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Note

Synthesis of methyl 3-deoxy-3-fluoro-β-D-galactopyranoside

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The known synthesis[1] of 3-deoxy-3-fluoro-D-galactose is based on an earlier observation[2] that the *endo*-sulfonyloxy group of 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-gulofuranose (**3**) readily undergoes SN2 displacement reactions with such nucleophiles as benzoate or azide ions, to give the corresponding D-galactose derivatives. Accordingly, Brimacombe *et al.*[1] treated **3** with tetrabutylammonium fluoride in acetonitrile for 48 h, and obtained a mixture of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**4**) and 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**9**). Because these products could not be separated either by thin-layer or column chromatography, **4** was isolated (41%) by column chromatography after hydrogenation of the mixture, whereby **9** is converted into the chromatographically much slower-moving 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose.

The synthesis of model compounds for use in study of the modes of binding between immunoglobulins and (1→6)-β-D-galacto-oligosaccharides required 3-deoxy-3-fluoro-D-galactose as the starting material. The present work describes improvements over the existing[1] synthesis of **4**, and its further conversion into the title glycoside **8**.

In the first approach, the (*p*-bromophenylsulfonyl)oxy (brosyloxy) group, instead of a tosyloxy[1] group, was used as the leaving group in the fluoride ion-induced displacement-reaction. Also, a commercially available, polymer-supported, ionic fluoride[3] that was easy to handle was used as the nucleophile. In this way, complete conversion of **2** into a mixture of **4** and **9** occurred within 12–16 h, compared to the 48 h required in the earlier work[1]. Although we have found for t.l.c. a solvent system that separates **4** from **9** (see Experimental section), large-scale isolation of **4** was more conveniently achieved, as suggested[1], after **9** had been hydrogenated.

In our second approach, the possibility of directly displacing the hydroxyl group in **1** (ref. 4) by use of diethylaminosulfur trifluoride (DAST) was explored. In a preliminary experiment (not described in the Experimental section), **1** was treated overnight with (*a*) plain DAST[5], and (*b*) DAST in dichloromethane[6]. In both reactions, only partial conversion into the desired product occurred, and **4**

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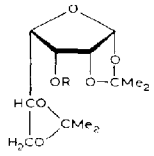
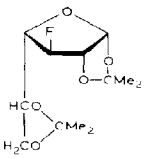


1 R = H
2 R = Brs
3 R = Ts



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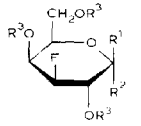
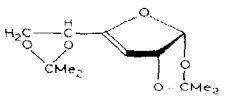


	R^1	R^2	R^3
5	OAc	H	Ac
6	H	OAc	Ac
7	OMe	H	Ac
8	OMe	H	H



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was isolated in ~30% yield, after column chromatography. Although addition of pyridine[7] to the reaction mixture improved the conversion somewhat, our use of a stronger base, 4-(dimethylamino)pyridine (DMAP) drove the reaction to completion and **4** was isolated (after chromatography) in ~90% yield.

When 3-deoxy-3-fluoro-D-galactose, prepared from **4** as described[1], was treated with a boiling mixture of acetic anhydride and fused sodium acetate for 10 min (the reaction conditions recommended[1]), two products were formed in equal amounts (t.l.c.). By prolonging the reaction time, the slower-moving compound, presumably 1,2,6-tri-*O*-acetyl-3-deoxy-3-fluoro-D-galactopyranose, was converted into the faster-moving one, and, after the usual work-up, **5** was isolated in substantially higher yield than previously reported (57 *vs.* 35% in ref. 1). The ^{13}C-n.m.r. spectrum of **5** showed the signal of C-1 at 91.5 p.p.m. as a doublet, $^3J_{C,F}$ 11 Hz. The material that remained in the mother liquor appeared as one spot in t.l.c., but its ^{13}C-n.m.r. spectrum showed it to be a mixture of acetates, and signals at 98.6–97 p.p.m. indicated that it contained furanose structures.

The presence of furanoses in a mixture of acetates is highly undesirable when they are to be converted into glycosyl halides to be used for synthesis of glycopyranosides or related oligosaccharides. Therefore, we examined the possibility of minimizing the formation of furanoid structures during the acetylation of 3-deoxy-3-fluoro-D-galactose. When this acetylation was conducted at 0° with acetic anhydride–pyridine, no furanose could be detected in the product by ^{13}C-n.m.r. spectroscopy. It had previously been found[8] that this reagent does not cause the forma-

tion of furanose peracetates, whereas they *had* been formed with sodium acetate–acetic anhydride. Also, the position of lines in the anomeric region of the ^{13}C-n.m.r. spectrum of the acetates so obtained was consistent with the sample's being a mixture of **5** and **6**.

Treatment of **5**, or of a mixture of the pyranose acetates **5** and **6**, with hydrogen bromide in acetic acid produced a glycosyl halide that reacted with methanol in the presence of mercuric cyanide to give **7**. Zemplen deacetylation of **7** then yielded the readily crystallizable **8**.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns melting-point apparatus. Optical rotations were measured with a Perkin–Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (t.l.c.) on precoated plates of silica gel GF (250 μm, Analtech) was performed with *A*, 5:1 toluene–acetone; *B*, 15:1 petroleum ether–acetone; *C*, 10:1 toluene–acetone; and *D*, 8:1 dichloromethane–methanol. Compounds were detected by charring with 5% sulfuric acid in ethanol, or by spraying with 0.1% potassium permanganate in acetone, with which alkenic components immediately appeared as yellow spots on a violet background. Column chromatography was performed on silica gel (Merck, Cat. No. 9385). Amberlyst A-26-F was a product of Fluka, A.G., and DAST was purchased from Aldrich Chemical Co. The solution of hydrogen bromide in acetic acid was obtained from Kodak Chemical Co. ^{13}C-N.m.r. spectra for solutions in $CDCl_3$ (internal standard, Me_4Si) or D_2O (internal standard MeOH, δ MeOH *vs.* Me_4Si 49.0) were recorded with a Jeol FX-100 spectrometer. Molecular sieves were activated by heating for 16 h at 160° at 133 Pa.

3-O-Brosyl-1,2:5,6-di-O-isopropylidene-α-D-gulofuranose (**2**). — Brosyl chloride (2 g, 7.8 mmol) was added to a solution of **1** (1 g, 3.84 mmol) in dry pyridine (2.5 mL), and the mixture was stirred at 60°, with the exclusion of atmospheric moisture, until t.l.c. (solvent *A*) showed complete conversion of the starting material into a faster-moving product. After being cooled to room temperature, the mixture was poured into an excess of aqueous sodium hydrogencarbonate solution. The precipitate formed was collected, washed with cold water, and processed in the usual way, to give, after evaporation of solvents, a solid residue (1.7 g, 92%) which was chromatographically homogeneous. Crystallization from dichloromethane–ethanol (twice) gave **2**; m.p. 127–128° (dec.), $[\alpha]_D^{20}$ −37° (*c* 0.91, chloroform).

Anal. Calc. for $C_{18}H_{23}BrOS$: C, 45.10; H, 4.83; S, 6.68. Found: C, 44.92; H, 4.96; S, 6.73.

3-Deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-galactofuranose (**4**). — (*a*) Commercial Amberlyst-A-26 (F^-) resin (25 g) was dehydrated by stirring in boiling benzene (150 mL) under reflux for 8 h in a Soxhlet extractor containing molecular sieve 3A. The brosyl derivative **2** (6.4 g) was introduced, and the mix-

ture was boiled overnight under reflux, with stirring and exclusion of atmospheric moisture. T.l.c. (solvent *B*) then showed that only traces of the starting material (R_F 0.1) remained. Two products (R_F 0.5 and 0.6) were formed, and the faster-moving one decolorized permanganate spray reagent. The mixture was cooled, and filtered, the resin was washed with several portions of dichloromethane, and the filtrate and washings were combined, and concentrated. The residue was dissolved in ethanol (100 mL), and hydrogenated at room temperature and atmospheric pressure in the presence of solid sodium hydrogencarbonate (2 g), using 5% palladium-on-charcoal as the catalyst (1 g). When the uptake of hydrogen ceased (~30 min), t.l.c. (solvent *B*) showed that the permanganate-positive component was no longer present, and that a new product had been formed (R_F 0.3). The component showing R_F 0.5, which had remained unchanged, was isolated by elution from a column of silica gel, to give the desired product **4** (1.8 g, 51.4%); m.p. 47–50° (lit.[1] m.p. 48–49°).

(*b*) DAST (1 mL) was slowly added to a mixture of **1** (1 g) and DMAP (1 g) in dry dichloromethane (5 mL) stirred at −10° under an inert gas. The mixture was allowed to warm, and was then kept for 24 h at room temperature. After being cooled to −20°, methanol (10 mL) was slowly added, and the mixture was partitioned between dichloromethane and aqueous sodium hydrogencarbonate solution. Concentration of the dichloromethane phase, and chromatography, gave **4** (0.9 g, 89.3%), which solidified on standing, and was identical with the afore-described compound.

*Acetylation of 3-deoxy-3-fluoro-*D*-galactose.* — (*a*) 3-Deoxy-3-fluoro-D-galactose (0.56 g, prepared from **4** by following the published directions[1]) was added to a stirred mixture of acetic anhydride (15 mL) and fused sodium acetate (300 mg) kept at 95–100°, and the mixture was stirred with the exclusion of atmospheric moisture for 10 min. T.l.c. (solvent *A*) then showed two spots (R_F 0.6 and 0.4) of about the same intensity. On prolonged reaction, the intensity of the spot having the lower R_F value diminished, and finally disappeared completely (1.5 h). The mixture was processed conventionally to give, after crystallization from ethanol–isopropyl ether, compound **5**, m.p. 126–128° (lit.[1] m.p. 126–127°); ^{13}C-n.m.r. data: δ 91.5 (d, $^3J_{CF}$ 11 Hz, C-1), 88.7 (d, $^1J_{CF}$ 195.3 Hz, C-3), 71.0 (d, $^3J_{CF}$ 3 Hz, C-5), 68.9 (d, $^2J_{CF}$ 19.5 Hz, C-2), 66.7 (d, $^2J_{CF}$ 17.1 Hz, C-4), and 61.1 (d, $^4J_{CF}$ 2.4 Hz, C-6). The ^{13}C-n.m.r. spectrum of the material that remained in the mother liquor showed, *inter alia*, signals at 98.6–97 p.p.m., suggesting that furanose structures were present.

(*b*) Cold (0°) acetic anhydride (3 mL) was added dropwise, with stirring, to a cold (0°) solution of 3-deoxy-3-fluoro-D-galactose (100 mg) in pyridine (2 mL). The mixture was kept for 30 min at 0°, and overnight at room temperature. T.l.c. (solvent *A*) then showed that the reaction was complete (single spot, R_F 0.6) and the product was isolated in the usual way. In addition to the lines present in the spectrum of **5** (see foregoing), the ^{13}C-n.m.r. spectrum of the product thus obtained showed definite signals, reflecting the presence of **6**, at δ 89.7 (d, $^3J_{CF}$ 8.6

Hz, C-1) and 85.4 (d, $^1J_{CF}$ 192.9 Hz, C-3). No lower-field anomeric signals indicative of furanoses were present.

Methyl 2,4,6-tri-O-acetyl-3-fluoro-β-D-galactopyranoside (**7**). — A solution (1 mL) of hydrogen bromide in acetic acid was added to a solution of **5**, or to a mixture of pyranose acetates **5** and **6** (200 mg), in dry dichloromethane (1 mL), and the solution was kept for 1 h at room temperature. T.l.c. (solvent *C*) then showed that the reaction was complete, and that one product (R_F 0.7; *cf.*, 0.4 for the starting material) was formed. The mixture was concentrated, the HBr and acetic acid were removed by co-distillation with toluene, and a solution of the residue in the minimal volume of dichloromethane was added to a mixture of methanol (7 mL), mercuric cyanide (150 mg), and Drierite (1.5 g) that had been prestirred for 2 h. After additional stirring for 30 min, t.l.c. (solvent *C*) showed that all of the glycosyl halide had reacted. The mixture was concentrated, the residue was extracted with dichloromethane, and the extract was successively washed with aqueous potassium bromide solution and water, dried, and concentrated. The residue was chromatographed on a column of silica gel, to give **7** (134 mg, 73%). Crystallization from ethanol–isopropyl ether afforded crystalline **7**, m.p. 81.5–82.5°, $[\alpha]_D^{25}$ −3.3° (*c* 0.87, chloroform); ^{13}C-n.m.r. data: δ 101.3 (d, $^3J_{CF}$ 11 Hz, C-1), 88.8 (d, $^1J_{CF}$ 192.9 Hz, C-3), 69.8 (d, $^3J_{CF}$ 6.1, C-5), 69.7 (d, $^2J_{CF}$ 19.5 Hz, C-2), 66.9 (d, $^2J_{CF}$ 17.1 Hz, C-4), 61.2 (s, C-6), and 56.9 (s, Me).

Anal. Calc. for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.94. Found: C, 48.65; H, 6.17.

Methyl 3-deoxy-3-fluoro-β-D-galactopyranoside (**8**). — A solution of sodium methoxide in methanol (M; 0.5 mL) was added to a solution of **7** (100 mg) in methanol (5 mL), and the mixture was kept overnight at room temperature. T.l.c. (solvent *D*) then showed that the reaction was complete, and that only one product (R_F 0.3) had been formed. After neutralization of the base with Dowex 50-W (H^+) resin, filtration, and concentration of the filtrate, compound **8** was obtained in almost theoretical yield; m.p. 161–162° (from ethanol–ethyl acetate), $[\alpha]_D^{25}$ −11° (*c* 0.85, water); ^{13}C-n.m.r. data: δ 103.2 (d, $^3J_{CF}$ 11 Hz, C-1), 93.2 (d, $^1J_{CF}$ 183.1 Hz, C-3), 74.0 (d, $^3J_{CF}$ 7.3 Hz, C-5), 69.5 (d, $^2J_{CF}$ 19.5 Hz, C-2), 67.0 (d, $^2J_{CF}$ 17.1 Hz, C-4), 60.7 (d, $^4J_{CF}$ 3.6 Hz, C-6), and 57.4 (s, Me).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.90; H, 6.70. Found: C, 42.95; H, 7.01.

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