane/Et_2O
18[a]	 **1f**	5	 **2o**	42.1	75	7:1-0:1 Pentane: Et_2O
19[a]	 **1g**	5	 **2p**	42.2	81	3:1 – 0:1 Pentane: Et_2O
20[e]	 **1h**	5	 **2q**	54	89	1:1 Pentane:Et_2O
21	 **1i**	5	 **2r**	61.3	90	1:1 Pentane:Et_2O
22[h,i]	 **1j**	180	 **2s**	30.6	51	95:5 CH_2Cl_2:MeOH

[a]To $La[N(SiMe_3)_2]_3$ (110 mg, 0.176 mmol), CH_2Cl_2 (1 mL), substrate (0.160 mmol, 1.0 M in CH_2Cl_2) and the nucleophile [dibutylamine (30 µL, 0.176 mmol)]. [b] Dibutylamine (81 µL, 0.48 mmol). [c] Nucleophile (0.21 mmol). [d] Nucelophile (0.3 mmol). [e] Nucleophile (0.6 mmol). [f] Nucleophile (20 mmol). [g] Was stirred for 10 min. before addition of nucleophile. [h] Was stirred for 30 min. before addition of nucleophile. [i] Nucleophile (0.42 mmol).

***N*1-benzyl-*N*2,N2-dibutyl-*N*1-methylethane-1,2-diamine (2a)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 5H), 3.58 (s, 2H), 2.66 (dd, *J* = 9.0, 5.5 Hz, 2H), 2.55 (dd, *J* = 9.2, 5.5 Hz, 2H), 2.51 – 2.42 (m, 4H), 2.28 (s, 3H), 1.48 – 1.29 (m, 8H), 0.96 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 129.2, 128.3, 127.0, 62.9, 55.6, 54.6, 52.4, 42.9, 29.4, 20.9, 14.2. HRMS calculated for $C_{18}H_{32}N_2$ $(M+H)^+$: 277.2638, found: 277.2639.

***N*-(2-(benzylthio)ethyl)-*N*-butylbutan-1-amine (4)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 5H), 3.73 (s, 2H), 2.64 – 2.55 (m, 2H), 2.53 – 2.44 (m, 2H), 2.42 – 2.29 (m, 4H), 1.46 – 1.20 (m, 8H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 129.0, 128.6, 127.1, 54.1, 53.9, 36.6, 29.5, 29.0, 20.8, 14.2. HRMS calculated for $C_{17}H_{29}NS$ $(M+H)^+$: 280.2093, found: 280.2096.

***N*-(2-(benzyloxy)ethyl)-*N*-butylbutan-1-amine (6)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 4.53 (s, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.49 – 2.38 (m, 4H), 1.48 – 1.22 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 128.5, 127.8, 127.6, 73.3, 69.1, 54.7, 53.7, 29.4, 20.8, 14.2. HRMS calculated for $C_{17}H_{29}NO$ $(M+H)^+$: 264.2321, found: 264.2323.

***N*,*N*-dibutyl-4-phenylbutan-1-amine (8)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.14 (m, 5H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.48 – 2.35 (m, 6H), 1.70 – 1.58 (m, 2H), 1.56 – 1.38 (m, 6H), 1.38 – 1.25 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 128.5, 128.4, 125.7, 54.2, 54.1, 36.1, 29.62, 29.44, 26.96, 20.93, 14.26. HRMS calculated for $C_{18}H_{31}N$ $(M+H)^+$: 262.2529, found: 262.2530.

***N*1-benzyl-*N*3,*N*3-dibutyl-*N*1-methylpropane-1,3-diamine (2n)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 5H), 3.48 (s, 2H), 2.49 – 2.33 (m, 8H), 2.18 (s, 3H), 1.66 (tt, *J* = 9.4, 6.4 Hz, 2H), 1.47 – 1.20 (m, 8H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 129.2, 128.3, 126.9, 62.5, 56.0, 54.1, 52.3, 42.4, 29.4, 25.2, 20.9, 14.2. HRMS calculated for $C_{19}H_{34}N_2$ $(M+H)^+$: 291.2794, found: 291.2796.

***N*-benzyl-*N*-methyl-2-morpholinoethan-1-amine (2b)**: ^{1}H NMR (400 MHz $CDCl_3$) δ 7.35 – 7.19 (m, 5H), 3.76 – 3.63 (m, 4H), 3.51 (s, 2H), 2.57 – 2.47 (m, 4H), 2.42 (dd, *J* = 5.7, 3.7 Hz, 4H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 129.1, 128.3, 127.1, 67.0, 62.9, 57.1, 54.3, 54.2, 42.9. HRMS calculated for $C_{14}H_{22}N_2O$ $(M+H)^+$: 235.1804, found: 235.1807.

***N*-benzyl-2-(1H-imidazol-1-yl)-*N*-methylethan-1-amine (2c)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.33 – 7.15 (m, 5H), 7.04 (s, 1H), 6.91 (s, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.53 (s, 2H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 137.5, 129.3, 128.8, 128.5, 127.3, 119.4, 62.7, 57.6, 45.3, 42.4. HRMS calculated for $C_{13}H_{17}N_3$ $(M+H)^+$: 216.1495, found: 216.1498.

***N*-benzyl-2-(benzylthio)-*N*-methylethan-1-amine (2d)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 10H), 3.69 (s, 2H), 3.49 (s, 2H), 2.62 – 2.51 (m, 4H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 138.6, 129.1, 129.0, 128.6, 128.3, 127.1, 127.0, 62.3, 56.6, 42.2, 36.4, 29.1. HRMS calculated for $C_{17}H_{21}NS$ $(M+H)^+$: 272.1467, found: 272.1470.

***N*-benzyl-2-(benzyloxy)-*N*-methylethan-1-amine (2e)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.16 (m, 10H), 4.53 (s, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.56 (s, 2H), 2.67 (t, *J* = 5.9 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.6, 129.2, 128.5, 128.3, 127.8, 127.6, 127.0, 73.2, 68.7, 62.8, 56.7, 43.0. HRMS calculated for $C_{17}H_{21}NO$ $(M+H)^+$: 256.1695, found: 256.1692.

2,2'-oxybis(*N*-benzyl-*N*-methylethan-1-amine) (2g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 10H; Ar), 3.64 (app dd, *J* = 10.8, 5.0 Hz, 8H, (Ph-C$\underline{H}_2$-N-)$_2$, -C$\underline{H}_2$-O-C$\underline{H}_2$-), 2.71 (t, *J* = 5.7 Hz, 4H, (-N-C$\underline{H}_2$-CH$_2$-)$_2$), 2.33 (s, 6H, -C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.9, 128.5, 127.6, 110.1, 68.9, 62.5, 56.2, 42.6. HRMS calculated for $C_{20}H_{28}N_2O$ $(M+H)^+$: 313.2274, found: 313.2269.

***N*-benzyl-*N*-methyl-2-(pyridin-2-yloxy)ethan-1-amine (2h)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 7H), 6.52 (ddd, *J* = 9.1, 1.4, 0.7 Hz, 1H), 6.13 (td, *J* = 6.7, 1.4 Hz, 1H), 4.01 (dd, *J* = 6.4, 5.7 Hz, 2H), 3.53 (s, 2H), 2.73 (dd, *J* = 6.4, 5.7 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 139.4, 138.9, 138.7, 128.8, 128.4, 127.1, 120.8, 105.4, 62.6, 55.7, 47.5, 42.5. HRMS calculated for $C_{15}H_{18}N_2O$ $(M+H)^+$: 243.1491, found: 243.1489.

***N*-benzyl-*N*-methyl-4-(trimethylsilyl)but-3-yn-1-amine (2l)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 3.54 (s, 2H), 2.68 – 2.60 (m, 2H), 2.47 – 2.39 (m, 2H), 2.24 (s, 3H), 0.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 129.0, 128.4, 127.1, 105.8, 85.4, 62.1, 56.1, 42.1, 18.7, 0.3. HRMS calculated for $C_{15}H_{23}NSi$ $(M+H)^+$: 246.1672, found: 246.1669.

2-(2-(benzyl(methyl)amino)ethyl)isoindoline-1,3-dione (2m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 – 7.67 (m, 2H), 7.14 (dd, *J* = 4.3, 1.4 Hz, 5H), 3.82 (t, *J* = 6.3 Hz, 2H), 3.52 (s, 2H), 2.67 (t, *J* = 6.3 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 139.0, 133.9, 132.4, 129.0, 128.2, 127.0, 123.3, 62.3, 54.7, 42.4, 36.1. HRMS calculated for $C_{18}H_{18}N_2O_2$ $(M+H)^+$: 295.1440, found: 295.1439.

***N*1,*N*2-dibenzyl-*N*1,*N*2-dimethyloctane-1,2-diamine (2o)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 10H), 3.73 – 3.58 (m, 2H), 3.57 – 3.42 (m, 2H), 2.80 – 2.73 (m, 1H), 2.61 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.24 (dd, *J* = 12.5, 6.7 Hz, 1H), 2.18 (app d, *J* = 2.0 Hz, 6H, 3 x N-C<u>H</u>$_3$), 1.54 – 1.25 (m, 10H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 139.5, 129.0, 128.6, 128.1, 128.0, 126.8, 126.6, 63.1, 60.2, 58.3, 58.2, 42.9, 36.6, 32.0, 30.3, 29.6, 27.2, 22.7, 14.2. HRMS calculated for $C_{24}H_{36}N_2$ $(M+H)^+$: 353.2951, found: 353.2948.

***N*,*N*-dibutyl-2-(piperidin-1-yl)octan-1-amine (2p)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 – 2.20 (m, 10H), 2.14 (dd, *J* = 12.6, 6.9 Hz, 1H), 1.57 – 1.18 (m, 24H), 0.93 – 0.87 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.9, 60.2, 56.9, 55.4, 54.8, 54.6, 50.0, 49.9, 32.0, 31.9, 31.8, 31.0, 30.3, 29.9, 29.6, 29.5, 29.3, 27.4, 27.2, 26.8, 26.2, 25.2, 24.6, 22.7, 20.7, 20.5, 14.2, 14.1, 14.1, 14.1. HRMS calculated for $C_{21}H_{44}N_2$ $(M+H)^+$: 325.3577, found: 325.3572.

***N*1-allyl-*N*1-benzyl-*N*2,*N*2-dibutylethane-1,2-diamine (2q)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 5H; Ar), 5.89 (ddt, *J* = 17.3, 10.2, 6.4 Hz, 1H; -N-CH_2-C<u>H</u>=CH_2), 5.19 (ddt, *J* = 17.2, 2.1, 1.5 Hz, 1H, -N-CH_2-CH=C<u>H</u>$_2$), 5.13 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H, -N-CH_2-CH=C<u>H</u>$_2$), 3.60 (s, 2H, N-C<u>H</u>$_2$-Ph), 3.11 (dt, *J* = 6.4, 1.4 Hz, 2H, -N-C<u>H</u>$_2$-CH=CH_2), 2.55 (s, 4H), 2.42 – 2.31 (m, 4H), 1.42 – 1.31 (m, 4H), 1.31 – 1.18 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 136.2, 129.0, 128.2, 126.9, 117.3, 58.9, 57.6, 54.6, 52.3, 51.6, 29.5, 20.9, 14.2. HRMS calculated for $C_{20}H_{34}N_2$ $(M+H)^+$: 303.2794, found: 303.2790.

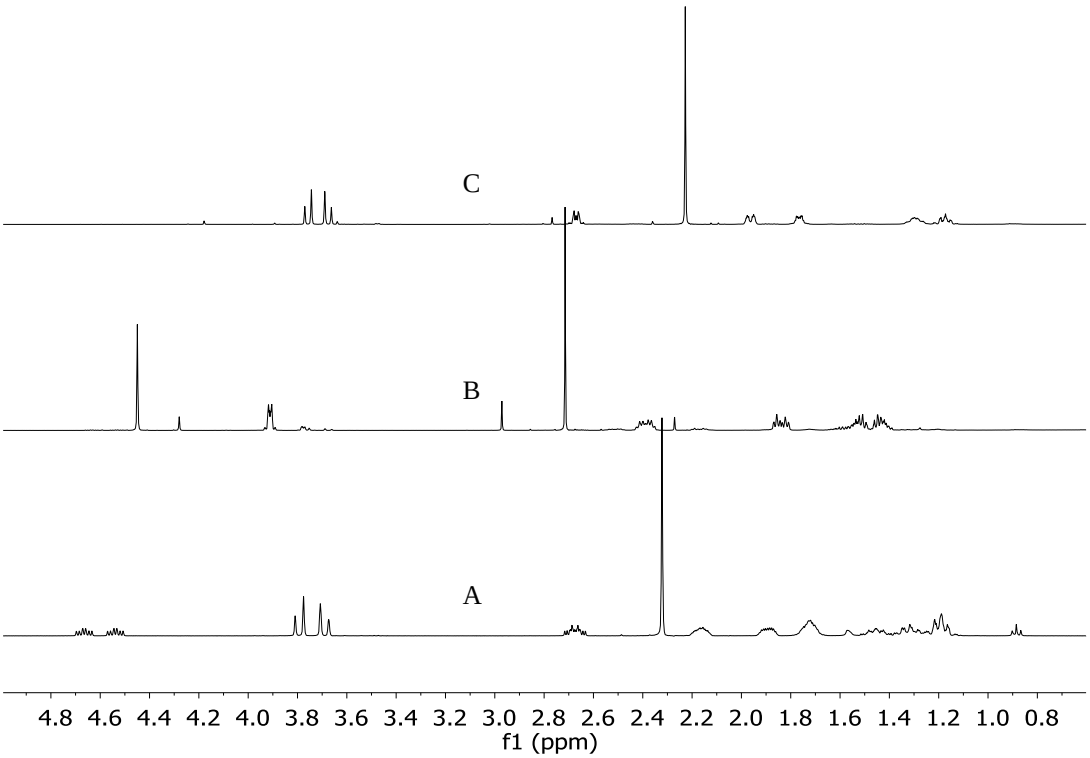
***N*1,*N*2-dibenzyl-*N*1-methyl-*N*2-((trimethylsilyl)methyl)ethane-1,2-diamine (2r)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 10H), 3.52 (s, 2H), 3.47 (s, 2H), 2.62 – 2.47 (m, 4H), 2.16 (s, 3H), 1.98 (s, 2H), 0.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 139.3, 129.1, 128.8, 128.3, 128.2, 127.0, 126.8, 62.8, 55.6, 55.4, 46.7, 42.9, -1.2. HRMS calculated for $C_{21}H_{32}N_2Si$ $(M+H)^+$: 341.2407, found: 341.2405.

4,4',4''-(propane-1,2,3-triyl)trimorpholine (2s): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 – 3.55 (m, 12H), 2.94 – 2.14 (m, 17H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.81, 67.26, 59.12, 58.68, 54.40, 49.60. HRMS calculated for $C_{15}H_{29}N_3O_3$ $(M+H)^+$: 300.2281, found: 300.2278.

NMR studies

^{1}H NMR study of (1*S*,2*S*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*anti*-1l)

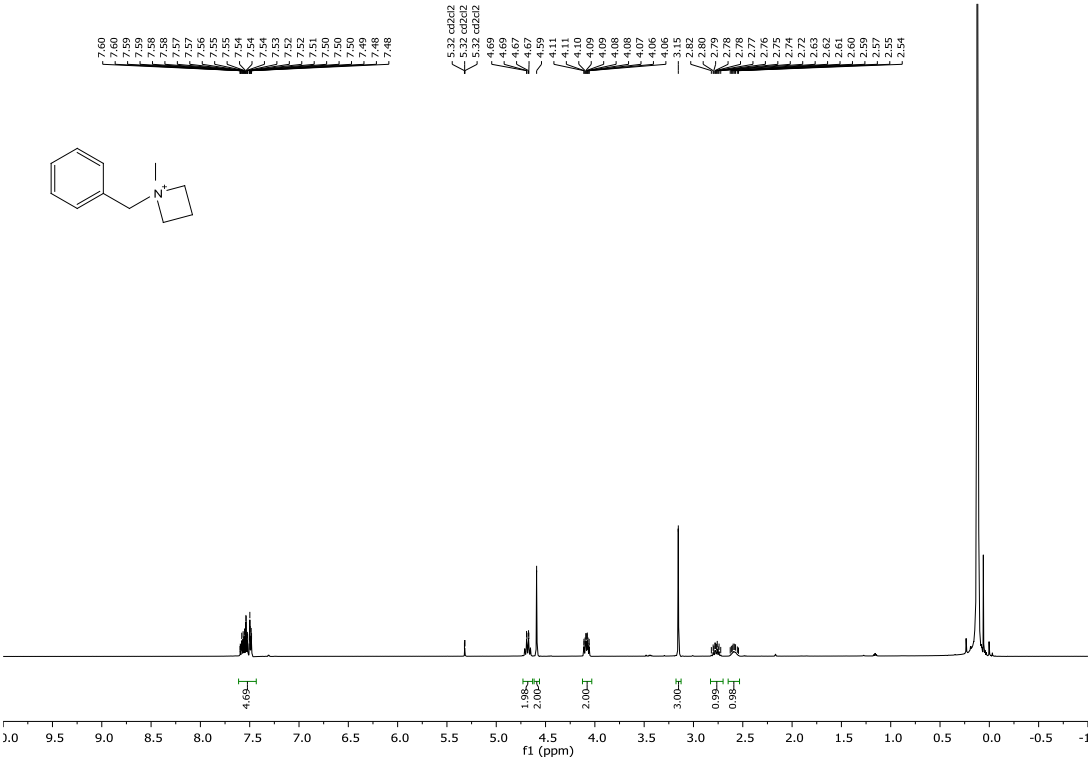
To La[N(SiMe$_3$)$_2$]$_3$ (50 mg, 0.08 mmol), in a NMR tube, was added CD_2Cl_2 (0.5 mL) followed by *anti*-**1l** (80 µL, 0.08 mmol, 1.0 M in CD_2Cl_2, **A**). ^{1}H NMR spectra was recorded. After aziridinium ion formation has been completed (**B**), *N*-benzyl methyl amine (10 µL, 0.08 mmol) was added and ^{1}H NMR spectra was recorded to follow the ring opening of the aziridinium ion (**C**). The *anti*-**2t** product that was obtained was in agreement with that previously reported.[22]



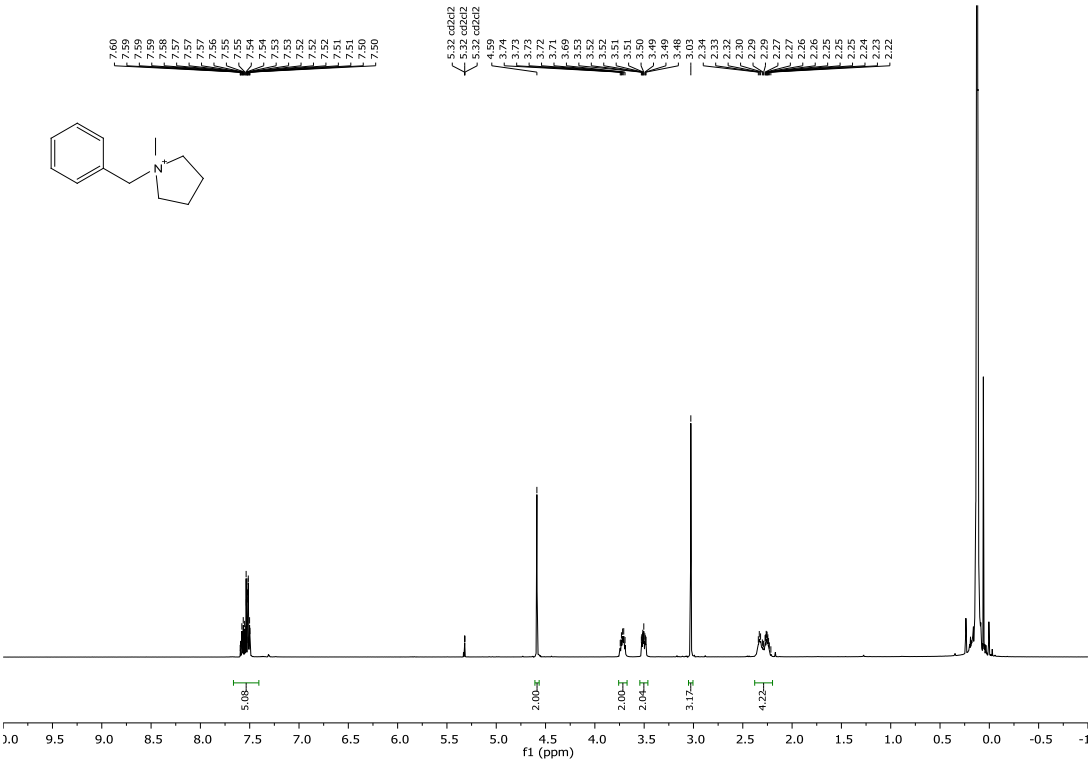
^{1}H NMR study of La[N(SiMe$_3$)$_2$]$_2$ mediated formation of 4-, 5-. 6-, and 7-membered cyclic ammonium ions

To La[N(SiMe$_3$)$_2$]$_3$ (50 mg, 0.08 mmol), in a NMR tube, was added CD_2Cl_2 (0.5 mL) followed by the substrate (80 µL, 0.08 mmol, 1.0 M in CD_2Cl_2). ^{1}H NMR spectra was recorded to follow the ring-closure.

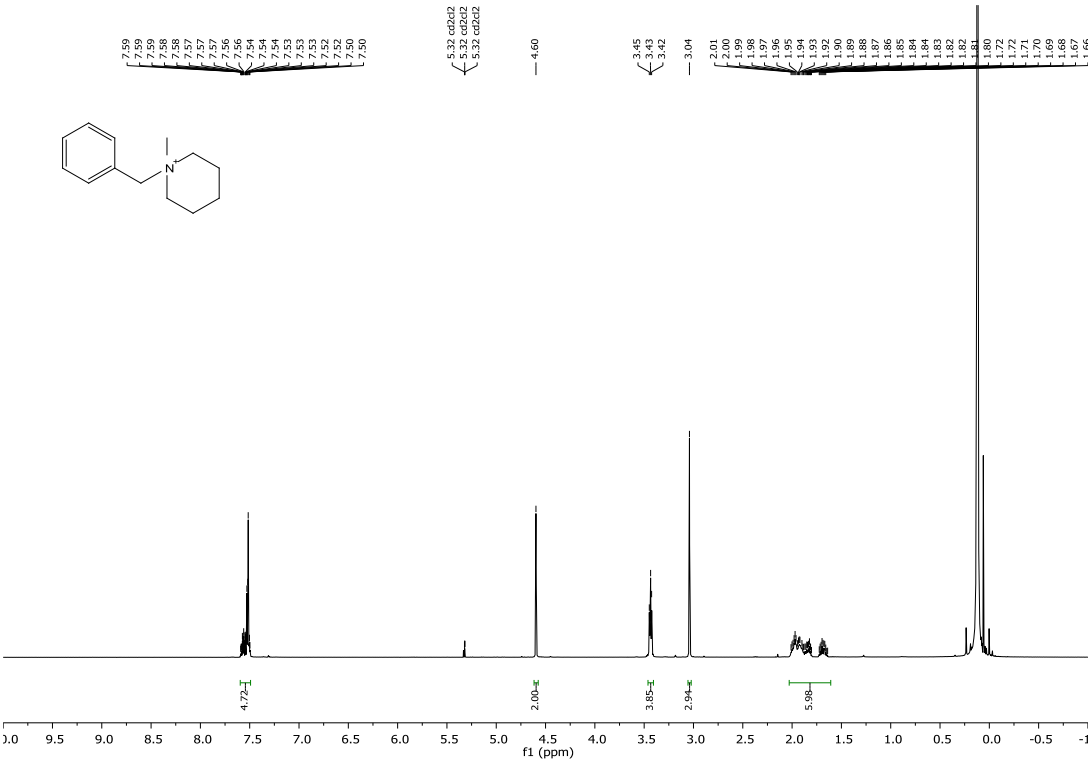
^{1}H NMR of the 4-membered cyclic ammonium ion



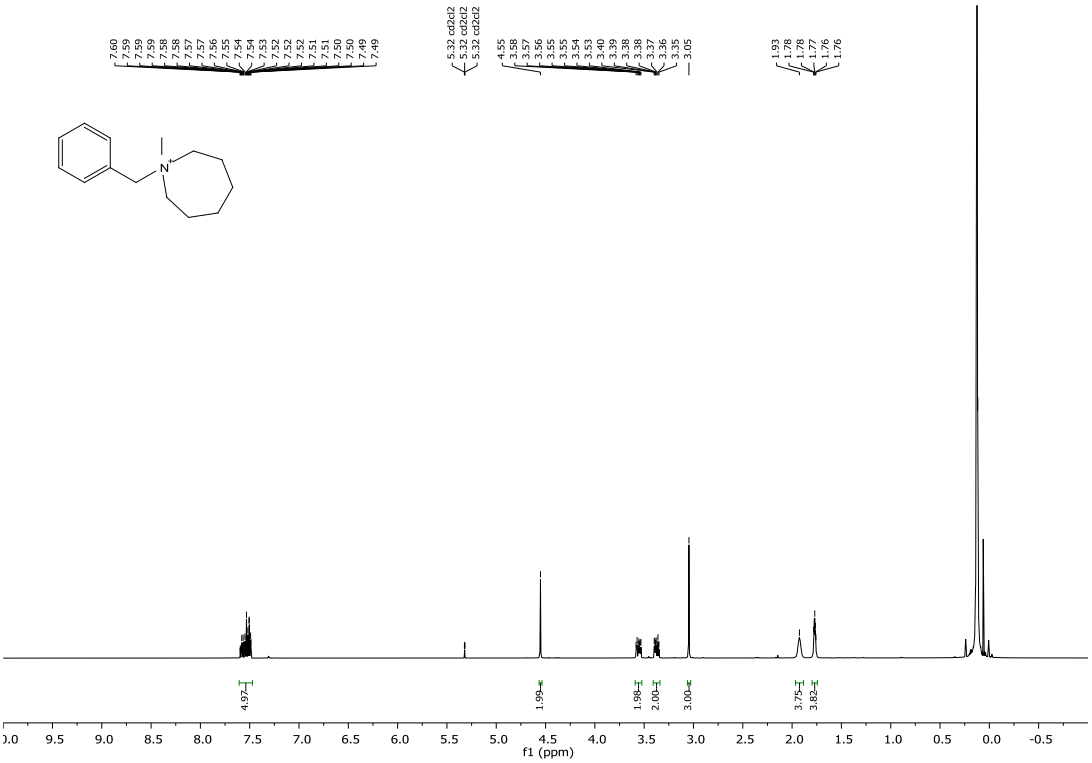
^{1}H NMR of the 5-membered cyclic ammonium ion



^{1}H NMR of the 6-membered cyclic ammonium ion

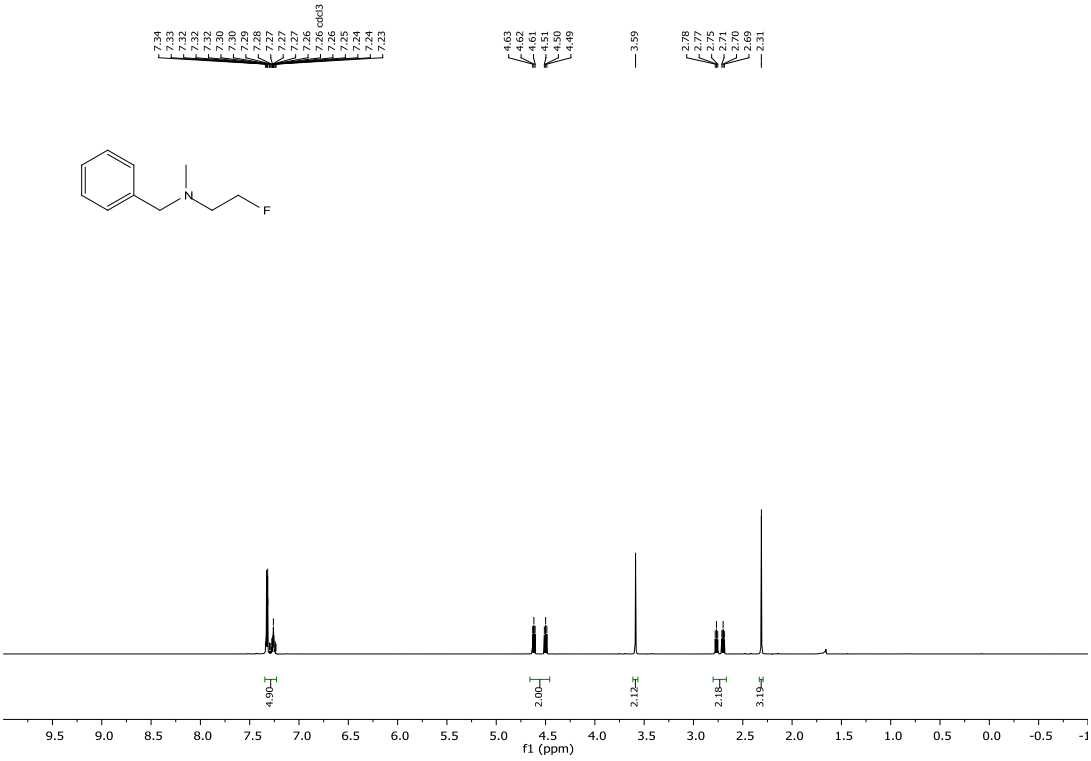


^{1}H NMR of the 7-membered cyclic ammonium ion

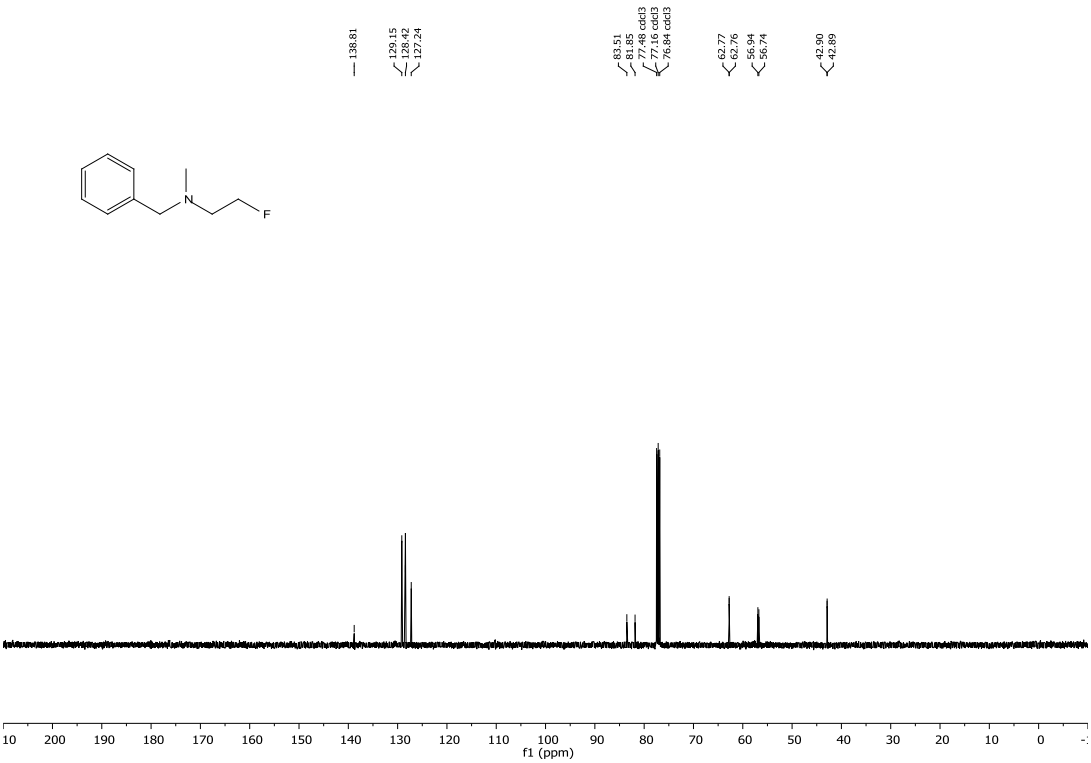


NMR Spectra

^{1}H NMR *N*-benzyl-*N*-methyl-2-fluoroethylamine (1a)

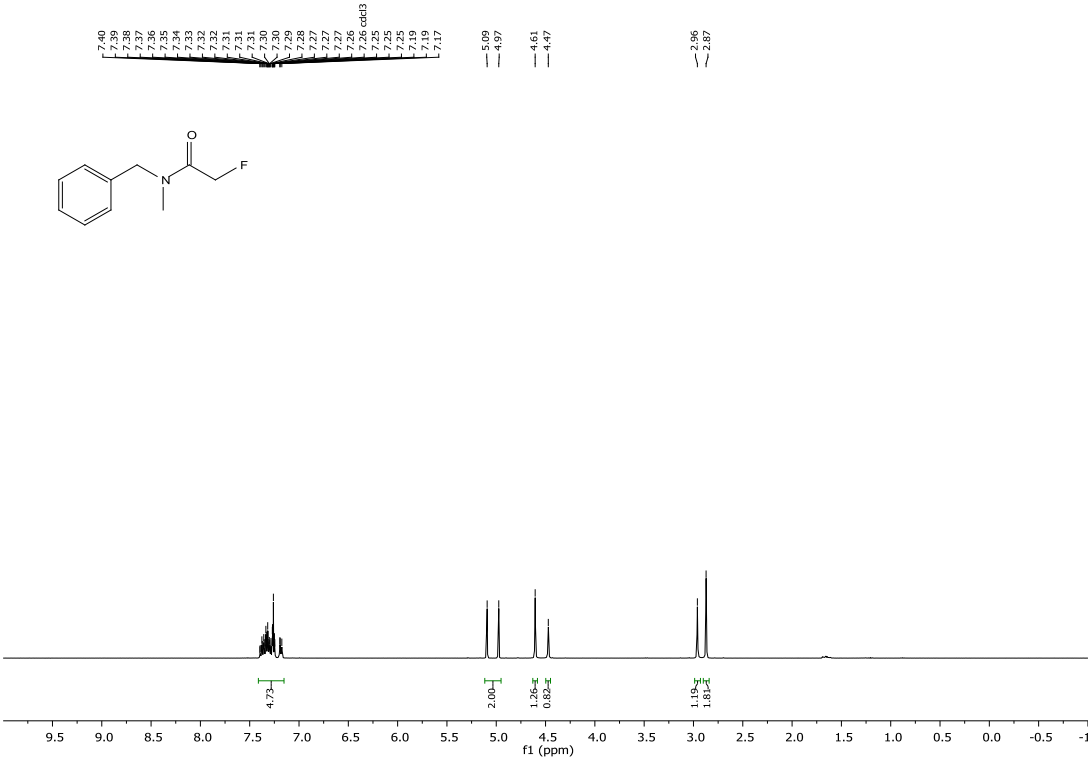


^{13}C NMR *N*-benzyl-*N*-methyl-2-fluoroethylamine (1a)

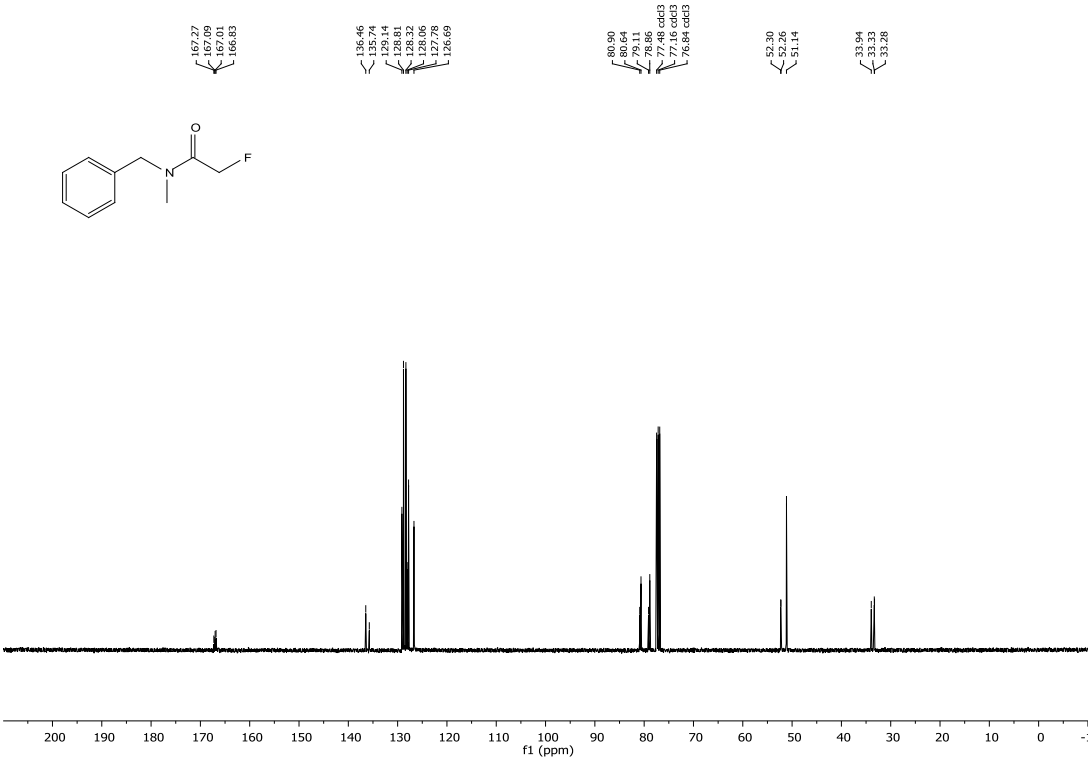


^{19}F NMR *N*-benzyl-*N*-methyl-2-fluoroethylamine (1a)

^{1}H NMR *N*-benzyl-2-fluoro-*N*-methylacetamide (9)

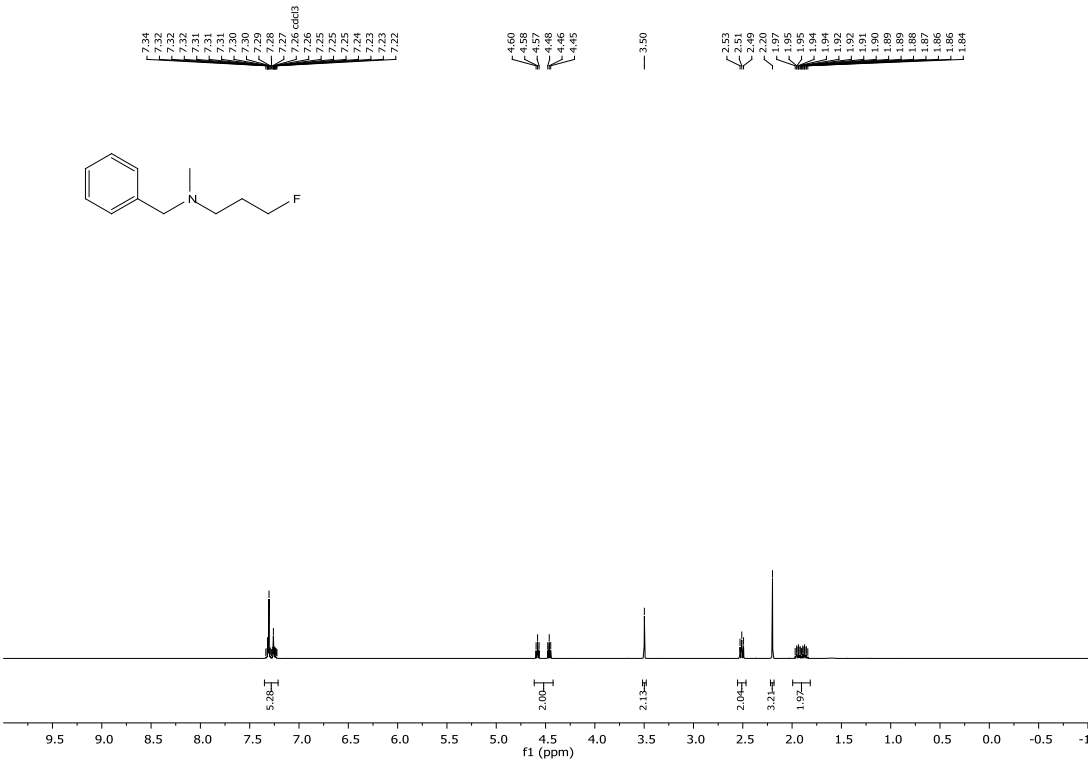


^{13}C NMR *N*-benzyl-2-fluoro-*N*-methylacetamide (9)

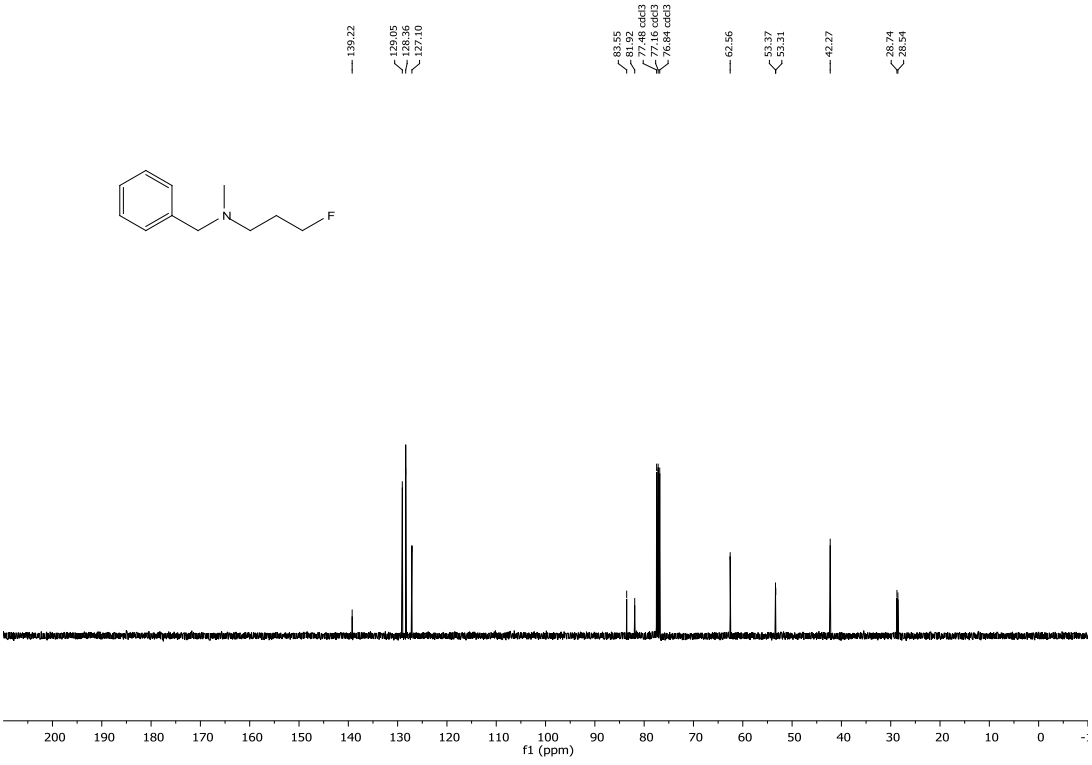


^{19}F NMR *N*-benzyl-2-fluoro-*N*-methylacetamide (9)

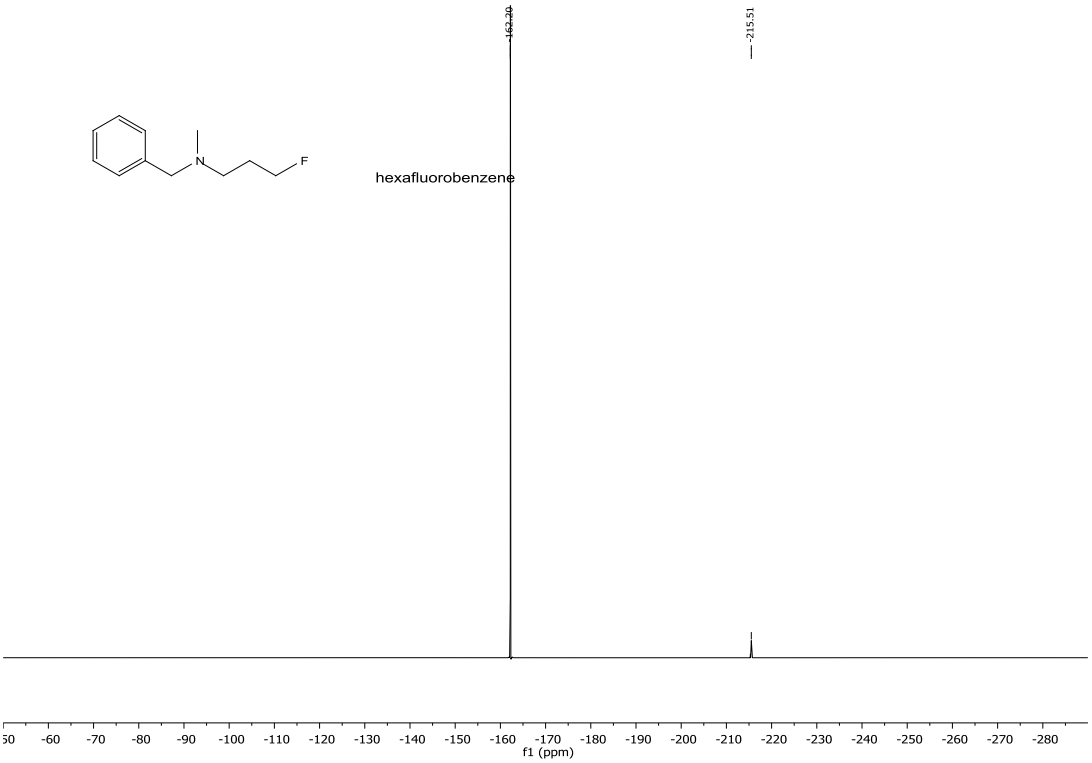
^{1}H NMR *N*-benzyl-3-fluoro-*N*-methylpropan-1-amine (1b)



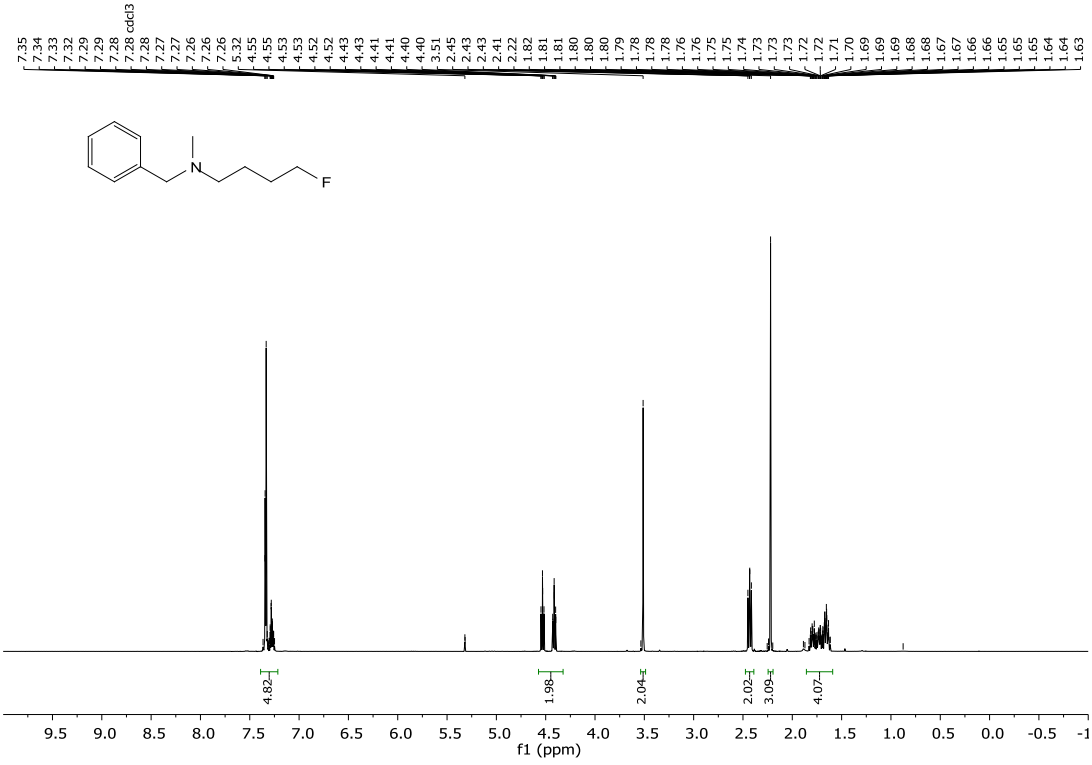
^{13}C NMR *N*-benzyl-3-fluoro-*N*-methylpropan-1-amine (1b)



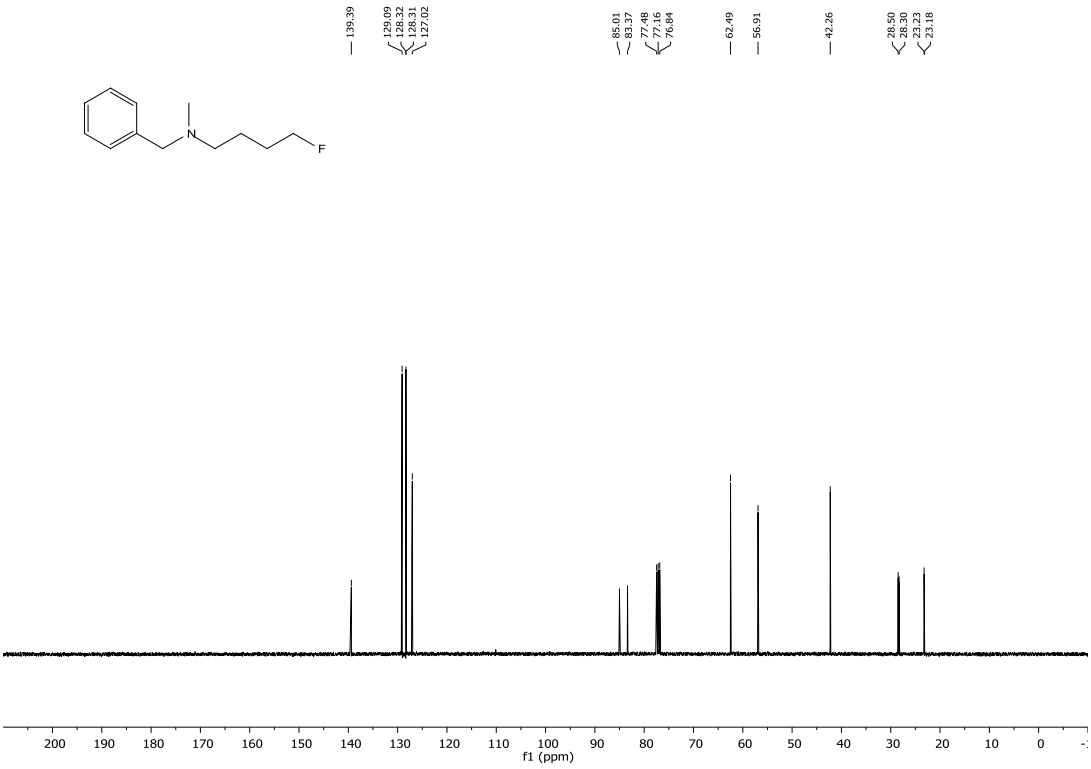
^{19}F NMR *N*-benzyl-3-fluoro-*N*-methylpropan-1-amine (1b)



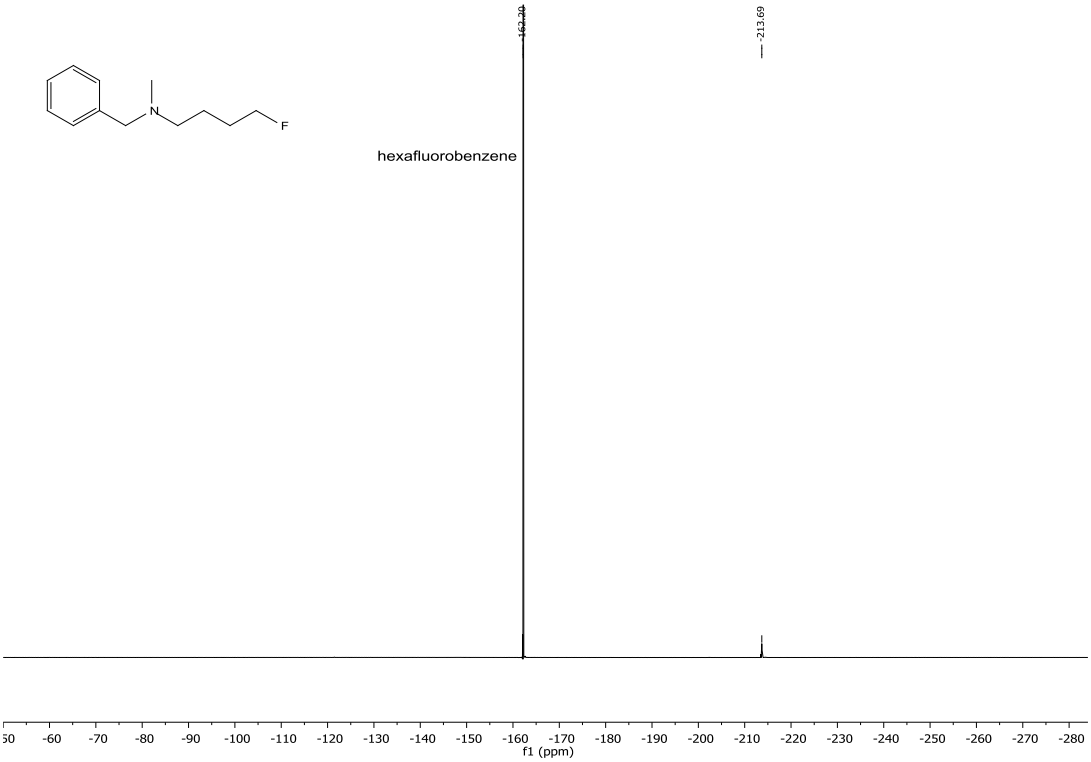
^{1}H NMR *N*-benzyl-4-fluoro-*N*-methylbutan-1-amine (1c)



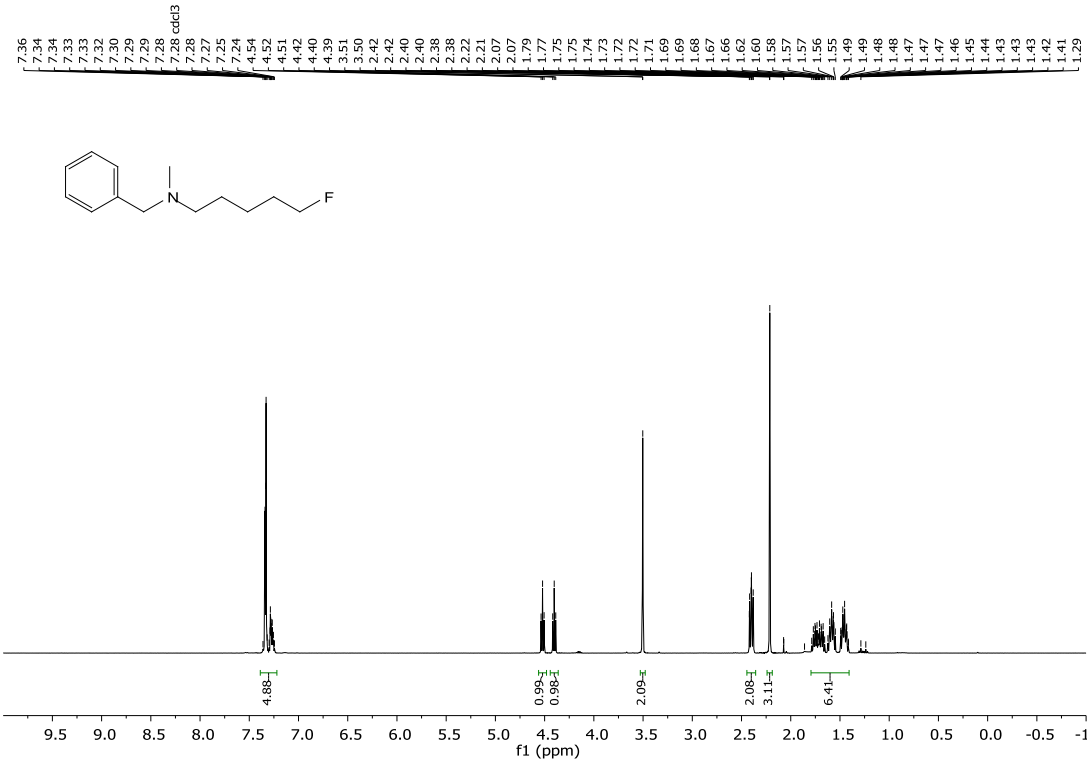
^{13}C NMR *N*-benzyl-4-fluoro-*N*-methylbutan-1-amine (1c)



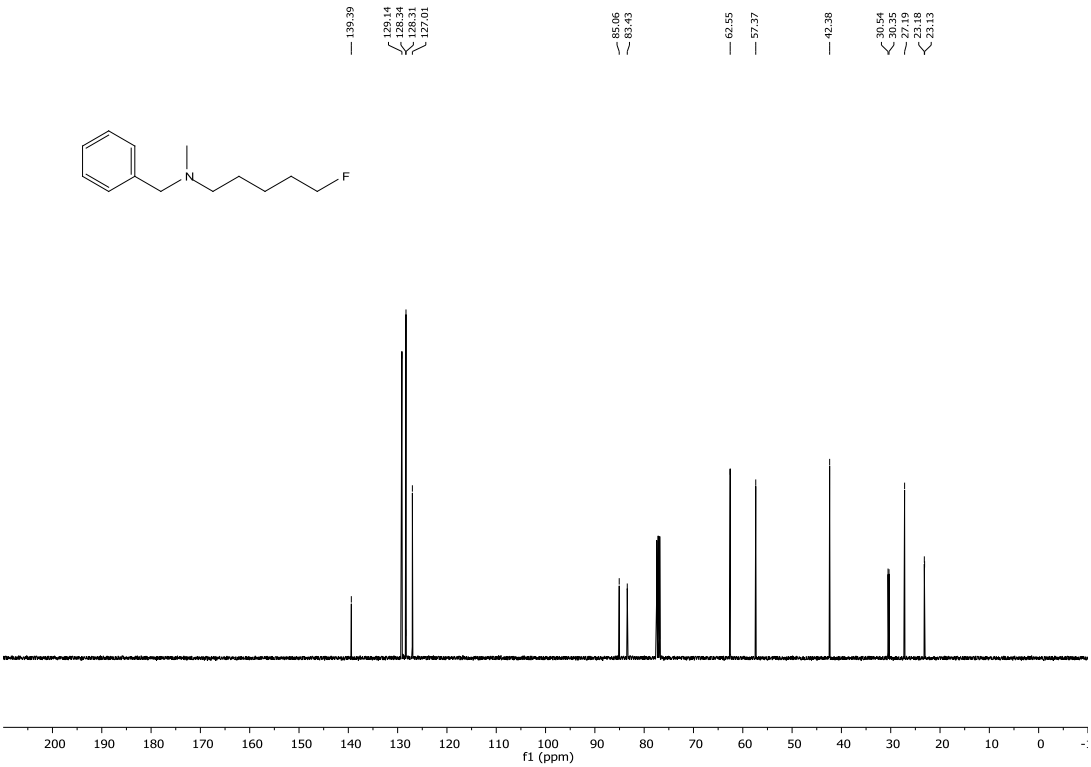
^{19}F NMR *N*-benzyl-4-fluoro-*N*-methylbutan-1-amine (1c)



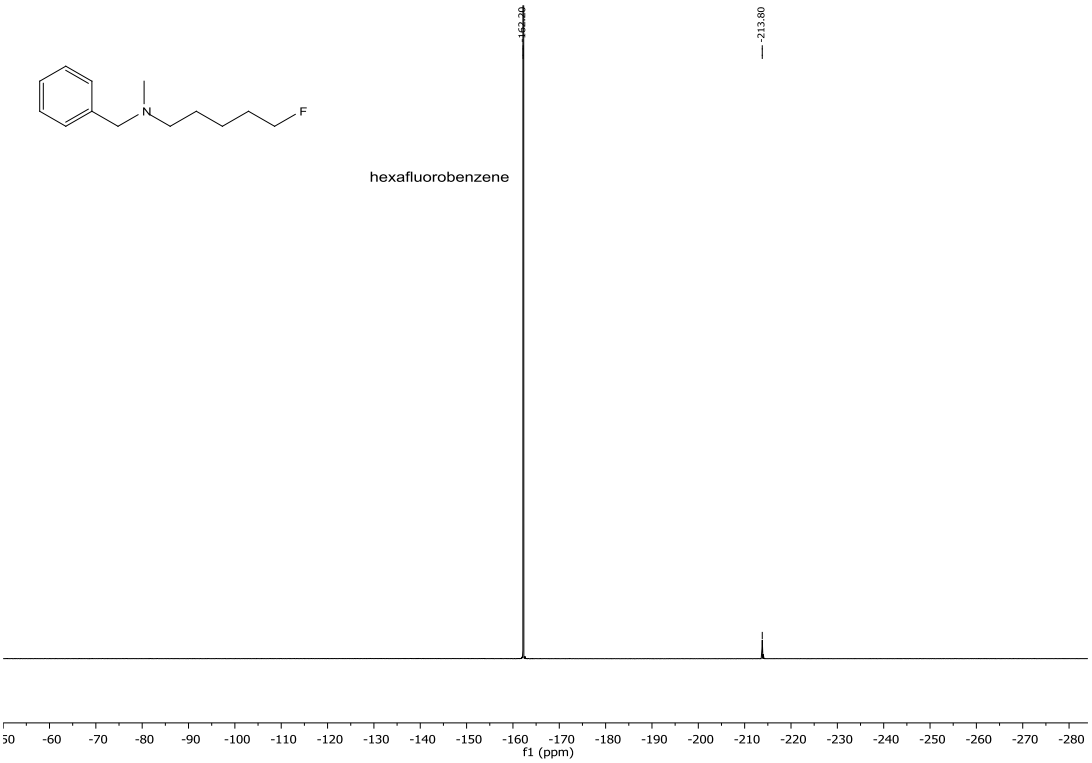
^{1}H NMR *N*-benzyl-5-fluoro-*N*-methylpentan-1-amine (1d)



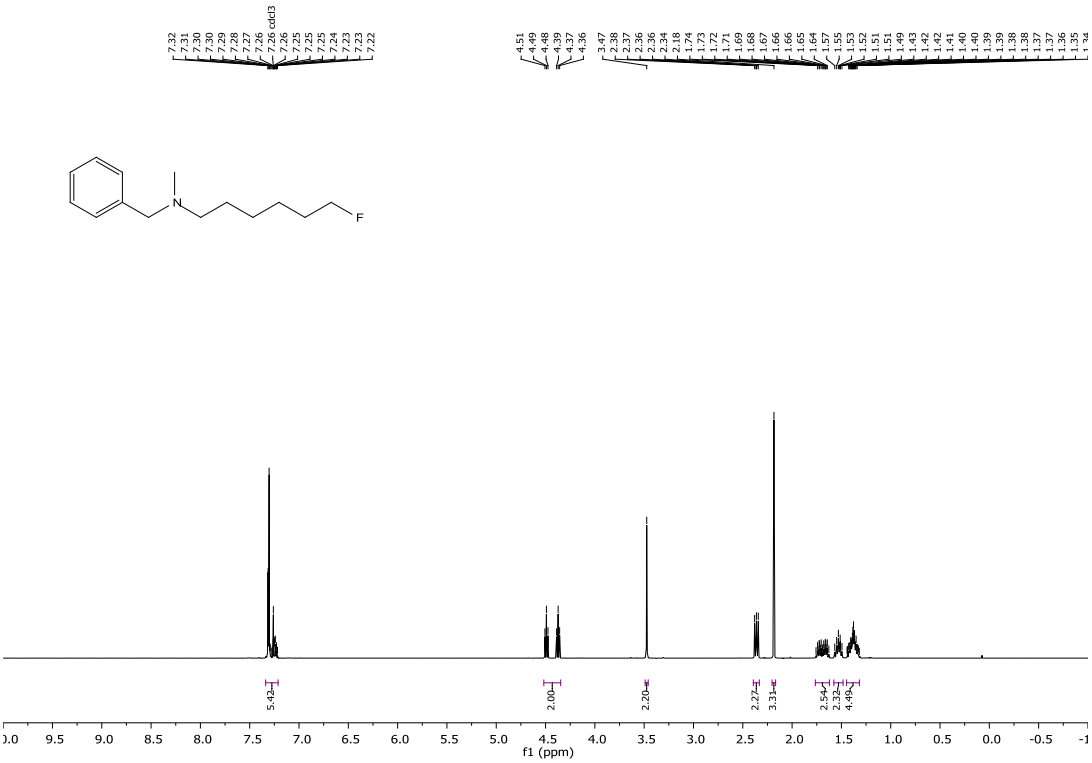
^{13}C NMR *N*-benzyl-5-fluoro-*N*-methylpentan-1-amine (1d)



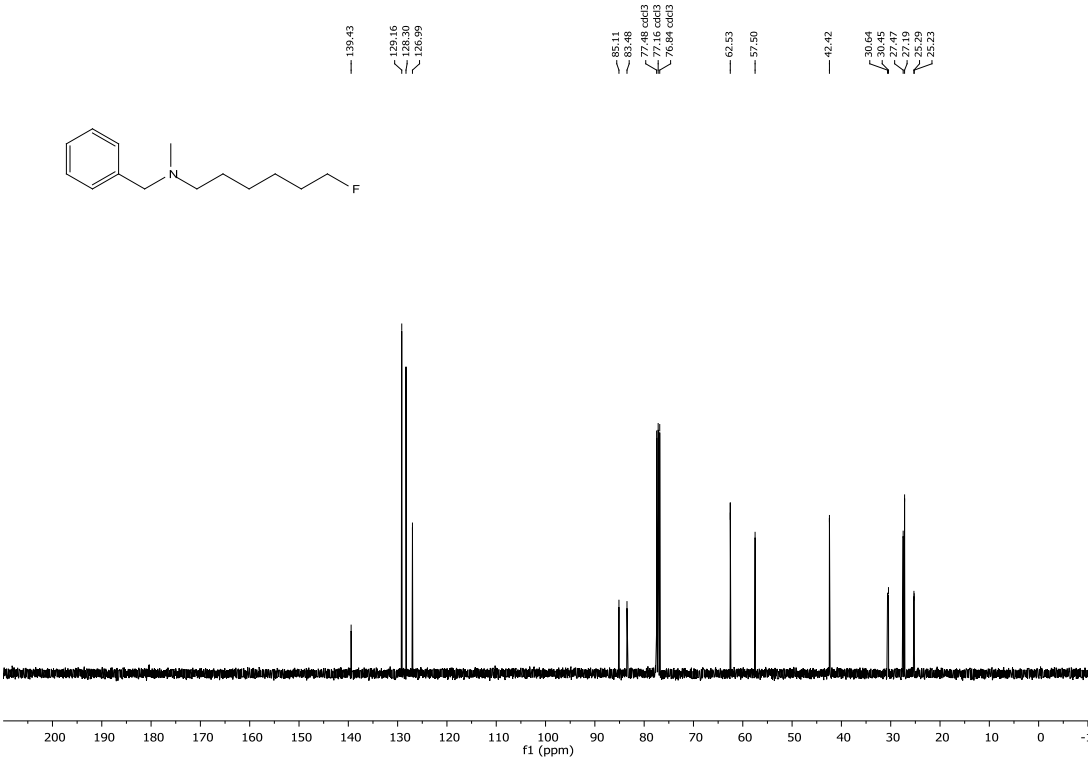
^{19}F NMR *N*-benzyl-5-fluoro-*N*-methylpentan-1-amine (1d)



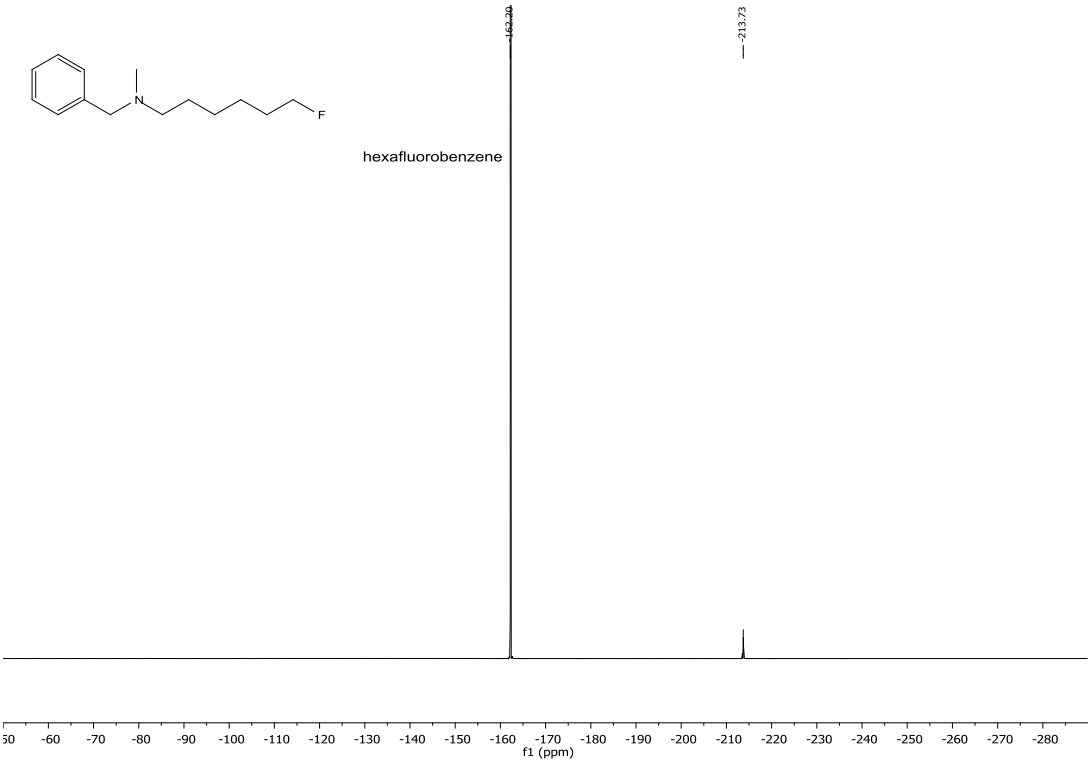
^{1}H NMR *N*-benzyl-6-fluoro-*N*-methylhexan-1-amine (1e)



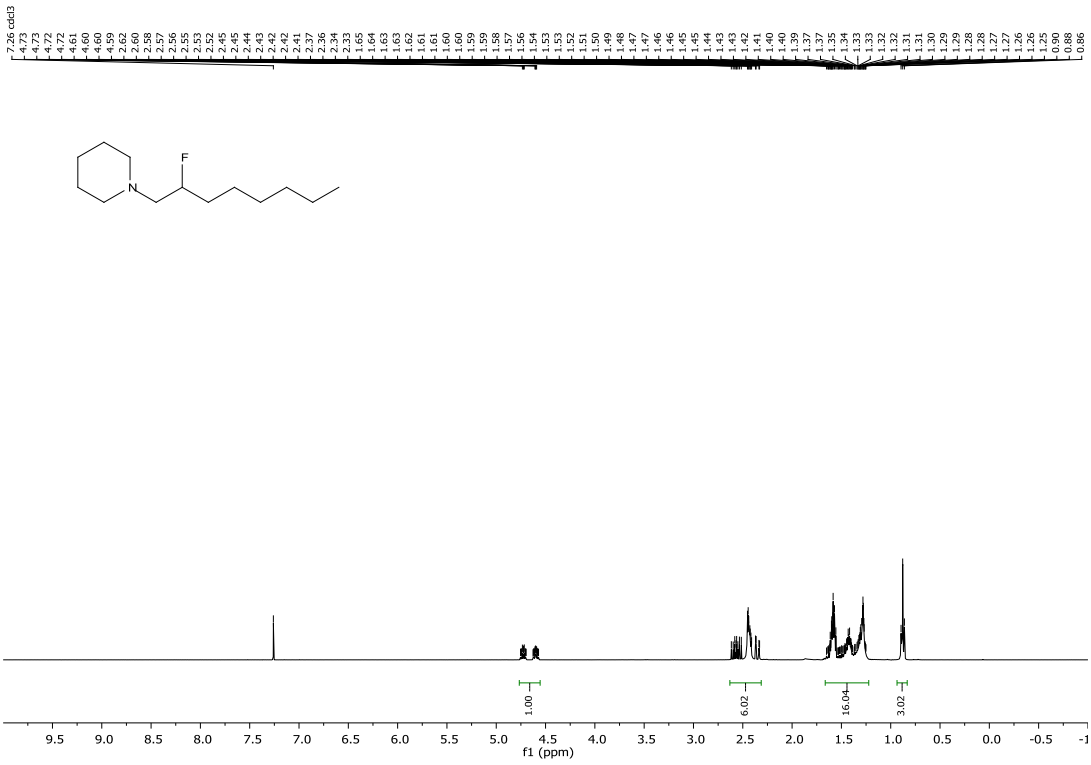
^{13}C NMR *N*-benzyl-6-fluoro-*N*-methylhexan-1-amine (1e)



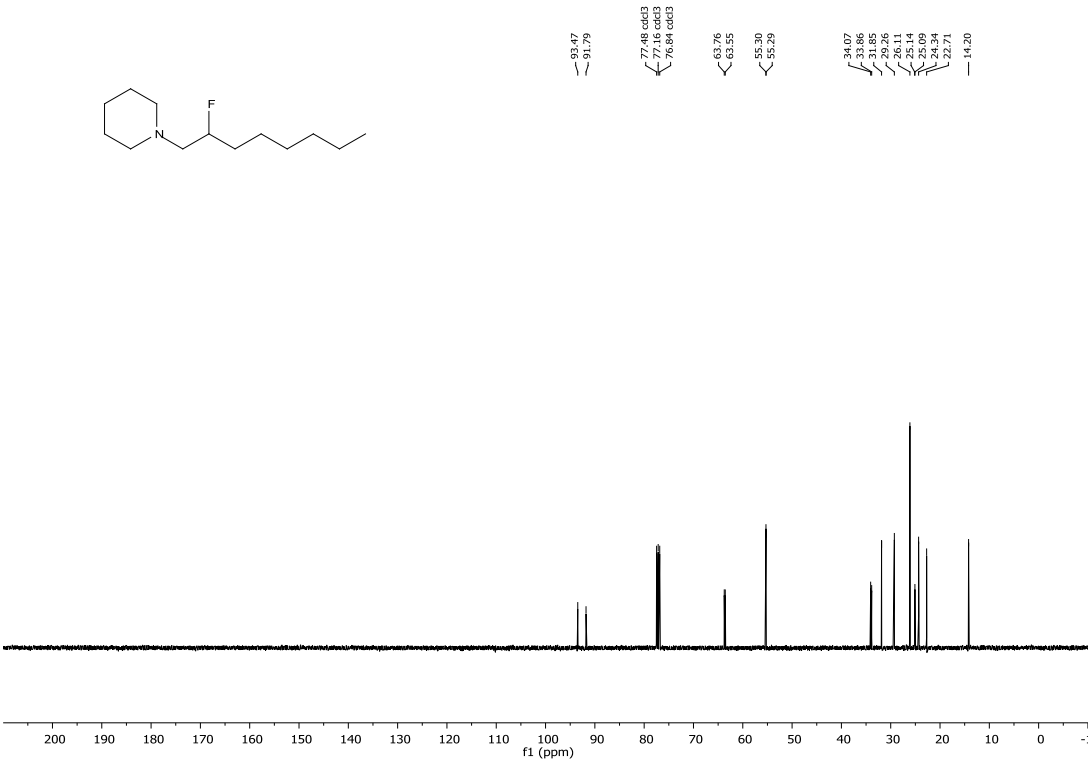
^{19}F NMR *N*-benzyl-6-fluoro-*N*-methylhexan-1-amine (1e)



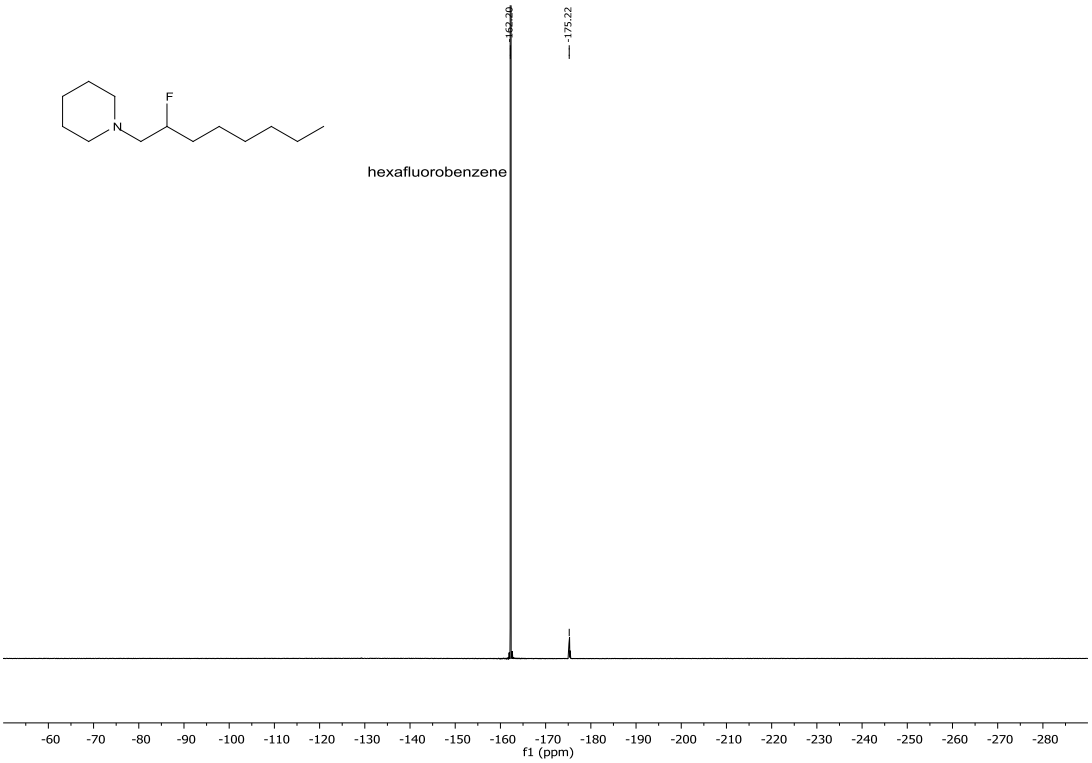
^{1}H NMR 1-(2-fluorooctyl)piperidine (1g)



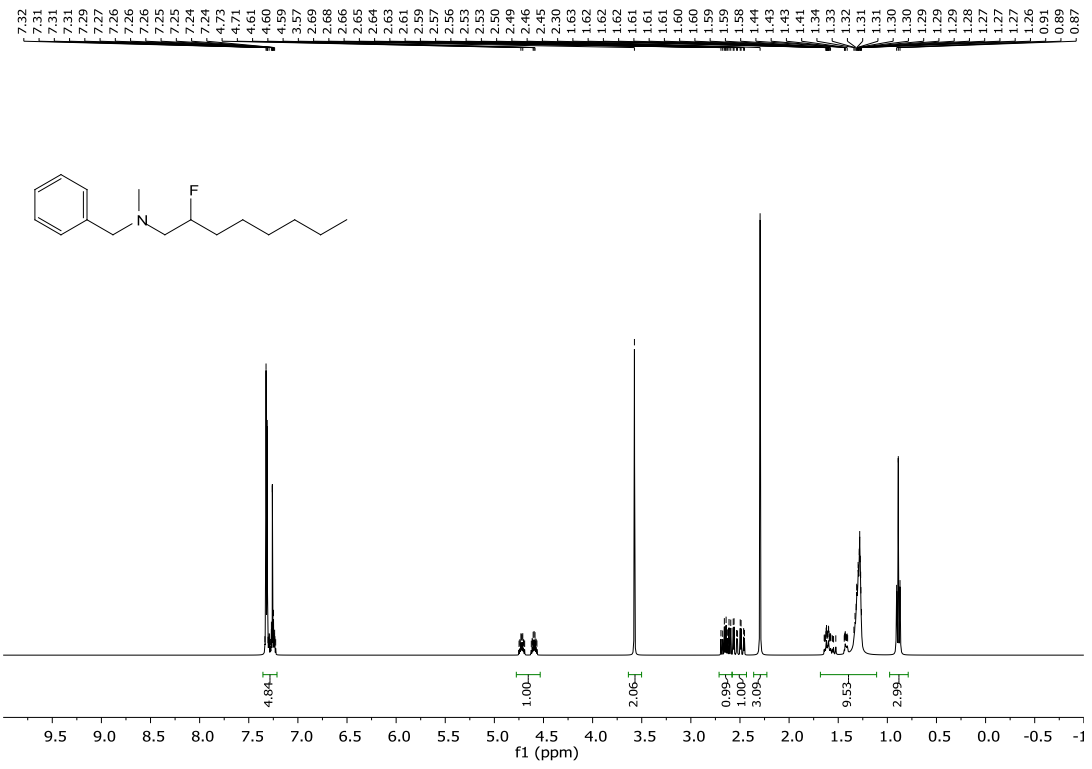
^{13}C NMR 1-(2-fluorooctyl)piperidine (1g)



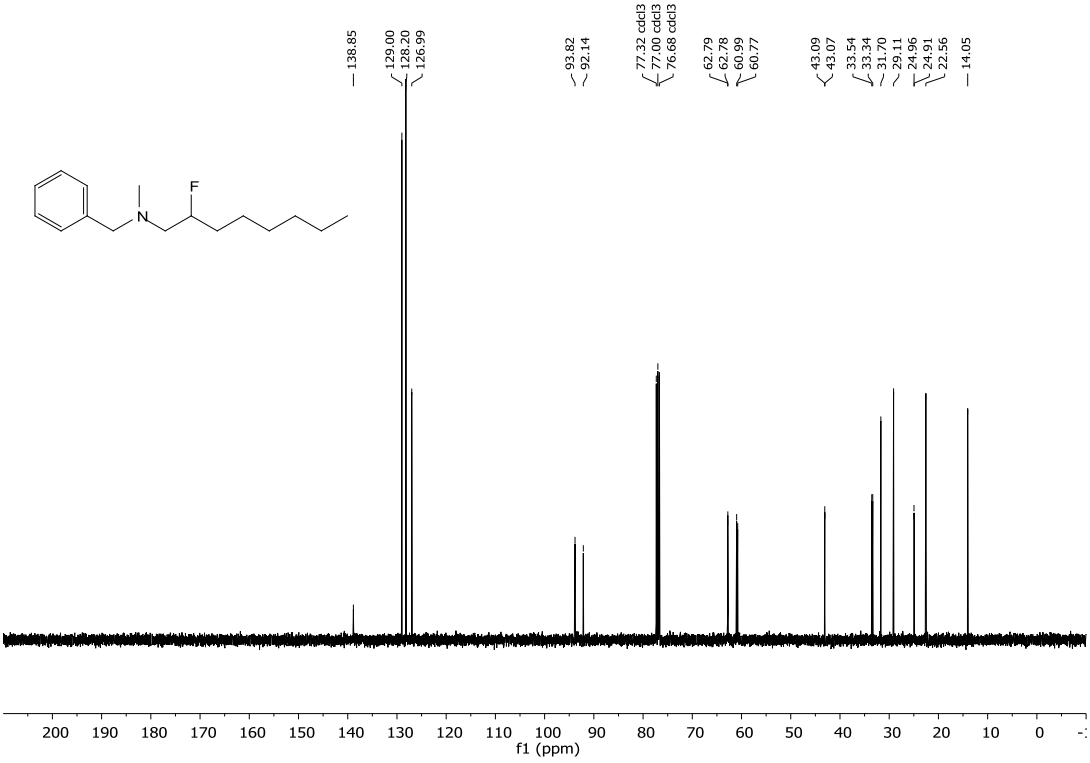
^{19}F NMR 1-(2-fluorooctyl)piperidine (1g)



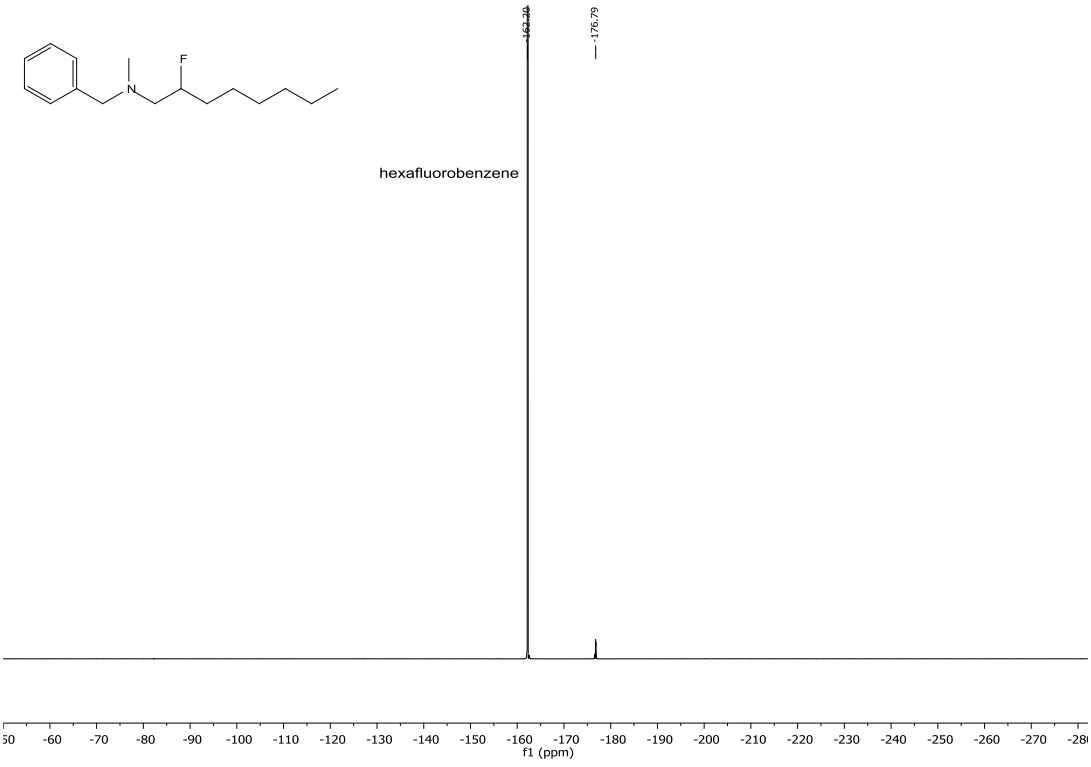
^{1}H NMR *N*-benzyl-2-fluoro-*N*-methyloctan-1-amine (1f)



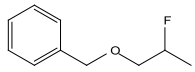
^{13}C NMR *N*-benzyl-2-fluoro-*N*-methyloctan-1-amine (1f)

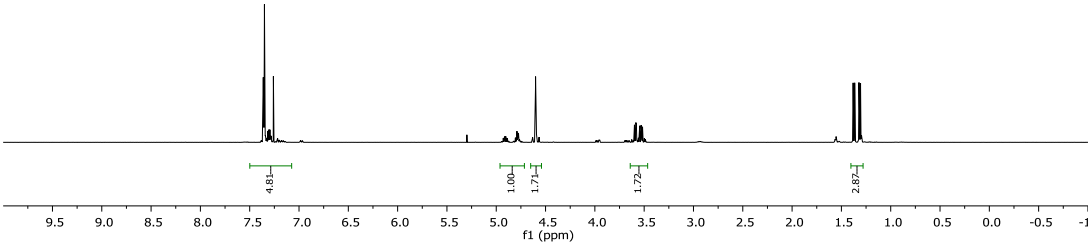


^{19}F NMR *N*-benzyl-2-fluoro-*N*-methyloctan-1-amine (1f)

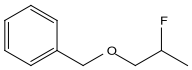


^{1}H NMR 2-fluorooctyl benzyl ether (5b)

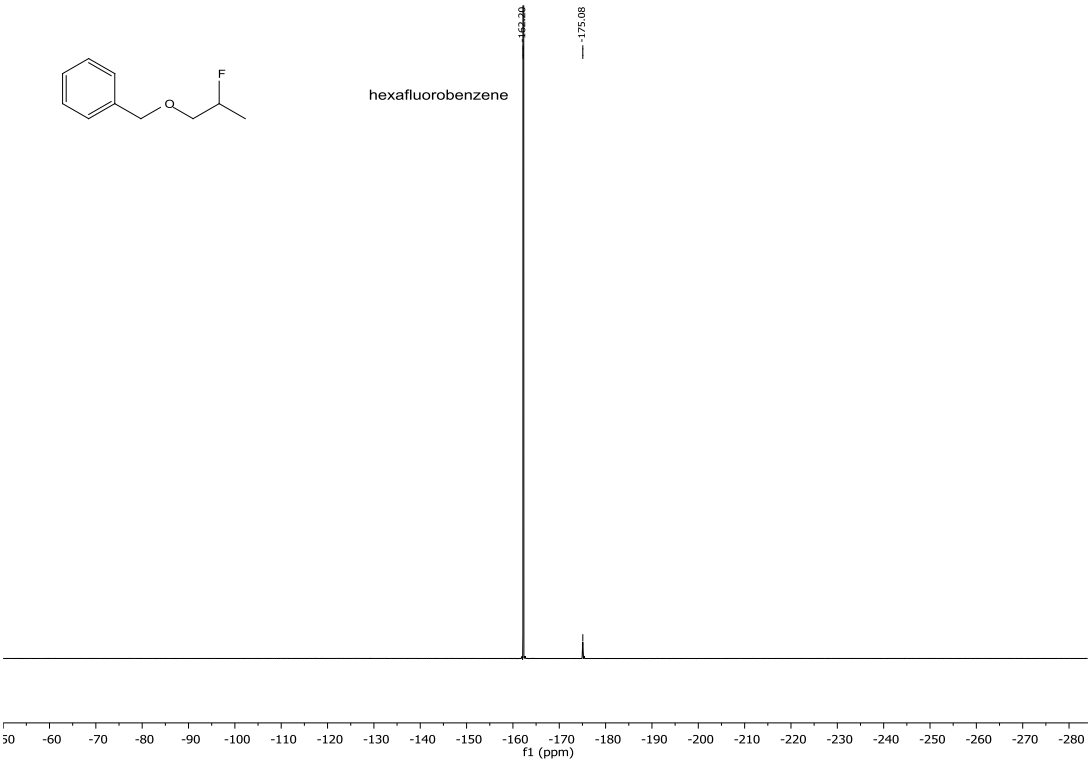




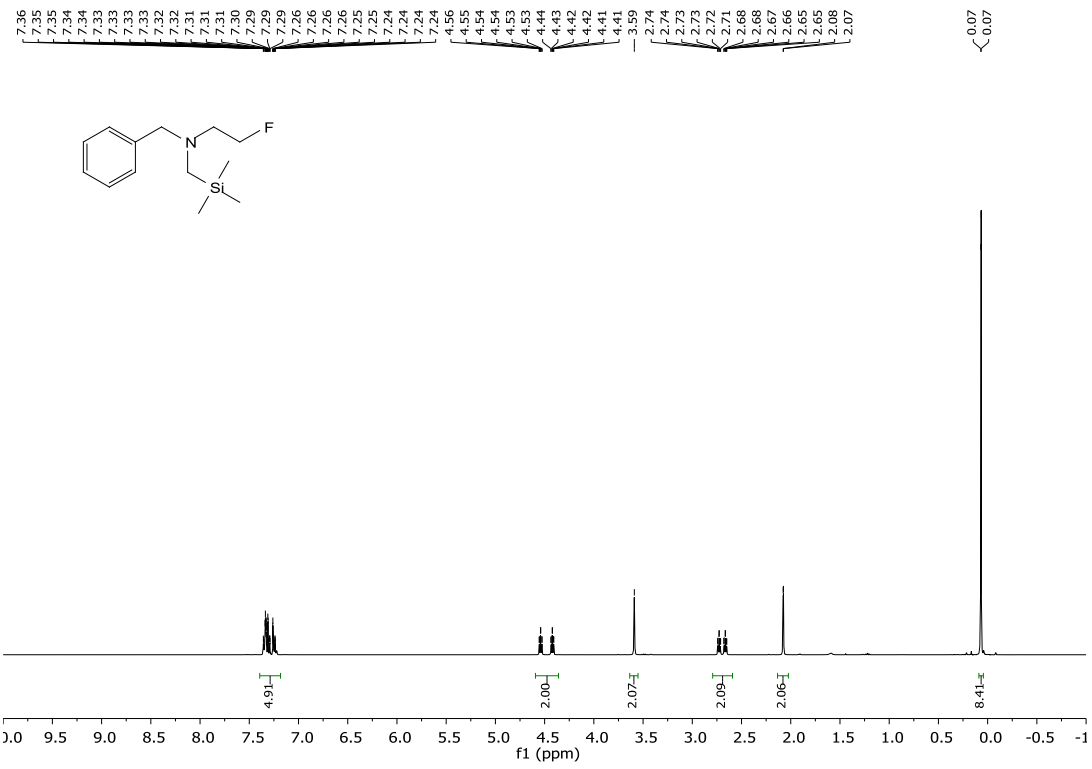
^{13}C NMR 2-fluorooctyl benzyl ether (5b)



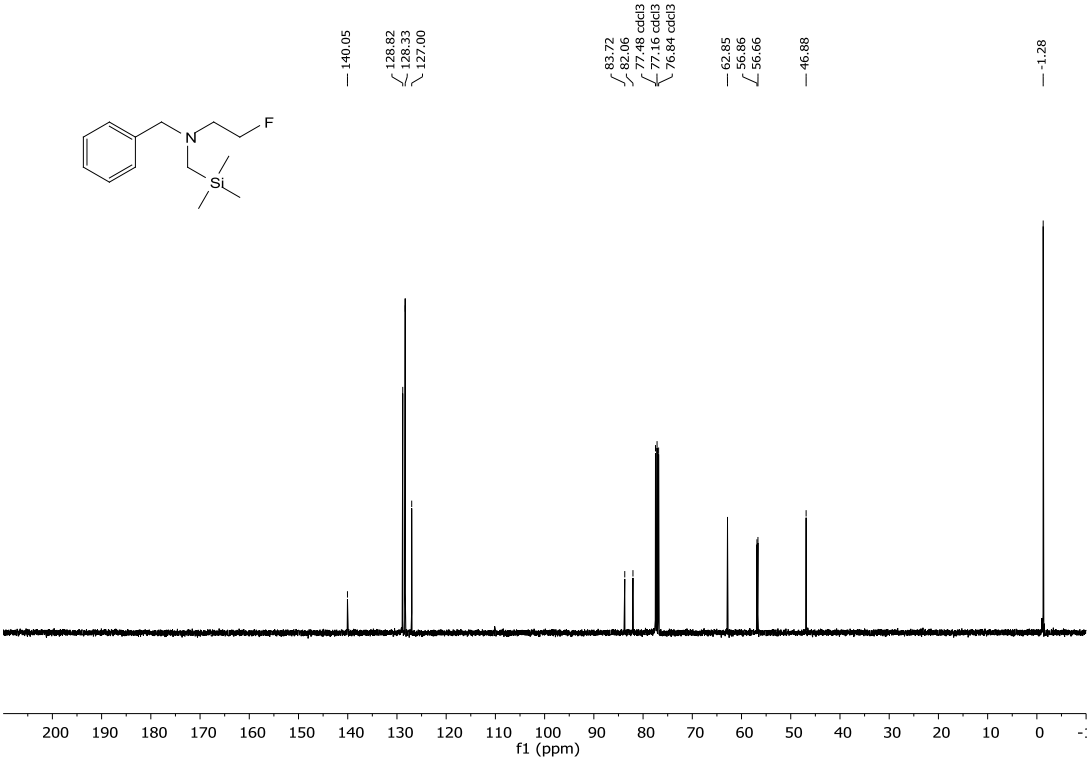
^{19}F NMR 2-fluorooctyl benzyl ether (5b)



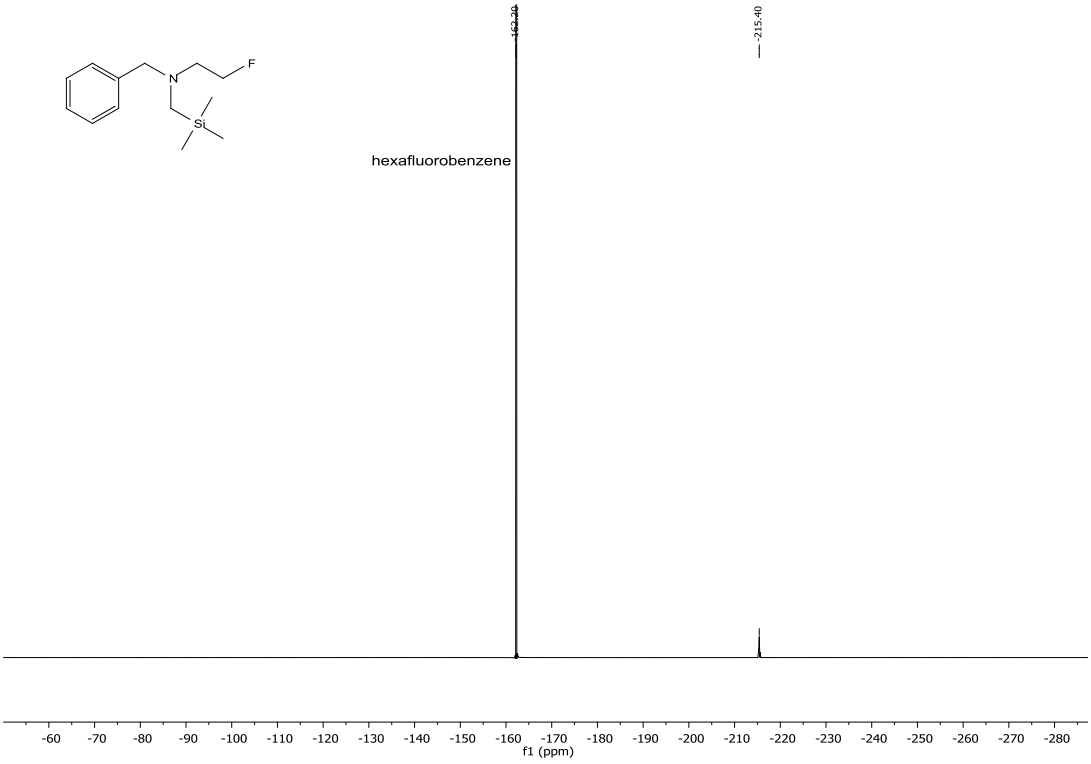
^{1}H NMR *N*-benzyl-2-fluoro-*N*-((trimethylsilyl)methyl)ethan-1-amine (1i)



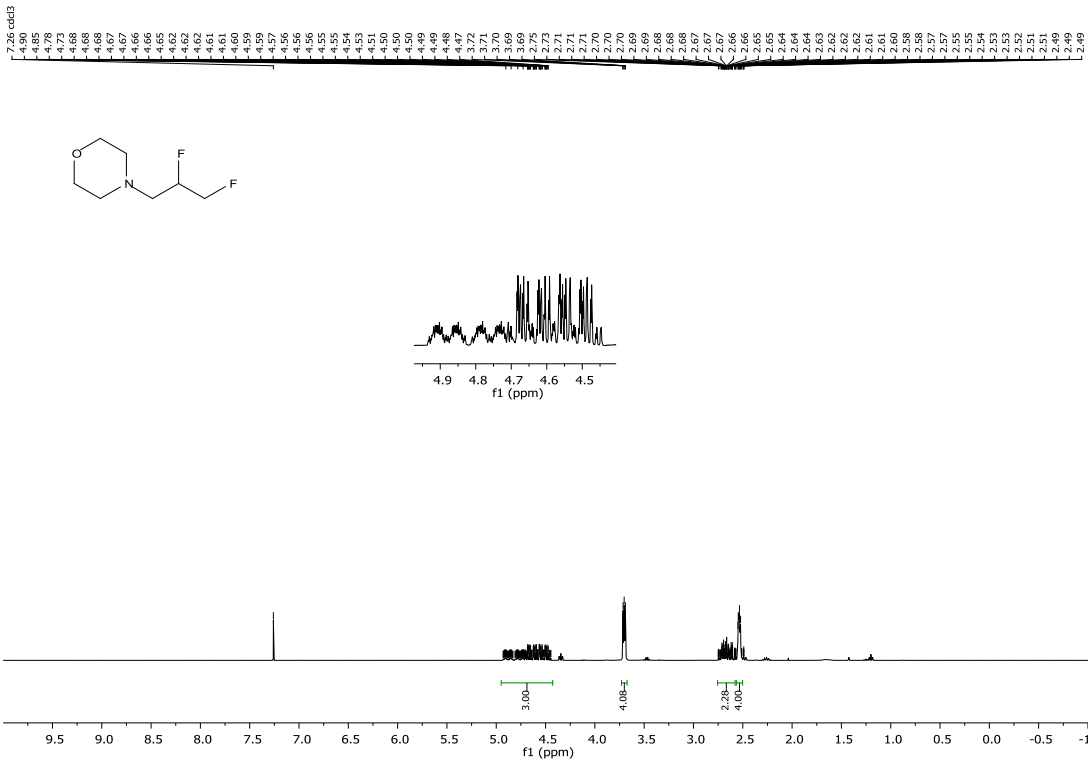
^{13}C NMR *N*-benzyl-2-fluoro-*N*-((trimethylsilyl)methyl)ethan-1-amine (1i)



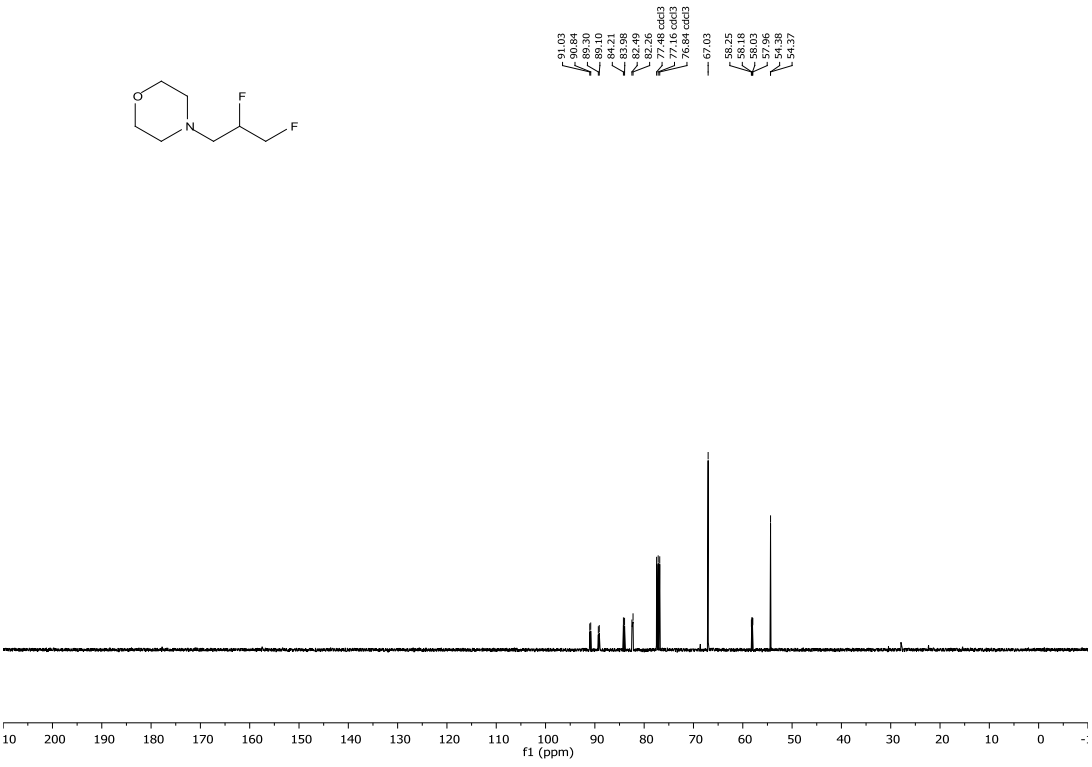
^{19}F NMR *N*-benzyl-2-fluoro-*N*-((trimethylsilyl)methyl)ethan-1-amine (1i)



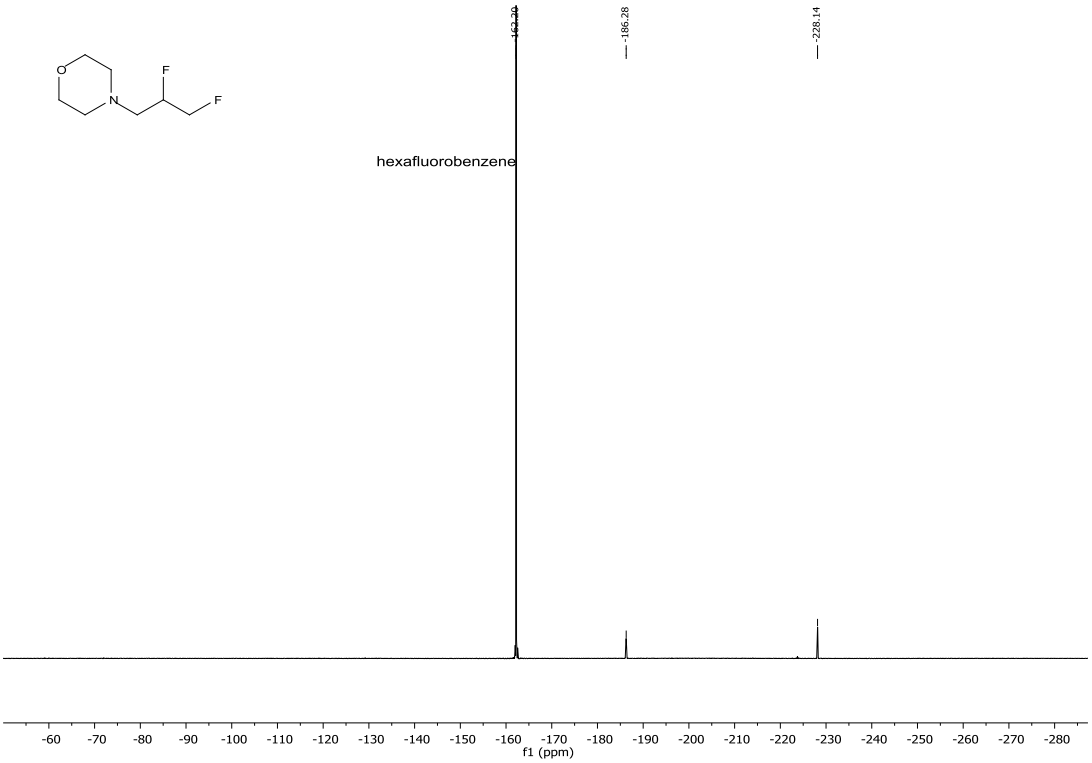
^{1}H NMR 4-(2,3-difluoropropyl)morpholine (1j)



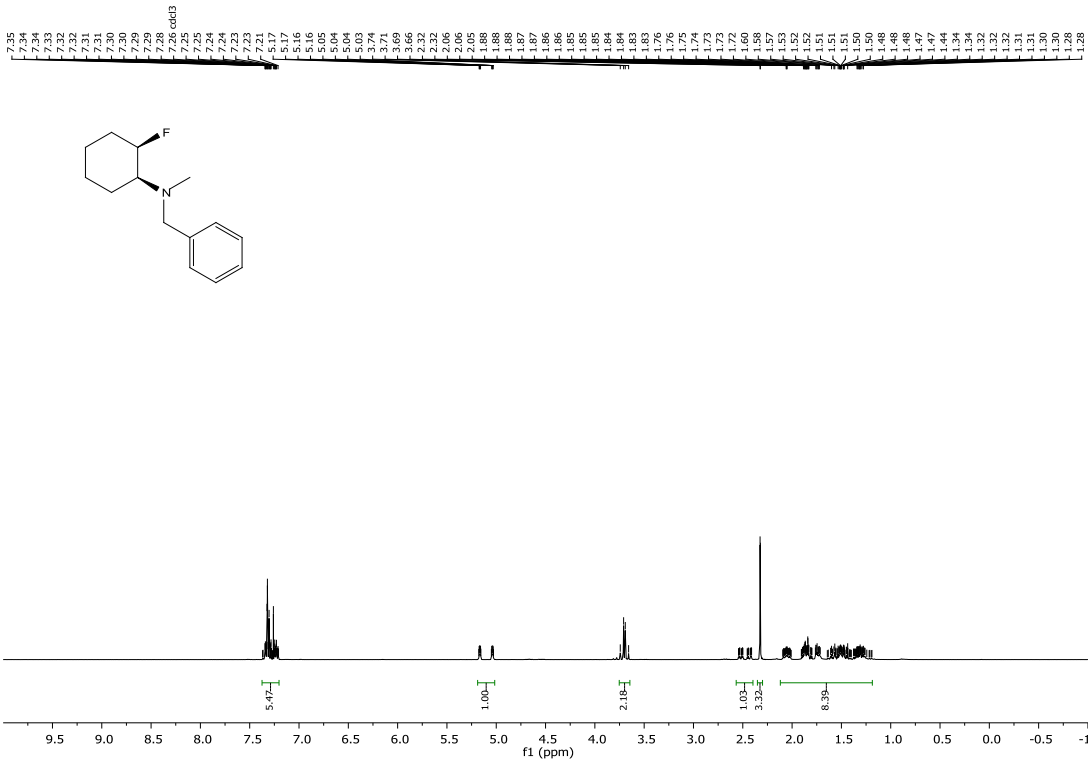
^{13}C NMR 4-(2,3-difluoropropyl)morpholine (1j)



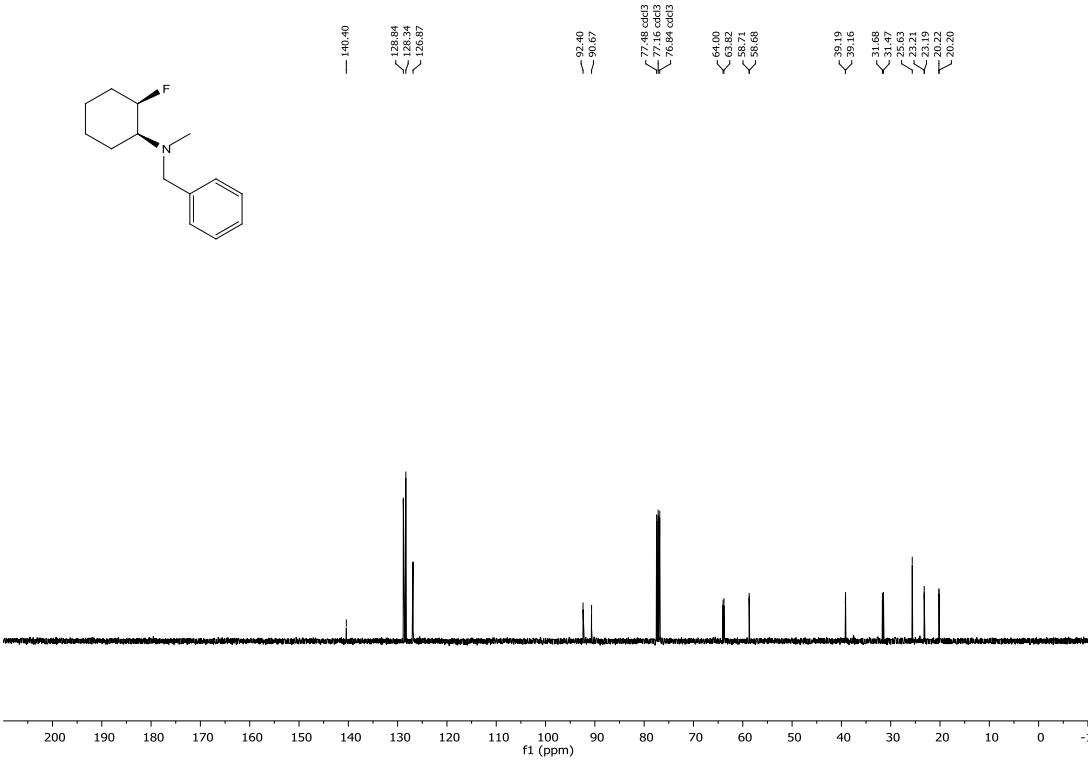
^{19}F NMR 4-(2,3-difluoropropyl)morpholine (1j)



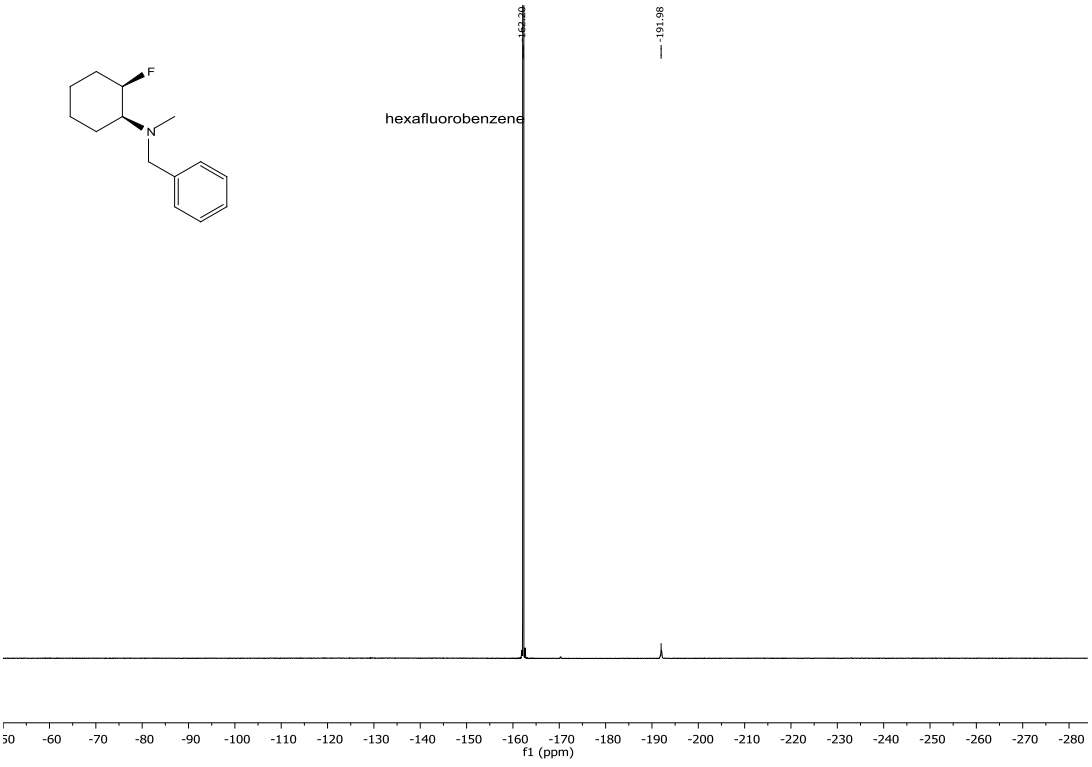
^{1}H NMR (1*S*,2*R*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*syn*-1l)



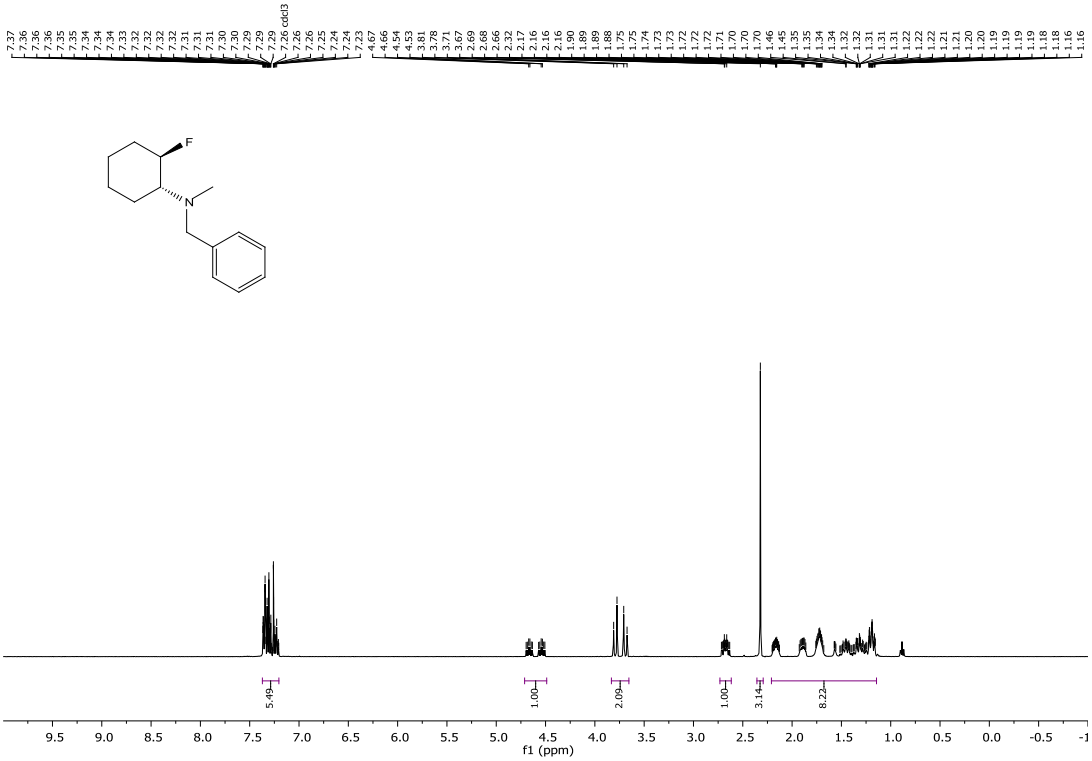
^{13}C NMR (1*S*,2*R*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*syn*-1l)



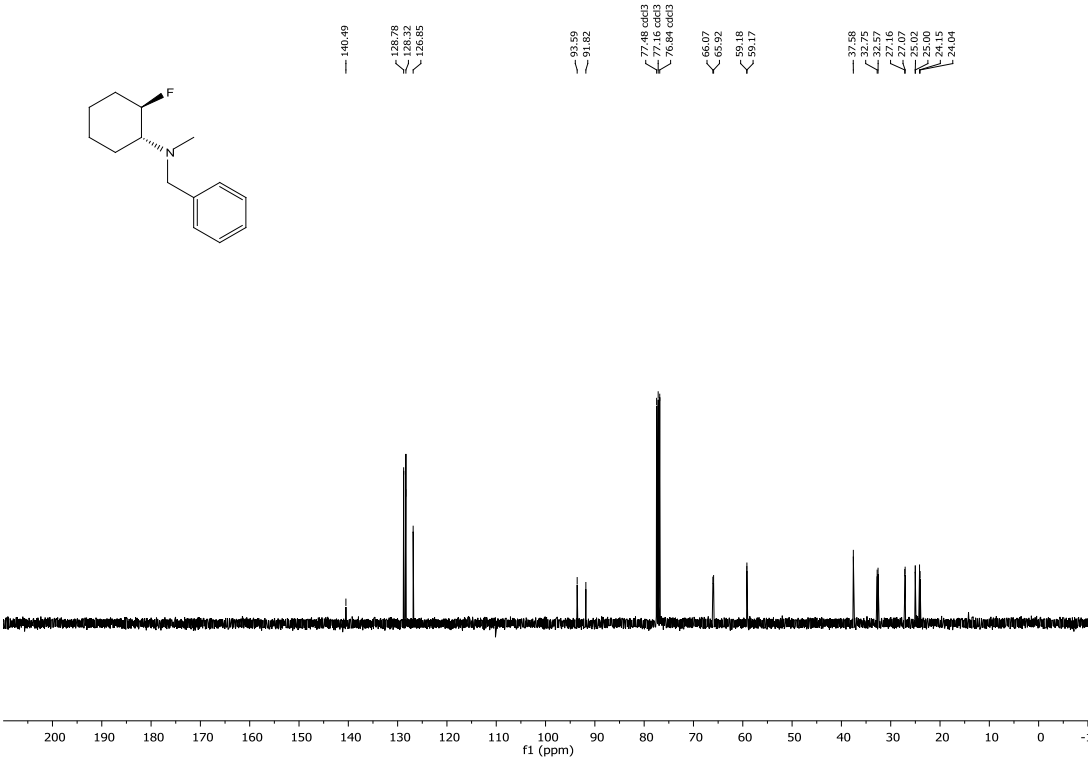
^{19}F NMR (1*S*,2*R*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*syn*-1l)



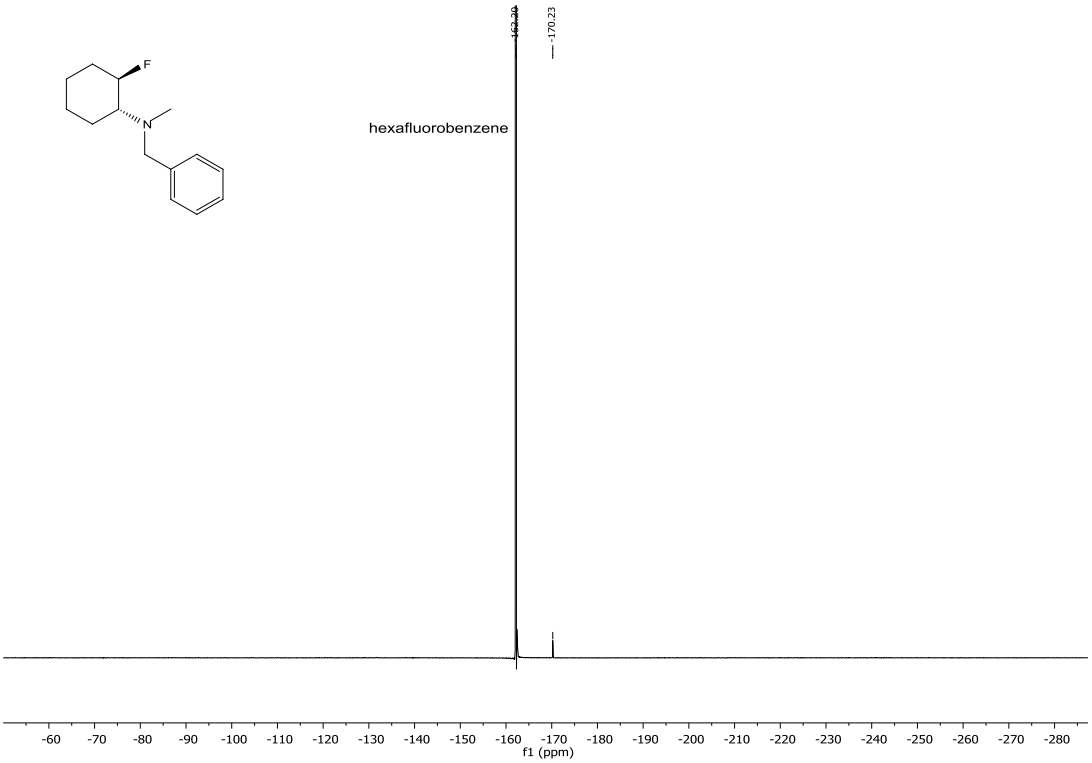
^{1}H NMR (1*S*,2*S*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*anti*-1l)



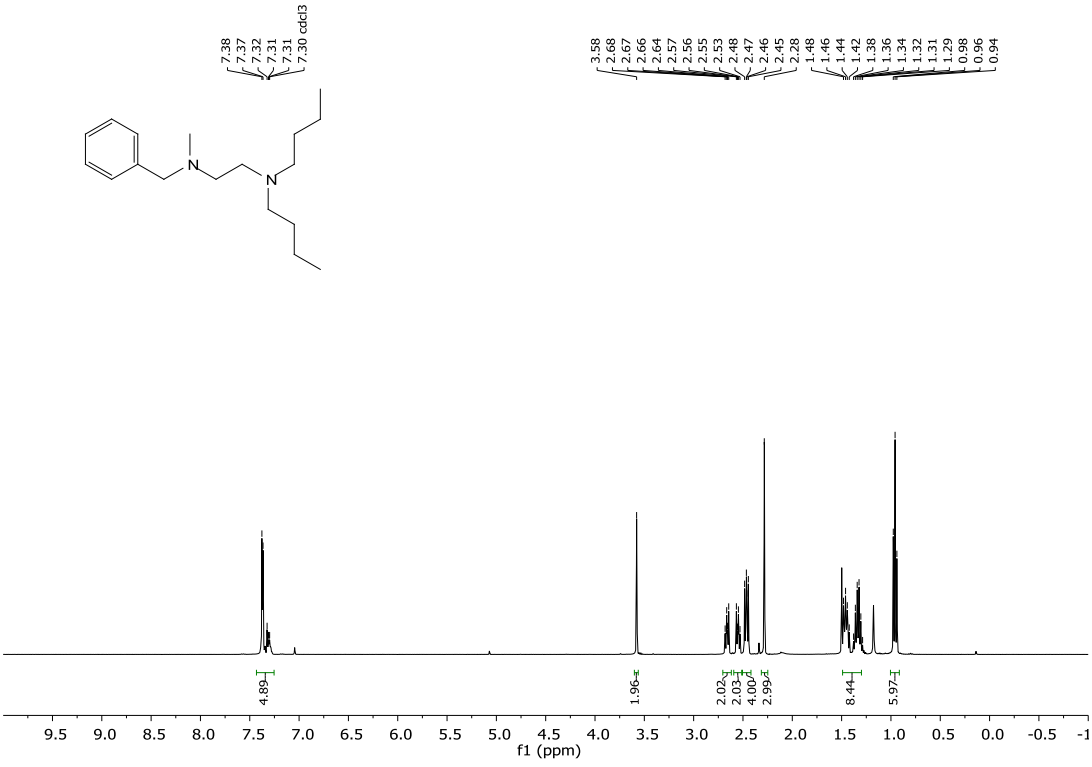
^{13}C NMR (1*S*,2*S*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*anti*-1l)



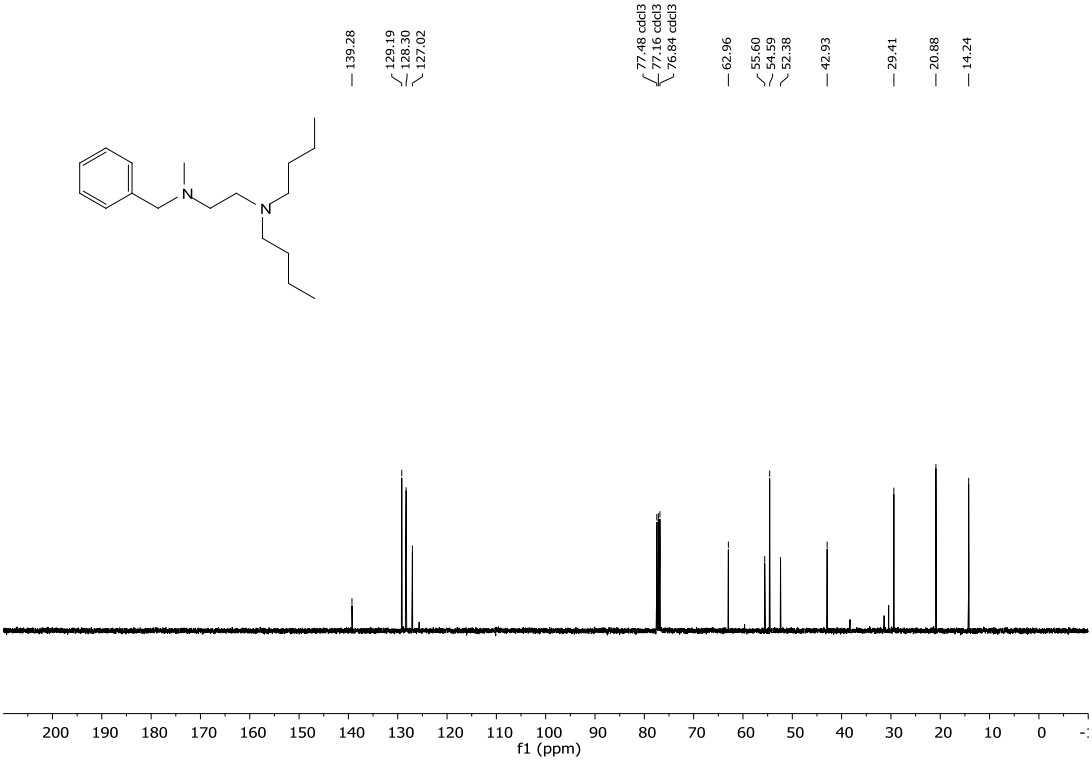
^{19}F NMR (1*S*,2*S*)-*N*-benzyl-2-fluoro-*N*-methylcyclohexan-1-amine (*anti*-1l)



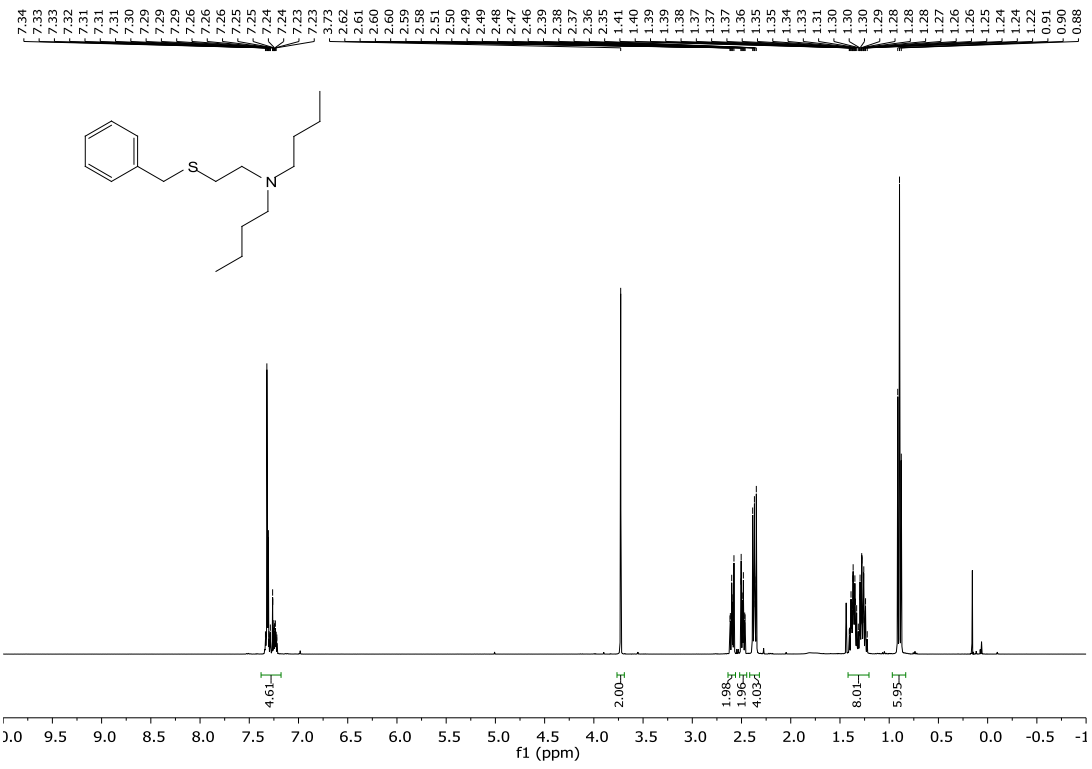
^{1}H NMR *N*1-benzyl-*N*2,*N*2-dibutyl-*N*1-methylethane-1,2-diamine (2a)



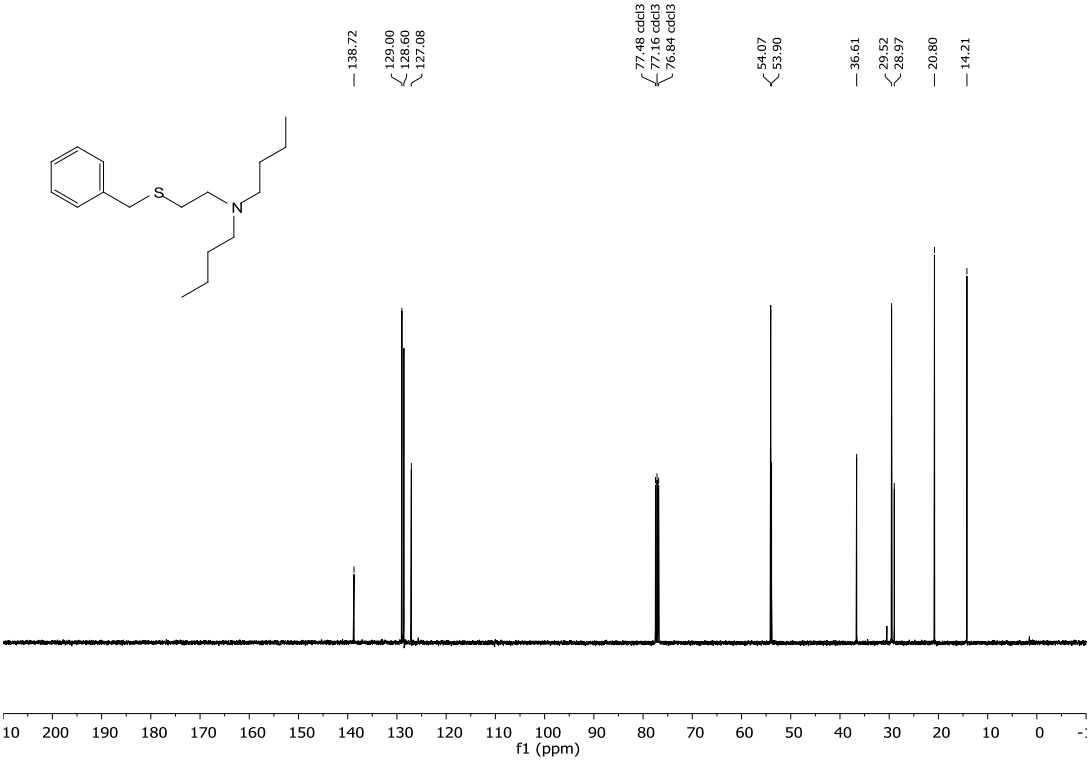
^{13}C NMR *N*1-benzyl-*N*2,*N*2-dibutyl-*N*1-methylethane-1,2-diamine (2a)



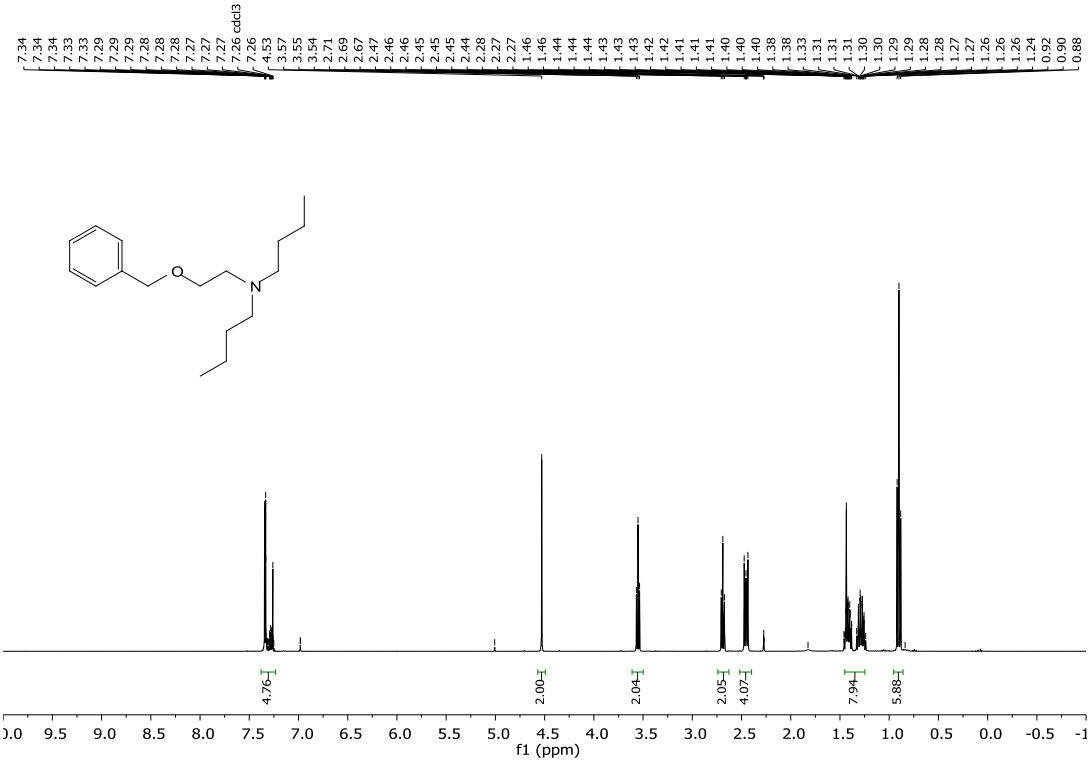
^{1}H NMR *N*-(2-(benzylthio)ethyl)-*N*-butylbutan-1-amine (4)



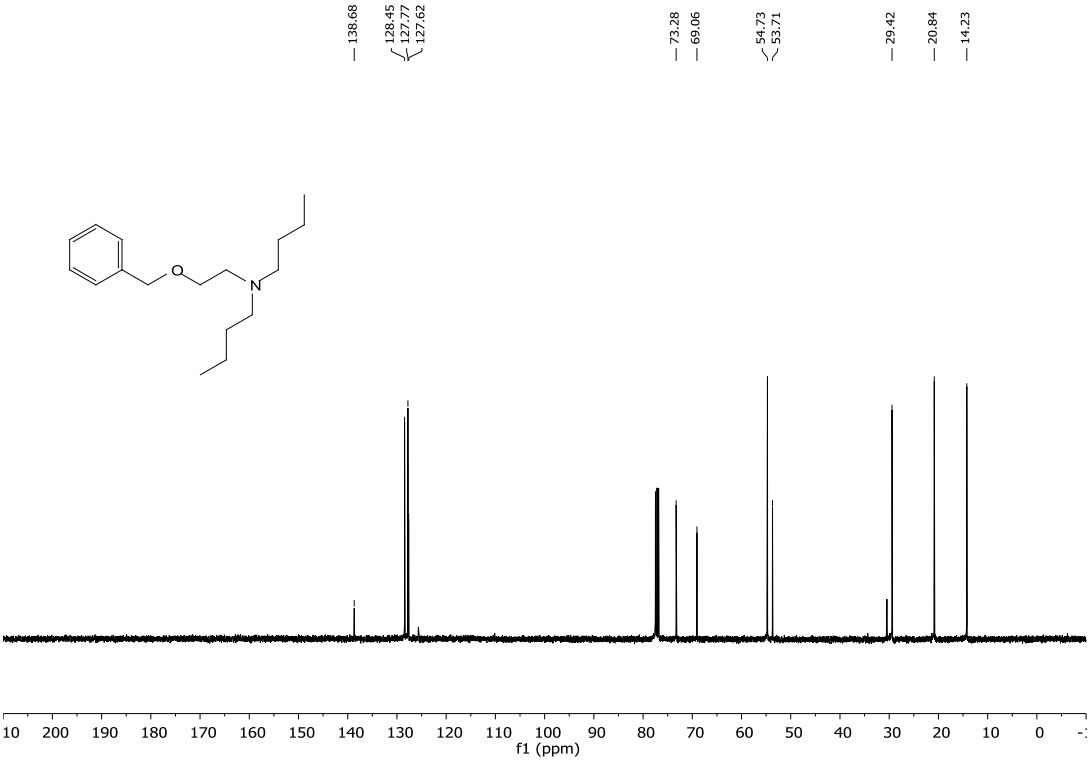
^{13}C NMR *N*-(2-(benzylthio)ethyl)-*N*-butylbutan-1-amine (4)



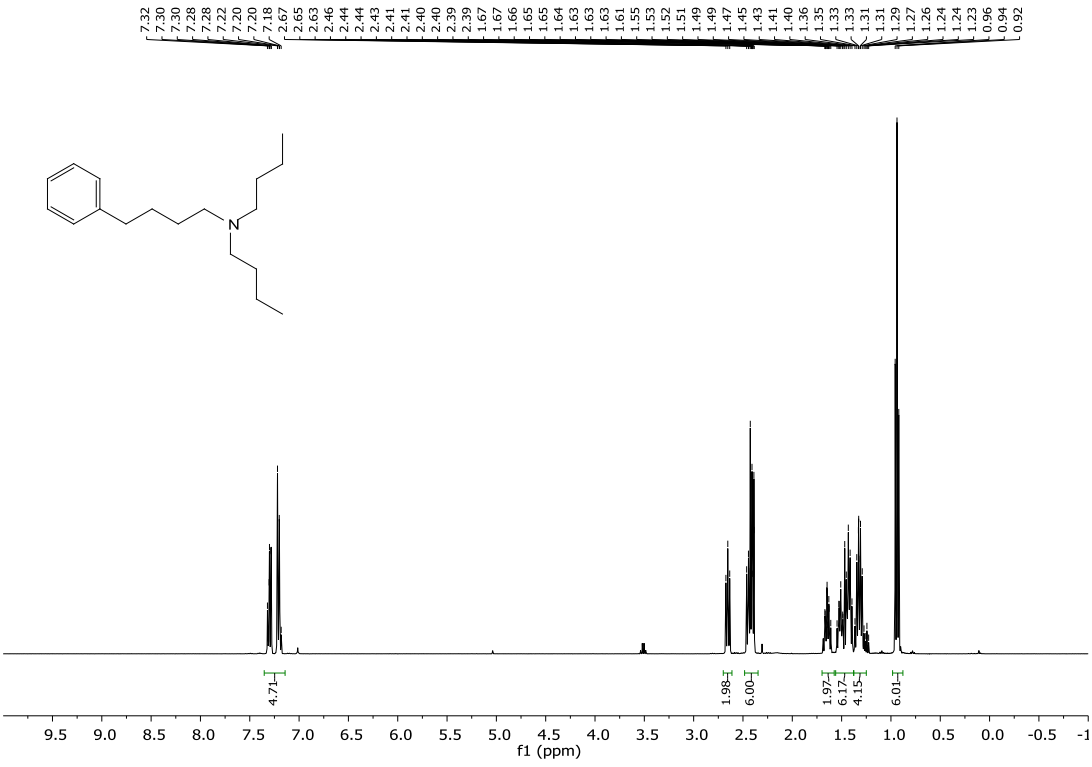
^{1}H NMR *N*-(2-(benzyloxy)ethyl)-*N*-butylbutan-1-amine (6)



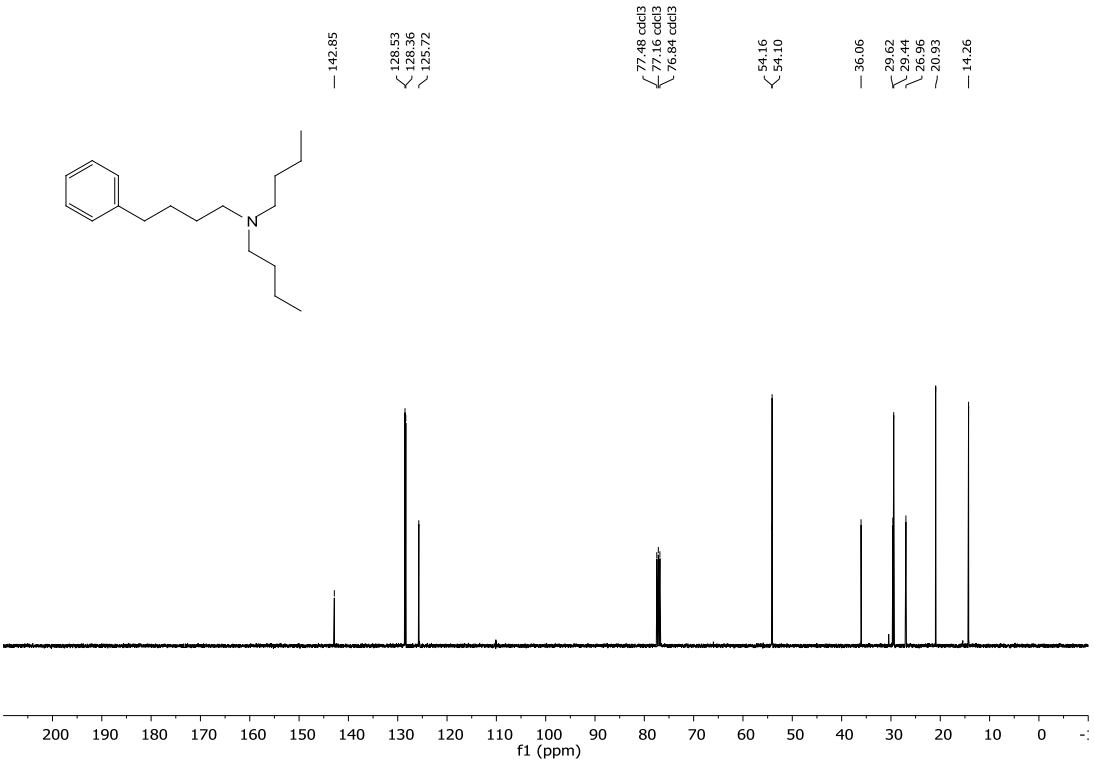
^{13}C NMR *N*-(2-(benzyloxy)ethyl)-*N*-butylbutan-1-amine (6)



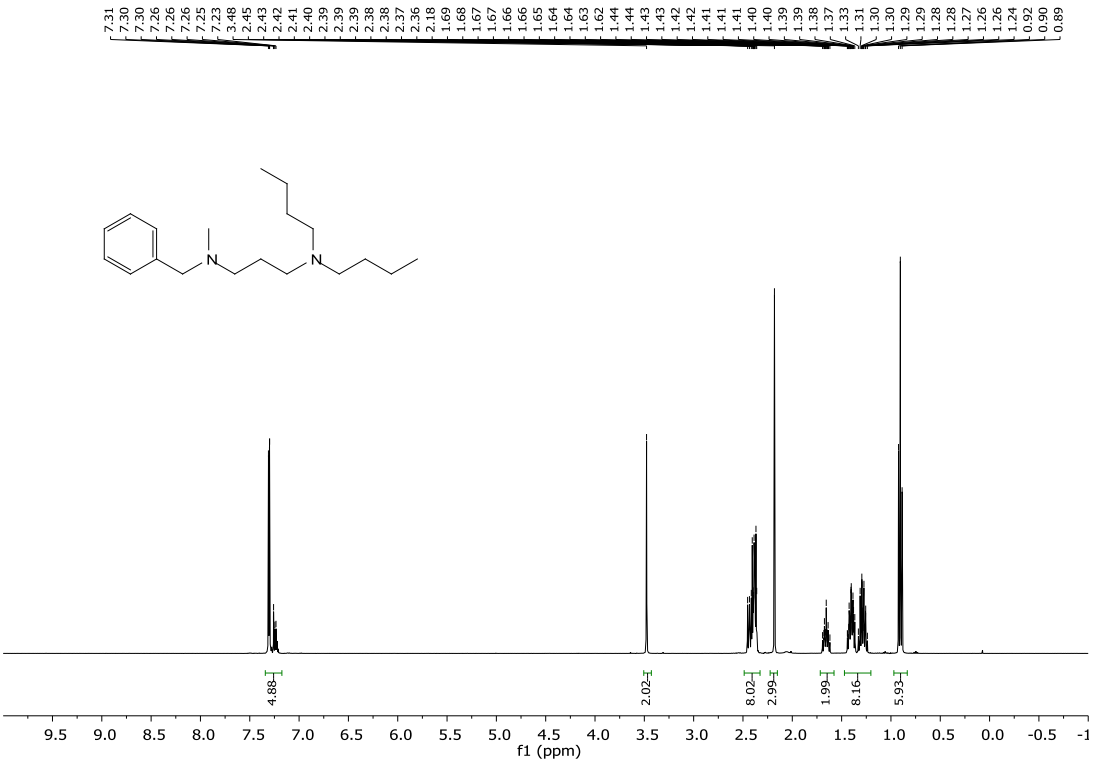
^{1}H NMR *N*,*N*-dibutyl-4-phenylbutan-1-amine (8)



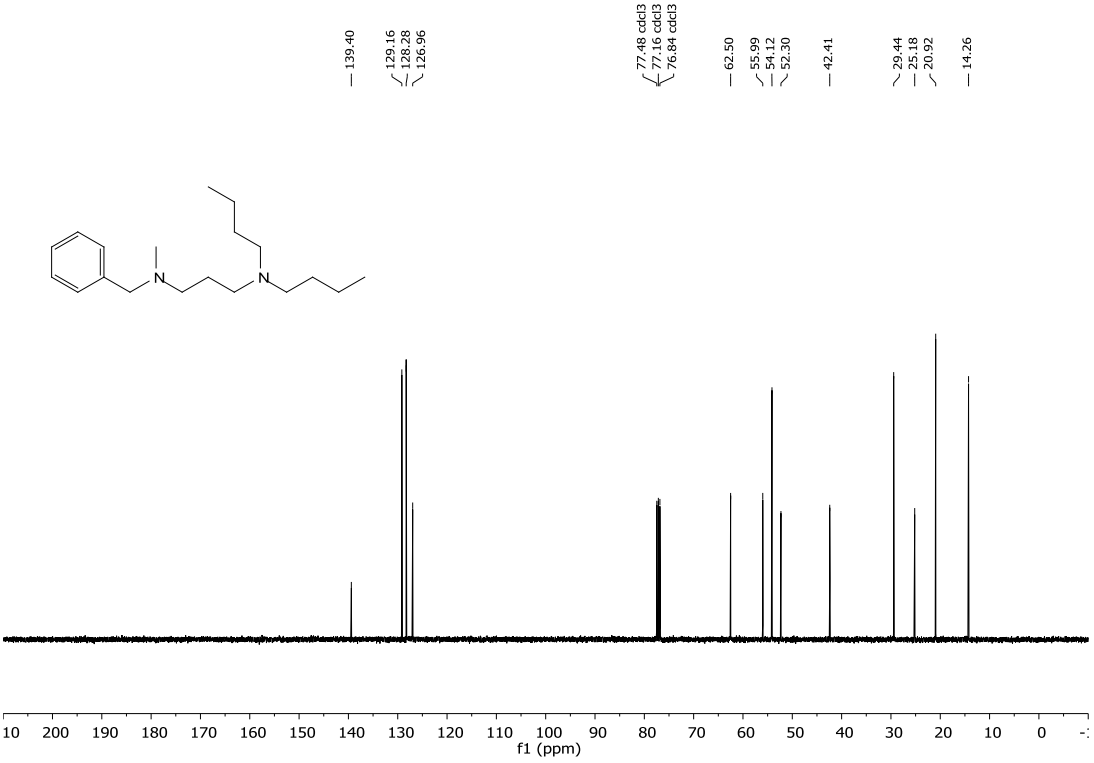
^{13}C NMR *N*,*N*-dibutyl-4-phenylbutan-1-amine (8)



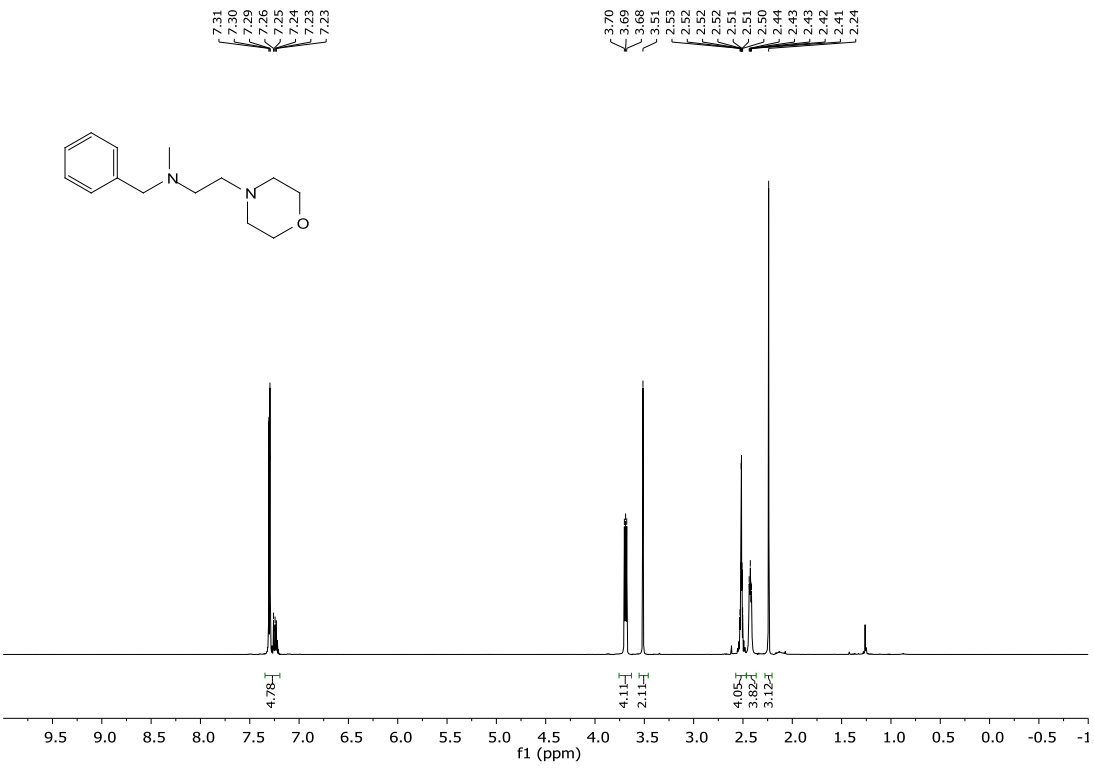
^{1}H NMR *N*1-benzyl-*N*3,*N*3-dibutyl-*N*1-methylpropane-1,3-diamine (2n)



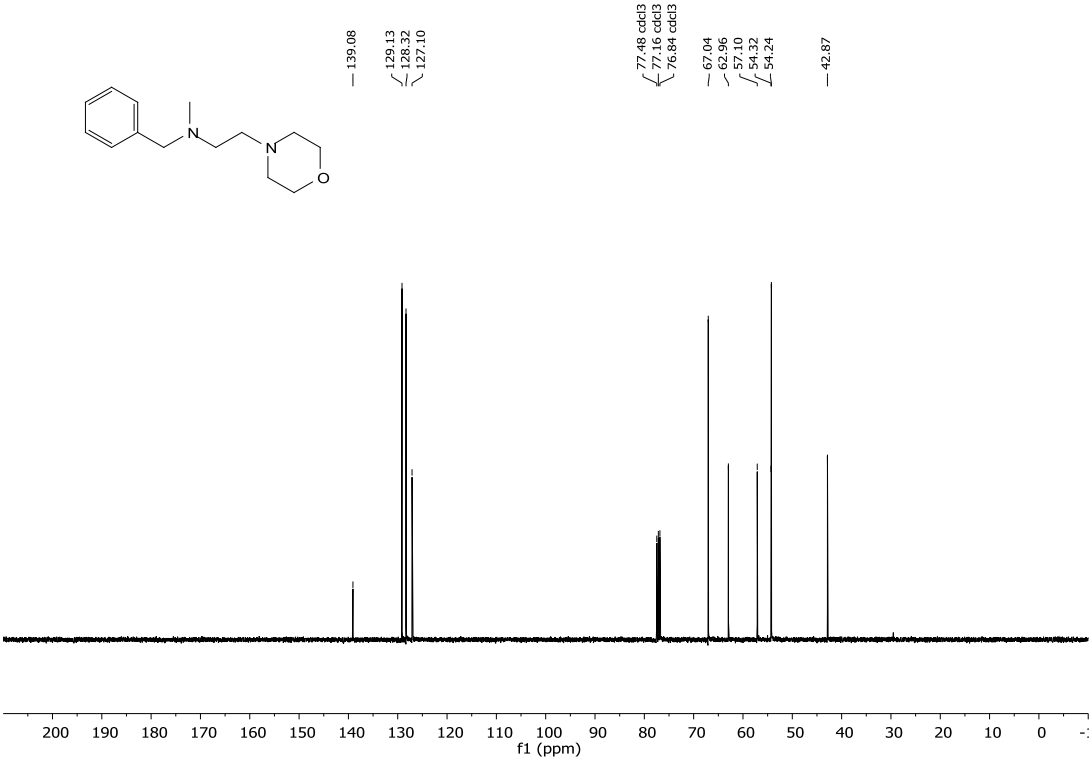
^{13}C NMR *N*1-benzyl-*N*3,*N*3-dibutyl-*N*1-methylpropane-1,3-diamine (2n)



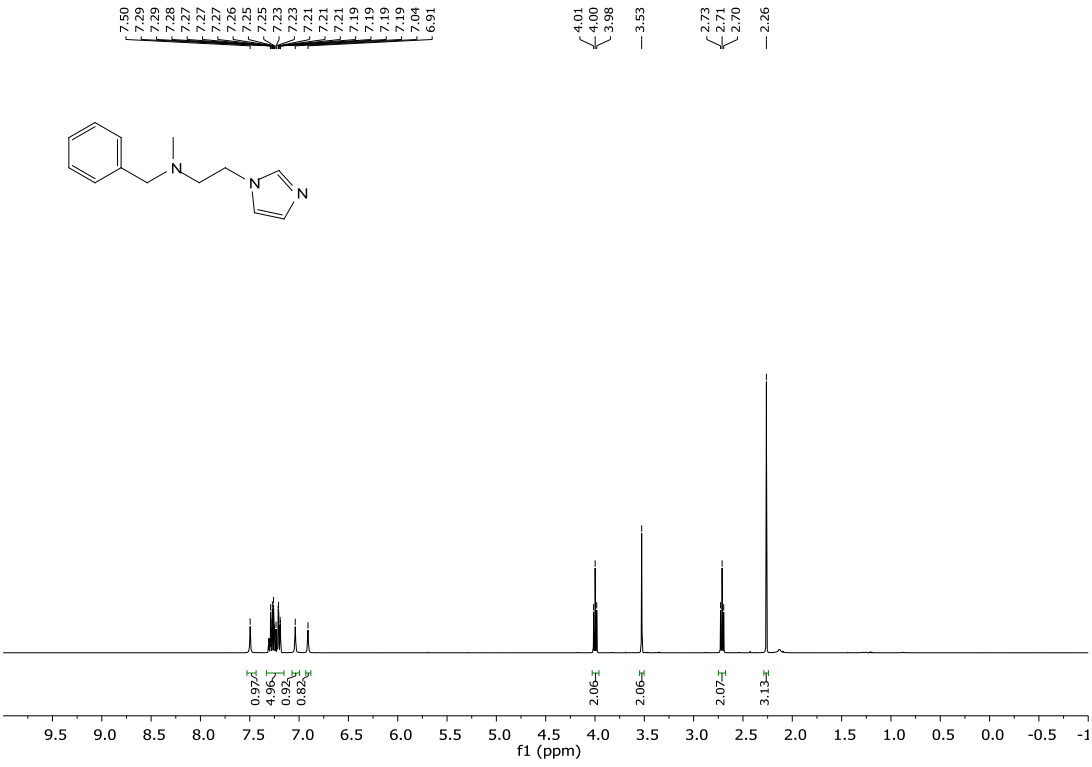
^{1}H NMR *N*-benzyl-*N*-methyl-2-morpholinoethan-1-amine (2b)



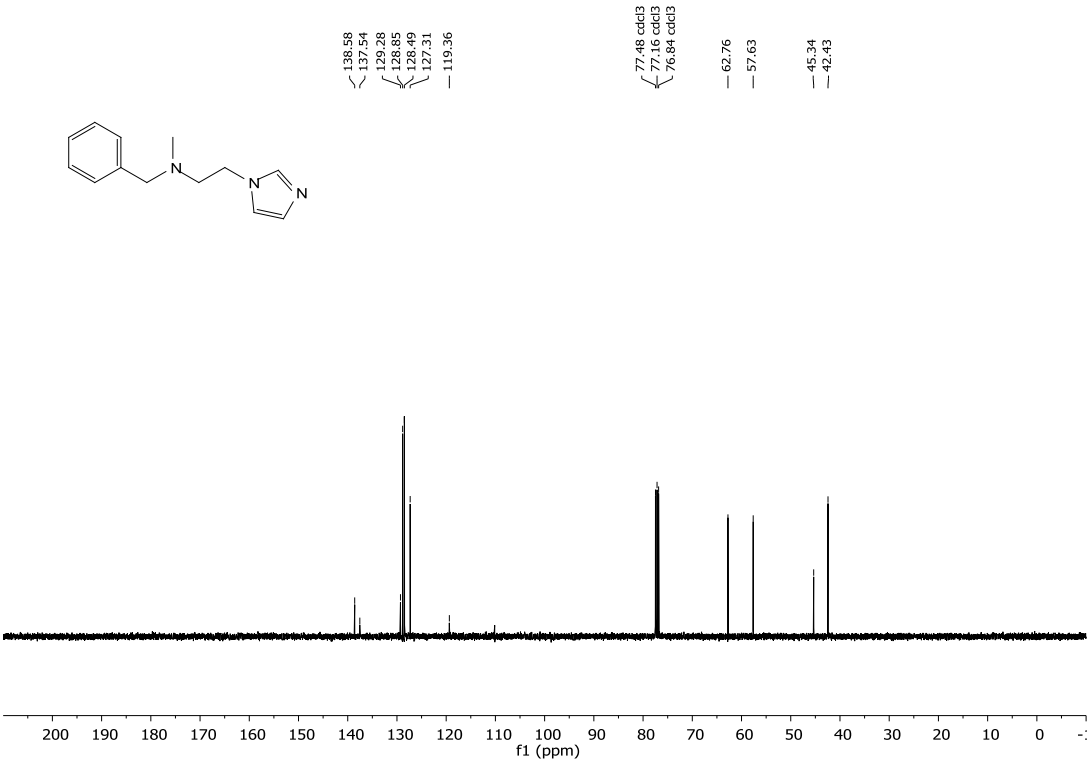
^{13}C NMR *N*-benzyl-*N*-methyl-2-morpholinoethan-1-amine (2b)



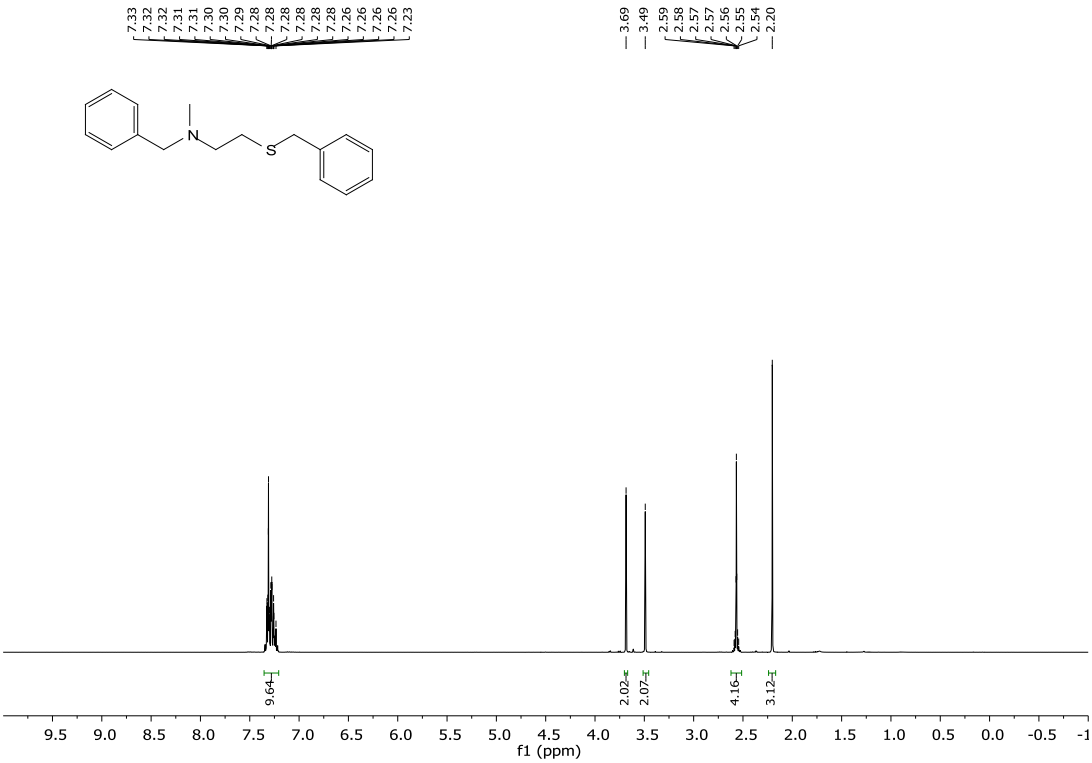
^{1}H NMR *N*-benzyl-2-(1H-imidazol-1-yl)-*N*-methylethan-1-amine (2c)



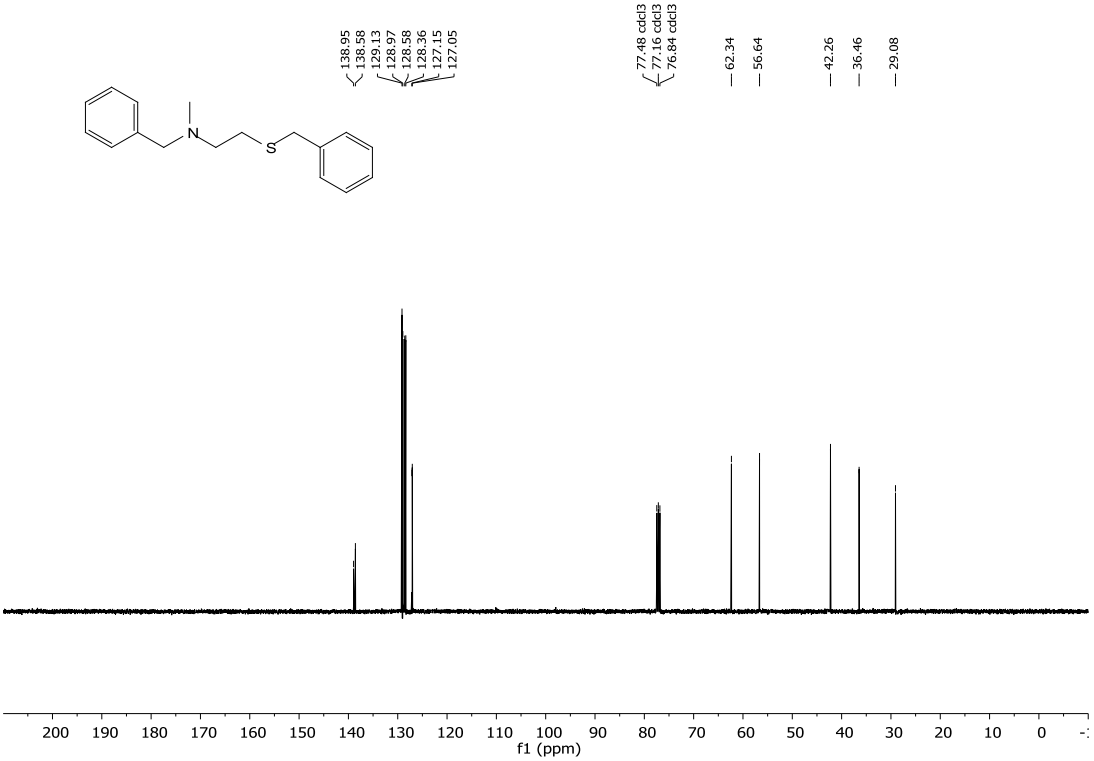
^{13}C NMR *N*-benzyl-2-(1H-imidazol-1-yl)-*N*-methylethan-1-amine (2c)



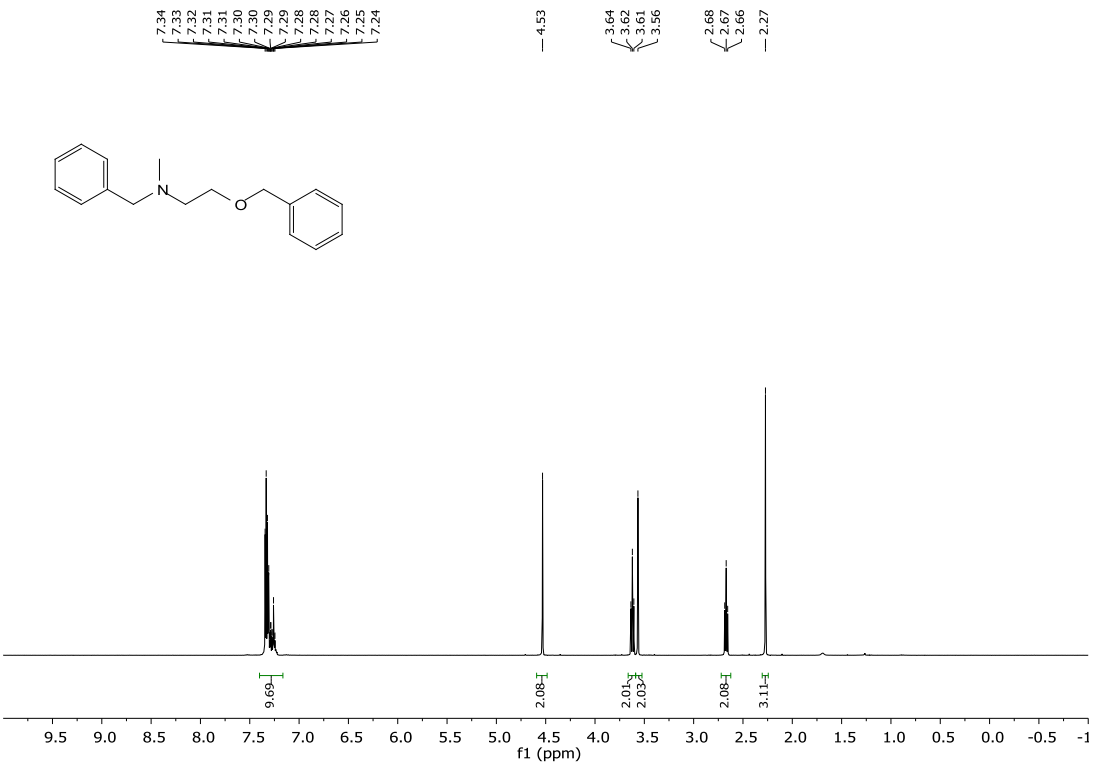
^{1}H NMR *N*-benzyl-2-(benzylthio)-*N*-methylethan-1-amine (2d)



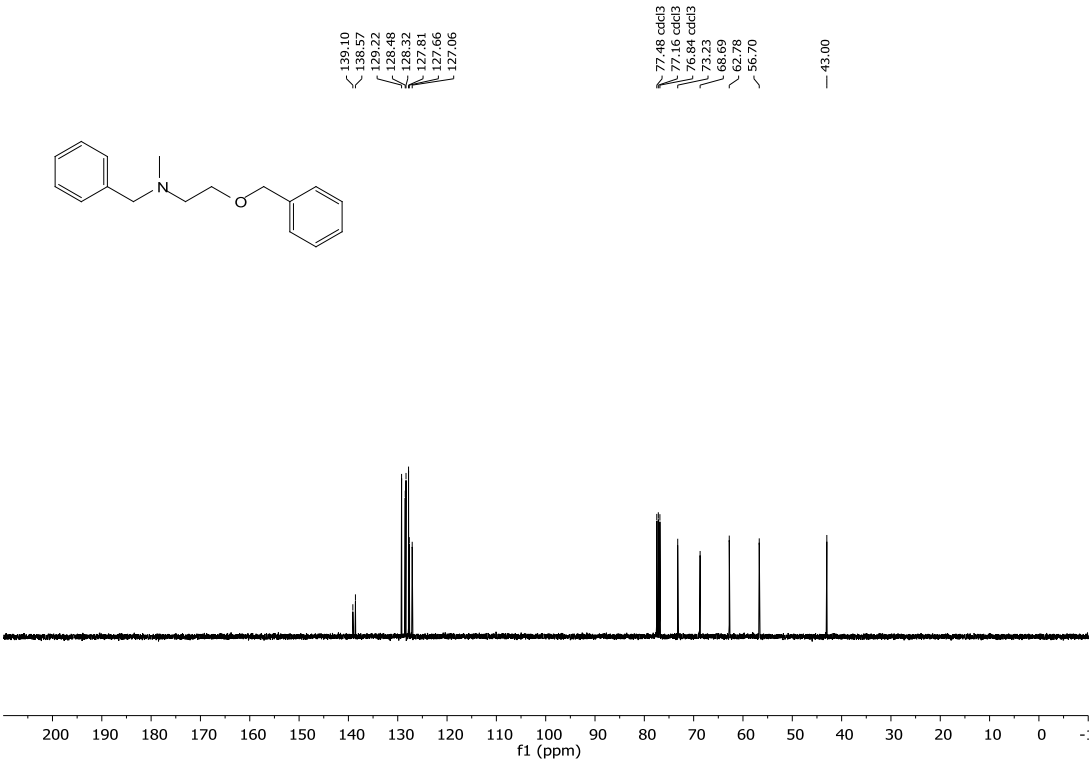
^{13}C NMR *N*-benzyl-2-(benzylthio)-*N*-methylethan-1-amine (2d)



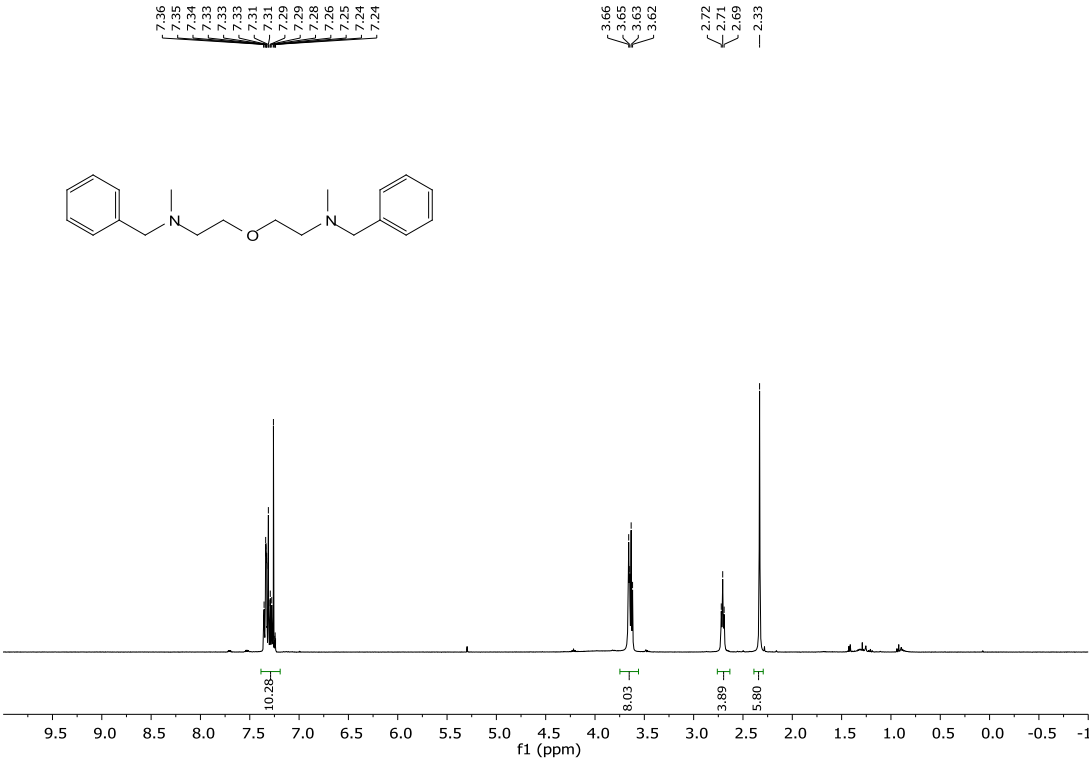
^{1}H NMR *N*-benzyl-2-(benzyloxy)-*N*-methylethan-1-amine (2e)



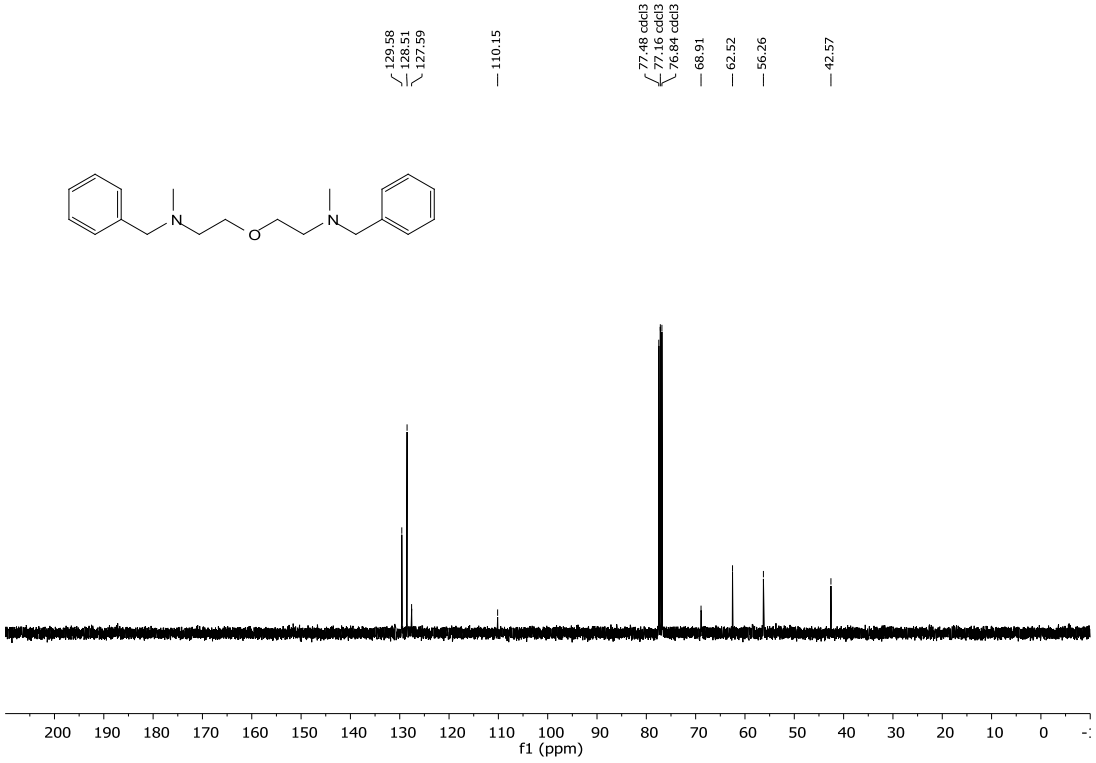
^{13}C NMR *N*-benzyl-2-(benzyloxy)-*N*-methylethan-1-amine (2e)



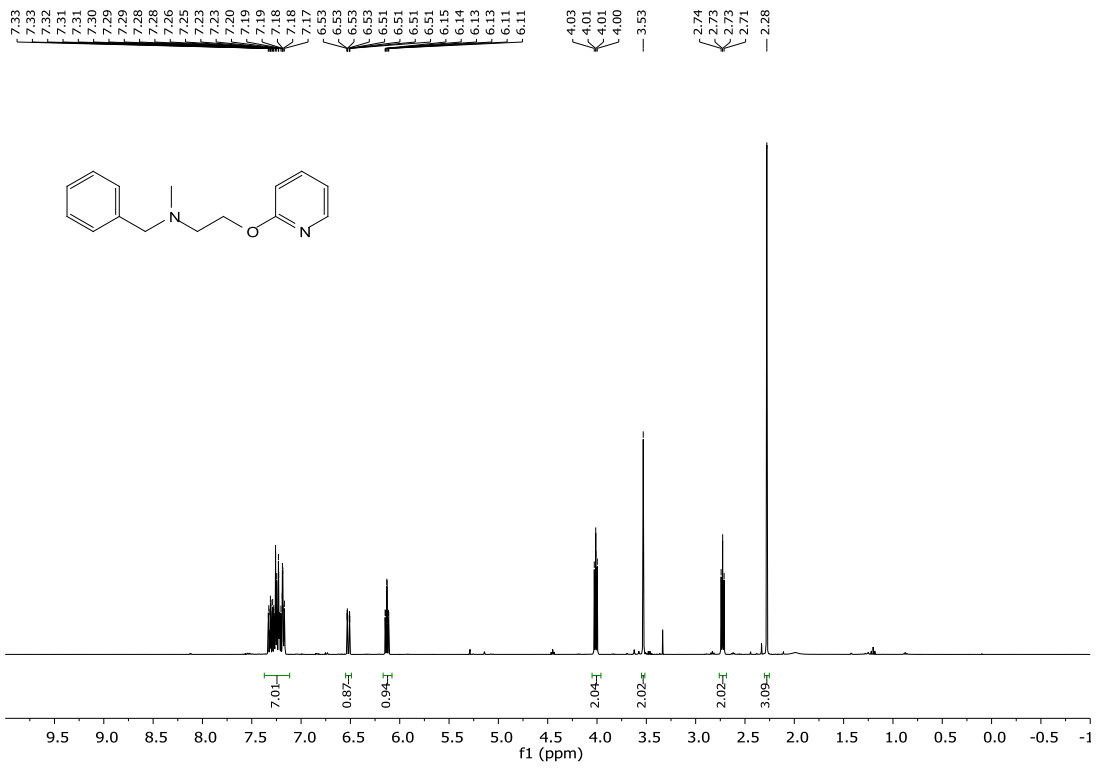
^{1}H NMR 2,2'-oxybis(*N*-benzyl-*N*-methylethan-1-amine) (2g)



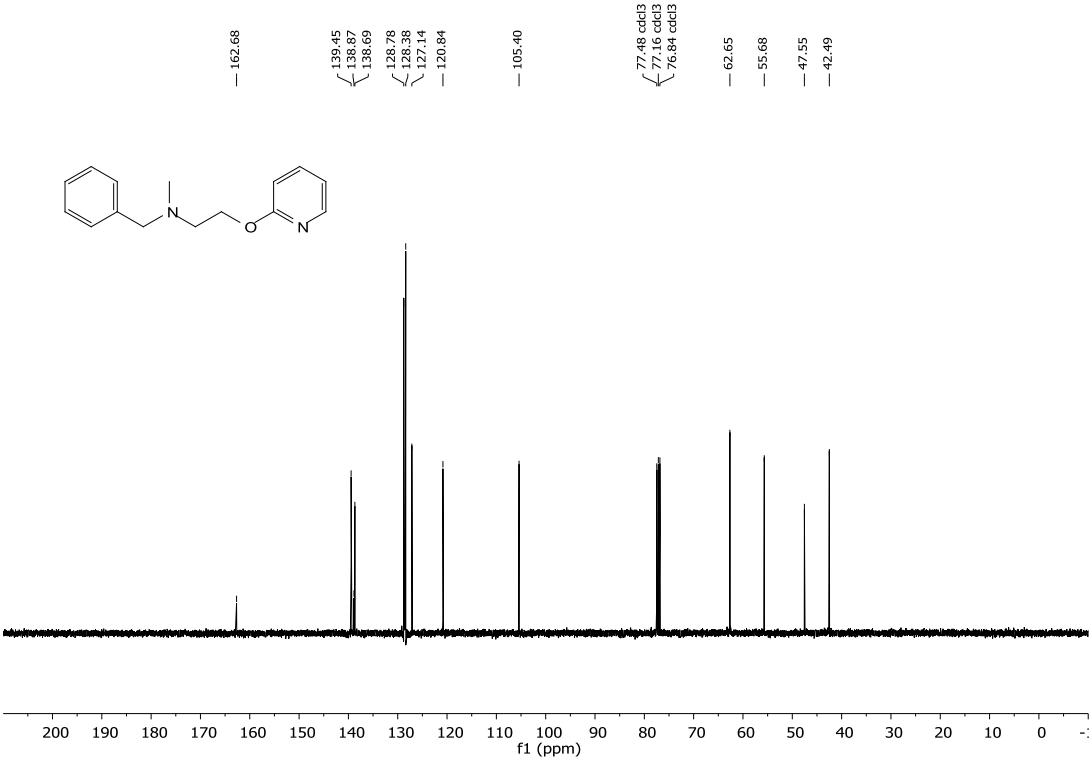
^{13}C NMR 2,2'-oxybis(*N*-benzyl-*N*-methylethan-1-amine) (2g)



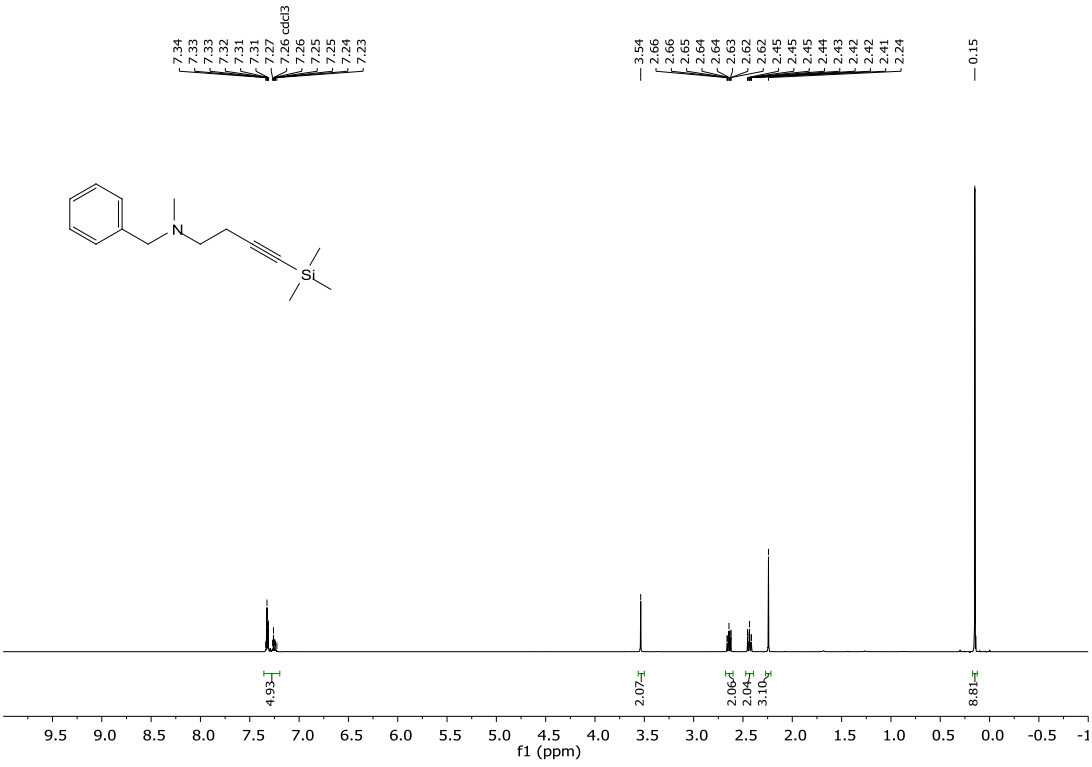
^{1}H NMR *N*-benzyl-*N*-methyl-2-(pyridin-2-yloxy)ethan-1-amine (2h)



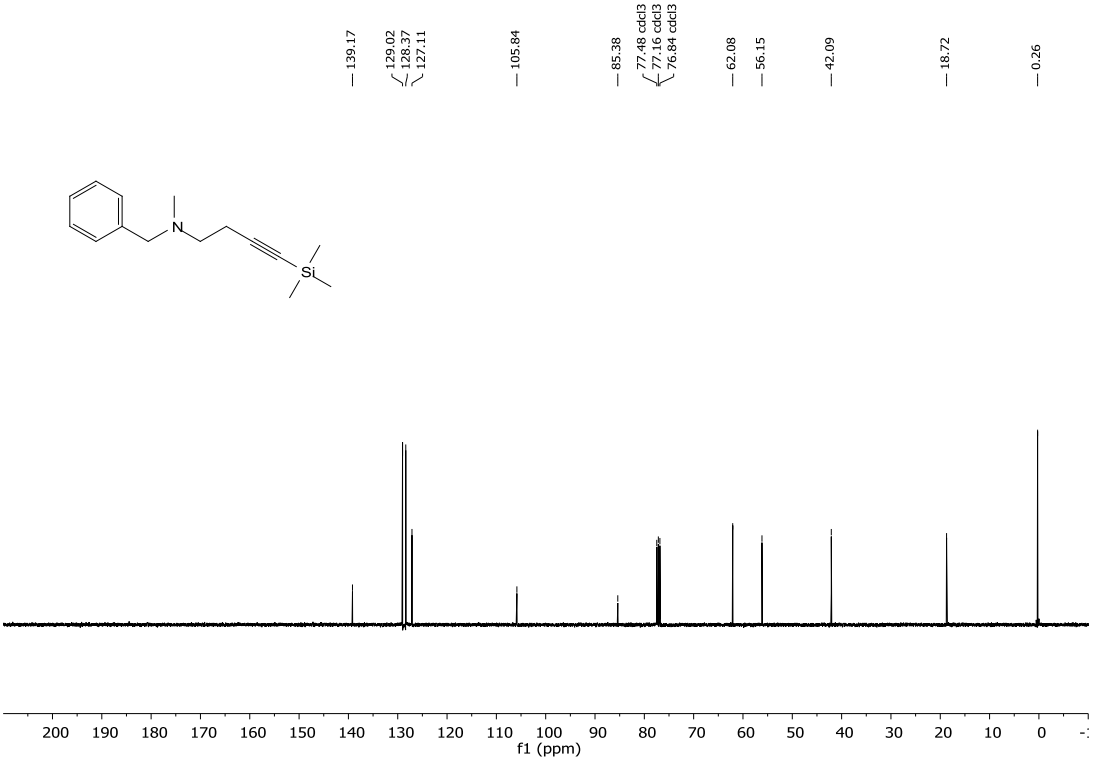
^{13}C NMR *N*-benzyl-*N*-methyl-2-(pyridin-2-yloxy)ethan-1-amine (2h)



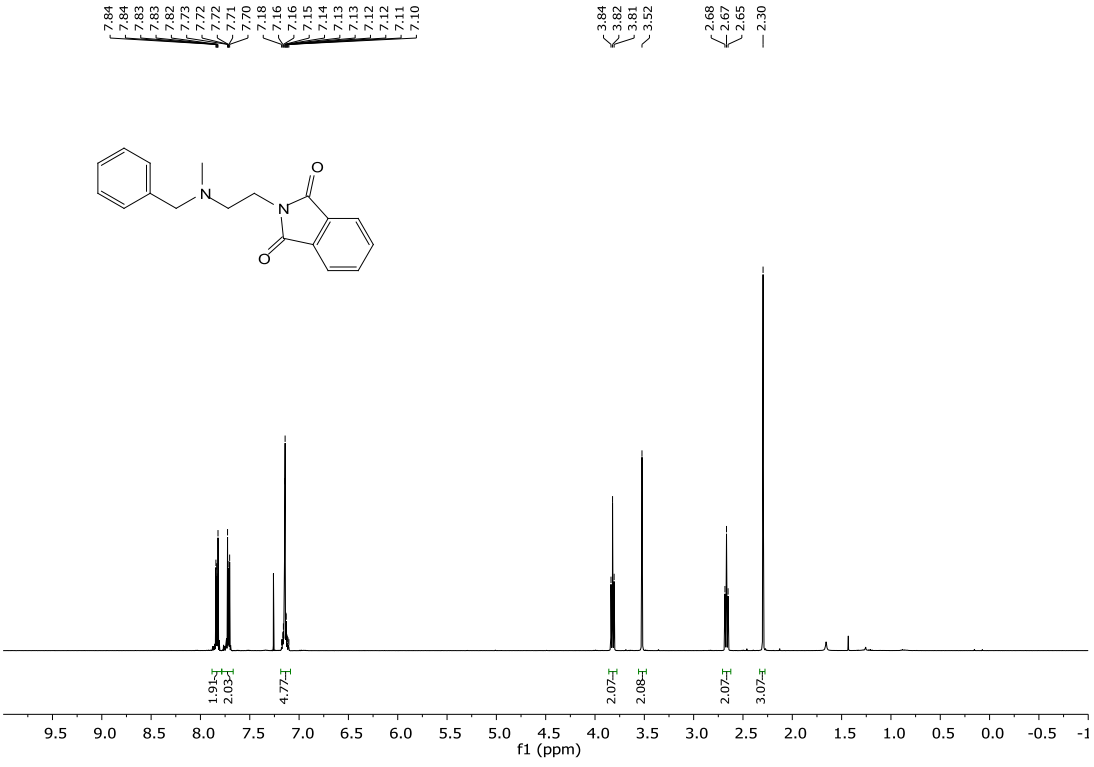
^{1}H NMR *N*-benzyl-*N*-methyl-4-(trimethylsilyl)but-3-yn-1-amine (2l)



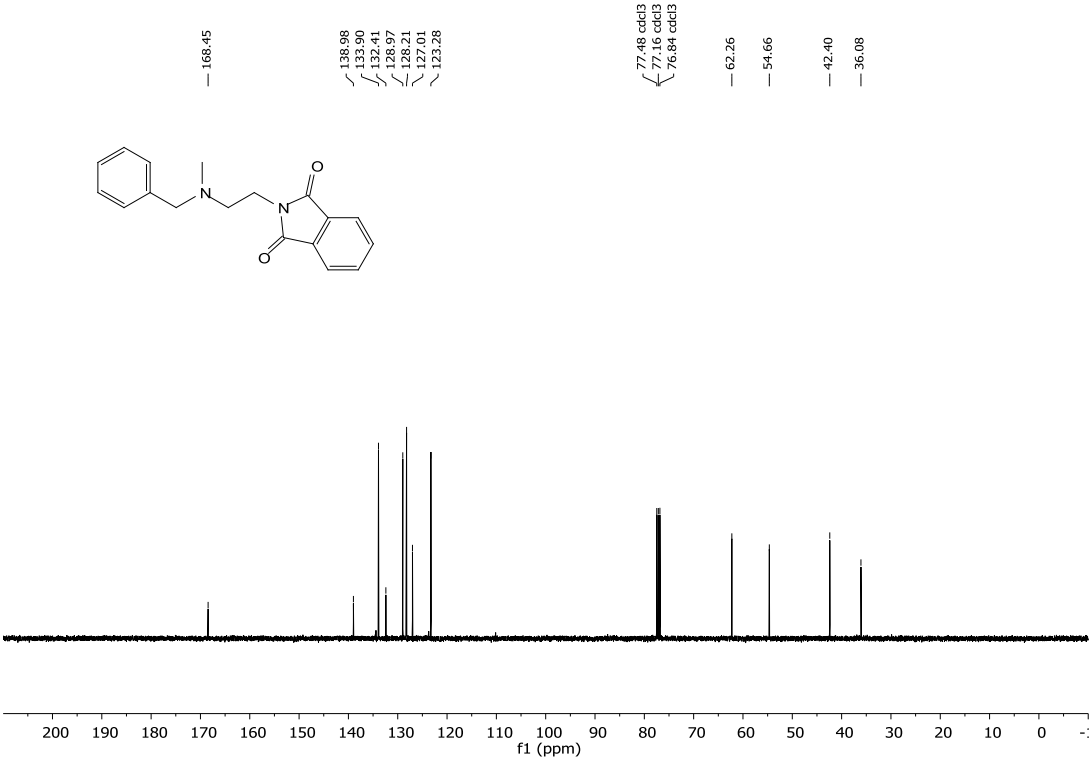
^{13}C NMR *N*-benzyl-*N*-methyl-4-(trimethylsilyl)but-3-yn-1-amine (2l)



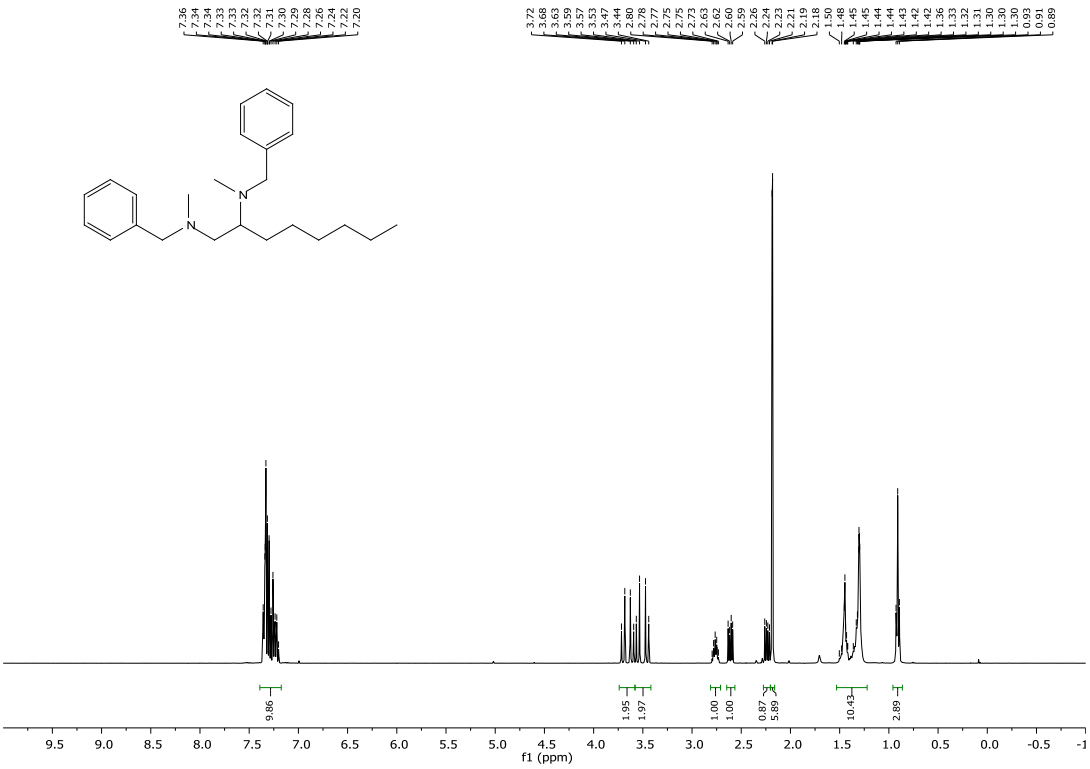
^{1}H NMR 2-(2-(benzyl(methyl)amino)ethyl)isoindoline-1,3-dione (2m)



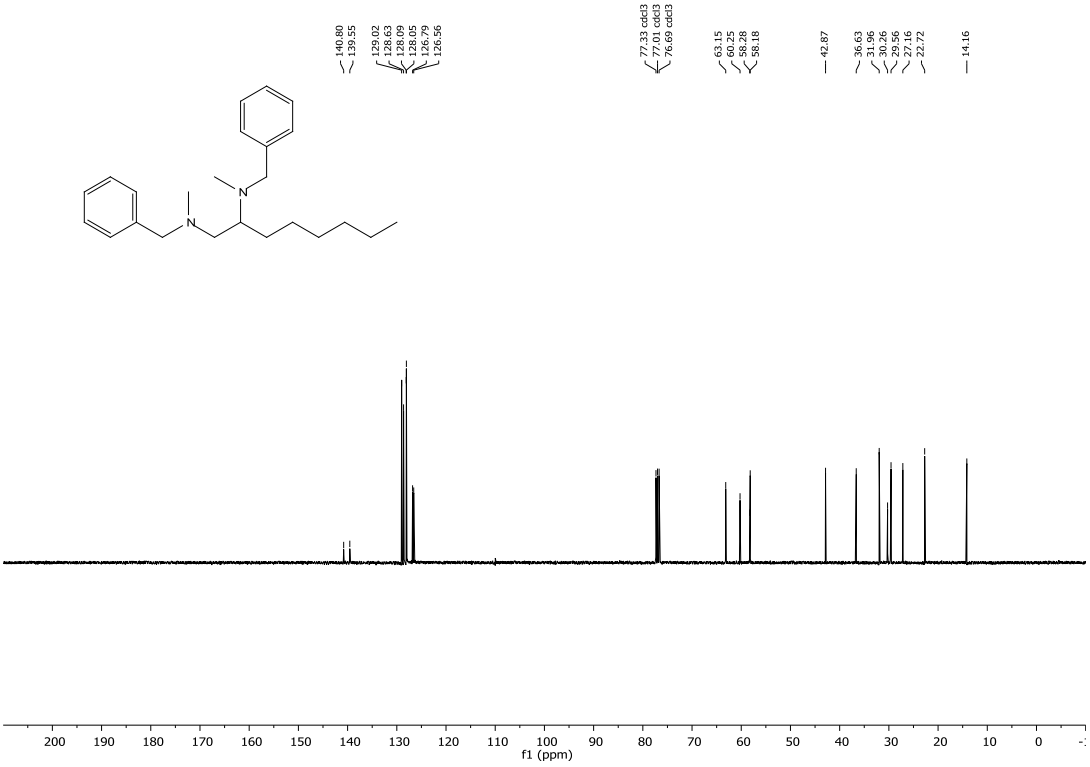
^{13}C NMR 2-(2-(benzyl(methyl)amino)ethyl)isoindoline-1,3-dione (2m)



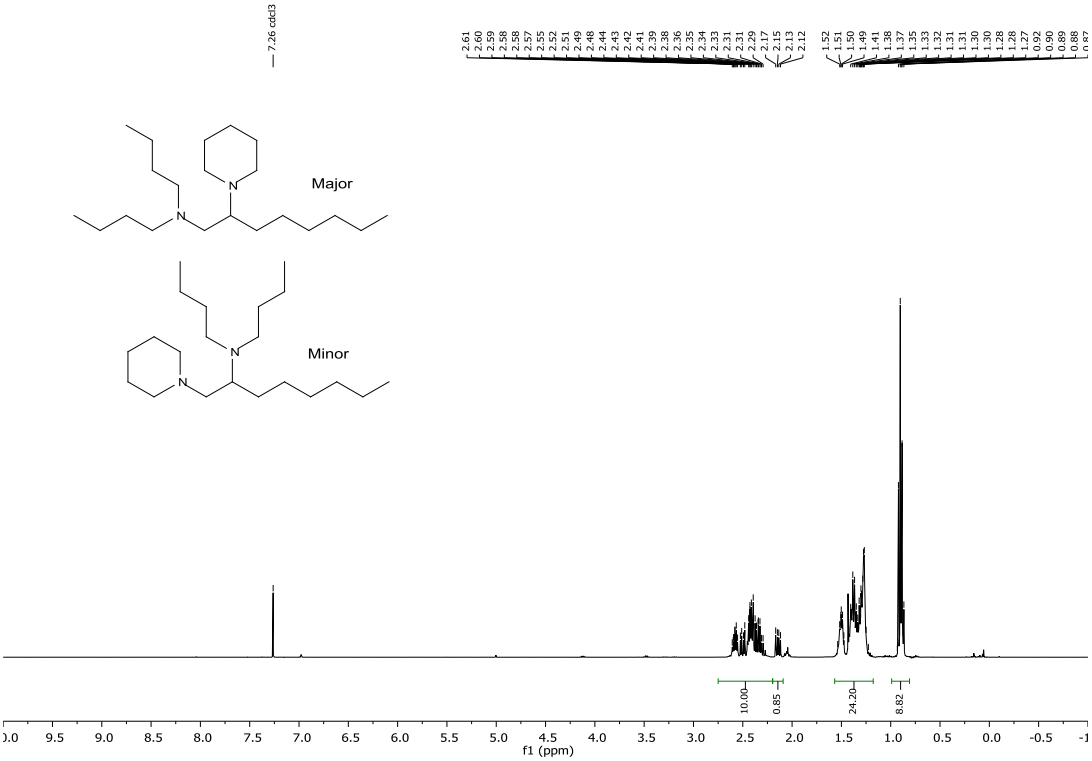
^{1}H NMR *N*1,*N*2-dibenzyl-*N*1,*N*2-dimethyloctane-1,2-diamine (2o)



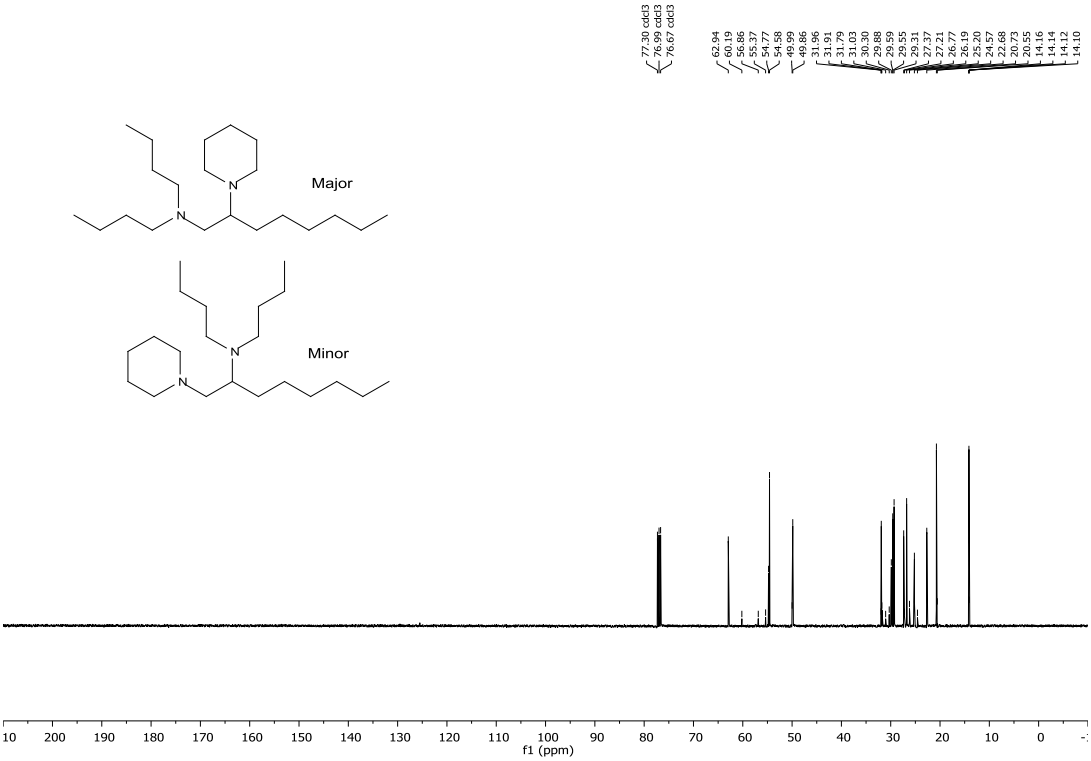
^{13}C NMR *N*1,*N*2-dibenzyl-*N*1,*N*2-dimethyloctane-1,2-diamine (2o)



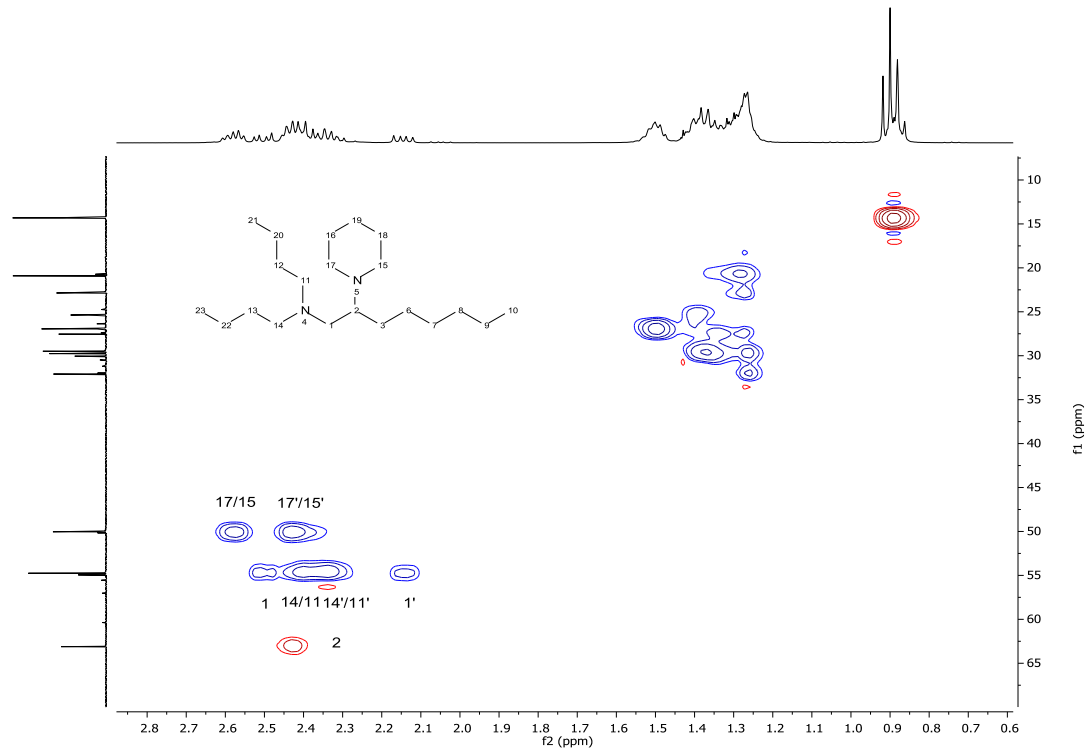
^{1}H NMR *N*,*N*-dibutyl-2-(piperidin-1-yl)octan-1-amine (2p)



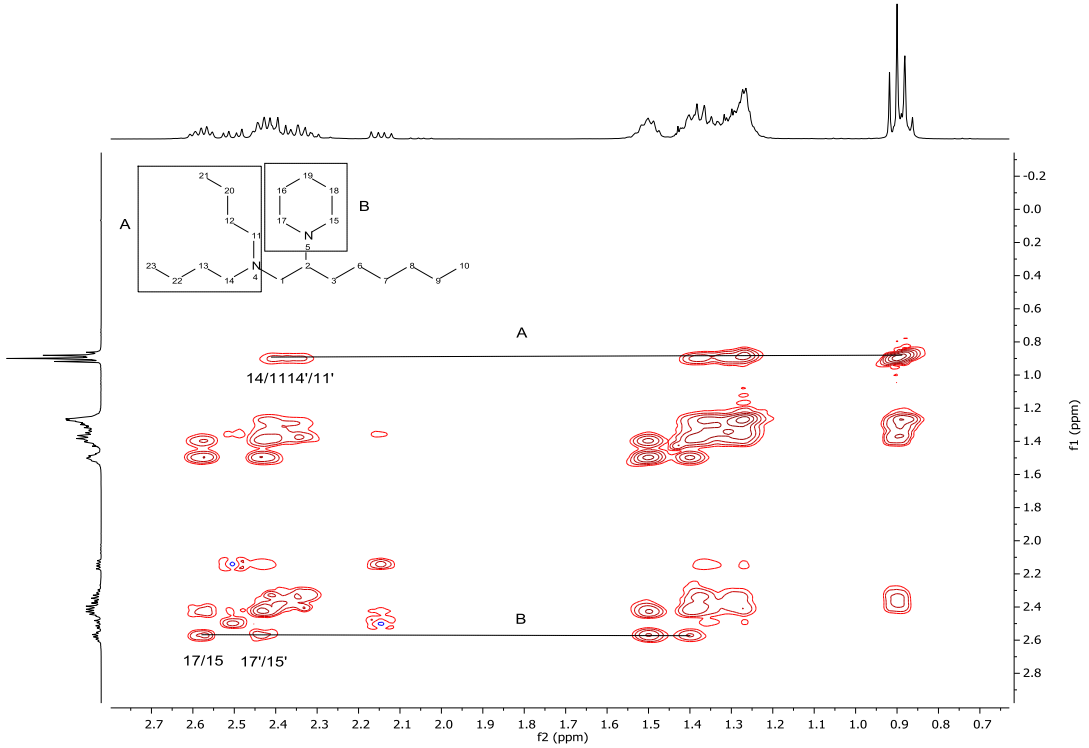
^{13}C NMR *N*,*N*-dibutyl-2-(piperidin-1-yl)octan-1-amine (2p)



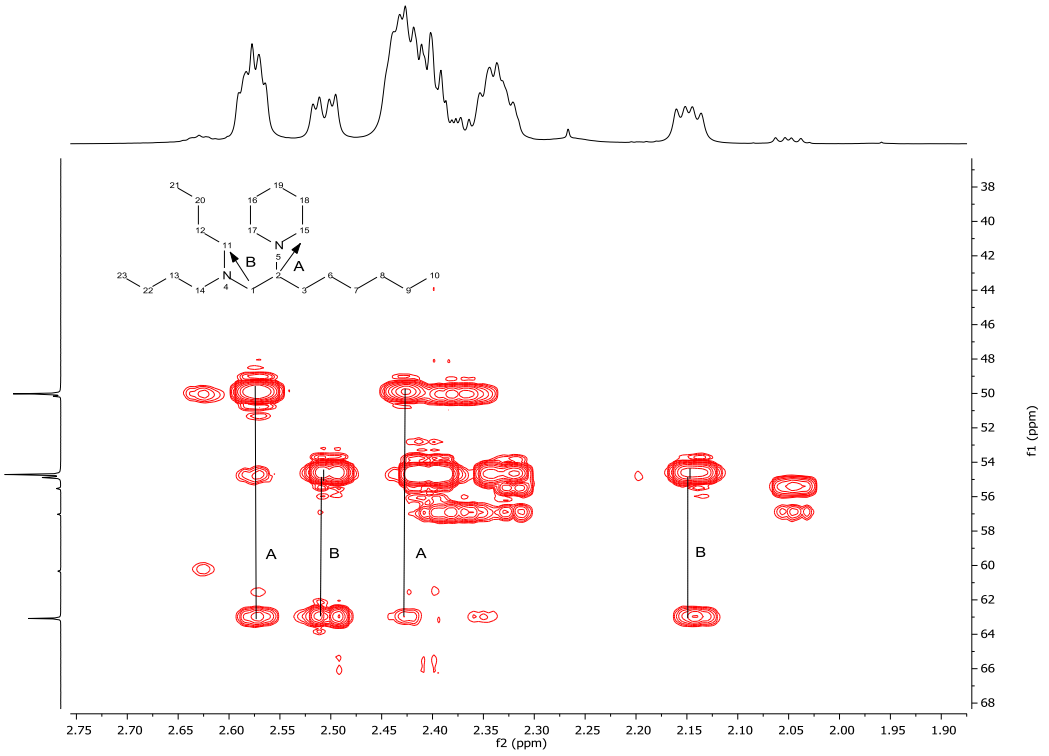
^{1}H-^{13}C HSQC NMR *N*,*N*-dibutyl-2-(piperidin-1-yl)octan-1-amine (2p)



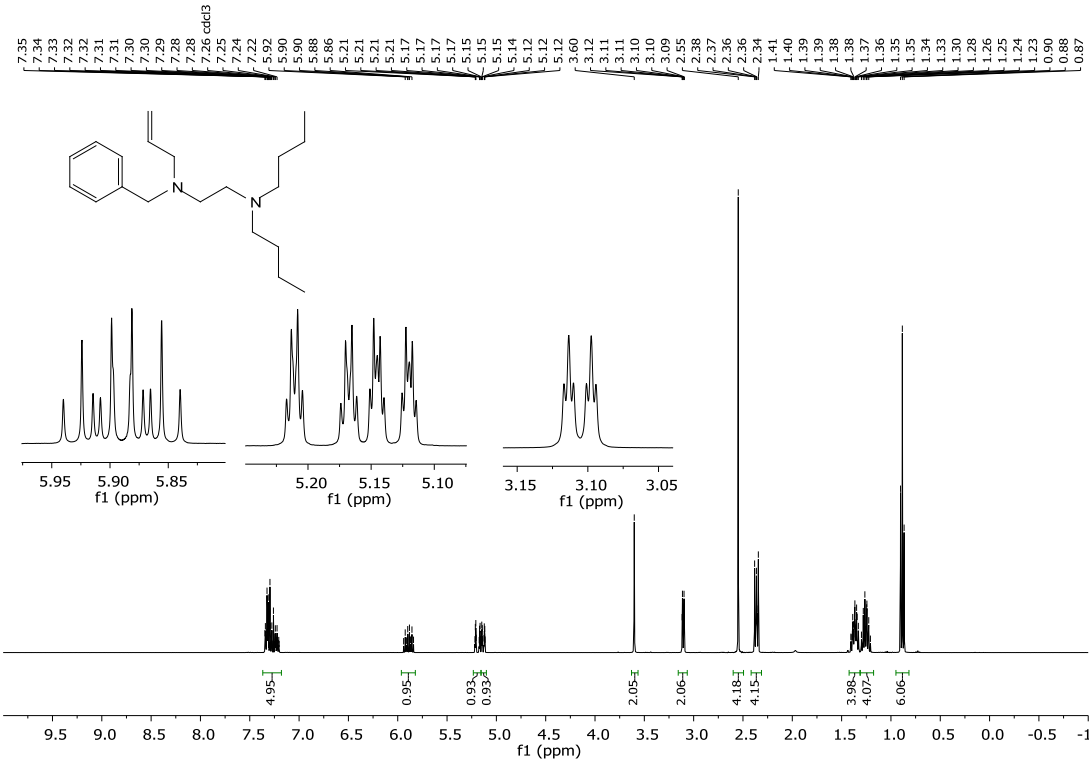
^{1}H-^{1}H TOCSY NMR *N*,*N*-dibutyl-2-(piperidin-1-yl)octan-1-amine (2p)



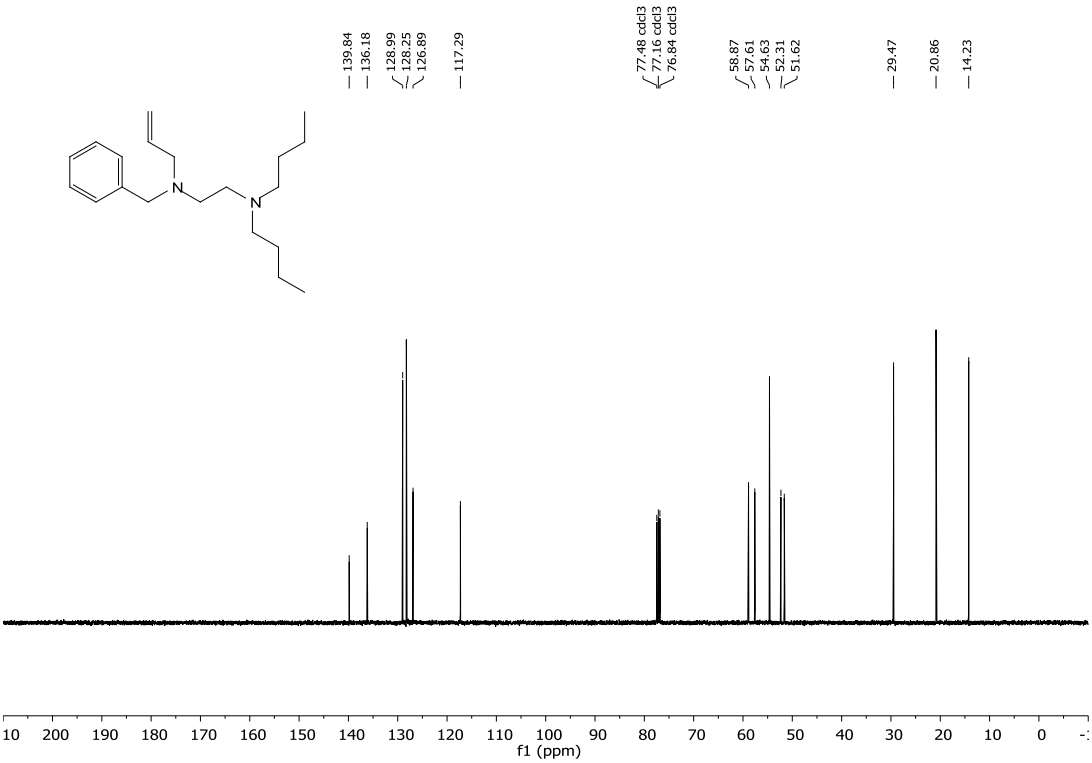
^{1}H-^{13}C HMBC NMR *N*,*N*-dibutyl-2-(piperidin-1-yl)octan-1-amine (2p)



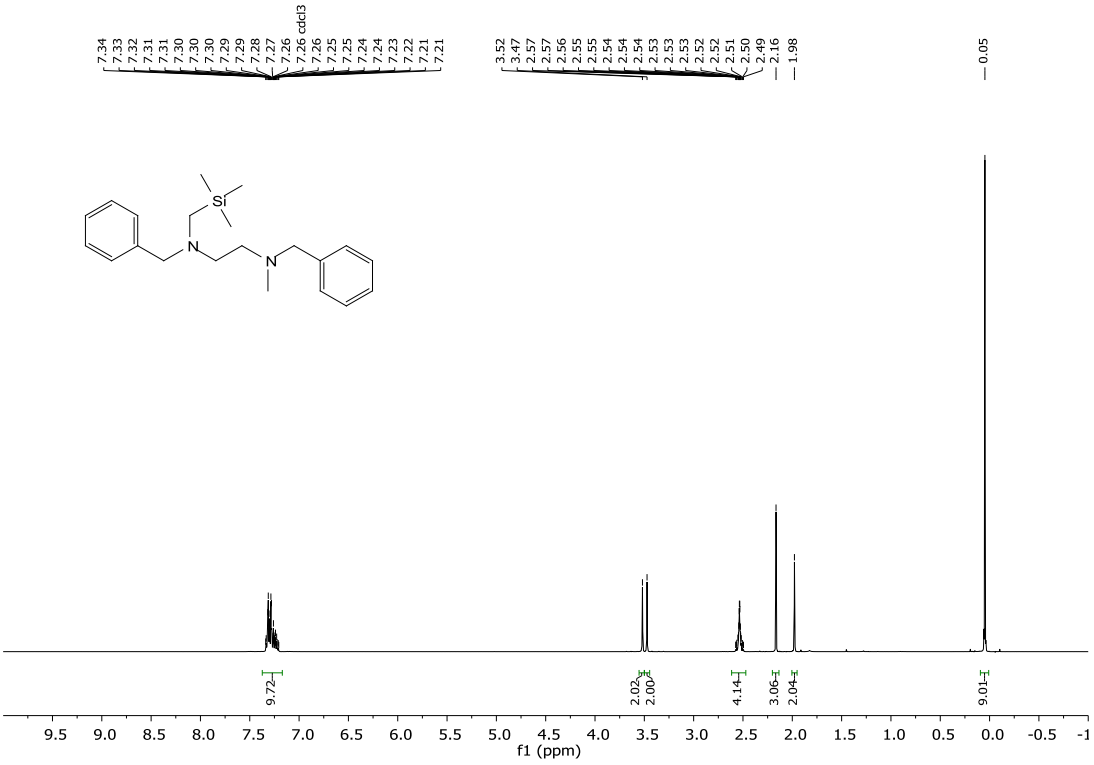
^{1}H NMR *N*1-allyl-*N*1-benzyl-*N*2,*N*2-dibutylethane-1,2-diamine (2q)



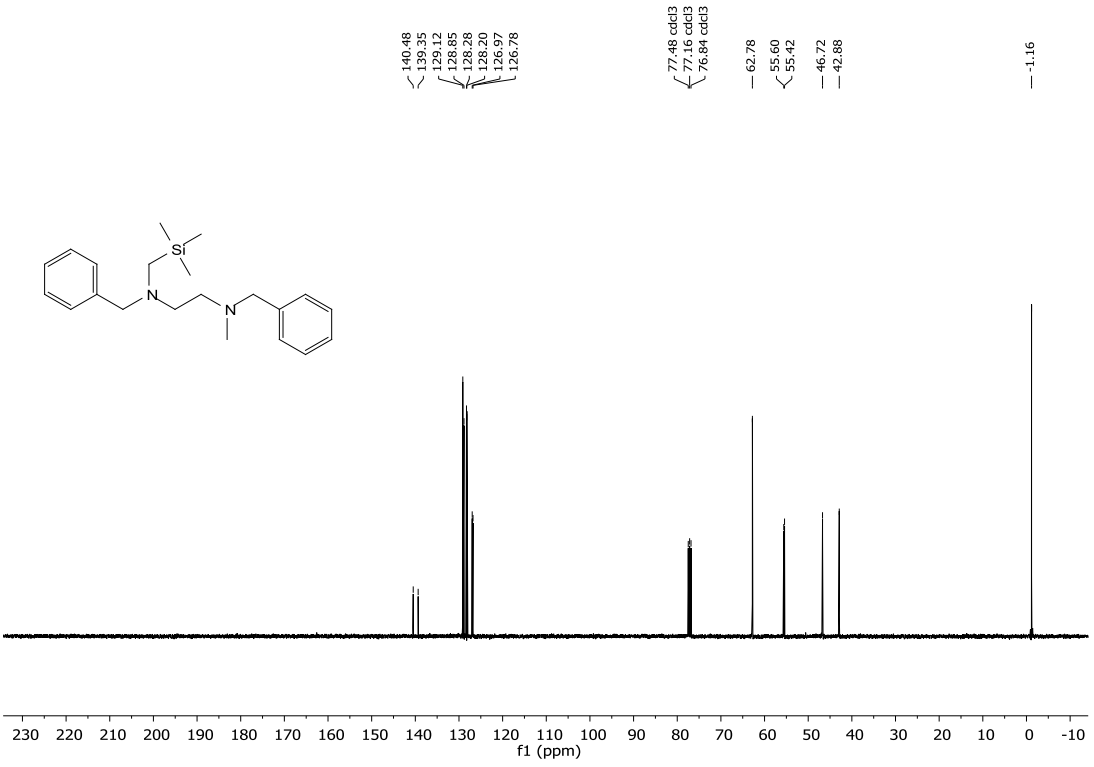
^{13}C NMR *N*1-allyl-*N*1-benzyl-*N*2,*N*2-dibutylethane-1,2-diamine (2q)



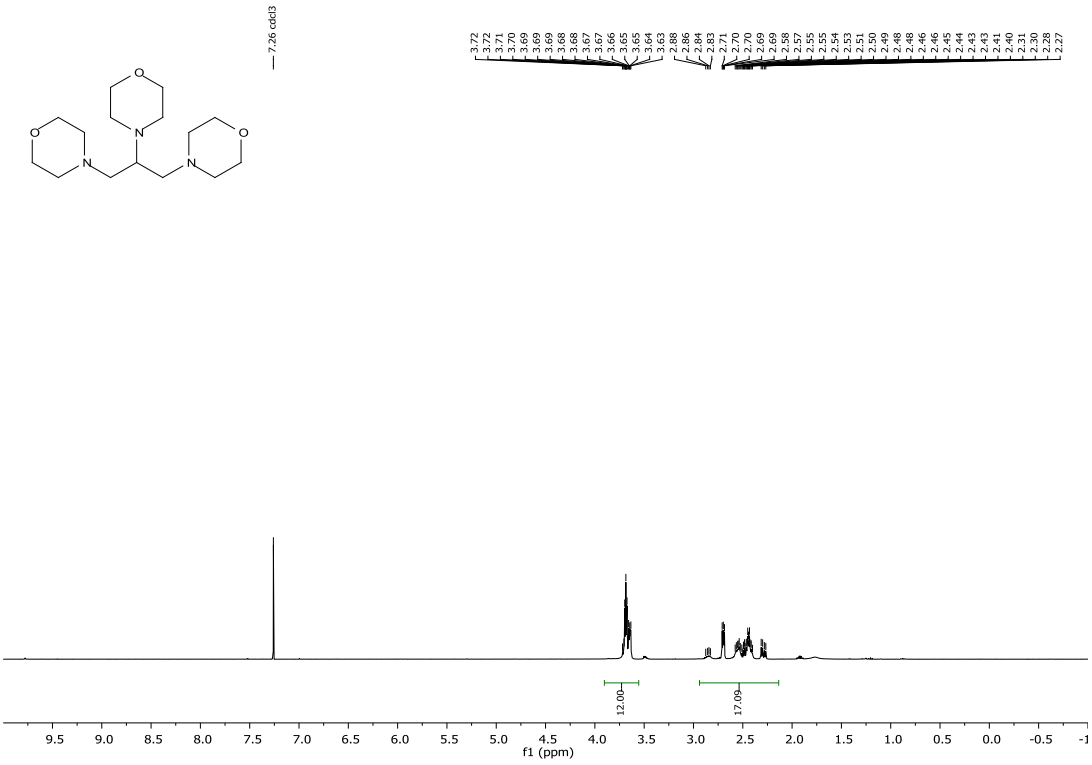
^{1}H NMR *N*1,*N*2-dibenzyl-*N*1-methyl-*N*2-((trimethylsilyl)methyl)ethane-1,2-diamine (2r)



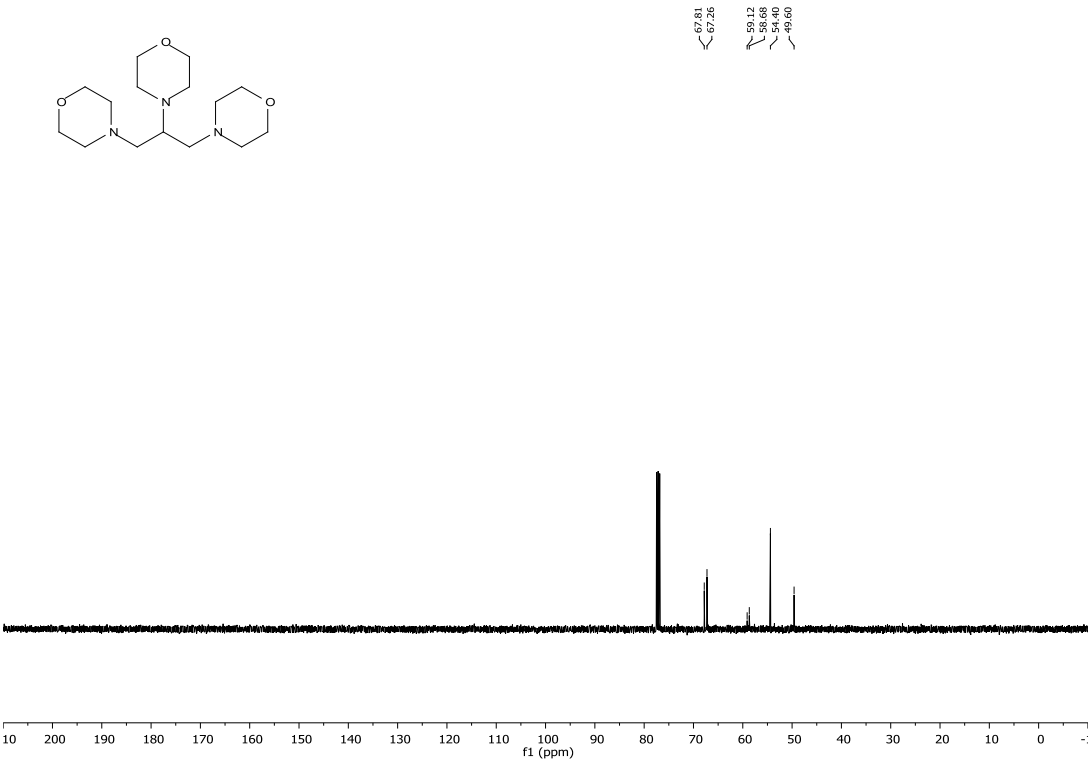
^{13}C NMR *N*1,*N*2-dibenzyl-*N*1-methyl-*N*2-((trimethylsilyl)methyl)ethane-1,2-diamine (2r)



^{1}H NMR 4,4',4''-(propane-1,2,3-triyl)trimorpholine (2s)



^{13}C NMR 4,4',4''-(propane-1,2,3-triyl)trimorpholine (2s)



References

1 W. R. Dolbier, *Guide to Fluorine NMR for Organic Chemists*, John Wiley & Sons Inc., Hoboken, New Jersey, USA, 2009.

2 C. Bunyagidj, H. Piotrowska and M. H. Aldridge, *J. Chem. Eng. Data*, 1981, **26**, 344.

3 S. Kobayashi, A. Yoneda, T. Fukuhara and S. Hara, *Tetrahedron*, 2004, **60**, 6923.

4 G. K. S. Prakash et al, *Org. Lett.*, 2009, **11**, 1127.

5 H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki and T. Ohshima, *Org. Lett.*, 2014, **16**, 2018.

6 D. Gao et al, *J. Am. Chem. Soc.*, 2011, **133**, 5921.

7 H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluorine Chem.*, 2010, **131**, 477.

8 A. D. Windhorst, L. Bechger, G. W. M. Visser, W. P. M. B. Menge, R. Leurs, H. Timmerman and J. D. M. Herscheid, *J. Fluorine Chem.*, 1996, **80**, 35.

9 S. Rozen and M. Brand, *J. Org. Chem.*, 1985, **50**, 3342.

10 M. Medoc and F. Sobrio, *RSC Adv.*, 2014, **4**, 35371.

11 E. A. Ilardi, C. E. Stivala and A. Zakarian, *Org. Lett.*,2008, **10**, 1727; X. Huo et al, *Org. Lett.*, 2014, **16**, 1570.

12 T. J. Barker and D. L. Boger, *J. Am. Chem. Soc.*, 2012, **134**, 13588.

13 R. K. Shiroodi, A. S. Dudnik and V. Gevorgyan, *J. Am. Chem. Soc.*, 2012, **134**, 6928.

14 Z. Wang, D. Pei, Y. Zhang, C. Wang and J. Sun, *Molecules*, 2012, **17**, 5151

15 M. Meguro, N. Asao and Y. Yamamoto, *J. Chem. Soc. Perkin Trans 1*, 1994, 2597

16 J. González-Sabin, V. Gotor and F. Rebolledo, *Tetrahedron Asymmetry*, 2004, **15**, 1335.

- 17 H.-S. Chong, X. Sun, Y. Chen and M. Wang, *Tetrahedron Lett.*, 2015, **56**, 946.

18 A. Clerici, A. Ghilardi, N. Pastori, C. Punta and O. Porta, *Org. Lett.*, 2008, **10**, 5063.

19 O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden and J. M. J. Williams, *Chem. Commun.*, 2010, **46**, 1541.

20 F. Chahdoura, C. Pradel and M. Gómez, *Adv. Synt. Catal.*, 2013, **355**, 3648.

21 G. L. Bihan et al, *J. Med. Chem.*, 1999, **42**, 1587.

22 J.-C. Kizirian, N. Cabello, L. Pinchard, J.-C. Caille and A. Alexakis, *Tetrahedron*, 2005, **61**, 8939.