

Supplementary information

Fluorosugars: Synthesis of the 2,3,4-trideoxy-2,3,4-trifluoro hexose analogues of D-glucose and D-altrose and assessment of their erythrocyte transmembrane transport

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General Experimental

All reagents were obtained from commercial sources and were used without further purification unless otherwise stated. Air- and moisture sensitive reactions were carried out under a positive pressure of argon in oven-dried (160 °C) glassware. Dry CH₂Cl₂ was obtained from the Solvent Purification System MB SPS-800. Chloroform was dried with K₂CO₃, refluxed with Na₂SO₄, distilled and stored under N₂ prior to use. Room temperature (RT) refers to 20-25 °C. Reaction temperatures of 0 °C were obtained in an ice/water bath. Reaction reflux conditions were obtained using an oil bath equipped with a contact thermometer. Solvent evaporations were carried out under reduced pressure on a Büchi rotary evaporator. Thin layer chromatography (TLC) was performed using Macherey-Nagel Polygram Sil G/UV254 plastic plates; visualisation was achieved by inspection under UV light (255 nm) or by the staining with a solution of basic potassium permanganate or phosphomolybdic acid. Column chromatography was performed using silica gel 60 (40–63 micron). All microwave-assisted reactions were performed in sealed vessels (vial size 2-5 cm³) on a Biotage Initiator 2.0 instrument under various temperature gradient conditions, the reaction was monitored by TLC. NMR spectra were recorded on Bruker AVANCE 300, 400 or 500 instruments. ¹H and ¹³C NMR spectra were recorded using deuterated solvent as the lock and residual solvent as the internal standard. ¹⁹F NMR spectra were referenced to CFC1₃ as the external standard. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The abbreviations for the multiplicity of the proton, carbon and fluorine signals are as follows: s singlet, d doublet, dd doublet of doublets, ddd doublet of doublet of doublets, dddd doublet of doublet of doublet of doublets, t triplet, dt double triplets, q quartet, m multiplet, app. apparent, br s broad singlet. When necessary, resonances were assigned using two-dimensional experiments (COSY, TOCSY, HMBC, HSQC, HMQC). IR spectra were recorded on a Nicolet Avatar 360 FT-IR from a thin film (either neat or combined with nujol) supported between NaCl plates. Optical rotations [α]_D are given in 10⁻¹ deg cm² g⁻¹ and were measured using a Perkin Elmer Model 341 polarimeter. Mass spectrometric (*m/z*) data was acquired by electrospray ionisation (ESI). High resolution mass analyses were recorded on a Micromass LCT TOF mass spectrometer using ES ionization in +ve ion mode.

2D EXSY NMR Spectroscopy

The human blood was spun down (4000 rpm, 5 min) and the plasma and buffy coat were discarded. The cells were washed four times in 3 volumes of saline buffer solution containing 123 mM NaCl, 15 mM Tris-HEPES and 5 mM ascorbic acid (the saline buffer solutions were filtered through sterile filters Nalgene 0.20 μ m cellulose acetate membranes before use). At each wash the supernatant was removed and the cells were collected by centrifugation. The red blood cells were then transferred to an eppendorf tube and diluted with one volume of saline buffer containing 123 mM NaCl, 15 mM Tris- HEPES, 5 mM ascorbic acid and 20 mM of fluorinated sugar (final hematocrit 0.5), carefully mixed and transferred into a WILMAD NMR tube with J Joung valve. A sealed capillary tube containing D₂O was then introduced into the NMR tube to provide deuterium signal for lock. A stream of carbon monoxide was bubbled through the cells for 3 minutes before sealing. Immediately after that the sample was sealed and analysed by NMR. 2D ¹⁹F spectra were recorded using Bruker AVANCE 500 MHz spectrometer equipped with double resonances ¹⁹F SEF probe at 310 K. The spectra were acquired using *noesyph* sequence which was adjusted by adding ¹H decoupling for directly detected dimension and the ¹H 180° refocusing pulse in the middle of *t*₁ evolution period to achieve decoupling in the F1 dimension. Each spectrum was digitised using 1024 points in F2 dimension and 256 points in F1 dimension which was later zero-filled to 1024 points. 8 scans were accumulated for each increment with interscan delay 2s. Sine squared window multiplication was used for all the spectra. Every sample was analysed using at least three different mixing times ranging from 0 to 800 ms. The program EXSYCalc (Mestrelab Research) was used to analyse integral intensities of crosspeaks according to a full relaxation matrix analysis.¹

Anomers Assignment

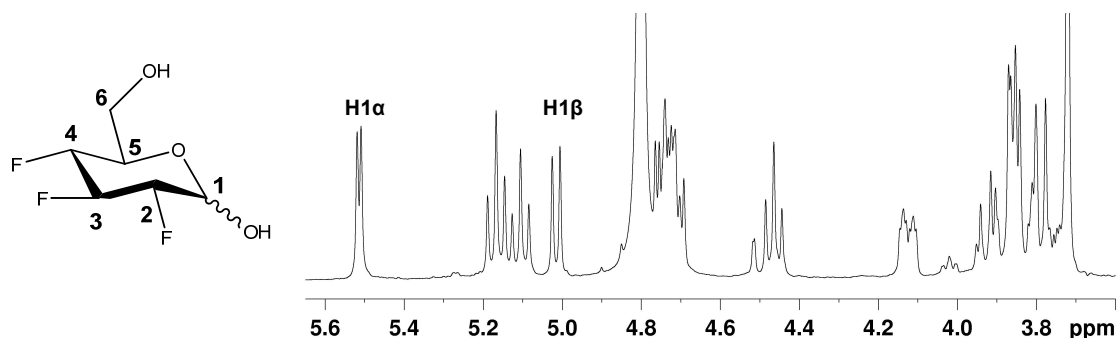


Figure 1 400.13 MHz $^1\text{H}\{^{19}\text{F}\}$ NMR spectrum of trifluoro-D-glucose **9** in D_2O -Tris- HEPES buffer recorded at room temperature. Two doublets at 5.51 ppm and 5.01 ppm show $^3J_{\text{HH}}$ coupling constants 3.8 and 8.2 Hz that enables assignment to hydrogen H1 of α - and β -anomer, respectively. The values of $^3J(\text{H1},\text{H2})$ coupling constants calculated using Altona equation for MMFF optimised geometries of α - and β -anomer are 3.4 and 6.3 Hz, respectively.

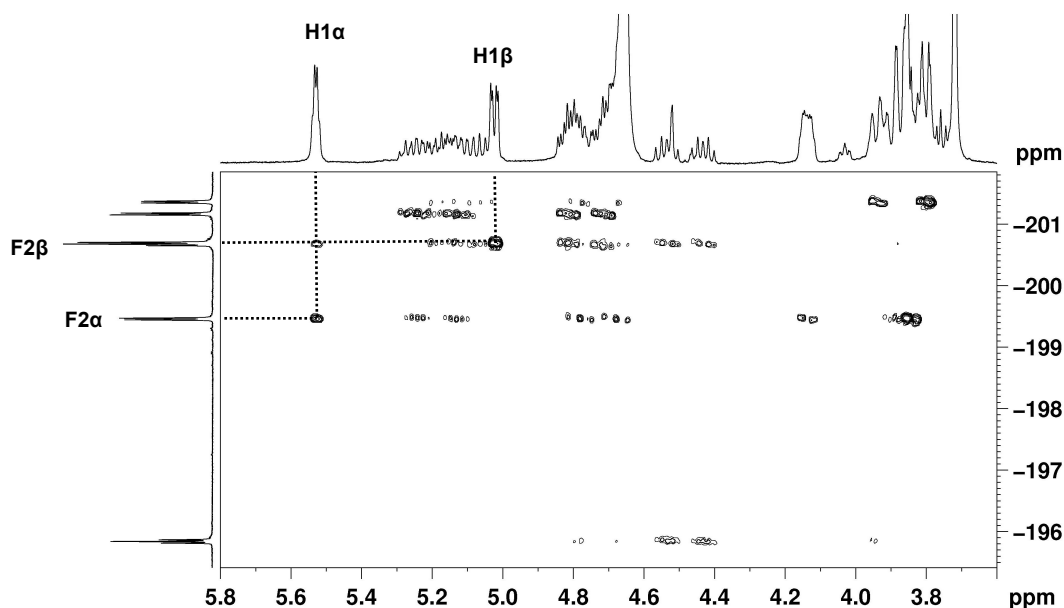


Figure 2 500 MHz $^1\text{H},^{19}\text{F}$ -HMBC spectrum of trifluoro-D-glucose **9** in D_2O -Tris- HEPES recorded at 310 K. The projection traces show ^1H and $^{19}\text{F}\{^1\text{H}\}$ spectra. Dashed lines highlight $^3J(\text{H1},\text{F2})$ crosspeaks which enable to assign ^{19}F doublets at -199.4 and -200.7 ppm to F2 of α - and β -anomer, respectively.

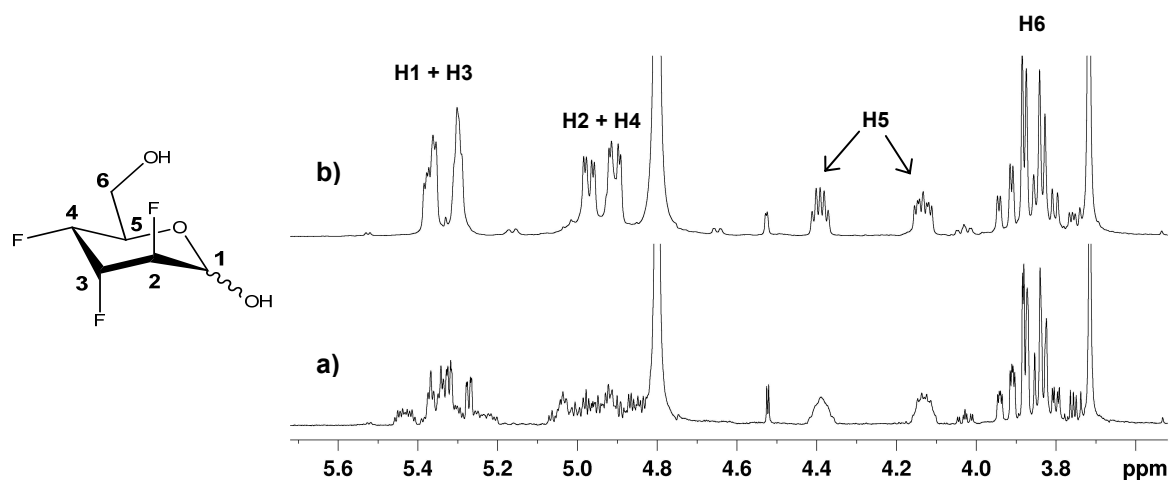


Figure 3 400.13 MHz ^1H (a) and $^1\text{H}\{^{19}\text{F}\}$ (b) spectra of trifluoro-D-altrose **10** in D_2O -Tris-HEPES. Overlap of H1 and H3 disables accurate measurement of $^3J_{\text{HH}}$ coupling constant and using them to discriminate the anomers. Moreover, the values of $^3J(\text{H1},\text{H2})$ coupling constants calculated using Altona equation for MMFF optimised geometries of α - and β -anomer (2.8 and 0.5 Hz, respectively) show only negligible difference.

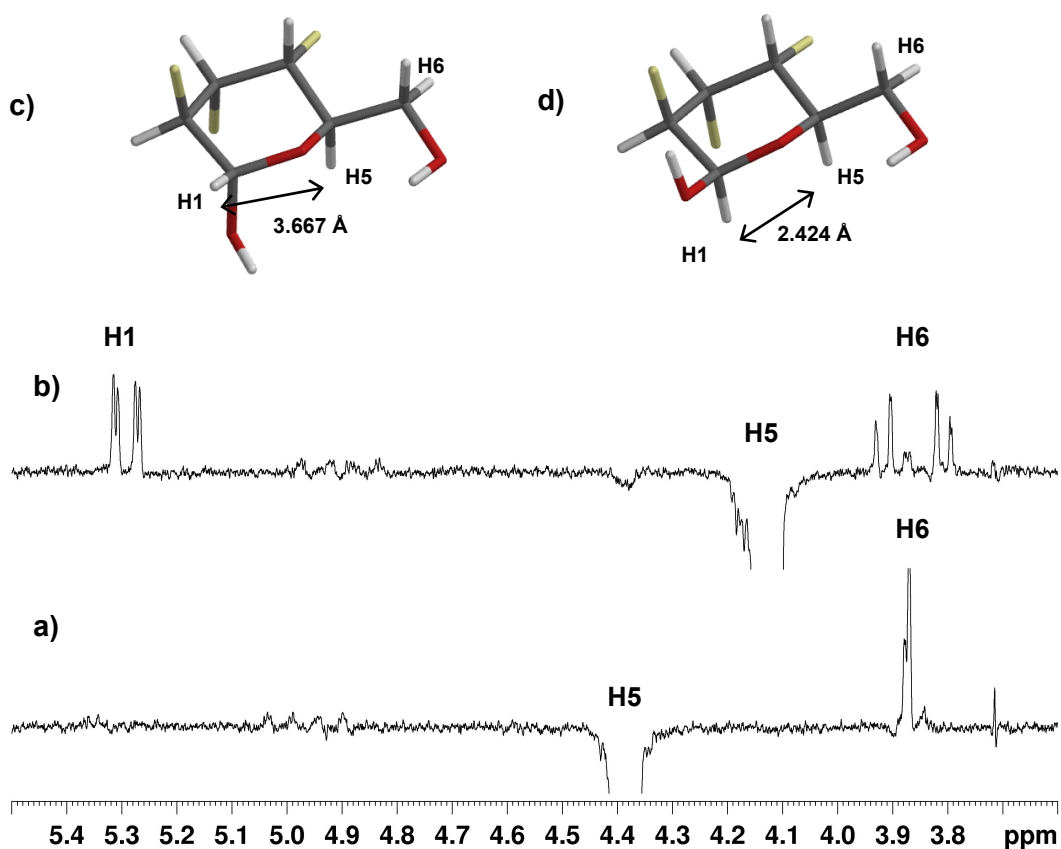


Figure 4 1D gradient NOESY spectra of trifluoro-D-altrose **10** in D₂O-Tris- HEPES. Spectrum (a) shows NOE between H5 resonance at 4.39 ppm and one H6 proton. Spectrum (b) shows NOE between H5 resonance at 4.13 ppm and H6 and H1 protons. MMFF optimised geometries of α -anomer (c) and β -anomer (d) show distances between H1 and H5 protons 3.667 and 2.424 Å. That enables to assign H5 resonance at 4.39 ppm to α -anomer and one at 4.13 ppm to β -anomer.

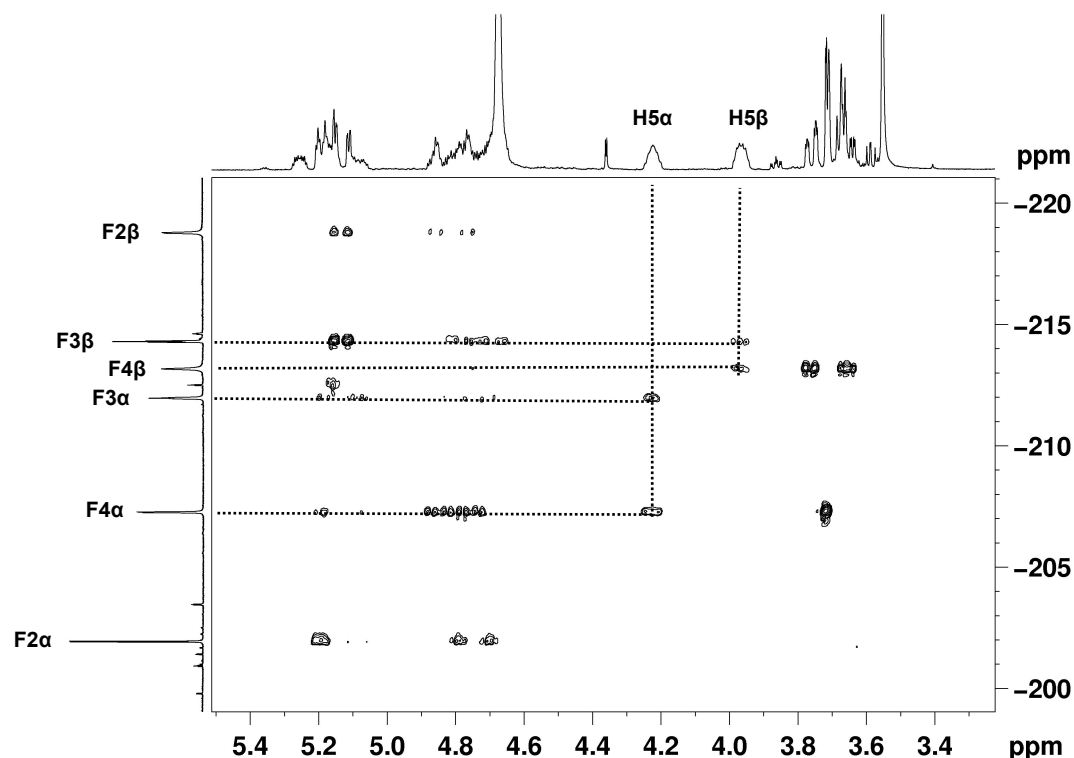
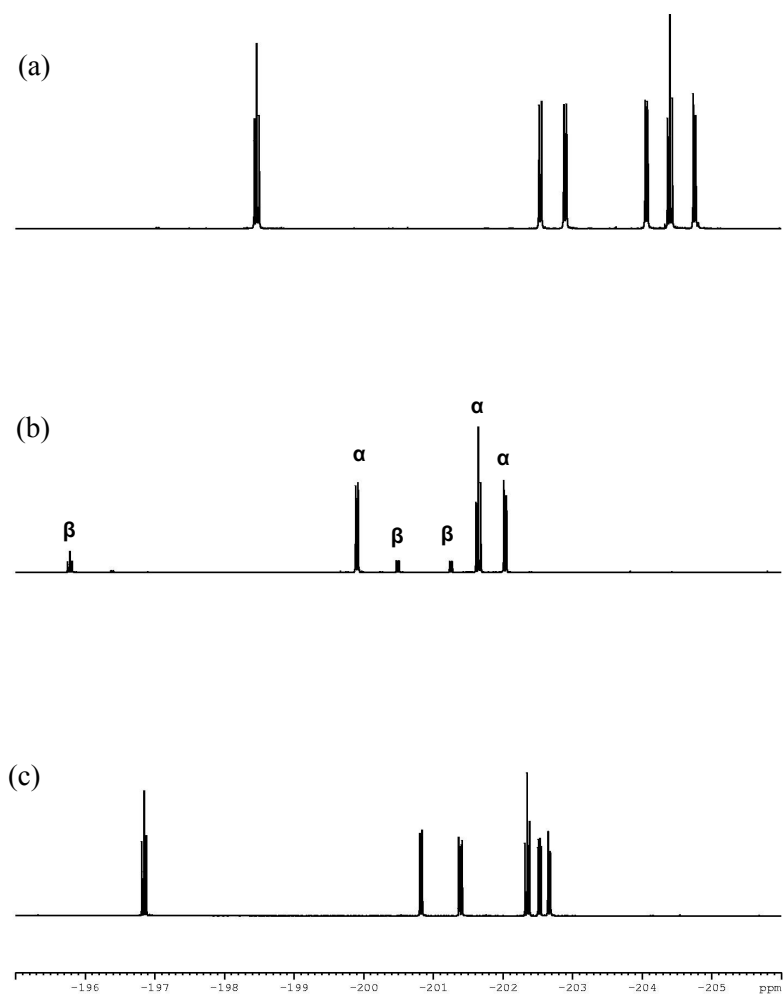


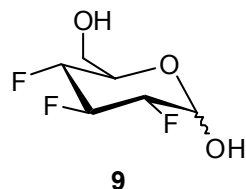
Figure 5 500 MHz ^1H , ^{19}F -HMBC spectrum of trifluoro-D-altrose in D₂O-Tris- HEPES buffer recorded. The projection traces show ^1H and $^{19}\text{F}\{^1\text{H}\}$ spectra. Dashed lines highlight $^3J(\text{H5},\text{F4})$ and $^4J(\text{H5},\text{F3})$ crosspeaks which enable to assign F3 and F4 resonances to corresponding anomers. F2 resonances were assigned using ^{19}F , ^{19}F -COSY (not shown)



$^{19}\text{F}\{^1\text{H}\}$ NMR showing the α/β anomer ratios of D-glucose analogue **9** in (a) $\text{THF-}d_8$, (b) CDCl_3 , (c) CD_3CN .

Experimental procedures and physical data of the obtained compounds

2,3,4-Tridehydroxy-2,3,4-trifluoroglucose (9). A mixture of crude **17** (0.035 g, 0.15 mmol) and anhydrous tin(II) chloride (0.058 g, 0.30 mmol) were stirred in dry CH₂Cl₂ (3.85 cm³) at

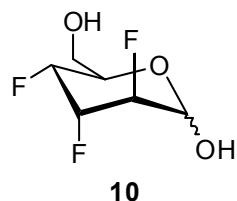


RT for 1 h. The undissolved tin(II) chloride was removed by filtration. Silica gel (1 g) was added to the filtrate. The resultant suspension was evaporated to dryness and purified over silica gel (9:1→1:9 hexane/ethyl acetate) to give **9** (0.016 g, 58%, mixture of α - and β -anomers) as a transparent oil. The product was recrystallised from CHCl₃. The relative stereochemistry of the β -anomer was determined by x-ray structure

analysis, mp 103–105 °C (from CHCl₃). The anomeric ratio in the anomeric mixture was α/β : 1/0.13 by ¹⁹F NMR (376.50 MHz, CDCl₃) and α/β : 1/0.2 by ¹H-NMR (400.13 MHz, CDCl₃).

Data for the anomeric mixture: $[\alpha]_D^{22} +40.1$ (c 1.15 in THF-*d*₈, 1/0.98 anomeric ratio); δ_H (400.13 MHz, CDCl₃) 5.56–4.78 (m, 4H), 4.77–4.21 (m, 4H), 4.20–3.26 (m, 6H), 3.30 (br s, OH), 1.78 (br s, OH); MS (ESI, +ve) m/z 208.99 [M-Na]⁺ (100); HRMS (ESI, +ve) C₆H₉F₃O₃Na⁺ requires m/z 209.0401, found 209.0405. **Data for α -anomer** δ_C (100.61 MHz, CDCl₃) 91.5–89.2 (m, CH), 90.5 (dd, J = 21.1, 9.7, CH), 88.0 (ddd, J = 192.8, 16.7, 8.1, CH), 86.6 (ddd, J = 186.0, 18.4, 7.7, CH), 68.7 (dd, J = 24.3, 6.3, CH), 60.9 (CH₂); δ_F (376.50 MHz, CDCl₃) -199.9 (dm, J = 51.0, 1F), -201.6 (dm, J = 55.0, 1F), -202.0 (dm, J = 49.6, 1F); $\delta_{F\{H\}}$ (376.50 MHz, CDCl₃) -199.9 (dd, J = 12.7, 2.0, 1F), -201.6 (dd, J = 13.2, 12.7, 1F), -202.0 (dd, J = 13.2, 2.0, 1F). **Data for β -anomer:** δ_F (376.50 MHz, CDCl₃) -195.8 (dm, J = 52.8, 1F), -200.5 (dm, J = 50.9, 1F), -201.3 (dm, J = 50.4, 1F); $\delta_{F\{H\}}$ (376.50 MHz, CDCl₃) -195.8 (dd, J = 13.2, 12.7, 1F), -200.5 (dd, J = 13.2, 2.8, 1F), -201.3 (dd, J = 12.7, 2.8, 1F).

2,3,4-Tridehydroxy-2,3,4-trifluoroaltrose (10). A mixture of crude **20** (0.035 g, 0.15 mmol) and anhydrous tin(II) chloride (0.058 g, 0.30 mmol) were stirred in dry CH₂Cl₂ (3.84 cm³) at



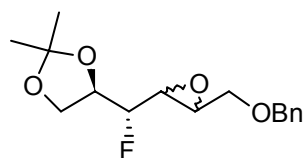
RT for 1 h. The undissolved tin(II) chloride was removed by filtration. Silica gel (1 g) was added to the filtrate. The resultant suspension was evaporated to dryness and purified over silica gel (9:1→1:9 hexane/ethyl acetate) to give **10** (0.013 g, 48%, mixture of α - and β -anomers) as a transparent oil. The product was recrystallised from CHCl₃. The relative stereochemistry of the β -anomer was determined by x-ray structure

analysis, mp 78–80 °C (from CHCl₃). The anomeric ratio in the anomeric mixture was α/β : 0.8/1 by ¹⁹F NMR (376.50 MHz, CDCl₃). **Data for the anomeric mixture:** δ_H (400.13 MHz, CDCl₃) 5.51–5.02 (m, 4H), 5.00–4.59 (m, 4H), 4.51–4.33 (m, 1H), 4.09–3.76 (m, 5H), 2.84 (br s, 2 x OH); MS (ESI, +ve) m/z 208.98 [M-Na]⁺ (100); HRMS (ESI, +ve) C₆H₉F₃O₃Na⁺ requires m/z 209.0401, found 209.0403. **Data for β -anomer:** δ_C (100.61 MHz, CDCl₃) 91.4 (d, J = 17.4, CH), 88.5–81.8 (m, CH), 72.2 (dd, J = 25.0, 2.8, CH), 61.4 (CH₂); δ_F (376.50 MHz, CDCl₃) 213.4 (dm, J = 44.4, 1F), -214.3 (dm, J = 48.8, 1F), -219.3 (dt, J = 46.5, 17.3, 1F); $\delta_{F\{H\}}$ (376.50 MHz, CDCl₃) -213.4 (d, J = 11.7, 1F), -214.3 (dd, J = 17.3, 11.7, 1F), -219.3 (d, J = 17.3, 1F). **Data for α -anomer:** δ_C (100.61 MHz, CDCl₃) 91.9 (d, J = 32.1, CH), 88.5–81.8 (m, CH), 66.1 (dd, J = 24.6, 2.8, CH), 61.5 (CH₂); δ_F (376.50 MHz, CDCl₃) -200.5

(dm, $J = 44.2$, 1F), -209.7 (dm, $J = 45.4$, 1F), -213.9 (dm, $J = 48.7$, 1F); $\delta_{F\{H\}}$ (376.50 MHz, $CDCl_3$) -200.5 (dd, $J = 17.7$, 2.1, 1F), -209.7 (dd, $J = 11.1$, 2.1, 1F), -213.9 (dd, $J = 17.7$, 11.1, 1F).

(*R*)-4-((*R*)-(3-(Benzyloxymethyl)oxiran-2-yl)fluoromethyl)-2,2-dimethyl-1,3-dioxolane

(12a, 12b). *m*-CPBA (4.994 g, 15.1 mmol) was added to a solution of (*R*)-11 (2.109 g, 7.5 mmol) in CH_2Cl_2 (38 cm^3) at 0 °C. After 1 minute the ice/water bath was removed and the solution was stirred for 5 days at RT. The resultant solution was then stirred with a mixture of 10% (w/v) aqueous Na_2SO_3 (50 cm^3) for 15 min then washed with saturated aqueous $NaHCO_3$ (50 cm^3). The organic layer was dried over Na_2SO_4 . The product was purified over silica gel (9:1→3:1



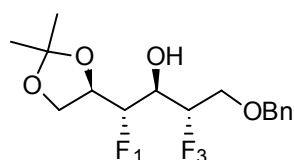
12a, 12b

hex:EtOAc) to give the inseparable mixture **12a/12b** (1.995 g, 89%, *dr* 1:0.7) as a clear oil.

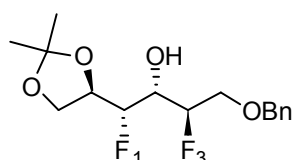
Data for both diastereoisomers: δ_H (400.13 MHz, $CDCl_3$) 7.42–7.26 (m, 10H), 4.65–4.17 (m, 8H), 4.16–4.08 (m, 2H), 4.06–3.98 (m, 2H), 3.85–3.75 (m, 2H), 3.60–3.46 (m, 2H), 3.38–3.12 (m, 4H), 1.44 (s, 3H), 1.42 (s, 3H), 1.36 (s, 6H); MS (ESI, +ve) m/z 319.02 $[M-Na]^+$ (100), 320.08 (20%); HRMS (ESI, +ve) $C_{16}H_{21}FO_4Na^+$ requires m/z 319.1322, found 319.1331. **Data for major diastereoisomer:** δ_C (100.61 MHz, $CDCl_3$) 137.9 (C), 128.6 (CH), 128.0 (CH), 127.9 (CH), 110.1 (C), 90.8 (d, $J = 180.1$, CH), 74.26 (d, $J = 29.0$, CH), 73.5 (CH₂), 69.4 (CH₂), 66.1 (d, $J = 2.8$, CH), 54.4–53.3 (m, CH), 26.7 (CH₃), 25.2 (CH₃); δ_F (376.50 MHz, $CDCl_3$) -201.3 (dm, $J = 47.7$, 1F); $\delta_{F\{H\}}$ (376.50 MHz, $CDCl_3$) -201.3 (s, 1F).

Data for minor diastereoisomer: δ_C (100.61 MHz, $CDCl_3$) 137.8 (C), 128.6 (CH), 128.0 (CH), 127.9 (CH), 110.3 (C), 90.2 (d, $J = 178.1$, CH), 74.3 (d, $J = 25.7$, CH), 73.5 (CH₂), 69.2 (CH₂), 65.7 (d, $J = 4.8$, CH), 54.4–53.3 (m, CH), 26.6 (CH₃), 25.3 (CH₃); δ_F (376.50 MHz, $CDCl_3$) -199.6 (dt, $J = 48.0$, 12.7, 1F); $\delta_{F\{H\}}$ (376.50 MHz, $CDCl_3$) -199.6 (s, 1F).

(1*S*,2*R*,3*R*)-4-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-difluorobutan-2-ol (13) and (1*S*,2*S*,3*S*)-4-(benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-difluorobutan-2-ol (14). A solution of **12a/12b** (0.114 g, 0.40 mmol, *dr* 1:0.7) in dry $CHCl_3$ (1288 μ l) was introduced in a microwave reaction glass vessel under an atmosphere of argon.



13



14

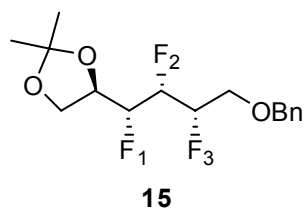
$Et_3N \cdot 3HF$ (514 μ l, 3.12 mmol) and dry Et_3N (118 μ l, 0.86 mmol) were then added and the reaction mixture was stirred for 2 h at 120 °C under microwave irradiation. After cooling, further $Et_3N \cdot 3HF$ (514 μ l, 3.12 mmol) was added and the reaction mixture

was stirred for 3 h at 100 °C, for 12 h at 120 °C, for 3 h at 130 °C and for 3 h at 140 °C under microwave irradiation. After cooling the reaction mixture was concentrated onto silica and subjected to flash chromatography over silica gel (9:1→4:1 hexane/ethyl acetate) to give separately **13** (0.02 g, 16%) and **14** (0.036 g, 29%) as clear oils. **Data for 13:** $[\alpha]_D^{22} -6.23$ (c

1.25 in CHCl₃), $\nu_{\max}$ (NaCl)/cm⁻¹ 3445, 3086, 3058, 3025, 2980, 2936, 1497, 1455, 1410, 1373, 1256, 1217, 1150, 1102, 1063, 845, 738, 699; δ_{H} (400.13 MHz, CDCl₃) 7.42–7.26 (m, 5H), 4.83 (dm, J = 46.4, 1H), 4.68–4.49 (m, 3H), 4.48–4.35 (m, 1H), 4.33–4.17 (m, 1H), 4.17–4.09 (m, 1H), 4.09–4.02 (m, 1H), 3.91–3.87 (m, 1H), 3.84–3.77 (m, 1H), 2.83 (d, J = 4.9, OH), 1.44 (s, 3H), 1.36 (s, 3H); δ_{C} (100.61 MHz, CDCl₃) 137.5 (C), 128.7 (CH), 128.2 (CH), 128.0 (CH), 110.1 (C), 91.7 (dd, J = 176.3, 3.6, CH), 90.6 (dd, J = 175.2, 6.2, CH), 73.9 (CH₂), 73.8 (d, J = 29.2, CH), 70.9 (dd, J = 24.1, 22.2, CH), 69.3 (d, J = 21.7, CH₂), 66.2 (d, J = 4.4, CH₂), 26.7 (CH₃), 25.3 (CH₃); δ_{F} (376.50 MHz, CDCl₃) -196.6 (dddd, J = 46.4, 27.2, 24.7, 9.4, F₃), -200.7 (ddd, J = 46.5, 14.0, 12.6, F₁); $\delta_{\text{F}\{\text{H}\}}$ (376.50 MHz, CDCl₃) -196.6 (s, F₃), -200.7 (s, F₁); MS (ESI, +ve) m/z 339.07 [M-Na]⁺ (100); HRMS (ESI, +ve) C₁₆H₂₂F₂O₄Na⁺ requires m/z 339.1384, found 339.1389. **Data for 14:** [α]_D²² -8.3 (c 1.25 in CHCl₃), $\nu_{\max}$ (NaCl)/cm⁻¹ 3440, 3087, 3070, 3025, 2986, 2930, 1455, 1373, 1256, 1217, 1069, 842, 738, 699; δ_{H} (400.13 MHz, CDCl₃) 7.42–7.26 (m, 5H), 4.82–4.48 (m, 4H), 4.46–4.33 (m, 1H), 4.23–4.00 (m, 3H), 3.94–3.78 (m, 2H), 2.54 (d, J = 6.2, OH), 1.42 (s, 3H), 1.37 (s, 3H); δ_{C} (100.61 MHz, CDCl₃) 137.5 (C), 128.7 (CH), 128.1 (CH), 128.0 (CH), 110.0 (C), 90.5 (dd, J = 178.1, 2.6, CH), 89.8 (dd, J = 176.3, 3.7, CH), 73.9 (CH₂), 73.0 (d, J = 29.8, CH), 69.4 (d, J = 21.0, CH₂), 68.5 (dd, J = 25.9, 17.6, CH), 66.5 (d, J = 2.7, CH₂), 26.9 (CH₃), 25.2 (CH₃); δ_{F} (376.50 MHz, CDCl₃) -195.3 (dm, J = 46.8, F₃), -212.0 (dm, J = 46.6, F₁); $\delta_{\text{F}\{\text{H}\}}$ (376.50 MHz, CDCl₃) -195.3 (d, J = 3.0, F₃), -212.0 (d, J = 3.0, F₁); MS (ESI, +ve) m/z 339.05 [M-Na]⁺ (100); HRMS (ESI, +ve) C₁₆H₂₂F₂O₄Na⁺ requires m/z 339.1395, found 339.1394.

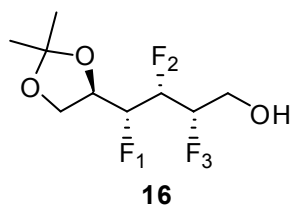
(*R*)-4-((1*R*,2*R*,3*S*)-4-(Benzyloxy)-1,2,3-trifluorobutyl)-2,2-dimethyl-1,3-dioxolane (15).

DeoxofluorTM (1.340 cm³, 3.15 mmol) was added to a solution of **13** (0.400 g, 1.26 mmol) in dry CH₂Cl₂ (25 cm³) at 0 °C. After addition the mixture was heated at vigorous reflux (oil bath temperature 70 °C) for 14 h. The reaction mixture was allowed to cool to RT, concentrated onto silica and subjected to flash chromatography over silica gel (9:1→5:1 hexane/ethyl acetate) to give **15** (0.229 g, 57%) as a yellow oil containing some impurities; $\nu_{\max}$ (NaCl)/cm⁻¹ 3033,



2989, 2941, 2868, 1497, 1452, 1382, 1371, 1250, 1216, 1150, 1119, 1071, 839, 741, 699; δ_{H} (400.13 MHz, CDCl₃) 7.43–7.27 (m, 5H), 5.18–4.76 (m, 2H), 4.66–4.50 (m, 3H), 4.41–4.30 (m, 1H), 4.23–4.01 (m, 2H), 3.95–3.70 (m, 2H), 1.37 (s, 3H), 1.36 (s, 3H); δ_{C} (125 MHz, CDCl₃) 137.3 (C), 128.6 (CH), 128.2 (CH), 127.9 (CH), 110.1 (C), 88.5–98.2 (m, CH), 74.0 (CH₂), 72.5 (dd, J = 29.1, 5.0, CH), 68.5 (dd, J = 21.7, 8.0, CH₂), 66.1 (m, CH) 26.8 (CH₃), 25.2 (CH₃); δ_{F} (376.50 MHz, CDCl₃) -198.3 (dm, J = 47.3, F₃), -209.4 (dm, J = 46.7, F₁), -214.2 (dm, J = 47.1, F₂); $\delta_{\text{F}\{\text{H}\}}$ (376.50 MHz, CDCl₃) -198.3 (d, J = 14.2, F₃), -209.4 (d, J = 9.9, F₁), -214.21 (dd, J = 14.2, 9.9, F₂); MS (ESI, +ve) m/z 340.98 [M-Na]⁺ (100); HRMS (ESI, +ve) C₁₆H₂₁F₃O₃Na⁺ requires m/z 341.1340, found 341.1334.

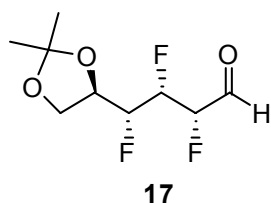
(2*S*,3*R*,4*R*)-4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3,4-trifluorobutan-1-ol (16). A solution of NaBrO₃ (0.096 g, 0.63 mmol) in water (2.1 cm³) was added to a solution of **15**



(0.068 g, 0.21 mmol) in ethyl acetate (2.85 cm³). This mixture was stirred at RT for 10 min and a solution of Na₂S₂O₄ (0.111 g, 0.54 mmol) in water (4.3 cm³) was added dropwise over 20 min at RT. The mixture was stirred for 1 h at RT. The mixture was then diluted with EtOAc and the organic phase was washed with aq. Na₂S₂O₃.

The product was purified by silica gel chromatography (9:1→5:1 hexane/ethyl acetate) to give **16** (0.026 g, 53%) as a clear oil; $[\alpha]_D^{22}$ -20.1 (c 0.57 in CHCl₃); $\nu_{\max}$ (NaCl)/cm⁻¹ 3434, 2986, 2958, 2936, 2896, 1634, 1457, 1385, 1373, 1256, 1222, 1150, 1113, 1066, 1049, 987, 945, 917, 842, 870, 786, 766, 708, 666; δ_H (400.13 MHz, CDCl₃) 5.13–4.73 (m, 2H), 4.60 (dm, *J* = 46.7, 1H), 4.45–4.31 (m, 1H), 4.22–3.79 (m, 4H) 1.91 (t, *J* = 6.3, OH), 1.43 (s, 3H), 1.37 (s, 3H); δ_C (125 MHz, CDCl₃) 110.2 (C), 93.3–88.2 (m, CH), 72.5 (dd, *J* = 29.0, 4.9, CH), 66.1 (m, CH), 61.7 (dd, *J* = 21.9, 8.1, CH₂) 26.9 (CH₃), 25.2 (CH₃); δ_F (376.50 MHz, CDCl₃) -202.0 (dm, *J* = 47.4, F₃), -209.4 (dm, *J* = 46.7, F₁), -215.0 (dm, *J* = 46.5, F₂); $\delta_{F\{H\}}$ (376.50 MHz, CDCl₃) -202.0 (d, *J* = 14.3, F₃), -209.4 (d, *J* = 9.6, F₁), -215.0 (dd, *J* = 14.3, 9.6, F₂); MS (ESI, +ve) *m/z* 251.03 [M-Na]⁺ (100); HRMS (ESI, +ve) C₉H₁₅F₃O₃Na⁺ requires *m/z* 251.0871, found 251.0872.

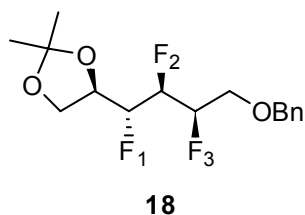
(2*S*,3*S*,4*R*)-4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3,4-trifluorobutanal (17). A solution of Dess-Martin periodinane reagent (0.133 g, 0.30 mmol) in dry CH₂Cl₂ (1.06 cm³) was



placed in an oven-dried round-bottom flask and stirred at RT for 5 min. Then a solution of **16** (0.035 g, 0.15 mmol) in dry CH₂Cl₂ (1.06 cm³) was added. After stirring for 40 min at RT, a mixture of hexane/ethyl acetate (9:1, 5 cm³) was added and the resultant suspension was quickly filtered through a silica plug (2.5 cm) by flushing 125 cm³ of 9:1 hexane/ethyl acetate. This provided aldehyde

17 (0.043 g) as a yellow oil containing impurities which was used in the next reaction without further purification due to its instability; δ_F (282.34 MHz, CDCl₃) -204.3 (dd, *J* = 11.1, 4.8, 1F); -212.5 (dd, *J* = 12.8, 11.1, 1F), -213.5 (dd, *J* = 12.8, 4.8, 1F).

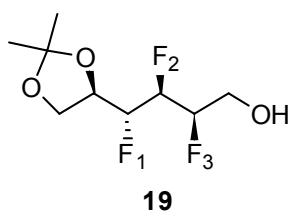
(*R*)-4-((1*R*,2*S*,3*R*)-4-(Benzyloxy)-1,2,3-trifluorobutyl)-2,2-dimethyl-1,3-dioxolane (18). DeoxofluorTM (1.340 cm³, 3.15 mmol) was added to a solution of **14** (0.400 g, 1.26 mmol)



in dry CH₂Cl₂ (25 cm³) at 0 °C. After addition the mixture was heated at vigorous reflux (oil bath temperature 70 °C) for 14 h. The reaction mixture was allowed to cool to RT, concentrated onto silica and subjected to flash chromatography over silica gel (9:1→5:1 hexane/ethyl acetate) to give **18** (0.241 g, 60%) as a yellow oil

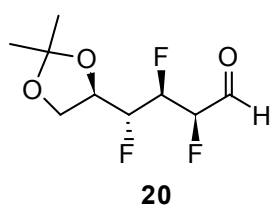
containing some impurities; $\nu_{\max}$ (NaCl)/ cm^{-1} 3089, 3058, 3025, 2986, 2930, 2874, 1497, 1455, 1379, 1370, 1259, 1214, 1147, 1108, 1066, 845, 744; δ_{H} (400.13 MHz, CDCl_3) 7.43–7.27 (m, 5H), 5.06–4.52 (m, 5H), 4.48–4.36 (m, 1H), 4.15–4.05 (m, 1H), 4.05–3.95 (m, 1H), 3.84–3.72 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H); δ_{C} (125 MHz, CDCl_3) 137.4 (C), 128.7 (CH), 128.2 (CH), 128.0 (CH), 110.1 (C), 91.1–87.8 (m, CH), 73.8 (CH_2), 73.4 (dd, $J = 25.1, 3.7$, CH), 67.6 (dd, $J = 25.2, 7.0$, CH_2), 65.3 (dd, $J = 5.7, 2.9$, CH_2) 26.2 (CH_3), 25.3 (CH_3); δ_{F} (376.50 MHz, CDCl_3) -201.3 (dm, $J = 45.9$, F_1), -203.3 (dm, $J = 47.8$, F_3), -213.6 (dm, $J = 47.1$, F_2); $\delta_{\text{F}\{\text{H}\}}$ (376.50 MHz, CDCl_3) -201.3 (dd, $J = 13.0, 5.7$, F_1), -203.3 (dd, $J = 10.7, 5.7$, F_3), -213.6 (dd, $J = 13.0, 10.7$, F_2); MS (ESI, +ve) m/z 341.07 $[\text{M}-\text{Na}]^+$ (100), 413.20 (30); HRMS (ESI, +ve) $\text{C}_{16}\text{H}_{21}\text{F}_3\text{O}_3\text{Na}^+$ requires m/z 341.1340, found 341.1344.

(2R,3S,4R)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3,4-trifluorobutan-1-ol (19). A solution of NaBrO_3 (0.096 g, 0.63 mmol) in water (2.1 cm^3) was added to a solution of **18**



(0.068 g, 0.21 mmol) in ethyl acetate (2.85 cm^3). This mixture was stirred for 10 min at RT and a solution of $\text{Na}_2\text{S}_2\text{O}_4$ (0.111 g, 0.54 mmol) in water (4.3 cm^3) was added dropwise over 20 min at room temperature. The mixture was stirred for 1 h at RT. The mixture was then diluted with EtOAc and the organic phase was washed with aq. $\text{Na}_2\text{S}_2\text{O}_3$. The product was purified by silica gel chromatography (9:1→5:1 hexane/ethyl acetate) to give **19** (0.024 g, 51%) as a clear oil; $[\alpha]_{\text{D}}^{22}$ -4.4 (c 0.39 in CHCl_3); $\nu_{\max}$ (NaCl)/ cm^{-1} 3446, 2986, 2930, 2891, 1636, 1483, 1457, 1382, 1376, 1258, 1211, 1152, 1063, 848; δ_{H} (400.13 MHz, CDCl_3) 5.03–4.64 (m, 3H), 4.52–4.36 (m, 1H), 4.18–4.10 (m, 1H), 4.07–4.00 (m, 1H), 3.99–3.84 (m, 2H), 1.97 (t, $J = 6.4$, OH), 1.44 (s, 3H), 1.37 (s, 3H); δ_{C} (125 MHz, CDCl_3) 110.3 (C), 92.0–87.8 (m, CH), 73.4 (dd, $J = 25.3, 4.1$, CH), 65.4 (dd, $J = 5.7, 2.9$, CH_2), 61.3 (dd, $J = 24.4, 7.2$, CH_2), 26.3 (CH_3), 25.2 (CH_3); δ_{F} (376.50 MHz, CDCl_3) -201.3 (dm, $J = 45.5$, F_1), -205.4 (m, F_3), -212.8 (dm, $J = 47.0$, F_2); $\delta_{\text{F}\{\text{H}\}}$ (376.50 MHz, CDCl_3) -201.3 (dd, $J = 12.7, 5.9$, F_1), -205.4 (dd, $J = 10.9, 5.9$, F_3), -212.8 (dd, $J = 12.7, 10.9$, F_2); MS (ESI, +ve) m/z 251.00 $[\text{M}-\text{Na}]^+$ (100); HRMS (ESI, +ve) $\text{C}_9\text{H}_{15}\text{F}_3\text{O}_3\text{Na}^+$ requires m/z 251.0871, found 251.0877.

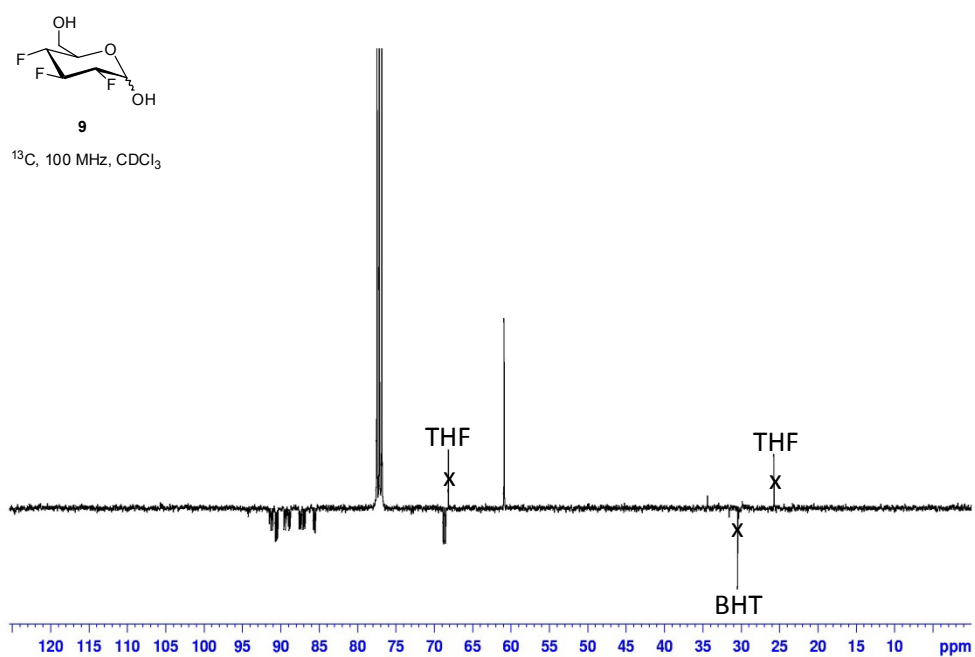
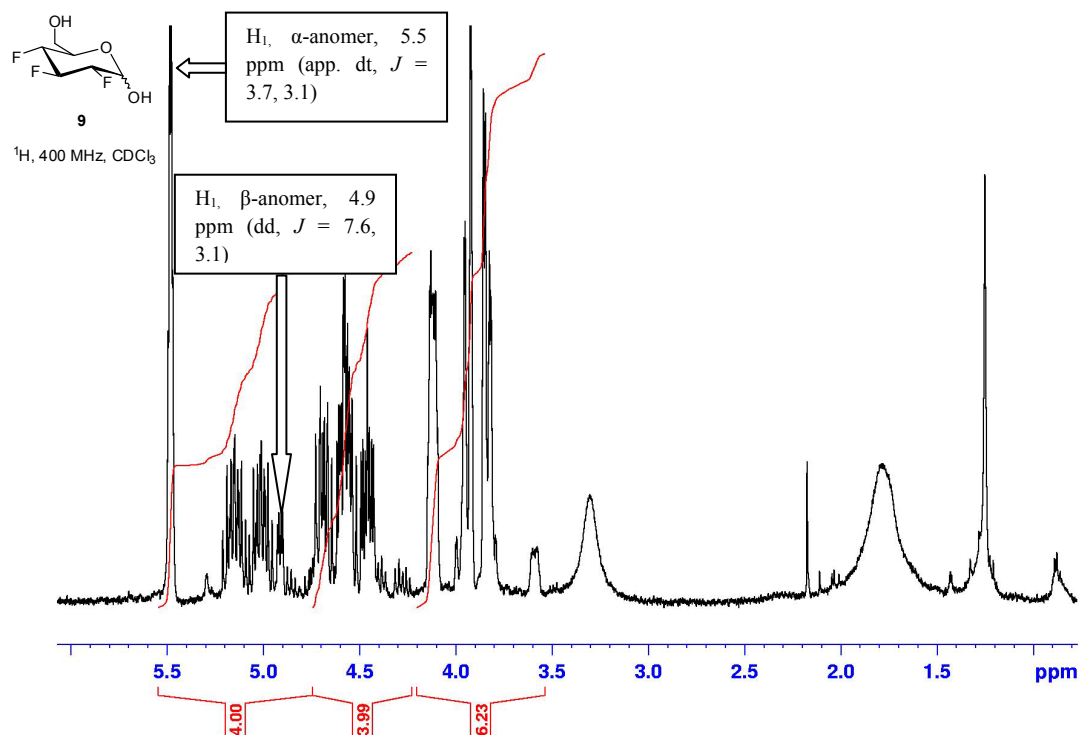
(2R,3R,4R)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3,4-trifluorobutanal (20). A solution of Dess-Martin periodinane reagent (0.133 g, 0.30 mmol) in dry CH_2Cl_2 (1.06 cm^3) was

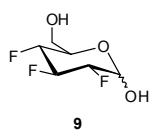


placed in an oven-dried round-bottom flask and stirred at RT for 5 min. Then a solution of **19** (0.035 g, 0.15 mmol) in dry CH_2Cl_2 (1.06 cm^3) was added. After stirring for 40 min, a mixture of hexane/ethyl acetate (9:1, 5 cm^3) was added and the resultant suspension was quickly filtered through a silica plug (2.5 cm) by flushing 125 cm^3 of 9:1 hexane/ethyl acetate. This provided aldehyde **20** (0.04 g) as a yellow oil containing impurities which was used in the next reaction without further

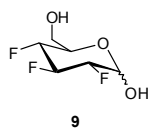
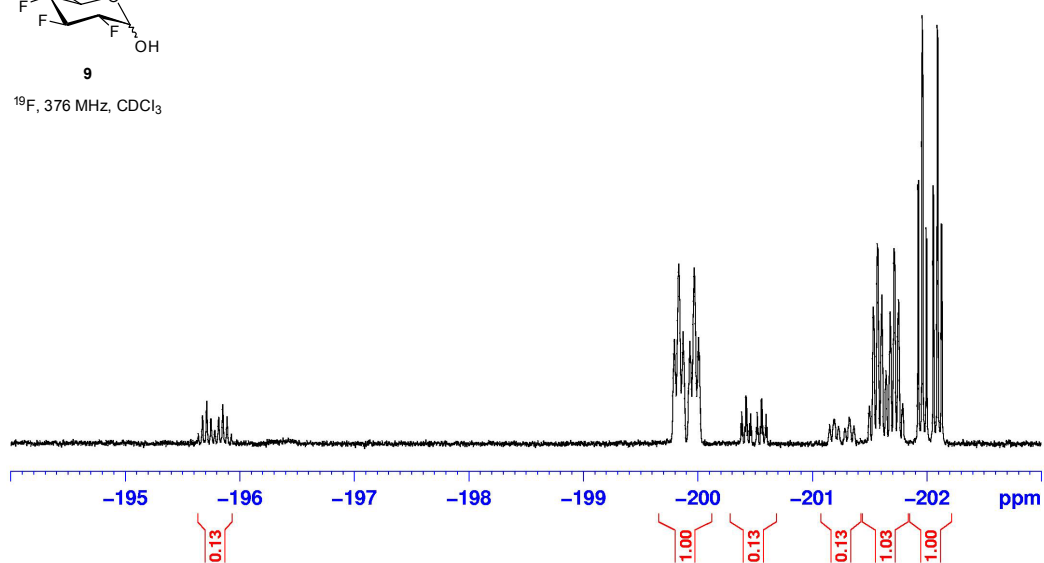
purification due to its instability; δ_F (282.34 MHz, $CDCl_3$) -201.5 (dd, $J = 13.4, 7.6, 1F$), -210.7 (dd, $J = 10.1, 13.4, 1F$), -217.0 (dd, $J = 10.1, 7.6, 1F$).

Reproduction NMR spectra for final products and intermediates

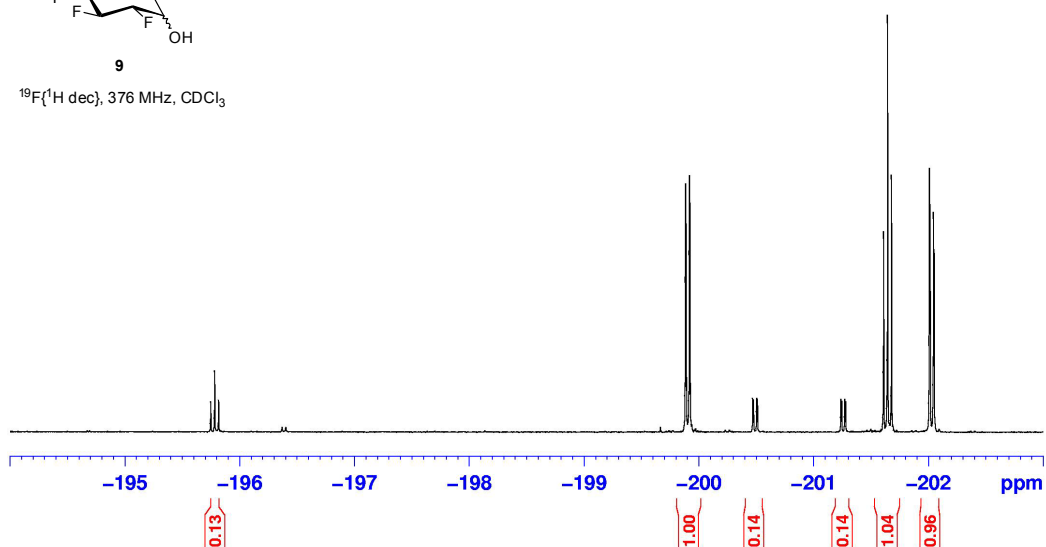


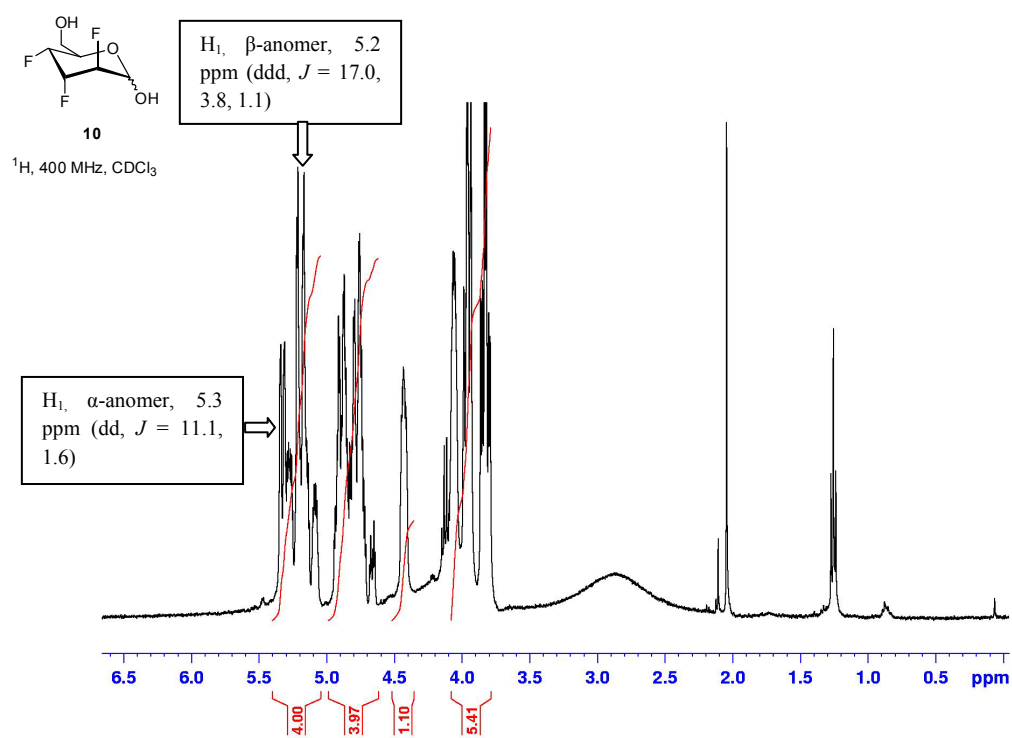
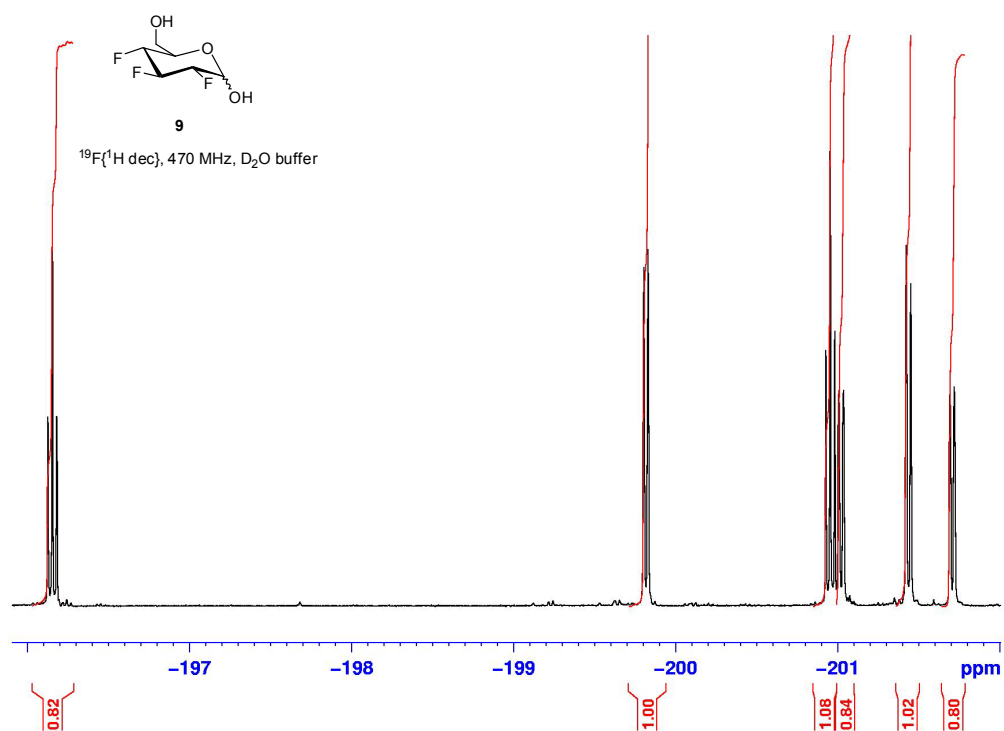


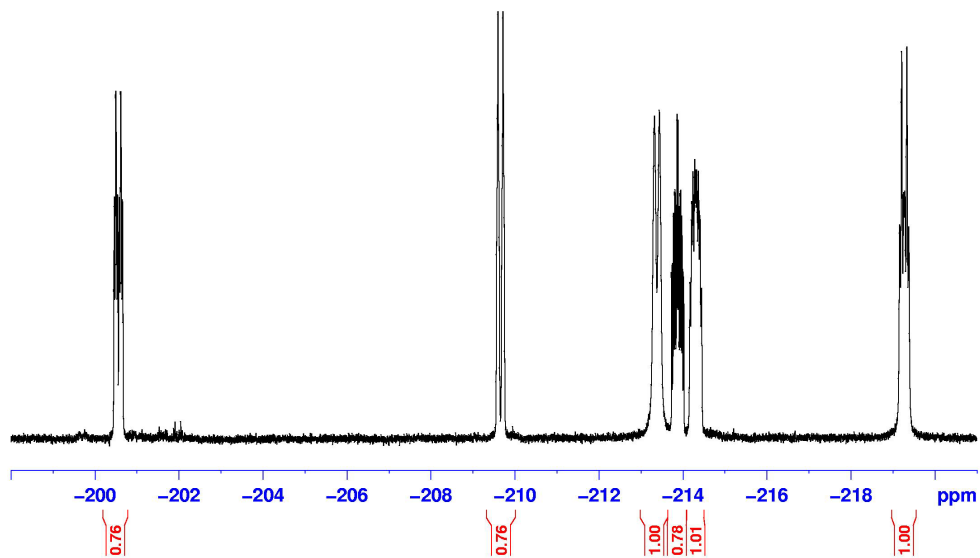
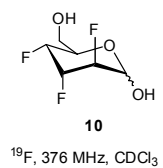
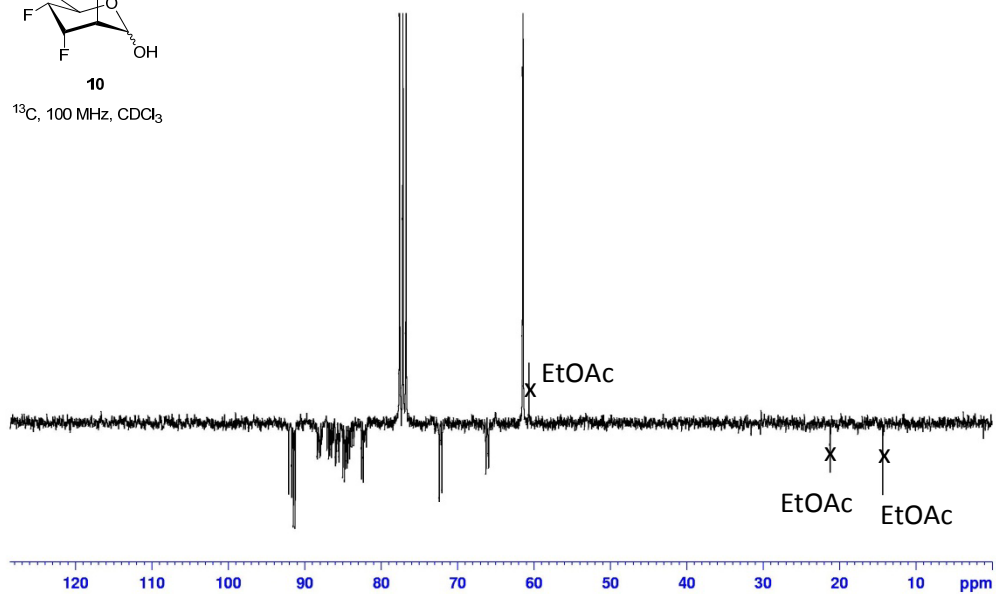
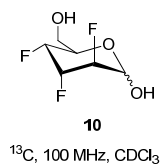
^{19}F , 376 MHz, CDCl_3

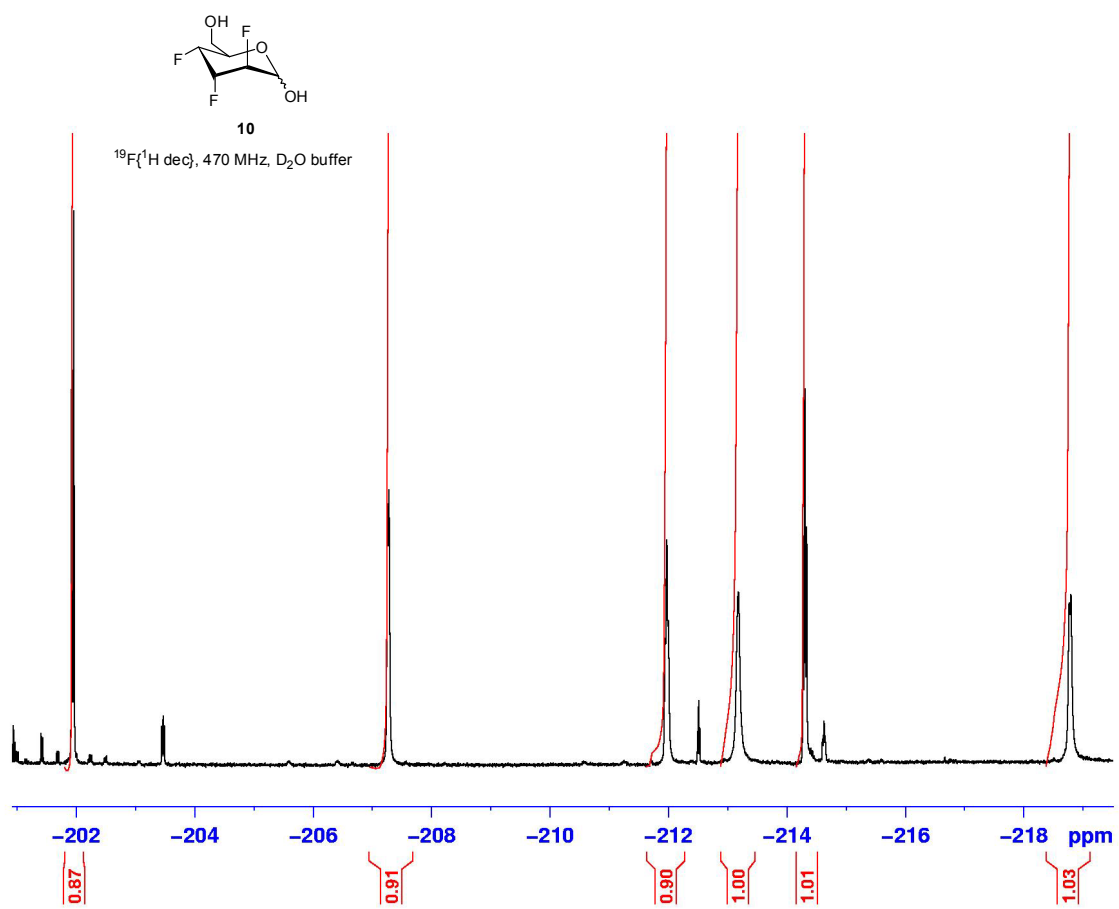
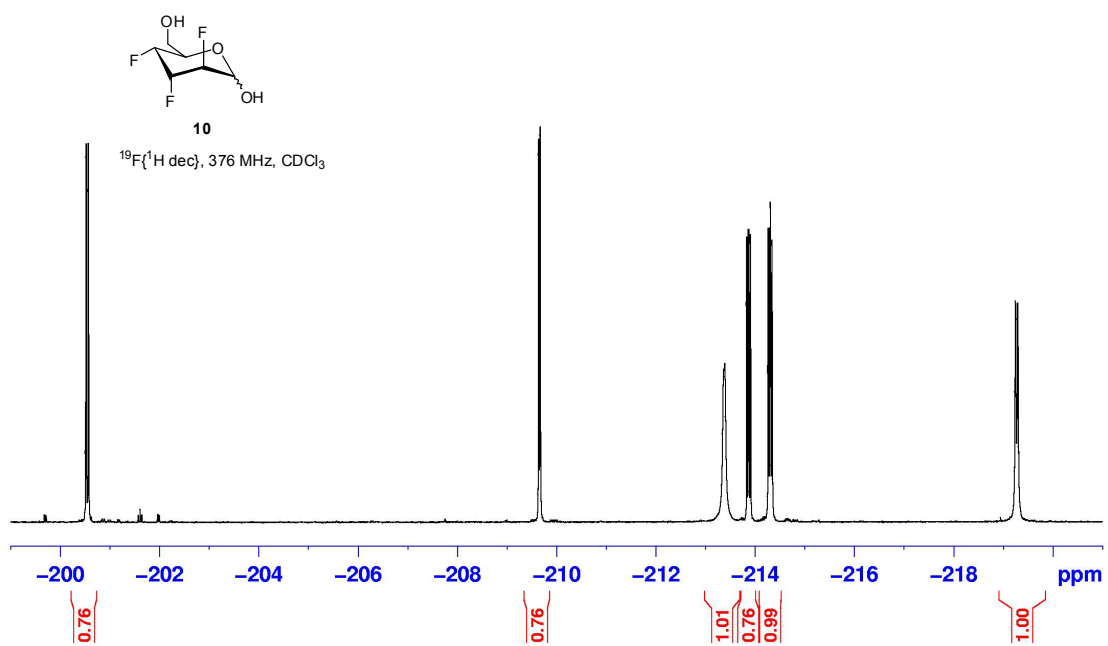


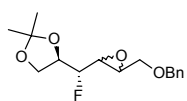
$^{19}\text{F}\{^1\text{H dec}\}$, 376 MHz, CDCl_3





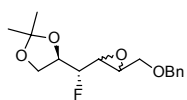
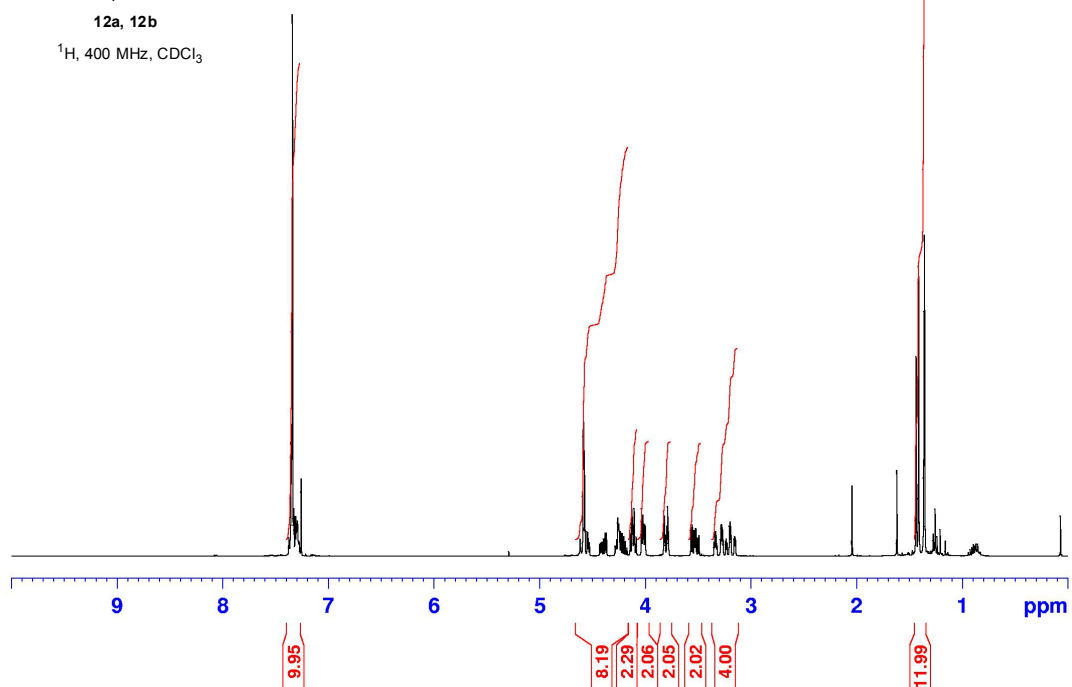






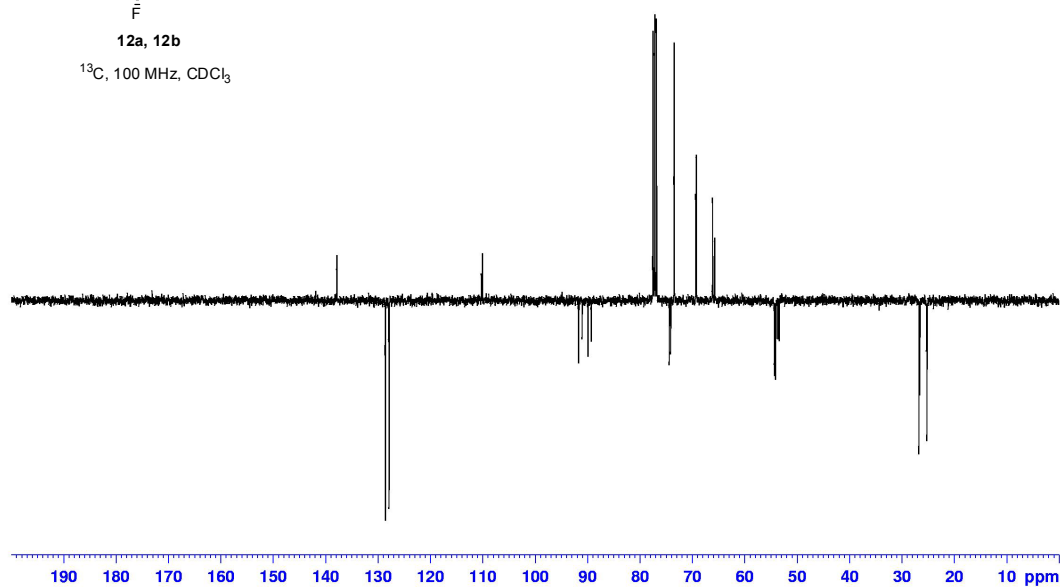
12a, 12b

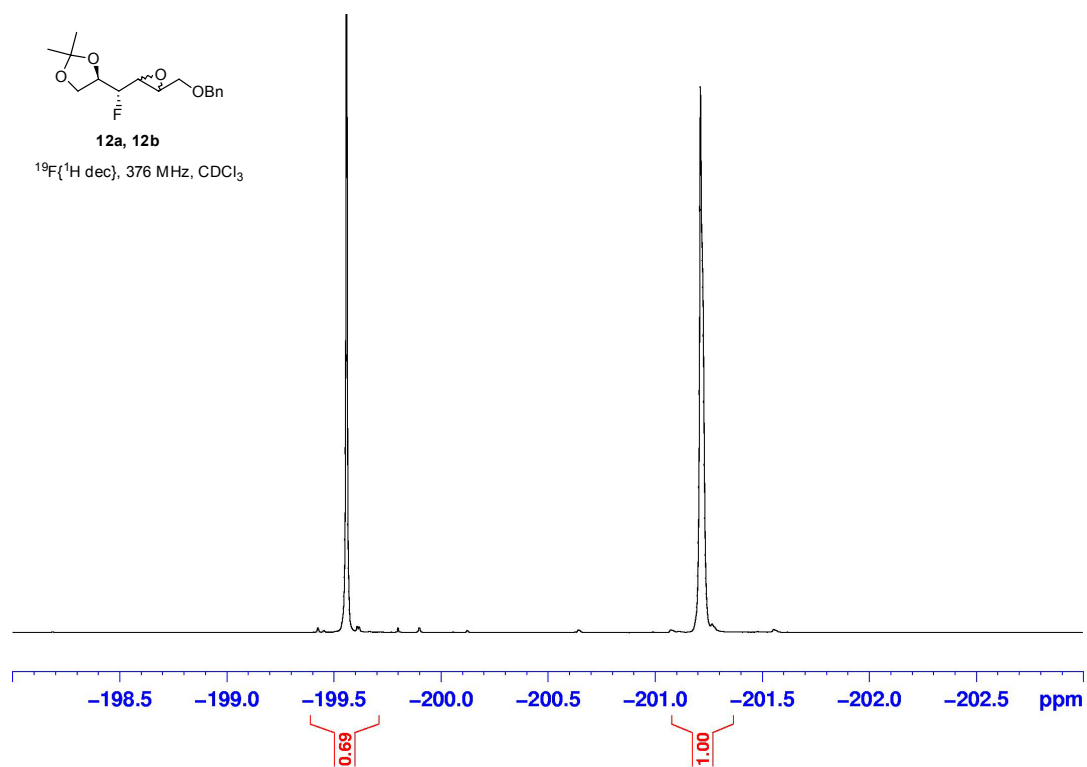
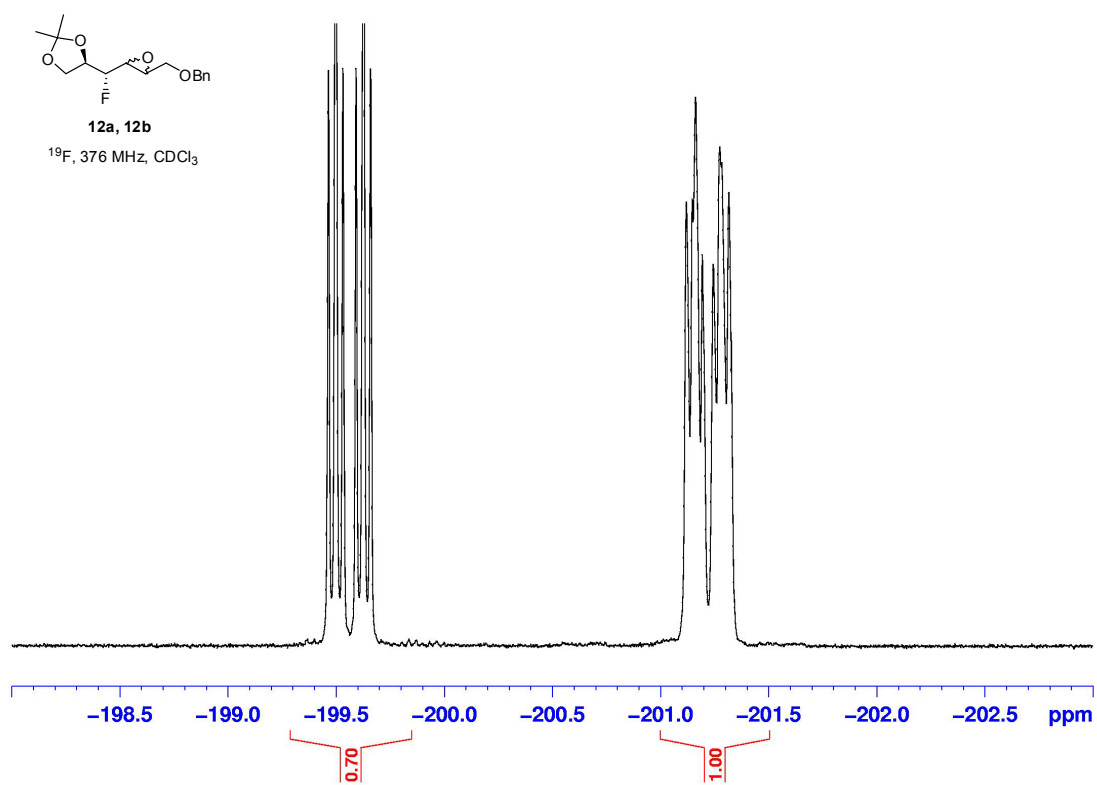
^1H , 400 MHz, CDCl_3

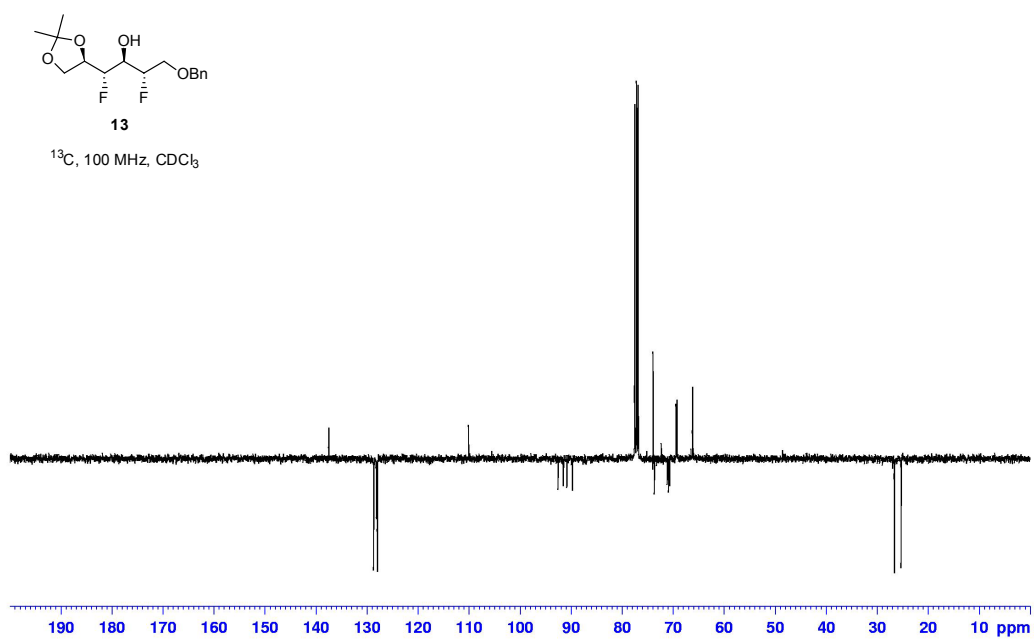
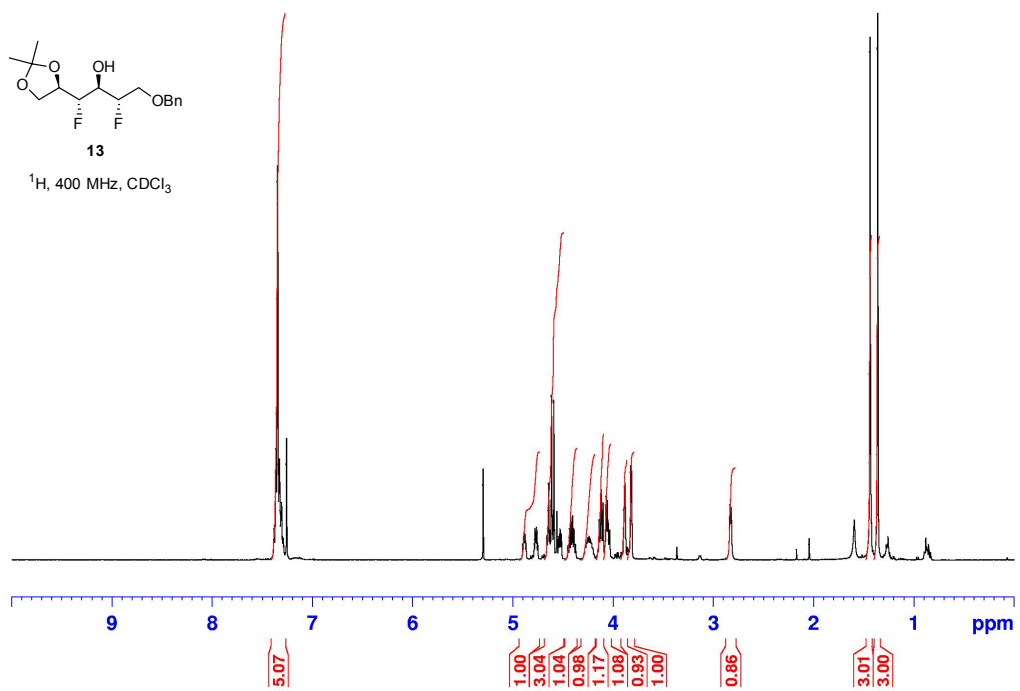


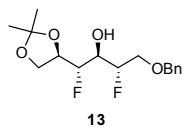
12a, 12b

^{13}C , 100 MHz, CDCl_3

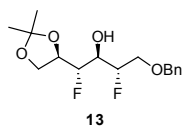
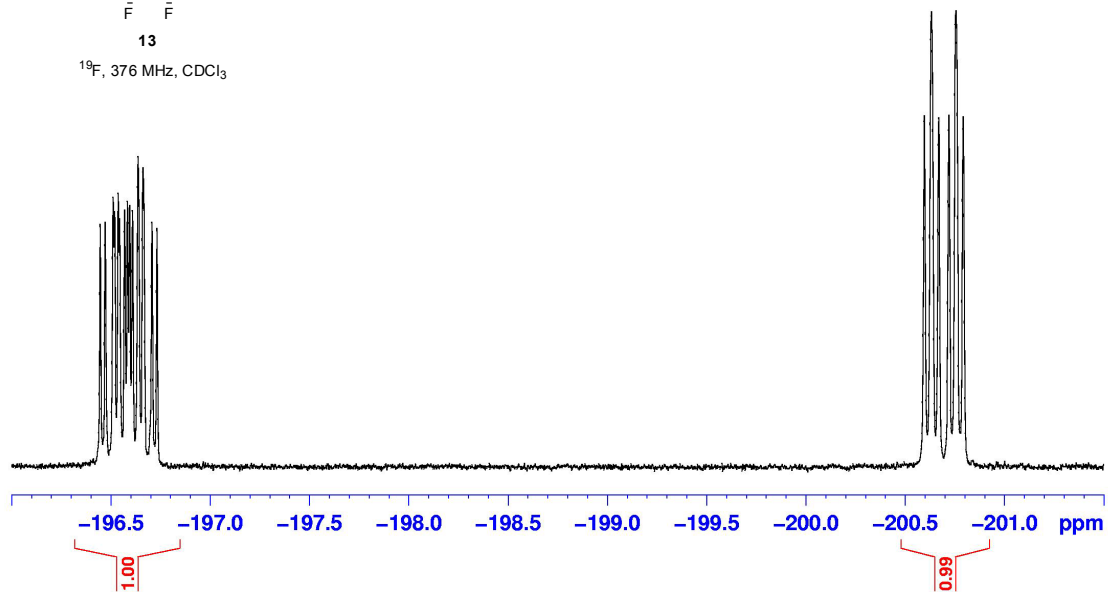




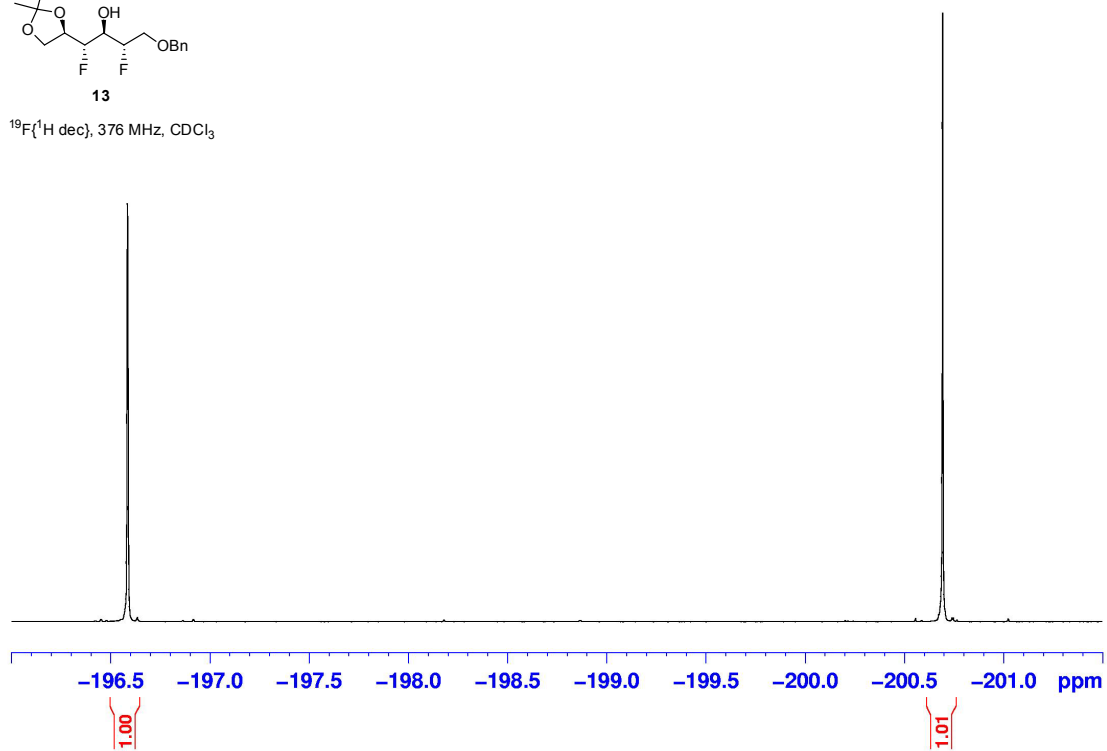


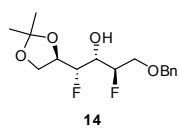


^{19}F , 376 MHz, CDCl_3

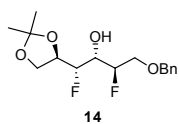
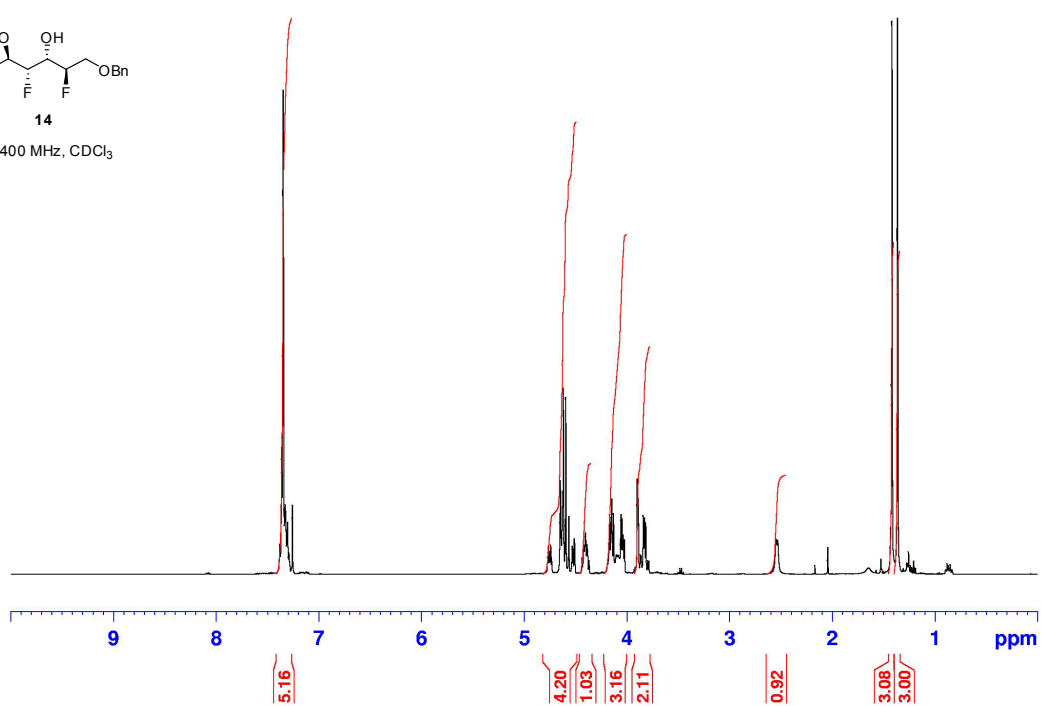


$^{19}\text{F}\{^1\text{H dec}\}$, 376 MHz, CDCl_3

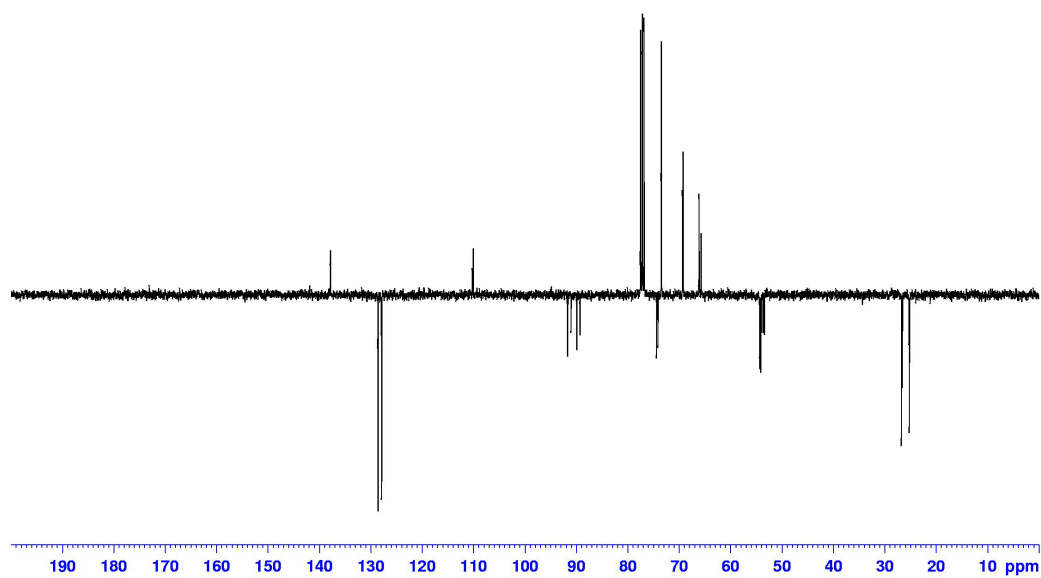


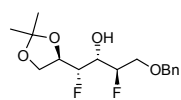


^1H , 400 MHz, CDCl_3



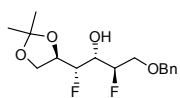
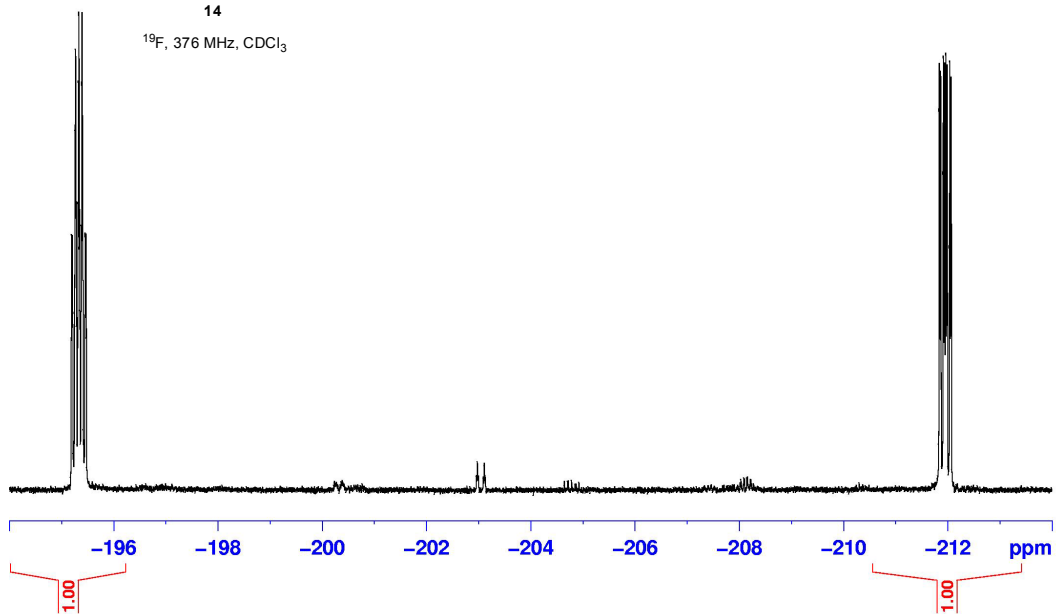
^{13}C , 100 MHz, CDCl_3





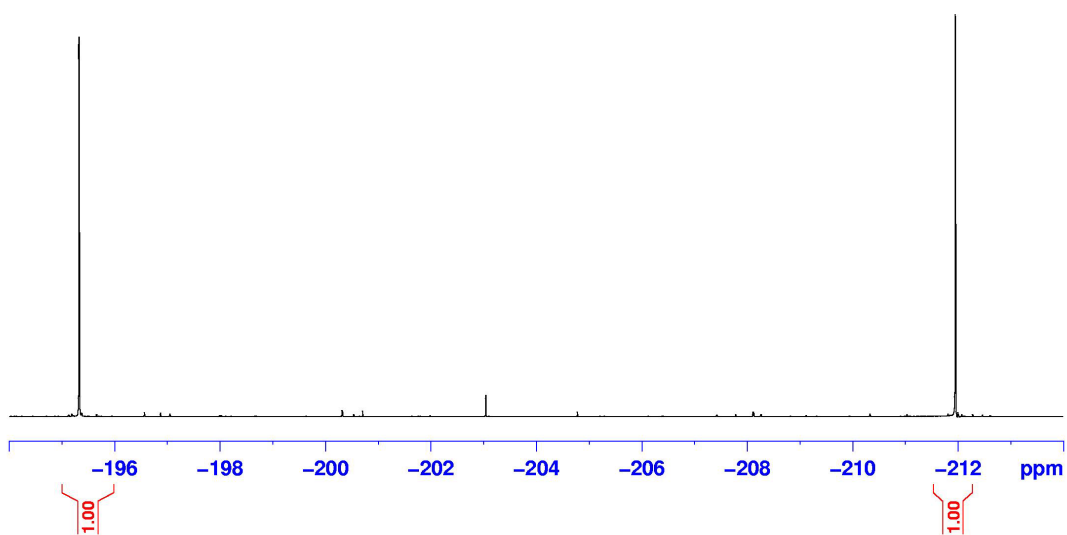
14

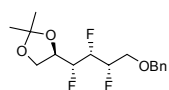
^{19}F , 376 MHz, CDCl_3



14

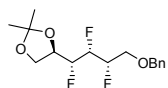
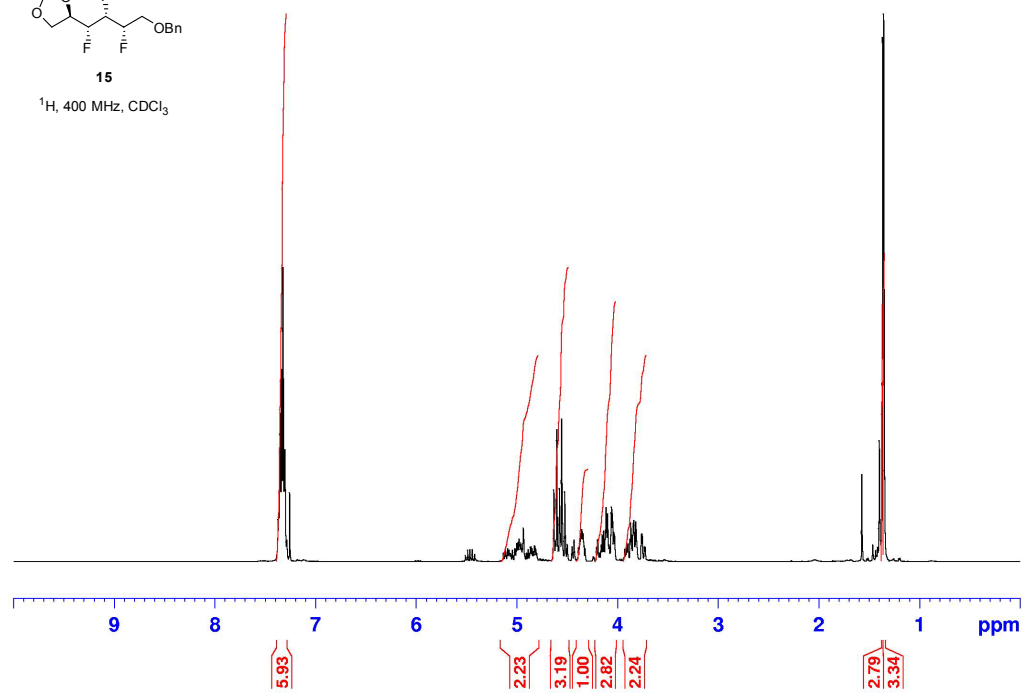
$^{19}\text{F}\{^1\text{H dec}\}$, 376 MHz, CDCl_3





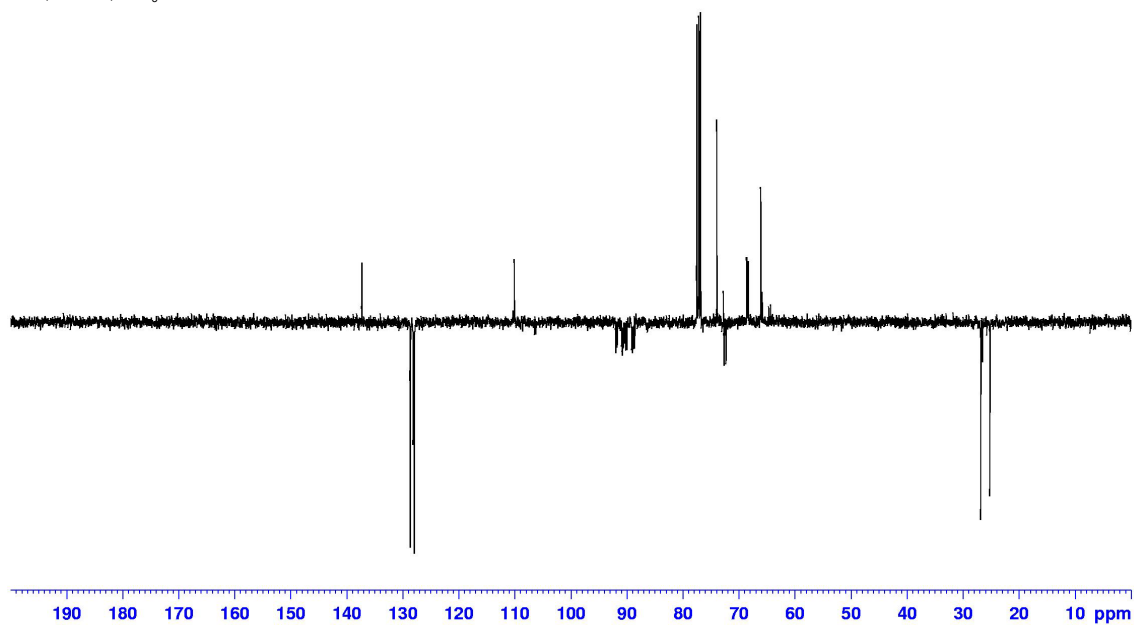
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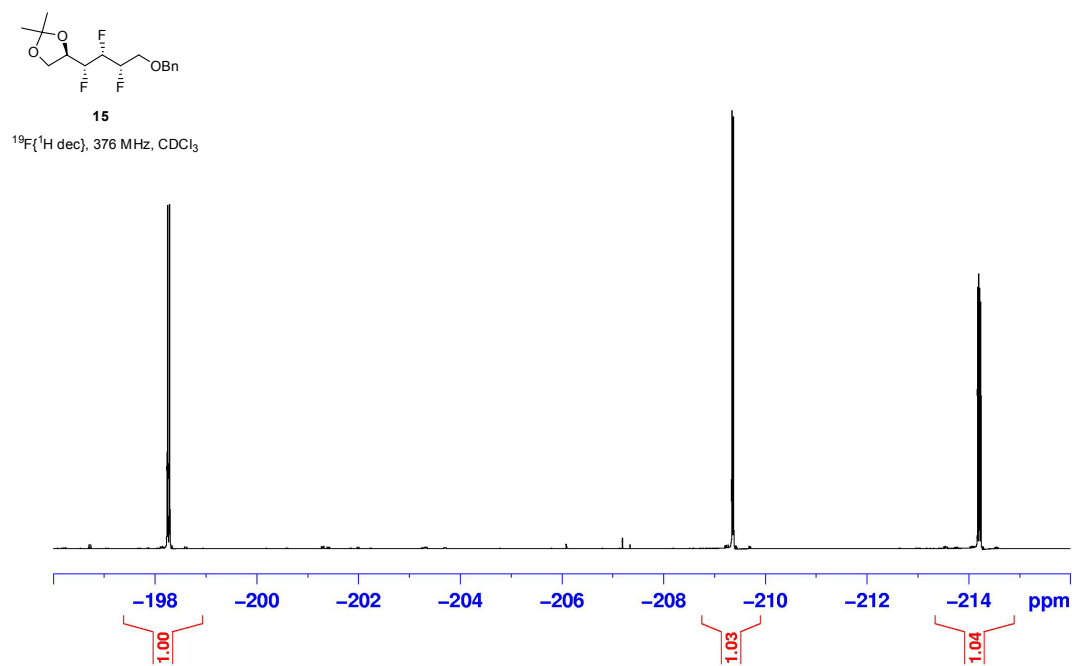
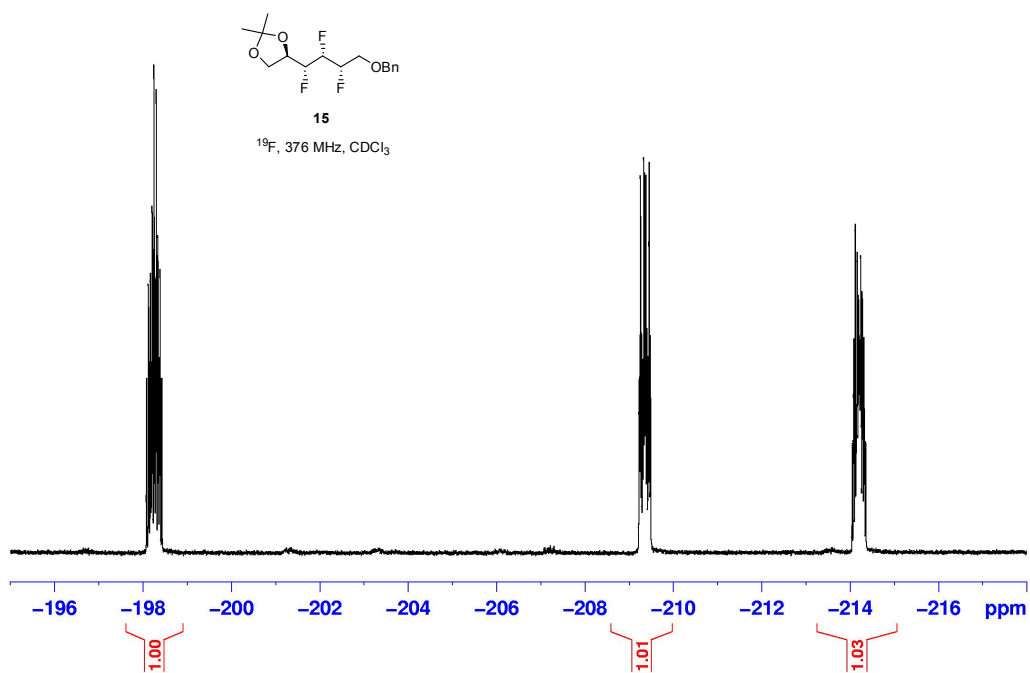
^1H , 400 MHz, CDCl_3

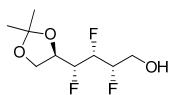


15

^{13}C , 100 MHz, CDCl_3

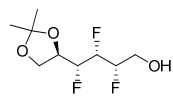
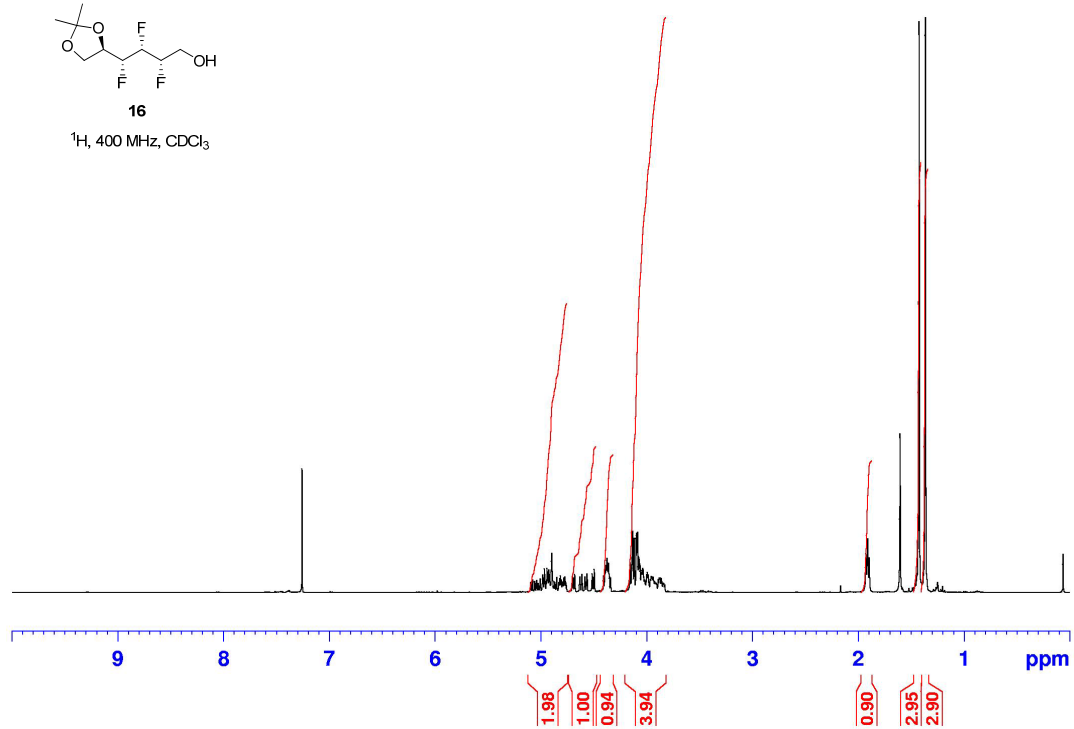






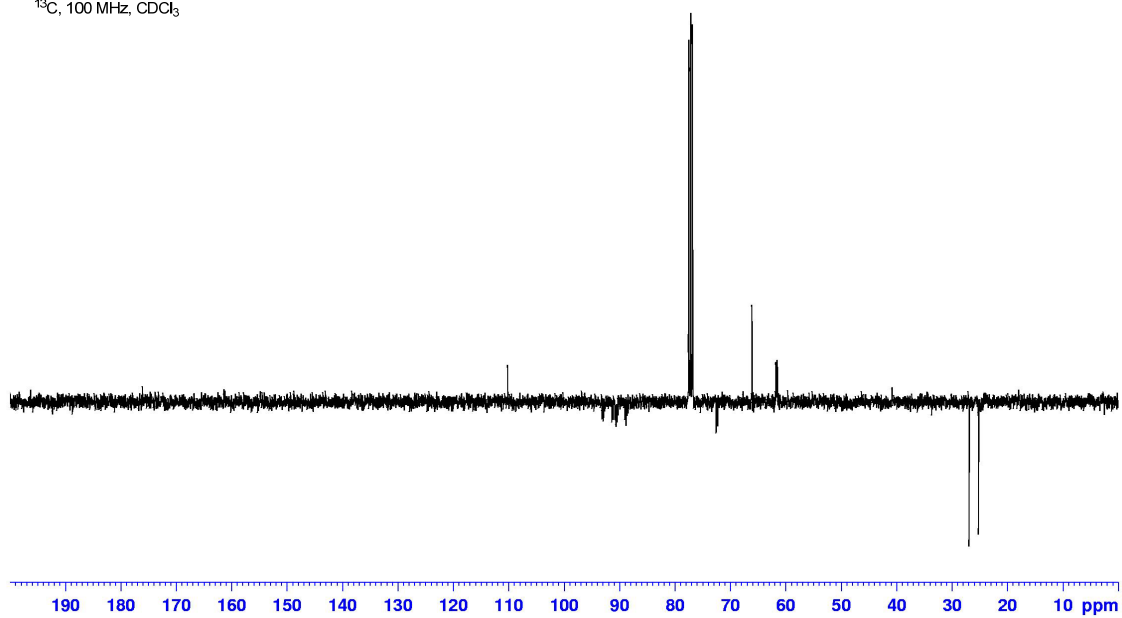
16

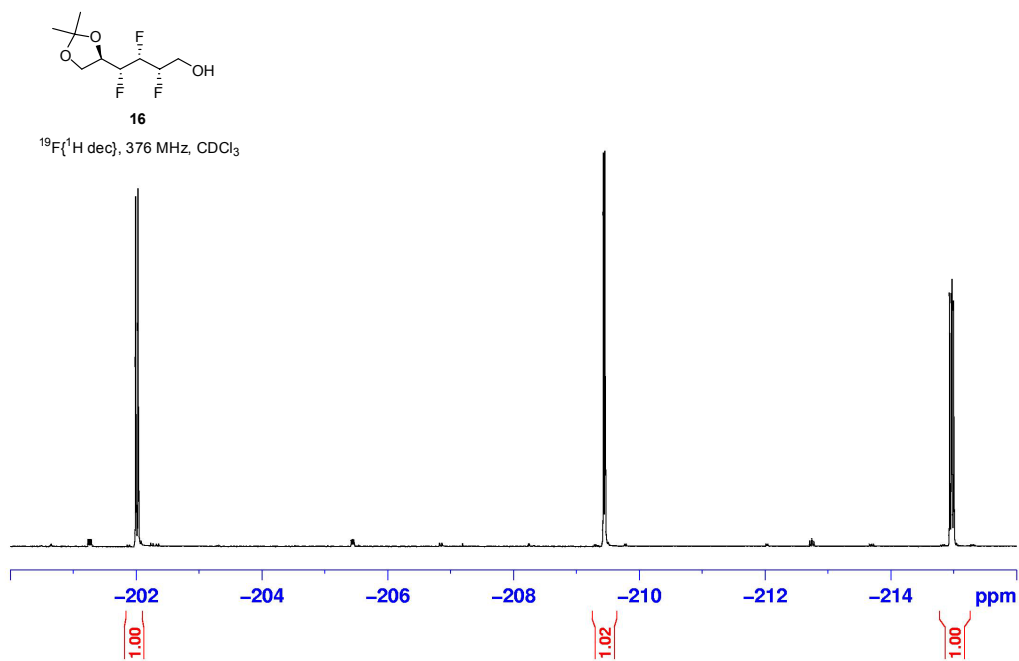
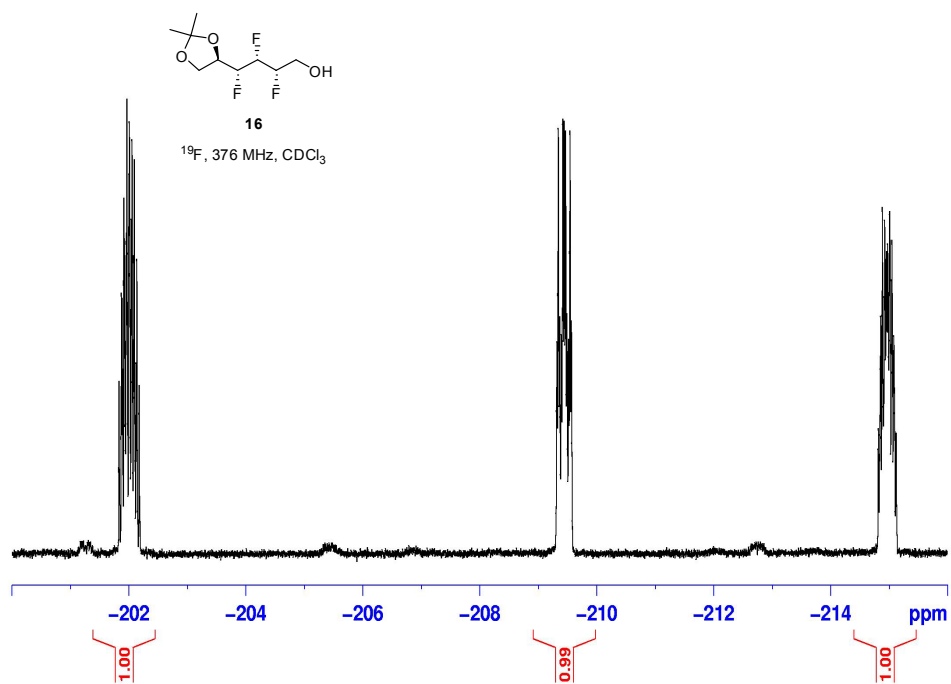
^1H , 400 MHz, CDCl_3



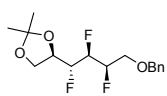
16

^{13}C , 100 MHz, CDCl_3



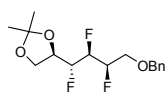
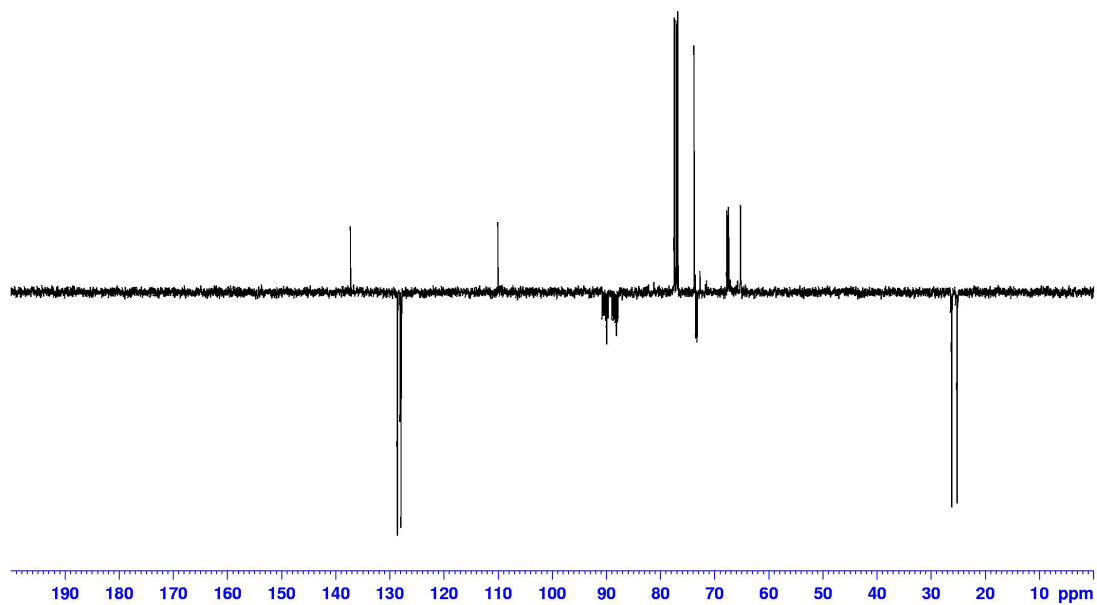


 $^{19}\text{F}\{^1\text{H dec}\}$, 282 MHz, CDCl_3 ¹H, 400 MHz, CDCl₃



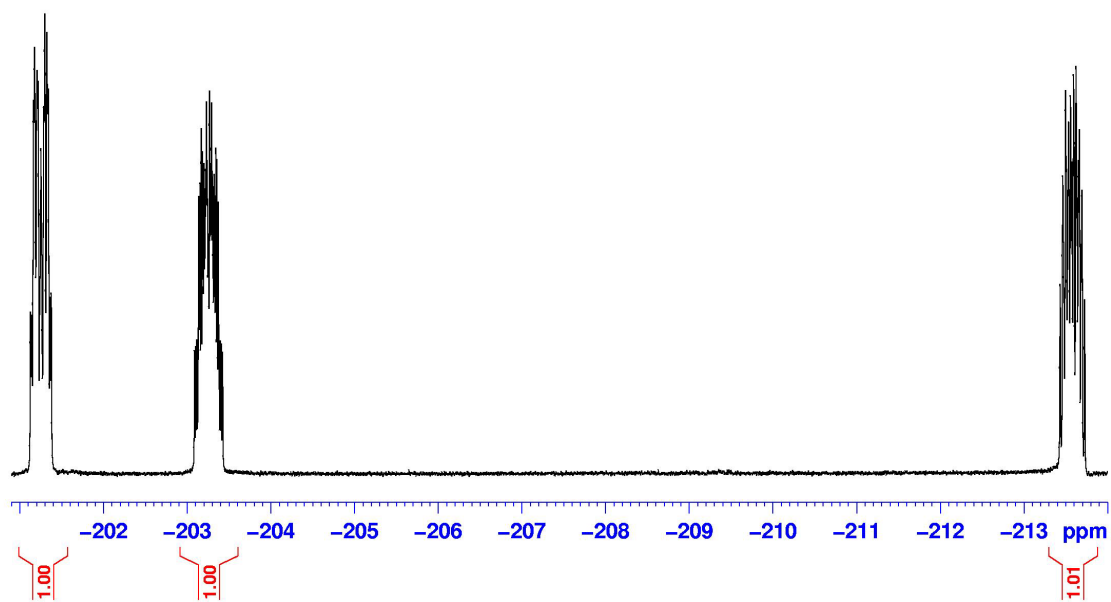
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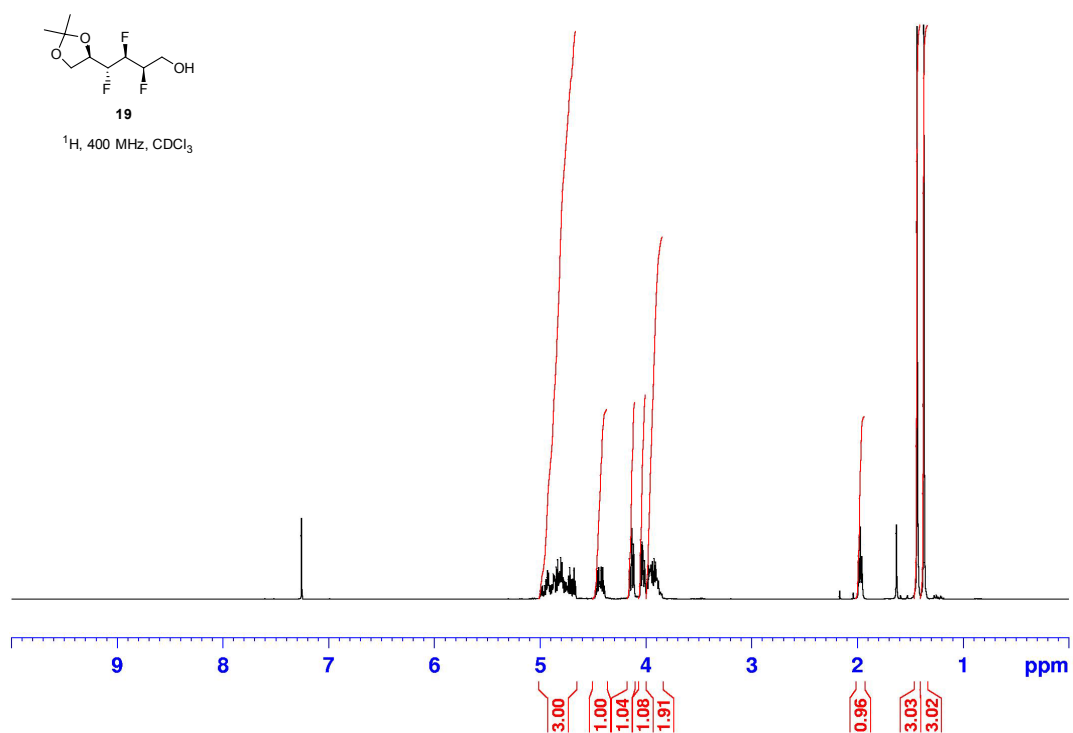
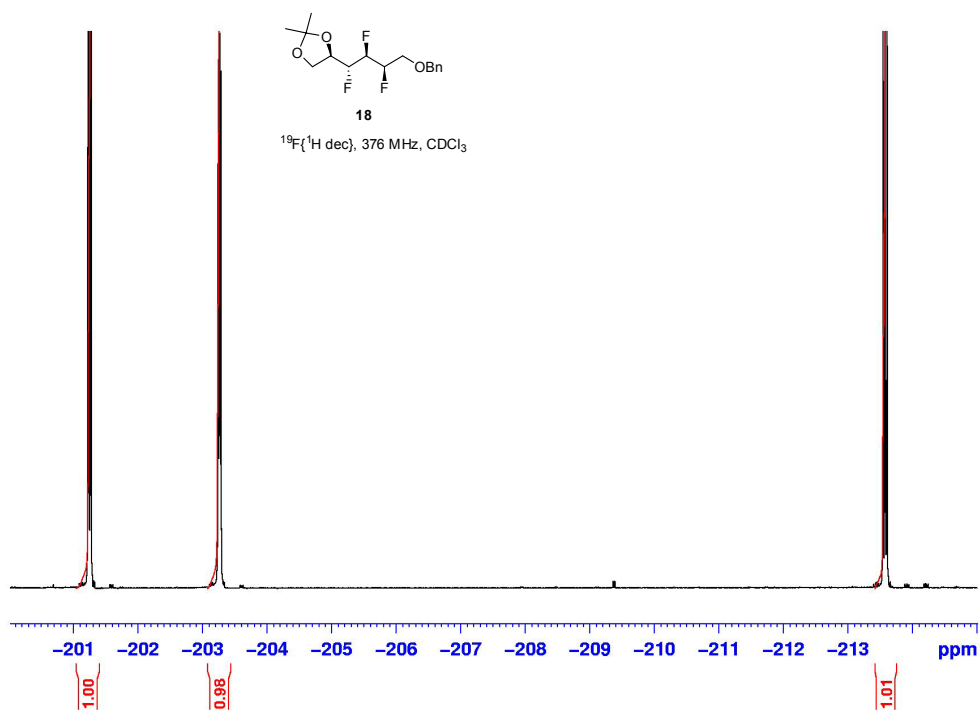
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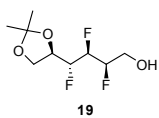


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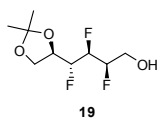
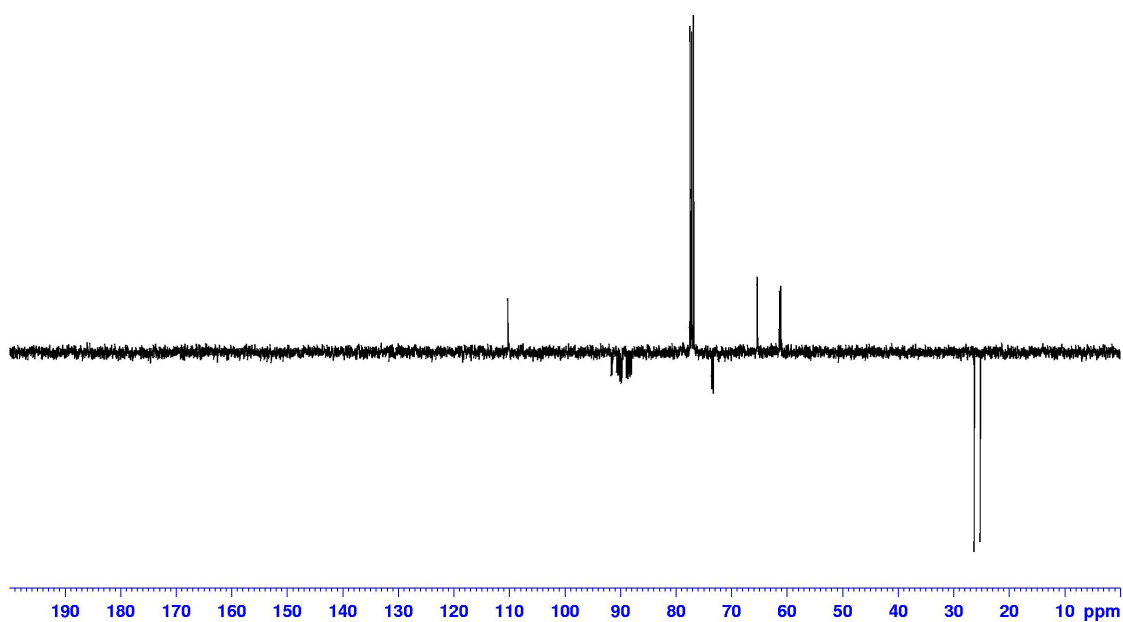
^{19}F , 376 MHz, CDCl_3



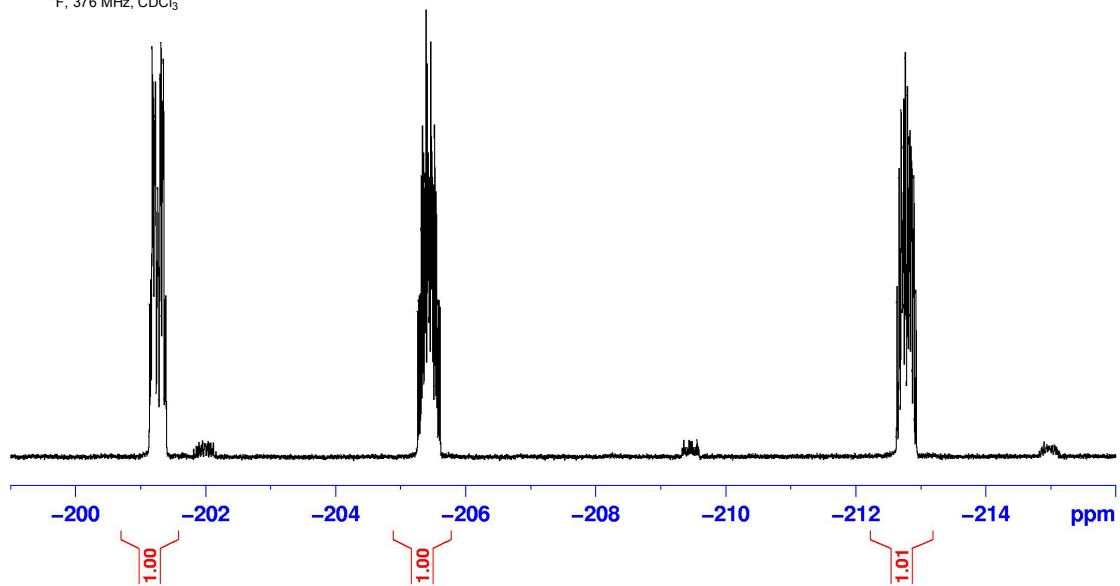


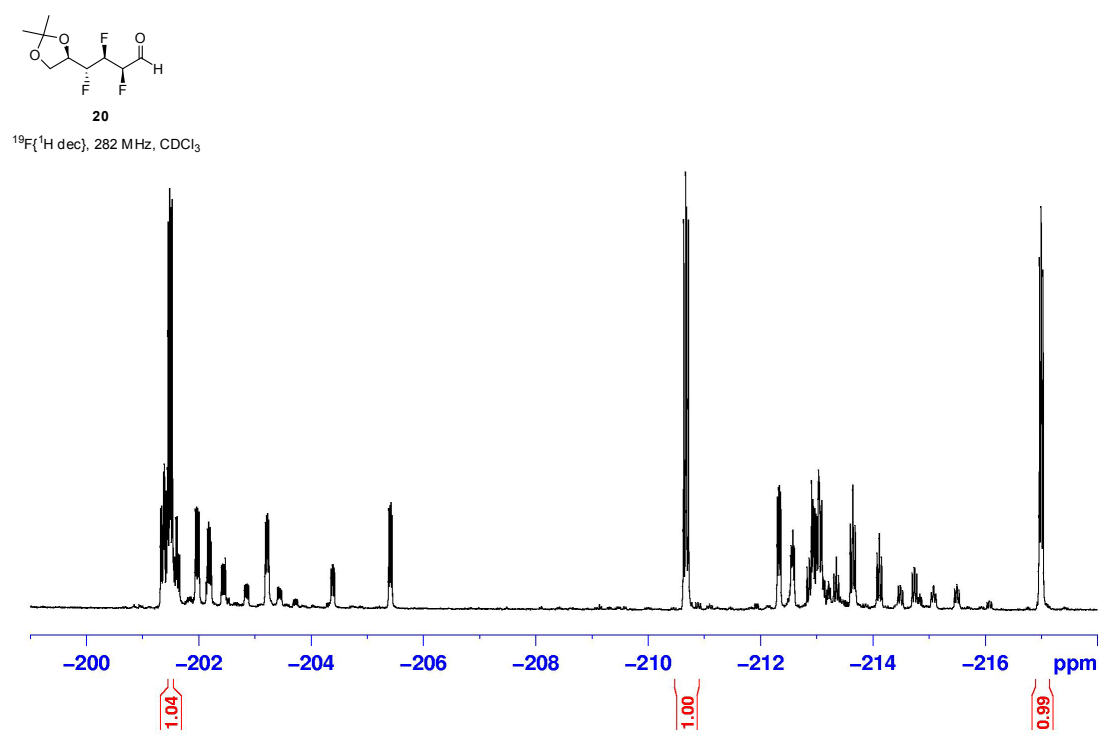
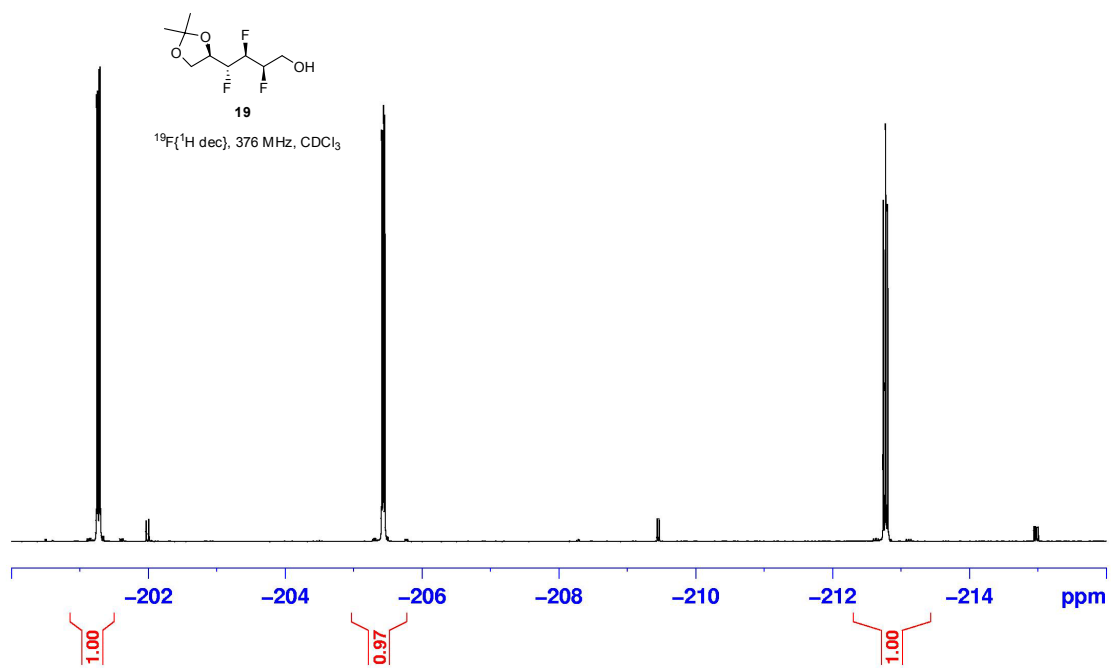


^{13}C , 100 MHz, CDCl_3



^{19}F , 376 MHz, CDCl_3





References for Supplementary Information

1. C. L. Perrin, T. J. Dwyer, *Chem. Rev.* 1990, **90**, 935-967.

See primary manuscript for references leading to the synthesis and the background to the ^{19}F -EXSY NMR experiments.