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Preliminary communication

Synthesis of 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone, a functional analog of daunorubicin

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The anthracycline antibiotics daunorubicin[1,2] (**1**), adriamycin[2,3] (**2**), and carminomycin[4] (**3**) are potent and clinically useful antitumor agents. Their scarcity and certain undesirable side-effects common to many antitumor drugs (such as bone-marrow damage, stomatitis, and alopecia), but, in particular, a cumulative, dose-related cardiotoxicity[5], have limited their broader utilization in chemotherapy. These aspects have led to continuing efforts towards syntheses* of these antibiotics that would be more advantageous than the fermentation route and, more important, offer a way to provide configurationally and/or functionally modified analogs having improved therapeutic indices. Derivatives[10] of the natural products, as well as several semi-synthetic anthracyclines[11,12], have already been prepared, and some of these appear to display significant antitumor activity and/or less toxicity than the parent agents.

We describe here a facile, high-yielding synthesis of 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**5**), a compound identical to the parent daunorubicin (**1**) except for replacement of the amino function in the sugar moiety by a hydroxyl group.

Peracetylation (pyridine–acetic anhydride, 2 days at 0°) of crystalline 2,6-dideoxy-α-L-*lyxo*-hexose[13] (**6**) afforded, in quantitative yield, the previously reported[14] triacetate **7** as a 2:1 mixture of the α and β anomers. The former† could be isolated pure by fractional crystallization (ethanol–hexane): m.p. 112°, $[\alpha]_D$ −137° (*c* 0.7, chloroform); ^{1}H-n.m.r. data for the anomeric mixture (in chloroform-*d*): δ 6.27 (dd, $J_{1,2e}$ 1.5, $J_{1,2a}$ 3.5 Hz, H-1 of α anomer), 5.80 (dd, $J_{1,2e}$ 5, $J_{1,2a}$ 7 Hz, H-1 of β anomer), 5.40–4.96 (m, H-3,4), 4.18 (q, $J_{5,6}$ 6.8 Hz, H-5 of α anomer), 3.85 (q, $J_{5,6}$ 6.4 Hz, H-5 of β anomer), 2.35–1.70 (m, H-2*e*,2*a*, partly obscured by *O*-acetyl signals), 2.12, 2.08, 2.07,

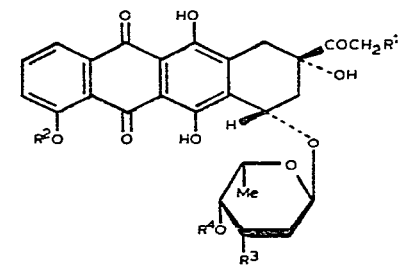
*Independent syntheses of the sugar daunosamine (see ref. 6), the aglycon daunomycinone (and carminomycinone) (see ref. 7), condensation of both to give **1** (see ref. 8), and conversion of **1** into **2** (see ref. 9) have been achieved.

†All compounds gave combustion analyses and/or mass spectra and ^{1}H-n.m.r. spectra (100 MHz) consistent with the reported structures; i.r. spectra were recorded for KBr mulls, and melting points are uncorrected.

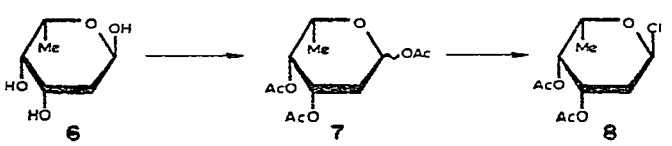
and 1.96 (4 s, OAc), 1,17 (d, H-6 of β anomer), and 1.10 (d, H-6 of α anomer).

The key intermediate for the glycosidation of daunomycinone, namely, 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride (8), was obtained as a syrup in theoretical yield by treatment of 7, dissolved in anhydrous ether, with dry hydrogen chloride at 0°; ^{1}H-n.m.r. (chloroform-*d*): δ 6.32 (dd, 1 H, $J_{1,2e}$ 1.5, $J_{1,2a}$ 3.7 Hz, H-1), 5.47 (ddd, 1 H, $J_{2a,3}$ 11.5, $J_{2e,3}$ 3, $J_{3,4}$ 5.2 Hz, H-3), 5.26 (m, 1 H, H-4), 4.36 (dq, 1 H, $J_{4,5}$ 1.5, $J_{5,6}$ 6.8 Hz, H-5), 2.38 (ddd, 1 H, $J_{2e,2a}$ 12.4 Hz, H-2*a*), ~2.10 (m, 1 H, obscured by *O*-acetyl signals, H-2*e*), 2.10, 1.94 (2 s, 3 H each, OAc), and 1.13 (d, 3 H, H-6).

When daunomycinone (1 molar equiv.) in anhydrous dichloromethane was treated with 8 (2 molar equiv.) under Koenigs–Knorr conditions (yellow mercuric oxide, mercuric bromide) in the presence of molecular sieve 4A for 24 h at 22°, only one product (R_F 0.55) was detected by t.l.c. on silica gel in 4:3:3 benzene–acetone–ether; it was observed as a red spot under u.v. and visible light and was contaminated with faster-migrating, sugar impurities. The excess of 8 was decomposed by adding methanol, the inorganic material was filtered off, and the solvent evaporated. Column chromatography on silica gel, using as eluant first 4:1 ether–petroleum ether (to remove the impurities) and then 2:3 benzene–acetone, afforded 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (4) as an amorphous (diffuse X-ray powder diffraction pattern) solid in 84% yield (based on daunomycinone), whose analysis indicated 4·0.5 H_2O); m.p. 134 138°, $[\alpha]_D$ +344° (*c* 0.03, methanol); λ_{max}^{MeOH} 235 nm (ϵ_{mM} 27.1), 257 (23.9), 270 (10.9), 292 (8.5), 474 (12.6), 495 (12.8), and 534 (6.9); ν_{max} 3490 (OH), 1750 (*O*-acetyl), 1720 (*C*-acetyl), 1620 and 1580 cm^{-1} (chelated quinone). The ^{1}H n.m.r. spectrum of 4 (in chloroform-*d*) was nearly identical with that[1a] of *N*-acetyldaunorubicin, except for the absence of an NH resonance and the paramagnetic shift of the signal for H-3′ (as anticipated for the replacement of the acetamido group in the latter by an acetoxyl substituent at C-3′ in 4). The α configuration of the glycosidic linkage was readily verified by inspection of the signal for the anomeric proton at δ 5.57 (broad s, ν ½ = 7 Hz).



	R^1	R^2	R^3	R^4
1	H	Me	NH_2	H
2	OH	Me	NH_2	H
3	H	H	NH_2	H
4	H	Me	OAc	Ac
5	H	Me	OH	H



Deacetylation was accomplished by treating a methanolic solution of **4** (200 mg/10 ml) with a catalytic amount of sodium methoxide for 30 h at 22°. De-ionization [Amberlite IRC-50 (OH^-) for 4 h at 0°] followed by evaporation of the solvent afforded crude 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**5**), which was recrystallized from acetone to yield pure, crystalline (X-ray powder diffraction pattern) **5** in two crops (79%); m.p. 252–254°, $[\alpha]_D$ +219° (*c* 0.03, methanol); λ_{max}^{MeOH} 235 nm (ϵ_{mM} 28.8), 254 (25.9), 272 (10.3), 292 (8.8), 474 (12.3), 497 (12.3), and 534 (6.4); ν_{max} 3470 (very broad, OH), 1715 (*C*-acetyl), 1620 and 1580 cm^{-1} (chelated quinone). Compound **5** is undergoing biological testing.

It is noteworthy that, as with the coupling of daunosamine[8] (and its 4-deoxy analog[12]) with the aglycon, the glycosidation of the deamino sugar analog **6** proceeds stereospecifically to furnish exclusively the α-L anomer. In contrast, it is expected[11] that coupling of other, stereochemically and /or functionally altered daunosamine analogs[13,15] will provide anomeric mixtures, and work in progress is focused on these aspects.

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