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Note

Novel 2,6-anhydro-β-D-hexopyranosyl fluorides by fluorination of 1,6-anhydro-α-D-hexopyranoses with diethylaminosulfur trifluoride

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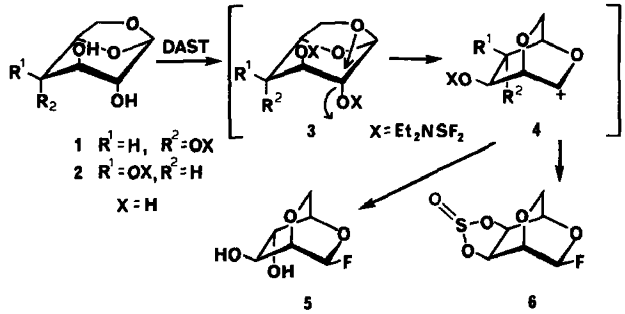
The preparation of selectively fluorinated carbohydrates is an active field of investigation because of the utility of these compounds in fundamental structural studies and because of their intrinsic biological activities. Although fluorinated derivatives of 1,6-anhydrohexopyranoses have been prepared before, the syntheses have generally involved multistep reaction-sequences[1]. As these anhydro sugars are conformationally rigid and internally protected by the 1,6-anhydride bridge against reaction at C-1 and C-6, they provide a convenient template on which the selectivity of fluorination[2] by diethylaminosulfur trifluoride (DAST) may be tested without any protection or deprotection steps in the process. Accordingly, we undertook the present study of fluorination of 1,6-anhydroglucose (**1**) and 1,6-anhydrogalactose (**2**) by DAST and observed the unexpected and novel rearrangement described in the text.

RESULTS AND DISCUSSION

Both 1,6-anhydroglucose (**1**) and 1,6-anhydrogalactose (**2**) were fluorinated by DAST according to a standard procedure[2]. Chromatographic analyses revealed mixtures of products in both cases, suggesting that the fluorination was non-selective. The major products **5** and **6** were isolated from the reactions of **1** and **2**, respectively, and spectral studies revealed that they no longer had the original 1,6-anhydro sugar structure. Instead, they are the rearranged products shown in the Scheme.

The ^{19}F-n.m.r. spectra of **5** and **6** showed doublets typical of β-glycosyl fluorides[3]. The ^{1}H-n.m.r. spectra did not show the characteristic acetal hydrogen resonances of 1,6-anhydroglycopyranoses; instead they showed the low-field resonances of anomeric hydrogen atoms of glycosyl fluorides. I.r. spectra showed the presence of an OH group in **5** but not in **6**; a sulfite absorption at 1210 cm^{-1} was



also observed for **6**. The 2-D COSY n.m.r. spectrum of **5** (Fig. 1) allowed us to identify and assign all proton resonances and coupling constants, and arrive at the structure shown in the Scheme. A similar 2-D COSY spectrum of **6** (not shown) led to the structure shown for **6**. One interesting observation in these 2-D COSY spectra is the small 5-bond H-1–H-6 coupling. This indicates an extended "W" arrangement and suggests the α-orientation of the anomeric hydrogen atoms, and

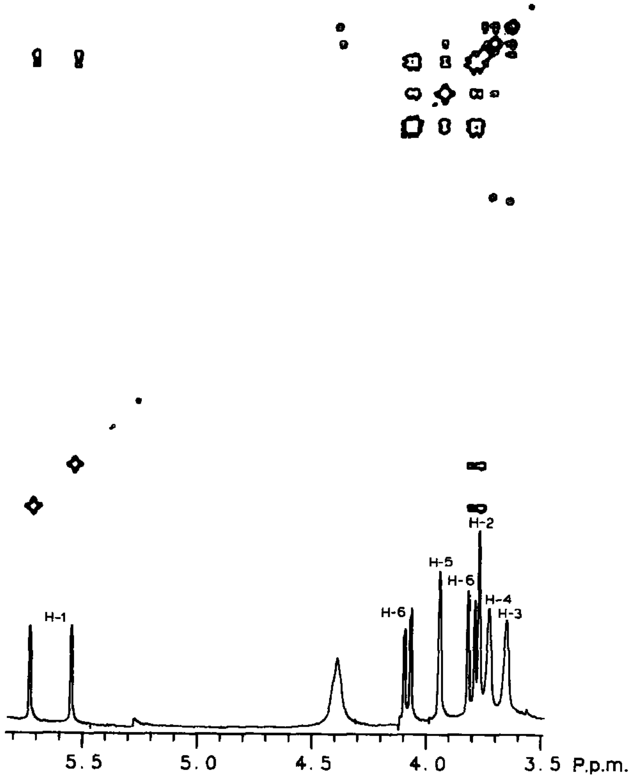


Fig. 1. 2-D COSY contour map of 2,6-anhydro-β-D-mannopyranosyl fluoride (**5**). The spectrum shown on the bottom is the actual high-resolution spectrum taken at the same width as the COSY spectrum. Some fold-backs and center anomalies are evident.

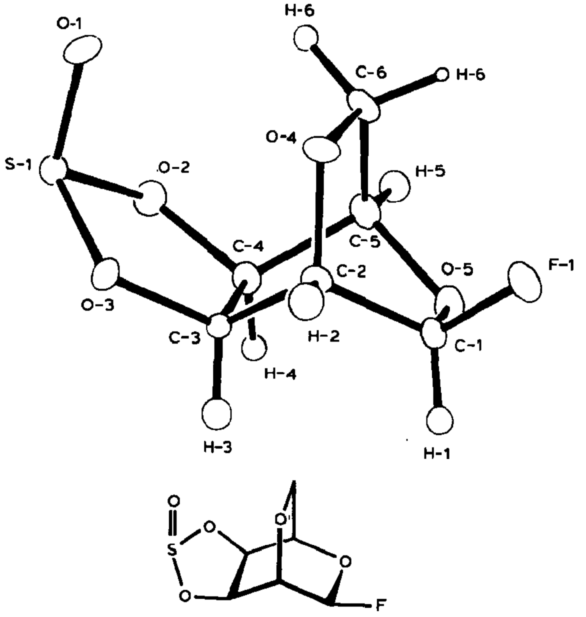


Fig. 2. Structure of 2,6-anhydro-β-D-talopyranosyl fluoride 3,4-sulfite (**6**) by X-ray crystallographic analysis.

also shows the close structural similarity of **5** and **6**. Finally, mass-spectral data for **5** and **6** and the single-crystal X-ray studies (see Fig. 2) of **6** (only **6** was obtained crystalline) clearly support the assigned structures.

These results clearly prove the 1,2-migration of the bridging oxygen atom during fluorination with DAST. The DAST-promoted rearrangement of 1,6-anhydrohexopyranoses to 2,6-anhydrohexopyranoses has been observed in few cases[4]. Generally, migration of O-6 in such a 1,2-shift has been observed when O-3 or its protecting group are incapable of neighboring-group participation, or when the leaving group at C-2 is lost so readily that internal capture of the carbonium ion by the bridging oxygen atom competes effectively with capture by an external nucleophile. In this study, we propose that the sulfenylated sugar intermediate **3** rearranges to **4** for the latter reason. The 3,4-cyclic sulfite **6** of 2,6-anhydro-β-D-talopyranosyl fluoride arises from incomplete hydrolysis of the DAST-derivatized sugar intermediates. This has been previously observed by us in other systems where a favorable and relatively rigid *syn* stereochemistry of vicinal OH groups exists[5]. In the present case, the sulfite is sufficiently stable that any attempts to liberate the OH groups were thwarted by simultaneous loss of the glycosyl fluoride.

EXPERIMENTAL

Materials. — 1,6-Anhydro-β-D-glucopyranose was from Fluka Corp. and 1,6-anhydrogalactose was prepared according to the method of Montgomery *et al.*[6]. Diethylaminosulfur trifluoride (DAST) was prepared by the method of Middleton[7].

2,6-Anhydro-β-D-mannopyranosyl fluoride (**5**). — A suspension of 1,6-anhydro-β-D-glucopyranose (1.00 g, 6.16 mmol) in CH_2Cl_2 (40 mL) was treated at −78° with DAST (3.98 g, 24.6 mmol). The mixture was warmed to 0° for 1 h and then to 25° for 5 h. The reaction was quenched with an excess of methanol at −40°. Solvent and volatiles were removed *in vacuo,* and the residue was dissolved in ethyl acetate, the mixture filtered, and the filtrate chromatographed on a column of silica gel. The final yield of **5** was 0.102 g (10%) as an off-white solid: m.p. 101–103.5°, $[\alpha]_D$ −66.8° (*c* 1.04, abs. EtOH); λ_{max}^{KBr} 3400, 1144, 1082, 989, 971, 905, and 858 cm^{-1}; ^{1}H-n.m.r. (acetone-d_6): δ 5.636 (ddd, *J* 63.5, 1.8, 1.0 Hz, anomeric H-1), 4.38 (broad, OH) 4.107 (ddd, *J* 10.0, 2.0, 0.6 Hz, H-6′ *endo* to fluoride), 3.946 (m, H-5), 3.821 (dddd, *J* 9.6, 1.0, 1.0, 1.0 Hz, H-6 *exo* to fluoride), 3.778 (ddd, *J* 1.8, 1.0, 1.0 Hz, H-2), 3.738 (m, H-4), and 3.640 (m, H-3); ^{19}F-n.m.r. (acetone-d_6): ϕ −122.83 p.p.m., d, *J* 63.5 Hz.

Anal. Exact mass for $C_6H_9FO_4$: calc. 164.0484. Found 164.0482.

2,6-Anhydro-β-D-talopyranosyl fluoride 3,4-cyclic sulfite (**6**). — A suspension of 1,6-anhydro-β-D-galactopyranose (1.62 g, 10.0 mmol) in CH_2Cl_2 (35 mL) −78° was treated with DAST (6.45 g, 40 mmol) and the mixture was warmed to 25° and maintained at this temperature for 20 h. Quenching with methanol and isolation as for **5**, with flash chromatography over silica gel with 1:2 ethyl acetate–hexane yielded 0.1313 g (6.2%) of **6** as a white solid that was recrystallized to colorless needles from Et_2O: m.p. 195–196.5°, $[\alpha]_D$ −35.6° (*c* 1.07, $CHCl_3$); λ_{max}^{KBr} 1220, 1210, 1151, 1070, 1053, 1007, 973, 891, 862, 822, 748, and 676 cm^{-1}; ^{1}H-n.m.r. (acetone-d_6): δ 5.808 (ddd, *J* 62.5, 1.7, 1.0 Hz, anomeric H-1), 5.70 (ddd, *J* 9.1, 2.0, 2.0 Hz, H-3), 5.016 (ddd, *J* 9.1, 4.5, 1.7 Hz, H-4), 4.330 (dm, *J* 10.5 Hz, H-6 *exo* to fluoride), 4.24 (dd, *J* 4.5, 1.5 Hz, H-5), 4.205 (m, H-2), and 4.156 (dm, *J* 10.5 Hz, H-6′ *endo* to fluoride); ^{19}F-n.m.r. (acetone-d_6): ϕ −128.43 p.p.m. (J = 62.5 Hz).

2-D J-*Correlation n.m.r.* — Two-dimensional, homonuclear shift-correlation (COSY)[8] spectra were obtained on a Nicolet 360 WB spectrometer using the standard $90° - \tau - 90°$ pulse sequence. The resulting contour-plot for **5** is shown in Fig. 1.

X-Ray crystal-structure analysis. — Three-dimensional X-ray intensity data were collected with a crystal 0.23 × 0.11 × 0.33 mm in size by using a Syntex P3 diffractometer with ω scan technique and MoKα radiation. Only **6** was obtained crystalline and the X-ray structure is shown in Fig. 2.

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