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SYNTHESIS AND ANTITUMOR ACTIVITY OF 3′-*C*-METHYL-DAUNORUBICIN

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ABSTRACT

Reaction of 1,5-anhydro-4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-L-*lyxo*-hex-1-enitol with daunomycinone in the presence of anhydrous toluene-*p*-sulfonic acid in benzene, followed by removal of the *N*- and *O*-protecting groups under mild conditions, gave 3′-*C*-methyldaunorubicin. The antitumor activity of the new anthracycline glycoside has been evaluated.

INTRODUCTION

Daunorubicin (**1**) and doxorubicin (**2**) are anthracycline glycosides[1,2] which are clinically useful antineoplastic agents. However, their utilisation is limited by undesirable side-effects such as cardiotoxicity[3]. The antitumor activity of **1** and **2** and their analogues is thought to be dependent on their ability to bind to nuclear DNA *via* an intercalative mechanism[4]. In this process, the presence of a 3′-amino group is critical as it stabilises the drug–DNA complex.

The synthesis of analogues of daunorubicin (**1**) and doxorubicin (**2**) in which the amino-sugar moiety is functionally and/or configurationally modified is of interest in relation to structure–activity relationships[5]. We now report the synthesis and preliminary biological evaluation of 3′-*C*-methyldaunorubicin (**3**) in which the natural amino sugar daunosamine is replaced by vancosamine, a branched-chain amino sugar (3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose) constituent of the glycopeptide antibiotic vancomycin[6].

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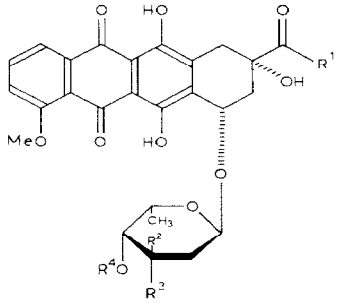

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2 R^1 = CH_2OH, R^2 = R^4 = H, R^3 = NH_2
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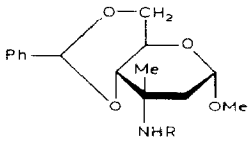

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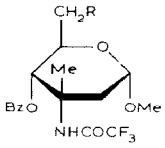

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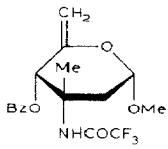

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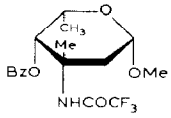

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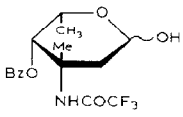

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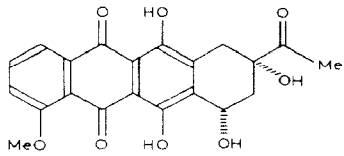

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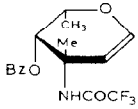

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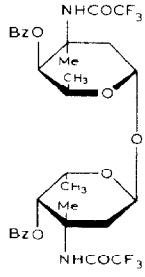

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RESULTS AND DISCUSSION

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*ribo*-hexopyranoside[7] (**5**), prepared in 80% yield, afforded 90% of the 6-bromo derivative **6**[7] upon treatment with *N*-bromosuccinimide in carbon tetrachloride. Dehydrobromination[8] of **6** furnished 88% of the 5,6-unsaturated glycoside **7**, hydrogenation of which with Raney nickel gave methyl 4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranoside (**8**, 78%) and the D-*ribo* isomer **9** which could be separated by chromatography. Acid hydrolysis of **8** afforded the *N*- and *O*-protected hexose derivative **10** as a 1:1 αβ-mixture (ratio based on ^{1}H-n.m.r. data).

The key intermediate for the glycosidation of daunomycinone (**11**), namely, the branched-chain glycal **12**, was obtained as a syrup in 89% yield by treatment of αβ-**10** with tosyl chloride in anhydrous pyridine, using a modification of the procedure developed by Tatsuta and co-workers[9]. Glycosidation of **11** with the glycal **12** in benzene at 45° for 10 min, using toluene-*p*-sulfonic acid as catalyst[10], yielded a mixture of products which was fractionated by column chromatography. Starting materials, separated from the desired glycoside **13**, could be re-utilised. Compound **14** was also isolated as a minor side-product. The yield of **13** was 38%, but longer reaction times and higher reaction temperatures favoured the formation of **14**.

The ^{1}H-n.m.r. data, especially the $J_{1,2}$ and δ H-1 values, indicated[5] **13** to be α-L. Removal of the *N*- and *O*-protective groups from **13** with 0.1M sodium hydroxide–tetrahydrofuran afforded 3′-*C*-methyldaunorubicin (**3**), which was isolated (43%) as the free amine.

The cytostatic activity of **3** against P388 leukemia cells *in vitro* (ID_{50} 0.25 μg/mL) was inferior to that (0.01 μg/mL) of doxorubicin (**2**), and **3** showed no activity against a doxorubicin-resistant P388 leukeumia cell subline. A similar pattern was observed for the *in vivo* tests against P388 and L1210 leukemias: **3** was less toxic than **2** and daunorubicin (**1**), but its range of active doses was greater. Thus, **3** and **1** had similar T/C × 100 values at optimal therapeutic doses against the P388 leukemia (**1**, 1 mg/kg, T/C × 100 = 131; **3**, 20 mg/kg, T/C × 100 = 167) and against the L1210 leukemia (**1**, 2 mg/kg, T/C × 100 = 130; **3**, 20 mg/kg, T/C × 100 = 124).

EXPERIMENTAL

General. — Melting points were determined with a Büchi apparatus and are uncorrected. A Perkin–Elmer Model 141 MC polarimeter (1-dm tube) was used for the measurement of optical rotations. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian A-60 (60 MHz) or Bruker HX 90E (90 MHz) spectrometer, and ^{13}C-n.m.r. spectra (22.63 MHz) with a Bruker HX 90E spectrometer. I.r. spectra were recorded with a Perkin–Elmer Model 257 instrument. Microanalyses were performed by the Service Central de Microanalyse du C.N.R.S. Kieselgel G (Merck) activated at 120° was used for t.l.c. and column chromatography.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-3-C-methyl-3-trifluoroacetamido-α-*D-ribo-*hexopyranoside* (**5**). — To a solution of the amine **4**[7] (2.5 g, 9 mmol) in dichloromethane (100 mL) containing anhydrous pyridine (5 mL) at 0° was added trifluoroacetic anhydride (5 mL). After stirring for 3 h, the solution was diluted with cold water (200 mL), dried, and concentrated. Column chromatography (dichloromethane–ether, 98:2) of the residue gave **5** (2.6 g, 80%), m.p. 110–111°, $[\alpha]_D^{22}$ +70° (*c* 1, chloroform) {lit.[7] m.p. 122–123°, $[\alpha]_D^{22}$ +76° (*c* 0.6, chloroform)}; ν_{max}^{KBr} 3340, 1730, and 1550 cm^{-1}. ^{1}H-N.m.r. data: δ 7.45 (m, 5 H, Ph), 7.20 (bs, 1 H, NH), 5.65 (s, 1 H, H-7), 4.75 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.50–3.50 (m, 4 H, H-4,5,6,6′), 3.35 (s, 3 H, OMe), 3.03 (d, 1 H, $J_{2e,a}$ 15 Hz, H-2*e*), 1.70 (dd, 1 H, $J_{1,2a}$ 4, $J_{2a,e}$ 15 Hz, H-2*a*), and 1.60 (s, 3 H, Me-3).

Anal. Calc. for $C_{17}H_{20}F_3NO_5$: C, 54.40; H, 5.33; N, 3.73. Found: C, 54.10; H, 5.40; N, 3.75.

*Methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy-3-C-methyl-3-trifluoroacetamido-α-*D-ribo-*hexopyranoside* (**6**). — A suspension of **5** (0.75 g, 2 mmol), *N*-bromosuccinimide (0.4 g, 2.2 mmol), and barium carbonate (0.8 g, 4 mmol) in dry carbon tetrachloride (70 mL) was boiled under reflux for 1 h and then filtered. Insoluble material was washed with dichloromethane (40 mL), the combined filtrate and washings were washed with aqueous sodium hydrogensulfite (5%, 200 mL), aqueous sodium hydrogencarbonate (200 mL), and water (300 mL), and then concentrated. The residue was subjected to column chromatography (dichloromethane–ether, 98:2) to give **6** (0.82 g, 90%), m.p. 108–109°, $[\alpha]_D^{22}$ −16° (*c* 1, chloroform) {lit.[7] m.p. 120–121°, $[\alpha]_D^{22}$ −16° (*c* 0.4, chloroform)}; ν_{max}^{KBr} 3320, 1730, and 1550 cm^{-1}. ^{1}H-N.m.r. data: δ 8.40–7.40 (m, 6 H, Ph and NH), 5.15 (d, 1 H, $J_{4,5}$ 10 Hz, H-4), 4.95 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.30–4.00 (m, 1 H, H-5), 3.50 (s, 3 H, OMe), 3.60–3.30 (m, 2 H, H-6,6′), 2.50–1.70 (m, 2 H, H-2,2′), and 1.67 (s, 3 H, Me-3).

Anal. Calc. for $C_{17}H_{19}BrF_3NO_5$: C, 44.93; H, 4.18; N, 3.08. Found: C, 44.70; H, 4.20; N, 3.12.

*Methyl 4-O-benzoyl-2,3,6-trideoxy-3-C-methyl-3-trifluoroacetamido-α-*D-erythro-*hex-5-enopyranoside* (**7**). — To a solution of **6** (0.53 g, 1.16 mmol) in dry pyridine (10 mL) was added silver fluoride (0.5 g, 2.2 mmol). The mixture was stirred in the dark for 24 h at room temperature, diluted with ether (100 mL), filtered through a column of silica gel, and concentrated to give **7** (0.38 g, 88%). Crystallisation from ether–hexane afforded material with m.p. 109–110°, $[\alpha]_D^{22}$ +27° (*c* 0.9, chloroform); ν_{max}^{KBr} 3370, 1730, 1660, and 1550 cm^{-1}. ^{1}H-N.m.r. data: δ 8.20–7.60 (m, 6 H, Ph and NH), 5.60 (t, 1 H, $J_{4,6} = J_{4,6'} = 1.5$ Hz, H-4), 4.99 (dd, 1 H, $J_{1,2e}$ 2, $J_{1,2a}$ 4 Hz, H-1), 4.80 (m, 2 H, H-6,6′), 3.53 (s, 3 H, OMe), 2.57 (dd, 1 H, $J_{1,2e}$ 2, $J_{2a,2e}$ 15 Hz, H-2*e*), 2.03 (dd, 1 H, $J_{1,2a}$ 4, $J_{2a,2e}$ 15 Hz, H-2*a*), and 1.72 (s, 3 H, Me-3).

Anal. Calc. for $C_{17}H_{18}F_3NO_5$: C, 54.69; H, 4.82; N, 3.75. Found: C, 54.40; H, 4.90; N, 3.80.

*Methyl 4-O-benzoyl-2,3,6-trideoxy-3-C-methyl-3-trifluoroacetamido-β-*L-lyxo-*hexopyranoside* (**8**). — A solution of **7** (1.9 g, 5 mmol) in ethanol (120 mL) was

hydrogenated overnight in the presence of freshly prepared Raney nickel (5 g) at normal pressure, filtered through Kieselguhr (Merck), and concentrated. The residual oil was subjected to column chromatography (ether–hexane, 3:7) to give **9** (0.08 g, 4%) and **8** (1.5 g, 78%), m.p. 121–123°, $[\alpha]_D^{22}$ +16° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 8.40–7.50 (m, 5 H, Ph), 6.85 (bs, 1 H, NH), 5.17 (s, 1 H, H-4), 4.67 (dd, 1 H, $J_{1,2e}$ 2, $J_{1,2a}$ 9 Hz, H-1), 4.10 (q, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 3.62 (s, 3 H, OMe), 2.70–1.90 (m, 2 H, H-2,2′), 1.77 (s, 3 H, Me-3), and 1.30 (d, 3 H, $J_{5,6}$ 6.5 Hz, Me-5).

Anal. Calc. for $C_{17}H_{20}F_3NO_5$: C, 54.40; H, 5.33; N, 3.73. Found: C, 54.10; H, 5.50; N, 3.79.

*4-O-Benzoyl-2,3,6-trideoxy-3-C-methyl-3-trifluoroacetamido-αβ-*L*-lyxo-hexopyranose* (**10**). — A solution of **8** (0.75 g, 2 mmol) in 0.05M sulfuric acid in 1,4-dioxane–water (30%, 50 mL) was kept at 80° for 15 h, neutralised ($BaCO_3$), filtered, and concentrated. The residue was subjected to column chromatography (chloroform–acetone, 95:5) to give syrupy αβ-**10** (0.67 g, 92%; αβ-ratio 1:1 as indicated by the ^{1}H-n.m.r. spectrum). ^{1}H-N.m.r. data: δ 8.30–7.40 (m, 5 H, Ph), 6.90 (s, 1 H, NH), 5.50 (bs, 0.5 H, H-1α), 5.20–4.90 (m, 1.5 H, H-4 and H-1β), 4.50 (q, 0.5 H, $J_{5,6}$ 6 Hz, H-5α), 4.10 (q, 0.5 H, $J_{5,6}$ 6 Hz, H-5β), 2.80–2.00 (m, 1 H, H-2), 1.90 (s, 1.5 H, Me-3α), 1.70 (s, 1.5 H, Me-3β), 1.27 and 1.24 (2 d, Me-5α and β).

*1,5-Anhydro-4-O-benzoyl-2,3,6-trideoxy-3-C-methyl-3-trifluoroacetamido-*L*-lyxo-hex-1-enitol* (**12**). — A solution of **10** (1.2 g, 3.3 mmol) in dry pyridine (10 mL) containing toluene-*p*-sulfonyl chloride (1.3 g, 0.7 mmol) was stirred for 5 h at 80°, and then concentrated under reduced pressure. The residue was subjected to column chromatography (dichloromethane–hexane, 3:7) to give **11** (1.02 g, 89%) as a syrup, $[\alpha]_D^{22}$ −2° (*c* 1, chloroform); ν_{max}^{KBr} 3300, 1720, 1650, and 1540 cm^{-1}. ^{1}H-N.m.r. data: 8.20–7.50 (m, 5 H, Ph), 6.52 (d, 2 H, $J_{1,2}$ 6 Hz, H-1 and NH), 5.50 (bs, 1 H, H-4), 5.10 (d, 1 H, $J_{1,2}$ 6 Hz, H-2), 4.40 (q, 1 H, $J_{5,6}$ 6 Hz, H-5), 1.78 (s, 3 H, Me-3), and 1.33 (d, 3 H, $J_{5,6}$ 6 Hz, Me-5).

Anal. Calc. for $C_{16}H_{16}F_3NO_4$: C, 55.97; H, 4.66; N, 4.08. Found: C, 55.60; H, 4.70; N, 4.12.

*7-O-[4-O-Benzoyl-2,3,6-trideoxy-3-C-methyl-3-trifluoroacetamido-α-*L*-lyxo-hexopyranosyl]daunomycinone* (**13**). — To a solution of daunomycinone (**11**; 0.15 g, 0.37 mmol) and **12** (0.3 g, 0.87 mmol) in dry benzene (120 mL) at 45° was added anhydrous toluene-*p*-sulfonic acid (50 mg, 0.29 mmol). The mixture was stirred for 10 min, cooled, washed with saturated aqueous sodium hydrogencarbonate (150 mL) and water (200 mL), dried, and concentrated. The residual oil was subjected to column chromatography (dichloromethane–ether, 97:3) to afford, first, **12** (0.15 g) and then 4-*O*-benzoyl-1-*O*-(4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranose (**14**, 18 mg), m.p. 245–247°, $[\alpha]_D^{22}$ −61° (*c* 1.3, chloroform); ν_{max}^{KBr} 3300, 1710, and 1550 cm^{-1}. N.m.r. data: ^{1}H, δ 8.30–7.40 (m, 5 H, Ph), 7.25 (bs, 1 H, NH), 5.47 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.10 (s, 1 H, H-4),

4.60–4.10 (q, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 2.85–2.10 (m, 2 H, H-2,2′), 1.87 (s, 3 H, Me-3), and 1.25 (d, 3 H, $J_{5,6}$ 6.5 Hz, Me-5); ^{13}C, δ 168.6 (C=O), 134.3, 130.2 (2C), 128.9 (2C), 128.0 (Ar), 110.0 (CF_3), 92.2 (C-1), 75.4 (C-4), 63.5 (C-5), 56.3 (C-3), 34.4 (C-2), 23.4 (Me-3), and 17.6 (Me-5).

Anal. Calc. for $C_{32}H_{34}F_6N_2O_9$: C, 54.54; H, 4.82; N, 3.97. Found: C, 54.20; H, 4.90; N, 4.00.

Eluted third was **13** (0.14 g, 38%), m.p. 240–242°, $[\alpha]_D^{22}$ −4° (*c* 0.5, chloroform). ^{1}H-N.m.r. data: δ 11.40 and 10.70 (2 s, 2 H, 2 Ar-OH), 8.10–7.30 (m, 8 H, aromatic protons), 6.80 (bs, 1 H, NH), 5.62 (d, 1 H, $J_{1,2}$ 4 Hz, H-1′), 5.22 (bs, 1 H, H-7), 5.10 (s, 1 H, H-4′), 4.42 (q, 1 H, $J_{5',6'}$ 6 Hz, H-5′), 4.18 (s, 1 H, HO-9), 4.08 (s, 3 H, OMe), 3.20 and 2.90 (2 s, 2 H, H-10a,10b), 2.41 (s, 3 H, COMe), 2.60–2.10 (m, 4 H, H-2′*a*,2′*e*,8a,8b), 1.72 (s, 3 H, Me-3′), and 1.20 (d, 3 H, $J_{5',6'}$ 6 Hz, Me-5′).

Anal. Calc. for $C_{37}H_{34}F_3NO_{12}$: C, 59.91; H, 4.58; N, 1.89. Found: C, 59.60; H, 4.60; N, 1.92.

*7-O-(3-Amino-2,3,6-trideoxy-3-C-methyl-α-*L*-lyxo-hexopyranosyl)daunomycinone (3′-C-methyldaunorubicin,* **3**). — To a solution of **13** (0.11 g, 0.15 mmol) in tetrahydrofuran (10 mL) at 0° was added 0.2M sodium hydroxide (10 mL). The solution was kept at 10° for 2.5 h, quenched with 0.33M citric acid (~3 mL), basified with aqueous sodium hydrogencarbonate (5%, 50 mL), and extracted with chloroform–methanol (9:1, 3 × 30 mL). The combined extracts were washed with saturated aqueous sodium chloride (100 mL), dried, and concentrated. The residual oil was subjected to column chromatography (chloroform–methanol–conc. ammonia, 90:9:1) to afford **3** (37 mg, 46%), m.p. 168–170° (dec.), $[\alpha]_D^{22}$ +215° (*c* 0.1, methanol). N.m.r. data: ^{1}H, δ 8.20–7.20 (m, 3 H, aromatic protons), 5.50 (bs, 1 H, H-1′), 5.25 (bs, 1 H, H-7), 4.05 (s, 3 H, OMe), 2.40 (s, 3 H, COMe), 1.38 (d, 3 H, $J_{5',6'}$ 6.5 Hz, Me-5′), and 1.22 (s, 3 H, Me-3′; ^{13}C, δ 160.9 (C-4), 156.1 (C-11), 155.3 (C-6), 135.6 (C-2 and C-12a), 135.4 (C-10a), 134.2 (C-6a), 119.7 (C-1 and C-4a), 118.5 (C-3), 100.3 (C-1′), 76.3 (C-9), 73.0 (C-4′), 69.4 (C-7), 64.7 (C-5′), 56.6 (OMe), 51.0 (C-3′), 36.6 (C-2′), 35.3 (C-8), 33.1 (C-10), 25.1 (Me-3′), 24.5 (C-14), and 17.0 (Me-5′). Signals due to C-5, C-5a, C-11a, C-12, and C-14 were not detected as a result of long relaxation times.

Anal. Calc. for $C_{28}H_{31}NO_{10} \cdot H_2O$: C, 60.10; H, 5.90; N, 2.50. Found: C, 59.31; H, 5.99; N, 2.71.

In vitro *inhibition of growth of P388 leukemia cells.* — Normal and doxorubicin-resistant P388 leukemia cells were grown at 37° in RP MI 1640 medium supplemented with 10% foetal-calf serum. Compounds were added on day 0, and final cell-numbers were counted on day 3. Drug effects were expressed in inhibitory doses (ID_{50}) which are obtained by plotting the log of drug concentration against the percent inhibition of cell growth and extrapolating the concentration required to inhibit 50% of cell growth.

In vivo *antitumor activity.* — B6 D2 F1 mice were grafted i.p. with 10^6 P388 cells or 10^5 L1210 cells on day 0, and treated i.p. on days 1, 2, 3, and 4 with the

compound. Results were expressed as T/C × 100 (T = median survival time of treated mice, C = median survival time of control mice).

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