Supporting Information

Nucleophilic Radiofluorination at Room Temperature via Aziridinium Intermediates

*Marie Médoc and Franck Sobrio**

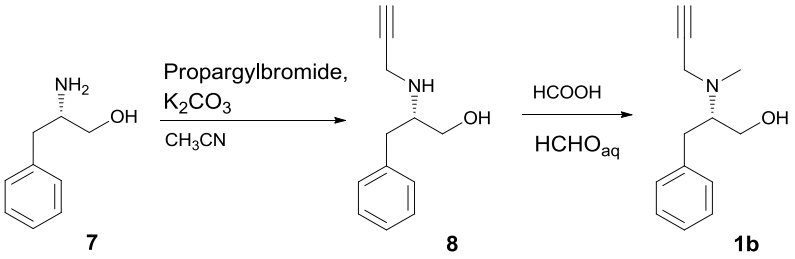
TABLE OF CONTENT

MATERIALS AND METHODS

Reagents and solvents used, unless stated otherwise, were of commercially available reagents grade quality and were used without further purification. Thin layer chromatographies (TLC) were run on pre-coated aluminum plates of silica gel $60F_{254}$ (Merck) and retention factor (R_f) were established using a UV-lamp at 254 nm or visualization with ninhydrin solution. Silica gel flash-chromatographies were performed on prepacked columns (20–40 µm, Flashmart, AIT, France). Optical rotations were determined on a JASCO P2000 polarimeter and are given in $cm^3.g^{-1}.dm^{-1}$ while the concentrations are given in $g.cm^{-3}$. Melting points were determined on a Barnstead Electrothermal IA 9100 melting point apparatus and are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer, at 400 MHz (^1H), 100.6 MHz (^{13}C) and 376.5 MHz (^{19}F). Fluorine-19 NMR spectra are coupled to proton. Chemical shifts were reported as parts per million (δ in ppm) using tetramethylsilane (TMS) as internal standard or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. Coupling patterns are abbreviated as: s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet). IR spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer and are given in cm^{-1}. High resolution mass spectra (HRMS) were obtained on a Waters Q-TOF micro spectrometer by electrospray ionization (ESI). Analytical HPLC was realized with a Waters 600 pump and controller system, a Waters 717plus autosampler and a Waters 996 photodiode arrays detector (198-380 nm) coupled with a NaI probe radioactive detector (Novelec, France). Purity was determined by HPLC on an analytical column (Macherey-Nagel, Nucleodur C18 Gravity, 250 × 4.6 mm, 5 µm; flow rate: 1 mL/min; UV-detection λ = 210 nm). The purity of compounds was found: to be more than 98%. Radioactivity measurements were carried out with a Capintec R15C ionization chamber. Radio-TLCs were performed using an Instant Imager® Packard apparatus.

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

Scheme S1: Synthesis of alcohol **1b**



(*S*)-2-(*N*-Propargylamino)-3-phenylpropan-1-ol (8)

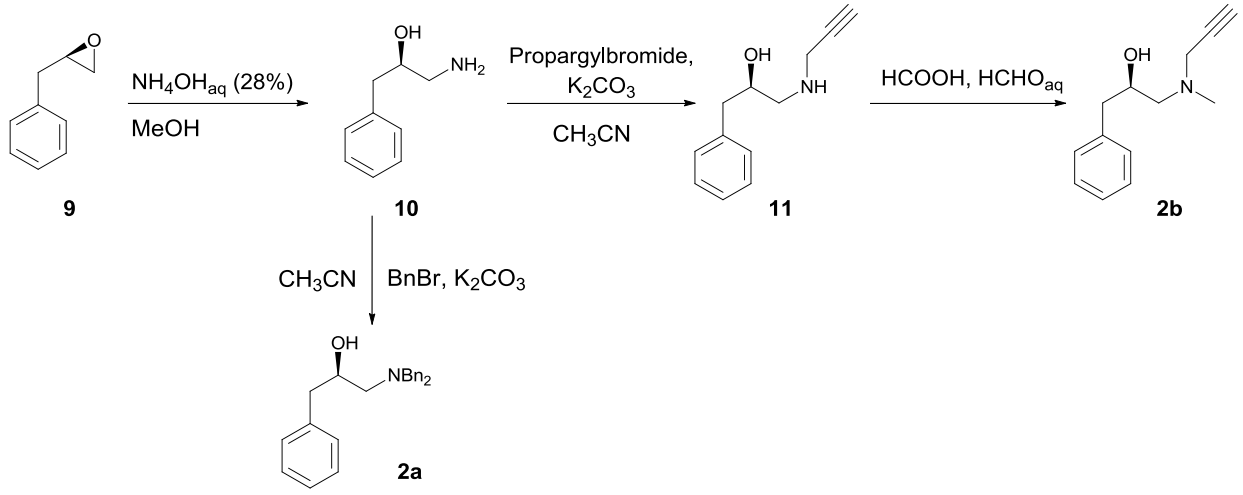
To a solution of (*S*)-2-amino-3-phenyl-propan-1-ol (**7**)[1] (502 mg, 3.32 mmol) in CH_3CN (10 mL) at 0 °C was added K_2CO_3 (1.00 g, 7.24 mmol) followed by a solution of propargylbromide in toluene (80 wt.%, 0.4 mL, 3.71 mmol). The mixture was warmed to RT and stirred overnight. The solvent was

evaporated before CH_2Cl_2 (30 mL) and water (30 mL) were added to the residue. The layers were separated and the aqueous layer was extracted further with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification by chromatography on silica gel (heptane/AcOEt, 80/20 to 60/40) gave compound **8** as a white solid (280 mg, 45%). m.p. 71-72°C; $[\alpha]_D^{20}$ +9.4 (*c* 1.00, $CHCl_3$); IR (ATR) ν_{max}: 3294, 2929, 1494, 1451, 1338, 1053, 743, 699; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.32-7.20 (m, 5H), 3.66 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 3.6 Hz, 1H), 3.44 (d, $^4J_{HH}$ = 2.4 Hz, 2H), 3.38 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 3.16-3.10 (m, 1H), 2.83-2.73 (m, 2H), 2.20 (t, $^4J_{HH}$ = 2.4 Hz, 1H), 1.97 (bs, 2H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 138.5, 129.6, 128.9, 126.8, 82.2, 71.9, 62.5, 58.9, 38.2, 36.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{16}NO$ 190.1232; Found 190.1223.

(*S*)-2-(*N*,*N*-Methylpropargylamino)-3-phenylpropan-1-ol (1b)

A mixture of **8** (200 mg, 1.06 mmol), formic acid (0.2 mL, 5.30 mmol) and formaldehyde (37% in water) (0.12 mL, 1.6 mmol) was stirred at 105 °C overnight. The mixture was cooled to RT and acidified to pH 1 with HCl (2 N). The solvent was evaporated and CH_2Cl_2 (20 mL) and water (20 mL) were added to the residue. The layers were separated and the aqueous layer was washed further with water (2 × 20 mL). The combined aqueous layers were brought to pH 8-9 by the addition of aqueous ammonia (28%) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Compound **1c** was obtained after purification by chromatography on silica gel (CH_2Cl_2/MeOH, 99/1) as colorless oil (154 mg, 72%). $[\alpha]_D^{20}$ -20.1 (*c* 1.00, $CHCl_3$); IR (ATR) ν_{max}: 3289, 2935, 2799, 1453, 1030,740, 699; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.30-7.16 (m, 5H), 3.50-3.32 (m, 4H), 3.11-3.06 (m, 2H), 2.43 (s, 3H), 2.42-2.35 (m, 1H), 2.29 (t, $^4J_{HH}$ = 2.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 139.3, 129.2, 128.7, 126.4, 80.5, 73.2, 65.5, 60.4, 43.8, 36.1, 32.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1388; Found 204.1387; HPLC purity: eluent MeOH/H_2O 65/35, t_r = 8.9 min.

Scheme S2: Synthesis of alcohols **2a** and **2b**



(*R*)-1-Amino-3-phenylpropan-2-ol (10)

To an emulsion of (*R*)-2-benzyloxirane (**9**)[2] (1.01 g, 7.53 mmol) in aqueous ammonia (28%, 9 mL) was added MeOH (about 9 mL) until the solution was limpid. The solution was then stirred at RT for 2 h. Ammonia (28%, 9 mL) and MeOH (9 mL) were added simultaneously and the solution was stirred further for 2 h at RT. The solvent was evaporated and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 80/20) to give compound **10** as a white solid (686 mg, 60%). m.p. 66-67°C; $[\alpha]_D^{20}$ +6.6 (*c* 1.00, $CHCl_3$); IR (ATR) ν_{max}: 2868, 1574, 1454, 1296, 1083, 743, 700; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.27-7.15 (m, 5H), 3.68-3.62 (m, 1H), 2.78 (bs, 3H), 2.65-2.60 (m, 3H), 2.47 (dd, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 8.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 138.6, 129.7, 128.8, 126.7, 73.2, 47.0, 41.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_9H_{14}NO$ 152.1075; Found: 152.1073.

(*R*)-1-(*N*,*N*-Dibenzylamino)-3-phenylpropan-2-ol (2a)

Compound **2a** was prepared following the procedure described for the synthesis of **8** starting from **10** (200 mg, 1.32 mmol), K_2CO_3 (400 mg, 2.89 mmol) and benzylbromide (0.33 mL, 2.77 mmol). Product **2a** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 95/5) as a white solid (364 mg, 83%). $[\alpha]_D^{20}$ -76.4 (*c* 0.84, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 11.4 min.

Characterization data are in accordance to the published data.[3]

(*R*)-1-(*N*-Propargylamino)-3-phenylpropan-2-ol (11)

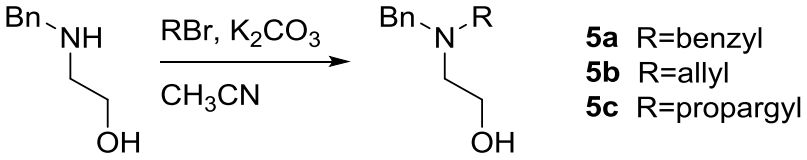
Compound **11** was prepared following the procedure described for the synthesis of **8** starting from **10** (704 mg, 4.66 mmol), K_2CO_3 (1.40 g, 10.13 mmol) and a solution of propargylbromide in toluene (80 wt.%, 0.4 mL, 3.71 mmol). Product **11** was obtained after purification by chromatography on silica gel (from 90/10 heptane/AcOEt to 100% AcOEt) as a white solid (358 mg, 41%). m.p. 62-63°C; $[\alpha]_D^{20}$ -39.4 (*c* 1.00, $CHCl_3$); IR (ATR) ν_{max}: 3283, 3150, 1603, 1462, 1441, 1333, 1102, 1077, 1030, 701, 647; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.35-7.23 (m, 5H), 3.96-3.89 (m, 1H), 3.46 (d, $^4J_{H-H}$ = 2.4 Hz, 2H), 2.91 (dd, $^2J_{H-H}$ = 12.2 Hz, $^3J_{H-H}$ = 3.0 Hz, 1H), 2.80 (d, $^3J_{H-H}$ = 6.4 Hz, 2H), 2.62 (dd, $^2J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 8.8 Hz, 1H), 2.42 (bs, 2H), 2.24 (t, $^4J_{H-H}$ = 2.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 138.4, 129.7, 128.9, 126.8, 82.0, 72.0, 71.0, 53.9, 41.9, 38.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{16}NO$ 190.1232; Found: 190.1228.

(*R*)-1-(*N*,*N*-Methylpropargylamino)-3-phenylpropan-2-ol (2b)

Compound **2b** was prepared following the procedure described for the synthesis of **1b** starting from **11** (270 mg, 1.43 mmol), formic acid (0.27 mL, 7.16 mmol) and formaldehyde (37% in H_2O) (0.32 mL, 4.27 mmol). Product **2b** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 85/15) as colorless oil (223 mg, 77%). $[\alpha]_D^{20}$ -26.7 (*c* 1.00, $CHCl_3$); IR (ATR) ν_{max}: 3286, 2845, 2797, 1602, 1330, 1086, 1029, 747, 699; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.32-7.20

(m, 5H), 3.92-3.85 (m, 1H), 3.40 and 3.34 (ABX system, $^2J_{AB}$ = 17.0 Hz, $^4J_{AX}$ = $^4J_{BX}$ = 2.2 Hz, 4H), 3.18 (bs, 1H), 2.79 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 7.2 Hz, 1H), 2.71 (dd, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 5.2 Hz, 1H), 2.38-2.35 (m, 1H), 2.33 (s, 3H), 2.21 (t, $^4J_{H-H}$ = 2.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 138.6, 129.7, 128.7, 126.7, 78.7, 73.6, 68.4, 61.5, 46.4, 41.9, 41.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{18}NO$ 204.1388; Found: 204.1380.

Scheme S3: Synthesis of alcohol **5a-c**



2-(*N,N*-Dibenzylamino)ethanol (5a)

Compound **5a** was prepared following the procedure described for the synthesis of **8** using commercial 2-benzyloaminoethanol (502 mg, 3.32 mmol), K_2CO_3 (1.01 g, 7.31 mmol) and benzylbromide (0.43 mL, 3.62 mmol). Product **5a** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 85/15) as a colorless oil (773 mg, 96%). IR (ATR) ν_{max}: 3420, 3026, 1494, 1452, 1049, 1026, 731; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.34-7.23 (m, 10H), 3.62 (s, 4H), 3.57 (t, $^3J_{HH}$ = 5.4 Hz, 2H), 2.66 (t, $^3J_{HH}$ = 5.4 Hz, 2H), 2.40 (bs, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 139.1, 129.3, 128.7, 127.5, 58.9, 58.5, 55.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{20}NO$ 242.1545; Found 242.1553; HPLC purity: eluent MeOH/H_2O 80/20, t_r = 8.5 min.

2-(*N,N*-Allylbenzylamino)ethanol (5b)

Compound **5b** was prepared following the procedure described for the synthesis of **8** using commercial 2-benzyloaminoethanol (501 mg, 3.31 mmol), K_2CO_3 (1.01 g, 7.31 mmol) and allylbromide (0.33 mL, 3.06 mmol). Product **5b** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 90/10) as an yellow oil (511 mg, 81%). IR (ATR) ν_{max}: 3395, 3026, 1642, 1452, 1048, 1027, 917, 737, 698; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.34-7.26 (m, 5H), 5.92-5.82 (m, 1H), 5.21-5.17 (m, 2H), 3.63 (s, 2H), 3.58 (t, $^3J_{HH}$ = 5.2 Hz, 2H), 3.14 (d, $^3J_{HH}$ = 6.4 Hz, 2H), 2.67 (t, $^3J_{HH}$ = 5.2 Hz, 2H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 139.1, 135.4, 129.3, 128.7, 127.5, 118.5, 58.7, 58.2, 56.8, 54.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{18}NO$ 192.1388; Found 192.1395; HPLC purity: eluent MeOH/H_2O 80/20, t_r = 5.3 min.

2-(*N,N*-Benzylpropargylamino)ethanol (5c)

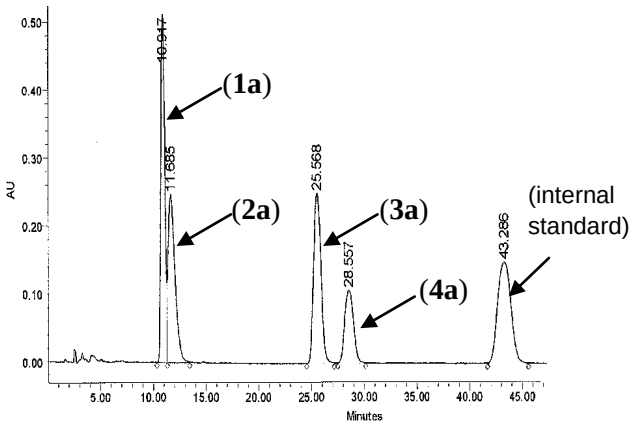
Compound **5c** was prepared following the procedure described for the synthesis of **8**, using commercial 2-benzyloaminoethanol (424 mg, 2.80 mmol), K_2CO_3 (0.85 g, 6.15 mmol) and a solution of propargylbromide in toluene (80 wt.%, 0.30 mL, 3.47 mmol). Product **5c** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 80/20) as a yellow oil (420 mg, 79%). IR (ATR) ν_{max}: 3398, 3289, 2928, 1453, 1050, 737, 698, 638; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS)

7.34-7.26 (m, 5H), 3.70 (s, 2H), 3.64 (t, $^{3}J_{HH}$ = 5.2 Hz, 2H), 3.34 (d, $^{4}J_{HH}$ = 2.4 Hz, 2H), 2.80 (t, $^{3}J_{HH}$ = 5.2 Hz, 2H), 2.59 (bs, 1H), 2.26 (t, $^{4}J_{HH}$ = 2.4 Hz, 2H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 138.3, 129.4, 128.8, 127.8, 78.4, 73.8, 58.7, 57.7, 55.1, 41.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{16}NO$ 190.1232; Found 190.1223; HPLC purity: eluent MeOH/H_2O 65/35, t_r = 7.8 min.

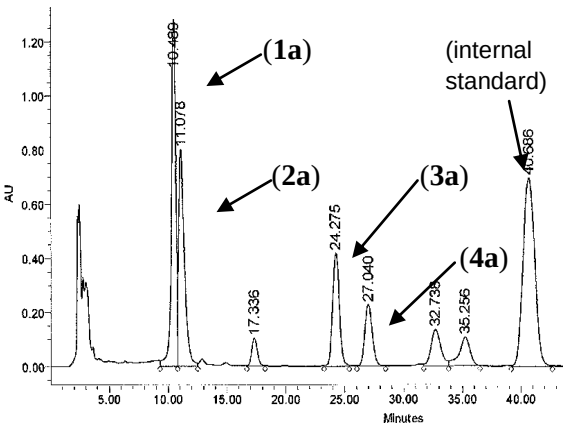
Optimization method for the fluorination of 1a

To a solution of alcohol (0.2 mmol) in dry CH_2Cl_2 (1.5 mL) in a conic vial under nitrogen atmosphere was added a solution of sulfonic anhydride (1 M in CH_2Cl_2, 0.22 mL). The solution was stirred for 1 h. Base was then added and after 1 minute stirring, the fluoride source solution was added. The reaction mixture was stirred further for 2 h at RT and quenched with aqueous NaOH (15%, 1 mL). The two layers were separated on a phase-separation column (chromabond® PTS, Macherey-Nagel) and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were concentrated under reduced pressure then dissolved in CH_3CN (10 mL). 0.5 mL of this solution were mixed to 0.5 mL of benzyl (*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylpropanoate solution in CH_3CN (internal standard: 2 mg/mL) before to be analyzed by HPLC. Compounds **3a** and **4a** were quantified by an internal standard method and were corrected to their corresponding UV absorbance factor. HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6 mm, 5 µm; Eluent: MeOH/H_2O 85/15; Flow rate: 1 mL/min; Injection volume: 10 µL; UV detection at λ = 198 nm. An example of chromatogram is provided in supporting information (Figure S1).

Figure S1: Chromatograms for the optimization of fluorination reaction



UV chromatogram of standard compounds at the same concentration.



UV chromatogram of typical crude reaction containing internal standard

Typical procedure for fluorination

To a solution of alcohol (0.2 mmol) in dry CH_2Cl_2 (1.5 mL) in a conic vial under nitrogen atmosphere was added a solution of trifluoromethanesulfonic anhydride (1 M in CH_2Cl_2, 0.22 mL). The solution

was stirred at RT for 1 h. *N*,*N*-Diisopropylethylamine (42 µL, 0.24 mmol) was then added and after 1 minute stirring, a solution of TBAF (1 M in THF, 0.4 mL) was added. The reaction mixture was stirred further for 2 h at RT and quenched with aqueous NaOH (15%, 1 mL). The two layers were separated on a phase-separation column (chromabond® PTS, Macherey-Nagel). The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL), the combined organic layers were concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

(*S*)-*N*,*N*-dibenzyl-1-fluoro-3-phenylpropan-2-amine (3a) and (*R*)-*N*,*N*-Dibenzyl-2-fluoro-3-phenylpropan-1-amine (4a)

Starting from (*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylpropan-1-ol **1a**,[4] isomers **3a** (18 mg, 27%) and **4a** (29 mg, 44%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 100/1) as colorless oils.

3a: $[\alpha]_D^{20}$ -19.9 (*c* 1.36, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 28.7 min. Characterization data are in accordance to the published data.[5]

4a: $[\alpha]_D^{20}$ -1.9 (*c* 2.48, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 25.5 min. Characterization data are in accordance to the published data.[5]

(*S*)-*N*,*N*-Methylpropargyl-1-fluoro-3-phenylpropan-2-amine and (3b) (*R*)-*N*,*N*-Methylpropargyl-2-fluoro-3-phenylpropan-1-amine (4b)

Starting from **1b** (121mg, 0.6 mmol), isomers **3b** (41 mg, 33%) and **4b** (44 mg, 36%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 90/10 to 85/15) as colorless oils.

3b: $[\alpha]_D^{20}$ -24.7 (*c* 0.36, $CHCl_3$); IR (ATR) ν_{max}: 3295, 2360, 1454, 1016, 740, 700, 648; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.35-7.22 (m, 5H), 4.62-4.33 (m, 2H), 3.55 (s, 2H), 3.16-3.00 (m, 2H), 2.77 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 10.0 Hz, 1H), 2.55 (s, 3H), 2.30 (t, $^4J_{HH}$ = 2.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 139.4, 129.6, 128.9, 126.7, 82.6 (d, $^1J_{CF}$ = 170.9 Hz), 80.5, 73.2, 64.2 (d, $^2J_{CF}$ = 17.5 Hz), 44.3 (d, $^4J_{CF}$ = 2.0 Hz), 38.5 (d, $^4J_{CF}$ = 1.7 Hz), 33.3 (d, $^3J_{CF}$ = 6.2 Hz); δ ^{19}F NMR (376.5 MHz, $CDCl_3$) -227.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{17}NF$ 206.1345; Found 206.1341; HPLC purity: eluent MeOH/H_2O/TFA 30/70/0.1, t_r = 10.1 min.

4b: $[\alpha]_D^{20}$ -17.3 (*c* 0.33, $CHCl_3$); IR (ATR) ν_{max}: 3295, 2945, 1454, 1030, 745, 700, 644; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.33-7.23 (m, 5H), 4.92-4.73 (m, 1H), 3.43 and 3.38 (ABX system, $^2J_{AB}$ = 17.2 Hz, $^4J_{AX}$ = $^4J_{BX}$ = 2.4 Hz, 2H), 3.00-2.92 (m, 2H), 2.70-2.57 (m, 2H), 2.37 (s, 3H), 2.21 (t, $^4J_{HH}$ = 2.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 137.3 (d, $^3J_{CF}$ = 4.6 Hz), 129.7, 128.8, 127.0, 93.2 (d, $^1J_{CF}$ = 172.0 Hz), 78.7, 73.6, 58.9 (d, $^2J_{CF}$ = 21.0 Hz), 46.7 (d, $^4J_{CF}$ = 1.7 Hz), 42.8, 40.0 (d, $^2J_{CF}$ = 21.2 Hz); δ ^{19}F NMR (376.5 MHz, $CDCl_3$) -180.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{17}NF$ 206.1345; Found 206.1342; HPLC purity: eluent MeOH/H_2O/TFA 30/70/0.1, t_r = 11.4 min.

***N*,*N*-Dibenzyl-2-fluoroethanamine (6a)**

Starting from **5a**, compound **6a** (16.7 mg, 35%) was obtained after purification by chromatography on silica gel (heptane/AcOEt, 100/1) as a colorless oil. HPLC purity: eluent MeOH/H_2O 80/20, t_r = 16.0 min Characterization data are in accordance to the published data.[6]

***N*,*N*-Allylbenzyl-2-fluoroethanamine (6b)**

Starting from **5b**, compound **6b** (16.2 mg, 42%) was obtained after purification by chromatography on silica gel (heptane/AcOEt, 98/2) as a colorless oil. IR (ATR) ν_{max}: 3029, 2970, 2802, 1738, 1453, 1027, 994, 919, 737, 698; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.28-7.16 (m, 5H), 5.85-5.77 (m, 1H), 5.16-5.07 (m, 2H), 4.44 (dt, $^2J_{HF}$ = 47.6 Hz, $^3J_{HH}$ = 5.4 Hz, 2H), 3.61 (s, 2H), 3.11 (d, $^3J_{HH}$ = 6.4 Hz, 2H), 2.72 (dt, $^3J_{HF}$ = 26.0 Hz, $^3J_{HH}$ = 5.4 Hz, 2H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 139.6, 136.0, 129.2, 128.6, 127.3, 118.0, 83.1 (d, $^1J_{CF}$ = 166.5 Hz), 59.0 (d, $^4J_{CF}$ = 1.0 Hz), 57.8 (d, $^4J_{CF}$ = 1.0 Hz), 53.3 (d, $^2J_{CF}$ = 20.3 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -219.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{17}NF$ 194.1345; Found 194.1338; HPLC purity: eluent MeOH/H_2O 80/20, t_r = 7.9 min.

***N*,*N*-Benzylpropargyl-2-fluoroethanamine (6c)**

Starting from **5c**, compound **6c** (20 mg, 52%) was obtained after purification by chromatography on silica gel (heptane/AcOEt, 90/10) as a colorless oil. IR (ATR) ν_{max}: 3296, 3030, 2951, 2828, 1454, 1028, 737, 698, 647; δ ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 7.32-7.18 (m, 5H), 4.50 (dt, $^2J_{HF}$ = 47.6 Hz, $^3J_{HH}$ = 5.2 Hz, 2H), 3.66 (s, 2H), 3.35 (d, $^4J_{HH}$ = 2.4 Hz, 2H), 2.84 (dt, $^3J_{HF}$ = 26.0 Hz, $^3J_{HH}$ = 5.2 Hz, 2H), 2.20 (t, $^4J_{HH}$ = 2.4 Hz, 1H); δ ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) 138.6, 129.4, 128.7, 127.6, 83.1 (d, $^1J_{CF}$ = 166.7 Hz), 78.7, 73.7, 58.6 (d, $^4J_{CF}$ = 1.0 Hz), 53.3 (d, $^2J_{CF}$ = 20.1 Hz), 42.7 (d, $^4J_{CF}$ = 1.6 Hz); δ ^{19}F NMR (376.5 MHz, $CDCl_3$) -219.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{15}NF$ 192.1189; Found 192.1190; HPLC purity: eluent MeOH/H_2O 70/30, t_r = 8.5 min.

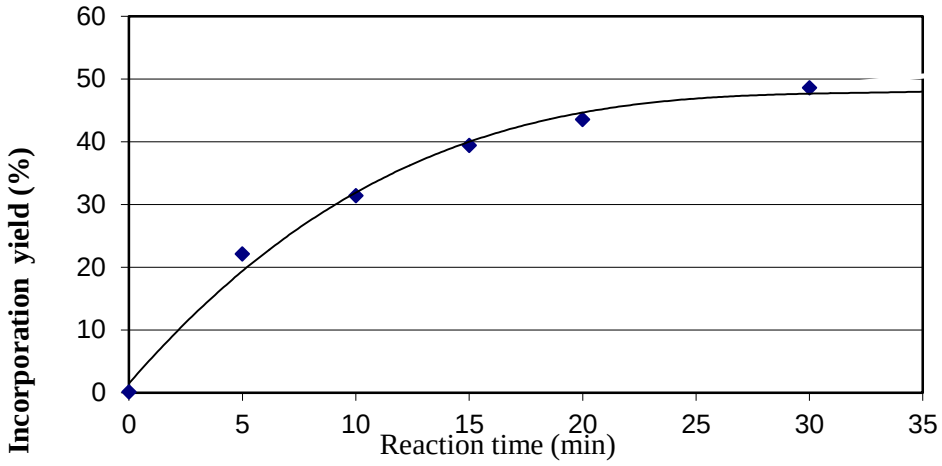
RADIOCHEMISTRY

Typical procedure for radiofluorination

No-carrier-added aqueous [^{18}F]-fluoride was produced by ^{18}O[p,n]^{18}F nuclear reaction of a target consisting of ^{18}O-enriched water (97%, Eurisotop, France) irradiated with a 18 MeV proton beam (IBA Cyclone 18/9 cyclotron). [^{18}F]-fluoride was trapped on a quaternary ammonium solid phase extraction cartridge (QMA Waters preconditioned with K_2CO_3, ABX, Germany) then eluted with tetrabutylammonium carbonate. After three azeotropic evaporations with acetonitrile at 90°C under nitrogen steam, dry [^{18}F]-fluoride was cooled down to RT. Triflic anhydride (1 M in CH_2Cl_2, 37 µL) was added to a solution of **1** (33 µmol) in CH_2Cl_2 (260 µL). After 1 h of reaction at RT, DIPEA (40 µmol) in CH_3CN (200 µL) was added to the crude and allowed to react for 1 min. Then, the reaction mixture was transferred into the vial containing dry [^{18}F]-fluoride (40 MBq) and tetrabutylammonium carbonate (23 µmol). The solution was stirred at RT for 30 min. Aliquot (0.025 mL) were taken off

and diluted in MeOH (0.2 mL). Analyses were performed by radio-TLC to establish the incorporation yield and by radio-HPLC to measure the isomer ratio. Identity of the radiofluorinated compounds was assessed by HPLC coelution with non-radioactive reference [^{19}F]-compounds. HPLC chromatograms shown below are the co-injection of the radioactive crude radiofluorination with non-radioactive reference product. Radioactivity detector (NaI probe, Novelec, France) is placed in line after the UV detector (996, Waters, France) generating a delay of 0.48 min between both signals.

Figure S2: Example of [^{18}F]-incorporation kinetics for [^{18}F]-**3a** and [^{18}F]-**4a** from **1a**

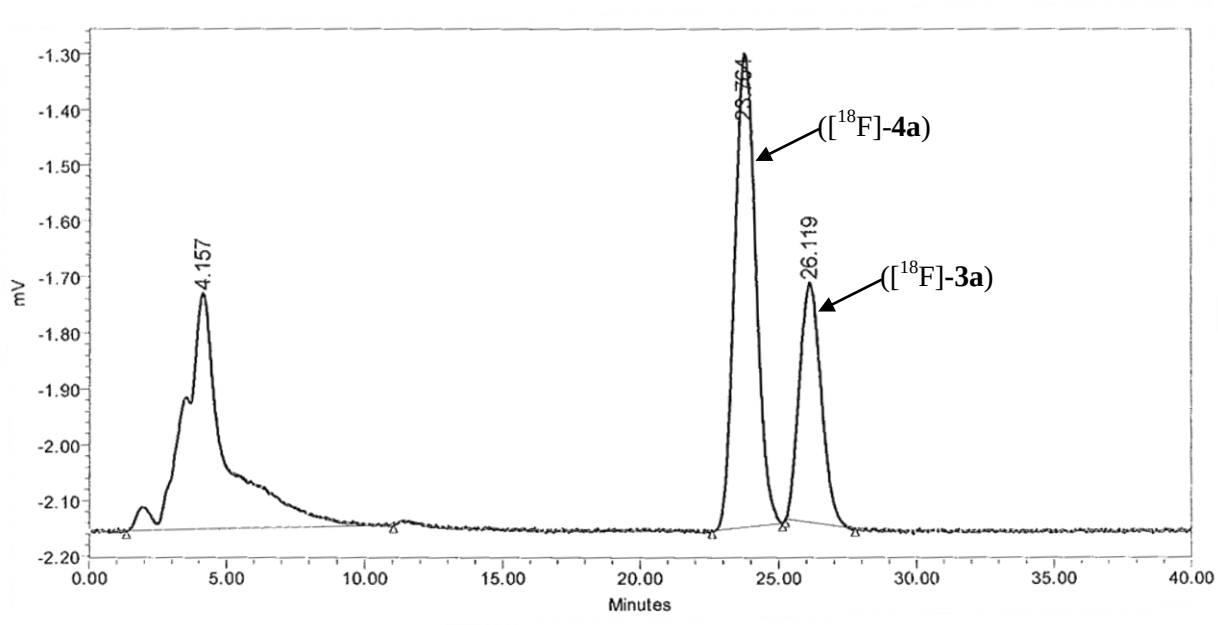


(*R*)-*N*,*N*-Dibenzyl-2-[^{18}F]-fluoro-3-phenylpropan-1-amine ([^{18}F]-3a) and (*S*)-*N*,*N*-dibenzyl-1-[^{18}F]-fluoro-3-phenylpropan-2-amine ([^{18}F]-4a) starting from precursor 1a

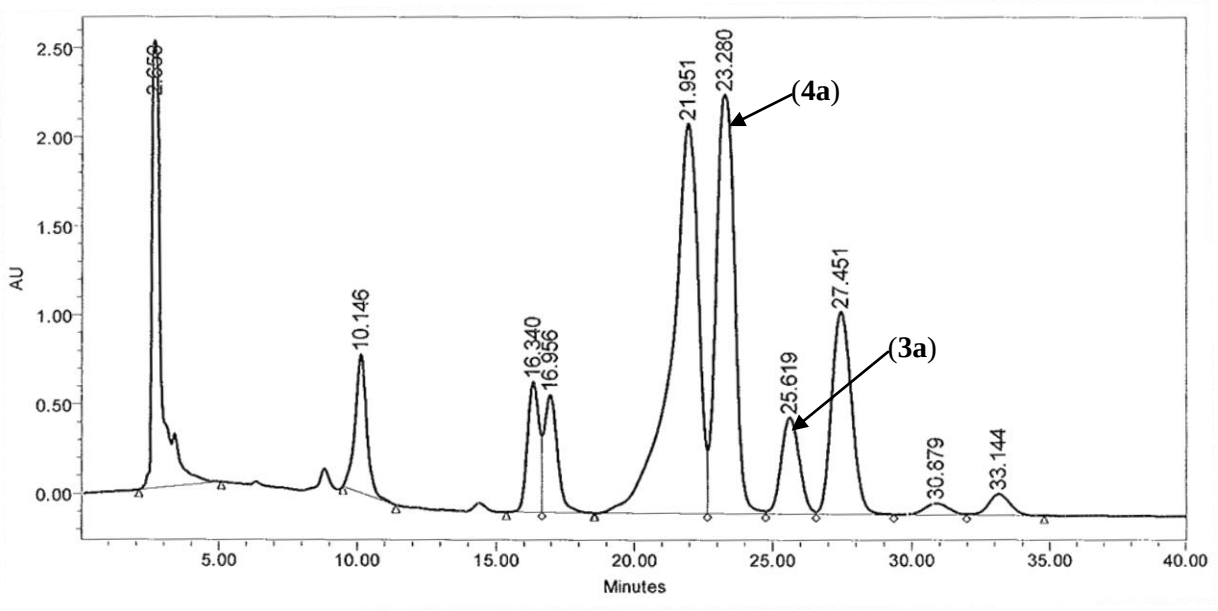
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O 85/15; Flow rate: 1 mL/min; UV detection at λ = 210 nm.

TLC conditions: heptane/AcOEt, 90/10.

Radioactive channel



UV channel

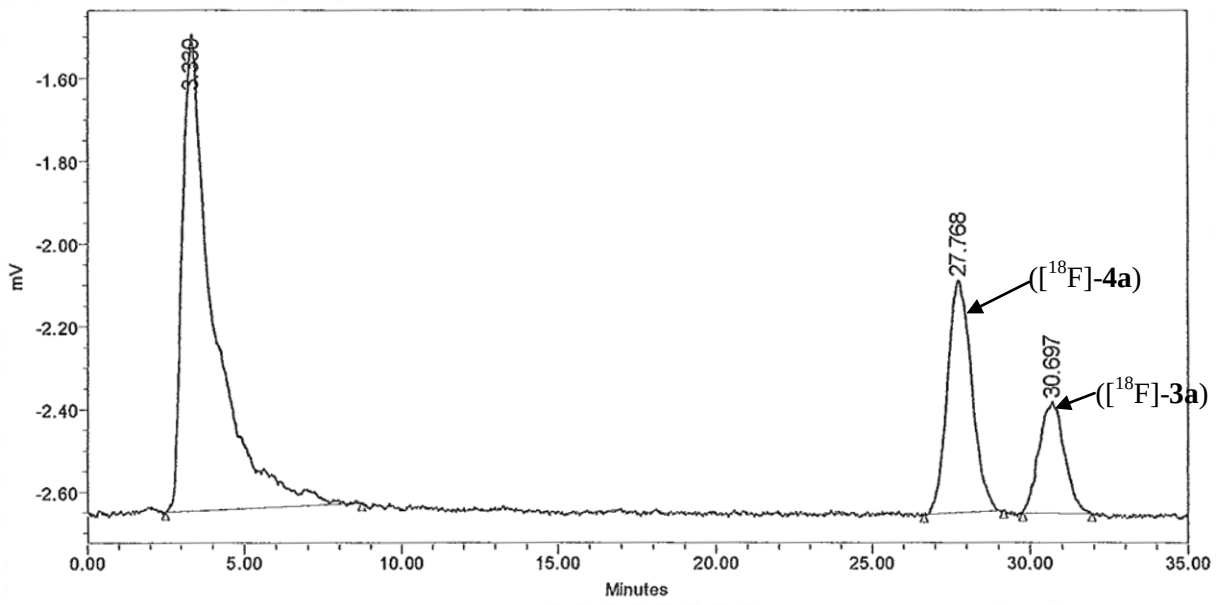


(*R*)-*N*,*N*-Dibenzyl-2-[^{18}F]-fluoro-3-phenylpropan-1-amine ([^{18}F]-3a) and (*S*)-*N*,*N*-dibenzyl-1-[^{18}F]-fluoro-3-phenylpropan-2-amine ([^{18}F]-4a) starting from precursor 2a

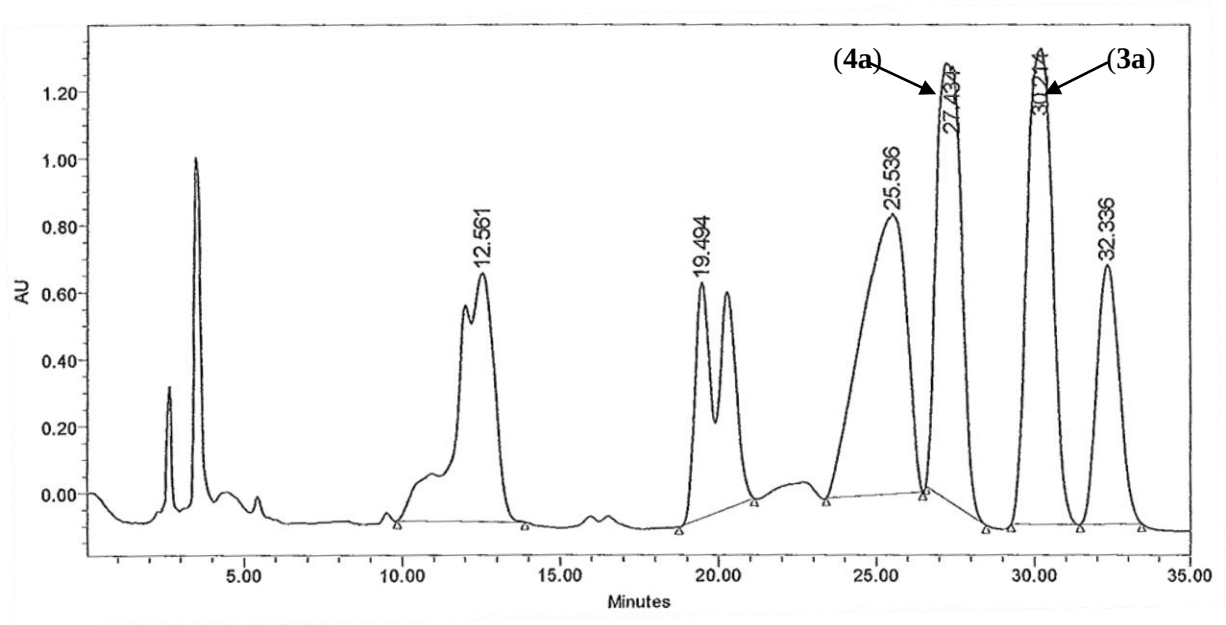
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O 85/15; Flow rate: 1 mL/min; UV detection at λ = 210 nm.

TLC conditions: heptane/AcOEt, 90/10.

Radioactive channel



UV channel

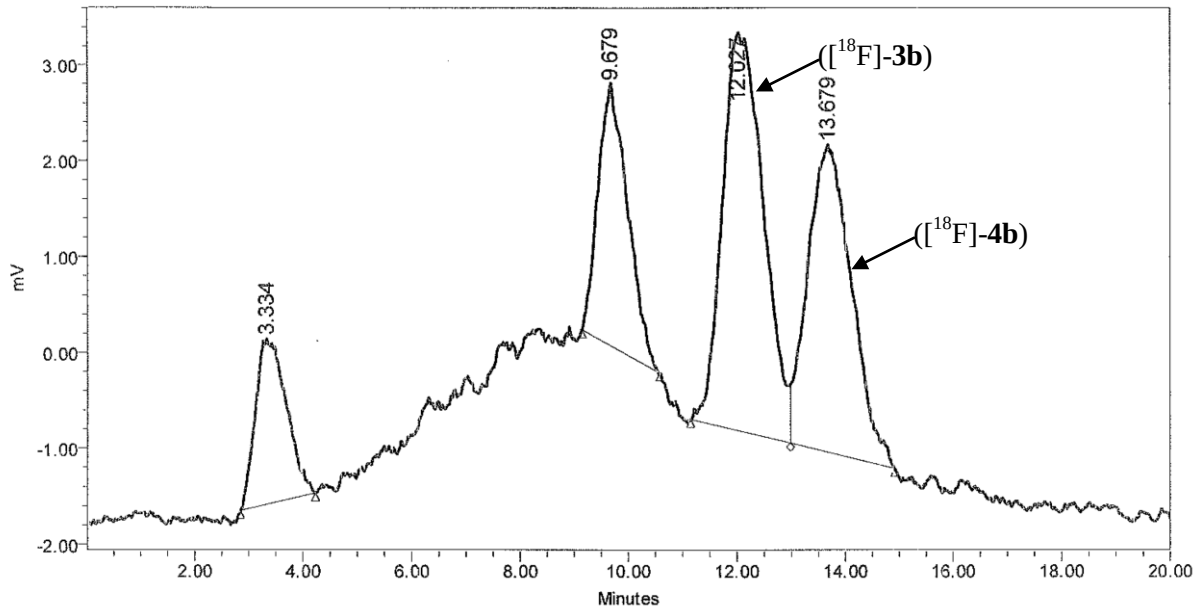


(*R*)-*N*-methyl,*N*-propargyl-2-[^{18}F]-fluoro-3-phenylpropan-1-amine ([^{18}F]-3b) and (*S*)-*N*-methyl,*N*-propargyl-1-[^{18}F]-fluoro-3-phenylpropan-2-amine ([^{18}F]-4b) starting from precursor 1b

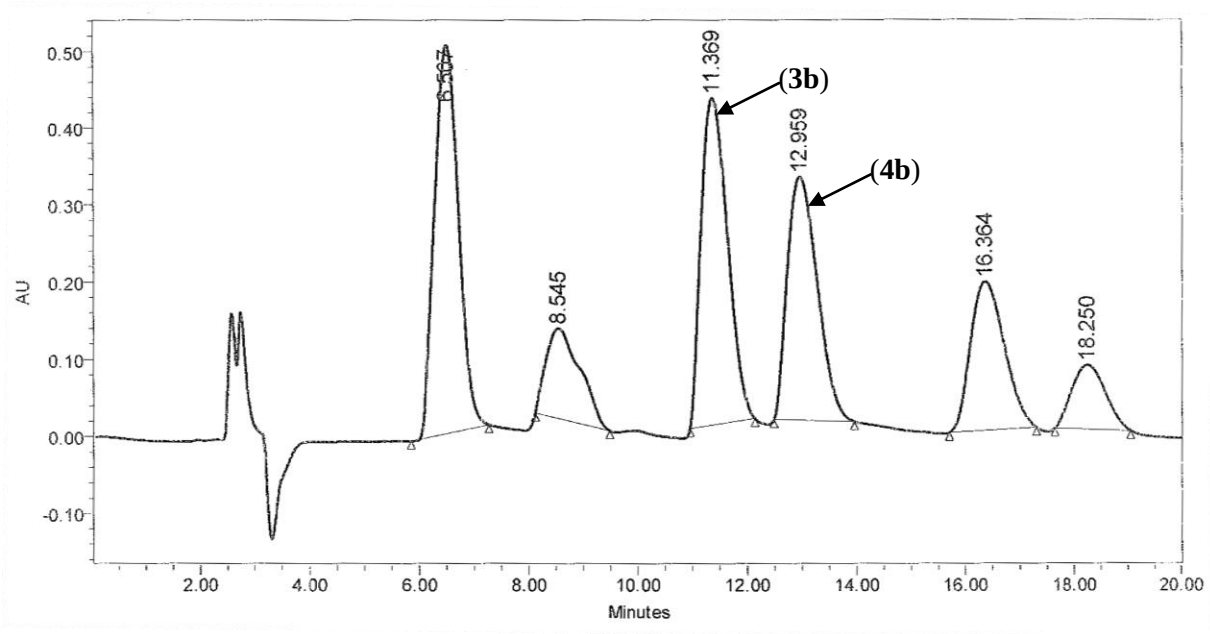
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O/TFA 30/70/0.1; Flow rate: 1 mL/min; UV detection at λ = 210 nm.

TLC conditions: heptane/AcOEt, 70/30.

Radioactive channel



UV channel

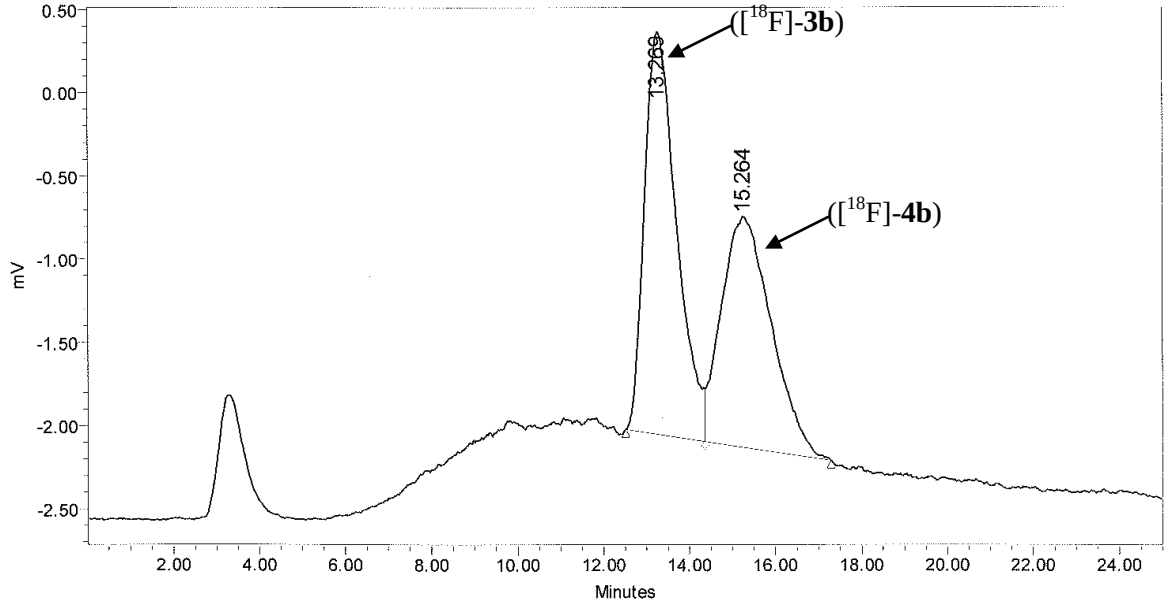


(*R*)-*N*-methyl,*N*-propargyl-2-[^{18}F]-fluoro-3-phenylpropan-1-amine ([^{18}F]-3b) and (*S*)-*N*-methyl,*N*-propargyl-1-[^{18}F]-fluoro-3-phenylpropan-2-amine ([^{18}F]-4b) starting from precursor 2b

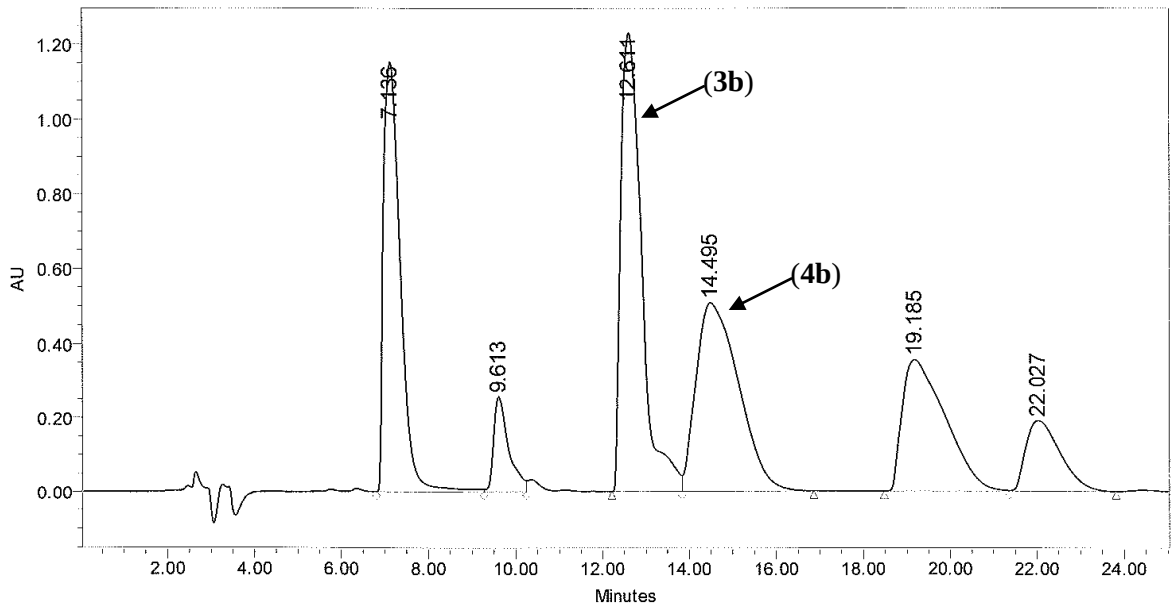
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O/TFA 30/70/0.1; Flow rate: 1 mL/min; UV detection at λ = 210 nm.

TLC conditions: heptane/AcOEt, 70/30.

Radioactive channel



UV channel

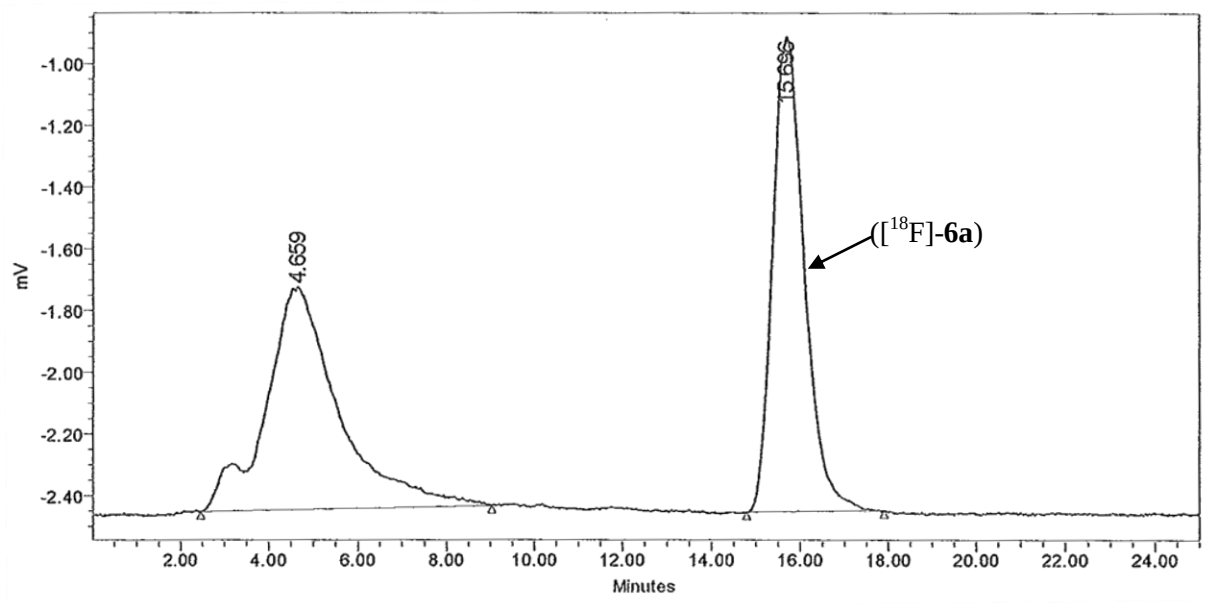


***N*,*N*-Dibenzyl-2-[^{18}F]-fluoroethanamine ([^{18}F]-6a)**

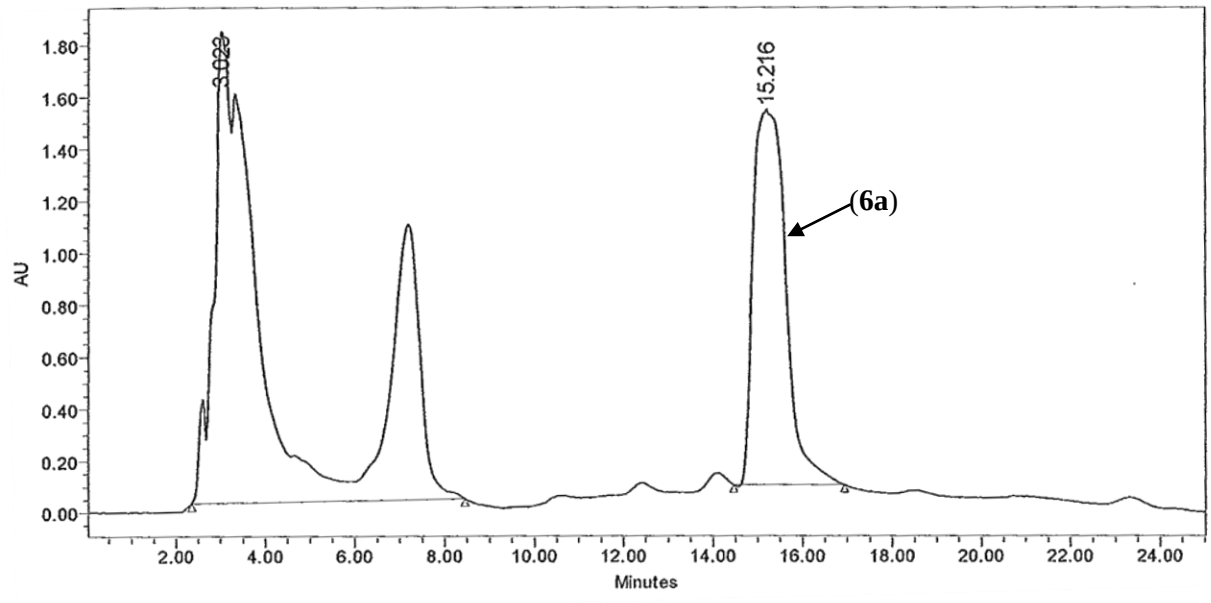
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O 80/20; Flow rate: 1 mL/min; UV detection at λ = 198 nm.

TLC conditions: heptane/AcOEt, 90/10.

Radioactive channel



UV channel

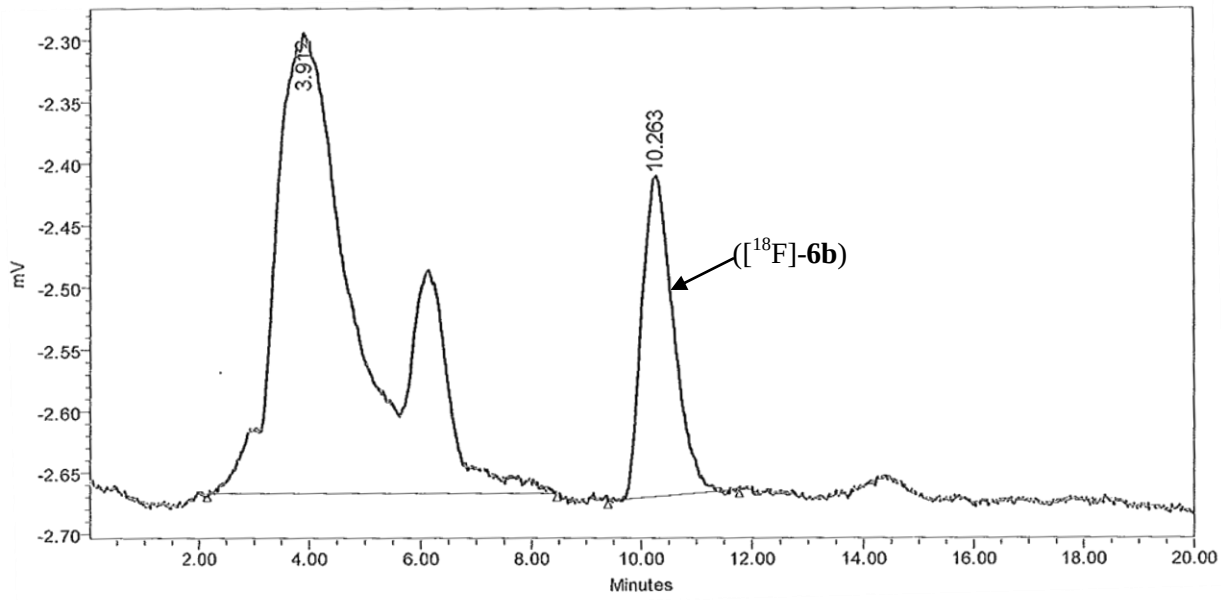


***N*,*N*-Allylbenzyl-2-[^{18}F]-fluoroethanamine ([^{18}F]-6b)**

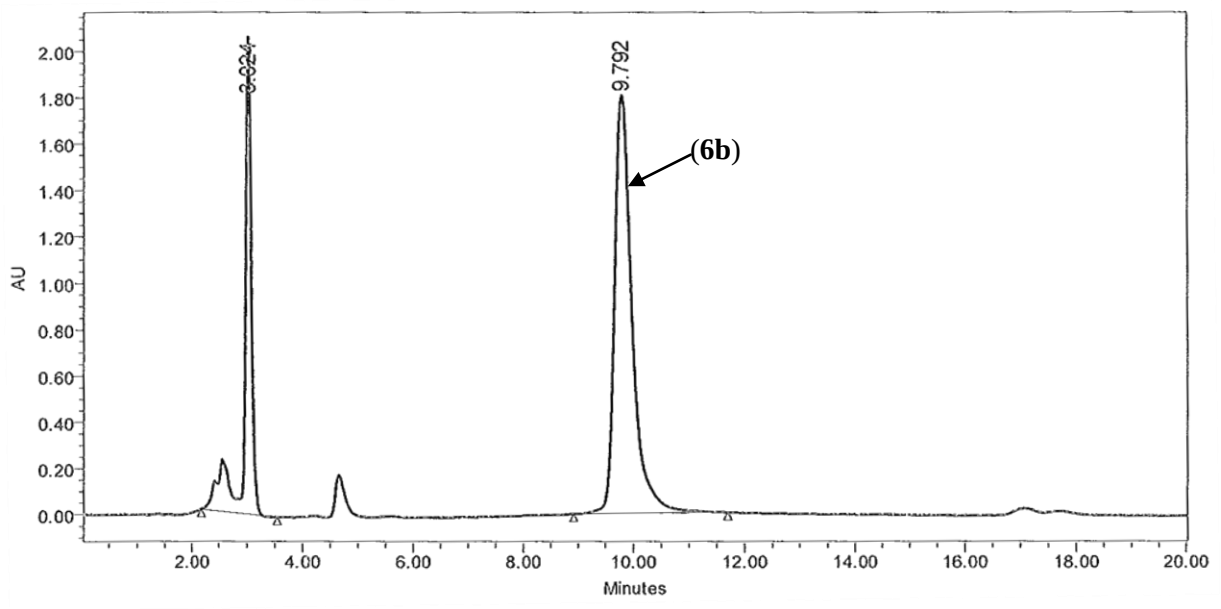
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O 70/30; Flow rate: 1 mL/min; UV detection at λ = 210 nm.

TLC conditions: heptane/AcOEt, 70/30.

Radioactive channel



UV channel

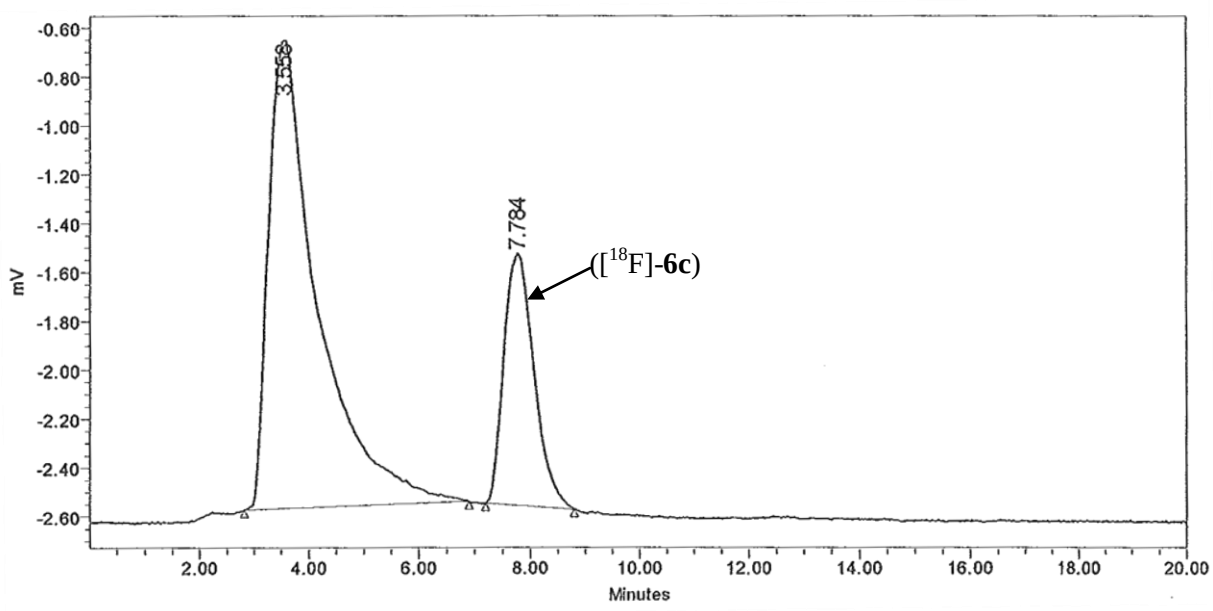


***N*,*N*-Benzylpropargyl-2-[^{18}F]-fluoroethanamine ([^{18}F]-6c)**

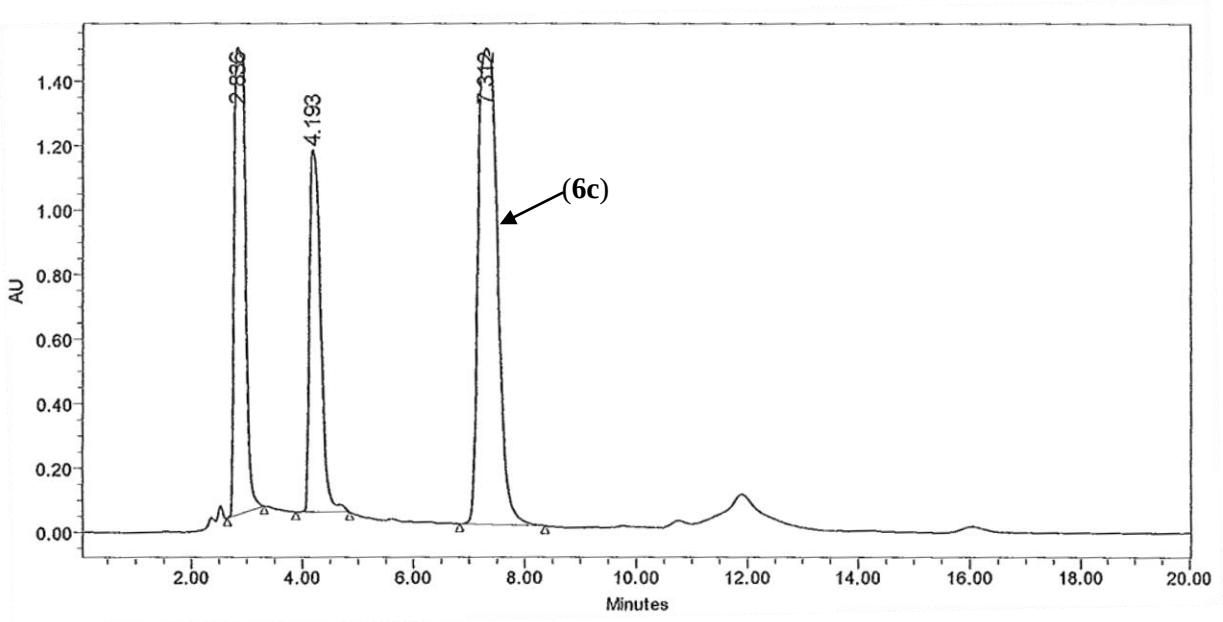
HPLC conditions: Column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; Eluent: MeOH/H_2O 70/30; Flow rate: 1 mL/min; UV detection at λ = 198 nm.

TLC conditions: heptane/AcOEt, 70/30.

Radioactive channel



UV channel



Radiosynthesis of [^{18}F]-3a and [^{18}F]-4a using a GE TRACERLab FX N Pro module

A solution of labeling precursor **1a** (11 mg, 33 µmol), triflic anhydride (37 µL, 37 µmol) in CH_2Cl_2 (0,55 mL) was stirred for 1 hour at RT before to be added in vial 4. The fluorine-18 produced by the cyclotron was trapped on an ion exchange resin (QMA light, Waters, ABX), separated from ^{18}O-enriched water then eluted with a solution of tetrabutylammonium carbonate (0.1 M in water, 200 µL) and acetonitrile (0.3 mL) (vial 1). The mixture was heated to 95 °C under reduced pressure under a flow of helium. 0.6 mL of acetonitrile (vial 2) was added and the mixture was further heated at 95 °C under reduced pressure. Then the reactor 1 was cooled down at RT (<28°C). Precursor solution (vial 4) and a solution of *N*,*N*-diisopropylethylamine (7 µL) in acetonitrile (193 µL) (vial 5) was added to the reactor. The fluorination reaction occurred during 30 min at RT under stirring before MeOH (2 mL)(vial 6) was added to the reactor. Then the reaction mixture was concentrated under vacuum at RT to eliminate CH_2Cl_2. HPLC eluent (2 mL)(vial 3) was added to the reactor to dissolve the reaction mixture for the HPLC injection (column: XTerra C18, 250 × 10 mm, Waters; eluent: MeOH/H_2O 75/25; flow rate: 5 mL/min). The both isomer products [^{18}F]-**3a** and [^{18}F]-**4a** were collected together (retention time: t_r(**3a**) = 20.5 min; t_r(**4a**) = 22.1 min). The collected fraction containing the two pure radiolabeled isomers was injected in HPLC to determine the ratio between both products, to measure the specific activity and to assess their identity by coelution with reference compounds (column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6mm, 5µm; eluent: MeOH/H_2O 85/15; flow rate: 1 mL/min; UV detection at λ = 210 nm). The radiosynthesis was performed within 75 min and the decay corrected radiochemical yields were between 3 and 10%.

REFERENCES

1 G. L. Grunewald, T. M. Caldwell, Q. Li, V. H. Dahanukar, B. McNeil, K. R. Criscione, *J. Med. Chem.* 1999, **42**, 4351.

2 O. D. Montagnat, G. Lessene, A. B. Hughes, *J. Org. Chem.* 2010, **75**, 390.

3 T. X. Métro, D. G. Pardo, J. Cossy, *J. Org. Chem.* 2007, **72**, 6556.

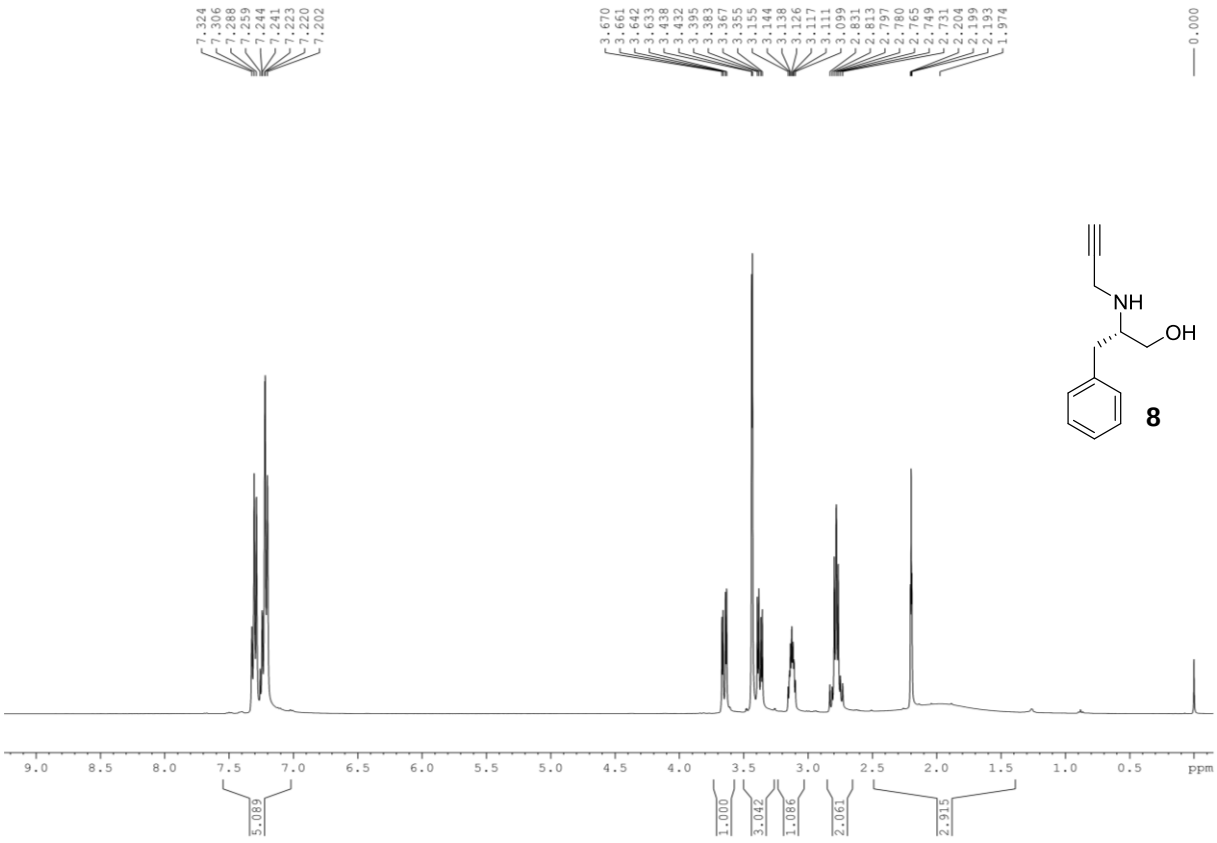
4 M. T. Reetz, M. W. Drewes, R. Schwickardi, *Org. Synth.* 1999, **coll. 76**, 110; O*rg. Synth.* 2004, **10,** 256.

5 B. Duthion, P. D. Gomez, J. Cossy, *Org. Lett.* 2010, **12**, 4620.

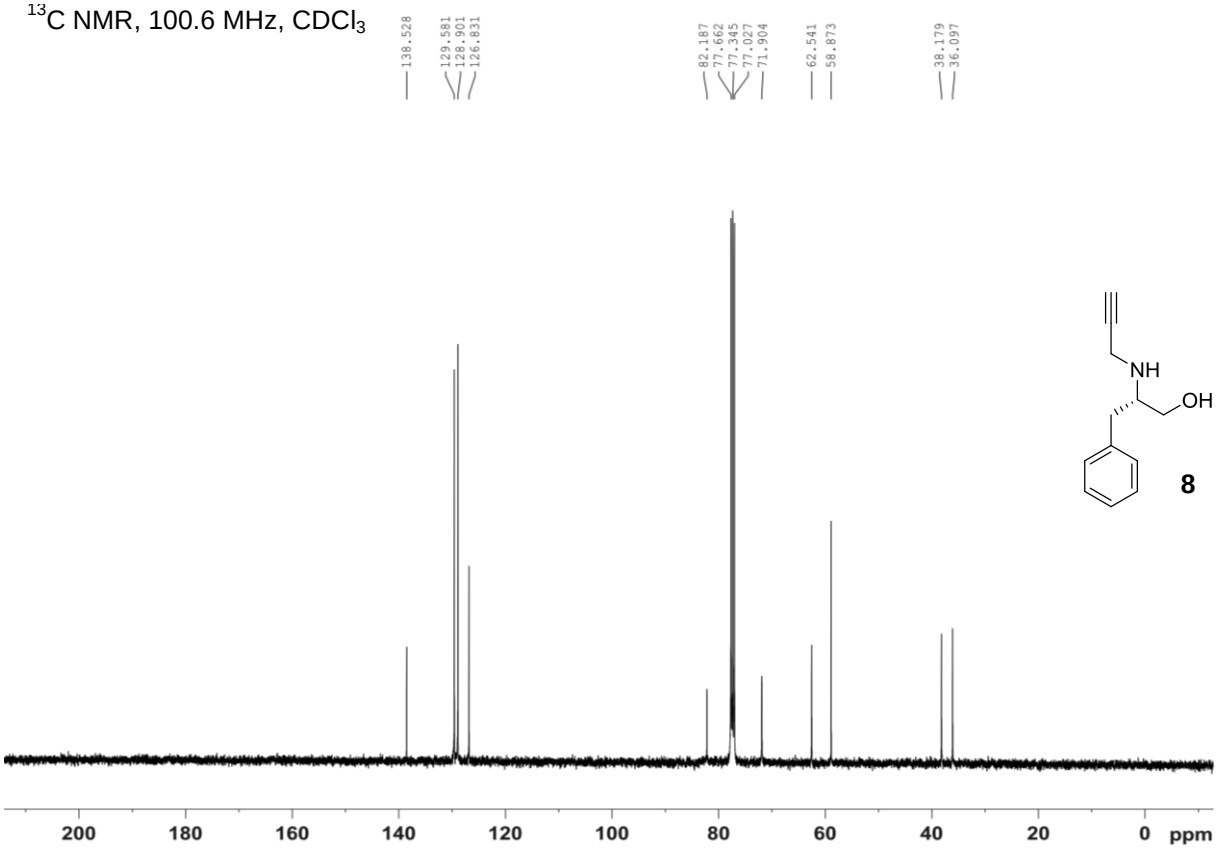
6 C. R. Briggs, M. J. A. Allen, D. O'Hagan, D. J. Tozer, A. M. Slawin, A. E. Goeta, J.A. K. Howard, *Org. Biomol. Chem.* 2004, **2**, 732.

***(S)*-2-(*N*-Propargylamino)-3-phenylpropan-1-ol (8)**

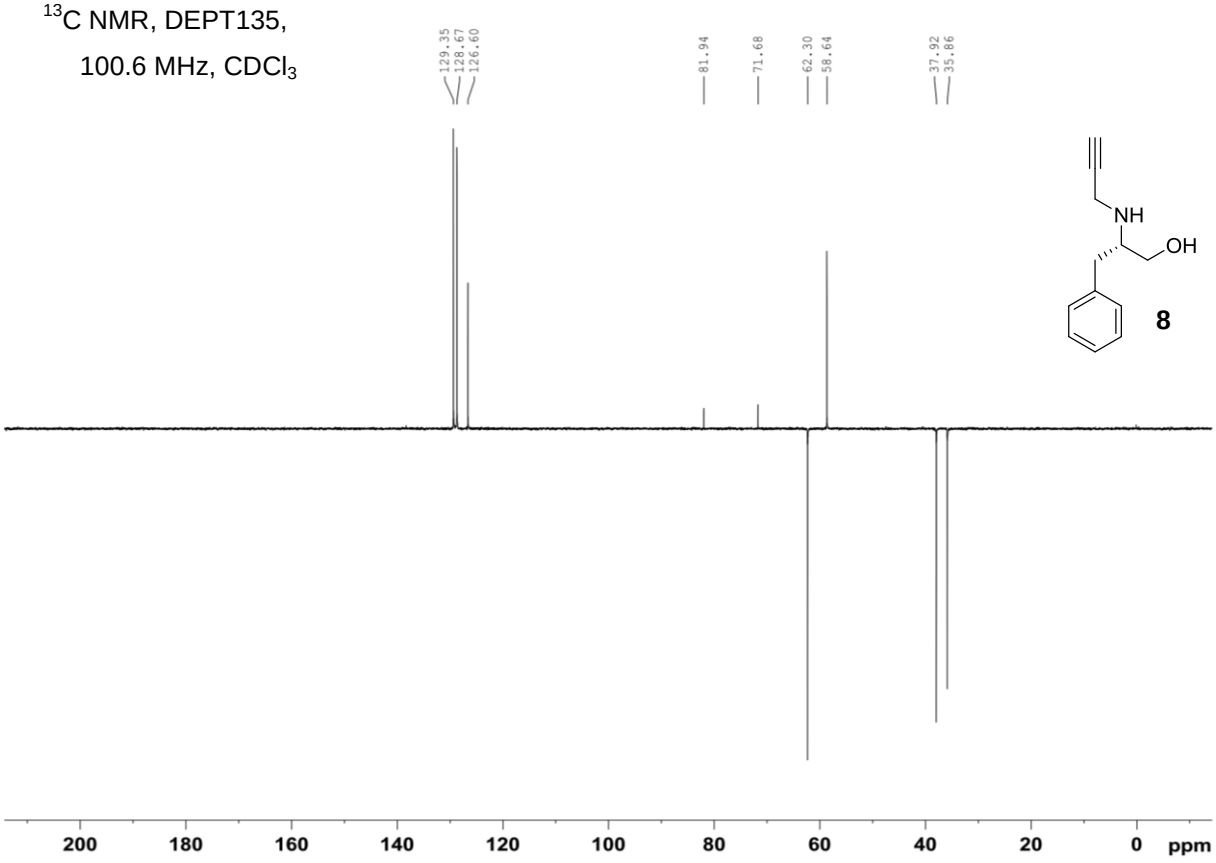
^{1}H NMR, 400 MHz, $CDCl_3$, TMS



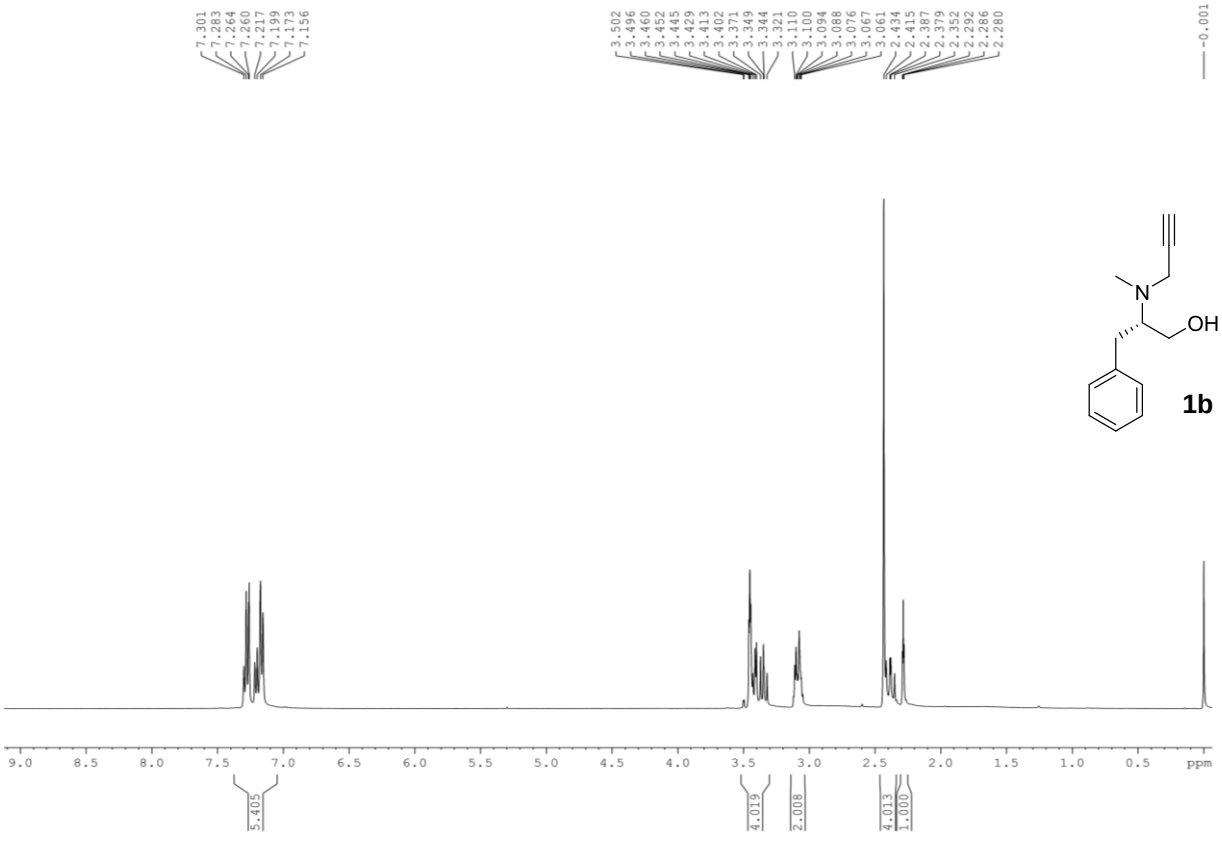
^{13}C NMR, 100.6 MHz, $CDCl_3$



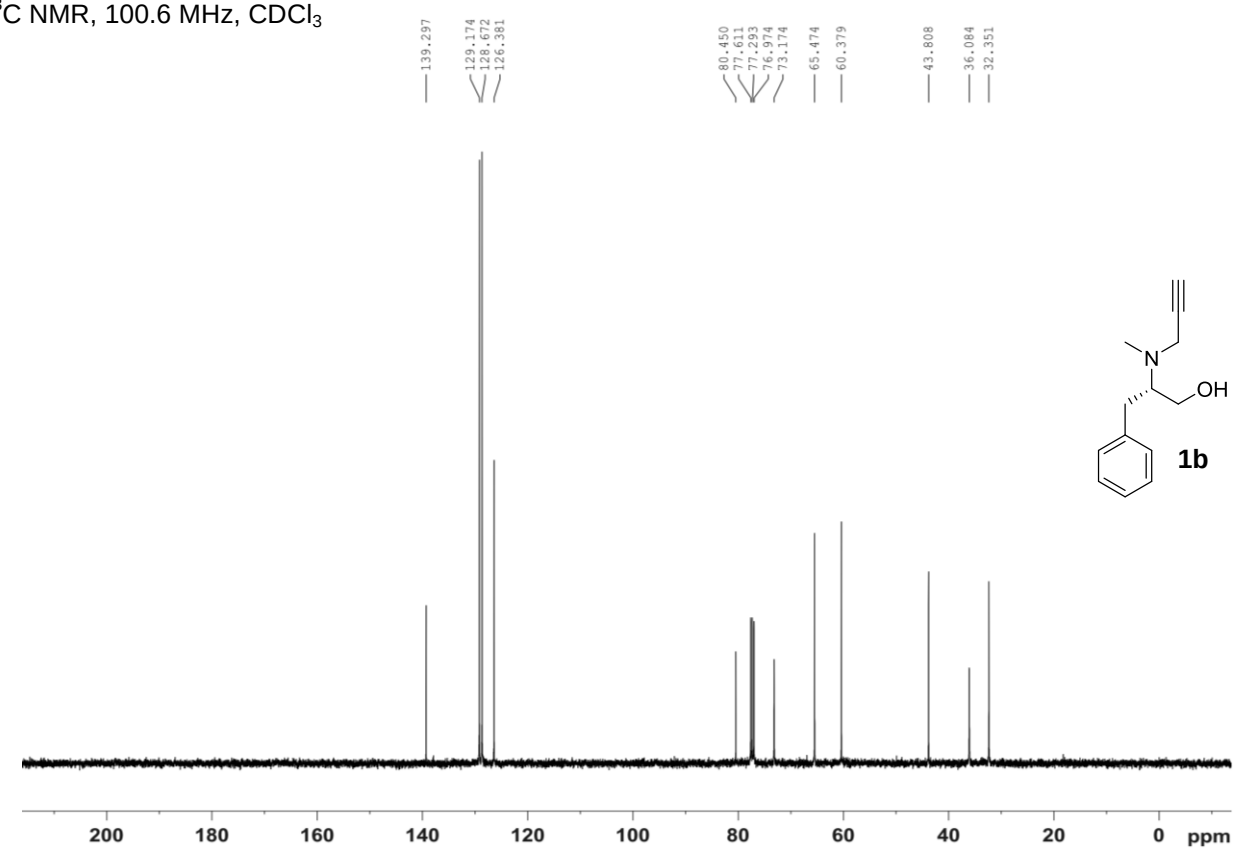
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



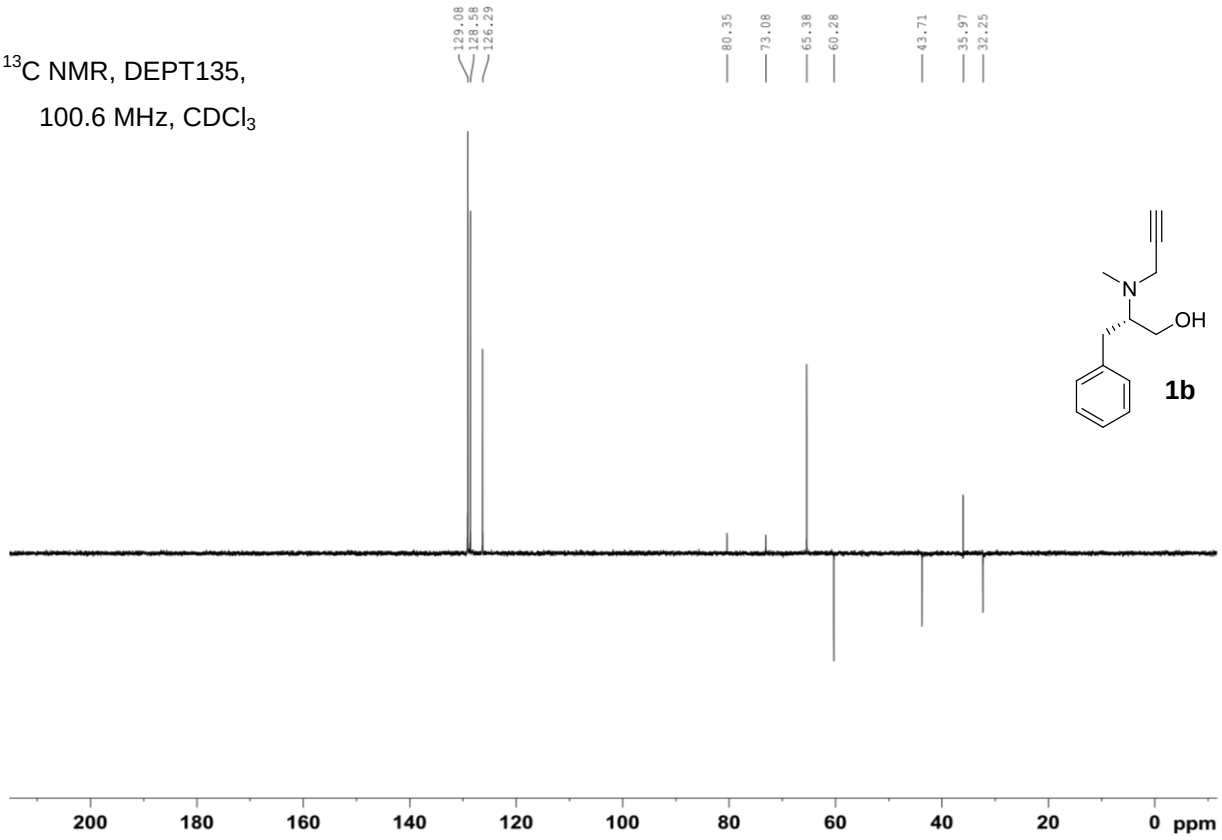
(*S*)-2-(*N*,*N*-Methylpropargylamino)-3-phenylpropan-1-ol (1b) ^{1}H NMR, 400 MHz, $CDCl_3$, TMS



^{13}C NMR, 100.6 MHz, $CDCl_3$

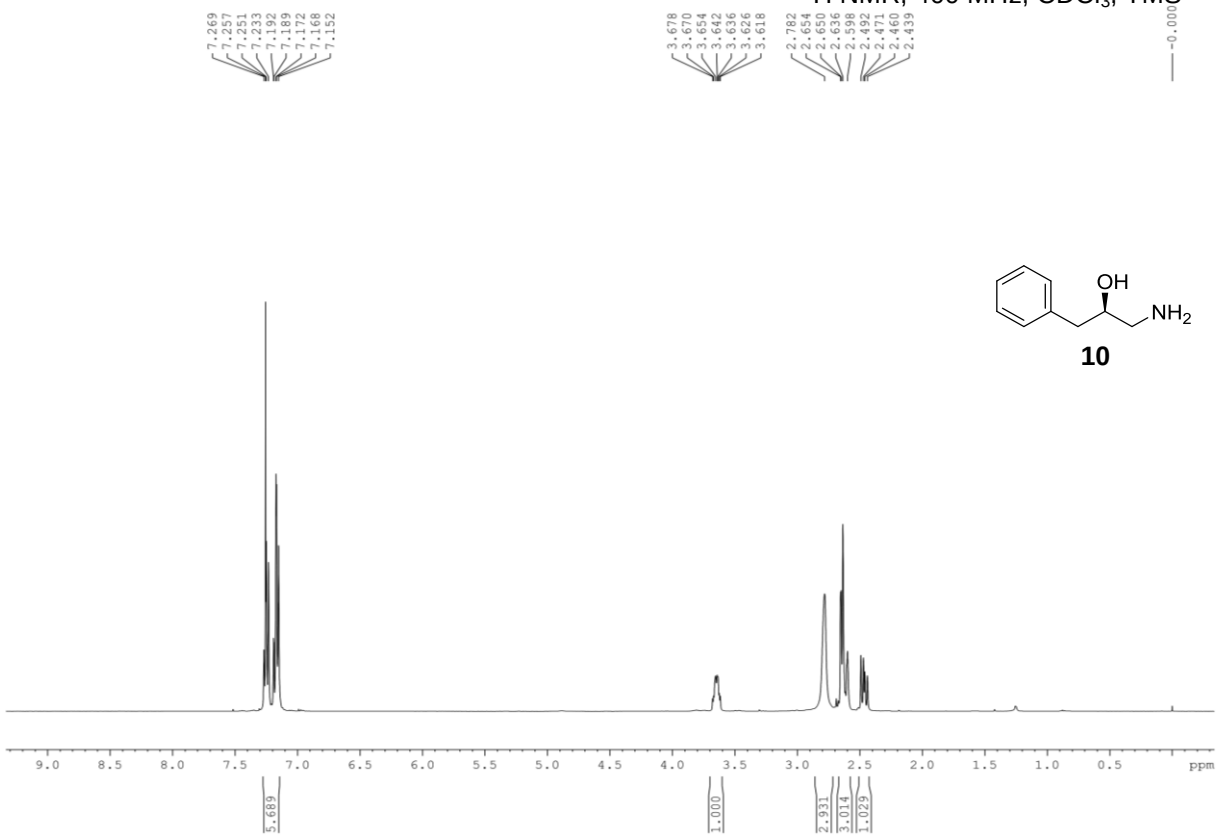


^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$

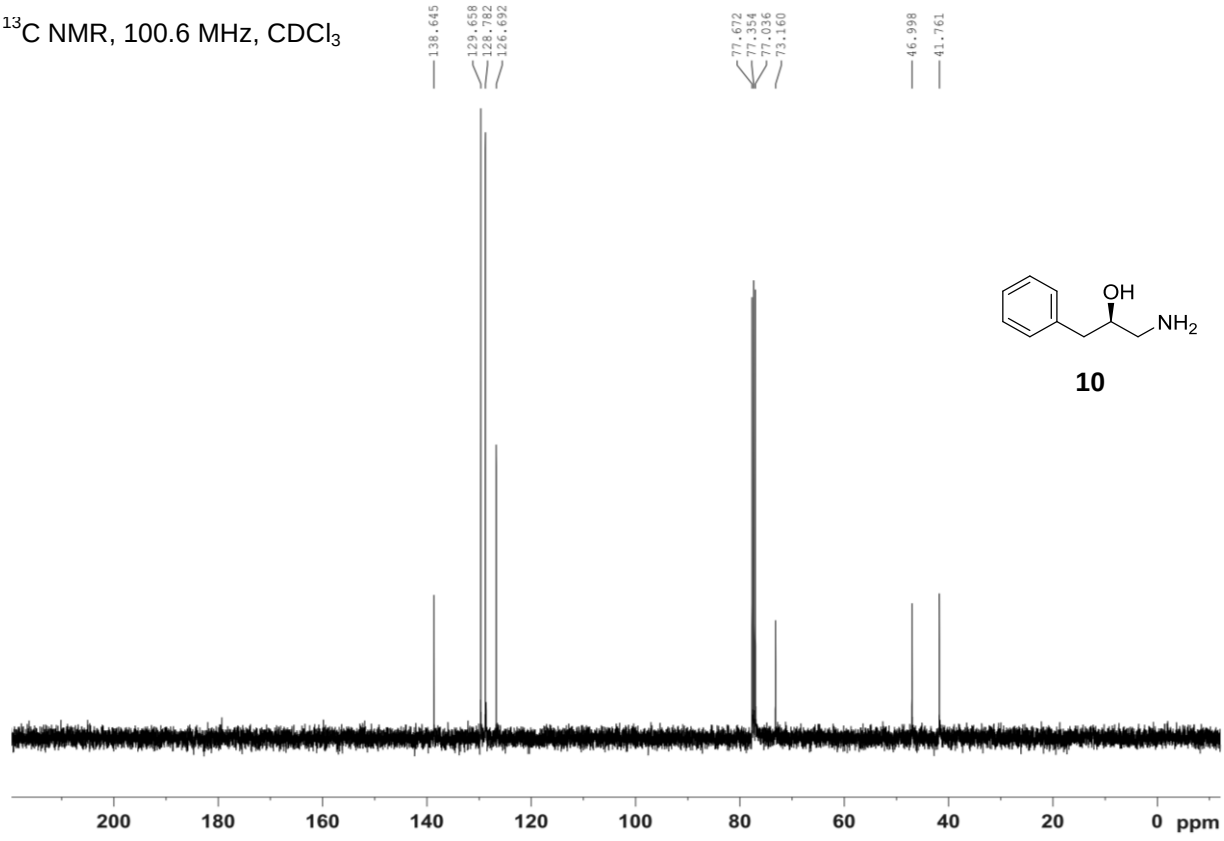


(*R*)-1-Amino-3-phenylpropan-2-ol (10)

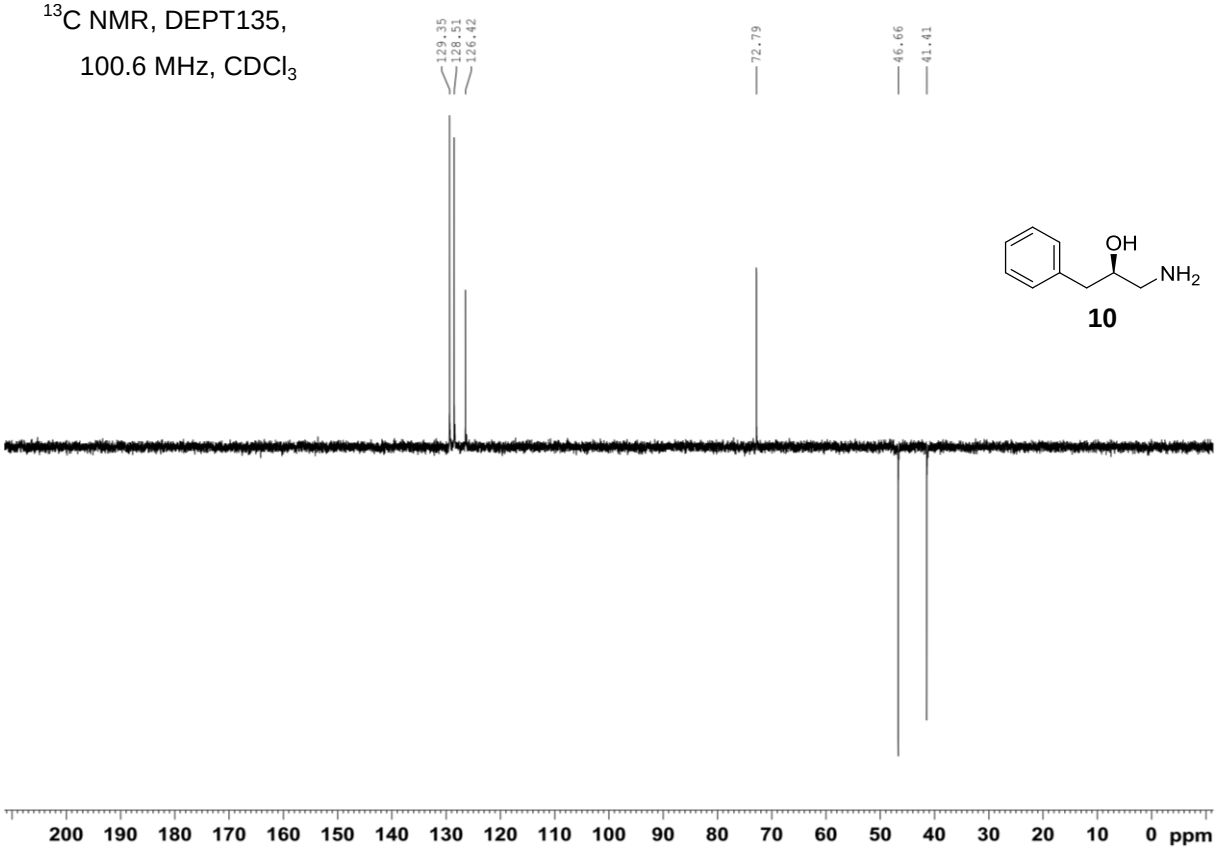
^{1}H NMR, 400 MHz, $CDCl_3$, TMS



^{13}C NMR, 100.6 MHz, $CDCl_3$

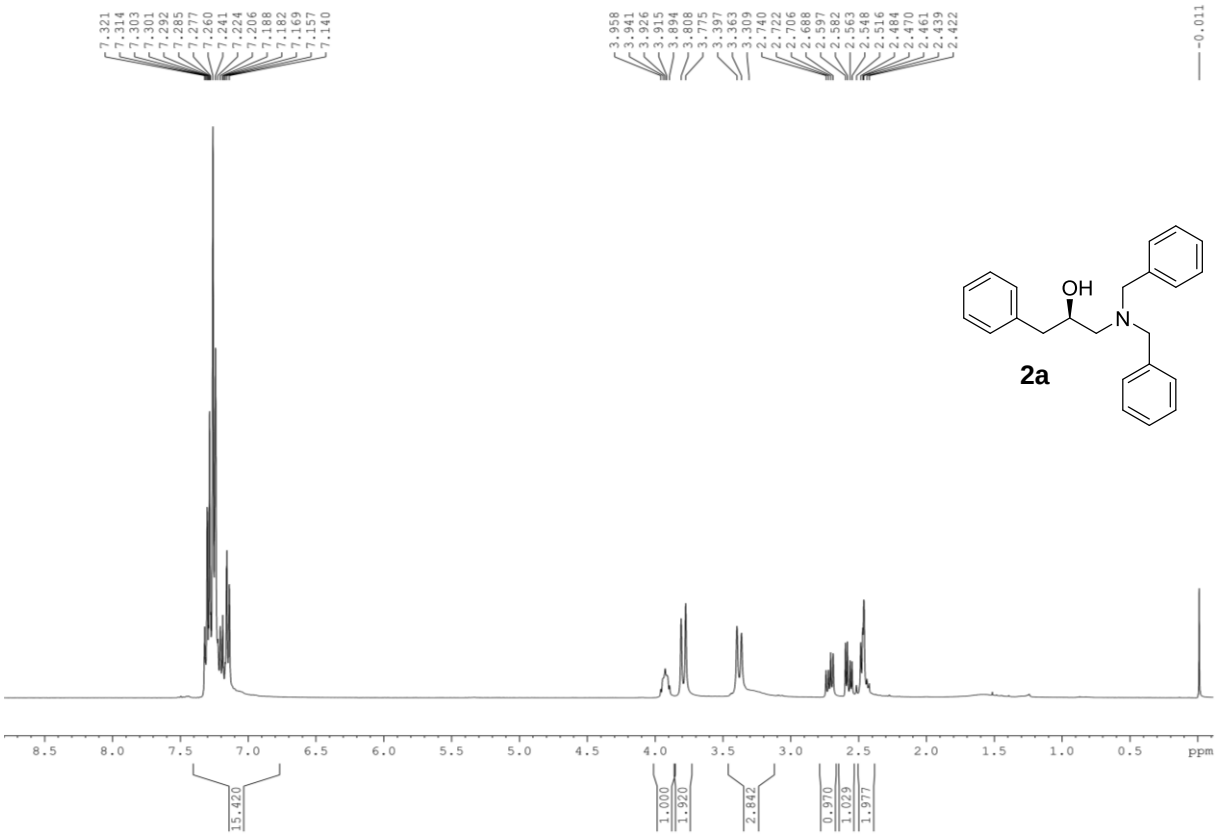


^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$

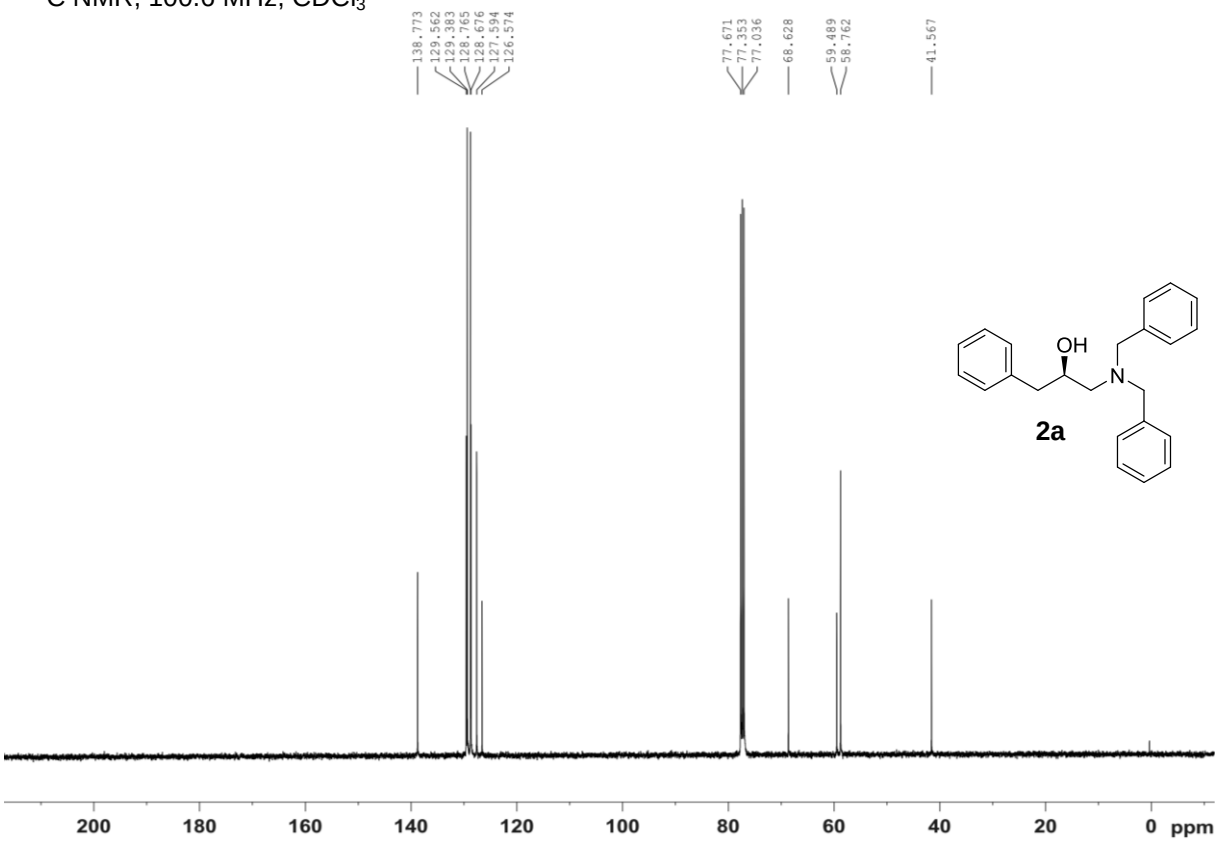


(*R*)-1-(*N*,*N*-Dibenzylamino)-3-phenylpropan-2-ol (2a)

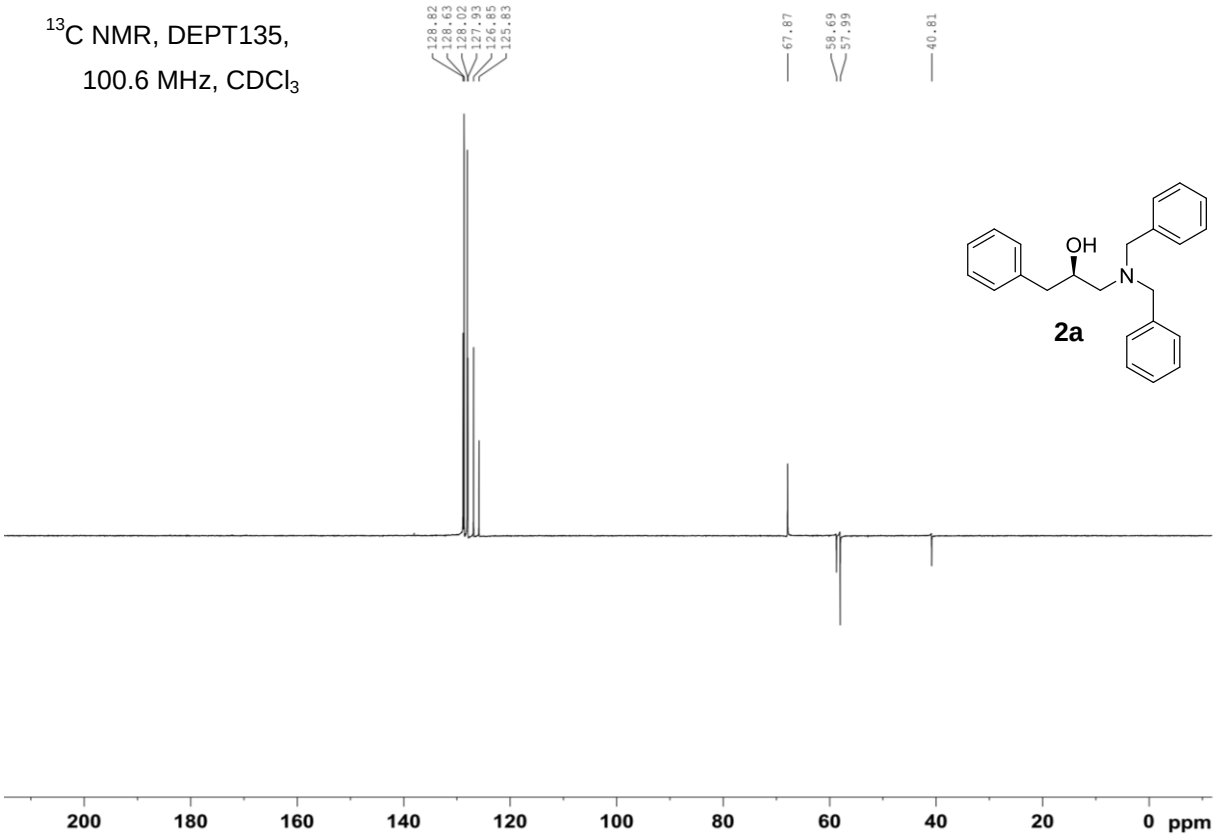
^{1}H NMR, 400 MHz, $CDCl_3$, TMS



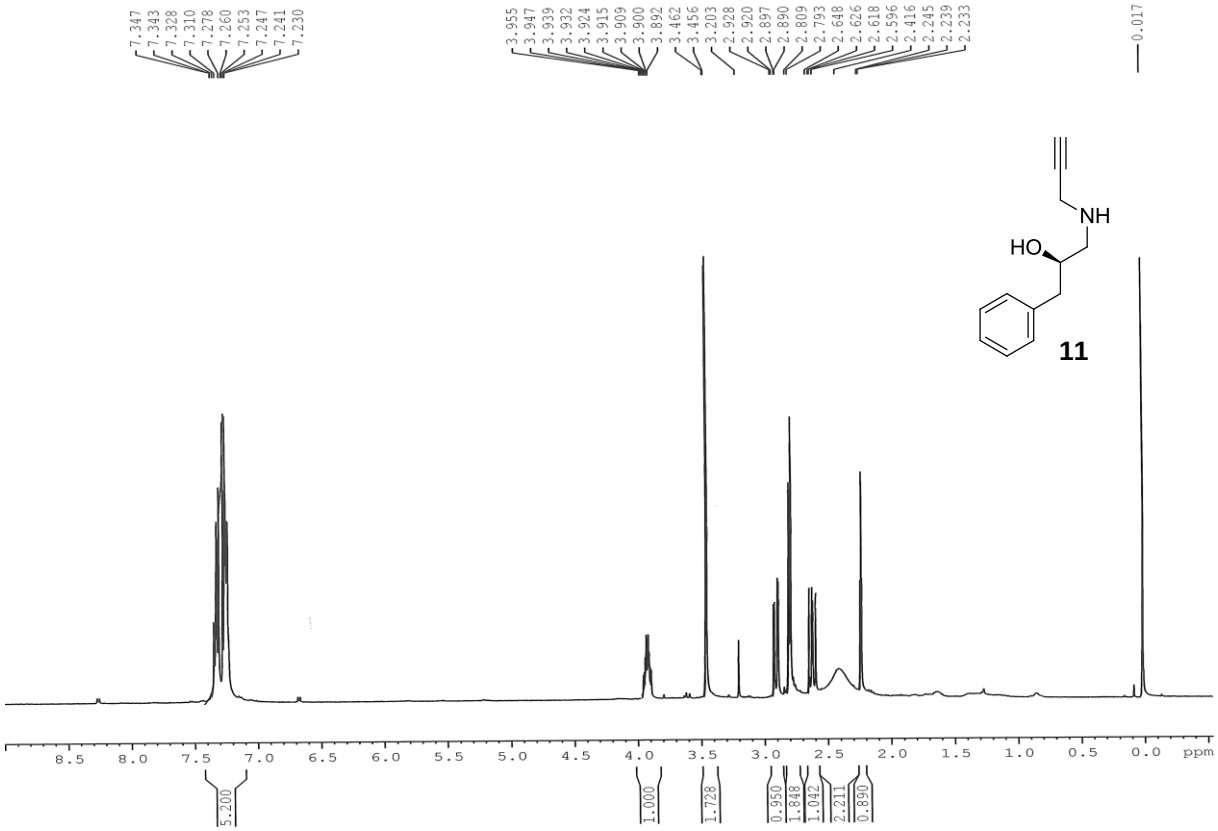
^{13}C NMR, 100.6 MHz, $CDCl_3$



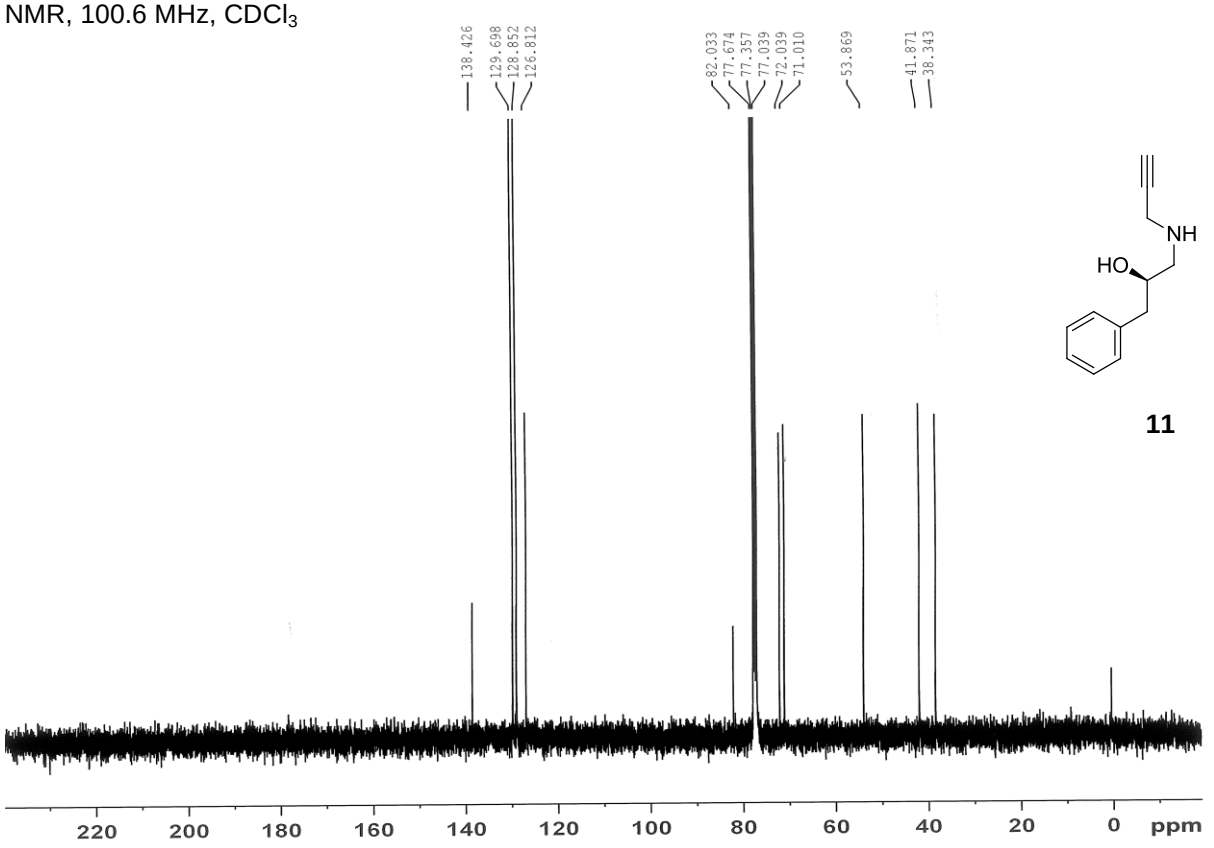
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



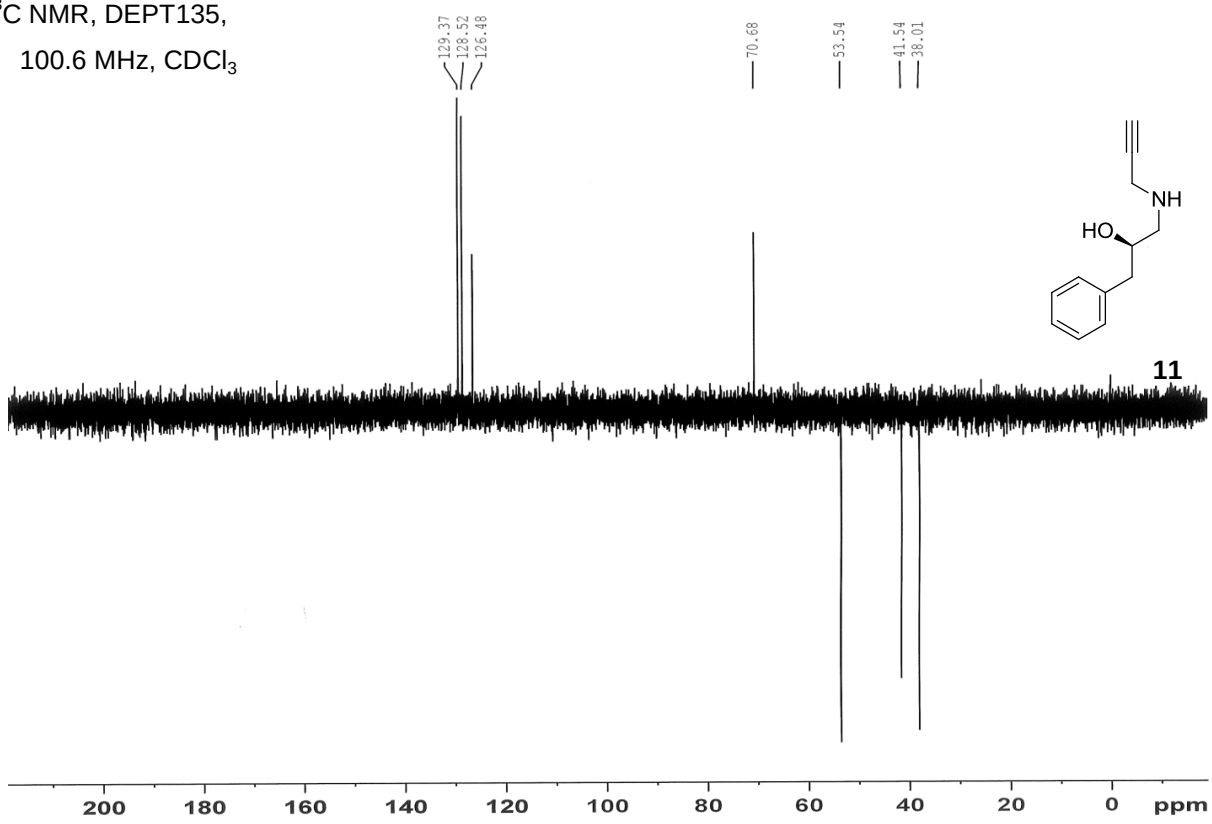
(*R*)-1-(*N*-Propargylamino)-3-phenylpropan-2-ol (11) ^{1}H NMR, 400 MHz, $CDCl_3$, TMS



^{13}C NMR, 100.6 MHz, $CDCl_3$



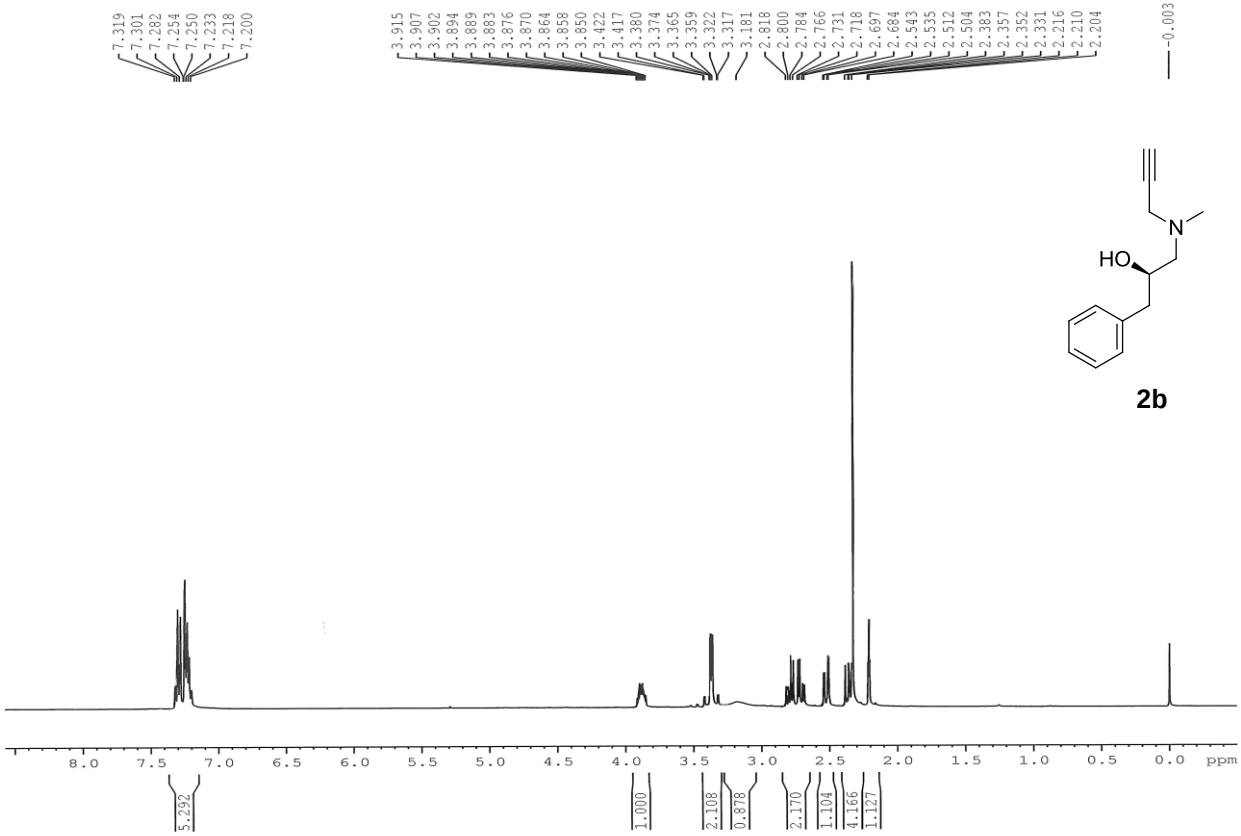
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



11

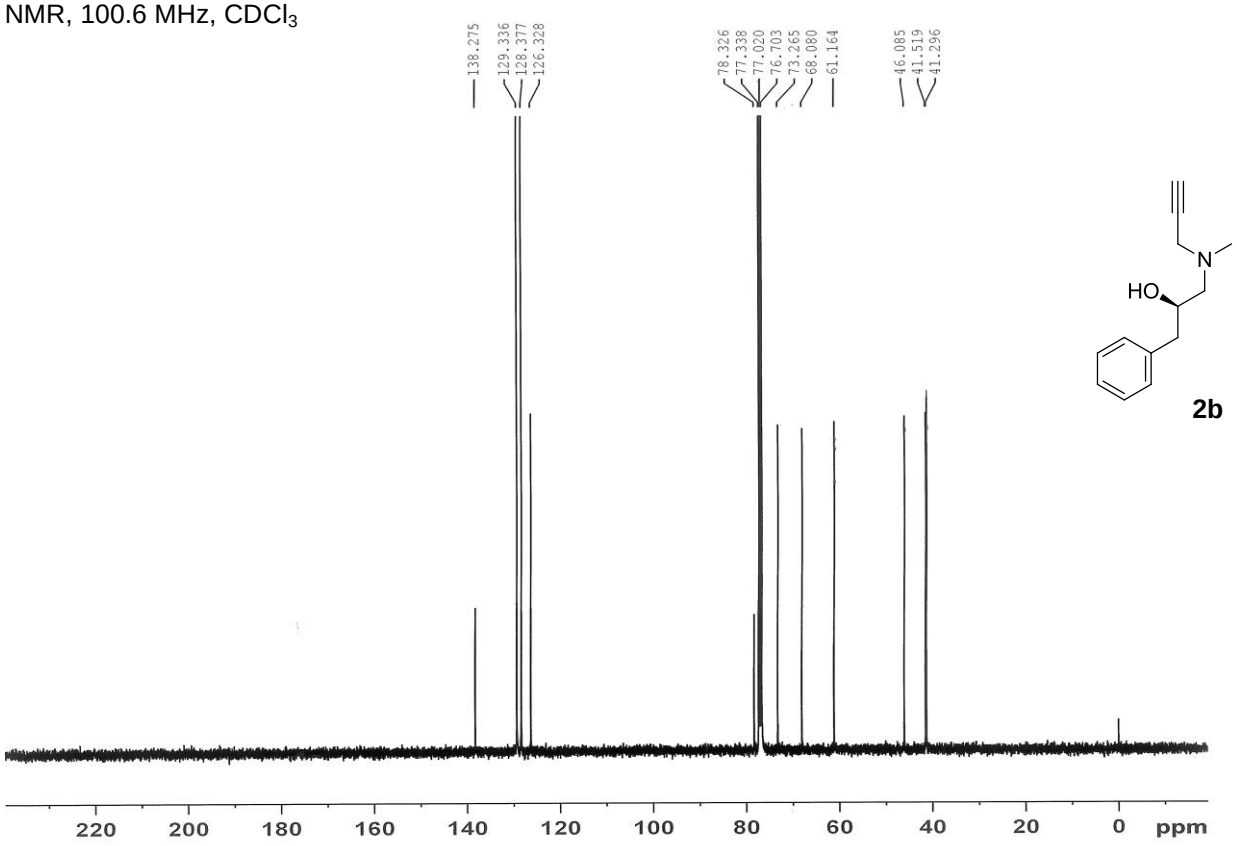
(*R*)-1-(*N*,*N*-Methylpropargylamino)-3-phenylpropan-2-ol (2b)

^{1}H NMR, 400 MHz, $CDCl_3$, TMS



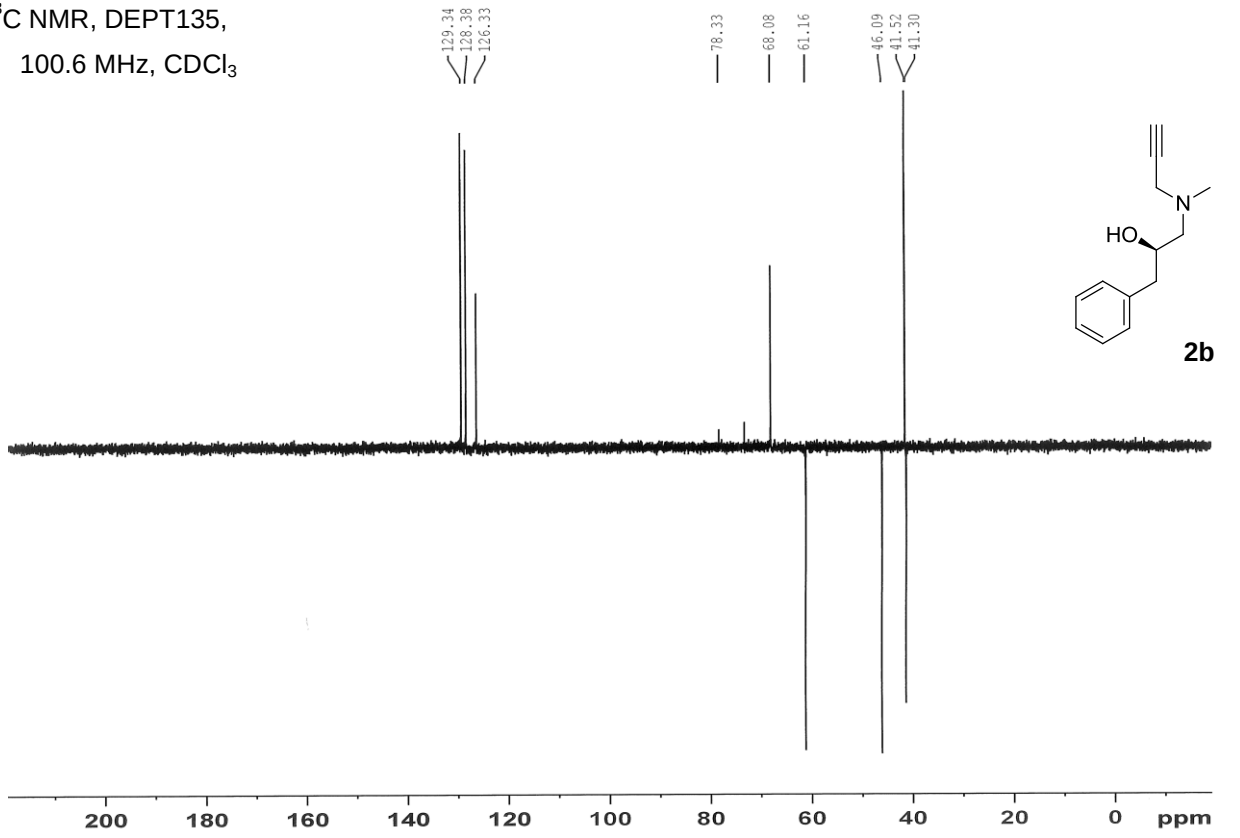
2b

^{13}C NMR, 100.6 MHz, $CDCl_3$



2b

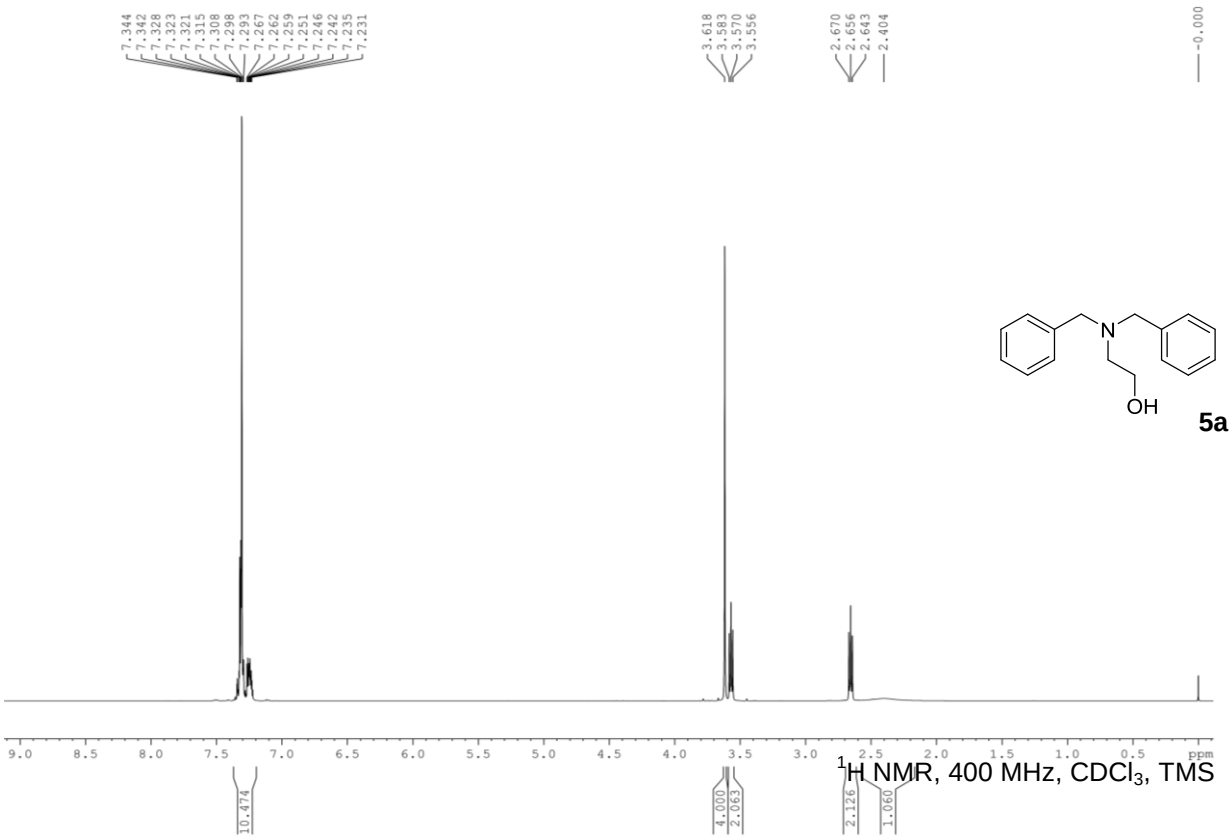
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



2b

2-(*N,N*-Dibenzylamino)ethanol (5a)

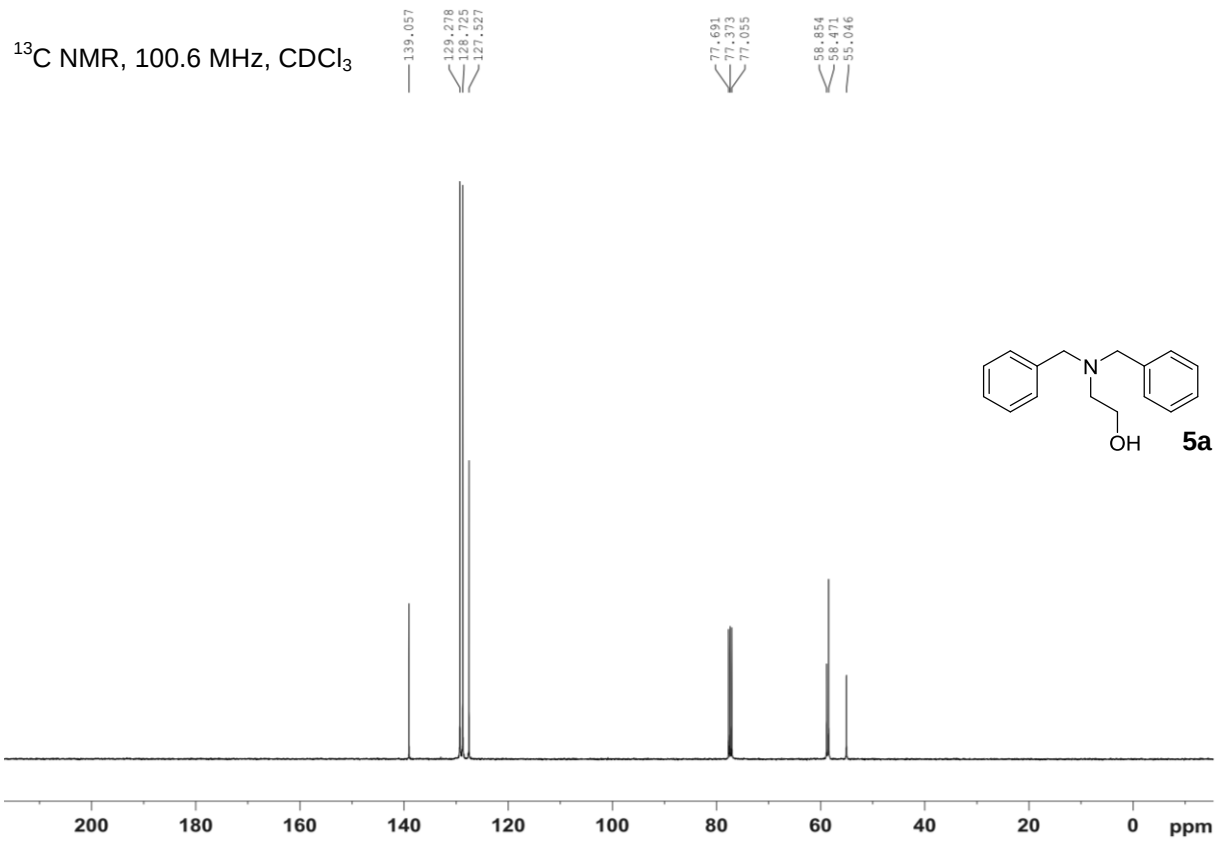
^{1}H NMR, 400 MHz, $CDCl_3$, TMS



5a

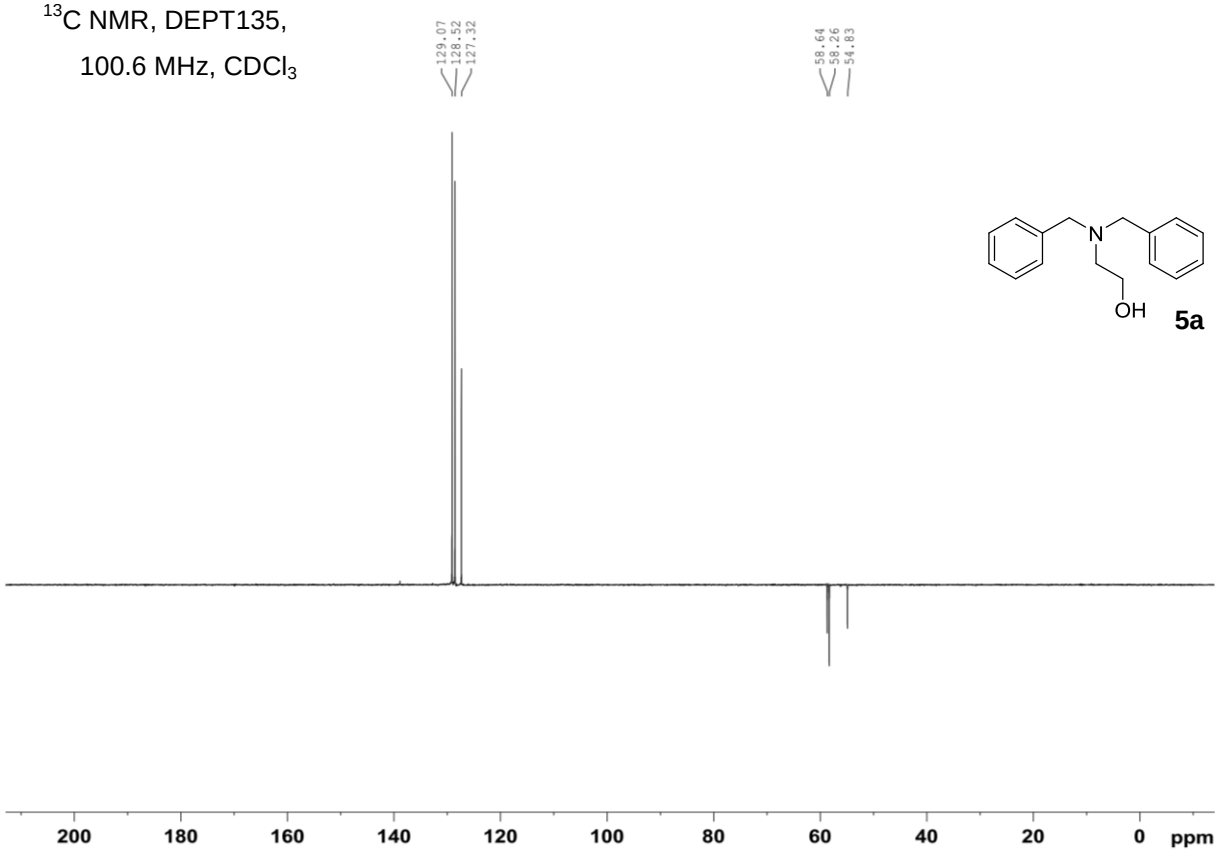
^{1}H NMR, 400 MHz, $CDCl_3$, TMS

^{13}C NMR, 100.6 MHz, $CDCl_3$



5a

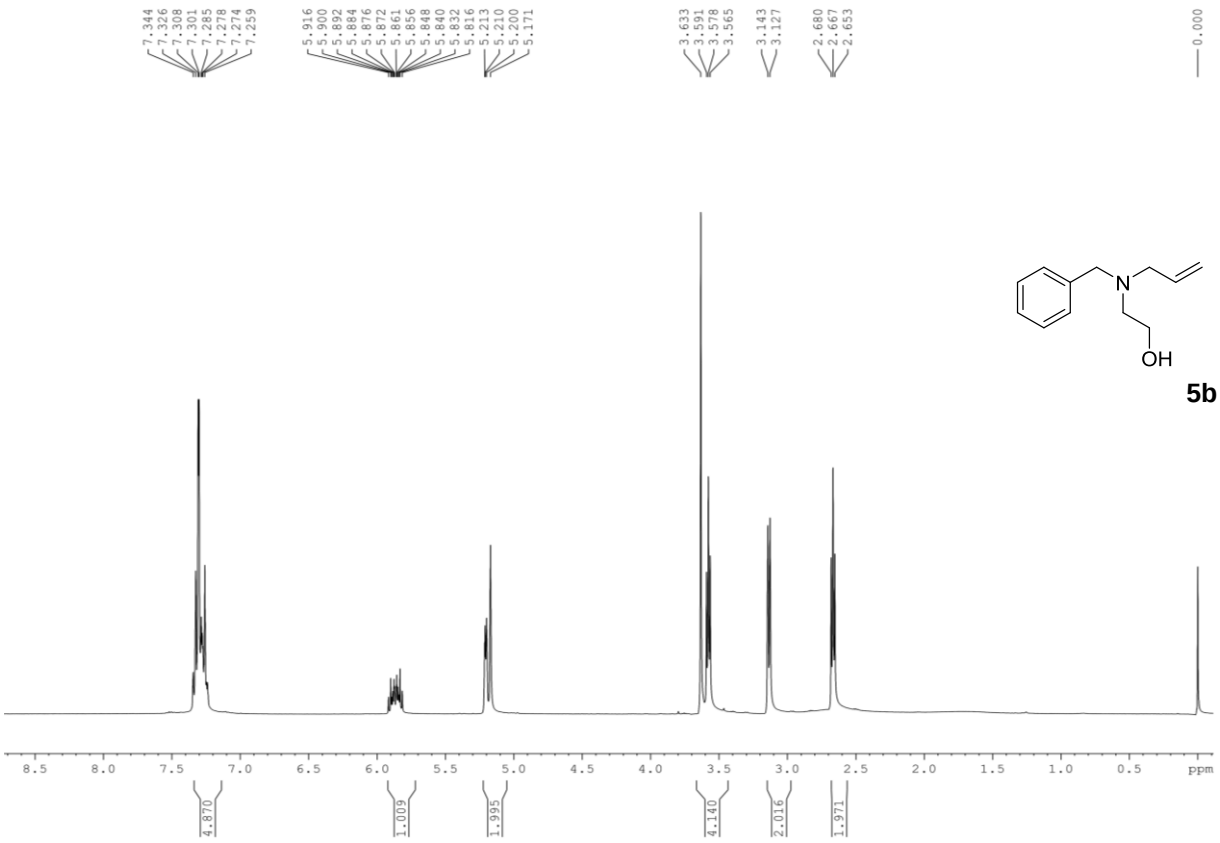
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



5a

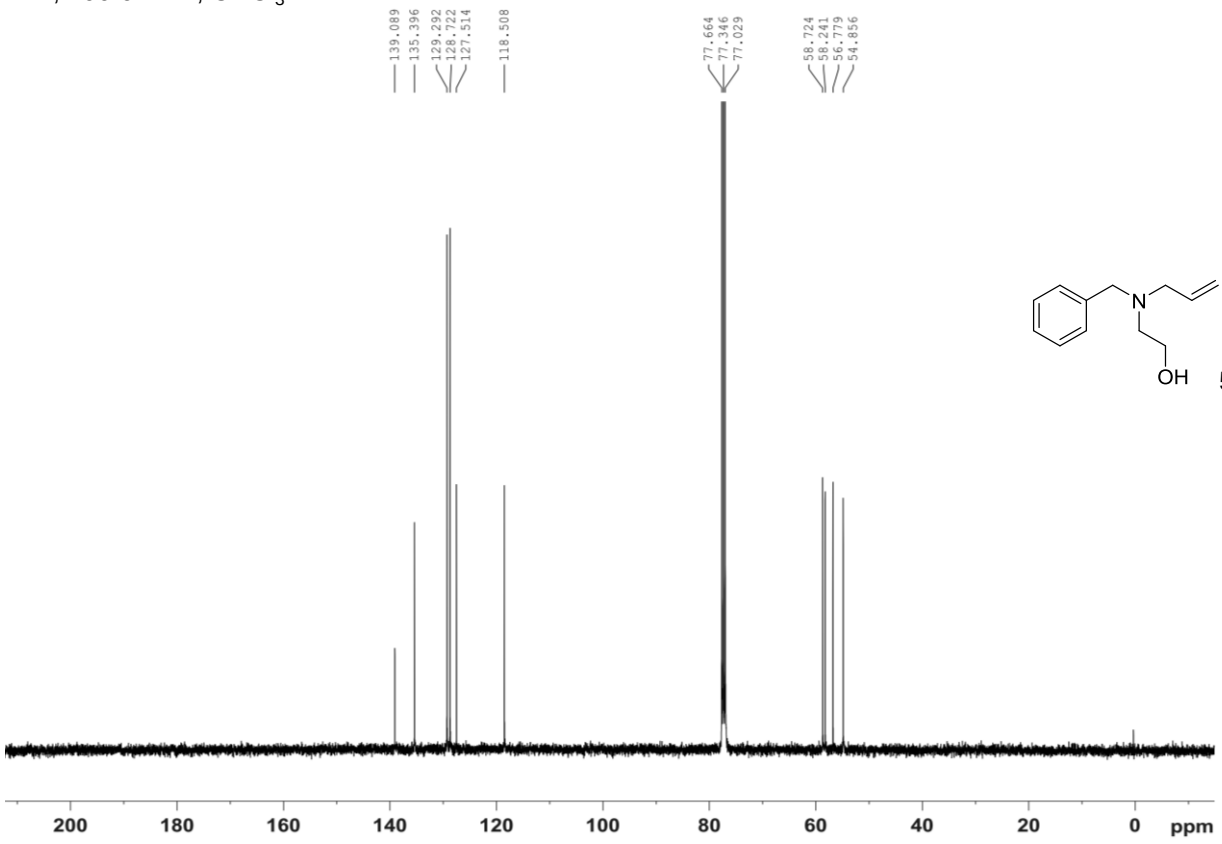
2-(*N,N*-Allylbenzylamino)ethanol (5b)

^{1}H NMR, 400 MHz, $CDCl_3$, TMS



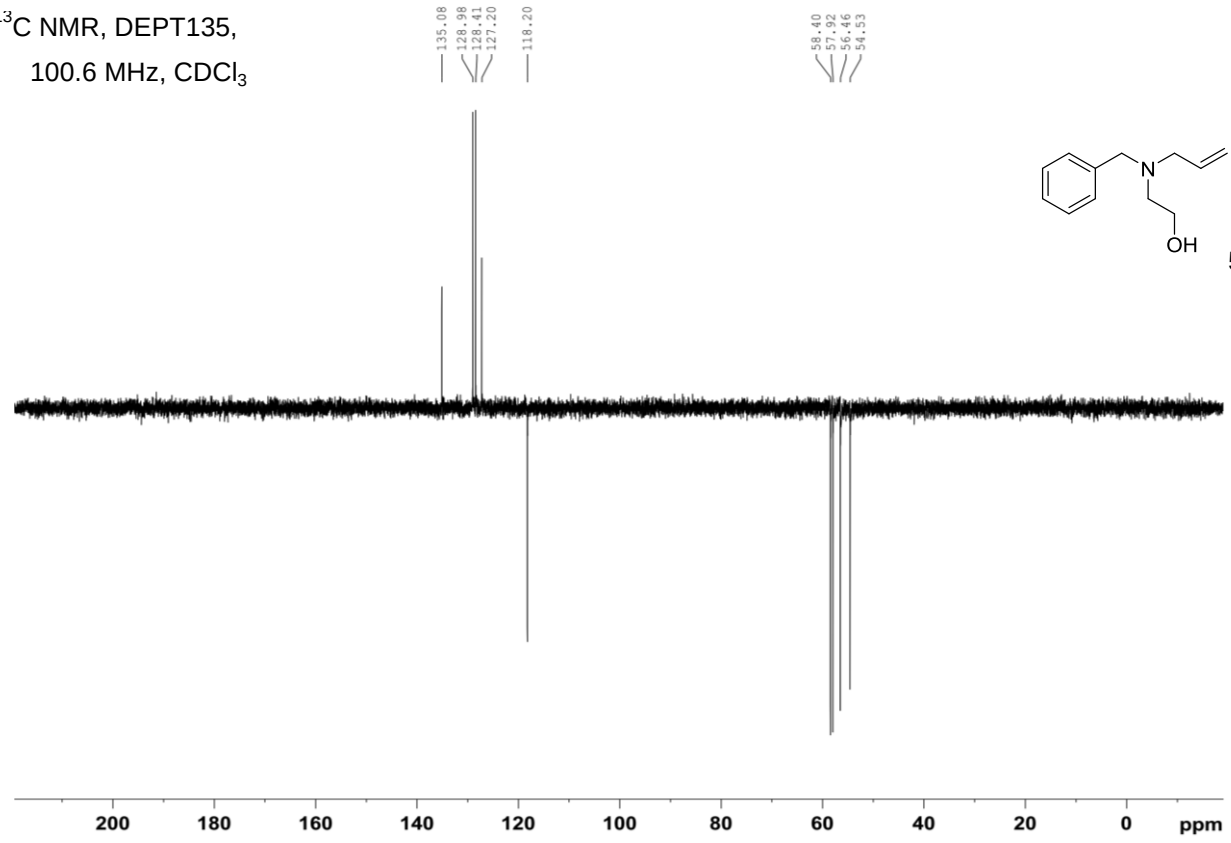
5b

^{13}C NMR, 100.6 MHz, $CDCl_3$



5b

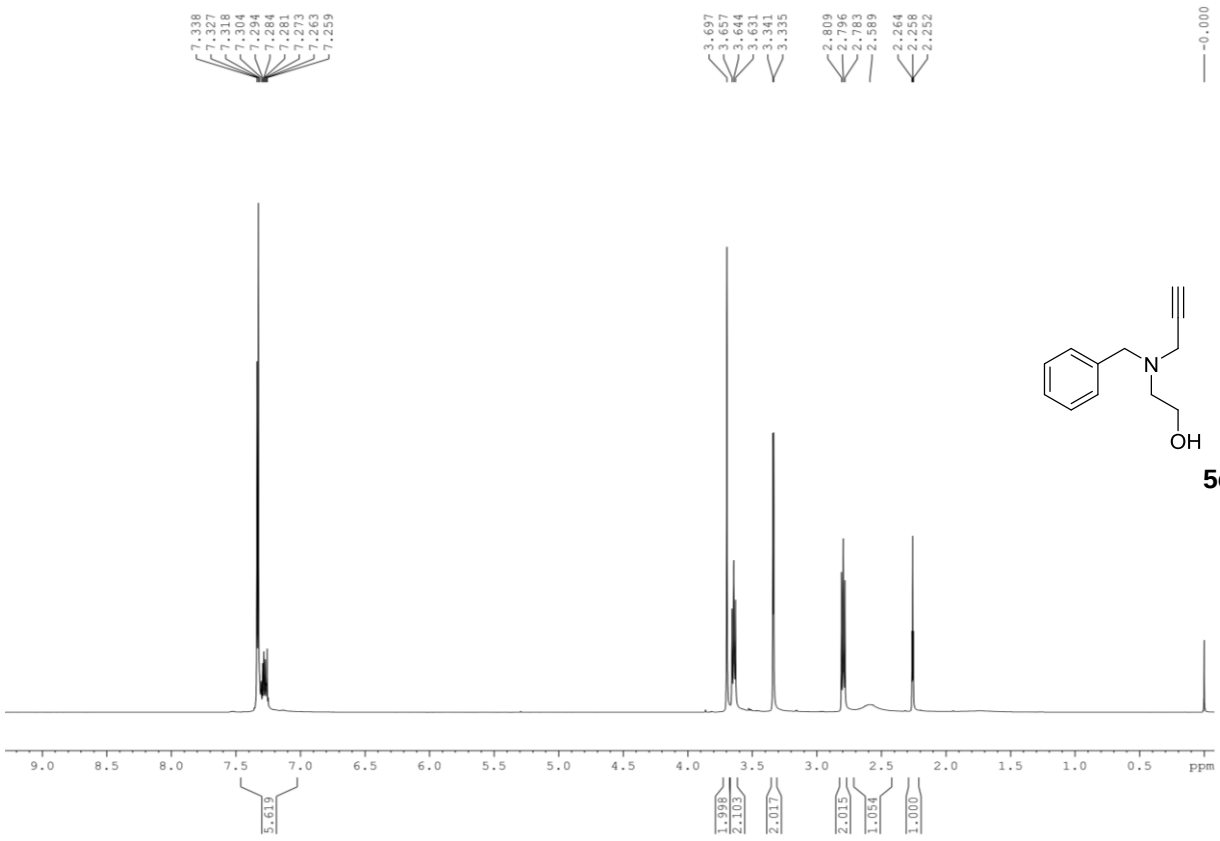
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



5b

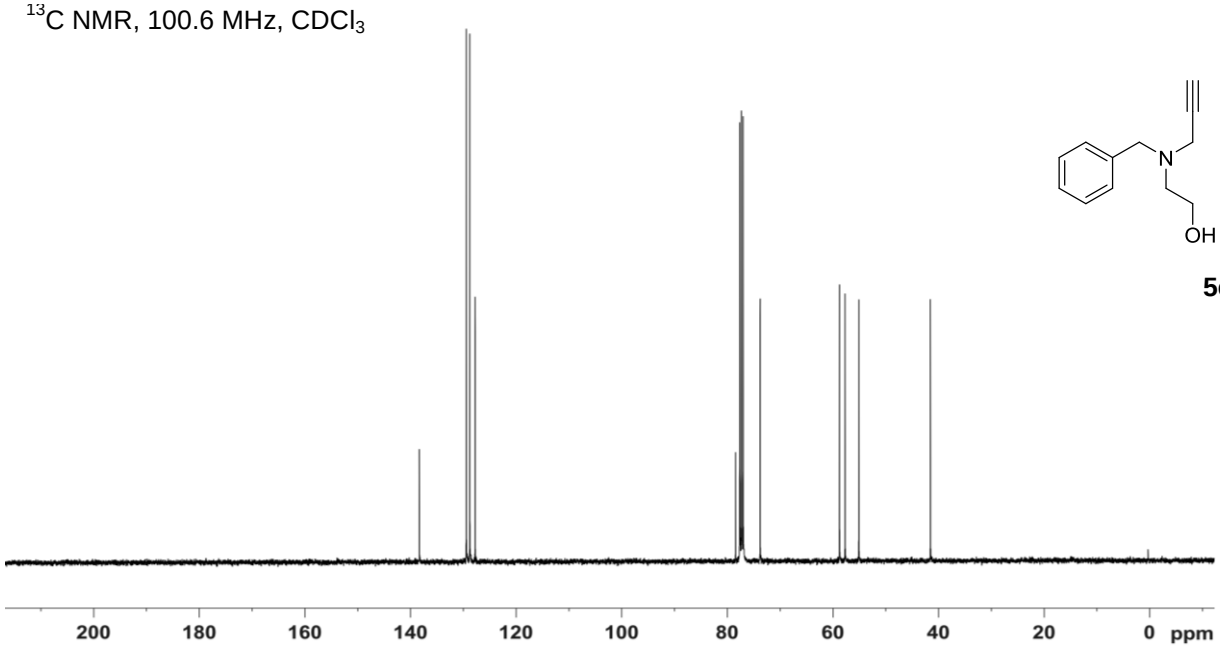
2-(*N*,*N*-Benzylpropargylamino)ethanol (5c)

^{1}H NMR, 400 MHz, $CDCl_3$, TMS



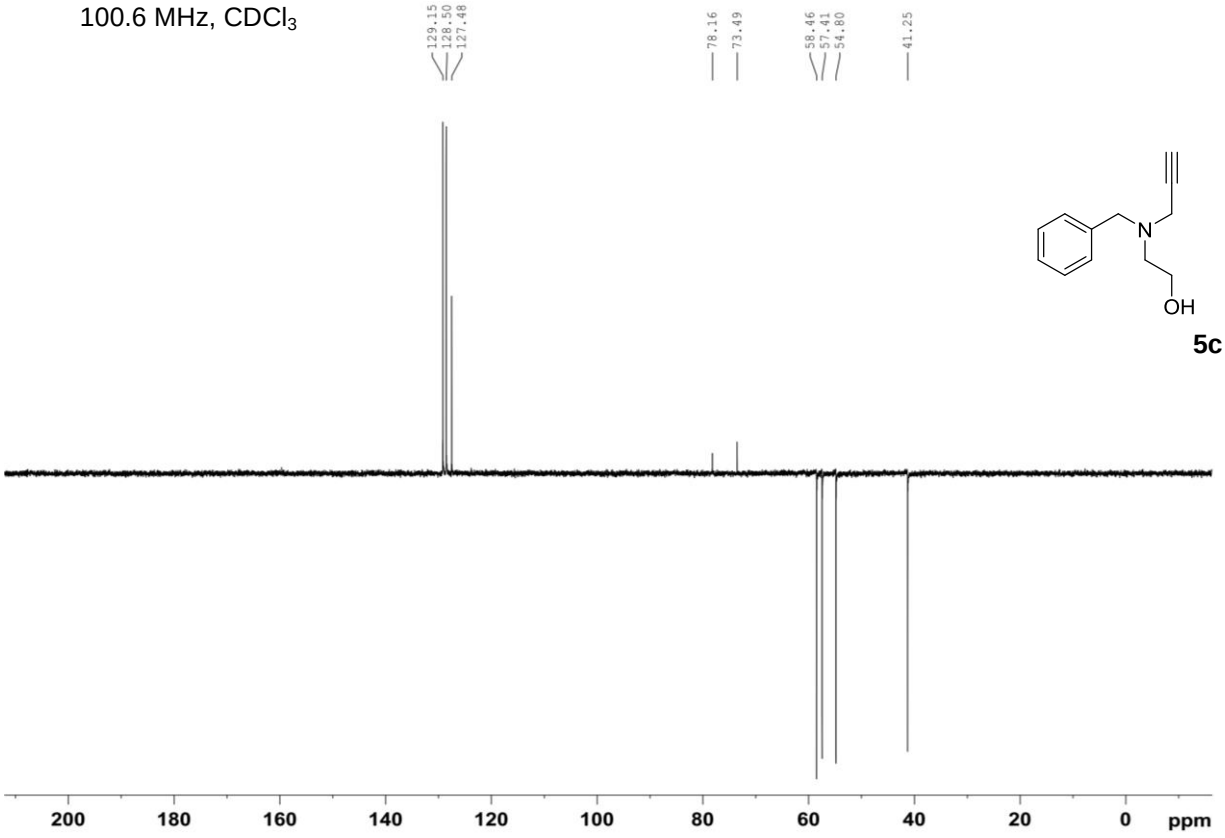
5c

^{13}C NMR, 100.6 MHz, $CDCl_3$



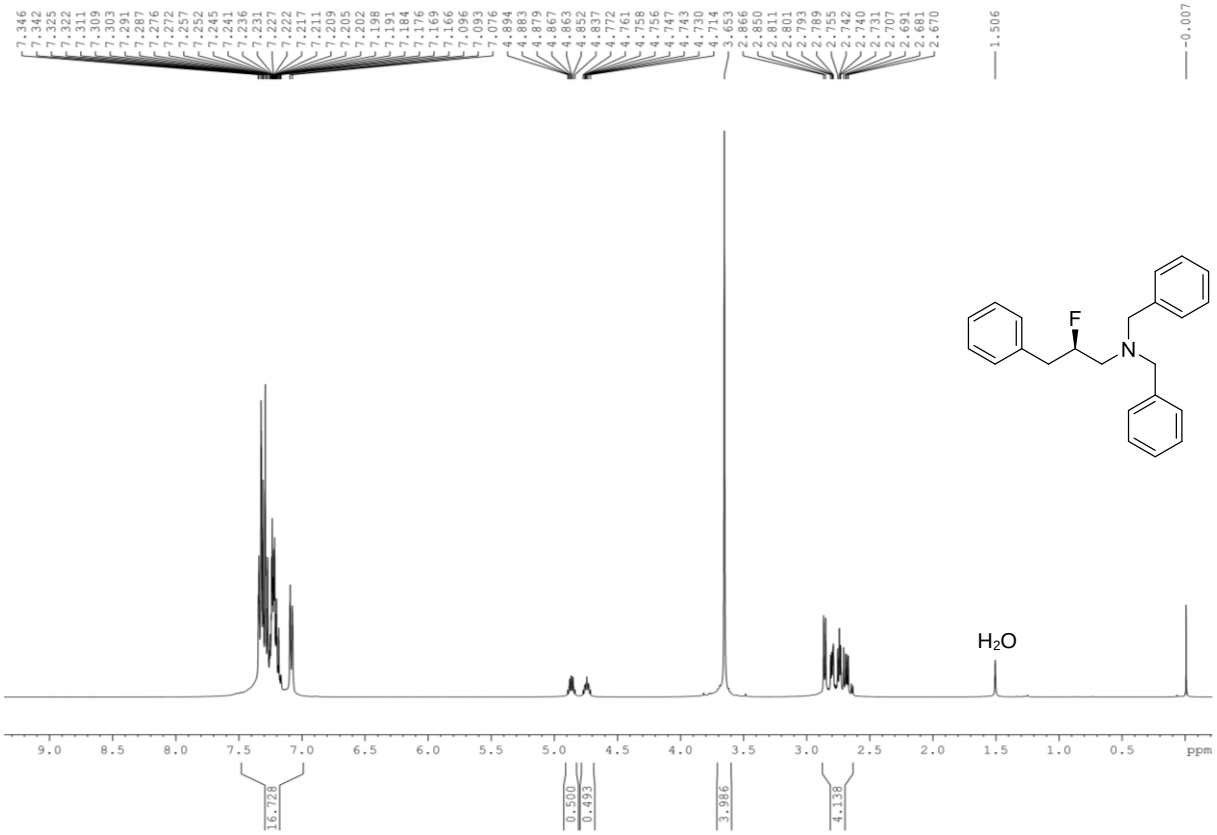
5c

^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



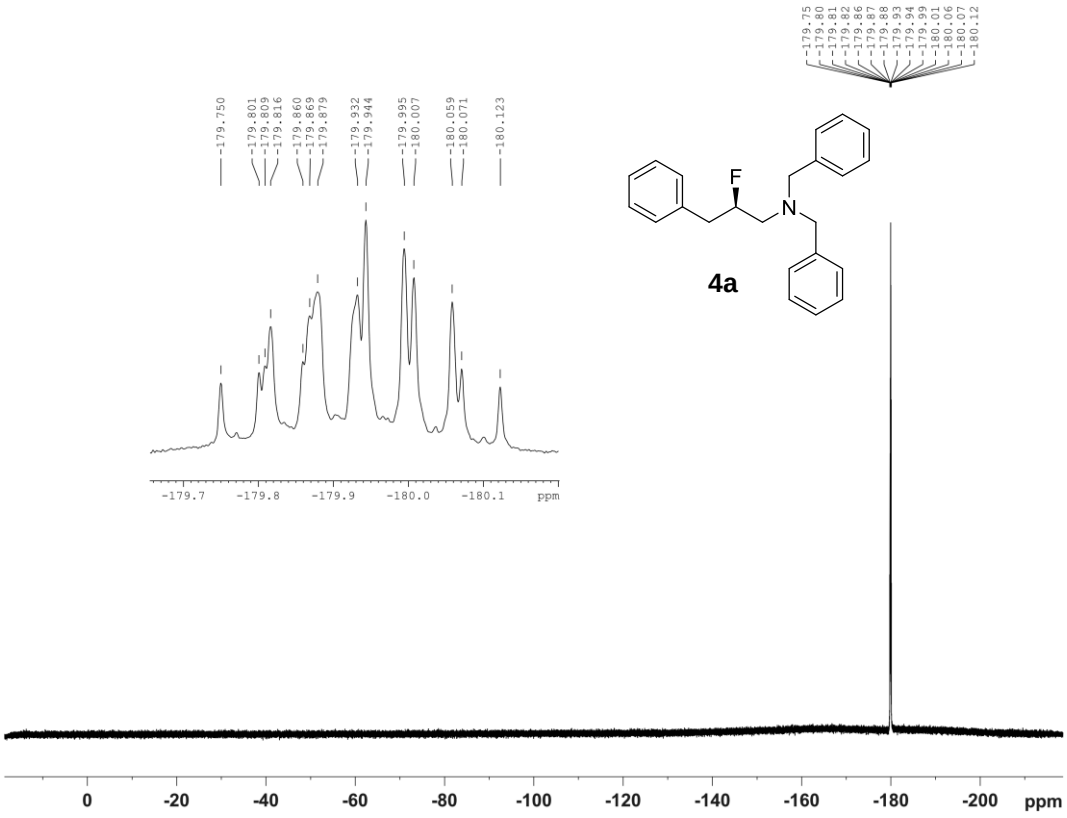
5c

(*R*)-*N*,*N*-Dibenzyl-2-fluoro-3-phenylpropan-1-amine (4a) ^{1}H NMR, 400 MHz, $CDCl_3$, TMS

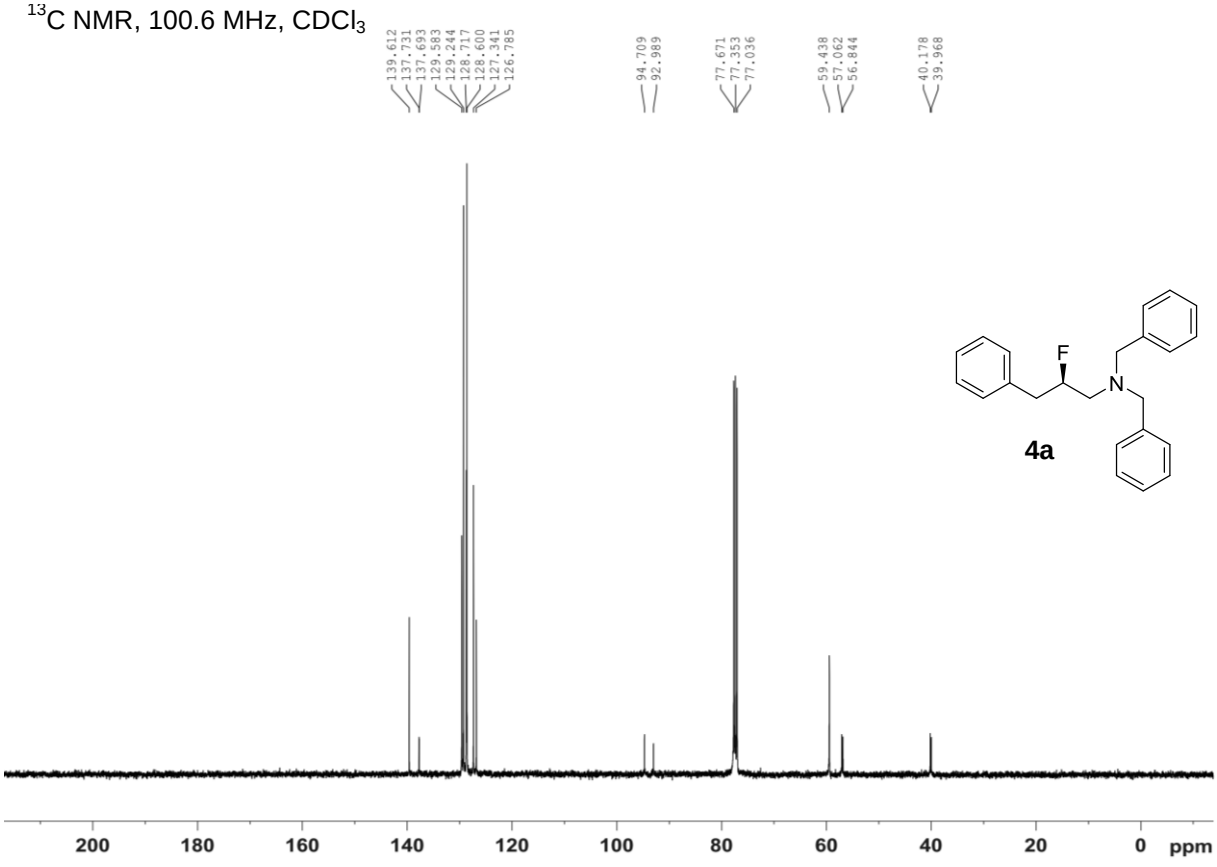


4a

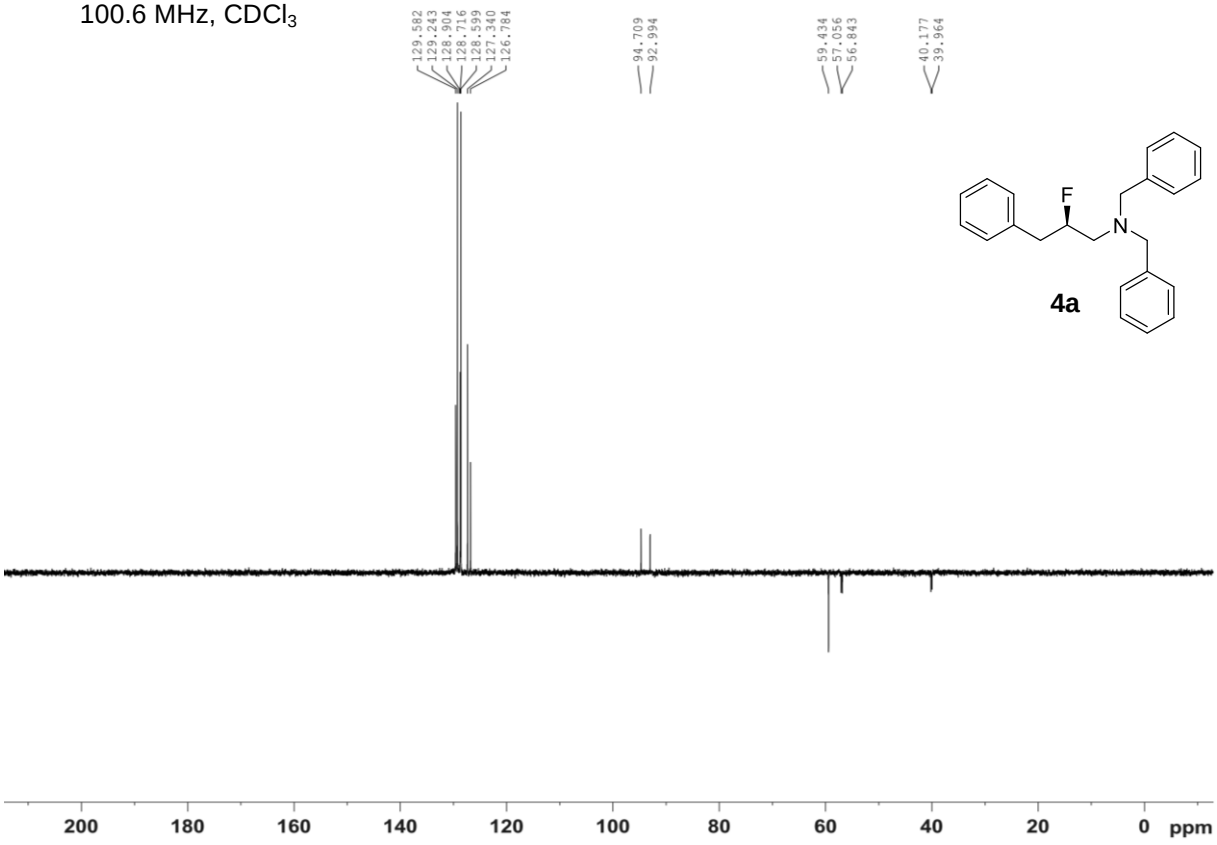
^{19}F NMR, 376.5 MHz, $CDCl_3$



^{13}C NMR, 100.6 MHz, $CDCl_3$

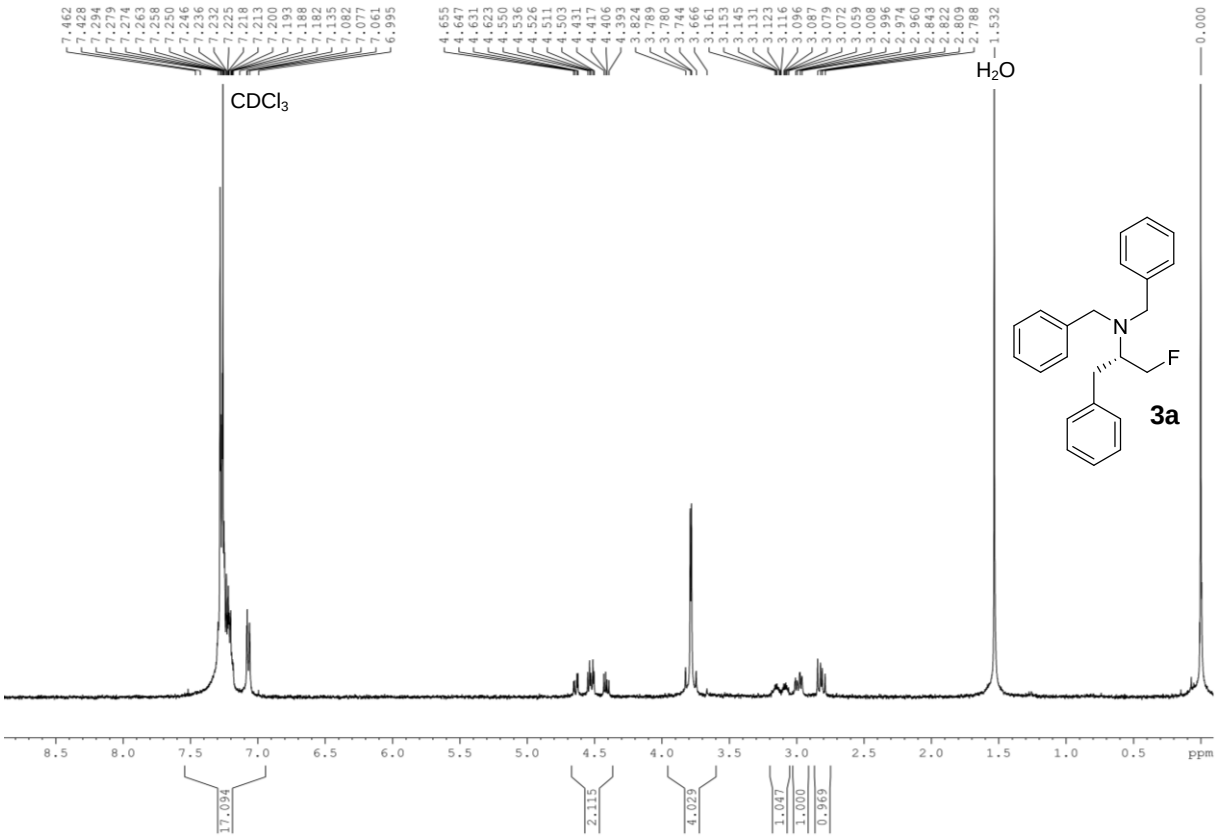


^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$

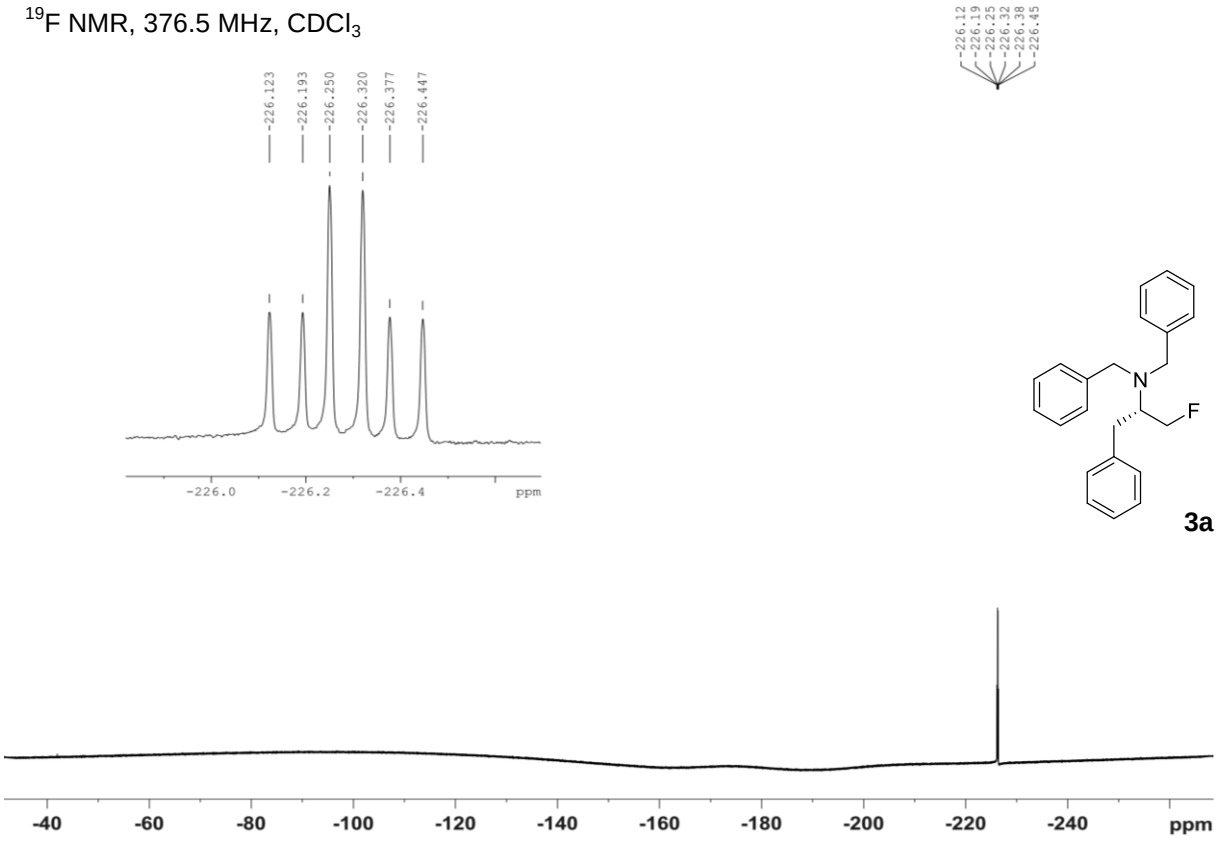


(*S*)-*N*,*N*-dibenzyl-1-fluoro-3-phenylpropan-2-amine (3a)

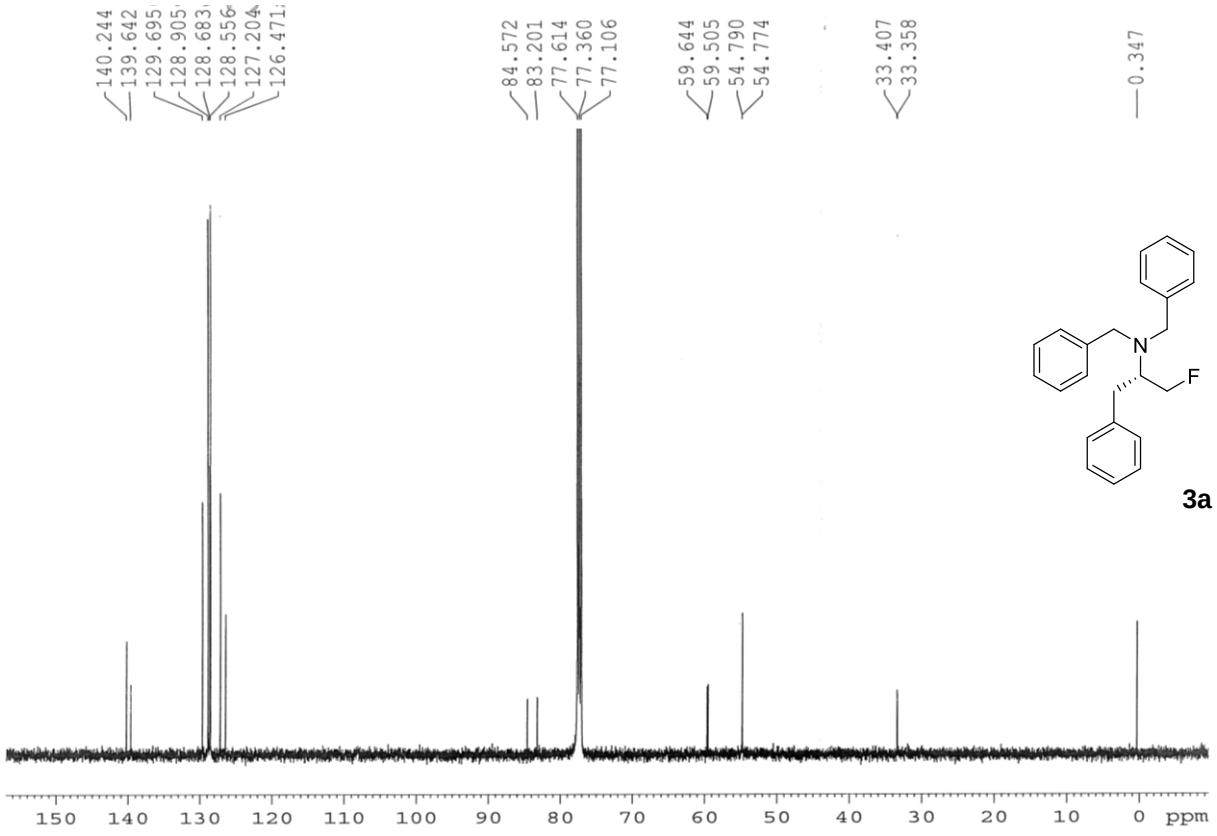
^{1}H NMR, 400 MHz, $CDCl_3$, TMS



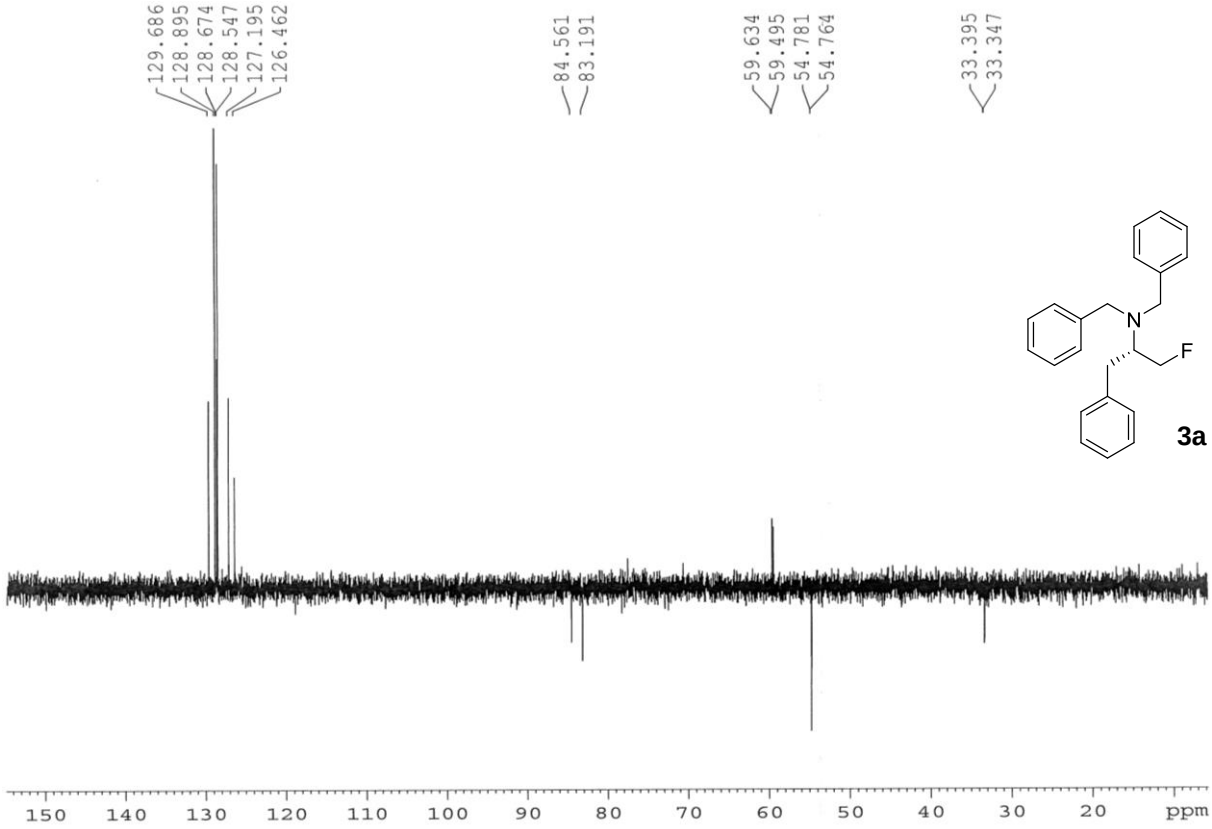
^{19}F NMR, 376.5 MHz, $CDCl_3$



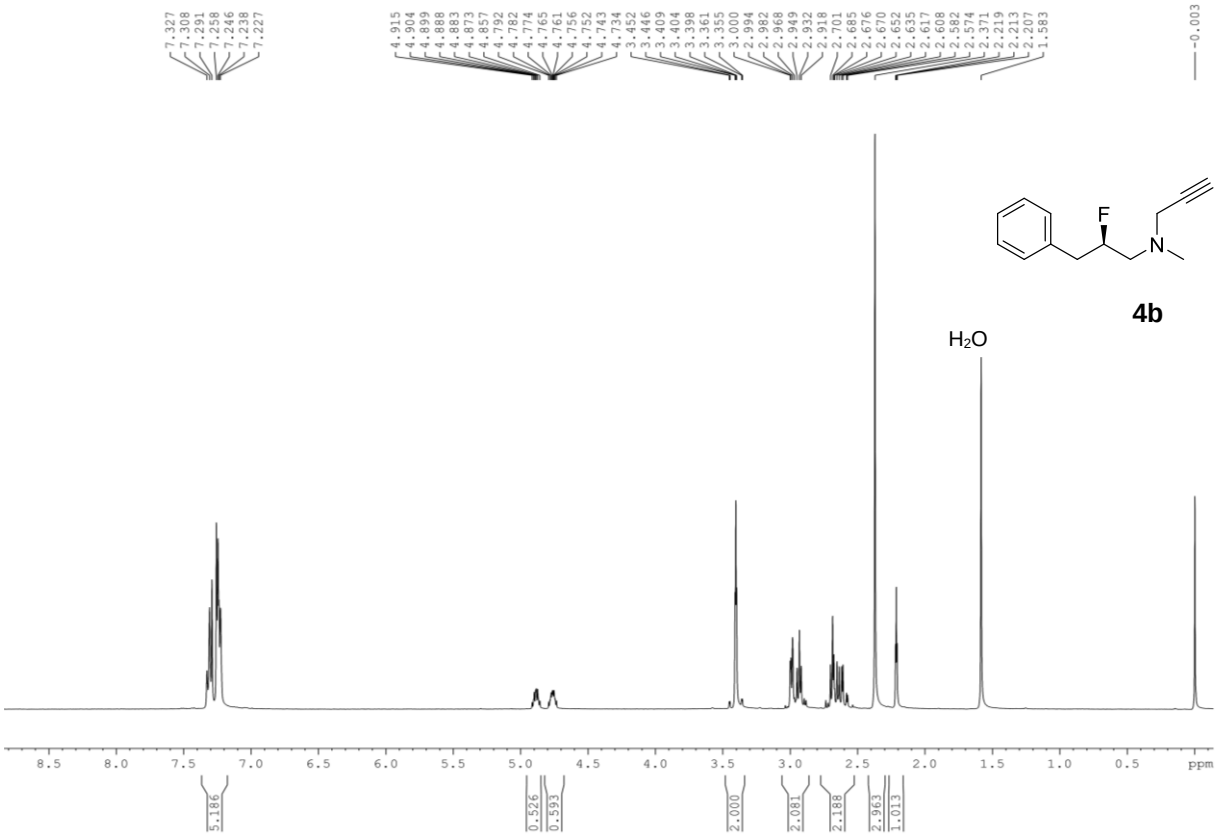
^{13}C NMR, 100.6 MHz, $CDCl_3$



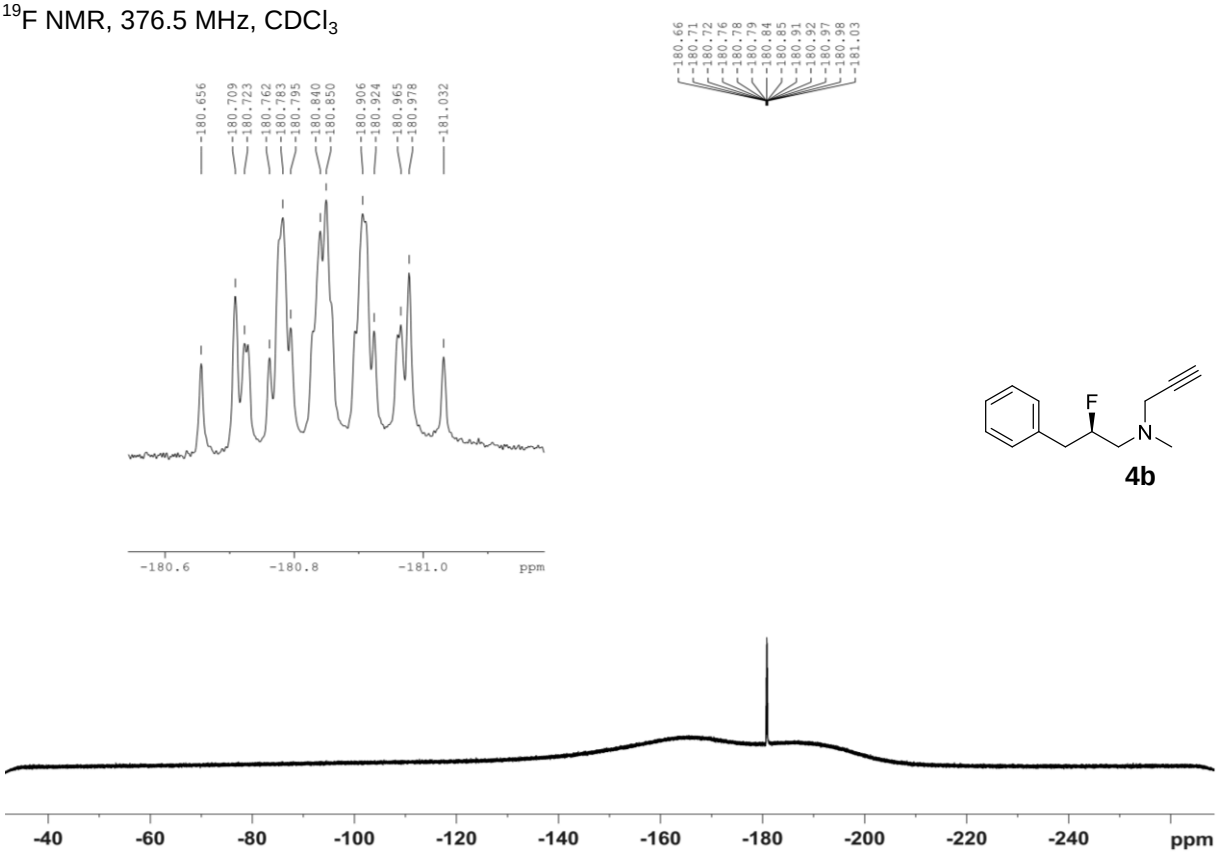
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



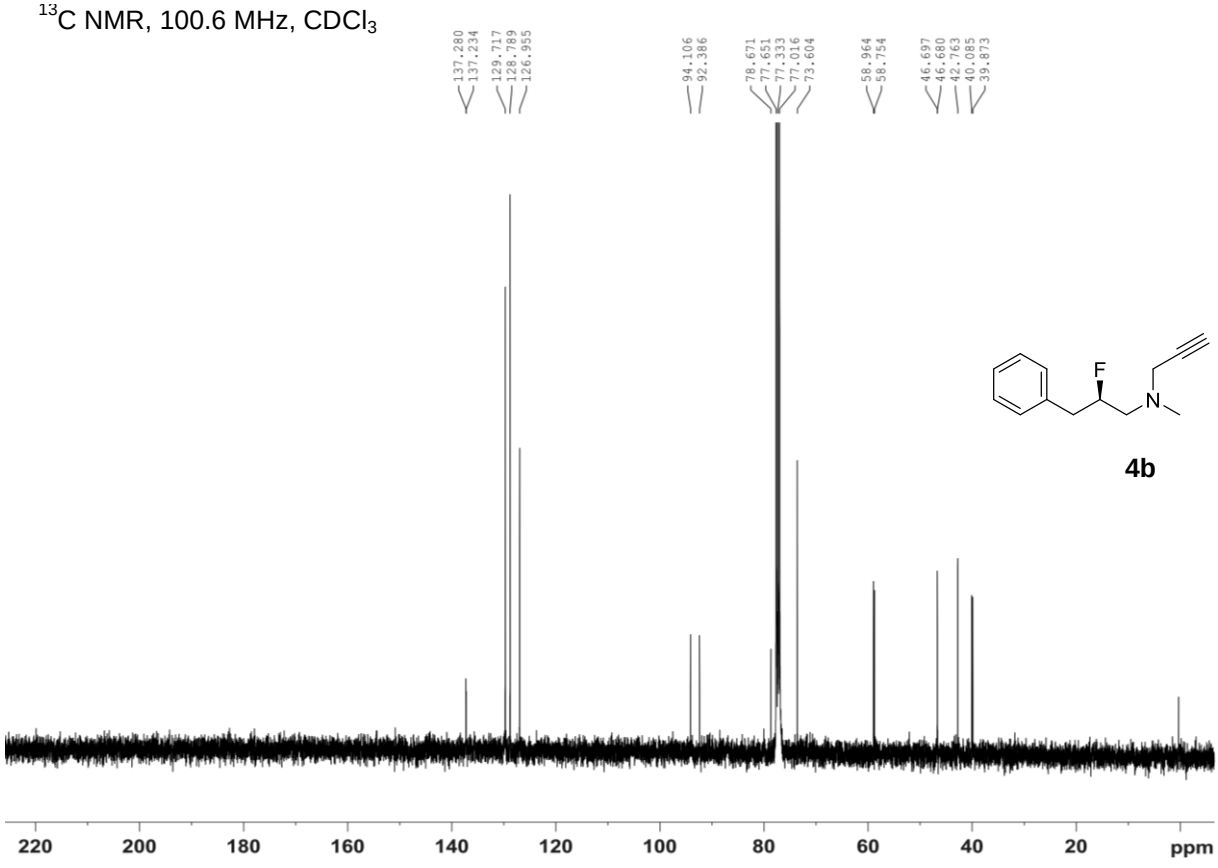
(*R*)-*N*,*N*-Methylpropargyl-2-fluoro-3-phenylpropan-1-amine (4b) ^{1}H NMR, 400 MHz, $CDCl_3$, TMS



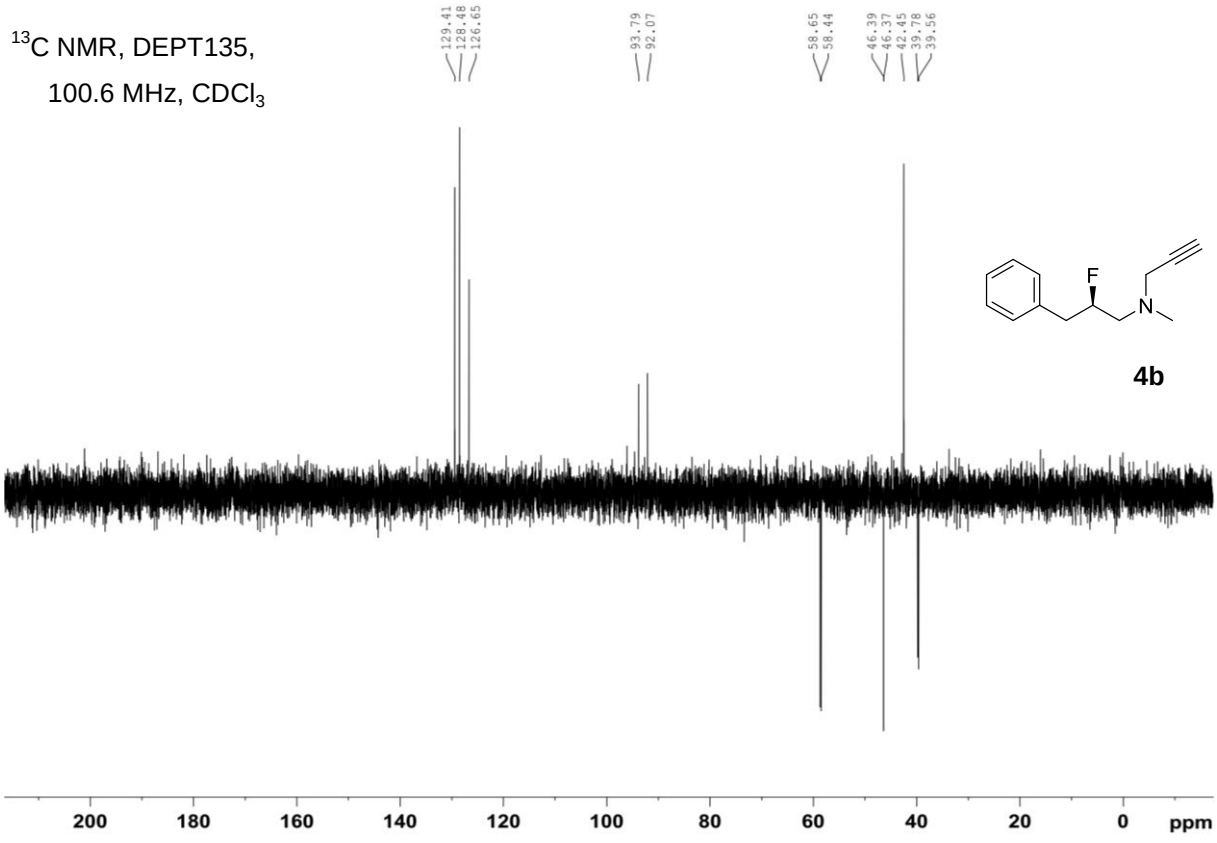
^{19}F NMR, 376.5 MHz, $CDCl_3$



^{13}C NMR, 100.6 MHz, $CDCl_3$



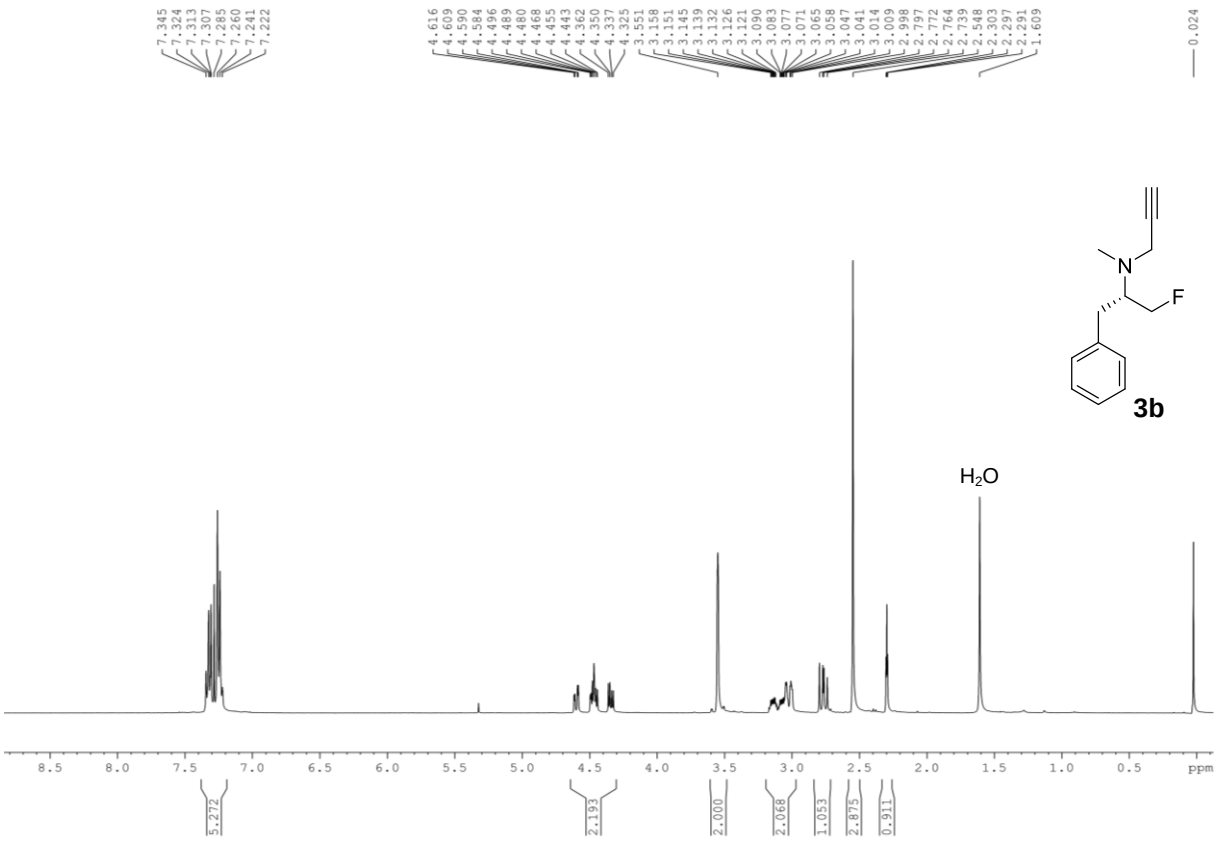
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



4b

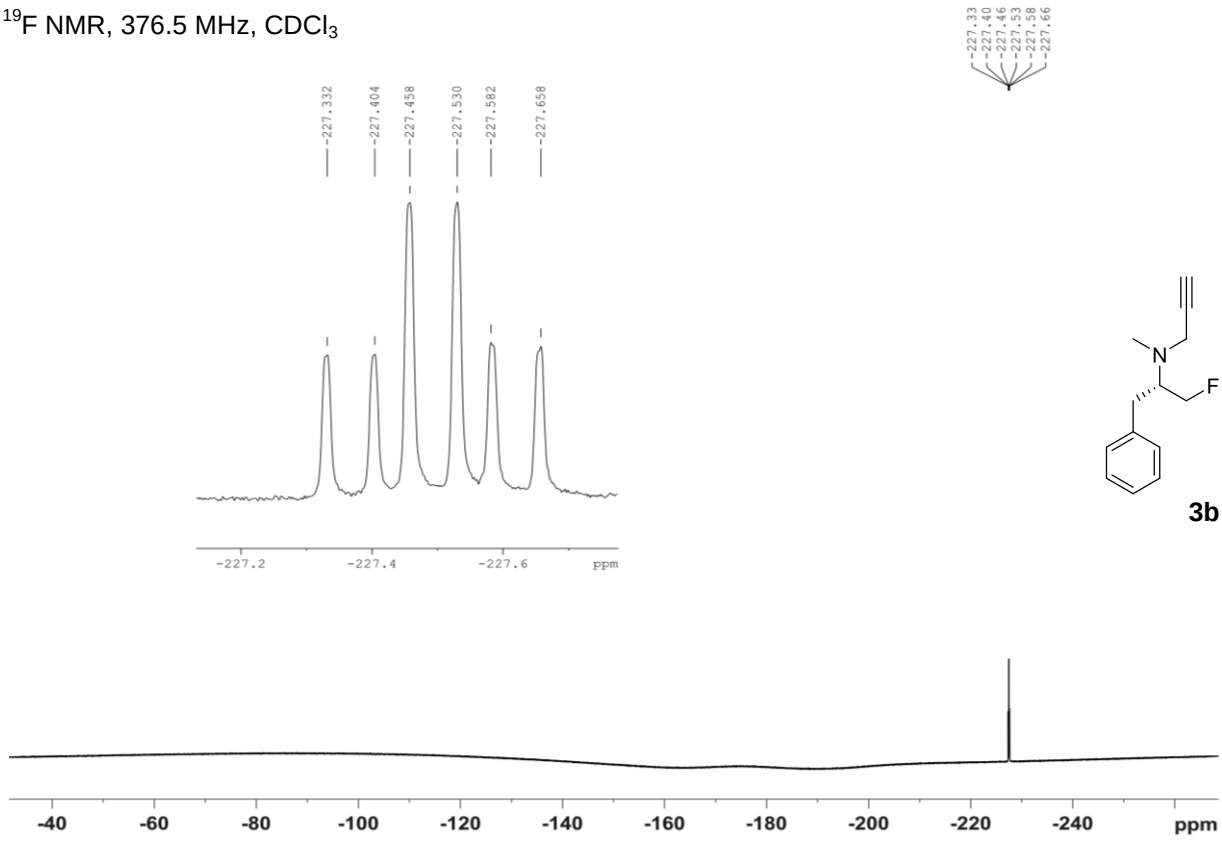
(*S*)-*N*,*N*-Methylpropargyl-1-fluoro-3-phenylpropan-2-amine (3b)

^{1}H NMR, 400 MHz, $CDCl_3$, TMS

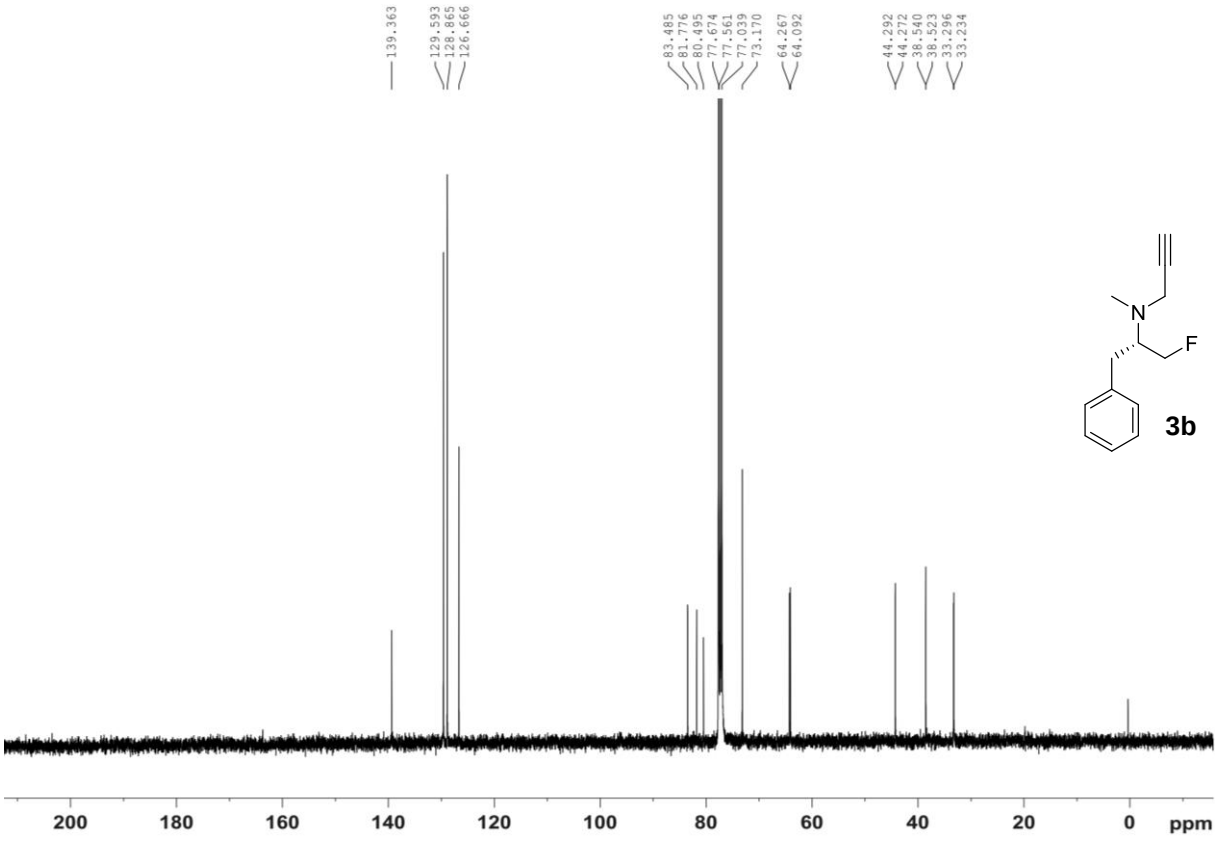


3b

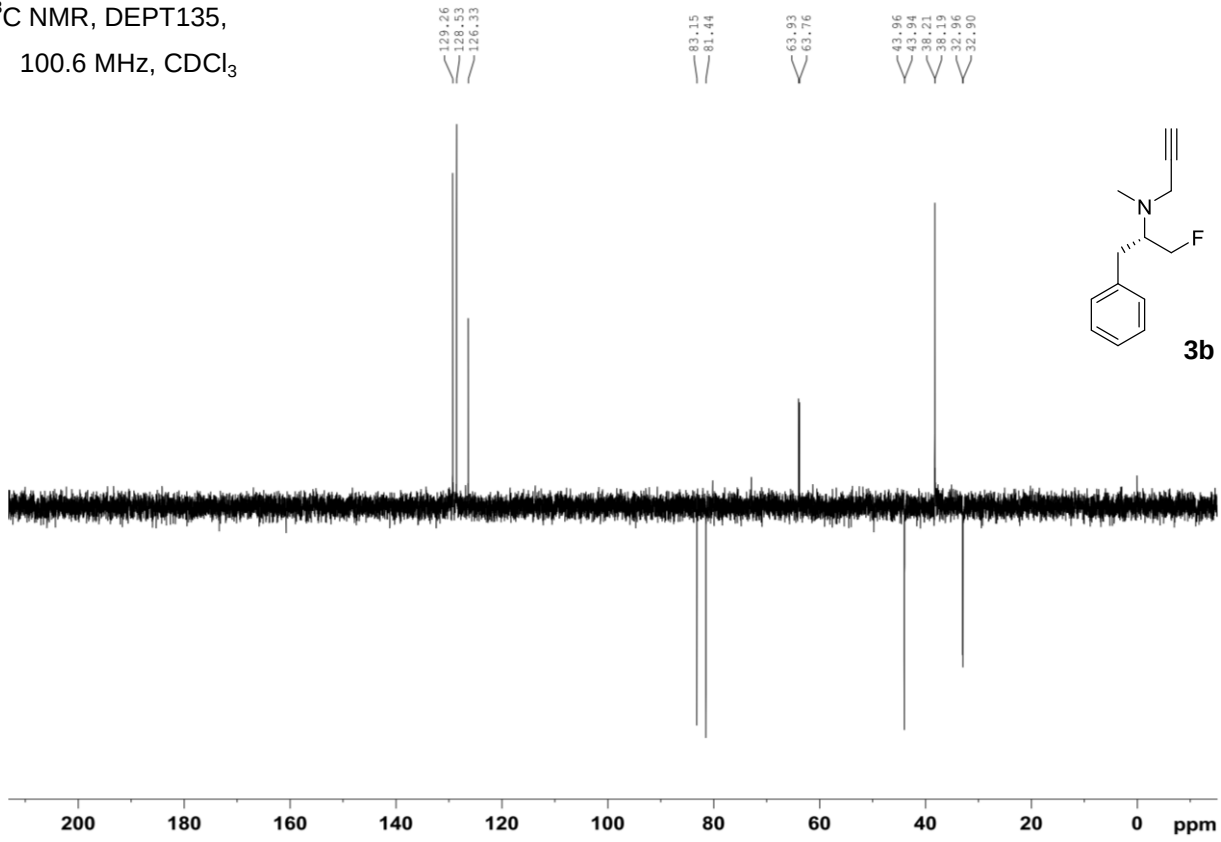
^{19}F NMR, 376.5 MHz, $CDCl_3$



^{13}C NMR, 100.6 MHz, $CDCl_3$

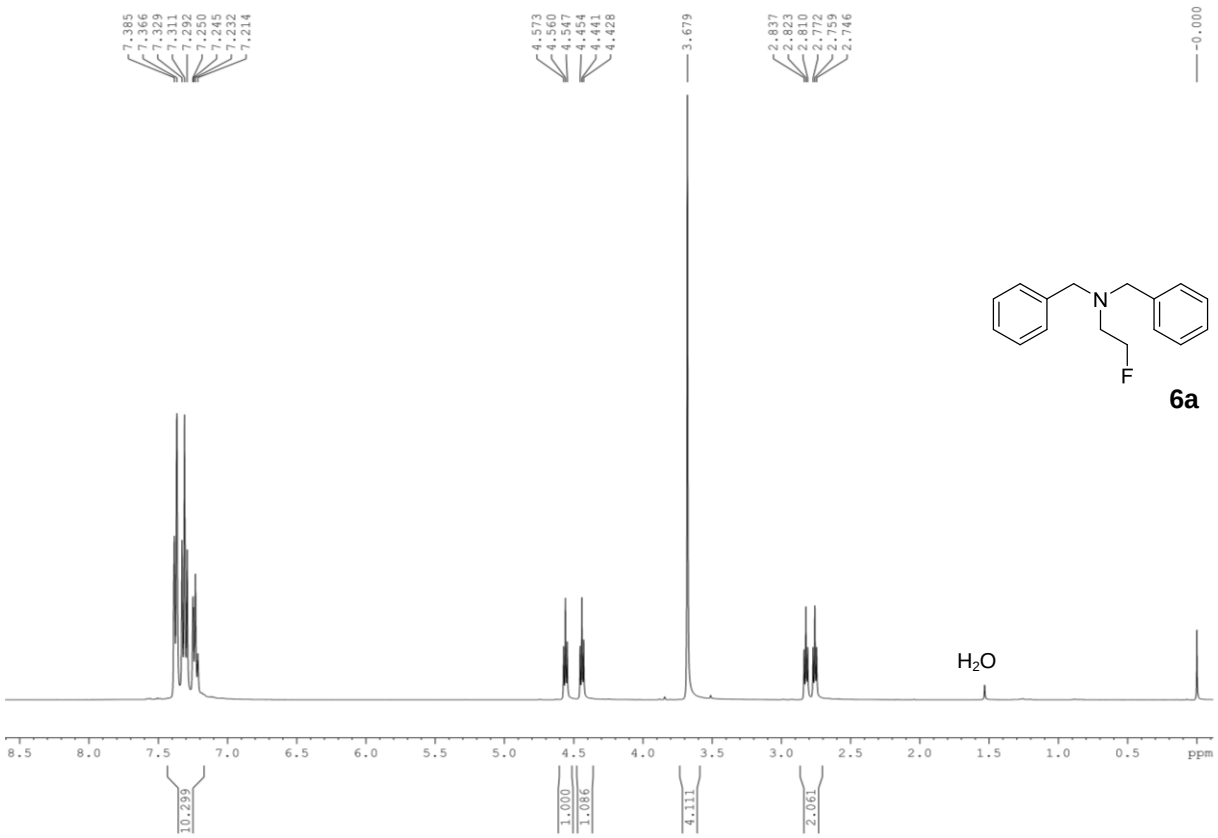


^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$

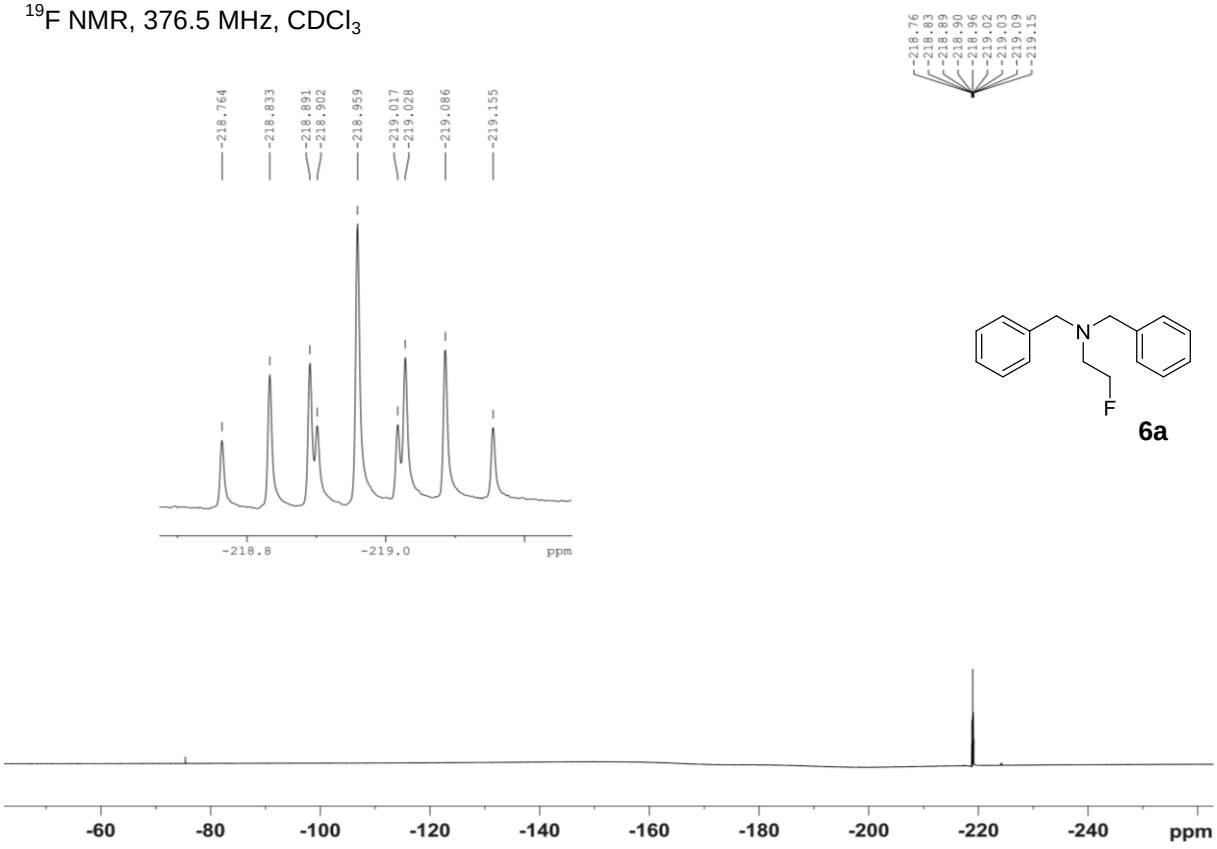


***N,N*-Dibenzyl-2-fluoroethanamine (6a)**

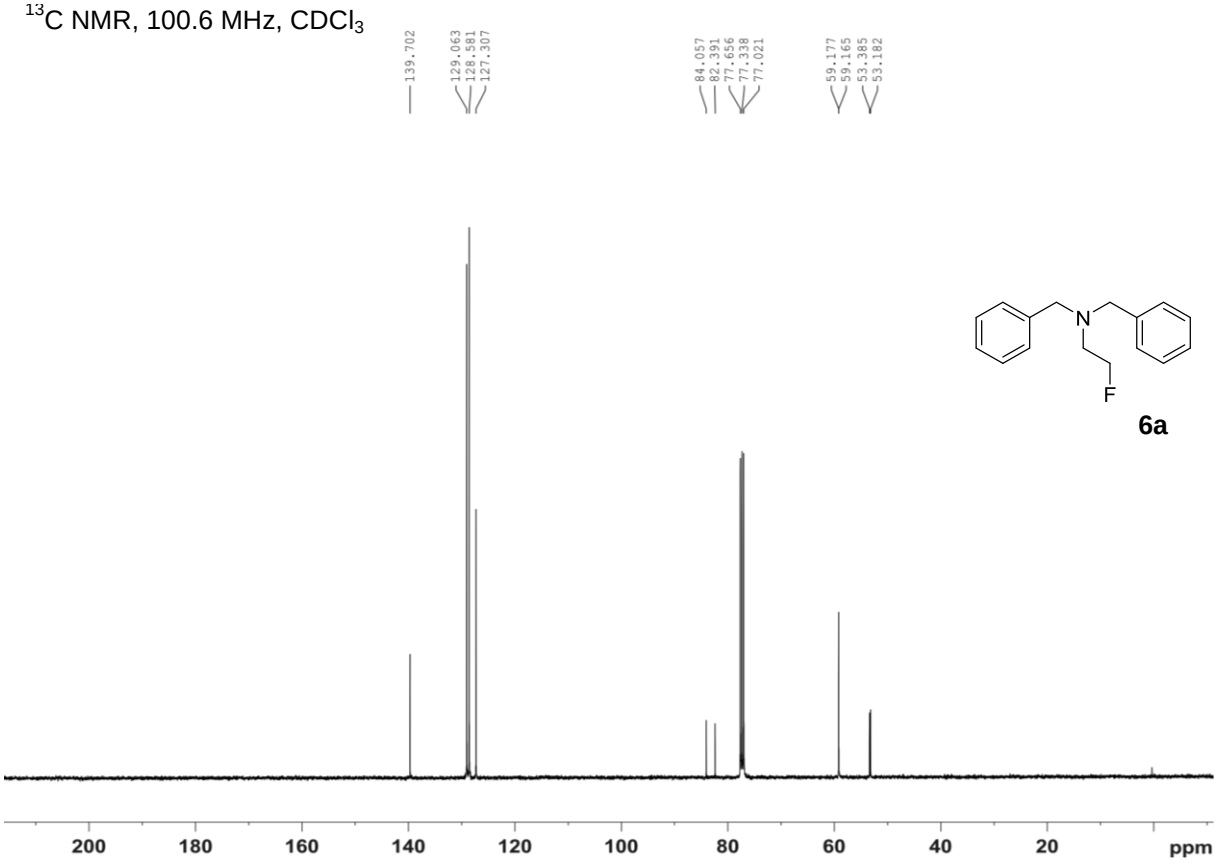
^{1}H NMR, 400 MHz, $CDCl_3$, TMS



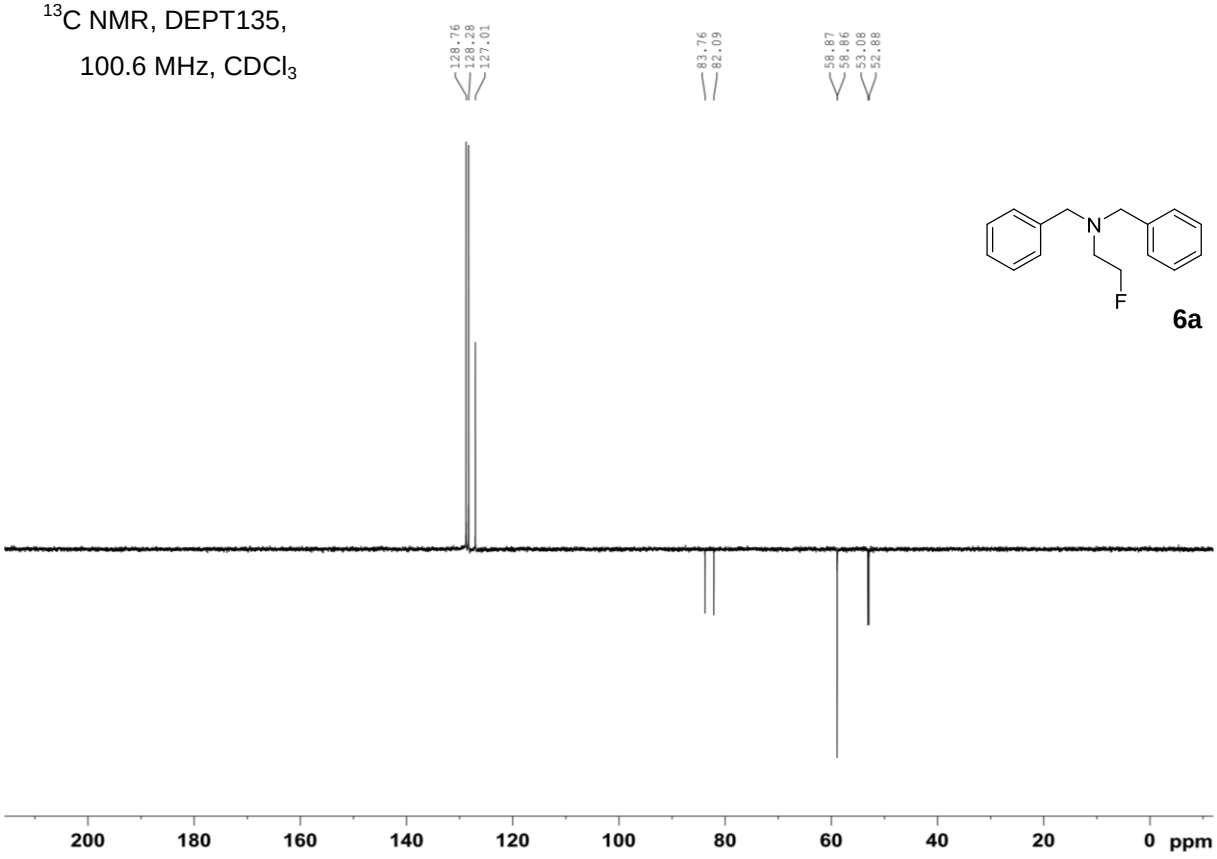
^{19}F NMR, 376.5 MHz, $CDCl_3$



^{13}C NMR, 100.6 MHz, $CDCl_3$



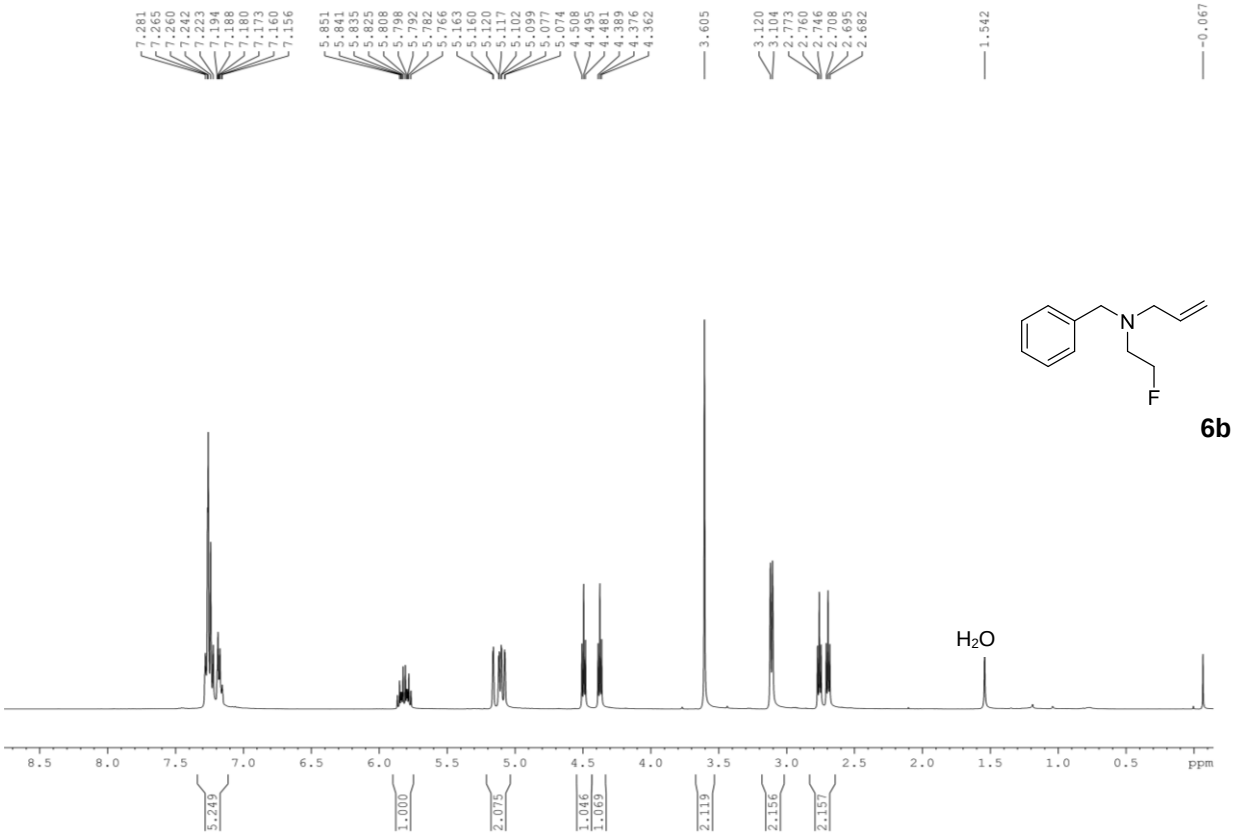
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



6a

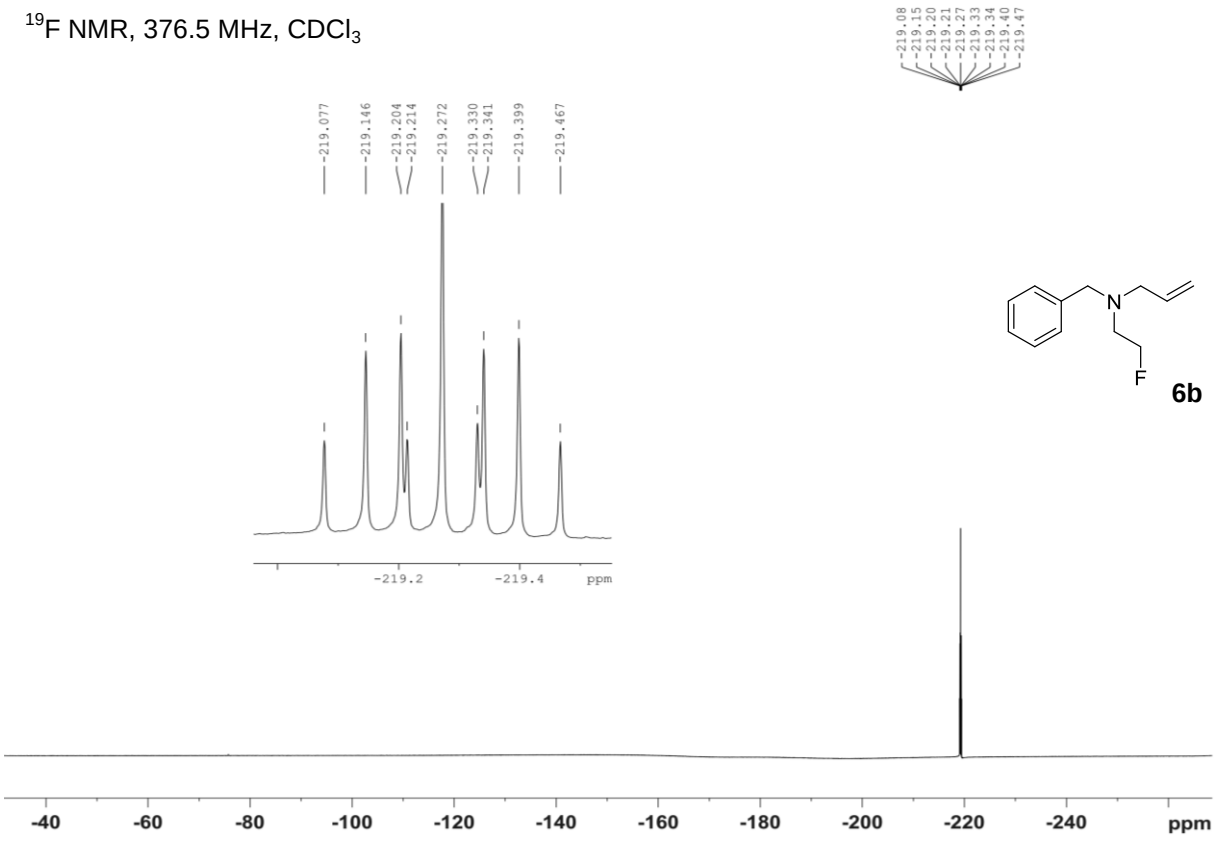
***N,N*-Allylbenzyl-2-fluoroethanamine (6b)**

^{1}H NMR, 400 MHz, $CDCl_3$, TMS

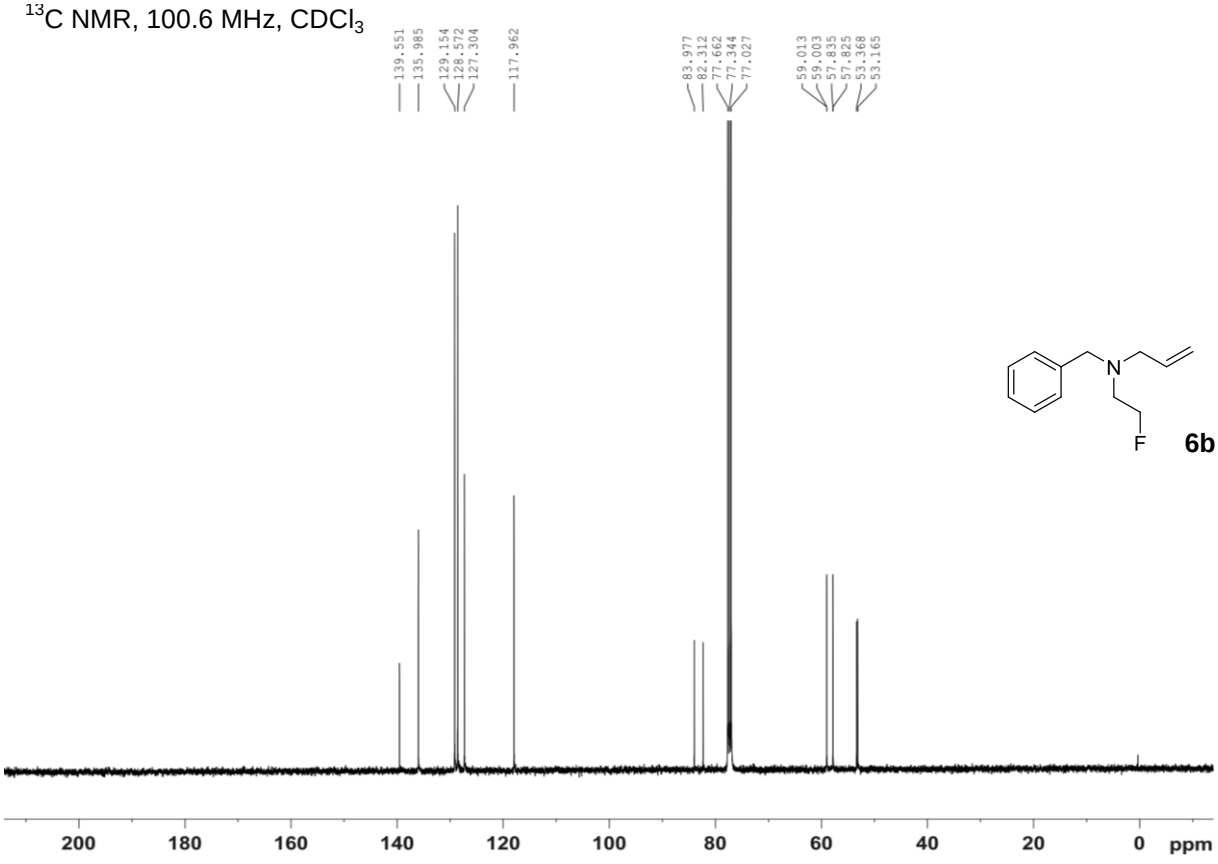


6b

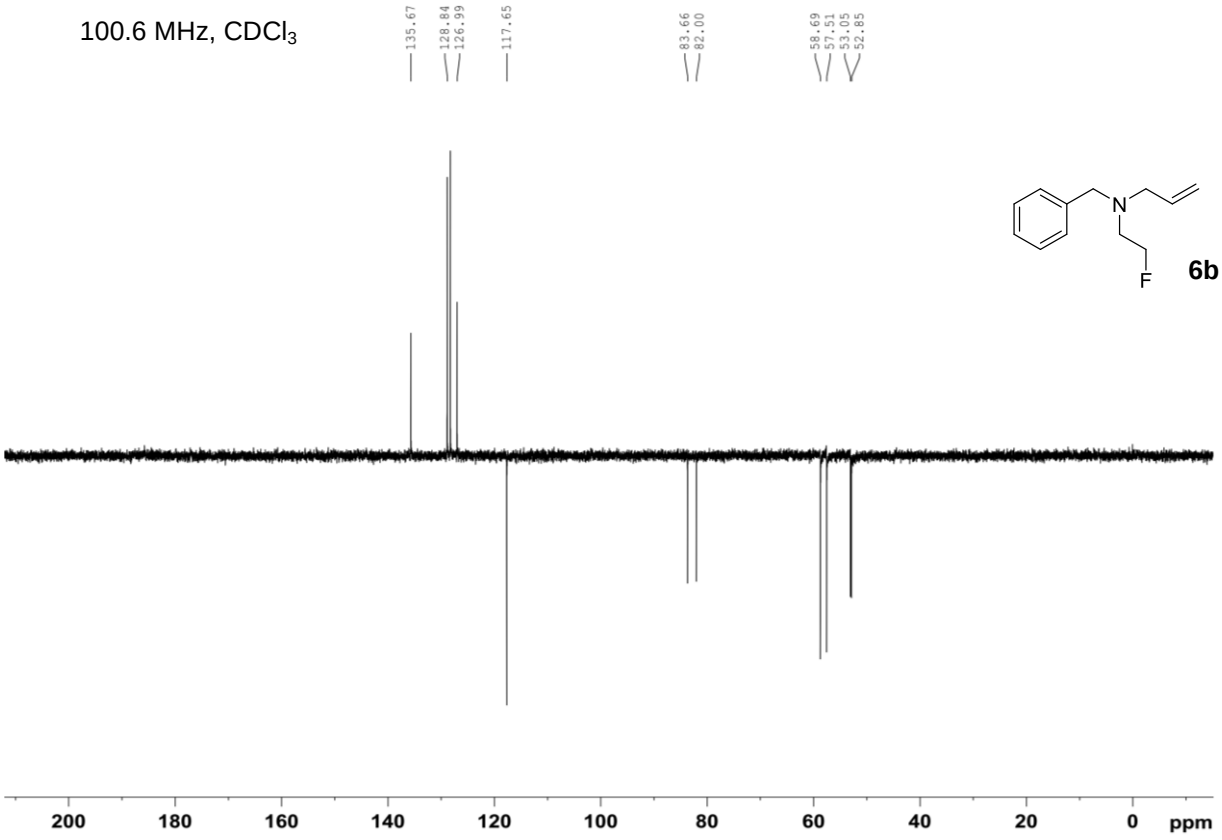
^{19}F NMR, 376.5 MHz, $CDCl_3$



^{13}C NMR, 100.6 MHz, $CDCl_3$



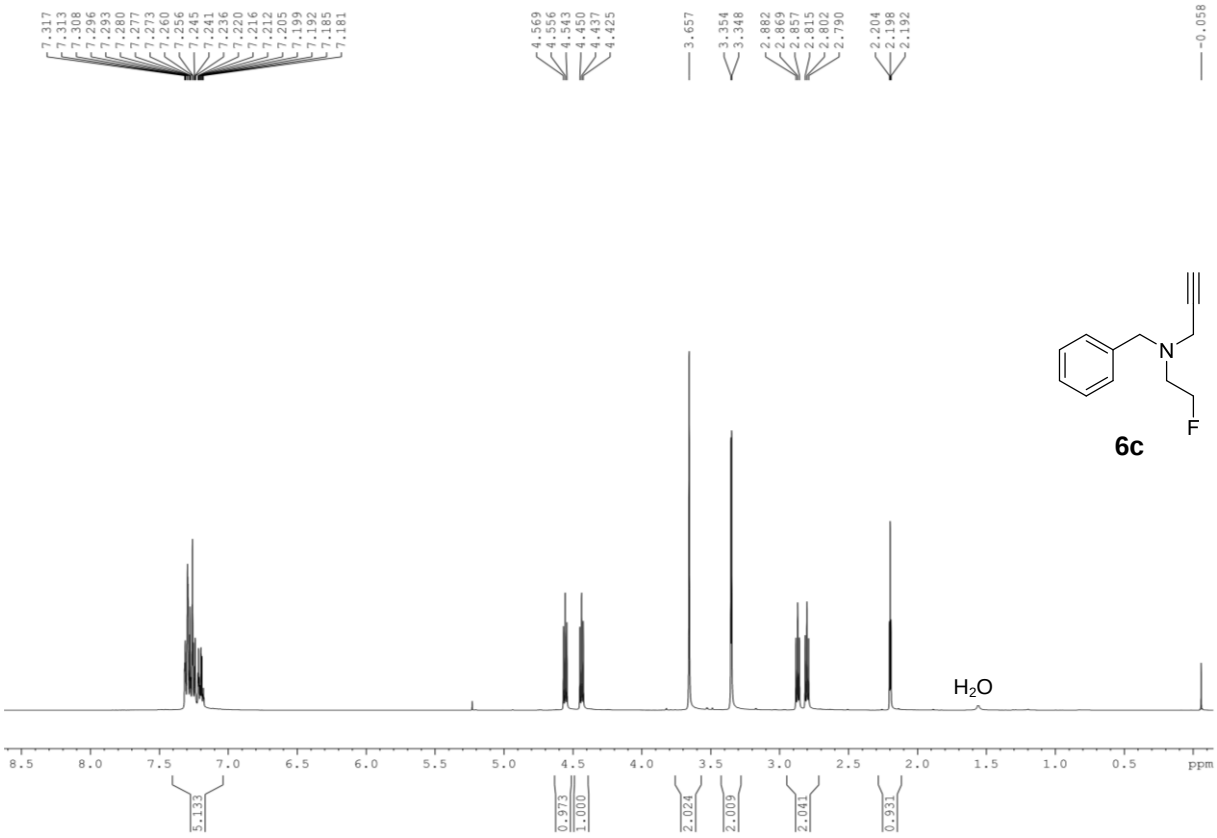
^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



6b

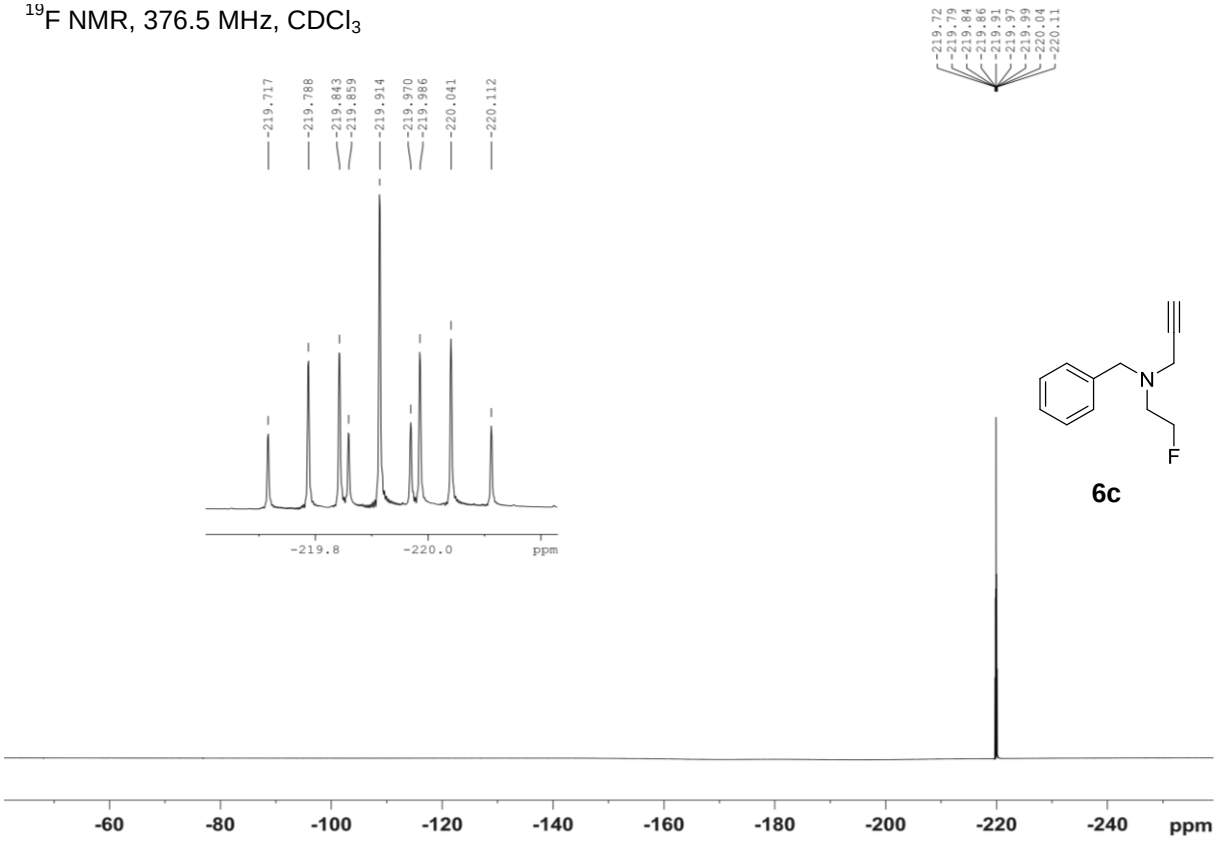
***N*,*N*-Benzylpropargyl-2-fluoroethanamine (6c)**

^{1}H NMR, 400 MHz, $CDCl_3$, TMS

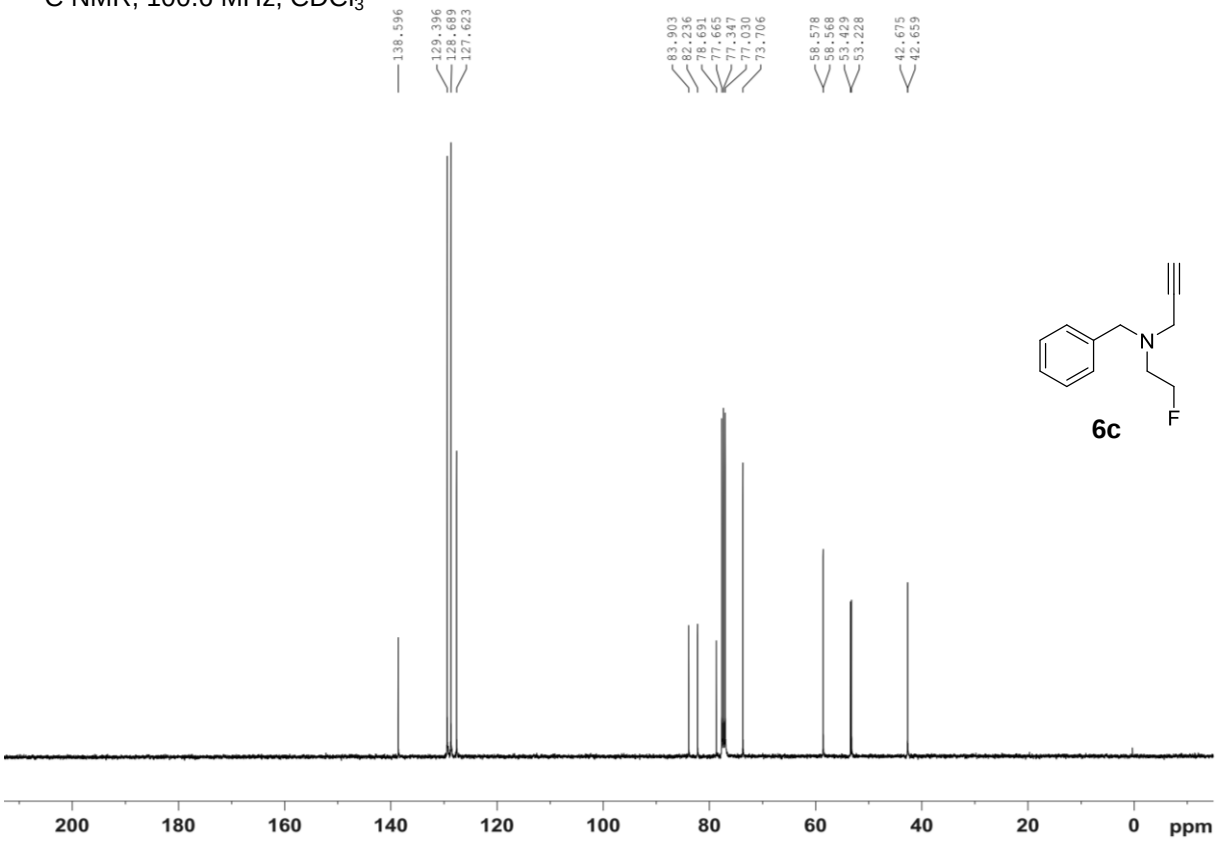


6c

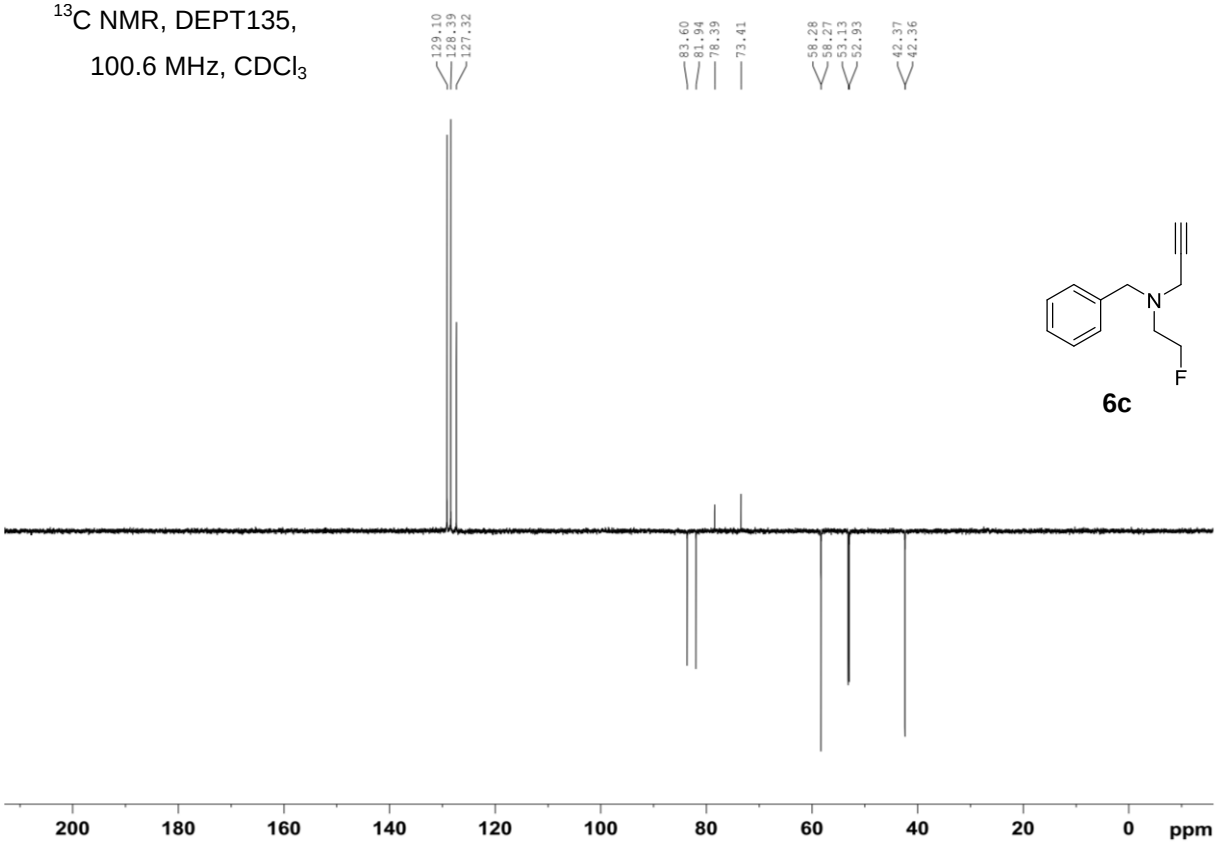
^{19}F NMR, 376.5 MHz, $CDCl_3$



^{13}C NMR, 100.6 MHz, $CDCl_3$



^{13}C NMR, DEPT135,
100.6 MHz, $CDCl_3$



6c