Supporting Information

Synthesis of the Positron-Emitting Radiotracer [^{18}F]-2-Fluoro-2-deoxy-D-glucose from Resin-Bound Perfluoroalkylsulfonates

Lynda J. Brown, Nianchun Ma, Denis R. Bouvet, Sue Champion, Alex M. Gibson, Yulai Hu, Alex Jackson, Imtiaz Khan, Nicholas Millot, Amy C. Topley, Harry Wadsworth, Duncan Wynn and Richard C. D. Brown*

Corresponding author rcb1@soton.ac.uk; FAX: +44 (0)23 80594108

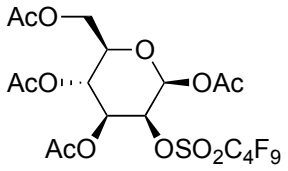
General Methods

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate adaptor or a Nicolet Impact 400 FTIR spectrometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AC300 (300, 75 and 282 MHz respectively) or a Bruker DPX400 (400 and 100 MHz respectively). Low resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. Elemental analyses were obtained from MEDAC Ltd., Egham, UK. Melting points were measured on a Gallenkamp electrothermal melting point apparatus. CH_2Cl_2 and Et_3N were distilled from CaH_2. THF was distilled from sodium/benzophenone prior to use. CH_3OH was distilled from Mg/I_2. All other anhydrous solvents were purchased from Aldrich. All reactions were performed under a dry argon atmosphere in oven dried glassware unless stated otherwise. Sulfonic halides and anhydrides were either purchased from Aldrich or prepared by following literature methods.[1] 1,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranoside was prepared following a literature procedure.[2]

Ion exchange HPLC was carried out using a Dionex system (gamma and electrochemical detectors) equiped with a Carbo Pac PA10 column (4 x 250 mm) with a Carbo Pac PA10 guard (4 x 50 mm), eluting with NaOH (50-52%)/H_2O (2 mL:600 mL, isocratic) at 1 mL/min. Reverse phase HPLC was carried out using a Gilson system (gamma and UV detection) equiped with a u-Bondapak column (3.9 x 300 mm), eluting with H_2O/CH_3CN (gradient 19:1 → 1:19) at 2 mL/min.

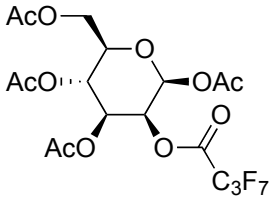
[1] P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85.
[2] V. Pozsgay, C. P. J. Glaudemans, J. B. Robbins, R. Schneerson, *Tetrahedron* **1992**, *48*, 10249.

1,3,4,6-Tetra-*O*-acetyl-2-(1,1,2,2,3,3,4,4,4-nonafluoro-butane-sulfonate)-β-D-mannopyranoside (8).[3]



To a solution of 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside[2] (**4**, 200 mg, 0.57 mmol) and pyridine (158 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) at –30°C was added $(F_9C_4SO_2)_2O$ (785 mg, 1.35 mmol). The reaction mixture was allowed to warm to rt over 1.5 h, whereupon $NaHCO_3$ (aq) was added and the organic layer was separated, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography, eluting with Et_2O/hexanes (4:1) afforded the title compound **8** as a pale yellow oil (129 mg, 0.205 mmol, 36 %). ^{1}H NMR ($CDCl_3$) ∂ 5.93 (1H, s), 5.31 (1H, tt, *J* = 1.5, 9.9 Hz), 5.16-5.23 (2H, m), 4.25 (1H, dd, *J* = 4.8, 12.4 Hz), 4.18 (1H, dd, *J* = 2.6, 12.4 Hz), 3.84 (1H, ddd, *J* = 2.6, 4.8, 9.9 Hz), 2.16 (3H, s), 2.11 (3H, s), 2.10 (3H, s), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$) ∂ 170.78, 170.00, 169.27, 168.16, 89.27, 81.63, 73.66, 69.81, 64.57, 61.73, 20.76, 20.70, 20.54; ^{19}F NMR ($CDCl_3$, ref. C_6F_6) ∂ 81.2, 51.6, 40.9, 35.9.

1,3,4,6-Tetra-*O*-acetyl-2-(perfluorobutanoate)-β-D-mannopyranoside (9).



To a mixture of AgOTf (118 mg, 0.46 mmol), $F_9C_4SO_2Cl$ (136 mg, 0.43 mmol) and pyridine (38 μL, 0.45 mmol) in THF (3 mL) was added 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside[2] (**5**, 100 mg, 0.287 mmol). After 2 h at rt the reaction was partitioned between Et_2O and water, and the organic layer was separated, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography, eluting with EtOAc/hexanes (1:9) afforded the title compound **9** as a pale yellow oil (70 mg, 0.132 mmol, 46 %). $[\alpha]_D$ – 1.8° (c = 0.0056, $CHCl_3$); ν_{max} (neat, cm^{-1}) 1750, 1369, 1209, 1085, 1054; (^{1}H NMR ($CDCl_3$) ∂ 5.94 (1H, d, *J* = 0.8 Hz), 5.60 (1H, d, *J* = 3.0 Hz), 5.32 (1H, t, *J* = 9.9 Hz), 5.22 (1H, dd, *J* = 3.0, 9.9 Hz), 4.28 (1H, dd, *J* = 4.3, 12.4 Hz), 4.18 (1H, dd, *J* = 2.2, 12.4 Hz), 3.84 (1H, ddd, *J* = 2.2, 4.3, 9.9 Hz), 2.11 (3H, s), 2.09 (3H, s), 2.06 (3H, s), 2.02 (3H, s); ^{13}C NMR ($CDCl_3$) ∂ 170.62, 169.69, 169.20, 168.12, 89.51, 73.27, 72.84, 70.10, 64.72, 61.49, 20.57, 20.48, 20.27; ^{19}F NMR ($CDCl_3$, ref. C_6F_6) ∂ 81.3, 42.7, 35.2; MS (ES^+) *m/z* 567.2 ($[M + Na]^+$, 100 %).

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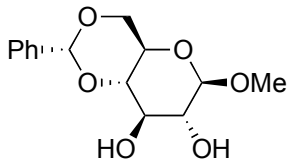
[3] (a) V. Pavliak, K. Pavol, *Carbohydr. Res.* **1991**, *210*, 333; (b) K. Hamacher, *Carbohydr. Res.* **1984**, *128*, 291.

Methyl 4,6-O-benzylidene-β-D-glucopyranoside (11).[4]



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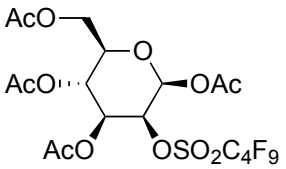
Following the method of Bundle: Methyl-β-D-glucopyranoside (5.1 g, 25 mmol), benzaldehyde dimethylacetal (15.2 g, 15 mL, 100 mmol) and 10-camphorsulfonic acid (58 mg, 0.25 mmol) were dissolved in anhydrous MeCN (75 mL) and the reaction stirred at room temperature for 4 h. Et_3N (0.5 mL) was added and the reaction filtered. The solid residue was washed with MeCN, the combined filtrates were concentrated in vacuo (~30 mL) and re-filtered. The combined solids were purified by crystallization from EtOAc: hexane and dried to afford the title compound as white crystals (**11**, 6.6 g, 93 %). Mp 198–200°C; Lit: 196.5–198°C;[4] ν_{max} (neat, cm^{-1}) 3373, 2872, 1378, 1087, 1022, 995; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.45 (2H, m), 7.40-7.33 (3H, m), 5.55 (1H, s), 4.37 (1H, dd, *J* = 4.7, 10.4 Hz), 4.34 (1H, d, *J* = 8.0 Hz), 3.85 (1H, t, *J* = 10.3 Hz), 3.78 (1H, t, *J* = 10.3 Hz), 3.59 (3H, s), 3.58-3.43 (3H, m), 2.83 (1H, br), 2.69 (1H, br); ^{13}C NMR (300 MHz, DMSO-d_6) δ 137.80, 128.85, 128.03, 126.35, 104.53, 100.67, 80.63, 74.27, 72.81, 67.97, 65.78, 56.40. Spectroscopic data consistent with those reported in the literature.[5]

[4] D. R. Bundle, *J. Chem. Soc.-Perkin Trans. 1* **1979**, 2751.
[5] A. Roën, J. I. Padron, J. T. Vazquez, *J. Org. Chem* **2003**, *68*, 4615.

^{1}H NMR Compound **8**



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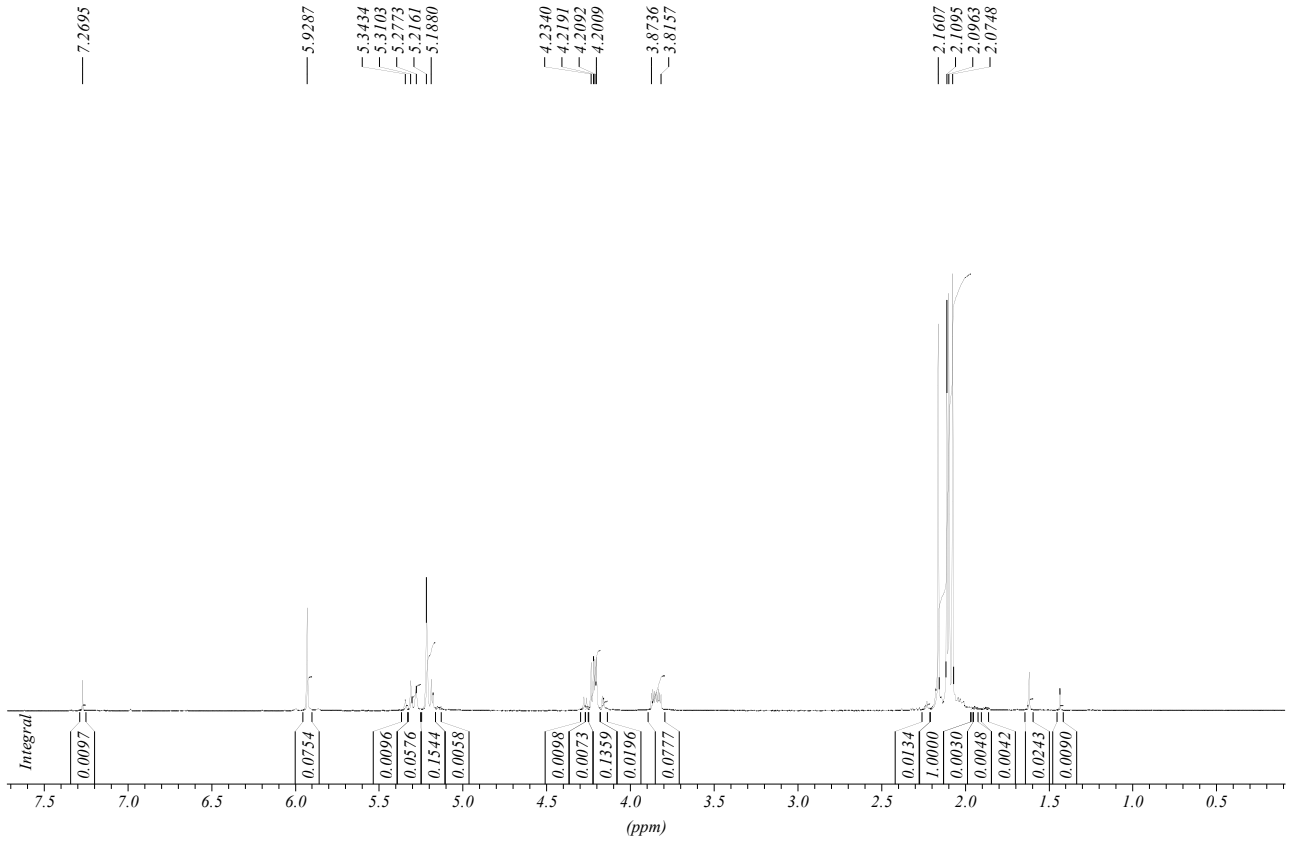

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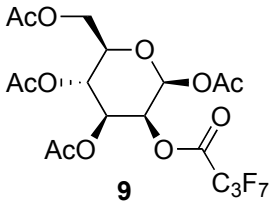

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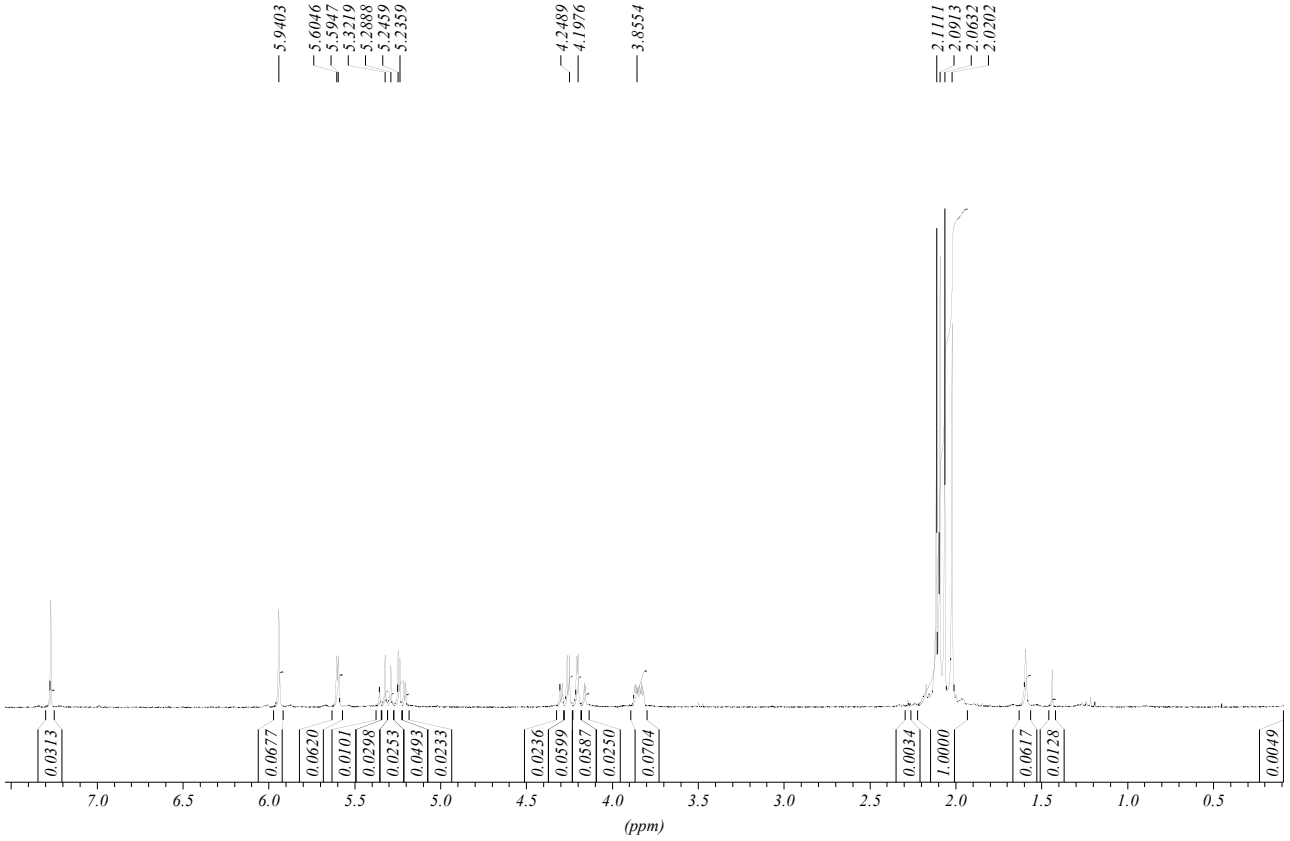

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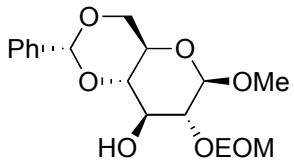

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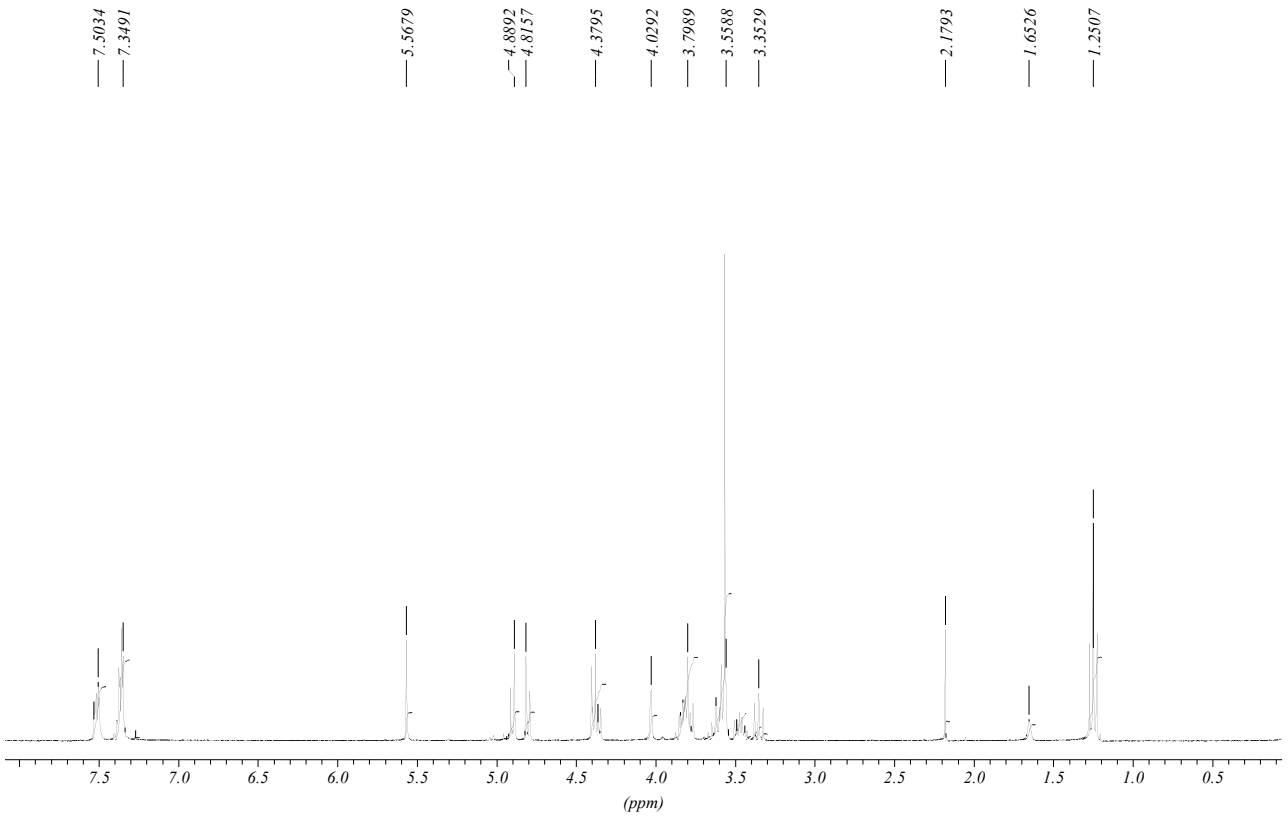

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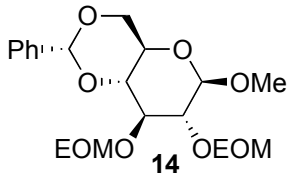

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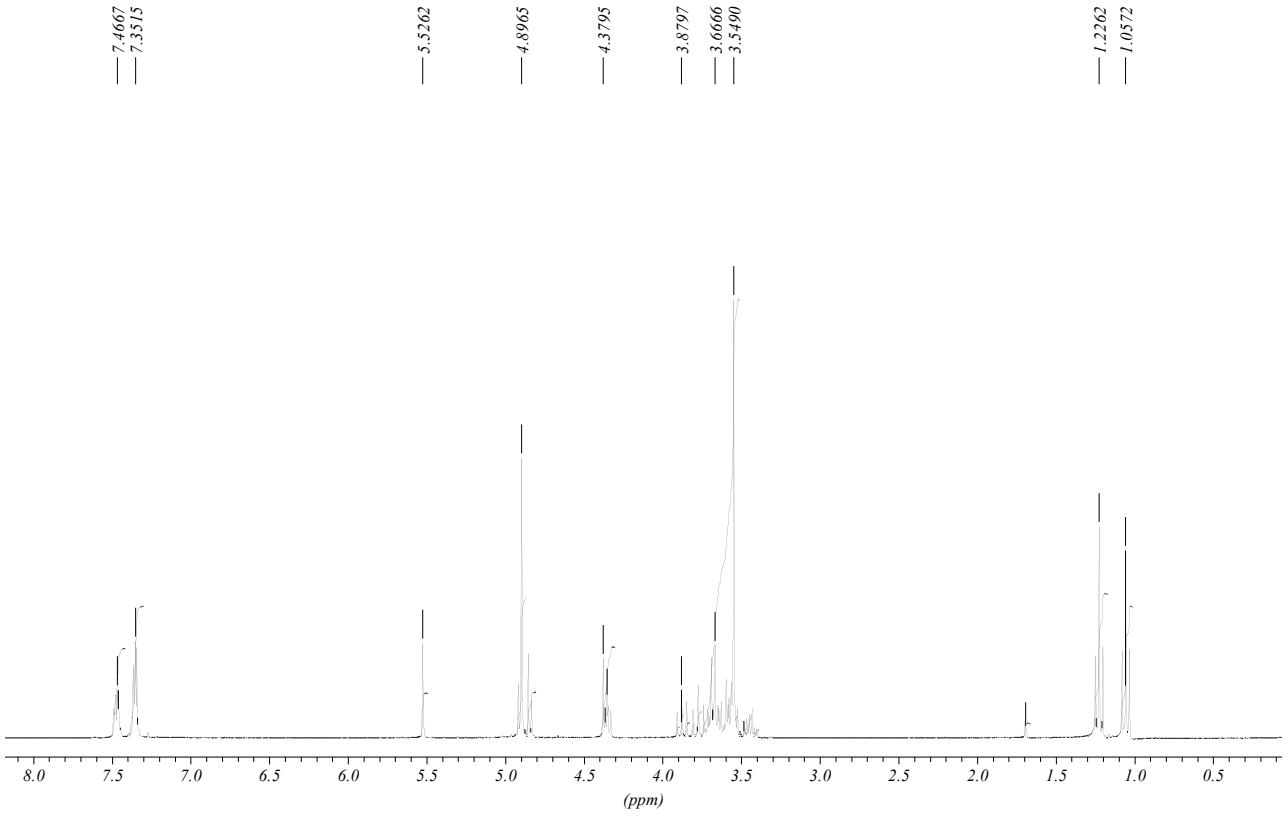

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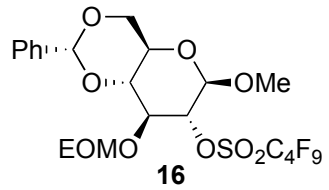

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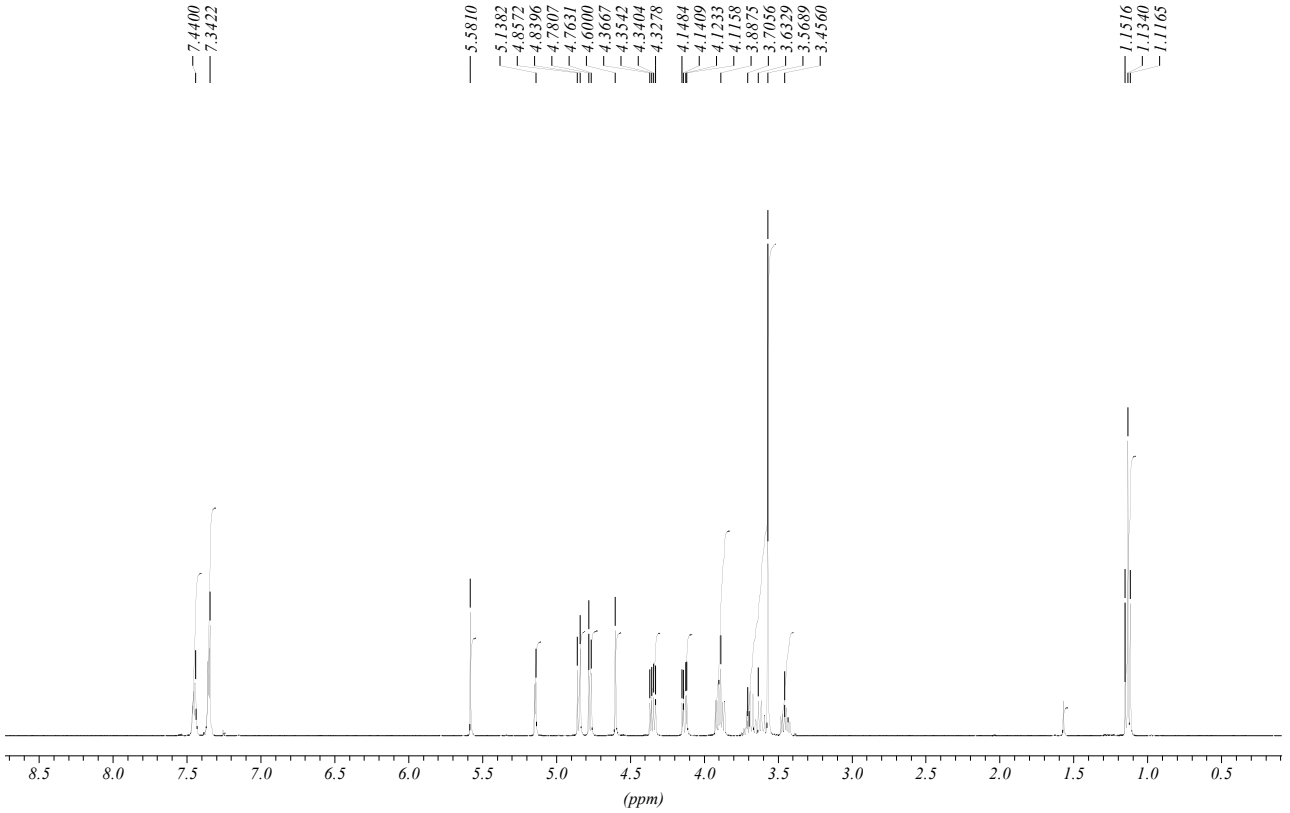

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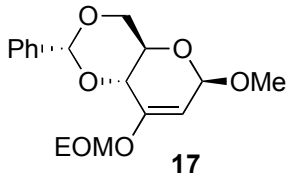

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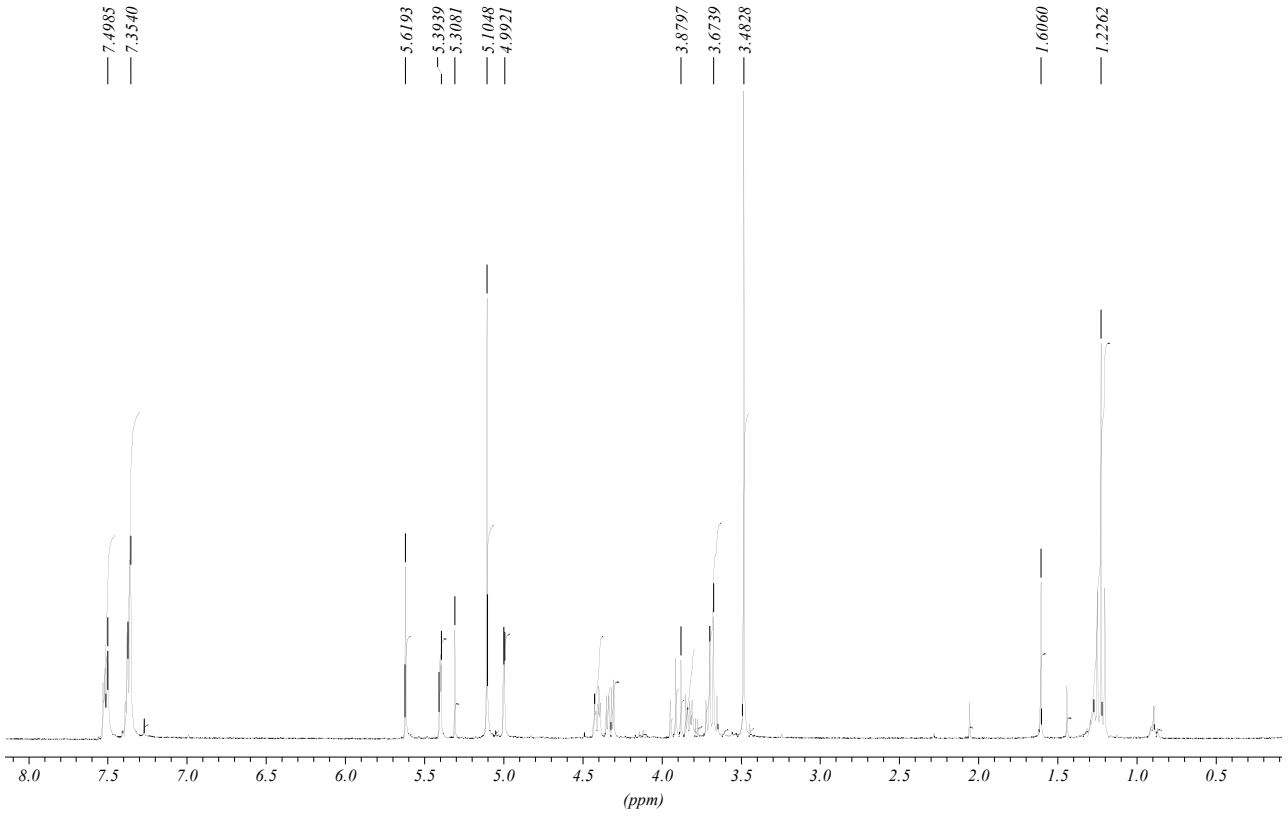

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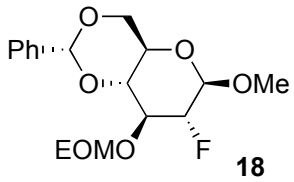

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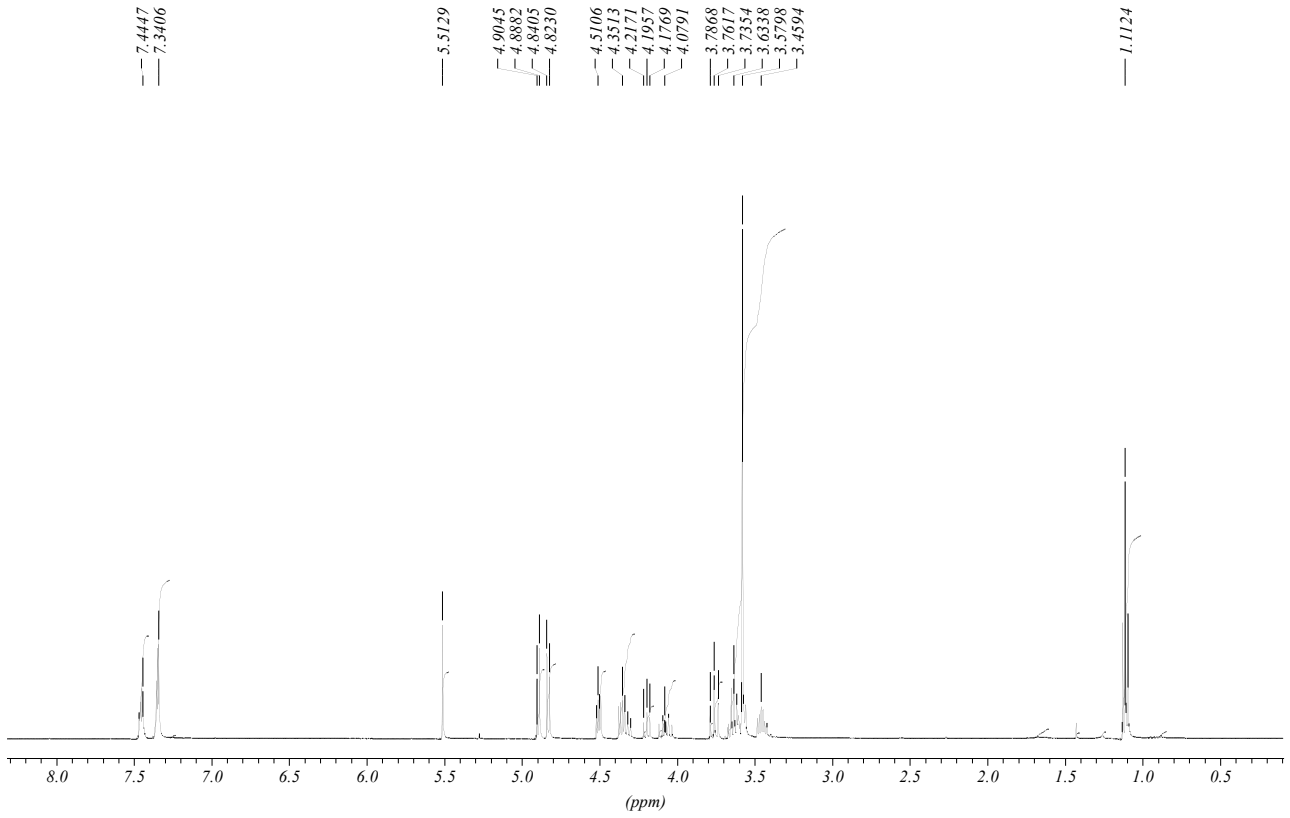

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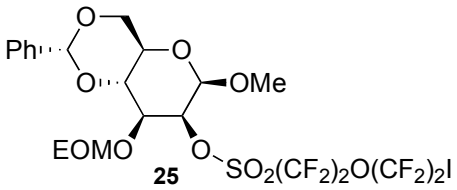

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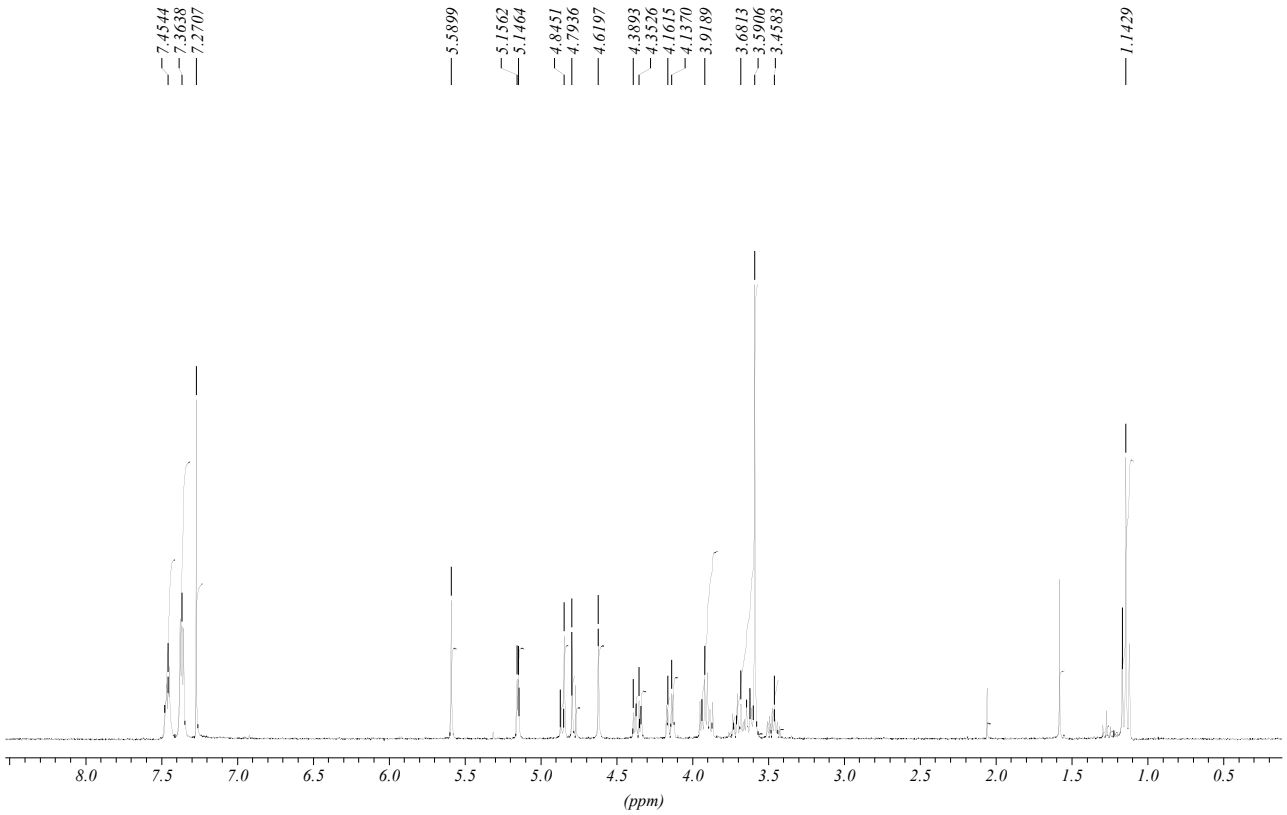

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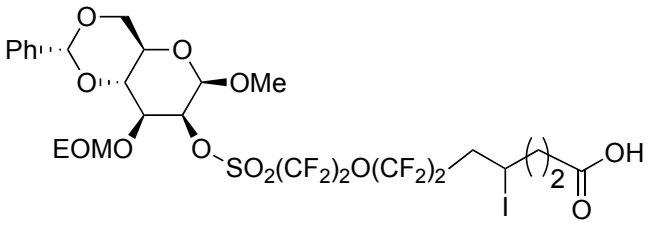
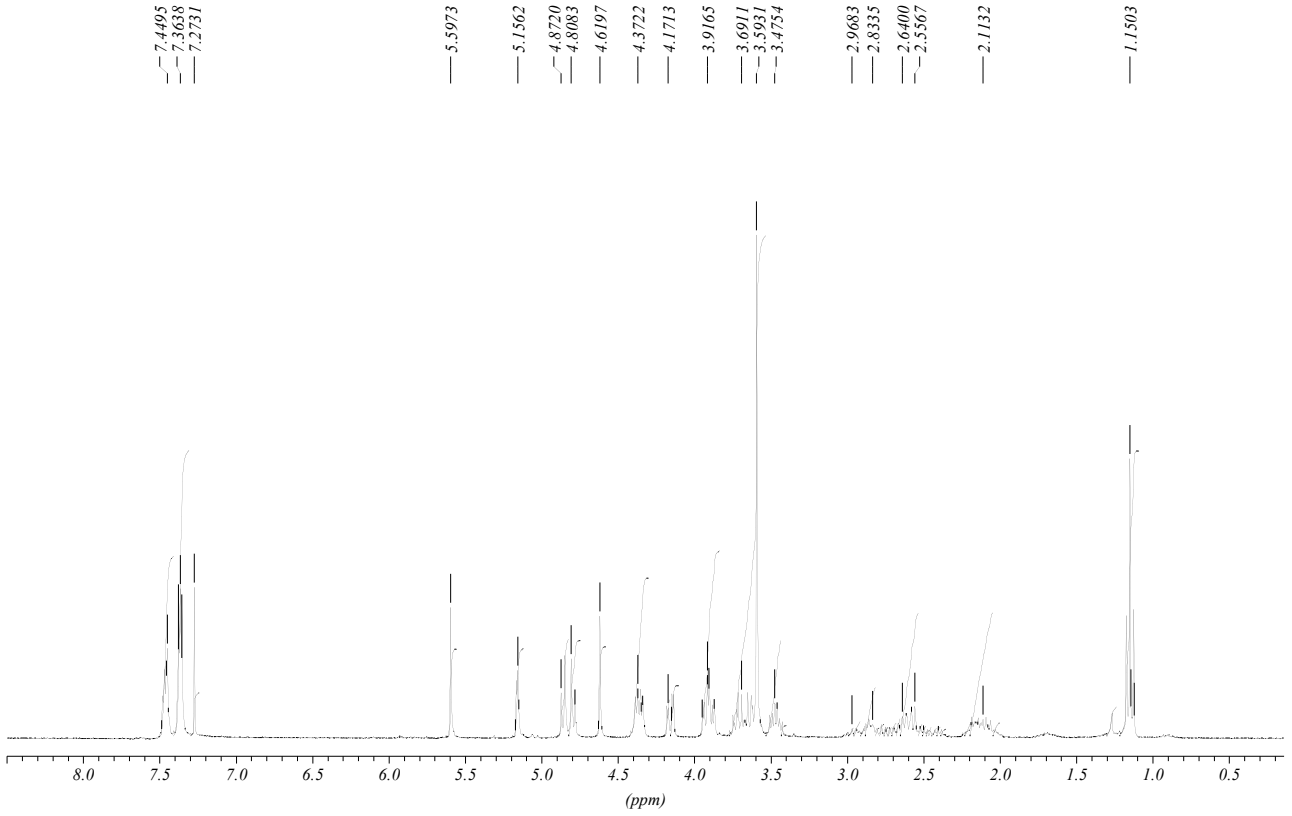

Ph
O
O
O
OMe
EOMO
O
SO2(CF2)2O(CF2)2
2
OH
I
O


7.4495
7.3638
7.2731
5.5973
5.1562
4.8720
4.8083
4.6197
4.3722
4.1713
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3.6911
3.5931
3.4754
2.9683
2.8335
2.6400
2.5567
2.1132
1.1503
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
2.5
2.0
1.5
1.0
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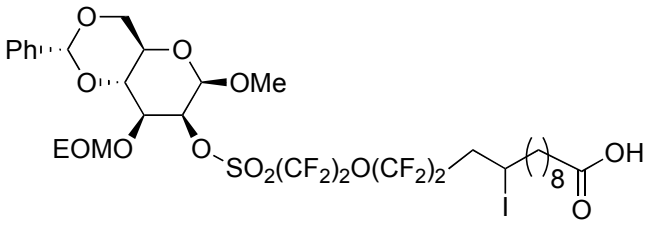
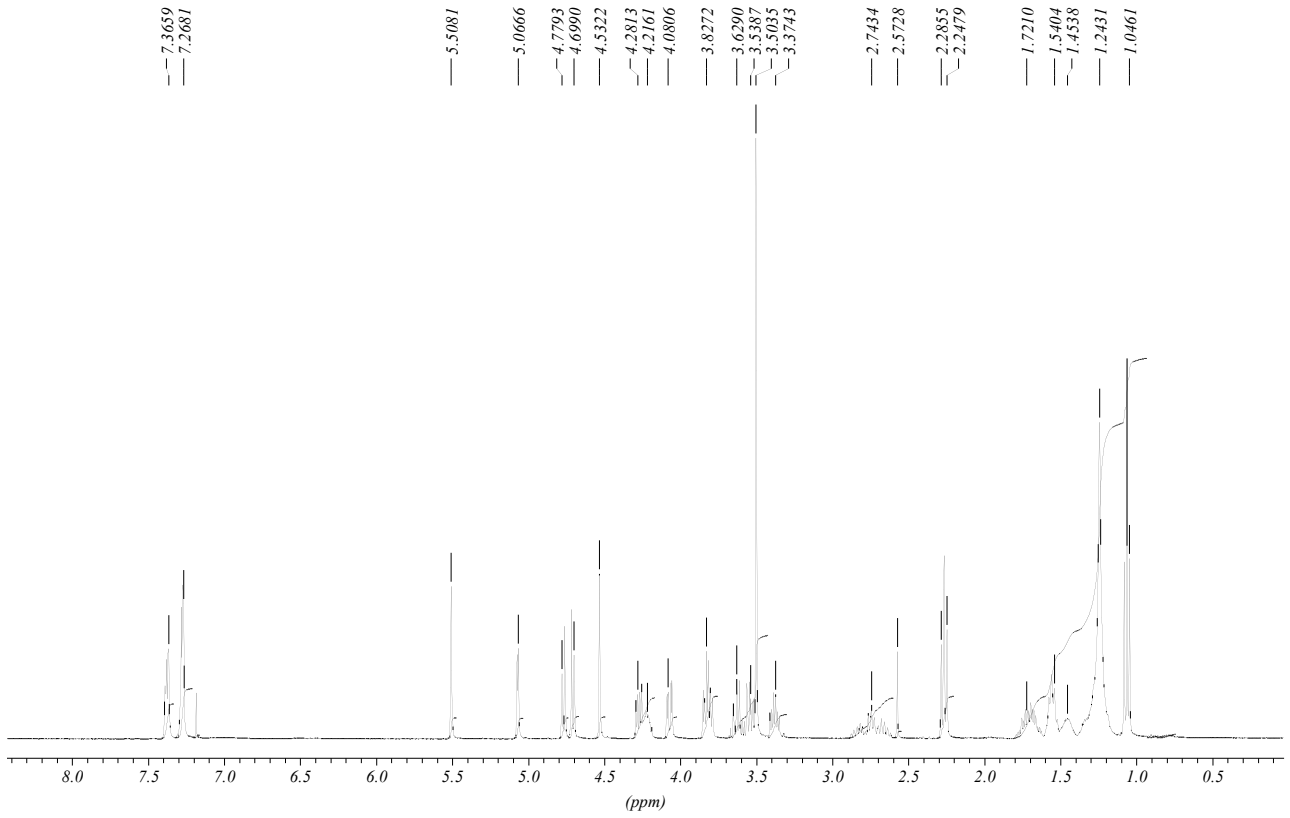
(ppm)

^{1}H NMR Compound **27**





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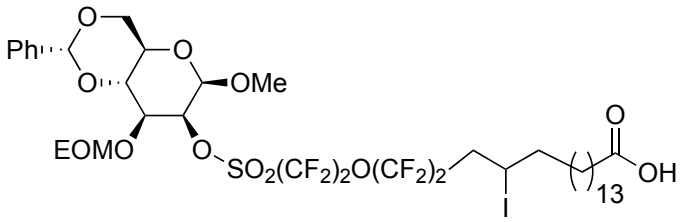

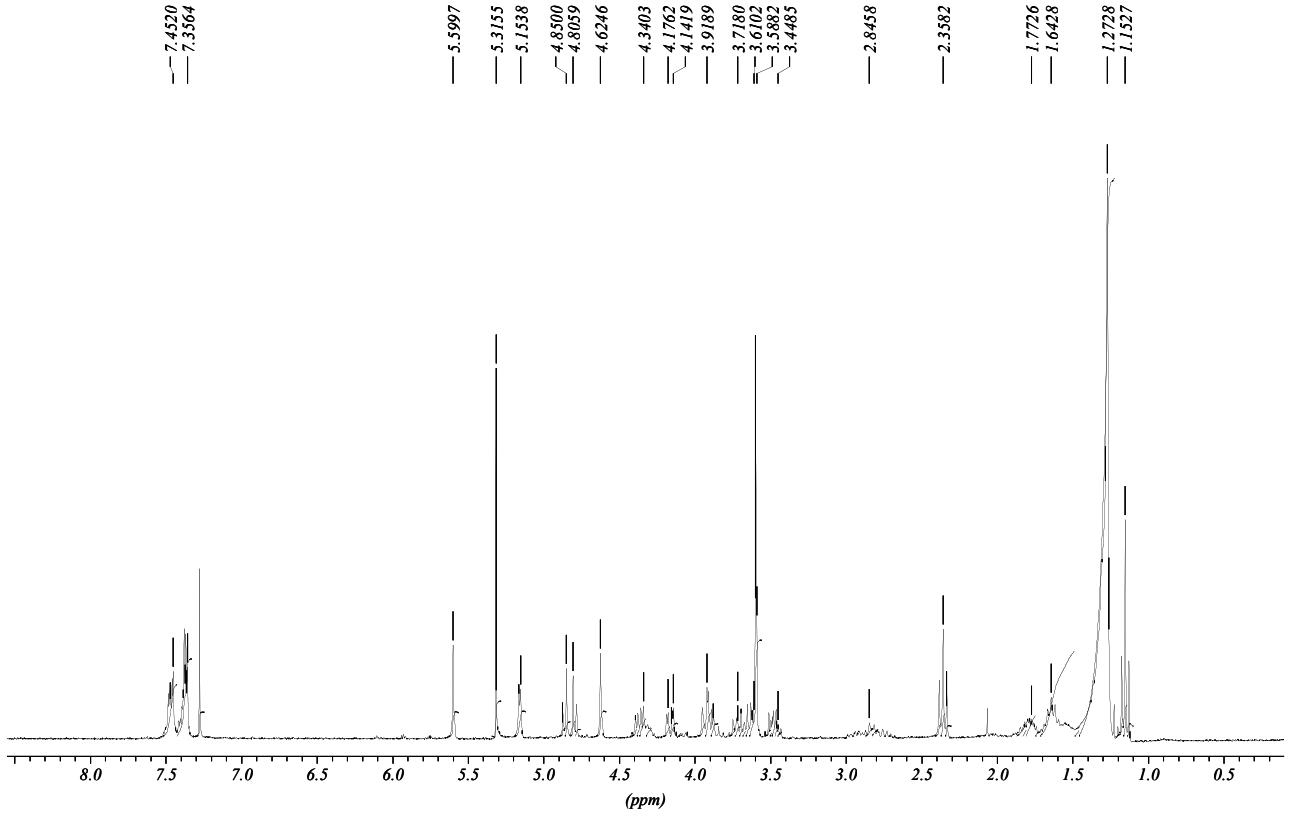

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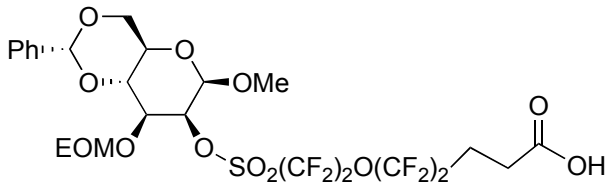

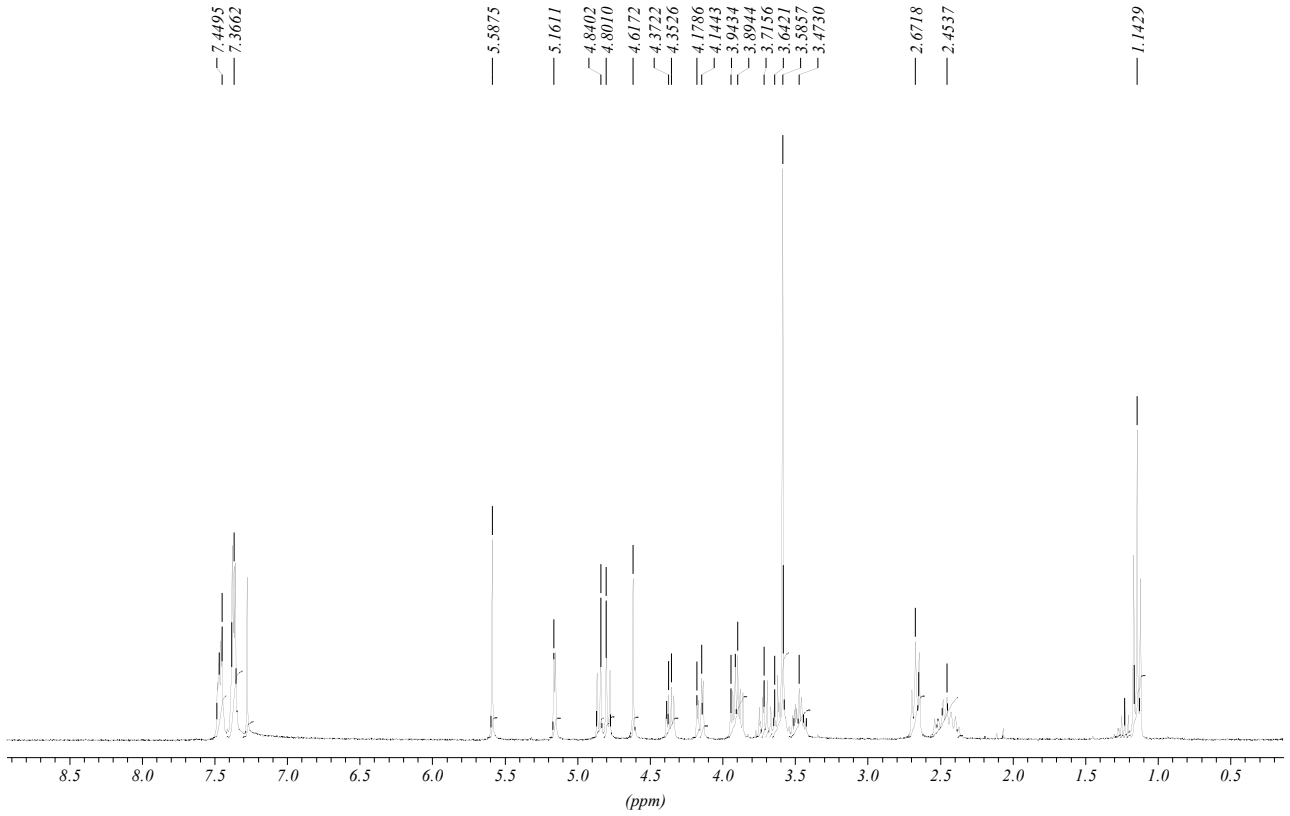

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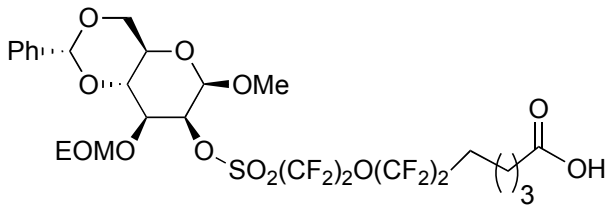

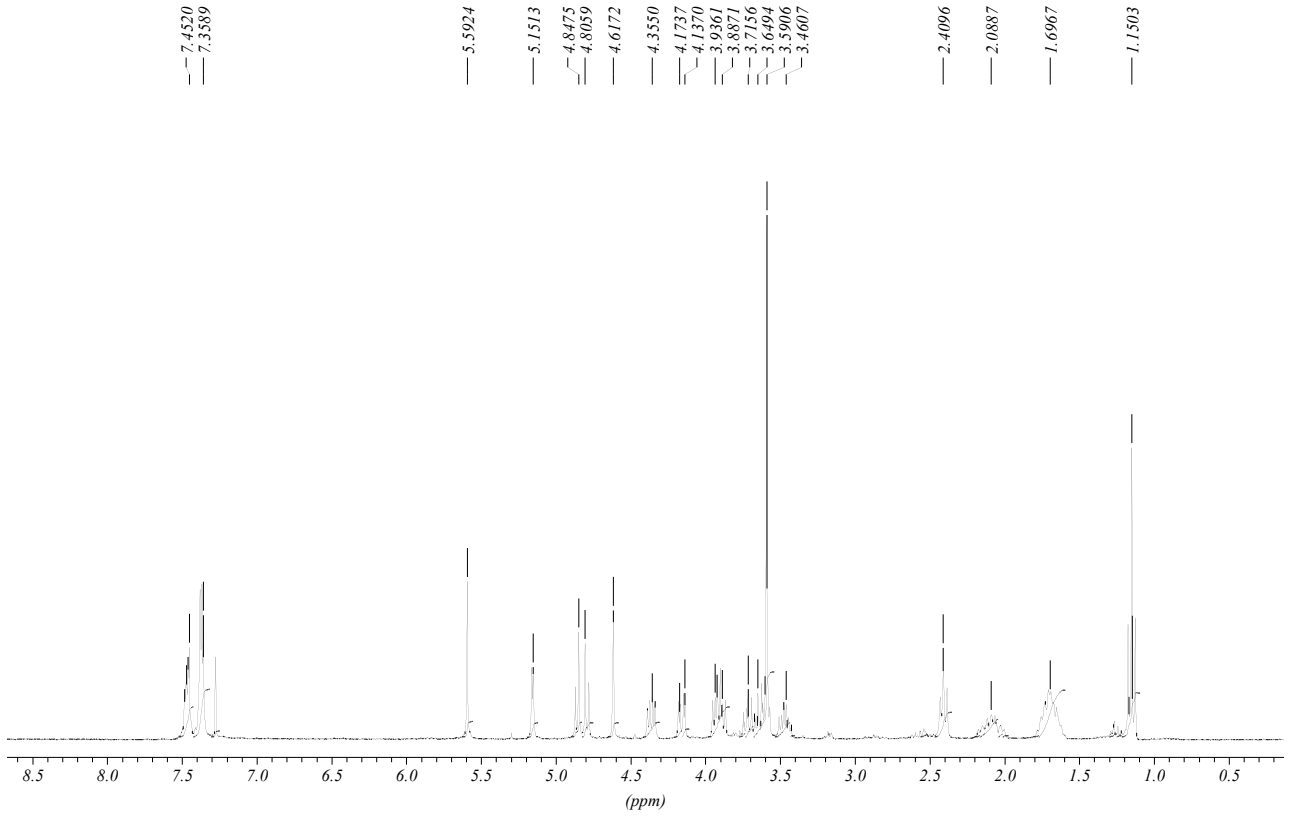

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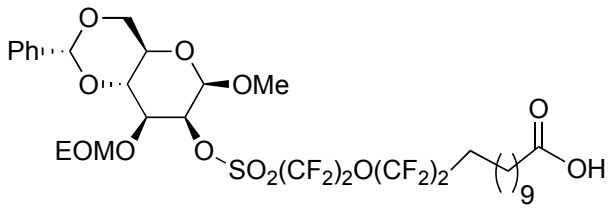

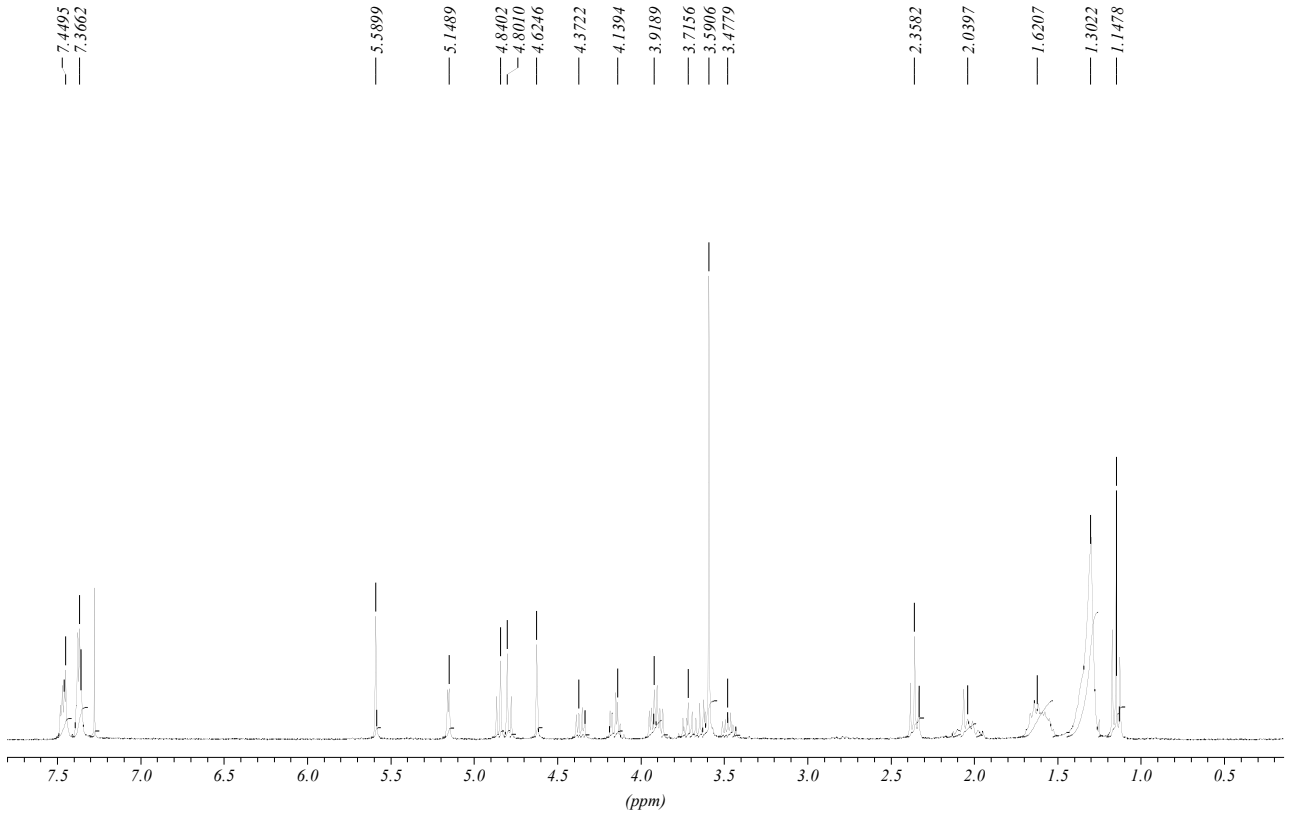

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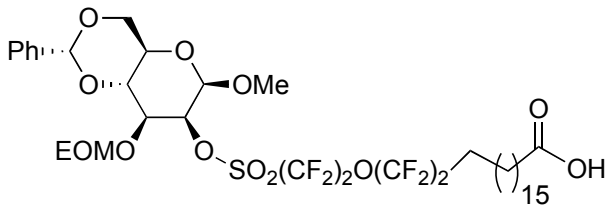
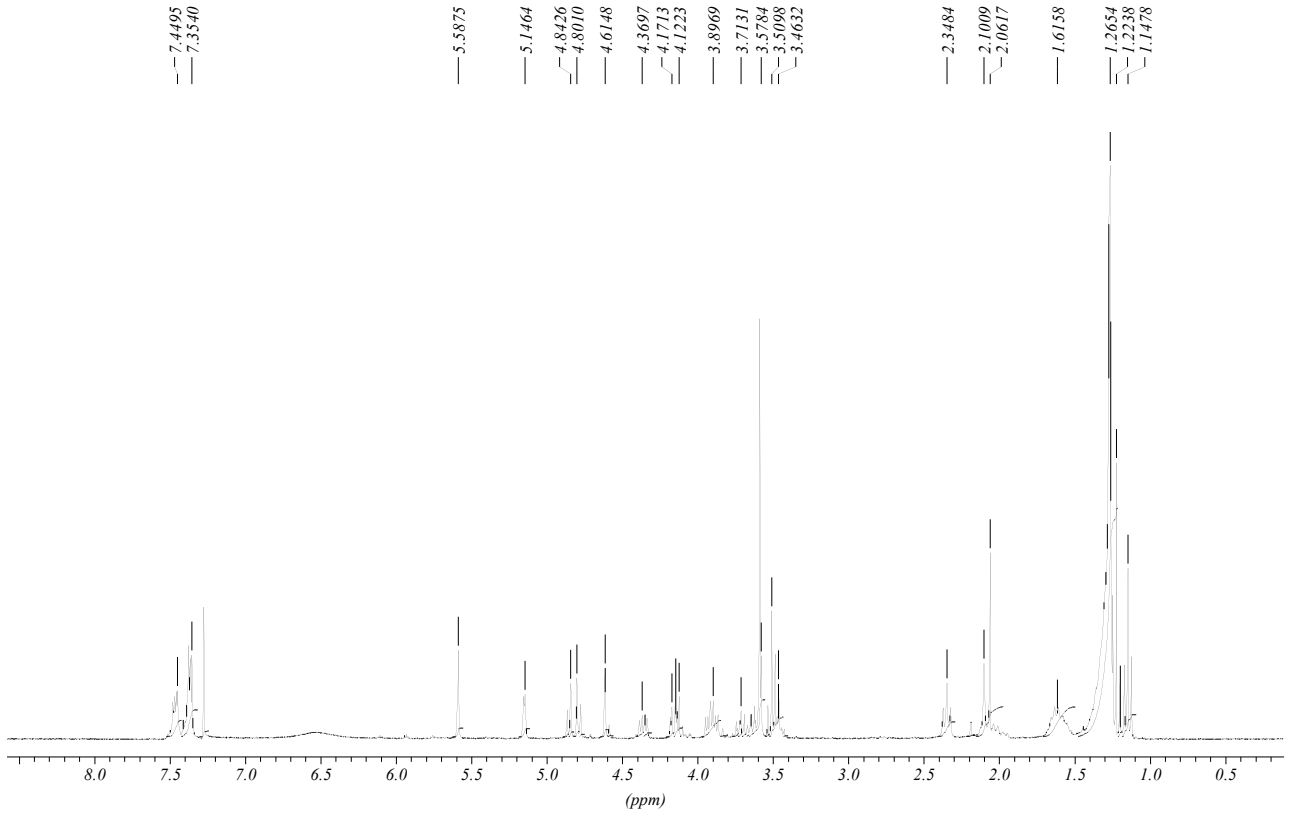
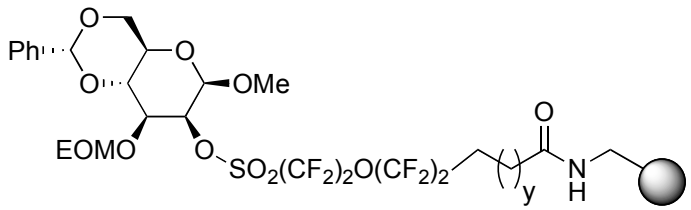




Gel-Phase ^{19}F NMR Compound **33** (Ref. $CFCl_3$)



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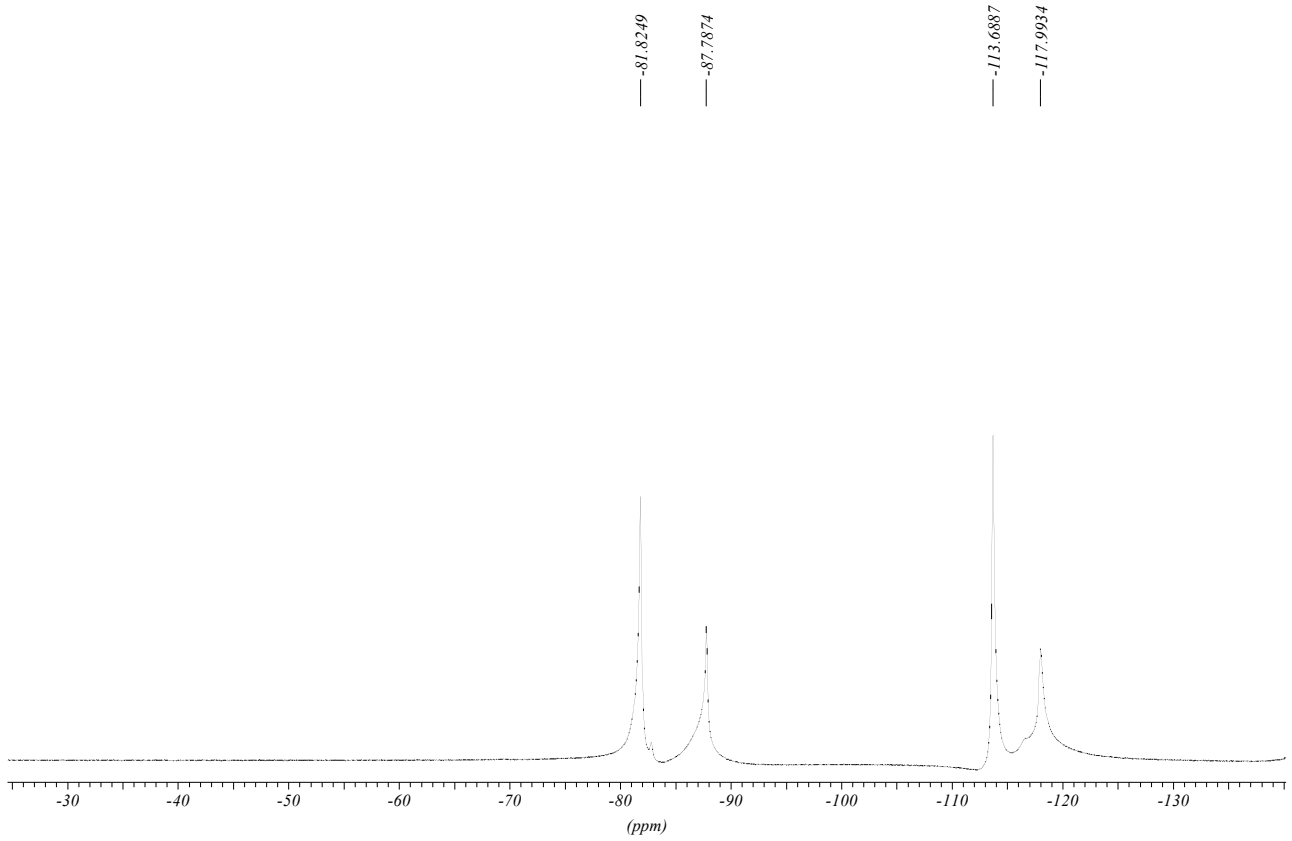
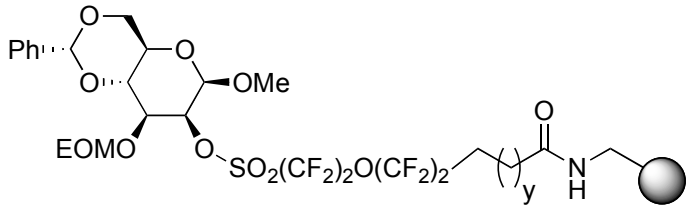


Gel-Phase ^{19}F NMR Compound **34** (Ref. $CFCl_3$)



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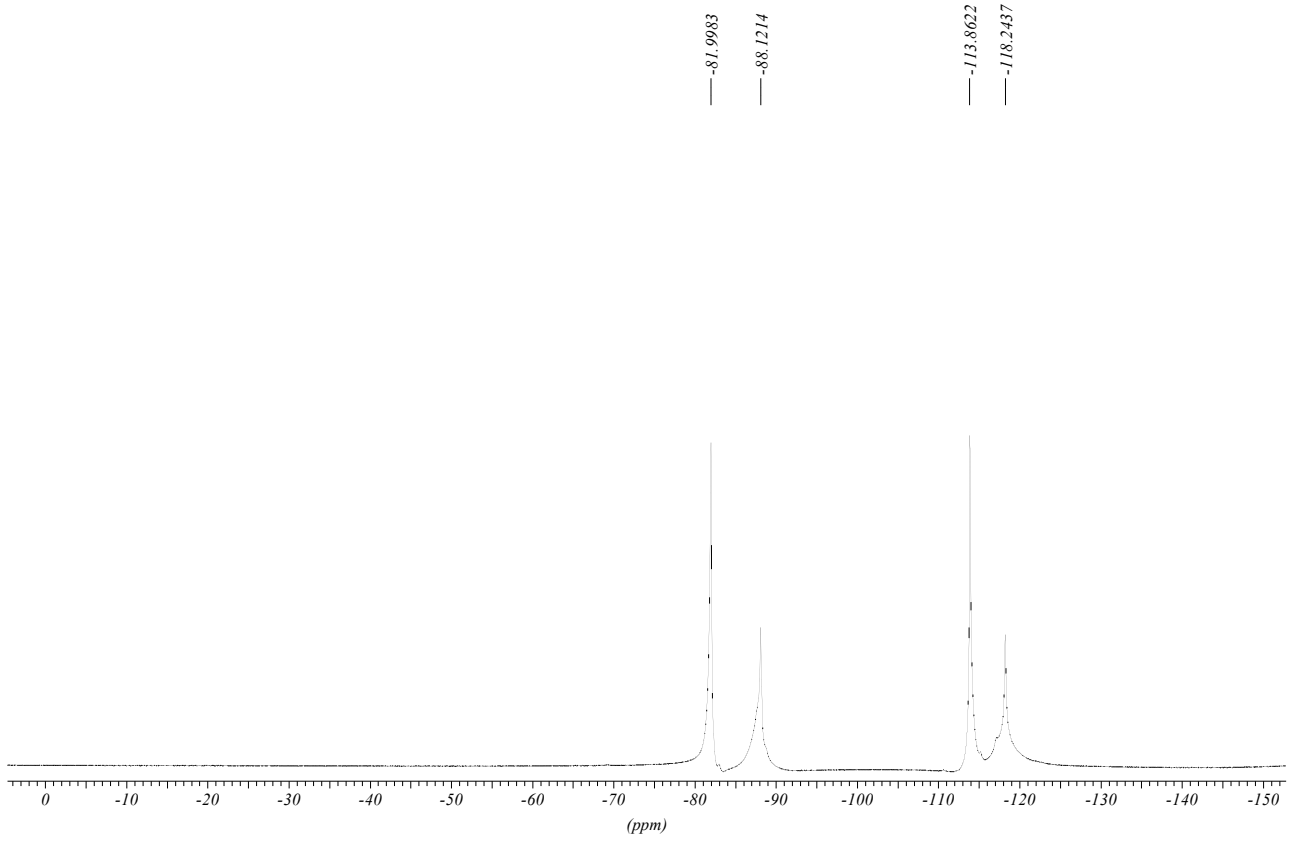
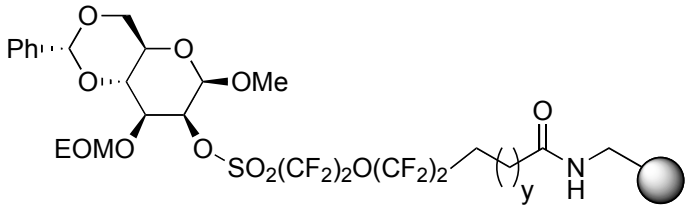
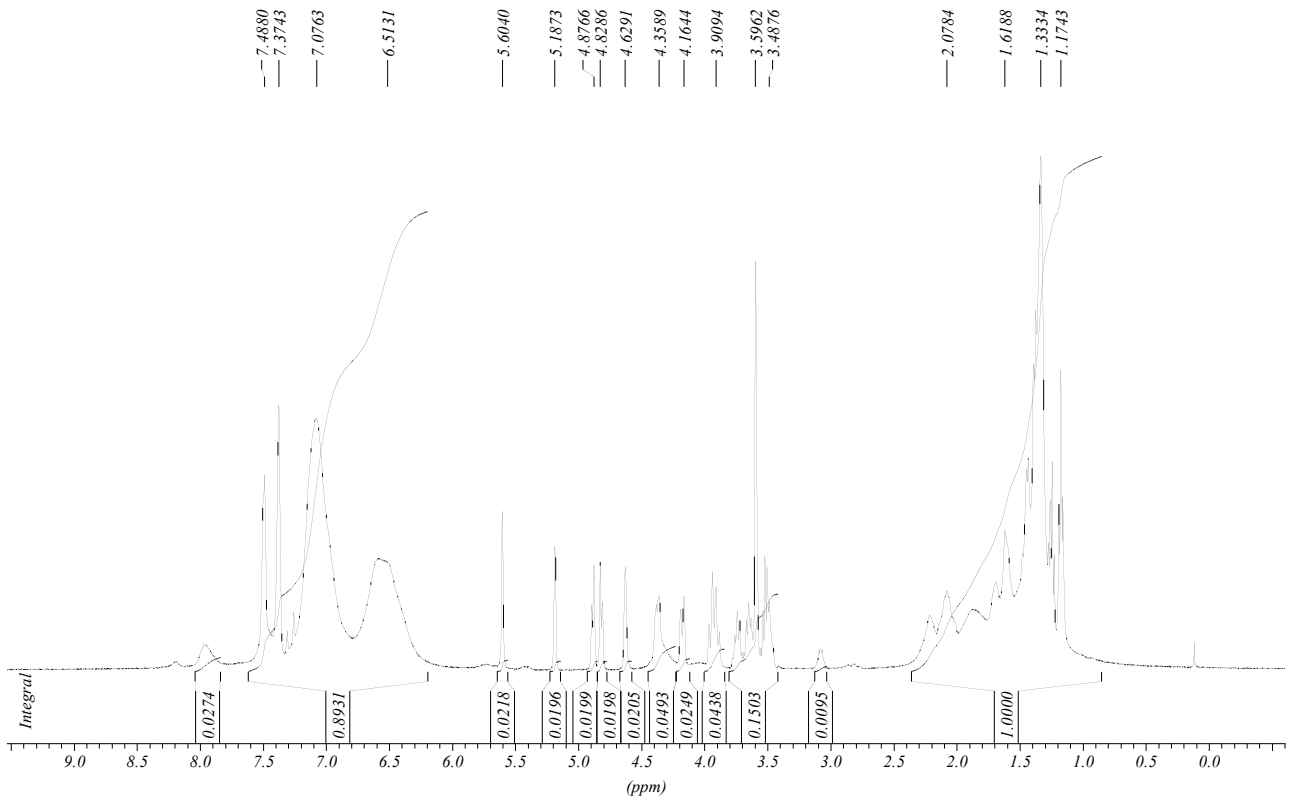


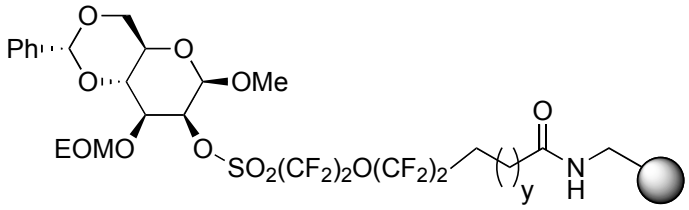
MAS ^{1}H NMR Compound **35** (0.59 mmol/g)



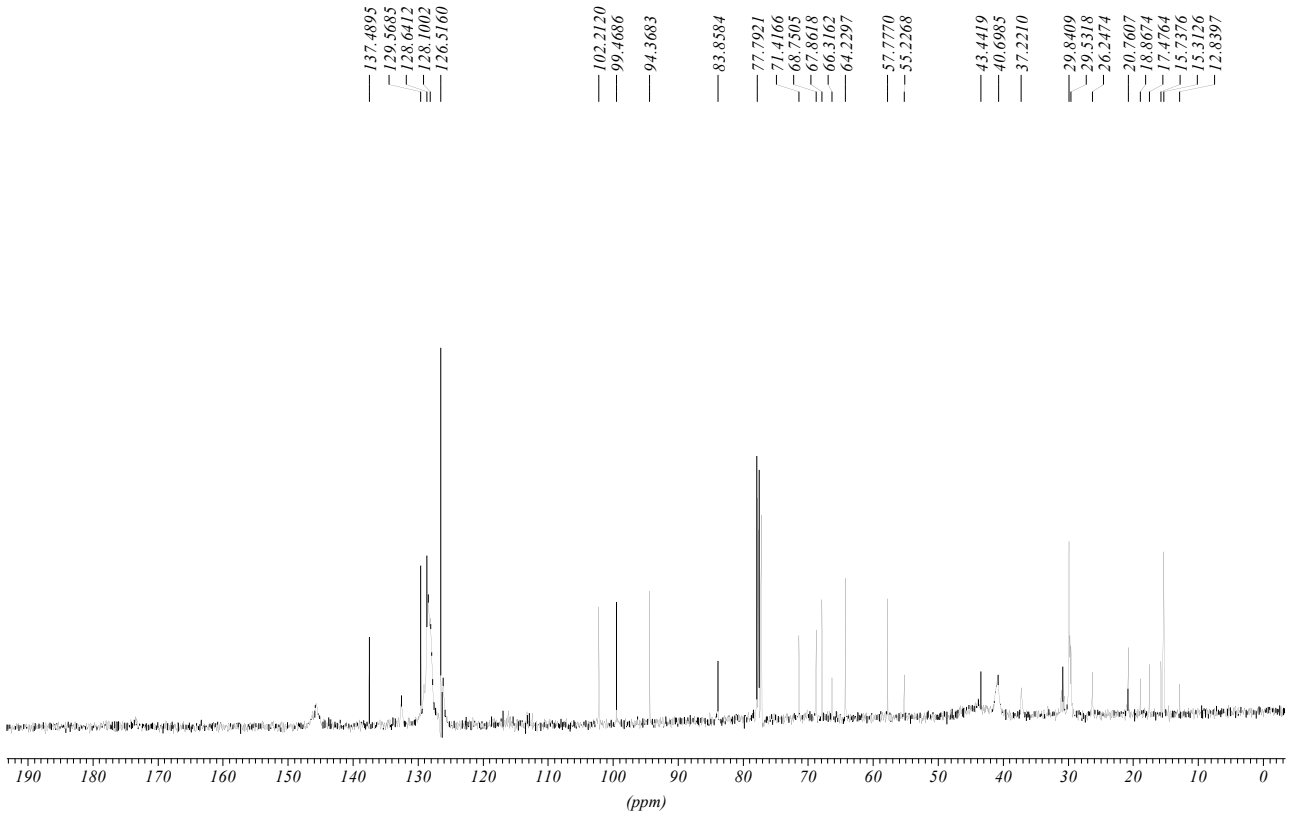
35 y = 9



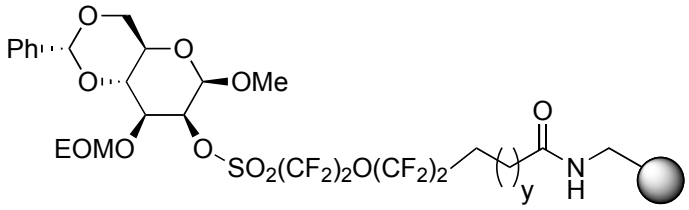
MAS ^{13}C NMR Compound **35** (0.59 mmol/g)



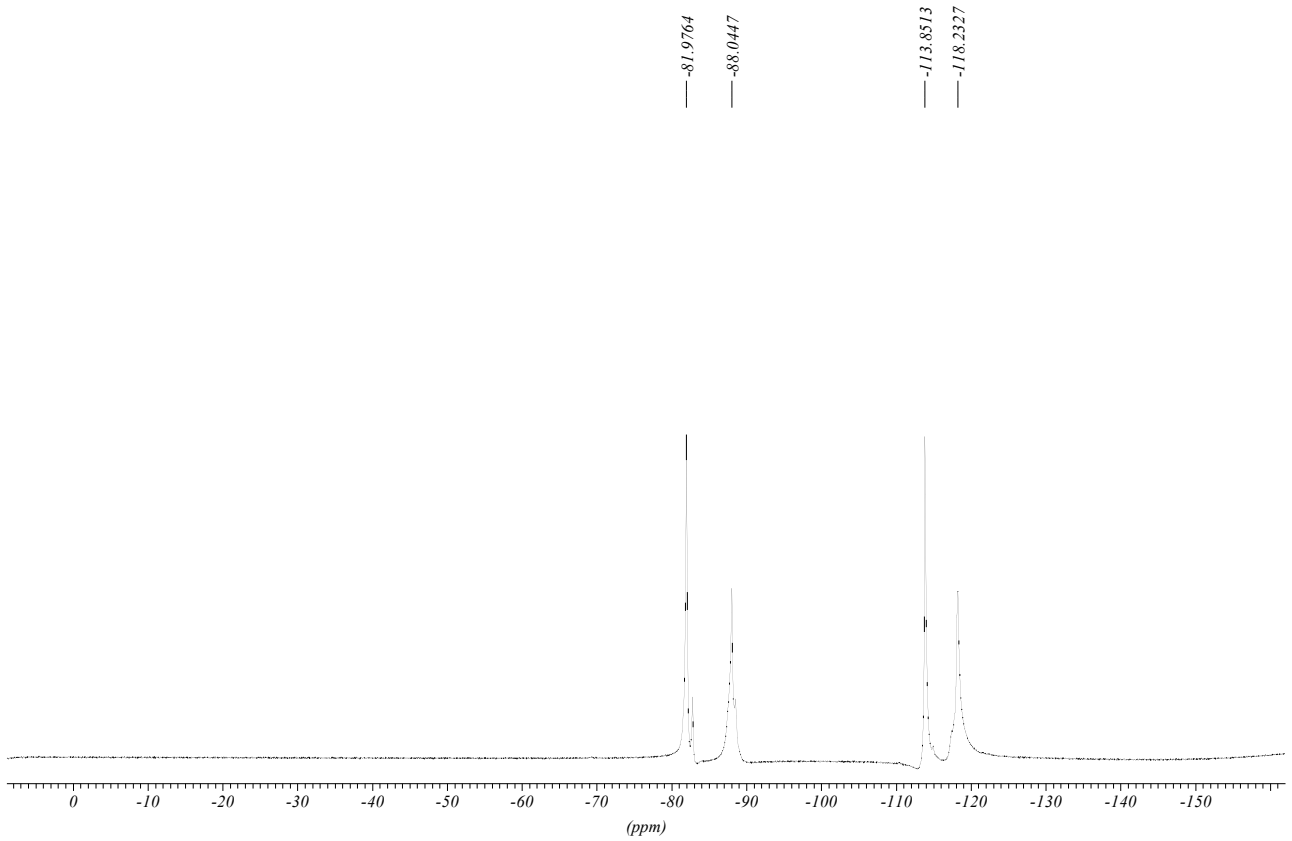
35 y = 9



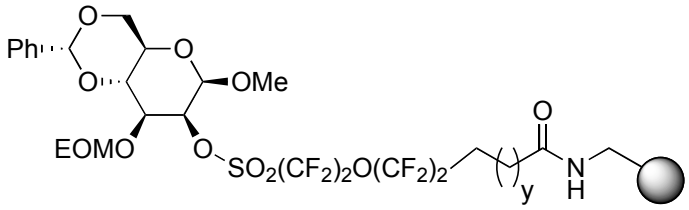
Gel-Phase ^{19}F NMR Compound **35** (Loading: 0.59 mmol/g, Ref. $CFCl_3$)



35 y = 9

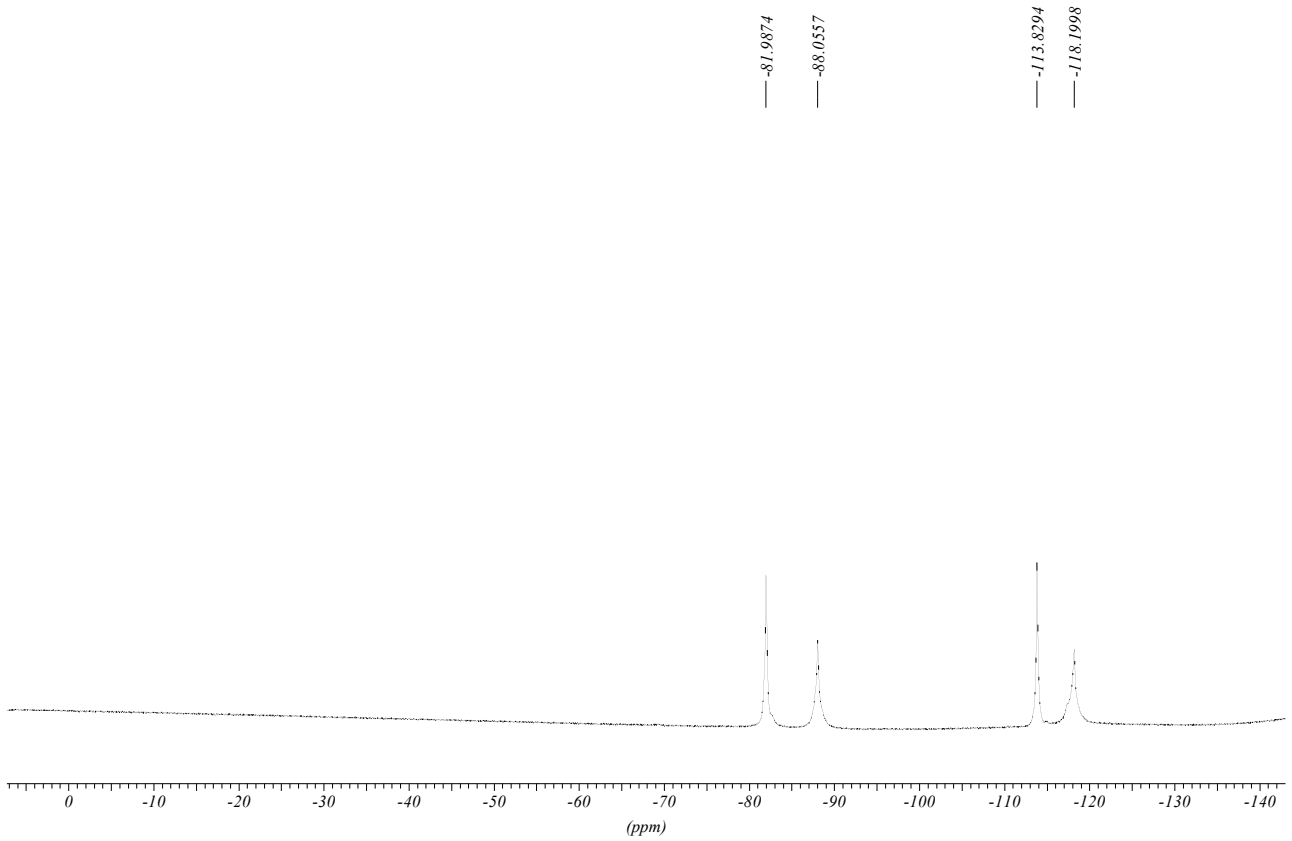


Gel-Phase ^{19}F NMR Compound **35** (Loading: 0.1 mmol/g, Ref. $CFCl_3$)

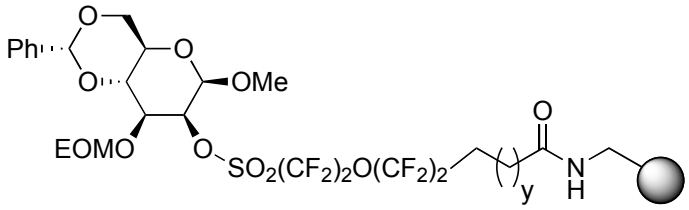


35 y = 9

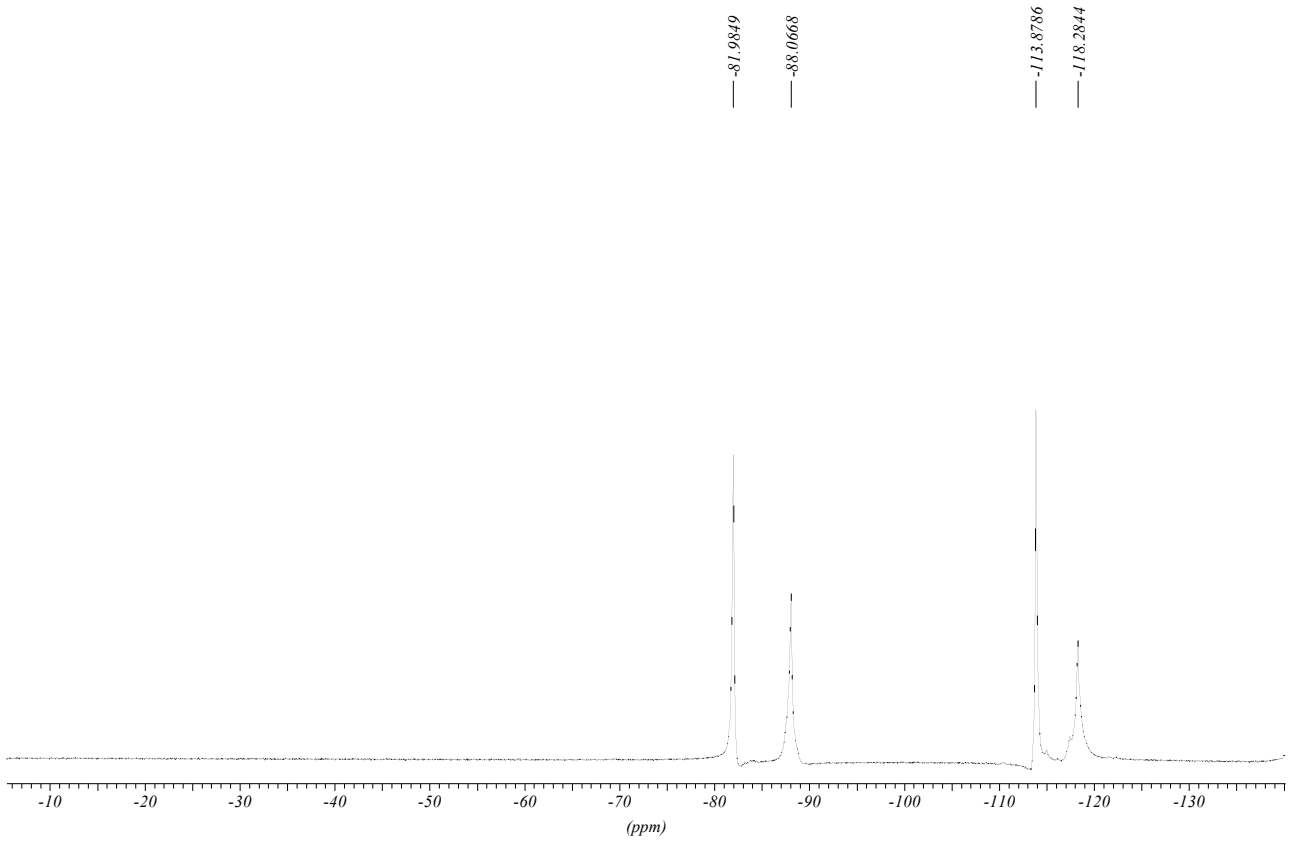
Gel phase 19F NMR referenced to CFCl3 (external) Compound 35 (0.1 mmol/g)



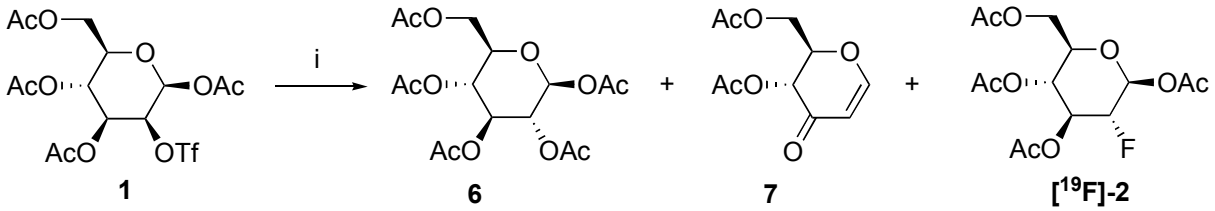
Gel-Phase ^{19}F NMR Compound **36** (Ref. $CFCl_3$)



36 y = 15

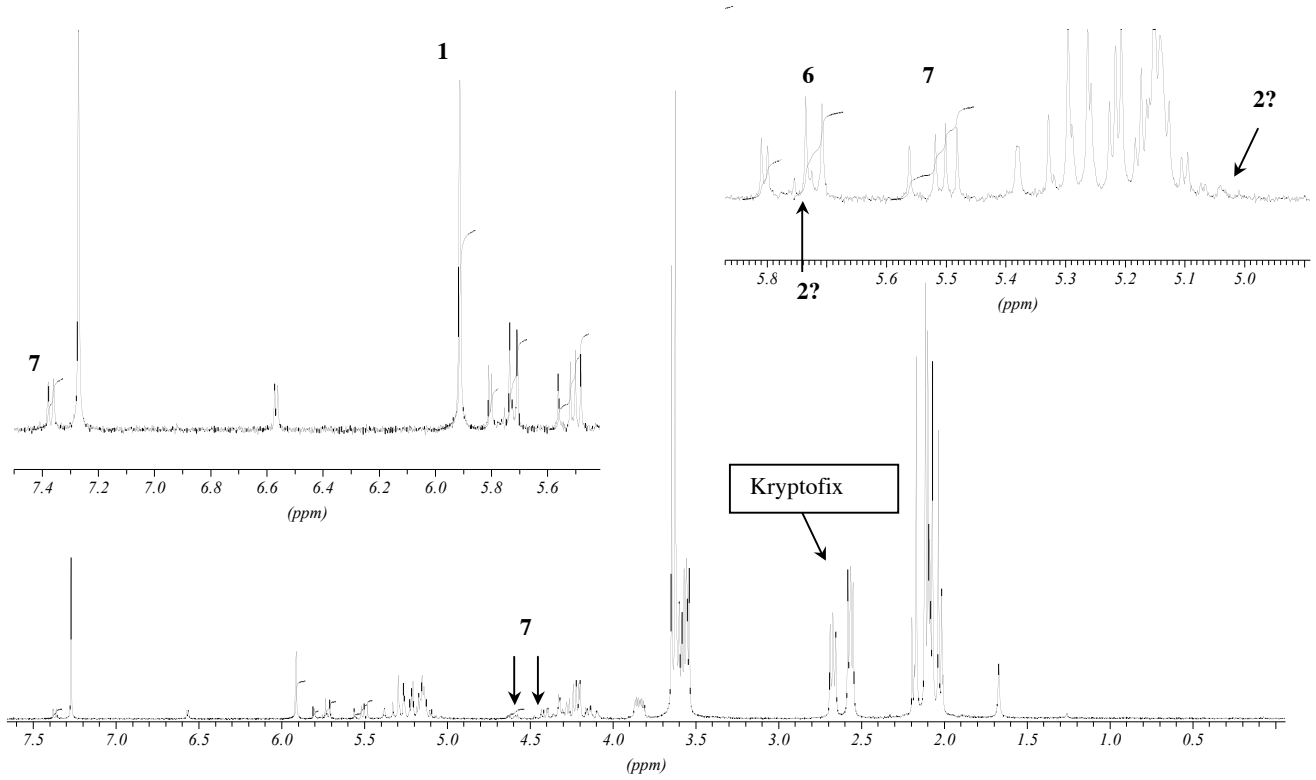


^{1}H NMR for fluoridation of **1** using K^{19}F/Kryprofix (crude). Reaction is incomplete with remaining **1**, elimination product **7** and acetate displacement product **6** clearly visible. Protected FDG **2** is not obvious in the spectrum, but we were able to isolate minor amounts (<5%) of **[^{19}F]-2** using this process.

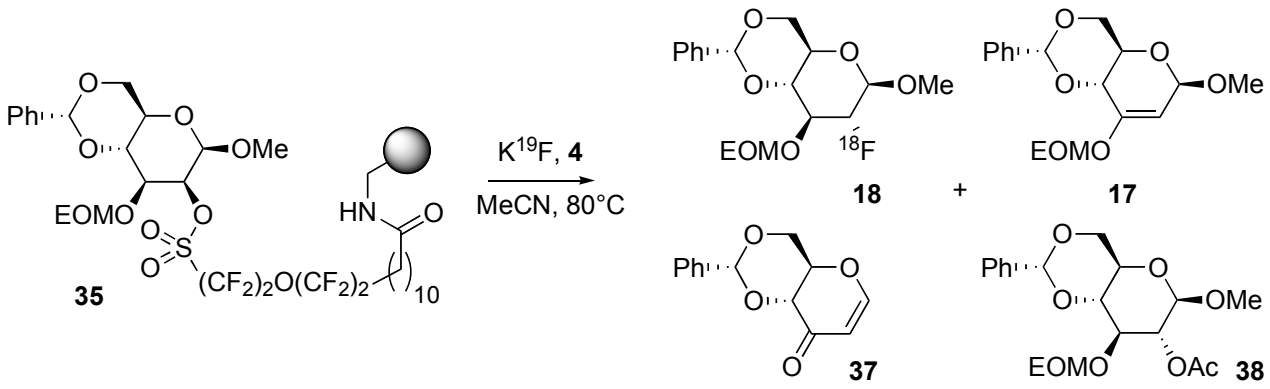


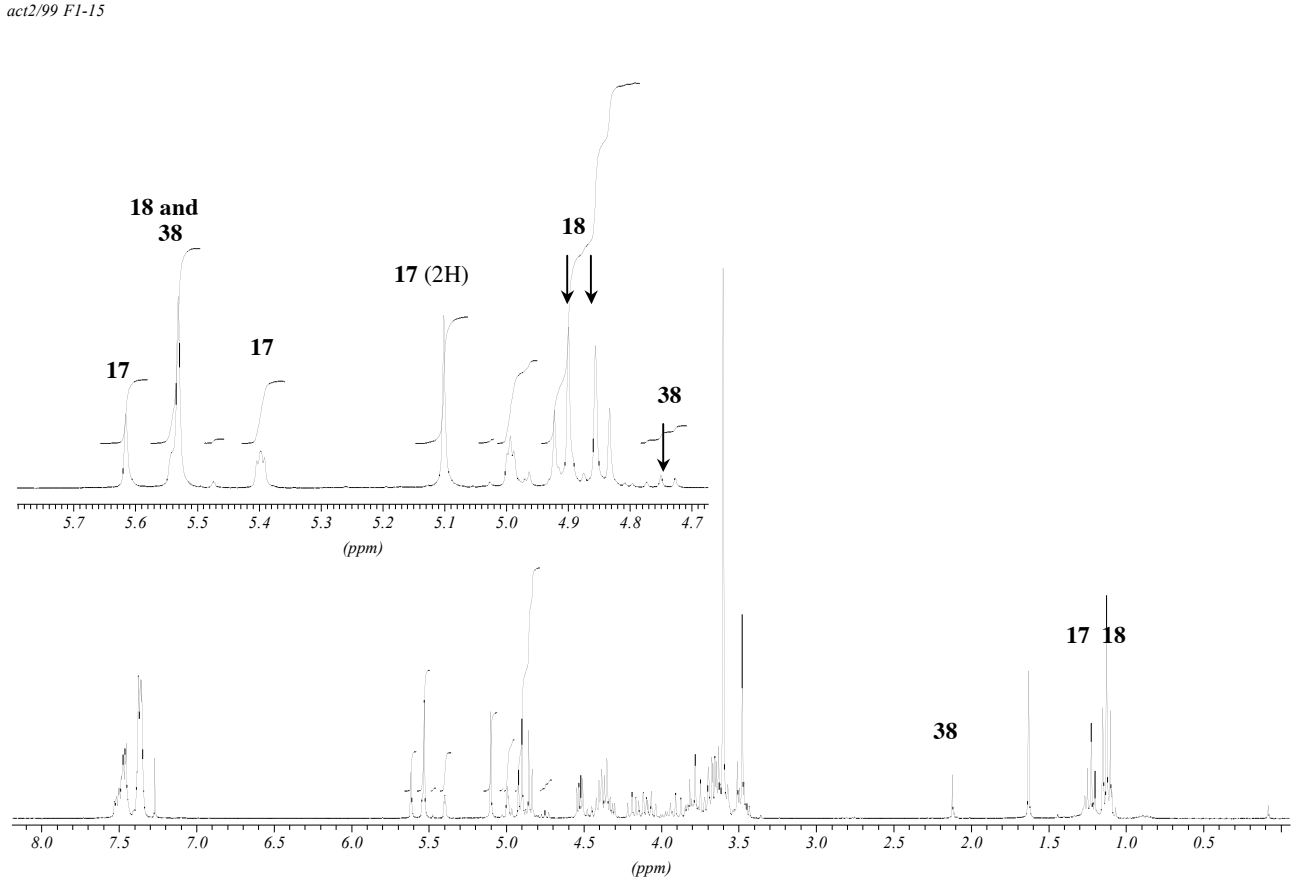
(i) K^{19}F, Kryptofix (**4**), MeCN, 80°C

Fluoridation of Compound 1



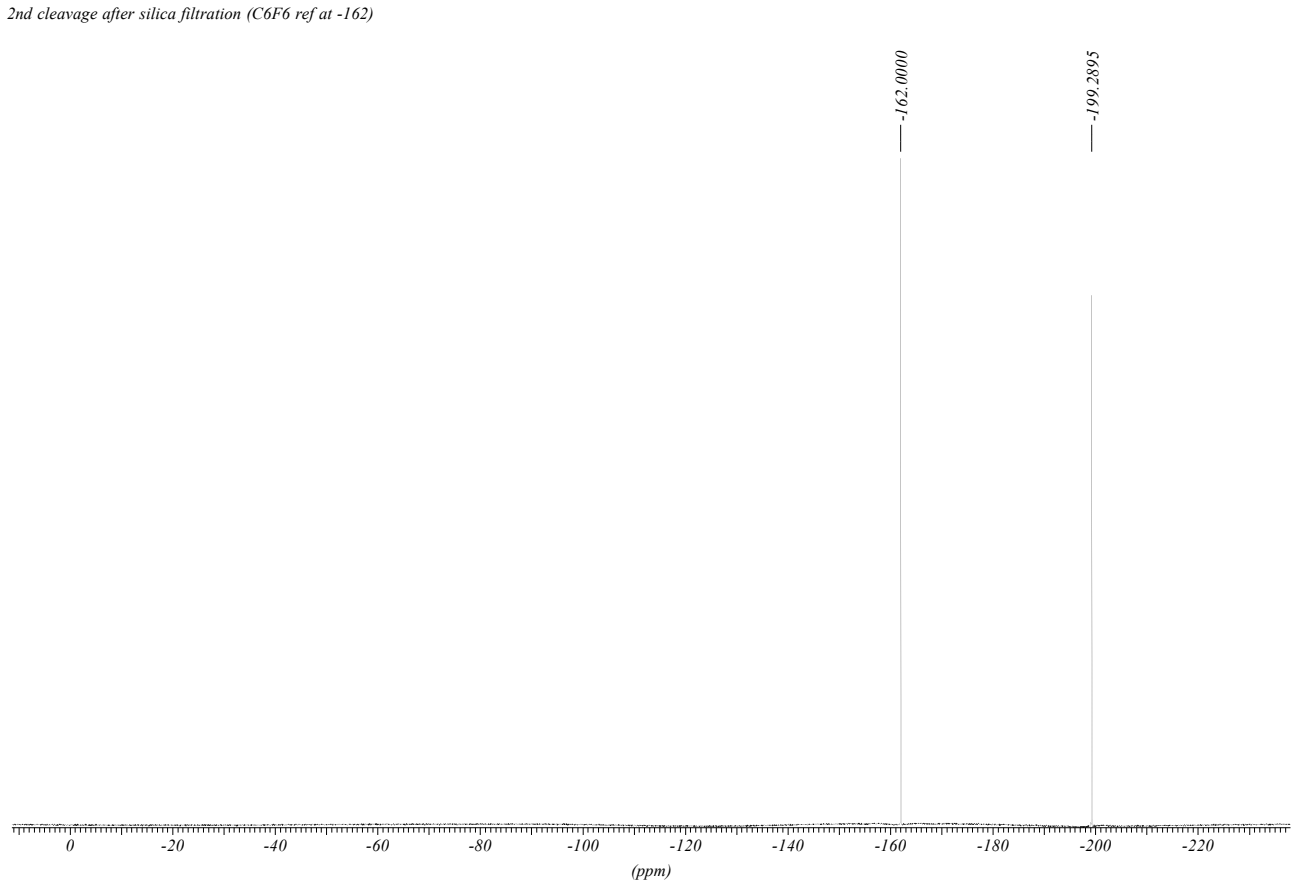
^{1}H NMR of the cleavage reaction mixture obtained from treatment of resin **35** (0.1 mmol/g) with K^{19}F/Kryptofix after filteration through a silica plug. In contrast to the solution-phase fluoridation of **2**, the protected FDG **18** can clearly be seen as the major product.



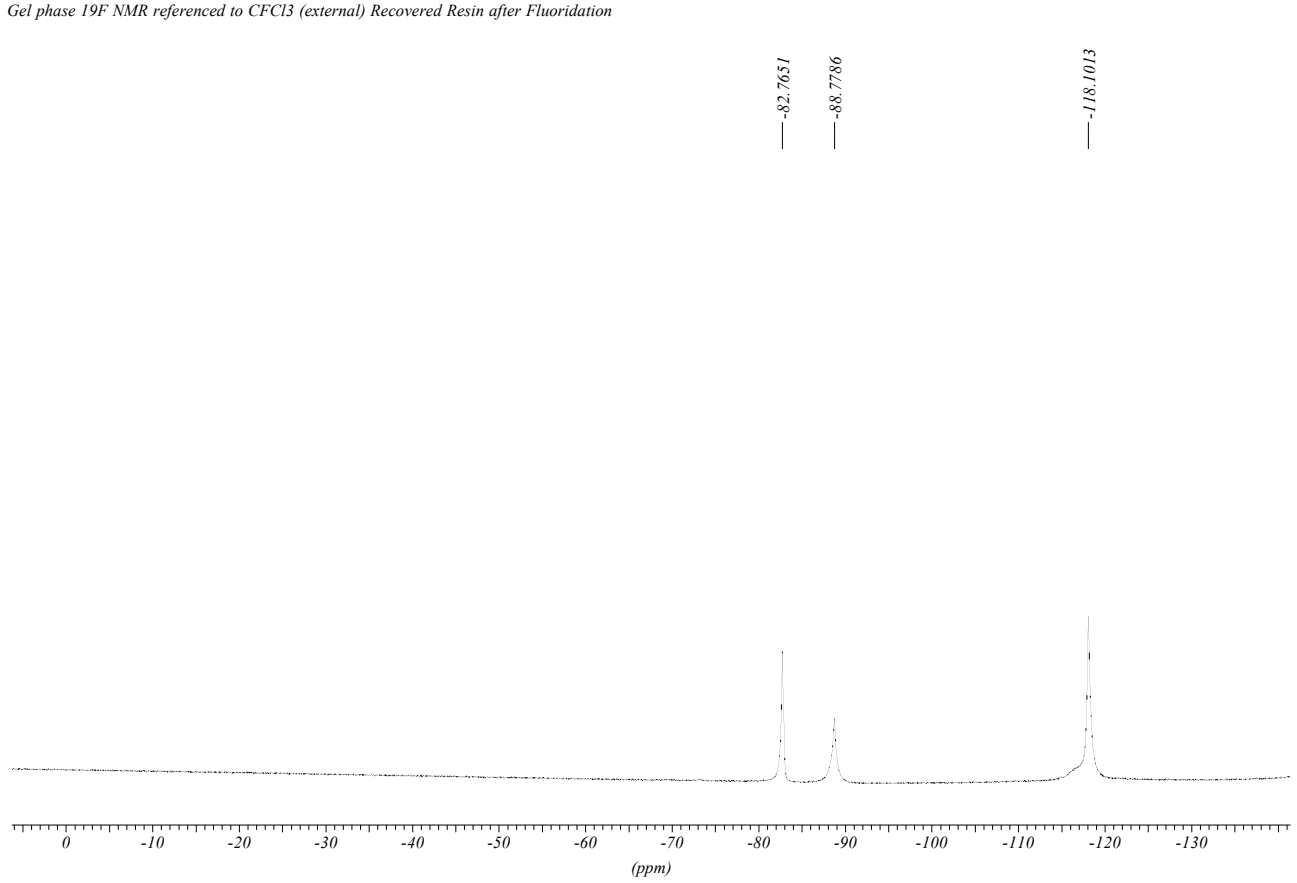


^{19}F NMR of the cleavage reaction mixture obtained from treatment of resin **35** (0.1 mmol/g) with K^{19}F/Kryptofix after filteration through a silica plug. Referenced to CCl_3F.

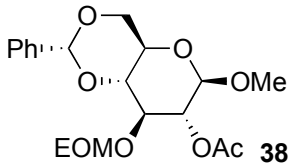
Peak at 162 ppm is C_6F_6 internal standard.

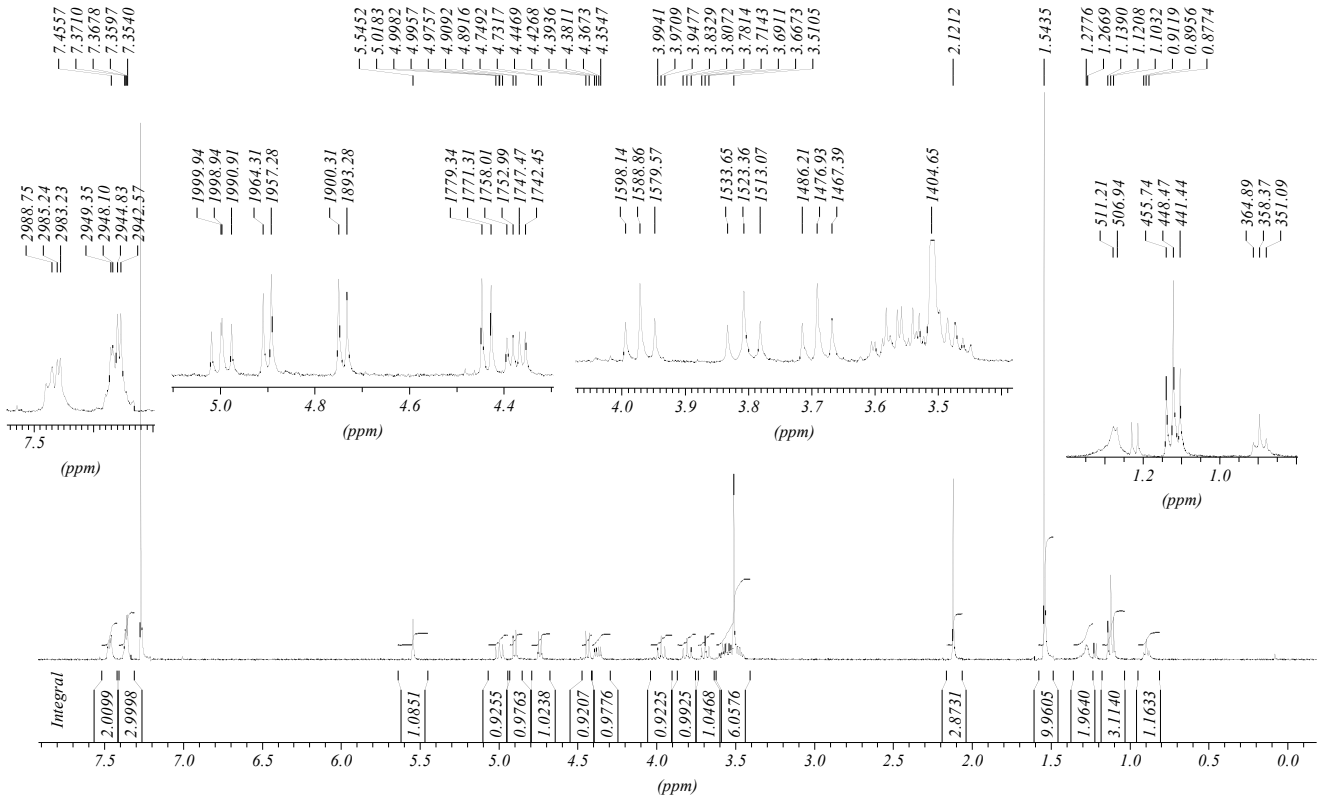


Resin recovered after fluoridation of resin **35** (0.1 mmol/g) with excess $K^{19}F$.



^{1}H NMR Compound **38**





Qualitative comparison of the chemical purity of the crude protected FDG [^{18}F]-18 from the resin precursor 35 against the crude protected FDG product [^{18}F]-2 obtained by conventional solution synthesis.

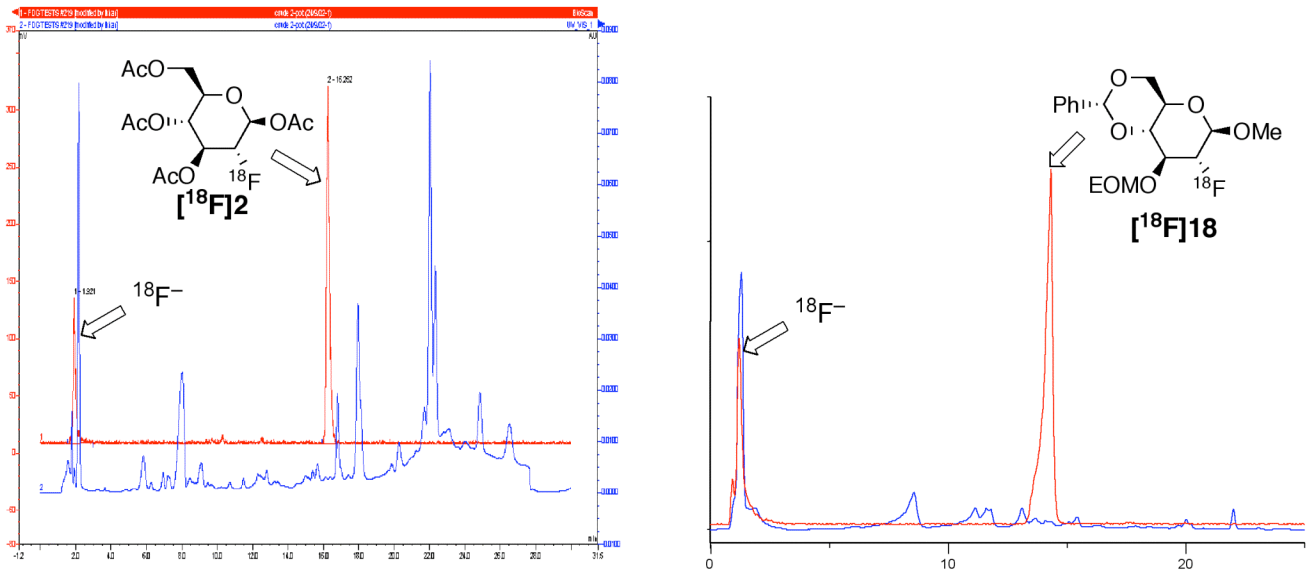


Figure 1. Reversed-phase HPLC chromatograms (C_{18} column) of the crude protected products **[^{18}F]-2** and **[^{18}F]-18** from conventional solution-phase FDG synthesis (left) and from the solid-phase precursor **35** (right). Red trace: Radioactivity; Blue trace: UV activity (210 nM).

The left chromatograms are of the crude product of a conventional solution tetracetoxy manose triflate fluoridation reaction before removal of unreacted [^{18}F]fluoride ion and Kryptofix. The blue UV trace indicates that a wide range of starting material decomposition products are produced. The red radioactive trace shows that there are only two radioactive materials present identified as fluoride running near the origin and the main radioactive peak of tetraacetoxy [^{18}F]FDG (**[^{18}F]-2**).

The right chromatograms are of the crude product of fluoridation of the solid phase precursor **35** before removal of the fluoride ion and Kryptofix. The blue UV trace shows that apart from material eluting from the column near the origin there is relatively less UV active material released from the solid phase. The radioactive (red) trace shows that there are two radioactive materials present. The peak eluting near the origin is assigned to unreacted [^{18}F]fluoride ion and the peak near 14 minutes is assigned as the protected [^{18}F]FDG (**[^{18}F]18**).