Formal Synthesis of the Juglomycins

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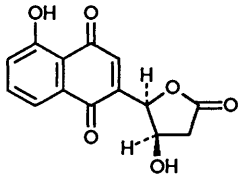
5'-Deoxyjuglomycin A **3** and 5'-methoxyjuglomycin A **4** have been synthesized *via* oxidative fragmentation of furo[3,2-*b*]naphtho[2,1-*d*]furans **9** and **10** respectively. Addition of 2-trimethylsiloxyfuran **5** to naphthoquinone sulfides **7**, **8** afforded the key adducts **9**, **10** which then underwent fragmentation to the quinone sulfides **11**, **14** using ceric ammonium nitrate. Treatment of the trimethylsilyl derivatives **13**, **15** of the sulfides **11**, **14** with *meta*-chloroperoxybenzoic acid effected conversion into the sulfoxides **16**, **18** which then underwent smooth desulfurization using tributyltin hydride to the quinones **21**, **23**. Finally, hydrolysis of the trimethylsilyl group completed the synthesis of 5'-deoxyjuglomycin A **3** and 5'-methoxyjuglomycin A **4**.

Juglomycins A **1** and B **2**, isolated from the culture filtrate of the fungus *Streptomyces sp.* 190-2, exhibit inhibitory activity



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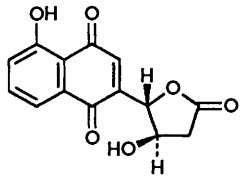

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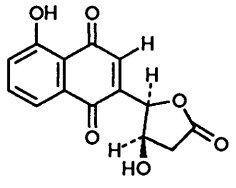
against a variety of organisms[1] and it has been proposed that they also act as bioreductive alkylating agents.[2] Subsequent determination of the structures of the dibromo derivatives of the juglomycins by X-ray crystallography[3] confirmed the individual configurational assignments of the hydroxy group on the lactone ring to be as depicted. The poor natural accessibility of these antibiotics prompted their synthesis which, hitherto, had only been *via* cyclization of a diol ester.[4] We now report the full details[5] of our synthesis of 5'-deoxyjuglomycin A **3** and 5'-methoxyjuglomycin A **4**, the latter representing a formal synthesis of juglomycins A **1** and B **2**.[4]



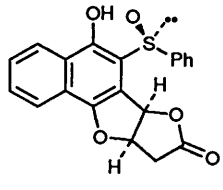
3 R = H
4 R = OMe

Our approach to the juglomycin ring system hinged on a ceric ammonium nitrate (CAN) oxidative cleavage of a furo[3,2-*b*]naphtho[2,1-*d*]furan (Scheme 1). Initial construction of the furo[3,2-*b*]naphtho[2,1-*d*]furan ring system has previously been reported[6,7] *via* the addition of 2-trimethylsiloxyfuran to a naphthoquinone bearing an acetyl substituent and was a key step in the synthesis of the pyranonaphthoquinone antibiotics kalafungin and frenolicin.[6,7]

The direct approach to the present target using this methodology hinged on the addition of 2-trimethylsiloxyfuran **5** to the naphthoquinone **6**. This approach proved fruitless in that the desired furofuran annulation did not occur in this case. Thus, it was envisaged that a substituent at C-3 on the naphthoquinone ring was required that would encourage formation of the furo[3,2-*b*]naphtho[2,1-*d*]furan ring system but could also be reductively removed either before or after the ceric ammonium nitrate step. In view of the fact that phenyl sulfides can be readily replaced by hydrogen using Raney nickel our synthesis therefore turned to the addition of 2-trimethylsiloxyfuran to naphthoquinones bearing a phenylsulfanyl group at C-3.

The ready availability[8] of the naphthoquinone **7** which lacks a methoxy group at C-5, focused our attention initially on the synthesis of 5'-deoxyjuglomycin **3** in order to test the feasibility of our synthetic route. Thus, addition of 2-trimethylsiloxyfuran **5** to naphthoquinone sulfide **7**[8] in acetonitrile afforded the furofuran adduct **9** in 51% yield.

At this point, removal of the phenylsulfanyl group could either precede or follow the oxidative opening to the naphthoquinone. Attempts to remove the sulfide reductively using Raney nickel lead to hydrogenolysis of the benzylic C–O bond; hence, oxidation of the sulfide **9** to the sulfoxide was considered as an alternative method to remove the substituent. Treatment of the sulfide **9** with *m*-chloroperoxybenzoic acid (MCPBA) afforded a 1:1 mixture of sulfoxides **25** and **26** in



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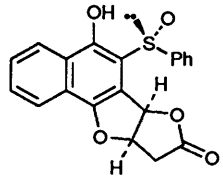

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85% yield which were separable by flash chromatography. Individual treatment of both sulfoxide isomers with Raney nickel, Mg–MeOH, Al–Hg or Na–Hg amalgams led to fragmentation of the furofuran system, and thus it was decided to effect the oxidation step before removal of the sulfur substituent.

Treatment of the sulfide **9** with ceric ammonium nitrate afforded the quinone **11** in 77% yield. Fragmentation of the central tetrahydrofuran ring was indicated in the ^{1}H NMR spectrum by the significant shift of the bridgehead proton 9a-H resonating at δ 5.68 in the starting furo[3,2-*b*]naphtho[2,1-*d*]furan **9** to δ 4.57–4.59 ppm in the quinone product **11**. The IR spectrum exhibited a carbonyl stretch at 1667 cm^{-1} assigned to the quinone carbonyl group and the ^{13}C NMR spectrum displayed resonances at δ 179.5 and 183.7 ppm further supporting the presence of a quinone.

The basic ring skeleton of juglomycin A having been prepared, removal of the phenylsulfanyl group at C-3' was now required. Treatment of the quinone sulfide **11** with Raney nickel

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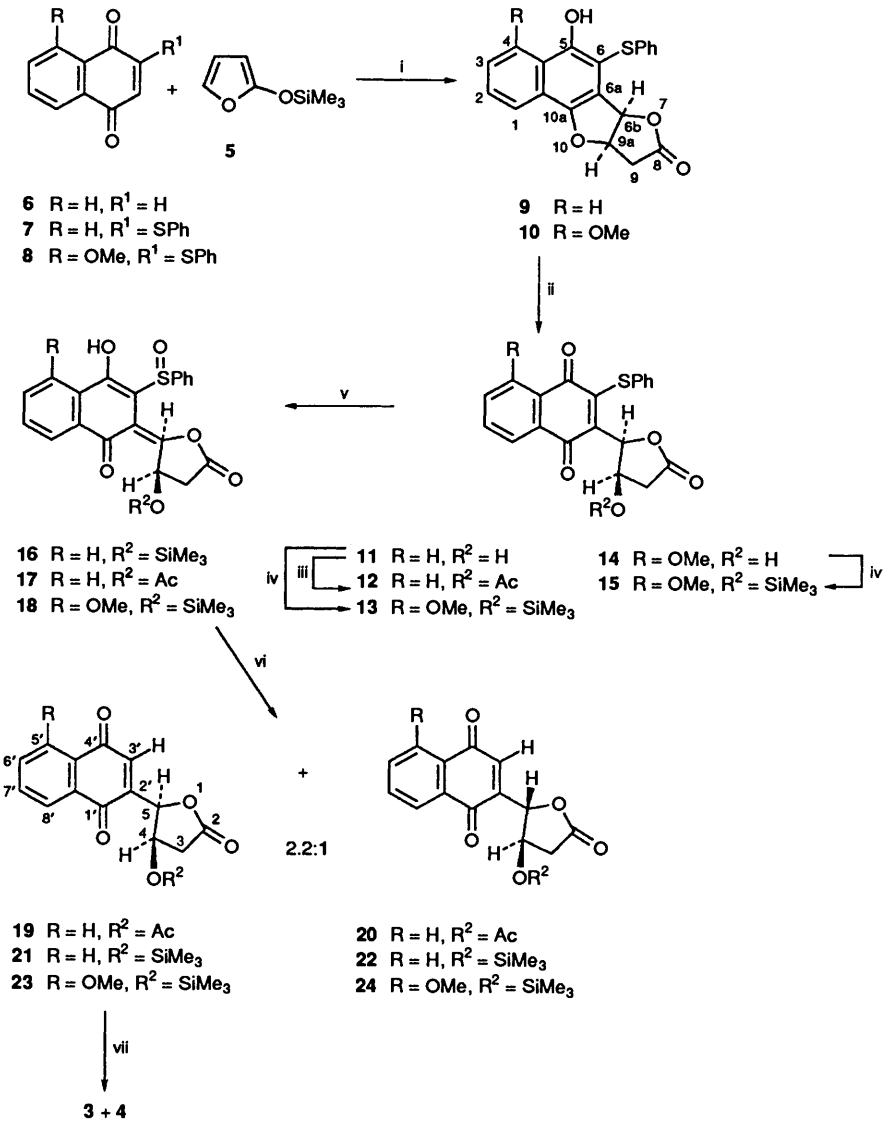
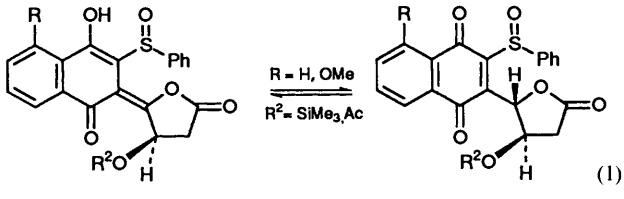


Scheme 1 *Reagents and conditions:* i, **5** (2 equiv), MeCN then MeOH (**9**, 51%); **5** (8 equiv.), MeOH (**10**, 66%); ii, CAN (2 equiv.), MeCN (**11**, 77%; **14**, 66%); iii, Ac_2O, Et_3N, DMAP, 89%; iv, 1-(trimethylsilyl)imidazole, CH_2Cl_2 (**13**, 94%; **14**, 80%); v, MCPBA, NaOAc, CH_2Cl_2 (**16**, 68%; **17**, 66%; **18**, 61%); vi, Bu_3SnH (2 equiv.), AIBN (cat.), toluene, reflux [**19** + **20**, 72%; **21** + **22**, 69%; **23** + **24**, 79%); vii, PPTS, MeOH (**3**, 65%; **4**, 69%)

resulted in cleavage of the C(2')–C(5) bond as did Mg–MeOH, Al–Hg or Na–Hg. Conversion into a sulfoxide was then considered a viable alternative. After conversion of the alcohol **11** into the acetate **12**, the sulfide was oxidized to the sulfoxide **17** using MCPBA buffered with sodium acetate in dichloromethane at room temperature. The ^1H NMR spectrum of the major product lacked the resonance at δ 6.51 ppm attributed to the methine proton at C-5 in the precursor **12**. This, together with the presence of a hydroxy group in the IR spectrum suggested the structure of the product to be the enol **17** rather than the quinone [eqn. (1)]. The signals in the ^1H NMR spectrum



(1)

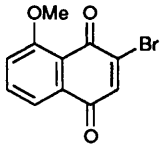
were very broad which may be attributed to the presence of two diastereoisomeric products, arising as a result of asymmetry associated with the chiral sulfur atom.

Removal of the sulfoxide group from **17** was finally achieved by treatment with tributyltin hydride and azoisobutyronitrile (AIBN) in toluene under reflux for 30 min. Purification by flash chromatography afforded, in 72% yield, a 2.2:1 mixture of the quinones **19** and **20** which were separable upon trituration with diethyl ether. Thus far, the synthesis of 5'-deoxyjuglomycin A acetate **19** and 5'-deoxyjuglomycin B acetate **20** had been successful. However, since removal of the acetate group proved problematic, the last described steps of the synthesis were repeated using a trimethylsilyl group.

Treatment of the quinone sulfide **11** with trimethylsilylimidazole afforded the trimethylsilyl ether **13** in 94% yield which then underwent oxidation to the sulfoxide **16** in 68% yield. Subsequent desulfurization using tributyltin hydride and AIBN then afforded the quinones **21** and **22** as a 2.2:1 mixture (^1H NMR) of *cis*:*trans* isomers. Trituration of the mixture with diethyl ether afforded the major isomer **21** which underwent deprotection to the alcohol **3** in 65% yield when stirred in methanol with Amberlite resin. Thus, with a synthesis of 5'-deoxyjuglomycin A **3** in hand, we turned our attention to the synthesis of juglomycin A **1** itself.

The synthesis of juglomycin A **1**, which bears a 5'-hydroxy group, using the above methodology required a synthesis of 5-

methoxynaphthoquinone **8**. This was prepared *via* substitution of the bromide **27** using potassium benzenethiolate,[9] the former



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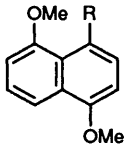


28 R = OH
29 R = CHO

being available from the naphthol **28** using the procedure reported by Rapoport *et al.*;[10] in turn, compound **28** was prepared by Vilsmeier formylation of 1,5-dimethoxynaphthalene to give the aldehyde **29**[10] which was then subjected to Baeyer–Villiger oxidation followed by *in situ* hydrolysis of the intermediate formate.[10]

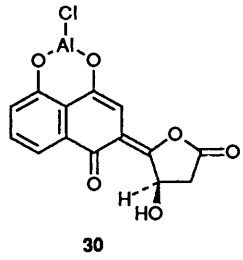
Because the naphthoquinone **8** was insoluble in acetonitrile the addition of 2-trimethylsiloxyfuran **5** was carried out in methanol at room temperature providing the furofuran annulation product **10** in 66% yield after purification by flash chromatography. Use of 8 equiv. of 2-trimethylsiloxyfuran, however, was critical to the success of this reaction. Using the methodology used in the synthesis of 5′-deoxyjuglomycin A **3**, the adduct **10** was converted into the naphthoquinone **14** in 66% yield. Fragmentation of the central tetrahydrofuran ring was indicated in the ^{1}H NMR spectrum by the significant shift of the bridgehead proton 9a-H resonating at δ 5.46 in the starting furo[3,2-*b*]naphtho[2,1-*d*]furan **10** to δ 4.41–4.54 ppm in the quinone product **14**. Additional evidence for the quinone product was found in the IR spectrum which showed absorbances at 3465, 1784 and 1662 cm^{-1} assigned to the hydroxy group, γ-lactone carbonyl and quinone group, respectively.

The alcohol **14** was protected as a trimethylsilyl ether **15** upon treatment with trimethylsilylimidazole before oxidation of the sulfide **15** to the sulfoxide **18** in 61% yield using MCPBA buffered with sodium acetate. Once again the ^{1}H NMR and IR spectra suggested the presence of the enol tautomer. Removal of the sulfoxide was then effected smoothly upon treatment of **18** with tributyltin hydride and AIBN in toluene after heating under reflux for 20 min.

The absence of a hydroxy group in the IR spectrum suggested the formation of the quinones **23** and **24** rather than their enol tautomers. Whilst separation of the individual isomers was not possible at this stage, removal of the trimethylsilyl ether, however, did allow separation. Thus, treatment of the isomeric mixture of the silyl ethers **23** and **24** with a catalytic quantity of pyridinium toluene-*p*-sulfonate (PPTS) in methanol at room temperature for 1 h afforded the *cis*-alcohol **4** in 69% yield as a yellow solid after purification by flash chromatography. Recrystallization from dichloromethane–hexane afforded pale yellow needles for which the melting point and ^{1}H NMR data were in agreement with the literature.[4]

Evidence for formation of the *cis*-isomer **4**, which has the same stereochemistry as juglomycin A **1**, was found upon examination of the resonance at δ 5.59 ppm assigned to the methine proton 5-H. This proton resonated as a double doublet with coupling constant, $J_{4,5}$ 4.4 Hz, clearly establishing that the two methine protons 4-H and 5-H were *syn* to each other. The magnitude of this coupling was also the same as that observed in juglomycin A **1** itself. In the *trans* natural product, juglomycin B **2**, no coupling was observed between the two methine protons 4-H and 5-H.

Having synthesized 5′-methoxyjuglomycin A **4** with the required *syn*-relationship between the methine protons 4-H and 5-H all that remained to complete the synthesis of the natural



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product juglomycin A **1** was to convert the methyl ether into the corresponding naphthol. Fortunately, *O*-demethylation of methyl ether **4** has been reported by Giles *et al.*[4] using aluminium chloride in dichloromethane to give a mixture of the diastereoisomers juglomycin A **1** (38%) and juglomycin B **2** (20%). The mixture of juglomycins formed by reaction with aluminium chloride probably arose by way of an intermediate such as **30** which would give rise to both products. Note that this proposed intermediate has a similar structure to enol **18** isolated upon oxidation of the sulfide **15**.

In summary, the successful synthesis of 5′-methoxyjuglomycin A **4** represents a formal synthesis of the natural antibiotics juglomycin A **1** and juglomycin B **2**. The synthetic route developed represents an efficient entry into this class of antibiotic in which the key step involves an oxidative fragmentation of a furo[3,2-*b*]naphtho[2,1-*d*]furan ring system using ceric ammonium nitrate.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Bio-Rad FTS 40V spectrophotometer as Nujol mulls or thin films between sodium chloride discs. ^{1}H NMR spectra were recorded at 270 MHz in $CDCl_3$ using tetramethylsilane as internal standard on a JEOL GX270 spectrometer. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL GX270 spectrometer. All *J* values are given in Hz. Mass spectra and accurate mass measurements were recorded on a VG70-250S double focusing magnetic sector mass spectrometer with an ionization potential of 70 eV. Microanalyses were performed at the microanalytical laboratory, University of Otago. Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) with the solvents described.

3-Phenylsulfanyl-1,4-naphthoquinone **7**.—The naphthoquinone **7** was prepared according to the method of Fieser and Brown[8] as a pale yellow solid, m.p. 158–160 °C (lit.,[8] m.p. 159–161 °C).

5-Methoxy-3-phenylsulfanyl-1,4-naphthoquinone **8**.—The naphthoquinone **8** was prepared from 3-bromo-5-methoxy-1,4-naphthoquinone **27** according to the method of d'Angelo *et al.*[9] as a yellow solid, m.p. 186–187 °C (lit.,[9] m.p. 186–187 °C).

3-Bromo-5-methoxy-1,4-naphthoquinone **27**.—The naphthoquinone **27** was prepared from 1,5-dimethoxy-4-naphthol **28** according to the procedure of Rapoport *et al.*[10] as an orange solid, m.p. 152–153 °C (lit.,[10] m.p. 154–155 °C).

1,5-Dimethoxy-4-naphthol **28**.—The naphthol **28** was prepared from 1,5-dimethoxynaphthalene-4-carbaldehyde **29** following the procedure of Rapoport *et al.*[10] as colourless plates, m.p. 155–156 °C (lit.,[10] m.p. 155–156 °C).

1,5-Dimethoxynaphthalene-4-carbaldehyde **29**.—The naphthalene-4-carbaldehyde **29** was prepared from 1,5-dimethoxy-

naphthalene following the procedure of Rapoport *et al.*[10] as a pale yellow solid, m.p. 125–126 °C (lit.,[10] 125–126 °C).

cis-5-*Hydroxy*-4-*methoxy*-6-*phenylsulfanyl*-6b,9a-*dihydrofuro*[3,2-b]*naphtho*[2,1-d]*furan*-8(9H)-*one* **10**.—2-Trimethylsiloxyfuran **5** (307 mg, 1.96 mmol) was added dropwise to an ice-cooled solution of quinone **8** (71 mg, 0.23 mmol) in methanol (18 cm^3) under an argon atmosphere. After 1 h, the reaction mixture was left to warm to room temperature and stirred for a further 18 h. Concentration of the filtrate at reduced pressure afforded a brown oil which was then purified by flash chromatography using hexane–ethyl acetate (4:1 v/v) as eluent to yield the *title compound* **10** (58 mg, 66%) as a colourless solid, m.p. 148–150 °C (Found: C, 66.3; H, 4.2; S, 8.0. $C_{21}H_{16}O_5S$ requires C, 66.3; H, 4.2; S, 8.4%); ν_{max}(Nujol)/cm^{-1} 3367 (OH) and 1782 (C=O, lactone); δ_H(270 MHz; $CDCl_3$) 3.08 (2 H, m, CH_2), 4.06 (3 H, s, OMe), 5.46 (1 H, m, 9a-H), 6.12 (1 H, d, $J_{6b,9a}$ 5.9, 6b-H), 6.94 (1 H, d, *J* 8.1, 1-H or 3-H), 7.10–7.30 (5 H, m, Ph), 7.45 (1 H, t, *J* 8.1, 2-H), 7.57 (1 H, d, *J* 8.1, 3-H or 1-H) and 9.78 (1 H, s, OH); δ_C(67.8 MHz; $CDCl_3$) 35.6 (CH_2, C-9), 56.4 (OMe), 81.4 (CH, C-9a), 85.0 (CH, C-6b), 106.8 (CH, C-1 or C-3), 108.1 (quat., C-6a), 116.0 (CH, C-3 or C-1), 116.6 (quat., C-4a), 121.5 (quat., C-6), 123.1 (quat., C-10b), 125.5 (CH, C-4′), 127.3 (CH, C-2′), 127.5 (CH, C-2), 128.8 (CH, C-3′), 137.0 (quat., C-1′), 149.9 (quat., C-10a), 151.5 (quat., C-4), 156.1 (quat., C-5) and 174.7 (quat., C-8); *m*/*z* 380 (M^+, 100%) and 365 (M − CH_3, 12).

cis-5-*Hydroxy*-6-*phenylsulfanyl*-6b,9a-*dihydrofuro*[3,2-b]-*naphtho*[2,1-d]*furan*-8(9H)-*one* **9**.—The furonaphthofuran **9** was prepared from 3-phenylsulfanyl-1,4-naphthoquinone **7** (500 mg, 1.8 mmol) and 2-trimethylsiloxyfuran **5** (554 mg, 3.5 mmol) in acetonitrile (10 cm^3) using a similar procedure to that described for the preparation of furonaphthofuran **10**. Purification by flash chromatography using hexane–ethyl acetate (4:1 v/v) afforded the *title compound* **9** (316 mg, 51%) as a colourless prisms (acetone), m.p. 178–180 °C (decomp., changes to needles at 155–158 °C) (Found: C, 68.6; H, 4.0; S, 9.1. $C_{20}H_{14}O_4S$ requires C, 68.6; H, 4.0; S, 9.15%); ν_{max}(Nujol)/cm^{-1} 3385 (OH) and 1762 (C=O, lactone); δ_H[270 MHz; $(CD_3)_2CO$] 3.01 (1 H, d, J_{gem} 18.7, 9-H), 3.28 (1 H, dd, J_{gem} 18.7, $J_{9',9a}$ 7.0, 9-H′), 5.68 (1 H, apparent t, *J* 6.2, 9a-H), 6.16 (1 H, d, $J_{6b,9a}$ 5.9, 6b-H), 7.10–7.30 (5 H, m, Ph), 7.65–7.70 (2 H, m, 2-H, 3-H), 7.97–8.00 (1 H, m, 1-H or 4-H) and 8.31–8.34 (1 H, m, 4-H or 1-H); δ_C[67.8 MHz; $(CD_3)_2CO$] 36.3 (CH_2, C-9), 84.0 (CH, C-9a), 86.1 (CH, C-6b), 106.9 (quat., C-6a), 121.3 (quat., C-6), 123.2 (quat., C-4a or C-10b), 125.2 (CH, C-4′), 125.3 (CH, C-1 or C-4), 127.7 (CH, C-4 or C-1), 127.9 (quat., C-4a or C-10b), 128.0 (CH, C-2′), 128.3, 129.2 (both CH, C-2, C-3), 130.4 (CH, C-3′), 137.6 (quat., C-1′), 151.8, 152.4 (both quat., C-5, C-10a) and 175.9 (quat., C-8); *m*/*z* 350 (M^+, 100%) and 305 (14).

(S^*_S,6bR*,9aR*)- and (R^*_S,6bR*,9aR*)-cis-5-*Hydroxy*-6-(*phenylsulfinyl*)-6b,9a-*dihydrofuro*[3,2-b]*naphtho*[2,1-d]*furan*-8(9H)-*one* **25** *and* **26**.—To a solution of the sulfide **9** (70 mg, 0.21 mmol) in dichloromethane (5 cm^3) was added 80% MCPBA (45 mg, 0.21 mmol). After the mixture had been stirred at room temperature for 2 h, it was concentrated under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (4:1 v/v) as eluent to give the (S^*_S,6bR*,9aR*)-*sulfoxide* **25** (32 mg, 42%) as colourless needles, m.p. 166–168 °C (decomp.) (Found: C, 65.6; H, 3.9; S, 8.9. $C_{20}H_{14}O_5S$ requires C, 65.6; H, 3.85; S, 8.75%); ν_{max}(Nujol)/cm^{-1} 3300–2900 (OH), 1788 (C=O, lactone) and 1038 (S=O); δ_H(270 MHz; $CDCl_3$) 3.11–3.14 (2 H, m, CH_2), 5.60 (1 H, ddd, $J_{9a,6b}$ 6.2, $J_{9a,9}$ 6.2, $J_{9a,9'}$ 2.9, 9a-H), 6.34 (1 H, d, $J_{6b,9a}$ 6.2, 6b-H) and 7.38–8.27 (9 H, m, ArH); *m*/*z* 366 (M^+, 2%), 350 (M − O, 10), 242 (63), 197 (100), 125 (44) and 77 (38), and the (R^*_S,6bR*,9aR*)-*sulfoxide* **26** (33 mg, 43%) as colourless prisms, m.p. 150–152 °C (decomp.) (Found: C, 65.6; H, 3.7; S, 8.8. $C_{20}H_{14}O_5S$ requires C, 65.6; H, 3.85; S, 8.75%); ν_{max}(Nujol)/cm^{-1} 3300–2900 (br., OH), 1788 (C=O, lactone) and 1038 (S=O); δ_H(270 MHz; $CDCl_3$) 3.03–3.08 (2 H, m, CH_2), 5.42–5.44 (1 H, m, 9a-H), 5.86 (1 H, d, $J_{6b,9a}$ 6.6, 6b-H) and 7.39–8.35 (9 H, m, ArH); *m*/*z* 366 (M^+, 3%), 350 (M − O, 8), 242 (63), 197 (100), 125 (46) and 77 (39).

(4R*,5R*)-5-(5-*Methoxy*-1,4-*dioxo*-3-*phenylsulfanyl*-1,4-*dihydro*-2-*naphthyl*)-4-*hydroxytetrahydrofuran*-2-*one* **14**.—To a rapidly stirred solution of the furo[3,2-*b*]naphtho[2,1-*d*]furan **10** (100 mg, 0.26 mmol) in acetonitrile (40 cm^3) was added a solution of ceric ammonium nitrate (285 mg, 0.52 mmol) in water (8 cm^3). The reaction mixture was poured into dichloromethane (150 cm^3) and washed with water (2 × 80 cm^3). The organic layer was separated, dried ($MgSO_4$), filtered through Florisil and evaporated under reduced pressure to give an orange oil. This was purified by flash chromatography using hexane–ethyl acetate (1:1 v/v) as eluent to yield the *title compound* **14** (68 mg, 66%) as an orange solid, m.p. 102–104 °C (Found: C, 63.25; H, 4.2; S, 7.9. $C_{21}H_{16}O_6S$ requires C, 63.6; H, 4.1; S, 8.1%); ν_{max}(Nujol)/cm^{-1} 3465 (OH), 1784 (C=O, lactone) and 1662 (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 2.84 (1 H, dd, J_{gem} 18.5, $J_{3,4}$ 3.5, 3-H), 3.00 (1 H, dd, J_{gem} 18.5, $J_{3',4}$ 7.9, 3-H′), 3.88 (3 H, s, OMe), 4.41–4.54 (1 H, m, 4-H), 6.15 (1 H, d, $J_{5,4}$ 6.6, 5-H) and 7.23–7.71 (8 H, m, ArH); δ_C(67.8 MHz; $CDCl_3$) 38.4 (CH_2, C-3), 56.4 (OMe), 69.0, 82.0 (both CH, C-4, C-5), 118.2, 119.5 (both CH, C-6′, C-8′), 120.3 (quat., C-3′), 128.3 (CH, C-4″), 129.6 (CH, C-2″), 131.6 (CH, C-3″), 133.3, 134.4 (both quat., C-1″, C-8a′), 135.2 (CH, C-7′), 140.6 (quat., C-2′), 152.6 (quat., C-5′), 174.6 (quat., C-2) and 178.6, 182.6 (both quat., C-1′, C-4′); *m*/*z* 396 (M^+, 31%) and 162 (100).

(4R*,5R*)-5-(1,4-*Dioxo*-3-*phenylsulfanyl*-1,4-*dihydro*-2-*naphthyl*)-4-*hydroxytetrahydrofuran*-2-*one* **11**.—Using the procedure described above for the preparation of the quinone **14**, the *title compound* **11** was prepared from the furonaphthofuran **9** (140 mg, 0.41 mmol), using ceric ammonium nitrate (452 mg, 0.83 mmol), as a red solid (116 mg, 77%), m.p. 168–169 °C; ν_{max}(Nujol)/cm^{-1} 3502 (OH), 1781 (C=O, lactone) and 1667 (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 2.83 (1 H, dd, J_{gem} 18.7, $J_{3,4}$ 3.7, 3-H), 3.01 (1 H, dd, J_{gem} 18.7, $J_{3',4}$ 3.7, 3-H′), 4.57–4.59 (1 H, m, 4-H), 6.27 (1 H, d, $J_{5,4}$ 6.6, 5-H) and 7.32–8.09 (9 H, m, ArH); δ_C(67.8 MHz; $CDCl_3$) 38.4 (CH_2, C-3), 69.0, 82.1 (both CH, C-4, C-5), 126.9, 127.3 (both CH, C-5′, C-8′), 128.3 (quat., C-1″), 128.4 (CH, C-4″), 129.6 (CH, C-2″), 131.4 (CH, C-3″), 132.1, 133.2 (both quat., C-4a′, C-8a′), 134.2, 134.3 (both CH, C-6′, C-7′), 143.3 (quat., C-2′), 150.2 (quat., C-3′), 174.6 (quat., C-2) and 179.5, 183.7 (quat., C-1′, C-4′); *m*/*z* 366 (M^+, 100). Conversion into the acetate derivative **12** provided an analytical sample.

(4R*,5R*)-4-*Acetoxy*-5-(1,4-*dioxo*-3-*phenylsulfanyl*-1,4-*dihydro*-2-*naphthyl*)*tetrahydrofuran*-2-*one* **12**.—To a solution of the alcohol **11** (75 mg, 0.2 mmol) in dichloromethane (5 cm^3) was added acetic anhydride (22 mg, 0.2 mmol), triethylamine (0.1 cm^3) and 4-dimethylaminopyridine (2 mg). After the mixture had been stirred at room temperature for 2 h it was concentrated under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (1:1 v/v) as eluent to afford the *title compound* **12** (73 mg, 89%) as orange needles, m.p. 164–165 °C (Found: C, 64.7; H, 3.8; S, 7.8. $C_{22}H_{16}O_6S$ requires C, 64.7; H, 3.95; S, 7.85%); ν_{max}(Nujol)/cm^{-1} 1788 (C=O, lactone), 1740 (C=O, ester) and 1654 (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.91 (3 H, s, $COCH_3$), 3.04–3.12 (2 H, m, CH_2CO), 5.65 (1 H, m, 4-H), 6.51 (1 H, d, $J_{5,4}$ 6.4, 5-H), 7.28–7.44 (5 H, m, Ph), 7.68–7.79 (2 H,

m, 6'-H, 7'-H), 7.94 (1 H, d, *J* 7.1, 5'-H or 8'-H) and 8.09 (1 H, d, *J* 7.1, 8'-H or 5'-H); *m/z* 408 (M^+, 74%), 348 (72), 320 (56) and 239 (52).

(4R*,5R*)-5-(5-*Methoxy*-1,4-*dioxo*-3-*phenylsulfanyl*-1,4-*dihydro*-2-*naphthyl*)-4-*trimethylsiloxytetrahydrofuran*-2-*one* **15**.—To a solution of alcohol **14** (68 mg, 0.17 mmol) in dry dichloromethane (10 cm^3) was added 1-(trimethylsilyl)-imidazole (24 mg, 0.17 mmol) and the reaction mixture was set aside at room temperature until no starting material could be detected by TLC (15 min). Removal of solvent under reduced pressure, followed by purification of the residue by flash chromatography using hexane–ethyl acetate (1 : 1 v/v) as eluent afforded the *title compound* **15** (64 mg, 80%) as an orange oil (Found: C, 61.3; H, 5.0. $C_{24}H_{24}O_6SSi$ requires C, 61.5; H, 5.2%); ν_{max}(Nujol)/cm^{-1} 1786 (C=O, lactone) and 1662 (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 0.05 (9 H, s, $SiMe_3$), 2.82–2.89 (2 H, m, CH_2), 3.84 (3 H, s, OMe), 4.92 (1 H, q, *J* 7.3, 4-H), 6.23 (1 H, br d, *J* 7.3, 5-H) and 7.21–7.22 (8 H, m, ArH); *m/z* 468 (M^+, 86%), 423 ($M - CO_2H$, 28), 323 (89), 162 (100) and 73 (82).

(4R*,5R*)-5-(1,4-*Dioxo*-3-*phenylsulfanyl*-1,4-*dihydro*-2-*naphthyl*)-4-*trimethylsiloxytetrahydrofuran*-2-*one* **13**.—Using the procedure described for the preparation of trimethylsilyl ether **15**, the *title compound* **13** was prepared in 94% yield from the alcohol **11** (75 mg, 0.2 mmol), using 1-(trimethylsilyl)-imidazole (32 mg, 0.2 mmol), as a red oil; δ_H(270 MHz; $CDCl_3$) 0.05 (9 H, s, $SiMe_3$), 2.89–2.92 (2 H, m, CH_2), 4.98 (1 H, q, *J* 7.3, 4-H), 6.36–6.42 (1 H, m, 5-H), 7.26–7.43 (5 H, m, Ph), 7.68–7.74 (2 H, m, 6'-H, 7'-H), 7.93 (1 H, d, *J* 7.3, 5'-H or 8'-H) and 8.10 (1 H, d, *J* 7.3, 8'-H or 5'-H); *m/z* 438 (M^+, 62%) and 293 (100).

5-(4-*Hydroxy*-5-*methoxy*-1-*oxo*-3-*phenylsulfinyl*-1,2-*dihydro*-2-*naphthylidene*)-4-*trimethylsiloxytetrahydrofuran*-2-*one* **18**.—To a solution of sulfide **15** (30 mg, 0.06 mmol) in dichloromethane (5 cm^3) was added anhydrous sodium acetate (40 mg) and 80% MCPBA (12.9 mg, 0.06 mmol). After being stirred for 1 h, the mixture was filtered to remove the sodium acetate and evaporated under reduced pressure to yield an orange oil. This was purified by flash chromatography using hexane–ethyl acetate (1 : 1 v/v) as eluent to give the *title compound* **18** (19 mg, 61%) as an orange solid, m.p. 160–161 °C (Found: C, 59.6; H, 5.1%; M^+, 484.0984. $C_{24}H_{24}O_7SSi$ requires C, 59.5; H, 5.0%; *M*, 484.1012); ν_{max}(Nujol)/cm^{-1} 3450–3200 (OH), 1793 (C=O, lactone), 1673 (C=O, quinone), 1591 (C=C) and 1060s (S=O); δ_H(270 MHz; $CDCl_3$) 0.04 (9 H, s, $SiMe_3$), 2.78–3.14 (2 H, m, CH_2), 3.91 (3 H, s, OMe), 4.96–5.16 (1 H, br m, 4-H) and 7.24–7.96 (8 H, m, ArH); *m/z* 484 (M^+, 8%), 394 ($M - C_3H_{10}OSi$, 6), 360 ($M - C_6H_4SO$, 5), 324 (27) and 73 ($SiMe_3$, 100).

5-(4-*Hydroxy*-1-*oxo*-3-*phenylsulfinyl*-1,2-*dihydro*-2-*naphthylidene*)-4-*trimethylsiloxytetrahydrofuran*-2-*one* **16**.—Using the procedure described for the preparation of the sulfoxide **18**, the sulfoxide **16** was prepared from sulfide **13** (90 mg, 0.21 mmol) in 68% yield as pale pink needles, m.p. 160–161 °C (Found: C, 58.35; H, 4.9; $C_{23}H_{22}O_6SSi$ requires C, 58.7; H, 4.7%); ν_{max}(Nujol)/cm^{-1} 3450–3200 (OH), 1786 (C=O, lactone), 1671 (C=O) and 1059 (S=O); δ_H(270 MHz; $CDCl_3$) 0.06 (9 H, s, $SiMe_3$), 2.72–3.09 (2 H, m, CH_2), 4.91–5.06 (1 H, br m, 4-H) and 7.48–8.08 (9 H, m, ArH); *m/z* 454 (M^+, 9%), 439 (10), 294 (20), 143 (36) and 73 (100).

4-*Acetoxy*-5-(4-*hydroxy*-1-*oxo*-3-*phenylsulfinyl*-1,2-*dihydro*-2-*naphthylidene*)*tetrahydrofuran*-2-*one* **17**.—Using the procedure described for the preparation of sulfoxide **18**, the sulfoxide **17** was prepared from the sulfide **12** (88 mg, 0.22 mmol) in 66% yield as an orange solid, m.p. 172–174 °C (Found: C, 62.0; H, 3.6; S, 7.7. $C_{22}H_{16}O_7S$ requires C, 62.3; H, 3.8; S, 7.55%); ν_{max}(Nujol)/cm^{-1} 3200–3460 (OH), 1807 (C=O, lactone), 1738 (C=O, ester), 1664 (C=O, quinone) and 1044 (S=O); δ_H(270 MHz; $CDCl_3$) 2.09 (3 H, s, $COCH_3$), 3.00 (1 H, dd, J_{gem} 18.7, $J_{3,4}$ 2.9, 3-H), 3.21 (1 H, dd, J_{gem} 18.7, $J_{3',4}$ 7.9, 3-H'), 5.76–5.80 (1 H, m, 4-H) and 7.48–8.11 (9 H, m, ArH); δ_C(67.8 MHz; $CDCl_3$) 20.9 ($COCH_3$), 35.7 (CH_2, C-3), 70.3 (CH, C-4), 124.9 (quat., C-2' or C-3'), 125.4 (CH, C-3''), 127.0, 127.1 (both CH, C-5', C-8'), 129.7 (quat., C-3' or C-2'), 131.2 (CH, C-4''), 131.5, 131.6 (both quat., C-4a', C-8a'), 134.8, 134.9 (both CH, C-6', C-7'), 141.4, 141.5 (both quat., C-1'', C-5), 142.8 (quat., C-4'), 170.2 (quat., *C*OCH_3), 173.3 (quat., C-2) and 182.1 (quat., C-1'); *m/z* 424 (M^+, 4%), 294 (9), 218 (58), 186 (91), 109 (62) and 43 (100).

(4R*,5R*)-5-(5-*Methoxy*-1,4-*dioxo*-1,4-*dihydro*-2-*naphthyl*)-4-*hydroxytetrahydrofuran*-2-*one* (5'-*Methoxyjuglomycin A*) **4**.—To a stirred solution of the sulfoxide **18** (29 mg, 0.06 mmol) in toluene (40 cm^3) were added tributyltin hydride (35 mg, 0.12 mmol) and azoisobutyronitrile (2 mg) under an atmosphere of nitrogen. The reaction mixture was gently heated for 20 min after which time, since no starting material was evident by TLC, it was evaporated under reduced pressure. The resultant oil was purified by flash chromatography using hexane–ethyl acetate (1 : 1 v/v) as eluent to give *trimethylsilyl ethers* **23** and **24** (17 mg, 79%) as a yellow oil (2.2 : 1 isomeric mixture by ^1H NMR). This isomeric mixture was redissolved in methanol (5 cm^3) and treated with pyridinium toluene-*p*-sulfonate (2 mg). After being stirred at room temperature for 1 h, the mixture was evaporated under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (1 : 1 v/v) as eluent to yield 5'-methoxyjuglomycin A **4** (10 mg, 69%) as a yellow solid, m.p. 189–191 °C (decomp.) [lit.,[4] m.p. 186–189 °C (decomp.)]; ν_{max}(Nujol)/cm^{-1} 1792 (C=O, lactone), 1660 (C=O, quinone) and 1590; δ_H[270 MHz; $(CD_3)_2SO$] 2.39 (1 H, d, J_{gem} 17.2, 3-H), 3.14 (1 H, dd, J_{gem} 17.2, $J_{3',4}$ 5.5, 3-H'), 3.93 (3 H, s, OMe), 4.62 (1 H, apparent q, *J* 4.4, 4-H), 5.50 (1 H, d, $J_{4,OH}$ 4.4, OH), 5.59 (1 H, dd, $J_{5,4}$ 4.4, $J_{5,3'}$ 1.6, 5-H), 6.60 (1 H, d, $J_{3',5}$ 1.6, 3'-H), 7.57–7.66 (2 H, m, 6'-H, 8'-H) and 7.83 (1 H, apparent t, *J* 8.4, 7'-H); δ_C[67.8 MHz; $(CD_3)_2SO$] 38.5 (CH_2, C-3), 56.4 (OCH_3), 68.5, 80.2 (both CH, C-4, C-5), 118.4, 119.2 (both CH, C-6', C-8'), 126.3 (quat., C-4a'), 129.3 (CH, C-3'), 135.4 (quat., C-8a'), 135.5 (CH, C-7'), 141.3 (quat., C-2'), 159.2 (quat., C-5'), 175.4 (quat., C-2) and 182.9, 183.6 (both quat., C-1', C-4'); *m/z* 288 (M^+, 29%), 218 ($C_{12}H_9O_4$, 100), 203 (64), 57 (78) and 43 (98).

(4R*,5R*)-5-(1,4-*Dioxo*-1,4-*dihydro*-2-*naphthyl*)-4-*hydroxytetrahydrofuran*-2-*one* (5'-*Deoxyjuglomycin A*) **3**.—Using the procedure described for the preparation of 5'-methoxyjuglomycin A **4**, the sulfoxide **16** (34 mg, 0.07 mmol) was treated with tributyltin hydride and the product purified by flash chromatography to give *trimethylsilyl ethers* **21** and **22** (17 mg, 69%), as a 2.2 : 1 mixture by ^1H NMR. Trituration of the mixture with diethyl ether afforded the *major isomer* **21** as a yellow solid, m.p. 181–183 °C (decomp.) (Found: M^+, 330.0925. $C_{17}H_{18}O_5Si$ requires *M*, 330.0923); δ_H(270 MHz; $CDCl_3$) −0.09 (9 H, s, $SiMe_3$), 2.53 (1 H, d, J_{gem} 17.6, 3-H'), 2.91 (1 H, dd, J_{gem} 17.6, $J_{3,4}$ 5.3, 3-H), 4.94 (1 H, dd, $J_{4,3}$ 5.3, $J_{4,5}$ 4.0, 4-H), 5.59 (1 H, dd, $J_{5,4}$ 4.0, $J_{5,3'}$ 2.0, 5-H), 7.11 (1 H, d, $J_{3',5}$ 2.0, 3'-H), 7.76–7.80 (2 H, m, 6'-H, 7'-H) and 8.07–8.14 (2 H, m, 5'-H, 8'-H); *m/z* 330 (M^+, 7%), 315 ($M - CH_3$, 31) and 162 (100). The trimethylsilyl ether **21** (12 mg, 0.035 mmol) was dissolved in methanol (1 cm^3) and treated with pyridinium toluene-*p*-sulfonate (2 mg). After the mixture had been stirred at room temperature for 1 h, it was evaporated under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (1 : 1 v/v) as eluent to yield 5'-deoxyjuglomycin A **3**

(6 mg, 65%) as a yellow solid, m.p. 200–201 °C (decomp.) [lit.,[4] m.p. 201–203 °C (decomp.)] for which the ^{1}H NMR data were in agreement with those of the literature.[4]

(4R*,5R*)- *and* (4R*,5S*)-4-*Acetoxy*-5-(1,4-*dioxo*-1,4-*dihydro*-2-*naphthyl*)*tetrahydrofuran*-2-*one* (*5'-Deoxyjuglomycin A Acetate and 5'-Deoxyjuglomycin B Acetate*) **19** *and* **20**.—Using the procedure described for the preparation of 5'-methoxyjuglomycin A **4**, the sulfoxide **17** (46 mg, 0.1 mmol) was treated with tributyltin hydride and the product purified by flash chromatography to give the *title compounds* **19** and **20** (22 mg, 72%), as a 2.2:1 mixture by ^{1}H NMR. Trituration of the mixture with diethyl ether afforded the *major acetate* **19** as a yellow solid, m.p. 148–150 °C (Found: C, 63.9; H, 3.8. $C_{16}H_{12}O_6$ requires C, 64.0; H, 4.0%); ν_{max}(Nujol)/cm^{-1} 1791 (C=O, lactone), 1743 (C=O, ester) and 1672 (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.89 (3 H, s, $COCH_3$), 2.75 (1 H, d, J_{gem} 18.3, 3-H'), 3.09 (1 H, dd, J_{gem} 18.3, $J_{3,4}$ 5.5, 3-H), 5.74–5.82 (2 H, m, 4-H, 5-H), 7.12 (1 H, d, $J_{3',5}$ 1.5, 3'-H), 7.76–7.83 (2 H, m, 6'-H, 7'-H) and 8.08–8.14 (2 H, m, 5'-H, 8'-H); δ_C(67.8 MHz; $CDCl_3$) 20.6 (CH_3), 36.5 (CH_2, C-3), 71.2, 78.0 (both CH, C-4, C-5), 126.6 (CH, C-3'), 131.5, 131.8 (both quat., C-4a', C-8a'), 134.2, 134.3, 134.5, 134.8 (all CH, C-5', C-6', C-7', C-8'), 142.9 (quat., C-2'), 169.5 (quat., OAc), 172.8 (quat., C-2) and 183.5, 183.9 (both quat., C-1', C-4'); *m/z* 258 (M − CH_2CO, 21%), 240 (46) and 188 (100), and the *minor acetate* **20** as a pale yellow solid, m.p. 167–171 °C (decomp.) (Found: M − CH_2CO, 258.0528. *M* − CH_2CO requires 258.0529); δ_H(270 MHz; $CDCl_3$) 2.18 (3 H, s, $COCH_3$), 2.67 (1 H, dd, J_{gem} 18.7, $J_{3,4}$ 2.2, 3-H), 3.16 (1 H, dd, J_{gem} 18.7, $J_{3',4}$ 7.1, 3-H'), 5.40–5.45 (2 H, m, 4-H, 5-H), 6.96 (1 H, d, $J_{3',5}$ 1.1, 3'-H), 7.78–7.81 (2 H, m, 6'-H, 7'-H) and 8.08–8.12 (2 H, m, 5'-H, 8'-H); *m/z* 258 (M − CH_2CO, 23%), 240 (43) and 188 (100).

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