

Diastereodivergent Access to *Syn* and *Anti* 3,4-Substituted β -Fluoropyrrolidines: Enhancing or Reversing Substrate Preference

Kasper Fjelbye,^{a,b} Mauro Marigo,^a Rasmus Prætorius Clausen,^b Karsten Juhl^{a,*}

^a Discovery Chemistry and DMPK, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Danmark

^b Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark

Supporting Information

Contents

General Methods.....	S2
General Procedure for the Diastereoselective Fluorination of Aldehydes.....	S2
General Procedure for the Reduction of Purified Aldehydes to the Corresponding Alcohols	S2
Fluorination of Aldehydes Using Pyrrolidine	S2
Kinetic Resolution using Organocatalysis	S6
Synthesis of Chiral Pyrrolidinyl Carbaldehydes	S7
Synthesis of Substrate (1a).....	S7
Synthesis of Substrate (1b)	S8
Synthesis of Substrate (1c).....	S9
Synthesis of Substrate (1d)	S9
Synthesis of Substrate (1e).....	S10
Synthesis of Substrate (1f).....	S11
Synthesis of Substrate (1g)	S12
Relative Configuration of Products.....	S14
Screening of Additional Catalysts.....	S16
Chiral SFC Data.....	S18
NMR Spectre	S20

General Methods

LCMS data were acquired using a Waters Acquity UPLC-MS consisting of a Waters Acquity system including column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nm), ELS detector, and TQ-MS equipped with APPI-source operating in positive ion mode. LC-conditions: The column was Acquity UPLC BEH C18 1.7 μ m; 2.1 \times 50 mm operating at 60 $^{\circ}$ C with 1.2 mL/min binary gradient consisting of H₂O+0.05% trifluoroacetic acid (TFA) (A) and MeCN+5% H₂O+0.05% TFA (B). Gradient: 0.00 min: 10% B; 1.00 min: 100% B; 1.01 min: 10% B; 1.15 min: 10% B. The retention times provided in the experimental section shall be compared to the total run time of 1.15 min. The LCMS data provided for determination of crude diastereomeric ratios are acquired on an Acquity UPLC BEH C18 1.7 μ m; 2.1x150mm column with a total run time of 3.60 min, and the extracted-ion chromatograms (XIC) were used for analysis of the crude diastereomeric ratios. HRMS data were acquired with a Bruker Daltonic MicroTOF with internal calibration using ESI in the positive mode. NMR data were collected with a Bruker 600-Avance-III spectrometer equipped with a 5 mm TCI cryoprobe operating at 600 and 151 MHz for ¹H and ¹³C, respectively. ¹⁹F NMR spectra were recorded with a Bruker 500-Avance spectrometer equipped with a 5 mm QNP probe operating at 470.6 Hz, using CFCl₃ as reference. The solvents used for NMR were CDCl₃, with reference signals for CHCl₃ (δ = 7.26 ppm, ¹H) and (δ = 77.16 ppm, ¹³C), and DMSO-*d*₆ with the reference signals for residual DMSO (δ = 2.50 ppm, ¹H) and (δ = 39.51 ppm, ¹³C) using TMS as internal reference. The chemical shifts are provided in ppm and broad proton signals are labeled (br). *N*-Fluorobenzenesulfonimide (NFSI), (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidine (*S*)-**7**, (*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidine (*R*)-**7**, (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one 2,2-dichloroacetate (*S*)-**8**, (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one 2,2-dichloroacetate (*R*)-**8** and NaBH₄ were purchased from Sigma-Aldrich. Due to hydrate formation during analysis, some of the fluorinated aldehydes were additionally characterized after reduction to the corresponding alcohols using a general procedure described below.

General Procedure for the Diastereoselective Fluorination of Aldehydes

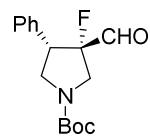
To a solution of **1a-g** in a specified solvent (0.5M) was added catalyst (10-20 mol%) and the mixture was stirred for 5 min at rt after which *N*-fluorobenzenesulfonimide (NFSI) (1.2 equiv) was added and the resulting mixture was stirred at 40 $^{\circ}$ C for 14-20 h. Unless otherwise noted, the reaction mixture was diluted with MTBE and loaded directly through a filter onto SiO₂ for flash chromatographic purification to yield **2a-g** or **3a-g**, respectively.

General Procedure for the Reduction of Purified Aldehydes to the Corresponding Alcohols

To a solution of the purified aldehyde in MeOH (0.02-0.1M) was added NaBH₄ (3 equiv) and the reaction mixture was stirred for 30 min. Subsequently, excess hydride donor was quenched by the addition of H₂O followed by EtOAc and the phases separated. The aqueous phase was then extracted with EtOAc and the combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to provide the corresponding alcohol.

Fluorination of Aldehydes Using Pyrrolidine

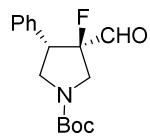
To a solution of each of the respective aldehydes (0.1 mmol) in MTBE (0.5M) was added pyrrolidine (0.020 mmol, 20 mol%) and the mixture was stirred for 5 min at rt after which *N*-fluorobenzenesulfonimide (0.12 mmol, 1.2 equiv) was added and the resulting mixture was stirred at 40 $^{\circ}$ C for 14-20 h. Subsequently, the reaction mixture was diluted with MTBE and loaded directly through a filter on SiO₂ for flash chromatographic purification to yield the fluorinated product.



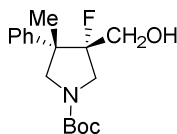
tert-Butyl (3*S*,4*S*)-3-fluoro-3-formyl-4-phenylpyrrolidine-1-carboxylate (2a**)** In accordance with the general procedure, **1a** (28 mg, 0.10 mmol) was reacted with (*R*)-**7** (6 mg, 0.01 mmol, 10 mol%) and NFSI (39 mg, 0.12 mmol, 97%) in MTBE for 14 h to provide **2a** (29 mg, 0.10 mmol, 100% yield, 98:2 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **11a** using NaBH₄ in MeOH on an analytical scale (*t*_R major = 2.54 min; *t*_R minor = 2.50 min, 96:4 dr). ¹H NMR (600 MHz, CDCl₃) δ 9.70 – 9.65 (m, 1H), 7.36 – 7.31 (m, 3H), 7.29 – 7.26 (m, 2H), 4.05 – 3.66 (m, 5H), 1.48 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 199.4 (d, *J* = 43.7 Hz), 154.0 (d, *J* = 24.5 Hz), 132.4, 129.7, 129.2, 129.1, 128.7, 128.7, 128.5, 128.4, 127.9, 80.4, 54.6 (d, *J* = 24.1 Hz), 54.4 (d, *J* = 24.0 Hz), 51.7 (d, *J* = 19.4 Hz), 51.1 (d, *J* = 19.6 Hz), 49.9, 49.3, 28.4. [α]_D²² = -35.1 $^{\circ}$ (*c* = 0.45, CHCl₃).

The product **2a** was additionally characterized after reduction in accordance with the general procedure to provide **11a**. ¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.28 (m, 5H), 3.99 – 3.69 (m, 5H), 3.64 – 3.57 (m, 1H), 3.43 – 3.27 (m, 1H), 1.50 – 1.47 (m, 9H).

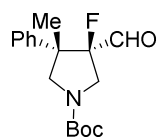
^{13}C NMR (151 MHz, CDCl_3) δ 154.3, 134.1, 134.1, 129.4, 128.5, 127.8, 79.9, 63.70 – 62.88 (m), 54.68 – 53.82 (m), 50.5, 49.8, 49.28 – 48.52 (m). 28.5 (conformers, the carbon bound to fluorine was not detected). ^{19}F NMR (471 MHz, CDCl_3) δ -63.23, -63.31, -176.93, -177.30 (conformers). HRMS-ESI: m/z for $\text{C}_{16}\text{H}_{22}\text{FNO}_3\text{Na}$ [MNa^+] calcd. 318.1476; found 318.1476.



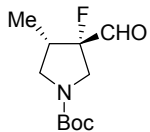
tert-Butyl (3R,4S)-3-fluoro-3-formyl-4-phenylpyrrolidine-1-carboxylate (3a) In accordance with the general procedure, **1a** (28 mg, 0.10 mmol) was reacted with (*S*)-**8** (7 mg, 0.020 mmol, 20 mol%) and NFSI (38 mg, 0.12 mmol) in 10% *i*-PrOH in THF for 16 h to provide **3a** (18.7 mg, 0.064 mmol, 64% yield, 98:2 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol using NaBH_4 in MeOH on an analytical scale (t_R major = 2.47 min; t_R minor = 2.52 min, 93:7 dr) ^1H NMR (600 MHz, CDCl_3) δ 9.41 (d, J = 4.2 Hz, 1H), 7.36 – 7.27 (m, 3H), 7.18 – 7.15 (m, 2H), 4.07 – 3.63 (m, 5H), 1.51 (s, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 197.3 – 196.6 (m), 154.2 – 154.0 (m), 134.4, 129.2, 128.3, 127.8, 80.5, 53.4, 52.4 – 51.2 (m), 51.3 – 49.5 (m), 28.4. ^{19}F NMR (471 MHz, CDCl_3) δ -159.49, -160.68 (two conformers), -167.56. HRMS-ESI: m/z for $\text{C}_{12}\text{H}_{13}\text{FNO}_3$ [$\text{MH}^+ - t\text{Bu}$] calcd. 238.0874; found 238.0874. $[\alpha]_D^{22}$ = -24.8° (c = 0.25, CHCl_3).



tert-Butyl (3S,4S)-3-fluoro-3-(hydroxymethyl)-4-methyl-4-phenylpyrrolidine-1-carboxylate (11b) In accordance with the general procedure, **1b** (73 mg, 0.25 mmol) was reacted with (*R*)-**7** (15 mg, 0.025 mmol, 10 mol%) and NFSI (95 mg, 0.3 mmol) in MTBE for 14 h to provide **2b** as a yellow oil. The semi-pure **2b** was diluted in MeOH (3 mL) after which NaBH_4 (29 mg, 0.76 mmol, 3 equiv) was added and the mixture was stirred for 30 min. EtOAc (5 mL) was added followed by H_2O (2 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 5 mL), the organic phases combined, dried over MgSO_4 , filtered and concentrated *in vacuo* to provide a yellow oil that was purified using silica gel chromatography to provide **11b** (58 mg, 0.187 mmol, 74% yield, 98:2 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) of the crude reaction mixture after reduction (t_R major = 2.56 min; t_R minor = 2.64 min, 96:4 dr). ^1H NMR (600 MHz, CDCl_3) δ 7.46 – 7.41 (m, 2H), 7.37 – 7.33 (m, 2H), 7.30 – 7.27 (m, 1H), 4.18 – 4.11 (m, 1H), 3.91 – 3.72 (m, 4H), 3.62 – 3.49 (m, 1H), 2.06 – 1.97 (m, 1H), 1.50 – 1.47 (m, 9H), 1.46 – 1.44 (m, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 155.0 (d, J = 22.8 Hz), 138.8 (d, J = 4.4 Hz), 128.4, 128.3, 128.1, 128.0, 127.4, 105.9 – 103.9 (m), 80.2, 63.0 – 62.6 (m), 57.5, 56.6, 54.3 – 53.7 (m), 28.7, 23.0, 23.0. ^{19}F NMR (471 MHz, CDCl_3) δ -162.08, -162.25 (conformers). HRMS-ESI: m/z for $\text{C}_{13}\text{H}_{17}\text{FNO}_3$ [$\text{MH}^+ - t\text{Bu}$] calcd. 254.1187; found 254.1183. $[\alpha]_D^{22}$ = -186° (c = 0.022, CHCl_3).

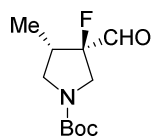


tert-Butyl (3R,4S)-3-fluoro-3-formyl-4-methyl-4-phenylpyrrolidine-1-carboxylate (3b) In accordance with the general procedure, **1b** (72 mg, 0.25 mmol) was reacted with (*S*)-**8** (17 mg, 0.05 mmol, 20 mol%) and NFSI (94 mg, 0.3 mmol) in 10% *i*-PrOH in THF for 16 h to provide **3b** (45 mg, 0.145 mmol, 59% yield, >99:1 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) from the crude reaction mixture after reduction to the alcohol **13b** using NaBH_4 in MeOH on an analytical scale (t_R major = 2.64 min; t_R minor = 2.56 min, 93:7 dr). ^1H NMR (600 MHz, CDCl_3) δ 9.50 (d, J = 5.1 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.29 – 7.25 (m, 3H), 4.01 – 3.97 (m, 1H), 3.92 – 3.62 (m, 4H), 1.57 (br, 3H), 1.53 – 1.49 (m, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 198.7 – 198.0 (m), 154.2 (d, J = 15.6 Hz), 140.1 (d, J = 26.2 Hz), 129.0, 127.8, 126.3, 126.2, 104.1 – 102.0 (m), 80.5, 80.5, 55.6, 55.0, 50.8 – 50.2 (m), 28.5, 28.4, 23.3 – 23.2 (m). ^{19}F NMR (471 MHz, CDCl_3) δ -175.84, -176.79 (conformers). HRMS-ESI: m/z for $\text{C}_{13}\text{H}_{15}\text{FNO}_3$ [$\text{MH}^+ - t\text{Bu}$] calcd. 252.1030; found 252.1026. $[\alpha]_D^{22}$ = -30.7° (c = 0.088, CHCl_3).



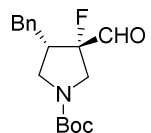
tert-Butyl (3S,4S)-3-fluoro-3-formyl-4-methylpyrrolidine-1-carboxylate (2c) In accordance with the general procedure, **1c** (222 mg, 1.04 mmol) was reacted with (*R*)-**7** (62 mg, 0.104 mmol, 10 mol%) and NFSI (394 mg, 1.25 mmol) in MTBE for 16 h to provide **2c** (210 mg, 0.908 mmol, 87% yield, 94:6 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **11c** using NaBH_4 in MeOH on an analytical scale (t_R major = 2.10 min; t_R minor = 1.99 min, 97:3 dr). The product can be isolated and handled as **2c**. ^1H NMR (600 MHz, CDCl_3) δ 9.84 – 9.82 (m, 1H), 3.86 – 3.44 (m, 3H), 3.18 – 3.02 (m, 1H), 2.70 – 2.10 (m, 1H), 1.49 – 1.42 (m, 9H), 1.10 – 0.97 (m, 3H).

Due to hydrate formation, **2c** was additionally characterized and the purity verified after reduction to the corresponding alcohol **11c** in accordance with the general procedure. ^1H NMR (600 MHz, CDCl_3) δ 3.93 – 3.85 (m, 1H), 3.76 – 3.51 (m, 4H), 3.16 – 3.08 (m, 1H), 2.35 – 1.97 (m, 2H), 1.46 (s, 9H), 1.08 – 1.05 (m, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.2, 104.0 – 100.8 (m), 79.6, 64.2 – 63.5 (m), 54.6 – 53.8 (m), 38.6 – 37.1 (m), 28.5, 10.0 – 9.8 (m). ^{19}F NMR (471 MHz, CDCl_3) δ -177.08, -177.21. HRMS-ESI: m/z for $\text{C}_7\text{H}_{11}\text{FNO}_3$ [MH^+] calcd. 234.1500; found 234.1498. $[\alpha]_D^{22}$ = +18.5° (c = 0.265, CHCl_3).

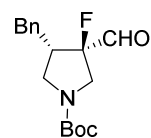


tert-Butyl (3R,4S)-3-fluoro-3-formyl-4-methylpyrrolidine-1-carboxylate (3c) In accordance with the general procedure, **1c** (135 mg, 0.633 mmol) was reacted with (*S*)-**8** (22 mg, 0.063 mmol, 10 mol%) and NFSI (240 mg, 0.76 mmol) in 10% *i*-PrOH in THF for 18 h to provide **3c** (91 mg, 0.393 mmol, 62% yield, 90:10 dr) as a yellow oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **13c** using NaBH₄ in MeOH on an analytical scale (*t*_R major = 2.01 min; *t*_R minor = 2.10 min, 87:13 dr). The product **3c** can be isolated and handled at the aldehyde stage. ¹H NMR (600 MHz, CDCl₃) δ 9.82 – 9.78 (m, 1H), 3.90 – 3.44 (m, 3H), 3.35 – 3.17 (m, 1H), 2.67 – 2.34 (m, 1H), 1.47 – 1.43 (m, 9H), 1.07 – 0.96 (m, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 199.2, 198.9, 198.3 – 197.5 (m), 154.6 – 154.2 (m), 129.3 – 128.6 (m), 106.0 – 103.3 (m), 89.8 – 89.6 (m), 80.3 – 80.1 (m), 52.7 – 50.5 (m), 41.1 – 40.7 (m), 40.1 – 39.8 (m), 28.5, 28.4, 14.0 – 13.7 (m) (conformers and hydrate formation). ¹⁹F NMR (471 MHz, CDCl₃) δ -160.84, -162.56. HRMS-ESI: *m/z* for C₇H₁₁FNO₃ [MH⁺-*t*Bu] calcd. 176.0717; found 176.0715. [α]_D²² = -2.7° (*c* = 0.488, CHCl₃).

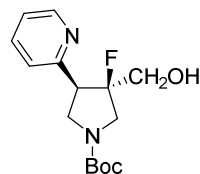
Due to hydrate formation, **3c** was additionally characterized and the purity verified after reduction to the corresponding alcohol **13c** in accordance with the general procedure. ¹H NMR (600 MHz, CDCl₃) δ 3.87 – 3.64 (m, 3H), 3.63 – 3.41 (m, 2H), 3.30 – 3.18 (m, 1H), 2.54 – 2.43 (m, 1H), 1.46 (s, 9H), 1.27 – 1.24 (m, 1H), 1.08 – 1.00 (m, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 154.8, 154.6, 106.6 – 104.4 (m), 79.8, 79.7, 62.7 (m), 52.5 – 51.6 (m), 51.6 – 50.6 (m), 38.7 (m), 28.5, 15.5 (m).



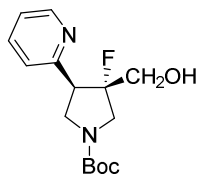
tert-Butyl (3S,4S)-4-benzyl-3-fluoro-3-formylpyrrolidine-1-carboxylate (2d) In accordance with the general procedure, **1d** (157 mg, 0.543 mmol) was reacted with (*R*)-**7** (32 mg, 0.054 mmol, 10 mol%) and NFSI (212 mg, 0.65 mmol) in MTBE for 16 h to provide **2d** (126 mg, 0.410 mmol, 76% yield, >99:1 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **11d** using NaBH₄ in MeOH on an analytical scale (*t*_R major = 2.63 min; *t*_R minor = 2.57 min, 98:2 dr). ¹H NMR (600 MHz, CDCl₃) δ 9.31 – 9.27 (m, 1H), 7.32 – 7.14 (m, 5H), 3.83 – 3.57 (m, 3H), 3.34 – 3.27 (m, 1H), 2.98 – 2.60 (m, 3H), 1.47 – 1.41 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 198.2 (d, *J* = 42.8 Hz), 153.8 (d, *J* = 30.5 Hz), 138.3, 128.9, 127.17, 127.15, 106.5 – 102.4 (m), 80.2, 55.0 – 54.4 (m), 50.4 – 49.8 (m), 50.0, 49.7, 32.3 – 32.1 (m), 28.44, 28.39. ¹⁹F NMR (471 MHz, CDCl₃) δ -180.51, -180.95 (two conformers); HRMS-ESI: *m/z* for C₁₃H₁₅FNO₃ [MH⁺-*t*Bu] calcd. 252.1030; found 252.1026. [α]_D²² = +31.9° (*c* = 2.64, CHCl₃).



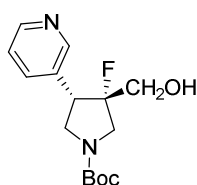
tert-Butyl (3R,4S)-4-benzyl-3-fluoro-3-formylpyrrolidine-1-carboxylate (3d) In accordance with the general procedure, **1d** (189 mg, 0.653 mmol) was reacted with (*S*)-**8** (23 mg, 0.065 mmol, 10 mol%) and NFSI (255 mg, 0.784 mmol) in 10% *i*-PrOH in THF for 18 h to provide **3d** (102 mg, 0.332 mmol, 51% yield, 98:2 dr) as a yellow oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **13d** using NaBH₄ in MeOH on an analytical scale (*t*_R major = 2.54 min; *t*_R minor = 2.61 min, 94:6 dr). ¹H NMR (600 MHz, CDCl₃) δ 9.87 – 9.83 (m, 1H), 7.34 – 7.19 (m, 3H), 7.13 – 7.10 (m, 2H), 4.01 – 3.85 (m, 1H), 3.67 – 3.48 (m, 2H), 3.42 – 3.29 (m, 1H), 2.90 – 2.77 (m, 2H), 2.46 – 2.39 (m, 1H), 1.48 – 1.43 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 198.4 (d, *J* = 43.3 Hz), 154.2 (d, *J* = 31.5 Hz), 138.0 (d, *J* = 22.0 Hz), 128.81, 128.79, 126.9, 104.7 – 102.5 (m), 52.0 – 51.3 (m), 80.3, 49.1, 48.9, 48.4 – 47.5 (m), 33.6 (d, *J* = 10.8 Hz), 28.4; ¹⁹F NMR (471 MHz, CDCl₃) δ -161.81, -162.56, -167.82, -168.11, -169.29, -169.61. (conformers and partial hydrate formation). HRMS-ESI: *m/z* for C₁₃H₁₅FNO₃ [MH⁺-*t*Bu] calcd. 252.1030; found 252.1037. [α]_D²² = +35° (*c* = 1.33, CHCl₃).



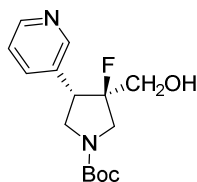
tert-Butyl (3R,4S)-3-fluoro-3-formyl-4-(pyridin-2-yl)pyrrolidine-1-carboxylate (11e) In accordance with the general procedure, **1e** (31 mg, 0.112 mmol) was reacted with (*S*)-**7** (13 mg, 0.022 mmol, 20 mol%) and NFSI (44 mg, 0.135 mmol) in MTBE for 16 h. Subsequently, MeOH (3 mL) was added followed by NaBH₄ (13 mg, 0.337 mmol, 3 equiv) and the resulting mixture was stirred for 30 min. Half sat. brine (1.5 mL) was added followed by a 1:1 mixture of THF/EtOAc (4 mL) and the phases were separated. The aqueous phase was extracted with a 1:1 mixture of THF/EtOAc (2 x 4 mL) and the organic phases combined, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a crude oil that was purified using silica gel chromatography to furnish **11e** (26.3 mg, 0.089 mmol, 79% yield, >99:1 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) (*t*_R major = 1.46 min; *t*_R minor = 1.66 min, 95:5 dr). ¹H NMR (600 MHz, CDCl₃) δ 8.57 – 8.52 (m, 1H), 7.77 – 7.71 (m, 1H), 7.32 – 7.25 (m, 2H), 4.12 – 3.99 (m, 1H), 3.93 – 3.88 (m, 1H), 3.86 – 3.68 (m, 5H), 1.50 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 154.6 – 154.2 (m), 148.74, 148.6, 137.4, 137.2, 123.1, 123.0, 122.8, 103.2 – 101.1 (m), 80.1, 62.6 – 62.1 (m), 54.8 – 54.1 (m), 50.8 – 49.9 (m), 48.1, 47.6, 28.5. ¹⁹F NMR (471 MHz, CDCl₃) δ -169.25, -169.56 (two conformers of the major isomer). HRMS-ESI: *m/z* for C₁₅H₂₂FN₂O₃ [MH⁺] calcd. 297.1609; found 297.1612. [α]_D²² = +56.8° (*c* = 0.176, CHCl₃).



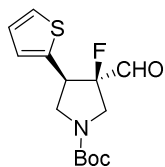
tert-Butyl (3S,4S)-3-fluoro-3-(hydroxymethyl)-4-(pyridin-2-yl)pyrrolidine-1-carboxylate (13e) In accordance with the general procedure, **1e** (71.4 mg, 0.258 mmol) was reacted with (*R*)-**8** (18 mg, 0.052 mmol, 20 mol%) and NFSI (101 mg, 0.31 mmol) in 10% *i*-PrOH in THF for 20 h. Subsequently, MeOH (5 mL) was added followed by NaBH₄ (29 mg, 0.775 mmol, 3 equiv) and the resulting mixture was stirred for 30 min. Half sat. brine (2 mL) was added followed by a 1:1 mixture of THF/EtOAc (6 mL) and the phases were separated. The aqueous phase was extracted with a 1:1 mixture of THF/EtOAc (2 x 6 mL) and the organic phases combined, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a crude oil that was purified using silica gel chromatography to furnish **13e** (33.5 mg, 0.113 mmol, 44% yield, >99:1) as a colorless oil. The crude dr was determined by LCMS (XIC) (*t_R* major = 1.66 min; *t_R* minor = 1.47 min, 99:1 dr). ¹H NMR (600 MHz, CDCl₃) δ 8.58 – 8.54 (m, 1H), 7.76 – 7.72 (m, 1H), 7.29 – 7.24 (m, 2H), 4.79 – 4.57 (m, 1H), 3.98 – 3.84 (m, 3H), 3.71 – 3.59 (m, 2H), 3.53 – 3.42 (m, 1H), 3.36 – 3.24 (m, 1H), 1.52 – 1.48 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 157.6 – 157.1 (m), 154.4, 149.34, 149.28, 138.0, 137.9, 122.9, 122.10, 122.05, 80.1 63.2 (d), 52.8 – 51.7 (2 x m), 49.6, 49.1, 28.52, 28.50. ¹⁹F NMR (471 MHz, CDCl₃) δ -150.58, -151.58 (two conformers of the major isomer). HRMS-ESI: *m/z* for C₁₅H₂₂FN₂O₃ [MH⁺] calcd. 297.1609; found 297.1608. [α]_D²² = +59.5° (*c* = 0.387, CHCl₃).



tert-Butyl (3S,4S)-3-fluoro-3-formyl-4-(pyridin-3-yl)pyrrolidine-1-carboxylate (11f) In accordance with the general procedure, **1f** (83 mg, 0.300 mmol) was reacted with (*R*)-**7** (36 mg, 0.06 mmol, 20 mol%) and NFSI (117 mg, 0.36 mmol) in MTBE for 16 h. Subsequently, MeOH (3 mL) was added followed by NaBH₄ (34 mg, 0.900 mmol, 3 equiv) and the resulting mixture was stirred for 30 min. Half sat. brine (1.5 mL) was added followed by a 1:1 mixture of THF/EtOAc (4 mL) and the phases were separated. The aqueous phase was extracted with a 1:1 mixture of THF/EtOAc (2 x 4 mL) and the organic phases combined, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a crude oil that was purified using silica gel chromatography to furnish **11f** (64.4 mg, 0.216 mmol, 72% yield, 96:4 dr) as a colorless oil. The crude dr was determined by LCMS (UV) (*t_R* major = 1.32 min; *t_R* minor = 1.34 min, 97:3 dr). ¹H NMR (600 MHz, CDCl₃) δ 8.53 – 8.42 (m, 2H), 7.77 – 7.71 (m, 1H), 7.30 – 7.27 (m, 1H), 4.82 (br, 1H), 3.98 – 3.45 (m, 7H), 1.49 – 1.44 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 154.6 (d, *J* = 3.4 Hz), 150.6, 150.5, 148.7, 148.6, 137.6, 131.1, 130.9, 123.9, 123.8, 103.34 – 101.32 (m), 80.33, 80.20, 61.2 – 60.6 (m), 54.4 – 53.7 (m), 50.3, 49.7, 46.2 – 45.2 (m), 28.6. ¹⁹F NMR (471 MHz, CDCl₃) δ -152.92 (trace amount of minor isomer), -170.19, -170.28 (two conformers of the major isomer). HRMS-ESI: *m/z* for C₁₅H₂₂FN₂O₃ [MH⁺] calcd. 297.1609; found 297.1608. [α]_D²² = -44.9° (*c* = 1.60, CHCl₃).

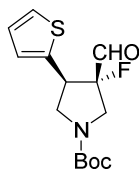


tert-Butyl (3R,4S)-3-fluoro-3-(hydroxymethyl)-4-(pyridin-3-yl)pyrrolidine-1-carboxylate (13f) In accordance with the general procedure, **1f** (83 mg, 0.300 mmol) was reacted with (*S*)-**8** (21 mg, 0.06 mmol, 20 mol%) and NFSI (117 mg, 0.36 mmol) in 10% *i*-PrOH in THF for 20 h. Subsequently, MeOH (3 mL) was added followed by NaBH₄ (34 mg, 0.900 mmol, 3 equiv) and the resulting mixture was stirred for 30 min. Half sat. brine (1.5 mL) was added followed by a 1:1 mixture of THF/EtOAc (4 mL) and the phases were separated. The aqueous phase was extracted with a 1:1 mixture of THF/EtOAc (2 x 4 mL) and the organic phases combined, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a crude oil that was purified using silica gel chromatography to provide the stereopure fluoroalcohol though contaminated by the catalyst. The catalyst was removed using preparative LCMS to yield **13f** (58 mg, 0.196 mmol, 65% yield, >99:1 dr) as a colorless oil. The crude dr was determined by LCMS (UV) (*t_R* major = 1.34 min; *t_R* minor = 1.33 min, 98:2 dr). ¹H NMR (600 MHz, CDCl₃) δ 8.53 – 8.49 (m, 2H), 7.57 – 7.53 (m, 1H), 7.30 – 7.27 (m, 1H), 4.02 – 3.95 (m, 1H), 3.81 – 3.61 (m, 3H), 3.59 – 3.30 (m, 3H), 1.51 – 1.48 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 154.5 (d, *J* = 17.6 Hz), 149.52, 149.44, 149.12, 135.31, 135.23, 134.6 – 134.2 (m), 124.15, 106.2 – 104.3 (m), 80.62, 62.9 – 62.4 (m), 52.1 – 51.5 (m), 51.22, 50.60, 48.4 – 47.3 (m) 28.65. ¹⁹F NMR (471 MHz, CDCl₃) δ -153.25, -153.31 (two conformers of the major isomer). HRMS-ESI: *m/z* for C₁₅H₂₂FN₂O₃ [MH⁺] calcd. 297.1609; found 297.1611.



tert-Butyl (3R,4R)-3-fluoro-3-formyl-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (2g) In accordance with the general procedure, **1g** (132.2 mg, 0.470 mmol) was reacted with (*S*)-**7** (28 mg, 0.047 mmol, 10 mol%) and NFSI (183 mg, 0.564 mmol) in MTBE for 14 h to provide **2g** (117 mg, 0.391 mmol, 83% yield, 89:11 dr) as a colorless oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **11g** using NaBH₄ in MeOH on an analytical scale (*t_R* major = 2.45 min; *t_R* minor = 2.38 min, 89:11 dr). ¹H NMR (600 MHz, CDCl₃) δ 9.75 – 9.71 (m, 1H), 7.28 – 7.26 (m, 1H), 6.99 – 6.94 (m, 2H), 4.10 – 3.65 (m, 5H), 1.49 – 1.42 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 198.9 (d, *J* = 42.9 Hz), 153.8 (d, *J* = 27.3 Hz), 134.0 (d, *J* = 5.8 Hz), 127.3, 127.21, 127.19, 126.98, 126.95, 126.7, 125.8, 125.7, 104.6 – 102.4 (m), 80.6, 54.3 – 53.8 (m), 51.0, 50.5, 47.2 – 46.4 (m), 28.5, 28.4.

For additional characterization, **2g** was reduced to the corresponding alcohol **11g** in accordance with the general procedure. ¹H NMR (600 MHz, CDCl₃) δ 7.28 – 7.26 (m, 1H), 7.02 – 6.98 (m, 2H), 4.05 – 3.62 (m, 7H), 1.97 – 1.82 (br, 1H), 1.49 – 1.46 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 135.8, 127.1, 126.7, 125.4, 80.0, 63.3 – 62.4 (m), 54.4 – 53.4 (m), 51.7, 51.1, 44.7 – 43.8 (m), 28.5. ¹⁹F NMR (471 MHz, CDCl₃) δ -155.65, -155.71 (two conformers from the trace amount of minor isomer), -170.09, -170.15 (two conformers of the major isomer). HRMS-ESI: *m/z* C₁₄H₂₁FNO₃S [MH⁺] calcd. 302.1221; found 302.1216. [α]_D²² = +37.2° (*c* = 0.223, CHCl₃).



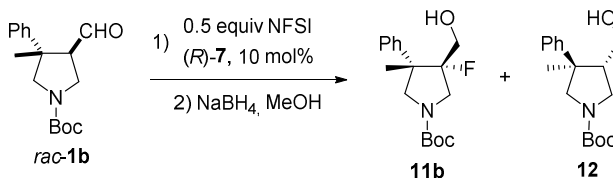
tert-Butyl (3S,4R)-3-fluoro-3-formyl-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (3g) In accordance with the general procedure, **1g** (136.3 mg, 0.484 mmol) was reacted with (*R*)-**8** (34 mg, 0.097 mmol, 20 mol%) and NFSI (189 mg, 0.581 mmol) in 10% *i*-PrOH in THF for 18 h to provide **3g** (106 mg, 0.354 mmol, 73% yield, 99:1 dr) as a yellow oil. The crude dr was determined by LCMS (XIC) after reduction to the alcohol **13g** using NaBH₄ in MeOH on an analytical scale (*t_R* major = 2.38 min; *t_R* minor = 2.44 min, 98:2 dr). ¹H NMR (600 MHz, CDCl₃) δ 9.49 (d, *J* = 3.2 Hz, 1H), 7.26 – 7.23 (m, 1H), 6.98 – 6.88 (m, 2H), 4.13 – 3.58 (m, 5H), 1.52 – 1.48 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 196.8 – 196.0 (m), 154.6 – 153.9 (m), 139.9 – 139.6 (m), 136.3 – 136.2 (m), 127.3, 126.90, 126.87, 126.4, 126.4, 125.7, 124.9, 106.3 – 101.6 (m), 89.7, 89.5, 80.7, 80.22, 80.20, 52.6 – 50.4 (m), 47.9 – 46.6 (m), 46.2 – 44.9 (m), 28.52, 28.48, 28.43. Partial hydrate formation and mixture of conformers.

For additional characterization, **3g** was reduced to the corresponding alcohol **13g** in accordance with the general procedure. ¹H NMR (600 MHz, CDCl₃) δ 7.23 – 7.21 (m, 1H), 6.98 – 6.95 (m, 1H), 6.94 – 6.91 (m, 1H), 3.97 – 3.90 (m, 1H), 3.89 – 3.48 (m, 6H), 1.82 (br, 1H), 1.53 – 1.49 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 154.3, 127.0, 125.8, 125.8, 124.9, 104.5, 80.2, 63.3 – 62.7 (m), 52.06, 51.7, 51.5, 51.4, 51.3, 51.1, 46.2 – 45.2 (m), 28.48, 28.46. ¹⁹F NMR (471 MHz, CDCl₃) δ -155.67, -155.71 (two conformers of the major isomer), -170.13 (trace amount of minor isomer). HRMS-ESI: *m/z* C₁₄H₂₁FNO₃S [MH⁺] calcd. 302.1221; found 302.1225. [α]_D²² = -9.7° (*c* = 0.248, CHCl₃).

Kinetic Resolution using Organocatalysis

Chiral resolution and concurrent formation of an enantioenriched fluorinated alcohol:

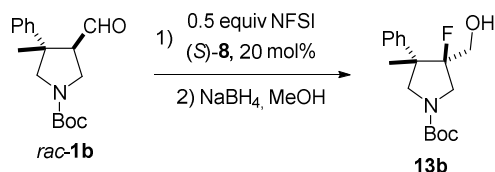
tert-Butyl (3S,4S)-3-fluoro-3-(hydroxymethyl)-4-methyl-4-phenylpyrrolidine-1-carboxylate (11b)



To a 20 mL microwave vial was added *rac*-**1b** (334 mg, 1.120 mmol, 97%) and (*R*)-**7** (67 mg, 0.112 mmol) in MTBE (400 μL) and the contents were stirred for 5 min at rt. Subsequently, NFSI (182 mg, 0.56 mmol, 97 %) was poured into the mixture and stirring was continued for 16 h at rt. MeOH (4 mL) was added followed by NaBH₄ (85 mg, 2.24 mmol, 2 equiv) and stirring was continued for 1 h at rt. Subsequently, half sat. brine (3 mL) was added followed by EtOAc (8 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 10 mL) and the organic phases combined, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a crude oil that was purified using silica gel chromatography to provide **11b** (106 mg, 0.343 mmol, 31% yield, 95% *ee*) as a colorless oil. The *enantiomeric excess* was determined using chiral SFC using a ChiralPak IA column using 10% modifier 0.1% diethylamine in EtOH (*t_R* major = 2.913 min; *t_R* minor = 2.577 min). The resolved non-fluorinated alcohol **12** (117 mg, 0.402 mmol, 36% yield, 79% *ee*) was also isolated as a colorless oil. The *enantiomeric excess* was determined using chiral SFC using a ChiralPak AS-H column using 10% modifier 0.1% diethylamine in EtOH (*t_R* major = 2.270 min; *t_R* minor = 1.827 min). Characterization data presented *vide supra*.

tert-Butyl (3R,4S)-3-fluoro-3-(hydroxymethyl)-4-methyl-4-phenylpyrrolidine-1-carboxylate (13b)

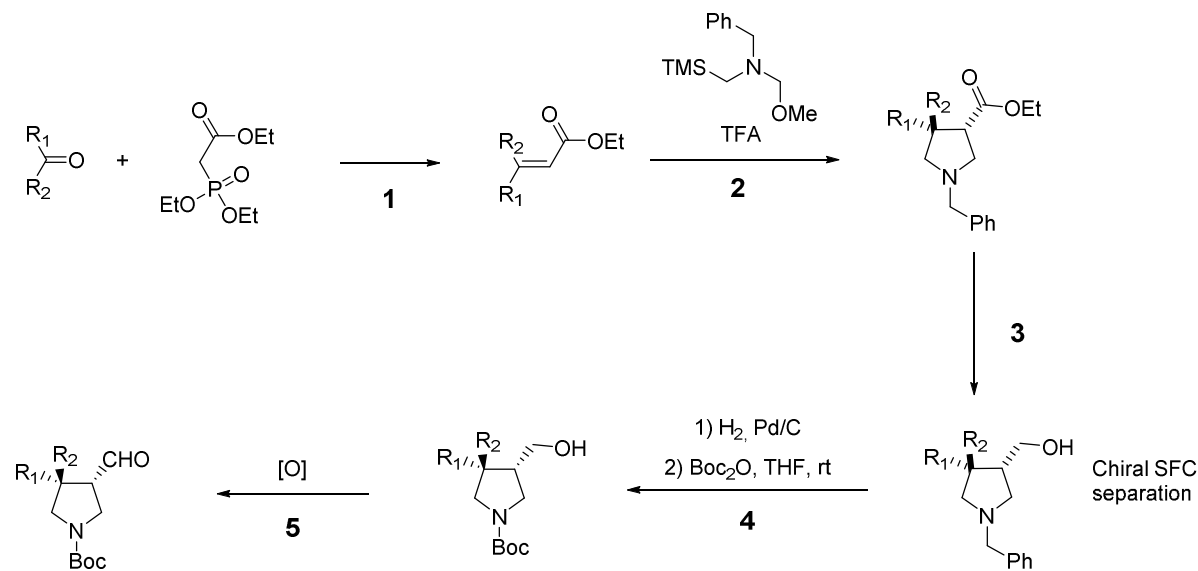
The following approach afforded **13b** as a racemate.



To a flask was added *rac-1b* (211 mg, 0.715 mmol, 98%) and (*S*)-**8** in THF/*i*-PrOH 9:1 (1.5 mL) and then stirred for 5 min at rt. Subsequently, NFSI (116 mg, 0.357 mmol, 97%) was poured into the mixture and stirring was continued for 16 h at 40 °C. MeOH (4 mL) was added followed by NaBH₄ (54 mg, 1.43 mmol, 2 equiv) and stirring was continued for 1 h at rt. Subsequently, half sat. brine (3 mL) was added followed by EtOAc (8 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 10 mL) and the organic phases combined, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a crude oil that was purified using silica gel chromatography to provide **13b** (76 mg, 0.246 mmol, 34% yield) as a colorless oil.

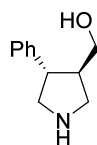
Synthesis of Chiral Pyrrolidinyl Carbaldehydes

With few exceptions, the chiral pyrrolidines were synthesized according to the following procedure using HWE olefination [1], 3+2 cycloaddition [2], reduction [3] followed by chiral SFC separation, debenzylation, Boc protection [4] and oxidation [5].



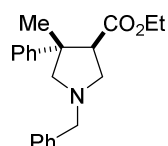
Synthesis of Substrate (1a)

(3*R*,4*S*)-tert-Butyl 3-formyl-4-phenylpyrrolidine-1-carboxylate (1a) To a solution of oxalyl chloride (1.24 g, 0.85 mL, 9.73 mmol) in anhydrous CH₂Cl₂ (10 mL) was added DMSO (1.52 g, 1.38 mL, 19.5 mmol) at -78 °C. The mixture was stirred for 5 min after which a solution of (3*R*,4*S*)-tert-butyl 3-(hydroxymethyl)-4-phenylpyrrolidine-1-carboxylate (1.08 g, 3.89 mmol) in CH₂Cl₂ (10 mL) was dropwise added and stirring was continued for 30 min. Subsequently, DIPEA (6.8 mL, 39 mmol) was dropwise added at -78 °C after which the temperature was elevated to 0 °C and stirring continued for 1 h. H₂O (3 mL) was then added followed by half sat. aq. NH₄Cl (10 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 40 mL), the organic extracts combined, washed with brine and dried over MgSO₄. Removal of solvents *in vacuo* provided a yellow oil that was purified using silica gel chromatography to provide **1a** (726 mg, 2.64 mmol, 68% yield) as a yellow oil. ¹H NMR (600 MHz, CDCl₃) δ 9.66 (br, 1H), 7.37 – 7.33 (m, 2H), 7.30 – 7.24 (m, 3H), 3.94 – 3.56 (m, 4H), 3.52 – 3.41 (m, 1H), 3.25 – 3.16 (m, 1H), 1.47 (s, *J* = 13.3 Hz, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 199.88, 154.11, 139.22, 138.98, 129.02, 127.57, 127.27, 79.95, 57.47, 56.54, 52.60, 52.06, 45.31, 45.20, 44.77, 28.46. HRMS-ESI: *m/z* C₁₆H₂₁NNaO₃ [MNa⁺] calcd. 298.1414; found 298.1422. [α]_D²² = +26° (*c* = 0.67, CHCl₃).

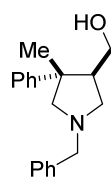


((3R,4S)-4-phenylpyrrolidin-3-yl)methanol (S1a) The absolute configuration of **1a** was confirmed by conversion to the corresponding *N*-deprotected alcohol **S1a**, which is reported in the literature.¹ A vial was charged with (3*S*,4*R*)-*tert*-butyl 3-(hydroxymethyl)-4-phenylpyrrolidine-1-carboxylate (75.55 mg, 0.272 mmol) after which CH₂Cl₂ (1 mL) was added followed by the dropwise addition of TFA (1 mL). This mixture was stirred for 30 min after which toluene (2 mL) was added and the resulting mixture concentrated *in vacuo* to provide a yellow substance that was suspended in sat. aq. NaHCO₃ (2 mL) and extracted with EtOAc (2 x 8 mL). The organic phases were combined, dried over MgSO₄, filtered and concentrated to provide **S1a** (42 mg, 0.237 mmol, 87% yield) as a yellow oil. [α]_D²² +34.2 (*c* 0.33 CHCl₃). The optical rotation is in accordance with the literature data.¹

Synthesis of Substrate (1b)

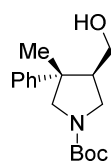


Ethyl *trans*-1-benzyl-4-methyl-4-phenylpyrrolidine-3-carboxylate (S1b) To a stirred solution of (*E*)-ethyl 3-phenylbut-2-enoate (2.96 g, 15.56 mmol) in toluene (26 mL) was added *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (4.43 g, 4.78 mL, 18.67 mmol) at 0 °C under N₂. After 20 min, a solution of TFA (0.120 mL, 1.56 mmol, 1M in CH₂Cl₂) was added slowly at 0 °C. The mixture was stirred for 40 min at 0 °C after which the cooling bath was removed and stirring continued for 12 h at rt. The solvent was removed *in vacuo* to provide a yellow oil that was purified using silica gel chromatography to provide **S1b** (2.44 g, 7.54 mmol, 49% yield) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.53 – 7.49 (m, 2H), 7.40 – 7.37 (m, 2H), 7.34 – 7.30 (m, 4H), 7.27 – 7.19 (m, 2H), 4.24 – 4.11 (m, 2H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.33 (t, *J* = 7.7 Hz, 1H), 3.11 – 3.05 (m, 2H), 2.93 (dd, *J* = 9.3, 8.3 Hz, 1H), 2.63 (d, *J* = 9.2 Hz, 1H), 1.39 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 173.30, 149.61, 139.41, 128.73, 128.45, 128.42, 127.12, 126.22, 68.34, 60.60, 60.23, 56.41, 54.55, 48.60, 24.95, 14.54. LRMS: (UV *t*_R = 0.52 min) *m/z* = 323.9. HRMS-ESI: *m/z* C₂₁H₂₆NO₂ [MH⁺] calcd. 324.1958; found 324.1957.

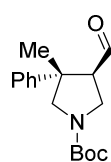


***trans*-1-Benzyl-4-methyl-4-phenylpyrrolidin-3-yl)methanol (S2b)** To a solution of **S1b** (2.44 g, 7.55 mmol) in THF (53 mL) was slowly added LiAlH₄ (8.30 mL, 8.3 mmol, 1M in THF) at 0 °C. The mixture was stirred at 0 °C for 45 min followed by the very slow addition of H₂O (3 mL), NaOH (5M, 5 mL) then H₂O (9 mL). The white suspension was heavily stirred for 30 min followed by filtration through Celite to provide **S2b** (2.03 g, 7.21 mmol, 96% yield) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.43 – 7.39 (m, 3H), 7.37 – 7.34 (m, 2H), 7.34 – 7.28 (m, 3H), 7.27 – 7.23 (m, 1H), 7.20 – 7.16 (m, 1H), 3.84 (dd, *J* = 10.6, 5.5 Hz, 1H), 3.72 – 3.63 (m, 3H), 2.99 (d, *J* = 9.4 Hz, 1H), 2.92 (dd, *J* = 9.1, 7.7 Hz, 1H), 2.72 (d, *J* = 9.3 Hz, 1H), 2.68 – 2.65 (m, 1H), 2.64 – 2.59 (m, 1H), 1.95 (br, *J* = 22.3 Hz, 1H), 1.43 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 150.3, 139.3, 128.8, 128.48, 128.47, 127.2, 126.1, 126.0, 69.4, 63.8, 60.5, 58.2, 50.8, 46.9, 23.6. HRMS-ESI: *m/z* for C₁₉H₂₄NO [MH⁺] calcd. 282.1852; found 282.1853.

Racemic **S2b** was separated using chiral SFC on a Lux Cellulose-2 column (*t*_R = 2.201 and 2.567 with 20% modifier 0.1% diethylamine in *i*-PrOH).



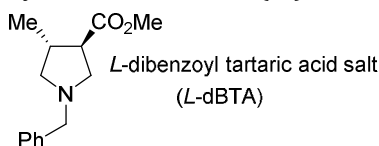
***tert*-Butyl (3*S*,4*R*)-4-(hydroxymethyl)-3-methyl-3-phenylpyrrolidine-1-carboxylate (S3b)** To an inert solution of (3*S*,4*R*)-**S2b** (786 mg, 2.79 mmol) in EtOH (38 mL) was added Pd(OH)₂ on carbon (102 mg, 0.73 mmol) 20% wt. The mixture was stirred under H₂ (7 bar, 50 °C) for 6 h and subsequently passed through a plug of Celite using THF (2 x 30 mL). To the filtrate was then added di-*tert*-butyl dicarbonate (726 mg, 3.33 mmol) and the mixture was stirred for 14 h at rt. The solvent was evaporated *in vacuo* and the resulting residue purified using silica gel chromatography to provide **S3b** (641 mg, 2.20 mmol, 79 % yield) as a dense colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.42 – 7.38 (m, 2H), 7.37 – 7.32 (m, 2H), 7.27 – 7.22 (m, 1H), 3.81 – 3.71 (m, 2H), 3.65 – 3.55 (m, 2H), 3.54 – 3.40 (m, 1H), 3.36 – 3.28 (m, 1H), 2.77 – 2.68 (m, 1H), 1.49 – 1.45 (m, 9H), 1.36 – 1.33 (m, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 154.9, 144.9, 128.8, 126.8, 126.2, 126.1, 79.6, 62.3, 62.2, 61.0, 60.1, 50.5, 49.5, 49.3, 48.8, 28.74, 28.72, 19.9. Mixture of conformers. HRMS-ESI: *m/z* for C₁₇H₂₅NNaO₃ [MNa⁺] calcd. 314.1727; found 314.1732.



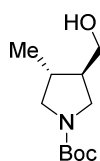
***tert*-Butyl (3*S*,4*R*)-4-formyl-3-methyl-3-phenylpyrrolidine-1-carboxylate (1b)** To a solution of oxalyl chloride (698 mg, 0.48 mL, 5.50 mmol) in anhydrous CH₂Cl₂ (10 mL) was added DMSO (0.78 mL, 11 mmol) at -78 °C. The mixture was stirred for 5 min after which a solution of **S3b** (641 mg, 2.20 mmol) in CH₂Cl₂ (6 mL) was added dropwise and further stirred for 30 min. Subsequently, diisopropylethylamine (2.84 g, 3.84 mL, 22 mmol) was added dropwise at -78 °C after which the temperature was elevated to 0 °C and stirring continued for 1 h. H₂O (3 mL) was then added followed by half sat. aq. NH₄Cl (10 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 40 mL), the organic extracts combined, washed with brine and dried over MgSO₄. Removal of volatiles *in vacuo* provided a yellow oil that was purified using silica gel chromatography to provide **1b** (436 mg, 1.51 mmol,

69% yield) as a yellow oil. ^1H NMR (600 MHz, CDCl_3) δ 9.74 - 9.72 (m, 1H), 7.43 - 7.36 (m, 4H), 7.31 - 7.27 (m, 1H), 3.87 - 3.78 (m, 1H), 3.73 - 3.59 (m, 2H), 3.58 - 3.51 (m, 1H), 3.41 - 3.32 (m, 1H), 1.49 - 1.47 (m, 9H), 1.46 - 1.44 (m, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 200.9, 154.7, 144.1, 144.0, 129.09, 129.07, 127.4, 126.03, 125.96, 80.1, 60.0, 59.44, 59.35, 58.3, 44.6, 44.5, 28.7, 22.1, 22.0 (mixture of conformers). HRMS-ESI: m/z for $\text{C}_{17}\text{H}_{24}\text{NO}_3$ $[\text{MH}^+]$ calcd. 290.1751; found 290.1750. $[\alpha]_{\text{D}}^{22} = -4.0^\circ$ ($c = 1.286$, CHCl_3).

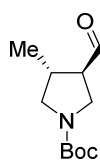
Synthesis of Substrate (1c)



(3R,4R)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate L-dBTAsalt To a solution of *trans*-1-benzyl-4-methylpyrrolidin-3-yl)methanol (10 g, 42.9 mmol, 1.0 equiv) in 4-methylpentan-2-one (43 mL, 1M) was added (-)-*O,O*-dibenzoyl-*L*-tartaric acid (9.98 g, 27.9 mmol, 0.65 equiv) and the mixture was heated to 70 °C and stirring was continued for 1 h. Subsequently, the mixture was cooled to rt and stirred for 4 h followed by collection of the precipitate. The precipitated salt was triturated with 4-methylpentan-2-one (10 mL) to afford the enantioenriched product as white solid. To the enantioenriched salt was then added EtOH (20 mL) and MTBE (40 mL) and the resulting suspension was stirred at 70 °C for 1 h and allowed to cool to rt over the course of 6 h. The resulting solid was collected by filtration and washed with MTBE (20 mL) to afford the single enantiomer (3R,4R)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (2R,3R)-2,3-bis(benzoyloxy)succinate (4 g, 6.76 mmol 16% yield) as white solid that was used directly in the next step without further characterization.

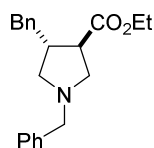


tert-Butyl (3R,4R)-3-(hydroxymethyl)-4-methylpyrrolidine-1-carboxylate (S1c) To a stirred suspension of (3R,4R)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (2R,3R)-2,3-bis(benzoyloxy)succinate (4 g, 6.76 mmol) in THF (100 mL) was added a solution of sat. aq. Na_2CO_3 (80 mL), the mixture was stirred for 30 min after which EtOAc was added and the phases separated. The aqueous phase was washed with EtOAc (3 x 125 mL) and the organic phases combined, washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to provide a crude oil. The crude oil was dissolved in THF (80 mL) at 0 °C after which LiAlH_4 (7.44 mL, 7.44 mmol, 1M in THF) was added and the mixture stirred for 1 h after which Et_2O (150 mL) was added. Subsequent "fieser work-up"; very slow addition of H_2O (134 μL , 7.44 mmol) followed by NaOH (137 μL , 5M) and H_2O (400 μL) followed by heavy stirring for 1 h. The precipitates were removed by filtration and the resulting clear filtrate was concentrated *in vacuo* to provide a colorless oil that was rediluted in EtOH (40 mL) under inert atmosphere at rt. To this solution was then poured Pd/C (720 mg, 0.676 mmol, 10%) through a slow stream of N_2 after which NH_4CHOO (4.26 g, 67.6 mmol) was added and the mixture was refluxed for 1 h. The solids were filtered off and to the filtrate was added THF (80 mL) and di-*tert*-butyl dicarbonate (1.623 g, 7.44 mmol) and the resulting solution was stirred overnight at rt. Removal of volatiles *in vacuo* provided a colorless oil that was purified by silica gel chromatography to provide **S1c** (1.219 g, 5.66 mmol, 84% yield) as a colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 3.75 - 3.63 (m, 1H), 3.61 - 3.45 (m, 3H), 3.18 - 3.07 (m, 1H), 2.91 - 2.81 (m, 1H), 2.03 - 1.84 (m, 2H), 1.41 (s, 9H), 1.04 - 0.98 (m, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.82, 154.79, 63.3, 63.1, 53.5, 52.9, 49.5, 49.0, 48.2, 47.5, 35.1, 34.4, 28.7, 17.0. Mixture of conformers. LRMS: RT_{TIC} (0.57 min) $m/z = 160.0$ $[\text{MH}^+ - t\text{-Bu}]$. HRMS-ESI: m/z for $\text{C}_{11}\text{H}_{22}\text{NO}_3$ $[\text{MH}^+]$ calcd. 216.1594; found 216.1593. $[\alpha]_{\text{D}}^{22} = +40.3^\circ$ ($c = 0.481$, CHCl_3).

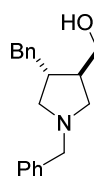


(3R,4R)-tert-Butyl 3-formyl-4-methylpyrrolidine-1-carboxylate (1c) To a solution of **S1c** (1.219 g, 5.66 mmol) in CH_2Cl_2 (33 mL, 0.17 M) was added Dess-Martin Periodinane (3.60 g, 8.49 mmol) at rt. To the stirred suspension was then slowly added H_2O (112 μL , 6.23 mmol). Stirring was continued for 30 min followed by the addition of Et_2O (150 mL) and the resulting suspension was gently concentrated *in vacuo* to a few mL after which Et_2O (150 mL) was added. The ethereal solution was washed with a 1:1 mixture of sat. aq. NaHCO_3 and 10% $\text{Na}_2\text{S}_2\text{O}_3$ until the phases became clear. The aqueous phase was back-extracted with Et_2O (100 mL) and the combined ethereal phases were washed with brine, dried over Na_2SO_4 , filtered, concentrated *in vacuo* and purified by silica gel chromatography to provide **1c** (950 mg, 4.45 mmol, 79% yield) as a colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 9.64 (br, 1H), 3.66 - 3.54 (m, 3H), 3.01 - 2.92 (m, 1H), 2.66 - 2.57 (m, 1H), 2.54 - 2.44 (m, 1H), 1.45 (s, 9H), 1.16 - 1.09 (m, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 200.8, 200.7, 79.9, 57.9, 57.0, 52.9, 52.5, 45.5, 45.4, 34.8, 34.2, 28.7, 17.2. Mixture of conformers. HRMS-ESI: m/z for $\text{C}_{11}\text{H}_{20}\text{NO}_3$ $[\text{MH}^+]$ calcd. 214.1438; found 214.1436. $[\alpha]_{\text{D}}^{22} = +14.3$ ($c = 1.2$, CHCl_3).

Synthesis of Substrate (1d)

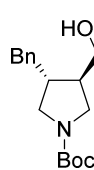


Ethyl *trans*-1,4-dibenzylpyrrolidine-3-carboxylate (S1d) To a stirred solution of (*E*)-ethyl 4-phenylbut-2-enoate (5.78 g, 23.39 mmol, 77%) in toluene (57 mL, 0.41M) was added *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (6.94 g, 7.48 mL, 28.1 mmol, 96%) at 0 °C under N₂. After 10 min, a solution of TFA (180 μL, 2.34 mmol) in CH₂Cl₂ (2.3 mL) was added over the course of 10 min at 0 °C. The mixture was stirred for 75 min at 0 °C after which the solvent was removed *in vacuo* to provide a yellow oil that was purified using silica gel chromatography to provide **S1d** (7.33 g, 22.66 mmol, 97% yield) as a colorless oil. The compound is known and characterized in the literature.²

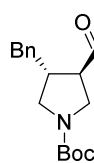


***trans*-1,4-Dibenzylpyrrolidin-3-ylmethanol (S2d)** To a solution of **S1d** (7.33 g, 22.66 mmol) in Et₂O (50 mL) was slowly added LiAlH₄ (24.93 mL, 24.93 mmol, 1M in THF) at 0 °C. The mixture was stirred at 0 °C for 45 min followed by the addition of H₂O (0.8 mL), NaOH (5M, 0.8 mL) then H₂O (2.4 mL). The white suspension was heavily stirred for 1 h followed by filtration and the resulting clear solution was concentrated *in vacuo* at 50 °C to provide a crystallizing oil that was recrystallized from boiling heptane to provide **S2d** (5.43 g, 19.30 mmol, 85% yield) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 7.32 – 7.22 (m, 7H), 7.20 – 7.16 (m, 3H), 3.60 – 3.51 (m, 3H), 3.40 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.15 (br, 1H), 3.01 – 2.97 (m, 1H), 2.74 – 2.68 (m, 3H), 2.54 (dd, *J* = 9.2, 7.1 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.05 – 1.98 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 140.5, 138.5, 128.8, 128.6, 128.4, 128.3, 127.1, 126.1, 67.3, 60.6, 60.1, 57.6, 44.9, 42.0, 41.3. LRMS: (UV t_R = 0.51 min) *m/z* = 282.1.

Racemic **S2d** was separated by chiral SFC using an Amy-C (20mm x 250mm, 5μm) column using 20% modifier with 0.1% NH₃ in MeOH (t_R peak 1 = 2.336 min; t_R peak 2 = 2.553 min). Peak 1 was used in the subsequent reaction.

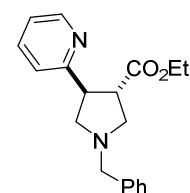


***tert*-Butyl (3*R*,4*R*)-3-benzyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate (S3d)** A flask was charged with (3*R*,4*R*)-**S2d** (2.34 g, 8.32 mmol) in EtOH (17 mL, 0.5M) and the solution was degassed with argon. Subsequently, Pd(OH)₂ on carbon (234 mg, 1.66 mmol) 20% wt was added and the mixture was placed on a Parr shaker apparatus at 3 bar, rt for 16 h. Subsequently, the reaction mixture was passed through Celite and to the filtrate was added THF (50 mL) and di-*tert*-butyl dicarbonate (1.996 g, 9.15 mmol) after which the mixture was stirred for 1.5 h and evaporated to dryness *in vacuo*. Purification using silica gel chromatography provided **S3d** (2.249 g, 7.72 mmol, 93% yield) as a colorless oil. [α]_D²² = +45° (*c* = 1, MeOH). The compound is known and characterized in the literature.²

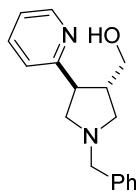


***tert*-Butyl (3*R*,4*R*)-3-benzyl-4-formylpyrrolidine-1-carboxylate (1d)** To a solution of **S3d** (2.24 g, 7.69 mmol) in CH₂Cl₂ (70 mL) was added Dess-Martin Periodinane (4.89 g, 11.53 mmol) at 0 °C. The mixture was allowed to stir overnight while allowing to reach rt. Na₂S₂O₃ (7.29 g, 46.1 mmol) was added followed by sat. aq. NaHCO₃ (20 mL) and the mixture was stirred for 2 h. The phases were separated and the aqueous phase extracted with EtOAc (2 x 80 mL). The organic phases were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to provide a colorless oil that was purified by silica gel chromatography to afford **1d** (2.159 g, 7.46 mmol, 97% yield) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 9.49 (d, *J* = 11.9 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.18 – 7.15 (m, *J* = 7.4 Hz, 2H), 3.71 – 3.40 (m, 3H), 3.20 – 3.10 (m, 1H), 2.82 – 2.71 (m, 4H), 1.45 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 200.5, 138.9, 129.1, 128.9, 127.0, 80.0, 55.5, 54.6, 51.1, 50.6, 45.2, 44.9, 41.5, 41.2, 38.7, 28.7. HRMS-ESI: *m/z* for C₁₇H₂₄NO₃[MH⁺] calcd. 290.1751; found 290.1745. [α]_D²² = +7.5° (*c* = 5.44, CHCl₃).

Synthesis of Substrate (1e)

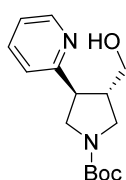


Ethyl *trans*-1-benzyl-4-(pyridin-2-yl)pyrrolidine-3-carboxylate (S1e) To a stirred solution of (*E*)-ethyl 3-(pyridin-2-yl)acrylate (3.08 g, 17.38 mmol) in toluene (42 mL, 0.41M) was added *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (4.53 g, 4.89 mL, 17.38 mmol, 91%) at 0 °C under N₂. After 10 min, a solution of TFA (134 μL, 1.74 mmol) in CH₂Cl₂ (3 mL) was added at once and the mixture stirred at 0 °C while allowing the mixture to reach rt overnight. Subsequently, the volatiles were removed *in vacuo* to provide a yellow oil that was purified by silica gel chromatography to provide **S1e** (4.69 g, 15.11 mmol, 87% yield) as a bright yellow oil. ¹H NMR (600 MHz, CDCl₃) δ 8.56 (ddd, *J* = 4.8, 1.8, 0.8 Hz, 1H), 7.58 (td, *J* = 7.6, 1.8 Hz, 1H), 7.35 (dd, *J* = 7.9, 1.0 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.11 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 4.15 – 4.09 (m, 2H), 3.88 – 3.83 (m, 1H), 3.69 (q, *J* = 13.0 Hz, 2H), 3.49 (ddd, *J* = 9.0, 7.3, 5.6 Hz, 1H), 3.15 – 3.10 (m, 2H), 2.98 (t, *J* = 9.3 Hz, 1H), 2.77 (dd, *J* = 9.1, 8.0 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 174.5, 162.1, 149.6, 139.0, 136.6, 128.9, 128.4, 127.2, 123.2, 121.8, 60.9, 60.9, 60.1, 57.2, 49.3, 49.1, 14.4. LRMS: (UV t_R = 0.44 min) *m/z* = 311.2. HRMS-ESI: *m/z* for C₁₉H₂₃N₂O₂ [MH⁺] calcd. 311.1754; found 311.1759.

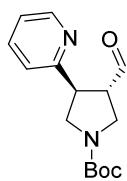


trans-(1-Benzyl-4-(pyridin-2-yl)pyrrolidin-3-yl)methanol (S2e) To a solution of **S1e** (4.67 g, 15.05 mmol) in Et₂O (130 mL) was slowly added LiAlH₄ (16.55 mL, 16.55 mmol, 1M in THF) at 0 °C. The mixture was stirred at 0 °C for 45 min followed by the very slow addition of H₂O (530 μL), NaOH (530 μL, 5M) then H₂O (1.6 mL). The white suspension was heavily stirred for 60 min followed by filtration and the resulting clear filtrate was concentrated *in vacuo* to provide a colorless oil that was purified using silica gel chromatography to provide **S2e** (2.97 g, 11.07 mmol, 74% yield) as a colorless dense oil. ¹H NMR (600 MHz, CDCl₃) δ 8.52 - 8.49 (m, 1H), 7.61 (td, J = 7.7, 1.8 Hz, 1H), 7.37 - 7.30 (m, 4H), 7.28 - 7.23 (m, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.14 - 7.11 (m, 1H), 3.78 - 3.72 (m, 2H), 3.70 (d, J = 12.9 Hz, 1H), 3.64 (d, J = 12.9 Hz, 1H), 3.47 (dd, J = 14.9, 7.8 Hz, 1H), 3.30 - 3.25 (m, 1H), 2.75 (t, J = 9.0 Hz, 1H), 2.71 (t, J = 8.8 Hz, 1H), 2.67 (dd, J = 9.3, 4.5 Hz, 1H), 2.62 - 2.57 (m, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 162.8, 148.9, 139.0, 137.0, 128.9, 128.5, 127.3, 121.6, 121.5, 67.1, 60.5, 59.7, 57.8, 50.3, 46.6. LC MS: (UV t_R = 0.30 min) *m/z* = 269.2. HRMS-ESI: *m/z* for C₁₇H₂₁N₂O [MH⁺] calcd. 269.1648; found 269.1649.

Racemic **S2e** was separated using chiral SFC on a ChiralPak AD (300×50 mm I.D., 10μm) column using 30% modifier with 0.1% NH₃H₂O in EtOH. (t_R peak 1 = 2.30 min; t_R peak 2 = 2.64 min). Peak 2 was used in the subsequent reaction.

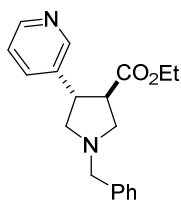


(3R,4R)-tert-Butyl 3-(hydroxymethyl)-4-(pyridin-2-yl)pyrrolidine-1-carboxylate (S3e) To an inert and degassed solution of (3R,4R)-**S2e** (1.29 g, 4.81 mmol) in MeOH (48 mL, 0.1M) was added Pd/C (512 mg, 0.481 mmol, 10%) followed by NH₄CHOO (3.0 g, 48 mmol). The mixture was refluxed for 1 h and subsequently allowed to reach rt followed by filtration of the catalyst by Celite. To the resulting filtrate was then added di-*tert*-butyl dicarbonate (1.154 g, 5.29 mmol) and stirring was continued for 2 h at rt. Evaporation of volatiles *in vacuo* provided a crude solid that was suspended in CH₂Cl₂ and filtered, the resulting filtrate was concentrated and subjected to silica gel chromatography to provide **S3e** (0.85 g, 3.1 mmol, 64% yield) as a dense colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 8.55 - 8.49 (m, 1H), 7.72 - 7.66 (m, 1H), 7.23 - 7.16 (m, 2H), 4.16 - 3.98 (m, 1H), 3.77 - 3.64 (m, 3H), 3.52 (t, J = 10.5 Hz, 1H), 3.46 - 3.36 (m, 1H), 3.21 - 3.10 (m, 1H), 2.75 - 2.67 (m, 1H), 1.47 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 159.7, 159.6, 154.6, 154.5, 148.8, 148.5, 137.7, 137.4, 122.6, 122.5, 122.4, 79.8, 64.3, 64.1, 51.7, 51.3, 50.3, 49.9, 49.0, 48.6, 46.0, 45.3, 28.7. Mixture of conformers. HRMS-ESI: *m/z* for C₁₅H₂₃N₂O₃ [MH⁺] calcd. 279.1703; found 279.1704. [α]_D²² = +8.5° (c = 0.176, CHCl₃).



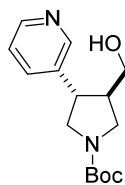
(3R,4R)-tert-Butyl 3-formyl-4-(pyridin-2-yl)pyrrolidine-1-carboxylate (1e) Synthesized using H₂O-accelerated DMP oxidation.³ To a solution of **S3e** (0.85 g, 3.1 mmol) in CH₂Cl₂ (18 mL, 0.17M) was added Dess-Martin Periodinane (1.94 g, 4.6 mmol) at rt. To the stirred suspension was then slowly added water (61 μL, 3.36 mmol). Stirring was continued for 30 min followed by the addition of Et₂O (150 mL) and the resulting suspension was gently concentrated *in vacuo* to a few mL after which Et₂O (150 mL) was added. The ethereal solution was washed with a 1:1 mixture of sat. aq. NaHCO₃ and 10% Na₂S₂O₃ until the phases became clear. The aqueous phase was back-extracted with Et₂O (100 mL) and the combined ethereal phases were washed with brine, dried over Na₂SO₄, filtered, concentrated *in vacuo* and purified by silica gel chromatography to provide **1e** (0.65 g, 2.35 mmol, 77% yield) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 9.77 (d, J = 10.9 Hz, 1H), 8.56 (d, J = 4.3 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.21 - 7.17 (m, 2H), 3.96 - 3.55 (m, 6H), 1.49 - 1.43 (m, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 200.5, 200.4, 158.6, 154.4, 150.0, 149.9, 137.0, 122.9, 122.8, 122.6, 80.0, 55.7, 55.1, 51.6, 51.2, 46.9, 46.4, 45.6, 28.7. Mixture of conformers. HRMS-ESI: *m/z* for C₁₅H₂₁N₂O₃ [MH⁺] calcd. 277.1547; found 277.1549. [α]_D²² = -12.9° (c = 0.94, CHCl₃).

Synthesis of Substrate (1f)



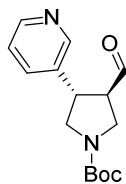
Ethyl trans-1-benzyl-4-(pyridin-3-yl)pyrrolidine-3-carboxylate (S1f) To a stirred solution of (*E*)-ethyl 3-(pyridin-3-yl)acrylate (3.43 g, 19.33 mmol) in toluene (47 mL, 0.41M) was added *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (5.04 g, 5.43 mL, 19.33 mmol, 91%) at 0 °C under N₂. After 10 min, a solution of TFA (149 μL, 1.93 mmol) in CH₂Cl₂ (4 mL) was added over the course of 5 min and stirring was continued at 0 °C while allowing the mixture to reach rt over 3 days. Subsequently, the solvent was removed *in vacuo* to provide a brown oil that was purified using silica gel chromatography to provide **S1f** (1.86 g, 5.99 mmol, 31% yield) as a yellow oil. ¹H NMR (600 MHz, CDCl₃) δ 8.58 (d, J = 2.2 Hz, 1H), 8.46 (dd, J = 4.7, 1.3 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.38 - 7.35 (m, 2H), 7.34 - 7.31 (m, 2H), 7.28 - 7.25 (m, 1H), 7.25 - 7.22 (m, 1H), 4.18 - 4.09 (m, 2H), 3.71 (d, J = 13.0 Hz, 1H), 3.68 - 3.63 (m, 2H), 3.14 (t, J = 8.9 Hz, 1H), 3.04 (dd, J = 14.9, 7.5 Hz, 1H), 2.96 (t, J = 8.8 Hz, 1H), 2.80 (ddd, J = 12.3, 9.3, 6.5 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 173.7,

149.3, 148.1, 140.1, 138.7, 134.9, 128.6, 128.4, 127.2, 123.6, 61.3, 61.0, 59.8, 57.3, 51.8, 44.4, 14.2. HRMS-ESI: m/z for $C_{19}H_{23}N_2O_2$ $[MH^+]$ calcd. 311.1754; found 311.1759.



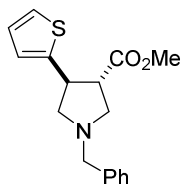
tert-Butyl trans-3-(hydroxymethyl)-4-(pyridin-3-yl)pyrrolidine-1-carboxylate (S2f) To a solution of **S1f** (1.86 g, 5.99 mmol) in THF (30 mL, 0.2M) at 0 °C, $LiAlH_4$ (6.59 mL, 6.59 mmol, 1M) was added and the mixture stirred for 30 min after which the mixture was diluted with Et_2O (100 mL). Subsequent "fieser work-up"; very slow addition of H_2O (0.204 mL) followed by NaOH (0.204 mL, 5M) and H_2O (0.612 mL) followed by heavy stirring for 30 min, filtration of precipitates, concentration of the filtrate *in vacuo* provided a colorless oil that was rediluted in MeOH (30 mL) and degassed with argon for 15 min. To the degassed solution was subsequently added Pd/C (638 mg, 0.60 mmol, 10%) and NH_4CHO_3 (3.78 g, 59.9 mmol) after which the mixture was refluxed for 35 min. The heating was discontinued and the mixture cooled to rt and passed through a plug of Celite. To the clear filtered solution was added THF (35 mL) and di-*tert*-butyl dicarbonate (1.37 g, 6.29 mmol) and the mixture was stirred for 2 h and concentrated *in vacuo* to yield a crude oil that was purified using silica gel chromatography to provide **S2f** (1.23 g, 4.42 mmol, 74% yield) as a colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 8.51 - 8.46 (m, 2H), 7.61 - 7.58 (m, 1H), 7.28 (dd, J = 7.9, 4.8 Hz, 1H), 3.91 - 3.72 (m, 2H), 3.69 - 3.64 (m, 1H), 3.55 (dd, J = 16.4, 8.7 Hz, 1H), 3.43 - 3.31 (m, 2H), 3.28 - 3.16 (m, 1H), 2.51 - 2.44 (m, 1H), 1.49 - 1.44 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 149.6, 148.6, 136.2, 135.1, 124.1, 124.0, 79.8, 62.1, 62.0, 60.6, 53.2, 52.6, 49.2, 48.7, 48.5, 47.5, 43.9, 43.2, 28.7, 21.3, 14.4. Mixture of conformers and a minor amount of EtOAc. LRMS: (UV t_R = 0.34 min) m/z = 279.1. HRMS-ESI: m/z for $C_{15}H_{23}N_2O_3$ $[MH^+]$ calcd. 279.1703; found 279.1709.

Racemic **S2f** was separated using chiral SFC on a Lux Cellulose-1 column with 20% modifier containing 0.1% diethylamine in EtOH. (t_R peak 1 = 2.740 min; t_R peak 2 = 3.286 min). Peak 2 was used in the subsequent reaction.

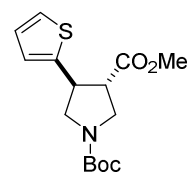


(3R,4S)-tert-Butyl 3-formyl-4-(pyridin-3-yl)pyrrolidine-1-carboxylate (1f) To a solution of (3R,4S)-**S2f** (525 mg, 1.886 mmol) in CH_2Cl_2 (11 mL, 0.17M) was added Dess-Martin Periodinane (1.20 g, 2.83 mmol) at rt. To the stirred suspension was then slowly added H_2O (37 μ L). Stirring was continued for 50 min followed by the addition of Et_2O (150 mL) and the resulting suspension was gently concentrated *in vacuo* to a few mL after which Et_2O (150 mL) was added. The ethereal solution was washed with a 1:1 mixture of sat. aq. $NaHCO_3$ and 10% $Na_2S_2O_3$ until the phases became clear. The aqueous phase was back-extracted with Et_2O (2 x 100 mL) and the combined ethereal phases were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to provide a crude oil that was purified by silica gel chromatography to provide **1f** (361 mg, 1.305 mmol, 69% yield) as a colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 9.71 - 9.68 (m, 1H), 8.56 - 8.54 (m, 1H), 8.54 - 8.51 (m, 1H), 7.62 - 7.58 (m, 1H), 7.33 - 7.28 (m, 1H), 3.94 - 3.65 (m, 4H), 3.53 - 3.43 (m, 1H), 3.26 - 3.17 (m, 1H), 1.50 - 1.45 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.12, 199.06, 154.0, 149.1, 149.0, 135.1, 135.0, 134.6, 123.8, 80.2, 57.2, 56.2, 52.2, 51.7, 45.3, 45.2, 42.3, 41.8, 28.4. Mixture of conformers.

Synthesis of Substrate (1g)

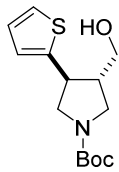


Methyl trans-1-benzyl-4-(thiophen-2-yl)pyrrolidine-3-carboxylate (S1g) To a stirred solution of (*E*)-methyl 3-(thiophen-2-yl)acrylate (1.56 g, 9.27 mmol) in toluene (23 mL, 0.41M) was added *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (2.75 g, 2.97 mL, 11.13 mmol, 96%) at 0 °C under N_2 . After 10 min, a solution of TFA (71 μ L, 0.93 mmol) in CH_2Cl_2 (2 mL) was added over the course of 10 min at 0 °C. The mixture was stirred for 1 h at 0 °C after which the solvent was removed *in vacuo* to provide a yellow oil that was purified using silica gel chromatography to afford **S1g** (2.1 g, 6.97 mmol, 75% yield) as a colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 7.39 - 7.30 (m, 4H), 7.27 - 7.24 (m, 1H), 7.15 (dd, J = 4.9, 1.4 Hz, 1H), 6.92 - 6.88 (m, 2H), 4.01 - 3.97 (m, 1H), 3.73 - 3.64 (m, 5H), 3.12 (dt, J = 8.8, 6.3 Hz, 1H), 3.07 - 3.00 (m, 2H), 2.88 (dd, J = 9.4, 6.3 Hz, 1H), 2.74 (dd, J = 9.2, 6.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 147.5, 138.7, 128.7, 128.3, 127.1, 126.6, 124.0, 123.8, 61.9, 59.7, 56.8, 52.1, 52.0, 42.4.



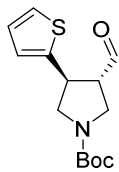
trans-1-tert-Butyl 3-methyl 4-(thiophen-2-yl)pyrrolidine-1,3-dicarboxylate (S2g) To a solution of **S1g** (2.455 g, 8.14 mmol) in toluene (80 mL) was added 1-chloroethyl carbonochloridate (2.33 g, 1.76 mL, 16.29 mmol) at rt and the mixture was refluxed for 3 h after which an additional equivalent of 1-chloroethyl carbonochloridate was added. The reflux was continued for 1 h after which the mixture was allowed to cool to rt. EtOAc (150 mL) was added and the organics were washed with sat. aq. $NaHCO_3$ (40 mL) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was dissolved in MeOH (55 mL) and refluxed for 2 h, allowed to cool to rt followed by removal of the volatiles *in vacuo*. Subsequently, CH_2Cl_2 (60 mL) was added followed by Et_3N (1.14 mL, 8.14 mmol) and di-*tert*-butyl dicarbonate (2.13 g, 9.77 mmol) at rt. The reaction mixture was stirred

for 2 h after which the volatiles were removed *in vacuo* and the crude product purified by silica gel chromatography to provide **S2g** (1.615 g, 5.19 mmol, 64% yield) as a colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 7.20 - 7.18 (m, 1H), 6.95 - 6.93 (m, 1H), 6.91 - 6.89 (m, 1H), 3.99 - 3.79 (m, 3H), 3.69 (s, 3H), 3.61 - 3.53 (m, 1H), 3.51 - 3.40 (m, 1H), 3.19 - 3.11 (m, 1H), 1.48 - 1.44 (m, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 172.62, 172.53, 154.12, 142.71, 142.55, 127.11, 124.86, 124.83, 124.30, 80.06, 53.12, 52.54, 52.46, 51.73, 50.76, 49.02, 48.69, 43.12, 42.42, 28.64. Mixture of conformers. LRMS: (UV t_{R} = 0.81 min) m/z = 256.0.



tert-Butyl trans-3-(hydroxymethyl)-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (S3g) To a solution of **S2g** (1.615 g, 5.19 mmol) in THF (26 mL, 0.2M) was slowly added LiAlH_4 (5.70 mL, 5.70 mmol, 1M in THF) at 0 °C and the mixture was stirred for 30 min after which Et_2O (100 mL) was added. Subsequent "fieser work-up"; very slow addition of H_2O (177 μL) followed by NaOH (177 μL , 5M) and H_2O (531 μL) followed by heavy stirring for 30 min, filtration of precipitates and concentration of the filtrate *in vacuo* to provide **S3g** (1.465 g, 5.17 mmol, 100% yield) as a colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 7.20 - 7.18 (m, 1H), 6.96 - 6.93 (m, 1H), 6.91 - 6.89 (m, 1H), 3.95 - 3.83 (m, 1H), 3.78 - 3.75 (m, 2H), 3.63 - 3.58 (m, 1H), 3.54 - 3.27 (m, 3H), 2.49 - 2.42 (m, 1H), 1.78 (br, 1H), 1.48 - 1.44 (m, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.54, 143.85, 143.78, 127.13, 124.86, 124.04, 79.70, 62.60, 62.37, 54.17, 53.53, 49.45, 49.21, 48.62, 48.58, 41.69, 41.03, 28.70.

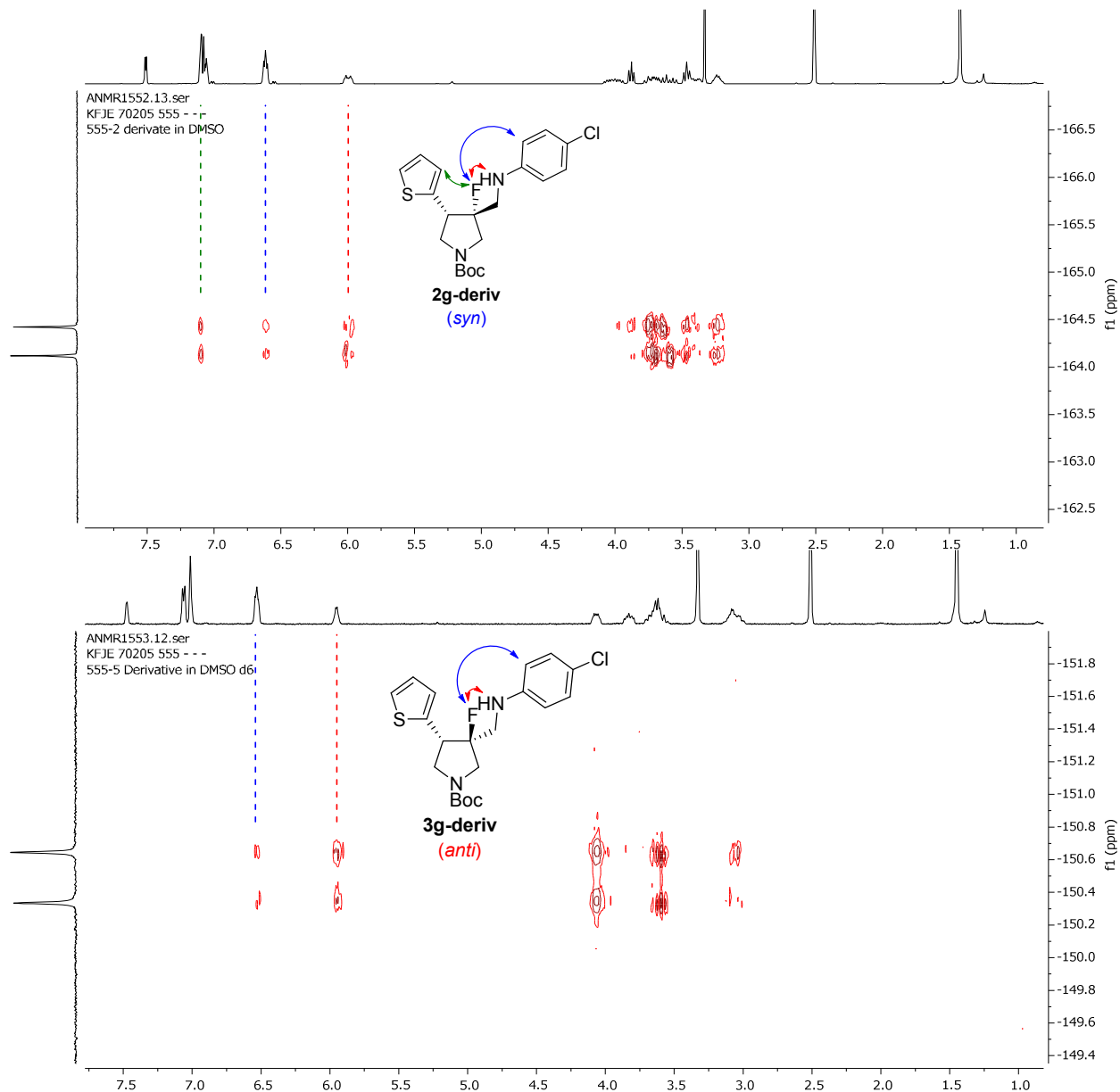
Racemic **S3g** was separated by chiral SFC on a Lux Cellulose-2 column using 40% modifier with 0.1% diethylamine in EtOH (t_{R} peak 1 = 1.892 min; t_{R} peak 2 = 2.229 min with 20% modifier). Peak 1 was used in the subsequent reaction.



(3S,4S)-tert-Butyl 3-formyl-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (1g) To a solution of (3*R*,4*R*)- **S3g** (442 mg, 1.560 mmol) in CH_2Cl_2 (9.17 mL, 0.17M) was added Dess-Martin Periodinane (992 mg, 2.340 mmol) at rt. To the stirred suspension was then slowly added H_2O (31 μL). Stirring was continued for 50 min followed by the addition of Et_2O (150 mL) and the resulting suspension was gently concentrated *in vacuo* to a few mL after which Et_2O (100 mL) was added. The ethereal solution was washed with a 1:1 mixture of sat. aq. NaHCO_3 and 10% $\text{Na}_2\text{S}_2\text{O}_3$ until the phases became clear. The aqueous phase was back-extracted with Et_2O (2 x 80 mL) and the combined ethereal phases were dried over MgSO_4 , filtered and concentrated *in vacuo* to provide a crude oil that was purified by silica gel chromatography to provide **1g** (435 mg, 1.546 mmol, 99% yield) as a colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 9.72 (br, 1H), 7.23 - 7.20 (m, 1H), 6.97 - 6.95 (m, 1H), 6.92 (br, 1H), 4.00 - 3.67 (m, 4H), 3.55 - 3.43 (m, 1H), 3.24 - 3.16 (m, 1H), 1.50 - 1.44 (m, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 199.68, 154.20, 142.82, 127.29, 125.05, 124.95, 124.62, 124.56, 80.26, 58.35, 57.46, 53.29, 52.81, 45.39, 45.22, 40.56, 40.11, 28.65. Mixture of conformers. LRMS: (UV t_{R} = 0.72) m/z = 226.0. HRMS-ESI: m/z for $\text{C}_{14}\text{H}_{20}\text{NO}_3\text{S}$ [MH^+] calcd. 282.1158; found 282.1158. $[\alpha]_{\text{D}}^{22} = -27.6^\circ$ (c = 1.2, CHCl_3).

Relative Configuration of Products

The relative configuration of the products was assigned using heteronuclear through-space NOE investigation on *p*-chloroaniline derivatives of **2g** and **3g**, namely **2g-deriv** and **3g-deriv**. As indicated below, the fluorine atom only interacts with the thienyl proton in the *syn*-product **2g-deriv**. The relative configurations of the other fluorinated products were assigned analogously.



Formation of the reduced amines **2g-deriv** and **3g-deriv**: To a solution of **2g** or **3g** (19mg, 0.063 mmol) in 1,2-dichloroethane (2 mL) was added 4-chloroaniline (8.1 mg, 0.063 mmol) followed by sodium triacetoxyborohydride (19 mg, 0.089 mmol) and the mixture was stirred at rt for 16 h followed by the addition of NaBH₄ (2.4 mg, 0.063 mmol) and continued stirring for 1 h. Subsequently, sat. aq. NaHCO₃ (1.5 mL) was added and the phases were separated followed by extraction of the aqueous phase with CH₂Cl₂ (2 x 3 mL) after which the combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide a crude residue that was purified using silica gel chromatography to provide the reduced amine **2g-deriv** or **3g-deriv**.

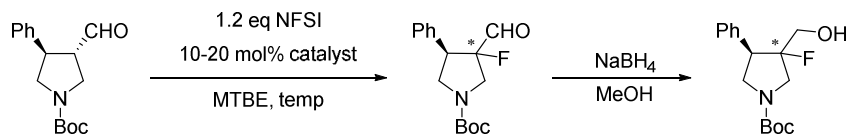
2g-deriv (12 mg, 0.029 mmol, 46% yield) as a yellow oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.51 (d, *J* = 5.1 Hz, 1H), 7.13 – 7.04 (m, 4H), 6.65 – 6.58 (m, 2H), 6.04 – 5.95 (m, 1H), 4.10 – 3.93 (m, 1H), 3.91 – 3.85 (m, 1H), 3.78 – 3.53 (m, 2H), 3.50 – 3.35 (m,

2H), 1.43 – 1.40 (m, 9H). ^{13}C NMR (151 MHz, DMSO-*d*6) δ 152.7, 152.6, 146.9, 146.9, 135.5, 135.3, 127.9, 127.8, 127.1, 126.2, 126.2, 126.2, 125.3, 125.3, 118.9, 118.8, 114.5, 113.0, 112.9, 102.4, 101.8, 101.2, 100.6, 78.4, 53.8, 53.7, 53.5, 53.4, 50.6, 50.3, 44.8, 44.6, 44.5, 44.3, 44.1, 44.0, 43.4, 43.3, 27.5, 27.4 (conformers). ^{19}F NMR (471 MHz, DMSO-*d*6) δ -164.12, -164.42 (two conformers). HRMS-ESI: m/z for $\text{C}_{20}\text{H}_{25}\text{ClFN}_2\text{O}_2\text{S}$ $[\text{MH}^+]$ calcd. 411.1304; found 411.1296.

3g-deriv (9 mg, 0.022 mmol, 35% yield) as a yellow oil. ^1H NMR (600 MHz, DMSO-*d*6) δ 7.49 – 7.45 (m, 1H), 7.08 – 7.04 (m, 2H), 7.02 – 6.99 (m, 2H), 6.55 – 6.49 (m, 2H), 5.99 – 5.94 (m, 1H), 4.10 – 4.02 (m, 1H), 3.86 – 3.77 (m, 1H), 3.70 – 3.53 (m, 3H), 3.13 – 2.98 (m, 2H), 1.47 – 1.42 (m, 9H). ^{13}C NMR (151 MHz, DMSO-*d*6) δ 152.9, 152.8, 147.0, 146.9, 139.5, 139.4, 127.8, 126.4, 125.8, 125.7, 124.9, 124.9, 118.8, 118.7, 112.9, 112.9, 104.7, 104.1, 103.5, 102.9, 78.6, 78.6, 51.7, 51.5, 51.4, 51.1, 50.6, 45.4, 45.2, 44.6, 44.6, 44.5, 27.5, 27.5 (conformers). ^{19}F NMR (471 MHz, DMSO-*d*6) δ -150.33, -150.64 (two conformers). HRMS-ESI: m/z for $\text{C}_{20}\text{H}_{25}\text{ClFN}_2\text{O}_2\text{S}$ $[\text{MH}^+]$ calcd. 411.1304; found 411.1302.

Screening of Additional Catalysts

The expanded screening of organocatalysts were performed on the enantiomer of **1a** ((3*S*,4*R*)-**1a**). Both the conversion and crude dr provided are obtained by LCMS after reduction to the alcohol.

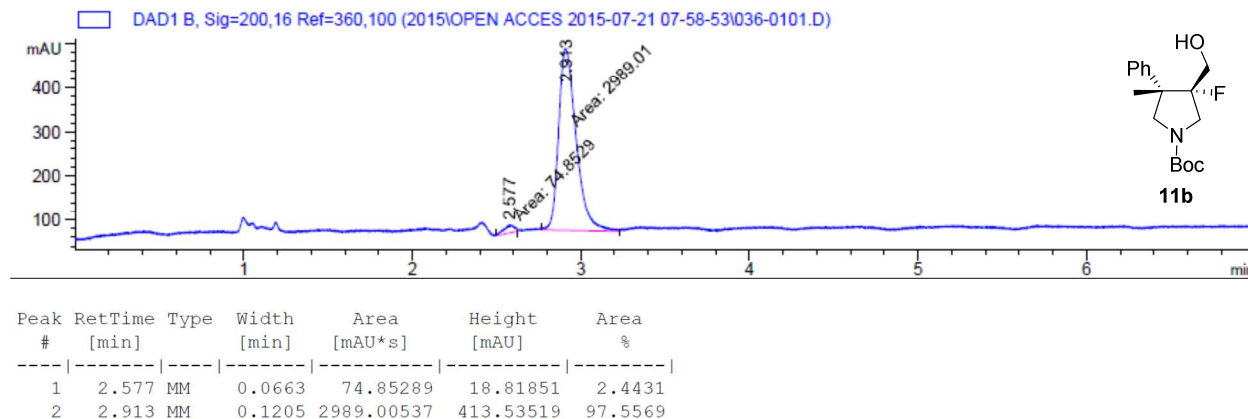


Entry	Catalyst	Temp [°C]	Conversion [%]	D.r. (fast : slow - TIC)
1		21	-	16 : 84
2		21	-	3 : 97
3		40	0	-
4		40	~50	93 : 7
5		40	~40	66 : 34
6		21	~15	65 : 35
7		40	~45	70 : 30
8		40	~33	89 : 11
9		40	~33	78 : 22
10		40	~66	69 : 31

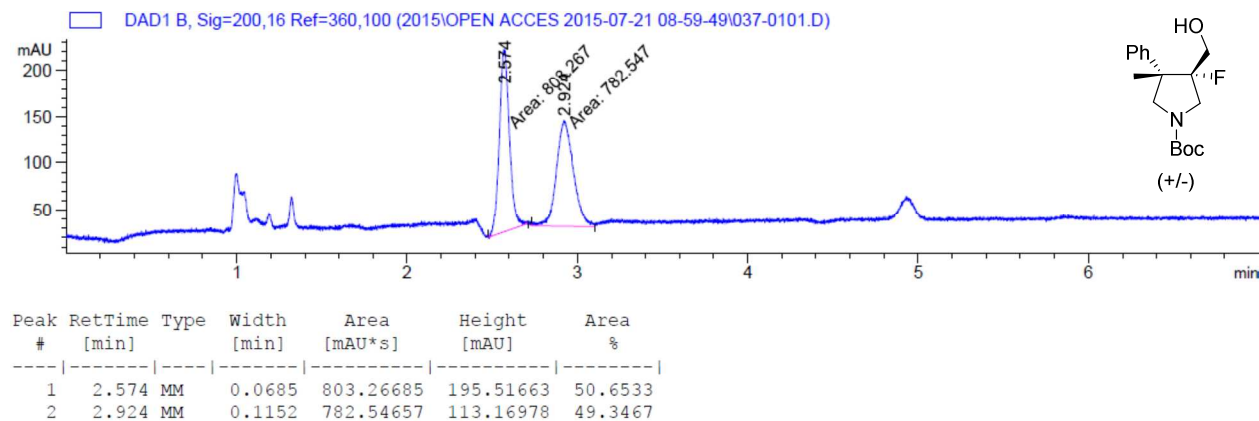
Chiral SFC Data

Determination of *ee* for **11b**.

Enantioenriched sample:

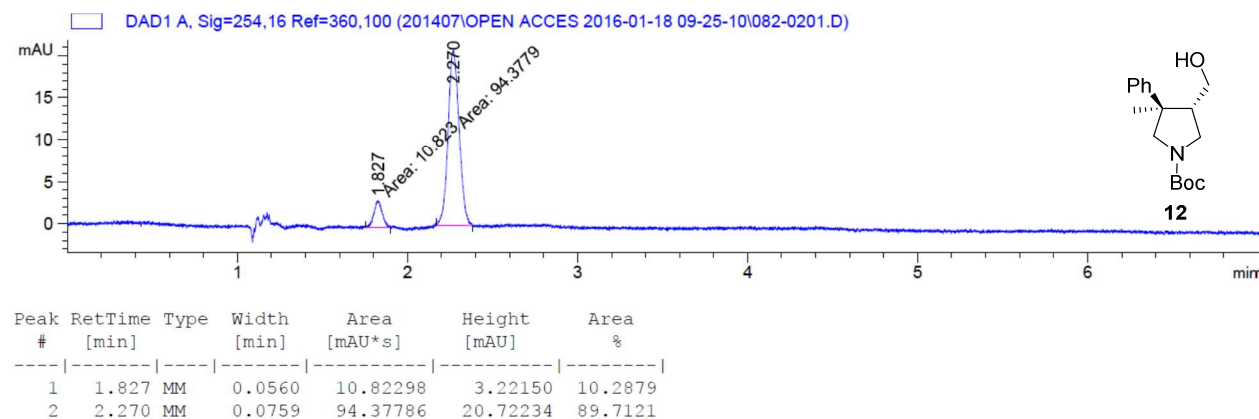


Racemic sample:

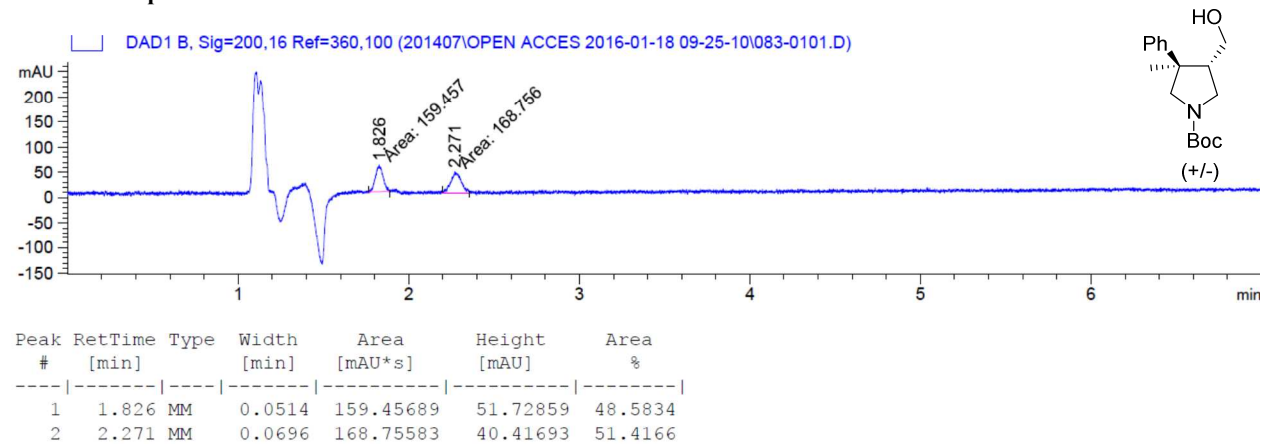


Determination of *ee* for **12**.

Enantioenriched sample:



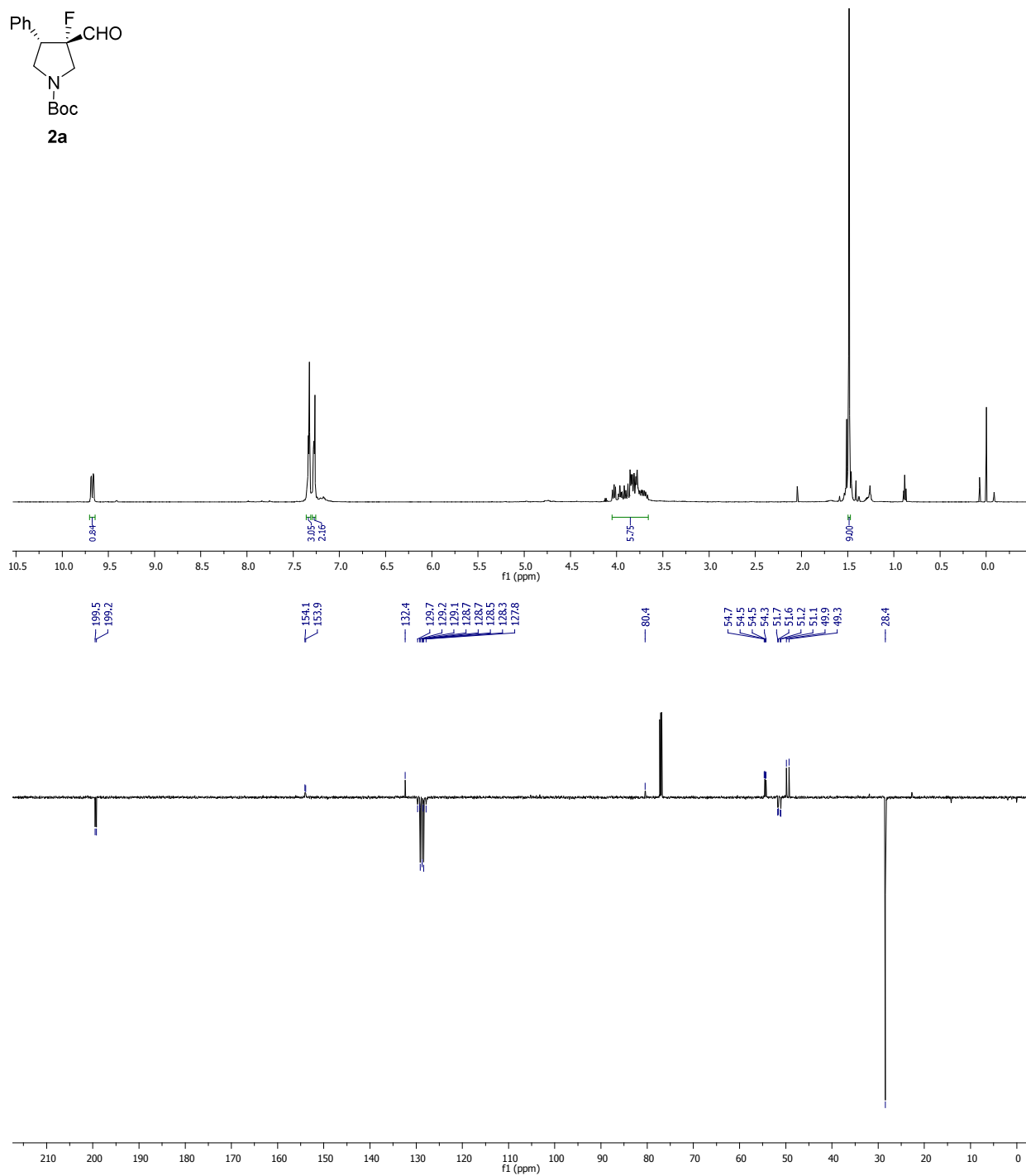
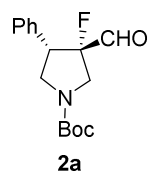
Racemic sample:

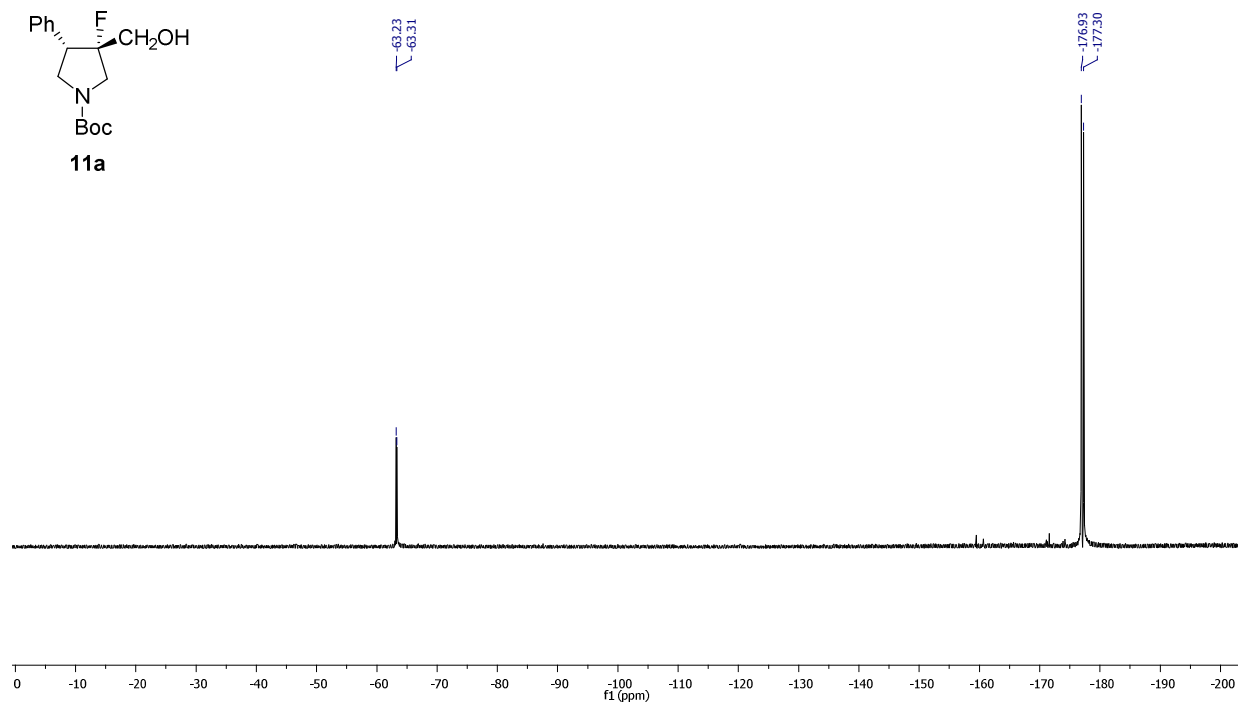
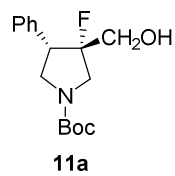


NMR Spectre

tert-Butyl (3*S*,4*S*)-3-fluoro-3-formyl-4-phenylpyrrolidine-1-carboxylate (**2a**)

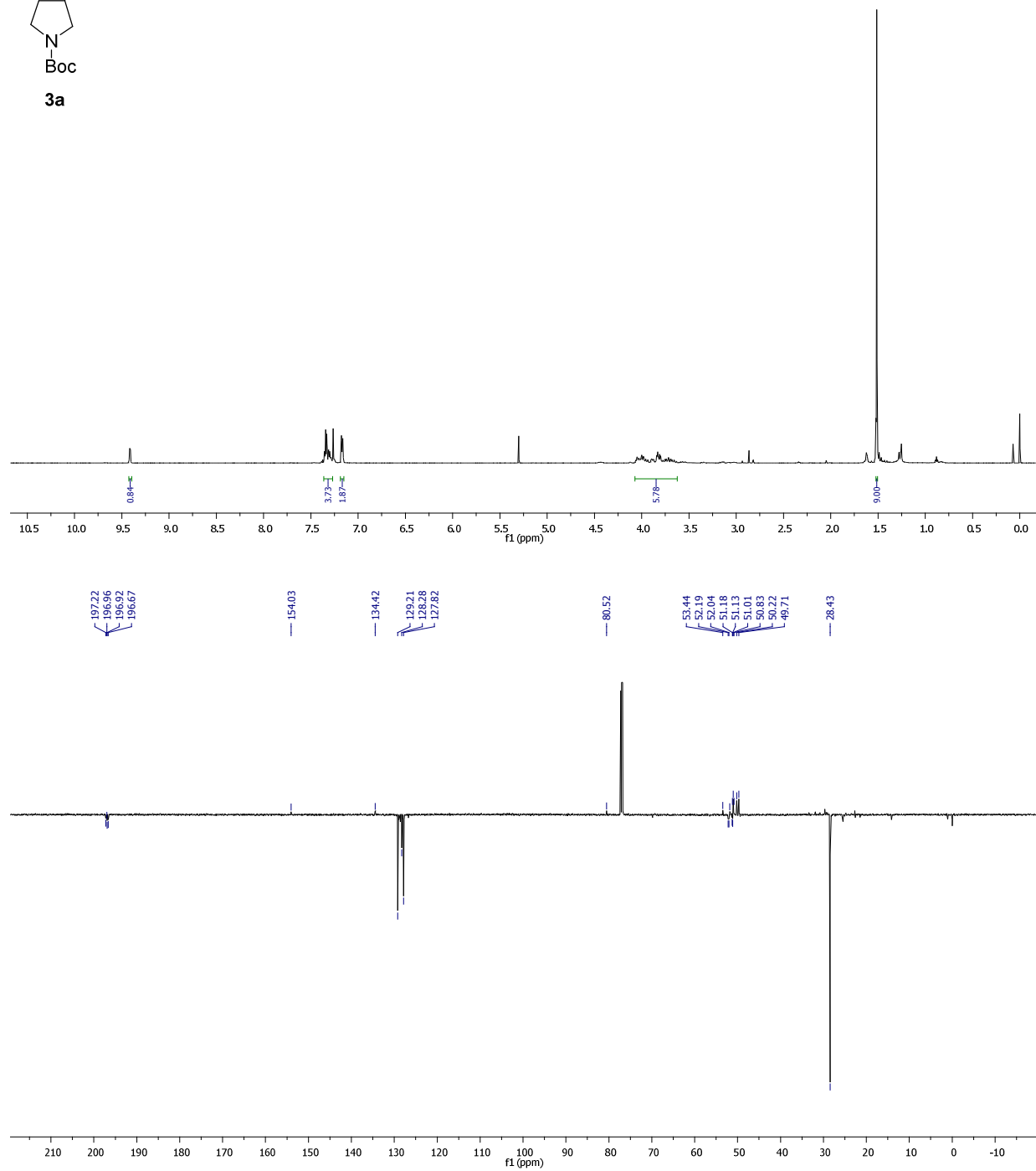
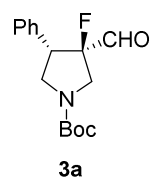
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

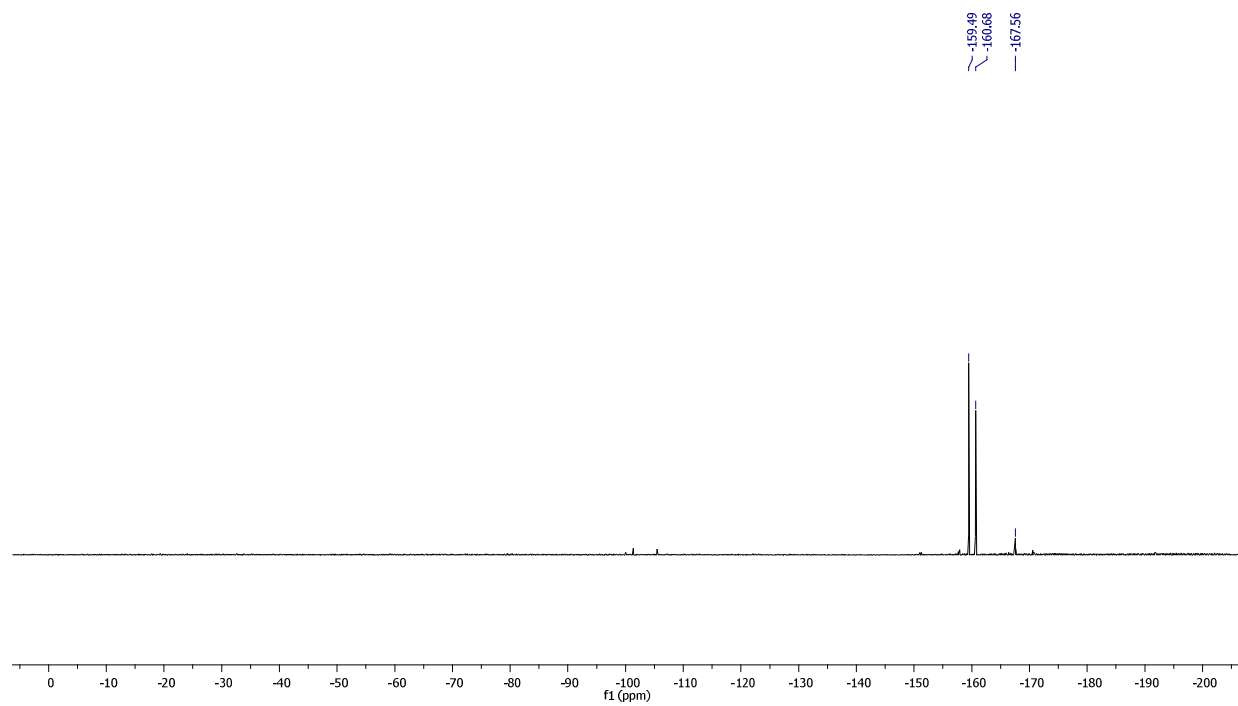




***tert*-Butyl (3*R*,4*S*)-3-fluoro-3-formyl-4-phenylpyrrolidine-1-carboxylate (3a)**

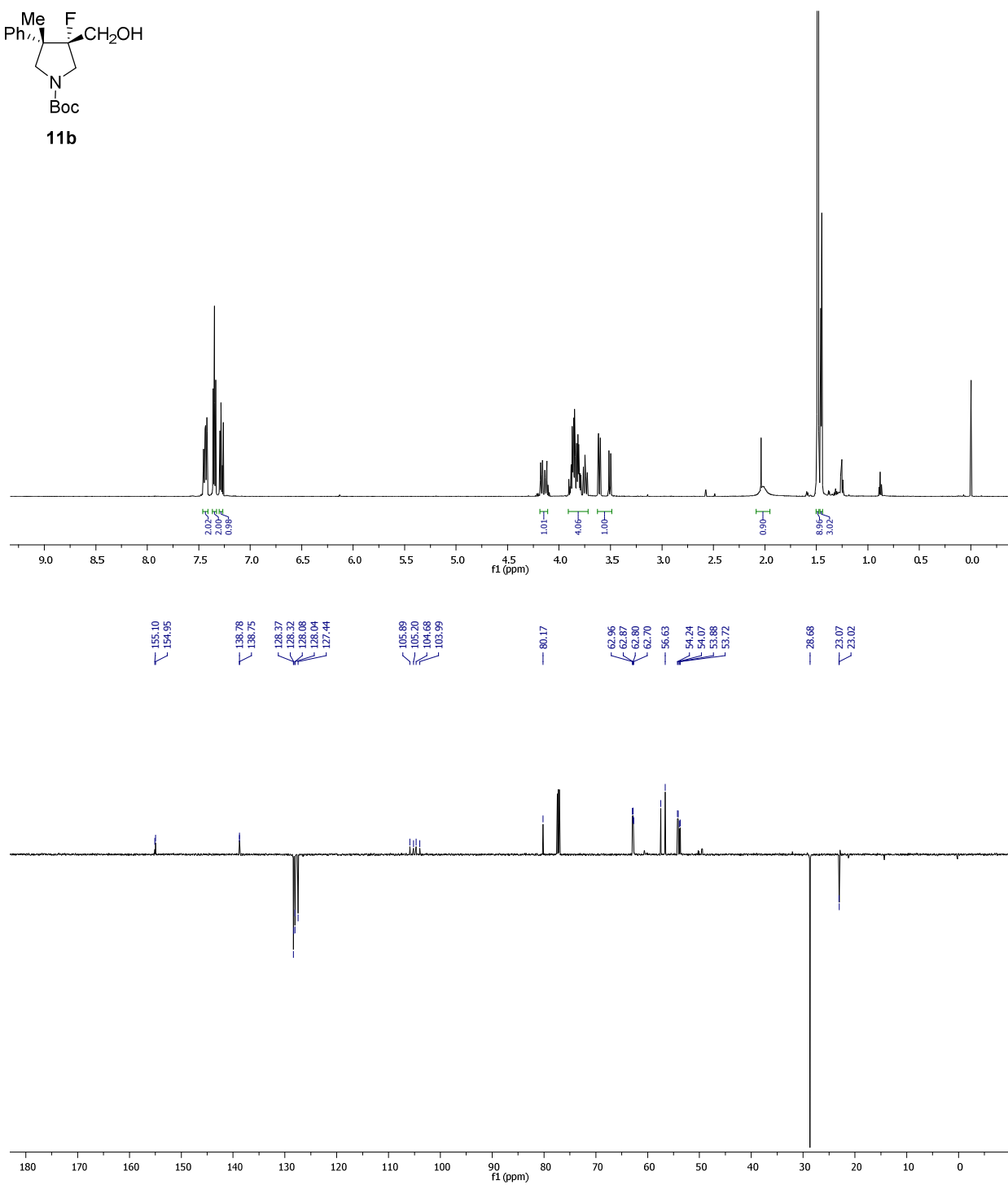
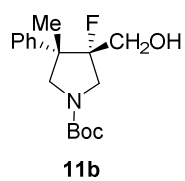
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

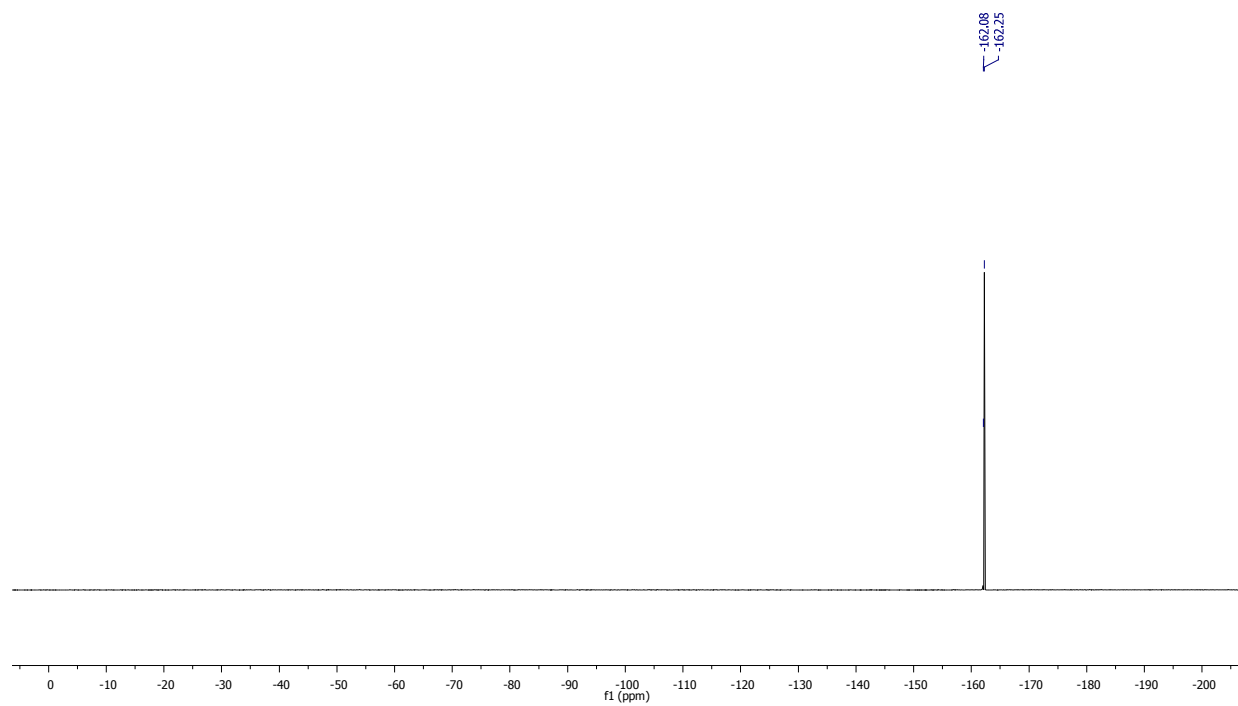




***tert*-Butyl (3*S*,4*S*)-3-fluoro-3-formyl-4-methyl-4-phenylpyrrolidine-1-carboxylate (11b)**

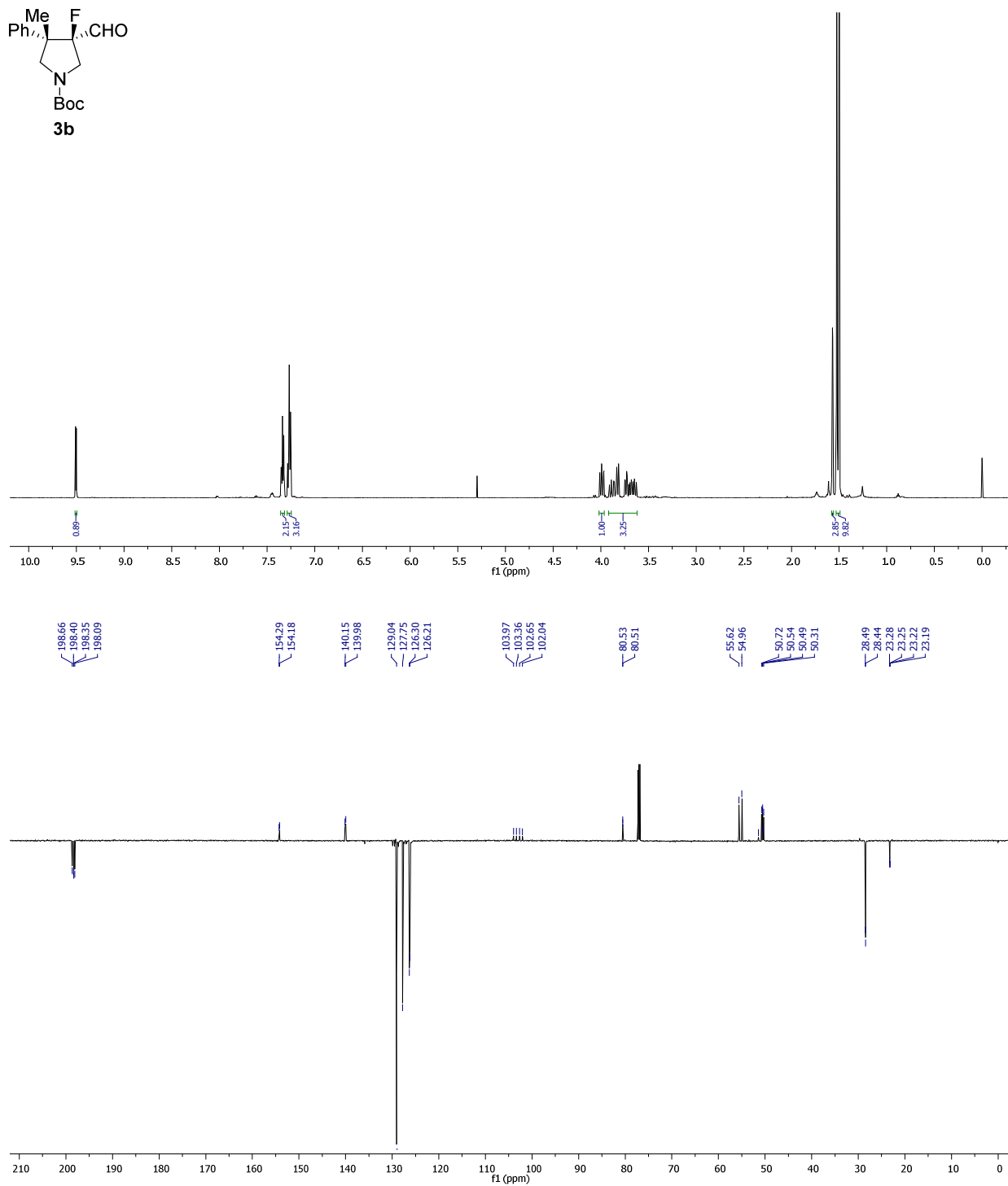
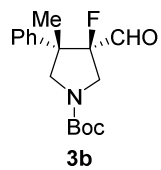
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

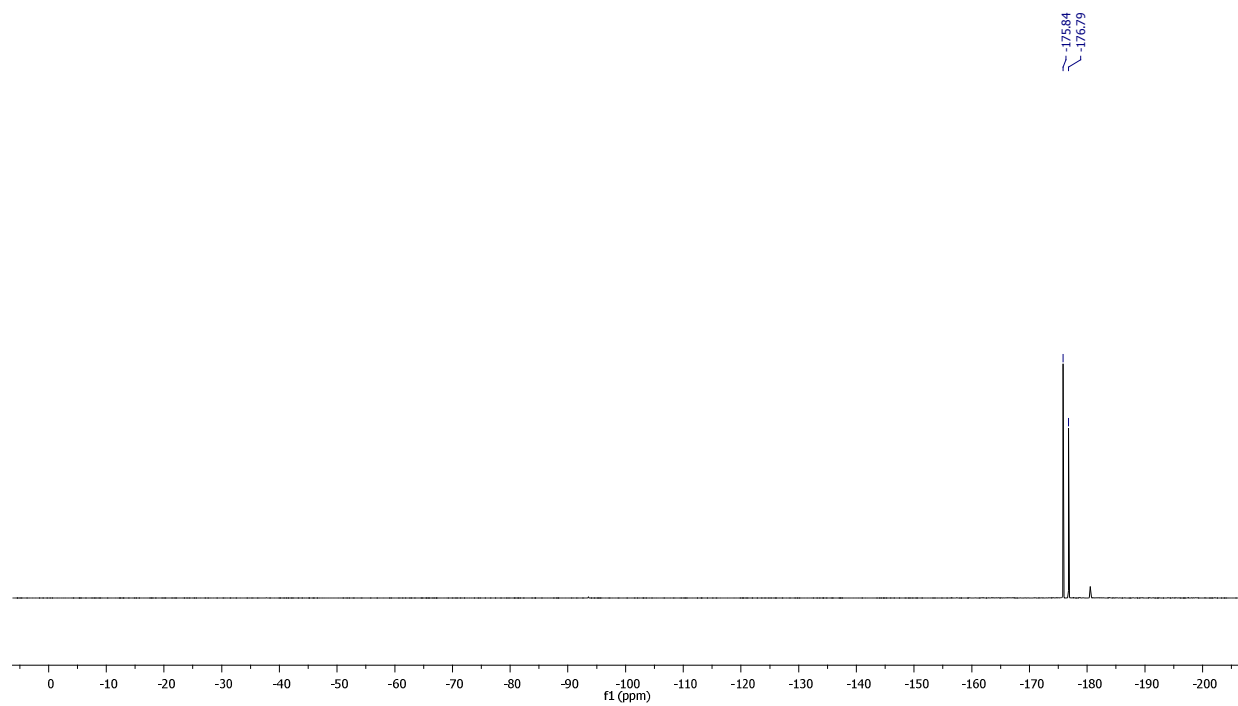




***tert*-Butyl (3*R*,4*S*)-3-fluoro-3-formyl-4-methyl-4-phenylpyrrolidine-1-carboxylate (3b)**

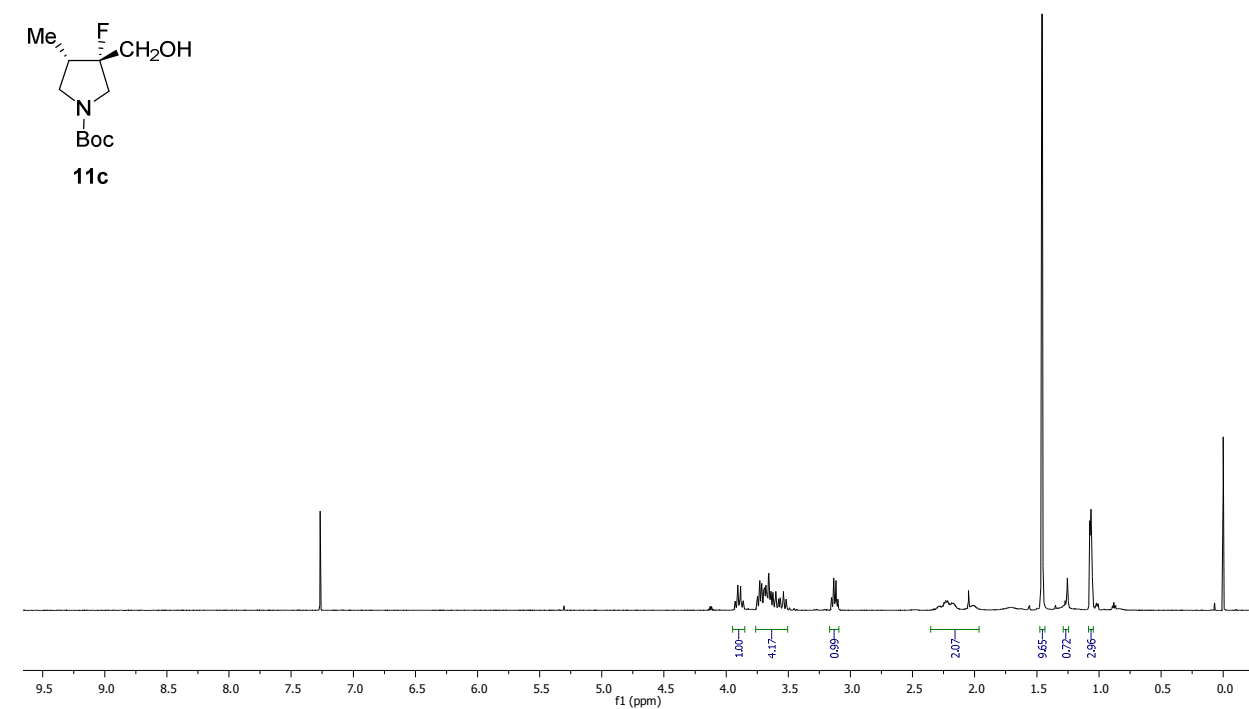
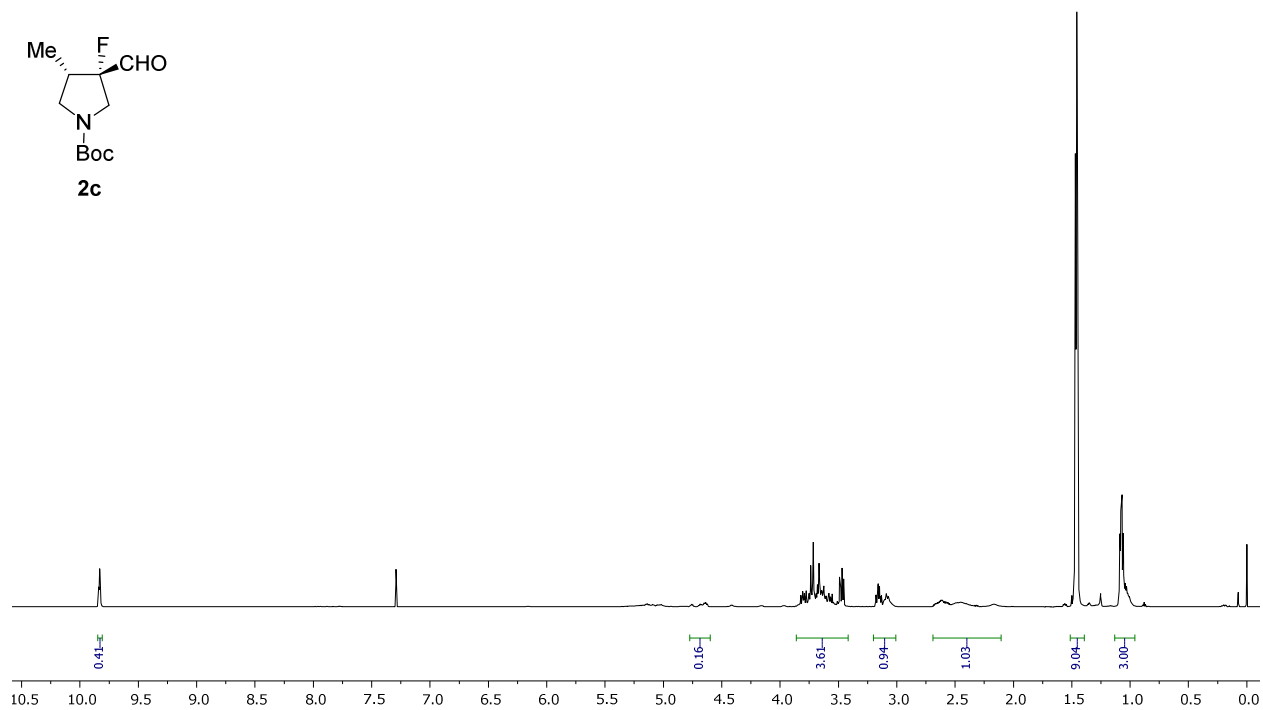
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

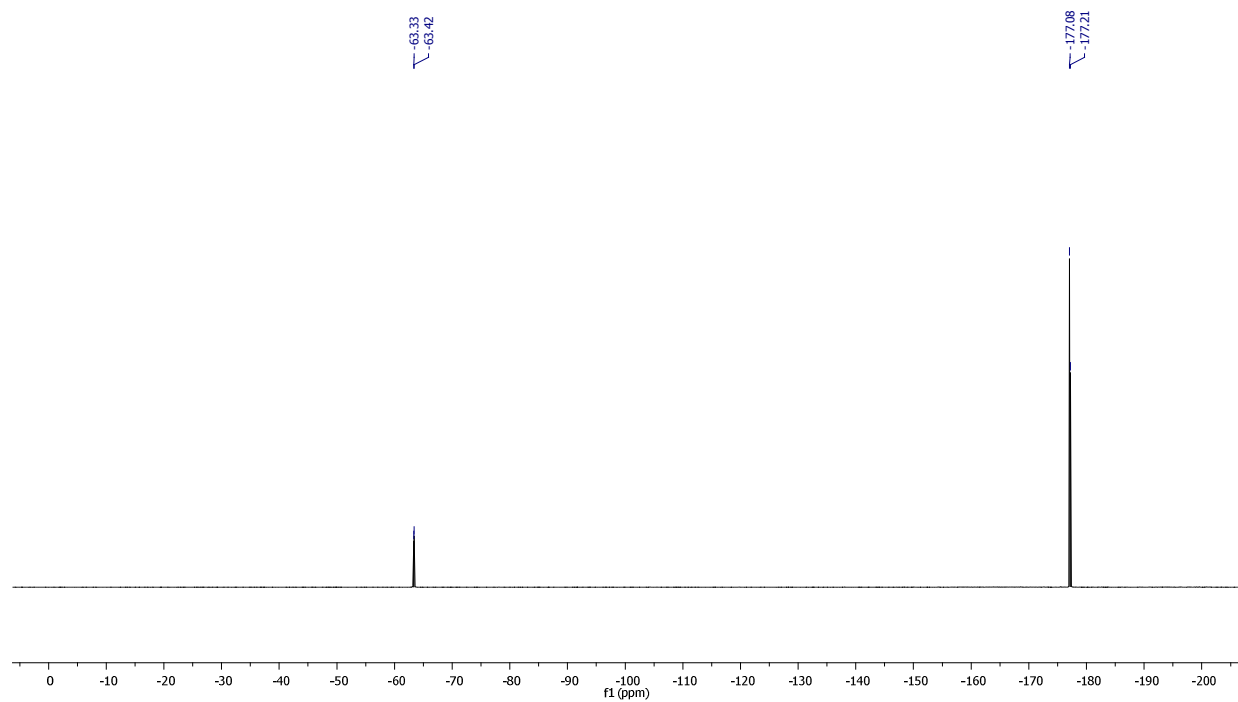
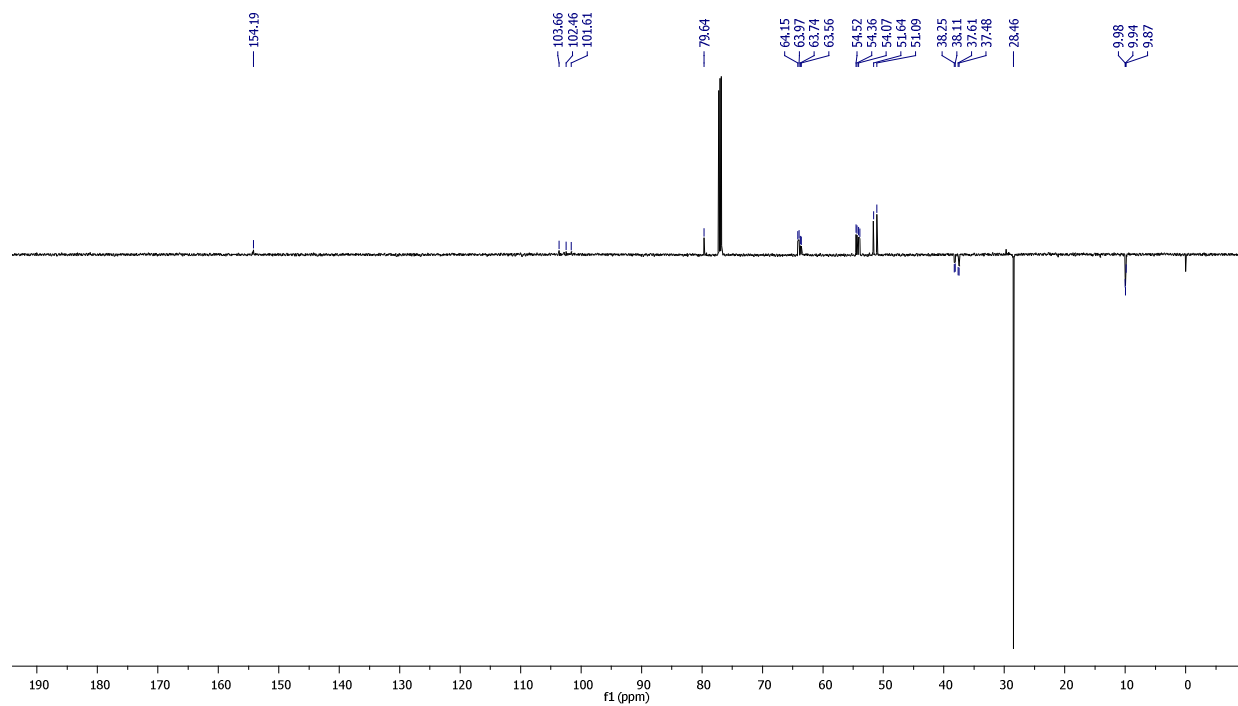




***tert*-Butyl (3*S*,4*S*)-3-fluoro-3-formyl-4-methylpyrrolidine-1-carboxylate (**2c**)**

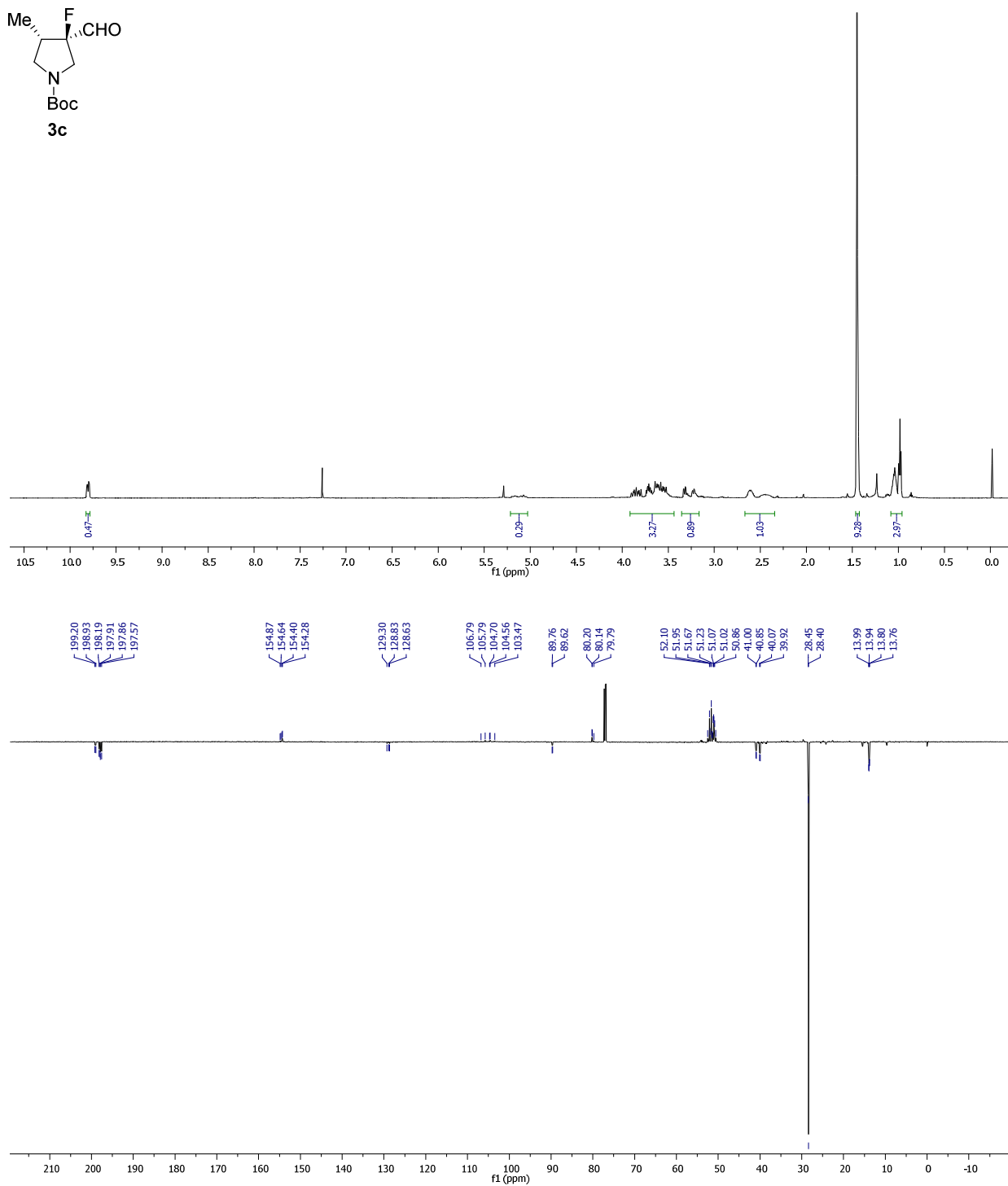
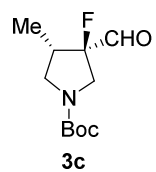
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

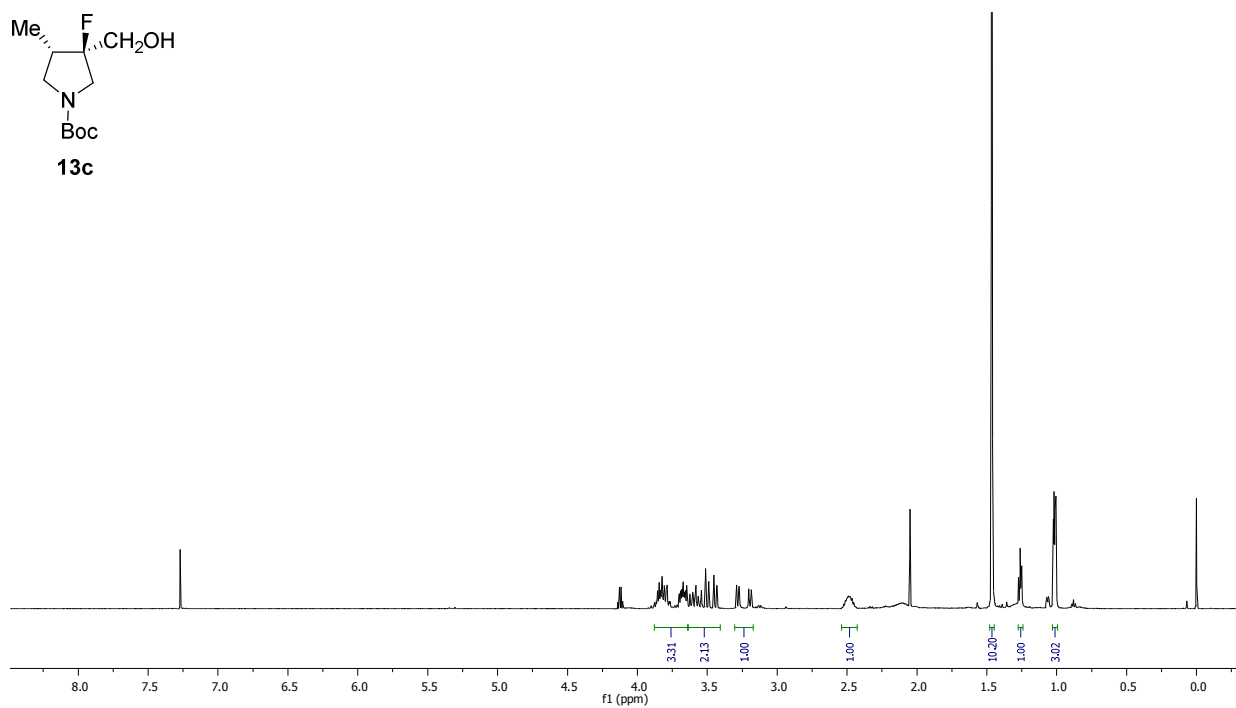
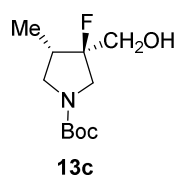
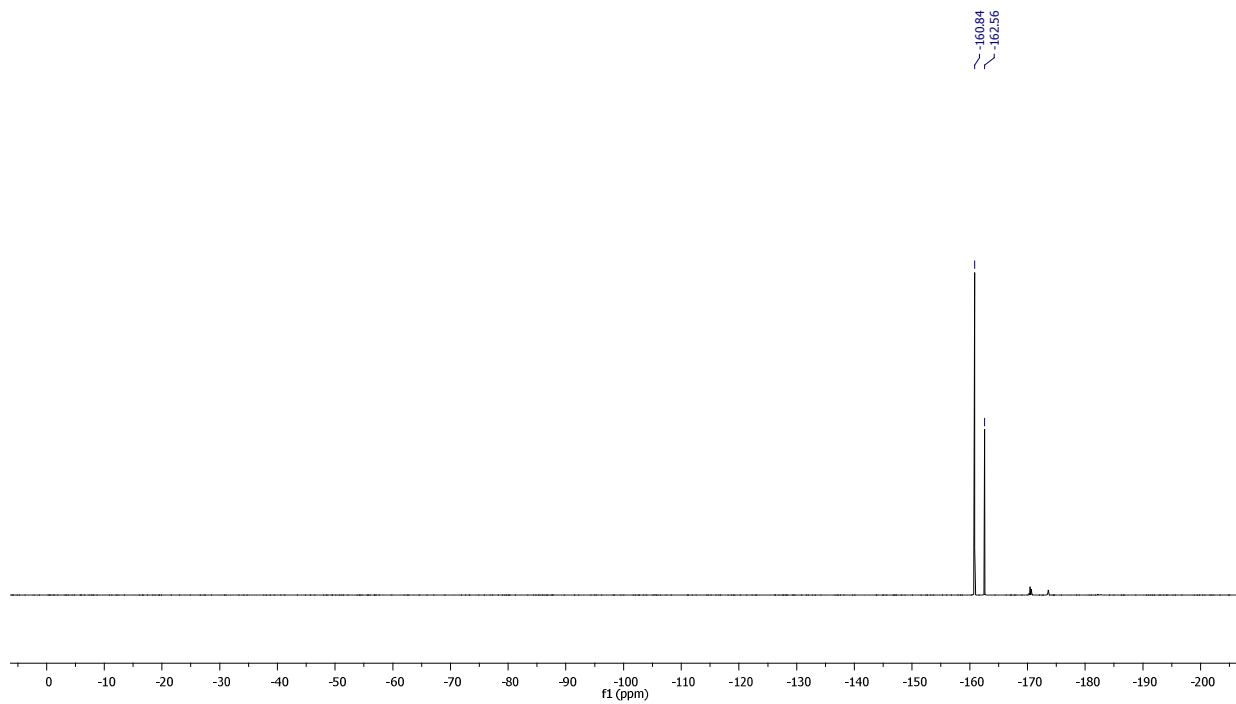


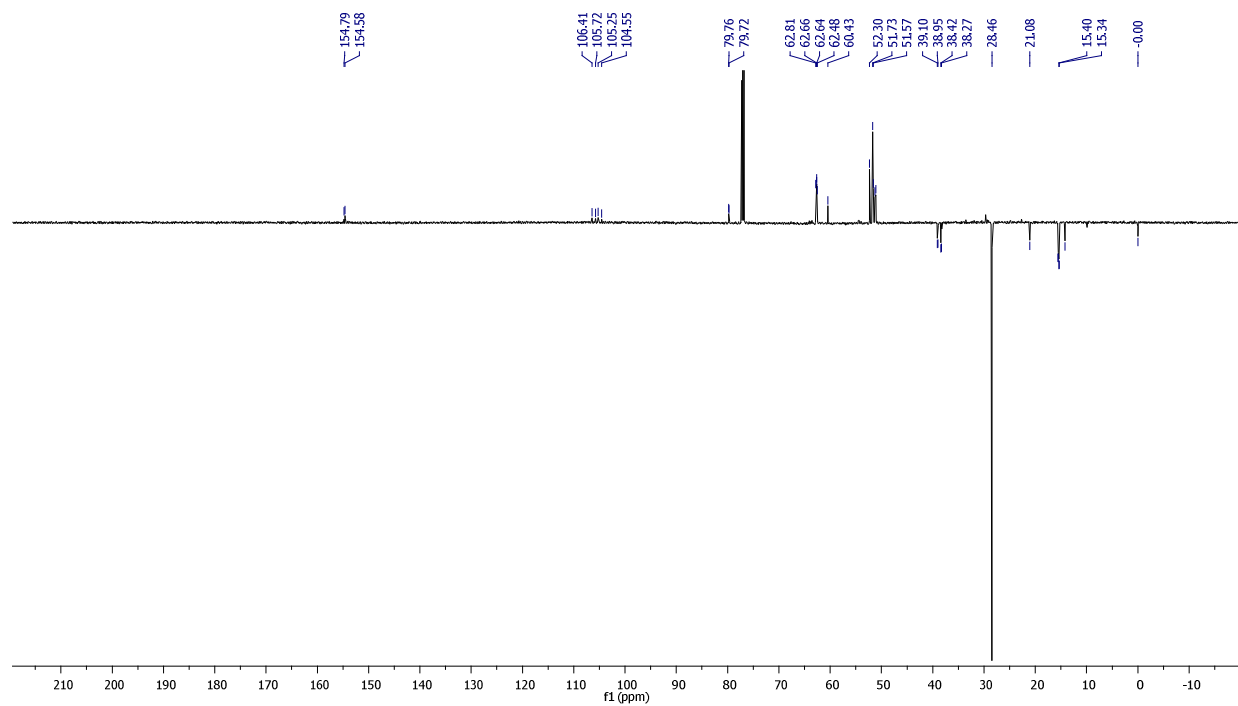


***tert*-Butyl (3*R*,4*S*)-3-fluoro-3-formyl-4-methylpyrrolidine-1-carboxylate (3c)**

The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

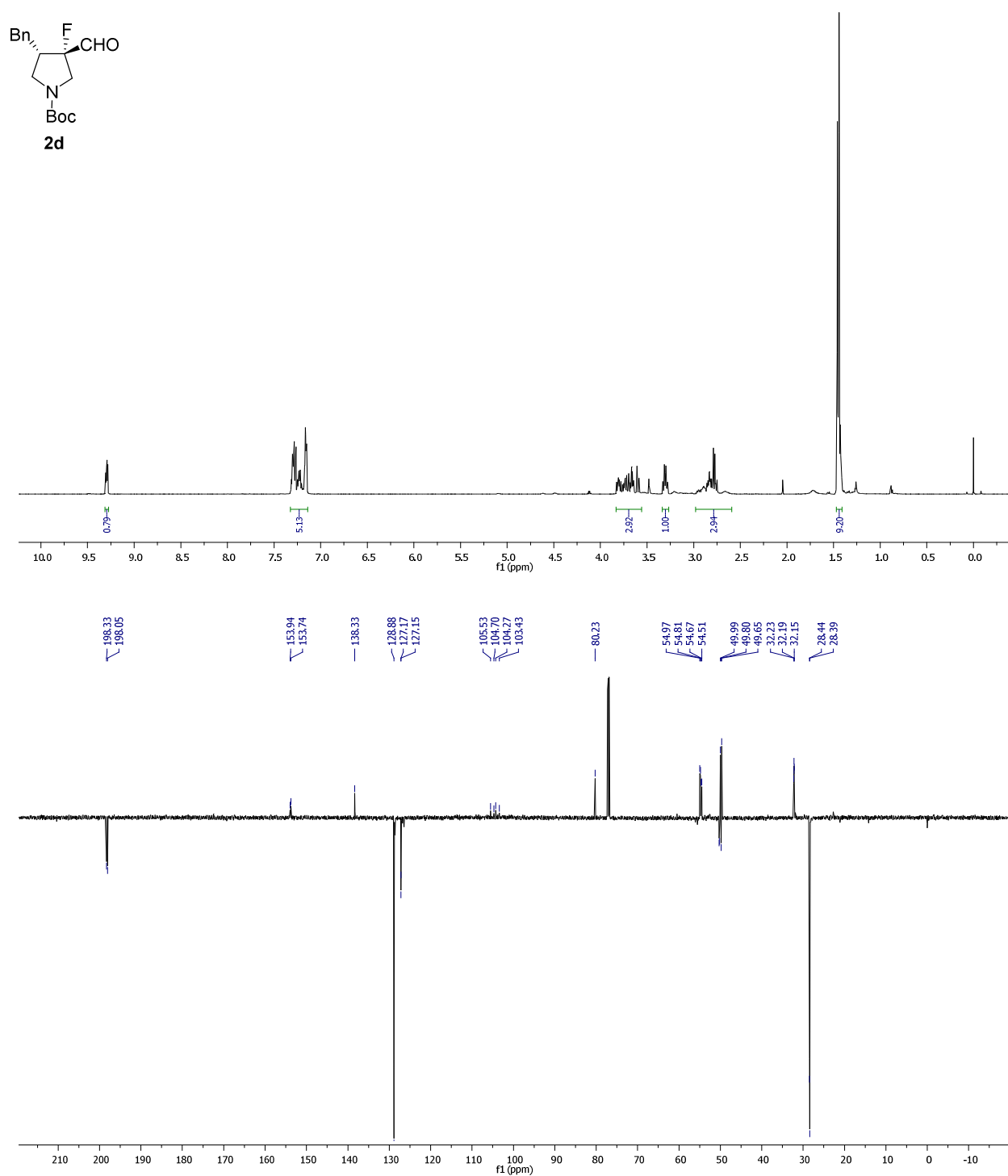


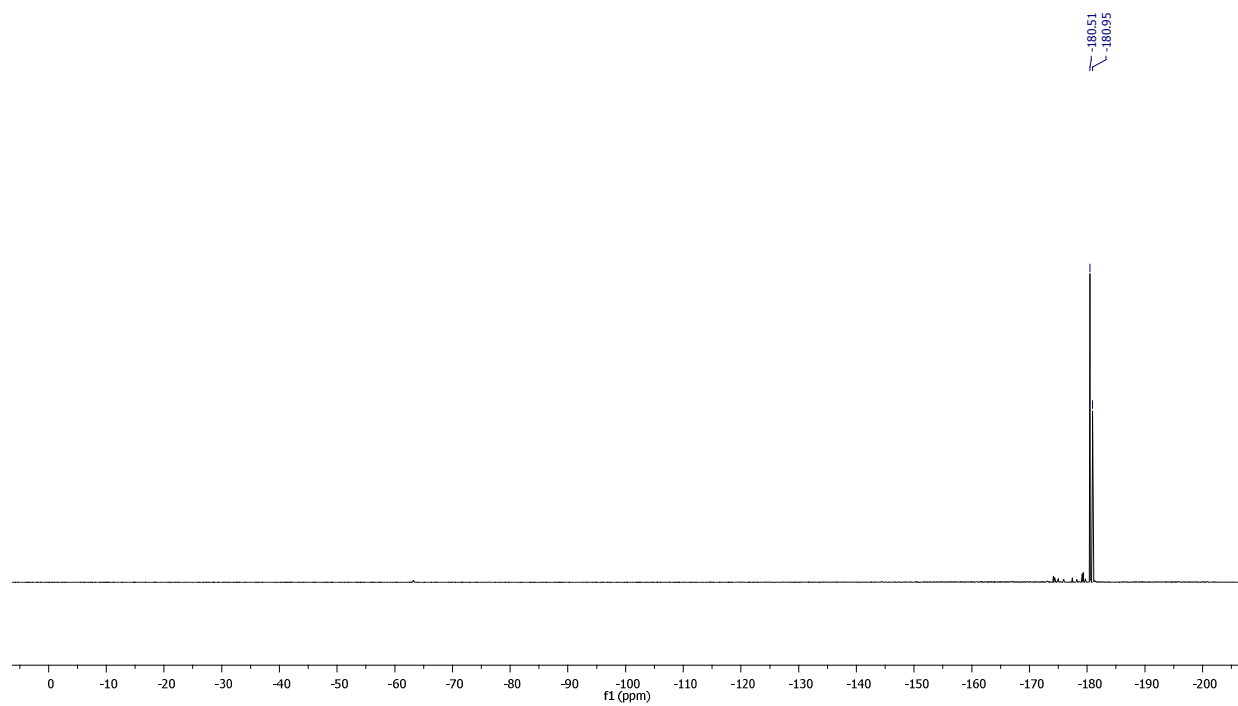




***tert*-Butyl (3*S*,4*S*)-4-benzyl-3-fluoro-3-formylpyrrolidine-1-carboxylate (2d)**

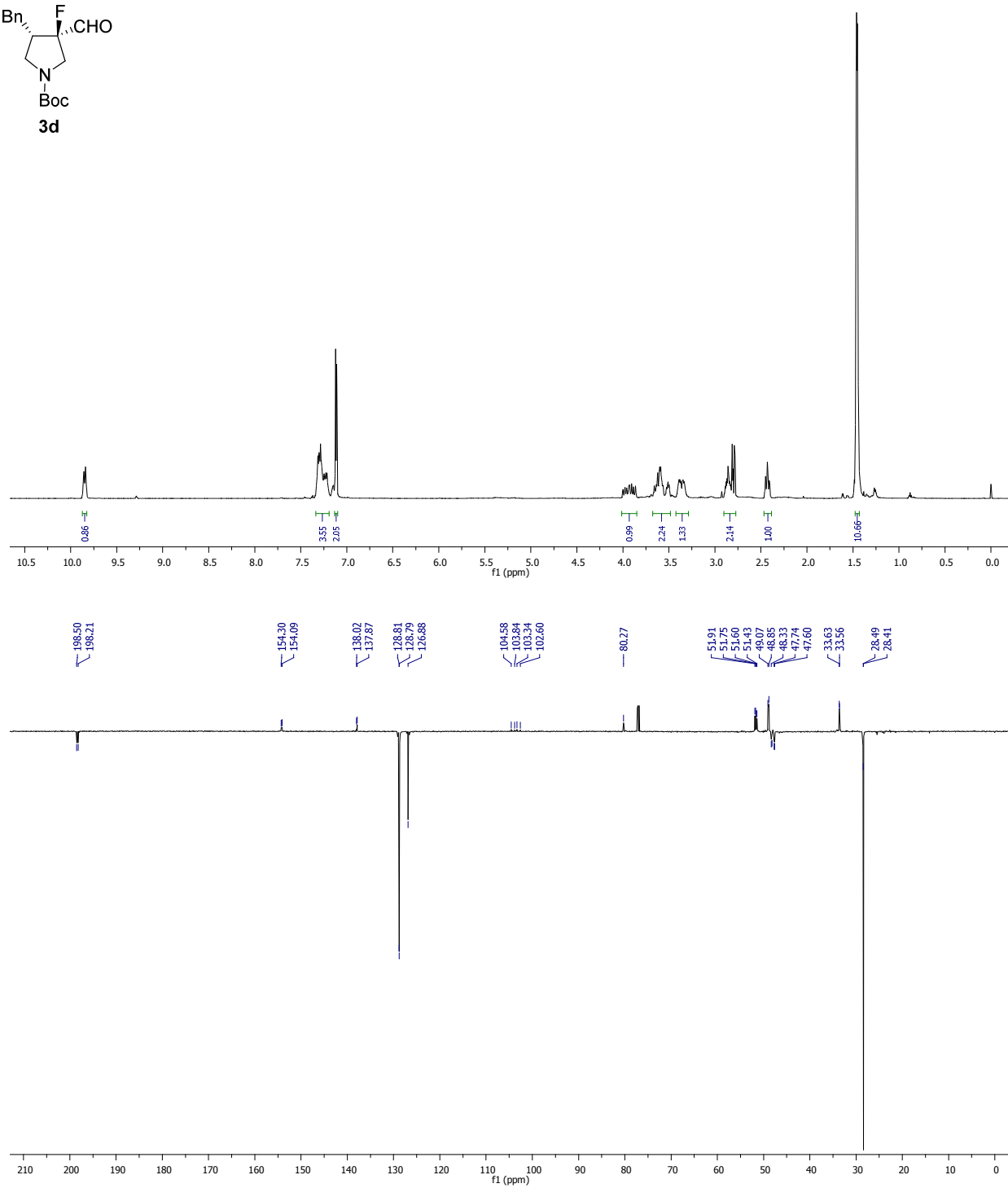
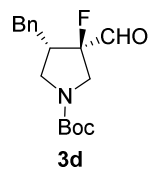
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

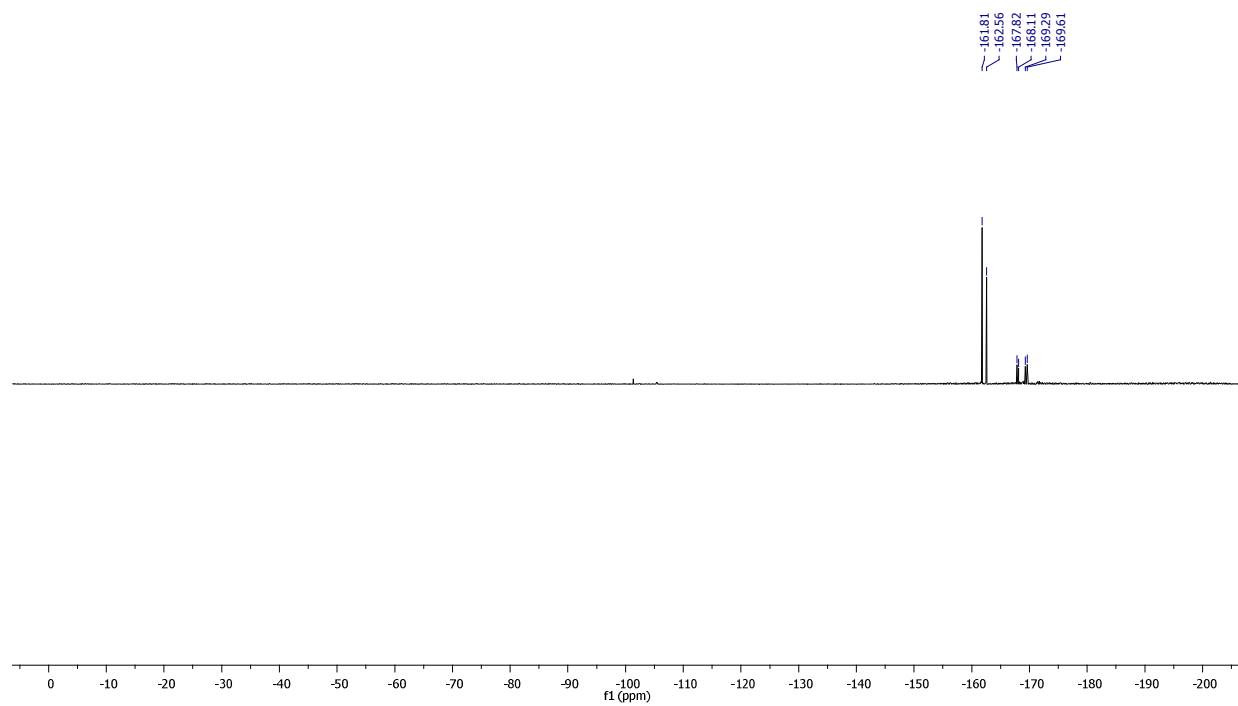




***tert*-Butyl (3*R*,4*S*)-4-benzyl-3-fluoro-3-formylpyrrolidine-1-carboxylate (3d)**

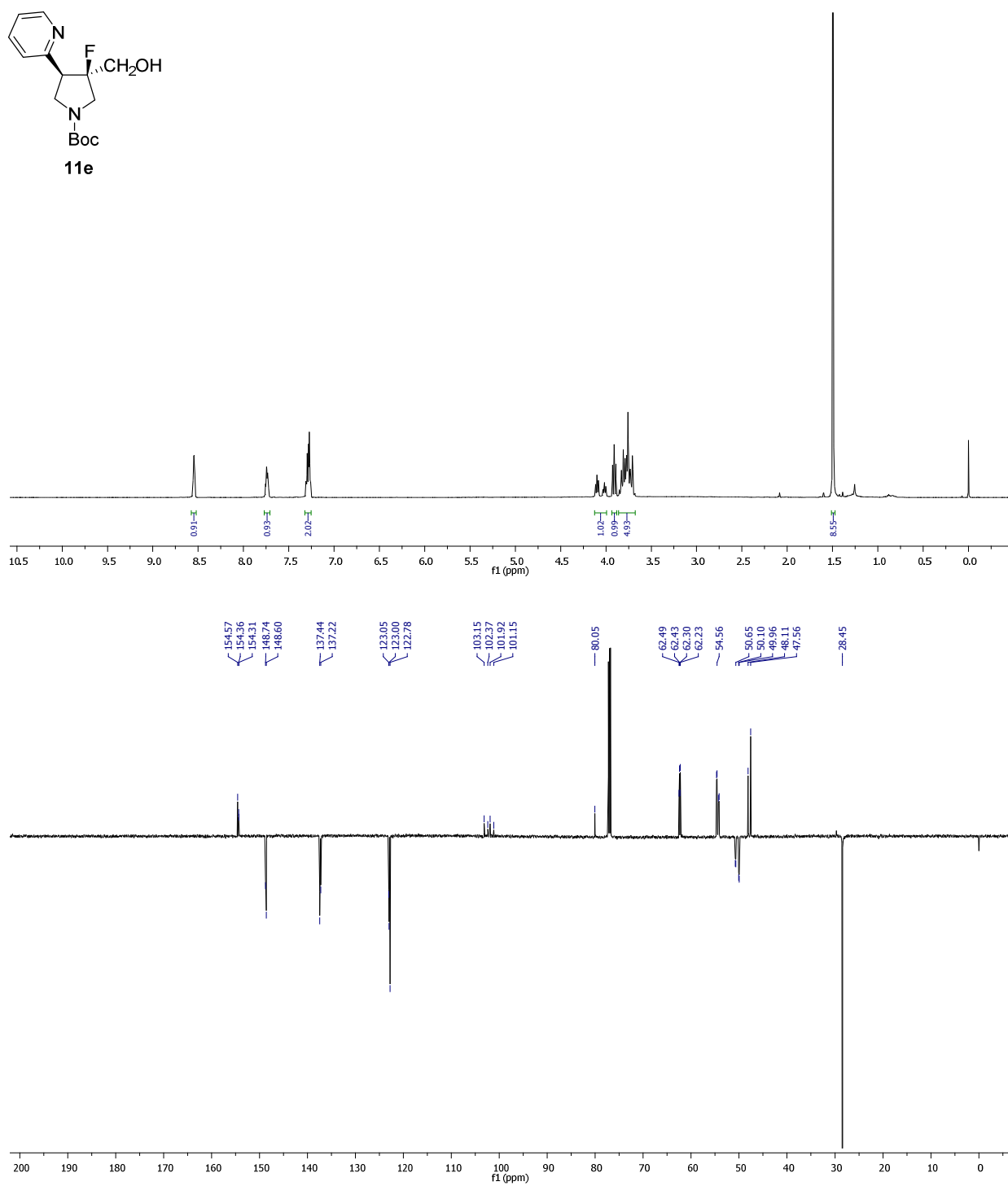
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

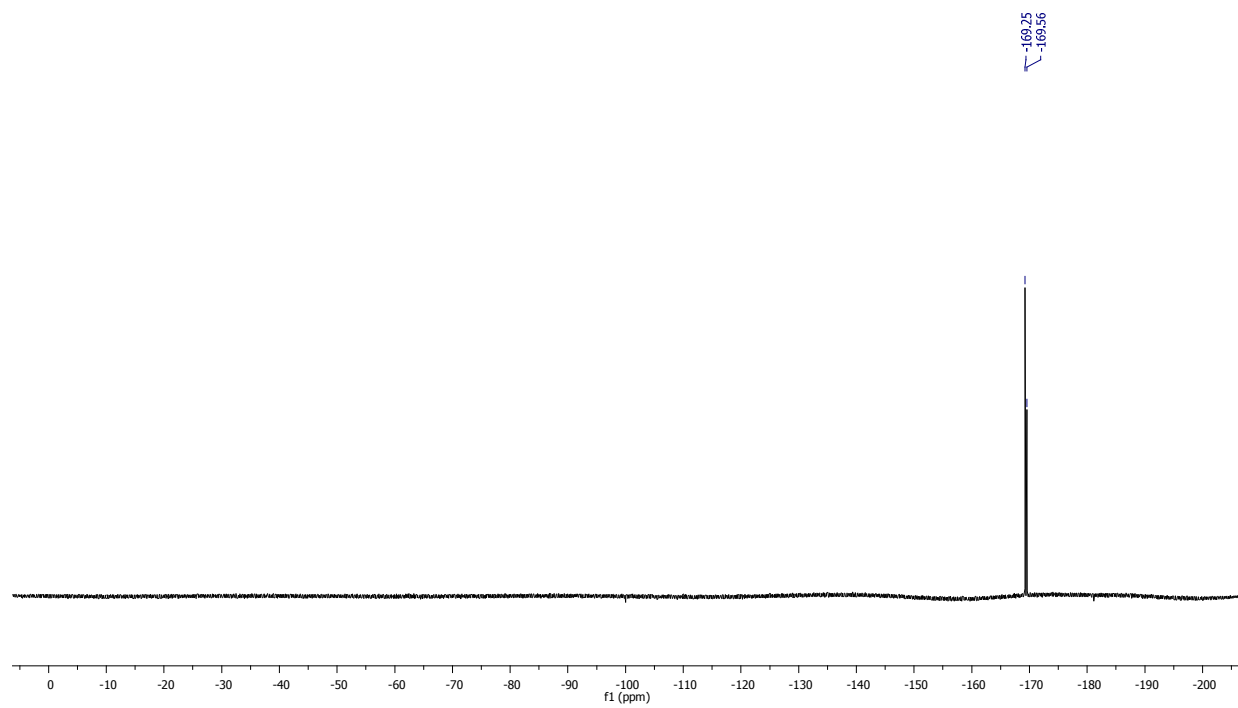




***tert*-Butyl (3*R*,4*S*)-3-fluoro-3-(hydroxymethyl)-4-(pyridin-2-yl)pyrrolidine-1-carboxylate (11e)**

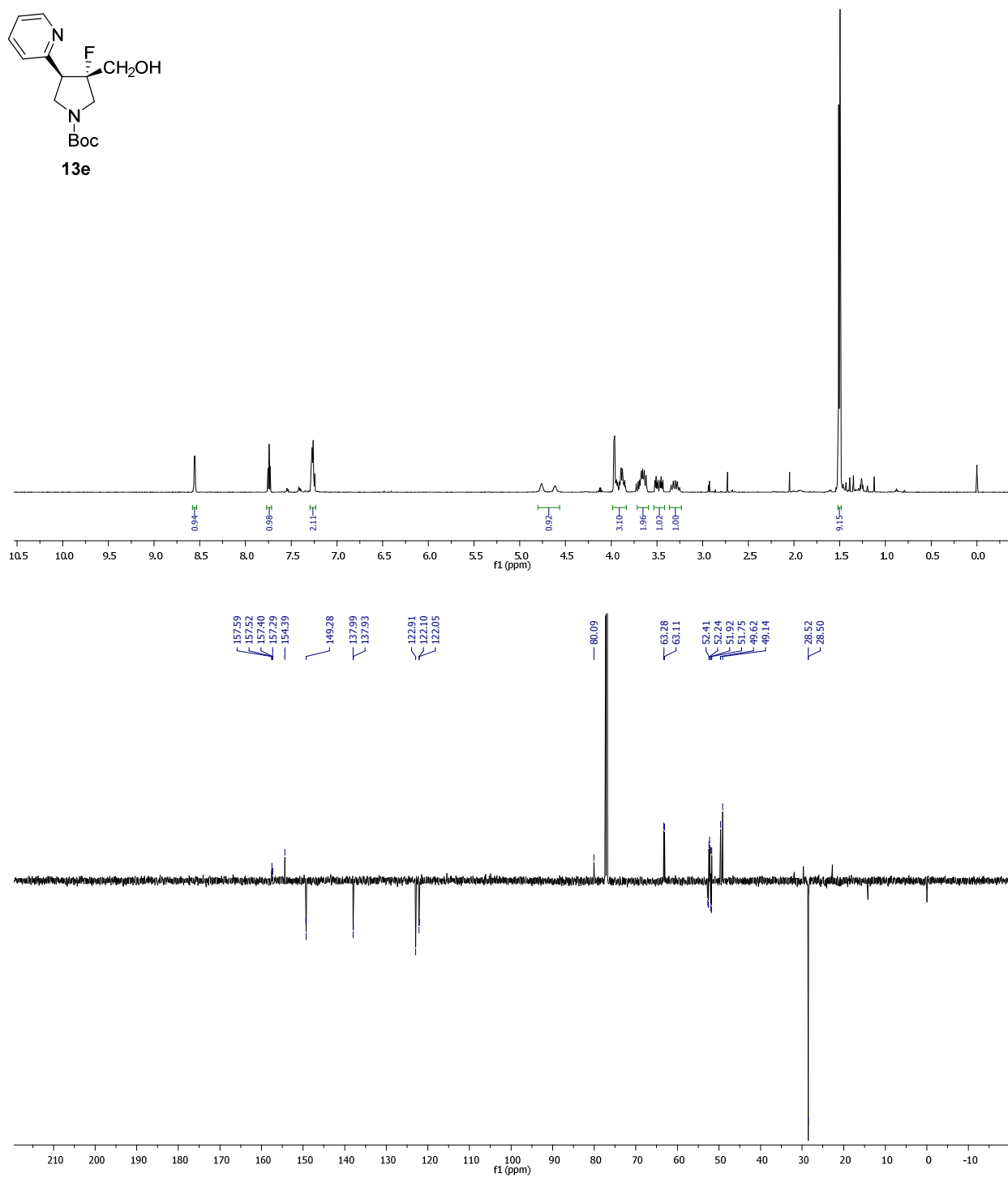
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

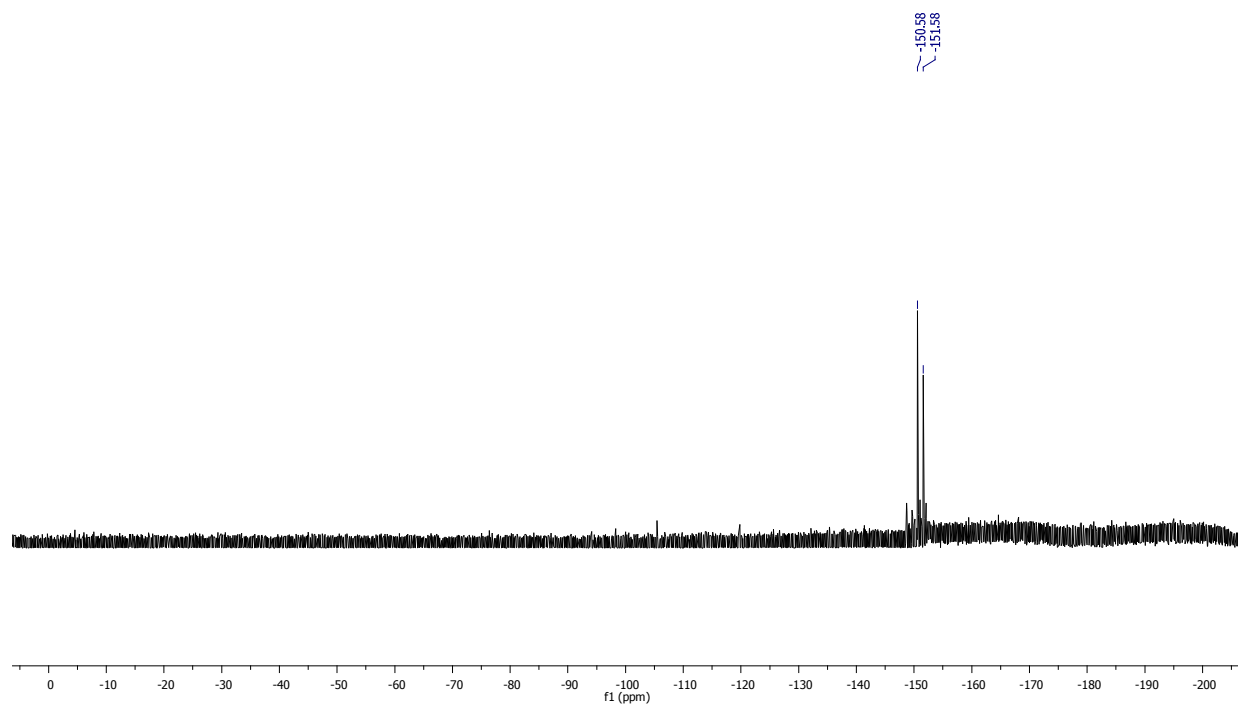




***tert*-Butyl (3*S*,4*S*)-3-fluoro-3-(hydroxymethyl)-4-(pyridin-2-yl)pyrrolidine-1-carboxylate (**13e**)**

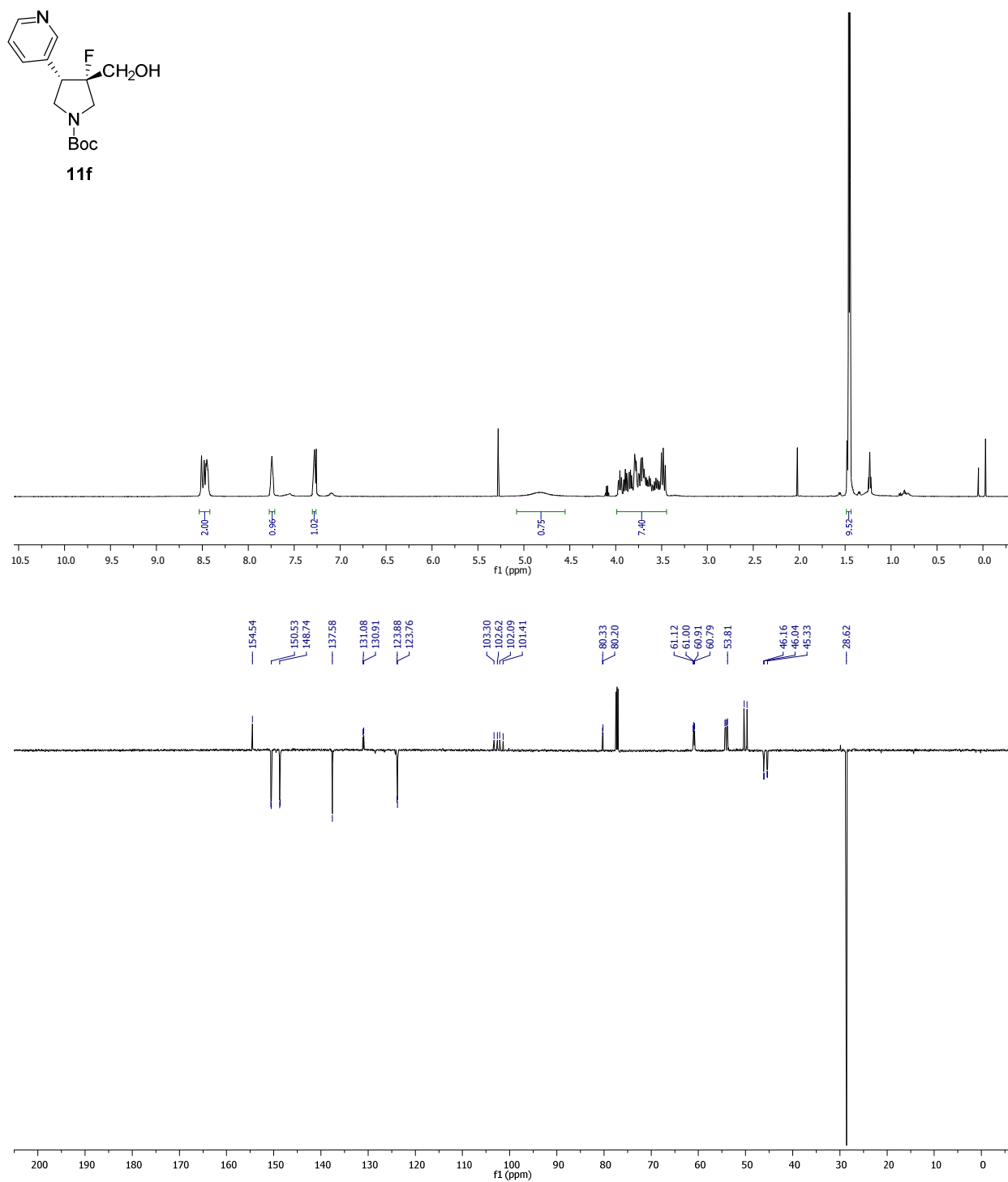
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

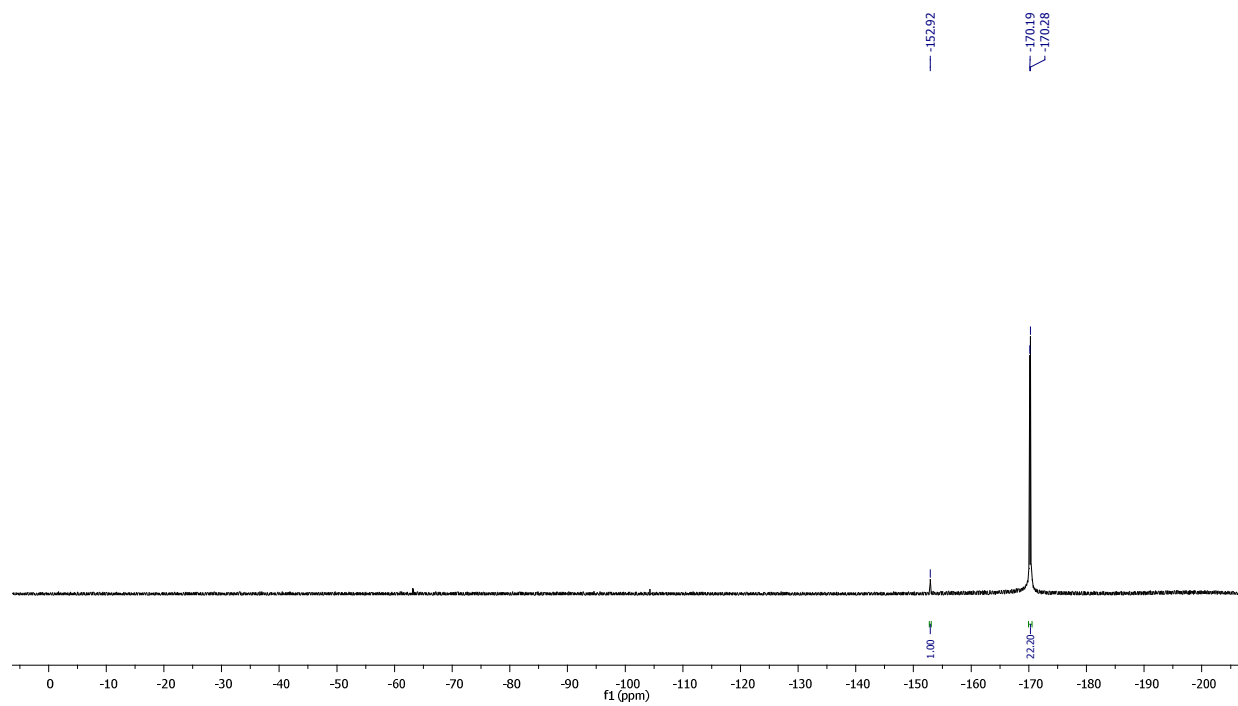




***tert*-Butyl (3*S*,4*S*)-3-fluoro-3-formyl-4-(pyridin-3-yl)pyrrolidine-1-carboxylate (11f)**

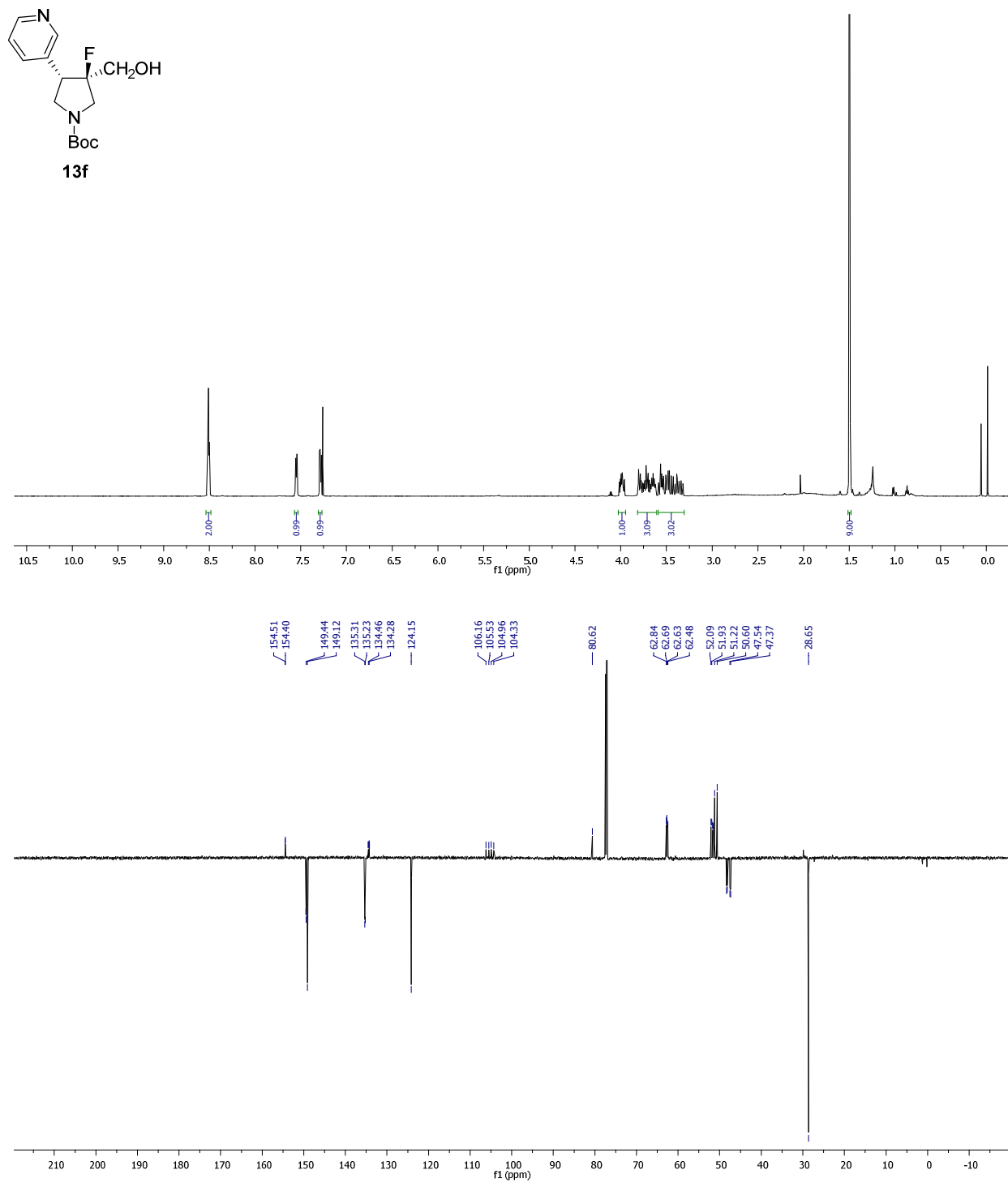
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .

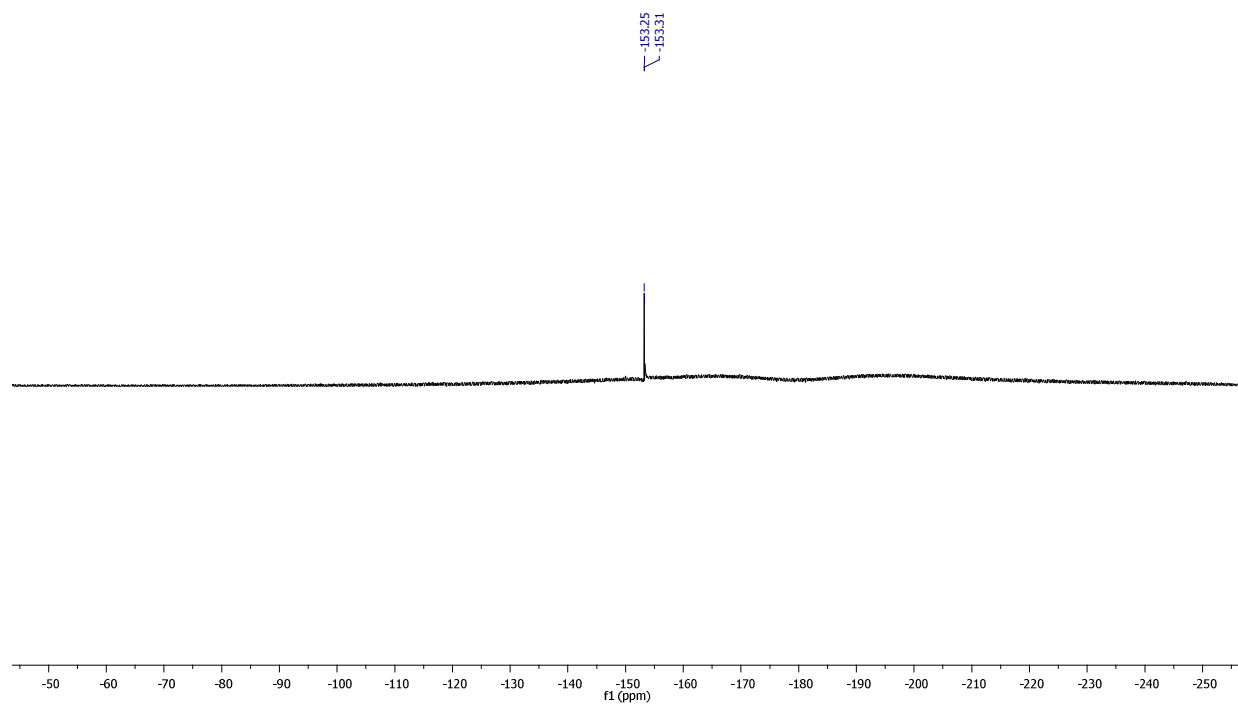




***tert*-Butyl (3*R*,4*S*)-3-fluoro-3-(hydroxymethyl)-4-(pyridin-3-yl)pyrrolidine-1-carboxylate (13f)**

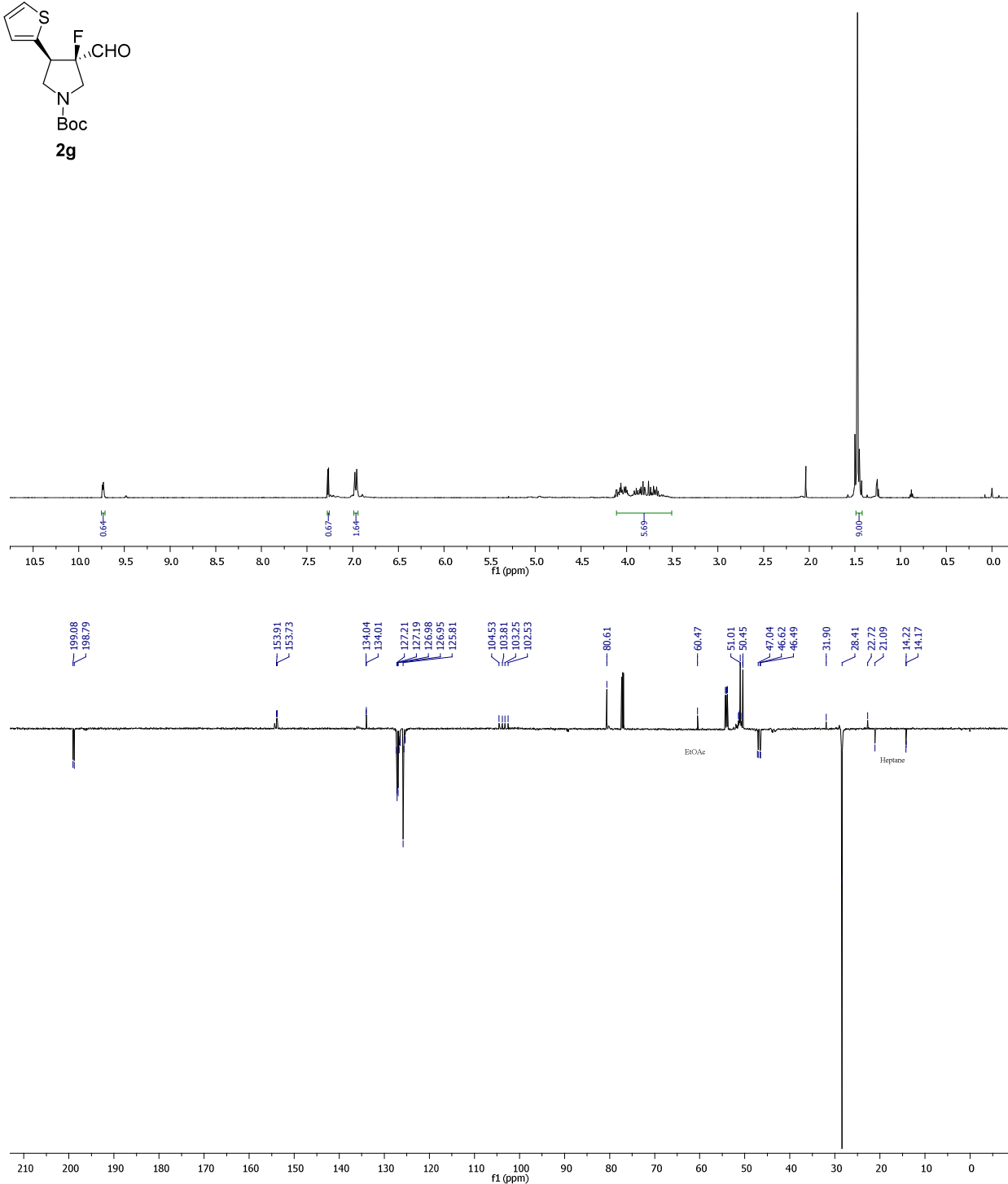
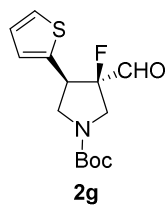
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .





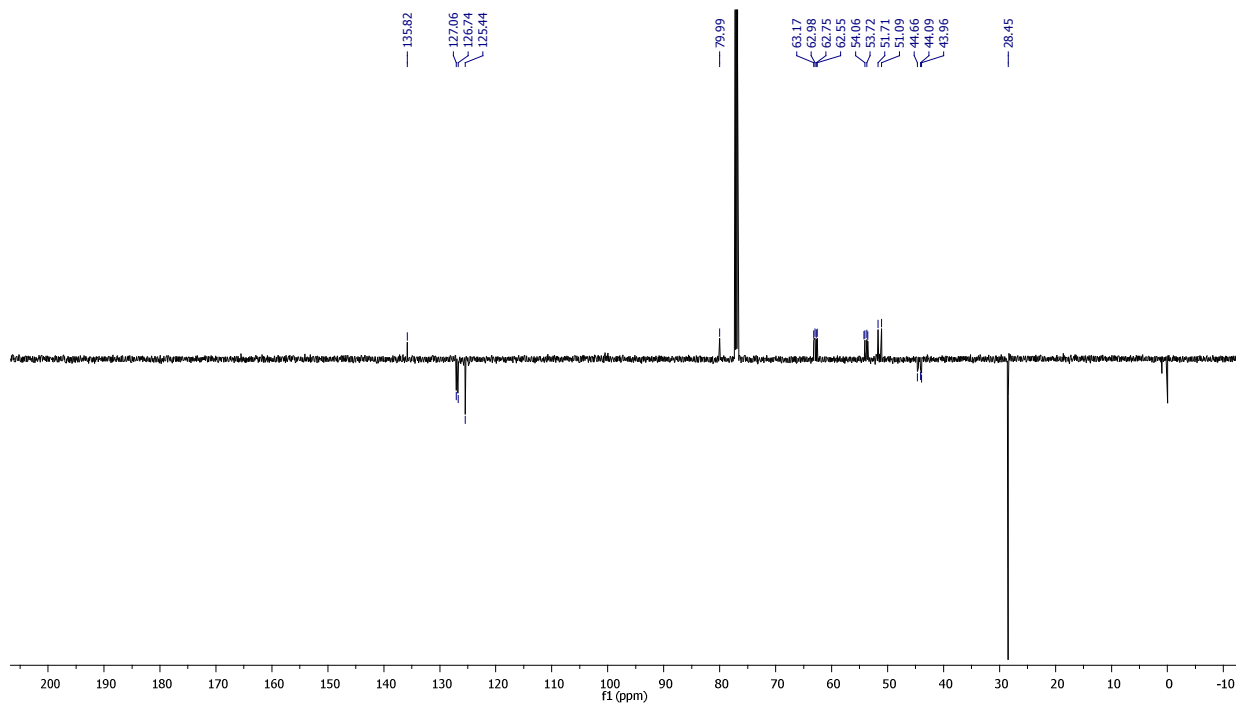
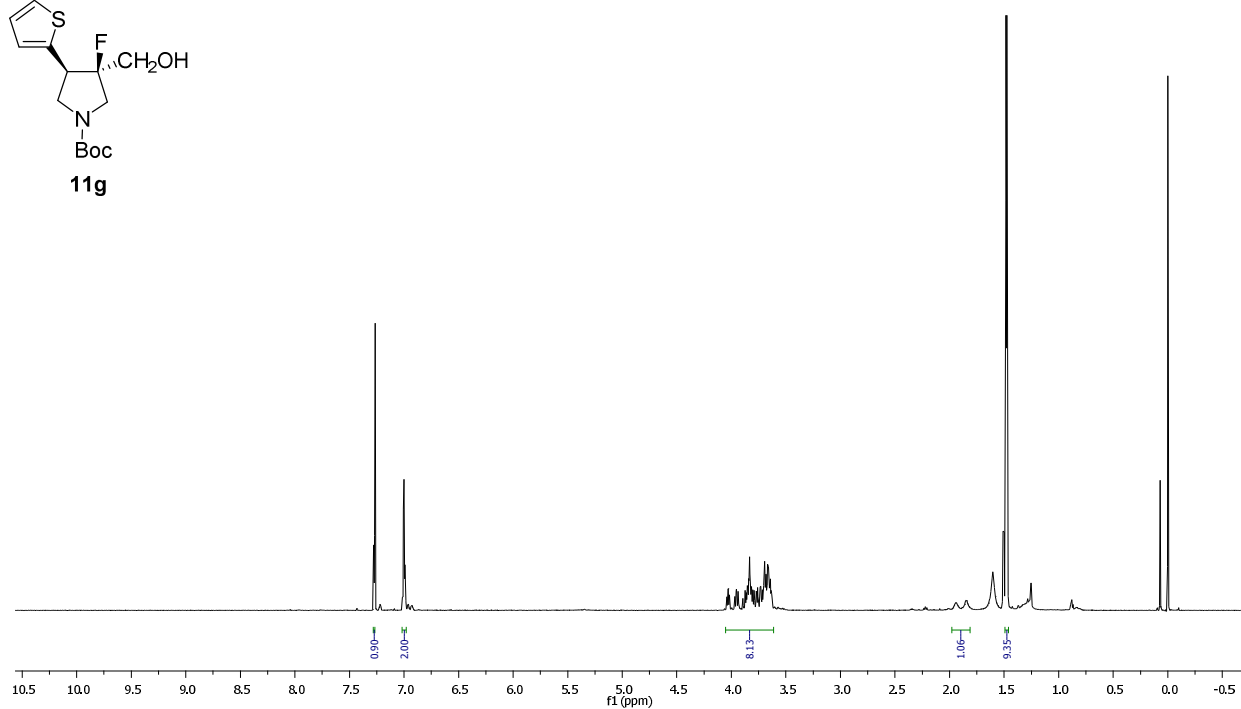
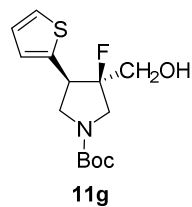
***tert*-Butyl (3*R*,4*R*)-3-fluoro-3-formyl-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (2g)**

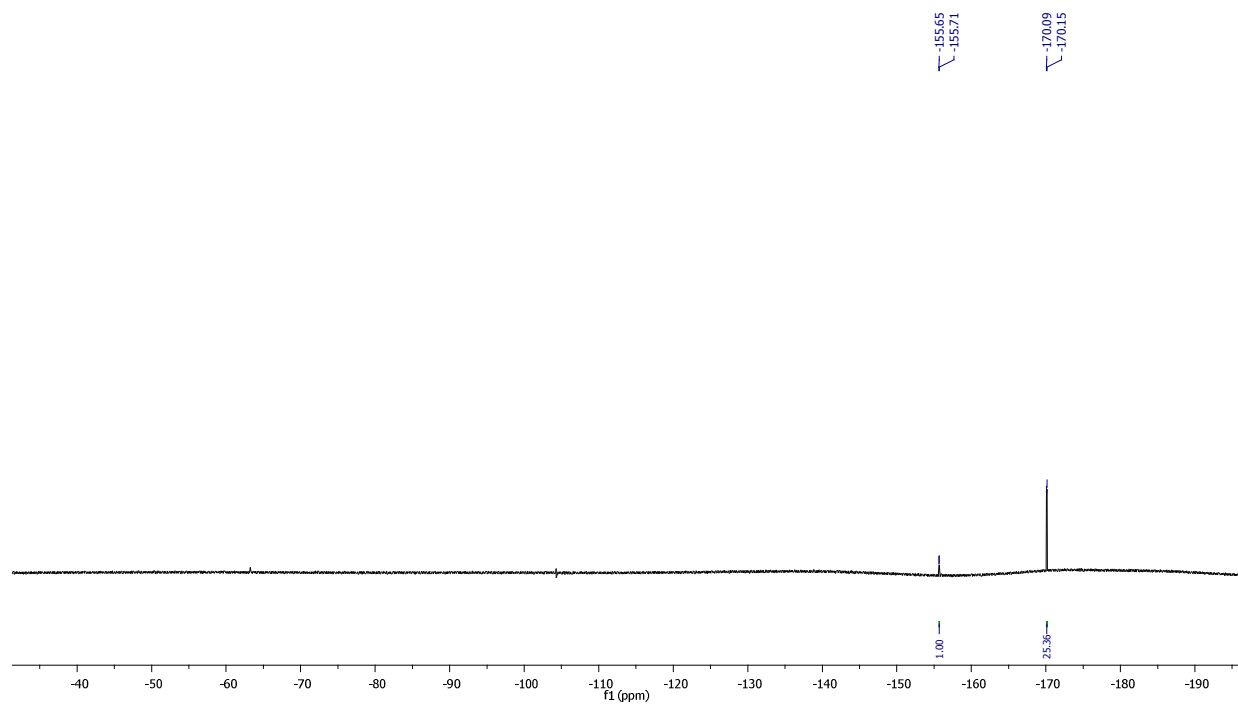
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .



***tert*-Butyl (3*R*,4*R*)-3-fluoro-3-(hydroxymethyl)-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (11g)**

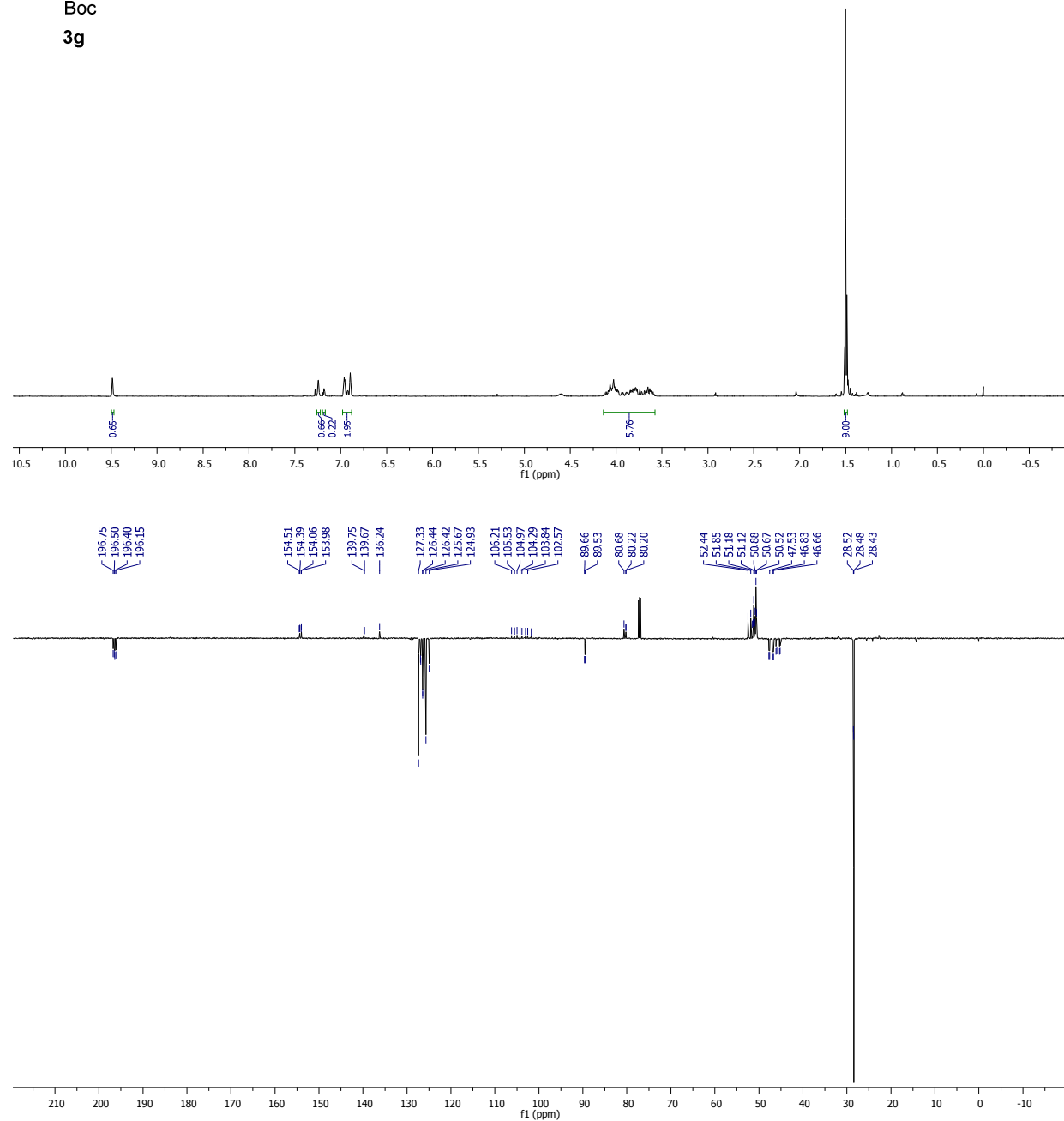
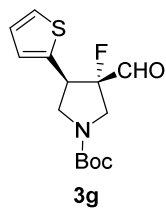
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .





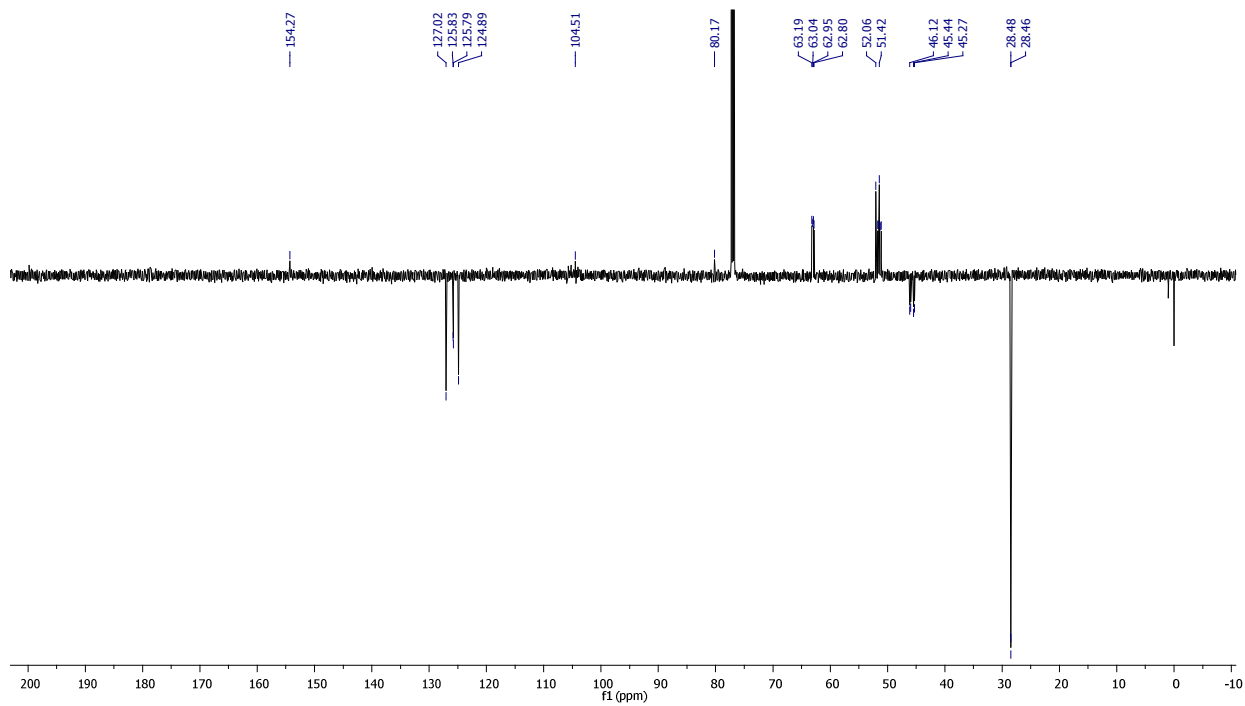
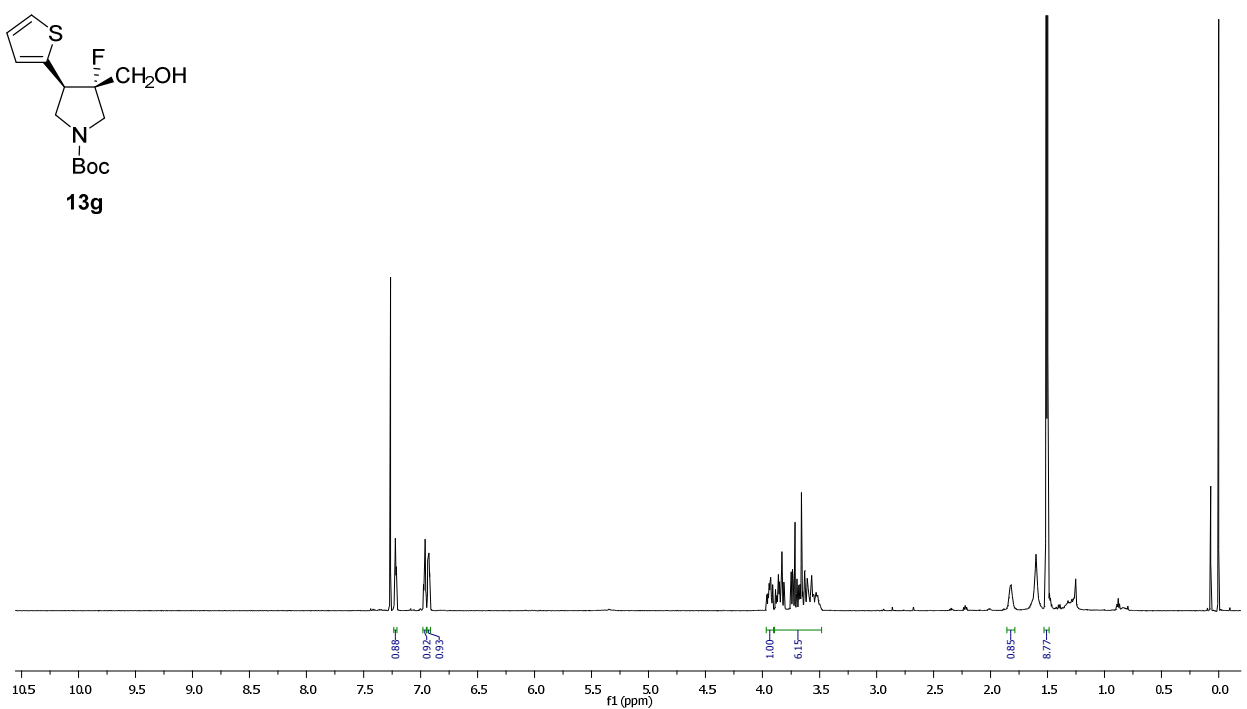
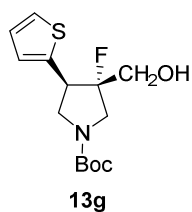
***tert*-Butyl (3*S*,4*R*)-3-fluoro-3-formyl-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (3g)**

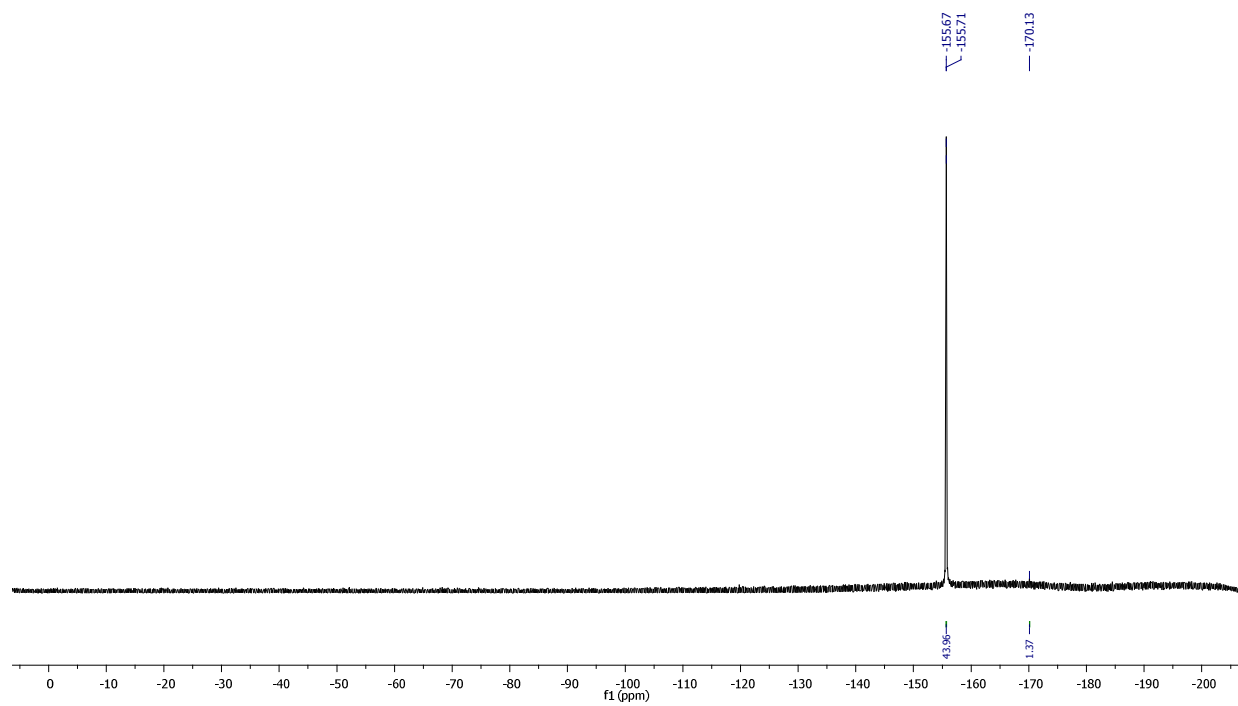
The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .



***tert*-Butyl (3*S*,4*R*)-3-fluoro-3-(hydroxymethyl)-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (13g)**

The NMR data was acquired at 600, 151 or 471 MHz for ^1H , ^{13}C or ^{19}F NMR respectively in CDCl_3 .





Reference List

1. Perlikowska, R.; Piekietna, J.; Mazur, M.; Koralewski, R.; Olczak, J.; do Rego, J. C.; Fichna, J.; Modranka, J.; Janecki, T.; Janecka, A. *Bioorg. Med. Chem.* **2014**, *22*, 4803.
2. Lorthiois, E.; Breitenstein, W.; Cumin, F.; Ehrhardt, C.; Francotte, E.; Jacoby, E.; Ostermann, N.; Sellner, H.; Kosaka, T.; Webb, R. L.; Rigel, D. F.; Hassiepen, U.; Richert, P.; Wagner, T.; Maibaum, J. *J. Med. Chem.* **2013**, *56*, 2207.
3. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.