245. Two New Syntheses of the Pyranojuglone Pigment α-Caryopterone

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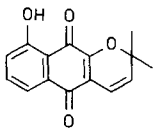
By a simple process, 3-methoxyjuglone (= 8-hydroxy-2-methoxy-1,4-naphthoquinone; **9**) has been synthesized from 1,2,4-trimethoxybenzene (**5**) and converted, after prenylation, to α-caryopterone (**1**; *Scheme 1*), a pyranojuglone pigment from *Caryopteris clandonensis*. On the other hand, juglone (= 5-hydroxy-1,4-naphthoquinone; **12**) was regioselectively prenylated at C(2) *via* its 1-methoxy-cyclohexa-1,3-diene adduct **15** *(Scheme 2)*. The 2-prenyljuglone (**4**) thus formed led to **1** after oxidation and other reactions.

1. Introduction. – In 1969 we reported the isolation and structure determination of α-caryopteron (**1**) [1], a red pyranojuglone from *Caryopteris clandonensis*. Its first synthesis was reported by *Giles* and *Roos* in 1975 [2] and later on by *Kapoor et al.* [3]. In the present paper, we describe two further syntheses of caryopterone.



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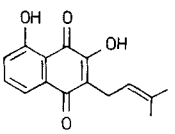

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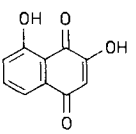

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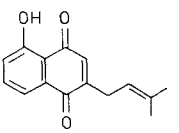

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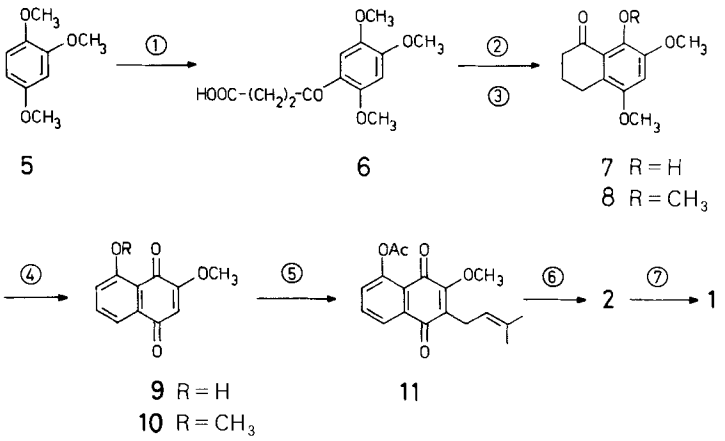
Since the pigment is supposedly derived from 3-hydroxy-2-prenyljuglon (**2**) *in vivo*, it seemed reasonable to synthesize it using 3-hydroxyjuglon (**3**) or 2-prenyljuglone (**4**) as an intermediate. However, regioselective hydroxylation at the C(3) position of juglone (= 5-hydroxy-1,4-naphthoquinone) is not necessarily so easy [4] [5]. Regioselective alkylation at C(2) of juglone is also expected to be difficult.

In our first synthesis (*Route A;* see *Scheme 1*), 3-methoxyjuglone (**9**) [5] was prepared by a new and simple process and used as an intermediate.

In the second synthesis (*Route B;* see *Scheme 2*), regioselective prenylation at C(2) of juglone was effected *via* its 1-methoxy-1,3-cyclohexadien adduct. The 2-prenyljuglon (**4**) thus obtained was then converted to **1** by oxidation.

2. Synthesis of α-Caryopterone by *Route A* *(Scheme 1)*. – *Clemmensen* reduction of 4-(2′,4′,5′-trimethoxyphenyl)-4-oxobutanoic acid (**6**) [6] [7] obtained from 1,2,4-trimethoxybenzene (**5**) and subsequent intramolecular acylation of the product with polyphos-

Scheme 1



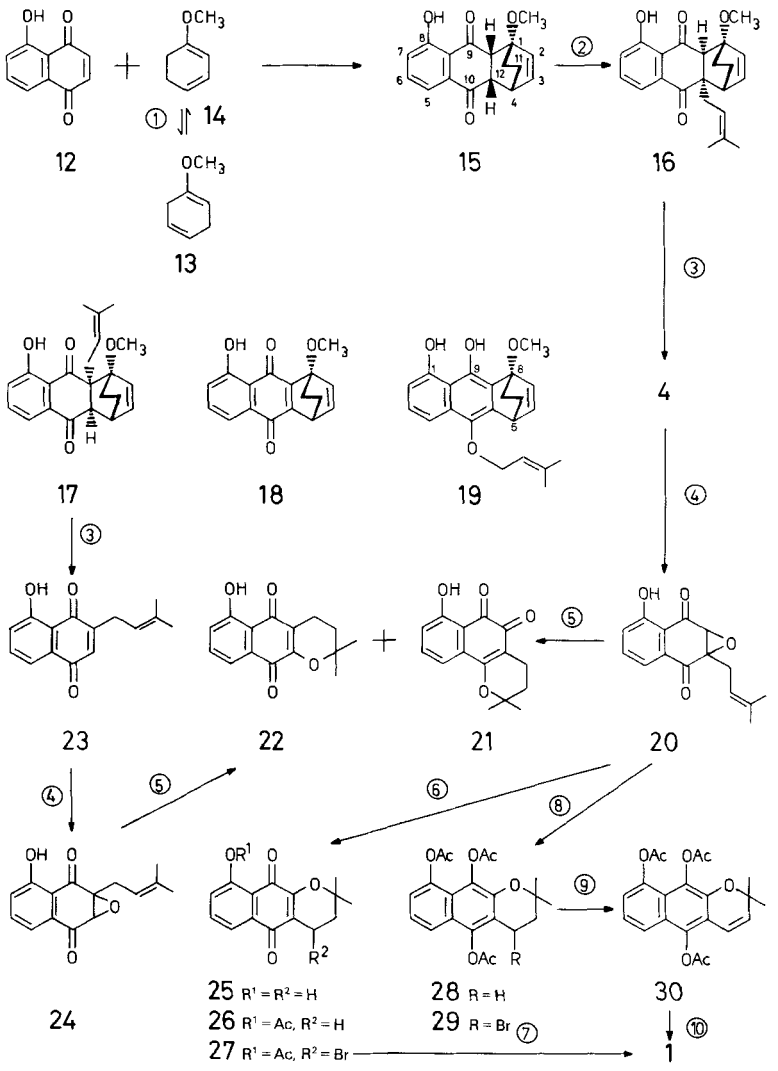
① Succinic anhydride/CS_2/$AlCl_3$ acc. [6b]; ② Zn/HCl; ③ PPS/ΔT; ④ DDQ/ΔT; ⑤ [1,3-η-(1,1-dimethylallyl)]nickel bromide/THF/−15°; ⑥ $Na_2CO_3/H_2O/\Delta T$; ⑦ DDQ/r.t.

phoric acid (PPS) at 100° for 3 h gave directly the monodemethylated tetralone **7**. At lower temperature (60°), 5,7,8-trimethoxytetralone (**8**) was produced, as also observed by other authors [6] [7]. From **7**, 3-methoxyjuglone (**9**) was prepared in one step by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 21% overall yield from **5**. Prenylation of the acetate **10** with [1-3-η-(1,1-dimethylallyl)]nickel bromide [8] under standard conditions [9] gave the desired compound **11** in acceptable yield (25%, see [9]) and 35% of the starting material. Alkaline hydrolysis immediately removed the AcO and MeO groups to afford dihydroxyquinone **2** which, upon treatment with DDQ (*cf.* [2]), furnished α-caryopterone (**1**) in one step in reasonable yield.

3. Synthesis of α-Caryopterone by *Route B* (*Scheme 2*). – In this approach, 2-prenyljuglone (**4**) was used as the starting material. Its preparation from the known juglone/1-methoxy-1,3-cyclohexadien adduct **15** [10] was conceived using the following assumptions: due to the steric hindrance, prenylation should occur more easily at C(4a) than at C(9a), and a *retro-Diels-Alder* reaction would recover the quinone system.

Several methods are known for the isomerization of 1-methoxy-1,4-cyclohexadiene (**13**) to 1-methoxy-1,3-cyclohexadien (**14**) [11]. However, all these methods require considerable skill. It turned out that simple heating of **13** in a $CHCl_3$ solution containing a small amount of CCl_4 at 55–60° brings about the equilibrium with **14**. Therefore, in the present study, a $CHCl_3$ solution of juglone (**12**) and the 1,4-diene **13** was treated under the above conditions to give the adduct **15** in 78% yield. The adduct **15** was then alkylated with prenyl bromide (= 3-methyl-2-buten-1-yl bromide) in the presence of LiN(i-Pr)$_2$ or *t*-BuOK at −45 to −50° to **16** in 27 and 53% yield, respectively. In addition to **16**, the by-products **17**, **18** [10], and **19** were also obtained in small amounts. The structures of **16** and **17** were deduced from their ^{1}H-NMR spectra, whilst the constitution of the *O*-alkylated product **19** was confirmed by its IR spectrum, which showed H-bonded OH bands at 3400 and 3250 cm^{-1} under high dilution conditions. The *rel*-(1*RS*,9a*RS*)-configuration of **16** was concluded from the presence of a long-range coupling (J = 1.6 Hz)

Scheme 2

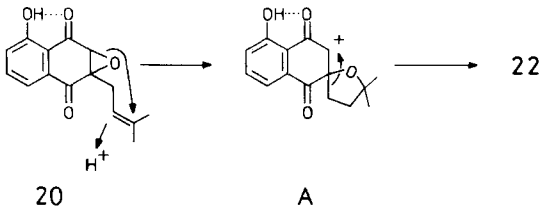


① $CHCl_3/CCl_4/\Delta T$; ② LiN(i-Pr)$_2$ or *t*-BuOK/THF/–45 to –50°/prenyl bromid; ③ ΔT; ④ sodium perborate; ⑤ conc. H_2SO_4; ⑥ $BF_3 \cdot OEt_2$ or BF_3/DDQ; ⑦ base; ⑧ Zn/Ac_2O; ⑨ pyridine; ⑩ $EtMgBr/Et_2O/H_3O^+/O_2$.

between H–C(9a) and one of the protons at C(11). Conversely, the (1*RS*,9a*SR*)-configuration was assigned to the starting material **15**, since no such coupling was observed (both in $CDCl_3$, 500 MHz). Thus, the alkylation presumably proceeded through the aromatized dienolate of **15**. *retro-Diels-Alder* reaction of **16** in toluene at 190–210° gave the desired 2-prenyljuglone (**4**) in 94% yield. Subsequent treatment of **4** with sodium perborate led to the epoxide **20** in 50% yield. However, treatment of **20** with conc. H_2SO_4 [12] afforded

o-quinone **21** [1] and an unexpected product **22** in low yields. The structure of the rearranged product **22** was confirmed by its synthesis (only product) from conc.-H_2SO_4 treatment of epoxide **24**, the latter being obtained from **17** *via* **23** by an analogous sequence of reactions to that above. The formation of **22** from **20** is rationalized as shown in *Scheme 3*. H-Bonding of the phenolic OH group to the CO group would reduce the double-bond character of the CO group and stabilize the carbocation of intermediate **A** in the rearrangement.

Scheme 3



20 A

In contrast to the reaction in H_2SO_4, treatment of the epoxide **20** with $BF_3 \cdot OEt_2$ in benzene gave dihydro-α-caryopterone (**25**; for its isolation from *Catalpa ovata*, see [13]) in 54% yield besides a small amount of **21**. An attempt to obtain α-caryopterone (**1**) directly from **20** by treating it with $BF_3 \cdot OEt_2$/DDQ was unsuccessful, but furnished exclusively **25** in improved yield (63%). Treatment of its acetate **26** with *N*-bromosuccinimide (NBS) in the presence of K_2CO_3 in CCl_4 yielded an unstable bromo compound **27**, which without further purification could be converted to α-caryopterone (**1**) by dehydrobromination and deacetylation. However, the yield was low. Therefore, an alternative route from **20** to **1** was examined and the overall yield of **1** significantly improved as follows. Epoxide **20** was first subjected to reductive acetylation (Zn dust/Ac_2O) to give a triacetate **28** (79%) which, on treatment with NBS and K_2CO_3 in CCl_4, produced a bromo derivative **29** in 83% yield. The latter was treated with pyridine to give **30**. Subsequent removal of the AcO groups with EtMgBr/Et_2O followed by hydrolysis and oxidation in air furnished α-caryopterone (**1**) in 47% overall yield from **29**.

Experimental Part

General. M.p. are uncorrected. Recording of spectra was carried out on the following apparatus; IR: *JASCO IR-S* and *Hitachi 285*. ^{1}H-NMR: *Hitachi R-20B* (60 MHz), *R-22* (90 MHz), *Jeol JNM-FX 100* (100 MHz), and *JNM-GX 500* (500 MHz). UV: *Hitachi 200*. MS: *Jeol JMS-D300* and *Hitachi RMU-6*.

Route A. – *3,4-Dihydro-8-hydroxy-5,7-dimethoxy-1(2H)-naphthalenone* (**7**). A mixture of 4-(2′,4′,5′-trimethoxyphenyl)-4-oxobutanoic acid (**6**) [6b] (6 g, 0.023 mol), 6N HCl (65 ml), and amalgamated Zn (12 g) was heated under reflux. After 30 min, a further amount (6 g) of **6** and 6N HCl (55 ml) were added and the refluxing continued for 5 h. After cooling, the products were extracted with 3× 30 ml of $CHCl_3$. The combined org. layers were shaken with 2N NaOH, from which, after acidification (2N HCl), the acidic material was extracted with $CHCl_3$. The combined org. layers were shaken with 2N NaOH, from which, after acidification (2N HCl), the acidic material was extracted with $CHCl_3$. The $CHCl_3$ soln. was washed with brine and dried. After evaporation, the crude product (3.6 g) was chromatographed on silica gel (benzene/EtOAc 1:1) to give 3.5 g (62%) of 4-(2′,4′,5′-trimethoxyphenyl)butanoic acid, m.p. 79.5–80° after crystallization from Et_2O ([7]: 78–80°; [6a]: 89–90°).

A mixture of polyphosphoric acid (110 g) and the above acid (22.3 g, 0.088 mol) was heated at 90–100° for 3 h with stirring. Crushed ice (300 g) was added to the deep-red mixture, and the product was extracted with $CHCl_3$. The org. layer was washed with brine and dried over anh. Na_2SO_4. Evaporation gave a semi-solid product (17.7 g), which was chromatographed on silica gel (350 g, $CHCl_3$) to afford 12.3 g of **7** as pale yellow crystals, m.p.

119.0–120.5° (recrystallized from benzene/hexane). UV (EtOH): 381 (3520), 270 (8520), 231 (16150). IR: 1660, 1645. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.02 (*quint.*, J = 6, 2 H–C(3)); 2.50–2.97 (*m*, 2 H–C(2), 2 H–C(4)); 3.79 (*s*, CH_3O); 3.88 (*s*, CH_3O); 6.73 (*s*, 1 arom. H); 12.10 (*s*, OH). MS: 223 (M^+ + 1), 222 (M^+), 207, 179, 147. Anal. calc. for $C_{12}H_{14}O_4$ (222.23): C 64.85, H 6.35; found: C 64.56, H 6.31.

3,4-Dihydro-5,7,8-trimethoxy-1(2H)-naphthalenone (**8**). By a method similar to that described above, 2.30 g of 4-(2′,4′,5′-trimethoxyphenyl)butanoic acid and polyphosphoric acid (11 g) were heated at 50–60° for 3 h to give **8** (1.73 g, 81%), m.p. 105–106° ([7]: 104–106°; [6]: 112°).

8-Hydroxy-2-methoxy-1,4-naphthoquinone (**9**). A mixture of **7** (18.2 g, 0.089 mol) and DDQ (44.4 g, 0.196 mol) in dry benzene (500 ml) was heated under reflux for 8 h. The precipitate was filtered off and the filtrate evaporated. The crude crystals (22 g) thus obtained were purified by silica-gel chromatography (400 g) with $CHCl_3$: **9** as yellow crystals (14.0 g, 84%). Recrystallization from benzene/hexane afforded a pure sample, m.p. 122.5–124.5°. The reported m.p. 222–222.5° [4] is probably attributable to a typing error.

(3-Methoxy-1,4-naphthoquinone-5-yl) Acetate (**10**). To a soln. of **9** (1.8 g, 8.8 mol) in $CHCl_3$ (100 ml) were added pyridine (50 ml) and Ac_2O (50 ml). The resulting mixture was allowed to stand at r.t. for 6 h. Solvent and excess reagents were evaporated and the crude **10** crystallized from $CHCl_3$/hexane. A pure sample of **10** was obtained as yellow needles, m.p. 158.0–161.0°. UV ($CHCl_3$): 342 (3870), 278 (15600), 273 (15800). IR (nujol): 3045, 1765, 1680, 1652, 1615, 1595, 1310, 1250, 1210, 1200, 1175. ^{1}H-NMR (60 MHz, $CDCl_3$): 2.43 (*s*, $COCH_3$); 3.88 (*s*, CH_3O); 6.13 (*s*, H–C(2)); 7.31 (*dd*, J = 7, 2, 1 arom. H); 7.73 (*t*, J = 7, 1 arom. H); 8.04 (*dd*, J = 7, 2, 1 arom. H). MS: 246 (M^+), 204 (100), 189, 173. Anal. calc. for $C_{13}H_{10}O_5$ (246.21): C 63.41, H 4.09; found: C 63.60, H 3.97.

[3-Methoxy-2-(3′-methyl-2′-butenyl)-1,4-naphthoquinon-5-yl] Acetate (**11**). To a soln. of **10** (1.47 g, 6.0 mmol) in dry THF (50 ml) was added 2.5 g (6.0 mmol) of [1-3-η-(1,1-dimethylallyl)]nickel bromide at −15° within 2 h. After additional 2 h, the solvent was evaporated and the residue diluted with 0.1N HCl (100 ml). The aq. soln. was extracted with $CHCl_3$, and the org. phase washed with brine and dried (Na_2SO_4). After evaporation, the residual viscous oil was purified by silica-gel chromatography (150 g). Compound **11** was eluted with $CHCl_3$/EtOAc 20:1 (474 mg, 25%). Further elution with the same solvent led to recovery of **10** (518 mg, 35%) and **4** (134 mg, 11%). Data of **11**: m.p. 80.0–80.5° (yellow needles, crystallized from Et_2O). UV (EtOH): 249 (20200), 273 (14400), 341 (4530). IR (nujol): 1780, 1664, 1645, 1615, 1600. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.66, 1.75 (2*s*, 2 CH_3); 2.38 (*s*, $COCH_3$); 3.22 (*d*, J = 7, 2 H–C(1′)); 3.99 (*s*, CH_3O); 5.08 (br. *t*, J = 7, H–C(2′)); 7.20 (*dd*, J = 7, 2, 1 arom. H); MS: 314 (M^+), 299, 272, 257, 239 (100). Anal. calc. for $C_{18}H_{18}O_5$ (314.32): C 68.78, H 5.77; found: C 68.92, H 5.98.

3,5-Dihydroxy-2-(3′-methyl-2′-butenyl)-1,4-naphthoquinone (**2**). Naphthoquinone **11** (0.10 g, 0.32 mmol) was heated in aq. 0.5N Na_2CO_3 at 73° for 28 h. The red soln. was acidified (pH 4) with 1N HCl, and the product was extracted with $CHCl_3$. The org. layer was washed with brine and dried over Na_2SO_4. Evaporation gave 75 mg of an orange solid, which was purified by prep. TLC (*Merck* silica gel *60*; benzene/EtOAc 20:1) to give 39 mg (48%) of **2** as orange needles. A sample for anal. was recrystallized from Et_2O, m.p. 121.5–123.0°. UV ($CHCl_3$): 417 (12300), 287 (12900). IR (nujol): 3400, 1628, 1597, 1583. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.69, 1.78 (2*s*, 2 CH_3); 3.30 (*d*, J = 7, 2 H–C(1′)); 5.20 (br. *t*, J = 7, H–C(2′)); 7.3–7.0 (*m*, 1 arom. H); 7.7–7.5 (*m*, 2 arom. H); 11.00 (*s*, OH). MS: 258 (M^+), 243, 215 (100). Anal. calc. for $C_{15}H_{14}O_4$ (258.26): C 69,75, H 5.46; found: C 69.86, H 5.43.

α-Caryopterone (= *9-Hydroxy-2,2-dimethyl-2H-naphtho[2,3-b]pyran-5,10-dione*; **1**). On stirring a mixture of **2** (50 mg, 0.194 mmol) and DDQ (150 mg, 0.66 mmol) in benzene (15 ml) at r.t. for 27 h, a precipitate was gradually formed. The precipitate was filtered off and the filtrate evaporated to give an oily product which was separated by prep. TLC ($CHCl_3$) giving 16 mg (32%) of **1**, m.p. 144–145.5°, and 17 mg (34%) of unchanged **2**.

Route B. – *1-Methoxy-1,3-cyclohexadiene* (**14**). A soln. of 42 ml of 1-methoxy-1,4-cyclohexadiene (**13**) and 42 ml of CCl_4 in 420 ml of $CHCl_3$, was heated with stirring at 55–60° under a *Dimroth* condenser and a drying ($CaCl_2$) tube. The mixture was checked by ^{1}H-NMR, and the reaction quenched when the intensity of the CH_3O signal of **14** became stronger than that of **13**. The mixture contained 25–30% of the **14**. ^{1}H-NMR (90 MHz, $CHCl_3$): 3.61 (CH_3O, **14**); 3.56 (CH_3O, **13**).

(1RS,4RS,4aSR,9aSR)-1,4-Ethano-1,4,4a,9a-tetrahydro-8-hydroxy-1-methoxyanthraquinone (**15**). A soln. of 100 mg (0.57 mmol) of juglone (**12**) and 0.16 ml (1.45 mmol) of **13** in a mixture of 1.6 ml of $CHCl_3$ and 0.16 ml of CCl_4 was heated with stirring at 55–60° for 3–3.5 h. The mixture was concentrated *in vacuo* and crystals of **15** which had separated out collected by filtration and washed with AcOEt. The filtrates were concentrated, and further deposited crystalline **15** was collected. Remaining **15** in the filtrates was isolated by prep. TLC with benzene/EtOAc 9:1. Total yield of **15**: 78% (127.7 mg). M.p. 144–147° ([6]: 145°). IR (KBr): 3430 (OH), 1685, 1645 (C=O), 1170 (C–OCH_3). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.54 (*m*, 2 H); 1.88 (*m*, 1 H); 2.03 (*m*, 1 H); 3.19 (*m*, $w_{1/2}$ = 13, H–C(4)); 3.26 (*dd*, J = 9.0, 2.9, H–C(4a)); 3.47 (*d*, J = 9.0, H–C(9a)); 3.50 (*s*, CH_3O); 6.00 (*d*, J = 8.9, H–C(2)); 6.06 (*dd*,

J = 8.7, 8.5, H–C(3)); 7.17 (*dd*, J = 7, 2, H–C(7)); 7.43 (*dd*, J = 7, 2, H–C(5)); 7.56 (*t*, J = 7, H–C(6)). MS: 284 (M^+), 174 ($M^+ - C_7H_{10}O$), 110 ($C_7H_{10}O^+$).

(1RS,4RS,4aRS,9aRS)-1,4-Ethano-1,4,4a,9a-tetrahydro-8-hydroxy-1-methoxy-4a-(3'-methyl-2'-butenyl)-anthraquinone (**16**). i) *Using Li N(i-Pr)$_2$*. To a soln. of 2 ml (0.014 mol) of freshly distilled (i-Pr)$_2$NH in 20 ml of dried THF under N_2 were added 6.7 ml of 2.3M BuLi in hexane and 2.7 ml (0.016 mol) of hexamethylphosphoric triamide (HMPT) through a syringe at −45 to −50°. After stirring for 25 min, 2 g (0.007 mol) of **15** in 16 ml of THF were added by syringe with continuous stirring, and the mixture was stirred for a further 15 min. Then, 1.6 ml (0.018 mol) of prenyl bromide were added, and the soln. was allowed to stand for 30–40 min at −45 to −50°. A sat. soln. of NH_4Cl was then added to the mixture, and this was extracted 3× with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The deposited crystals of **15** were removed by filtration, and the filtrate was evaporated to give a residue which was chromatographed on a silica-gel column with benzene to yield 0.66 g (26.7%) of **16**, small amounts of **17–19**, and recovered **15**. The total amount of **15** consumed was 0.84 g.

ii) *Using t-BuOK*. A mixture of 300 mg of K (7.69 mmol) in 6 ml of *t*-BuOH was refluxed with stirring under N_2 for 3 h. After cooling to 0°, 500 mg (1.76 mmol) of **15** in 5 ml of DMF was added and the mixture allowed to stand for 10 min before adding 0.4 ml (4.50 mmol) of prenyl bromide. The mixture was left to stand for 10–15 min, poured into ice/H_2O, acidified with 3N HCl to pH 5, and extracted 3× with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica-gel column with hexane/Et_2O 4:1 to give, besides **18** and **19**, 330 mg (53%) of **16**, which was recrystallized from Et_2O, m.p. 99.4–101.2°. IR (KBr): 3430 (OH), 1670, 1630 (C=O). ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.20–1.34 (*m*, CH_2CH_2); 1.49, 1.54 (*d*, each 3 H, $(CH_3)_2C$=); 2.01 (*dd*, J = 13, 9, H–C(1')); 2.75 (*dd*, J = 13, 6, H–C(1')); 2.86 (*d*, J = 1.6, H–C(9a)); 2.94 (*ddd*, J = 7.1, 4.0, 3.0, H–C(4)); 3.57 (3*s*, CH_3O); 4.71 (*ddq*, J = 9.0, 6.0, 1.0, H–C(2')); 6.42 (*dd*, J = 8.6, 7.1, H–C(3)); 6.53 (*d*, J = 8.6, H–C(2)); 7.27 (*dd*, J = 8.0, 2.0, 1 arom. H); 7.60 (*dd*, J = 8.0, 2.0, 1 arom. H); 7.64 (*t*, J = 7.0, 1 arom. H). MS: 352 (M^+). Anal. calc. for $C_{22}H_{24}O_4$ (352.41): C 74.97, H 6.86; found: C 74.92, H 6.90.

(1RS,4RS,4aRS,9aRS)-1,4-Ethano-1,4,4a,9a-tetrahydro-8-hydroxy-1-methoxy-9a-(3'-methyl-2'-butenyl)-anthraquinone (**17**). M.p. 121–122°. IR (KBr): 3420 (OH), 1680, 1625 (C=O). ^{1}H-NMR (90 MHz, CCl_4): 1.46, 1.51 (2*s*, each 3 H, $(CH_3)_2C$=); 0.96–2.07 (*m*, H–C(4), CH_2CH_2); 2.47 (br. *d*, J = 1, H–C(4a)); 2.83, 3.16 (2*m*, each 1 H, 2 H–C(1')); 3.36 (*s*, 3 H, CH_3O); 4.62 (*m*, H–C(2')); 6.12–6.49 (*m*, H–C(2), H–C(3)); 7.10 (*dd*, J = 8, 2, 1 arom. H); 7.27 (*t*, J = 8, 1 arom. H); 7.51 (*dd*, J = 8, 2, 1 arom. H); 12.42 (*s*, OH). MS: 352 (M^+). Anal. calc. for $C_{22}H_{24}O_4$ (352.41): C 74.97, H 6.86; found: C 74.99, H 6.82.

(1RS,4RS)-1,4-Ethano-1,4-dihydro-8-hydroxy-1-methoxyanthraquinone (**18**). M.p. 197–198° ([6]: 128°). IR (KBr): 3420 (OH), 1620 (C=O). ^{1}H-NMR (90 MHz, CCl_4): 1.18–1.98 (*m*, CH_2CH_2); 3.58 (*s*, CH_3O); 4.31–4.51 (*m*, H–C(4)); 6.28 (*dd*, J = 8, 6, H–C(3)); 6.51 (*dd*, J = 8, 2, H–C(2)); 7.04 (*t*, J = 5, H–C(7)); 7.62 (*d*, J = 5, H–C(6), H–C(8)); 12.17 (*s*, OH). MS: 282 (M^+).

(5RS,8RS)-5,8-Ethano-5,8-dihydro-8-methoxy-10-[(3'-methyl-2'-butenyl)oxy]anthracene-1,9-diol (**19**). M.p. 143–143.5° (recrystallized from $CHCl_3$). IR (KBr): 3360 (OH), 3150 (OH), 1635 (C=C), 1610, 1500 (arom). IR (2.2×10^{-4}M in CCl_4): 3400, 3250 (intramol. H-bonded OH). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.62, 1.79 (*s*, $(CH_3)_2C$=); 1.36–1.96 (*m*, CH_2CH_2); 1.96–2.20 (*m*, H–C(5)); 3.68 (*s*, CH_3O); 4.40 (*d*, J = 8, 2 H–C(1')); 5.62 (*m*, H–C(2')); 6.46 (*d*, J = 14, H–C(7)); 6.52 (*dd*, J = 14, 2, H–C(6)); 6.79 (*dd*, J = 7, 2, H–C(2)); 7.24 (*t*, J = 7, H–C(3)); 7.44 (*dd*, J = 7, 2, H–C(4)); 9.54, 10.20 (2 br. *s*, each 1 H, 2 OH). MS: 352 (M^+). Anal. calc. for $C_{22}H_{24}O_4$ (352.41): C 74.97, H 6.86; found: C 74.77, H 6.84.

5-Hydroxy-2-(3'-methyl-2'-butenyl)-1,4-naphthoquinone (**4**). A soln. of 58.8 mg of **16** in 20 ml of toluene was heated at 190–210° for 30 min in a sealed tube. The mixture was evaporated and the oily residue chromatographed on silica-gel plates with hexane/Et_2O 2:1 to give 38 mg (93%) of **4**. This was recrystallized from EtOAc/EtOH yielding pure **4**, m.p. 57–58°. IR (KBr): 1670, 1645 (C=O). ^{1}H-NMR (90 MHz, CCl_4): 1.66, 1.74 (2*s*, each 3 H, $(CH_3)_2C$=); 3.12 (br. *d*, J = 7, 2 H–C(1')); 5.08 (br. *t*, J = 7, H–C(2')); 6.47 (*t*, J = 1, H–C(3)); 7.02 (*m*, H–C(6), H–C(7)); 7.36 (*m*, H–C(8)); 11.64 (*s*, OH). MS: 242 (M^+). Anal. calc. for $C_{15}H_{14}O_3$ (242.26): C 74.36, H 5.83; found: C 74.37, H 5.87.

2,3-Epoxy-2,3-dihydro-5-hydroxy-2-(3'-methyl-2'-butenyl)-1,4-naphthoquinone (**20**). To a soln. of 100 mg (0.65 mmol) of sodium perborate ($NaBO_3$) in 13.5 ml of H_2O was added 50 mg (0.21 mmol) of **4** in 20 ml of EtOH and the mixture stirred for 30 min at r.t. The mixture was filtered and the filtrate acidified with 3N HCl and extracted 3× with EtOAc. The combined extracts were washed with brine, dried over anh. $MgSO_4$, and evaporated to dryness. The crude product was purified by prep. TLC (hexane/Et_2O 2:1) to give a crystalline material which was recrystallized from $CHCl_3$ yielding 27 mg (50%) of pure **20**, m.p. 30.5–31.5°. IR (KBr): 1690, 1655 (C=O). ^{1}H-NMR (90 MHz, CCl_4): 1.70, 1.74 (2*s*, each 3 H, $(CH_3)_2C$=); 2.53, 2.99 (2 br. *dd*, J = 14, 8, 2 H–C(1')); 3.67 (*s*,

H–C(3)); 5.04 (br. *t*, *J* = 8, H–C(2')); 7.14 (*dd*, *J* = 7, 2, 1 arom. H); 7.46 (*dd*, *J* = 7, 2, 1 arom. H); 7.58 (*t*, *J* = 7, 1 arom. H); 11.09 (*s*, OH). MS: 258 (M^+). Anal. calc. for $C_{15}H_{14}O_4$ (258.00): C 69.75, H 5.46; found: C 69.58, H 5.33.

*3,4-Dihydro-6-hydroxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione* (**22**). A mixture of 75 mg (0.29 mmol) of **20** and 1.5 ml of conc. H_2SO_4 was stirred for 10 min at r.t. Ice/H_2O was added to the mixture which was then stirred for 5–6 min. After addition of $CHCl_3$, insoluble material was removed by filtration. The filtrate was extracted 3× with $CHCl_3$, and the combined extracts were washed with brine, dried over anh. $MgSO_4$, and evaporated. The crude product was purified by prep. TLC using benzene/EtOAc 9:1 to yield 7.3 mg (2.8%) of **22** and 5.6 mg (2.1%) of **21**. The isomer **21** was identified by comparison with an authentic sample prepared from **25** according to a known procedure [1]. Recrystallization of **22** from $CHCl_3$ gave a pure material, m.p. 170.8–183.6°. IR ($CHCl_3$): 1680, 1625 (C=O). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.44 (*s*, 2 CH_3); 1.83 (*t*, *J* = 7, 2 H–C(3)); 2.60 (*t*, *J* = 7, 2 H–C(4)); 7.21 (*dd*, *J* = 6, 3, 1 arom. H); 7.36 (*t*, *J* = 6, 1 arom. H); 7.58 (*dd*, *J* = 6, 3, 1 arom. H); 12.37 (*s*, OH). MS (HR): 258.0913 (M^+, $C_{15}H_{14}O_4$, calc. 258.0893).

8-Hydroxy-2-(3'-methyl-2'-butenyl)-1,4-naphthoquinone (**23**). A mixture of 300 mg of **16**/**17** (*ca.* 1:1) in 60 ml of toluene was heated at 180–200° for 30 min in a sealed tube. The mixture was evaporated to give 115 mg of **4**/**23**, a portion of which (21 mg) was purified by prep. TLC with hexane/Et_2O 4:1 to yield 7.8 mg of **4** and 6.5 mg of **23**. Data of **23**. IR (neat): 1665 (C=O), 1640 (C=O), 1605 (C=C). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.63, 1.76 (2*s*, each 3 H, $(CH_3)_2C$=); 3.19 (*d*, *J* = 7, 2 H–C(1')); 5.12 (br. *t*, *J* = 7, H–C(2')); 6.59 (*t*, *J* = 1, H–C(3)); 7.09 (*dd*, *J* = 4, 2, 1 arom. H); 7.40–7.47 (*m*, 2 arom. H); 11.87 (br. *s*, OH). MS (HR): 242.0937 (M^+, $C_{15}H_{14}O_3$, calc. 242.0942).

2,3-Epoxy-2,3-dihydro-8-hydroxy-2-(3'-methyl-2'-butenyl)-1,4-naphthoquinone (**24**). To a soln. of 200 mg (1.3 mmol) of $NaBO_3$ in 27 ml of H_2O was added 94 mg (0.2 mmol) of **23** in 10 ml of EtOH and 8.5 ml of H_2O, and the mixture was stirred for 30 min at r.t. The mixture was filtered, the filtrate acidified with 3N HCl and extracted 3× with EtOAc. The combined extracts were washed with brine, dried over anh. $MgSO_4$, and evaporated. Purification of the crude product by prep. TLC (cyclohexane/EtOAc 4:1) yielded 29.5 mg of **23** and 21.6 mg of **24**. Data of **24**. IR (neat): 1695 (C=O), 1655 (C=O). ^{1}H-NMR (90 MHz, CCl_4): 1.70, 1.74 (2*s*, each 3 H, $(CH_3)_2C$=); 2.47 (*dd*, *J* = 14, 8, H–C(1')); 3.00 (*dd*, *J* = 14, 8, H–C(1')); 3.63 (*s*, H–C(3)); 5.04 (*m*, H–C(2')); 7.04 (*dd*, *J* = 8, 1, 1 arom. H); 7.28 (*dd*, *J* = 8, 1, 1 arom. H); 7.48 (*t*, *J* = 8, 1 arom. H); 11.21 (*s*, OH). MS (HR): 258.0891 (M^+, $C_{15}H_{14}O_3$, calc. 258.0891).

22 *from* **24**. A mixture of 15 mg (0.06 mmol) of **24** and 1.5 ml of conc. H_2SO_4 was stirred for 10 min at r.t. Ice/H_2O was added and the mixture filtered. The filtrate was extracted with $CHCl_3$, and the extracts were dried over anh. Na_2SO_4 and evaporated. Purification of the residue by prep. TLC (benzene/EtOAc 9:1) yielded 2.2 mg (14.7%) of **22**, which was identical in all respects with the previously obtained sample.

Dihydro-α-caryopterone (= *3,4-Dihydro-9-hydroxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione;* **25**). i) *In the Presence of DDQ*. To a mixture of 185 mg (0.81 mmol) of DDQ and 123 mg (0.48 mmol) of **20** in 12.3 ml of dry benzene was added dropwise 0.25 ml (0.20 mmol) of $BF_3 \cdot Et_2O$ under N_2. The mixture was stirred until all the starting material had disappeared (TLC). The mixture was filtered, the filtrate neutralized with aq. $NaHCO_3$ soln. and then extracted 4× with EtOAc. The combined extracts were dried over anh. $MgSO_4$ and evaporated. Purification of the residue on silica-gel plates ($CHCl_3$) yielded 77 mg (63%) of **25** which was recrystallized from $CHCl_3$ to give pure **25**, m.p. 114.5–115° ([1]: 110.5–111°). IR (KBr): 1645, 1600 (C=O). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.40 (*s*, 2 CH_3); 1.78 (*t*, *J* = 6, 2 H–C(3)); 2.57 (*t*, *J* = 6, 2 H–C(4)); 7.04–7.23 (*m*, 1 arom. H); 7.51 (*m*, 2 arom. H). MS: 258 (M^+). Anal. calc. for $C_{15}H_{14}O_4$ (258.26): C 69.75, H 5.46; found: C 69.89, H 5.49.

ii) *Preparation without DDQ*. The reaction was carried out in essentially the same way as above, but without using DDQ. From 60 mg (0.23 mmol) of **20**, 32.5 mg (54%) of **25** and 3.2 mg (5.3%) of **21** were obtained, after prep. TLC (benzene/EtOAc).

*3,4,5,10-Tetrahydro-2,2-dimethyl-5,10-dioxo-2*H*-naphtho[2,3-*b*]pyran-9-yl Acetate* (**26**). A soln. of 224 mg (0.87 mmol) of **25** and 0.16 ml (1.95 mmol) of Ac_2O in 1 ml of pyridine was allowed to stand for 2.5 h at r.t. Ice/H_2O was added and the mixture extracted 3× with EtOAc. The combined extracts were washed with brine, dried over anh. Na_2SO_4, and evaporated to give **26** (*ca.* 100%). Recrystallization from EtOAc/EtOH afforded pure **26**. M.p. 175–179°. IR (KBr): 1760, 1670, 1650 (C=O), 1200 (AcO). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.40 (*s*, 2 CH_3); 1.79 (*t*, *J* = 6, 2 H–C(3)); 2.42 (*s*, $COCH_3$); 2.59 (*t*, *J* = 6, 2 H–C(4)); 7.27 (*dd*, *J* = 8, 1, 1 arom. H); 7.68 (*t*, *J* = 8, 1, 1 arom. H); 8.04 (*dd*, *J* = 8, 1, 1 arom. H). MS: 300 (M^+). Anal. calc. for $C_{17}H_{16}O_5$ (300.30): C 67.99, H 5.37; found: C 67.93, H 5.31.

α-Caryopterone (**1**). A mixture of 247 mg (0.82 mmol) of **26**, 172 mg (0.97 mmol) of NBS and 605 mg of K_2CO_3 in 136 ml of CCl_4 was refluxed with stirring for 2.5 h. The mixture was filtered, and the filtrate evaporated to give a powder which was extracted with CCl_4. The extracts were concentrated to afford a crystalline bromo compound **27** (*ca.* 100%). This bromo compound was immediately transferred to a flask under N_2, and 60 ml of dry pyridine

were added. The mixture was refluxed overnight. After evaporation, the oily residue was purified by prep. TLC with benzene/EtOAc 9:1 to afford 14.6 mg of **1**. Recrystallization from $CHCl_3$ yielded a pure sample. M.p. 147–151° ([1]: 143.5–145.5°). IR (KBr): 3430 (OH), 1685, 1645 (C=O). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.56 (*s*, 2 CH_3); 5.70 (*d*, *J* = 10, H–C(3)); 6.60 (*d*, *J* = 10, H–C(4)); 7.06–7.70 (*m*, 3 arom. H).

*[3,4-Dihydro-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,9-10-triyl] Triacetate* (**28**). A mixture of 27.6 mg (0.107 mmol) of **20**, 552 mg of Zn dust, and 138 mg (1.68 mmol) of NaOAc in 5 ml of Ac_2O was refluxed for 25 min. The mixture was filtered, the filtrate was poured into ice/H_2O and then extracted with EtOAc. The combined extracts were evaporated, and the residue was purified by prep. TLC using benzene/EtOAc. A pale yellow band on the plates was collected to give 32.5 mg (79.1%) of **28** which was recrystallized from Et_2O/benzene. M.p. 172.5–173.5°. IR (KBr): 1760 ($COCH_3$). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.36 (*s*, 2 CH_3); 1.88 (*t*, *J* = 7, 2 H–C(3)); 2.40 (*s*, 2 $COCH_3$); 2.49 (*s*, $COCH_3$); 2.81 (*t*, *J* = 7, 2 H–C(4)); 7.17 (*dd*, *J* = 7, 2, 1 arom. H); 7.36 (*dd*, *J* = 8, 7, 1 arom. H); 7.68 (*dd*, *J* = 8, 2, 1 arom. H). MS (HR): 386.1372 (M^+, $C_{21}H_{22}O_4$, 386.1365).

*[4-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,9,10-triyl] Triacetate* (**29**). A mixture of 40 g (0.104 mmol) of **28**, 30 mg (0.169 mmol) of NBS and 95 mg of K_2CO_3 in 21.6 ml of CCl_4 was refluxed for 2.5 h. The mixture was filtered and the filtrate evaporated to give a residue, which was taken up in CCl_4. Insoluble material was removed by filtration. The filtrate was evaporated and the residue purified by prep. TLC with benzene/EtOAc 4:1 to give 40.1 mg (83.4%) of **29**. IR (KBr): 1750 (C=O). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.34, 1.56 (2*s*, each 3 H, 2 CH_3); 2.39 (*s*, 2 $COCH_3$); 2.56 (*s*, $COCH_3$); 2.53–2.62 (*m*, 2 H–C(3)); 5.47 (*t*, *J* = 6, H–C(4)); 7.17 (*dd*, *J* = 8, 1, 1 arom. H); 7.38 (*t*, *J* = 8, 1 arom. H); 7.72 (*dd*, *J* = 8, 1, 1 arom. H). MS (HR): 464.0435 ($C_{21}H_{21}BrO_4$, calc. 464.0438).

*2,2-Dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,9,10-triyl Triacetate* (**30**). A mixture of 39 mg (0.084 mmol) of **29** in 4 ml of pyridine was refluxed for 2 h. After evaporation, the residue was chromatographed on a short silica-gel column with benzene/EtOAc 92:8 to give 15 mg (46.5%) of **30**. IR (neat): 1760 (C=O). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.44 (*s*, 2 CH_3); 2.38 (*s*, 2 $COCH_3$); 2.47 (*s*, $COCH_3$); 5.94 (*d*, *J* = 10, H–C(3)); 6.48 (*d*, *J* = 10, H–C(4)); 7.09 (*dd*, *J* = 8, 2, 1 arom. H); 7.33 (*t*, *J* = 8, 1 arom. H); 7.63 (*dd*, *J* = 8, 2, 1 arom. H). MS (HR): 384.1259 ($C_{21}H_{20}O_4$, calc. 384.1209).

α-Caryopterone (**1**). To a *Grignard* reagent prepared from 292 mg (2.68 mmol) of EtBr and 51 mg (2.10 mol-equiv.) of Mg in 0.4 ml of Et_2O under N_2 was added dropwise 12.5 mg (0.033 mmol) of **30** in 0.9 ml of Et_2O. The mixture was allowed to stand for 1 h at r.t., and excess *Grignard* reagent was decomposed by dropwise addition of 0.5N HCl under ice-cooling. Insoluble solid was removed by filtration and the filtrate extracted with $CHCl_3$. The combined extracts were dried over anh. $MgSO_4$ and evaporated to give 8.9 mg (100%) of red crystals, which were recrystallized from EtOH yielding pure **1**, m.p. 145.5–148.5°.

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