A Novel Synthetic Approach to Isoatisirene-related Compounds *via* an Intramolecular Diels-Alder Reaction[1]

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A new synthesis of 2-oxo-18-norisoatisirene (**2**), a potential intermediate for the synthesis of isoatisirene (**1**), *via* 3-methoxy-7-methyl-9-phenylthio-4bβ,5,6,8a,9,10-hexahydro-6α,8aα-ethanophenanthren-8(7*H*)-one (**4a**) and 3-methoxy-7-methyl-7-phenylthio-4bβ,5,6,7,8,8a,9,10-octahydro-6α,8aα-ethanophenanthrene (**4b**) [which were prepared by a thermolysis of 5-methoxy-1-(2-methyl-3-oxo-4-phenylthiomethylenecyclohexylmethyl)-1,2-dihydrocyclobutabenzene (**6a**), and 5-methoxy-1-(2-methyl-4-methylenecyclohexylmethyl)-1,2-dihydrocyclobutabenzene (**6b**) respectively] is described.

There have been many studies[2–7] of the bridged bicyclo-[2.2.2]octane system, since this unique ring system constitutes an integral part of the structure of a large class of diterpenoids and diterpene alkaloids.[8,9] In connection with our interest[10–13] in the development of synthetic cycloaddition reactions of *o*-quinodimethanes based on dihydrocyclobutabenzenes, we have investigated a facile route to the potential intermediate (**2**) for the synthesis of isoatisirene (**1**). The most challenging feature of this study is the cycloaddition reaction of the *o*-quinodimethanes derived from the thermolysis of the dihydrocyclobutabenzenes (**6a**) and (**6b**) through a conformationally unfavoured intermediate in either the *exo*-(**A**) or *endo*-(**B**) forms (*i.e.* having a boat-like conformation of the cyclohexane ring) leading to (**4a**) and (**4b**), or (**5a**) and (**5b**) respectively, rather than the conformationally favoured intermediate (C) which has a chair-like conformation and in which the diene and dienophile are too far apart to interact with each other.

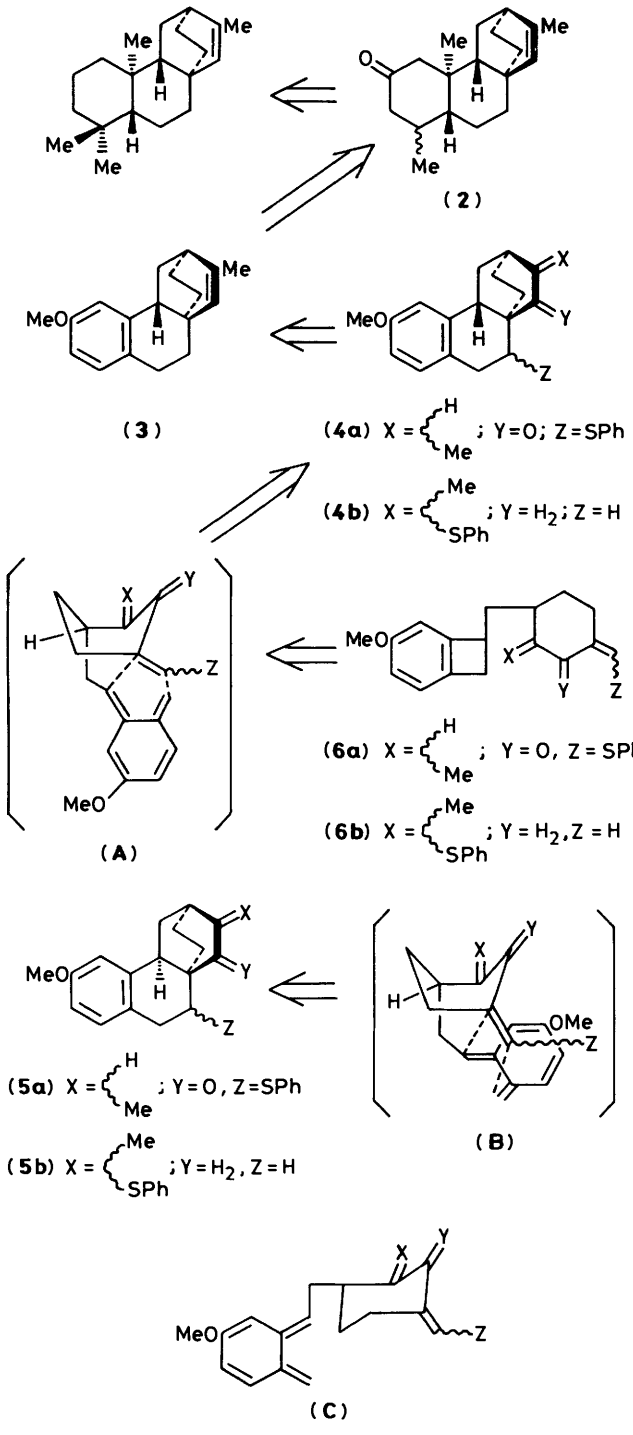
The synthesis of the dihydrocyclobutabenzene (**6a**), a source for generating the *o*-quinodimethane, was carried out as follows.

The sulphoxide (**9**), prepared in 85.5% overall yield from the toluene-*p*-sulphonate (**7**)[13] *via* the sulphide (**8**) by successive treatment with sodium thiophenoxide in dimethylformamide (DMF) and *m*-chloroperbenzoic acid (MCPBA) in dichloromethane (CH_2Cl_2) was condensed with 2-methylcyclohex-2-enone[14] in hexamethylphosphoric triamide (HMPA) and tetrahydrofuran (THF) in the presence of lithium di-isopropylamide (LDA) to give the alcoholic sulphoxide (**10**) in 85% yield. The enone (**12**), obtained in 81% overall yield by treating (**10**) with pyridinium chlorochromate (PCC) in CH_2Cl_2, and the resulting product (**11**) with zinc in acetic acid, was hydrogenated in methanol in the presence of palladium–carbon to afford the cyclohexanone (**13**) in 88% yield. The dienophile moiety was introduced into the cyclohexanone (**13**) to give (**6a**) in 75% overall yield by successive treatment of (**13**) with ethyl formate in benzene in the presence of sodium hydride (NaH) and then of the product (**14**) with mesyl chloride, followed by thiophenol in pyridine.

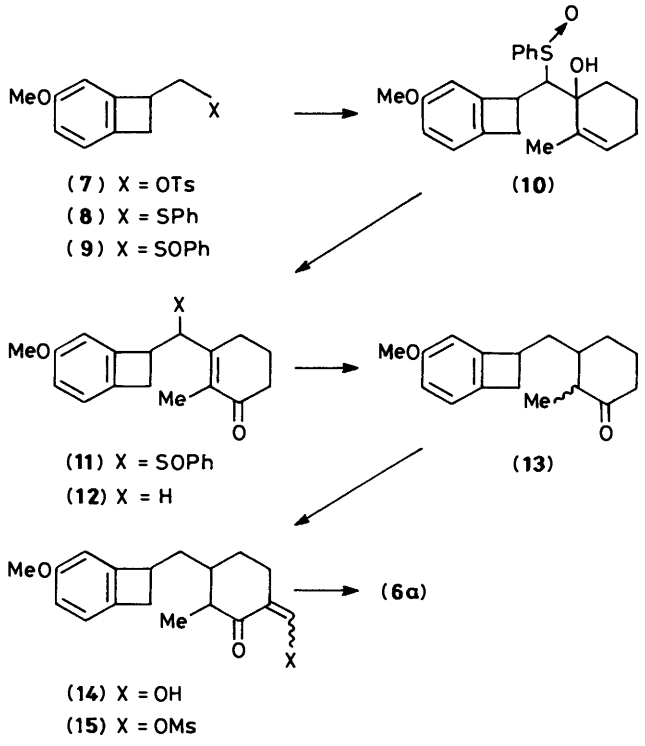
Compound (**6a**), when heated in *o*-dichlorobenzene at 200 °C for 10 h in a current of nitrogen, afforded the tetracyclic compounds (**4a**) and (**5a**) as an inseparable stereoisomeric mixture in 95% yield. The stereochemistry at the ring junction of (**4a**) and (**5a**) was easily deduced by converting (**4a**) and (**5a**) into the styrenes (**17**) and (**21**) and then into (**3**) and (**24**), respectively.

Thus, oxidation of (**4a**) and (**5a**) with MCPBA and then elimination of the phenylsulphinyl group from the resulting sulphoxides (**16**) and (**20**) gave the styrenes (**17**) and (**21**) in 16 and 37% overall yields respectively, after chromatography. The n.m.r. spectra of (**17**) and (**21**) were diagnostic for the stereochemical assignment, *i.e.* an olefinic proton at C-9 of (**17**), suffering from the deshielding effect of the carbonyl group, was observed at δ 6.08 as a doublet (*J* 10 Hz). For (**21**), the corresponding olefinic proton would not be expected to be deshielded by the carbonyl group and the resonances were observed as doublets at their positions (δ 5.35 and 5.38, *J* 10 Hz). Next, the olefinic ketones (**17**) and (**21**) were hydrogenated in methanol in the presence of palladium–carbon to give the ketones (**18**) and (**22**) in 45 and 59% yields, respectively. The tosylhydrazides (**19**) and (**23**) prepared from the ketones (**18**) and (**22**) in 49 and 53% yields, respectively, were subjected to the Shapiro reaction using n-butyl-lithium in THF, to furnish the olefinic tetracyclic compounds (**3**) and (**24**) in 32 and 80% yields respectively. Thus, although we could have shown that the stereochemical course of the cycloaddition of the *o*-quinodimethane based on the dihydrocyclobutabenzene (**6a**) is *via* (**A**) and (**B**), overcoming the conformational disadvantage, unfortunately the main reaction course was *via* (**B**) rather than (**A**), the product (**4a**) of which could be a potential intermediate for the synthesis of isoatisirene (**1**). One might expect that the bulky substituents at C-2 on the cyclohexane ring of dihydrocyclobutabenzene (**6a**) might alter the stereochemical course of the cycloaddition to favour the intermediate (**A**), there being steric repulsion between X and the *o*-quinodimethane moiety in the intermediate (**B**). Thus, we have investigated the cycloaddition of *o*-quinodimethane derived from the thermolysis of dihydrocyclobutabenzene (**6b**), and developed a more effective synthetic route to (**3**).

The dihydrobenzocyclobutenylcyclohexenone (**27**) was prepared in 81% yield by a Michael addition of 1-cyano-5-methoxybenzocyclobutene (**25**)[15] to 3-methyl-4-methylenecyclohex-2-enone (**26**)[16] in HMPA and THF in the presence of LDA. Compound (**27**) was then converted into the conjugated cyclohexenone (**30**) in 46% overall yield *via* the cyano acetal (**28**) and decyanated acetal (**29**) by successive treatment with ethylene glycol in benzene in the presence of toluene-*p*-sulphonic acid, with sodium in liquid ammonia and THF in the presence of ethanol, and with 10% hydrochloric acid in methanol. Next, compound (**30**) was treated with thiophenol in triethylamine (TEA) to give the 1,4-addition product (**31**) in 52% yield. This was then subjected to the Wittig reaction by using triphenylphosphonium methylide in THF to give the *exo*-methylene derivative (**6b**) in 62% yield. Compound (**6b**), when heated in *o*-dichlorobenzene at 200 °C for 5 h in a current of nitrogen, gave the tetracyclic compounds (**4b**) and (**5b**) as an inseparable mixture in 66% yield.



Scheme 1



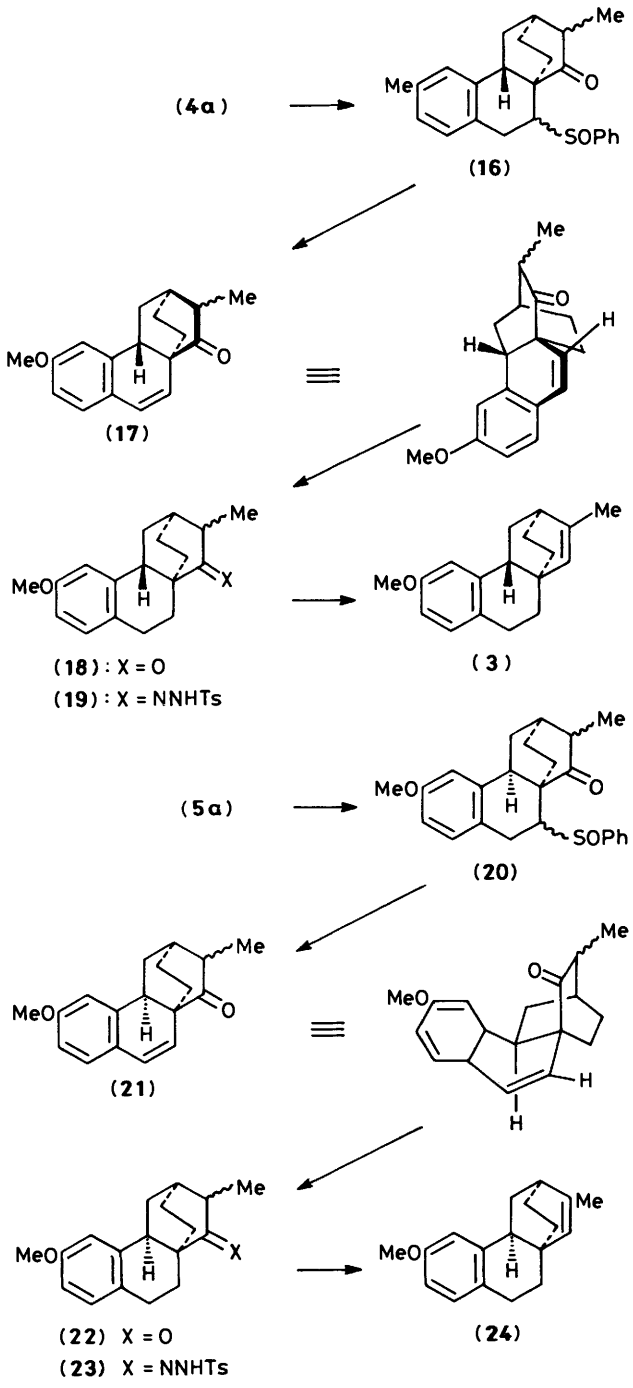
Scheme 2

The stereochemistry at the ring junction of (**4b**) and (**5b**) was determined by converting (**4b**) and (**5b**) *via* the sulphoxides (**32**) and (**33**) into compounds (**3**) and (**24**) by oxidation with MCPBA and then elimination of the phenylsulphinyl group from the resulting sulphoxides (**32**) and (**33**). Compounds (**3**) and (**24**) thus obtained in a 1:1 ratio were identical with those described above. Since the ratio of (**3**):(**24**) derived from (**4a**) and (**5a**) was calculated to be 1:8, we could improve the stereochemical course of the cycloaddition reaction of the *o*-quinodimethane. Although the precise reasons for the different stereochemical outcome of the thermolyses of (**6a**) and (**6b**) were not clear, one of the possible reasons could be the presence of the bulky substituents at the C-2 position of its cyclohexane ring. The transformation of the compound (**3**) into 2-oxo-18-norisoatisirene (**2**) was carried out as follows. The enone (**34**), prepared in 34% overall yield from compound (**3**) by Birch reduction using sodium in liquid ammonia and THF in the presence of ethanol, followed by acid treatment of the resulting product, was treated with 30% hydrogen peroxide in methanol in the presence of 10% sodium hydroxide solution to give the epoxide (**35**) in 41% yield. This was then subjected to the Eschenmoser's ring-opening reaction by using toluene-*p*-sulphonylhydrazine in acetic acid and CH_2Cl_2 to afford the keto acetylenic compound (**36**) in 42% yield. The hydroxyacetylenic compound (**37**), derived from the reaction of (**36**) with methyl-lithium in ether in 77% yield, was converted into the tetracyclic ketonic compound (**38**) in 52% yield by successive treatment of (**37**) with trifluoroacetic anhydride in trifluoroacetic acid followed by 10% hydrochloric acid in methanol and acetone. The stereochemistry at the C-10 position of (**38**) was deduced by the analogous reaction of our previous studies;[13] namely, because of the steric interference of the bicyclo-octane system, the stereochemical course of the cyclization of the hydroxy acetylenic compound (**37**) was expected to proceed from the β-face, giving rise to 10α-methyl derivative (**38**). Finally, the enone (**39**), prepared in 67% yield, by the oxidation[17] of (**38**) with palladium chloride in concentrated hydrochloric acid, was treated with lithium dimethylcuprate in ether to furnish 2-oxo-18-norisoatisirene (**2**) in 47% yield.

Experimental

General.—M.p.s were taken with a Yanagimoto micro-melting-point apparatus (MP-S2). I.r. spectra were measured with a Hitachi 260-10 recording spectrophotometer, n.m.r. spectra with a JEOL-PMX-60 and a JEOL-PS-100 using tetramethylsilane as an internal reference, and mass spectra with Hitachi M-52-G and JEOL-JMS-01SG-2.

5-Methoxybenzocyclobut-1-enyl Phenyl Sulphide (**8**).—To a



Scheme 3

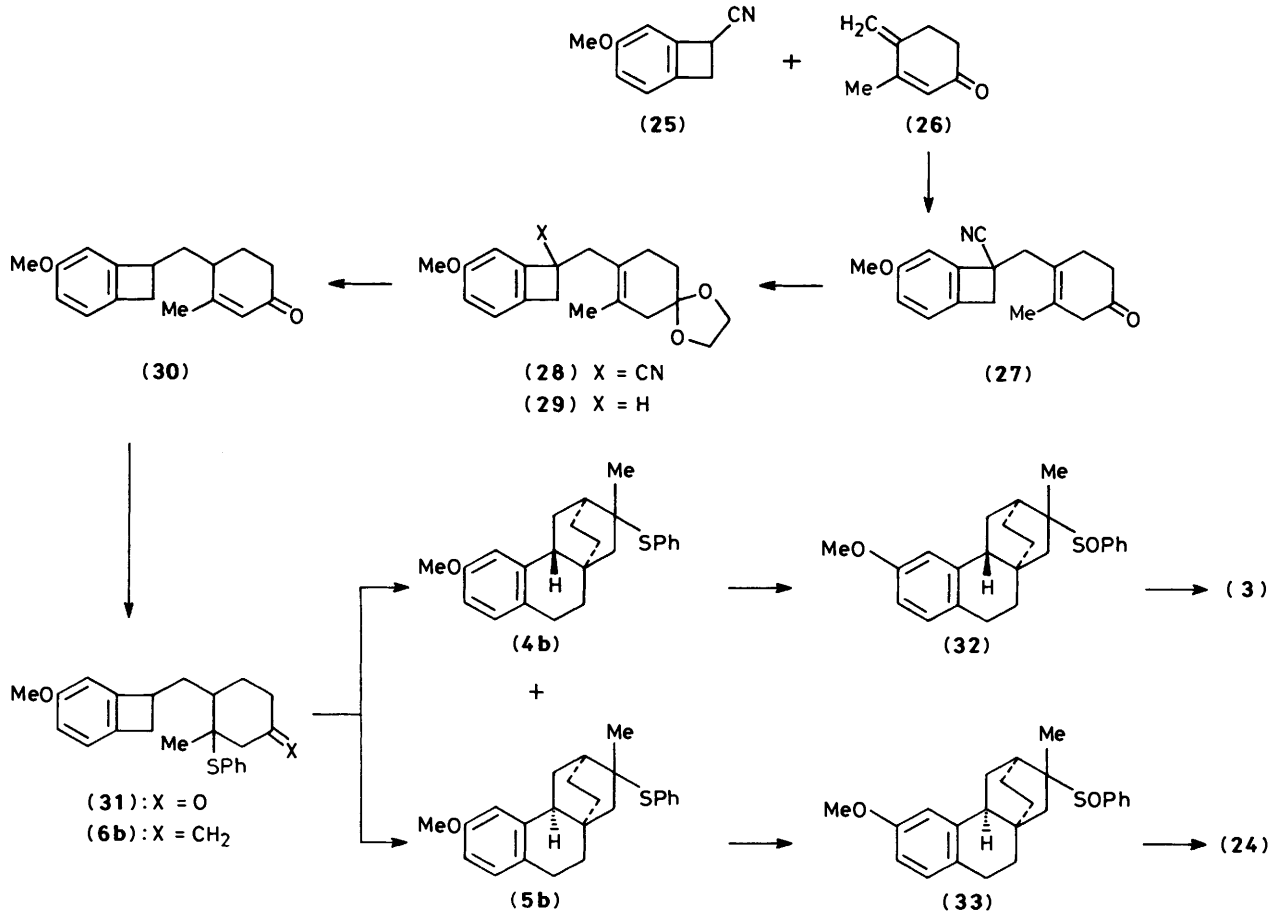
stirred solution of sodium thiophenoxide [prepared from NaH (1.4 g, 60% in oil) and thiophenol (3.8 ml)] in anhydrous DMF (60 ml) was added a solution of 5-methoxybenzocyclobuten-1-yl toluene-*p*-sulphonate[13] (**7**) (10.7 g) in anhydrous DMF (30 ml) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, quenched with water (200 ml), and extracted with benzene (×3). The combined benzene extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica gel (100 g) using n-hexane–benzene (1:1, v/v) as eluant gave the *sulphide* (**8**) (8.5 g, 95%) as a colourless oil (Found: C, 75.1; H, 5.95. $C_{16}H_{16}OS$ requires C, 74.95; H, 6.3%); *m/z* 256 (M^+); $\delta_H(CCl_4)$ 2.98 (2 H, d, *J* 6.0 Hz, SCH_2), 3.03 (2 H, d, *J* 8.0 Hz, $ArCH_2$), 3.61 (1 H, m, ArC*H*), 6.50—7.00 (3 H, m, ArH), and 7.40 (5 H, br s, ArH).

5-Methoxybenzocyclobut-1-enylmethyl Phenyl Sulphoxide (**9**).—To a solution of the sulphide (**8**) (8.7 g) in CH_2Cl_2 (80 ml) was added dropwise a solution of MCPBA (6.4 g) in CH_2Cl_2 (30 ml) with stirring at room temperature. The resulting reaction mixture was stirred for 30 min at the same temperature and then neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel (100 g), with $CHCl_3$ as an eluant, gave a colourless powder which crystallized from n-hexane–CH_2Cl_2 (1:1 v/v) to afford the *sulphoxide* (**9**) (7.7 g, 90%) as colourless needles, m.p. 84—85 °C (Found: C, 70.05; H, 6.1. $C_{16}H_{16}O_2S$ requires C, 70.55; H, 5.9%); *m/z* 272 (M^+); $\delta_H(CCl_4)$ 3.60, 3.66 (3 H, each s, OMe), 6.33—7.00 (3 H, m, ArH), and 7.58 (5 H, br s, ArH).

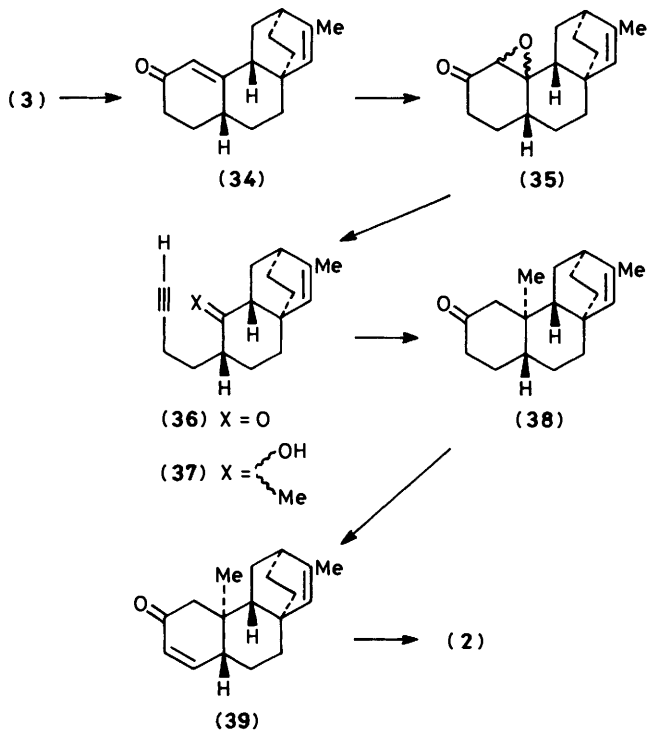
1-[1-*Hydroxy-2-methylcyclohex-2-enyl*(*phenylsulphinyl*)*methyl*]-5-*methoxy*-1,2-*dihydrocyclobutabenzene* (**10**).—To a stirred solution of LDA [prepared by addition of n-butyllithium (1.56M; 1.18 ml) to a solution of di-isopropylamine (0.28 ml) in anhydrous THF (30 ml) at −78 °C] was added dropwise a solution of the sulphoxide (**9**) (520 mg) in anhydrous THF (5 ml). Stirring was continued for 15 min at the same temperature. After addition of HMPA (0.34 ml) and a solution of 2-methylcyclohex-2-enone (273 mg) in anhydrous THF (5 ml), the reaction mixture was stirred for 1 h at the same temperature, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (×3). The combined Et_2O extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica gel (15 g) with benzene as eluant afforded the *alcoholic sulphoxide* (**10**) (672 mg, 85%) as a pale yellowish oil (Found: C, 72.25; H, 6.5. $C_{23}H_{26}O_3S$ requires C, 72.2; H, 6.85%); *m/z* 382 (M^+); $\nu_{max.}(CHCl_3)$ 3 600 cm^{-1} (OH); $\delta_H(CCl_4)$ 3.66 (3 H, s, OMe), 5.70 (2 H, br s, OH, C=C*H*); 6.30—6.93 (3 H, m, ArH), and 7.30 (5 H, br s, ArH).

5-Methoxy-1-[2-*methyl*-3-*oxocyclohex*-1-*enyl*(*phenylsulphinyl*)*methyl*]-1,2-*dihydrocyclobutabenzene* (**11**).—To a slurry of PCC (2.7 g) in CH_2Cl_2 (20 ml) was added a solution of the alcoholic sulphoxide (**10**) (2.25 g) in CH_2Cl_2 (20 ml). The mixture was stirred for 12 h at room temperature and then treated with Florisil and filtered through Celite. The filtrate was evaporated and the residue chromatographed on silica gel (30 g) with n-hexane–AcOEt (7:3 v/v) as eluant to give the *enone* (**11**) (2.01 g, 90%) as a pale yellowish oil (Found: C, 73.05; H, 6.35. $C_{23}H_{24}O_3S$ requires C, 72.6; H, 6.35%); *m/z* 380 (M^+); $\nu_{max.}(CHCl_3)$ 1 650 cm^{-1} (CO); $\delta_H(CCl_4)$ 3.60 (3 H, s, OMe), 6.20—7.16 (3 H, m, ArH), and 7.50 (5 H, br s, ArH).

5-Methoxy-1-(2-*methyl*-3-*oxocyclohex*-1-*enylmethyl*)-1,2-*dihydrocyclobutabenzene* (**12**).—To a solution of the compound (**11**) (3.65 g) in AcOH (30 ml) zinc (26 g) was added in portions. The reaction mixture was stirred for 1 h at room temperature and then filtered through Celite to remove the inorganic compounds. The filtrate was diluted with water (100 ml), and extracted with benzene (×3). The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (100 g) using benzene as an eluant to afford the *desulphoxide enone* (**12**) (2.23 g, 90%) as a colourless oil (Found: C, 79.8; H, 7.75. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.85%); *m/z* 256 (M^+); $\nu_{max.}(CHCl_3)$ 1 650 cm^{-1} (CO); δ_H (CCl_4) 1.60 (3 H, br s, Me), 3.67 (3 H, s, OMe), and 6.36—6.98 (3 H, m, ArH).



Scheme 4



Scheme 5

5-Methoxy-1-(2-methyl-3-oxocyclohexylmethyl)-1,2-dihydrocyclobutabenzene (**13**).—A mixture of the enone (**12**) (8.53 g), 10% palladium on carbon (1.0 g), and MeOH (100 ml) was stirred for 12 h under an atmosphere of hydrogen. The mixture was filtered through Celite and the filtrate was evaporated to give the residue which was chromatographed on silica gel (100 g) using benzene as an eluant to afford the *cyclohexanone* (**13**) (7.59 g, 88%) as a colourless oil (Found: C, 79.0; H, 8.05. $C_{17}H_{22}O_2$ requires C, 79.05; H, 8.6%); *m/z* 258 (M^+); $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.00 (3 H, d, *J* 8 Hz, Me), 3.70 (3 H, s, OMe), and 6.45—6.98 (3 H, m, ArH).

1-(4-Hydroxymethylene-2-methyl-3-oxocyclohexylmethyl)-5-methoxy-1,2-dihydrocyclobutabenzene (**14**).—To a solution of the cyclohexanone (**13**) (3.9 g) and NaH (1.2 g, 60% in oil) in anhydrous benzene (50 ml) was added a solution of ethyl formate (1.8 ml) in anhydrous benzene (10 ml). The mixture was stirred for 3 h at room temperature and then treated with saturated aqueous NH_4Cl solution and 10% aqueous HCl. The organic layer was separated and the aqueous layer extracted with benzene. The combined organic extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (70 g) with benzene as eluant to give the hydroxymethylene compound (**14**) (4.14 g, 89%) as a pale yellowish oil; *m/z* 286 (M^+); $\nu_{max.}(CHCl_3)$ 1 640 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.30 (3 H, d, *J* 8.0 Hz, Me), 3.70 (3 H, s, OMe), 6.40—6.96 (3 H, m, ArH), and 8.56 (1 H, br s, OH).

5-Methoxy-1-(2-methyl-3-oxo-4-phenylthiomethylenecyclohexylmethyl)-1,2-dihydrocyclobutabenzene (**6a**).—Methanesulphonyl chloride (0.14 ml) was added to a solution of the hydroxymethylene compound (**14**) (264 mg) in pyridine (10 ml) and stirring was continued for 30 min at room temperature.

After addition of thiophenol (0.13 ml), the reaction mixture was stirred for 2 h at room temperature, diluted with water (5 ml) and extracted with benzene. The combined extract was washed with saturated aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (10 g) with benzene as an eluant to give the *thiomethylene* compound (**6a**) (292 mg, 84%) as a pale yellowish oil (Found: C, 76.3; H, 6.9. $C_{24}H_{26}O_2S$ requires C, 76.15; H, 6.9%); *m/z* 378 (M^+); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1} (CO); δ_H(CCl_4) 1.20 (3 H, d, *J* 8.0 Hz, Me), 3.60 (3 H, s, OMe), 6.30—6.90 (3 H, m, ArH), and 7.30 (6 H, br s, ArH, C=CH).

3-*Methoxy*-7-*methyl*-9-*phenylthio*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**4a**) and 3-*Methoxy*-7-*methyl*-9-*phenylthio*-4bα,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**5a**).—A solution of the thiomethylene compound (**6a**) (207 mg) in *o*-dichlorobenzene (20 ml) was refluxed for 10 h under an atmosphere of nitrogen. The solvent was evaporated, and the residue was chromatographed on silica gel (5 g), with n-hexane–benzene (1:1 v/v) as eluant, to give a mixture of the tetracyclic compounds (**4a**) and (**5a**) (196 mg, 94%) as a pale yellowish oil (Found: C, 76.15; H, 7.2. Calc. for $C_{24}H_{26}O_2S$: C, 76.15; H, 6.9%); *m/z* 378 (M^+); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO); δ_H(CCl_4) 0.82—1.20 (3 H, m, Me), 3.70 (3 H, s, OMe), 6.30—6.93 (3 H, m, ArH), and 7.20 (5 H, br s, ArH).

3-*Methoxy*-7-*methyl*-9-*phenylsulphinyl*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**16**) and 3-*Methoxy*-7-*methyl*-9-*phenylsulphinyl*-4bα,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**20**).—To a solution of the mixture of the sulphide (**4a**) and (**5a**) (984 mg) in CH_2Cl_2 (5 ml) was added dropwise a solution of MCPBA (449 mg) in CH_2Cl_2 (3 ml) with stirring at 0 °C. The mixture was stirred for 30 min at room temperature, after which it was neutralized with saturated aqueous $NaHCO_3$; the organic layer was then separated, washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel (20 g) with AcOEt as eluant to give a mixture of the sulphoxides (**16**) and (**20**) (816 mg, 62%) as a colourless oil (Found: C, 75.25; H, 7.0. $C_{24}H_{28}O_2S$ requires C, 75.75; H, 7.4%); *m/z* 394 (M^+); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO); δ_H(CCl_4) 0.82—1.50 (3 H, m, Me), 3.70 (3 H, s, OMe), 6.30—7.06 (3 H, m, ArH), and 7.60 (5 H, br s, ArH).

3-*Methoxy*-7-*methyl*-4bβ,5,6,8a-*tetrahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**17**) and 3-*Methoxy*-7-*methyl*-4bα,5,6,8a-*tetrahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**21**).—A solution of the mixed (**16**) and (**20**) (139 mg) in toluene (5 ml) was refluxed for 1 h. Evaporation of the solvent gave the residue which was chromatographed on silica gel (5 g). From the first fraction using n-hexane–benzene (4:1 v/v) as eluant, a colourless powder was obtained which crystallized from n-hexane–benzene (3:1 v/v) to give the *styrene* (**21**) (76 mg, 60%) as colourless needles, m.p. 133—134 °C (Found: M^+, *m/z* 268.1469. $C_{18}H_{20}O_2$ requires *M*, 268.1471); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO); δ_H($CDCl_3$) 0.98, 1.10 (3 H, each d, *J* 8 Hz, Me), 3.76 (3 H, s, OMe), 5.35, 5.38 (1 H, each d, *J* 10 Hz, ArC=C*H*), 6.34 (1 H, d, *J* 10 Hz, ArC*H*=C), and 6.60—7.04 (3 H, m, ArH).

From the second fraction with benzene as eluant, the *styrene* (**17**) (33 mg, 26%) was obtained as a colourless oil (Found: M^+, *m/z* 268.1458. $C_{18}H_{20}O_2$ requires *M*, 268.1471); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO); δ_H($CDCl_3$) 1.15, 1.26 (3 H, each d, *J* 6 Hz, Me), 3.70 (3 H, s, OMe), 6.08 (1 H, d, *J* 10 Hz, ArC=C*H*), 6.30 (1 H, d, *J* 10 Hz, ArC*H*=C), and 6.60—7.00 (3 H, m, ArH).

3-*Methoxy*-7-*methyl*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**18**).—A mixture of the styrene (**17**) (33 mg), 5% palladium–carbon (10 mg), and MeOH (5 ml) was stirred for 3 h under an atmosphere of hydrogen. The mixture was filtered through Celite and the filtrate was evaporated to give the residue which was chromatographed on silica gel (1 g) with $CHCl_3$ as an eluant to afford the *ketone* (**18**) (15 mg, 45%) as a colourless oil (Found: M^+, *m/z* 270.1623. $C_{18}H_{22}O_2$ requires *M*, 270.1620); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO); δ_H($CDCl_3$) 1.08, 1.26 (3 H, each d, *J* 7 Hz, Me), 3.70 (3 H, s, OMe), and 6.33—7.03 (3 H, m, ArH).

3-*Methoxy*-7-*methyl*-4bα,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* (**22**).—By following the same procedure described for the ketone (**18**), the *ketone* (**22**) was obtained from the styrene (**21**) as a colourless oil in 59% yield (Found: M^+, *m/z* 270.1623. $C_{18}H_{22}O_2$ requires *M*, 270.1620); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO); δ_H($CDCl_3$) 1.20, 1.33 (3 H, each d, *J* 7 Hz, Me), 3.80 (3 H, s, OMe), and 6.60—7.20 (3 H, m, ArH).

3-*Methoxy*-7-*methyl*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* *Toluene*-p-*sulphonylhydrazone* (**19**).—A mixture of the ketone (**18**) (190 mg), toluene-*p*-sulphonylhydrazine (144 mg), concentrated H_2SO_4 (0.05 ml), and MeOH (5 ml) was refluxed for 3 h. The reaction mixture was then neutralized with saturated aqueous $NaHCO_3$, diluted with water (50 ml), and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was chromatographed on silica gel (2 g) with $CHCl_3$ as eluant to afford the *hydrazone* (**19**) (120 mg, 49%) as a colourless oil (Found: M^+, *m/z* 438.1978. $C_{25}H_{30}N_2O_3S$ requires *M*, 438.1978); $\nu_{max.}$($CHCl_3$) 3 250 cm^{-1} (NH); δ_H($CDCl_3$) 1.18 (3 H, d, *J* 7 Hz, Me), 2.39 (3 H, s, Me), 3.75 (3 H, s, OMe), 6.35—6.85 (3 H, m, ArH), 7.00 (2 H, d, *J* 8 Hz, ArH), and 7.52 (2 H, d, *J* 8 Hz, ArH).

3-*Methoxy*-7-*methyl*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthren*-8(7H)-*one* *Toluene*-p-*sulphonylhydrazone* (**23**).—By following the same procedure as described for the hydrazone (**19**), the *hydrazone* (**23**) was obtained from the ketone (**22**) as colourless prisms (53% yield), m.p. 203—204 °C (from MeOH) (Found: M^+, *m/z* 438.1978. $C_{25}H_{30}N_2O_3S$ requires *M*, 438.1978); $\nu_{max.}$($CHCl_3$) 3 250 cm^{-1} (NH); δ_H($CDCl_3$) 1.10 (3 H, d, *J* 7 Hz, Me), 2.40 (3 H, s, Me), 3.80 (3 H, s, OMe), 6.30—6.90 (3 H, m, ArH), 7.05 (2 H, d, *J* 8 Hz, ArH), and 7.60 (2 H, d, *J* 8 Hz, ArH).

3-*Methoxy*-7-*methyl*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthrene* (**3**).—To a solution of the hydrazone (**19**) (120 mg) in anhydrous THF (5 ml) was added n-butyl-lithium in n-hexane (1.56M; 1 ml) at −78 °C. The reaction mixture was stirred for 30 min at the same temperature and for 1 h at room temperature, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O. The combined extract was washed with saturated aqueous NaCl and then dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (1 g) with benzene as eluant to give the *olefinic tetracyclic compound* (**3**) (28 mg, 32%) as a colourless oil (Found: M^+, *m/z* 254.1683. $C_{18}H_{22}O$ requires *M*, 254.1671); δ_H($CDCl_3$) 1.76 (3 H, d, *J* 1.0 Hz, Me), 3.70 (3 H, s, OMe), 5.60 (1 H, br s, C=C*H*), and 6.50—7.00 (3 H, m, ArH).

3-*Methoxy*-7-*methyl*-4bα,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthrene* (**24**).—By following the same procedure as described for the compound (**3**), the *olefinic tetracycle* (**24**) was obtained from the hydrazone (**23**) in 80% yield as a colourless oil (Found: M^+, *m/z* 254.1683. $C_{18}H_{22}O$ requires *M*, 254.1671); δ_H($CDCl_3$) 1.70 (3 H, d, *J* 1.0 Hz, Me), 3.76 (3 H, s, OMe), 5.60 (1 H, br s, C*H*=C), and 6.42—7.00 (3 H, m, ArH).

1-*Cyano*-5-*methoxy*-1-(2-*methyl*-4-*oxocyclohex*-1-*enylmethyl*)-1,2-*dihydrocyclobutabenzene* (**27**).—To a stirred solution of LDA [prepared by addition of n-butyl lithium (1.56M; 1.25 ml) to a solution of di-isopropylamine (0.3 ml) in anhydrous THF (10 ml) at −78 °C] was added dropwise a solution of 1-cyano-5-methoxybenzocyclobutene (**25**) (282 mg) in anhydrous THF (10 ml). Stirring was continued for 20 min at the same temperature. After addition of HMPA (0.5 ml) and a solution of 3-methyl-4-methylenecyclohex-2-enone (**26**) (197 mg) in anhydrous THF (5 ml), the reaction mixture was stirred for 1 h at the same temperature, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica gel (5 g) with CH_2Cl_2 as eluant afforded the β,γ-*unsaturated enone* (**27**) (248 mg, 81%) as a colourless oil (Found: C, 76.45; H, 6.7; N, 4.85. $C_{18}H_{19}NO_2$ requires C, 76.85; H, 6.8; N, 5.0%); *m/z* 281 (M^+); $\nu_{max.}$($CHCl_3$) 2 200 (C≡N) and 1 705 cm^{-1} (CO); δ_H(CCl_4) 1.63 (3 H, s, Me), 2.15—2.60 (4 H, m, CH_2CH_2C=O), 2.80 (4 H, s, CH_2C=CCH_2CO), 3.30, 3.45 (2 H, each s, ArCH_2), 3.70 (3 H, s, OMe), and 6.55—7.15 (3 H, m, ArH).

1-*Cyano*-1-(4,4-*ethylenedioxy*-2-*methylcyclohex*-1-*enylmethyl*)-5-*methoxy*-1,2-*dihydrocyclobutabenzene* (**28**).—A mixture of the ketone (**27**) (13.0 g), ethylene glycol (3.6 g), catalytic amount of toluene-*p*-sulphonic acid, and benzene (100 ml) was refluxed for 2 h, with removal of water generated. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried (Na_2SO_4). Removal of the solvent gave the residue which was chromatographed on silica gel (150 g) with benzene as eluant to afford the *acetal* (**28**) (11.0 g, 73%) as a pale yellowish oil (Found: C, 73.6; H, 7.2; N, 4.15. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1; N, 4.3%); *m/z* 325 (M^+); $\nu_{max.}$($CHCl_3$) 2 200 cm^{-1} (C≡N); δ_H(CCl_4) 1.47 (3 H, br s, Me), 3.26, 3.40 (2 H, each d, *J* 14 Hz, ArCH_2), 3.70 (3 H, s, OMe), 3.86 (4 H, s, OCH_2CH_2O), and 6.54—7.00 (3 H, m, ArH).

1-(4,4-*Ethylenedioxy*-2-*methylcyclohex*-1-*enylmethyl*)-5-*methoxy*-1,2-*dihydrocyclobutabenzene* (**29**).—To a stirred solution of the cyano acetal (**28**) (2.7 g), absolute EtOH (1 ml), anhydrous THF (20 ml), and liquid NH_3 (50 ml) was added sodium (0.38 g) at −78 °C. The solution was then stirred for 3 h at the same temperature. After evaporation of the solvent, the residue was diluted with water (100 ml) and extracted with Et_2O. The combined ethereal extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Removal of the solvent gave a yellowish gum, which was chromatographed on silica gel (50 g) with benzene as an eluant to afford the decyanated acetal (**29**) (2.0 g, 80%) as a colourless oil, *m/z* 300 (M^+); δ_H(CCl_4) 1.53 (3 H, br s, Me), 3.43 (2 H, br s, ArCH_2), 3.66 (3 H, s, OMe), 3.83 (4 H, s, OCH_2CH_2O), and 6.46—6.96 (3 H, m, ArH).

5-*Methoxy*-1-(2-*methyl*-4-*oxocyclohex*-2-*enylmethyl*)-1,2-*dihydrocyclobutabenzene* (**30**).—A mixture of the acetal (**29**) (18.0 g), 10% HCl solution (2 ml), and MeOH (200 ml) was stirred for 5 h at room temperature. After evaporation of the solvent, the residue was diluted with water (100 ml) and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl and dried (Na_2SO_4). Removal of the solvent gave a yellowish oil, which was chromatographed on silica gel (300 g) using CH_2Cl_2 as an eluant to afford the *enone* (**30**) (12.0 g, 78%) as a pale yellowish oil (Found: C, 79.65; H, 7.9. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.85%); *m/z* 256 (M^+); $\nu_{max.}$($CHCl_3$) 1 650 cm^{-1} (CO); δ_H(CCl_4) 1.93 (3 H, br s, Me), 3.06—3.62 (3 H, m, ArCH, ArCH_2), 5.66 (1 H, br s, C=CHCO), and 6.50—7.00 (3 H, m, ArH).

5-*Methoxy*-1-(2-*methyl*-4-*oxo*-2-*phenylthiocyclohexylmethyl*)-1,2-*dihydrocyclobutabenzene* (**31**).—A mixture of the enone (**30**) (10.8 g), Et_3N (50 ml), and thiophenol (4.5 ml) was stirred for 12 h at room temperature and then neutralized with 10% HCl solution. The reaction mixture was extracted with benzene and the combined extracts were then washed with saturated aqueous NaCl solution and dried (Na_2SO_4). Evaporation of the solvent left a colourless powder which was crystallized from Et_2O to give the *addition compound* (**31**) (8.0 g, 52%) as a colourless powder, m.p. 158—160 °C (Found: C, 75.85; H, 7.3. $C_{23}H_{26}O_2S$ requires C, 75.35; H, 7.15%); *m/z* 366 (M^+); $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (CO); δ_H(CCl_4) 1.10, 1.20 (3 H, each s, Me), 3.70 (3 H, s, OMe), 6.40—7.00 (3 H, m, ArH), and 7.23 (5 H, br s, ArH).

5-*Methoxy*-1-(2-*methyl*-4-*methylenecyclohexylmethyl*)-1,2-*dihydrocyclobutabenzene* (**6b**).—To a stirred solution of triphenylphosphonium methylide [prepared from methyltriphenylphosphonium bromide (12.4 g) and 1.56M-n-butyllithium solution (21.5 ml) in n-hexane] in anhydrous THF (30 ml) was added a solution of the ketone (**31**) (8.5 g) in anhydrous THF (50 ml) at 0 °C. The reaction mixture was stirred for 1 h and then treated with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue resulting from evaporation of the solvent was chromatographed on silica gel (200 g) with benzene as eluant to give the exo-*methylene derivative* (**6b**) (5.2 g, 62%) as a pale yellowish oil (Found: C, 78.85; H, 7.85. $C_{24}H_{28}OS$ requires C, 79.05; H, 7.75%); *m/z* 364 (M^+); δ_H(CCl_4) 1.20 (3 H, s, Me), 3.70 (3 H, s, OMe), 4.60 (1 H, br s, C=CH), 4.80 (1 H, br s, C=CH), 6.50—7.00 (3 H, m, ArH), and 7.25 (5 H, br s, ArH).

3-*Methoxy*-7-*methyl*-7-*phenylthio*-4bβ,5,6,7,8,8a,9,10-*octahydro*-6α,8aα-*ethanophenanthrene* (**4b**) and 3-*Methoxy*-7-*methyl*-7-*phenylthio*-4bα,5,6,7,8,8a,9,10-*octahydro*-6α,8aα-*ethanophenanthrene* (**5b**).—A solution of the *exo*-methylene compound (**6b**) (5.0 g) in *o*-dichlorobenzene (200 ml) was refluxed for 5 h under an atmosphere of nitrogen. After evaporation of the solvent, the residue was chromatographed on silica gel (100 g) with benzene as eluant to give a mixture of the *tetracyclic sulphides* (**4b**) and (**5b**) (3.3 g, 66%) as a pale yellowish oil (Found: C, 79.2; H, 7.85. $C_{24}H_{28}OS$ requires C, 79.05; H, 7.75%); *m/z* 364 (M^+); δ_H(CCl_4) 1.36 (3 H, s, Me), 3.68 (3 H, s, OMe), 6.33—6.93 (3 H, m, ArH), and 7.20 (5 H, br s, ArH).

3-*Methoxy*-7-*methyl*-4bβ,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthrene* (**3**) and 3-*Methoxy*-7-*methyl*-4bα,5,6,8a,9,10-*hexahydro*-6α,8aα-*ethanophenanthrene* (**24**) via *the Sulphoxides* (**32**) *and* (**33**).—To a solution of the mixed sulphides (**4b**) and (**5b**) (4.3 g) in CH_2Cl_2 (150 ml) was added dropwise a solution of MCPBA (2.1 g) in CH_2Cl_2 (30 ml) with stirring at 0 °C. The mixture was stirred for 30 min at room temperature, and then neutralized with saturated aqueous $NaHCO_3$; the organic layer was separated, washed with saturated aqueous NaCl solution, and then dried (Na_2SO_4). The residue resulting from evaporation of the solvent was chromatographed on silica gel (70 g) with AcOEt as eluant to give a mixture of the sulphoxides (**32**) and (**33**) (3.05 g, 68%); *m/z* 380 (M^+); δ_H(CCl_4) 1.00 (3 H, s, Me), 3.72 (3 H, s, OMe), 6.45—7.10 (3 H, m, ArH), and 7.40 (5 H, br s, ArH).

A solution of the mixed sulphoxides (**32**) and (**33**) (3.05 g) in toluene (80 ml) was refluxed for 2 h. Evaporation of the solvent gave a residue which was chromatographed on silica gel (60 g) to give the olefinic tetracyclic compounds (**3**) (0.12 g, 6%) and (**24**) (0.12 g, 6%) as a colourless oil with n-hexane and n-hexane–benzene (9:1 v/v) respectively. The compounds (**3**) and (**24**) thus obtained were identical with those prepared by the Shapiro

reaction of the hydrazones (**19**) and (**23**) respectively in all aspects.

2-*Oxo*-$\Delta^{1,10}$-18,19,20-*trinorisoatisirene* (**34**).—To a solution of lithium (20 mg) in liquid NH_3 (10 ml), a solution of the compound (**3**) (31 mg) in anhydrous THF (5 ml) and absolute EtOH (0.2 ml) was added at −78 °C. The reaction mixture was then stirred for 2 h at the same temperature, before addition of EtOH (2 ml), and evaporation of the solvent. The residue was diluted with MeOH (5 ml) and CH_2Cl_2 (3 ml) and treated with 10% HCl solution (0.5 ml). After the reaction mixture had been stirred for 3 h at room temperature, the residue resulting from evaporation of the solvent was extracted with Et_2O. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to give the residue which was chromatographed on silica gel (1 g) with CH_2Cl_2 as eluant to afford the *enone* (**34**) (10 mg, 34%) as a colourless oil (Found: M^+, *m/z* 242.1688. $C_{17}H_{22}O$ requires *M*, 242.1671); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1} (CO); δ_H(CCl_4) 1.76 (3 H, d, *J* 1.0 Hz, Me), 5.50 (1 H, br s, C=C*H*), and 5.83 (1 H, br s, C=C*H*CO).

1,10-*Epoxy*-2-*oxo*-18,19,20-*trinorisoatisirene* (**35**).—To a solution of the enone (**34**) (23 mg) in MeOH (5 ml) was added H_2O_2 (30%; 0.5 ml) and 10% aqueous NaOH (0.5 ml) at 0 °C. After being stirred for 1 h at the same temperature the reaction mixture was diluted with water (30 ml) and extracted with Et_2O. The combined extracts were washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent left a colourless oil which was chromatographed on silica gel (1 g) with benzene as eluant to give the *epoxide* (**35**) (10 mg, 41%) as a colourless oil (Found: M^+, *m/z* 258.1667. $C_{17}H_{22}O_2$ requires *M*, 258.1620); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (CO); δ_H(CCl_4) 1.76 (3 H, d, *J* 1.0 Hz, Me), 3.80 (1 H, br s, OCC*H*CO), and 5.60 (1 H, br s, C=C*H*).

2α-*But*-3-*ynyl*-6-*methyl*-3,4,4a,7,8,8a-*hexahydro*-4α,7α-*ethanonaphthalen*-1(2H)-*one* (**36**).—A solution of the epoxide (**35**) (68 mg) and toluene-*p*-sulphonylhydrazine (58 mg) in AcOH (2 ml) and CH_2Cl_2 (2 ml) was stirred for 1 h at −20 °C and then 12 h at room temperature. The reaction mixture was diluted with water (30 ml) and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent left a yellow gum, which was chromatographed on silica gel (2 g) with CH_2Cl_2 as eluant to afford the *acetylenic ketone* (**36**) (27 mg, 42%) as a yellowish oil (Found: M^+, *m/z* 242.1688. $C_{17}H_{22}O$ requires *M*, 242.1671); $\nu_{max.}$($CHCl_3$) 3 310 (C≡CH) and 1 700 cm^{-1} (CO); δ_H(CCl_4) 1.80 (3 H, d, *J* 1.0 Hz, Me), and 5.60 (1 H, br s, C=C*H*).

2α-*But*-3-*ynyl*-1,6-*dimethyl*-1,2,3,4,4a,7,8,8a-*octahydro*-4α,7α-*ethanonaphthalen*-1-*ol* (**37**).—To a solution of the acetylenic ketone (**36**) (27 mg) in Et_2O (1 ml) was added 1.2M-methyl-lithium solution in Et_2O (5 ml) at 0 °C. The mixture was stirred for 15 min at the same temperature and then 10 min at room temperature, before being treated with water (5 ml). The organic layer was separated, washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated. The residue was then chromatographed on silica gel (1 g) with benzene as eluant to give the *acetylenic alcohol* (**37**) (23 mg, 77%) as a colourless oil (Found: M^+, *m/z* 258.1983. $C_{18}H_{26}O$ requires *M*, 258.1983); $\nu_{max.}$($CHCl_3$) 3 550 (OH) and 3 300 cm^{-1} (C≡CH); δ_H(CCl_3) 1.05 (3 H, s, Me), 1.76 (3 H, d, *J* 1.0 Hz, Me), and 5.58 (1 H, br s, C=C*H*).

2-*Oxo*-18,19-*dinorisoatisirene* (**38**).—To a mixture of CF_3CO_2H (2 ml) and $(CF_3CO)_2O$ (1 ml) was added the acetylenic alcohol (**37**) (9.6 mg) at −18 °C. The resulting mixture was stirred for 30 min at the same temperature and then evaporated. The residue was dissolved in a mixture of acetone (2 ml) and MeOH (2 ml), and the resulting solution was treated with 10% HCl solution (0.2 ml) and then stirred for 10 h at room temperature. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, the solvent removed, and the residue extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent left a yellowish gum, which was chromatographed on silica gel (500 mg) with benzene as eluant to give the 2-*oxo*-18,19-*dinorisoatisirene* (**38**) (5 mg, 52%) as a colourless oil (Found: M^+, *m/z* 258.1623. $C_{18}H_{26}O$ requires *M*, 258.1620); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (CO); δ_H(CCl_4) 0.80 (3 H, s, Me), 1.78 (3 H, d, *J* 1.0 Hz, Me), and 5.60 (1 H, br s, C=C*H*).

2-*Oxo*-18,19-*dinor*-Δ^3-*isoatisirene* (**39**).—To the residue resulting from the removal of solvent from a solution of $PdCl_2$ (3 mg) in concentrated HCl (0.3 ml) was added Bu^tOH (2 ml) and a solution of the ketone (**38**) (3.0 mg) in Bu^tOH (1 ml). The reaction mixture was stirred for 24 h at 80 °C, filtered through Celite, and the filtrate diluted with water (10 ml) and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent left a residue which was chromatographed on silica gel (100 mg) with benzene as eluant to afford the *enone* (**39**) (2.0 mg, 67%) (Found: M^+, *m/z* 256.1656. $C_{18}H_{24}O$ requires *M*, 256.1617); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1} (CO); δ_H(CCl_4) 0.80 (3 H, s, Me), 1.80 (3 H, d, *J* 1 Hz, Me), 5.60 (1 H, br s, C=C*H*), 5.90 (1 H, br s, C*H*=CCO), and 6.08 (1 H, br s, C=C*H*CO).

2-*Oxo*-18-*norisoatisirene* (**2**).—To a stirred solution of lithium dimethylcuprate [prepared from CuI (5.0 mg) and 1.2M-methyl-lithium solution in Et_2O (5 ml)] was added a solution of the enone (**39**) (2.0 mg) in anhydrous Et_2O (1 ml) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution. The ethereal layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to give a residue which was chromatographed on silica gel (100 mg) with $CHCl_3$ as eluant to give the 2-*oxo*-18-*norisoatisirene* (**2**) (1.0 mg, 47%) as a colourless oil; *m/z* 272 (M^+); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (CO); δ_H($CDCl_3$) 0.82 (3 H, s, Me), 0.89 (3 H, d, *J* 6 Hz, Me), 1.80 (3 H, br s, Me), and 5.60 (1 H, br s, C=CH).

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