Anthracyclinones. Part 1. A Versatile Synthesis of the Anthracyclinone System using a Chiral Template derived from a Carbohydrate

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Condensation of *aldehydo*-2,3:4,5-di-*O*-isopropylidene-D-arabinose (7) with *leuco*-quinizarin (6a) or 5-hydroxy-*leuco*-quinizarin (6b) in alkaline solution at 0 °C followed by aerial oxidation gave a good yield of 2-(1-hydroxy-D-arabinityl)quinizarin (8a) and the 5-hydroxy-derivative (8b). Reaction of (8a) with acid furnished the monoisopropylidene derivative (9) and further treatment gave the fully deblocked derivative (10). The monoisopropylidene derivative (9) with periodate, cold alkaline dithionite aerial oxidation, and mild acid treatment gave the novel tetrahydroxy (in ring A) anthracyclinone (12). Structures of the compounds were confirmed by u.v., mass, i.r., and ^{1}H n.m.r. spectroscopy.

The anthracyclines continue to be among the most promising subjects for the development of new drugs for the treatment of cancer.[1] There exists intense sustained interest in the synthesis of adriamycin (1a), daunomycin (1b), and carminomycin (1c), clinically the most important representatives of this class. Synthetic approaches towards the anthracycline antibiotics and potential routes to new analogues have been reviewed.[2-5]

A major problem which arises in the synthesis of aglycones corresponding to (1a—c) is regiospecificity and the construction and functionalisation of ring A.[1] A potential route to the tetracyclic system would involve the extension of a suitable anthraquinone derivative such as quinizarin (2a) by attachment of a fourth ring and concomitant introduction of appropriate chiral centres. In an attempt to achieve such a synthesis we have been interested in using a carbohydrate as an aldehyde and chiral-template source in the Marschalk reaction.[6,7] This reaction involves the condensation of an aldehyde with an anthraquinone, such as quinizarin (2a), in hot alkaline sodium dithionate solution followed by aerial oxidation of the intermediate *leuco*-form when good yields of the corresponding 2-alkyl quinizarins (2b) are generally obtained.

In preliminary experiments using simple monosaccharides, we obtained evidence which suggested that the proposed synthesis was feasible, but, under the normal conditions of the Marschalk reaction, mixtures of products were obtained which proved difficult to separate and identify. In an attempt to produce the 2-D-xylitylquinizarin (3a) we have examined the reaction of quinizarin with a two-fold excess of D-xylose under typical Marschalk conditions. In addition to much unchanged quinizarin, 2-methylquinizarin and 2-(2-hydroxyethyl)quinizarin [isolated as the diacetate (2 f)] were identified among the reaction products together with a highly insoluble fraction. The latter compound (2 f) undoubtedly arises from reaction of *leuco*-quinizarin and glycolaldehyde formed by the well-known reverse aldol reaction of xylose in the presence of sodium hydroxide.[8] Acetylation of the insoluble fraction gave a mixture of products, exhaustive column chromatography of which on silica gel led to the isolation of a homogeneous (t.l.c.) yellow solid in low yield (4%) whose mass spectrum [*m/e* 626 (M^+), 584, 542, 470, 398, 368, 326, 266, 254, and 240] possessed the breakdown features expected for the desired hexaacetate (3b). A complicating feature of the D-xylose condensation involved the formation of a water soluble, highly crystalline monosubstituted quinizarin containing sulphur and sodium, the structure of which was not determined. Under milder reaction conditions (using pure *leuco*-quinizarin in alkaline solution at 0 °C in the absence of reducing agent), D-xylose gave no evidence of reaction. Similar evidence was obtained for the occurrence of analogous reactions with other simple sugars, including D-glucose, D-glucosamine, and maltose.

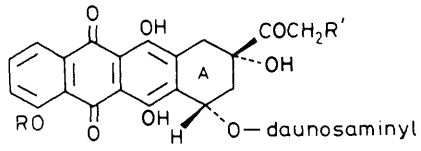
In a separate experiment, condensation of the acyclic 2,4:3,5-di-*O*-benzylidene-L-xylose [9] (4) with quinizarin under identical conditions to those used for the mono- and disaccharides also proved unsatisfactory. Despite peaks in the mass spectrum of the product which suggested the presence of the desired alkylation product (5), this compound was not isolated in a pure form, and the major reaction product (96%) was identified as 2-benzylquinizarin (2c),[10] presumably formed by cleavage of the acetal under the reducing conditions to generate benzaldehyde which reacted with the anthraquinone.

The low yield and complex mixtures produced in these early experiments led us to modify the Marschalk reaction conditions to produce stereospecifically hydroxyglycitylquinizarins which are readily convertible into anthracyclinones. A preliminary account of the work has appeared.[11]

Reaction of pure recrystallized *leuco*-quinizarin (6a) and one molar equivalent of *aldehydo*-2,3:4,5-di-*O*-isopropylidene-D-arabinose (7) [12] with aqueous sodium hydroxide in methanolic tetrahydrofuran (THF) solution at 0 °C for 30 min under nitrogen, followed by aerial oxidation gave a good yield (56%) of the crystalline 2-(1-hydroxy-D-arabinityl)quinizarin (8a) after a single chromatographic purification on silica gel.

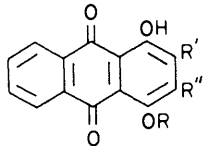
The structure assigned to (8a) was confirmed by elemental analysis, by its i.r. [*e.g.* $\nu_{max.}$ 1 380 cm^{-1} (CMe_2)] and mass [*e.g.* *m/e* 470 (M^+)] absorptions (typical of monosubstituted quinizarins), and ^{1}H n.m.r. [*e.g.* absence of signal for 2-H, signals at δ 7.52 (3-H) and 3.1 (d, 1′-OH), and full assignment of all other protons] spectra, and by its subsequent reactions.

The spectroscopic data and homogeneity of the material on t.l.c. in several solvent systems suggested that compound (8a) was a single diastereoisomer. In particular, ^{1}H n.m.r. studies (spin-decoupling experiments), whilst unable to point unequivocally to the absolute configuration at C-1′, have confirmed this belief. The 1′-H proton signal (centred at δ 5.35) appears as a double doublet (J 2.6, 8.9 Hz). The proton signal of the benzylic hydroxy-group (1′-OH) centred at δ 3.1, is a sharp doublet (J 8.9 Hz). The coupling of the 1′-H proton and the 1′-OH proton was demonstrated by double irradiation of



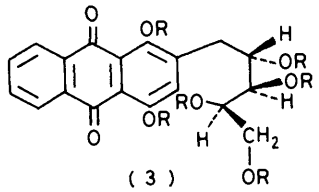
(1)

a; R = CH_3, R′ = OH Adriamycin
b; R = CH_3, R′ = H Daunomycin
c; R = H, R′ = H Carminomycin



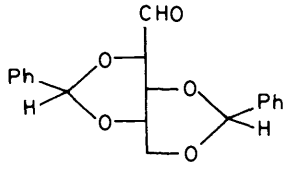
(2)

a; R = R′ = R″ = H
b; R = R″ = H, R′ = CH_2R'''
c; R = R″ = H, R′ = CH_2Ph
d; R = R″ = H, R′ = CH_2OH
e; R = R″ = H, R′ = $CH(OH)CH_3$
f; R = $COCH_3$, R′ = $CH_2CH_2OCOCH_3$, R″ = H

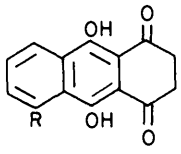


(3)

a; R = H
b; R = Ac

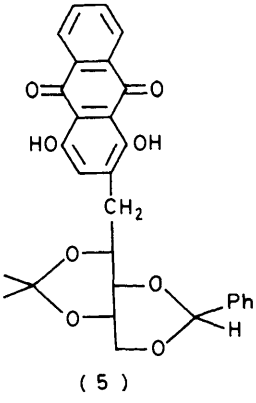


(4)

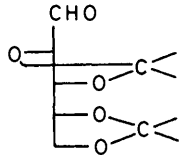


(6)

a; R = H
b; R = OH



(5)



(7)

the signal for 1′-H, whereupon the OH signal collapsed to a singlet, indicating that the compound was a single diastereoisomer and that the OH doublet is not composed of two signals.

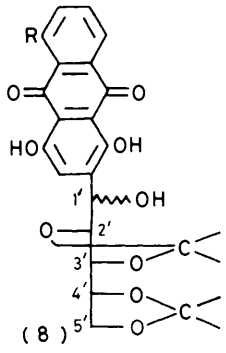
Reciprocally, upon double irradiation of the 1′-OH signal, the 1′-H signal collapsed, essentially to a fine doublet (J 2.6 Hz) arising from the smaller coupling to the adjacent 2′-H. Double irradiation of the 2′-H signal (multiplet centred at δ 4.4) caused the 1′-H signal to appear as a well-defined doublet (J 8.9 Hz). The magnitude of the coupling $J_{1',1'\text{-OH}}$ suggests a near *trans* diaxial relationship and significant rigidity of the O–H function within the molecule.

From an examination of a space-filling model of the anthraquinone (8a) and the application of an extension of Cram's Rule of asymmetric induction [13] (derived from a theoretical treatment of carbonyl reduction by organometallic hydride transfer reagents) one would predict the *S*-configuration at C-1′ as in (8c). It is known that when *aldehydo*-2,3:4,5-di-*O*-isopropylidene-D-arabinose (7) was treated with phenyl-, cyclohexyl-, and 1-naphthyl-magnesium halides, it produced after hydrolysis a series of 1-*C*-substituted pentitols, and in each case only one of the two possible diastereoisomers was isolated.[14] The D-glucitol configuration for the 1-*C*-phenyl-D-pentitol was later established and this is consistent with the assignment [15] (8c).

A definitive assignment of the absolute configuration at C-1′ will be made on completion of *X*-ray crystallographic studies which will be reported elsewhere.

Some simple hydroxyalkylquinizarins analogous to (8a) have been described in the literature. 2-Hydroxymethylquinizarin (2d) [16–18] also occurs naturally in *Digitalis ferruginea*.[19] 2-(1-Hydroxyethyl)quinizarin (2e) and higher homologous products of hydroxyalkylation of quinizarin with aldehydes [21,22] have also been reported previously.

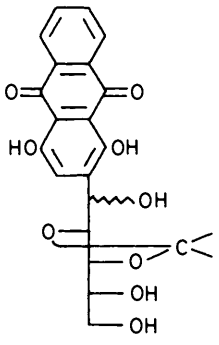
Treatment of the di-isopropylidene derivative (8a) with aqueous acetic acid (70%) at 48 °C readily removed the terminal isopropylidene group to produce in high yield (95%) the monoisopropylidene derivative (9) which readily crystallised. Further treatment of (9) with refluxing 80% aqueous acetic acid gave (100% yield) the fully deprotected crystalline 2-(1-hydroxy-D-arabinityl)quinizarin (10). The structure assigned to the monoisopropylidene derivative (9) was confirmed by elemental analysis, by its mass [*e.g.* M^+ 430, *m/e* 415 ($M - CH_3$)] and ^{1}H n.m.r. [*e.g.* δ 1.48 (3 H, s) 1.66 (3 H, s, CMe_2)] spectroscopic data and, in addition, by its reaction with one molar equivalent of periodate to give the aldehyde (11) which was obtained in solid form, homogeneous on t.l.c. This compound [*m/e* 398 (M^+); $\nu_{max.}$ 1 380 cm^{-1} (CMe_2) and 1 700 cm^{-1} (CHO)] did not readily cyclise (δ 9.3 CHO), but when it was converted into the *leuco*-form with sodium dithionite in alkaline solution at 0 °C it rapidly cyclised to give, after treatment with aqueous acetic acid, the fully deblocked anthracyclinone derivative (12) which was obtained in crystalline form in high yield (70%). The cyclic isopropylidene derivative (13) could be isolated as a solid intermediate in this reaction sequence. The structure of (12) was confirmed by elemental analysis and spectroscopic data [*m/e* = 358 (M^+), no ^{1}H n.m.r. signal at δ 7.52 corresponding to loss of 3-H, full assignment of all other signals and absorption spectra typical of a 2,3-disubstituted quinizarin]. The synthesis of compound (12) is of special interest since substitution at all positions in ring A is achieved. Tetrasubstituted (ring A) derivatives of this type are uncommon and include the naturally occurring steffimycins.[23] The conformations of most anthracyclinones which have been examined from various sources, are related to the crystallographically determined conformation of *N*-bromoacetyldaunomycin.[24] Most models for intercalation of the compounds into DNA are based on this conformation. It is known, however, that modification of the substituent pattern in ring A, as in certain trisubstituted derivatives, may



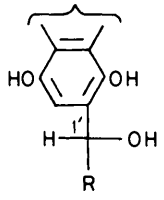
(8)

a; R = H

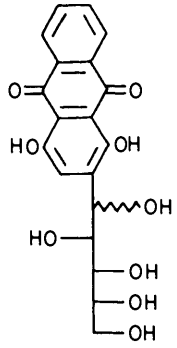
b; R = OH



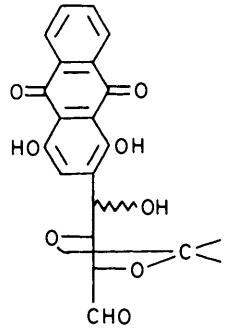
(9)



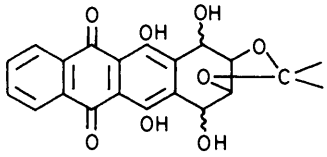
(8c)



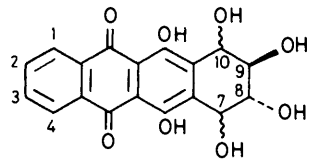
(10)



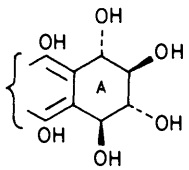
(11)



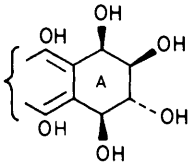
(13)



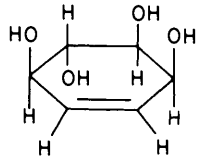
(12)



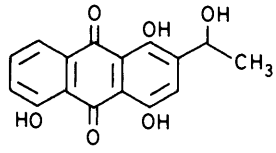
(12a)



(12b)



(14)



(15)

also produce a different conformation.[25] In our example, tetrasubstitution may have special implications regarding conformation in ring A and subsequent interaction with DNA. The relatively high activity shown by this compound (12) in the L1210 assay (see later) would suggest that tetrasubstitution of this particular type and conformation is of potential value in the design of useful anti-tumour agents.

The intramolecular cyclisation of (11) proceeds with introduction of a benzylic hydroxy-group so producing in ring A the second of two new chiral centres at C-7, and C-10. A logical treatment of the mechanism of cyclisation suggested that it would perhaps be analogous to the initial condensation of (6a) with (7) and that the OH groups at C-7 and C-10 would have a *transoid* arrangement with respect to the known chiral centres at C-8 and C-9 as in compound (12a). *cisoidal* (1,3) Arrangement of OH groups is known to be thermodynamically preferred (6 : 1 ratio).[26] This arrangement, however, is inconsistent with the ^{1}H n.m.r. spectral data for compound (12). Because of the symmetry of the all *transoid* arrangement (assuming the half-chair conformation for ring A) only two signals would be expected for the hydroxy-protons at C-7, C-10, and C-8, C-9 respectively, due to their identical chemical and magnetic environments. However, four independent OH signals (in addition to signals for the two phenolic OH groups) were present in the ^{1}H n.m.r. spectrum, each integrating to one proton which exchanged in D_2O. These results indicate that the anthracyclinone has the unsymmetrical structure (12b), which has the same configuration of OH groups as the model compound, unsymmetrical conduritol F[27] (1,2,3,4-tetrahydroxycyclohex-5-ene) (14) where the splitting pattern of the 2-H and 3-H protons, which form part of an A_2B_2 system, closely resembles that of the 8-H and 9-H protons of (12b). These results do not indicate of course whether the *cis*-diol in (12b) was introduced at the final cyclisation step or in the initial condensation.

Methanesulphonylation of compound (12b) with methanesulphonyl chloride in pyridine at 0 °C gave a crystalline monomethanesulphonyl derivative, probably either the 8-*O*- or 9-*O*-methanesulphonate of (12b) since its mass spectrum showed the characteristic retro-Diels–Alder fragment *m/e* 298 expected of either of these compounds. The structure was further confirmed by elemental analysis.

Intramolecular conventional Marschalk alkylations under normal conditions have also been used in the quinizarin and 5-methoxyquinizarin series to produce anthracyclinone analogues, but the overall yields were relatively low and ring A achiral and poorly functionalised.[28] In one example, using a modified Marschalk reaction, an OH group was introduced on cyclisation at C-10 in ring A in the synthesis of ε-rhodomycinone, but this naturally resulted in a mixture of C-10 epimers.[29] Some racemic rhodomycinones have similarly been obtained [30] by base-catalysed cyclisation of an anthraquinone ketoester, and a mixture of epimers of a citromycinone derivative were very recently obtained by an intramolecular Marschalk cyclisation.[31]

Marschalk alkylation of 1,4,5-trihydroxyanthraquinone (5-hydroxyquinizarin) has been shown to be directed to either the 2- or 3-position with high regioselectivity.[32] The 2-hydroxyethyl derivative (15) has been prepared from the *leuco*-form of 5-hydroxyquinizarin (6b) *in situ*.[22]

We have condensed *aldehydo*-2,3 : 4,5-di-*O*-isopropylidene-D-arabinose with *leuco*-5-hydroxyquinizarin in the absence of reducing agent to produce a single diastereoisomer (of unassigned absolute configuration at C-1′) of the 2-(1-hydroxy-D-arabinityl) derivative (8b) which readily crystallized. The

Table. Inhibitory activity of anthraquinone derivatives on murine L1210 cell growth [a]

Compound	ID_{50} (μg/ml) [b]	Average values (standard deviation)
(8a)	36, 29, 48	37.67 (±7.84)
(10)	52, 52, 33.7	45.90 (±8.62)
(12b)	3.65, 3.20, 2.50, 2.90	3.06 (±0.51)
8(9)-Mono-*O*-methanesulphonate of (12b)	3.88, 3.20	3.54 (±0.34)
(1a)	0.170, 0.180, 0.162	0.170 (±0.007)
(1b)	0.017, 0.015, 0.020, 0.017	0.0173 (±0.0018)

[a] The complete procedure for measuring inhibition of murine L1210 cell growth *in vitro* has been described elsewhere (see E. de Clercq, J. Balzarini, P. F. Torrence, M. P. Mertes, C. L. Schmidt, D. Shugar, P. J. Barr, A. S. Jones, G. Verhelst, and R. T. Walker, *Mol. Pharmacol.*, 1981, **19**, 321). [b] Individual values for two to four separate experiments.

structure of (8b) was confirmed by elemental analysis, mass [*e.g.* *m/e* 486 (M^+), 471 ($M - CH_3$)], i.r. [*e.g.* $\nu_{max.}$ (KBr) 1 605 (quinone), 1 380 cm^{-1} (CMe_2)], and ^1H n.m.r. spectra [*e.g.* δ 3.05 (d, 1′-OH), 5.33 (1′-H), absence of signal for 2-H, and full assignment of all other protons]. The conversion of this compound into analogues of carminomycinone (1c) will be the subject of a future publication.

Numerous brief communications have appeared in the last five years concerned with the synthesis of the aglycone portion of the anthracyclines. Much of this research effort has been directed towards the regioselective incorporation of the 4-methoxy-group into the anthracyclinone system whereas recent work shows that activity is maintained when the 4-OMe substituent is omitted,[33,34] and probably the 9-side chain [35] as well, whereas the 9-OH group is essential. Compound (12) has shown promising activity in the experimental L1210 system and this is exceptional among anthracyclinones since activity is normally almost always associated with the intact anthracycline glycosides. The results of the determination of the inhibitory activity of some anthraquinone derivatives on murine leukemia L1210 cell growth are presented in the Table. The results reflect the difference in activity between compound (12b), its mono-*O*-methanesulphonyl derivative, and its 2-substituted quinizarin precursors, and also the values for adriamycin and daunomycin in the same assay system are included.

We believe that the method outlined represents the best available for the synthesis of a wide variety of anthracyclinones utilising an existing wealth of well characterised *aldehydo*-carbohydrate derivatives. In particular, the ability to introduce centres of known chirality is in itself novel and much modification of OH groups in these positions is possible.

Experimental

Evaporations were carried out with a Buchi rotary evaporator, under water-pump vacuum with a flask temperature below 40 °C, unless otherwise stated. U.v. spectra were measured with a Unicam SP800 spectrophotometer, i.r. spectra with a Perkin-Elmer 681 spectrophotometer, ^1H n.m.r. (100 Hz) spectra with a JEOL JNM-MH-100 spectrometer (tetramethylsilane as internal standard), unless otherwise stated, and mass spectra with an A.E.I. MS 903 spectrometer. We thank P.C.M.U. and I.C.I. Ltd for high resolution ^1H n.m.r., and field-desorption mass spectra. Silica gel (0.05—0.2 mm, 70—270 mesh; Machery-Nagel and Co.) and cellulose powder CC31 (Whatman) were used for column chromatography. Thin-layer chromatograms were run on silica gel 60 F_{254} (0.2-mm thick) pre-coated aluminium plates (Merck) and Cellulose F_{254} (0.1-mm thick) pre-coated aluminium plates (Merck) in the systems (A) toluene–ethyl acetate (4 : 1); (B) toluene–ethyl acetate (1 : 1); (C) ethyl acetate; (D) butan-1-ol–acetic acid–water (5 : 4 : 1).

1,4-*Dihydroxy*-2-(1-*hydroxy*-2,3 : 4,5-*di*-O-*isopropylidene*-D-*arabinityl*)-9,10-*anthraquinone* (8a).—*aldehydo*-2,3:4,5-Di-*O*-isopropylidene-D-arabinose [12] (7) (43 g, 0.187 mol) in methanol (50 cm^3) was added to a solution of *leuco*-quinizarin (6a) (45 g, 0.186 mol) in THF (960 cm^3) and methanol (780 cm^3) cooled to 0 °C. A solution of sodium hydroxide (32 g) in water (150 cm^3) was added to the mixture and the reactants maintained at 0 °C for 25 min under nitrogen. The brown solution was aerated for 2 h and the resultant purple solution was added dropwise with rapid stirring to a mixture of hydrochloric acid (100 cm^3; 36% w/w), water (200 cm^3) and crushed ice (200 g). The resulting orange-red precipitate was filtered off, washed with water and air-dried to give an orange-red solid (78.4 g) which afforded the anthraquinone (8a) in 56% overall yield after chromatographic purification as follows: a solution of the foregoing product (30 g) in toluene–ethyl acetate (4 : 1) was applied to a silica-gel column (10 × 60 cm) and eluted by the same solvent mixture. The product fraction (R_F 0.42, system A), on evaporation yielded 1,4-*dihydroxy*-2-(1-*hydroxy*-2,3:4,5-*di*-O-*isopropylidene*-D-*arabinityl*)-9,10-*anthraquinone* (8a) (18.7 g) which recrystallized from ethanol as orange-red laths, m.p. 167 °C (Found: C, 63.8; H, 5.6%; M^+, 470. $C_{25}H_{26}O_9$ requires C, 63.85; H, 5.55%; *M*, 470); *m/e* 470, 455 ($M - CH_3$), 270, and 143; $\nu_{max.}$ (KBr) 1 624, 1 590 (chelated quinone), and 1 380 cm^{-1} (CMe_2); $\lambda_{max.}$ (EtOH) (log ε) 227sh (4.25), 250 (4.56), 256sh (4.47), 284 (3.94), 320 (3.45), 482 (3.99), and 518 nm (3.82); δ ($CDCl_3$; 220 MHz) 1.36—1.55 (12 H, 2 CMe_2), 3.1 (d, *J* 8.9 Hz, 1′-OH), 4.05 (m, 4′-H), 4.2 (3 H, m, 3′-H and 5′-CH_2), 4.4 (q, 2′-H), 5.35 (dd, 1′-H, $J_{1'2'}$ 2.6 Hz, $J_{1'1'-OH}$ 8.9 Hz), 7.52 (s, 3-H), AA′BB′ signal [δ_A 7.75—7.9 (6-, 7-H), δ_B 8.25—8.4 (5-, 8-H)], 12.88 (s, 4-OH), and 13.45 (s, 1-OH).

1,4-*Dihydroxy*-2-(1-*hydroxy*-2,3-O-*isopropylidene*-D-*arabinityl*)-9,10-*anthraquinone* (9).—A solution of the foregoing di-isopropylidene derivative (8a) (3 g) in acetic acid (210 cm^3) was diluted with water (45 cm^3) then set aside at 48 °C for 1 h. T.l.c. examination (system B) revealed complete disappearance of starting material (R_F 0.79) and emergence of two new compounds R_F 0.16 (major) and R_F = 0.0 (trace) corresponding to compounds (9) and (10), respectively. The solution was evaporated (<30 °C) using an oil pump, to a gum which solidified when re-evaporated with toluene. Compound (9) was separated from the highly insoluble (10) by cold ethyl acetate extraction and evaporation of the extract yielded 1,4-*dihydroxy*-2-(1-*hydroxy*-2,3-O-*isopropylidene*-D-*arabinityl*)-9,10-*anthraquinone* (9) as a chromatographically homogeneous orange-red solid (2.6 g, 95% yield) which crystallised from propan-2-ol–ether as orange-red prisms, m.p. 178 °C (Found: C, 61.4; H, 5.0%; M^+, 430. $C_{22}H_{22}O_9$ requires C, 61.4; H, 5.15%; *M*, 430); *m/e* 430, 415 ($M - CH_3$), and 270; $\nu_{max.}$ (KBr) 1 622, 1 593 (chelated quinone), and 1 379 cm^{-1} (CMe_2); $\lambda_{max.}$ (EtOH) (log ε) 226sh (4.21), 251 (4.57), 256sh (4.48), 286 (3.93), 320 (3.41), 486 (3.86), and 518 nm (3.63); δ ([$^2H_5$]pyridine) 1.48 (3 H, s), 1.66 (3 H, s,

CMe_2); δ ($CDCl_3$) AA'BB' signal [δ_A7.7–7.84 (6-H, 7-H, δ_B 8.24—8.39 (5-H, 8-H)].

1,4-*Dihydroxy*-2-(1-*hydroxy*-D-*arabinityl*)-9,10-*anthraquinone* (10).—A solution of compound (8a) (1 g) in aqueous acetic acid (100 cm^3, 80%) was refluxed for 1 h, then evaporated and re-evaporated with toluene to dryness. The residue was homogeneous on t.l.c. examination, R_F 0.72 (system D). 1,4-*Dihydroxy*-2-(1-*hydroxy*-D-*arabinityl*)-9,10-*anthraquinone* (10) (0.82 g, 100% yield), crystallised from ethanol as orange silky needles, m.p. 229 °C (Found: C, 58.35; H, 4.55%; M^+, 390. $C_{19}H_{18}O_9$ requires C, 58.45; H, 4.5%; *M*, 390); *m/e* 390 and 270; $\nu_{max.}$ (KBr) 1 630 and 1 595 cm^{-1} (quinone); $\lambda_{max.}$ (EtOH) (log ε) 227sh (3.80), 250 (4.26), 256sh (4.18), 287 (3.63) 322 (3.19), and 480 (3.82); δ [$(CD_3)_2SO$–D_2O] 3.66 (4'-H), 3.94 (3 H, m, 3'-H and 5'-CH_2), 4.09 (2'-H), 5.15 (1'-H, dd, *J* 4.8, 1.6 Hz), 7.5 (s, 3-H), and AA'BB' signal [δ_A 7.94—8.10 (6-H, 7-H), δ_B 8.25—8.41 (5-H, 8-H)].

7,8,9,10-*Tetrahydro*-6,7(S),8(S),9(R),10(R),11-*hexahydroxynaphthacene*-5,12-*dione* (12b).—A solution of the monoisopropylidene derivative (9) (2.6 g) in methanol (300 cm^3) was treated with a solution of sodium metaperiodate (1.4 g, 1.1 mol equiv.) in water (90 cm^3) at room temperature for 45 min. The solution was then concentrated under reduced pressure (<30 °C) to *ca.* 100 cm^3 and extracted with chloroform (3 × 40 cm^3). The extracts were combined, washed with water, dried ($MgSO_4$), filtered and evaporated to give the *aldehyde* (11) as a red solid (2.4 g) which was homogeneous on t.l.c. examination [R_F 0.78, system C; starting material (9) had R_F 0.58] (Found: M^+ 398. $C_{21}H_{18}O_9$ requires *M*, 398); *m/e* 383 (*M* − CH_3) and 270; $\nu_{max.}$ (KBr) 1 700 (CHO) and 1 380 cm^{-1} (CMe_2); δ ($CDCl_3$) 9.3 (1 H, s, CHO). It was used immediately in the next step without further purification as follows. The aldehyde (11) (2.4 g) was dissolved in methanol (200 cm^3) and THF (30 cm^3) and treated at 0 °C with an aqueous solution of sodium hydroxide (1.5%, 50 cm^3) containing sodium dithionite (1.32 g) for 15 min under nitrogen. The yellow solution was aerated for 20 min to produce a purple solution which was added dropwise with stirring to 5M-hydrochloric acid (700 cm^3) at 0 °C. The resulting red solid precipitate was collected by centrifugation, washed with water, and evaporated from a methanol suspension to give a solid which was homogeneous on t.l.c. examination (R_F 0.64, system B). The solid was dissolved in hot acetic acid and the solution diluted with water to incipient turbidity (*ca.* 60%) to afford on cooling a crystalline precipitate. 7,8,9,10-*Tetrahydro*-6,7(S),8(S),9(R),10(R),11-*hexahydroxynaphthacene*-5,12-*dione* (12b) *hemihydrate* (1.51 g, 70%), recrystallised from aqueous acetic acid as orange-red laths, m.p. 240 °C (decomp.). A second crop (0.350 g) of (12b) (R_F 0.7, system D) was obtained after concentration of the mother liquor (Found: C, 59.0; H, 4.2%; M^+, 358. $C_{18}H_{14}O_8 \cdot 0.5H_2O$ requires C, 58.85; H, 4.1%; *M*, 358); *m/e* 354, 322, 298, and 270; $\nu_{max.}$ (KBr) 3 430sh (OH), 1 625, and 1 589 cm^{-1} (quinone); $\lambda_{max.}$ (EtOH) (log ε) 227sh (4.03), 235sh (4.06), 252 (4.32), 256sh (4.22), 285 (3.71), 325sh (3.20), 460 (3.55), 485 (3.62), and 519 nm (3.38); δ [$(CD_3)_2SO$; 300 MHz] 3.89—4.20 (2 H, m, 8-H, 9-H), 4.60—4.95 (2 H, m, 7-H, 10-H), 5.0, 5.1, 5.33, 5.44 (each 1 H d, 7-OH, 8-OH, 9-OH, 10-OH, all exchangeable with D_2O), 13.35 (1 H, s, 6-O*H*, exch. D_2O), 13.48 (1 H, s, 11-O*H*, exch. D_2O), AA'BB' signal [δ_A 7.9—8.08 (2-H, 3-H), δ_B 8.21—8.38 (1-H, 4-H)].

Methanesulphonylation of (12b) [methanesulphonyl chloride (1.5 mol equiv.) in pyridine at 0 °C for 45 min, then poured into water and the red precipitate filtered off] afforded the 8(9)-*mono*-O-*methanesulphonate* which crystallised from methanol as red prisms, m.p. 200 °C (decomp.) (Found: C, 52.15; H, 3.8%; M^+, 436. $C_{19}H_{16}O_{10}S$ requires C, 52.3; H, 3.7%; *M*, 436). Under identical conditions, use of toluene-4-sulphonyl chloride gave only unchanged (12b).

1,4,5-*Trihydroxy*-2-(1-*hydroxy*-2,3:4,5-*di*-O-*isopropylidene*-D-*arabinityl*)-9,10-*anthraquinone* (8b).—A solution of 1,4,5-trihydroxyanthraquinone (3.0 g) in aqueous sodium hydroxide (2%, 250 cm^3) was heated at 80 °C for 25 min with sodium dithionite (6.0 g) under nitrogen. The solution was cooled then acidified with an excess of 5M-hydrochloric acid and the yellow-brown precipitate of *leuco*-5-hydroxyquinizarin (6b) was filtered off, washed with water and dried *in vacuo* (P_2O_5). A solution of this compound (2.8 g) in THF (50 cm^3) and methanol (50 cm^3) was treated with *aldehydo*-2,3:4,5-di-*O*-isopropylidene-D-arabinose (7) (2.5 g) in methanol (30 cm^3). The solution was cooled to 0 °C, treated with aqueous sodium hydroxide (8%, 20 cm^3) under nitrogen for 30 min, then allowed to warm to room temperature (22 °C) and set aside for 12 h. T.l.c. examination of the solution revealed (system A) the presence of several compounds including the starting material (R_F 0.86) and other compounds [R_F 0.52 (trace), R_F 0.44 corresponding to compound (15), and R_F = 0.0]. The brown reaction mixture was aerated for 30 min and added dropwise with stirring to aqueous 5M-hydrochloric acid (50 cm^3) at 0 °C when a red-brown precipitate was obtained. This was filtered off and washed with water to give a red solid (4.8 g). A sample of the solid (1 g) was dissolved in the minimum amount of a solution of toluene–ethyl acetate (4 : 1) and a small amount of undissolved material was filtered off. The solution was applied to a silica-gel column (7 × 12 cm) and eluted by the same solvent mixture. The fraction containing the product was evaporated to dryness to give a red solid. 1,4,5-*Trihydroxy*-2-(1-*hydroxy*-2,3:4,5-*di*-O-*isopropylidene*-D-*arabinityl*)-9,10-*anthraquinone* (8b), crystallized from ethanol as red lustrous platelets, m.p. 172 °C (0.438 g, 39% overall yield) (Found: C, 61.8; H, 5.2%; M^+, 486. $C_{25}H_{26}O_{10}$ requires C, 61.75; H, 5.4%; *M*, 486); *m/e* 486, 471 (*M* − CH_3), and 286; $\lambda_{max.}$ (MeOH) (log ε) 219sh (4.0), 233 (4.39), 252 (4.17), 274 (3.61), 292 (3.72), and 462 (3.67); δ ($CDCl_3$) 1.24—1.63 (12 H, m, 2 CMe_2), 3.05 (1 H, d, 1'-OH, *J* 10.7 Hz), 5.33 (1 H, dd, *J* 10.7, 3.5 Hz, 1'-H), 7.35 (1 H, d, 6-H), 7.52 (1 H, s, 3-H), 7.74 (1 H, t, 7-H), 7.9 (1 H, d, 8-H), 12.24 (1 H, s, 4-OH), 12.31 (1 H, s, 1-OH), and 13.45 (1 H, s, 5-OH); $\nu_{max.}$ (KBr) 1 605 (quinone) and 1 380 cm^{-1} (CMe_2).

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