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The synthesis of mono- and difluorinated 2,3-dideoxy-D-glucopyranoses

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ABSTRACT

The synthesis of 2,3-dideoxy-2,3-difluoro-D-glucose and 2,3-dideoxy-3-fluoro-D-glucose is reported in, respectively, 5 and 6 steps from D-glucal, using a fluorination strategy.

1. Introduction

Carbohydrates are central to many fundamental processes [1], and the glycosylation of proteins and natural products can have a significant impact on their biological activity [2]. Yet, the affinity of carbohydrates to proteins is typically rather low, which mainly originates from their highly hydrophilic character. The design of carbohydrate-based analogues with greater affinity to carbohydrate-processing proteins is of interest for use as probes or therapeutics [3].

An appealing strategy to increase protein–carbohydrate affinity consists of replacing multiple CHOH groups in the sugar ring with CF_2 groups [4], thus creating a hydrophobic environment without significantly altering the shape of the sugar. Hydrophobic desolvation is known to increase affinity, and perfluoroalkyl desolvation energy is higher compared to that of hydrocarbons, due to their larger surface [5]. In addition, the highly polarised C–F bond is able to engage in stabilising electrostatic interactions with various cationic or polar protein residues [6]. These are weak interactions, but negligible in aqueous medium (when the ligand is in the unbound state). The combination of these two effects has been coined 'polar hydrophobicity' [4]. It has been demonstrated that a hexafluorinated pyranose **1** (Fig. 1) crosses the erythrocyte membrane 10 times as fast as D-glucose [4]. This process is transporter-mediated, and the result was interpreted as due to a better binding of the ligand to the protein. Interestingly, the corresponding 2,3,4-trideoxy-2,3,4-trifluoro-D-glucose **2** was shown to have a slightly lower transport rate than D-glucose [7].

Our group has been involved in the synthesis of heavily fluorinated sugars, such as tetrafluorinated D-glucose **3** [8], that still contain a non-anomeric chiral alcohol group within the ring, believed to be important for the selectivity aspect of binding events involving carbohydrates [9]. The difference in membrane transport rates between **1** and **2** clearly illustrates the fundamental difference between the two fluorination motifs of these sugars. Key parameters include a difference in molecular lipophilicity, hydrogen bond accepting/donating properties of the adjacent alcohol groups [10], and the electron density of the fluorine atoms involved (as illustrated by their different chemical shift values) impacting on their capacity for intermolecular interactions with proteins [11].

Hence, we became interested to extend our studies involving **3** to D-glucose analogues with a hydrophobic moiety at C2–C3 (or C3–C4) having a lighter fluorination pattern. Here we describe the synthesis and characterisation of the novel sugars 2,3-dideoxy-2,3-difluoro-D-glucose **4** (Fig. 2) and 2,3-dideoxy-3-fluoro-D-glucose **5** from a common precursor [12].

2. Results and discussion

The common intermediate, 1,6:2,3-anhydro-4-*O*-benzyl-β-D-mannopyranose **6** (Scheme 1) was obtained in two steps from

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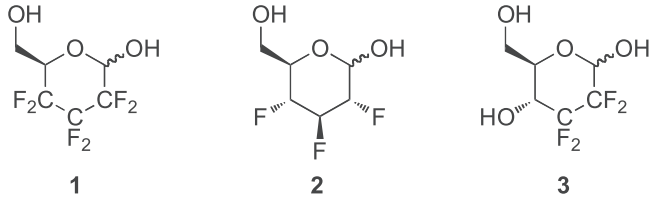


Fig. 1. Fluorinated D-glucose derivatives.

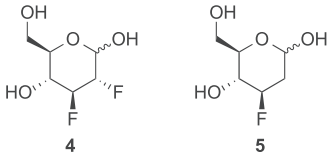


Fig. 2. Target D-glucose derivatives.

D-glucal as described, using well-established methodology [13–15]. From **6**, the synthesis of **4** started by a regioselective epoxide opening with potassium hydrogen bifluoride in refluxing ethylene glycol [16–17], in a reasonable 65% yield (74% on small scale). Jensen recently reported a 40% yield under these conditions, which they could improve to 69% when conducted in a sealed vessel under microwave conditions at 220 °C [18]. However, in our hands this procedure gave lower yields. DAST-mediated deoxofluorination of the 3-OH, already described by Sarda et al. [19], gave the difluoride **8** in excellent yield. As noted by Sarda et al. [19], the retention of configuration was clearly proven by the small $^{3}J_{H3-H2/4}$ values (<5 Hz). In addition, given the axial position of the OBn substituent, the $^{2}J_{C4-F}$ value of 26.3 Hz clearly indicates an axial C–F bond, and the small (2.3 Hz) $^{3}J_{C5-F}$ value indicates a *gauche* dihedral angle between C3–F and C4–C5 [20]. This stereochemical outcome may be due to anchimeric assistance by the axial benzyloxy group [21], given the steric hindrance exerted by the axial OBn and F groups at C4 and C2. Benzyl deprotection and concomitant anomeric hydrolysis was achieved in one pot by treatment of **8** with BCl_3 followed by quenching with water, leading to pure **4** in 79% yield.

The resulting chair inversion in comparison with the levoglucosan **8** was clearly observed from ^{13}C NMR analysis in that the abovementioned 26.3 Hz $^{2}J_{C4-F}$ value reduced to 17.6 Hz, (equatorial F *gauche* to C4–OH) [22]. The $^{3}J_{C5-F3}$ value increased to 8.0 Hz in **4**, indicating the equatorial C3–F is antiperiplanar to C4–C5.

The synthesis of **5** is shown in Scheme 2. Regioselective epoxide reduction [22] of **6** led to the 2-deoxyderivative **9** in excellent yield. On larger scale (±4 g), a workup involving dilution with Et_2O and addition of $MgSO_4$ after quenching with water/aq. NaOH was found important to ensure consistent high yields. Deoxofluorination reaction with DAST then gave **10**. Interestingly, this deoxyfluorination proceeded again with overall retention of configuration, despite no axial C–F bond is now present at C2. This was again clear from the small $^{3}J_{H3-H2/4}$ coupling values (<5 Hz), the $^{2}J_{C4-F}$ value of 26.2 Hz, and the very small (in this case unobserved) $^{3}J_{C5-F}$ value (indicating a *gauche* dihedral angle between C3–F and C4–C5). The 1,6-anhydro derivative **10** was hydrolysed in excellent yield to give the 4-*O*-benzyl pyranose **11**, which was easily purified. The resulting chair inversion going from **10** to **11** was again clear from ^{13}C NMR analysis, in that the $^{2}J_{C4-F}$ value reduced to a value of 16.1 Hz, and the $^{3}J_{C5-F}$ value increased to 8.1–9.5 Hz, all indicative of an equatorial C–F bond. Final hydrogenolysis then resulted in colourless **5** in almost quantitative yield.

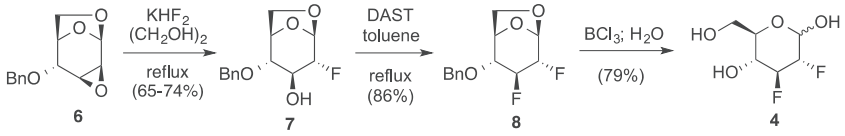
3. Conclusion

The novel sugars 2,3-dideoxy-2,3-difluoro-D-glucose, and its lighter fluorinated analogue, 2,3-dideoxy-3-fluoro-D-glucose, have been synthesised from D-glucal. A sugar fluorination approach has been employed, with the fluorine at the 2-position introduced by fluoride mediated epoxide opening, and the fluorine at the 3-position by a deoxofluorination reaction. Interestingly, the latter reaction proceeded with retention of configuration, even when the 2-position is unsubstituted. All steps proceeded in excellent yield. These sugar analogues having a hydrophobic domain within the ring will be used as probes to study the physical and biological properties of this class of compounds. This work is in progress in our group.

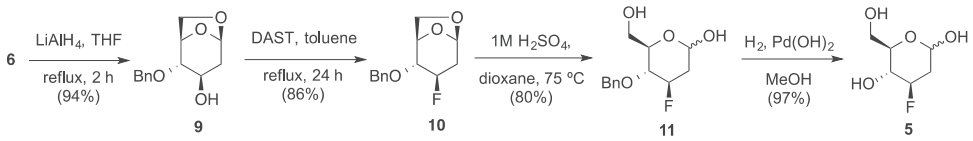
4. Experimental

*4.1. 1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranoside (**7**)*

The epoxide **6** (0.515 g, 2.20 mmol) was boiled with potassium hydrogen difluoride (10.280 g, 131.57 mmol) in ethylene glycol (40 mL) for 2.5 h under nitrogen. After completion of the reaction, the mixture was cooled and then poured into 5% K_2CO_3 (20 mL). The mixture was then extracted with chloroform (5 × 30 mL). After drying over $MgSO_4$ and evaporation of solvent, the obtained syrup was chromatographed on silica gel (chloroform/acetone 95:05) and afforded **7** as a colourless oil (0.412 g, 1.62 mmol, 74%). **Mw** 254.25 ($C_{13}H_{15}FO_4$); **Rf** 0.32 (chloroform/acetone 95:05); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (5H, m, H_{Ar}), 5.56 (1H, d, *J* 5.4 Hz, H_1), 4.73 (1H, d, *J* 12.2 Hz, H_7), 4.67 (1H, d, *J* 12.2 Hz, $H_{7'}$), 4.63 (1H, br. d, *J* 4.6 Hz, H_5), 4.27 (1H, br. dd, *J* 47.4, 3.2 Hz, H_2), 4.01 (1H, m, *J* 19.6 Hz can be observed, H_3), 3.89 (1H, br. dd, *J* 7.6, 0.5 Hz, H_6), 3.70 (1H, br. dd, *J* 7.3, 5.4 Hz, $H_{6'}$), 3.35 (1H, br. d, *J* 3.2 Hz, H_4) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.5 (C_{Ar}), 128.6 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 99.7 (d, *J* 30.1 Hz,C_1), 89.9 (d, *J* 183.4 Hz,C_2), 78.4 (d, *J* 6.6 Hz,C_4), 75.1 (C_5), 71.8 (C_7), 70.2 (d, *J* 26.4 Hz,C_3), 66.3 (C_6) ppm;



Scheme 1. Synthesis of **4**.



Scheme 2. Synthesis of **5**.

^{19}F NMR (376 MHz, $CDCl_3$) δ − 187.8 (1F, ddd, *J* 47.8, 20.0, 5.2 Hz). NMR data correspond to literature data [18].

4.2. 1,6-Anhydro-4-O-benzyl-2,3-dideoxy-2,3-difluoro-β-D-glucopyranoside (**8**)

To a solution of **7** (4.3 g, 16.91 mmol) in dry toluene (80.0 mL) DAST was added slowly (11.17 mL, 84.56 mmol) at rt. The mixture was refluxed under nitrogen atmosphere for 24 h when TLC indicated completion of the reaction. Quenching of excess reagent was carried out by adding dry MeOH (10 mL) very slowly at −20 °C. The solvent was evaporated and the sample dried under high vacuum. Column chromatography (EtOAc/PE 20:80) with addition of 0.5% TEA afforded **8** as a colourless oil (3.67 g, 86%). **Mw** 256.25 ($C_{13}H_{14}F_2O_3$); **Rf** 0.38 (EtOAc/PE 20:80); **$[\alpha]_D$** − 33.4 (c 1.00, acetone, 24 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 − 7.29 (5H, m, H_{Ar}), 5.58 (1H, br. d., *J* 3.0 Hz, simplifies to s upon F-decoupling, H_1), 4.77 (1H, m, *J* 44.3, 16.1 Hz can be observed, which disappear upon F-decoupling, H_3), 4.78 (1H, d, *J* 12.2 Hz, H_7), 4.68 (1H, d, *J* 12.4 Hz, $H_{7'}$), 4.66 (br. dd, *J* 5.7, 1.0 Hz, simplifies to d, *J* 1.0 Hz upon F-decoupling, H_5), 4.42 (1H, br. dd, *J* 45.6, 15.6 Hz, simplifies to bs upon F-decoupling, H_2), 3.87 (1H, d, *J* 7.3 Hz, changes to dd, *J* 7.7, 0.7 Hz upon F-decoupling, H_6), 3.76 (1H, app t, changes to dd, *J* 7.6, 5.9 Hz upon F-decoupling, H_6), 3.49 (1H, br. d, *J* 16.9 Hz, simplifies to br. S upon F-decoupling, H_4) ppm; **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 137.1 (C_{Ar}), 128.7 (C_{Ar}), 128.2 (C_{Ar}), 127.92 (C_{Ar}), 98.7 (dd, *J* 29.3, 2.9 Hz,C_1), 88.6 (dd, *J* 179.6, 30.4 Hz,C_3), 85.9 (dd, *J* 183.0, 27.5 Hz,C_2), 74.8 (dd, *J* 26.4, 4.6 Hz,C_4), 74.3 (d, *J* 2.3 Hz,C_5), 71.7 (C_7), 65.5 (d, *J* 2.3 Hz,C_6)ppm; **^{19}F NMR** (470.6 MHz, $CDCl_3$) δ − 186.9 (1F, ddt, *J* 44.9, 16.1, 13.3 Hz, F_3), −192.32 (1F, dddd app as m, *J* 45.6, 15.8, 12.8, 3.1 Hz, F_2); ppm; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ − 187.2 (d, *J* 12.9 Hz, F_3), −192.4 (d, *J* 12.9 Hz, F_2) ppm; **ESI$^+$MS**: *m*/*z* 320.1 $[M + MeCN + Na]^+$ (83%). ^{13}C NMR spectra details corresponded to those reported by Sarda et al. [19]. The ^{1}H NMR and ^{19}F NMR data were not reported.

4.3. 2,3-Dideoxy-2,3-difluoro-D-glucopyranose (**4**)

To a stirred solution of **8** (0.444 g, 1.73 mmol) in DCM at 0 °C was added a solution of BCl_3 in DCM (1 M, 2.3 mL, 2.30 mmol). After 30 min at 0 °C the solution was allowed to reach room temperature and the solution was stirred for 2 h. The reaction mixture was quenched with H_2O (16 mL), then the solvents were removed under vacuum. The crude product was then purified by column chromatography (PE/acetone 70:30) to yield **4** as a colourless oil (0.253 g, 1.38 mmol, 79%). **Mw** 184.14; **Rf** 0.30 ($MeOH/CH_2Cl_2$ 10:90); **Rf** 0.12 (PE/acetone 60:40); **$[\alpha]_D$** + 50.6 (c 0.08, acetone, 19 °C); **IR** (neat) 3315 (br, m), 1024 (s, CO) cm^{-1}; **^{1}H NMR** (500 MHz, acetone-d_6) δ 6.30 (1H, d, *J* 6.5 Hz, $OH_{1\beta}$), 6.07 (1H, d, *J* 4.3 Hz, $OH_{1\alpha}$), 5.38 (1H, app q, *J* 3.9 Hz, simplifies to app t, *J* 3.9 Hz upon F-decoupling, $H_{1\alpha}$), 4.92 (1H, d, *J* 5.3 Hz, OH_β), 4.87 − 4.77 (2H, m, $H_{1\beta}$ + OH), 4.76 (1H, ddt, *J* 55.4, 13.7, 8.7 Hz, simplifies to t, *J* 8.7 Hz upon F-decoupling, $H_{3\alpha}$), 4.57 (1H, ddt, *J* 53.6, 16.0, 8.6 Hz, simplifies to t, *J* 8.7 Hz upon F-decoupling, $H_{3\beta}$), 4.45 (1H, dddd, *J* 51.1, 12.9, 9.1, 3.7 Hz, simplifies to dd, *J* 9.0, 3.8 Hz upon F-decoupling, $H_{2\alpha}$), 4.17 (1H, dddd, *J* 52.2, 14.5, 8.5, 7.7 Hz, simplifies to app t, *J* 7.9 Hz upon F-decoupling, $H_{2\beta}$), 3.83 (2H, m, *J* 9.9, 4.4, 2.7 Hz, $H_{5\alpha}$ + $H_{6\alpha}$), 3.80 − 3.66 (6H, m, $H4_{\alpha,\beta}$, $H_{6\beta}$, $H_{6'\alpha,\beta}$, OH), 3.61 (2H, app t, *J* 6.1 Hz, OH_α), 3.38 (1H, dddd, *J* 9.6, 4.7, 2.7, 1.3 Hz, simplifies to ddd, *J* 9.8, 4.7, 2.7 Hz upon F-decoupling, $H5_\beta$) ppm; **^{13}C NMR** (101 MHz, acetone-d_6) δ 95.5 (dd, *J* 183.4, 17.6 Hz,$C_{3\beta}$), 93.9 (dd, *J* 22.0, 11.0 Hz,$C_{1\beta}$), 93.6 (dd, *J* 179.7, 15.4 Hz,$C_{3\alpha}$), 91.9 (dd, *J* 187.1, 17.6 Hz,$C_{2\beta}$) 90.3 (dd, *J* 20.5, 10.3 Hz,$C_{1\alpha}$), 88.7 (dd, *J* 191.5, 17.6 Hz,$C_{2\alpha}$), 75.3 (dd, *J* 7.3, 1.5 Hz,$C_{5\beta}$), 71.3 (dd, *J* 7.3, 1.5 Hz,$C_{5\alpha}$), 68.74 (dd, *J* 17.6, 6.6 Hz, $C4_\beta$), 68.71 (dd, *J* 17.6, 6.6 Hz, $C4_\alpha$), 61.13 ($C6_\beta$), 61.08 ($C6_\alpha$) ppm; **^{19}F NMR** (471 MHz, acetone-d_6) δ − 195.4 (dq, *J* 53.2, 14.6 Hz, simplifies to d, *J* 14.0 Hz upon H-decoupling, F_β), −199.5 (dddd, *J* 52.3, 16.1, 13.8, 2.5 Hz, simplifies to d, *J* 14.0 Hz upon H-decoupling, F_β), −200.9 (dt, 50.9, 13.6 Hz, simplifies to d, *J* 14.0 Hz upon H-decoupling, F_α), −201.1 (ddtdd, *J* 55.3, 15.1, 13.4, 3.6, 1.7 Hz, simplifies to d, *J* 12.9 Hz upon H-decoupling, F_α) ppm; **ESI$^-$-MS:** *m*/*z* 183 $[M–H]^-$ (35%).

4.4. 1,6-Anhydro-4-O-benzyl-2-deoxy-D-glucopyranoside (**9**)

To a refluxed solution of $LiAlH_4$ (1 M in THF, 18.4 mL, 18.40 mmol) in THF (40 mL) was added drop wise a solution of **6** (4.102 g, 17.51 mmol) in THF (20 mL). Reflux was continued for additional 2 h. The reaction mixture was cooled to ambient temperature and quenched by successive addition of water (4 mL) and 15% aq. NaOH (22 mL). Ether (80 mL) was then added to ensure even stirring, followed by $MgSO_4$ (30 g), and the mixture was left stirring overnight. The solid was filtered and rinsed with ether (6 × 40 mL), then the filtrate was evaporated under vacuum. The crude product was then purified by column chromatography (7:3 PE/acetone) to yield **9** as a colourless oil (3.899 g, 16.50 mmol, 94%). **Mw** 236.26; **Rf** 0.23 (acetone/PE 30:70); **IR** (neat) 3451 (br, m), 1126 (s), 1070 (s) cm^1; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28–7.42 (5H, m, H_{Ar}), 5.66 (1H, br. d, *J* 1.2 Hz, H_1), 4.71 (1H, d, *J* 12.2 Hz, H_7), 4.66 (1H, d, *J* 12.3 Hz, $H_{7'}$), 4.60 (1H, m, *J* 5.4 Hz can be observed, H_5), 4.19 (1H, dd, *J* 7.5, 0.7 Hz, H_6), 3.93 (1H, m, H_3), 3.72 (1H, dd, *J* 7.6, 5.4 Hz, $H_{6'}$), 3.46 (1H, br d (app q), *J* 1.1 Hz, H_4), 2.69 (1H, d, *J* 8.0 Hz, OH_3), 2.22 (1H, ddd, *J* 15.0, 5.3, 1.6 Hz, H_2), 1.84 (1H, br m, *J* 15.0 Hz can be observed, $H_{2'}$) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8 (C_{Ar}), 128.6 (2C,C_{Ar}), 127.9 (C_{Ar}), 127.8 (2C,C_{Ar}), 101.0 (C_1), 77.8 (C_4), 74.5 (C_5), 71.6 (C_7), 66.6 (C_3), 65.2 (C_6), 35.9 (C_2) ppm; **ESI$^+$-MS:** *m*/*z* 275.2 $[+K]^-$ (53%). This is a known compound, [23] but no NMR data had been reported.

4.5. 1,6-Anhydro-4-benzyl-2,3-dideoxy-3-fluoro-D-glucopyranose (**10**)

To a solution of **9** (2.6 g, 11.0 mmol) in dry toluene (40.0 mL) DAST was slowly added (7.3 mL, 55.0 mmol) at rt. The mixture was refluxed under argon for 24 h. Decomposition of excess reagent was carried out by adding dry MeOH (10 mL) very slowly at −20 °C. The solvent was evaporated and the sample dried under vacuum. Column chromatography (EtOAc/PE 20:80) afforded **10** as a brown oil (1.9 g, 73%). **Mw** 238.25 ($C_{13}H_{15}FO_3$); **Rf** 0.3 (EtOAc/PE 20:80); **$[\alpha]_D$** − 55.6 (c 0.25, $CHCl_3$, 19 °C); **IR** (neat) 2952 (m), 1493 (w), 1452 (w), 1039 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 − 7.28 (5H, m, H_{Ar}), 5.58 (1H, br. s, H_1), 4.74 (1H, m, *J* 45.9 Hz can be observed, which disappears upon F-decoupling, H_3), 4.72 (1H, d, *J*, 12.2 Hz, H_7), 4.69 (1H, d, *J* 12.2 Hz, $H_{7'}$), 4.61 (1H, br. d, *J* 5.9 Hz, H_5), 4.06 (1H, br. dt, *J* 7.5 Hz, *J* 1.0 Hz, simplifies to 1H, dd, *J* 7.5 Hz, 1.0 Hz upon F-decoupling, H_6), 3.76 (1H, ddd, *J* 7.4, 6.0, 3.6 Hz, simplifies to dd, *J* 7.3 6.0 Hz upon F-decoupling, $H_{6'}$), 3.53 (1H, br. dd, *J* 13.9, 1.2 Hz, simplifies to br. d, *J* 1.0 Hz upon F-decoupling, H_4), 2.15 (1H, dddd, *J* 40.2, 15.6, 4.9, 2.0 Hz, simplifies to ddd, *J* 15.6, 4.9, 2.0 Hz upon F-decoupling, H_{2ax}), 2.03 (1H, br. dd, *J* 22.6, 15.5 Hz, simplifies to br. d, *J* 15.4 Hz upon F-decoupling, H_{2eq}) ppm. **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 128.66 (C_{Ar}), 128.17 (C_{Ar}), 127.87 (C_{Ar}), 99.42 (d, *J* 1.2, C_1), 86.52 (d, *J* 175.3 Hz,C_3), 75.16 (d, *J* 26.2 Hz,C_4), 73.38 (C_5), 71.77 (C_7), 64.48 (C_6), 33.87 (d, *J* 20.0 Hz,C_2) ppm; **^{19}F NMR** (470.5 MHz, $CDCl_3$) δ − 176.28 ppm (1F, ddddd, *J* 46.0, 40.1, 22.7, 13.9, 3.5 Hz)ppm; **EI-MS**: *m*/*z* 91 (100), 238 ($M^{+\bullet}$, 0.3).

4.6. 4-O-Benzyl-2,3-dideoxy-3-fluoro-D-glucopyranose (**11**)

To a stirred solution of **10** (515 mg, 2.16 mmol) in dioxane (10 mL) was added an aqueous solution of H_2SO_4 (1 M, 32.5 mL,

32.5 mmol), followed by heating at 75 °C for 3 h. The reaction mixture was cooled to ambient temperature and quenched by addition of sat $NaHCO_3$ (80 mL). The mixture was extracted with ethyl acetate (4 × 150 mL), the combined organic layers were dried over $MgSO_4$ and solvent was removed under vacuum. The crude product was then purified by HPLC (petroleum hexane/acetone 65:35) to yield **11** as a slight yellow oil (445 mg, 1.74 mmol, 80%). **Mw** 256.27 ($C_{13}H_{17}FO_4$); **Rf** 0.22 (PE/acetone 70:30); **$[\alpha]_D$** + 59.0 (c 1.02, acetone, 21 °C); **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.39 – 7.26 (5H, m, H_{Ar}), 5.79 (1H, dd, *J* 6.6, 1.4 Hz, simplifies to d, *J* 6.4 Hz upon F-decoupling, $OH_{1\beta}$), 5.40 (1H, dd, *J* 3.7, 1.9 Hz, $OH_{1\alpha}$), 5.36 (1H, m (bq, simplifies to bt upon F-decoupling), $H_{1\alpha}$), 5.00 (1H, dddd, *J* 52.4, 11.5, 8.5, 5.6 Hz, simplifies to ddd, *J* 11.4, 8.5, 5.6 Hz upon F-decoupling, $H_{3\alpha}$), 4.89-4.79 (3H, m, $H_{1\beta}$, $H_{7\beta}$, $H_{7'\beta}$ (and half of $H3_\beta$), simplifies to the following: 4.86 (1H, ddd, *J* 9.6, 6.4, 1.9 Hz, $H_{1\beta}$), 4.85 (1H, d, *J* 11.1 Hz, $H_{7\alpha}$), and 4.83 (1H, d, *J* 11.1 Hz, $H_{7\beta}$) upon F-decoupling, 4.77 (1H, dddd, *J* 51.1, 11.7, 8.4, 5.6 Hz, simplifies to ddd, *J* 11.7, 8.4, 5.6 Hz upon F-decoupling, $H3_\beta$), 4.68 (1H, d, *J* 11.4 Hz, $H_{7'\alpha}$), 4.67 (1H, d, *J* 11.4 Hz, $H_{7'\beta}$), 3.83 – 3.79 (2H, m, $H_{5\alpha}$, $H_{6\alpha}$), 3.77 – 3.68 (3H, m, $H_{6\alpha}$, $H_{6\beta}$, OH), 3.71 (ddd, *J* 11.7, 7.1, 4.7 Hz, $H_{6\beta}$), 3.62 (ddd, *J* 13.3, 9.7, 8.6 Hz, simplifies to app t, *J* 9.2 Hz upon F-decoupling, $H_{4\alpha}$), 3.60 (dd, *J* 7.1, 6.0 Hz, $H_{6\beta}$), 3.55 (1H, ddd, *J* 13.3, 9.3, 8.6 Hz, simplifies to app t, *J* 9.1 Hz upon F-decoupling, $H_{4\beta}$), 3.47 (1H, dd, *J* 6.6, 5.9 Hz, OH), 3.27 (1H, dddd, *J* 9.5, 4.6, 2.2, 1.5 Hz, simplifies to ddd, *J* 9.5, 4.6, 2.2 Hz upon F-decoupling, $H5_\beta$), 2.36 (1H, dtd, *J* 12.0, 5.2, 1.7 Hz, simplifies to ddd, *J* 12.1, 5.7, 1.9 Hz upon F-decoupling, $H_{2eq,\beta}$), 2.24 (1H, dtd, *J* 12.4, 5.4, 1.4 Hz, simplifies to ddd, *J* 12.4, 5.6, 1.3 Hz upon F-decoupling, $H_{2eq,\alpha}$), 1.76 (1H, dtdd, *J* 12.5, 11.3, 3.5, 1.9 Hz, simplifies to dddd *J* 12.4, 11.5, 3.4, 1.7 Hz upon F-decoupling, $H_{2ax,\alpha}$), 1.65 (1H, dq, *J* 11.7, 9.6 Hz, simplifies to dt, *J* 11.7, 9.6 Hz upon F-decoupling, $H_{2ax,\beta}$) ppm; **^{13}C NMR** (100.6 MHz, acetone-d_6) δ 139.0 ($C_{Ar,\alpha \text{ or } \beta}$), 138.9 ($C_{Ar,\ \beta \text{ or } \alpha}$), 128.2 ($4C_{Ar,\alpha\ +\ \beta}$), 127.7 ($2C_{Ar,\alpha \text{ or } \beta}$), 127.6 ($2C_{Ar,\ \beta \text{ or } \alpha}$), 127.44 ($C_{Ar,\alpha \text{ or } \beta}$), 127.40 ($C_{Ar,\ \beta \text{ or } \alpha}$), 93.9 (d, *J* 126.9 Hz,$C_{3\alpha \text{ or } \beta}$), 93.2 (d, *J* 16.4 Hz,$C_{1\alpha \text{ or } \beta}$), 92.1 (d, *J* 125.4 Hz,$C_{3\beta \text{ or } \alpha}$), 91.4 (d, J 16.1 Hz,$C_{1\beta \text{ or } \alpha}$), 77.7 (d, *J* 16.1 Hz,$C_{4\alpha \text{ or } \beta}$), 77.3 (d, *J* 16.1 Hz,$C_{4\beta \text{ or } \alpha}$), 74.6 (d, *J* 9.5 Hz,$C_{5\alpha \text{ or } \beta}$), 73.9 (1d, *J* 2.2 Hz,$C_{7\alpha \text{ or } \beta}$), 73.8 (1d, J 2.2 Hz,$C_{7\beta \text{ or } \alpha}$), 71.1 (1 C, d, *J* 8.1 Hz,$C_{5\beta \text{ or } \alpha}$), 61.7 (d, *J* 2.2 Hz,$C_{6\alpha \text{ or } \beta}$), 61.6 (d, *J* 1.4 Hz,$C_{6\beta \text{ or } \alpha}$), 39.0 (d, *J* 16.9 Hz,$C_{2\alpha \text{ or } \beta}$) 36.6 (d, J 17.6 Hz,$C_{2\beta \text{ or } \alpha}$) ppm; **^{19}F NMR** δ (470.6 MHz, acetone-*d*6) δ ppm – 180.49 (1F, m, *J* 50.8, 12.1 Hz is visible, $F3_\beta$), –184.71 (1F, m, *J* 52.5, 12.2 Hz is visible, $F3_\alpha$) ppm.

4.7. 2,3-Dideoxy-3-fluoro-D-glucopyranose (*5*)

To a solution of **11** (0.443 g, 1.73 mmol) in methanol (1.4 mL) was added 20 wt% $Pd(OH)_2/C$ (0.038 g, 0.05 mmol). The solution was stirred overnight under hydrogen atmosphere. The catalyst was filtered through celite and the solvent removed under vaccum. This afforded **6** as a colourless oil (0.2803 g, 1.69 mmol, 97%). **Mw** 166.15 ($C_6H_9O_3$); **Rf** 0.23 (MeOH/CH_2Cl_2 20:80); 0.10 (PE/acetone 60:40); **$[\alpha]_D$** + 68.7 (c 1.00, acetone, 20 °C); **IR** (neat) 3312 (br,m), 1058 (s), 968 (s) cm^{-1}; **^{1}H NMR** (500 MHz, acetone-d_6) δ (500 MHz, acetone-*d6*) δ ppm 5.76 (1H, b.s, $OH_{1\beta}$), 5.38 – 5.32 (2H, m, $H_{1\alpha}$, $OH1_\alpha$), 4.88 – 4.79 (1.5H, m-overlap with $H_{3\alpha}$, which simplifies as br. ddd, *J* 9.6, 6.2, 1.6 Hz upon F-decoupling, $H_{1\beta}$), 4.78 (1H, dddd, *J* 46.4, 11.5, 8.6, 5.5 Hz, simplifies to ddd, *J* 11.4, 8.5, 5.5 Hz upon F-decoupling, $H_{3\alpha}$), 4.62 – 4.52 (2.5H, m-overlap with $H3_\beta$, $OH_{\alpha\ +\ \beta}$), 4.52 (1H, dddd, *J* 51.1, 11.6, 8.5, 5.6 Hz, simplifies to ddd, *J* 11.6, 8.5, 5.5 Hz, $H_{3\beta}$), 3.84 – 3.65 (3H, m, $H_{6\alpha\ +\ \beta}$ + $H_{5\alpha}$), 3.63 – 3.48 (4H, m, $H_{4\alpha\ +\ \beta}$ + $OH_{6\alpha\ +\ \beta}$, simplifies upon F-decoupling to: 3.58 (2H, app dt visible for $H_{4\alpha}$, *J* 8.9, 4.5 Hz, overlaps with $OH_{6\beta}$), 3.50 (app dt, *J* 9.2, 4.7 Hz, $H_{4\beta}$), and 3.43 (1H, m, $OH_{6\alpha}$)), 3.21 (1H, m, simplifies to br. ddd, *J* 9.4, 5.0, 3.1 Hz upon F-decoupling, $H5_\beta$), 2.88 (2H, m, OH), 2.31 (1H, m, simplifies to ddd, *J* 12.0, 5.5, 1.9 Hz upon F-decoupling, $H_{2eq,\beta}$), 2.19 (1H, m, simplifies to ddd, *J* 12.4, 5.5, 1.1 Hz upon F-decoupling, $H_{2eq,\alpha}$), 1.69 (1H, m, $H_{2ax,\alpha}$), 1.58 (1H, qd, *J* 11.5, 9.7 Hz, simplifies to td, *J* 11.9, 9.6 Hz upon F-decoupling, $H_{2ax,\beta}$); **^{13}C NMR** (101 MHz, acetone-d_6) δ 93.2 (d, *J* 16.9 Hz,$C_{1\beta}$), 92.8 (d, *J* 177.5 Hz,$C_{3\beta}$), 91.5 (d, *J* 14.7 Hz,$C_{1\alpha}$), 91.4 (d, *J* 175.3 Hz,$C_{3\alpha}$), 75.3 (d, *J* 8.1 Hz,$C_{5\beta}$), 71.8 (d, *J* 6.6 Hz,$C_{5\alpha}$), 70.5 (d, *J* 16.9 Hz,$C_{4\alpha}$), 70.0 (d, *J* 17.6 Hz,$C_{4\beta}$), 61.7 (m, $C_{6\alpha}$ + $C_{6\beta}$), 38.7 (d, *J* 17.6 Hz,$C_{2\beta}$), 36.3 (d, *J* 16.9 Hz,$C_{2\alpha}$) ppm; **^{19}F NMR** (282 MHz, acetone-d_6) δ – 184.5 (br. app dt, *J* 51.6, 12.9 Hz, F_β), –188.9 (1F, br. d, *J* 52.4 Hz, F_α) ppm; **EI-MS**: *m*/*z* 166, ($M^{+\bullet}$, 0.1).

5. Supporting information

General information, copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all compounds.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.08.023.

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