Introduction of the 4,4,4-Trifluorobut-2-ene Chain Exploiting a Regioselective Tsuji-Trost Reaction Catalyzed by Palladium Nanoparticles

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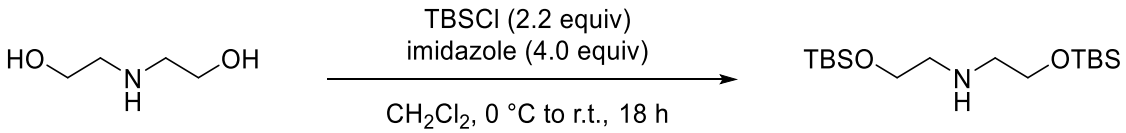
General information

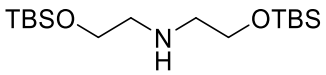
Materials and Methods. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Unless otherwise noted, all commercial reagents were used without further purification. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Silicyle silica gel 60Å F254 TLC Plates and visualized under UV (λ =254 nm) or by staining with $KMnO_4$ solution or *p*-anisaldehyde solution followed by heating. Flash column chromatography was carried out on Silicycle Silica Gel 60 Å, 230 X 400 mesh. NMR spectrum were pectra were recorded using Agilent DD2 500 and Varian Inova 400 spectrometers ^1H, ^{13}C and ^{19}F spectra were respectively recorded at 500, 125 and 470 MHz using $CDCl_3$ as the solvent at ambient temperature using tetramethylsilane for ^1H NMR (δ = 0 ppm) or residual $CHCl_3$ for ^1H (δ = 7.26 ppm) or ^{13}C NMR (δ = 77.16 ppm) as the internal standard and $CFCl_3$ for ^{19}F NMR as the external standard. Coupling constants (*J*) are measured in hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. Copies of the NMR spectra were prepared using MestReNova. High-resolution mass spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI) on a time-of-flight (TOF) spectrometer. Melting points were obtained on a Stanford ResearchSystem OptiMelt with open capillary tubes and are uncorrected. IR spectra were measured on a Thermo Scientific Nicolet 380 FT-IR spectrometer. Enantiomeric excesses were determined by HPLC analysis with a Hewlett Packard Series 1100 using a CHIRALCEL® OJ-H column. The nucleophiles (phenols, amines, malonates or thiophenol) were obtained from commercial sources or prepared as described below.

Synthesis of nucleophiles

Synthesis of various amines



bis(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amine (**SI-1**)

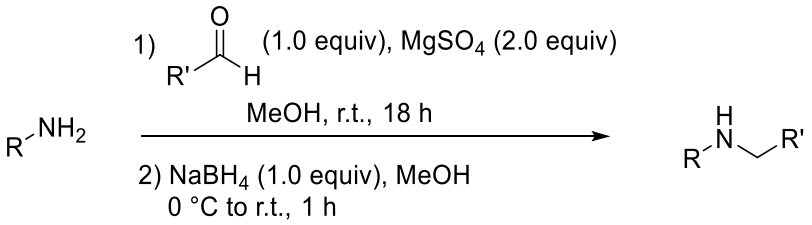


To a solution of diethanolamine (300 mg, 2.8 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) at 0°C under inert atmosphere were successively added imidazole (770 mg, 11.4 mmol, 4.0 equiv) and TBSCl (940 mg, 6.3 mmol, 2.2 equiv) diluted in the minimum amount of dry CH_2Cl_2. The resulting mixture was stirred overnight. Water was then added and the mixture was extracted with CH_2Cl_2. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel by using EtOAc as the eluent to afford **SI-1** as a colorless oil (710 mg, 75%). Spectral data were identical to those previously reported.[1]

^1H NMR (500 MHz, $CDCl_3$): δ = 3.74-3.71 (m, 4H), 2.73-2.71 (m, 4H), 1.97 (br s, 1H), 0.88 (s, 18H), 0.05 (s, 12H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.7, 51.9, 26.1, 18.4, –5.2.

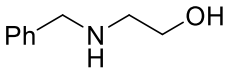
[1] Wang, W.; Li, R.; Gokel, G. W. *Chem. Eur. J.* **2009**, *15*, 10543.

Synthesis of amines by reductive amination



General procedure 1: To a solution of the primary amine (or the aniline) (1.0 equiv) in technical grade methanol were successively added $MgSO_4$ (2.0 equiv) and an aldehyde (1.0 equiv). The resulting mixture was stirred at room temperature overnight. The solution was then cooled to 0 °C and $NaBH_4$ was added portionwise (1.0 equiv) (Caution: exothermic reaction). The mixture was stirred at 0 °C for one hour before the addition of water. The mixture was then extracted with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel if necessary.

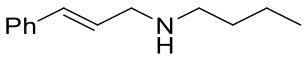
2-(benzylamino)ethan-1-ol (**SI-2**)



Following the general procedure 1: ethanolamine (500 mg, 8.2 mmol, 1.0 equiv) in methanol (15 mL), $MgSO_4$ (1.9 g, 16.4 mmol, 2.0 equiv), benzaldehyde (870 mg, 8.2 mmol, 1.0 equiv) and $NaBH_4$ (310 mg, 8.2 mmol, 1.0 equiv). **SI-2** was obtained as a colorless oil and was used without any further purification (1.2 g, 95%). Spectral data were identical to those previously reported.[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.26 (m, 5H), 3.82 (s, 2H), 3.68-3.66 (m, 2H), 2.84-2.81 (m, 2H), 2.11 (br s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.2, 128.6, 128.2, 127.2, 61.1, 53.6, 50.6.

N-cinnamylbutan-1-amine (**SI-3**)

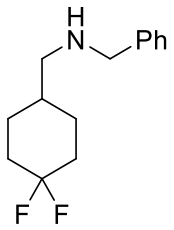


Following the general procedure 1: *n*-butylamine (500 mg, 6.8 mmol, 1.0 equiv) in methanol (10 mL), $MgSO_4$ (900 mg, 13.6 mmol, 2.0 equiv), *trans*-cinnamaldehyde (900 mg, 6.8 mmol, 1.0 equiv) and $NaBH_4$ (260 mg, 6.8 mmol, 1.0 equiv). The crude product was purified by column chromatography on silica gel by using EtOAc as the eluent to afford **SI-3** as a colorless oil (1.1 g, 86%). Spectral data were identical to those previously reported.[3]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (m, 1H), 7.33-7.30 (m, 2H), 7.23 (m, 1H), 6.54 (dt, 1H, *J* = 15.9, 2.0 Hz), 6.33 (dt, 1H, *J* = 15.9, 6.3 Hz), 3.43 (dd, 2H, *J* = 6.3, 1.5 Hz), 2.68-2.66 (m, 2H), 1.55-1.49 (m, 2H), 1.41-1.34 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.3, 131.2, 128.9, 128.6, 127.4, 126.4, 52.2, 49.4, 32.5, 20.6, 14.2.

[2] Jiang, X.-J.; Lo, P.-C.; Tsang, Y.-M.; Yeung, S.-L.; Fong, W.-P.; Ng, D. K. P. *Chem. Eur. J.* **2010**, *16*, 4777.
[3] Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275.

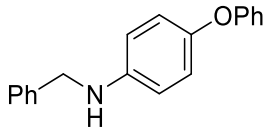
N-benzyl-1-(4,4-difluorocyclohexyl)methanamine (**SI-4**)



To a solution of (4,4-difluorocyclohexane)methylamine hydrochloride (200 mg, 1.1 mmol, 1.0 equiv) in dry CH_2Cl_2 (5.0 mL) were successively added $MgSO_4$ (260 mg, 2.2 mmol, 2.0 equiv), triethylamine (0.75 mL, 5.4 mmol, 5.0 equiv) and benzaldehyde (0.11 mL, 1.1 mmol, 1.0 equiv). The resulting mixture was stirred at room temperature for 48 h. Solvent was then evaporated under reduced pressure and MeOH (5.0 mL) was added. The reaction mixture was cooled to 0 °C before the slow addition of $NaBH_4$ (41 mg, 1.1 mmol, 1.0 equiv). After one hour, water was added to quench the reaction. The mixture was then extracted with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/EtOAc: 40/60 as the eluent to afford **SI-4** as a colorless oil (0.18 g, 71%). Spectral data were identical to those previously reported.[4]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.25 (m, 5H), 3.80 (s, 2H), 2.54 (d, 2H, *J* = 6.7 Hz), 1.89-1.82 (m, 2H), 1.79-1.63 (m, 2H), 1.55 (m, 1H), 1.33-1.25 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.6, 128.6, 128.1, 127.0, 123.9 (dd, *J* = 239.5, 242.0 Hz), 54.6 (d, *J* = 2.7 Hz), 54.3, 36.5 (d, *J* = 1.4 Hz), 33.4 (dd, *J* = 22.5, 25.4 Hz), 27.3 (d, *J* = 9.5 Hz).
^{19}F NMR (470 MHz, $CDCl_3$): δ = –91.3 (d, 1F, *J* = 234.2 Hz), –101.9 (d, 1F, *J* = 234.2 Hz).

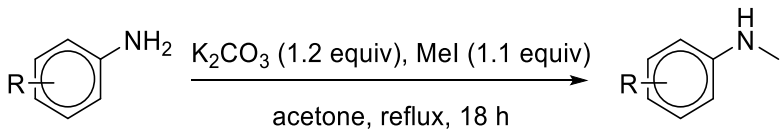
N-benzyl-4-phenoxyaniline (**SI-5**)



By using general procedure 1: 4-phenoxyaniline (940 mg, 5.1 mmol, 1.0 eq) in methanol (10 mL), $MgSO_4$ (1.22 g, 10.1 mmol, 2.0 eq), benzaldehyde (540 mg, 5.1 mmol, 1.0 eq) and $NaBH_4$ (190 mg, 5.1 mmol, 1.0 eq). The crude product was purified by column chromatography on silica gel using hexane/EtOAc: 90/10 as the eluent to afford **SI-5** as a pale brown viscous oil (1.18 g, 85 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.37 (m, 4H), 7.33-7.28 (m, 3H), 7.03 (m, 1H), 6.97-6.95 (m, 2H), 6.94-6.92 (m, 2H), 6.65 (m, 2H), 4.34 (s, 2H), 3.99 (br s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 147.9, 144.9, 139.4, 129.6, 128.8, 127.7, 127.4, 122.0, 121.3, 117.2, 113.9, 49.0.
HRMS-ESI calcd for $C_{19}H_{17}NO$ $[M+H]^+$ 276.1383, found 276.1385.
IR (ATR, ZnSe) ν (cm^{-1}) = 1587, 1507, 1485, 1224, 830, 747, 690.

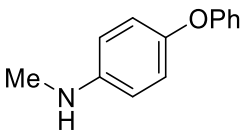
Synthesis of *N*-methylaniline derivatives



General procedure 2: to a solution of the aniline derivative (1.0 equiv) in technical grade acetone were successively added K_2CO_3 (1.2 equiv) and methyl iodide (1.1 equiv). The resulting mixture was refluxed for 18 h. The crude product was then filtrated through Celite and the organic phase was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

[4] Hamel, J.-D.; Drouin, M.; Paquin, J.-F. *J. Fluorine Chem.* **2015**, in press. (DOI: 10.1016/j.jfluchem.2014.07.012).

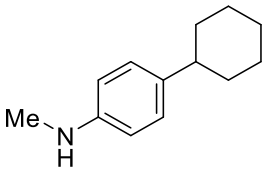
N-methyl-4-phenoxyaniline (**SI-6**)



Following the general procedure 2: 4-phenoxyaniline (1.0 g, 5.4 mmol, 1.0 equiv) in acetone (10 mL), K_2CO_3 (740 mg, 6.5 mmol, 1.2 equiv) and methyl iodide (0.37 mL, 5.9 mmol, 1.1 equiv). The crude product was purified by column chromatography on silica gel using hexane/EtOAc: 90/10 as the eluent to afford **SI-6** as a brown oil which crystallized slowly in the fridge (100 mg, 10%).

mp = 55-57 °C.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30-7.27 (m, 2H), 7.02 (m, 1H), 6.95-6.93 (m, 4H), 6.64-6.61 (m, 2H), 3.66 (br s, 1H), 2.86 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 147.6, 146.1, 129.6, 122.0, 121.4, 117.1, 113.4, 31.4.
HRMS-ESI calcd for $C_{13}H_{13}NO$ $[M+H]^+$ 200.1070, found 200.1065.
IR (ATR, ZnSe) ν (cm^{-1}) = 3410, 1511, 1481, 1197, 866, 832, 753, 689.

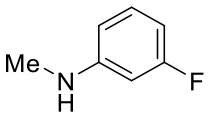
4-cyclohexyl-*N*-methylaniline (**SI-7**)



Following the general procedure 2: 4-cyclohexylaniline (1.0 g, 5.7 mmol, 1.0 equiv) in acetone (10 mL), K_2CO_3 (940 mg, 6.8 mmol, 1.2 equiv) and methyl iodide (0.39 mL, 6.3 mmol, 1.1 equiv). The crude product was purified by column chromatography on silica gel using hexane/EtOAc: 90/10 as the eluent to afford **SI-7** as a brown oil (80 mg, 7%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, 2H, *J* = 8.4 Hz), 6.58 (d, 2H, *J* = 8.4 Hz), 3.54 (br s, 1H), 2.84 (s, 3H), 2.41 (m, 1H), 1.88-1.83 (m, 4H), 1.75 (m, 1H), 1.41-1.37 (m, 4H), 1.25 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6, 137.3, 127.6, 112.6, 43.8, 34.9, 31.2, 27.2, 26.4.
HRMS-ESI calcd for $C_{13}H_{19}N$ $[M+H]^+$ 190.1590, found 190.1593.
IR (ATR, ZnSe) ν (cm^{-1}) = 2920, 2848, 1615, 1519, 1446, 1315, 1260, 1183, 815.

3-fluoro-*N*-methylaniline (**SI-8**)

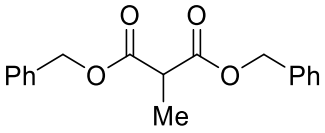


Following the general procedure 2: 3-fluoroaniline (1.0 g, 5.4 mmol, 1.0 equiv) in acetone (10 mL), K_2CO_3 (740 mg, 6.5 mmol, 1.2 equiv) and methyl iodide (0.37 mL, 5.9 mmol, 1.1 equiv). The crude product was purified by column chromatography on silica gel using hexane/EtOAc: 95/5→90/10 as the eluent to afford **SI-8** as a pale yellow oil (100 mg, 10%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (m, 1H), 6.42-6.37 (m, 2H), 6.30 (m, 1H), 3.84 (br s, 1H), 2.84 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4 (d, *J* = 242.5 Hz), 151.2 (d, *J* = 10.8 Hz), 130.3 (d, *J* = 10.2 Hz), 108.4 (d, *J* = 2.2 Hz), 103.6 (d, *J* = 21.5 Hz), 99.0 (d, *J* = 25.3 Hz), 30.7.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –113.1 (m, 1F).
HRMS-ESI calcd for C_7H_8FN $[M+H]^+$ 126.0714, found 126.0710.
IR (ATR, ZnSe) ν (cm^{-1}) = 3423, 1621, 1588, 1511, 1496, 1333, 1262, 1176, 1159, 1147.

Synthesis of malonates

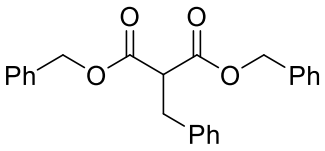
dibenzyl 2-methylmalonate (**SI-9**)



Using a slightly modified protocol,[5] to a solution of dibenzyl malonate (800 mg, 2.8 mmol, 1.0 equiv) in anhydrous acetone (6.0 mL) were added potassium carbonate (420 mg, 3.1 mmol, 1.1 equiv) and iodomethane (0.31 mL, 3.4 mmol, 1.2 equiv). The resulting mixture was refluxed overnight. The solution was then filtrated through Celite. The organic phase was concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/EtOAc: 90/10 as the eluent to afford **SI-9** as a colorless oil (690 mg, 82%).Spectral data were identical to those previously reported.[6]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 10H), 5.16 (s, 4H), 3.56 (q, 1H, *J* = 7.3 Hz), 1.48 (d, 3H, *J* = 7.3 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 135.5, 128.7, 128.4, 128.2, 67.2, 46.3, 13.7.

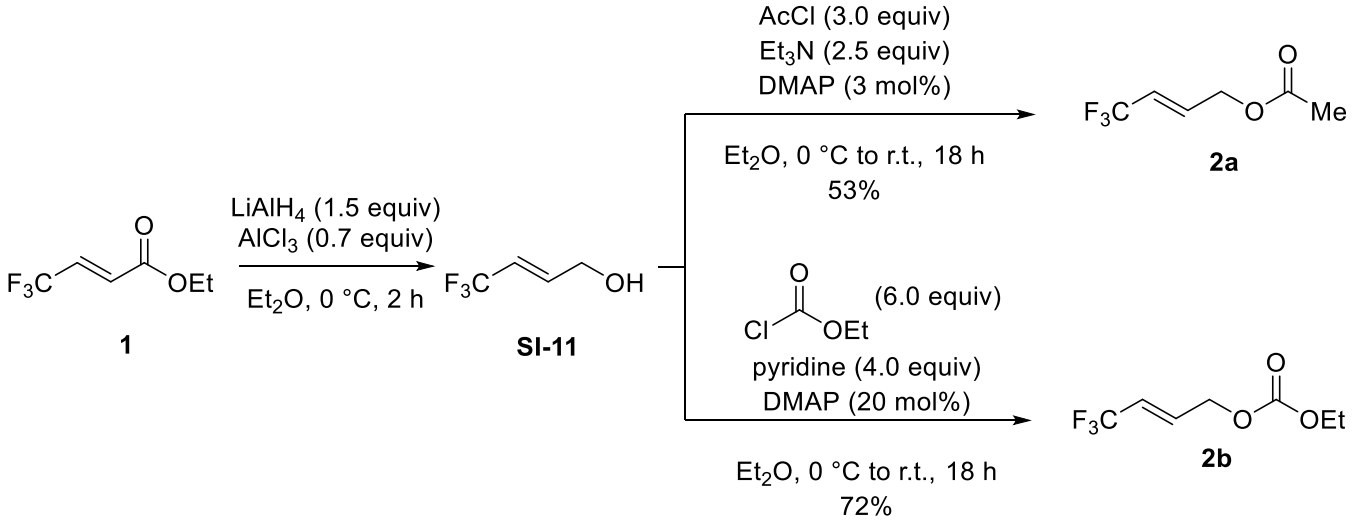
dibenzyl 2-benzylmalonate (**SI-10**)



To a solution of dibenzyl malonate (500 mg, 1.7 mmol, 1.0 equiv) in anhydrous THF (6.0 mL) under inert atmosphere at 0°C were successively added NaH (70 mg, 1.7 mmol, 1.0 eq, 60% dispersed in oil) and benzylbromide (0.21 mL, 1.7 mmol, 1.0 equiv). The resulting mixture was stirred at room temperature overnight. Water was then added and the mixture was extracted with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified using hexane/EtOAc: 90/10 as the eluent to afford **SI-10** as a colorless oil (520 mg, 81%).Spectral data were identical to those previously reported.[7]

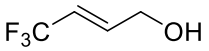
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33-7.31 (m, 6H), 7.27-7.21 (m, 7H), 7.18-7.16 (m, 2H), 5.12 (s, 4H), 3.79 (t, 1H, *J* = 7.9 Hz), 3.27 (d, 2H, *J* = 7.9 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 137.7, 135.3, 128.9, 128.7, 128.6, 128.4, 128.2, 126.9, 67.3, 53.9, 34.8.

Synthesis of acetate and carbonate derivatives



[5] Wang, W.; Li, R.; Gokel, G. W. *Chem. Eur. J.* **2009**, *15*, 10543.
[6] Jiang, X.-J.; Lo, P.-C.; Tsang, Y.-M.; Yeung, S.-L.; Fong, W.-P.; Ng, D. K. P. *Chem. Eur. J.* **2010**, *16*, 4777.

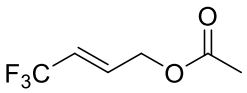
(*E*)-4,4,4-trifluorobut-2-en-1-ol (**SI-11**)



To a solution of $LiAlH_4$ (1.35 g, 35.5 mmol, 1.5 equiv) in dry Et_2O (13.0 mL) under argon atmosphere was added dropwise a solution of $AlCl_3$ (2.22 g, 16.6 mmol, 0.7 equiv) in dry Et_2O (6.5 mL). After 20 min of stirring at 0°C, a solution of ethyl (*E*)-4,4,4-trifluorocrotonate (4.00 g, 23.8 mmol, 1.0 equiv) in dry Et_2O was added dropwise. The resulting mixture was allowed to stir at 0°C for 2 hours. A saturated solution of Na_2SO_4 was then added (Caution: very exothermic reaction). The mixture was filtrated and the solid was washed several times with Et_2O. The organic layers were combined and washed with brine and dried over $MgSO_4$. The solvent was removed by thorough distillation at atmospheric pressure to afford **SI-11** as a colorless oil that was used without any further purification. Spectral data were in accordance with the literature.[7]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.51 (dtq, 1H, *J* = 15.7, 3.8, 1.7 Hz), 5.97 (dqt, 1H, *J* = 15.7, 6.5, 2.2 Hz), 4.31-4.35 (m, 2H), 1.62 (t, 1H, *J* = 5.3 Hz).
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.1 (m, 3F).

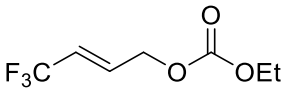
(*E*)-4,4,4-trifluorobut-2-en-1-yl acetate (**2a**)



To a stirred solution of (*E*)-4,4,4-trifluorobut-2-en-1-ol **SI-11** (1.50 g, 11.9 mmol, 1.0 equiv) in Et_2O (9 mL) was added triethylamine (4.20 mL, 29.8 mmol, 2.5 equiv) and DMAP (43 mg, 0.35 mmol, 0.03 equiv). The reaction mixture was cooled to 0 °C then acetyl chloride (1.70 mL, 23.8 mmol, 2.0 equiv) was added dropwise. The mixture was stirred at room temperature for 18 hours. Then, the reaction was quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted 3 times using Et_2O. The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed by distillation at atmospheric pressure. The crude product was purified by column chromatography on silica gel using pentane/Et_2O: 90/10 as the eluent. The solvents were removed by distillation at atmospheric pressure affording the product **2a** (1.07 g, 53% over two steps) as a colorless oil. Spectral data were in accordance with the literature.[8]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.43 (dtq, 1H, *J* = 15.8, 4.4, 2.0 Hz), 5.88 (dqt, 1H, *J* = 15.8, 6.3, 2.0 Hz), 4.69 (m, 2H), 2.13 (s, 3H).
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.6 (m, 3F).

(*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate (**2b**)

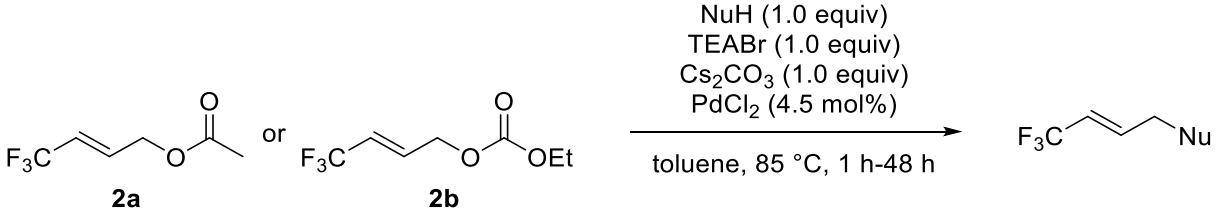


To a solution of (*E*)-4,4,4-trifluorobut-2-en-1-ol **SI-11** (2.90 g, 23.0 mmol, 1.0 equiv) in anhydrous Et_2O (92.0 mL) at 0 °C under inert atmosphere were successively added pyridine (7.40 mL, 92.0 mmol, 4.0 equiv), DMAP (560 mg, 4.60 mmol, 0.2 equiv) and ethyl chloroformate (13.7 mL, 0.14 mol, 6.0 equiv). The solution immediately turned white after the addition of ethyl chloroformate. The mixture was stirred at room temperature overnight. Water was then added to quench the reaction and the mixture was extracted with Et_2O. The organic layers were combined and washed with 3 N HCl then with a saturated solution of $NaHCO_3$. Organic solvent were removed by thorough distillation at atmospheric pressure. The crude product was purified by column chromatography on silica gel by using pentane/Et_2O: 90/10 as the eluent. Solvents were once again removed by thorough distillation at atmospheric pressure. The last traces of solvent were removed by Kugelrohr distillation under reduced pressure (T = 75 °C, P = 41 mmHg) to afford **2b** as a colorless oil (3.28 g, 72% over two steps).

[7] Jiang, Z.-X.; Qing, F.-L. *J. Org. Chem.* **2004**, *69*, 5486.
[8] US2004147789A1

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.44 (dtq, 1H, *J* = 15.8, 4.4, 2.3 Hz), 5.95 (dqt, 1H, *J* = 15.8, 6.3, 2.0 Hz), 4.78-4.74 (m, 2H), 4.25 (q, 2H, *J* = 7.1 Hz), 1.34 (t, 3H, *J* = 7.1 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 133.4 (q, *J* = 6.5 Hz), 122.6 (q, *J* = 269.3 Hz), 120.2 (q, *J* = 34.5 Hz), 64.9, 64.4, 14.4.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.7 (m, 3F).
HRMS-ESI calcd for $C_7H_9F_3O_3$ $[M+H]^+$ 199.0577, found 199.0577.
IR (ATR, ZnSe) ν (cm^{-1}) = 1747, 1691, 1244, 1117, 1038, 999, 959, 789.

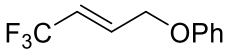
Tsuji-Trost reaction



General procedure A: To a 2-5 mL microwave vial were successively charged, (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (0.25 mmol, 1.0 equiv), the nucleophile (0.25 mmol, 1.0 equiv), tetraethylammonium bromide (0.25 mmol, 1.0 equiv), cesium carbonate (0.25 mmol, 1.0 equiv), $PdCl_2$ (4.5 mol%) and toluene (0.5 M). The vial was then sealed with a cap and resulting mixture was heated for 1 h at 85 °C in a preheated oil bath. Water was then added to quench the reaction, and the mixture was extracted three times with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography.

General procedure B: To a 2-5 mL microwave vial were successively charged, (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (0.30 mmol, 1.0 equiv) in toluene (1 M), tetraethylammonium bromide (0.30 mmol, 1.0 equiv), the nucleophile (0.30 mmol, 1.0 equiv), cesium carbonate (0.30 mmol, 1.0 equiv) and $PdCl_2$ (4.5 mol%). The vial was then sealed with a cap and resulting mixture was heated for 48 h at 85 °C. Water was then added to quench the reaction, and the mixture was extracted three times with Et_2O. The organic layers were combined and washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography.

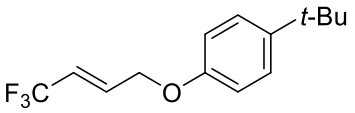
(*E*)-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3a**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), phenol (23 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3a** as a colorless oil (31 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 1H), 7.01 (m, 1H), 6.95-6.92 (m, 2H), 6.58 (dtq, 1H, *J* = 15.8, 3.9, 1.8 Hz, 1H), 6.09 (dqt, 1H, *J* = 15.8, 6.5, 2.2 Hz), 4.68-4.65 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 135.0 (q, *J* = 6.4 Hz), 129.8, 123.0 (q, *J* = 269.3 Hz), 121.7, 119.6 (q, *J* = 34.3 Hz), 114.7, 65.7.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-APPI calcd for $C_{10}H_9F_3O$ $[M^*]^+$ 202.0605, found 202.0605.
IR (ATR, ZnSe) ν (cm^{-1}) = 1599, 1496, 1239, 1117, 1084, 959, 751, 639.

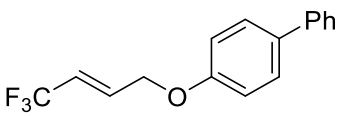
(*E*)-1-(tert-butyl)-4-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3b**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 4-*tert*-butylphenol (38 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3b** as a colorless oil (46 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, 2H, *J* = 8.9 Hz), 6.88 (d, 2H, *J* = 8.9 Hz), 6.58 (dtq, 1H, *J* = 15.8, 4.0, 1.9 Hz), 6.10 (dqt, 1H, *J* = 15.7, 6.5, 2.2 Hz), 4.67-4.64 (m, 2H), 1.34 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8, 144.4, 135.3 (q, *J* = 6.5 Hz, CH), 126.5, 123.1 (q, *J* = 269.2 Hz), 119.4 (q, *J* = 34.2 Hz), 114.2, 65.8, 34.2, 31.6.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.3 (m, 3F).
HRMS-APPI calcd for $C_{14}H_{17}F_3O$ $[M^*]^+$ 258.1231, found 258.1235.
IR (ATR, ZnSe) ν (cm^{-1}) = 2963, 1513, 1315, 1307, 1240, 1119, 1078, 958, 834, 822, 670.

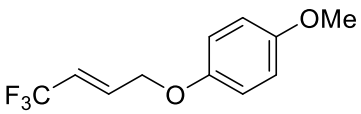
(*E*)-4-((4,4,4-trifluorobut-2-en-1-yl)oxy)-1,1'-biphenyl (**3c**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 4-phenylphenol (42 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82.0 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3c** as a colorless oil (42 mg, 60%).

mp = 102-103 °C
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 4H), 7.46-7.42 (m, 2H), 7.32 (m, 1H), 7.02-6.98 (m, 2H), 6.59 (dtq, 1H, *J* = 15.8, 4.0, 1.9 Hz), 6.11 (dqt, 1H, *J* = 15.8, 6.4, 2.1 Hz), 4.71-4.69 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.5, 140.7, 135.0 (q, *J* = 6.4 Hz), 134.8, 128.9, 128.4, 127.0, 126.9, 123.1 (q, *J* = 269.2 Hz), 119.6 (q, *J* = 34.3 Hz), 115.0, 65.8.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-APPI calcd for $C_{16}H_{13}F_3O$ $[M^*]^+$ 278.0918, found 278.0915.
IR (ATR, ZnSe) ν (cm^{-1}) = 1487, 1318, 1310, 1266, 1246, 1098, 1073, 959, 830, 763, 693.

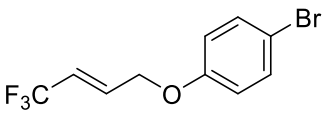
(*E*)-1-methoxy-4-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3d**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 4-methoxyphenol (31 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3d** as a colorless oil (38 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (br s, 4H), 6.56 (dm, 1H, *J* = 15.5 Hz), 6.07 (dqt, 1H, *J* = 15.5, 6.5, 2.1 Hz), 4.62-4.60 (m, 2H), 3.79 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 152.2, 135.4 (q, *J* = 6.4 Hz), 123.0 (q, *J* = 269.2 Hz), 119.3 (q, *J* = 34.2 Hz), 115.8, 114.5, 66.5, 55.8.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-APPI calcd for $C_{11}H_{11}F_3O_2$ $[M^*]^+$ 232.0711, found 232.0715.
IR (ATR, ZnSe) ν (cm^{-1}) = 1506, 1313, 1227, 1107, 1078, 1035, 959, 822, 692.

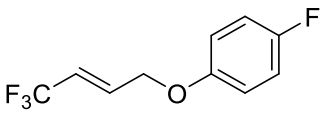
(*E*)-1-bromo-4-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3e**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 4-bromophenol (44 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3e** as a colorless oil (41 mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.40 (m, 2H), 6.82-6.80 (m, 2H), 6.55 (dtq, 1H, *J* = 15.8, 4.0, 1.9 Hz), 6.06 (dqt, 1H, *J* = 15.8, 6.4, 2.2 Hz), 4.64-4.61 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1, 134.6 (q, *J* = 6.5 Hz), 132.6, 122.9 (q, *J* = 269.0 Hz), 119.8 (q, *J* = 34.4 Hz), 116.5, 113.9, 65.9.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-APPI calcd for $C_{10}H_8BrF_3O$ $[M^*]^+$ 279.9711, found 279.9738.
IR (ATR, ZnSe) ν (cm^{-1}) = 1487, 1311, 1237, 1113, 1078, 1070, 1023, 1003, 959, 819.

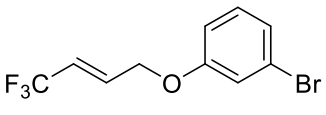
(*E*)-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3f**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 4-fluorophenol (28 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3f** as a colorless oil (38 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.03-6.99 (m, 2H), 6.89-6.84 (m, 2H), 6.56 (dtq, 1H, *J* = 15.8, 4.0, 1.8 Hz), 6.07 (dqt, 1H, *J* = 15.8, 6.4, 2.2 Hz), 4.64-4.60 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.7 (d, *J* = 269.3 Hz), 154.1 (d, *J* = 2.4 Hz), 134.9 (q, *J* = 6.5 Hz), 122.9 (q, *J* = 269.3 Hz), 119.6 (q, *J* = 34.3 Hz), 116.1 (d, *J* = 23.0 Hz), 115.8 (d, *J* = 8.1 Hz), 66.4.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F), –122.8 (tt, 1F, *J* = 8.2, 4.2 Hz).
HRMS-APPI calcd for $C_{10}H_9F_3O$ $[M^*]^+$ 220.0511, found 220.0535.
IR (ATR, ZnSe) ν (cm^{-1}) = 1505, 1314, 1211, 1116, 1097, 1078, 959, 826, 775, 693.

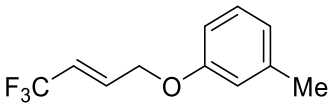
(*E*)-1-bromo-3-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3h**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 3-bromophenol (44 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3h** as a colorless oil (41 mg, 58%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19-7.13 (m, 2H), 7.08 (m, 1H), 6.85 (ddd, 1H, *J* = 8.0, 2.3, 1.2 Hz), 6.54 (dtq, 1H, *J* = 15.8, 4.0, 1.9 Hz), 6.06 (dqt, 1H, *J* = 15.8, 6.4, 2.1 Hz), 4.64-4.62 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7, 134.4 (q, *J* = 6.5 Hz), 130.9, 124.9, 123.1, 122.9 (q, *J* = 269.3 Hz), 119.8 (q, *J* = 34.4 Hz), 118.1, 113.7, 65.9.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.6 (m, 3F).
HRMS-APPI calcd for $C_{10}H_8BrF_3O$ $[M^*]^+$ 279.9711, found 279.9726.
IR (ATR, ZnSe) ν (cm^{-1}) = 1589, 1575, 1474, 1310, 1225, 1116, 1076, 958, 840, 764, 678.

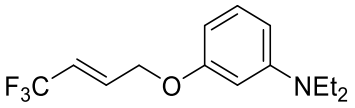
(*E*)-1-methyl-3-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3i**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), (34 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3i** as a colorless oil (37 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (t, 1H, *J* = 7.5 Hz), 6.83 (ddd, 1H, *J* = 7.5, 1.5, 0.8 Hz), 6.76 (m, 1H), 6.73 (ddd, 1H, *J* = 7.5, 1.5, 0.8 Hz), 6.57 (dtq, 1H, *J* = 15.8, 4.0, 1.8 Hz), 6.08 (dqt, 1H, *J* = 15.8, 6.5, 2.2 Hz), 4.66-4.63 (m, 2H), 2.36 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 139.9, 135.2 (q, *J* = 6.5 Hz), 129.5, 123.0 (q, *J* = 269.1 Hz), 122.5, 119.4 (q, *J* = 34.2 Hz), 115.6, 111.5, 65.6, 21.7.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-APPI calcd for $C_{11}H_{11}F_3O$ $[M^*]^+$ 216.0762, found 216.0765.
IR (ATR, ZnSe) ν (cm^{-1}) = 1585, 1489, 1312, 1257, 1159, 1118, 1082, 958, 768, 688.

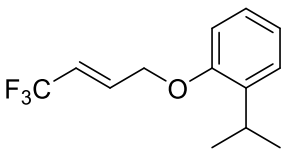
(*E*)-*N*,*N*-diethyl-3-((4,4,4-trifluorobut-2-en-1-yl)oxy)aniline (**3j**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 3-diethylaminophenol (42 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3j** as a colorless oil (43 mg, 63%).

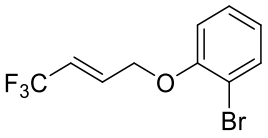
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 (t, 1H, *J* = 8.2Hz), 6.57 (dm, 1H, *J* = 15.8 Hz), 6.37 (ddd, 1H, *J* = 8.2, 2.3, 0.6 Hz), 6.25 (t, 1H, *J* = 2.3 Hz), 6.21 (ddd, 1H, *J* = 8.2, 2.3, 0.6 Hz), 6.09 (dqt, 1H, *J* = 15.8, 6.5, 2.2 Hz), 4.66-4.63 (m, 2H), 3.35 (q, 4H, *J* = 7.1 Hz), 1.18 (t, 6H, *J* = 7.1 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5, 149.4, 135.6 (q, *J* = 6.5 Hz), 130.2, 123.2 (q, *J* = 269.2 Hz), 119.4 (q, *J* = 34.1 Hz), 105.8, 100.6, 99.0, 65.7, 44.5, 12.7.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.3 (m, 3F).
HRMS-ESI calcd for $C_{14}H_{18}F_3NO$ $[M+H]^+$ 274.1413, found 274.1418.
IR (ATR, ZnSe) ν (cm^{-1}) = 2972, 1610, 1571, 1499, 1307, 1256, 1213, 1117, 1082, 958, 743, 685.

(*E*)-1-isopropyl-2-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3k**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 2-isopropylphenol (34 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3k** as a colorless oil (32 mg, 52%).
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (dd, 1H, *J* = 7.5, 1.7 Hz), 7.19 (ddd, 1H, *J* = 8.2, 7.5, 1.7 Hz), 7.00 (dt, 1H, *J* = 7.5, 1.0 Hz), 6.82 (dd, 1H, *J* = 8.2, 1.0 Hz), 6.62 (dtq, 1H, *J* = 15.8, 3.8, 1.6 Hz), 6.11 (dqt, 1H, *J* = 15.7, 6.5, 2.2 Hz), 4.69-4.66 (m, 2H), 3.39 (sept, 1H, *J* = 6.9 Hz), 1.28 (d, 6H, *J* = 6.9 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 137.4, 135.5 (q, *J* = 6.5 Hz), 126.8, 126.5, 123.1 (q, *J* = 269.1 Hz), 121.7, 119.0 (q, *J* = 34.2 Hz), 111.6, 65.9, 27.0, 22.8.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.3 (m, 3F).
HRMS-APPI calcd for $C_{13}H_{15}F_3O$ $[M^*]^+$ 244.1075, found 244.1090.
IR (ATR, ZnSe) ν (cm^{-1}) = 1490, 1447, 1311, 1234, 1116, 1091, 958, 747.

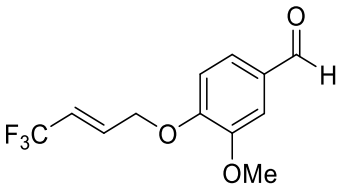
(*E*)-1-bromo-2-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzene (**3l**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 2-bromophenol (44 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82.0 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **3l** as a colorless oil (37 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.29 (m, 1H), 6.90 (m, 1H), 6.88 (dd, 1H, *J* = 8.2, 1.3 Hz), 6.58 (dtq, 1H, *J* = 15.2, 3.6, 1.5 Hz), 6.24 (dqt, 1H, *J* = 15.2, 6.5, 2.2 Hz), 4.73-4.70 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3, 134.2 (q, *J* = 6.5 Hz), 133.8, 128.7, 123.0 (q, *J* = 269.3 Hz), 122.9, 119.8 (q, *J* = 34.3 Hz), 113.4, 112.5, 66.6.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-APPI calcd for $C_{10}H_8BrF_3O$ $[M^*]^+$ 279.9711, found 279.9710.
IR (ATR, ZnSe) ν (cm^{-1}) = 1480, 1443, 1311, 1264, 1248, 1115, 1075, 1031, 959, 744, 663.

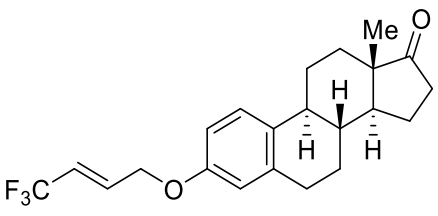
(*E*)-3-methoxy-4-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzaldehyde (**3m**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), vanilline (38 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 80/20 as the eluent to afford **3m** as a colorless solid (43 mg, 65%).

mp = 50-52 °C.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.87 (s, 1H), 7.46-7.44 (m, 2H), 6.94 (dd, 1H, *J* = 8.6, 0.7 Hz), 6.59 (m, 1H), 6.13-6.06 (m, 1H), 4.81-4.79 (m, 2H), 3.96 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 152.7, 150.1, 134.0 (q, *J* = 6.4 Hz), 131.0, 126.5, 122.8 (q, *J* = 269.4 Hz), 120.3 (q, *J* = 34.4 Hz), 112.2, 109.7, 66.7, 56.2.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.5 (m, 3F).
HRMS-ESI calcd for $C_{12}H_{11}F_3O_3$ $[M+H]^+$ 261.0733, found 261.0735.
IR (ATR, ZnSe) ν (cm^{-1}) = 1680, 1585, 1510, 1313, 1266, 1236, 1125, 1097, 1067, 1033, 959, 804, 655.

(8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(((*E*)-4,4,4-trifluorobut-2-en-1-yl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one (**3n**)

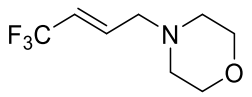


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), estrone (68 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 80/20 as the eluent to afford **3n** as a white solid (82 mg, 87%).

mp = 117-119 °C.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, 1H, *J* = 8.6 Hz), 6.73 (dd, 1H, *J* = 8.6, 2.8 Hz), 6.67 (d, 1H, *J* = 2.8 Hz), 6.56 (dtq, 1H, *J* = 15.8, 4.0, 1.8 Hz), 6.07 (dqt, 1H, *J* = 15.8, 6.5, 2.2 Hz), 4.65-4.62 (m, 2H), 2.92-2.90 (m, 2H), 2.52 (m, 1H), 2.41 (m, 1H), 2.27 (m, 1H), 2.17 (m, 1H), 2.10-2.01 (m, 2H), 1.96 (m, 1H), 1.68-1.41 (m, 6H), 0.93 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 221.0, 156.1, 138.2, 135.3 (q, *J* = 6.5 Hz), 133.1, 126.6, 123.0 (q, *J* = 269.2 Hz), 119.3 (q, *J* = 34.2 Hz), 114.9, 112.3, 65.8, 50.5, 48.1, 44.1, 38.4, 36.0, 31.7, 29.8, 26.6, 26.0, 21.7, 14.0.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.3 (m, 3F).
HRMS-ESI calcd for $C_{22}H_{25}F_3O_2$ $[M+H]^+$ 378.1879, found 378.1880.
IR (ATR, ZnSe) ν (cm^{-1}) = 2931, 2874, 1732, 1494, 1248, 1132, 1054, 971, 809.

(*E*)-4-(4,4,4-trifluorobut-2-en-1-yl)morpholine (**4a**)

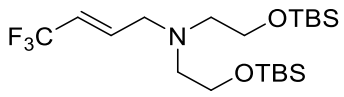


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), morpholine (22 µL, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4a** as a colorless oil (20 mg, 41%).

Following the general procedure B: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv), morpholine (26 µL, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was purified using hexane/Et_2O: 90/10 as the eluent to afford **4a** as a colorless oil (35 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (dtq, 1H, *J* = 15.8, 4.2, 2.1 Hz), 5.85 (dqt, 1H, *J* = 15.8, 6.4, 1.7 Hz), 3.74-3.72 (m, 4H), 3.11-3.08 (m, 2H), 2.48-2.46 (m, 4H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.0 (q, *J* = 6.3 Hz), 123.0 (q, *J* = 269.2 Hz), 121.1 (q, *J* = 33.7 Hz), 67.0, 59.0, 53.7.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.2 (m, 3F).
HRMS-ESI calcd for $C_8H_{12}F_3NO$ $[M+H]^+$ 196.0944, found 196.0948.
IR (ATR, ZnSe) ν (cm^{-1}) = 1308, 1275, 1259, 1109, 1069, 870.

(*E*)-*N*,*N*-bis(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4,4,4-trifluorobut-2-en-1-amine (**4b**)

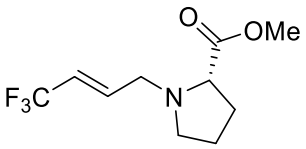


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), bis(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amine **SI-1** (83 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4b** as a colorless oil (72 mg, 65%).

Following the general procedure B: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv), bis(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amine **SI-1** (99 mg, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was purified using hexane/Et_2O: 90/10 as the eluent to afford **4b** as a colorless oil (68 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.39 (dtq, 1H, *J* = 15.8, 4.8, 2.7 Hz), 5.90 (dqt, 1H, *J* = 15.7, 6.6, 1.7 Hz), 3.67 (t, 4H, *J* = 6.2 Hz), 3.35-3.34 (m, 2H), 2.67 (t, 4H, *J* = 6.2 Hz), 0.90 (s, 18H), 0.06 (s, 12H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9 (q, *J* =6.2 Hz), 123.3 (q, *J* = 269.1 Hz), 119.6 (q, *J* = 33.5 Hz), 62.2, 57.0, 56.2, 26.0, 18.4, –5.2.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.9 (m, 3F).
HRMS-ESI calcd for $C_{20}H_{42}F_3NO_2Si_2$ $[M+H]^+$ 442.2779, found 449.2773.
IR (ATR, ZnSe) ν (cm^{-1}) = 2954, 2929, 2857, 1472, 1292, 1253, 1105, 937, 831, 810, 773.

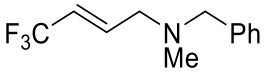
methyl (*E*)-(4,4,4-trifluorobut-2-en-1-yl)-*L*-prolinate (**4c**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), L-Proline methyl ester hydrochloride (42 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), triethylamine (38 µL, 0.27 mmol, 1.1 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 90/10 as the eluent to afford **4c** as a colorless oil (36 mg, 61%)

$[\alpha]_D^{22}$ –17.20 (CH_2Cl_2, c 0.5).
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.45 (dtq, 1H, *J* = 15.8, 4.2, 2.1 Hz), 5.81 (dqt, 1H, *J* = 15.7, 6.4, 1.7 Hz), 3.71 (s, 3H), 3.42 (m, 1H), 3.26-3.19 (m, 2H), 3.15 (m, 1H), 2.42 (dd, 1H, *J* = 16.8, 8.0 Hz), 2.15 (m, 1H), 2.00-1.90 (m, 2H), 1.83 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4, 137.5 (q, *J* = 6.3 Hz), 122.8 (q, *J* = 269.3 Hz), 120.3 (q, *J* = 33.7 Hz), 65.5, 54.9, 53.8, 52.0, 29.6, 23.4.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.3 (m, 3F).
HRMS-ESI calcd for $C_{10}H_{14}F_3NO_2$ $[M+H]^+$ 238.1049, found 238.1052.
IR (ATR, ZnSe) ν (cm^{-1}) = 1735, 1683, 1437, 1273, 1111, 1071, 970, 683.

(*E*)-*N*-benzyl-4,4,4-trifluoro-*N*-methylbut-2-en-1-amine (**4d**)

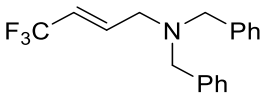


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), *N*-methylbenzylamine (32 µL, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4d** as a colorless oil (41 mg, 72%).

Following the general procedure B with a reaction time of 18 hours: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv),, *N*-methylbenzylamine (38 µL, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was purified using hexane/Et_2O: 95/5 as the eluent to afford **4d** as a colorless oil (53 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.27 (m, 5H), 6.44 (dtq, 1H, *J* = 15.8, 4.2, 2.1 Hz), 5.86 (dqt, 1H, *J* = 15.8, 6.4, 1.7 Hz), 3.54 (s, 2H), 3.14-3.11 (m, 2H), 2.24 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6, 138.2 (q, *J* = 6.3 Hz), 129.0, 128.5, 127.4, 123.0 (q, *J* = 269.3 Hz), 120.2 (q, *J* = 33.6 Hz), 62.2, 57.4, 42.5.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.1 (m, 3F).
HRMS-ESI calcd for $C_{12}H_{14}F_3N$ $[M+H]^+$ 230.1151, found 230.1162.
IR (ATR, ZnSe) ν (cm^{-1}) = 1308, 1277, 1260, 1112, 737, 697.

(*E*)-*N*,*N*-dibenzyl-4,4,4-trifluorobut-2-en-1-amine (**4e**)

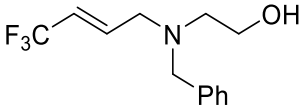


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), dibenzylamine (48 µL, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4e** as a colorless oil (56 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43-7.36 (m, 8H), 7.32-7.29 (m, 2H), 6.47 (dtq, 1H, *J* = 15.8, 4.1, 1.9 Hz), 5.92 (dqt, 1H, *J* = 15.8, 6.4, 1.7 Hz), 3.64 (s, 4H), 3.22-3.19 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 138.4 (q, *J* = 6.2 Hz), 128.8, 128.5, 127.3, 123.1 (q, *J* = 269.3 Hz), 120.1 (q, *J* = 33.7 Hz), 58.4, 53.7.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.4 (m, 3F).
HRMS-ESI calcd for $C_{18}H_{18}F_3N$ $[M+H]^+$ 306.1464, found 306.1469.
IR (ATR, ZnSe) ν (cm^{-1}) = 1308, 1269, 1112, 1069, 733, 696.

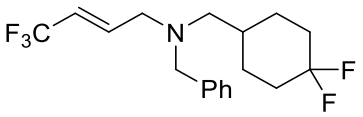
(*E*)-2-(benzyl(4,4,4-trifluorobut-2-en-1-yl)amino)ethan-1-ol (**4f**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 2-(benzylamino)ethan-1-ol **SI-2** (38 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 70/30 as the eluent to afford **4f** as a colorless oil (31 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.28 (m, 5H), 6.42 (dtq, 1H, *J* = 15.8, 4.2, 2.1 Hz), 5.82 (dqt, 1H, *J* = 15.8, 6.3, 1.6 Hz), 3.66 (s, 2H), 3.65-3.63 (m, 2H), 3.28-3.25 (m, 2H), 2.72-2.69 (m, 2H), 2.47 (br s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.1, 137.4 (q, *J* = 6.2 Hz), 128.8, 128.5, 127.5, 122.7 (q, *J* = 269.4 Hz), 120.8 (q, *J* = 33.8 Hz), 58.8, 58.4, 55.4, 54.1.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.1 (m, 3F).
HRMS-ESI calcd for $C_{13}H_{16}F_3NO$ $[M+H]^+$ 260.1257, found 260.1259.
IR (ATR, ZnSe) ν (cm^{-1}) = 1681, 1453, 1271, 1111, 1058, 977, 736, 698.

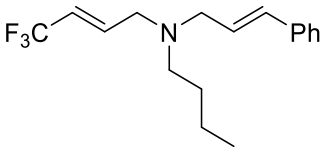
(*E*)-*N*-benzyl-*N*-((4,4-difluorocyclohexyl)methyl)-4,4,4-trifluorobut-2-en-1-amine (**4g**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), *N*-benzyl-1-(4,4-difluorocyclohexyl)methanamine **SI-4** (60 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4g** as a colorless oil (52 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.26 (m, 5H), 6.40 (dtq, 1H, *J* = 15.8, 4.2, 2.1 Hz), 5.85 (dqt, 1H, *J* = 15.8, 6.4, 1.7 Hz), 3.57 (s, 2H), 3.16-3.13 (m, 2H), 2.31 (d, 2H, *J* = 7.2 Hz), 2.11-2.04 (m, 2H), 1.92-1.88 (m, 2H), 1.75-1.62 (m, 2H), 1.58 (m, 1H), 1.23-1.15 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.0, 138.4 (q, *J* = 6.2 Hz), 128.8, 128.5, 127.4, 123.9 (dd, *J* = 239.7 Hz, *J* = 241.9 Hz), 123.0 (q, *J* = 269.1 Hz), 120.1 (q, *J* = 33.7 Hz), 59.6 (d, *J* = 2.5 Hz), 59.3, 54.7, 34.3 (d, *J* = 0.9 Hz), 33.3 (dd, *J* = 22.5 Hz, *J* = 25.4 Hz), 27.3 (d, *J* = 9.4 Hz).
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.0 (m, 3F), –91.5 (d, 1F, *J* = 234.5 Hz), –101.7 (d, 1F, *J* = 234.5 Hz).
HRMS-ESI calcd for $C_{18}H_{22}F_5N$ $[M+H]^+$ 348.1745, found 348.1742.
IR (ATR, ZnSe) ν (cm^{-1}) = 2936, 1450, 1356, 1299, 1267, 1112, 984, 962, 909, 738, 698.

(*E*)-*N*-butyl-*N*-cinnamyl-4,4,4-trifluorobut-2-en-1-amine (**4h**)

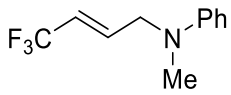


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), *N*-cinnamylbutan-1-amine **SI-3** (48 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4h** as a colorless oil (51 mg, 68%).

Following the general procedure B: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv), *N*-cinnamylbutan-1-amine **SI-3** (56 mg, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was purified using hexane/Et_2O: 90/10 as the eluent to afford **4h** as a colorless oil (52 mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.40 (m, 2H), 7.36-7.33 (m, 2H), 7.26 (m, 1H), 6.46 (dtq, 1H, *J* = 15.8, 5.9, 2.1 Hz), 6.26 (dt, 1H, *J* = 15.9, 6.6 Hz), 5.88 (dqt, 1H, *J* = 15.8, 6.5, 1.7 Hz), 3.27 (dd, 2H, *J* = 6.6, 1.3 Hz), 3.25-3.22 (m, 2H), 2.52-2.49 (m, 2H), 1.53-1.47 (m, 2H), 1.40-1.33 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6 (q, *J* = 6.2 Hz), 137.1, 132.8, 128.7, 127.7, 127.2, 126.4, 123.0 (q, *J* = 269.3 Hz), 120.0 (q, *J* = 33.5 Hz), 56.7, 54.2, 53.8, 29.5, 20.6, 14.1.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.5 (m, 3F).
HRMS-ESI calcd for $C_{17}H_{22}F_3N$ $[M+H]^+$ 298.1777, found 298.1772.
IR (ATR, ZnSe) ν (cm^{-1}) = 2931, 1312, 1294, 1266, 1116, 967, 907, 731, 691.

(*E*)-*N*-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl)aniline (**4i**)

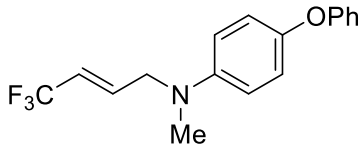


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), freshly distilled *N*-methylaniline (27 µL, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 95/5 as the eluent to afford **4i** as a colorless oil (51 mg, 95%).

Following the general procedure B with a reaction time of 24 hours: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv), freshly distilled *N*-methylaniline (32 µL, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was purified using hexane/Et_2O: 90/10 as the eluent to afford **4i** as a colorless oil (39 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (m, 1H), 6.79 (m, 1H), 6.73-6.71 (m, 2H), 6.45 (dm, 1H, *J* = 15.8 Hz), 5.80 (dqt, 1H, *J* = 15.8, 6.5, 1.7 Hz), 4.06-4.04 (m, 2H), 2.99 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.0, 136.6 (q, *J* = 5.9 Hz), 129.4, 123.2 (q, *J* = 269.3 Hz), 119.3 (q, *J* = 33.9 Hz), 117.4, 112.5, 53.5, 38.5.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.7 (m, 3F).
HRMS-ESI calcd for $C_8H_{12}F_3NO$ $[M+H]^+$ 216.0995, found 216.0999.
IR (ATR, ZnSe) ν (cm^{-1}) = 1599, 1505, 1292, 1254, 1109, 747, 690.

(*E*)-*N*-methyl-4-phenoxy-*N*-(4,4,4-trifluorobut-2-en-1-yl)aniline (**4j**)

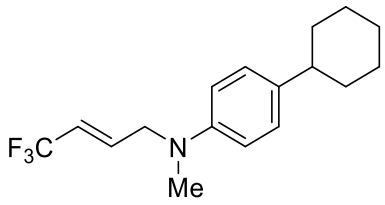


Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), *N*-methyl-4-phenoxyaniline **SI-6** (50 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **4j** as a colorless oil (51 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.30 (m, 2H), 7.05 (m, 1H), 7.01-6.97 (m, 4H), 6.72-6.70 (m, 2H), 6.46 (dtq, 1H, *J* = 15.8, 4.3, 2.1 Hz), 5.83 (dqt, 1H, *J* = 15.7, 6.4, 2.0 Hz), 4.04-4.01 (m, 2H), 2.98 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 148.0, 145.9, 136.7 (q, *J* = 5.9 Hz), 129.7, 125.3 (q, *J* = 269.2 Hz), 122.2, 121.1, 119.5 (q, *J* = 34.0 Hz), 117.4, 113.8, 54.1, 38.9.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.7 (m, 3F).

HRMS-ESI calcd for $C_{17}H_{16}F_3N$ $[M+H]^+$ 292.1308, found 292.1309.
IR (ATR, ZnSe) ν (cm^{-1}) = 1509, 1488, 1293, 1231, 1109, 867, 825, 754, 689.

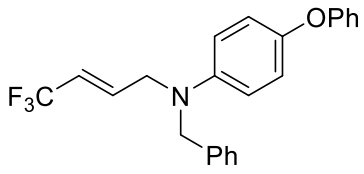
(*E*)-4-cyclohexyl-*N*-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl)aniline (**4k**)



Following the general procedure A: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 4-cyclohexyl-*N*-methylaniline **SI-7** (48 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **4k** as a colorless oil (49 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15-7.12 (m, 2H), 6.70-6.67 (m, 2H), 6.46 (dtq, 1H, *J* = 15.8, 4.3, 2.0 Hz), 5.84 (dqt, 1H, *J* = 15.6, 6.6, 2.0 Hz), 4.03-4.00 (m, 2H), 2.97 (s, 3H), 2.45 (m, 1H), 1.90-1.85 (m, 4H), 1.77 (m, 1H), 1.46-1.38 (m, 4H), 1.28 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.3, 137.0 (q, *J* = 6.0 Hz), 127.6, 123.3 (q, *J* = 269.2 Hz), 119.4 (q, *J* = 33.8 Hz), 112.7, 53.9, 43.6, 38.5, 34.8, 27.1, 26.3.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.7 (m, 3F).
HRMS-ESI calcd for $C_{17}H_{22}F_3N$ $[M+H]^+$ 298.1777, found 298.1772.
IR (ATR, ZnSe) ν (cm^{-1}) = 2922, 2850, 1613, 1518, 1292, 1253, 1113, 1028, 946, 810.

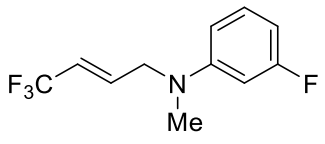
(*E*)-*N*-benzyl-4-phenoxy-*N*-(4,4,4-trifluorobut-2-en-1-yl)aniline (**4l**)



Following general procedure A with a reaction time of 24 hours: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), *N*-benzyl-4-phenoxyaniline **SI-5** (70 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **4l** as a colorless oil (56 mg, 58 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.35 (2H), 7.32-7.25 (m, 4H), 7.06-7.02 (m, 1H), 6.98-6.93 (m, 5H), 6.71-6.69 (m, 2H), 6.45 (dtq, 1H, *J* = 15.8, 4.3, 2.2 Hz), 5.82 (dqt, 1H, *J* = 15.8, 6.4, 2.0 Hz), 4.56 (s, 2H), 4.12-4.10 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8, 148.1, 145.1, 138.2, 136.4 (q, *J* = 6.0 Hz), 129.7, 128.9, 127.3, 126.9, 123.1 (q, *J* = 269.3 Hz), 122.3, 121.1, 119.7 (q, *J* = 34.0 Hz), 117.6, 114.0, 57.8, 51.5.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.70 (m, 3F).
HRMS-ESI calcd for $C_{23}H_{20}F_3NO$ $[M+H]^+$ 384.1570, found 384.1588.
IR (ATR, ZnSe) ν (cm^{-1}) = 1508, 1487, 1292, 1222, 1115, 730, 690.

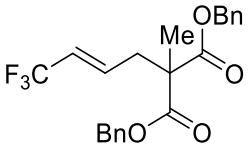
(*E*)-3-fluoro-*N*-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl)aniline (**4m**)



Following the general procedure A with a reaction time of 24 hours: (*E*)-ethyl (4,4,4-trifluorobut-2-en-1-yl) carbonate **2b** (50 mg, 0.25 mmol, 1.0 equiv), 3-fluoro-*N*-methylaniline **SI-8** (31 mg, 0.25 mmol, 1.0 equiv), tetraethylammonium bromide (53 mg, 0.25 mmol, 1.0 equiv), cesium carbonate (82 mg, 0.25 mmol, 1.0 equiv), $PdCl_2$ (2.0 mg, 11 µmol, 4.5 mol%) and toluene (0.5 mL). The crude product was purified using hexane/EtOAc: 98/2 as the eluent to afford **4l** as a colorless oil (33 mg, 57%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (m, 1H), 6.47-6.36 (m, 4H), 5.75 (m, 1H), 4.05-4.02 (m, 2H), 2.98 (s, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2 (d, *J* = 242.6 Hz), 150.5 (d, *J* = 10.5 Hz), 135.9 (q, *J* = 6.0 Hz), 130.4 (d, *J* = 10.3 Hz), 123.0 (q, *J* = 269.4 Hz), 119.5 (q, *J* = 34.0 Hz), 107.8 (d, *J* = 2.3 Hz), 103.7 (d, *J* = 21.6 Hz), 99.4 (d, *J* = 26.1 Hz), 53.3, 38.6.
^{19}F NMR (470 MHz, $CDCl_3$): δ = −63.8 (m, 3F), −112.2 (m, 1F).
HRMS-ESI calcd for $C_{11}H_{11}F_4N$ $[M+H]^+$ 234.0900, found 234.0917.
IR (ATR, ZnSe) ν (cm^{-1}) = 1619, 1579, 1500, 1292, 1259, 1160, 1112, 942, 823, 754, 680.

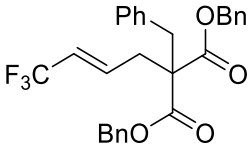
dibenzyl (*E*)-2-methyl-2-(4,4,4-trifluorobut-2-en-1-yl)malonate (**6b**)



Following general procedure B: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv), dibenzyl 2-methylmalonate **SI-9** (90 mg, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was using hexane/Et_2O: 90/10 as the eluent to afford **6b** as a colorless oil (80 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (m, 6H), 7.26 (m, 4H), 6.27 (dm, 1H, *J* = 15.6 Hz), 5.63 (dqt, 1H, *J* = 15.6, 5.6, 1.5 Hz), 5.13 (m, 4H), 2.72 (dq, J = 5.1, 1.6 Hz, 2H), 1.47 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 135.3, 134.9 (q, *J* = 6.6 Hz), 128.7, 128.6, 128.3, 122.53 (q, *J* = 33.7 Hz), 122.50 (q, *J* = 269.6 Hz), 67.5, 53.5, 37.9, 20.2.
^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.3 (m, 3F).
HRMS-ESI calcd for $C_{22}H_{21}F_3O_4$ $[M+H]^+$ 407.1465, found 407.1464.
IR (ATR, ZnSe) ν (cm^{-1}) = 3035, 2944, 1731, 1270, 1110, 732, 696.

dibenzyl (*E*)-2-benzyl-2-(4,4,4-trifluorobut-2-en-1-yl)malonate (**6c**)



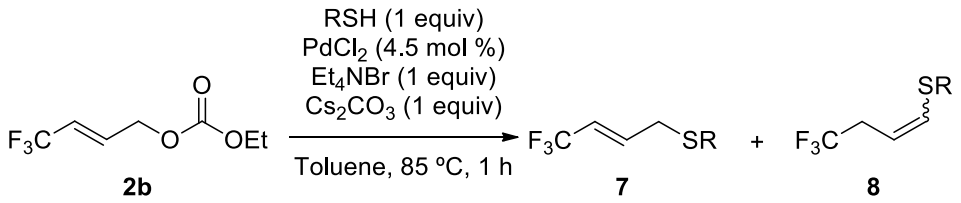
Following general procedure B: (*E*)-4,4,4-trifluorobut-2-en-1-yl acetate **2a** (50 mg, 0.30 mmol, 1.0 equiv), dibenzyl 2-benzylmalonate **SI-10** (112 mg, 0.30 mmol, 1.0 equiv), tetraethylammonium bromide (62 mg, 0.30 mmol, 1.0 equiv), cesium carbonate (97 mg, 0.30 mmol, 1.0 equiv), $PdCl_2$ (2.4 mg, 13 µmol, 4.5 mol%) and toluene (0.3 mL). The crude product was using hexane/Et_2O: 90/10 as the eluent to afford **6c** as a colorless oil (80 mg, 56%). Reaction time was 24 hours.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, 6H), 7.27 (m, 4H), 7.22 (m, 3H), 6.98 (m, 2H), 6.29 (dm, 1H, *J* = 15.7 Hz), 5.59 (dqt, 1H, *J* = 15.7, 6.3, 1.3 Hz), 5.13 (m, 4H), 3.29 (s, 2H), 2.63 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 135.14, 135.06 (q, *J* = 6.6 Hz), 135.0, 130.0, 128.8, 128.69, 128.68, 128.6, 127.4, 122.5 (q, *J* = 269.6 Hz), 122.4 (q, *J* = 33.6 Hz), 67.6, 58.7, 39.0, 34.8.
^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.3 (m, 3F).
HRMS-ESI calcd for $C_{28}H_{25}F_3O_4$ $[M+H]^+$ 483.1778, found 483.1778.
IR (ATR, ZnSe) ν (cm^{-1}) = 3034, 2959, 1731, 1270, 1146, 1118, 731, 696.

Reaction with thiols

The general procedure A was used with thiophenol, 4-methoxythiophenol, benzyl mercaptan or 2-methyl-1-propanethiol. The crude products were analyzed by NMR and the results are shown in the Table S1.

Table S1: Reaction of 2b with thiols.



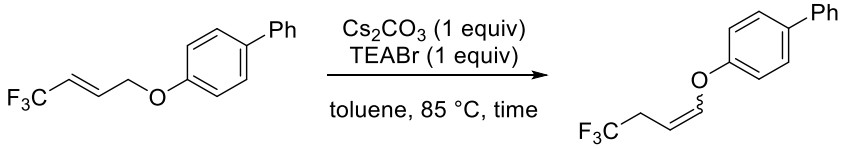
2b **7** **8**

Entry	R	Conversion (%)[a]	**7** (%)[a]	**8** (%)[a]	Fluorinated side-products (%)[a]
1	Ph	46	6	14 (*Z*/*E* = 58/42)	9
2	4-MeO-C_6H_4	30	0	5 (*Z*/*E* = 58/42)	7
3	Bn	58	2	13 (*Z*/*E* = 63/37)	15
4	*i*-Bu	50	0	6 (*Z*/*E* = 66/34)	8

[a] Determined by ^{1}H and ^{19}F NMR analysis of the crude mixture.

The isomerization reaction

Table S2: Selected examples for the isomerization without palladium catalyst.

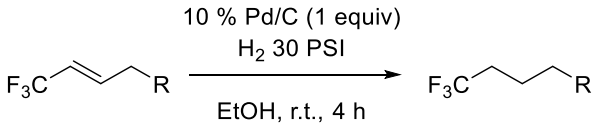


3c **5c**

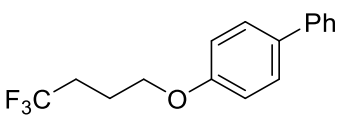
Entry	Time	Conversion[a]	**5c** *E*/*Z*[a]
1	1 h	11 %	5/95
2	24 h	45 %	2/98

[a] Determined by ^{1}H and ^{19}F NMR analysis of the crude mixture.

Hydrogenation reaction



4-(4,4,4-trifluorobutoxy)-1,1'-biphenyl (**9**)



To a solution of **3c** (20 mg, 72 µmol, 1.0 equiv) in technical grade EtOH (1.5 mL) was added 10% Pd/C (8 mg, 72 µmol, 1.0 equiv). The resulting suspension was put under 30 PSI H_2 atmosphere for 4 hours at room temperature. The mixture was then filtrated through Celite to remove the residual Pd/C. The solvent was removed under reduced pressure, and the crude product was then purified by column chromatography on silica gel using hexane/EtOAc: 98/2 as the eluent to afford **9** as a white solid (20 mg, quant).

mp = 92-94 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 4H), 7.46-7.42 (m, 2H), 7.33 (m, 1H), 7.00-6.97 (m, 2H), 4.08 (t, 2H, *J* = 6.0 Hz), 2.41-2.31 (m, 2H), 2.12-2.07 (m, 2H).

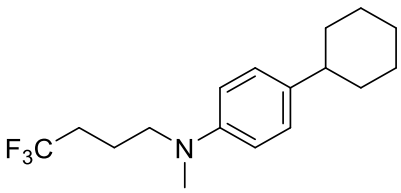
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3, 140.8, 134.3, 128.9, 128.4, 126.0 (q, *J* = 241.2 Hz), 114.8, 66.2, 30.8 (q, *J* = 29.2 Hz), 22.3 (q, *J* = 3.0 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –66.3 (t, 3F, *J* = 10.9 Hz).

HRMS-APPI calcd for $C_{16}H_{15}F_3O$ $[M^*]^+$ 280.1075, found 280.1098.

IR (ATR, ZnSe) ν (cm^{-1}) = 1475, 1389, 1298, 1281, 1223, 1132, 1025, 835, 717, 692, 656.

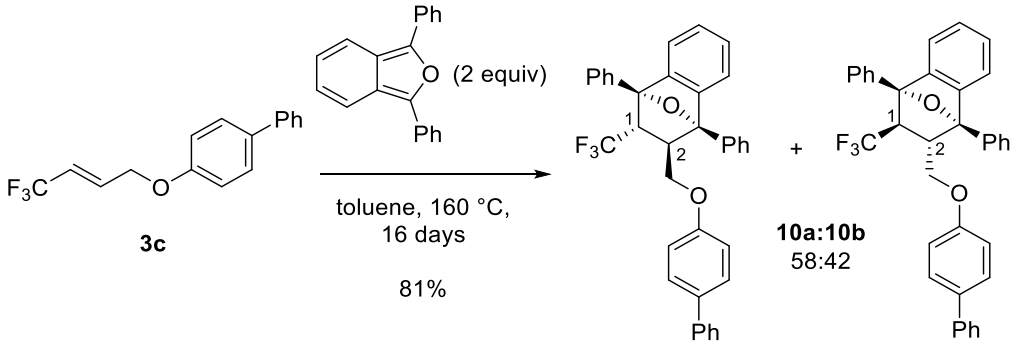
4-cyclohexyl-*N*-methyl-*N*-(4,4,4-trifluorobutyl)aniline (**SI-12**)



To a solution of **4k** (50 mg, 0.16 mmol, 1.0 equiv) in technical grade EtOH (1.5 mL) was added 10% Pd/C (18 mg, 0.16 mmol, 1.0 equiv). The resulting suspension was put under 30 PSI H_2 atmosphere for 4 hours at room temperature. The mixture was then filtrated through Celite to remove the residual Pd/C. The solvent was removed under reduced pressure, and the crude product was then purified by column chromatography on silica gel using hexane/EtOAc: 98/2 as the eluent to afford 4-cyclohexyl-*N*-methyl-*N*-(4,4,4-trifluorobutyl)aniline **SI-12** as a colorless oil (21 mg, 42%).

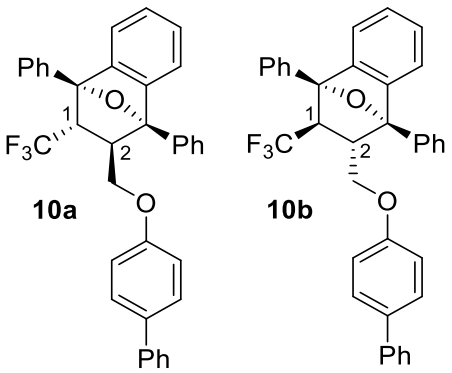
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13-7.09 (m, 2H), 6.72-6.64 (m, 2H), 3.35 (t, 2H, *J* = 7.3 Hz), 2.91 (s, 3H), 2.40 (m, 1H), 2.19-2.06 (m, 2H), 1.89-1.83 (m, 6H), 1.74 (m, 1H), 1.43-1.34 (m, 4H), 1.25 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6, 136.8, 127.6, 127.3 (q, *J* = 276.2 Hz), 112.8, 52.0, 43.6, 38.5, 34.9, 31.5 (q, *J* = 29.0 Hz), 27.2, 26.4, 19.9 (q, *J* = 2.4 Hz).
^{19}F NMR (470 MHz, $CDCl_3$): δ = –66.0 (t, 3F, *J* = 10.9 Hz).
HRMS-ESI calcd for $C_{17}H_{24}F_3N$ $[M+H]^+$ 300.1934, found 300.1938.
IR (ATR, ZnSe) ν (cm^{-1}) = 2923, 2850, 1613, 1518, 1370, 1250, 1150, 1091, 1021, 987, 810.

Diels-Alder reaction



(1*S*,2*S*,3*R*,4*R*)-2-(([1,1'-biphenyl]-4-yloxy)methyl)-1,4-diphenyl-3-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (**10a**)
(1*S*,2*R*,3*S*,4*R*)-2-(([1,1'-biphenyl]-4-yloxy)methyl)-1,4-diphenyl-3-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (**10b**)

To a solution of **3c** (20 mg, 72 µmol, 1.0 equiv) in toluene (0.5 mL) was added 1,3-diphenylisobenzofuran (39 mg, 0.14 mmol, 2.0 equiv). The resulting mixture was heated at 150 °C in a sealed vial for 16 days. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using hexane/EtOAc: 98/2 as the eluent to afford a mixture of **10a** and **10b** as a white solid (39 mg, 81%, Ratio **10a**:**10b**: 58:42 determined by NMR analysis on the crude mixture).
NB: **10a** and **10b** were separated by column chromatography on silica gel for characterization.



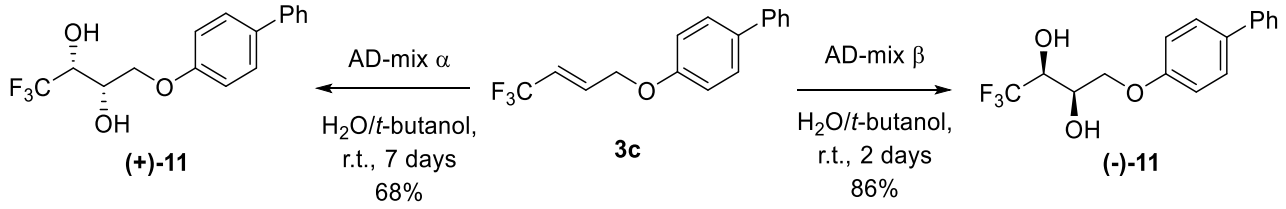
10a
mp = 154-156 °C
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81-7.79 (m, 2H), 7.65-7.63 (m, 2H), 7.54-7.49 (m, 7H), 7.45 (d, 2H, *J* = 8.7 Hz), 7.42-7.39 (m, 3H), 7.32-7.23 (m, 5H), 6.80 (d, 2H, *J* = 8.7 Hz), 4.08 (dd, 1H, *J* = 5.2, 9.5 Hz), 3.83 (t, 1H, *J* = 9.5 Hz), 3.81 (dq, 1H, *J* = 3.7, 8.6 Hz, H^1), 3.09 (m, 1H, H^2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1, 147.7, 144.4, 140.9, 135.5, 135.4, 134.4, 129.3, 128.83, 128.78, 128.71, 128.6, 128.2, 128.1, 127.8, 127.5, 126.84, 126.81, 125.8, 125.7 (q, *J* = 289.1 Hz), 122.3, 119.2, 114.8, 89.4, 89.3 (q, *J* = 1.8 Hz), 69.1, 52.8 (q, *J* = 26.4 Hz), 48.3.
^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.8 (d, 3F, *J* = 8.6 Hz).
HRMS-APPI calcd for $C_{36}H_{27}F_3O_2$ $[M^*]^+$ 548.1963, found 548.1980.
IR (ATR, ZnSe) ν (cm^{-1}) = 1487, 1267, 1249, 1237, 1188, 1157, 1102, 749, 698, 666.

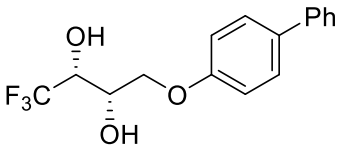
10b

mp = 154-156 °C
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88-7.86 (m, 2H), 7.72-7.70 (m, 2H), 7.55-7.49 (m, 7H), 7.46 (d, 2H, *J* = 8.9 Hz), 7.43-7.38 (m, 4H), 7.31 (m, 1H), 7.28 (m, 1H), 7.25 (m, 1H), 7.19 (m, 1H), 6.73 (d, 2H, *J* = 8.8 Hz), 3.77 (d, 2H, *J* = 6.5 Hz), 3.66 (dt, 1H, *J* = 4.7, 6.5 Hz, H^2), 2.89 (dq, 1H, *J* = 4.7, 8.9 Hz, H^1).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.8, 146.9, 145.5, 140.8, 136.1, 134.8, 134.3, 129.1, 128.9, 128.6, 128.3, 128.24, 128.17, 128.0, 127.7, 126.90, 126.85, 126.4 (q, *J* = 280.4 Hz), 126.3, 121.9, 119.6, 114.6, 89.6, 88.0 (br q), 68.2, 54.4 (q, *J* = 25.4 Hz), 47.3,
^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.1 (d, 3F, *J* = 8.9 Hz).
HRMS-APPI calcd for $C_{36}H_{27}F_3O_2$ $[M^*]^+$ 548.1963, found 548.1979.
IR (ATR, ZnSe) ν (cm^{-1}) = 1486, 1268, 1241, 1152, 1123, 750, 695, 653.

Dihydroxylation reaction



(2*R*,3*S*)-4-([1,1'-biphenyl]-4-yloxy)-1,1,1-trifluorobutane-2,3-diol ((+)-**11**)

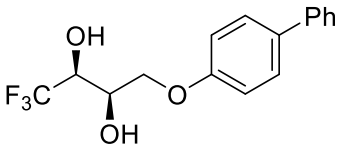


Using a modified procedure,[9,10] to a solution of **3c** (20 mg, 72 µmol, 1.0 equiv) in H_2O/*tert*-butanol (4 mL, 1/1) mixture was added AD-mix α (200 mg). The resulting mixture was stirred at room temperature for 7 days. The mixture was extracted with EtOAc and all volatiles were removed under reduced pressure. The crude product was then purified by column chromatography on silica gel using hexane/EtOAc: 70/30 as the eluent to afford (+)-**11** as a white solid (15 mg, 68%).

mp = 163-165 °C
$[\alpha]_D^{22}$ + 13.30 (CH_2Cl_2, c 0.38).
ee >99% determined by HPLC with a OJ-H chiral column (hexane/*i*PrOH: 80/20, 1mL/min) retention time: 26.8 min.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57-7.55 (m, 4H), 7.45-7.42 (m, 2H), 7.33 (m, 1H), 7.02-6.99 (m, 2H), 4.42 (t, 1H, *J* = 6.0 Hz), 4.15 (d, 2H, *J* = 6.0 Hz), 4.14 (m, 1H), 3.13 (d, 1H, *J* = 8.1 Hz), 2.60 (br s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.5, 140.6, 135.1, 128.9, 128.5, 127.1, 126.9, 124.5 (q, *J* = 282.7 Hz), 115.0, 69.2 (q, *J* = 30.7 Hz), 68.3, 66.9 (q, *J* = 1.6 Hz).
^{19}F NMR (470 MHz, $CDCl_3$): δ = –77.0 (d, 3F, *J* = 7.0 Hz).
HRMS-ESI calcd for $C_{16}H_{15}F_3O_3$ $[M+H]^+$ 313.1046, found 313.1042.
IR (ATR, ZnSe) ν (cm^{-1}) = 3249, 2959, 1605, 1488, 1282, 1269, 1165, 1125, 1046, 834, 761, 669.

(2*S*,3*R*)-4-([1,1'-biphenyl]-4-yloxy)-1,1,1-trifluorobutane-2,3-diol ((–)-**11**)

[9] Xiao, N.; Jiang, Z.-X.; Yu, Y. B. *Pept. Sci.* **2007**, *88*, 781.
[10] Jiang, Z.-X.; Qing, F.-L. *J. Org. Chem.* **2004**, *69*, 5486.



To a solution of **3c** (20 mg, 72 µmol, 1.0 equiv) in H_2O/*tert*-butanol (4 mL, 1/1) mixture was added AD-mix β (200 mg). The resulting mixture was stirred at room temperature for 2 days. Mixture was then extracted with EtOAc and all volatiles were removed under reduced pressure. The crude product was then purified by column chromatography on silica gel using hexane/EtOAc: 70/30 as the eluent to afford (-)-**11** as white solid (19 mg, 86%).

mp = 163-165 °C

$[\alpha]_D^{22}$ –11.58 (CH_2Cl_2, c 0.38).

ee >99% determined by HPLC with a OJ-H chiral column (hexane/*i*PrOH: 80/20, 1mL/min) retention time: 30.0 min

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57-7.55 (m, 2H), 7.45-7.42 (m, 2H), 7.33 (m, 1H), 7.00 (d, 2H, *J* = 8.7 Hz), 4.43 (m, 1H), 4.15 (d, 2H, *J* = 6.0 Hz), 4.14 (m, 1H), 3.11 (d, 1H, *J* = 8.8 Hz), 2.58 (d, 1H, *J* = 4.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.5, 140.6, 135.1, 128.9, 128.5, 127.1, 126.9, 124.5 (q, *J* = 282.9 Hz), 115.0, 69.3 (q, *J* = 30.8 Hz), 68.3 (q, *J* = 0.8 Hz), 66.9 (q, *J* = 1.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –77.0 (d, 3F, *J* = 7.1 Hz).

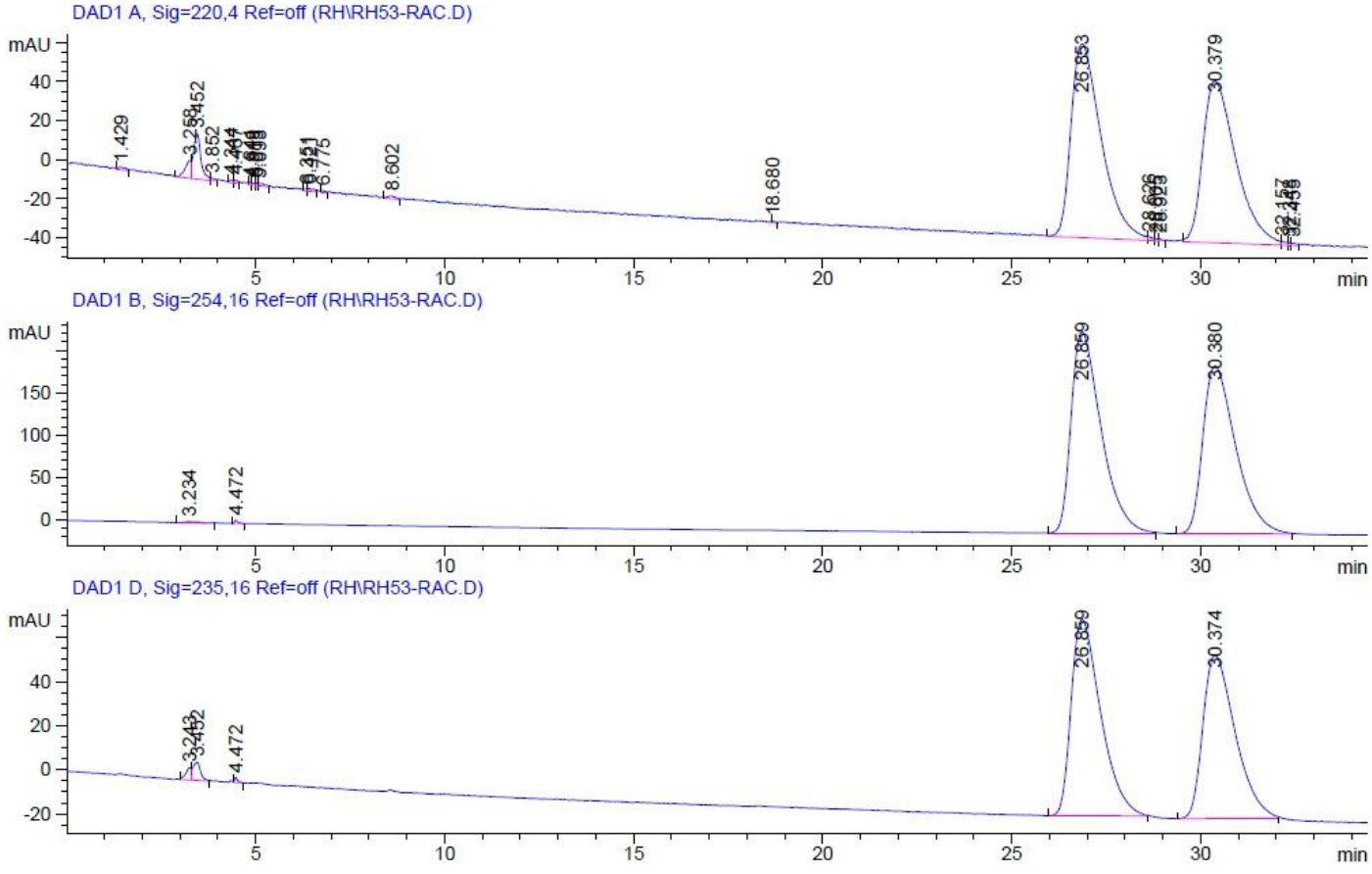
HRMS-ESI calcd for $C_{16}H_{15}F_3O_3$ $[M+H]^+$ 313.1046, found 313.1042.

IR (ATR, ZnSe) ν (cm^{-1}) = 3265, 1605, 1489, 1321, 1282, 1269, 1165, 1128, 1081, 1047, 835, 762, 691, 670.

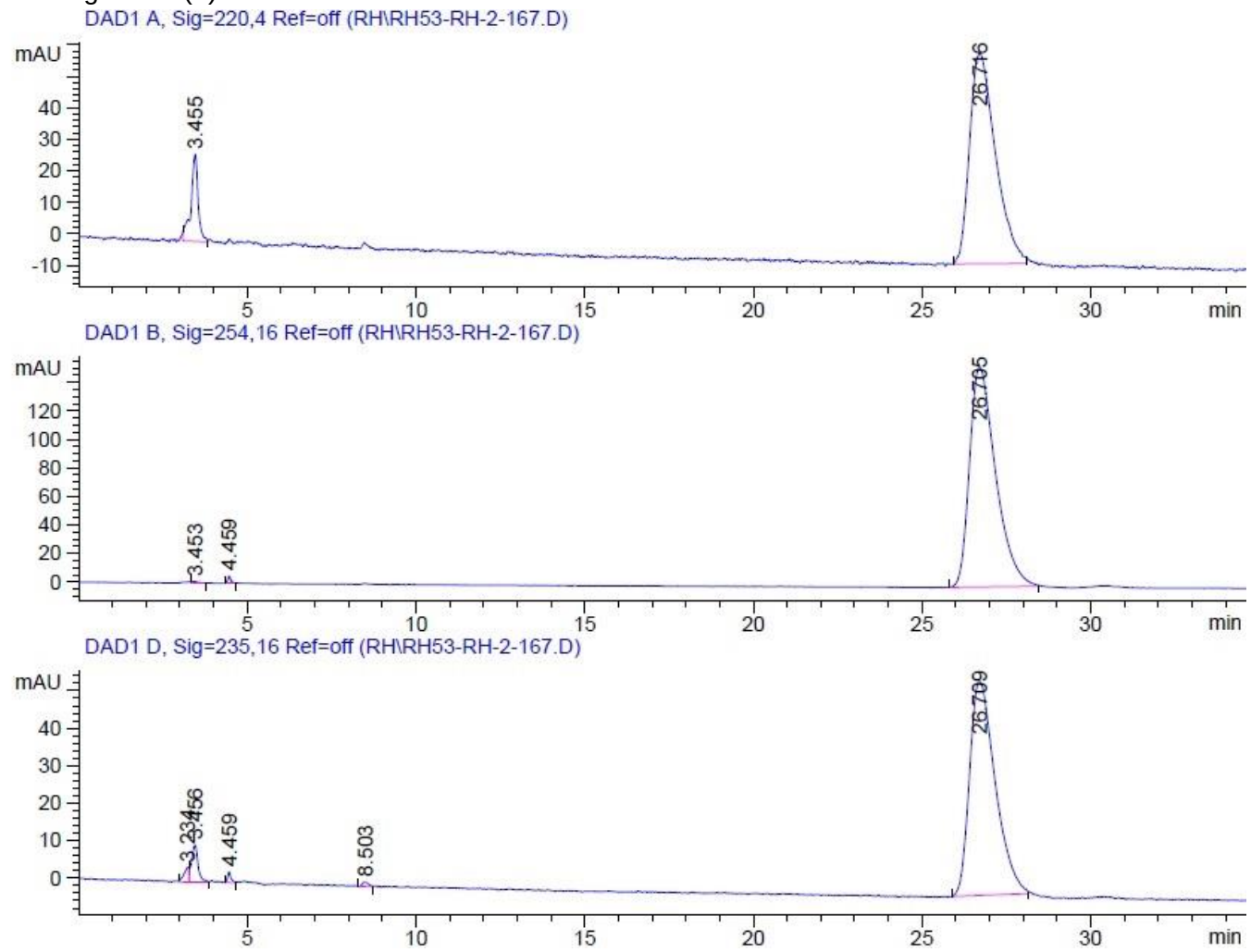
<u>ee determination</u>:

Chromatogram for the racemic sample was obtained by mixing (+)-**11** and (–)-**11** (since reaction did not proceed using OsO_4).

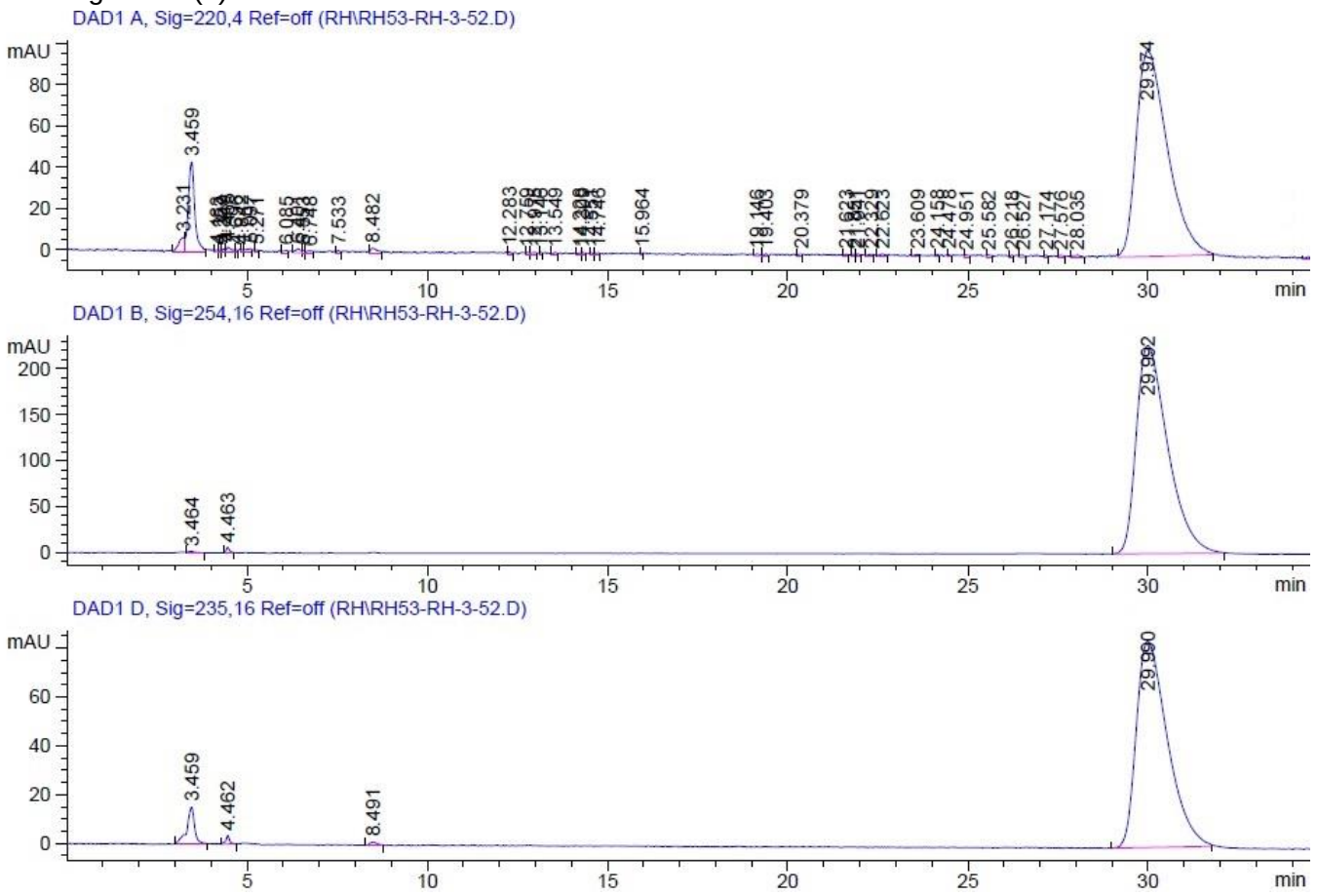
Chromatogram of (+)-**11** + (–)-**11**:



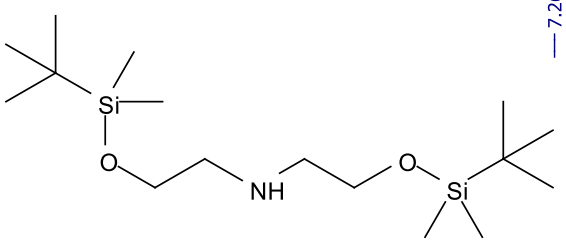
Chromatogram of (+)–**11**:



Chromatogram of (–)-**11**:

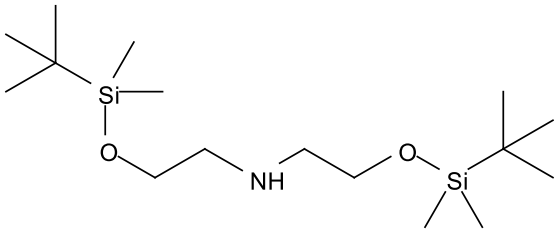


^{1}H NMR and ^{13}C NMR spectra of previously reported compounds



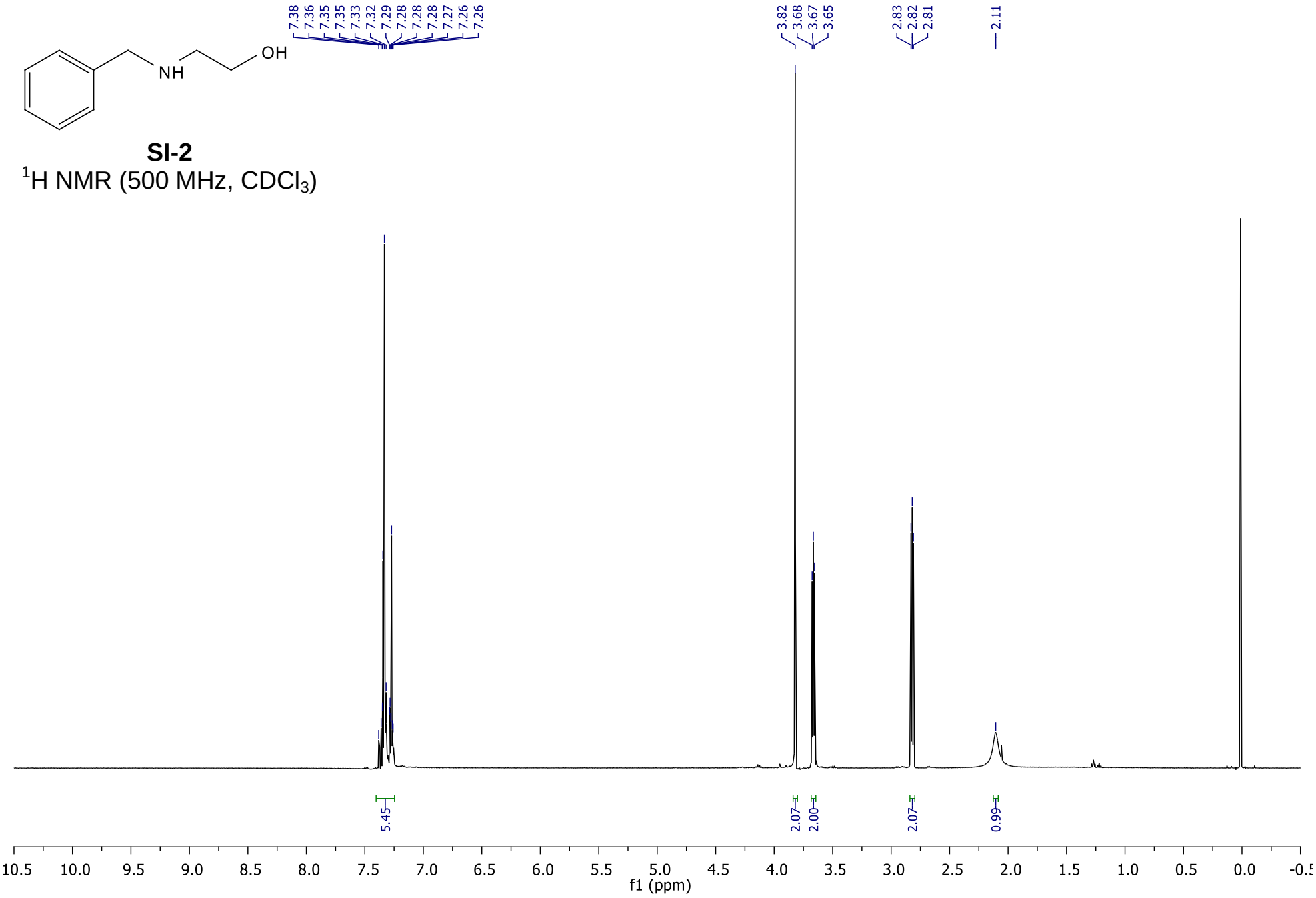
SI-1

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



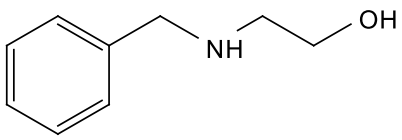
SI-1

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



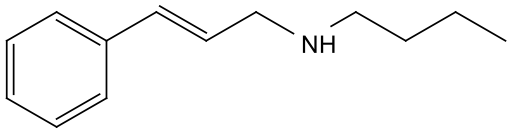
SI-2

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



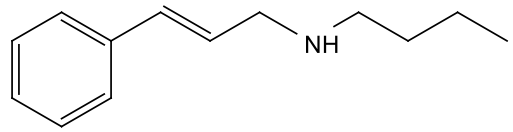
SI-2

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



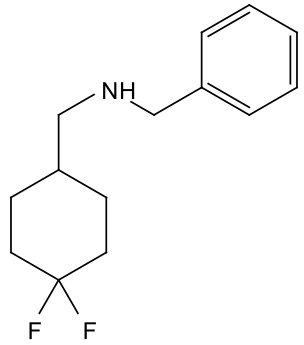
SI-3

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



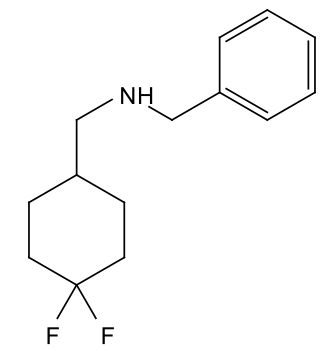
SI-3

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



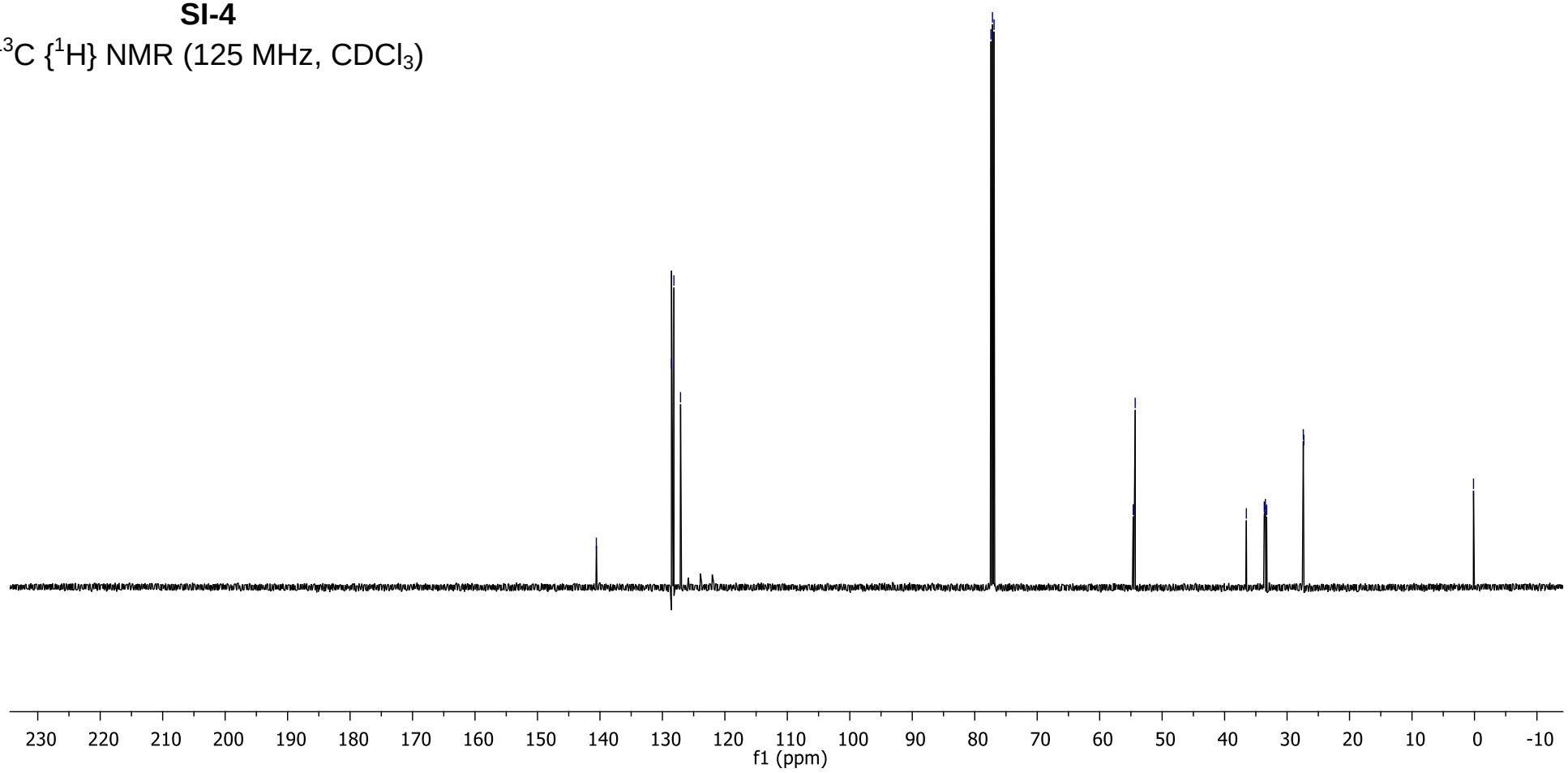
SI-4

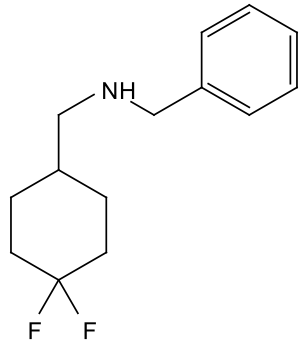
^{1}H NMR (500 MHz, $CDCl_3$)



SI-4

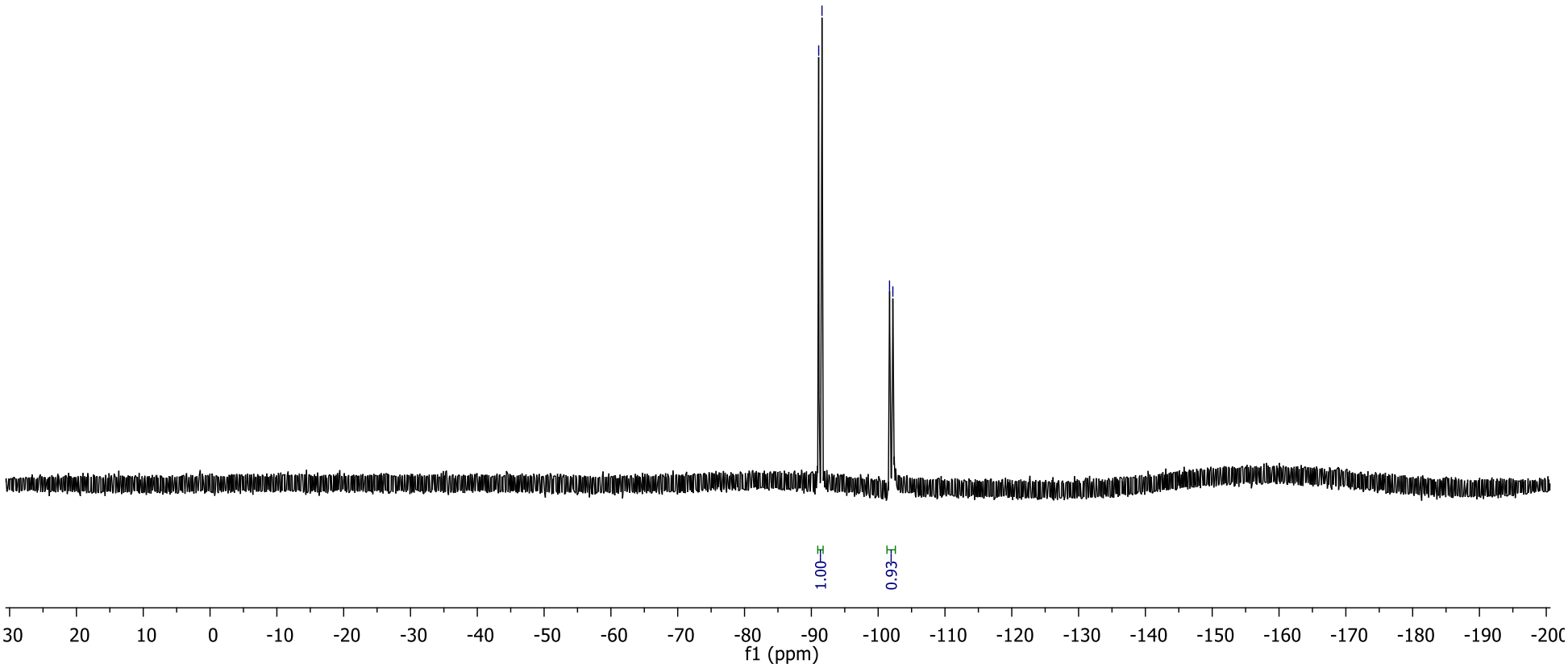
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)

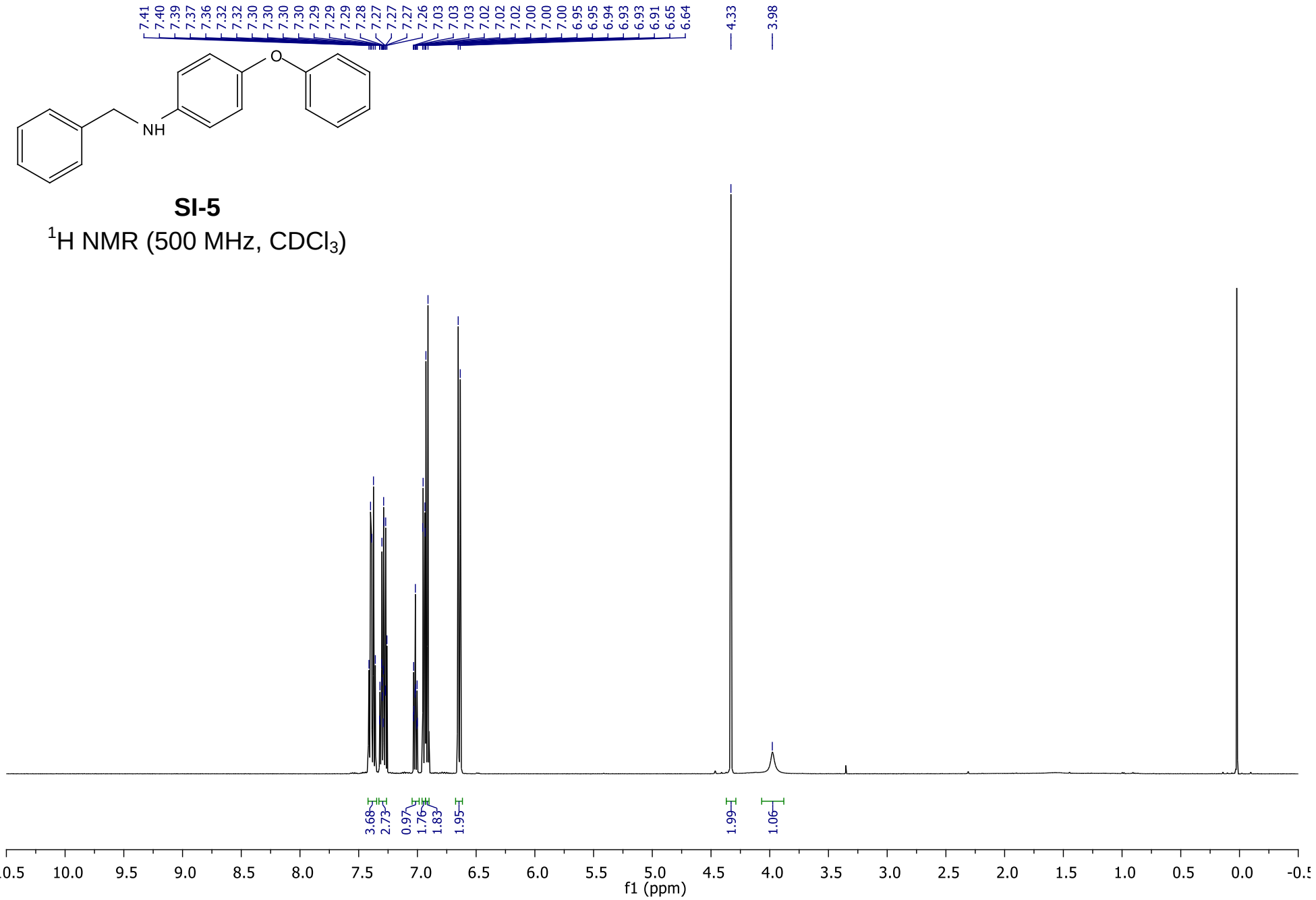




SI-4

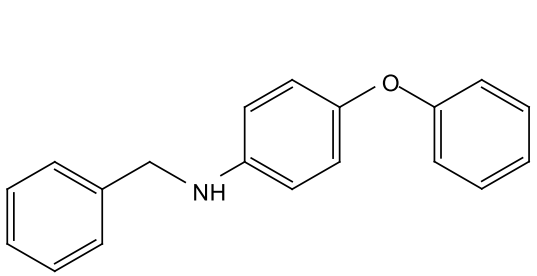
^{19}F NMR (470 MHz, $CDCl_3$)





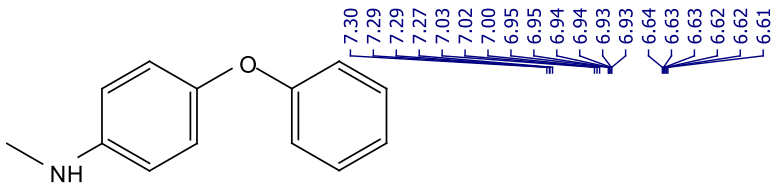
SI-5

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



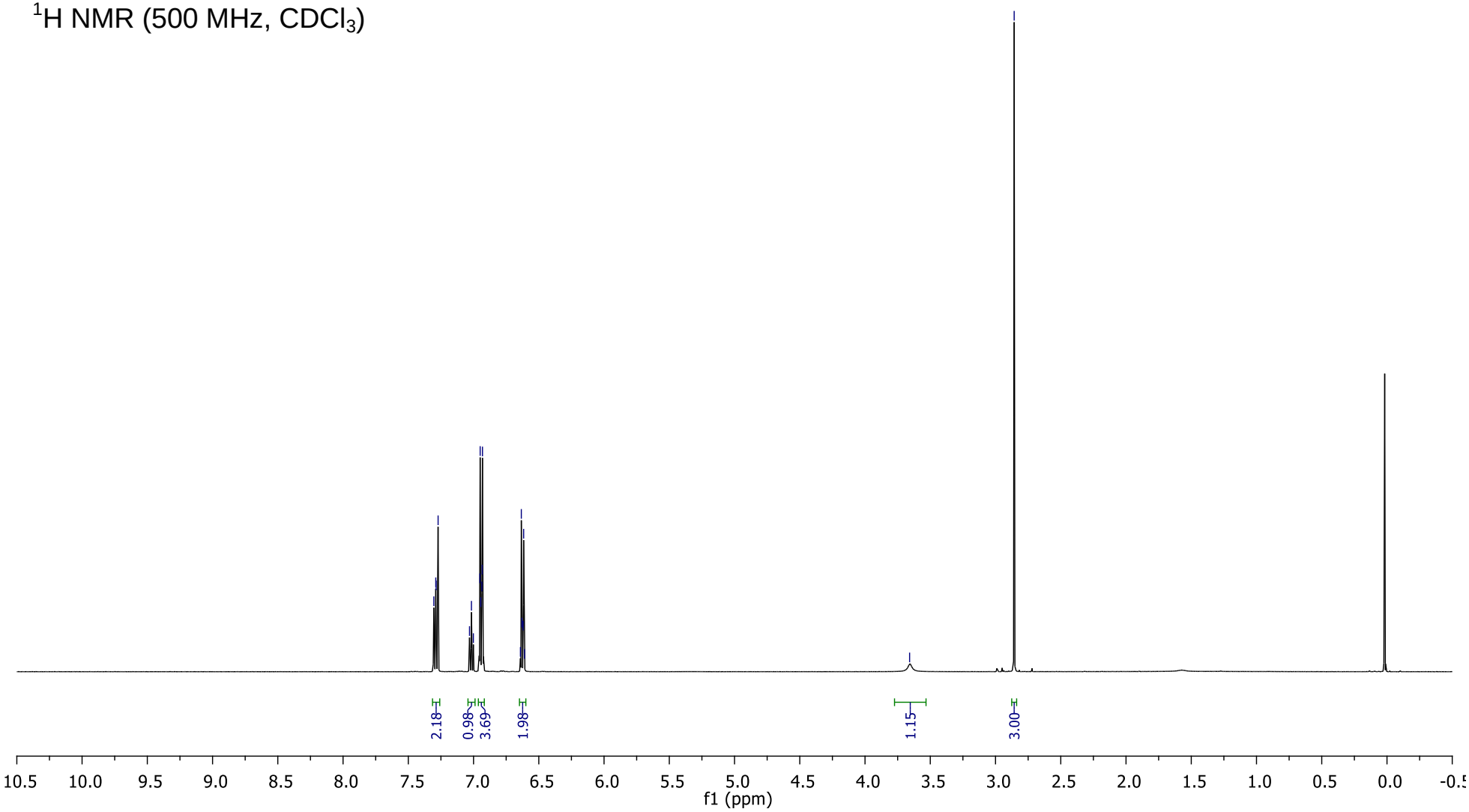
SI-5

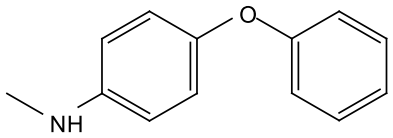
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



SI-6

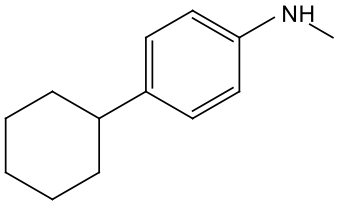
^{1}H NMR (500 MHz, $CDCl_3$)





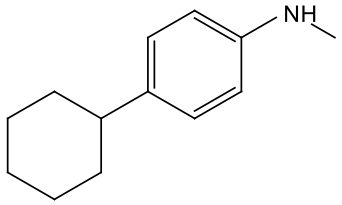
SI-6

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



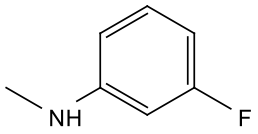
SI-7

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



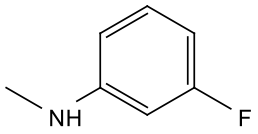
SI-7

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



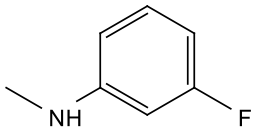
SI-8

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



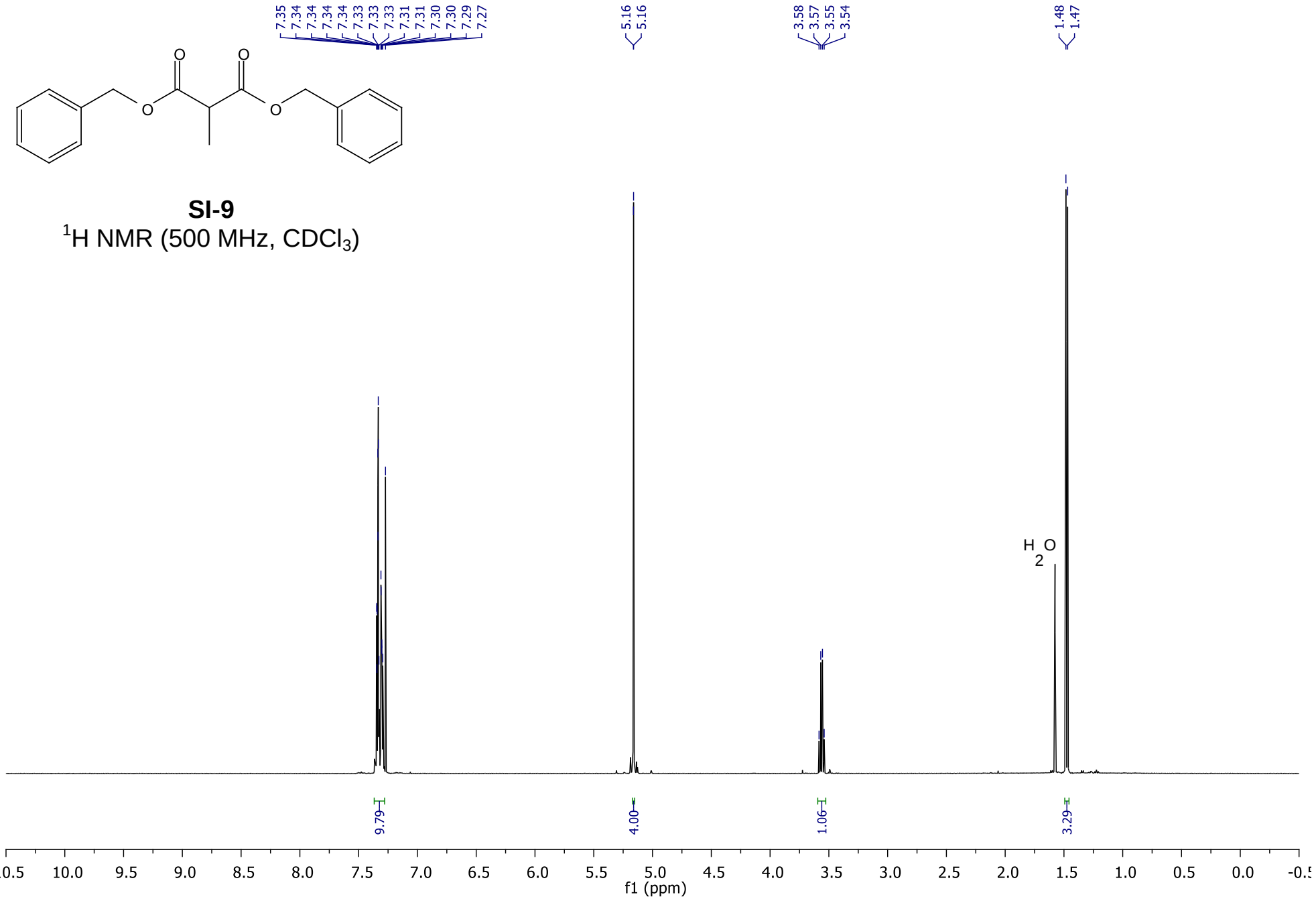
SI-8

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



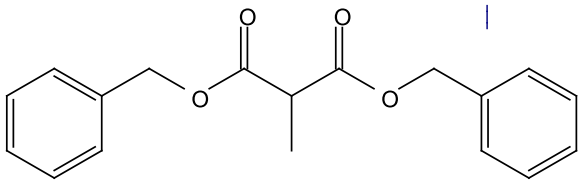
SI-8

^{19}F NMR (470 MHz, $CDCl_3$)



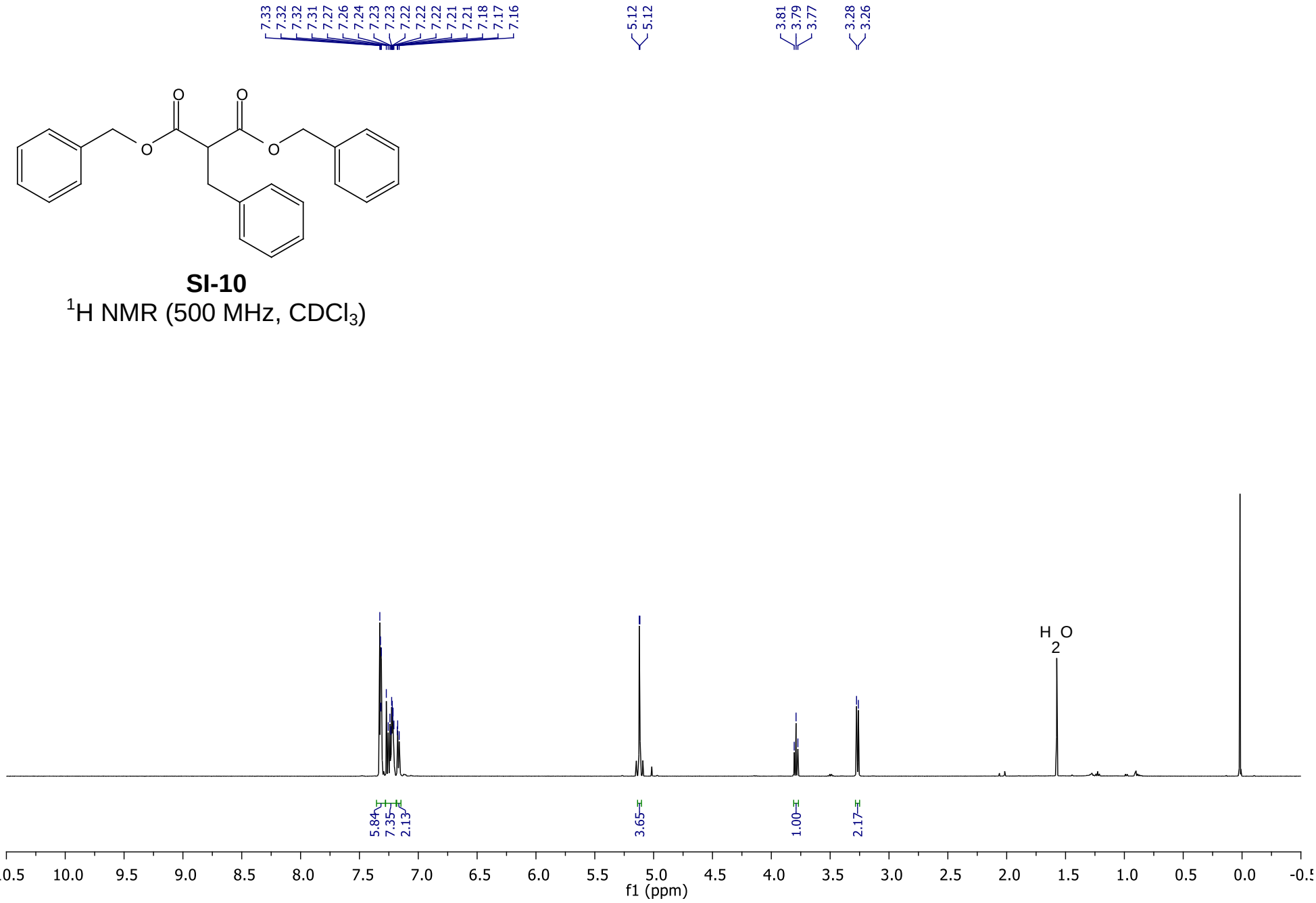
SI-9

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



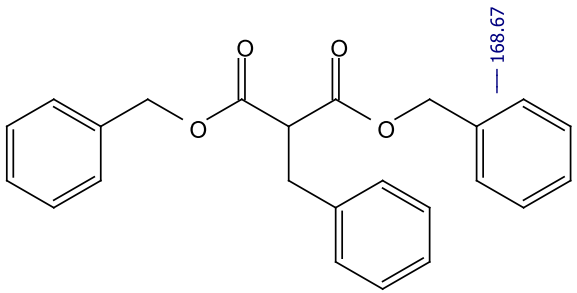
SI-9

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



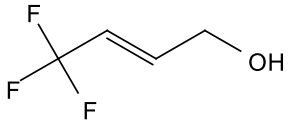
SI-10

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



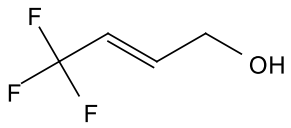
SI-10

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



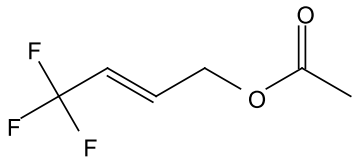
SI-11

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



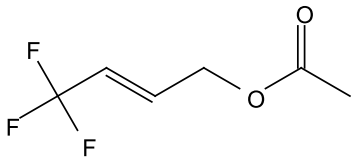
SI-11

^{19}F NMR (470 MHz, $CDCl_3$)



2a

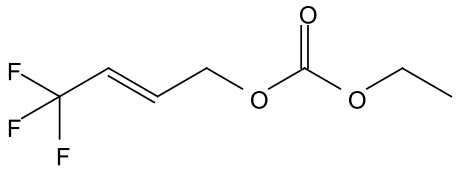
^{1}H NMR (500 MHz, $CDCl_3$)



2a

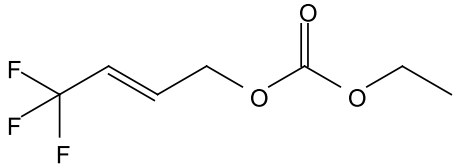
^{19}F NMR (470 MHz, $CDCl_3$)

NMR spectra of all new compounds



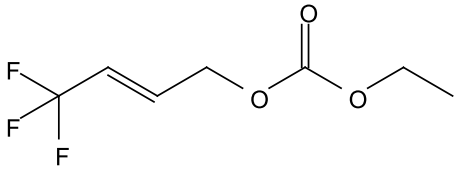
2b

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



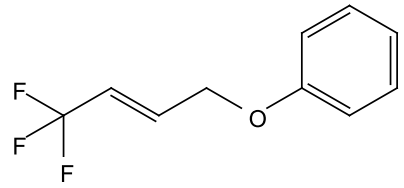
2b

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



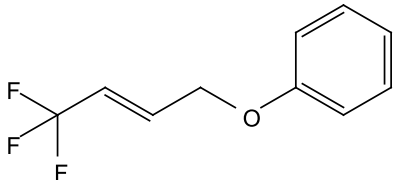
2b

^{19}F NMR (470 MHz, $CDCl_3$)



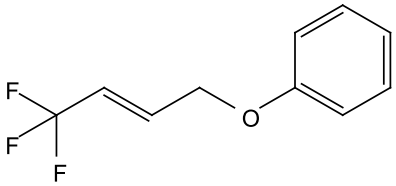
3a

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



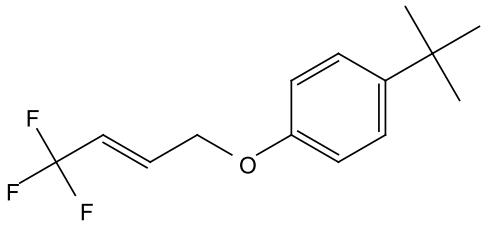
3a

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



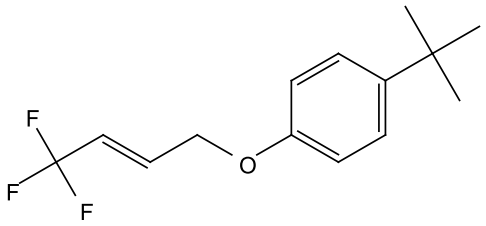
3a

^{19}F NMR (470 MHz, $CDCl_3$)



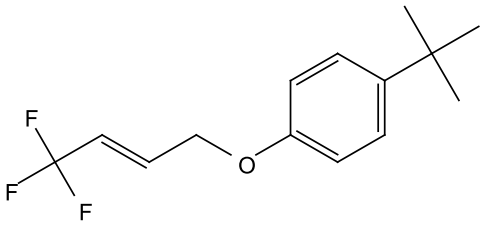
3b

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



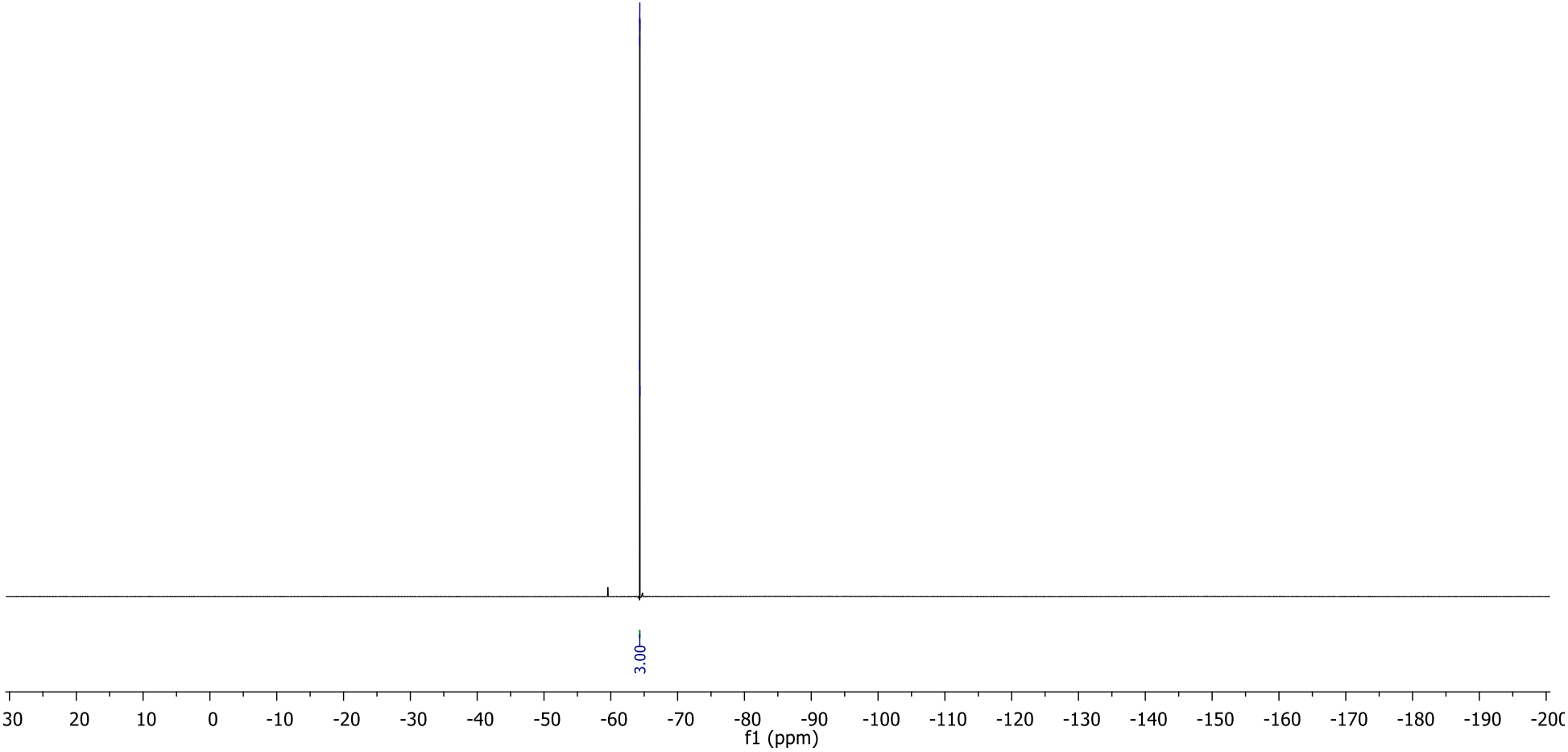
3b

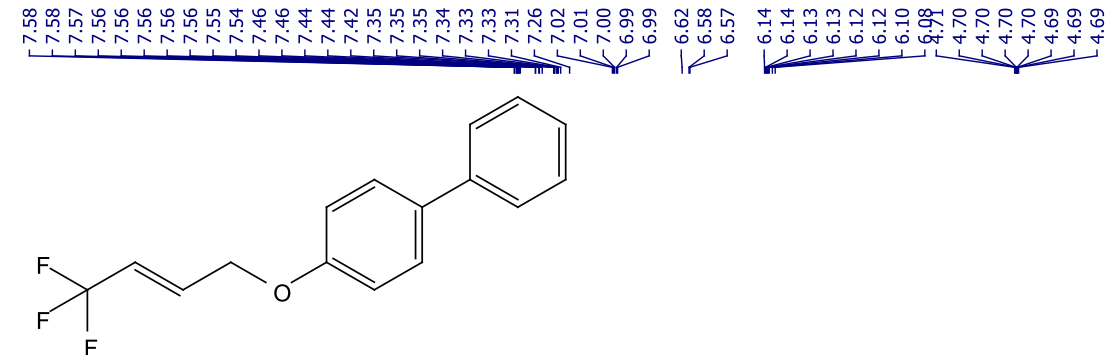
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



3b

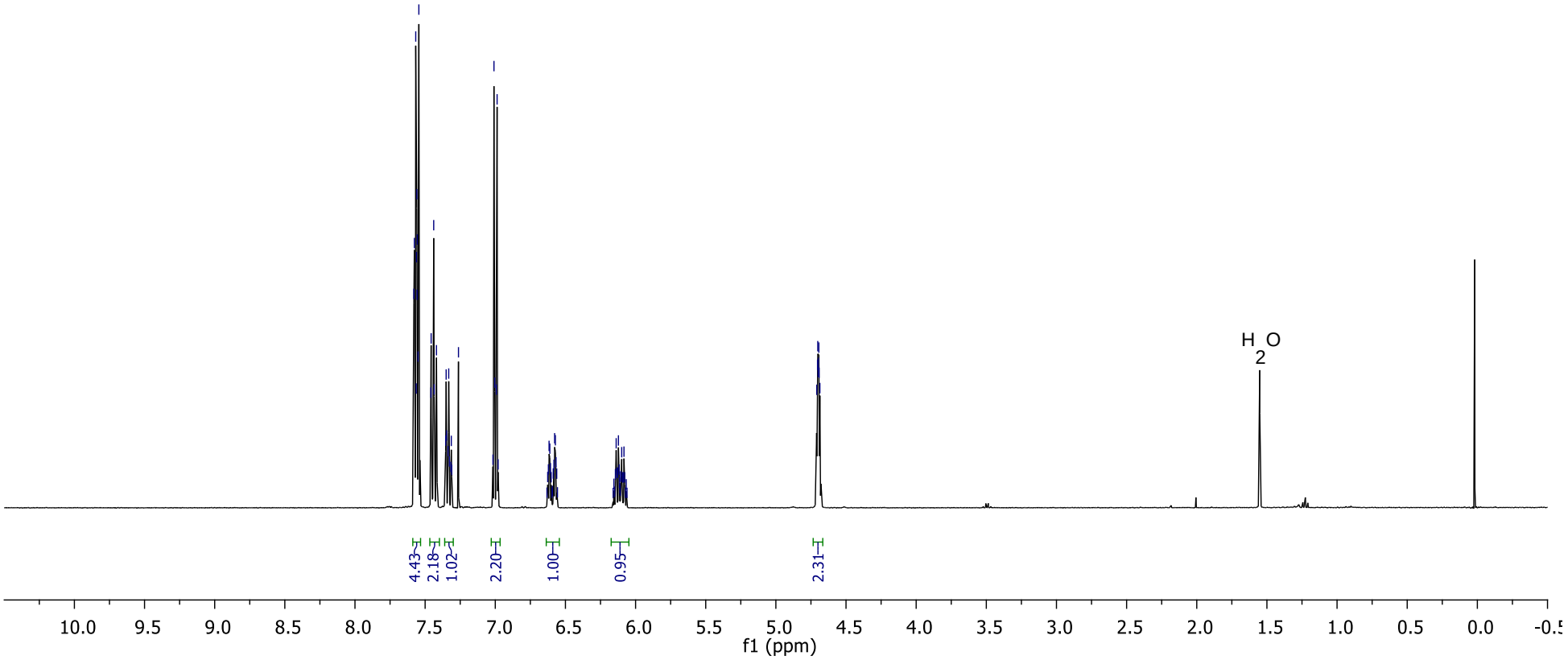
^{19}F NMR (470 MHz, $CDCl_3$)

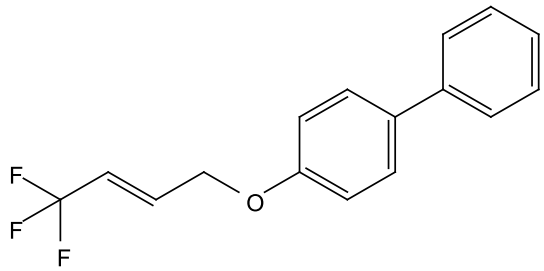




3c

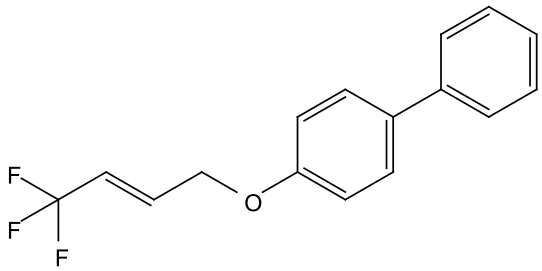
^{1}H NMR (500 MHz, $CDCl_3$)





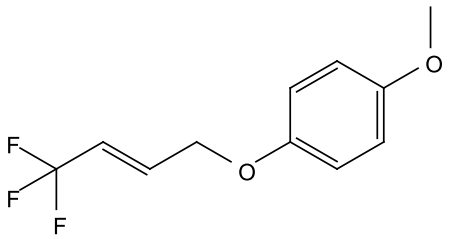
3c

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



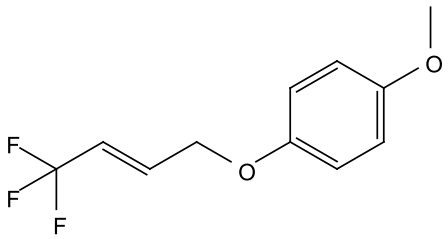
3c

^{19}F NMR (470 MHz, $CDCl_3$)



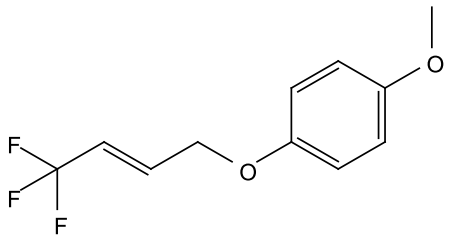
3d

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



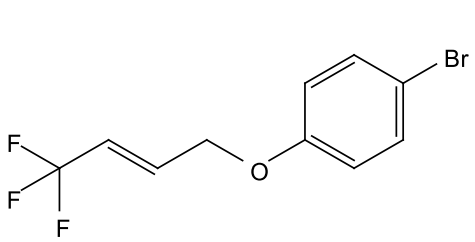
3d

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



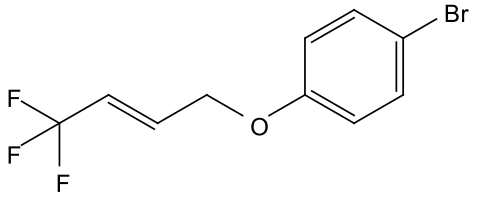
3d

^{19}F NMR (470 MHz, $CDCl_3$)



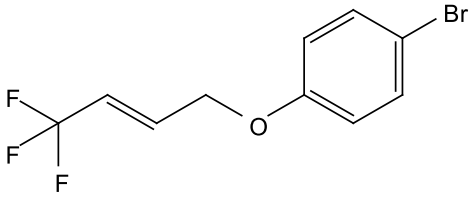
3e

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



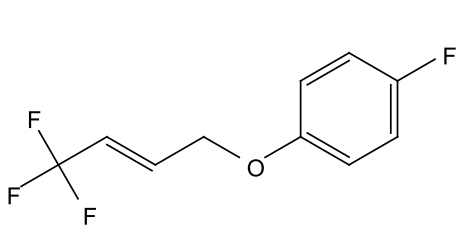
3e

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



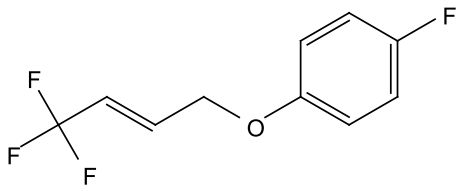
3e

^{19}F NMR (470 MHz, $CDCl_3$)



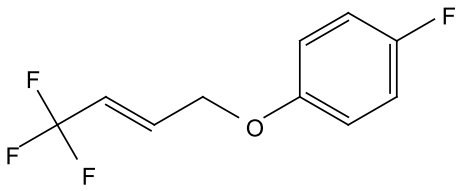
3f

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



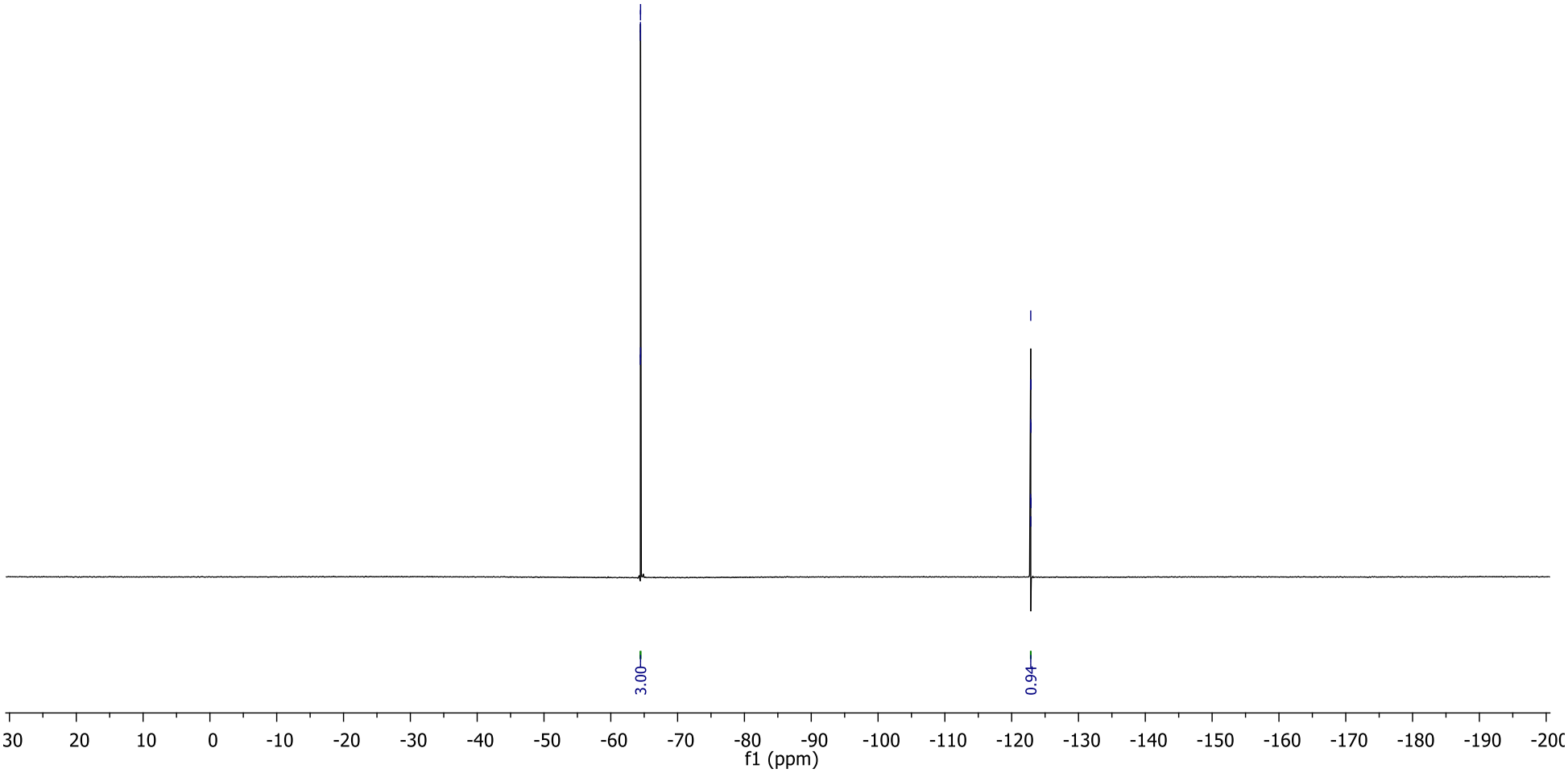
3f

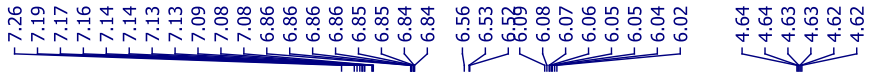
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)

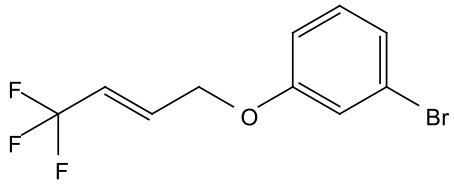


3f

^{19}F NMR (470 MHz, $CDCl_3$)

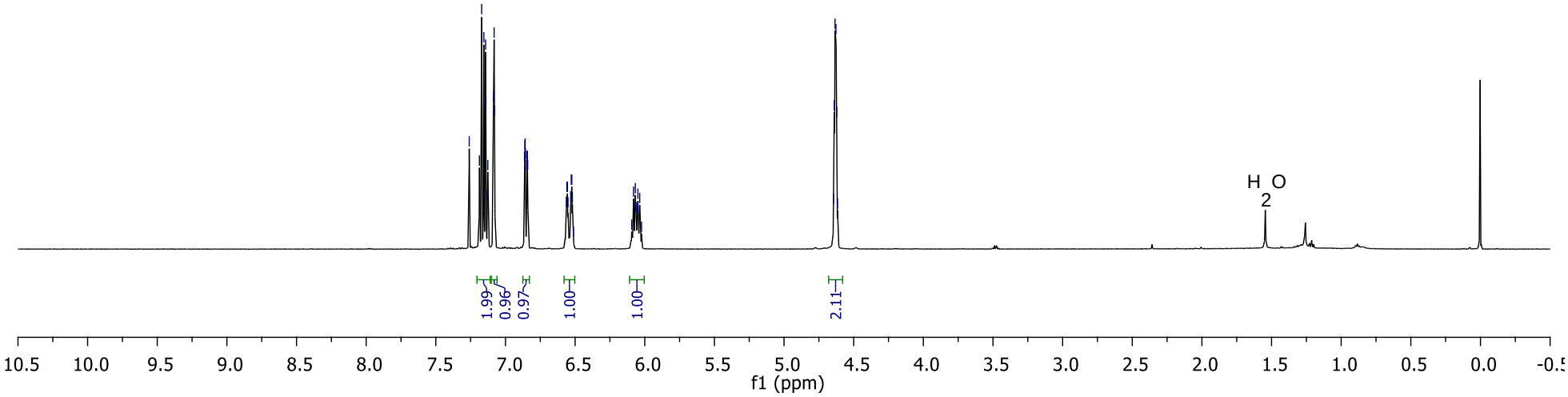


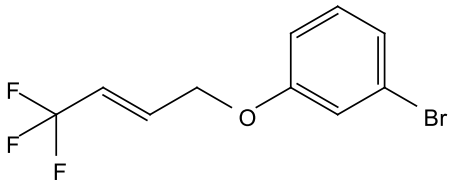




3h

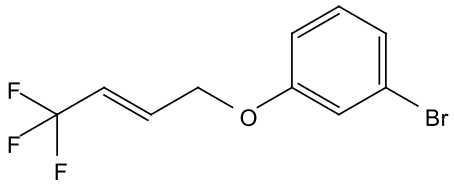
^{1}H NMR (500 MHz, $CDCl_3$)





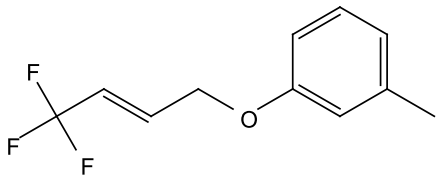
3h

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



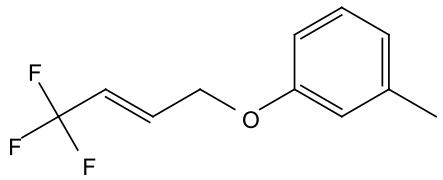
3h

^{19}F NMR (470 MHz, $CDCl_3$)



3i

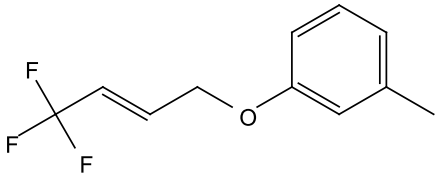
^{1}H NMR (500 MHz, $CDCl_3$)



3i

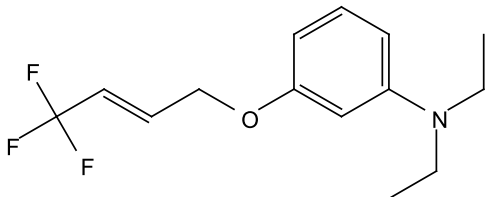
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)

t



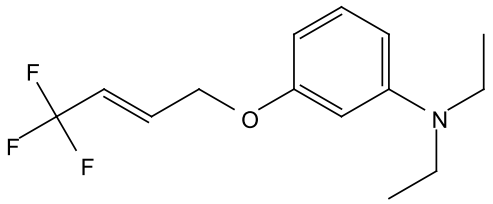
3i

^{9}F NMR (470 MHz, $CDCl_3$)



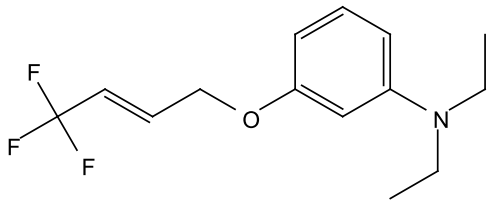
3j

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



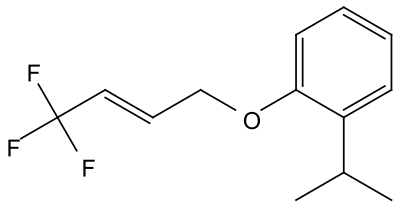
3j

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



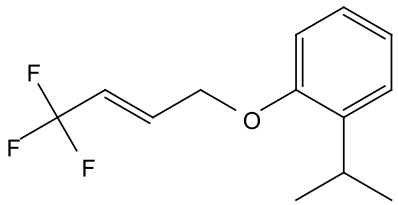
3j

^{19}F NMR (470 MHz, $CDCl_3$)



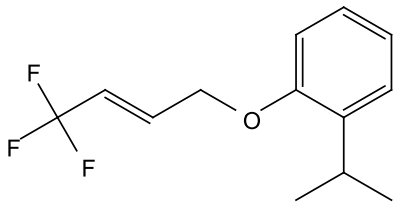
3k

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



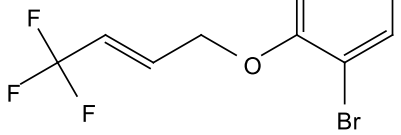
3k

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



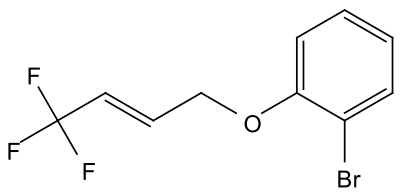
3k

^{19}F NMR (470 MHz, $CDCl_3$)



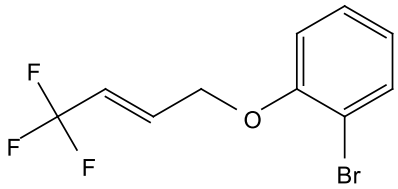
3l

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



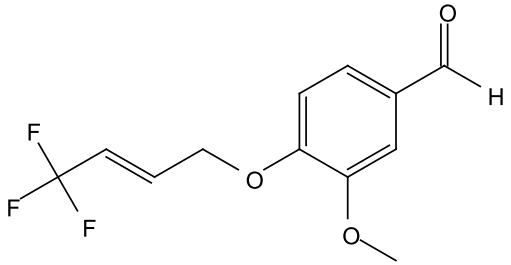
3l

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



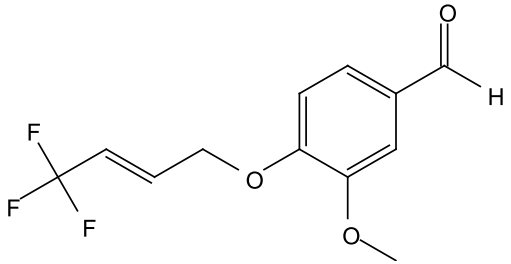
3l

^{19}F NMR (470 MHz, $CDCl_3$)



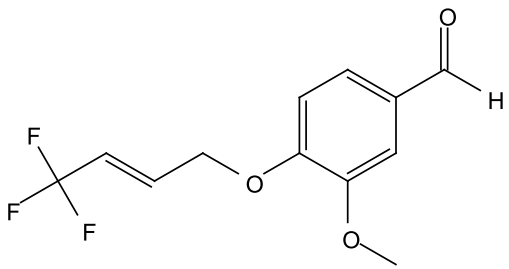
3m

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



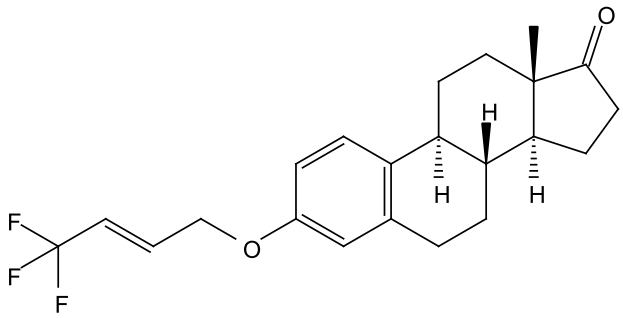
3m

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



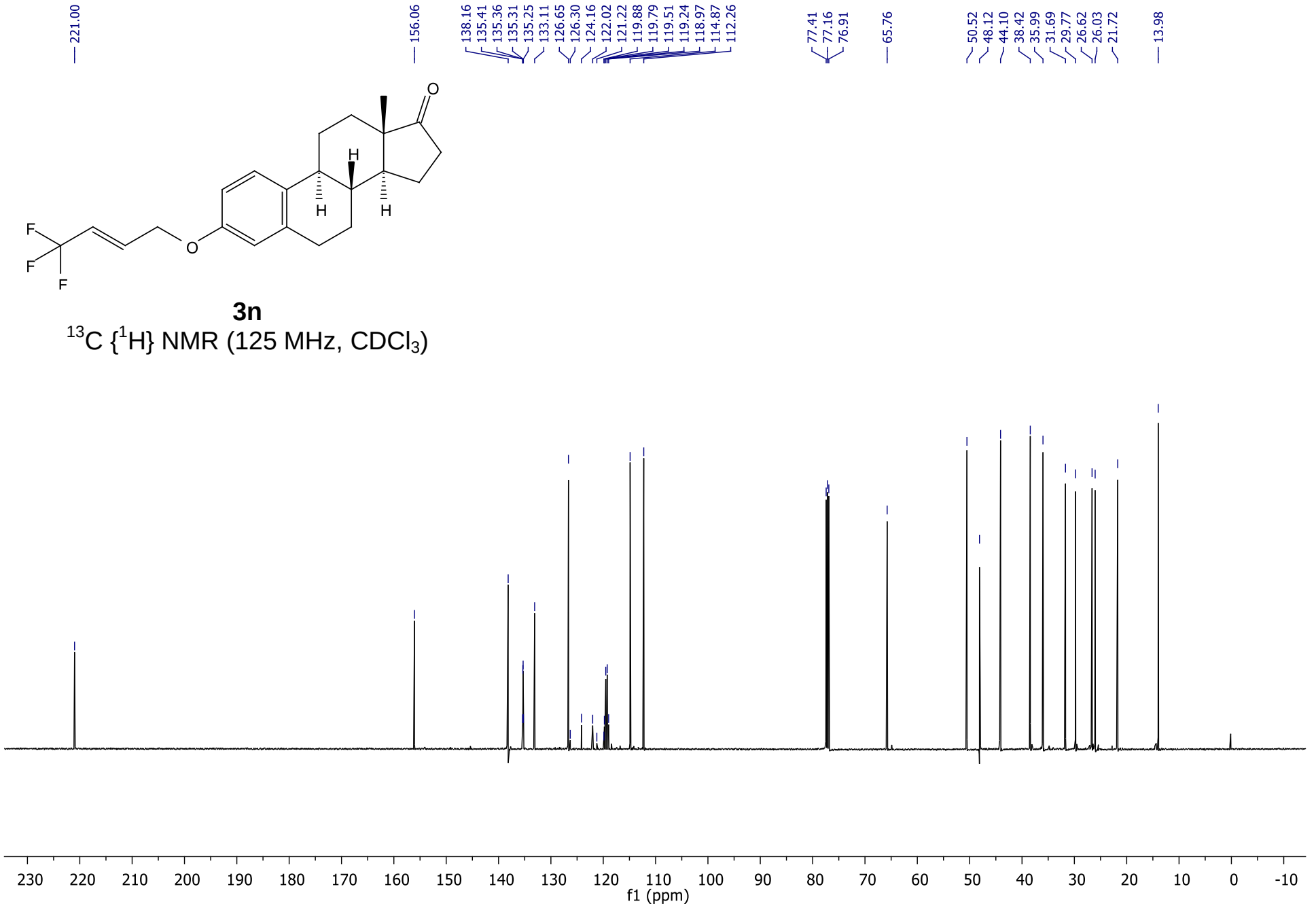
3m

^{19}F NMR (470 MHz, $CDCl_3$)



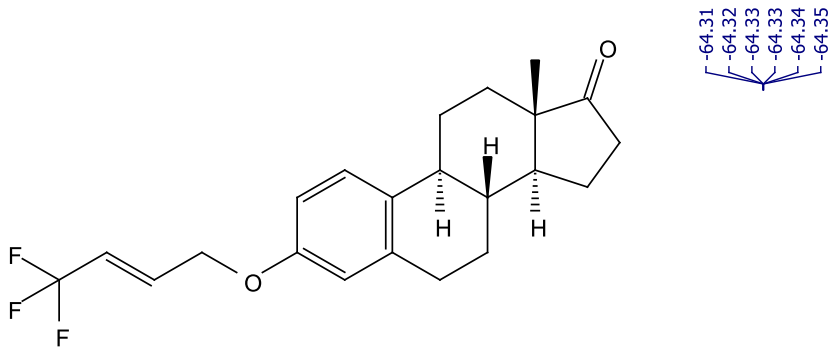
3n

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



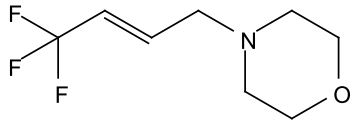
3n

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



3n

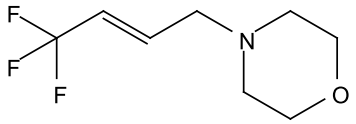
^{19}F NMR (470 MHz, $CDCl_3$)



4a

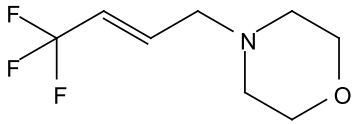
^{1}H NMR (500 MHz, $CDCl_3$)

hh



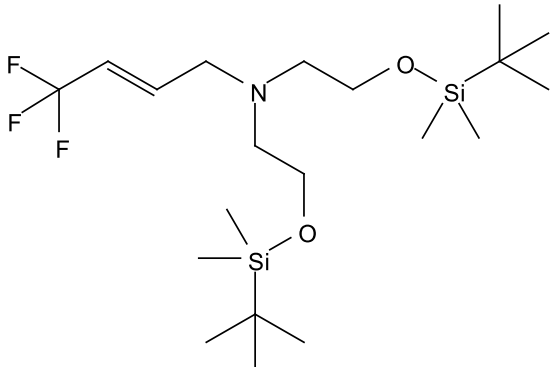
4a

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



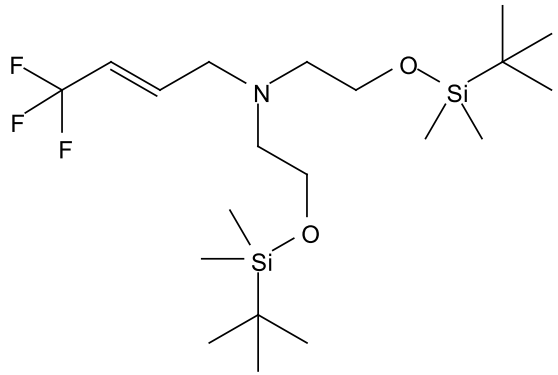
4a

^{19}F NMR (470 MHz, $CDCl_3$)



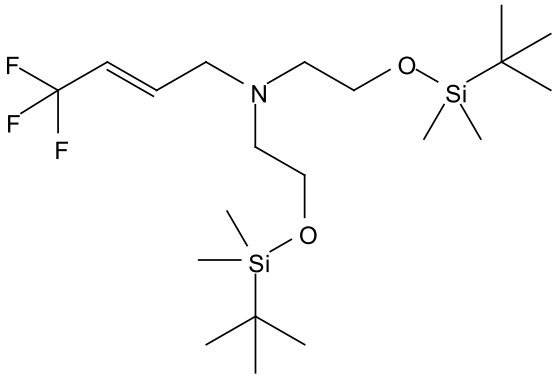
4b

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



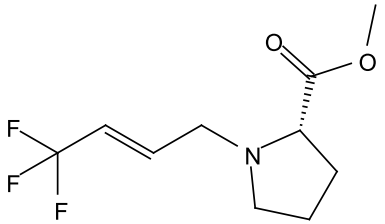
4b

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



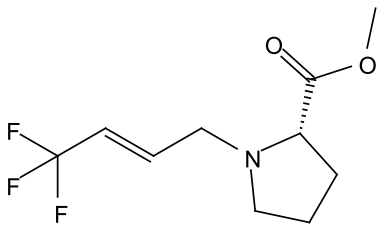
4b

^{19}F NMR (470 MHz, $CDCl_3$)



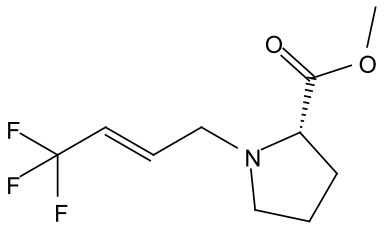
4c

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



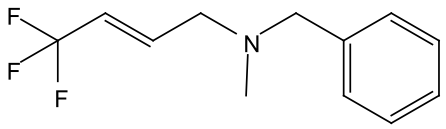
4c

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



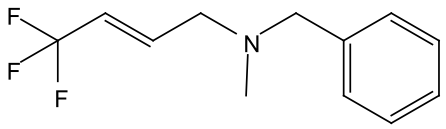
4c

^{19}F NMR (470 MHz, $CDCl_3$)



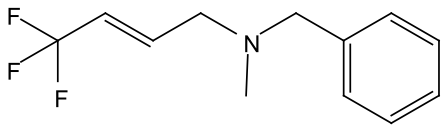
4d

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



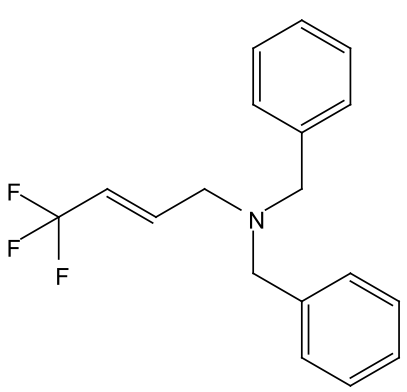
4d

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



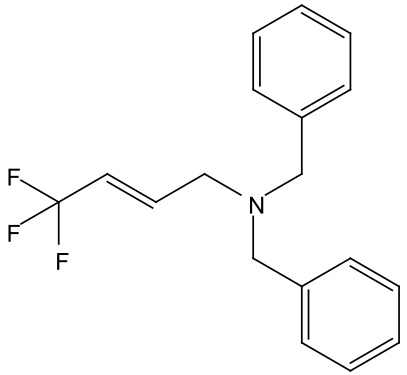
4d

^{19}F NMR (470 MHz, $CDCl_3$)



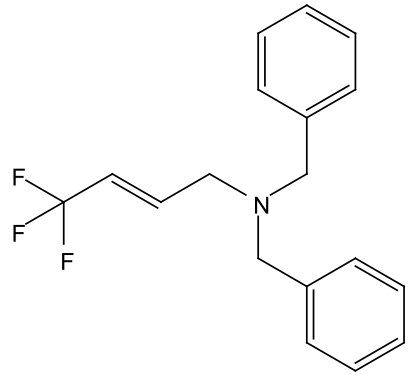
4e

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



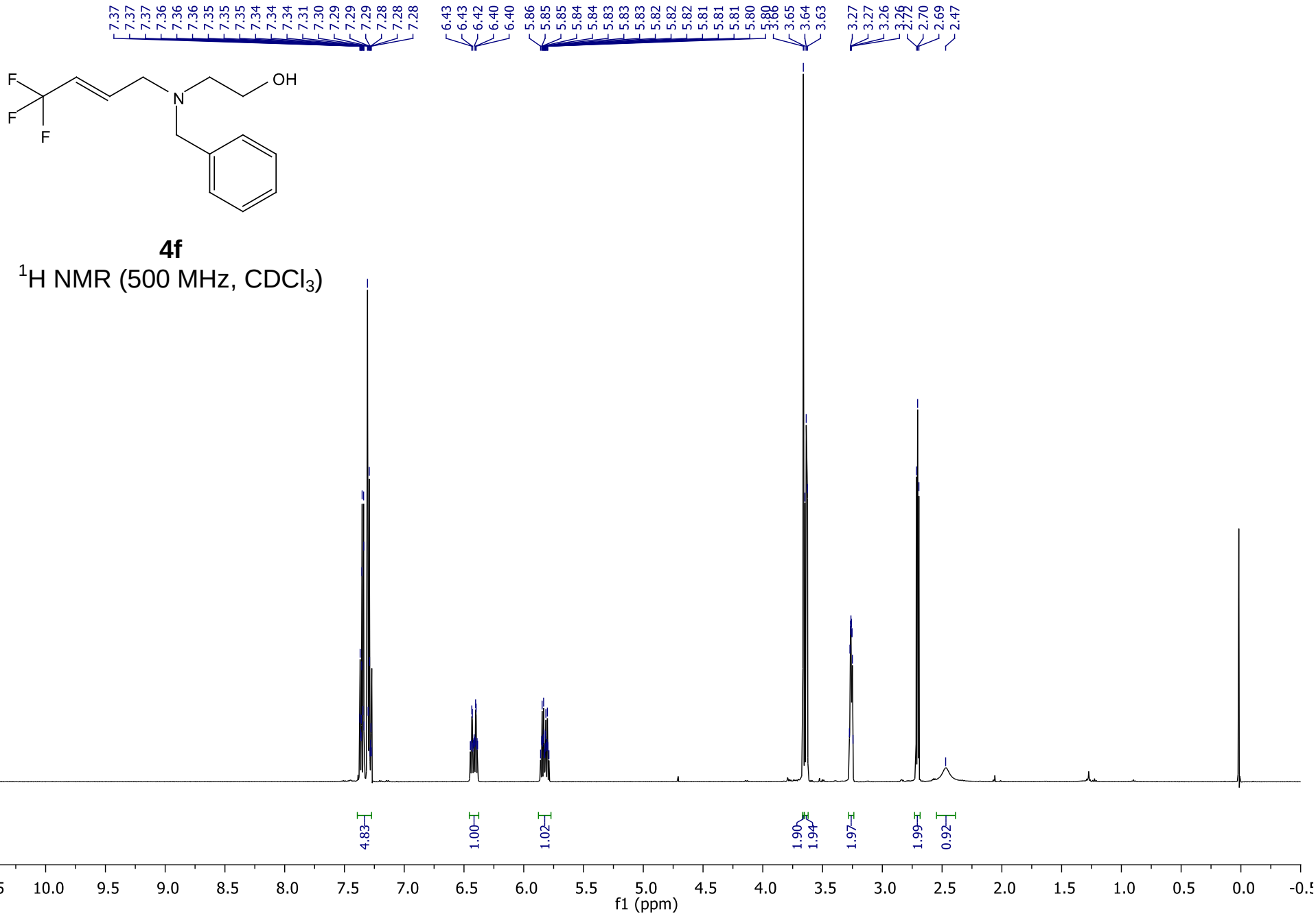
4e

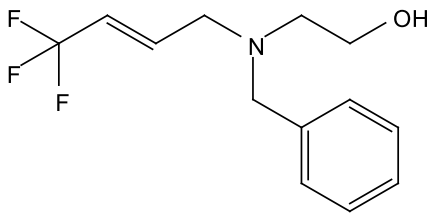
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



4e

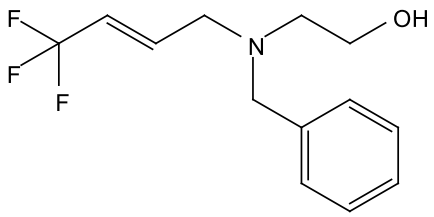
^{19}F NMR (470 MHz, $CDCl_3$)


F
F
F
N
OH
4f
1H NMR (500 MHz, CDCl3)
7.37 7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.34 7.31 7.30 7.29 7.29 7.29 7.28 7.28 7.28
6.43 6.43 6.42 6.40 6.40
5.86 5.85 5.85 5.84 5.84 5.83 5.83 5.83 5.82 5.82 5.82 5.81 5.81 5.81 5.80 5.80
3.65 3.64 3.63
3.27 3.27 3.26 2.72 2.70 2.69 2.47
4.83 1.00 1.02 1.90 1.94 1.97 1.99 0.92
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



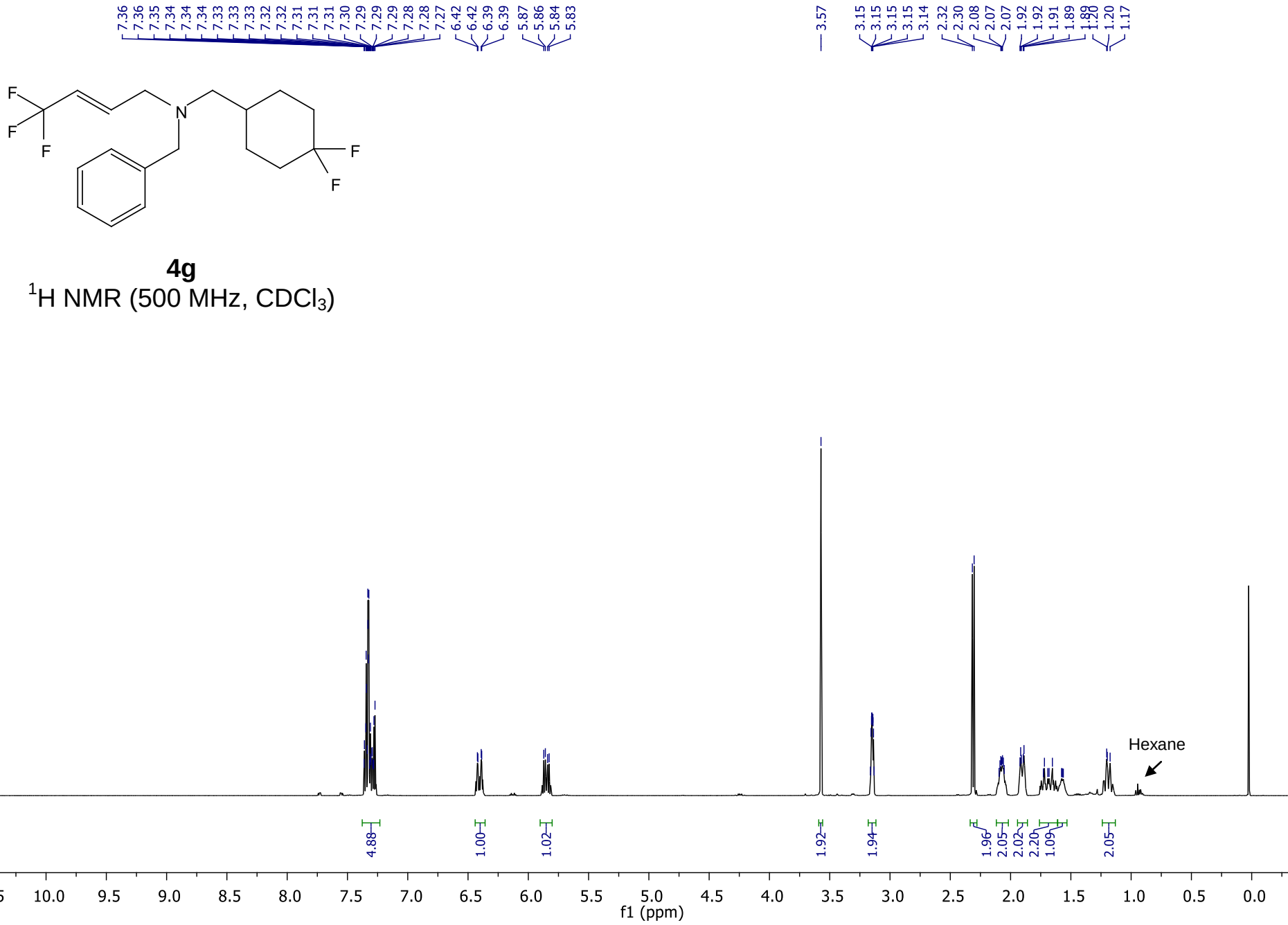
4f

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



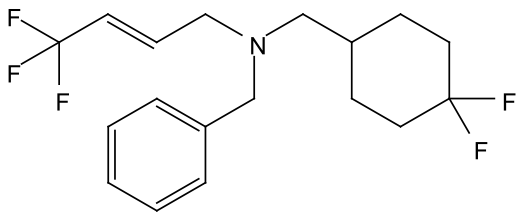
4f

^{19}F NMR (470 MHz, $CDCl_3$)



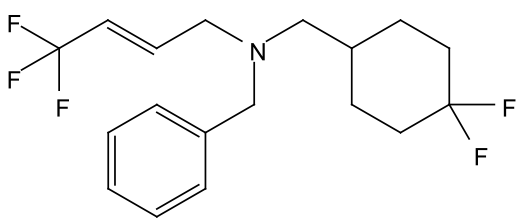
4g

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



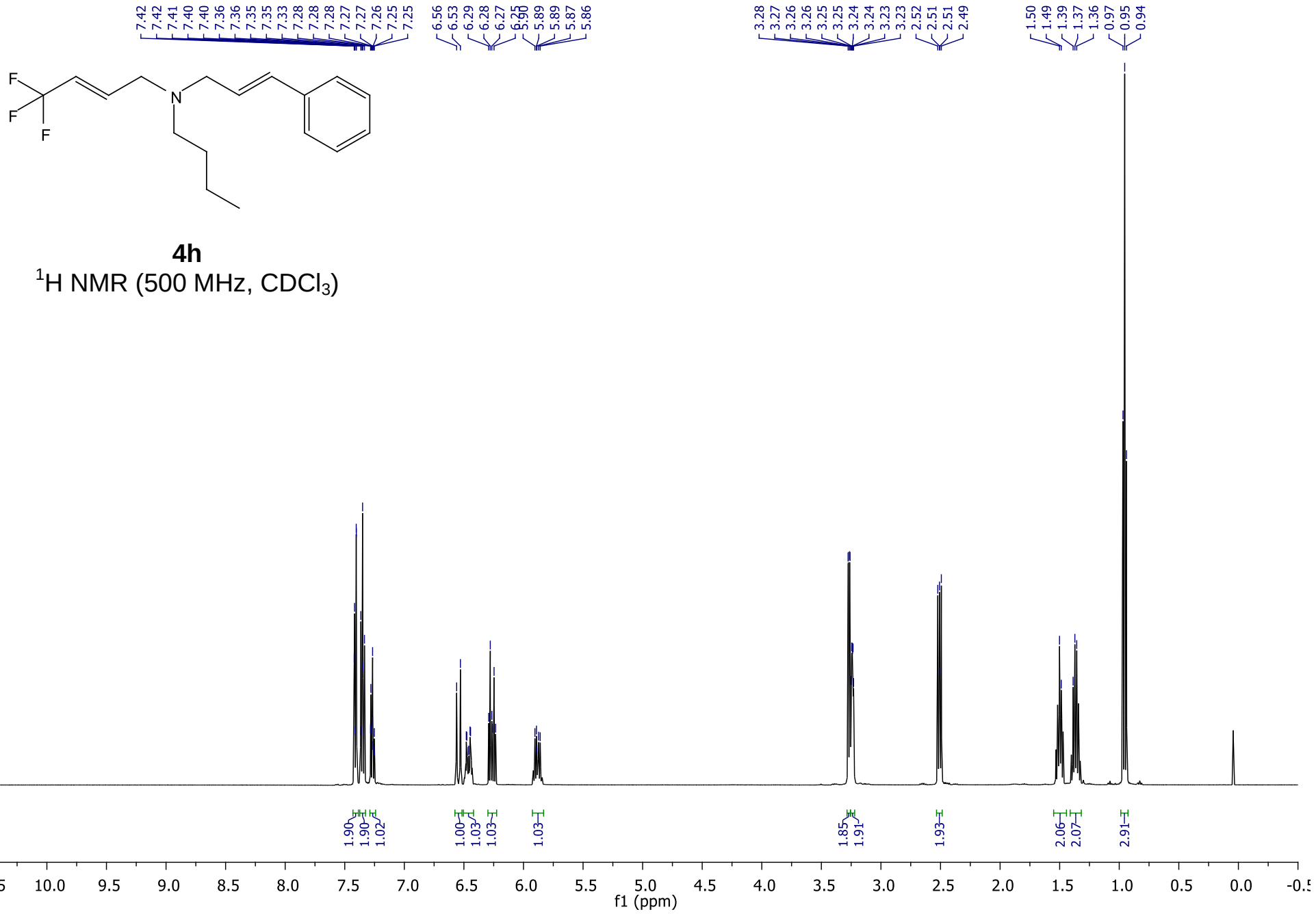
4g

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



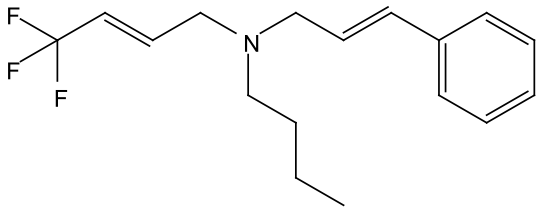
4g

^{19}F NMR (470 MHz, $CDCl_3$)



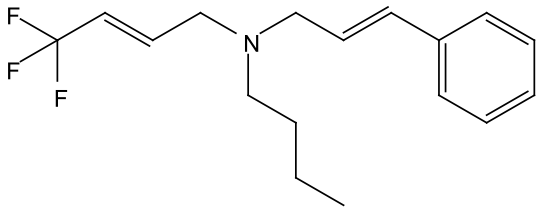
4h

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



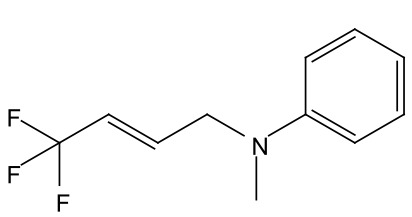
4h

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



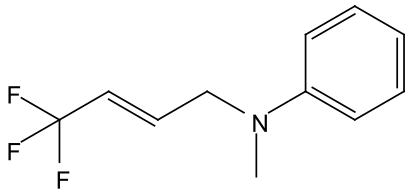
4h

^{19}F NMR (470 MHz, $CDCl_3$)



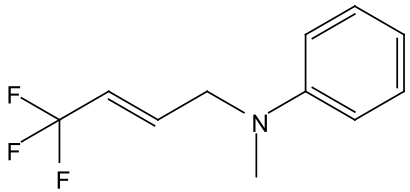
4i

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



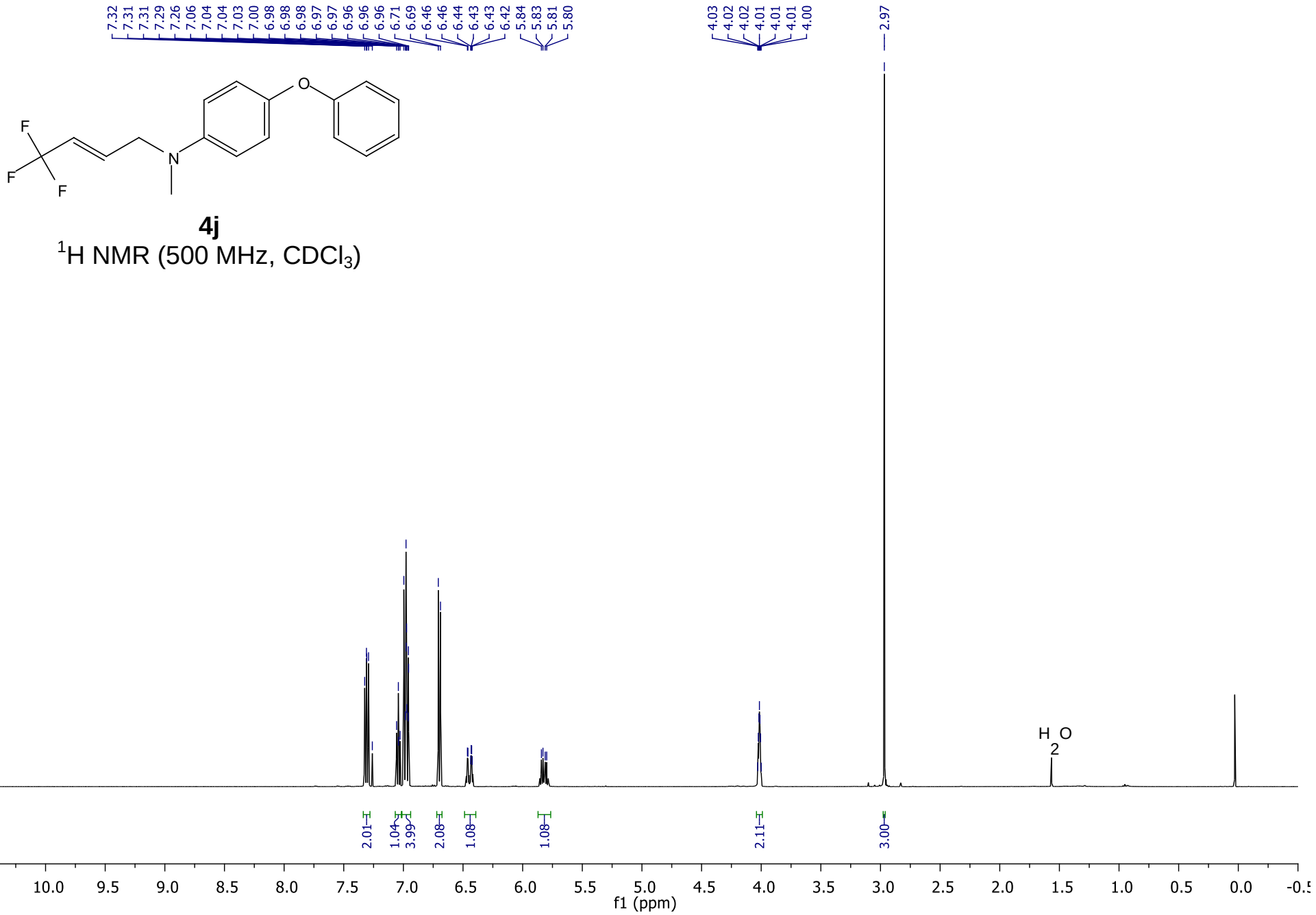
4i

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



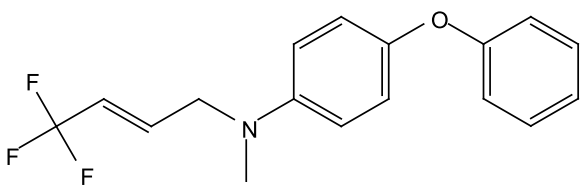
4i

^{19}F NMR (470 MHz, $CDCl_3$)



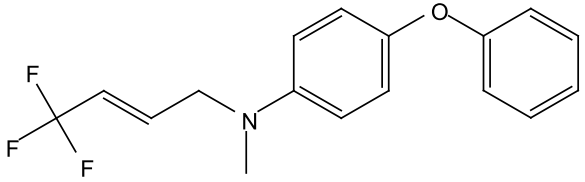
4j

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



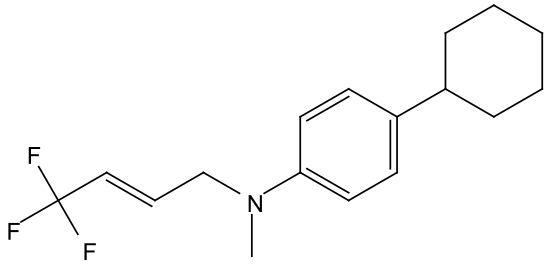
4j

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



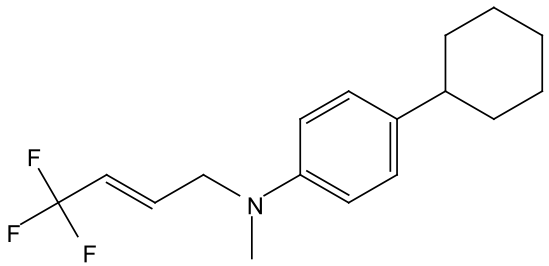
4j

^{19}F NMR (470 MHz, $CDCl_3$)



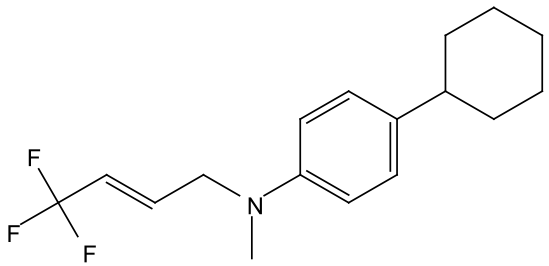
4k

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



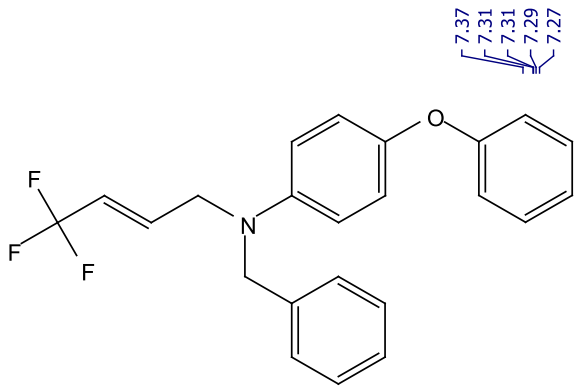
4k

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



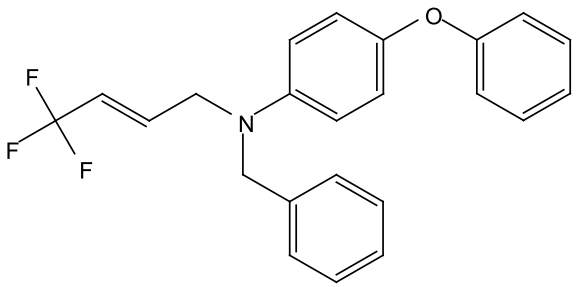
4k

^{19}F NMR (470 MHz, $CDCl_3$)



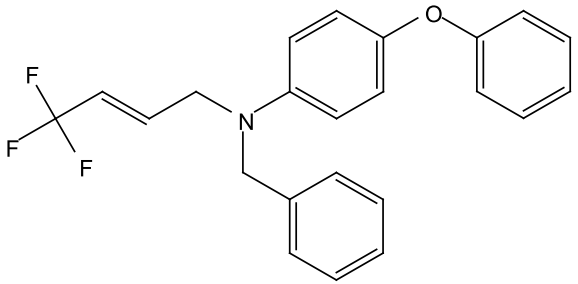
4l

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



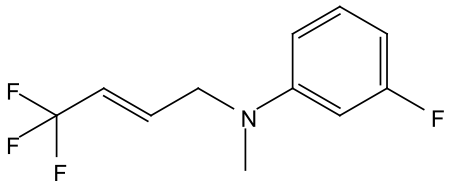
4l

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



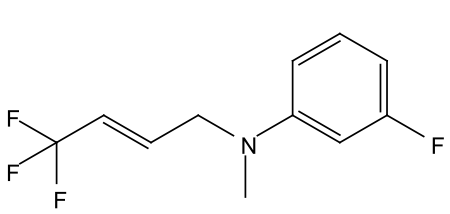
4l

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



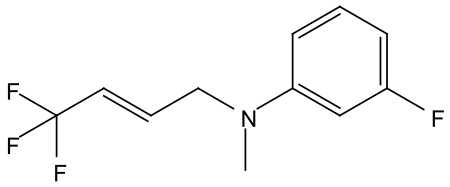
4m

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



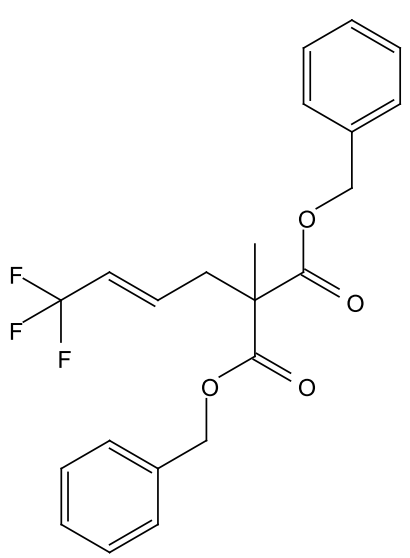
4m

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



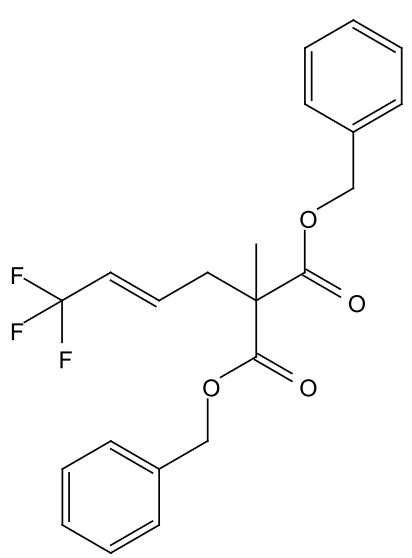
4m

^{19}F NMR (470 MHz, $CDCl_3$)



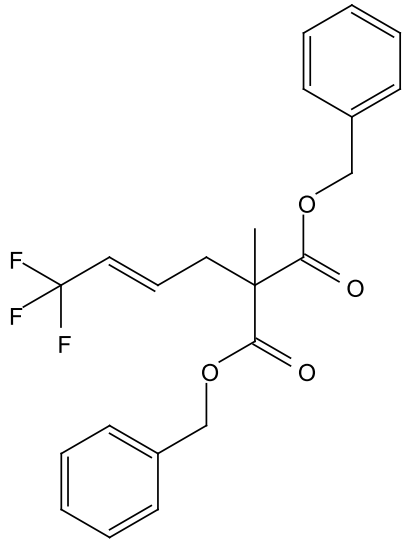
6b

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



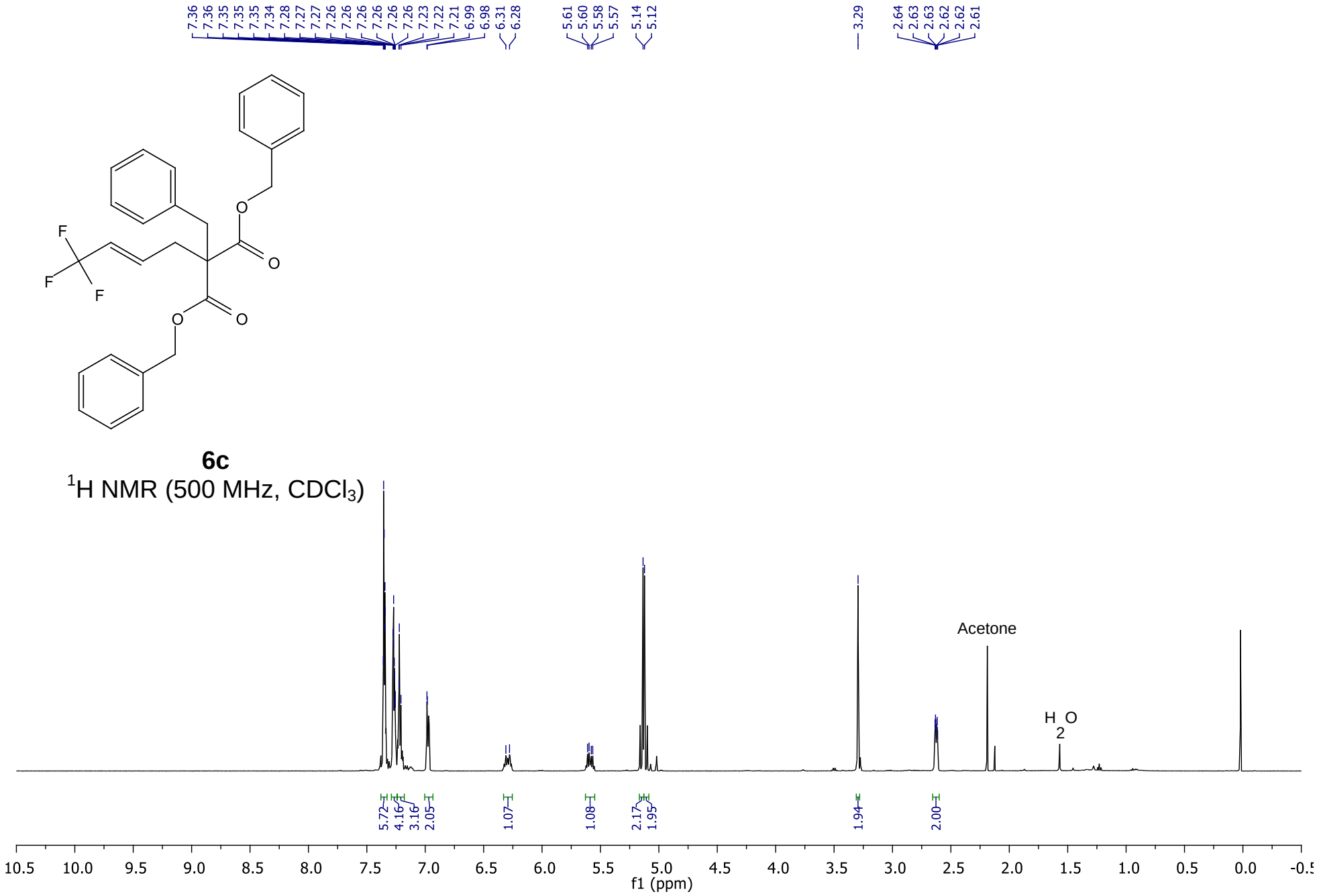
6b

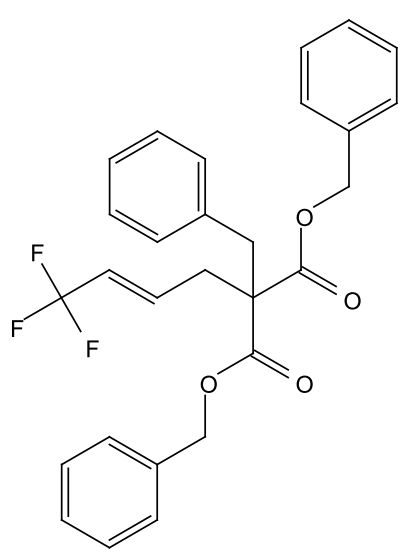
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



6b

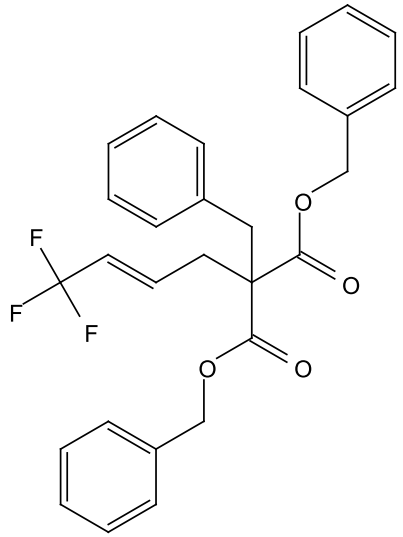
^{19}F NMR (470 MHz, $CDCl_3$)


7.36
7.36
7.35
7.35
7.35
7.34
7.28
7.27
7.27
7.26
7.26
7.26
7.26
7.26
7.26
7.23
7.22
7.21
6.99
6.98
6.31
6.28
5.61
5.60
5.58
5.57
5.14
5.12
3.29
2.64
2.63
2.63
2.62
2.62
2.61
F
F
F
O
O
O
O
6c
1H NMR (500 MHz, CDCl3)
Acetone
H2O
5.72
4.16
3.16
2.05
1.07
1.08
2.17
1.95
1.94
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



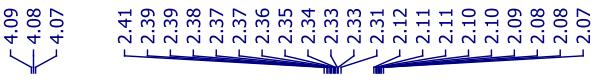
6c

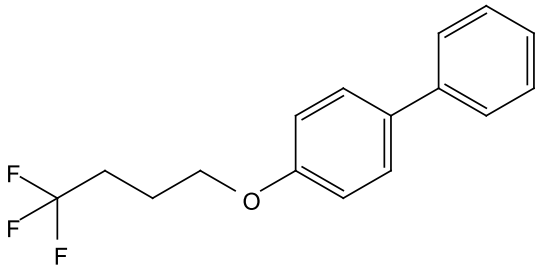
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



6c

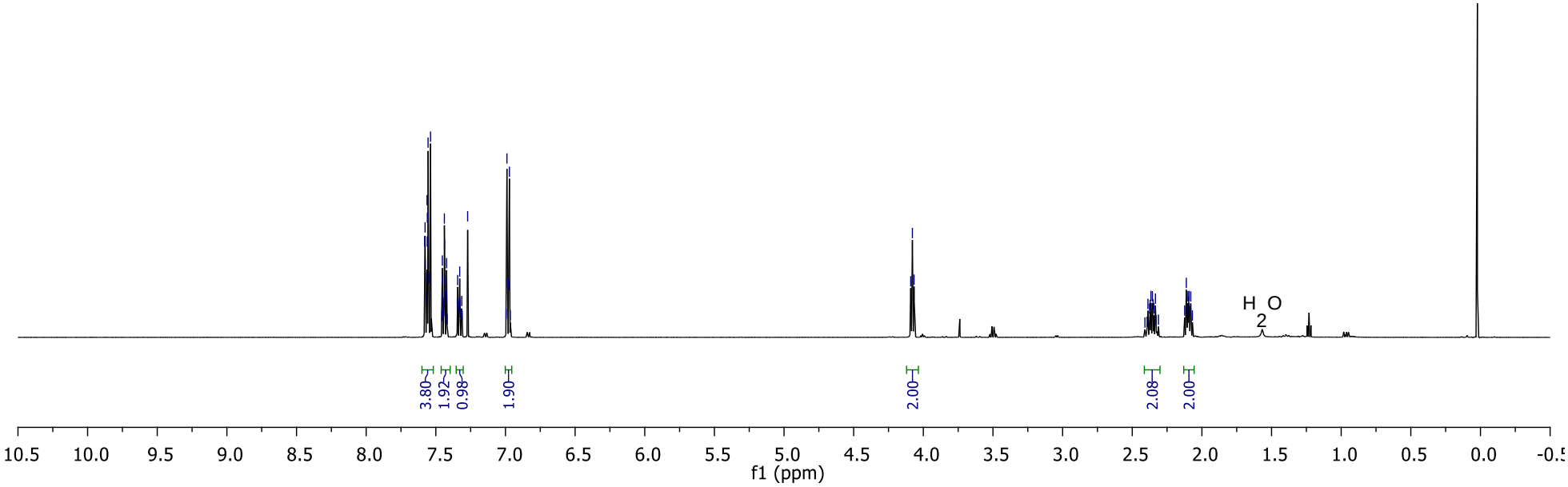
^{19}F NMR (470 MHz, $CDCl_3$)

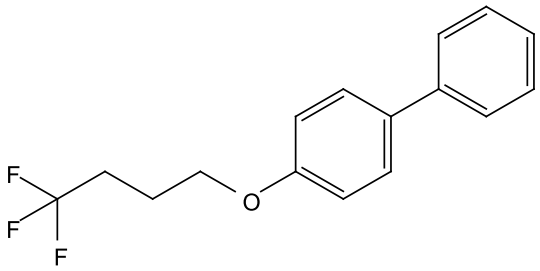




9

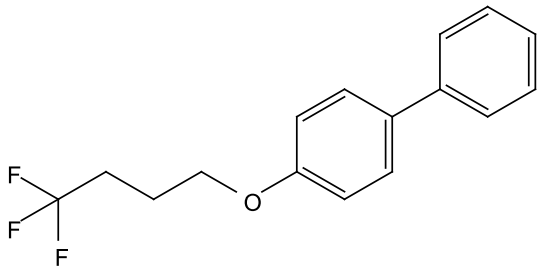
^{1}H NMR (500 MHz, $CDCl_3$)





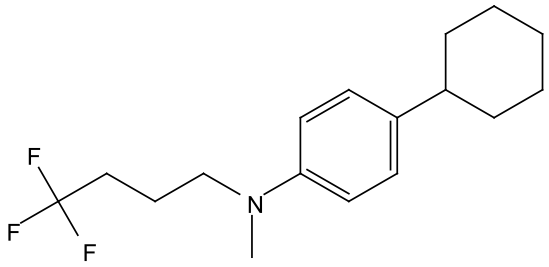
9

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



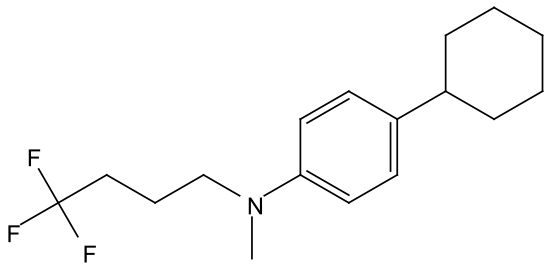
9

^{19}F NMR (470 MHz, $CDCl_3$)



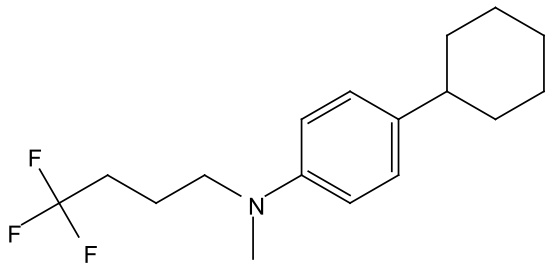
SI-12

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



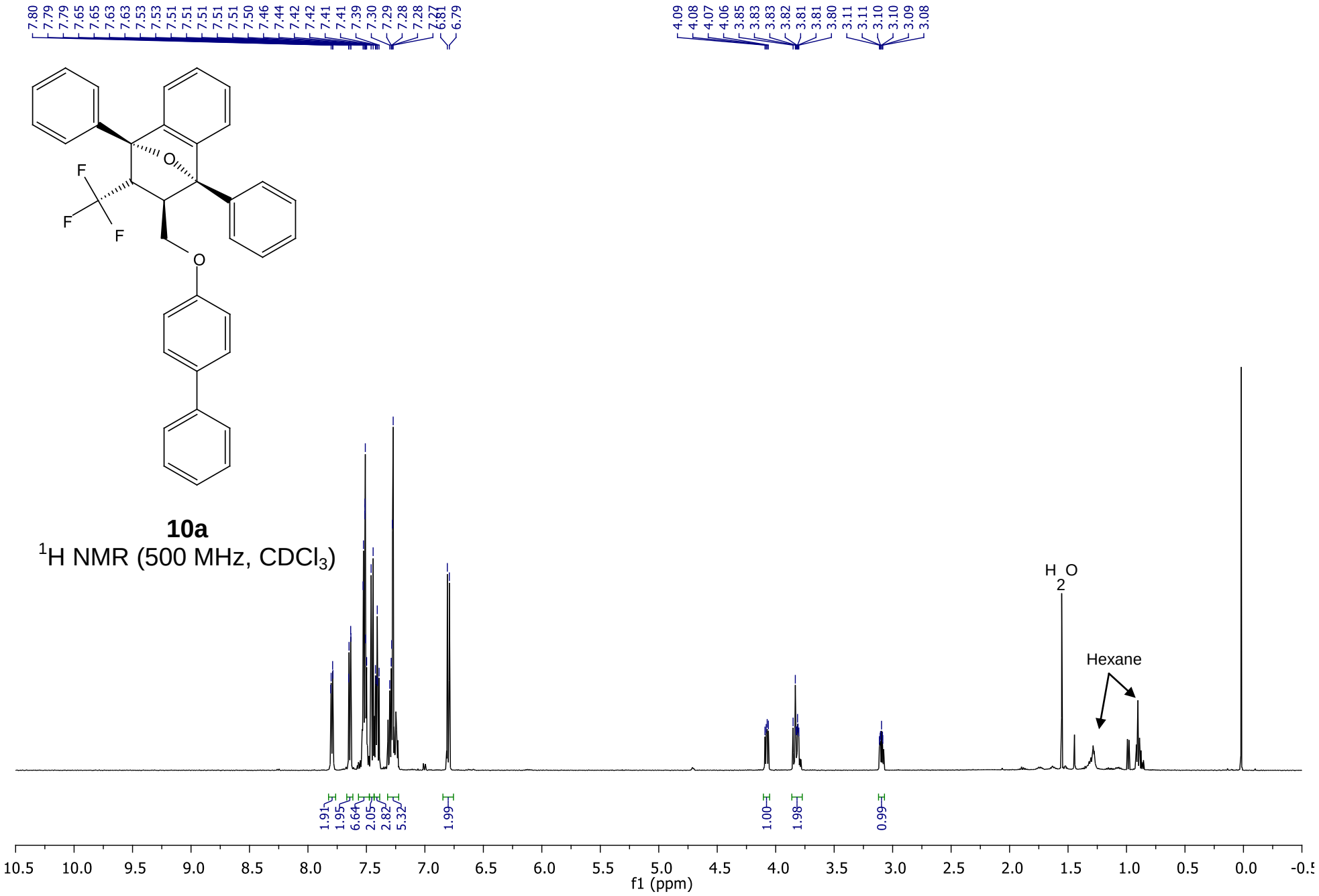
SI-12

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



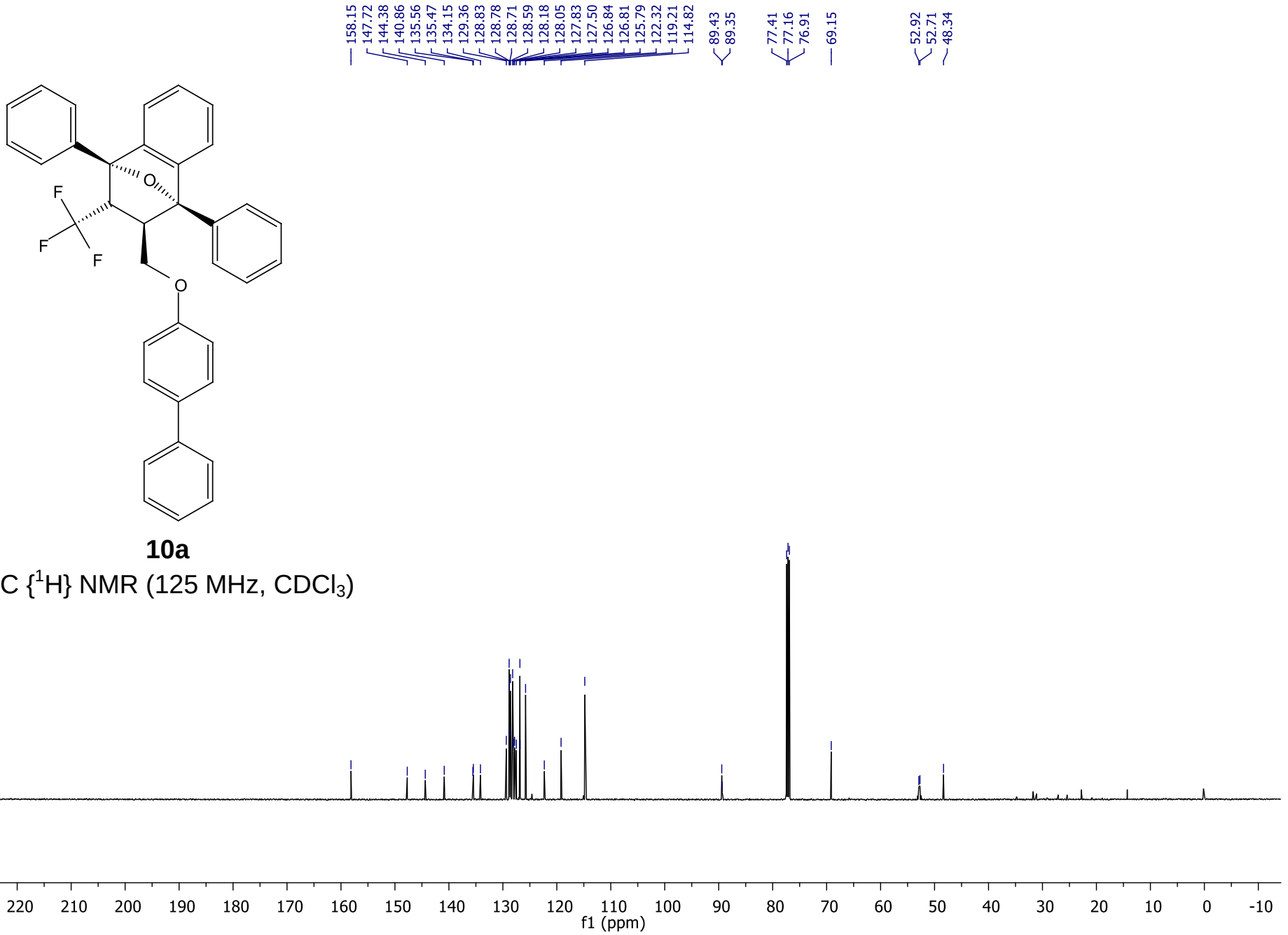
SI-12

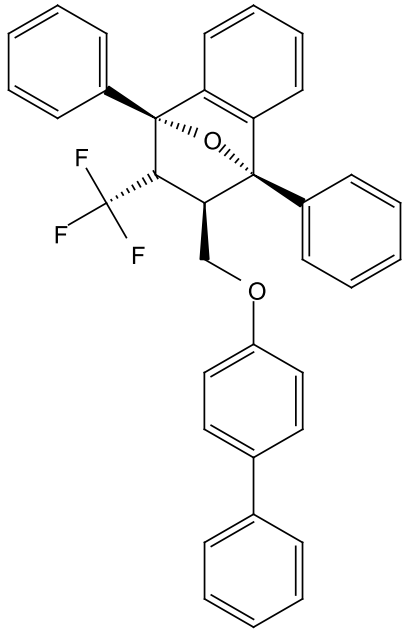
^{19}F NMR (470 MHz, $CDCl_3$)



10a

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


158.15
147.72
144.38
140.86
135.56
135.47
134.15
129.36
128.83
128.78
128.71
128.59
128.18
128.05
127.83
127.50
126.84
126.81
125.79
122.32
119.21
114.82
89.43
89.35
77.41
77.16
76.91
69.15
52.92
52.71
48.34
F
F
F
O
O
10a
13C {1H} NMR (125 MHz, CDCl3)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

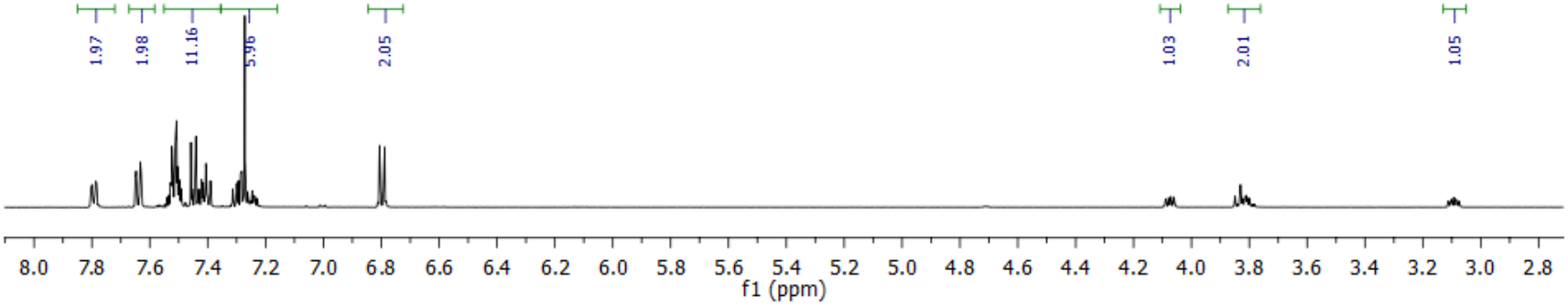


10a

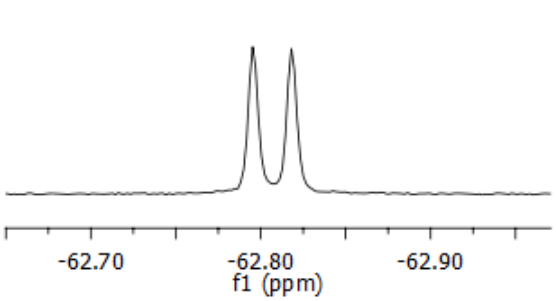
^{19}F NMR (470 MHz, $CDCl_3$)

CF_3-C*H* assignment

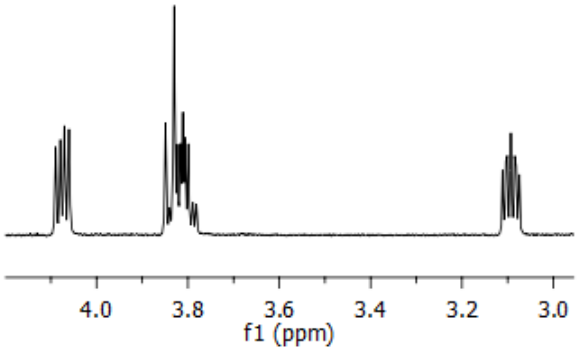
1H NMR (500 MHz, CDCl3)

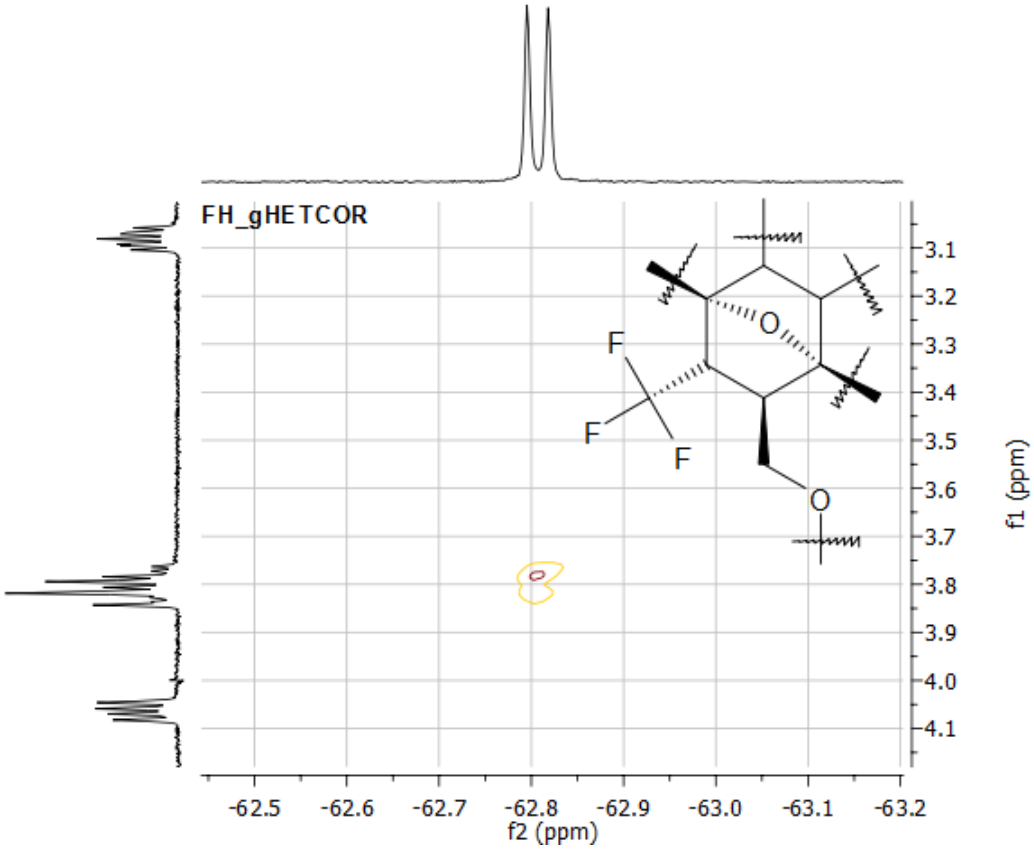


19F NMR (470 MHz, CDCl3)

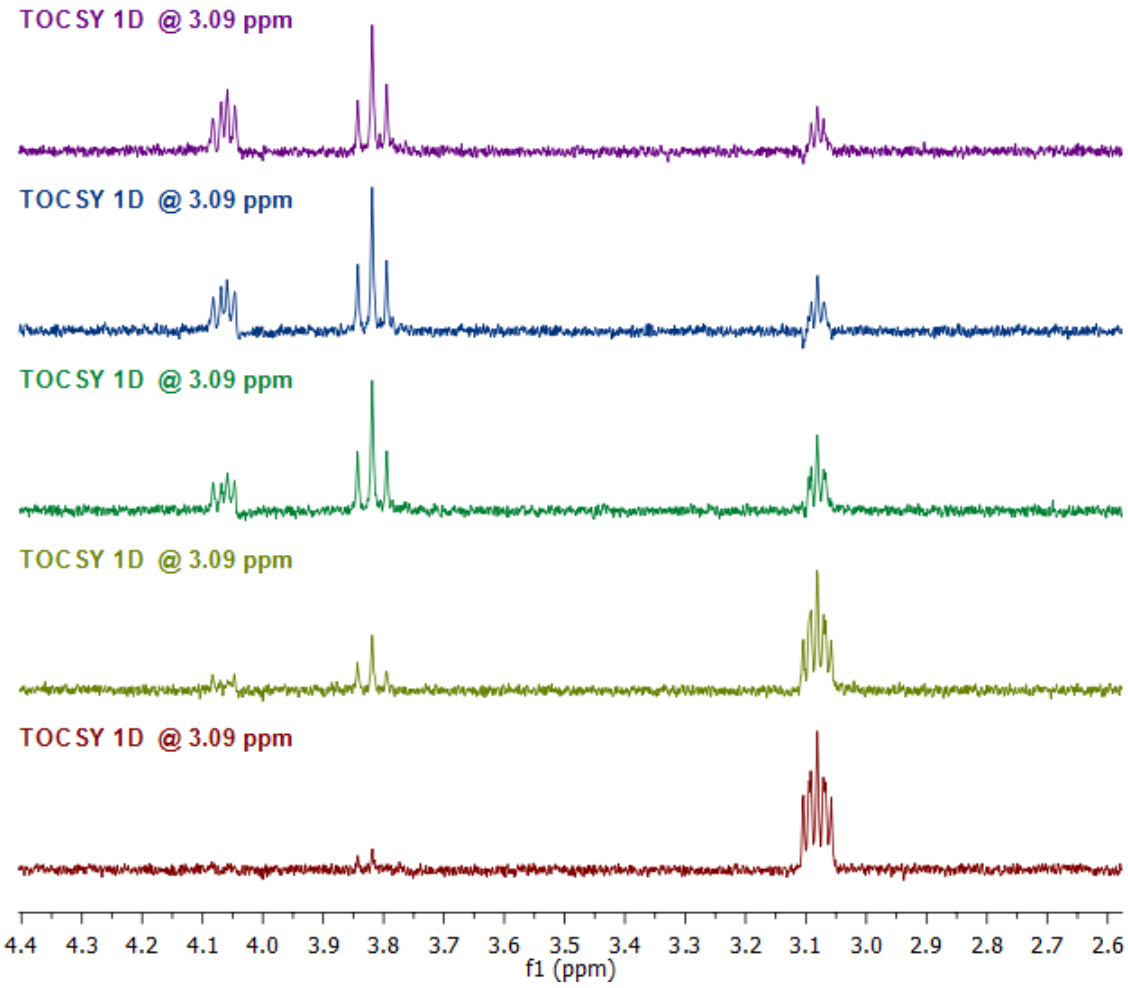


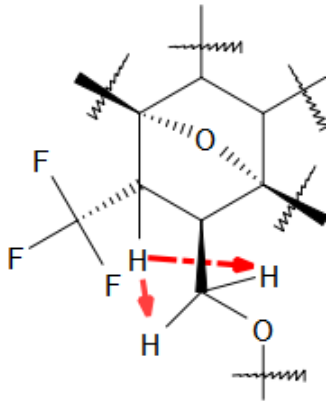
1H NMR (500 MHz, CDCl3)



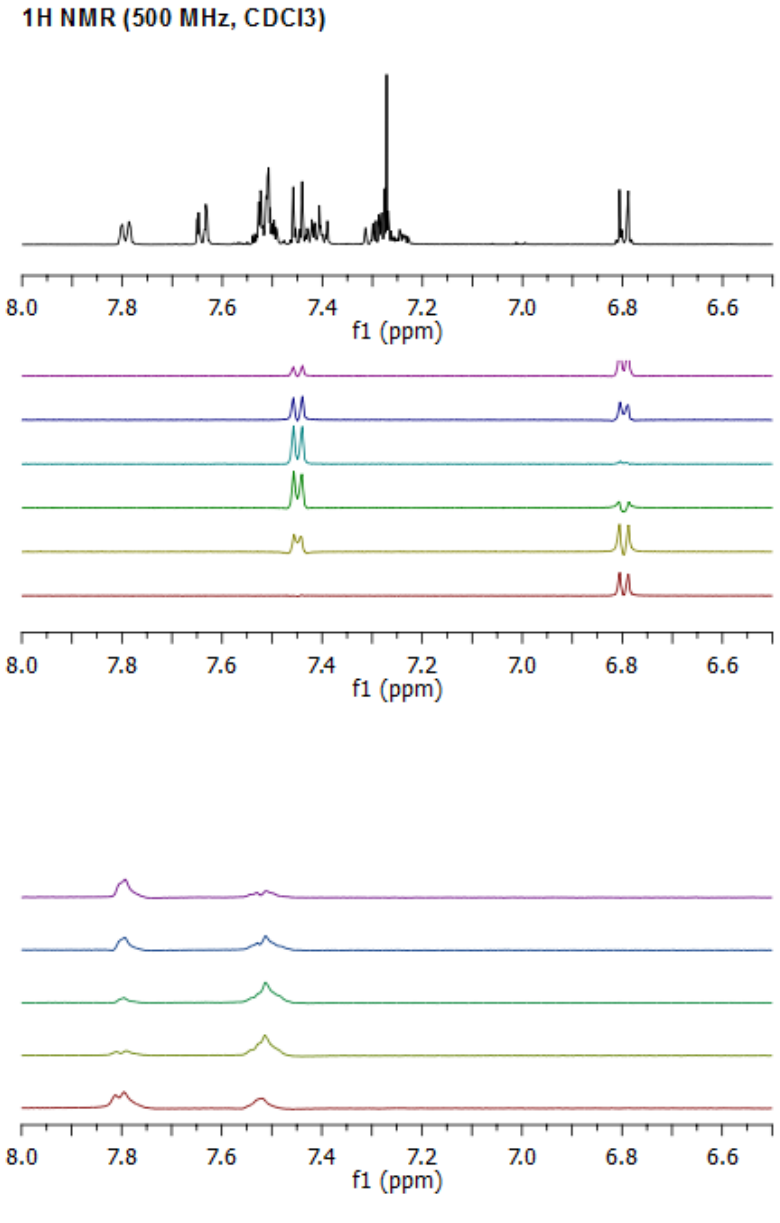


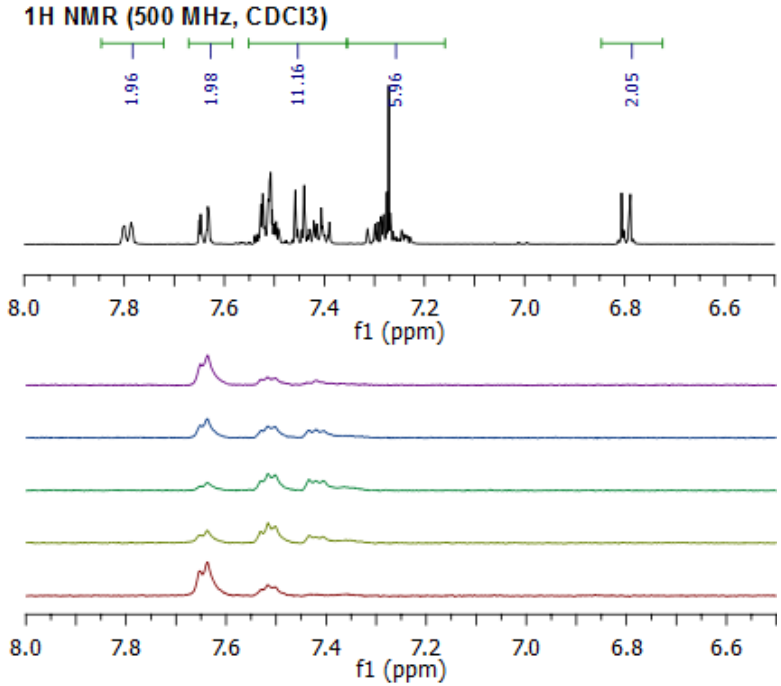
Aliphatic assignment

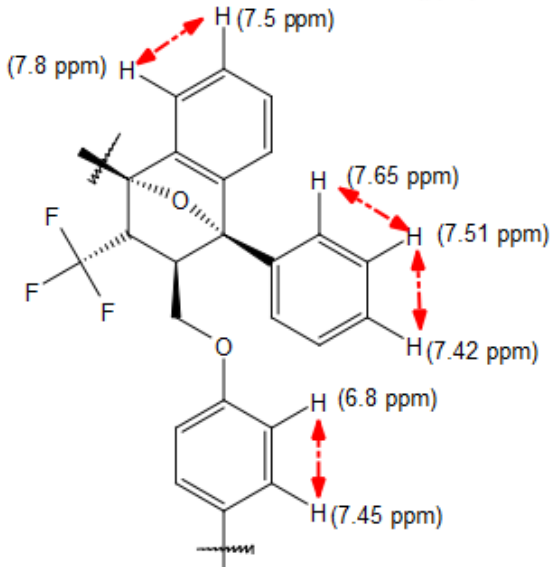




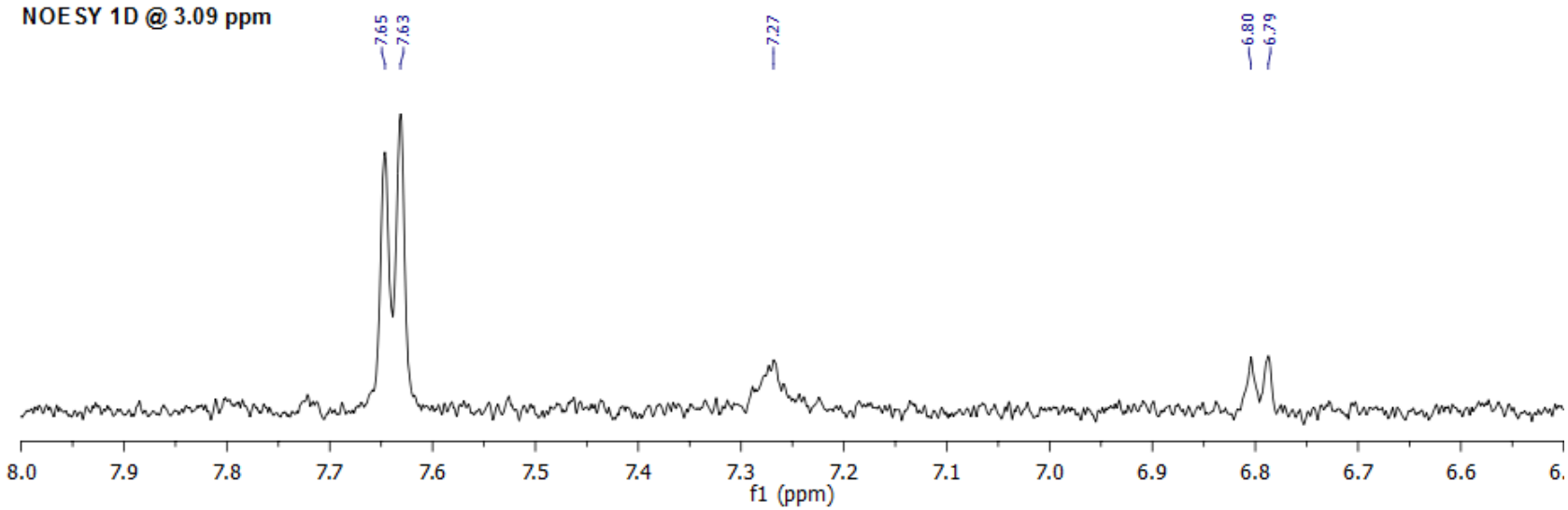
Aromatic assignment

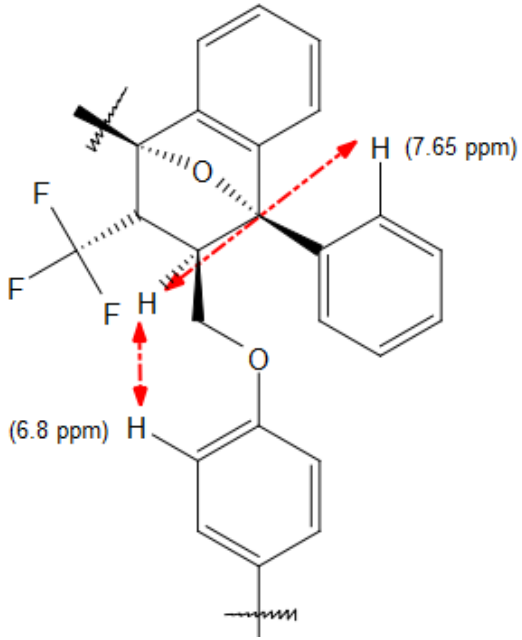






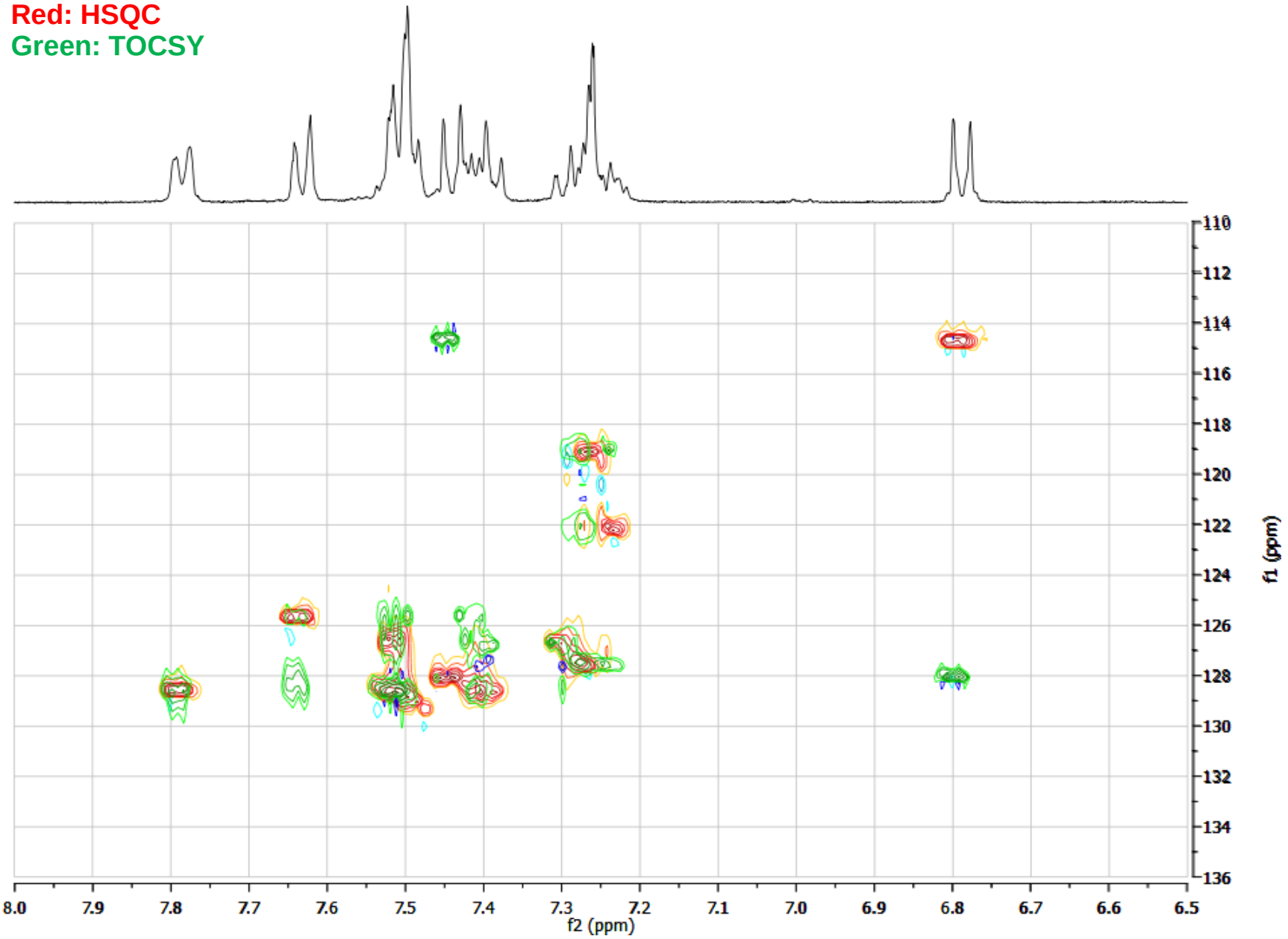
NOESY study


NOESY 1D @ 3.09 ppm
7.65
7.63
7.27
6.80
6.79
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
f1 (ppm)

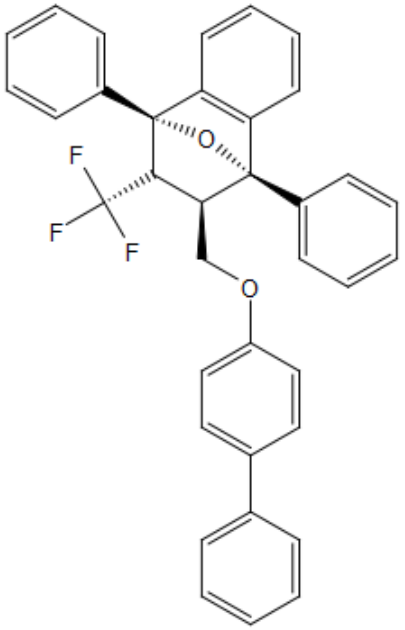

H (7.65 ppm)
O
F
F
F
H
O
(6.8 ppm) H

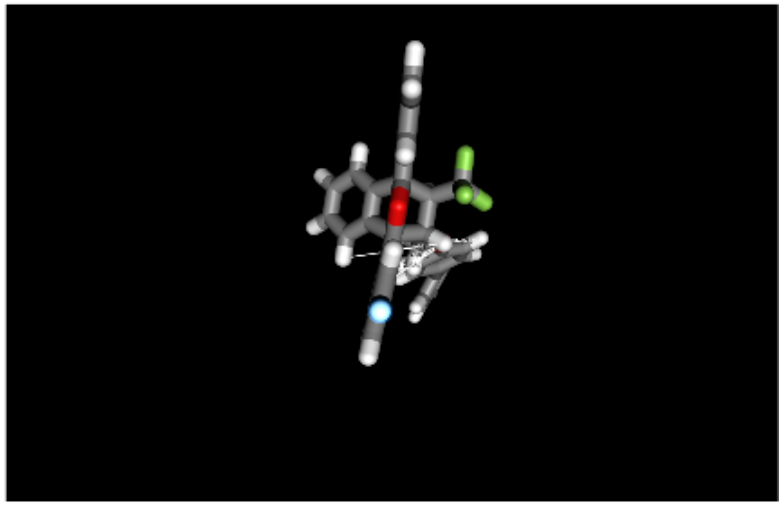
Superimposed HSQC and TOCSY in the aromatic region

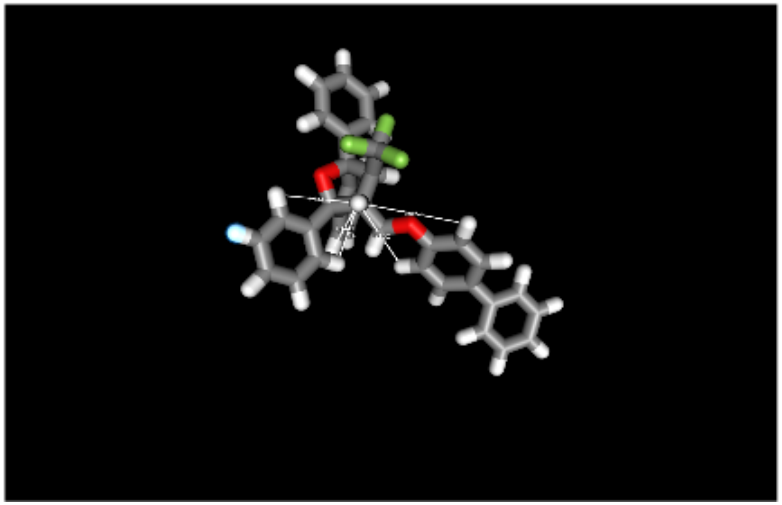
Red: HSQC
Green: TOCSY

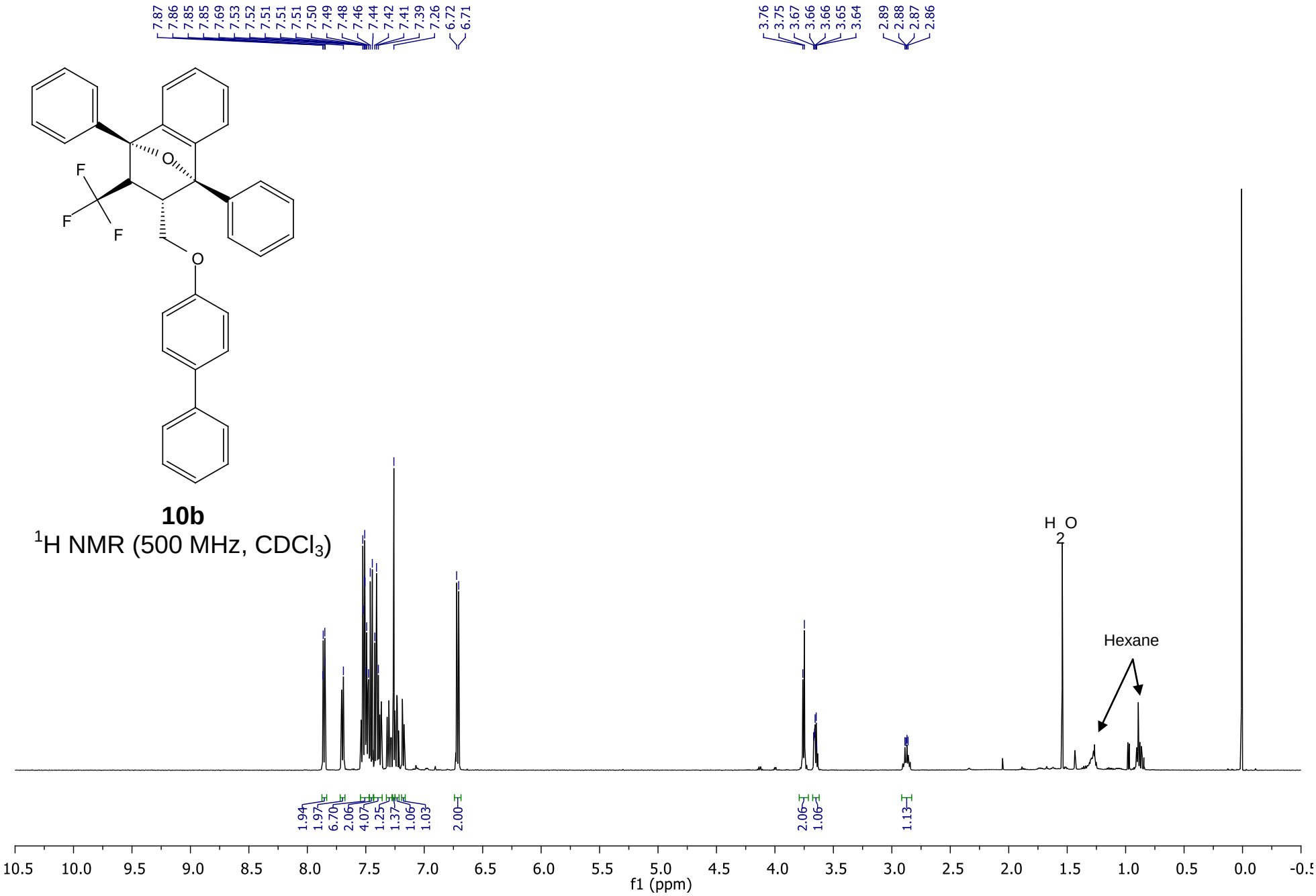


Proposed structure



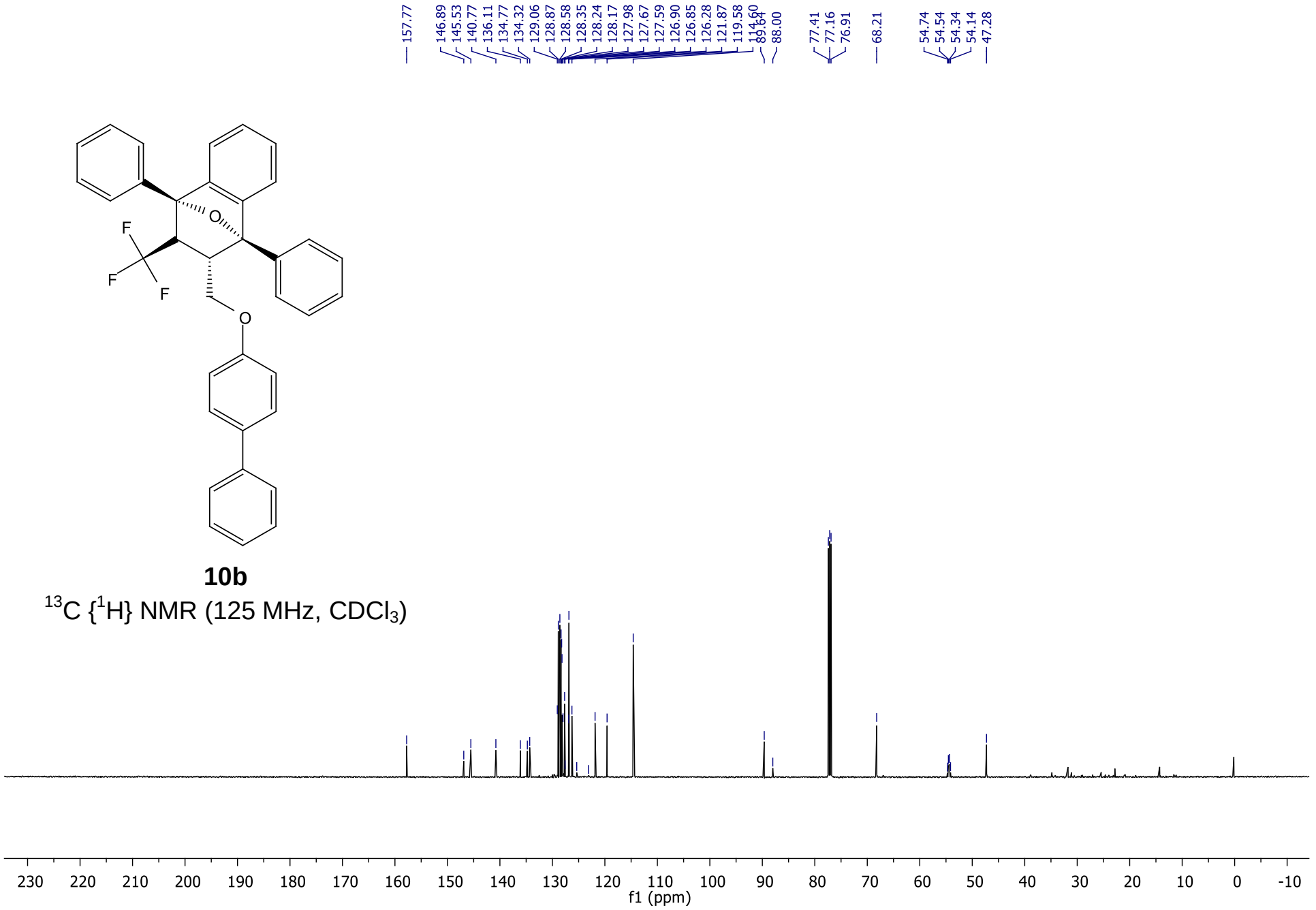






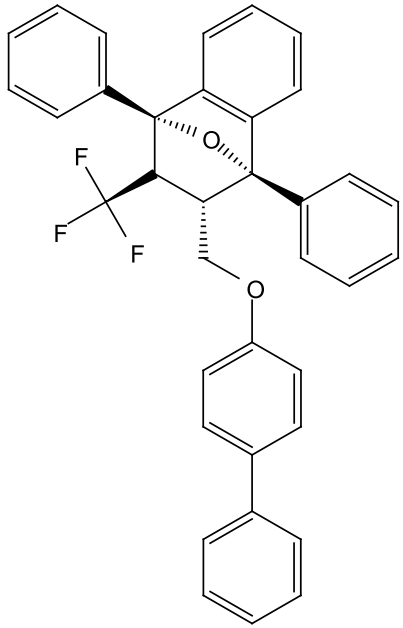
10b

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



10b

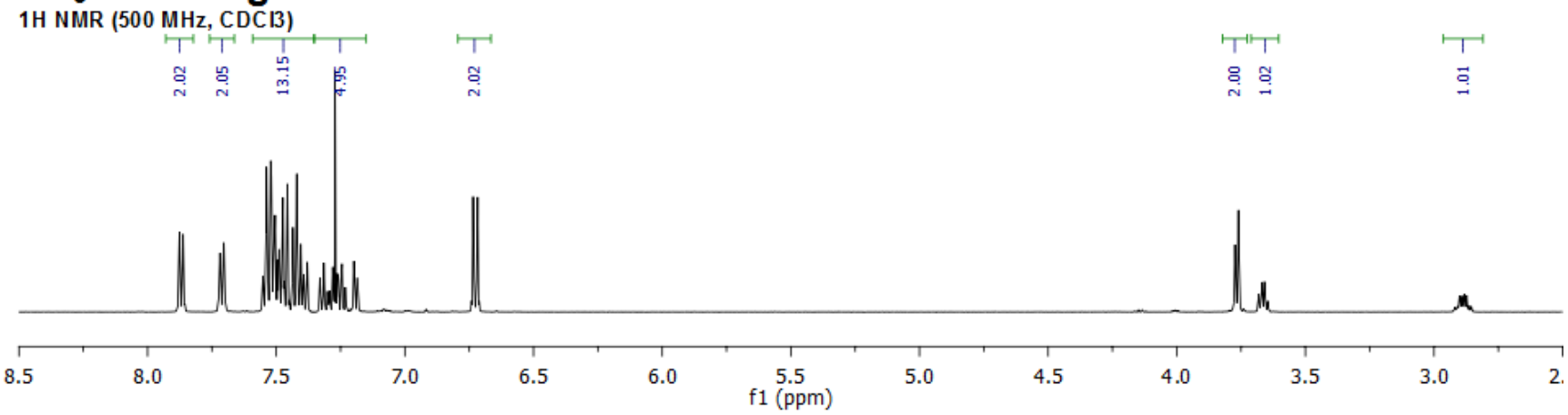
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)

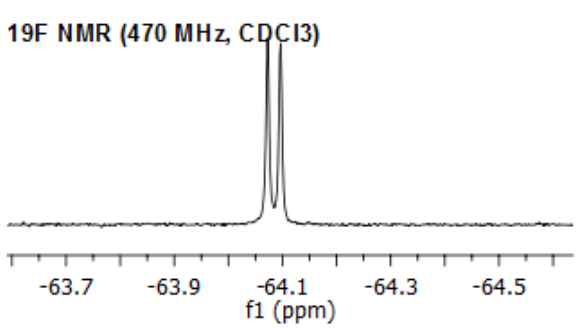


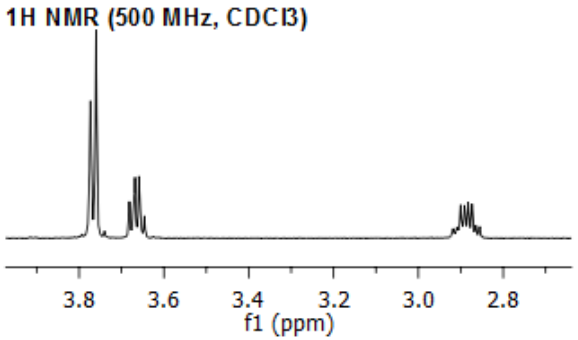
10b

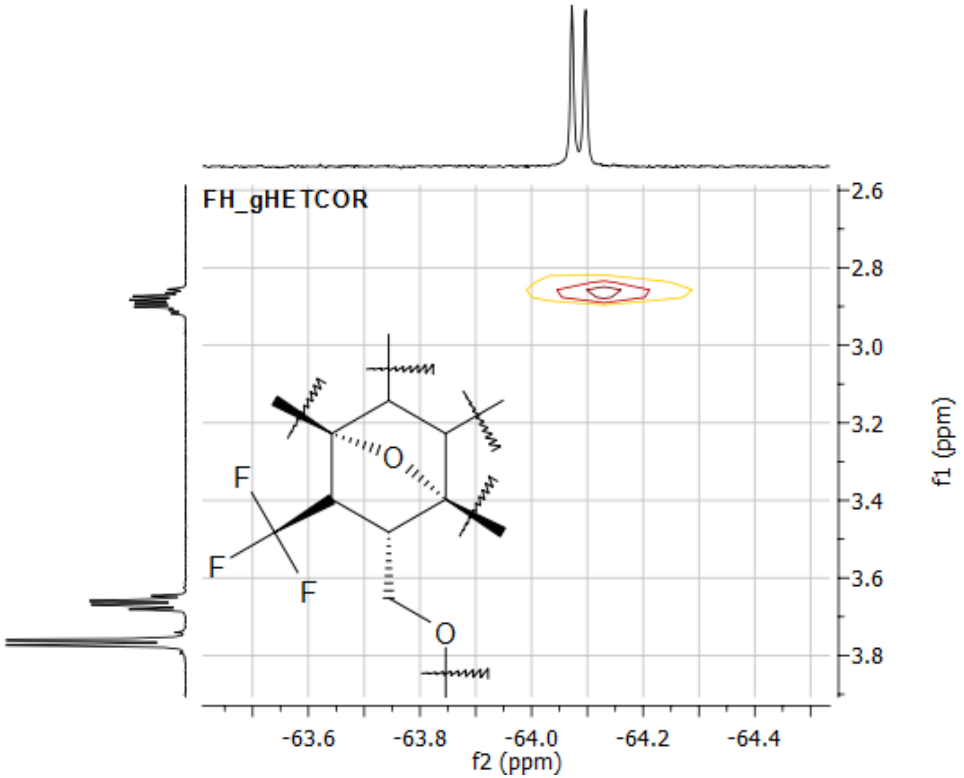
^{19}F NMR (470 MHz, $CDCl_3$)

CF_3-C*H* assignment

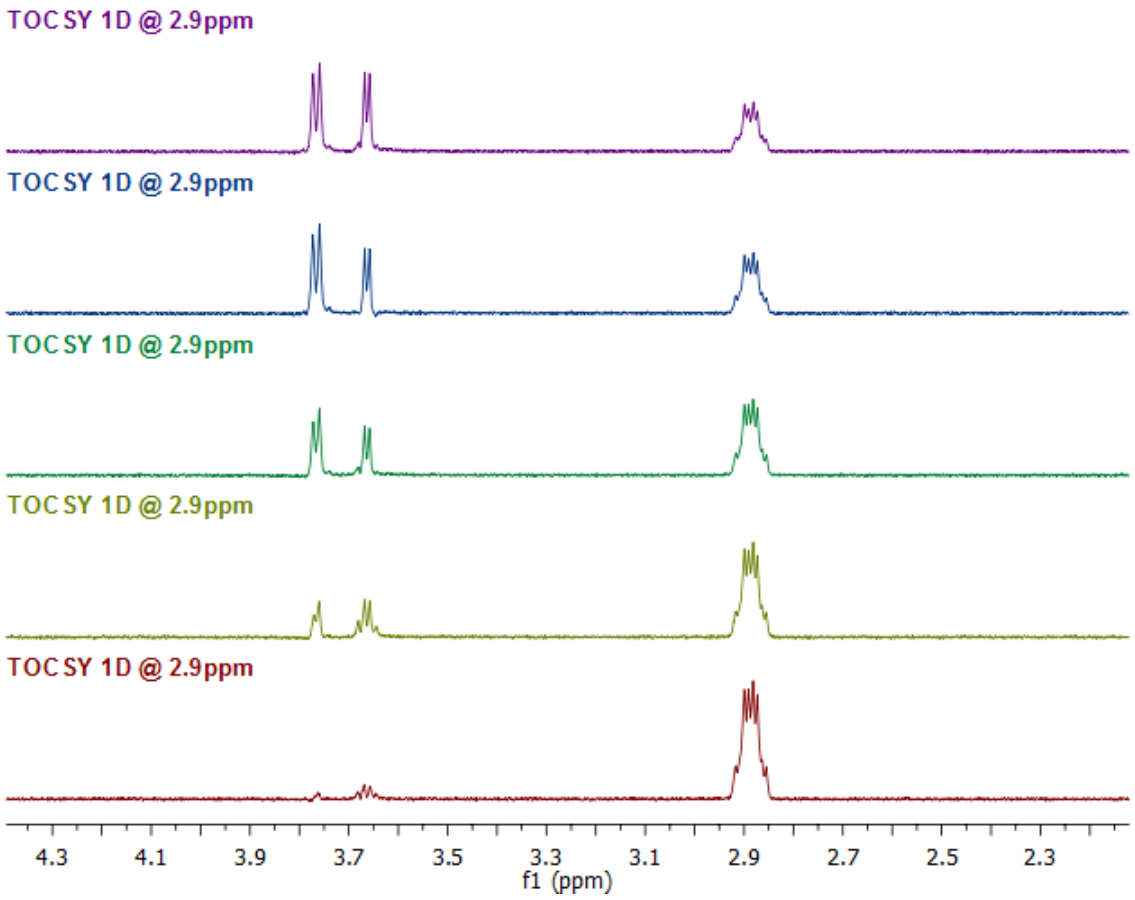


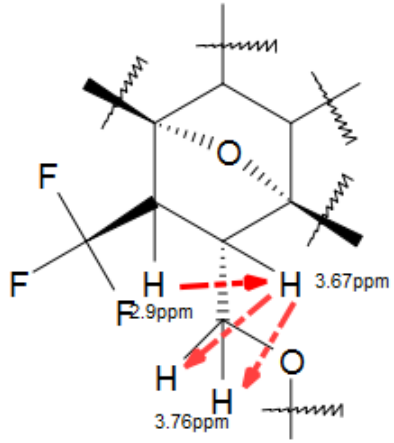




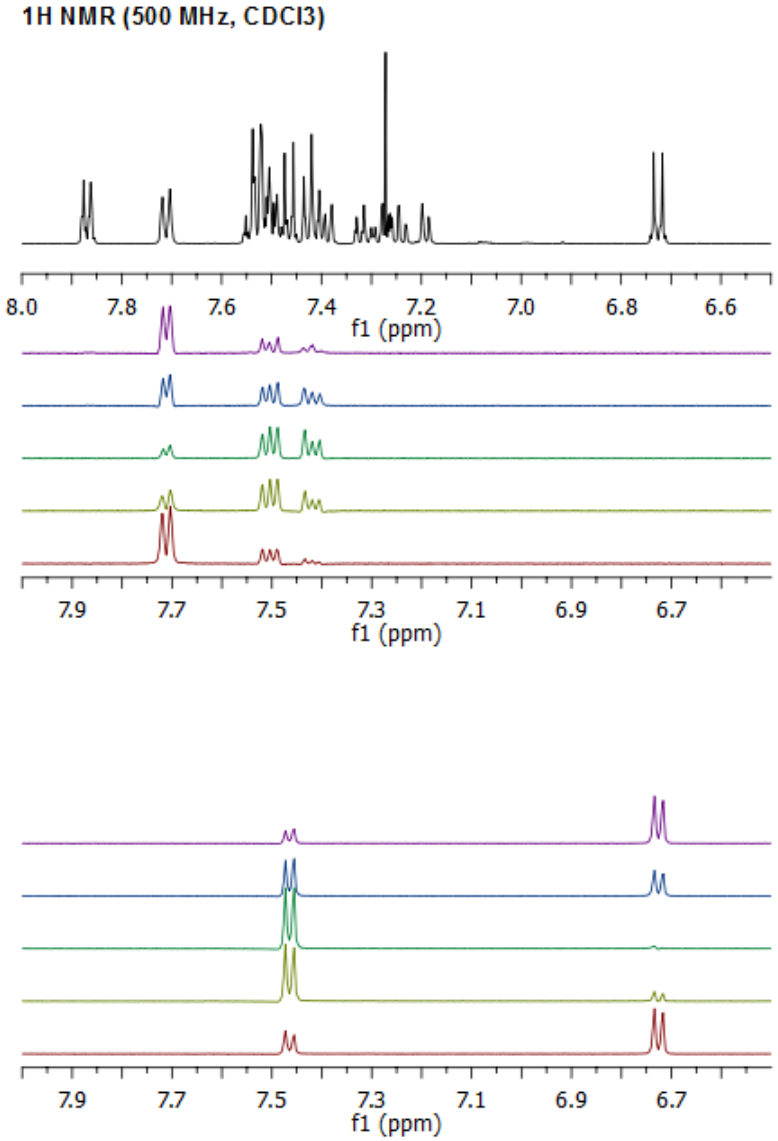


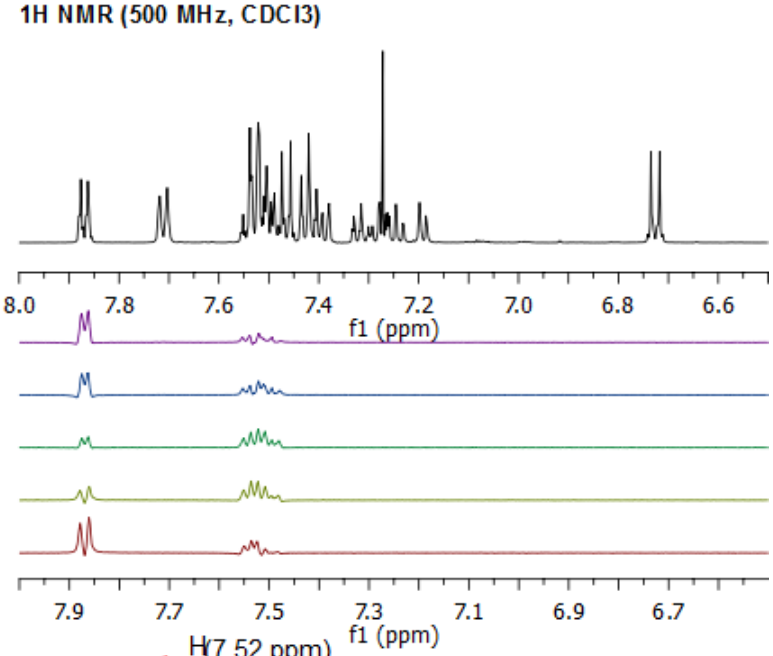
Aliphatic assignment

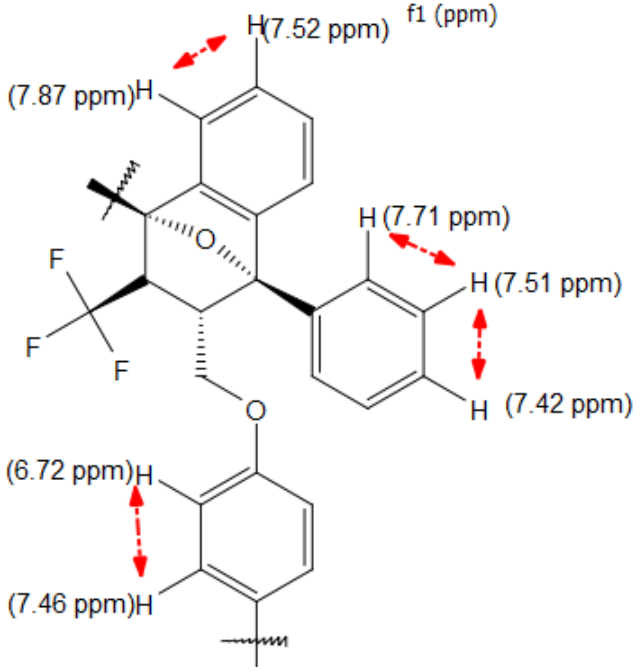




Aromatic assignment

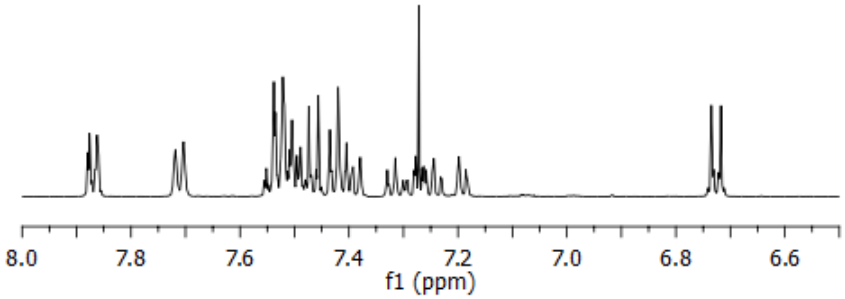




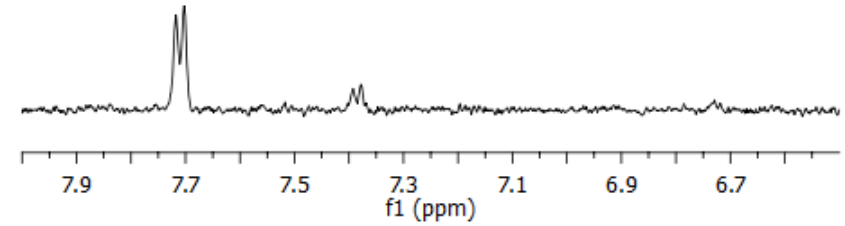


NOESY study

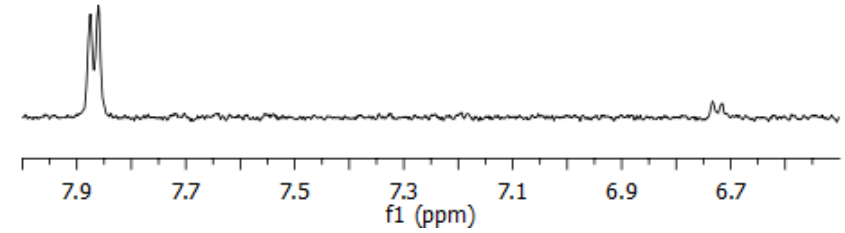
1H NMR (500 MHz, CDCl3)

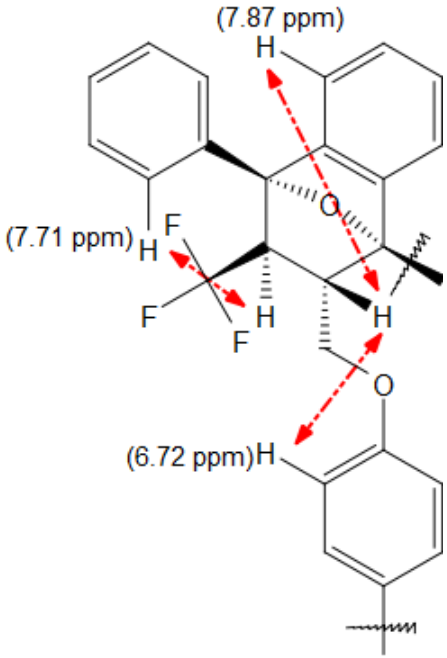


NOE SY 1D @ 2.88ppm



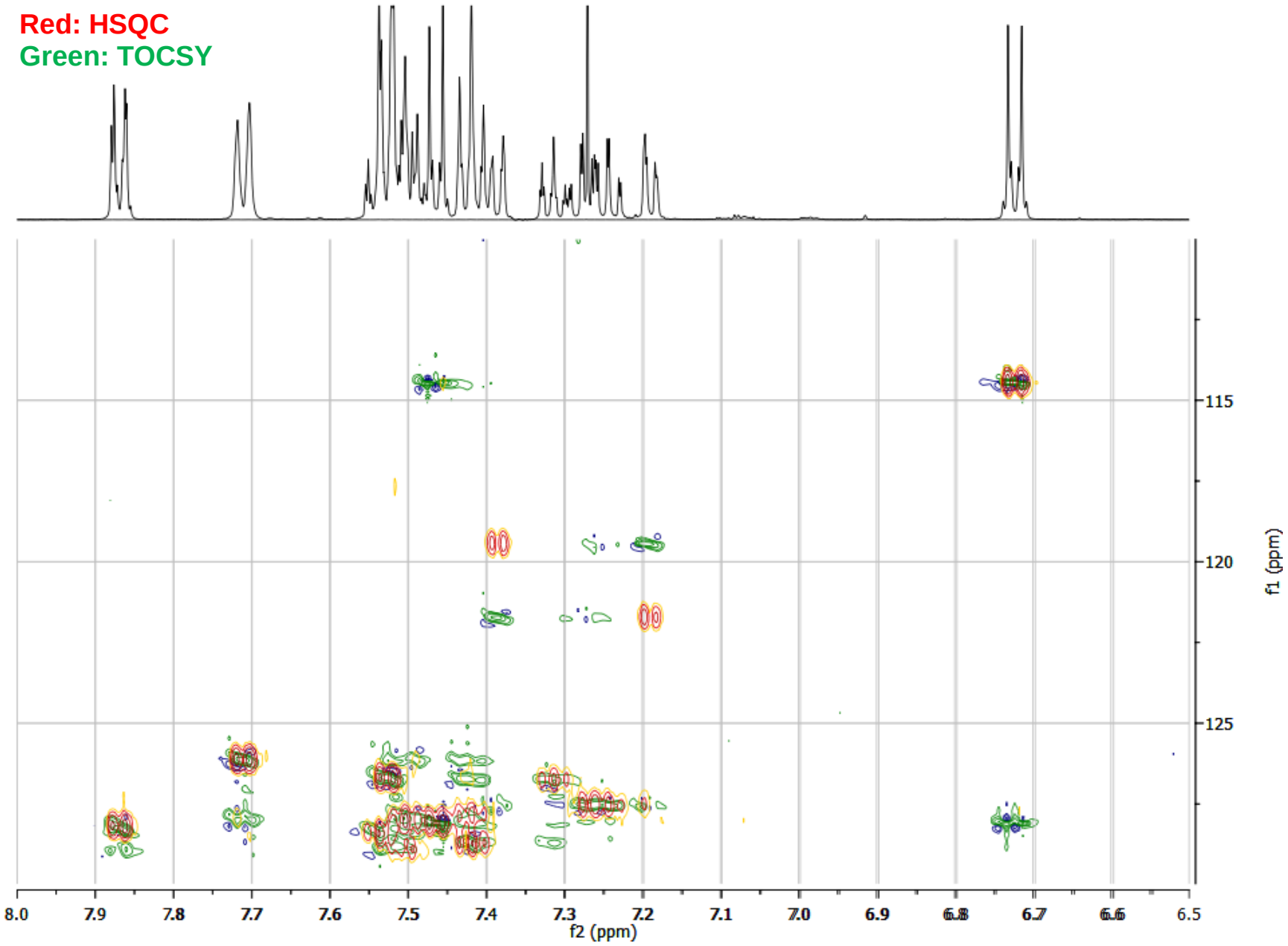
NOE SY 1D @ 3.66ppm



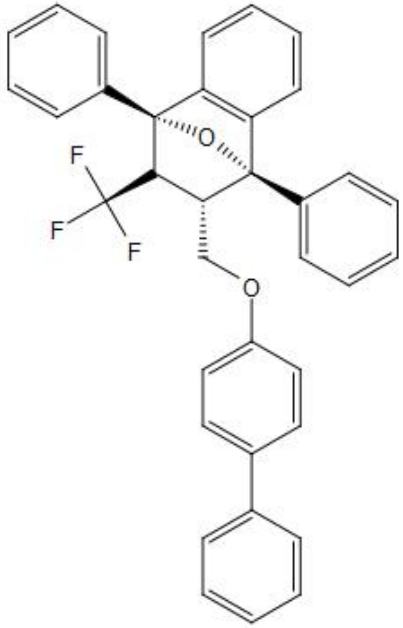


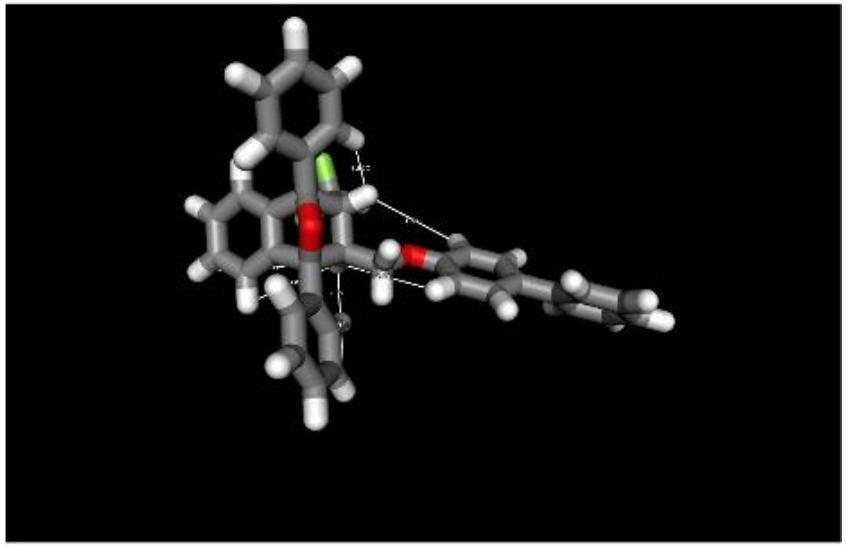
Superimposed HSQC et TOCSY aromatic region

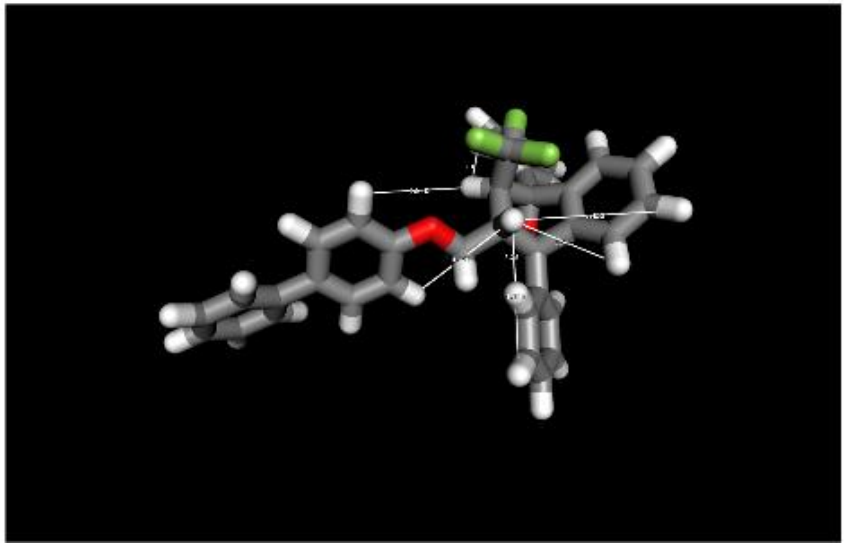
Red: HSQC
Green: TOCSY

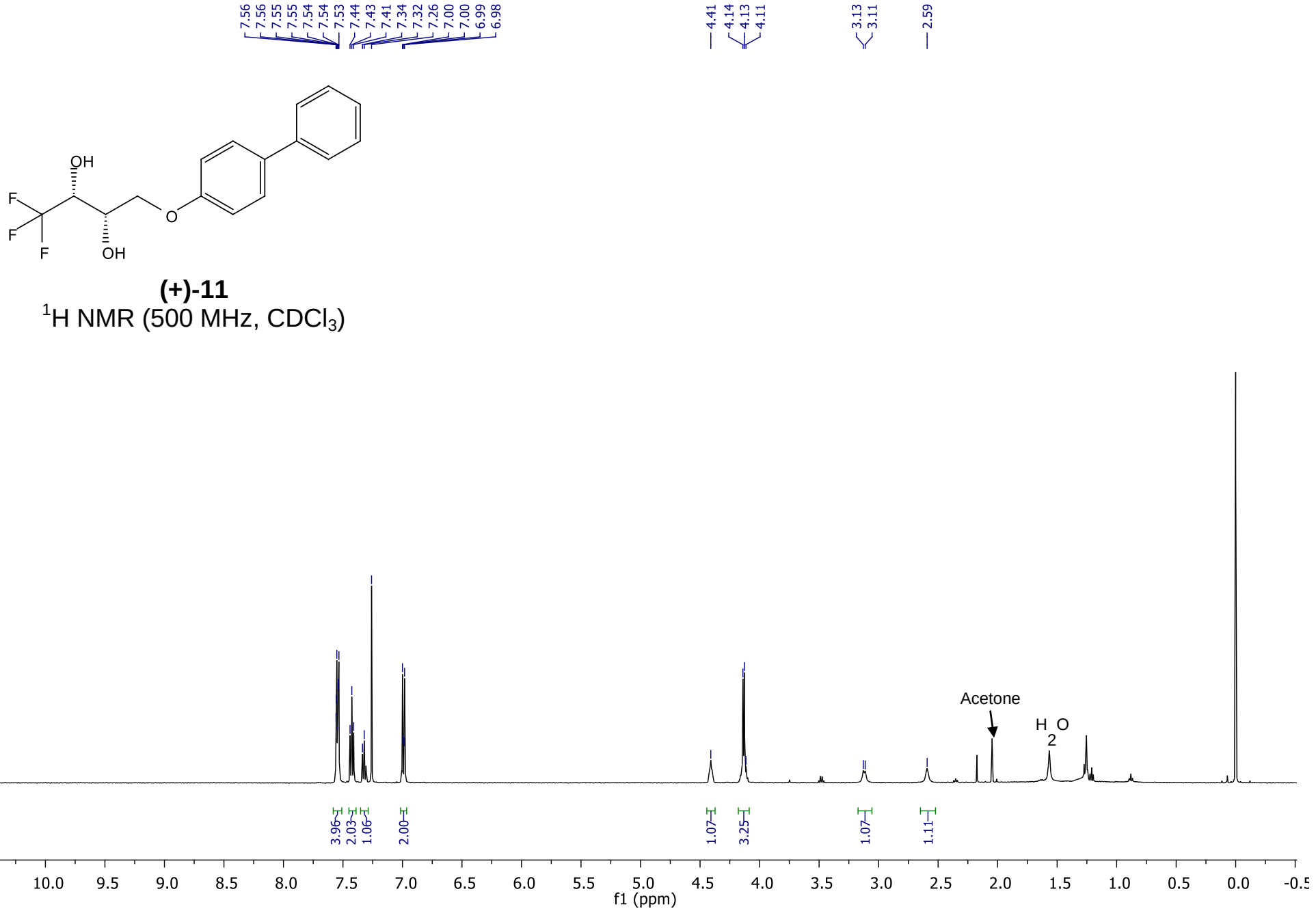


Proposed structure



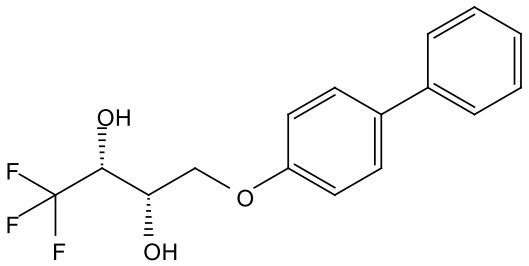






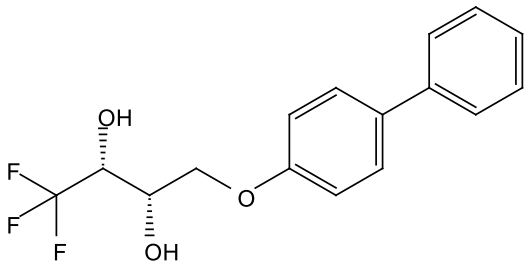
(+)-11

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



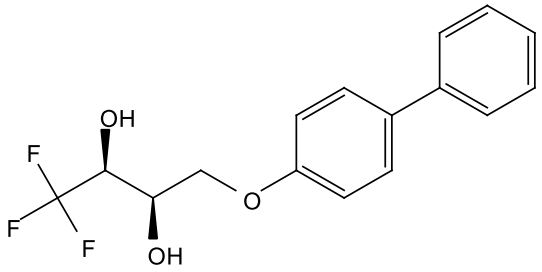
(+)-11

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



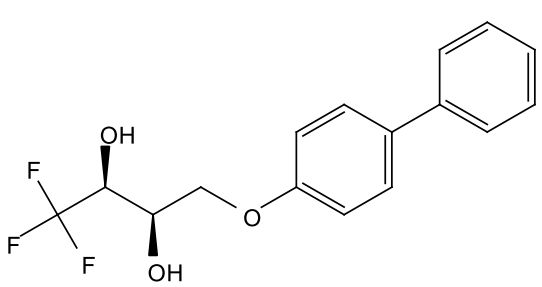
(+)-11

^{19}F NMR (470 MHz, $CDCl_3$)



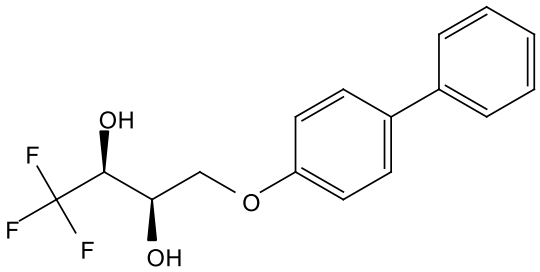
(-)-11

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



(-)-11

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



(-)-11

^{19}F NMR (470 MHz, $CDCl_3$)