2-Benzopyran-3-ones as Synthetic Building Blocks; Regioselective Diels–Alder Additions with Simple Olefins leading to Aromatic Steroids

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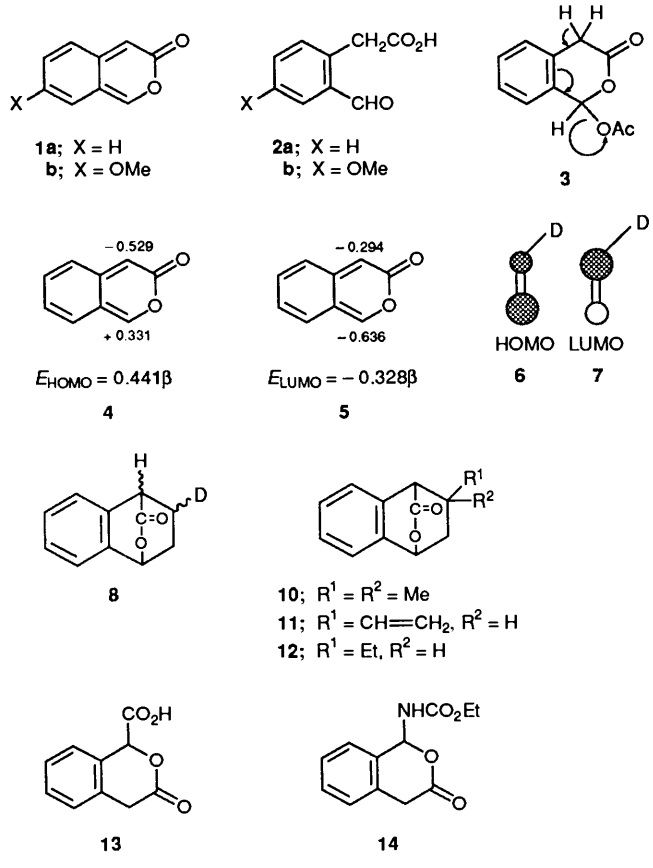
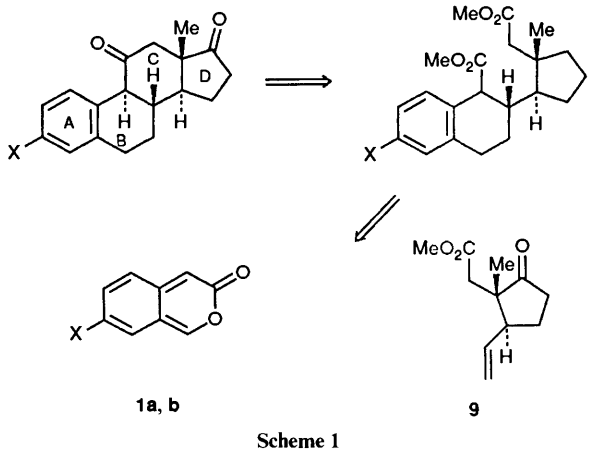
2-Benzopyran-3-one **1a** undergoes strongly regioselective Diels–Alder additions to buta-1,3-diene, 2-methylpropene, but-1-ene and the olefin **9**. The main adducts **17a** and **17b** from **1a** and **1b** respectively and the olefin **9**(≡**16**) are derived by *endo*- and *exo*-addition to the *re*-face of **9**(≡**16**). These adducts are converted into the 8α,9α-steroids **22a** and **22b** by a four-step sequence including Dieckmann cyclisation of **21a** and **21b** as the key step. The derived 8α,9α-steroids **24a** and **24b** can be epimerised at C-8 *via* the enones **26a** and **26b** and lithium–ammonia reduction. Other aromatic steroids obtained by this general route are the equilenin derivative **28** and the dihydronaphthalene **29**.

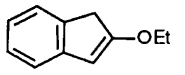
2-Benzopyran-3-one **1a** is a reactive intermediate responsible for the yellow colour of hot acetic anhydride solutions of *o*-formylphenylacetic acid **2a**.[1] Unlike many other *o*-quinonoid compounds **1a** does not appear to dimerise/oligomerise readily.[2,3] This greater resistance to dimerisation of **1a** in comparison with *e.g.* α-cyano-*o*-quinodimethane† may be due to the method of its generation which provides only a very small concentration of the *o*-quinodimethane associated with the non-destructive equilibrium **3** ⇌ **1a** + HOAc. When **1a** is produced in high concentration small quantities of dimers as well as much oligomeric/polymeric material is produced.[1] 2-Benzopyran-3-ones are therefore good dienes in intermolecular Diels–Alder reactions. The parent **1a** is efficiently trapped not only by electron-deficient dienophiles[2] but also with simple olefins like cyclopentene and *cis*-but-2-ene.[5] The additions of *cis*-but-2-ene and cyclopentene to **1a** are *endo*-selective[5] and this has been attributed to secondary interactions involving alkyl groups (steric attraction).[3,5] Both the HOMO and LUMO of **1a** derived from a Huckel calculation show large differences in magnitude at C-1 and C-4 as shown in **4** and **5**. Since the HOMO and LUMO of electron-donor (D) substituted olefins are biased as indicated in **6** and **7** the addition of such olefins to **1a** should lead to the regioisomer shown in **8**.[6] This is true whether such additions are truly inverse electron demand additions or not, although the energies of the HOMO and LUMO shown in **4** and **5** suggest that in the addition to ethylene and donor substituted ethylenes the LUMO-pyrone ↔ HOMO-olefin interaction should be the more important. On the other hand electron-acceptor substituted olefins would be expected to add to **1a** with opposite regioselectivity. These characteristics of the 2-benzopyran-3-one system suggested that these molecules could be useful building blocks in synthesis. In particular, a range of functionalised naphthalenes, as well as dihydro- and tetrahydro-naphthalenes should be readily prepared *via* intermolecular Diels–Alder additions. Thus, natural products of the aromatic steroid, podophyllotoxin, and anthracyclinone type might be accessible. Herein we explore the possibility of making aromatic steroids *via* the retrosynthesis of Scheme 1. The steroid ring-B would be formed by a regioselective Diels–Alder addition and ring-C by a Dieckmann cyclisation. The olefin 9



† When generated from 1-cyanobenzocyclobutene in the presence of a trap *ca.* 33% of this diene is dimerised.[4]



Scheme 1



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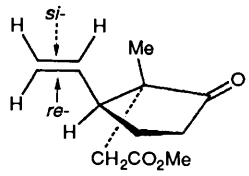

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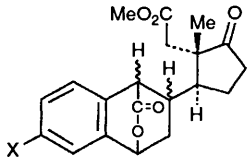
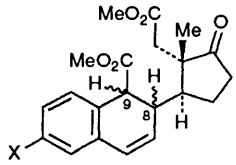


17a; X = H
b; X = OMe



18a; X = H
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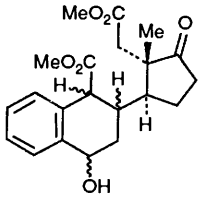

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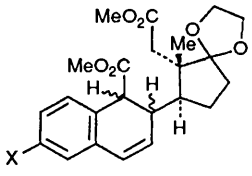


20a; X = H
b; X = OMe

required for this route is readily available having been prepared for steroid synthesis *via* intramolecular addition to an *o*-quinodimethane;[7,8] the preparation of **9** due to Ito and his collaborators[7b] is particularly attractive in providing the highest *trans*:*cis* ratio.

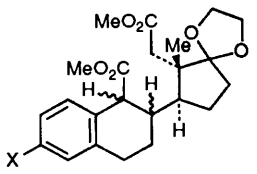
In agreement with the prediction of FMO theory the addition of simple olefins to **1a** was found to be strongly regioselective. Isobutene gave the adduct **10**, and butadiene gave *endo*- and *exo*-**11** (ratio 5.5:1) as the only isolable products. But-1-ene gave a 3.5:1 mixture of regioisomers with *endo*- and *exo*-**12** predominating (*endo*:*exo* ratio, 3.5:1).

Dehydration of **2a*** in boiling acetic anhydride in the presence of the olefin **9** (2.2 equiv.) gave, in 70% yield, a mixture of adducts in which the adducts of correct regiochemistry for steroid synthesis predominated (ratio 5.1:1, 400 MHz ^{1}H NMR). The four adducts of correct regiochemistry derive by *endo*- and *exo*- addition to the diastereotopic faces of the olefin **9**. Subsequent transformation of the adducts **17a** shows that addition to the *re*-face of the olefin (see **16**) leading to steroids of unnatural 8α-configuration† is preferred (ratio 3.25:1). If **16** is indeed the favoured conformation of the olefin, approach to the *re*-face is less hindered. However, epimerisation at C-8 is readily achieved as described later. With boiling methanolic hydrogen chloride the adducts **17a** gave four 1,2-dihydronaphthalenes **18a**. Equilibration at the benzylic centre of **18a** with 1,5-diazabicyclo[3.4.0]non-5-ene (DBN) gave the two *trans*-1,2-dihydronaphthalenes **18a** (8α, 9β†) and **18a** (8β, 9α†) separated by short-column chromatography on silica in benzene–diethyl ether (9:1). Whilst the former was obtained in a pure form by this procedure the latter was contaminated with a regioisomeric material not removed by recrystallisation. Pure **18a** (8β, 9α) was obtained by chromatography of the mixture of adducts to give polar and non-polar fractions. The polar fraction after treatment with methanolic hydrogen chloride gave **18a** (8α, 9β) and an easily separable regioisomer. The less polar adduct fraction was hydrolysed with NaOH–H_2O–EtOH and the resulting acids treated with diazomethane to give a mixture of three hydroxy esters, **19** (6α, 8α, 9α) which was the less polar material on chromatography and was readily converted into **18a** (8α, 9β) by treatment with methanolic hydrogen chloride followed by epimerisation at C-9 with DBN. The other hydroxy esters **19** (6β, 8β, 9β) and its isomer epimeric at C-6 and C-9 were not separable by chromatography and treatment with methanolic hydrogen chloride followed by DBN gave **18a** (8β, 9α). The small $J_{9\text{-H},10\text{-H}}$ values for **18a** (8α, 9β) (1.5 Hz) and **18a** (8β, 9α) (2.5 Hz)[10] together with their formation from their 9-epimers with DBN show these compounds to be *trans*-dihydronaphthalenes. Protection of the keto group in the stereoisomers **18a** prior to attempted Dieckmann reaction was accomplished using a boiling mixture of ethylene glycol and trimethyl orthoformate (2:1 v/v) and toluene-*p*-sulphonic acid as catalyst. The high pot temperature achieved with this mixture was required to obtain reaction;[11] the classical Dean–Stark procedure in benzene or xylene was ineffective. In addition to acetalisation some transesterification occurred and ester hydrolysis and esterification (CH_2N_2) were required to obtain the isomers **20a** (8α, 9β) and **20a** (8β, 9α). Acetalisation using the bistrimethylsilyl ether of ethylene glycol and trimethylsilyl trifluoromethanesulphonate[12] was also effective but was likewise accompanied by transesterification. Catalytic reduction (H_2/Pd-C) of the individual acetals gave the dihydro derivatives **21a** (8β, 9α) and **21a** (8α, 9β). Dieckmann cyclisation of the former with sodium hydride in boiling THF (tetrahydrofuran) containing a trace of methanol gave a mixture of the β-keto esters **22a** (8β) epimeric at C-9. The two isomers were separated by chromatography and fully characterised. Compound **22a** (8β, 9α) showed $J_{8\text{-H},9\text{-H}}$ and $J_{8\text{-H},14\text{-H}}$ both equal to 12 Hz in agreement with the axial orientation of 8-H, 9-H and 14-H. In contrast **22a** (8β, 9β) showed $J_{8\text{-H},14\text{-H}}$ 12 Hz and a $J_{8\text{-H},9\text{-H}}$ value of 6 Hz indicating the equatorial nature of 9-H. The isolation of the *trans*-**22a** (8β, 9α) and *cis*-**22a** (8β, 9β) isomers in a ratio of 3:2 respectively is in agreement with earlier observations and calculations[13] which reveal the 9α-isomer of **23** to be kinetically favoured but the 9β-isomer to be the more thermodynamically stable.

Dieckmann cyclisation of **21a** (8α, 9β) under the same conditions produced a single product **22a** (8α, 9α) which showed $J_{8\text{-H},9\text{-H}}$ 7 Hz and $J_{8\text{-H},14\text{-H}}$ 4 Hz in agreement with structure **22a** in which 9-H, 8-H and 14-H are respectively axial, equatorial and axial with respect to ring-C. Reaction of **22a** (8α, 9α) with barium hydroxide in boiling water containing some ethanol gave the demethoxycarbonylated product **24a** (8α, 9α). Related attempted demethoxycarbonylation of **22a** (8β, 9α) was unsuccessful, but the Krapcho procedure using calcium chloride in hot dimethyl sulphoxide (DMSO) converted **22a** (8β, 9β) into a mixture of **24a** (8β, 9β) and **24a** (8β, 9α). Conversion of the unnatural steroid **24a** (8α, 9α) into its 8β isomer was achieved in an overall yield of 40% *via* enol silylation [Me_3SiCl, Et_3N, dimethylformamide (DMF)] to **25a**, dehydrosilylation [$Pd(OAc)_2$, MeCN, 80 °C] to the enone **26a**, and reduction (Li, NH_3, Bu^{t}OH, THF). In addition to **24a** (8β, 9α) the metal–ammonia reduction gave small quantities of **24a** (8α, 9α) and

* The existing preparation of **2a** *via* **13** (ref. 9*a*) involving Curtius rearrangement to **14** and hydrolysis to **2a** (4 steps) proceeded poorly as did the one-step alternative for Curtius rearrangement using diphenyl phosphorazidate (ref. 9*b*) (18% yield). Reaction of **13** with lead tetraacetate followed by hydrolysis of the supposed intermediate **3** (*cf.* ref. 9*c*) was little better (a 30% yield that decreased on scale up). Ozonolysis of the readily available enol ethyl ether **15** (ref. 9*d*) of indan-2-one (ref. 9*e*) followed by acid hydrolysis gave **2a** in 54% yield based on indan-2-one. Ozonolysis of the related enol silyl ether has now been reported (ref. 9*f*).

† Steroid numbering and nomenclature, α and β referring to the positions of hydrogen atoms. All compounds are racemates.



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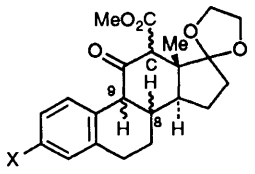
b; X = OMe



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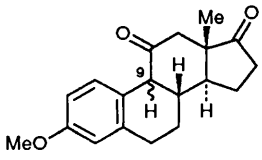

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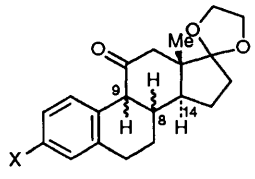

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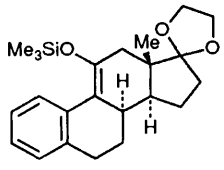

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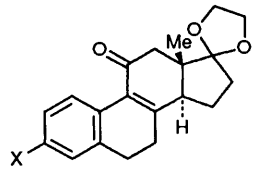

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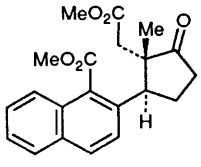

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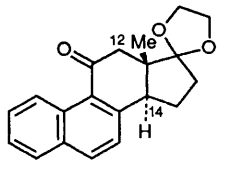

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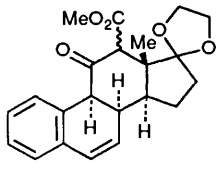

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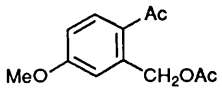

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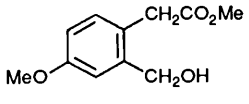

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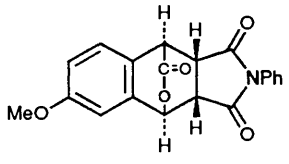

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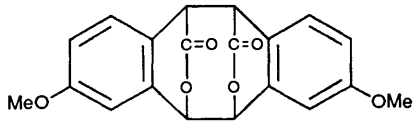

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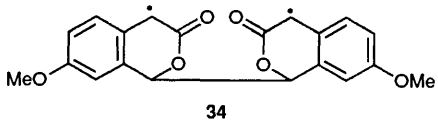

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24a (8β, 9β). Epimerisation at C-9 of **24a** (8β, 9α) gave the more stable 9β-isomer. The mixture of 1,2-dihydronaphthalenes **18a** can be dehydrogenated [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), PhCl, 132 °C] to the naphthalene **27** (50% yield) which after acetalisation [$(CH_2OSiMe_3)_2$, cat. trimethylsilyl trifluoromethanesulphonate, CH_2Cl_2, −25 °C, 14 d], Dieckmann cyclisation, and demethoxycarbonylation ($CaCl_2$·$2H_2O$, Me_2SO, 150 °C) gives the equilenin derivative **28**. Attempted use of barium hydroxide to achieve the demethoxycarbonylation step gave mostly the 14β-epimer of **28**. The implied acidity of 14-H in **28** is noteworthy. The ethylene acetals of the dihydronaphthalenes **18a** can also be individually cyclised (NaH–THF, cat. MeOH) and the 8α,9α-isomer **29** smoothly dehydrogenated (DDQ, benzene, 80 °C) to the 12-methoxycarbonyl derivative of **28**.

Synthesis of 3-Methoxy Steroids.—Hückel calculations revealed very little difference in the bias of the HOMO and LUMO of **1b** when compared with the corresponding orbitals of **1a**. Accordingly, similar regioselectivity in the addition of **1a** and **1b** to **9** and hence ready synthesis of natural 3-oxygenated steroids was expected. The methoxy acid **2b** required to generate the pyrone **1b** was made from the methyl ketone **30** in turn obtained by Friedel–Crafts acetylation of 3-methoxybenzyl acetate.[14] Oxidative rearrangement using the McKillop[15] variant of the Willgerodt reaction [$Tl(NO_3)_3$. $3H_2O$, MeOH, $HClO_4$, 20 °C] converted **30** into a mixture of **31** and the corresponding δ-lactone. Hydrolysis of the mixture (NaOH, H_2O, EtOH, 100 °C, 4 h), acidification at 0–5 °C and immediate reaction with diazomethane gave the pure methyl ester **31** which gave **2b** after Swern oxidation and acid hydrolysis (34% yield over the four steps). When heated with acetic anhydride in the presence of *N*-phenylmaleimide **2b** gave the *endo*-adduct **32** of the methoxypyrone **1b**. In view of the apparent reluctance of **1a** to dimerise it was surprising to find that in the absence of *N*-phenylmaleimide generation of **1b** gave considerable amounts of the *syn*- and *anti*-dimers **33**. More ready dimerisation of **1b** than **1a** may be associated with stabilisation of the biradical intermediate **34** by the *para*-methoxy group; a degree of merostabilisation is also possible. The more ready dimerisation of **1b** could be largely avoided in the addition of **1b** to the olefin **9** by slow addition of **2b** to boiling acetic anhydride containing a large excess of **9**; the excess **9** was readily recovered in pure form for recycling. The adducts **17b** were thus obtained in *ca.* 60% yield and the dimers **33** in *ca.* 12% yield. As in the X = H series the adducts were readily separated chromatographically into more and less polar fractions, and the polar fraction after treatment with methanolic hydrogen chloride gave **18b** (8α, 9β). The non-polar fraction after treatment with methanolic hydrogen chloride and epimerisation with DBN gave **18b** (8β, 9α) and more **18b** (8α, 9β). The more abundant **18b** (8α, 9β) was acetalised to **20b** (8α, 9β) reduced to **21b** (8α, 9β) cyclised to **22b** (8α, 9α) and demethoxycarbonylated to **24b** (8α, 9α). This was epimerised at C-8 as described for the X = H series *via* the enol silyl ether **25b**, and the enone **26b**.

The regioselective Diels–Alder addition of **1a** and **1b** and the transformations of their adducts described herein auger well for the use of 2-benzopyran-3-ones as synthetic building blocks. This is, affirmed by the regioselective additions of **1a** to vinyl ethers which was reported[9f] as a route to AB-ring analogues of anthracyclinones after most of our own work was complete. More recently we have described syntheses of podophyllotoxin based on Diels–Alder additions to an *o*-quinonoid pyrone.[16]

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and

are uncorrected. Unless otherwise stated, IR spectra refer to Nujol mulls, UV spectra to ethanol solutions and ^1H NMR spectra to solutions in deuteriochloroform measured at 90 MHz with a Perkin-Elmer R32 or a JEOL FX90Q instrument. 400 MHz spectra were obtained on a Bruker WH-400 instrument. *J* Values are given in Hz. Low resolution mass spectra were obtained with a Kratos MS25 instrument and accurate mass measurements were made using a Kratos MS9150 instrument. Where accurate mass measurement was used to establish molecular formulae the purity of the sample was checked by TLC in more than one solvent system as well as by NMR measurements, and for crystalline material by crystallisation to constant m.p. Chromatography on silica refers to short-column chromatography[17] over Kieselgel G (Merck). Ether refers to diethyl ether and light petroleum to the fraction b.p. 60–80 °C.

o-Formylphenylacetic Acid by Oxidative Decarboxylation of 3-Oxoisochroman-1-carboxylic Acid with Lead Tetraacetate.—3-Oxoisochroman-1-carboxylic acid **3** (2.0 g, 10.4 mmol), anhydrous sodium acetate (8.56 g) and glacial acetic acid (32 cm^3; distilled from Ac_2O and deoxygenated) were heated together (oil bath temperature 110 °C) under an argon atmosphere with stirring. Lead tetraacetate (5.72 g, 12. 9 mmol) was added in three approximately equal portions to the solution. After each addition vigorous effervescence was observed and allowed to subside (1–2 min) before further lead tetraacetate was added. The mixture was stirred (0.5 h) to leave a clear solution and then allowed to cool. Before crystallisation occurred the mixture was poured into water and extracted several times with ether. The ether layers were washed with saturated brine, dried ($MgSO_4$) and evaporated. The residue and water (20 cm^3) were boiled under reflux with stirring (1 h). This procedure was repeated four times using a total of 9.4 g of 3-oxoisochroman-1-carboxylic acid. After the usual acid extraction procedure the combined products were chromatographed on silica in benzene–ether–acetic acid (17:2:1) to yield pure *o*-formylphenylacetic acid (2.40 g, 29%), m.p. 104–107 °C (lit.,[9a] 107–108 °C and NMR spectroscopic comparison).

o-Formylphenylacetic Acid **2a**.—2-Ethoxyindene[9d] was prepared from indan-2-one *via* 2,2-diethoxyindane according to the literature procedure but in 71.5% yield (*cf.* lit., 48% yield); this product (22 g) in dichloromethane (88 cm^3) and methanol (352 cm^3) was cooled to −30 °C and a stream of ozonised oxygen passed through the solution until a blue colour persisted (*ca.* 1 h). A stream of argon was passed through the solution to remove the excess of ozone when dimethyl sulphide (166 cm^3) was added at −30 °C. The temperature was kept at −30 °C (1 h) and then allowed to attain room temperature overnight. The mixture was evaporated, the residue taken up in ether, and the solution washed with water (4 ×), dried ($MgSO_4$), and evaporated. Recrystallisation of the product from light petroleum gave ethyl 2-formylphenylacetate (23.23 g, 88% yield), m.p. 52–54 °C. This product, concentrated hydrochloric acid (72.5 cm^3) and water (72.5 cm^3) were boiled under reflux in an inert atmosphere (argon) (1 h). Upon cooling at 0–5 °C a small quantity of dark oil separated and was removed. The residual solution was extracted with dichloromethane and the organic extracts dried ($MgSO_4$) and evaporated to *ca.* 50 cm^3 and cooled in ice when *o*-formylphenylacetic acid was obtained in two crops (14.7 g), m.p. 90–105 °C. Evaporation of the mother liquor gave a residue (5.2 g) containing *ca.* 50% acid and 50% unhydrolysed ester. This mixture gave an additional quantity of *o*-formylphenylacetic acid (2.2 g), m.p. 96–105 °C upon boiling with hydrochloric acid–water (1:1) for 2 h and work-up as above. The acid obtained in this way is suitable for most purposes (86% yield on the ester hydrolysis step and 54% yield from indan-2-one).

Diels–Alder Addition of 2-Benzopyran-3-one with 2-Methylpropene.—*o*-Formylphenylacetic acid (100 mg), 2-methylpropene (4 cm^3) and acetic anhydride (distilled, 6 cm^3) were heated together in a steel bomb at 140 °C (oil bath; 15 h). The volatile components were removed under reduced pressure (water pump) on a steam bath and the residue chromatographed on silica in benzene–ether (24:1). The adduct was recovered (94 mg), as an oil, in a homogeneous state according to TLC analysis (2 elutions; benzene–ether, 24:1); no other significant components were identified. Adduct **10** (Found: M^+, 202.0992. $C_{13}H_{14}O_2$ requires *M*, 202.0994), ν_{max}(neat)/cm^{-1} 2980, 1755, 1170, 1005, 975, 765 and 755; δ_H 7.25 (4 H, s), 5.50 (1 H, dd, *J* 5 and 2), 3.45 (1 H, s), 2.18 (1 H, dd, *J* 14 and 5), 1.48 (1 H, dd, *J* 14 and 2), 1.27 (3 H, s) and 0.70 (3 H, s); *m/z* 202, 158, 146, 143, 141, 128, 118 and 115 (10.6, 46.6, 85.9, 97.3, 26.1, 48.3, 100 and 29.5%).

Diels–Alder Addition of 2-Benzopyran-3-one to Butadiene.—2-Formylphenylacetic acid (120 mg), butadiene (4 cm^3) and acetic anhydride (distilled, 5.0 cm^3) were heated together in a steel bomb at 140 °C (oil bath; 17 h). The reaction mixture was evaporated to dryness under reduced pressure (water pump) at 100 °C, and the residue chromatographed on silica in benzene–ether (49:1). The oil recovered was homogeneous according to TLC (2 elutions, benzene–ether, 49:1) and appeared to be almost pure *endo*-isomer according to its 90 MHz NMR spectrum, apart from a signal at δ 2.1. The oil slowly crystallized at 0 °C (from pentane) and was recrystallized (3 ×, from trace benzene–pentane) but the signal at δ 2.1 was only slightly reduced; the 400 MHz NMR spectrum revealed the crystalline material as a mixture of *endo*- and *exo*- adducts in a ratio of 5–5.5:1 respectively (integral trace), m.p. 64–65.5 °C (from trace benzene–pentane) (Found: C, 77.8; H, 6.05. $C_{13}H_{12}O_2$ requires C, 78.0; H, 6.05); ν_{max}/cm^{-1} 1755, 1465, 1450, 1185, 1005, 995, 975, 935, 920, 770 and 760; δ_H(400 MHz) *endo*-isomer 7.38–7.26 (4 H, m, aromatic), 5.61 (1 H, dd, *J* 4 and 1.8), 5.13 (1 H, ddd, *J* 17, 9.8 and 7.3, olefinic methine H), 5.01 (1 H, ddd, *J* 17, 1.8 and 1, *cis*-olefinic H), 4.93 (1 H, ddd, *J* 9.8, 1.8 and 1, *trans*-olefinic H), 3.83 (1 H, d, *J* 2.8), 3.03 (1 H, m, methine H), 2.69 (1 H, ddd, 7 lines, *J* 14, 10 and 4, *exo*-H) and 1.48 (1 H, ddd, *J* 14, 4 and 1.8, *endo*-H); *exo*-isomer 7.38–7.26 (4 H, m, aromatic), 5.87 (1 H, ddd, *J* 17, 10 and 8.3, olefinic methine H), 5.60 (1 H, 2 lines visible, downfield signals overlapping with lines due to major isomer, only smaller *J* 1.8 coupling constant visible, H_{C-O}), 5.22 (1 H, ddd, 6 lines, *J* 17, 1.3 and 1.3, *cis*-olefinic hydrogen), 5.17 (1 H, ddd, 6 lines of which the highest field line overlaps with line due to major isomer, *J* 10, 1.3 and 1.3, *trans*-olefinic hydrogen), 3.84 (1 H, one line visible and one overlapping with signal due to major isomer, H_{C-CO}), 2.59 (1 H, m, methine H), 2.17 (1 H, ddd, AB system, *J* 14, 5.5 and 3.8, *exo*-H) and 2.07 (1 H, ddd, AB system, *J* 14, 10 and 1.8, *endo*-H); *m/z* 200, 156, 155, 146, 141, 129, 128, 118 and 115 (11.4, 65.1, 21.4, 41.1, 43.8, 27.0, 100, 81.0 and 41.3%).

Hydrogenation of Butadiene Adducts.—The mixture of butadiene adducts (ratio *ca.* 5:1 respectively) (23 mg) and 10% palladized charcoal (5 mg) in ethyl acetate (distilled, 3.0 cm^3) were stirred together under an atmosphere of hydrogen at room temperature until uptake ceased (0.5 h). The filtered residue (24 mg), consisting of a mixture of *endo*- and *exo*-but-1-ene adducts was homogenous by TLC (3 elutions, benzene–ether, 99:1); the 90 MHz NMR spectrum only indicated the obvious presence of the *endo*-isomer, diagnostic signals due to the *exo*-isomer are masked at this field strength (Found: M^+, 202.0993. $C_{13}H_{14}O_2$

requires *M*, 202.0994); $\nu_{max}(CCl_4)/cm^{-1}$ 2960, 2930, 1765br, 1365, 1175, 1165sh and 1000; δ_H 7.3 (4 H, m, aromatic), 5.55 (1 H, dd, *J ca.* 4 and 1), 3.85 (1 H, d, *J* 3), 2.62 (1 H, ddd, 7 lines, *J* 13, 10 and 3), 2.25 (1 H, m) and 2.0–0.85 (6 H, m); *m/z* 202, 158, 129, 128, 86 and 84 (1.2, 18.1, 100.0, 27.8, 23.5 and 35.5%).

Diels–Alder Addition of 2-Benzopyran-3-one with But-1-ene.—*o*-Formylphenylacetic acid (110 mg), but-1-ene (4 cm^3) and acetic anhydride (distilled, 5.0 cm^3) were heated together in a steel bomb at 140 °C (oil bath; 16 h). The reaction mixture was evaporated to dryness under reduced pressure (water pump) at 100 °C, and the residue chromatographed on silica in benzene–ether (99:1). The oil recovered (112 mg) was homogeneous according to TLC (3 elutions; benzene–ether, 99:1); the 90 MHz ^1H NMR spectrum revealed the signal at δ 5.55, observed for the mixture of *endo-* and *exo*-adducts, prepared by hydrogenation of the butadiene adducts, and the presence of an additional signal at δ 5.4, presumably due to the regioisomeric *endo*-isomer (ratio of signals at 5.55 and 5.4, *ca.* 4:1 respectively).

The IR and mass spectra corresponded exactly to those recorded for the adducts prepared by hydrogenation of the butadiene adducts. The 400 MHz ^1H NMR spectrum gave a ratio of *ca.* 3.5:1 for the signals at δ 5.55 [overlapping dd's due to *endo*-**12** and *exo*-**12** and δ 5.4 [two d due to *endo* and *exo* regioisomeric adducts; signals of diagnostic value are analysed as follows, *endo*-**12**; 7.35–7.26 (4 H, m, aromatic), 5.55 (1 H, dd, *J* 4 and 1.5, H_{C-O}), 3.86 (1 H, d, *J* 2.5, H_{C-CO}), 2.59 (1 H, ddd, 7 lines, *J* 13.5, 10 and 4, H_{endo}), 2.20 (1 H, ddd, *J* 10, 4, 2.5 and 7, methine hydrogen), 1.20 (1 H, ddd, *J* 13.5, 4 and 1.5, H_{exo}) and 1.0–0.85 (5 H, m); *exo*-**12**, diagnostic signals at δ 5.55 (1 H, dd, masked by signal due to *endo*-isomer **12**, two downfield lines visible, *J* 1.8, H_{C-O}), 3.83 (1 H, d, *J* 2, H_{C-CO}), 1.99 (1 H, ddd, part of AB system, *J* 13.5, 10 and 2.3, H_{exo}), 1.89 (1 H, ddd, part of AB system, *J* 13.5, 5.5 and 4, H_{endo}) and 1.77 (1 H, m, methine), *endo*-regioisomer of **12**, diagnostic signals at δ 5.41 (1 H, d, *J* 3.3, H_{C-O}) and 3.86 (signal obscured, one line visible due to H_{C-CO}), the existence of the *exo*-regioisomer of **12** is tentatively proposed, due to the signal at δ 5.43 (d, *J* 1, H_{C-O}).

Reaction between 2-Benzopyran-3-one and the Olefin **9**.—*o*-Formylphenylacetic acid (1.21 g, 7.38 mmol), the olefin **9** (2.96 g, 15.1 mmol) and acetic anhydride (8.0 cm^3) were boiled under reflux in an argon atmosphere (3 h). After evaporation of acetic anhydride, chromatography on silica in benzene–ether (4:1) gave first recovered olefin (*ca.* 1.8 g) followed by a gum (742 mg) comprising a copolar mixture of adducts from *exo-re* and *endo* and *exo-si* attack (Found: M^+, 342.1461. $C_{20}H_{22}O_5$ requires *M*, 342.1467); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 sh and 1730; the 400 MHz ^1H NMR spectrum indicated the presence of the forementioned isomers and a regioisomer. Assignments are as follows: 7.4–7.25 (4 H, m, aromatic), 5.61–5.53 [1H, including δ 5.61 (overlapping signals due to major isomer from *exo-re* attack and product of either *endo* or *exo-si* attack, one dd visible, 3 lines, *J* 5 and 2.5, HC-O), 5.59 (dd, *J* 4.5 and 1.3, H_{C-O} in product of either *endo-* or *exo-si*-attack) and 5.53 (d, *J* 3.3, H_{C-O} in a regioisomer], 3.99–3.91 [1 H, including δ 3.99 (d, *J* 2, H_{C-CO} in *exo-re* adduct), 3.96 (d, *J* 2.5, H_{C-CO} in *endo-si* adduct), 3.94 (d, *J* 1.8, H_{C-CO} in *exo-si* adduct), and 3.91 (dd, *J* 3.5 and 2.5, H_{C-CO} in regioisomer)], 3.68–3.59 [3 H, including δ 3.68 (s, CO_2Me in either regioisomer, or *exo-si* adduct, 3.67 (s, CO_2 Me in *exo-re* adduct), 3.61 (s, CO_2Me in a regioisomer or *exo-si*-adduct) and 3.59 (s, CO_2Me in *endo-si*-adduct), 3.1–1.3 (10 H, m) and 1.07–0.82 [3 H, including δ 1.07 (s, Me in either the regioisomer or *exo-si*-adduct), 1.03 (s, Me, in *endo-si*-adduct), 0.97 (s, Me in either the regioisomer or *exo-si*-adduct) and 0.82 (s, Me in *exo-re*-adduct)]; *m/z* 342, 155, 154, 129, 128 and 118 (9.2, 45.9, 100, 91.8, 93.8 and 52.4%). The NMR spectrum also showed the presence of *ca.* 5% of the 2-benzopyran-3-one dimers.

Continued elution afforded a copolar mixture of *endo-re*-adduct and a regioisomer (ratio *ca.* 5:1) as a solid (890 mg); δ_H(400 MHz), signals due to major *endo-re* isomer, 7.4–7.3 (4 H, m), 5.61 (1 H, dd, *J* 4 and 1.5, H_{C-O}), 4.00 (1 H, d, *J* 2.5, H_{C-CO}), 3.25 (3 H, s), 2.92 (1 H, d, part of AB system, *J* 16, CH_2CO_2Me), 2.62 (1 H, ddd, 7 lines, *J* 13, 9 and 4, *exo*-H from CH_2), 2.45–2.32 (2 H, m), 2.28–2.17 (3 H, m, including δ 2.22, 1 H, d, part of AB system, *J* 16, CH_2CO_2Me), 1.60 (1 H, m), 1.47 (1 H, ddd, *J* 13, 4.5 and 1.5, *endo*-H from CH_2), 1.34 (1 H, m) and 0.93 (3 H, s); analytically useful signals due to the regioisomer are, δ 5.57 (1 H, d, *J* 3.3, H_{C-O}), 3.92 (1 H, dd, *J* 3.5 and 2.5), 3.29 (3 H, s), 2.90 (1 H, d, part of AB-system, *J* 16.5, CH_2CO_2Me) and 0.96 (3 H, s).

Preparation of **18a** (8α, 9β)* *by Reaction of the More Polar Adduct Mixture with* MeOH–HCl.—The *endo-re* adduct (310 mg) (contaminated with *ca.* 20% of copolar regioisomeric impurity) was heated in refluxing methanol (5 cm^3) previously saturated with dry hydrogen chloride (1 h). The cooled product was neutralised with saturated aqueous sodium hydrogen carbonate, saturated with sodium chloride and extracted with dichloromethane. Evaporation of the dried (Na_2SO_4) dichloromethane solution and chromatography on silica in benzene–ether (19:1) gave first the regioisomeric *dihydronaphthalene* (40 mg), m.p. 130–131 °C (from benzene–ether–pentane) (Found: C, 70.9; H, 6.8. $C_{21}H_{24}O_5$ requires C, 70.8; H, 6.8%); ν_{max}/cm^{-1} 1735 and 1725; λ/nm(ε) 268 and 223(sh) (12 000, 11 000); δ_H 7.26–7.0 (4 H, m), 6.30 (1 H, br s), 3.8 (1 H, m, obscured, benzylic), 3.68 (6 H, s, 2 × CO_2Me), 3.15 (1 H, m), 2.89 (2 H, s, CH_2CO_2Me), 2.74–1.9 (6 H, m) and 0.85 (3 H, s). Continued elution of the column gave the *dihydronaphthalene* **18a** (8α, 9β) (233 mg), m.p. 119–120 °C (from ether–pentane) (Found: C, 70.85, H, 6.7%); ν_{max}/cm^{-1} 1740 and 1730; λ_{max}/nm(ε) 261 and 221sh (8300, 14 600); δ_H(400 MHz) 7.25–7.18 (3 H, m), 7.03 (1 H, dd, *J* 6 and 2, 4-H), 6.48 (1 H, d, *J* 10, 6-H), 6.06 (1 H, ddd, *J* 10, 6 and 1, 7-H), 3.71 (1 H, br s, $W_{\frac{1}{2}}$ 4 Hz, 9-H), 3.60 (3 H, s), 3.39 (3 H, s), 2.90 (1 H, ddd, *J* 11, 6 and 1.5, 8-H), 2.86 (1 H, d, *J* 17, CH_2CO_2Me), 2.57 (1 H, d, *J* 17, CH_2CO_2Me), 2.38 (1 H, ddd, *J* 18.5, 9 and 1.5, 16α-H), 2.30 (1 H, ddd, *J* 18.5, 12 and 9, 16β-H), 2.19 (1 H, ddd, 6 lines, *J* 12, 11 and 6, 14-H), 2.10 (1 H, dddd, *J* 12, 9, 6 and 1.5, 15β-H), 1.56 (1 H, dddd, 8 lines, *J* 12, 12, 12 and 9, 15α-H) and 1.05 (3 H, s); *m/z* 356, 324, 237, 181, 155, 129 and 128 (9.2, 24.9, 27.5, 30.6, 35.5, 25.9 and 100%).

Conversion of the Less Polar Adduct Mixture into **18a** (8α, 9β) *and* **18a** (8β, 9α).—The mixture of adducts (639 mg), aqueous sodium hydroxide (4 mol dm^{-3}; 12 cm^3), and ethanol (12 cm^3) were boiled under reflux under argon (3.5 h). After removal of as much ethanol as possible (rotary evaporator) the aqueous solution was cooled to 0–5 °C, and acidified to pH 1 (conc. hydrochloric acid), saturated with sodium chloride, and extracted with ethyl acetate (4 ×). The combined organic phases were washed with saturated brine, dried ($MgSO_4$) and evaporated. The residue in ether containing a little methanol was treated with an excess of ethereal diazomethane at 20 °C, the solution evaporated, and the residue chromatographed on silica in benzene–ether (4:1) to give first hydroxytetralin **19** (6α, 8α, 9α)† (198 mg), m.p. 168–170 °C (from benzene–light

* Methyl 2-(2-methoxycarbonylmethyl-2-methyl-3-oxocyclopentyl)-1β,2α-dihydronaphthalene-1-carboxylate.

† Methyl 4-hydroxy-2-(2-methoxycarbonylmethyl-2-methylcyclopentyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate.

petroleum) (Found: C, 67.55; H, 7.05. $C_{21}H_{26}O_6$ requires C, 67.4; H, 7.0%); ν_{max}/cm^{-1} 3510, 1740, 1725 and 1710; δ_H(400 MHz) 7.62 (1 H, d, *J* 7.5), 7.34–7.20 (3 H, m), 4.79 (1 H, dd, 3 lines, *J* 9 and 8, 6-H), 3.92 (1 H, d, *J* 5, H-9), 3.68 (3 H, s), 3.63 (3 H, s), 3.00 and 2.70 (2 H, AB-system, *J* 17, CH_2CO_2Me), 2.49–2.20 (6 H, m), 2.03 (1 H, dddd, 15 lines, *J* 12.5, 11, 4.5 and 3.5), 1.50 (1 H, m), 1.25 (1 H, br s, OH) and 0.94 (3 H, s). Continued elution gave 80 mg of a mixture of three components, and then a gum (298 mg) comprising a mixture of the *hydroxytetralins* **19** (6α, 8β, 9α) and **19** (6β, 8β, 9β) in a ratio of *ca.* 4:1 (Found: M^+, 374.1732. $C_{21}H_{26}O_6$ requires *M*, 374.1729); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400br, 2950 and 1735br; δ_H 7.7–7.1 (4 H, m), 4.8 (1 H, m, 6-H), 3.8–3.4 [7 H, m, 2 × CO_2Me and 9-H including signals for major isomer **19** (6α, 8β, 9α) δ 3.71, s, CO_2Me and 3.47, s, CO_2Me and for minor isomer **19** (6β, 8β, 9β), δ 3.65, s, CO_2Me and 3.61, s, CO_2Me], 3.0–1.3 (11 H, m) and 1.0–0.9 (3 H, including major isomer, δ 1.00, s, Me and minor isomer, δ 0.91, s, Me). The less polar hydroxytetralin **19** (6α, 8α, 9α) (480 mg) was boiled under reflux with methanolic hydrogen chloride (10 cm^3) as described above for the more polar adduct and the crude product (464 mg) treated with DBN (0.4 cm^3) in boiling benzene (9 cm^3) (4 h) to give the previously prepared dihydronaphthalene **18a** (8α, 9β) (224 mg). In the same way the more polar mixture of **19** (6α, 8β, 9α) and **19** (6β, 8β, 9β) (300 mg) was converted into isomeric *dihydronaphthalene* **18a** (8β, 9α) (190 mg), m.p. 135–136 °C (from benzene–light petroleum) (Found: C, 70.55; H, 6.75%); $\nu_{max}(CCl_4)/cm^{-1}$ 1745; $\lambda_{max}/nm(\varepsilon)$ 261 and 221sh (8650 and 14 600); δ(400 MHz) 7.25–7.14 (2 H, m, 2-H and 3-H), 7.13 (1 H, m, 1-H), 7.06 (1 H, dd, *J* 7 and 1.5, 4-H), 6.51 (1 H, d, *J* 10, 6-H), 6.02 (1 H, ddd, *J* 10, 6.5 and 1, 7-H), 3.69 (1 H, d, *J* 2.5 9-H), 3.63 (3 H, s), 3.39 (3 H, s), 3.03 (1 H, ddd, 7 lines, *J* 9, 6.5 and 2.5, 8-H), 2.96 and 2.60 (2 H, AB system, *J* 17, CH_2CO_2Me), 2.35–2.29 (2 H, m, 16-H), 2.24 (1 H, ddd, *J* 12, 9 and 6.5, 14-H), 2.03 (1 H, m, 15β-H), 1.62 (1 H, m, 15α-H) and 1.05 (3 H, s).

The Acetals of Dihydronaphthalenes **18a** (8β, 9α) *and* **18a** (8α, 9β).—A slightly impure sample of **18a** (8α, 9β) (containing 5–10% of copolar regioisomeric dihydronaphthalene) (1.90 g), ethylene glycol (dry, 10.0 cm^3), trimethyl orthoformate (distilled, 5 cm^3) and anhydrous toluene-*p*-sulphonic acid (25 mg) were heated together under reflux (oil bath temp. 160 °C), with stirring, under an argon atmosphere (16 h). The product was poured into aqueous sodium hydrogen carbonate and isolated in the usual way. The crude product (2.57 g), sodium hydroxide solution (4 mol dm^{-3}; 10 cm^3) and ethanol (10 cm^3) were stirred at 20 °C (16 h). After acidification to pH 5 (2 mol dm^{-3} hydrochloric acid followed by acetic acid) the product was isolated in the usual way in dichloromethane. The product, in ether, was treated briefly with diazomethane in ether and the product after evaporation chromatographed on silica in benzene–ether (19:1) to give the *acetal* **20a*** (8α, 9β) (1.43 g), m.p. 87–88 °C (from ether–pentane) (Found: C, 69.2; H, 7.1. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.05%); ν_{max}/cm^{-1} 1725; λ_{max}/nm (ε) 261 and 221sh (9100, 13 000); δ 7.25–6.95 (4 H, m), 6.43 (1 H, d, *J* 10, H-6), 6.05 (1 H, dd, *J* 10 and 6, 7-H), 3.80 (4 H, m, acetal), 3.55 (3 H, s, and 1 H, obscured, 9-H), 3.45 (3 H, s), 2.90 (1 H, dd with further spitting, *J* 10 and 6, 8-H), 2.35 (2 H, s, CH_2CO_2Me), 2.3–1.35 (5 H, m) and 1.23 (3 H, s). In a similar way the dihydronaphthalene **18a** (8β, 9α) was converted into its acetal (84%) the chromatography being conducted in benzene–ether (9:1) to give dihydronaphthalene *acetal* **20a**† (8β, 9α) m.p. 73–74 °C (from ether–pentane) (Found: C, 69.1; H, 7.1%); ν_{max}/cm^{-1} 1735 and 1725; $\lambda_{max}/nm(\varepsilon)$ 261 and 221sh (8800, 14 200); δ 7.25–6.95 (4 H, m), 6.50 (1 H, d, *J* 10, 6-H), 5.95 (1 H, dd, *J* 10 and 6, 7-H), 3.85 (4 H, br s, acetal), 3.80 (1 H, partially obscured, 9-H), 3.63 (6 H, s, 2 × Me), 3.20 (1 H, dd with further splitting, *J* 10 and 4), 2.40 (2 H, s, CH_2CO_2Me), 2.30 (1 H, m, partially obscured) 1.8–1.3 (4 H, m) and 1.12 (3 H, s).

Catalytic Hydrogenation of Acetals **20a** (8α, 9β) *and* **20a** (8β, 9α).—A solution of the acetal **20a** (8α, 9β) (1.43 g) in ethyl acetate (20 cm^3), and palladized charcoal (10% Pd, 300 mg) were stirred in a hydrogen atmosphere at atmospheric pressure (1.5 h). Filtration of the catalyst (Filter-aid) and evaporation of the filtrate gave the *tetralin* **21a**‡ (8α, 9β) (1.46 g) as a colourless gum (Found: M^+, 402.2047. $C_{23}H_{30}O_6$ requires *M*, 402.2042); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725; δ 7.1 (4 H, br s), 3.85 (4 H, br s, acetal), 3.70 (1 H, obscured by neighbouring CO_2Me signal, 9-H), 3.63 (3 H, s), 3.58 (3 H, s), 2.90–1.30 (15 H, m) and 1.13 (3 H, s).

In the same way **20a** (8β, 9α) gave the *tetralin* **21a**§ (8β, 9α) (quantitative yield) as a gum (Found: M^+, 402.2047. $C_{23}H_{30}O_6$ requires *M*, 402.2042); $\nu_{max}(CCl_4)/cm^{-1}$ 1735; δ 7.1 (4 H, br s), 3.85 (4 H, br s, acetal), 3.82 (1 H, obscured by neighbouring acetal signal, 9-H), 3.68 (3 H, s), 3.52 (3 H, s), 2.95–1.40 (15 H, m) and 1.15 (3 H, s).

Methyl 17,17-*Ethylenedioxy*-11-*oxo*-8α-*estra*-1,3,5(10)-*triene*-12ξ-*carboxylate*.—A dispersion of sodium hydride (58% w/w in oil; 380 mg, 9.2 mmol) was washed oil-free with several portions of dry benzene under an oxygen-free, argon atmosphere and suspended in THF (tetrahydrofuran) (dry, 1.0 cm^3). Compound **21a** (8α, 9β) (370 mg, 0.920 mmol), dissolved in THF (8.5 cm^3), was added to the stirred suspension of sodium hydride at 20 °C and the reaction initiated by addition of methanol (0.02 cm^3) in THF (0.5 cm^3). A deep lemon-yellow colour soon appeared and the reaction mixture was heated under reflux (4.5 h). After cooling to 20 °C the product was treated with methanol (0.75 cm^3) and then glacial acetic acid (1.3 cm^3), and partitioned between saturated aqueous ammonium chloride and benzene–ether (*ca.* 1:1). The aqueous phase was re-extracted with benzene–ether (1:1) 2×) and the combined organic phase were washed with brine, dried (Na_2SO_4), evaporated and chromatographed on silica in benzene–ether (19:1) to give the *title compound* **22a** (8α, 9α) (236 mg, 69.4%), m.p. 170–172 °C (from benzene–light petroleum) (Found: C, 71.35; H, 6.95. $C_{22}H_{26}O_5$ requires C, 71.3; H, 7.05); ν_{max}/cm^{-1} 1755 and 1705; δ_H(400 MHz) 7.07–7.20 (3 H, m), 6.96 (1 H, d, *J* 6.5), 4.09 (1 H, s, 12-H), 3.85–4.0 (3 H, m, acetal), 3.80 (1 H, br d, *J* 6.5, 9-H), 3.70 (3 H, s) 3.70 (1 H, m, acetal), 2.85 (2 H, m, 6-H and 14-H), 2.62 (1 H, ddd, *J* 17, 12 and 4.5, 6-H), 2.56 (1 H, dddd, *J* 12.5, 6.5, 4 and 2, 8-H simplified to a ddd, *J* 12.5, 4 and 2 upon irradiation of the 9-H signal at δ 3.8), 1.71 (1 H, m), 1.57 (1 H, qd, *J* 12.5 and 4, 7-H) and 1.21 (3 H, s). Irradiation of 8-H (δ 2.56) affects signals at 1.57 (7-H), 2.85 [6-H and 14-H (?)] as well as δ 3.8 (9-H). Irradiation of 6-H and 14-H (?) at 2.85 affects signals at 1.57 (7-H), 2.56 (8-H) and 2.62 (6-H).

Methyl 17,17-*Ethylenedioxy*-11-*oxoestra*-1,3,5(10)-*triene*-12ξ-*carboxylate and its* C-9 *Epimer*.—A mixture of **21a** (8β, 9α) (and a presumed regioisomeric impurity, in the ratio *ca.* 3.5:1) (273 mg) was cyclised as described in the preceding experiment. The products were isolated by chromatography on silica in benzene–ether (19:1). 17,17-*Ethylenedioxy*-11-*oxo*-9β-*estra*-1,3,5(10)-*triene*-12ξ-*carboxylate* **22a** (8β, 9β) was eluted first (46 mg, 29%) m.p. 126–127 °C (from ether) (Found: C, 71.6; H,

* Methyl 2-(3,3-ethylenedioxy-2-methoxycarbonylmethyl-2-methylcyclopentyl)-1β,2α,-dihydronaphthalene-1-carboxylate.
† Methyl 2-(3,3-ethylenedioxy-2-methoxycarbonylmethyl-2-methylcyclopentyl)-1α,2β-dihydronaphthalene-1-carboxylate.
‡ Methyl 2-(3,3-ethylenedioxy-2-methoxycarbonylmethyl-2-methylcyclopentyl)-1β,2α,3,4-tetrahydronaphalenene-1-carboxylate.
§ Methyl 2-(3,3-ethylenedioxy-2-methoxycarbonylmethyl-2-methylcyclopentyl)-1α,2β3,4-tetrahydronaphalene-1-carboxylate.

7.0%) ν_{max}/cm^{-1} 1750 and 1695; δ_H(400 MHz) 7.1–7.2 (3 H, m), 7.0 (1 H, br d, *J* 8), 3.8 (1 H, obscured by acetal, 9-H), 3.70 (3 H, s), 3.68 (1 H, s, 12-H), 3.60–3.90 (4 H, m, acetal), 2.90 (1 H, ddd, *J* 17, 13, 6, 6α-H), 2.725 (1 H, ddd, *J* 17.0, 6.0, 2.0, 6β-H), 2.39 (1 H, ddt, *J* 12, 5.5, 3.5, 8-H), 2.32 (1 H, td, *J* 12, 7, 14-H), 1.81–2.01 (4 H, m, 1 × 7-H, 1 × 15-H, 2 × 16-H), 1.765 (1 H, tdd, *J* 13.0, 5.5, 3.0, 7-H), 1.5 (1 H, m, 15-H) and 1.22 (3 H, s). Continued elution of the column with the same solvent gave a mixed fraction (10 mg) followed by *compound* **22a** (8β, 9α) (84 mg, 53%), m.p. 147–150 °C (from ether) (Found: C, 71.3; H, 6.9%); ν_{max}/cm^{-1} 1750 and 1710; δ_H(400 MHz), 7.35 (1 H, m), 7.15 (2 H, m), 7.08 (1 H, m), 4.05 (1 H, br s, 12-H), 3.87–3.97 (3 H, m, acetal), 3.70 (1 H, m, acetal), 3.73 (3 H, s), 3.60 (1 H, br d, *J* 11.5, 9-H), 2.84 (2 H, m, 2 × 6-H), 2.38 (1 H, td, *J* 11.5 and 7.5, 14-H), 1.82–2.07 (5 H, m), 1.55 (2 H, m) and 1.17 (3 H, s). The signal at 2.38 is unaffected by irradiation at δ 2.84 (6-H) or 3.60 (9-H) and is not therefore due to 8-H. Irradiation at δ 2.38 (14-H) affects 1.55 (7-H ?) and 1.83 (8-H ?).

17,17-*Ethylenedioxy*-11-*oxo*-8α-*estra*-1,3,5(10)*triene* **24a** (8α, 9α).—The β-keto ester **22a** (8α, 9α) (68 mg) and barium hydroxide octahydrate (300 mg) were heated in boiling ethanol (0.8 cm^3) and water (2.0 cm^3) in an argon atmosphere (16 h). The product was cooled to 20 °C and glacial acetic acid (1.0 cm^3) added to dissolve the barium salts. The product was isolated in ether in the usual way. Evaporation of the dried ($MgSO_4$) ether layer gave a crude product (63 mg) which was chromatographed on silica in benzene–ether (9:1) to give the title compound **24a** (8α, 9α) (40 mg) as an oil. The yield rose to 87% when reaction was carried out on a larger scale (575 mg). The *title compound* had m.p. 135–136 °C (from ether–light petroleum) (Found: C, 76.9; H, 7.45%; M$^+$, 312.1725. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312.1727); ν_{max}(CCl_4)/cm^{-1} 1715; δ_H 7.25–6.85 (4 H, m), 4.1–3.65 (5 H, m, acetal and 6-H), 3.0–2.4 (5 H, m), 2.3–1.3 (7 H, m) and 0.98 (3 H, s).

17,17-*Ethylenedioxy*-11-*oxoestra*-1,3,5(10)*triene* **24a** (8β, 9α) *and its* 9β-*Epimer* **24a** (8β, 9β).—Compound **22a** (8β, 9β) (42 mg), calcium chloride dihydrate (90 mg) and dimethyl sulphoxide (DMSO) (1 cm^3) were heated in an argon atmosphere under a reflux condenser in an oil-bath at 160 °C (14 h). The product was cooled, poured into water and isolated by ether extraction and chromatography on silica in benzene–ether (9:1). This gave first the 9β-epimer (13 mg) and then the natural 9α-epimer (4 mg). These products were fully characterised when produced by epimerisation as described below.

Epimerisation of 17,17-*Ethylenedioxy*-11-*oxo*-8α-*estra*-1,3,5(10)-*triene at* C-8.—This was accomplished *via* enol silylation, palladium acetate dehydrosilylation and reduction of the enone with lithium in liquid ammonia as later described in detail for the corresponding 3-methoxy compound.

17,17-*Ethylenedioxy*-11-*oxoestra*-1,3,5(10),8(9)-*tetraene* **26a** (56% yield; 73% based on recovered saturated ketone) was isolated by chromatography on silica in ether–benzene (2:3), m.p. 158–159 °C (from ether) (Found: C, 77.35; H, 7.2%; M$^+$, 310.1568. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%; *M*, 310.1569); ν_{max}(CH_2Cl_2film)/cm^{-1} 1665; δ(90 MHz) 8.0 (1 H, m), 7.10–7.35 (3 H, m), 3.90–4.00 (4 H, m), 3.4–1.1 (11 H, complex resonance) and 0.99 (3 H, s).

17,17-*Ethylenedioxy*-11-*oxoestra*-1,3,5(10)-*triene* **24a** (8β, 9α) (66% yield) separated by chromatography on silica in benzene–ether (9:1) from its less polar 9β-isomer (4.2% yield) and more polar 8α,9α-isomer (9.4% yield), m.p. 136–139 °C (from ether) (Found: C, 77.05; H, 7.65%; M$^+$, 312.1722. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312.1725); ν_{max}/cm^{-1} 1702; δ(400 MHz) 7.30 (1 H, m), 7.15 (2 H, m), 7.08 (1 H, m), 3.81–4.20 (4 H, m, acetal), 3.60 (1 H, br d, *J* 11.5, 12α-H), 2.88 (1 H, dq, *J* 11.5 and < 1, 9-H), 2.83 (2 H, m, 2 × 6-H), 2.33 (1 H, td, *J* 12 and 7.5), 2.24 (1 H, d, *J* 11.5), 2.10 (1 H, ddd, *J* 14.5, 12.0 and 3.5), 1.99 (2 H, m), 1.88 (1 H, m), 1.81 (1 H, *J* 11.5 and 2.5, either td or qd), 1.55 (1 H, qd, *J* 12.0 and 6.0), 1.45 (1 H, qd, *J* 12 and 6.5) and 0.885 (3 H, d, *J* < 1, Me).

17,17-*Ethylenedioxy*-11-*oxo*-9β-*estra*-1,3,5(10)-*triene* **24a** (8β, 9β), m.p. 162–165 °C (from ether–light petroleum) (Found: M$^+$, 312.1717. $C_{20}H_{24}O_3$ requires *M*, 312.1725); δ_H(400 MHz) 7.07–7.18 (3 H, m), 6.99 (1 H, br d, *J* 8), 3.685 (1 H, partly obscured, 9-H), 3.66–3.90 (4 H, m, acetal), 2.93 (1 H, ddd, *J* 17.5, 14.0 and 6.0, 6α-H), 2.72 (1 H, br dd, *J* 17.5 and 5, 6β-H), 2.54 (1 H, dd, *J* 12.5 and 1.0, 12α-H), 2.29 (2 H, m), 2.04 (1 H, dd, *J* 12.5 and 1.5, 12β-H), 1.99–2.10 (1 H, m), 1.81–1.97 (3 H, m), 1.76 (1 H, tdd, *J* 13.5, 5.5 and 3.0), 1.41 (1 H, m) and 0.92 (3 H, d, *J* 0.9).

17,17-*Ethylenedioxy*-11-*oxoestra*-1,3,5,6,8(9)-*pentaene* **28**.—A mixture of the stereoisomeric adducts, *i.e.* without separation into more and less polar fractions (2.08 g), was treated with boiling methanolic hydrogen chloride as previously described to give stereoisomeric dihydronaphthalenes (1.95 g). Part of this mixture (438 mg), DDQ (460 mg) and chlorobenzene (6 cm^3) were boiled under reflux (16 h) in a nitrogen atmosphere. Evaporation of solvent and chromatography on silica in ether–benzene (1:9) gave the *naphthalene* **27*** (220 mg), m.p. 143–145 °C (from ether–light petroleum) (Found: M$^+$, 354.1466. $C_{21}H_{22}O_5$ requires *M*, 354.1467), δ 7.37–8.00 (6 H, m), 4.1 (1 H, m), 3.95 (3 H, s), 3.70 (3 H, s), 2.1–2.8 (6 H, m) and 0.87 (3 H, s). This ketone (200 mg), ethylene glycol bistrimethylsilyl ether (233 mg), dichloromethane (2 cm^3) and five drops of TMSOTf were stored at −25 °C (48 h) under argon in a sealed flask. The recovered mixture (206 mg), dichloromethane (2 cm^3) and ethylene glycol bistrimethylsilyl ether (466 mg) were kept at −25 °C (2 d) when the usual work-up showed almost complete acetalisation. Chromatography of the crude product (209 mg) on silica in benzene–ether (9:1) gave the *ethylene–acetal* of **27** (136 mg), m.p. 129–132 °C (from methanol). Chromatography of the mother liquor gave a further 17 mg of the acetal (total yield, 68%) (Found: M$^+$, 398.1729. $C_{23}H_{26}O_6$ requires *M*, 398.1729).

Dieckmann cyclisation of this acetal was conducted as previously described and the product purified by chromatography on silica in benzene–ether (9:1) to give *methyl* 17,17-*ethylenedioxy*-11-*oxoestra*-1,3,5,6,8(9)-*pentaene*-12ξ-*carboxylate* (177 mg, 87%), m.p. 113–116 °C (from ether–pentane with aid of a trace of methanol) (Found: C, 72.25; H, 6.2. $C_{22}H_{22}O_5$ requires C, 72.1; H, 6.05%); ν_{max}/cm^{-1} 1745 and 1670; λ_{max}/nm(ε) 320 and 246 (7850 and 19 000); δ_H 9.30 (1 H, d, *J* 8.6, 1-H), 8.1–7.3 (5 H, m), 4.19 (1 H, s, 12-H), 4.15–3.85 (4 H, m, acetal), 3.79 (3 H, s), 3.55 (1 H, m, 14-H), 2.50–1.89 (4 H, m, 15-H and 16-H) and 1.02 (3 H, s).

Reaction of this keto ester with calcium chloride dihydrate in DMSO in the usual way gave *methyl* 17,17-*ethylenedioxy*-11-*oxoestra*-1,3,5,6,8(9)-*pentaene*-1-*carboxylate* **28** (55%), m.p. 88–90 °C (from ethanol) (Found: M$^+$, 308.1412. $C_{20}H_{20}O_3$ requires *M*, 308.1412); ν_{max}/cm^{-1} 1595, 1620 and 1665; δ_H 9.38 (1 H, br d, *J* 8), 7.95 (1 H, d, *J* 8), 7.88–7.38 (3 H, m), 7.23 (1 H, d, *J* 8), 3.95 (4 H, m, acetal), 3.54 (1 H, m, 14-H), 3.08 (1 H, d, *J* 18, 12-H), 2.58 (1 H, d, *J* 18, 12-H), 1.58–2.58 (4 H, m, 15-H and 16-H) and 0.86 (3 H, s). Attempted demethoxycarbonylation using baryta [$Ba(OH)_2$] gave mainly (86%) the 14β-epimer which showed methyl resonance at δ 1.1, 14-H resonance at δ 3.3 and the AB-system for the C-12 hydrogens centred at δ 2.73.

Methyl 17,17-*Ethylenedioxy*-11-*oxoestra*-1,3,5(10),6-*tetraene*-12ξ-*carboxylate* **29**.—Cyclisation of the diester **20a** (8α,

* Methyl 2-(2-methoxycarbonylmethyl-2-methyl-3-oxocyclopentyl)-naphthalene-1-carboxylate.

9β) with sodium hydride and work-up of the reaction mixture was conducted as previously described. Chromatography on silica in benzene–ether (19:1) gave first the previously described naphthalene (30 mg), followed by the *title compound* (123 mg), m.p. 161–163 °C (from methanol with aid of a trace of light petroleum) (Found: C, 71.55; H, 6.6. $C_{22}H_{24}O_5$ requires C, 71.7; H, 6.55%); ν_{max}/cm^{-1} 1745 and 1710; λ_{max}/nm(ε) 266sh, 258 and 223 (9100, 9350, 20 250); δ(400 MHz), 7.24–7.17 (2 H, m), 7.08 (1 H, dd, *J* 7 and 1.5), 6.98 (1 H, dd, *J* 7 and 1), 6.40 (1 H, dd, *J* 9.5 and 3.5, 6-H), 6.03 (1 H, dd, *J* 9.5 and 2.5, 7-H), 4.02 (1 H, s, 12-H), 3.98–3.86 (3 H, m, acetal), 3.68 (1 H, m, acetal), 3.65 (3 H, s), 3.62 (1 H, d, *J* 8, 9-H), 3.38 (1 H, dddd, 8 lines, *J* 8, 5, 3.5 and 2.5, 8-H), 2.90 (1 H, m, 14-H), 2.10–2.00 (3 H, m), 1.79 (1 H, m) and 1.28 (3 H, s).

With DDQ (33 mg) in boiling benzene (3 cm^3) (10 min) this acetal gave the previously prepared naphthalene (>90% yield) isolated by chromatography on silica in benzene–ether (9:1).

Methyl Ester and δ-Lactone of 2-Hydroxymethyl-4-methoxyphenylacetic Acid.—2-Acetyl-5-methoxybenzyl acetate (2.22 g) was added in methanol (10 cm^3) to a mixture of methanol (25 cm^3), 70% perchloric acid (5 cm^3) and thallium(III) nitrate (4.44 g) which had been allowed to reach room temperature. The mixture was stirred at *ca.* 17 °C (16 h) and then filtered to remove thallium(I) nitrate; the filtrate was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water (3×), dried ($MgSO_4$) and evaporated. The NMR spectrum of the crude product (1.65 g, 93% recovery) showed a 2:1 mixture of the title lactone and methyl ester which was satisfactory for the next stage of the synthesis. The products were separated on silica in benzene–ether (9:1) to give first the *δ-lactone* of *2-hydroxymethyl-4-methoxyphenylacetic acid* (0.89 g, 50%) (Found: M$^+$, 178.0631. $C_{10}H_{10}O_3$ requires *M*, 178.06299); ν_{max}(film)/cm^{-1} 1593, 1615 and 1750; δ(90 MHz) 7.13 (1 H, d, *J* 8), 6.85 (1 H, dd, *J* 8 and *ca.* 2), 6.80 (1 H, d, *J ca.* 2), 5.25 (2 H, s), 3.8 (3 H, s) and 3.65 (2 H, s). Continued elution of the column gave *methyl 2-hydroxymethyl-4-methoxyphenylacetate* **31** (0.523 g, 25%) (Found: M$^+$, 210.0893. $C_{14}H_{14}O_4$ requires *M*, 210.0892); ν_{max}/cm^{-1} 3450 br, 1735, 1612 and 1582; δ_H(90 MHz) 7.14 (1 H, d, *J* 8), 6.96 (1 H, d, *J ca.* 2), 6.78 (1 H, dd, *J* 8 and *ca.* 2), 4.6 (2 H, br s), 3.79 (3 H, s), 3.69 (5 H, apparent s, OMe and CH_2) and 2.86 (1 H, br s, OH).

Methyl 2-Formyl-4-methoxyphenylacetate.—The foregoing mixture of methyl ester and δ-lactone (1.70 g), 2 mol dm^{-3} aqueous sodium hydroxide (29 cm^3) and ethanol (6.8 cm^3) were boiled under reflux in an atmosphere of argon (3.5 h). The cooled product was washed with ether and cooled to 0–5 °C before addition of *ca.* 6 mol dm^{-3} hydrochloric acid dropwise to reduce the pH to 1. The product was extracted into ether and the solution treated at once with ethereal diazomethane. Evaporation of the solution at *ca.* 40 °C under reduced pressure gave the title compound sufficiently pure for the next step (1.355 g). Purification could be achieved by chromatography on silica in benzene–ether (4:1). Oxalyl chloride (255 mg) in dry CH_2Cl_2 was cooled to −55 °C and DMSO (314 mg) added in CH_2Cl_2 (1.1 cm^3) with stirring under argon. After 3 min the foregoing hydroxy ester (384 mg) in CH_2Cl_2 (2.5 cm^3) was added over 5 min by syringe. After the mixture had been stirred at −55 °C for 20 min, triethylamine (925 mg) was added and stirring continued (5 min); the mixture was then allowed to warm to 20 °C. It was then diluted with water, extracted with CH_2Cl_2 and the organic layer washed with water (3×), dried ($MgSO_4$) and evaporated to give the *title compound* (0.36 g); if required, the latter could be freed from lactone by chromatography on silica in benzene–ether (9:1) (Found: M$^+$, 208.0734. $C_{11}H_{12}O_4$ requires *M*, 208.0736); ν_{max}/cm^{-1} 1575, 1610, 1695 and 1740; δ_H(90 MHz) 10.08 (1 H, s), 7.35 (1 H, d, *J ca.* 2), 7.22 (1 H, d, *J* 8), 7.06 (1 H, dd, *J* 8 and 2), 3.98 (2 H, s), 3.86 (3 H, s) and 3.69 (3 H, s).

2-Formyl-4-methoxyphenylacetic Acid.—The foregoing ester (725 mg), water (5.75 cm^3), acetic acid (5.75 cm^3), and concentrated hydrochloric acid (5.75 cm^3) were boiled under reflux in an argon atmosphere (70 min). The *title compound* **2b** was isolated by ether extraction in the usual way and formed crystals, m.p. 121–122 °C (from chloroform) (Found: C, 62.0; H, 5.25%; M$^+$, 194.0578. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.15%; *M*, 194.0579); ν_{max}/cm^{-1} 2400–3400, 1695, 1705sh, 1614 and 1576; δ_H(90 MHz) 10.8 (1 H, br s), 10.0 (1 H, s), 7.32 (1 H, d, *J ca.* 2), 7.2 (1 H, d, *J* 8), 7.06 (1 H, dd, *J* 8 and *ca.* 2), 3.98 (2 H, s) and 3.84 (3 H, s).

Dehydration of 2-Formyl-4-methoxyphenylacetic Acid in the Absence of a Trap.—The title acid (50 mg) and acetic anhydride (2 cm^3) were boiled under reflux in an argon atmosphere (3 h). After evaporation of the acetic anhydride under reduced pressure at 100 °C the residue was chromatographed on silica in benzene–ether (4:1) to give first the anti-*dimer* of *7-methoxy-2-benzopyran-3-one* **33** (9 mg), m.p. 304–305 °C (from dichloromethane–ethanol) (Found: M$^+$, 352.0956. $C_{20}H_{16}O_6$ requires *M*, 352.0947); ν_{max}/cm^{-1} 1662 and 1758; δ_H[90 MHz, $(CD_3)_2$SO] 7.36 (2 H, d, *J* 8), 7.13 (2 H, d, *J ca.* 2), 6.95 (2 H, dd, *J* 8 and *ca.* 2), 6.09 (2 H, s), 4.54 (2 H, s) and 3.81 (6 H, s). Continued elution of the column gave the syn-*dimer* of *7-methoxy-2-benzopyran-3-one* **33** (10 mg), m.p. 274–275 °C (from chloroform–ethanol) (Found: M$^+$, 352.0953. $C_{20}H_{16}O_6$ requires *M*, 352.0947); ν_{max}/cm^{-1} 1611 and 1759; δ_H[90 MHz, $(CD_3)_2$SO] 6.9 (2 H, d, *J* 8), 6.75 (2 H, d, *J ca.* 2), 6.63 (2 H, dd, *J* 8 and *ca.* 2), 6.05 (2 H, s), 4.6 (2 H, s) and 3.62 (6 H, s).

N-Phenylmaleimide Adduct of 7-Methoxy-2-benzopyran-3-one.—2-Formyl-4-methoxyphenylacetic acid (50 mg), *N*-phenylmaleimide (58 mg) and acetic anhydride (2 cm^3) were boiled under reflux in an argon atmosphere (1.5 h). Evaporation of acetic anhydride under reduced pressure at 100 °C and crystallisation of the residue from ethanol (2×) gave the *title compound* **32** (60 mg, 63%), m.p. 222–224 °C (Found: M$^+$, 349.0952. $C_{20}H_{15}NO_5$ requires *M*, 349.0950); ν_{max}/cm^{-1} 1720 and 1770; δ_H(90 MHz) 7.3 (4 H, m), 6.95 (2 H, m), 6.55 (2 H, m), 5.91 (1 H, d, *J* 4.5), 4.4 (1 H, d, *J* 3), 3.9 (1 H, m), 3.79 (3 H, s) and 3.60 (1 H, m).

Addition of 7-Methoxy-2-benzopyran-3-one to the Olefin **9**.—2-Formyl-4-methoxyphenylacetic acid (1.0 g) was added in *ca.* 20 mg portions over 4 h to a refluxing mixture of acetic anhydride (20 cm^3) and the olefin **9** (4.04 g) under argon. Boiling under reflux was continued for a further 1.25 h and the acetic anhydride removed at 100 °C under a water-pump vacuum. Chromatography on silica in benzene–ether (7:3), gave recovered olefin **9** (2.38 g), and a less polar (0.53 g) and a more polar adduct fraction (0.63 g) but allowed separation of only a part (50 mg) of the more polar pyrone dimer. Rechromatography of the adduct fractions on silica in ether–dichloromethane (1:9) separated the adducts from the less polar dimers but failed to separate the adducts. The less polar adduct fraction gave the less polar dimer (10 mg) and adducts (0.52 g). The more polar adduct fraction gave dimer (60 mg) and more polar adducts (0.59 g). The yield of adducts is 58% and that of dimers 12%.

Conversion of the More Polar Adduct into Dihydronaphthalene **18b** (8α, 9β).—More polar adduct (1.94 g), and methanol saturated with dry hydrogen chloride (35 cm^3) were boiled under reflux (1.75 h). After cooling the crystalline precipitate was filtered off (1.24 g). A further quantity (0.110 g) of this crystalline product was obtained by evaporation of the meth-

anol, washing the residue in CH_2Cl_2 with saturated aqueous sodium hydrogen carbonate, evaporation of the dried ($MgSO_4$) CH_2Cl_2 solution and trituration with ether. The methoxy 8α, 9β-*dihydronaphthalene* had m.p. 145–147 °C (from ether–light petroleum) (Found: C, 68.5; H, 6.8%; M^+, 386.1724. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.7%; *M*, 386.1729), ν_{max}/cm^{-1} 1730 and 1740sh), δ(90 MHz) 7.11 (1 H, d, *J* 8), 6.73 (1 H, dd, *J* 8 and *ca.* 2), 6.6 (1 H, d, *J ca.* 2), 6.43 (1 H, d, *J* 9), 6.05 (1 H, dd, *J* 9 and *ca.* 6), 3.78 (3 H, s), 3.66 br (1 H, s), 3.60 (3 H, s), 3.41 (3 H, s), 2.85 (1 H, d, *J* 17), 2.56 (1 H, d, *J* 17) and 1.04 (3 H, s); in addition the region 1.2–3.05 contains complicated ill-resolved resonance for 6 H *cf.* the 400 MHz spectrum of the demethoxy compound.

Conversion of the Less Polar Adducts into Dihydronaphthalenes **18b** (8β, 9α) *and* **18b** (8α, 9β).—The less polar adduct fraction (1.51 g) was treated with boiling MeOH–HCl in the same way, after which the methanol was evaporated and the product in CH_2Cl_2 washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated. The product (1.57 g), benzene (31.5 cm^3), and DBN (1.57 cm^3) were boiled under reflux in an argon atmosphere (4 h). The product in CH_2Cl_2 was washed with 2 mol dm^{-3} hydrochloric acid and water, dried ($MgSO_4$) and evaporated. The crude product (1.49 g) was chromatographed on silica in CH_2Cl_2–Et_2O (95:5). Rechromatography of the overlap region (2 ×) gave a total of 0.604 g of the 8β,9α-*methoxydihydronaphthalene* **18b**;* (8β, 9α) and its 8α,9β-isomer described above (0.644 g). The 8β,9α-isomer had m.p. 154–5 °C (from ether–light petroleum) (Found: C, 68.5; H, 6.9; *M*, 386.1730) ν_{max}/cm^{-1} 1728 and 1743, δ_H(90 MHz) 7.1 (1 H, d, *J* 9), 6.73 (1 H, dd, *J* 9 and *ca.* 2), 6.68 (1 H, d, *J ca.* 2), 6.51 (1 H, d, *J* 9), 3.8 (3 H, s), 3.64 (3 H, s), 3.69 (1 H, br), 3.45 (3 H, s), 3.0 (1 H, m) and (1 H, d, *J* 18), 2.64 (1 H, d, *J* 18), 1.05 (3 H, s) and 1.05–2.48 (5 H, complex resonance) *cf.* the 400 MHz spectrum of the demethoxy compound **18a** (8β, 9α).

Ethylene Acetals **20b** (8α, 9β) *and* **20b** (8β, 9α).—The ketone **18a** (8α, 9β) (436 mg), ethylene glycol bis-trimethylsilyl derivative (0.79 g), dry dichloromethane (8 cm^3) and trimethylsilyl triflate (0.1 cm^3) were held at −25 °C (14 d). The product was treated with pyridine (200 mg) at −25 °C and then poured into aqueous sodium hydrogen carbonate and isolated in dichloromethane in the usual way. The crude product, 4 mol dm^{-3} aqueous sodium hydroxide (7.2 cm^3) and ethanol (4 cm^3) were stirred at 20 °C (16 h) under argon. The mixture was acidified with 2 mol dm^{-3} hydrochloric acid, isolated in dichloromethane in the usual way and treated with ethereal diazomethane. Chromatography on silica (150 g) in dichloromethane–ether (95:5) gave first recovered ketone (68 mg) followed by the 8α,9β-*methoxydihydronaphthalene acetal* **20b**† (8α, 9β) (300 mg), m.p. 118–120 °C (from ether) (Found: C, 67.0; H, 7.1%; M^+, 430.1987. $C_{24}H_{30}O_7$ requires C, 67.0; H, 7.0%; *M*, 430.1991); δ_H 7.12 (1 H, d, *J* 8), 6.75 (1 H, dd, *J* 8 and *ca.* 2), 6.7 (1 H, d, *J ca.* 2), 6.44 (1 H, d, *J* 10), 6.15 (1 H, dd, *J* 10 and 6), 3.82 (7 H, m, overlapping OMe and OCH_2CH_2O signals), 3.62 (4 H, OMe singlet and obscured 1 H singlet), 3.52 (3 H, s), 2.9 (1 H, m), 2.45–1.3 (5 H, m) and 1.25 (3 H, s).

In a similar way the stereoisomeric ketone **18b** (8β, 9α) was converted into its ethylene acetal **20b** (8β, 9α). Any unchanged ketone could be removed by adding ether to the crude product; the acetal dissolved leaving the crystalline ketone to be recycled. The acetal was purified by chromatography on silica in dichloromethane–ether (95:5); the yield of acetal with one recycle of unchanged ketone was 69%. The *acetal* **20b**† (8β, 9α) was a gum that resisted attempted crystallisation (Found: M^+, 430.1983. $C_{24}H_{30}O_7$ requires *M*, 430.1991); δ_H 7.12 (1 H, d, *J* 8), 6.73 (1 H, dd, *J* 8 and *ca.* 2), 6.68 (1 H, d, *J ca.* 2), 6.55 (1 H, d, *J* 10), 6.01 (1 H, dd, *J* 10 and 6), 3.9 (br) and 3.83 (s) (overlapping OCH_2CH_2O and OMe signals), 3.75 obscured (1 H, br, 9-H), 3.20 (1 H, m), 2.4 (2 H, br s, CH_2CO_2Me), 2.30 (1 H, m, partly obscured), 1.8–1.25 (4 H, m) and 1.13 (3 H, s).

Methyl 17,17-*Ethylenedioxy*-3-*methoxy*-11-*oxo*-8α-*estra*-1,3,5(10)-*triene*-12ξ-*carboxylate* **22b** (8α, 9α).—The foregoing 8α,9β-acetal **20b** (8α, 9β) was catalytically hydrogenated and the product directly cyclised with NaH as described for the corresponding demethoxy compound. The *title compound* was isolated by chromatography on silica in benzene–ether (19:1) (77%), m.p. 134–139 °C (from ethanol (Found: C, 68.75; H, 7.05%; M^+, 400.1889. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.0%; *M*, 400.1885); ν_{max}/cm^{-1} 1710, 1725sh and 1745; δ_H(400 MHz) 6.88 (1 H, d, *J* 8.5, 1-H), 6.73 (1 H, dd, *J* 2.5 and 8.5, 2-H), 6.63 (1 H, d, *J* 2.5, 4-H), 4.06 (1 H, s, 12-H), 3.85–4.0 (3 H, m, acetal), 3.77 (3 H, s), 3.74 (1 H, br d, *J* 6.5, 9-H), 3.68 (3 H, s), 3.62–3.70 (1 H, m, acetal), 2.83 (2 H, m, 14-H and 6-H), 2.61 (1 H, ddd, *J* 17.0, 12.5 and 5, 6-H), 2.54 (1 H, dddd, *J* 12.5, 6.5, 4.5 and 2.0, 8-H), 1.85–2.10 (4 H, m), 1.71 (1 H, m), 1.54 (1 H, qd, *J* 13 and 4.5, 7-H) and 1.22 (3 H, s).

Methyl 17,17-*Ethylenedioxy*-3-*methoxy*-11-*oxoestra*-1,3,5(10)-*triene*-12ξ-*carboxylate and its* 9β-*Epimer*.—Hydrogenation of the 8β,9α-dihydronaphthalene acetal **20b** (8β, 9α) and Dieckmann cyclisation of the product were conducted as described for the corresponding demethoxy compounds. The title compounds were separated by chromatography on silica in benzene–ether (9:1) to give first *methyl* 17,17-*ethylenedioxy*-3-*methoxy*-11-*oxo*-9β-*estra*-1,3,5(10)-*triene*-12ξ-*carboxylate* (19%) as a gum (Found: M^+, 400.1883. $C_{23}H_{28}O_6$ requires *M*, 400.1886), ν_{max}(CH_2Cl_2 film)/cm^{-1} 1708, 1730 and 1756; δ(400 MHz) 6.91 (1 H, br d, *J* 8.5, 1-H), 6.71 (1 H, dd, *J* 8.5 and 2.5, 2-H), 6.65 (1 H, d, *J* 2.5, 4-H), 3.77 (3 H, s), 3.72 (1 H, br d, *J* 5, 9-H), 3.69 (3 H, s), 3.685 (1 H, s, 12-H), 3.57–3.85 (4 H, m), 2.875 (1 H, ddd, *J* 18.0, 13.0, 6.0), 2.685 (1 H, br dd, *J* 18 and 5.0, 6β-H), 2.35 (2 H, m, 8-H and 14-H), 1.79–2.00 (4 H, m, 1 7-H, 2 × 16-H and 1 × 15-H), 1.74 (1 H, tdd, *J* 14.0, 6.0 and 3.0, 7-H), 1.49 (1 H, m, 15-H) and 1.215 (3 H, s). Irradiation of the signal at δ 3.725 9-H) causes a signal at *ca.* δ 2.37 to become a dt (*J* 12 and 3) which must therefore be due to 8-H which shows *J* values of 5, 12, 3, and 3; 14-H at δ 2.31 is also clarified as a td (*J* 12 and 6.5). Continued elution gave the 9α-*epimer* **22b** (8β, 9α), m.p. 116–118 °C (from ether–light petroleum) (Found: M^+, 400.189) ν_{max}/cm^{-1} 1713, 1725 sh and 1760; δ(400 MHz) 7.275 (1 H, d, *J* 9), 6.73 (1 H, dd, *J* 9 and 2.5), 6.60 (1 H, d, *J* 2.5), 4.02 (1 H, br s, 12-H), 3.98–3.85 (3 H, m, acetal), 3.77 (3 H, s), 3.73 (3 H, s), 3.65–3.72 (1 H, m, acetal), 3.535 (1 H, br d, *J* 11.5, 9-H), 2.85 (1 H, m, 6-H, 'leans' to following signal), 2.78 (1 H, ddd, 17.5 and 2, 6-H, leans to preceding signal), 2.38 (1 H, td, *J* 11.5 and 7.5, 14-H ?), 1.80–2.06 (5 H, m), 1.53 (2 H, m) and 1.16 (3 H, s).

17,17-*Ethylenedioxy*-3-*methoxy*-11-*oxo*-8α-*estra*-1,3,5(10)-*triene*.—The title compound was prepared by demethoxycarbonylation of the corresponding methyl 12ξ-carboxylate using barium hydroxide as described for the corresponding demethoxy compound. The product was purified by chromatography on silica in ether–dichloromethane (1:19) to give the *title compound* (86%), m.p. 134–136 °C (from ethanol) (Found: C, 73.55; H, 7.75%; M^+, 342.1832. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.6%; *M*, 342.1831), ν_{max}/cm^{-1} 1608 and 1712; δ(400 MHz) 6.87 (1 H, d, *J* 8.5), 6.75 (1 H, dd, *J* 8.5 and 2.5), 6.64 (1 H, d, *J* 2.5), 3.85–4.02 (3 H, m, acetal), 3.80–3.85 (1 H, m, acetal), 3.78 (3 H, s), 3.70 (1 H, br d, *J* 6.5, 9-H), 2.875 (1

* Methyl 6-methoxy-2-(2-methoxycarbonylmethyl-2-methyl-3-oxocyclopentyl)-1β,2α-dihydronaphthalene-1-carboxylate.

† Methyl 6-methoxy-2-(3,3-ethylenedioxy-2-methoxycarbonylmethyl-2-methylcyclopentyl)-1β,2α-dihydronaphthalene-1-carboxylate.

H, dq, *J* 12 and <1, 12-H), 2.75–2.85 (2 H, m, 14-H and 6-H), 2.63 (1 H, ddd, *J* 16, 7.5 and 5.0, 6-H), 2.55 (1 H, dddd, *J* 2.5, 5.0, 6.5 and 14.5, 8-H), 2.24 (1 H, d, *J* 12.0, 12-H), 2.08 (1 H, ddd, *J* 14, 11 and 4.0, 16β-H, 'leans' to following signal), 2.01 (1 H, ddd, *J* 14.0, 9.5 and 6.0, 16α-H), 1.81 (1 H, qd, *J* 13 and 6.0, 15β-H), 1.70 (1 H, m, 15α-H), 1.51 (1 H, qd, *J* 13 and 4.75, 7β-H), 0.965 (3 H, br s). An NOE difference experiment with irradiation of the 13-methyl showed the following enhancements: δ 3.8–3.85 (1%, acetal 1 H), 2.8–2.9 (negative, 12α), 2.24 (5%, 12β-H), 2.08 (5%, 16β-H), 1.81 (6%, 15β-H) and 1.51 (14%, 7β-H).

Epimerisation of 17,17-*Ethylenedioxy*-3-*methoxy*-11-*oxo*-8α-*estra*-1,3,5(10)-*triene* **24b** (8α, 9α) *at* C-8.—(*a*) The ketone **24b** (8α, 9α) (0.44 g), dimethylformamide (9.8 cm^3), triethylamine (4.2 cm^3) and trimethylsilyl chloride (2.1 cm^3) were boiled under reflux under argon (16 h) (bath temperature 110 °C). The cooled product was poured into ether and washed with water (3 ×), and the organic layer dried ($MgSO_4$) and evaporated to give the almost pure silyl ether. The product was warmed with ether, the mixture cooled in ice, and the ether decanted to give pure 17,17-*ethylenedioxy*-11-*trimethylsiloxyestra*-1,3,5(10),9-*tetraene* **25b** (0.48 g, 90%), m.p. 147–149 °C (Found: M^+, 414.2233. $C_{24}H_{34}O_4Si$ requires *M*, 414.2226); ν_{max}/cm^{-1} 1604 and 1633; δ_H(90 MHz) 8.04 (1 H, d, *J ca.* 8, 1-H), 6.75 (1 H, dd, *J ca.* 8 and 2, 2-H), 3.97 (4 H, br s, acetal), 3.83 (3 H, s), 1.03 (3 H, s) and 0.12 (9 H, s); proton resonance in the δ 0.3 region was poorly resolved.

(*b*) The foregoing enol silyl ether (345 mg) was dissolved in dry degassed acetonitrile (8.25 cm^3) and palladium acetate (301 mg) added in an argon atmosphere. The mixture was boiled under reflux (5.5 h) and the product chromatographed on silica in benzene–ether (9:1) to give 17,17-*ethylenedioxy*-3-*methoxy*-11-*oxoestra*-1,3,5,8(9)-*tetraene* **26b** (178 mg, 63%), m.p. 186–187 °C (from methanol) (Found: C, 74.1; H, 7.05%; M^+, 340.1672. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%; *M*, 340.1674); δ(90 MHz) 8.08 (1 H, d, *J* 8, 1-H), 6.85 (1 H, dd, *J* 8 and *ca.* 2, 2-H), 6.8 (1 H, d, *J ca.* 2, 4-H), 4.1–3.9 (4 H, br m, acetal), 3.85 (3 H, s), 3.4–1.5 (11 H, m's) and 0.99 (3 H, s).

(*c*) To the foregoing $\Delta^{8(9)}$-ene-11-one **26b** (149 mg) in THF (5 cm^3) and liquid ammonia (15 cm^3) containing *tert*-butyl alcohol (71 mg) in a Dewar vessel was added small pieces of lithium metal (23 mg). The deep blue colour persisted for 85 min when the product was quenched with saturated aqueous ammonium chloride and extracted into dichloromethane. Evaporation of the dried ($MgSO_4$) organic extract and chromatography of the residue on silica in benzene–ether (9:1) gave 17,17-*ethylenedioxy*-3-*methoxy*-11-*oxoestra*-1,3,5(10)-*triene* **24b** (8β, 9α) (106 mg) as well as its previously described 8-epimer **24b** (8α, 9α) (24 mg). Compound **24b** (8β, 9α), m.p. 154–156 °C (from ethanol) (Found: C, 73.5; H, 7.7 5%; M^+, 342.1827. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.6; *M*, 342.1831); ν_{max}/cm^{-1} 1580, 1612 and 1710; δ_H(400 MHz) 7.25 (1 H, br d, *J* 8.5, 1-H), 6.76 (1 H, dd, *J* 8.5 and 2.5, 2-H), 6.62 (1 H, d, *J* 2.5, 4-H), 3.81–4.015 (4 H, m, acetal), 3.775 (3 H, s), 3.53 (1 H, br d, *J* 11.5, 9-H), 2.87 (1 H, dq, *J* 11.5 and <1, 12α-H), 2.84 (1 H, m, obscured, 6-H), 2.71 (1 H, ddd, *J* 16.5, 5 and 2, 6-H, partly obscured and leaning to preceding signal), 2.325 (1 H, td, *J* 12 and 7.5, 14-H ?), 2.25 (1 H, d, *J* 11.5, 12-H) 210 (1 H, ddd, *J* 14.5, 12.0 and 3.5), 1.93–2.04 (2 H, m), 1.86 (1 H, m), 1.79 (1 H, *J* 11.5 and 2.5, either td or qd), 1.53 (1 H, qd, *J* 12.0 and 6.0), 1.44 (1 H, qd, *J* 11.5 and 6.5) and 0.875 (3 H, br s).

17,17-*Ethylenedioxy*-3-*methoxy*-11-*oxo*-9β-*estra*-1,3,5(10)-*triene*.—The 9α-ketone **24b** (8β, 9α) (30 mg), benzene (3 cm^3) and DBN (0.2 cm^3) were boiled under reflux in an argon atmosphere (3 h). The cooled product was dissolved in ether and the solution washed with 2 mol dm^{-3} hydrochloric acid, and aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated, and the residue chromatographed on silica in ether–benzene (1:9) to give the 9β-ketone **24b** (8β, 9β) (24 mg), m.p. 163–165 °C (from ethanol) (Found: C, 73.35; H, 7.5%; M^+, 342.1824. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.6%; *M*, 342.1831); ν_{max}/cm^{-1} 1578, 1612 and 1702; δ(400 MHz) 6.90 (1 H, d, *J* 8.5, 1-H), 6.675 (1 H, dd, *J* 8.5 and 2.5, 2-H), 6.66 (1 H, br s, $W_{\frac{1}{2}}$ 4 Hz, 4-H), 3.77 (3 H, s), 3.67–3.90 (4 H, m, acetal), 3.61 (1 H, br d, *J* 3.0, 9-H), 2.91 (1 H, ddd, *J* 17.5, 14.0 and 6.0, 6α-H), 2.685 (1 H, br dd, *J* 17.5 and 5.0, 6β-H), 2.545 (1 H, dd, *J* 13.0 and 0.8, 12α-H), 2.28 (2 H, m), 2.05 (1 H, m), 2.015 (1 H, dd, *J* 13.0 and 1.5, 16β-H), 1.79–1.95 (3 H, m), 1.73 (1 H, tdd, *J* 13.5, 5.5 and 2.5), 1.405 (1 H, m) and 0.91 (3 H, d, *J* 0.8, 18-H). Continued elution of the column gave recovered 9α-ketone **24b** (8β, 9α) (6 mg). The same 9β-ketone was obtained together with its 9α-isomer by boiling the ester **22b** (8β, 9β) (23 mg), water (2 cm^3) and ethanol (1 cm^3) with barium hydroxide (300 mg) for 23 h in an argon atmosphere under reflux. After work-up chromatography of the product on silica in benzene–ether (9:1) gave the 9β-ketone (3 mg) and the 9α-ketone (2 mg).

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