Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of B-Ring-fluorinated (-)-Epicatechin Gallate Derivatives

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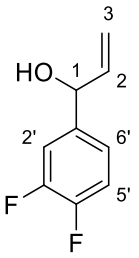
1 GENERAL METHODS

All reactions were performed under a nitrogen atmosphere using established Schlenk techniques. The glassware was dried at 120 °C for two hours and cooled under evacuation using a high vacuum rotary vane oil pump (vacuubrand RZ 6). Chemicals and solvents were purchased from Alfa Aesar, Fluka, TCI, VWR, Merck or Sigma Aldrich and used without further purification, unless otherwise stated. Dry solvents (tetrahydrofuran, toluene, dichloromethane, diethylether) were taken from a MBraun Solvent Purification System (MB-SPS-800). *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 and stored over molecular sieve (4 Å). Other chemicals or solvents were purified according to common laboratory methods. For thin-layer chromatography (TLC) analysis, Macherey-Nagel precoated plates (ALUGRAM® Xtra G/UV254) with fluorescence indicator were used. The detection occurred by UV radiation (254 nm) and by staining with cerium molybdophosphoric acid solution (16.0 mL concentrated H_2SO_4, 200 mL distilled water, 5.00 g molybdophosphoric acid, 2.00 g $Ce(SO_4)_2$ x 4 H_2O). For preparative silica-gel chromatography or flash chromatography Macherey-Nagel silica-gel (60 Mesh, 0.04-0.063 mm) was used. Medium pressure chromatography (MPLC) was done using a Büchi Sepacore® X50 system.

^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded on a Bruker Avance III 300 or 600 spectrometer. The NMR samples were dissolved in deuterated chloroform ($CDCl_3$) or methanol (CD_3OD). The recorded spectra were calibrated on the corresponding solvent signal ($CDCl_3$: ^{1}H-NMR - δ = 7.26 pmm; ^{13}C-NMR - δ = 77.0 ppm; CD_3OD: ^{1}H-NMR - δ = 4.87 pmm; ^{13}C-NMR – δ = 49.0 ppm). Chemical shifts are expressed in parts per million (ppm). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Jasco FT/IR 6200 as a thin film on a NaCl single crystal at 499 – 4000 cm^{-1} and a resolution of 4 cm^{-1}. Enantiomeric excesses were measured using a VWR-Hitachi LaChrom ELITE® HPLC system with Daicel CHIRALPAK® columns (length: 25 cm, diameter: 0.46 cm). Optical rotations were measured on a Perkin Elmer Polarimeter (341) at 589 nm. For High resolution electrospray ionization mass spectra (HRMS ESI) a Bruker Daltonics UHR-QTOF maXis 4G was used.

2 EXPERIMENTAL SECTION

2.1 1-(3,4-Difluorophenyl)prop-2-en-1-ol (9)



Synthesis by addition of vinylmagnesium bromide to 3,4-difluorobenzaldehyde (8)

A solution of 3,4-difluorobenzaldehyde (**8**) (2.00 mL, 18.2 mmol, 1.00 eq.) in THF (40 mL) was cooled to −78 °C. Vinylmagnesium bromide (1.0 M in THF, 21.7 mL, 21.7 mmol, 1.19 eq.) was added dropwise over a period of 15 minutes and the mixture was stirred for 3.5 hours until full conversion was indicated by TLC analysis on silica plates deactivated with 1 % (v/v) Et_3N. Saturated NH_4Cl solution (3.30 mL) and H_2O (40.0 mL) were added and the reaction mixture was allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (5 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (*n*-hexane/CH_2Cl_2 = 1:1.25) on deactivated silica gel (1 % (v/v) NEt_3) gave 1-(3,4-difluorophenyl)prop-2-en-1-ol (**9**) (2.58 g, 15.2 mmol, 84%) as a slightly yellowish oil.

R_f = 0.38 (*n*-hexane/CH_2Cl_2 = 1:1.25).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.25−7.03 (m, 3H, arom.-*H*), 5.96 (ddd, *J* = 17.1, 10.3, 6.2 Hz, 1H, *H*-2), 5.33 (dt, *J* = 17.1, 1.3 Hz, 1H, *H*-3a), 5.22 (dt, *J* = 10.3, 1.2 Hz, 1H, *H*-3b), 5.14 (d, *J* = 6.2 Hz, 1H, *H*-1), 2.24 (s, 1H, O*H*).

^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = −137.43 (d, *J* = 21.0 Hz), −139.50 (d, *J* = 21.0 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 151.8 (dd, *J* = 45.7, 12.8 Hz), 148.5 (dd, *J* = 45.2, 12.7 Hz), 139.7, 139.7-139.6 (m), 122.4 (dd, *J* = 6.4, 3.6 Hz), 117.3 (d, *J* = 17.3 Hz), 116.1, 115.5 (d, *J* = 17.9 Hz), 74.4.

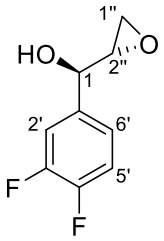
IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3427, 3069, 3001, 2925, 1612, 1520, 1435, 1380, 1283, 1210, 1143, 1116, 1075, 1042, 967, 946, 925, 826, 768, 751, 709, 656, 562.

HRMS (ESI) *m/z* calculated for $C_9H_7F_2O$ $[M + H]^+$ 169.0470, found 169.0465.

Attempted enantioselective addition of divinylzinc to 3,4-difluorobenzaldehyde (8) in the presence of (–)-MIB[1] (14)

Vinylmagnesium bromide (1.0 M in THF, 5.44 mL, 5.44 mmol, 4.00 eq) was added over 10 minutes to a solution of zinc chloride (1.0 M in Et_2O, 2.72 mL, 2.72 mmol, 2.00 eq.) at 0 °C. The mixture was stirred for 2 h at room temperature. 1,4-dioxane (1.65 mL, 19.3 mmol, 14.2 eq.) was added and the grey precipitate was filtered off using a Schlenk-frit and rinsed with 1,4-dioxane (4 x 6 mL). The solution of divinyl zinc was concentrated in vacuo at room temperature. Et_2O (30 mL), (−)-MIB[1] (16.0 mg, 66.8 µmol , 4.91 mol%), diethylzinc (1.0 M in *n*-hexane, 4.22 mL, 4.22 mmol, 3.10 eq.) and 3,4-difluorobenzaldehyde (**8**) (0.15 mL, 1.36 mmol, 1.00 eq.) were added. After 2 h, saturated NH_4Cl (5 mL) solution was added and the mixture was stirred for 30 minutes. The white precipitate was filtered off and rinsed with EtOAc (3 x 20 mL). H_2O (10 mL) was added and the aqueous phase was extracted with EtOAc (5 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/CH_2Cl_2 = 1:1.25, on deactivated silica-gel: 1 % (v/v) NEt_3) to give allylic alcohol **9** (199 mg, 1.17 mmol, 86%) as a slightly yellowish oil in racemic form (Chiral HPLC: Chiralpak IA, flow 0.9 mL/min., *n*-hexane/isopropanol 99.5:0.5).

2.2 (1*R*,2*S*)-3-(3,4-Difluorophenyl)-glycidol (10)



A solution of freshly distilled Ti(O*i*Pr)$_4$ (17.5 mL, 58.8 mmol, 1.00 eq.) in CH_2Cl_2 (500 mL) was dried over molecular sieve (4 Å, 40.0 g) that was crushed and baked out at 200 °C in vacuo overnight and cooled to –25 °C. (–)-D-DIPT (13.5 mL, 64.4 mmol, 1.10 eq.) was added and the mixture was stirred for 30 minutes. TBHP (5.5 M in *n*-decane, 5.35 mL, 29.4 mmol, 0.501 eq.) was added and stirring was continued for another 30 minutes. A solution of 1-(3,4-difluorophenyl)prop-2-en-1-ol (**9**) (10.0 g, 58.8 mmol, 1.00 eq.) in CH_2Cl_2 (100 mL) that was dried over molecular sieve (4 Å, 8.00 g) was added via transfer cannula. Aliquots were taken for monitoring conversion. The mixture was stirred for 62 h until 50% conversion was indicated by ^{19}F-NMR-spectroscopy. It was poured into an ice-cold solution of $FeSO_4 \cdot 7H_2O$ (11.4 g, 41.1 mmol, 0.700 eq.) and (+)-L-tartaric acid (9.72 g, 64.8 mmol, 1.10 eq.) in H_2O (240 mL). After stirring for 30 minutes at room temperature, the solid was filtered off and washed with Et_2O (3 x 100 mL). The aqueous phase was extracted with Et_2O (5 x 300 mL) and the combined organic layers were dried over Na_2SO_4, before the solvent was removed under reduced pressure at room temperature. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 1:1) to give (1*R*,2*S*)-3-(3,4-difluorophenyl)-glycidol (**10**) (4.46 g, 24.0 mmol, 41%) as a colorless oil with 97% *ee* (Chiral HPLC: Chiralpak IB, flow 0.9 mL/min., *n*-hexane/isopropanol 95:5).

In an entirely analogous fashion, but running the reaction at -35 °C, the product was isolated in 22% yield and >99% ee.

R_f = 0.33 (*n*-hexane/EtOAc = 1:1). $[\alpha]_D^{27}$ = –65.2 (c = 1.5, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.28–7.08 (m, 3H, arom.-*H*), 4.90 (d, *J* = 3.1 Hz, 1H, *H*-1), 3.19 (ddd, *J* = 4.0, 3.2, 2.7 Hz, 1H, *H*-2''), 2.91 (ddd, *J* = 4.9, 2.7, 0.6 Hz, 1H, *H*-1''a), 2.77 (dd, *J* = 4.9, 3.9 Hz, 1H, *H*-1''b), 2.30 (d, *J* = 2.2 Hz, 1H, O*H*).

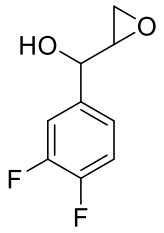
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –137.05 (d, *J* = 21.4 Hz), –138.50 (d, *J* = 21.0 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 152.1 (dd, *J* = 26.3, 12.5 Hz), 148.8 (*J* = 26.2, 12.5 Hz), 136.6 (dd, *J* = 5.3, 3.7 Hz), 122.5 (dd, *J* = 6.4, 3.7 Hz), 117.5 (d, *J* = 17.4 Hz), 115.5 (d, *J* = 18.1), 70.0, 54.9, 43.6.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3428, 3069, 3001, 2925, 1612, 1519, 1435, 1283, 1210, 1143, 1116, 1075, 1042, 967, 946, 925, 850, 826, 768, 751, 708, 656, 626, 562.

HRMS (ESI) *m/z* calculated for $C_9H_7F_2O_2$ $[M - H]^-$ 185.0420, found 185.0414.

2.3 3-(3,4-Difluorophenyl)-glycidol (mixture of stereoisomers)



A solution of 1-(3,4-difluorophenyl)prop-2-en-1-ol (**8**) (200 mg, 1.18 mmol, 1.00 eq.) in CH_2Cl_2 (10.0 mL) was cooled to –30 °C and a solution of *m*CPBA (378 mg, 2.19 mmol, 1.86 eq.) in CH_2Cl_2 (5.0 mL) was added via syringe. The mixture was stirred for 25 h at –30 °C and for 21 h at –10 °C. After addition of additional *m*CPBA (388 mg, 2.25 mmol, 1.91 eq.) from another batch the mixture was stirred for 26 – 10 °C. Na_2SO_3 solution (10 % in water, 12.0 mL) was added. The organic phase was washed with Na_2SO_3 solution (10 % in water,

2 x 19 mL) and saturated $NaHCO_3$ solution (3 x 13 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure and column chromatography (*n*-hexane/EtOAc = 1:1, deactivated with 1 vol% NEt_3) gave the racemic diastereomeric mixture (60.6 mg, 0.326 mmol, 28 %) as a colourless oil.

R_f = 0.33 (*n*-hexane/EtOAc = 1:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.30–7.04 (m, 6H, arom.-*H*), 4.86 (d, *J* = 3.1 Hz, erythro-*H*-1), 4.44 (d, *J* = 5.3 Hz, 1H, threo-*H*-1), 3.27–3.09 (m, 2H, *H*-2''), 2.93–2.86 (m, 1H, *H*-1''a), 2.82 (dd, *J* = 4.8, 2.7 Hz, 1H, threo-*H*-1''b), 2.77 (dd, *J* = 4.9, 3.9 Hz, 1H, erythro-*H*-1''b), 2.74–2.33 (br-s, 2H, O*H*).

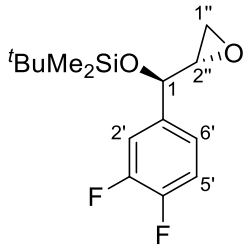
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –136.98 (d, *J* = 21.0 Hz), –137.08 (d, *J* = 21.0 Hz), –138.58 (d, *J* = 7.4 Hz), -138.58 (d, *J* = 7.7 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 152.2 (dd, *J* = 12.6, 2.15 Hz), 151.9 (dd, *J* = 12.6, 2.3 Hz), 148.9 (dd, *J* = 12.6, 2.3 Hz), 148.6 (dd, *J* = 12.5, 2.5 Hz), 137.2 (dd, *J* = 5.2, 3.8 Hz), 136.6 (dd, *J* = 5.4, 3.7 Hz), 122.4 (ddd, *J* = 8.2, 6.4, 3.7 Hz), 117.5 (dd, *J* = 17.3, 5.5 Hz), 115.5 (d, *J* = 17.9 Hz), 73.3, 69.9, 55.8, 54.9, 45.5, 43.6.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3423, 3068, 3002, 2894, 1611, 1566, 1520, 1435, 1284, 1210, 1143, 1116, 1050, 962, 922, 879, 854, 826, 809, 768, 752, 625.

HRMS (ESI) *m/z* calculated for $C_9H_7F_2O_2$ $[M + H]^+$ 185.0420, found 185.0416.

2.4 (1*R*,2*S*)-(*O*)-*tert*-Butyldimethylsilyl-3-(3,4-difluorophenyl)-glycidol (17)



A solution of (1*R*,2*S*)-3-(3,4-difluorophenyl)-glycidol (**10**) (955 mg, 5.13 mmol, 1.00 eq.) in CH_2Cl_2 (10.3 mL) was cooled to −10 °C before TBDMSCl (1.96 g, 13.0 mmol, 2.54 eq.) and imidazole (1.06 g, 15.6 mmol, 3.03 eq.) were added. After 14.5 h saturated $NaHCO_3$ solution (20.0 mL) and H_2O (20.0 mL) were added and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (5 x 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 9:1) to give (1*R*,2*S*)-(*O*)-*tert*-butyldimethylsilyl-3-(3,4-difluorophenyl)-glycidol (**17**) (1.33 g, 4.43 mmol, 86%) as a colorless oil.

R_f = 0.65 (*n*-hexane/EtOAc = 9:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = −42.1 (c = 1.77, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.26–7.02 (m, 3H, arom.-*H*), 4.60 (d, *J* = 4.0 Hz, 1H, *H*-1), 2.98 (td, *J* = 3.9, 2.5 Hz, 1H, *H*-2''), 2.79 (dd, *J* = 5.4, 2.6 Hz, 1H, *H*-1''a), 2.72 (dd, *J* = 5.4, 3.8 Hz, 1H, *H*-1''b), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, SiCH_3), −0.02 (s, 3H, SiCH_3).

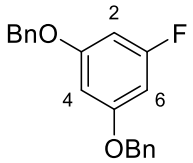
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = −137.52 (d, *J* = 21.0 Hz), −139.45 (d, *J* = 21.2 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 151.9 (dd, *J* = 37.3, 12.7 Hz), 148.6 (dd, *J* = 36.6, 12.6 Hz), 138.77 (m), 122.2 (dd, *J* = 6.4, 3.6 Hz), 117.2 (d, *J* = 17.3 Hz), 115.3 (d, *J* = 17.9 Hz), 72.6, 72.6, 55.7, 44.6, 25.8, 18.4, 1.2, -4.7, -4.8.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3063, 2956, 2930, 2887, 2858, 1729, 1611, 1519, 1472, 1434, 1362, 1288, 1257, 1209, 1146, 1115, 1084, 1004, 961, 939, 839, 778, 673, 625, 583.

HRMS (ESI) *m/z* calculated for $C_{15}H_{23}F_2O_2Si$ $[M + H]^+$ 301.1430, found 301.1428.

2.5 3,5-Bis(benzyloxy)fluorobenzene (20)



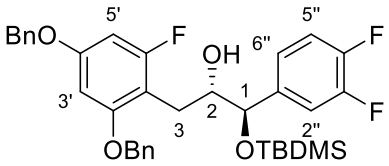
A solution of NaH (60% in mineral oil, 4.60 g, 115 mmol, 2.98 eq.) in *N*-methyl-2-pyrrolidon (60.0 mL) was cooled to 0 °C. Benzyl alcohol (9.90 mL, 95.2 mmol, 2.46 eq.) was added dropwise and the solution was stirred for 1 h at 0 °C. 1,3,5-Trifluorobenzene (**19**) (4.00 mL, 38.7 mmol, 1.00 eq.) was added at 0 °C and the mixture was stirred for 3 h at room temperature and for 2.5 h at 100 °C. After cooling to 0 °C, H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (3x). The combined organic extracts were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The yellow oil crystallized overnight. Benzyl alcohol and *N*-methyl-2-pyrrolidon were separated by column chromatography (*n*-hexane/EtOAc = 32:1) and the resulting mixture of 3,5-bis(benzyloxy)fluorobenzene (**20**) and 1,3,5-tris(benzyloxy)benzene was purified by repetitive recrystallization (*n*-hexane/EtOAc = 6.5:1–3:1). The residue was purified by column chromatography (*n*-hexane/EtOAc = 32:1). The reaction gave 3,5-bis(benzyloxy)fluorobenzene (**20**) (10.3 g, 29.0 mmol, 75%) as a white solid.

R_f = 0.19 (*n*-hexane/EtOAc 99:1); 0.65 (*n*-hexane /EtOAc 90:10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm] = 7.30–7.46 (m, 10H, OC_6H_5), 6.41 (td, *J* = 2.2, 1.0 Hz, 1H, *H*-4), 6.33 (dd, *J* = 10.5, 2.2 Hz, 2H, *H*-2, *H*-6), 5.01 (s, 4H, OCH_2Ph).

^{19}F-NMR (282 MHz, $CDCl_3$): δ_F [ppm] = −110.76 (s).

2.6 (1*R*,2*S*)-3-(2,4-Bis(benzyloxy)-6-fluorophenyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluorophenyl)propan-2-ol (18)



A solution of 3,5-bis(benzyloxy)fluorobenzene (**20**) (821 mg, 2.66 mmol, 1.99 eq.) in THF (23.0 mL) was cooled to −78 °C, before *n*-BuLi (2.5 M in *n*-hexane, 1.16 mL, 2.90 mmol, 2.16 eq.) was added and the mixture was stirred for 1 h at −78 °C. (1*R*,2*S*)-(*O*)-*tert*-Butyldimethylsilyl-3-(3,4-difluorophenyl)-glycidol (**17**) (402 mg, 1.34 mmol, 1.00 eq.) and freshly distilled $BF_3{\cdot}OEt_2$ (0.35 mL, 2.76 mmol, 2.06 eq.) were added and the mixture was stirred for 5 minutes at −78 °C before the reaction was quenched by the addition of MeOH (4.00 mL) and brine (6.00 mL). After warming up to room temperature, H_2O (20.0 mL) was added and the aqueous phase was extracted with EtOAc (5 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC (gradient over 2 h: *n*-hexane/CH_2Cl_2 = 2.3:1 → 1:1.5, flow: 30 mL/min., length: 15 cm, diameter: 4 cm) to give (1*R*,2*S*)-3-(2,4-bis (benzyloxy)-6-fluorophenyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluoro-phenyl)propan-2-ol (**18**) (620 mg, 1.02 mmol, 76%) as a white solid.

R_f = 0.22 (*n*-hexane/EtOAc = 19:1). $[\alpha]_D^{27}$ = −36.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.44–7.27 (m, 10H, arom.-*H*), 7.22–7.12 (m, 1H, *H*-6''), 7.08–6.96 (m, 2H, *H*-2'', *H*-5''), 6.38 (dd, *J* = 2.3, 1.4 Hz, 1H, *H*-3'), 6.32 (dd, *J* = 11.2, 2.3 Hz, 1H, *H*-5'), 4.97 (d, *J* = 7.67 Hz, 4H, OCH_2Ph), 4.65 (d, *J* = 4.4 Hz, 1H, *H*-1), 3.84 (dq, *J* = 9.9, 4.9 Hz, 1H, *H*-2), 2.79–2.63 (m, 2H, *H*-3a, *H*-3b), 2.04 (d, *J* = 9.9 Hz, 1H, O*H*), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), −0.13 (s, 3H, $SiCH_3$).

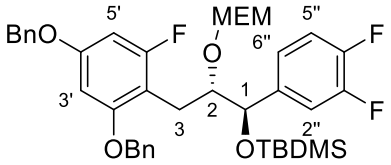
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = −114.86, –137.93 (d, *J* = 21.4 Hz), −139.99 (d, *J* = 21.3 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 164.1, 160.9, 158.8 (d, *J* = 14.0 Hz), 158.4 (d, *J* = 11.2 Hz), 151.5 (dd, *J* = 45.6, 12.7 Hz), 148.3 (dd, *J* = 45.6, 12.7 Hz), 139.0 (m), 136.6, 136.4, 128.8, 128.3, 127.7, 127.5, 122.7 (dd, *J* = 6.2, 3.5 Hz), 116.8 (d, *J* = 17.3 Hz), 115.8 (d, *J* = 17.7 Hz), 107.3 (d, *J* = 19.2 Hz), 96.5 (d, *J* = 2.5 Hz), 94.6 (d, *J* = 28.1 Hz), 77.3, 70.7, 70.5, 25.9, 24.8, 18.3, −4.6, −4.9.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3033, 2929, 2857, 2337, 1628, 1589, 1516, 1500, 1455, 1436, 1377, 1279, 1257, 1207, 1144, 1105, 1029, 939, 836, 777, 749, 697, 617.

HRMS (ESI) *m/z* calculated for $C_{35}H_{39}F_3O_4Si$ $[M + H]^+$ 609.2635, found 609.2642.

2.7 (1*R*,2*S*)-3-(2,4-Bis(benzyloxy)-6-fluorophenyl)-1-((*tert*-butyl-dimethylsilyl)oxy)-1-(3,4-difluorophenyl)-2-((2-methoxyethoxymethyl)oxy)propan



A solution of (1*R*,2*S*)-3-(2,4-bis(benzyloxy)-6-fluorophenyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluorophenyl)propan-2-ol (**18**) (100 mg, 0.164 mmol, 1.00 eq.) in CH_2Cl_2 (0.47 mL) was cooled to 0 °C. Diisopropylethylamine (0.34 mL, 2.00 mmol, 12.2 eq.), MEMCl (0.11 mL, 0.962 mmol, 5.87 eq.) and *n*-Bu_4NI (3.5 mg, 9.5 µmol, 0.058 eq.) were added and the mixture was stirred at room temperature for 24.5 h. Saturated $NaHCO_3$ solution (1.75 mL) and H_2O (10.0 mL) were added and the aqueous phase was extracted with EtOAc (5 x 15 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by MPLC (gradient over 2 h: *n*-hexane/EtOAc = 9:1 → 4:1, flow: 30 mL/min., length: 15 cm, diameter: 4 cm) gave (1*R*,2*S*)-3-(2,4-bis(benzyloxy)-6-fluorophenyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluoro-phenyl)-2-((methoxyethoxy-methyl)oxy)propan (107 mg, 0.154 mmol, 94%) as a white solid.

R_f = 0.23 (*n*-hexane/EtOAc = 9:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = −45.9 (c = 1.0, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.44–7.27 (m, 10H, $OCH_2C_6H_5$), 7.22–7.13 (m, 1H, *H*-6''), 7.03–6.90 (m, 2H, *H*-2'', *H*-5''), 6.34 (dd, *J* = 2.4, 1.3 Hz, 1H, *H*-3'), 6.29 (dd, *J* = 11.0, 2.3 Hz, 1H, *H*-5'), 4.96 (d, *J* = 8.4 Hz, 4H, OCH_2Ph), 4.63 (d, *J* = 4.3 Hz, 1H, *H*-1), 4.39 (d, *J* = 7.1 Hz, 1H, OCH_2O), 4.31 (d, *J* = 7.0 Hz, 1H, OCH_2O), 4.02 (dt, *J* = 8.8, 4.3 Hz, 1H, *H*-2), 3.27 (s, 3H, OCH_3), 3.21–2.96 (m, 4H, OCH_2CH_2O), 2.88–2.72 (m, 2H, *H*-3a, *H*-3b), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), −0.16 (s, 3H, $SiCH_3$).

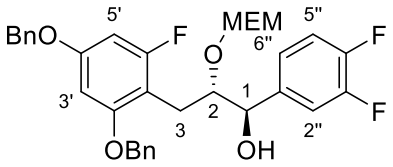
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = −114.17 (s), −138.19 (d, *J* = 21.1 Hz), −140.22 (d, *J* = 21.3 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 164.1, 160.9, 158.6 (d, *J* = 3.4 Hz), 158.5, 151.3 (dd, *J* = 45.2, 12.3 Hz), 148.0 (dd, *J* = 44.8, 12.8 Hz), 139.4 (m), 136.5, 136.4, 128.7, 128.6, 128.2, 128.0, 127.5, 127.3, 122.9 (m), 116.5 (dd, *J* = 30.7, 17.4 Hz), 107.6 (d, *J* = 18.9 Hz), 96.1 (d, *J* = 2.4 Hz), 94.8, 94.2 (d, *J* = 28.0 Hz), 80.2, 76.2, 71.5, 70.4, 70.3, 66.6, 58.9, 29.7, 25.8, 24.1, 18.2, -4.8, -5.0.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 2928, 2885, 2856, 1626, 1589, 1517, 1500, 1456, 1436, 1376, 1280, 1254, 1219, 1170, 1146, 1111, 1039, 984, 952, 913, 837, 773, 697, 627.

HRMS (ESI) *m/z* calculated for $C_{39}H_{51}NF_3O_6Si$ $[M + NH_4]^+$ 714.3432, found 714.3432.

2.8 (1*R*,2*S*)-3-(2,4-Bis(benzyloxy)-6-fluorophenyl)-1-(3,4-difluorophenyl)-2-((2-methoxyethoxy)meth-oxy)propan-1-ol (21)



To a solution of (1*R*,2*S*)-3-(2,4-bis(benzyloxy)-6-fluorophenyl)-1-((*tert*-butyldimethyl-silyl)oxy)-1-(3,4-difluorophenyl)-2-((methoxyethoxy-methyl)oxy)propane (1.99 g, 2.85 mmol, 1.00 eq.) in THF (180 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 3.76 mL, 3.76 mmol, 1.32 eq.) and the mixture was stirred for 22 h at room temperature. Phosphate buffer solution (pH = 7, 100 mL) was added and stirring was continued for 1 h before the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with water (3 x 50 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by MPLC (gradient over 2 h: *n*-hexane/EtOAc = 2.3:1 → 1.5:1, flow: 30 mL/min., length: 15 cm, diameter: 4 cm) gave (1*R*,2*S*)-3-(2,4-bis(benzyloxy)-6-fluorophenyl)-1-(3,4-difluorophenyl)-2-((2-methoxyethoxy)methoxy)-propan-1-ol (**21**) (1.63 g, 2.80 mmol, 98%) as a white solid.

R_f = 0.53 (*n*-hexane/EtOAc = 1.5:1). $[\alpha]_D^{22}$ = +11.5 (c = 1.0, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.43–7.28 (m, 10H, $OCH_2C_6H_5$), 7.25–7.15 (m, 1H, *H*-6''), 7.03–6.87 (m, 2H, *H*-2'', *H*-5''), 6.37 (dd, *J* = 2.3, 1.4 Hz, 1H, *H*-3'), 6.31 (dd, *J* = 11.2, 2.3 Hz, 1H, *H*-5'), 4.97 (d, *J* = 10.3 Hz, 4H, OCH_2Ph), 4.76 (t, *J* = 4.1 Hz, 1H, *H*-1), 4.62 (d, *J* = 7.3 Hz, 1H, OCH_2O), 4.53 (d, *J* = 7.2 Hz, 1H, OCH_2O), 4.10 (dt, *J* = 8.2, 4.0 Hz, 1H, *H*-2), 3.55–3.32 (m, 7H, $OCH_2CH_2OCH_3$), 2.87 (ddd, *J* = 14.1, 8.5, 1.1 Hz, 1H, *H*-3b), 2.54 (ddd, *J* = 14.1, 4.2, 1.7 Hz, 1H, *H*-3a), 2.36 (s, 1H, O*H*).

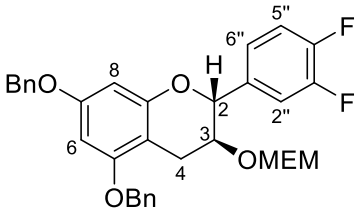
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –113.72, –138.15 (d, *J* = 21.1 Hz), –140.32 (d, *J* = 21.4 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 164.1, 161, 158.8 (d, *J* = 14.1 Hz), 158.5 (d, *J* = 11.3 Hz), 137.8 (m), 136.5, 136.2, 129.2, 128.8, 128.4, 128.4, 127.7, 122.8 (m), 116.7 (d, *J* = 17.3 Hz), 116.0 (d, *J* = 17.9 Hz), 106.9 (d, *J* = 19.2 Hz), 96.4, 95.0, 94.7, 94.4, 80.8, 73.5, 71.7, 70.8, 70.5, 67.4, 59.0, 22.60.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 2924, 2854, 2370, 2325, 1625, 1588, 1558, 1541, 1519, 1456, 1436, 1375, 1278, 1220, 1170, 1143, 1104, 1030, 913, 820, 772, 697.

HRMS (ESI) *m/z* calculated for $C_{39}H_{51}NF_3O_6Si$ $[M + NH_4]^+$ 714.3432, found 714.3432.

2.9 (2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)-3-((2-methoxyethoxy)methoxy)chromane (22)



To a solution of (1*R*,2*S*)-3-(2,4-bis(benzyloxy)-6-fluorophenyl)-1-(3,4-difluorophenyl)-2-((2-methoxyethoxy)-methoxy)propan-1-ol (**21**) (500 mg, 0.859 mmol, 1.00 eq.) in DMF (500 mL) was slowly added a solution of KO^{t}Bu (144 mg, 1.28 mmol, 1.49 eq.) in DMF (24.0 mL) using a syringe pump (1 mL/h). After 24 h, the syringe was replaced and another solution of KO^{t}Bu (144 mg, 1.28 mmol, 1.49 eq.) in DMF (24 mL) was added over 24 h. Phosphate buffer solution (pH = 7, 750 mL) was added and the aqueous phase was extracted with EtOAc (5 x 150 mL). The combined organic layers were washed with H_2O (150 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by MPLC (gradient over 2 h: *n*-hexane/EtOAc = 2.3:1 → 1.5:1, flow: 30 mL/min., length: 15 cm, diameter: 4 cm) gave

(2*R*,3*S*)-5,7-bis(benzyloxy)-2-(3,4-difluorophenyl)-3-((2-methoxyethoxy)methoxy) chromane (**16**) (296 mg, 0.527 mmol, 61%) as a white solid.

R_f = 0.48 (*n*-hexane/EtOAc = 2.33:1). $[\alpha]_D^{22}$ = +17.8 (c = 1.0, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.48–7.25 (m, 10H, $OCH_2C_6H_5$), 7.28–7.10 (m, 3H, *H*-2', *H*-5', *H*-6'), 6.28 (d, *J* = 2.3 Hz, 1H, *H*-6), 6.25 (d, *J* = 2.3 Hz, 1H, *H*-8), 5.02 (d, *J* = 5.42 Hz, 4H, OCH_2Ph), 4.91 (d, *J* = 7.4 Hz, 1H, *H*-2), 4.75 (d, *J* = 7.1 Hz, 1H, OCH_2O), 4.50 (d, *J* = 7.2 Hz, 1H, OCH_2O), 4.09 (td, *J* = 7.5, 5.4 Hz, 1H, *H*-3), 3.57 – 3.30 (m, 7H, $OCH_2CH_2OCH_3$), 3.00 (dd, *J* = 16.6, 5.4 Hz, 1H, *H*-4b), 2.72 (dd, *J* = 16.5, 7.7 Hz, 1H, *H*-4a).

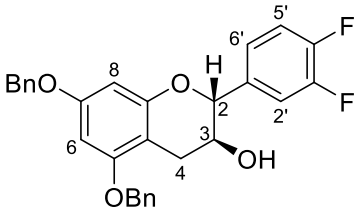
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –137.37 (d, *J* = 21.0 Hz), –138.68 (d, *J* = 21.0 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.0, 157.8, 154.8, 151.9 (dd, *J* = 18.4, 12.4 Hz), 148.6 (dd, *J* = 18.5, 12.4 Hz), 138.0, 137.0, 136.3, 129.2, 128.7, 128.4, 128.2, 128.0, 127.7, 127.4, 125.4, 123.3 (dd, *J* = 6.3, 3.6 Hz), 117.2 (d, *J* = 17.2 Hz), 116.1 (d, *J* = 18.2 Hz), 101.9, 94.5, 94.1, 93.9, 78.9, 72.2, 71.7, 70.3, 70.2, 67.0, 59.1, 25.3, 21.6.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 2916, 2364, 1619, 1593, 1520, 1498, 1436, 1376, 1280, 1219, 1149, 1115, 1053, 814, 772, 697, 510.

HRMS (ESI) *m/z* calculated for $C_{33}H_{33}F_2O_6$ $[M + H]^+$ 563.2240, found 563.2241.

2.10 (2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (23)



A solution of (2*R*,3*S*)-5,7-bis(benzyloxy)-2-(3,4-difluorophenyl)-3-((2-methoxyethoxy)methoxy)chromane (**22**) (258 mg, 0.459 mmol, 1.00 eq.) in CH_2Cl_2 (10.0 mL) was cooled to 0 °C. Phloroglucinol (177 mg, 1.41 mmol, 3.07 eq.) and *p*-TsOH·H_2O (382 mg, 2.01 mmol, 4.37 eq.) were added and the mixture was stirred for 14 days at room temperature. Saturated $NaHCO_3$ solution (30 mL) and H_2O (30 mL) were added and the aqueous phase was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by MPLC (gradient over 2 h: *n*-hexane/EtOAc = 2.3:1 → 1.5:1, flow: 30 mL/min., length: 15 cm, diameter: 4 cm) afforded (2*R*,3*S*)-5,7-bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (**23**) (174 mg, 0.367 mmol, 80%) as a white solid.

R_f = 0.54 (*n*-hexane/EtOAc = 2.33:1). $[\alpha]_D^{22}$ = –10.0 (c = 1.0, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.46–7.11 (m, 13H, $OCH_2C_6H_5$, *H*-2', *H*-5', *H*-6'), 6.29 (d, *J* = 2.3 Hz, 1H, *H*-6), 6.23 (d, *J* = 2.3 Hz, 1H, *H*-8), 5.02 (d, *J* = 5.5 Hz, 4H, OCH_2Ph), 4.75 (d, *J* = 7.8 Hz, 1H, *H*-2), 4.40 (tt, *J* = 8.2, 5.2 Hz, 1H, *H*-3), 3.08 (dd, *J* = 16.5, 5.6 Hz, 1H, *H*-4b), 2.69 (dd, *J* = 16.5, 8.5 Hz, 1H, *H*-4a), 1.76 (d, *J* = 4.7 Hz, 1H, O*H*).

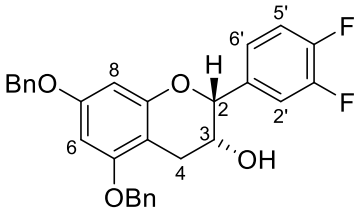
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –136.66 (d, *J* = 21.1 Hz), –137.88 (d, *J* = 21.2 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 159.1, 157.9, 154.9, 152.2 (t, *J* = 12.9 Hz), 148.9 (t, *J* = 12.9 Hz), 136.9, 135.5 (m), 128.7, 128.2, 128.1, 127.7, 127.3, 123.4 (dd, *J* = 6.4, 3.6 Hz), 117.6 (d, *J* = 17.3 Hz), 116.2 (d, *J* = 17.9 Hz), 102.0, 94.5, 94.2, 80.6, 70.3, 70.1, 68.3, 27.7.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3284, 3032, 2869, 2346, 1619,1499,1455,1434,1376,1341,1276, 1221, 1154, 1115, 1088, 1049, 913, 813, 772, 744, 699, 627, 512.

HRMS (ESI) *m/z* calculated for $C_{29}H_{25}F_2O_4$ $[M + H]^+$ 475.1715, found 475.1721.

2.11 (2*R*,3*R*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (24)



For the inversion of configuration of secondary alcohol **23** a modified protocol reported by Li and Chan was followed.[2] To a solution of (2*R*,3*S*)-5,7-bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (**23**) (50.1 mg 0.106 mmol, 1.00 eq.) in CH_2Cl_2 (5.0 mL) was added Dess-Martin periodinane (59.5 mg, 0.140 mmol, 1.32 eq.). After 85 minutes the solvent was evaporated at room temperature. The residue was dissolved in THF (5.0 mL) and the solution was cooled to –78 °C. A solution of L-Selectride (1.0 m in THF, 0.25 mL, 0.25 mmol, 2.4 eq.) was added dropwise and stirring was continued overnight. After 18.5 h saturated $NaHCO_3$ solution (3 mL) and H2O (10 mL) were added and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (*n*-hexane/EtOAc = 90:10) gave (2*R*,3*R*)-5,7-bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (24) (36.7 mg, 77.4 µmol, 73%) as a white solid.

R_f = 0.33 (*n*-hexane/EtOAc = 9:1). $[\alpha]_D^{26}$ = –17.8 (c = 1.0, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.48–7.15 (m, 13H, $OCH_2C_6H_5$, *H*-2', *H*-5', *H*-6'), 6.30 (d, *J* = 2.4 Hz, 1H, *H*-6), 6.28 (d, *J* = 2.4 Hz, 1H, *H*-8), 5.03 (d, *J* = 2.0 Hz, 4H, OCH_2Ph), 4.96 (s, 1H, *H*-2), 4.28 (dt, *J* = 7.0, 3.4 Hz, 1H, *H*-3), 3.00 (2x dd, *J* = 3.6 Hz, 2H, *H*-4), 1.69 (d, *J* = 7.2 Hz, 1H, O*H*).

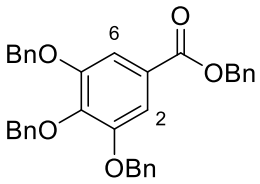
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –137.21 (d, *J* = 21.1 Hz), –138.79 (d, *J* = 21.4 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) δ_C [ppm] = 159.1, 158.5, 155.0, 137.0, 136.9, 135.5 (m), 128.8, 128.7, 128.2, 128.1, 127.7, 127.4, 122.5 (dd, *J* = 6.3, 3.6 Hz), 117.4 (d, *J* = 17.3 Hz), 116.2 (d, *J* = 18.3 Hz), 100.7, 94.8, 94.5, 77.8, 70.3, 70.2, 66.4, 28.7.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 2924, 2359, 1618, 1592, 1519, 1497, 1439, 1376, 1278, 1219, 1148, 1114, 1062, 1029, 772, 737, 696.

HRMS (ESI) *m/z* calculated for $C_{29}H_{25}F_2O_4$ $[M + H]^+$ 475.1715, found 475.1713.

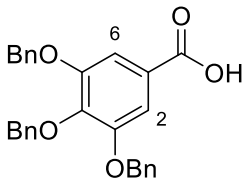
2.12 Benzyl-3,4,5-tris(benzyloxy)benzoate[3]



A mixture of gallic acid monohydrate (20.0 g, 106 mmol, 1.00 eq.) and K_2CO_3 (120 g, 869 mmol, 8.20 eq.) in DMF (550 mL) was stirred for 1 h at room temperature. The mixture was heated to 40 °C and benzyl bromide (151 mL, 1.27 mol, 12.0 eq.) was added over 45 minutes using a dropping funnel. After refluxing for 16 h and stirring at room temperature for additional 48 h the solid was filtered off and EtOAc (100 mL) was added. The solution was washed with water (5 x 250 mL), dried over Na_2SO_4 and concentrated in vacuo. Recrystallization from EtOH gave benzyl-3,4,5-tris(benzyloxy)benzoate (37.9 g, 71.2 mmol, 67%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.47–7.27 (m, 22H, $OCH_2C_6H_5$, *H*-2, *H*-6), 5.33 (s, 2H, $C(O)OCH_2Ph$), 5.13 (d, J = 2.2 Hz, 6H, OCH_2Ph).

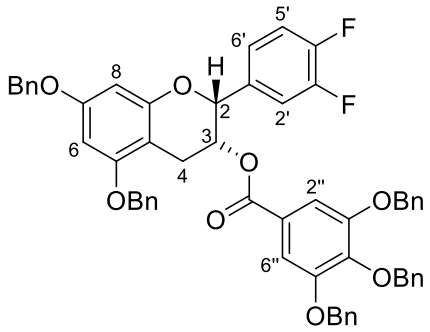
2.13 3,4,5-Tris(benzyloxy)benzoic acid[3]



Benzyl-3,4,5-tris(benzyloxy)benzoate (41.7 g, 78.6 mmol, 1.00 eq.) was dissolved in a solution of KOH (350 g, 6.24 mol, 78.6 eq.) in MeOH (1450 mL) and the mixture was refluxed for 3 h, stirred over night at room temperature and refluxed again for 3 h. After cooling to room temperature, the precipitate was filtered off and dissolved in EtOAc (3 L). The pH value was adjusted to pH = 1 by the addition of concentrated HCl. The organic phase was washed with water (12 L), dried over Na_2SO_4 and concentrated in vacuo. Recrystallization from MeOH gave 3,4,5-tris(benzyloxy)benzoic acid (32.5 g, 73.4 mmol, 93%) as white needles.

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H [ppm] = 7.48 – 7.26 (m, 17H, $OCH_2C_6H_5$, *H*-2, *H*-6), 5.15 (d, *J* = 2.4 Hz, 6H, OCH_2Ph).

2.14 (2*R*,3*R*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-yl-3,4,5-tris(benzyloxy)benzoate (25)



To a solution of (2*R*,3*R*)-5,7-bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (**24**) (15.0 mg, 31.6 µmol, 1.00 eq.) in CH_2Cl_2 (2 mL) were added 3,4,5-tris(benzyloxy)benzoic acid (26.0 mg, 59.0 µmol, 1.87 eq.), DMAP (2.0 mg, 16.4 µmol, 0.518 eq.) and EDC·HCl (16.0 mg, 103 µmol, 3.26 eq.). The mixture was stirred for 4 d, before H_2O (10 mL) was added and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Dissolving the residue in Et_2O and precipitation with *n*-pentane gave pure (2*R*,3*R*)-5,6-bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-yl-3,4,5-tris(benzyloxy) benzoate (**25**) (25 mg, 27.9 µmol, 88%) as a white solid.

R_f = 0.36 (*n*-hexane/EtOAc = 4:1). $[\alpha]_D^{22}$ = –51.5 (c = 0.75, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$) δ_H [ppm] = 7.47–7.24 (m, 26H, $OCH_2C_6H_5$, *H*-6'), 7.18 (s, 2H, *H*-2'', *H*-6''), 7.11–6.98 (m, 2H, *H*-2', *H*-5'), 6.37 (d, *J* = 2.3 Hz, 1H, *H*-6), 6.33 (d, *J* = 2.3 Hz, 1H, *H*-8), 5.59 (d, *J* = 3.8 Hz, 1H, *H*-2), 5.14–5.00 (m, 11H, OCH_2Ph, *H*-3), 3.10 (2x d, *J* = 3.9 Hz, 2H, *H*-4).

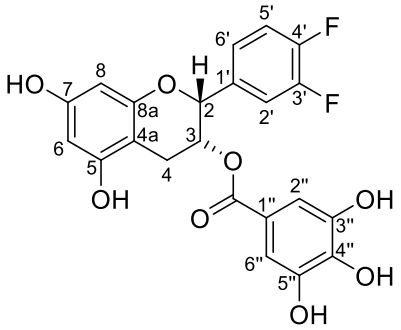
^{19}F-NMR (282 MHz, $CDCl_3$) δ_F [ppm] = –137.09 (d, *J* = 21.4 Hz), –138.39 (d, *J* = 21.3 Hz).

^{13}C-NMR (151 MHz, $CDCl_3$) δ_C [ppm] = 165.2, 159.1, 158.1, 155.2, 152.5, 142.7, 137.5, 136.9, 136.8, 136.7, 135.0 (m), 128.8, 128.7, 128.3, 128.2, 128.1, 127.6, 127.4, 124.7, 122.5 (m), 117.3 (d, *J* = 17.4 Hz), 115.9 (d, *J* = 18.7 Hz), 109.1, 100.8, 94.7, 94.3, 76.7, 75.2, 71.2, 70.4, 70.2, 68.6, 26.0.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 2359, 1716, 1591, 1541, 1520, 1428, 1220, 1149, 1114, 1028, 772, 695.

HRMS (ESI) *m/z* calculated for $C_{57}H_{50}F_2NO_8$ $[M + NH_4]^+$ 914.3499, found 914.3499.

2.15 (2*R*,3*R*)-2-(3,4-Difluorophenyl)-5,7-dihydroxychroman-3-yl-gallate (26)



(2*R*,3*R*)-5,6-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-yl-3,4,5-tris(benzyloxy)benzoate (**25**) (34.3 mg, 38.3 µmol, 1.00 eq.) was dissolved in a degassed solvent mixture of HPLC-grade MeOH and freshly distilled, peroxide free THF (1:1 v/v, 3 mL) and transferred into a Schlenk-flask containing $Pd(OH)_2/C$ (20 %, 36.0 mg, 5.13 µmol, 13 mol%). After rinsing with the degassed solvent mixture (2 x 3.0 mL) the flask was connected to a hydrogen balloon and flushed with hydrogen. The mixture was stirred for 20 h until full conversion was indicated by TLC. Then, the hydrogen balloon was removed and the flask was flushed with argon. A syringe with two merged syringe filters (PTFE, pore diameter = 0.45 µm) was flushed with argon and used to withdraw the mixture into the syringe. The reaction flask was rinsed with the degassed solvent mixture (3 x 3 mL). Removal of the solvent under reduced pressure gave (2*R*,3*R*)-2-(3,4-difluorophenyl)-5,7-dihydroxychroman-3-yl 3,4,5-trihydroxybenzoate (**26**) as a grey solid. The sample was purified by a short filter column (CH_2Cl_2 → *n*-pentane → MeOH).

R_f = 0.86 (MeOH). $[\alpha]_D^{22}$ = – 55.7 (c = 0.15, CH_3OH).

^{1}H-NMR (600 MHz, CD_3OD) δ_H [ppm] = 7.42 (ddd, *J* = 11.7, 7.7, 2.1 Hz, 1H, *H*-6‘), 7.31 (dd, *J* = 9.0, 3.9 Hz, 1H, *H*-2‘), 7.20 (dt, *J* = 10.4, 8.3 Hz, 1H, *H*-5‘), 6.92 (s, 2H), 6.00 (s, 2H), 5.60 (dt, *J* = 4.3, 1.9 Hz, 1H), 5.20 (s, 1H), 3.05 (dd, *J* = 17.5, 4.6 Hz, 1H), 2.89 (dd, *J* = 17.6, 2.2 Hz, 1H).

^{19}F-NMR (565 MHz, CD_3OD) δ_F [ppm] = –140.81 (d, *J* = 21.2 Hz), –142.04 (d, *J* = 20.6 Hz)

^{13}C-NMR (126 MHz, CD_3OD) δ_C [ppm] = 167.3 (C=O), 158.0 (m, C-5/C-7), 157.9 (m, C-5/C-7), 156.7 (m, C-8a), 152.2 (m, C-4‘), 150.3 (d, *J* = 33.1, 12.8 Hz, C-3’), 146.4 (C-3‘‘, C-5‘‘), 139.9 (C-4‘‘), 137.5 (m, C-1’), 124.1 (m, C-2’), 121.2 (C-1‘‘), 117.9 (d, *J* = 17.8 Hz C-5’), 116.8 (d, *J* = 18.8 Hz C-6’), 110.2 (C-2‘‘, C-6‘‘), 99.3 (C-4a), 97.0 (C-6/C-8), 95.9 (C-6/C-8), 77.6 (C-2), 69.6 (C-3), 26.7 (C-4).

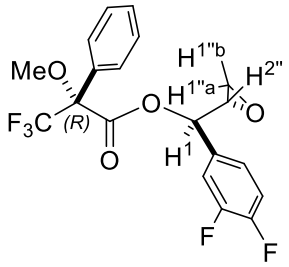
IR (film on NaCl) $\tilde{\upsilon}$ $[cm^{-1}]$ = 3710, 3679, 3649, 2950, 2865, 2844, 2356, 2333, 2229, 2074, 1753, 1614, 1558, 1522, 1455, 1435, 1274, 1242, 1170, 1119, 1055, 1033, 1015, 823, 767, 719.

HRMS (ESI) *m/z* calculated for $C_{22}H_{17}F_2O_8$ $[M + H]^+$ 447.0886, found 447.0882.

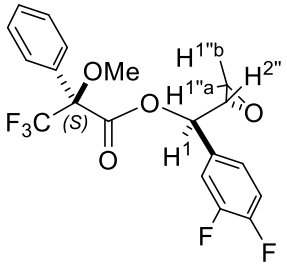
2.16 Evaluation of stability of (2*R*,3*R*)-2-(3,4-difluorophenyl)-5,7-dihydroxychroman-3-yl-gallate (26) at high pH conditions

Into a Young tube containing a solution of B-ring fluorinated ECG (2.00 mg, 4.48 µmol) in deuterated MeOD (0.600 mL) was added a degassed solution of NaOD in D_2O (0.300 mL) previously adjusted to pH = 10.02 using a pH meter (Metrohm 744). The Young tube was closed and thoroughly mixed by repeated flipping to ensure a homogeneous solution, before it was subjected to ^{1}H-NMR-spectroscopy. To obtain sharp signals, all NMR measurements were performed at 50 °C. NMR spectra were repeatedly measured and compared with the chemical shifts and coupling constants of B-ring fluorinated ECG. Thereby, no signs of racemization, epimerization or degradation were observed after 24 h.

2.17 (1R,2S)-3-(3,4-Difluorophenyl)-glycidyl-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (Mosher´s esters)



(*R*)-MTPA-ester



(*S*)-MTPA-ester

To a solution of (1R,2S)-3-(3,4-difluorophenyl)-glycidol (**10**) (50.0 mg, 268 µmol, 1.00 eq.) in CH_2Cl_2 (4.3 mL) were subsequently added (*R*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoic acid (MTPA) (195 mg, 833 µmol, 3.11 eq.), DCC (172 mg, 834 µmol, 3.11 eq.) and DMAP (102 mg, 835 µmol, 3.12 eq.). The mixture was stirred for 20 h at room temperature. The white precipitate was filtered off and the solvent was removed under reduced pressure at room temperature. The residue was purified by column chromatography (*n*-hexane/EtOAc = 4:1) to give the product (48.2 mg, 130 µmol, 48%) as a white solid. In an entirely analogous fashion, (1R,2S)-3-(3,4-difluorophenyl)-glycidyl-(S)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (53.6 mg, 144 µmol, 54%) was prepared using (*S*)-(−)-MTPA.

(*R*)-(−)-MTPA ester:

$[\alpha]_D^{22}$ = –3.5 (c = 0.75, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ_H [ppm] = 7.46 – 7.34 (m, 5H, MTPA-C_5H_5), 7.16 – 7.01 (m, 3H, arom.-*H*), 6.03 (d, *J* = 3.6 Hz, 1H, *H*-1), 3.56 (q, J = 1.2 Hz, 3H, MTPA-OCH_3), 3.26 (td, J = 3.8, 2.5 Hz, 1H, *H*-2''), 2.80 (dd, *J* = 5.1, 3.9 Hz, 1H, *H*-1''a, trans to H-2''), 2.71 (dd, *J* = 5.1, 2.5 Hz, 1H, *H*-1''b, cis to H-2'').

^{19}F-NMR (565 MHz, $CDCl_3$) δ_F [ppm] = –71.54 (s), –136.33 (d, *J* = 21.4 Hz), –136.56 (d, *J* = 21.2 Hz).

^{13}C-NMR (151 MHz, $CDCl_3$) δ_C [ppm] = 165.6, 150.8 (dd, *J* = 247.3, 9.2 Hz), 150.4 (dd, *J* = 253.2, 16.2 Hz), 132.0, 131.9, 131.9, 129.9, 128.6, 127.4, 124.0 (dd, *J* = 6.6, 3.8 Hz), 123.4 (q, 288.6 Hz), 117.7 (d, *J* = 17.5 Hz), 116.82 (d, *J* = 18.2 Hz), 84.82 (q, *J* = 27.9 Hz), 74.4, 55.7, 52.4, 44.4.

IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3003, 2952, 2851, 1755, 1613, 1523, 1440, 1278, 1244, 1172, 1120, 1082, 1054, 1020, 997, 914, 877, 822, 788, 766, 746, 719, 698, 655, 563.

(*S*)-(−)-MTPA ester:

$[\alpha]_D^{22}$ = –58.8 (c = 1.0, $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$) δ_H [ppm] = 7.48 – 7.35 (m, 5H, MTPA-C_5H_5), 7.23 – 7.11 (m, 3H, arom.-*H*), 6.03 (d, *J* = 4.0 Hz, 1H, *H*-1), 3.48 (t, *J* = 1.3 Hz, 3H, MTPA-OCH_3), 3.20 (td, *J* = 3.9, 2.5 Hz, 1H, *H*-2''), 2.75 (dd, *J* = 5.1, 3.9 Hz, 1H, *H*-1''a, trans to H-2''), 2.61 (dd, *J* = 5.0, 2.5 Hz, 1H, *H*-1''b, cis to H-2'').

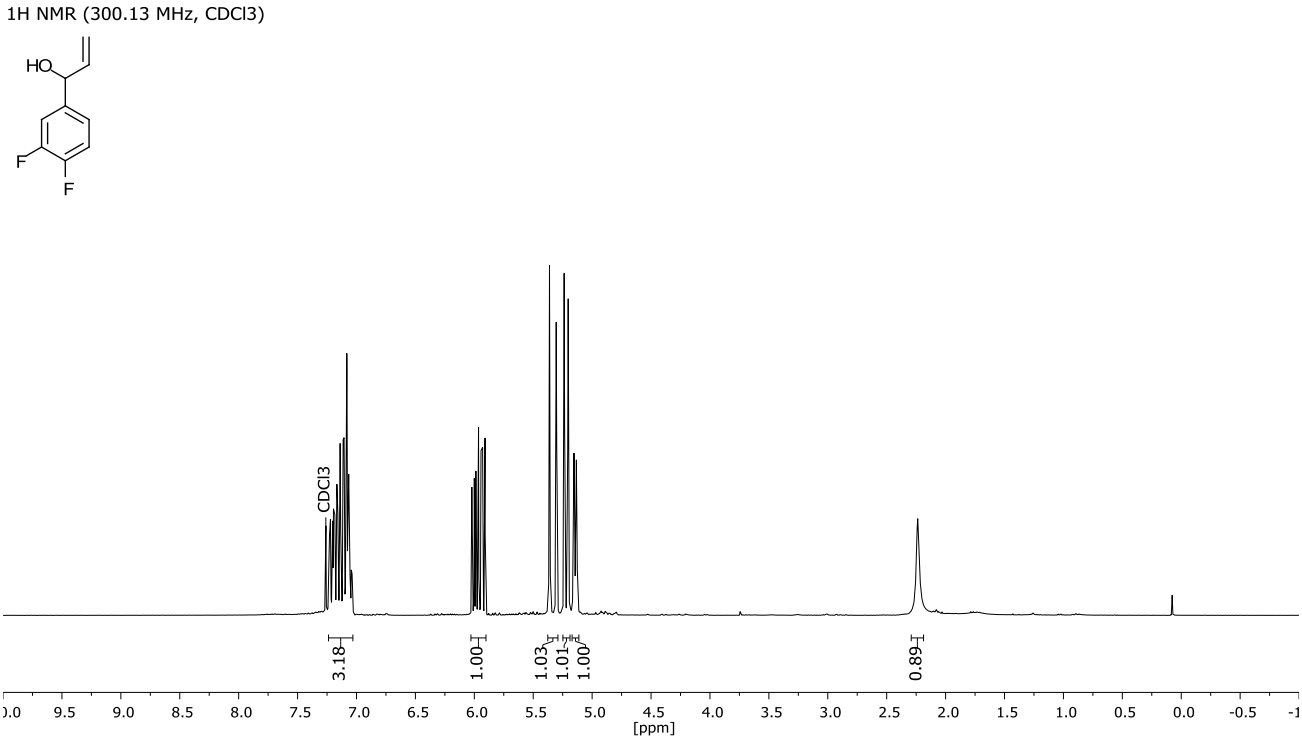
^{19}F-NMR (565 MHz, $CDCl_3$) δ_F [ppm] = –71.41 (s), –136.14 (d, J = 21.3 Hz), –136.36 (d, *J* = 20.7 Hz).

^{13}C-NMR (151 MHz, $CDCl_3$) δ_C [ppm] = 165.5, 151.9 (dd, *J* = 246.6, 8.3 Hz), 149.8 (dd, *J* = 252.9, 15.8 Hz), 131.9, 131.8 (m), 129.9, 128.6, 127.3, 123.9 (dd, *J* = 6.5, 3.8 Hz), 123.3 (q, *J* = 288.6 Hz), 117.8 (d, *J* = 17.4 Hz), 116.8 (d, *J* = 18.1 Hz), 84.8 (q, *J* = 27.9 Hz), 74.6, 55.5, 52.3, 44.5.

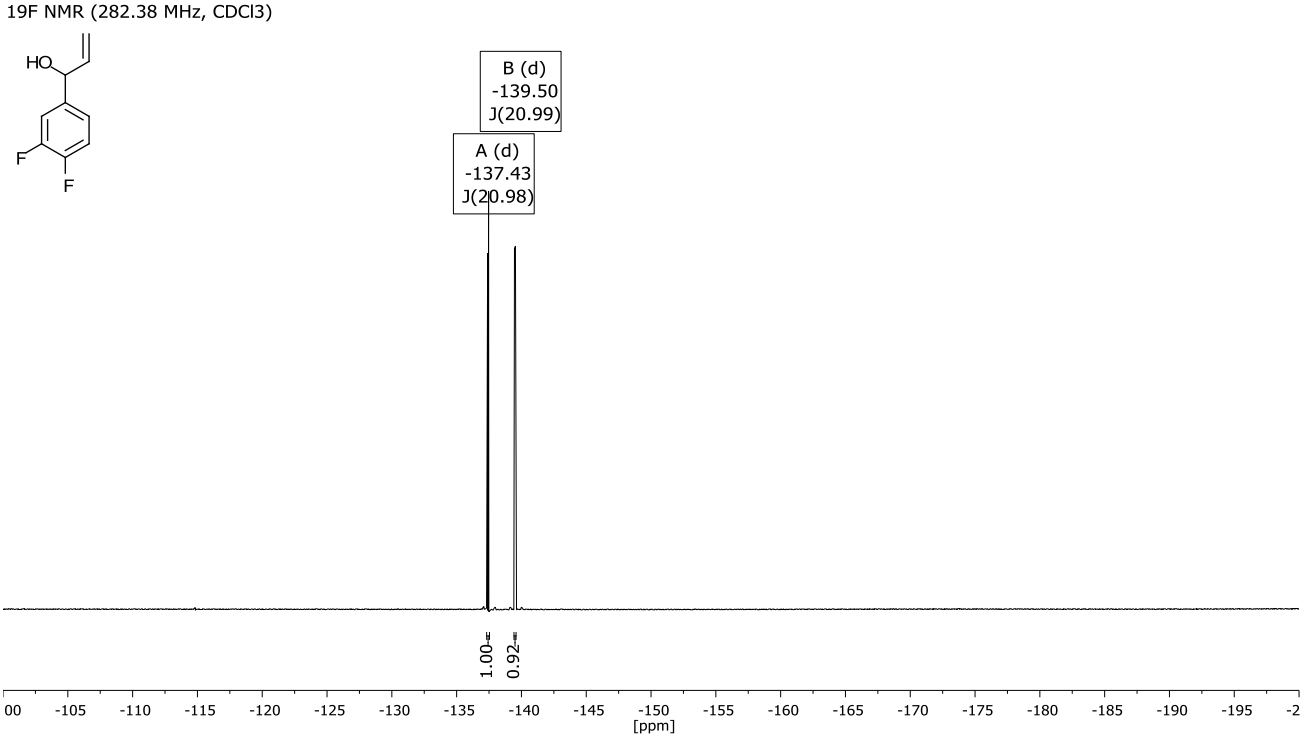
IR (film on NaCl) $\tilde{\upsilon}$ [cm^{-1}] = 3066, 3002, 2951, 2851, 2117, 1756, 1613, 1523, 1440, 1275, 1244, 1172, 1120, 1082, 1053, 1019, 996, 914, 877, 823, 786, 766, 748, 718, 698, 636, 563.

3 SPECTRA

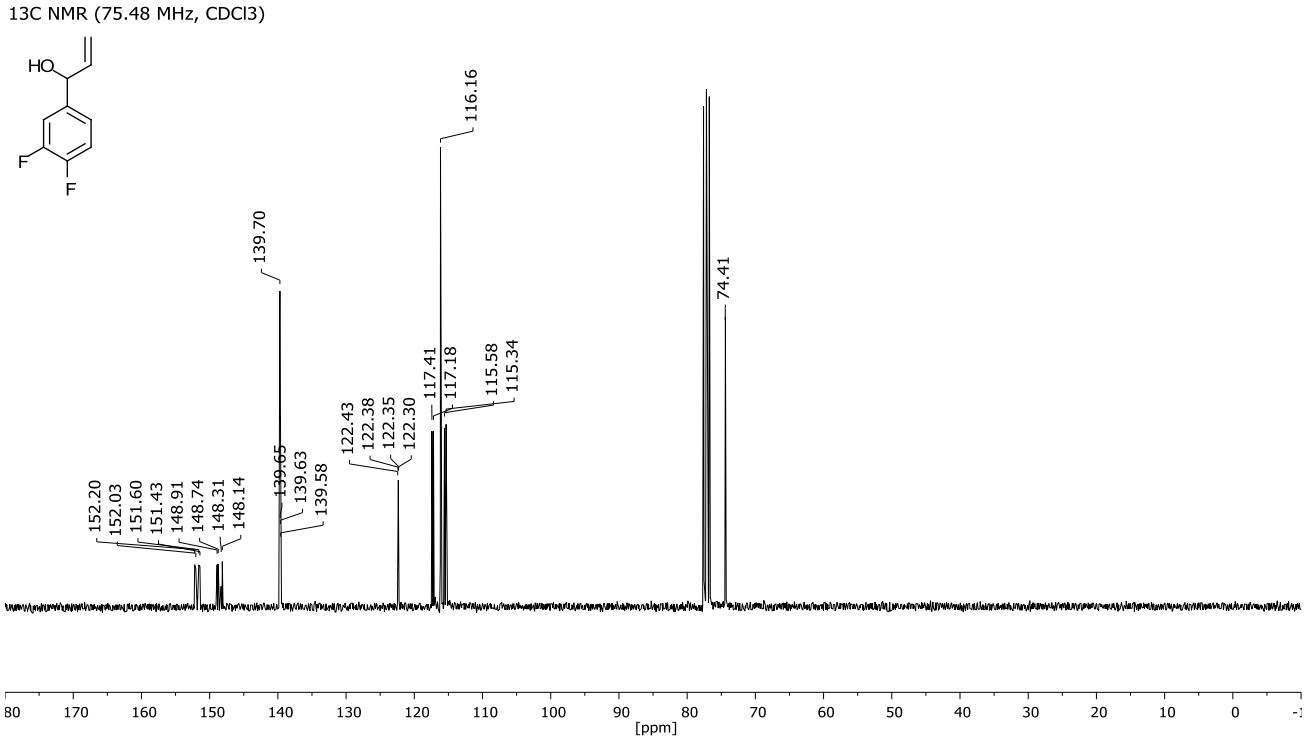
3.1 1-(3,4-Difluorophenyl)prop-2-en-1-ol (9)



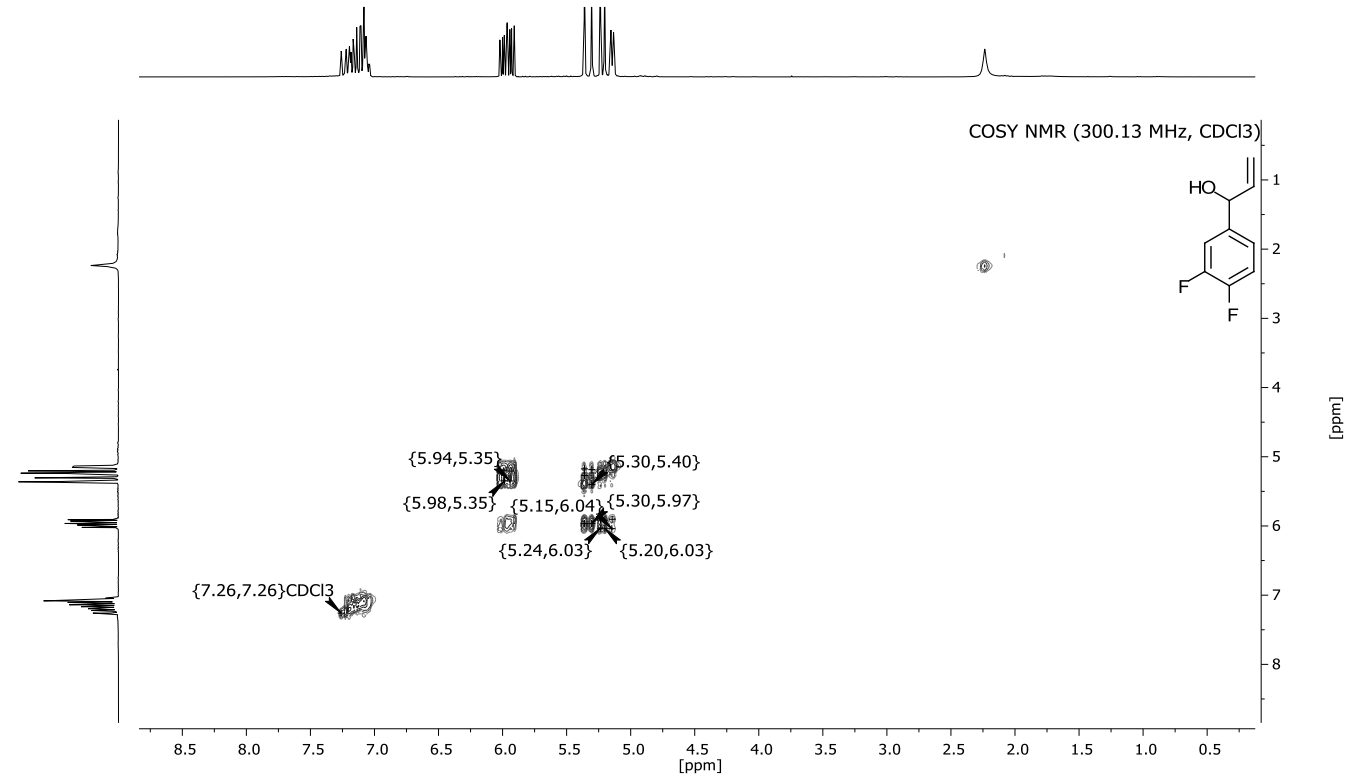
Spectrum 1. ^{1}H-NMR, 300 MHz, $CDCl_3$.



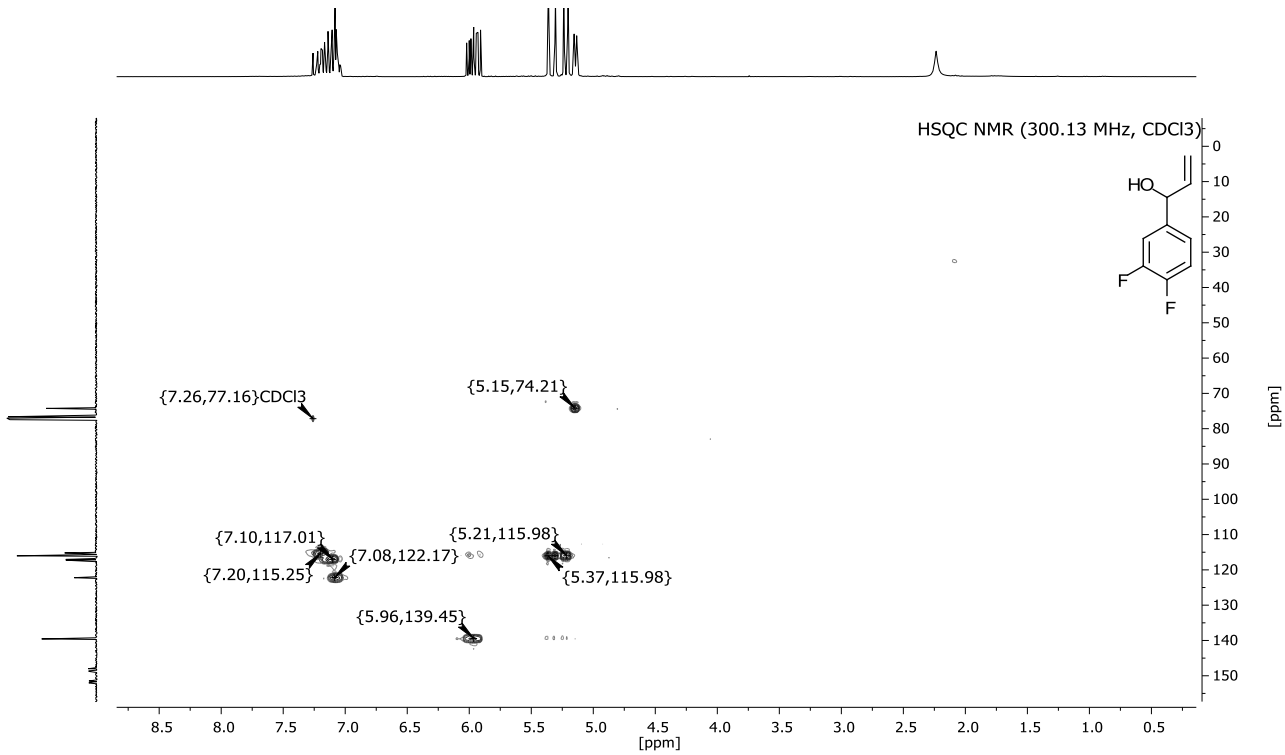
Spectrum 2. ^{19}F-NMR, 282 MHz, $CDCl_3$.



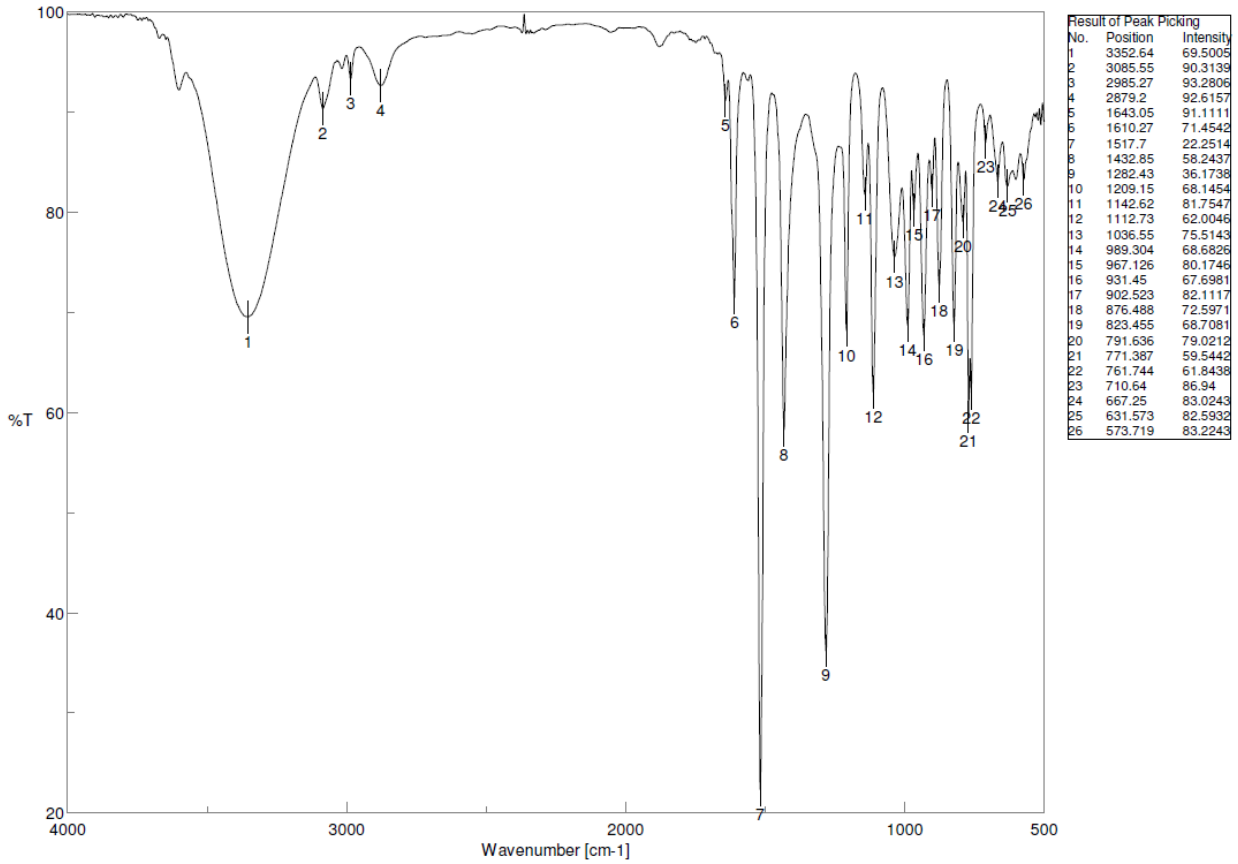
Spectrum 3. ^{13}C-NMR, 75 MHz, $CDCl_3$.



Spectrum 4. COSY-NMR, 300 MHz, $CDCl_3$.



Spectrum 5. HSQC-NMR, 300 MHz, $CDCl_3$.

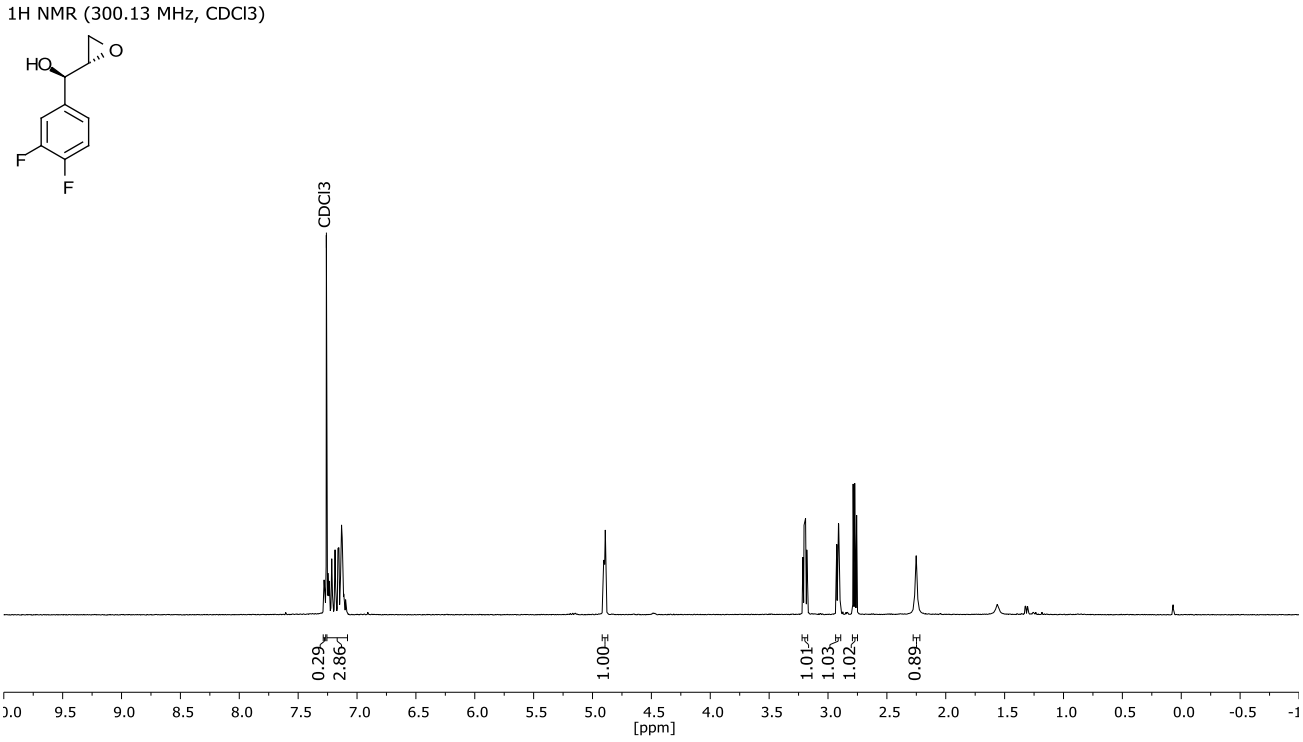


Result of Peak Picking

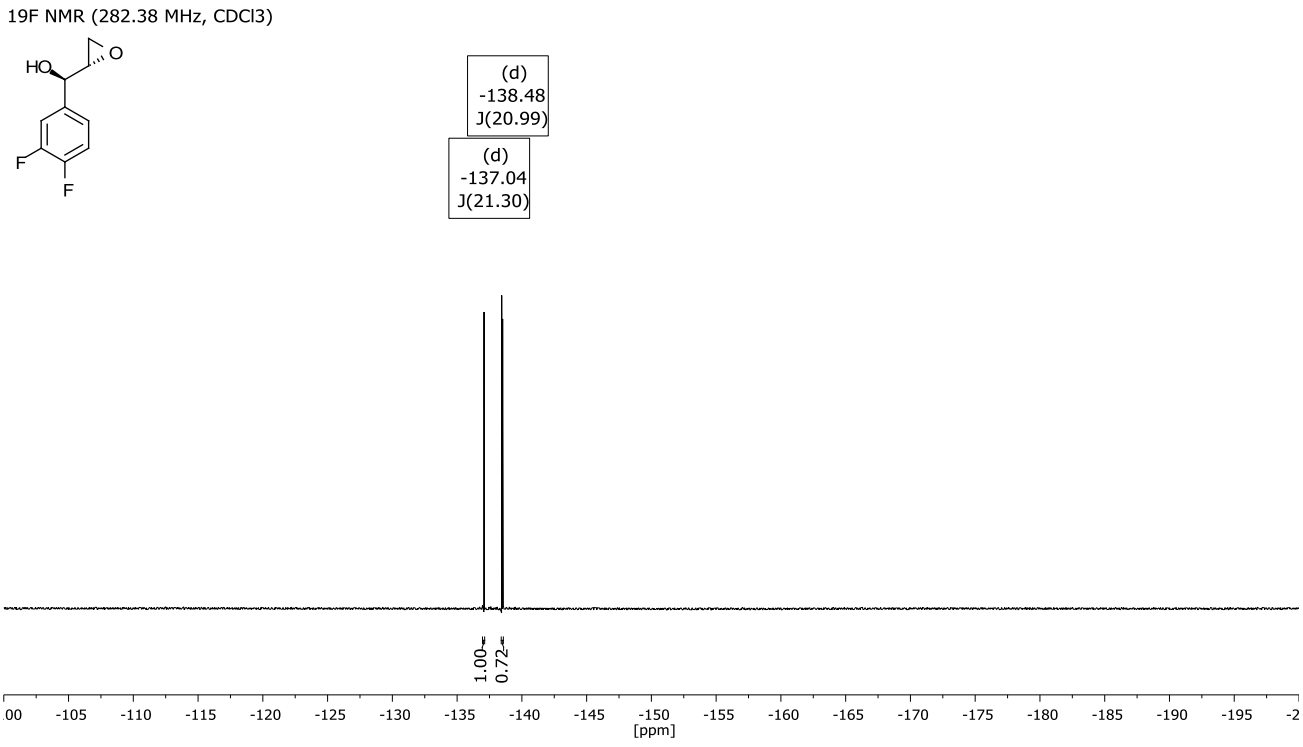
No.	Position	Intensity
1	3352.64	69.5005
2	3085.55	90.3139
3	2985.27	93.2806
4	2879.2	92.6157
5	1643.05	91.1111
6	1610.27	71.4542
7	1517.7	22.2514
8	1432.85	58.2437
9	1282.43	36.1738
10	1209.15	68.1454
11	1142.62	81.7547
12	1112.73	62.0046
13	1036.55	75.5143
14	989.304	68.6826
15	967.126	80.1746
16	931.45	67.6981
17	902.523	82.1117
18	876.488	72.5971
19	823.455	68.7081
20	791.636	79.0212
21	771.387	59.5442
22	761.744	61.8438
23	710.64	86.94
24	667.25	83.0243
25	631.573	82.5932
26	573.719	83.2243

Spectrum 6. IR, film on NaCl.

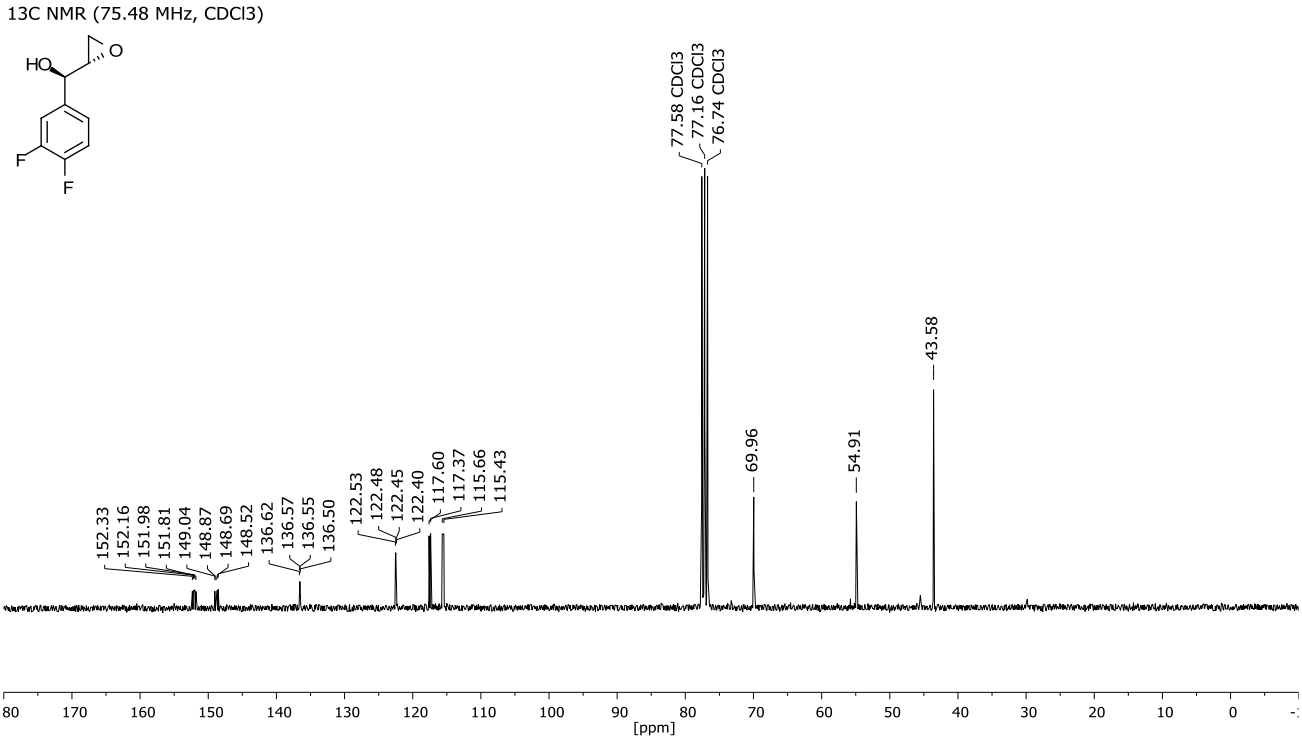
3.2 (1*R*,2*S*)-3-(3,4-Difluorophenyl)-glycidol (10)



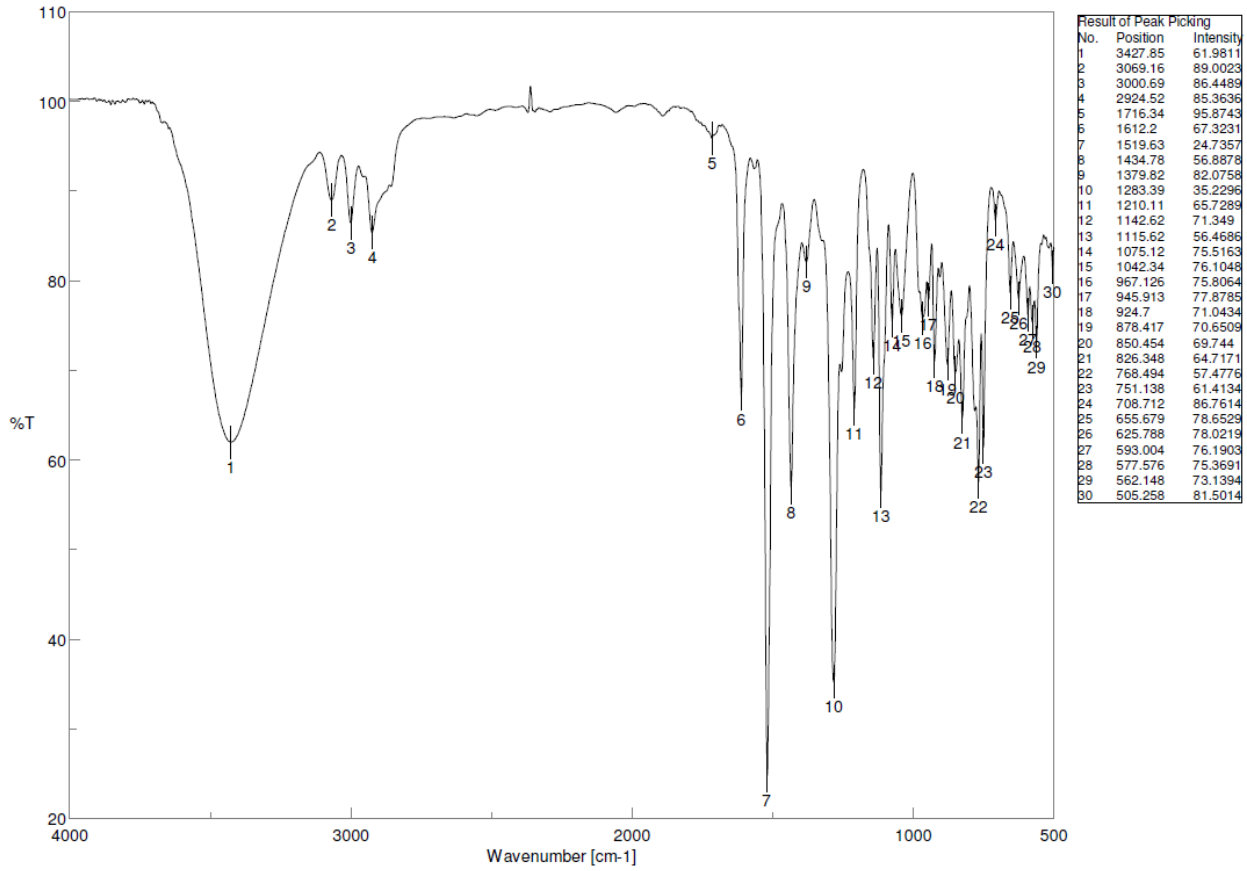
Spectrum 7. ^{1}H-NMR, 300 MHz, $CDCl_3$.



Spectrum 8. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 9. ^{13}C-NMR, 75 MHz, $CDCl_3$.

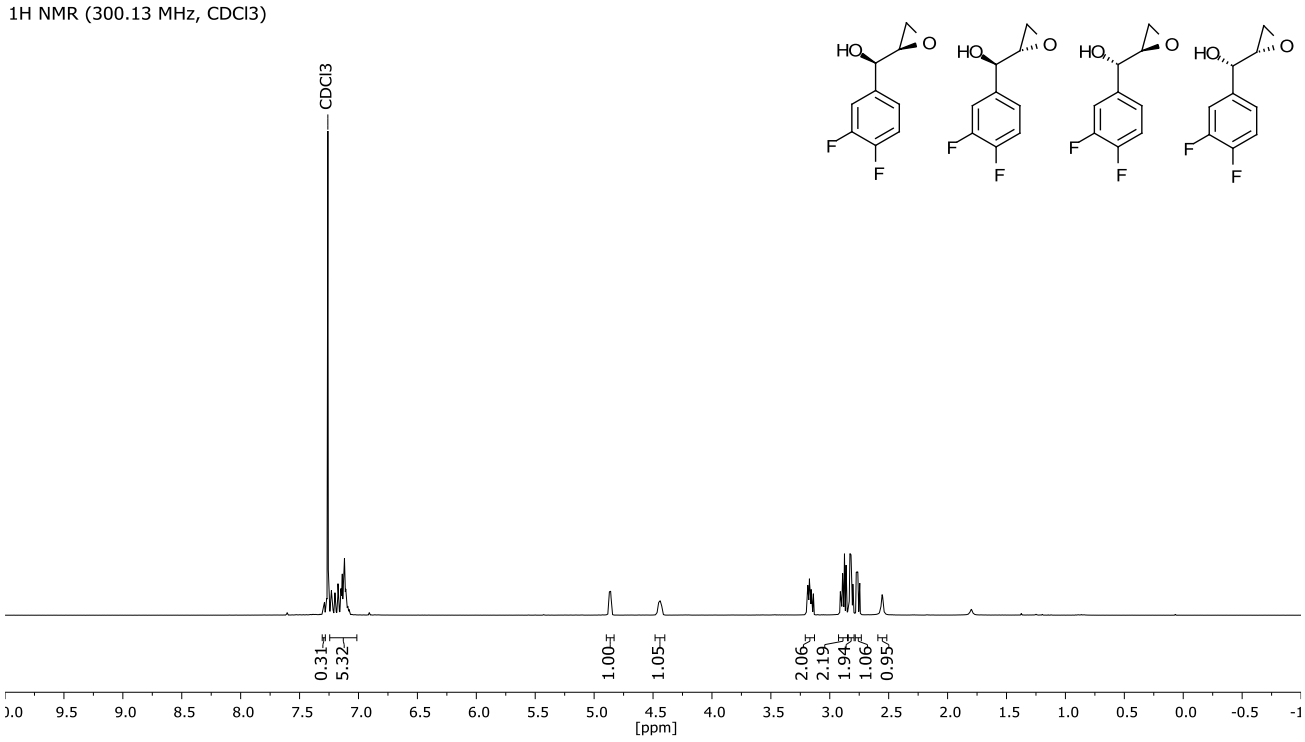


Result of Peak Picking

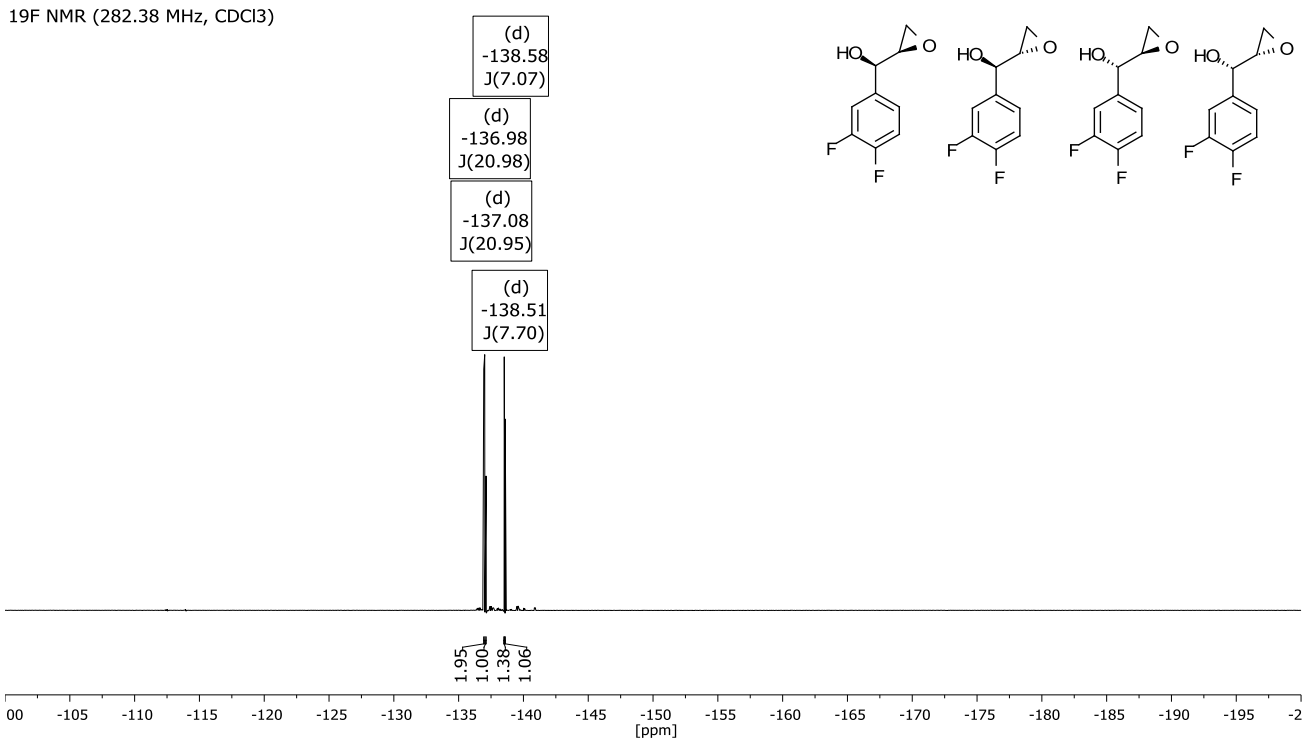
No.	Position	Intensity
1	3427.85	61.9811
2	3069.16	89.0023
3	3000.69	86.4489
4	2924.52	85.3636
5	1716.34	95.8743
6	1612.2	67.3231
7	1519.63	24.7357
8	1434.78	56.8878
9	1379.82	82.0758
10	1283.39	35.2296
11	1210.11	65.7289
12	1142.62	71.349
13	1115.62	56.4686
14	1075.12	75.5163
15	1042.34	76.1048
16	967.126	75.8064
17	945.913	77.8785
18	924.7	71.0434
19	878.417	70.6509
20	850.454	69.744
21	826.348	64.7171
22	768.494	57.4776
23	751.138	61.4134
24	708.712	86.7614
25	655.679	78.6529
26	625.788	78.0219
27	593.004	76.1903
28	577.576	75.3691
29	562.148	73.1394
30	505.258	81.5014

Spectrum 10. IR, film on NaCl.

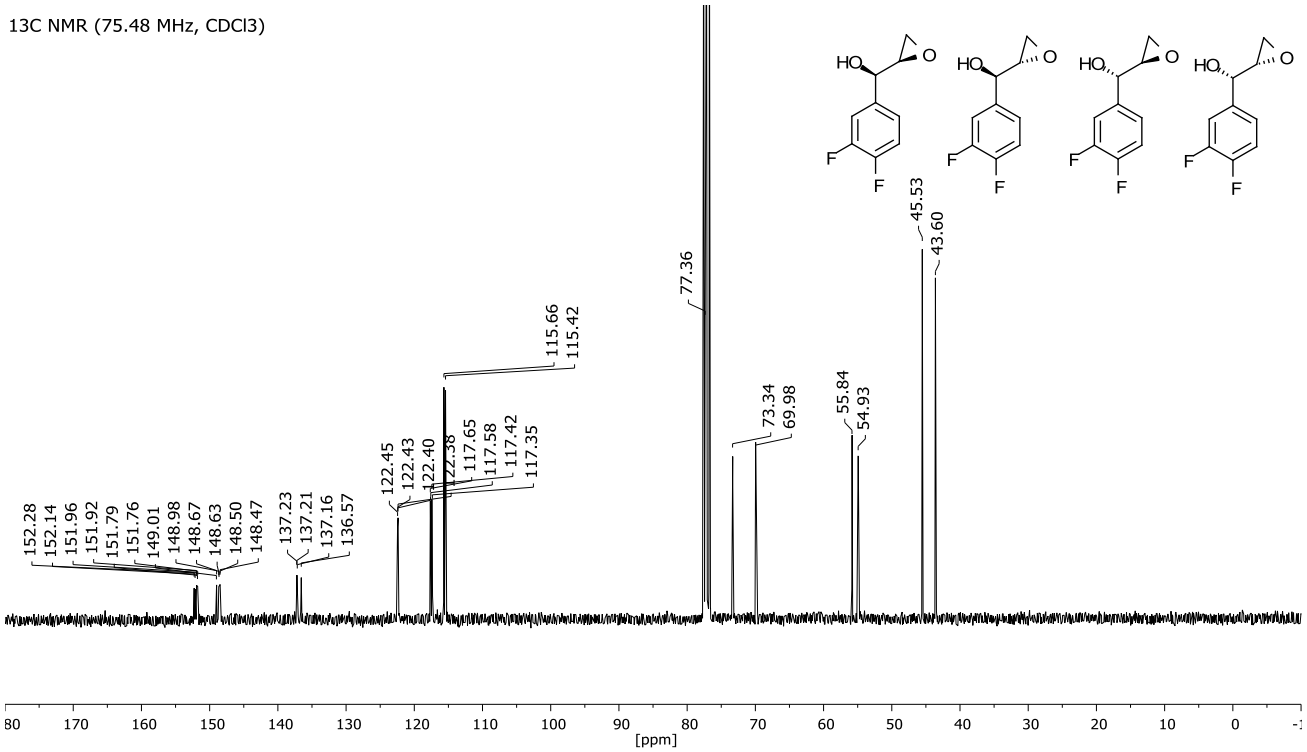
3.3 3-(3,4-Difluorophenyl)-glycidol (mixture of stereoisomers)



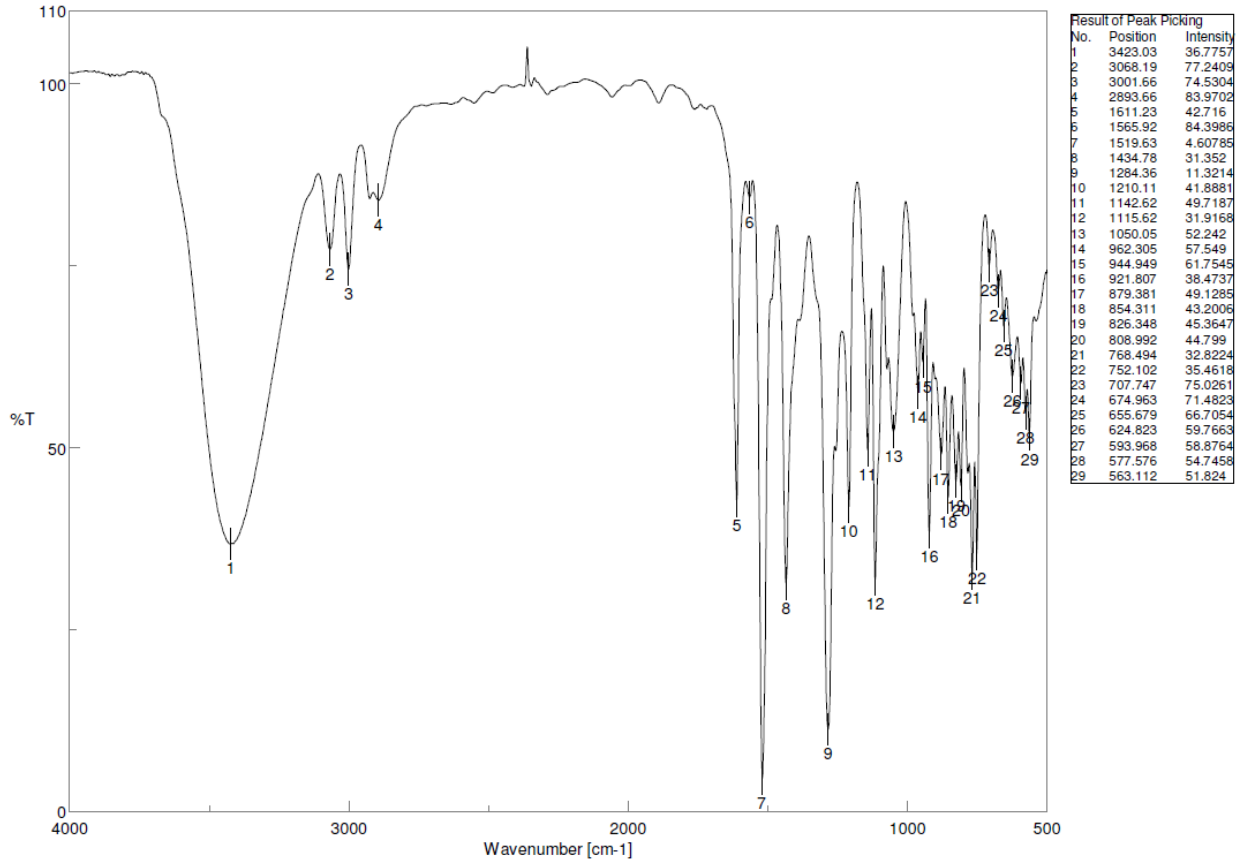
Spectrum 11. ^{1}H-NMR, 300 MHz, $CDCl_3$.



Spectrum 12. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 13. ^{13}C-NMR, 75 MHz, $CDCl_3$.

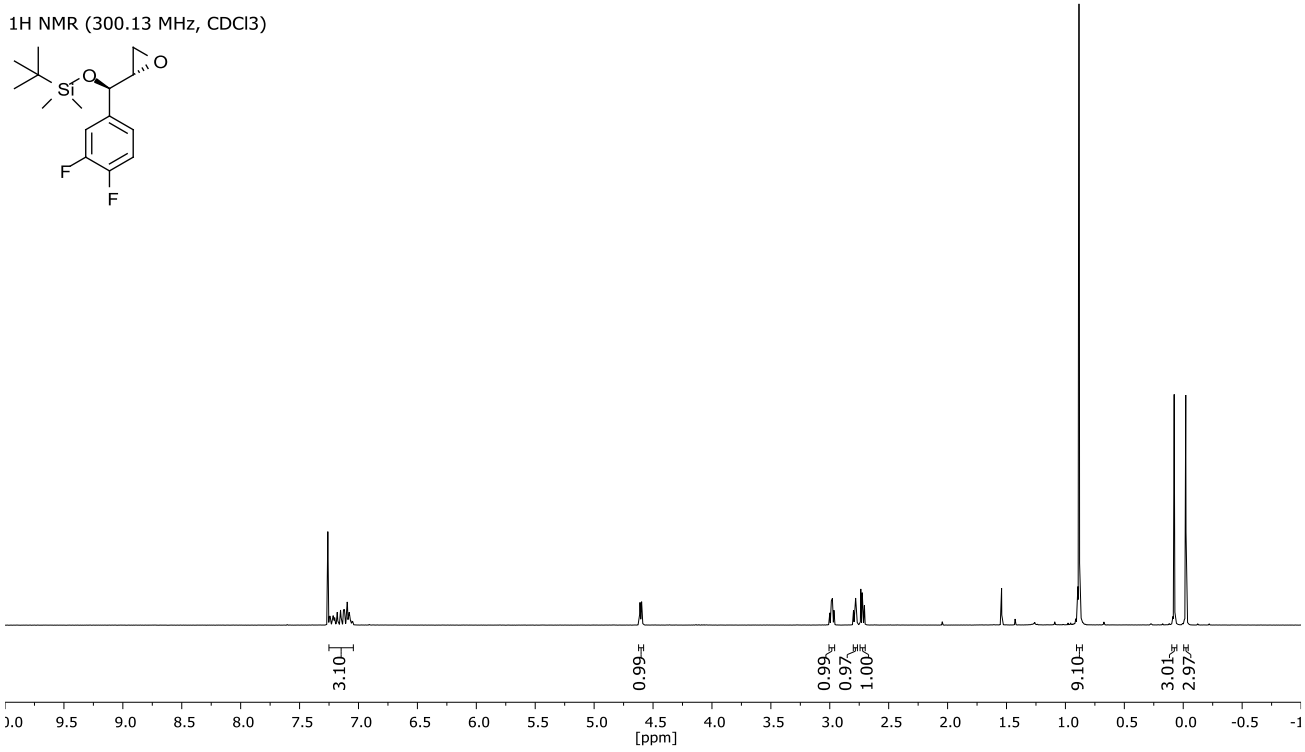


Result of Peak Picking

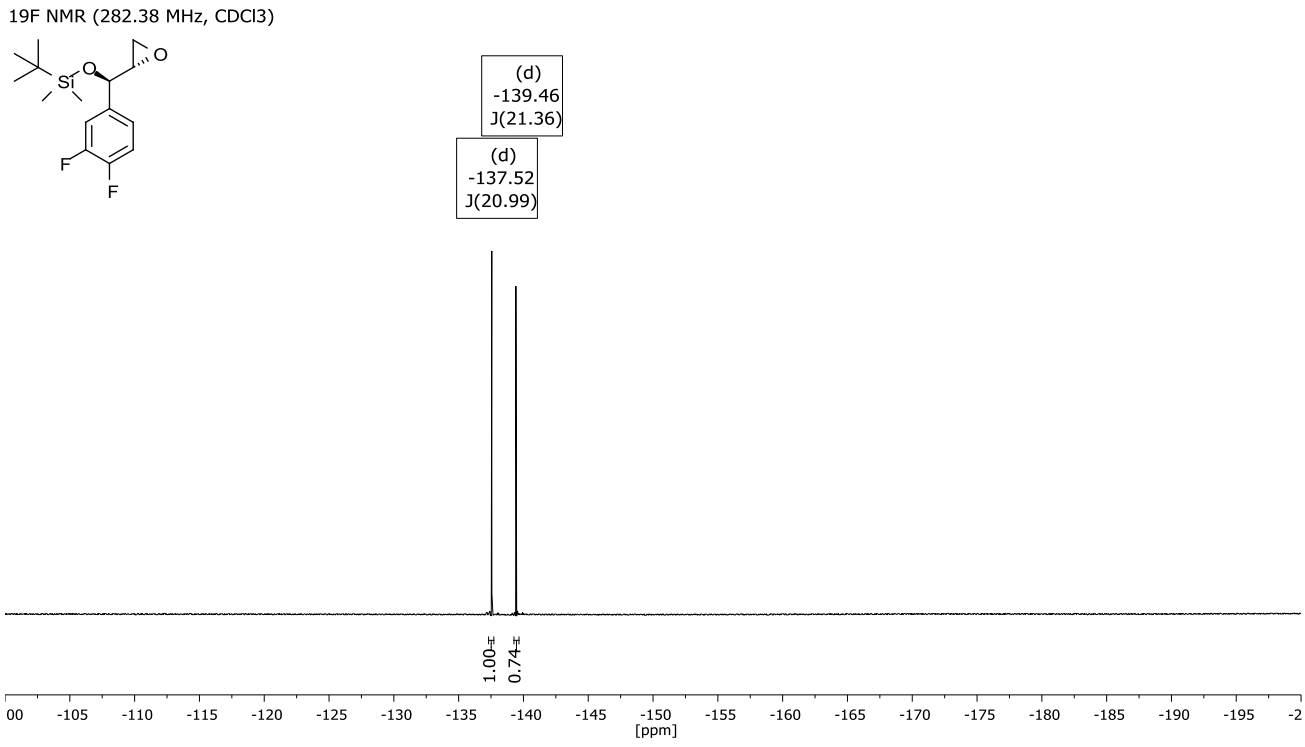
No.	Position	Intensity
1	3423.03	36.7757
2	3068.19	77.2409
3	3001.66	74.5304
4	2893.66	83.9702
5	1611.23	42.716
6	1565.92	84.3986
7	1519.63	4.60785
8	1434.78	31.352
9	1284.36	11.3214
10	1210.11	41.8881
11	1142.62	49.7187
12	1115.62	31.9168
13	1050.05	52.242
14	962.305	57.549
15	944.949	61.7545
16	921.807	38.4737
17	879.381	49.1285
18	854.311	43.2006
19	826.348	45.3647
20	808.992	44.799
21	768.494	32.8224
22	752.102	35.4618
23	707.747	75.0261
24	674.963	71.4823
25	655.679	66.7054
26	624.823	59.7663
27	593.968	58.8764
28	577.576	54.7458
29	563.112	51.824

Spectrum 14. IR, film on NaCl.

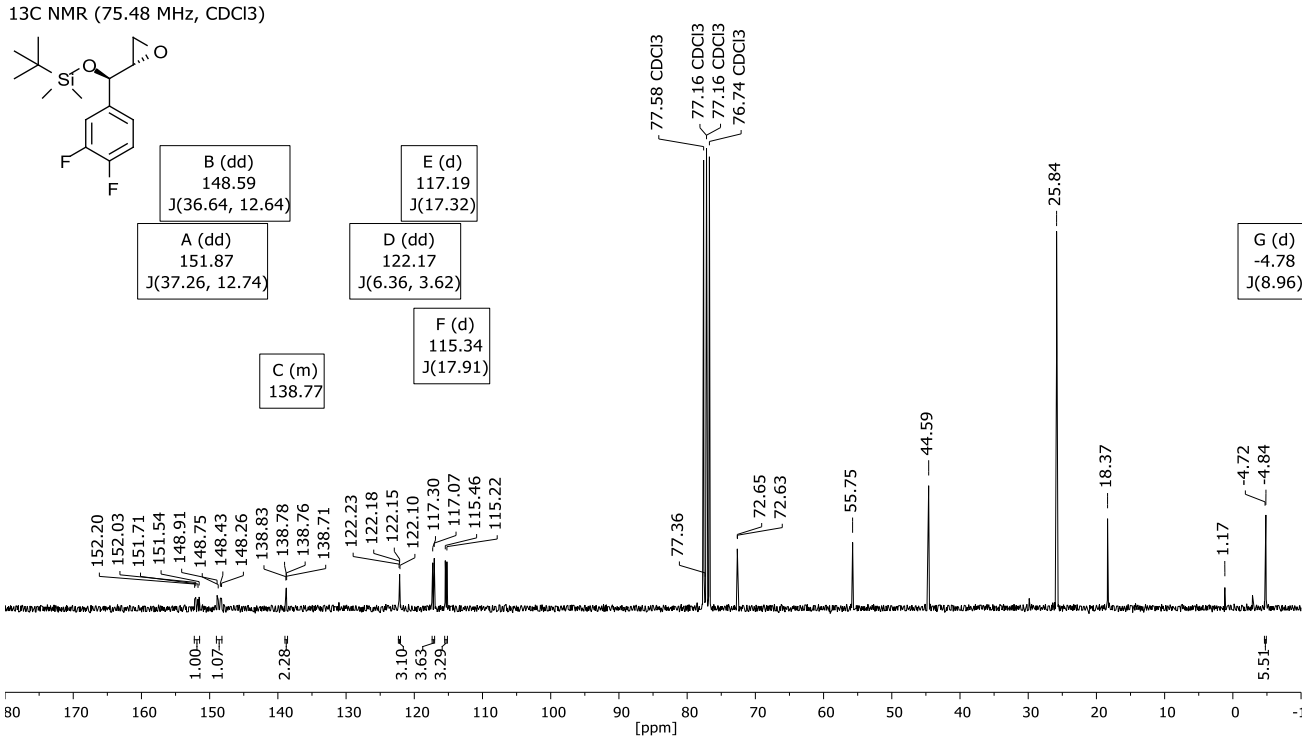
3.4 (1*R*,2*S*)-(*O*)-*tert*-Butyldimethylsilyl-3-(3,4-difluorophenyl)-glycidol (17)



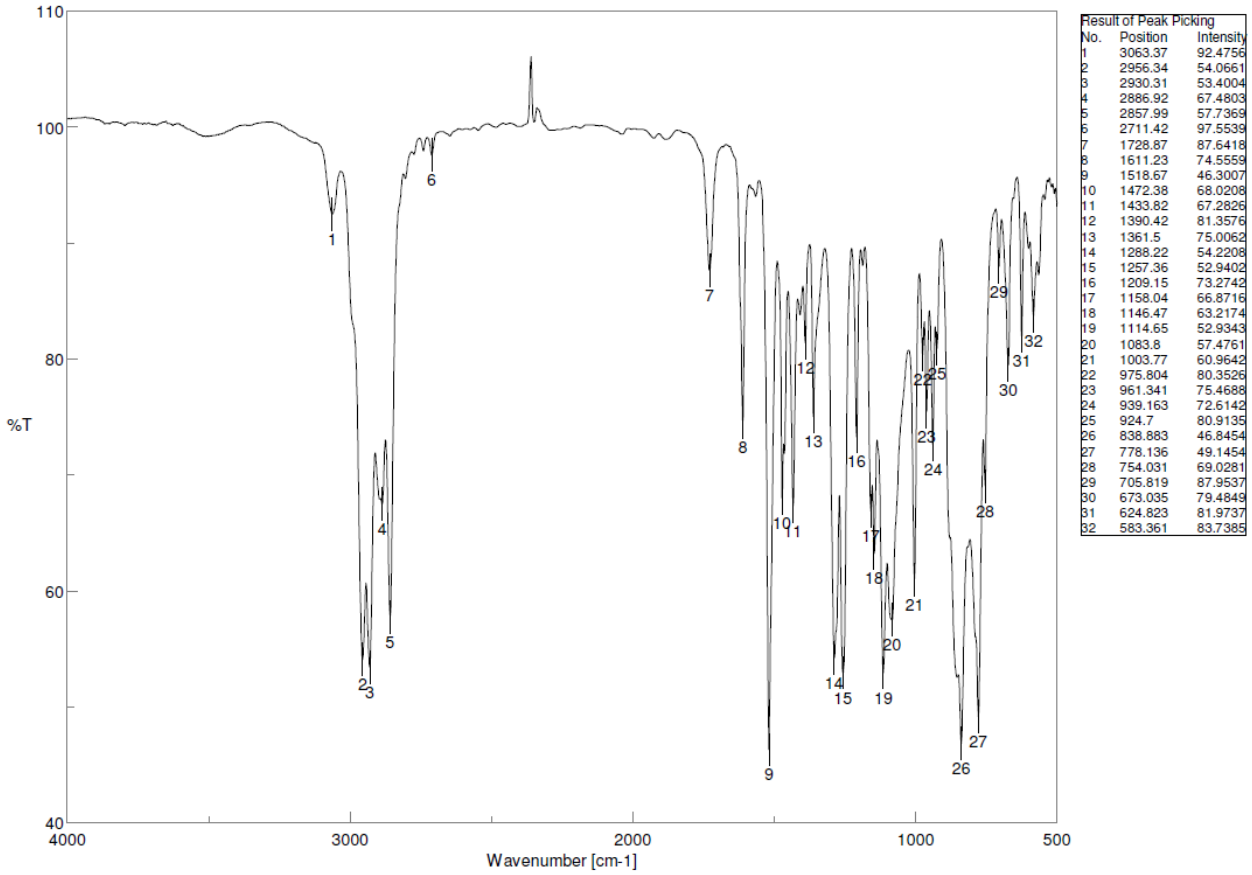
Spectrum 15. ^{1}H-NMR, 300 MHz, $CDCl_3$.



Spectrum 16. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 17. ^{13}C-NMR, 75 MHz, $CDCl_3$.

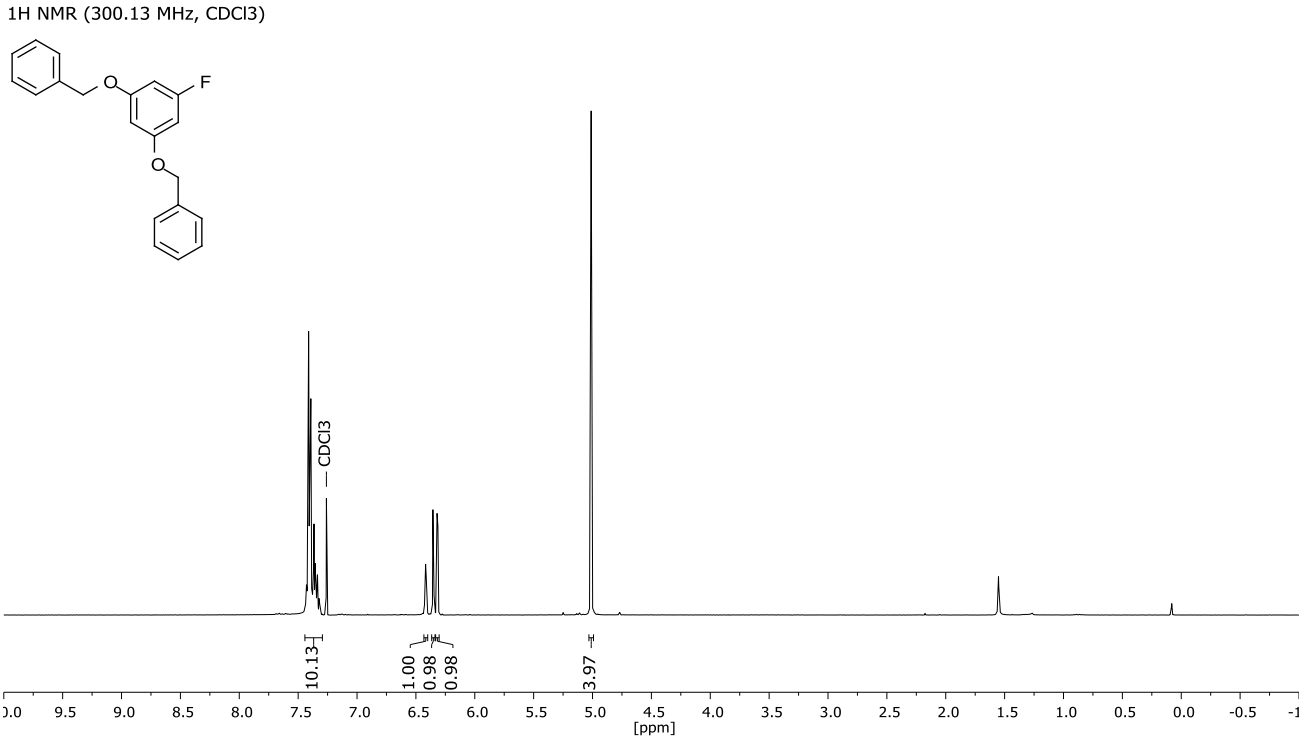


Result of Peak Picking

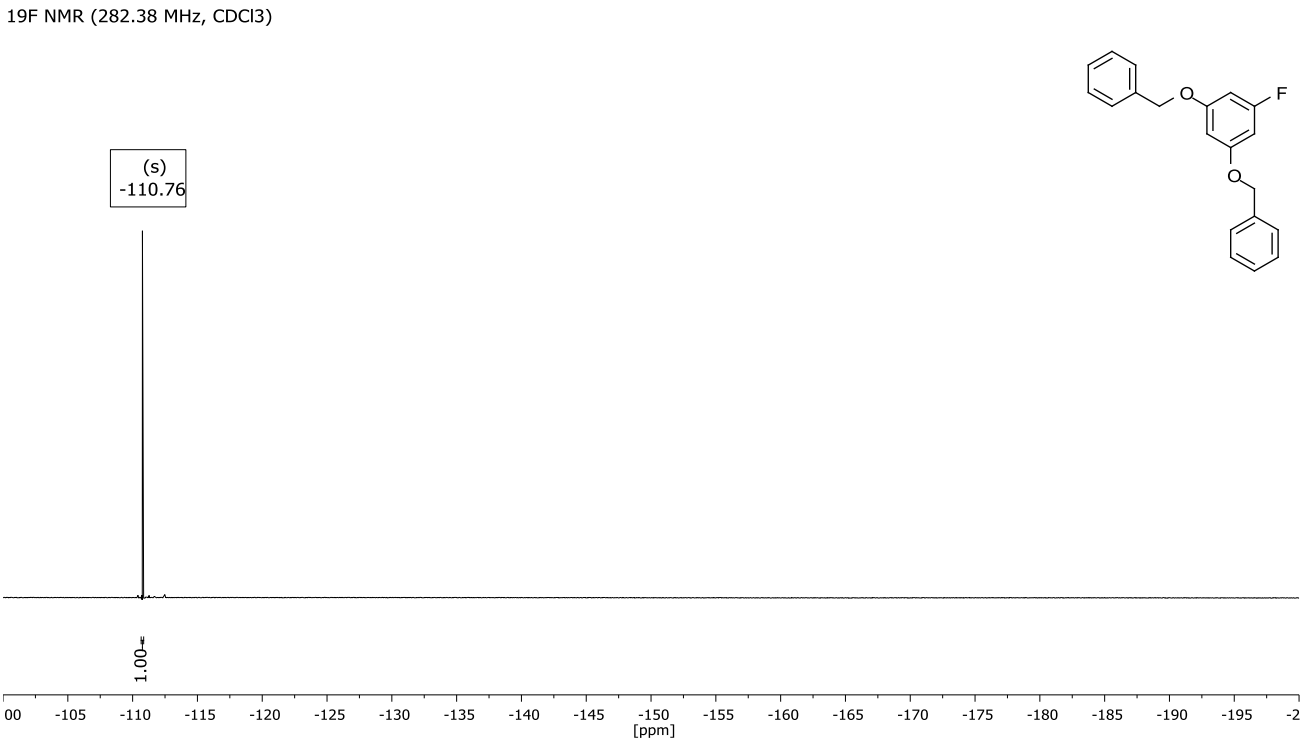
No.	Position	Intensity
1	3063.37	92.4756
2	2956.34	54.0661
3	2930.31	53.4004
4	2886.92	67.4803
5	2857.99	57.7369
6	2711.42	97.5539
7	1728.87	87.6418
8	1611.23	74.5559
9	1518.67	46.3007
10	1472.38	68.0208
11	1433.82	67.2826
12	1390.42	81.3576
13	1361.5	75.0062
14	1288.22	54.2208
15	1257.36	52.9402
16	1209.15	73.2742
17	1158.04	66.8716
18	1146.47	63.2174
19	1114.65	52.9343
20	1083.8	57.4761
21	1003.77	60.9642
22	975.804	80.3526
23	961.341	75.4688
24	939.163	72.6142
25	924.7	80.9135
26	838.883	46.8454
27	778.136	49.1454
28	754.031	69.0281
29	705.819	87.9537
30	673.035	79.4849
31	624.823	81.9737
32	583.361	83.7385

Spectrum 18. IR, film on NaCl.

3.5 3,5-Bis(benzyloxy)fluorobenzene (20)

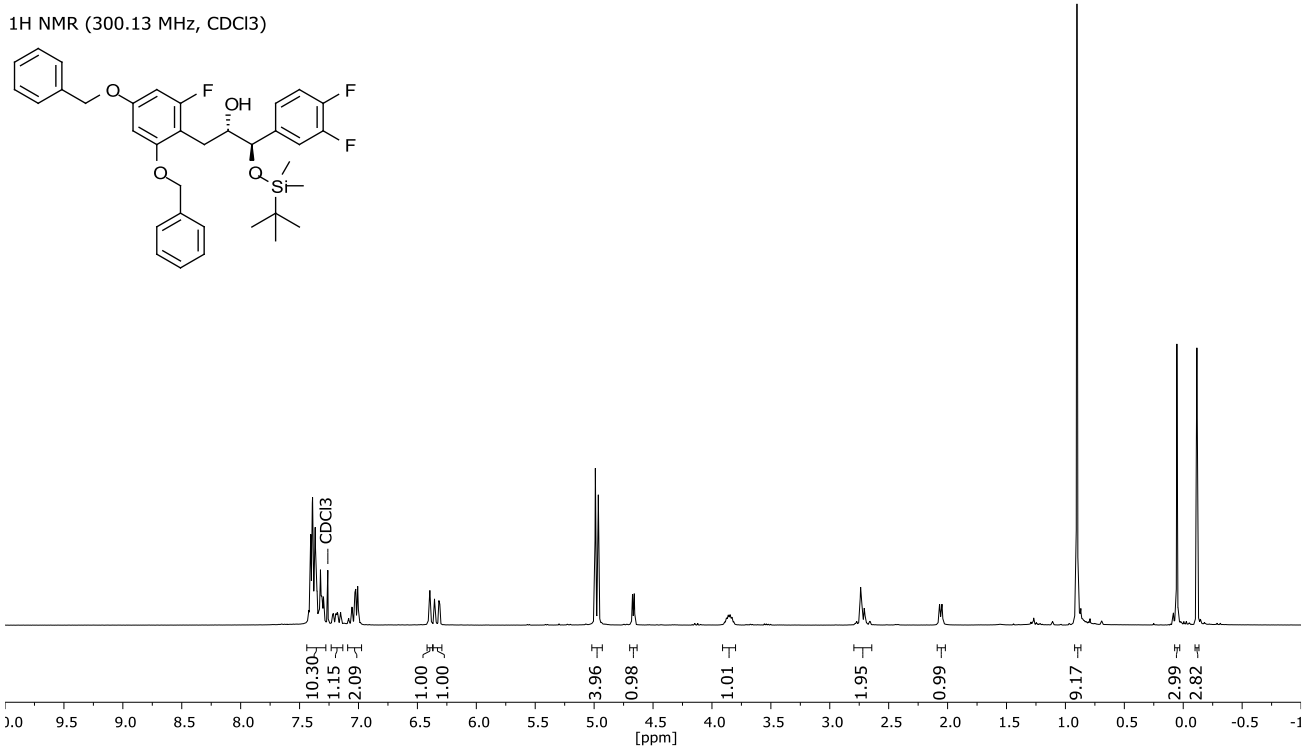


Spectrum 19. ^{1}H-NMR, 300 MHz, $CDCl_3$.

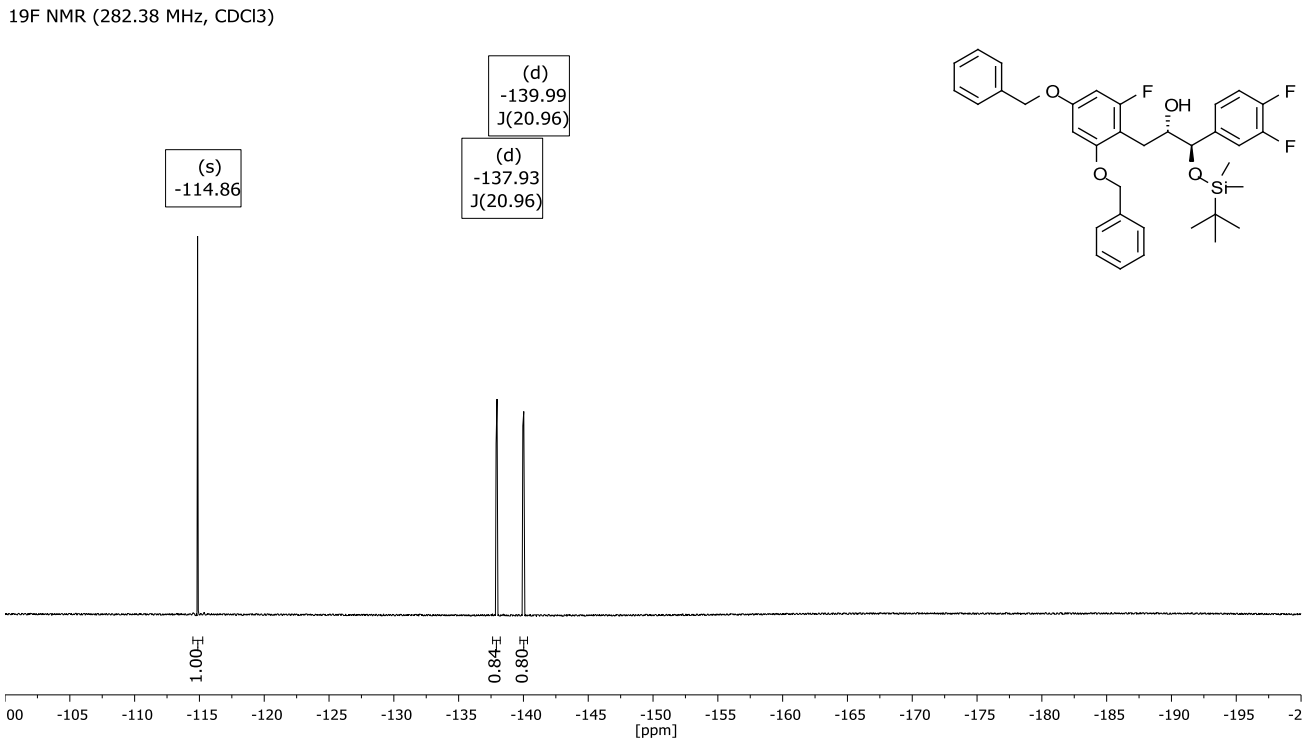


Spectrum 20. ^{19}F-NMR, 282 MHz, $CDCl_3$.

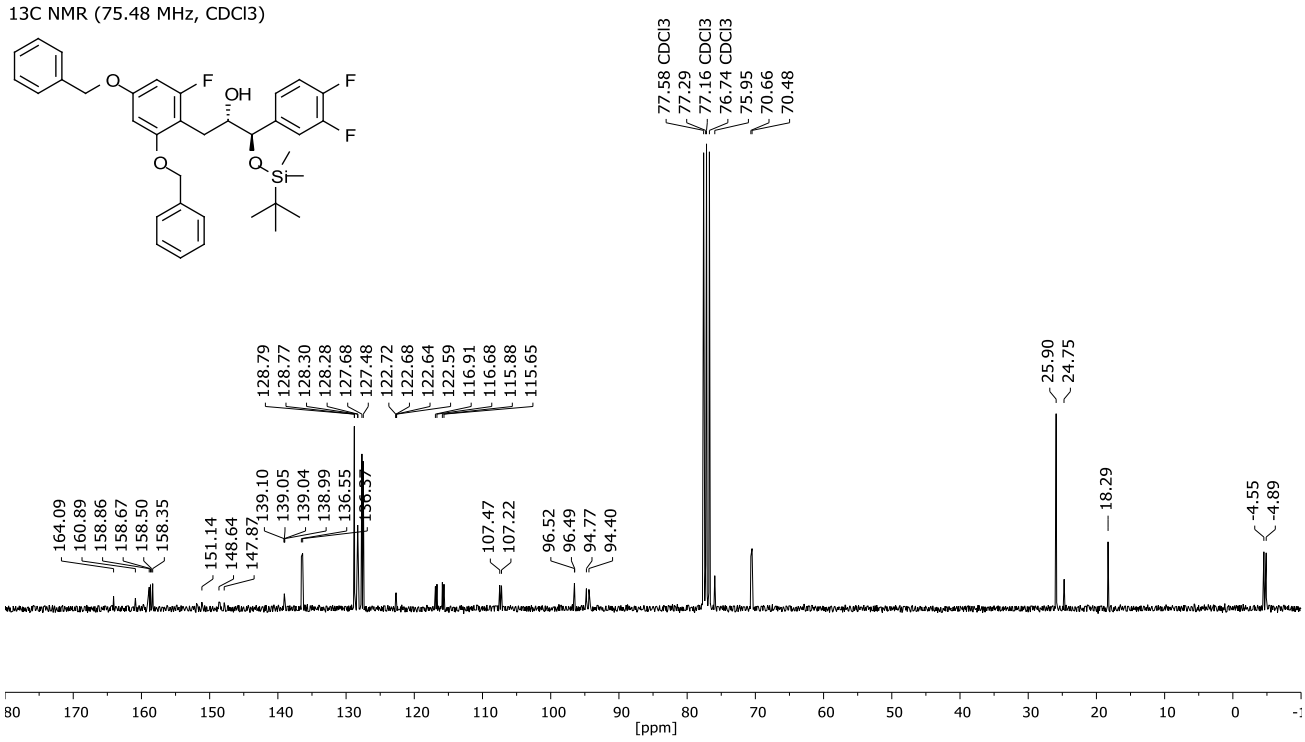
3.6 (1*R*,2*S*)-3-(2,4-Bis(benzyloxy)-6-fluorphenyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluorphenyl)propan-2-ol (18)



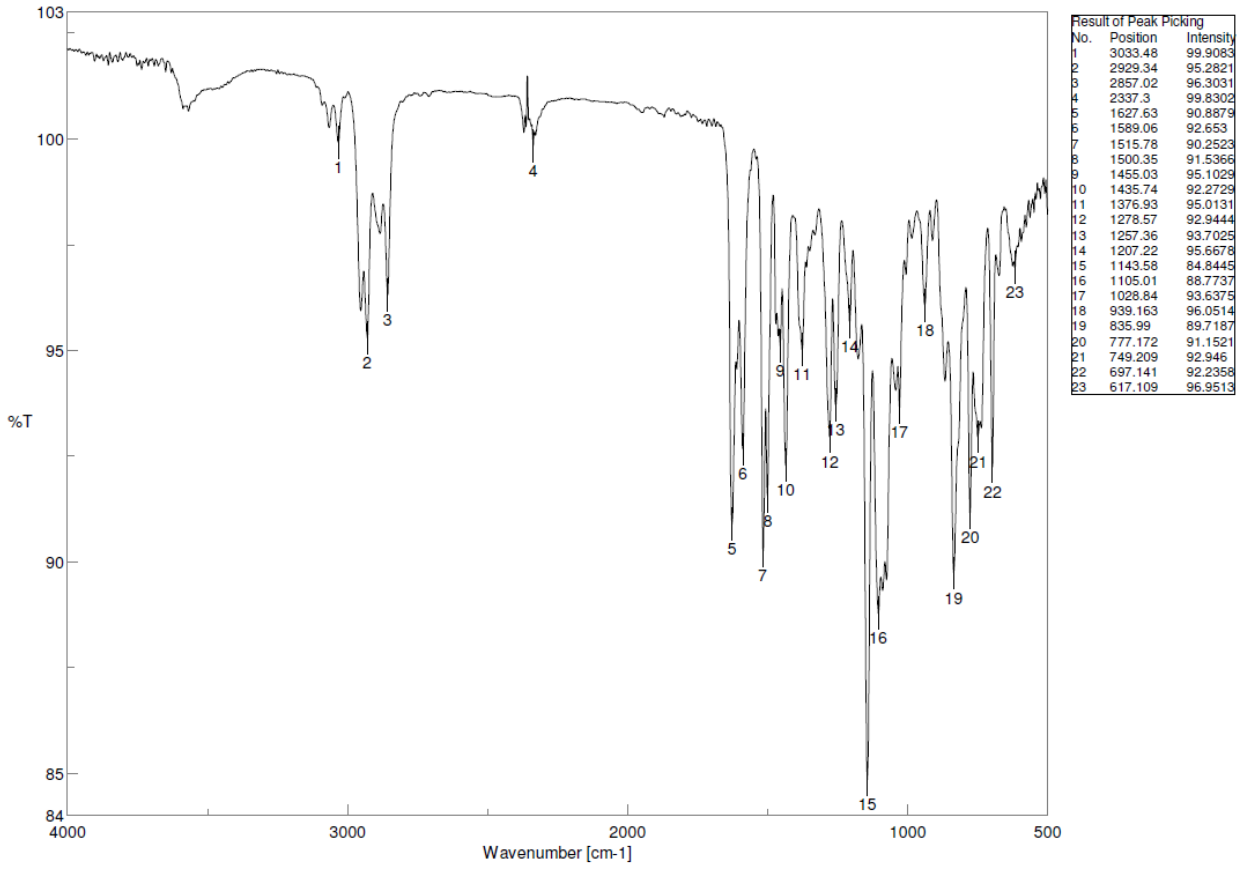
Spectrum 21. ^{1}H-NMR, 300 MHz, $CDCl_3$.



Spectrum 22. ^{19}F-NMR, 282 MHz, $CDCl_3$.

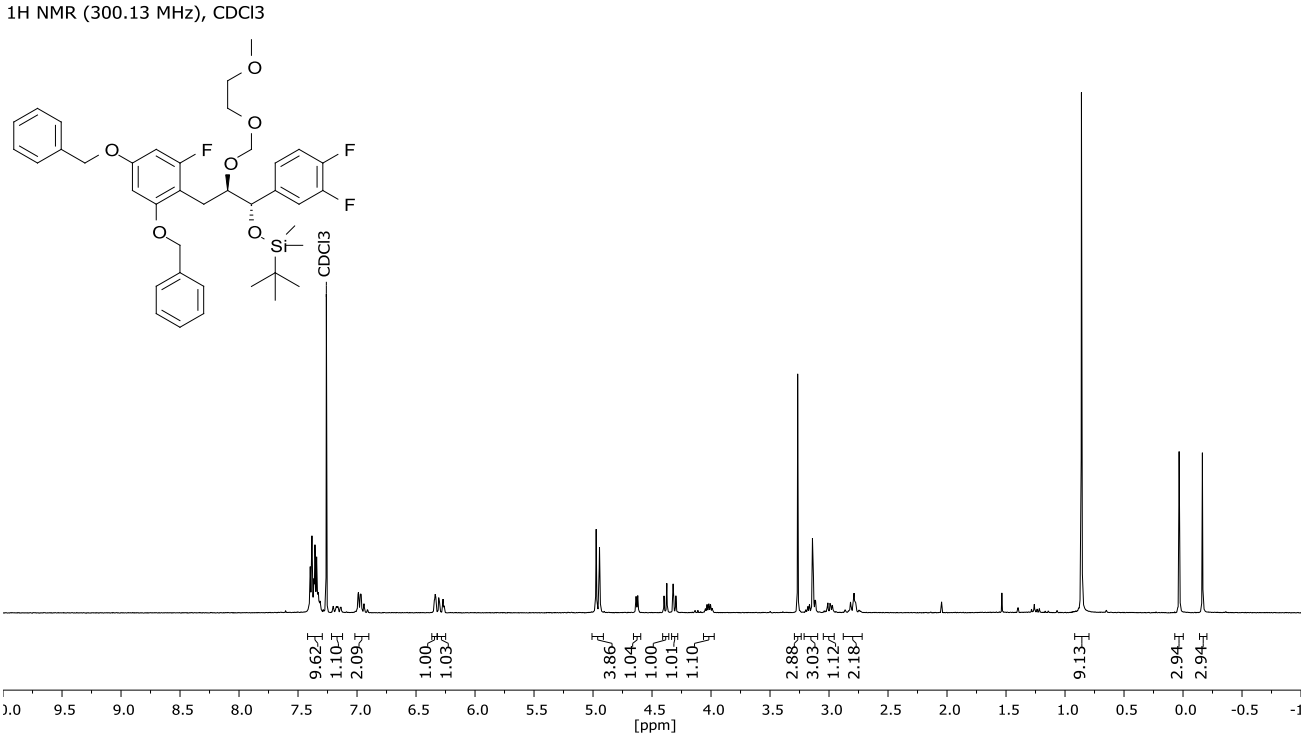


Spectrum 23. ^{13}C-NMR, 75 MHz, $CDCl_3$.

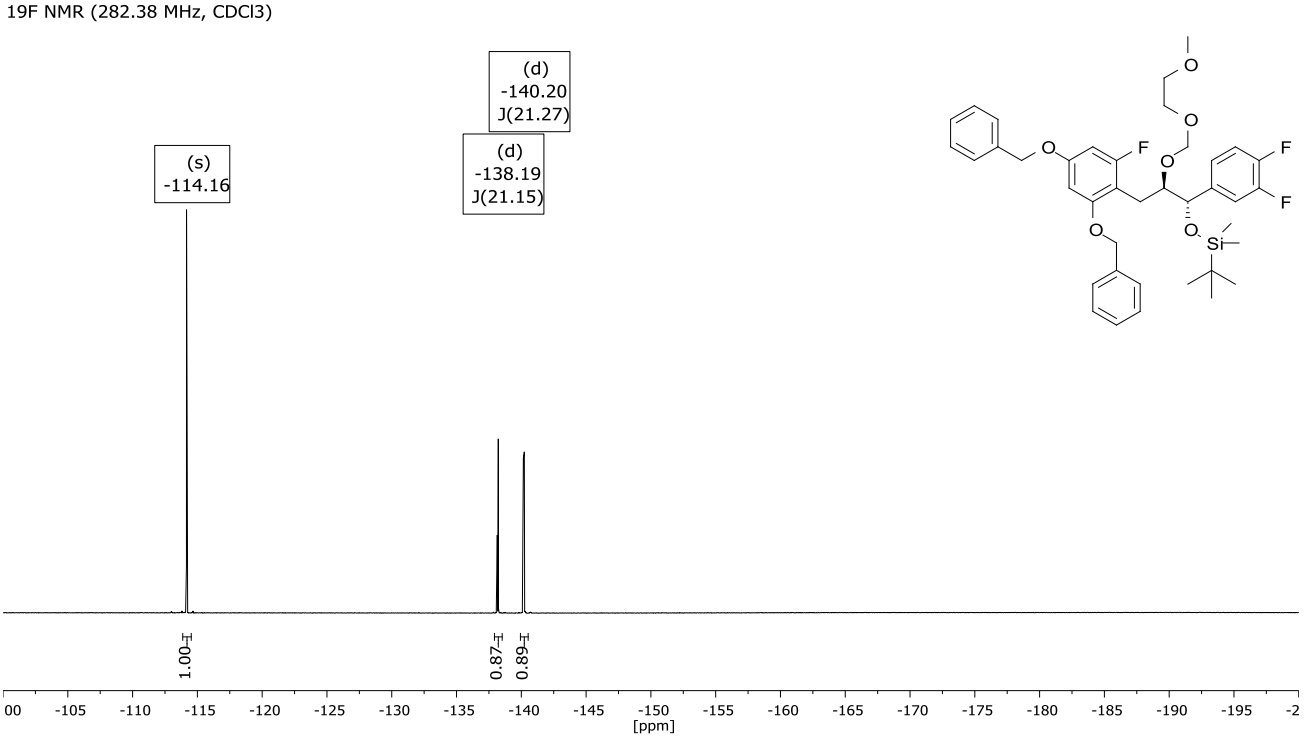


Spectrum 24. IR, film on NaCl.

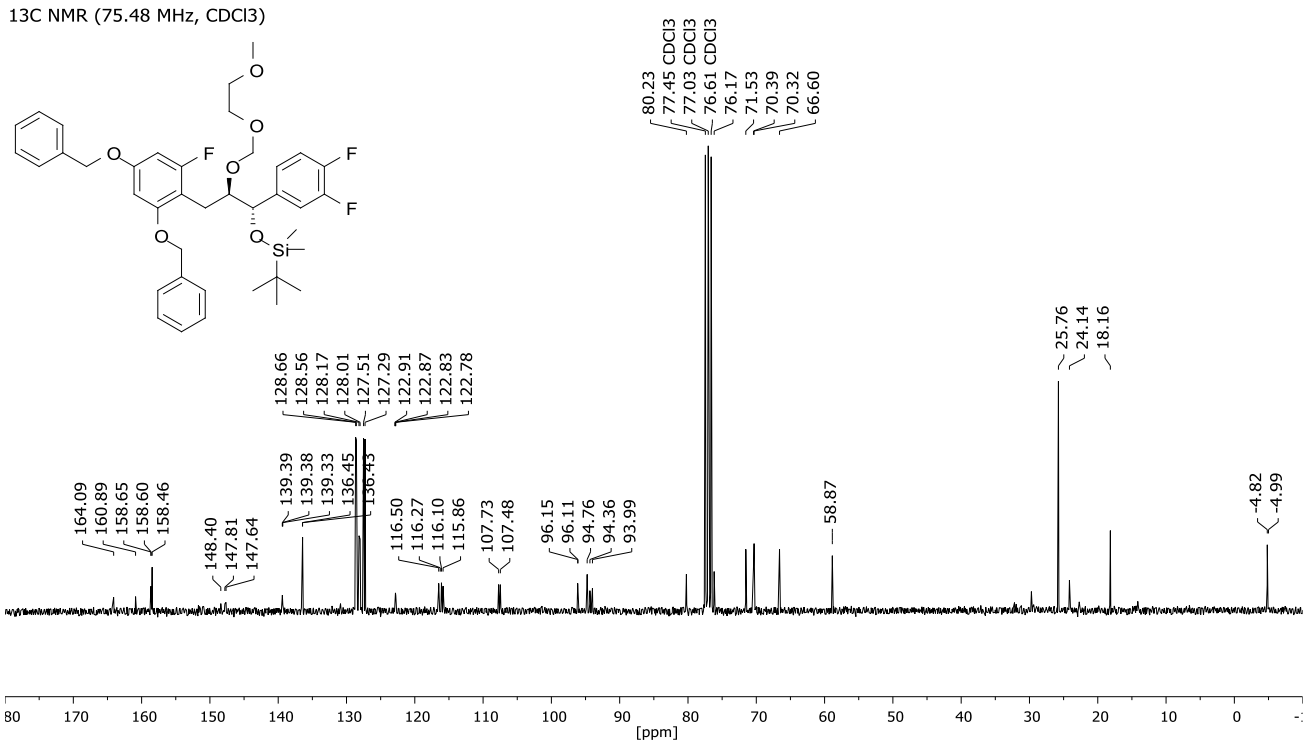
3.7 (1*R*,2*S*)-3-(2,4-Bis(benzyloxy)-6-fluorbenzyl)-1-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluorphenyl)-2-((2-methoxyethoxymethyl)oxy)propan



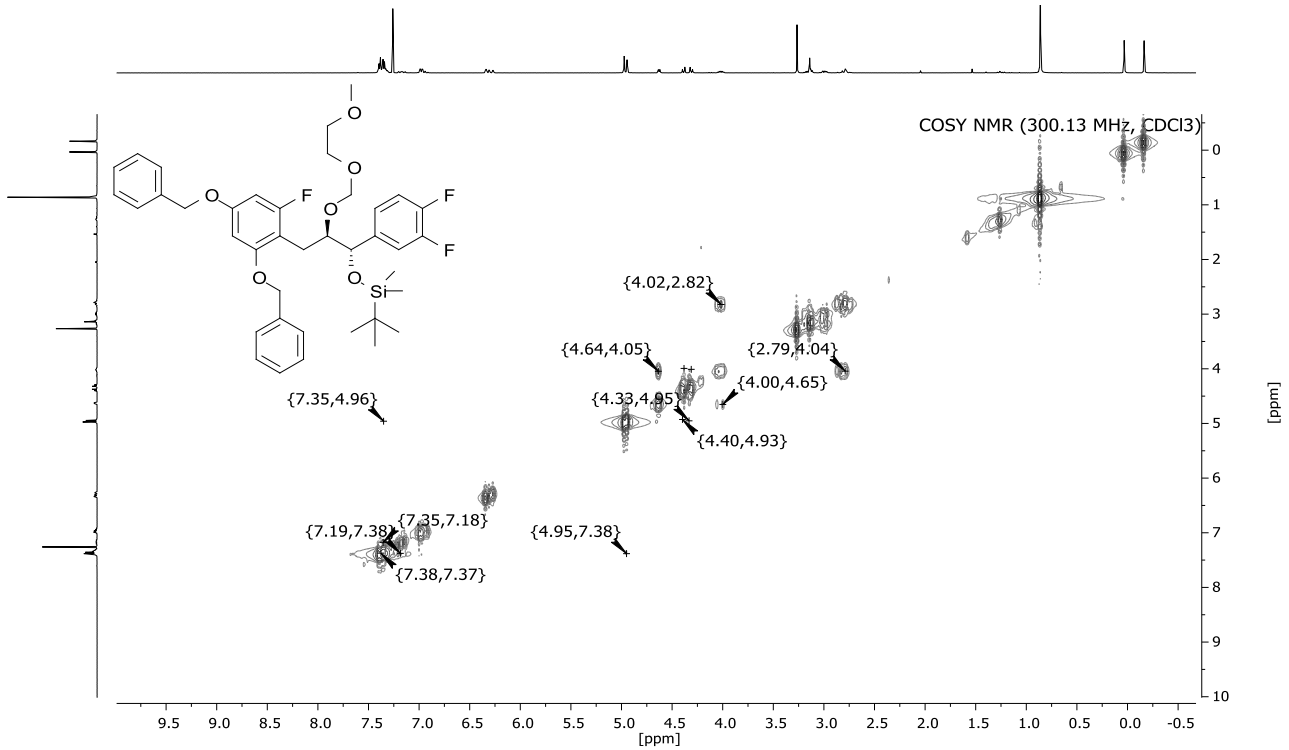
Spectrum 25. ^{1}H-NMR, 300 MHz, $CDCl_3$.



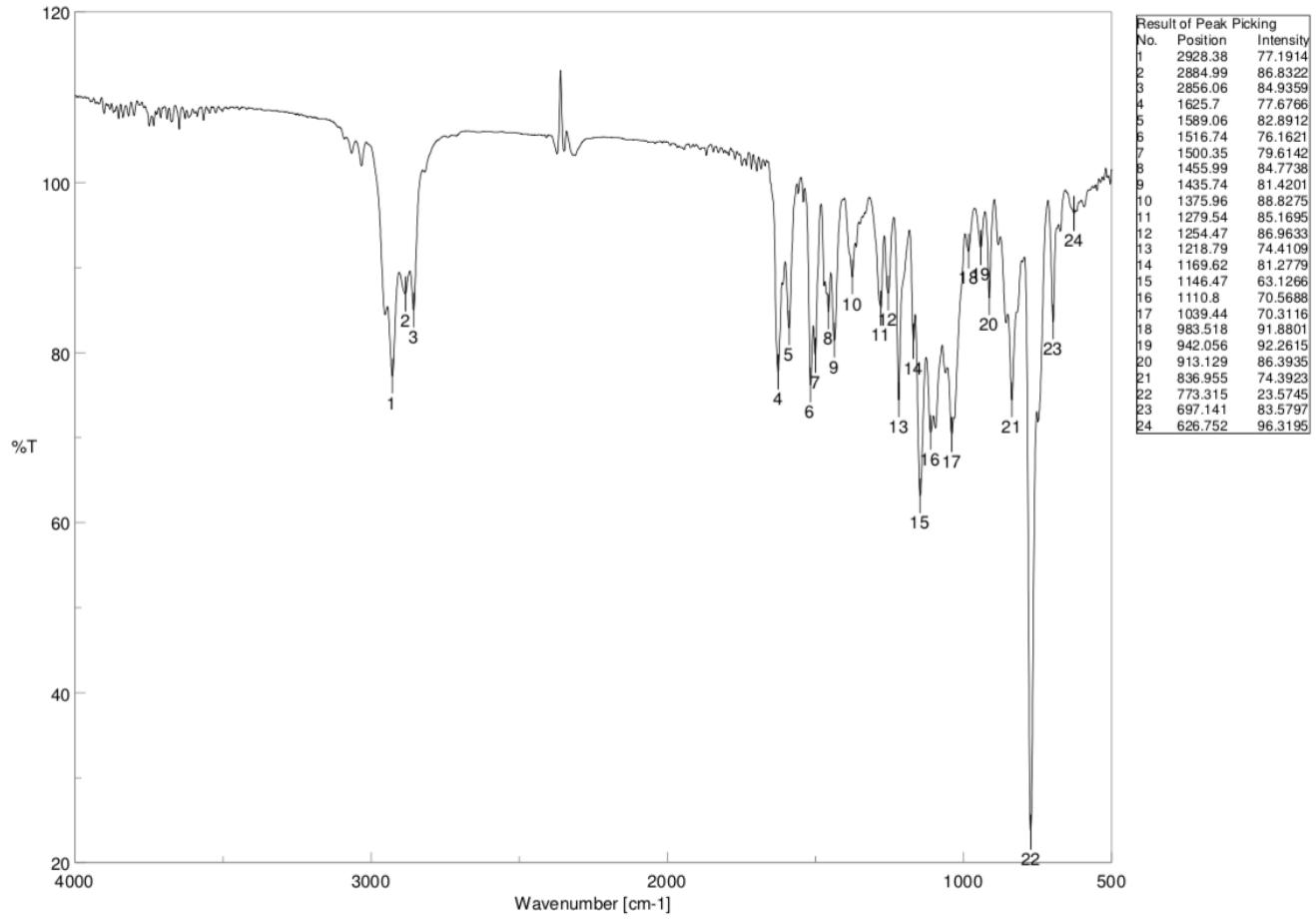
Spectrum 26. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 27. ^{13}C-NMR, 75 MHz, $CDCl_3$.



Spectrum 28. COSY-NMR, 300 MHz, $CDCl_3$.

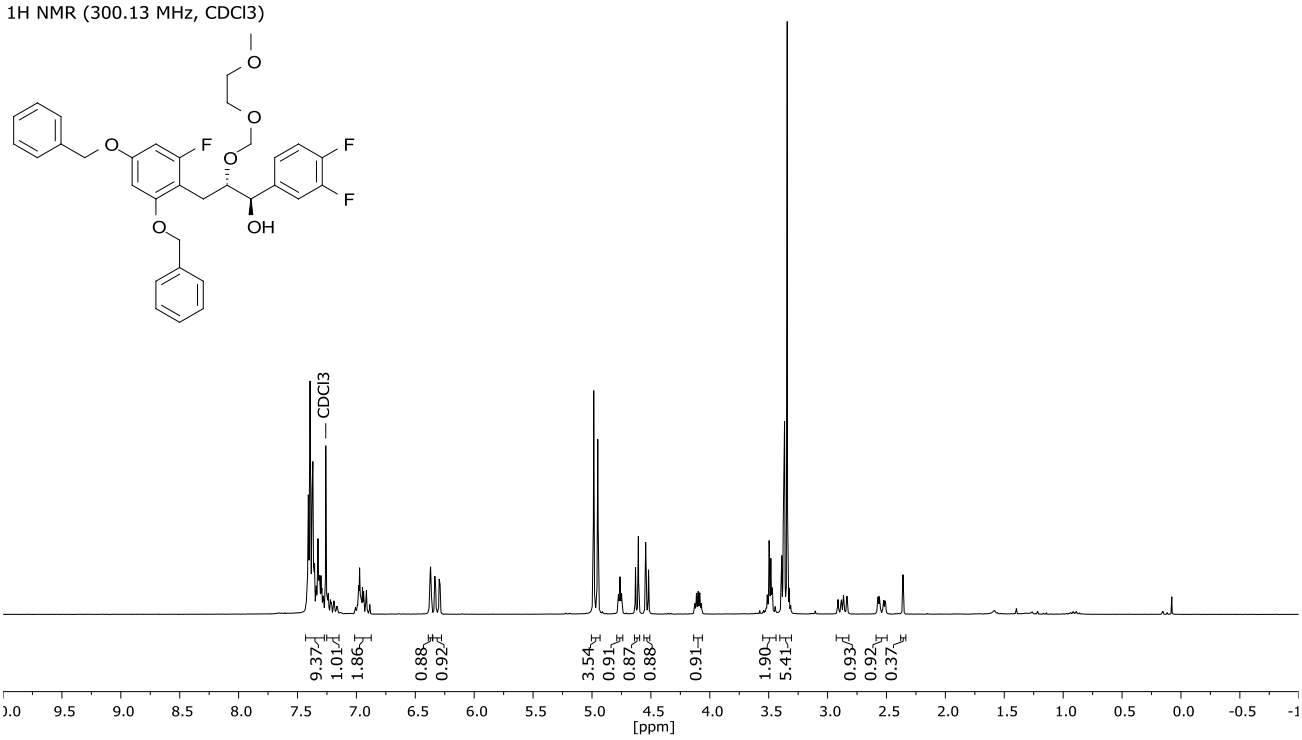


Result of Peak Picking

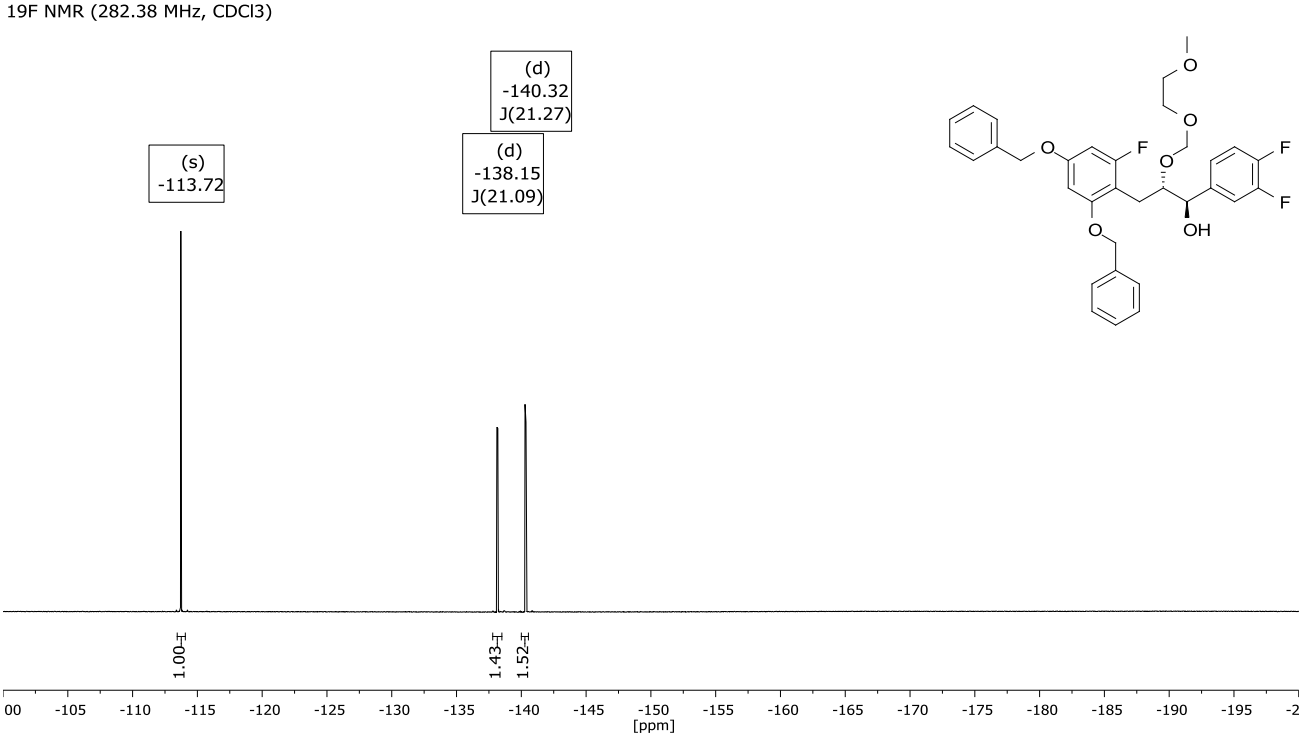
No.	Position	Intensity
1	2928.38	77.1914
2	2884.99	86.8322
3	2856.06	84.9359
4	1625.7	77.6766
5	1589.06	82.8912
6	1516.74	76.1621
7	1500.35	79.6142
8	1455.99	84.7738
9	1435.74	81.4201
10	1375.96	88.8275
11	1279.54	85.1695
12	1254.47	86.9633
13	1218.79	74.4109
14	1169.62	81.2779
15	1146.47	63.1266
16	1110.8	70.5688
17	1039.44	70.3116
18	983.518	91.8801
19	942.056	92.2615
20	913.129	86.3935
21	836.955	74.3923
22	773.315	23.5745
23	697.141	83.5797
24	626.752	96.3195

Spectrum 29. IR, film on NaCl.

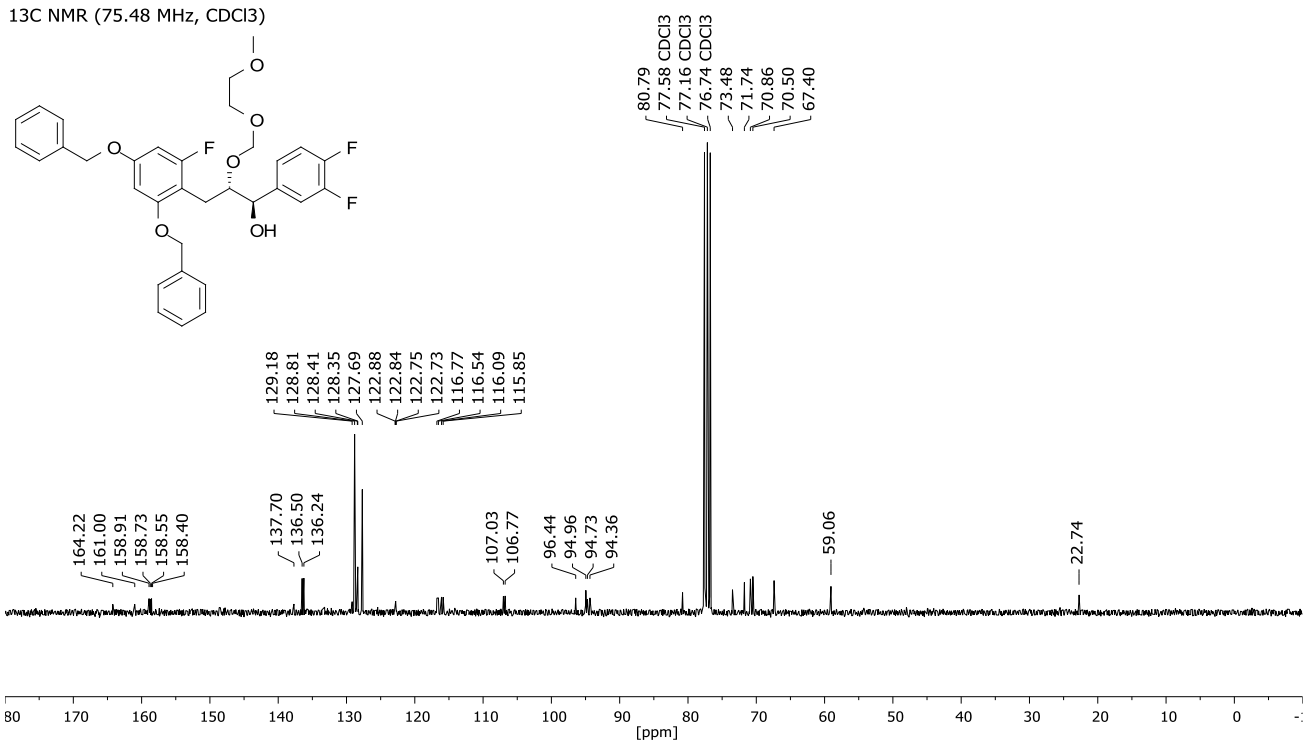
3.8 (1*R*,2*S*)-3-(2,4-Bis(benzyloxy)-6-fluorphenyl)-1-(3,4-difluorphenyl)-2-((2-methoxy-ethoxy)methoxy)propan-1-ol (21)



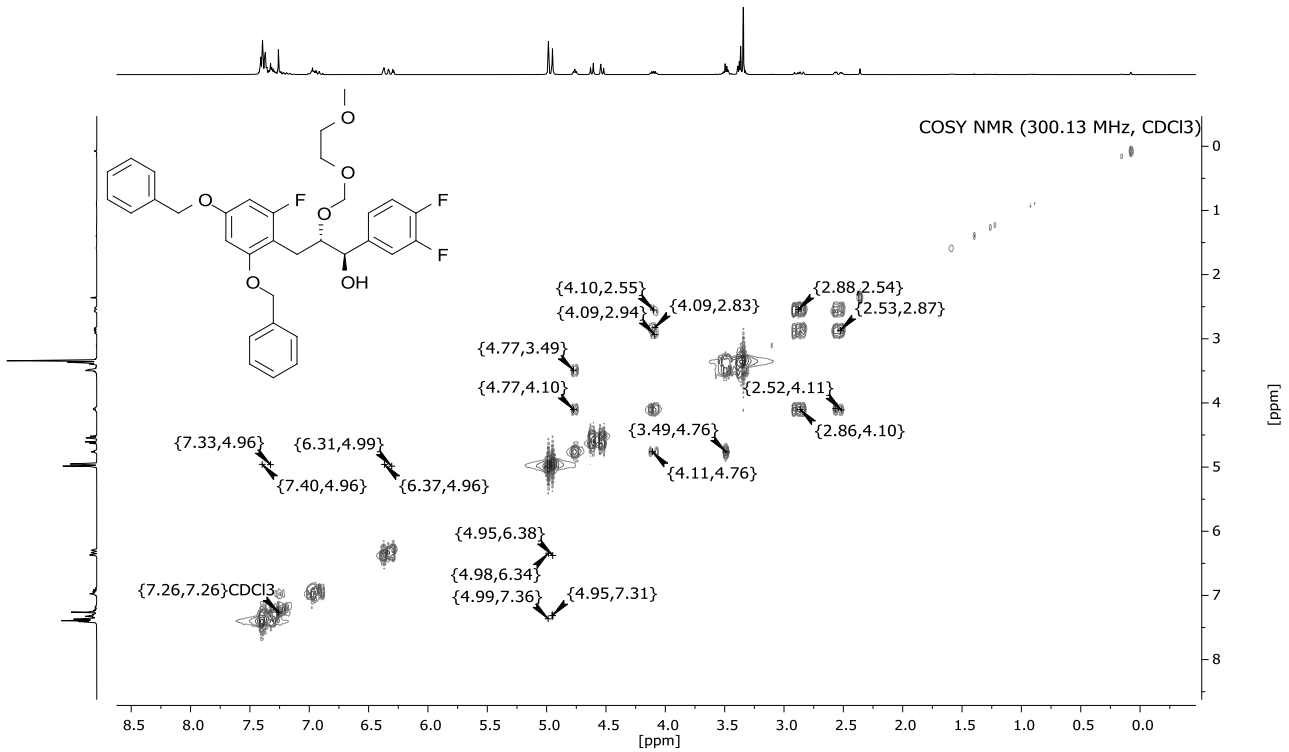
Spectrum 30. ^{1}H-NMR, 300 MHz, $CDCl_3$.



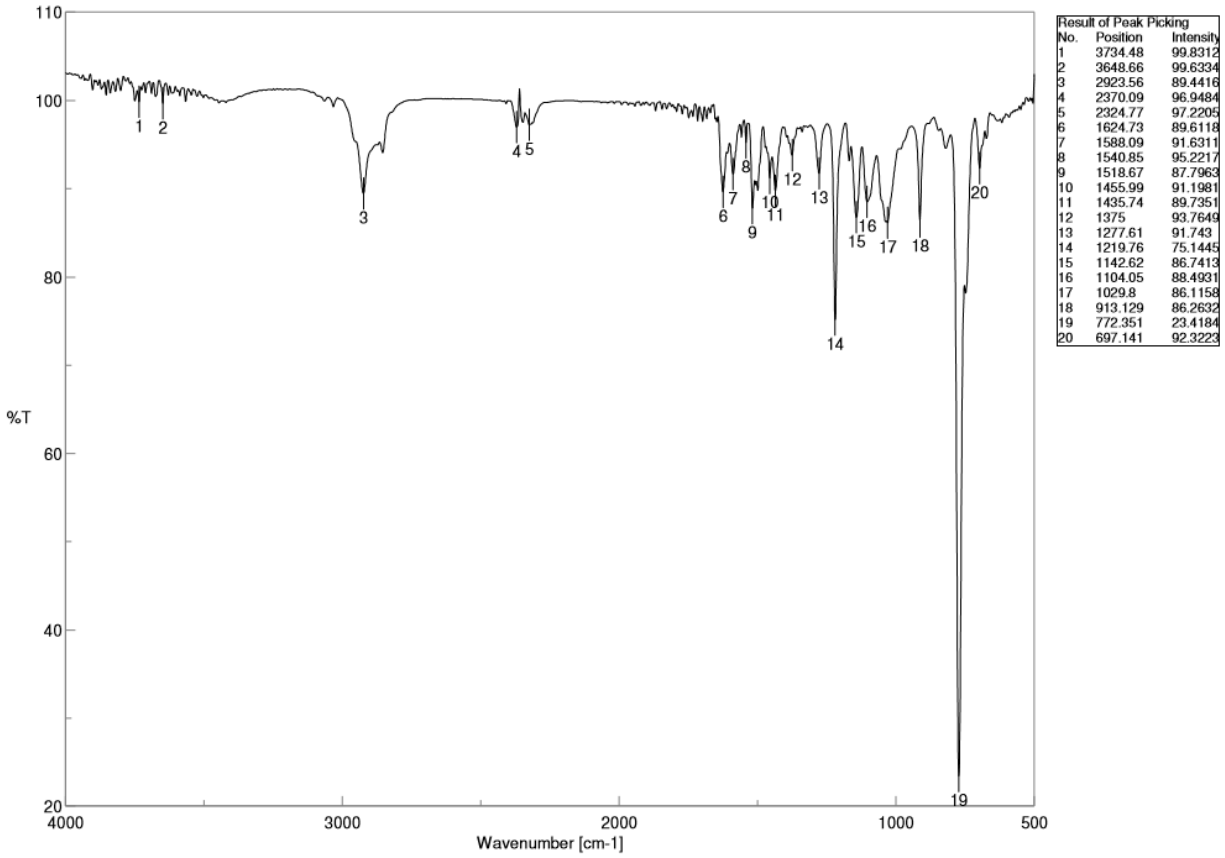
Spectrum 31. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 32. ^{13}C-NMR, 75 MHz, $CDCl_3$.



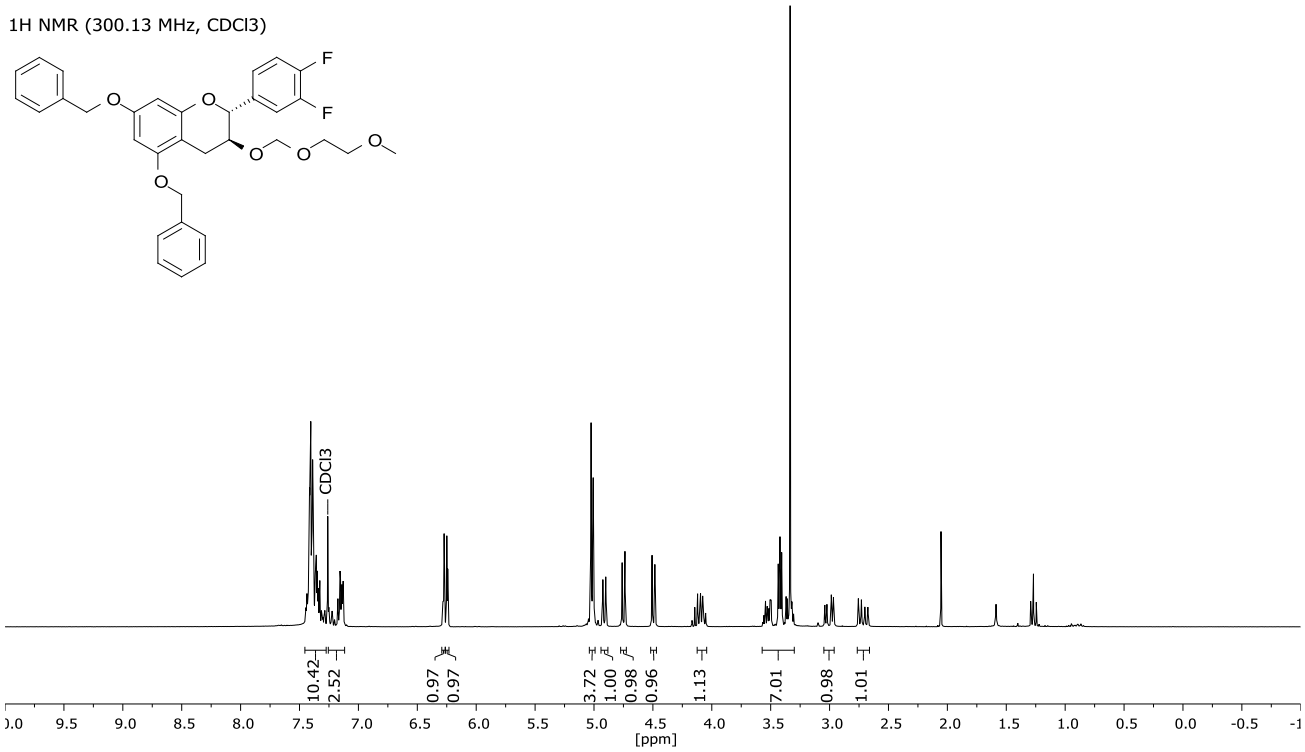
Spectrum 33. COSY-NMR, 300 MHz, $CDCl_3$.



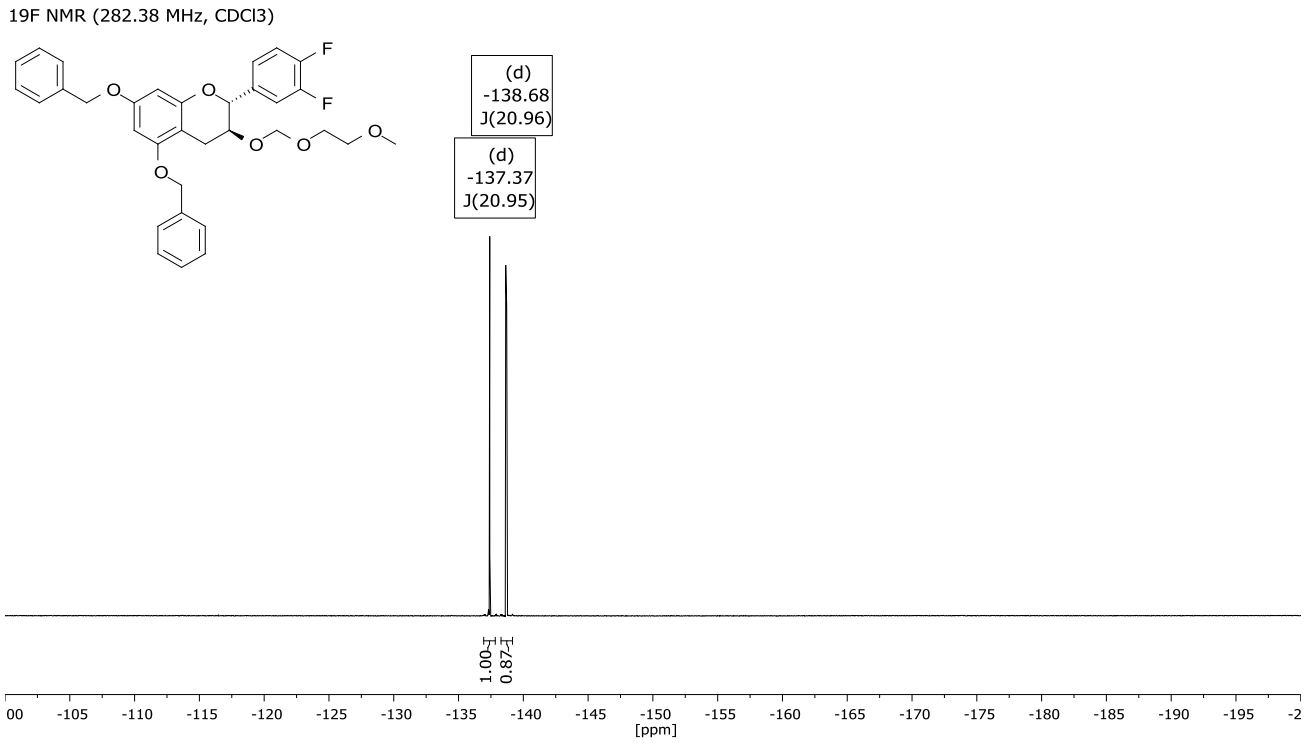
Result of Peak Picking		
No.	Position	Intensity
1	3734.48	99.8312
2	3648.66	99.6334
3	2923.56	89.4416
4	2370.09	96.9484
5	2324.77	97.2205
6	1624.73	89.6118
7	1588.09	91.6311
8	1540.85	95.2217
9	1518.67	87.7963
10	1455.99	91.1981
11	1435.74	89.7351
12	1375	93.7649
13	1277.61	91.743
14	1219.76	75.1445
15	1142.62	86.7413
16	1104.05	88.4931
17	1029.8	86.1158
18	913.129	86.2632
19	772.351	23.4184
20	697.141	92.3223

Spectrum 34. IR, film on NaCl.

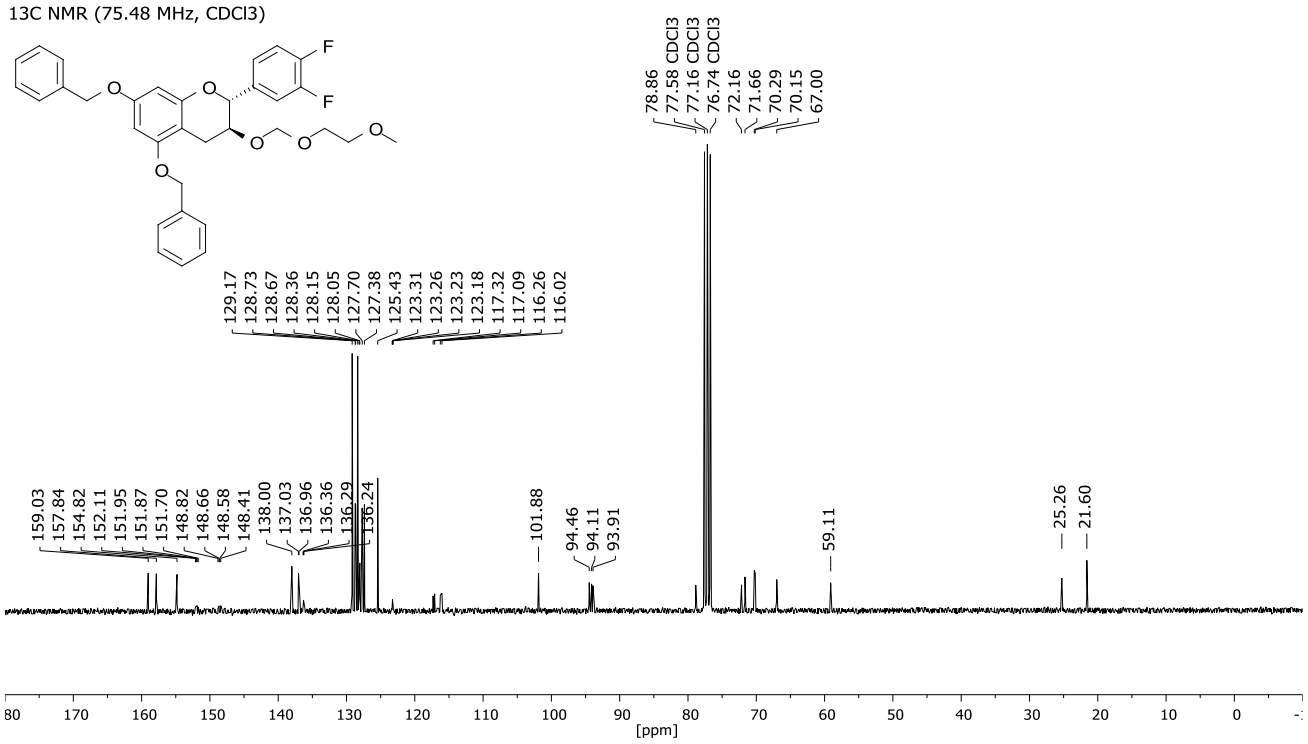
3.9 (2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)-3-((2-methoxyethoxy)methoxy)chromane (22)



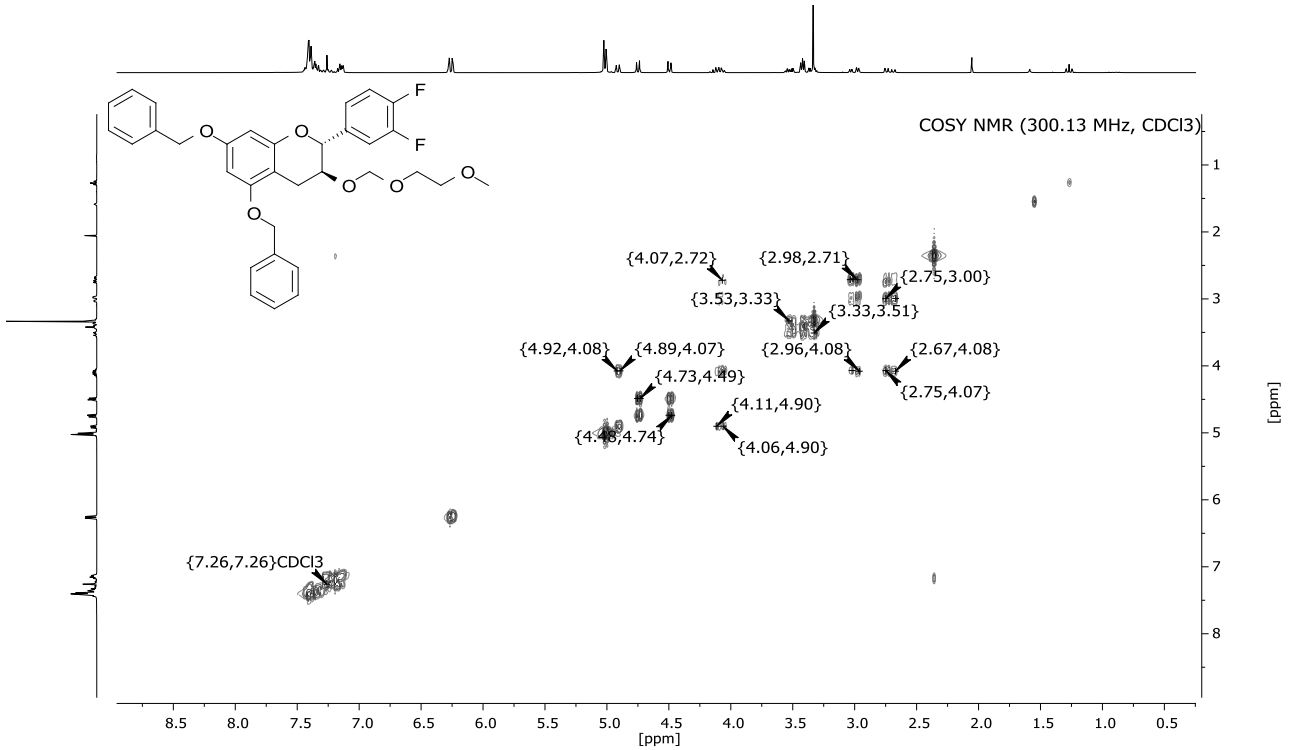
Spectrum 35. ^{1}H-NMR, 300 MHz, $CDCl_3$.



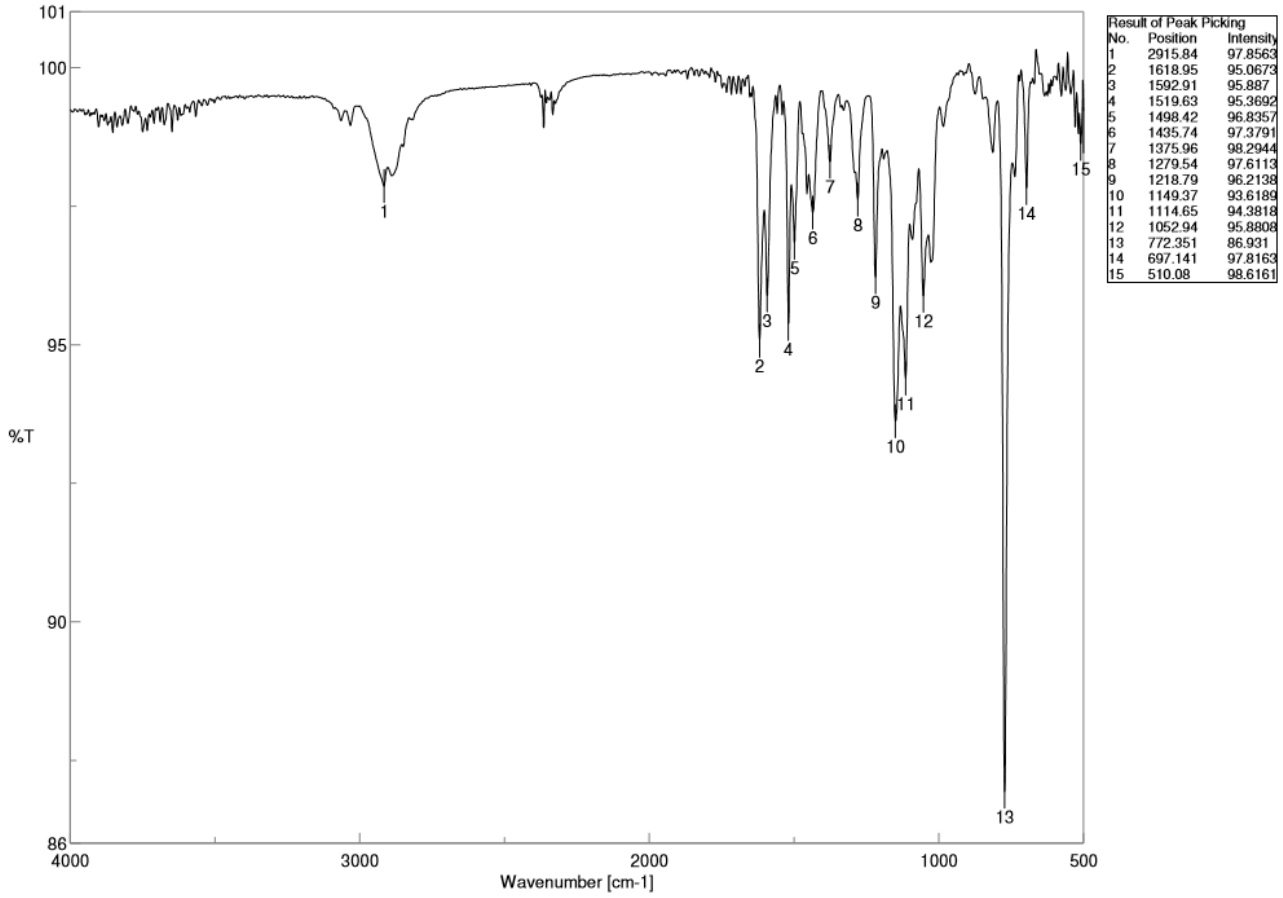
Spectrum 36. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 37. ^{13}C-NMR, 75 MHz, $CDCl_3$.

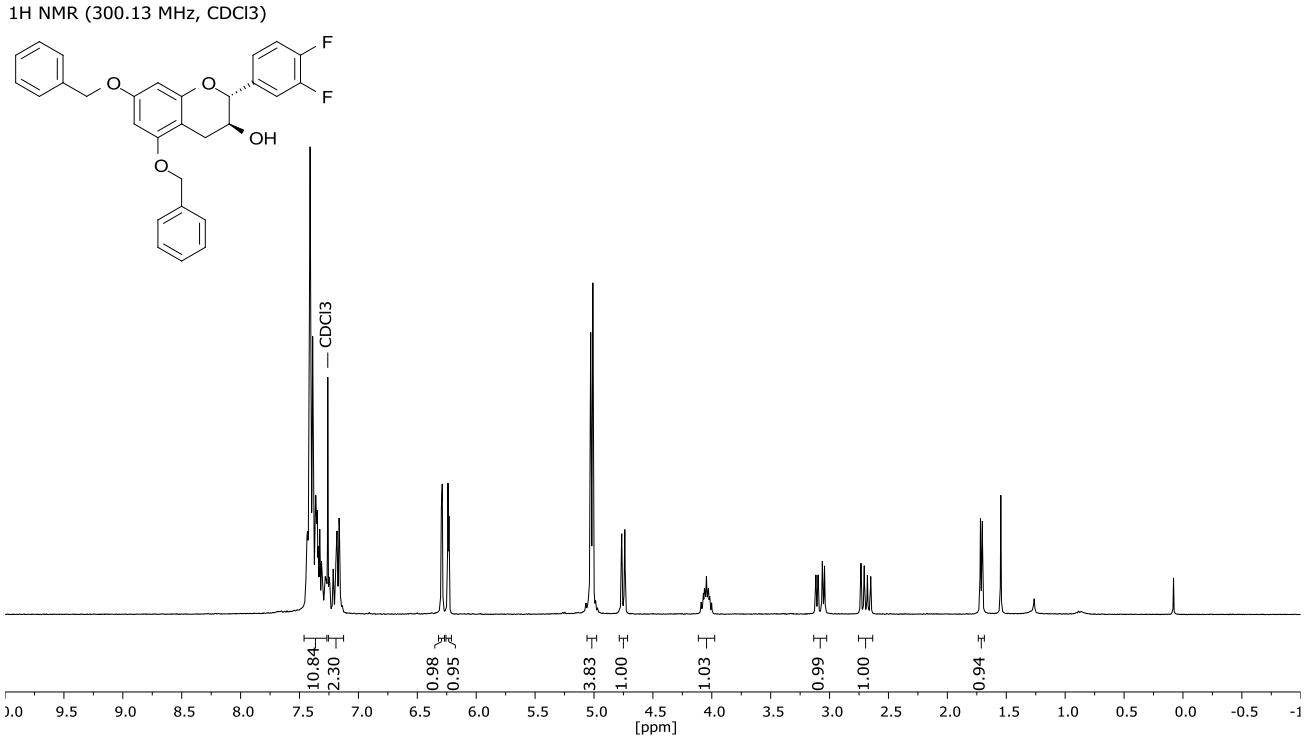


Spectrum 38. COSY-NMR, 300 MHz, $CDCl_3$.

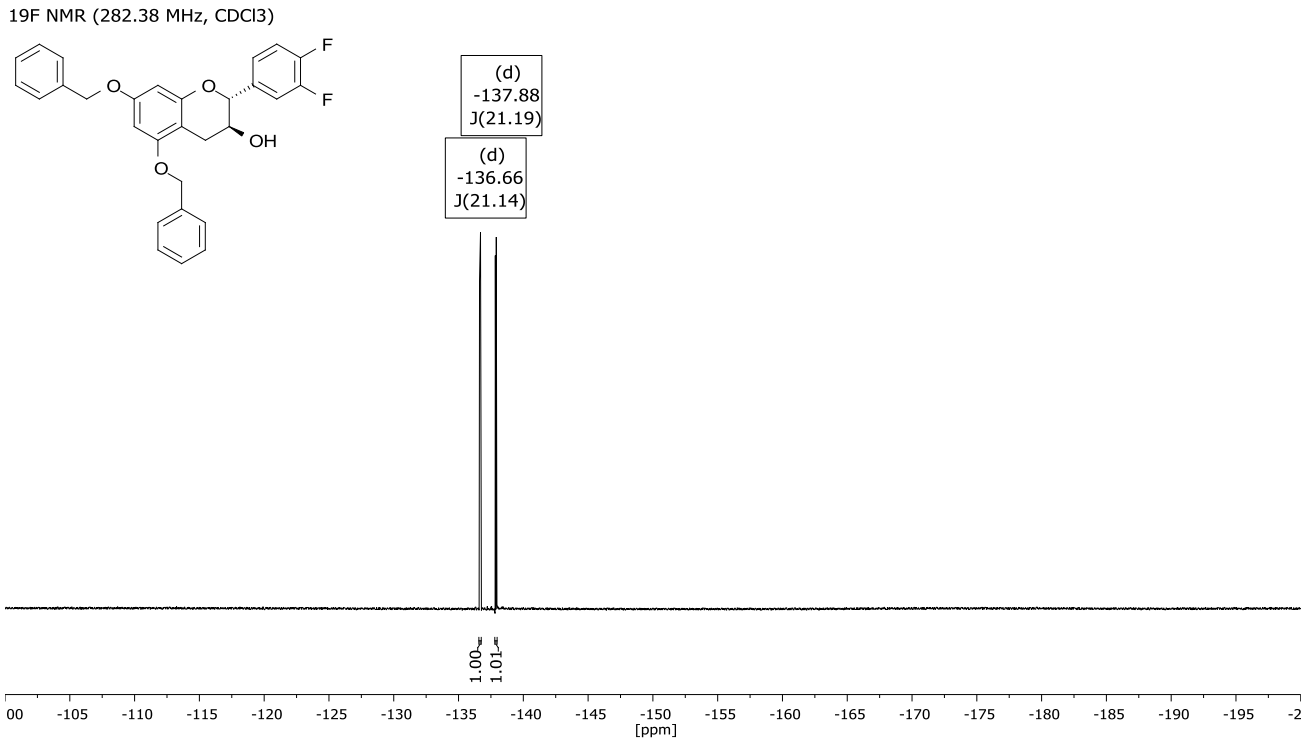


Spectrum 39. IR, film on NaCl.

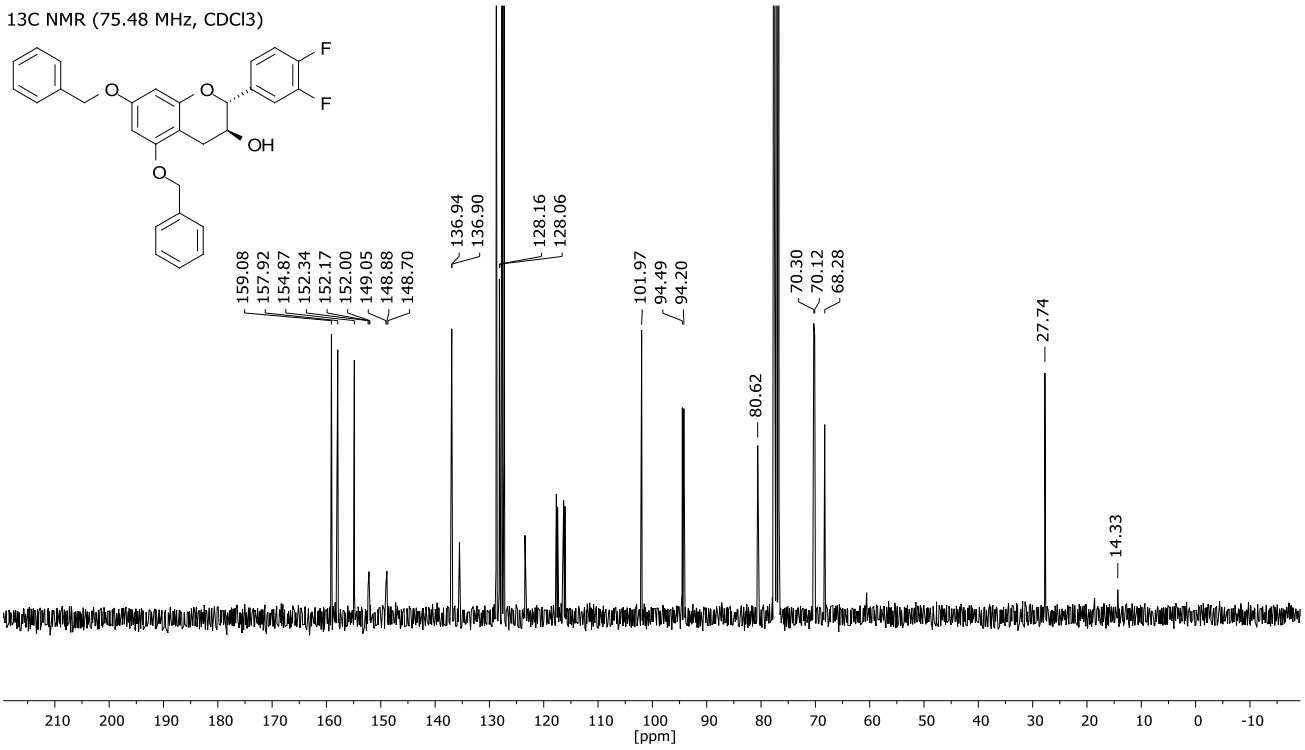
3.10 (2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (23)



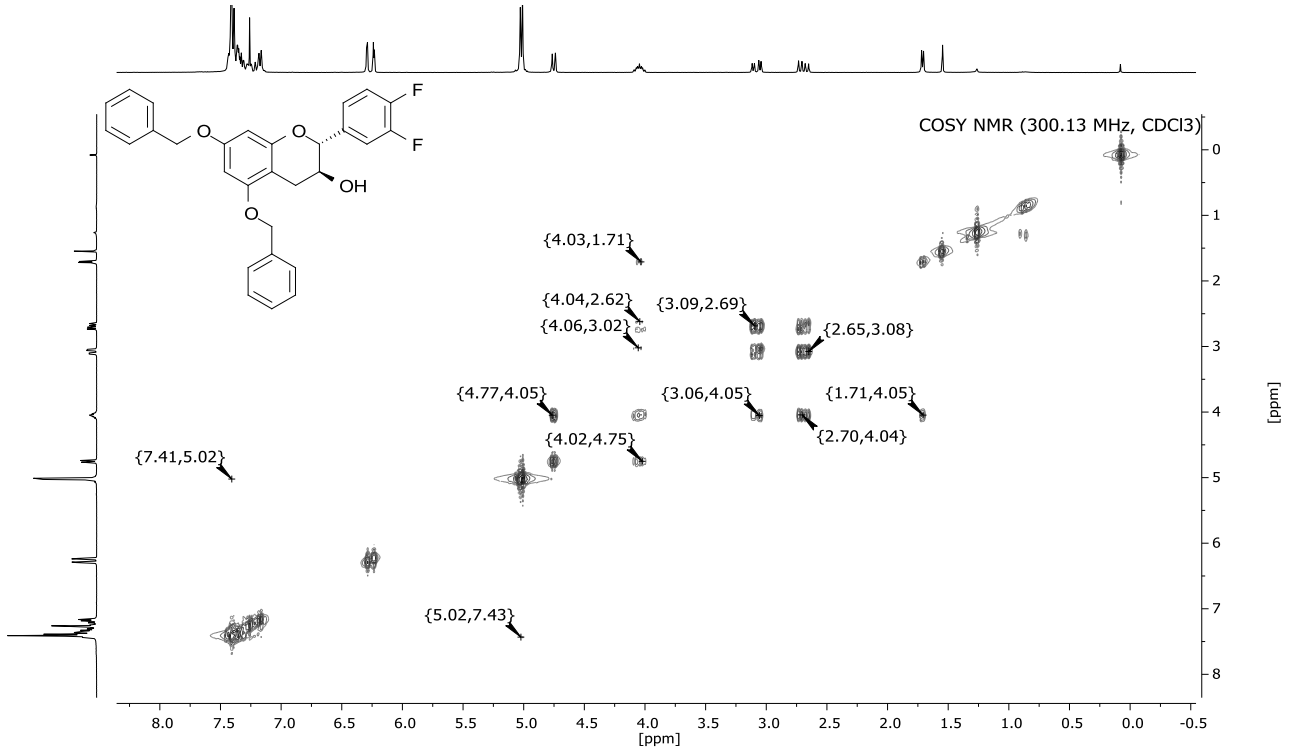
Spectrum 40. ^{1}H-NMR, 300 MHz, $CDCl_3$.



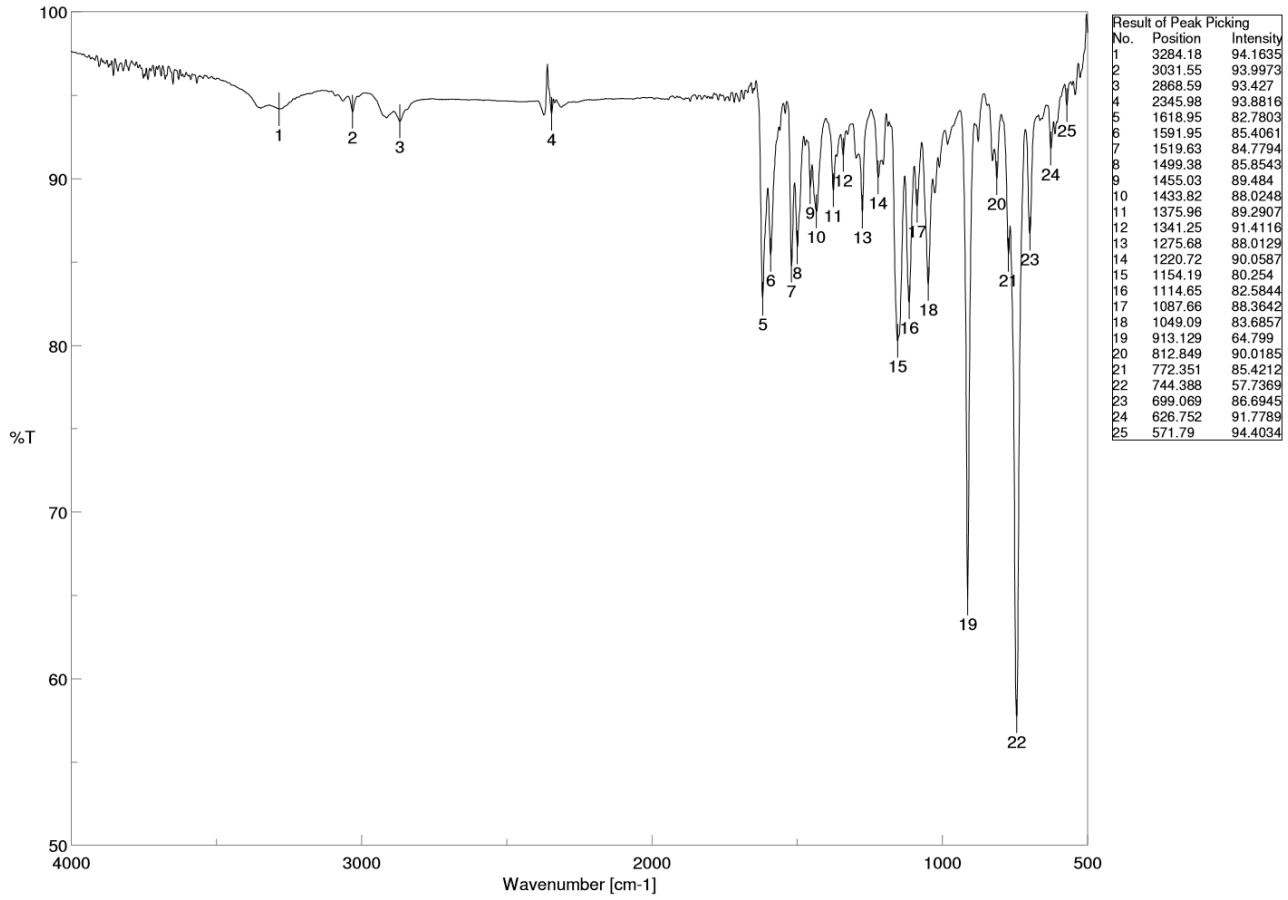
Spectrum 41. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 42. ^{13}C-NMR, 75 MHz, $CDCl_3$.



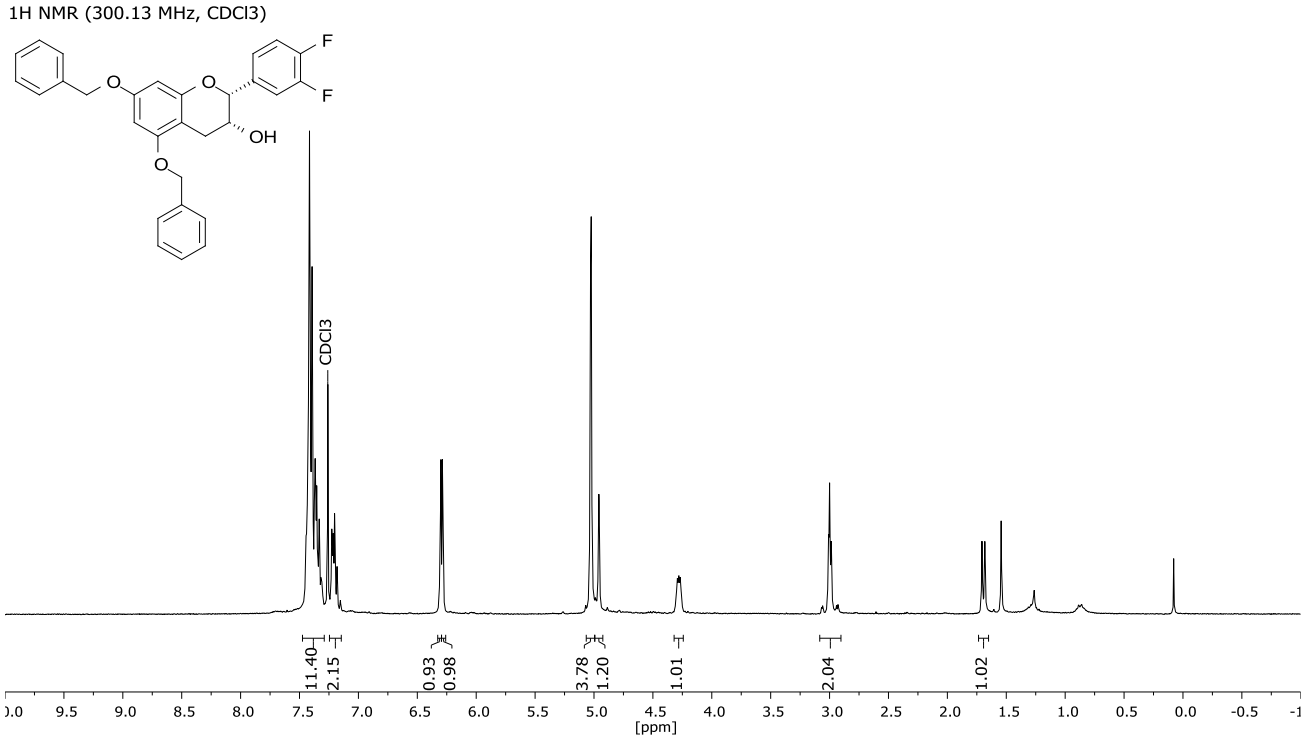
Spectrum 43. COSY-NMR, 300 MHz, $CDCl_3$.



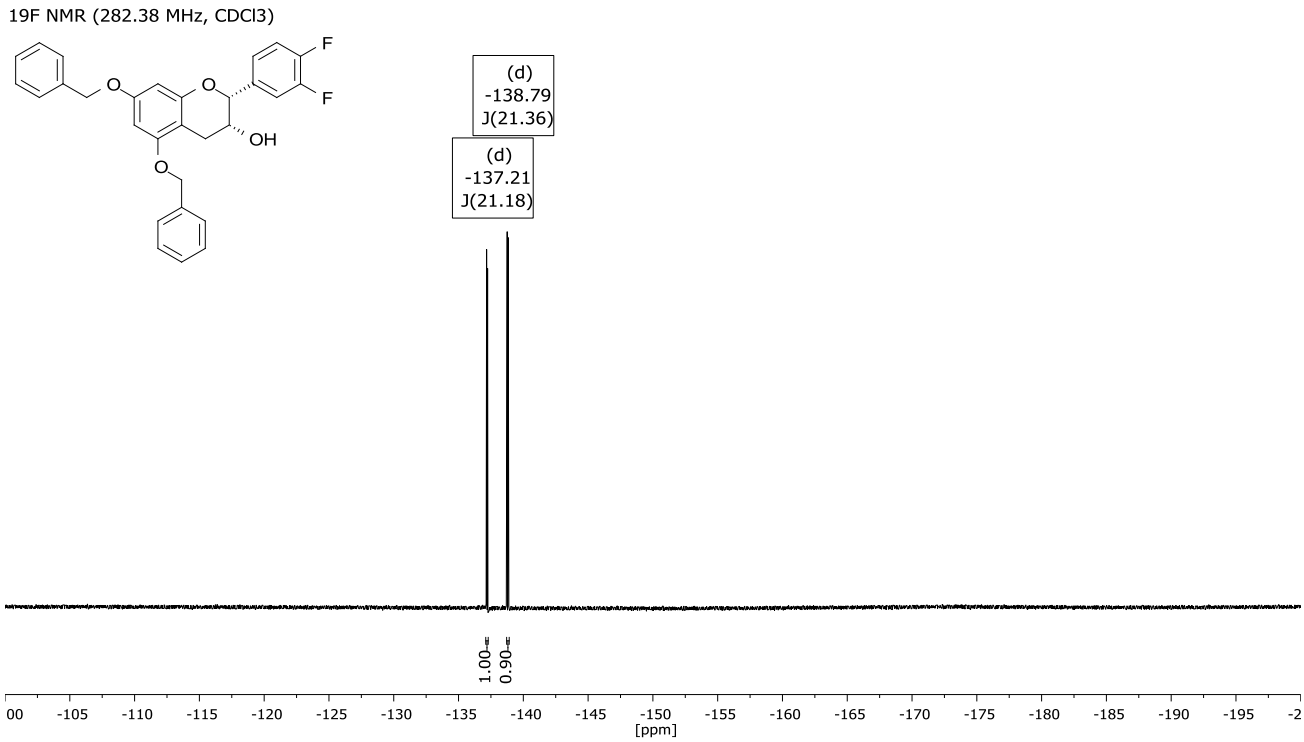
Result of Peak Picking		
No.	Position	Intensity
1	3284.18	94.1635
2	3031.55	93.9973
3	2868.59	93.427
4	2345.98	93.8816
5	1618.95	82.7803
6	1591.95	85.4061
7	1519.63	84.7794
8	1499.38	85.8543
9	1455.03	89.484
10	1433.82	88.0248
11	1375.96	89.2907
12	1341.25	91.4116
13	1275.68	88.0129
14	1220.72	90.0587
15	1154.19	80.254
16	1114.65	82.5844
17	1087.66	88.3642
18	1049.09	83.6857
19	913.129	64.799
20	812.849	90.0185
21	772.351	85.4212
22	744.388	57.7369
23	699.069	86.6945
24	626.752	91.7789
25	571.79	94.4034

Spectrum 44. IR, film on NaCl.

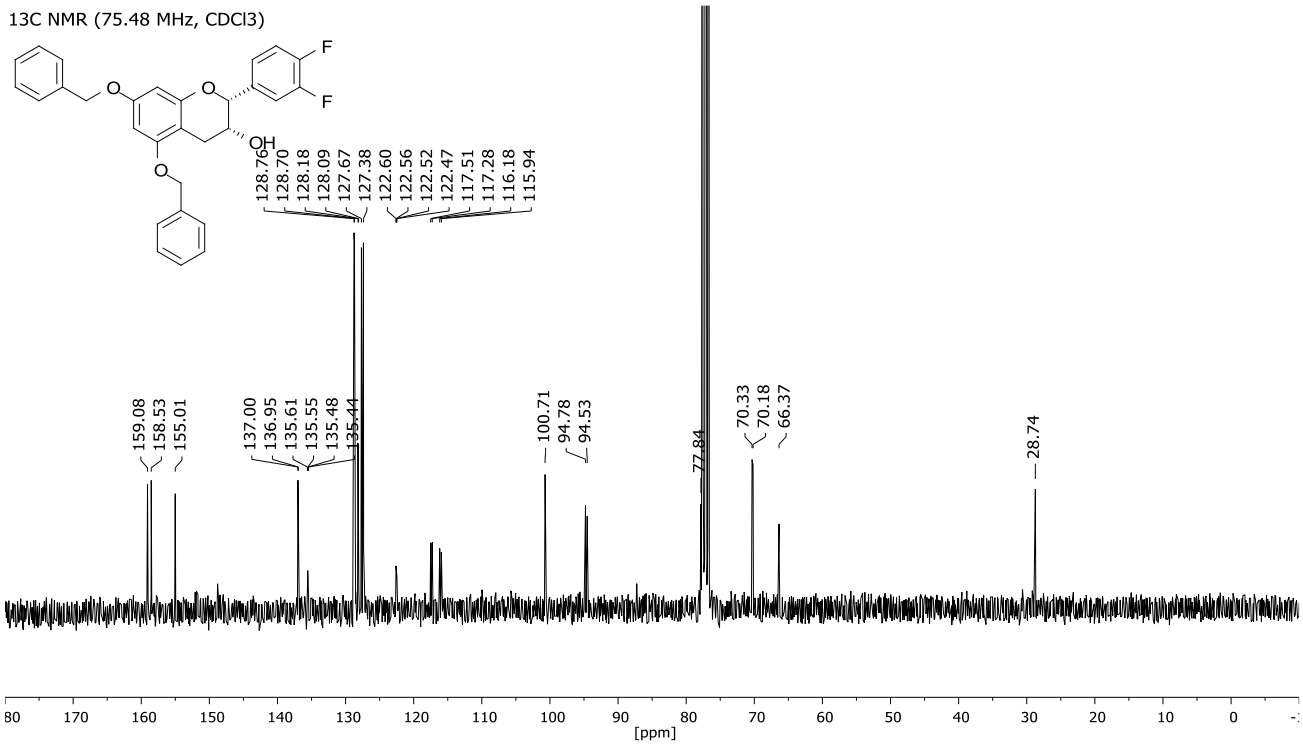
3.11 (2*R*,3*R*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-ol (24)



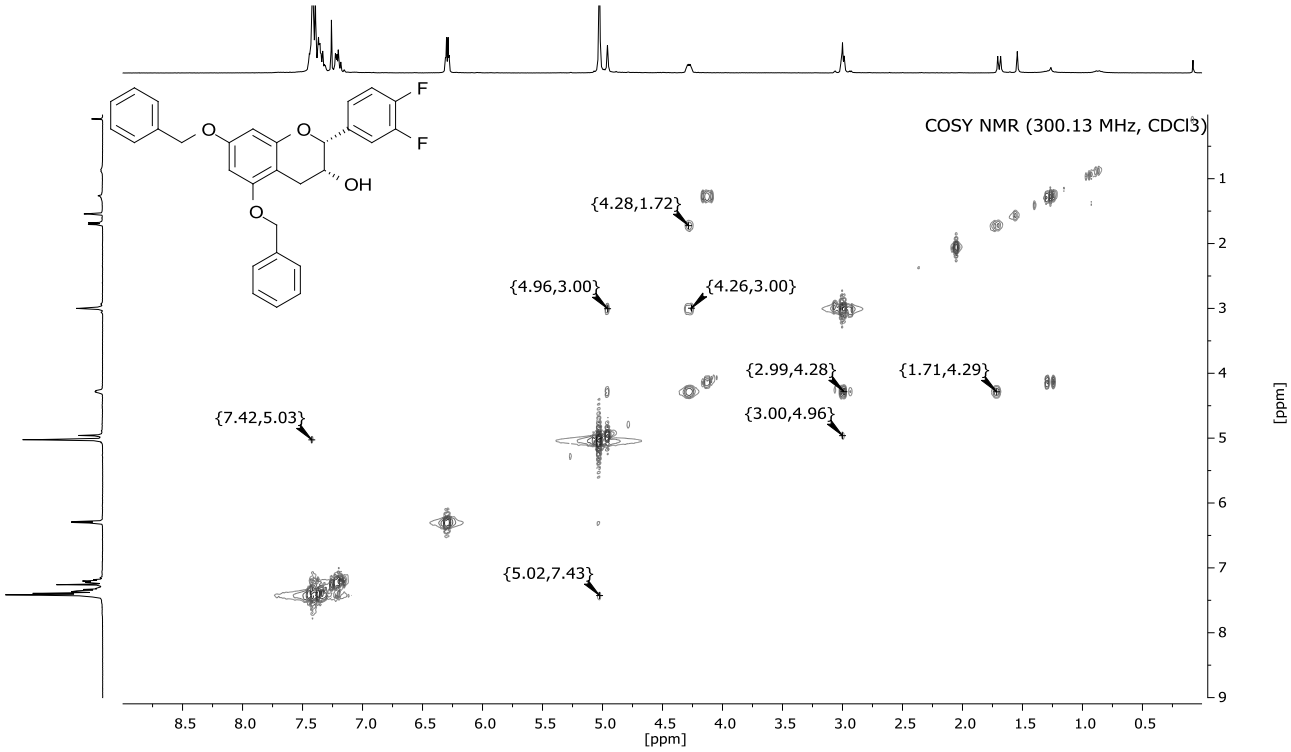
Spectrum 45. ^{1}H-NMR, 300 MHz, $CDCl_3$.



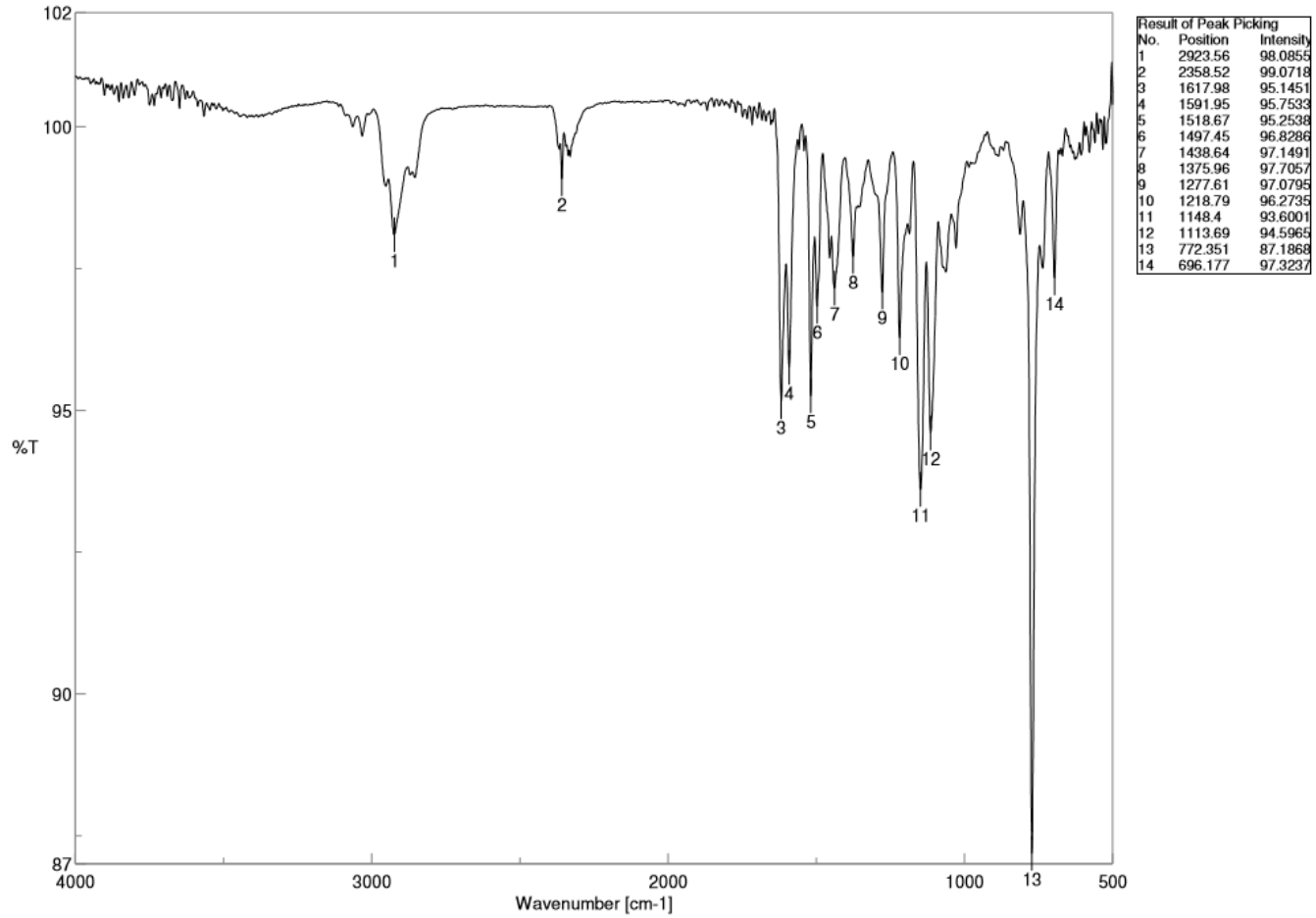
Spectrum 46. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 47. ^{13}C-NMR, 75 MHz, $CDCl_3$.

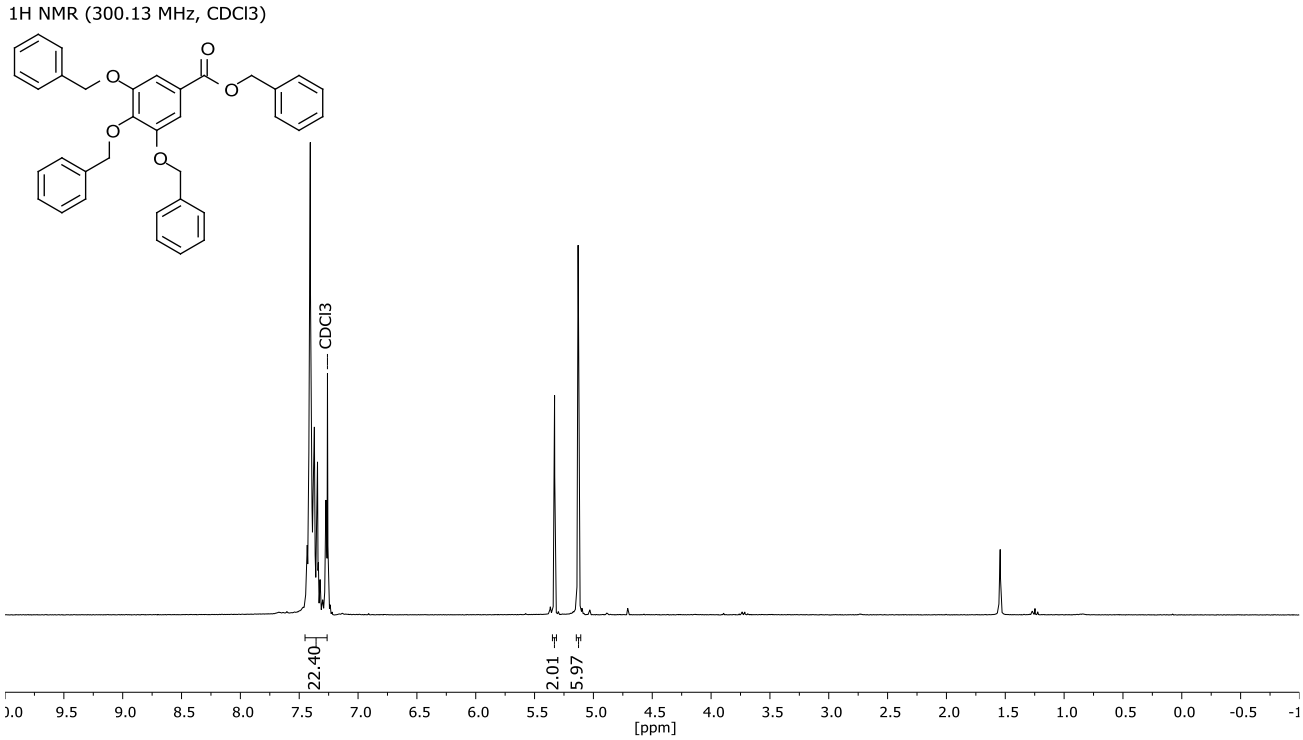


Spectrum 48. COSY-NMR, 300 MHz, $CDCl_3$.



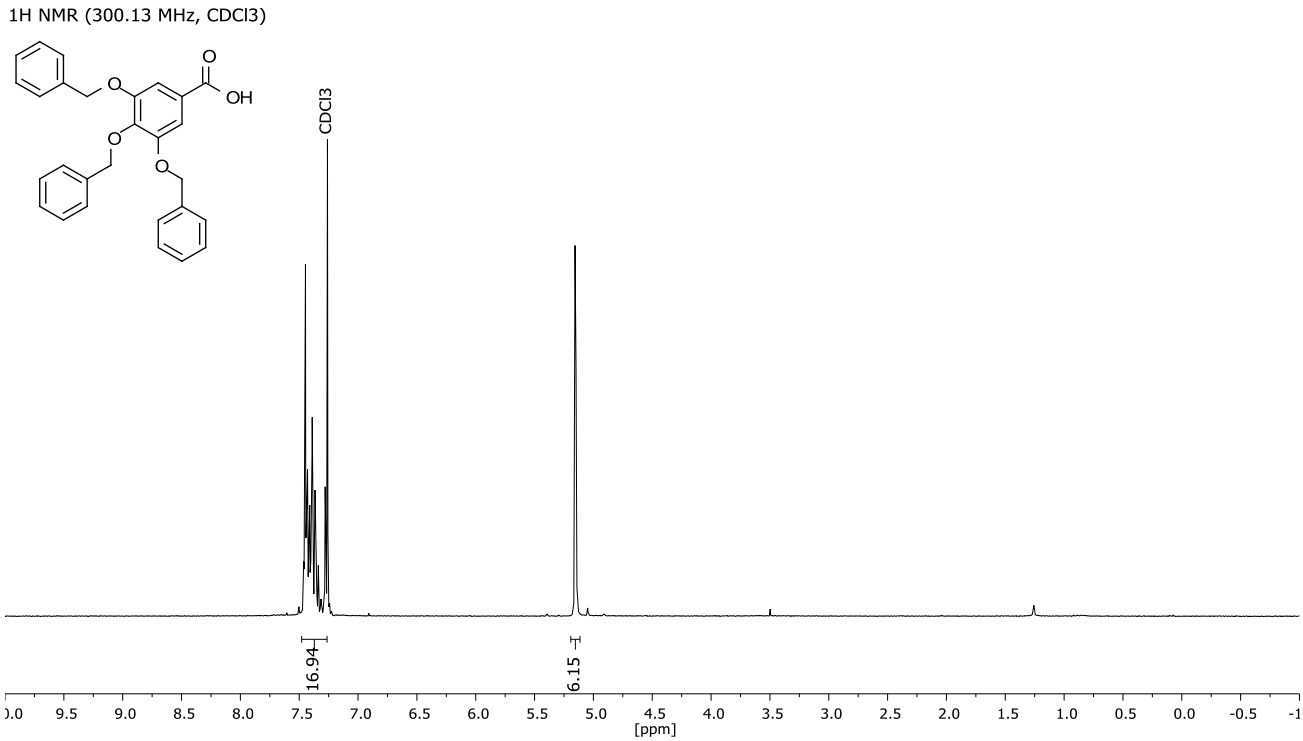
Spectrum 49. IR, film on NaCl.

3.12 Benzyl-3,4,5-tris(benzyloxy)benzoate



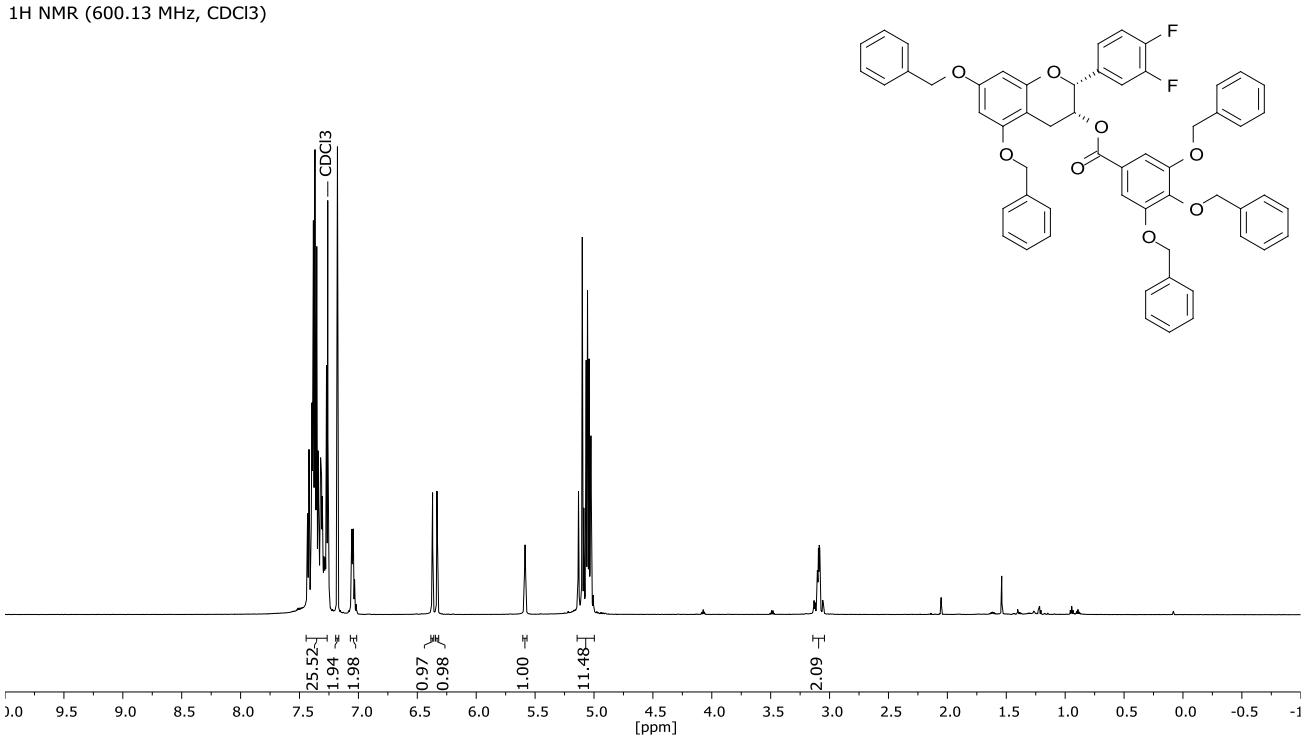
Spectrum 50. ^{1}H-NMR, 300 MHz, $CDCl_3$.

3.13 3,4,5-Tris(benzyloxy)benzoic acid

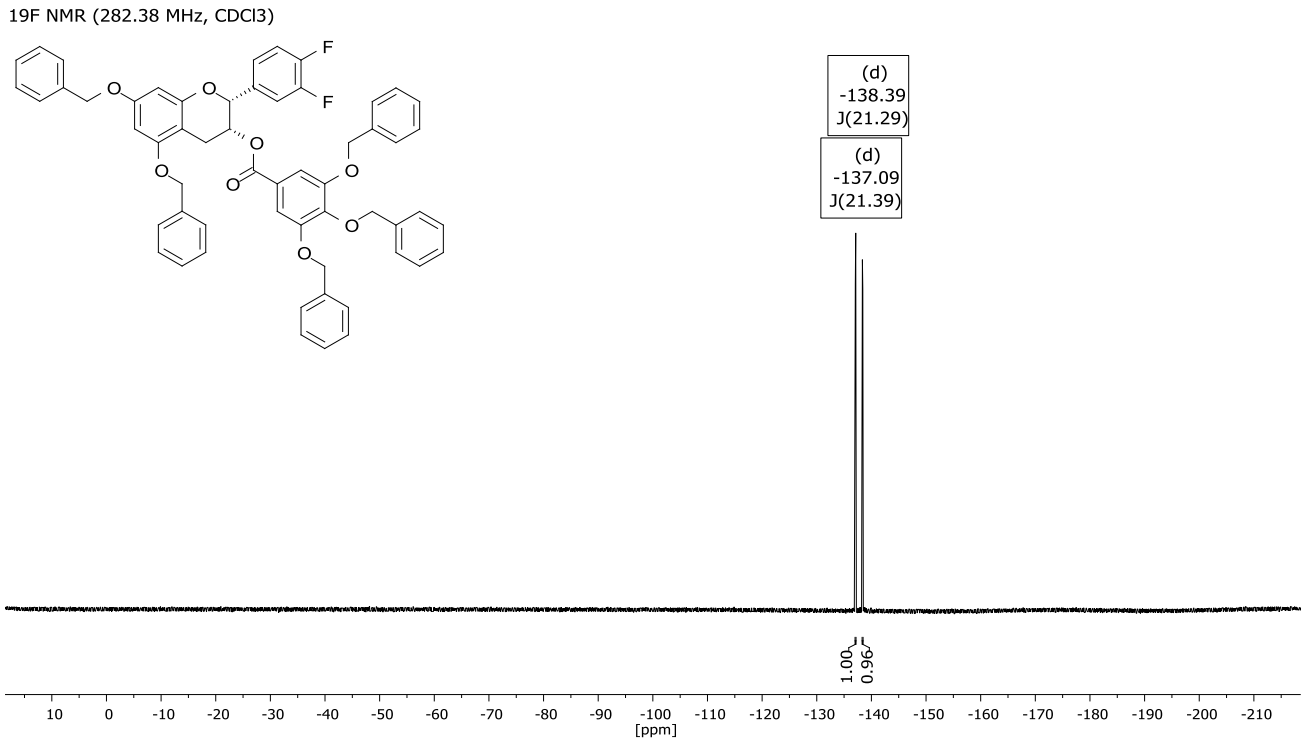


Spectrum 51. ^{1}H-NMR, 300 MHz, $CDCl_3$.

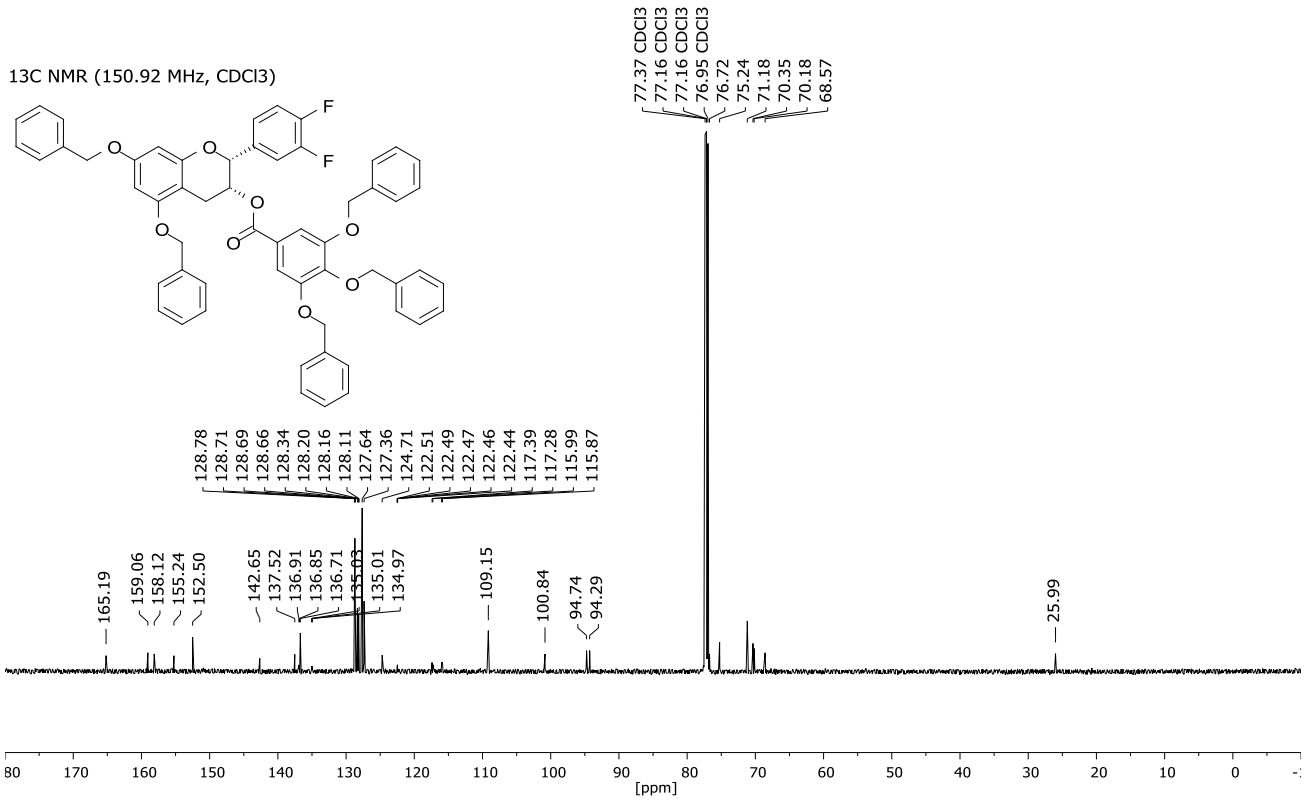
3.14 (2*R*,3*R*)-5,7-Bis(benzyloxy)-2-(3,4-difluorophenyl)chroman-3-yl-3,4,5-tris(benzyloxy)benzoate (25)



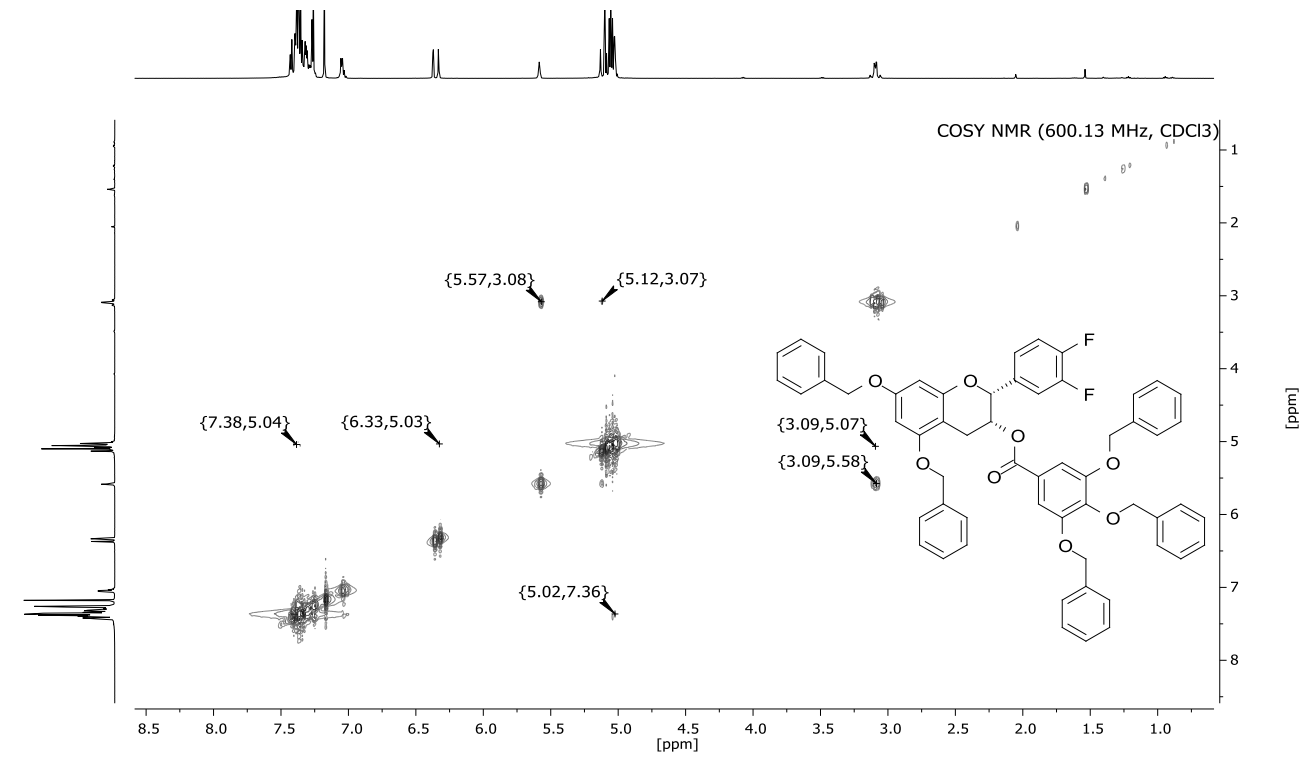
Spectrum 52. ^{1}H-NMR, 600 MHz, $CDCl_3$.



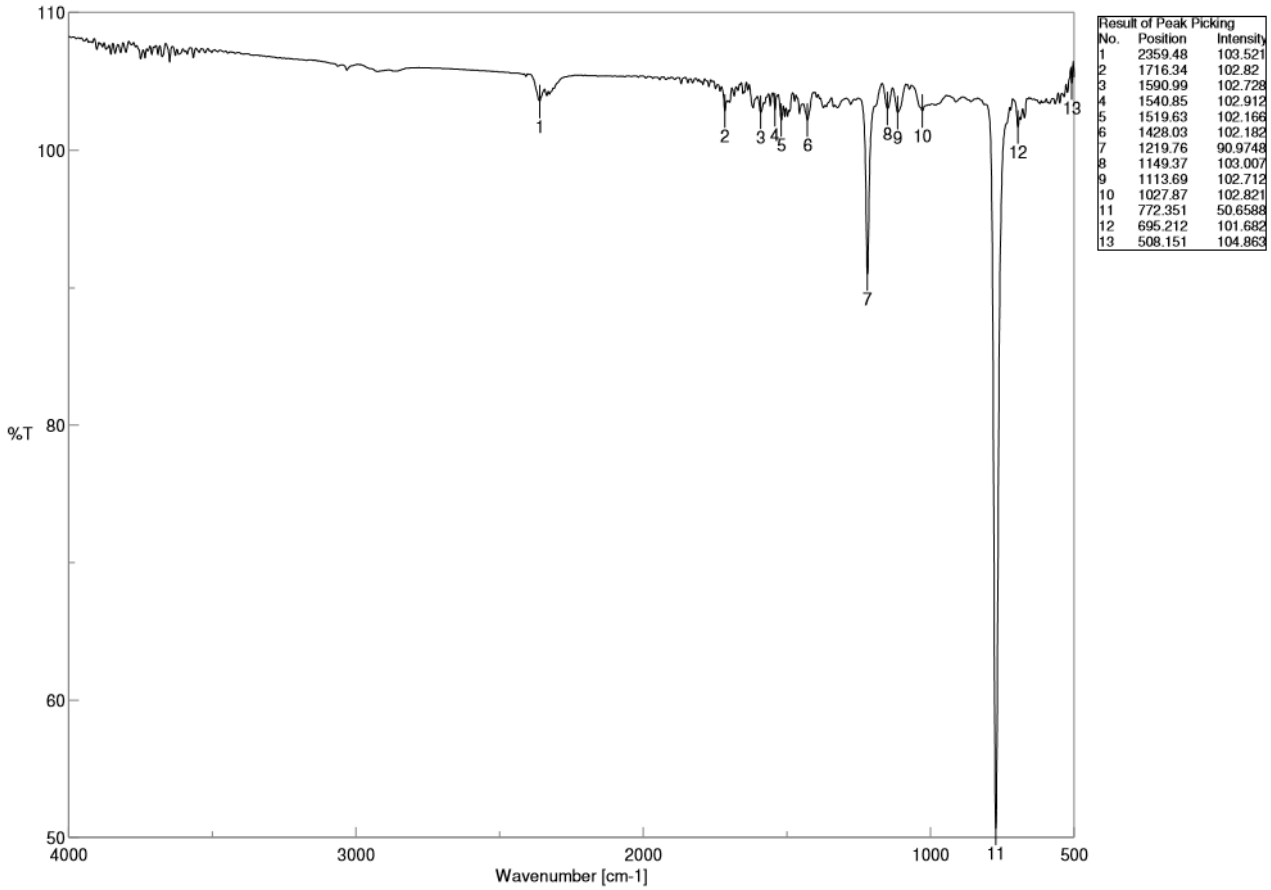
Spectrum 53. ^{19}F-NMR, 282 MHz, $CDCl_3$.



Spectrum 54. ^{13}C-NMR, 151 MHz, $CDCl_3$.



Spectrum 55. COSY-NMR, 600 MHz, $CDCl_3$.

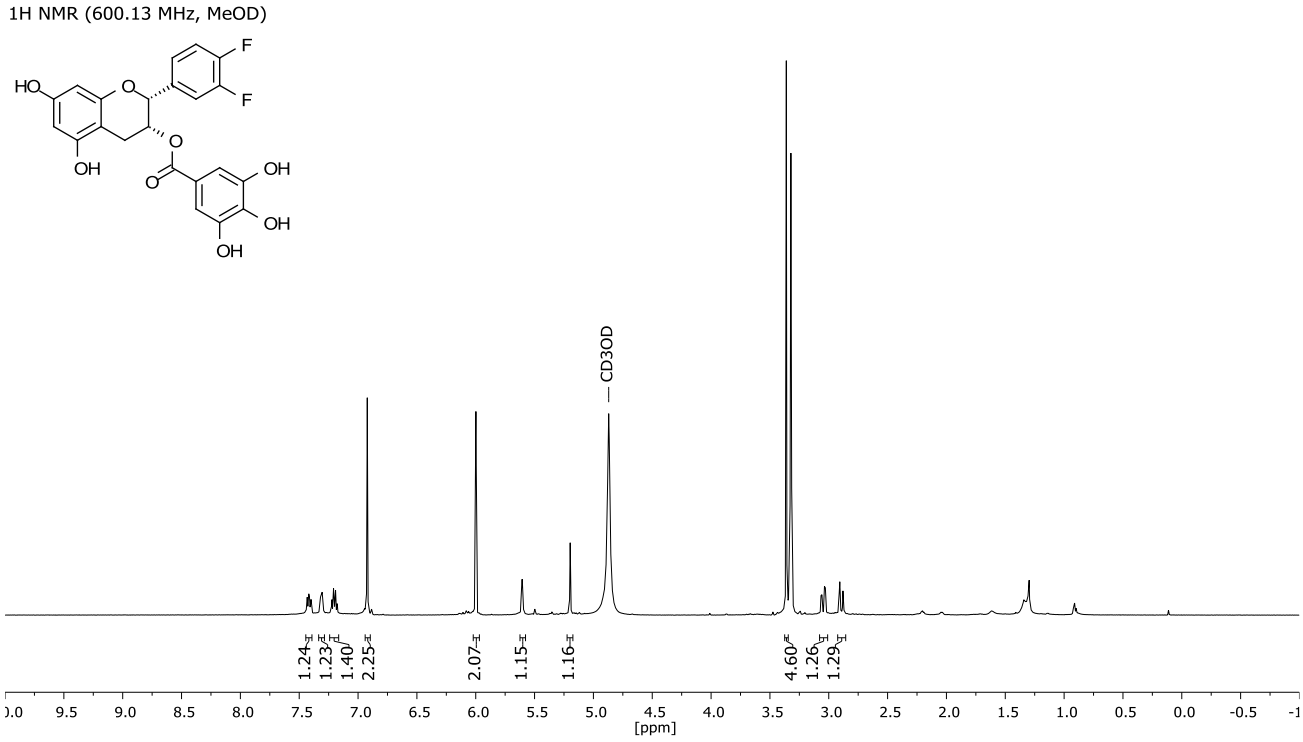


Result of Peak Picking

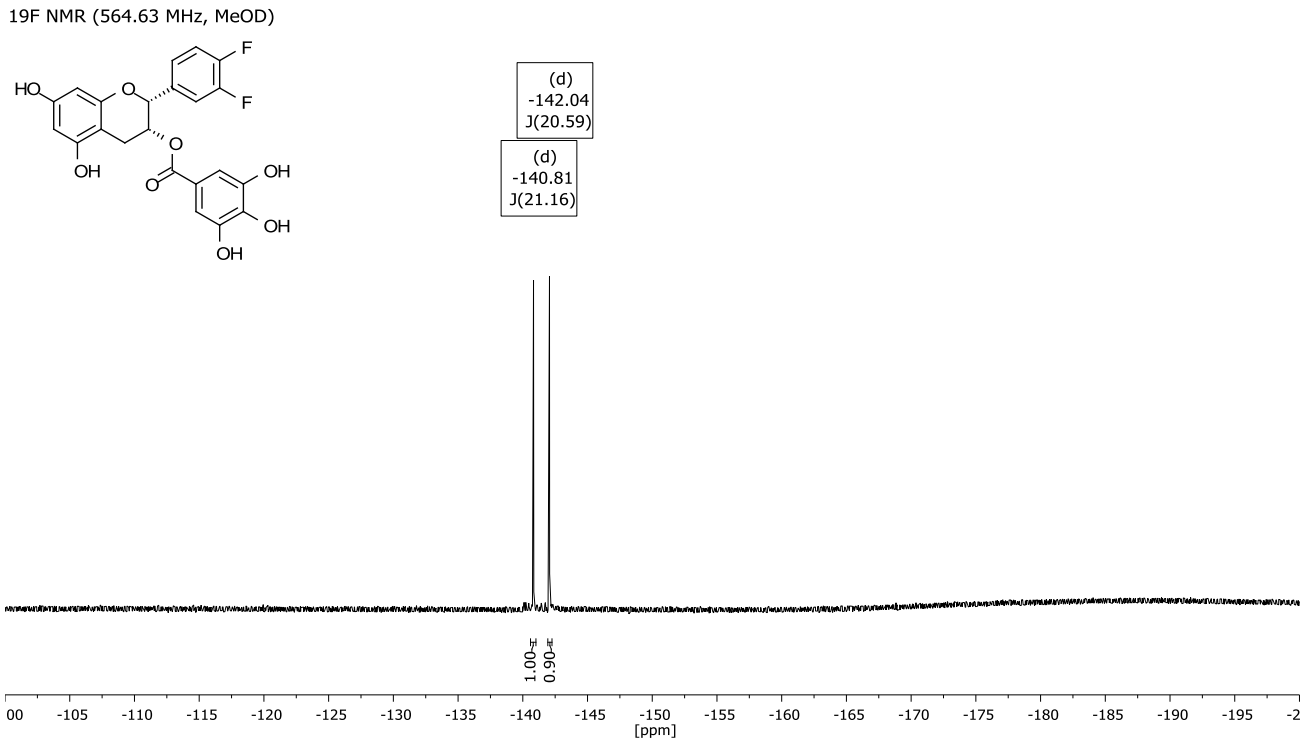
No.	Position	Intensity
1	2359.48	103.521
2	1716.34	102.82
3	1590.99	102.728
4	1540.85	102.912
5	1519.63	102.166
6	1428.03	102.182
7	1219.76	90.9748
8	1149.37	103.007
9	1113.69	102.712
10	1027.87	102.821
11	772.351	50.6588
12	695.212	101.682
13	508.151	104.863

Spectrum 56. IR, film on NaCl.

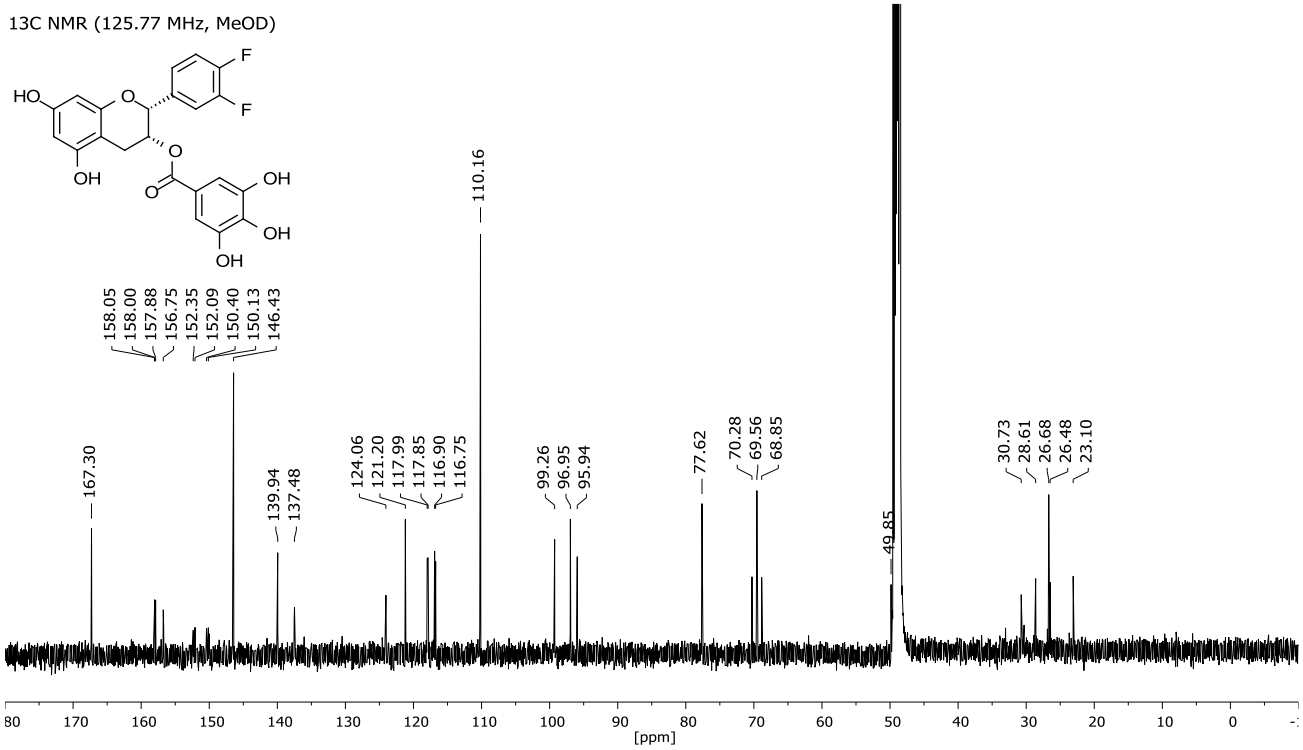
3.15 (2*R*,3*R*)-2-(3,4-Difluorophenyl)-5,7-dihydroxychroman-3-yl-gallate (26)



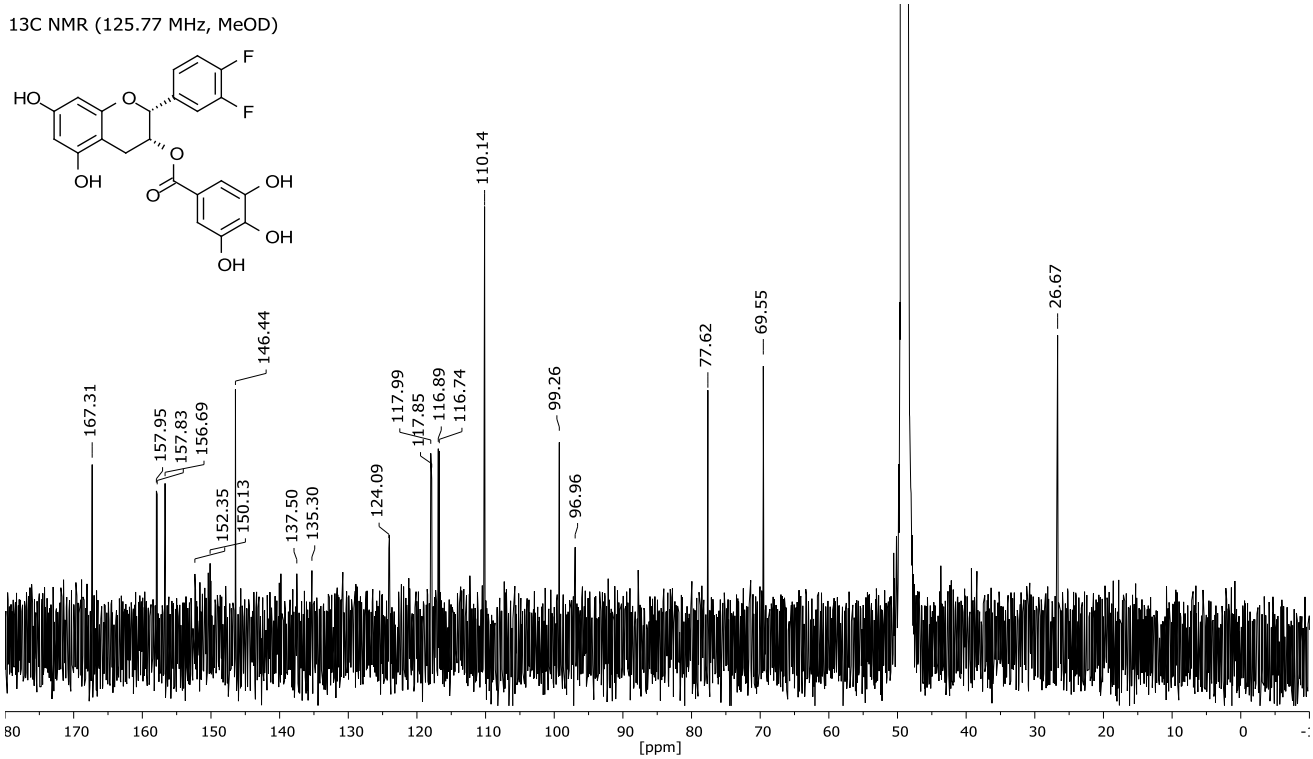
Spectrum 57. ^{1}H-NMR, 600 MHz, MeOD.



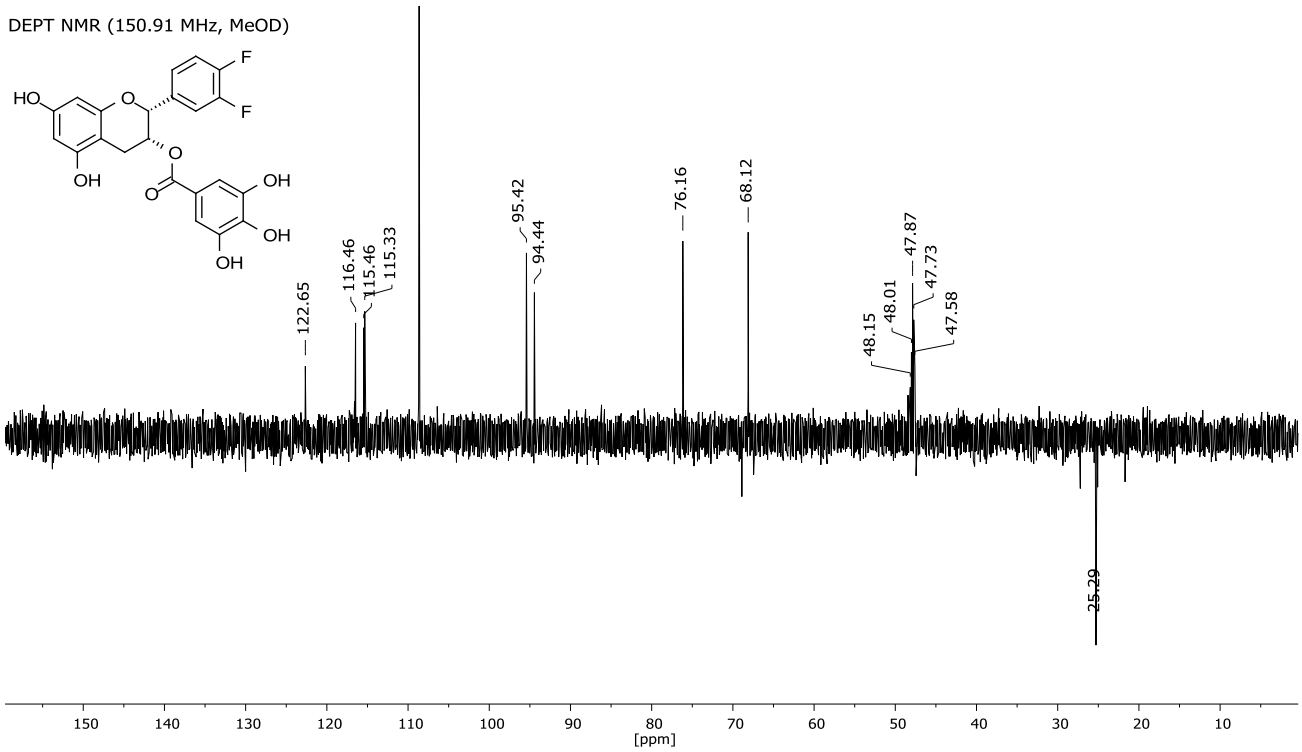
Spectrum 58. ^{19}F-NMR, 282 MHz, MeOD.



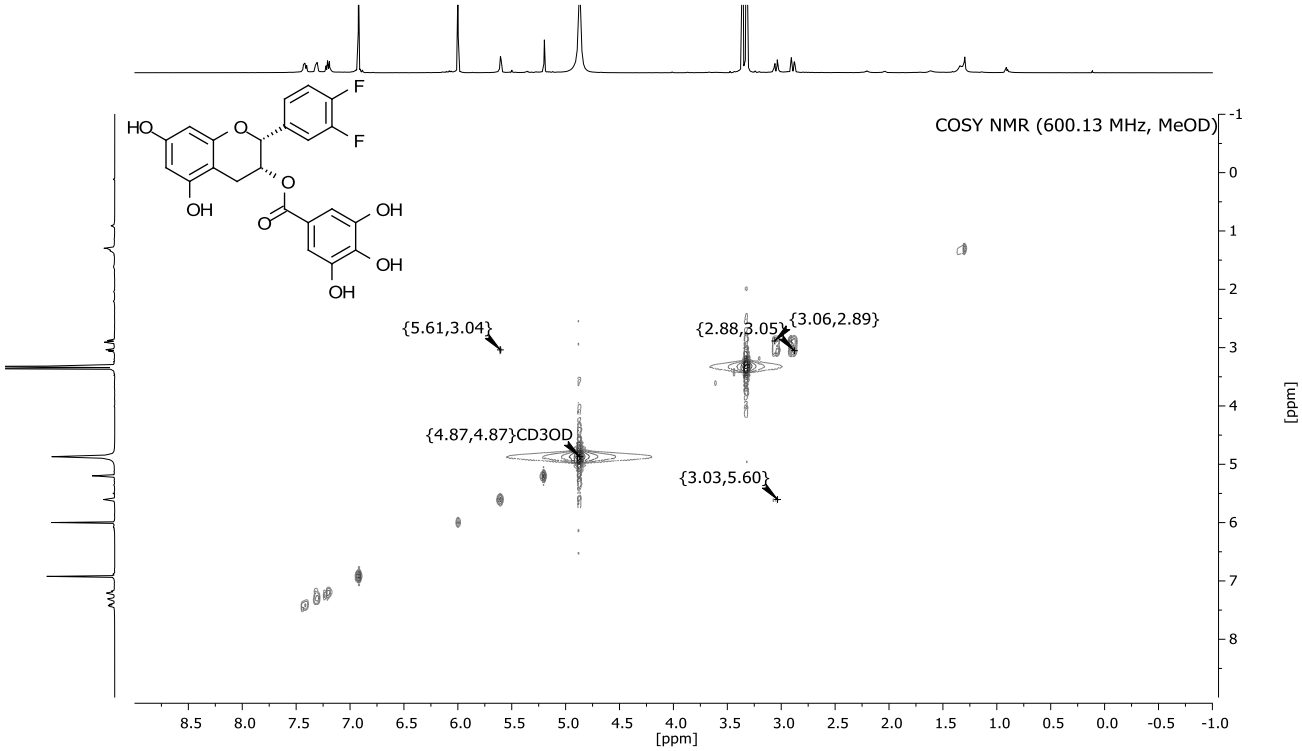
Spectrum 59. ^{13}C-NMR, 126 MHz, MeOD, crude material.



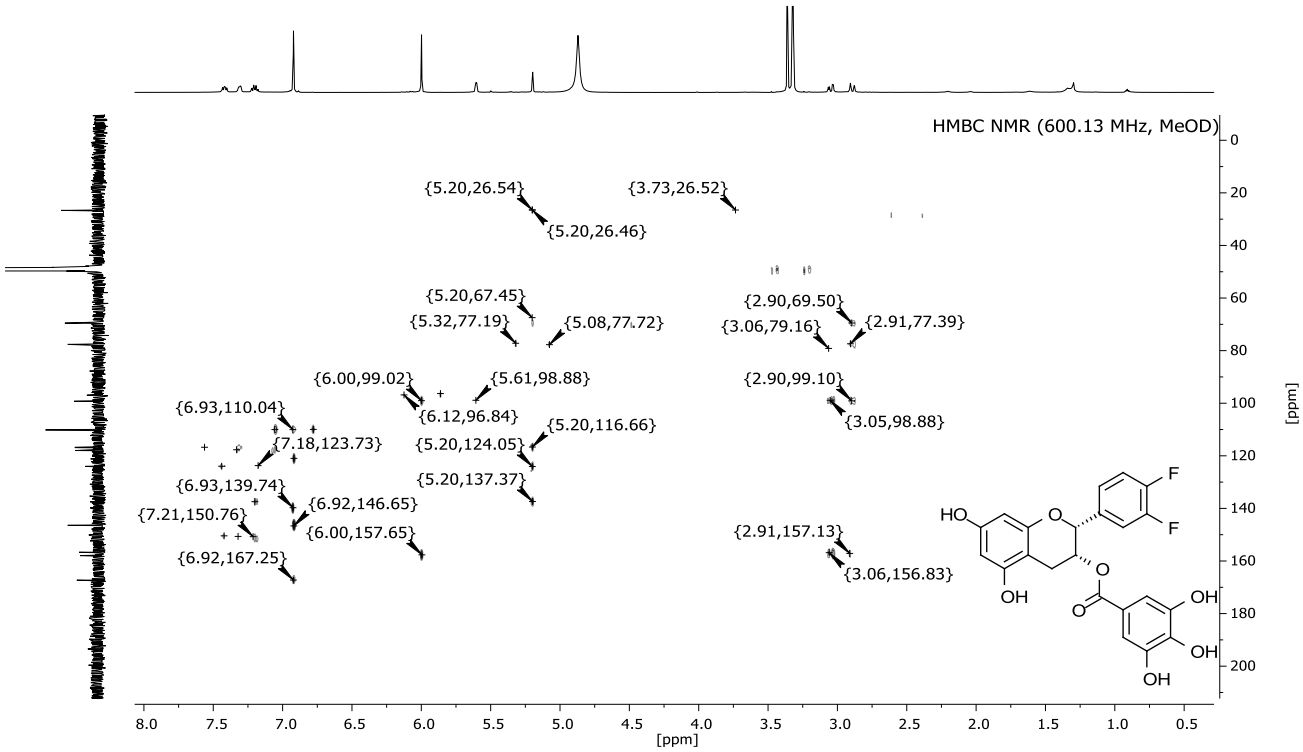
Spectrum 60. ^{13}C-NMR, 126 MHz, MeOD.



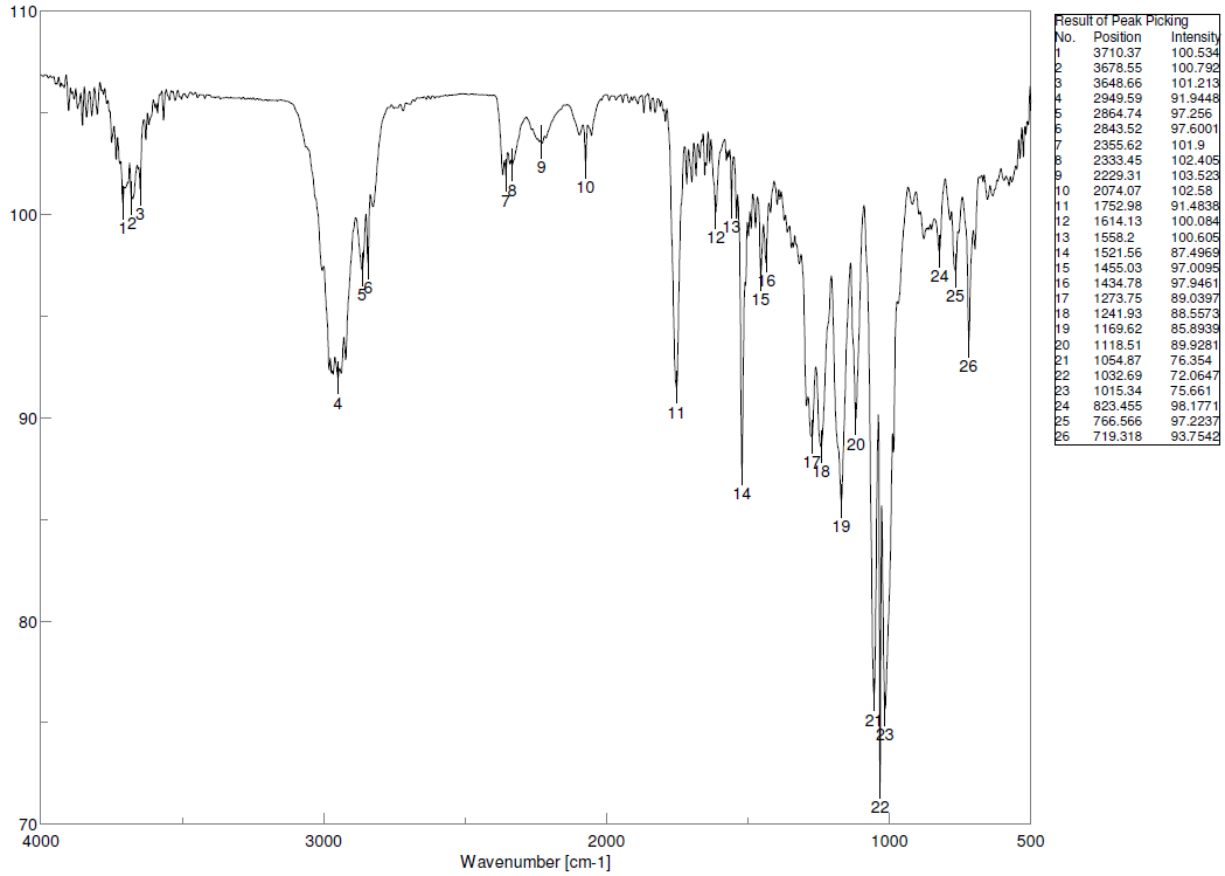
Spectrum 61. DEPT-NMR, 151 MHz, MeOD.



Spectrum 62. COSY-NMR, 600 MHz, MeOD.



Spectrum 63. HMBC-NMR, 600 MHz, MeOD.

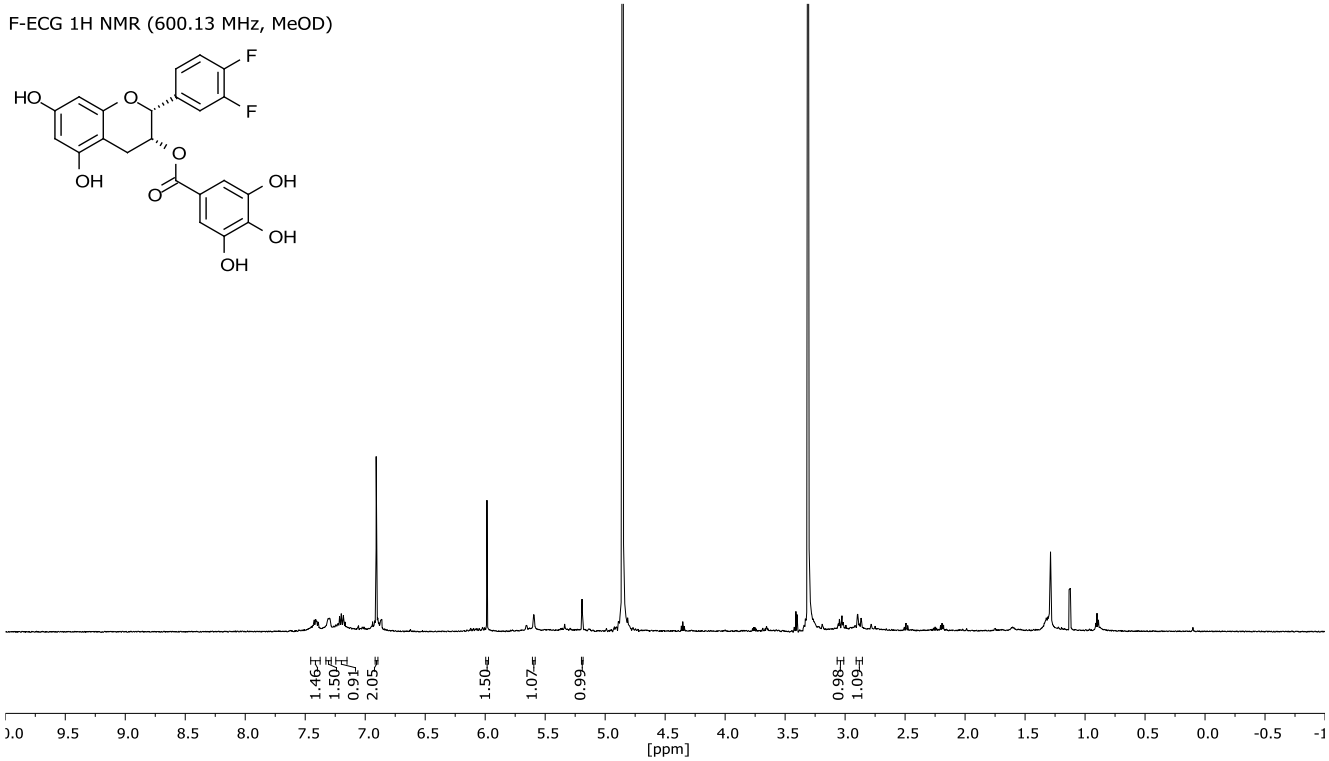


Result of Peak Picking

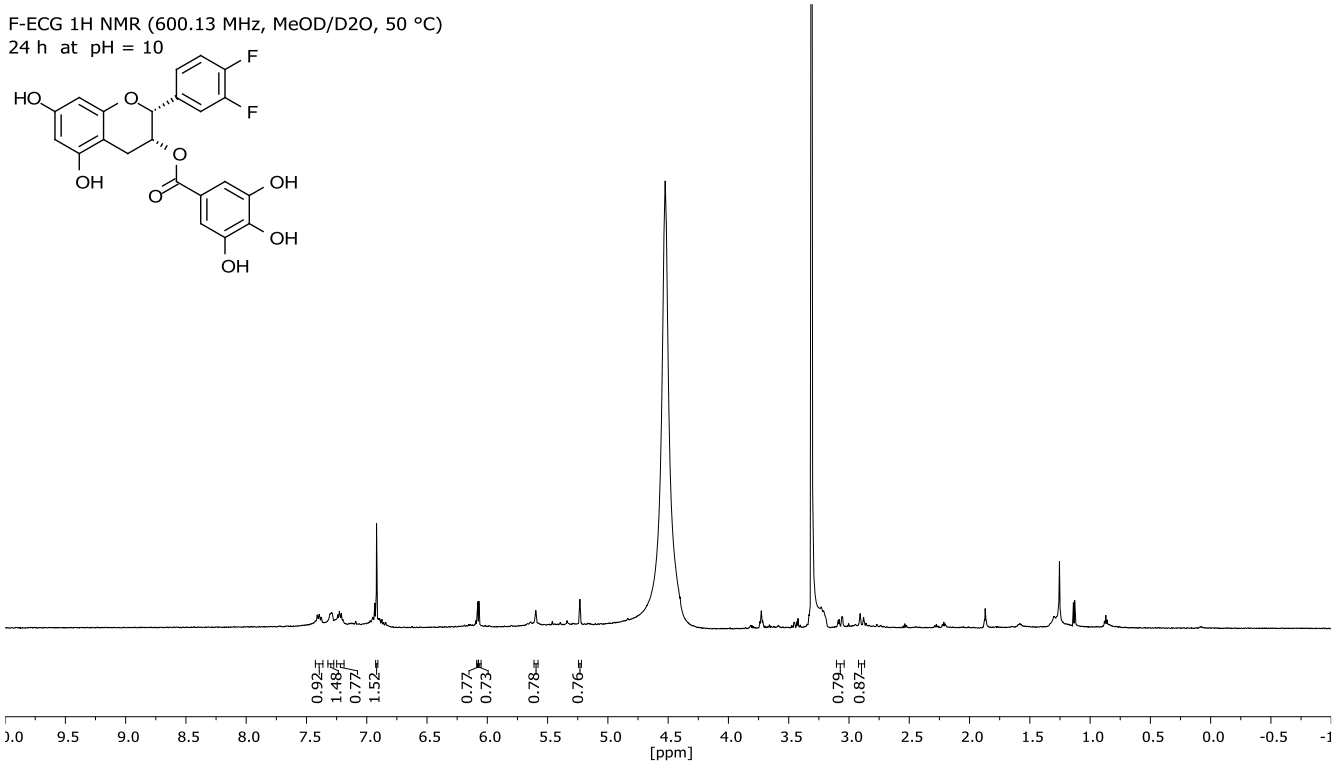
No.	Position	Intensity
1	3710.37	100.534
2	3678.55	100.792
3	3648.66	101.213
4	2949.59	91.9448
5	2864.74	97.256
6	2843.52	97.6001
7	2355.62	101.9
8	2333.45	102.405
9	2229.31	103.523
10	2074.07	102.58
11	1752.98	91.4838
12	1614.13	100.084
13	1558.2	100.605
14	1521.56	87.4969
15	1455.03	97.0095
16	1434.78	97.9461
17	1273.75	89.0397
18	1241.93	88.5573
19	1169.62	85.8939
20	1118.51	89.9281
21	1054.87	76.354
22	1032.69	72.0647
23	1015.34	75.661
24	823.455	98.1771
25	766.566	97.2237
26	719.318	93.7542

Spectrum 64. IR, film on NaCl.

3.16 (2*R*,3*R*)-2-(3,4-Difluorophenyl)-5,7-dihydroxychroman-3-yl-gallate (26) at pH 10



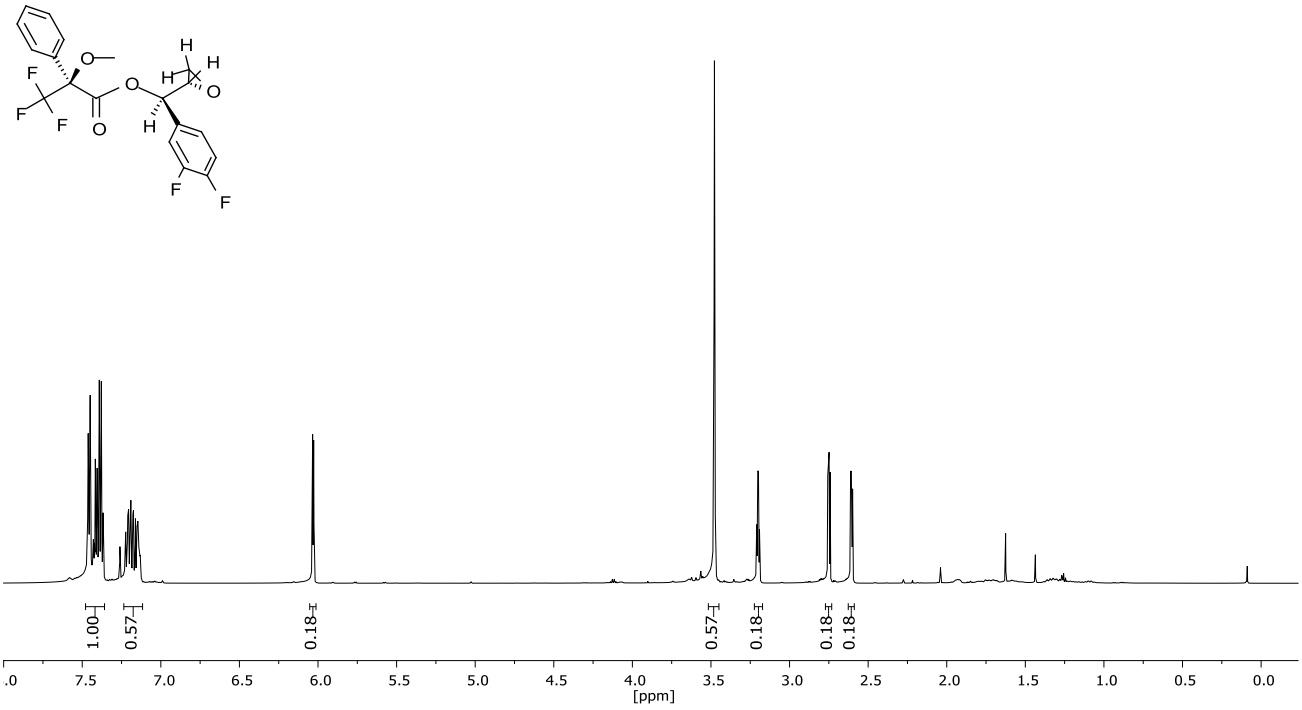
Spectrum 65. ^{1}H-NMR, 600 MHz, MeOD.



Spectrum 66. ^{1}H-NMR, 600 MHz, 50 °C, MeOD and NaOD/D_2O after 24 h.

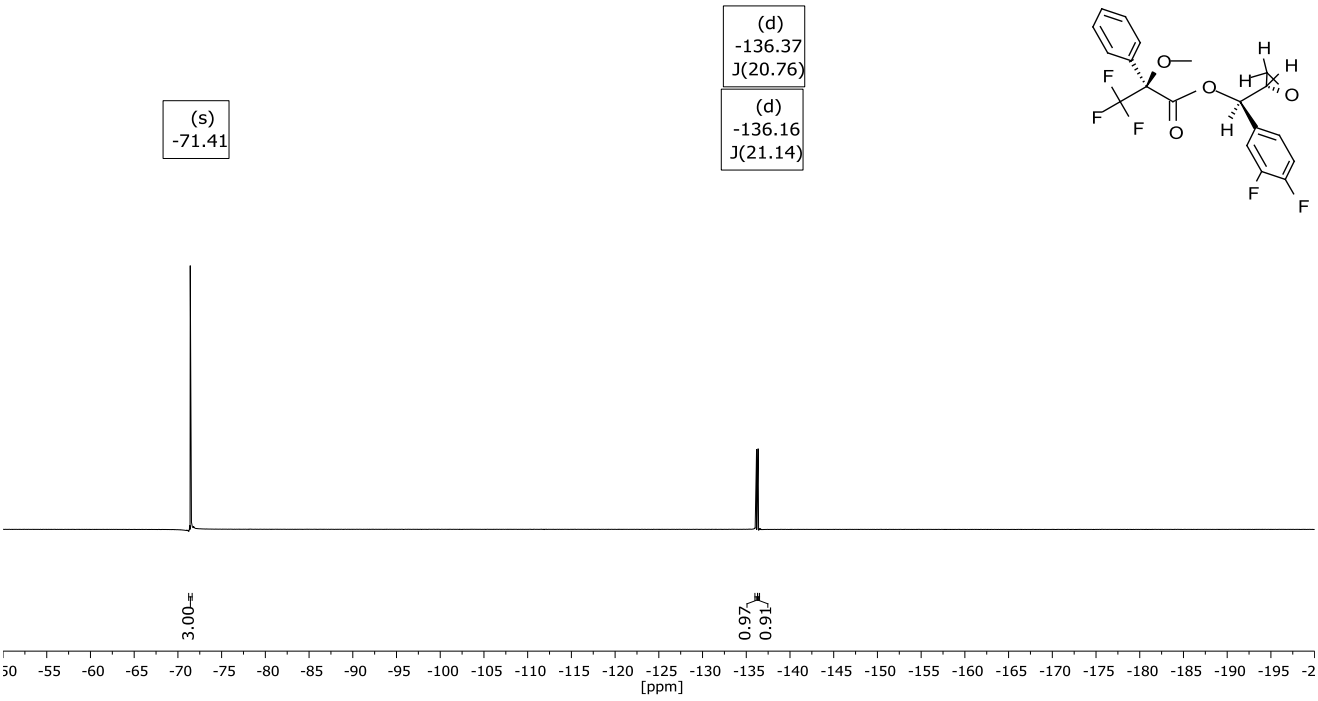
3.17 (1*R*,2*S*)-3-(3,4-Difluorophenyl)-glycidyl-(*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate

1H NMR (600.13 MHz, CDCl3) (S)-MTPA-ester

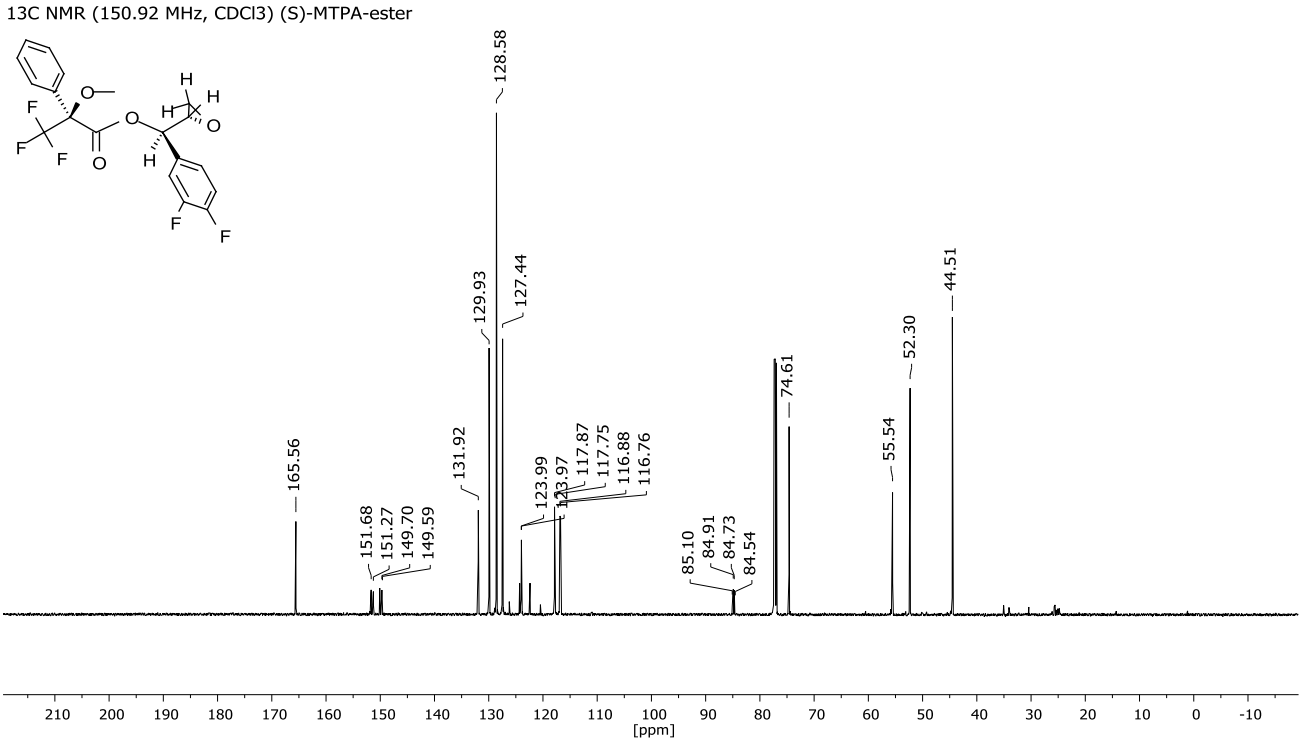


Spectrum 67. ^{1}H-NMR, 600 MHz, $CDCl_3$.

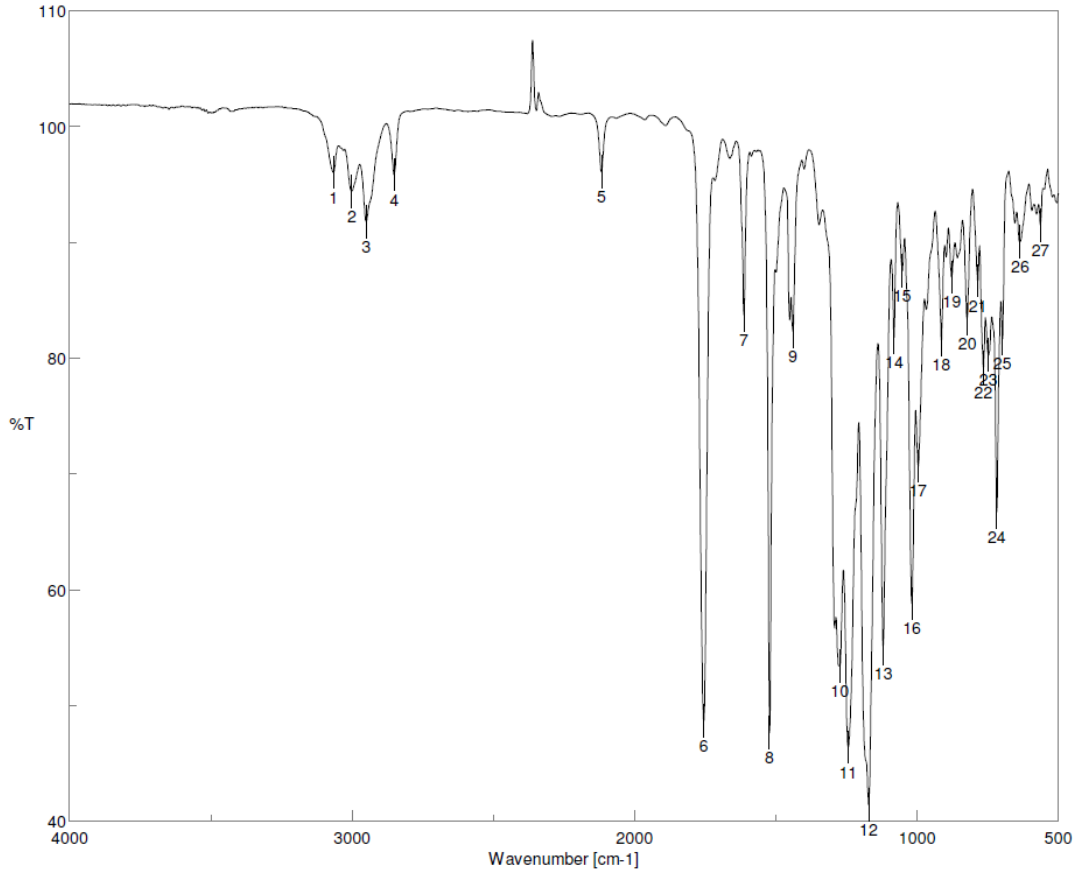
19F NMR (564.63 MHz, CDCl3) (S)-MTPA-ester



Spectrum 68. ^{19}F-NMR, 565 MHz, $CDCl_3$.



Spectrum 69. ^{13}C-NMR, 151 MHz, $CDCl_3$.



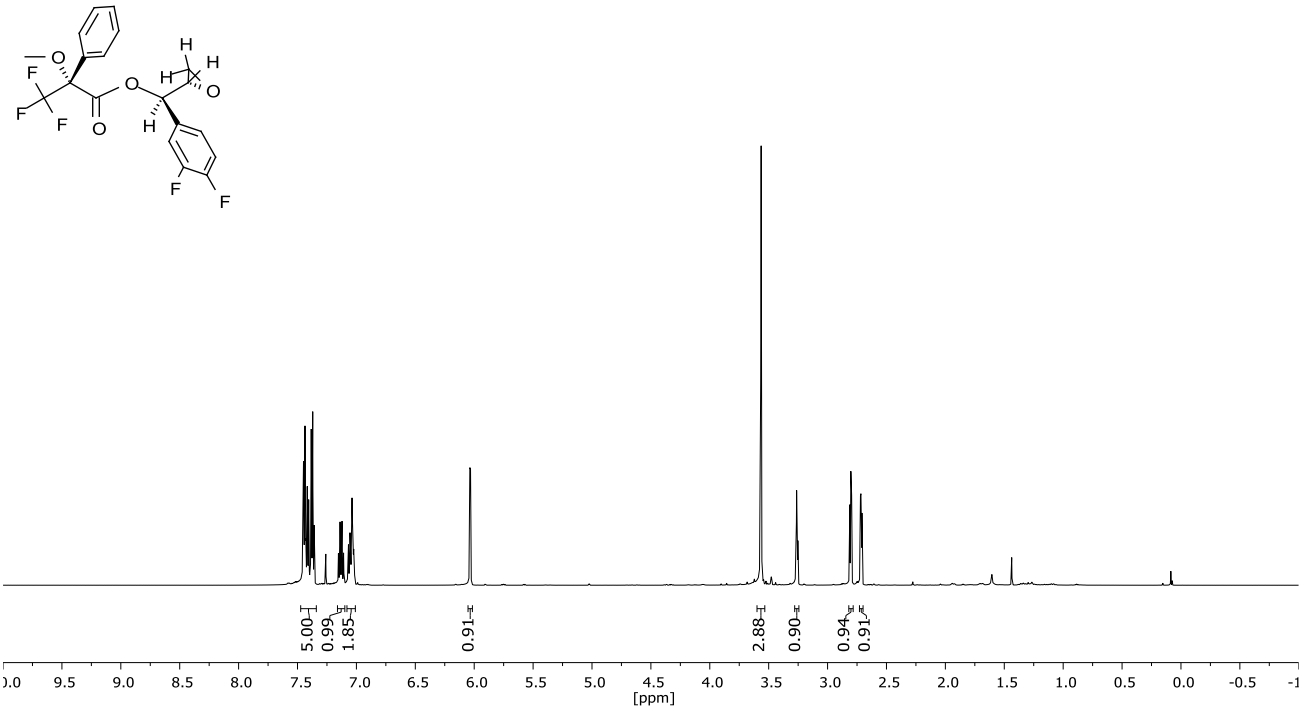
Result of Peak Picking

No.	Position	Intensity
1	3066.26	96.0276
2	3001.66	94.4069
3	2950.55	91.785
4	2851.24	95.8239
5	2117.46	96.0761
6	1755.87	48.693
7	1613.16	83.6876
8	1522.52	47.6389
9	1439.6	82.289
10	1274.72	53.3984
11	1243.86	46.3791
12	1171.54	41.383
13	1120.44	54.9256
14	1081.87	81.7889
15	1052.94	87.5113
16	1019.19	58.7962
17	996.053	70.6518
18	914.093	81.5309
19	877.452	86.9732
20	823.455	83.334
21	785.85	86.6425
22	765.601	79.2148
23	748.245	80.246
24	718.354	66.6676
25	698.105	81.6352
26	636.394	90.0177
27	563.112	91.4338

Spectrum 70. IR, film on NaCl.

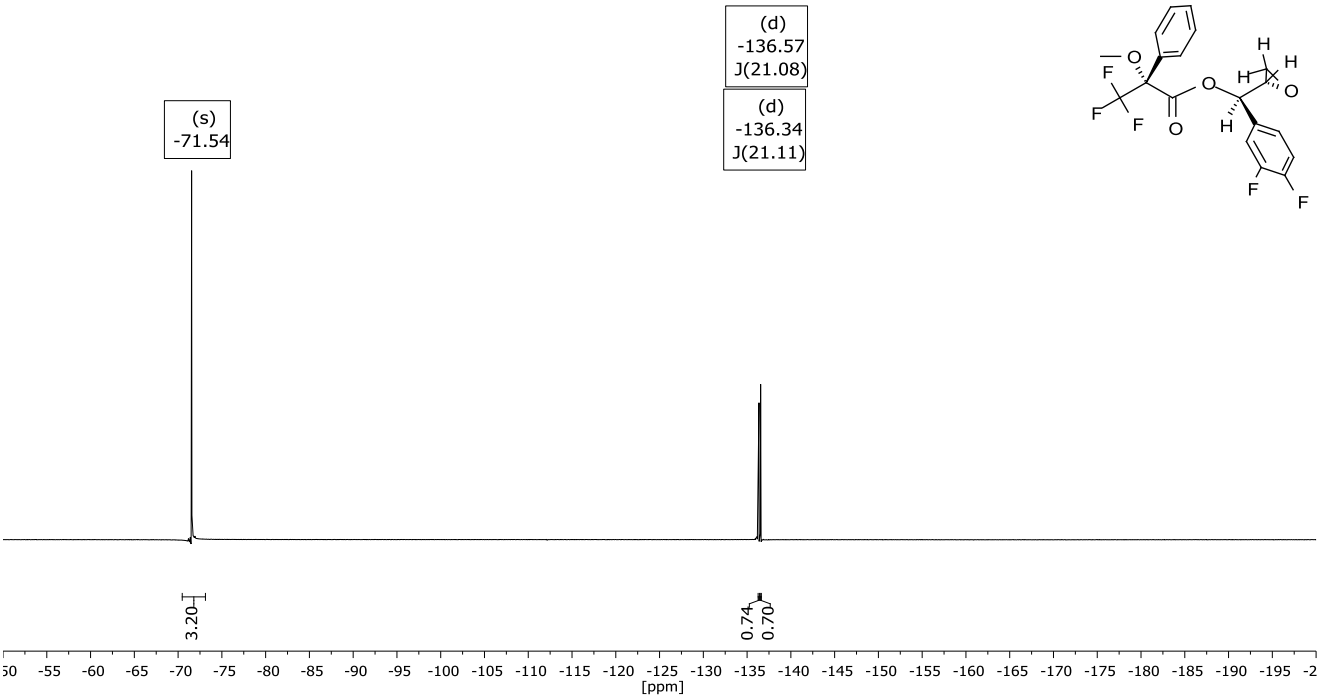
(1*R*,2*S*)-3-(3,4-Difluorophenyl)-glycidyl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate

1H NMR (600.13 MHz, CDCl3) (R)-MTPA-ester



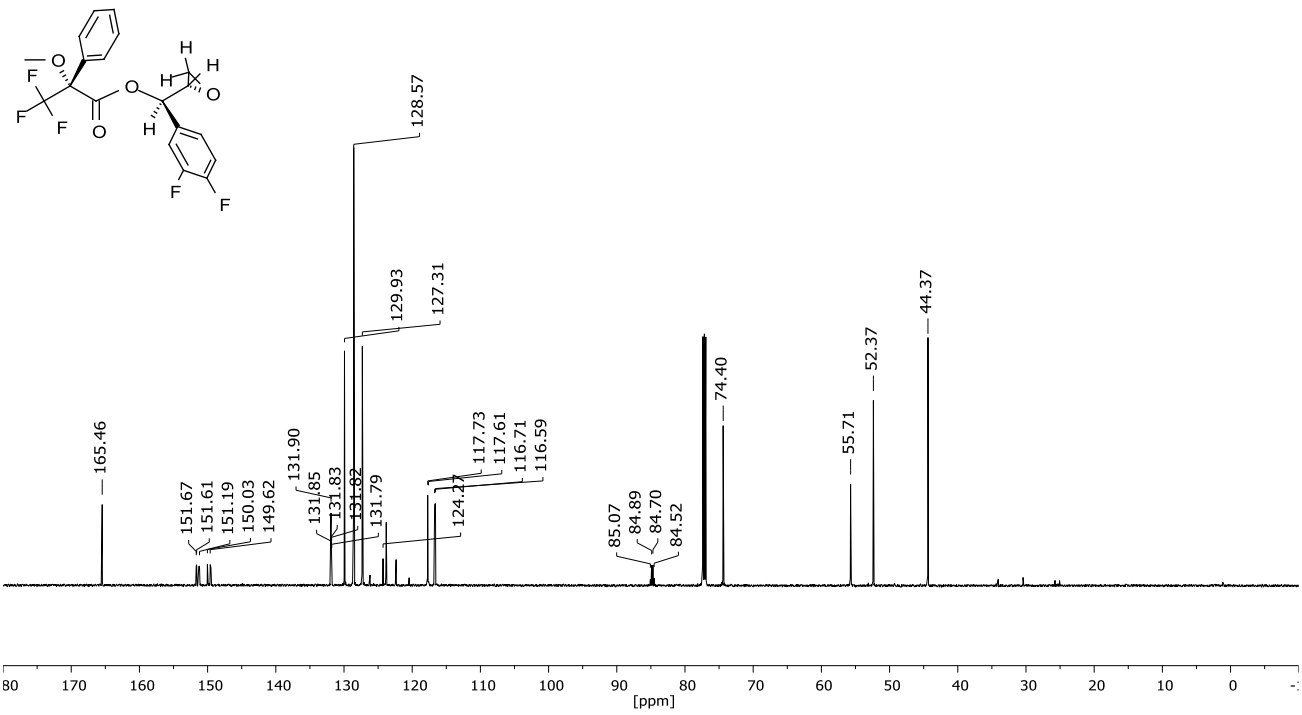
Spectrum 71. ^{1}H-NMR, 600 MHz, $CDCl_3$.

19F NMR (564.63 MHz, CDCl3) (R)-MTPA-ester

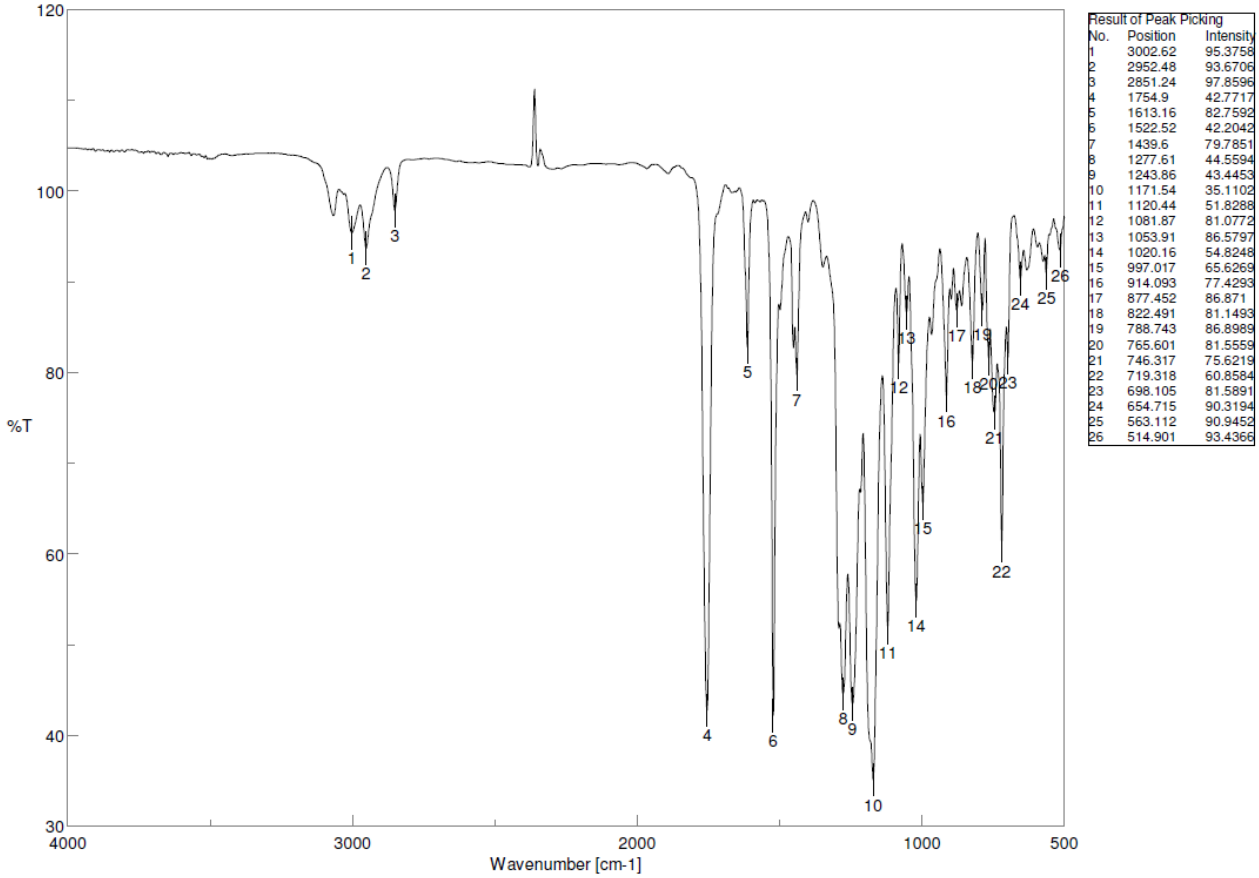


Spectrum 72. ^{19}F-NMR, 565 MHz, $CDCl_3$.

13C NMR (150.92 MHz, CDCl3) (R)-MTPA-ester



Spectrum 73. ^{13}C-NMR, 151 MHz, $CDCl_3$.



Result of Peak Picking

No.	Position	Intensity
1	3002.62	95.3758
2	2952.48	93.6706
3	2851.24	97.8596
4	1754.9	42.7717
5	1613.16	82.7592
6	1522.52	42.2042
7	1439.6	79.7851
8	1277.61	44.5594
9	1243.86	43.4453
10	1171.54	35.1102
11	1120.44	51.8288
12	1081.87	81.0772
13	1053.91	86.5797
14	1020.16	54.8248
15	997.017	65.6269
16	914.093	77.4293
17	877.452	86.871
18	822.491	81.1493
19	788.743	86.8989
20	765.601	81.5559
21	746.317	75.6219
22	719.318	60.8584
23	698.105	81.5891
24	654.715	90.3194
25	563.112	90.9452
26	514.901	93.4366

Spectrum 74. IR, film on NaCl.

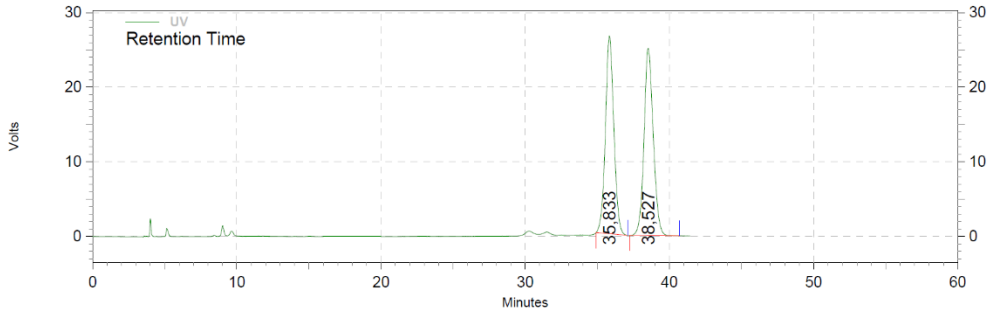
4 HPLC TRACES

4.1 1-(3,4-Difluorophenyl)prop-2-en-1-ol (9)

Attempted enantioselective addition of divinylzinc to 3,4-difluorobenzaldehyde in the presence of (–)-MIB

ChiralPak IA, *n*-hexane/isopropanol 99.5:0.5, Flow: 0.9 mL/min

Acquired: 03.08.2017 17:32:00
Printed: 03.08.2017 18:21:02



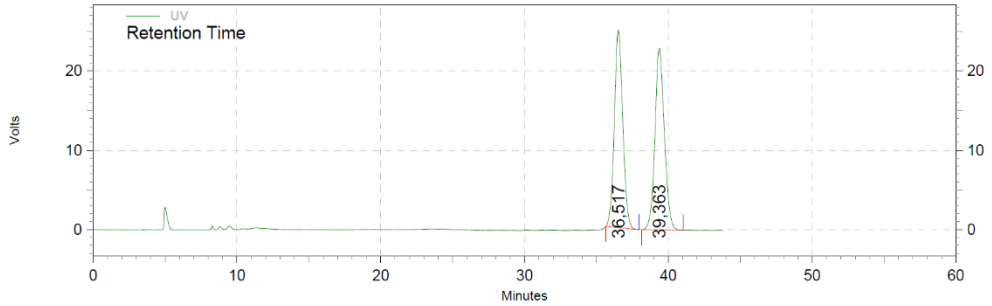
UV Results

Retention Time	Area	Area %	Height	Height %
35,833	4310454	49,06	106045	51,36
38,527	4476514	50,94	100436	48,64

1-(3,4-Difluorophenyl)prop-2-en-1-ol – Racemic reference

ChiralPak IA, *n*-hexane/isopropanol 99.5:0.5, Flow: 0.9 mL/min

Acquired: 03.08.2017 16:45:43
Printed: 03.08.2017 18:17:08



UV Results

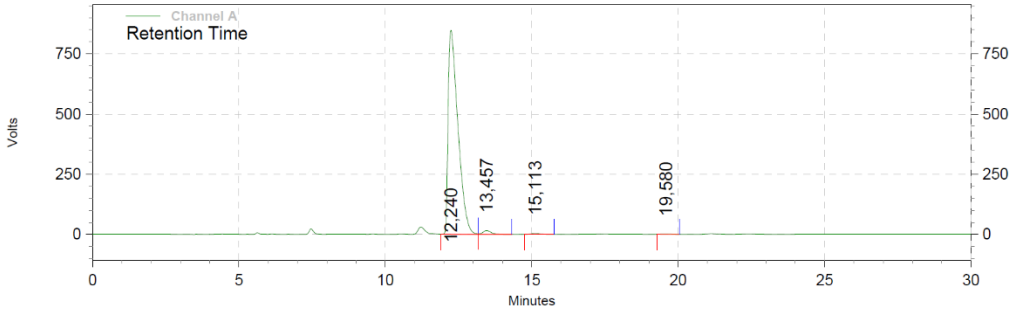
Retention Time	Area	Area %	Height	Height %
36,517	4059209	49,27	99702	52,09
39,363	4179421	50,73	91704	47,91

4.2 3-(3,4-Difluorophenyl)-glycidol (10)

Sharpless epoxidation at –25 °C

ChiralPak IB, *n*-hexane/isopropanol 95:5, Flow: 0.9 mL/min

Acquired: 08.05.2017 14:44:48
Printed: 20.03.2020 16:04:17



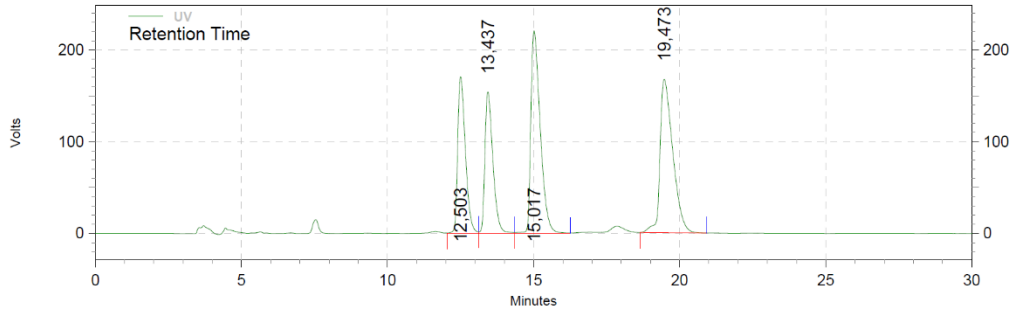
Channel A Results

Retention Time	Area	Area %	Height	Height %
12,240	78816537	97,84	3385707	97,48
13,457	1255927	1,56	63387	1,82
15,113	361631	0,45	18528	0,53
19,580	120062	0,15	5687	0,16

3-(3,4-Difluorophenyl)-glycidol – Racemic reference

ChiralPak IB, *n*-hexane/isopropanol 95:5, Flow: 0.9 mL/min

Acquired: 08.05.2017 13:33:56
Printed: 08.05.2017 14:04:21



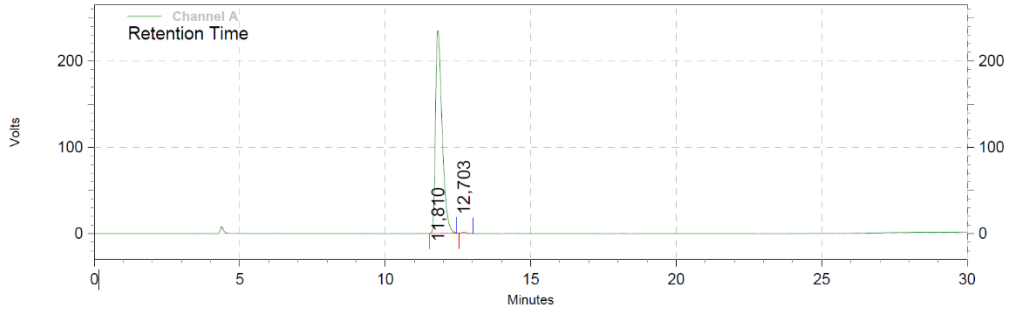
UV Results

Retention Time	Area	Area %	Height	Height %
12,503	12414500	19,44	680484	23,94
13,437	11581360	18,14	614443	21,61
15,017	19559979	30,64	880626	30,98
19,473	20288893	31,78	667466	23,48

Sharpless epoxidation at −35 °C

ChiralPak IB, *n*-hexane/isopropanol 95:5, Flow: 0.9 mL/min

Acquired: 14.06.2017 12:37:38
Printed: 20.03.2020 15:09:40



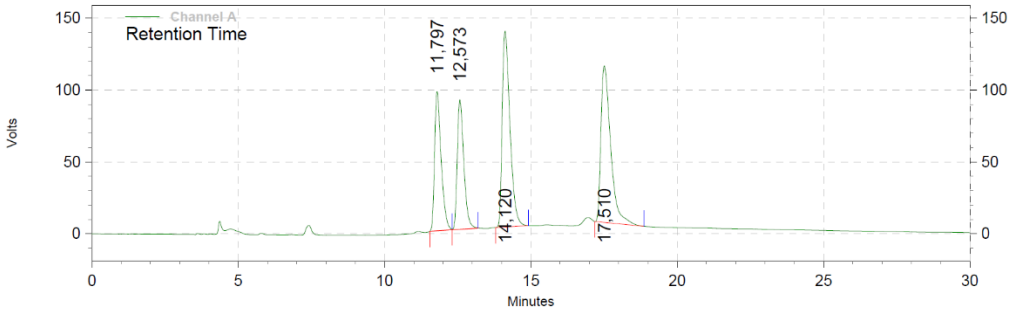
Channel A Results

Retention Time	Area	Area %	Height	Height %
11,810	14842024	99,70	939018	99,62
12,703	44697	0,30	3535	0,38

3-(3,4-Difluorophenyl)-glycidol – Racemic reference

ChiralPak IB, *n*-hexane/isopropanol 95:5, Flow: 0.9 mL/min

Acquired: 14.06.2017 13:28:30
Printed: 20.03.2020 15:21:03



Channel A Results

Retention Time	Area	Area %	Height	Height %
11,797	6002290	18,96	386616	22,38
12,573	5602166	17,70	360443	20,86
14,120	9987981	31,55	545051	31,55
17,510	10063261	31,79	435689	25,22

5 REFERENCES

[1] M. M. Hussain and P. J. Walsh, *Org. Synth.*, 2013, **90**, 25-40.

[2] L. Li and T. H. Chan, *Org. Lett.*, 2001, **3**, 739-741.

[3] H. Yin and K. Cheng, PCT/US2013/052517 (WO2014022287A1), 2013.