High Diastereoselection in the Intramolecular Diels–Alder Reaction of *o*-Quinodimethanes: an Expedient Entry to *trans*-Benzoperhydrindans. A Highly Stereoselective Total Synthesis of (±)-Estrone and (±)-Adrenosterone‡

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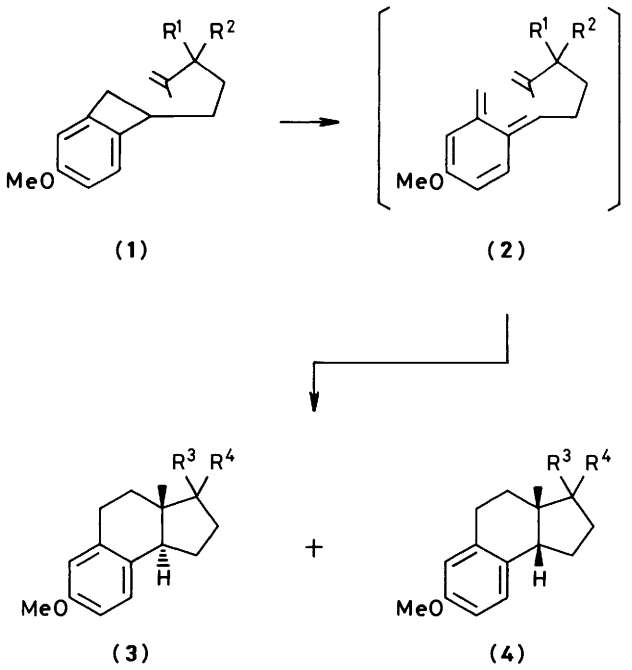
A substituent effect on the diastereoselectivity of an intramolecular Diels–Alder reaction of *o*-quinodimethanes has been studied and a highly diastereoselective synthesis of *trans*-benzoperhydrindan, which is a key intermediate for the synthesis of steroids, has been achieved by the thermolysis of 2-[2-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)ethyl]-2-isopropenyl-1,3-dioxolane, followed by acid hydrolysis of the initial product in quantitative yield. *trans*-Benzoperhydrindan was subsequently converted into (±)-estrone and (±)-adrenosterone.

Angularly alkylated *trans*-perhydrindans are widely encountered in a variety of natural products [1] and a large volume of research [2] has been devoted to the construction of this skeleton. In particular, the stereoselective synthesis, useful for practical production of properly functionalised *trans*-perhydrindans, is now an important subject for synthetic organic chemists since such skeletons constitute an essential part of many physiologically important steroids and could be useful synthons. Thus, we undertook an investigation into the stereoselective synthesis of the *trans*-benzoperhydrindan (**3**) *via* an intramolecular Diels–Alder reaction§ of the *o*-quinodimethane (**2**) (see Scheme 1). In so doing, we took advantage (1) of the above reaction for the rapid creation of the desired ring system (2) the ease of access [3] to the substrate (**1**), and (3) the promising utility [3a,d,e] of product (**3**) for the synthesis of steroids. Here, we report our observations on the high diastereoselection in an intramolecular Diels–Alder reaction of *o*-quinodimethanes which provides access to *trans*-benzoperhydrindans in an effective total synthesis of (±)-estrone [4] and (±)-adrenosterone, [5] the latter of which is an important intermediate in corticosteroid syntheses.

Synthesis of trans-*Benzoperhydrindan*.—The substrates (**1b, g**) for the thermolysis were prepared by a standard acetalisation process of (**1a**) [3f,g] by using methyl orthoformate for (**1b**) and the corresponding diol for (**1d—g**). Compound (**1c**) was prepared by a treatment of (**1b**) with trimethylsilyl iodide [6] and compound (**1h**) was obtained by a reaction of the lithio derivative of dithiane (**5**) [7] with the iodide (**6**) (see Scheme 2). [8]

The results of the cyclisations are reported in the Table. Although, in the case of (**1a**), the stereoselection on ring juncture formation was not high, high stereoselectivity in the series (**1b—h**) was observed. This was especially so for (**1f**) and (**1g**), where the reaction provided both a high yield and high diastereoselection.

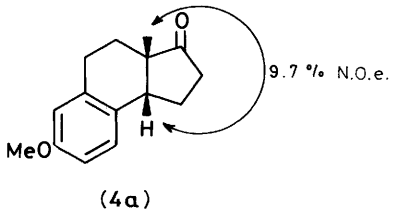
Although compound (**1h**) afforded the cyclised product with high stereoselectivity, the deprotection process did not occur smoothly. These contrasting stereochemical features of the cyclisation suggest considerable steric repulsion in the transition state between *o*-quinodimethanes and R^1 and R^2 which lead to the *cis*-isomer (**4**).¶ Thus, with (**1f**) and (**1g**), since the conformational rigidity of the five-membered ring compared with that of (**1b—e**) brings about serious steric congestion in



Scheme 1.

† Deceased October, 1988.
‡ A preliminary communication of part of this work appeared in *Tetrahedron Lett.*, 1988, **29**, 4959.
§ Previous similar type of approach to *trans*-perhydrindans [2iii] and *trans*-benzoperhydrindans [3] has shown that only moderate selectivities (60—80% *trans*) were observed.

¶ The relative stereochemistry of (**4a**) was determined on the basis of n.O.e. experiments, in which 9.7% n.O.e. between the angular methyl proton and methine proton was observed.

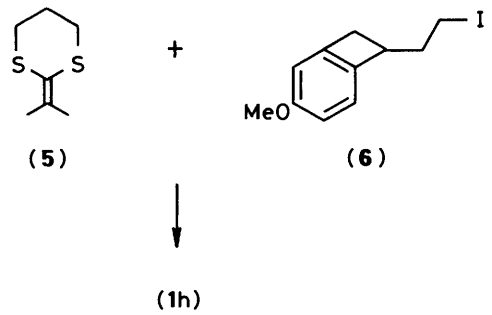


(4a)

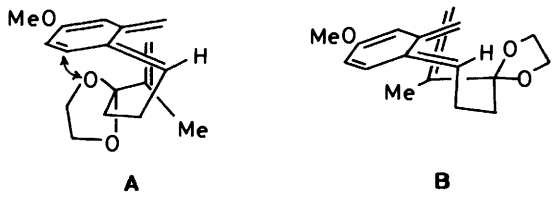
Table.[a]

Entry	Substrates	Reaction time (h)	Products* Ratio of (**3a**) to (**4a**)[c]	Products* Yield (%)
1	(**1a**; $R^1 = R^2 = O$)[d]	3	59:41	74
2[b]	(**1b**; $R^1 = R^2 = OMe$)	3	95:5	41[e]
3[b]	[**1c**; MeC(=CH_2)C(OMe)C=CH~)	3	91:9	25[f]
4[b]	[**1d**; $R^1 = R^2 = O(CH_2)_3O$]	3	87:13	90
5[b]	[**1e**; $R^1 = R^2 = OCH(Me)CH_2CH(Me)O$]	2	88:12	92
6[b]	[**1f**; $R^1 = R^2 = O(CH_2)_2O$]	5	95:5	96
7[b]	[**1g**; $R^1 = R^2 = OCH(Me)CH(Me)O$]	5	95:5	98
8[b]	[**1h**; $R^1 = R^2 = S(CH_2)_3S$]	6	100:0	51

[a] All reactions were conducted in *o*-dichlorobenzene at 180 °C. [b] Initial products were directly hydrolysed (for entries 2—7: 10%HCl, acetone, room temperature; for entry 8: MeI, $NaHCO_3$, MeCN, 50 °C, 7 h) to the corresponding ketones and then analysed. [c] (**3a**; $R^3 = R^4 = O$); (**4a**; $R^3 = R^4 = O$). [d] Ref. 3*f*. [e] (**1a**) Was recovered in 31% yield. [f] (**1a**) Was recovered in 51% yield.
* The signal due to the angular methyl group in its ^1H n.m.r. spectrum was the most diagnostically useful and was used for the analysis of the products ratios: namely, δ 0.72 and 1.12 for (**3a**) and (**4a**) respectively.



Scheme 2.



Scheme 3.

transition state **A** leading to the *cis*-isomer (**4**), the reaction might be forced to proceed *via* transition state **B** leading to the *trans*-isomer (**3**) (see Scheme 3).

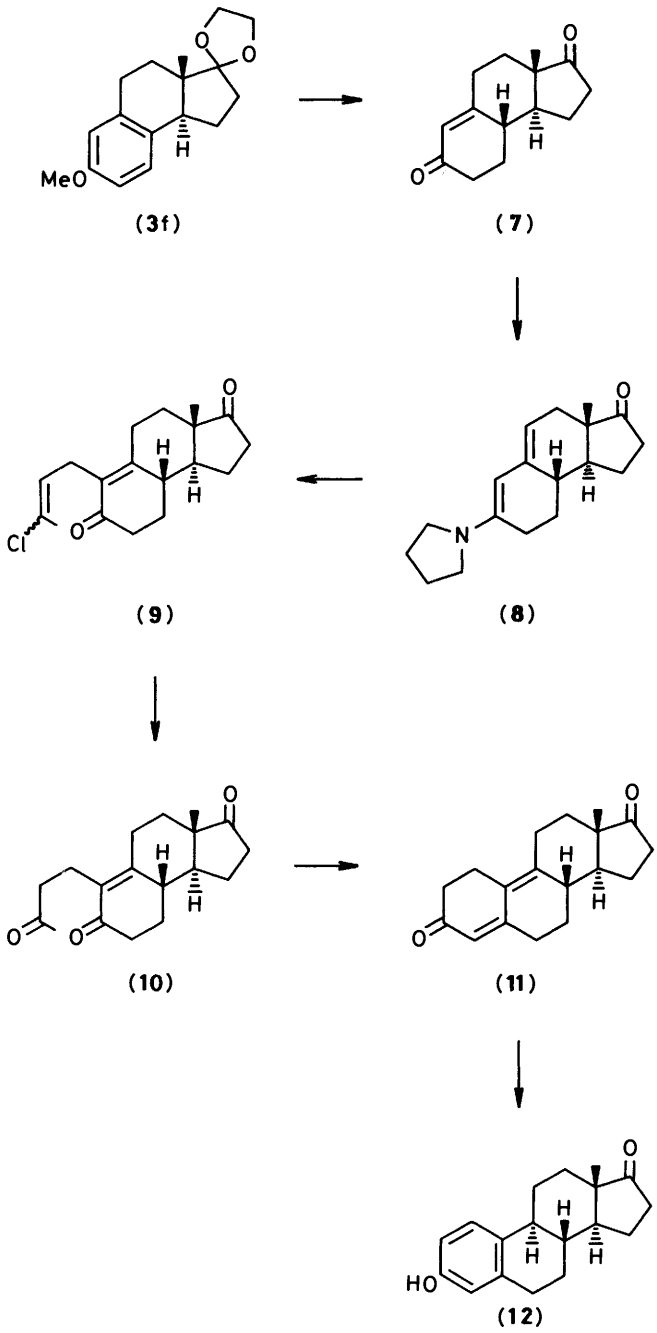
The difference in atomic size between oxygen and sulphur also appears to be a major factor which influences the stereoselectivities of (**1h**) and (**1d**).

Synthesis of (±)-*Estrone* (**12**).—Since, from a synthetic point of view, compounds (**1f**) or (**1g**) would be compounds of choice for the synthesis of 17-oxosteroids, a simple and stereoselective synthesis of (±)-estrone (**12**) was investigated as follows (see Scheme 4).

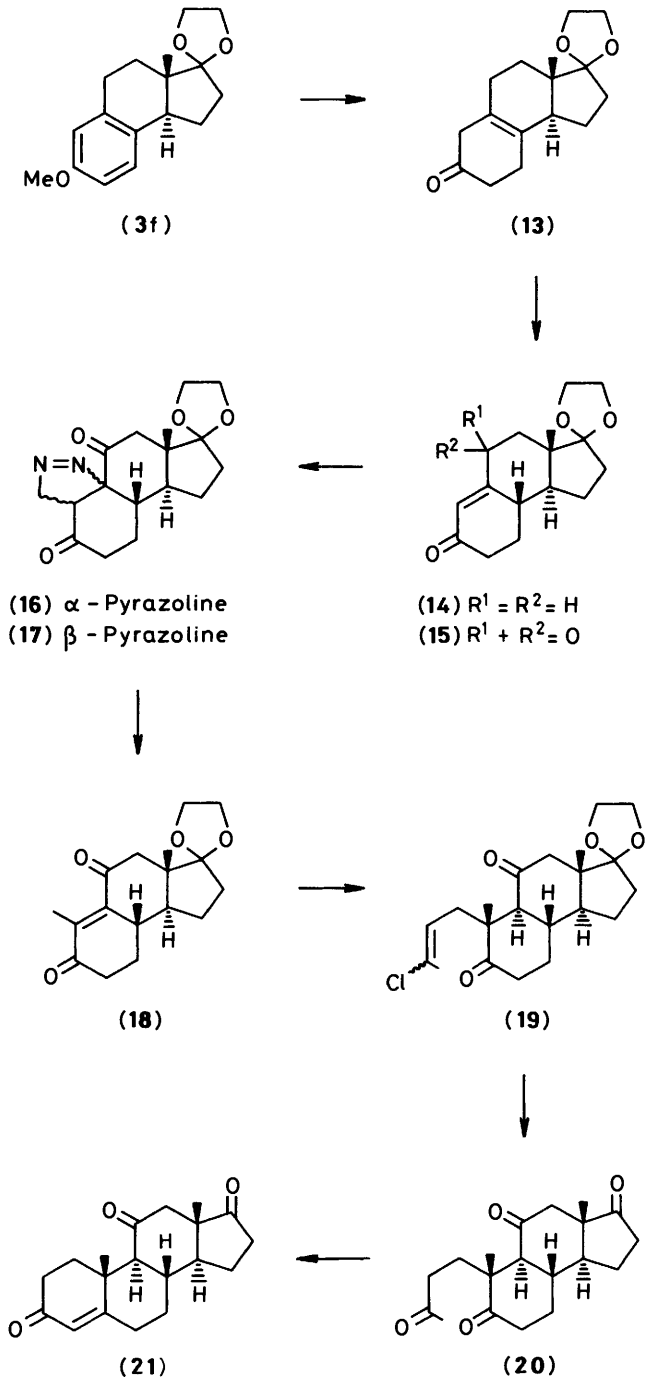
First, the *trans*-benzoperhydrindan (**3f**), which was easily obtained in 90% yield by crystallisation of the crude product derived from the thermolysis of (**1f**) (entry 6 in the Table), was successively subjected to Birch reduction (Li, EtOH, liq. NH_3, THF) and acid hydrolysis (10% HCl, MeOH) to give the enone (**7**) [*m*/*z* 218 (M^+)] in 82% overall yield. Treatment of the latter with pyrrolidine then produced the enamine (**8**), which reacted with Wichterle's reagent (1,3-dichlorobut-2-ene)[9] in DMF to afford (**9**) in 82% overall yield. Finally, hydrolysis (97% H_2SO_4, AcOH) followed by cyclisation (NaOPent^t, toluene) of (**10**) afforded in 62% overall yield the dienedione (**11**) (m.p. 108—109 °C, di-isopropyl ether) [*m*/*z* 218 (M^+)] whose spectral properties (i.r., ^1H n.m.r. 500 MHz, ^{13}C n.m.r. 125.65 MHz) and t.l.c. behaviour were identical with those of an authentic sample.[10] Since the conversion of the (+)-dienedione (**11**) into (+)-estrone (**12**) has already been achieved,[4a,11] this work constitutes a formal total synthesis of (±)-estrone (**12**).

Synthesis of (±)-*Adrenosterone* (**21**).—Although we have previously developed a novel route to (±)-11-oxoprogesterone[3e] *via* a compound similar to the dienedione (**11**), stereoselectivity in the introduction of the 19-methyl group and the total yield of this synthesis were unsatisfactory. Therefore, a new and stereoselective synthesis of (±)-adrenosterone (**21**) was investigated as follows (see Scheme 5). First, the *trans*-benzoperhydrindan (**3f**) was subjected to Birch reduction (Li, EtOH, liq. NH_3, THF) and acid hydrolysis [$(CO_2H)_2$, EtOH, H_2O] to give the β,γ-unsaturated ketone (**13**) [*m*/*z* 262 (M^+)] in 92% overall yield. The subsequent conjugation of the β,γ-unsaturated ketone (**13**) into the α,β-unsaturated ketone (**14**) [*m*/*z* 262 (M^+)] was effected by using a catalytic amount of *N*,*N*-dimethylethylenediamine in 78% yield. Other catalysts such as 2,2,2-trifluoroethylamine hydrochloride and 2,2,2-trifluoroethylamine[12] did not give satisfactory results. Next, the α,β-unsaturated enone (**14**) was oxidized[13] (3,5-dimethylpyrazole–chromium trioxide complex, CH_2Cl_2) to give the enedione (**15**) [*m*/*z* 276 (M^+)] in 66% yield. Treatment of the enedione (**15**) with diazomethane[14] afforded a separable mixture of the α-pyrazoline (**16**) and the β-pyrazoline (**17**) in the ratio of 3:2 in 93% yield. A mixture of the α-pyrazoline (**16**) and the β-pyrazoline (**17**) was heated (180 °C, *o*-dichlorobenzene) to afford the methylated compound (**18**) [*m*/*z* 290 (M^+)] in 72% yield. The transformation of (**18**) into (±)-adrenosterone (**21**) was straightforward as follows. Reduction[5b] (Li, liq. NH_3, THF) of (**18**), followed by trapping of the resulting dienolate with 1-bromo-3-chlorobut-2-ene[5b] afforded a 72% yield of (**19**) [*m*/*z* 381, 379 ($M^+ + 2$), (M^+)]. Finally, hydrolysis (H_2SO_4, AcOH) followed by cyclisation [KOH, MeOH, H_2O] of (**20**) furnished the initial target compound (±)-adrenosterone (**21**) [*m*/*z* 300 (M^+)] (m.p. 184—185 °C, ethyl acetate)[15] in 56% overall yield whose spectral properties (i.r., ^1H n.m.r. 500 MHz) and t.l.c. behaviour were identical with those of natural sample.* Thus, the series of reaction we have developed provide efficient access to *trans*-benzoperhydrindans and an effective method for the synthesis of (±)-estrone and (±)-adrenosterone.

* Commercially available (+)-adrenosterone was used as a natural sample.



Scheme 4.



Scheme 5.

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 obtained on a JEOL PS-100, JEOL FX-90, and JNM GX-500 spectrometers. Chemical shifts were reported as δ values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M-52G and JEOL-TMS-01SG-2 spectrometers. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue obtained when the organic layer was separated, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. All new compounds described in this Experimental sections were homogeneous on t.l.c.

1-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-3,3-*dimethoxy*-4-*methylpent*-4-*ene* (**1b**).—To a stirred solution of the enone (**1a**) (105 mg, 0.46 mmol) in anhydrous methanol (4 ml) was added trimethyl orthoformate (1.94 g, 18.2 mmol) and D-camphor-10-sulphonic acid (catalytic amount) at room temperature, and the mixture was stirred for 3 h at the same temperature. The mixture was neutralized with saturated aqueous sodium hydrogen carbonate and the solvent was then evaporated. The residue was diluted with water (20 ml) and extracted with ether, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) to give the *dimethyl acetal* (**1b**) (118.5 mg, 94%) as an oil; $\nu_{max.}(CHCl_3)$ 1 135 cm^{-1} (C–O); δ_H(100 MHz; $CDCl_3$) 1.66 (3 H, s, C=CMe), 3.10 (3 H, s, OMe),

3.12 (3 H, s, OMe), 3.74 (3 H, s, OMe), 5.04 (1 H, br s, C=CH_2), 5.21 (1 H, br s, C=CH_2), and 6.58—7.04 (3 H, m, ArH) (Found: M^+, 276.1716. $C_{17}H_{24}O_3$ requires M, 276.1724).

1-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-3-*methoxy*-4-*methylpenta*-2,4-*diene* (**1c**).—To a stirred solution of the dimethyl acetal (**1b**) (30.6 mg, 0.11 mmol) in dichloromethane (2 ml) was added trimethylsilyl iodide (35 mg, 0.17 mmol) and hexamethyldisilazane (31 mg, 0.19 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. The mixture was diluted with water (10 ml) and extracted with dichloromethane, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) to afford the *dienol ether* (**1c**) (19 mg, 70%) as an oil; $\delta_H(CDCl_3)$ 1.84 (3 H, br s, C=CMe), 3.53 (3 H, s, OMe), 3.68 (3 H, s, OMe), 4.59 (1 H, t, *J* 8 Hz, MeOC=CH), 4.86—5.28 (2 H, m, C=CH_2), and 6.60—7.04 (3 H, m, ArH) (Found: M^+, 244.1464. $C_{16}H_{20}O_2$ requires M, 244.1464).

1-[(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-1,3-*dioxane* (**1d**).—To a solution of the enone (**1a**) (151 mg, 0.66 mmol) in benzene (16 ml) was added toluene-*p*-sulphonic acid (catalytic amount) and propane-1,3-diol (251 mg, 3.3 mmol). The reaction mixture was refluxed in a flask fitted with a Dean-Stark trap for 6 h and then diluted with benzene (30 ml); the benzene solution was then washed with saturated aqueous sodium hydrogen carbonate and saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (97:3, v/v) to yield the *acetal* (**1d**) (151 mg, 79%) as an oil; $\delta_H(CDCl_3)$ 1.70 (3 H, s, C=CMe), 3.72—3.88 (4 H, m, OCH_2), 3.75 (3 H, s, OMe), 5.08 (1 H, br s, C=CH_2), 5.14 (1 H, br s, C=CH_2), and 6.55—7.00 (3 H, m, ArH) (Found: M^+, 288.1709. $C_{18}N_{24}O_3$ requires M, 288.1726).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-4,6-*dimethyl*-1,3-*dioxane* (**1e**).—Similar treatment of the enone (**1a**) (200 mg, 0.87 mmol), as described for (**1d**), afforded the *acetal* (**1e**) (216 mg, 79%) as an oil (Found: C, 75.7; H, 9.2. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%); $\delta_H(CDCl_3)$ 1.14 (6 H, d, *J* 6 Hz, OCH*Me*), 1.65 (3 H, s, C=CMe), 3.70 (3 H, s, OMe), 4.95 (1 H, br s, C=CH_2), 5.05 (1 H, br s, C=CH_2), and 6.60—7.00 (3 H, m, ArH); *m*/*z* 316 (M^+).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-1,3-*dioxolane* (**1f**).—Similar treatment of the enone (**1a**) (4.0 g, 17.4 mmol), as described for (**1d**), afforded the *ethylene acetal* (**1f**) (4.6 g, 95%) as an oil (Found: C, 74.6; H, 8.4. $C_{17}H_{22}O_3$ requires C, 74.05; H, 8.1%); $\delta_H(CDCl_3)$ 1.73 (3 H, s, C=CMe), 3.73 (3 H, s, OMe), 3.83 (4 H, br s, OCH_2CH_2O), 4.83 (1 H, br s, C=CH_2), 5.06 (1 H, br s, C=CH_2), and 6.50—7.00 (3 H, m, ArH); *m*/*z* 274 (M^+).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-4,5-*dimethyl*-1,3-*dioxolane* (**1g**).—Similar treatment of the enone (**1a**) (143 mg, 0.62 mmol), as described for (**1d**), afforded the *dioxolane* (**1g**) (169 mg, 90%) as an oil (Found: C, 75.25; H, 8.85. $C_{19}H_{26}O_3$ requires C, 75.45; H, 8.65%); $\delta_H(CDCl_3)$ 1.04—1.24 (6 H, m, OCH*Me*), 1.66 (3 H, br s, C=CMe), 3.50—3.61 (1 H, m, OCH), 3.75 (3 H, s, OMe), 3.98—4.19 (1 H, m, OCH), 4.84 (1 H, br s, C=CH_2), 5.12 (1 H, br s, C=CH_2), and 6.60—7.02 (3 H, m, ArH); *m*/*z* 302 (M^+).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-1,3-*dithiane* (**1h**).—To a stirred solution of 2-isopropylidene-1,3-dithiane (**5**) (125 mg, 0.78 mmol) in anhydrous tetrahydrofuran (4 ml) and hexamethylphosphoramide (420 mg, 2.4 mmol) was added butyl-lithium (1.33M hexane solution; 0.61 ml, 0.81 mmol) at −78 °C. After the mixture had been stirred for 1 h at −20 °C, 2-(1,2-dihydro-4-methoxybenzocyclobutenyl)ethyl iodide (**6**) (155 mg, 0.54 mmol) in anhydrous tetrahydrofuran (2 ml) was added to it at −20 °C, and stirring was continued for 15 min at the same temperature. After being quenched with saturated aqueous ammonium chloride (5 ml), the mixture was extracted with ether and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) to give the *thioacetal* (**1h**) (132 mg, 76%) as a pale yellow oil; $\delta_H(CDCl_3)$ 1.84 (3 H, br s, C=CMe), 3.75 (3 H, s, OMe), 5.22 (1 H, br s, C=CH_2), 5.42 (1 H, br s, C=CH_2), and 6.60—7.04 (3 H, m, ArH) (Found: M^+, 320.1275. $C_{18}H_{24}OS_2$ requires M, 320.1268).

Thermolysis of (**1a**).—A solution of the enone (**1a**) (92 mg, 0.4 mmol) in *o*-dichlorobenzene (10 ml) was heated at 180 °C for 3 h. Removal of the solvent gave a crude mixture of the ketones (**3a**) and (**4a**) [$\delta_H(CDCl_3)$ 0.72 (1.77 H, s, Me), 1.12 (1.23 H, s, Me), 3.75 (3 H, s, OMe), and 6.50—7.10 (3 H, m, ArH)]. The mixture was chromatographed with hexane–ethyl acetate (19:1, v/v) to yield the *ketone* (**4a**) (7 mg, 8%) as an oil; $\nu_{max.}(CHCl_3)$ 1 730 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.12 (3 H, s, CMe), 1.50—1.60 (2 H, m), 1.75—1.85 (2 H, m), 2.30—2.43 (2 H, m), 2.67 (1 H, dt, *J* 5.5, 16 Hz), 2.78 (1 H, ddd, *J* 5.5, 9, 16 Hz), 3.19 (1 H, t, *J* 7.4 Hz), 3.78 (3 H, s, OMe), 6.63 (1 H, d, *J* 2 Hz, ArH), 6.77 (1 H, dd, *J* 2, 6.2 Hz, ArH), and 7.12 (1 H, d, *J* 6.2 Hz, ArH) (Found: M^+, 230.1305. $C_{15}H_{18}O_2$ requires M, 230.1305). From the later fractions, a mixture of (**3a**) and (**4a**) (42 mg, 46%) was obtained as an oil. From the later fractions, the pure *ketone* (**3a**) (18 mg, 20%) was obtained as needles after recrystallisation from hexane, which was identical with an authentic sample.[3a]

General Procedure for Thermolysis of the Acetals (**1b**—**g**).—A solution of the acetal (0.25 mmol) in *o*-dichlorobenzene (12 ml) was heated at 180 °C for 3 h. After removal of the solvent, the residue was dissolved in acetone (5 ml) containing 10% aqueous hydrochloric acid (3 ml) and stirred for 1 h at room temperature. The mixture was basified with sodium hydrogen carbonate and the solvent was evaporated. The residue was diluted with water (10 ml) and extracted with ether, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) to give (**3**) and (**4**).

Thermolysis of (**1h**) *and Synthesis of* trans-7-*Methoxy*-3aβ-*methyl*-3a,4,5,9b-*tetrahydro*-1H-*benz*[e]*inden*-3-*one* (**3a**).—A solution of the thioacetal (**1h**) (4.9 mg, 0.015 mmol) in *o*-dichlorobenzene (2.5 ml) was heated at 180 °C for 6 h. After removal of the solvent, the residue was dissolved in acetonitrile (1.2 ml) and water (0.3 ml). This solution was treated with methyl iodide (70.6 mg, 0.49 mmol) and sodium carbonate (25 mg, 0.24 mmol) for 7 h at 50 °C. The mixture was diluted with water (10 ml) and extracted with ether, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) to give the ketone (**3a**)[3a] (1.8 mg, 51%).

trans-3,3-*Ethylenedioxy*-7-*methoxy*-3aβ-*methyl*-3a,4,5,9b-*tetrahydro*-1H-*benz*[e]*indene* (**3f**).—A solution of the acetal (**1f**) (3.3 g, 12.2 mmol) in *o*-dichlorobenzene (180 ml) was heated at 180 °C for 5 h. After removal of the solvent, the residue was recrystallized from ether to furnish trans-*benzoperhydrindan* (**3f**) (3.0 g, 90%) as needles, m.p. 78—79 °C (Found: C, 74.05; H, 8.15. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.1%); $\delta_H(CDCl_3)$ 0.72 (3 H, s, Me), 3.75 (3 H, s, OMe), 3.92 (4 H, br s, OCH_2), and 6.52—6.98 (3 H, m, ArH); *m*/*z* 274 (M^+).

anti-trans-3aβ-*Methyl*-3a,4,5,9,9a,9b-*hexahydro*-1H-*benz*[e]-*indene*-3,7-*dione* (**7**).—A solution of *trans*-benzoperhydrindan

(**3f**) (6.5 g, 23.7 mmol) in anhydrous tetrahydrofuran (160 ml) and ethanol (20 ml) was added cautiously to liquid ammonia (400 ml). To this solution was added lithium (890 mg, 127.1 mmol) at −78 °C. After the mixture had been stirred for 30 min at −78 °C, ethanol (20 ml) was added dropwise, and the solvent was then evaporated. The residue was diluted with water (100 ml) and the mixture was extracted with ether and the extract was washed with saturated brine. The extract was evaporated to give the residue which was dissolved in methanol (250 ml) containing 10% aqueous hydrochloric acid (15 ml) and refluxed for 12 h. The mixture was basified with sodium hydrogen carbonate and the solvent was then evaporated. The residue was diluted with water (30 ml) and extracted with ether, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl aceate (3:1, v/v) to afford the *enone* (**7**) (4.2 g, 82%) as needles after recrystallisation from methanol, m.p. 121—122 °C (Found: C, 76.65; H, 8.55. $C_{14}H_{18}O_2$ requires C, 77.05; H, 8.3%); $\nu_{max.}$($CHCl_3$) 1 665 and 1 742 cm^{-1} (C=O); δ_H($CDCl_3$) 1.04 (3 H, s, Me) and 5.88 (1 H, s, CHCO); *m/z* 218 (M^+).

anti-trans-6-(3-*Chlorobut*-2-*enyl*)-3aβ-*methyl*-3a,4,5,9,9a,9b-*hexahydro*-1H-*benz*[e]*indene*-3,7-*dione* (**9**).—The enone (**7**) (1.2 g, 5.5 mmol) was dissolved in pyrrolidine (0.735 ml) and the mixture was diluted with methanol to give the *monoenamine* (**8**) (1.24 g, 83%) as pale green needles, m.p. 93—94 °C; $\nu_{max.}$($CHCl_3$) 1 742 cm^{-1} (C=O); δ_H($CDCl_3$) 0.91 (3 H, s, Me), 3.04—3.30 (4 H, m, CH_2NCH_2), 4.89 (1 H, s, NC=CH), and 5.02 (1 H, br s, NC=CHC=C*H*) (Found: M^+, 271.1922. $C_{18}H_{25}NO$ requires *M*, 271.1934).

To a stirred solution of the monoenamine (**8**) (1.24 g, 4.6 mmol) in dimethylformamide (20 ml) was added potassium iodide (939 mg, 5.7 mmol) and 1,3-dichlorobut-2-ene (962 mg, 5.7 mmol) at 0 °C, and the mixture was stirred for 1 h at the same temperature. It was then diluted with water (10 ml) and 10% aqueous hydrochloric acid (2 ml), and the resulting mixture was heated at 100 °C for 3 h. After this the mixture was diluted with water (20 ml) and extracted with chloroform, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (4:1, v/v) to afford the *butenyl chloride* (**9**) (1.39 g, 99%) as a pale yellow oil (Found: C, 70.85; H, 7.35; Cl, 11.9. $C_{18}H_{23}ClO_2$ requires, C. 70.45; H, 7.55; Cl, 11.55%); $\nu_{max.}$($CHCl_3$) 1 665 and 1 740 cm^{-1} (C=O); δ_H($CDCl_3$) 1.05 (3 H, s, Me), 2.18 (3 H, s, Me), and 5.34 (1 H, t, *J* 7 Hz, ClC=CH); *m/z* 308 (M^+ + 2) and 306 (M^+).

anti-trans-3aβ-*Methyl*-3-*oxobutyl*-3a,4,5,9,9a,9b-*hexahydro*-1H-*benz*[e]*indene*-3,7-*dione* (**10**).—To a stirred solution of (**9**) (8.6 mg, 0.028 mmol) in acetic acid (0.04 ml) was added concentrated sulphuric acid (0.18 ml) at 0 °C. After being stirred for 5 min at the same temperature, the reaction mixture was warmed to room temperature and stirred for 40 min. It was then diluted with water (10 ml) and extracted with chloroform, and the extract was washed with saturated brine. The residue upon work-up was chromatographed using benzene–ethyl acetate (4:1, v/v) to give the *triketone* (**10**) (8 mg, 99%) as an oil (Found: C, 74.7; H, 8.5. $C_{18}H_{24}O_3$ requires C, 74.95; H, 8.4%); $\nu_{max.}$($CHCl_3$) 1 660, 1 715, and 1 740 cm^{-1} (C=O); δ_H($CDCl_3$) 1.02 (3 H, s, Me) and 2.12 (3 H, s, COMe); *m/z* 288 (M^+).

Estra-4,9(10)-*diene*-3,17-*dione* (**11**).—To a solution of 2-methylbutan-2-ol (210 mg, 2.38 mmol) in anhydrous toluene (25 ml) was added sodium (48 mg, 2.08 mmol) at room temperature, and the mixture was refluxed for 12 h. The resulting mixture was cooled to room temperature, and the triketone (**10**) (419 mg, 1.45 mmol) in anhydrous toluene (2 ml) was added dropwise. The reaction mixture was stirred for 2 h at the same temperature, after which it was quenched with acetic acid and the solvent evaporated. The residue was diluted with water (30 ml) and extracted with chloroform, and the extract was washed with saturated brine. The residue upon work-up was chromatographed using benzene–ethyl acetate (9:1, v/v) to afford the *dienedione* (**11**) (247 mg, 63%) as needles after recrystallisation from di-isopropyl ether, m.p. 108—109 °C; $\nu_{max.}$($CHCl_3$) 1 655 and 1 740 cm^{-1} (C=O); δ_H($CDCl_3$) 1.02 (3 H, s, Me), 1.32—1.54 (4 H, m), 1.65 (1 H, ddd, *J* 7, 10, 19 Hz), 1.93 (1 H, ddd, *J* 3, 5, 12 Hz), 1.98—2.07 (2 H, m), 2.13 (1 H, t, *J* 9 Hz), 2.17 (1 H, t, *J* 9 Hz), 2.36—2.60 (7 H, m), 2.86—2.95 (2 H, m), and 5.71 (1 H, br s, COCH); δ_C($CDCl_3$) 13.2, 21.9, 25.2, 25.9, 26.6, 30.7, 31.5, 35.9, 37.1, 38.8, 47.5, 51.3, 122.7, 126.4, 144.6, 156.44, 199.5, and 219.6; *m/z* 218 (M^+), whose spectral data were identical with those of an authentic sample.[10]

trans-3,3-*Ethylenedioxy*-3aβ-*methyl*-3a,4,5,6,9,9b-*hexahydro*-1H-*benz*[e]*inden*-7-*one* (**13**).—A solution of the acetal (**3f**) (1.8 g, 6.57 mmol) in anhydrous tetrahydrofuran (48 ml) and ethanol (5.6 ml) was added cautiously to liquid ammonia (112 ml). Lithium (241 mg, 34.4 mmol) was then added to this solution at −78 °C. After the mixture had been stirred for 30 min at −78 °C, ethanol was added dropwise, and the solvent was then evaporated. The residue was diluted with water (60 ml), the mixture was extracted with ether, and the extract was washed with saturated brine and evaporated to give a residue. This was dissolved in ethanol (55 ml) and water (5.9 ml) and the solution treated with oxalic acid (618 mg, 6.87 mmol) for 2 h at room temperature. The mixture was neutralized with a 10% aqueous sodium hydroxide and the solvent was then evaporated. The residue was diluted with water (60 ml) and extracted with ether, and the extract was washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) to afford the β,γ-*unsaturated enone* (**13**) (1.58 g, 92%) as prisms after recrystallisation from ether, m.p. 65—67 °C (Found: C, 73.35; H, 8.65. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%); $\nu_{max.}$(CHCl) 1 720 cm^{-1} (C=O); δ_H($CDCl_3$) 0.84 (3 H, s, CMe) and 3.80—4.00 (4 H, m, OCH_2CH_2O); *m/z* 262 (M^+).

anti-trans-3,3-*Ethylenedioxy*-3aβ-*methyl*-3a,4,5,9,9a,9b-*hexahydro*-1H-*benz*[e]*inden*-7-*one* (**14**).—To a solution of *N*,*N*-dimethylethylenediamine (40 mg, 0.046 mmol) in methanol (80 ml) was added a soluton of the β,γ-unsaturated enone (**13**) (1.47 g, 5.6 mmol) in methanol (10 ml). The reaction mixtue was refluxed for 15 h. After removal of the solvent, the residue was chromatographed with hexane–ethyl acetate (87:13, v/v) to yield the α,β-*unsaturated enone* (**14**) (1.1 g, 78%) as prisms after recrystallisation from ether, m.p. 114—115 °C (Found: C, 73.35; H, 8.65. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%); $\nu_{max.}$($CHCl_3$) 1 655 cm^{-1} (C=O); δ_H($CDCl_3$) 1.05 (3 H, s, CMe), 3.80—4.00 (4 H, m, OCH_2CH_2O), and 5.85 (1 H, br s, COCH); *m/z* 262 (M^+).

anti-trans-3,3-*Ethylenedioxy*-3aβ-*methyl*-3a,9,9a,9b-*tetrahydro*-1H-*benz*[e]*indene*-5,7-*dione* (**15**).—To a stirred suspension of chromium trioxide (159 mg, 1.59 mmol) in dichloromethane (1 ml) was added a solution of 3,5-dimethylpyrazole (153 mg, 1.59 mmol) in dichloromethane (1 ml) at −20 °C. After the mixture had been stirred for 1 h, a solution of the α,β-unsaturated enone (**14**) (11.9 mg, 0.045 mmol) in dichloromethane (0.5 ml) was added to it at −20 °C; the reaction mixture was then stirred for 20 h at the room temperature. 10% Aqueous sodium hydroxide (2 ml) was then added and the mixture was stirred for 1 h at 0 °C after which it was diluted with water (4 ml) and extracted with dichloromethane. The extract was washed with 10% aqueous hydrochloric acid and saturated brine. The residue upon work-up was chromatographed using

hexane–ethyl acetate (17:3, v/v) to give the *enedione* (**15**) (8.3 mg, 66%) as prisms after recyrstallisation from ether; m.p. 123—124 °C (Found: C, 69.4; H, 7.35. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.3%); $\nu_{max.}$(CHCl$_3$) 1 680 cm^{-1} (C=O); δ_H(CDCl$_3$) 1.00 (3 H, s, CMe) and 3.80—4.00 (4 H, m, OCH_2CH_2O); *m/z* 276 (M^+).

1,3-*Dipolar Cycloaddition of* (**15**) *with Diazomethane*.—To a stirred solution of the enedione (**15**) (14.7 mg, 0.053 mmol) in chloroform (1 ml) was added a solution of diazomethane in ether (2 ml) at 0 °C, and the reaction mixture was stirred for 3.5 h at the same temperature. After removal of the solvent, the residue was chromatographed with hexane–ethyl acetate (17:3, v/v) to afford the α-pyrazoline (**16**) (9.6 mg, 57%) as an oil; $\nu_{max.}$(CHCl$_2$) 1 710 and 1 725 cm^{-1} (C=O); δ_H(CDCl$_3$) 1.00 (3 H, s, CMe), 3.80—4.00 (4 H, m, OCH_2CH_2O), 4.28 (1 H, dd, *J* 18.5, 8.6 Hz, N_2CH_2), and 5.17 (1 H, dd, *J* 18.5, 1 Hz, N_2CH_2); *m/z* 290 (M^+ − 28). From the later fractions (hexane–ethyl acetate, 4:1 v/v), the β-pyrazoline (**17**) (6.1 mg, 36%) was obtained as an oil; $\nu_{max.}$(CHCl$_3$) 1 710 cm^{-1} (C=O); δ_H(CDCl$_3$) 1.18 (3 H, s, CMe), 3.80—4.00 (4 H, m, OCH_2CH_2O), 4.42 (1 H, dd, *J* 18.5, 8.6 Hz, N_2CH_2), and 4.99 (1 H, dd, *J* 18.5, 1 Hz, N_2CH_2); *m/z* (M^+ − 28).

anti-trans-3,3-*Ethylenedioxy*-3aβ,6-*dimethyl*-3a,9,9a,9b-*tetrahydro*-1H-*benz*[e]*indene*-5,7-*dione* (**18**).—A solution of the mixture of the pyrazoline (**16**) and (**17**) (9.3 mg, 0.029 mmol) in *o*-dichlorobenzene (3 ml) was heated at 180 °C for 5 min. After removal of the solvent, the residue was chromatographed with hexane–ethyl acetate (83:17, v/v) to give the *methylated compound* (**18**) (6.1 mg, 72%) as needles after recrystallisation from ether, m.p. 145—147 °C (Found: C, 69.95; H, 7.35. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.65%); $\nu_{max.}$(CHCl$_3$) 1 680 cm^{-1} (C=O); δ_H(CDCl$_3$) 0.96 (3 H, s, CMe), 1.90 [3 H, d, *J* 2.8 Hz, COC(Me)=CCO], and 3.80—4.00 (4 H, m, OCH_2CH_2O); *m/z* 290 (M^+).

trans-anti-trans-6a-(3-*Chlorobut*-2-*enyl*)-3,3-*ethylenedioxy*-3aβ,6β-*dimethyl*-3a,5a,6,9,9a,9b-*hexahydro*-1H-*benz*[e]*indene*-5,7-*dione* (**19**).—A solution of the dione (**18**) (48 mg, 0.17 mmol) in anhydrous tetrahydrofuran (8 ml) was added cautiously in liquid ammonia (10 ml). To this solution was added lithium (8 mg, 1.14 mmol) at −78 °C. The resulting mixture was warmed to −20 °C over 20 min, and then stirred for 1 h at the same temperature. To this mixture was added 1-bromo-3-chlorobut-2-ene (334 mg, 1.37 mmol) in anhydrous tetrahydrofuran (2 ml) at −20 °C and the reaction mixture was stirred for 40 min at the same temperature. After being quenched with ethanol (1 ml), the solvent was then evaporated. The residue was diluted with water (5 ml), and the mixture was extracted with chloroform, and the extract was washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) to afford the *alkylated compound* (**19**) (45 mg, 72%) as a pale yellow oil; $\nu_{max.}$(CHCl$_3$) 1 705 cm^{-1} (C=O); δ_H(CDCl$_3$) 0.88 (3 H, s, CMe), 1.32 (3 H, s, COCMe), 1.95 (3 H, br s, C=CM), 3.80—4.00 (4 H, m, OCH_2CH_2O), and 5.32—5.90 (1 H, m, C=CH) (Found: M^+ + 2, 381.1662, M^+, 379.1678. $C_{21}H_{29}ClO_4$ requires M^+ + 2, 381.1647, *M*, 379.1676).

trans-anti-trans-3,3-*Ethylenedioxy*-3aβ,6β-*dimethyl*-6α-(3-*oxobutyl*)-3a,5a,6,9,9a,9b-*hexahydro*-1H-*benz*[e]*indene*-5,7-*dione* (**20**).—To a stirred solution of the alkylated compound (**19**) (20.0 mg, 0.52 mmol) in acetic acid (0.06 ml) was added concentrated sulphuric acid (0.3 ml) cautiously at 0 °C, and the mixture was stirred for 5 min at the same temperature. The mixture was warmed to room temperature and stirred for a further 45 min at the same temperature, after which it was diluted with water (4 ml) and extracted with chloroform; the extract was washed with saturated brine. The residue upon work-up was chromatographed using chloroform to give the *tetraketone* (**20**) (10.2 mg, 60%) as an oil; $\nu_{max.}$(CHCl$_3$) 1 710 and 1 740 cm^{-1} (C=O); δ_H(CDCl$_3$) 0.89 (3 H, s, CMe), 1.32 (3 H, s, CMe), 2.11 (3 H, s, COMe), and 1.40—2.90 (17 H, m) (Found: M^+, 318.1839. $C_{19}H_{26}O_4$ requires *M*, 318.1831).

(±)-*Adrenosterone* (**21**).—To a stirred solution of the tetraketone (**20**) (10.0 mg, 0.031 mmol) in methanol (4 ml) was added 10% aqueous potassium hydroxide (0.4 ml) at the room temperature. After being stirred for 1 h at 50 °C, the mixture was diluted with water (5 ml), and extracted with chloroform, and the extract was washed with saturated brine. The residue upon work-up was chromatographed with chloroform to yield (±)-adrenosterone (**21**) (8.9 mg, 94%) as needles after recrystallisation from ethyl acetate, m.p. 184—185 °C; $\nu_{max.}$(CHCl$_3$) 1 660, 1 710, and 1 740 cm^{-1} (C=O); δ_H(CDCl$_3$) 0.89 (3 H, s, CMe), 1.31 (1 H, m), 1.44 (3 H, s, CMe), 1.63—1.74 (2 H, m), 1.87—1.95 (2 H, m), 2.03—2.18 (3 H, m), 2.25—2.38 (4 H, m), 2.42—2.62 (4 H, m), 2.78 (1 H, ddd, *J* 3.2, 5.5, 13.9 Hz), and 5.75 (1 H br s); *m/z* 300 (M^+); the spectral data for this compound were identical with those of a natural sample.*

* Commercially available (+)-adrenosterone was used as a natural sample.

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