Anthracyclines. Part 3. The Total Synthesis of 4-Demethoxydaunomycin

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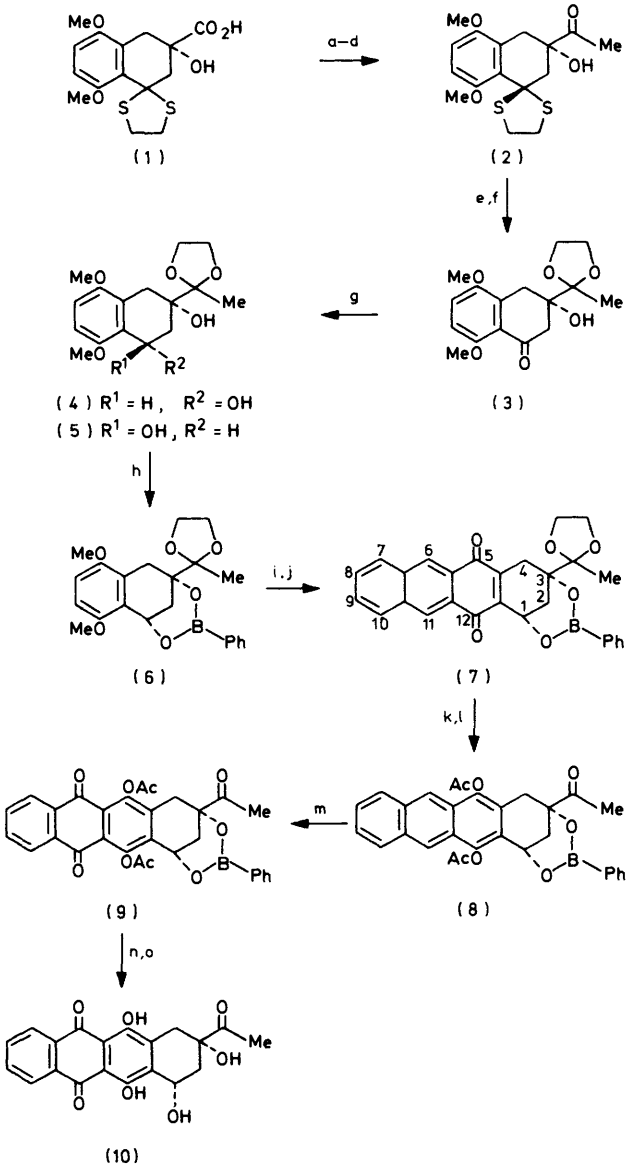
Procedures selected from our earlier work have been applied to the synthesis of (+)-4-demethoxydaunomycinone (10) and (−)-4-demethoxy-7,9-bisepidaunomycinone. 4-Demethoxydaunomycin has been prepared from the (+)-aglycone by specific glycosidation using 1-chloro-4-*O*-*p*-nitrobenzoyl-3-*N*-trifluoroacetyldaunosamine and silver trifluoromethanesulphonate as catalyst. Analogous glycosidation of the (−)-algycone has given 4-demethoxy-7,9-bisepidaunomycin whose properties differ from those previously reported.

In the preceding paper [1] several approaches to the synthesis of 4-demethoxyanthracyclinones were described, culminating in a practicable synthesis of (±)-4-demethoxydaunomycinone. We have now undertaken the synthesis of the isomer (+)-4-demethoxydaunomycinone, which has the chirality of natural daunomycin at both centres of asymmetry. This utilises a route that could be applied to the large-scale preparation of this compound and its analogues.

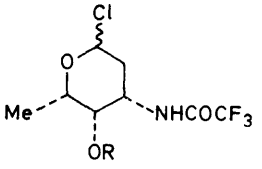
The enantiomers prepared from the racemic bicyclic hydroxy-acid (1) [1] were converted into the corresponding ketones [*e.g.* (2)] (Scheme); the absolute configurations were elucidated by an *X*-ray diffraction study. When the (*S*)-ketone (3) was reduced with lithium borohydride, the resultant mixture of *cis*- and *trans*-diols (4) and (5) could be converted entirely into the *cis*-boronate (6) by the action of benzeneboronic acid in the presence of toluene-4-sulphonic acid. The subsequent stages in the preparation of (+)-4-demethoxydaunomycinone *via* the tetracyclic quinone (7) utilised the reaction conditions described in the preceding paper.[1] The product (10) had the same characteristics as those reported for (+)-4-demethoxydaunomycinone.[2–4] The isomer (−)-4-demethoxy-7,9-bisepidaunomycinone was synthesised in a similar manner from the (*R*)-ketone corresponding to (3).

Several procedures have been investigated for the glycosidation of anthracyclinones.[5,6] The conventional Koenigs–Knorr method, when used with 1-chloro-3-*N*,4-*O*-bistrifluoroacetyldaunosamine (11), gave mixtures of α- and β-glycosides with both the anthracyclinone (10) and (−)-4-demethoxy-7,9-bisepidaunomycinone.[3] Smith and his co-workers [7] have shown that, with daunomycinone, similar reaction conditions employing the 4-*O*-*p*-nitrobenzoyl derivative (12) gave the α-glycoside exclusively. A high degree of stereospecificity is also achieved in glycosidations catalysed by silver trifluoromethane sulphonate. The reaction of daunomycinone or 4-demethoxydaunomycinone with a variety of glycosyl halides gave α-glycosides exclusively.[8] On the other hand, in the case of the sodium trifluoromethane sulphonate-catalysed condensation of 4-demethoxy-7,9-bisepidaunomycinone with bistrifluoroacetyldaunosamine (11), the product was reported to be the β-glycoside exclusively.[2,9]



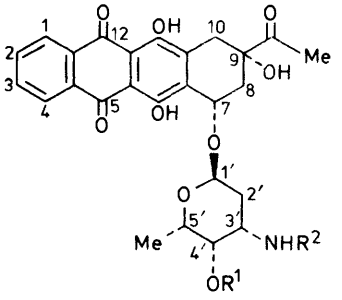
Scheme *Reagents*: a, Brucine; b, $BF_3(MeOH)_2$; c, $CH_3SO-CH_2^-Na^+$; d, Al–Hg; e, $HOCH_2CH_2OH$; f, Hg^{2+}; g, $LiBH_4$; h, $PhB(OH)_2$; i, Ce^{4+}; j, (21); k, HCl; l, H_2, Pd–C, Ac_2O, pyridine; m, CrO_3; n, BCl_3; o, $(CH_3)_2C(OH)CH_2CH(OH)CH_3$

In this work we have employed the silver trifluoromethane sulphonate-catalysed reaction of the aglycones with the 4-*O*-*p*-nitrobenzoyl sugar (12). Condensation of 4-demethoxydaunomycinone with compound (12) under the reaction conditions employed by Arcamone

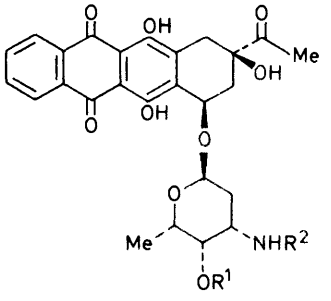


(11) R = $COCF_3$
(12) R = $CO \cdot C_6H_4 \cdot NO_2$-*p*

et al.[2,8] gave the expected glycoside (13) in rather poor yield. Isolation of the product was complicated by the presence of unchanged aglycone and several by-products. Modification of the reaction conditions gave the glycoside (13) in 84% yield. The ^1H n.m.r. spectrum established



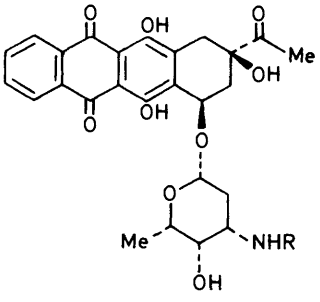
(13) $R^1 = CO \cdot C_6H_4 \cdot NO_2$-*p*, $R^2 = COCF_3$
(14) $R^1 = H$, $R^2 = COCF_3$
(15) $R^1 = R^2 = H$



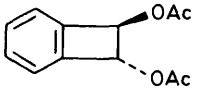
(16) $R^1 = CO \cdot C_6H_4 \cdot NO_2$-*p*, $R^2 = COCF_3$
(17) $R^1 = H$, $R^2 = COCF_3$
(18) $R^1 = R^2 = H$

that the product was the α-glycoside; it included a broad singlet at δ 5.70 due to the anomeric 1′-proton.[10—12] From the evidence set out below, we have established that the anomeric proton of α-glycosides of 2-deoxy-sugars gives rise to a narrow multiplet (W_H *ca.* 6 Hz) whereas β-glycosides exhibit a double doublet (*J ca.* 10 and 2 Hz). Stepwise hydrolysis of compound (13) gave *N*-trifluoroacetyl-4-demethoxydaunomycin (14), and 4-demethoxydaunomycin (15), each with characteristics in good agreement with those reported.[3,4,9]

Analogous glycosidation of 4-demethoxy-7,9-bisepidaunomycinone also gave a single glycoside. The stereochemistry of the glycoside linkage could not, however, be determined unambiguously from its n.m.r. spectrum because of the proximity of overlapping signals due to the 1′-, 4′-, and 7-protons in the region δ 5.62—5.35. Stepwise hydrolysis of the *p*-nitrobenzoyl-glycoside gave the corresponding *N*-trifluoroacetyl-anthracycline and the anthracycline hydrochloride, respectively. Contrary to our expectations, however, the physical properties of these products did not agree with those reported [4] for the α-glycosides (17) and (18), o,r indeed, for the corresponding β-glycosides (19) and (20) (Table 1). Microanalyses of the reaction products gave empirical formulae consistent with structures (16), (17), and (18), and their u.v. and visible spectra were almost identical with those of the corresponding glycosides (13), (14), and (15), derived from 4-demethoxydaunomycinone.



(19) R = $COCF_3$
(20) R = H



(21)

The structure of the *N*-trifluoroacetyl-glycoside derived from 4-demethoxy-7,9-bisepidaunomycinone was established unequivocally by a detailed study of its 400 MHz n.m.r. spectrum, facilitated by a series of double resonance experiments (Table 2). Definition of the glycoside stereochemistry required the determination of the coupling constants between the anomeric 1′-proton and the 2′-protons. The n.m.r. spectrum included signals at δ 5.55 and 5.35 due to the 7-proton and the 1′-proton. Irradiation at δ 5.55 abolished a splitting of 2 Hz in the signal due to the equatorial 8-proton. The signal at δ 5.55 could therefore be assigned to the 7-proton, and that at δ 5.35 to the 1′-proton. Signals due to the 2′-methylene protons formed part of a complex 4-proton multiplet in the region δ 1.98—1.84. After the assignment, based on double resonance experiments, of the 4′-hydroxy and the axial 8-protons, the 2′-protons could be assigned to a double triplet at δ 1.93 and a double doublet at δ 1.87. The signal at δ 1.93 was shown to be due to the axial 2′-proton when irradiation of the 3′-proton abolished a large (12.5 Hz) splitting resulting from a *trans*-diaxial relationship. The coupling constant between the axial 2′-proton and the

TABLE 1

Physical properties of 7,9-bisepianthracyclines

Compound	Literature [a]		Observed	
	$[\alpha]_D^{20}$/°	m.p./°C	$[\alpha]_D^{20}$/°	m.p./°C
(17)	−91 [a]	210—215		
(19)	−270 [a]	165—167		
N-Trifluoroacetylanthracycline			−359 [a]	137—147
(18) hydrochloride	−80 [b]	205—207		
(20) hydrochloride	−250 [b]	185—187		
Anthracycline hydrochloride			−317 [b]	164—166

[a] 0.1% in Dioxan. [b] 0.1% in Methanol.

TABLE 2

^{1}H N.m.r. data of compound (17) [a]

Hydrogen atom	δ [b]	*J* (H_i, H_j) Hz [c]	Double resonance experiments [d]
1 and 4	8.39—8.34 (m)		
2 and 3	7.88—7.84 (m)		
6-OH and 11-OH	13.77 (s), 13.35 (s)		
7	5.55 (dd)	3 ($7,8_{ax}$)	8_{ax} ⟶ br s
		2 ($7,8_{eq}$)	
8_{ax}	1.96 (dd)	15.5 (8_{ax}, 8_{eq})	
		3 (8_{ax}, 7)	7 ⟶ d
8_{eq}	2.46 (dt)	15.5 (8_{ax}, 8_{eq})	
		1.5 (8_{eq}, 10_{eq})	10_{eq} ⟶ dd
		2 (8_{eq},) 7	7 ⟶ dd
9-COMe	2.41 (s)		
9-OH	4.47 (s)		
10_{ax}	3.05 (d)	19.5 (10_{ax}, 10_{eq})	
10_{eq}	3.32 (dd)	19.5 (10_{ax}, 10_{eq})	
		1.5 (10_{eq}, 8_{eq})	
1′	5.35 (br d)	3.5 (1′,$2'_{ax}$)	$2'_{ax}$ and $2'_{eq}$ ⟶ s
		<0.5 (1′,$2'_{eq}$)	
$2'_{ax}$	1.93 (dt)	12.5 ($2'_{ax}$, $2'_{eq}$)	
		12.5 ($2'_{ax}$, 3′)	3′ ⟶ dd
		3.5 ($2'_{ax}$, 1′)	1′ ⟶ t
$2'_{eq}$	1.87 (dd)	12.5 ($2'_{ax}$, $2'_{eq}$)	
		4.5 ($2'_{eq}$, 3′)	3′ ⟶ d
		<0.5 (1′, $2'_{eq}$)	1′ ⟶ sharper dd
3′	4.30 (dddd)	12.5 ($2'_{ax}$, 3′)	$2'_{ax}$ and $2'_{eq}$ ⟶ dd
		4.5 ($2'_{eq}$, 3′)	
		2.5 (3′, 4′)	4′ ⟶ ddd
		8 (3′, 3′-NH)	3′-NH ⟶ ddd
3′-NH	6.67 (br d)	8 (3′, 3′-NH)	
4′	3.61 (br d)	8 (4′, 4′-OH)	4′-OH ⟶ br s
		2.5 (3′, 4′)	3′ ⟶ sh d
		<0.5 (4′, 5′)	
4′-OH	1.95 (d)	8 (4′, 4′-OH)	4′ ⟶ s
5′	4.52 (q)	6.5 (5′, 6′)	
		<0.5 (4′, 5,)	4′ ⟶ sharper q
6′-Me	1.30 (d)	6.5 (5′, 6′)	

[a] Recorded as a solution in $CDCl_3$ at 400 MHz on a Bruker WH 400 spectrometer. [b] Chemical shifts and multiplicity of signals. [c] Coupling constants; coupled hydrogen atoms are given in parentheses. [d] The hydrogen atom which irradiation is performed and the resulting multiplicity of the signal under consideration.

anomeric 1′-proton was 3.5 Hz, establishing the equatorial orientation of the latter. A *trans*-diaxial relationship would give rise to a much greater interaction.[13] This showed the product to be the α-glycoside (17). Analogous methods have been applied to the elucidation of the glycoside stereochemistry in other anthracyclines [10-12] and in other 2-deoxy-sugar derivatives.[14-17] We did not have sufficient physical data to be able to identify the structures of the glycosides derived from 4-demethoxy-7,9-bisepidaunomycinone, which were reported in earlier work.[4,9]

This synthetic route to 4-demethoxyanthracyclines proceeds in good overall yield and thus facilitates the preparation of products in sufficient quantity for biological evaluation. In subsequent papers we shall report the application of this synthesis to the preparation of a variety of novel 4-demethoxyanthracyclines.

EXPERIMENTAL

M.p.s were determined on a Büchi melting point apparatus. I.r. spectra were recorded on a Unicam SP 1 000 spectrophotometer for Nujol mulls, u.v. and visible spectra were recorded with a Unicam SP 8000 spectrophotometer, and ^{1}H n.m.r. spectra were recorded on a Varian XL 100 spectrometer for deuteriochloroform solutions with tetramethylsilane as internal reference, unless otherwise stated. Mass spectra were recorded using an A.E.I. MS 902 mass spectrometer with a direct insertion probe. Optical

rotations were determined on a Perkin-Elmer 141 MC polarimeter, and microanalyses were carried out using a Perkin-Elmer elemental analyser. Organic solutions were dried over magnesium sulphate. Silica gel used for column chromatography was Kieselgel 60, 70—230 mesh (Merck).

1′,2′,3′,4′-Tetrahydro-3′-hydroxy-5′,8′-dimethoxyspiro[1,3-dithiolan-2,1′-naphthalene]-3′-carboxylic Acid (1).—A solution of methyl 1,1-ethylenedioxy-1,2,3,4-tetrahydro-3-hydroxy-5,8-dimethoxynaphthalene-3-carboxylate [1] (137.10 g) in dichloromethane (423 ml) was stirred and cooled to 0 °C. Ethanedithiol (56.0 ml) was added to the solution, followed by boron trifluoride–diethyl ether (56.0 ml). The mixture was stirred at 0 °C for 15 min and then poured into diethyl ether (2.80 l). The solution was washed with 5% aqueous sodium hydroxide (3 × 700 ml) and evaporated to give a yellow oil which was dissolved in methanol (2.80 l). 5% Aqueous sodium hydroxide (1.40 l) was added and the mixture stirred at room temperature for 1.5 h. The solution was concentrated to *ca.* 1.5 l, diluted with water (3.0 l), and washed with diethyl ether (4 × 1.0 l). The aqueous solution was cooled and acidified with concentrated hydrochloric acid, and the resulting precipitate was collected and dried *in vacuo*. The crude product was recrystallised from ethyl acetate (2.1 l) to give the *acid* (1) (121.76 g, 84%) as colourless crystals, m.p. 189.5—190.5 °C (Found: C, 52.85; H, 5.4; S, 18.75. $C_{15}H_{18}O_5S_2$ requires C, 52,6; H, 5.3; S, 18.7%); δ (DMSO) 6.8 (2 H, s, ArH), 3.75 (3 H, s, OMe), 3.7 (3 H, s, OMe), 3.6—3.2 (4 H, m, SCH_2CH_2S), 2.8 (2 H, s, CH_2), and 2.63 (2 H, s, CH_2).

Resolution of the Hydroxy-acid (1).—A suspension of the (±)-acid (1) (79.6 g, 0.23 mol) and brucine dihydrate (118.0 g, 0.27 mol) in ethyl acetate (3.90 l) was stirred under reflux until a clear solution was obtained. After being seeded with (*R*)-acid salt, the solution was allowed to cool slowly to room temperature and then left for 2 d. The crystalline solid (97.75 g) was collected and the mother liquor retained. The solid was dissolved in boiling ethyl acetate (11.45 l) and additional brucine dihydrate (49.0 g, 0.11 mol) was added. The solution was concentrated to 8.0 l and left to cool slowly. The resulting solid (46.56 g) was collected and the mother liquor was combined with the ethyl acetate mother liquor obtained earlier. The solid was suspended in ethyl acetate (700 ml) and shaken with 5M-hydrochloric acid (2 × 200 ml) and saturated aqueous sodium chloride (4 × 400 ml). The ethyl acetate solution was dried and evaporated and the residue was triturated with hexane (500 ml); the solid was collected to give the (R)- *acid* (17.07 g) as white crystals, m.p. 147—149 °C, $[\alpha]_D^{20}$ +13.8° (*c* 0.5 in dioxan).

The combined ethyl acetate mother liquors obtained above were concentrated to 3.0 l and shaken with 5M-hydrochloric acid (2 × 200 ml), washed with saturated aqueous sodium chloride (4 × 400 ml), dried, and evaporated. The solid residue was suspended in ethyl acetate (1.0 l) and refluxed for 30 min. The solution was allowed to cool and left at room temperature for 2 d. The resulting crystalline solid was collected to give recovered (±)-acid (35.47 g). The mother liquor was evaporated and the residue was taken up in boiling diethyl ether (1.70 l). The solution was cooled and filtered to give further (±)-acid (3.44 g). The mother liquor was evaporated and the residue was recrystallised from diethyl ether–hexane to give the (S)-*acid* (16.56 g) as a white crystalline solid, m.p. 145—148 °C, $[\alpha]_D^{20}$ −13.5° (*c* 0.5 in dioxan).

(S)-*3′-Acetyl-1′,2′,3′,4′-tetrahydro-3′-hydroxy-5′,8′-dimethoxyspiro[1,3-dithiolan-2,1′-naphthalene]* (2).—Boron trifluoride–methanol complex (20.0 ml) was added to a stirred suspension of (*S*)-(−)-1′,2′,3′,4′-tetrahydro-3′-hydroxy-5′,8′-dimethoxyspiro[1,3-dithiolan-2,1′-naphthalene]-3′-carboxylic acid (20.0 g) in methanol (200 ml). The mixture was stirred at room temperature for 4 h and then poured into water (800 ml) and extracted with dichloromethane (3 × 400 ml). The combined extracts were washed with water (500 ml), 10% aqueous potassium hydrogen carbonate (200 ml), and saturated aqueous sodium chloride (200 ml), and then dried and evaporated to give the methyl ester as a colourless gum (21.1 g) which was used without purification in the next step.

The methyl ester prepared above was treated with sodium methylsulphinyl methanide according to our earlier procedure,[1] and the product was reduced with aluminium amalgam [1] to give the *ketone* (2) (12.96 g, 61% overall) as a white crystalline solid, m.p. 178.5—179.5 °C, $[\alpha]_D^{20}$ −24.4° (*c* 0.5 in chloroform) (Found: C, 56.5; H, 6.0; S, 18.6. $C_{16}H_{20}O_4S_2$ requires C, 56.45; H, 5.9; S, 18.85%).

(S)-*3-[1-(1,1-Ethylenedioxy)ethyl]-1,2,3,4-tetrahydro-3-hydroxy-5,8-dimethoxynaphthalenone* (3).—The ketone (2) (17.30 g) was treated with ethylene glycol by our earlier procedure [1] to give (S)-*3′-[1-(1,1-ethylenedioxy)ethyl]-1′,2′,3′,4′-tetrahydro-3′-hydroxy-5′,8′-dimethoxyspiro[1,3-dithiolan-2,1′-naphthalene]* (17.17 g, 88%) as a white solid, m.p. 144—146 °C, $[\alpha]_D^{20}$ −42.4° (*c* 0.5 in chloroform) (Found: C, 56.25; H, 6.3; S, 16.7. $C_{18}H_{24}O_5S_2$ requires C, 56.2; H, 6.15; S, 16.65%).

The product obtained above (11.28 g) was treated with mercuric oxide and mercuric chloride according to our earlier procedure to give the tetralone (3) (7.80 g, 86%) as a white solid, m.p. 182.5—184 °C, $[\alpha]_D^{20}$ +14.0° (*c* 0.5 in chloroform).

(3S)-cis-*[1-(1,1-Ethylenedioxy)ethyl]-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene-1,3-diyl Benzeneboronate* (6).—The (*S*)-tetralone (3) (10.72 g) was reduced with lithium borohydride according to our earlier procedure [1] to give a mixture of the cis- (4) and the trans-*diol* (5). This mixture was treated with benzeneboronic acid in the presence of toluene-4-sulphonic acid [1] to give the benzeneboronate (6) (12.89 g, 93.5%) as a white crystalline solid, m.p. 126—127 °C, $[\alpha]_D^{20}$ +35.8° (*c* 0.5 in chloroform) (Found: C, 61.95; H, 7.05. $C_{22}H_{25}BO_6$ requires C, 61.9; H, 7.15%).

(S)-cis-*3-[1-(1,1-Ethylenedioxy)ethyl]-1,2,3,4,5,12-hexahydro-5,12-dioxonaphthacene-1,3-diyl Benzeneboronate* (7).—The benzeneboronate (6) (10.11 g) was treated with ammonium ceric nitrate according to our earlier procedure [1] to give (S)-cis-*3-[1-(1,1-ethylenedioxy)ethyl]-1,2,3,4,5,8-hexahydro-5,8-dioxonaphthalene-1,3-diyl benzeneboronate* as a yellow gum (9.10 g). This was treated with *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene (21) [18] according to our earlier procedure [1] to give the *quinone* (7) (9.39 g, 79%) as a bright yellow crystalline solid, m.p. 235—240 °C, $[\alpha]_D^{20}$ +127° (*c* 0.25 in chloroform) (Found: C, 72.1; H, 5.0. $C_{28}H_{23}BO_6$ requires C, 72.1; H, 5.0%).

(S)-cis-*5,12-Diacetoxy-3-acetyl-1,2,3,4-tetrahydronaphthacene-1,3-diyl Benzeneboronate* (8).—The acetal (7) (6.76 g) was treated with hydrochloric acid in dioxan [1] to give (S)-cis-*3-acetyl-1,2,3,4,5,12-hexahydro-5,12-dioxonaphthacene-1,3-diyl benzeneboronate* (5.45 g, 89%) as a bright yellow solid, m.p. 246—247 °C, $[\alpha]_D^{20}$ +121° (*c* 0.5 in dioxan) (Found: C, 73.7; H, 4.45. $C_{26}H_{19}BO_5$ requires C, 73.95; H, 4.5%); M^+, 422; $\nu_{max.}$ 1 710, 1 670, 1 660, 1 630, 1 620,

and 1 590 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 244, 272sh, 280sh, 290, 301, and 423 nm (log ε 4.47, 4.16, 4.19, 4.27, 4.31, and 3.74); δ 8.70 (1 H, s, ArH), 8.61 (1 H, s, ArH), 8.13—7.99 (2 H, m, 7- and 10-ArH), 7.90—7.76 (2 H, m, ArH), 7.74—7.62 (2 H, m, 8- and 9-ArH), 7.46—7.25 (3 H, m, ArH), 5.76 (1 H, t, *J* 3 Hz, 1-H), 3.20 (2 H, s, 4-H_2), 2.57 (3 H, s, Ac), and 2.26 (2 H, m, 2-H_2).

Reductive acetylation of the ketone prepared above (3.90 g) according to our earlier procedure gave the *diacetate* (8) (3.874 g, 82.5%) as a light brown solid, m.p. 271.5—272 °C, $[\alpha]_D^{20}$ +263° (*c* 0.5 in dioxan) (Found: C, 71.1; H, 5.1. $C_{30}H_{25}BO_7$ requires C, 70.9; H, 5.0%); M^+, 508; $\nu_{max.}$ 1 760, 1 710, 1 640, and 1 600 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 258sh, 265, 324, 338, 353, 372, and 392 nm (log ε 4.94, 5.26, 3.13, 3.45, 3.71, 3.85, and 3.80); δ 8.36 (1 H, s, ArH), 8.26 (1 H, s, ArH), 8.04—7.90 (2 H, m, 7- and 10-ArH), 7.82—7.70 (2 H, m, ArH), 7.56—7.42 (2 H, m, 8- and 9-ArH), 7.40—7.26 (3 H, m, ArH), 5.68 (1 H, t, *J* 3 Hz, 1-H), 3.29 (2 H, s, 4-H_2), 2.68 (3 H, s, Ac), 2.57 (3 H, s, Ac), 2.55 (3 H, s, Ac), and 2.36 (2 H, m, 2-H_2).

(S)-cis-5,12-*Diacetoxy*-3-*acetyl*-1,2,3,4,6,11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl Benzeneboronate* (9).—Oxidation of the diacetate (8) (4.17 g) by our earlier procedure [1] gave the *quinone* (9) (2.52 g, 57%) as a light brown solid, m.p. 191—200 °C, $[\alpha]_D^{20}$ +171° (*c* 0.5 in dioxan) (Found: C, 66.8; H, 4.6. $C_{30}H_{23}BO_9$ requires C, 66.9; H, 4.3%); M^+, 538; $\nu_{max.}$ 1 770, 1 720, 1 670, and 1 590 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 260 and 340 nm (log ε 4.62 and 3.75); δ 8.24—8.10 (2 H, m, ArH), 7.82—7.64 (4 H, m, ArH), 7.44—7.24 (3 H, m, ArH), 5.58 (1 H, br s, 1-H), 3.24 (2 H, br s, 4-H_2), 2.65 (3 H, s, Ac), 2.56 (3 H, s, Ac), 2.52 (3 H, s, Ac), 2.31 (2 H, m, 2-H_2).

(S)-cis-3-*Acetyl*-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* [(+)-4-*Demethoxydaunomycinone*] (10).—Treatment of the quinone (9) (1.859 g) with boron trichloride according to our earlier procedure [1] gave (S)-cis-3-*acetyl*-1,2,3,4,6,11-*hexahydro*-5,12-*dihydroxy*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* as a red gum. A sample was crystallised from diethyl ether to give bright orange crystals, m.p. 220—222 °C, $[\alpha]_D^{20}$ +353° (*c* 0.1 in dioxan) (Found: C, 68.7; H, 4.15. $C_{26}H_{19}BO_7$ requires C, 68.75; H, 4.2%); M^+, 454; $\nu_{max.}$ 3 100—2 500, 1 715, 1 620, and 1 580 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 253, 259, 288, 330sh, 487, 508sh, and 522 sh nm (log ε 4.61, 4.58, 4.00, 3.46, 4.03, 3.88 and 3.79); δ 13.53 (1 H, s, ArOH), 13.24 (1 H, s, ArOH), 8.42—8.28 (2 H, m, ArH), 7.94—7.78 (4 H, m, ArH), 7.50—7.30 (3 H, m, ArH), 5.84 (1 H, t, *J* 3 Hz, 1-H), 3.36 (1 H, d, *J* 20 Hz, 4-*eq*-H), 3.26 (1 H, d, *J* 20 Hz, 4-*ax*-H), 2.58 (3 H, s, Ac), and 2.32 (2 H, m, 2-H_2).

The product prepared above was treated with 2-methylpentane-2,4-diol [1] to give the naphthacene [(+)-4-demethoxydaunomycinone] (10) (1.031 g, 81%) as a bright red crystalline solid, m.p. 182.5—183 °C (lit.,[2,3] m.p. 184—186 °C), $[\alpha]_D^{20}$ +164.5° (*c* 0.1 in dioxan) (lit., $[\alpha]_D^{20}$ +170°,[2] +140° [3]) (Found: C, 65.1; H, 4.1. Calc. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.4%); M^+, 368; $\lambda_{max.}$ ($CHCl_3$) 252, 259, 289, 330sh, 475sh, 486, and 518sh nm (log ε 4.61, 4.57, 4.02, 3.43, 3.98, 4.01, and 3.77); δ [$CDCl_3$–$(CD_3)_2SO$] 13.58 (1 H, s, ArOH), 13.33 (1 H, s, ArOH), 8.40—8.28 (2 H, m, 7- and 10-ArH), 7.91—7.79 (2 H, m, 8- and 9-ArH), 5.56 (1 H, s, 3-OH), 5.26 (1 H, m, 1-H), 4.88 (1 H, d, *J* 7 Hz, 1-OH), 3.20 (1 H, dd, $J_{4\text{-}eq,4\text{-}ax}$ 19.5 Hz, $J_{4\text{-}eq,2\text{-}eq}$ 2 Hz, 4-*eq*-H), 2.98 (1 H, d, *J* 19.5 Hz, 4-*ax*-H), 2.44 (3 H, s, Ac), 2.36 (1 H, dt, $J_{2\text{-}ax,2\text{-}eq}$ 14 Hz, $J_{2\text{-}eq,4\text{-}eq}$ 2 Hz, $J_{2\text{-}eq,1}$ 2 Hz, 2-*eq*-H), and 2.06 (1 H, dd, $J_{2\text{-}eq,2\text{-}ax}$ 14 Hz, $J_{2\text{-}ax,1}$ 5 Hz, 2-*ax*-H).

(*R*)-(+)-1′,2′,3′,4′-Tetrahydro-3′-hydroxy-5′,8′-dimethoxyspiro[1,3-dithiolan-2,1′-naphthalene]-3′-carboxylic acid was converted into (*R*)-*cis*-3-acetyl-1,2,3,4,6,11-hexahydro-1,3,5,12-tetrahydroxy-6,11-quinone [(−)-4-demethoxy-7,9-bisepidaunomycinone] *via* a similar reaction sequence.

4′-O-p-*Nitrobenzoyl*-3′-N-*trifluoroacetyl*-4-*demethoxydaunomycin* (13).*—A suspension of 2,3,6-trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-lyxohexopyranose [7] † (814 mg, 1.5 mmol) in dichloromethane (24 ml) was stirred at 0 °C and hydrogen chloride was bubbled through for 3 min. The mixture was allowed to stand at room temperature for 10 min, and was then filtered and the filtrate evaporated to give the chlorosugar (12) as a colourless gum. This was dissolved in dry tetrahydrofuran (THF) (10 ml) and added to a stirred solution of (+)-4-demethoxydaunomycinone (10) (920 mg, 2.5 mmol) in THF (124 ml) at −3 °C. A solution of silver trifluoromethanesulphonate (540 mg, 2.0 mmol) in anhydrous diethyl ether (17 ml) was added during 20 min, and the mixture was stirred at −3 °C for 2 h. Additional chlorosugar (1.5 mmol) in THF (10 ml) was added, followed by a solution of silver trifluoromethanesulphonate (540 mg) in diethyl ether (17 ml), and the mixture was stirred at −3 °C for a further 1.5 h. The reaction mixture was poured into a mixture of 10% aqueous sodium hydrogen carbonate (700 ml) and ethyl acetate (300 ml) and filtered. The organic layer was washed with water (2 × 1.0 l), dried and evaporated. The residue was chromatographed on a column of silica gel (140 g), using light petroleum (b.p. 60—80 °C)–ethyl acetate (2 : 1 v/v) as eluant, to give the glycoside (13) (1.549 g, 83.5%) as bright orange crystals, m.p. 171—175 °C, $[\alpha]_D^{20}$ −89.8° (*c* 0.1 in dioxan) (Found: C, 56.7; H, 4.2; N, 4.0. $C_{35}H_{29}F_3N_2O_{13}$ requires C, 56.6; H, 3.9; N, 3.8%); $\lambda_{max.}$ ($CHCl_3$) 253, 259, 487, and 520 nm (log ε 4.69, 4.68, 3.97, and 3.75); δ 13.65 (1 H, s, ArOH), 13.30 (1 H, s, ArOH), 8.45—8.25 (6 H, m, ArH), 7.93—7.80 (2 H, m, ArH), 6.43 (1 H, br d, *J* 8 Hz, 3′-NH), 5.70 (1 H, br s, W_H 6 Hz, 1′-H), 5.50 (1 H, br s, W_H 6 Hz, 4′-H), 5.31 (1 H, br s, W_H 6 Hz, 7-H), 4.8—4.4 (2 H, m, 3′- and 5′-H), 4.24 (1 H, s, 9-OH), 3.26 (1 H, d, *J* 19 Hz, 10-*eq*-CH), 2.98 (1 H, d, *J* 19 Hz, 10-*ax*-CH), 2.45 (3 H, s, Ac), 2.4—2.0 (4 H, m, 2′- and 8-H_2), and 1.27 (3 H, d, *J* 6 Hz, 6′-Me).

3′-N-*Trifluoroacetyl*-4-*demethoxydaunomycin* (14).—A solution of the *p*-nitrobenzoyl-glycoside (13) (1.514 g) in dichloromethane (12 ml) was added to methanol (1.33 l) and the mixture was stirred under nitrogen and cooled to 0 °C. 0.1M-Aqueous sodium hydroxide (20 ml) was added and the deep purple solution was stirred at 0 °C for 20 min. Glacial acetic acid was added until the solution became bright orange and it was then concentrated to *ca.* 1.5 l and poured into water (2.30 l). The resulting suspension was extracted with ethyl acetate (2 × 400 ml) and the combined extracts were dried and evaporated. The residue was chromatographed on a column of silica gel (225 g), using dichloromethane (1.50 l) and dichloromethane–acetone (9 : 1, v/v; 1.50 l) as eluants. The product was triturated with diethyl ether to give 3′-*N*-trifluoroacetyl-4-demethoxydaunomycin

* Compounds (13)—(18) have been named by the anthracydine system of nomenclature. The numbering used in the spectral assignments for these compounds is therefore different to that in the foregoing compounds, and is as shown in structure (13).

† We are grateful to Dr. M. R. Uskokovic, Hoffmann-La Roche, Nutley, for supplying the intermediate methyl 3-acetamido-2,3,6-trideoxy-β-L-lyxohexopyranoside, which was prepared from D-mannose by a procedure based on that of Horton and Weckerle.[19]

(14) (0.865 g, 71.5%) as a bright orange crystalline solid, m.p. 155—156 °C (lit.,[3] m.p. 155—157 °C), $[\alpha]_D^{20}$ +190° (*c* 0.1 in dioxan) (lit.,[3] $[\alpha]_D^{20}$ +188°) (Found: C, 56.4; H, 4.4; N, 2.35. Calc. for $C_{28}H_{26}F_3NO_{10}$: C, 56.7; H, 4.4; N, 2.4%); $\lambda_{max.}$ ($CHCl_3$) 253, 259, 290, 487, 507sh, and 520 nm (log ε 4.60, 4.57, 4.01, 4.03, 3.87, and 3.81); δ 13.65 (1 H, s, ArOH), 13.36 (1 H, s, ArOH), 8.45—8.30 (2 H, m, 1- and 4-ArH), 7.94—7.80 (2 H, m, 2- and 3-ArH), 6.67 (1 H, br d, *J* 8 Hz, 3'-NH), 5.53 (1 H, br d, *J* 3 Hz, 1'-H), 5.30 (1 H, dd, $J_{7,8\text{-}ax}$ 4 Hz, $J_{7,8\text{-}eq}$ 2 Hz, 7-H), 4.4—4.1 (2 H, m, 3'- and 5'-H), 4.30 (1 H, s, 9-OH), 3.69 (1 H, m, 4'-H), 3.30 (1 H, dd, $J_{10\text{-}eq,10\text{-}ax}$ 19 Hz, $J_{10\text{-}q,8\text{-}eq}$ 1.5 Hz, 10-*eq*-H), 2.99 (1 H, d, *J* 19 Hz, 10-*ax*-H), 2.44 (3 H, s, Ac), 2.35 (1 H, ddd, $J_{8\text{-}eq,8\text{-}ax}$ 15 Hz, $J_{8\text{-}eq,7}$ 2 Hz, $J_{8\text{-}q,10\text{-}eq}$ 1.5 Hz, 8-*eq*-CH), 2.16 (1 H, dd, $J_{8\text{-}eq,8\text{-}ax}$ 15 Hz, $J_{8\text{-}ax,7}$ 4 Hz, 8-*ax*-H), 2.10—1.80 (2 H, m, 2'-H_2), and 1.32 (3 H, d, *J* 6.5 Hz, 6'-Me).

4-*Demethoxydaunomycin Hydrochloride* (15).—A solution of the *N*-trifluoroacetyl-glycoside (14) (188 mg) in 0.1M-aqueous sodium hydroxide (35 ml) was stirred under nitrogen at room temperature for 30 min. The solution was adjusted to pH 8 with 5M-hydrochloric acid and extracted with chloroform (5 × 50 ml). The combined extracts were washed with water (50 ml), dried and evaporated. The residue was dissolved in a mixture of methanol (1 ml) and chloroform (9 ml) and 0.25M-methanolic hydrogen chloride (1.3 ml) was added. Diethyl ether (40 ml) was added to precipitate 4-demethoxydaunomycin hydrochloride (15) (129 mg, 76%) as a bright orange solid, m.p. 172—174 °C (lit.,[3] m.p. 183—185 °C), $[\alpha]_D^{20}$ +187°, $[\alpha]_{578}^{20}$ +215° (*c* 0.1 in methanol) (lit.,[3] $[\alpha]_D^{20}$ +205°) (Found: C, 58.3; H, 5.4; Cl, 6.6; N, 2.8. Calc. for $C_{26}H_{28}ClNO_9$: C, 58.5; H, 5.3; Cl, 6.6; N, 2.6%), $\lambda_{max.}$ (MeOH) 205, 252, 256sh, 288, 470sh, 484, and 515 nm (log ε 4.41, 4.61, 4.57, 3.99, 3.99, 4.02, and 3.82); δ [$(CD_3)_2SO$] 13.5 (1 H, br band, exch. D_2O, ArOH), 13.3 (1 H, br band, exch. D_2O, ArOH), 8.34—8.18 (2 H, m, 1- and 4-ArH), 8.05—7.89 (2 H, m, 2- and 3-ArH), 5.6—5.4 (2 H, m, exch. D_2O, 9- and 4'-OH), 5.32 (1 H, br s, W_H 6 Hz, 1'-H), 4.94 (1 H, br s, W_H 8 Hz, 7-H), 4.26 (1 H, m, 5'-H), 3.66 (1 H, m, 4'-H), 3.6—3.25 (m, H_2O and 3'-H), 2.98 (2 H, br s, 10-H_2), 2.32 (3 H, s, Ac), 2.3—1.7 (4 H, m, 2'- and 8-CH_2), and 1.20 (3 H, d, *J* 6 Hz, 6'-Me).

4'-O-p-*Nitrobenzoyl*-3'-N-*trifluoroacetyl*-4-*demethoxy*-7,9-*bisepidaunomycin* (16).—Glycosidation of 4-demethoxy-7,9-bisepidaunomycinone (461 mg) as described above for the (*S*)-aglycone gave the α-*glycoside* (16) (583 mg, 63%) as a bright orange crystalline solid, m.p. 167—177 °C (Found: C, 55.0; H, 4.0; N, 3.8. $C_{35}H_{29}F_3N_2O_{13}\cdot H_2O$ requires C, 55.3; H, 4.1; N, 3.7%); $[\alpha]_D^{20}$ −226.5° (*c* 0.1 in dioxan); $\lambda_{max.}$ ($CHCl_3$) 253, 259, 488, 508sh, and 523 nm (log ε 4.69, 4.69, 3.98, 3.82, and 3.76); δ 13.81 (1 H, s, ArOH), 13.34 (1 H, s, ArOH), 8.45—8.25 (6 H, m, ArH), 7.95—7.79 (2 H, m, ArH), 6.44 (1 H, br d, *J* 8 Hz, 3'-NH), 5.62—5.35 (3 H, m, 1'-, 4'- and 7-H), 4.9—4.3 (3 H, m, 3'-, 5'-H and 9-OH), 3.33 (1 H, d, *J* 20 Hz, 10-*eq*-H), 3.05 (1 H, d, *J* 20 Hz, 10-*ax*-H), 2.52 (1 H, br d, *J* 14 Hz, 8-*eq*-H), 2.43 (3 H, s, Ac), 2.25—1.80 (3 H, m, 8-*ax*-H and 2'-H_2), and 1.26 (3 H, d, *J* 6 Hz, 6'-Me).

3'-N-*Trifluoroacetyl*-4-*demethoxy*-7,9-*bisepidaunomycin* (17).—Base-catalysed hydrolysis of the *p*-nitrobenzoyl-glycoside (16) (454 mg) as for the preparation of compound (14) gave the α-*glycoside* (17) (310 mg, 85%) as a bright orange solid, m.p. 137—147 °C, $[\alpha]_D^{20}$ −359° (*c* 0.1 in dioxan) (Found: C, 56.4; H, 4.6; N, 2.3. $C_{28}H_{26}F_3NO_{10}$ requires C, 56.7; H, 4.4; N, 2.4%); $\lambda_{max.}$ ($CHCl_3$) 253, 259, 287, 488, and 523 nm (log ε 4.57, 4.54, 3.99, 4.00, and 3.79); n.m.r. data are in Table 2.

4-*Demethoxy*-7,9-*bisepidaunomycin Hydrochloride* (18).—Alkaline hydrolysis of the *N*-trifluoroacetyl glycoside (17) (80 mg) gave 4-*demethoxy*-7,9-*bisepidaunomycin hydrochloride* (18) (35 mg, 49%) as a bright orange solid, m.p. 164—166 °C, $[\alpha]_D^{20}$ −317° (*c* 0.1 in methanol) (Found: C, 58.9; H, 5.25; Cl, 6.9; N, 2.9. $C_{26}H_{28}ClNO_9$ requires C, 58.5; H, 5.3; Cl, 6.6; N, 2.6%); $\lambda_{max.}$ (MeOH) 205, 252, 256sh, 288, 470sh, 485, and 515 nm (log ε 4.41, 4.63, 4.59, 4.01, 4.03, 4.05, and 3.85); δ [$(CD_3)_2SO$] * 13.5 (2 H, br band, exch. D_2O, ArOH), 8.5—7.5 (3 H, br band, exch. D_2O, 3'-NH_3^+), 8.26—8.23 (2 H, m, 1- and 4-ArH), 8.00—7.97 (2 H, m, 2- and 3-ArH), 5.49 (1 H, s, exch. D_2O, 9-OH), 5.22 (1 H, d, *J* 6 Hz, exch. D_2O, 4'-OH), 5.31 (1 H, d, $J_{1',2'\text{-}ax}$ 2.5 Hz, 1'-H), 5.17 (1 H, dd, $J_{7,8\text{-}ax}$ 4.5 Hz, $J_{7,8\text{-}eq}$ 2.5 Hz, 7-H), 4.21 (1 H, q, *J* 7 Hz, 5'-H), 3.60 (1 H, br d, *J* 6 Hz, 4'-H), 3.3 (m, 3'-H and H_2O), 3.02 (1 H, d, *J* 18 Hz, 10-*eq*-H), 2.95 (1 H, d, *J* 18 Hz, 10-*ax*-H), 2.41 (1 H, br d, $J_{8\text{-}eq,8\text{-}ax}$ 15 Hz, $J_{8\text{-}eq,7}$ 2.5 Hz, 8-*eq*,-H), 2.30 (3 H, s, Ac), 1.91 (1 H, dt, $J_{2'\text{-}ax,2'\text{-}eq}$ 12.5 Hz, $J_{2'\text{-}ax,3'}$ 12.5 Hz, $J_{2'\text{-}ax,1'}$ 2.5 Hz, 2'-*ax*-H), 1.90 (1 H, dd, $J_{8\text{-}ax,8\text{-}eq}$ 15 Hz, $J_{8\text{-}ax,7}$ 4.5 Hz, 8-*ax*-H), 1.68 (1 H, dd, $J_{2'\text{-}eq,2'\text{-}ax}$ 12.5 Hz, $J_{2'\text{-}eq,3'}$ 4 Hz, 2'-*eq*-H), and 1.13 (3 H, d, *J* 7 Hz, 6'-Me).

We are grateful to Dr. J. Daly, Hoffmann-La Roche, Basle for carrying out *X*-ray analyses, to Dr. G. Englert, Hoffmann-La Roche, Basle for recording the 400 MHz n.m.r. spectra of compounds (17) and (18), and Dr. W. A. Thomas for helpful discussions on the interpretation of the data.

[2/067 *Received*, 14*th January*, 1982]

* The n.m.r. spectrum was recorded at 400 MHz on a Bruker WH 400 spectrometer.

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