The Syntheses of (±)-Juglomycin A and (±)-Juglomycin B, Racemates of two Isomeric Naturally Occurring Naphthoquinonoid Antibiotics

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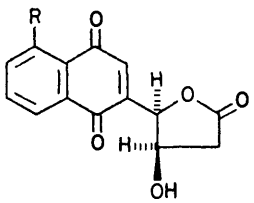
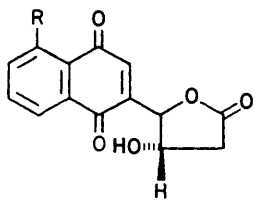
Syntheses of the diastereoisomeric 5-hydroxy-2-(4′-hydroxy-γ-butyrolacton-5′-yl)-1,4-naphthoquinones (1) and (2) and their 5-deoxy-analogues (3) and (4) are described. The stereochemistries of the latter, being defined through unambiguous synthesis, permit the assignment of the configurations of (1) and (2) (which were obtained from a single precursor) and also those of the natural products, juglomycins A and B.

THE juglomycins A and B have been isolated by a Japanese group from the culture filtrate of the fungus *Streptomyces* sp 190-2.[1] In preliminary trials these two compounds showed some inhibitory action against a variety of organisms. However, the relatively high toxicity and poor natural accessibility of these antibiotics favour the use of alternatives.

Two structures, (1) and (2), were put forward for the two juglomycins on the basis of their spectral data and chemical properties, which differed only in the diastereoisomeric nature of the γ-lactone groupings, but individual assignments were not made.[2] The lactone rings were attached to C-2 relative to the 5-OH of juglone, from biogenetic considerations and a comparison with the known structurally related kalafungin.[2,3]



(1) R = OH
(3) R = H
(16) R = OMe



(2) R = OH
(4) R = H

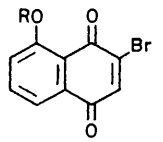
We wished to confirm these structures by synthesis, make relative individual configurational assignments for A and B, and clarify the anomalous appearance of the quinonoid proton in the published ^{1}H n.m.r. spectrum of juglomycin B.[2]

RESULTS AND DISCUSSION

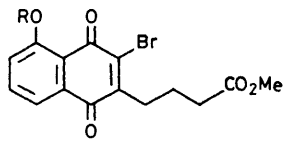
Preliminary syntheses of the 5-deoxy-juglomycins A and B [(3) and (4)] were undertaken [4] to (*a*) assess the feasibility of our proposed routes to, and (*b*) define the relative stereochemistry of, each of the lactone rings. Having established the stereochemistries for the model systems by unambiguous divergent routes, it was found more convenient for the natural products themselves to obtain both in a final step from a single precursor (16) and to identify the stereochemistry of each product by comparison with the appropriate model (3) or (4) (see below). Unfortunately neither of the natural samples was available for comparison with our synthetic materials.

Our proposed strategy essentially involved blocking the juglone nucleus at C-3 with bromine, which could readily be removed after appropriate alkylation at C-2 with a substituent which lent itself to subsequent elaboration to the lactone rings. Initially, 3-bromojuglone (5) [5] was converted to its *O*-methyl ether (6), but this resisted alkylation with monomethyl glutarate using the method of Jacobsen and Torssell.[6] However bromojuglone (5) itself underwent alkylation with this acid to afford the 2-(3-methoxycarbonylpropyl)quinone (7) in good yield. Attempts to regiospecifically alkylate juglone itself at C-2 gave rise to a mixture which was not further investigated.

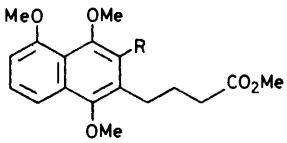
The quinone (7) was readily *O*-methylated with methyl iodide and silver(I) oxide to afford the corresponding product (8), the concomitant ^{1}H n.m.r. spectra showing the replacement of a one-proton singlet at δ 11.77 by a three-proton singlet at δ 4.00. This compound was reductively methylated using sodium dithionite followed by treatment with dimethyl sulphate to give the bromonaphthalene (9). Debromination was effected in a yield of 96% by catalytic hydrogenolysis over palladium–carbon in acetic acid, giving rise to product (10).



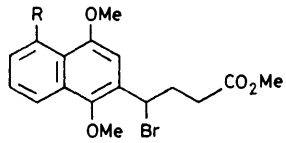
(5) R = H
(6) R = Me



(7) R = H
(8) R = Me



(9) R = Br
(10) R = H



(11) R = H
(12) R = OMe

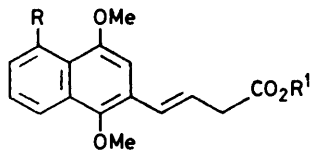
In the case of the syntheses of the model 5-deoxy-juglomycins (3) and (4), *N*-bromosuccinimide bromination of the 5-demethoxy-analogue of (10) [4,7] readily afforded the product (11) of benzylic bromination. Under the same conditions, however, the more electron-rich naphthalene (10) gave considerable quantities of

material brominated in the less substituted nucleus, as indicated in the ^{1}H n.m.r. spectra by the replacement of signals due to three adjacent protons by those due to two *ortho*-protons. Specific benzylic bromination was, however, achieved in a very much more dilute solution [8] to afford compound (12), the n.m.r. spectrum of which indicated retention of three adjacent aromatic protons, and a single benzylic proton at δ 5.62—5.82 as a multiplet coupled to its two diastereotopic neighbours. The product (12) was unstable and was therefore dehydrobrominated without further purification in boiling 2,6-lutidine to give only the *trans*-olefin (13) in an overall yield of 84% from its precursor (10). The stereochemistry of the double bond was given by the olefinic proton coupling constant of 16 Hz.

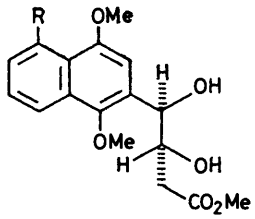
Treatment of the *trans*-olefin (13) with osmium tetraoxide in pyridine followed by work-up with sodium hydrogensulphite afforded the (1′*R*,2′*R*)-1′,2′-diol (14) (and its enantiomer),* which was converted directly into the γ-lactone (15) under acidic conditions with retention of stereochemistry at the asymmetric centres (see below). The naphthalene lactone (15) was oxidatively demethylated with silver(II) oxide using Rapoport's method [9] to give the quinonoid lactone (16). This was smoothly *O*-demethylated with aluminium chloride in methylene chloride to give a mixture of the diastereoisomers juglomycin A and juglomycin B [(1) and (2)], which were readily separated chromatographically. No doubt the mixture of juglomycins formed by reaction with aluminium chloride arose by way of an intermediate such as (17) (or the protonated equivalent), which would give rise to both products.

It remained to assign individual structures to the two products. This was possible from a comparison of the ^{1}H n.m.r. spectra of the natural [2] and synthetic materials in [$^2H_6$]dimethyl sulphoxide. One of the synthetic compounds afforded a spectrum identical with that reported for juglomycin A the lactone signals of these spectra also being virtually identical with those for the methyl ether (16) in the same solvent, and also with those of the model compound (3), prepared from bromide (11) by the related route (11) → (18) [7] → (19) → (20) → (3). Thus juglomycin A can be assigned structure (1). Structure (2) can therefore be adduced for juglomycin B, and this is supported by a comparison of the n.m.r. spectrum of the alternative synthetic isomer with that published [2] for juglomycin B. These were identical with the exception of two signals. As anticipated earlier, the quinonoid signal for the synthetic material (in [$^2H_6$]dimethyl sulphoxide) appeared as a sharp, allylic coupled (*J* 2 Hz) doublet at δ 6.70, rather than the very broad signal recorded at about the same chemical shift for the natural material. A similar broad signal at *ca.* δ 5.3 appeared in the synthetic compound as a sharp doublet (*J* 2 Hz) at δ 5.38. Otherwise, the lactone signals of synthetic and natural juglomycin B were virtually identical with those of the model (4).

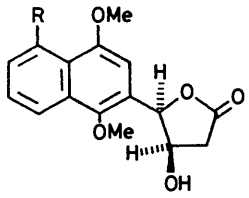
Quinone (4) was prepared by an alternative sequence [4] involving hydroxide-promoted hydrolysis of the ester (18) to the acid (21) (without isomerisation of the double bond), followed by reaction of this acid with both sodium hydrogencarbonate and *m*-chloroperbenzoic acid (either in water–acetonitrile, or in a two-phase water–methylene chloride system) to afford the lactone (22) of alternative stereochemistry. This cyclisation no doubt proceeded *via* the intermediate (23), in which the initially formed epoxide underwent intramolecular nucleophilic ring-opening by carboxylate. Oxidative demethylation [9] gave rise to quinone (4). Inspection of the ^{1}H n.m.r. spectra of the crude lactones (15), (20), and (22) showed each to be stereochemically pure. The lactone signals for (15) and (20) were very similar and readily distinguishable from those of (22).



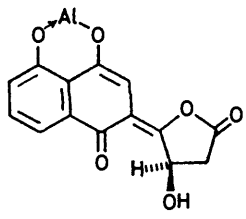
(13) R = OMe, R^1 = Me
(18) R = H, R^1 = Me
(21) R = R^1 = H



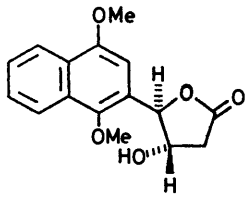
(14) R = OMe
(19) R = H



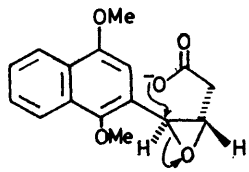
(15) R = OMe
(20) R = H



(17)



(22)



(23)

As the natural products were not available for direct comparison with synthetic material, it is not possible to confirm the structures of the former with total certainty. However, with the exception noted above, the u.v., i.r., ^{1}H n.m.r., and mass spectra of natural and synthetic materials were in very close agreement, and lend strong support to the gross structural assignments.[2] The syntheses of the racemates also achieved the objective of providing the relative stereochemistry of each of the natural products.

* All compounds capable of optical activity were prepared as their racemates.

EXPERIMENTAL

Unless otherwise stated, n.m.r. spectra were measured for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference, while i.r. spectra were measured for films (in the case of oils) or for solutions in chloroform (solids). Preparative layer chromatography was performed on glass plates coated with Merck Kieselgel 60 F 254, while column chromatography refers to dry-packed columns using the same gel (70—230 mesh). Light petroleum refers to the fraction of b.p. 60—80 °C. The phrase ' residue obtained upon work-up ' refers to the residue when the organic phase was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

3-Bromo-5-hydroxy-2-(3'-methoxycarbonylpropyl)-1,4-naphthoquinone (7).—A freshly prepared solution of ammonium peroxidisulphonate (7.0 g) in water (40 ml) was added dropwise during 65 min to a vigorously stirred solution of 3-bromojuglone (5) (2.0 g) in acetonitrile (100 ml) and water (100 ml) containing silver(I) nitrate (0.4 g) and monomethyl glutarate (1.4 g). During addition the bath temperature was maintained at 80 °C. The reaction mixture was cooled and extracted with methylene chloride. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate in light petroleum) to afford starting material (0.74 g, 37%). Later fractions gave rise to the orange *product* (1.32 g, 78% based on unrecovered starting material), m.p. 89—90 °C (ethanol) (Found: C, 50.8; H, 3.65. $C_{15}H_{13}BrO_5$ requires C, 51.0; H, 3.7%); $\nu_{max.}$ 1 730, 1 665, 1 640, and 1 590 cm^{-1}, δ 1.94 (2 H, quintet, *J* 7 Hz, 2'-CH_2), 2.48 (2 H, t, *J* 7 Hz, 3'-CH_2), 2.93 (2 H, t, *J* 7 Hz, 1'-CH_2), 3.71 (3 H, s, OMe), 7.20—7.40 (1 H, m, 6-H), 7.50—7.80 (2 H, m, 7- and 8-H), and 11.77 (1 H, s, OH).

3-Bromo-5-methoxy-2-(3'-methoxycarbonylpropyl)-1,4-naphthoquinone (8).—The quinone (7) (1.65 g) in chloroform (125 ml) containing anhydrous magnesium sulphate (1 g) and silver(I) oxide (1 g) was treated with methyl iodide (2 ml). Further quantities of the latter two reagents (1 g and 2 ml, respectively) were added at intervals of 6 h until t.l.c. showed the absence of starting material. The solution was filtered and the solvent evaporated to afford the *quinone* (1.58 g, 92%), m.p. 110.5—111.5 °C (methanol) (Found: C, 51.95; H, 4.1. $C_{16}H_{15}BrO_5$ requires C, 52.3; H, 4.1%); $\nu_{max.}$ 1 725, 1 665, 1 605, and 1 558 cm^{-1}; δ 1.91 (2 H, quintet, *J* 7 Hz, 2'-CH_2), 2.42 (2 H, t, *J* 7 Hz, 3'-CH_2), 2.82 (2 H, t, *J* 8 Hz, 1'-CH_2), 3.68 (3 H, s, CO_2Me), 4.00 (3 H, s, ArOMe), 7.20—7.40 (1 H, m, 6-H), and 7.55—7.80 (2 H, m, 7- and 8-H).

3-Bromo-1,4,5-trimethoxy-2-(3'-methoxycarbonylpropyl)-naphthalene (9).—The quinone (8) (1.38 g) was dissolved in a minimum of ether and shaken with an excess of aqueous sodium dithionite until the orange layer became colourless. The residue upon work-up was immediately dissolved in actone (100 ml) and anhydrous potassium carbonate (6 g) and dimethyl sulphate (10 ml) were added. The mixture was vigorously stirred under reflux for 2.5 h under nitrogen, then cooled, filtered, and the solvent evaporated. The residue was dissolved in ether and shaken successively with concentrated aqueous ammonia, water, dilute hydrochloric acid, and finally water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate in light petroleum) to afford the oily *product* (1.19 g) (80%) (Found: C, 53.9; H, 5.5. $C_{18}H_{21}BrO_5$ requires C, 54.4; H, 5.35%); $\nu_{max.}$ 1 730, 1 620, 1 597, and 1 580 cm^{-1}; δ 2.00 (2 H, quintet, *J* 7 Hz, 2'-CH_2), 2.46 (2 H, t, *J* 7 Hz, 3'-CH_2), 3.02 (2 H, t, *J* 7 Hz, 1'-CH_2), 3.68 (3 H, s, CO_2Me), 3.88 (6 H, s, 2 × ArOMe), 3.99 (3 H, s, ArOMe), 6.88 (1 H, d, *J* 8 Hz, 6-H), 7.42 (1 H, t, *J* 8 Hz, 7-H), and 7.64 (1 H, d, *J* 8 Hz, 8-H).

1,4,5-Trimethoxy-2-(3'-methoxycarbonylpropyl)naphthalene (10).—The bromonaphthalene (9) (1.80 g), dissolved in acetic acid (100 ml) containing sodium acetate (1.2 g) and a catalytic quantity of 10% palladium–carbon, was stirred at 45 °C (bath) under a hydrogen atmosphere until 1 mol equiv. of H_2 had been adsorbed, when t.l.c. (eluant 20% ethyl acetate in light petroleum) indicated complete conversion into a single product. The mixture was filtered, the solvent evaporated, and the residue chromatographed (eluant as above) to afford the oily *product* (1.38 g) (96%) (Found: C, 67.6; H, 6.95. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%); $\nu_{max.}$ 1 730, 1 615, 1 597, and 1 580 cm^{-1}; δ 2.02 (2 H, quintet, *J* 7 Hz, 2'-CH_2), 2.42 (2 H, t, *J* 8 Hz, 3'-CH_2), 2.82 (2 H, t, *J* 8 Hz, 1'-CH_2), 3.67 (3 H, s, CO_2Me), 3.83, 3.93, and 3.96 (3 H each, s, 3 × ArOMe), 6.65 (1 H, s, 3-H), 6.82 (1 H, d, *J* 8 Hz, 6-H), 7.58 (1 H, t, *J* 8 Hz, 7-H), and 7.65 (1 H, d, *J* 8 Hz, 8-H).

trans-*1,4,5-Trimethoxy-2-(3'-methoxycarbonylprop-1'-enyl)-naphthalene* (13).—The alkylnaphthalene (10) (500 mg), *N*-bromosuccinimide (340 mg), and di-t-butyl peroxide (6 ml) were dissolved in carbon tetrachloride (300 ml) and refluxed for 35 min. The volume of the solution was reduced under diminished pressure to *ca.* 50 ml, the solution filtered, and the solvent evaporated. The ^{1}H n.m.r. spectrum of the residue showed no starting material, but instead a product with δ 2.30—2.85 (4 H, m, 2'- and 3'-CH_2), 3.84 (3 H, s, CO_2Me), 3.94 (6 H, s, 2 × ArOMe), 3.98 (3 H, s, ArOMe), 5.62—5.82 (1 H, m, 1'-CH), 7.84 (1 H, d, *J* 8 Hz, 6-H), 7.88 (1 H, s, 3-H), 8.38 (1 H, t, *J* 8 Hz, 7-H), and 8.66 (1 H, d, *J* 8 Hz, 8-H). The residue was refluxed in lutidine (25 ml) for 1.5 h; the solution was then cooled, filtered, and the solvent evaporated. The residue was chromatographed (eluant 20% ethyl acetate in light petroleum) to afford the oily *product* (417 mg, 84%) (Found: C, 67.95; H, 6.25. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%); $\nu_{max.}$ 1 735 and 1 595 cm^{-1}; δ 3.36 (2 H, d, *J* 7 Hz, 3'-CH_2), 3.74 (3 H, s, CO_2Me), 3.84 (3 H, s, ArOMe), 3.96 (6 H, s, 2 × ArOMe), 6.42 (1 H, dt *J* 7 and 16 Hz, 2'-CH), 6.87 (1 H, d, *J* 8 Hz, 6-H), 6.94 (1 H, s, 3-H), 6.98 (1 H, d, *J* 16 Hz, 1'-CH), 7.40 (1 H, t, *J* 8 Hz, 7-H), and 7.70 (1 H, d, *J* 8 Hz, 8-H).

2-[(2'R,3'R)-3'-*Hydroxy-5'-oxotetrahydrofuran-2'-yl*]-*1,4,5-trimethoxynaphthalene* (15) *and its Enantiomer*.—The olefin ester (13) (370 mg) and osmium tetraoxide (300 mg) in dry pyridine (50 ml) were stirred at room temperature for 3 h. A solution of sodium hydrogensulphite (1.3 g) in water (20 ml) was then added and the solution stirred for a further 0.5 h. Further water was added and the solution washed with methylene chloride. An n.m.r. spectrum of the residue obtained upon work-up showed the virtually pure oily 2-(1',2'-dihydroxy-3'-methoxycarbonylpropyl)-1,4,5-trimethoxynaphthalene (14); δ 2.33 (1 H, dd, J_{gem} 17 and $J_{2',3'}$ 4 Hz, 3'-H), 2.56 (1 H, dd, J_{gem} 17, $J_{2',3'}$ 8 Hz, 3'-H), 3.28 br (2 H, s, 2 × OH), 3.62 (3 H, s, CO_2Me), 3.85 (3 H, s, ArOMe), 3.95 (6 H, s, 2 × ArOMe), 4.17 (1 H, dt, $J_{1',2'}$ 7.5, $J_{2',3'}$ 4, $J_{2',3''}$ 8 Hz, 2'-H), 5.05 (1 H, d, $J_{1',2'}$ 7.5 Hz, 1'-H), 6.86 (1 H, d, *J* 8 Hz, 6-H), 6.90 (1 H, s, 3-H), 7.38 (1 H, t, *J* 8 Hz, 7-H), and 7.62 (1 H, d, *J* 8 Hz, 8-H). The diol was dissolved in tetrahydrofuran (10 ml), concentrated hydrochloric acid (3 drops) was added, and the solution stirred overnight. Chloroform was added and the organic layer washed with water. The residue obtained upon work-up was chromato-

graphed (eluant 1% ethanol in methylene chloride) to give first the diol (14) (80 mg, 20%). Later fractions afforded the oily *lactone* (175 mg, 58% based on unrecovered diol) (Found: C, 63.8; H, 5.55. $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.7%); $\nu_{max.}$ 3 600, 1 780, 1 600, and 1 582 cm^{-1}; δ 1.90 (1 H, br s, OH), 2.71 (1 H, d, J_{gem} 17 Hz, 4'-H), 2.98 (1 H, dd, J_{gem} 17, $J_{4'.3'}$ 5 Hz, 4'-H), 3.90 (3 H, s, OMe), 3.97 (6 H, s, 2 × OMe), 4.86 (1 H, apparent t, $J_{4'.3'}$ 5, $J_{3'.2'}$ 4 Hz, 3'-H), 5.86 (1 H, d, $J_{3'.2'}$ 4 Hz, 2'-H), 6.91 (1 H, s, 3-H), 6.92 (1 H, d, J 8 Hz, 6-H), 7.44 (1 H, apparent t, J 8 and 9 Hz, 7-H), and 7.62 (1 H, d, J 9 Hz, 8-H).

2-[(2'R,3'R)-3'-*Hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-1,4-*dimethoxynaphthalene* (20) *and its Enantiomer*.—The olefin (18) [7] (65 mg) when treated as above with osmium tetraoxide (70 mg) afforded 2-(1',2'-dihydroxy-3'-methoxycarbonylpropyl)-1,4-dimethoxynaphthalene (19) as a clear oil (72 mg, 73%); $\nu_{max.}$ 3 460, 1 787, 1 635, and 1 602 cm^{-1}; δ 2.34 (1 H, dd, J_{gem} 17, $J_{2'.3'}$ 4 Hz, 3'-H), 2.58 (1 H, dd, J_{gem} 17, $J_{2'.3'}$ 8 Hz, 3'-H), 3.58 (3 H, s, CO_2Me), 3.65 (2 H, br s, 2 × OH), 3.88 (3 H, s, ArOMe), 3.96 (3 H, s, ArOMe), 4.21 (1 H, dt, $J_{1'.2'}$ 7.5, $J_{2'.3'}$ 4, $J_{2'.3'}$ 8 Hz, 2'-H), 5.08 (1 H, d, $J_{1'.2'}$ 7.5 Hz, 1'-H), 6.85 (1 H, s, 3-H), 7.3—7.6 (2 H, m, 6- and 7-H), 7.9—8.1 and 8.1—8.3 (1 H each, m, 5- and 8-H). The diol (62 mg) was cyclised as above, but with stirring for only 4 h, to give the *lactone* (20) (40 mg, 85% based on unrecovered diol) (Found: M^+, 288.099 160. $C_{16}H_{16}O_5$ requires M, 288.099 088); δ 2.00 br (1 H, s, OH), 2.66 (1 H, d, J_{gem} 17 Hz, 4'-H), 2.92 (1 H, dd, J_{gem} 17, $J_{4'.3'}$ 5 Hz, 4'-H), 3.90 (3 H, s, OMe), 3.98 (3 H, s, OMe), 4.80 (1 H, apparent t, $J_{4'.3'}$ 5, $J_{3'.2'}$ 4 Hz, 3'-H), 5.85 (1 H, d, $J_{3'.2'}$ 4 Hz, 2'-H), 6.86 (1 H, s, 3-H), 7.45—7.65 (2 H, m, 6- and 7-H), 7.9—8.1 and 8.2—8.35 (1 H each, m, 5- and 8-H).

2-[(2'R,3'R)-3'-*Hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-5-*methoxy*-1,4-*naphthoquinone* (16) *and its Enantiomer*.—The naphthalene lactone (15) in dioxan (10 ml) containing silver(II) oxide (450 mg) was treated at room temperature with nitric acid (6M, 1 ml). After stirring the mixture for 1.5 min, water (10 ml) and chloroform (40 ml) were added. The residue obtained upon work-up was chromatographed (eluant 1% ethanol in methylene chloride) to afford the *quinone* (180 mg, 69%), m.p. 187—188 °C (decomp.) (methylene chloride–light petroleum) (Found: C, 62.1; H, 4.35%; M^+ 288.062 34. $C_{15}H_{12}O_6$ requires C, 62.5; H, 4.2%; M, 288.063); $\nu_{max.}$ 1 794, 1 660, and 1 590 cm^{-1}; δ 2.64 (1 H, d, J_{gem} 17 Hz, 4'-H), 2.97 (1 H, dd, J_{gem} 17 and $J_{4'.3'}$ 5 Hz, 4'-H), 3.00 (1 H, br s, OH), 3.91 (3 H, s, OMe), 4.96 (1 H, apparent t, $J_{4'.3'}$ 5, $J_{3'.2'}$ 4 Hz, 3'-H), 5.47 (1 H, dd, $J_{3'.2'}$ 4, $J_{3,2'}$ 2 Hz, 2'-H), 6.80 (1 H, d, $J_{3.2'}$ 2 Hz, 3-H), 7.16 (1 H, dd, $J_{6.7}$ 9, $J_{6.8}$ 4 Hz, 6-H), and 7.40—7.70 (2 H, m, 7- and 8-H); δ ([$^2H_6$]DMSO) 2.39 (1 H, d, J_{gem} 17 Hz, 4'-H), 3.16 (1 H, dd, J_{gem} 17, $J_{4'.3'}$ 5 Hz, 4'-H), 3.94 (3 H, s, OMe), 4.65 (1 H, q, $J_{4'.3'} = J_{3'.2'} = J_{3'.OH}$ 5 Hz, 3'-H), 5.58 (1 H, d, $J_{3'.OH}$ 5 Hz, OH, D_2O exchangeable), 5.61 (1 H, dd, $J_{3'.2'}$ 5, $J_{3'.2'}$ 2 Hz, 2'-H), 6.62 (1 H, d, $J_{3.2'}$ 2 Hz, 3-H), 7.57 (1 H, d, J 9 Hz, 6-H), 7.65 (1 H, d, J 7 Hz, 8-H), and 7.84 (1 H, apparent t, $J_{6.7}$ 9, $J_{7.8}$ 7 Hz, 7-H).

5-*Hydroxy*-2-[(2'R,3'R)-3'-*hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-1,4-*naphthoquinone* (*Juglomycin A*) (1) *and* 5-*Hydroxy*-2-[(2'R,3'S)-3'-*hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-1,4-*naphthoquinone* (*Juglomycin B*) (2) *and their Enantiomers*.—The quinone methyl ether (16) (105 mg) in methylene chloride (5 ml) containing anhydrous aluminium trichloride (240 mg) was stirred at room temperature for 1.5 h. Water was added and the aqueous layer washed with ethyl acetate. The residue upon work-up was chromatographed (eluant 1% ethanol in methylene chloride) to afford juglomycin B (2) (20 mg, 20%), m.p. 168—169 °C (decomp.) (chloroform) (Found: M^+, 274.044 69. $C_{14}H_{10}O_6$ requires M, 274.044 72); $\lambda_{max.}$ (ethanol) 212, 249, and 415 nm; $\nu_{max.}$ 1 790, 1 643, and 1 616 cm^{-1}; $\nu_{max.}$ (KBr disc) 3 400, 1 780, 1 675, 1 645, and 1 625 cm^{-1}; δ ([$^2H_6$]DMSO) 2.29 (1 H, dd, J_{gem} 19, $J_{4'.3'}$ 2 Hz, 4'-H), 2.94 (1 H, dd, J_{gem} 19, $J_{4'.3'}$ 6 Hz, 4'-H), 4.42 (1 H, dt, $J_{4'.3'} = J_{3'.OH}$ 6, $J_{4'.3'}$ 2 Hz, 3'-H, gives dd on D_2O exchange), 5.38 (1 H, d, $J_{3.2'}$ 2 Hz, 2'-H), 6.02 (1 H, d, J 6 Hz, OH, D_2O exchangeable), 6.70 (1 H, d, $J_{3.2'}$ 2 Hz, 3-H), 7.37 (1 H, dd, $J_{6.7}$ 9, $J_{6.8}$ 2 Hz, 6-H), 7.57 (1 H, dd, $J_{7.8}$ 8, $J_{6.8}$ 2 Hz, 8-H), 7.79 (1 H, apparent t, $J_{6.7}$ 9, $J_{7.8}$ 8 Hz, 7-H), and 11.71 (1 H, s, OH). Later fractions afforded juglomycin A (1) (38 mg, 38%), m.p. 189 °C (decomp.) (acetone) (Found: C, 61.0; H, 4.0%; M^+, 274.047 38. $C_{14}H_{10}O_6$ requires C, 61.3; H, 3.7%; M, 274.047 72); $\lambda_{max.}$ (ethanol) 212, 249, and 415 nm; $\nu_{max.}$ (acetone) 1 790, 1 657, and 1 590 cm^{-1}; $\nu_{max.}$ (KBr disc) 3 420, 1 780, 1 670, 1 650, and 1 620 cm^{-1}; δ ([$^2H_6$]DMSO) 2.40 (1 H, d, J_{gem} 19 Hz, 4'-H), 3.16 (1 H, dd, J_{gem} 19, $J_{4'.3'}$ 5 Hz, 4'-H), 4.67 (1 H, q, $J_{4'.3'} = J_{3'.2'} = J_{3'.OH}$ 5 Hz, 3'-H, gives t on D_2O exchange), 5.53 (1 H, d, $J_{3'.OH}$, 5 Hz, D_2O exchangeable, OH), 5.65 (1 H, dd, $J_{3.2'}$ 3, $J_{3'.2'}$ 5 Hz, 2'-H), 6.80 (1 H, d, $J_{3.2'}$ 3 Hz, 3-H), 7.38 (1 H, dd, $J_{6.7}$ 9, $J_{6.8}$ 2 Hz, 6-H), 7.58 (1 H, dd, $J_{7.8}$ 8, $J_{6,8}$ 2 Hz, 8-H), 7.80 (1 H, apparent t, $J_{6.7}$ 9, $J_{7.8}$ 8 Hz, 7-H), and 11.76 (1 H, s, OH).

2-[(2'R,3'R)-3'-*Hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-1,4-*naphthoquinone* (3), *and its Enantiomer*.—The naphthalene dimethyl ether (20) (40 mg) was oxidatively demethylated as described for the synthesis of (16) above, to give the pale yellow *quinone* (3) (26 mg, 72%), m.p. 201—203 °C (decomp.) (ethyl acetate–light petroleum) (Found: M^+, 258.050 56. $C_{14}H_{10}O_5$ requires M, 258.052 81); $\nu_{max.}$ 3 460, 1 775, 1 728, and 1 664 cm^{-1}; δ ([$^2H_6$]DMSO) 2.42 (1 H, d, J_{gem} 18 Hz, 4'-H), 3.17 (1 H, dd, J_{gem} 18, $J_{4'.3'}$ 5 Hz, 4'-H), 4.68 (1 H, apparent q, $J_{4'.3'}$ 5, $J_{3'.2'} = J_{3'.OH}$ 4 Hz, 3'-H), 5.47 (1 H, d, J 4 Hz, OH, D_2O exchangeable), 5.66 (1 H, dd, $J_{3'.2'}$ 4, $J_{3,2'}$ 2 Hz, 2'-H), 6.77 (1 H, d, $J_{3.2'}$ 2 Hz, 3-H), and 6.8—7.2 (4 H, m, Ar-H).

trans-2-(3'-*Carboxyprop*-1'-*enyl*)-1,4-*dimethoxynaphthalene* (21).—The olefin ester (18) [7] (90 mg) was refluxed in 5% aqueous potassium hydroxide for 3 h. The cooled solution was washed with ether to remove any starting material (10 mg recovered) and then acidified with dilute hydrochloric acid. This solution was extracted with chloroform. The residue on work-up was purified by p.l.c. (eluant 2% ethanol in methylene chloride) to afford the *acid* (21) (70 mg, 92%) as white needles, m.p. 139—140 °C (methylene chloride–light petroleum) (Found: M^+, 272.105 330. $C_{16}H_{16}O_4$ requires M, 272.104 840); $\nu_{max.}$ 3 540—2 600, 1 712, and 1 598 cm^{-1}; δ 3.44 (2 H, d, J 7 Hz, CH_2), 3.90 and 4.03 (3 H each, s, OMe), 6.38 (1 H, dt, J 7 and 16 Hz, 2'-CH), 6.89 (1 H, s, 3-H), 7.06 (1 H, d, J 16 Hz, 1'-CH), 7.4—7.62 (2 H, m, 6- and 7-H), 8.0—8.3 (2 H, m, 5- and 8-H), and 8.70 (1 H, br s, OH).

2-[(2'R,3'S)-3'-*Hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-1,4-*dimethoxynaphthalene* (22) *and its Enantiomer*.—(*a*) The acid (21) (100 mg) in a mixture of acetonitrile (10 ml) and aqueous sodium hydrogencarbonate (0.5M, 10 ml) was treated with *m*-chloroperbenzoic acid (3 mol equiv.) in small portions. (Additions of peracid were made when starch–iodide tests indicated consumption of the previous portion.) The mixture was stirred for a further 4 h, then partitioned between chloroform and water. The residue upon work-up afforded the oily *lactone* (22) (54 mg, 50%), which was

purified by p.l.c. (eluant, methylene chloride) (Found: M^+, 288.099 160. $C_{16}H_{16}O_5$ requires M, 288.099 088); $\nu_{max.}$ 3 410, 1 780, 1 630, and 1 597 cm^{-1}, δ 2.69 (1 H, dd, J_{gem} 18, $J_{4',3'}$ 6 Hz, 4'-H), 3.00 (1 H, dd, J_{gem} 18, $J_{4',3'}$ 7 Hz, 4'-H), 3.14 (1 H, br s, OH), 3.94 and 3.96 (3 H each, s, OMe), 4.54 (1 H, deformed q, $J_{3',2'}$ 5.5, $J_{4',3'}$ 6, $J_{4',3'}$ 7 Hz, 3'-H), 5.71 (1 H, d, $J_{3',2'}$ 5.5 Hz, 2'-H), 6.64 (1 H, s, 3-H), 7.45—7.7 (2 H, m, 6- and 7-H), and 8.9—9.1 and 9.2—9.35 (1 H each, m, 5- and 8-H).

(*b*) The acid (21) (100 mg) in methylene chloride (10 ml) and aqueous sodium hydrogencarbonate (0.5M, 10 ml) was treated with *m*-chloroperbenzoic acid (100 mg, 85% peracid) in small portions as in (*a*) above. The mixture was stirred for a further 10 h at room temperature. More methylene chloride and water were added for partition and the organic layer was worked up to afford the lactone as in (*a*) (50 mg, 47%).

2-[(2'R,3'S)-3'-*Hydroxy*-5'-*oxotetrahydrofuran*-2'-*yl*]-1,4-*naphthoquinone* (4) *and its Enantiomer*.—The lactone (22) (80 mg) was oxidatively demethylated as for the syntheses of (16) and (3) above to give the *quinone* (4) (57 mg, 80%), m.p. 166—168 °C (decomp.) (methylene chloride–light petroleum) (Found: M^+, 258.053 110. $C_{14}H_{10}O_5$ requires M, 258.052 810); $\nu_{max.}$ 3 325, 1 788, 1 728, 1 667, and 1 600 cm^{-1}; δ ([$^2H_6$]DMSO) 2.33 (1 H, dd, J_{gem} 18, $J_{4',3'}$ 2 Hz, 4'-H), 2.97 (1 H, dd, J_{gem} 18, $J_{4',3'}$ 6 Hz, 4'-H), 4.47 (1 H, dt, $J_{4',3'}$ 2, $J_{4',3'} = J_{3',OH}$ 6 Hz, 3'-H), 5.42 (1 H, d, $J_{3,2'}$ 2 Hz, 2'-H), 6.02 (1 H, d, $J_{3',OH}$ 6 Hz, OH), 6.72 (1 H, d, $J_{3,2'}$ 2 Hz, 3-H), and 7.7—8.3 (4 H, m, Ar-H).

Financial support from the Council of the University of Cape Town and the Council for Scientific and Industrial Research is gratefully acknowledged.

[0/1975 *Received*, 23*rd December*, 1980]

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