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# AN EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE 4-DEMETHOXY ANTHRACYCLINONES

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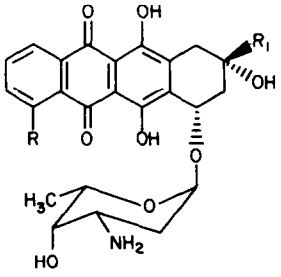
**Abstract**—Optically active 4-demethoxy-anthracyclinones related to daunorubicin were synthesized in several steps from lactose as chiral precursor of ring A and from leucoquinizarine as precursor of rings B, C and D.

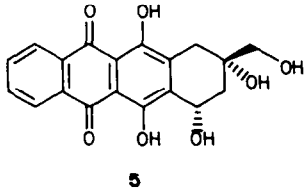
The total synthesis of naturally occurring anthracyclines, daunorubicin **1** and doxorubicin or adriamycin **2** and of related structural analogs has been the subject of intense studies over the last decade.[1] However, only a limited number of reported syntheses are adaptable to the preparation of the aglycone portion of these molecules on a large scale[2] and/or in optically pure form.[3] The synthesis of chiral aglycones is of particular importance as loss of the valuable sugar moiety as a result of the formation of diastereoisomeric products in the final glycosidation step can thus be avoided.

It was with this fact in mind that we decided to develop a chiral synthesis of several aglycones following routes which could be scaled up to the preparative level.

As recent findings indicate that 4-demethoxy daunorubicin **3** is approximatively five or ten times more potent than daunorubicin[2a,4] and that substitution of the acetyl side chain of **3** by an hydroxymethyl group as in **4** (NSC 272681) does not result in a significant loss of the activity,[5] our first target was the daunomycinone analog, 4-demethoxy-9-deacetyl-9-hydroxymethyl daunomycinone, **5**, bearing both these modifications.†



**1** R = $OCH_3$, $R_1$ = $COCH_3$
**2** R = $OCH_3$, $R_1$ = $COCH_2OH$
**3** R = H, $R_1$ = $COCH_3$
**4** R = $OCH_3$, $R_1$ = $CH_2OH$



**5**

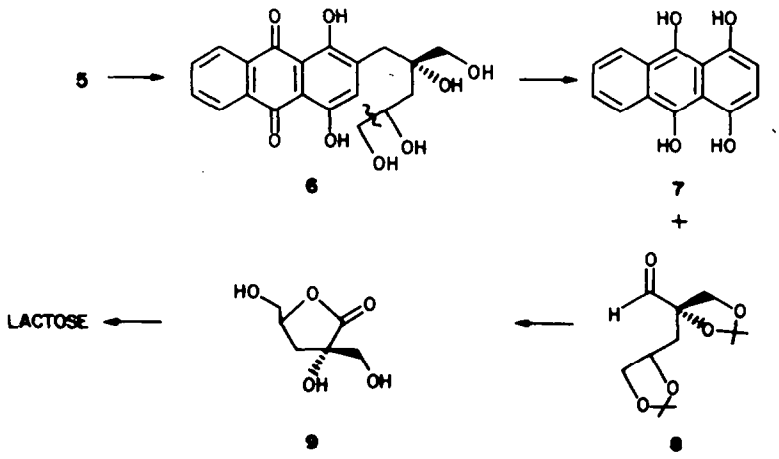
Formula 1.

From the retrosynthetic analysis presented in the Scheme 1, it can be seen that aglycone **5** could be constructed by means of an intermolecular aldolisation reaction under Lewis[7] or Marschalk[8] conditions between leucoquinizarine **7** and the synthon **8** (followed by suitable transformations of the adduct **6**). The aldehyde **8** itself can be prepared from a readily available precursor, α-D-isosaccharino-1,4 lactone **9** obtained on a large scale (400 or 500 g) from lactose. The choice of this carbohydrate avoids, as we shall see, the major problem of introducing the hydroxyl groups at C-7 and/or at C-9.[3b]

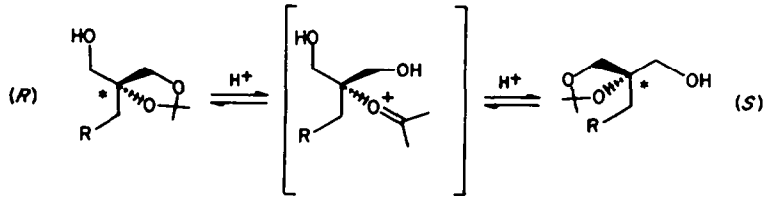
α-D-isosaccharino-1,4 lactone **9** was prepared by treatment of lactose with calcium hydroxide[9] and its vicinal diol protected as an isopropylidene. Reaction of the isopropylidene derivative **10**[10] with borane-methylsulfid complex[11] (94% yield) or LAH (90% yield) gave the alditol **11a** characterized as its tri-O-acetyl derivative **11b**. It was expected that the conversion of **11a** to aldehyde **8** could be achieved in two steps: (a) protection of the vicinal diol, (b) oxidation of the primary alcohol. Unfortunately, treatment of **11a** with either a mixture of acetone-HCl or with 2,2-dimethoxypropane-*p*TsOH in DMF led invariably to a mixture of the diastereoisomers **12** and **13**, separated by column chromatography on silica gel. The spectroscopic data for these compounds were consistent with bis-acetonide structures and their formation could be explained by racemization of the quaternary center according to the Scheme 2.

In view of this result and with large amounts of the alditol **11a** available, we modified the above approach in order to prepare aldehyde **14**. With this purpose the alditol **11a** was reacted with sodium periodate to afford **14** (hemiacetal form as shown by IR and NMR spectra) which was subsequently condensed with leucoquinizarine **5** under Lewis conditions[7] (refluxing

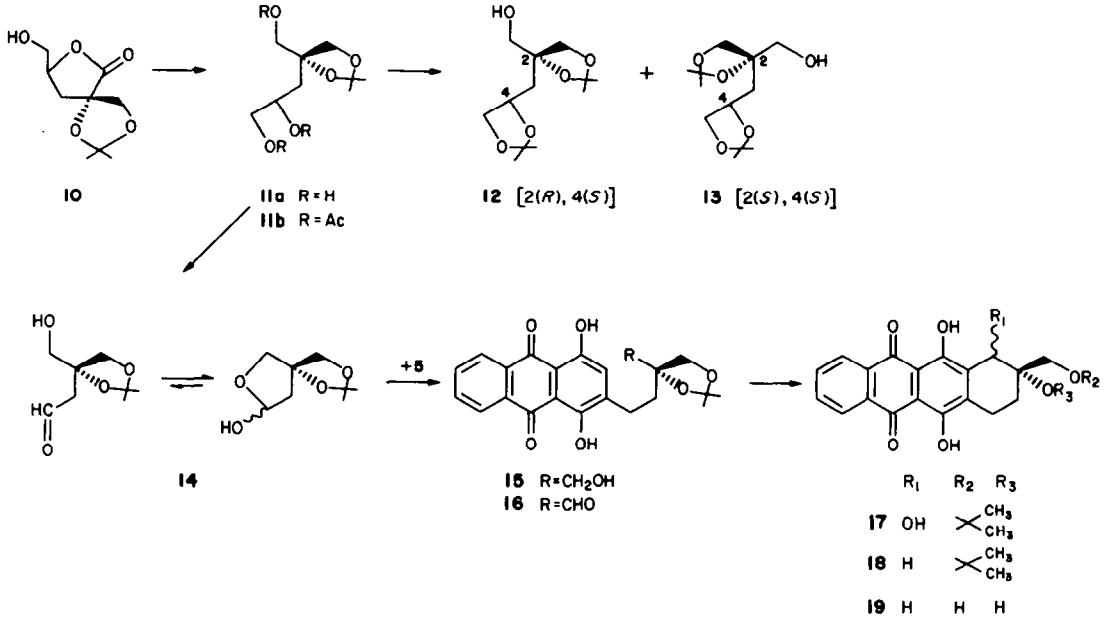
† During the course of this work a different approach to the 13-acetyl derivative of **5** has been published by Broadhurst *et al.* as well as the corresponding daunosaminyl and 4'-epi-daunosaminyl glycosides.[6]




Scheme 1.




Scheme 2.




Scheme 3.

isopropanol-piperidinium acetate, $N_2$ atm). This led after aerial oxidation, extraction and chromatographic purification, to the anthraquinone derivative **15** in good yield (75%).

Treatment of **15** under various oxidation conditions†—DMSO-acetic anhydride,[12] DMSO-trifluoroacetic anhydride,[13] N-iodo-succinimide-tetrabutylammonium iodide[14]—resulted in either the recovery of starting material or the formation of **16** along with many side-products. It was eventually found that **15** could be efficiently oxidized to **16** using N-chlorosuccinimide-$Me_2S$-$Et_3N$[15] or Moffatt oxidation[16] (DMSO-DCC-pyridinium trifluoroacetate) in 60 and 80% yields respectively. The intramolecular cyclization of **16** was carried out under Marschalk

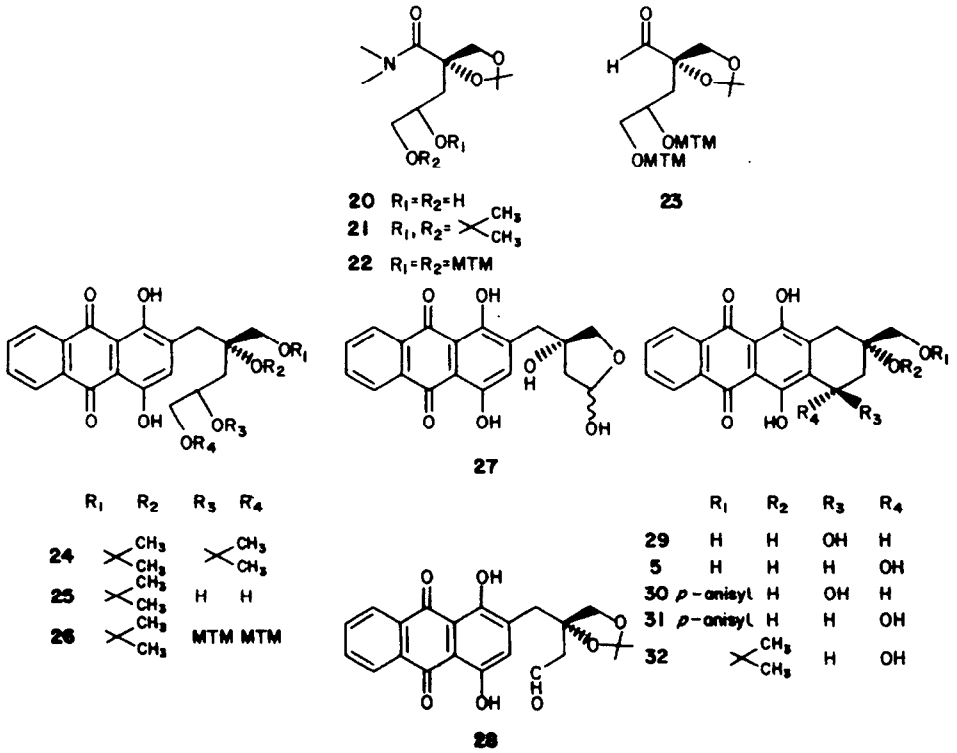
† Similar difficulties have been encountered by S. Terashima *et al.*[3c] during oxidation of closely related structural analog.

conditions[8] (sodium dithionite-KOH-THF) at 0° to give **17** (60% yield). As shown by TLC examination and by $^1$H-NMR spectroscopy at 270 MHz (Experimental) **17** was in fact a diastereoisomeric mixture of C-10 alcohols produced in the ratio of 3 : 2. Hydrogenolysis of this mixture in the presence of palladium on barium sulfate and in ethanol followed by acid hydrolysis gave the 7-deoxy-anthracyclinones **18** and **19** (overall yield for the last two steps = 80%).

At this stage, in order to obtain directly our target molecule having the hydroxyl group present at C-7, we decided to reinvestigate the preparation of the aldehyde **8**. With this goal in mind, lactone **10** was converted into the dimethylamido derivative **20** ($Me_2NH$—$CHCl_3$—r.t., 65% yield) so that the terminal vicinal diol could be protected without epimerization of the quaternary carbon atom under acid catalysis. Thus **20** led to the fully protected bis-acetonide **21** in 90% yield. Subsequent reduction of **21** with LAH in ether at −40° afforded the aldehyde derivative **8** in 78% yield.†

vicinal diol was carried out using one molar equivalent of sodium periodate in the presence of acetic acid. The aldehyde **27** as shown by IR and NMR spectra (400 MHz) exists in its hemiacetal form (mixture of anomers). Mass spectroscopy (E.I.) and analysis were in full agreement with this structure.

Intramolecular cyclization of **27** under Marschalk conditions[8] at room temperature afforded the 7-deoxy anthracyclinone **19** in 80% yield. In contrast when this reaction was carried out at 0°, two others anthracyclinones, slightly more polar ($R_f$ 0.30 and 0.28) than **19** ($R_f$ 0.46) were also detected by TLC examination. ($CH_2Cl_2$—MeOH, 95 : 5). Their structures were unambiguously established as the corresponding 7-hydroxy derivatives and the configuration of the C-7 was deduced from their $^1$H-NMR spectra at 400 MHz in pyridine-$d_5$. The structure of *trans* derivative 7(R), 9(S) was attributed to the less polar compound **29** ($\delta$ 5.86 ppm and $J = J' = 6$ Hz for the 7-H signal) while the broad singlet at $\delta$ 5.69 ppm




Formulae 2 and 3.

Condensation of **8** with leucoquinizarine **7** in the presence of piperidinium acetate[7] at reflux for 20 hr led to **24** in 75% yield after chromatography on silica gel. Deprotection of **24** by stirring in a mixture of THF—MeOH containing N hydrochloric acid afforded the tetrol **6**. Selective cleavage of the terminal

† The lack of reactivity of **21** toward lithium triethoxyaluminohydride in ether solution can be understood in terms of steric hindrance of the amide function.[17] This can explain also the formation of only small amounts of the alcohol **13** during the reduction with LAH.[18] As already observed with various N,N-disubstituted amides the reaction sequence stops at the amino alcohol stage.

($\nu_{1/2}$ : 7.5 Hz) observed for the 7-H in the more polar **9** was in agreement with a configuration 7(*S*), 9(*S*) of *cis* derivative. Mass spectra and analysis of **29** and **30** were in full agreement with these structures. Owing to the difficulty of separating these compounds by column chromatography (poor recoveries) the crude product mixture was reacted with *p*-methoxytriphenylmethyl chloride (or *p*-anisyl chloride) giving the expected ethers **30** and **31**. These derivatives were readily separated by column chromatography on silica gel.

As this protecting group did not appear to be stable under several attempts of glycosidation of **31** (although it has already been used in adriamycinone chemistry) we chose to reinvestigate the last steps of the synthesis.

Selective hydrolysis of **24** led to the mono-acetonide

derivative **25**† (90% yield) which was treated with sodium periodate producing aldehyde **28** in essentially quantitative yield. Intramolecular cyclization under Marschalk conditions at −10° gave the *cis* anthracyclinone, 7(*S*), 9(*S*), **32**, *exclusively* in 75% yield after crystallization. Such a high asymmetric induction may be due to the presence of the bulky isopropylidene ring present in the molecule.

## EXPERIMENTAL

*General procedures.* M.ps were determined on a Kŏfler hot stage microscope and are uncorrected. Microanalyses were performed by the "Laboratoire de Microanalyse du CNRS", Gif sur Yvette and Lyon.

IR spectra were recorded on a Perkin-Elmer Model 257 Spectrophotometer, calibrated against polystyrene film and are expressed in $cm^{-1}$. PMR spectra at 270 MHz were obtained on a Brucker HX 270 and at 400 MHz on an IEF instrument built at the "Institut d'Electronique d'Orsay, France" (P. Gonord, S. K. Kan and M. J. Sauzade, *J. Magn. Res.* **24**, 457 (1976) and S. K. Kan, P. Gonord, M. Fan, M. J. Sauzade and J. Courtieu, *Rev. Sci. Instrum.* **49**, 785 (1978)).

Chemical shifts are reported in ppm relative to internal TMS with the notations indicating the multiplicity of the signal. Spin multiplicity is given by s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. The coupling constants are expressed as J values in units of Hertz.

Mass spectra were recorded on a Nermag R 1010 and for E.I. are obtained at an ionizing voltage of 70 eV.

Silica gel for column chromatography was Merck Silica Gel H Type 60 no 7736.

Analytical TLC were performed on Merck Silica Gel 60 F-254.

*α-D-isosaccharino 1,4-lactone* (**9**). This was obtained as described by Whistler and BeMiller.[9]

*2,2' - Isopropylidene - α - D - isosaccharino 1,4 - lactone* (**10**) was obtained in accordance with the procedure described by Whistler and BeMiller:[10] m.p. 56° $|\alpha|_D$ +43° (*c* 1, $CHCl_3$); IR (film $\nu_{max}$: 1775, 1220 and 1060 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 400 MHz): 4.72 (1H, m, 4-H); 4.34 (1H, d) and 4.12 (1H, d) (AB signal, J = 9, 2'-H); 3.97 (1H, dd) and 3.60 (1H, dd) (ABX signal, J = 13, J' = 3, 5-H); 3.01 (1H, OH); 2.46 (1H, m) and 2.34 (1H, m) (ABX signal, J = 14, J' = 7, 3-H); 1.48 (3H, s) and 1.43 (3H, s) ($CMe_2$); $^{13}$C-NMR: 176.5 (1-C), 112.4 ($CMe_2$), 81.1 (4-C), 78.1 (2-C), 71.8 (2'-C), 63 (5-C), 26.4 and 25.7 (Me isopropyl.); MS (E.I.): *m/z*: 203 (M+1, traces), 187 (M-15, 100%), 145 (M+1−58, 12%), 128 (12%), 85 (19%) and 43 (36%). (Found: C, 53.54; H, 7.02; O, 39.57. Calc for $C_9H_{14}O_5$ (202.20): C, 53.46; H, 6.98; O, 39.56%).

*3-Deoxy-2-C-hydroxymethyl-2,2'-O-isopropylidene-D-glycero-pentitol* (**11a**)

(a) *By reduction with* $BH_3$—$Me_2S$ *complex.*[11] To a soln of **10** (10 g, 49.2 mmol) in dry THF (235 ml), a 2M diborane-methyl sulfide soln (120 ml) was added dropwise at room temp. After stirring for 24 hr, the excess of diborane was destroyed by cautious addition of water at 0°. The water was then removed under reduced pressure and the residue was taken up in MeOH and evaporated. This was repeated three times affording a syrupy residue (9.4 g), pure enough for the following reaction.

(b) *By reduction with LAH.* To a stirred soln of **10** (10 g, 49.2 mmol) in dry THF (200 ml) cooled to 0°, was added, in small portions over 2.5 hr, LAH (4 g). The mixture was left at r.t. overnight and the excess of LAH was destroyed by sequential addition of water (4 ml), 15% NaOH aq (4 ml) and $H_2O$ (12 ml).[21] After filtration, concentration under reduced pressure of the filtrate led to 9.5 g of **11a** as a syrupy residue, homogeneous on TLC (hexane–acetone 1:1).

This product was described as its tri-O acetylated derivative **11b**.

*3-Deoxy-2-C-hydroxymethyl-2,2' - O-isopropylidene-D-glycero-pentitol 1,4,5 triacetate* (**11b**)

To a stirred soln of **11a** (200 mg) in pyridine (3 ml) was added $Ac_2O$ (1 ml). After 12 hr, the soln was diluted with ice-water and extracted with ether in a usual work up. The crude product was purified by preparative TLC (hexane–acetone 2:1).

Pure **11b** was isolated as a syrup, $|\alpha|_D$ −16° (*c* 1, $CHCl_3$); IR (film): $\nu_{max}$: 1740, 1235, 1050 (CO ester) and 1375 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 5.27 (1H, m, 4-H); 4.34 (1H, dd, J = 12; J' = 3.5) and 5.08 (1H, dd, J' = 6) (ABX, 5-H); 4.15 (1H, d) and 4.02 (1H, d) (AB signal, J = 11.5, 2'-H): 3.98 (1H, d) and 3.78 (1H, d) (AB signal, J = 9, 1-H); 2.19–1.90 (2H, m, 3-H); 2.10 (3H, s), 2.07 (3H, s) and 2.05 (3H, s) (3 OAc); 1.40 (3H, s) and 1.39 (3H, s) ($CMe_2$). (Found: C, 54.27; H, 7.14; O, 38.63. Calc for $C_{15}H_{24}O_8$ (332.34): Calc C, 54.35; H, 7.27; O, 38.51%).

*3-Deoxy-2(R),4(S)-2-C-hydroxymethyl-2,2':4,5-di-O-isopropylidene-D-glycero-pentitol* (**12**) *and its diastereoisomer* 2(S),4(S) (**13**)

To a stirred soln of **11a** (800 mg, 3.9 mmol) in 2,2-dimethoxypropane (2.5 ml) was added dry *p*-TsOH (96 mg). After 12 hr the mixture was poured into a soln of cold 10% $NaHCO_3$ aq and extracted with ether. Concentration under reduced pressure gave a syrupy residue (622 mg) which showed two spots by TLC examination (hexane–AcOEt 1:1). Chromatography on silica gel (60 g, same solvent as for TLC) provided respectively **12** and **13**.

*Compound* **12**: syrup: $|\alpha|_D$ −10° (*c* 1, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 270 MHz): 4.32 (1H, m, 4-H); 4.10 (1H, dd, J = 8.5, J' = 6) and 3.49 (1H, t, J' = 8) (ABX signal, 5-H); 4.01 (1H, d) and 3.75 (1H, d) (AB signal, J = 9, 2'-H); 3.63 (1H, d) and 3.57 (1H, d) (AB signal, J = 12, 1-H); 1.87 (2H, m, 3-H); 1.37 (6H, s), 1.36 (3H, s) and 1.35 (3H, s) ($2CMe_2$).

*Compound* **13**: syrup $|\alpha|_D$ 0° (*c* 1, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 270 MHz): 4.13 (1H, m, 4-H); 4.04 (1H, dd) and 3.52 (1H, dd) (ABX signal, J = 8; J' = 6, 5-H); 4.01 (1H, d) and 3.87 (1H, d) (AB signal J = 9.5, 2'-H); 3.52 (2H, m, 1-H); 1.89 (2H, m, 3-H); 1.40 (9H, s) and 1.34 (3H, s) ($2CMe_2$); MS (E.I.): *m/z* 231 ($M^+$ −15, 52%), 216 (11%), 215 (68%), 173 (M−58−15, 18%), 101 (100%). (Found: C, 58.67; H, 9.04; O, 32.38. Calc for $C_{12}H_{22}O_5$ (246.30): C, 58.51; H, 9.00; O, 32.48%).

The 2-C configuration of **12** and hence of **13** has been deduced from comparison of spectroscopic data with a sample obtained from **21** (*vide infra*).

*3-Deoxy-2-C-hydroxymethyl-2,2':4,5-di-O-isopropylidene-D-ribose* (**8**) and *3-deoxy-2-C-hydroxymethyl-2,2':4,5-di-O-isopropylidene-D-glyceropentitol* (**12**)

(a) *Reduction at low temperature.* To a stirred suspension of LAH (1.32 g, 35 mmol) in anhyd ether (200 ml) at −40° was added dropwise a soln of ribonamide derivative **21** (10 g, 35 mmol) in anhyd ether (100 ml). After 4 hr, the mixture was quenched at −40° with EtOAc (≃50 ml) and was allowed to warm to 0°. This was followed by addition of water (50 ml) with subsequent addition of N NaOH (50 ml). The suspension was filtered through celite and the filtrate extracted with EtOAc. Usual work up followed by concentration under reduced pressure yielded **8** (7 g, 78% yield) containing less than 5% of alcohol **12** and pure enough for the following step. Chromatography of an aliquot on silica gel (hexane–EtOAc 2:1) gave an analytical sample of **8**: syrup $|\alpha|_D$ −53° (*c* 1, $CHCl_3$); IR (film) $\nu_{max}$: 2840, 1730 (CH=O) and 1375 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 4.31 (1H, m, 4-H); 4.23 (1H, d) and 3.83 (1H, d) (AB signal, J = 9, 2'-H); 4.12 (1H, dd)

† Alternatively the partial reduction of the amide derivative **22** (where the C-4 and C-5 OH groups are protected as their MTM ethers[19]) to the aldehyde **23** followed by condensation with leucoquinizarine gave the adduct **26** wherein the MTM groups could be selectively cleaved by reaction with HgO—$HgCl_2$[20] to lead to **25**.

and 3.59 (1H, dd) (ABX signal, J = 8, J' = 6, 5-H); 2.15 (1H, dd, J = 13.5 and J' = 9) and 1.84 (1H, dd, J' = 4) (ABX signal, 3-H), 1.46 (3H, s); 1.45 (3H, s); 1.35 (3H, s) and 1.32 (3H, s) (2 $CMe_2$). (Found: C, 57.00; H, 8.35; O, 34.84. Calc for $C_{12}H_{20}O_5$, 0.5 $H_2O$ (253.28): C, 56.91; H, 8.36; O, 34.72%).

(b) *Reduction at room temperature.* When the preceding procedure was carried out at room temp for 3 hr, **21** (927 mg) led to **8** (460 mg) and **12** (154 mg) which could be separated by chromatography on silica gel as described above. Spectroscopic data of **12** were identical in all respects with **12** as obtained from **11** (*vide supra*).

3-C-*Hydroxymethyl*-3,3' - O-*isopropylidene*-D-*glycero-tetrose* (**14**)

To a stirred soln of **11a** (21.6 g, 104.8 mmol) in MeOH (200 ml) was added dropwise a soln of sodium periodate (27 g, 106 mmol) in $H_2O$ (200 ml). After 1 hr, the mixture was poured into a sat $NaHCO_3$ aq and filtered. The insoluble material was washed with MeOH and then combined organic layers were evaporated under reduced pressure to *ca* 200 ml. Extraction with EtOAc and removal of the solvent under reduced pressure gave pure **14** as shown by TLC ($CH_2Cl_2$—MeOH, 95:5) (15.6 g, 86%) which crystallized out slowly under low temp: m.p. $<20°$; $|\alpha|_D + 18°$ (*c* 1, EtOH equil.); IR (film) $\nu_{max}$: 3410 (OH), 1730, 1725 (CH=O) and 1375 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 5.65 (1H, dd, J = 4, J' = 2) and 5.46 (1H, d, J = 4) (total 1H, 2-H); 4.10–3.78 (4H, m, 4'-H and 4-H); 2.28–2.00 (2H, m, 2-H); MS (E.I.): *m/z* 159 (M − 15, 100%), 143 (M − $CH_2OH$, 30) and 131 (M − $CH_2CHO$, 1.5). (Found: C, 55.32; H, 8.07, O, 36.70. Calc for $C_8H_{14}O_4$ (174.19): C, 55.16; H, 8.10; O, 36.74%).

1,4-*Dihydroxy*-2-(3(R),4-*dihydroxy*-3,3' - O-*isopropylidene*-3-*hydroxymethylbutyl*)-9,10-*anthraquinone* (**15**)

To a stirred soln of piperidine (120 ml) and iPrOH (150 ml) at 0° under an argon atm was added dropwise AcOH (36.5 ml). After 15 min were added successively, **14** (7 g, 40.2 mmol), iPrOH (50 ml) and a soln of leucoquinizarine (15.5 g, 64.25 mmol) in iPrOH (50 ml). The mixture was heated under reflux overnight and then, after being cooled to room temp, was oxidized by bubbling air through it for 30 min to 1 hr. The crude mixture was acidified by the addition of 1N HCl and the ppt was filtered and washed with water. The filtrate was extracted with $CH_2Cl_2$ in usual manner. After removal of the solvent under reduced pressure the crude residue was collected with the ppt to give after drying 15 g of **15**. A flash chromatography (hexane–$CH_2Cl_2$ 1:1, then pure $CH_2Cl_2$) afforded 12 g (75% yield) of homogeneous and crystalline **15**: m.p. 203–205° (acetone); $[\alpha]_D + 26°$ (*c* 0.1, $CHCl_3$); IR (Nujol) $\nu_{max}$: 3460 (OH), 1635 and 1600 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 400 MHz): 8.26 (2H, m) and 7.76 (2H, m) (AA'BB' signal, aromat. 4H); 7.10 (1H, s, 2-H); 3.87 (1H, d) and 3.76 (1H, d) (AB signal, J = 9, 3''-H); 3.67 (1H, d) and 3.61 (1H, d) (AB signal, J = 12, 4'-H); 2.79 (2H, m, 1'-H); 2.16 (1H, s, OH); 1.96 (2H, t, J = J' = 8.5, 2'-H); 1.49 (3H, s) and 1.46 (3H, s) ($CMe_2$); MS (E.I.): *m/z* 398 ($M^+$, 17%), 383 (M − 15, 10%), 340 (M-acetone, 5%), 309 (M − 89, 100%); (DCI/$NH_3$): *m/z*: 416 (M + 18) 399 (base peak, M + 1), 383, 341, 325 and 309. (Found: C, 66.43; H, 5.63; O, 28.22. Calc for $C_{22}H_{22}O_7$ (398.40): C, 66.32; H, 5.57; O, 28.11%).

4-[2-(1,4-*Dihydroxy*-9,10-*anthraquinyl*)]-2(R)-*hydroxy*-2-*hydroxymethyl*-2,2' O-*isopropylidene-butanal* (**16**)

(a) *Oxidation with* N-*chlorosuccinimide*-$Me_2S$[15]. To a stirred soln of N-chlorosuccinimide (1.5 g, 11.27 mmol) in anhyd toluene (25 ml) was added at 0° methylsulfide (1.1 ml, 15 mmol). A white ppt appeared while the mixture was cooled to −25° before adding a soln of **15** (1 g, 2.5 mmol) in 50 ml of a mixture of toluene–THF (1:1). After 2 hr a soln of $Et_3N$ (0.5 ml) in toluene (10 ml) was then added and the mixture was allowed to warm to room temp and stirred overnight. It was poured into water and extracted with ether. Usual work up followed by concentration under reduced pressure provided **16** pure enough for the next step. A flash chromatography (hexane–EtOAc 4:1) gave an analytical sample of crystalline **16**: m.p. 94–98°; $|\alpha|_D + 8°$ (*c* 0.1, acetone) and $+17°$ (*c* 0.1, dioxane); IR (Nujol) $\nu_{max}$ 1730 (CHO), 1625 and 1590 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 400 MHz): 8.23 (2H, m) and 7.75 (2H, m) (AA', BB' signal, aromat. 4H); 7.05 (1H, s, 3-H); 4.23 (1H, d) and 3.90 (1H, d) (AB signal, J = 9, 2''-H); 2.87 (1H, m) and 2.65 (1H, m) (ABXY signal, J = 14, J' = 12, J'' = 5, 4'-H); 2.15 (1H, m) and 1.98 (1H, m) (ABXY signal, J = 14; J' = 12, J'' = 5, 3'-H); 1.52 (3H, s) and 1.46 (3H, s) ($CMe_2$). (Found: C, 66.43; H, 5.20; O, 28.17. Calc for $C_{22}H_{20}O_7$ (396.38): C, 66.66; H, 5.09; O, 28.25%).

(b) *Oxidation according to Pfitzner-Moffatt method.*[16] To a soln of **15** (1g, 2.51 mmol) in a mixture of dry dimethylsulfoxide (30 ml) and anhyd toluene (100 ml) were successively added pyridine (0.4 ml, 4.9 mmol), trifluoroacetic acid (0.1 ml, 1.38 mmol) and DCCl (1.83, 8.88 mmol). The mixture was allowed to stir at room temp for 4 hr and the mixture was taken up in ether. Then usual work up followed by flash chromatography on silica gel (hexane–$CH_2Cl_2$ 1:1 then pure $CH_2Cl_2$) afforded pure crystalline **16** identical with the sample prepared by the precedent method, on the basis of analytical and spectral comparisons.

1,2,3,4,6,11-*Hexahydro*-2(R),1(R or S),5,12-*tetrahydroxy*-2-*hydroxymethyl*-2,13-O-*isopropylidene*-6,11-*naphthacene dione* (**17**)†

To a stirred soln of **16** (1.15 g, 2.9 mmol) in a mixture of MeOH–THF (200 ml, 1:1) at 0° was added under argon atm a soln of KOH (365 mg) and sodium dithionite (504 mg, 2.9 mmol) in water (25 ml). After stirring for 3 hr at 0°, the mixture was allowed to warm to room temp and oxidized by bubbling air through it for 30 min. After acidification with a 1N HCl (10 ml), usual work up followed by chromatography on silica gel ($CH_2Cl_2$ as eluant) gave **17** (690 mg, 60% yield). Examination by TLC using hexane–EtOAc as eluant (3:1) showed two spots corresponding to the C-1 isomers as confirmed by $^1$H-NMR spectrum in pyridine-$d_5$ at 270 MHz: 13.78 (broad signal, 2H, chelated OH); 8.35 (2H, m) and 7.73 (2H, m) (AA' and BB' signal aromat. 4H); 5.40 (s) and 5.36 (s) (total 1H, 1-H); 4.74 (d) and 4.17 (d), then 4.07 (d) and 3.87 (d) (AB signals, J = 9 Hz, 13-H); 3.25–3.03 and 2.94–2.68 (m, total 2H, 4-H); 2.09–1.87 (2H, m, 3-H); MS (DCI/$NH_3$): *m/z* 397 (M + 1 base peak), 381 (M − 15), 339 (M − 1 − 58) and 321 and 225. (Found: C, 66.55; H, 5.12; O, 28.37. Calc for $C_{22}H_{20}O_7$ (396.38): C, 66.66; H, 5.09; O, 28.25%).

1,2,3,4,6,11-*Hexahydro*-2(R),5,12-*trihydroxy*-2-*hydroxymethyl*-2,13-O-*isopropylidene*-6,11-*naphthacene dione* (**18**)

An ethanolic soln of **17** (30 mg into 10 ml) was stirred under $H_2$ atm in the presence of Pd on $BaSO_4$ 10% (20 mg) for 1 hr. The catalyst was removed by filtration and the filtrate was oxidized by bubbling air through it for 10 min. The solvent was then evaporated *in vacuo* and the residue was crystallized from acetone to give 25 mg of pure **18** (85% yield) m.p. 232–234°; $|\alpha|_D$ −52° (*c* 0.01, $CHCl_3$); IR ($CHCl_3$): $\nu_{max}$ 1625 and 1590 (chelated quinone), 1375 $cm^-$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 270 MHz): 13.42 (s) and 13.40 (s) (2 chelated OH); 8.32 (2H, m) and 7.81 (2H, m) (AA' and BB' signal, aromat. 4H); 3.89 (2H, s, 13-H), 3.05–2.81 (m, 4H, 1-H and 4-H), 2.17–2.04 (1H, m) and 1.86–1.70 (1H, m) (3-H); 1.43 (s, 3H) and 1.42 (s, 3H) ($CMe_2$); MS (DCI/$NH_3$) = *m/z* 398 (M + 18), 381 (M + 1, base peak), 323 (M + 1 − 58). (Found: C, 69.53; H, 5.27; O, 25.17. Calc for $C_{22}H_{20}O_6$ (380.38): C, 69.46; H, 5.30; O, 25.24%).

† Compounds **17–19**, **29–32** and **5** have been named by the anthracycline 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 on structure **17**.

1,2,3,4,6,11-*Hexahydro*-2(R),5,12-*trihydroxy*-2-*hydroxymethyl*-6,11-*naphthacene dione* (**19**)

(a) *From* **18**. To a stirred soln of **18** (90 mg, 2.6 mmol) in MeOH (20 ml) was added an N HCl soln (4 ml). After 4 hr the mixture was neutralized by filtration over 45 ($OH^-$) Amberlite ion-exchange resin and evaporated under reduced pressure to give 80 mg (98%) of pure crystalline **19**: m.p. 235–238°: $|\alpha|_D$ −32° (*c* 0.06, dioxane); IR (Nujol) $\nu_{max}$: 1625 and 1585 $cm^{-1}$ (chelated quinone): $^1$H-NMR (pyridine-$d_5$, 400 MHz): 8.39 (2H, m) and 7.75 (2H, m) (AA', BB' signal, aromat. 4H); 4.09 (2H, s, 13-H); 3.44 (1H, d) and 3.21 (1H, d) (AB signal, J = 19, 1-H); 3.39–3.11 (4H, m, 4-H and OH); 2.30 (1H, m) and 2.08 (1H, m) (3-H); MS (E.I): *m/z* 340 (M+, 6%); 322 (M − 18, 100%), 304 (M − 18 − 18, 20%), 291 (M − 31 − 18, 30%), 278 (25%); (DCI/$NH_3$): *m/z* 358 (M + 18, base peak), 341 (M + 1), 321 (M − 18), 309 (M − $CH_2OH$); $C_{19}H_{16}O_6$ requires *m/z* 340.332, measured 340.330.

(b) *From* **27**. A soln of NaOH (0.8 g) and sodium dithionite (1.5 g, 8.6 mmol) in water (10 ml) was added to a soln of **27** (2 g, 5.6 mmol) in THF (100 ml) and MeOH (100 ml) at room temp, under argon atm. After stirring for 2 hr, TLC examination of the soln ($CH_2Cl_2$–acetone 3:1) revealed the total disappearance of the starting material. Reoxydation by air for 30 min was followed by dropwise addition of 0.5N HCl (100 ml) at 0°. Extraction by EtOAc in usual work up and removal of the solvent under reduced pressure followed by flash chromatography purification ($CH_2Cl_2$–acetone 3:1, then 2:1) led to **19** (1.6 g, 80% yield) which had identical spectral data with those previously described (*vide supra*).

3-*Deoxy*-2-C-*hydroxymethyl*-2,2'-O-*isopropylidene*-N,N-*dimethyl*-D-*ribonamide* (**20**)

To a stirred soln of **10** (50 g, 25 mmol) in $CHCl_3$ (150 ml) was added dropwise at 0° a $CHCl_3$ soln of dimethylamine (100 ml into 500 ml of $CHCl_3$). The mixture was allowed to stand at room temp and was then stirred for 48 hr. TLC examination (hexane–acetone 1:1) revealed complete disappearance of starting material. Concentration *in vacuo* followed by flash chromatography on silica gel (hexane–acetone 2:1 then 1:1) afforded 39.5 g of pure **20** (65%): syrup $|\alpha|_D$ −27° (*c* 1, $CHCl_3$); IR (film) $\nu_{max}$: 1620 (amide), 1380 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 4.68 (1H, d) and 3.98 (1H, d) (AB signal, J = 9, 2'-H); 3.77 (1H, m, 4-H); 3.90 and 2.70 (2H, s, OH); 3.45 (1H, dd, J = 11.5 and J' = 6.5) and 3.55 (1H, dd, J' = 3.5) (ABX signal, 5-H); 3.27 (3H, s) and 2.95 (3H, s) $NMe_2$); 2.00 (1H, dd, J = 14.5 and J' = 10.5) and 1.89 (1H, dd, J' = 2) (ABX signal 3-H); 1.42 (3H, s) and 1.34 (3H, s) ($CMe_2$).

3-*Deoxy*-2-C-*hydroxymethyl*-2,2':4,5-*di*-O-*isopropylidene*-N,N-*dimethyl*-D-*ribonamide* (**21**)

To a soln of **20** (39 g, 158 mmol) in DMF (50 ml) were added 2,2-dimethoxypropane (130 ml) and camphorsulfonic acid (8 g, 34 mmol). After stirring overnight, the mixture was poured into sat of ice-cooled $NaHCO_3$ aq and after 15 min the soln was filtered to remove the insoluble materials and the filtrate was extracted with a mixture of ether–EtOAc (1:1) in a standard work up to afford **21** (41 g, 90% yield) as a syrup homogenous on TLC examination (hexane–acetone 1:1): $|\alpha|_D$ −30° (*c* 1, $CHCl_3$); IR (film) $\nu_{max}$: 1675 and 1630 (amide) and 1375 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 4.59 (1H, d) and 3.97 (1H, d) (AB signal, J = 9, 2'-H); 4.17 (1H, m, 4-H); 4.08 (1H, dd, J = 8 and J' = 5.5) and 3.48 (1H, dd, J' = 7.5) (ABX signal 5-H); 3.27 (3H, s) and 2.96 (3H, s) ($NMe_2$); 2.25 (1H, dd, J = 13, J' = 7) and 1.95 (1H, dd, J' = 5) (ABX signal 3-H); 1.45 (3H, s), 1.39 (3H, s), 1.35 (3H, s) and 1.34 (3H, s) (2 $CMe_2$), (Found: C, 58.65; H, 8.92; N, 4.77; O, 27.80. Calc for $C_{14}H_{25}NO_5$ (287.35): C, 58.51; H, 8.77; N, 4.87; O, 27.84%).

3-*Deoxy*-2-C-*hydroxymethyl*-2,2'-O-*isopropylidene*-4,5-*di*-O-*methylthiomethyl*-N,N-*dimethyl*-D-*ribonamide* (**22**)

To a stirred soln of **20** (6.5 g, 26.3 mmol) in DMSO (70 ml) were added at room temp, $Ac_2O$ (46.2 ml) and AcOH (14 ml). After 48 hr, the mixture was poured into a cold 20% $Na_2CO_3$ aq. Extraction with ether followed by flash chromatography (hexane–acetone 6:1, then 3:1) gave **22** (5 g, 52%): syrup: $|\alpha|_D$ +26.5° (*c* 1.38, $CHCl_3$); IR (film) $\nu_{max}$: 1630 (CO amide) and 1380 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 4.78–4.67 (4H, m, $2CH_2S$); 3.94 (2H, d, 2'-H); 3.79 (1H, m, 4-H); 3.63 (2H, d, J = 4.5, 5-H); 3.30 (3H, s) and 3.01 (3H, s) ($NMe_2$); 2.25 (3H, s) and 2.20 (3H, s) (2 SMe); 2.25–2.09 (2H, m, 3-H); 1.48 (3H, s) and 1.40 (3H, s) ($CMe_2$). (Found: C, 48.87; H, 8.01; O, 21.65. Calc for $C_{15}H_{29}O_5S_2N$ (367.49): C, 49.02; H, 7.95; O, 21.76%).

3-*Deoxy*-2-C-*hydroxymethyl*-2,2'-O-*isopropylidene*-4,5-O-*methylthiomethyl*-D-*ribose* (**23**)

To a suspension of LAH (0.3 g, 7.9 mmol) in ether (100 ml) at −40° was added a soln of **22** (2.5 g, 6.8 mmol) in ether with stirring. After 4 hr the mixture was hydrolyzed by the method of Fieser and Fieser.[21] Insoluble was removed by filtration and the filtrate was evaporated under reduced pressure to give **23** (2 g, 90% yield) as a syrup: $|\alpha|_D$ −61° (*c* 1.38, $CHCl_3$); IR (film) $\nu_{max}$: 1730 (CO) and 1380 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 4.71–4.62 (4H, m, $2CH_2S$); 4.18 (1H, d) and 3.82 (1H, d) (AB signal, J = 9, 2'-H); 4.04 (1H, m, 4-H); 3.63 (2H, m, 5-H); 2.19 (3H, s) and 2.15 (3H, s) (2 SMe); 2.28 (1H, m, J = 14; J' = 10.5) and 1.93 (1H, m, J' = 3.5) (ABX signal, 3-H); 1.47 (6H, s, $CMe_2$).

1,4-*Dihydroxy*-2-(1,3-*dideoxy*-2-C-*hydroxymethyl*-2,2':4,5-*di*-O-*isopropylidene*-D-*ribityl*)-9,10-*anthraquinone* (**24**)

To a stirred soln of piperidine (90 ml, 900 mmol) in iPrOH (450 ml) at 0° under argon atm were successively added, AcOH (59.8 ml, 1.02 mol), a soln of **8** (13.7 g, 56 mmol) in iPrOH (170 ml) and then a soln of **7** (13.5 g, 56 mmol) in iPrOH (170 ml). The mixture was warmed under reflux for 20 hr, cooled to room temp, aerated for 30 min and then added dropwise with stirring to aqueous 3M-HCl (180 ml) at 0°. A red-brown precipitate was obtained. This was filtered off and washed with water to give a red solid (26 g). This afforded the pure crystalline **24** (19.2 g, 75% yield) after flash chromatography (hexane–$CH_2Cl_2$ 8:1, then 4:1 and 2:1 as eluent). For analytical purpose, a sample was recrystallized from hexane–acetone: m.p. 130°; $|\alpha|_D$ −70° (*c* 0.15, dioxane); IR ($CHCl_3$) $\nu_{max}$ 1640 and 1600 (chelated quinone), 1385 $cm^{-1}$ ($CMe_2$); $^1$H-NMR ($CDCl_3$, 400 MHz): 13.58 (1H, s) and 12.88 (1H, s) (chelated OH); 8.35 (2H, m) and 7.84 (2H, m) (AA' BB' signal, aromat. 4H); 7.48 (1H, s, 3-H); 4.43 (1H, m, J = J' = 7.5, J'' = J''' = 5.5, 4'-H); 4.12 (1H, dd, J = 8, J' = 5.5) and 3.35 (1H, dd, J' = 7.5) (ABX signal, 5'-H); 3.97 (1H, d) and 3.95 (1H, d) (AB signal, J = 9.5, 2''-H); 3.26 (1H, d) and 3.11 (1H, d) (AB signal, J = 14, 1'-H); 1.90 (2H, m, 3'-H); 1.44 (3H, s), 1.40 (6H, s) and 1.26 (3H, s) (2 $CMe_2$); MS (E.I.) *m/z*: 468 (M+, traces), 411 (M − 58, 10%), 395 (M − 58 − 15, 15%), 253 (13%), 215 (35%) and 101 (100%); (DCI/$NH_3$): *m/z* 486 (M + 18), 469 (M + 1, base peak), 453, 428, 411 and 393. (Found: C, 66.75; H, 6.00; O, 27.43. Calc for $C_{26}H_{28}O_8$ (468.48): C, 66.65; H, 6.02; O, 27.32%).

1,4-*Dihydroxy*-2-(1,3-*dideoxy*-2-C-*hydroxymethyl*-D-*ribityl*)-9,10-*anthraquinone* (**6**)

To a stirred soln of the foregoing **24** (14.5 g, 30 mmol) in THF (250 ml) and MeOH (250 ml) was added an N HCl soln (500 ml) and the reactants heated at 70° for 3 hr. The soln was then concentrated under reduced pressure to *ca* 500 ml. A red ppt appeared and, before collecting it, water (250 ml) and crushed ice were added. After stirring for 15 min the precipitate was filtered off and air-dried to give the anthraquinone **6** (12 g, = 100%). A sample for analytical purpose was recrystallized from MeOH–acetone: m.p. 90–92°; $|\alpha|_D$ +12.5° (*c* 0.08, dioxane); IR (Nujol) $\nu_{max}$: 3350 (OH), 1640 and 1600 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CD_3OD$, 400 MHz): 8.29 (2H, m) and 7.87 (2H, m) (AA' BB' signal, aromat. 4H); 7.38 (1H, s, 3-H); 4.02 (1H, m, 4'-H); 3.56 ($A_2$ signal, 2''-H); 3.41 (2H, m, 5'-H); 3.17 (1H, d) and 2.81 (1H, d) (AB signal, J = 13.5, 1'-H); 1.80 (1H, dd, J = 15; J' = 2) and 1.53 (1H, dd, J' = 10) (ABX signal, 3'-H); MS (E.I.): *m/z* 388 (M+, traces), 370 (M − 18, traces), 321 (7%), 254 (100%); (DCI/$NH_3$): *m/z*: 389 (M + 1,

base peak), 373, 254, 238. (Found: C, 62.02; H, 5.17; O, 32.80. Calc for $C_{20}H_{20}O_8$ (388.27): C, 61.85; H, 5.18; O, 32.94%).

1,4-*Dihydroxy*-2(1,3-*dideoxy*-2-C-*hydroxymethyl*-2,2'-O-*isopropylidene*-D-*ribityl*)-9,10-*anthraquinone* (**25**)

(a) *Preparation from the di-isopropylidene derivative* **24**. A soln of **24** (4 g, 8.3 mmol) in AcOH (200 ml) was diluted with water (45 ml) and stirred for 1 hr at room temp. TLC examination (hexane–acetone, 2:1) revealed nearly complete disappearance of starting material and emergence of one new product corresponding to **25**. The reaction was quenched by careful addition of sat $NaHCO_3$ aq. Extraction with EtOAc followed by column chromatography on silica gel ($CH_2Cl_2$–MeOH 99:1) afforded successively starting material **24** (0.5 g, 12% yield) and **25** (3.5 g, 88% yield). For analytical purpose, a sample of **25** was recrystallized from acetone: m.p. 165–166°C, $|\alpha|_D + 60°$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$: 3620 (OH), 1625 and 1590 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 270 MHz): 13.42 (1H, s) and 12.69 (1H, s) (chelated OH phenoliques); 8.17 (2H, m) and 7.74 (2H, m) (AA' and BB' signal, aromat. 4H); 7.31 (1H, s, 3-H); 4.08 (1H, m, 4'-H); 4.00 (2H, s, 5'-H); 3.58 (1H, d) and 3.43 (1H, d) (AB signal, J = 11, H-2"); 3.16 (1H, d) and 2.99 (1H, d) (AB signal, J = 14, 1'-H); 1.76 (1H, m, 3'-H); 1.41 (3H, s) and 1.33 (3H, s) ($CMe_2$). MS (DCI/$NH_3$): *m/z*: 429 (M + 1, 100%), 371 (M + 1 − 58, 16%), 353 (M + 1 − 58 − 18, 17%). (Found: C, 64.59; H, 5.77; O, 29.97. Calc for $C_{23}H_{24}O_8$ (428.42): C, 64.48; H, 5.65; O, 29.88%).

(b) *Preparation from* **26**. To a soln of **26** (800 mg, 1.46 mmol) in a mixture of $CH_3CN$ (50 ml) and $H_2O$ (10 ml) were added $HgCl_2$ (2.3 g, 8 mmol) and yellow HgO (1.95 g, 7.4 mmol). The suspension was stirred overnight at room temp and then diluted with water. The mixture was filtered on celite and the filtrate extracted with a mixture of ether–EtOAc (2:1). The organic layer was washed with water, dried ($Na_2SO_4$) and evaporated *in vacuo* to give a crude product (800 mg) which was purified by flash chromatography (hexane–EtOAc 2:1). This led to 462 mg (74% yield) of pure **25**.

1,4-*Dihydroxy*-2-(2,2'-O-*isopropylidene*-4,5-*di*-O-*methylthiomethyl*-2-*hydroxymethyl*-*pentyl*)-9,10-*anthraquinone* (**26**)

Using the procedure described for the preparation of **24** (piperidinium acetate) and starting from **23**, **26** was obtained as a red-brown syrup (1.8 g, 50% yield) purified by flash chromatography (hexane–$CH_2Cl_2$ then $CH_2Cl_2$): $|\alpha|_D$ − 168° (*c* 0.09, THF); IR ($CHCl_3$) $\nu_{max}$: 1590 and 1625 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 400 MHz): 13.47 (1H, s) and 12.78 (1H, s) (chelated OH); 8.26 (2H, m) and 7.78 (2H, m) (AA' BB' signal, aromat. 4H); 7.40 (1H, s, 3-H) 4.81 (2H, s) and 4.63 (2H, s) (2 $CH_2S$); 4.19 (1H, m, 4'-H); 3.98 (1H, d) and 3.87 (1H, d) (AB signal, J = 8.5, 2"-H); 3.66 (1H, dd, J = 10.5; J' = 4) and 3.54 (1H, dd) (ABX signal, 5'-H); 3.24 (1H, d) and 3.10 (1H, d) (AB signal, J = 14, 1'-H); 2.26 (3H, s) and 2.3 (3H, s) (2 SMe); 1.94 (2H, d, J = 7, 3'-H); 1.37 (3H, s) and 1.24 (3H, s) ($CMe_2$).

4-(2-(1,4-*Dihydroxy*-9,10-*anthraquinonyl*))-3(S)-*hydroxy*-3-*hydroxymethyl butanal* (**27**)

To a stirred soln of **6** (2.4 g, 6.18 mmol) in THF (100 ml) and MeOH (100 ml) at room temp, were added a soln of sodium periodate (1.4 g, 6.5 mmol) in water (15 ml) and AcOH (8 ml). After 3 hr, the mixture was filtered and the filtrate was concentrated under reduced pressure to *ca* 50 ml. Extraction with EtOAc gave a syrup which solidified when re-evaporated twice with toluene (2 × 50 ml). Compound **27** (2.16 g, 98% yield) was pure enough for the following step but an analytical sample was obtained by crystallization from hexane–acetone m.p. 95–100°; $|\alpha|_D + 78°$ (*c* 0.05, dioxane); IR (Nujol) $\nu_{max}$ 3400 (OH), 1640 and 1600 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 400 MHz) (mixture of anomers): 8.33 (2H, m) and 7.85 (2H, m) (AA' BB' signal, aromat. 4H); 5.73 (1H, dd, J = 5, J' = 3.5) and 5.53 (1H, dd, J' = 1) (1'-H); 4.18–3.93 (2H, m, 3"-H); 3.78 (1H, d, OH); 3.23 (1H, s) and 3.14 (1H, s) ($A_2$ signal, 1'-H); 2.16 (1H, m) and 2.05 (1H, m) (2'-H); 1.69 (1H, s, OH). MS (E.I.): *m/z* 356 (M+, 5%), 338 (M − 18, 4%); 320 (M − 18 − 18, 50%), 312 (M–$CH_2CHO$, 30%), 253 (100%). (Found: C, 64.25; H, 4.50; O, 31.25. Calc for $C_{19}H_{16}O_7$ (356.32): C, 64.04; H, 4.53; O, 31.43%).

4-[2-(1,4-*Dihydroxy*-9,10-*anthraquinonyl*)]-3(S)-*hydroxy*-3-*hydroxymethyl*-3,3'-O-*isopropylidene*-*butanal* (**28**)

The derivative **25** (1.4 g, 3.27 mmol) was treated in a similar manner (100 ml MeOH, 50 ml THF, 14 g $IO_4Na$ (6.5 mmol), 15 ml $H_2O$ and 16 ml AcOH) to that used for the preparation of **27**. This gave **28** (1.3 g, quantitative) homogeneous on TLC (hexane–acetone, 2:1). For analytical purpose sample was recrystallized from hexane: m.p. 186–189°; $|\alpha|_D + 51°$ (*c* 0.07, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$: 1720 (CHO), 1625 and 1590 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 270 MHz): 13.24 (1H, s) and 12.64 (1H, s) (chelated OH); 9.65 (1H, s, CHO); 8.30 (2H, m) and 7.72 (2H, m) (AA' BB' signal, aromat. 4H); 7.18 (1H, s, 3-H); 4.10 (1H, d) and 3.97 (1H, d) (AB signal, J = 9, 3"-H); 3.21 (1H, d) and 2.99 (1H, d) (AB signal, J = 13, 4'-H); 2.85 (1H, d) and 2.58 (1H, d) (AB signal, J = 17, 2'-H); 1.40 (6H, s, $CMe_2$). MS (DCI/$NH_3$): *m/z*: 414 (M + 18, 2%), 397 (M + 1, 100%), 381 (M − 15, 20%), 356 (2%), 339 (M + 1 − 58, 15%), 323 (7%) and 321 (7%). (Found: C, 66.80; H, 5.12; O, 28.33. Calc for $C_{22}H_{20}O_7$ (396.38): C, 66.66; H, 5.09; O, 28.25%).

1,2,3,4,6,11-*Hexahydro*-1(R),3(S),5,12-*tetrahydroxy*-3-*hydroxymethyl*-6,11-*naphthacene dione* (**29**) *and its isomer* 1(S),3(S) (**5**)

Similar procedure as described (cf. preparation of **19** from **27** but at −10° and then at 0° for 1.5 hr after addition of the reactants) afforded crude product (840 mg from 1.2 g of **27**). As shown by TLC examination it was a mixture of two diastereoisomers which can be separated by chromatography on silica gel either directly, or after protection of the 13-C hydroxyl as a *p*-methoxytriphenyl ether (or *p*-anisyl). Direct chromatography (84 g silica gel) ($CH_2Cl_2$–MeOH, 999:1) allowed us to isolate first the *trans* derivative 1(R),3(S), **29** (82 mg), a mixture of **29** and **5** and then the corresponding *cis* derivative, 1(*S*),3(*S*), **5** (76 mg).

*Compound* **29**: m.p. 210–212°; $|\alpha|_D$ − 108° (*c* 0.05, THF); IR ($CHCl_3$) $\nu_{max}$: 3250 (OH), 1620 and 1590 $cm^{-1}$ (chelated quinone); $^1$H-NMR (pyridine-$d_5$, 400 MHz): 8.39 (2H, m) and 7.75 (2H, m) (AA' BB' signal aromat. 4H); 5.86 (1H, t, J = J' = 6, 1-H); 4.28 (1H, d) and 4.21 (1H, d) (AB signal, J = 10.5, 13-H); 3.60 (1H, d) and 3.39 (1H, d) (AB signal J = 18, 4-H); 2.77 (1H, m, J = 13.5, J' = 6, J" = 1, 2-H) and 2.67 (1H, dd, J' = 6.5, 2-H); MS (E.I.): *m/z* 356 (M+, 20%), 338 (M − 18, 27%), 320 (M − 18 − 18, 13%), 307 (M − 18 − 31, 100%) and 279 (32%). (Found: C, 64.16; H, 4.48; O, 31.50. Calc for $C_{19}H_{16}O_7$ (356.32): C, 64.04; H, 4.53; O, 31.43%).

*Compound* **5**: m.p. 230° $|\alpha|_D + 95°$ (*c* 0.05, THF); IR (*cf* **29**); $^1$H-NMR (pyridine-$d_5$, 400 MHz): 8.37 (2H, m) and 7.73 (2H, m) (AA' BB', signal aromat. 4H); 5.69 (1H, broad s, 1-H); 4.11 (1H, d) and 4.06 (1H, d) (AB syst. J = 11, 13-H); 3.67 (1H, dd, J = 18.5, J' = 2, 4-H) and 3.24 (1H, d, 4-H); 2.72 (1H, m, J = 14; J' = J" = 2, 2-H) and 2.30 (1H, dd, J = 14, J' = 4.5, 2-H). MS (E.I.): *m/z* 356 (M+, 55%), 338 (M − 18, 100%), 320 (M − 18 − 18, 68%), 307 (88%) and 279 (60%). (Found: C, 64.12; H, 4.55; O, 31.40. Calc for $C_{19}H_{16}O_7$ (356.52): C, 64.04; H, 4.53; O, 31.43%).

1,2,3,4,6,11-*Hexahydro*-1(R),3(S),5,12-*tetrahydroxy*-3-*hydroxymethyl*-13-p-*methoxytriphenylmethyl*-6,11-*naphthacene dione* (**30**) *and its isomer*-1(S),3(S) (**31**)

To a stirred soln of crude mixture of **29** and **5** (resulting from the Marschalk cyclization of **27**) (1 g, 2.8 mmol) in pyridine (10 ml) at −10° was added *p*-methoxytriphenylmethyl chloride (3.3 g, 11.3 mmol). After addition the mixture was allowed to warm at room temp for 24 hr. Dilution with MeOH (5 ml) was followed by stirring for 15 min, dilution with water and then extraction with $CH_2Cl_2$. Usual work up afforded a residue (1.1 g) which was chromatographed on 150 g of silica gel ($CH_2Cl_2$–MeOH 999/1). This allowed to isolate first the *trans* isomer **30** and then the *cis* isomer **31** in a 1:1 ratio.

*Compound* **30**: NMR ($CDCl_3$, 400 MHz): 8.28 (2H, m) and 7.80 (2H, m) (AA' BB' signal, aromat. 4H); 7.52 (2H, d, J = 9) and 6.82 (2H, d, J = 8) (AA' BB' signal, *p*-anisyl); 7.37–7.18 (10 H, m, Ar); 5.33 (1H, dd, J = 8, J' = 6.5, 1-H); 4.06 (1H, m, OH); 3.74 (3H, s, OMe anisyl); 3.27 (2H, s, 13-H); 2.92 (1H, d) and 2.81 (1H, d) (AB signal, J = 18, 4-H); 2.49 (1H, m, J = 14, J' = 6.5, J'' = 1.5) and 1.83 (1H, m) (2-H).

*Compound* **31**: NMR ($CDCl_3$, 400 MHz): 8.25 (2H, m) and 7.79 (2H, m) (AA' BB' signal, aromat. 4H); 7.50 (2H, d, J = 9) and 6.87 (2H, d, J = 9) (AA' BB' signal, *p*-anisyl); 7.47–7.15 (10H, m, Ar); 5.16 (1H, dd, J = 4, J' = 1, 1-H); 3.79 (3H, s, OMe anisyl); 3.24 (2H, s, 13-H); 2.70 (1H, d) and 2.32 (1H, d) (AB signal, J = 19, 4-H); 2.09–1.82 (2H, m, 2-H).

Due to their instability these compounds have not been more described but were hydrolyzed to give the corresponding anthracyclinones **29** and **5**.

1,2,3,4,6,11-*Hexahydro*-1(S),3(S),5,12-*tetrahydroxy*-3-*hydroxymethyl*-3,13-O-*isopropylidene*-6,11-*naphthacene dione* (**32**)

To a stirred soln of **28** (250 mg, 0.63 mmol) in THF (20 ml) and MeOH (20 ml) at −10° was added dropwise under argon atm NaOH aq (10 ml) (120 mg of Na; 3 mmol) and sodium dithionite (150 mg, 0.86 mmol). After 15 min the reaction was quenched at −10° by bubbling air through it for 5 min. Addition of N HCl aq dropwise until the purple mixture became yellow-brown was followed by dilution with water and extraction with EtOAc. This provided a crude crystalline product (240 mg) which was almost homogeneous on TLC examination (toluene–acetone, 95:5) ($R_f$ 0.25) while starting material ($R_f$ 0.47) was completely disappeared. This crude product was crystallized from THF–MeOH to give 185 mg (75% yield) of pure **32**: m.p. 270–274° $|\alpha|_D$ + 96° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$: 3500 (OH), 1625 and 1590 $cm^{-1}$ (chelated quinone); $^1$H-NMR ($CDCl_3$, 270 MHz): 13.32 (1H, s) and 13.12 (1H, s) (chelated OH); 8.17 (2H, m) and 7.72 (2H, m) (AA', BB' signal, aromat. 4H); 5.14 (1H, m, J = 10, J' = 5, J'' = 2, 1-H); 4.08 (1H, d, J = 10, OH); 3.96 (2H, s, 13-H); 3.21 (1H, dd, J = 18.5, J' = 1.5, 4-H) and 2.70 (1H, d, J = 18.5, 4-H); 2.43 (1H, m, J = 14, J' = 2, J'' = 1.5) and 1.98 (1H, dd, J' = 5) (ABX signal, 2-H); 1.48 (3H, s) and 1.43 (3H, s) ($CMe_2$); MS (DCI/$NH_3$): *m/z*: 414 (M + 18), 396 (base peak = M +), 379, 338 and 320; (DCI/$ND_3$): *m/z*: 421 ($M' + ND_4^+$), 401 (base peak = M' + D), 385, 370 and 325. (Found: C, 66.79; H, 5.15; O, 28.18. Calc for $C_{22}H_{20}O_7$ (396.38): C, 66.66; H, 5.09; O, 28.25%).

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