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Synthesis of 6-Deoxy-6,6-Difluoro-α-D-Glucopyranosyl Fluoride

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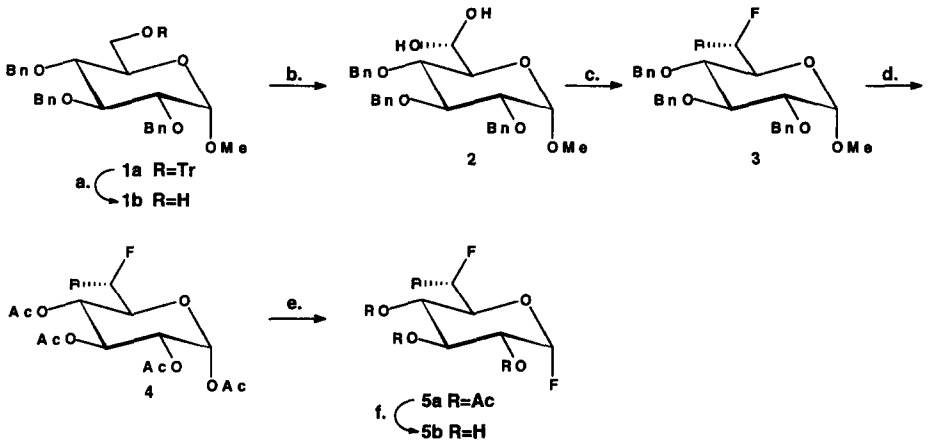
Abstract: The synthesis of 6-deoxy-6,6-difluoro-α-D-glucopyranosyl fluoride from the benzyl-protected methylglucoside was accomplished in six steps. © 1997 Elsevier Science Ltd.

Glycosyl fluorides have been used as substrates to study the specificity and kinetics of numerous glucantransferases,[1] glycosidases,[2,3] and phosphorylases.[4] Several substituted glycosyl fluorides including 6-deoxy-6-fluoro-α-D-glucopyranosyl fluoride were found to be enzyme inhibitors. Consequently, 6-deoxy-6,6-difluoro-α-D-glucopyranosyl fluoride was synthesized for its use with inhibition studies of sucrose phosphorylase from *Leuconostoc mesenteroides* using α-D-glucopyranosyl fluoride as substrate.

Several gem-difluorosaccharides have been prepared from the corresponding carbonyl compounds using diethylaminosulfur trifluoride (DAST). The 2-deoxy-2,2-and 4-deoxy-4,4-difluoropentopyranosides[5] and 6-deoxy-6,6-difluorogalactose[6] were prepared from their respective isopropylidene derivatives. The synthesis of a 6-deoxy-6,6-difluoroglucose derivative has been described[3] using a similar approach that is reported here.

Attempts to use the acetate-protected glucoside gave unsatisfactory results. The Moffatt oxidation of the 1,2,3,4-tetraacetylglucose gave a good yield of the aldehyde. However, fluorination of the aldehyde with DAST gave a poor yield of the desired 1,2,3,4-tetra-O-acetyl-6-deoxy-6,6-difluoro-β-D-glucopyranose (9%) and an elimination product, 1,2,3-tri-O-acetyl-4,6-dideoxy-6,6-difluoro-α-L-*threo*-hex-4-enopyranose (2%). Each compound was identified by its nmr spectra.

The successful synthesis (Scheme 1) relied on the oxidation of the benzyl-protected sugar **1b**, which was obtained from the benzylation of methyl 6-*O*-triphenylmethyl-α-D-glucopyranoside, followed by acid-catalyzed removal of the trityl group. The oxidation employed 1,3-diisopropylcarbodiimide in methyl sulfoxide[7] to yield methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-hexodialdo-1,5-pyranose hydrate, **2**. Compound **2** (2.5 mmol) in CH_2Cl_2 was treated with DAST (6.8 mmol) at -40°C, and stirred overnight at 0°C. After the reaction mixture was quenched with MeOH, separation by silica gel chromatography (ethyl acetate-hexanes, 1:9, v/v) gave the difluoro compound **3**[8] (in 23% yield from **1b**). After conversion to the peracetylated difluoro compound **4**, it was reacted with HF-pyridine (70:30, v/v)[9] to give 2,3,4-tri-*O*-acetyl-6-deoxy-6,6-difluoro-α-D-glucopyranosyl fluoride, **5a**,[10] in 31% yield. The acetate ester hydrolysis with catalytic sodium methoxide in methanol afforded pure fluoride **5b** which was used in enzymatic assays without additional purification.



Scheme 1. a.) Amberlyst® 15 (H^+), hexanes, wet MeOH, 50°C, 3 days; b.) diisopropylcarbodiimide, Me_2SO, PhH, pyr, trifluoroacetic acid, 14 h, then oxalic acid in MeOH; c.) DAST, CH_2Cl_2, -40→0°C; d.) HOAc/Ac_2O, 3:7, v/v, 0°C, H_2SO_4; e.) HF-pyridine 7:3 v/v, CH_2Cl_2; f.) NaOMe, MeOH.

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8. **3**: $[\alpha]_D$+9.5 (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35-7.25 (m, 15H, aromatic), 5.76 (td, 1H, $J_{6,F}$ 54.0, $J_{5,6}$ 1.1 Hz, H-6), 5.00, 4.89, 4.81, 4.80, 4.64, 4.59 (6d, 6H, $J_{H,H}$ 10.8 10.9, 12.1 Hz, 3 OCH^AH^BPh), 4.63 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.01 (dd, 1H, $J_{2,3}$9.7, $J_{3,4}$ 8.7 Hz, H-3), 3.84 (dddd, 1H, $J_{5,F}$ 18.4, $J_{5,F}$ 8.7, $J_{4,5}$ 8.4, $J_{5,6}$ 1.1 Hz, H-5), 3.58 (t, 1H, $J_{3,4}$ 8.7, $J_{4,5}$ 8.4 Hz, H-4), 3.53 (dd, 1H, $J_{2,3}$ 9.7, $J_{1,2}$ 3.6 Hz, H-2), 3.39 (s, 3H, OCH_3); ^{19}F NMR ($CDCl_3$): δ -132.6 (ddd, $J_{F,F}$ 283.7, $J_{F,6}$ 53.7, $J_{F,5}$ 8.7 Hz), -135.2 (ddd, $J_{F,F}$ 283.7, $J_{F,6}$ 54.4, $J_{F,5}$ 18.4 Hz); ^{13}C NMR ($CDCl_3$): δ 138.3-127.5 (aromatic), 113.6 (t, $J_{6,F}$ 243.8 Hz, C-6), 97.9 (C-1), 81.5 (C-3), 79.4 (C-2), 76.6 (d, $J_{4,F}$ 4.8 Hz ,C-4), 75.6, 74.9, 73.3 ($3OCH_2Ph$), 68.6 (t, $J_{5,F}$ 19.9 Hz, C-5), 55.2 (OCH_3). Anal. Calculated for $C_{28}H_{30}F_2O_5$: C, 69.41; H, 6.24; F, 7.84; Found C, 69.28, H, 6.21, F, 7.98.
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10. **5a**: m.p. 118.5-120°C (from ether-hexanes); ^1H NMR ($CDCl_3$): δ 5.84 (td, 1H, $J_{6,F}$ 54.1, $J_{5,6}$ 2.7 Hz, H- 6), 5.80 (dd, 1H, $J_{1,F}$ 52.4, $J_{1,2}$ 2.8 Hz, H-1), 5.54 (t, 1H, $J_{2,3}$ 10.1, $J_{3,4}$ 9.7 Hz, H-3), 5.32 (t, 1H, $J_{4,5}$ 9.8, $J_{3,4}$ 9.7 Hz, H-4), 4.94 (ddd, 1H, $J_{2,F}$ 24.1, $J_{2,3}$ 10.1, $J_{1,2}$ 2.8 Hz, H-2), 4.21 (dddd, 1H, $J_{5,F}$ 11.0, $J_{5,F}$ 10.1, $J_{4,5}$ 9.8, $J_{5,6}$ 2.7 Hz, H-5), 2.11, 2.06, 2.05 (3s, 9H, 3 CH_3C=O); ^{19}F NMR($CDCl_3$): δ -128.3 (ddd, $J_{F6,F6}$ 295.0, $J_{F6,H6}$ 53.6, $J_{F6,H5}$ 10.1 Hz, F- 6b), -132.0 (ddd, $J_{F6,F6}$ 295.0, $J_{F6,H6}$ 54.1, $J_{F6,H5}$ 11.1Hz, F-6a), -150.8 (dd, $J_{F1,H1}$ 52.4, $J_{F1,H2}$ 24.1 Hz, F-1); ^{13}C NMR ($CDCl_3$): δ 169.8, 169.8, 169.1 (3s, CH_3C=O), 112.8 (t, $J_{6,F6}$ 246.5 Hz, C-6), 103.2 (d, $J_{1,F1}$ 230.7 Hz, C-1), 69.7 (d, $J_{2,F1}$ 24.3 Hz, C-2), 69.5 (td, $J_{5,F6}$ 23.6, $J_{5,F1}$ 4.3 Hz, C-5), 68.7 (C-3), 66.0 (dd, $J_{4,F6}$ 4.1, $J_{4,F6}$ 1.9 Hz, C-4), 20.5, 20.4, 20.3 (3s, CH_3C=O). Anal. Calculated for $C_{12}H_{15}F_3O_7$: C, 43.91, H, 4.61, F, 17.36; Found: C, 44.14, H, 4.61, F, 17.10.

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