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Note

The synthesis of derivatives of 3-amino-2,3-dideoxy-2-fluoro-D-altrose

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In pursuit of a synthesis of the fluoro analogues of 2-amino-2-deoxy-D-glucose, we have investigated the reaction of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside[1] (**1**) with fluoride anion. Although direct S_N2 displacement of the 3-sulphonate is probably unfavourable[2], participation by the neighbouring *N*-benzoyl group was expected to occur, thereby enhancing the displacement with overall retention of configuration to give a derivative of the 3-fluoroglucoside.

When **1** was heated with tetrabutylammonium fluoride in either acetonitrile or hexamethylphosphoric triamide, it was rapidly converted into the *N*-benzoylepimine **2** and then into a faster-moving component (t.l.c.) and two less-mobile compounds. Column chromatography gave the former (35%) as a glass, which was identified as methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**4**);

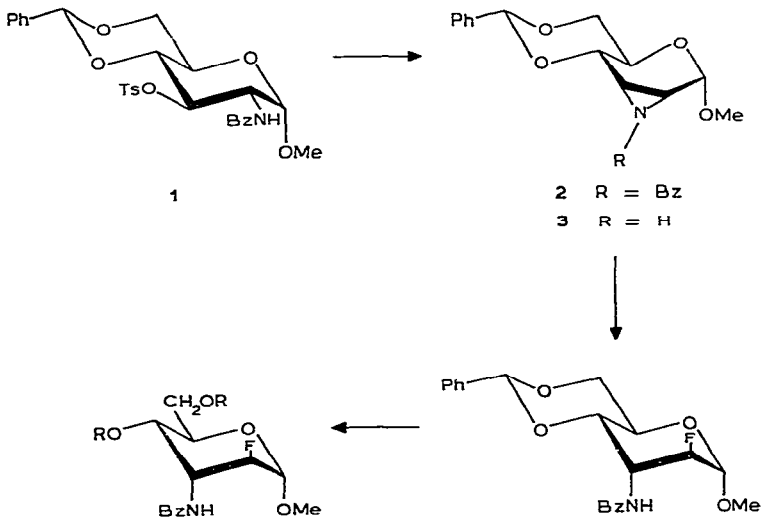

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TABLE I

^{1}H-N.M.R. PARAMETERS[a]

Compound	**4**[b]	**5**[c]	**6**[c]
H-1	4.85dt	5.00dt	4.92dt
H-2	4.29ddd	4.67ddd	4.60ddd
H-3	5.06m	5.35m	5.13m
H-4	3.87dd	5.63ddd	5.18ddd
H-5		4.40dt	4.12dt
H-6a		4.67dd	4.25cm
H-6b		4.47dd	
OCH_3	3.49s	3.54s	3.57s
C*H*Ph	5.63s		
N*H*	6.88d		
$J_{1,2}$	1.5	1.5	1.5
$J_{1,3}$	1.5	1.5	1.2
$J_{2,3}$	3.0	3.6	3.5
$J_{3,4}$	2.5	4.6	4.5
$J_{4,5}$	9.0	9.6	10.0
$J_{5,6a}$		2.6	4.0
$J_{5,6b}$		6.0	4.0
$J_{6a,6b}$		12.0	—
$J_{F-2,H-2}$	45	44.0	45
$J_{F-2,H-1}$	9	8.0	8
$J_{F-2,H-3}$		9.0	—
$J_{F-2,H-4}$	~1	2.0	1.5

[a]For solutions in $CDCl_3$ (internal Me_4Si); chemical shifts on δ scale, and J in Hz. [b]At 100 MHz. [c]At 220 MHz.

the latter components could not be separated, but neither exhibited a ^{19}F-n.m.r. resonance and one was probably the *N*-debenzoylated epimine **3**.

Compound **4** showed a single ^{19}F-n.m.r. resonance which appeared as a double triplet (J ~8.6, 8.6, and 44.1 Hz) at −28.5 p.p.m. (relative to the signal for C_6F_6). Unfortunately, the ^{1}H-n.m.r. spectrum of **4** was not readily interpretable, but debenzylidenation of **4** followed by acetylation or benzoylation afforded, respectively, the 4,6-diacetate **6** or the 4,6-dibenzoate **5**. The ^{1}H-n.m.r. spectrum of **5** (see Table I) was clearly incompatible with a 3-fluoroglycopyranoside, particularly inasmuch as the resonance (δ 5.63) at lowest field, due to H-4, was a double double-doublet with splittings of 9.6, 4.6, and 2 Hz. Upon irradiation of the ^{19}F resonance, the 2-Hz splitting disappeared; the small magnitude of this internuclear coupling indicated that the fluorine was probably not vicinal to H-4. The remaining possibility that ring-opening of the *N*-benzoylepimine **2** had occurred by axial attack at C-2, to give the 2-fluoroaltroside **4**, was supported by the ^{1}H-n.m.r. parameters. The H-1 resonance occurred at δ 5.00 as a double triplet (J 8, 1.5, and 1.2 Hz). Upon irradiation at the ^{19}F resonance, the large coupling (8 Hz) was diminished to ~4 Hz, although complete decoupling did not occur, suggesting that H-1 was vicinal to the fluorine.

TABLE II

^{19}F-N.M.R. PARAMETERS[a]

Compound	**4**[b]	**5**[c]	**6**[b]
F-2	−28.5dt	−30.8dt	−30.4dt
$J_{F-2,H-2}$	46	44	46
$J_{F-2,H-1}$	8.5	8.5	8.6
$J_{F-2,H-3}$	8.5	8.5	8.6

[a]For solutions in $CDCl_3$ (internal C_6F_6); chemical shifts on δ scale. [b]At 56.46 MHz. [c]At 94.1 MHz.

Furthermore, the small, residual proton–proton couplings ($J_{1,2} \sim J_{1,3} \sim 1.5$ Hz) were in accord with the $^4C_1$ conformation of an α-altropyranoside (as in **5**). The H-2 resonance appeared as a double double-doublet (J 44, 3.6, and 4.6 Hz) and H-3 as a complex multiplet. The ^{1}H-n.m.r. spectrum of the 4,6-diacetate **6** gave further support to the structure of the 2-fluoroaltroside **4** (Table I).

The results reveal that fluoride displacement of **1** occurs *via* **2**, involving *N*- rather than *O*-participation from the benzamido group. *N*-Participation in **1** occurs[1] under basic conditions, whereas *O*-participation occurs under neutral conditions[1]. Presumably, *N*-participation must be due to the high basicity of fluoride anion. Although Guthrie and Murphy reported[3] that **2** underwent predominant *trans*-diequatorial ring-opening on reaction with azide and other nucleophiles, it was concluded later[4] that "diaxial ring-opening" predominated. Our findings provide a further example of the predominant, if not exclusive, formation of a *trans*-diaxial product from **2**.

EXPERIMENTAL

Esters of methyl 3-benzamido-2,3-dideoxy-2-fluoro-α-D-altropyranoside. — (*a*) *4,6-Dibenzoate* (**5**). A solution of the 3-tosylate[1] **1** (4 g, 7.4 mmol) and anhydrous tetrabutylammonium fluoride[5] (16 g, 61 mmol) in hexamethylphosphoric triamide (20 ml) was heated at 85° and the reaction monitored by t.l.c. Within 5 min, **1** was totally consumed, giving the *N*-benzoylepimine **2**. A portion (~0.5 ml) of the reaction mixture was removed after ~15 min and processed as described below, to give a product that was identical (i.r., m.p., mixture m.p.) with authentic[6] **2**. On further reaction, **2** was slowly converted into the faster-moving **4** together with the two slower-moving compounds of similar mobility. After 6 h, the reaction mixture was poured into water, the solid was collected, and a solution in ethyl acetate was washed with water, dried ($MgSO_4$), and concentrated onto a little silica gel. Dry-packed column chromatography[7] with cyclohexane–ethyl acetate (4:1) then gave **4** as a colourless glass (1 g, 35%) (Found: C, 65.0; H, 5.65; N, 3.35. $C_{21}H_{22}FNO_5$ calc.: C, 65.1; H, 5.7; N, 3.6).

The reaction followed the same course when acetonitrile was used as solvent, but the initial conversion of **1**→**2** required at least 20 min for completion.

A solution of **4** (0.3 g, 0.78 mmol) in methanol (75 ml) containing conc. hydrochloric acid (2.5 ml) was heated under reflux for 15 min; t.l.c. then indicated the complete conversion of **4** into a slower-moving product. The solution was cooled, neutralised ($PbCO_3$), and concentrated, and the syrupy residue was conventionally benzoylated using dry pyridine (15 ml) and benzoyl chloride (1 ml) to give **5** (0.28 g, 71%), m.p. 162.5–164° [from dichloromethane–light petroleum (b.p. 60–80°)], $[\alpha]_D$ +149° (*c* 0.7, chloroform) (Found: C, 66.0; H, 5.0; F, 4.0; N, 2.7. $C_{28}H_{26}FNO_7$ calc.: C, 66.3; H, 5.10; N, 2.75; F, 3.75).

(*b*) *4,6-Diacetate* (**6**). The syrupy product obtained from **4** (0.5 g, 1.3 mmol) as described in (*a*) was treated conventionally with pyridine (20 ml) and acetic anhydride (6 ml), to give **6** (0.25 g, 51%), m.p. 102–104° [from ether–light petroleum (b.p. 60–80°)], $[\alpha]_D$ +129° (*c* 0.5, chloroform) (Found: C, 56.6; H, 5.7; N, 3.55. $C_{18}H_{22}FNO_7$ calc.: C, 56.4; H, 5.75; N, 3.65).

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