Acknowledgment. This work was supported by Research Grants CA 17263 and CA 19118 from the National Cancer Institute, National Institutes of Health. Mass spectra were kindly provided by Ed Henson of the Children's Hospital Medical Center, Boston. We thank Adria Laboratories Inc., Columbus, OH, and Farmitalia, Milan, Italy, for the generous supplies of daunorubicin and adriamycin used in this work.

Adriamycin Analogues. Novel Anomeric Ribofuranoside Analogues of Daunorubicin[1]

Mervyn Israel,* John E. Airey, Robert J. Murray, and John W. Gillard

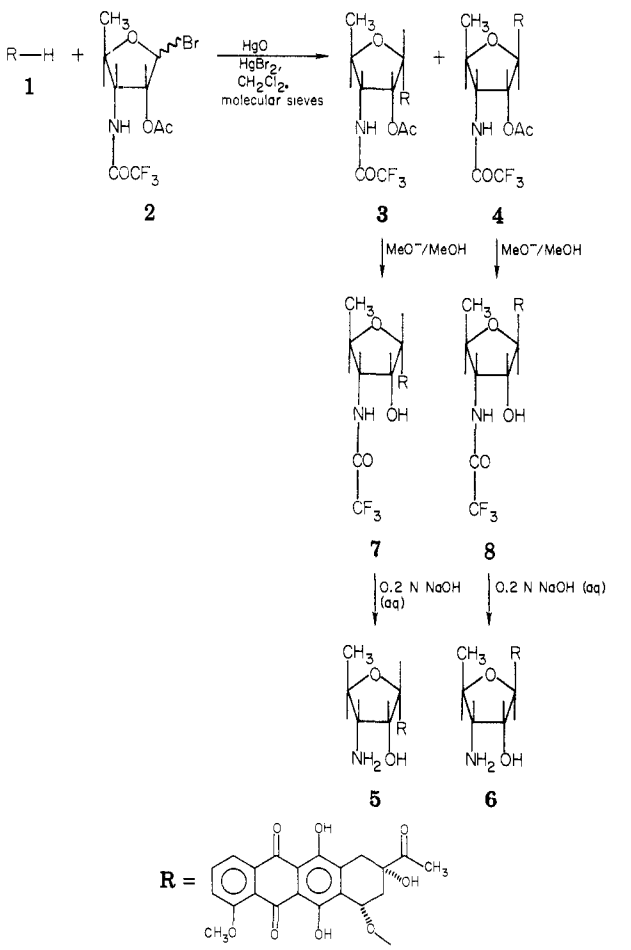
Division of Pharmacology, The Sidney Farber Cancer Institute, Boston, Massachusetts 02115. *Received March 13, 1981*

The synthesis, cell growth-inhibitory activity, in vivo antileukemic activity, and extent of DNA binding of the α- and β-anomeric 7-*O*-(3-amino-3,5-dideoxy-D-ribofuranosyl)daunomycinones and their trifluoroacetamides are described. These compounds are unique in that they are the first reported furanoside analogues of the antitumor antibiotics daunorubicin and adriamycin. Continuing analysis of structure–activity relationships amongst natural and semisynthetic anthracyclines fails to reveal a predictable relationship between in vivo antitumor activity and the in vitro properties of DNA complexation and cell growth inhibition.

This report concerns the synthesis and preliminary biological evaluation of the α and β anomers of 7-*O*-(3-amino-3,5-dideoxy-D-ribofuranosyl)daunomycinone and their trifluoroacetamide derivatives. These compounds are analogues of the anthracycline antitumor agents adriamycin, daunorubicin, and carminomycin and of AD 32 [*N*-(trifluoroacetyl)adriamycin 14-valerate],[2] an experimentally therapeutically superior and less toxic adriamycin analogue developed in these laboratories and currently in phase II clinical trial. The present aminofuranosides are unique in that, in so far as we are aware, no anthracycline analogue has yet been reported in which the naturally occurring 6-carbon daunosamine pyranose sugar has been replaced by a 5-carbon furanose moiety.

Adriamycin is one of the most important agents in cancer medicine today because of its use, either alone or in combination, in the treatment of leukemias and a range of solid tumors normally refractory to drug therapy.[3-5] Acute myelosuppression and concern about congestive heart failure are dose-limiting factors related to the use of this drug. Thus, anthracycline analogues which may further extend the antitumor spectrum of the parent antibiotic and/or reduce toxicity continue to be a worthwhile goal. Furthermore, although the mechanism of adriamycin-induced cardiomyopathy is not known, it has been suggested[6] that the development of cardiac toxicity may somehow be associated with the presence of the daunosamine moiety. Anthracycline analogues without the daunosamine moiety which continue to show biological activity may, if nothing else, contribute significantly to the elaboration of the molecular features which are associated with the problem of cardiotoxicity. The expectation that anthracycline analogues with fraudulent glycosides may be of value as antitumor agents derives, in practice, from

Scheme I



our own work with AD 32, a drug which does not bind to DNA, and from the retained antitumor activity of 7-*O*-β-D-glucosaminyldaunomycinone and 7-*O*-β-D-glucosaminyladriamycinone,[7] compounds which also do not fit the general accepted structure–activity hypothesis for adriamycin.[4] Furthermore, from theoretical considerations, it has been argued that conformational or configurational changes in the attached glycoside should continue to result

(1) A preliminary report of this work has appeared. See M. Israel and R. J. Murray in "Abstracts of Papers", 173rd National Meeting of the American Chemical Society, New Orleans, LA, Mar 1977, American Chemical Society, Washington, DC, 1977, Abstr MEDI 59.
(2) M. Israel, E. J. Modest, and E. Frei III, *Cancer Res.*, **35**, 1365 (1975).
(3) A. DiMarco and L. Lenaz in "Cancer Medicine", J. F. Holland and E. Frei III, Eds., Lea and Febiger, Philadelphia, PA, 1973, p 826.
(4) A. DiMarco and F. Arcamone, *Arzneim.-Forsch.*, **25**, 368 (1975).
(5) T. Skovsgaard and N. I. Nissen, *Dan. Med. Bull.*, **22**, 62 (1975).
(6) R. A. Adamson, *Cancer Chemother. Rep.*, **58**, 293 (1974).
(7) M. Israel and R. J. Murray, *J. Med. Chem.*, preceding paper in this issue.

0022-2623/82/1825-0028$01.25/0

Table I. Some Biological Properties of Anomeric 7-*O*-(3-Amino-3,5-dideoxy-D-ribofuranosyl)daunomycinones and Their Trifluoroacetamides

compound	ID_{50},[a] μM	extent of DNA binding: A/A_0 (λ 480 nm)[b]	in vivo antitumor act.[c] optimal dose, mg/kg × 4	% ILS
adriamycin	0.066[d]	0.62	4.0	+66
α-ribofuranoside-NH_2 (5)	0.28	0.80	15.0	+22
β-ribofuranoside-NH_2 (6)	0.21	0.86	50.6	+55
AD 32	0.24[d]	0.96[e]	50.0	curative
α-ribofuranoside trifluoroacetamide (7)	0.89		45.0	+55
β-ribofuranoside trifluoroacetamide (8)	1.08		70.0	+66
7-*O*-(β-D-glucosaminyl)daunomycinone[f]	3.04	0.82	90.0	+60

[a] Versus CCRF-CEM cells in culture; 48-h continuous drug exposure. [b] Calf thymus DNA; pH 7.0 Tris buffer; drug/DNA molar ratio = 0.1. [c] Versus murine L1210 leukemia, 10^5 tumor inoculum ip on day 0, treatment once daily ip on days 1–4. % ILS = increase in life span of treated animals relative to untreated controls. [d] Reference 2. [e] Reference 23. [f] Reference 7.

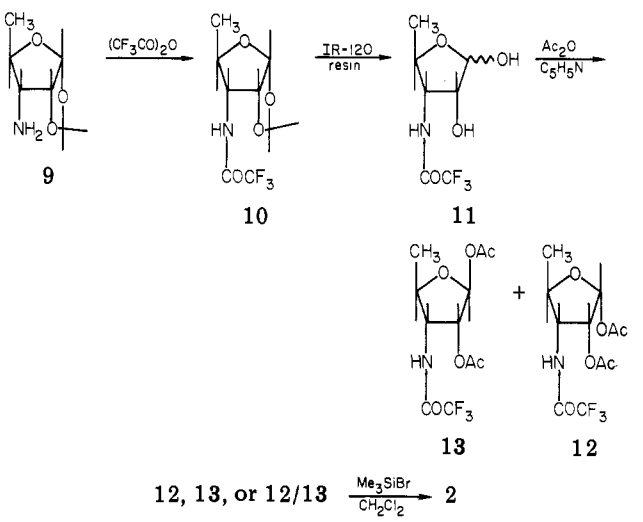
in analogues with biological activity.[8]

Chemistry. The preparation of the furanosides of daunomycinone, compounds **5–8**, was carried out as outlined in Scheme I. Condensation of daunomycinone (**1**) with 2-*O*-acetyl-3,5-dideoxy-3-[(trifluoroacetyl)amido]-D-ribofuranosyl bromide (**2**) under Koenigs–Knorr glycosidation conditions gave in good yield a 1:3.8 mixture of the α- and β-furanosides **3** and **4**, respectively. Separation of the mixture into the individual components by column chromatography, followed by methanolysis at 0 °C for 24 h, gave the respective α- and β-trifluoroacetamides, **7** and **8**, as amorphous powders. Finally, basic hydrolysis of each led to the free α- and β-amines, **5** and **6**.

Epimerization of the carbohydrate 2 position has been observed with sugars structurally related to **2**, especially under fusion reaction conditions.[9,10] That no epimerization at the C-2′ position of **2** to give the arabino configuration had taken place during the coupling reaction was shown by the observation that both **5** and **6** reacted quantitatively with phosgene to give within a few minutes the corresponding cyclic carbamates (IR, C=O, 1780 cm^{-1}).

The anomeric assignments were established by analysis of the NMR spectra of the fully protected coupled products **3** and **4**. The Karplus equation[11] predicts that the observed coupling constants of the anomeric proton and the C-2 proton of the sugar moiety ($J_{1',2'}$) can vary from 3.5 to 8.0 Hz for the α-glycoside and 0.0 to 8.0 Hz for the β-glycoside. Thus, when both anomers are available, an assignment of the β configuration can be made if the coupling constant is found to be less than 3.5 Hz. The fact that the anomeric proton for **4** appears as a singlet and that for **3** as a partially exposed doublet led to the assignment as made. Additional supportive evidence for these assignments was found in the observation of the multiplicities of the absorption of the C-2′ protons. In **3**, as in the α-acetate **12**, the C-2′ proton appears as a double doublet, whereas in **4**, as in β-acetate **13**, the C-2′ proton appears simply as a doublet. Finally, the benzylic proton at C-7 appears at higher field in the β-anomer **4** than in **3**, a result consistent with the findings in the α and β anomers of daunomycin and its 4′-epi derivative.[12,13]

Scheme II



The bromo sugar **2** used for coupling was prepared by an adaptation of the method of Vince[14] for the preparation of the analogous *N*-acetyl chloro sugar derivative (see Scheme II). Thus, treatment of amine **9**[15] with trifluoroacetic anhydride gave the amide **10** as a colorless oil. Subsequent cleavage of the 1,2-acetal with ion exchange (H^+), followed by acetylation of the crude diol **11**, gave a 1:2 mixture of the α and β acetates **12** and **13**, which were separable initially by column chromatography and subsequently by fractional crystallization. Both the α- and β-acetates were readily converted into an identical anomeric bromo sugar mixture by the trimethylsilyl bromide bromination procedure recently described by us,[16] a method vastly superior to the Br_2 in CH_2Cl_2 or HOAc procedures used in the earlier stages of this work.

Biology. The biological properties of the target compounds prepared in this study, together with data on several reference compounds, are given in Table I.

Compounds **5–8** were assayed for growth-inhibitory activity against CCRF-CEM cells, a lymphoblastic leukemic line of human origin, serially propagated in suspension cultures.[17,18] As seen in the table, adriamycin is strongly growth inhibitory in this system, a concentration of 0.066

(8) H. Berg and K. Eckardt, *Z. Naturforsch.*, **25**, 362 (1970).
(9) J. A. Montgomery, K. Hewson, A. G. Laseter, and M. C. Thorpe, *J. Am. Chem. Soc.*, **94**, 7176 (1972).
(10) R. Vince and R. G. Almquist, *Carbohydr. Res.*, **36**, 214 (1974).
(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(12) F. Arcamone, S. Penco, and A. Vigevani, *Cancer Chemother. Rep., Part 3*, **6**, 123 (1975).
(13) F. Arcamone, S. Penco, A. Vigevani, S. Redaelli, G. Franchi, A. DiMarco, A. Casazza, T. Dasdia, F. Formelli, A. Necco, and C. Soranzo, *J. Med. Chem.*, **18**, 703 (1975).
(14) R. G. Almquist and R. Vince, *J. Med. Chem.*, **16**, 1396 (1973).
(15) J. M. J. Tronchet and R. Graf, *Helv. Chim. Acta*, **55**, 2286 (1972).
(16) J. W. Gillard and M. Israel, *Tetrahedron Lett.*, **22**, 513 (1981).
(17) G. E. Foley, H. Lazarus, S. Farber, B. G. Uzman, B. A. Boone, and R. E. McCarthy, *Cancer*, **18**, 522 (1965).
(18) G. E. Foley and H. Lazarus, *Biochem. Pharmacol.*, **16**, 659 (1967).

μM producing 50% inhibition of growth (ID_{50} value). The furanoside analogues **5** and **6**, with unsubstituted amino groups, were also significantly inhibitory of growth, somewhat less active than adriamycin but with ID_{50} values in the same range as the potent adriamycin analogue AD 32.[2] The parent amino compounds **5** and **6** were 3 to 5 times more active than their corresponding trifluoroacetamides **7** and **8**, about the same relationship that exists between adriamycin and its trifluoroacetamide[19] or between adriamycin and AD 32.[2] Compounds **3** and **4** were also assayed in the CEM cell culture system and were found to be inactive up to a concentration of 3.0 μM, the highest dose level tested.

The antitumor activity of the target compounds was determined in the murine L1210 leukemia system according to the standard National Cancer Institute protocol,[20] except that treatment was given once daily on days 1–4 instead of on days 1–9. While the α-aminoribofuranoside (**5**) was only marginally active, its β-anomer **6** at its optimal dose was essentially as active as adriamycin itself. The ability of **6** and its trifluoroacetamide **8** to prolong the survival of mice bearing the L1210 leukemia was essentially equivalent. It was interesting to find, however, that trifluoroacetylation of **5** (i.e., **7**) resulted in an improvement in antitumor efficacy.

It has generally been accepted that the therapeutic activity of adriamycin and related agents was a consequence of their DNA-binding capability.[4,5] This view has been challenged, in part, by the observation of greater therapeutic efficacy for AD 32 compared to adriamycin,[2,21,22] despite the inability of AD 32 to bind to calf thymus DNA,[23,24] and also by the findings of these laboratories and of Tong et al.[25] that some adriamycin analogues, which in vitro bind as strongly to DNA as adriamycin, are less active as antitumor agents in vivo. Structure–DNA binding activity relationships are further explored here with the finding of a low order of DNA interaction for **5** and **6** despite their significant in vitro growth-inhibitory activity. The extent of DNA binding was determined by the spectral shift method[26,27] by calculating the ratio of the absorbances of drug–DNA mixtures to drug alone at 480 nm; with this method, the closer the ratio A/A_0 is to unity the lesser is the degree of drug–DNA complexation.

Comparison of the biological data for adriamycin vs. the non-DNA binding analogue AD 32 and for adriamycin vs. **5**, **6**, and also 7-*O*-β-D-glucosaminyldaunomycinone,[7] another DNA weak complexing analogue, demonstrates that among these anthracyclines no predictable relationship appears to exist between DNA binding, growth-inhibitory activity in vitro, and in vivo antitumor activity.

The DNA-binding properties of adriamycin result in the persistence of drug in body tissues and thereby probably contributes to the toxicity seen with this agent. In contrast, the non-DNA binding analogue AD 32 is very much more rapidly excreted and produces significantly less toxicity. The growth-inhibitory properties of **5** and **6**, as well as the low DNA binding which, if similar to AD 32, should lead to rapid clearance of these agents in vivo, have encouraged us to pursue the synthesis of the corresponding and other adriamycinone furanosides for in vivo biological evaluation, with the expectation that such agents may show improved properties compared to the parent anthracyclines.

Experimental Section

Melting points were taken on a Kofler hot stage with microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 137B Infracord. Proton NMR spectra were obtained on a Varian T60-A System spectrometer, with tetramethylsilane as internal standard, and are expressed as δ values. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6E double-focusing spectrometer operated at 70-eV ionizing energy. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and are within ±0.4% of theoretical values, unless otherwise noted. TLC on silica gel G (Analtech) with chloroform–acetone (9:1; system A), chloroform–methanol (49:1, system B), or chloroform–methanol–water (120:20:1, system C) as irrigant was used for identification and for analysis of homogeneity. Column chromatography was done on BioSil A silicic acid (100–200 mesh, Bio-Rad) or on washed and reactivated silicic acid.[28]

3-Amino-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (9) was prepared in six steps in 43.5% overall yield starting with commercially available 1,2-*O*-isopropylidene-D-xylofuranose (Pfanstiehl), according to the procedure outlined by Almquist and Vince:[14] TLC (solvent system A) R_f 0.15.

3,5-Dideoxy-3-(trifluoroacetamido)-1,2-*O*-isopropylidene-α-D-ribofuranose (10). To 1.22 g (7.0 mmol) of **9** dissolved in 75 mL of dry ether and cooled to 0 °C was added, in rapid drops, 4.0 mL of TFAA. After stirring at 0 °C for 0.5 h, the reaction mixture was allowed to warm to room temperature and then was stirred for an additional 30 min. Removal of the solvent at reduced pressure afforded 2.0 g (100%) of the amide as a colorless syrup, TLC (solvent system A) R_f 0.81, which was used without purification for the next reaction.

3,5-Dideoxy-3-(trifluoroacetamido)-D-ribofuranose (11). To a solution of 1.0 g (3.71 mmol) of the 1,2-acetal **10** in 30 mL of H_2O heated in an oil bath at 60 °C was added 12 mL of IR-120 resin (H^+) suspended in 20 mL of H_2O. After the mixture was stirred at 60 °C for 1.5 h, the resin was filtered and the filtrate was evaporated under reduced pressure to afford 0.57 g (67.3%) of the diol as a yellow semisolid: TLC (solvent system A) R_f 0.10.

1,2-Di-*O*-acetyl-3,5-dideoxy-3-(trifluoroacetamido)-α- and -β-D-ribofuranose (12 and 13). To 4.0 g (17.45 mmol) of the crude diol **11** dissolved in 100 mL of dry pyridine and cooled in an ice bath was added, dropwise, 15 mL (158.97 mmol) of acetic anhydride. After the addition was complete (ca. 15 min), the ice bath was removed, and the yellow solution was allowed to stir at room temperature for 16 h. The reaction was then poured into 300 mL of an ice–H_2O mixture, and the aqueous solution was extracted with $CHCl_3$ (4 × 250 mL). The $CHCl_3$ extracts were combined, cooled to 0 °C, washed with 5 N H_2SO_4 in ice and then with saturated $NaHCO_3$ solution (3 × 75 mL), dried (Na_2SO_4), and evaporated to give 6.0 g of a viscous oil. Chromatography of the oil in BioSil, chloroform elution, afforded 1.2 g (21.8%) of the pure α-acetate **12**, recrystallized from ether–petroleum ether [mp 89–90.5 °C; R_f 0.68; NMR ($CDCl_3$) δ 1.40 (d, 3 H, J = 6 Hz, C_5 CH_3), 2.10 (s, 6 H, C_1 and C_2 $COCH_3$), 4.00–4.43 (m, 2 H, C_3 and C_4 H), 5.30 (dd, 1 H, C_2 H), 6.40 (d, 1 H, J = 4 Hz, C_1 H), 6.80 (br m, 1 H, NH, exchangeable with D_2O). Anal. ($C_{11}H_{14}F_3NO_6$) C, H, F, N], 1.50 g (27.4%) of the pure β-acetate **13**,

(19) M. Israel, W. J. Pegg, R. Seshadri, and L. M. Parker, Abstracts, Fifth International Symposium on Medicinal Chemistry, Paris, France, July 1976, Imprimerie Levert, Paris, 1976, p 63.
(20) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 3, 1 (1972).
(21) L. M. Parker, M. Hirst, and M. Israel, *Cancer Treat. Rep.*, 62, 119 (1978).
(22) A. Vecchi, M. Cairo, A. Mantovani, M. Sironi, and F. Spreafico, *Cancer Treat. Rep.*, 62, 111 (1978).
(23) S. K. Sengupta, R. Seshadri, E. J. Modest, and M. Israel, *Proc. Am. Assoc. Cancer Res. and Am. Soc. Clin. Oncol.*, 17, 109 (1976).
(24) L. F. Chuang, R. T. Kawahata, and R. Y. Chuang, *FEBS Lett.*, 117, 247 (1980).
(25) G. L. Tong, H. Y. Wu, T. H. Smith, and D. W. Henry, *J. Med. Chem.*, 22, 912 (1979).
(26) I. H. Goldberg, M. Rabinowitz, and E. Reich, *Proc. Natl. Acad. Sci. U.S.A.*, 48, 2094 (1962).
(27) A. Rusconi, *Biochim. Biophys. Acta*, 123, 627 (1966).
(28) N. R. Bachur, K. Masek, K. L. Melmon, and S. Udenfriend, *J. Biol. Chem.*, 240, 1019 (1965).

recrystallized from ether–petroleum ether [mp 107–109 °C; TLC (solvent system A) R_f 0.60; NMR ($CDCl_3$) δ 1.40 (d, 3 H, J = 6 Hz, C_5 CH_3), 2.10 and 2.13 (2 s, 6 H, C_1 and C_2 $COCH_3$), 4.00–4.70 (m, 2 H, C_3 and C_4 H), 5.17 (d, 1 H, J = 4.0 Hz, C_2 H), 6.06 (s, 1 H, C_1 H), 6.70–6.90 (br d, 1 H, NH, exchangeable with D_2O). Anal. ($C_{11}H_{14}F_3NO_6$) C, H, F, N], and 2.6 g (47%) of a mixture of **12** and **13**, which were separated by fractional crystallization from ether–petroleum ether.

2-*O*-Acetyl-3,5-dideoxy-3-(trifluoroacetamido)-D-ribofuranosyl Bromide (12). To 2.0 g (6.38 mmol) of pure α-acetate **12** dissolved in dry CH_2Cl_2 and cooled to 0 °C was added dropwise 2.0 mL of trimethylsilyl bromide. The reaction was allowed to come to room temperature and was monitored by NMR by removal of solvent and reagent in vacuo from aliquots. The pure α-acetate (C_1 H, δ 6.40, d, J = 6 Hz) was converted quantitatively into a mixture of α- and β-bromides in a ratio of 1:2 after 80 min (C_1 H_α, δ 6.80, d, J = 6.2 Hz; C_1 H_β δ 6.38, s).

Similarly, pure β-acetate (C_1 H, δ 6.8, s) was converted into a 1:2 ratio of α/β bromides but required 6 h for completion of the reaction.

7-*O*-[2-Acetoxy-3,5-dideoxy-3-(trifluoroacetamido)-α- and -β-D-ribofuranosyl]daunomycinones (3 and 4). To 1.0 g (2.51 mmol) of daunomycinone (**1**) dissolved in 110 mL of dry CH_2Cl_2 were added successively 10 g of type 4Å molecular sieves, ground fine and baked under vacuum, 3.0 g (13.86 mmol) of HgO, 0.750 g (2.08 mmol) of HgBr, and 2.40 g (7.18 mmol) of the bromo sugar **2** dissolved in 12 mL of dry CH_2Cl_2. After stirring for 2.5 h in the dark (foil-covered flask), the reaction mixture was filtered, and the filtrate was evaporated to a red viscous oil, which showed three major spots on TLC (solvent system B) at R_f 0.35, 0.25, and 0.22, corresponding to compounds **3**, **4**, and **1**, respectively. Chromatography on BioSil using CH_2Cl_2 afforded the coupled products **3** (242 mg) and **4** (866 mg), which were subjected to a two-stage hydrolytic conversion to **5** and **6** as described below.

Analytically pure samples of **3** and **4** were obtained by crystallization of the individual anomeric products from chloroform–petroleum ether.

3: mp 175–185 °C; TLC (solvent system B) R_f 0.35; NMR ($CDCl_3$) δ 1.43 (d, 3 H, J = 6 Hz, C_5 CH_3), 1.60–2.40 (m, 2 H, C_8 H), 2.03 (s, 3 H, $C_{2'}$ $COCH_3$), 2.40 (s, 3 H, C_9 $COCH_3$), 2.66–3.43 (m, 2 H, C_{10} H_2), 4.06 (s, 3 H, C_4 OCH_3), 4.13 (s, 1 H, C_9 OH, D_2O exchangeable), 4.33–4.66 (m, 2 H, $C_{3'}$ and $C_{4'}$ H), 5.00–5.30 (m, 1 H, $C_{2'}$ H), 5.46 (m, 2 H, $C_{1'}$ and C_7 H), 7.23 (br m, 1 H, NH, D_2O exchangeable), 7.30–8.20 (m, 3 H, aromatic), 13.20 and 13.90 (2 s, 2 H, phenolic OH, D_2O exchangeable); mass spectrum, m/e 651; $[\alpha]^{19}_D$ +213°. Anal. ($C_{30}H_{28}F_3NO_{12}\cdot H_2O$) C, H, N.

4: mp 332–334 °C; TLC (solvent system B) R_f 0.22; NMR ($CDCl_3$) δ 1.48 (d, 3 H, J = 6 Hz, $C_{5'}$ CH_3), 1.73–1.93 (m, 2 H, C_8 H), 2.17 (s, 3 H, $C_{2'}$ $COOH_3$), 2.43 (s, 3 H, C_9 $COCH_3$), 2.63–3.40 (m, 2 H, C_{10} H), 4.06 (s, 3 H, C_4 OCH_3), 4.20–4.56 (m, 2 H, $C_{3'}$ and $C_{4'}$ H), 4.26 (s, 1 H, C_9 OH, D_2O exchangeable), 5.23 (m, 2 H, $C_{3'}$ and $C_{4'}$ H), 4.26 (s, 1 H, $C_{1'}$ H), 6.43 (br m, 1 H, NH, D_2O exchangeable), 7.40–8.03 (m, 3 H aromatic), 13.13 and 13.89 (2 s, 2 H, phenolic OH, D_2O exchangeable); mass spectrum, m/e 651; $[\alpha]$ +206°. Anal. ($C_{30}H_{28}F_3NO_{12}$) C, H, F, N.

7-*O*-[3,5-Dideoxy-3-(trifluoroacetamido)-α- and -β-D-ribofuranosyl]daunomycinones (7 and 8). The products **3** and **4** (100 mg of each) were separately dissolved in 75 mL of dry MeOH and cooled to 0 °C. Under N_2, 4 mL of a 5% solution of NaOMe in MeOH was added, and the reaction was allowed to come to room temperature. After 16 h, 1.0 g of IR 120 (H^+) resin was added to each solution, the solutions were then filtered, and the resin was well washed with $MeOH/CH_2Cl_2$. Concentration in vacuo, followed by precipitation from petroleum ether, produced **7** and **8** in essentially quantitative yield.

Recrystallization from $CHCl_3$–petroleum ether produced **7**-hydrate [mp 132–136 °C. Anal. ($C_{27}H_{26}F_3NO_{11}\cdot H_2O$) C, H, F, N] and **8**-sesquihydrate [mp 145–148 °C. Anal. ($C_{27}H_{26}F_3NO_{11}\cdot 1.5H_2O$) C, H, F, N].

7-*O*-(3-Amino-3,5-dideoxy-α- and -β-D-ribofuranosyl)daunomycinones (5 and 6). The products **7** and **8**, from above, separately dissolved in acetone and cooled to 0 °C in an ice bath, were treated with 0.1 N NaOH solution. After cooling to 0 °C in an ice bath, they were treated with 0.1 N NaOH solution. After the solutions were stirred at 0 °C for 1 h, the pH was adjusted to 8.4 by the dropwise addition of 0.1 N HCl, and the solutions were repeatedly extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The solid residues were chromatographed on washed and reactivated silicic acid using 5% MeOH in $CHCl_3$ as eluent, and the fractions containing **5** and **6** were combined and evaporated to a small volume (~2 mL) separately. Treatment of the individual solutions with the stoichiometric amount of 0.7 N methanolic HCl, followed by the addition of dry ether, gave the respective hydrochloride salts of **5** (72 mg, 80%) and **6** (65 mg, 75%) as red amorphous solids. **5**: mp 200–202 °C; TLC (solvent system C) R_f 0.55. Anal. ($C_{26}H_{27}NO_{10}\cdot HCl\cdot 3H_2O$) C, H, N. **6**: mp 221–224 °C; TLC (solvent system C) R_f 0.66. Anal. ($C_{26}H_{27}NO_{10}\cdot HCl\cdot H_2O$) C, H, N.

Acknowledgment. This investigation was supported by research Grants CA 17263 and CA 19118 from the National Cancer Institute, National Institutes of Health. The authors are grateful to Dr. Ramakrishnan Seshadri for determination of the DNA-binding data, to Drs. Herbert Lazarus and J. M. Idriss for the cell culture determinations, and to Ed Henson, The Children's Hospital Medical Center, Boston, for the mass spectral determinations. The daunorubicin used in this work was generously provided by Farmitalia, Milan, Italy, and Adria Laboratories Inc., Columbus, OH.