Double furofuran annulation to a bis-naphthoquinone: an approach to dimeric pyranonaphthoquinones

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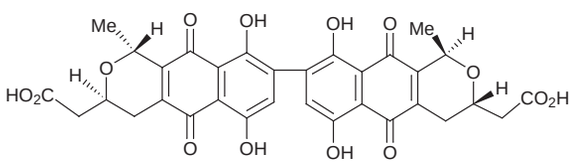
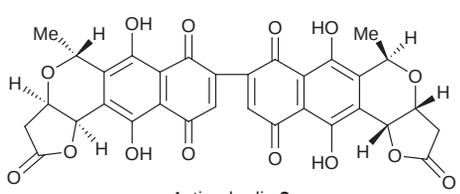
The preparation of bis-naphthoquinone **7**, a key intermediate in the synthesis of dimeric pyranonaphthoquinones related to the actinorhodins is described. Initial efforts directed to **7** which focussed on a double Fries rearrangement of bis-acetate **14** to 2-acetylnaphthol **13** were low yielding. Use of a Stille coupling reaction between dimeric bromonaphthalene **20** and (α-ethoxyvinyl)tri-*n*-butyltin **19** as a means to introduce the acetyl groups at C-2 was also low yielding. The optimum route to bis-naphthoquinone **7** involved the synthesis of 2-acetylnaphthol **13** from bromide **25** using a Suzuki–Miyaura coupling. Addition of 2-trimethylsilyloxyfuran to bis-naphthoquinone **7** afforded the bis-annulation adducts **30**,**31** which underwent double oxidative rearrangement to bis-lactols **32**,**33**. Reduction of the bis-lactols to bis-ethers **34**,**35** completed the first synthesis of a dimeric pyranonaphthoquinone.

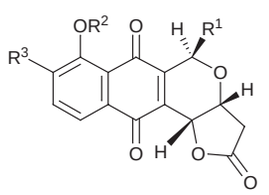
Streptomyces coelicolor produces[1–3] a pigment which displays litmus-type properties, bright blue in alkali and red in acid. The structure of this pigment was subsequently determined by mass spectral studies[4] and extensive chemical degradation[5,6] and shown to be the dimeric pyranonaphthoquinone actinorhodin **1**. The point of dimerization has subsequently been unequivocally determined from biosynthetic studies.[7] Several other actinorhodin congeners isolated[8] from the cultures of *Streptomyces coelicolor* including the bis-lactone γ-actinorhodin **2**, all possess an oxygen atom *ortho* to the linkage site. Apart from the reported activity of actinorhodin **1** against *Staphylococcus aureus*[2] 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 compounds have been proposed to act as bioreductive alkylating agents.[9] In contrast to the monomeric pyranonaphthoquinones no total synthesis of a dimeric pyranonaphthoquinone has been reported.



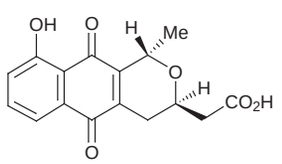
Actinorhodin **1**



γ-Actinorhodin **2**



Kalafungin **3** R^1 = Me, R^2 = H, R^3 = H
Frenolicin B **5** R^1 = Pr, R^2 = H, R^3 = H
Arizonin C1 **6** R^1 = Me, R^2 = Me, R^3 = OMe



Nanaomycin A **4**

An efficient synthesis of several monomeric members of the pyranonaphthoquinone antibiotics, namely kalafungin **3**,[10] nanaomycin A **4**, frenolicin B **5**[11] and arizonin C1 **6**[12] has been achieved in which the key step involved furofuran annulation of a naphthoquinone to a furo[3,2-*b*]naphtho[2,1-*d*]furan followed by oxidative rearrangement to a furo[3,2-*b*]naphtho[2,3-*d*]-pyran. In order to apply this methodology to the synthesis of dimeric pyranonaphthoquinones, at some point in the synthesis formation of a new C–C bond between each half of the molecule was required. Initial work therefore, focussed on construction of the monomeric unit with a view to effecting dimerization in the final step. Towards this end, the synthesis[13] of the monomeric unit of actinorhodin **1** was completed, however attempts to effect oxidative coupling to the dimer proved unsuccessful.

Given these disappointing results, an alternative synthetic strategy was proposed wherein the binaphthyl linkage is introduced at an earlier stage in the synthesis using a palladium(0) catalysed cross-coupling reaction. The binaphthyl is then converted to the key intermediate bis-naphthoquinone **7** which bears acetyl groups at C-2 as required for the ensuing double furofuran annulation reaction with 2-trimethylsilyloxyfuran. The key steps in our initial approach to **7** involved construction of the binaphthyl linkage *via* a Suzuki coupling reaction[14] followed by a double Fries rearrangement to introduce the acetyl groups at C-2 onto the dimeric naphthalene (Scheme 1).

We have previously reported[15] the synthesis of benzyl ether **8** in 8 steps from 1,5-dihydroxynaphthalene. In earlier work,[15] we found that the inherent basicity of highly oxygenated naphthyl anions possessing *ortho*-methoxy substituents prevented an efficient reaction with bulky tin electrophiles. In our case[15] and in related examples[16] protonated naphthalenes were the major products isolated from the reaction mixture. Metallation of bromonaphthalene **8** in tetrahydrofuran at −78 °C with *n*-

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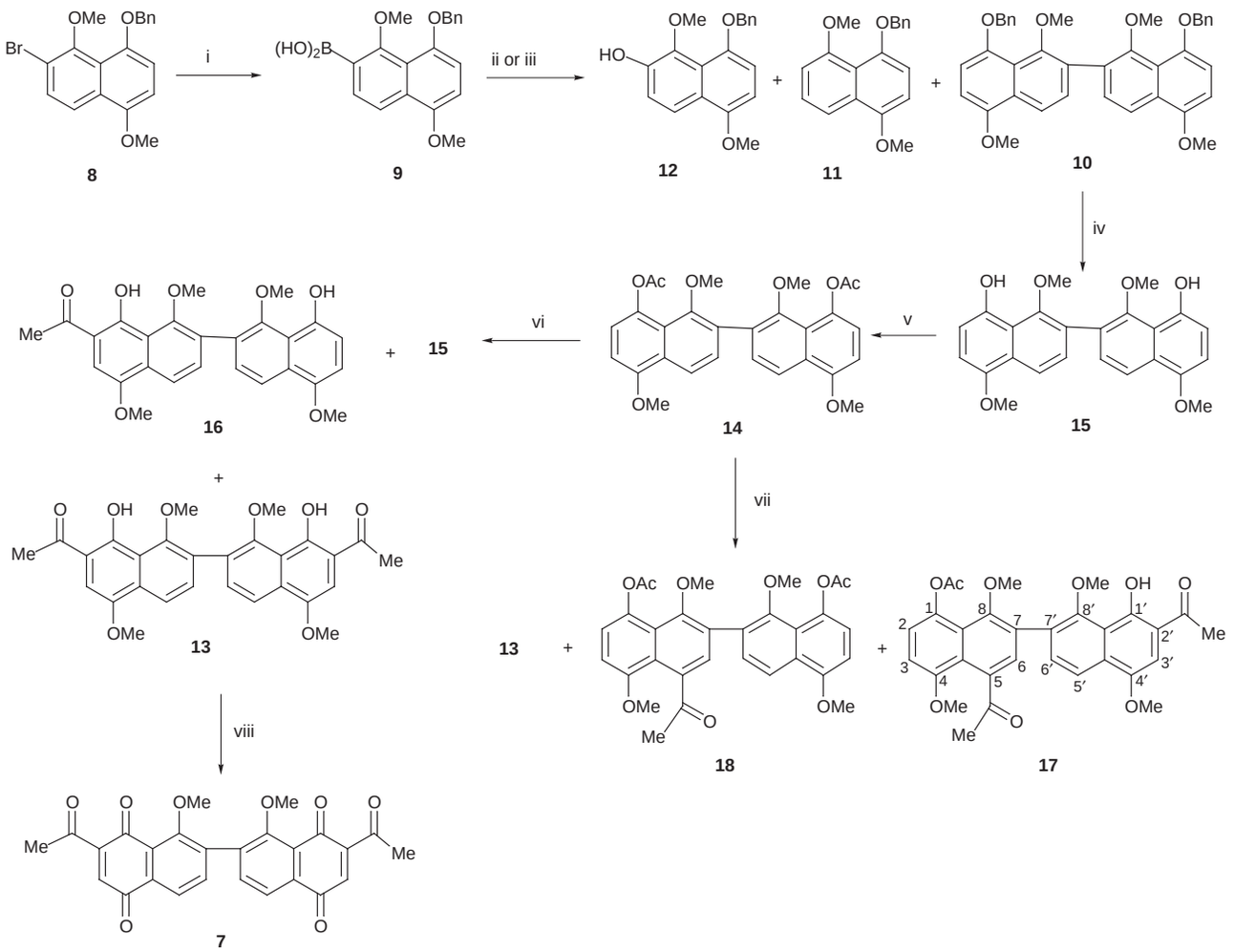


Scheme 1 *Reagents and conditions*: i, a: *n*-BuLi (2 equiv.), THF, N_2, −78 °C then immediately $B(O^iPr)_3$, −78 °C to RT, 1 h; b: 10% HCl, 87%; ii, **8**, $PdCl_2(dppf)$, 2 M Na_2CO_3, toluene or ethanol, argon, reflux, **11** 19% and **10** 74%; iii, **8**, $PdCl_2(dppf)$, $Ba(OH)_2$, DME, N_2, 80 °C, **8** 66%, **11** 19% and **12** 68%; iv, H_2 Pd/C, EtOAc, RT, 93%; v, Ac_2O, NEt_3, DMAP (catalytic), CH_2Cl_2, RT, 68%; vi, $BF_3{\cdot}OEt_2$, 220 °C, argon, **13** 21%, **15** 15% and **16** 15%; vii, $BF_3{\cdot}OEt_2$, Ac_2O, 140 °C, argon, **13** 34%, **17** 37% and **18** 9%; viii, AgO (16 equiv.), HNO_3, dioxane, RT, 72%.

butyllithium followed by immediate quenching with triisopropyl borate gave the desired boronic acid **9** in 87% yield (Scheme 1). In dramatic contrast to earlier stannylation reactions, no protonated naphthalene was observed. With boronic acid **9** in hand, attention then focussed on the use of a Suzuki coupling [14,17] to effect dimerisation.

Coupling of boronic acid **9** and bromonaphthalene **8** using 2 M sodium carbonate solution as base and $PdCl_2(PPh_3)_2$ as catalyst afforded the desired binaphthyl **10** in low yield (18%) together with substantial quantities of unreacted bromide **8** (25%) and naphthalene **11** (24%) arising from competitive hydrolytic protodeboronation.[18,19,20] The ^1H NMR spectrum for dimeric naphthalene **10** showed a significant upfield shift in the resonance of the C-5 methoxy group adjacent to the site of dimerisation at δ 3.42 relative to the bromide **8** where it resonated at δ 3.78. A model of dimer **10** places the methoxy protons at C-5 in close proximity to the neighbouring aromatic ring thereby accounting for the observed shielding.

Using toluene as solvent, the coupling of **8** and **9** in the presence of the chelating ligand [18,21–24] $PdCl_2(dppf)$ (10 mol%) with two equivalents of sodium carbonate afforded the desired binaphthyl **10** in 74% yield together with protonated naphthalene **11** (19%). Use of dimethylformamide or dioxane with potassium phosphate in the presence of $PdCl_2(dppf)$ afforded binaphthyl **10** in only moderate yields whilst use of $Pd(OAc)_2$ with triphenylphosphine [or $PdCl_2(dppf)$] and triethylamine [25,26] afforded significant quantities of protonated naphthalene **11**. Use of barium hydroxide in 1,2-dimethoxyethane [14,19,20] mainly afforded naphthol **12** (68%) [27] whereas use of caesium fluoride [28] in 1,2-dimethoxyethane with $PdCl_2(dppf)$ as catalyst yielded the desired binaphthyl **10** in 69% yield.

With binaphthyl **10** in hand, attention then focussed on its transformation to bis-naphthoquinone **7**. It was initially envisaged that oxidation of acetylnaphthol **13**, obtained *via* double Fries rearrangement of bis-acetate **14** would provide the desired naphthoquinone **7** (Scheme 1). Bis-acetate **14** in turn was available from naphthol **15**. With this in mind, deprotection of benzyl ether **10** to naphthol **15** was achieved in 93% yield by hydrogenation over palladium on charcoal.

After smooth acetylation of **15** under standard conditions (68% yield), double Fries rearrangement of bis-acetate **14** using boron trifluoride–diethyl ether at 150 °C afforded starting material and naphthol **15** (formed by cleavage of ester **14**). Heating **14** to 220 °C under argon followed by treatment with boron trifluoride–diethyl ether furnished acetylnaphthol **13** in a disappointing 21% yield. Two other minor products were deacetylated naphthol **15** (15%) and the half Fries product mono-ketone **16** (15%).

The double Fries rearrangement proved difficult to reproduce giving rise to variable yields of acetylnaphthol **13**. Use of milder conditions [29] (70 °C for 30 min) afforded predominantly deacetylated naphthol **15** (15%) and mono-ketone **16** (17%) with none of the required acetylnaphthol **13** being formed.

It was proposed that use of acetic anhydride as co-solvent would minimise loss of the acetate groups whilst reducing the reaction temperature. Boron trifluoride–diethyl ether was added to a solution of bis-acetate **14** in acetic anhydride heated to 140 °C under argon affording the desired acetylnaphthol **13**

(34%) together with less polar material (Scheme 1) which exhibited multiple methoxy and methyl signals in the ^{1}H NMR spectrum. Further purification of this material by HPLC identified the components as the regioisomeric aryl ketones **17** and **18** isolated in 37 and 9% yield respectively and the desired acetylnaphthol **13** (34% yield).

Formation of aryl ketone **17** from the Fries rearrangement of bis-acetate **14** is consistent with similar observations on a related monomeric system.[30] The observed acylation at C-5 can be rationalised on the basis of the combined electron donating effects of 8-OMe and 1-OH in **15** which activate this position toward electrophilic attack despite unfavourable steric hindrance at this site. In aryl ketone **18** no *ortho*-acylation had occurred rather acylation at C-5 on one half of the dimer took place.

Attempts to effect direct *ortho*-acylation[30] of naphthol **15** using trifluoroacetic anhydride in boiling glacial acetic acid followed by base mediated hydrolysis of the intermediate ester resulted in exclusive formation of bis-acetate **14** in 65% yield. The use of acetic acid in toluene[31] and scandium triflate[31,32] was also unsuccessful further illustrating the inherent reluctance of bis-acetate **14** to undergo a double Fries rearrangement.

The work described herein constitutes the first reported investigation of a double Fries rearrangement on dimeric naphthyl acetates, however, given that only low yields of the desired acetylnaphthol **13** were obtained, an alternative strategy for introduction of the C-2 acetyl groups onto the dimeric naphthalene was sought.

The second strategy for the synthesis of bis-naphthoquinone **7** focussed on introduction of the acetyl groups *via* a palladium catalysed coupling reaction between vinylstannane **19** and bromonaphthalene **20** (Scheme 2).[33,34] Acid hydrolysis of the resultant enol ether **21** would afford diketone **22**, a precursor to naphthoquinone **7**. Bromonaphthalene **20** in turn, is derived from bisnaphthol **15** by selective *ortho*-bromination followed by methylation of the hydroxy groups.

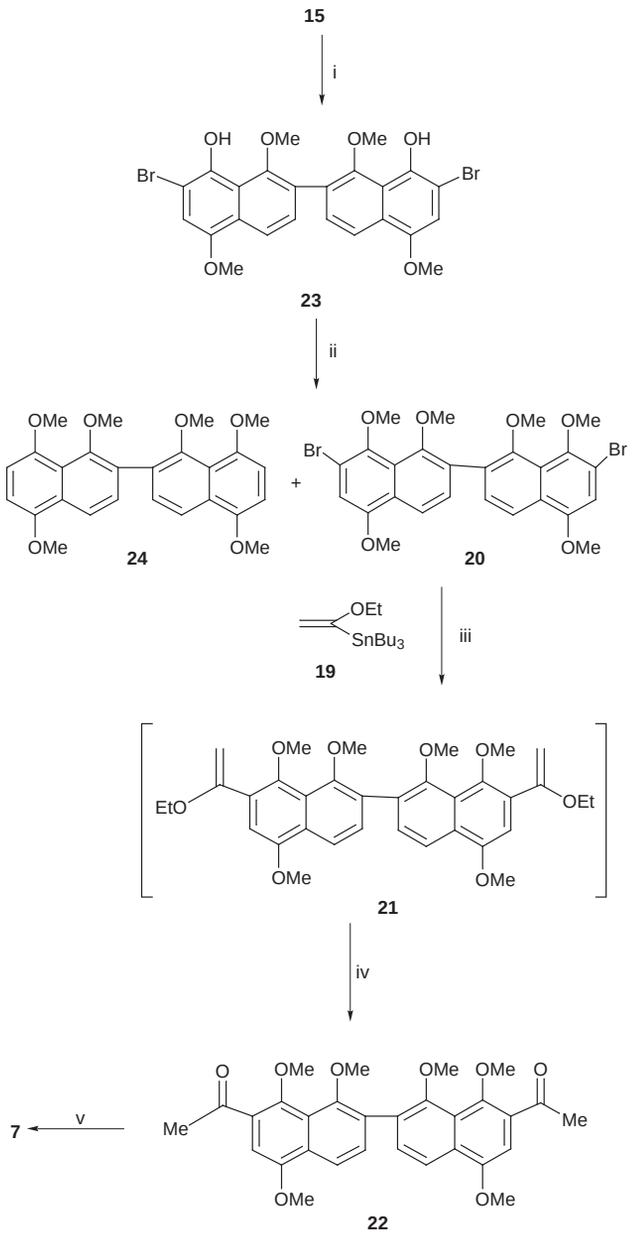
Selective *ortho*-bromination of bisnaphthol **15** to bromonaphthol **23** was achieved in 74% yield using bromine (2.5 equivalents) in carbon tetrachloride (Scheme 2). Bromonaphthol **23** was unstable upon standing thus it was taken directly to the methylation step.

An extensive investigation of different procedures for the methylation of bromonaphthol **23** was undertaken, however, in all cases the major product was naphthalene **24**, the methylated product formed from debrominated naphthol **23**. The optimum yield of methyl ether **20** (39%) was achieved by addition of a reducing agent, namely sodium dithionite to the reaction mixture prior to the addition of dimethyl sulfate and potassium hydroxide, however naphthalene **24** was still the major product (50% yield).

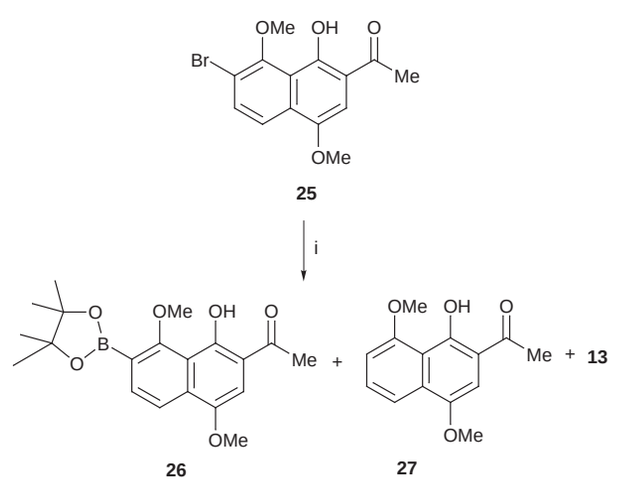
With methyl ether **20** in hand, transformation of the bromine group to the required acetyl group was investigated. Thus, **20** was heated under reflux with an excess of vinylstannane **19**[34] in toluene using $PdCl_2(PPh_3)_2$ as catalyst. Hydrolysis of the intermediate enol ether using 10% hydrochloric acid afforded the required diketone **22** in 70% overall yield.

Acetylnaphthol **13** and its methyl ether derivative **22** are precursors to the activated bis-naphthoquinone **7** required for the subsequent furofuran annulation reaction with 2-trimethylsilyloxyfuran. Oxidation of **13** and **22** with an excess of freshly prepared silver(II) oxide[35] in dioxane afforded bis-naphthoquinone **7** in 72 and 66% yields respectively. The vast excess of oxidant and longer reaction times needed to effect complete oxidation was somewhat unexpected given the facile oxidation of similar monomeric compounds.[10,11,12]

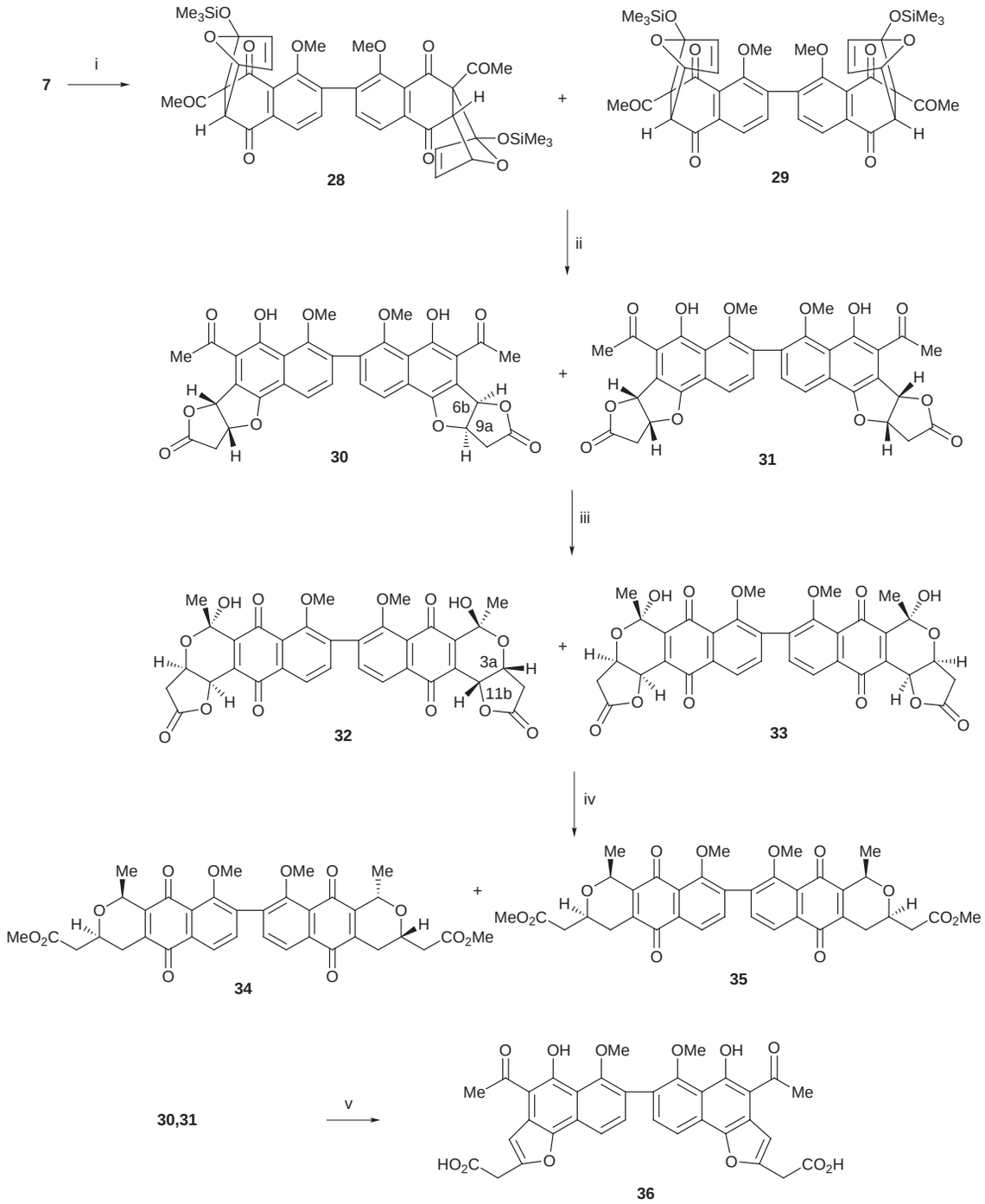
The double Fries rearrangement approach to bis-naphthoquinone **7** reported above is low yielding hence an alternative strategy wherein the Fries rearrangement was carried out before construction of the binaphthyl linkage was investigated.[37] Suzuki–Miyaura[38] coupling between boronate ester **26** and



Scheme 2 *Reagents and conditions*: i, Br_2 (2.5 equiv.), CCl_4, 0 °C, 74%; ii, $Na_2S_2O_4$, Me_2SO_4, KOH, THF, DMF, 0 °C to RT, **24** 50% and **20** 39%; iii, $PdCl_2(PPh_3)_2$, toluene, argon, reflux, 36 h; iv, 10% HCl, RT, 70% over two steps; v, AgO (16 equiv.), HNO_3, dioxane, RT, 66%.



Scheme 3 *Reagents and conditions*: i, $PdCl_2$(dppf), CsF (4 equiv.), bis(pinacolato)diboron (4 equiv.), THF, reflux, 25 h, **26** 19%, **27** 20%, **13** 53%.



Scheme 4 *Reagents and conditions*: i, 2-trimethylsilyloxyfuran, CH_3CN, 0 °C, 1 h; ii, silica gel, EtOAc–hexane (2:1), 51%; iii, CAN (4 equiv.), CH_3CN, H_2O, 0 °C, 0.25 h, 55%; iv, 10% Pd/C, H_2, EtOAc, 2 h, then excess CH_2N_2, Et_2O, 78%; v, $CHCl_3$, RT, 0.25 h, 100%.

bromonaphthol **25**[36] affords the required dimeric acetylnaphthol **13** (Scheme 3). Bromonaphthol **25** was therefore treated with bis(pinacolato)diboron[39] (4 equiv.), $PdCl_2$(dppf) and caesium fluoride (4 equiv.) in tetrahydrofuran affording boronate ester **26** (19%), naphthol **27** (20%) and binaphthyl **13** (53%). The *in situ* coupling facilitates construction of the desired dimeric acetylnaphthol **13** in a single operation. Acetylnaphthol **13** was then oxidised to bis-naphthoquinone **7** as described above.

With an efficient synthesis of bis-naphthoquinone **7** in hand, examination of its bis-annulation reaction with 2-trimethylsilyloxyfuran was undertaken (Scheme 4). Addition of 2-trimethylsilyloxyfuran (3 equiv.) to bis-naphthoquinone **7** in acetonitrile at 0 °C resulted in initial formation of a Diels–Alder adduct, tentatively assigned as bis-*endo*-adducts **28** and **29**. Attempts to obtain a pure sample of these cycloadducts were unsuccessful due their facile rearrangement to bis-furonaphthofurans **30** and **31**.

The ^{1}H NMR data reported by Jurczak *et al.*[40] for the analogous *endo*-adduct formed by addition of 1,4-benzoquinone to furan offers support for the intermediacy of *endo*-cycloadducts **28** and **29** in the formation of the diastereomeric furofuran adducts **30** and **31**. In particular, the vinylic protons at δ 6.12–6.14 and the bridgehead proton (a broad doublet at δ 5.17) resonated at similar chemical shifts to those reported for the analogous protons in the *endo* 1,4-benzoquinone–furan adduct. The allylic bridgehead proton appeared as a doublet at δ 3.90 with the coupling constant $J_{9a,1}$ 5.2 Hz also consistent with the formation of *endo*-adducts.[40]

Purification of the crude reaction mixture using flash silica (Merck Kieselgel 60) resulted in rearrangement of the Diels–Alder adducts **28** and **29** to the diastereomeric furofuran

adducts **30** and **31** in 51% yield. Due to accidental equivalence of the signals in the ^{1}H NMR and ^{13}C NMR spectra, it appeared that only one diastereomer had formed. However analysis of the furonaphthofurans **30** and **31** by HPLC established that it was in fact a 1 : 1 mixture of the two diastereomers. Adducts **30** and **31** proved to be very unstable and underwent ring opening of the γ-lactone ring affording bis-carboxylic acid **36** upon standing. The driving force for the ring opening of the γ-lactone is the aromatisation of the dihydrofuran ring.

With furonaphthofurans **30** and **31** in hand, double oxidative rearrangement to the pyranonaphthoquinone ring system was then investigated. Treatment of **30** and **31** with ceric ammonium nitrate (4 equiv.) in aqueous acetonitrile at 0 °C afforded a 1 : 1 inseparable mixture of hemiacetals **32** and **33** in 55% yield (Scheme 4). The bridgehead protons resonated at similar chemical shifts to those reported for the analogous monomeric furonaphthopyrans[10,11,13] and the coupling constant of $J_{3a,11b}$ 3.2 Hz supported the presence of a *cis*-fused furonaphthopyran ring system.[13] In the aromatic region, four one proton doublets at δ 7.81, 7.82, 7.97 and 7.98 established the presence of a 1 : 1 mixture of diastereomeric adducts. The stereochemistry of hemiacetals **32** and **33** was assigned by analogy to the monomeric system.[13]

Attempted reduction of hemiacetals **32** and **33** to a cyclic ether using triethylsilane and trifluoroacetic acid in dichloromethane afforded baseline material (on HPLC), thus an alternative procedure was sought. Hydrogenation of hemiacetals **32** and **33** over palladium on charcoal resulted in reduction of the hemiacetal group to a cyclic ether together with concomitant hydrogenolysis of the γ-lactone. Immediate treatment of the resultant carboxylic acid with an ethereal solution of diazomethane afforded (78% yield) a 1 : 1 mixture of bis-methyl esters **34** and **35** which are closely related to the bis-methyl ester of actinorhodin **1**. The stereochemistry of the methyl esters **34** and **35** was also assigned by analogy to the monomeric system.[13]

In conclusion, the work described herein constitutes the first synthesis of a dimeric pyranonaphthoquinone employing a double furofuran annulation/oxidative rearrangement strategy. This novel approach should allow access to more elaborate pyranonaphthoquinone dimers in the future.

Experimental

Mps were determined using a Kofler hot stage apparatus or a Reichert heating stage with microscope, and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 Fourier Transform infra-red spectrophotometer as Nujol mulls, thin films or solutions. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200.13 MHz), Bruker AM 400 (400.12 MHz), Bruker AMX 400 (400.13 MHz) or a Bruker DRX 400 (400.12 MHz) spectrometer. OH resonances were assigned by exchange with deuterium oxide. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz), a Bruker AM 400 (100.6 MHz), a Bruker AMX 400 (100.4 MHz) or a Bruker DRX 400 (100.51 MHz) spectrometer and assignments were made with the aid of DEPT spectra. Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or a AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV (EI, CI). High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Elemental analyses were carried out by the Microanalytical Laboratory, University of Otago, New Zealand or the Microanalytical Laboratory, University of New South Wales, Sydney, Australia. High performance liquid chromatography (HPLC) was carried out using a Waters Associates system consisting of, a Model M-6000A pump, a millipore model U6K injector, a model 440 ultra-violet detector at 256 nm and a R401 differential refractometer. Separation was carried out using the indicated solvents on a Partisil 10 M9 semi-preparative column of the following dimensions; outer diameter 12.80 mm, inner diameter 9.40 mm, length 500.0 mm and particle size 10.0 μm.

4-Benzyloxy-6-bromo-1,5-dimethoxynaphthalene 8

To a solution of 7-bromo-4,8-dimethoxy-1-naphthol[36] (818 mg, 2.89 mmol) in dimethylformamide (15 cm^3) cooled to 0 °C under an atmosphere of nitrogen was added sodium hydride (231 mg of a 60% dispersion in oil, 5.78 mmol). The resultant suspension was allowed to warm to room temperature for 15 min. After cooling to 0 °C, benzyl bromide (0.34 cm^3, 2.89 mmol) was added dropwise and the mixture stirred at room temperature for 12 h. The solution was quenched with ice-cold water (15 cm^3) and the reaction mixture extracted with dichloromethane (4 × 50 cm^3). The combined extracts were washed with water (100 cm^3), brine (100 cm^3) and dried (sodium sulfate). Removal of the solvent under reduced pressure afforded an oily solid which was purified by flash chromatography using hexane–ethyl acetate (99 : 1) as eluent to afford the title compound **8** (949 mg, 88%) as a colourless solid, mp 79–80 °C (Found: C, 61.2; H, 4.6. $C_{19}H_{17}O_3Br$ requires C, 61.1; H, 4.6%); ν_{max}(Nujol)/cm^{-1} 1616, 1376 (C=C) and 1054 (C–O); δ_H(200 MHz, $CDCl_3$) 3.78 (3H, s, 5-OCH_3), 3.93 (3H, s, 1-OCH_3), 5.11 (2H, s, OCH_2), 6.71 (1H, d, $J_{3,2}$ 8.4, 3-H), 6.89 (1H, d, $J_{2,3}$ 8.4, 2-H), 7.35–7.43 (3H, m, 3′-H and 4′-H), 7.54–7.57 (2H, m, 2′-H), 7.59 (1H, d, $J_{7,8}$ 9.0, 7-H) and 7.92 (1H, d, $J_{8,7}$ 9.0, 8-H); δ_C(100 MHz, $CDCl_3$) 55.7 (OCH_3), 61.9 (OCH_3), 72.7 (CH_2, OCH_2), 104.2 (CH, C-2), 110.2 (CH, C-3), 116.4 (C-6), 119.6 (CH, C-8), 122.7 (C-4a), 127.6 (CH, C-4′), 127.7 (CH, C-3′), 128.0 (C-8a), 128.4 (CH, C-2′), 129.9 (CH, C-7), 137.3 (C-1′), 148.1, 150.1 (C-4 and C-5) and 152.8 (C-1); *m*/*z* 372/374 (M^+, 30%), 281/283 (M − CH_2Ph, 100) and 202 (M − CH_2PhBr, 48).

4-Benzyloxy-1,5-dimethoxy-6-naphthylboronic acid 9

A solution of compound **8** (220 mg, 0.59 mmol) in tetrahydrofuran (5 cm^3) was cooled to −78 °C under an atmosphere of nitrogen. To this was added *n*-butyllithium (0.78 cm^3 of a 1.5 mol dm^{-3} solution in hexane, 1.18 mmol) followed immediately by triisopropyl borate (0.27 cm^3, 1.18 mmol). After stirring at −78 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for 1 h. The resulting suspension was quenched with 10% hydrochloric acid (10 cm^3) and extracted with ethyl acetate (3 × 20 cm^3). The combined extracts were washed with brine (2 × 20 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure to give a pale yellow solid. Trituration with diethyl ether afforded the title compound **9** (173 mg, 87%) as a colourless solid, mp 108–109 °C (Found: C, 67.8; H, 5.7. $C_{19}H_{19}O_5B$ requires C, 67.5; H, 5.7%); ν_{max}(Nujol)/cm^{-1} 3276 (OH); δ_H(200 MHz, d^6-acetone), 2.83 (2H, s, OH), 3.77 (3H, s, 5-OCH_3), 3.96 (3H, s, 1-OCH_3), 5.19 (2H, s, OCH_2), 6.92 (1H, d, $J_{3,2}$ 8.5, 3-H), 7.03 (1H, d, $J_{2,3}$ 8.5, 2-H), 7.33–7.46 (3H, m, 3′-H and 4′-H), 7.60–7.64 (2H, m, 2′-H), 7.85 (1H, d, $J_{7,8}$ 8.5, 7-H) and 8.01 (1H, d, $J_{8,7}$ 8.5, 8-H); δ_C(50 MHz, d^6-acetone) 55.8 (OCH_3), 64.3 (OCH_3), 72.5 (CH_2, OCH_2), 105.2 (CH, C-2), 109.0 (CH, C-3), 118.4 (CH, C-8), 120.1 (C-4a), 127.6 (CH, C-4′), 127.9 (CH, C-3′), 128.5 (CH, C-2′), 131.0 (C-8a), 131.3 (CH, C-7), 137.5 (C-1′), 148.8 (C-4 and C-5), 150.1 (C-1) and 163.8 (C-6); *m*/*z* 294 [M − $B(OH)_2$, 42%] and 203 [M − CH_2Ph-$B(OH)_2$, 100].

4-Benzyloxy-6-(4-benzyloxy-1,5-dimethoxy-6-naphthyl)-1,5-dimethoxynaphthalene 10 and 4-benzyloxy-1,5-dimethoxynaphthalene 11

To a suspension of bromonaphthalene **8** (182 mg, 0.49 mmol), boronic acid **9** (189 mg, 0.56 mmol) and $PdCl_2$(dppf) (40 mg, 0.049 mmol) in toluene (8 cm^3) and ethanol (2 cm^3) was added sodium carbonate (0.49 cm^3 of a 2 mol dm^{-3} solution, 0.97 mmol). The reaction mixture was heated under reflux under argon for 24 h. After cooling to room temperature, brine (8 cm^3) was added and the reaction mixture extracted with dichloro-

methane (3 × 15 cm^3). The organic phase was washed with brine (2 × 10 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure to give a dark oil. Flash chromatography using hexane–ethyl acetate (8:2) as eluent yielded binaphthyl **10** (211 mg, 74%) as a colourless crystalline solid, mp 134–135 °C [Found: C, 77.5; H, 6.1%. M^+ (EI), 586.2346; $C_{38}H_{34}O_6$ requires C, 77.8; H, 5.8%; *M*, 586.2355]; $\nu_{max}(CH_2Cl_2$ solution)/cm^{-1} 1600 (C=C) and 1050 (C–O); δ_H(400 MHz, $CDCl_3$) 3.42 (3H, s, 5-OCH_3), 3.97 (3H, s, 1-OCH_3), 5.24 (2H, s, CH_2), 6.68 (1H, d, $J_{3,2}$ 8.5, 3-H), 6.85 (1H, d, $J_{2,3}$ 8.5, 2-H), 7.24 (1H, d, $J_{4',3'}$ 7.3, 4′-H), 7.30 (2H, t, $J_{3',4'}$ 7.3, $J_{3',2'}$ 7.3, 3′-H), 7.48 (2H, d, $J_{2',3'}$ 7.3, 2′-H), 7.57 (1H, d, $J_{7,8}$ 8.7, 7-H) and 8.04 (1H, d, $J_{8,7}$ 8.7, 8-H); δ_C(100 MHz, $CDCl_3$) 55.7 (OCH_3), 61.9 (OCH_3), 73.0 (CH_2, OCH_2), 103.9 (CH, C-2), 109.8 (CH, C-3), 117.3 (CH, C-8), 122.0 (C-4a), 127.6 (CH, C-4′), 127.8 (CH, C-3′), 128.5 (CH, C-2′), 128.6 (C-8a), 129.7 (CH, C-7), 130.5 (C-6), 137.7 (C-1′), 149.2, 150.4 (C-4 and C-5) and 153.7 (C-1); *m*/*z* 586 (M^+, 40%), 495 (M − CH_2Ph, 65) and 91 (100), and naphthalene **11** (59 mg, 19%) as a colourless solid, mp 63–64 °C for which the ^1H NMR data were in agreement with those reported in the literature.[15]

4-Benzyloxy-1,5-dimethoxy-6-naphthol 12

A flask equipped with a reflux condenser, a septum inlet and a magnetic stirring bar was charged with bromonaphthalene **8** (39 mg, 0.11 mmol), boronic acid **9** (42 mg, 0.13 mmol), $PdCl_2$(dppf) (9 mg, 0.011 mmol) and barium hydroxide (42 mg, 0.22 mmol). The flask was flushed with nitrogen and charged with 1,2-dimethoxyethane (3 cm^3) and water (0.5 cm^3). The reaction mixture was heated in an oil bath at 80 °C for 4 h. After cooling to room temperature, brine (10 cm^3) was added and the reaction mixture extracted with dichloromethane (3 × 15 cm^3). The organic phase was washed with brine (2 × 15 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to yield the title compound **12** (27 mg, 68%) as a pink solid, mp 75–76 °C [Found (EI): M^+, 310.1210; $C_{19}H_{18}O_4$ requires *M*, 310.1205]; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3417 (OH), 1453, 1263 and 1050 (C–O); δ_H(400 MHz, $CDCl_3$) 3.70 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.04 (2H, s, OCH_2), 6.11 (1H, br s, OH), 6.48 (1H, d, $J_{3,2}$ 8.4, 3-H), 6.78 (1H, d, $J_{2,3}$ 8.4, 2-H), 7.16 (1H, d, $J_{7,8}$ 9.1, 7-H), 7.27–7.36 (3H, m, 3′-H and 4′-H), 7.49 (2H, d, $J_{2',3'}$ 7.4, 2′-H) and 7.92 (1H, d, $J_{8,7}$ 9.1, 8-H); δ_C(100 MHz, $CDCl_3$) 54.7 (OCH_3), 61.7 (OCH_3), 71.7 (CH_2, OCH_2), 100.3 (CH, C-2), 108.8 (CH, C-3), 115.3 (CH, C-7), 118.5 (CH, C-8), 120.6, 122.0 (C-4a and C-8a), 126.7 (CH, C-4′), 126.8 (CH, C-3′), 127.3 (CH, C-2′), 136.5 (C-1′), 138.9 (C-6), 146.6 (C-4 and C-5) and 149.6 (C-1); *m*/*z* 310 (M^+, 20%), 219 (M − CH_2Ph, 100), 201 (38) and 91 (88) and bromonaphthalene **8** (26 mg, 66%) as a colourless solid mp 79–80 °C, for which the ^1H NMR data were in agreement with those reported earlier and naphthalene **11** (13 mg, 19%) as a colourless solid, mp 63–64 °C. for which the ^1H NMR data were also in agreement with those reported above.

7-(1-Hydroxy-4,8-dimethoxy-7-naphthyl)-4,8-dimethoxy-1-naphthol 15

To a suspension of binaphthyl **10** (110 mg, 0.19 mmol) in dry ethyl acetate (50 cm^3) was added palladium on charcoal (50 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 4 h, then filtered through Celite. The solvent was removed under reduced pressure to give an orange solid which was purified by trituration with diethyl ether to yield the title compound **15** (72 mg, 93%) as a tan solid, mp 196–197 °C [Found (EI): M^+, 406.1411; $C_{24}H_{22}O_6$ requires *M*, 406.1416]; $\nu_{max}(CH_2Cl_2$ solution)/cm^{-1} 3370 (OH) and 1601 (C=C); δ_H(400 MHz, d^6-acetone) 3.50 (3H, s, 8-OCH_3), 3.86 (3H, s, 4-OCH_3), 6.68 (1H, d, $J_{2,3}$ 8.4, 2-H), 6.81 (1H, d, $J_{3,2}$ 8.4, 3-H), 7.50 (1H, d, $J_{6,5}$ 8.7, 6-H), 7.96 (1H, d, $J_{5,6}$ 8.7, 5-H) and 9.10 (1H, s, OH); δ_C(100 MHz, d^6-acetone) 56.7 (OCH_3), 62.7 (OCH_3), 107.8 (CH, C-3), 111.0 (CH, C-2), 120.1 (CH, C-5), 127.2, 129.7 (C-8a and C-4a), 129.8 (CH, C-6), 130.0 (C-7), 132.4 (C-1) and 149.2, 149.5 (C-4 and C-8); *m*/*z* 406 (M^+, 60%), 360 (M − OC_2H_6, 40), 167 (58) and 149 (100).

7-(1-Acetoxy-4,8-dimethoxy-7-naphthyl)-4,8-dimethoxy-1-naphthyl acetate 14

To a solution of binaphthol **15** (103 mg, 0.25 mmol) in dichloromethane (8 cm^3) was added triethylamine (0.16 cm^3, 1.17 mmol), acetic anhydride (0.096 cm^3, 1.02 mmol) and 4-dimethylaminopyridine (2 mg). After stirring at room temperature for 1.5 h the reaction mixture was quenched with water (5 cm^3), extracted with dichloromethane (3 × 10 cm^3) and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a pale yellow oil that was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford the title compound **14** (84 mg, 68%) as a cream solid, mp 164–166 °C (Found: C, 68.7; H, 5.1. $C_{28}H_{26}O_8$ requires C, 68.6; H, 5.3%); ν_{max}(Nujol)/cm^{-1} 1760 (C=O), 1595 (C=C) and 1049 (C–O); δ_H(200 MHz, $CDCl_3$) 2.30 (3H, s, OAc), 3.50 (3H, s, 8-OCH_3), 4.01 (3H, s, 4-OCH_3), 6.80 (1H, d, $J_{3,2}$ 8.3, 3-H), 7.05 (1H, d, $J_{2,3}$ 8.3, 2-H), 7.57 (1H, d, $J_{6,5}$ 8.8, 6-H) and 8.11 (1H, d, $J_{5,6}$ 8.8, 5-H); δ_C(50 MHz, $CDCl_3$) 20.8 (CH_3, OAc), 55.8 (OCH_3), 61.6 (OCH_3), 103.6 (CH, C-3), 118.0 (CH, C-2), 119.4 (CH, C-5), 122.3 (C-4a), 128.1 (C-8a), 129.4 (CH, C-6), 129.8 (C-7), 139.3 (C-1), 152.3, 153.7 (C-4 and C-8) and 170.4 (C=O); *m*/*z* 490 (M^+, 22%), 448 (M − $COCH_2$, 70), 406 [M − $(CH_2CO)_2$, 100] and 360 (32).

2-Acetyl-7-(1-hydroxy-4,8-dimethoxy-7-naphthyl)-4,8-dimethoxy-1-naphthol 16 and 2-acetyl-7-(2-acetyl-1-hydroxy-4,8-dimethoxy-7-naphthyl)-4,8-dimethoxy-1-naphthol 13

Bis-acetate **14** (53 mg, 0.11 mmol) was heated to *ca*. 220 °C under argon and boron trifluoride–diethyl ether (0.07 cm^3, 0.55 mmol) was added. Vigorous evolution of ether was accompanied by formation of a dark red oil. After 2 min the reaction mixture was cooled to room temperature and the solid decomposed by the addition of water (5 cm^3) and dichloromethane (5 cm^3). After extraction into dichloromethane (3 × 8 cm^3), the organic phase was washed with water (2 × 8 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure to yield a brown oil. Flash chromatography using hexane–ethyl acetate (7:3) as eluent afforded mono-ketone **16** (7 mg, 15%) as a yellow solid, mp 173–175 °C [Found (EI): M^+, 448.1539; $C_{26}H_{24}O_7$ requires *M*, 448.1522]; $\nu_{max}(CH_2Cl_2$ solution)/cm^{-1} 3355 (OH), 1620 (C=O) and 1044 (C–O); δ_H(400 MHz, $CDCl_3$) 2.67 (3H, s, $COCH_3$), 3.49 (3H, s, 8′-OCH_3), 3.56 (3H, s, 8-OCH_3), 3.91 (3H, s, 4′-OCH_3), 3.95 (3H, s, 4-OCH_3), 6.74 (1H, d, $J_{2',3'}$ 8.4, 2′-H), 6.79 (1H, d, $J_{3',2'}$ 8.4, 3′-H), 6.93 (1H, s, 3-H), 7.50 (1H, d, $J_{6',5'}$ 8.7, 6′-H), 7.70 (1H, d, $J_{6,5}$ 8.6, 6-H), 8.02 (1H, d, $J_{5',6'}$ 8.7, 5′-H), 8.04 (1H, d, $J_{5,6}$ 8.6, 5-H), 9.25 (1H, s, 1′-OH) and 14.09 (1H, s, 1-OH); δ_C(50 MHz, $CDCl_3$) 27.6 (CH_3, $COCH_3$), 52.7 (2 × OCH_3), 62.0 (2 × OCH_3), 102.5 (CH, C-3), 106.1 (CH, C-3′), 109.5 (CH, C-2′), 113.7 (C-8a), 117.9 (C-8a′), 118.2 (CH, C-5), 118.7 (CH, C-5′), 119.7 (C-4a), 126.0 (C-4a′), 127.5 (C-1′), 128.9 (CH, C-6′), 129.7 (C-7), 132.4 (C-2 and C-7′), 132.9 (CH, C-6), 147.0 (C-1), 147.6, 148.3 (C-4′ and C-8′), 153.3 (C-8), 158.2 (C-4) and 203.2 (C=O); *m*/*z* 448 (M^+, 100%), 402 (70) and 43 (62) and acetylnaphthol **13** (11 mg, 21%) as a fluorescent yellow solid, mp 119–120 °C [Found (EI): M^+, 490.1576; $C_{28}H_{26}O_8$ requires *M*, 490.1627]; $\nu_{max}(CH_2Cl_2$ solution)/cm^{-1} 3354 (OH), 1619 (C=O) and 1049 (C–O); δ_H(200 MHz, $CDCl_3$) 2.74 (3H, s, $COCH_3$), 3.62 (3H, s, 8-OCH_3), 4.01 (3H, s, 4-OCH_3), 6.98 (1H, s, 3-H), 7.82 (1H, d, $J_{6,5}$ 8.7, 6-H), 8.07 (1H, d, $J_{5,6}$ 8.7, 5-H) and 14.07 (1H, s, OH); δ_C(50 MHz, $CDCl_3$) 20.9 (CH_3, $COCH_3$), 55.9 (OCH_3), 61.9 (OCH_3), 102.3 (CH, C-3), 114.2 (C-8a), 117.7 (CH, C-5), 119.5 (C-4a), 129.4

(C-7), 132.4 (C-2), 133.7 (CH, C-6), 147.1 (C-1), 153.7 (C-8), 158.1 (C-4) and 207.2 (C=O); *m/z* 490 (M^+, 40%), 448 (M − $COCH_2$, 42), 406 [M − $(COCH_2)_2$, 30] and 43 (100) and bis-naphthol **15** (6 mg, 15%) as a tan solid, mp 196–197 °C. for which the ^{1}H NMR data were in agreement with those reported earlier.

5-Acetyl-7-(2-acetyl-1-hydroxy-4,8-dimethoxy-7-naphthyl)-4,8-dimethoxy-1-naphthyl acetate 17 and 7-(1-acetoxy-4,8-dimethoxy-7-naphthyl)-5-acetyl-4,8-dimethoxy-1-naphthyl acetate 18

To a solution of bis-acetate **14** (46 mg, 0.094 mmol) in acetic anhydride (0.2 cm^3) heated to *ca*. 140 °C under argon was added boron trifluoride–diethyl ether (0.05 cm^3, 0.37 mmol). Vigorous evolution of diethyl ether was accompanied by the formation of a yellow oil. After 2 min, the reaction mixture was cooled to room temperature and decomposed by the addition of water (0.5 cm^3) and dichloromethane (1 cm^3). After extraction with dichloromethane (3 × 5 cm^3), the organic phase was washed with water (2 × 8 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a brown oil. Purification by flash chromatography using hexane–ethyl acetate (6:4) as eluent yielded a yellow oil (24 mg) which was further purified by HPLC on a Partisil 10 M9 semi-preparative column using dichloromethane–ethyl acetate (98:2) as eluent to afford ketone **17** (19 mg, 37%) as a fluorescent yellow oil [Found (EI): M^+, 532.1740; $C_{30}H_{28}O_9$ requires *M*, 532.1733]; ν_{max}(film)/cm^{-1} 3354 (OH), 1760 (C=O, acetate), 1619 (C=O, acetyl) and 1043 (C–O); δ_H(200 MHz, $CDCl_3$) 2.35 (3H, s, OAc), 2.39 (3H, s, 5-$COCH_3$), 2.75 (3H, s, 2′-$COCH_3$), 3.56 (3H, s, 8′-OCH_3), 3.65 (3H, s, 8-OCH_3), 3.95 (3H, s, 4-OCH_3), 4.02 (3H, s, 4′-OCH_3), 6.23 (1H, s, 6-H), 6.95 (1H, d, $J_{2,3}$ 8.5, 2-H), 6.98 (1H, s, 3′-H), 7.19 (1H, d, $J_{3,2}$ 8.5, 3-H), 7.74 (1H, d, $J_{6',5'}$ 8.6, 6′-H), 8.08 (1H, d, $J_{5',6'}$ 8.6, 5′-H) and 14.37 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 20.8 (CH_3, OAc), 24.4 (CH_3, 5-CH_3), 27.7 (CH_3, 2-CH_3), 55.9, 56.1, 61.9, 62.1 (OCH_3), 101.9 (CH, C-3′), 102.7 (CH, C-3), 106.5 (CH, C-6), 113.3 (C-8a′), 118.1 (CH, C-5′), 121.5 (CH, C-2), 123.4 and 124.4 (C-4a′ and C-4a), 126.9 (C-8a), 128.2, 128.7 (C-7 and C-7′), 131.8 (CH, C-6′), 132.7 (C-2′), 133.2 (C-5), 139.4 (C-1), 147.2 (C-1′), 153.2 (C-8′), 155.5, 156.4 (C-4 and C-8), 158.2 (C-4′), 170.0 [C=O (acetate)], 191.4 [C=O (C-5)] and 204.0 [C=O (C-2′)]; *m/z* 532 (M^+, 52%), 490 (M − OC_2H_2, 58), 448 (M − $O_2C_4H_4$, 14) and 43 (100) and ketone **18** (4.5 mg, 9%) as a fluorescent yellow oil [Found (EI); M^+, 532.1724; $C_{30}H_{28}O_9$ requires *M*, 532.1733]; ν_{max}(film)/cm^{-1} 1761 (C=O, acetate) and 1726 (C=O, acetyl), 1548 and 1048 (C–O); δ_H(200 MHz, $CDCl_3$) 2.32 (3H, s, OAc), 2.34 (3H, s, OAc), 2.38 (3H, s, $COCH_3$), 3.51 (3H, s, 8-OCH_3 or 8′-OCH_3), 3.52 (3H, s, 8′-OCH_3 or 8-OCH_3), 3.93 (3H, s, 4-OCH_3), 4.01 (3H, s, 4′-OCH_3), 6.19 (1H, s, 6-H), 6.82 (1H, d, $J_{2',3'}$ 8.3, 2′-H), 6.92 (1H, d, $J_{2,3}$ 8.5, 2-H), 7.07 (1H, d, $J_{3',2'}$ 8.3, 3′-H), 7.16 (1H, d, $J_{3,2}$ 8.5, 3-H), 7.48 (1H, d, $J_{6',5'}$ 8.8, 6′-H) and 8.12 (1H, d, $J_{5',6'}$ 8.8, 5′-H); *m/z* 532 (M^+, 72%), 490 (M − OC_2H_2, 68), 417 (18) and 43 (100) and acetylnaphthol **13** (16 mg, 34%) as a fluorescent yellow solid, mp 119–120 °C for which the ^{1}H NMR data were in agreement with those reported earlier.

2-Bromo-7-(2-bromo-1-hydroxy-4,8-dimethoxy-7-naphthyl)-4,8-dimethoxy-1-naphthol 23

To a solution of binaphthol **15** (86 mg, 0.21 mmol) in carbon tetrachloride (6 cm^3) cooled to 0 °C under an atmosphere of nitrogen, was added bromine [0.34 cm^3 of a solution prepared from Br_2 (85 mg, 0.53 mmol) in CCl_4 (0.5 cm^3)] dropwise, and the resulting suspension stirred for 10 min. After quenching with saturated aqueous sodium thiosulfate (8 cm^3), the reaction mixture was extracted with dichloromethane (3 × 10 cm^3), washed with water (2 × 10 cm^3) and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded a brown oil which was purified by trituration with diethyl ether to give the title compound **23** (89 mg, 74%) as a tan solid, mp 180–181 °C [Found (EI): M^+, 561.9628; $C_{24}H_{20}O_6Br_2$ requires *M*, 561.9628]; ν_{max}(CH_2Cl_2 solution)/cm^{-1} 3307 (OH), 1595 (C=C) and 1049 (C–O); δ_H(200 MHz, $CDCl_3$) 3.53 (3H, s, 8-OCH_3), 3.96 (3H, s, 4-OCH_3), 6.99 (1H, s, 3-H), 7.56 (1H, d, $J_{6,5}$ 8.8, 6-H), 8.08 (1H, d, $J_{5,6}$ 8.8, 5-H) and 10.00 (1H, s, OH); δ_C(50 MHz, $CDCl_3$) 56.1 (OCH_3), 62.6 (OCH_3), 103.6 (CH, C-3), 110.4 (C-4a), 118.1 (C-2), 119.6 (CH, C-5), 126.4 (C-8a), 127.0 (C-7), 128.6 (CH, C-6), 144.2 (C-1), 148.3 (C-4) and 152.6 (C-8); *m/z* 564 (M^+, 43%), 484/486 (M − Br, 18), 406 (M − Br_2, 10) and 94 (100).

3-Bromo-6-(3-bromo-1,4,5-trimethoxy-6-naphthyl)-1,4,5-trimethoxynaphthalene 20 and 1,4,5-trimethoxy-6-(1,4,5-trimethoxy-6-naphthyl)naphthalene 24

A solution of bromonaphthol **23** (41 mg, 0.073 mmol) in dimethylformamide (1 cm^3) was cooled to 0 °C under an atmosphere of argon. A solution of sodium dithionite (13 mg, 0.073 mmol) in water (0.2 cm^3) was added followed by tetrahydrofuran (0.5 cm^3) and dimethyl sulfate (0.03 cm^3, 0.29 mmol). After stirring for 10 min potassium hydroxide (21 mg, 0.37 mmol) in water (0.2 cm^3) was added dropwise and stirring continued for a further 15 min. The reaction mixture was poured into ethyl acetate (5 cm^3) and the aqueous phase extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were washed with water (15 cm^3), brine (20 cm^3) and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a red oil, which was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluent to afford bromonaphthalene **20** (17 mg, 39%) as a pale orange solid, mp 135–136 °C [Found (EI): M^+, 589.9948; $C_{26}H_{24}O_6Br_2$ requires *M*, 589.9941]; ν_{max}(CH_2Cl_2 solution)/cm^{-1} 1584 (C=C), 1402, 1320 and 1055 (C–O); δ_H(200 MHz, $CDCl_3$) 3.54 (3H, s, 5-OCH_3), 3.87 (3H, s, 4-OCH_3), 4.00 (3H, s, 1-OCH_3), 6.98 (1H, s, 2-H), 7.54 (1H, d, $J_{7,8}$ 8.7, 7-H) and 8.07 (1H, d, $J_{8,7}$ 8.7, 8-H); δ_C(50 MHz, $CDCl_3$) 56.0 (OCH_3), 61.9 (OCH_3), 62.1 (OCH_3), 108.7 (CH, C-2), 114.9 (C-3), 118.0 (CH, C-8), 123.9 (C-4a), 127.9 (C-8a), 129.3 (CH, C-7), 131.2 (C-6), 146.1, 152.4 (C-1 and C-4) and 152.6 (C-5); *m/z* 592 (M^+, 100%), 546 (20), 516 (12) and 45 (40) and naphthalene **24** (15.8 mg, 50%) as a tan solid, mp 175–176 °C [Found (EI): M^+, 434.1715; $C_{26}H_{26}O_6$ requires *M*, 434.1729]; ν_{max}(CH_2Cl_2 solution)/cm^{-1} 1595 (C=C), 1337, 1255 and 1054 (C–O); δ_H(200 MHz, $CDCl_3$) 3.56 (3H, s, 5-OCH_3), 3.96 (3H, s, 1-OCH_3 or 4-OCH_3), 3.98 (3H, s, 4-OCH_3 or 1-OCH_3), 6.75 (1H, d, $J_{3,2}$ 8.5, 3-H), 6.81 (1H, d, $J_{2,3}$ 8.5, 2-H), 7.67 (1H, d, $J_{7,8}$ 8.7, 7-H) and 8.08 (1H, d, $J_{8,7}$ 8.7, 8-H); δ_C(50 MHz, $CDCl_3$) 55.8 (OCH_3), 56.7 (OCH_3), 61.6 (OCH_3), 103.8 (CH, C-2), 105.8 (CH, C-3), 117.2 (CH, C-8), 121.3 (C-4a), 128.4 (C-8a and C-6), 130.0 (CH, C-7), 149.6, 150.2 (C-1 and C-5) and 157.1 (C-4); *m/z* 434 (M^+, 100%), 338 (17) and 343 (10).

2-Acetyl-7-(2-acetyl-1,4,8-trimethoxy-7-naphthyl)-1,4,8-trimethoxynaphthalene 22

To a suspension of compound **20** (15 mg, 0.025 mmol) and $PdCl_2(PPh_3)_2$ (2 mg, 0.003 mmol) in dry toluene (2 cm^3) under an atmosphere of argon, was added (α-ethoxyvinyl)tri-*n*-butyltin **19** (37 mg, 0.10 mmol). The reaction mixture was heated under reflux for 18 h. Additional (α-ethoxyvinyl)tri-*n*-butyltin **19** (37 mg, 0.10 mmol) and $PdCl_2(PPh_3)_2$ (2 mg, 0.003 mmol) were added and heating continued for a further 18 h. After cooling to room temperature, 10% hydrochloric acid (3 cm^3) was added, the reaction mixture stirred for 5 min, then extracted with dichloromethane (3 × 10 cm^3). The combined extracts were washed vigorously with saturated potassium fluoride solution (5 × 10 cm^3), water (2 × 10 cm^3) and dried (Na_2SO_4). Removal of the solvent under reduced pressure

afforded a yellow oil which was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to yield a colourless oil which upon trituration with hexane gave the title compound **22** (9 mg, 70%) as a colourless solid, mp 184–185 °C [Found (EI): M^+, 518.1960; $C_{30}H_{30}O_8$ requires *M*, 518.1941]; ν_{max}(film)/cm^{-1} 2919, 1661 (C=O), 1330 and 1049 (C–O); δ_H(200 MHz, $CDCl_3$) 2.81 (3H, s, $COCH_3$), 3.62 (3H, s, 8-OCH_3), 3.88 (3H, s, 1-OCH_3), 4.04 (3H, s, 4-OCH_3), 7.10 (1H, s, 3-H), 7.64 (1H, d, $J_{6,5}$ 8.6, 6-H) and 8.14 (1H, d, $J_{5,6}$ 8.6, 5-H); δ_C(50 MHz, $CDCl_3$) 31.5 (CH_3, $COCH_3$), 55.9 (OCH_3), 62.2 (OCH_3), 63.9 (OCH_3), 103.0 (CH, C-3), 118.0 (CH, C-5), 123.0, 128.6 (C-4a and C-8a), 129.5 (C-7), 130.9 (C-2), 131.2 (CH, C-6), 151.8 (C-1 and C-8), 154.1 (C-4) and 201.1 (C=O); *m*/*z* 518 (M^+, 82%), 476 (M − OC_2H_2, 76), 247 (18) and 43 (100).

7-(2-Acetyl-8-methoxy-1,4-dioxonaphthalen-7-yl)-2-acetyl-8-methoxy-1,4-naphthoquinone 7

(i) Oxidation of acetylnaphthol 13. Compound **13** (21 mg, 0.043 mmol) and freshly prepared AgO (ref. 35) (41 mg, 0.34 mmol) were mixed in dioxane (3 cm^3). To this was added HNO_3 (0.06 cm^3 of a 6 mol dm^3 solution) and the reaction mixture stirred for 10 min in air, after which time further AgO (41 mg, 0.34 mmol) and HNO_3 (0.06 cm^3 of a 6 mol dm^3 solution) were added. After stirring an additional 10 min the reaction mixture was quenched with water (5 cm^3) and extracted into dichloromethane (4 × 10 cm^3). The organic layer was washed with water (20 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure to yield the title compound **7** (14 mg, 72%) as an orange solid, mp 211–213 °C [Found (EI): M^+, 458.1015; $C_{26}H_{18}O_8$ requires *M*, 458.1002]; ν_{max}(CH_2Cl_2 solution)/cm^{-1} 1700 (C=O, acetyl) and 1655 (C=O, quinone); δ_H(200 MHz, $CHCl_3$) 2.60 (3H, s, $COCH_3$), 3.63 (3H, s, OCH_3), 7.09 (1H, s, 3-H), 7.73 (1H, d, $J_{6,5}$ 7.9, 6-H) and 7.97 (1H, d, $J_{5,6}$ 7.9, 5-H); *m*/*z* 462 (M + 4, 48%), 460 (M + 2, 76), 458 (M^+, 76), 427 (M − OCH_3, 58) and 385 (50).

(ii) Oxidation of diketone 22. Compound **22** (10 mg, 0.019 mmol) and freshly prepared AgO (ref. 35) (19 mg, 0.15 mmol) were mixed in dioxane (2 cm^3). To this was added HNO_3 (0.04 cm^3 of a 6 mol dm^3 solution) and the reaction mixture stirred for 10 min in air, after which time further AgO (19 mg, 0.15 mmol) and HNO_3 (0.04 cm^3 of a 6 mol dm^3 solution) were added. After stirring an additional 15 min the reaction mixture was quenched with water (5 cm^3) and extracted into dichloromethane (4 × 10 cm^3). The organic layer was washed with water (2 × 10 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure to yield the title compound **7** (5.7 mg, 66%) as an orange solid, mp 211–213 °C for which the ^{1}H NMR data were in agreement with those reported above.

In situ coupling of bromonaphthol 25

A flask equipped with a reflux condenser, septum inlet and magnetic stirring bar was charged with 2-acetyl-7-bromo-4,8-dimethoxy-1-naphthol **25**[36] (41 mg, 0.13 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl-4′,4′,5′,5′-tetramethyl-1′,3′,2′-dioxaboralane [bis(pinacolato)diboron][39] (130 mg, 0.51 mmol), $PdCl_2$(dppf) (41 mg, 0.051 mmol) and caesium fluoride (39 mg, 0.26 mmol). The flask was flushed with argon, charged with dry tetrahydrofuran (4 cm^3) and the reaction mixture heated under reflux for 5 h. Additional $PdCl_2$(dppf) (41 mg, 0.051 mmol) and caesium fluoride (39 mg, 0.26 mmol) were added and the reaction mixture heated under reflux for a further 10 h. After cooling to room temperature, the reaction mixture was partitioned between water (4 cm^3) and ethyl acetate (4 cm^3). The aqueous layer was extracted with ethyl acetate (3 × 10 cm^3) and the combined organic layers were washed with water (2 × 10 cm^3) and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded a dark oil which was purified by flash chromatography using hexane–ethyl acetate (8:2) then (6:4) as eluent to yield 2-acetyl-4,8-dimethoxy-1-naphthol **27** (6.4 mg, 20%) as a yellow solid, mp 133–135 °C (lit.,[41] mp 133–135 °C); *2-acetyl-4,8-dimethoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-1-naphthol* **26** (9.2 mg, 19%) as a yellow solid, mp 75–78 °C; [Found (EI): M^+, 372.1754; $C_{20}H_{25}O_6B$ requires *M*, 372.1744]; ν_{max}(film)/cm^{-1} 3290 (OH), 1617 (C=O), 1373, 1280 and 1125; δ_H(200 MHz, $CDCl_3$) 1.37 (12H, s, 4 × CH_3), 2.69 (3H, s, $COCH_3$), 3.94 (3H, s, OMe), 3.96 (3H, s, OMe), 6.99 (1H, s, 3-H), 7.84 (1H, d, $J_{6,5}$ 8.5, 6-H), 7.94 (1H, d, $J_{5,6}$ 8.5, 5-H) and 13.40 (1H, s, OH); δ_C(50 MHz, $CDCl_3$) 24.5 (CH_3, CH_3), 28.8 (CH_3, $COCH_3$), 55.8 (CH_3, OMe), 64.4 (CH_3, OMe), 83.8 (C-OB), 103.5 (CH, C-3), 107.2 (C-7), 114.1, 114.7 (C-4a and C-8a), 117.6 (CH, C-5), 129.9 (C-2), 134.2 (C-8), 135.8 (CH, C-6), 146.9 (C-1), 157.3 (C-4) and 202.0 (C=O); *m*/*z* 372 (M^+, 45%), 272 (20), 257 (16), 84 (100) and 43 (60); binaphthol **13** (17 mg, 53%) was also isolated as a yellow solid, mp 119–120 °C for which the ^{1}H NMR data were in agreement with those reported above.

(6b*R**,9a*R**,6b′*S**,9a′*S**)-6-Acetyl-3-{6-acetyl-6b,8,9,9a-tetrahydro-5-hydroxy-4-methoxy-8-oxofuro[3,2-*b*]naphtho[2,1-*d*]-furan-3-yl}-6b,9a-dihydro-5-hydroxy-4-methoxyfuro[3,2-*b*]-naphtho[2,1-*d*]furan-8(9*H*)-one 30 and (6b*R**,9a*R**,6b′*R**, 9a′*R**)-6-acetyl-3-{6-acetyl-6b,8,9,9a-tetrahydro-5-hydroxy-4-methoxy-8-oxofuro[3,2-*b*]naphtho[2,1-*d*]furan-3-yl}-6b,9a-dihydro-5-hydroxy-4-methoxyfuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one 31 ‡

To a solution of bis-naphthoquinone **7** (51 mg, 0.11 mmol) in acetonitrile (6 cm^3) cooled to 0 °C under an atmosphere of nitrogen was added dropwise, over a period of 2 min a solution of 2-trimethylsilyloxyfuran (0.056 cm^3, 0.33 mmol) in acetonitrile (1 cm^3). After stirring for 1 h at 0 °C the solvent was removed under reduced pressure to afford an orange oil. Purification by flash chromatography using hexane–ethyl acetate (1:2) as eluent afforded a 1:1 mixture of *adducts* **30** and **31** (35 mg, 51%) as a yellow oil [Found (FAB): M + H 627.1530; $C_{34}H_{27}O_{12}$ requires *M* + H 627.1503]; ν_{max}(CH_2Cl_2 solution)/cm^{-1} 3243 (OH), 1782 (C=O, lactone) and 1625 (C=O, acetyl); δ_H(400 MHz, $CDCl_3$) 2.83 (6H, s, CH_3), 3.06 (2H, dd, J_{gem} 19.1 and $J_{9,9a}$ 2.4, 9-H), 3.12 (2H, dd, J_{gem} 19.1 and $J_{9',9a}$ 5.7, 9′-H), 3.62 (6H, s, OMe), 5.47 (2H, ddd, $J_{9a,9}$ 5.7, $J_{9a,6b}$ 5.7 and $J_{9a,9}$ 2.4, 9a-H), 6.52 (2H, d, $J_{6b,9a}$ 5.7, 6b-H), 7.71 (2H, d, $J_{2,1}$ 8.5, 2-H), 7.77 (2H, d, $J_{1,2}$ 8.5, 1-H) and 13.33 (2H, s, OH); δ_C(100 MHz, $CDCl_3$) 32.3 (CH_3, $COCH_3$), 36.3 (CH_2, C-9), 63.1 (CH_3, OMe), 81.8 (CH, C-9a), 86.3 (CH, C-6b), 113.9, 114.8, 121.6, 126.4, 130.5 (C-3, C-4a, C-6, C-6a, C-10b), 119.4 (CH, C-1), 134.0 (CH, C-2), 150.9, 156.9, 158.3 (C-4, C-5, C-10a), 175.0 [C=O (lactone)] and 202.2 [C=O (ketone)]; *m*/*z* (FAB) 627 (M + H, 100%), 550 (12) and 491 (84).

(3a*R**,5*S**,11b*R**,3a′*S**,5′*R**,11b′*S**)-3,3a,5,11b-Tetrahydro-8-{3,3a,5,11b-tetrahydro-5-hydroxy-7-methoxy-5-methyl-2,6,11-trioxo-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-8-yl}-5-hydroxy-7-methoxy-5-methyl-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 32 and (3a*R**,5*S**,11b*R**,3a′*R**,5′*S**,11b′*R**)-3,3a,5,11b-tetrahydro-8-{3,3a,5,11b-tetrahydro-5-hydroxy-7-methoxy-5-methyl-2,6,11-trioxo-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-8-yl}-5-hydroxy-7-methoxy-5-methyl-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]-pyran-2,6,11-trione 33 ‡

To a vigorously stirred solution of bis-adducts **30** and **31** (29.1 mg, 0.046 mmol) in acetonitrile (1 cm^3) at 0 °C was added a solution of ceric ammonium nitrate (105 mg, 0.19 mmol) in water (2 cm^3). After 15 min the reaction mixture was extracted with dichloromethane (2 × 10 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and the sol-

‡ The use of primed numbers to donate the stereochemistry in these names refers to the positions in the cyclic substituent attached to the parent molecule.

vent removed under reduced pressure to afford a yellow oil. Purification by flash chromatography using hexane–ethyl acetate (3 : 7) then ethyl acetate as eluent afforded a 1 : 1 mixture of *hemiacetals* **32** and **33** (16 mg, 55%) as a yellow oil [Found (CI): M + H, 659.1354; $C_{34}H_{27}O_{14}$ requires *M* + H, 659.1400]; ν_{max}(film)/cm^{-1} 3443 (OH), 1783 (C=O, lactone) and 1666 (C=O, quinone); δ_H[400 MHz, $(CD_3)_2O$]§ 1.83 (3H, s, CH_3), 1.84* (3H, s, CH_3), 2.51 (2H, d, J_{gem} 17.6, 3-H), 3.20 (2H, dd, J_{gem} 17.6 and $J_{3',3a}$ 5.2, 3-H′), 3.67 (6H, s, OCH_3), 5.00 (2H, dd, $J_{3a,3'}$ 5.2, $J_{3a,11b}$ 3.2, 3a-H), 5.40 (2H, d, $J_{11b,3a}$ 3.2, 11b-H), 5.90 (2H, br s, OH), 7.81 (1H, d, $J_{9,10}$ 8.0, 9-H), 7.82* (1H, d, $J_{9,10}$ 8.0, 9-H), 7.97 (1H, d, $J_{10,9}$ 8.0, 10-H) and 7.98* (1H, d, $J_{10,9}$ 8.0, 10-H); δ_C[100 MHz, $(CD_3)_2O$] 26.8 (CH_3, CH_3), 36.8 (CH_2, C-3), 62.3 (CH_3, OMe), 67.2 (CH, C-3a), 69.7 (CH, C-11b), 93.8 (C-5), 122.0 (CH, C-10), 122.1 (C-8), 125.9, 134.4, 139.8, 148.4 (C-5a, C-6a, C-10a, C-11a), 136.7 (CH, C-9), 158.7 (C-7), 175.2 [C=O (C-2)] and 183.2, 183.5 [C=O (C-6 and C-11)]; *m*/*z* 659 (M + H, 16%), 643 (M − O, 22), 627 (M − O_2, 28), 599 (M − $C_2H_4O_2$, 100) and 553 (580).

(1*S,3*R**,1′*R**,3′*R**)-Methyl 3,4,5,10-tetrahydro-8-{3,4,5,10-tetrahydro-9-methoxy-1-methyl-5,10-dioxo-3-methoxycarbonylmethyl-1*H*-naphtho[2,3-*c*]pyran-8-yl}-9-methoxy-1-methyl-5,10-dioxo-1*H*-naphtho[2,3-*c*]pyran-3-ylacetate 34 and (1*S**,3*R**,1′*S**,3′*S**)-methyl 3,4,5,10-tetrahydro-8-{3,4,5,10-tetrahydro-9-methoxy-1-methyl-5,10-dioxo-3-methoxycarbonylmethyl-1*H*-naphtho[2,3-*c*]pyran-8-yl}-9-methoxy-1-methyl-5,10-dioxo-1*H*-naphtho[2,3-*c*]pyran-3-ylacetate 35‡**

To a solution of hemiacetals **32** and **33** (10 mg, 0.015 mmol) in ethyl acetate (5 cm^3) was added 10% palladium on charcoal (20 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 1.5 h, then filtered through Celite. The solvent was removed under reduced pressure to afford a red oil to which ethyl acetate (15 cm^3) and an excess of ethereal diazomethane (1.5 cm^3) were added with stirring. Removal of the solvent under reduced pressure afforded a 1 : 1 mixture of *methyl esters* **34** and **35** (7.8 mg, 78%) as a yellow oil [Found (FAB): M^+, 659.2084. $C_{36}H_{35}O_{12}$ requires *M*, 659.2183]; ν_{max}(film)/cm^{-1} 1737 (C=O, ester) and 1660 (C=O, ketone); δ_H(400 MHz, $CDCl_3$) 1.46 (6H, d, J_{vic} 6.4, CH_3), 2.25 (2H, ddd, J_{gem} 18.4, $J_{4ax,3ax}$ 10.6 and $J_{4ax,1}$ 2.8, 4-pseudoaxial-H), 2.56 (2H, dd, J_{gem} 15.6 and *J* 5.4, C$H_A$$CO_2$Me), 2.68 (2H, dd, J_{gem} 15.6 and *J* 7.6, C$H_B$$CO_2$Me), 2.83 (2H, br d, *J* 18.4, 4-pseudoequatorial-H), 3.56 (6H, s, OMe), 3.67 (6H, s, CO_2-Me), 3.84–3.93 (2H, m, 3-H), 4.81–4.88 (2H, m, 1-H), 7.56 (1H, d, $J_{7,6}$ 8.0, 7-H), 7.58* (1H, d, $J_{7,6}$ 8.0, 7-H), 7.85 (1H, d, $J_{6,7}$ 8.0, 6-H) and 7.87* (1H, d, $J_{6,7}$ 8.0, 6-H); *m*/*z* 659 (M + H, 2%), 154 (100) and 107 (26).

4-Acetyl-7-(4-acetyl-2-carboxymethyl-5-hydroxy-6-methoxynaphtho[1,2-*b*]furan-7-yl)-5-hydroxy-6-methoxynaphtho[1,2-*b*]furan-2-ylacetic acid 36

A 1 : 1 mixture of furonaphthofurans **30** and **31** (20.5 mg, 0.03 mmol) in chloroform (0.5 mL) was allowed to stand for 20 min. The solvent was removed *in vacuo* to afford the title compound **36** (20.5 mg, 100%) as a yellow oil [Found (EI): M + H, 626.1436. $C_{34}H_{26}O_{12}$ requires *M* + H, 626.1424]; ν_{max}(film)/cm^{-1} 3200 (OH), 1723 (C=O, acid) and 1623 (C=O, *o*-hydroxyaryl ketone); δ_H[400 MHz, $(CD_3)_2SO$] 2.82 (6H, s, $COCH_3$), 3.57 (6H, s, OCH_3), 4.00 (4H, s, C$H_2$$CO_2$H), 7.19 (2H, s, furan-H), 7.87 (2H, d, *J* 11.8, Ar*H*), 8.00 (2H, d, *J* 11.8, Ar*H*) and 14.45 (2H, s, O*H*); δ_C[100.6 MHz, $(CD_3)_2SO$] 31.7 (COCH_3), 34.3 (CH_2CO_2H), 61.9 (OCH_3), 107.5 (CH), 109.3 (CH), 115.3 (CH), 116.0 (C), 122.0 (C), 126.0 (C), 127.9 (C), 134.6 (CH), 143.2 (C), 152.9 (C), 156.8 (C), 160.3 (C), 170.3 (C=O, acid) and 203.1(C=O, ketone).

§ * Denotes resonance for diastereomer.

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