technical assistance and Christiane Callebaut for her fine editorial help.

Registry No. 8, 127915-66-6; 8 dephosphorylated derivative, 69304-47-8; 9, 127915-67-7; 9 dephosphorylated derivative, 59277-89-3; 15, 127943-59-3; 16, 127915-68-8; 17, 127915-69-9; 18, 127915-70-2; 19a, 127915-71-3; 19b, 127915-77-9; 19c, 127915-78-0; 20, 119672-65-0; 21, 127915-72-4; 22, 127943-60-6; 23, 127915-73-5; 24, 127915-74-6; 25a, 127915-75-7; 26a, 127915-76-8; 9-[(2-chloroethoxy)methyl]guanine, 127302-85-6; thymidine, 50-89-5.

Synthesis and Antitumor Activity of Novel 4-Demethoxyanthracyclines

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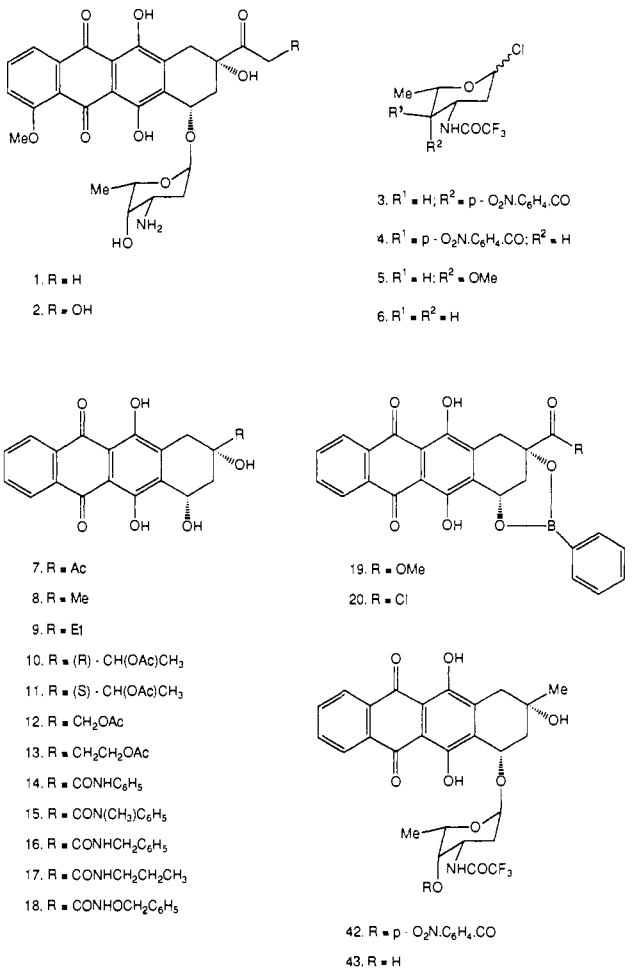
A versatile and efficient synthetic route to 4-demethoxyanthracyclinones has been utilized in the preparation of a number of aglycons having 9-alkyl, 9-(hydroxylalkyl), or 9-carbamoyl substituents. Silver trifluoromethanesulfonate catalyzed coupling of these aglycons with various daunosamine derivatives has yielded a series of novel anthracyclines which have been evaluated as antitumor agents. 9-Alkylanthracyclines **22**, **23**, **33**, and **34** have higher efficacy vs L-1210 leukemia than the parent 4-demethoxydaunorubicin (**21**), or the natural anthracyclines daunorubicin (**1**) and doxorubicin (**2**). 9-(Hydroxyalkyl) derivatives have in most cases high efficacy but are slightly less potent than **21**. 9-Methyl analogue **22** has higher efficacy vs P388 leukemia than other anthracyclines tested, while 9-(hydroxymethyl) derivative **37** retains similar efficacy to anthracyclines **1**, **2**, and **21** but is considerably more potent. The N-substituted 9-carbamoylanthracyclines are devoid of antitumor activity.

The anthracyclines daunorubicin (daunomycin, **1**; Chart I) and, particularly, doxorubicin (adriamycin, **2**) are widely used for the treatment of human tumors.[1-3] However, the clinical use of these agents is hampered by a number of undesirable side effects, particularly a dose-related and irreversible cardiotoxicity. Consequently a major goal for anthracycline research is the identification of new analogues with reduced toxicity, as well as a broader spectrum of antitumor activity, and this objective has stimulated considerable research activity in various industrial and academic laboratories.[4] Some structure–activity relationships have been established for the anthracyclines, but these are largely derived from the investigation of analogues obtained through chemical modification of fermentation-derived products.[5] This has limited the range of new structures since the natural products have labile functions at positions 7 and 9 which are essential for good biological activity. We have therefore undertaken to extend the understanding of structure–activity relationships by utilizing a new method of total synthesis which facilitates the preparation of the substantial quantities of novel anthracylinones necessary for subsequent glycosidation and biological evaluation.[6,7] We have selected as targets for synthesis a number of novel 4-demethoxyanthracyclines because 4-demethoxydaunorubicin (**21**) and 4-demethoxydoxorubicin are claimed to be more potent and less toxic than the parent compounds[8] and are effective in human therapy.[9,10] The choice of position 9 substituents is supported by various observations. Some natural products such as aclacinomycin A,B[11] and cinerubin A[12] which lack a C-13 oxo function show interesting antitumor activities. Besides being a potent antitumor agent, aclacinomycin A is claimed to be considerably less cardiotoxic than doxorubicin, while cinerubin A shows low but reproducible activity against a doxorubicin-resistant strain of P-388 leukemia.[13] In addition, both daunorubicin (**1**) and doxorubicin (**2**) have been converted to 13-deoxy derivatives with retention of considerable antitumor activity.[14] As one of the principal metabolic reactions of the anthracyclines **1** and **2** in man[15] and in animal tissues[16-19] involves reduction of the C-13 oxo function to give 13-dihydroanthracyclines, analogues which lack this function

Chart I



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(1) Brown, J. R. *Prog. Med. Chem.* **1978**, *15*, 125.
(2) Henry, D. W. *Cancer Chemotherapy*; ACS Symposium Series 30; American Chemical Society: Washington, DC, 1976; pp 15–57.

0022-2623/90/1833-2375$02.50/0

might show markedly different biological properties. The finding that the 13-dihydroanthracyclines themselves possess significant antitumor activity[20,21] has stimulated considerable interest in their preparation. Reduction of the parent anthracyclines has been carried out by microbial[22,23] and by chemical methods,[24] but the configuration at C-13 has not been established in these studies. Recently Cassinelli et al. reported the microbial reduction of 4-demethoxydaunorubicin (**21**) to a 13-dihydro derivative,[25] which was shown to be identical with the major metabolite obtained from the urine of patients treated with **21**, and formulated this as the (13*R*)-dihydro derivative.[25] By means of total synthesis of both the (13*R*)- and (13*S*)-dihydroanthracyclines **24** and **25**, we have now established that the mammalian and microbial metabolites possess the 13*S* configuration[26] and this has recently been confirmed by Penco et al.[27] In view of the fact that 13*S* dihydro metabolite **25** may be partly responsible for the clinical activity of **21**, we have synthesized other hydroxyalkyl analogues. Following the observation that a 9-carbamoyl anthracycline obtained through side-chain degradation of doxorubicin shows good activity against solid tumors in mice[28] we have prepared a number of N-substituted 9-carbamoyl analogues of 4-demethoxydaunorubicin.

Finally, as it has been shown that modification of anthracyclines **1** and **2** in the sugar residue at the 4′-position may confer advantageous biological properties,[29] a number of novel 4′-modified analogues have been synthesized.

Chemistry

The synthesis of aglycons **7–13** has been described previously.[30] Aglycons **14–18** were prepared through treatment of acid chloride **20** (derived from the corresponding methyl ester **19**[30]) with the appropriate amine or hydroxylamine followed by removal of the benzeneboronate protecting group. Chloro sugars **3–6** were synthesized by published procedures.[29,31] Coupling to aglycons **7–18** was catalyzed by silver triflate to give high yields of the desired α-glycosides as shown by the presence of a narrow multiplet in the region δ 5.3–5.4 in the ^{1}H NMR spectrum for the anomeric proton. In no case was an appreciable amount of the β-glycoside obtained. Stepwise deprotection of the resulting glycosides through treatment with a trace of base in methanol to remove the *p*-nitrobenzoyl residue, followed by hydrolysis of the *N*-trifluoroacetyl group and simultaneously, the side-chain *O*-acetate residue, if present, gave the desired anthracyclines **22–41** which were isolated as hydrochlorides.

Results and Discussion

Biological activity of the new 4-demethoxyanthracyclines against L-1210 leukemia in mice is shown in Table I. The compounds possessing an amide side chain at C-9 (**27–30** and hydroxamate **31**) were devoid of antitumor activity. These results were unexpected in view of the reported activity of a doxorubicin analogue with a primary amide side chain[28] and the significant antitumor activity of analogues with large acyl groups at C-9.[32,33] In contrast the compounds with simple alkyl or hydroxylalkyl side chains had potent activity. 9-Methyl and 9-ethyl analogues **22**, **33** and **23**, **34** were highly efficacious, giving survival times markedly better than those of **21**, daunorubicin (**1**), and doxorubicin (**2**). Compounds with hydroxyalkyl side chains were in most cases highly potent but with slightly reduced efficacy. Results for selected compounds tested against p-388 leukemia by using the stringent q4d 5,9, 13-test regimen[34] are shown in Table II. The best efficacy was obtained with **22** (T/C = 1.92) while **37** retained the antitumor activity of doxorubicin (**2**) (T/C = 1.74) but with much greater potency. Interestingly, in this test **37** was considerably more potent than the parent 4-methoxy-

(3) Arcamone, F. *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood: Chichester, 1978; Vol. 2, pp 99–239.
(4) Arcamone, F. *Doxorubicin Anticancer Antibiotics*; Academic Press: New York, 1981; Chapter 2.
(5) Arcamone, F.; Cassinelli, G.; Penco, S. *Anthracycline Antibiotics*, Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 159–73.
(6) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 158.
(7) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2249.
(8) Arcamone, F.; Bernardi, L.; Giardino, P.; Patelli, P.; DiMarco, A.; Casazza, A. M.; Pratesi, G.: Reggiani, P. *Cancer Treat. Rep.* **1976**, *60*, 829.
(9) Bonadonna, G.; Bonfante, V. *Anthracycline Antibiotics in Cancer Therapy*; Muggia, F. M., Young, C. A., Carter, S. K. Ed.; Martinus Nijhoff: The Hague, 1982; pp 455–465.
(10) DiMarco, A.; Casazza, A. M.; Guiliani, F.; Pratesi, G.; Arcamone, F.; Bernardi, L.; Franchi, G.; Giardino, P.; Patelli, B.; Penco, S. *Cancer Treat. Rep.* **1978**, *62*, 375.
(11) Oki, T.; Matsuzawa, Y.; Yoshimoto, A.; Numata, I.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Naganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1975**, *28*, 830.
(12) Ettlinger, L.; Gaumann, E.; Hütter, R.; Keller-Schierlein, W.; Kradolfer, E.; Niepp, L.; Prelog, V.; Reusser, P.; Zähner, H. *Chem. Ber.* **1959**, *92*, 1867.
(13) Johnson, R. K.; Overjera, A. A.; Goldin, A. *Cancer Treat. Rep.* **1976**, *60*, 99.
(14) Smith, T. H.; Fujiwara, A. N.; Henry, D. W. *J. Med. Chem.* **1978**, *21*, 280.
(15) Bachur, N. R. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 573.
(16) Bachur, N. R.; Cradock, J. C. *J. Pharmacol. Exp. Ther.* **1970**, *175*, 331.
(17) Bachur, N. R.; Gee, M. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 567.
(18) Bachur, N. R.; Huffman, D. H. *Br. J. Pharmacol.* **1971**, *43*, 828.
(19) Felsted, R. L.; Gee, M.; Bachur, N. R. *J. Biol. Chem.* **1974**, *249*, 3672.
(20) Cassinelli, G.; Grein, A.; Masi, P.; Suarato, A.; Bernardi, L.; Arcamone, F.; DiMarco, A.; Casazza, A. M.; Pratesi, G.; Soranzo, C. *J. Antibiot.* **1978**, *31*, 178.
(21) DiMarco, A.; Casazza, A. M.; Dasdia, T.; Guiliani, F.; Lenaz, L.; Necco, A.; Soranzo, C. *Cancer Chemother. Rep., Part 1* **1973**, *57*, 269.
(22) Aszalos, A. A.; Bachur, N. R.; Hamilton, B. K.; Langlykke, A. F.; Roller, P. P.; Sheikh, M. Y.; Sutphin, M. S.; Thomas, M. C.; Wareheim, D. A.; Wright, L. H. *J. Antibiot.* **1977**, *30*, 50.
(23) Marshall, V. P.; McGovern, J. P.; Richard, F. A.; Richard, R. E.; Wiley, P. F. *J. Antibiot.* **1978**, *31*, 336.
(24) Jolles, G.; Ponsinet, G. German Patent 2202690; *Chem. Abstr.* **1972**, *77*, 164320*v*.
(25) Cassinelli, G.; Grein, A.; Merli, S.; Penco, S.; Rivola, G.; Vigevani, A.; Zini, P.; Arcamone, F. *Gazz. Chim. Ital.* **1984**, *114*, 185.
(26) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Tetrahedron Lett.* **1984**, 6059.
(27) Penco, S.; Cassinelli, G.; Vigevani, A.; Zini, P.; Rivola, G.; Arcamone, F. *Gazz. Chim. Ital.* **1985**, *115*, 195.
(28) Tong, G. L.; Henry, D. W.; Acton, E. M. *J. Med. Chem.* **1979**, *22*, 36.
(29) Arcamone, F. *Doxorubicin Anticancer Antibiotics*; Academic Press: New York, 1981; Chapter 6.
(30) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Tetrahedron* **1984**, *40*, 4649.
(31) Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653.
(32) Arcamone, F.; Franceschi, G.; Minghetti, A.; Penco, S.; Redaelli, S.; DiMarco, A.; Casazza, A. M.; Dasdia, T.; DiFranzo, G.; Guiliani, F.; Lenaz, L.; Necco, A.; Soranzo, C. *J. Med. Chem.* **1974**, *17*, 335.
(33) Smith, T. H.; Fujiwara, A. N.; Henry, D. W. *J. Med. Chem.* **1979**, *22*, 40.
(34) Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chmother. Rep., Part 3* **1972**, *3*, 9.

daunorubicin (21) while retaining similar efficacy.

Whether any of the new anthracyclines offer real advantages over compounds currently in the clinic will require further careful evaluation. However, preliminary in vitro investigations indicate that 22 may have useful activity against some doxorubicin resistant cell lines.[35-37]

Further studies on the antitumor activity of 22 and other analogues are in progress and will be reported in due course.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL 100 spectrometer for $(CD_3)_2SO$ solutions unless otherwise stated. Optical rotations were determined on a Perkin-Elmer 141 MC polarimeter and microanalyses were carried out with a Perkin-Elmer elemental analyzer. Silica gel used for column chromatography was Kieselgel 60 (70–230 mesh, Merck).

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-methyl-5,12-naphthacenedione Hydrochloride (22). (i). A solution of naphthacenedione 8 (1.0 g, 2.94 mmol) in dry tetrahydrofuran (100 mL) was cooled to −5 °C with stirring under nitrogen and a solution of the chloro sugar 3 [prepared[31] from 2,3,6-trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-(trifluoroacetamido)-L-lyxohexopyranose (1.0 g, 1.84 mmol)] in dry tetrahydrofuran (15 mL) was added. A solution of silver trifluoromethanesulfonate (0.5 g, 1.85 mmol) in anhydrous diethyl ether (15 mL) was added during 20 min, and the mixture was stirred at −5 °C for 2 h. Additional chloro sugar (1.84 mmol) in tetrahydrofuran (15 mL) was added, followed by a solution of silver trifluoromethanesulfonate (0.5 g) in diethyl ether (15 mL) and the mixture was stirred at −5 °C for a further 1.5 h. The reaction mixture was poured into a mixture of 10% aqueous sodium hydrogen carbonate (300 mL) and dichloromethane (100 mL) and filtered. The organic layer was separated and the aqueous layer was extracted with three additional portions of dichloromethane (100 mL). The combined dichloromethane extracts were washed with water (2 × 200 mL), dried, and evaporated. The residue was chromatographed on a column of silica gel (200 g), using hexane–ethyl acetate (1:1 v/v) as eluent to give glycoside **42** (1.12 g, 53%) as a bright red, crystalline solid: mp 225–6 °C; $[\alpha]^{20}_D$ −94° (*c* 0.1% in $CHCl_3$).

(ii). Glycoside **42** (1.12 g) was dissolved in a mixture of dichloromethane (100 mL) and methanol (250 mL), and the solution was cooled to 0 °C with stirring in a nitrogen atmosphere. A 0.1 M aqueous sodium hydroxide solution (20 mL) was added and the purple solution was stirred at 0 °C for 30 min. Glacial acetic acid was added until the solution became bright orange and the mixture was poured into water (1 L) and extracted with dichloromethane (3 × 300 mL). The combined dichloromethane extracts were dried and evaporated, and the residue was triturated with ether to give glycoside **43** (0.8 g, 88%) as a bright red, crystalline solid: mp 253–4 °C; $[\alpha]^{20}_D$ +181° (*c* 0.1% in $CHCl_3$).

(iii). A solution of glycoside **43** (0.565 g) in tetrahydrofuran (20 mL) was added to 0.1 M aqueous sodium hydroxide (90 mL) and the solution stirred in a nitrogen atmosphere for 1 h. The solution was then adjusted to pH 8 with 5 M hydrochloric acid and extracted with 5% ethanol in dichloromethane (5 × 80 mL). The combined extracts were washed with water (200 mL), dried, and evaporated. The residue was dissolved in a mixture of dichloromethane (12 mL) and methanol (3 mL) and filtered, and the filtrate was treated with 0.25 M methanolic hydrogen chloride (4 mL). The solution was concentrated to ca. 5 mL and anhydrous diethyl ether (50 mL) was added with swirling to precipitate the hydrochloride of glycoside **22** (0.47 g, 93%) as a bright orange solid: mp 174–6 °C; $[\alpha]^{20}_D$ +160° (*c* 0.05% in MeOH); NMR δ 1.20 (d, 3, 6′-H_3), 1.26 (s, 3, 13-H_3), 1.55–2.22 (m, 4, 2′-H_2 and 8-H_2), 2.58 (d, 1, 10-H), 2.94 (d, 1, 10-H), 3.20–3.50 (m, H_2O and 3′-H), 3.64 (m, 1, 4′-H), 4.17 (q, 1, 5′-H), 4.46 (s, 1, exch D_2O, 9-OH), 4.88 (br s, 1, 7-H), 5.36 (br s, 1, 1′-H), 5.44 (d, 1, exch D_2O, 4′-OH), 7.88–8.07 (m, 2, 2-H and 3-H), 8.18–8.35 (m, 2, 1-H and 4-H). Anal. ($C_{25}H_{27}NO_8$·HCl·2.25H_2O) C, H, N, Cl.

Similar procedures were employed in the synthesis of the following compounds.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-9-ethyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (23) was obtained in a yield of 38% over three steps from **9** and **3**: mp 174–6 °C; $[\alpha]^{20}_D$ +176° (*c* 0.1% in MeOH); NMR δ 0.96 (t, 3, 14-H_3), 1.17 (d, 3, 6′-H_3), 1.4–2.25 (m, 6, 2′-H_2, 8-H_2 and 13-H_2), 2.54 (d, 1, 10-H), 2.92 (d, 1, 10-H), 3.2–3.45 (m, H_2O and 3′-H), 3.62 (m, 1, 4′-H), 4.16 (q, 1, 5′-H), 4.16 (s, 1, exch D_2O, 9-OH), 4.88 (br s, 1, 7-H), 5.31 (br s, 1, 1′-H), 5.41 (d, 1, exch D_2O, 4′-OH), 7.90–8.06 (m, 2, 2-H and 3-H), 8.20–8.36 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{29}NO_8$HCl·1.2H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(*R*)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (24) was obtained in 50% yield over three steps from **10** and **3**: mp 180–2 °C; $[\alpha]^{20}_D$ +142° (*c* 0.05% in MeOH); NMR (300 MHz) δ 1.16 (d, 3, H_3), 1.17 (d, 3, H_3), 1.65–2.1 (m, 4, 2′-H_2 and 8-H_2), 2.61 (d, 1, 10-H), 2.93 (d, 1, 10-H), 3.3–3.45 (m, H_2O and 3′-H), 3.53 (m, 1, 13-H), 3.60 (m, 1, 4′-H), 4.10 (s, 1, exch D_2O, 9-OH), 4.21 (q, 1, 5′-H), 4.81 (d, 1, exch D_2O, OH), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1′-H), 5.48 (d, 1, exch D_2O, OH), 7.92–7.98 (m, 2, 2-H and 3-H), 8.22–8.28 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{29}NO_9$·HCl·1.2H_2O) C, H, N, Cl.

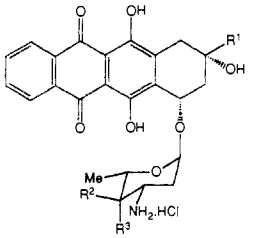
(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(*S*)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (25) was obtained in 45% yield over three steps from **11** and **3**: mp 174–5 °C; $[\alpha]^{20}_D$ +141° (*c* 0.05% in MeOH); NMR (300 MHz) δ 1.15 (d, 3, H_3), 1.17 (d, 3, H_3), 1.65–1.96 (m, 3, 2′-H_2 and 8-H), 2.23 (d, 1, 8-H), 2.74 (d, 1, 10-H), 2.83 (d, 1, 10-H), 3.27–3.44 (m, H_2O and 3′-H), 3.55 (m, 1, 13-H), 3.60 (m, 1, 4′-H), 4.06 (s, 1, exch D_2O, 9-OH), 4.23 (q, 1, 5′-H), 4.82 (d, 1, exch D_2O, OH), 4.92 (br s, 1, 7-H), 5.27 (br s, 1, 1′-H), 5.48 (d, 1, exch D_2O, OH), 7.93–8.00 (m, 2, 2-H and 3-H), 8.22–8.29 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{29}NO_9$·HCl·1.5H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione hydrochloride (26) was obtained in 31% yield over three steps from **12** and **3**: mp 183–6 °C; $[\alpha]^{20}_D$ +153° (*c* 0.05% in MeOH); NMR δ 1.16 (d, 3, 6′-H_3), 1.55–2.28 (m, 4, 2′-H_2 and 8-H_2), 2.81 (m, 2, 10-H_2), 3.22–3.45 (m, H_2O, 3′-H and 13-H_2), 3.62 (m, 1, 4′-H), 4.22 (q, 1, 5′-H), 4.28 (s, 1, exch D_2O, 9-OH), 4.85 (t, 1, exch D_2O, 13-OH), 4.94 (br s, 1, 7-H), 5.30 (br s, 1, 1′-H), 5.38 (d, 1, exch D_2O, 4′-OH), 7.95–8.06 (m, 2, 2-H and 3-H), 8.20–8.38 (m, 2, 1-H and 4-H). Anal. ($C_{25}H_{27}NO_9$·HCl·1.75H_2O) C, H, N, Cl.

(7*S*,9*S*)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-(*N*-phenylcarbamoyl)-5,12-naphthacenedione (14). A suspension of methyl ester **19** (2.0 g, 4.25 mmol) in tetrahydrofuran (40 mL) was treated with 0.1 M aqueous sodium hydroxide (140 mL) and the resulting dark purple solution was stirred at ambient temperature for 5.5 h. The solution was then acidified by dropwise addition of concentrated hydrochloric acid and the majority of the tetrahydrofuran was removed by evaporation. The precipitate was filtered off and dried in vacuo over P_2O_5 to give a red solid (1.6 g) which was finely powdered and suspended in dry dichloromethane (400 mL) and treated with oxalyl chloride (1.6 g) and 2 drops of dimethylformamide. The mixture was stirred at ambient temperature for 2.5 h to give a clear orange solution which was evaporated to remove solvent and excess oxalyl chloride to give acid chloride **20** as a red gum. This material was dissolved in dichloromethane (20 mL), the solution was cooled to 0 °C, and a solution of aniline (0.4 g, 4.3 mmol) in dichloromethane (10 mL) was added dropwise with stirring during 10 min. After a further 10 min the solution was washed with 2 M hydrochloric acid (100 mL) and water (100 mL), dried, and evaporated to give a red gum which was dissolved in a mixture of dichloromethane (60 mL), 2-methyl-pentane-2,4-diol (10 mL), and acetic acid (1 mL). The mixture was warmed at 60 °C for 15 min and then allowed to stand at room temperature for 2 days. Chloroform (400 mL) and

(35) Twentyman, P. R.; Fox, N. E.; Wright, K. A.; Workman, P.; Broadhurst, M. J.; Martin, J. A. *Br. J. Cancer* **1986**, *53*, 585.
(36) Scott, C. A.; Westmacott, D.; Broadhurst, M. J.; Thomas, G. J.; Hall, M. J. *Br. J. Cancer* **1986**, *53*, 595.
(37) Twentyman, P. R.; Workman, P.; Bleehen, N. M. *Invest. New Drugs* **1987**, *5*, 76.

Table I. Activity vs L-1210 Leukemia[a]



compd	R^1	R^2	R^3	optimal dose, mg/kg ip	% T/C
21	Ac	H	OH	0.05	230
22	Me	H	OH	0.5	400
23	Et	H	OH	0.5	420 (1)
24	(*R*)-CH(OH)CH_3	H	OH	0.125	250
25	(*S*)-CH(OH)CH_3	H	OH	0.125	220
26	CH_2OH	H	OH	0.1	230
27	$CONHC_6H_5$	H	OH	16	120
28	$CON(CH_3)C_6H_5$	H	OH	16	120
29	$CONHCH_2C_6H_5$	H	OH	4	130
30	$CONHCH_2CH_2CH_3$	H	OH	2	120
31	$CONHOCH_2C_6H_5$	H	OH	8	100
32	Ac	OH	H	0.5	240
33	Me	OH	H	2	470 (2)
34	Et	OH	H	0.5	460 (3)
35	(*R*)-CH(OH)CH_3	OH	H	0.125	270
36	(*S*)-CH(OH)CH_3	OH	H	0.125	360
37	CH_2OH	OH	H	0.125	340 (1)
38	CH_2CH_2OH	OH	H	0.25	450
39	Ac	H	OMe	0.25	230
40	CH_2OH	H	OMe	0.125	350
41	CH_2OH	H	H	0.125	280
1				0.5	290 (1)
2				2	330 (3)

[a] Aqueous solutions of test compounds were administered ip daily, five times a week for 4 weeks or until death. Groups of five female BDF_1 mice were used for each dose. Efficacy is expressed as the ratio T/C of mean survival time of treated animals to that of untreated controls, and the optimal dose is that which gave the highest T/C value. Animals surviving for 4 weeks are deemed long-term survivors. Where long-term survivors occurred, their number is shown in parentheses. Evidence of leucopenia was observed at the doses indicated for **23**, **29**, **32**, daunorubicin (**1**), and doxorubicin (**2**).

Table II. Activity vs P388 Leukemia[34]

compd	optimal dose,[a] mg/kg ip	% T/C[b]	ref
22	6.25	192	
23	3.0	155	
34	4.0	184	
37	0.38	174	
1	8.0	143	39
2	8.0	174	39
21	2.4	174	39

[a] Dose giving the highest value of T/C. [b] Ratio of mean survival time of treated animals to untreated controls.

methanol (50 mL) were then added, and the mixture was warmed to dissolve the precipitated solid. After cooling, the solution was washed with water (2 × 200 mL), dried, and evaporated. Trituration of the residue with ethyl acetate gave naphthacenedione **14** (1.48 g, 78%) as orange-red crystals: mp 228–30 °C; $[\alpha]^{20}_D$ +157° (*c* 0.05% in dioxane); NMR ($CDCl_3$) δ 2.48 (m, 2, 8-H_2) 3.36 (m, 3, part. exch D_2O, 10-H_2 and 7-OH), 5.13 (s, 1, exch D_2O, 9-OH), 5.43 (m, 1, 7-H), 7.14–7.73 (m, 5, ArH) 7.79–7.91 (m, 2, 2-H and 3-H), 8.30–8.45 (m, 2, 1-H and 4-H), 9.13 (br s, 1, NH), 13.24 (s, 1, exch D_2O, OH), 13.60 (s, 1, exch D_2O, OH). Anal. ($C_{25}H_{19}NO_7 \cdot 0.2H_2O$) C, H, N.

Similar procedures were employed in the synthesis of the following naphthacenediones.

(7*S*,9*S*)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-(*N*-methyl-*N*-phenylcarbamoyl)-5,12-naphthacenedione (15) was obtained in 76% yield over four steps from **19** and *N*-methylaniline: mp 245–7 °C; $[\alpha]^{20}_D$ +204° (*c* 0.05% in $CHCl_3$); NMR ($CDCl_3$ + DMSO) δ 2.04 (dd, 1, 10-H), 2.45 (dt, 1, 10-H), 3.07 (d, 1, 8-H), 3.36 (dd, 1, 8-H), 3.42 (s, 3, 15-H_3), 4.52 (d, 1, exch D_2O, 7-OH), 5.04 (s, 1, exch D_2O, 9-OH), 5.08 (m, 1, 7-H), 7.26–7.56 (m, 5, ArH), 7.78–7.92 (m, 2, 2-H and 3-H), 8.28–8.42 (m, 2, 1-H and 4-H), 13.36 (br s, 1, OH), 13.56 (br s, 1, OH). Anal. ($C_{26}H_{21}NO_7 \cdot 1.1H_2O$) C, H, N.

(7*S*,9*S*)-9-(*N*-Benzylcarbamoyl)-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-5,12-naphthacenedione (16) was obtained in 76% yield over four steps from **19** and benzylamine: mp 257–8 °C; $[\alpha]^{20}_D$ +87.5° (*c* 0.05% in dioxane); NMR δ 2.18 (m, 2, 8-H_2), 3.10 (br s, 2, 10-H_2), 4.37 (m, 2, 15-H_2), 5.13 (m, 1, 7-H), 7.30 (s, 5, ArH), 7.90–8.06 (m, 2, 2-H and 3-H), 8.39–8.49 (m, 2, 1-H and 4-H), 8.56 (br s, 1, NH). Anal. ($C_{26}H_{21}NO_7$) C, H, N.

(7*S*,9*S*)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-(*N*-propylcarbamoyl)-5,12-naphthacenedione (17) was obtained in 65% yield over four steps from **19** and *n*-propylamine: mp 253–6 °C; $[\alpha]^{20}_D$ +157° (*c* 0.05% in dioxane); NMR δ 0.88 (t, 3, 17-H_3), 1.53 (m, 2, 16-H_2), 2.14 (m, 2, 8-H_2), 2.99–3.20 (m, 4, 10-H_2 and 15-H_2), 5.12 (m, 1, 7-H), 5.66 (br s, 1, exch D_2O, 7-OH), 6.01 (s, 1, exch D_2O, 9-OH), 7.88–8.08 (m, 2, 2-H and 3-H), 8.22–8.38 (m, 2, 1-H and 4-H), 13.37 (br s, 2, exch D_2O, OH). Anal. ($C_{22}H_{21}NO_7 \cdot 0.2H_2O$) C, H, N.

(7*S*,9*S*)-9-[*N*-(Benzyloxy)carbamoyl]-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-5,12-naphthacenedione (18) was obtained in 75% yield over four steps from **19** and *O*-benzylhydroxylamine: mp 233–4 °C; $[\alpha]^{20}_D$ +59° (*c* 0.05% in dioxane); NMR δ 2.14 (m, 2, 8-H_2), 3.07 (s, 2, 10-H_2), 4.87 (s, 2, 16-H_2), 5.13 (m, 1, 7-H), 5.97 (br s, 1, exch D_2O), 7.41 (m, 5, ArH), 7.92–8.08 (m, 2, 2-H and 3-H), 8.24–8.38 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{21}NO_8$) C, H, N.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(*N*-phenylcarbamoyl)-5,12-naphthacenedione Hydrochloride (27). Silver triflate catalyzed coupling of chloro sugar **3** with aglycon **14** followed by stepwise deprotection gave **27** (54% over three steps): mp 180–1 °C; $[\alpha]^{20}_D$ +158° (*c* 0.05% in MeOH); NMR (300 MHz) δ 1.17 (d, 3, 6′-H_3), 1.74 (dd, 1, 2′-H), 1.93 (dt, 1, 2′-H), 2.24 (dd, 1, 8-H), 2.45 (dd, 1, 8-H), 3.14 (m, 2, 10-H_2), 3.30–3.47 (m, H_2O and 3′-H), 3.64 (m, 1, 4′-H), 4.29 (q, 1, 5′-H), 5.00 (br s, 1, 7-H), 5.37 (br s, 1, 1′-H), 5.48 (d, 1, exch D_2O, 4′-OH), 5.91 (s, 1, exch D_2O, 9-OH), 7.08 (t, 1, ArH), 7.32 (t, 2, ArH), 7.79 (d, 2, ArH), 7.98 (m, 2, 2-H and 3-H), 8.27 (m, 2, 1-H and 4-H), 10.00 (s, 1, NH). Anal. ($C_{31}H_{30}N_2O_9 \cdot HCl \cdot 2.0H_2O$) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(*N*-methyl-*N*-phenylcarbamoyl)-5,12-naphthacenedione hydrochloride (28) was obtained in 50% yield over three steps from **15** and **3**: mp 170–2 °C; $[\alpha]^{20}_D$ +134° (*c* 0.05% in MeOH); NMR δ 1.19 (d, 3, 6′-H_3), 1.70–2.27 (m, 4, 2′-H_2 and 8-H_2), 2.68 (d, 1, 10-H), 2.94 (d, 1, 10-H), 3.17–3.68 (m, H_2O, 3′-H and 15-H_3), 3.96 (q, 1, 5′-H), 5.04 (br s, 1, 7-H), 5.28 (m, 2, part exch D_2O, 4′-OH and 1′-H), 5.54 (s, 1, exch D_2O, 9-OH), 7.33 (m, 5, ArH), 7.93–8.08 (m, 2, 2-H and 3-H), 8.20–8.37 (m, 2, 1-H and 4-H). Anal. ($C_{32}H_{32}N_2O_9 \cdot HCl \cdot 2H_2O$) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-9-(*N*-benzylcarbamoyl)-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (29) was obtained in 18% yield over three steps from **16** and **3**: mp 174–6 °C; $[\alpha]^{20}_D$ +127° (C 0.05% in MeOH); NMR δ 1.15 (d, 3, 6′-H_3), 1.56–2.33 (m, 4, 2′-H_2 and 8′-H_2), 2.95–3.72 (m, H_2O, 3′-H and 10-H_2), 4.12–4.44 (m, 3, 5′-H and 15-H_2), 4.94 (br s, 1, 7-H), 5.32 (br s, 1, 1′-H), 5.54 (d, 1 exch D_2O, 4′-OH), 5.60 (s, 1, exch D_2O, 9-OH), 7.32 (m, 5, ArH), 7.84–8.05 (m, 2, 2-H and 3-H), 8.16–8.32 (m, 2, 1-H and 4-H), 8.52 (br t, 1, NH), 13.42 (br s, 2, exch D_2O, OH). Anal. ($C_{32}H_{32}N_2O_9 \cdot HCl \cdot 1.5H_2O$) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(*N*-propylcarbamoyl)-5,12-naphthacenedione hydrochloride (30) was obtained in 22% yield over three steps from **17** and **3**: mp 168–70 °C; $[\alpha]^{20}_D$ +148° (*c* 0.05% in MeOH); NMR δ 0.78 (t, 3, 17-H_3), 1.15 (d, 3, 6′-H_3), 1.50 (m, 2, 16-H_2), 1.54–2.34 (m, 4, 2′-H_2 and 8-H_2), 2.90–3.76 (m, H_2O, 3′-H, 10-H_2 and 15-H_2), 4.22 (q, 1, 5′-H), 4.96 (br s, 1, 7-H), 5.27–5.48 (m, 3, part. exch D_2O, 1′-H, 4′-OH and 9-OH), 7.90–8.14 (m, 3, NH, 2-H and 3-H), 8.18–8.38

(m, 2, 1-H and 4-H), 13.30 (br s, 1, exch D_2O, OH), 13.57 (br s, 1 exch D_2O, OH). Anal. ($C_{28}H_{32}N_2O_9$·HCl·1.6H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-lyxohexopyranosyl)oxy]-9-[*N*-(benzyloxy)carbamoyl]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (31) was obtained in 25% yield over three steps from 18 and 3: mp 173–5 °C; $[\alpha]^{20}_D$ +147° (*c* 0.05% in MeOH); NMR δ 1.16 (d, 3, 6′-H_3), 1.56–2.34 (m, 4, 2′-H_2 and 8-H_2), 2.96–3.70 (m, H_2O, 3′-H and 10-H_2), 4.20 (q, 1, 5′-H), 4.86 (s, 2, 16-H_2), 4.96 (br s, 1, 7-H), 5.36 (m, 2, part. exch D_2O, 4′-OH and 1′-H), 5.54 (s, 1, exch D_2O, 9-OH), 7.38 (m, 5, ArH), 7.88–8.08 (m, 3, NH, 2-H and 3-H), 8.20–8.36 (m, 2, 1-H and 4-H), 13.48 (br s, 2, exch D_2O, OH). Anal. ($C_{32}H_{32}N_2O_{10}$·HCl·2.3H_2O) C, H, N, Cl.

(7*S*,9*S*)-9-Acetyl-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione Hydrochloride (32). Silver triflate catalyzed coupling of chloro sugar **4** with 4-demethoxydaunomycinone (**7**) followed by stepwise deprotection gave **32** (25% over three steps): mp 173–5 °C; $[\alpha]^{20}_D$ +200° (0.05% in MeOH); NMR (300 MHz) δ 1.24 (d, 3, 6′-H_3), 1.75–2.3 (m, 4, 2′-H_2 and 8-H_2), 2.27 (s, 3, 14-H_3), 3.0 (m, 2, 10-H_2), 3.1–3.4 (m, H_2O and 3′-H and 4′-H), 4.0 (m, 1, 5′-H), 4.98 (br s, 1, 7-H), 5.30 (br s, 1, 1′-H), 5.60 (s, 1, exch D_2O, OH), 5.78 (s, 1, exch D_2O, OH), 7.94–8.02 (m, 2, 2-H and 3-H), 8.24–8.32 (m, 2, 1-H and 4-H), 13.33 (s, 1, exch D_2O, OH), 13.56 (s, 1, exch D_2O, OH). Anal. ($C_{26}H_{27}NO_9$·HCl·1.5H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-methyl-5,12-naphthacenedione hydrochloride (33) was obtained in 30% yield over three steps from **8** and **4**: mp 181–3 °C; $[\alpha]^{20}_D$ +243° (*c* 0.05% in MeOH); NMR δ 1.24 (m, 6, 6′-H_3 and 13-H_3), 1.70–2.20 (m, 4, 2′-H_2 and 8-H_2), 2.36 (d, 1, 10-H), 2.76 (d, 1, 10-H), 2.94–3.40 (m, H_2O and 3′-H and 4′-H), 3.96 (m, 1, 5′-H), 4.44 (d, 1, exch D_2O, OH), 4.90 (br s, 1, 7-H), 5.34 (br s, 1, 1′-H), 5.64 (br s, 1, exch D_2O, OH), 7.86–8.02 (m, 2, 2-H and 3-H), 8.15–8.32 (m, 2, 1-H and 4-H), 13.30 (br s, 1, exch D_2O, OH), 13.60 (br s, 1, exch D_2O, OH). Anal. ($C_{25}H_{27}NO_8$·HCl·1.8H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexopyranosyl)oxy]-9-ethyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (34) was obtained in 44% yield over three steps from **9** and **4**: mp 186–7 °C; $[\alpha]^{20}_D$ +240° (*c* 0.01% in MeOH); NMR [$(CD_3)_2SO$–$CDCl_3$] δ 1.00 (t, 3, 14-H_3), 1.23 (d, 3, 6′-H_3), 1.55–2.40 (m, 6, 2′-H_2, 8-H_2, and 13-H_2), 2.60 (d, 1, 10-H), 3.14 (d, 1, 10-H), 3.3–3.7 (m, H_2O and 3′-H and 4′-H), 3.9 (m, 1, 5′-H), 4.85 (br s, 1, 7-H), 5.30 (br s, 1, 1′-H), 7.58–7.78 (m, 2, 2-H and 3-H), 7.96–8.16 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{30}NO_8$·HCl·1.8H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(*R*)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (35) was obtained in 40% yield over three steps from **10** and **4**: mp 187–9 °C; $[\alpha]^{20}_D$ +213° (*c* 0.1% in MeOH); NMR (300 MHz) δ 1.17 (d, 3, H_3), 1.21 (d, 3, H_3), 1.75–2.2 (m, 4, 2′-H_2 and 8-H_2), 2.65 (d, 1, 10-H), 2.93 (d, 1, 10-H), 3.03–3.17 (m, 2, 3′-H and 4′-H), 3.52 (m, 1, 13-H), 3.95 (m, 1, 5′-H), 4.10 (s, 1, 9-OH), 4.80 (br s, 1, exch D_2O, OH), 4.94 (br s, 1, 7-H), 5.29 (br s, 1, 1′-H), 5.73 (d, 1, exch D_2O, OH), 7.95–8.01 (m, 2, 2-H and 3-H), 8.22–8.08 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{29}NO_9$·HCl·H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(*S*)-hydroxyethyl]-5,12-naphthacenedione hydrochloride (36) was obtained in 49% yield over three steps from **11** and **4**: mp 185–7 °C; $[\alpha]^{20}_D$ +192° (*c* 0.05% in MeOH); NMR δ 1.23 (m, 6, 6′-H_3 and 13-H_3), 1.67–2.45 (m, 4, 2′-H_2 and 8-H_2), 2.83 (m, 2, 10-H_2), 3.05–3.53 (m, 3′-H, 4′-H, and H_2O), 3.93 (s, 1, 9-OH), 3.96 (m, 1, 5′-H), 4.76 (br s, 1, exch D_2O, OH), 5.02 (br s, 1, 7-H), 5.33 (br s, 1, 1′-H), 5.67 (d, 1, exch D_2O, OH), 7.92–8.12 (m, 2, 2-H and 3-H), 8.24–8.43 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{29}NO_9$·HCl·1.2H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione hydrochloride (37) was obtained in 50% yield over three steps from **12** and **4**: mp 189–3 °C; $[\alpha]^{20}_D$ +216° (*c* 0.05% in MeOH); NMR δ 1.23 (d, 3, 6′-H_3), 1.60–2.22 (m, 4, 2′-H_2 and 8-H_2), 2.79 (m, 2, 10-H_2), 3.03–3.44 (m, H_2O, 3′-H, 4′-H, and 13-H_2), 3.98 (m, 1, 5′-H), 4.22 (s, 1, exch D_2O, 9-OH), 4.82 (br s, 1, exch D_2O, OH), 4.96 (br s, 1, 7-H), 5.32 (br s, 1, 1′-H), 5.64 (br m, 1, exch D_2O, OH), 7.89–8.04 (m, 2, 2-H and 3-H), 8.17–8.36 (m, 2, 1-H and 4-H), 13.36 (br s, 1, OH), 13.58 (br s, 1, OH). Anal. ($C_{25}H_{27}NO_9$·HCl·1.5H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-arabinohexopyranosyl)oxy]-9-(2-hydroxyethyl)-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (38) was obtained in 5% yield over three steps from **13** and **4**: mp 176–8 °C; $[\alpha]^{20}_D$ +172° (0.05% in MeOH); NMR (300 MHz) δ 1.22 (d, 3, 6′-H_3), 1.65–2.20 (m, 6, 2′-H_2, 8-H_2, and 13-H_2), 2.75 (d, 1, 10-H), 2.91 (d, 1, 10-H), 3.03–3.15 (m, 2, 3′-H and 4′-H), 3.65 (m, 2, 14-H_2), 3.87 (m, 1, 5′-H), 4.42 (s, 1, exch D_2O, 9-OH), 4.46 (d, 1, exch D_2O, OH), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1′-H), 5.71 (d, 1, exch D_2O, OH), 7.97–8.03 (m, 2, 2-H and 3-H), 8.28–8.33 (m, 2, 1-H and 4-H). Anal. ($C_{26}H_{29}NO_9$·HCl·2H_2O) C, H, N, Cl.

(7*S*,9*S*)-9-Acetyl-7-[(3′-amino-2′,3′,6′-trideoxy-4′-*O*-methyl-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione Hydrochloride (39). Coupling of 4-demethoxydaunomycinone (**7**) with sugar **5** followed by treatment with 0.1 M NaOH gave product **39** (39% over two steps): mp 195–6 °C (lit.[38] mp 189–90 °C); $[\alpha]^{20}_D$ +223° (0.05% in MeOH); NMR (300 MHz) δ 1.24 (d, 3, 6′-H_3), 1.68–2.2 (m, 4, 2′-H_2 and 8-H_2), 2.28 (s, 3, 14-H_3), 2.95 (br s, 2, 10-H_2), 3.3–3.5 (m, H_2O and 3′-H and 4′-H), 3.50 (s, 3, 4′-OMe), 4.25 (m, 1, 5′-H), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1′-H), 5.57 (s, 1, exch D_2O, 9-OH) 7.96–8.03 (m, 2, 2-H and 3-H), 8.25–8.32 (m, 1, 1-H and 4-H). Anal. ($C_{27}H_{29}NO_9$·HCl·1.5H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,6′-trideoxy-4′-*O*-methyl-α-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione hydrochloride (40) was obtained in 20% yield over three steps from **12** and **5**: mp 190–5 °C; $[\alpha]^{20}_D$ +132° (*c* 0.05% in MeOH); NMR δ 1.25 (d, 3, 6′-H_3), 1.62–2.18 (m, 4, 2′-H_2 and 8-H_2), 2.76 (m, 2, 10-H_2), 3.12–3.50 (m, H_2O and 3′-H and 4′-H), 3.54 (s, 3, 4′-OMe), 4.28 (m, 1, 5′-H), 4.92 (br s, 1, 7-H), 5.33 (br s, 1, 1′-H), 7.86–8.08 (m, 2, 2-H and 3-H), 8.11–8.38 (m, 5, part. exch D_2O, 1-H and 4-H and 3′-NH_3), 13.29 (br s, 1, OH), 13.55 (br s, 1, OH). Anal. ($C_{26}H_{29}NO_9$·HCl·2.1H_2O) C, H, N, Cl.

(7*S*,9*S*)-7-[(3′-Amino-2′,3′,4′,6′-tetradeoxy-α-L-threohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxymethyl)-5,12-naphthacenedione Hydrochloride (41). Silver triflate catalyzed coupling of chloro sugar **6** with aglycon **12** followed by treatment with 0.1 M NaOH gave product **41** (32% over three steps): mp 179–81 °C; $[\alpha]^{20}_D$ +200° (*c* 0.05% in MeOH); NMR δ 1.19 (d, 3, 6′-H_3), 1.13–2.16 (m, 6, 2′-H_2, 4′-H_2, and 8-H_2), 2.78 (m, 2, 10-H_2), 3.14–3.49 (m, H_2O, 3′-H), 4.20 (m, 1, 5′-H), 4.29 (s, 1, exch D_2O, 9-OH), 4.90 (m, 2, part. exch D_2O, 7-H and OH), 5.40 (br s, 1, 1′-H), 7.92–8.08 (m, 2, 2-H and 3-H), 8.18–8.36 (m, 2, 1-H and 4-H). Anal. ($C_{25}H_{27}NO_8$·HCl·0.7H_2O) C, H, N, Cl.

Biological Evaluation. For determination of antitumor activity against L-1210 leukemia BDF_1 mice were injected intraperitoneally with 10^5 viable L-1210 ascites tumor cells, and intraperitoneal administration of aqueous solutions of test compounds started on the same day. Test compounds were administered daily, five times a week for 4 weeks or until death. Groups of five female mice were used for each dose. Efficacy is expressed as the ratio T/C of mean survival time of treated animals to that of untreated controls. Animals surviving for 4 weeks were deemed long-term survivors. At the doses reported, apart from evidence of leucopenia with some compounds, no specific toxic effects were observed.

Selected compounds were evaluated against P-388 leukemia at the NCI by using the q4d 5,9,13-test regimen.[34]

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(38) Penco, S.; Casazza, A. M.; Franchi, G.; Barbieri, B.; Bellini, O.; Podesta, A.; Savi, G.; Pratesi, G.; Geroni, C.; DiMarco, A.; Arcamone, F. *Cancer Treat. Rep.* **1983**, *67*, 665.

(39) Benton Naff, M.; Plowman, J.; Narayanan, V. L. *Anthracycline Antibiotics*; El Khadem, Ed.; Academic Press: New York, 1982; pp 1–57.