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ANTHRACYCLINONES. PART VIII.[1] SYNTHESIS OF A 9-METHYL ANTHRACYCLINONE FROM D-GLUCOSE

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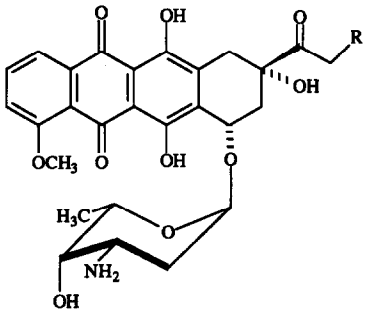
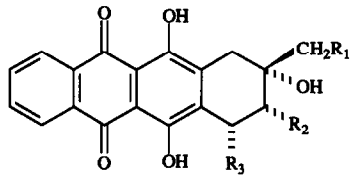
Abstract : The chiral pool synthesis of enantiomerically pure anthracyclinone **6** from leucoquinizarin **10**, and from 3-*O*-benzyl-1,2-*O*-isopropylidene-3-C-methyl-α-D-ribo-pentodialdo-1,4-furanose (**9**) readily obtained from diacetone glucose, is reported.

The clinical efficacy of daunorubicin (or daunomycin) **1** and doxorubicin (or adriamycin) **2** as antitumor agents[2] has motivated the search for new anthracyclines devoid of their well-known cumulative dose-dependent cardiotoxicity.[3] Although a large number of studies have been directed toward the synthesis of aglycones closely related to daunomycinone, only a limited number of asymmetric syntheses have been reported.[4] For our part, we have been engaged in a broad program to develop the chiral pool synthesis of new aglycone moieties and, as a result, aglycones **3** and **4** were obtained from α-D-isosaccharinolactone[1,5] and, more recently, aglycones **5** and **6** from α-D-glucosaccharino-1,4- lactone.[6]



1 R = H

2 R = OH

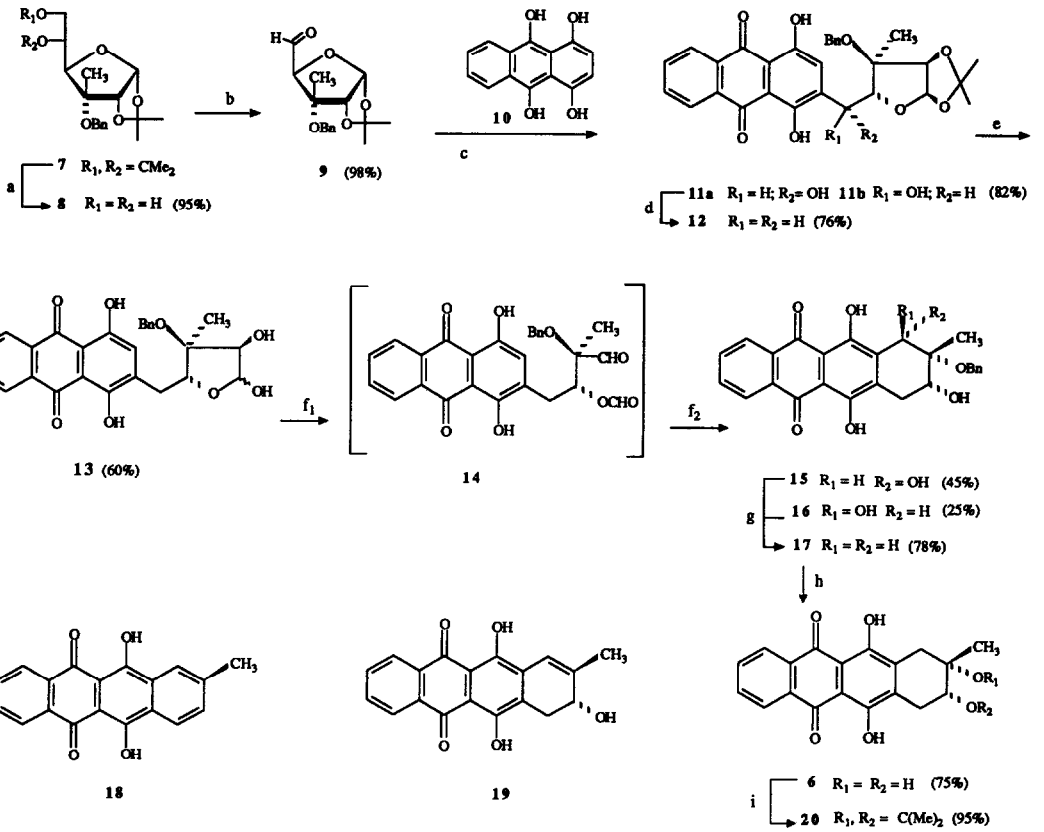


	R_1	R_2	R_3
3	OH	H	OH
4	H	H	OH
5	H	OH	OH
6	H	OH	H

**Dedicated to Professor Gabor Fodor on the occasion of his 75th birthday

Recent reports have shown that 9-alkyl anthracyclines[7] and in particular, 9-alkyl anthracyclines combined with a 3'-morpholino-3'-deamino daunosaminyl (or 2,3,6-trideoxy-3-morpholino-L-*lyxo*-hexopyranosyl) moiety exhibit high antitumor activity even against a number of doxorubicin-resistant cell lines.[8] This has prompted us to search for a versatile synthon for the synthesis of various 9-alkyl aglycones. Commercially available diacetone glucose seemed to be the most suitable and in this paper [9] we report in detail the synthesis of the 9-methyl anthracyclinone **6** from **7**.

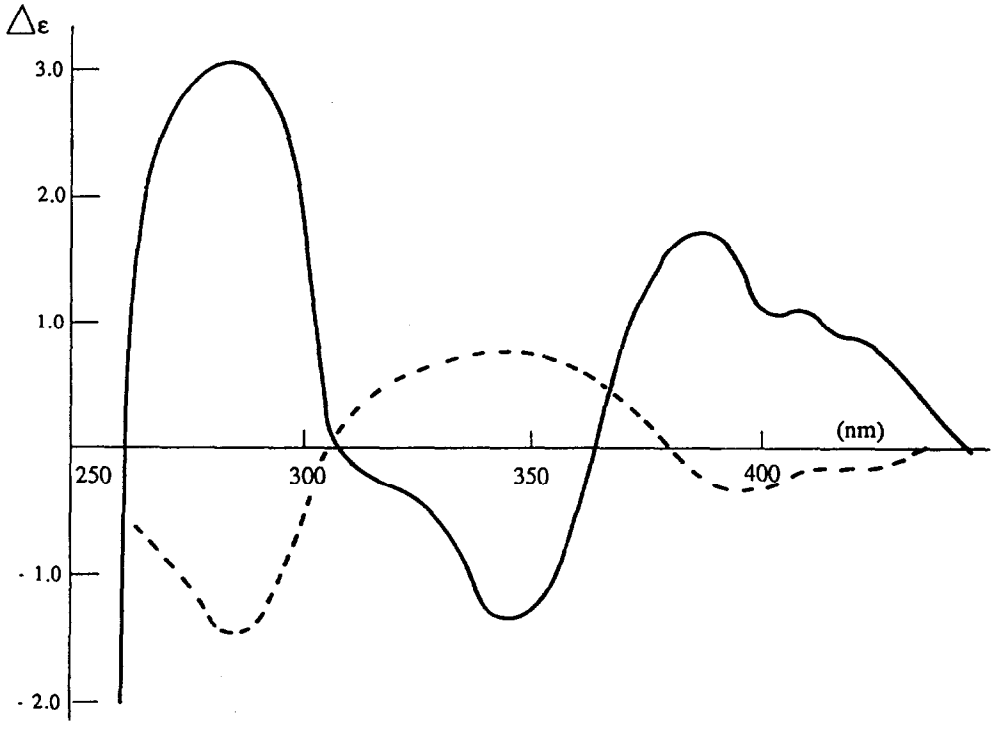
The starting material, 3-*O*-benzyl-3-C-methyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **7** was readily obtained from diacetone-glucose according to Brimacombe *et al*[10] and Funabashi *et al*.[11] This branched -chain sugar was then converted (Scheme 1) into the corresponding mono-isopropylidene derivative **8**,



Reagents and conditions. (a) aq. 75% AcOH, H_2O, r.t., 18 h (b) $NaIO_4$, H_2O,MeOH, r.t. 15h (c) DBU, DMF, r.t. 5 min (d) $Na_2S_2O_4$, DMF, 80°C, H_2O, 30 min (e) 75% AcOH, reflux, 10 h (f) 1/ $NaIO_4$, H_2O, THF, 3 h 2/ MeOH, THF, KOH,$Na_2S_2O_4$,r.t., 12 h (g) $Na_2S_2O_4$, H_2O, 30 min (h) BBr_3, CH_2Cl_2, - 78°C, 1h --> r.t. 1h (i)α,α - Dimethoxypropane, CSA, DMF, r.t., 18h.

SCHEME 1.

using 75% aqueous acetic acid. The aldehyde **9** was subsequently prepared by treatment of **8** with sodium metaperiodate. On reacting **9** with leucoquinizarin **10** under Shaw conditions[12] (DBU in DMF), the alkylanthraquinone **11** was isolated in 82% yield as a mixture of diastereoisomers in a 1.5:1 ratio as determined by NMR spectroscopy. Both diastereoisomers **11a** and **11b** could be isolated as pure compounds by column chromatography with toluene-acetone (98:2) as eluent and the C-5 configuration of these diastereoisomers was assigned by comparison with literature data.[13] Removal of the benzylic OH was achieved on heating **11** in dry DMF in the presence of sodium dithionite to give **12** in 76% yield. Alternatively, alkylanthraquinone **12** could be readily prepared in 61% yield by condensation of **9** with leucoquinizarin under Lewis conditions[14] (piperidinium acetate for 24 h at room temperature). Conversion of **12** into the corresponding diol **13** was carried out (60% yield) by treatment with 75% aqueous acetic acid. Intermediate **13** was subsequently converted to a mixture of **15** (45%) and **16** (25%) of (10S) and (10R) configuration, respectively, by the following sequence of reactions: sodium metaperiodate cleavage, alkaline deformylation of the intermediate species and, intramolecular aldolisation under Marschalk conditions[15] (KOH and sodium dithionite). Configurations at C-10 were deduced from examination of the CD spectra of **15** and **16**. Thus, the 10R configuration of **16** was unequivocally assigned by comparison of its CD curve with the curve of γ-rhodomycinone[16] as shown in Figure 2. The almost opposite CD curve obtained for **15** correlated with the corresponding S configuration at C-10.[1]



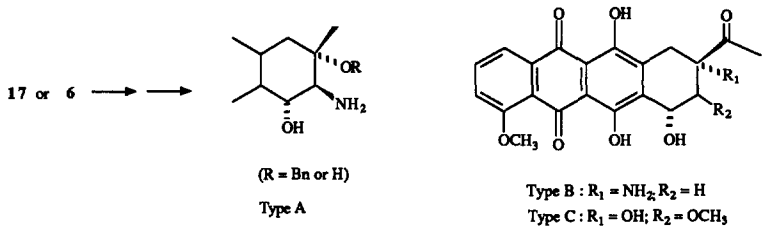
— **15** - - - **16**

Figure 2

Circular dichroism of compounds **15** and **16**

Benzylic deoxygenation of both diastereoisomers using sodium dithionite in THF gave **17** in only 30% yield along with the formation of side-products including fully aromatized **18** (20%) and unsaturated compound **19** (30%) . Better results were observed when DMF was used as the solvent. Under these conditions **17** was isolated in 78% yield with only a small amount of **19** (15%). Treatment of **17** with boron tribromide in dichloromethane at -78°C provided the anthracyclinone **6** (75%) whereas further treatment with α,α-dimethoxypropane in the presence of camphorsulfonic acid gave **20** (72%). Compounds **6** and **20** were fully correlated (m.p., $[\alpha]_D$ and spectral data) with the (-)-(8R,9S)-7,8,9,10-tetrahydro-6,8,9,11-tetrahydroxy-9-methyl-5,12-naphthacene quinone and its corresponding isopropylidene derivative, respectively, already obtained[6] from glucosaccharino-1,4-lactone.[17].

Having thus secured the stereochemical identity of aglycon **6**, several options were considered for the manipulation of the 8-OH group *en route* to the required (8R,9S) intermediate aglycon (scheme 2), bearing a 9-amino function (type A). This compound bears a direct relation to the two aglycons of highly antitumor anthracyclines, 9-amino-9-deoxy daunomycinone[18] (type B), and (8S)-methoxy daunomycinone[19](type C). This will be reported later on.



SCHEME 2

EXPERIMENTAL SECTION

Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer Model 1710 and ^1H NMR spectra on a spectrophotometer Bruker (270MHz) using TMS as an internal standard. Mass spectra were registered on a Nermag R10.10C (DCI/NH_3) spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter and circular dichroism with a Jobin-Yvon Mark V apparatus. Flash chromatographies[20] were performed on Merck silica gel 60 (Art. 9385). Elemental analyses were carried out at the "Service Central de Micronanalyse du CNRS".

3-O-Benzyl-3-C-methyl-1,2-O-isopropylidene-α-D-allofuranose (8).

Branched-chain sugar **7**[11] (800 mg, 2.2 mmol) was stirred overnight in aqueous acetic acid (75%, 20 mL). After evaporation under reduced pressure, followed by co-evaporations with toluene (2x 20 mL), a flash-chromatography with hexane-acetone (2:1) as eluent gave **8** (680 mg, 95%) as a crystalline compound mp 117°C (lit.[10] mp 119-120°C from EtOH); $[\alpha]_D^{20}$ + 44° (c 1, chloroform); IR ($CHCl_3$): ν 3500 and 1380cm^{-1}; ^1H-NMR δ 7.36-7.31 (m, 5H, CH_2Bn), 5.75 (d, 1H, J=3.5 Hz, 1-H), 4.70 and 4.60 (2d, 2x1H,

CH_2Bn), 4.30 (d, 1H, J=3.5Hz, 2-H), 4.04 (d, 1H, J=8.5Hz, 4-H), 3.89-3.73 (m, 2H, 6-H), 3.73-3.61 (m, 1H, 5-H), 2.74 and 2.15 (2s, 2x1H, 2 OH), 1.56, 1.40 and 1.25 (3s, 3x3H, Me and CMe_2); MS (DCI/NH_3): *m/z* 342 $[M+ NH_4]^+$, 325 $[M+ H]^+$, 284 $[M+ NH_4- 58]^+$, 267 $[M+H -58]^+$, 91.

3-O-Benzyl-1,2-O-isopropylidene-3-C-methyl-α-D-ribopentodialdo-1,4-furanose (9).

To a methanolic solution of **8** (500 mg, 1.54 mmol in 10 mL), an aqueous solution of sodium metaperiodate (363 mg, 1.69 mmol in 10 mL) was added dropwise. After stirring at room temperature for 15 min, the mixture was filtered and the filtrate was extracted with EtOAc. Usual work-up quantitatively afforded **9** (450 mg) as crystals mp 40°C (petroleum ether); lit.[12] mp 40°C; $[\alpha]_D^{20}$ + 71° (c 0.9, chloroform); IR ($CHCl_3$) 1740, 1600 and 1320cm^{-1}; ^{1}H-NMR δ 9.63 (s, 1H, CHO), 7.62-7.50 (m, 5H, CH_2Bn), 5.26 (d, 1H, J=4.5 Hz, 1-H), 4.61 (s, 2H, CH_2Bn), 4.36 (d, 1H, J=4.5Hz, 2-H), 1.60, 1.36 and 1.25 (3s, 3x3H, Me and CMe_2); MS (DCI/NH_3): *m/z* 310 $[M+ NH_4]^+$, 293 $[M+ H]^+$, 252 $[M+ NH_4- 58]^+$, 235 $[M+H -58]^+$, 143, 81.

(5R) and (5S) 3-O-benzyl-1,2-0-isopropylidene-3-C-methyl-5-(9',10'-dihydro-1',4'-dihydroxy-9',10'-dioxo -2'-anthryl)-α-D-ribofuranose (11a) and (11b).

Leucoquinizarin (91 mg, 0.37 mmol) and DBU (0.22 mL, 1.5 mmol) were added to a solution of **9** (100 mg, 0.34 mmol) in dry DMF (20 mL). After 5 min, the solution was reoxidized by bubbling air, diluted with dichloromethane, and 1N HCl was added dropwise until pH 2-3. Separation of the organic layer and usual work-up followed by flash chromatography of the residue with toluene-acetone as eluent (95:5) gave 150 mg of **10** (82%) as a mixture of diastereoisomers. Chromatography on silica gel with toluene-acetone (98:2) allowed to isolate small amounts of each diastereoisomer **11a** and **11b**, which could be characterized as follows:

Isomer 11a : mp 120-125°C (MeOH); litt.[12] mp 127°C; $[\alpha]_D^{20}$ - 256° (c 0.1, chloroform)[13] ; IR ($CHCl_3$): ν 3620, 1620 and 1590 cm^{-1}; ^{1}H-NMR: δ 13.49 and 12.89 (2s, 2x 1H, chelated phenols), 8.32 (m, 2H, Ar), 7.82 (m, 2H, Ar), 7.54 (s, 1H, Ar), 7.25-7.13 (m, 5H, CH_2Ph), 5.77 (d, 1H, J=3.5 Hz, 1-H), 5.32 (dd, 1H, J=8, J'=3 Hz, 5-H), 4.62 and 4.56 (2d, 2 x 1H, J=11 Hz, CH_2Ph), 4.39 (d, 1H, J=3.5Hz, 2-H), 4.38 (d, 1H, J=8 Hz, 4-H), 3.34 (d, 1H, J=3 Hz, OH), 1.58, 1.45 and 1.33 (3s, 3x3H, Me and CMe_2); MS (DCI/NH_3) *m/z* 550 $[M+ NH_4]^+$, 533 $[M+ H]^+$.

Analysis calcd. for $C_{30}H_{28}O_9$ C, 67.67; H, 5.30. Found C, 67.31; H, 5.36.

Isomer 11b : amorphous solid; $[\alpha]_D^{20}$ +160° (c 0.2, chloroform) [litt.[12]:mp 189°C]; IR ($CHCl_3$): cf. **11a**: ^{1}H-NMR δ 13.49 and 12.78 (2s, 2 x 1H, chelated phenols), 8.28 (m, 2H, Ar), 7.80 (m, 2H, Ar), 7.46 (s, 1H, Ar), 7.05-7.02 (m, 5H, CH_2Ph), 5.82 (d, 1H, J=3.5 Hz, 1-H), 5.27 (dd, 1H, J=5.5 Hz, 5-H), 4.52 and 4.45 (2d, 2 x 1H, J=11 Hz, CH_2Ph), 4.41 (d, 1H, J=5.5Hz, 4-H), 4.35 (d, 1H, J=3.5 Hz, 2-H), 3.04 (d, 1H, J=6 Hz, OH), 1.57, 1.42 and 1.34 (3s, 3x3H, Me and CMe_2); MS (DCI/NH_3): *m/z* 550 $[M+ NH_4]^+$, 533 $[M+ H]^+$, 492, 475, 310.

Analysis calcd. for $C_{30}H_{28}O_9$ C, 67.67; H, 5.30. Found C, 67.36; H, 5.40.

3-O-Benzyl-1,2-O-isopropylidene-3-C-methyl-5-deoxy-5-(quinizarin-2-yl)-α-D-ribofuranose (12).

1) From **11.** To a stirred solution of **11** (1.05 g, 1.97 mmol) in dry DMF (25 mL) heated at 80°C, sodium dithionite (500 mg, 2.87 mmol) in water (20 mL) was added under inert atmosphere. The red solution became immediately yellow-brown and, 30 min later, turned to red color. After dilution with water (20 mL), and

extraction with ether (200 mL), flash chromatography with toluene-acetone (95:5) as eluent afforded 740 mg (76%) of **12**which crystallized from acetone mp 88-89°C; $[\alpha]_D^{20}$ - 43° (c 0.18, chloroform); IR ($CHCl_3$): ν 1625, 1590 and 1375 cm^{-1}; ^{1}H-NMR: δ (13.89 and 12.87 (2s, 2x 1H, chelated phenols), 8.25 (m, 2H, Ar), 7.74 (m, 2H, Ar), 7.26 (m, 1H, Ar), 5.78 (d, 1H, J=3.8 Hz, 1-H), 4.67 and 4.60 (2d, 2x 1H, J=11Hz, $\underline{CH_2}$Bn), 4.47 (dd, 1H, J=10, J'=3.5Hz, 4-H), 4.38 (d, 1H, J=3.8 Hz, 2-H), 3.07 (dd, 1H, J=15, J'=3.5Hz, 5a-H), 2.81 (dd, 1H, J=15, J'=10, 5b-H), 1.59, 1.35 and 1.34 (3s, 3x3H, Me and CMe_2); MS (DCI/NH_3): *m/z* 534 $[M+ NH_4]^+$, 517 $[M+ H]^+$, 476, 459.
Analysis calcd. for $C_{30}H_{28}O_8$ C, 69.75; H, 5.46. Found C, 69.83; H, 5.21.

2) From **9** and leucoquinizarin To a degased solution of dry 2-propanol (50 mL), freshly distilled piperidine (18.8 mL, 190 mmol) and acetic acid (5.60 mL, 95 mmol) were added. The mixture was kept under argon atmosphere and cooled to 0°C. After 30 min, a solution of aldehyde **9** (1.77 g, 6.06 mmol) in propanol (40 mL), and a solution of leucoquinizarin (4.60 g, 18.8 mmol) in THF (10 mL) were added. The mixture was allowed to reach room temperature and then kept for 24h with stirring before reoxidation by bubbling air through it, dilution with dichloromethane and acidification by addition of 1N HCl. Separation of the organic layer followed by usual work-up afforded a residue (4g) and flash chromatography (toluene-acetone, 98:2) led to 1.74g (61%) of **12.**

3-O-Benzyl-3-C-methyl-5-deoxy-5-(quinizarin-2-yl)-α-D-ribofuranose (13).

A solution of the foregoing compound **12** (470 mg, 0.9 mmol) in 75% aqueous acetic acid (15 mL) was stirred for 10h under reflux. Evaporation of the solvent followed by co-evaporation with toluene (2x 10mL) afforded a red residue, and chromatography on silica gel (toluene-acetone, 95:5) gave **13** (260 mg, 60%) as an amorphous solid: $[\alpha]_D^{20}$ + 100° (c 0.2, THF, after equilibrium); IR ($CHCl_3$): ν 3500, 1624 and 1590cm^{-1}; ^{1}H-NMR (anomeric mixture): δ 13.53, 13.44, 13.43 and 12.88 (4s, total 2H, H-ar), 7.73 and 7.68 (m, total 2H, H-ar), 7.22 (m, 5H, Bn), 7.17 (s, 1H, Ar), 5.24 (m, 1H, 1-H), 4.70-4.33 (m, 3H, $\underline{CH_2}$Bn and 4-H), 4.06 (d, 1H, exch. D_2O, J=10Hz, OH), 3.74 (m, 1H, 2-H), 3.13 (dd, 1H, J=14, J'=4 Hz, 5a-H), 2.95 (d, 1H, exch. D_2O, J=4Hz, OH), 2.60 (dd, 1H, J=14, J'=10Hz, 5b-H), 1.53 and 1.26 (2s, total 3H, 5-CH_3); MS (DCI/NH_3): *m/z* 494 $[M+ NH_4]^+$, 476 $[M+ NH_4- H_2O]^+$, 459.

(8R,9R,10S)-9-O-Benzyl-7,8,9,10-tetrahydro-6,8,9,10,11-pentahydroxy-9-methyl-5, 12 naphthacenequinone (15) and its (8R,9R,10R)- diastereoisomer (16)

Sodium metaperiodate (3.12 g) in water (40 mL) was added to a solution of **13** (3.5 g, 7.35 mmol) in 60 mL of THF. After stirring for 3 h at room temperature, extraction with EtOAc (300 mL) and evaporation under reduced pressure afforded a crude residue which was dissolved in a mixture of MeOH and THF (7/1, 100 mL). Addition of an aqueous solution of KOH (1.52 g in 35 mL) was followed, after stirring for 30 min at room temperature, by addition of sodium dithionite (1.1 g, 6.32 mmol) in 17 mL of water. Stirring was maintained for 12 h at room temperature and for 30 min, after a new amount of sodium dithionite (1.1 g, 6.32 mmol) had been added. Subsequent addition of 1N NaOH (coloration becoming purple), reoxidation by bubbling air through the reaction mixture, neutralization with 1N HCl and extraction with EtOAc (3x 500 mL) led to 3 g of crude red residue. Chromatography on silica gel with toluene-acetone (90:10) gave successively **15** (1.64 g, 45%) and **16** (1.08 g, 25%).
Isomer 15 mp 252-254°C (MeOH); $[\alpha]_D^{20}$ - 210° (c 0.1, chloroform); ^{1}H-NMR: δ 13.68 and 13.40 (2s, 2 x 1H, chelated phenols), 8.36 (m, 2H, Ar), 7.82 (m, 2H, Ar), 7.52-7.35 (m, 5H, Ar), 5.22 (br s, J=1 Hz,

10-H), 4.98 and 4.82 (2d, 2 x 1H, J=10 Hz, $C\underline{H_2}Bn$), 4.35 (m, 1H, 8-H), 3.84 (d, 1H, J=10Hz, OH), 3.52 (dd, 1H, J=20, J'=3 Hz, 7a-H), 3.00 (dd, 1H, J=20, J'=5.5Hz, 7b-H), 1.30 (s, 3H, 9-CH_3); MS (DCI/NH_3): *m/z* 464 $[M+ NH_4]^+$, 447 $[M+ H]^+$, 429, 411.
Analysis calcd. for $C_{26}H_{22}O_7$ (446.19) C, 69.94; H, 4.96. Found C, 69.93; H, 5.16.
Isomer 16 mp 210-212°C (MeOH-THF); $[\alpha]_D^{20}$ - 32° (c 0.1, chloroform); ^{1}H-NMR: δ 13.80 and 13.30 (2s, 2 x 1H, chelated phenols), 8.35 (m, 2H, Ar), 7.82 (m, 2H, Ar), 7.25 (m, 5H, Ar), 5.32 (d, 1H, J=3 Hz, 10-H), 4.75 (s, 2H, $C\underline{H_2}Bn$), 4.22 (ddd, 1H, J=J'=7, J"=6Hz, 8-H), 3.50 (d, 1H, disp. D_2O, J=3Hz, 10-OH), 3.22 (dd, 1H, J=18, J'=6Hz, 7a-H), 3.05 (dd, 1H, J=18, J'=7Hz, 7b-H), 2.35 (d, 1H, disp. D_2O, J=7Hz, 8-OH), 1.30 (s, 3H, 9-CH_3); MS (DCI/NH_3): *m/z* 447 $[M+ H]^+$.
Analysis calcd. for $C_{22}H_{22}O_7$ C, 69.94; H, 4.96. Found C, 70.20; H, 5.19.

(8R,9S)-9-O-Benzyl-7,8,9,10-tetrahydro-6,8,9,10,11-pentahydroxy-9-methyl-5,12 naphthacene quinone (17).
a) By reduction of **15** (or **16**) with sodium dithionite in THF.

Compound **15** (or compound **16**) (100 mg, 0.22 mmol) was dissolved in dry THF (20 mL) in the presence of sodium dithionite (200 mg, 1.37 mmol) dissolved in water (25 mL). The mixture was stirred for 30 min, whereas bubbling of argon was maintained during the reaction. After work-up, flash chromatography with toluene, toluene-acetone (90:10) led to **18** (20 mg, 20%), **19** (30 mg, 30%), and to **17** (30 mg, 30%).

b) by reduction of **15** (or **16**) with sodium dithionite in DMF.

Compound **15** (or compound **16**) (400 mg, 0.89 mmol) was dissolved in dry DMF (30 mL) and treated as above with sodium dithionite (830 mg, 2.18 mmol) in water (15 mL). The mixture was treated as above and flash chromatography led to **19** (60 mg, 15%) then to **17** (300 mg,78%).
Compound 17 : mp 187-188°C (MeOH); $[\alpha]_D^{20}$ - 54° (c 0.12, chloroform) and - 32° (c 0.12, THF); IR ($CHCl_3$): ν 1623 and 1589cm^{-1}; ^{1}H-NMR: δ 13.45 and 13.32 (2s, 2 x 1H, chelated phenols), 8.30 (m, 2H, Ar), 7.79 (m, 2H, Ar), 7.25 (s, 5H, Ar), 4.68 (s, 2H, $C\underline{H_2}Bn$), 4.02 (dd, 1H, J=J'=4Hz, 8-H), 3.13 and 2.92 (2 dd, 2x 1H, J=18, J'=4Hz, 7-H), 3.08 and 2.96 (2d, 2x 1H, J=18Hz, 10-H), 1.30 (s, 3H, 9-CH_3); MS (DCI/NH_3): *m/z* 448 $[M+ NH_4]^+$, 431 $[M+ H]^+$, 430 $[M+ NH_4\text{-}H_2O]^+$.
Analysis calcd. for $C_{26}H_{22}O_6$ C, 72.52; H, 5.15. Found C, 72.72; H, 5.20.

9,10-Dihydro-6,8,11-trihydroxy-9-methyl-5,12-naphthacene dione (19) [21]

Amorphous solid; $[\alpha]_D^{20}$ - 137° (c 0.12, $CHCl_3$); IR (KBr): ν 1620 and 1585cm^{-1}; ^{1}H-NMR: δ 13.46 and 13.34 (2s, 2x 1H, chelated phenols), 8.28 (m, 2H, Ar), 7.83 (m, 2H, Ar), 6.85 (d, 1H, J=1Hz, 10-H), 4.67 (dd, 1H, 8-H), 3.42 (d, 1H) and 2.93 (d, 1H, CH_2-7), 2.10 (d, 3H, J=1Hz, 9-CH_3); MS (DIE): *m/z* 322 $[M^{+\cdot}$, 70%], 307 $[M^{+\cdot}$- 15, 50%), 304 $[M^{+\cdot}$-18, 55%], 279.
Analysis calcd. for $C_{19}H_{14}NO_5$ (322.32) C, 70.80; H, 4.37. Found C, 70.85; H, 4.30.

(8S,9R)-7,8,9,10-Tetrahydro-6,8,9,11-tetrahydroxy-9-methyl-5,12-naphthacene quinone (6)

A solution of **17** (760 mg, 1.76 mmol) in dry CH_2Cl_2 (300 mL) was treated at -78°C under N_2 with a solution of BBr_3 in CH_2Cl_2 (1M, 5.3 mL). The mixture, which became purple, was stirred for 1h at room temperature, treated with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. Usual work-up gave a crude residue (580 mg) and flash chromatography with toluene, and then toluene-acetone (70/30) provided 450 mg (75%) of

6 as a crystalline compound mp 254°C; $[\alpha]_D^{20}$ -18° (c 0.1, dioxane); [lit.[6] mp 255-257°C; $[\alpha]_D^{20}$ - 27° (C 0.14, dioxane)]; $[\alpha]_D^{20}$ - 20° (c 0.1, MeOH).

(8R,9S)-7,8,9,10-Tetrahydro-6,8,9,11-tetrahydroxy-8,9-O-isopropylidene-9-methyl-5,12-naphthacene quinone (20)

To a solution of **6** (50 mg, 0.14 mmol), in dry DMF (3 mL) were added α,α-dimethoxypropane (0.12 mL), and camphorsulfonic acid (5 mg) as catalyst. After stirring overnight at room temperature under inert atmosphere, extraction with ethyl acetate and neutralization with aqueous $NaHCO_3$, afforded 53 mg (95%) of **20**. Crystallization from MeOH gave mp 213-214°C; $[\alpha]_D^{20}$ +88° (c 0.1, chloroform); [Lit.[6] mp 210-213°C (MeOH); $[\alpha]_D^{20}$ +89° (c 0.25, chloroform)]; ^{1}H-NMR spectrum was in full agreement with that previously reported[6].

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Références and Notes:

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13. From sample provided by Prof. G. Shaw: $(\alpha)_D^{20}$ - 255° (c 0.2, $CHCl_3$); ^{1}H NMR superimposable.
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17. It is important to note that in the closely related synthesis reported by Shaw *et al.*[12] the configuration at C-8 and C-9 in compounds 19a-k given by these authors do not correspond to that determined by us for compounds **6** and **20**. The structures for compounds 19a-k may, therefore, require revision.
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