A New Synthetic Approach to Quassinoids *via* an Intramolecular Diels–Alder Reaction: A Stereoselective Construction of the Klaineanone Ring System †

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Thermolysis of the benzocyclobutene derivative (25) prepared from norcamphor (6) gave stereoselectively the tetracyclic compound (27), which was converted into the D-deoxyquassinoid derivative (2) possessing the same ABCD-ring fusion as that of klaineanone (1).

Quassinoids, which are a kind of bitter principle, are highly oxygenated and degraded triterpenes found in *Simarubaceae*.[1] Recent interest in them has focussed on the potent anti-leukemic activity of the C-15 acyloxylated derivatives, such as bruceantin, as reported by Kupchan.[2] Moreover, the complex stereostructure coupled with the oxygen functionality present in quassinoids together the biogenetic interest have stimulated a great deal of synthetic activity.[3] Recently Grieco elegantly synthesized (±)-quassin [4] and (±)-castelanoide [5] by employing an intermolecular Diels–Alder reaction. We have investigated the synthesis of this type of terpene by thermolysis of benzocyclobutenes,[6] and have envisioned a stereoselective construction of the tetracyclic compound (2),‡ having the same ABCD ring fusion as that of klaineanone (1),[7] by an intramolecular Diels–Alder reaction [8] of the *o*-quinodimethane (4) derived from the benzocyclobutene (5) and norcamphor (6). Here we report our results.

In the above synthetic approach we have three types of problem; the first is stereoselectivity in the Diels–Alder reaction, and the second building of the D-ring *via* a Baeyer-Villiger reaction of the cycloaddition product. The third centres around modification of the A-aromatic ring to give the methylated cyclohexane system possessing an oxygen function. Initially we investigated the first two problems by using the model compound (20) as follows.

Methylation of the lactone (7), [9] derived from norcamphor (6), with methyl iodide in the presence of lithium di-isopropylamide under kinetically controlled conditions gave, in 87.2% yield, exclusively one stereoisomer (8), the stereostructure of which was assigned on consideration of the approach of the methyl group to the enolate anion from the less hindered side.[10] In this way, the relative configuration between the C-13 and C-14 positions of klaineanone (1) was fixed. After reduction (82.5% yield) of (8) with lithium aluminium hydride, the secondary hydroxy group of the resulting diol (9) was selectively oxidised with ceric ammonium nitrate [11] in the presence of sodium bromate in aqueous acetonitrile at room temperature to the ketone (10). The resulting product was treated with tosyl chloride and pyridine to give the keto tosylate (11) in 94.9% overall yield. This compound was also obtained in 37.8% yield by selective tosylation of the secondary hydroxy group with tosyl chloride and pyridine, followed by Jones oxidation of the resulting monotosylate (12). After protection of the carbonyl group by acetalisation, the tosylate (13) was treated with potassium cyanide in dimethylformamide to give, in 74.2% yield, the nitrile (14), which was converted, on reduction with di-isobutylaluminium hydride and successive hydrolysis, into the aldehyde (15) in 80.3% yield. Aldol-type condensation of this aldehyde (15) with 1-cyanobenzocyclobutene (5) [12] in the presence of sodium amide in liquid ammonia afforded the alcohol (16) as a stereoisomeric mixture at the C-1 position on the benzocyclobutene. The stereochemical relationship between the α and γ positions on the side-chain of the main constituent of the benzocyclobutene was assumed by an examination of a Dreiding model; thus, the benzocyclobutenyl anion would approach the formyl group as shown in A. This assignment was confirmed by an *X*-ray analysis of the tetracyclic compound (24) derived from (16) in the later stage of the synthesis.

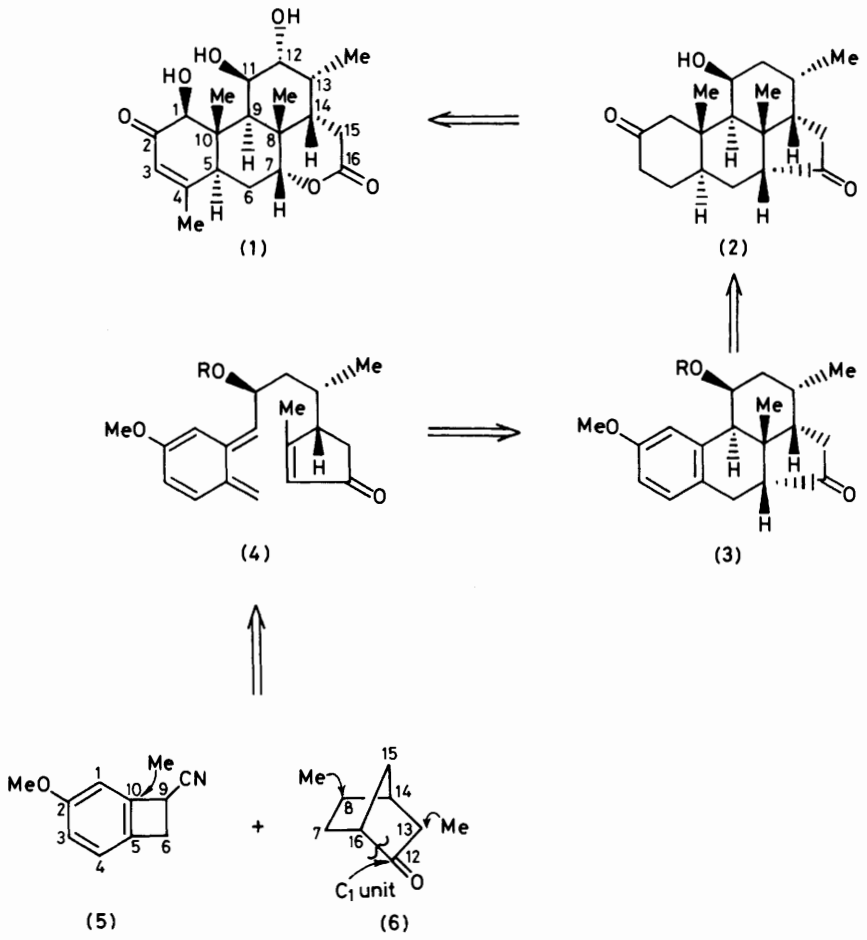
Treatment of the condensation product (16) with sodium in liquid ammonia in order to remove the unwanted cyano group,[6,13] followed by deprotection of the acetal group in product (17) afforded, in 56.7% yield, the alcohol (18) in addition to the corresponding dehydroxylated compound (19).[6] The desired keto alcohol (18) was obtained in >80% yield from the aldehyde (15) in a one-pot reaction; namely, the reaction of the aldehyde (15) with the benzocyclobutene (5), in the presence of sodium amide in liquid ammonia for 0.5 h and then treatment of this reaction mixture with sodium in the same solvent gave the expected decyanated compound (17) without any dehydroxylated one. This one-pot process is better than the stepwise method in terms both of yield and procedure.

Formation of the silyl enol ether from (18), followed by a dehydrogenation with palladium acetate by the Saegusa method [14] furnished the enone (20) [i.r. ($CHCl_3$) 1 721 cm^{-1}] in 53.9% yield.

As a model experiment in order to investigate whether the intramolecular Diels–Alder reaction proceeds in a regio- or stereo-selective manner, thermolysis of the enone (20) was examined. Heating of the enone (20) in *o*-dichlorobenzene at 230 °C for 2.5 h in a sealed tube afforded, regio- and stereoselectively and in 81% yield, the tetracyclic compound (22), *via* the *o*-quinodimethane (21) formed initially by a conrotatory ring-opening of the benzocyclobutene system. It is considered that *endo* forms would be disfavoured during the cycloaddition [15] because of serious interaction between the aromatic ring and the methyl group or hydrogens. One, B, of the two *exo*-modes would be a preferred conformation and form the BC(*trans*), BC(*cis*), and CD(*cis*) fused product (22), while other conformations would have considerable non-bonding interaction between the diene and the allylic hydro-

† This paper forms Part 999 of 'Studies on the Syntheses of Heterocyclic Compounds and Natural Products' by T. Kametani. Part 998. T. Kametani, N. Kanaya, T. Mochizuki, and T. Honda, *Tetrahedron Lett.*, 1983, **24**, 1511, and a part of this work has been reported in *Tetrahedron Lett.*, 1982, **23**, 2973.

‡ All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.



Scheme 1.

gen. The expected relative configuration was suggested from the n.m.r. spectrum of the desilylated compound (23), m.p. 184 °C [i.r. ($CHCl_3$) 1 740 cm^{-1}; *m/z* 286 (M^+)], in which the methine hydrogen present at the C-1 position was observed at low field, 4.66 p.p.m., due to deshielding by the benzene ring.

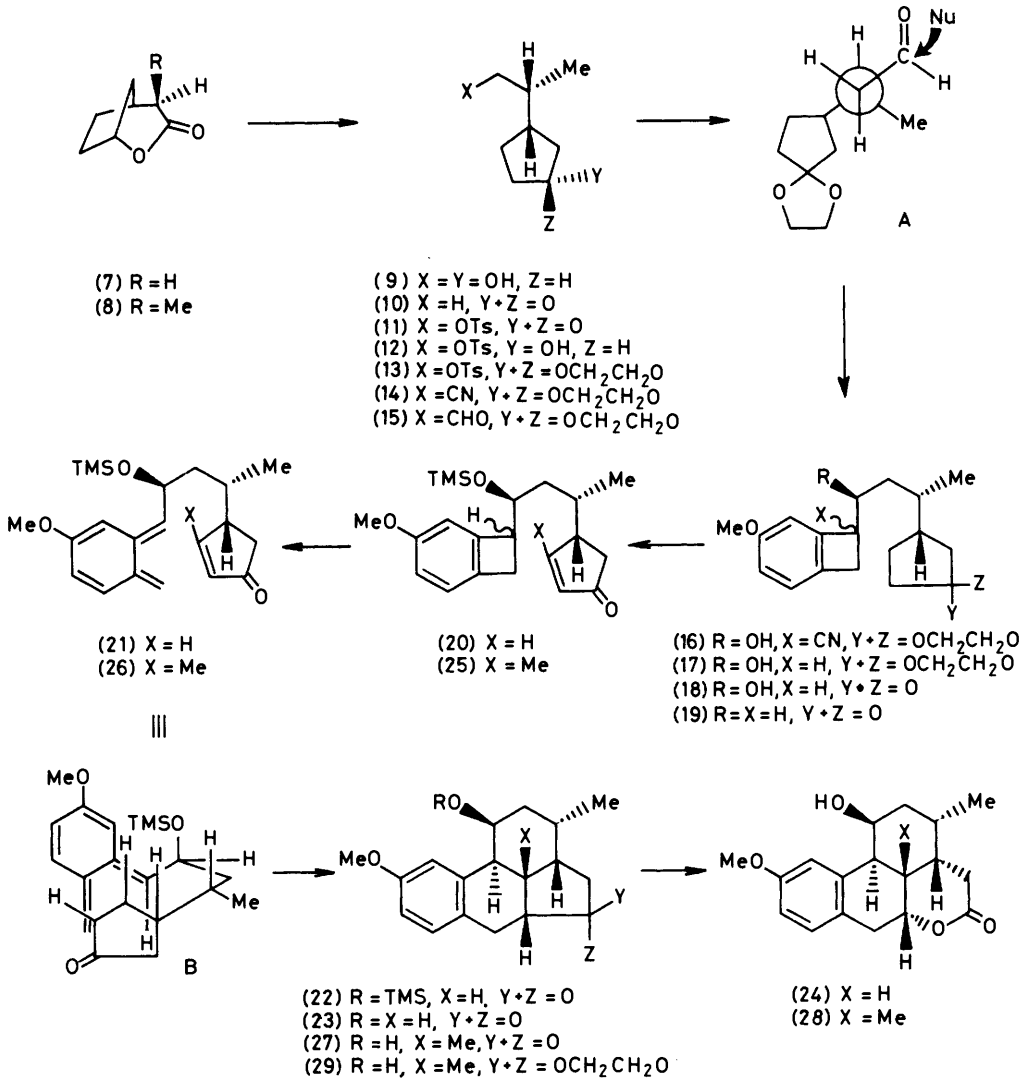
Baeyer-Villiger oxidation of the migrating tertiary carbon of (23) was achieved by the action of *m*-chloroperbenzoic acid in the presence of toluene-*p*-sulphonic acid. The stereochemistry of the resulting lactone (67.6% yield) (24), m.p. 218 °C [i.r. ($CHCl_3$) 1 720 cm^{-1}; *m/z* 302 (M^+)] was unambiguously established by a single-crystal *X*-ray analysis.* The projection of the lactone (24) including bond lengths and bond angles is shown in the Figure. It is now made clear that the relative stereochemistry at all six chiral centres of (24) is identical with that of klaineanone (1) as expected.

Thus we have demonstrated both that the intramolecular cycloaddition of the *o*-quinodimethane (21) proceeds stereoselectively to the correct array in klaineanone (1) and that a Baeyer-Villiger reaction is useful for construction of the D ring. With this knowledge, our attention was directed to the synthesis of A-aromatic 12-deoxyklaineanone (28) as follows.

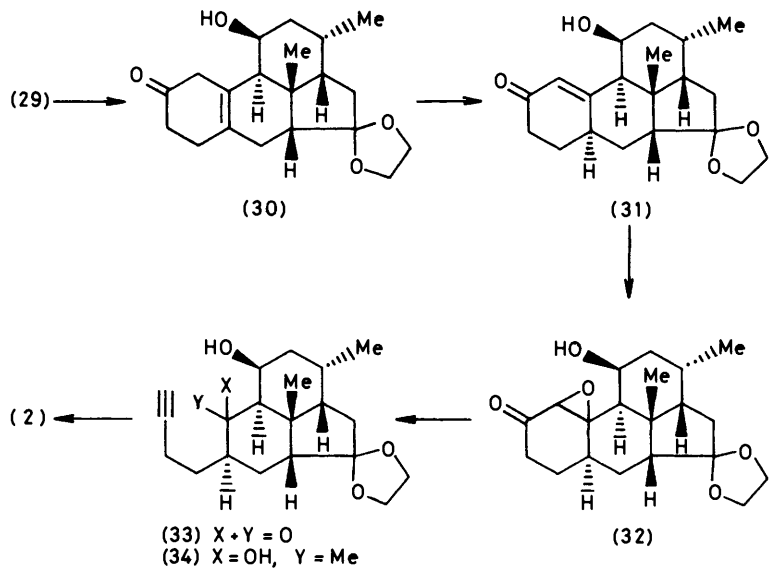
Introduction of a methyl group into the enone (20) was carried out *via* conjugate addition using dimethyl copper-lithium followed by quenching with trimethylsilyl chloride. Oxidation of this product with palladium acetate by the Saegusa method [14] afforded the methylated enone (25) [i.r. ($CHCl_3$) 1 680 cm^{-1}; *m/z* 372 (M^+); n.m.r. δ_H 2.04 (3 H, s, Me)] in 42.6% yield. Thermolysis of a solution of (25) in *o*-dichlorobenzene at 210—230 °C for 3 h and subsequent deblocking of the silyl group with 10% hydrochloric acid and tetra-n-butylammonium bromide furnished, in 57% yield, the tetracyclic ketone (27), m.p. 161 °C [i.r. ($CHCl_3$) 1 740 cm^{-1}; *m/z* 300 (M^+): n.m.r. δ_H 1.12 (3 H, s, Me)] *via* the *o*-quinodimethane (26), which was converted into the desired A-aromatic klaineanone (28), m.p. 114 °C [i.r. ($CHCl_3$) 1 725 cm^{-1}; *m/z* 316 (M^+)] by Baeyer-Villiger reaction under the previously described conditions.

Finally, our attention focussed on the conversion of the aromatic ring into the cyclohexanone system having a methyl group. This transformation has been achieved stereoselectively by a method we developed in the synthesis of hibaol.[17] Treatment of the tetracyclic ketone (27) with ethylene glycol and toluene-*p*-sulphonic acid gave the acetal (29), which was subjected to a Birch reduction with lithium in liquid ammonia in the presence of t-butyl alcohol, followed by treatment with pyridinium toluene-*p*-sulphonate to afford the β,γ-unsaturated ketone (30)] [i.r. ($CHCl_3$) 1 710 cm^{-1}] in 58.2% overall yield. The conversion of this into the corresponding α,β-unsaturated ketone (31) [i.r. ($CHCl_3$) 1 670 cm^{-1}] was achieved by a reaction of (30) with pyridinium toluene-*p*-sulphonate in refluxing benzene in 80% yield. Oxidation of the enone (31) with hydrogen peroxide in the presence of sodium hydroxide at 50—60 °C gave, in 51% yield, the epoxide (32) which was treated with tosylhydrazide in acetic acid at −40 °C to afford

* Orthorhombic, space group $Pna2_1$ with a = 20.511(2), b = 5.153(1), c = 14.332(2) Å; D_c = 1.326 g/cm³ for Z = 4. Final R value was 0.045 for 1 168 observed reflections.



Scheme 2.



Scheme 3.

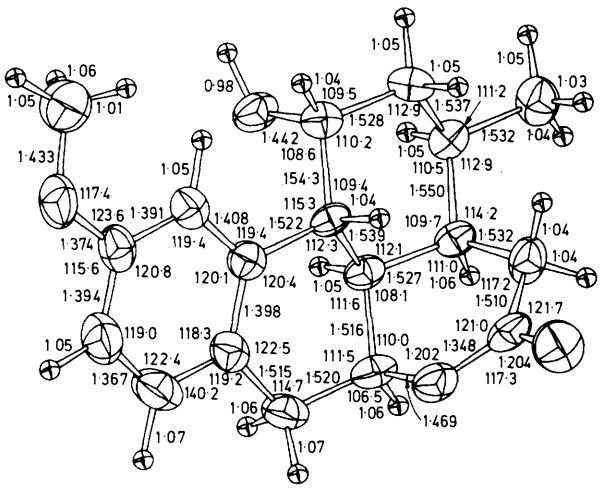


Figure. Projection of the lactone (24) including bond lengths and bond angles

the acetylenic ketone (33) [i.r. ($CHCl_3$) 3 320, 2 130, and 1 700 cm^{-1}; *m/z* 332 (M^+)]. Reaction of (33) with methyl-lithium in ether at 0 °C yielded the methylated acetylenic alcohol (34) (71.8%) [*m/z* 348 (M^+)] which was successively treated with trifluoroacetic anhydride and trifluoroacetic acid at 60 °C and then 10% aqueous potassium hydroxide at room temperature to furnish the target compound (2) [i.r. ($CHCl_3$) 1 730 and 1 700 cm^{-1}; *m/z* 304 (M^+); n.m.r. δ_H 0.91 (3 H, d, *J* 7 Hz, 3-Me), 1.07 (3 H, d, *J* 1 Hz, 10aβ-Me), 1.26 (3 H, s, 10cβ-Me), and 4.24 (1 H, m, 1α-H)]. The stereochemical assignment of (2) was based on an appearance of a 10a-methyl resonance as a doublet having *J* 1 Hz; this fact indicates that this methyl group possesses three anti-coplanar protons.[18]

Thus we have developed a new and stereoselective method for the construction of the quassinoid ring system, a route which has considerable potential for the synthesis of quassinoid terpenes.

Experimental

General Methods.—M.p.s are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured on a JEOL JNM-PMX-60 spectrometer and JEOL PS 100 spectrometer. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M-52G spectrometer and JEOL-TMS-O1SG-2 spectrometer. All new compounds described in Experimental section were homogenous on t.l.c.

4-*Methyl*-2-*oxabicyclo*[3.2.1]*octan*-3-*one* (8).—To a stirred solution of lithium di-isopropylamide [from di-isopropylamine (97.5 g, 0.97 mol) and n-butyl-lithium (62 g, 0.97 mol) in anhydrous tetrahydrofuran (1 l) was added the lactone (7) (116.1 g, 0.92 mol) in anhydrous tetrahydrofuran (200 ml) at −78 °C. After the mixture had been stirred for 1.5 h at the same temperature, methyl iodide (137.5 g, 0.97 mol) was added to it and the whole stirred first for 1 h at −78 °C and then for 1 h at room temperature. The reaction mixture was then treated with a small amount of water and, after evaporation of most of the solvent, the residue was extracted with methylene chloride. The organic layer was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of solvent under reduced pressure and subsequent distillation afforded the *lactone* (8) (112.3 g, 87.2%) as an oil, b.p. 149—151 °C (20 mmHg) (Found: C, 68.8; H, 8.85. $C_8H_{12}O_2$ requires C, 68.55; H, 8.65%), $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, d, *J* 7 Hz, Me), and 4.70 (1 H, m, CH-O); *m/z* 140 (M^+).

2-(3-*Hydroxycyclopentyl*)*propan*-1-*ol* (9).—To a suspension of lithium aluminium hydride (81 g, 2.13 mol) in anhydrous tetrahydrofuran (3 l) was added the lactone (8) (330 g, 2.36 mmol) in anhydrous tetrahydrofuran (200 ml) and the resulting mixture was stirred for 1 h at 0 °C. After the reaction mixture had been quenched with 15% aqueous sodium hydroxide (80 ml), the solution was decanted and the remaining suspension was filtered through Celite and washed twice with ether. Removal of the combined organic layer under reduced pressure and subsequent distillation afforded the *diol* (9) (280 g, 82.5%) as a viscous syrup, b.p. 125—130 °C (1 mmHg) (Found: C, 66.6; H, 11.05. $C_8H_{16}O_2$ requires C, 66.65; H, 11.2%), $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH); δ_H (60 MHz; $CDCl_3$) 0.97 (3 H, d, *J* 7 Hz, Me), 2.17 (2 H, s, OH), 3.40—3.67 (2 H, m, CH_2OH), and 4.20—4.43 (1 H, m, *CH*OH); *m/z* 144 (M^+).

2-(3-*Oxocyclopentyl*)*propyl Toluene*-p-*sulphonate* (11).—*Method A.* To a solution of the diol (9) (40 g, 278 mmol) in 30% aqueous acetonitrile (400 ml) were added crystalline sodium bromate (42 g, 278 mmol) and ceric ammonium nitrate (9.6 g, 18 mmol). After being stirred for 48 h at room temperature, the reaction mixture was extracted thrice with ether (300 ml) and the extract dried (Na_2SO_4). Evaporation of the solvent afforded the crude unstable hydroxy ketone (10) (38 g) which was used for the next reaction without further purification. A mixture of the crude product (10) (38 g), pyridine (52 ml, 643 mmol) toluene-*p*-sulphonyl chloride (60 g, 315 mmol) and methylene chloride (300 ml) was stirred for 40 h at room temperature. The reaction mixture was washed with saturated aqueous potassium hydrogensulphate and saturated aqueous sodium chloride and then dried (Na_2SO_4). Evaporation of the solvent afforded a crude product which was recrystallised from ethanol to give the *tosylate* (11) (78 g, 95%) as needles, m.p. 60—61 °C (Found: C, 60.7; H, 6.9. $C_{15}H_{20}O_4S$ requires C, 60.8; H, 6.8%), $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 1.00 (3 H, d, *J* 7 Hz, Me), 2.58 (3 H, s, Me), 3.90 (2 H, d, *J* 5 Hz, CH_2-OTs), 7.30 (2 H, d, *J* Hz, ArH), and 7.70 (2 H, d, *J* 8 Hz, ArH); *m/z* 296 (M^+).

Method B. A mixture of the diol (9) (160 mg, 1.1 mmol), toluene-*p*-sulphonyl chloride (210 mg, 1.1 mmol) and pyridine (1.5 ml) was stirred for 45 min at room temperature. After addition of chloroform (30 ml), the organic layer was washed with saturated aqueous potassium hydrogensulphate and saturated aqueous sodium chloride and then dried (Na_2SO_4). Removal of the solvent gave a yellow oil which was chromatographed on silica gel using benzene–acetone (20 : 1, v/v) as an eluant to give the *tosylate* (12) (170 mg, 51.4%) as a syrup (Found: C, 59.6; H, 7.45. $C_{15}H_{22}O_4S$ requires C, 60.4; H, 7.45%); δ_H (60 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6 Hz, Me), 2.47 (3 H, s, ArMe) 7.43 (2 H, d, *J* 8 Hz, ArH), and 7.86 (2 H, d, *J* 8 Hz, ArH). To a solution of the tosylate (12) (2.7 g, 9.1 mmol) in acetone (80 ml) was added 4M-solution of chromic acid (10 ml) [prepared from chromium trioxide (2.7 g), concentrated sulphuric acid (2.3 ml), and enough water to make the total volume of 10 ml as a solution] at 0 °C and stirring was continued for 2 h at room temperature. Solid sodium hydrogensulphite was added to this reaction mixture until it showed a pale blue colour. The separated substances were removed by decantation and the resulting solution was washed with saturated aqueous potassium carbonate and dried (K_2CO_3). Evaporation of the solvent gave a solid which was recrystallised from ethanol to give the ketone (11) (2 g, 74.4%) as needles, m.p.

60—61 °C, which was identical with the sample prepared by method A.

3-[3,3-(1,2-*Ethylenedioxy*)*cyclopentyl*]*butyronitrile* (14).—To a solution of the tosylate (11) (136 g, 459 mmol) in benzene (1 l) were added a catalytic amount of toluene-*p*-sulphonic acid and ethylene glycol (42.3 g, 682 mmol). The mixture was refluxed in a flask fitted with a Dean-Stark trap for 3 h to remove water, and cooled. The benzene layer was washed with saturated aqueous sodium carbonate and dried (Na_2SO_4). Removal of the solvent afforded the crude compound (13), which was used in the next reaction without purification. A solution of the crude compound (13), potassium cyanide (38 g, 584 mmol), and dimethylformamide (1.2 l) was stirred for 12 h at 70 °C. After removal of the solvent under reduced pressure, the residue was extracted with benzene and the extract washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation of the solvent and subsequent distillation afforded the *nitrile* (14) (66.6 g, 74.2%) as an oil, b.p. 115—117 °C (0.5 mmHg) (Found: C, 67.2; H, 8.85; N, 7.15. $C_{11}H_{17}NO_2$ requires C, 67.65; H, 8.8; N, 7.15%), $\nu_{max.}$ ($CHCl_3$) 2 220 cm^{-1} (CN); δ_H (60 MHz; $CDCl_3$) 1.10 (3 H, d, *J* 7 Hz, Me), and 3.87 (4 H, s, OCH_2CH_2O); *m/z* 195 (M^+).

3-[3,3-(1,2-*Ethylenedioxy*)*cyclopentyl*]*butyraldehyde* (15).—To a stirred solution of the nitrile (14) (26.2 g, 134 mmol) in toluene (200 ml) was added dropwise di-isobutylaluminium hydride (28.7 g, 202 mmol) at −78 °C. After 1 h, the reaction temperature was raised to room temperature and treated with water (40 ml). The solution was then decanted and the remaining suspension filtered off through glass filter and washed twice with benzene. The combined filtrates were washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Careful removal of the solvent afforded a crude adduct which was chromatographed on silica gel using benzene–ethyl acetate (19 : 1, v/v) to give the unstable aldehyde (15) (21.3 g, 80.3%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1} (CHO); δ_H (60 MHz; $CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, Me), 3.87 (4 H, s, OCH_2CH_2O), and 9.73 (1 H, t, *J* 2 Hz, CHO); *m/z* 198 (M^+).

3-[(4-*Hydroxy*-4-(5-*methoxybenzocyclobutenyl*)*butan*-2-*yl*]-*cyclopentan*-1-*one* (18).—*Method A*. To a stirred solution of sodium amide [from sodium (1.3 g, 56.5 mg-atom)] and 1-cyano-5-methoxybenzocyclobutene (5) (7.1 g, 44.4 mmol) in liquid ammonia (100 ml), and anhydrous tetrahydrofuran (20 ml) was added the aldehyde (15) (8.8 g, 44.4 mmol) in anhydrous tetrahydrofuran (50 ml) at −78 °C. After being stirred for 0.5 h at the same temperature, the reaction mixture was treated with an excess of solid ammonium chloride and the solvent evaporated. The residue was diluted with saturated aqueous ammonium chloride (100 ml), and the resulting mixture extracted three times with methylene chloride. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded a reddish gum which was subjected to silica-gel column chromatography. Elution with benzene–ethyl acetate (9 : 1, v/v) gave the *cyano alcohol* (16) (7 g) as an oil (Found: C, 70.35; H, 7.95; N, 4.05. $C_{21}H_{27}NO_4$ requires C, 70.55; H, 7.6; N, 3.9%), $\nu_{max.}$ ($CHCl_3$) 3 575 (OH) and 2 230 cm^{-1} (CN); δ_H (60 MHz; $CDCl_3$) 0.77—1.10 (3 H, m, Me), 3.78 (3 H, s, OMe), and 3.88 (4 H, s, OCH_2CH_2O); *m/z* 357 (M^+).

To a solution of sodium (2.3 g, 100 mg-atom) in liquid ammonia (250 ml) was added a solution of (16) (17.7 g, 49.6 mmol) in anhydrous tetrahydrofuran (100 ml) at −78 °C. After being stirred for 0.5 h at −78 °C, the reaction mixture was quenched with an excess of crystalline ammonium chloride, and the solvent removed by evaporation. The resulting residue was extracted three times with methylene chloride. This extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation of the solvent left (17) as a residue, and this was dissolved in methanol (50 ml) and 3% hydrochloric acid (5 ml). The mixture was stirred for 2 h at room temperature and then basified with saturated aqueous sodium hydrogencarbonate. After evaporation of methanol at 50 °C under reduced pressure, the residue was extracted with methylene chloride, and the extract washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent by distillation gave a viscous syrup which was chromatographed on silica gel. Elution with benzene–ethyl acetate (9 : 1, v/v) gave the *hydroxy ketone* (18) (8.1 g, 56.7%) as a yellow oil (Found: C, 74.85; H, 8.65. $C_{18}H_{24}O_3$ requires C, 74.95; H, 8.4%), $\nu_{max.}$ ($CHCl_3$) 3 500 (OH) and 1 740 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.97 (3 H, d, *J* 6 Hz, Me), 3.70—4.00 (1 H, m, C*H*OH), 3.77 (3 H, s, OMe), and 6.60—7.20 (3 H, m, ArH); *m/z* 288 (M^+), and the *dehydroxylated ketone* (19) (24.9 g, 17.8%) as a yellow oil; δ_H (60 Mz; $CDCl_3$) 0.93 (3 H, d, *J* 6 Hz, Me), 3.77 (3 H, s, OMe), and 6.57—7.13 (3 H, m, ArH); *m/z* 272 (M^+).

Method B. The aldehyde (15) (14 g, 70.4 mmol) in anhydrous tetrahydrofuran (50 ml) was added in one portion to a stirred solution of 1-cyano-5-methoxybenzocyclobutene (5) (11.2 g, 70.4 mmol) and sodium amide [prepared from sodium (2 g, 87.0 mg-atom)] in liquid ammonia (700 ml) at −78 °C. The reaction mixture was stirred for 0.5 h. After addition of anhydrous tetrahydrofuran (250 ml), sodium (4 g, 173.9 mg-atom) was added in small portions, and the reaction mixture stirred for 0.5 h at −78 °C. The reaction mixture was treated with an excess of solid ammonium chloride and the solvent evaporated. The residue was diluted with saturated aqueous ammonium chloride, and the resulting mixture extracted thrice with methylene chloride. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded a gummy adduct (17) which was used in the next reaction without purification. To a stirred solution of compound (17) in methanol (50 ml) was added at 0 °C a 3% aqueous hydrochloric acid solution (5 ml). After the reaction mixture had been stirred for 1 h at room temperature a small amount of crystalline sodium hydrogencarbonate was added to it. Removal of most of the solvent afforded the product which was extracted with methylene chloride and washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation of the solvent afforded a gummy product which was chromatographed on silica gel with benzene–ethyl acetate (9 : 1 v/v) as eluant to give the alcohol (18) (16.2 g, 80.3%) as a yellow oil, which was identical with the sample prepared by the method A.

4-[4-(5-*Methoxybenzocyclobuten*-1-*yl*)*trimethylsilyloxy*-*butan*-2-*yl*]*cyclopent*-2-*en*-1-*one* (20).—To a stirred solution of lithium di-isopropylamide [prepared from di-isopropylamine (4.8 g, 47.4 mmol) and n-butyl-lithium (2.1 g, 32.8 mmol)] in anhydrous tetrahydrofuran (40 ml) was added slowly the keto alcohol (18) (3.3 g, 11.4 mmol) in anhydrous tetrahydrofuran (40 ml) at −78 °C. After being stirred for 0.5 h at −78 °C, a mixture of trimethylsilyl chloride (4.8 g, 44.2 mmol) and hexamethylphosphoric triamide (1.5 ml) was added in small portions to the reaction mixture and stirring was continued for 3 h at −78 °C; the temperature was then raised to 0 °C. The reaction mixture was twice washed with saturated aqueous sodium hydrogencarbonate and cold water and then dried (Na_2SO_4). After removal of solvent, the crude product was dissolved in acetonitrile (20 ml). This solution was added to a stirred solution of palladium acetate (2.23 g, 10 mmol) in acetonitrile (45 ml) and the reaction mixture was stirred for 1 h. Removal of the solvent gave a black residue which was dissolved in methylene chloride (30 ml) and filtered through

glass filter. Evaporation of the solvent afforded a crude product which was chromatographed on silica gel using benzene–ethyl acetate (19 : 1, v/v) as an eluant to give the *enone* (20) (2.21 g, 53.9%) (Found: C, 70.5; H, 8.5. $C_{21}H_{30}O_3Si$ requires C, 70.35; H, 8.45%); $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) −0.03 (9 H, s, $OSiMe_3$), 0.92 (3 H, d, *J* 7 Hz, Me), 3.80—4.60 (1 H, m, C*H*O$SiMe_3$), 3.73 (3 H, s, OMe), 6.18 (1 H, dd, *J* 2 and 6 Hz, =CHCO), and 7.66 (1 H, dd, *J* 3 and 6 Hz, C*H*=CHCO); *m/z* 385 (M^+) and a regioisomer (553 mg, 13.5%).

1α,2,3β,3aβ,4,5β,5aβ,6,10bα,10cβ-*Decahydro*-1β-*hydroxy*-9-*methoxy*-3α-*methylacephenanthrylen*-5-*one* (23).—A solution of the enone (20) (500 mg, 1.4 mmol) in *o*-dichlorobenzene (25 ml) was heated in a sealed tube for 2.5 h at 230 °C. After the mixture had been cooled to room temperature, the solvent was removed under reduced pressure and the residue chromatographed on silica gel with benzene–ethyl acetate (49 : 1, v/v) as eluant to give the tetracyclic compound (22) (405 mg, 81%) as an amorphous powder, $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.08 (9 H, s, $OSiMe_3$), 0.80 (3 H, d, *J* 7 Hz, Me), 3.68 (3 H, s, OMe), 4.61 (1 H, m, C*H*O$SiMe_3$), and 6.41—7.08 (3 H, m, ArH); *m/z* 358 (M^+).

A stirred solution of compound (22) (405 mg, 1.13 mmol) in methylene chloride–methanol (4 : 1, v/v; 10 ml) was treated at 0 °C with a 2% hydrochloric acid solution (1 ml) and then stirred for 1 h. The reaction mixture was then basified with saturated aqueous sodium hydrogencarbonate, washed with saturated aqueous sodium chloride, and dried (Na_2SO_4). Removal of the solvent afforded a yellow solid which was recrystallised from methanol to give the *hydroxy ketone* (23) (270 mg, 83.5%) as needles, m.p. 184 °C (Found: C, 75.25; H, 8.05. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.75%); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 740 cm^{-1} (C=O); δ_H (100 MHz; $CDCl_3$) 1.00 (3 H, d, *J* 7 Hz, Me), 3.77 (3 H, s, OMe), 4.66br (1 H, s, C*H*OH), 6.69 (1 H, dd, *J* 2 and 8 Hz, ArH), 6.86 (1 H, d, *J* 2 Hz, ArH), and 7.04 (1 H, d, *J* 8 Hz, ArH); *m/z* 286 (M^+).

1α,2,3β,3aβ,6aβ,7,11bα,11cβ-*Octahydro*-1β-*hydroxy*-10-*methoxy*-3α-*methyl*-4H,5H-*phenanthro*[10,1-bc]*pyran*-5-*one* (24).—A solution of the hydroxy ketone (23) (14 mg, 0.049 mmol), *m*-chloroperbenzoic acid (18.5 mg, 0.107 mmol), a catalytic amount of toluene-*p*-sulphonic acid in methylene chloride (3 ml) was stirred for 5 h at room temperature. The reaction mixture was washed with water and dried (Na_2SO_4). Removal of the solvent and subsequent purification by silica gel column chromatography afforded the lactone (24) (10 mg, 67.6%) which crystallised from methanol as needles, m.p. 218 °C; $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.90 (3 H, d, *J* 7 Hz, Me), 3.78 (3 H, s, OMe), 4.90br (2 H, s, 6a-H and 1-H); *m/z* 302 (M^+).

4-[(5-*Methoxybenzocyclobuten*-1-*yl*)*trimethylsilyloxybutan*-2-*yl*]-3-*methylcyclopent*-2-*en*-1-*one* (25).—To anhydrous ether (90 ml) containing dimethyl copperlithium [prepared from cuprous iodide (1.66 g, 8.72 mmol) and a 1.5M ethereal solution of methyl-lithium (11.65 ml, 17.48 mmol)] was added dropwise the enone (20) (2.6 g, 7.26 mmol) in anhydrous ether (110 ml). After being stirred for 0.5 h at 0 °C, a mixture of trimethylsilyl chloride (1.89 g, 17.4 mmol), hexamethylphosphoric triamide (1.4 ml), and triethylamine (3 ml) was added portionwise to the reaction mixture and stirring was continued for 2 h at room temperature. To this mixture was added ice–water (20 ml). The organic layer was washed with water (20 ml) and dried (Na_2SO_4). Evaporation of the solvent gave a yellow unstable residue which was used in the next reaction without purification. To a stirred solution of palladium acetate (800 mg, 3.6 mmol) and *p*-benzoquinone (400 mg, 3.7 mmol) in acetonitrile (80 ml) was added the above crude adduct in acetonitrile (20 ml). After further stirring for 2 h at 40—50 °C, the solvent was removed and the residue extracted twice with methylene chloride; the extract was filtered through a glass filter. Removal of the solvent afforded a black gum which was chromatographed on silica gel with benzene–ethyl acetate (47 : 3, v/v) as eluant to give the enone (25) (1.15 g, 42.6%) as a yellow syrup, $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.00 (9 H, s, $OSiMe_3$), 0.93 (3 H, d, *J* 7 Hz, Me), 2.04 (3 H, s, Me), 3.88—3.93 (1 H, m, C*H*O$SiMe_3$), 3.67 (3 H, s, OMe), and 5.90br (1 H, s, =CHC=O); *m/z* 372 (M^+).

1α,2,3β,3aβ,4,5,5aβ,6,10bα,10c-*Decahydro*-1β-*hydroxy*-3α,10cβ-*dimethyl*-9-*methoxyacephenanthrylen*-5-*one* (27).—A solution of the enone (25) (50 mg, 0.134 mmol) in *o*-dichlorobenzene (3.5 ml) was heated at 210—230 °C for 3 h in a sealed tube. After evaporation of the solvent under reduced pressure, the residue was dissolved in methylene chloride–methanol (5 : 1, v/v; 6 ml), and treated with a 2% hydrochloric acid solution (1 ml) containing a catalytic amount of tetra-n-butylammonium bromide. The mixture was refluxed for 20h. After cooling to room temperature, the reaction mixture was washed with water and dried (Na_2SO_4). Removal of the solvent afforded a solid which was chromatographed on silica gel with benzene–ethyl acetate (9 : 1, v/v) as eluant to give the *cyclized compound* (27) (23 mg, 57.2%) as needles after recrystallisation from methanol, m.p. 161 °C (Found: C, 75.7; H, 8.05. $C_{19}H_{24}O_3$ requires C, 75.95; H, 8.05%); $\nu_{max.}$ ($CHCl_3$) 3 625 (OH) and 1 740 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 1.00 (3 H, d, *J* 7 Hz, 3-Me), 1.12 (3 H, s, 10c-Me), 3.77 (3 H, s, OMe), 4.70br (1 H, s, 1-H), 6.68 (1 H, dd, *J* 2 and 8 Hz, ArH), 6.90 (1 H, d, *J* 2 Hz, ArH), and 7.05 (1 H, d, *J* 8 Hz, ArH); *m/z* 300 (M^+).

1α,2,3β,3aβ,6aβ,7,11bα,11c-*Octahydro*-1β-*hydroxy*-10-*methoxy*-3α,11cβ-*dimethyl*-4H,5H-*phenanthro*[10,1-bc]*pyran*-5-*one* (28).—A mixture of the tetracyclic compound (27) (20 mg, 0.067 mmol), *m*-chloroperbenzoic acid (25.2 mg, 0.146 mmol), and a catalytic amount of toluene-*p*-sulphonic acid in methylene chloride (3 ml) was stirred for 14 h at room temperature. After removal of the solvent the residue was chromatographed on silica gel using benzene–ethyl acetate (17 : 3, v/v) as eluant to afford the *lactone* (28) (5 mg, 23.7%) which crystallised from methanol as needles, m.p. 114 °C; $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 725 cm^{-1} (C=O); δ_H (100 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 3-Me), 1.16 (3 H, s, 11c-Me), 3.77 (3 H, s, OMe), 4.20 (1 H, dd, *J* 2 and 4 Hz, 6a-H), 4.72—4.92 (1 H, m, 1-H), 6.70 (1 H, dd, *J* 2 and 8 Hz, ArH), 6.86 (1 H, d, *J* 2 Hz, ArH), and 7.06 (1 H, d, *J* 8 Hz, ArH) (Found: M^+ *m/z*, 316.1669. $C_{19}H_{24}O_4$ requires *M*, 316.1674).

5,5-*Ethylenedioxy*-1α,2,3β,3aβ,4,5,5aβ,6,10bα,10c-*decahydro*-1β-*hydroxy*-9-*methoxy*-3α,10cβ-*dimethylacephenanthrylene* (29).—To a solution of the tetracyclic ketone (27) (200 mg, 0.667 mmol) in benzene (30 ml) was added a catalytic amount of toluene-*p*-sulphonic acid and ethylene glycol (1.1 g, 17.9 mmol). The mixture was refluxed in a flask fitted with a Dean-Stark trap for 5 h, after which it was cooled to room temperature. The benzene layer was washed with saturated aqueous sodium hydrogencarbonate and saturated aqueous sodium chloride and then dried (Na_2SO_4). Removal of the solvent afforded a crude solid which was chromatographed on silica gel with benzene–ethyl acetate (23 : 2, v/v) as eluant to give the *acetal* (29) (196 mg, 85.5%) as needles after crystallisation from methanol; m.p. 158—159 °C (Found: C, 72.65; H, 8.25. $C_{21}H_2,O_4 \cdot 0.25H_2O$ requires C, 72.3; H, 8.15%); $\nu_{max.}$

($CHCl_3$) 3 600 cm^{-1} (OH); δ_H (60 MHz; $CDCl_3$) 0.92 (3 H, d, *J* 6 Hz, 3-Me), 0.93 (3 H, s, 10-Me), 3.77 (3 H, s, OMe), 3.87 (4 H, s, OCH_2CH_2O), 4.67 (1 H, m, 1-H), and 6.53—7.17 (3 H, m, ArH); *m/z* 344 (M^+).

5,5-*Ethylenedioxy*-1α,2,3β,3aβ,4,5,5aβ,6,7,8,9,10,10bα,10c-*tetradecahydro*-1β-*hydroxy*-3α,10cβ-*dimethylacephenanthrylen*-9-*one* (30).—To a solution of lithium (36 mg, 5.1 mg-atom) in liquid ammonia (10 ml) was added at −78 °C a solution of (29) (137 mg, 0.398 mmol) in anhydrous tetrahydrofuran (5 ml), and t-butyl alcohol (5 ml). The reaction mixture was stirred for 1 h. After addition of an excess of crystalline ammonium chloride to the reaction mixture, the solvent was evaporated leaving a residue which was extracted three times with methylene chloride. The combined extracts were washed with water and dried (Na_2SO_4). After removal of the solvent, the product was dissolved in methylene chloride–water (7 : 3, v/v; 10 ml). To the resulting solution was added a catalytic amount of pyridinium toluene-*p*-sulphonate and the reaction mixture was stirred for 48 h at room temperature. The organic layer was separated from the reaction mixture and the aqueous layer was twice extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and the solvent removed by evaporation under reduced pressure. The residue was chromatographed on silica gel with benzene–ethyl acetate (17 : 3, v/v) as eluant to give the *tetradecahydrogenated compound* (30) (77 mg, 58.2%) as an unstable compound; $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 710 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 7 Hz, 3-Me), 1.17 (3 H, s, 10c-Me), 3.90br (4 H, s, OCH_2CH_2O), and 4.23 (1 H, m, 1-H).

5,5-*Ethylenedioxy*-1α,2,3β,3aβ,4,5,5aβ,6,6aα,7,8,9,10bα,10c-*tetradecahydro*-1β-*hydroxy*-3α,10cβ-*dimethylacephenanthylen*-9-*one* (31).—A mixture of the ketone (30) (75 mg, 0.226 mmol), a catalytic amount of pyridinium toluene-*p*-sulphonate, and anhydrous benzene (25 ml) was refluxed for 1 h. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate (10 ml) and water (10 ml) and then dried (Na_2SO_4). After removal of the solvent, the residue was subjected to silica gel column chromatography. Elution with benzene–ethyl acetate (17 : 3, v/v) gave the *enone* (31) (60 mg, 80%) as needles after recrystallisation from methanol, m.p. 247—248 °C (Found: C, 71.95; H, 8.55. $C_{20}H_{28}O_9$ requires C, 72.25; H, 8.5%); $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.85 (3 H, d, *J* 7 Hz, 3-Me), 1.15 (3 H, s, 10c-Me), 3.90br (4 H, s, OCH_2CH_2O), 4.25 (1 H, m, 1-H), and 6.33 (1 H, s, 10-H); *m/z* 332 (M^+).

Epoxidation of (31).—To a solution of (31) (15 mg, 0.045 mmol) in methanol (2 ml) was added three drops of 30% hydrogen peroxide and two drops of 10% sodium hydroxide solution at room temperature. After the mixture had been stirred for 3 h at 50 °C, water (5 ml) and methylene chloride (15 ml) were added and the organic layer separated and dried (Na_2SO_4). Removal of the solvent left a residue, which was chromatographed on silica gel with benzene–ethyl acetate (93 : 7, v/v) as eluant to give the *epoxide* (32) (8 mg, 50.9%), $\nu_{max.}$ ($CHCl_3$) 3 630 (OH) and 1 700 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 7 Hz, 3-Me), 1.20 (3 H, s, 10c-Me), 3.77 (1 H, m, 10-H), 3.90br (4 H, s, OCH_2CH_2O), and 4.10 (1 H, m, 1-H) (Found: M^+, *m/z* 348.1921. $C_{20}H_{28}O_5$ requires *M*, 348.1936).

7β-(*But*-3-*ynyl*)-1,1-*ethylenedioxy*-1,2,2aβ,2b,3β,4,5α,5aα,-6,7,8,8aβ-*dodecahydro*-5β-*hydroxy*-2bβ,3α-*dimethylacenaphthylen*-6-*one* (33).—A solution of the epoxide (32) (29 mg, 0.083 mmol) and toluene-*p*-sulphonylhydrazide (18.6 mg, 0.1 mmol) in acetic acid (2 ml) and methylene chloride (2 ml) was stirred for 14 h at −40 °C and for 4 h at room temperature. The reaction mixture was diluted with methylene chloride (10 ml) and then washed with saturated aqueous sodium hydrogencarbonate; the organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent left a yellow solid which was chromatographed on silica gel with benzene–ethyl acetate (47 : 3, v/v) as eluant to give the *acetylenic ketone* (33) (16 mg, 57.8%); $\nu_{max.}$ ($CHCl_3$) 3 320, 2 130 (C≡C) and 1 700 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 7 Hz, 3-Me), 1.13 (3 H, s, 2b-Me), 3.97br (4 H, s, OCH_2CH_2O), and 4.27 (1 H, m, 5-H) (Found: M^+, *m/z* 332.1990. $C_{20}H_{28}O_4$ requires *M*, 332.1988).

7β-(*But*-3-*ynyl*)-1,1-*ethylenedioxy*-1,2,2aβ,2b,3β,4,5α,5aα,-6,7,8,8aβ-*dodecahydro*-5β,6-*dihydroxy*-2bβ,3α,6-*trimethylacenaphthylene* (34).—To a solution of the acetylenic ketone (33) (16 mg, 0.048 mmol) was added a 1.5M ethereal solution of methyl-lithium (0.26 ml, 0.39 mmol) at 0 °C and the mixture was stirred for 15 min at the same temperature. Water (1.5 ml) was added slowly to this mixture, which was then extracted with an excess of ether and dried (Na_2SO_4). Removal of the solvent left a residue which was subjected to silica gel column chromatography with benzene–ethyl acetate (23 : 2, v/v) as eluant to afford the *acetylenic alcohol* (34) (12 mg, 71.8%); $\nu_{max.}$ ($CHCl_3$) 3 320 and 2 130 cm^{-1} (C≡C); δ_H (60 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 7 Hz, 3-Me), 1.33 (3 H, s, 2b-Me), 1.47 (3 H, s, 6-Me), 3.87 (4 H, m, OCH_2CH_2O), and 4.50 (1 H, m, 5-H) (Found: M^+, *m/z* 348.2333. $C_{21}H_{32}O_4$ requires *M*, 348.2301).

1α,2,3β,3aβ,4,5,5aβ,6,6aα,7,8,9,10,10a,10bα,10c-*Hexadecahydro*-1β-*hydroxy*-3α,10aβ,10cβ-*trimethylacephenanthrylene*-5,9-*dione* (2).—A mixture of the acetylenic alcohol (34) (12 mg, 0.034 mmol), trifluoroacetic acid (4 ml), and trifluoroacetic anhydride (2 ml) was refluxed for 12 h. Excess of reagent and solvent were removed under reduced pressure and the residue dissolved in methanol (3 ml); to this solution was added 2 drops of 10% aqueous potassium hydroxide. After the mixture had been stirred for 1 h at room temperature most of the solvent was removed and the residue was twice extracted with methylene chloride. The extract was washed with water (5 ml) and dried (Na_2SO_4). Evaporation of the solvent left a yellow residue which was chromatographed on silica gel with benzene–ethyl acetate (22 : 3, v/v) as eluant to give the *tetracyclic compound* (2) (4 mg, 38.2%) as a viscous syrup; $\nu_{max.}$ ($CHCl_3$) 1 730 and 1 700 cm^{-1} (C=O); δ_H (100 MHz; $CDCl_3$) 0.91 (3 H, d, *J* 7 Hz, 3-Me), 1.07 (3 H, d, *J* 1 Hz, 10a-Me), 1.26 (3 H, s, 10c-Me), and 4.24 (1 H, m, 1-H) (Found: M^+, *m/z* 304.2052. $C_{19}H_{28}O_3$ requires *M*, 304.2039).

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