Synthesis of arizonin C1

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The first syntheses of the pyranonaphthoquinone antibiotics 5-*epi*-arizonin B1 **16**, 5-*epi*-arizonin C1 **15** and arizonin C1 **3** are described. The key steps involve addition of 2-trimethylsilyloxyfuran **12** to the 2-acetylnaphthoquinone **11** affording the adduct **13** which undergoes oxidative rearrangement to a pyranonaphthoquinone system **14** upon treatment with ceric ammonium nitrate. The regioselective synthesis of naphthoquinone **11** *via* oxidation of ketone **10** is described wherein **10** is prepared *via* addition of furan to 3,4-dimethoxydehydrobenzene followed by treatment with acid.

The arizonins **1–6** were first isolated from the fermentation broth of *Actinoplanes arizonensis* by Hochlowski *et al.*[1,2] in 1987 and were found to exhibit antimicrobial activity against pathogenic strains of Gram-positive bacteria. In particular, arizonins A1 **1** and B1 **2** exhibited moderate to potent *in vitro* activity. The six arizonins differ from a simpler member of the pyranonaphthoquinone family of antibiotics, kalafungin **7**, in that they possess a 7,8-dioxygenated nucleus with the individual arizonins differing from one another in the degree and position of *O*-methylation of the aromatic ring.

Our interest in the synthesis of the pyranonaphthoquinone family of antibiotics stems from the proposal that this class of compound can act as bioreductive alkylating agents.[3] We herein report the full details[4] of the first synthesis of arizonin C1 **3** based on the methodology which we have previously applied to the syntheses of a C-5 epimer of kalafungin[5] and deoxyfrenolicin.[6]

Results and discussion

Our synthetic strategy (Scheme 1) rested on the addition of 2-trimethylsilyloxyfuran **12** to a 2-acetyl-1,4-naphthoquinone **11** followed by ceric ammonium nitrate rearrangement to the desired pyranonaphthoquinone ring system. Hence a synthesis of the appropriately substituted naphthoquinone **11** was pivotal to this approach. The unsymmetrical nature of naphthoquinone **11** necessitated a synthesis in which the regiochemistry of the acetyl group could be controlled.

The most desirable route to naphthoquinone **11** would be *via* oxidation of naphthalenol **18** bearing a methoxy substituent at C-4. Naphthalenol **18** would be prepared by Fries rearrangement of acetate **19** which, in turn, would be prepared from naphthalenol **21**. Giles *et al.*[7] have reported efficient methodology for the construction of oxygenated naphthalenols *via* the addition of furan or 2-methoxyfuran to methoxydidehydrobenzenes. However, reaction of 3,4-dimethoxydidehydrobenzene with 2-methoxyfuran afforded predominantly naphthalenol **22** (55%) whilst the naphthalenol **21**, required for our synthesis, was isolated in only 8% yield.

The second approach to naphthoquinone **11** was to proceed *via* oxidation of naphthalenol **10** that is unsubstituted at C-4. Naphthalenol **10** would be prepared by Fries rearrangement of acetate **9** which, in turn, is derived from naphthalenol **8**. Giles *et al.*[7] have reported that the reaction of 3,4-dimethoxydidehydrobenzene with furan gave the desired naphthalenol **8** (74%) with only a small amount of the undesired isomer **23** being formed. It was therefore decided that this was the most suitable route to naphthoquinone **11**.

Using the procedure of Giles *et al.*,[7] 7,8-dimethoxynaphthalen-1-ol **8** was prepared in the following manner. 2,3-Dimethoxyphenol was converted into the bromosulfonate **20** by reaction with toluene-*p*-sulfonyl chloride and triethylamine in dichloromethane for 1 h, followed by subsequent treatment with bromine in carbon tetrachloride at room temperature for 16 h. The bromo sulfonate **20** was then treated with butyllithium in the presence of furan at −78 °C for 45 min to give an initial Diels–Alder adduct which was not isolated but heated directly with concentrated hydrochloric acid in methanol to give naphthalenol **8** (76%). None of the minor isomer **23** was observed.

Acetylation of naphthalenol **8** using acetic anhydride, triethylamine and 4-dimethylaminopyridine (DMAP; catalytic quantity) gave acetate **9** (95%). Subsequent Fries rearrangement of acetate **9** was effected using boron trifluoride–diethyl ether to give 2-acetylnaphthol **10** (90%). Spectroscopic data were in agreement with the structure of naphthol **10**. The IR spectrum showed a ketone carbonyl stretch at 1623 cm^{-1}. The ^1H NMR spectrum exhibited a downfield shift of the methyl group from δ_H 2.37 in acetate **9** to δ_H 2.68 in ketone **10**. The ^{13}C NMR spectrum showed a shift in the resonance assigned to the carbonyl carbon from δ_C 169.9 in acetate **9** to δ_C 203.8 in ketone **10**.

Although, in general, the ketone **10** could be prepared in good yield from this rearrangement, several minor products were also observed on several occasions. In one instance, ketone **10** was obtained in only 43% yield and two other products were also isolated. One product, less polar by TLC than the ketone **10**, was found to be the naphthalenol **8** (19%) formed by cleavage of ester **9**. This did not present a problem since it could be recycled back into the synthesis. The second product, more polar by TLC than ketone **10**, was identified as naphthalenediol (7%) **24**, formed by Fries rearrangement of ester **9** with concomitant deprotection of one methyl ether group.

Finally, it remained to oxidise naphthalenol **10** to naphthoquinone **11**. Use of silver(II) oxide and concentrated nitric acid in dioxane afforded naphthoquinone **11** (54%). However, this reagent was found to give variable results, when repeating the synthesis, with yields ranging from 24 to 47%. Ceric ammonium nitrate also gave variable yields and no improvement was observed when the reaction was buffered with sodium acetate. This oxidation was also attempted unsuccessfully using Fremy's salt. Finally it was found that the most reliable method to effect the oxidation involved the use of salcomine[8] [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II);

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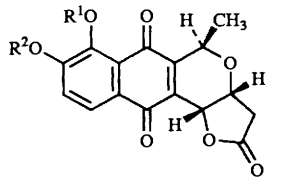
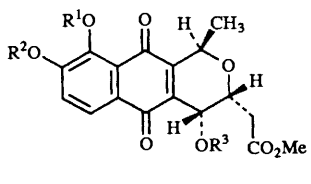
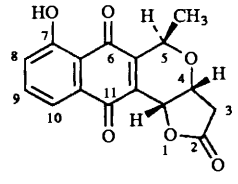


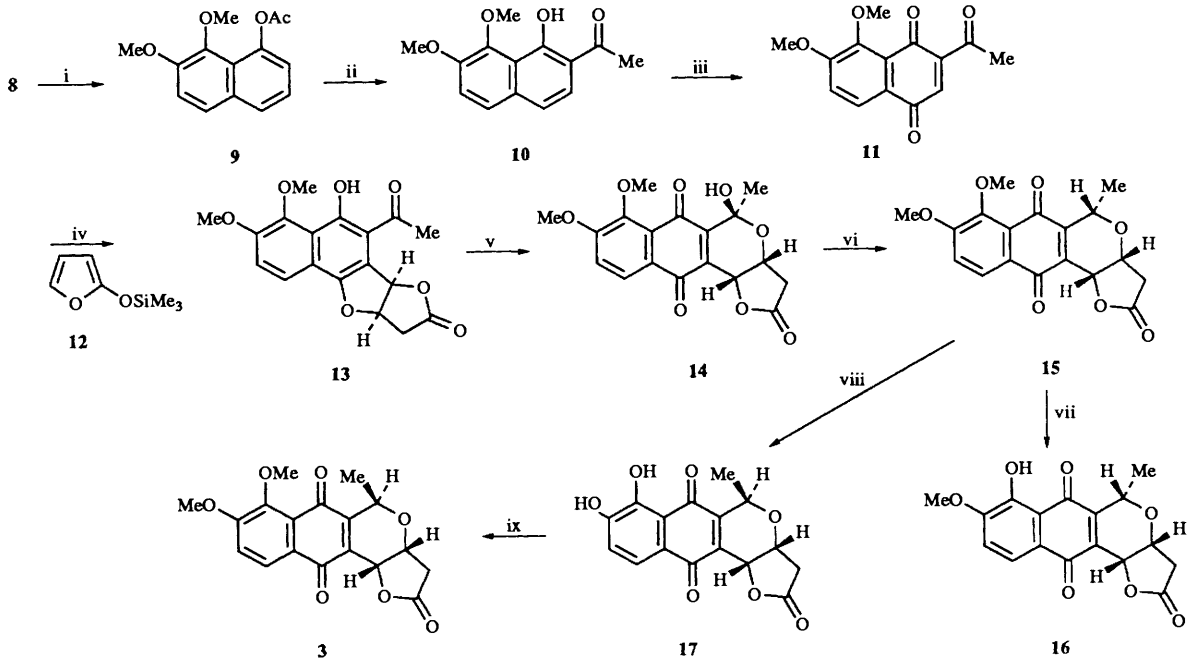
Arizonin A1 **1**, $R^1 = CH_3$, $R^2 = H$
Arizonin B1 **2**, $R^1 = H$, $R^2 = CH_3$
Arizonin C1 **3**, $R^1 = R^2 = CH_3$



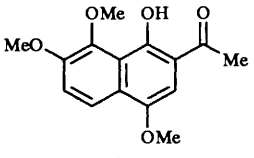
Arizonin A2 **4**, $R^1 = CH_3$, $R^2 = R^3 = H$
Arizonin B2 **5**, $R^1 = H$, $R^2 = CH_3$, $R^3 = H$
Arizonin C3 **6**, $R^1 = R^2 = R^3 = CH_3$



Kalafungin **7**



Scheme 1 *Reagents and conditions:* i, Et_3N, Ac_2O, DMAP(cat.), CH_2Cl_2, 48 h, 95%; ii, BF_3–Et_2O, 95 °C, 90%; iii, salcomine (0.5 equiv.), O_2, THF, 56%; iv, MeCN, **12**, 0 °C, 57%; v, CAN (2.0 equiv.), MeCN, H_2O, 62%; vi, Et_3SiH, TFA, CH_2Cl_2, 3 h, 84%; vii, BBr_3 (2.0 equiv.), CH_2Cl_2, −78 °C to room temp., 56%; viii, BBr_3 (3.3 equiv.), CH_2Cl_2, −48 °C to room temp., 87%; ix, Ag_2O (18 equiv.), MeI (excess), CH_2Cl_2, 75%



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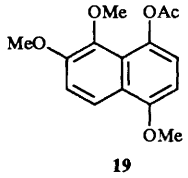

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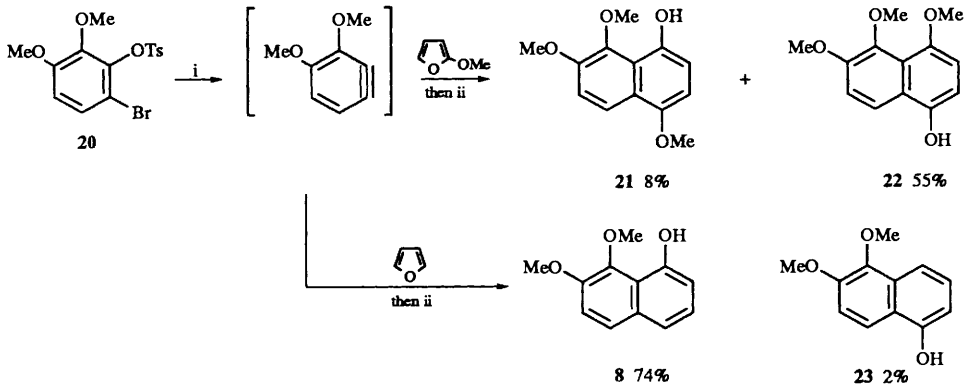
(0.5 equiv.)] and oxygen in tetrahydrofuran as solvent. This latter method afforded naphthoquinone **11** reproducibly in 56% yield after purification by flash chromatography.

With the required naphthoquinone **11** in hand, our attention then focused on the furofuran annulation (Scheme 1). 2-Trimethylsilyloxyfuran **12** (2 equiv.) was added to naphthoquinone **11** in acetonitrile at 0 °C under an atmosphere of argon. The reaction mixture was warmed to room temperature and after 3 h solvent was removed under reduced pressure. Purification by flash chromatography gave the desired adduct **13** (57%) as a pale yellow solid.

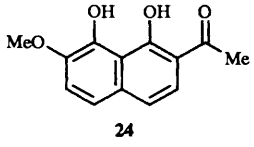
The mass spectrum showed a molecular ion at *m/z* 344 and the accurate mass measurement was consistent with the molecular formula $C_{18}H_{16}O_7$. The ^1H NMR spectrum exhibited a double doublet at δ_H 5.57 and a doublet at δ_H 6.56, assigned as the bridgehead protons 9a-H and 6b-H respectively. These protons resonated at similar chemical shifts to those reported for analogous furo[3,2-*b*]naphtho[2,1-*d*]furans.[5,6] The coupling constant $J_{9a,6b}$ 6.0 Hz was consistent with the *cis* fused ring junction of the two furan rings. The ^{13}C NMR spectrum was also consistent with the proposed structure, exhibiting a methylene carbon at δ_C 35.3 assigned as C-9, two methine carbons at δ_C 82.1 and 85.1 assigned to the two bridgehead carbons C-9a and C-6b respectively and two carbonyl carbons at δ_C 175.2 and 201.0 assigned to the γ-lactone and ketone carbons respectively.

The rearrangement of furo[3,2-*b*]naphtho[2,1-*d*]furan **13** was then carried out by treatment of adduct **13** with ceric(IV) ammonium nitrate (2 equiv.) in aqueous acetonitrile at room temperature. This afforded furo[3,2-*b*]naphtho[2,3-*d*]pyran **14** (62%) as a pale yellow solid. Spectral data were in agreement with the proposed structure with the mass spectrum exhibiting a molecular ion at *m/z* 360 and the IR spectrum displaying an OH stretch at 3404 cm^{-1} and absorbances at 1764 and 1673 cm^{-1} due to the carbonyl group of the γ-lactone and quinone, respectively. The ^1H NMR spectrum showed an upfield shift in the resonances of the bridgehead protons relative to the initial adduct **13**. The doublet of doublets at δ_H 4.76 was assigned as 3a-H and the doublet at δ_H 5.28 was assigned as 11b-H. Thus these protons appeared at chemical shifts similar to those reported for the analogous furo[3,2-*b*]naphtho[2,3-*d*]-pyrans.[5,6] The bridgehead coupling constant of $J_{3a,11b}$ 2.9 Hz also supported the presence of a *cis* fused 2*H*-furo[3,2-*b*]-naphtho[2,3-*d*]pyran system.

Reduction of the hemiacetal **14** to the ether **15** was



Scheme 2 *Reagents and conditions:* i, Bu^{n}Li, furan or 2-methoxyfuran, THF, −78 °C, 0.75 h; ii, conc. HCl, MeOH, reflux, 3 h



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accomplished using the method of Kraus *et al.*[9] Thus, the hemiacetal **14** was stirred with triethylsilane and trifluoroacetic acid in dichloromethane at room temperature for 3 h to give the ether **15** (84%). A comparison of the ^{1}H NMR data of the ether **15** with that of *epi*-7-O-methylkalafungin[5] suggested a *cis* relationship between the groups at C-5 and C-3a, consistent with axial delivery of hydride from triethylsilane as reported by Kraus.[9] The ^{1}H NMR spectrum of ether **15** showed a doublet of doublets at δ_H 4.34 assigned to 3a-H and a double quartet at δ_H 4.78 assigned to 5-H. *epi*-7-*O*-Methylkalafungin[5] exhibited comparable chemical shifts for these same protons at δ_H 4.33 and 4.79 whereas in the *trans* isomer 9-*O*-methylnanaomycin D[10] these protons resonated further downfield at δ_H 4.69 and 5.09 respectively.

Several methods were considered for the deprotection of the methyl ether **15**. It was thought that selective deprotection could be achieved by using a reagent which combined a strongly chelating cation with a nucleophilic anion. To this end, magnesium iodide was generated *in situ*[11] but this failed to give any of the deprotected methyl ether. Greater success was realised using boron tribromide.[12] The methyl ether **15** was treated with boron tribromide (2 equiv.) in dichloromethane at −78 °C. The reaction mixture was warmed to room temperature and quenched with aqueous sodium hydrogen carbonate (5%). Isolation and purification gave 5-*epi*-arizonin B1 **16** (56%) as an orange solid. Spectroscopic data supported the deprotection of only the *peri* methyl ether group. The mass spectrum showed a molecular ion at *m/z* 330 with the accurate mass measurement being consistent with the molecular formula $C_{17}H_{14}O_7$. The ^{1}H NMR spectrum showed only one methyl ether singlet at δ_H 4.01. The chemical shifts of the protons 3a-H and 5-H were δ_H 4.33 and 4.78 respectively, similar to those for the dimethyl ether **15** suggesting that no epimerisation had occurred. Arizonin B1[1] showed chemical shifts for these protons at δ_H 4.68 and 5.08, as expected for the *trans* isomer. The ^{13}C NMR spectrum recorded for **16** exhibited data similar to the data reported by Hochlowski *et al.*[1] for arizonin B1 **2**. In particular, for arizonin B1 **2** the signal at δ_C 188.6 was assigned as the C-7 hydrogen-bonded carbonyl due to its relative downfield shift from δ_C 182.4 in arizonin C1 **3** and δ_C 182.7 in arizonin A1 **1**.[1] The monomethyl ether **16** showed a signal at δ_C 189.2 assigned as the C-7 hydrogen-bonded carbonyl, compared to δ_C 184.0 for the dimethyl ether **15**. Thus, at this point selective demethylation at C-7 and a synthesis of 5-*epi*-arizonin B1 **16** and 5-*epi*-arizonin C1 **15** had been achieved.

The question remained as to whether treatment of 5-*epi*-arizonin C1 **15** with a larger excess of boron tribromide would effect demethylation as well as epimerisation of the groups on C-3a or C-5 to generate the correct *trans* stereochemistry between these two groups. Thus, 5-*epi*-arizonin C1 **15**, was treated with boron tribromide (3.3 equiv.) in dichloromethane affording dihydroxynaphthoquinone **17** as red crystals (87%) after purification by flash chromatography. Thus, additional boron tribromide not only effected demethylation at C-7 and C-8 but also the desired epimerisation to afford the *trans* stereochemistry between the groups on C-5 and C-3a.

Evidence for the formation of the *trans* isomer in the dihydroxynaphthoquinone **17** came from the observation of the characteristic downfield shifts of the resonances assigned to 3a-H and 5-H. The doublet of doublets assigned to the bridgehead proton 3a-H shifted downfield from δ_H 4.34 in the *cis* isomer **15** to δ_H 4.68 in the *trans* isomer **17** and the double quartet assigned to 5-H, shifted from δ_H 4.78 in the *cis* isomer **15** to δ_H 5.07 in the *trans* isomer **17** where it resonated as a quartet. This observed loss of long-range coupling between 5-H and 11b-H is consistent with conversion of the *cis* isomer into the *trans* isomer. The lack of methoxy group resonances in the ^{1}H NMR spectrum at δ_H 3.93 and 3.99, together with the IR spectrum which exhibited a broad OH stretch at 3854 cm^{-1} supported the formation of the dihydroxynaphthoquinone **17**. Furthermore, in the mass spectrum a molecular ion measured at high resolution at *m/z* 316.0582 supported the molecular formula $C_{16}H_{12}O_7$, thereby confirming the presence of two hydroxy groups.

Attempts to effect isomerisation of the *cis* isomer, 5-*epi*-arizonin B1 **16**, to the *trans* isomer, arizonin B1 **2**, were unsuccessful in that further treatment of **16** with boron tribromide afforded the *trans*-dihydroxynaphthoquinone **17** as the sole product.

The correct *trans* stereochemistry at C-3a and C-5 in the dihydroxynaphthoquinone **17** having been obtained, methylation at C-7 and/or C-8 was attempted in order to complete the synthesis of arizonin A1, B1 or C1. No matter what the outcome of the methylation, synthesis of an arizonin natural product should be achieved.

Methylation of dihydroxynaphthoquinone **17** was initially attempted using diazomethane. However this afforded a complex mixture for which the ^{1}H NMR spectrum showed the absence of a methoxy group. Methylation of kalafungin has been attempted by Hoeksema and Krueger using diazomethane.[13] However, in this case, methylation of the quinone

carbonyl group occurred in preference to methylation of the hydroxy group.

Methylation of dihydroxynaphthoquinone **11** was successfully achieved upon treatment with silver(I) oxide and an excess of methyl iodide for 0.5 h at room temperature. This method afforded arizonin C1 **3** (92%) wherein methylation at both C-7 and C-8 had occurred.

Evidence for the synthesis of the *trans* isomer once again came from the characteristic downfield shift of the resonances assigned to 3a-H and 5-H. A downfield shift of the resonance assigned to 3a-H from δ_H 4.34 in the *cis* isomer **15** to δ_H 4.66 in the *trans* isomer **3** together with the downfield shift of the resonance assigned to 5-H from δ_H 4.78 to δ_H 5.06 supported assignment as the *trans* isomer. The ^{1}H NMR spectrum further confirmed the *trans* stereochemistry at C-3a and C-5 by the presence of a doublet of doublets at δ_H 4.66 with coupling constants $J_{3a,3}$ 6.6 and $J_{3a,11b}$ 3.0 Hz, assigned to 3a-H, and a quartet at δ_H 5.06 with a coupling constant J_{vic} 6.9 Hz, assigned to 5-H. Two methoxy signals at δ_H 3.99 and 3.93 in the ^{1}H NMR spectrum and the molecular ion measured at high resolution at *m/z* 344.0893 establishing the molecular formula as $C_{18}H_{16}O_7$ also confirmed the synthesis of arizonin C1 **3**. The spectroscopic data and melting point were also in agreement with those reported in the literature for arizonin C1 isolated from natural sources.[1]

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 and assignments were made with the aid of DEPT spectra. 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 ionisation energy of 70 eV. Microanalyses were performed by the microanalytical laboratory, University of Otago. Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) with the solvents described. Standard extractive work-up refers to three extractions with the specified solvent, washing of the combined organic extracts with water and then brine, drying ($MgSO_4$) and removal of the solvent from the mixture using a rotary evaporator.

6-Bromo-2,3-dimethoxyphenyl toluene-*p*-sulfonate 20

To a solution of 2.3-dimethoxyphenol (2.0 g, 13 mmol) and triethylamine (1.57 g, 15.6 mmol) in dichloromethane (20 cm^3) at 0 °C was added toluene-*p*-sulfonyl chloride (3.0 g, 15.6 mmol) in dichloromethane (25 cm^3). The solution was stirred at room temperature for 1 h. Standard extractive work-up (dichloromethane) including an aq. $NaHCO_3$ wash, gave the crude product which was purified by flash chromatography (hexane then hexane–ethyl acetate, 2:1 then ethyl acetate) to give a sulfonate (3.62 g, 90%) as an amber oil; δ_H(270 MHz, $CDCl_3$) 2.43 (3 H, s, CH_3), 3.71 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3) 6.73–6.96 (3 H, m, ArH) and 7.31, 7.80 (4 H, AA'BB', *J* 8.4, C_6H_4). To a solution of this sulfonate (3.62 g, 11.8 mmol) in carbon tetrachloride (20 cm^3) was added a solution of bromine (2.35 g, 14.7 mmol) in carbon tetrachloride (4.7 cm^3). The reaction mixture was stirred at room temperature for 16 h after which the solvent was removed under reduced pressure. The crude product was recrystallised from hexane–dichloromethane (1:1) to give the bromosulfonate **20** (3.18 g, 70%) as an off-white solid, mp 115–117 °C (lit.,[7] mp 118.5–119.5 °C): δ_H(60 MHz, $CDCl_3$) 2.46 (3 H, s, CH_3), 3.65 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 6.72 and 7.23 (2 H, AB, *J* 9.1, ArH) and 7.37, 7.95 (4 H, AA'BB', *J* 8.4, ArH).

7,8-Dimethoxynaphthalen-1-ol 8

To a solution of the toluene-*p*-sulfonate **20** (5.0 g, 12.92 mmol) in anhydrous THF (50 cm^3)-furan (37 cm^3) at −78 °C under argon was added butyllithium (1.25 mol dm^{-3} in hexane: 10.45 cm^3, 13.1 mmol). The reaction mixture was stirred at −78 °C for 0.75 h and then warmed to room temperature over 0.5 h, diluted with water and subjected to a standard extractive work-up (ethyl acetate). The crude epoxide was dissolved in methanol (60 cm^3) containing conc. hydrochloric acid (0.5 cm^3) and heated under reflux for 3 h. Methanol was removed from the mixture under reduced pressure and the residue diluted with water and subjected to a standard extractive work-up (ethyl acetate). Flash chromatography (hexane–ethyl acetate, 4:1) gave the title compound **8** (2.0 g, 76%) as a yellow oil; δ_H(60 MHz, $CDCl_3$) 3.99 (3 H, s, OCH_3), 4.10 (3 H, s, OCH_3), 6.89–7.69 (5 H, m, ArH) and 9.66 (1 H, s, OH) which is in agreement with the literature.[7]

7,8-Dimethoxy-1-naphthyl ethanoate 9

To a solution of the naphthalenol **8** (4.27 g, 21 mmol) in dichloromethane (50 cm^3) was added triethylamine (4.23 g, 41.8 mmol), acetic anhydride (2.56 g, 25.2 mmol) and 4-dimethylaminopyridine (catalytic quantity). The reaction mixture was stirred at room temperature under argon for 48 h after which the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue the title compound gave **9** (4.9 g, 95%) as a white solid, mp 90–93 °C (lit.,[7] mp 92–93 °C): ν_{max}(Nujol) 1756 (C=O, ester) and 1603 cm^{-1} (C=C, aromatic): δ_H(270 MHz) 2.37 (3 H, s, CH_3), 3.88 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3) and 7.05–7.65 (5 H, m, ArH); δ_C 20.7 (CH_3), 56.5 (OCH_3), 61.5 (OCH_3), 115.0, 119.9, 125.0, 126.4, 131.4 (CH, C-2, C-3, C-4, C-5, C-6), 122.2, 123.3 (quat., C-4a, C-8a), 141.8 (quat., C-1), 145.1, 149.9 (quat., C-7, C-8) and 169.9 (quat., C=O): *m/z* 246 (M$^+$, 33%), 204 (M − C_2H_3O, 100) and 189 (75).

2-Acetyl-7,8-dimethoxy-1-naphthol 10

The ethanoate **9** (4.39 g, 17.85 mmol) was heated to *ca.* 95 °C under argon and boron trifluoride–diethyl ether (2.90 g, 20.6 mmol) was added dropwise to it. Vigorous evolution of ether was accompanied by the formation of a dark red solid. After 5 min the reaction mixture was cooled to room temperature and the resulting solid was decomposed by the addition of water. Standard extractive work-up (ethyl acetate) gave a brown oil, flash chromatography (hexane–ethyl acetate, 4:1) of which gave the title compound **10** (3.93 g, 90%) as fluorescent yellow needles, mp 123–124 °C (Found: C, 68.4; H, 5.6. $C_{14}H_{14}O_4$ requires C, 68.28; H, 5.73%); ν_{max}(Nujol) 1623 cm^{-1} (C=O, ketone): δ_H(270 MHz, $CDCl_3$) 2.68 (3 H, s, CH_3), 3.98 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 7.14 and 7.48 (2 H, AB, *J* 8.95, ArH), 7.38 and 7.49 (2 H, AB, *J* 8.95, ArH) and 14.31 (1 H, s, OH): δ_C(67.8 MHz, $CDCl_3$) 27.6 (CH_3), 57.0 (OCH_3), 61.8 (OCH_3), 114.0 and 120.5 (quat., C-4a, C-8a), 118.3, 118.6, 123.2, 124.1 (CH, C-3, C-4, C-5, C-6), 133.9 (quat., C-2), 146.95 and 150.35 (quat., C-7, C-8), 163.0 (s, C-1) and 203.8 (s, C=O): *m/z* 246 (M$^+$, 100%), (231 (M − CH_3, 59) and 203 (M − C_2H_3O, 19).

2-Acetyl-7,8-dimethoxy-1,4-naphthoquinone 11

A solution of the 1-naphthol **10** (30 mg, 0.122 mmol) in tetrahydrofuran (4.5 cm^3) was treated with salcomine (20 mg) and the reaction mixture stirred at room temperature under an atmosphere of oxygen for 50 h. Evaporation of the mixture

under reduced pressure, gave a brown oil which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford the title compound **11** (18 mg, 56%) as red crystals, mp 129.5–131.5 °C; ν_{max}(Nujol) 1662 cm^{-1} (C=O, quinone); δ_H(270 MHz, $CDCl_3$) 2.61 (3 H, s, CH_3), 3.95 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 7.02 (1 H, s, 3-H) and 7.23 and 7.91 (2 H, AB, *J* 8.8, ArH); *m/z* 260 (M^+, 100%), 245 (M − CH_3, 64) and 217 (M − CH_3CO, 66). Because of its instability the material was used in the subsequent step without further purification.

6-Acetyl-*cis*-6b,9a-dihydro-5-hydroxy-3,4-dimethoxyfuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one 13

To a solution of the naphthoquinone **11** (32 mg, 0.12 mmol) in acetonitrile (1 cm^3) at 0 °C under argon was added freshly distilled 2-trimethylsilyloxyfuran **12** (32 mg, 0.20 mmol) in acetonitrile (0.25 cm^3). The reaction mixture was warmed to room temperature and after 3 h the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (hexane–ethyl acetate, 2:1) to give the title compound **13** (23 mg, 57%) as a pale yellow solid, mp 111–113 °C (decomp.) (Found: C, 62.7; H, 4.6%; M^+, 344.0894. $C_{18}H_{16}O_7$ requires C, 62.79; H, 4.68%; *M*, 344.0896); ν_{max}(Nujol) 3163 (OH), 1762 (C=O, γ-lactone) and 1648 cm^{-1} (C=O, *o*-hydroxyaryl ketone); δ_H[270 MHz; $(CD_3)_2CO$] 2.69 (3 H, s, CH_3), 2.92 (1 H, d, J_{gem} 19.0, 9-H), 3.26 (1 H, dd, J_{gem} 19.0 and $J_{9',9a}$ 7.1, 9-H'), 4.01 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 5.57 (1 H, dd, $J_{9a,9'}$ 7.1 and $J_{9a,6b}$ 6.0, 9a-H), 6.56 (1 H, d, $J_{6b,9a}$ 6.0, 6b-H) and 7.60 and 7.70 (2 H, AB, *J* 9.0, ArH) and 14.21 (1 H, s, OH); δ_C[67.8 MHz, $(CD_3)_2SO$] 31.7 (CH_3, C-2'), 35.3 (CH_2, C-9), 56.6 (OCH_3), 61.8 (OCH_3), 82.1 (CH, C-9a), 85.1 (CH, C-6b), 111.7, 113.6, 118.1, 120.5 (quat., C-4a, C-6, C-6a, C-10b), 118.5, 119.0 (CH, C-1, C-2), 145.2, 150.0, 151.0, 154.6 (quat., C-3, C-4, C-5, C-10a), 175.2 (quat., C-8) and 201.0 (quat., C-1'); *m/z* 344 (M^+, 100%), 329 (M − CH_3, 39) and 299 (20).

(3a*R**,5*S**,11b*R**)-3,3a,5,11b-Tetrahydro-5-hydroxy-7,8-dimethoxy-5-methylfuro[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 14

To a solution of the adduct **13** (59 mg, 0.17 mmol) in acetonitrile (7 cm^3) was added a solution of ceric ammonium nitrate (0.19 g, 0.34 mmol) in water (3 cm^3). After 5 min the reaction mixture was subjected to standard extractive work-up (dichloromethane) to give the crude product, flash chromatography (hexane–ethyl acetate, 2:1 then ethyl acetate) of which gave the title compound **14** (38 mg, 62%) as a pale yellow solid, 204–206 °C (decomp.) [Found (EI): M^+, 360.0835. $C_{18}H_{16}O_8$ requires *M*, 360.0845]; ν_{max}(Nujol) 3404 (OH), 1764 (C=O, γ-lactone) and 1673 cm^{-1} (C=O, quinone); δ_H[270 MHz; $(CD_3)_2SO$] 1.67 (3 H, s, CH_3), 3.20 (1 H, dd, J_{gem} 17.6 and $J_{3,3a}$ 5.1, 3-H), 3.79 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.76 (1 H, dd, $J_{3a,3}$ 4.8 and $J_{3a,11b}$ 2.9, 3a-H), 5.28 (1 H, d, $J_{11b,3a}$ 2.9, 11b-H) and 7.50 and 7.85 (2 H, AB, *J* 8.8, ArH); δ_C[67.8 MHz; $(CD_3)_2SO$] 26.1 (CH_3), 36.1 (CH_2, C-3), 56.5 (OCH_3), 60.8 (OCH_3), 65.9 (CH, C-3a), 69.1 (CH, C-11b), 92.6 (quat., C-5), 116.8, 123.7 (CH, C-9, C-10), 124.4, 125.5, 133.3, 147.4 (quat., C-5a, C-6a, C-10a, C-11a), 148.4, 158.9 (quat., C-7, C-8), 175.4 (quat., C-2) and 182.0 and 182.1 (quat., C-6, C-11); *m/z* 360 (M^+, 75%), 345 (M − CH_3, 100), 299 (48) and 290 (93).

(3a*R**,5*S**,11b*R**)-3,3a,5,11b-Tetrahydro-7,8-dimethoxy-5-methylfuro[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 15

To a solution of the hemi-acetal **14** (73 mg, 0.20 mmol) in dichloromethane (10 cm^3) at 0 °C under argon was added trifluoroacetic acid (0.23 g, 2.0 mmol) followed by triethylsilane (0.23 g, 2.0 mmol). After 15 min, the reaction mixture was warmed to room temperature and stirred for a further 3 h. The mixture was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexane–ethyl acetate, 2:1 then 3:7) to give the title compound **15** (59 mg, 84%) as an amber solid, mp 191–194 °C (decomp.) (Found: C, 62.6; H, 4.5%; M^+, 344.0909. $C_{18}H_{16}O_7$ requires C, 62.79; H, 4.68%; *M*, 344.0896); ν_{max}(CH_2Cl_2) 1790 (C=O, γ-lactone) and 1664 cm^{-1} (C=O, quinone); δ_H(270 MHz, $CDCl_3$) 1.56 (3 H, d, J_{vic} 7.0, CH_3), 2.72 (1 H, d, J_{gem} 17.6, 3-H'), 2.91 (1 H, dd, J_{gem} 17.6 and $J_{3,3a}$ 4.8, 3-H), 3.93 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 4.34 (1 H, dd, $J_{3a,3}$ 4.8 and $J_{3a,11b}$ 2.6, 3a-H), 4.78 (1 H, dq, J_{vic} 7.0 and $J_{5,11b}$ 1.8, 5-H), 5.28 (1 H, dd, $J_{11b,3a}$ 2.2 and $J_{11b,5}$ 1.8, 11b-H) and 7.21 and 7.93 (2 H, AB, *J* 8.8, ArH); δ_C(67.8 MHz, $CDCl_3$) 19.8 (CH_3), 37.2 (CH_2, C-3), 56.3 (OCH_3), 61.6 (OCH_3), 68.9, 69.7 (CH, C-3a, C-11b), 71.2 (CH, C-5), 116.0, 124.6 (CH, C-9, C-10), 125.1, 125.9, 133.1, 148.9 (quat., C-5a, C-6a, C-10a, C-11a), 152.0, 158.9 (quat., C-7, C-8), 174.5 (quat., C-2) and, 181.3 and 184.0 (quat., C-6, C-11); *m/z* 344 (M^+, 42%), 300 (M − CO_2, 79) and 285 (M − $C_2H_3O_2$, 100).

(3a*R**,5*S**,11b*R**)-3,3a,5,11b-Tetrahydro-7-hydroxy-8-methoxy-5-methylfuro[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 16

To a solution of dimethyl ether **15** (25 mg, 0.073 mmol) in dichloromethane (5 cm^3) at −78 °C under argon was added a solution of boron tribromide (38 mg, 0.15 mmol) in dichloromethane (0.80 cm^3). After 5 min the temperature was raised to 0 °C. After a further 10 min the reaction mixture was treated with aq. $NaHCO_3$ (5%). The aqueous phase was extracted with $CHCl_3$ (3 × 5 cm^3) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–ethyl acetate, 4:1, 2:1 then 1:1) gave the title compound **16** (13 mg, 56%) as an orange solid, mp 197–200 °C [Found (EI): M^+, 330.0727. $C_{17}H_{14}O_7$ requires *M*, 330.0739]; ν_{max} 1791 cm^{-1} (C=O, γ-lactone); δ_H(270 MHz, $CDCl_3$) 1.64 (3 H, d, J_{vic} 6.6, CH_3), 2.73 (1 H, d, J_{gem} 17.2, 3-H'), 2.89 (1 H, dd, J_{gem} 17.6 and $J_{3,3a}$ 4.4, 3-H), 4.01 (3 H, s, OCH_3), 4.33 (1 H, dd, $J_{3a,3}$ 4.4 and $J_{3a,11b}$ 2.6, 3a-H), 4.78 (1 H, dq, J_{vic} 6.6 and $J_{5,11b}$ 1.8, 5-H), 5.26 (1 H, dd, $J_{11b,3a}$ 2.6 and $J_{11b,5}$ 1.8, 11b-H) and 7.13 and 7.72 (2 H, AB, $J_{8,7}$, ArH); δ_C(67.8 MHz, $CDCl_3$) 20.6 (CH_3), 37.3 (CH_2, C-3), 56.5 (OCH_3), 68.6, 69.9 (CH, C-3a, C-11b), 71.1 (CH, C-5), 115.2, 123.3, 136.4, 149.9 (quat., C-5a, C-6a, C-10a, C-11a), 152.4, 154.5 (quat., C-7, C-8), 174.2 (quat., C-2), 180.5 (quat., C-11) and 189.2 (quat., C-6); *m/z* 330 (M^+, 100%), 315 (M − CH_3, 8), 286 (28), 271 (34) and 259 (30).

(3a*R**,5*R**,11b*R**)-3,3a,5,11b-Tetrahydro-7,8-dihydroxy-5-methylfuro[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 17

To a solution of dimethyl ether **15** (5 mg, 0.015 mmol) in dichloromethane (0.75 cm^3) at −48 °C under an atmosphere of nitrogen, boron tribromide in dichloromethane (1.0 mol dm^{-3}; 0.048 cm^3, 0.048 mmol) was added dropwise. After 5 min the reaction mixture was allowed to warm to room temperature and stirring was continued for a further 1 h. Water (1 cm^3) was added to the reaction mixture after which it was stirred for 30 min. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 4 cm^3). The combined organic layer and extracts were washed with water (4 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a red solid which was purified by flash chromatography using hexane–ethyl acetate (1:1 then 1:2) as eluent to afford the *title compound* **17** (4 mg, 87%) as red crystals, mp 157.5–158.5 °C (Found: M^+, 316.0582. $C_{16}H_{12}O_7$ requires *M*, 316.0583); ν_{max}(CH_2Cl_2) 1777 (C=O, γ-lactone) and 1646 cm^{-1} (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.56 (3 H, d, J_{vic} 6.7, CH_3), 2.69 (1 H, d, J_{gem} 17.7, 3'-H), 2.97 (1 H, dd, J_{gem} 17.7 and

$J_{3,3a}$ 5.0, 3-H), 4.68 (1 H, dd, $J_{3a,3}$ 5.0 and $J_{3a,11b}$ 3.0, 3a-H), 5.07 (1 H, q, J_{vic} 6.7, 5-H), 7.24 (1 H, d, $J_{11b,3a}$ 3.0, 11b-H), 7.24 (1 H, d, $J_{9,10}$ 8.6, 9-H), 7.71 (1 H, d, $J_{10,9}$ 8.6, 10-H) and 12.00 (1 H, s, OH); *m/z* 316 (M^+, 100%) and 43 ($M - C_{14}H_9O_6$, 25).

Arizonin Cl 3

To a solution of the dihydroxynaphthoquinone **17** (4 mg, 0.013 mmol) in dichloromethane (0.5 cm^3) was added silver(I) oxide (42 mg, 0.181 mmol) and iodomethane (0.5 cm^3, 8.03 mmol). The reaction mixture was stirred for 30 min and then filtered through a Celite pad and evaporated under reduced pressure to afford arizonin Cl **3** as an orange solid, mp 110–114 °C (lit.,[1] mp 110–135 °C) (Found: M^+, 344.0893; $C_{18}H_{16}O_7$ requires M, 344.0896); $\nu_{max}(CH_2Cl_2)$ 1789 (C=O, γ-lactone) and 1660 cm^{-1} (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.55 (3 H, d, J_{vic} 6.9, CH_3), 2.68 (1 H, d, J_{gem} 17.8, 3-H′), 2.95 (1 H, dd, J_{gem} 17.8 and $J_{3,3a}$ 6.6, 3-H). 3.93, 3.99 (each 3 H, s, OMe), 4.66 (1 H, dd, $J_{3a,3}$ 6.6 and $J_{3a,11b}$ 3.0, 3a-H), 5.06 (1 H, q, J_{vic} 6.9, 5-H), 5.26 (1 H, d, $J_{11b,3a}$ 3.0, 11b-H), 7.23 (1 H, d, $J_{9,10}$ 8.6, 9-H) and 8.00 (1 H, d, $J_{10,9}$ 8.6, 10-H); *m/z* 344 (M^+, 100%), 330 ($M - CH_2$, 75) and 285 ($M - C_2H_5$, 60). The ^1H NMR data were in agreement with those given in the literature.[1]

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