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## Note

# Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside*

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Although several syntheses[1] of daunosamine, the sugar component of adriamycin, daunomycin, *etc.*, have been described, very few efforts have been made to prepare analogues of daunosamine with a view to improving the therapeutic index. Fluoro analogues of steroids[2] have better activity than their parent compounds, and fluorine substitution in sporaricin A lowered the toxicity of the antibiotic[3]. Prior to studying the effect of fluorodaunosamine on the antibiotic activity of anthracyclines, we have synthesised the 2-fluorodaunosamine derivative **6**.

Methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside[4] (**1**) was prepared (61%) by a modification of the literature procedure. Reaction of **1** with *N*-bromosuccinimide[5] in carbon tetrachloride opened the 1,3-dioxane ring and gave 83% of the 6-bromide **2**. The $^1$H-n.m.r. spectrum of **2** was not amenable to first-order analysis, but the loss of the benzylidene group was clear from the absence of a signal for a benzylidene acetal proton. Further proof of the structure of **2** was obtained by its reductive debromination with Raney nickel to give the deoxy compound **3**, the $^1$H-n.m.r. spectrum of which showed a doublet at δ 1.31 for H-6,6′,6″ and a multiplet at δ 4.15 for H-5. The resonances due to the remaining protons were consistent with the product's being methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-α-D-altropyranoside (**3**).

Dehydrobromination[6] of **2** was effected with 1,5-diazabicyclo[5.4.0]undec-5-ene in hexamethylphosphoric triamide under nitrogen for 96 h, to furnish 73% of the 5,6-ene **4**. The $^1$H-n.m.r. spectrum of **4** contained two narrow triplets for H-6 and H-6′ at δ 4.82 and 4.97. Hydrogenation[7] of **4** over palladised carbon in ethyl acetate and chromatography of the products gave, first, methyl 3-benzamido-2,3,4,6-tetradeoxy-2-fluoro-α-D-*threo*-hex-4-enopyranoside (**5**), which was identified on the basis of $^1$H-n.m.r. data (a singlet corresponding to vinylic methyl at δ

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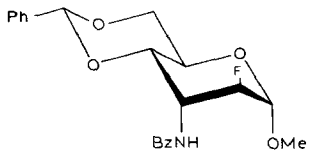


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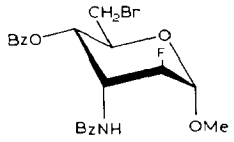


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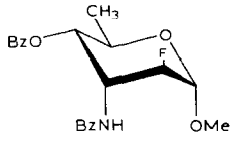


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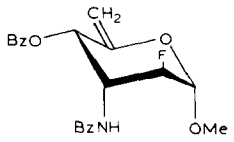


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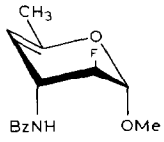


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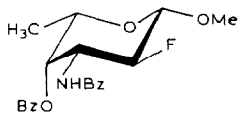


6

1.85) and the mass spectrum (signal for $M^+$ at *m/z* 265) which suggested the assigned structure[8].

The second fraction, obtained in almost equal amount, was methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside (**6**). The L configuration was assigned on the basis of the $[\alpha]_D$ value (−152.5°) and by comparison with the deoxy sugar **3**. The $^1$H-n.m.r. spectrum was in agreement with the structure (**6**) assigned.

The coupling of **6** with 4-demethoxydaunomycinone is being investigated.

## EXPERIMENTAL

The general methods have been described[1]. $^1$H-n.m.r. spectra were recorded with a Bruker WH 90 FT NMR spectrometer. Optical rotations were measured with a JASCO DIP-181 polarimeter.

*Methyl 3-benzamido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-α-D-altropyranoside* (**2**). — To a solution of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside[9] (2 g, 3.7 mmol) in dry tetrahydrofuran (5 mL) under nitrogen was added M tetrabutylammonium fluoride in tetrahydrofuran (30 mL, 30 mmol). The mixture was boiled under reflux for 6 h, diluted with water, and extracted repeatedly with ethyl acetate. The organic layer was concentrated and the residue was subjected to column chromatography on silica gel (ethyl acetate–light petroleum, 1:5) to give **1** (0.88 g, 61%) as a colourless glass. The $^1$H-n.m.r. spectrum was in agreement with that reported[4] for **1**.

To a stirred solution of **1** (0.6 g, 1.55 mmol) in carbon tetrachloride (20 mL) containing barium carbonate (0.68 g) and benzoyl peroxide (5 mg) was added *N*-bromosuccinimide (0.3 g, 1.68 mmol). The mixture was heated under reflux for 3 h, filtered, washed with aqueous sodium hydrogensulfite, aqueous sodium carbonate, and water, dried, and concentrated. The residue was eluted from a short

column of silica gel with ethyl acetate–light petroleum (1:4) to afford **2** (0.6 g, 83%), m.p. 110°, $[\alpha]_D$ +95° (*c* 0.45, chloroform). $^1$H-n.m.r. data ($CDCl_3$): $\delta$ 3.66 (s, 3 H, OMe), 3.5–4.3 (m, 3 H, H-5,6,6'), 4.77 (ddd, 1 H, $J_{2,F}$ 46, $J_{1,2}$ 1.5, $J_{2,3}$ 3 Hz, H-2), 5.02 (bd, 1 H, $J_{1,F}$ 9 Hz, H-1), 5.1–5.5 (m, 2 H, H-3,4), and 7.2–8.0 (m, 10 H, 2 Ph).

*Anal.* Calc. for $C_{21}H_{21}BrFNO_5$: C, 54.1; H, 4.5; N, 3.0. Found: C, 53.8; H, 4.5; N, 2.9.

*Methyl 3-benzamido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-*D*-altropyranoside* (**3**). — A solution of **2** (0.1 g) in ethanol–ethyl acetate (5 mL) was hydrogenated at normal pressure and room temperature for 16 h in the presence of W-2 Raney nickel (0.5 g). The catalyst was then removed and the filtrate was concentrated to afford **3** (0.08 g), m.p. 121°, $[\alpha]_D$ +148° (*c* 0.53, chloroform). $^1$H-n.m.r. data ($CDCl_3$): $\delta$ 1.31 (d, 3 H, *J* 6 Hz, H-6,6',6''), 3.57 (s, 3 H, OMe), 4.15 (m, 1 H, H-5), 4.66 (ddd, 1 H, $J_{2,F}$ 46, $J_{1,2}$ 1.5, $J_{2,3}$ 3 Hz, H-2), 4.88 (bd, 1 H, $J_{1,F}$ 9 Hz, H-1), 5.3 (m, 2 H, H-3,4), and 7–8.2 (m, 10 H, 2 Ph).

*Anal.* Calc. for $C_{21}H_{22}FNO_5$: C, 65.1; H, 5.7. Found: C, 64.8; H, 5.7.

*Methyl 3-benzamido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-*D*-*arabino*-hex-5-enopyranoside* (**4**). — To a solution of **2** (0.2 g, 0.43 mmol) in dry hexamethylphosphoric triamide (2 mL) under nitrogen was added 1,5-diazabicyclo[5.4.0]undec-5-ene (0.076 g, 0.5 mmol) at room temperature. After 96 h, the mixture was diluted with ether, washed successively with aqueous sodium hydrogensulfate, aqueous sodium hydrogencarbonate, and water, dried, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate–light petroleum, 1:4) to give **4** (0.12 g, 74%), $[\alpha]_D$ +113° (*c* 0.49, chloroform). $^1$H-n.m.r. data ($CDCl_3$): $\delta$ 3.62 (s, 3 H, OMe), 4.77 (ddd, 1 H, $J_{2,F}$ 46, $J_{1,2}$ 2, $J_{2,3}$ 4 Hz, H-2), 4.82 (t, 1 H, H-6), 4.97 (t, 1 H, H-6'), 5.0 (bd, 1 H, $J_{1,F}$ 8 Hz, H-1), 5.26 (m, 1 H, H-3), 5.97 (m, 1 H, H-4), and 7.0–8.2 (m, 10 H, 2 Ph).

*Anal.* Calc. for $C_{21}H_{20}FNO_5$: C, 65.45; H, 5.2; N, 3.6. Found: C, 64.8; H, 5.1; N, 3.45.

*Hydrogenation of the 5,6-ene* **4**. — A solution of **4** (0.12 g, 0.31 mmol) in ethyl acetate (5 mL) was hydrogenated at normal pressure and room temperature for 8 h over 5% Pd/C (0.05 g). T.l.c. (ethyl acetate–light petroleum, 1:1) then indicated two products and no **4**. The mixture was filtered and concentrated, and the residue was subjected to column chromatography on silica gel (ethyl acetate–light petroleum, 1:4).

Eluted first was methyl 3-benzamido-2,3,4,6-tetradeoxy-2-fluoro-α-D-*threo*-hex-4-enopyranoside (**5**; 0.032 g, 39%), m.p. 112°, $[\alpha]_D$ −69° (*c* 0.37, chloroform). $^1$H- n.m.r. data ($CDCl_3$): $\delta$ 1.85 (s, 3 H, Me), 3.53 (s, 3 H, OMe), 4.66 (ddd, 1 H, $J_{2,F}$ 46, $J_{1,2}$ 1.5, $J_{2,3}$ 3.5 Hz, H-2), 4.77 (m, 1 H, H-3), 4.84 (bd, 1 H, $J_{1,F}$ 9 Hz), 5.11 (m, 1 H, H-4), 6.55 (d, 1 H, *J* 8 Hz, N-H), and 7.0–8.2 (m, 5 H, Ph). Mass spectrum: *m/z* 265 ($M^+$), 245 ($M^+$ − HF), and 233 ($M^+$ − MeOH).

*Anal.* Calc. for $C_{14}H_{16}FNO_3$: C, 63.4; H, 6.0. Found: C, 63.1; H, 5.95.

Eluted second was methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-

β-L-galactopyranoside (**6**; 0.05 g, 41%), m.p. 108°, $[\alpha]_D$ −152.5° (*c* 0.32, chloroform). $^1$H-n.m.r. data ($CDCl_3$): δ 1.28 (d, 3 H, *J* 6.5 Hz, H-6,6′,6″), 3.66 (s, 3 H, OMe), 4.04 (m, 1 H, H-5), 4.49 (ddd, 1 H, $J_{2,F}$ 46, $J_{1,2}$ 10.5, $J_{2,3}$ 8 Hz, H-2), 4.60 (d, 1 H, H-1), 4.84 (m, 1 H, H-3), 5.65 (m, 1 H, H-4), 6.20 (d, 1 H, *J* 8 Hz, NH), and 7.0–8.2 (m, 10 H, 2 Ph).

*Anal.* Calc. for $C_{21}H_{22}FNO_5$: C, 65.1; H, 5.7; N, 3.6. Found: C, 64.95; H, 5.7; N, 3.4.

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