Synthesis of a Pyranonaphthoquinone-spiroacetal [1]

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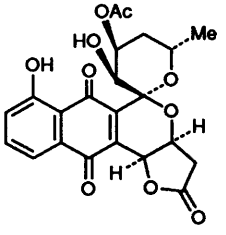
A synthesis of pyranonaphthoquinone-spiroacetal **12** is reported which represents an efficient entry to the pentacyclic framework of the pyranonaphthoquinone antibiotic griseusin A. The key step involves assembly of the furo[3,2-*b*]naphtho[2,3-*d*]pyran **11** *via* a ceric ammonium nitrate oxidative rearrangement of the furo[3,2-*b*]naptho[2,1-*d*]furan **10**. This latter heterocycle **10** in turn was constructed *via* the uncatalysed 1,4-addition of 2-trimethylsilyloxyfuran **9** to naphthoquinone **8**. Naphthoquinone **8** is readily available from 1,4-dimethoxynaphthalene-2-carbaldehyde **3** and acetylene **4**.

Griseusins A and B, **1** and **2**, produced by a strain of *Streptomyces griseus* [2] are members of the pyranonaphthoquinone



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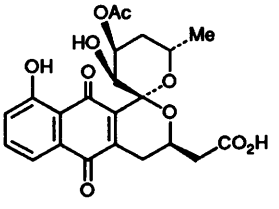

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family of antibiotics which have aroused interest due to their inhibitory activity against gram-positive bacteria, pathogenic fungi and yeasts.[2] They have also been proposed to act as bioreductive alkylating agents [3] and are distinguished from simpler members of the family which include kalafungin [4] and the nanaomycins A and D [5] by the presence of the 1,7-dioxaspiro[5,5]undecane ring system.

Despite the biological activity exhibited by these compounds only one synthesis of Griseusins A and B has been reported by Yoshii *et al.*[6,7,8] in which the spiroacetal ring system was assembled *via* intramolecular ketalization of a δ,δ′-dihydroxy ketone derived from a bromohydrin. We now wish to report an efficient entry to the basic pentacyclic framework of Griseusin A in which the furo[3,2-*b*]naphtho[2,3-*d*]pyran ring system is assembled *via* ceric ammonium nitrate (CAN) oxidative rearrangement of a furo-[3,2-*b*]naphtho[2,1-*d*]furan (Scheme 1). This strategy has recently been employed by us [9] to synthesize *epi*-7-deoxykalafungin and *epi*-7-*O*-methylkalafungin.

The synthesis of the initial furo[3,2-*b*]naphtho[2,1-*d*]furan **10** involved the uncatalysed addition of 2-trimethylsilyloxyfuran **9** to the naphthoquinone **8**. Naphthoquinone **8** was prepared from readily available 1,4-dimethoxynaphthalene-2-carbaldehyde **3** and protected alcohol **4**. Initially alcohol **4c** was protected as an acetate **4a** but it proved difficult to remove this group in the presence of the γ-lactone functionality at a later stage in the synthesis. Hence subsequent work used *tert*-butyldimethylsilyl ether **4b** which proved to be successful.

Generation of the lithium acetylide of acetylene **4b** with butyllithium in tetrahydrofuran (THF) at −78 °C for 1 h followed by the addition of 1,4-dimethoxynaphthalene-2-carbaldehyde **3** afforded an isomeric mixture of the alcohol **5b** in 86% yield. Oxidation of the benzylic alcohol **5b** to the ketone **6b** was then easily effected using activated manganese dioxide in 76% yield. Hydrogenation of keto acetylene **6b** over 5% palladium on charcoal in ethyl acetate gave the saturated ketone **7b** in 93% yield which underwent smooth oxidation using ceric ammonium nitrate (1.9 equiv.) in aqueous acetonitrile to give the desired saturated quinone **8b** in excellent yield.

Having successfully prepared quinone **8b**, its subsequent reaction with 2-trimethylsilyloxyfuran **9** was investigated. Using acetonitrile as solvent, 2-trimethylsilyloxyfuran **9** (2.0 equiv.) was added to the quinone **8b** at 0 °C under nitrogen. Addition of methanol followed by purificati n by flash-chromatography afforded the furo[3,2-*b*]naphtho[2,1-*d*]furan **10b** in 71% yield.

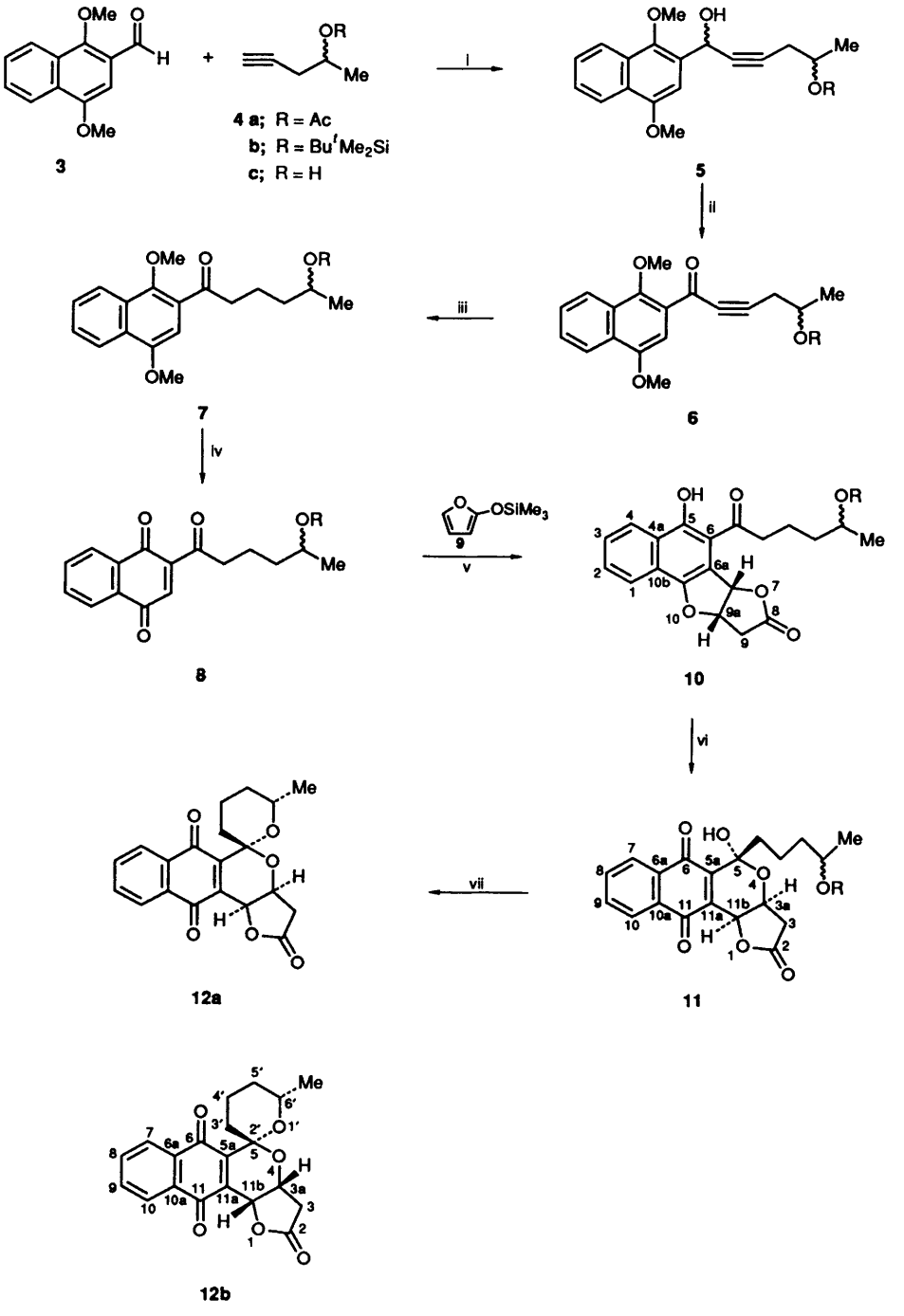
^{1}H NMR spectroscopy indicated a 1:1 mixture of diastereoisomers, which, although not differentiated by TLC were able to be separated by recrystallisation from diethyl ether, affording the least soluble isomer of adduct **10b** as yellow needles, m.p. 132–135 °C. The ^{1}H NMR spectrum of this isomer exhibited a double double doublet at δ_H 5.54 and a doublet at δ_H 6.46 assigned to the bridgehead protons 9a-H and 6b-H respectively, and the bridgehead coupling constant, 6.3 Hz, was consistent with *cis* fusion of the two furan rings. These protons resonated at similar positions to those reported for the analogous protons in related furo[3,2-*b*]naphtho[2,1-*d*]furans.[9]

In our initial work using an acetate protecting group, addition of 2-trimethylsilyloxyfuran **9** to naphthoquinone **8a** resulted in formation of the enol **13** in 80% yield when addition of methanol to the reaction mixture was omitted. A similar intermediate **14** was isolated in previous work [9] directed towards the synthesis of kalafungin. Hence addition of methanol before work-up was crucial to the formation of the desired furo[3,2-*b*]naphtho[2,1-*d*]furan ring system.

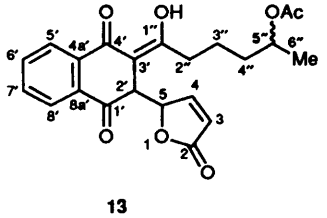
The ^{1}H NMR spectrum of enol **13** exhibited a multiplet at δ_H 4.92–5.04, a double doublet at δ_H 6.15 and a multiplet at δ_H 7.33–7.37, assigned to the protons 5-H, 3-H and 4-H respectively of the butenolide. Similar resonances for these protons were observed for the simpler enol **14**.[9] The presence of a 1:1 mixture of diastereoisomers was also indicated in the ^{1}H NMR spectrum of **13** by the presence of two resonances at δ_H 2.04 and 2.05 assigned to the acetate group.

Returning to the adduct **10b**, it now remained to investigate the ceric ammonium nitrate rearrangement to the furo[3,2-*b*]naphtho[2,3-*d*]pyran. Treatment of the 1:1 isomeric mixture of the adduct **10b** with ceric ammonium nitrate (2.0 equiv.) resulted in the formation of the expected rearranged hemiacetal **11b** with the *tert*-butyldimethylsilyl group still intact, as well as a more polar minor product identified as the diol **11c**. It was decided to capitalize on this fortuitous loss of the protecting group in the ceric ammonium nitrate rearrangement and thus, treatment of adduct **10b** with CAN (8.0 equiv.) effected rearrangement and complete loss of the *tert*-butyldimethylsilyl group, giving the desired diol **11c** in 87% yield after purification by flash chromatography.

The product **11c** obtained from the isomeric mixture of



Scheme 1 *Reagents and conditions:* i, **4**, BuLi (1.1 equiv.), THF, −78 °C, 1 h, then **3**, −78 °C to −60 °C, 86%; ii, excess MnO_2 (activated), dichloromethane, room temp., 76%; iii, H_2, 5% Pd on C, ethyl acetate, room temp., 1 h, 93%; iv, ceric ammonium nitrate (1.9 equiv.), CH_3CN, H_2O, room temp., 0.25 h, 90%; v, CH_3CN, 0 °C, 1 h, then room temp., MeOH, 18 h, 71%; vi, ceric ammonium nitrate (8.0 equiv.), CH_3CN, H_2O, room temp., 0.5 h, 87%; vii, dichloromethane, reflux, camphorsulfonic acid (cat.), 3 d, 64%



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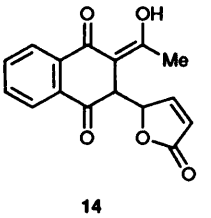

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adduct **10b** was itself found to be a 1:1 mixture of isomers using ^{1}H NMR spectroscopy. However, recrystallization from hexane–ethyl acetate did afford the least soluble isomer of diol **11c** as a yellow solid, m.p. 151–153 °C. The ^{1}H NMR spectrum revealed an upfield shift in the resonances of the bridgehead protons relative to the initial adduct **10b**. The double doublet at δ_H 4.90 and the doublet at δ_H 5.33 assigned to 3a-H and 11b-H respectively resonated at similar positions to that reported for the analogous protons in 5-methyl substituted 2*H*-furo[3,2-*b*]-naphtho[2,3-*d*]pyran-2,6,11-triones.[9] The resonance assigned to the protons of the methylene group (1′-CH_2) in hemiacetal **11c** moved upfield from δ_H 3.07–3.27 (2′-CH_2) in the ketone adduct **10b** to δ_H 1.21–2.14 consistent with attachment to an sp^3 hybridised carbon rather than a carbonyl carbon. In the ^{13}C NMR spectrum the bridgehead carbons C-3a and C-11b of **11c**

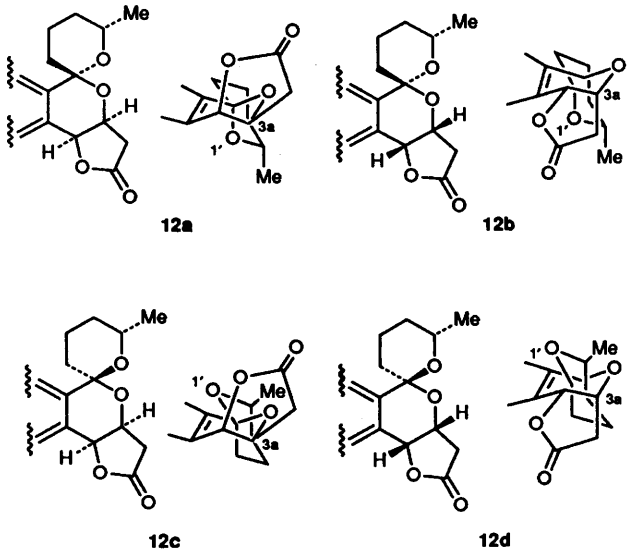

Fig. 1

resonated at δ_C 67.8 and 70.5 respectively, which is in good agreement with data recorded for analogous compounds.[9] The structure assigned from NOE experiments is that in which the hydroxy group is axial and *cis* to the bridgehead protons 3a-H and 11b-H due to the stability gained from the anomeric effect.[10]

Finally, it remained to effect cyclisation of diol **11c** to form the spiroacetal ring. The 1:1 isomeric mixture of diol **11c** was heated under reflux with camphorsulfonic acid (catalytic quantity) in dichloromethane for three days affording two isomers of spiroacetal **12** as racemic mixtures which in this case were easily separated by flash chromatography. The less polar isomer **12a** was isolated as a yellow solid in 42% yield, m.p. 206–208 °C and the more polar isomer **12b** as a yellow solid in 22% yield, m.p. 174–177 °C. Yoshii *et al.*[8] have reported the preparation of isomer **12a** by an independent route with m.p. 107–109 °C for which the ^{1}H NMR spectroscopic data is in agreement with ours but with the omission of a resonance at δ_H 3.86–3.97 assigned to 6'-H. In a personal communication Professor Yoshii acknowledged the omission of this NMR signal and questioned the melting point reported for this isomer.

The stereochemistry * of the two spiroacetals **12a**, **12b** (Fig. 1) was assigned on the basis that the spiroacetal functionality is formed under thermodynamic control. Of the four possible isomers **12a–d**, **12a** and **12b** are preferred due to the stability gained from the anomeric effect[10] when the oxygen atom of each ring occupies a position axial with respect to the C–O bond of the adjacent ring. Based on these considerations, it was assumed that the two products **12a**, **12b** isolated adopted this favoured conformation of the spiroacetal ring. The major product was assigned to isomer **12a** where the fused γ-lactone occupies an equatorial position at C-3a, and is favoured over isomer **12b** where the methylene group occupies an axial position and exhibits unfavourable steric interactions with the oxygen atom O-1'.

Comparison of the ^{1}H NMR spectra for the two isomers **12a** and **12b** supported the assigned conformations. The ^{1}H NMR spectrum for **12b** exhibited a multiplet at δ_H 4.60 assigned to the bridgehead proton 3a-H which, in the less polar isomer **12a** resonated as a double doublet at δ_H 4.72. The deshielding of this proton in isomer **12a** is ascribed to the 1,3-diaxial interactions present between 3a-H and the oxygen (O-1') of the spiroacetal ring.

In summary, the successful synthesis of spiroacetal **12a** represents an efficient entry to the basic ring system present in the pyranonaphthoquinone antibiotic griseusin A **1**. Future work will investigate methodology to introduce the oxygenated substituents at C-3', C-4' and C-7 required for the natural product.

* Similar stereochemical arguments have been described by Yoshii *et al.*[8]

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP3-200S or 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 the solvents stated using tetramethylsilane as internal standard on a JEOL GX270 spectrometer. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL GX270 spectrometer. All *J* values are given in Hz. Mass spectra and accurate mass measurements were recorded on a VG70-250S double focusing magnetic sector mass spectrometer with an ionisation potential of 70 eV. Microanalyses were performed by the microanalytical laboratory, University of Otago. Solvents were purified and dried according to the method of Perrin, Perrin and Armarego.[11] Column chromatography was carried out on Merck Kiesel gel 60 (230–400 mesh) with the solvents described according to the method of Still *et al.*[12]

2-tert-*Butyldimethylsilyloxypent*-4-*yne* **4b**.—To a solution of pent-4-yn-2-ol **4c** (1.60 g, 19 mmol) in dimethylformamide (20 cm^3) was added *tert*-butyldimethylsilyl chloride (2.87 g, 19 mmol) and imidazole (6.37 g, 94 mmol). The reaction mixture was stirred for 30 h at room temperature, poured into diethyl ether (40 cm^3) and washed with water (3 × 15 cm^3). After drying over sodium sulfate the diethyl ether was removed at reduced pressure to yield a pale liquid which upon distillation afforded the *title compound* **4b** (2.73 g, 72%) as a colourless liquid, b.p. 170–172 °C/760 mmHg; ν_{max}(thin film)/cm^{-1} 3316s (HC≡C) and 2130w (C≡C); δ_H (60 MHz; $CDCl_3$) 0.07 (6 H, s, Me_2), 0.89 (9 H, s, Bu^t), 1.24 (3 H, d, *J* 6, Me), 1.97 (1 H, t, *J* 3, HC≡C), 2.21–2.35 (2 H, m, CH_2) and 3.97 (1 H, h, *J* 6, CHOSi); *m*/*z* 197 (*M* − H, 58) and 57 (C_4H_9, 100).

2-(5-tert-*Butyldimethylsilyloxy*-1-*hydroxyhex*-2-*ynyl*)-1,4-*dimethoxynaphthalene* **5b**.—To a solution of 2-*tert*-butyldimethylsilyloxypent-4-yne **4b** (1.32 g, 6.65 mmol) in tetrahydrofuran (THF) (20 cm^3), cooled to −78 °C under nitrogen, was added butyllithium (4.88 cm^3 of a 1.5 mol dm^{-3} solution in hexane, 7.32 mmol). After approximately 1 h, during which time the reaction temperature was raised to −60 °C, a solution of 1,4-dimethoxynaphthalene-2-carbaldehyde **3** (1.08 g, 4.99 mmol) in THF (10 cm^3) was added. The reaction was quenched after a further 1 h by the addition of aqueous ammonium chloride (5 cm^3). Following extraction with diethyl ether (2 × 15 cm^3) the organic layer was washed with water (2 × 7 cm^3) and dried over sodium sulfate. The solvent was removed under reduced pressure to give a yellow oil, which upon purification by flash chromatography using hexane–ethyl acetate (8:2) as eluent afforded the *title compound* **5b** (1.79 g, 86%) as a yellow oil (Found: C, 69.8; H, 8.6. $C_{24}H_{34}O_4Si$ requires C, 69.5; H, 8.3%); ν_{max}(thin film)/cm^{-1} 3600–3130br (OH) and 2240w (C≡C); δ_H(270 MHz; $CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.86, 0.87 (9 H, s, Bu^t), 1.23 (3 H, d, *J* 5.9, Me), 2.34–2.43 (2 H, m, $CH_2C{\equiv}C$), 2.74–2.85 (1 H, m, CHOSi), 3.97 (3 H, s, 1-OMe or 4-OMe), 4.00 (3 H, s, 4-OMe or 1-OMe), 5.98 (1 H, br.s, C*H*OH), 7.01 (1 H, s, 3-H), 7.45–7.57 (2 H, m, 6-H and 7-H), 8.01–8.05 (1 H, m, 5-H or 8-H) and 8.21–8.24 (1 H, m, 8-H or 5-H); δ_C(67.8 MHz; $CDCl_3$) −4.7,

−4.8 (q, $SiMe_2$), 18.1 [s, $C(CH_3)_3$], 23.4 (q, C-6′), 25.8 [q, $C(CH_3)_3$], 29.8 (t, C-4′), 55.6, 63.1 (q, 2 × OMe), 60.1 (d, C-1′), 67.5 (d, C-5′), 81.8, 84.4 (s, C-2′, C-3′), 102.2 (d, C-3), 122.0, 122.5 (d, C-5, C-8), 125.8, 126.7 (d, C-6, C-7), 126.6 (s, C-2), 128.3, 129.2 (s, C-4a, C-8a) and 146.3, 152.3 (s, C-1, C-4); *m/z* 414 (M^+, 14), 357 ($M - C_4H_9$, 24) and 75 (Me_2SiOH, 84).

2-(5-tert-*Butyldimethylsilyloxy*-1-*oxohex*-2-*ynyl*)-1,4-*dimethoxynaphthalene* **6b**.—A mixture of alcohol **5b** (959 mg, 2.31 mmol) and manganese dioxide (1.1 g, 13 mmol) in dichloromethane (30 cm^3) was stirred vigorously at room temperature until all starting material had disappeared (TLC). The suspension was filtered through a Celite pad and the solvent removed at reduced pressure to give a yellow oil that was purified by flash chromatography, using hexane–ethyl acetate (8:2) as eluent, to give the *title compound* **6b** (724 mg, 76%) as a yellow oil (Found: C, 69.8; H, 8.0. $C_{24}H_{32}O_4Si$ requires C, 69.9; H, 7.8%), ν_{max}(thin film)/cm^{-1} 2235m (C≡C) and 1647m (C=O); δ_H(270 MHz; $CDCl_3$) 0.10 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.36 (3 H, d, *J* 6.2, Me), 2.56–2.74 (2 H, m, $CH_2C{\equiv}C$), 4.02 (3 H, s, 1-OMe or 4-OMe), 4.04 (3 H, s, 4-OMe or 1-OMe), 4.11–4.18 (1 H, m, CHOSi), 7.29 (1 H, s, 3-H), 7.59–7.65 (2 H, m, 6-H and 7-H) and 8.22–8.27 (2 H, m, 5-H and 8-H); δ_C(67.8 MHz; $CDCl_3$) −4.7, −4.8 (q, $SiMe_2$), 18.1 [s, $C(CH_3)_3$], 23.6 (q, C-6′), 25.8 [q, $C(CH_3)_3$], 30.3 (t, C-4′), 55.7, 64.1 (q, 2 × OMe), 67.1 (d, C-5′), 83.7 (s, C-2′), 92.5 (s, C-3′), 102.5 (d, C-3), 122.5, 123.8 (d, C-5, C-8), 125.6 (s, C-2), 127.2, 128.5 (d, C-6, C-7), 129.1, 129.6 (s, C-4a, C-8a), 151.5, 153.4 (s, C-1, C-4) and 176.4 (s, C-1′); *m/z* 412 (M^+, 12), 355 ($M - C_4H_9$, 67), 296 ($M - C_6H_{16}OSi$, 100), 215 ($M - C_{11}H_{21}OSi$, 27), 73 (Me_3Si, 57) and 57 (C_4H_9, 7).

2-(5-tert-*Butyldimethylsilyloxy*-1-*oxohexyl*)-1,4-*dimethoxynaphthalene* **7b**.—To acetylene **6b** (1.32 g, 3.2 mmol) dissolved in ethyl acetate (30 cm^3) was added 5% palladium on charcoal (catalytic quantity). The reaction vessel was flushed with hydrogen from a reservoir, and the contents stirred vigorously at room temperature until all the starting material had disappeared (TLC). After removal of the catalyst by filtration through a Celite pad the filtrate was concentrated at reduced pressure to give a yellow oil that was purified by flash chromatography, using hexane–ethyl acetate (8:2) as eluent to give the *title compound* **7b** (1.24 g, 93%) as a yellow oil (Found: C, 69.0; H, 8.7 $C_{24}H_{36}O_4Si$ requires C, 69.2; H, 8.7%); ν_{max}(thin film)/cm^{-1} 1672m (C=O); δ_H(270 MHz; $CDCl_3$) 0.04, 0.05 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 1.15 (3 H, d, *J* 6.2, Me), 1.48–1.78 (4 H, m, 2 × CH_2), 3.16 (2 H, t, *J* 7.3, CH_2CO), 3.80–3.86 (1 H, m, CHOSi), 3.92 (3 H, s, 1-OMe or 4-OMe), 4.00 (3 H, s, 4-OMe or 1-OMe), 6.99 (1 H, s, 3-H), 7.56–7.60 (2 H, m, 6-H and 7-H), 8.13–8.17 (1 H, m, 5-H or 8-H) and 8.23–8.27 (1 H, m, 8-H or 5-H); δ_C(67.8 MHz; $CDCl_3$) −4.4, −4.7 (q, $SiMe_2$), 18.1 [s, $C(CH_3)_3$], 20.9 (t, C-3′), 23.8 (q, C-6′), 25.9 [q, $C(CH_3)_3$], 39.3 (t, C-4′), 43.1 (t, C-2′), 55.7, 63.9 (q, 2 × OMe), 68.5 (d, C-5′), 102.2 (d, C-3), 122.5, 123.1 (d, C-5, C-8), 127.1, 127.5 (d, C-6, C-7), 127.7, 128.7 (s, C-4a, C-8a), 150.7, 151.8 (s, C-1, C-4) and 203.4 (s, C-1′); *m/z* 416 (M^+, 10), 359 ($M - C_4H_9$, 59), 344 ($M - CH_3 - C_4H_9$, 29), 259 ($M - C_7H_{17}OSi$, 93), 227 ($M - C_9H_{23}OSi$, 73), 215 ($M - C_{11}H_{25}OSi$, 47), 75 [$(CH_3)_2SiOH$, 64] and 57 (C_4H_9, 57).

2-(5-tert-*Butyldimethylsilyloxy*-1-*oxohexyl*)-1,4-*naphthoquinone* **8b**.—A solution of ceric ammonium nitrate (1.50 g, 2.74 mmol) in water (4 cm^3) was added dropwise to a solution of dimethoxynaphthalene **7b** (602 mg, 1.44 mmol) in acetonitrile (28 cm^3) at room temperature until no starting material could be detected by TLC (0.25 h). The reaction mixture was then diluted with dichloromethane (30 cm^3), washed with water (2 × 20 cm^3), and dried over sodium sulfate. Evaporation of the solvent at reduced pressure yielded the *title compound* **8b** (502 mg, 90%) as an orange oil; ν_{max}(thin film)/cm^{-1} 1670s (C=O, aryl ketone); δ_H(60 MHz; $CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 1.15 (3 H, d, *J* 6, Me), 1.48–1.78 (4 H, m, 2 × CH_2), 2.94 (2 H, t, *J* 7, CH_2CO), 3.58–4.03 (1 H, m, CHOSi), 7.06 (1 H, s, 3-H) and 7.34–8.24 (4 H, m, 6-H, 7-H, 5-H and 8-H); *m/z* 388 (M + 2H, 8), 256 [$M - (CH_3)_2SiOH$-C_4H_9, 54], 187 ($M - C_{11}H_{23}OSi$, 53) and 75 [$(CH_3)_2SiOH$, 100]. The quinone was used in the subsequent step without further purification.

6-(5-tert-*Butyldimethylsilyloxy*-1-*oxohexyl*)-cis-6b,9a-*dihydro*-5-*hydroxyfuro*[3,2-b]*naphtho*[2,1-d]*furan*-8(9H)-*one* **10b**.—A solution of 2-trimethylsilyloxyfuran **9** (406 mg, 2.60 mmol) in acetonitrile (6 cm^3) was added dropwise to an ice cooled solution of quinone **8b** (502 mg, 1.30 mmol) in acetonitrile (30 cm^3), under an atmosphere of nitrogen. After 1 h, the reaction mixture was left to warm to room temperature and then methanol (2 cm^3) was added. After a further 18 h, the solvent was removed under reduced pressure to give an orange oil, which was then purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to afford the *title compound* (434 mg, 71%) as a yellow solid (1:1 isomeric mixture by ^1H NMR spectroscopy), m.p. 120–123 °C. Fractional crystallisation from diethyl ether afforded the less soluble isomer of **10b** as yellow needles, m.p. 132–135 °C (Found: C, 66.4; H, 7.3. $C_{26}H_{34}O_6Si$ requires C, 66.35; H, 7.3%); ν_{max}(Nujol)/cm^{-1} 3600–3100br (OH), 1790s (C=O, γ-lactone) and 1632 (C=O, *o*-hydroxyaryl ketone); δ_H(270 MHz; $CDCl_3$) 0.07, 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 1.17 (3 H, d, *J* 6.0, Me), 1.58–1.89 (4 H, m, 2 × CH_2), 3.07–3.27 (2 H, m, CH_2CO), 3.18 (2 H, d, $J_{9,9a}$ 4.1, 9-H and 9′-H), 3.85–3.90 (1 H, m, CHOSi), 5.54 (1 H, ddd, $J_{9a,6b}$ 6.3, $J_{9a,9}$ 4.1 and $J_{9a,9'}$ 4.1, 9a-H), 6.46 (1 H, d, $J_{6b,9a}$ 6.3, 6b-H), 7.63–7.74 (2 H, m, 2-H and 3-H), 7.92–7.96 (1 H, m, 1-H or 4-H), 8.49–8.52 (1 H, m, 4-H or 1-H) and 14.75 (1 H, s, OH); δ_C(67.8 MHz; $CDCl_3$) −4.6 (q, $SiMe_2$), 18.2 [s, $C(CH_3)_3$], 20.0 (t, C-3′), 23.7 (q, C-6′), 25.9 [q, $C(CH_3)_3$], 35.7 (t, C-9), 39.1 (t, C-4′), 41.5 (t, C-2′), 68.5 (d, C-5′), 80.7 (d, C-9a), 86.3 (d, C-6b), 109.4 (s, C-6), 110.8 (s, C-6a), 122.1, 125.4 (d, C-1, C-4), 124.4, 127.9 (s, C-4a, C-10b), 128.1, 130.5 (d, C-2, C-3), 150.5 (s, C-10a), 160.1 (s, C-5), 174.1 (s, C-8) and 205.1 (s, C-1′); *m/z* 470 (M^+, 30), 413 (M − C_4H_9, 100), 269 ($M - C_{11}H_{25}OSi$, 68) and 75 [$(CH_3)_2SiOH$, 31].

5-[3′-(5″-*Acetoxy*-1″-*hydroxyhexylene*)-1′,2′,3′,4′-*tetrahydro*-1′,4′-*dioxonaphth*-2′-*yl*]*furan*-2(5H)-*one* **13**.—A solution of 2-trimethylsilyloxyfuran **9** (231 mg, 1.48 mmol) in acetonitrile (7 cm^3) was added dropwise to an ice cooled solution of quinone **8a** (233 mg, 0.74 mmol) in acetonitrile (35 cm^3), under an atmosphere of nitrogen. After 1 h the reaction mixture was left to warm to room temperature, and the solvent then removed under reduced pressure. The resultant orange oil was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent to yield the *title compound* **13** (236 mg, 80%) as an orange oil. Trituration from diethyl ether afforded a pale yellow solid (1:1 mixture of isomers), m.p. 99–102 °C (Found: C, 66.05; H, 5.45. $C_{22}H_{22}O_7$ requires C, 66.3; H, 5.6%); ν_{max}(Nujol)/cm^{-1} 3600–3150br (OH), 1763s (C=O, α,β-unsaturated lactone), 1724s (C=O, acetate) and 1681s (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.24 (3 H, d, *J* 6.3, Me), 1.38–1.92 (4 H, m, 3″-CH_2, 4″-CH_2), 2.04, 2.05 (3 H, s, $COCH_3$), 2.54–2.56 (2 H, m, 2″-CH_2), 3.95, 3.97 (1 H, d, $J_{2',5}$ 6.8, 2′-H), 4.92–5.04 (2 H, m, 5″-H and 5-H), 6.15 (1 H, dd, $J_{3,4}$ 5.7 and $J_{3,5}$ 2.1, 3-H), 7.33–7.37 (1 H, m, 4-H), 7.66–7.71 (1 H, m, 6′-H or 7′-H), 7.79–7.85 (1 H, m, 7′-H or 6′-H), 7.96–7.99 (1 H, m, 5′-H or 8′-H), 8.19–8.22 (1 H, m, 8′-H or 5′-H) and 16.79 (1 H, s, OH); δ_C(67.8 MHz; $CDCl_3$) 20.0 (q, C-6″), 20.5, 20.6 (t, C-3″), 21.3 (q, $COCH_3$), 35.4 (t, C-4″), 36.1 (t, C-2″), 51.9 (d, C-2′), 70.2, 70.4 (d, C-5″), 83.8 (d, C-5), 103.8 (s, C-3′), 122.9 (d, C-3), 126.6, 126.7 (d, C-5′, C-8′), 131.9, 134.1 (s,

C-4a′, C-8a′), 133.1, 135.4 (d, C-6′, C-7′), 152.7 (d, C-4), 171.0 (s, C-1″ and $COCH_3$), 172.8 (s, C-2) and 194.2, 199.4 (s, C-1′, C-4′); *m/z* 398 (M^+, 55), 38 ($M - CH_3 - CO_2H$, 86), 269 ($M - C_7H_{13}O_2$, 100) and 43 (CH_3CO, 18).

3,3a,5,11b-*Tetrahydro-5-hydroxy-5-(4-hydroxypentyl)-2H-furo*[3,2-b]*naphtho*[2,3-d]*pyran*-2,6,11-*trione* **11c**.—The *title compound* **11c** (232 mg, 87%) was prepared following the procedure for quinone **8b**, from adduct **10b** (338 mg, 0.72 mmol of a 1:1 isomeric mixture) and ceric ammonium nitrate (3.16 g, 5.76 mmol). Purification by flash chromatography using hexane–ethyl acetate (1:2) as eluent gave a yellow solid (1:1 isomeric mixture by ^1H NMR spectroscopy). Fractional crystallization from hexane–ethyl acetate (1:2) afforded the less soluble isomer as a yellow solid, m.p. 151–153 °C (Found: C, 64.7; H, 5.6. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%); ν_{max}(Nujol)/cm^{-1} 3600–3100br (OH), 1790s (C=O, γ-lactone) and 1670s (C=O, quinone); δ_H(270 MHz; [$^2H_6$]-acetone) 0.95 (3 H, d, *J* 6.2, Me), 1.21–1.32 and 1.91–2.14 (6 H, m, 3 × CH_2), 2.47 (1 H, d, J_{gem} 17.4, 3-H_a), 3.14 (1 H, dd, J_{gem} 17.4 and $J_{3,3a}$ 4.8, 3-H_b), 3.51–3.55 (1 H, m, C*H*OH), 4.90 (1 H, dd, $J_{3a,3}$ 4.8 and $J_{3a,11b}$ 2.9, 3a-H), 5.33 (1 H, d, $J_{11b,3a}$ 2.9, 11b-H), 7.85–7.90 (2 H, m, 8-H and 9 H) and 8.05–8.09 (2 H, m, 7-H and 10-H); δ_C(67.8 MHz; [$^2H_6$]-acetone) 21.9, 22.2 (t, C-2′, C-3′), 24.4 (q, C-5′), 37.5 (t, C-3), 40.7 (t, C-1′), 67.4 (d, C-4′), 67.8 (d, C-3a), 70.5 (d, C-11b), 96.5 (s, C-5), 127.2, 127.8 (d, C-7, C-10), 132.8, 133.7 (s, C-10a, C-6a), 135.6, 135.8 (d, C-8, C-9), 138.0 (s, C-11a), 176.0 (s, C-2) and 184.1 (s, C-6, C-11); *m/z* 372 (M^+, 3), 354 ($M - H_2O$, 17), 268 ($M - C_5H_{12}O_2$, 41), 240 ($M - C_6H_{12}O_3$, 100) and 43 (CH_3CO, 100).

cis-3′,3a,4′,5′,6′,11b-*Hexahydro-6′-methylspiro*[5H-*furo*[3,2-b]*naphtho*[2,3-d]*pyran*-5′,2′-[2H]*pyran*]-2,6,11(3H)-*trione* **12**.—To a solution of diol **11c** (232 mg, 0.62 mmol, as a 1:1 isomeric mixture) in dichloromethane (30 cm^3) was added camphorsulfonic acid (catalytic quantity). The reaction was heated under reflux for 3 d at the end of which time two products were visible by TLC. Removal of solvent at reduced pressure gave a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent, to give: (i) Spiroacetal **12a** [76 mg, 42%; R_f 0.77 (1:1 hexane–ethyl acetate)] as a yellow solid, m.p. 206–208 °C (decomp.) (Found: C, 67.8; H, 5.2. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%); ν_{max}(Nujol)/cm^{-1} 1795s (C=O, γ-lactone) and 1670s (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.20 (3 H, d, J 6.2, Me), 1.51–1.70 (5 H, m, 5′$_{ax}$-H, 5′$_{eq}$-H, 4′$_{ax}$-H, 4′$_{eq}$-H and 3′$_{eq}$-H), 2.68 (1 H, ddd, J_{gem} 13.7, $J_{3'ax,4'ax}$ 13.7 and $J_{3'ax,4'eq}$ 4.8, 3′$_{ax}$-H), 2.75 (1 H, d, J_{gem} 17.4, 3-H_a), 2.98 (1 H, dd, J_{gem} 17.4 and $J_{3,3a}$ 4.9, 3-H_b), 3.86–3.97 (1 H, m, 6′-H), 4.72 (1 H, dd, $J_{3a,3}$ 4.9 and $J_{3a,11b}$ 2.9, 3a-H), 5.31 (1 H, d, $J_{11b,3a}$ 2.9, 11b-H), 7.75–7.81 (2 H, m, 8-H and 9-H) and 8.08–8.13 (2 H, m, 7-H and 10-H); δ_C(67.8 MHz; $CDCl_3$) 18.7 (t, C-4′), 21.8 (q, Me), 30.3, 31.6 (t, C-3′, C-5′), 36.6 (t, C-3), 65.4 (d, C-6′), 68.4 (d, C-3a), 69.6 (d, C-11b), 95-4 (s, C-5), 126.3, 126.8 (d, C-7, C-10), 131.2, 132.6 (s, C-6a, C-10a). 134.0, 134.5 (d, C-8, C-9), 136.2 (s, C-11a), 144.8 (s, C-5a), 174.4 (s, C-2) and 180.4, 182.4 (s, C-6, C-11); *m/z* 354 (M^+, 34), 285 ($M - C_5H_9$, 100) and 43 (CH_3CO, 20).

(ii) Spiroacetal **12b** [38 mg, 22%; R_f 0.66 (1:1 hexane–ethyl acetate)] as a yellow solid, m.p. 174–177 °C (Found: C, 67.6; H, 5.1. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%); ν_{max}(Nujol)/cm^{-1} 1788s (C=O, γ-lactone) and 1670s (C=O, quinone); δ_H(270 MHz; $CDCl_3$) 1.16 (3 H, d, *J* 6.2, Me), 1.52–1.82 (5 H, m, 5′$_{ax}$-H, 5′$_{eq}$-H 4′$_{ax}$-H, 4′$_{eq}$-H and 3′$_{eq}$-H), 2.34 (1 H, ddd, J_{gem} 14.1, $J_{3'ax,4'ax}$ 14.1 and $J_{3'ax,4'eq}$ 4.7, 3′$_{ax}$-H), 2.84 (1 H, d, J_{gem} 17.6, 3-H_a), 2.96 (1 H, dd, J_{gem} 17.6, and $J_{3,3a}$ 5.1, 3-H_b), 4.13–4.17 (1 H, m, 6′-H), 4.60 (1 H, m, 3a-H), 5.33 (1 H, d, $J_{11b,3a}$ 3.3, 11b-H), 7.72–7.81 (2 H, m, 8-H and 9-H) and 8.07–8.12 (2 H, m, 7-H and 10-H); δ_C(67.8 MHz; $CDCl_3$) 18.6 (t, C-4′), 21.8 (q, Me), 28.2, 31.5 (t, C-3′, C-5′), 36.9 (t, C-3), 68.2, 68.3 (d, C-3a, C-6′), 69.1 (d, C-11b), 96.8 (s, C-5), 126.3, 126.8 (d, C-7, C-10), 131.3, 132.7 (s, C-6a, C-10a), 133.9, 134.4 (d, C-8, C-9), 135.5 (s, C-11a), 145.9 (s, C-5a), 174.0 (s, C-2) and 181.8, 183.0 (s, C-6, C-11); *m/z* 354 (M^+, 36), 285 ($M - C_5H_9$, 100) and 43 (CH_3CO, 5). Unreacted diol **11c** (52 mg, 22%) was also recovered.

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References

1 Preliminary Communication: M. A. Brimble and M. R. Nairn, *J. Chem. Soc., Perkin Trans 1*, 1990, 169.
2 N. Tsuji, M. Kobayashi, Y. Wakisaka, Y. Kawamura, M. Mayama and K. Matsumoto, *J. Antibiot.*, 1976, **29**, 7; N. Tsuji, M. Kobayashi, Y. Terui and K. Tori, *Tetrahedron*, 1976, **32**, 2207.
3 H. W. Moore, *Science*, 1977, **197**, 527; H. W. Moore and R. Czerniak, *Med. Res. Rev.*, 1981, **1**, 249.
4 M. K. Bergy, *J. Antibiot.*, 1968, **21**, 454; H. Hoeksama and W. C. Krueger, *J. Antibiot.*, 1976, **29**, 704.
5 S. Omura, H. Tanaka, Y. Okada and H. Marumo, *J. Chem. Soc., Chem. Commun.*, 1976, 320.
6 Synthesis of (+)-griseusin A: T. Kometani, Y. Takeuchi and E. Yoshii, *J. Org. Chem.*, 1983, **48**, 2311.
7 Synthesis of (+)-Deoxygriseusin A: T. Kometani, Y. Takeuchi and E. Yoshii, *J. Org. Chem.*, 1982, **47**, 4725.
8 Model work for synthesis of griseusin A: K. Matsumoto, Y. Takeuchi, K. Takeda and E. Yoshii, *Heterocycles*, 1981, **16**, 1659.
9 M. A. Brimble and S. J. Stuart, *J. Chem. Soc., Perkin Trans 1*, 1990, 881.
10 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983.
11 D. D. Perrin, D. R. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1966.
12 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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