Supporting Information

Synthesis of Enantioenriched Spirocyclic 2-Arylpiperidines *via* Kinetic Resolution

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Contents

1. General information

Reagents were obtained from commercial suppliers and were used without further purification or after distillation; *n*-BuLi was titrated before use. Solvents were obtained from a Grubbs dry solvent system. 2-Aryl-4-methylenepiperidines **1a–f** were synthesised using previously reported methods.[1] Thin layer chromatography was performed on Merck silica gel 60F254 plates and visualised by UV irradiation at 254 nm or by staining with an alkaline KMnO4 dip. Flash column chromatography was performed using DAVISIL or Geduran silica gel (40-63 micron mesh). Melting points were recorded on a Gallenkamp hot stage and were uncorrected. InfraRed spectra were recorded on a Perkin Elmer Spectrum RX Fourier Transform – IR System and only selected peaks are reported. ^{1}H NMR spectra were recorded on a Bruker AC400 (400 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J values) are quoted to the nearest 0.5 Hz with values in Hertz (Hz). ^{13}C NMR spectra were recorded on the above instrument at 100 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Walters LCT instrument for Electro–Spray (ES).

Intensity data for X-ray crystal structures were collected at 100 K on a Bruker D8 Venture diffractometer using a Cu Kα microfocus X-ray source. Suitable crystals were mounted on a MiTiGen microloop using fomblin oil and transferred directly to the cold nitrogen stream at 100 K for data collection on a Bruker D8 VENTURE diffractometer equipped with an Oxford 700+ cryostream, a PHOTON 100 CMOS detector and using Cu-Kα micro-focus X-ray source. Intensity data was collected in shutterless mode with a final fast scan collected at lower incident beam intensity to enable correction for any detector saturation for low-angle data. Data reduction was performed using the Bruker Apex3 software.[2] Intensity data were corrected for absorption using empirical methods (SADABS) based upon symmetry equivalent

reflections combined with measurements at different azimuthal angles.[3] The crystal structure was solved using ShelXT[4] and refined against all F^2 values using the SHELXL[5] accessed via the Olex2 program.[6] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with idealized geometries and then refined by employing a riding model and isotropic displacement parameters.

All calculations were performed using density functional theory, employing the B3LYP[7] functional as implemented in the D.01 version of Gaussian 09.[8] Calculations included dispersion corrections using the GD3-BJ[9] method. Calculations used the def2TZVP[10] basis set. Solvent was included via the PCM method[11] as implemented in Gaussian with the default parameters for THF.

2. General procedures

2.1 General procedure A: Synthesis of difluoro spiropiperidines 2a–f

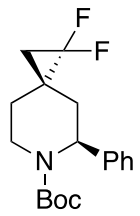
To a solution of 2-aryl-4-methylene-piperidine[1] (1 eq) in THF (0.5 M) was added NaI (0.36 eq) followed by the dropwise addition of $TMSCF_3$ (7 eq). The mixture was heated under reflux for 16 h and then was cooled to room temperature. The solvent was evaporated to give the crude product which was purified by column chromatography on silica gel to give the spiropiperidine.

2.2 General procedure B: Racemic lithiation–trapping of spiropiperidines

To a solution of the spiropiperidine (1 eq) in THF (0.25 M) under an argon atmosphere was added *n*-BuLi (1.2 eq, 2.0**–**2.4 M in hexanes) at –40 °C or –78 °C. After 10 min the electrophile (1.2**–**3.5 eq) was added and the mixture was warmed to room temperature over 16 h. MeOH (1 mL) was added and the solvent was evaporated to give the crude product.

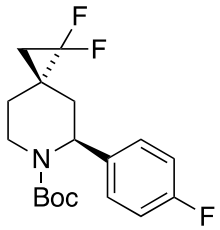
3. Preparation of Spiropiperidines 2a–f, 5, 8

(±)-*tert*-Butyl 1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-6-carboxylate **2a**



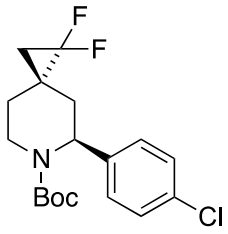
Using general procedure A, piperidine **1a** (800 mg, 2.93 mmol), NaI (158 mg, 1.05 mmol) and $TMSCF_3$ (3 mL, 21 mmol) in THF (6 mL) gave, after purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), the spiropiperidine **2a** (796 mg, 84%) as a white amorphous solid; mp 55–57 °C (petrol−EtOAc); R_f 0.47 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1687 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.29 (m, 2H), 7.25–7.14 (m, 3H), 5.49 (br s, 1H), 4.24 (br d, *J* = 13.0 Hz, 1H), 3.15 (td, *J* = 13.0, 3.5 Hz, 1H), 2.25 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.09 (br d, *J* = 14.5 Hz, 1H), 1.94 (td, *J* = 13.0, 5.0 Hz, 1H), 1.42 (s, 9H), 1.30 (br d, *J* = 13.0 Hz, 1H), 0.94–0.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 155.5, 140.3, 128.5, 126.6, 125.9, 114.8 (t, *J* = 287.5 Hz), 80.2, 53.4, 38.4, 31.1 (d, *J* = 5.0 Hz), 28.3, 28.2 (d, *J* = 5.5 Hz), 24.4 (t, *J* = 10.5 Hz), 21.7 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –139.67 (dd, J = 157.0, 12.5 Hz), –141.85 (dd, J = 157.0, 12.5 Hz); HRMS *m/z* (ES) Found: MNa^+ 346.1598. $C_{18}H_{23}F_2NO_2Na$ requires MNa^+ 346.1590; LRMS *m/z* (ES) 224 (20%), 268 (100%), 269 (25%), 346 (25%, MNa^+). Resolution between the enantiomers of spiropiperidine **2a** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 6.9 min and 8.4 min.

(±)-*tert*-Butyl 5-(4-Fluorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate **2b**



Using general procedure A, piperidine **1b** (460 mg, 1.58 mmol), NaI (85 mg, 0.57 mmol) and $TMSCF_3$ (1.6 mL, 11 mmol) in THF (3.2 mL) gave, after purification by column chromatography on silica gel, eluting with hexane−EtOAc (93:7), the spiropiperidine **2b** (455 mg, 84%) as a white amorphous solid; mp 41–43 °C (hexane−EtOAc); R_f 0.46 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1686 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.20–7.09 (m, 2H), 7.07–6.97 (m, 2H), 5.44 (br s, 1H), 4.22 (br d, *J* = 13.0 Hz, 1H), 3.12 (td, *J* = 13.0, 3.5 Hz, 1H), 2.24 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.03 (br d, *J* = 14.5 Hz, 1H), 1.94 (td, *J* = 13.0, 5.0 Hz, 1H), 1.42 (s, 9H), 1.31 (br d, *J* = 13.0 Hz, 1H), 0.96–0.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.6 (d, *J* = 245.0 Hz), 155.4, 136.1, 127.4 (d, *J* = 8.0 Hz), 115.4 (d, *J* = 21.5 Hz), 114.7 (t, *J* = 287.0 Hz), 80.3, 53.0, 38.4, 31.3 (d, *J* = 5.0 Hz), 28.3, 28.1 (d, *J* = 5.5 Hz), 24.2 (t, *J* = 11.0 Hz), 21.7 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –116.57 (s), –139.69 (dd, *J* = 157.5, 12.5 Hz), –141.86 (dd, *J* = 157.5, 12.5 Hz); HRMS *m/z* (ES) Found: MNa^+ 364.1494. $C_{18}H_{22}F_3NO_2Na$ requires MNa^+ 364.1495; LRMS *m/z* (ES) 222 (15%), 242 (45%), 286 (100%), 287 (45%), 364 (45%, MNa^+). Resolution between the enantiomers of spiropiperidine **2b** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 7.5 min and 9.1 min.

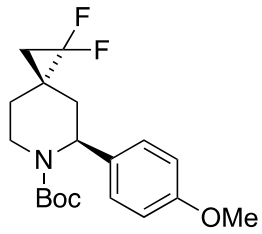
(±)-*tert*-Butyl 5-(4-Chlorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate **2c**



Using general procedure A, piperidine **1c** (4.4 g, 14 mmol), NaI (0.77 g, 5.2 mmol) and $TMSCF_3$ (14.8 mL, 100 mmol) in THF (29 mL) gave, after purification by column chromatography on silica gel, eluting with petrol−EtOAc (93:7) the spiropiperidine **2c** (3.6 g, 70%) as a white amorphous solid; mp 66–68 °C (petrol−EtOAc); R_f 0.52 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1691 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 5.43 (br s, 1H), 4.23 (br d, *J* = 13.0 Hz, 1H), 3.10 (td, *J* = 13.0, 3.5 Hz, 1H), 2.24 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.03 (br d, *J* = 14.5 Hz,

1H), 1.93 (td, *J* = 13.0, 5.0 Hz, 1H), 1.42 (s, 9H), 1.31 (br d, *J* = 13.0 Hz, 1H), 0.95–0.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C-F couplings not observed) δ = 155.3, 139.1, 132.4, 128.7, 127.3, 114.6, 80.4, 53.1, 38.4, 31.1, 28.3, 28.0, 24.3, 21.7 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –139.65 (dd, *J* = 157.5, 12.5 Hz), –141.87 (dd, *J* = 157.5, 12.5 Hz); HRMS *m/z* (ES) Found: MNa^+ 380.1220. $C_{18}H_{22}F_2{}^{35}ClNO_2Na$ requires MNa^+ 380.1200; MNa^+ 382.1190. $C_{18}H_{22}F_2{}^{37}ClNO_2Na$ requires MNa^+ 382.1170; LRMS *m/z* (ES) 258 (20%) 302 (100%), 304 (35%), 380 (25%, MNa^+ for ^{35}Cl), 382 (10%, MNa^+ for ^{37}Cl). Resolution between the enantiomers of spiropiperidine **2c** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 6.9 min and 8.3 min.

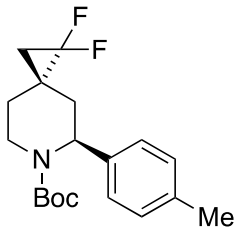
(±)-*tert*-Butyl 5-(4-Methoxyphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate **2d**



Using general procedure A, piperidine **1d** (356 mg, 1.17 mmol), NaI (63 mg, 0.42 mmol) and $TMSCF_3$ (1.2 mL, 8.2 mmol) in THF (2.3 mL) gave, after purification by column chromatography on silica gel, eluting with petrol−EtOAc (85:15), the spiropiperidine **2d** (0.4 g, 97%) as a white amorphous solid; mp 51–53 °C (petrol−EtOAc); R_f 0.45 [petrol−EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 1689 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.08 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.44 (br s, 1H), 4.21 (br d, *J* = 13.0 Hz, 1H), 3.80 (s, 3H), 3.11 (td, *J* = 13.0, 3.5 Hz, 1H), 2.22 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.04 (br d, *J* = 14.5 Hz, 1H), 1.92 (td, *J* = 13.0, 5.0 Hz, 1H), 1.43 (s, 9H), 1.28 (br d, *J* = 13.0 Hz, 1H), 0.95–0.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 158.2, 155.5, 132.1, 127.0, 114.8 (t, *J* = 289.5 Hz), 113.9, 80.1, 55.3, 52.9, 38.2, 31.0 (d, *J* = 5.0 Hz), 28.4, 28.3 (d, *J* = 5.0 Hz), 24.4 (t, *J* = 11.0 Hz), 21.8 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –139.64 (dd, *J* = 157.5, 12.5 Hz), –141.91 (dd, *J* = 157.5, 12.5 Hz); HRMS *m/z* (ES) Found: MNa^+ 376.1692. $C_{19}H_{25}F_2NO_3Na$ requires MNa^+ 376.1695; LRMS *m/z* (ES) 190 (100%), 254 (80%), 298 (90%), 376 (75%, MNa^+). Resolution between the enantiomers of

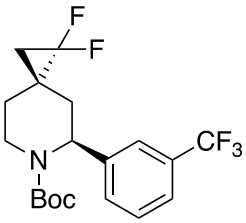
spiropiperidine **2d** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 11.3 min and 13.2 min.

(±)-*tert*-Butyl 5-(4-Methylphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate **2e**



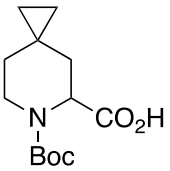
Using general procedure A, piperidine **1e** (536 mg, 1.86 mmol), NaI (100 mg, 0.67 mmol) and $TMSCF_3$ (1.9 mL, 13 mmol) in THF (3.7 mL) gave, after purification by column chromatography on silica gel, eluting with petrol−EtOAc (92:8), the spiropiperidine **2e** (0.58 g, 92%) as a clear oil; R_f 0.43 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1692 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.13 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 5.46 (br s, 1H), 4.22 (br d, *J* = 13.0 Hz, 1H), 3.11 (td, *J* = 13.0, 3.5 Hz, 1H), 2.33 (s, 3H), 2.23 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.07 (br d, *J* = 14.5 Hz, 1H), 1.92 (td, *J* = 13.0, 5.0 Hz, 1H), 1.43 (s, 9H), 1.28 (br d, *J* = 13.0 Hz, 1H), 0.95–0.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 155.5, 137.0, 136.1, 129.2, 125.8, 114.9 (t, *J* = 287.0 Hz), 80.1, 53.2, 38.3, 30.9 (d, *J* = 5.0 Hz), 28.4, 28.3 (d, *J* = 5.0 Hz), 24.4 (t, *J* = 11.0 Hz), 21.8 (t, *J* = 10.0 Hz), 20.9; ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –139.65 (dd, *J* = 157.5, 14.5 Hz), –141.90 (dd, *J* = 157.5, 14.5 Hz); HRMS *m/z* (ES) Found: MNa^+ 360.1761. $C_{19}H_{25}F_2NO_2Na$ requires MNa^+ 360.1746; LRMS *m/z* (ES) 282 (100%), 283 (20%), 360 (20%, MNa^+). Resolution between the enantiomers of spiropiperidine **2e** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 7.6 min and 9.1 min.

(±)-*tert*-Butyl 1,1-Difluoro-5-(3-(trifluoromethyl)phenyl)-6-azaspiro[2.5]octane-6-carboxylate **2f**



Using general procedure A, piperidine **1f** (583 mg, 1.49 mmol), NaI (80 mg, 0.54 mmol) and $TMSCF_3$ (1.5 mL, 10 mmol) in THF (3 mL) gave, after purification by column chromatography on silica gel, eluting with petrol−EtOAc (93:7), the spiropiperidine **2f** (0.56 g, 95%) as a clear oil; R_f 0.40 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1693 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.58–7.34 (m, 4H), 5.47 (br s, 1H), 4.24 (br d, *J* = 13.5 Hz, 1H), 3.21–3.06 (m, 1H), 2.28 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.08 (br d, *J* = 14.5 Hz, 1H), 1.96 (td, *J* = 13.5, 5.0 Hz, 1H), 1.42 (s, 9H), 1.35 (br d, *J* = 13.5 Hz, 1H), 0.99–0.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, no coupling observed for CF_3 quaternary carbon) δ = 155.3, 142.0, 131.0 (q, *J* = 32.5 Hz), 129.3, 129.1, 125.4, 123.8 – 123.5 (m), 122.8 – 122.6 (m), 114.5 (t, *J* = 287.0 Hz), 80.6, 53.5, 38.6, 31.2 (d, *J* = 5.0 Hz), 28.3, 27.9 (d, *J* = 5.5 Hz), 24.1 (t, *J* = 11.0 Hz), 21.7 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –62.67 (s), –139.74 (dd, *J* = 157.5, 12.5 Hz), –141.74 (dd, *J* = 157.5, 12.5 Hz); HRMS *m/z* (ES) Found: MNa^+ 414.1454. $C_{19}H_{22}F_5NO_2Na$ requires MNa^+ 414.1463; LRMS *m/z* (ES) 292 (60%), 336 (100%), 337 (30%), 414 (30%, MNa^+). Resolution between the enantiomers of spiropiperidine **2f** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 5.6 min and 6.2 min.

(±)-6-*tert*-Butyl 6-Azaspiro[2.5]octane-5,6-dicarboxylate **4**



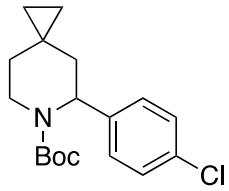
Following a related method,[12] *N*-Boc-4-methylenepiperidine **3**[13] (5 g, 25.3 mmol), benzyltriethylammonium chloride (560 mg, 2.5 mmol) and $CHCl_3$ (70 mL) were heated to 50 °C then

NaOH (10 g, 250 mmol) in water (20 mL) was dropwise. After 3 h, the mixture was cooled to room temperature. After 16 h, $CHCl_3$ (150 mL) and water (150 mL) were added and the organic phase was separated, washed with water (200 mL), brine (200 mL) and dried ($MgSO_4$). The solvent was evaporated to give the dichlorocyclopropane product (6.0 g, 85%) as a white solid; m.p. 70–72 °C. This was used directly in the next step.

The dichlorospiropiperidine (3.5 g, 12.5 mmol) in *tert*-butanol (100 mL) and Et_2O (200 mL) was heated under reflux. Li granules (800 mg, 700 mmol) were added to the mixture portionwise over 48 h. Water was added and the mixture was extracted with Et_2O (3 x 100 mL). The organic layers were washed with water (200 mL), brine (150 mL) and were dried ($MgSO_4$). The solvent was evaporated and the mixture was purified by column chromatography on silica gel, eluting with hexane–EtOAc (9:1), to give the spiropiperidine (2.4 g, 92%) as an oil; R_f 0.7 [hexane–EtOAc (9:1)]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.45 (t, 4H, *J* = 4 Hz), 1.49 (s, 9H), 1.34 (t, 4H, *J* = 4 Hz), 0.34 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 79.2, 43.6, 34.9, 28.4, 17.6, 11.3; ^{1}H NMR data as reported.[14]

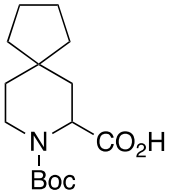
sec-BuLi (24 mL, 13.6 mmol) was added to the spiropiperidine (2.4 g, 11.4 mmol) and TMEDA (7 mL, 45.4 mmol) in Et_2O (60 mL) at –40 °C. After 3 h, dry CO_2 was added (prepared[15] from 100 g dry ice crushed in a mortar and pestle under a continuous flow of nitrogen and mixed into anhydrous THF under nitrogen and filtered). The mixture was allowed to warm to room temperature. After 1 h, the solvent was evaporated, water (150 mL) was added, and the mixture was adjusted to pH to 2 by adding aqueous HCl (1 M). The mixture was extracted with EtOAc (3 x 50 mL), washed with brine (100 mL) and dried ($MgSO_4$) to give the carboxylic acid **4** (1.6 g, 56%) as a white solid; m.p. 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ~1:1 mixture of rotamers) δ = 8.50 (br s, 1H), 4.97 (br s, 0.5H), 4.79 (br s, 0.5H), 4.06 (br d, 0.5H, *J* = 12 Hz), 3.96 (br d, 0.5H, *J* = 12 Hz), 3.26–3.15 (m, 1H), 2.20 (dd, 1H, *J* = 12, 4 Hz), 1.92 (td, 1H, *J* = 12 Hz, 4 Hz), 1.60–1.58 (m, 1H), 1.49 (s, 9H), 0.88–0.79 (m, 1H), 0.43–0.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 178.2, 178.1, 156.1, 155.6, 80.4, 54.7, 53.6, 41.3, 40.4, 35.0, 34.1, 33.8, 29.7, 28.3, 22.7, 15.2, 14.1, 10.8, 10.5; HRMS *m/z* (ES) Found: [MH^+ – Boc] 156.1028. $C_8H_{14}NO_2$ requires MH^+ – Boc 156.1025; ^{1}H NMR data as reported.[16]

(±)-*tert*-Butyl 5-(4-Chlorophenyl)-6-azaspiro[2.5]octane-6-carboxylate **5**



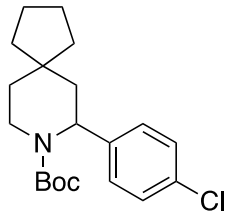
The carboxylic acid **4** (510 mg, 2 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (15 mg, 14 μmol), 1-chloro-4-iodobenzene (806 mg, 3.3 mmol), nickel(II)chloride·glyme (30 mg, 0.14 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (54 mg, 0.20 mmol), cesium carbonate (655 mg, 2.0 mmol) in DMF (50 mL) were degassed (freeze pump thaw with liquid nitrogen). The mixture was irradiated with a blue LED (34 W, 460 nm) with a cooling fan. After 24 h, saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography on silica gel, eluting with hexane–EtOAc (9:1), gave the carbamate **5** (398 mg, 62%) as an oil; R_f 0.8 [hexane–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2976, 2931, 1687, 1491, 1409, 1391, 1152, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30–7.27 (m, 2H), 7.15–7.13 (m, 2H), 5.38 (br d, 1H, *J* = 5 Hz), 4.16 (ddd, 1H, *J* = 13, 5, 1 Hz), 3.08 (td, 1H, *J* = 13, 5 Hz), 2.32 (ddd, 1H, *J* = 13, 5, 1 Hz), 1.94 (tdd, 1H, *J* = 13, 5, 1 Hz), 1.60–1.55 (m, 1H), 1.44 (s, 9H), 0.88–0.85 (m, 1H), 0.30–0.22 (m, 2H), 0.18–0.14 (m, 1H), 0.09–0.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 140.2, 131.8, 128.3, 127.5, 79.8, 53.9, 39.9, 37.7, 34.5, 28.3, 14.2, 12.7, 10.5; HRMS *m/z* (ES) Found: MH^+–C_4H_8 266.0954. $C_{14}H_{17}{}^{35}ClNO_2$ requires MH^+–C_4H_8 266.0948. The enantiomers were resolved using a Beckman system fitted with a Lux Cellulose–2 column (250 mm x 4.6 mm i.d.) as the stationary phase with a mixture of n-hexane–isopropanol (95:5 v/v) as the mobile phase at a flow rate of 0.8 mL/min; room temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 20 mg in 1 mL of the eluent. Retention times 17.6 and 19.8 min.

(±)-8-*tert*-Butyl 8-Azaspiro[4.5]decane-7,8-dicarboxylate **7**



8-Azaspiro[4.5]decane-7,9-dione (5 g, 30 mmol) in THF (100 mL) was added slowly to a suspension of $LiAlH_4$ (6 g, 150 mmol) in THF (200 mL) at 0 °C.[17] After 15 min, the mixture was warmed to room temperature and was then heated under reflux. After 16 h, the mixture was cooled 0 °C and was quenched with water and aqueous NaOH. The white solid formed was filtered and the mixture was extracted with EtOAc (3 x 200 mL), washed with water (200 mL), brine (200 mL) and dried ($MgSO_4$). The solvent was evaporated, the crude product was dissolved in THF (200 mL) and was cooled to 0 °C. Boc_2O (4.0 g, 18.3 mmol) was added, the mixture was stirred for 16 h then the solvent was evaporated. The mixture was dissolved in EtOAc (250 mL), washed with water (200 mL), brine (200 mL) and was dried ($MgSO_4$). Purification by column chromatography on silica gel, eluting with hexane–EtOAc (4:1), gave the spiropiperidine **6** (3 g, 42%) as an oil; R_f 0.8 [hexane–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1738, 1438, 1365, 1231, 1216, 1208, 800; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.38 (t, 4H, *J* = 4 Hz), 1.65–1.62 (m, 4H), 1.47 (s, 9H), 1.46–1.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 79.1, 42.2, 41.0, 37.6, 37.3, 28.5, 24.2. sec-BuLi (8.3 mL, 10.0 mmol, 1.2 M in cyclohexane) was added to the spiropiperidine **6** (2.0 g, 8.4 mmol) and TMEDA (5 mL, 33 mmol) in Et_2O (35 mL) at –40 °C. After 3 h, dry CO_2 was added (prepared[15] from 60 g dry ice crushed in a mortar and pestle under a continuous flow of nitrogen and mixed into anhydrous THF under nitrogen and filtered). The mixture was allowed to warm to room temperature. After 1 h, the solvent was evaporated, water (100 mL) was added, and the mixture was adjusted to pH to 2 by adding aqueous HCl (2 M). The mixture was extracted with EtOAc (3 x 50 mL) and the solvent was dried ($MgSO_4$) to give the carboxylic acid **7** (2.0 g, 86%) as a white solid; m.p. 99–101 °C; FT-IR ν_{max} (film)/cm^{-1} 2950, 2871, 1738, 1697, 1394, 1366, 1253, 1140, 951, 773; ^{1}H NMR (400 MHz, $CDCl_3$, ~1:1 mixture of rotamers) δ = 8.95 (br s, 1H), 4.83 (br s, 0.5H), 4.66 (br s, 0.5H), 3.90 (br s, 1H), 3.13 (br s, 1H), 2.13–2.10 (m, 1H), 1.85–1.79 (m, 1H), 1.68–1.60 (m, 4H), 1.46–1.27 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 179.2, 179.0, 156.0, 155.6, 80.2, 53.8, 52.7, 41.6, 40.4, 39.5, 38.5, 37.3, 35.5, 33.0, 28.3, 24.5, 22.9; HRMS *m/z* (ES) Found: [MH^+ – Boc] 184.1329. $C_{10}H_{18}NO_2$ requires MH^+ – Boc 184.1338.

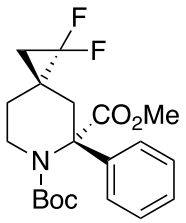
(±)-*tert*-Butyl 7-(4-Chlorophenyl)-8-azaspiro[4.5]decane-8-carboxylate **8**



The carboxylic acid **7** (566 mg, 2 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (15 mg, 14 μmol), 1-chloro-4-iodobenzene (806 mg, 3.3 mmol), nickel(II)chloride·glyme (30 mg, 0.14 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (54 mg, 0.20 mmol), cesium carbonate (655 mg, 2.0 mmol) in DMF (50 mL) were degassed (freeze pump thaw with liquid nitrogen). The mixture was irradiated with a blue LED (34 W, 460 nm) with a cooling fan. After 24 h, saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography on silica gel, eluting with hexane–EtOAc (9:1), gave the carbamate **8** (405 mg, 58%) as an oil; R_f 0.7 [hexane–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2936, 2868, 1692, 1491, 1421, 770 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, 2H, *J* = 8 Hz), 7.11 (d, 2H, *J* = 8 Hz), 5.22 (t, 1H, *J* = 4 Hz), 4.10 (dt, 1H, *J* = 13, 4 Hz), 3.39–3.36 (m, 1H), 3.10 (ddd, 1H, *J* = 13, 11.5, 4 Hz), 2.05–2.00 (m, 1H), 1.93 (dd, 1H, *J* = 14, 4 Hz), 1.64–1.61 (m, 1H), 1.55–1.50 (m, 3H), 1.43–1.41 (m, 3H), 1.39 (s, 9H), 1.09–0.03 (m, 1H), 0.97–0.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 141.3, 131.7, 128.4, 126.8, 79.7, 53.3, 41.5, 40.6, 38.4, 37.5, 35.7, 28.3, 24.2, 24.1, 22.6; HRMS *m/z* (ES) Found: MH$^+$–^{t}Bu 294.1266. $C_{16}H_{21}{}^{35}ClNO_2$ requires MH$^+$–^{t}Bu 294.1261. The enantiomers were resolved using a Beckman system fitted with a Lux Amylose–2 column (250 mm x 4.6 mm i.d.) as the stationary phase with a mixture of n-hexane–isopropanol (95:5 v/v) as the mobile phase at a flow rate of 0.8 mL/min; room temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 20 mg in 1 mL of the eluent. Retention times 7.08 and 7.93 min.

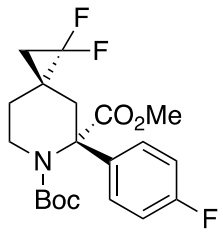
4. Preparation of racemic disubstituted products

(±)-6-*tert*-Butyl 5-Methyl 1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-5,6-dicarboxylate **9a**



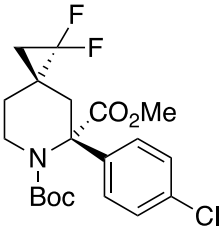
Using general procedure B, *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and spiropiperidine **2a** (100 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and MeOCOCl (0.08 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with pentane−EtOAc (9:1), the carbamate **9a** (100 mg, 85%) as an oil; R_f 0.39 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1746, 1694; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.29–7.22 (m, 1H), 4.07 (dt, *J* = 13.5, 5.5 Hz, 1H), 3.76 (s, 3H), 3.69–3.52 (m, 1H), 2.45 (br d, *J* = 14.5 Hz, 1H), 2.25–2.10 (m, 2H), 1.54–1.48 (m, 1H), 1.28 (br s, 9H), 0.84–0.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 172.5, 155.3, 127.7, 127.1, 127.0, 114.2 (t, *J* = 288.0 Hz), 81.1, 66.7, 52.5, 39.9, 28.0, 26.9, 22.5 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –138.13 – –141.05 (m); HRMS *m/z* (ES) Found: MNa^+ 404.1658. $C_{20}H_{25}F_2NO_4Na$ requires MNa^+ 404.1644; LRMS *m/z* (ES) 282 (100%), 283 (60%), 373 (15%), 401 (30%), 404 (95%, MNa^+). Resolution between the enantiomers of carbamate **9a** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 11.5 min and 16.0 min.

(±)-6-(*tert*-Butyl) 5-Methyl 5-(4-Fluorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate **9b**



Using general procedure B, *n*-BuLi (0.17 mL, 0.37 mmol, 2.2 M in hexanes) and spiropiperidine **2b** (105 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and MeOCOCl (0.08 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with hexane−EtOAc (92:8), the carbamate **9b** (111 mg, 90%) as a white amorphous solid; mp 92–94 °C (hexane−EtOAc); R_f 0.38 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1747, 1696; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.50–7.34 (m, 2H), 7.07–6.97 (m, 2H), 4.05 (dt, *J* = 13.5, 5.5 Hz, 1H), 3.76 (s, 3H), 3.66–3.52 (m, 1H), 2.42 (br d, *J* = 14.5 Hz, 1H), 2.25–2.14 (m, 1H), 2.10 (br d, *J* = 14.5 Hz, 1H), 1.54–1.46 (m, 1H), 1.28 (br s, 9H), 0.89–0.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 172.5, 161.9 (d, *J* = 246.0 Hz), 155.1, 128.7 (d, *J* = 7.5 Hz), 114.5 (d, *J* = 21.5 Hz), 114.1 (t, *J* = 288.0 Hz), 81.3, 66.2, 52.6, 39.8, 28.0, 26.8, 22.6 (t, *J* = 9.5 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –115.96 (s), –138.10 – –141.87 (m); HRMS *m/z* (ES) Found: MNa^+ 422.1556. $C_{20}H_{24}F_3NO_4Na$ requires MNa^+ 422.1550; LRMS *m/z* (ES) 300 (100%), 363 (15%), 391 (20%), 419 (15%), 422 (90%, MNa^+). Resolution between the enantiomers of carbamate **9b** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 8.9 min and 11.0 min.

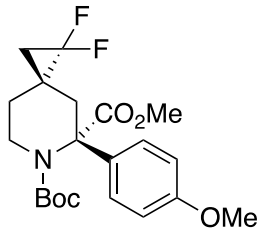
(±)-6-(*tert*-Butyl) 5-Methyl 5-(4-Chlorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate **9c**



Using general procedure B, *n*-BuLi (0.15 mL, 0.35 mmol, 2.3 M in hexanes) and spiropiperidine **2c** (105 mg, 0.29 mmol) in THF (1.2 mL) at –40 °C and MeOCOCl (0.08 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol−EtOAc (92:8), the carbamate **9c** (108 mg, 89%) as a white amorphous solid; mp 120–122 °C (petrol−EtOAc); R_f 0.36 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1743, 1694; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.45–7.36 (m, 2H), 7.33–7.28 (m, 2H), 4.04 (dt, *J* = 13.5, 5.5 Hz, 1H), 3.76 (s, 3H), 3.65–3.55 (m, 1H), 2.41 (br d, *J* = 14.5 Hz, 1H), 2.25–2.14 (m, 1H), 2.10 (br d, *J* = 14.5 Hz, 1H), 1.54–1.46 (m, 1H), 1.28 (br s, 9H), 0.92–0.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 172.3, 133.1, 128.4, 127.9, 114.0 (t, *J* = 288.0 Hz), 81.4, 66.3, 52.6, 39.8, 28.0, 26.8, 22.7 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –138.58 – –140.99 (m); HRMS *m/z* (ES) Found: MNa^+ 438.1243. $C_{20}H_{24}F_2{}^{35}ClNO_4Na$ requires MNa^+ 438.1255; Found: MNa^+ 440.1226. $C_{20}H_{24}F_2{}^{37}ClNO_4Na$ requires MNa^+ 440.1225; LRMS *m/z* (ES) 316 (100%), 318 (30%), 438 (35%, MNa^+ for ^{35}Cl), 440 (10%, MNa^+ for ^{37}Cl). Resolution between the enantiomers of carbamate **9c** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 9.6 min and 12.8 min.

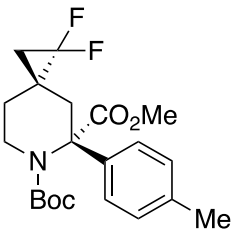
(±)-6-(*tert*-Butyl) 5-Methyl 5-(4-Methoxyphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate

9d



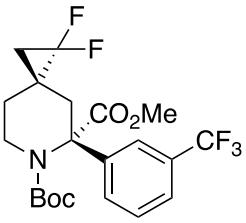
Using general procedure B, *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and spiropiperidine **2d** (109 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and MeOCOCl (0.08 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with pentane−EtOAc (9:1), the carbamate **9d** (79 mg, 62%) as an oil; R_f 0.23 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1744, 1694; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.29 (m, 2H), 6.90–6.82 (m, 2H), 4.05 (dt, *J* = 13.5, 5.5 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.62–3.49 (m, 1H), 2.44 (br d, *J* = 14.5 Hz, 1H), 2.22–2.05 (m, 2H), 1.54–1.43 (m, 1H), 1.30 (br s, 9H), 0.85–0.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 172.8, 158.6, 155.3, 128.2, 114.2 (t, *J* = 288.0 Hz), 113.0, 81.1, 66.3, 55.3, 52.4, 40.8, 39.9, 28.1, 26.9, 22.5 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –138.47 – –141.05 (m); HRMS *m/z* (ES) Found: MNa^+ 434.1752. $C_{21}H_{27}F_2NO_5Na$ requires MNa^+ 434.1750; LRMS *m/z* (ES) 312 (100%), 431 (35%), 434 (70%, MNa^+). Resolution between the enantiomers of carbamate **9d** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (98:2 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 10.5 min and 16.8 min.

(±)-6-(*tert*-Butyl) 5-Methyl 5-(4-Methylphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate **9e**



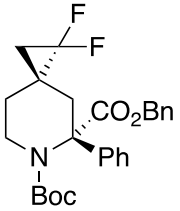
Using general procedure B, *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and spiropiperidine **2e** (104 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and MeOCOCl (0.08 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with pentane−EtOAc (9:1), the carbamate **9e** (106 mg, 86%) as an oil; R_f 0.29 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1746, 1697; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.07 (dt, *J* = 13.5, 5.5 Hz, 1H), 3.74 (s, 3H), 3.62–3.49 (m, 1H), 2.44 (d, *J* = 14.5 Hz, 1H), 2.33 (s, 3H), 2.23–2.07 (m, 2H), 1.54–1.42 (m, 1H), 1.30 (br s, 9H), 0.87–0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 172.7, 136.8, 128.4, 126.9, 114.3 (t, *J* = 288.0 Hz), 81.1, 66.5, 52.4, 39.9, 28.0, 27.0, 22.5 (t, *J* = 9.5 Hz), 20.9; ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –137.73 – –142.48 (m); HRMS *m/z* (ES) Found: MNa^+ 418.1818. $C_{21}H_{27}F_2NO_4Na$ requires MNa^+ 418.1801; LRMS *m/z* (ES) 296 (100%), 297 (60%), 415 (25%), 418 (80%, MNa^+). Resolution between the enantiomers of carbamate **9e** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 10.9 min and 16.7 min.

(±)-6-(*tert*-Butyl) 5-Methyl 1,1-Difluoro-5-(3-(trifluoromethyl)phenyl)-6-azaspiro[2.5]octane-5,6-dicarboxylate **9f**



Using general procedure B, *n*-BuLi (0.17 mL, 0.37 mmol, 2.2 M in hexanes) and spiropiperidine **2f** (121 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and MeOCOCl (0.08 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with pentane−EtOAc (93:7), the carbamate **9f** (116 mg, 83%) as an oil; R_f 0.34 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1745, 1698; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.80–7.64 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 4.10–4.01 (m, 1H), 3.78 (s, 3H), 3.73–3.58 (m, 1H), 2.43 (d, *J* = 14.5 Hz, 1H), 2.28–2.18 (m, 1H), 2.14 (d, *J* = 14.5 Hz, 1H), 1.61–1.53 (m, 1H), 1.26 (br s, 9H), 0.92–0.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 172.1, 130.6, 128.2, 124.1–123.9 (m), 123.6–123.4 (m), 114.0 (t, *J* = 288.5 Hz), 81.5, 66.4, 52.7, 27.9, 26.7, 22.9–22.6 (m); ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –62.51 (s), –136.78 – –141.71 (m); HRMS *m/z* (ES) Found: MNa^+ 472.1520. $C_{21}H_{24}F_5NO_4Na$ requires MNa^+ 472.1518; LRMS *m/z* (ES) 350 (100%), 413 (15%), 441 (15%), 472 (85%, MNa^+). Resolution between the enantiomers of carbamate **9f** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 6.1 min and 7.1 min.

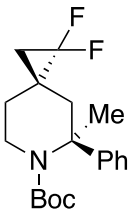
(±)-6-*tert*-Butyl 5-Benzyl 1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-5,6-dicarboxylate **10**



Using general procedure B, *n*-BuLi (0.16 mL, 0.37 mmol, 2.3 M in hexanes) and spiropiperidine **2a** (100 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and BnOCOCl (0.07 mL, 0.5 mmol) gave, after

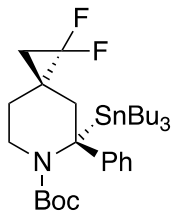
purification by column chromatography on silica gel, eluting with petrol−EtOAc (94:6), the carbamate **10** (94 mg, 66%) as an oil; R_f 0.40 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1743, 1692; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.52–7.14 (m, 10H), 5.22–5.04 (m, 2H), 4.04–3.92 (m, 1H), 3.77–3.50 (m, 1H), 2.50 (d, *J* = 14.5 Hz, 1H), 2.21–1.99 (m, 2H), 1.54–1.36 (m, 1H), 1.21 (br s, 9H), 0.81–0.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, some C could not be observed) δ = 171.9, 155.4, 135.6, 128.5, 128.3, 128.2, 127.8, 127.2, 127.1, 114.1 (t, *J* = 288.5 Hz), 81.2, 67.4, 66.8, 40.3, 28.0, 27.1, 22.5 (t, *J* = 9.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –137.72 – –142.47 (m); HRMS *m/z* (ES) Found: MNa^+ 480.1958. $C_{26}H_{29}F_2NO_4Na$ requires MNa^+ 480.1957; LRMS *m/z* (ES) 358 (100%), 359 (80%), 477 (25%), 480 (85%, MNa^+). Resolution between the enantiomers of carbamate **10** was achieved using a Agilent system fitted with a CHIRAL ART Cellulose-SC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 210 nm. Injection volume was 5 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 21.8 min and 27.1 min.

(±)-*tert*-Butyl 1,1-Difluoro-5-methyl-5-phenyl-6-azaspiro[2.5]octane-6-carboxylate **11**



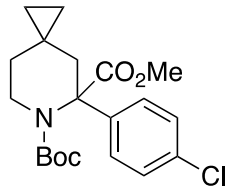
Using general procedure B, *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and spiropiperidine **2a** (100 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and MeI (0.07 mL, 1 mmol) gave, after purification by column chromatography on silica gel, eluting with pentane−EtOAc (9:1), the carbamate **11** (87 mg, 83%) as an oil; R_f 0.43 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1682; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.24 (m, 4H), 7.22–7.14 (m, 1H), 3.99–3.74 (m, 2H), 2.21–2.07 (m, 2H), 1.81–1.68 (m, 4H), 1.64–1.57 (m, 1H), 1.14–0.87 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz, one C could not be observed) 155.5, 149.2, 128.1, 126.0, 124.4, 114.8 (t, *J* = 288.5 Hz), 79.8, 59.6, 43.6 (d, *J* = 3.0 Hz), 40.2, 28.0, 27.9 (d, *J* = 4.5 Hz), 23.6, 23.2 (t, *J* = 10.0 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ = –137.05 (dd, *J* = 152.5, 12.5 Hz), –137.93 – –139.07 (m); HRMS *m/z* (ES) Found: MNa^+ 360.1756. $C_{19}H_{25}F_2NO_2Na$ requires MNa^+ 360.1746; LRMS *m/z* (ES) 238 (20%), 282 (100%), 360 (35%, MNa^+).

(±)-6-*tert*-Butyl 5-(Tributylstannyl)-1,1-difluoro-5-phenyl-6-azaspiro[2.5]octane-5,6-dicarboxylate **12**



Using general procedure B, *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and spiropiperidine **2a** (100 mg, 0.31 mmol) in THF (1.3 mL) at –40 °C and Bu_3SnCl (0.10 mL, 0.37 mmol) gave, after purification by column chromatography on a mixture of silica gel and K_2CO_3 (10% w/w), eluting with pentane−EtOAc (97:3), the carbamate **12** (122 mg, 64%) as an oil; R_f 0.73 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 1668; ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ = 7.34–7.21 (m, 2H), 7.09–6.98 (m, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 4.20–4.08 (m, 0.4H), 4.01 (dt, *J* = 13.0, 4.0 Hz, 0.6H), 3.05 (td, *J* = 13.0, 3.0 Hz, 0.4H), 2.97 (td, *J* = 13.0, 3.0 Hz, 0.6H), 2.61–2.26 (m, 2H), 1.92 (td, *J* = 13.0, 4.0 Hz, 0.4H), 1.83–1.72 (m, 0.6H), 1.63– 1.45 (m, 10H), 1.42–0.98 (m, 14H), 0.85 (t, *J* = 7.0 Hz, 9H), 0.80–0.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers, some C could not be observed) δ = 157.3, 157.2, 144.2, 143.7, 128.4, 128.1, 124.0, 123.8, 123.7, 115.6 (t, *J* = 288.0 Hz), 115.1 (t, *J* = 288.0 Hz), 80.4, 80.2, 57.6, 40.7, 39.2, 35.5, 33.9, 29.0, 28.4, 27.7, 22.9 (t, *J* = 10.0 Hz), 22.1 (t, *J* = 10.0 Hz), 13.7, 13.5, 13.4; ^{19}F NMR ($CDCl_3$, 377 MHz, rotamers) δ = –129.8 – –143.2 (m); HRMS *m/z* (ES-TOF) Found: MH^+ 614.2834. $C_{30}H_{50}F_2NO_2Sn$ requires MH^+ 614.2826; LRMS *m/z* (ES) 222 (20%), 556 (100%), 614 (5%, MNa^+).

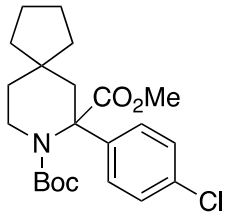
(±)-6-(*tert*-Butyl) 5-Methyl 5-(4-Chlorophenyl)-6-azaspiro[2.5]octane-5,6-dicarboxylate **13**



Using general procedure B, *n*-BuLi (0.16 mL, 0.4 mmol, 2.4 M in hexanes) and spiropiperidine **5** (108 mg, 0.34 mmol) in THF (1.5 mL) at –78 °C and MeOCOCl (0.14 mL, 1.7 mmol) gave, after purification by column chromatography on silica gel, eluting with hexane−EtOAc (9:1), the carbamate **13** (110 mg, 60%) as an oil; R_f 0.7 [hexane−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2977, 2929, 2874, 1741, 1693, 1492, 1365, 1157, 1011, 775; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.27 (m, 4H), 3.95–3.92 (m, 1H), 3.76 (s, 3H), 3.61 (br, 1H), 2.38 (d, 1H, *J* = 12 Hz), 1.86 (d, 1H, *J* = 12 Hz), 1.79–1.73 (m, 1H),

1.39 (br, 1H), 1.29 (s, 9H), 0.32–0.24 (m, 2H), 0.13–0.08 (m, 1H), –0.01– –0.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, one C could not be observed) δ = 172.9, 156.1, 132.4, 128.4, 127.6, 80.8, 67.7, 52.3, 45.9, 42.3, 33.2, 28.0, 13.6, 12.5, 11.4; HRMS *m/z* (ES) Found: MH^+–Boc 280.1104. $C_{15}H_{19}{}^{35}ClNO_4$ requires MH^+ – Boc 280.1104. Resolution between the enantiomers of carbamate **13** was achieved using a Beckman system fitted with a Lux Amylose–2 column (250 mm x 4.6 mm i.d.) as the stationary phase with a mixture of n-hexane–isopropanol (90:10 v/v) as the mobile phase at a flow rate of 1.0 mL/min; room temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 20 mg in 1 mL of the eluent. Under these conditions, the components were eluted at 16.4 and 18.5 min.

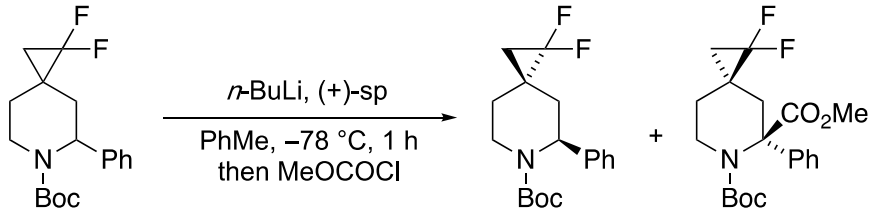
(±)-8-(*tert*-Butyl) 7-Methyl 7-(4-Chlorophenyl)-8-azaspiro[4.5]decane-7,8-dicarboxylate **14**



Using general procedure B, *n*-BuLi (0.21 mL, 0.51 mmol, 2.4 M in hexanes) and spiropiperidine **5** (150 mg, 0.43 mmol) in THF (2 mL) at –78 °C and MeOCOCl (0.17 mL, 2.1 mmol) gave, after purification by column chromatography on silica gel, eluting with hexane−EtOAc (9:1), the carbamate **14** (111 mg, 64%) as an oil; R_f 0.7 [hexane−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2949, 2874, 1740, 1701, 1365, 1217, 748; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.19 (m, 4H), 3.72–3.69 (m, 1H), 3.66 (s, 3H), 3.51 (br s, 1H), 2.26 (d, 1H, *J* = 12 Hz), 1.98 (d, 1H, *J* = 12 Hz), 1.56–1.49 (m, 1H), 1.47–1.42 (m, 3H), 1.39–1.33 (m, 4H), 1.21 (br s, 9H), 0.81–0.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, one C could not be observed) δ = 173.3, 155.7, 132.5, 128.8, 127.5, 80.8, 66.8, 52.4, 40.3, 40.1, 39.8, 34.6, 28.4, 28.3, 28.0, 23.6, 22.3; HRMS *m/z* (ES) Found: MH^+–Boc 308.1422. $C_{17}H_{23}{}^{35}ClNO_4$ requires MH^+ – Boc 308.1417. Resolution between the enantiomers of carbamate **14** was achieved using a Beckman system fitted with a Lux Amylose–2 column (250 mm x 4.6 mm i.d.) as the stationary phase with a mixture of n-hexane–isopropanol (95:5 v/v) as the mobile phase at a flow rate of 0.8 mL/min; room temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 20 mg in 1 mL of the eluent. Under these conditions, the components were eluted at 7.8 and 14.2 min.

5. Kinetic resolution of racemic substrates 2a–f

tert-Butyl (3*S*,5*S*)-1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-6-carboxylate (3*S*,5*S*)-**2a** and 6-(*tert*-Butyl) 5-Methyl (3*R*,5*R*)-1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*R*,5*R*)-**9a**



(±)-**2a** (3*S*,5*S*)-**2a** (3*R*,5*R*)-**9a**

Reaction with 200 mg of spiropiperidine **2a**:

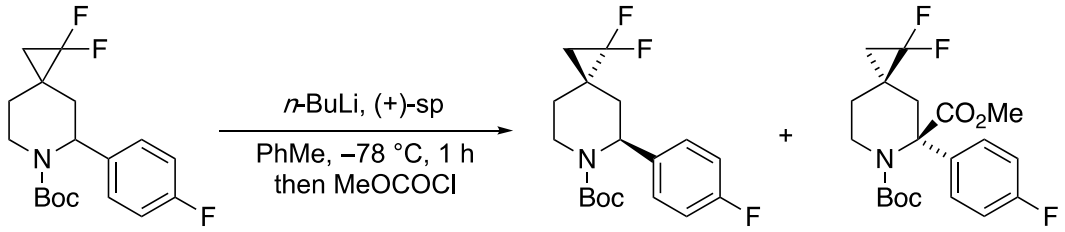
n-BuLi (0.22 mL, 0.50 mmol, 2.3 M in hexanes) was added to a mixture of (+)-sparteine (131 mg, 0.56 mmol) and the racemic spiropiperidine **2a** (200 mg, 0.62 mmol) in dry PhMe (2.5 mL) at –78 °C. After 1 h, MeOCOCl (0.12 mL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (93:7), to give recovered spiropiperidine (3*S*,5*S*)-**2a** (82 mg, 41%) as an oil; data as above; the enantiomeric ratio was determined to be 97:3 by CSP-HPLC as described above (major component eluted at 8.4 min); $[\alpha]_D^{22}$ –62 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9a** (115 mg, 49%) was isolated as an oil, data as above; the enantiomeric ratio was determined to be 86:14 by CSP-HPLC (major component eluted at 11.5 min); $[\alpha]_D^{22}$ +20 (*c* 1.0, $CHCl_3$).

Reaction with 2 g of spiropiperidine **2a**:

n-BuLi (2.2 mL, 5.0 mmol, 2.3 M in hexanes) was added to a mixture of (+)-sparteine (1.3 g, 5.6 mmol) and the racemic spiropiperidine **2a** (2.0 g, 6.2 mmol) in dry PhMe (25 mL) at –78 °C. After 1 h, MeOCOCl (1.2 mL, 16 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (10 mL) was added. The solvent was evaporated, and the residue was diluted with Et_2O (200 mL) and water (100 mL). The aqueous layer was adjusted to pH 1 using aq HCl (2 M) and the organic layer was separated, dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (94:6), gave recovered spiropiperidine (3*S*,5*S*)-

2a (0.65 g, 33%) as a clear oil; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC as described above (major component eluted at 8.4 min); $[\alpha]_D^{20}$ –70 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9a** (1.4 g, 58%) was isolated as a white amorphous solid; mp 100–102 °C (petrol−EtOAc); remaining data as above; the enantiomeric ratio was determined to be 75:25 by CSP-HPLC (major component eluted at 11.1 min); $[\alpha]_D^{20}$ +12 (*c* 1.0, $CHCl_3$). Note: The aqueous layer from the extraction was adjusted to pH 14 using NaOH pellets and Et_2O (200 mL) was added. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to give crude recovered (+)-sparteine. Purification by short path distillation gave recovered (+)-sparteine (1.1 g, 85%) as an oil.

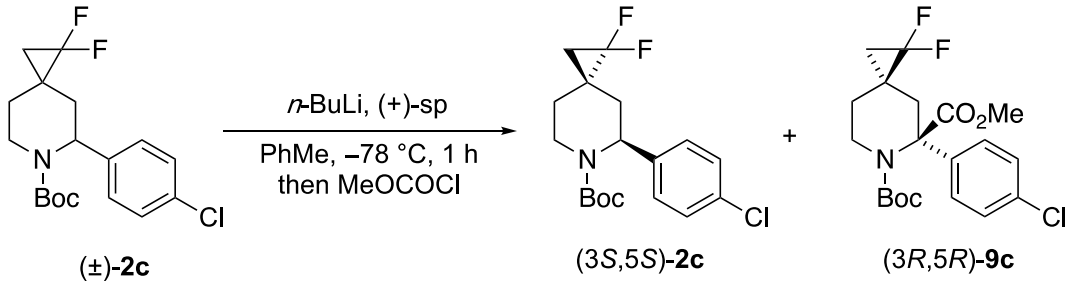
tert-Butyl (3*S*,5*S*)-5-(4-Fluorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate (3*S*,5*S*)-**2b** and 6-(*tert*-Butyl) 5-Methyl (3*R*,5*R*)-5-(4-fluorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*R*,5*R*)-**9b**



(±)-**2b** (3*S*,5*S*)-**2b** (3*R*,5*R*)-**9b**

n-BuLi (0.22 mL, 0.50 mmol, 2.3 M in hexanes) was added to a mixture of (+)-sparteine (131 mg, 0.56 mmol) and the racemic spiropiperidine **2b** (211 mg, 0.62 mmol) in dry PhMe (2.5 mL) at –78 °C. After 1 h, MeOCOCl (0.12 mL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (94:6), to give recovered spiropiperidine (3*S*,5*S*)-**2b** (90 mg, 41%) as an oil; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC as described above (major component eluted at 9.2 min); $[\alpha]_D^{20}$ –53 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9b** (141 mg, 57%) was isolated as an oil, data as above; the enantiomeric ratio was determined to be 76:24 by CSP-HPLC (major component eluted at 9.0 min); $[\alpha]_D^{20}$ +13 (*c* 1.0, $CHCl_3$).

tert-Butyl (3*S*,5*S*)-5-(4-Chlorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate (3*S*,5*S*)-**2c** and 6-(*tert*-Butyl) 5-Methyl (3*R*,5*R*)-5-(4-Chlorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*R*,5*R*)-**9c**



(±)-**2c** (3*S*,5*S*)-**2c** (3*R*,5*R*)-**9c**

Reaction with 200 mg of spiropiperidine **2c**:

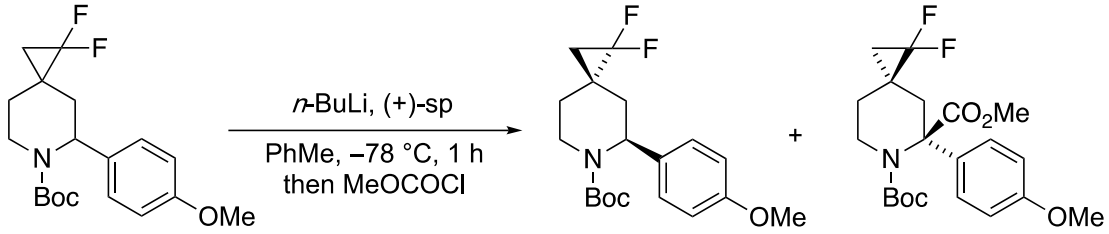
n-BuLi (0.28 mL, 0.62 mmol, 2.2 M in hexanes) was added to a mixture of (+)-sparteine (159 mg, 0.68 mmol) and the racemic spiropiperidine **2c** (221 mg, 0.62 mmol) in dry PhMe (5 mL) at –78 °C. After 1 h, MeOCOCl (0.12 mL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give recovered spiropiperidine (3*S*,5*S*)-**2c** (90 mg, 41%) as an oil; data as above; the enantiomeric ratio was determined to be 94:6 by CSP-HPLC as described above (major component eluted at 8.5 min); $[\alpha]_D^{18}$ –57 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9c** (138 mg, 54%) was isolated as a clear oil, data as above; the enantiomeric ratio was determined to be 79:21 by CSP-HPLC (major component eluted at 9.7 min); $[\alpha]_D^{18}$ +11 (*c* 1.0, $CHCl_3$).

Reaction with 1 g of spiropiperidine **2c**:

n-BuLi (1.0 mL, 2.2 mmol, 2.2 M in hexanes) was added to a mixture of recovered (+)-sparteine (590 mg, 2.52 mmol) and the racemic spiropiperidine **2c** (1.0 g, 2.8 mmol) in dry PhMe (12 mL) at –78 °C. After 1 h, MeOCOCl (0.54 mL, 7.0 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (5 mL) was added. The solvent was evaporated, and the residue was diluted with Et_2O (150 mL) and water (100 mL). The aqueous layer was adjusted to pH 1 using aq HCl (2 M) and the organic layer was separated, dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (94:6), gave recovered spiropiperidine (3*S*,5*S*)-**2c** (0.25 g, 25%) as an oil; data as above; the enantiomeric ratio was

determined to be 99:1 by CSP-HPLC as described above (major component eluted at 8.4 min); $[\alpha]_D^{20}$ –72 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9c** (0.83 g, 72%) was isolated as a white amorphous solid; mp 108–110 °C (petrol−EtOAc); remaining data as above; the enantiomeric ratio was determined to be 66:34 by CSP-HPLC (major component eluted at 9.5 min); $[\alpha]_D^{20}$ +6 (*c* 1.0, $CHCl_3$). Note: The aqueous layer from the extraction was adjusted to pH 14 using NaOH pellets and Et_2O (150 mL) was added. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated to give crude recovered (+)-sparteine (0.53 g) as an oil.

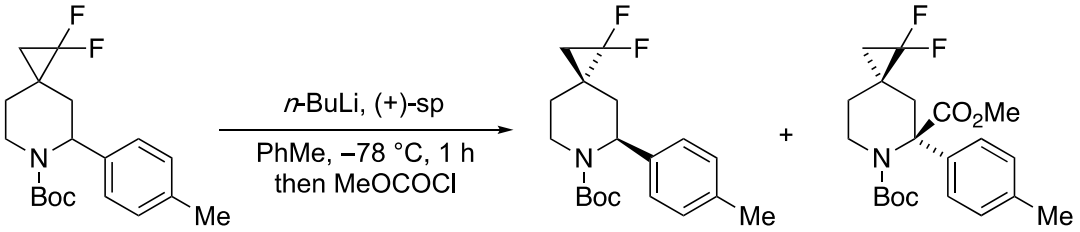
tert-Butyl (3*S*,5*S*)-5-(4-Methoxyphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate (3*S*,5*S*)-**2d** and 6-(*tert*-Butyl) 5-Methyl (3*R*,5*R*)-5-(4-Methoxyphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*R*,5*R*)-**9d**



(±)-**2d** (3*S*,5*S*)-**2d** (3*R*,5*R*)-**9d**

n-BuLi (0.20 mL, 0.93 mmol, 2.3 M in hexanes) was added to a mixture of (+)-sparteine (232 mg, 0.989 mmol) and the racemic spiropiperidine **2d** (218 mg, 0.62 mmol) in dry PhMe (5 mL) at –78 °C. After 1 h, MeOCOCl (0.12 mL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give recovered spiropiperidine (3*S*,5*S*)-**2d** (41 mg, 19%) as an oil; data as above; the enantiomeric ratio was determined to be 90:10 by CSP-HPLC as described above (major component eluted at 13.2 min); $[\alpha]_D^{20}$ –51 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9d** (183 mg, 72%) was isolated as an oil, data as above; the enantiomeric ratio was determined to be 62:38 by CSP-HPLC (major component eluted at 10.3 min); $[\alpha]_D^{20}$ +10 (*c* 1.0, $CHCl_3$).

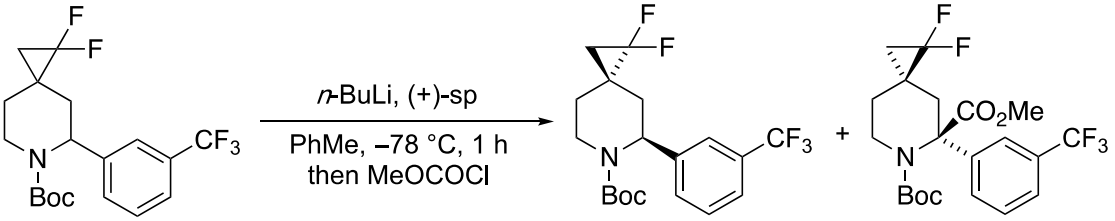
tert-Butyl (3*S*,5*S*)-5-(4-Methylphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate (3*S*,5*S*)-**2e** and 6-(*tert*-Butyl) 5-Methyl (3*R*,5*R*)-5-(4-Methylphenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*R*,5*R*)-**9e**



(±)-**2e** (3*S*,5*S*)-**2e** (3*R*,5*R*)-**9e**

n-BuLi (0.28 mL, 0.61 mmol, 2.2 M in hexanes) was added to a mixture of (+)-sparteine (157 mg, 0.67 mmol) and the racemic spiropiperidine **2e** (206 mg, 0.61 mmol) in dry PhMe (5 mL) at –78 °C. After 1 h, MeOCOCl (0.12 mL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (92:8), to give recovered spiropiperidine (3*S*,5*S*)-**2e** (88 mg, 43%) as an oil; data as above; the enantiomeric ratio was determined to be 92:8 by CSP-HPLC as described above (major component eluted at 8.9 min); $[\alpha]_{\mathrm{D}}^{18}$ –60 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9e** (114 mg, 47%) was isolated as an oil, data as above; the enantiomeric ratio was determined to be 84:16 by CSP-HPLC (major component eluted at 10.5 min); $[\alpha]_{\mathrm{D}}^{18}$ +22 (*c* 1.0, $CHCl_3$).

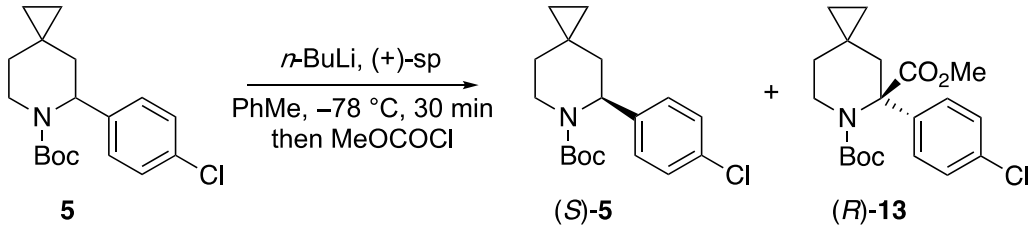
tert-Butyl (3*S*,5*S*)-1,1-Difluoro-5-(3-(trifluoromethyl)phenyl)-6-azaspiro[2.5]octane-6-carboxylate (3*S*,5*S*)-**2f** and 6-(*tert*-Butyl) 5-Methyl (3*R*,5*R*)-1,1-Difluoro-5-(3-(trifluoromethyl)phenyl)-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*R*,5*R*)-**9f**



(±)-**2f** (3*S*,5*S*)-**2f** (3*R*,5*R*)-**9f**

n-BuLi (0.20 mL, 0.44 mmol, 2.2 M in hexanes) was added to a mixture of (+)-sparteine (116 mg, 0.49 mmol) and the racemic spiropiperidine **2f** (215 mg, 0.55 mmol) in dry PhMe (2.2 mL) at –78 °C. After 1 h, MeOCOCl (0.11 mL, 1.4 mmol) was added and the mixture was allowed to warm to room temperature over 16 h then MeOH (1 mL) was added. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (93:7), to give recovered spiropiperidine (3*S*,5*S*)-**2f** (73 mg, 34%) as an oil; data as above; the enantiomeric ratio was determined to be 88:12 by CSP-HPLC as described above (major component eluted at 5.9 min); $[\alpha]_D^{20}$ –41 (*c* 1.0, $CHCl_3$). In addition, the carbamate (3*R*,5*R*)-**9f** (146 mg, 59%) was isolated as an oil, data as above; the enantiomeric ratio was determined to be 72:28 by CSP-HPLC (major component eluted at 6.6 min); $[\alpha]_D^{20}$ +8 (*c* 1.0, $CHCl_3$).

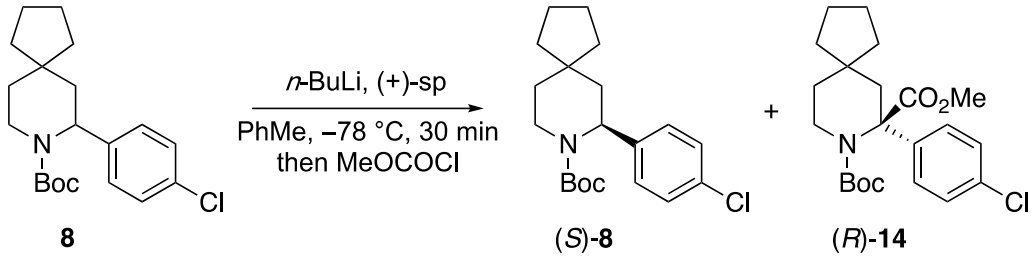
tert-Butyl (5*S*)-5-(4-Chlorophenyl)-6-azaspiro[2.5]octane-6-carboxylate (*S*)-**5** and 6-(*tert*-Butyl) 5-Methyl (5*R*)-5-(4-Chlorophenyl)-6-azaspiro[2.5]octane-5,6-dicarboxylate (*R*)-**13**



5 (*S*)-**5** (*R*)-**13**

n-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) was added to a mixture of (+)-sparteine (118 mg, 0.50 mmol) and the racemic spiropiperidine **5** (200 mg, 0.62 mmol) in dry PhMe (7.5 mL) at –78 °C. After 0.5 h, MeOCOCl (0.24 mL, 3.1 mmol) was added and the mixture was allowed to warm to room temperature. After 1 h, MeOH (2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with *n*-hexane–EtOAc (90:10), to give recovered spiropiperidine (*S*)-**5** (88 mg, 44%) as an oil; data as above; the enantiomeric ratio was determined to be 92:8 by CSP-HPLC as described above (major component eluted at 19.9 min); $[\alpha]_D^{20}$ –34 (*c* 1.0, $CHCl_3$). In addition, the carbamate (*R*)-**13** (99 mg, 42%) was isolated as an oil, data as above; the enantiomeric ratio was determined to be 90:10 by CSP-HPLC (major component eluted at 16.3 min); $[\alpha]_D^{20}$ +42 (*c* 1.0, $CHCl_3$).

tert-Butyl (7*S*)-7-(4-Chlorophenyl)-8-azaspiro[4.5]decane-8-carboxylate (S)-**8** and (7*R*)-8-(*tert*-Butyl) 7-Methyl 7-(4-Chlorophenyl)-8-azaspiro[4.5]decane-7,8-dicarboxylate (*R*)-**14**

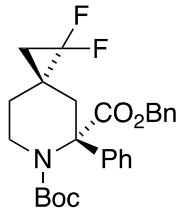


8 (*S*)-**8** (*R*)-**14**

n-BuLi (0.14 mL, 0.34 mmol, 2.4 M in hexanes) was added to a mixture of (+)-sparteine (108 mg, 0.46 mmol) and the racemic spiropiperidine **8** (200 mg, 0.57 mmol) in dry PhMe (6.8 mL) at –78 °C. After 0.5 h, MeOCOCl (0.22 mL, 2.85 mmol) was added and the mixture was allowed to warm to room temperature. After 1 h, MeOH (2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with *n*-hexane–EtOAc (90:10), to give recovered spiropiperidine (*S*)-**8** (90 mg, 45%) as an oil; data as above; er 97:3 by CSP-HPLC as described above (major component eluted at 7.7 min); $[\alpha]_{\mathrm{D}}^{20}$ –40 (*c* 1.0, $CHCl_3$). In addition, the carbamate (*R*)-**14** (88 mg, 38%) was isolated as an oil, data as above; er 96:4 by CSP-HPLC (major component eluted at 8.0 min); $[\alpha]_{\mathrm{D}}^{20}$ +62 (*c* 1.0, $CHCl_3$).

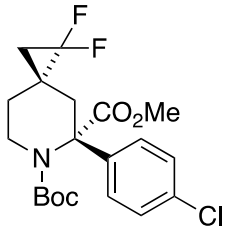
6. Further functionalisation of enantioenriched compounds

6-*tert*-Butyl 5-Benzyl (3*S*,5*S*)-1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*S*,5*S*)-**10**



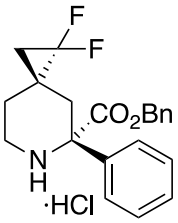
Using general procedure B (page S-4), *n*-BuLi (0.73 mL, 1.7 mmol, 2.3 M in hexanes) and (3*S*,5*S*)-**2a** (0.45 g, 1.4 mmol, er 99:1) in THF (5.6 mL) at –78 °C and BnOCOCl (0.30 mL, 2.1 mmol) gave, after purification by column chromatography on silica gel, eluting with hexane−EtOAc (94:6), the carbamate (3*S*,5*S*)-**10** (0.46 g, 72%) as an oil; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC (major component eluted at 21.2 min); $[\alpha]_D^{20}$ −11 (*c* 1.0, $CHCl_3$).

6-(*tert*-Butyl) 5-Methyl (3*S*,5*S*)-5-(4-Chlorophenyl)-1,1-difluoro-6-azaspiro[2.5]octane-5,6-dicarboxylate (3*S*,5*S*)-**9c**



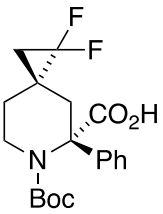
Using general procedure B (page S-4), *n*-BuLi (0.18 mL, 0.41 mmol, 2.2 M in hexanes) and (3*S*,5*S*)-**2c** (121 mg, 0.338 mmol, er 99:1) in THF (1.4 mL) at –78 °C and MeOCOCl (0.1 mL, 1.2 mmol) gave, after purification by column chromatography on silica gel, eluting with hexane−EtOAc (94:6), the carbamate (3*S*,5*S*)-**9c** (110 mg, 78%) as a white amorphous solid; m.p. 145–147 °C (Et_2O); remaining data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC (major component eluted at 12.5 min); $[\alpha]_D^{20}$ −20 (*c* 0.5, $CHCl_3$).

Benzyl (3*S*,5*S*)-1,1-Difluoro-5-phenyl-6-azaspiro[2.5]octane-5-carboxylate hydrochloride (3*S*,5*S*)-**15**



HCl (0.82 mL, 3.3 mmol, 4 M in dioxane) was added to carbamate (3*S*,5*S*)-**10** (150 mg, 0.328 mmol, er 99:1) in CH_2Cl_2 (3.3 mL) at 0 °C then the mixture was warmed to room temperature. After 16 h, the solvent was evaporated and the oily residue and was suspended in Et_2O (15 mL). The solvent was evaporated to give hydrochloride salt (3*S*,5*S*)-**15** (125 mg, 97%) as an amorphous off-white solid; m.p. 102–104 °C (Et_2O); R_f 0.15 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1742; ^{1}H NMR (DMSO-d^6, 400 MHz) δ = 10.55 (br s, 2H), 7.69–7.58 (m, 2H), 7.54–7.45 (m, 3H), 7.32–7.23 (m, 3H), 7.13–7.03 (m, 2H), 5.30 (d, *J* = 12.5 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 3.52–3.29 (m, 2H), 2.89–2.68 (m, 2H), 2.20–2.00 (m, 1H), 1.80 (d, *J* = 14.5 Hz, 1H), 1.63–1.46 (m, 2H); ^{13}C NMR (DMSO-d^6, 100 MHz, some C could not be observed) δ = 135.0, 130.2, 129.6, 128.8, 128.75, 128.1, 126.7, 69.7, 68.3, 65.5, 42.1, 32.4, 24.6, 21.8 (t, *J* = 10.0 Hz); ^{19}F NMR (DMSO-d^6, 377 MHz) δ = –135.6 (d, *J* = 152.0 Hz), –138.2 (d, *J* = 152.0 Hz); HRMS *m/z* (ES) Found: MH$^+$ 358.1615. $C_{21}H_{22}F_2NO_2Na$ requires MH$^+$ 358.1613; LRMS *m/z* (ES) 358 (100%, MNa$^+$); $[\alpha]_D^{20}$ +72 (*c* 0.5, MeOH).

(3*S*,5*S*)-6-(*tert*-Butoxycarbonyl)-1,1-difluoro-5-phenyl-6-azaspiro[2.5]octane-5-carboxylic acid (3*S*,5*S*)-**16**



To a solution of carbamate (3*S*,5*S*)-**10** (158 mg, 0.34 mmol) in MeOH (12 mL) was added 10% wt Pd/C (100 mg, 0.086 mmol). The mixture was stirred at room temperature under a hydrogen gas atmosphere (1 atm) for 16 h. The mixture was filtered and the solvent was removed under reduced pressure to give carboxylic acid (3*S*,5*S*)-**16** (113 mg, 89% yield) as a white amorphous solid; mp >250 °C (MeOH); R_f 0.01 [petrol−EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 1742, 1637; ^{1}H NMR (DMSO-d^6, 400 MHz) δ = 12.80

(br s, 1H), 7.47–7.16 (m, 5H), 3.98–3.76 (m, 1H), 3.53–3.26 (m, 2H), 2.39 (br d, *J* = 14.5 Hz, 1H), 2.20 (br d, *J* = 14.5 Hz, 1H), 2.08–1.79 (m, 1H), 1.36–0.66 (m, 11H); ^{13}C NMR (DMSO-d^6, 100 MHz, some C could not be observed) δ = 173.2, 155.2, 127.8, 127.0, 115.5, 80.3, 66.8, 28.2, 26.7, 23.4–23.1 (m), 22.3–21.9 (m); ^{19}F NMR (DMSO-d^6, 377 MHz, rotamers) δ = –136.19 – –139.68 (m); HRMS *m/z* (ES) Found: MNa^+ 390.1498. $C_{19}H_{23}F_2NO_4Na$ requires MNa^+ 390.1487; LRMS *m/z* (ES) 196 (15%), 268 (100%), 390 (75%, MNa^+); $[\alpha]_D^{20}$ −25 (*c* 1.0, MeOH).

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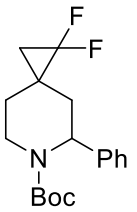
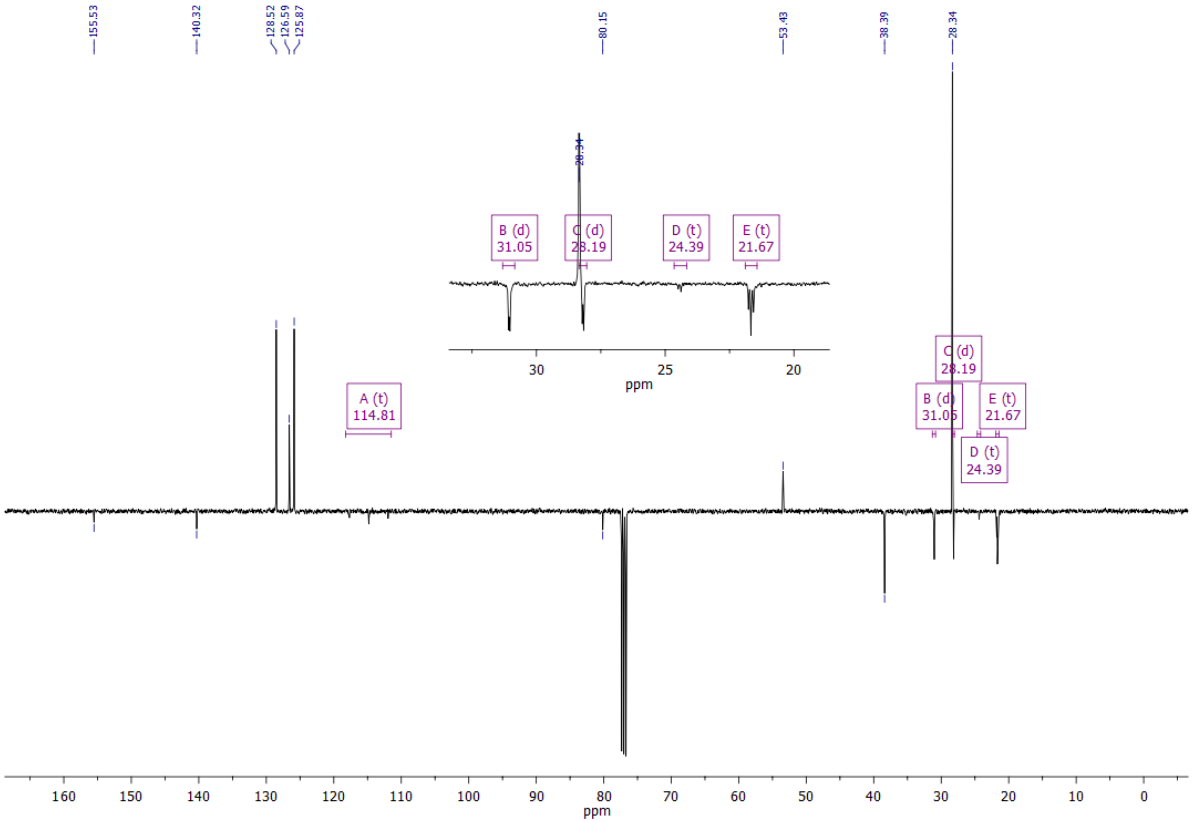
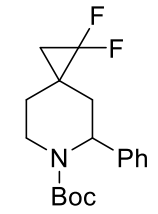
7. ^{1}H, ^{19}F and ^{13}C NMR spectra (all in $CDCl_3$ unless stated)



2a

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F
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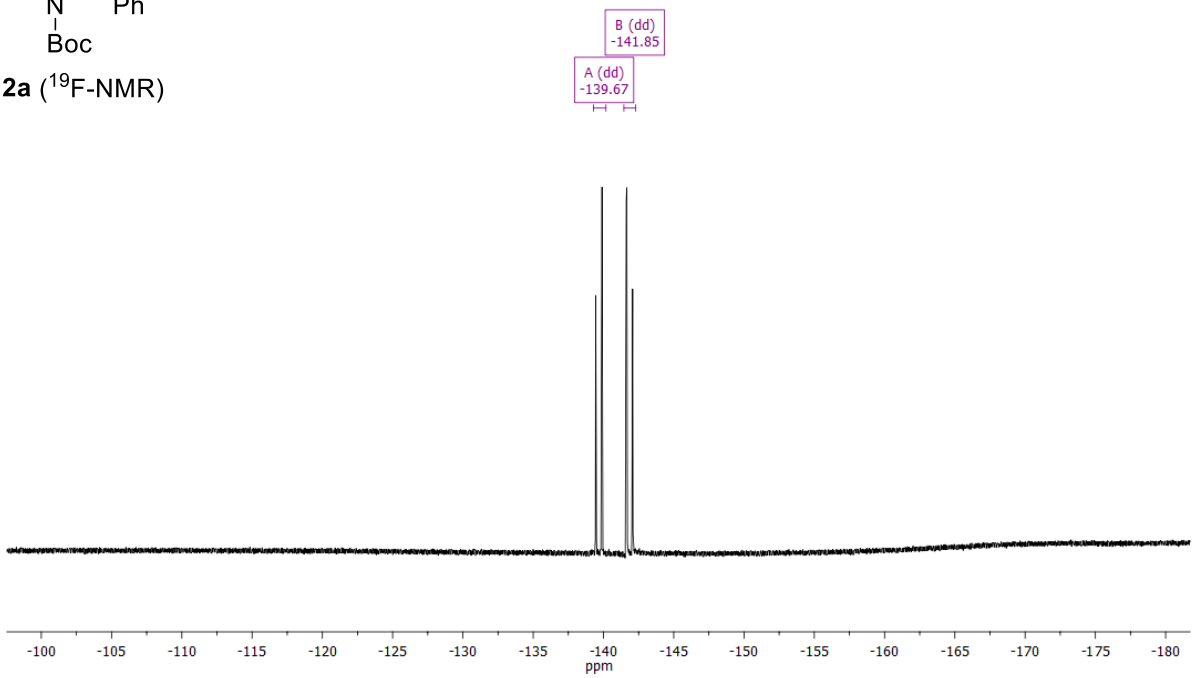
Ph
Boc

2a (^{19}F-NMR)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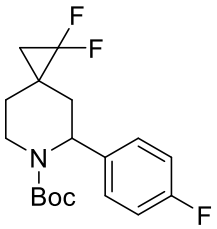
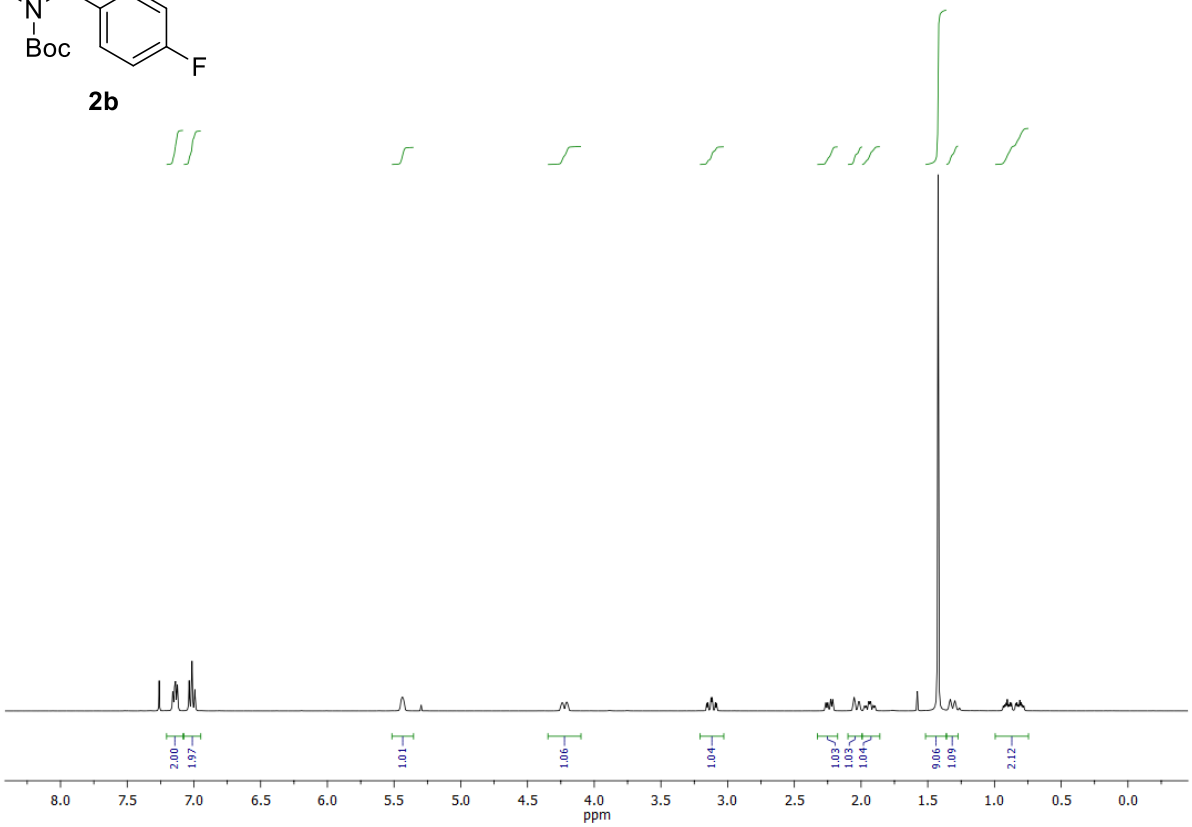
-180
ppm


F
F
N
Boc
F

2b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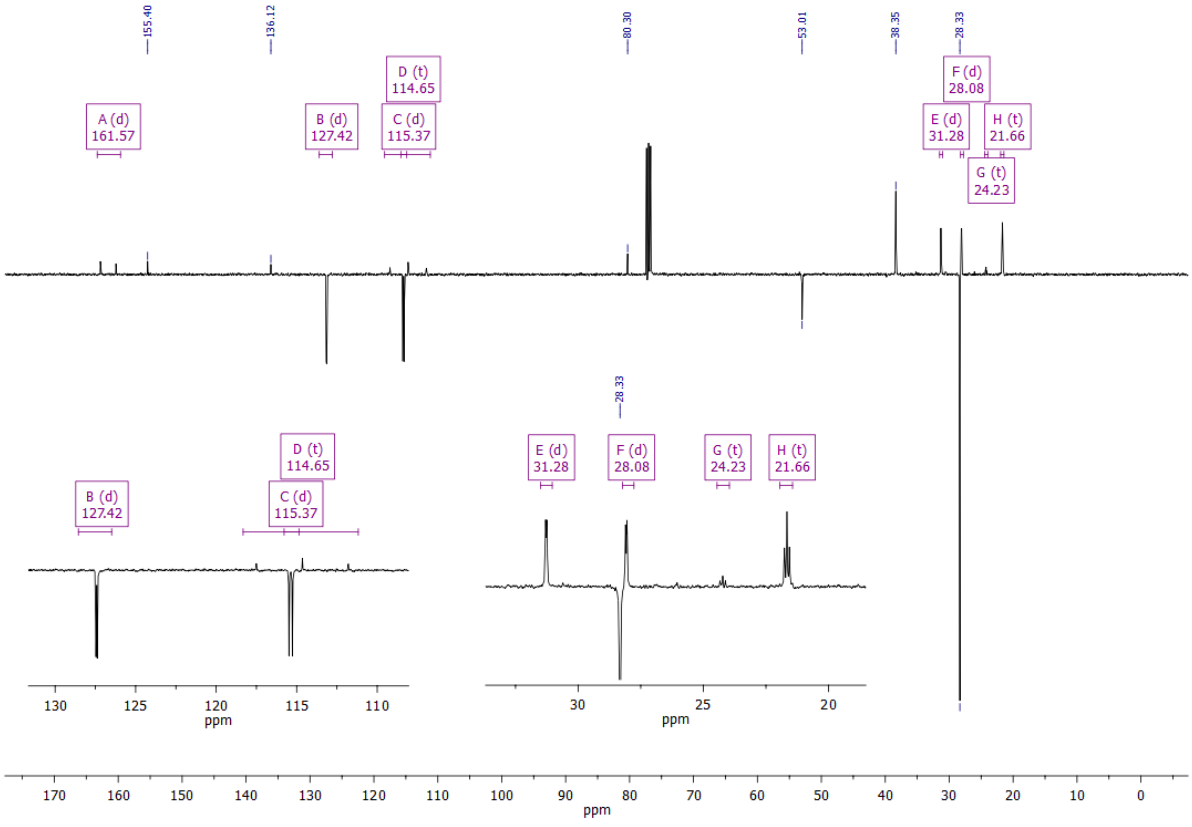
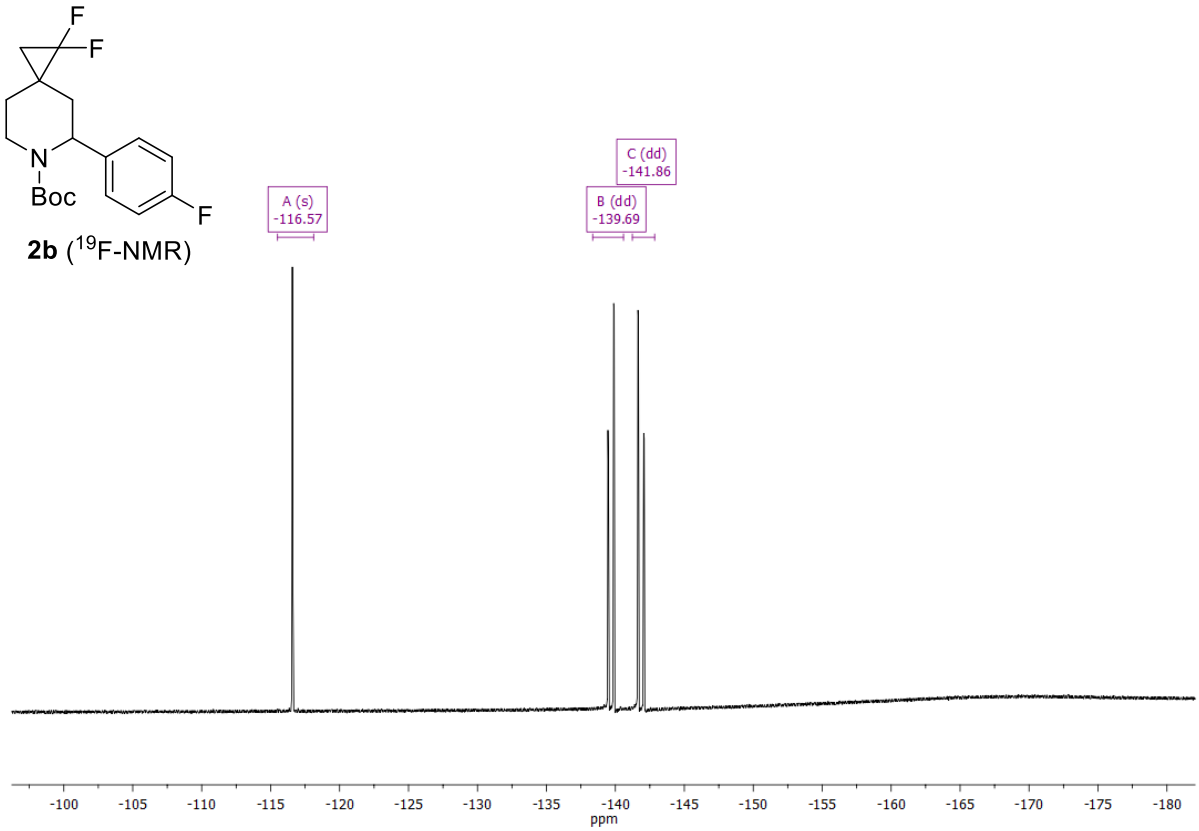
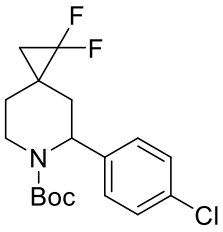
1.97
1.01
1.06
1.04
1.03
1.03
1.04
9.06
1.09
2.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

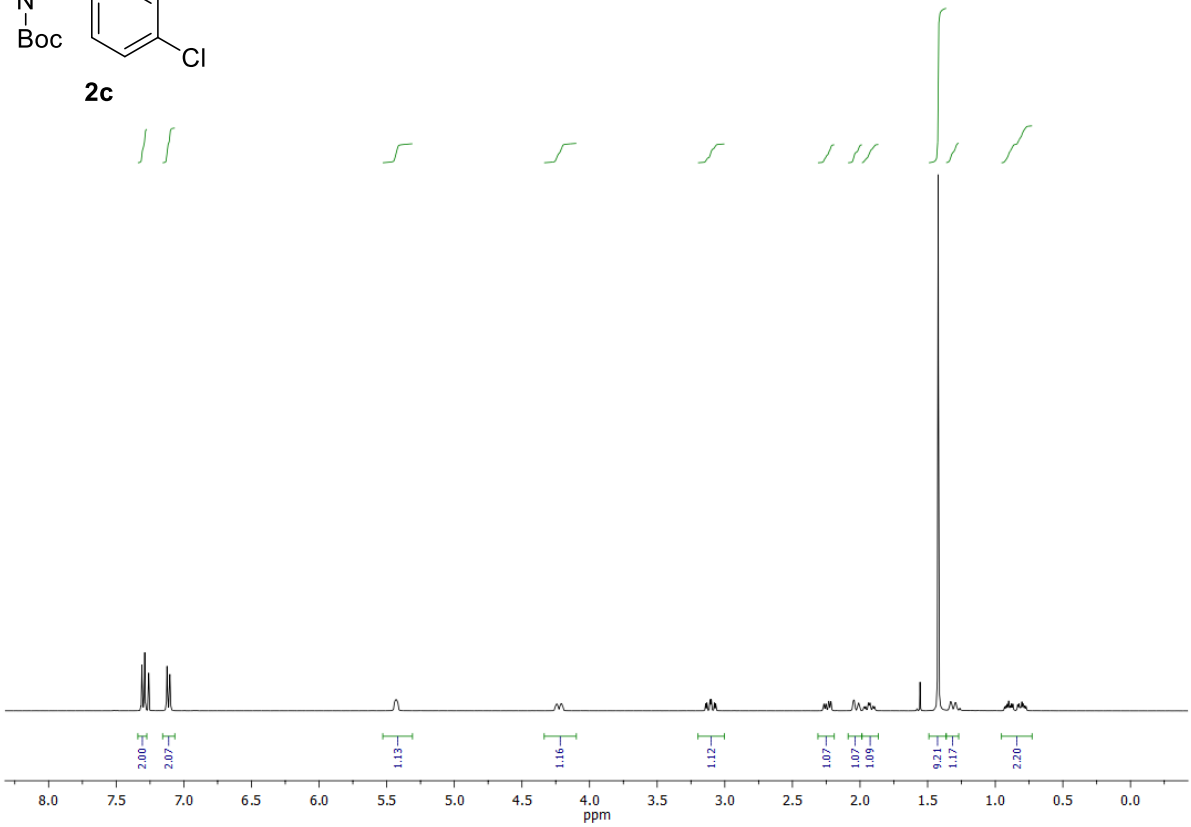

155.40
136.12
80.30
53.01
38.35
28.33
A (d)
161.57
B (d)
127.42
D (t)
114.65
C (d)
115.37
F (d)
28.08
E (d)
31.28
H (t)
21.66
G (t)
24.23
28.33
E (d)
31.28
F (d)
28.08
G (t)
24.23
H (t)
21.66
D (t)
114.65
B (d)
127.42
C (d)
115.37
130
125
120
115
110
ppm
30
25
20
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

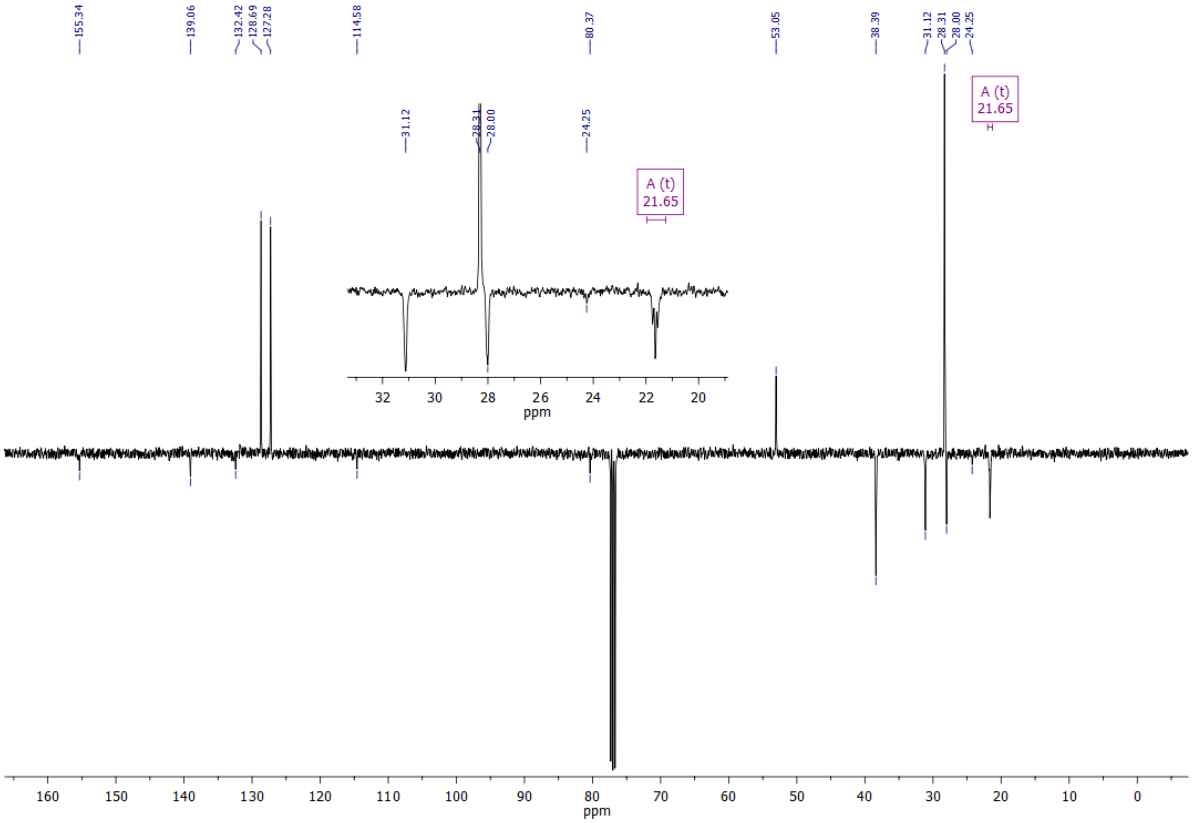

F
F
N
Boc
F
A (s)
-116.57
B (dd)
-139.69
C (dd)
-141.86
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm

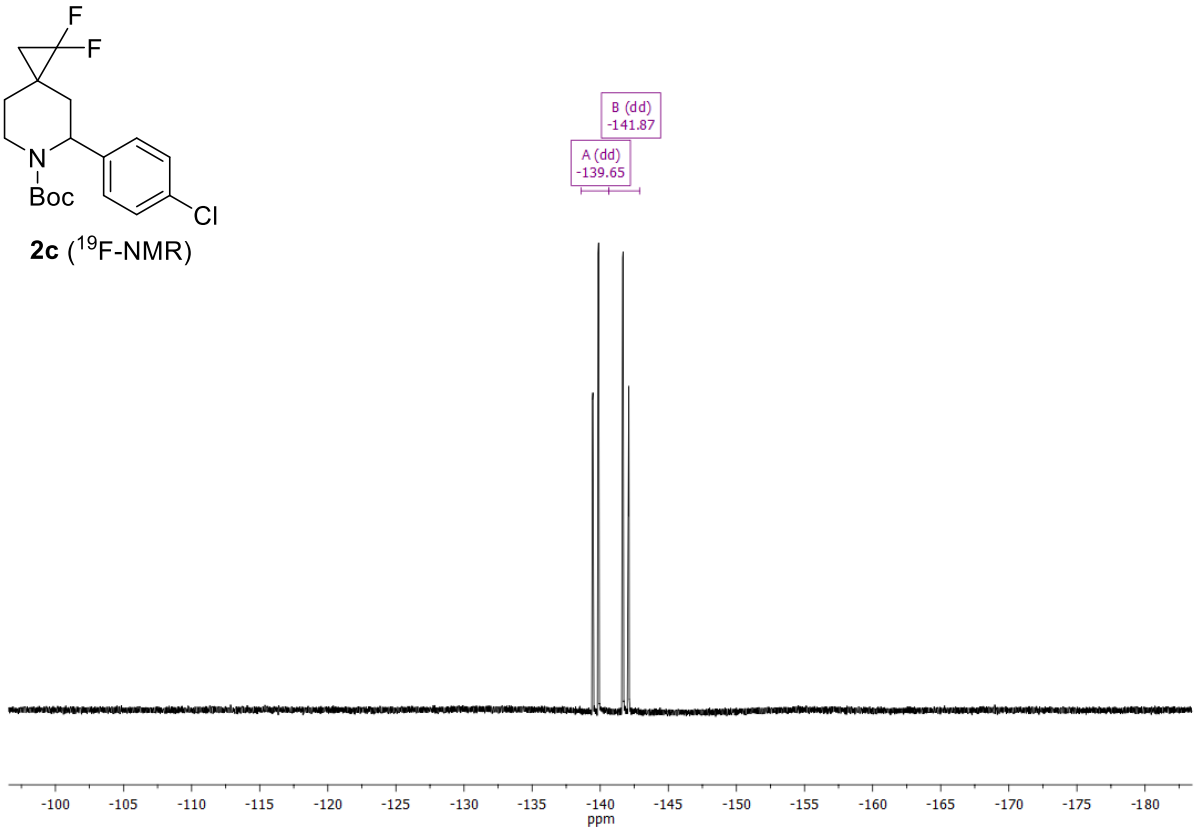
2b (^{19}F-NMR)


F
F
N
Boc
Cl

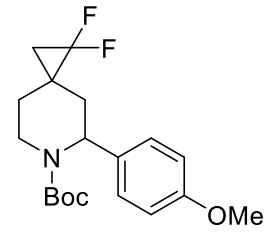
2c


2.00
2.07
1.13
1.16
1.12
1.07
1.07
1.09
9.21
1.17
2.20
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
ppm

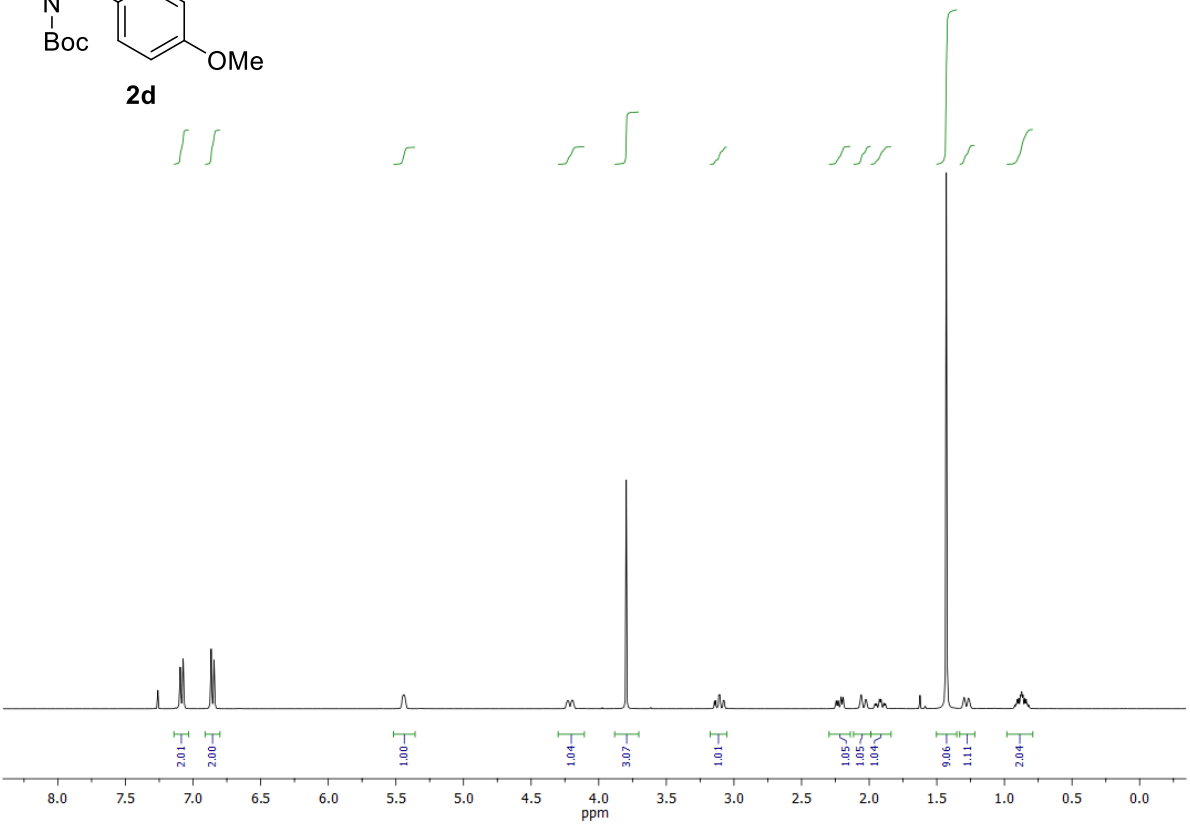

155.34
139.06
132.42
128.69
127.28
114.58
80.37
53.05
38.39
31.12
28.31
28.00
24.25
A (t)
21.65
A (t)
21.65
32
30
28
26
24
22
20
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

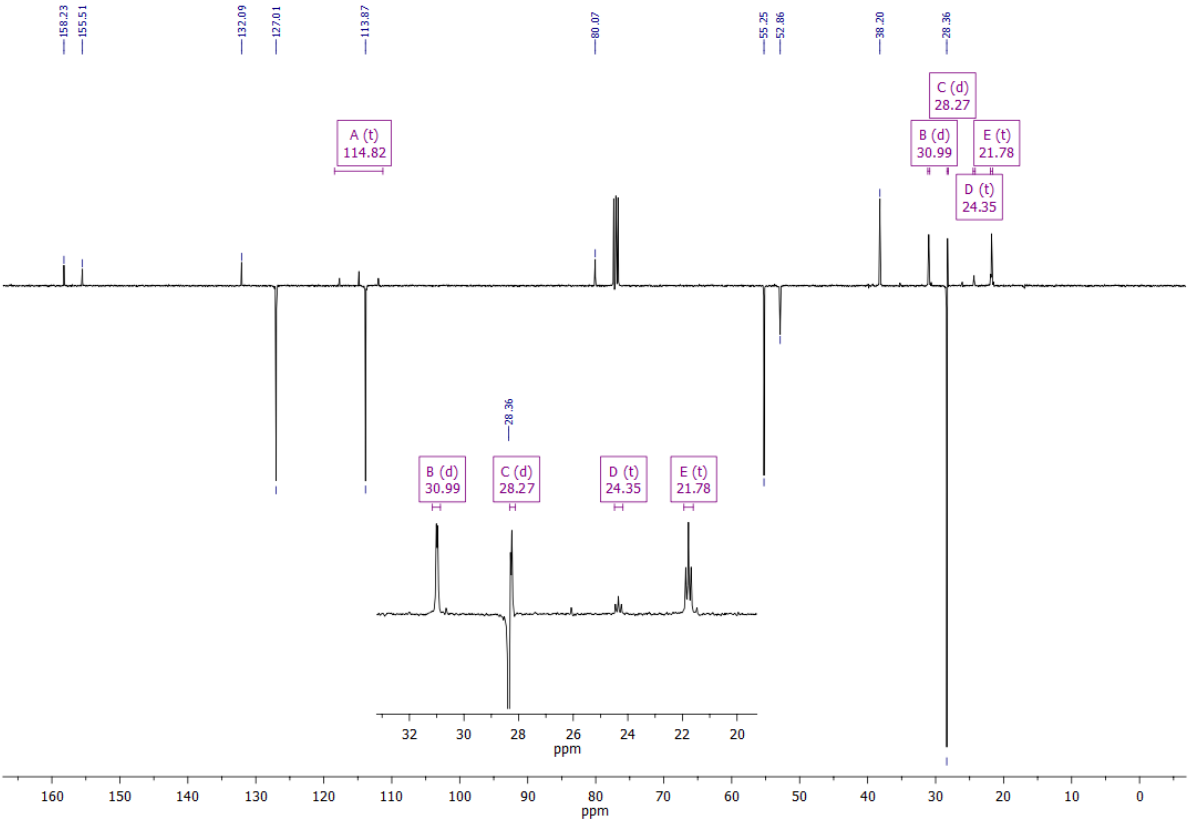

F
F
N
Boc
Cl
B (dd)
-141.87
A (dd)
-139.65
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm

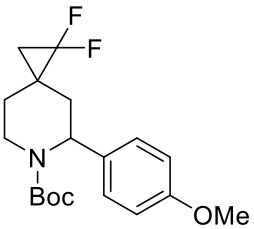
2c (^{19}F-NMR)


F
F
N
Boc
OMe

2d

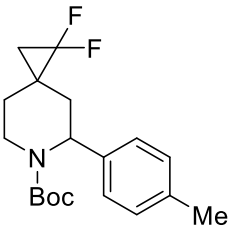

2.01
2.00
1.00
1.04
3.07
1.01
1.05
1.05
1.04
9.66
1.11
2.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


158.23
155.51
132.09
127.01
113.87
80.07
55.25
52.86
38.20
28.36
A (t)
114.82
C (d)
28.27
B (d)
30.99
E (t)
21.78
D (t)
24.35
28.36
B (d)
30.99
C (d)
28.27
D (t)
24.35
E (t)
21.78
32
30
28
26
24
22
20
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

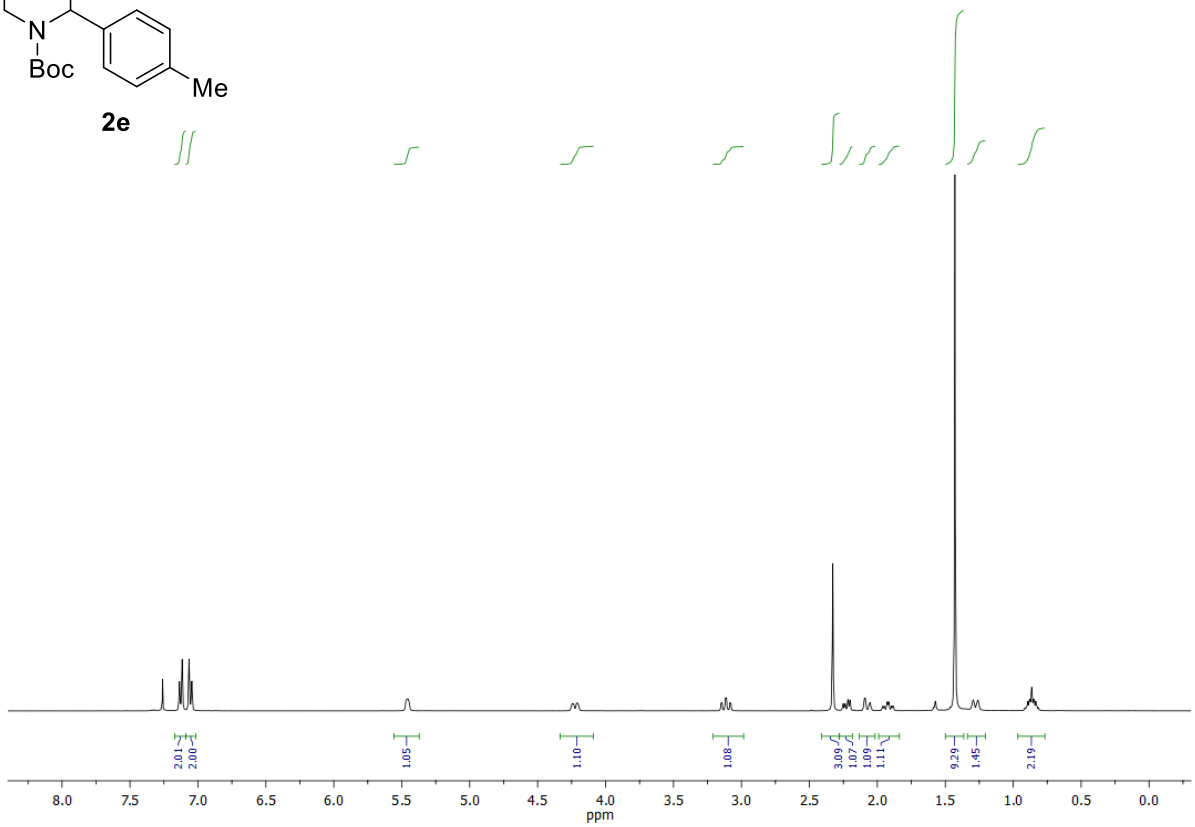

F
F
N
Boc
OMe

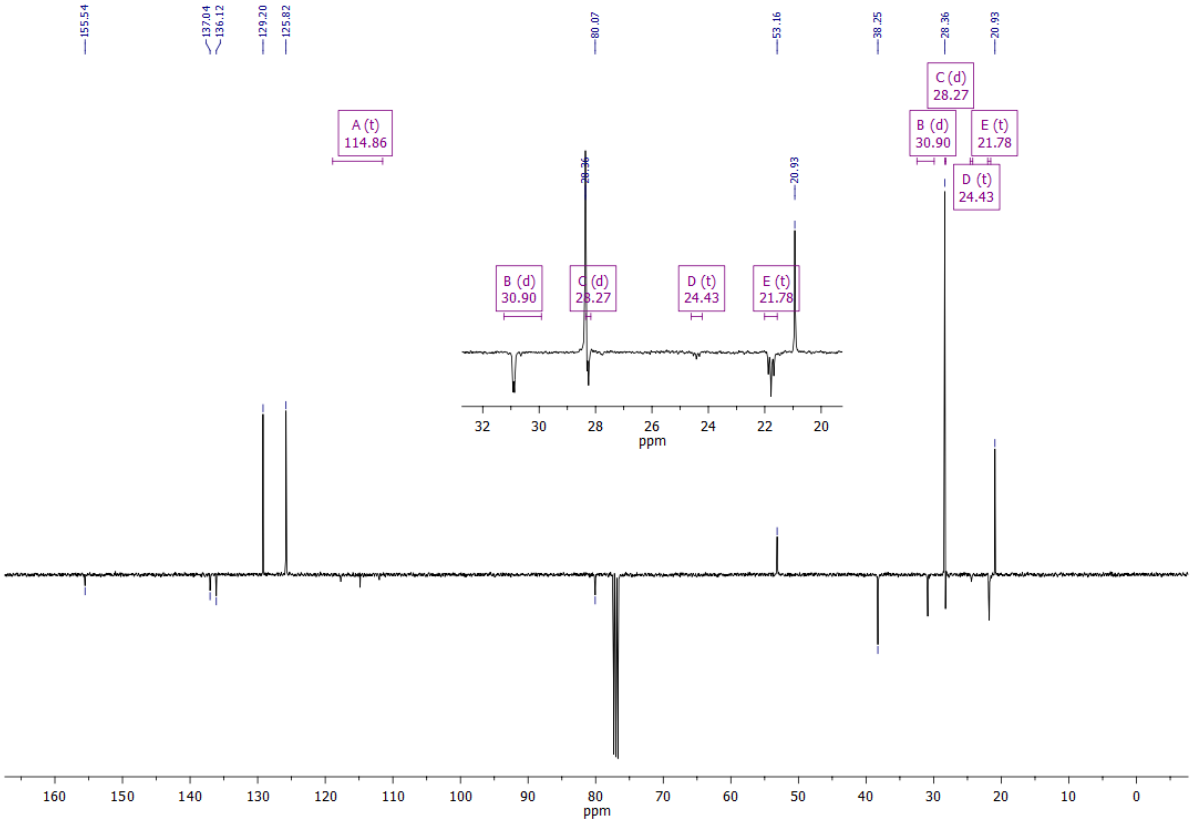
2d (^{19}F-NMR)

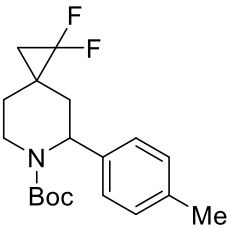
B (dd)
-141.91
A (dd)
-139.64
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
N
Boc
Me

2e

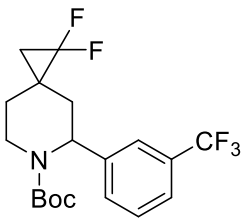

2.01
2.00
1.05
1.10
1.08
3.09
1.07
1.09
1.11
9.29
1.45
2.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


155.54
137.04
136.12
129.20
125.82
80.07
53.16
38.25
28.36
20.93
A (t)
114.86
C (d)
28.27
B (d)
30.90
E (t)
21.78
D (t)
24.43
B (d)
30.90
C (d)
28.27
D (t)
24.43
E (t)
21.78
32
30
28
26
24
22
20
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

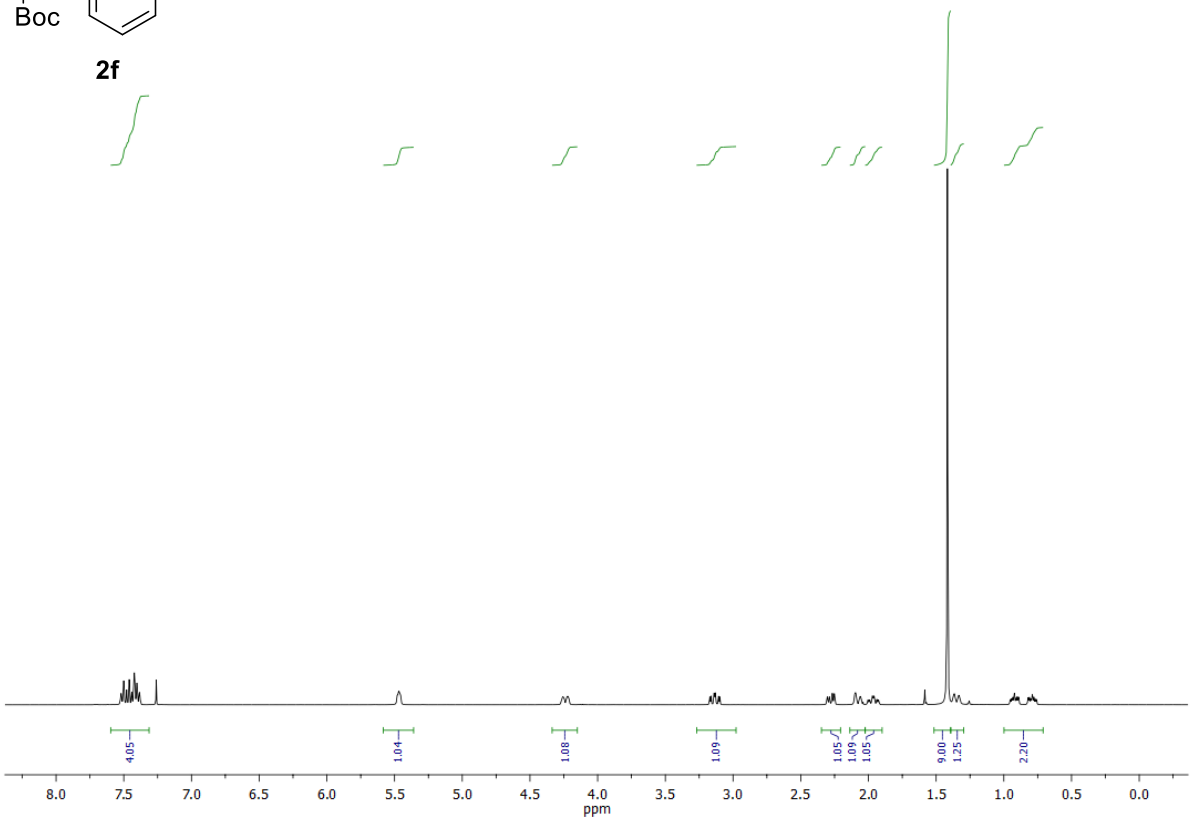

F
F
N
Boc
Me

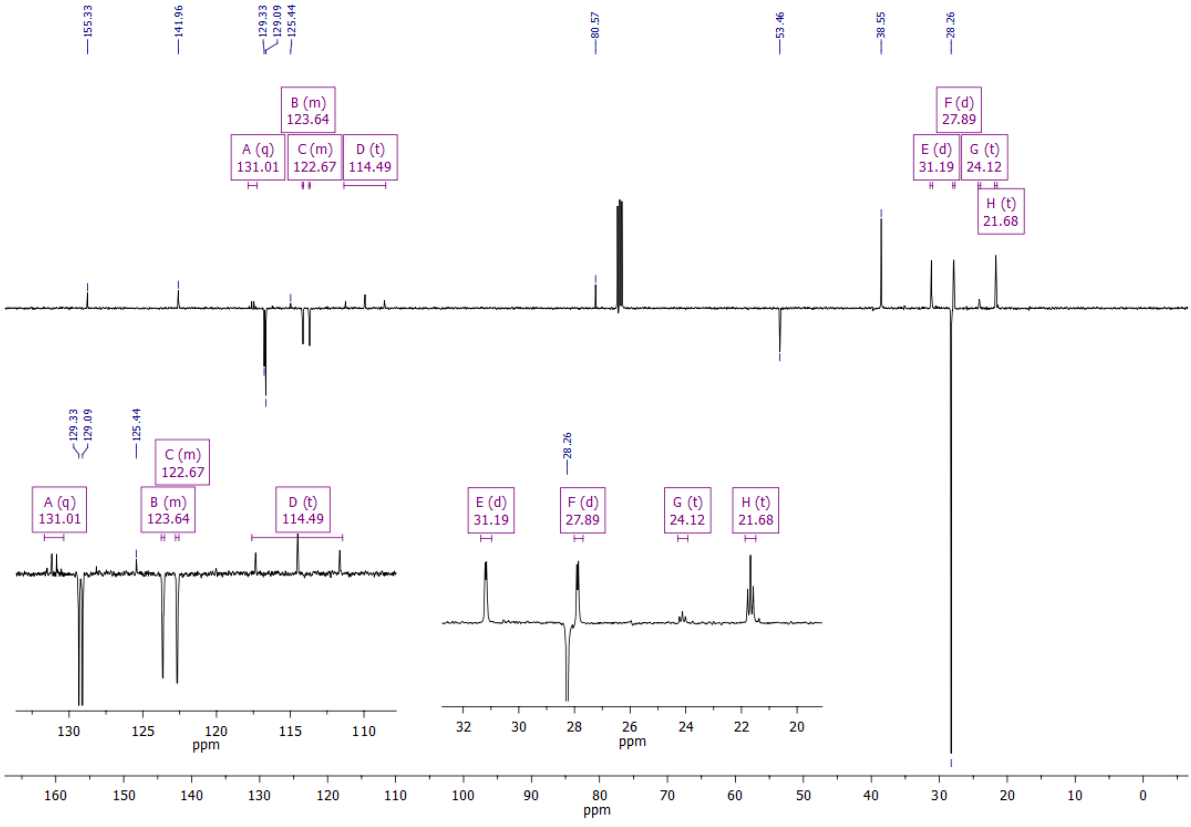
2e (^{19}F-NMR)

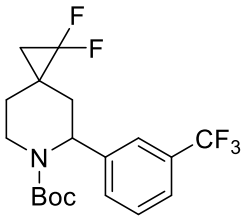
B (dd)
-141.90
A (dd)
-139.65
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
CF3
N
Boc

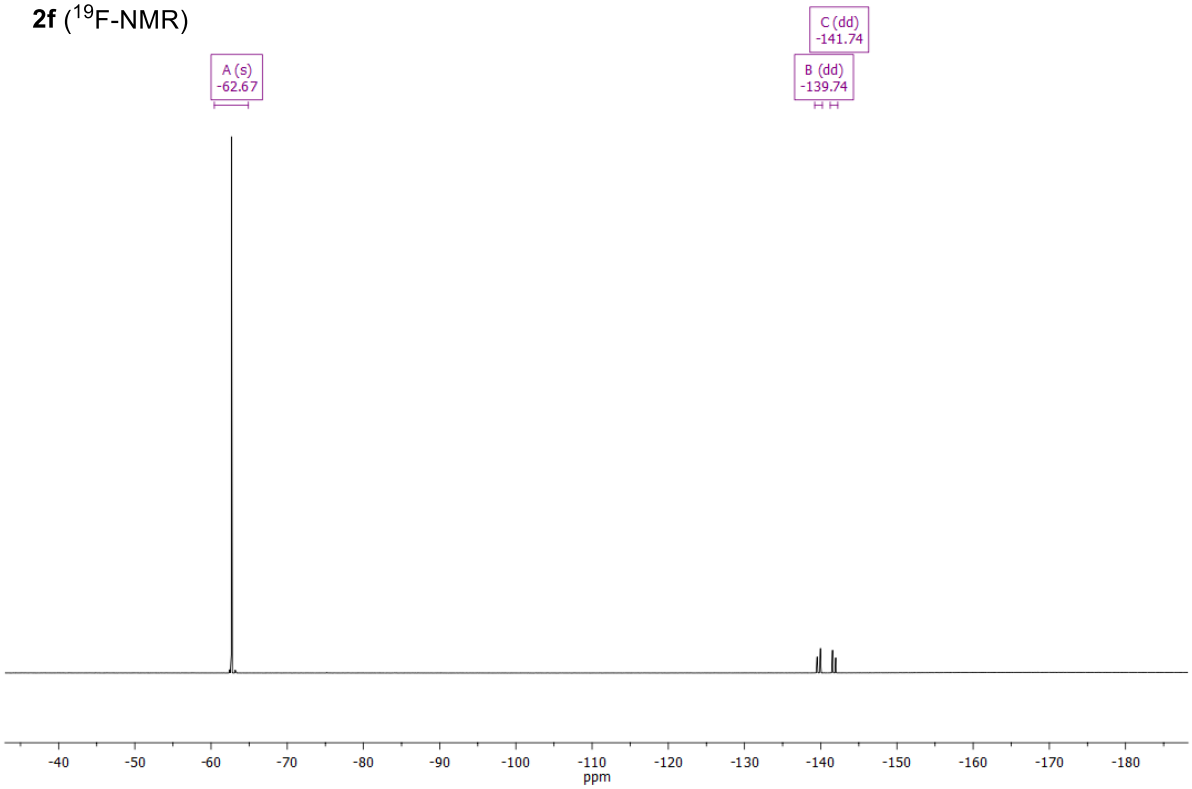
2f


4.05
1.04
1.00
1.09
1.05
1.09
1.05
9.00
1.25
2.20
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
ppm

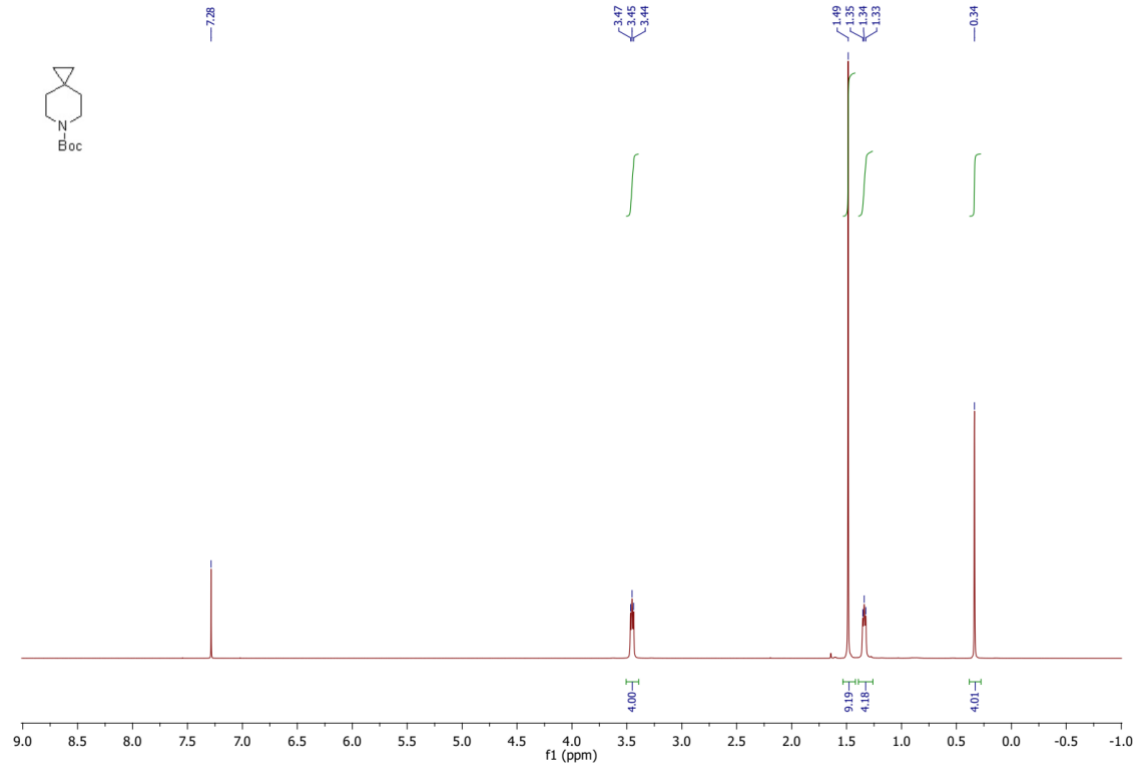

155.33
141.96
129.33
129.09
125.44
80.57
53.46
38.55
28.26
B (m)
123.64
A (q)
131.01
C (m)
122.67
D (t)
114.49
F (d)
27.89
E (d)
31.19
G (t)
24.12
H (t)
21.68
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
F
CF3
N
Boc

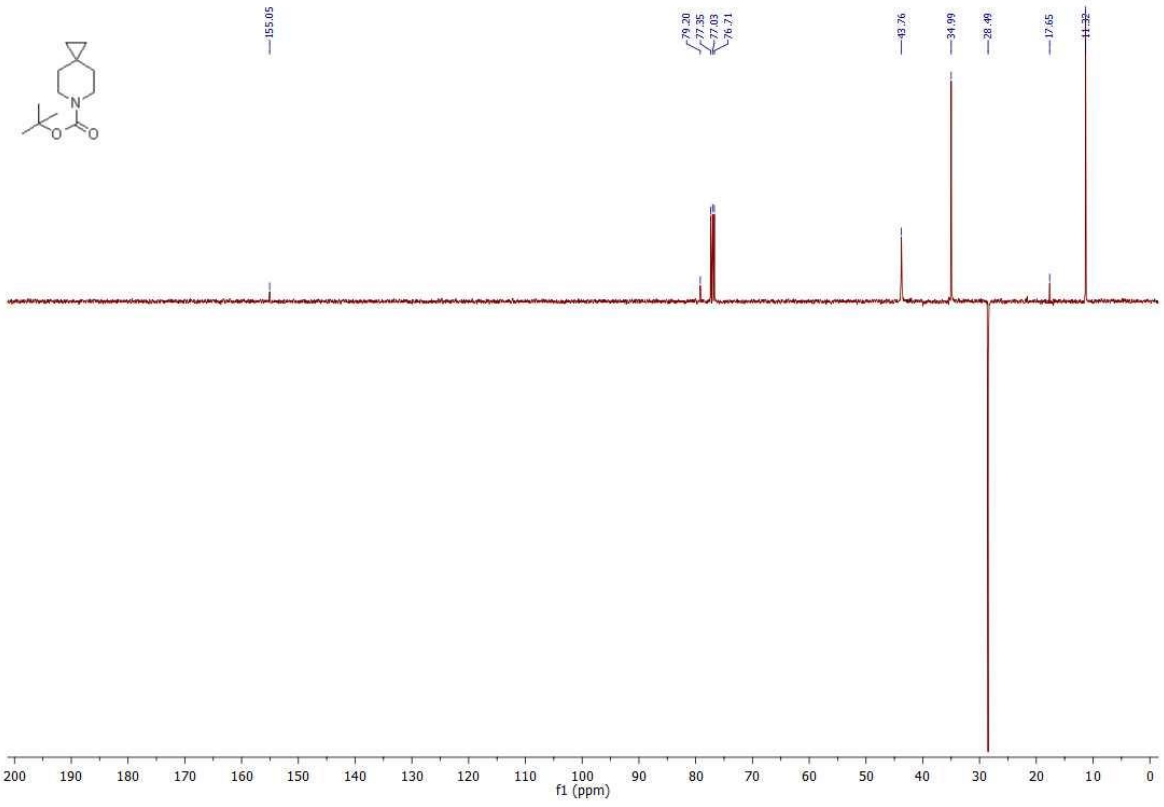
2f (^{19}F-NMR)


A (s)
-62.67
C (dd)
-141.74
B (dd)
-139.74
-40
-50
-60
-70
-80
-90
-100
-110
ppm
-120
-130
-140
-150
-160
-170
-180

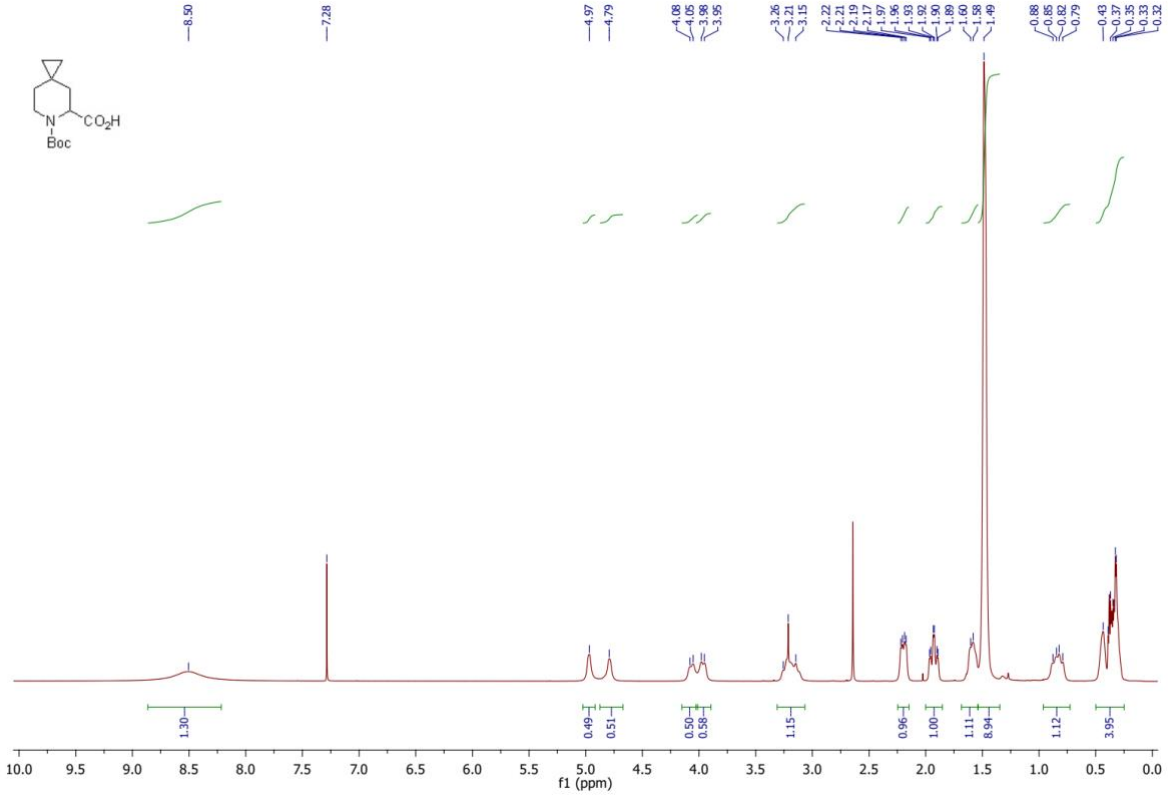
Precursor to compound **4** (^{1}H NMR, $CDCl_3$)



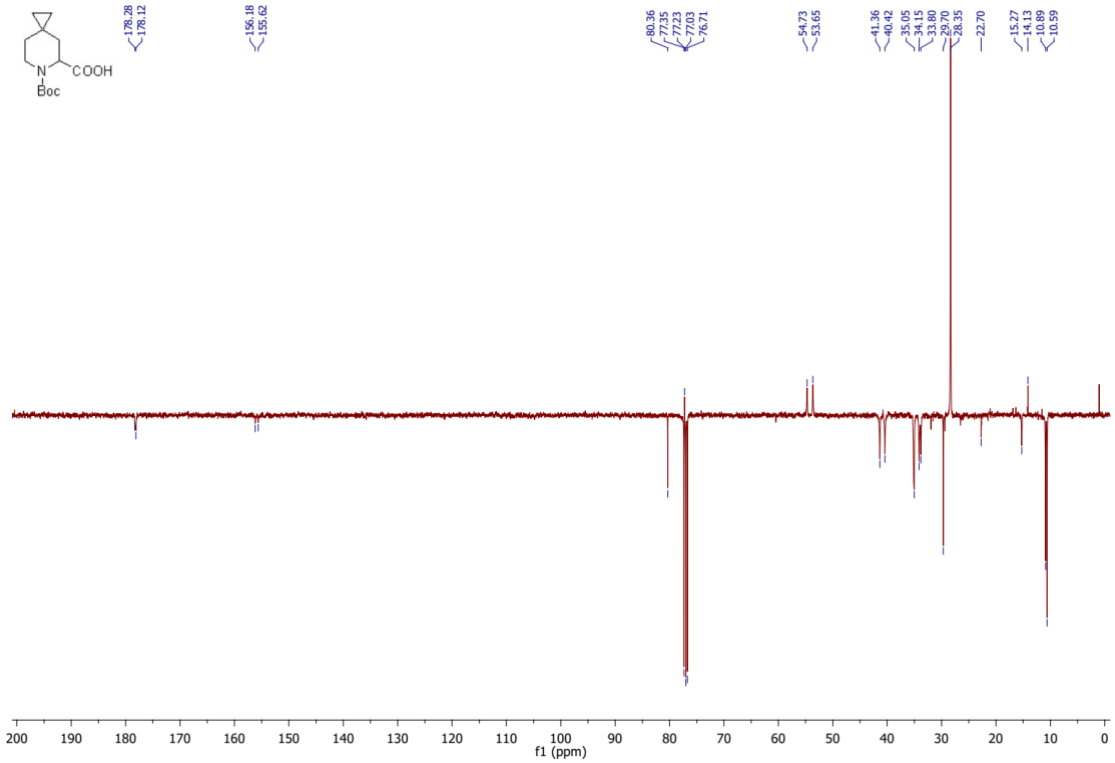
Precursor to compound **4** (^{13}C NMR, $CDCl_3$)



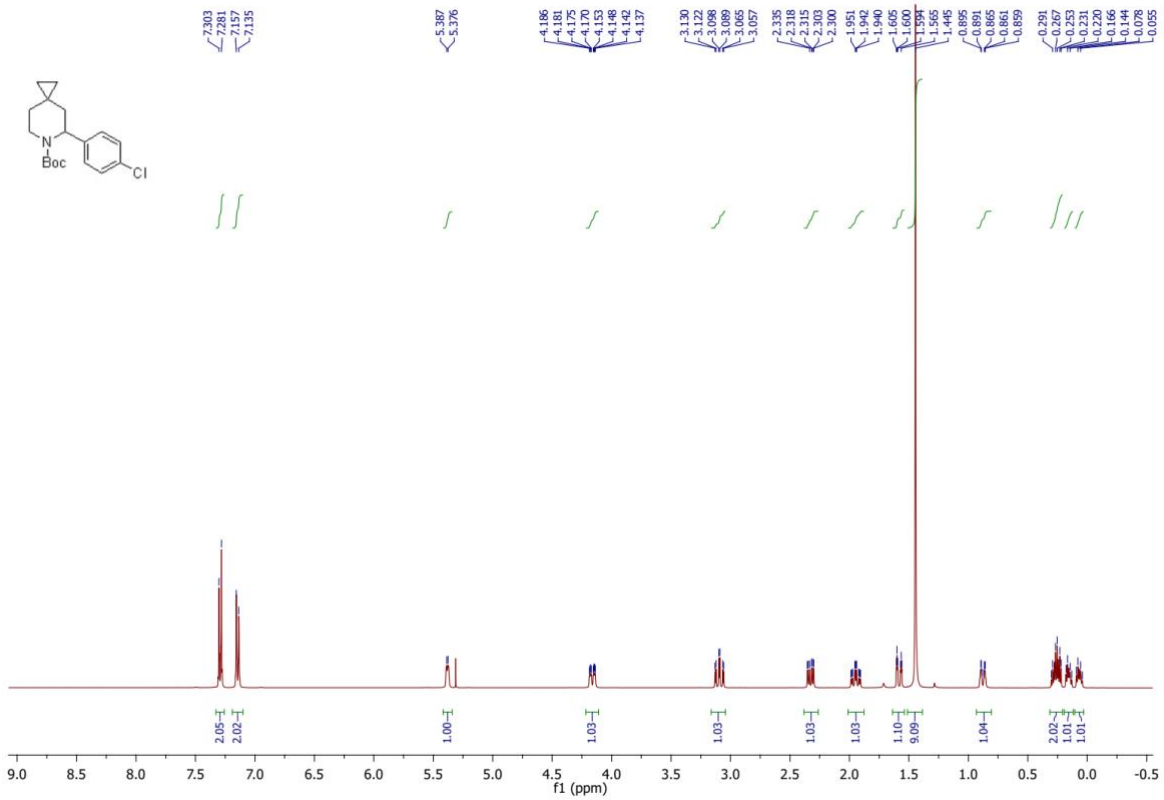
Compound **4** (^{1}H NMR, $CDCl_3$)



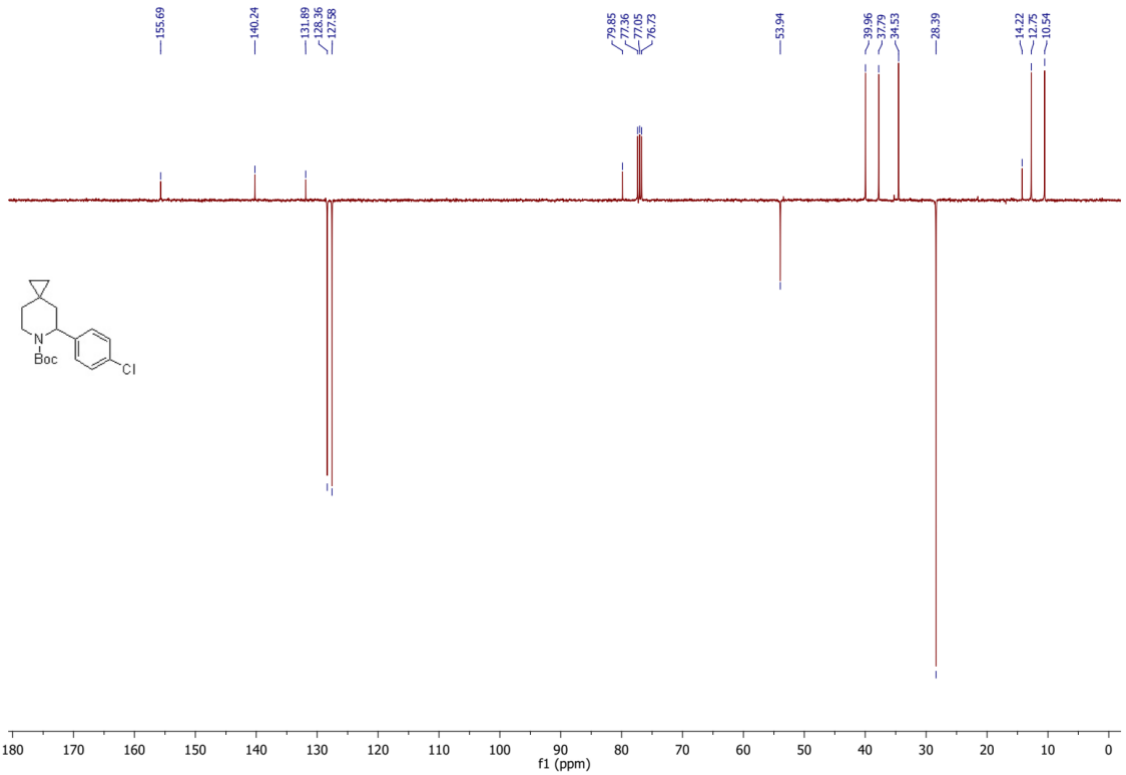
Compound **4** (^{13}C NMR, $CDCl_3$)



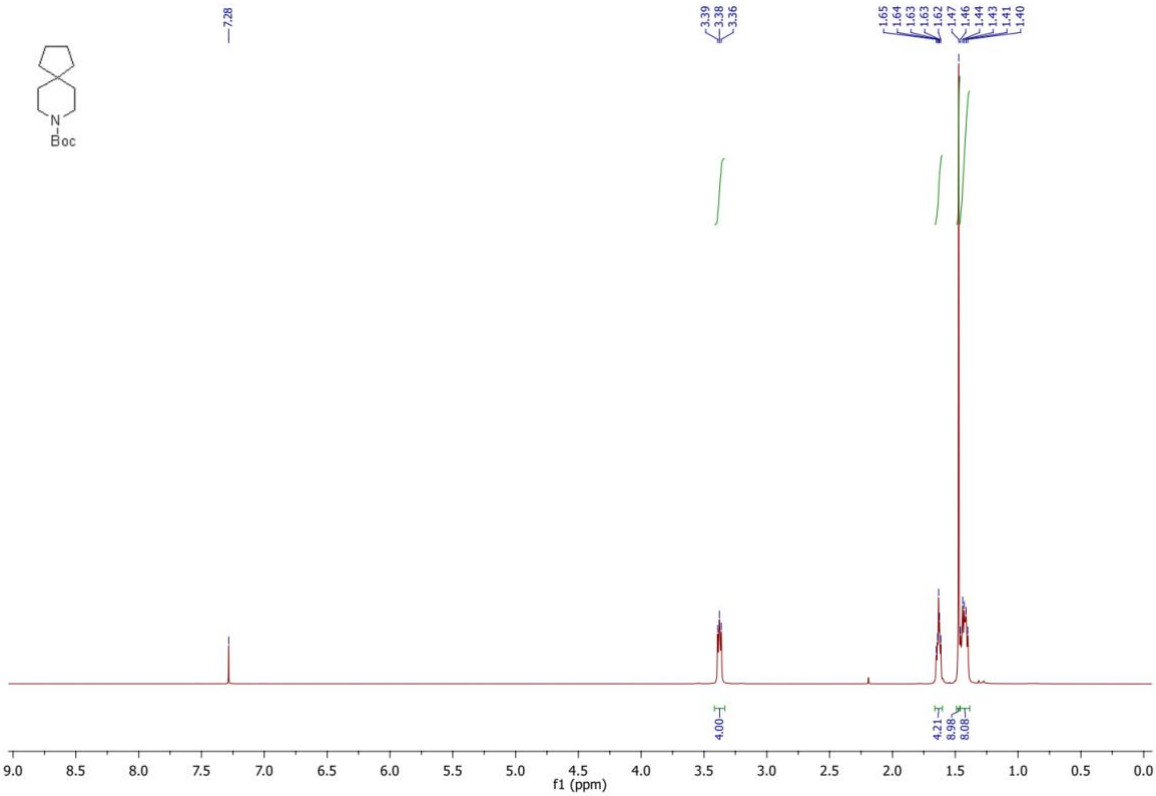
Compound **5** (^{1}H NMR, $CDCl_3$)



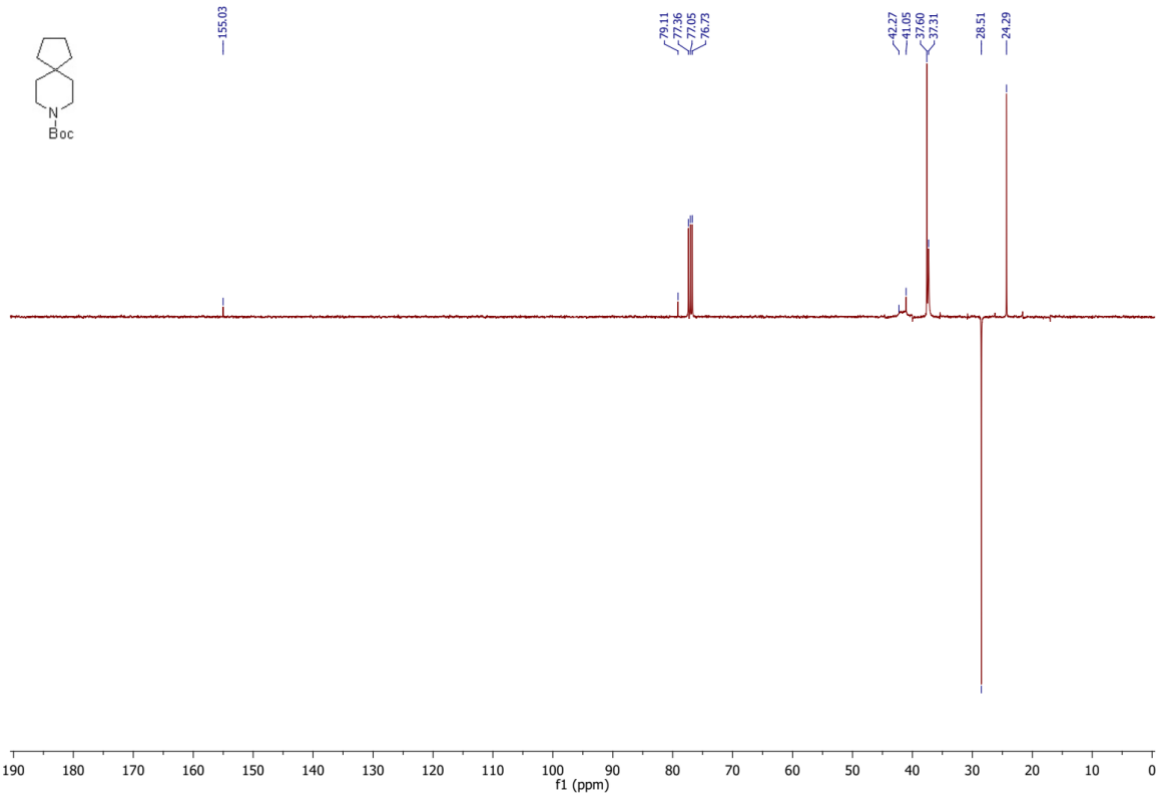
Compound **5** (^{13}C NMR, $CDCl_3$)



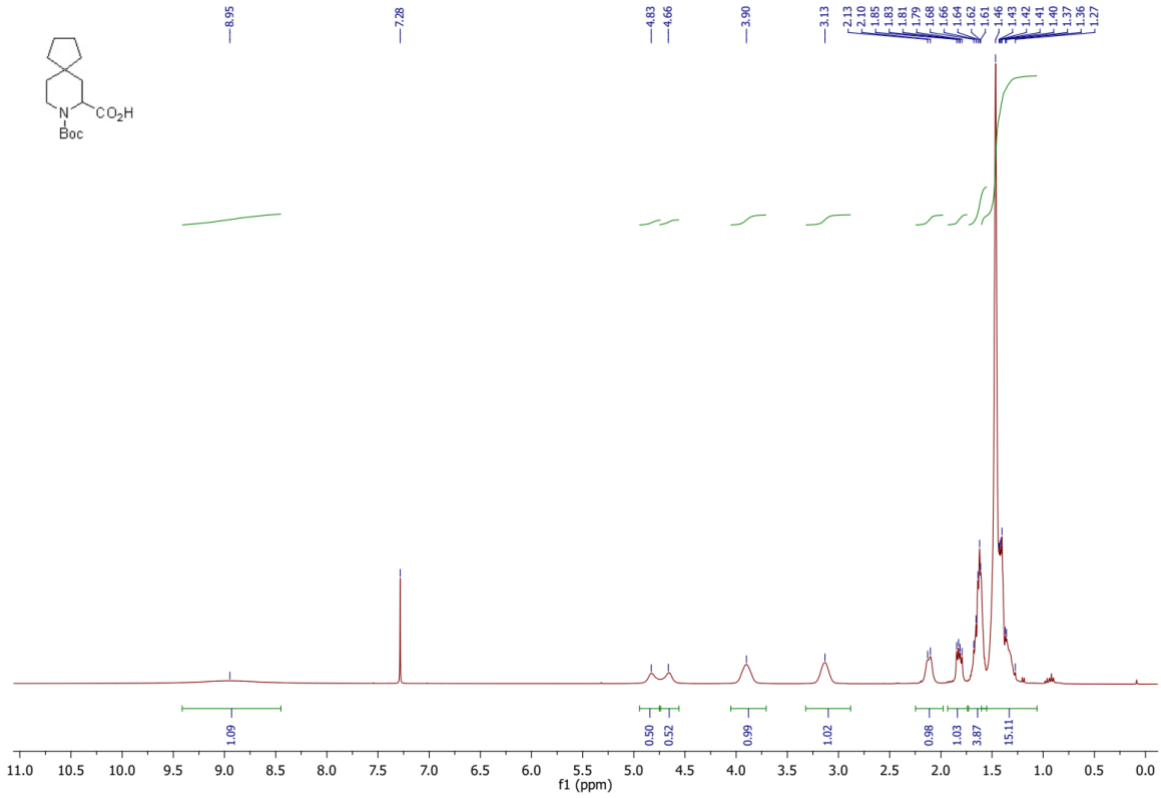
Compound **6** (^{1}H NMR, $CDCl_3$)



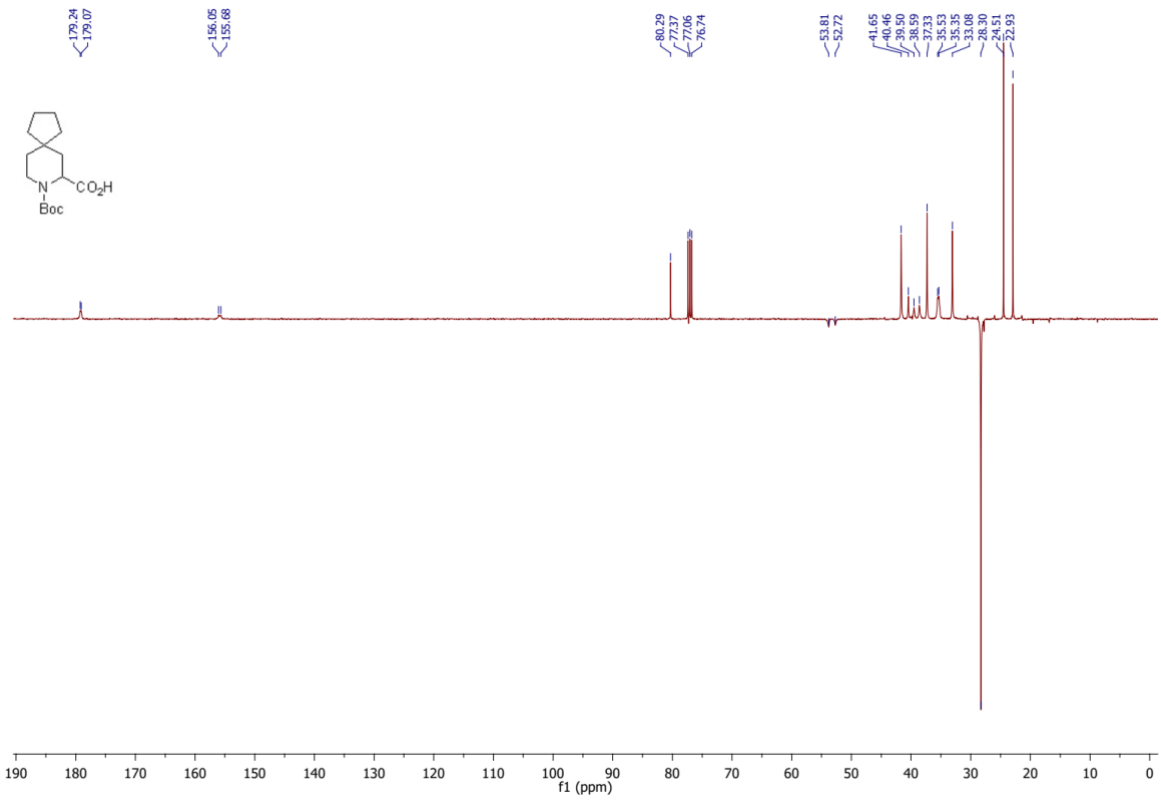
Compound **6** (^{13}C NMR, $CDCl_3$)



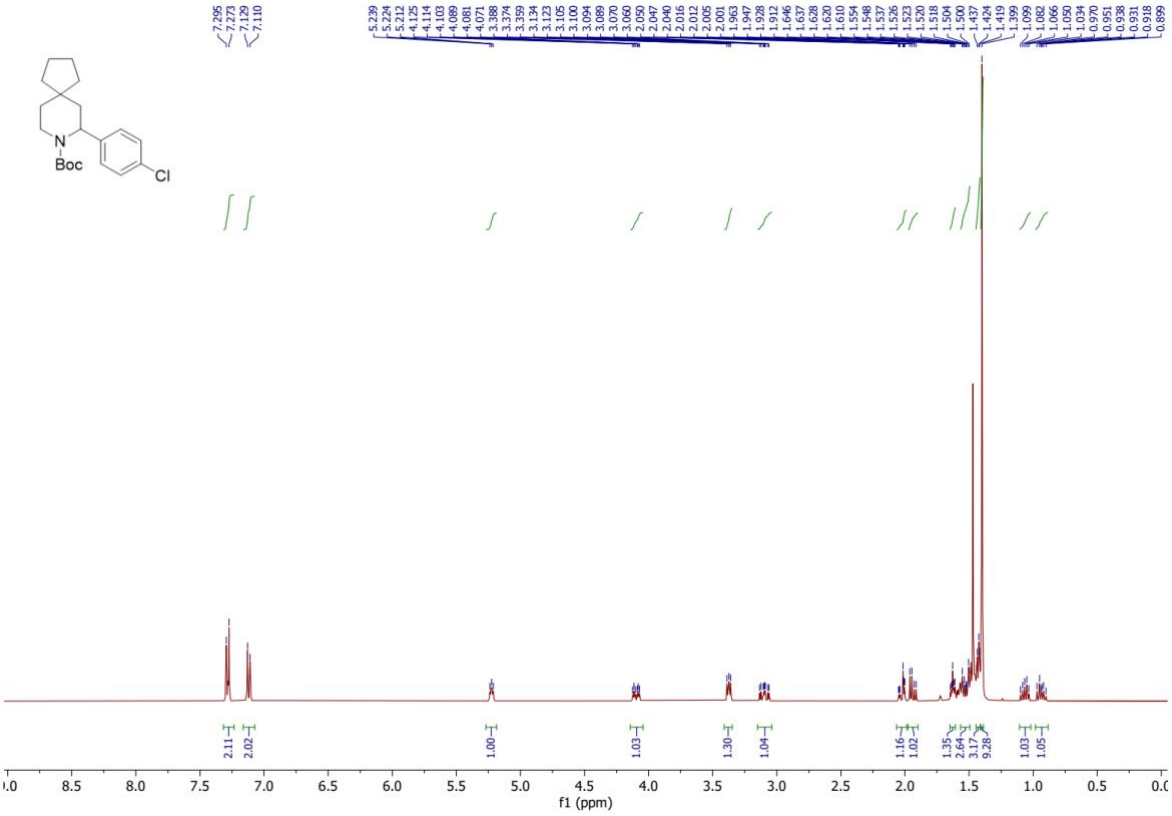
Compound **7** (^{1}H NMR, $CDCl_3$)



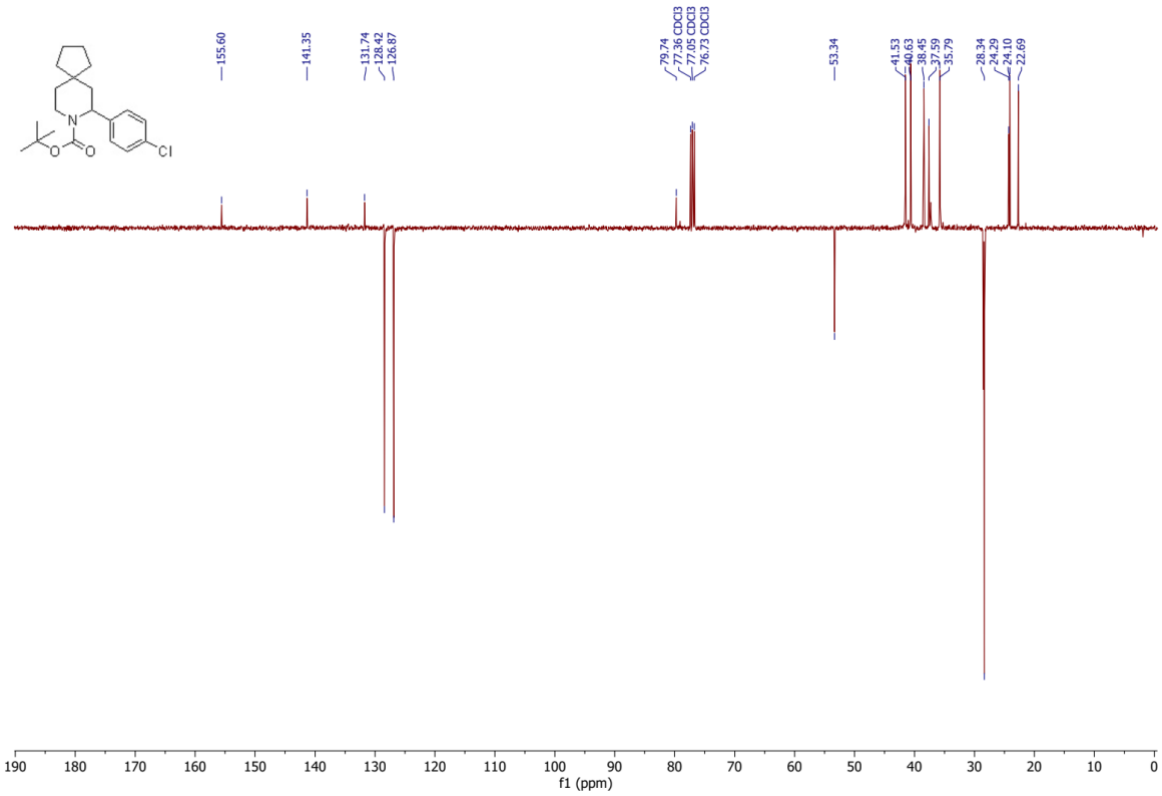
Compound **7** (^{13}C NMR, $CDCl_3$)

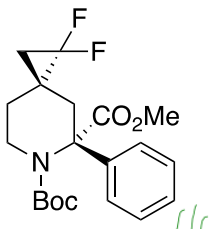


Compound **8** (^{1}H NMR, $CDCl_3$)

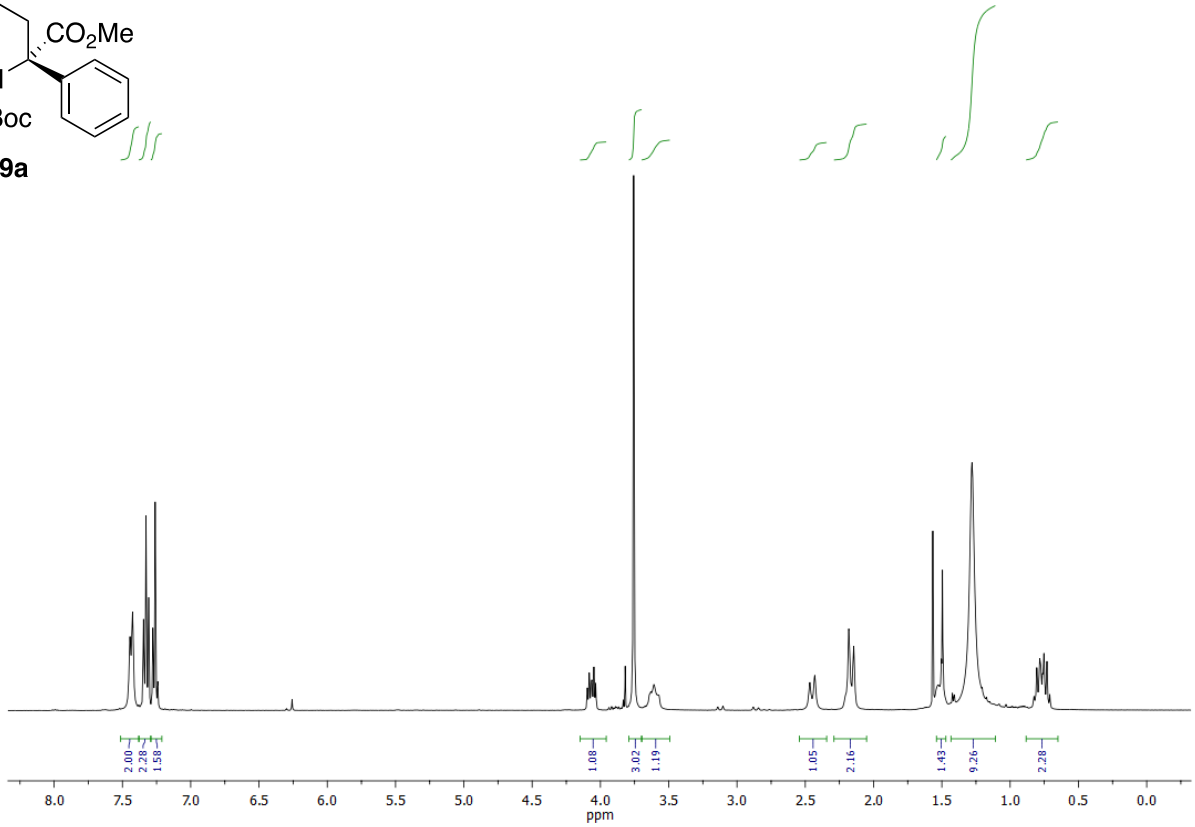


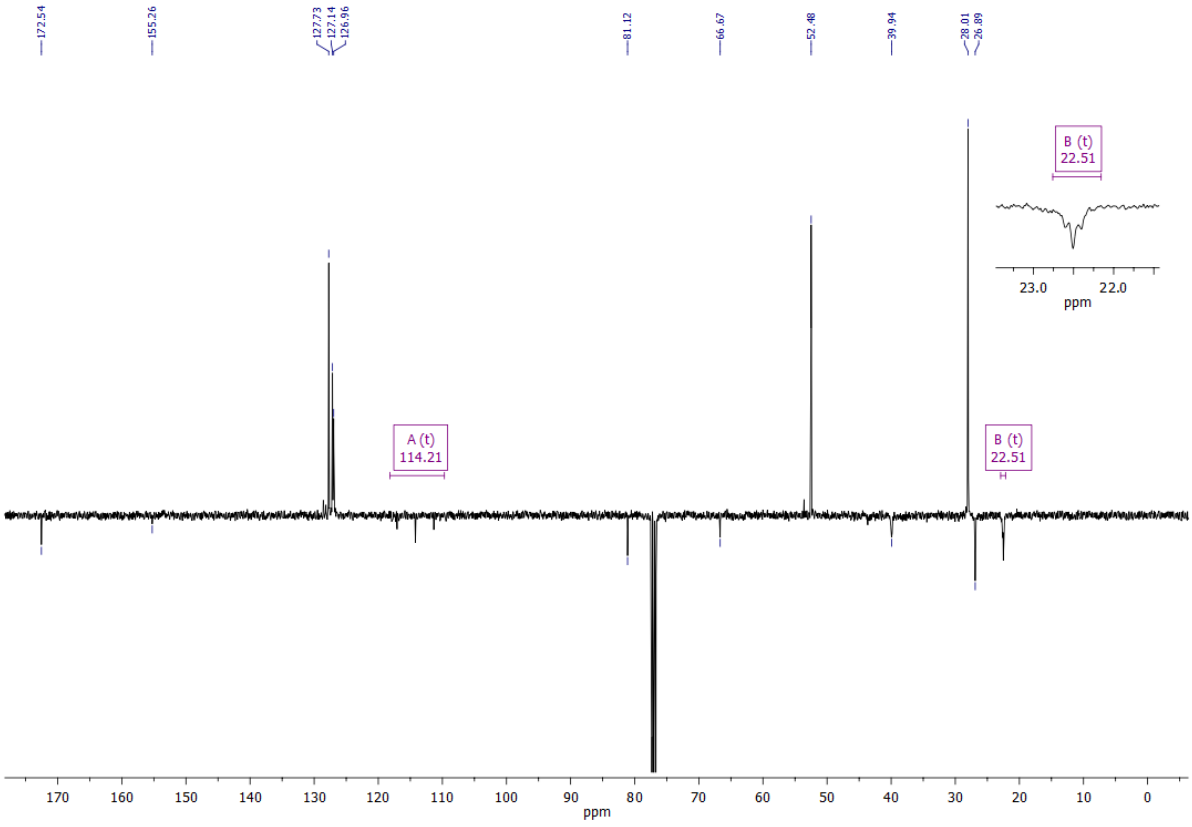
Compound **8** (^{13}C NMR, $CDCl_3$)

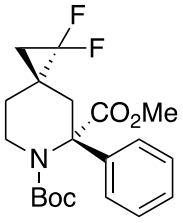



F
F
CO2Me
N
Boc

9a

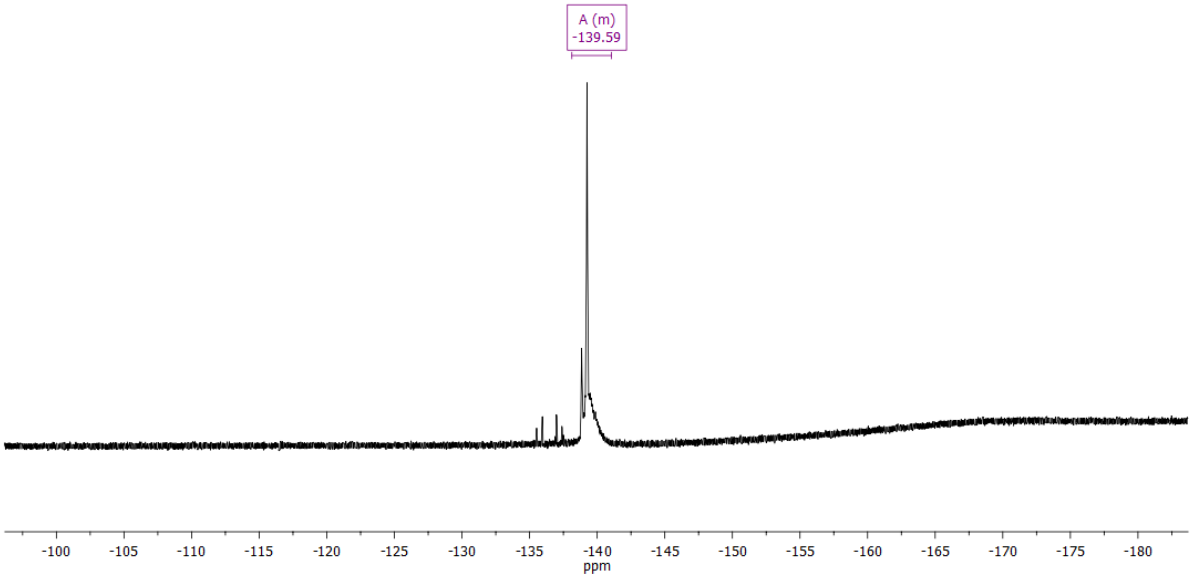

2.00
2.28
1.58
1.08
3.02
1.19
1.05
2.16
1.43
9.26
2.28
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

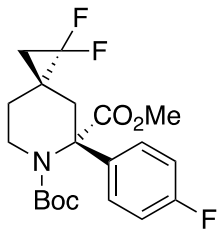

172.54
155.26
127.73
127.14
126.96
81.12
66.67
52.48
39.94
28.01
26.89
B (t)
22.51
23.0
22.0
ppm
A (t)
114.21
B (t)
22.51
H
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
F
CO2Me
N
Boc

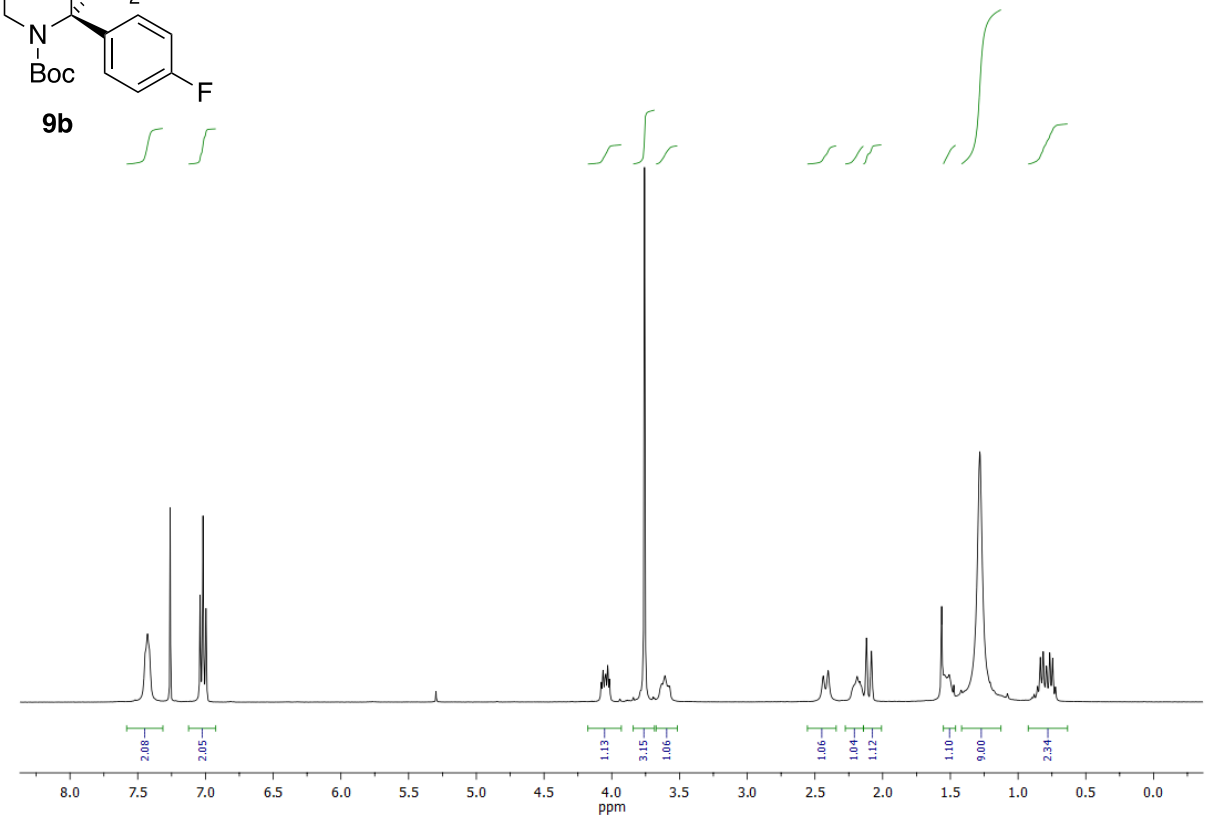
9a

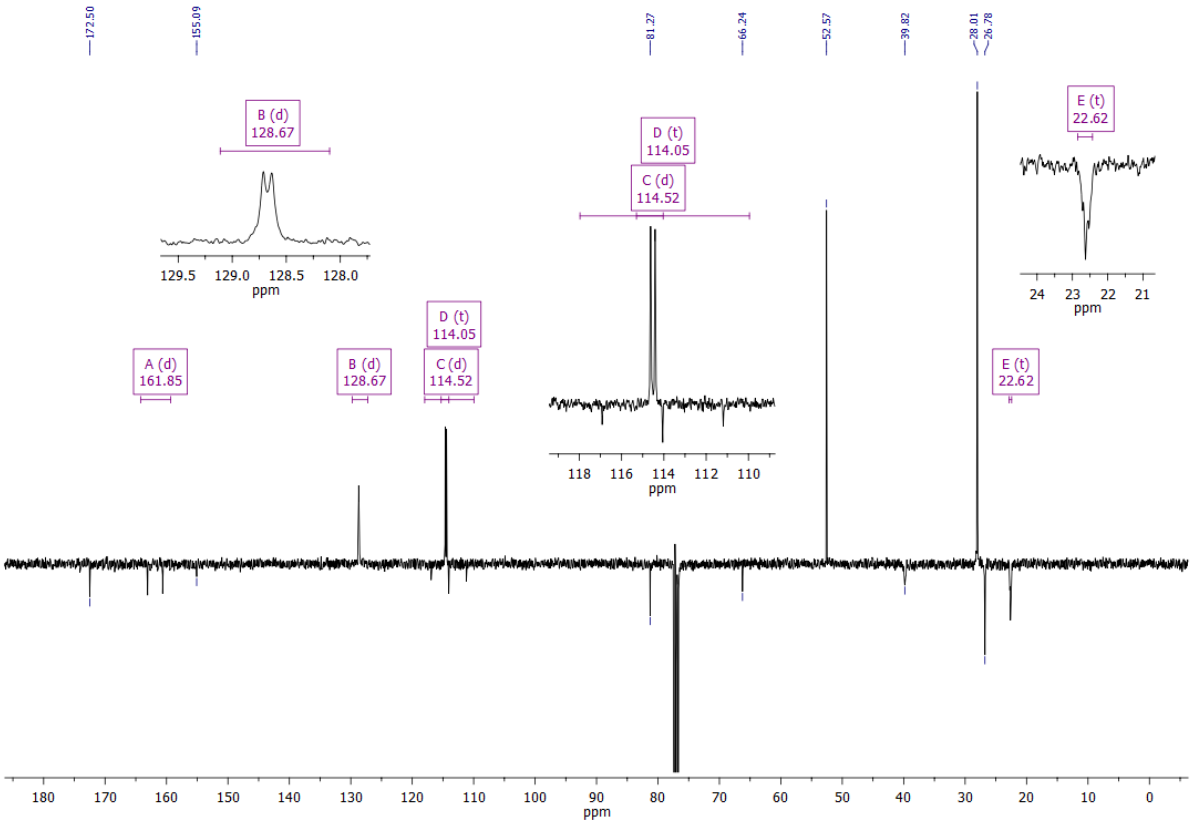
(^{19}F NMR)

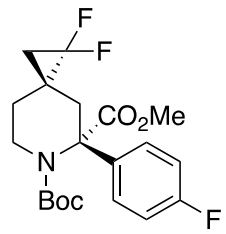

A (m)
-139.59
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
CO2Me
N
Boc
F

9b

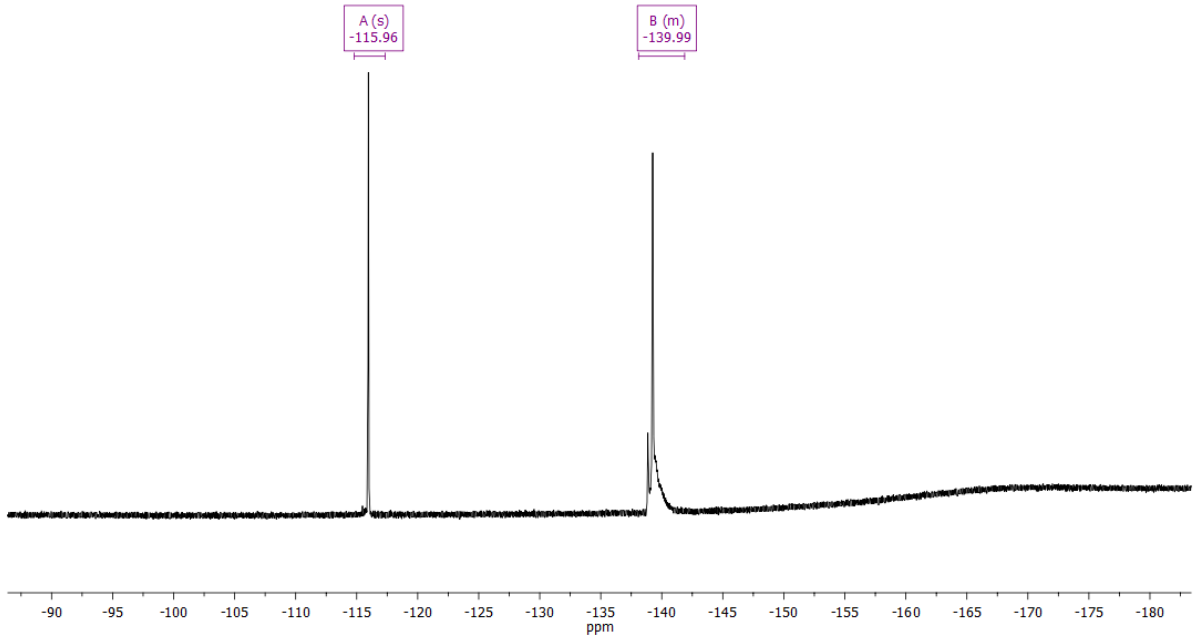

2.08
2.05
1.13
3.15
1.06
1.06
1.04
1.12
1.10
9.00
2.34
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

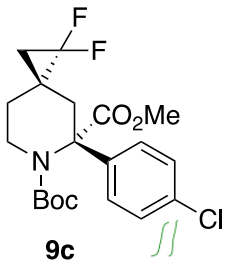

172.50
155.09
81.27
66.24
52.57
39.82
28.01
26.78
B (d)
128.67
129.5 129.0 128.5 128.0
ppm
D (t)
114.05
C (d)
114.52
118 116 114 112 110
ppm
E (t)
22.62
24 23 22 21
ppm
A (d)
161.85
B (d)
128.67
D (t)
114.05
C (d)
114.52
E (t)
22.62
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


F
F
CO2Me
N
Boc
F

9b

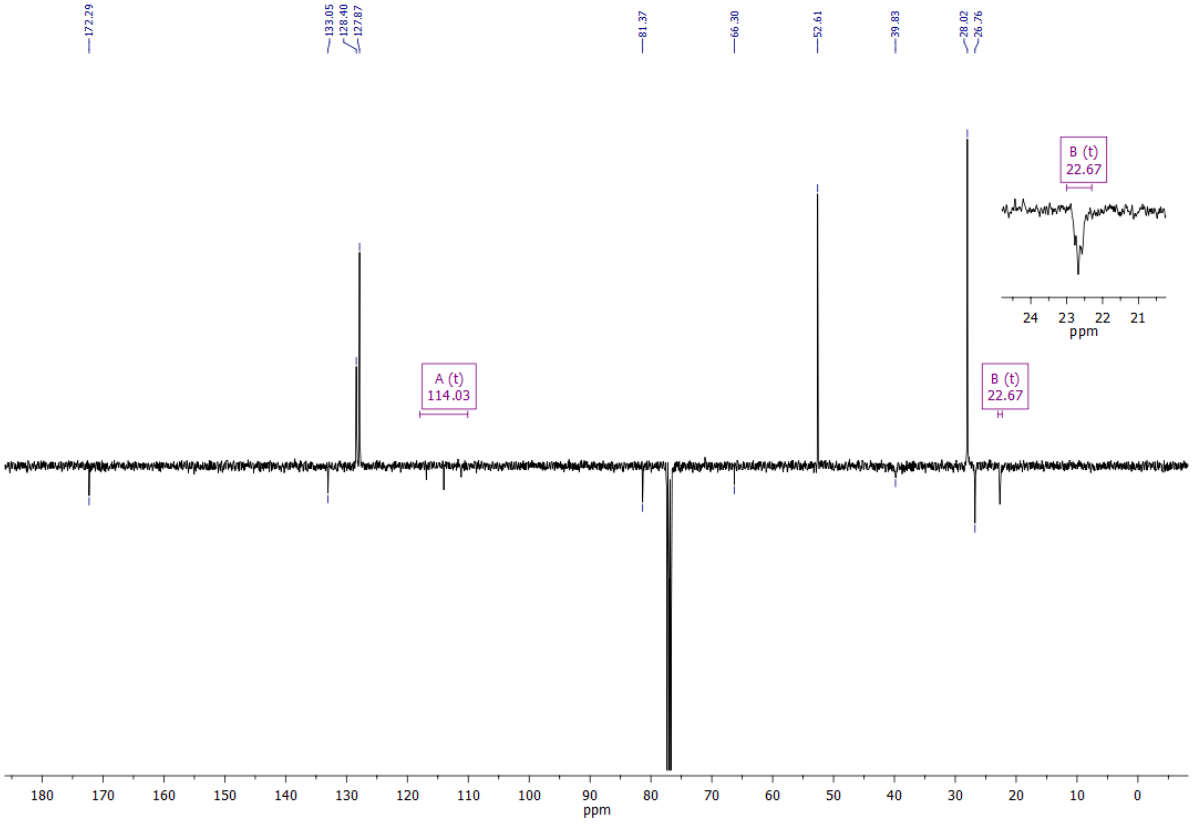
(^{19}F NMR)

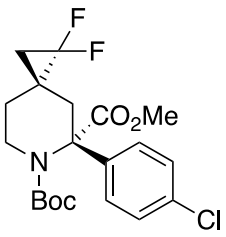

A (s)
-115.96
B (m)
-139.99
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
CO2Me
N
Boc
Cl

9c

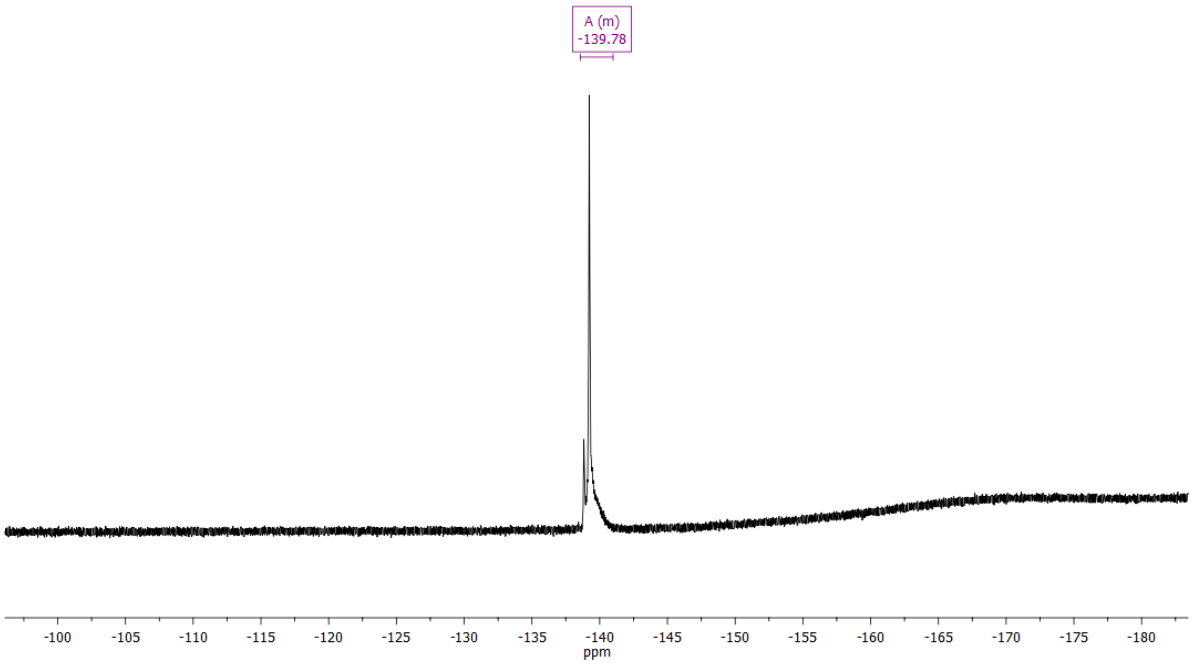
2.00
2.11
1.09
3.15
1.17
1.07
1.04
1.14
1.08
9.08
2.40
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

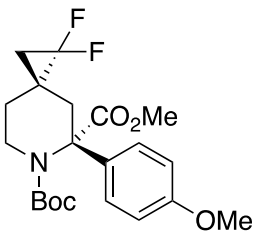

172.29
133.05
128.40
127.87
81.37
66.30
52.61
39.83
28.02
26.76
A (t)
114.03
B (t)
22.67
B (t)
22.67
24
23
22
21
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
F
CO2Me
N
Boc
Cl

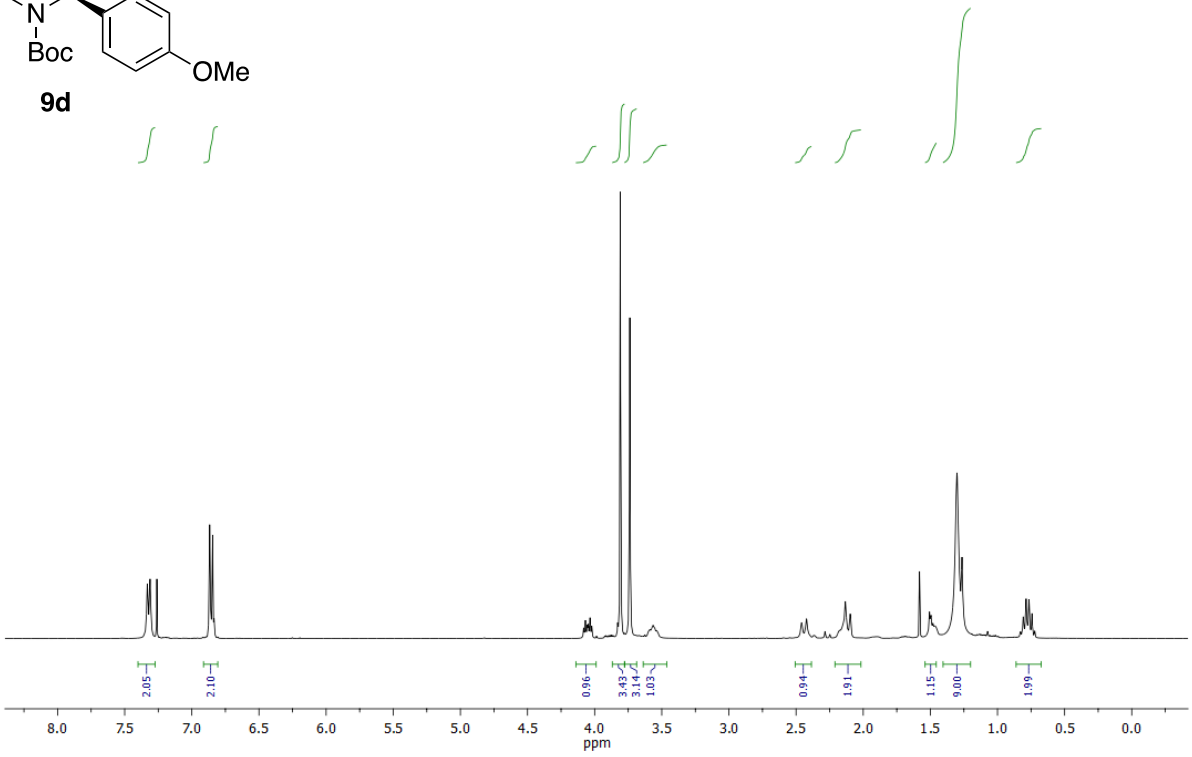
9c

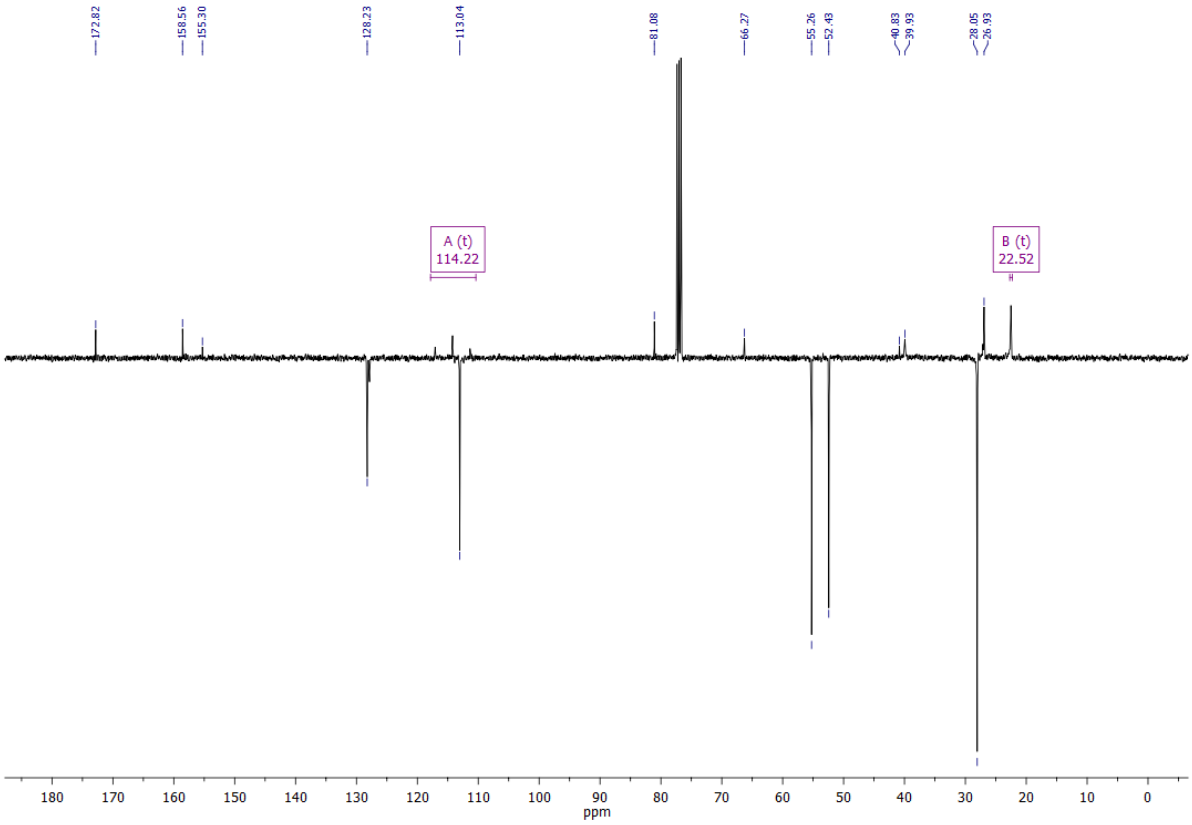
(^{19}F NMR)

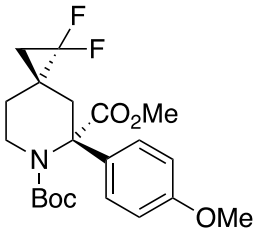

A (m)
-139.78
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
CO2Me
N
Boc
OMe

9d

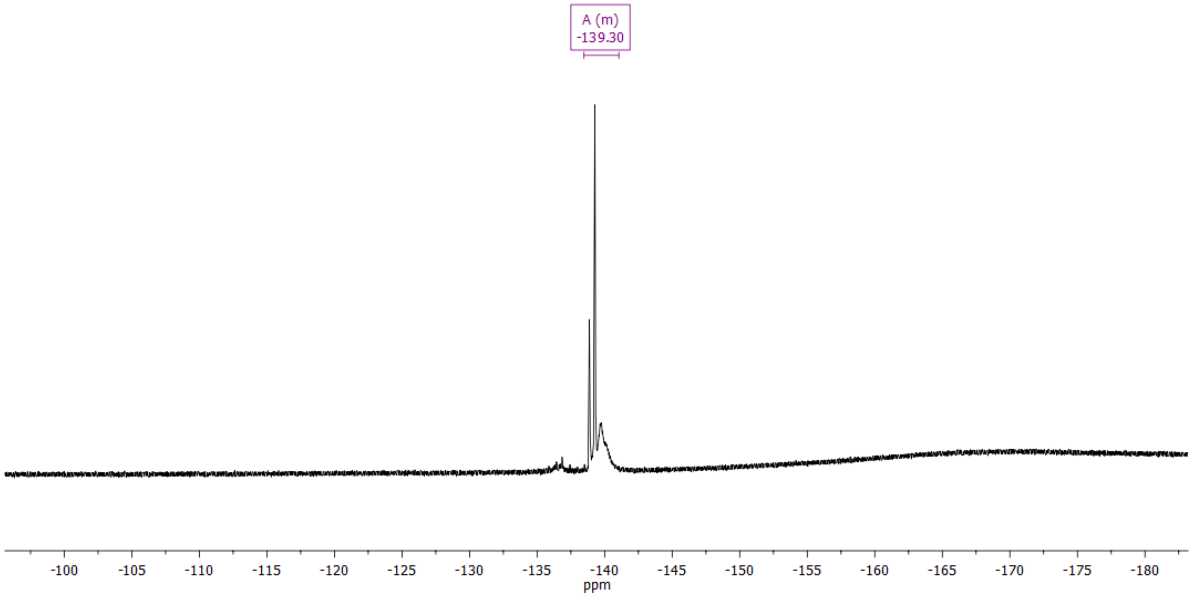

2.05
2.10
0.96
3.43
3.14
1.03
0.94
1.91
1.15
9.00
1.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

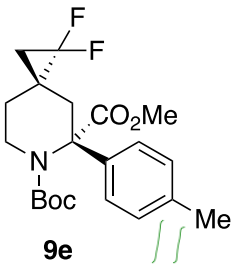

172.82
158.56
155.30
128.23
113.04
81.08
66.27
55.26
52.43
40.83
39.93
28.05
26.93
A (t)
114.22
B (t)
22.52
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
F
CO2Me
N
Boc
OMe

9d

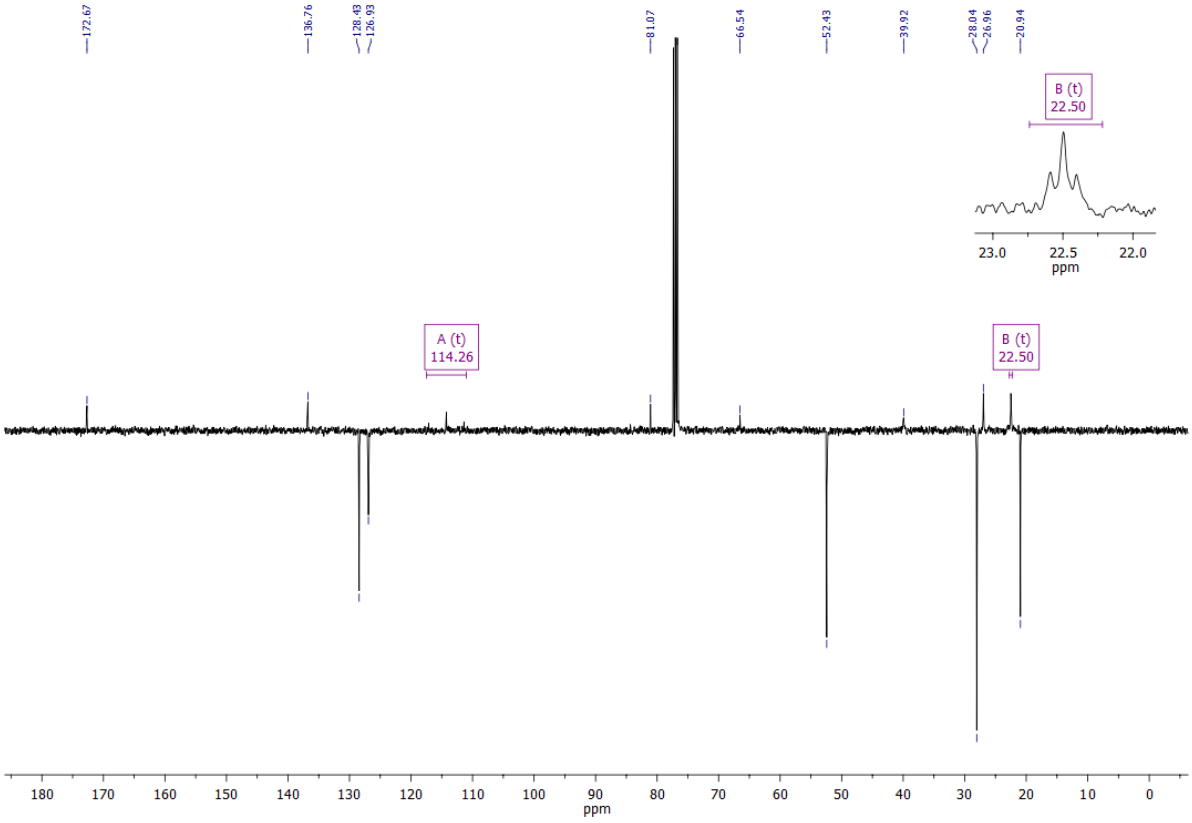
(^{19}F NMR)

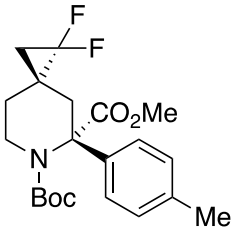

A (m)
-139.30
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
CO2Me
N
Boc
Me

9e

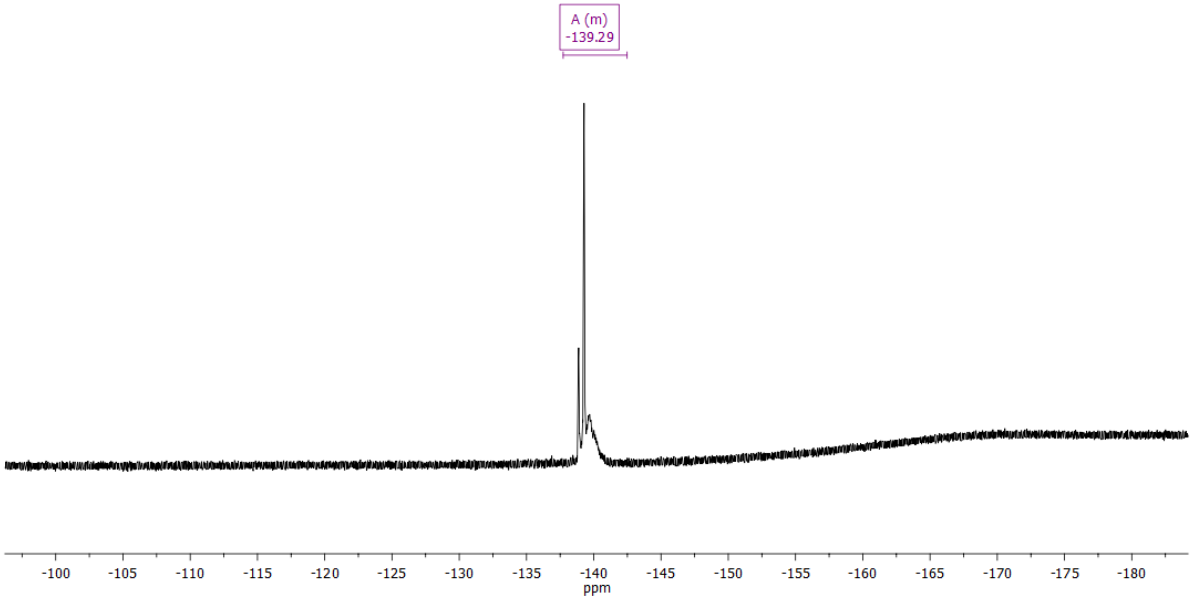
2.47
2.07
1.06
3.11
1.08
1.04
3.21
2.12
1.55
9.00
2.23
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

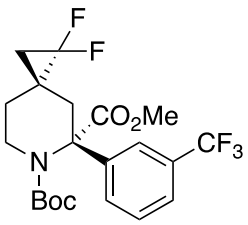

172.67
136.76
128.48
126.93
81.07
66.54
52.43
39.92
28.04
26.96
20.94
B (t)
22.50
23.0
22.5
22.0
ppm
A (t)
114.26
B (t)
22.50
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
F
CO2Me
N
Boc
Me

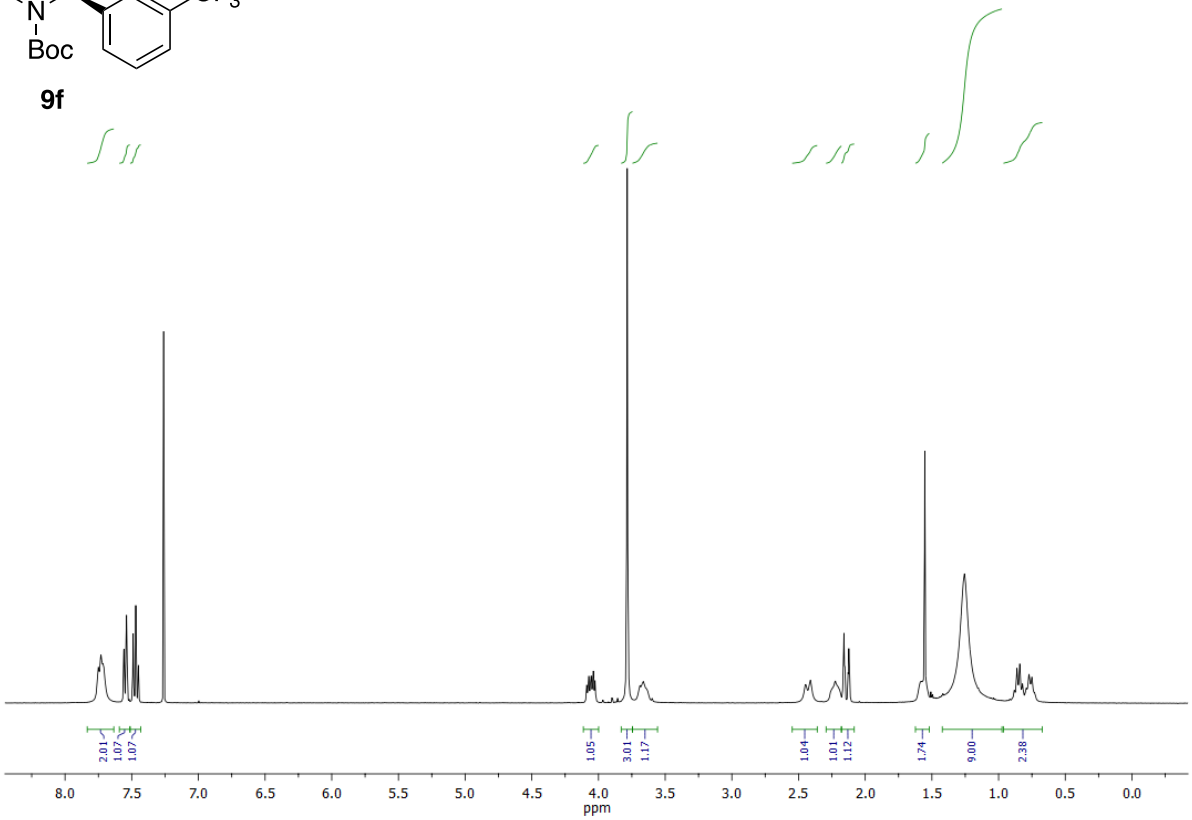
9e

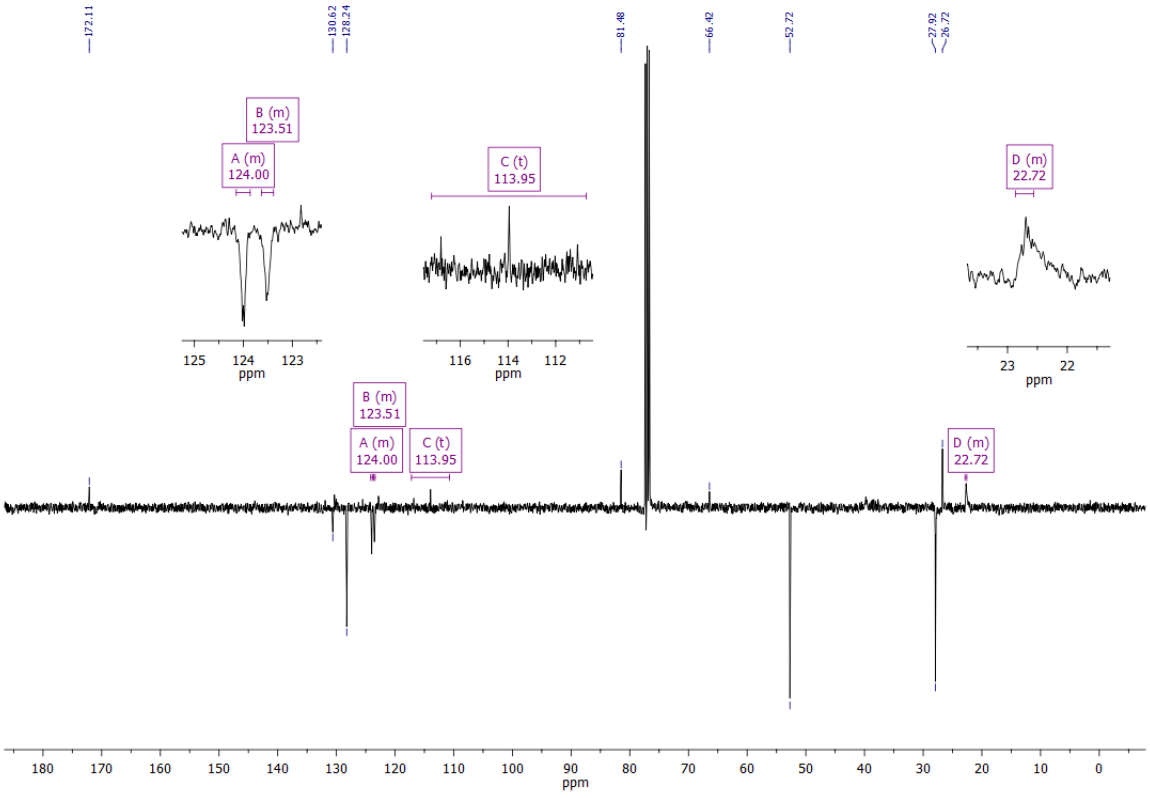
(^{19}F NMR)

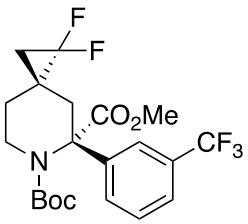

A (m)
-139.29
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
CO2Me
CF3
N
Boc

9f

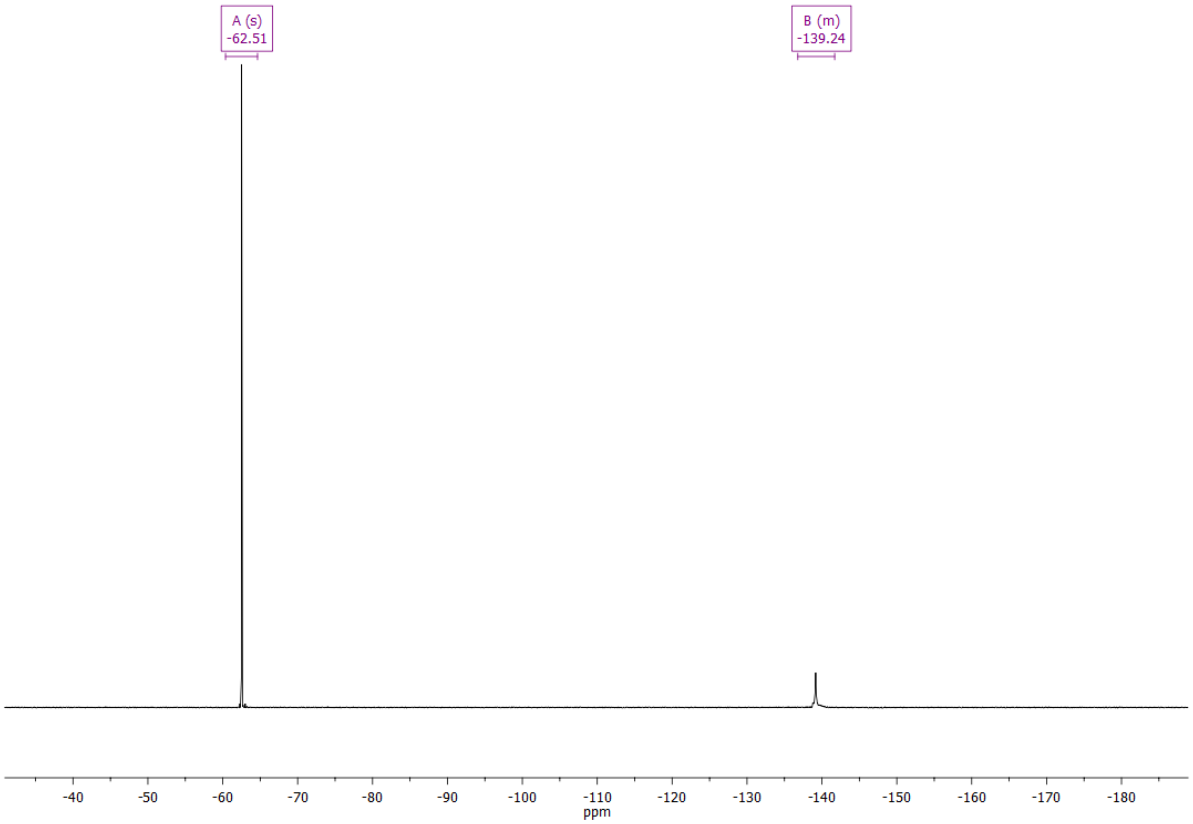

2.01
1.07
1.07
1.05
3.01
1.17
1.04
1.01
1.12
1.74
9.00
2.38
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

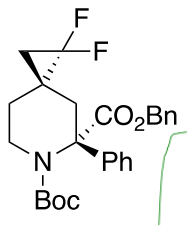

172.11
130.62
128.24
81.48
66.42
52.72
27.92
26.72
B (m)
123.51
A (m)
124.00
C (t)
113.95
D (m)
22.72
125
124
123
116
114
112
23
22
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F
F
CO2Me
CF3
N
Boc

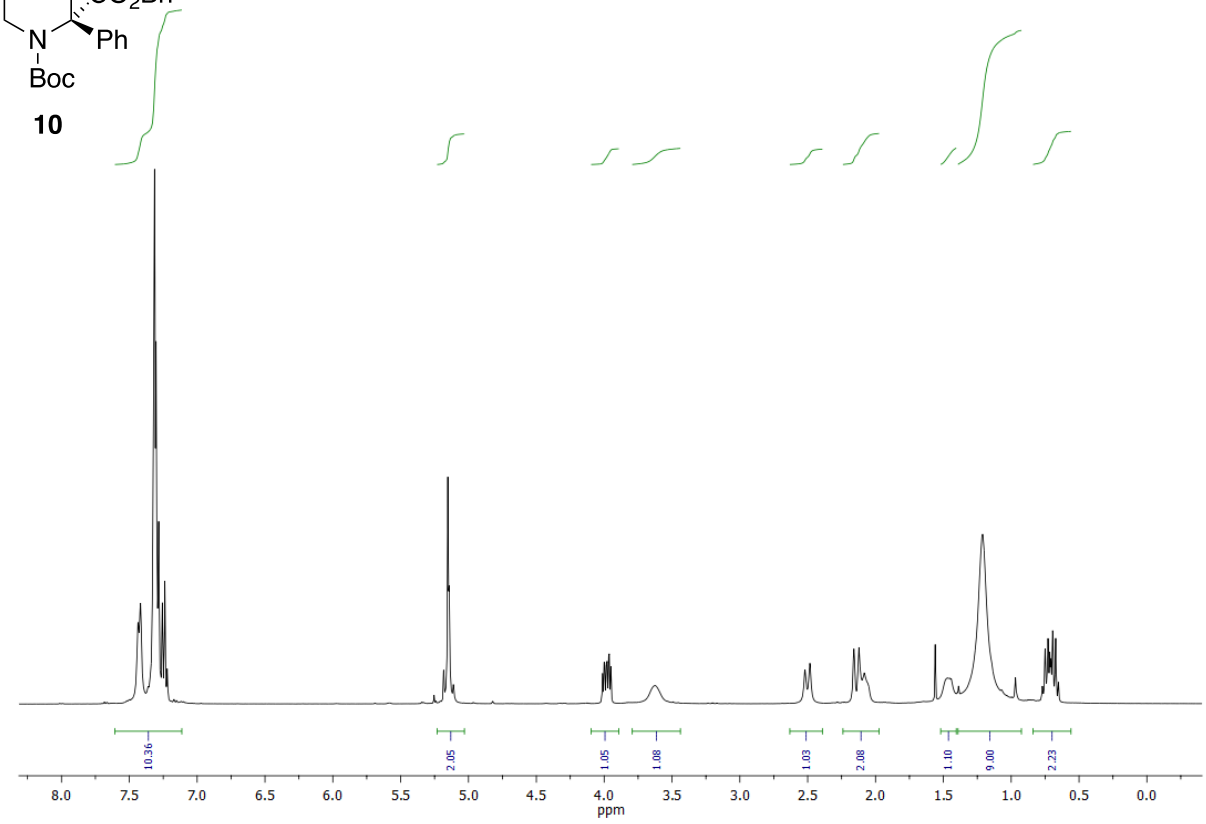
9f

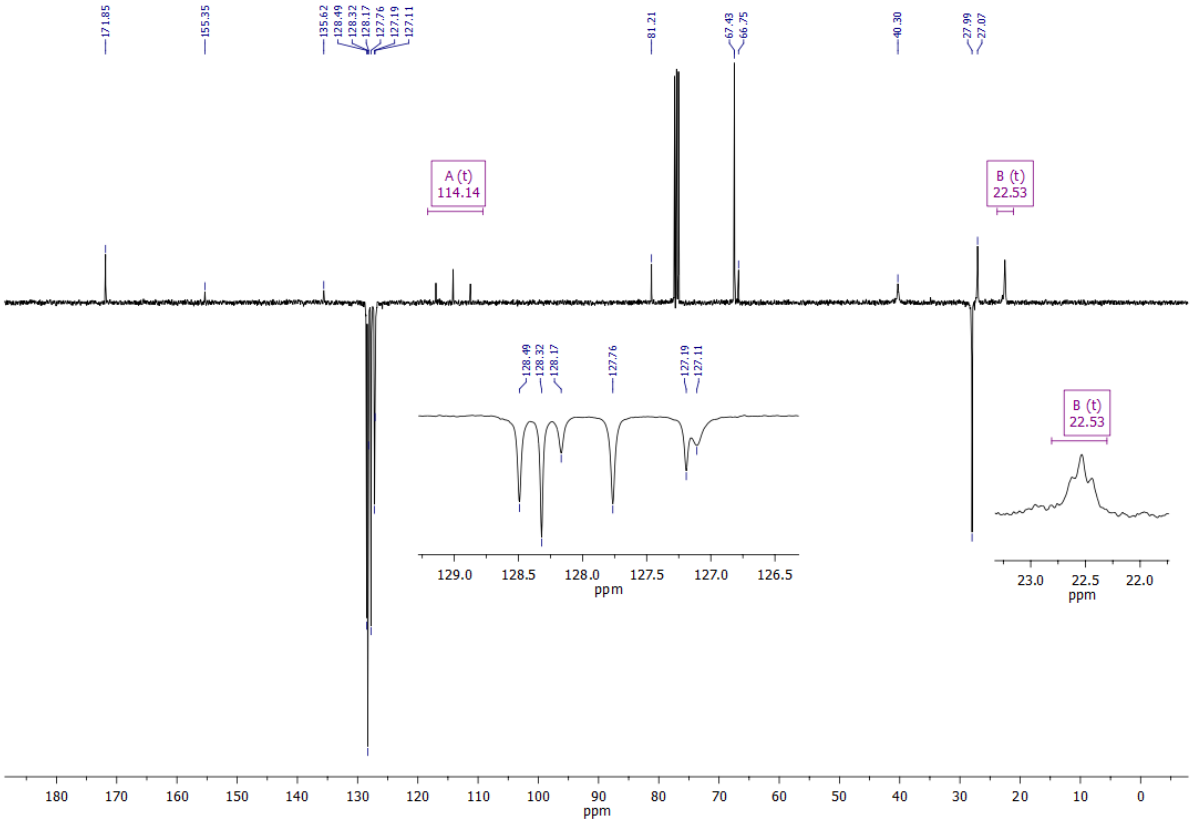
(^{19}F NMR)

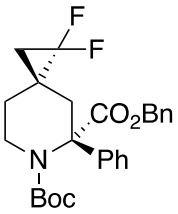

A (s)
-62.51
B (m)
-139.24
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm


F
F
CO2Bn
N
Ph
Boc

10

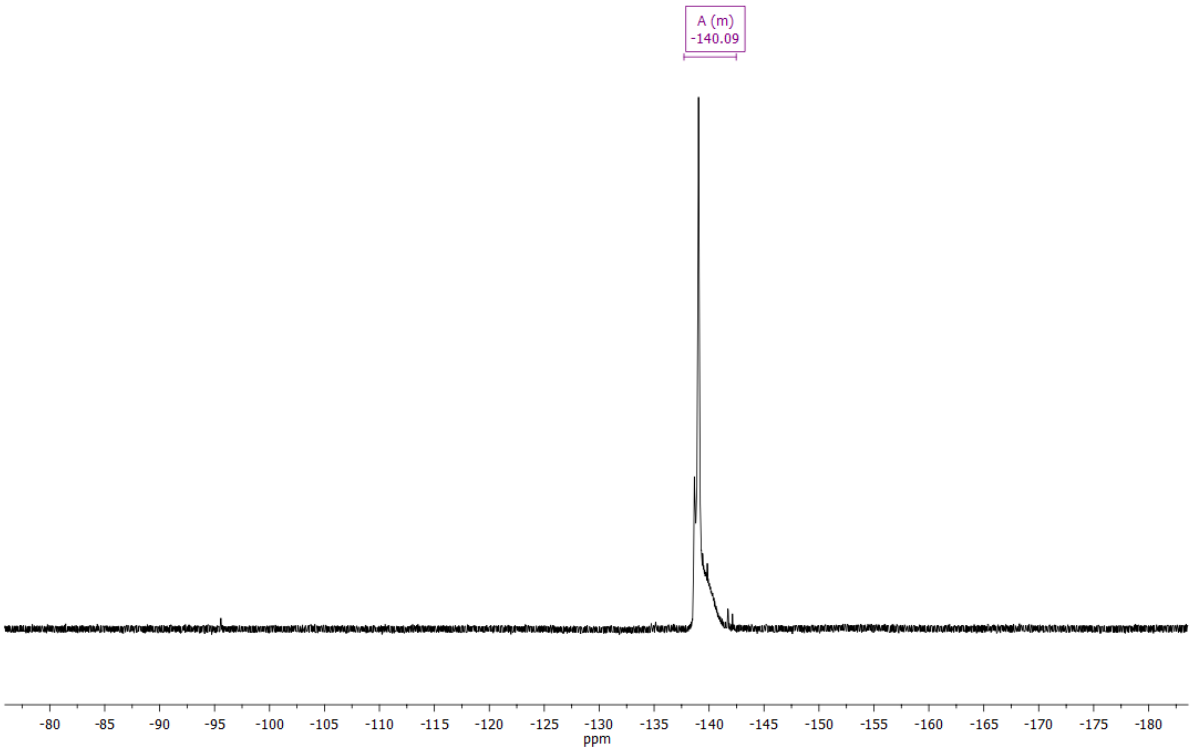

10.36
2.05
1.05
1.08
1.03
2.08
1.10
9.00
2.23
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

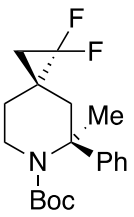

171.85
155.35
135.62
128.49
128.32
128.17
127.76
127.19
127.11
81.21
67.43
66.75
40.30
27.99
27.07
A (t)
114.14
B (t)
22.53
128.49
128.32
128.17
127.76
127.19
127.11
129.0
128.5
128.0
127.5
127.0
126.5
ppm
B (t)
22.53
23.0
22.5
22.0
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
F
CO2Bn
N
Ph
Boc

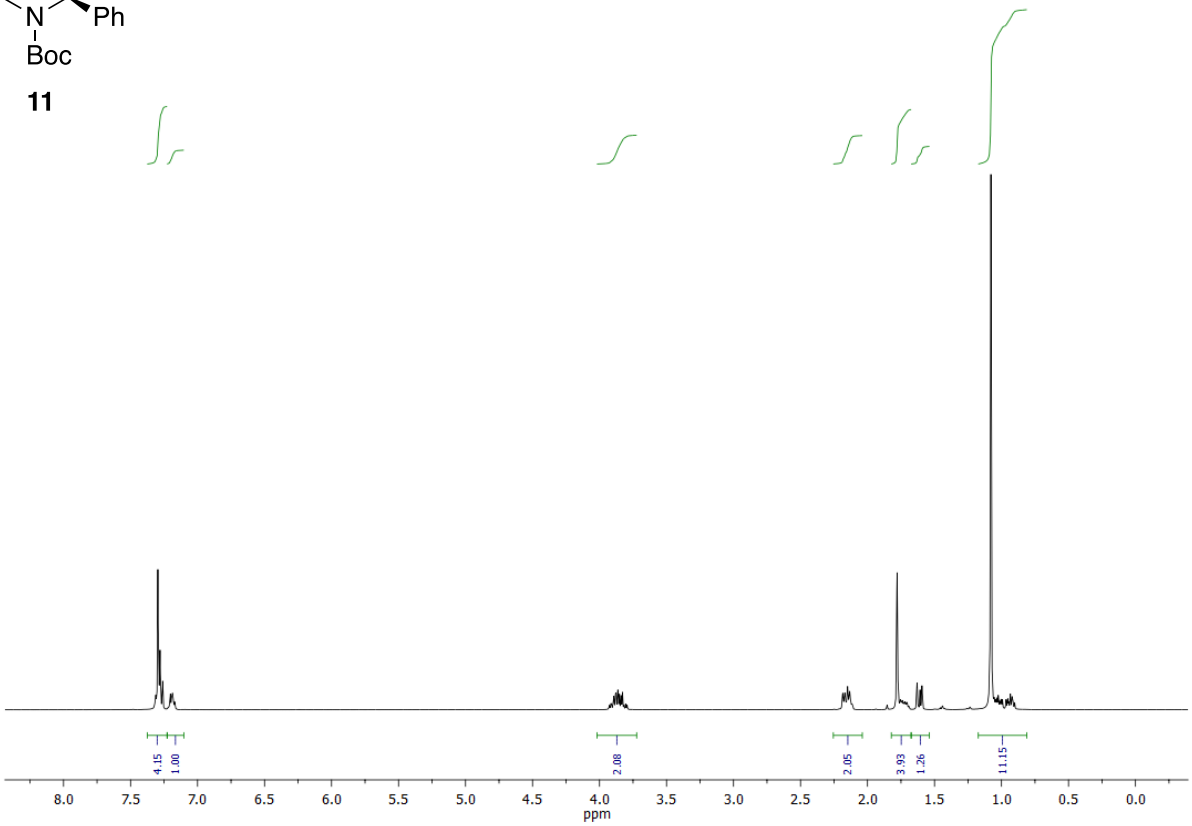
10

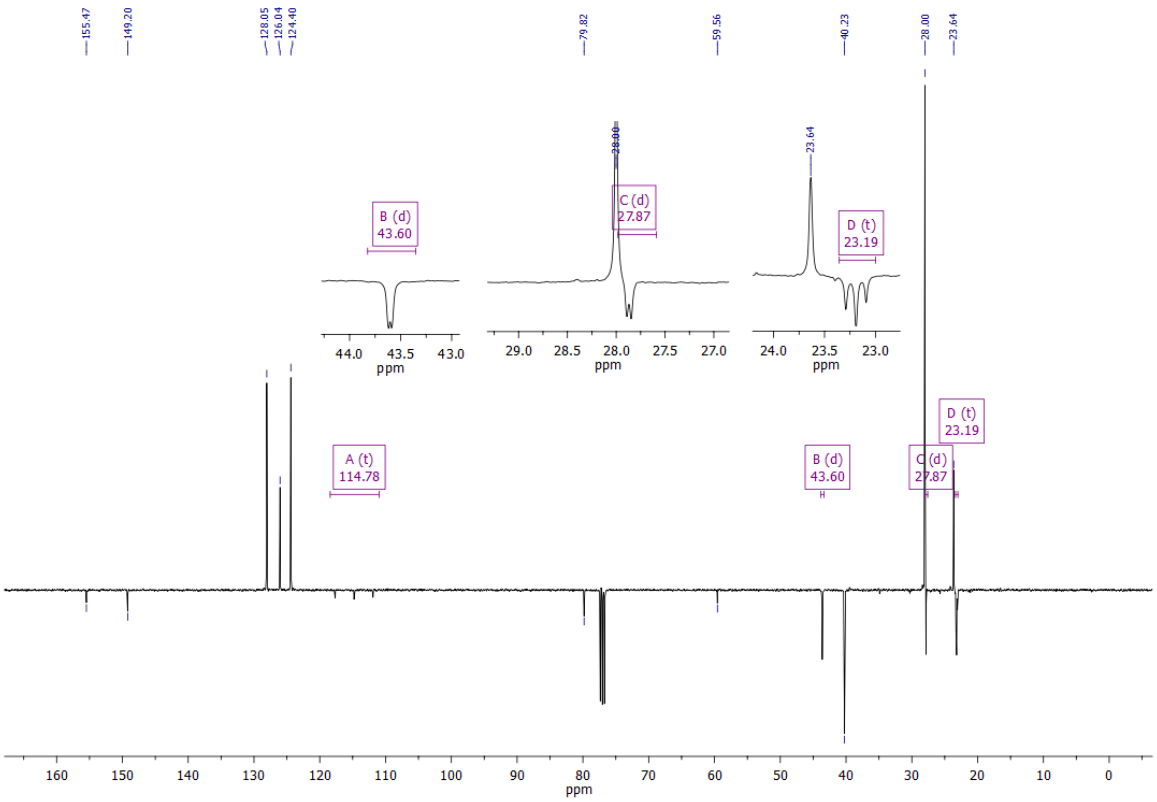
(^{19}F NMR)

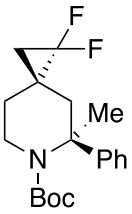

A (m)
-140.09
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm


F
F
Me
N
Ph
Boc

11

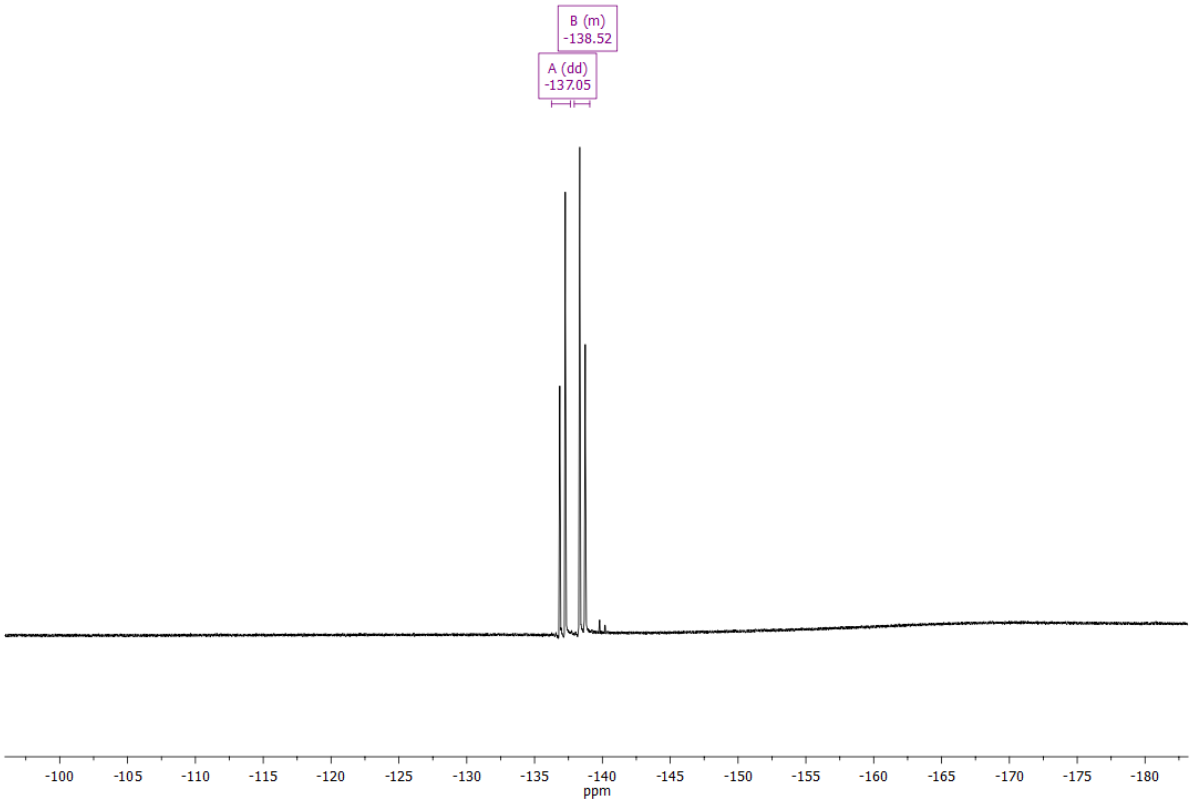

4.15
1.00
2.08
2.05
3.93
1.26
11.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

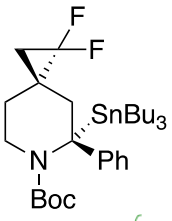

155.47
149.20
128.05
126.64
124.40
79.82
59.56
40.23
28.00
23.64
B (d)
43.60
C (d)
27.87
D (t)
23.19
A (t)
114.78
44.0
43.5
43.0
29.0
28.5
28.0
27.5
27.0
24.0
23.5
23.0
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F
F
Me
N
Ph
Boc

11

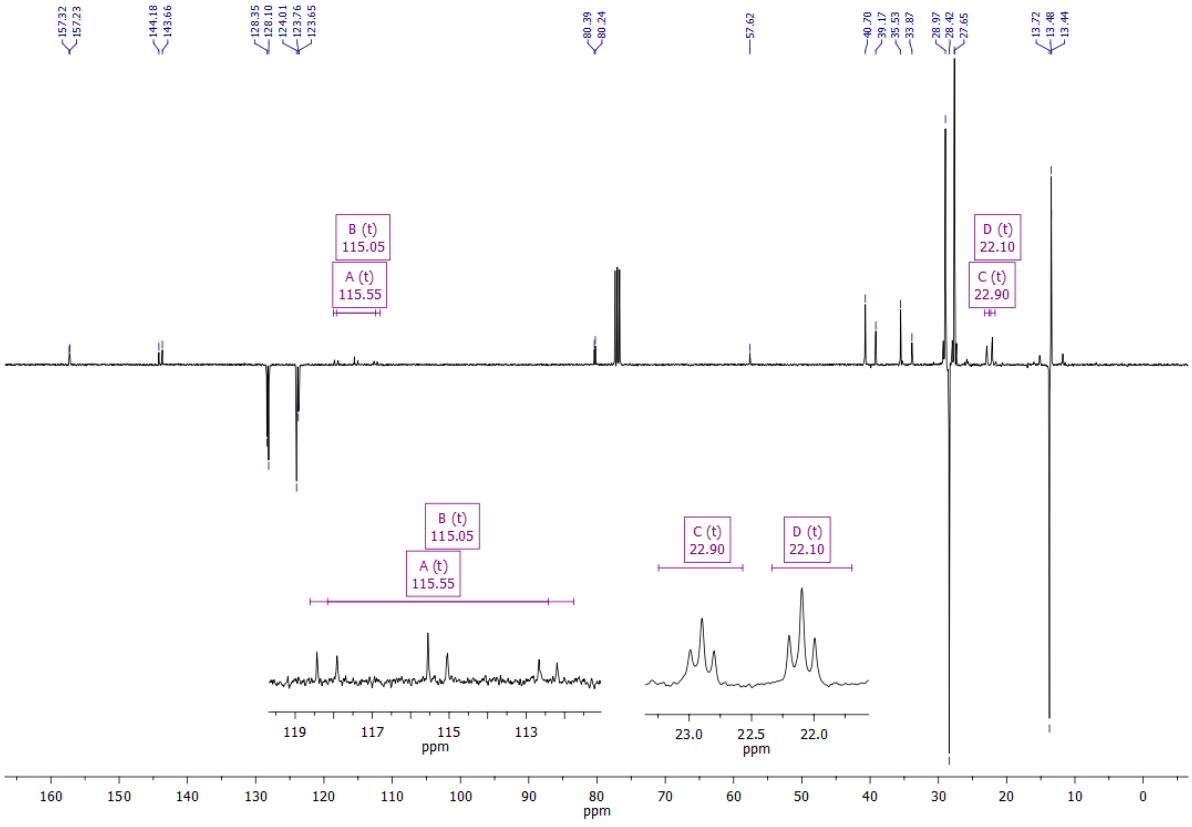
(^{19}F NMR)


B (m)
-138.52
A (dd)
-137.05
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm

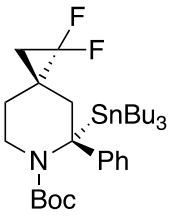

F
F
SnBu3
N
Ph
Boc

12

2.15
1.04
2.00
0.47
0.61
0.48
0.59
2.16
0.48
0.63
9.82
14.54
9.31
6.19
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
ppm

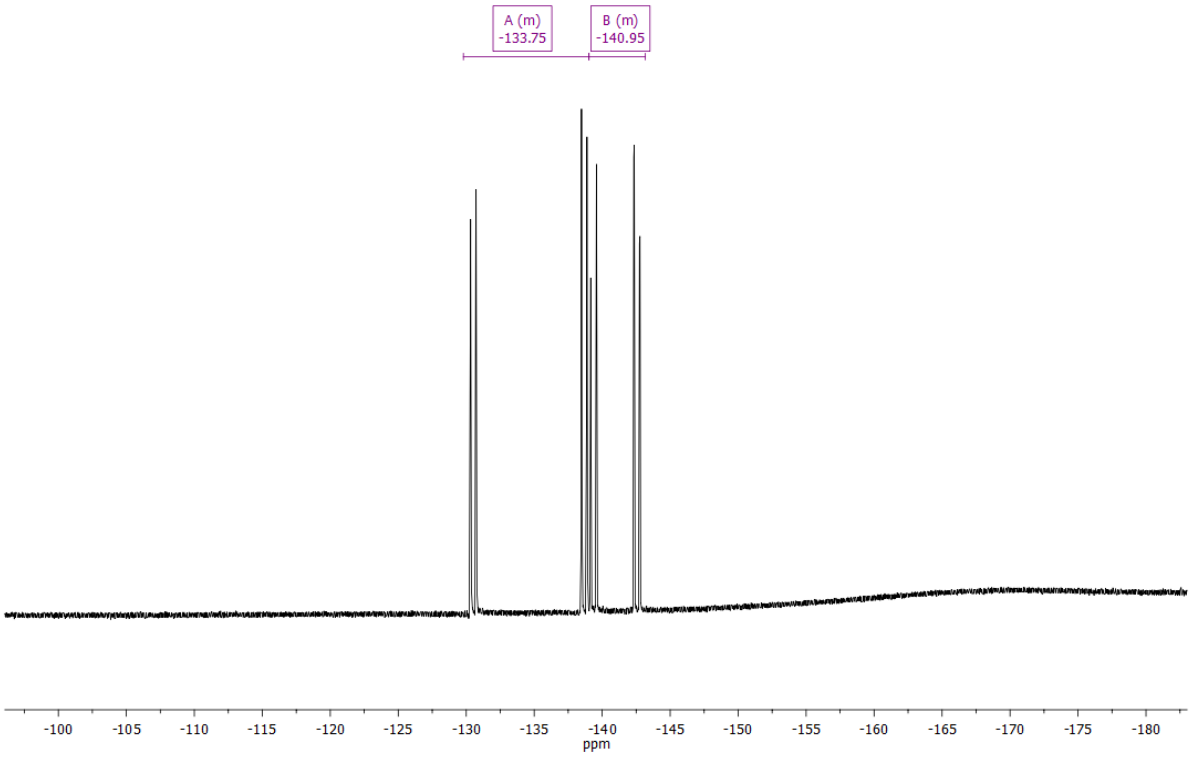

157.32
157.23
144.18
143.66
128.35
128.10
124.01
123.76
123.65
80.39
80.24
57.62
40.70
39.17
35.53
33.87
28.97
28.42
27.65
13.72
13.48
13.44
B (t)
115.05
A (t)
115.55
D (t)
22.10
C (t)
22.90
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

B (t)
115.05
A (t)
115.55
C (t)
22.90
D (t)
22.10
119
117
115
113
ppm
23.0
22.5
22.0
ppm

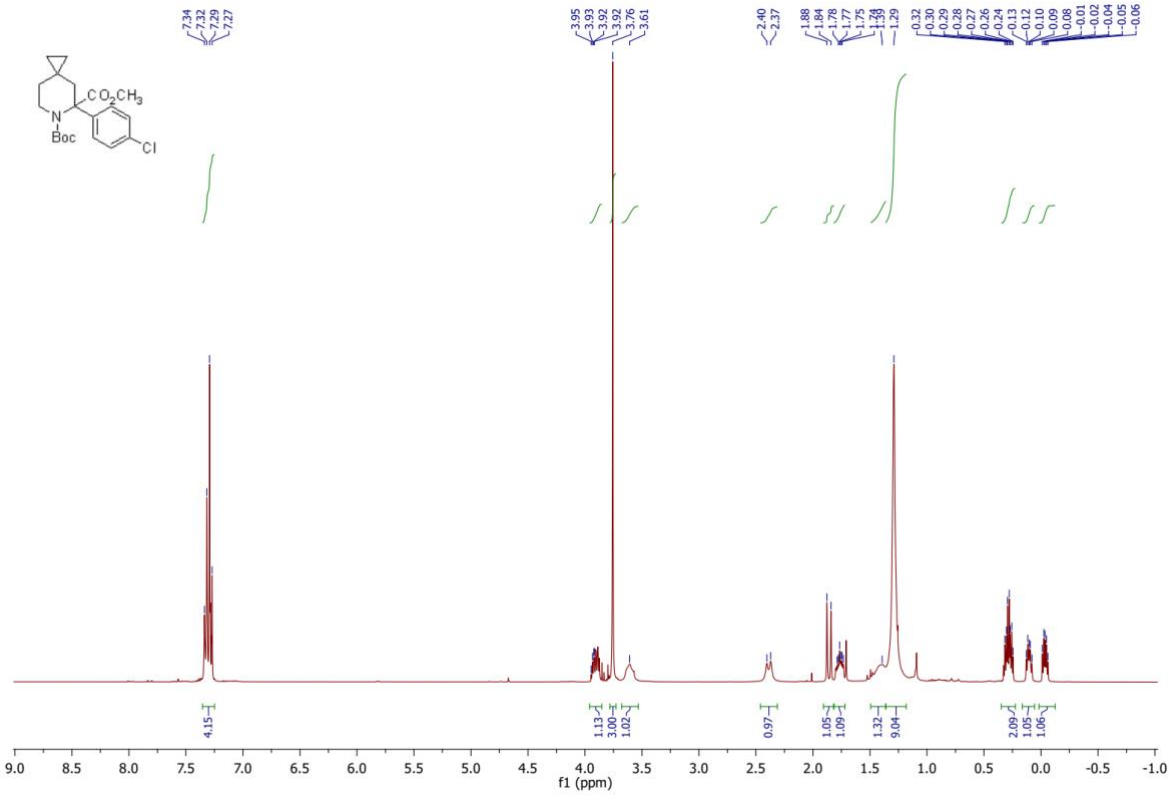

F
F
SnBu3
N
Ph
Boc

12

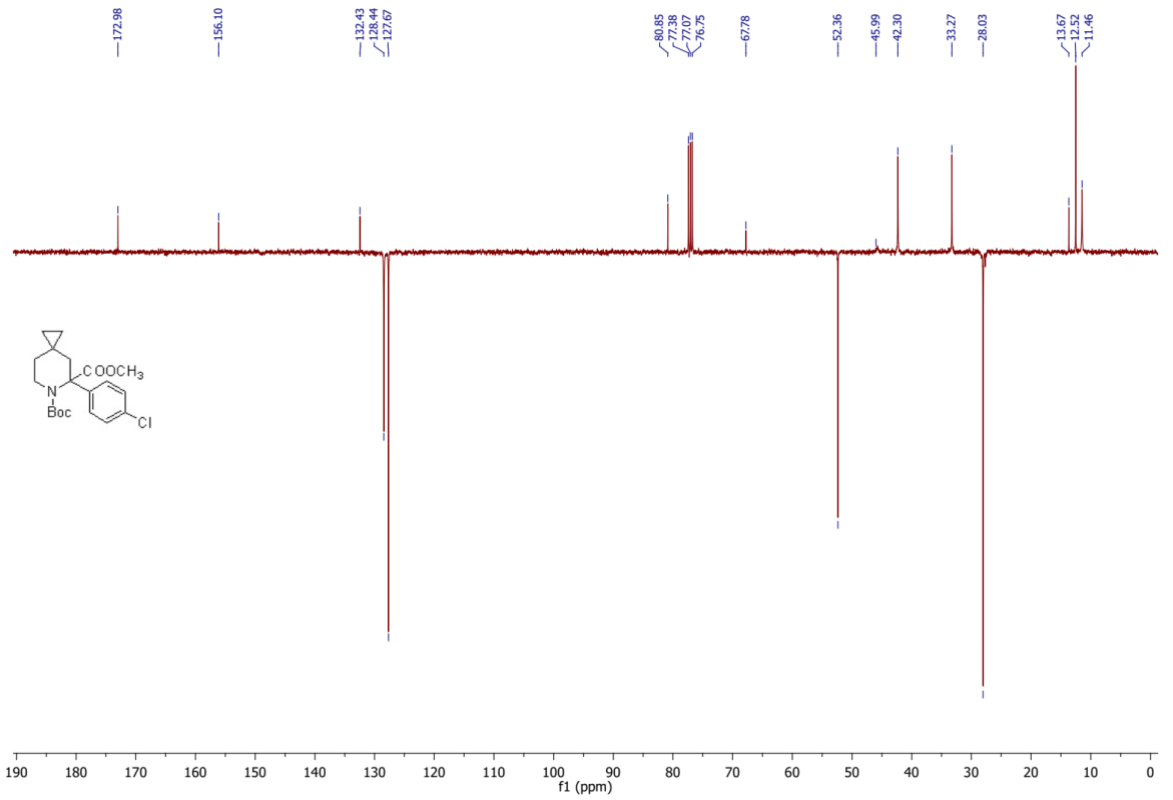
(^{19}F NMR)


A (m)
-133.75
B (m)
-140.95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
ppm

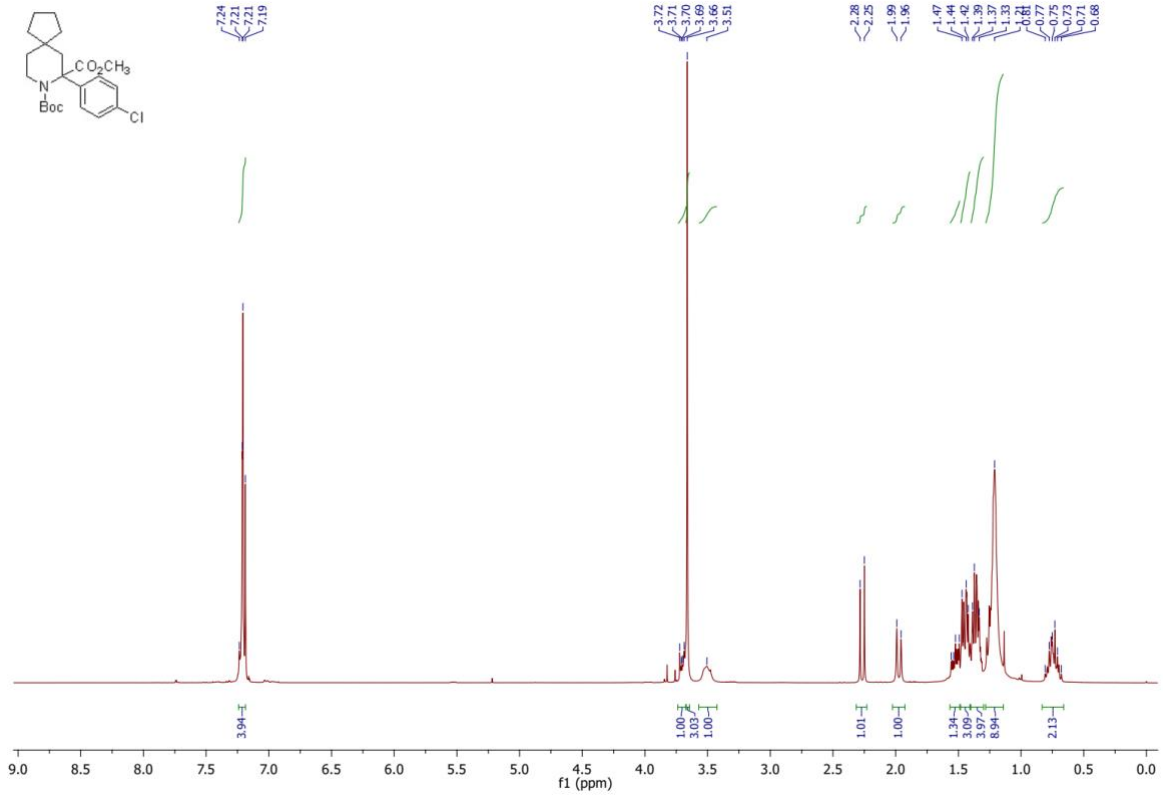
Compound **13** (^{1}H NMR, $CDCl_3$)



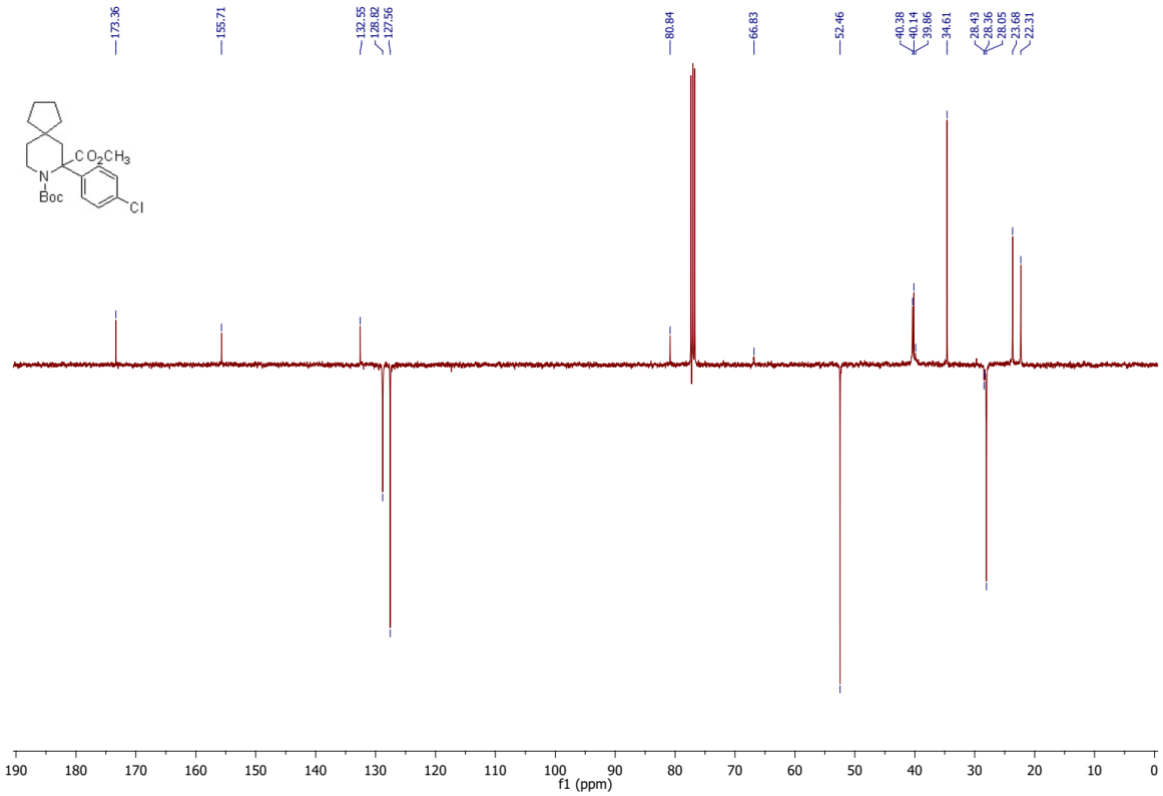
Compound **13** (^{13}C NMR, $CDCl_3$)

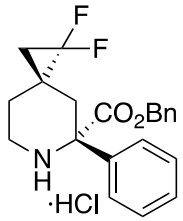


Compound **14** (^{1}H NMR, $CDCl_3$)

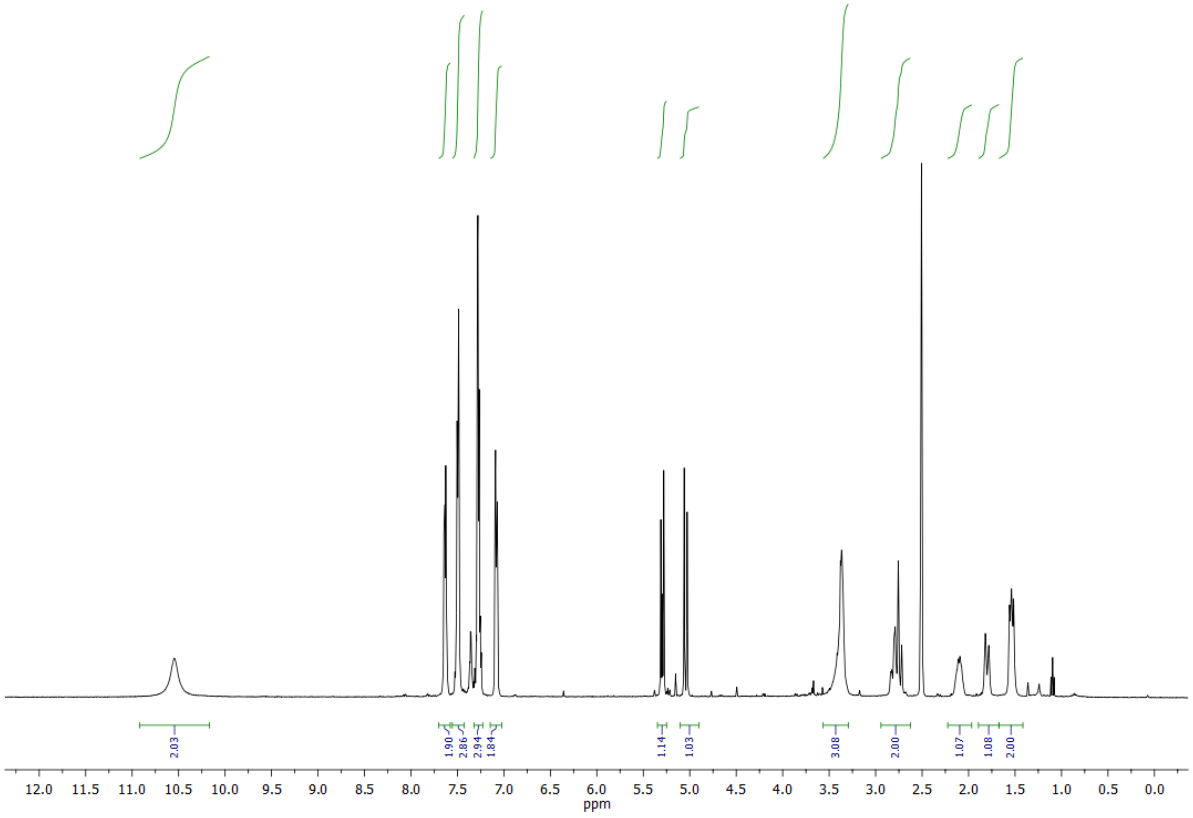


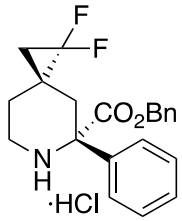
Compound **14** (^{13}C NMR, $CDCl_3$)



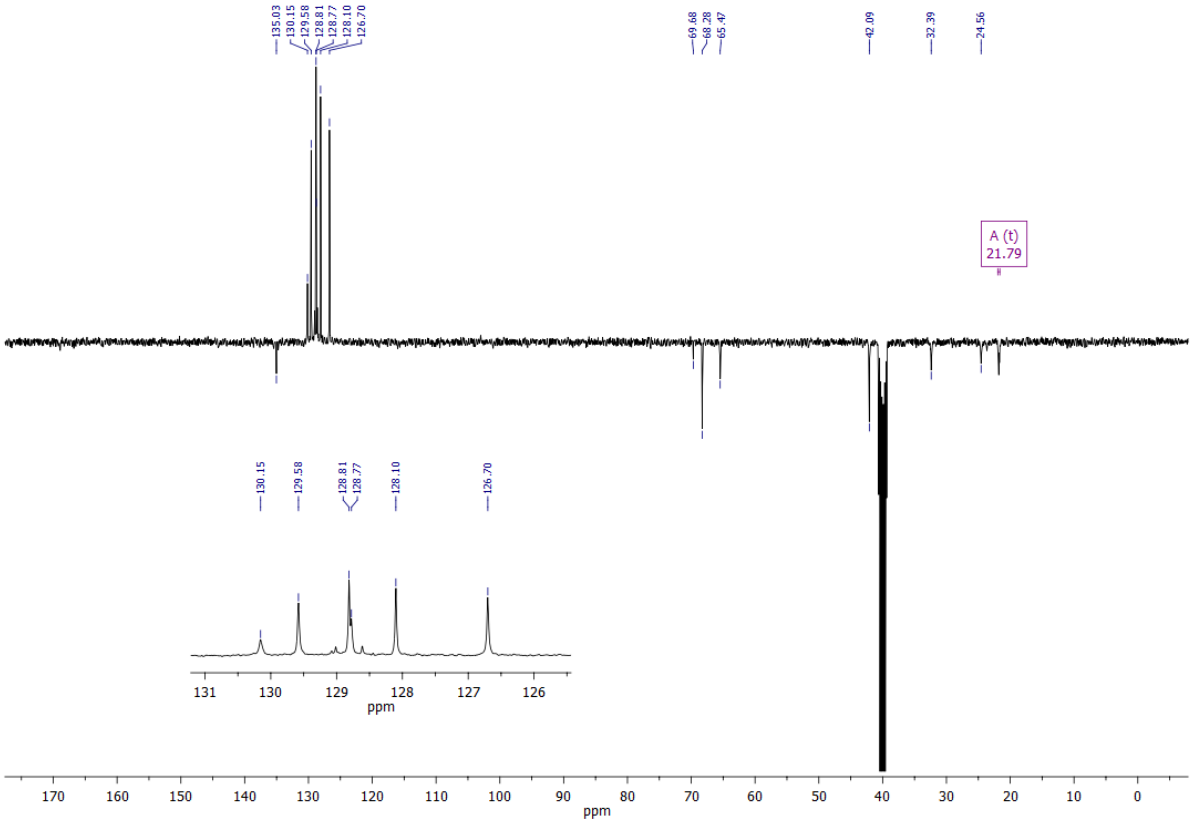

F
F
CO2Bn
N
H
·HCl

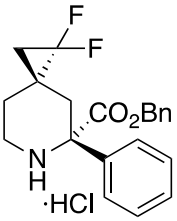
15
[in d_6-DMSO]


2.03
1.90
2.86
2.94
1.84
1.14
1.03
3.08
2.00
1.07
1.08
2.00
12.0 11.5 11.0 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
ppm


F
F
CO2Bn
N
H
·HCl

15
[in d_6-DMSO]

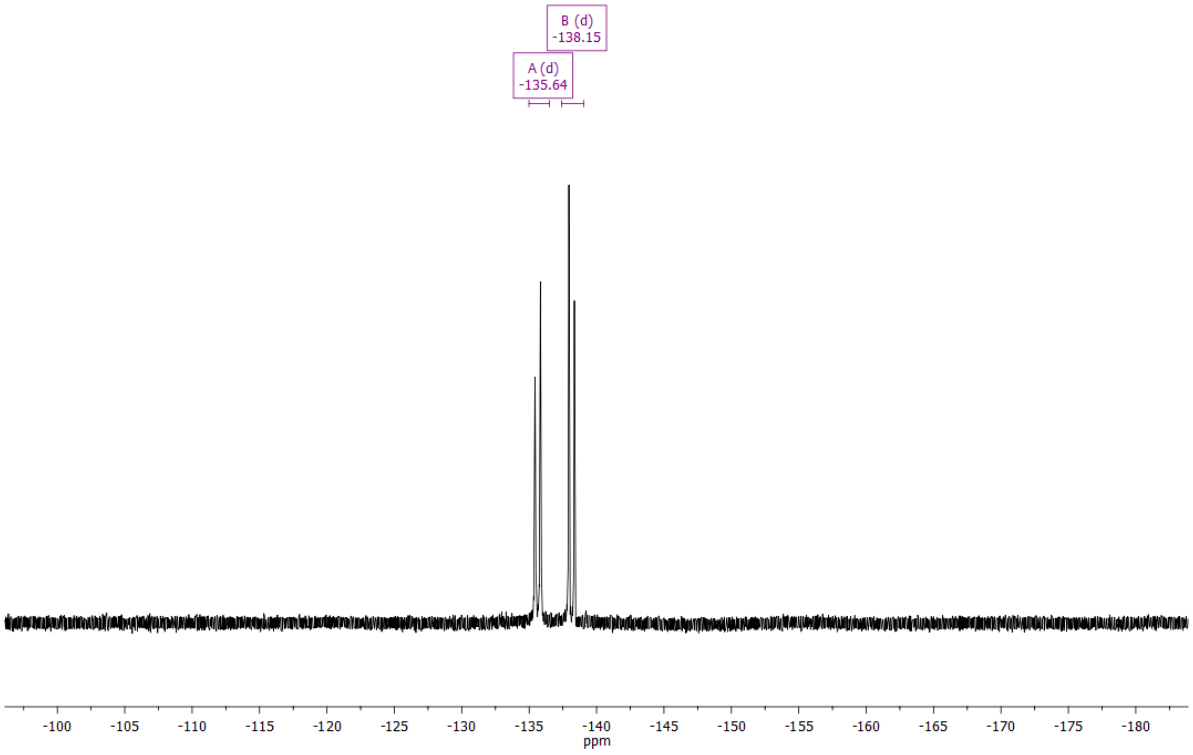

135.03
130.15
129.58
128.81
128.77
128.10
126.70
69.68
68.28
65.47
42.09
32.39
24.56
A (t)
21.79
130.15
129.58
128.81
128.77
128.10
126.70
131
130
129
128
127
126
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

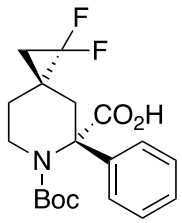


15

[in d_6-DMSO]

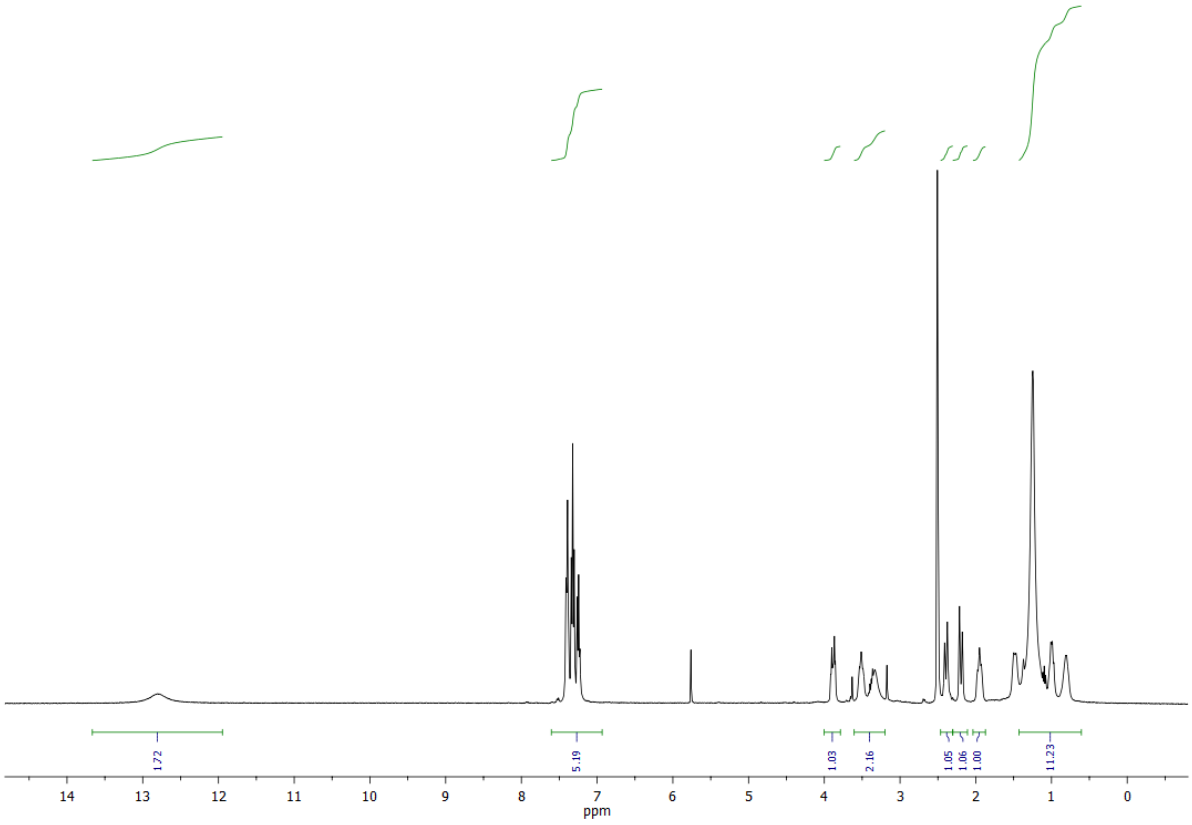
(^{19}F NMR)

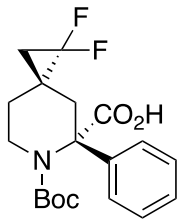



F
F
CO2H
N
Boc

16

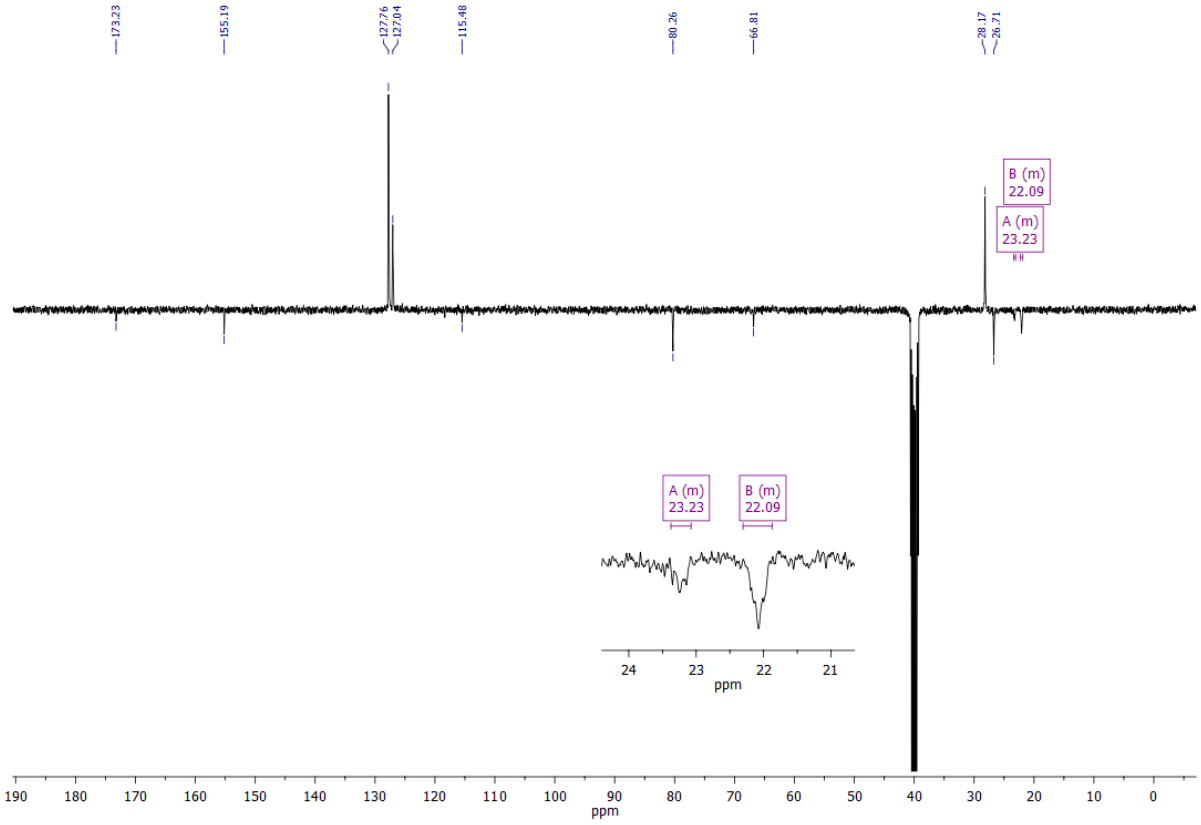
[in d_6-DMSO]

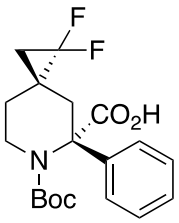

1.72
5.19
1.03
2.16
1.05
1.06
1.00
11.23
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


F
F
CO2H
N
Boc

16

[in d_6-DMSO]

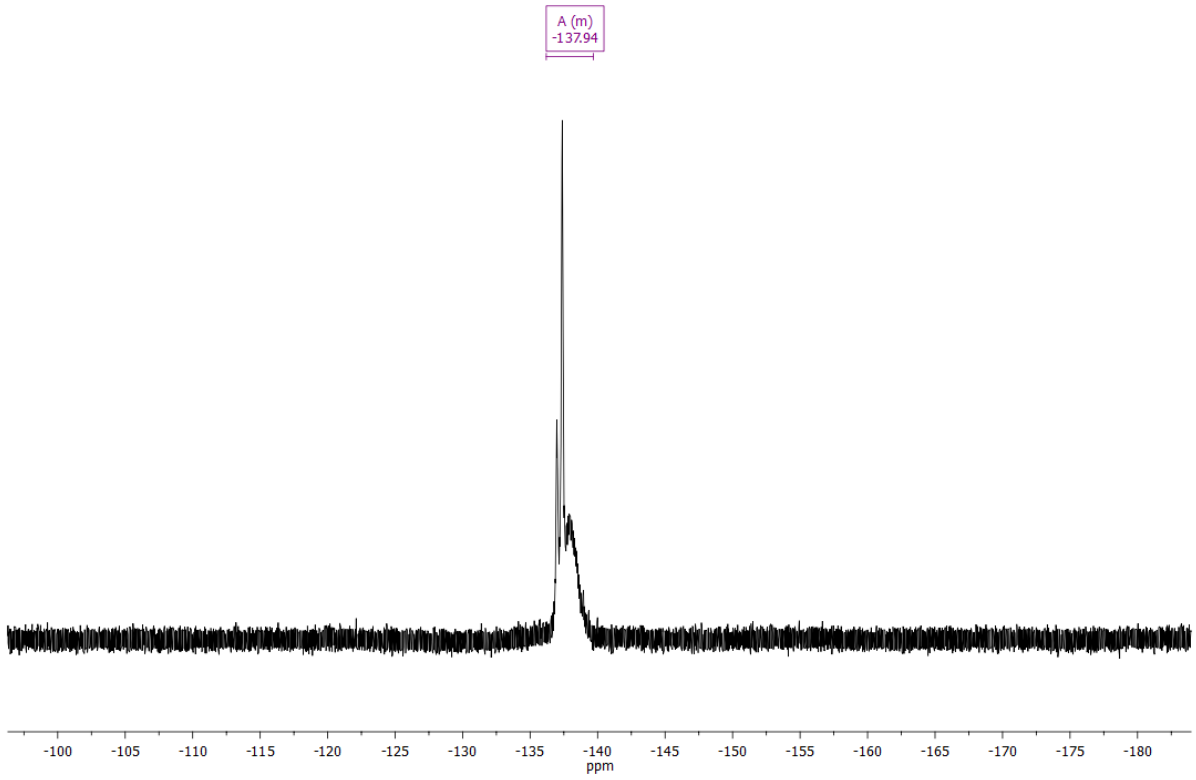

173.23
155.19
127.76
127.04
115.48
80.26
66.81
28.17
26.71
B (m)
22.09
A (m)
23.23
A (m)
23.23
B (m)
22.09
24
23
22
21
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



16

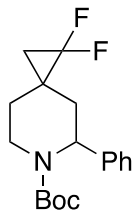
[in d_6-DMSO]

(^{19}F NMR)



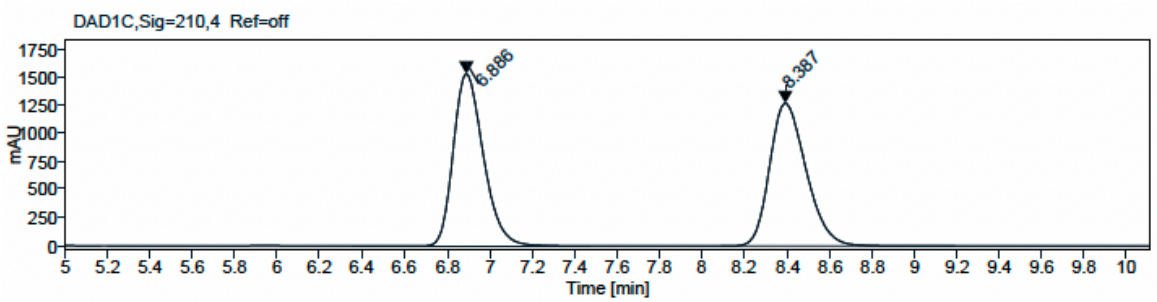
8. HPLC traces

HPLC of (±)-**2a** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

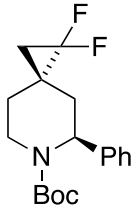


(±)-**2a**

	R_t/min	Area	Area/%
1	6.886	15248.6781	49.93
2	8.387	15292.9410	50.07
	Total	30541.6191	100.00

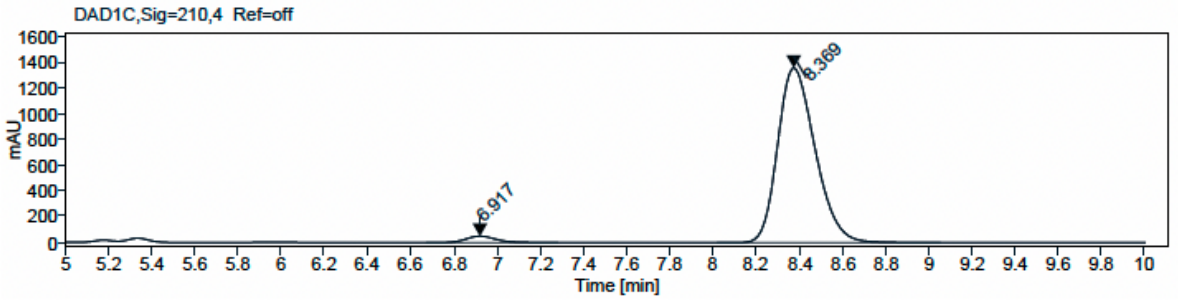


HPLC of (3*S*,5*S*)-**2a** (er 97:3) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

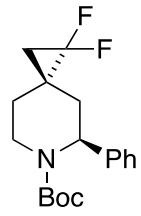


(3*S*,5*S*)-**2a**
(er 97:3)

	R_t/min	Area	Area/%
1	6.917	499.6881	2.95
2	8.369	16453.7999	97.05
	Total	16953.4881	100.00

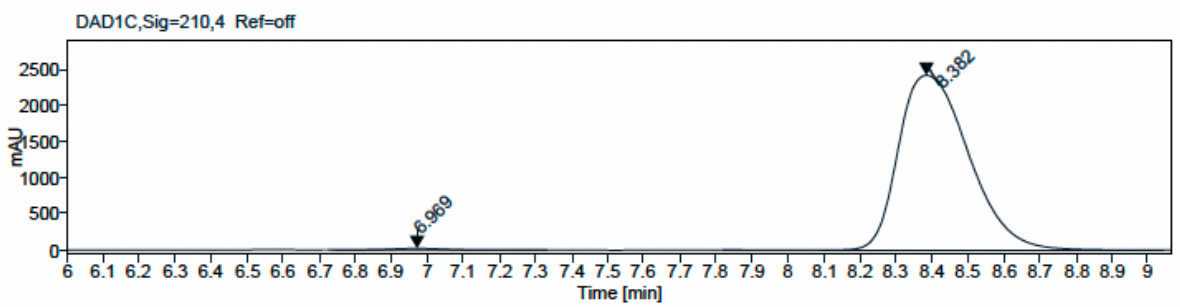


HPLC of (3*S*,5*S*)-**2a** (er 99:1) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

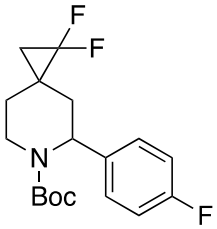


(3*S*,5*S*)-**2a**
(er 99:1)

	R_t/min	Area	Area/%
1	6.969	198.8356	0.60
2	8.382	32831.4113	99.40
	Total	33030.2469	100.00

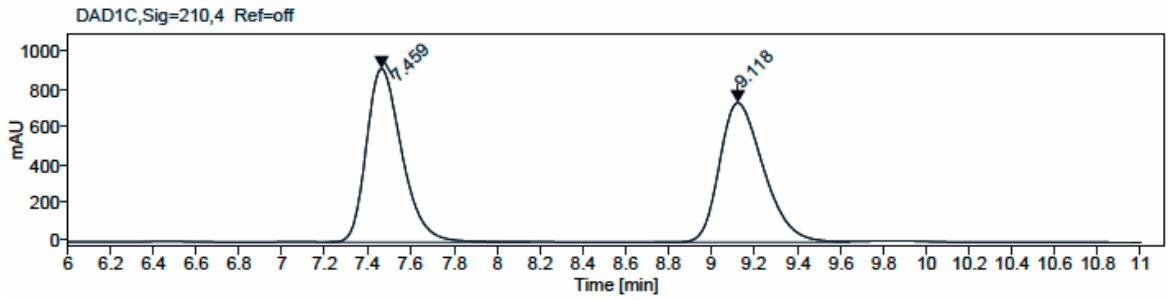


HPLC of (±)-**2b** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

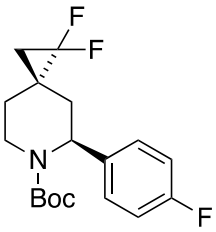


(±)-**2b**

	R_t/min	Area	Area/%
1	7.459	10577.5933	50.01
2	9.118	10572.3395	49.99
	Total	21149.9328	100.00

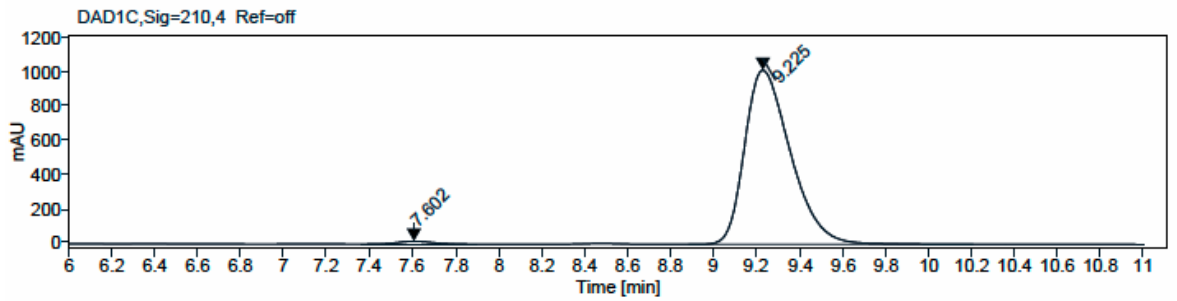


HPLC of (3*S*,5*S*)-**2b** (er 99:1) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

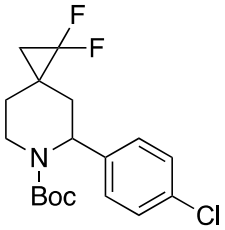


(3*S*,5*S*)-**2b**
(er 99:1)

	R_f/min	Area	Area/%
1	7.602	191.2280	1.25
2	9.225	15068.7051	98.75
	Total	15259.9332	100.00

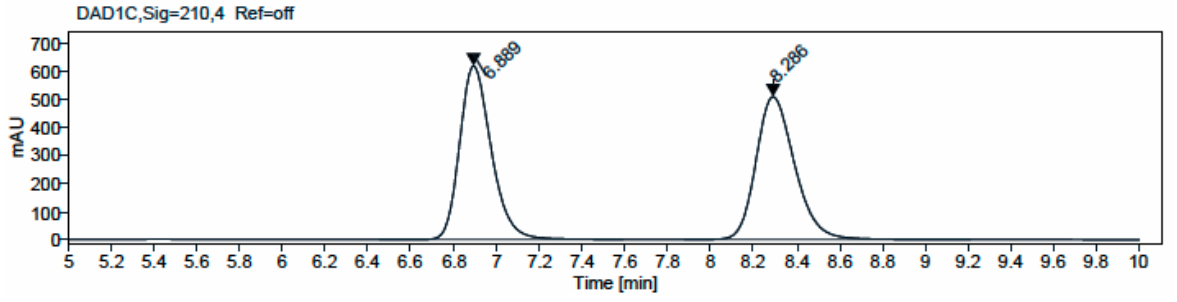


HPLC of (±)-**2c** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

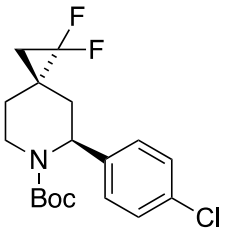


(±)-**2c**

	R_f/min	Area	Area/%
1	6.889	6359.6704	49.90
2	8.286	6384.5720	50.10
	Total	12744.2424	100.00

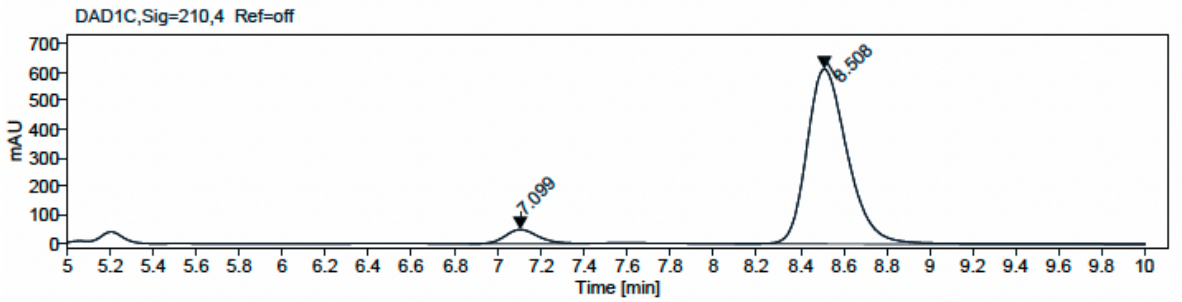


HPLC of (3*S*,5*S*)-**2c** (er 94:6) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

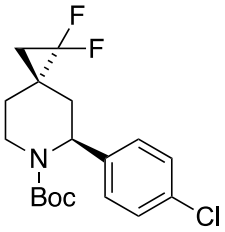


(3*S*,5*S*)-**2c**
(er 94:6)

	R_f/min	Area	Area/%
1	7.099	549.0053	6.39
2	8.508	8040.1616	93.61
	Total	8589.1669	100.00

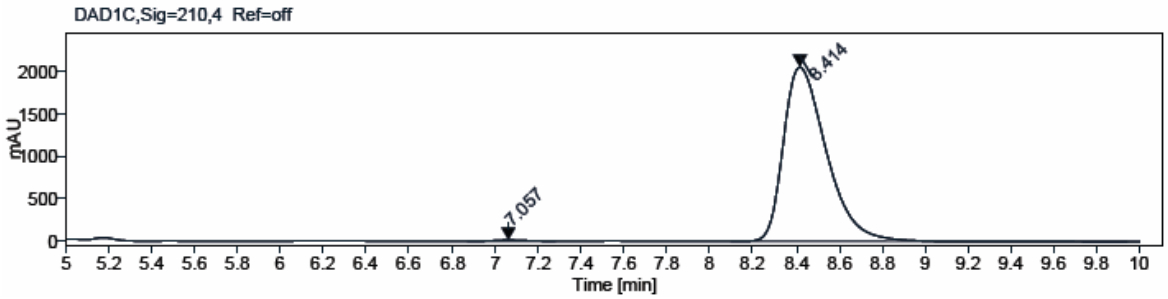


HPLC of (3*S*,5*S*)-**2c** (er 99:1) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

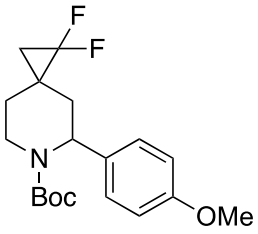


(3*S*,5*S*)-**2c**
(er 99:1)

	R_f/min	Area	Area/%
1	7.057	145.2179	0.50
2	8.414	28809.9305	99.50
	Total	28955.1483	100.00

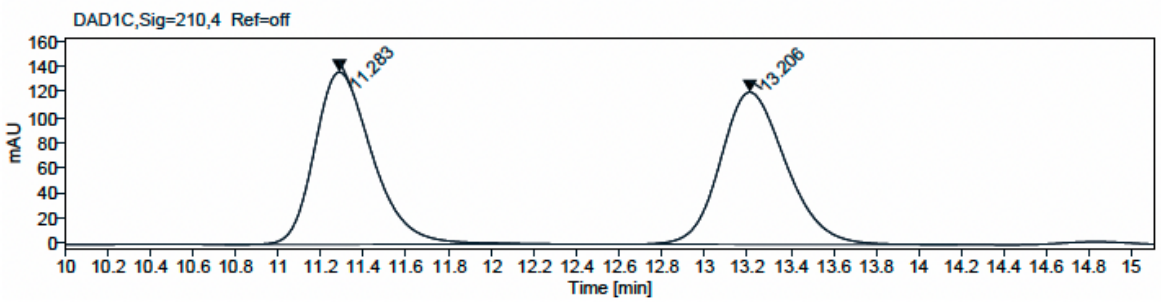


HPLC of (±)-**2d** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

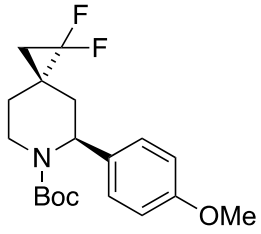


(±)-**2d**

	R_f/min	Area	Area/%
1	11.283	2588.2621	49.97
2	13.206	2591.1975	50.03
	Total	5179.4596	100.00

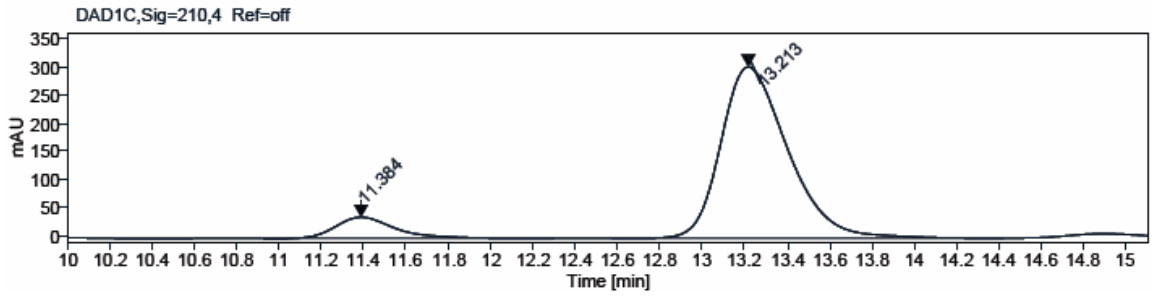


HPLC of (3*S*,5*S*)-**2d** (er 90:10) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

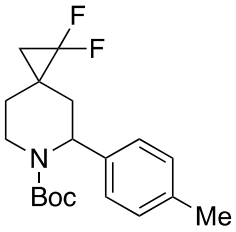


(3*S*,5*S*)-**2d**
(er 90:10)

	R_f/min	Area	Area/%
1	11.384	718.6112	9.77
2	13.213	6634.7685	90.23
	Total	7353.3796	100.00

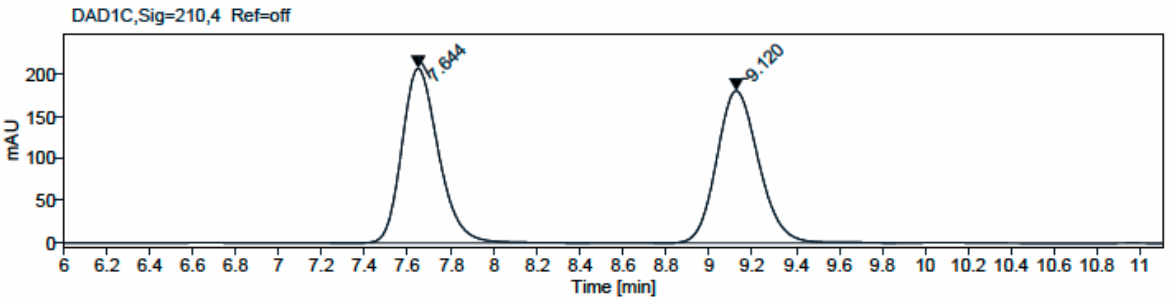


HPLC of (±)-**2e** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

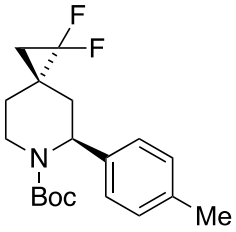


(±)-**2e**

	R_f/min	Area	Area/%
1	7.644	2449.8495	50.01
2	9.120	2448.5302	49.99
	Total	4898.3797	100.00

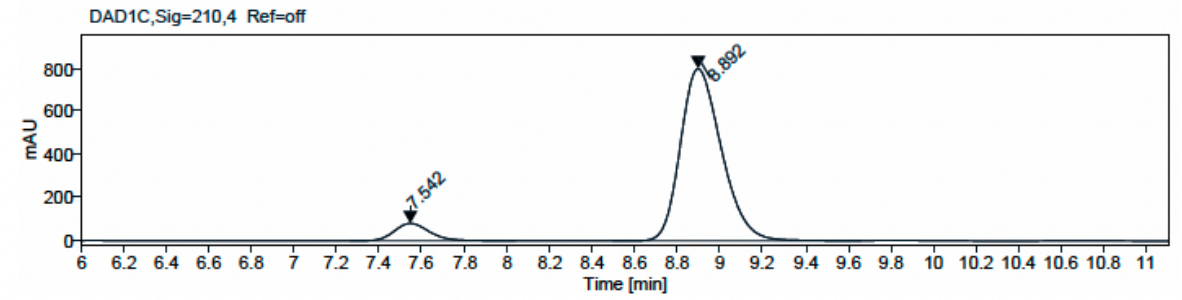


HPLC of (3*S*,5*S*)-**2e** (er 92:8) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

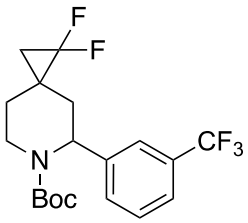


(3*S*,5*S*)-**2e**
(er 92:8)

	R_f/min	Area	Area/%
1	7.542	927.9051	7.99
2	8.892	10686.6779	92.01
	Total	11614.5830	100.00

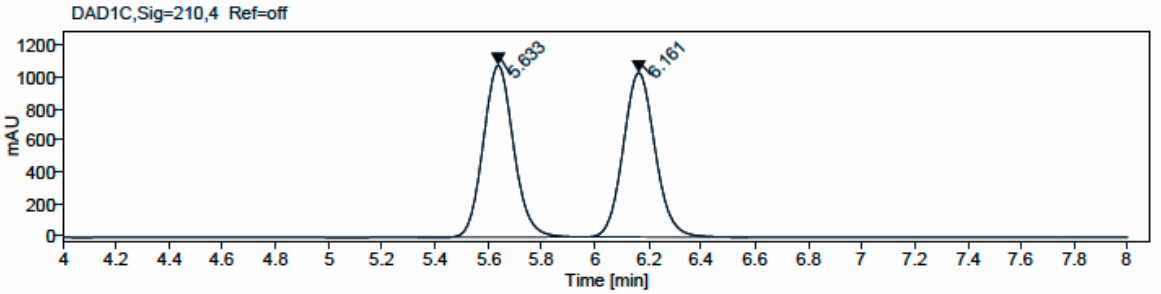


HPLC of (±)-**2f** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

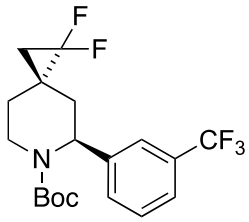


(±)-**2f**

	R_f/min	Area	Area/%
1	5.633	8551.2074	49.90
2	6.161	8586.0122	50.10
	Total	17137.2196	100.00

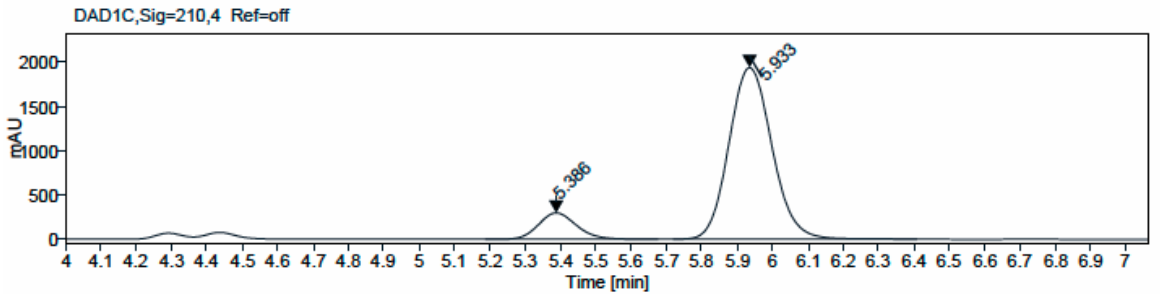


HPLC of (3*S*,5*S*)-**2f** (er 88:12) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

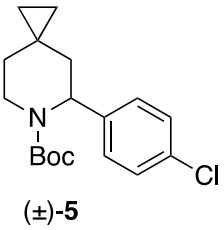


(3*S*,5*S*)-**2f**
(er 88:12)

	R_f/min	Area	Area/%
1	5.386	2222.0088	11.87
2	5.933	16502.1968	88.13
	Total	18724.2056	100.00

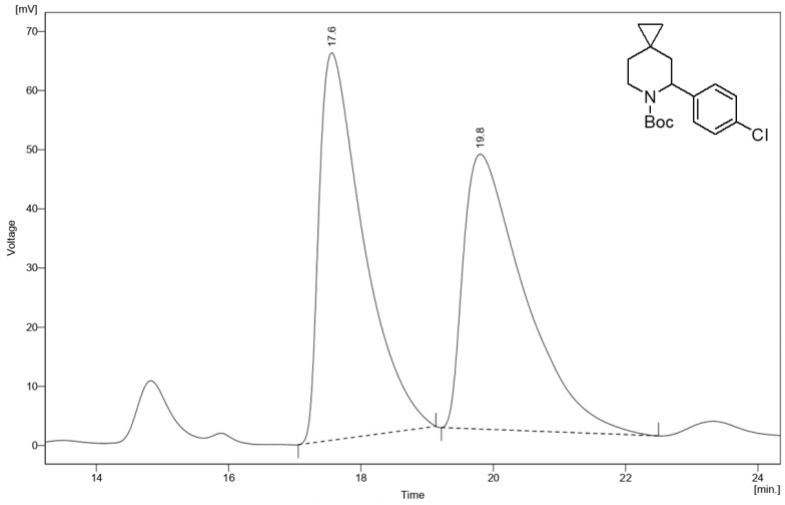


HPLC of (±)-**5** from Beckman system fitted with a Lux Cellulose–2 column:

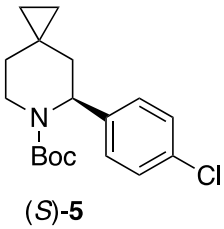


(±)-**5**

	R_f/min	Area	Area/%
1	17. 6	1157.419	47.9
2	19.8	1256.427	52.1
	Total	2413.846	100.00

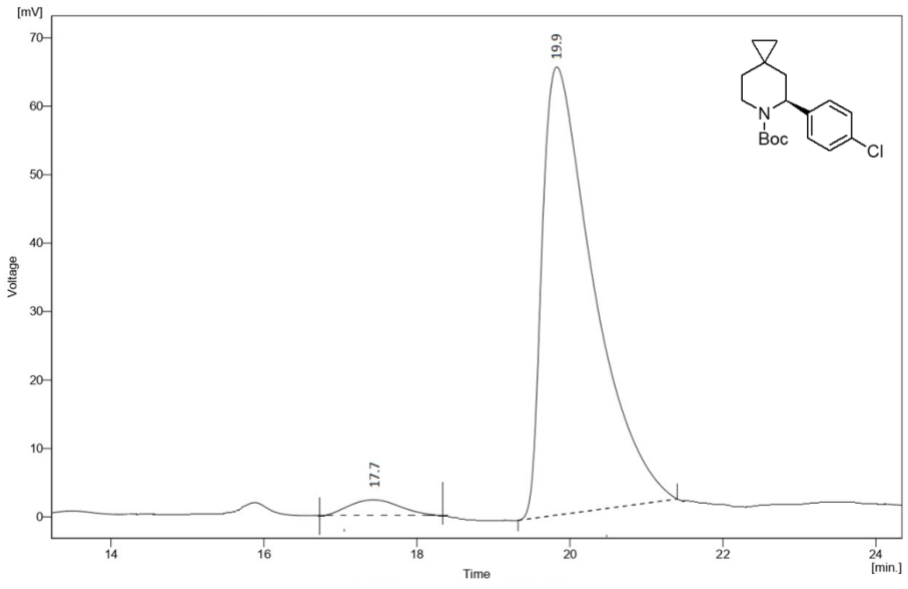


HPLC of (*S*)-**5** from Beckman system fitted with a Lux Cellulose–2 column:

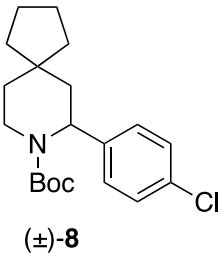


(*S*)-**5**

	R_f/min	Area	Area/%
1	17. 7	85.855	7.8
2	19.9	1016.057	92.2
	Total	1101.912	100.00

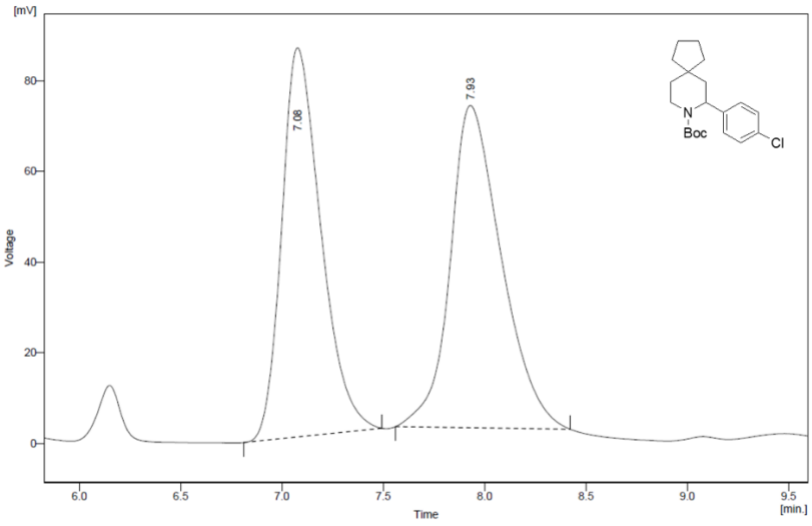


HPLC of (±)-**8** from Beckman system fitted with a Lux Amylose–2 column:

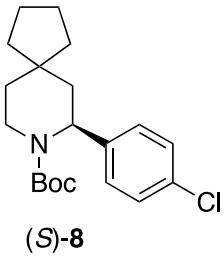


(±)-**8**

	R_f/min	Area	Area/%
1	7.08	38848.46	49.6
2	7.93	39549.28	50.4
	Total	78397.74	100.00

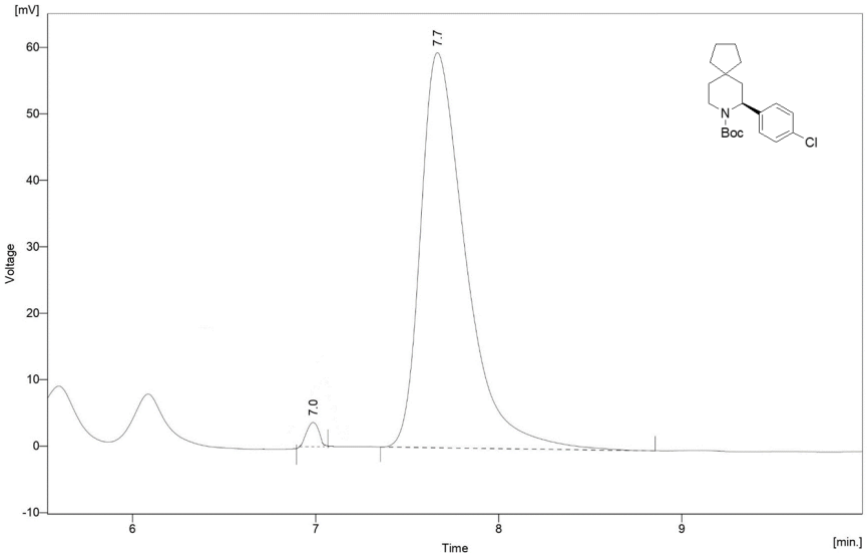


HPLC of (*S*)-**8** from Beckman system fitted with a Lux Amylose–2 column:

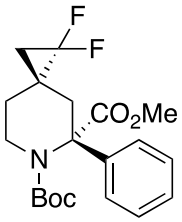


(*S*)-**8**

	R_f/min	Area	Area/%
1	7.0	257.636	3.1
2	7.7	5681.100	96.9
	Total	5938.736	100.00

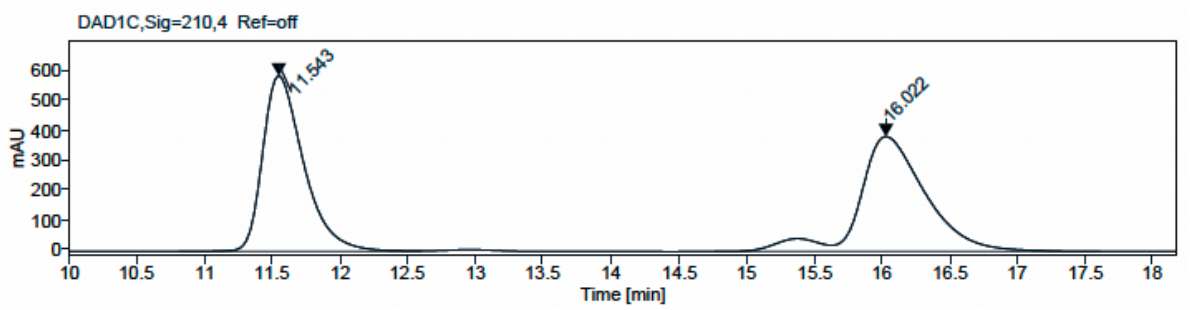


HPLC of (±)-**9a** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

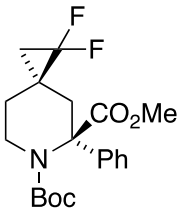


(±)-**9a**

	R_t/min	Area	Area/%
1	11.543	12297.7516	48.48
2	16.022	13070.9555	51.52
	Total	25368.7071	100.00

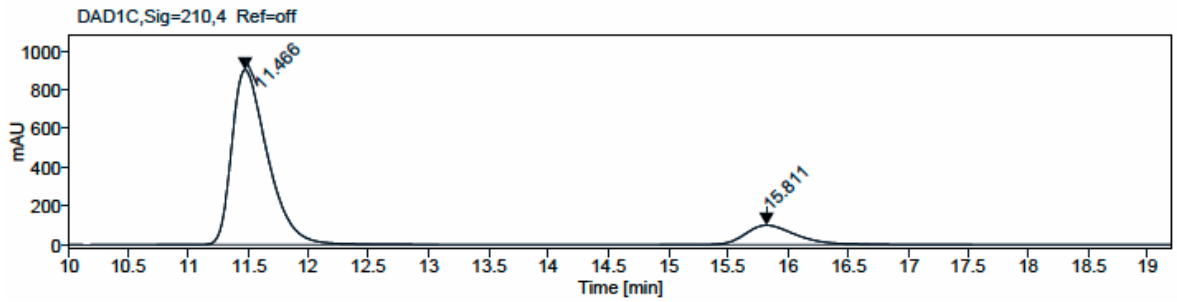


HPLC of (3*R*,5*R*)-**9a** (er 86:14) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

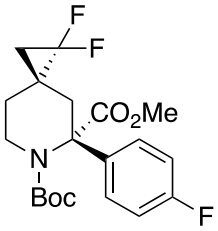


(3*R*,5*R*)-**9a**
(er 86:14)

	R_t/min	Area	Area/%
1	11.466	18787.2635	86.27
2	15.811	2989.2703	13.73
	Total	21776.5338	100.00

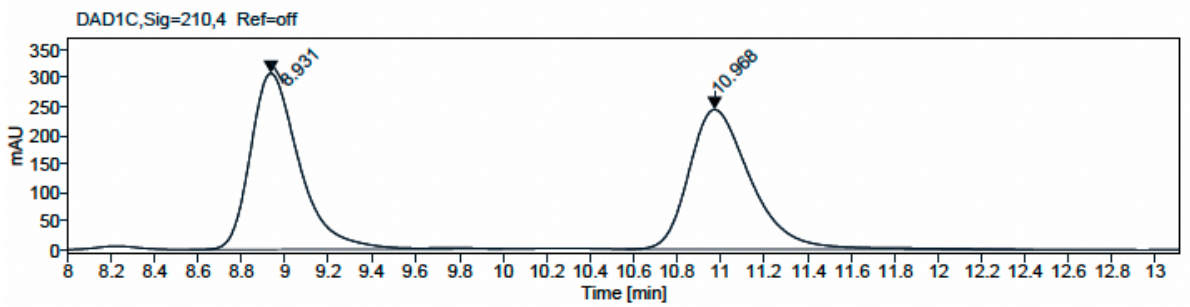


HPLC of (±)-**9b** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

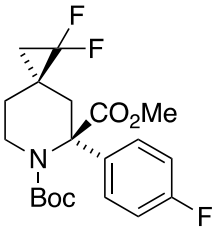


(±)-**9b**

	R_t/min	Area	Area/%
1	8.931	4844.7521	49.91
2	10.968	4862.6680	50.09
	Total	9707.4201	100.00

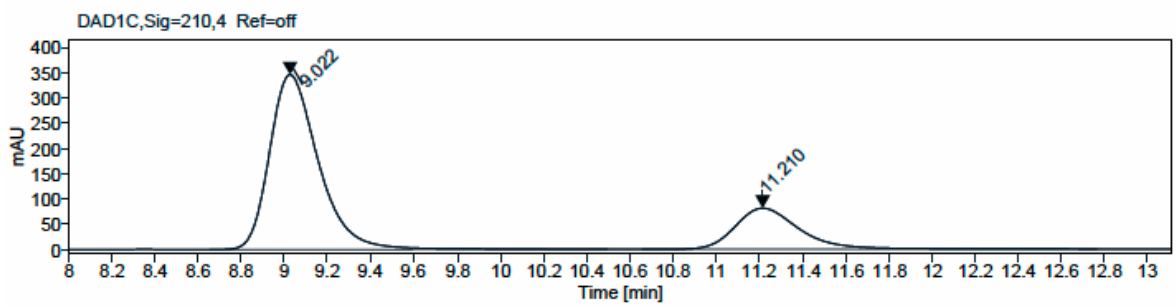


HPLC of (3*R*,5*R*)-**9b** (er 76:24) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

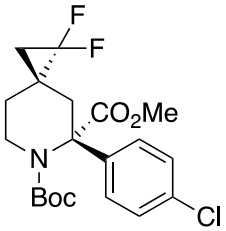


(3*R*,5*R*)-**9b**
(er 76:24)

	R_t/min	Area	Area/%
1	9.022	5434.9551	76.17
2	11.210	1700.3942	23.83
	Total	7135.3493	100.00

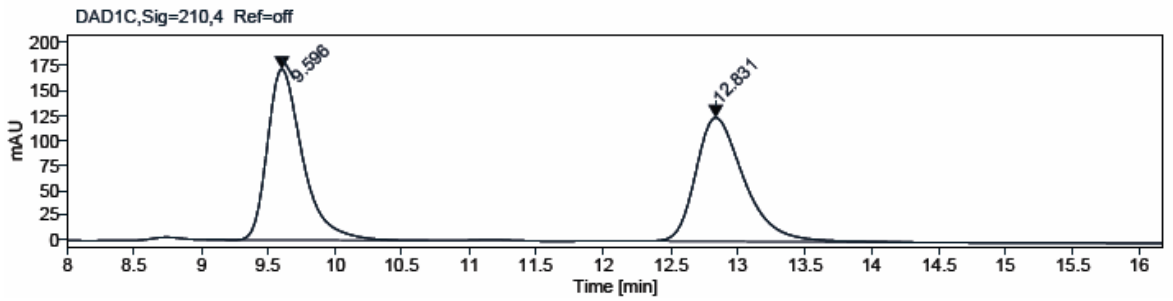


HPLC of (±)-**9c** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

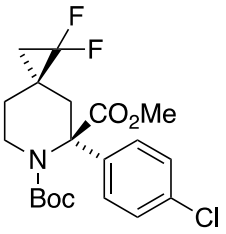


(±)-**9c**

	R_t/min	Area	Area/%
1	9.596	3141.4616	50.06
2	12.831	3133.7045	49.94
	Total	6275.1662	100.00

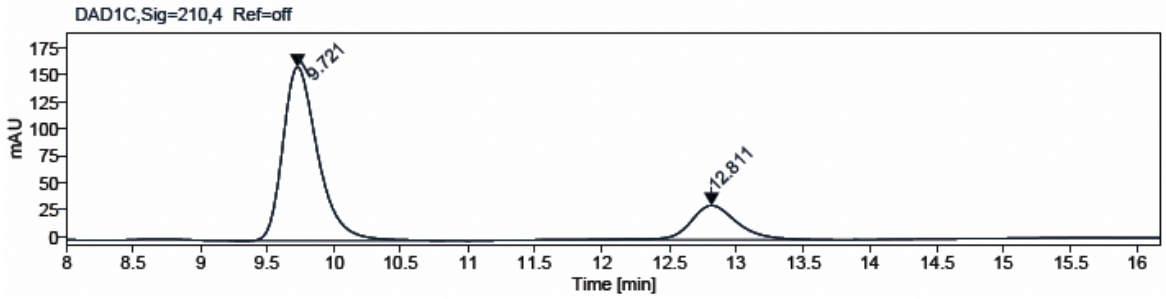


HPLC of (3*R*,5*R*)-**9c** (er 79:21) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

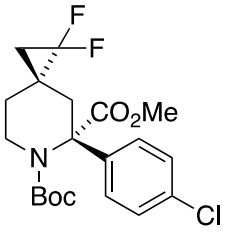


(3*R*,5*R*)-**9c**
(er 79:21)

	R_t/min	Area	Area/%
1	9.721	2914.8609	78.70
2	12.811	789.0472	21.30
	Total	3703.9081	100.00

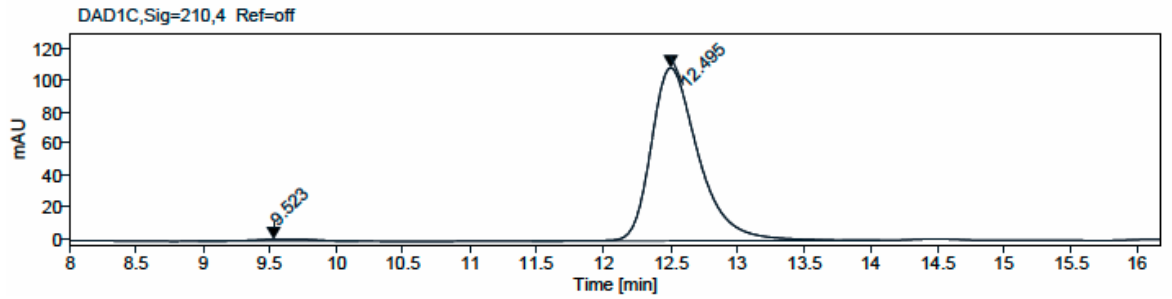


HPLC of (3*S*,5*S*)-**9c** (er 99:1) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

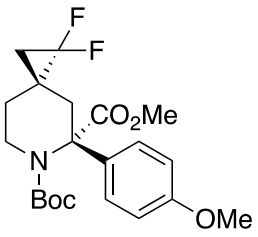


(3*S*,5*S*)-**9c**
(er 99:1)

	R_t/min	Area	Area/%
1	9.523	35.3430	1.30
2	12.495	2678.7830	98.70
	Total	2714.1261	100.00

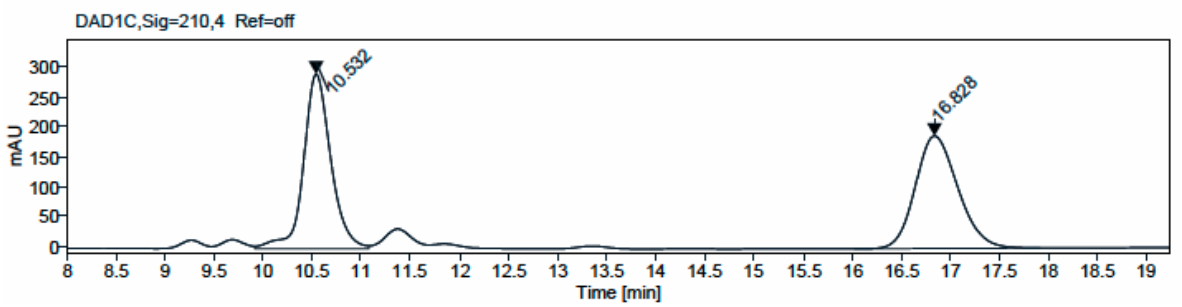


HPLC of (±)-**9d** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

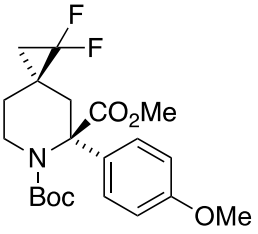


(±)-**9d**

	R_f/min	Area	Area/%
1	10.532	5647.1188	49.95
2	16.828	5658.4015	50.04
	Total	11305.5203	100.00

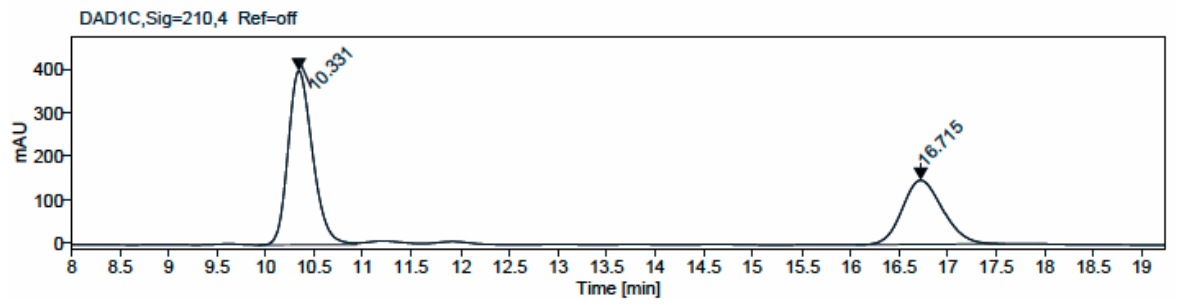


HPLC of (3*R*,5*R*)-**9d** (er 62:38) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

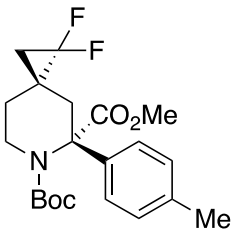


(3*R*,5*R*)-**9d**
(er 62:38)

	R_f/min	Area	Area/%
1	10.331	7019.9956	62.23
2	16.715	4260.6957	37.77
	Total	11280.6913	100.00

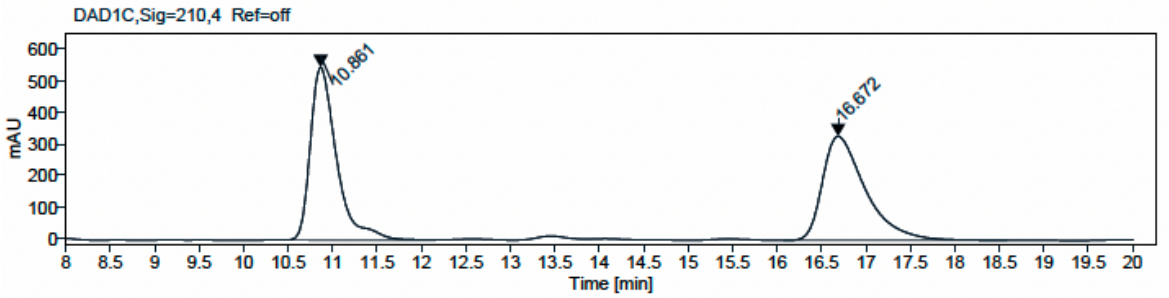


HPLC of (±)-**9e** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

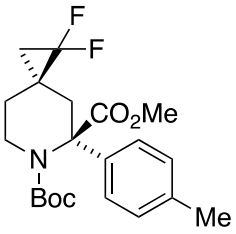


(±)-**9e**

	R_f/min	Area	Area/%
1	10.861	11169.1168	50.36
2	16.672	11010.0858	49.64
	Total	22179.2026	100.00

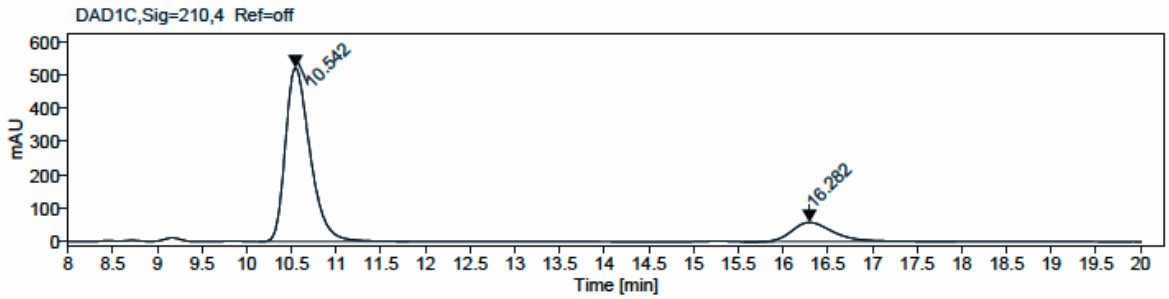


HPLC of (3*R*,5*R*)-**9e** (er 84:16) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

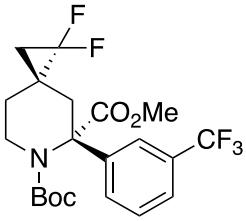


(3*R*,5*R*)-**9e**
(er 84:16)

	R_f/min	Area	Area/%
1	10.542	10137.8176	84.10
2	16.282	1916.1275	15.90
	Total	12053.9451	100.00

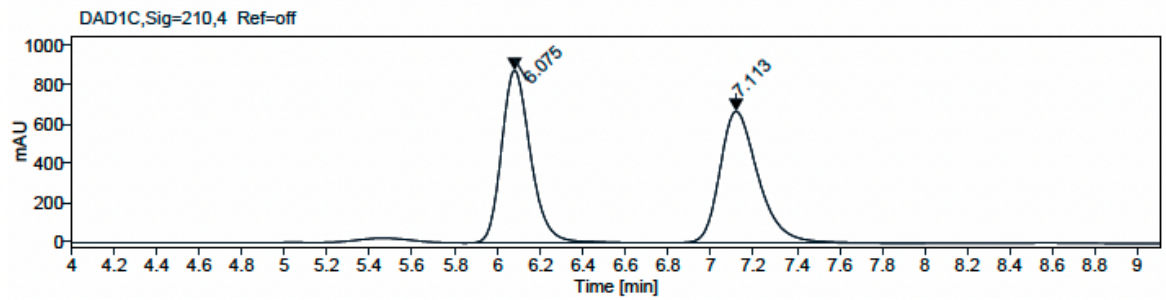


HPLC of (±)-**9f** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

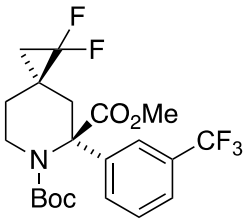


(±)-**9f**

	R_f/min	Area	Area/%
1	6.075	8230.1892	49.81
2	7.113	8293.6463	50.19
	Total	16523.8356	100.00

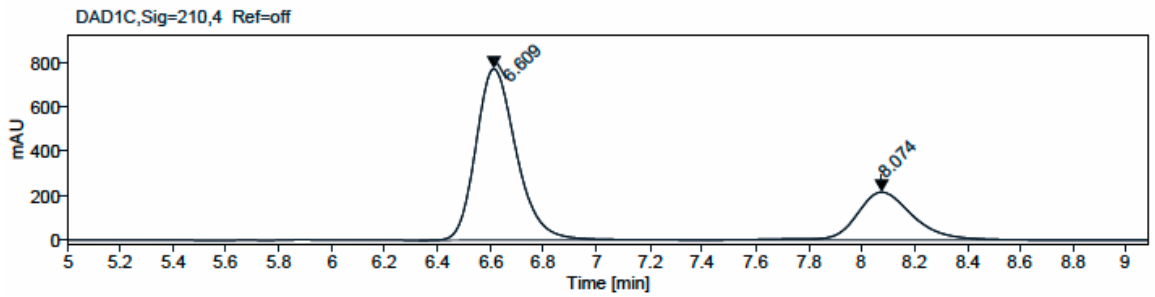


HPLC of (3*R*,5*R*)-**9f** (er 72:28) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

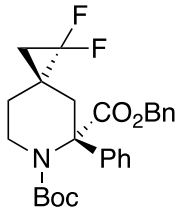


(3*R*,5*R*)-**9f**
(er 72:28)

	R_f/min	Area	Area/%
1	6.609	8235.8640	71.86
2	8.074	3224.6532	28.14
	Total	11460.5172	100.00

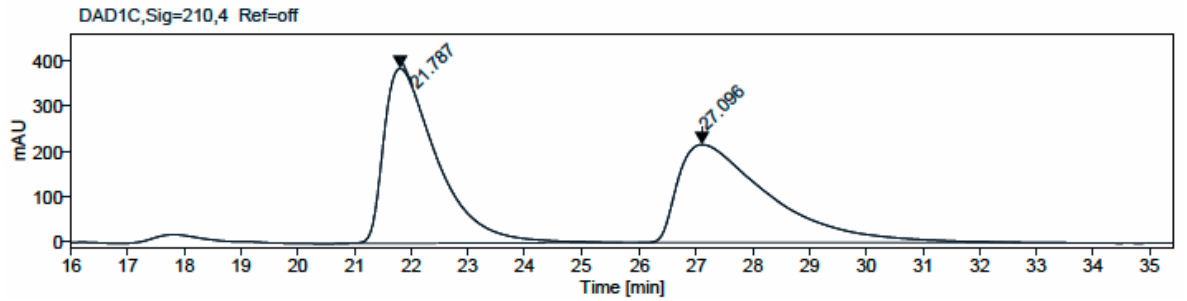


HPLC of (±)-**10** from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

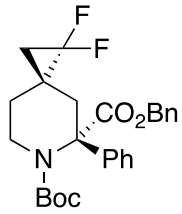


	Rf/min	Area	Area/%
1	21.787	25118.4965	50.79
2	27.096	24341.5611	49.21
	Total	49460.0576	100.00

(±)-**10**

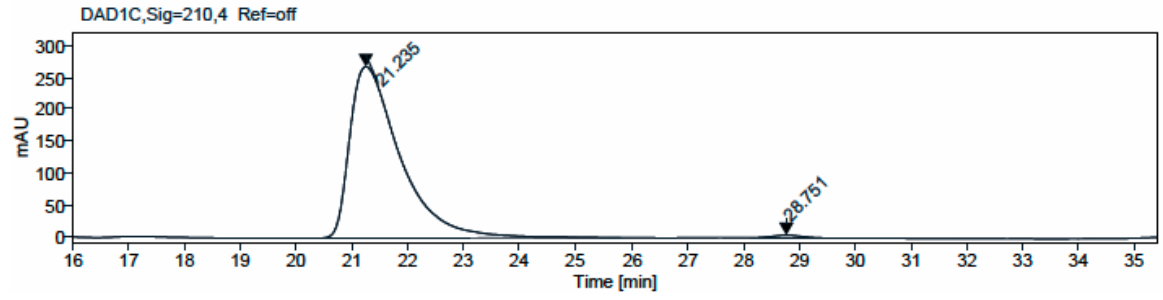


HPLC of (3*S*,5*S*)-**10** (er 99:1) from Agilent system fitted with a CHIRAL ART Cellulose-SC column:

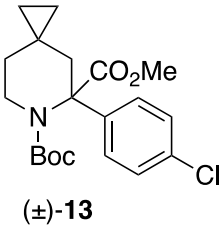


	Rf/min	Area	Area/%
1	21.235	16821.4506	98.99
2	28.751	171.0768	1.01
	Total	16992.5274	100.00

(3*S*,5*S*)-**10**

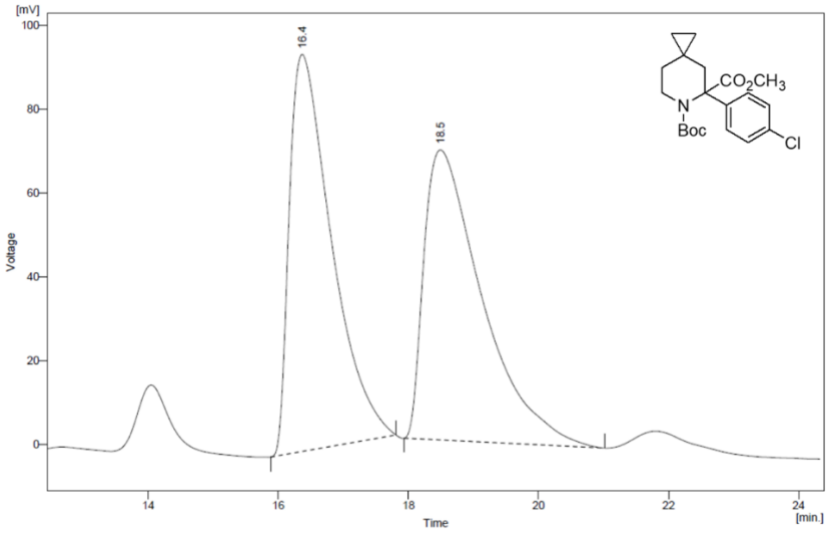


HPLC of (±)-**13** from Beckman system fitted with a Lux Amylose–2 column:

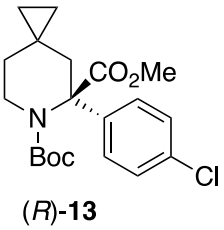


(±)-**13**

	R_f/min	Area	Area/%
1	16.4	3893.83	50.5
2	18.5	3813.25	49.5
	Total	7707.08	100.00

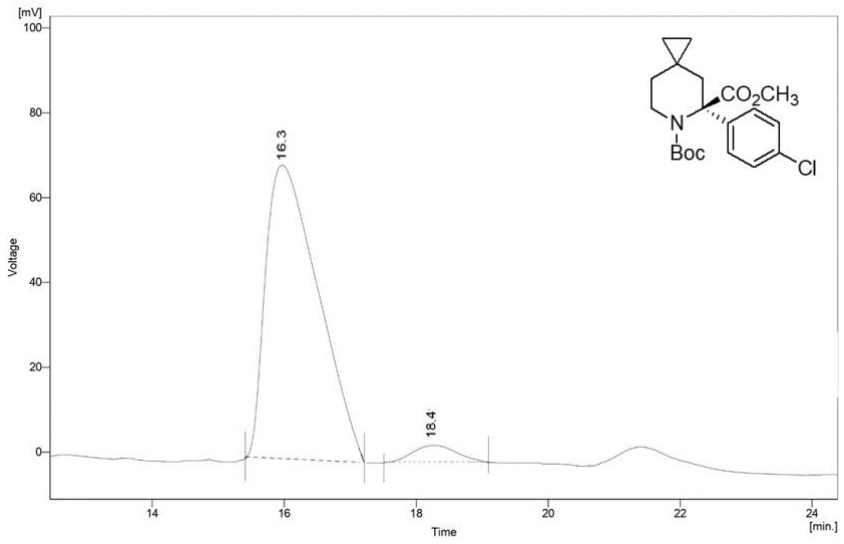


HPLC of (*R*)-**13** from Beckman system fitted with a Lux Amylose–2 column:

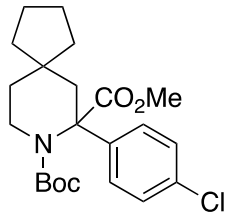


(*R*)-**13**

	R_f/min	Area	Area/%
1	16.3	22727.95	90.2
2	18.4	2807.15	9.8
	Total	25535.10	100.00

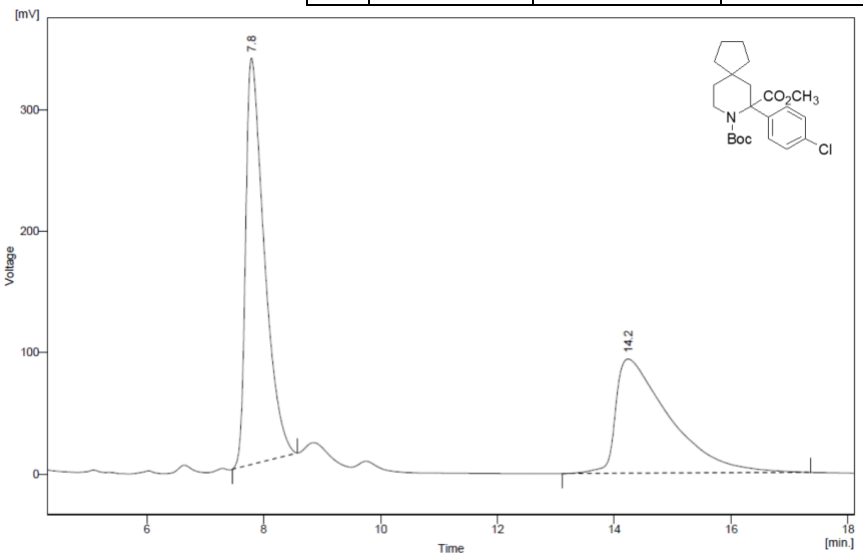


HPLC of (±)-**14** from Beckman system fitted with a Lux Amylose–2 column:

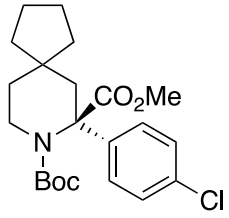


(±)-**14**

	R_f/min	Area	Area/%
1	7.8	7036.12	48.6
2	14.2	6405.50	51.4
	Total	13441.62	100.00

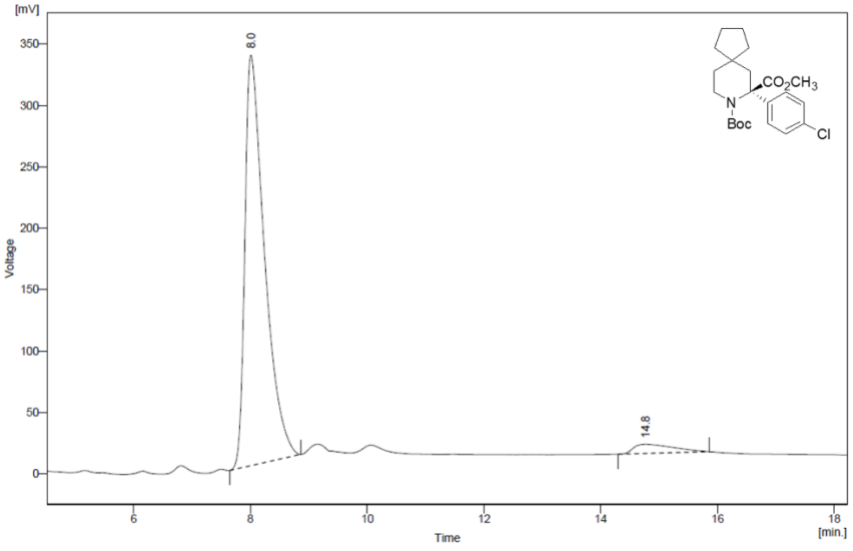


HPLC of (*R*)-**14** from Beckman system fitted with a Lux Amylose–2 column:



(*R*)-**14**

	R_f/min	Area	Area/%
1	8.0	28550.72	96.1
2	14.8	806.48	3.9
	Total	29357.20	100.00



9. X-Ray crystallography data for spiropiperidine (±)-2d

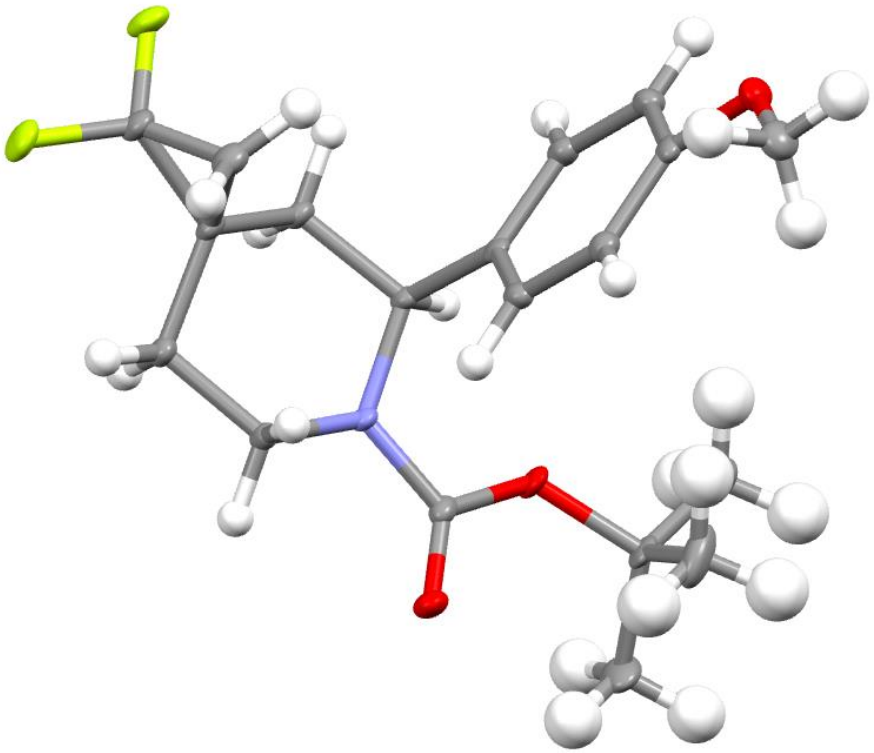
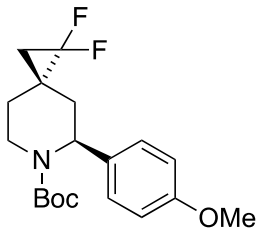


Figure S-1 X-ray for (±)-**2d**



(±)-**2d**

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Table S-1 Crystal data and structure refinement for OIC327s_0m (2d).

Identification code	OIC327s_0m
Empirical formula	$C_{19}H_{25}F_2NO_3$
Formula weight	353.40
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	6.496(3)
b/Å	11.821(5)
c/Å	12.772(5)
α/°	73.748(8)
β/°	83.671(9)
γ/°	75.267(8)
Volume/Å^3	909.8(6)
Z	2
ρ_{calc}g/cm^3	1.290
μ/mm^{-1}	0.100
F(000)	376.0
Crystal size/mm^3	0.5 × 0.5 × 0.45
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.324 to 57.834
Index ranges	$-8 \leq h \leq 8$, $-16 \leq k \leq 15$, $-17 \leq l \leq 17$
Reflections collected	36476
Independent reflections	4707 [R_{int} = 0.0802, R_{sigma} = 0.0456]
Data/restraints/parameters	4707/0/230
Goodness-of-fit on F^2	1.041
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.1094
Final R indexes [all data]	R_1 = 0.0488, wR_2 = 0.1173
Largest diff. peak/hole / e Å^{-3}	0.34/-0.32

Table S-2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for OIC327s_0m. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
F1	7167.1(11)	556.8(6)	7610.8(6)	23.83(17)
F2	9956.1(10)	902.5(6)	6532.9(6)	24.52(17)
O1	8528.5(12)	838.5(7)	854.8(7)	19.88(18)
O2	553.3(12)	4773.6(7)	3555.6(7)	18.72(18)
O3	3557.2(12)	5337.1(7)	2701.3(6)	17.67(18)
N1	3824.9(13)	3917.4(8)	4293.8(7)	13.07(18)
C1	6127.7(15)	3590.3(9)	3999.4(8)	12.7(2)
C2	7426.8(16)	2975.4(9)	5025.4(8)	14.1(2)
C3	6456.0(16)	2023.9(9)	5823.9(8)	14.2(2)
C4	4218.3(16)	2573.3(10)	6186.1(9)	15.9(2)
C5	2841.2(16)	3106.3(10)	5193.5(8)	14.8(2)
C6	6643.6(15)	2832.7(9)	3173.0(8)	13.2(2)
C7	8645.4(16)	2740.5(10)	2619.4(9)	16.5(2)
C8	9225.9(17)	2075.4(10)	1855.3(9)	18.1(2)
C9	7811.5(16)	1470.3(9)	1625.8(8)	15.4(2)
C10	5812.7(17)	1554.3(9)	2157.1(9)	15.6(2)
C11	5246.7(16)	2240.3(9)	2923.5(9)	14.8(2)
C12	7123.2(19)	213.1(11)	595.4(10)	23.0(2)
C13	6932.0(18)	713.6(10)	5668.5(9)	19.2(2)
C14	7829.5(17)	979.2(10)	6556.2(9)	18.1(2)
C15	2470.9(16)	4684.0(9)	3508.4(8)	13.8(2)
C16	2610.8(18)	6023.5(10)	1644.7(9)	18.3(2)
C17	4486(2)	6483.0(14)	1004.7(11)	34.6(3)
C18	1927(3)	5179.5(13)	1124.8(11)	36.7(3)
C19	789(2)	7074.5(12)	1780.6(11)	30.9(3)

Table S-3 Anisotropic Displacement Parameters ($Å^2×10^3$) for OIC327s_0m. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	26.8(4)	23.1(4)	14.6(3)	6.6(3)	-6.8(3)	-3.7(3)
F2	16.2(3)	26.0(4)	23.5(4)	2.9(3)	-8.7(3)	2.0(3)
O1	19.3(4)	22.6(4)	15.8(4)	-7.3(3)	0.6(3)	0.5(3)
O2	13.4(3)	21.2(4)	16.6(4)	-1.3(3)	-4.3(3)	2.3(3)
O3	16.9(4)	17.7(4)	11.5(4)	5.1(3)	-5.0(3)	0.2(3)
N1	11.3(4)	12.7(4)	10.4(4)	1.0(3)	-2.0(3)	1.9(3)
C1	10.5(4)	12.3(5)	11.4(5)	0.6(4)	-1.8(3)	0.8(3)
C2	12.7(4)	14.4(5)	12.4(5)	-0.3(4)	-3.9(4)	-0.5(4)
C3	14.1(4)	13.3(5)	11.6(5)	0.5(4)	-4.5(4)	0.7(4)
C4	14.9(5)	17.3(5)	11.0(5)	0.6(4)	-1.8(4)	0.0(4)
C5	12.3(4)	16.0(5)	11.8(5)	0.7(4)	-1.3(4)	0.0(4)
C6	13.2(4)	11.4(4)	9.7(5)	1.9(4)	-2.9(4)	2.4(3)
C7	13.1(5)	18.8(5)	14.5(5)	-0.6(4)	-2.3(4)	-1.5(4)
C8	12.9(5)	21.2(5)	15.3(5)	-1.8(4)	0.2(4)	1.1(4)
C9	16.8(5)	13.7(5)	10.0(5)	0.3(4)	-2.5(4)	3.3(4)
C10	16.0(5)	14.4(5)	13.5(5)	-0.9(4)	-2.4(4)	-0.6(4)
C11	12.2(4)	15.1(5)	13.3(5)	-0.8(4)	-0.6(4)	0.4(4)
C12	25.5(6)	21.0(6)	22.1(6)	-9.0(5)	0.7(5)	-1.6(4)
C13	20.6(5)	14.3(5)	18.8(5)	-0.6(4)	-5.3(4)	0.4(4)
C14	16.1(5)	17.5(5)	14.8(5)	3.1(4)	-4.7(4)	-0.1(4)
C15	16.2(5)	11.3(4)	11.0(5)	-2.0(4)	-2.7(4)	1.7(4)
C16	21.1(5)	16.0(5)	10.6(5)	3.0(4)	-5.9(4)	3.6(4)
C17	27.9(6)	40.7(8)	19.3(6)	13.2(5)	-2.1(5)	-2.5(6)
C18	65.7(10)	26.8(7)	16.6(6)	-1.2(5)	-14.3(6)	-8.8(6)
C19	33.2(7)	21.2(6)	23.4(6)	2.9(5)	-3.1(5)	11.4(5)

Table S-4 Bond Lengths for OIC327s_0m.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
F1	C14	1.3615(14)	C3	C13	1.5650(16)
F2	C14	1.3587(14)	C3	C14	1.4741(15)
O1	C9	1.3704(13)	C4	C5	1.5233(15)
O1	C12	1.4272(15)	C6	C7	1.4040(15)
O2	C15	1.2192(14)	C6	C11	1.3883(15)
O3	C15	1.3519(13)	C7	C8	1.3821(16)
O3	C16	1.4744(13)	C8	C9	1.3974(16)
N1	C1	1.4805(13)	C9	C10	1.3907(15)
N1	C5	1.4768(13)	C10	C11	1.4015(15)
N1	C15	1.3717(14)	C13	C14	1.4705(17)
C1	C2	1.5350(15)	C16	C17	1.5217(18)
C1	C6	1.5254(15)	C16	C18	1.5148(19)
C2	C3	1.5099(15)	C16	C19	1.5171(16)
C3	C4	1.5128(15)			

Table S-5 Bond Angles for OIC327s_0m.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C9	O1	C12	117.20(9)	O1	C9	C8	115.61(9)
C15	O3	C16	121.71(9)	O1	C9	C10	124.59(10)
C5	N1	C1	121.02(8)	C10	C9	C8	119.79(10)
C15	N1	C1	118.65(9)	C9	C10	C11	119.46(10)
C15	N1	C5	115.51(9)	C6	C11	C10	121.51(9)
N1	C1	C2	110.80(8)	C14	C13	C3	58.01(7)
N1	C1	C6	113.24(8)	F1	C14	C3	120.09(9)
C6	C1	C2	111.72(8)	F1	C14	C13	120.08(10)
C3	C2	C1	112.34(9)	F2	C14	F1	108.22(9)
C2	C3	C4	110.87(9)	F2	C14	C3	119.57(9)
C2	C3	C13	119.78(9)	F2	C14	C13	119.35(10)
C4	C3	C13	118.03(9)	C13	C14	C3	64.21(8)
C14	C3	C2	119.95(9)	O2	C15	O3	125.46(10)
C14	C3	C4	121.25(9)	O2	C15	N1	124.11(10)
C14	C3	C13	57.78(7)	O3	C15	N1	110.41(9)
C3	C4	C5	109.02(9)	O3	C16	C17	101.43(9)
N1	C5	C4	112.33(9)	O3	C16	C18	109.92(10)
C7	C6	C1	118.02(9)	O3	C16	C19	110.88(9)
C11	C6	C1	124.09(9)	C18	C16	C17	111.17(12)
C11	C6	C7	117.88(10)	C18	C16	C19	112.26(12)
C8	C7	C6	121.42(10)	C19	C16	C17	110.67(11)
C7	C8	C9	119.93(10)				

Table S-6 Torsion Angles for OIC327s_0m.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C9	C10	C11	-179.25(9)	C5	N1	C1	C2	-38.57(12)
N1	C1	C2	C3	45.39(11)	C5	N1	C1	C6	87.88(11)
N1	C1	C6	C7	163.44(9)	C5	N1	C15	O2	4.66(15)
N1	C1	C6	C11	-15.71(14)	C5	N1	C15	O3	-176.91(8)
C1	N1	C5	C4	42.41(13)	C6	C1	C2	C3	-81.89(11)
C1	N1	C15	O2	160.35(10)	C6	C7	C8	C9	-0.43(16)
C1	N1	C15	O3	-21.22(13)	C7	C6	C11	C10	0.97(15)
C1	C2	C3	C4	-59.39(11)	C7	C8	C9	O1	179.82(9)
C1	C2	C3	C13	83.52(11)	C7	C8	C9	C10	0.89(16)
C1	C2	C3	C14	151.24(10)	C8	C9	C10	C11	-0.43(16)
C1	C6	C7	C8	-179.70(9)	C9	C10	C11	C6	-0.52(16)
C1	C6	C11	C10	-179.88(9)	C11	C6	C7	C8	-0.49(16)
C2	C1	C6	C7	-70.60(12)	C12	O1	C9	C8	179.73(10)
C2	C1	C6	C11	110.25(11)	C12	O1	C9	C10	-0.87(15)
C2	C3	C4	C5	61.06(11)	C13	C3	C4	C5	-82.58(11)
C2	C3	C13	C14	108.62(11)	C13	C3	C14	F1	111.31(12)
C2	C3	C14	F1	140.36(10)	C13	C3	C14	F2	110.60(12)
C2	C3	C14	F2	2.27(15)	C14	C3	C4	C5	150.03(10)
C2	C3	C14	C13	108.33(11)	C15	O3	C16	C17	174.85(10)
C3	C4	C5	N1	-50.94(12)	C15	O3	C16	C18	-57.12(14)
C3	C13	C14	F1	111.32(11)	C15	O3	C16	C19	67.59(13)
C3	C13	C14	F2	110.92(11)	C15	N1	C1	C2	167.12(9)
C4	C3	C13	C14	111.04(11)	C15	N1	C1	C6	-66.43(12)
C4	C3	C14	F1	-5.80(16)	C15	N1	C5	C4	-162.53(9)
C4	C3	C14	F2	143.89(10)	C16	O3	C15	O2	-15.57(16)
C4	C3	C14	C13	105.51(11)	C16	O3	C15	N1	166.02(9)

Table S-7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for OIC327s_0m.

Atom	*x*	*y*	*z*	U(eq)
H1	6568.1	4366.12	3645.59	15
H2A	8892.06	2593.17	4808.42	17
H2B	7520.66	3597.82	5388.37	17
H4A	4242.83	3216.68	6538.25	19
H4B	3619.22	1943.26	6723.92	19
H5A	2602.04	2438.06	4932.8	18
H5B	1436.97	3565.87	5409.96	18
H7	9621.93	3144.08	2773.23	20
H8	10584.96	2029.61	1486.5	22
H10	4838.9	1149.93	2001.75	19
H11	3875.62	2301.26	3280.48	18
H12A	7795.62	-180.66	22.08	35
H12B	5791.56	791.77	337.61	35
H12C	6817.39	-401.4	1248.39	35
H13A	5776.11	274.18	5859.57	23
H13B	7901.89	534.98	5050.72	23
H17A	4865.37	7046.07	1344.38	52
H17B	4092.75	6902.5	251.04	52
H17C	5708	5796.44	1006.67	52
H18A	3101.11	4468.05	1130.82	55
H18B	1549.64	5604.25	369.87	55
H18C	688.72	4920.31	1537.34	55
H19A	-409.37	6761.35	2184.39	46
H19B	337.28	7592.45	1060.26	46
H19C	1263.05	7548.52	2185.1	46

Crystal structure determination of OIC327s_0m

Crystal Data for $C_{19}H_{25}F_2NO_3$ (*M* =353.40 g/mol): triclinic, space group P-1 (no. 2), *a* = 6.496(3) Å, *b* = 11.821(5) Å, *c* = 12.772(5) Å, α = 73.748(8)°, β = 83.671(9)°, γ = 75.267(8)°, *V* = 909.8(6) Å^3, *Z* = 2, *T* = 100 K, μ(MoKα) = 0.100 mm^{-1}, *Dcalc* = 1.290 g/cm^3, 36476 reflections measured (3.324° ≤ 2Θ ≤ 57.834°), 4707 unique (R_{int} = 0.0802, R_{sigma} = 0.0456) which were used in all calculations. The final R_1 was 0.0410 (I > 2σ(I)) and wR_2 was 0.1173 (all data).

10. X-Ray crystallography data for carbamate (*S*,*S*)-9c

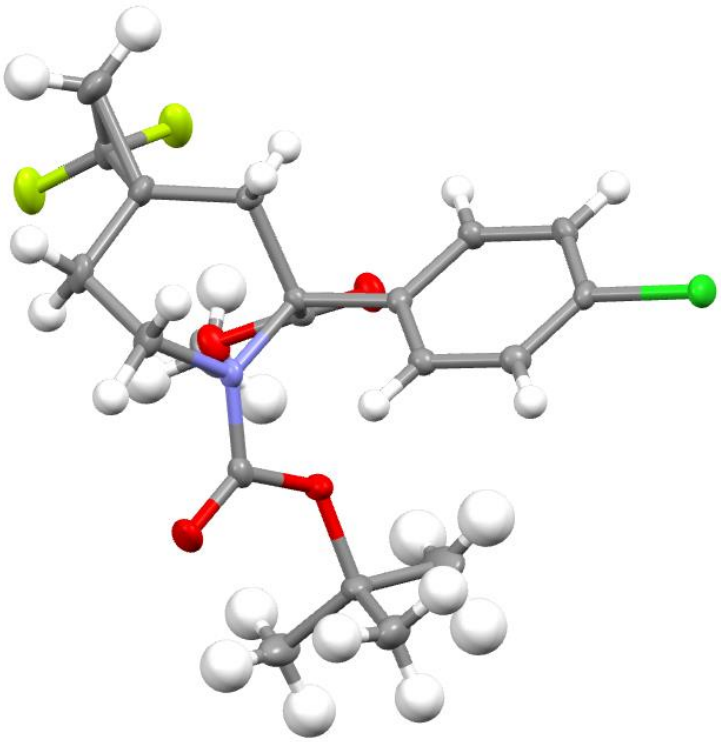
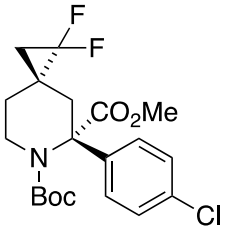


Figure S-2 X-ray for (*S*,*S*)-**9c**



(3*S*,5*S*)-**9c**

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Table S-8 Crystal data and structure refinement for OIC326s_0m (9c).

Identification code	OIC326s_0m
Empirical formula	$C_{20}H_{24}ClF_2NO_4$
Formula weight	415.85
Temperature/K	100.00
Crystal system	monoclinic
Space group	$P2_1$
a/Å	8.252(7)
b/Å	10.441(11)
c/Å	12.226(10)
α/°	90
β/°	100.816(10)
γ/°	90
Volume/Å^3	1034.7(16)
Z	2
ρ_{calc}g/cm^3	1.335
μ/mm^{-1}	0.227
F(000)	436.0
Crystal size/mm^3	0.334 × 0.254 × 0.177
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.392 to 57.424
Index ranges	$-10 \leq h \leq 11$, $-13 \leq k \leq 13$, $-16 \leq l \leq 16$
Reflections collected	19144
Independent reflections	5317 [R_{int} = 0.0481, R_{sigma} = 0.0477]
Data/restraints/parameters	5317/1/257
Goodness-of-fit on F^2	1.025
Final R indexes [I>=2σ (I)]	R_1 = 0.0347, wR_2 = 0.0751
Final R indexes [all data]	R_1 = 0.0416, wR_2 = 0.0794
Largest diff. peak/hole / e Å^{-3}	0.21/-0.22
Flack parameter	0.02(3)

Table S-9 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for OIC326s_0m. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	10921.3(7)	942.2(5)	8359.8(5)	22.88(13)
F1	3661(2)	8859.2(15)	8786.7(14)	34.8(4)
F2	6008.3(19)	8198.0(15)	9783.1(13)	33.4(4)
O1	8829(2)	7015.3(16)	8243.5(15)	23.1(4)
O2	6395(2)	7826.2(15)	7398.2(14)	22.1(4)
O3	4315(2)	5668.5(18)	4950.8(13)	27.0(4)
O4	6996.3(18)	5905.8(17)	5823.9(12)	19.8(3)
N1	5103(2)	5513.9(17)	6845.8(15)	15.5(4)
C1	6432(3)	5602.4(19)	7833.8(17)	13.9(4)
C2	5607(3)	5624(2)	8882.9(18)	18.0(5)
C3	4174(3)	6543(2)	8786(2)	20.8(5)
C4	2889(3)	6409(2)	7711(2)	24.2(5)
C5	3398(3)	5323(2)	7011(2)	21.3(5)
C6	7595(3)	4442(2)	7936.6(18)	14.6(4)
C7	8939(3)	4350(2)	8828.8(18)	17.7(5)
C8	9961(3)	3281(2)	8957.8(19)	18.6(5)
C9	9633(3)	2290(2)	8192.5(19)	16.9(4)
C10	8313(3)	2339(2)	7314.2(19)	18.0(5)
C11	7291(3)	3416(2)	7193.0(19)	16.4(4)
C12	7393(3)	6869(2)	7833.6(18)	16.3(4)
C13	7196(4)	9067(2)	7417(3)	32.7(6)
C14	3573(4)	6903(3)	9882(2)	34.1(6)
C15	4449(3)	7823(2)	9301(2)	26.0(6)
C16	5376(3)	5702(2)	5789.0(18)	18.0(5)
C17	7703(3)	5925(3)	4796.3(18)	23.2(5)
C18	9505(3)	6153(4)	5265(3)	42.9(8)
C19	7457(4)	4624(3)	4233(2)	31.8(6)
C20	6961(4)	7015(3)	4036(2)	36.7(7)

Table S-10 Anisotropic Displacement Parameters ($Å^2×10^3$) for OIC326s_0m. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	26.5(3)	19.9(2)	22.9(3)	3.5(2)	6.3(2)	10.2(2)
F1	34.7(9)	25.7(7)	39.8(9)	-9.3(7)	-3.6(7)	15.2(7)
F2	28.1(9)	34.1(9)	33.5(9)	-15.8(7)	-5.8(7)	7.6(7)
O1	16.9(9)	21.1(9)	28.8(9)	0.5(7)	-1.9(7)	-2.8(6)
O2	22.8(9)	13.5(7)	27.4(9)	3.0(7)	-1.7(7)	-0.9(6)
O3	20.2(9)	39.1(11)	18.5(8)	-4.8(7)	-4.9(7)	6.3(7)
O4	15.4(8)	29.6(8)	14.3(7)	1.7(7)	2.7(6)	1.0(8)
N1	9.2(9)	19.0(9)	17.6(9)	-1.3(7)	0.4(7)	0.2(7)
C1	13.2(10)	14.2(10)	13.5(10)	-0.2(7)	0.5(8)	1.3(7)
C2	20.7(12)	17.8(11)	17.1(10)	1.7(8)	7.3(9)	4.5(8)
C3	19.1(12)	23.6(12)	21.4(12)	-1.4(9)	7.7(10)	6.2(9)
C4	13.3(11)	28.3(12)	30.6(13)	-6.3(10)	2.9(10)	3.2(9)
C5	13.0(11)	24.4(12)	27.2(13)	-4.6(10)	5.3(10)	-2.4(9)
C6	15.3(11)	14.1(10)	15.0(10)	2.3(8)	4.6(8)	1.7(8)
C7	18.9(12)	17.8(10)	15.9(11)	-0.9(8)	2.1(9)	2.6(9)
C8	15.1(12)	22.9(11)	16.7(11)	2.1(9)	0.5(9)	3.2(9)
C9	17.6(12)	15.4(10)	19.5(11)	3.5(8)	7.8(9)	5.8(8)
C10	22.0(13)	14.7(10)	17.5(11)	0.0(8)	4.3(9)	0.0(9)
C11	16.0(12)	17.8(10)	15.1(11)	0.8(8)	2.4(9)	-0.5(8)
C12	18.9(12)	16.1(10)	13.7(10)	0.5(8)	2.2(9)	1.1(9)
C13	33.7(16)	16.3(12)	42.8(16)	7.0(11)	-6.6(13)	-4.7(10)
C14	32.5(16)	45.8(16)	27.0(14)	-4.2(12)	13.5(12)	13.3(13)
C15	21.8(13)	28.3(13)	26.0(13)	-8.2(10)	-0.7(11)	9.9(10)
C16	16.8(11)	17.3(11)	18.7(10)	-0.9(8)	0.0(9)	4.1(8)
C17	24.5(12)	31.1(12)	15.8(10)	6.2(11)	8.3(9)	6.9(11)
C18	25.4(15)	73(2)	33.0(15)	6.8(15)	13.2(12)	-5.2(15)
C19	38.0(17)	33.5(14)	26.5(14)	0.8(11)	12.4(12)	11.6(12)
C20	56(2)	32.1(15)	26.6(14)	11.4(12)	18.5(14)	17.9(14)

Table S-11 Bond Lengths for OIC326s_0m.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	C9	1.753(3)	C2	C3	1.510(3)
F1	C15	1.355(3)	C3	C4	1.532(4)
F2	C15	1.368(3)	C3	C14	1.560(3)
O1	C12	1.207(3)	C3	C15	1.477(4)
O2	C12	1.340(3)	C4	C5	1.526(3)
O2	C13	1.453(3)	C6	C7	1.406(3)
O3	C16	1.217(3)	C6	C11	1.397(3)
O4	C16	1.346(3)	C7	C8	1.390(3)
O4	C17	1.481(3)	C8	C9	1.387(3)
N1	C1	1.474(3)	C9	C10	1.380(3)
N1	C5	1.472(3)	C10	C11	1.396(3)
N1	C16	1.367(3)	C14	C15	1.464(4)
C1	C2	1.561(3)	C17	C18	1.509(4)
C1	C6	1.536(3)	C17	C19	1.519(4)
C1	C12	1.542(3)	C17	C20	1.524(4)

Table S-12 Bond Angles for OIC326s_0m.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C12	O2	C13	114.5(2)	C8	C9	Cl1	118.86(18)
C16	O4	C17	121.46(17)	C10	C9	Cl1	119.57(17)
C5	N1	C1	118.63(19)	C10	C9	C8	121.6(2)
C16	N1	C1	122.45(19)	C9	C10	C11	119.0(2)
C16	N1	C5	118.72(18)	C10	C11	C6	121.2(2)
N1	C1	C2	107.62(18)	O1	C12	O2	123.6(2)
N1	C1	C6	112.02(17)	O1	C12	C1	125.0(2)
N1	C1	C12	110.92(17)	O2	C12	C1	111.21(19)
C6	C1	C2	107.83(17)	C15	C14	C3	58.35(17)
C6	C1	C12	111.27(18)	F1	C15	F2	107.6(2)
C12	C1	C2	106.93(17)	F1	C15	C3	120.2(2)
C3	C2	C1	113.60(18)	F1	C15	C14	120.8(2)
C2	C3	C4	114.5(2)	F2	C15	C3	120.0(2)
C2	C3	C14	117.2(2)	F2	C15	C14	119.3(2)
C4	C3	C14	118.6(2)	C14	C15	C3	64.10(18)
C15	C3	C2	119.1(2)	O3	C16	O4	125.8(2)
C15	C3	C4	118.3(2)	O3	C16	N1	124.9(2)
C15	C3	C14	57.54(18)	O4	C16	N1	109.37(18)
C5	C4	C3	109.2(2)	O4	C17	C18	101.36(19)
N1	C5	C4	110.35(19)	O4	C17	C19	109.4(2)
C7	C6	C1	120.51(19)	O4	C17	C20	110.5(2)
C11	C6	C1	121.2(2)	C18	C17	C19	110.6(2)
C11	C6	C7	118.1(2)	C18	C17	C20	111.6(3)
C8	C7	C6	121.1(2)	C19	C17	C20	112.8(2)
C9	C8	C7	119.0(2)				

Table S-13 Torsion Angles for OIC326s_0m.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Cl1	C9	C10	C11	179.74(17)	C5	N1	C1	C12	-123.3(2)
N1	C1	C2	C3	-46.9(2)	C5	N1	C16	O3	-3.5(3)
N1	C1	C6	C7	179.83(19)	C5	N1	C16	O4	177.57(18)
N1	C1	C6	C11	-4.0(3)	C6	C1	C2	C3	167.92(19)
N1	C1	C12	O1	-150.3(2)	C6	C1	C12	O1	-24.9(3)
N1	C1	C12	O2	34.8(2)	C6	C1	C12	O2	160.21(18)
C1	N1	C5	C4	58.3(3)	C6	C7	C8	C9	-0.4(3)
C1	N1	C16	O3	-178.2(2)	C7	C6	C11	C10	-1.4(3)
C1	N1	C16	O4	2.8(3)	C7	C8	C9	Cl1	179.87(17)
C1	C2	C3	C4	50.2(3)	C7	C8	C9	C10	-0.5(3)
C1	C2	C3	C14	-164.3(2)	C8	C9	C10	C11	0.4(3)
C1	C2	C3	C15	-98.1(3)	C9	C10	C11	C6	0.6(3)
C1	C6	C7	C8	177.3(2)	C11	C6	C7	C8	1.3(3)
C1	C6	C11	C10	-177.4(2)	C12	C1	C2	C3	72.3(2)
C2	C1	C6	C7	-61.6(3)	C12	C1	C6	C7	55.4(3)
C2	C1	C6	C11	114.3(2)	C12	C1	C6	C11	-128.8(2)
C2	C1	C12	O1	92.6(3)	C13	O2	C12	O1	2.3(3)
C2	C1	C12	O2	-82.3(2)	C13	O2	C12	C1	177.3(2)
C2	C3	C4	C5	1.3(3)	C14	C3	C4	C5	-143.8(2)
C2	C3	C14	C15	108.7(3)	C14	C3	C15	F1	-112.0(3)
C2	C3	C15	F1	142.6(2)	C14	C3	C15	F2	110.4(3)
C2	C3	C15	F2	5.0(4)	C15	C3	C4	C5	149.8(2)
C2	C3	C15	C14	-105.4(3)	C16	O4	C17	C18	-178.9(2)
C3	C4	C5	N1	-52.8(3)	C16	O4	C17	C19	-62.1(3)
C3	C14	C15	F1	111.2(3)	C16	O4	C17	C20	62.7(3)
C3	C14	C15	F2	-111.4(2)	C16	N1	C1	C2	168.12(18)
C4	C3	C14	C15	-107.1(3)	C16	N1	C1	C6	-73.5(2)
C4	C3	C15	F1	-4.5(4)	C16	N1	C1	C12	51.5(3)
C4	C3	C15	F2	-142.1(2)	C16	N1	C5	C4	-116.6(2)
C4	C3	C15	C14	107.5(3)	C17	O4	C16	O3	-9.3(3)
C5	N1	C1	C2	-6.6(2)	C17	O4	C16	N1	169.7(2)
C5	N1	C1	C6	111.7(2)					

Table S-14 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for OIC326s_0m.

Atom	*x*	*y*	*z*	U(eq)
H2A	5214.88	4750.63	9011.38	22
H2B	6448.53	5863.17	9539.79	22
H4A	1793.29	6222.13	7893.41	29
H4B	2808.96	7220.76	7286.05	29
H5A	3314.03	4494.9	7389.8	26
H5B	2643.69	5296.77	6278.87	26
H7	9152.82	5029.91	9352.43	21
H8	10869.98	3229.11	9561.24	22
H10	8101.44	1649.8	6799.64	22
H11	6373.86	3451.6	6594.12	20
H13A	8121.69	9009.99	7020	49
H13B	7607.17	9323.95	8189.75	49
H13C	6401.46	9703	7052.36	49
H14A	2374.79	7032.01	9844.8	41
H14B	4171.63	6532.96	10589.16	41
H18A	9643.71	7003.61	5607.91	64
H18B	10138.35	6103.04	4663.45	64
H18C	9903.31	5499.87	5826.85	64
H19A	7981.81	3961.99	4749.3	48
H19B	7955.62	4626.13	3566.47	48
H19C	6273.73	4443.72	4021.21	48
H20A	5811.32	6812.37	3711.58	55
H20B	7592.08	7125.06	3438.7	55
H20C	7001.6	7808.46	4468.2	55

Crystal structure determination of OIC326s_0m

Crystal Data for $C_{20}H_{24}ClF_2NO_4$ (*M* =415.85 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 8.252(7) Å, *b* = 10.441(11) Å, *c* = 12.226(10) Å, *β* = 100.816(10)°, *V* = 1034.7(16) Å^3, *Z* = 2, *T* = 100.00 K, μ(MoKα) = 0.227 mm^{-1}, *Dcalc* = 1.335 g/cm^3, 19144 reflections measured (3.392° ≤ 2Θ ≤ 57.424°), 5317 unique (R_{int} = 0.0481, R_{sigma} = 0.0477) which were used in all calculations. The final R_1 was 0.0347 (I > 2σ(I)) and wR_2 was 0.0794 (all data).

11. DFT data

DFT calculations on structure (3*S*,5*S*)-**9c** were carried out using the methods described in the general procedures. Having obtained the X-ray crystal structure for compound (3*S*,5*S*)-**9c** a frequency calculation was performed. The outcome of this calculation showed 27 imaginary frequencies indicating that this structure was not optimised. An optimisation calculation was then performed to give the structure shown in Figure S-3a. The next calculations performed were optimisation calculations on the chair conformations of (3*S*,5*S*)-**9c**. In line with previous work, the *p*-chlorophenyl group could adopt an axial or equatorial position. Optimisation of the axial chair conformation gave the structure shown in Figure S-3b, while optimisation of the equatorial chair conformation gave the structure shown in Figure S-3c.

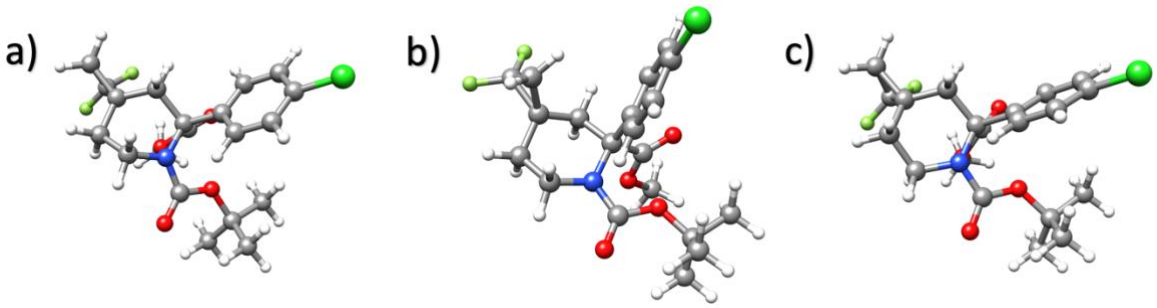
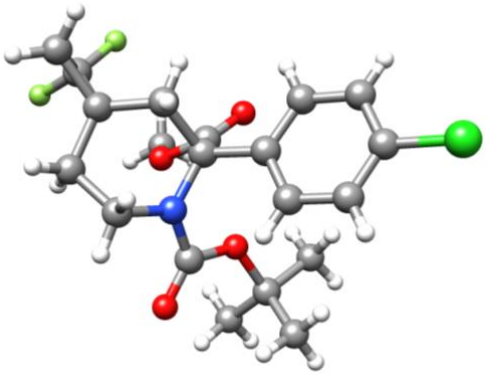


Figure S-3. Calculated conformations of **9c**

Frequency Calculation Performed on X-ray Crystal Structure of (3*S*,5*S*)-**9c**:



Route : # freq b3lyp scrf=(solvent=thf) geom=connectivity def2tzvp empiricaldispersion=gd3bj int=ultrafine pop=(regular,mk)

SMILES : COC(=O)C2(c1ccc(Cl)cc1)CC3(CCN2C(=O)OC(C)(C)C)CC3(F)F

Formula : $C_{20}H_{24}ClF_2NO_4$

Charge : 0

Multiplicity : 1

Dipole : 2.7865 Debye

Energy : -1792.56472910 a.u.

Gibbs Energy : -1792.191838 a.u.

Number of imaginary frequencies : 27

Cartesian Coordinates (XYZ format)

52

Cl	5.43056000	-2.36082400	0.06740900
F	-4.71669900	-0.72066600	0.17985800
F	-3.36185100	-1.87464000	1.46813500
O	-0.38403600	-0.26153300	2.28099700
O	-1.95914100	0.76429700	1.05349700
O	-0.40511400	2.60224300	-1.98854100
O	0.46310900	1.94200000	0.01652700
N	-0.59879100	0.44956200	-1.22721400
C	-0.35745400	-0.52472900	-0.14754700
C	-1.20188100	-1.79878600	-0.46464600
H	-0.76708500	-2.29505600	-1.20265800
H	-1.20501400	-2.38627500	0.33230000
C	-2.62942500	-1.49688000	-0.85382100
C	-2.77900600	-0.43485000	-1.94836000
H	-3.26888600	-0.81536000	-2.72053400
H	-3.29663500	0.33426700	-1.60152800
C	-1.39434700	0.02912100	-2.39214100
H	-0.93117300	-0.70857800	-2.86134400
H	-1.48480800	0.78715900	-3.02260900
C	1.11790900	-0.94530000	-0.07055000

C	1.54552500	-1.87268200	0.89493500
H	0.92170200	-2.21017300	1.52698600
C	2.86600900	-2.30417700	0.94083900
H	3.14708200	-2.92772500	1.59988600
C	3.76758100	-1.81143400	0.00882400
C	3.38090500	-0.91303100	-0.96407200
H	4.00973200	-0.58903200	-1.59845700
C	2.05114700	-0.48762700	-1.00383000
H	1.77691600	0.12410700	-1.67678900
C	-0.85592900	0.01905500	1.20657900
C	-2.52742500	1.26180500	2.29432900
H	-1.85187300	1.78514700	2.77552600
H	-2.81153500	0.50668500	2.84970500
H	-3.29971800	1.83079800	2.09513000
C	-3.64190000	-2.68262100	-0.82124300
H	-4.34944000	-2.70846800	-1.51385300
H	-3.31088200	-3.56822400	-0.52693600
C	-3.69017500	-1.60461300	0.16774200
C	-0.20208800	1.75448700	-1.13923600
C	1.20601600	3.19465600	0.28637900
C	1.78069500	2.91075400	1.65224600
H	1.05272600	2.83418400	2.30325200
H	2.37742200	3.64321200	1.91387400
H	2.28609500	2.07166000	1.62614800
C	2.31673200	3.35305000	-0.73803100
H	2.91198400	2.57510800	-0.69739500
H	2.82754800	4.16572400	-0.54349100
H	1.92677700	3.41852200	-1.63506600
C	0.25488600	4.38425900	0.31370700
H	-0.05712700	4.57411100	-0.59597700
H	0.72296600	5.16869400	0.66861700
H	-0.51300700	4.17554500	0.88537200

Frequencies

Mode	IR frequency	IR intensity	Raman intensity
1	-1174.74300000	0.00870000	0.00000000
2	-1157.96740000	0.10420000	0.00000000
3	-1149.93500000	0.16890000	0.00000000
4	-1144.78150000	0.23660000	0.00000000
5	-1128.77130000	106.27340000	0.00000000
6	-1088.01860000	1.43420000	0.00000000
7	-943.36000000	0.31150000	0.00000000
8	-922.96370000	0.01060000	0.00000000
9	-808.85400000	5.91640000	0.00000000
10	-776.11590000	9.40980000	0.00000000
11	-733.63380000	7.84850000	0.00000000
12	-726.48290000	2.33870000	0.00000000
13	-707.67610000	0.91630000	0.00000000
14	-692.00510000	2.75400000	0.00000000
15	-681.77640000	0.48340000	0.00000000

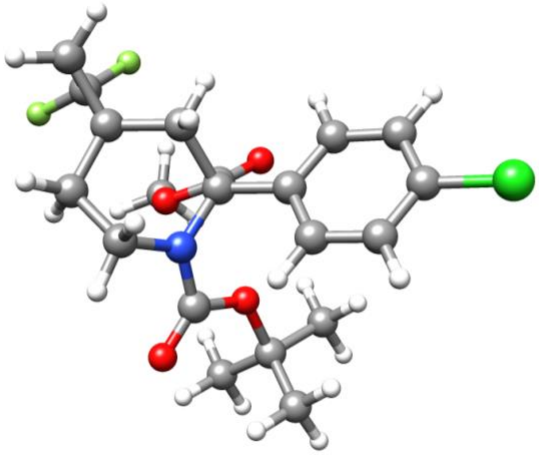
16	-651.04390000	0.09970000	0.00000000
17	-642.05040000	0.68330000	0.00000000
18	-631.77940000	0.65210000	0.00000000
19	-558.93200000	6.56310000	0.00000000
20	-530.49910000	10.38890000	0.00000000
21	-512.48120000	2.07940000	0.00000000
22	-414.48710000	2.74600000	0.00000000
23	-373.55030000	0.96930000	0.00000000
24	-301.20280000	17.39370000	0.00000000
25	-184.70070000	15.22260000	0.00000000
26	-89.76540000	1.12910000	0.00000000
27	-71.33890000	1.17770000	0.00000000
28	70.29710000	0.33240000	0.00000000
29	85.60560000	0.33530000	0.00000000
30	106.64320000	4.77730000	0.00000000
31	116.30570000	4.17070000	0.00000000
32	125.85800000	1.12700000	0.00000000
33	131.07460000	3.19380000	0.00000000
34	137.88590000	0.82690000	0.00000000
35	169.67990000	2.44230000	0.00000000
36	183.82190000	2.73830000	0.00000000
37	221.52050000	0.32660000	0.00000000
38	223.37840000	0.11720000	0.00000000
39	229.52260000	2.64270000	0.00000000
40	245.23870000	4.19990000	0.00000000
41	254.29080000	8.25860000	0.00000000
42	276.30000000	2.04790000	0.00000000
43	304.14350000	17.54150000	0.00000000
44	349.69460000	1.84810000	0.00000000
45	362.52270000	4.07530000	0.00000000
46	376.75950000	5.23860000	0.00000000
47	385.16200000	0.05710000	0.00000000
48	419.04790000	2.89630000	0.00000000
49	428.01610000	26.16340000	0.00000000
50	437.06420000	31.97110000	0.00000000
51	498.75400000	10.33450000	0.00000000
52	519.55760000	20.37250000	0.00000000
53	521.80630000	7.60370000	0.00000000
54	536.13840000	3.95740000	0.00000000
55	546.05910000	0.10790000	0.00000000
56	573.00980000	3.20470000	0.00000000
57	587.13490000	9.80140000	0.00000000
58	595.80370000	6.23000000	0.00000000

59	600.45030000	1.53030000	0.00000000
60	609.40890000	2.37930000	0.00000000
61	633.67610000	2.56070000	0.00000000
62	637.52480000	0.46170000	0.00000000
63	662.32040000	4.57330000	0.00000000
64	682.42070000	17.81500000	0.00000000
65	705.76860000	2.25720000	0.00000000
66	717.05010000	2.82970000	0.00000000
67	720.02390000	10.55850000	0.00000000
68	723.37280000	0.98190000	0.00000000
69	725.81070000	2.28710000	0.00000000
70	758.48910000	4.95330000	0.00000000
71	762.92920000	27.60720000	0.00000000
72	783.79060000	1.73870000	0.00000000
73	786.66360000	37.75430000	0.00000000
74	791.94300000	13.82650000	0.00000000
75	819.29130000	7.53590000	0.00000000
76	828.70850000	7.16780000	0.00000000
77	850.32510000	1.84610000	0.00000000
78	855.14510000	5.38700000	0.00000000
79	884.28950000	9.76160000	0.00000000
80	903.73720000	27.41740000	0.00000000
81	904.78520000	39.39540000	0.00000000
82	906.79320000	67.62750000	0.00000000
83	914.46930000	8.86210000	0.00000000
84	944.36900000	22.84440000	0.00000000
85	944.95220000	34.55090000	0.00000000
86	963.87160000	100.22630000	0.00000000
87	989.06420000	93.18390000	0.00000000
88	999.52550000	80.28880000	0.00000000
89	1033.45260000	291.62640000	0.00000000
90	1037.33230000	140.35110000	0.00000000
91	1041.87370000	132.36380000	0.00000000
92	1054.26690000	16.75810000	0.00000000
93	1061.88110000	39.03940000	0.00000000
94	1067.72130000	130.49660000	0.00000000
95	1081.82870000	47.51680000	0.00000000
96	1121.64990000	14.84990000	0.00000000
97	1156.70660000	164.99260000	0.00000000
98	1158.53450000	59.81970000	0.00000000
99	1163.16430000	65.98820000	0.00000000
100	1178.15440000	17.54420000	0.00000000
101	1180.26030000	87.67850000	0.00000000

102	1183.52700000	75.68540000	0.00000000
103	1187.74470000	4.83060000	0.00000000
104	1206.39460000	79.80430000	0.00000000
105	1215.84800000	2.94700000	0.00000000
106	1220.59120000	16.73420000	0.00000000
107	1223.43460000	0.60300000	0.00000000
108	1228.06700000	19.87070000	0.00000000
109	1233.26570000	32.13610000	0.00000000
110	1238.38270000	23.89550000	0.00000000
111	1239.71260000	44.49000000	0.00000000
112	1276.93990000	48.64020000	0.00000000
113	1280.71450000	13.56380000	0.00000000
114	1284.37680000	66.69480000	0.00000000
115	1290.47280000	293.01340000	0.00000000
116	1305.03140000	15.58280000	0.00000000
117	1307.01000000	9.15840000	0.00000000
118	1326.75390000	26.65240000	0.00000000
119	1368.78760000	47.76420000	0.00000000
120	1375.71790000	65.44900000	0.00000000
121	1395.84620000	499.30230000	0.00000000
122	1453.64180000	201.86960000	0.00000000
123	1549.46720000	30.84510000	0.00000000
124	1596.83500000	9.84100000	0.00000000
125	1721.10510000	931.92280000	0.00000000
126	1761.26330000	259.60030000	0.00000000
127	4055.43340000	19.54200000	0.00000000
128	4057.07410000	0.70770000	0.00000000
129	4059.84000000	3.03070000	0.00000000
130	4066.31190000	27.31360000	0.00000000
131	4117.36250000	10.02420000	0.00000000
132	4118.35120000	16.16810000	0.00000000
133	4121.91330000	9.75440000	0.00000000
134	4130.02080000	23.80940000	0.00000000
135	4141.51680000	6.37650000	0.00000000
136	4147.33140000	1.20220000	0.00000000
137	4155.52330000	7.41090000	0.00000000
138	4187.60420000	0.02220000	0.00000000
139	4263.92640000	4.53180000	0.00000000
140	4265.92180000	7.12910000	0.00000000
141	4268.58550000	8.07190000	0.00000000
142	4270.06940000	7.44580000	0.00000000
143	4271.22720000	25.60240000	0.00000000
144	4274.04020000	9.55720000	0.00000000

145	4274.16430000	19.62820000	0.00000000
146	4287.23820000	4.79500000	0.00000000
147	4624.11790000	0.33110000	0.00000000
148	4626.26930000	0.16050000	0.00000000
149	4633.27030000	0.18570000	0.00000000
150	4634.99030000	0.28080000	0.00000000

Optimisation Calculation Performed on X-ray Crystal Structure of (3*S*,5*S*)-**9c** (Figure S-3a):



Route : # opt freq b3lyp scrf=(solvent=thf) geom=connectivity def2tzvp empiricaldispersion=gd3bj int=ultrafine pop=(regular,mk)

SMILES : COC(=O)C2(c1ccc(Cl)cc1)CC3(CCN2C(=O)OC(C)(C)C)CC3(F)F

Formula : $C_{20}H_{24}ClF_2NO_4$

Charge : 0

Multiplicity : 1

Dipole : 2.7554 Debye

Energy : -1792.79065084 a.u.

Gibbs Energy : -1792.432752 a.u.

Number of imaginary frequencies : 0

Cartesian Coordinates (XYZ format)

52

Cl	-5.48230300	-2.28995500	-0.09668500
F	4.70059600	-0.86694800	-0.19402100
F	3.30555100	-1.94314200	-1.51342200
O	0.36233100	-0.13561400	-2.26482100
O	1.96272800	0.76259500	-0.98221300
O	0.42453200	2.54326400	2.04864400
O	-0.48832700	1.93918100	0.05284800
N	0.57187500	0.40346200	1.25475400
C	0.32034300	-0.53090600	0.15438100
C	1.14196100	-1.82938000	0.41608800
H	0.64319700	-2.37767500	1.21578600
H	1.08300500	-2.45313300	-0.47276700
C	2.57931100	-1.57499700	0.81251600
C	2.74553100	-0.52966200	1.91405000
H	3.29164300	-0.94289900	2.76319000
H	3.31375600	0.32060200	1.53733800
C	1.38047800	-0.04162800	2.38455400
H	0.85052400	-0.83000500	2.92467000
H	1.48477300	0.80348500	3.05634600

C	-1.15304800	-0.93625800	0.06256300
C	-1.60316600	-1.77768600	-0.95605700
H	-0.92664500	-2.10573200	-1.72911200
C	-2.92600300	-2.19440600	-1.01179600
H	-3.26324300	-2.83911800	-1.81091100
C	-3.81170600	-1.77392100	-0.03094400
C	-3.38803900	-0.95544300	1.00341100
H	-4.08169600	-0.63803200	1.76892700
C	-2.06102500	-0.54682700	1.04280500
H	-1.74179900	0.08622400	1.85672200
C	0.84258200	0.06443300	-1.17897500
C	2.58684200	1.31124400	-2.15595900
H	1.90768400	2.00254800	-2.65180300
H	2.86413300	0.51312100	-2.84140700
H	3.46878300	1.83199000	-1.79732600
C	3.53478100	-2.79106700	0.77268900
H	4.29668200	-2.84506600	1.53891400
H	3.12984900	-3.73714800	0.43861800
C	3.63524400	-1.70627600	-0.21479200
C	0.18905500	1.71447500	1.18732900
C	-1.07477400	3.24602600	-0.28222100
C	-1.73648600	2.97013500	-1.62589000
H	-0.99668300	2.65241800	-2.36041600
H	-2.22467900	3.87465500	-1.98897800
H	-2.48444400	2.18323700	-1.52765100
C	-2.11459900	3.62656500	0.76450500
H	-2.84840000	2.82676700	0.87342900
H	-2.63717700	4.52727100	0.43963500
H	-1.65196800	3.81905000	1.72902300
C	0.02744100	4.28835700	-0.42086300
H	0.50789700	4.48274800	0.53443300
H	-0.40284600	5.21838300	-0.79498100
H	0.77990600	3.95003900	-1.13437400

Frequencies

Mode	IR frequency	IR intensity	Raman intensity
1	21.93750000	0.14830000	0.00000000
2	35.65980000	0.16290000	0.00000000
3	40.11980000	0.67570000	0.00000000
4	48.19430000	0.57080000	0.00000000
5	51.70700000	2.45230000	0.00000000
6	65.53270000	1.23520000	0.00000000
7	82.02640000	2.83240000	0.00000000
8	89.11030000	1.51550000	0.00000000
9	93.18090000	2.61500000	0.00000000
10	106.71680000	0.90140000	0.00000000
11	119.60210000	0.69090000	0.00000000
12	134.20370000	0.95190000	0.00000000
13	141.58170000	0.74540000	0.00000000
14	149.16490000	0.51510000	0.00000000

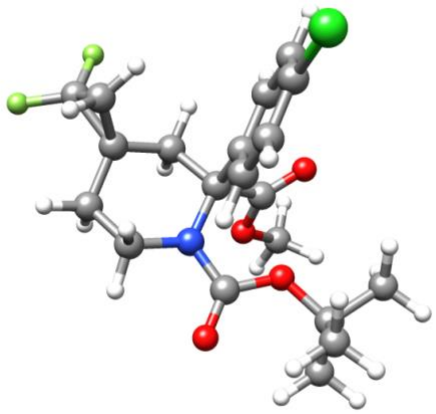
15	168.61400000	1.04150000	0.00000000
16	184.08900000	0.08920000	0.00000000
17	199.60250000	0.85770000	0.00000000
18	206.91990000	1.75290000	0.00000000
19	210.37280000	4.74050000	0.00000000
20	233.00130000	0.47280000	0.00000000
21	238.12750000	5.06020000	0.00000000
22	247.34250000	0.22220000	0.00000000
23	261.54390000	5.83050000	0.00000000
24	269.93400000	0.97690000	0.00000000
25	286.17500000	2.28120000	0.00000000
26	324.23620000	6.91930000	0.00000000
27	342.22590000	0.72840000	0.00000000
28	345.46560000	4.03530000	0.00000000
29	353.73770000	3.42370000	0.00000000
30	361.83800000	15.42260000	0.00000000
31	371.92920000	9.01830000	0.00000000
32	378.96010000	15.96920000	0.00000000
33	401.55640000	6.31240000	0.00000000
34	419.49040000	2.65540000	0.00000000
35	427.06540000	0.41090000	0.00000000
36	434.21790000	5.57200000	0.00000000
37	442.78680000	7.13160000	0.00000000
38	460.88060000	13.70540000	0.00000000
39	466.15060000	3.43880000	0.00000000
40	471.69750000	6.71850000	0.00000000
41	485.13120000	16.14380000	0.00000000
42	507.84010000	12.52670000	0.00000000
43	524.60830000	15.36540000	0.00000000
44	549.64950000	3.13810000	0.00000000
45	590.33640000	39.02640000	0.00000000
46	616.27290000	8.26450000	0.00000000
47	649.69560000	0.89280000	0.00000000
48	712.79470000	9.83890000	0.00000000
49	722.16140000	9.36640000	0.00000000
50	729.99770000	3.18530000	0.00000000
51	746.11540000	17.29960000	0.00000000
52	768.61560000	11.76050000	0.00000000
53	774.70110000	5.50420000	0.00000000
54	780.10070000	14.60930000	0.00000000
55	782.89950000	46.99420000	0.00000000
56	814.85480000	10.62770000	0.00000000
57	841.26530000	8.08540000	0.00000000

58	850.68600000	46.34200000	0.00000000
59	864.60040000	45.67990000	0.00000000
60	877.00400000	7.88050000	0.00000000
61	885.31680000	14.19880000	0.00000000
62	907.57710000	40.02330000	0.00000000
63	914.57110000	38.79580000	0.00000000
64	932.08820000	0.34720000	0.00000000
65	933.31340000	0.60570000	0.00000000
66	962.35500000	21.37210000	0.00000000
67	974.73120000	0.09930000	0.00000000
68	978.31620000	0.10350000	0.00000000
69	990.50540000	0.76930000	0.00000000
70	993.32460000	56.36780000	0.00000000
71	1012.70830000	41.17290000	0.00000000
72	1025.11830000	137.87610000	0.00000000
73	1029.70150000	152.28270000	0.00000000
74	1040.43080000	20.83320000	0.00000000
75	1046.13990000	10.47440000	0.00000000
76	1054.87740000	0.76570000	0.00000000
77	1060.35420000	14.73860000	0.00000000
78	1069.77050000	17.43240000	0.00000000
79	1078.34800000	13.48710000	0.00000000
80	1108.87630000	77.08430000	0.00000000
81	1141.12240000	56.48100000	0.00000000
82	1152.46290000	82.70820000	0.00000000
83	1161.22280000	39.00400000	0.00000000
84	1173.97860000	3.68290000	0.00000000
85	1179.62920000	381.92750000	0.00000000
86	1189.12110000	192.83850000	0.00000000
87	1200.31290000	138.02150000	0.00000000
88	1212.42350000	38.14140000	0.00000000
89	1214.37230000	4.90480000	0.00000000
90	1226.07370000	90.36760000	0.00000000
91	1236.74860000	127.56000000	0.00000000
92	1256.95590000	54.41460000	0.00000000
93	1271.54330000	24.35940000	0.00000000
94	1280.37030000	141.93900000	0.00000000
95	1291.20550000	207.10760000	0.00000000
96	1292.99720000	30.31040000	0.00000000
97	1315.13340000	39.74260000	0.00000000
98	1327.59710000	53.06340000	0.00000000
99	1339.80920000	1.80920000	0.00000000
100	1356.66260000	15.54890000	0.00000000

101	1370.66220000	55.99190000	0.00000000
102	1397.83430000	100.01490000	0.00000000
103	1399.06140000	26.17110000	0.00000000
104	1402.61570000	28.37510000	0.00000000
105	1413.60960000	72.55860000	0.00000000
106	1419.99340000	265.99520000	0.00000000
107	1427.53690000	41.61160000	0.00000000
108	1432.81910000	21.60920000	0.00000000
109	1466.96800000	0.16390000	0.00000000
110	1472.29510000	20.49770000	0.00000000
111	1480.73950000	12.28420000	0.00000000
112	1483.08190000	21.89240000	0.00000000
113	1484.49810000	5.60930000	0.00000000
114	1484.85060000	3.52650000	0.00000000
115	1485.78680000	28.71300000	0.00000000
116	1487.98510000	6.40330000	0.00000000
117	1490.46110000	20.26620000	0.00000000
118	1493.01740000	95.30750000	0.00000000
119	1498.08690000	1.52580000	0.00000000
120	1512.23690000	22.67080000	0.00000000
121	1518.76460000	26.44600000	0.00000000
122	1528.90230000	103.14370000	0.00000000
123	1615.06210000	9.05250000	0.00000000
124	1636.42380000	11.36930000	0.00000000
125	1716.36450000	810.07100000	0.00000000
126	1776.14330000	288.33590000	0.00000000
127	3035.74950000	41.78200000	0.00000000
128	3044.58170000	12.23410000	0.00000000
129	3045.48940000	35.00880000	0.00000000
130	3052.76760000	20.03020000	0.00000000
131	3057.83370000	35.92690000	0.00000000
132	3062.98750000	41.40120000	0.00000000
133	3070.24360000	20.89690000	0.00000000
134	3100.52450000	28.60610000	0.00000000
135	3105.48080000	10.09120000	0.00000000
136	3107.14290000	25.60280000	0.00000000
137	3116.85300000	44.49600000	0.00000000
138	3120.87930000	55.31630000	0.00000000
139	3126.02340000	5.50820000	0.00000000
140	3134.69040000	5.18300000	0.00000000
141	3137.70420000	21.63880000	0.00000000
142	3143.08340000	1.01250000	0.00000000
143	3146.22630000	24.19380000	0.00000000

144	3154.76850000	4.88990000	0.00000000
145	3170.61820000	12.62670000	0.00000000
146	3200.63320000	2.42290000	0.00000000
147	3202.32590000	2.85180000	0.00000000
148	3218.05810000	5.48460000	0.00000000
149	3226.86590000	1.47500000	0.00000000
150	3229.31630000	2.42310000	0.00000000

Optimisation Calculation Performed on Chair Conformation of (3*S*,5*S*)-**9c** with *p*-Chlorophenyl Group Axial (Figure S-3b):



Route : # opt freq b3lyp scrf=(solvent=thf) geom=connectivity def2tzvp empiricaldispersion=gd3bj int=ultrafine pop=(regular,mk)

SMILES : COC(=O)C2(c1ccc(Cl)cc1)CC3(CCN2C(=O)OC(C)(C)C)CC3(F)F

Formula : $C_{20}H_{24}ClF_2NO_4$

Charge : 0

Multiplicity : 1

Dipole : 2.6912 Debye

Energy : -1792.79018093 a.u.

Gibbs Energy : -1792.432280 a.u.

Number of imaginary frequencies : 0

Cartesian Coordinates (XYZ format)

52

C	1.49404800	-1.39245500	0.77584700
C	2.43809300	-1.52447200	-0.38723400
C	1.79284800	-2.29310700	-1.51102200
C	0.54837000	-1.55388900	-1.96484200
C	0.17371400	-0.65638400	0.39123400
H	2.46407000	-2.40419900	-2.36195200
H	1.24003500	-2.39542900	1.11956100
H	1.95190600	-0.86799200	1.60965200
H	0.85012300	-0.63652100	-2.48194800
H	-0.01880500	-2.15257300	-2.66926600
H	1.53292400	-3.29468800	-1.15938500
N	-0.36178700	-1.21912300	-0.85817200
C	3.40148100	-0.36174200	-0.73439300
H	3.38112800	0.51445100	-0.10226200
H	3.60654700	-0.18429100	-1.78140600
C	3.89023500	-1.61943000	-0.14588400
F	4.36879700	-1.62704600	1.12629400
F	4.64450000	-2.46972800	-0.88946600

C	-1.67291100	-1.01204000	-1.22241300
O	-2.13523500	-1.35621100	-2.29463700
O	-2.35073100	-0.37970400	-0.25720000
C	-3.76873200	0.00031100	-0.39821800
C	-3.92743500	0.96396600	-1.56792500
C	-4.62728100	-1.24895600	-0.54406000
C	-4.05221300	0.70842900	0.91956300
H	-3.24847800	1.80997400	-1.45284300
H	-3.72787300	0.47330200	-2.51663200
H	-4.94899200	1.34615000	-1.57807800
H	-4.43934200	-1.93652100	0.28153700
H	-5.68008900	-0.96455500	-0.51737400
H	-4.42568700	-1.75869100	-1.48252300
H	-5.08525000	1.05606200	0.93313700
H	-3.89958900	0.03599900	1.76291900
H	-3.39153100	1.56655000	1.04137600
C	-0.76750000	-0.99006600	1.57751400
O	-0.99390700	-0.25095900	2.50005800
O	-1.18760300	-2.25619800	1.51679600
C	0.41647600	0.85311500	0.29322400
C	0.09308600	1.56802700	-0.85554000
C	0.99537700	1.55015600	1.35538700
C	0.33970400	2.93191600	-0.95640100
H	-0.35922800	1.07557800	-1.70192900
C	1.24807400	2.91123500	1.27536500
H	1.24601700	1.03821400	2.27183000
C	0.91864000	3.59391200	0.11311100
H	0.08295700	3.46883100	-1.85833200
H	1.69374200	3.43575500	2.10844800
Cl	1.23796900	5.30909900	-0.00069200
C	-2.01283200	-2.70437500	2.60570300
H	-2.92359500	-2.11023800	2.65622100
H	-2.24726200	-3.74077800	2.38429200
H	-1.47401200	-2.62456500	3.54824200

Frequencies

Mode	IR frequency	IR intensity	Raman intensity
1	24.04800000	0.06870000	0.00000000
2	30.35410000	0.23900000	0.00000000
3	34.41930000	0.09110000	0.00000000
4	55.25640000	1.67430000	0.00000000
5	60.94370000	1.38630000	0.00000000
6	76.99310000	1.59520000	0.00000000
7	85.60280000	2.94540000	0.00000000
8	86.78390000	1.22510000	0.00000000
9	94.42690000	1.79330000	0.00000000
10	103.19600000	1.71520000	0.00000000
11	128.16760000	0.73440000	0.00000000
12	131.70710000	2.70970000	0.00000000
13	140.98800000	0.50190000	0.00000000

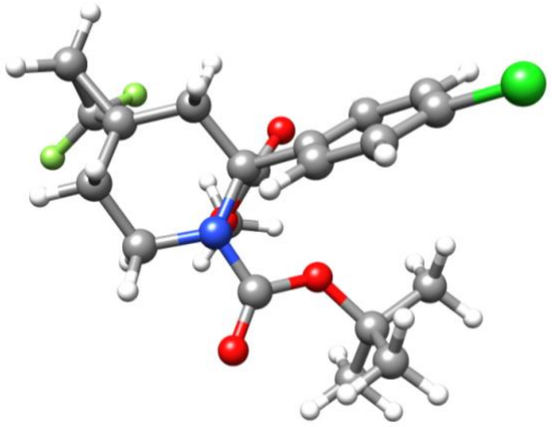
14	155.14650000	0.67510000	0.00000000
15	165.35390000	1.97120000	0.00000000
16	174.57940000	0.57790000	0.00000000
17	192.49990000	4.15430000	0.00000000
18	202.70350000	0.30420000	0.00000000
19	214.04090000	1.45920000	0.00000000
20	224.39030000	5.78760000	0.00000000
21	238.57930000	1.37180000	0.00000000
22	245.24090000	0.38980000	0.00000000
23	258.50440000	1.06630000	0.00000000
24	269.37840000	4.40560000	0.00000000
25	272.85880000	2.40850000	0.00000000
26	305.41890000	4.39440000	0.00000000
27	327.77470000	7.97410000	0.00000000
28	344.42380000	0.51490000	0.00000000
29	349.36270000	6.15460000	0.00000000
30	356.04500000	2.63940000	0.00000000
31	369.66470000	15.67360000	0.00000000
32	383.09180000	5.82090000	0.00000000
33	407.87430000	8.32740000	0.00000000
34	417.32920000	11.27110000	0.00000000
35	426.01940000	5.07530000	0.00000000
36	431.43610000	8.00730000	0.00000000
37	442.22570000	1.61840000	0.00000000
38	448.11550000	1.80720000	0.00000000
39	462.29300000	6.95820000	0.00000000
40	473.74720000	4.96740000	0.00000000
41	482.96980000	25.06140000	0.00000000
42	489.84660000	1.69860000	0.00000000
43	518.32670000	18.70920000	0.00000000
44	568.39670000	19.39500000	0.00000000
45	580.61150000	32.54280000	0.00000000
46	648.56890000	6.93690000	0.00000000
47	655.28020000	8.20340000	0.00000000
48	705.47320000	25.76990000	0.00000000
49	723.04150000	10.77440000	0.00000000
50	734.87410000	1.97630000	0.00000000
51	756.20990000	31.44080000	0.00000000
52	770.40330000	3.33310000	0.00000000
53	784.16280000	29.98780000	0.00000000
54	785.87780000	21.53770000	0.00000000
55	800.75000000	12.61430000	0.00000000
56	801.99520000	19.99310000	0.00000000

57	841.24350000	3.91790000	0.00000000
58	847.16050000	26.05870000	0.00000000
59	856.83630000	49.35990000	0.00000000
60	859.29810000	40.96960000	0.00000000
61	890.83470000	7.21300000	0.00000000
62	911.14240000	48.14460000	0.00000000
63	915.03320000	9.18230000	0.00000000
64	931.54190000	0.07570000	0.00000000
65	933.02950000	0.65480000	0.00000000
66	959.48650000	40.25770000	0.00000000
67	974.95730000	0.18130000	0.00000000
68	979.18860000	1.58480000	0.00000000
69	988.26310000	0.03700000	0.00000000
70	1000.74920000	22.13360000	0.00000000
71	1025.86770000	78.11940000	0.00000000
72	1029.86520000	118.35400000	0.00000000
73	1036.83330000	93.41290000	0.00000000
74	1042.96200000	32.67970000	0.00000000
75	1046.98410000	24.92820000	0.00000000
76	1053.99280000	29.42150000	0.00000000
77	1054.36090000	1.10850000	0.00000000
78	1063.86440000	3.98640000	0.00000000
79	1098.53290000	62.67130000	0.00000000
80	1110.61820000	117.75970000	0.00000000
81	1143.83040000	57.43870000	0.00000000
82	1150.67490000	190.10490000	0.00000000
83	1161.48540000	36.13920000	0.00000000
84	1170.90470000	23.00920000	0.00000000
85	1173.07390000	3.15100000	0.00000000
86	1182.11760000	148.06360000	0.00000000
87	1190.10890000	394.22910000	0.00000000
88	1202.53540000	68.84760000	0.00000000
89	1210.48280000	31.17510000	0.00000000
90	1218.04150000	4.19950000	0.00000000
91	1250.08560000	100.33120000	0.00000000
92	1252.82850000	522.38280000	0.00000000
93	1271.59240000	30.22360000	0.00000000
94	1282.75010000	31.97710000	0.00000000
95	1296.19880000	63.81300000	0.00000000
96	1305.57830000	74.52790000	0.00000000
97	1314.51880000	48.36130000	0.00000000
98	1324.76300000	25.99690000	0.00000000
99	1341.45900000	4.79790000	0.00000000

100	1362.36680000	192.04800000	0.00000000
101	1381.96370000	26.62720000	0.00000000
102	1386.43960000	275.62700000	0.00000000
103	1398.80580000	25.15360000	0.00000000
104	1403.42740000	45.09970000	0.00000000
105	1414.21460000	48.36290000	0.00000000
106	1425.46080000	6.54780000	0.00000000
107	1427.02180000	18.31760000	0.00000000
108	1434.53740000	23.48970000	0.00000000
109	1467.11410000	0.07330000	0.00000000
110	1472.00490000	14.85710000	0.00000000
111	1480.21260000	11.25480000	0.00000000
112	1482.62100000	7.26850000	0.00000000
113	1483.93750000	2.31400000	0.00000000
114	1485.97100000	3.34740000	0.00000000
115	1488.02420000	11.99510000	0.00000000
116	1489.06210000	22.35880000	0.00000000
117	1494.81580000	155.45500000	0.00000000
118	1498.56310000	2.77290000	0.00000000
119	1501.11510000	21.17090000	0.00000000
120	1508.51850000	11.41000000	0.00000000
121	1517.78770000	21.69350000	0.00000000
122	1531.64690000	86.73830000	0.00000000
123	1616.39890000	11.04000000	0.00000000
124	1637.90120000	18.28590000	0.00000000
125	1714.81560000	739.86230000	0.00000000
126	1774.82920000	283.47410000	0.00000000
127	3005.82300000	45.07840000	0.00000000
128	3044.26780000	37.17060000	0.00000000
129	3046.15180000	37.12100000	0.00000000
130	3046.76620000	10.28250000	0.00000000
131	3054.14940000	20.79330000	0.00000000
132	3060.59730000	46.25390000	0.00000000
133	3072.93150000	22.23560000	0.00000000
134	3103.97050000	23.60430000	0.00000000
135	3106.11120000	12.26380000	0.00000000
136	3107.64340000	26.79150000	0.00000000
137	3120.07460000	47.50880000	0.00000000
138	3123.20910000	49.89570000	0.00000000
139	3133.09920000	23.73060000	0.00000000
140	3137.44470000	10.69710000	0.00000000
141	3143.53140000	4.14730000	0.00000000
142	3144.70830000	2.53270000	0.00000000

143	3147.70170000	7.86560000	0.00000000
144	3147.96900000	23.21840000	0.00000000
145	3167.21400000	14.41630000	0.00000000
146	3202.00120000	4.28190000	0.00000000
147	3203.42100000	1.21390000	0.00000000
148	3219.07580000	5.71210000	0.00000000
149	3225.53950000	5.46180000	0.00000000
150	3236.42000000	0.72350000	0.00000000

Optimisation Calculation Performed on Chair Conformation of (3*S*,5*S*)-**9c** with *p*-Chlorophenyl Group Equatorial (Figure S-3c):



Route : # opt freq b3lyp scrf=(solvent=thf) geom=connectivity def2tzvp empiricaldispersion=gd3bj int=ultrafine pop=(regular,mk)

SMILES : COC(=O)C2(c1ccc(Cl)cc1)CC3(CCN2C(=O)OC(C)(C)C)CC3(F)F

Formula : $C_{20}H_{24}ClF_2NO_4$

Charge : 0

Multiplicity : 1

Dipole : 1.8449 Debye

Energy : -1792.78846948 a.u.

Gibbs Energy : -1792.431337 a.u.

Number of imaginary frequencies : 0

Cartesian Coordinates (XYZ format)

52

C	-1.96596300	0.64864400	-1.84641800
C	-2.67412900	-0.66995000	-2.08934200
C	-2.80195500	-1.42845800	-0.79457300
C	-1.44343100	-1.71404800	-0.21516400
C	-0.56842500	-0.44247700	0.01538100
H	-3.64693400	-0.46071400	-2.53299800
H	-2.63184300	1.31903300	-1.29538900
H	-1.72589600	1.12665100	-2.79078800
H	-1.49563900	-2.24363900	0.73379000
H	-0.91505600	-2.35824000	-0.91827200
H	-2.11243600	-1.28534700	-2.79712000
C	0.87805600	-0.96730800	0.09146300
C	1.54262100	-1.20967800	-1.11198500
C	1.53165000	-1.28119600	1.27804000
C	2.83375100	-1.71227700	-1.13740900
H	1.05495300	-0.97964700	-2.04857400
C	2.82685000	-1.78854200	1.26932600
H	1.04300600	-1.12109000	2.22429700

C	3.47211700	-1.99349200	0.06219500
H	3.33906700	-1.87919500	-2.07806600
H	3.32752200	-2.01458700	2.20015600
C	-1.07431800	0.18654800	1.33514000
O	-0.94076600	-0.31057200	2.42638400
O	-1.76396000	1.30640500	1.11951900
C	0.07063000	1.65370300	-1.11418600
O	-0.04429200	2.52375300	-1.95739900
O	0.93277000	1.67723900	-0.09421600
C	2.00338200	2.68242700	0.01699100
C	2.90216200	2.61861300	-1.21162400
C	1.39374600	4.06189700	0.23188800
C	2.75795000	2.22319600	1.25766500
H	3.26153700	1.59959100	-1.36076200
H	2.37710100	2.94592100	-2.10531500
H	3.76569300	3.26669900	-1.05619700
H	0.71291200	4.04314900	1.08419100
H	2.18946300	4.77687700	0.44613900
H	0.84974300	4.39382500	-0.64824600
H	3.57785200	2.91119200	1.46478500
H	2.09443700	2.20183600	2.12273100
H	3.16631100	1.22413900	1.11028600
C	-2.34862900	1.92963800	2.27834100
H	-3.03310600	1.23940000	2.76696900
H	-1.56783600	2.22972300	2.97479600
H	-2.87970400	2.79752300	1.90123500
C	-3.91298700	-2.48693500	-0.63447300
H	-3.68382400	-3.36961700	-0.05246700
H	-4.58480000	-2.62974000	-1.47026300
C	-3.97230000	-1.20046700	0.08070000
F	-3.82485900	-1.17723900	1.43144000
F	-4.90700300	-0.27596300	-0.26058300
Cl	5.10814900	-2.61446700	0.04568200
N	-0.70128400	0.50819600	-1.10217900

Frequencies

Mode	IR frequency	IR intensity	Raman intensity
1	22.16750000	0.63060000	0.00000000
2	29.62470000	1.44240000	0.00000000
3	37.60290000	0.26200000	0.00000000
4	40.64840000	2.86990000	0.00000000
5	49.42170000	1.56060000	0.00000000
6	54.24010000	1.61210000	0.00000000
7	67.74400000	0.18170000	0.00000000
8	82.51690000	2.67690000	0.00000000
9	104.10070000	2.56860000	0.00000000
10	117.01490000	0.72760000	0.00000000
11	120.37250000	0.42750000	0.00000000
12	138.43450000	0.98080000	0.00000000
13	143.83310000	0.20160000	0.00000000

14	148.80730000	1.88200000	0.00000000
15	167.58260000	1.57570000	0.00000000
16	172.23040000	1.57240000	0.00000000
17	196.02340000	6.29160000	0.00000000
18	205.39530000	2.92990000	0.00000000
19	209.94150000	0.06560000	0.00000000
20	227.29180000	0.35390000	0.00000000
21	245.26020000	0.24250000	0.00000000
22	246.48720000	1.72420000	0.00000000
23	270.15400000	2.39170000	0.00000000
24	279.33210000	0.33280000	0.00000000
25	289.34290000	1.81970000	0.00000000
26	311.85040000	2.50340000	0.00000000
27	338.26390000	19.99470000	0.00000000
28	348.54700000	9.33170000	0.00000000
29	354.54990000	2.49640000	0.00000000
30	360.76450000	5.79470000	0.00000000
31	365.68690000	20.31290000	0.00000000
32	384.92890000	21.06300000	0.00000000
33	388.77070000	1.84020000	0.00000000
34	408.21280000	1.23510000	0.00000000
35	420.49660000	0.16670000	0.00000000
36	433.32600000	4.02440000	0.00000000
37	442.72710000	8.36450000	0.00000000
38	456.40700000	3.04070000	0.00000000
39	467.47390000	6.48140000	0.00000000
40	474.20410000	3.68650000	0.00000000
41	488.68180000	22.82370000	0.00000000
42	516.73340000	5.63600000	0.00000000
43	529.75890000	7.58300000	0.00000000
44	548.36110000	2.16500000	0.00000000
45	569.05120000	5.52230000	0.00000000
46	609.95920000	41.04570000	0.00000000
47	650.78960000	0.65330000	0.00000000
48	710.97560000	9.17700000	0.00000000
49	720.37760000	12.70610000	0.00000000
50	737.17270000	9.61270000	0.00000000
51	749.04740000	13.93990000	0.00000000
52	765.66490000	12.36740000	0.00000000
53	775.37680000	18.67020000	0.00000000
54	791.92720000	44.07170000	0.00000000
55	811.01690000	22.57540000	0.00000000
56	819.25910000	10.77950000	0.00000000

57	846.57520000	2.83530000	0.00000000
58	853.10630000	11.15020000	0.00000000
59	856.97030000	98.53710000	0.00000000
60	873.32760000	17.40000000	0.00000000
61	886.13020000	10.80390000	0.00000000
62	910.77660000	49.29250000	0.00000000
63	916.42780000	15.31540000	0.00000000
64	931.98760000	0.46770000	0.00000000
65	932.26800000	0.02570000	0.00000000
66	966.00400000	5.69670000	0.00000000
67	974.80730000	0.14060000	0.00000000
68	984.73370000	0.30320000	0.00000000
69	996.56050000	0.36420000	0.00000000
70	1009.48680000	48.49370000	0.00000000
71	1018.11850000	72.46260000	0.00000000
72	1023.20230000	60.96880000	0.00000000
73	1036.24290000	179.57140000	0.00000000
74	1039.36290000	31.65090000	0.00000000
75	1048.88460000	5.53870000	0.00000000
76	1054.40080000	2.07640000	0.00000000
77	1058.28210000	14.67230000	0.00000000
78	1067.25840000	10.95810000	0.00000000
79	1080.02000000	27.09940000	0.00000000
80	1109.48610000	62.56310000	0.00000000
81	1140.90530000	68.04660000	0.00000000
82	1147.46960000	58.46790000	0.00000000
83	1165.07480000	96.73390000	0.00000000
84	1172.88440000	0.65740000	0.00000000
85	1173.92970000	18.83830000	0.00000000
86	1183.31900000	507.85630000	0.00000000
87	1193.32680000	132.13240000	0.00000000
88	1203.26910000	78.30150000	0.00000000
89	1209.81130000	26.42700000	0.00000000
90	1218.61560000	63.40970000	0.00000000
91	1236.34240000	112.82320000	0.00000000
92	1260.84620000	121.85620000	0.00000000
93	1271.60560000	25.64660000	0.00000000
94	1281.48500000	54.42030000	0.00000000
95	1293.76070000	81.25360000	0.00000000
96	1306.31120000	161.93930000	0.00000000
97	1315.11220000	39.17990000	0.00000000
98	1324.16240000	45.45610000	0.00000000
99	1336.94120000	17.29160000	0.00000000

100	1352.22740000	219.85070000	0.00000000
101	1373.53700000	266.36320000	0.00000000
102	1383.01860000	12.26930000	0.00000000
103	1398.04740000	24.77550000	0.00000000
104	1402.21970000	37.85100000	0.00000000
105	1414.86050000	15.76600000	0.00000000
106	1425.04690000	22.41520000	0.00000000
107	1427.30820000	12.20720000	0.00000000
108	1434.37380000	23.55820000	0.00000000
109	1467.62200000	0.23930000	0.00000000
110	1470.87900000	15.05350000	0.00000000
111	1478.35300000	6.27730000	0.00000000
112	1480.39500000	12.88360000	0.00000000
113	1485.03960000	3.46150000	0.00000000
114	1485.78840000	1.16650000	0.00000000
115	1487.03090000	5.47260000	0.00000000
116	1488.27860000	18.08780000	0.00000000
117	1488.56710000	22.75410000	0.00000000
118	1497.66270000	2.33990000	0.00000000
119	1503.03890000	130.28120000	0.00000000
120	1512.95570000	9.19620000	0.00000000
121	1517.06440000	22.67490000	0.00000000
122	1525.76910000	134.25210000	0.00000000
123	1613.67040000	6.37270000	0.00000000
124	1634.88300000	1.42880000	0.00000000
125	1715.47990000	738.24860000	0.00000000
126	1765.03600000	256.73440000	0.00000000
127	3027.40130000	36.77370000	0.00000000
128	3042.44080000	44.34670000	0.00000000
129	3043.71550000	13.04450000	0.00000000
130	3044.53810000	34.15040000	0.00000000
131	3051.91090000	21.99840000	0.00000000
132	3064.18850000	36.96270000	0.00000000
133	3068.06410000	20.62260000	0.00000000
134	3102.54640000	27.65470000	0.00000000
135	3103.76760000	14.00380000	0.00000000
136	3107.01270000	17.29050000	0.00000000
137	3115.14750000	57.84340000	0.00000000
138	3124.17840000	4.80630000	0.00000000
139	3124.38920000	35.27290000	0.00000000
140	3136.78970000	7.07720000	0.00000000
141	3136.98690000	10.40500000	0.00000000
142	3140.08760000	18.61170000	0.00000000

143	3141.80440000	5.55920000	0.00000000
144	3146.81920000	19.64880000	0.00000000
145	3171.94620000	12.32600000	0.00000000
146	3194.53620000	2.14850000	0.00000000
147	3201.45700000	3.43310000	0.00000000
148	3208.65440000	3.12650000	0.00000000
149	3228.99130000	0.96610000	0.00000000
150	3245.21330000	9.30730000	0.00000000