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Preliminary communication

A one-step synthesis of methyl 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside

CHANDRASIRI W. SOMAWARDHANA*
Department of Chemistry, University of Missouri–St. Louis, St. Louis, MO 63121 (U.S.A.)
and ERIC G. BRUNNGRABER
Department of Biochemistry, Missouri Institute of Psychiatry, School of Medicine, University of Missouri–Columbia, St. Louis, MO 63139 (U.S.A.)

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Fluorinated carbohydrates may possess antitumor and other biological activities[1–4]; they have been used as inhibitors in examining the active sites of hexokinases[4], and may prove to have value in studies of the biosynthesis and function of glycoproteins as well as of lectin–carbohydrate interactions[5]. The synthesis of a difluoro derivative of methyl α-D-galactopyranoside reported here is a pilot procedure on the feasibility of fluorination of biologically active oligosaccharides or glycopeptides, or both, prior to structural analysis by ^{19}F-n.m.r. spectroscopy. We are interested in ^{19}F and ^{13}C chemical-shifts and ^{19}F, ^{19}F coupling-constants of multifluorinated sugars. We have found that diethylamine-sulfur trifluoride[6] selectively reacts with the 4- and 6-hydroxyl groups of methyl α-D-glucopyranoside (1), to afford 3. The reaction at C-4 involves a Walden inversion thereof, and presumably proceeds through an (unisolated) intermediate[7], 2, in which one of the fluorine atoms of diethylamine-sulfur trifluoride has been replaced by the oxygen atom of the 4-hydroxyl group of the sugar. As no trace of products retaining the configuration at C-4 was found, it is proposed that the reaction involves an SN2 type of displacement mechanism under the conditions used, rather than a fluoride-ion transfer in an ion-pair.

Methyl 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside (3) was characterized by its ^{1}H-, ^{13}C-, and ^{19}F-n.m.r. spectra. The H-1 signal appears as a doublet at δ 4.88, without being affected by the long-range coupling of the 4-fluorine atom. The fluorine atoms on C-4 and C-6 resonate at δ 219.7 and 229.9, respectively, upfield from the internal $CFCl_3$ signal (0.2 M solution in acetone-d_6). The proton-coupled spectrum shows $J_{F-4,H-3} = J_{F-4,H-5} = 30.6$, $J_{F-4,H-4}$ 50.3, $J_{F-6,H-5}$ 13.8, and $J_{F-6,H-6}$ 46.6 Hz. The mass spectrum of 3 shows its molecular ion at m/z 198, and an intense peak at m/z 120 that is characteristic for the 4,6-dideoxy-4,6-difluoroaldohexoses[8,9].

Methyl α-D-glucopyranoside (1) (1 g, 5 mmol), dried over P_2O_5 at 100°, was added to diethylamine–sulfur trifluoride (3.8 mL, 4.75 g, 30 mmol) at room temperature

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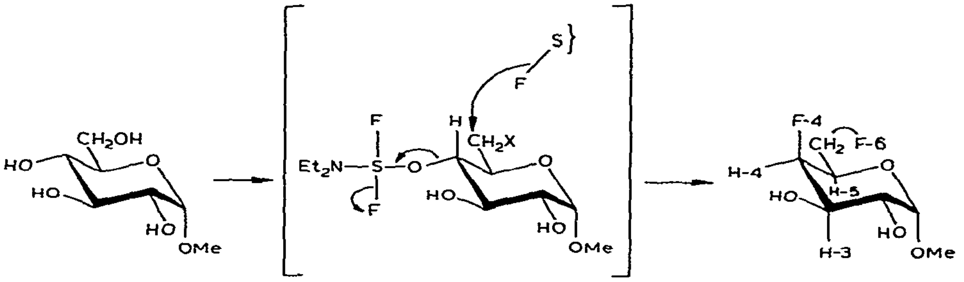
*To whom enquiries should be addressed.



1

X = —OSF_2NEt_2

2

3

and the mixture was stirred overnight at the same temperature. (Temperature increase leads to violent decomposition.) Methanol (10 mL) was slowly added to the clear solution at −10°, the temperature of the mixture being maintained. The mixture was evaporated and the residue was chromatographed on a column of silica gel G with 5:1 (v/v) chloroform–methanol as the eluant. The same solvent-system was used to irrigate the t.l.c. plates (Analtech, Uniplate). The product (3), R_F 0.57, was isolated in 60% yield, and was recrystallized from absolute ethanol, m.p. 135–136°, $[\alpha]_D^{22}$ + 282.9° (in absolute ethanol). *Anal.* Calc. for $C_7H_{12}F_2O_4$: C, 42.42; H, 6.06; F, 19.19. Found: C, 42.41; H, 6.22; F, 18.95.

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