

Synthesis and Antitumor Activity of 9-[(Carbamoyloxy)alkyl]anthracyclines: A Novel Class of Anthracycline Derivatives

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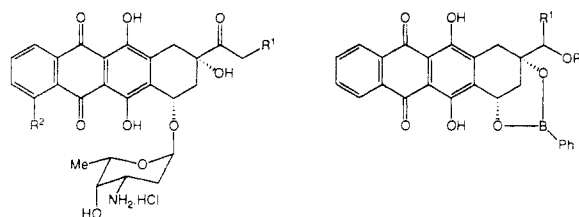
A number of 4-demethoxyanthracyclines having hydroxylalkyl functions at the 9-position have previously been synthesized and shown to have potent antitumor activity. A series of carbamate derivatives of these (hydroxyalkyl)anthracyclines have now been prepared, many of which possess considerably greater efficacy in an L-1210 leukemia test system than do the parent alcohols or the known anthracyclines daunorubicin (1), doxorubicin (2), and 4-demethoxydaunorubicin (3). Phenylcarbamate **8a** was more active than methyl analogue **8b**, while the 4'-deoxy and 4'-*epi* phenylcarbamates **17** and **18** showed particularly high efficacy at optimal dose levels similar to that of doxorubicin. Secondary carbamates were more potent, with the 13*R* isomer **23** having significantly higher efficacy than 13*S* analogue **24**.

Although the anthracyclines daunorubicin (daunomycin, 1; Chart I) and, particularly, doxorubicin (adriamycin, 2) are widely employed clinically as anticancer agents,¹⁻³ a number of undesirable side effects, especially cardiotoxicity, have limited their use. This has stimulated considerable interest in the synthesis of new analogues with reduced toxicity, as well as a broader spectrum of activity.⁴ Among the synthetic anthracyclines evaluated to date, 4-demethoxydaunorubicin (3) and 4-demethoxydoxorubicin are particularly interesting as they are reported to be more potent and less toxic than the parent compounds⁵ and are effective in human therapy.^{6,7} We have previously developed a versatile and practicable synthetic route to the 4-demethoxyaglycons⁸⁻¹⁰ and have recently employed this methodology in the synthesis of novel 4-demethoxyanthracyclines having a variety of alkyl, hydroxyalkyl, or carbamoyl substituents in the 9-position.¹¹ The 9-alkylanthracyclines exhibited high efficacy in an L-1210 leukemia test system, giving survival times markedly longer than those of the parent compounds 1-3, and they also showed good in vitro antitumor activity vs a number of doxorubicin-resistant cell lines.¹² In general, the 9-(hydroxyalkyl)anthracyclines had similar efficacy to daunorubicin (1) and doxorubicin (2) but were significantly more potent. This, together with the observation that one of the principal metabolic reactions of anthracyclines 1 and 2 in man involves reduction of the C-13 oxo function to give 13-dihydroanthracyclines¹³ and that these metabolites may be partly responsible for the clinical activity of 1 and 2,^{14,15} has prompted us to synthesize a number of derivatives of the 9-(hydroxyalkyl)anthracyclines. Such derivatives would be expected to have different physicochemical properties than the parent compounds, resulting in a different spectrum of biological activity, and might, in addition, act as prodrugs of the (hydroxyalkyl)anthracyclines. Among the most interesting derivatives studied were a series of carbamates.¹⁶ We now wish to report the synthesis and antitumor activity of these 9-[(carbamoyloxy)alkyl]anthracyclines.

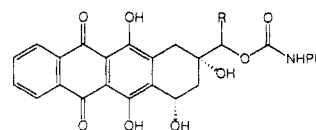
Chemistry

The synthesis of 9-(acetoxymethyl)aglycons, protected as benzenboronate esters **4**, **9**, and **11**, has been described previously.¹⁰ Following base-catalyzed hydrolysis of acetate **4** (Scheme I), alcohol **5** was treated with either an alkyl or aryl isocyanate or the corresponding acyl azide to give, after removal of the benzenboronate protecting group, 9-[(carbamoyloxy)methyl]anthracyclines **6a-e**. Silver triflate catalyzed glycosidation gave high yields of α -glycosides as shown by a narrow multiplet in the region δ

Chart I

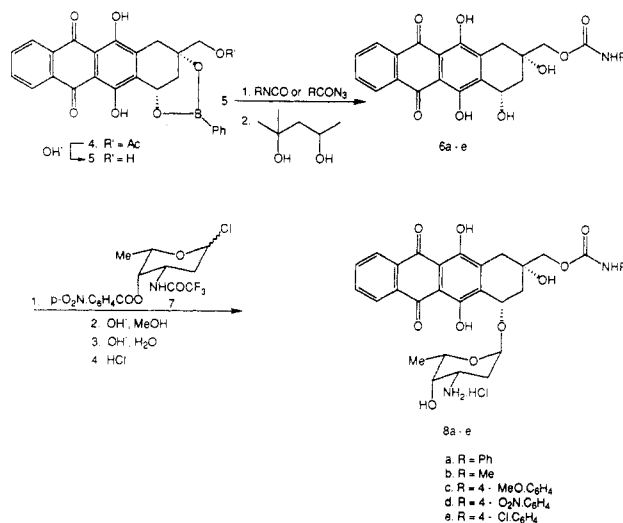


1. $R^1 = H, R^2 = OMe$
 2. $R^1 = OH, R^2 = OMe$
 3. $R^1 = R^2 = H$
 9. $R^1 = (R) \cdot Me, R^2 = Ac$
 10. $R^1 = (R) \cdot Me, R^2 = H$
 11. $R^1 = (S) \cdot Me, R^2 = Ac$
 12. $R^1 = (S) \cdot Me, R^2 = H$



13. $R = (R) \cdot Me$
 14. $R = (S) \cdot Me$

Scheme I

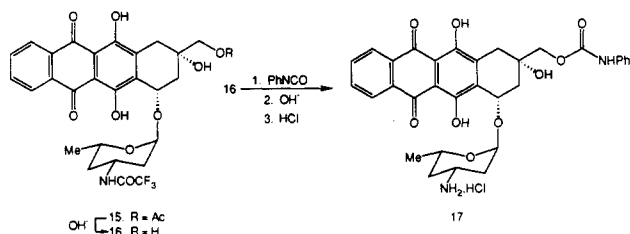
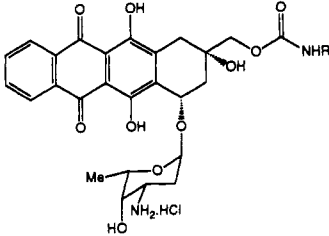


5.3-5.6 in the ¹H NMR spectrum for the anomeric proton. Stepwise removal of 4-nitrobenzoyl and trifluoroacetyl

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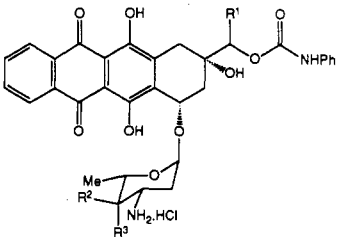
Scheme II

Table I. Activity vs L-1210 Leukemia^a


compd	R	optimal dose, mg/kg ip	% T/C
8a	C ₆ H ₅	2.0	380 (3)
8b	Me	4.0	280
8c	4-MeOC ₆ H ₄	2.0	230
8d	4-O ₂ NC ₆ H ₄	4.0	210
8e	4-ClC ₆ H ₄	2.0	370
1		0.5	290 (1)
2		2.0	330 (3)
3		0.05	230

^a Aqueous solutions of test compounds or, if insoluble, suspensions in propylene glycol were administered ip daily, five times a week for 4 weeks or until death. Groups of five female BDF₁ 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 at 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 8a, 8b, daunorubicin (1), and doxorubicin (2).

protecting groups gave the anthracyclines 8a–e which were isolated as hydrochlorides. The secondary carbamates 22–24 were similarly prepared from 9 and 11. For the

Table II. Activity vs L-1210 Leukemia^a


compd	R ¹	R ²	R ³	optimal dose, mg/kg ip	% T/C
8a	H	H	OH	2.0	380 (3)
17	H	H	H	2.0	500 (4)
18	H	OH	H	1.0	560 (3)
19	H	H	OMe	2.0	230
20	H	OMe	H	4.0	480 (5)
21	H	H	OCH ₂ C ₆ H ₅	16.0	470 (4)
22	(R)-Me	H	OH	0.25	420 (1)
23	(R)-Me	OH	H	0.125	400 (3)
24	(S)-Me	OH	H	1.0	280
1				0.5	290 (1)
2				2.0	330 (3)
3				0.05	230

^a Route and schedule of administration of test compounds as described in Table I. Efficacy is expressed as the ratio of 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 8a, 17, 18, 19, 20, daunorubicin (1), and doxorubicin (2).

synthesis of anthracyclines which lack a hydroxyl function at the 4'-position, an alternative route could be employed in which treatment of a preformed glycoside such as 16 with an isocyanate and removal of the trifluoroacetyl protecting group gave carbamate 17 directly (Scheme II).

Results and Discussion

Antitumor activity of a series of carbamates having different residues at the 9-position against L-1210 leukemia in mice is shown in Table I. Phenylcarbamate 8a had significantly higher efficacy than any of the standard anthracyclines 1–3 and was also clearly superior to methylcarbamate 8b. Substitution of the aryl residue (8c–e) did not appear to confer any increase in either potency or efficacy. Based on these results a number of phenylcarbamates having modified sugar residues (17–21) were evaluated, as well as the secondary phenylcarbamates 22–24 (Table II). The 4'-deoxy and 4'-epi analogues 17 and 18 showed particularly high efficacy, with potencies in the same range as daunorubicin (1) and doxorubicin (2). As with the free hydroxyglycosides 8a and 18, arabinomethyl ether 20 had significantly higher efficacy than lyxo isomer 19. Benzyl ether 21 was highly efficacious but considerably less potent than the other analogues. The secondary carbamates (22, 23) having the R configuration in the side chain were significantly more potent than unsubstituted analogues 8a and 18 and also had greater potency and efficacy than the S isomer 24. This contrasts with the case of the free secondary alcohols, where both diastereomers have similar activity,¹¹ and this may well imply a difference in the extent of metabolic cleavage of the carbamate moiety in vivo.

Further studies will be required in order to establish whether these carbamates act as prodrugs of the corresponding hydroxyalkyl anthracyclines, or are active per se. However, the results presented above indicate that derivatization of (hydroxyalkyl)anthracyclines as phe-

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nylcarbamates yields potent antileukemic agents which have considerably higher efficacy than the parent alcohols. Preliminary studies indicate that the phenylcarbamate 18 possesses a broad spectrum of antitumor activity, is active by the oral route of administration, and is considerably less cardiotoxic than the parent anthracyclines 1–3. A more detailed account of the biological properties of 18 and other analogues will be presented in due course.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian XL 100 spectrometer for $(\text{CD}_3)_2\text{SO}$ 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).

(7S,9S)-5,7,8,9,10,12-Hexahydro-6,11-dihydroxy-9-(hydroxymethyl)-5,12-dioxo-7,9-naphthacenediyl Benzeneboronate (5). A solution of acetate 4^{10} (1.00 g, 2.1 mmol) in a mixture of dichloromethane (100 mL) and methanol (100 mL) was stirred and sufficient 0.1 M sodium hydroxide solution was added to give a deep purple color. After stirring for 4 h at room temperature, glacial acetic acid was added to give a bright orange solution. Evaporation of the solvent and trituration of the residue with methanol yielded hydroxymethyl derivative 5 (0.70 g, 77%) as orange-red crystals: mp 258–9 °C; $[\alpha]_D^{20} +355^\circ$ (c 0.1% in dioxane); NMR [$\text{CDCl}_3 + (\text{CD}_3)_2\text{SO}$] δ 2.12 (dd, 1, 8-H), 2.33 (dd, 1, 8-H), 3.17 (d, 2, 10-H), 3.84 (d, 2, 13-H₂), 5.53 (t, 1, exch D_2O , OH), 5.80 (t, 1, 7-H), 7.20–7.40 (m, 3, ArH), 7.70–7.96 (m, 4, ArH), 8.22–8.44 (m, 2, ArH), 13.25 (s, 1, OH), 13.53 (s, 1, OH). Anal. ($\text{C}_{25}\text{H}_{19}\text{BO}_7$) C, H.

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

(7S,9S)-5,7,8,9,10,12-Hexahydro-6,11-dihydroxy-9-[1(R)-hydroxyethyl]-5,12-dioxo-7,9-naphthacenediyl Benzeneboronate (10). Base-catalyzed hydrolysis of acetate 9^{10} gave alcohol 10 as a red gum: 78%; NMR δ 1.44 (d, 3, 14-H₃), 2.07 (dd, 1, 8-H), 2.40 (br d, 1, 8-H), 2.96 (d, 1, 10-H), 3.32 (d, 1, 10-H), 4.05 (q, 1, 13-H), 5.81 (t, 1, 7-H), 7.20–7.50 (m, 3, ArH), 7.70–7.92 (m, 4, ArH), 8.23–8.44 (m, 2, ArH), 13.29 (s, 1, OH), 13.52 (s, 1, OH).

(7S,9S)-5,7,8,9,10,12-Hexahydro-6,11-dihydroxy-9-[1(S)-hydroxyethyl]-5,12-dioxo-7,9-naphthacenediyl Benzeneboronate (12). Base-catalyzed hydrolysis of 11^{10} gave 12 as a red solid: 80%; mp 244–6 °C; $[\alpha]_D^{20} +270^\circ$ (c 0.05% in dioxane). This material was used without further purification for the preparation of compound 20.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-[[phenylcarbamoyloxy]methyl]-5,12-naphthacenedione (6a). A solution of alcohol 5 (0.08 g, 1.81 mmol) and phenyl isocyanate (0.90 g, 7.6 mmol) in pyridine (100 mL) was stirred at 60 °C for 45 min and the solvent was then evaporated. The residue was taken up in dichloromethane (100 mL) and the solution was filtered and then washed with 5 M hydrochloric acid (2 × 50 mL) and water (2 × 50 mL), dried, and evaporated. The residue was dissolved in a mixture of dichloromethane (30 mL), 2-methyl-2,4-pentanediol (30 mL), and acetic acid (3 mL), and the solution was left to stand at room temperature overnight. The mixture was then diluted with dichloromethane (100 mL), washed with water (3 × 100 mL), dried, and evaporated. The residue was trituated with a mixture of ethyl acetate and diethyl ether to give carbamate 6a (0.82 g, 95%) as a red, crystalline solid, mp 225–6 °C; $[\alpha]_D^{20} +136^\circ$ (c 0.05% in dioxane); NMR [$\text{CDCl}_3 + (\text{CD}_3)_2\text{SO}$] δ 1.91 (dd, 1, 8-H), 2.42 (br d, 1, 8-H), 2.70 (d, 1, 10-H), 3.30 (d, 1, 10-H), 4.25 (s, 2, 13-H₂), 5.24 (br s, 1, 7-H), 6.92–7.60 (m, 5, ArH), 7.76–7.95 (m, 2, 2-H and 3-H), 8.22–8.48 (m, 2, 1-H and 4-H), 8.75 (br s, 1, NH), 13.37 (s, 1, OH), 13.58 (s, 1, OH). Anal. ($\text{C}_{26}\text{H}_{21}\text{NO}_8$) C, H, N.

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

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-[[methylcarbamoyloxy]methyl]-5,12-naphthacenedione (6b) was obtained in a yield of 64% over two steps from alcohol 5 and methyl isocyanate: mp 216–8 °C; $[\alpha]_D^{20} +130^\circ$ (c 0.05%

in dioxane); NMR [$\text{CDCl}_3 + (\text{CD}_3)_2\text{SO}$] δ 1.84 (dd, 1, 8-H), 2.34 (br d, 1, 8-H), 2.79 (d, 3, NCH_3), 2.81 (d, 1, 10-H), 3.26 (br d, 1, 10-H), 4.17 (s, 2, 13-H₂), 5.25 (m, 2, 7-H and OH), 6.04 (br s, 1, NH), 7.70–7.95 (m, 2, 2-H and 3-H), 8.20–8.46 (m, 2, 1-H and 4-H), 13.40 (br s, 2, OH). Anal. ($\text{C}_{27}\text{H}_{19}\text{NO}_8$) C, H, N.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-[[[(4-methoxyphenyl)carbamoyloxy]methyl]-5,12-naphthacenedione (6c). Treatment of 5 with *p*-methoxybenzoyl azide and removal of the benzeneboronate residue gave 6c: 84% over two steps; mp 196–7 °C; $[\alpha]_D^{20} +157^\circ$ (c 0.05% in dioxane); NMR (CDCl_3) δ 1.88 (dd, 1, 8-H), 2.44 (br d, 1, 8-H), 2.60 (d, 1, 10-H), 3.24 (d, 1, 10-H), 3.78 (s, 3, OCH_3), 4.00 (m, 2, 7-OH and 9-OH), 4.25 (s, 2, 13-H₂), 5.24 (br s, 1, 7-H), 6.84 (d, 2, ArH), 7.06 (br s, 1, NH), 7.32 (d, 2, ArH), 7.80–7.91 (m, 2, 2-H and 3-H), 8.16–8.40 (m, 2, 1-H and 4-H), 13.22 (br s, 1, OH), 13.43 (br s, 1, OH). Anal. ($\text{C}_{27}\text{H}_{23}\text{NO}_9$) C, H, N.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-[[[(4-nitrophenyl)carbamoyloxy]methyl]-5,12-naphthacenedione (6d). Treatment of 5 with *p*-nitrobenzoyl azide and deprotection gave 6d: 81% over two steps; mp 237–9 °C; $[\alpha]_D^{20} +117^\circ$ (c 0.05% in dioxane); NMR δ 1.96 (dd, 1, 8-H), 2.24 (br d, 1, 8-H), 2.75 (d, 1, 10-H), 3.14 (d, 1, 10-H), 4.22 (s, 2, 13-H₂), 5.12 (br s, 1, 7-H), 5.32 (br s, 1, exch D_2O , OH), 5.56 (s, 1, exch D_2O , OH), 7.75 (d, 2, ArH), 7.88–8.10 (m, 2, 2-H and 3-H), 8.12–8.40 (m, 4, 1-H, 4-H, and ArH), 10.33 (br s, 1, NH), 13.31 (br s, 2, OH). Anal. ($\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_{10} \cdot 2\text{H}_2\text{O}$) C, H, N, H_2O .

(7S,9S)-9-[[[(4-chlorophenyl)carbamoyloxy]methyl]-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-5,12-naphthacenedione (6e). Treatment of 5 with *p*-chlorophenyl isocyanate and deprotection gave 6e: 82% over two steps; mp 264–5 °C; $[\alpha]_D^{20} +125^\circ$ (c 0.05% in dioxane); NMR δ 1.94 (dd, 1, 8-H), 2.22 (br d, 1, 8-H), 2.72 (d, 1, 10-H), 3.12 (d, 1, 10-H), 4.17 (s, 2, 13-H₂), 5.08 (br s, 1, 7-H), 5.30 (br s, 1, exch D_2O , OH), 5.54 (s, exch D_2O , OH), 7.34 (d, 2, ArH), 7.56 (d, 2, ArH), 7.92–8.10 (m, 2, 2-H and 3-H), 8.18–8.38 (m, 2, 4-H and 1-H), 9.90 (br s, 1, NH), 13.30 (br s, 2, OH). Anal. ($\text{C}_{26}\text{H}_{20}\text{ClNO}_8$) C, H, N.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-[1(R)-[(phenylcarbamoyloxy)ethyl]-5,12-naphthacenedione (13). Treatment of alcohol 10 with phenyl isocyanate followed by removal of the benzeneboronate residue gave aglycon 13: 80%; mp 218–30 °C; $[\alpha]_D^{20} +220^\circ$ (c 0.1% in dioxane); NMR δ 1.45 (d, 3, 14-H₃), 1.90 (dd, 1, 8-H), 2.36 (br d, 1, 8-H), 2.76 (d, 1, 10-H), 3.35 (d, 1, 10-H), 4.66 (m, 2, 7-OH and 9-OH), 4.90 (q, 1, 13-H), 5.25 (br s, 1, 7-H), 6.96–7.56 (m, 5, ArH), 7.75–7.86 (m, 2, 2-H and 3-H), 8.26–8.43 (m, 2, 1-H and 4-H), 13.40 (s, 1, OH), 13.60 (s, 1, OH). Anal. ($\text{C}_{27}\text{H}_{23}\text{BO}_8$) C, H, N.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-[1(S)-[(phenylcarbamoyloxy)ethyl]-5,12-naphthacenedione (14). Treatment of alcohol 12 with phenyl isocyanate and deprotection gave 14: 86% over two steps; mp 155–60 °C; $[\alpha]_D^{20} +62^\circ$ (c 0.05% in dioxane); NMR (CDCl_3) δ 1.47 (d, 3, 14-H₃), 1.86 (dd, 1, 8-H), 2.48 (br d, 1, 8-H), 2.60 (d, 1, 10-H), 3.22 (d, 1, 10-H), 3.79 (d, 1, exch D_2O , 7-OH), 3.88 (s, 1, exch D_2O , 9-OH), 5.00 (q, 1, 13-H), 5.28 (br s, 1, 7-H), 6.98 (br s, 1, NH), 7.04–7.52 (m, 5, ArH), 7.74–7.95 (m, 2, 2-H and 3-H), 8.24–8.41 (m, 2, 1-H and 4-H), 13.31 (s, 1, OH), 13.53 (s, 1, OH). Anal. ($\text{C}_{27}\text{H}_{23}\text{NO}_8$) C, H, N.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[phenylcarbamoyloxy]methyl]-5,12-naphthacenedione Hydrochloride (8a). (i). A solution of aglycon 6a (1.30 g, 2.7 mmol) in tetrahydrofuran (100 mL) was cooled to –5 °C and a solution of 2,3,6-trideoxy-4-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-L-lyxohexopyranosyl chloride (7^{17}) (1.30 g, 3.5 mmol) in dichloromethane (10 mL) was added. A solution of silver trifluoromethanesulfonate (0.65 g, 2.5 mmol) in diethyl ether (15 mL) was added over 20 min. Additional chloro sugar (1.30 g, 3.5 mmol) in dichloromethane (10 mL) was then added, followed by a solution of silver trifluoromethanesulfonate (0.65 g, 2.5 mmol) in diethyl ether (15 mL), and the mixture was stirred at –5 °C for 30 min. The reaction mixture was poured into 10% potassium hydrogen carbonate solution (300 mL) and extracted with di-

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chloromethane (4 × 100 mL). The combined extracts were dried and evaporated, and the residue was chromatographed on a column of silica gel using ethyl acetate-hexane (1:1 v/v) as eluent to give the glycoside (1.16 g, 50%) which, without further purification, was treated as described below.

(ii). The glycoside prepared above (1.70 g, 2.1 mmol) was dissolved in a mixture of dichloromethane (100 mL) and methanol (100 mL) and the solution cooled to 0 °C. A 0.1 M aqueous sodium hydroxide solution was added to produce a deep purple color and the solution was stirred at 0 °C for 1.5 h. Acetic acid was added to give a bright orange solution which was poured into water (250 mL) and extracted with dichloromethane (4 × 100 mL). The combined extracts were dried and concentrated, and diethyl ether was added to precipitate (7S,9S)-7-[(3',6'-trideoxy-3'-(trifluoroacetamido)- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione] as an orange solid (1.3 g, 93%): mp 160–70 °C; $[\alpha]_D^{20} + 137^\circ$ (c 0.1% in chloroform); NMR δ (CDCl₃) 1.27 (d, 3, H₃), 1.70–2.52 (m, 4, 2'-H₂ and 8-H₂), 2.72 (d, 1, 10-H), 3.36 (d, 1, 10-H), 3.64 (m, 1, 4'-H), 3.98 (s, 1, exch D₂O, 9-OH), 4.04–4.46 (m, 4, 3'-H, 5'-H, and 13-H₂), 5.22 (m, 1, 7-H), 5.50 (br d, 1, 1'-H), 6.69 (br s, 1, NH), 6.70 (br d, 1, NH), 7.00–7.46 (m, 5, ArH), 7.74–7.92 (m, 2, 2-H and 3-H), 8.20–8.42 (m, 1, 1-H and 4-H), 13.22 (s, 1, OH), 13.46 (s, 1, OH). Anal. (C₃₄H₃₁F₃N₂O₁₁·0.75H₂O) C, H, N, H₂O.

(iii). A solution of the above glycoside (680 mg, 1.1 mmol) in tetrahydrofuran (10 mL) was added to cold 0.1 M aqueous sodium hydroxide (60 mL) and the solution stirred at 0 °C for 45 min and then at room temperature for a further 30 min. The solution was adjusted to pH 8 with 0.1 M hydrochloric acid and was repeatedly extracted with 10% ethanol in dichloromethane. The combined extracts were washed with water, dried, and evaporated. The residue was taken up in a mixture of dichloromethane (15 mL) and methanol (3 mL), and filtered, and the filtrate was treated with 0.25 M methanolic hydrogen chloride (4 mL). Diethyl ether (250 mL) was added to precipitate hydrochloride 8a (540 mg, 80%): mp 175–7 °C dec; $[\alpha]_D^{20} + 159^\circ$ (c 0.05% in MeOH); NMR δ 1.18 (d, 3, H₃), 1.64–2.21 (m, 4, 2'-H₂ and 8-H₂), 2.76 (d, 1, 10-H), 3.08 (d, 1, 10-H), 3.20–3.40 (m, H₂O and 3'-H), 3.62 (m, 1, 4'-H), 3.98–4.36 (m, 3, 5'-H and 13-H₂), 4.69 (s, 1, exch D₂O, 9-OH), 5.00 (br s, 1, 7-H), 5.35 (br s, 1, 1'-H), 5.40 (d, 1, exch D₂O, 4'-OH), 6.85–7.40 (m, 5, ArH), 7.88–8.10 (m, 2, 2-H and 3-H), 8.21–8.40 (m, 2, 1-H and 4-H), 9.60 (s, 1, NH), 13.35 (s, 1, OH), 13.60 (s, 1, OH). Anal. (C₃₂H₃₂N₂O₁₀·HCl·0.8H₂O) C, H, N, Cl.

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

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(methylcarbamoyl)oxy]methyl]-5,12-naphthacenedione] hydrochloride (8b) was obtained in a yield of 40% over three steps from aglycon 6b and sugar 7: mp 170–3 °C; $[\alpha]_D^{20} + 144^\circ$ (c 0.05% in MeOH); NMR δ 1.17 (d, 3, H₃), 1.67–2.18 (m, 4, 2'-H₂ and 8-H₂), 2.57 (s, 3, NCH₃), 2.62 (d, 1, 10-H), 2.95 (d, 1, 10-H), 3.05–3.46 (m, H₂O and 3'-H), 3.59 (m, 1, 4'-H), 3.82–4.37 (m, 3, 5'-H and 13-H₂), 4.58 (s, 1, exch D₂O, 9-OH), 4.92 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.48 (d, 1, exch D₂O, 4'-OH), 6.94 (br s, 1, NH), 7.86–8.06 (m, 2, 2-H and 4-H), 8.16–8.34 (m, 2, 1-H and 4-H), 13.52 (s, 1, OH), 13.81 (s, 1, OH). Anal. (C₂₇H₃₀N₂O₁₀·HCl·2.5H₂O) C, H, N, Cl, H₂O.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(4-methoxyphenyl)carbamoyl]oxy]methyl]-5,12-naphthacenedione hydrochloride (8c) was obtained in 46% yield over three steps from 6c and 7: mp 183–5 °C dec; $[\alpha]_D^{20} + 153^\circ$ (c 0.5% in MeOH); NMR δ 1.18 (d, 3, H₃), 1.58–2.35 (m, 4, 2'-H₂ and 8-H₂), 2.71–3.21 (m, 2, 10-H₂), 3.21–3.66 (m, H₂O, 3'-H and 4'-H), 3.71 (s, 3, OCH₃), 3.92–4.41 (m, 3, 5'-H and 13-H₂), 4.77 (s, 1, exch D₂O, 9-OH), 5.00 (br s, 1, 7-H), 5.35 (br s, 1, 1'-H), 5.46 (d, 1, exch D₂O, 4'-OH), 6.79 (d, 2, ArH), 7.38 (d, 2, ArH), 7.90–8.10 (m, 2, 2-H and 3-H), 8.17–8.42 (m, 2, 1-H and 4-H), 9.46 (s, 1, NH). Anal. (C₃₂H₃₄N₂O₁₁·HCl·3.0H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(4-nitrophenyl)carbamoyl]oxy]methyl]-5,12-naphthacenedione hydrochloride (8d) was obtained in 25% yield over three steps from 6d and 7: mp 175–8 °C dec; $[\alpha]_D^{20}$

+152° (c 0.05% in MeOH); NMR δ 1.17 (d, 3, H₃), 1.46–2.34 (m, 4, 2'-H₂ and 8-H₂), 2.82 (d, 1, 10-H), 3.09 (d, 1, 10-H), 3.23–3.50 (m, H₂O and 3'-H), 3.66 (m, 1, 4'-H), 3.97–4.42 (m, 3, 5'-H and 13-H₂), 4.82 (s, 1, exch D₂O, 9-OH), 5.04 (br s, 1, 7-H), 5.46 (br s, 1, 1'-H), 5.52 (d, 1, exch D₂O, 4'-OH), 7.60–8.34 (m, 8, ArH), 13.34 (s, 1, OH), 13.58 (s, 1, OH). Anal. (C₃₂H₃₁N₃O₁₂·HCl·H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-9-[[[(4-chlorophenyl)carbamoyl]oxy]methyl]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione hydrochloride (8e) was obtained in 37.5% yield over three steps from 6e and 7: mp 177–9 °C; $[\alpha]_D^{20} + 160^\circ$ (c 0.05% in MeOH); NMR δ 1.18 (d, 3, H₃), 1.62–2.22 (m, 4, 2'-H₂ and 8-H₂), 2.78 (d, 1, 10-H), 3.10 (d, 1, 10-H), 3.14–3.50 (m, H₂O and 3'-H), 3.64 (m, 1, 4'-H), 3.96–4.36 (m, 3, 5'-H and 13-H₂), 4.72 (s, 1, exch D₂O, 9-OH), 5.05 (br s, 1, 7-H), 5.38 (br s, 2, 1'-H and 4'-OH), 7.20 (d, 2, ArH), 7.46 (d, 2, ArH), 7.88–8.07 (m, 2, 2-H and 3-H), 8.22–8.50 (m, 2, 1-H and 4-H), 9.73 (s, 1, NH), 13.33 (s, 1, OH), 13.57 (s, 1, OH). Anal. (C₃₂H₃₁ClN₂O₁₀·HCl·H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione] Hydrochloride (18). Silver trifluoromethanesulfonate catalyzed coupling of 2,3,6-trideoxy-4-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-L-arabinohexopyranosyl chloride¹⁸ with aglycon 6a followed by stepwise deprotection gave 18: 38% over three steps; mp 183–5 °C dec; $[\alpha]_D^{20} + 207^\circ$ (c 0.05% in MeOH); NMR δ 1.22 (d, 3, H₃), 1.66–2.24 (m, 4, 2'-H₂ and 8-H₂), 2.80 (d, 1, 10-H), 3.06 (d, 1, 10-H), 3.06–3.50 (m, 3'-H, 4'-H, and H₂O), 3.80–4.30 (m, 3, 5'-H and 13-H₂), 4.70 (s, 1, exch D₂O, 9-OH), 5.03 (br s, 1, 7-H), 5.32 (br s, 1, 1'-H), 5.65 (br d, 1, exch D₂O, 4'-OH), 6.80–7.52 (m, 5, ArH), 7.86–8.06 (m, 2, 2-H and 3-H), 8.18–8.36 (m, 2, 1-H and 4-H), 9.58 (s, 1, NH). Anal. (C₃₂H₃₂N₂O₁₀·HCl·1.5H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy-4'-O-methyl- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione] Hydrochloride (19). Coupling of aglycon 6a with 2,3,6-trideoxy-4-O-methyl-3-(trifluoroacetamido)-L-lyxohexopyranosyl chloride¹⁸ followed by treatment with aqueous sodium hydroxide gave 19: 26% over two steps; mp 183–5 °C dec; $[\alpha]_D^{20} + 172^\circ$ (c 0.05% in MeOH); NMR δ 1.26 (d, 3, H₃), 1.63–2.22 (m, 4, 2'-H₂ and 8-H₂), 2.78 (d, 1, 10-H), 3.06 (d, 1, 10-H), 3.06–3.80 (m, H₂O, 3'-H and 4'-H), 3.55 (s, 3, OCH₃), 3.90–4.34 (m, 3, 5'-H and 13-H₂), 4.68 (s, 1, exch D₂O, 9-OH), 5.05 (br s, 1, 7-H), 5.36 (br s, 1, 1'-H), 6.86–7.54 (m, 5, ArH), 7.92–8.10 (m, 2, 2-H and 3-H), 8.22–8.42 (m, 2, 1-H and 4-H), 9.58 (s, 1, NH). Anal. (C₃₃H₃₄N₂O₁₀·HCl·1.8H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy-4'-O-methyl- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione] Hydrochloride (20). Coupling of aglycon 6a with 2,3,6-trideoxy-4-O-methyl-3-(trifluoroacetamido)-L-arabinohexopyranosyl chloride¹⁸ followed by treatment with aqueous sodium hydroxide gave 20: 26% over two steps; mp 212–4 °C dec; $[\alpha]_D^{20} + 204^\circ$ (c 0.05% in MeOH); NMR δ 1.26 (d, 3, H₃), 1.64–2.28 (m, 4, 2'-H₂ and 8-H₂), 2.68–3.60 (m, H₂O, 3'-H, 4'-H, and 10-H₂), 3.44 (s, 3, OCH₃), 3.84–4.32 (m, 3, 5'-H and 13-H₂), 4.78 (s, 1, exch D₂O, 9-OH), 5.04 (br s, 1, 7-H), 5.33 (br s, 1, 1'-H), 6.84–7.56 (m, 5, ArH), 7.88–8.11 (m, 2, 2-H and 3-H), 8.22–8.41 (m, 2, 1-H and 4-H), 9.66 (s, 1, NH). Anal. (C₃₃H₃₄N₂O₁₀·HCl·0.7H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy-4'-O-benzyl- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[[(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione] Hydrochloride (21). 4-O-Benzyl-2,3,6-trideoxy-3-(trifluoroacetamido)-L-lyxohexopyranosyl chloride was prepared through treatment of methyl 3-acetamido-2,3,6-trideoxy- β -L-lyxohexopyranoside with excess benzyl bromide and silver oxide¹⁹ in DMF followed by an analogous sequence of reactions to that employed for the corresponding 4-O-methyl

(18) Reference 4, Chapter 6.

(19) Lee, W. W.; Wu, H. Y.; Christensen, J. E.; Goodman, L.; Henry, D. W. *J. Med. Chem.* 1975, 18, 768.

derivative.¹⁸ Glycosidation of aglycon **6a** followed by treatment with aqueous sodium hydroxide gave **21**: 26% over two steps; mp 175–8 °C dec; $[\alpha]_D^{20} +61^\circ$ (c 0.05% in MeOH); NMR δ 1.81 (d, 3, H₃), 1.64–2.26 (m, 4, 2'-H₂ and 8-H₂), 2.78 (d, 1, 10-H), 3.10 (d, 1, 10-H), 3.14–3.86 (m, H₂O, 3'-H and 4'-H), 3.95–4.42 (m, 3, 5'-H and 13-H₂), 4.60–4.98 (q, 2, H₂), 4.76 (s, 1, exch D₂O, 9-OH), 5.04 (br s, 1, 7-H), 5.42 (br s, 1, 1'-H), 6.84–7.43 (m, 10-ArH), 7.91–8.12 (m, 2, 2-H and 3-H), 8.23–8.43 (m, 2, 1-H and 4-H), 9.62 (s, 1, NH). Anal. (C₃₉H₂₈N₂O₁₀·HCl·1.7H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(R)-[(phenylcarbamoyl)oxy]ethyl]-5,12-naphthacenedione Hydrochloride (22). Glycosidation of **13** with **7** and stepwise deprotection gave **22**: 16% over three steps; mp 169–71 °C; $[\alpha]_D^{20} +217^\circ$ (c 0.1% in MeOH); NMR δ 1.19 (d, 3, H₃), 1.38 (d, 3, H₃), 1.60–2.18 (m, 4, 2'-H₂ and 8-H₂), 2.71 (d, 1, 10-H), 2.96 (d, 1, 10-H), 3.20–3.50 (m, H₂O and 3'-H), 3.62 (m, 1, 4'-H), 4.23 (q, 1, 5'-H), 4.52 (s, 1, exch D₂O, 9-OH), 4.83 (q, 1, 13-H), 5.00 (br s, 1, 7-H), 5.35 (br s, 1, 1'-H), 5.40 (d, 1, exch D₂O, 4'-OH), 6.90–7.57 (m, 5, ArH), 7.90–8.08 (m, 2, 2-H and 3-H), 8.22–8.38 (m, 2, 1-H and 4-H), 13.36 (s, 1, OH), 13.56 (s, 1, OH). Anal. (C₃₃H₃₄N₂O₁₀·HCl·1.5H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(R)-[(phenylcarbamoyl)oxy]ethyl]-5,12-naphthacenedione Hydrochloride (23). Coupling of aglycon **13** with 2,3,6-trideoxy-4-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-L-arabinohexopyranosyl chloride and deprotection gave **23**: 13% over three steps; mp 175–8 °C; $[\alpha]_D^{20} +271^\circ$ (0.1% in MeOH); NMR δ 1.24 (d, 3, H₃), 1.36 (d, 3, H₃), 1.70–2.25 (m, 4, 2'-H₂ and 8-H₂), 2.76 (d, 1, 10-H), 3.00–3.50 (m, 3'-H, 4'-H, 10-H, and H₂O), 3.90–4.10 (m, 1, 5'-H), 4.51 (s, 1, exch D₂O, 9-OH), 4.84 (q, 1, 13-H), 5.02 (br s, 1, 7-H), 5.33 (br s, 1, 1'-H), 5.70 (br s, 1, exch D₂O, 4'-OH), 6.90–7.60 (m, 5, ArH), 7.94–8.09 (m, 2, 2-H and 3-H), 8.24–8.39 (m, 2, 1-H and 4-H), 9.58 (s, 1, exch D₂O, OH), 10.30 (br s, 1, exch D₂O, OH). Anal. (C₃₃H₃₄N₂O₁₀·HCl·H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',6'-trideoxy- α -L-arabinohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[1-(S)-[(phenylcarbamoyl)oxy]ethyl]-5,12-naphthacenedione Hydrochloride (24). Coupling of aglycon **14** with 2,3,6-trideoxy-4-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-L-arabinohexopyranosyl chloride and deprotection gave **24**: 38% over three steps; mp 188–90 °C dec; $[\alpha]_D^{20} +180^\circ$ (c 0.05% in MeOH); NMR δ 1.18 (d, 3, H₃), 1.33 (d, 3, H₃), 1.74–2.28 (m, 4, 2'-H₂ and 8-H₂), 2.78 (d, 1, 10-H), 2.97 (d, 1, 10-H), 3.07–3.42 (m, H₂O, 3'-H and 4'-H), 3.90–4.03 (m, 1, 5'-H), 4.48 (s, 1, exch D₂O, 9-OH), 4.88 (q, 1, 13-H), 5.03 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.72 (d, 1, exch D₂O, 4'-OH), 6.86–7.45 (m, 5, ArH), 7.93–8.04 (m, 2, 2-H and 3-H), 8.06 (br s, 3, NH₃), 8.22–8.30 (m, 2, 1-H and 4-H), 9.50 (s, 1, NH), 13.29 (s, 1, OH), 13.52 (s, 1, OH). Anal. (C₃₃H₃₄N₂O₁₀·HCl·2H₂O) C, H, N, Cl.

(7S,9S)-7-[(3'-Amino-2',3',4',6'-tetraideoxy- α -L-threohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[1-(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione Hydrochloride (17). (i). A solution of (7S,9S)-9-(acetoxymethyl)-7-[(2',3',4',6'-tetraideoxy-3'-(trifluoroacetamido)- α -L-threohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trideoxy-5,12-naphthacenedione (**15**;¹¹ 0.05 g, 0.82 mmol) in a mixture of dichloromethane (200 mL) and methanol (200 mL) was stirred, and sufficient 0.1 M sodium hydroxide solution was added to give

a deep purple color. The mixture was stirred at room temperature for 6 h and acetic acid was then added to give an orange solution which was poured into water (250 mL) and extracted with dichloromethane (4 \times 100 mL). The combined extracts were dried and evaporated, and the residue was triturated with diethyl ether to give hydroxymethyl derivative **16** (0.36 g, 77%) as an orange, crystalline solid: mp 240–2 °C; $[\alpha]_D^{20} +228^\circ$ (c 0.05% in dioxane); NMR δ 1.28 (d, 3, H₃), 1.30–2.24 (m, 6, 2'-H₂, 4'-H₂, and 8-H₂), 2.68 (d, 1, 10-H), 3.20 (d, 1, 10-H), 3.42–3.75 (m, 3, 13-CH₂ and OH), 3.92–4.46 (m, 3, 3'-H, 5'-H, and 9-OH), 5.26 (m, 1, 7-H), 5.58 (br d, 1, 1'-H), 7.77–7.92 (m, 2, 2-H and 3-H), 7.98 (br d, 1, NH), 8.24–8.44 (m, 2, 1-H and 4-H), 13.62 (s, 1, OH), 13.87 (s, 1, OH). Anal. (C₂₇H₂₆F₃NO₉) C, H, N.

(ii). A mixture of alcohol **16** (50 mg, 0.09 mmol) and phenyl isocyanate (100 mg, 0.84 mmol) in pyridine (5 mL) was stirred at 70 °C for 30 min. The solvent was evaporated and the residue was taken up in dichloromethane (30 mL) and filtered. The filtrate was evaporated and the residue was chromatographed on a column of silica gel, eluting with dichloromethane–acetone (95:5, v/v) to give (7S,9S)-7-[(2',3',4',6'-tetraideoxy-3'-(trifluoroacetamido)- α -L-threohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-[[1-(phenylcarbamoyl)oxy]methyl]-5,12-naphthacenedione (52 mg, 86%) as orange-red crystals: mp 155–60 °C; $[\alpha]_D^{20} +185^\circ$ (c 0.05% in dioxane); NMR δ 1.26 (d, 3, H₃), 1.40–2.57 (m, 6, 2'-H₂, 4'-H₂, and 8-H₂), 2.74 (d, 1, 10-H), 3.37 (d, 1, 10-H), 3.96–4.44 (m, 5, 3'-H, 5'-H, 13-H₂, and 9-OH), 5.28 (m, 1, 7-H), 5.58 (br d, 1, 1'-H), 5.96 (br d, 1, NH), 6.70–7.50 (m, 5, ArH), 7.74–7.94 (m, 2, 2-H and 3-H), 8.30–8.44 (m, 2, 1-H and 4-H), 13.37 (s, 1, OH), 13.62 (s, 1, OH). Anal. (C₃₄H₃₁F₃N₂O₁₀) C, H, N.

(iii). A solution of the above product (0.60 g, 0.88 mmol) in a mixture of tetrahydrofuran (20 mL) and a 0.1 M sodium hydroxide solution (60 mL) was stirred at 0 °C for 3 h. The solution was adjusted to pH 8 with 0.1 M hydrochloric acid and was repeatedly extracted with dichloromethane–ethanol (9:1, v/v). The combined extracts were washed with water, dried, and evaporated. The residue was taken up in dichloromethane (20 mL) and filtered, and 0.25 M methanolic hydrogen chloride (4 mL) was added to the filtrate. Diethyl ether (200 mL) was added and the resulting precipitate was collected to give hydrochloride **17** (0.44 g, 80%) as an orange-red solid: mp 173–5 °C dec; $[\alpha]_D^{20} +205^\circ$ (0.05% in MeOH); NMR δ 1.19 (d, 3, H₃), 1.33–2.29 (m, 6, 2'-H₂, 4'-H₂, and 8-H₂), 2.80 (d, 1, 10-H), 3.10 (d, 1, 10-H), 3.20–3.50 (m, H₂O and 3'-H), 3.94–4.41 (m, 3, 5'-H and 13-H₂), 3.75 (s, 1, exch D₂O, 9-OH), 5.05 (br s, 1, 7-H), 5.45 (br s, 1, 1'-H), 6.88–7.62 (m, 5, ArH), 7.94–8.14 (m, 2, 2-H and 3-H), 8.24–8.40 (m, 2, 1-H and 4-H), 9.68 (s, 1, NH). Anal. (C₃₂H₃₂N₂O₉·HCl·2.5H₂O) C, H, N, Cl.

Biological Evaluation. For evaluation of antitumor activity against L-1210 leukemia, BDF₁ mice were injected intraperitoneally with 10⁵ viable L-1210 ascites tumor cells, and intraperitoneal administration of aqueous solutions or, if insoluble, suspensions in propylene glycol 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.