and 0.9 Å (*h*) for *a* and 6.1 (*d*) and 0.15 Å (*h*) for *b*.
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(19) The dibenzosuberone derivatives which were reduced to the 5-ol compounds as precursors for **9c** and **9d** are described in E. Englehardt, H. Zell, W. Saari, M. Christy, C. Colton, C. Stone, J. Stavorski, H. Wenger, and C. Ludden, *J. Med. Chem.*, **8**, 928 (1965).
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Synthesis and Antitumor Activity of Sugar-Ring Hydroxyl Analogues of Daunorubicin[1]

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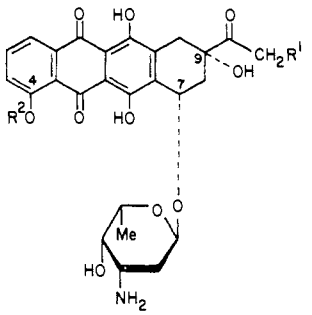
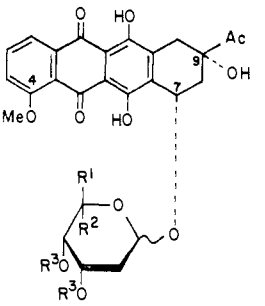
Daunorubicin analogues in which the natural amino sugar, daunosamine, is replaced by neutral 2,6-dideoxyhexopyranosyl residues have been prepared in high yields. Glycosidation of 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride (**13**) with daunomycinone under Koenigs–Knorr conditions yielded exclusively the protected α-anomeric product **4**, which was converted into the free glycoside **5**. In contrast, the 1-chloro-D-*ribo* isomer **19**, bearing *p*-nitrobenzoyl groups for hydroxyl-group protection, furnished a 5:3 mixture of the α (**6**) and β (**7**) glycosides. Separation and individual deprotection afforded the target compounds **8** (from **6**) and **9** (from **7**). Whereas all of the D-*ribo* analogues (**6–9**) are inactive as antitumor agents in vivo against P388 lymphocytic leukemia in mice, the protected L-*lyxo* glycoside **4** (T/C 186) and also the free glycoside **5** (T/C 183) are highly effective in this test system; **5** is also active (T/C 146) in vivo against murine B16 melanocarcinoma.

The anthracycline antibiotics[2,3] daunorubicin (**1**; NSC-82151) and adriamycin (doxorubicin, **2**; NSC-123127)



1, R^1 = H; R^2 = Me
2, R^1 = OH; R^2 = Me
3, R^1 = H; R^2 = H

are potent and clinically useful antitumor agents. Similarly, the closely related carminomycin (**3**; NSC-180024) is considered a highly promising anticancer drug under clinical trial. Their broader utilization in chemotherapy is hampered,[4] however, by their scarcity and by certain undesirable side effects common to many antitumor drugs (such as bone-marrow damage, stomatitis, alopecia, and mutagenic behavior) but, in particular, a cumulative, dose-limiting cardiotoxicity (congestive heart failure). The scarcity factor has led to continuing efforts toward the total synthesis of **1–3** as a more economical alternative to the fermentation route, and the undesirable side effects have stimulated increasing interest in the preparation of analogues (derivatives of the parent antibiotics and semisynthetic and totally synthetic analogues) that may display more favorable therapeutic characteristics than the parent drugs. As part of our program aimed toward the development of new semisynthetic analogues, we now report the synthesis of 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone ("3′-hydroxydaunorubicin", **5**;



	Anomer	R^1	R^2	R^3
4	α	H	Me	Ac
5	α	H	Me	H
6	α	Me	H	$O_2NC_6H_4CO$
7	β	Me	H	$O_2NC_6H_4CO$
8	α	Me	H	H
9	β	Me	H	H

NSC-284682) in which the natural amino sugar, daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), in **1** has been replaced by the corresponding 3-hydroxyl analogue (2-deoxy-L-fucose, **10**). Biological evaluation of **5** was expected to shed some light on the role of the amino group at C-3 of the sugar moiety. Structural features of the sugar component are considered to exert a decisive influence on the pharmacological properties of members of this class of antitumor drugs. In addition, we present here the synthesis and results of an initial biological evaluation of the anomeric glycosides **8** (NSC-294987) and **9** (NSC-297279) in which 2,6-dideoxy-D-*ribo*-hexose (digitoxose, **14**)

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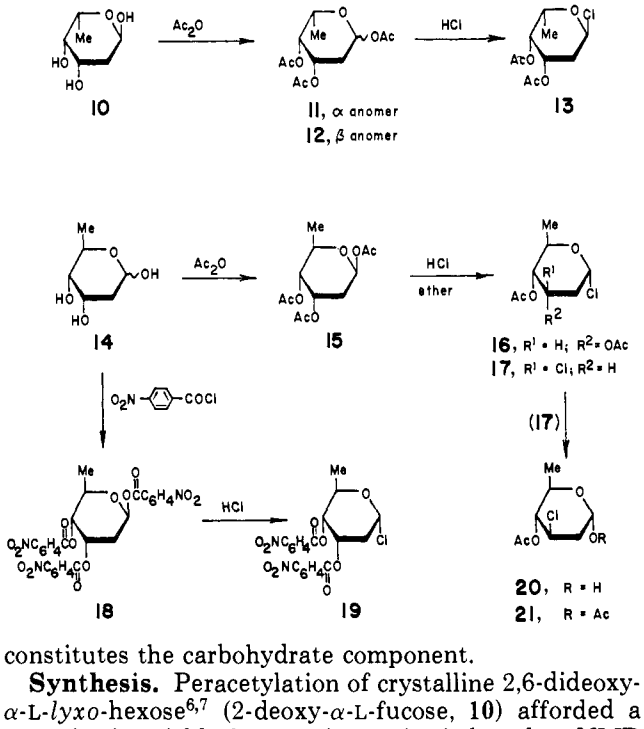

constitutes the carbohydrate component.

Synthesis. Peracetylation of crystalline 2,6-dideoxy-α-L-*lyxo*-hexose[6,7] (2-deoxy-α-L-fucose, **10**) afforded a quantitative yield of a 2:1 mixture (ratio based on NMR spectral analysis) of the peracetates having the α (**11**) and β (**12**) anomeric configuration. Although separation of the two components was not required for the subsequent conversion into the 1-chloro derivative **13**, the preponderant α anomer **11** could be isolated pure by fractional crystallization from ethanol–hexane. The physical constants (mp and optical rotation) corresponded well with data reported for this compound as prepared[8] from a hydrolyzate of cinerubine A.

Treatment of the mixture of **11** and **12** with dry hydrogen chloride in ether furnished a quantitative yield of the syrupy chloride **13**, the key intermediate for the preparation of novel anthracycline glycosides.[9] The excellent, first-order NMR spectrum (Table I) of **13** affirmed the anomeric purity of **13** and established its configuration as α-L. Compound **13** may also be prepared from a glycal precursor.[10]

Coupling of daunomycinone with the 1-chloro derivative **13** was achieved under Koenigs–Knorr conditions (Helferich modification) to give exclusively, in 78% yield, the protected α-glycoside **4** as an amorphous (diffuse X-ray powder diffraction pattern) solid. The ^{1}H NMR spectrum of **4** (Table I) was comparable to that[11] of *N*-acetyldaunorubicin, except that the NH resonance was absent, and paramagnetic shifts of the H-3′ and H-4′ resonances were observed as anticipated for replacement of the acetamido and hydroxyl groups in the latter by acetoxyl subsituents in **4**. In addition to establishing anomeric purity, the NMR spectrum readily allowed attribution of the α configuration to the product, as indicated from the characteristic broad ($\nu_{1/2}$ = 7 Hz) singlet at δ 5.57 for the anomeric proton.

Removal of the protecting groups by catalytic transesterification afforded the crystalline target compound **5** in 68% yield. In subsequent, scaled-up preparations of **5**, the procedure just described was slightly modified (see Experimental Section); isolation of the intermediate, protected glycoside **4**, was avoided, as was the need of purifying the product by column chromatography. Thus, an overall yield of 90% on a multigram scale could be achieved for the two-step conversion of **13** into **5**.

A further extension involved the preparation of daunorubicin analogues **8** and **9** in which the natural amino sugar, daunosamine, was replaced by 2,6-dideoxy-D-*ribo*-hexose (digitoxose, **14**). Following the same synthetic strategem as before, the known[12] 1,3,4-tri-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (**15**) was treated with dry hydrogen chloride under conventional conditions. However, the crystalline product formed in high yield turned out to be a dichloro derivative (**17**). Even under less severe conditions (lower temperature, shorter reaction time, and equimolar stoichiometry), the action of hydrogen chloride on **15** did not afford the desired 1-chloride **16** in adequate purity; immediate glycosidation with daunomycinone in the presence of mercury salts led to a complex, inseparable mixture of products that was not investigated further.

The crystalline product **17** obtained in the foregoing reaction was formulated as 4-*O*-acetyl-3-chloro-2,3,6-trideoxy-α-D-*arabino*-hexopyranosyl chloride on the basis of microanalysis (two chlorine atoms per molecule) and spectral (IR, NMR, and MS) data. The distinctive upfield shift (~1.1 ppm) of the H-3 signal in the NMR spectrum (Table I) of **17** relative to that of its precursor **15** clearly demonstrated[13] that chlorine displacement had taken place at C-3. Furthermore, the large values (9.8 Hz) for $J_{2a,3}$, $J_{3,4}$, and $J_{4,5}$ are indicative of four consecutive, trans diaxially disposed protons at C-2–C-5. In combination with the narrow multiplet for H-1 (characteristic of an equatorial orientation of the anomeric proton), these data unequivocally established the α-D-*arabino* configuration for **17**.

Additional evidence for the proposed structure was provided by converting **17** into the reducing sugar **20** and its peracetate **21**, both of which were obtained crystalline and were fully characterized by spectroscopic (IR, NMR, and MS) and elemental analysis.

Evidently, the acetyl groups that had proven compatible with the chloride-exchange conditions for the L-*lyxo* (and L-*arabino*[10]) system were inadequate for hydroxyl-group protection in the D-*ribo* series because of their susceptibility to displacement by chlorine. Similar results have been reported in comparable systems[12-14] and the mechanism for introduction of chlorine is considered[13] to involve a 2,3-unsaturated (pseudoglycal) intermediate.

A suitably derivatized coupling precursor of digitoxose (**14**) was secured in the crystalline derivative 2,6-dideoxy-3,4-di-*O*-(*p*-nitrobenzoyl)-α-D-*ribo*-hexopyranosyl chloride (**19**), which was prepared according to a literature procedure[12] via the peracylated derivative **18**. Glycosidation of **19** with daunomycinone under Koenigs–Knorr conditions proceeded effectively to afford a two-component mixture (contaminated with sugar impurities) that could be readily separated by column chromatography on silica gel into the pure, protected glycosides **6** and **7** (α and β anomer, respectively). The anomeric configurations were readily determined by ^{1}H NMR spectroscopy from the pattern of the H-1 signals (Table I).

Deprotection of the individual anomers **6** and **7** was accomplished by treatment with alkali to afford the crystalline target compounds **8** and **9**, each in 63% yield.

Antitumor Activity. The new anthracycline glycosides **5**, **8**, and **9** were assayed in vivo against transplanted P388 lymphocytic leukemia in mice. The results are summarized in Table II and are compared with data obtained for daunorubicin (**1**) and adriamycin (**2**) as well as for the fully protected glycosides **4**, **6**, and **7**. At the tested dose levels, all four D-*ribo* derivatives (**6–9**) were completely devoid of antitumor activity. However, both L-*lyxo* analogues substantially increased the survival time of tumor-bearing animals; at the most effective dose level (50 mg/kg) the

Table I. ^{1}H NMR Spectral Data of 2,6-Dideoxyhexopyranose Derivatives

	chemical shifts, δ[b] (first-order couplings, Hz)									
compd[a]	H-1 ($J_{1,2a}$)	H-2e ($J_{1,2e}$)	($J_{2e,2a}$)	H-2a ($J_{2a,3}$)	H-3 ($J_{2e,3}$)	H-4 ($J_{3,4}$)	H-5 ($J_{4,5}$)	H-6 ($J_{5,6}$)	1-OR	3,4-OR
4[c]	5.57 br s (W_h = 7)	~2.2 m		~1.85 m	---5.30-4.94 m----		4.30 m	1.16 d (6.0)	*e*	2.35 s 2.12 s
6[c]	5.43 br s (3.0)	~2.37 m[d]	(15.5)	1.94 m (3.0)	---5.75-5.55 m----		4.49 m	1.35 d (5.8)	*e*	8.30-7.45 m
7[c]	5.65 dd (8.8)	----2.30-2.05 m---- (2.5)			5.89 m	5.02 dd (2.9)	4.37 m (10.0)	1.40 d (6.2)	*e*	8.45-7.36 m
8[c]	5.30 br s (W_h = 7.5)	----2.40-1.80 m----			----4.45-3.60 m----			1.27 d (6.0)	*e*	*f*
9[c]	5.34 dd (9.8)	~2.00 m[d] (1.5)	(13.5)	1.65 m_b (3.2)	----4.95-3.60 m----			1.35 d (6.3)	*e*	*f*
11	6.27 dd (3.5)	----2.35-1.70 m---- (1.5)			---5.40-5.18 m----		4.17 q (>1)	1.10 d (6.8)	2.12 s	2.05 s 1.95 s
12[g]	5.80 dd (7.0)	----2.35-1.70 m---- (5.0)			---5.40-4.96 m---		3.85 q (>1)	1.17 d (6.4)	2.08 s	2.07 s 1.96 s
13	6.32 dd (3.7)	~2.10 m[d] (1.5)	(12.4)	2.38 ddd (1.5)	5.47 ddd (3.0)	5.26 m (5.2)	4.38 dq (1.5)	1.13 d (6.8)		2.10 s 1.94 s
15	6.06 dd (8.0)	----2.20-1.75 m[d]---- (3.8)		(3.6)	5.50 m_4 (3.6)	4.65 dd (3.0)	4.08 dq (9.6)	1.21 d (6.0)	2.08 s	2.08 s 2.00 s
17	6.16 br d (3.0)	----2.90-2.10 m---- (~1)		(9.8)	4.42 m_c (5.0)	4.88 m_3 (9.8)	4.11 dq (9.8)	1.19 d (6.5)		2.11 s
18[c,h]	6.58 dd (9.0)	----2.15-1.75 m[d]---- (4.2)		(3.3)	6.07 m_4 (3.3)	5.25 dd (3.6)	4.68 dq (10.0)	1.34 d (7.5)	---8.40-8.20 m----	
19	6.23 br s	----2.70-2.50 m----			5.84 m_4	5.08 dd (3.0)	4.74 dq (10.4)	1.30 d (6.2)		8.25-7.90 m
20[i] α	5.23 br s (3.0)	----2.58-1.84 m---- (1.2)		(10.0)	4.28 m_c (4.5)	4.73 m_3 (10.2)	3.99 dq (10.2)	1.08 d (6.6) 1.16 d (6.6)	3.45 br	2.04 s
β	4.25 dd (7.8)	----2.58-1.84 m---- (2.0)		(10.0)						

[a] 100-MHz continuous-wave spectra in chloroform-*d*, unless otherwise stated. [b] Signal multiplicities: br, broadened; d, doublet; m, multiplet; m_x, *x*-line pattern; q, quartet; s, singlet; t, triplet. [c] 90-MHz Fourier-transform spectrum. [d] Partly obscured signal. [e] Chemical shifts of the aglycon portion are but little affected by the various sugar species; as representative data, those of compound 8 are given: 13.91 and 13.22 (two s, 1 each, chelated OH), 8.00 (dd, 1, $J_{1,2}$ = 8.0 Hz, $J_{1,3}$ = 1.3 Hz, H-1), 7.77 (t, 1, $J_{2,3}$ = 8.0 Hz, H-2), 7.38 (dd, 1, H-3), 5.30 (narrow m, H-7), 4.08 (s, 3, OMe), 3.17 (dd, 1, $J_{10A,10B}$ = 20 Hz, $J_{8,10}$ = 1.5 Hz, H-10A), 2.87 (d, 1, H-10B), 2.43 (s, 3, CAc), 2.50-1.95 (m, partly obscured by CAc and C-2 protons of the glycon, H-8A, 8B). [f] Proton exchanged by deuterium. [g] Taken from the NMR spectrum of a 2:1 mixture of the anomers 11 and 12. [h] In acetone-d_6. [i] Upon dissolution in chloroform-*d*, 20 mutarotated to form a 4:1 mixture of the α and β anomers.

unprotected glycoside **5** even surpassed adriamycin (**2**) in efficacy, albeit at doses 6 to 12 times higher than those (8 and 4 mg/kg) used for **2**. However, this lower potency on a weight basis might be more than compensated if the cardiotoxicity potential of **5** were decreased, and this aspect is being evaluated. Assay of **5** in vivo againt B16 melanocarcinoma in mice (Table III) showed activity comparable to that of adriamycin (**2**) and much higher than that of daunorubicin (**1**).

Discussion

It is noteworthy that glycosidation of 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride (**13**) proceeds stereospecifically, despite the lack of a participating substituent at C-2, to furnish exclusively the α-L anomer **4**. This behavior is analogous[16] to the coupling of the stereochemically related daunosamine[17] and its 4-deoxy analogue[18] with daunomycinone. In contrast, Koenigs–Knorr reaction with the D-*ribo* isomer **19** as the glycosylating agent provides a mixture of anomeric glycosides (**6** and **7**), as is generally observed[19] in the glycosidation of 2-deoxy sugars.

Among the numerous daunomycinone/adriamycinone glycosides that have thus far been reported in the literature, the biologically inactive 7-*O*-(β-D-glucopyranosyl)daunomycinone[20] constitutes, to the best of our knowledge, the only example that does not contain an aminodeoxy sugar as the carbohydrate moiety. It appears that, until now, the 3′-amino-2′,3′-dideoxy portion of the sugar was considered essential for biological activity in any anthracycline analogue modified in the daunosamine residue. However, our results (Table II) clearly establish what was hinted at in a recent study[9] on glycosides of ϵ-rhodomycinone, namely, that neutral 2-deoxy sugars (which are more readily accessible and simpler to work with in chemical synthesis than their aminodeoxy counterparts) must be considered seriously as carbohydrate building blocks in the quest for effective, new, anthracycline-type antitumor agents.

The rationale for coupling a sugar (**14**) of the D series to daunomycinone was to evaluate the dependence of biological activity upon stereochemical requirements at C-5 of the sugar moiety. The close relationship between 2-deoxy-α-L- (as in most of the active compounds thus far reported) and 2-deoxy-β-D-hexopyranosides in the appropriate conformation may be readily visualized; in the present instance, when derivatives of the L-*lyxo* (**10**) and D-*ribo* (**14**) isomers are encountered, the only difference lies in the orientation of the substituent (methyl group) at C-5. The lack of any bioactivity for compound **9** (Table II) now suggests that, at least for the 3′-hydroxyl analogue (**5**) of daunorubicin, inversion at the 5′ position decreases antitumor activity.

Experimental Section

TLC was performed on precoated plates of silica gel 60 (E. Merck, Darmstadt); zones of colorless compounds were detected by spraying the plates with sulfuric acid and subsequently heating. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Infrared spectra were recorded with a Perkin-Elmer Model 457 grating spectrophotometer. Ultraviolet–visible spectra were obtained on a Cary-14 spec-

Table II. Activity[a] of Daunorubicin (1), Adriamycin (2), and the Hydroxyl Analogues 4-9 on P388 Lymphocytic Leukemia in Mice[b]

compd	NSC no.	dose,[c] mg/kg	T/C,[d,e] %
1	82151	32	97
		16	122
		8	151
		4	123
		2	116
2	123127	16	114
		8	150
		4	149
		2	132
		1	118
4	283158	200	186
		100	155
		50	110
		25	108
		12.5	100
5	284682	400	89
		200	
		100	156
		50	183
		25	125
6	293151	50	105
		25	107
		12.5	110
		6.25	106
		3.13	101
7	293152	50	101
		25	106
		12.5	99
		6.25	100
		3.13	98
8	294987	50	101
		25	101
		12.5	100
		6.25	100
		3.13	99
9	297279	50	102
		25	100
		12.5	97
		6.25	102
		3.13	100

[a] Data obtained under the auspices of the National Cancer Institute, Division of Cancer Treatment, Drug Research and Development Branch. [b] CDF_1 mice are injected ip with 10^6 P388 lymphocytic leukemia cells on day 0 and treated ip on days 5, 9, and 13 with the drug dose specified. Detailed protocols are described in ref 15. [c] Six (for compound 5, five) mice per dose level. [d] Ratio of median survival time expressed as percent of untreated controls. [e] The average survival time of untreated controls was approximately 11 days. At none of the dose levels reported were significant, acute, toxic-drug deaths (survival for less than 5 days after injection of treatment) seen.

trophotometer. Mass spectra were recorded with an AEI MS-9 double-focusing, high-resolution spectrometer (ionizing and accelerating potentials, 70 eV and 8 kV). NMR spectra were measured at 100 MHz with a Varian HA-100 spectrometer or at 90 MHz with a Bruker HX-90 instrument; chemical shifts refer to an internal standard of tetramethylsilane (δ 0.00) and are listed, together with spin-coupling values (Hz), in Table I. X-Ray powder diffraction data give interplanar spacings, Å, for Cu Kα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities. Analyses for indicated elements were within ±0.4%, unless otherwise stated.

1,3,4-Tri-*O*-acetyl-2,6-dideoxy-α- and 1,3,4-Tri-*O*-acetyl-2,6-dideoxy-β-L-*lyxo*-hexopyranose (11 and 12). Treatment of crystalline 2,6-dideoxy-α-L-*lyxo*-hexose[6,7] (**10**; 7.41 g, 50 mmol) with 1:2 acetic anhydride–pyridine (120 mL) for 18 h at 25 °C afforded, after conventional processing, a syrupy 2:1 mixture (as judged from NMR data) of the anomeric peracetates **11** and **12**: yield 13.7 g (theoretical). The preponderant product, the α anomer **11**, was isolated pure by fractional crystallization from ethanol–hexane: mp 112 °C; $[\alpha]^{23}_D$ −137° (*c* 0.7, chloroform); MS *m/e* 274 ($M^{+\cdot}$, absent), 215 (0.8%, $M^{+\cdot}$ − AcO·), 154 (4%, $M^{+\cdot}$ − 2HOAc); X-ray powder diffraction data 10.71 (m), 8.46 (vw), 6.88 (vs, 1, 1), 5.98 (m), 5.43 (s, 2, 2, 2), 5.03 (vs, 1, 1), 4.45 (m), 4.31 (m), 3.90 (s, 3), 3.79 (s, 2, 2, 2), 3.62 (s, 2, 2, 2), 3.43 (w). Anal. ($C_{12}H_{18}O_7$) C, H.

The peracetates **11** and **12**, prepared from a hydrolyzate of cinerubine A, have been reported[8] to have a mp 109–110 °C, $[\alpha]_D$ −137° in chloroform, and a mp 67–70 °C, $[\alpha]_D$ −39° in chloroform, respectively.

3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl Chloride (13). A stream of dry hydrogen chloride was passed for 10 min into a cold (0 °C) solution of syrupy **11** and **12** (4.16 g, 15.2 mmol) in dry ether (250 mL). After storing the solution for 18 h at +5 °C, the solvent was removed under diminished pressure (bath temperature <30 °C) to give the chloride **13** in quantitative yield (3.7 g) as a pale-yellow syrup that was subjected, without delay, to the coupling reaction described next. The NMR spectrum (Table I) of this product was in good accord with data reported[10] for compound **13** prepared by an independent route.

7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (4). A mixture of the chloride **13** (1.8 g, 7.18 mmol), daunomycinone (796 mg, 2.0 mmol), yellow mercuric oxide (1.65 g, 7.62 mmol), mercuric bromide (500 mg, 1.39 mmol), and granular molecular sieve 4Å (15 g) in anhydrous dichloromethane (150 mL) was stirred for 30 h at 22 °C. TLC (4:3:3 benzene–acetone–ether) revealed at this point that all of the anthraquinone had reacted to form a single product (R_f 0.55) observable as a red spot under UV and visible light. The inorganic material was filtered off and thoroughly washed with dichloromethane. The combined filtrates were evaporated, and the remaining residue was placed on a short column of silica gel (E. Merck No. 7734, 63–200 μm). Sugar impurities were eluted first with 4:1 ether–petroleum ether, and then the product was recovered by eluting the column with 2:3 benzene–acetone and evaporation of the solvent. The crude product was dissolved in ethanol (150 mL), and the clear solution was concentrated to about one-fifth its original volume, whereupon, after cooling, compound **4** precipitated as an amorphous (diffuse X-ray powder diffraction

Table III. Activity[a] of Daunorubicin (1), Adriamycin (2), and the 3′-Hydroxyl Analogue 5 on B16 Melanocarcinoma in Mice[b]

compd	NSC no.	dose,[c] mg/kg	T/C,[d,e] %
1	82151	16	*f*
		8	
		4	96
		2	127
		1	122
2	123127	16	156
		8	150
		4	132
		2	122
		1	118
5	284682	200	*f*
		100	*f*
		50	146
		25	126
		12.5	113

[a] Data obtained under the auspices of the National Cancer Institute, Division of Cancer Treatment, Drug Research and Development Branch. [b] BDF_1 mice are implanted ip with B16 melanocarcinoma cells on day 0 and treated ip on day 5 with the drug dose specified. [c] Ten mice per dose level. [d] Ratio of median survival time expressed as percent of untreated controls. [e] At the lower dose levels, no acute toxic drug deaths were observed. [f] Toxic dose.

pattern) solid: yield 970 mg (78%, based on daunomycinone); mp 134–138 °C; $[\alpha]^{23}_D$ + 344° (c 0.03, methanol); IR (KBr) ν_{max} 3490 (OH), 1750 (*O*-acetyl), 1720 (*C*-acetyl), 1620, 1580 cm^{-1} (chelated quinone); UV (MeOH) λ_{max} 233 nm ($\epsilon \times 10^{-3}$ 36.1), 251 (26.8), 288 (9.3), 313 (2.8), 327 (3.4), 388 (2.8), 450 (9.0), 473 (12.2), 480 (12.4), 496 (12.5), 519 (8.1), 532 (7.0), 578 (0.4). The ^1H NMR spectrum of **4** (in chloroform-*d*) was similar to that[11] of *N*-acetyldaunorubicin except for the absence of an NH resonance and the paramagnetic shifts of the H-3′ and H-4′ signals. Anal. ($C_{31}H_{32}O_{13}\cdot 0.5H_2O$) C, H.

7-*O*-(2,6-Dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (5). (A) From 4 by Catalytic Transesterification. To a solution of the protected anthracycline glycoside **4** (620 mg, 1.0 mmol) in absolute methanol (20 mL) was added 1 M sodium methoxide (200 μL), and the mixture was kept for 12 h at 25 °C. TLC (2:3 benzene–acetone) indicated complete conversion of **4** into a new product (R_f 0.4). Methanol (400 mL) was added to the dark-blue solution, which was then treated with Amberlite IRC-50 (H^+) (4 mL, 4 h, 0 °C), whereupon the color changed to red. Evaporation of the solvent afforded crude **5** that was recrystallized from acetone–hexane: yield 360 mg (68%); mp 252–254 °C; $[\alpha]^{22}_D$ +219° (c 0.03, methanol); IR (KBr) ν_{max} 3470 (very broad, OH), 1715 (*C*-acetyl), 1620 and 1580 cm^{-1} (chelated quinone); UV (MeOH) λ_{max} 233 nm ($\epsilon \times 10^{-3}$ 35.4), 251 (25.6), 288 (9.1), 313 (3.6), 327 (3.2), 385 (2.5), 449 (8.5), 473 (11.9), 480 (12.1), 497 (12.4), 517 (8.6), 532 (7.0), 580 (0.5); X-ray powder diffraction data 12.02 (m, 2), 10.52 (vw), 7.89 (m, 1), 6.94 (vw), 6.00 (w), 5.02 (vw), 4.77 (w), 4.31 (vw), 4.14 (vw), 3.86 (m, 3), 3.40 (w), 1.95 (m). Anal. ($C_{27}H_{28}O_{11}$) C, H.

(B) Simplified Preparation of 5: Preparative-Scale Glycosidation–Saponification. A mixture of daunomycinone (4.0 g, 10 mmol), yellow mercuric oxide (12.7 g, 58.6 mmol), mercuric bromide (3.7 g, 10.3 mol), and molecular sieve 3Å (50 g) in anhydrous dichloromethane (500 mL) was stirred for 1 h at 15 °C. A solution of the chloride **13** (5.0 g, 20 mmol) in anhydrous dichloromethane (50 mL) was then added. TLC (2:3 benzene–acetone) after 90 min indicated the reaction to be complete. The mixture was filtered and the inorganic filter cake washed thoroughly with dichloromethane. The combined filtrates were successively washed with aqueous potassium iodide (30%), aqueous sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated. To the residue was added cold (0 °C) aqueous 0.2 M sodium hydroxide (500 mL), and the suspension was stirred at 0 °C until a clear, violet solution was obtained (~2 h). The pH then was adjusted to 6 by the careful addition of 1 M hydrochloric acid with ice cooling. The clear red solution was saturated with sodium chloride and kept overnight at 5 °C. Compound **5** precipitated, was collected by filtration, dried over phosphorus pentaoxide in vacuo and recrystallized from dichloromethane–hexane to give pure **5** (4.77 g, 90%). This product was identical in all respects with the foregoing sample.

1,3,4-Tri-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (15). 2,6-Dideoxy-D-*ribo*-hexose[7,21] (**14**; 1.4 g, 7.0 mmol) was treated with 1:2 acetic anhydride–pyridine (18 mL) for 48 h at 0 °C. The mixture was poured into ice–water (500 mL), and the few crystals that formed were collected. The aqueous phase was then extracted with dichloromethane (three 50-mL portions), and the combined extracts were dried (magnesium sulfate) and evaporated. Toluene (three 10-mL portions) was successively added to and evaporated from the residue, which crystallized readily upon seeding with the foregoing crystals. Recrystallization from ether–hexane afforded pure **15**: yield 1.6 g (83%); mp 85–86.5 °C; $[\alpha]^{23}_D$ +38° (c 0.6, chloroform) (lit.[12] dimorphic, mp 75.5–76.5 and 86.5–87.5 °C; $[\alpha]_D$ +36.2° in chloroform); IR (KBr) ν_{max} 1755, 1740 cm^{-1} (C=O); MS *m/e* 231 (0.3%, M – Ac·), 154 (2%, M – 2AcOH); X-ray powder diffraction data 13.08 (vs, 2), 6.75 (vs, 1), 6.22 (vw), 5.69 (vw), 5.32 (m), 5.06 (w), 4.50 (m), 4.34 (m, 3), 4.04 (m), 3.87 (w). Anal. ($C_{12}H_{18}O_7$) C, H.

Chloride Substitution at C-1 in 15: 3,4-Di-*O*-acetyl-2,6-dideoxy-α-D-*ribo*- (16) and 4-*O*-Acetyl-3-chloro-2,3,6-trideoxy-α-D-*arabino*-hexopyranosyl Chloride (17). The peracetate **15** (1 g, 3.6 mmol) in dry ether (30 mL) was treated with dry hydrogen chloride as described for the preparation of **13** to give, after conventional processing, a semicrystalline residue. The crystals (**17**) were filtered off in a dry atmosphere (glove box) with the aid of a little hexane; they were extremely sensitive to moist air. In several experiments, the yield of **17** varied from 243 (29%) to 510 mg (62%): mp 78–98 °C dec; IR (film) ν_{max} 1740 (C=O), 693 cm^{-1} (CCl); MS *m/e* 191 (2.3% , M – HCl), 131 (23%, 191 – AcOH). Anal. ($C_8H_{12}Cl_2O_3$) H, Cl; C: calcd, 42.31; found, 41.80.

Formation of the dichloro derivative **17** was drastically decreased by limiting the treatment with hydrogen chloride to not more than 10 min at 0 °C. Rapid evaporation of the solvent in vacuo at 25 °C afforded a syrupy residue (**16**) that contained only traces of **15** (TLC; 1:1 hexane–ethyl acetate) and, in all probability, some **17**, yield 850 mg (94%). Similar results were obtained by treating **15** (1 g, 3.6 mmol), suspended in dichloromethane (20 mL), for 4 h at 0 °C with 1 mol-equiv of hydrogen chloride, dissolved in dichloromethane.

Because of the instability and high reactivity characteristic of glycosyl halides, chromatographic purification of **16** was precluded. Immediate glycosidation of the crude chloride **16** with daunomycinone in the presence of mercury salts (by analogy with the preparations of **4**–**7**) led to a complex mixture of products that proved inseparable, even by LC.

4-*O*-Acetyl-3-chloro-2,3,6-trideoxy-α-D-*arabino*-hexose (20). To a solution of the dichoro derivative **17** (500 mg, 2.2 mmol) in acetone (10 mL) was added a slurry of silver carbonate (1.8 g, 6.5 mmol) in 1:1 acetone–water (15 mL). The mixture was stirred for 15 min at 23 °C, the inorganic material was filtered off, and the filtrate was evaporated. The remaining solid was recrystallized from hexane to give analytically pure **20**: yield 297 mg (65%); mp 84–85.5 °C; $[\alpha]^{23}_D$ + 63.1° (30 min), +59.2° (12 h, equilibrium; c 0.9, chloroform); IR (KBr) ν_{max} 3390 (OH), 1740 (C=O), 570 cm^{-1} (CCl); MS *m/e* 191 (0.2%, M – ·OH), 173 (0.1%, M – Cl·); X-ray powder diffraction data 7.08 (vs, 1), 4.70 (vs, 2), 4.57 (m), 4.22 (m), 3.87 (m), 3.56 (m, 3), 3.42 (m), 3.25 (w), 3.10 (w), 2.90 (w). Anal. ($C_8H_{13}ClO_4$) C, H, Cl.

1,4-Di-*O*-acetyl-3-chloro-2,3,6-trideoxy-α-D-*arabino*-hexopyranose (21). Treatment of the reducing sugar **20** (100 mg, 0.48 mmol) with 1:2 acetic anhydride–pyridine (6 mL) for 20 h at 23 °C afforded, after conventional processing, crude **21** that was recrystallized from hexane: yield 107 mg (89%); mp 80–81 °C; $[\alpha]^{23}_D$ +89.9° (c 1.14, chloroform); IR (chloroform) ν_{max} 1750 (C=O), 558 cm^{-1} (CCl); MS *m/e* 207 (0.2%, M – Ac·), 191 (9%, M – AcO·), 155 (3.3%, 191 – HCl), 95 (5%, methylpyrylium cation); X-ray powder diffraction data 8.52 (m), 7.13 (s, 1), 6.70 (w), 5.31 (m), 4.95 (s, 2), 4.45 (vw), 4.19 (m), 4.07 (s, 3), 3.95 (m), 3.65 (w). Anal. ($C_{10}H_{15}ClO_5$) C, H, Cl.

1,3,4-Tri-*O*-(*p*-nitrobenzoyl)-2,6-dideoxy-β-D-*ribo*-hexopyranose (18). 2,6-Dideoxy-D-*ribo*-hexose[7,21] (**14**; 1.04 g, 7.0 mmol) was peracylated by the procedure described by Zorbach and Payne[12] to afford, after recrystallization from acetone, pure **18**: yield 3.58 g (86%); mp 183–185 °C; $[\alpha]^{27}_D$ +35.6° (c 0.4, acetone) (lit.[12] dimorphic, mp 181–182 and 182-205 °C dec; $[\alpha]_D$ +55.6° in chloroform and +42.8° in acetone]; IR (KBr) ν_{max} 1740, 1734 (C=O), 1610, 720 (nitro-substituted phenyl), 1530, 1350 cm^{-1} (NO_2); MS *m/e* 261 (13%, M – $2O_2NC_6H_4CO_2H$), 150 (100%, $O_2NC_6H_4CO^+$), 95 (18%, methylpyrylium cation); X-ray powder diffraction data 11.01 (w), 9.68 (m), 8.13 (m), 7.38 (w), 6.87 (m), 6.28 (m), 5.61 (vs, 1), 5.13 (vs, 2), 4.57 (m), 4.29 (w), 4.27 (w), 4.06 (m). Anal. ($C_{27}H_{21}N_3O_{13}$) C, H, N.

2,6-Dideoxy-3,4-di-*O*-(*p*-nitrobenzoyl)-α-D-*ribo*-hexopyranosyl Chloride (19). The perester **18** (3.45 g, 5.8 mmol) was treated as described by Zorbach and Payne[12] with dry hydrogen chloride (11 mmol) in anhydrous dichloromethane (100 mL) for 10 h at 23 °C. The precipitate (*p*-nitrobenzoic acid) was filtered off and the filtrate evaporated. The resulting solid was recrystallized from 2:3 dichloromethane–ether (30 mL) to afford pure **19**: yield 2.24 g (83%); mp 96–104 °C dec [lit.[12] 96–103 °C (with effervescence)]; IR (KBr) ν_{max} 1725 (C=O), 1610 and 720 (nitro-substituted phenyl), 1530 and 1355 (NO_2), 561 cm^{-1} (CCl); MS *m/e* 262 (5%, M – Cl· – $O_2NC_6H_4CO_2H$), 95 (26%, 262 – $O_2NC_6H_4CO_2H$).

Moist air caused rapid hydrolysis of **19**, and an elemental analysis within acceptable limits could not be obtained.

7-*O*-[2,6-Dideoxy-3,4-di-*O*-(*p*-nitrobenzoyl)-α-D-*ribo*-hexopyranosyl]daunomycinone (6) and Its β Anomer 7. A mixture of the chloride **19** (2.02 g, 3.45 mmol), daunomycinone (868 mg, 2.18 mmol), yellow mercuric oxide (1.9 g, 8.77 mmol), mercuric bromide (521 mg, 1.45 mmol), and granular molecular

sieve 4Å (19 g) in anhydrous dichloromethane (200 mL) was stirred for 48 h at 23 °C under protection from moisture. TLC (9:1 benzene–acetone) then indicated that all of the daunomycinone had reacted and revealed the presence of two new components (R_f 0.3 and 0.2, observable as red zones under UV and visible light), together with some sugar impurities. After the excess of chloride 19 had been decomposed by the addition of methanol (30 mL), the inorganic material was filtered off and the solvent was evaporated. The remaining residue was placed on a column of silica gel that was eluted with 18:1 benzene–acetone. Recrystallization of the component having R_f 0.2 from acetone–hexane afforded the pure α anomer **6**: yield 1.05 g (58%); mp 151 °C (with sintering); $[\alpha]^{23}_D$ +756° (*c* 0.07, chloroform); IR (chloroform) ν_{max} 3490 (OH), 1730 (*C*- and *O*-acetyl), 1615 and 1580 (chelated quinone), 1530, 1355 cm^{-1} (NO_2); UV (chloroform) λ_{max} 253 nm ($\epsilon \times 10^{-3}$ 39.7), 483 (11.1), 498 (11.0), 532 (6.2); X-ray powder diffraction data 11.74 (s, 1), 9.63 (w), 7.47 (m, 2), 6.84 (w), 6.47 (w), 6.01 (vw), 5.82 (m), 5.04 (m, 3). Anal. ($C_{41}H_{34}N_2O_{17}$) C, H, N.

Recrystallization of the other fraction (R_f 0.3) from ethyl acetate afforded the pure β anomer **7**: yield 626 mg (35%, based on daunomycinone); mp 216–218 °C; $[\alpha]^{25}_D$ −276° (*c* 0.03, chloroform); IR (chloroform) ν_{max} 3520 (OH), 1735 (*C*- and *O*-acetyl), 1625 and 1580 (chelated quinone), 1530 and 1355 cm^{-1} (NO_2); UV (chloroform) λ_{max} 253 nm ($\epsilon \times 10^{-3}$ 43.4), 488 (11.0), 505 (11.0), and 540 (6.1); X-ray powder diffraction data 11.00 (s, 3), 8.60 (s), 6.39 (vw), 5.84 (s, 2), 5.32 (m), 5.04 (m), 4.66 (w), 3.42 (vs, 1). Anal. ($C_{41}H_{34}N_2O_{17}$) C, H, N.

7-*O*-(2,6-Dideoxy-α-D-*ribo*-hexopyranosyl)daunomycinone (8). To a cold (0 °C) solution of the protected glycoside **6** (232 mg, 0.28 mmol) in oxolane (20 mL) was added 0.1 M sodium hydroxide (20 mL), and the mixture was kept for 24 h at 0 °C. After this time, no starting material was detectable by TLC (2:3 benzene–acetone). Sodium acetate (1 g) was added and the product was extracted with chloroform (five 25-mL portions). Evaporation of the dried (magnesium sulfate) extract afforded crude **8** that was recrystallized from acetone–hexane: yield 93 mg (63%); mp 179–181 °C; $[\alpha]^{22}_D$ +244° (*c* 0.03, chloroform); IR (chloroform) ν_{max} 3520 (OH), 1740 (*C*-acetyl), 1625 and 1585 cm^{-1} (chelated quinone); UV (chloroform) λ_{max} 252 nm ($\epsilon \times 10^{-3}$ 19.4), 288 (7.1), 480 (10.5), 496 (10.3), 530 (5.4); X-ray powder diffraction data 11.58 (s, 1), 7.59 (vw), 5.78 (m, 2), 5.17 (w, 3), 4.75 (vw). Anal. ($C_{27}H_{28}O_{11}$) C, H.

7-*O*-(2,6-Dideoxy-β-D-*ribo*-hexopyranosyl)daunomycinone (9). Deprotection of **7** (210 mg, 0.25 mmol) was accomplished in the same way as described for **6** in the preceding experiment to afford, after recrystallization from acetone–hexane, 84 mg (63%) of **9**: mp 190–192 °C; $[\alpha]^{22}_D$ +58° (*c* 0.03, chloroform); IR (chloroform) ν_{max} 3490 (OH), 1715 (*C*-acetyl), 1620 and 1582 cm^{-1} (chelated quinone); UV (chloroform) λ_{max} 253 nm ($\epsilon \times 10^{-3}$ 24.2), 289 (8.2), 486 (12.4), 499 (12.7), 535 (7.4); X-ray powder diffraction data 10.97 (vs, 1), 7.98 (s, 2), 6.55 (m), 6.20 (w), 4.88 (w), 4.46 (m), 4.22 (m, 3), 3.96 (m), 3.66 (w), 3.53 (w). Anal. ($C_{27}H_{28}O_{11}\cdot 0.5H_2O$) C, H.

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