Synthesis of the monomeric unit of γ-actinorhodin

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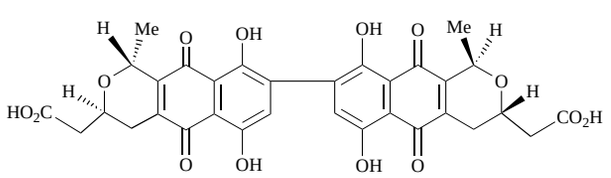
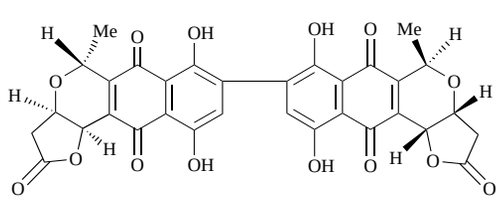
The first syntheses of the monomeric units of actinorhodin 19 and 5-*epi*-γ-actinorhodin 18 are described. The key steps involve addition of 2-trimethylsilyloxyfuran 14 to the 2-acetylnaphthoquinone 13 affording the adduct 15 which undergoes oxidative rearrangement to a pyranonaphthoquinone system 16 upon treatment with ceric ammonium nitrate. Naphthoquinone 13 is prepared from naphthol 11 which, in turn, is prepared *via* addition of furan 5 to 1,4-dimethoxy-2,3-dehydrobenzene followed by treatment with acid.

The red pigment actinorhodin **1** was first isolated[1] from the mycelia of an actinomyces species *Streptomyces coelicolor* and displayed litmus-like properties—bright blue in alkaline and red in acid. The presence of the dimeric isochromanquinone skeleton in actinorhodin **1** was determined by extensive chemical degradation and mass spectral studies[2] and the point of dimerization has been established unequivocally.[3] Six other congeners of actinorhodin **1**, including γ-actinorhodin **2**, which all contain an oxygen atom in the position *ortho* to the linkage site have been isolated[4,5] from *Streptomyces coelicolor*. Apart from the reported activity of actinorhodin **1** against *Staphylococcus aureus*,[6] the biological activity of these dimeric pyranonaphthoquinones has been relatively unexplored, although kalafungin **3** and nanaomycin A **4**, which are closely related to the monomeric units of these dimeric structures, have been proposed to act as bioreductive alkylating agents.[7]

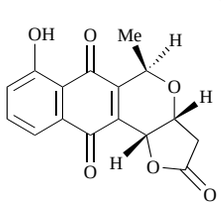
Despite the fact that molecular cloning systems[8,9] have been developed to produce actinorhodin **1** and hybrids of actinorhodin **1**, no total synthesis of actinorhodin **1** or γ-actinorhodin **2** has been reported. A partial synthesis of actinorhodin **1** starting from a degradation product of the antibacterial metabolite α-naphthocyclinone has been reported by Laatsch,[10] in which the key step hinged on an oxidative coupling of a naphthol derivative. We herein report the full details of our synthesis[11] of the monomeric unit of actinorhodin **19** based on earlier methodology we have developed for the synthesis of related pyranonaphthoquinone antibiotics, *e.g.* kalafungin **3**[12] and arizonin C1.[13]



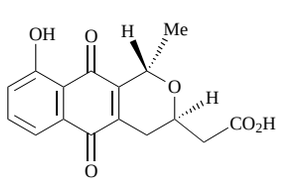
Actinorhodin **1**



γ-Actinorhodin **2**



Kalafungin **3**



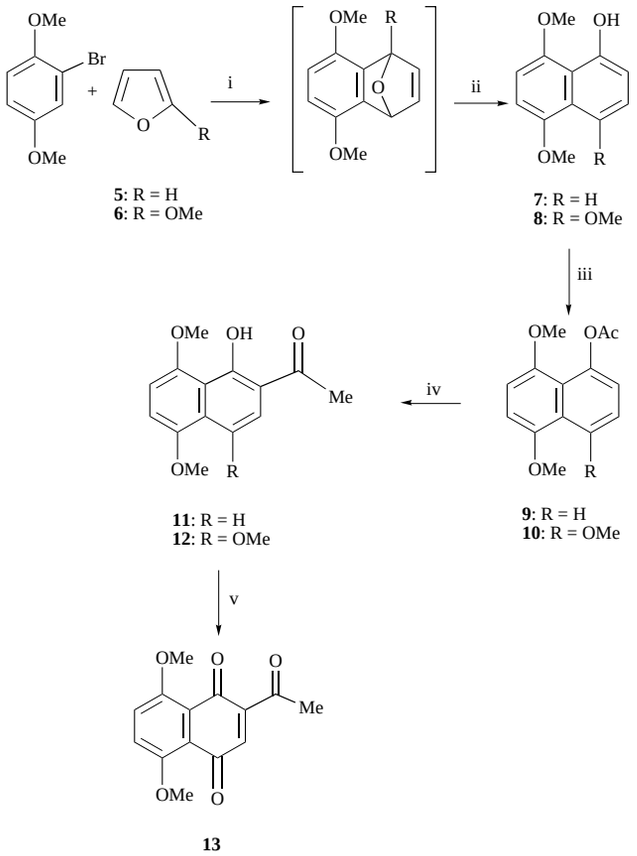
Nanaomycin A **4**

The key steps in our approach to **19** involved addition of 2-trimethylsilyloxyfuran **14** to a naphthoquinone **13** bearing an acetyl group at C-2, followed by oxidative rearrangement of the resultant furo[2′,3′-*d*]naphtho[1,2-*b*]furan **15** to a furo[2′,3′-*e*]naphtho[2,3-*c*]pyran **16** (Scheme 2). Our initial goal was therefore to prepare naphthoquinone **13**.

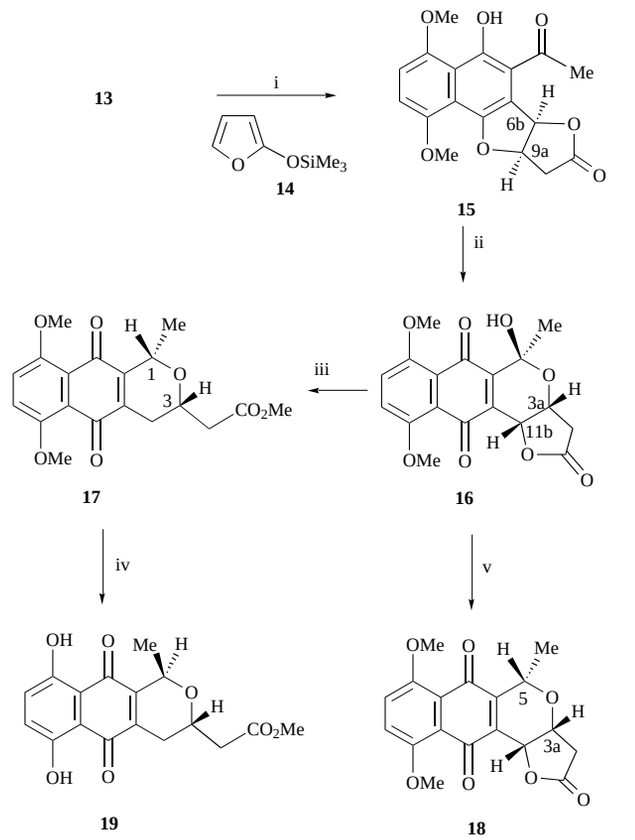
It was initially envisaged that oxidation of 2-(1-oxoethyl)-4,5,8-trimethoxy-1-naphthol **12**, obtained *via* Fries rearrangement of the acetate **10** (prepared from naphthol **8**) would provide the desired naphthoquinone **12** (Scheme 1). Naphthol **8** has previously been prepared[14] albeit in 13% overall yield using a four-step procedure starting from naphthazarin. It was therefore hoped that methodology developed by Giles *et al.*[15] to prepare oxygenated naphthols *via* the addition of furan **5** or 2-methoxyfuran **6** to methoxydidehydrobenzenes would afford a more efficient preparation of naphthol **8**.

Towards this end, 1-bromo-2,5-dimethoxybenzene was stirred with sodium amide and 2-methoxyfuran **6** at 50 °C in tetrahydrofuran. After acidic work-up the desired naphthol **8** was isolated only in very low yield due to reaction of sodium amide with 2-methoxyfuran **6**. Hence it was necessary to generate the dehydrobenzene intermediate before addition of 2-methoxyfuran **6** rather than have this present during dehydrobenzene formation. Using this modified procedure, the desired naphthol **8** was still only isolated in 22% yield. The low yield in this case was attributed to competitive reaction of the dehydrobenzene intermediate with sodium amide which was not improved by use of lithium diisopropylamide. After conversion of naphthol **8** into the acetate **10**, Fries rearrangement using boron trifluoride–diethyl ether and aluminium trichloride also proved problematic, in that concomitant loss of the methoxy groups resulted in only complex mixtures being obtained.

At this point it was decided to investigate an alternative synthesis of naphthoquinone **13** starting from naphthol **7** which lacks the additional methoxy group at C-4. In this case, naphthol **7** had been previously prepared by Giles *et al.*[15] in good yield by treatment of 1-bromo-2,5-dimethoxybenzene with sodium amide in the presence of furan **5** followed by treatment with hydrochloric acid. After smooth acetylation under standard conditions (72% yield), Fries rearrangement of acetate **9** was effected using boron trifluoride–diethyl ether affording 2-acetylnaphthol **11** (70%). On some occasions, lower yields were



Scheme 1 *Reagents and conditions:* i, $NaNH_2$, THF, 50 °C, 45 h; ii, conc. HCl, MeOH, reflux, 3 h, 76% (R = H); iii, Et_3N, Ac_2O, DMAP (cat.), CH_2Cl_2, room temp., 48 h, 72% (R = H); iv, $BF_3{\cdot}OEt_2$, 140 °C, 70% (R = H); v, CAN (2.0 equiv.), MeCN, H_2O, room temp., 46%



Scheme 2 *Reagents and conditions:* i, **14**, MeCN, 0 °C, 66%; ii, CAN (2.0 equiv.), MeCN, H_2O, room temp., 75%; iii, Et_3SiH, TFA, CH_2Cl_2, room temp., 24 h then CH_2N_2, 68%; iv, BBr_3 (10 equiv.), CH_2Cl_2, −78 °C to room temp., 82%; v, Et_3SiH, TFA, CH_2Cl_2, room temp., 7 h, 84%

obtained for this reaction when a second product was formed. This by-product was identified as naphthol **7** which could be recycled back into the synthesis and was, therefore, not problematic.

Finally it remained only to oxidize naphthol **11** to naphthoquinone **13**. The optimum yield obtained for this step using 2 equiv. of ceric ammonium nitrate in aqueous acetonitrile was 46%. Use of silver(II) oxide and Fremy's salt afforded even lower yields of the desired naphthoquinone **13**.

With the required naphthoquinone **13** in hand, addition of 2-trimethylsilyloxyfuran **14** afforded the desired adduct **15** in 66% yield (Scheme 2). The mass spectrum showed a molecular ion at *m/z* 344 and the accurate mass was consistent with the molecular formula $C_{18}H_{16}O_7$. The ^{1}H NMR spectrum exhibited a double doublet at δ_H 5.42 and a doublet at δ_H 6.37, assigned as the bridgehead protons 9a-H and 6b-H, respectively. These protons resonated at similar chemical shifts to those reported for the analogous protons in the furo[3,2-*b*]benzofurans.[12,13] The coupling constant $J_{9a,6b}$ 5.9 Hz was consistent with the *cis*-fused ring junction of the two furan rings.[12,13] The ^{13}C NMR spectrum was also consistent with the proposed structure, exhibiting a methylene carbon at δ_C 35.4 assigned as C-9, two methine carbons at δ_C 81.5 and 83.4 assigned as the two bridgehead carbons C-9a and C-6b, respectively and two carbonyl carbons at δ_C 175.4 and 200.2 assigned as the γ-lactone and ketone respectively.

Thus, with the furo[2′,3′-*d*]naphtho[1,2-*b*]furan **15** in hand, rearrangement to a pyranonaphthoquinone was investigated. This was based on a similar rearrangement previously reported for the synthesis of kalafungin **3**.[12] Such a conversion was based on the work of Castagnoli *et al.*[16] who reported that ceric ammonium nitrate could be used to oxidize a variety of hydroquinone methyl ethers to the corresponding quinones. On this basis, it was proposed that furonaphthofuran **15**, a cyclic ether of a hydroquinone, would undergo an analogous oxidative dealkylation reaction to give a β-hydroxy lactone. Subsequent nucleophilic attack of the hydroxy group onto the methyl ketone then affords the hemiacetal **16**.

Ceric(IV) ammonium nitrate oxidation of the adduct **15** in aqueous acetonitrile at room temperature, gave the desired furo[2′,3′-*e*]naphtho[2,3-*c*]pyran **16** in 75% yield. Spectral data were in agreement with the proposed structure. The mass spectrum showed a molecular ion at *m/z* 360 while the IR spectrum exhibited a hydroxy band at 3680 cm^{-1} and bands at 1790 and 1662 cm^{-1} due to the carbonyl group of the γ-lactone and quinone respectively. The ^{1}H NMR spectrum showed an upfield shift in the resonances of the bridgehead protons relative to the initial adduct **15**. The doublet of doublets at δ_H 4.88 was assigned as 3a-H and the doublet at δ_H 5.35 was assigned as 11b-H. The bridgehead protons resonated at similar positions to that reported for the analogous furo[3′,2′-*e*]naphtho[2,3-*c*]pyrans[12,13] and the coupling constant of $J_{3a,11b}$ 2.9 Hz also supported the presence of a *cis*-fused 2*H*-furo[2′,3′-*e*]naphtho[2,3-*c*]pyran system.

Reduction of hemiacetal **16** to the ether **18** was accomplished using the method of Kraus *et al.*[17] Thus, hemiacetal **16** was stirred with triethylsilane and trifluoroacetic acid in dichloromethane at room temperature for 7 h to give ether **18** in 84% yield. A comparison of the ^{1}H NMR data of ether **18** with that of *epi*-7-*O*-methylkalafungin[12] suggested a *cis*-relationship between the groups at C-5 and C-3a as expected and consistent with axial delivery of hydride from triethylsilane as reported by Kraus.[17] The ^{1}H NMR spectrum of ether **18** showed a doublet of doublets at δ_H 4.39 assigned as 3a-H and a double quartet at δ_H 4.70 assigned as 5-H. *epi*-7-*O*-Methylkalafungin[12] showed similar chemical shifts at δ_H 4.33 and 4.79, in comparison to the downfield shifts exhibited by the *trans*-isomer 9-*O*-methylnanaomycin D at δ_H 4.69 and 5.09.[12]

The work to date constituted a synthesis of the monomeric unit of 5-*epi*-γ-actinorhodin dimethyl ether **18**. It now remained to convert the hemiacetal **16** into the monomeric unit of actinorhodin methyl ester **19**. It was discovered in this laboratory that the triethylsilane reduction of a hemiacetal to an ether by the method of Kraus[17] would also effect cleavage of the lactone ring of a pyranonaphthoquinone to give the corresponding acid, if the reaction time was increased.

Thus, treatment of hemiacetal **16** with triethylsilane and trifluoroacetic acid followed by diazomethane afforded ester **17** in 68% yield as a yellow–orange solid. The ^{1}H NMR spectrum lacked the bridgehead proton at δ_H 5.31 assigned to 11b-H in the ether **18** and was, therefore, consistent with cleavage of the γ-lactone ring. The double double doublet at δ_H 2.16 was assigned to the pseudoaxial proton at C-4 and the double double doublet at δ_H 2.86 to the C-4 pseudoequatorial proton. The 3-H signal was at δ_H 3.86–3.92 which is considerably upfield from its position in the hemiacetal **16** (as 3a-H) where it resonated at δ_H 4.88. The multiplet at δ_H 4.80–4.84 was assigned to 1-H and was consistent with the reduction of the hemiacetal to a cyclic ether. The three-proton singlet at δ_H 3.70 was consistent with the presence of a methyl ester group and the two, three-proton singlets at δ_H 3.92 and 3.93 were consistent with the presence of two methyl ether groups.

Deprotection of dimethyl ether **17** to dihydroxynaphthoquinone **19** was then achieved in 82% yield using an excess of boron tribromide. Under these conditions epimerization at C-1 was also effected to give the isomer in which the protons at C-1 and C-3 are *trans* to each other. The NMR data for **19** were in agreement with those reported by Laatsch.[10]

The synthesis of **19** constitutes a synthesis of the monomeric unit of the dimeric pyranonaphthoquinone actinorhodin **1** whilst **18** is a dimethyl ether epimer of the monomeric unit of γ-actinorhodin **2**. Several attempts were made to effect oxidative coupling of the monomeric naphthazarin **19** to form a dimer using various oxidizing agents such as silver(I) oxide–triethylamine and CuCl(OH)·TMEDA/O_2. These reagents have been reported by Laatsch[18] and Koga,[19] respectively, as suitable reagents to effect oxidative coupling of juglone derivatives. Unfortunately, in the present work only unchanged starting material was recovered from these reactions after prolonged reaction times.

Experimental

Mps 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 ionization energy of 70 eV. Microanalyses were performed by the microanalytical laboratory, University of Otago, New Zealand. 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 using a rotary evaporator.

4,5,8-Trimethoxynaphthalen-1-ol 8

To a suspension of sodium amide (2.0 g, 51 mmol) in anhydrous tetrahydrofuran (50 ml) was added 1-bromo-2,5-dimethoxybenzene (5.53 g, 25.5 mmol). The reaction mixture was stirred at 50 °C under argon for 1 h after which 2-methoxyfuran **6** (5.0 g, 51 mmol) was added dropwise to it. The reaction mixture was heated at 50 °C for 18 h and then quenched with conc. hydrochloric acid (2 ml) and stirred at room temperature for 10 min. Standard extractive work-up (ethyl acetate) gave a brown oil, flash chromatography (hexane–ethyl acetate, 4:1) of which gave (i) *N*,*N*-bis(1,4-dimethoxybenzyl)amine (0.4 g); δ_H(60 MHz) 3.75 (6 H, s, 2 × OCH_3), 3.83 (6 H, s, 2 × OCH_3) and 6.22–7.13 (6 H, m, ArH); *m/z* 289 (M^+, 89%), 274 (M − CH_3, 26) and 243 (M − C_2H_6O, 100); (ii) *N*,*N*,*N*-tris(1,4-dimethoxybenzyl)amine (0.85 g); δ_H(270 MHz) 3.53–3.86 (18 H, s, 6 × OCH_3) and 6.37–7.13 (9 H, m, ArH); *m/z* 425 (M^+, 100%) and 379 (M − C_2H_6O, 92); (iii) 4,5,8-trimethoxynaphthalen-1-ol **8** (1.08 g, 22%), mp 149–150 °C (lit.,[14] mp 148–149 °C).

4,5,8-Trimethoxy-1-naphthyl ethanoate 10

To a solution of 4,5,8-trimethoxynaphthalen-1-ol **8** (1.91 g, 8.16 mmol) in dichloromethane (40 ml) was added triethylamine (1.65 g, 16.3 mmol) followed by acetic anhydride (0.1 g, 9.79 mmol) and 4-dimethylaminopyridine (catalytic quantity). The reaction mixture was stirred at room temperature under argon for 18 h after which solvent was removed under reduced pressure and the crude product flash chromatographed (hexane–ethyl acetate, 4:1) to give the title compound **10** (0.93 g, 73%) as a colourless solid, mp 132–134 °C (Found: C, 65.3; H, 5.9. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%); ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1753 (C=O, ester) and 1598 (C=C, aromatic); δ_H(270 MHz) 2.33 (3 H, s, CH_3), 3.84 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 6.80 (1 H, d, *J* 8.6, ArH), 6.82 (1 H, d, *J* 8.6, ArH), 6.83 (1 H, d, *J* 8.6, ArH) and 6.91 (1 H, d, *J* 8.6, ArH); δ_C 20.8 (CH_3), 56.6 (OCH_3), 56.8 (OCH_3), 57.7 (OCH_3), 106.6, 107.4, 108.5 (CH, C-3, C-6, C-7), 119.8 (CH, C-2), 120.3, 121.5 (quat., C-4a, C-8a), 139.7 (quat., C-1), 149.3, 151.3, 155.0 (quat., C-4, C-5, C-8) and 170.5 (quat., C=O); *m/z* 276 (M^+, 52%), 234 (M − $COCH_3$, 100) and 219 (M − C_3H_6O, 90).

2-(1-Oxoethyl)-4,5,8-trimethoxynaphthalen-1-ol 12

The ester **10** (0.88 g, 3.19 mmol) was heated to *ca.* 140 °C under argon and then boron trifluoride–diethyl ether (0.52 g, 3.67 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 solid decomposed by the addition of water. Standard extractive work-up (ethyl acetate) gave a brown oil, flash chromatography (hexane–ethyl acetate, 9:1 then 4:1) of which gave the title compound **12** (0.181 g, 18%) as a yellow oil [Found (EI): M^+, 262.0842. $C_{14}H_{14}O_5$ requires *M*, 262.0841]; ν_{max}-(CH_2Cl_2 solution)/cm^{-1} 3393 (OH) and 1623 (C=O, ketone); δ_H(270 MHz) 2.67 (3 H, s, CH_3), 3.98 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 6.79 (1 H, d, *J* 8.6, ArH), 6.92 (1 H, d, *J* 8.6, ArH), 7.11 (1 H, s, 3-H) and 9.21 (1 H, s, OH); δ_C 28.2 (CH_3), 56.6 (OCH_3), 56.8 (OCH_3), 56.9 (OCH_3), 106.5, 109.1, 109.2 (CH, C-3, C-6, C-7), 115.4, 118.2, 120.9 (quat., C-2, C-4a, C-8a), 145.4, 149.7 (quat., C-1, C-4), 154.3, 155.7 (quat., C-5, C-8) and 203.2 (quat., C=O); *m/z* 262 (M^+, 100%), 247 (M − CH_3, 95), 232 (M − 2 × CH_3, 15) and 217 (M − 3 × CH_3, 29).

5,8-Dimethoxynaphthalen-1-ol 7

To a suspension of sodium amide (2.0 g, 51.28 mmol) in anhydrous tetrahydrofuran (17 ml) was added furan **5** (14 ml) and the mixture warmed to 50 °C under argon. 1-Bromo-2,5-dimethoxybenzene (2.86 g, 13.18 mmol) was added to the reaction mixture which was then stirred at 50 °C for 45 h. After this it was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. This was dissolved in methanol (60 ml) containing conc. hydrochloric acid (1 ml) and the mixture heated at reflux for 3 h. Methanol was removed from the mixture under reduced pressure and the residue partitioned between ethyl acetate and

water. The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue gave 5,8-dimethoxynaphthalen-1-ol **7** (2.03 g, 76%) as a white solid, mp 102–104 °C (lit.,[15] mp 103–104 °C).

5,8-Dimethoxy-1-naphthyl ethanoate 9

To a solution of compound **7** (0.63 g, 3.09 mmol) in dichloromethane (10 ml) was added triethylamine (0.63 g, 6.18 mmol) followed by acetic anhydride (0.38 g, 3.71 mmol) and 4-dimethylaminopyridine (catalytic quantity). The reaction mixture was stirred at room temperature under argon for 48 h, after which standard extractive work-up (dichloromethane) followed by flash chromatography (hexane–ethyl acetate, 4:1) gave the title compound **9** (0.55 g, 72%) as a white solid, mp 134–135 °C (Found: C, 68.1; H, 5.7. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%); ν_{max}(Nujol)/cm^{-1} 1761 (C=O, ester) and 1603 (C=C, aromatic); δ_H(270 MHz), 2.33 (3 H, s, CH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 6.64 (1 H, d, *J* 7.9, 6-H or 7-H), 6.66 (1 H, d, *J* 7.9, 7-H or 6-H), 7.09 (1 H, dd, $J_{2,3}$ 7.7 and $J_{2,4}$1.5, 2-H), 7.41 (1 H, dd, $J_{3,4}$ 8.4 and $J_{3,2}$ 7.7, 3-H) and 8.15 (1 H, dd, $J_{4,3}$ 8.4 and $J_{4.2}$ 1.5, 4-H); δ_C 20.8 (CH_3), 55.6 (OCH_3), 56.2 (OCH_3), 103.9, 105.8, 119.9, 120.3 (CH, C-2, C-4, C-6, C-7), 125.4 (CH, C-3), 119.6, 128.3 (quat., C-4a, C-8a), 146.1, 148.7, 149.4 (quat., C-1, C-5, C-8) and 170.1 (quat., C=O); *m/z* 246 (M^+, 43%), 204 (M − C_2H_2O, 90) and 189 (M − C_3H_5O, 100).

5,8-Dimethoxy-2-(1-oxoethyl)-1-naphthol 11

The ester **9** (0.74 g, 3.01 mmol) was heated to *ca*. 140 °C under argon after which boron trifluoride–diethyl ether (0.49 g, 3.46 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 solid 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 **11** as a yellow solid (0.52 g, 70%), mp 129–130 °C (yellow needles, EtOAc) (Found: C, 68.55; H, 5.9. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%); ν_{max}(Nujol)/cm^{-1} 3400 (OH) and 1620 (C=O, ketone); δ_H(270 MHz) 2.69 (3 H, s, CH_3), 3.92 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 6.76 (1 H, d, *J* 8.5, 6-H or 7-H), 6.86 (1 H, d, *J* 8.5, 7-H or 6-H), 7.64 (1 H, d, *J* 8.7, 3-H or 4-H), 7.66 (1 H, d, *J* 8.7, 4-H or 3-H) and 14.08 (1 H, br s, OH); δ_C 28.0 (CH_3), 55.8 (OCH_3), 56.6 (OCH_3), 106.1, 108.2, 112.2, 125.6 (CH, C-3, C-4, C-6, C-7), 115.2, 116.8 (quat., C-4a, C-8a), 131.0 (quat., C-2), 149.0, 152.8 (quat., C-5, C-8), 163.0 (quat., C-1) and 203.4 (quat., C=O); *m/z* 246 (M^+, 100%), 231 (M − CH_3, 95) and 201 (40).

2-(1-Oxoethyl)-5,8-dimethoxy-1,4-naphthoquinone 13

(i) Ceric ammonium nitrate. To a solution of compound **11** (0.46 g, 1.87 mmol) in acetonitrile (10 ml) at 0 °C was added a solution of ceric ammonium nitrate (2.25 g, 4.11 mmol) in water (5 ml). After *ca*. 3 min the reaction mixture was diluted with water and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–ethyl acetate, 4:1 then 1:1 then ethyl acetate) of the residue yielded naphthoquinone **13** (0.23 g, 46%) as red needles, mp 164–166 °C [Found (EI): M^+, 260.0681. $C_{14}H_{12}O_5$ requires *M*, 260.0685]; ν_{max}(CH_2Cl_2 solution)/cm^{-1} 1656 (C=O, quinone); δ_H(270 MHz) 2.61 (3 H, s, CH_3), 3.97 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 6.99 (1 H, s, 3-H), 7.37 (1 H, d, *J* 8.5, 6-H or 7-H) and 7.38 (1 H, d, *J* 8.5, 7-H or 6-H); δ_C 30.9 (CH_3), 56.8 (2 × OCH_3), 120.4, 120.8 (CH, C-6, C-7), 136.7 (CH, C-3), 144.6, 144.8 (quat., C-4a, C-8a), 153.4, 153.7 (quat., C-5, C-8), 183.1, 184.4 (quat., C-1, C-4) and 198.1 (quat., C=O); *m/z* 260 (M^+, 100%), 247 (M − CH_3, 28) and 217 (M − $COCH_3$, 42).

(ii) Silver(II) oxide. To a solution of compound **11** (0.40 g, 1.63 mmol) in dioxane (20 ml) containing silver(II) oxide (0.81 g, 6.5 mmol) was added conc. nitric acid (0.5 ml). The reaction mixture was stirred for 5 min at room temperature after which standard extractive work-up (dichloromethane) followed by column chromatography (hexane–ethyl acetate, 2:1) gave naphthoquinone **18** (52 mg, 12%) as red needles for which the spectroscopic data (NMR, IR) were in agreement with those reported above.

(6b*R,9a*R**)-6-Acetyl-6b,9a-dihydro-1,4-dimethoxy-5-hydroxyfuro[2′,3′-*d*]naphtho[1,2-*b*]furan-8(9*H*)-one 15**

To a solution of naphthoquinone **13** (30 mg, 0.115 mmol) in acetonitrile (4 ml) at 0 °C under argon was added distilled 2-trimethylsilyloxyfuran **14** (36 μl, 0.23 mmol). The reaction mixture was warmed to room temperature and after 0.75 h methanol (5 ml) was added to it. Stirring was continued for 17 h, after which, the solvent was removed under reduced pressure from the reaction mixture. The resulting yellow oil was triturated in methanol to give the title compound **15** (26 mg, 66%) as a yellow solid, mp 161–163 °C [Found: C, 62.6; H, 4.6%; M^+, 344.0885. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%; *M*, 344.0896]; ν_{max}(CH_2Cl_2)/cm^{-1} 3304br (OH), 1776 (C=O, γ-lactone) and 1666 (C=O, *o*-hydroxyaryl ketone); δ_H(270 MHz, [$^2H_6$]-DMSO) 2.65 (3 H, s, CH_3), 2.86 (1 H, d, J_{gem} 18.6, 9-H), 3.30 [1 H, m (obscured), 9-H′], 3.81 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 5.42 (1 H, dd, $J_{9a,9'}$ 6.6 and $J_{9a,6b}$ 5.9, 9a-H), 6.37 (1 H, d, $J_{6b,9a}$ 5.9, 6b-H), 7.04 (1 H, d, *J* 8.8, 2-H or 3-H), 7.11 (1 H, d, *J* 8.8, 3-H or 2-H) and 10.76 (1 H, s, OH); δ_C([$^2H_6$]-DMSO) 30.7 (CH_3), 35.4 (CH_2, C-9), 56.3 (OCH_3), 57.1 (OCH_3), 81.5 (CH, C-9a), 83.4 (CH, C-6b), 106.0, 115.7, 116.8, 117.4 (quat., C-4a, C-6, C-6a, C-10b), 108.5, 109.2 (CH, C-2, C-3), 150.2, 150.5, 150.3, 150.8 (quat., C-1, C-4, C-5, C-10a), 175.4 (quat., C-8) and 200.2 (quat., C=O); *m/z* 344 (M^+, 100%), 329 (M − CH_3, 68) and 299 (25).

(3a*R,5*S**,11b*R**)-3,3a,5,11b-Tetrahydro-7,10-dimethoxy-5-hydroxy-5-methyl-2*H*-furo[2′,3′-*e*]naphtho[2,3-*c*]pyran-2,6,11-trione 16**

To a solution of compound **15** (70 mg, 0.20 mmol) in dichloromethane (8 ml) at room temperature was added a solution of ceric ammonium nitrate (0.22 g, 0.41 mmol) in water (2 ml). After 5 min the reaction mixture was subjected to a standard extractive work-up (dichloromethane) to give a pale brown oil which was purified by flash chromatography (hexane–ethyl acetate, 7:3 then ethyl acetate) to give the title compound **16** (54 mg, 75%) as a red–orange solid, mp 190–192 °C [Found (EI): M^+, 360.0853. $C_{18}H_{16}O_8$ requires *M*, 360.0845]; ν_{max}-(CH_2Cl_2)/cm^{-1} 3680 (OH), 1790 (C=O, γ-lactone) and 1662 (C=O, quinone); δ_H(270 MHz) 1.74 (3 H, s, CH_3), 2.74 (1 H, d, J_{gem} 18.0, 3-H), 2.96 (1 H, dd, J_{gem} 17.6 and $J_{3,3a}$ 4.8, 3-H′), 3.70 (1 H, s, OH), 3.96 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 4.88 (1 H, dd, $J_{3,3a}$ 4.8 and $J_{3a,11b}$ 2.9, 3a-H), 5.35 (1 H, d, $J_{11b,3a}$ 2.9, 11b-H) and 7.35 (2 H, s, ArH); δ_C 27.3 (CH_3), 36.7 (CH_2, 3-H), 56.8 (2 × OCH_3), 67.4 (CH, C-3a), 68.3 (CH, C-11b), 93.1 (quat., C-5), 120.5, 120.8 (CH, C-8, C-9), 132.9, 146.4 (quat., C-5a, C-6a, C-10a, C-11a), 153.4, 153.7 (quat., C-7, C-10), 174.4 (quat., C-2) and 184.6, 184.7 (quat., C-6, C-11); *m/z* 360 (M^+, 27%), 344 (M − O, 10), 329 (M − OCH_3, 7), 300 (M − $C_2H_4O_2$, 100) and 285 (72).

(3a*R,5*S**,11b*R**)-3,3a,5,11b-Tetrahydro-7,10-dimethoxy-5-methyl-2*H*-furo[2′,3′-*e*]naphtho[2,3-*c*]pyran-2,6,11-trione 18**

To a solution of compound **16** (17 mg, 0.047 mmol) in dichloromethane (2.5 ml) at room temperature under argon was added trifluoroacetic acid (54 mg, 0.47 mmol) followed by triethylsilane (55 mg, 0.47 mmol). The reaction mixture was stirred at room temperature for 7 h after which the solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 3:7 then ethyl acetate) gave the title compound **18** (13.5 mg, 84%) as an orange solid, mp 209–211 °C (Found: C, 62.7; H, 4.6%; M^+, 344.0904. $C_{18}H_{16}O_7$ requires C,

62.8; H, 4.7%; *M*, 344.0896); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1789 (C=O, γ-lactone) and 1661 (C=O, quinone); δ_H(270 MHz; [$^2H_6$]-DMSO) 1.37 (3 H, d, J_{vic} 6.6, CH_3), 3.17 (1 H, dd, J_{gem} 17.6 and $J_{3,3a}$ 5.1, 3-H), 3.31 [1 H, m (obscured), 3-H′], 3.86 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.39 (1 H, dd, $J_{3a,3}$ 4.8 and $J_{3a,11b}$ 2.6, 3a-H), 4.70 (1 H, dq, J_{vic} 6.6 and $J_{5,11b}$ 1.8, 5-H), 5.31 (1 H, dd, $J_{11b,3a}$ 2.6 and $J_{11b,5}$ 1.8, 11b-H) and 7.57 (2 H, s, ArH); δ_C([$^2H_6$]-DMSO) 19.0 (CH_3), 36.7 (CH_2, C-3), 56.6 (2 × OCH_3), 67.9, 69.5, 71.6 (CH, C-3a, C-5, C-11b), 119.6, 120.6, 133.4, 142.1 (quat., C-5a, C-6a, C-10a, C-11a), 121.3 (CH, C-8, C-9), 152.6, 152.9 (quat., C-7, C-10), 175.4 (quat., C-2) and 180.9, 183.4 (quat., C-6, C-11); *m/z* 344 (M^+, 100%), 300 (M − CO_2, 22) and 285 (M − CH_3CO_2, 48).

(1*S,3*R**)-Methyl 6,9-dimethoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-ylacetate 17**

To a solution of lactol **16** (43 mg, 0.12 mmol) in dichloromethane (6 ml) at room temperature under argon was added trifluoroacetic acid (68 mg, 0.6 mmol) followed by triethylsilane (70 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 24 h after which the solvent was removed under reduced pressure. The residual crude acid was dissolved in methanol (3 ml) and treated with an excess of diazomethane, after which the solvent was removed at reduced pressure. Standard extractive work-up (ethyl acetate) followed by flash chromatography (hexane–ethyl acetate, 1:1 then 3:7 then ethyl acetate) afforded the title compound **17** (29 mg, 68%) as a yellow–orange solid, mp 133–135 °C [Found: C, 63.2; H, 5.4%; M^+, 360.1212. $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6%; *M*, 360.1209]; ν_{max}/cm^{-1} 1737 (C=O, ester) and 1655 (C=O, quinone); δ_H(270 MHz) 1.46 (3 H, d, J_{vic} 6.6, CH_3), 2.16 (1 H, ddd, J_{gem} 18.0, $J_{4ax,3ax}$ 10.6 and $J_{4ax,1}$ 3.7, 4-pseudoaxial-H), 2.58 (1 H, dd, J_{gem} 15.8 and *J* 5.5, CH_ACH_BCO_2CH_3), 2.68 (1 H, dd, J_{gem} 15.8 and *J* 7.7, CH_ACH_BCO_2CH_3), 2.86 (1 H, ddd, J_{gem} 18.0, $J_{4eq,3ax}$ 2.6 and $J_{4eq,1}$ 4.0, 4-pseudoequatorial-H), 3.70 (3 H, s, CO_2CH_3), 3.86–3.92 (1 H, m, 3-H), 3.92 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 4.80–4.84 (1 H, m, 1-H) and 7.25 (2 H, apparent s, 7-H, 8-H); δ_C 20.2 (CH_3), 27.5 (CH_2, C-4), 40.4 (CH_2, $CH_2CO_2CH_3$), 51.8 (CO_2CH_3), 56.8 (OCH_3), 56.9 (OCH_3), 69.5, 70.1 (CH, C-1, C-3), 119.7, 120.1 (CH, C-7, C-8), 121.4, 121.5 (quat., C-5a, C-9a), 140.5, 146.5 (quat., C-4a, C-10a), 153.3, 153.5 (quat., C-6, C-9), 171.2 (quat., CO_2CH_3) and 183.2, 183.8 (quat., C-5, C-10); *m/z* 360 (M^+, 100%), 345 (M − CH_3, 18) and 287 (M − $CH_2CO_2CH_3$, 93).

(1*R,3*R**)-Methyl 6,9-dihydroxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-ylacetate 19**

To a solution of dimethyl ether **17** (12 mg, 0.033 mmol) in dichloromethane (2.5 ml) at −78 °C under argon was added boron tribromide (83 mg, 0.33 mmol) in dichloromethane (1.9 ml). The resulting dark-red solution was maintained at −78 °C for 5 min then warmed to 0 °C. After 10 min the reaction mixture was treated with 5% aqueous sodium hydrogen carbonate. Standard extractive work-up (chloroform) followed by flash chromatography (hexane–ethyl acetate, 4:1 then 1:1) gave the title compound **19** (9 mg, 82%) as a dark-red solid, mp 169–171 °C (red needles, MeOH) (lit.,[10] mp 171 °C) [Found (EI): M^+, 332.0897. $C_{17}H_{16}O_7$ requires *M*, 332.0896]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1736 (C=O, ester) and 1608 (C=O, quinone); δ_H(270 MHz) 1.58 (3 H, d, J_{vic} 6.6, CH_3), 2.37 (1 H, m, 4-pseudoaxial-H), 2.67 (1 H, dd, J_{gem} 15.1, J_{vic} 6.0, CH_ACH$_B$CO_2CH_3), 2.69 (1 H, dd, J_{gem} 15.1, J_{vic} 7.1, CH$_A$CH_BCO_2CH_3), 2.88 (1 H, ddd, J_{gem} 19.1, $J_{4eq,3}$ 3.3, $J_{4eq,1}$ 0.5, 4-pseudoequatorial-H), 3.75 (3 H, s, CO_2CH_3), 4.33–4.36 (1 H, m, 3-H), 5.04 (1 H, qdd, $J_{1,Me}$ 6.6, $J_{1,4ax}$ 1.8, $J_{1,4eq}$ 0.5, 1-H), 7.28 (2 H, apparent s, 7-H, 8-H), 12.48 (1 H, s, OH) and 12.52 (1 H, s, OH); δ_C 19.3 (CH_3), 27.5 (CH_2, C-4), 40.4 (CH_2, $CH_2CO_2CH_3$), 51.8 (CO_2CH_3), 63.2, 67.5 (CH, C-1, C-3), 111.4, 111.3 (quat., C-5a, C-9a), 130.1, 130.3 (CH, C-7, C-8), 141.6 (quat., C-4a), 147.1 (quat., C-10a), 159.9, 160.0 (quat., C-6, C-9), 171.0 (quat., CO_2CH_3), 183.6 (quat., C-5) and 184.1 (quat., C-10); *m/z* 332 (M^+, 100%), 314 (M − H_2O, 74), 300 (40), 258 (80), 243 (55) and 230 (43). The NMR data were in agreement with the literature.[10]

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