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Note

Synthesis of methyl 3-acetamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-mannopyranoside: a protected 2-fluoro analogue of acosamine

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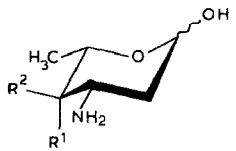
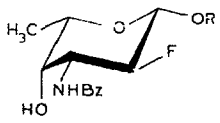
Acosamine (**1**) and daunosamine (**2**) are amino sugar components of some antibiotics of the anthracycline group which are effective in the treatment of solid tumors[1].

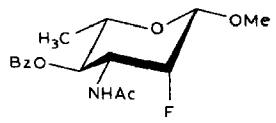
Efforts have been made to prepare analogues of these antibiotics, modified in the amino sugar moiety, with a view to improving their therapeutic index[2]. Interest in fluorinated carbohydrates was awakened by enhancement of biological activity and/or lowering of toxicity of fluorinated derivatives when compared to their parent compounds[3]. We have described[4] syntheses of methyl (**3**) and benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside (**4**), which are protected analogues of daunosamine having an equatorial fluorine substituent at position 2, and we now report the synthesis of a derivative (**5**) of 2-fluoroacosamine in which the amino and fluoro groups are *cis*.



1 R^1 = H, R^2 = OH
2 R^1 = OH, R^2 = H



3 R = Me
4 R = Bzl



5

Reaction of the known[5] azido-alcohol **6**, readily available from D-galactose, with trifluoromethanesulfonic anhydride in pyridine furnished 82% of the 2-triflate **7**. Treatment of **7** in dry *N,N*-dimethylformamide with 8 equiv. of anhydrous tetra-

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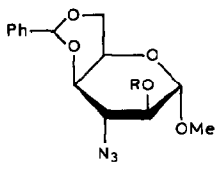
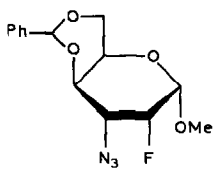
butylammonium fluoride[6] afforded 78% of the 2-fluoro derivative **8**. The *gulo* configuration of **8** was ascertained on the basis of ^{1}H- and ^{13}C-n.m.r. data. Thus, the ^{1}H data, $J_{1,2} = J_{2,3} = 4$ Hz indicated H-2 to be axial, $J_{C\text{-}1,F}$ 22.3, $J_{C\text{-}3,F}$ 16.6 Hz revealed[7] the fluorine and the substituents attached to the coupled carbon to be *cis*, and $J_{C\text{-}4,F}$ 6.1 Hz accorded with a *trans* relationship between these nuclei[7].

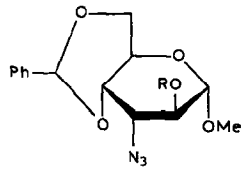
The introduction of the 2-fluorine substituent in **8** by an S_N2-like reaction may be explained by the conformational flexibility of the α-D-*ido* derivative **7** which can adopt a $^1C_4$ conformation. The *J* values of **7** indicated a $^4C_1 \rightleftharpoons {}^1C_4$ equilibrium. When the same treatment was applied to a more rigid system such as **10** (readily prepared from **9**[8]), the reaction was unsuccessful.



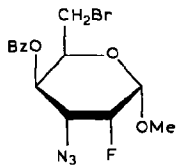
6 R = H
7 R = CF_3SO_2



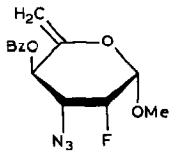
8



9 R = H
10 R = CF_3SO_2



11



12

The transformation of methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-gulopyranoside (**8**) into **12** was carried out according to known methodology[9]. The opening of the 1,3-dioxane ring in **8** with *N*-bromosuccinimide gave **11** (56%) which, on treatment with silver fluoride, afforded the unsaturated compound **12** (72%).

Catalytic hydrogenation of **12** under *N*-acetylating conditions afforded methyl 3-acetamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-mannopyranoside (**5**, 60%). The ^{1}H-n.m.r. data for **5** ($J_{3,4} = J_{4,5} = 10$ Hz) accorded with a $^1C_4$ conformation, and hence the L configuration. This conclusion was also corroborated by the low-field chemical shift (71.9 p.p.m.) of the C-5 resonance[4] and the lower $J_{C\text{-}4,F}$ value of **5** in comparison with those of **8**, **11**, and **12**[7].

EXPERIMENTAL

General methods. — Melting points were determined with a Reichert hot-stage microscope and are uncorrected. Optical rotations were measured with a Carl

Zeiss photoelectric polarimeter. I.r. spectra were recorded with a Perkin–Elmer 399 B spectrophotometer. ^{1}H-N.m.r. spectra (400, 360, and 100 MHz) were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Varian spectrometers, and ^{13}C-n.m.r. spectra (100.56 and 25.2 MHz) for solutions in $CHCl_3$ with Varian spectrometers [$\delta(Me_4Si) = \delta(CHCl_3) + 77.2$ p.p.m.].

Silica gel 60 (70–230 mesh) (Merck) was used for column chromatography and silica gel GF_{254} for t.l.c., with detection by charring with sulphuric acid.

All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. The term "standard work-up" means that the organic layer was washed with water, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure.

*Methyl 3-azido-4,6-O-benzylidene-3-deoxy-2-O-trifluoromethanesulphonyl-α-*D*-idopyranoside* (**7**). — To a solution of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-idopyranoside[5] (**6**; 1.03 g, 3.5 mmol) in dry pyridine (8 mL) at −10° was added trifluoromethanesulphonic anhydride (1.89 g, 6.7 mmol) dropwise. The mixture was stirred for 2 h at 0°, then poured into ice–water, and extracted with chloroform. The combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate and then with water. After standard work-up, column chromatography (hexane–chloroform, 1:1) of the crude product gave **7** (1.21 g, 82%), m.p. 114–116° (from chloroform–light petroleum), $[\alpha]_D$ +81° (*c* 1, chloroform); ν_{max}^{KBr} 2120 cm^{-1} (N_3). Mass spectrum: *m/z* 439 (M^+). N.m.r. data: ^{1}H (400 MHz), δ 3.58 (s, 3 H, OMe), 3.92 (m, 1 H, H-5), 4.17 (m, 2 H, H-3,4), 4.25 and 4.44 (2 dd, 2 H, J_{gem} 13.8, $J_{5,6}$ 1.5, $J_{5,6'}$ 2.0 Hz, H-6,6'), 4.83 (dd, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 5 Hz, H-2), 5.08 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5.67 (s, 1 H, H-7), 7.46–7.63 (m, 5 H, Ph); ^{13}C (25.2 MHz), δ 55.9 (OCH_3), 59.8* (C-5), 60.0* (C-3), 68.7 (C-6), 73.2 (C-4), 78.9 (C-2), 98.7 (C-1), 100.7 (C-7).

Anal. Calc. for $C_{15}H_{16}F_3N_3O_7S$: C, 41.0; H, 3.7; N, 9.6. Found: C, 40.5; H, 3.7; N, 9.4.

*Methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-2-fluoro-α-*D*-gulopyranoside* (**8**). — A solution of **7** (1.23 g, 2.8 mmol) in dry *N,N*-dimethylformamide (5 mL) was added dropwise to anhydrous tetrabutylammonium fluoride[6] (5.85 g, 22.4 mmol) under argon and at room temperature. The mixture was stirred for 5 h, then poured into ice–water, and extracted with chloroform (5 × 30 mL). After standard work-up of the combined organic extracts, column chromatography (hexane–ether, 9:1 then 8.5:1.5) of the product gave **8** (0.67 g, 78%), m.p. 91.5–92.5° (from methanol–ether), $[\alpha]_D$ +191° (*c* 0.85, chloroform); ν_{max}^{KBr} 2110 cm^{-1} (N_3). Mass spectrum: *m/z* 309 (M^+). N.m.r. data: ^{1}H (400 MHz), δ 3.53 (s, 3 H, OMe), 3.86 (bd, 1 H, *J* 1.5–2.0 Hz, H-5), 4.04 (m, 1 H, H-4), 4.07 and 4.29 (2 dd, 2 H, J_{gem} 12.5, $J_{5,6}$ 1.5, $J_{5,6'}$ 2.0 Hz, H-6,6'), 4.24 (m, 1 H, H-3), 5.03 (dt, 1 H, $J_{2,F}$ 44.8, $J_{1,2} = J_{2,3} = 4.0$, $J_{1,F}$ ~0 Hz, H-2), 5.05 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.53 (s, 1 H, H-7), 7.36–7.48 (m, 5 H, Ph); ^{13}C (25.2 MHz), δ 56.3 (OCH_3), 57.9 (d, $J_{3,F}$ 16.6 Hz, C-3), 58.9

*Assignments may be interchanged.

(C-5), 69.0 (C-6), 75.8 (d, $J_{4,F}$ 6.1 Hz, C-4), 85.6 (d, $J_{2,F}$ 190.7 Hz, C-2), 97.4 (d, $J_{1,F}$ 22.3 Hz, C-1), 101.1 (C-7).

Anal. Calc. for $C_{14}H_{16}FN_3O_4$: C, 54.4; H, 5.2; N, 13.6. Found: C, 54.4; H, 5.2; N, 13.7.

Methyl 3-azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-α-D-gulopyranoside (**11**). — To a solution of **8** (0.42 g, 1.4 mmol) in carbon tetrachloride (15 mL) were added *N*-bromosuccinimide (0.37 g, 2.1 mmol) and barium carbonate (1.36 g, 6.9 mmol). The suspension was heated under reflux for 1 h and then filtered hot through Celite. The Celite was washed with chloroform, and the combined filtrate and washings were concentrated to dryness. The residue was dissolved in chloroform and, after standard work-up, column chromatography (hexane–ether, 9.8:0.2) of the crude product gave **11** (0.29 g, 56%) as a syrup, $[\alpha]_D$ +166° (*c* 1.8, chloroform); ν_{max}^{film} 2110 (N_3), 1725 cm^{-1} (*C*OPh). N.m.r. data: ^1H (400 MHz), δ 3.50 (d, 2 H, $J_{5,6} = J_{5,6'} = 4.5$ Hz, H-6,6'), 3.71 (s, 3 H, OMe), 4.44 (q, 1 H, $J_{2,3} = J_{3,4} = J_{3,F} = 4$ Hz, H-3), 4.54 (bt, 1 H, $J_{4,5} \sim 1$, $J_{5,6} = J_{5,6'} = 4.5$ Hz, H-5), 5.04 (dt, 1 H, $J_{2,F}$ 44, $J_{1,2} = J_{2,3} = 4$ Hz, H-2), 5.17 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.38 (td, 1 H, $J_{3,4} = J_{4,F} = 4$, $J_{4,5} \sim 1$ Hz, H-4), 7.54–8.15 (m, 5 H, Ph); ^{13}C (25.2 MHz), δ 29.1 (C-6), 56.4 (OCH_3), 57.2 (d, $J_{3,F}$ 17.1 Hz, C-3), 65.8 (C-5), 71.0 (d, $J_{4,F}$ 5.6 Hz, C-4), 85.5 (d, $J_{2,F}$ 193.7 Hz, C-2), 97.1 (d, $J_{1,F}$ 22.3 Hz, C-1), 164.8 (*C*OPh).

Methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-lyxo-hex-5-enopyranoside (**12**). — A mixture of **11** (0.23 g, 0.6 mmol) and silver fluoride (0.51 g, 4.0 mmol) in dry pyridine (6 mL) was stirred for 12 h at room temperature in the dark, and then poured dropwise into ether (200 mL). The resulting mixture was filtered through Celite and concentrated. Column chromatography (hexane–ether, 9.2:0.8) of the residue gave **12** (0.13 g, 72%), m.p. 57.5–59°, $[\alpha]_D$ +86° (*c* 1, chloroform); ν_{max}^{KBr} 2105 (N_3), 1735 (*C*OPh), 1670 (C=C), 880 cm^{-1} (C=CH_2). Mass spectrum: *m/z* 307 (M^+). N.m.r. data: ^1H (400 MHz), δ 3.64 (s, 3 H, OMe), 4.02 (ddd, 1 H, $J_{3,F}$ 16, $J_{3,4}$ 6.5, $J_{2,3}$ 3 Hz, H-3), 4.88 (dd, 1 H, $J_{1,F}$ 8.5, $J_{1,2} \sim 2.5$ Hz, H-1), 4.83 and 4.96 (2 bs, 2 H, $J_{gem} \sim 1.5$ Hz, H-6,6'), 5.07 (dt, 1 H, $J_{2,F}$ 47, $J_{1,2} = J_{2,3} = 3$ Hz, H-2), 5.77 (dd, 1 H, $J_{3,4}$ 6.5, $J_{4,F}$ 1.5 Hz, H-4), 7.46–8.08 (m, 5 H, Ph); ^{13}C (25.2 MHz), δ 57.1 (OCH_3), 59.5 (d, $J_{3,F}$ 17.7 Hz, C-3), 69.5 (d, $J_{4,F}$ 4.5 Hz, C-4), 86.7 (d, $J_{2,F}$ 192.1 Hz, C-2), 99.4 (d, $J_{1,F}$ 19.3 Hz, C-1), 101.5 (C-6), 149.3 (C-5), 164.5 (*C*OPh).

Anal. Calc. for $C_{14}H_{14}FN_3O_4$: C, 54.7; H, 4.6; N, 13.7. Found: C, 54.5; H, 4.5; N, 13.7.

Methyl 3-acetamido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-mannopyranoside (**5**). — A solution of **12** (16 mg, 0.017 mmol) in dry methanol (5 mL) and dry acetic anhydride (0.3 mL, 3 mmol) was hydrogenated for 12 h at atmospheric pressure in the presence of 10% Pd/C (20 mg). The suspension was filtered through Celite and concentrated. Preparative t.l.c. (2 × chloroform–methanol, 0.5%) of the residue gave **5** (10 mg, 60%), m.p. 184.5–185.5° (from dichloromethane–light petroleum), $[\alpha]_D$ +32° (*c* 0.3, chloroform); ν_{max}^{KBr} 3300 (N-H), 1720 (*C*OPh), 1650 (NH*C*OCH_3). Mass spectrum: *m/z* 326 (MH^+, 100%), 294 ($MH^+ - OMe$, 46%).

N.m.r. data: ^{1}H (400 MHz), δ 1.46 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.00 (s, 3 H, OAc), 3.71 (s, 3 H, OMe), 3.85 (m, 1 H, H-5), 4.53 (dbt, 1 H, $J_{3,F}$ 31.3, $J_{3,NH} = J_{3,4} = 10$, $J_{2,3}$ ~2 Hz, H-3), 4.64 (d, 1 H, $J_{1,F}$ 19.4 Hz, H-1), 4.83 (dd, 1 H, $J_{2,F}$ 50.5, $J_{2,3}$ 2 Hz, H-2), 5.16 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 6.12 (d, 1 H, $J_{NH,3}$ 9.5 Hz, N-H), 7.54–8.12 (m, 5 H, Ph); ^{13}C (100, 56 MHz), δ 17.6 (C-6), 23.1 ($COCH_3$), 52.3 (d, $J_{3,F}$ 16.5 Hz, C-3), 57.4 (OCH_3), 71.4 ($J_{4,F}$ ~0 Hz, C-4), 71.9 (C-5), 89.1 (d, $J_{2,F}$ 183.7 Hz, C-2), 99.7 (d, $J_{1,F}$ 16.5 Hz, C-1).

Anal. Calc. for $C_{16}H_{20}FNO_5$: C, 59.1; H, 6.2; N, 4.3. Found: C, 59.1; H, 6.2; N, 4.4.

*Methyl 3-azido-4,6-O-benzylidene-3-deoxy-2-O-trifluoromethanesulphonyl-α-*D*-altropyranoside* (**10**). — To a solution of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside[8] (**9**; 0.77 g, 2.5 mmol) in dry pyridine (6 mL) at −10° was added trifluoromethanesulphonic anhydride (1.34 g, 4.8 mmol) dropwise. The mixture was stirred for 2 h at 0° and then poured into ice–water. Column chromatography (hexane–chloroform, 1:1) of the crude product gave **10** (0.82 g, 75%), m.p. 131–133° (from chloroform–light petroleum), $[\alpha]_D$ +45° (*c* 1.4, chloroform); ν_{max}^{KBr} 2120 cm^{-1} (N_3). Mass spectrum: 439 (M^+). N.m.r. data: ^{1}H (100 MHz), δ 3.46 (s, 3 H, OMe), 3.67–4.46 (m, 5 H, H-3,4,5,6,6'), 4.77 (bs, $J_{1,2}$ ~1 Hz, H-1), 4.90 (dd, $J_{1,2}$ ~1, $J_{2,3}$ 2 Hz, H-2), 5.66 (s, 1 H, H-7), 7.34–7.60 (m, 5 H, Ph); ^{13}C (25.2 MHz), δ 56.1 (OCH_3), 57.9* (C-5), 58.6* (C-3), 68.6 (C-6), 74.9 (C-4), 81.1 (C-2), 98.1 (C-1), 102.3 (C-7).

Anal. Calc. for $C_{15}H_{16}F_3N_3O_7S$: C, 41.0; H, 3.7; N, 9.6. Found: C, 40.8; H, 3.7; N, 9.5.

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*Assignments may be interchanged.

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