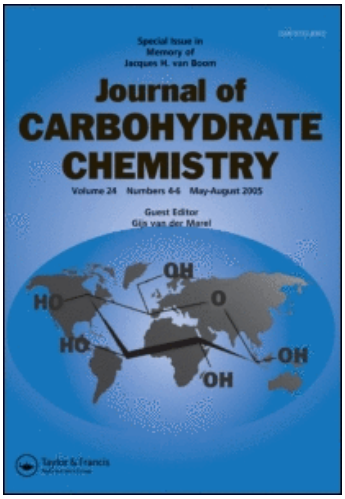

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STEREOSPECIFIC ACCESS TO 2,3,4-TRIDEOXY-2,3,4-TRIFLUORO-D-GLUCOSE AND D-GALACTOSE DERIVATIVES

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ABSTRACT

Fluorodehydroxylation of 1,6-anhydro-β-D-gluco- and galactopyranose derivatives was investigated on compounds having only one free hydroxy group. The reaction proceeded with complete retention and inversion of configuration at C-3 and C-4 respectively and allowed the stereospecificic preparation of 1,6-anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-gluco- and galactopyranose. Acid catalyzed opening of their 1,6-anhydro bridge gave the corresponding 1,6-di-O-acetyl gluco- and galactopyranose derivatives.

INTRODUCTION

Because of their widespread utility, considerable interest has been devoted in recent years to the synthesis of fluorinated carbohydrates.[1] Specifically fluorinated compounds have been largely exploited in biological investigations.[2] However, in view of the difficulty associated with the introduction of fluo-

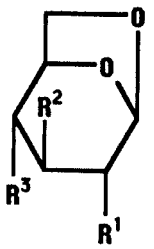
rine into carbohydrates, very few derivatives containing several fluorine atoms have been reported.[3] We were interested in synthesizing carbohydrates in which all hydroxy groups would be replaced by fluorine and in this paper we present a strategy which allows stereospecific access to 2,3,4-trideoxy-2,3,4-trifluoro-D-glucose and -D-galactose derivatives. The subsequent introduction of fluorine at C-1 and C-6 appears trivial in the light of well-established methodology.[4]

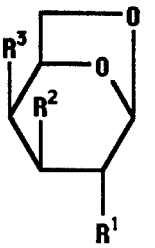
RESULTS AND DISCUSSION

In connection with the synthesis of fluoro analogues of antibiotic sugars, on the basis of a few examples, we made the statement in a recent paper[5] that axial alcohols involved in vicinal diaxial systems undergo fluorodehydroxylation with configurational retention in the presence of diethylaminosulfur trifluoride (DAST). This observation prompted us to investigate the possibility of the simultaneous introduction with DAST of axial fluorine atoms into 1,6-anhydro-β-D-glucopyranose 1. However, under a variety of conditions, the reaction furnished only a complex mixture from which the major product, the recently described 2,6-anhydro-β-D-manopyranosyl fluoride 2[6] of rearranged structure could be isolated in modest yield. Therefore, we decided to use as starting material of our scheme 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose 3 whose preparation has been known for a number of years.[7] Fluorodehydroxylation of 3 proceeded in the presence of DAST with configurational retention affording 4 in nearly quantitative yield. Stereochemical proof for the configuration of the second fluorine atom at C-3 was based on geminal and vicinal ^{13}C-^{19}F coupling constants[8] in the ^{13}C NMR spectrum of 5 obtained by hydrogenolysis of the benzyl group of 4. The large geminal coupling constants $^{2}J_{C-2,F-3}$ = 29.2 Hz and $^{2}J_{C-4,F-3}$ = 26.0 Hz reveal a trans-diaxial relationship between the substituents of the pyranose ring. Additional support was

provided by the very small vicinal coupling constants $^{3}J_{C-1,F-3} \cong {}^{3}J_{C-5,F-3} < 1$ Hz, indicating a cis arrangement of F-3 with respect to both C-1 and C-5.

Introduction of the third axial fluorine atom at C-4 into the 1,6-anhydro-β-D-glucopyranose framework was attempted by DAST treatment of 5. The reaction proceeded cleanly and furnished unexpectedly a trideoxy-trifluoro sugar in good yield with configurational inversion at C-4 6 belonging to the D-galacto series. The ^{13}C NMR spectrum of the crude reaction mixture did not reveal the presence of any trace of an epimeric trifluoro sugar. Stereochemical proof for the configuration of the third fluorine atom at C-4 in 6 was provided by the relatively small geminal coupling constant $^{2}J_{C-3,F-4} = 15.3$ Hz revealing a cis relationship between the C-3 and C-4 substituents of the pyranose ring. This result, being in contrast with our earlier statement[5] concerning the expected configurational retention, was interesting. In order to prepare a 1,6-anhydro trideoxy trifluoro sugar with D-gluco configuration, the inversion of the stereochemistry at C-4 of difluro sugar 5 was undertaken. The triflate 7 prepared from 5 was treated with sodium benzoate and the resulting material 8 was debenzoylated using a catalytic amount of sodium methoxide in methanol giving 9. Carbon-13 NMR spectroscopy of 8 afforded proof for the configurational inversion at C-4. The cis-relationship between the C-3 and C-4 substituents of 8 was evident from the relatively small geminal coupling constant $^{2}J_{C-4,F-3} = 15.6$ Hz. When the 1,6-anhydro-β-D-galactose derivative 9 was treated with DAST a trideoxy-2,3,4-trifluoro-2,3,4 sugar 10 of D-gluco configuration was obtained as the exclusive product of the reaction. Stereochemical proof for the C-4 configuration was based on the very large geminal coupling constant $^{2}J_{C-3,F-4} = 34.4$ Hz reflecting a trans relationship between the substituents of C-3 and C-4.





1 $R^1 = R^2 = R^3 = OH$

3 $R^1 = F; R^2 = OH; R^3 = OBzl$

4 $R^1 = R^2 = F; R^3 = OBzl$

5 $R^1 = R^2 = F; R^3 = OH$

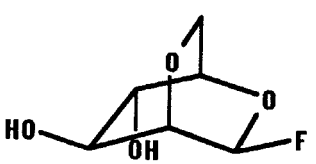
7 $R^1 = R^2 = F; R^3 = OTf$

10 $R^1 = R^2 = R^3 = F$

6 $R^1 = R^2 = R^3 = F$

8 $R^1 = R^2 = F; R^3 = OBz$

9 $R^1 = R^2 = F; R^3 = OH$



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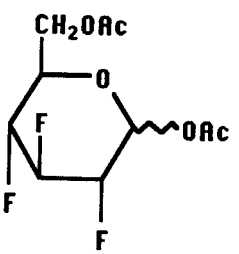

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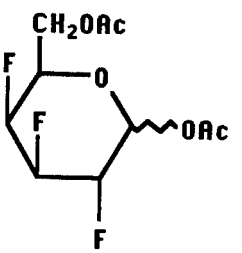

12

Treatment of 1,6-anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-gluco 10 and galactopyranose 6 with acetic acid containing sulfuric acid gave respectively anomeric mixtures of 1,6-O-diacetyl-2,3,4-trideoxy-2,3,4-trifluoroglucopyranose 11 and -galactopyranose 12 ready for transformation to perfluorinated pyranosyl systems.

No appropriate explanation can be advanced at this time as to why the fluorodehydroxylation reaction, as a result of DAST treatment of hindered secondary alcohols, occurs in some cases with complete retention and in some others with complete inversion of configuration.

EXPERIMENTAL

General Procedures. The melting points were determined with a Buchi apparatus and are uncorrected. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. ^1H NMR spectra of the fluorinated compounds was difficult to analyze without the help of two-dimensional experiments. Therefore, structures are based on their carbon-13 NMR spectra measured at 50.31 MHz with a Bruker WP-200 spectrometer. Carbon-13 chemical shifts for aromatic carbons are not given. Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica gel 60 PF_{254} (Merck) activated at 120°C was the support for TLC and for column chromatography. The term "standard workup" means that the organic layer was washed with water, dried over Na_2SO_4, and filtered and the solvent was removed at reduced pressure.

1,6-Anhydro-4-O-benzyl-2,3-dideoxy-2,3-difluoro-β-D-glucopyranose (4). To a solution of 3 (16 g, 62.9 mmol) in dry toluene (160 mL) was added slowly at room temperature diethylaminosulfur trifluoride (42 mL, 315 mmol) and the mixture was refluxed in an argon atmosphere for 24 h. Destruction of excess reagent was

carried out by adding dry methanol (35 mL) very slowly at -20°C. After the usual workup and column chromatography, pure syrupy 4 (11.3 g, 70%) was obtained; $[\alpha]_D^{22}$ = -36° (c = 2.85, chloroform); mass spectrum m/z 256 ($M^{+\cdot}$); ^{13}C NMR ($CDCl_3$) δ: 98.8 (d, $J_{C-1,F-2}$ = 29.2 Hz, C-1), 89.0 (dd, $J_{C-2,F-2}$ = 180.1 Hz, $J_{C-2,F-3}$ = 30.7 Hz, C-2), 86.3 (dd, $J_{C-3,F-3}$ = 182.1 Hz, $J_{C-3,F-2}$ = 27.2 Hz, C-3), 75.3 (dd, $J_{C-4,F-3}$ = 25.7 Hz, $J_{C-4,F-2}$ = 9 Hz, C-4), 74.3 (CH_2Ph), 71.6 (C-5), 65.6 (C-6).

Anal. Calcd for $C_{13}H_{14}F_2O_3$: C, 60.93; H, 5.47; F, 14.84. Found: C, 61.01; H, 5.40; F, 14.71.

1,6-Anhydro-2,3-dideoxy-2,3,-difluoro-β-D-glucopyranose (5). To a solution of 4 (10 g, 39 mmol) in ethyl acetate (300 ml) was added 10% Pd/C (5 g) and the mixture was stirred overnight in a hydrogen atmosphere at 5 kg pressure. After filtration of the catalyst and evaporation of the solvent, crude homogenous 5 was obtained (6.2 g, 96%), mp = 97-98°C; $[\alpha]_D^{22}$ = -59° (c = 0.7, chloroform); mass spectrum m/z 166 ($M^{+\cdot}$); ^{13}C NMR (pyridine-d_5) δ: 99.7 (d, $J_{C-1,F-2}$ = 30.2 Hz, C-1),92.6 (dd, $J_{C-3,F-3}$ = 181.2 Hz, $J_{C-3,F-2}$ = 27.6 Hz, C-3), 87.7 (dd, $J_{C-2,F-2}$ = 178.5 Hz, $J_{C-2,F-3}$ = 29.2 Hz, C-2), 77.7 (C-5), 69.7 (dd, $J_{C-4,F-3}$ = 26.0 Hz, $J_{C-4,F-2}$ = 9 Hz, C-4), 66.3 (C-6).

Anal. Calcd for $C_6H_8F_2O_3$: C, 43.37; H, 4.82; F, 22.89. Found: C, 43.25; H, 4.91; F, 23.00.

1,6-Anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-galactopyranose (6). To a solution of 5 (1.46 g, 8.8 mmol) in dry dichloromethane (30 ml) was added diethylaminosulfur trifluoride (3.5 mL, 26.5 mmol) slowly at -20°C and the mixture was refluxed in an argon atmosphere for 24 h. Product isolation was carried out as for 4. Pure 6 (1.12 g, 72%) was obtained, $[\alpha]_D^{22}$ = -19° (c = 0.7, chloroform); mass spectrum m/z 168 ($M^{+\cdot}$); ^{13}C NMR (pyridine-d_5) δ: 99.0 (d, $J_{C-1,F-2}$ = 25.7 Hz, C-1), 87.9 (dd, $J_{C-2,F-2}$ = 182.1 Hz, $J_{C-2,F-3}$ = 28.7 Hz, C-2), 85.8 (ddd, $J_{C-3,F-2}$ = 31.7 Hz,

$J_{C-3,F-3}$ = 184.1 Hz, $J_{C-3,F-4}$ = 15.3 Hz, C-3), 83.3 (dd, $J_{C-4,F-3}$ = 16.0 Hz, $J_{C-4,F-4}$ = 192.6 Hz, C-4), 72.2 (C-5); 64.4 (C-6).

Anal. Calcd for $C_6H_7F_3O_2$: C, 42.86; H, 4.17; F, 33.93. Found: C, 42.99; H, 4.10; F, 33.85.

1,6-Anhydro-4-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-galactopyranose (8). To a solution of 5 (2.56 g, 15.4 mmol) in dry dichloromethane (20 mL) was added a solution of trifluoromethanesulfonic anhydride (3.6 mL, 16.8 mmol) in dry pyridine (1.4 mL) and the mixture was stirred for 3 h in an argon atmosphere. After dilution with cold water and chromatography 1,6-anhydro-2,3-dideoxy-2,3-difluro-2-O-[trifluoromethyl-sulfonyl]-β-D-glucopyranose 7 (4.41 g, 98%), mass spectrum, m/z 298 ($M^{+\cdot}$) was obtained. To a solution of 7 (4.3 g, 14.4 mmol) in N,N'-dimethylformamide (70 mL) was added sodium benzoate (10.4 g, 72 mmol) and the mixture was heated to 80°C for 24 h in an argon atmosphere. After standard workup and chromatography pure 8 (3.8 g, 97%) was obtained as fine needles, mp 89-90°C; $[\alpha]_D^{22}$ = -31° (c = 1.72, chloroform); mass spectrum m/z 270 ($M^{+\cdot}$); ^{13}C NMR (pyridine-d_5) δ: 99.2 (d, $J_{C-1,F-2}$ = 26.2 Hz, C-1), 88.4 (dd, $J_{C-2,F-2}$ = 181.5 Hz, $J_{C-2,F-3}$ = 28.5 Hz, C-2), 84.8 (dd, $J_{C-3,F-2}$ = 31.3 Hz, $J_{C-3,F-3}$ = 183.7 Hz, C-3), 72.4 (C-5), 67.1 ($J_{C-4,F-3}$ = 16.2 Hz, C-4), 65.0 (C-6).

Anal. Calcd for $C_{13}H_{12}F_2O_4$: C, 55.77; H, 4.44; F, 14.08. Found: C, 57.81; H, 4.48; F, 14.20.

1,6-Anhydro-2,3,-dideoxy-2,3-difluoro-β-D-galactopyranose (9). To a solution of 8 (2.91 g, 10.7 mmol) in methanol (10 ml) was added a solution of sodium methoxide (0.1M) in methanol (40 mL) and the mixture was stirred overnight at room temperature in an argon atmosphere. After standard workup, pure 9 (1.61 g, 90%) was obtained, mp = 117-119°C; $[\alpha]_D^{22}$ = -39° (c = 1.05, chloroform); mass spectrum m/z 166 ($M^{+\cdot}$)

Anal. Calcd for $C_6H_8F_2O_3$: C, 43.37; H, 4.82; F, 22.89. Found: C, 43.21; H, 5.00; F, 22.84.

1,6-Anhydro-2,3,4-trideoxy-2,3,4-trifluoro-β-D-glucopyranose (10). To a solution of 9 (1.1 g, 6.6 mmol) in dry dichloromethane (25 mL) was added diethylaminosulfur trifluoride (2.6 mL, 20 mmol) slowly at -20°C and the mixture was refluxed in an argon atmosphere for 24 h. Product isolation was carried out as for 4 and 6. Pure 10 (1 g, 90%) was obtained; $[\alpha]_D^{22}$ = -56° (c = 1.32, chloroform); mass spectrum m/z 168 ($M^{+\cdot}$); ^{13}C NMR (pyridine-d_5) δ: 99.2 (d, $J_{C-1,F-2}$ = 29.3 Hz, C-1), 88.5 (ddd, $J_{C-3,F-2}$ = 34.4 Hz, $J_{C-3,F-3}$ = 177.8 Hz, $J_{C-3,F-4}$ = 34.4 Hz, C-3), 87.6 (dd, $J_{C-2,F-2}$ = 181.1 Hz, $J_{C-2,F-3}$ = 30.6 Hz, C-2), 85.8 (dd, $J_{C-4,F-3}$ = 26.6 Hz, $J_{C-4,F-4}$ = 178.6 Hz, C-4), 74.3 (C-5), 64.7 (C-6).

Anal. Calcd for $C_6H_7F_3O_2$: C, 42.86; H, 4.17; F, 33.93. Found: C, 43.01; H, 4.08; F, 33.85.

1,6-di-O-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α- and β-D-glucopyranose (11). To a solution of 10 (0.75 g, 4.48 mmol) in acetic anhydride (6 mL) was added a solution of acetic anhydride (0.6 mL) containing sulfuric acid (0.06 mL) and the mixture was stirred at room temperature for 7 days. After neutralization with a 5% cold solution of sodium hydrogenocarbonate, standard workup and chromatography, a mixture of α and β anomers of 11 g, 93%) was obtained; mass spectrum, m/z 270 ($M^{+\cdot}$).

1,6-di-O-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α-and β-D-galactopyranose (12). From 6 (0.76 g, 4.52 mmol) was obtained 12 (0.91 g, 75%), mass spectrum, m/z 270 (M), as described for the preparation of 11 from 10.

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