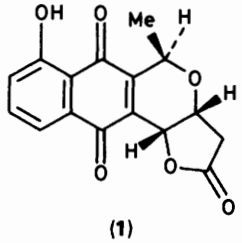
Synthesis of 5-*epi*-7-Deoxykalafungin and 5-*epi*-7-*O*-Methylkalafungin[1]

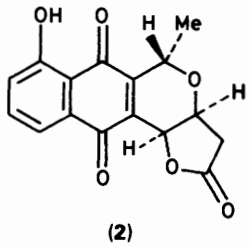
Margaret A. Brimble* and Susan J. Stuart
Department of Chemistry and Biochemistry, Massey University, Palmerston North, New Zealand

The syntheses of 5-*epi*-7-deoxykalafungin (**12a**) and 5-*epi*-7-*o*-methylkalafungin (**12b**), compounds closely related to the pyranonaphthoquinone antibiotic kalafungin (**1**), have been completed making use of the transformation of one tricyclic ring system into another. The uncatalysed 1,4-addition of 2-trimethylsilyloxyfuran (**4**) to the 2-acetyl-1,4-naphthoquinones (**8**) gave the furo[3,2-*b*]naphtho[2,1-*d*]furans (**9**) which underwent facile oxidative rearrangement, in 72–76% yield using cerium(IV) ammonium nitrate, to the furo[3,2-*b*]naphtho[2,3-*d*]pyrans (**11**) which contain the same ring system as the natural product kalafungin (**1**). Reduction of the hemiacetals (**11**) to the cyclic ethers (**12**) was effected using triethylsilane in trifluoroacetic acid. The analogous rearrangement of the furo[3,2-*b*]benzofuran (**5a**) to the furo[3,2-*b*][2]benzopyran (**6**) proceeded in only 27% yield. Further insight into the mechanism of the initial 1,4-addition reaction was gained by isolation of the intermediate (**13**) in the reaction of 2-trimethylsilyloxyfuran (**4**) with the naphthoquinone (**8a**).

Kalafungin (**1**)[2] and its enantiomer nanaomycin D (**2**)[3] are members of the pyranonaphthoquinone class of antibiotics which also includes granaticin,[4] medermycin,[5] and griseusins A and B.[6] These natural products are potent antimicrobial agents[7] and have been proposed to be transformed into bisalkylating agents upon bioreduction in a similar fashion to the drug



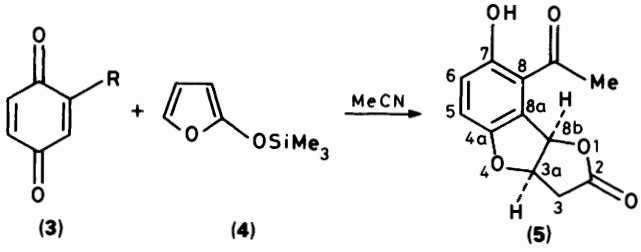
(**1**)



(**2**)

mitomycin.[8] As a consequence of their biological activity these compounds have been synthesized both in racemic[9] and optically active[10] form. We now report the synthesis of 5-*epi*-7-deoxykalafungin (**12a**) and 5-*epi*-7-O-methylkalafungin (**12b**), making use of a rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan to a pyranonaphthoquinone.[1]

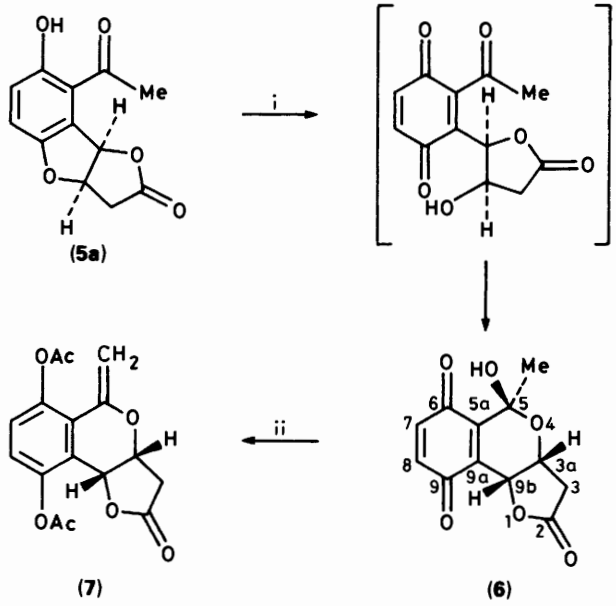
We have recently reported[11] the synthesis of the *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-one (**5**) ring system *via* the uncatalysed addition of 2-trimethylsilyloxyfuran (**4**) to 1,4-benzoquinones (**3**) containing an electron-withdrawing substituent at C-2 (Scheme 1). In our initial model work using the



(**3**) (**4**) (**5**)

Scheme 1.

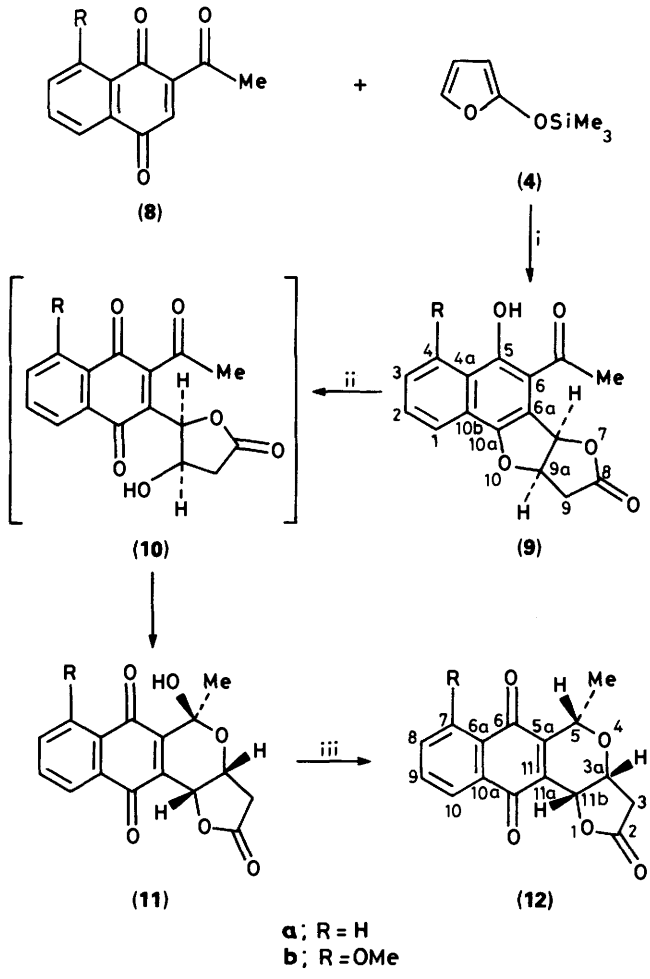
a; R = COMe
b; R = CO_2Me
c; R = SOPh



(**5a**) (**7**) (**6**)

Scheme 2. *Reagents and conditions:* i, CAN, MeCN, H_2O, room temp.; ii, Ac_2O (excess), Et_3N, DMAP, room temp., 17 h.

furo[3,2-*b*]benzofurans we found that treatment of the adduct (**5a**) containing an acetyl group at C-8 with cerium(IV) ammonium nitrate (CAN) effected an oxidative rearrangement to the furo[3,2-*b*][2]benzopyran ring system (**6**) albeit in 27% yield (Scheme 2). The reaction was also accompanied by formation of a high molecular weight product for which the ^1H NMR spectrum indicated the presence of both the initial furo[3,2-*b*]benzofuran-2(3*H*)-one ring system and the ring system arising from the desired rearrangement. Attempted acetylation of the alcohol (**6**) with acetic anhydride and triethylamine using 4-dimethylaminopyridine (DMAP) as catalyst gave the cyclic enol ether (**7**) providing further evidence for this interesting rearrangement. Thus, it was envisaged that extension of the trimethylsilyloxyfuran addition reaction and the subsequent CAN rearrangement to the corresponding naphthoquinones (**8**) would provide an entry into the ring system required for the synthesis of kalafungin (**1**) (Scheme 3).

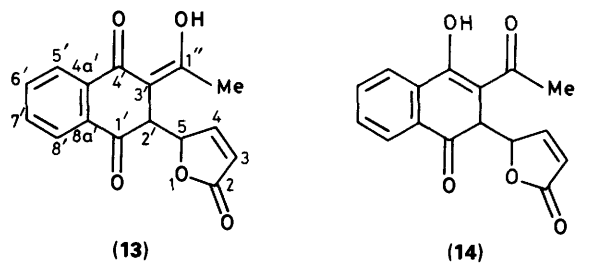


Scheme 3. *Reagents and conditions:* i, MeCN, room temp., then MeOH; ii, CAN (2.0 equiv.), MeCN, H_2O, room temp.; iii, Et_3SiH, CF_3CO_2H −78 °C to room temp.

Moreover, it was hoped that the extra aromatic ring in the naphthoquinone series would inhibit the formation of the polymeric product found in the benzoquinone series.

Addition of 2-trimethylsilyloxyfuran (**4**) to the naphthoquinones (**8**) containing an acetyl group at C-2 gave the desired furo[3,2-*b*]naphtho[2,1-*d*]furans (**9**) in 73–81% yield respectively. The resonances at δ_H 5.55 (δ_H 5.53) and δ_H 6.45 (δ_H 6.50) for (**9a**) [data for (**9b**) in parentheses] assigned to the bridgehead protons 9a–H and 6b–H respectively, together with the magnitude of the bridgehead coupling constants, $J_{9a,6b}$ 6.6 Hz (*J* 5.9 Hz), was consistent with the *cis*-ring junction.[11]

Further insight into the mechanism of the 1,4-addition was gained when the intermediate (**13**) in the reaction of naphthoquinone (**8a**) with 2-trimethylsilyloxyfuran (**4**) was also isolated in 5% yield. The ^{1}H NMR spectrum of this less soluble product exhibited a doublet of triplets at δ_H 5.06, a double doublet at δ_H 6.16, and a double doublet at δ_H 7.37 assigned to protons 5-H, 3-H, and 4-H of the butenolide. The ^{13}C NMR spectrum together with the two-dimensional HETCOR spectrum were also consistent with the presence of a 5-substituted butenolide. An upfield shift in the resonance assigned to the methyl group in the ^{13}C NMR spectrum from δ_C 30.2 in the ketone adduct (**9a**) to δ_C 24.2 in the butenolide (**13**) was consistent with its attachment to a vinylic carbon rather than a carbonyl carbon. This was also supported by the upfield shift of the protons of the methyl group from δ_H 2.84 in the adduct (**9a**) to δ_H 2.30 in the butenolide (**13**). These latter observations together with the lack of a resonance



at δ_C 202.9 as observed in the adduct (**9a**) due to the carbonyl carbon of the methyl ketone, suggested the structure of the butenolide product as the enol (**13**) and not the methyl ketone (**14**).

Cyclization of the butenolide (**13**) to the desired adduct (**9a**) was, however, easily achieved through the addition of methanol. The cyclization was monitored by UV spectroscopy by the disappearance of the band at 326 nm due to the butenolide (**13**) and the appearance of a band at 398 nm due to the adduct (**9a**). Thus, with a synthesis of the furo[3,2-*b*]naphtho[2,1-*d*]furans (**9**) in hand, their rearrangement to a pyranonaphthoquinone was investigated.

Castagnoli, Jr. *et al.*[12] have reported that CAN in aqueous acetonitrile can be used to oxidize a variety of hydroquinone methyl ethers to the corresponding quinones. On this basis, it was proposed that the 6-acetyl-5-hydroxylactones (**9**), as cyclic ethers of a hydroquinone, might undergo an analogous oxidative dealkylation reaction to give the β-hydroxylactones (**10**). Subsequent nucleophilic attack of the hydroxy group on the methyl ketone would then give rise to the hemiacetals (**11**) (Scheme 3). During the course of this work a similar reaction was reported by Kraus *et al.*[13]

Addition of an aqueous solution of CAN (2.0 equiv.) to a solution of the methyl ketone adducts (**9**) in acetonitrile at room temperature afforded the desired pyranonaphthoquinones (**11**) in 72–76% yield after purification by flash chromatography.[14] The ^{1}H NMR spectra showed an upfield shift in the resonances of the bridgehead protons relative to the initial adducts (**9**). The double doublet at δ_H 4.77 (δ_H 4.76) was assigned to 3a-H, and the doublet at δ_H 5.31 (δ_H 5.28) to 11b-H. These protons resonated at similar positions to that recorded for the analogous 5*H*-furo[3,2-*c*][2]benzopyran (**6**). The bridgehead coupling constant, $J_{3a,11b}$ 2.9 Hz, also supported the presence of a *cis*-fused 2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran system.[15] Both the ^{1}H and the ^{13}C NMR spectra indicated that only one hemiacetal was present. The structure assigned was that in which the hydroxy group is axial and *cis* with respect to the bridgehead protons 3a-H and 11b-H. This was assigned on the basis of the anomeric effect and the observation of a nuclear Overhauser enhancement (NOE) between the protons of the methyl group at C-5 and one of the protons of the methylene group, 3-H′.

In order to complete the synthesis of the ring system present in the pyranonaphthoquinone antibiotic kalafungin it remained to reduce the hemiacetal to a cyclic ether. Thus, using the method of Kraus *et al.*,[13] the hemiacetals (**11**) were reduced in 92–95% yield using triethylsilane and trifluoroacetic acid to the ethers (**12**) with a *cis*-relationship between the groups at C-5 and C-3a. This was consistent with axial delivery of hydride from triethylsilane as reported by Kraus *et al.*[13] Evidence for formation of the *cis*-isomer (**12a**) came from the observation of an NOE between the protons resonating at δ_H 4.80 and 4.36 assigned to H-5 and H-3a respectively. Furthermore the upfield shift of both the resonance assigned to the bridgehead proton H-3a from δ_H 4.69 in the *trans*-isomers nanaomycin D (**2**)[10] and 9-*O*-methylnanaomycin D[10] to δ_H 4.33 in the *cis*-isomer (**12b**), together with the upfield shift of the resonance assigned to H-5

from δ_H 5.09 to 4.79 in the *cis*-isomer (**12b**) was consistent with similar upfield shifts of these protons when comparing the *cis*- and *trans*-isomers of an analogous furobenzopyran.[16] Similar shifts were also observed when comparing the 9-deoxy *cis*-isomer (**12a**) with the *trans*-isomer 9-deoxykalafungin.[17]

Whilst the reduction using triethylsilane gave the opposite relative stereochemistry to that present in kalafungin (**1**) the acid-catalysed epimerisation of the *cis*-isomer to the *trans*-isomer has been well documented for related pyranonaphthoquinones which did not contain a fused γ-lactone.[9,10,18,19] We have, however, been unable to effect this epimerisation step using these literature precedents.

In summary, the syntheses of *epi*-7-deoxykalafungin (**12a**) and *epi*-7-*o*-methylkalafungin (**12b**) have been completed making use of the transformation of one tricyclic ring system into another. The methodology demonstrated by the syntheses of these previously unreported compounds closely related to kalafungin (**1**) has the potential to become the focal point of syntheses of more complex pyranonaphthoquinone antibiotics such as granaticin and griseusin A.

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 spectrophotometer as Nujol mulls between sodium chloride discs. UV spectra were recorded on a Shimadzu UV 160 spectrophotometer. ^{1}H NMR spectra were recorded in the solvents stated using tetramethylsilane as internal standard on either a Varian T-60, a Bruker WP-80SY, or a Jeol GX270 spectrometer. ^{13}C NMR spectra were recorded at 20 MHz on a Bruker WP-80SY or at 67.8 MHz on a Jeol GX270 spectrometer. Mass spectra and accurate mass measurements were recorded on a AEI MS9 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.[20] Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) with the solvents described according to the method of Still *et al.*[14] Compounds were visualised on TLC by UV fluorescence or by spraying with vanillin in methanolic sulphuric acid.

3,3a,5,9b-*Tetrahydro*-5-*hydroxy*-5-*methyl*-2H-*furo*[3,2-b]-[2]*benzopyran*-2,6,9-*trione* (**6**).—A solution of cerium(IV) ammonium nitrate (CAN) (345 mg, 0.63 mmol) in water (5 ml) was added dropwise to *cis*-3a,8b-dihydro-8-acetyl-7-hydroxyfuro[3,2-*b*]benzofuran-2(3*H*)-one (**5a**)[11] (50 mg, 0.21 mmol) dissolved in acetonitrile (15 ml). The solution was diluted with water (30 ml) and extracted with dichloromethane (50 ml). After the organic phase had been washed with water (30 ml) and dried over sodium sulphate, solvent was removed at reduced pressure to give a yellow oil. Flash chromatography using hexane–ethyl acetate as eluant afforded the *title compound* (**6**) (14 mg, 27%) as a yellow solid, m.p. 200 °C (decomp.) (Found: C, 57.5; H, 4.0. $C_{12}H_{10}O_6$ requires C, 57.6; H, 4.0%); λ_{max}(EtOH) 204.5 (log ε 3.8), 244.5 (4.0), and 302.0 nm (3.2); ν_{max}(Nujol) 3 370br (OH), 1 760s (C=O, γ-lactone), and 1 653 cm^{-1} (C=O, quinone); δ_H [80 MHz; $(CD_3)_2CO$] 1.75 (3 H, s, Me), 2.44 (1 H, d, J_{gem} 17 Hz, 3-H_A), 2.88 (1 H, br s, OH), 3.14 (1 H, dd, J_{gem} 17, $J_{3,3a}$ 4.9 Hz, 3-H_B), 4.89 (1 H, dd, $J_{3a,3}$ 4.9, $J_{3a,9b}$ 2.9 Hz, 3a-H), 5.16 (1 H, d, $J_{9b,3a}$ 2.9 Hz, 9b-H), and 6.88 (2 H, s, 7-H and 8-H); δ_C[20 MHz; $(CD_3)_2CO$] 27.0 (q, Me), 37.0 (t, C-3), 67.3 (d, C-3a), 69.7 (d, C-9b), 93.5 (s, C-5), 134.1 (s, C-9a), 136.4 (d, C-7 or C-8), 138.6 (d, C-8 or C(7), 144.5 (s, C-5a), 175.4 (s, C-2), 186.0 (s, C-6 or C-9), and 186.4 (s, C-9 or C-6); *m/z* 235 (M − CH_3, 100%).

6,9-*Diacetoxy*-3,3a,5,9b-*tetrahydro*-5-*methylene*-2H-*furo*[3,2-c][2]*benzopyran*-2-*one* (**7**).—To a solution of the quinone (**6**) (20 mg, 0.08 mmol) in dichloromethane (5 ml) was added acetic anhydride (41 mg, 0.4 mmol), triethylamine (80 mg, 0.8 mmol) and 4-dimethylaminopyridine (catalytic quantity). After standing at room temperature overnight the solvent was removed at reduced pressure and the residue purified by flash chromatography using hexene–ethyl acetate as eluant to give the *title compound* (**7**) (16 mg, 62%) as a colourless solid, m.p. 143–144 °C (Found: C, 60.2; H, 4.3. $C_{16}H_{14}O_7$ requires C, 60.4; H, 4.4%); λ_{max}(MeOH) 229 (log ε 3.9) and 288 (3.25); ν_{max}(Nujol) 1 750–1 780s cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 2.35, 2.37 (6 H, s, 2 × $COCH_3$), 2.89 (1 H, d, J_{gem} 17 Hz, 3-H_A), 2.91 (1 H, dd, J_{gem} 17 and $J_{3,3a}$ 4.6 Hz, 3-H_B), 4.68 (1 H, m, 3a-H), 5.16 (1 H, d, J 1.3 Hz, C=H), 5.29 (1 H, d, $J_{9b,3a}$ 3.3 Hz, 9b-H), 5.41 (1 H, d, J 1.3 Hz, C=CH), and 7.22 (2 H, s, 7-H and 8-H); δ_C (67.8 MHz; $CDCl_3$) 20.96, 21.37 (q, 2 × $COCH_3$), 37.2 (t, C-3), 71.2, 73.7 (d, C-3a, C-9b), 101.7 (t, C=CH_2), 121.7 (s, C-5a or C-9a), 123.2 (d, C-7 or C-8), 124.3 (s, C-9a or C-5a), 125.8 (d, C-8 or C-7), 144.6, 147.8, 149.1 (s, C-5, C-6, C-9), 168.8, 169.9 (s, 2 × $COCH_3$), and 174.0 (s, C-2); *m/z* 318 (M^+, 9%), 276 (M − CH_2CO, 22), 234 (M − 2 × CH_2CO, 100), and 175 ($C_{10}H_7O_3$, 48).

2-*Acetyl*-1,4-*naphthoquinone* (**8a**).—2-Acetyl-1,4-naphthoquinone (**8a**) was prepared from 2-acetyl-1,4-dimethoxynaphthalene[21] using silver(II) oxide (prepared according to the method of Hammer and Kleinberg[22]), as orange crystals, m.p. 81–82 °C (lit.,[21] m.p. 83.5–84 °C).

3-*Acetyl*-5-*methoxy*-1,4-*naphthoquinone* (**8b**).—3-Acetyl-5-methoxy-1,4-naphthoquinone (**8b**) was prepared from 3-acetyl-1,5-dimethoxy-4-naphthol[18] using CAN as yellow needles, m.p. 102–104 °C (decomp.) (lit.,[18] m.p. 101–105 °C).

cis-6-*Acetyl*-6b,9a-*dihydro*-5-*hydroxyfuro*[3,2-b]*naphtho*[2,1-d]*furan*-8(9H)-*one* (**9a**).—A solution of 2-trimethylsilyloxyfuran (**4**)[11] (441 mg, 3.1 mmol) in acetonitrile (40 ml) was added dropwise to an ice-cooled solution of 2-acetyl-1,4-naphthoquinone (**8a**) (315 mg, 1.6 mmol) in acetonitrile (15 ml), under an atmosphere of nitrogen. After 1 h, the reaction mixture was left to warm to room temperature and then methanol (2 ml) was added. After a further 18 h, dichloromethane (50 ml) was added and the solution washed with water (2 × 30 ml) and brine (20 ml), and dried over sodium sulphate. Removal of the solvent at reduced pressure yielded an orange oil which on addition of ether gave a yellow crystalline solid that was fractionally crystallised from acetone to give (i) *the title compound* (**9a**) (331 mg, 73%) as yellow needles, m.p. 197–198 °C (decomp.) (Found: C, 67.6; H, 4.0. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.25%); λ_{max}(MeOH) 224 (log ε 4.3), 270 (4.3), and 398 nm (3.7); ν_{max}(Nujol) 3 600–3 100br (OH), 1 780s (C=O, γ-lactone), and 1 620s cm^{-1} (C=O, *o*-hydroxyaryl ketone); δ_H(270 MHz; $CDCl_3$) 2.84 (3 H, s, COMe), 3.18 (2 H, d, $J_{9,9a}$ 4.2 Hz, 9-H and 9-H'), 5.55 (1 H, ddd, $J_{9a,6b}$ 6.6, $J_{9a,9}$ 4.2, and $J_{9a,9'}$ 4.2 Hz, 9a-H), 6.45 (1 H, d, $J_{6b,9a}$ 6.6 Hz, 6b-H), 7.61–7.75 (2 H, m, 2-H and 3-H), 7.92–7.96 (1 H, m, 1-H or 4-H), 8.48–8.52 (1 H, m, 4-H or 1-H), and 14.65 (1 H, s, OH); δ_C (67.8 MHz; $CDCl_3$) 30.3 (q, Me), 35.7 (t, C-9), 80.7 (d, C-9a), 86.0 (d, C-6b), 109.4 (s, C-6), 111.0 (s, C-6a), 122.1 (d, C-4 or C-1), 124.6 (s, C-4a or C-10b), 125.5 (d, C-1 or C-4), 128.1 (s, C-10b or C-4a), 128.2 (d, C-2 or C-3), 130.7 (d, C-3 or C-2), 150.4 (s, C-10a), 160.2 (s, C-5), 174.1 (s, C-8), and 202.9 (s, COMe); *m/z* 284 (M^+, 100%), 269 ($M-CH_3$, 14), 239 ($M-CO_2H$, 55), and 225 ($M-CH_2CO_2H$, 20); (ii) 5-[1,2,3,4-*tetrahydro*-3-(1-*hydroxyethylidene*)-1,4-*dioxo*-2-*naphthyl*]*furan*-2-(5H)-*one* (**13**) (23 mg, 5%) as pale yellow needles, m.p. 192–192.5 °C (decomp.) with change in crystalline form at 141–143 °C (Found: C, 67.45; H, 4.3. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.25%); λ_{max}(MeCN) 230 (log ε 4.1), 268 (4.2), and 326 nm (3.7); ν_{max}(Nujol) 3 600–2 400br (OH), 1 745s (C=O, γ-lactone),

1 670m (C=O), and 1 600 cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 2.30 (3 H, s, CH_3), 3.94 (1 H, d, $J_{2',5}$ 6.8 Hz, 2'-H; numbering as on displayed formula), 5.06 (1 H, ddd, $J_{5,2'}$ 6.8, $J_{5,4}$ 1.8, and $J_{5,3}$ 1.8 Hz, 5-H), 6.16 (1 H, dd, $J_{3,4}$ 5.8, and $J_{3,5}$ 1.8 Hz, 3-H), 7.37 (1 H, dd, $J_{4,3}$ 5.8, and $J_{4,5}$ 1.8 Hz, 4-H), 7.66–7.72 (1 H, m, 6'-H or 7'-H), 7.79–7.85 (1 H, m, 7'-H or 6'-H), 7.765–7.80 (1 H, m, 5'-H or 8'-H), 8.195–8.22 (1 H, m, 8'-H or 5'-H), and 16.8 (1 H, s, OH); δ_C (67.8 MHz; $CDCl_3$) 24.2 (q, CH_3), 52.6 (d, C-2'), 83.9 (d, C-5), 104.0 (s, C-3'), 123.0 (d, C-3), 126.7 (d, C-5' and C-8'), 132.0 (s, C-4a' or C-8a'), 133.2 (d, C-6' or C-7'), 134.2 (s, C-8a' or C-4a'), 135.4 (d, C-7' or C-6'), 152.7 (d, C-4), 171.0 (s, COH), 173.4 (s, C-2), 194.3 (s, C-1' or C-4'), and 196.3 (s, C-4' or C-1'); *m/z* 284 (M^+, 100%), 239 ($M - CO_2H$, 52), and 201 ($C_{12}H_9O_3$, 57).

cis-6-*Acetyl*-6b,9a-*dihydro*-5-*hydroxy*-4-*methoxyfuro*[3,2-*b*]*naphtho*[2,1-d]*furan*-8(9H)-*one* (**9b**).—The *title compound* (**9b**) was prepared from 3-acetyl-5-methoxy-1,4-naphthoquinone (**8b**) (330 mg, 1.44 mmol) and 2-trimethylsilyloxyfuran (**4**) (449 mg, 2.88 mmol) using the procedure described for adduct (**9a**) as a pale yellow flocculent solid (366 mg, 81%), m.p. 213–215 °C (decomp.) (Found: C, 64.7; H, 4.6. $C_{17}H_{14}O_6$ requires C, 65.0; H, 4.5%); λ_{max}(MeOH) 228 (log ε 4.4), 332 (3.5), and 382 nm (3.9); ν_{max}(Nujol) 3 260 (OH), 1 770s (C=O, γ-lactone), and 1 630 cm^{-1} (C=O, *o*-hydroxyaryl ketone); δ_H [270 MHz; $(CD_3)_2SO$] 2.69 (3 H, s, COMe), 2.96 (1 H, d, J_{gem} 19 Hz, 9-H), 3.31 (1 H, dd, J_{gem} 19, and $J_{9a,9'}$ 6.8 Hz, 9-H'), 4.07 (3 H, s, OMe), 5.53 (1 H, dd, $J_{9a,6b}$ 5.9, and $J_{9a,9'}$ 6.8 Hz, 9a-H), 6.50 (1 H, d, $J_{6b,9a}$ 5.9 Hz, 6b-H), 7.20 (1 H, d, *J* 7.8 Hz, 1-H or 3-H), 7.47 (1 H, d, *J* 7.8 Hz, 3-H or 1-H), and 7.64 (1 H, t, *J* 7.8 Hz, 2-H); δ_C (67.8 MHz; $CDCl_3$) 32.1 (q, Me), 35.2 (t, C-9), 56.7 (q, OMe), 82.0 (d, C-9a), 84.7 (d, C-6b), 108.4 (s, C-6), 114.7, 114.9 (d, C-1, C-3), 115.2, 116.0 (s, C-4a, C-6a), 124.2 (s, C-10b), 130.3 (d, C-2), 149.6 (s, C-10a), 153.4 (s, C-4), 157.7 (s, C-5), 175.2 (s, C-8), and 199.5 (s, COMe); *m/z* 314 (M^+, 100%), 299 ($M - CH_3$, 34), 269 ($M - CO_2H$, 14), and 255 ($M - CH_2CO_2H$, 21).

3,3a,5,11b-*Tetrahydro*-5-*hydroxy*-5-*methyl*-2H-*furo*[3,2-b]-*naphtho*[2,3-d]*pyran*-2,6,11-*trione* (**11a**).—A solution of CAN (960 mg, 1.75 mmol) in water (6 ml) was added dropwise to a solution of compound (**9a**) (248 mg, 0.87 mmol) in acetonitrile (45 ml) until no starting material could be detected by TLC. The mixture was then diluted with dichloromethane (50 ml), washed with water (2 × 30 ml), and dried over sodium sulphate. Evaporation under reduced pressure yielded an orange oil. Purification by flash chromatography using hexane–ethyl acetate as eluant gave the *title compound* (**11a**) (189 mg, 72%) as a pale yellow solid, m.p. 194–196 °C (decomp.) (Found: C, 63.5; H, 3.8. $C_{16}H_{12}O_6$ requires C, 64.0; H, 4.0%); λ_{max}(MeOH) 248 (log ε 4.2) and 332 nm (3.4); ν_{max}(Nujol) 3 450m (OH), 1 765s (C=O, γ-lactone), and 1 665s cm^{-1} (C=O, quinone); δ_H[270 MHz; $(CD_3)_2SO$] 1.73 (3 H, s, Me), 2.46 (1 H, d, J_{gem} 17 Hz, 3-H'), 3.21 (1 H, dd, J_{gem} 17, and $J_{3,3a}$ 4.9 Hz, 3-H), 4.77 (1 H, dd, $J_{3a,3}$ 4.9 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.31 (1 H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 7.84–7.95 (2 H, m, 8-H and 9-H), and 8.00–8.08 (2 H, m, 7-H and 10-H); δ_C [67.8 MHz; $(CD_3)_2SO$] 26.5 (q, Me), 36.2 (t, C-3), 66.0 (d, C-3a), 69.3 (d, C-11b), 92.6 (s, C-5), 125.7, 126.4 (d, C-10, C-7), 130.8, 132.1 (s, C-10a, C-6a), 134.3, 134.7 (d, C-9, C-8), 145.9 (s, C-5a), 175.5 (s, C-2), and 182.4, 183.3 (s, C-11, C-6); *m/z* 300 (M^+, 2%) and 285 ($M - CH_3$, 100).

3,3a,5,11b-*Tetrahydro*-5-*hydroxy*-7-*methoxy*-5-*methyl*-2H-*furo*[3,2-b]*naphtho*[2,3-d]*pyran*-2,6,11-*trione* (**11b**).—The *title compound* (**11b**) was prepared from the adduct (**9b**) (120 mg, 0.38 mmol) and CAN (419 mg, 0.76 mmol) using the procedure described for the hemiacetal (**11a**) as a yellow solid (95 mg, 76%), m.p. 246–248 °C (decomp.) (Found: C, 61.5; H, 4.3. $C_{17}H_{14}O_7$ requires C, 61.8; H, 4.3%); λ_{max}(MeOH) 210 (log ε 4.4) and 249 nm (4.1); ν_{max}(Nujol) 3 400m (OH), 1 760s (C=O, γ-lactone), and 1 665s cm^{-1} (C=O, quinone); δ_H [270 MHz; $(CD_3)_2SO$] 1.67 (3 H, s, Me), 2.46 (1 H, d, J_{gem} 17 Hz, 3-H'), 3.20 (1 H, dd, J_{gem} 17 and $J_{3,3a}$ 4.9 Hz, 3-H), 3.93 (3 H, s, OMe), 4.76 (1 H, dd, $J_{3a,3}$ 4.9 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.28 (1 H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 7.62 (1 H, d, *J* 8.3 Hz, 8-H or 10-H), 7.63 (1 H, d, *J* 8.3 Hz, 10-H or 8-H), and 7.82 (1 H, t, *J* 8.3 Hz, 9-H); δ_C [67.8 MHz; $(CD_3)_2SO$] 26.3 (q, Me), 36.1 (t, C-3), 56.4 (q, OMe), 65.9 (d, C-3a), 69.2 (d, C-11b), 92.7 (s, C-5), 118.0, 119.5 (d, C-8, C-10), 119.7 (s, C-6a), 135.4 (d, C-9), 138.9 (s, C-10a), 147.5 (s, C-5a), 159.3 (s, C-7), 175.4 (s, C-2), and 182.6, 183.3 (s, C-6, C-11); *m/z* 330 (M^+, 6%) and 315 ($M - CH_3$, 100).

cis-3,3a,5,11b-*Tetrahydro*-5-*methyl*-2H-*furo*[3,2-b]*naphtho*-[2,3-d]*pyran*-2,6,11-*trione* (**12a**) (epi-7-*deoxykalafungin*).—To a solution of the hemiacetal (**11a**) (100 mg, 0.33 mmol) in dichloromethane (15 ml) cooled to −78 °C under nitrogen was added trifluoroacetic acid (0.14 ml, 1.8 mmol) followed by triethylsilane (0.3 ml, 1.8 mmol). The reaction mixture was slowly warmed to room temperature over 3 h. After removal of solvent at reduced pressure the residue was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluant to give the *title compound* (**12a**) (86 mg, 92%) as yellow needles, m.p. 190–193 °C (decomp.) (from hexane–diethyl ether), (Found: C, 67.6; H, 4.2. $C_{16}H_{12}O_5$ requires C 67.6; H, 4.3%); λ_{max}(MeOH) 248 (log ε 4.25) and 338 nm (3.1); ν_{max}(Nujol) 1 775s(C=O, γ-lactone) and 1 660s cm^{-1} (C=O, quinone); δ_H (270 MHz; $CDCl_3$) 1.60 (3 H, d, J_{vic} 6.6 Hz, Me), 2.75 (1 H, d, J_{gem} 17 Hz, 3-H'), 2.91 (1 H, dd, J_{gem} 17 and $J_{3,3a}$ 4.5 Hz, 3-H), 4.36 (1 H, dd, $J_{3a,3}$ 4.5 and $J_{3a,11b}$ 2.6 Hz, 3a-H), 4.80 (1 H, dq, J_{vic} 6.6 and $J_{5,11b}$ 1.8 Hz, 5-H), 5.31 (1 H, dd, $J_{11b,3a}$ 2.6 and $J_{11b,5}$ 1.8 Hz, 11b-H), 7.72–7.82 (2 H, m, 8-H and 9-H), and 8.05–8.16 (2 H, m, 7-H and 10-H); δ_C (67.8 MHz; $CDCl_3$) 20.3 (q, Me), 37.3 (t, C-3), 68.8, 69.8 (d, C-3a, C-11b), 71.2 (d, C-5), 126.5, 126.7 (d, C-7, C-10), 131.5, 132.3 (s, C-10a, C-6a), 134.3, 134.4 (d, C-8, C-9), 134.5 (s, C-11a), 150.4 (s, C-5a), 174.3 (s, C-2), and 182.3, 184.0 (s, C-6, C-11); *m/z* 284 (M^+, 100) and 240 ($M - CO_2$, 37).

cis-3,3a,5,11b-*Tetrahydro*-7-*methoxy*-5-*methyl*-2H-*furo*[3,2-b]*naphtho*[2,3-d]*pyran*-2,6,11-*trione* (**12b**) (epi-7-o-*methylkalafungin*).—The *title compound* (**12b**) was prepared from the hemiacetal (**11b**) (50 mg, 0.15 mmol) using the procedure described for *epi*-7-deoxykalafungin (**12a**) as an orange solid (44 mg, 95%), m.p. 188–190 °C (decomp.) (Found: C, 65.0; H, 4.6. $C_{17}H_{14}O_6$ requires C, 65.0; H, 4.5%); λ_{max}(MeOH) 211 (log ε 4.3), 226 (4.0), and 353 nm (3.5); ν_{max}(Nujol) 1 770s (C=O, γ-lactone) and 1 665s cm^{-1} (C=O, quinone); δ_H (270 MHz; $CDCl_3$) 1.56 (3 H, d, J_{vic} 6.6 Hz, Me), 2.73 (1 H, *d*, J_{gem} 17 Hz, 3-H'), 2.90 (1 H, dd, J_{gem} 17 and $J_{3,3a}$ 4.4 Hz, 3-H), 4.33 (1 H, dd, $J_{3a,3}$ 4.4 and $J_{3a,11b}$ 2.6 Hz, 3a-H), 4.79 (1 H, dq, J_{vic} 6.6 and $J_{5,11b}$ 1.8 Hz, 5-H), 5.29 (1 H, dd, $J_{11b,3a}$ 2.6 and $J_{11b,5}$ 1.8 Hz, 11b-H), 7.29–7.33 (1 H, m, Ar-H), and 7.67–7.79 (2 H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 20.0 (q, Me), 37.3 (t, C-3), 56.6 (q, OMe), 69.1, 69.7 (d, C-3a, C-11b), 71.2 (d, C-5), 118.1, 119.3 (d, C-8, C-10), 132.2, 133.7 (s, C-6a, C-10a), 135.4 (d, C-9), 152.5 (s, C-5a), 159.4 (s, C-7), 174.4 (s, C-2), and 182.5, 183.4 (s, C-6, C-11); *m/z* 314 (M^+, 54%) and 270 ($M - CO_2$, 54).

Acknowledgements

We thank Dr. K. W. Jolley and Professor R. Hodges for recording the high field NMR and mass spectra. We thank the Massey University Research Fund for financial support.

References

1 Preliminary communication: M. A. Brimble, R. Hodges, and S. J. Stuart, *Tetrahedron Lett.*, 1988, **29**, 5987.
2 M. E. Bergy, *J. Antibiot.*, 1968, **21**, 454; H. Hoeksama and W. C. Krueger, *ibid.*, 1976, **29**, 704.

3 S. Omura, H. Tanaka, Y. Okada, and H. Marumo, *J. Chem. Soc., Chem. Commun.*, 1976, 320.
4 W. Keller-Schierlein, M. Brufani, and S. Barcza, *Helv. Chim. Acta*, 1968, **51**, 1256.
5 H. Ogura and K. Puruhata, 9th International Congress of Heterocyclic Chemistry, Tokyo, August 1983, Abstr. No. S-IV-6.
6 N. Tsuji, M. Kobayashi, Y. Wakisaka, Y. Kawamura, M. Mayama, and K. Matsumoto, *J. Antibiot.*, 1976, **29**, 7.
7 L. E. Johnson and A. Dietz, *Appl. Microbiol.*, 1968, **16**, 1815.
8 H. W. Moore, *Science*, 1977, **197**, 527.
9 G. A. Kraus, H. Cho, S. Crowley, B. Roth, H. Sugimoto, and S. Prugh, *J. Org. Chem.*, 1983, **48**, 3439; T. Li and R. H. Ellison, *J. Am. Chem. Soc.*, 1978, **100**, 6263; review: Y. Naruta and K. Maruyama, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 415.
10 K. Tatsuta, K. Akimoto, M. Annaka, Y. Ohno, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1699.
11 M. A. Brimble, M. T. Brimble, and J. J. Gibson, *J. Chem. Soc., Perkin Trans. 1*, 1989, 179.
12 P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, 1976, **42**, 3627.
13 G. A. Kraus, M. T. Molina, and J. A. Walling, *J. Org. Chem.*, 1987, **52**, 1273.
14 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
15 D. C. Aldridge and W. B. Turner, *J. Chem. Soc. C*, 1970, 2598.
16 M. F. Semmelhack, C. Bodurow, and M. Baum, *Tetrahedron Lett.*, 1984, **25**, 3171.
17 G. A. Kraus and B. Roth, *J. Org. Chem.*, 1978, **43**, 4923.
18 H. Uno, *J. Org. Chem.*, 1986, **51**, 350.
19 M. S. South and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1984, **106**, 4181.
20 D. D. Perrin, D. R. Perrin, and W. L. F. Armarego, 'Purification of Laboratory Chemicals,' Pergamon, Oxford, 1966.
21 T. A. Chorn, R. G. F. Giles, I. R. Green, V. I. Hugo, P. R. K. Mitchell, and S. C. Yorke, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1339.
22 N. Hammer and J. Kleinberg, *Inorg. Synth.*, 1953, **4**, 12.

Paper 9/02791B
Received 30*th June* 1989
Accepted 23*rd September* 1989