A New Synthetic Approach to Bruceantin *via* an Intramolecular Diels–Alder Reaction: Stereoselective Construction of the Pentacyclic Model System[1]

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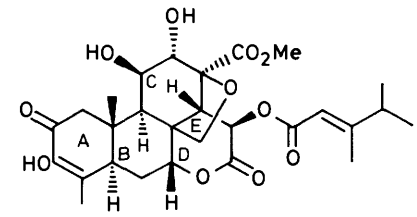
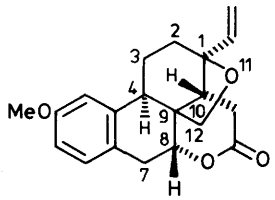
An efficient synthesis of the pentacyclic system (**2**) as a model for bruceantin (**1**) is described. The key feature of the synthesis was a stereoselective intramolecular Diels–Alder reaction of the benzocyclobutene derivatives (**15**) and (**16**), which were conveniently derived from the aldehyde (**6**) in 7 steps. The tetracyclic cycloadducts (**17**) and (**19**) were converted, *via* two separate routes, into the alcohol (**26**), which was then transformed stereoselectively to the pentacyclic lactone (**2**).

In 1973, during the course of a search for tumour inhibitors from plant sources, Kupchan *et al.*[2] disclosed the isolation of the antitumour quassinoid bruceantin from *Brucea antidysenterica*, a plant used in Ethiopia in the treatment of cancer. This compound showed significant inhibitory activity against the L-1210 lymphoid leukaemia and two solid murine tumour systems, the Lewis lung carcinoma and the B-16 melanocarcinoma. Preliminary chemical and spectroscopic studies led to the assignment of the pentacyclic structure (**1**) to this compound. Bruceantin (**1**) is a challenging synthetic target owing to the presence of ten asymmetric centres, a high degree of functionalization, and its promising antitumour activity.† Although extensive synthetic studies[3] on this quassinoid have been reported in recent years by many groups, a total synthesis has not yet been accomplished.

In connection with a possible synthetic approach to bruceantin, we became interested in the stereoselective construction of the pentacyclic model system (**2**),‡ with an aromatic A ring and five contiguous asymmetric centres on the BCDE ring juncture, since there are few efficient routes to compounds with the basic pentacyclic carbon framework of bruceantin. We herein detail our experiments in which the pentacyclic lactone (**2**), as a model for bruceantin, was successfully synthesized.



(**1**)



(**2**)

Non-systematic numbering scheme

Our initial synthetic strategy entailed the dissection of (**2**) as outlined in Scheme 1. We envisaged that the pentacyclic lactone (**2**) might be prepared from the tetracyclic ketones (**3**) and (**4**) *via* two separate routes. The ketones (**3**) and (**4**) in turn might be constructed by a stereoselective intramolecular Diels–Alder reaction[4,5] using the benzocyclobutene derivative (**5**) which, with a dihydrofuranone moiety ready to become the future E ring, should be derived from the aldehyde (**6**) by successive introduction of a vinyl group, a C_3 unit, and a dienophile.

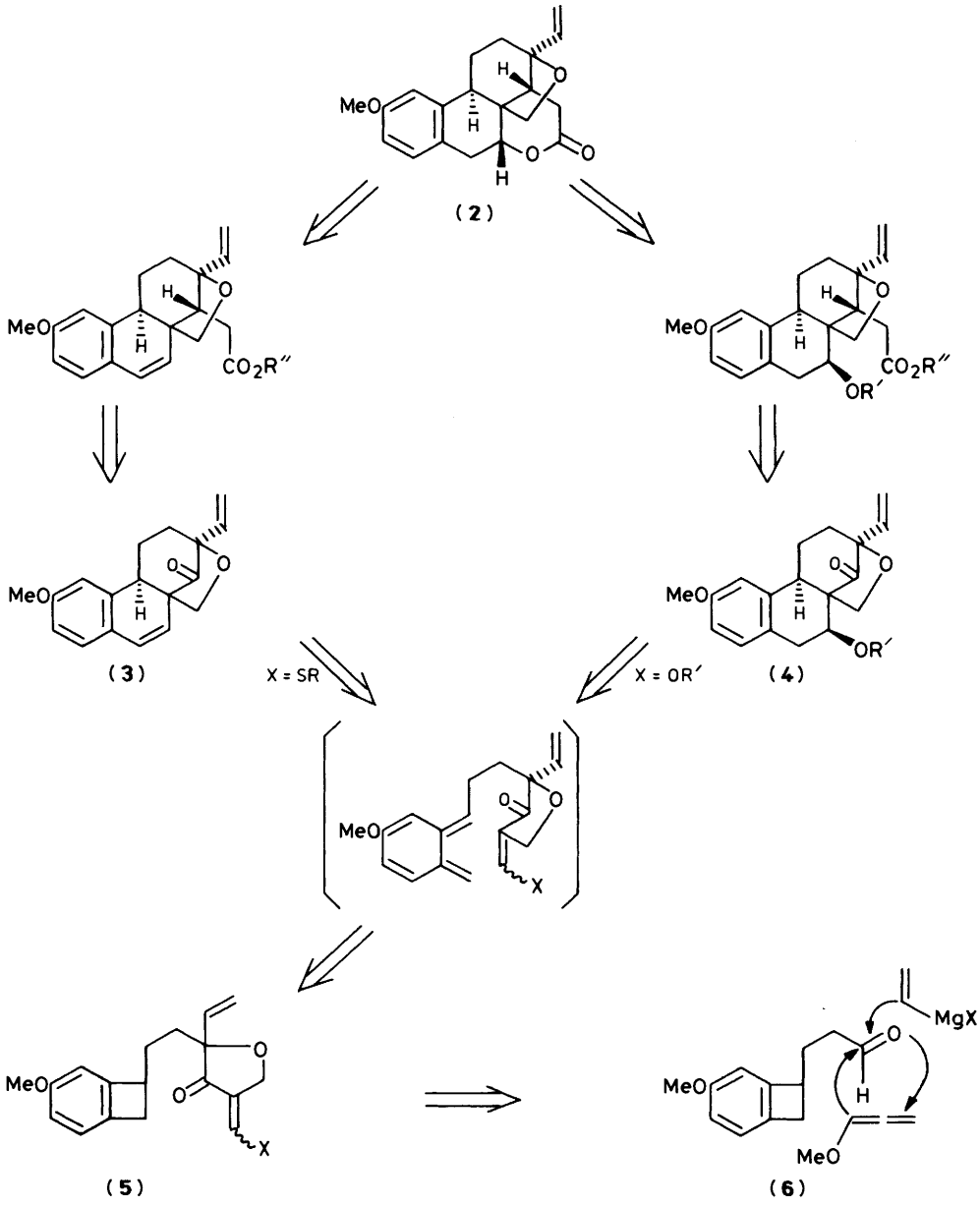
Our approach to the dihydrofuranone (**12**) began with the Grignard reaction of the aldehyde (**6**), derived from the acetal (**7**), with vinylmagnesium bromide. The resulting allylic alcohol (**8**) was oxidized with pyridinium chlorochromate to the enone (**9**) which was treated with α-lithio-α-methoxyallene, prepared *in situ* from methoxyallene[6] with n-butyl-lithium, to give the 1,2-adduct (**10**). According to Magnus' procedure,[7] the crude alcohol (**10**) was treated with potassium t-butoxide in the presence of 18-crown-6 to afford the cyclized enol ether (**11**) which was then, without isolation, hydrolysed with 6M-hydrochloric acid to the desired ketone (**12**) [$\nu_{max.}$($CHCl_3$) 1 743 cm^{-1}] in 61% yield from (**9**). Introduction of two different dienophiles to the α position to the carbonyl group in (**12**) was accomplished by the procedure described as follows. Formylation of (**12**) was effected with ethyl formate and sodium hydride as a base to yield the labile hydroxymethylene (**13**). Sequential mesylation [to give (**14**)] and substitution with thiophenol provided the vinylogous phenyl thioester (**15**)§ [$\nu_{max.}$($CHCl_3$) 1 700 cm^{-1}; δ_H 4.70 (2 H, d, *J* 2 Hz) and 7.65 (1 H, t, *J* 2 Hz); *m/z* 392 (M^+)], a substrate for thermolysis, in 87% yield. On the other hand, the other substrate (**16**)§ [$\nu_{max.}$($CHCl_3$) 1 780 and 1 733 cm^{-1}; δ_H 4.77 (2 H, d, *J* 2.5 Hz) and 8.11 (1 H, t, *J* 2.5 Hz); *m/z* 342 (M^+)], with the acetoxymethylene unit as a dienophile moiety, was prepared in 78% yield by acetylation of the hydroxymethylene (**13**). These reactions are given in Scheme 2.

Having the desired benzocyclobutenes (**15**) and (**16**) in hand, we proceeded to examine the key transformation of the synthetic sequence. On heating the thiomethylene (**15**) in *o*-dichlorobenzene at 180 °C for 15 h, the tetracyclic adduct

† A recent paper on the biological activity of (**1**) reports that preliminary results from phase-two clinical trials in humans have not been overly encouraging; see R. J. Pariza and P. L. Fuchs, *J. Org. Chem.*, 1983, **48**, 2306.

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

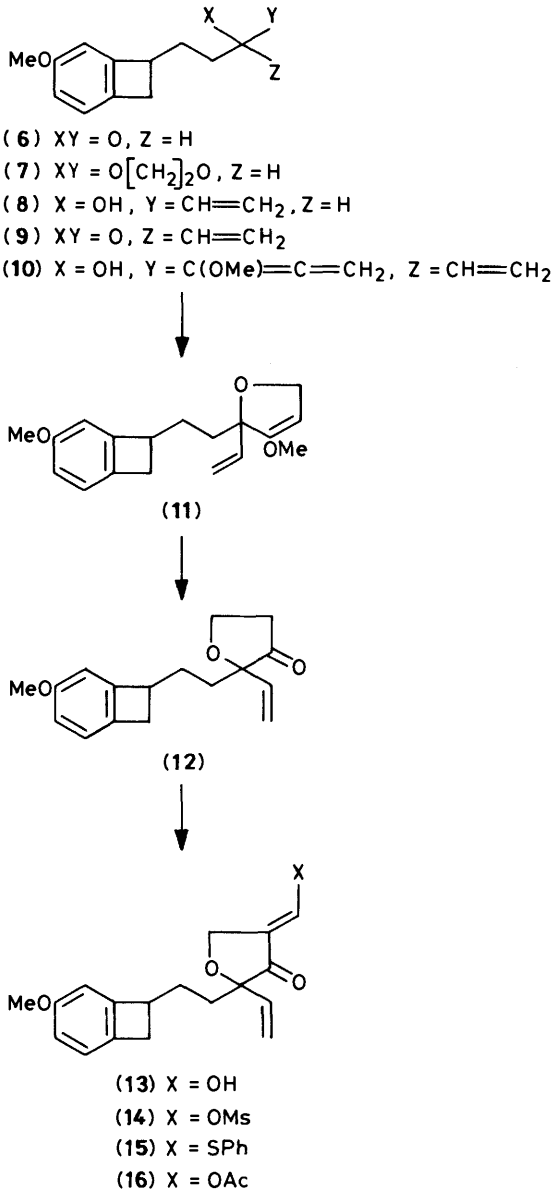
§ On the basis of the chemical shifts of the olefinic protons at the thiophenyl and the acetoxy-bearing carbon, *E* geometry for the dienophile moiety in (**15**) and (**16**) was assigned; *cf.* S. Danishefsky, J. Morris, G. Mullen, and R. Gammill, *J. Am. Chem. Soc.*, 1982, **104**, 7591.



Scheme 1.

[$\nu_{max.}$(CHCl$_3$) 1 755 cm^{-1}; *m/z* 392 (M^+)] was obtained in 89% yield as an inseparable diastereoisomeric mixture of (**17**) and (**18**). The mixture of the adducts was then submitted to the oxidation–elimination sequence to give a 6.7:1 mixture of the olefins (**3**) and (**21**), readily separable by chromatography, in 66.7% yield. Examination of the transition state during the thermolysis reveals that a non-bonding interaction develops between one of the methylene protons and an olefinic proton on the quinodimethane ring in the *endo* transition state $(\mathbf{T}_2)^{\ddagger}$, whereas this type of interaction is absent altogether in the *exo* transition state $(\mathbf{T}_1)^{\ddagger}$ (Scheme 3). From this consideration, the major isomer, generated from the *exo*-conformer, was tentatively assigned as (**17**) with the desired stereochemistry at C-1, -4, and -9 (non-systematic numbering scheme). The configuration at C-4 in (**17**) was supported on the basis of a higher field shift, owing to an anisotropy of the newly formed double bond at C-7, and the W-type long-range coupling (with 4-H) of the *exo*-proton at C-12 at δ_H 3.70 as a double doublet with *J* 1 and 8 Hz in the ^{1}H n.m.r. spectrum of (**3**).

For the acetoxymethylene (**16**), the thermolysis similarly gave the cycloadduct as an inseparable diastereoisomeric mixture of (**19**) and (**20**) in 74.5% yield. Subsequent hydrolysis of the mixture provided the alcohols (**27**) and (**28**) in the ratio 6:1, which were easily separated by chromatography. The expected stereochemistry of the major isomer was deduced from the n.m.r. spectrum of the acetate (**29**) [which also showed $\nu_{max.}$(CHCl$_3$) 1 765 and 1 735 cm^{-1}; *m/z* 342 (M^+)], derived from acetylation of (**27**), in which the *exo*-proton at C-12 was observed at δ_H 4.32 as a double doublet with *J* 1 and 8 Hz due to a W-type long-range coupling with 4-H. On the other hand, that proton of the minor acetate (**30**) [which also showed $\nu_{max.}$(CHCl$_3$) 1 765 and 1 735 cm^{-1}; *m/z* 342 (M^+)] showed no long-range coupling with 4-H indicating that (**28**) would be the C-4 epimer of (**27**). Concerning the configuration at C-8 in (**29**), the acetoxy group could be considered as being β-orientated from the n.m.r. spectral signal of 8-H at δ_H 5.37 as a double doublet with *J* 6 and 11 Hz in the hydrogenated acetate (**32**) prepared by catalytic hydrogenation of (**29**). The



(6) XY = O, Z = H
(7) XY = O[CH_2]$_2$O, Z = H
(8) X = OH, Y = CH=CH_2, Z = H
(9) XY = O, Z = CH=CH_2
(10) X = OH, Y = C(OMe)=C=CH_2, Z = CH=CH_2

Scheme 2.

stereoselective introduction of the C_2 unit, necessary to construct the D ring, to C-10 in (**3**) and (**27**) could be achieved in excellent yield. Thus, Emmons–Horner reaction of (**3**) and (**27**) with triethyl phosphonoacetate in the presence of sodium hydride gave an inseparable *E,Z* mixture of the α,β-unsaturated esters (**22**) [$\nu_{max.}$($CHCl_3$) 1 710 cm^{-1}; *m/z* 352 (M^+)] and (**31**) [$\nu_{max.}$($CHCl_3$) 3 400 and 1 712 cm^{-1}; *m/z* 370 (M^+)] in 90 and 91% yield, respectively. The successful selective reduction of a conjugate double bond in the presence of isolated olefins was carried out employing sodium hydrotelluride[8] as a reducing agent. Reaction of (**22**) and (**31**) with sodium hydrotelluride, prepared *in situ* from tellurium powder with sodium borohydride in ethanol, gave the reduced products (**23**) [$\nu_{max.}$($CHCl_3$) 1 720 cm^{-1}; *m/z* 354 (M^+)] and (**26**) [$\nu_{max.}$($CHCl_3$) 3 455 and 1 720 cm^{-1}; *m/z* 372 (M^+)], each as a single compound, in 92 and 84% yield, respectively. The remarkable stereoselectivity in the reduction might be attributed to attack from the β-face in (**22**) and (**31**). At this point, a series of experiments on the carboxylic acid prepared by a saponification of (**23**) was conducted in an attempt to lactonize selectively at one of the two olefin functions; however, no satisfactory result was obtained even under various conditions for the lactonization. Accordingly, the diene (**23**) was selectively converted into the monoepoxide (**24**) which was then submitted to acid-catalysed rearrangement with boron trifluoride–diethyl ether to yield the keto ester (**25**) [$\nu_{max.}$($CHCl_3$) 1 720 cm^{-1}; *m/z* 370 (M^+)] as a single product in 54% yield from (**23**). Reduction of (**25**) with sodium borohydride afforded a single alcohol which was identical with the alcohol (**26**) prepared above. The stereoselective reduction of the C-8 carbonyl group might be explainable in terms of ethoxycarbonyl-directed hydride transfer from the α-face in (**25**). These reaction are set out in Scheme 4.

To set the stage for assembling the δ-lactone with S_N2 inversion at C-8, it was necessary to activate the hydroxy group at C-8 in the hydroxy acid * (**33**) [$\nu_{max.}$($CHCl_3$) 3 400 and 1 700 cm^{-1}; *m/z* 344 (M^+)], derived from (**26**). After several ineffective trials, treatment of the hydroxy acid (**33**) with an excess of methanesulphonyl chloride in the presence of triethylamine gave the dimesylate[9] which was then selectively hydrolysed with an aqueous solution of sodium hydrogen carbonate followed by acidification to afford the expected pentacyclic lactone (**2**) in 70.9% yield. Examination of the ^1H n.m.r. spectrum of (**2**) at 400 MHz revealed the methine proton of 8-H as a doublet with *J* 4 Hz at δ_H 4.63 which was indicative of the desired configuration at C-8, and the *exo*-proton at C-12 as a double doublet with *J* 1.5 and 8 Hz, long-range-coupled with 4-H, at δ_H 3.59. Furthermore, the ^{13}C n.m.r. spectrum showed the lactone carbonyl carbon at δ_C 169.725 p.p.m. and the i.r. spectrum exhibited a lactone carbonyl absorption at 1 725 cm^{-1}. Finally, the whole structure and the stereochemistry of (**2**) were unambiguously established by a single-crystal *X*-ray analysis (Figure).† Thus we have developed an efficient and stereoselective route for constructing the pentacyclic system as a model for bruceantin; this methodology should provide a basis for the total synthesis of the antitumour quassinoid bruceantin.

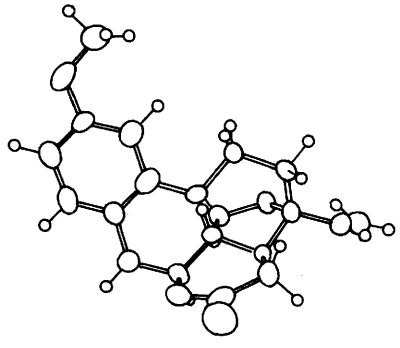


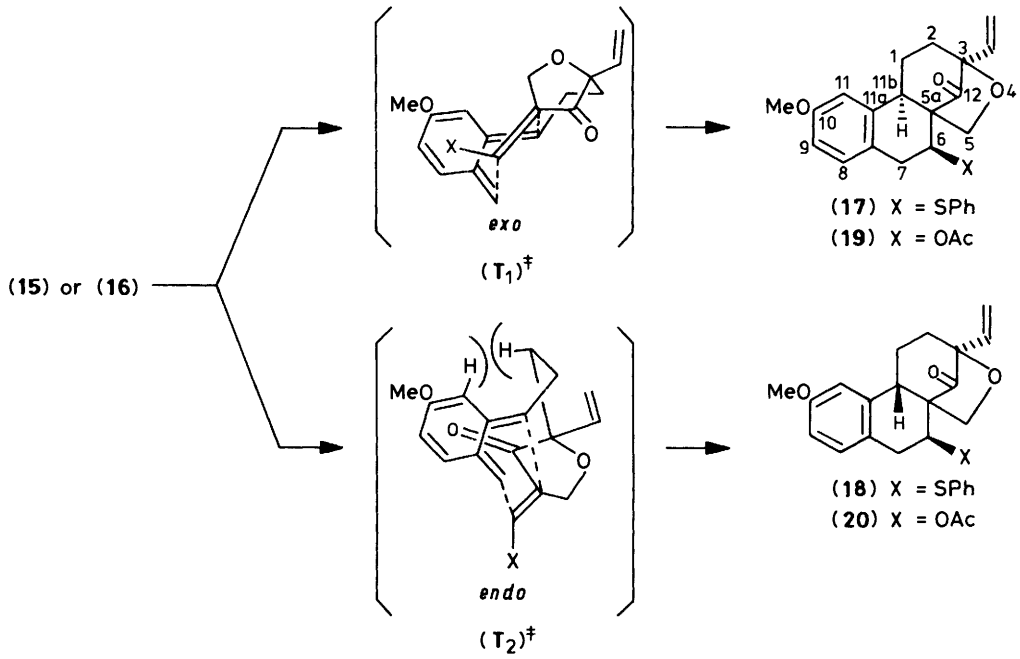
Figure. Projection drawing of the lactone (**2**)

Experimental

General Methods.—M.p.s were determined on a Yanagimoto MP-22 apparatus and 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, JEOL PS-100, and JEOL JNM-GX-400 spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Mass spectra

* At this point, the examinations of the standard acid-catalysed lactonization of (**33**) showed only recovery of starting material. This fact supported the β-orientation of the hydroxy group at C-8.

† Monoclinic, space group $P2_1/a$ with a = 11.440(2), b = 13.537(2), c = 10.491(3) Å; β = 90.47(3)°; D_c = 1.33 g/cm^3 for Z = 4. Final R value was 0.095.



Scheme 3. Systematic numbering shown for tetracycles

were taken on a Hitachi M-52G spectrometer and JEOL-TMS-01SG-2 spectrometer. All reactions were carried out under dry argon. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. All new compounds described in this Experimental section were homogeneous on t.l.c.

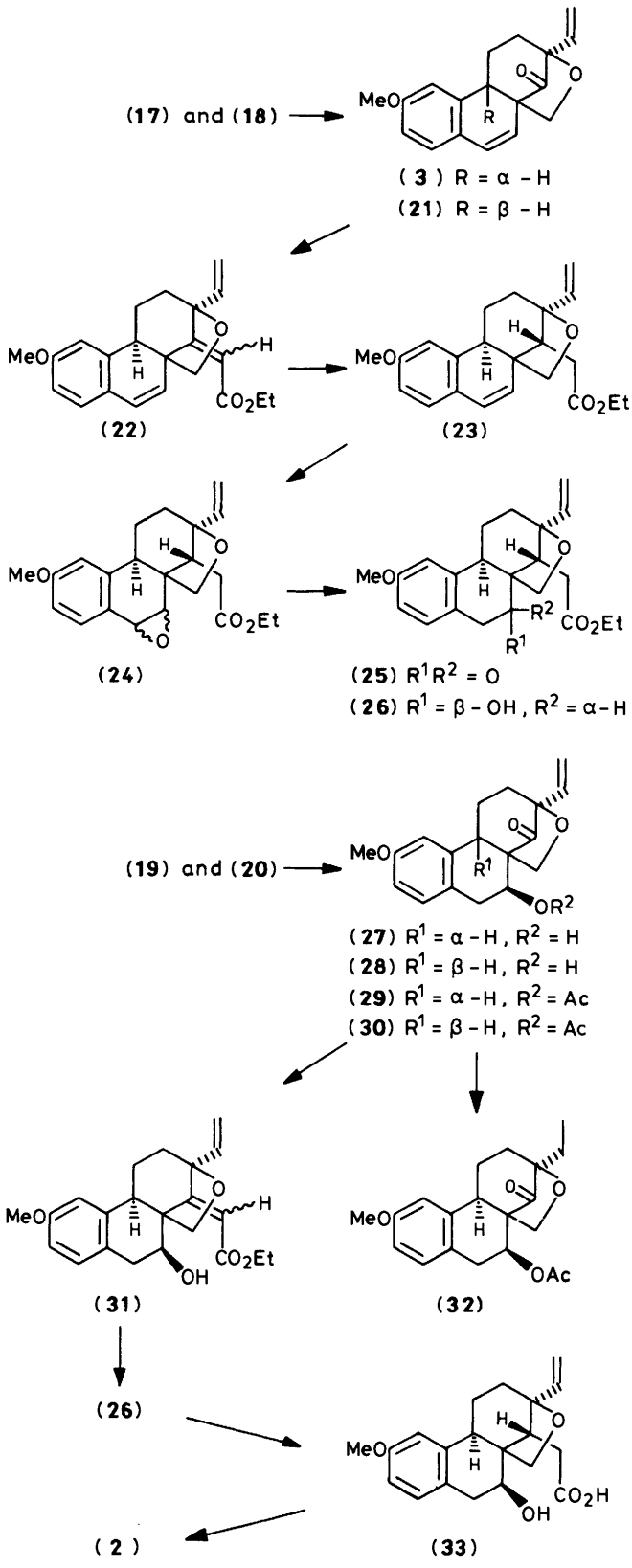
3-(1,2-*Dihydro*-5-*methoxybenzocyclobutenyl*)*propanal Ethylene Acetal* (**7**).—To a stirred solution of sodium amide [from sodium (1.73 g, 75.2 mg-atom)] and 1-cyano-1,2-dihydro-5-methoxybenzocyclobutene[10] (10 g, 62.9 mmol) in liquid ammonia (500 ml) and anhydrous tetrahydrofuran (THF) (10 ml) was added a solution of 3,3-ethylenedioxypropyl bromide[11] (11.4 g, 63.0 mmol) in anhydrous THF (20 ml) at −33 °C, and the reaction mixture was stirred for 3 h. After addition of anhydrous THF (3 ml) and anhydrous ethanol (3 ml), sodium (2.89 g, 125.7 mg-atom) was added in small portions at −78 °C and the reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was then treated with an excess of ethanol and the solvent was evaporated. The residue was diluted with water (100 ml) and the resulting mixture was extracted with chloroform. The extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using benzene-ethyl acetate (99:1, v/v) to give the *acetal* (**7**) (12.6 g, 85%) as an oil (Found: C, 71.95; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.75; H, 7.75%); δ_H (60 MHz; $CDCl_3$) 3.76 (3 H, s, OMe), 3.90 (4 H, br s, OCH_2CH_2O), 4.90 (1 H, m, 1-H), and 6.60—7.10 (3 H, m, ArH); *m/z* 234 (M^+).

3-(1,2-*Dihydro*-5-*methoxybenzocyclobutenyl*)*propanol* (**6**).—A solution of the acetal (**7**) (7.0 g, 29.9 mmol) in acetic acid (3 ml) and water (3 ml) was stirred for 16 h at room temperature. The reaction mixture was diluted with saturated aqueous sodium chloride (3 ml) and extracted with benzene. The extract was washed successively with water and saturated aqueous sodium hydrogen carbonate. The residue upon work-up was chromatographed using benzene–ethyl acetate (99:1, v/v) to give the *aldehyde* (**6**) (5.6 g, 97.7%) as an oil (Found: C, 75.75; H, 7.65. $C_{12}H_{14}O_2$ requires C, 75.75; H, 7.4%); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.67 (3 H, s, OMe), 6.40—6.90 (3 H, m, ArH), and 9.60 (1 H, br s, CHO); *m/z* 190 (M^+).

5-(1,2-*Dihydro*-5-*methoxybenzocyclobutenyl*)-3-*hydroxypent*-1-*ene* (**8**).—To a stirred solution of vinylmagnesium bromide [from magnesium (2.56 g, 105.3 mg-atom) and vinyl bromide (9.38 g, 87.7 mmol)] in anhydrous THF (100 ml) was added a solution of the aldehyde (**6**) (5.56 g, 29.2 mmol) in anhydrous THF (20 ml) at room temperature, and the resulting mixture was stirred for 4 h at the same temperature. After addition of saturated aqueous ammonium chloride (20 ml), the mixture was filtered through Celite and the filtrate was extracted with benzene. The extract was washed successively with water and saturated aqueous sodium chloride. The residue upon work-up was chromatographed using benzene–ethyl acetate (19:1, v/v) to afford the *alcohol* (**8**) (5.35 g, 83.8%) as an oil (Found: C, 76.8; H, 8.6. $C_{14}H_{18}O_2$ requires C, 77.05; H, 8.3%); $\nu_{max.}$($CHCl_3$) 3 450 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.59 (1 H, s, OH, D_2O exchangeable), 1.50—2.00 (4 H, m, CH_2CH_2), 3.73 (3 H, s, OMe), 4.13 (1 H, br s, C*H*OH), 5.00—5.40 (2 H, m, $=CH_2$), and 5.76 (1 H, dd, *J* 6 and 10 Hz, C*H*=CH_2); *m/z* 218 (M^+).

5-(1,2-*Dihydro*-5-*methoxybenzocyclobutenyl*)*pent*-1-*en*-3-*one* (**9**).—To a stirred solution of pyridinium chlorochromate (10.48 g, 48.6 mmol) in anhydrous methylene dichloride (100 ml) was added a solution of the alcohol (**8**) (5.3 g, 24.3 mmol) in anhydrous methylene dichloride (50 ml) at room temperature and the mixture was stirred for 2 h. After addition of Florisil (10 g), the mixture was diluted with anhydrous ether (100 ml) and filtered through Celite. The filtrate was washed successively with water and saturated aqueous sodium hydrogen carbonate. The residue upon work-up was chromatographed using benzene–ethyl acetate (19:1, v/v) to afford the *enone* (**9**) (3.3 g, 62%) as an oil (Found: C, 78.05; H, 7.55. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.45%); $\nu_{max.}$($CHCl_3$) 1 672 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.75 (3 H, s, OMe), 5.67—6.50 (3 H, m, CH=CH_2), and 6.50—7.10 (3 H, m, ArH); *m/z* 216 (M^+).

2-[2-(1,2-*Dihydro*-5-*methoxybenzocyclobutenyl*)*ethyl*]-2-*ethenyl*-2,3,4,5-*tetrahydrofuran*-3-*one* (**12**).—To a stirred solu-



Scheme 4.

tion of n-butyl-lithium (1.56M n-hexane solution; 107 ml, 166.9 mmol) in anhydrous THF (207 ml) was added methoxyallene[6] (9.7 g, 138.6 mmol) at −78 °C and the mixture was stirred for 1 h at the same temperature. A solution of the enone (**9**) (10 g, 46.3 mmol) in anhydrous THF (20 ml) was then added to the reaction mixture and the mixture was stirred for 2 h at −78 °C. After being quenched with saturated aqueous ammonium chloride (10 ml), the mixture was extracted with methylene dichloride and the extract was washed with water. The residue upon work-up gave the alcohol (**10**) (13.24 g) as a yellow oil, which was used in the next reaction without further purification.

A solution of the crude alcohol (**10**) (13.24 g) in anhydrous t-butyl alcohol (100 ml) was treated with potassium t-butoxide (26 g, 231.7 mmol) in the presence of 18-crown-6 (1 g, 3.8 mmol) and the resulting mixture was heated under reflux for 2 h. After addition of 6M-hydrochloric acid (80 ml) to the ice-cooled solution, the reaction mixture was stirred for 2 h at room temperature, and then basified with sodium hydrogen carbonate. The resulting mixture was extracted with methylene dichloride and the extract was washed with water. The residue upon work-up was chromatographed using benzene–ethyl acetate (99:1, v/v) to afford the *furanone* (**12**) (7.7 g, 61%) as a yellow oil (Found: C, 75.05; H, 7.55. $C_{17}H_{20}O_3$ requires C, 74.95; H, 7.4%); $\nu_{max.}$($CHCl_3$) 1 743 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 2.50 (2 H, t, *J* 8 Hz, $COCH_2CH_2$), 3.78 (3 H, s, OMe), 4.26 (2 H, t, *J* 8 Hz, CH_2CH_2O), 5.10—5.75 (3 H, m, $CH=CH_2$), and 6.60—7.10 (3 H, m, ArH); *m/z* 272 (M^+).

2-[2-(1,2-*Dihydro*-5-*methoxybenzocyclobutenyl*)*ethyl*]-2-*ethenyl*-2,3,4,5-*tetrahydro*-4-*phenylthiomethylenefuran*-3-*one* (**15**).—To a suspension of sodium hydride (60% in oil; 220 mg, 4.4 mmol) in anhydrous benzene (10 ml) was added a solution of the furanone (**12**) (300 mg, 1.1 mmol) in anhydrous benzene (5 ml) at 0 °C and the mixture was stirred for 1 h at the same temperature. To the reaction mixture was then added dropwise ethyl formate (340 mg, 4.4 mmol) and, after being stirred for 0.5 h, the mixture was diluted with water (5 ml), acidified with 10% hydrochloric acid, extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up gave the unstable hydroxymethylene compound (**13**) as a brown oil which was used in the next reaction without further purification.

To a stirred solution of the crude (**13**) (395 mg) in anhydrous pyridine (12 ml) was added methanesulphonyl chloride (164 mg, 1.4 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was treated with thiophenol (145 mg, 1.3 mmol) for 12 h at room temperature. The resulting mixture was then diluted with 10% aqueous sodium hydroxide (15 ml), extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using methylene dichloride to afford the *phenylthiomethylene compound* (**15**) (375 mg, 87%) as a yellow oil (Found: C, 73.15; H, 6.1. $C_{24}H_{24}O_3S$ requires C, 73.45; H, 6.15%); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.74 (3 H, s, OMe), 4.70 (2 H, d, *J* 2 Hz, OCH_2), 5.05—6.00 (3 H, m, $CH=CH_2$), 6.60—7.10 (3 H, m, ArH), and 7.65 (1 H, t, *J* 2 Hz, $C=CH$SPh); *m/z* 392 (M^+).

4-*Acetoxymethylene*-2-[2-(1,2-*dihydro*-5-*methoxybenzocyclobutenyl*)*ethyl*]-2-*ethenyl*-2,3,4,5-*tetrahydrofuran*-3-*one* (**16**).—A solution of the crude hydroxymethylene (**13**) (200 mg, 0.67 mmol) in anhydrous methylene dichloride (5 ml) was treated with acetic anhydride (205 mg, 2 mmol), 4-dimethylaminopyridine (catalytic amount), and anhydrous pyridine (164 mg, 2 mmol) for 10 h at room temperature. After removal of the solvent, the residue was chromatographed using benzene–ethyl acetate (23:2, v/v) to yield the *acetate* (**16**) (178 mg, 78%) as an oil (Found: C, 70.65; H, 7.0%; M^+, 342.1450. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.5%; *M*, 342.1466); $\nu_{max.}$($CHCl_3$) 1 780, 1 733, and 1 660 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 2.20 (3 H, s, COMe), 3.73 (3 H, s, OMe), 4.77 (2 H, d, *J* 2.5 Hz, OCH_2), 5.05—

5.90 (3 H, m, CH=CH_2), 6.56—7.10 (3 H, m, ArH), and 8.11 (1 H, t, *J* 2.5 Hz, C=C*H*OAc).

Thermolysis of (**15**).—A solution of the benzocyclobutene (**15**) (759 mg, 1.9 mmol) in *o*-dichlorobenzene (75 ml) was heated at 180 °C for 15 h. After removal of the solvent, the residue was chromatographed using benzene–ethyl acetate (9:1, v/v) to give the adducts (**17**) and (**18**) (673 mg, 89%), an inseparable C-4 epimeric mixture, as a pale yellow oil (Found: C, 73.8; H, 6.3. Calc. for $C_{24}H_{24}O_3S$: C, 73.45; H, 6.15%); $\nu_{max.}$($CHCl_3$) 1 755 cm^{-1}; δ_H* (60 MHz; $CDCl_3$) 3.71 (3 H, s, OMe), 4.15 (1 H, d, *J* 8 Hz, 5-H), 4.39 (1 H, br d, *J* 8 Hz, 5-H), 6.50—7.00 (3 H, m, ArH), and 7.00—7.70 (5 H, m, ArH); *m/z* 392 (M^+).

Thermolysis of (**16**).—A solution of the benzocyclobutene (**16**) (745 mg, 2.2 mmol) in *o*-dichlorobenzene (75 ml) was heated at 180 °C for 11 h. After removal of the solvent, the residue was chromatographed using benzene–ethyl acetate (9:1, v/v) to give a mixture of the adducts (**19**) and (**20**) (555 mg, 74.5%) as a pale yellow oil, which was then saponified with sodium hydroxide (153 mg, 3.8 mmol) in water (1 ml), methanol (5 ml), and methylene dichloride (3 ml) for 2 h at room temperature. Evaporation of the solvent gave a residue which was extracted with methylene dichloride and the extract was washed successively with 10% aqueous hydrochloric acid and water. The residue upon work-up was chromatographed using chloroform–methanol (49:1, v/v) to yield the *alcohol* (**27**) (131 mg, 61%) as a pale yellow oil (Found: C, 71.7; H, 6.4. $C_{18}H_{20}O_4$ requires C, 71.8; H, 6.7%); $\nu_{max.}$($CHCl_3$) 3 450 and 1 760 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.71 (3 H, s, OMe), 4.01 (1 H, d, *J* 8 Hz, 5-H), 4.36 (1 H, d, *J* 8 Hz, 5-H), 5.10—6.20 (3 H, m, CH=CH_2), and 6.50—7.10 (3 H, m, ArH); *m/z* 300 (M^+). From the later fractions, the isomeric *alcohol* (**28**) (49.5 mg, 10%) was obtained as a pale yellow oil, $\nu_{max.}$($CHCl_3$) 3 450 and 1 760 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 4.23 (1 H, d, *J* 8 Hz, 5-H) and 4.46 (1 H, d, *J* 8 Hz, 5-H) (Found: M^+, 300.1347. $C_{18}H_{20}O_4$ requires *M*, 300.1362.

3α-*Ethenyl*-1,2,3,11bα-*tetrahydro*-10-*methoxy*-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12(5H)-*one* (**3**) *and* 3α-*Ethenyl*-1,2,3,11bβ-*tetrahydro*-10-*methoxy*-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12(5H)-*one* (**21**).—To a stirred solution of a mixture of the sulphides (**17**) and (**18**) (673 mg, 1.7 mmol) in anhydrous methylene dichloride (30 ml) was added a solution of *m*-chloroperbenzoic acid (70%; 420 mg, 1.7 mmol) in anhydrous methylene dichloride (5 ml) at −78 °C. After being stirred for 2 h at the same temperature, the reaction mixture was diluted with water (5 ml) and the organic layer was separated. The aqueous layer was extracted with methylene dichloride and the combined extracts were washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue upon work-up was the crude sulphoxide (689 mg, 99.3%) which was submitted to the following reaction without further purification.

A solution of the crude sulphoxide (215 mg, 0.53 mmol) in anhydrous toluene (35 ml) was refluxed for 6 h. After removal of the solvent, the residue was chromatographed using benzene–ethyl acetate (9:1, v/v) to give the *olefin* (**3**) (80 mg, 58%) as needles after recrystallisation from benzene–n-hexane, m.p. 112 °C; $\nu_{max.}$($CHCl_3$) 1 755 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 3.72 (1 H, dd, *J* 1 and 8 Hz, 5-H_{exo}), 3.80 (3 H, s, OMe), 4.24 (1 H, d, *J* 8 Hz, 5-H_{endo}), 5.29 (1 H, dd, *J* 2 and 11 Hz, $H\!>\!C\!=\!C\!<^{H}_{H}$), 5.39 (1 H, dd, *J* 2 and 17 Hz, $H\!>\!C\!=\!C\!<^{H}_{H}$), 5.74 (1 H, d, *J* 10 Hz, 6-H), 5.97 (1 H, dd, *J* 11 and 17 Hz, CH=CH_2), 6.57 (1 H, d, *J* 10 Hz, 7-H), and 6.58 (1H, d, *J* 10 Hz, 7-H (Found: M^+, 282.1247. $C_{18}H_{18}O_3$ requires *M*, 282.1256). From the later fractions, the isomeric *olefin* (**21**) (12 mg, 8.7%) was obtained as needles after recrystallisation from benzene–n-hexane, m.p. 101 °C; δ_H (100 MHz; $CDCl_3$) 3.79 (3 H, s, OMe), 4.24 (1 H, d, *J* 8 Hz, 5-H), 4.54 (1 H, d, *J* 8 Hz, 5-H), 5.20 (1 H, dd, *J* 2 and 11 Hz, $H\!>\!C\!=\!C\!<^{H}_{H}$), 5.32 (1 H, dd, *J* 2 and 17 Hz, $H\!>\!C\!=\!C\!<^{H}_{H}$), 5.48 (1 H, d, *J* 10 Hz, 6-H), and 5.83 (1 H, dd, *J* 11 and 17 Hz, C*H*=CH_2) (Found: M^+, 282.1261. $C_{18}H_{18}O_3$ requires *M*, 282.1256).

3α-*Ethenyl*-12-(E *and* Z)-*ethoxycarbonylmethylene*-1,2,3,11bα-*tetrahydro*-10-*methoxy*-5H-3,5aα-*methanonaphth*[2,1-c]*oxepine* (**22**).—To a stirred suspension of sodium hydride (60% in oil; 89 mg, 2.23 mmol) in dimethoxyethane (6 ml) was added triethyl phosphonoacetate (417 mg, 1.86 mmol) at 0 °C. After the mixture had been stirred for 1 h, a solution of the ketone (**3**) (105 mg, 0.37 mmol) in dimethoxyethane (4 ml) was added dropwise at 0 °C and then the mixture was refluxed for 0.5 h. The resulting mixture was diluted with water (5 ml) and extracted with methylene dichloride, and the extract was washed with water. The residue upon work-up was chromatographed using methylene dichloride to give the unsaturated ester (**22**) (119 mg, 90%), a mixture of *E* and *Z* olefin isomers, as an oil, $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 3.42 (1 H, dd, *J* 1 and 8 Hz, 5-H_{exo}), 3.71 (1.2 H, s, OMe), 3.73 (1.8 H, s, OMe), 3.92 (0.6 H, d, *J* 8 Hz, 5-H_{endo}), 4.08 (0.4 H, d, *J* 8 Hz, 5-H_{endo}), 5.56 (0.4 H, d, *J* 10 Hz, 6-H), 5.62 (0.6 H, d, *J* 10 Hz, 6-H), 5.74 (0.4 H, s, C=C*H*CO_2Et), 5.77 (0.6 H, s, C=C*H*CO_2Et), 6.42 (0.6 H, d, *J* 10 Hz, 7-H), and 6.52 (0.4 H, d, *J* 10 Hz, 7-H) (Found: M^+, 352.1641. $C_{22}H_{24}O_2$ requires *M*, 352.1673).

Ethyl 3α-*Ethenyl*-1,2,3,11bα-*tetrahydro*-10-*methoxy*-5H-3,4aα-*methanonaphth*[2,1-c]*oxepin*-12-endo-*ylacetate* (**23**).—To a stirred suspension of tellurium powder (172 mg, 1.3 mg-atom) and sodium borohydride (130 mg, 3.4 mmol) in ethanol (6 ml) was added a solution of the unsaturated ester (**22**) (119 mg, 0.34 mmol), as a mixture of *E* and *Z* olefin isomers, in ethanol (3 ml) at room temperature and the mixture was stirred for 48 h. After the addition of 10% aqueous hydrochloric acid (1 ml), the mixture was filtered through Celite. The filtrate was extracted with methylene dichloride and the extract was washed with water. The residue upon work-up was chromatographed using benzene–ethyl acetate (9:1, v/v) to afford the *ester* (**23**) (110 mg, 91.9%) as an oil, $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.16 (3 H, t, *J* 8 Hz, OCH_2CH_3), 3.33 (1 H, dd, *J* 1 and 8 Hz, 5-H_{exo}), 3.72 (3 H, s, OMe), 4.17 (1 H, d, *J* 8 Hz, 5-H_{endo}), 5.42 (1 H, d, *J* 10 Hz, 6-H), and 6.35 (1 H, d, *J* 10 Hz, 7-H) (Found: M^+, 354.1824. $C_{22}H_{26}O_4$ requires *M*, 354.1829).

Ethyl 6,7-*Epoxy*-3α-*ethenyl*-1,2,3,6,7,11bα-*hexahydro*-10-*methoxy*-5H-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12-endo-*ylacetate* (**24**).—To a stirred solution of the ester (**23**) (135 mg, 0.38 mmol) in methylene dichloride (10 ml) was added disodium hydrogen phosphate (433 mg, 3.05 mmol) and *m*-chloroperbenzoic acid (112 mg, 0.46 mmol) at −78 °C. After being stirred for 3 h at the same temperature, the mixture was diluted with water (2 ml) and extracted with methylene dichloride, and the extract was washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue upon work-up was chromatographed using benzene–ethyl acetate (19:1, v/v) to give the *epoxide* (**24**) (181 mg, 100%) as a pale yellow oil,

* Systematic numbering used here and for the other compounds in this section.

$\nu_{max.}$($CHCl_3$) 1 720 cm $^{-1}$; δ_H (60 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 8 Hz, OCH_2CH_3), 3.80 (3 H, s, OMe), and 5.00—6.20 (3 H, m, $CH{=}CH_2$) (Found: M^+, 370.1790. $C_{22}H_{26}O_5$ requires *M*, 370.1780).

Ethyl 3α-*Ethenyl*-1,2,3,4,7,11bα-*hexahydro*-10-*methoxy*-6-*oxo*-5H-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12-endo-*ylacetate* (**25**).—To a stirred solution of the epoxide (**24**) (160 mg, 0.42 mmol) in anhydrous benzene (7 ml) was added boron trifluoride–diethyl ether (184 mg, 1.29 mmol) at 0 °C and the mixture was stirred for 7 h at room temperature. After removal of the solvent, the residue was chromatographed using benzene–ethyl acetate (19:1, v/v) to yield the *keto ester* (**25**) (57 mg, 54%) as an amorphous solid, $\nu_{max.}$($CHCl_3$) 1 720 cm $^{-1}$; δ_H (60 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 8 Hz, OCH_2CH_3), 3.58 (2 H, br s, $ArCH_2CO$), 4.85—6.15 (3 H, m, $CH{=}CH_2$), and 6.50—7.10 (3 H, m, ArH) (Found: M^+, 370.1742. $C_{22}H_{26}O_5$ requires *M*, 370.1778).

6β-*Acetoxy*-3α-*ethenyl*-1,2,3,6,7,11bα-*hexahydro*-10-*methoxy*-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12(5H)-*one* (**29**).—To a stirred solution of the alcohol (**27**) (10 mg, 0.027 mmol) in anhydrous methylene dichloride (1 ml) was added pyridine (9.8 mg, 0.12 mmol), acetic anhydride (10.8 mg, 0.11 mmol), and a catalytic amount of 4-dimethylaminopyridine at room temperature and the resulting mixture was stirred for 3 h at the same temperature. Evaporation of the solvent gave a residue which was chromatographed using chloroform–methanol (99:1, v/v) to afford the *acetate* (**29**) (11 mg, 96%) as a pale yellow oil (Found: C, 70.35; H, 6.6. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.5%); $\nu_{max.}$($CHCl_3$) 1 765 and 1 735 cm $^{-1}$; δ_H* (100 MHz; $CDCl_3$) 1.97 (3 H, s, $OCOCH_3$), 2.42 (1 H, dd, *J* 11 and 16 Hz, 7-H), 3.17 (1 H, dd, *J* 6 and 16 Hz, 7-H), 3.72 (3 H, s, OMe), 4.12 (1 H, d, *J* 8 Hz, 5-H_{endo}), 4.32 (1 H, dd, *J* 1 and 8 Hz, 5-H_{exo}), 5.27 (1 H, dd, *J* 2 and 10 Hz, $H{>}C{=}C{<}^{H}_{H}$), 5.32 (1 H, dd, *J* 2 and 18 Hz, $H{>}C{=}C{<}^{H}_{H}$), 5.41 (1 H, dd, *J* 6 and 11 Hz, 6-H), 5.92 (1 H, dd, *J* 10 and 18 Hz, $CH{=}CH_2$), and 6.50—6.96 (3 H, m, ArH) (Found: M^+, 342.1462. $C_{20}H_{22}O_5$ requires *M*, 342.1467).

6β-*Acetoxy*-3α-*ethenyl*-1,2,3,6,7,11bβ-*hexahydro*-10-*methoxy*-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12(5H)-*one* (**30**).—The *acetate* (**30**) (10.5 mg, 91%) was obtained from the alcohol (**28**) (10 mg, 0.027 mmol) by the same method as described for (**29**); $\nu_{max.}$($CHCl_3$) 1 765 and 1 635 cm $^{-1}$; δ_H* (100 MHz; $CDCl_3$) 1.96 (3 H, s, $OCOCH_3$), 2.68 (1 H, dd, *J* 4 and 17 Hz, 7-H), 3.67 (1 H, dd, *J* 7 and 17 Hz, 7-H), 4.14 (1 H, d, *J* 8 Hz, 5-H), 4.37 (1 H, d, *J* 8 Hz, 5-H), and 5.19 (1 H, dd, *J* 4 and 7 Hz, 6-H) (Found: M^+, 342.1485. $C_{20}H_{22}O_5$ requires *M*, 342.1467).

6β-*Acetoxy*-3α-*ethyl*-1,2,3,6,7,11bα-*hexahydro*-10-*methoxy*-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12(5H)-*one* (**32**).—A solution of the acetate (**29**) (5 mg, 0.015 mmol) in methanol (2 ml) was hydrogenated over 5% palladium–carbon (5 mg) under atmospheric pressure at room temperature for 12 h. After removal of the catalyst by filtration, the filtrate was evaporated to leave a residue which was chromatographed using benzene–ethyl aceate (9:1, v/v) to give the *hydrogenated acetate* (**32**) (5 mg, 100%) as an amorphous solid, $\nu_{max.}$($CHCl_3$) 1 765 and 1 735 cm $^{-1}$; δ_H (100 MHz; $CDCl_3$) 0.80 (3 H, t, *J* 8 Hz, CH_2CH_3), 1.95 (3 H, s, $OCOCH_3$), 3.68 (3 H, s, OMe), 4.03 (1 H, d, *J* 8 Hz, 5-H_{endo}), 4.20 (1 H, dd, *J* 1 and 8 Hz, 5-H_{exo}), 5.37 (1 H, dd, *J* 6 and 11 Hz, 6-H), and 6.52—6.94 (3 H, m, ArH) (Found: M^+, 344.1619. $C_{20}H_{24}O_5$ requires *M*, 344.1622).

* The assignment of the coupled protons shown here was made on the basis of decoupling experiments.

3α-*Ethenyl*-12-(E *and* Z)-*ethoxycarbonylmethylene*-1,2,3,6,7,11bα-*hexahydro*-6β-*hydroxy*-10-*methoxy*-5H-3,5aα-*methanonaphth*[2,1-c]*oxepine* (**31**).—To a stirred suspension of sodium hydride (60% in oil; 288 mg, 7.2 mmol) in dimethoxyethane (20 ml) was added triethyl phosphonoacetate (1.0 g, 4.5 mmol) at 0 °C. After the mixture had been stirred for 1 h at room temperature, a solution of the alcohol (**27**) (300 mg, 1 mmol) in dimethoxyethane (5 ml) was added dropwise at 0 °C and the mixture was stirred for 7 h at room temperature. The resulting mixture was acidified with 10% aqueous hydrochloric acid and extracted with methylene dichloride, and the extract was washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue upon work-up was chromatographed using benzene–ethyl acetate (9:1, v/v) to afford the unsaturated ester (**31**) (340 mg, 91%), a mixture of *E* and *Z* olefin isomers, as an oil (Found: C, 71.3; H, 7.05%; M^+, 370.1758. Calc. for $C_{22}H_{26}O_5$: C, 71.2; H, 7.05%; *M*, 370.1779); $\nu_{max.}$($CHCl_3$) 3 400 and 1 712 cm $^{-1}$; δ_H (60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 8 Hz, OCH_2CH_3), 3.77 (3 H, s, OMe), and 5.74 (1 H, s, $C{=}CHCO_2Et$).

Ethyl 3α-*Ethenyl*-1,2,3,6,7,11bα-*hexahydro*-6β-*hydroxy*-10-*methoxy*-5H-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12-endo-*ylacetate* (**26**).—(a) *Sodium borohydride reduction of* (**25**). To a stirred solution of the ketone (**25**) (10 mg, 0.027 mmol) in ethanol (2 ml) was added sodium borohydride (10 mg, 0.26 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 15 min. After removal of the solvent, the residue was diluted with water (2 ml) and extracted with methylene dichloride, and the extract was washed with water. The residue upon work-up was chromatographed using chloroform–methanol (99:1, v/v) to afford the *alcohol* (**26**) (10.5 mg, 100%) as an oil, $\nu_{max.}$($CHCl_3$) 3 455 and 1 720 cm $^{-1}$; δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 8 Hz, OCH_2CH_3), 3.70 (3 H, s, OMe), 4.13 (2 H, q, *J* 8 Hz, OCH_2CH_3), 4.90—6.20 (3 H, m, $CH{=}CH_2$), and 6.40—7.00 (3 H, m, ArH) (Found: M^+, 372.1912. $C_{22}H_{28}O_5$ requires *M*, 372.1935).

(b) *Sodium hydrotelluride reduction of* (**31**).—To a stirred suspension of tellurium powder (22 mg, 0.17 mg-atom) and sodium borohydride (13.7 mg, 0.36 mmol) in ethanol (2 ml) was added a solution of the unsaturated ester (**31**) (65.4 mg, 0.17 mmol) in ethanol (1 ml) at room temperature and the mixture was stirred for 48 h. After the addition of 10% aqueous hydrochloric acid (0.5 ml), the mixture was filtered through Celite. The filtrate was extracted with methylene dichloride and the extract was washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue upon work-up was chromatographed using chloroform–methanol (99:1, v/v) to give the hydroxy ester (**26**) (24 mg, 84% based on the consumed starting material), which was identical with the compound prepared by method (a).

3α-*Ethenyl*-1,2,3,6,7,11bα-*hexahydro*-6β-*hydroxy*-10-*methoxy*-5H-3,5aα-*methanonaphth*[2,1-c]*oxepin*-12-endo-*ylacetic Acid* (**33**).—A solution of the ester (**26**) (178 mg, 0.48 mmol) in ethanol (5 ml) was stirred with potassium hydroxide (500 mg, 8.9 mmol) at room temperature for 0.5 h. After removal of the solvent, the residue was acidified with 10% aqueous hydrochloric acid (5 ml) and extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using chloroform–methanol (9:1, v/v) to afford the *hydroxy acid* (**33**) (157 mg, 100%) as needles after recrystallisation from benzene–n-hexane, m.p. 220—224 °C; $\nu_{max.}$($CHCl_3$) 3 400 and 1 700 cm $^{-1}$; δ_H (100 MHz; $CDCl_3$) 3.70 (3 H, s, OMe), 5.14 (1 H, dd, *J* 1 and 17 Hz, $H{>}C{=}C{<}^{H}_{H}$), 5.15 (1 H, dd, *J* 1 and 10 Hz,

$H\diagdown C{=}C\diagup^{H}_{H}$), 5.86 (1 H, dd, *J* 10 and 17 Hz, C*H*=CH_2), and 6.50—7.00 (3 H, m, ArH) (Found: M^+, 344.1614. $C_{20}H_{24}O_5$ requires *M*, 344.1622).

Lactonization of the Hydroxy Acid (**33**).—To a stirred solution of the hydroxy acid (**33**) (20 mg, 0.058 mmol) and triethylamine (166 mg, 1.16 mmol) in anhydrous methylene dichloride (2 ml) was added methanesulphonyl chloride (26.6 mg, 0.23 mmol) and a catalytic amount of 4-dimethylaminopyridine at 0 °C. After being stirred at room temperature for 18 h, the mixture was diluted with water (1 ml) and extracted with methylene dichloride, and the extract was washed with water. The residue upon work-up was taken up with methylene dichloride (1 ml) and the solution was stirred with saturated aqueous sodium hydrogen carbonate (1 ml) at room temperature for 14 h. After acidification with 10% aqueous hydrochloric acid, the mixture was extracted with methylene dichloride and the extract was washed with water. The residue upon work-up was chromatographed using chloroform–methanol (99:1, v/v) to yield the *lactone* (**2**) (13.4 mg, 70.9%) as needles after recrystallisation from benzene–n-hexane, m.p. 167—168 °C; $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.59 (1 H, dd, *J* 1.5 and 8 Hz, 5-H_{exo}), 3.79 (3 H, s, OMe), 3.84 (1 H, d, *J* 8 Hz, 5-H_{endo}), 4.63 (1 H, d, *J* 4 Hz, 6-H), 5.20 (1 H, dd, *J* 1 and 11 Hz, $H\diagdown C{=}C\diagup^{H}_{H}$), 5.26 (1 H, dd, *J* 1 and 17.5 Hz, $\overset{H}{\underset{H}{}}C{=}C\overset{H}{\underset{}{}}$), 5.93 (1 H, dd, *J* 11 and 17.5 Hz, C*H*=CH_2), 6.76 (1 H, dd, *J* 2 and 8 Hz, ArH), 6.82 (1 H, d, *J* 2 Hz, ArH), and 7.00 (1 H, d, *J* 8 Hz, ArH); δ_C (25 MHz; $CDCl_3$) 23.307, 29.120, 29.237, 30.177, 32.819, 43.680, 49.023, 55.481, 70.804, 81.311, 83.073, 112.193, 112.428, 115.307, 130.041, 137.265, 139.613, 158.223, 158.687, and 169.725 p.p.m. (Found: M^+, 326.1514. $C_{20}H_{22}O_4$ requires *M*, 326.1516).

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