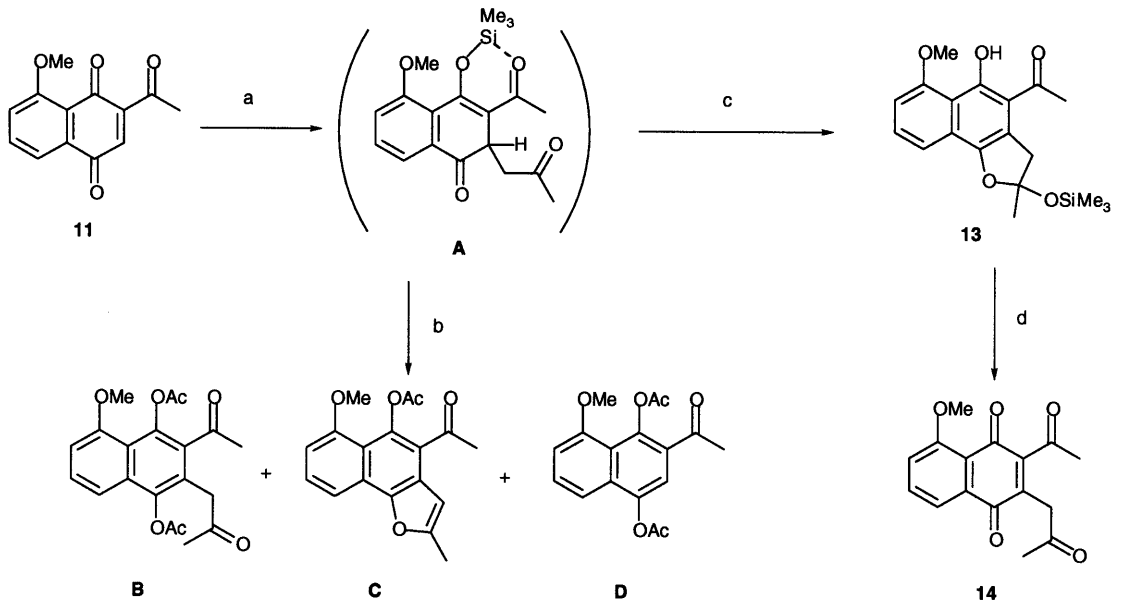
Preparation of acetonylquinones

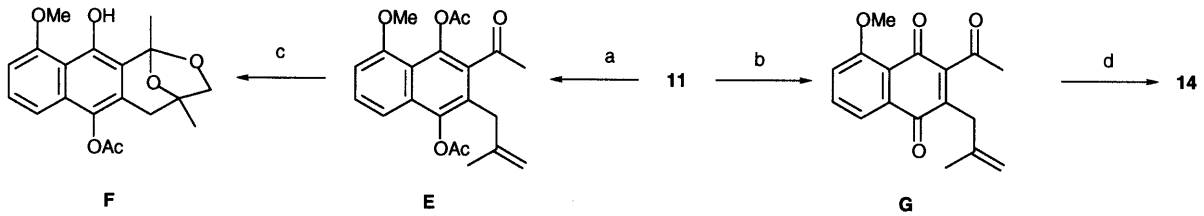
We examined the reaction of **11** with the commercially available 2-(trimethylsiloxy)propene. Since the quinone **11** did not react with 2-(trimethylsiloxy)propene in CH_2Cl_2 at room temperature, some Lewis acids were employed as a promoter. In the presence of $SnCl_4$ (1.2 equiv.), the starting quinone **11** smoothly disappeared within 1 h at –78 °C probably to give adduct **A** (Scheme A). As attempted isolation of **A** failed, the reaction mixture was treated with acetic anhydride and pyridine to give a mixture of the aimed acetonylated hydroquinone diacetate **B**, naphthofuran **C**, and the simple hydroquinone diacetate **D** in respective yields of 16, 65, and 11%. The diacetate **D** would be formed by simple reduction of the quinone followed by acetylation. When the initial adduct was treated with ethyldiisopropylamine, hydroquinone monosilyl ether **13** was obtained in rather low yield (40%). Conversion of **13** to the quinone **14** was accomplished by the oxidation with CAN in quantitative yield. Change of the Lewis acid to $BF_3 \cdot OEt_2$ or of the solvent to ether did not improve the yield of acetonylated hydroquinones.



Scheme A. Acetonylation of **11**. *Reagents and conditions*: a) 2-(trimethylsiloxy)propene, $SnCl_4$, CH_2Cl_2, –78 °C. b) Ac_2O, pyridine, rt. c) *i*-Pr_2EtN, rt. d) CAN, aq MeCN, rt.

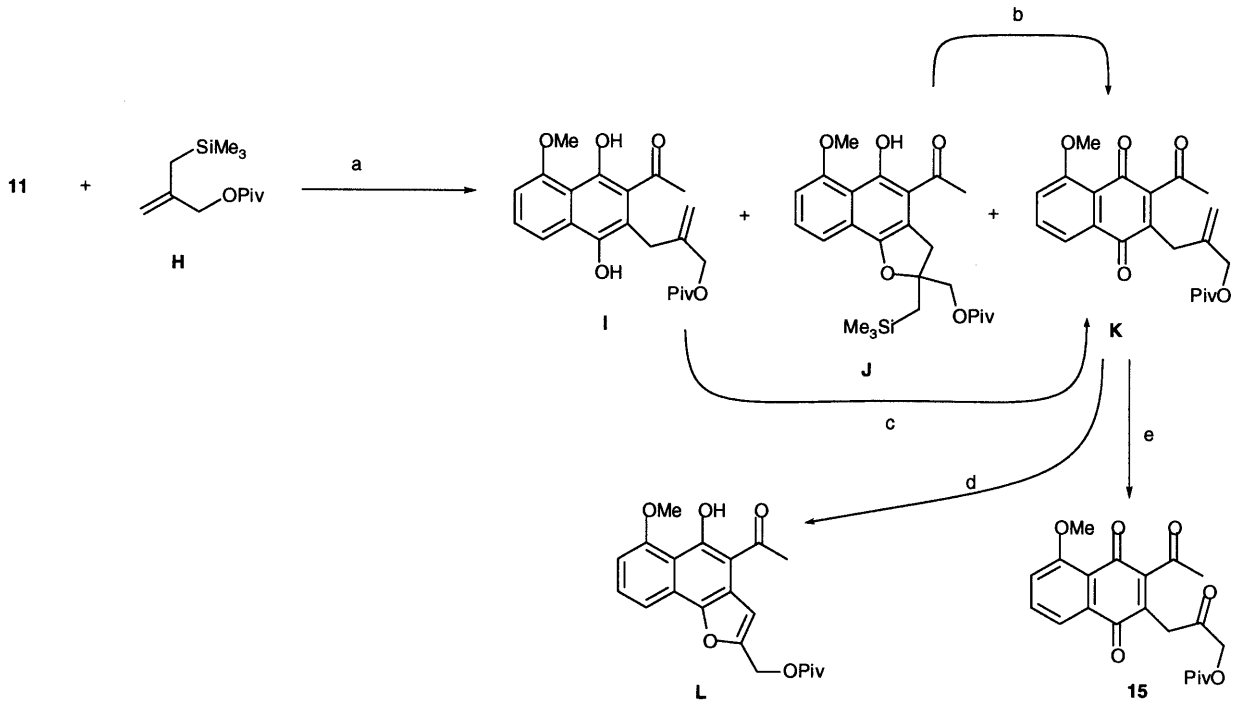
In order to prepare the acetonyl quinone **14** efficiently, we examined the indirect acetonylation: 2-methyl-2-propenylation followed by oxidation (Scheme B). 2-Methyl-2-propenyl hydroquinone diacetate **E**,[1] readily prepared from the reaction of **11** with 2-methyl-2-propenylstannane, was

employed as the starting material. Dihydroxylation of the 2-methyl-2-propenyl group of **E** with OsO_4 brought about the intramolecular acetal formation and concomitant deprotection of one acetyl group to give naphthol **F** in 68% yield. A similar intramolecular acetal formation was utilized for the preparation of isagarin.[2] Ozonolysis of **E** failed to convert the 2-methyl-2-propenyl to acetonyl group, and a complex mixture was obtained. Failure of the ozonolysis would be due to the highly electron-rich nature of the hydroquinone skeleton. Therefore, the corresponding quinone **G**,[1] which was obtained by saponification of **E** followed by oxidation with Ag_2O, was subject to ozonolysis, and the target compound **14** was obtained in good yield.



Scheme B. Preparation of **14** from **11**. *Reagents and conditions*: a) CH_2=C(Me)CH_2SnMe_3, BF_3·OEt_2, CH_2Cl_2, –78 °C; Ac_2O, pyridine, rt. b) CH_2=C(Me)CH_2SiR_3, $SnCl_4$, CH_2Cl_2, –78 °C; CAN, aq MeCN, rt. c) OsO_4, NMO, acetone, rt. d) O_3, CH_2Cl_2, –78 °C; Me_2S, rt.

For the preparation of aloe-emodin (**2**), introduction of a hydroxylated acetonyl group was required. We employed 2-[(trimethylsilyl)methyl]-2-propenyl pivaloate (**H**) as the reagent, because commercially available 2-[(trimethylsilyl)methyl]-2-propenyl acetate, Trost's tri(methylene)methane precursor,[3] may not be suitable when the reaction mixture has to be protected by acetylation. The reaction of **11** with the reagent **H** in the presence of $SnCl_4$ occurred smoothly at –78 °C to give adducts, silica-gel chromatography of which gave hydroquinone **I**, dihydronaphthofuran **J**, and naphthoquinone **K** in respective yields of 9, 63, and 24%. The former two compounds were converted to the naphthoquinone **K** in almost quantitative yield by the treatment with Ag_2O or cerium(IV) ammonium nitrate (CAN), respectively. Treatment of **K** with ozone at –78 °C followed by PPh_3 gave naphthofuran **L** as a sole product in 49% yield. The naphthofuran **L** would be formed by the reduction of the aimed naphthoquinone **15** with excess PPh_3 followed by cyclization. Therefore, Me_2S was used as the milder reducing reagent of an intermediary ozonide and the reaction gave the desired quinone **15** in 60% yield.



Scheme C. Preparation of **15**. *Reagents and conditions*: a) $SnCl_4$, CH_2Cl_2, –78 °C. b) CAN, aq MeCN, rt. c) Ag_2O, ether, rt. d) O_3, CH_2Cl_2, –78 °C; PPh_3, rt. e) O_3, CH_2Cl_2, –78 °C; Me_2S, rt.

Experimental

Reaction of 11 with 2-(trimethylsiloxy)propene

Work-up with acetylation—To a solution of compound **11**[1] (115 mg, 0.5 mmol) in dry CH_2Cl_2 (15 mL) was added $SnCl_4$ (1.0 mol·L^{-1} in CH_2Cl_2, 0.6 mL) and 2-(trimethylsiloxy)propene (0.10 mL, 0.6 mmol) at –78 °C. After the addition, the mixture was stirred for 1 h at the temperature. The reaction was quenched with water. The combined organic phase was separated and the aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated by a rotary evaporator to give a crude product. Acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added. The mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$. The mixture was extracted with ether. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated by a rotary evaporator. The residue was purified by silica-gel chromatography (30—50% EtOAc/hexane) to give 30 mg (16%) of 1-(1,4-diacetoxy-3-acetyl-5-methoxy-2-naphthyl)-2-propanone (**B**), 102 mg (65%) of 5-acetoxy-4-acetyl-6-methoxy-2-methylnaphtho[1,2-*b*]furan (**C**), and 17 mg (11%) of 1-(1,4-diacetoxy-8-methoxy-2-naphthyl)ethanone (**D**). **B**: yellow oil; R_f (50% EtOAc/hexane) 0.35; δ_H 2.16 (3 H, s), 2.36 (3 H, s), 2.45 (3 H, s), 2.57 (3 H, s), 3.76 (2 H, br s), 3.93 (3 H, s), 6.90 (1 H, d, J = 7.0), 7.31 (1 H, d, J = 8.4) and 7.48 (1 H, dd, J = 8.4 and 7.0); δ_C 20.5, 20.9, 29.6, 31.9,

42.0, 56.2, 107.4, 114.2, 118.7, 121.6, 128.7, 130.0, 132.3, 141.8, 143.2, 155.8, 168.7, 169.0, 203.1 and 204.5; ν_{max} ($CDCl_3$) 1766, 1710br, 1368, 1270, 1236, 1208, 1190 and 1070 cm^{-1}. **C**: pale yellow needles (Found: C, 69.2; H, 5.2%. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.2%), R_f (50% EtOAc/hexane) 0.6; mp 150—152 °C (CH_2Cl_2/hexane); δ_H 2.40 (3 H, s, OCO*Me*), 2.52 (3 H, d, J = 1.0, 2-Me), 2.65 (3 H, s, 4-CO*Me*), 3.92 (3 H, s, 6-OMe), 6.79 (1 H, q, J = 1.0, H^3), 6.79 (1 H, dd, J = 8.3 and 1.0, H^7), 7.50 (1 H, t, J = 8.3, H^8) and 7.83 (1 H, dd, J = 8.3 and 1.0, H^9); δ_C 14.4 (4-Ac), 21.5 (OAc), 32.1 (2-Me), 56.4 (OMe), 104.6 (C3), 106.2 (C9), 113.1 (C7), 115.3, 123.0, 123.4, 125.0, 129.3 (C8), 142.6, 148.2, 156.7, 157.0, 170.2 (O*C*OMe) and 199.3 (4-*C*OMe); IR (KBr) 1764, 1662, 1632, 1572 and 1360 cm^{-1}; *m/z* (rel. intensity) 312 (M^+, 23), 270 (100), 255 (67), 240 (15), 237 (11) and 139 (11). **D**: pale yellow needles (Found: C, 64.2; H, 5.1%. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%), R_f (50% EtOAc/hexane) 0.5; mp 184—186 °C (CH_2Cl_2/hexane); δ_H 2.42 (3 H, s), 2.44 (3 H, s), 2.62 (3 H, s), 3.94 (3 H, s), 6.92 (1 H, d, J = 7.6), 7.43—7.55 (2 H, m) and 7.61 (1 H, s); ν_{max} (KBr) 1762, 1662, 1630, 1572, 1380, 1370, 1210, 1192 and 1040 cm^{-1}; *m/z* (rel. intensity) 316 (M^+, 7), 274 (23), 270 (11), 232 (100) and 217 (31).

2-Acetonyl-3-acetyl-5-methyl-1,4-naphthoquinone (14) from G

Ozone was bubbled into a solution of **G** (284 mg, 1.0 mmol) in CH_2Cl_2 (100 mL) at –78 °C. After the yellow color of the solution became dark (40 min), excess ozone was purged by oxygen. Me_2S (1.0 mL) was added at the temperature and then the mixture was allowed to warm up to room temperature. The mixture was vigorously stirred for 1 h and then the volatile material was removed by evaporation. The residue was triturated with CH_2Cl_2/ether/hexane to give 141 mg (50%) of **14** as yellow powdery crystals.

Ozonolysis of E

To a solution of **E** (185 mg, 0.5 mmol) and N-methylmorpholin N-oxide monohydrate (64 mg, 0.55 mmol) in 1% aqueous acetone (1.0 mL) was added a solution (0.25 mL) of OsO_4 in *t*-BuOH (0.02 $mol \cdot L^{-1}$) at room temperature, and the mixture was stirred overnight. After consumption of **E** was checked by TLC, the reaction was quenched with $Na_2S_2O_3$ (30 mg), brine (1 mL) and EtOAc (10 mL). The mixture was filtered through a Celite pad. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica-gel (30-50% EtOAc/hexane) to give 116 mg (68%) of 6-acetoxy-10-methoxy-1,4-dimethyl-1,4-epoxy-1,3,4,5-

tetrahydronaphtho[2,3-*c*]oxepin-11-ol (**F**) as pale white crystals. Conformational interconversion was observed in the ^{1}H NMR spectra of the naphthol **F**. At ambient temperature, naphthylic methylene protons appeared as broad signals, which became one pair of sharp well-resolved AB-quartet signals at 55 °C. The interconversion between the two conformers was frozen at –50 °C and the ratio of the conformers was 1:1.3. **F**: pale yellow crystals, (Found: C, 66.0; H, 6.0%. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.85%); mp 254—256 °C; R_f (60% EtOAc/hexane) 0.70; δ_H (ambient temperature) 1.57 (3 H, s), 2.19 (3 H, s), 2.42 (3 H, s), 2.69 (1 H, br m), 2.95 (1 H, br m), 3.66 (1 H, d, J = 7.3), 3.73 (1 H, d, J = 7.3), 4.05 (3 H, s), 6.78 (1 H, d, J = 7.8), 7.23 (1 H, d, J = 8.8), 7.33 (1 H, dd, J = 8.8 and 7.8) and 9.89 (1 H, s); (55 °C) 1.56 (3 H, s), 2.18 (3 H, s), 2.40 (3 H, s), 2.67 (1 H, d, J = 17.1), 2.96 (1 H, d, J = 17.1), 3.64 (1 H, d, J = 7.3), 3.73 (1 H, d, J = 7.3), 4.04 (3 H, s), 6.77 (1 H, d, J = 7.8), 7.22 (1 H, d, J = 8.3), 7.31 (1 H, dd, J = 8.3 and 7.8) and 9.83 (1 H, s); (–50 °C) 1.63 (3 H, s), 2.22 (3 H, s), 2.52 (3 H, s), 2.54 (1 H of minor conformer, d, J = 17.1), 2.87 (1 H of major conformer, d, J = 16.9), 2.92 (1 H of major conformer, d, J = 16.9), 3.13 (1 H of minor conformer, d, J = 17.1), 3.76 (2 H, m), 4.15 (3 H, s), 6.83 (1 H of minor conformer, d, J = 7.8), 6.84 (1 H of major conformer, d, J = 7.8), 7.23 (1 H of minor conformer, d, J = 8.3), 7.27 (1 H of major conformer, d, J = 8.3), 7.40 (1 H of minor conformer, dd, J = 8.3 and 7.8), 7.41 (1 H of major conformer, dd, J = 8.3 and 7.8), 10.07 (1 H of minor conformer, s) and 10.09 (1 H of major conformer, s); δ_C (ambient temperature) 20.4, 24.5, 40.0, 56.5, 74.4, 76.7, 77.9, 104.5, 106.6, 114.5, 119.4, 125.4, 126.8, 128.9, 136.3, 149.2,157.0 and 168.9; ν_{max} (KBr) 3345, 1755, 1637, 1610, 1585, 1450, 1394, 1371, 1207 and 1024 cm^{-1}; *m/z* (rel. intensity) 344 (M^+, 62), 302 (100), 272 (28), 257 (26) and 241 (15).

2-[(Trimethylsilyl)methyl]-2-propenyl pivaloate (H)

To a solution of 2-[(trimethylsilyl)methyl]-2-propenol[3] (1.821 g, 12.6 mmol) in CH_2Cl_2 (14 mL) were added successively pyridine (3.5 mL) and pivaloyl chloride (2.64 mL, 21.5 mmol) at room temperature. After being stirred for 1.5 h, the mixture was diluted with ether. The ethereal solution was washed with sat. $NaHCO_3$, sat. $CuSO_4$, water and brine, dried over Na_2SO_4 and concentrated. The residual oil was distilled by a Kugelrohr apparatus to give 1.804 g (63%) of **H** as a colorless oil (Found: C, 63.3; H, 10.8%. $C_{12}H_{24}OSi$ requires C, 63.1; H, 10.6%): bp 95—105 °C/1.7 x 10^3 Pa; δ_H 0.00 (9 H, s), 1.19 (9 H, s), 1.49 (2 H, s), 4.38 (2 H, s), 4.65 (1 H, m) and 4.82 (1 H, m); δ_C –1.5, 23.5, 26.5, 27.2, 67.4, 108.6, 142.0 and 178.1; ν_{max} (neat) 2960, 1734, 1150, and 844 cm^{-1};

m/z (rel. intensity) 228 (M^+, 6), 171 (8), 159 (29), 144 (5), 103 (5), 85 (11) and 73 (100).

Reaction of 11 with H

To a solution of **11**[1] (230 mg, 1.0 mmol) in dry CH_2Cl_2 (30 mL) were added $SnCl_4$ (1.0 M in CH_2Cl_2, 1.2 mL) and **H** (274 mg, 1.2 mmol) at –78 °C. After the addition, the mixture was stirred for 1 h at the temperature. The reaction was quenched with water. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated by a rotary evaporator to give a crude material. To the crude material in DMF (3 mL) were added *t*-butyldimethylsilyl chloride (TBSCl; 226 mg, 1.5 mmol) and imidazole (225 mg, 3.3 mmol). The mixture was stirred overnight at room temperature. The reaction was quenched with water. The mixture was extracted with ether. The ethereal phase was washed with water and brine, dried over Na_2SO_4 and concentrated by a rotary evaporator to give a residue. The residual oil was dissolved in MeCN (16 mL) and 50% HF (1.8 mL, 60 mmol) was added. After being stirred for 20 h, the mixture was quenched with sat. $NaHCO_3$ (10 mL) and ether. The organic phase was separated and the aqueous phase was extracted with ether. The combined ethereal phase was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated by a rotary evaporator. The residue was chromatographed on silica gel (30—50% EtOAc/hexane) to give 36 mg (9%) of 3-acetyl-5-methoxy-2-[2-(pivaloyloxymethyl)-2-propenyl]-1,4-naphthalenediol (**I**), 289 mg (63%) of 4-acetyl-6-methoxy-2-[2-(pivaloyloxymethyl)-2-propenyl]-2-(trimethylsilylmethyl)-2,3-dihydronaphtho[1,2-*b*]furan-5-ol (**J**), and 92 mg (24%) of 3-acetyl-5-methoxy-2-[2-(pivaloyloxymethyl)-2-propenyl]-1,4-naphthoquinone (**K**). **I**: pale yellow oil; R_f (50% EtOAc/hexane) 0.5; δ_H 1.23 (9 H, s), 2.58 (3 H, s), 3.51 (2 H, s), 4.02 (3 H, s), 4.54 (2 H, s), 4.83 (1 H, br s), 5.13 (1 H, br s), 5.76 (1 H, br, OH), 6.79 (1 H, d, J = 7.8), 7.34 (1 H, dd, J = 8.6 and 7.8), 7.76 (1 H, d, J = 8.6) and 9.26 (1 H, br, OH); δ_C 27.1, 30.5, 32.5, 38.8, 56.1, 66.7, 104.9, 114.0, 114.2, 115.8, 117.0, 124.1, 126.4, 128.1, 135.4, 142.2, 145.8, 156.2, 178.4 and 205.9; ν_{max} (neat) 3380, 1727, 1693, 1627, 1604, 1400, 1284 and 1153 cm^{-1}; *m/z* (rel. intensity) 386 (M^+, 18), 284 (100), 269 (46), 266 (29) and 241 (17). **J**: pale yellow needles (Found: C, 65.25; H, 7.5%. $C_{25}H_{34}O_6Si$ requires C, 65.5; H 7.5%), mp 103—105 °C (CH_2Cl_2/hexane); R_f (40% EtOAc/hexane) 0.75; δ_H 0.04 (9 H, s), 0.98 (9 H, s), 1.25 (1 H, d, J = 14.7), 1.36 (1 H, d, J = 14.7), 2.69 (3 H, s), 3.41 (1 H, d, J = 17.1), 3.55 (1 H, d, J = 17.1), 4.08 (3 H, s), 4.12 (1 H, d, J = 11.5), 4.21 (1 H, d, J = 11.5), 6.82 (1 H, d, J = 7.3), 7.38—7.48 (2 H, m) and 11.24 (1 H, br,

OH); δ_C 0.0 ($SiMe_3$), 26.9 (CMe_3), 27.2 (CH_2Si), 32.5 (CO*Me*), 38.7 (CMe_3), 43.1 (C3), 56.2 (OMe), 70.2 (CH_2O), 88.8 (C2), 105.3 (C9), 114.8, 115.3 (C7), 116.4, 118.9, 124.9, 128.5 (C8), 147.1, 153.5, 157.8, 178.1 (O_2CCMe_3) and 201.1 (*C*OMe); ν_{max} (KBr) 3284, 2956, 1738, 1646, 1634, 1474, 1150 and 1016 cm^{-1}; *m/z* (rel. intensity) 458 (M^+, 30), 356 (18), 341 (27), 338 (22), 267 (11), 266 (19) and 73 (100). **K**: yellow needles (Found: C, 68.5; H, 6.3%. $C_{22}H_{24}O_6$ requires C, 68.7; H, 6.3%), mp 148—149 °C (CH_2Cl_2/hexane); R_f (40% EtOAc/hexane) 0.45; δ_H 1.21 (9 H, s), 2.46 (3 H, s), 3.26 (2 H, s), 4.02 (3 H, s), 4.56 (2 H, s), 4.90 (1 H, br s), 5.14 (1 H, br s), 7.33 (1 H, dd, J = 7.8 and 1.5), 7.71 (1 H, t, J = 7.8) and 7.76 (1 H, dd, J = 7.8 and 1.5); δ_C 27.2, 29.4, 31.8, 38.8, 56.5, 66.6, 114.9, 118.1, 119.1, 120.0, 133.7, 135.5, 140.3, 140.4, 148.2, 159.7, 178.0, 182.8, 184.5 and 201.4; *m/z* (rel. intensity) 384 (M^+, 8), 341 (8), 299 (21), 282 (100), 269 (40), 267 (22), 239 (16) and 115 (34); ν_{max} (KBr) 2976, 1730, 1710, 1658, 1644, 1582, 1476, 1280, 1266 and 1152 cm^{-1}.

Conversion of I to K

To a solution of **I** (104 mg, 0.27 mmol) in ether (5 mL) was added $MgSO_4$ (800 mg) and Ag_2O (800 mg) at room temperature. After being stirred for 30 min, the reaction mixture was filtered. The filtrate was concentrated and the residue was purified by silica-gel chromatography (30—50% EtOAc/hexane) to give 78 mg (75%) of **K**.

Conversion of J to K

The dihydronaphthofuran **J** (50 mg, 0.11 mmol) was dissolved in MeCN (2 mL) and CAN (150 mg, 0.27 mmol) in water (0.8 mL) was added at room temperature. After 10 min, the mixture was extracted with $CHCl_3$. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (30—50% EtOAc/hexane) to give 42 mg (100%) of **K**.

Ozonolysis of K

PPh_3 work-up—Ozone was bubbled into a solution of **K** (50 mg, 0.091 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After the yellow color of the solution became dark (40 min), excess ozone was purged by oxygen. A solution of PPh_3 (200 mg, 0.76 mmol) in dry CH_2Cl_2 (10 mL) was added at the temperature and then the mixture was allowed to warm up to room temperature. After 1 h, the mixture was concentrated and the residue was purified by silica-gel chromatography (30—50% EtOAc/hexane) to give 24 mg (49%) of 4-acetyl-6-methoxy-2-(pivaloyloxymethyl)naphtho[1,2-

b]furan-5-ol (**L**) as yellow needles (Found: C, 67.8; H, 6.0%. $C_{21}H_{22}O_6$ requires C, 68.1; H, 6.0%): mp 132—134 °C (CH_2Cl_2/hexane); R_f (50% EtOAc/hexane) 0.7; δ_H 1.24 (9 H, s), 2.77 (3 H, s), 4.07 (3 H, s), 5.25 (2 H, s), 6.88 (1 H, dd, J = 7.6 and 1.0), 7.15 (1 H, s), 7.56 (1 H, dd, J = 8.3 and 7.6), 7.78 (1 H, dd, J = 8.3 and 1.0) and 13.38 (1 H, br); δ_C 27.1, 31.9, 38.8, 56.3, 58.4, 106.1, 108.7, 110.0, 113.2, 113.4, 121.8, 126.7, 130.7, 144.5, 152.4, 159.1, 160.5, 178.0 and 201.2; ν_{max} (KBr) 3288, 2976, 1724, 1644, 1634, 1594, 1392 and 1150 cm^{-1}; *m/z* (rel. intensity) 370 (M^+, 70), 355 (8), 285 (8) and 269 (100).

Me_2S work-up—The reaction of **K** (240 mg, 0.624 mmol) was carried out according to the similar procedure described for conversion of **G** to **14**. Chromatographic purification gave 144 mg (60%) of 3-acetyl-5-methoxy-2-[2-oxo-3-(pivaloyloxy]propyl]-1,4-naphthoquinone (**15**).

References

1 H. Uno, *J. Org. Chem.*, 1986, **51**, 350.

2 B. Kesteleyn, L. V. Puyvelde and N. D. Kimpe, *J. Org. Chem.*, 1999, **64**, 438.

3 B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 1983, **105**, 2315.