Cycloaddition of Phenyl Vinyl Sulphone to 3-Methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl Acetate: Synthesis of 14-Functionalised 19-Norpregnane Derivatives†

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Diels–Alder reaction of 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate **3** with phenyl vinyl sulphone affords three 14,17-cycloadducts; the two major products (*ca.* 37% each) are the regioisomers derived from *endo* addition on the β-face, whereas the minor product (*ca.* 14%) is the *endo* isomer of *meta*-directed attack on the α-face. Sequential reductive desulphonylation, hydroxylation, and oxidative cleavage of the major products is described, and the derived 14-hydroxymethyl-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one **16** is converted into 14α-hydroxymethyl and 14α-formyl analogues of 19-norprogesterone. A route to 3-methoxy-14-methyl-19-norpregna-1,3,5(10)-trien-20-one **27** is described.

We have recently described a synthetic route to 14α,17α-ethano-19-norsteroids, based upon cycloaddition of an ethylene equivalent to estrone-derived 14,16-dien-17-yl acetates.[1] The method provides scope for modification of the intermediates to 14-alkyl or 14-functionalised alkyl systems.[1,2] It was considered that an extension of this approach, to starting materials bearing a 16-methyl group, might provide an entry to 14α-functionalised alkyl 19-norpregnane analogues.

In this work, we describe the regio- and stereo-chemical outcome of phenyl vinyl sulphone cycloaddition to 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate **3**, and conversion of the cycloadducts into 14α-formyl, 14α-hydroxymethyl and 14α-methyl analogues of 19-norprogesterone.[3]

Estrone 3-methyl ether **1** was converted into 3-methoxy-16-methylestra-1,3,5(10),15-tetraen-17-one **2** through sequential 16-methylenation, catalytic hydrogenation (to 16β-methyl 17-one), bromination (mainly to 16α-bromo-16β-methyl 17-one), and dehydrobromination.[4] Conversion of enone **2** into the derived dienyl acetate **3** proceeded efficiently under forcing conditions (Scheme 1).

Treatment of the dienyl acetate **3** with phenyl vinyl sulphone[5] in xylene at 140 °C (sealed tube) for 120 h resulted in *ca.* 90% conversion into a mixture of cycloadducts (*ca.* 2.5:1:2.5; TLC). When the mixture was cooled, the product **5** of intermediate R_f precipitated, and was recovered essentially quantitatively. Chromatography of the remaining material resulted in separation of the two major cycloadducts **4** and **6**. (In practice, this separation was not essential, for further transformation of the intermediates, see later.)

NMR examination of the compounds **4**–**6** revealed their gross structural similarity as 14,17-cycloadducts. Although the C*H*(SO_2Ph) signals were consistent with *endo* orientation of the substituent in all cases,[1] these and other spectroscopic data failed to distinguish between the three of four possible *endo* isomers. However, only one isomer **4** underwent base-mediated cleavage, to give the 14β-(2-phenylsulphonylethyl) compound **7**, thereby confirming the 16α-location of the phenylsulphonyl group in **4**,[1,2] and by exclusion, the absence of vicinal acetoxy–phenylsulphonyl relationships in **5** and **6**. The latter compounds merely suffered bridgehead hydrolysis under similar reaction conditions, to give the respective 17-alcohols **8** and **9**.

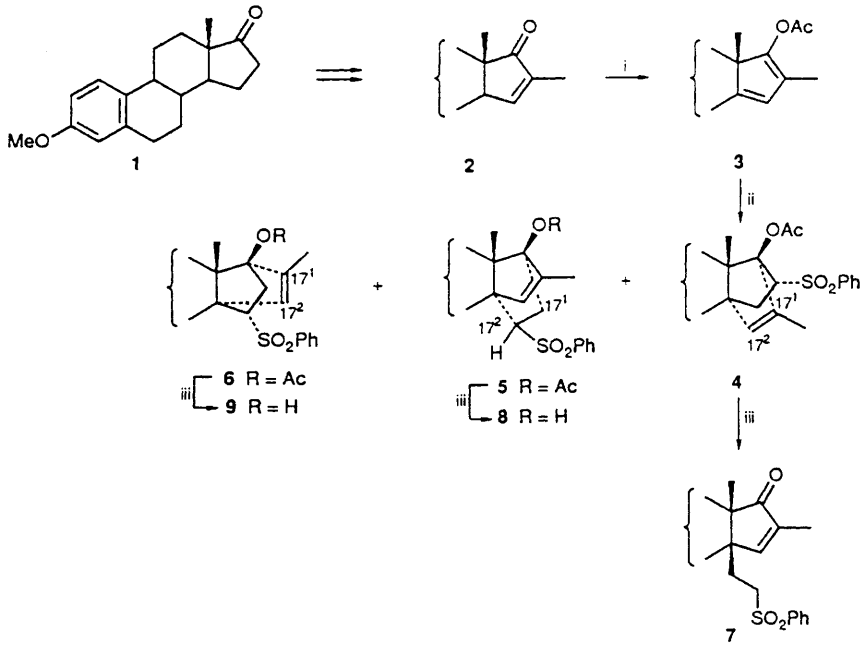
† Parts of the experimental work described in this paper were carried out by the authors whilst employed at the former National Chemical Research Laboratory, Pretoria.

The foregoing evidence was insufficient to assign overall 14,17-configuration to the products, but subsequent transformations demonstrated that the two major cycloadducts **4** and **6** are regioisomers (see later), and it seemed improbable that the presence of the 16-methyl group in **3** would result in an overall reversal of the β-face stereoselectivity which has now been widely demonstrated in cycloadditions to steroidal 14,16-dienes.[1,6–9] Consequently, we concluded that the cycloadducts **4** and **6** arose from β-face *endo* attack by phenyl vinyl sulphone, whereas the minor product **5** is the *endo* isomer arising from *meta*-directed addition upon the α-face.[10]

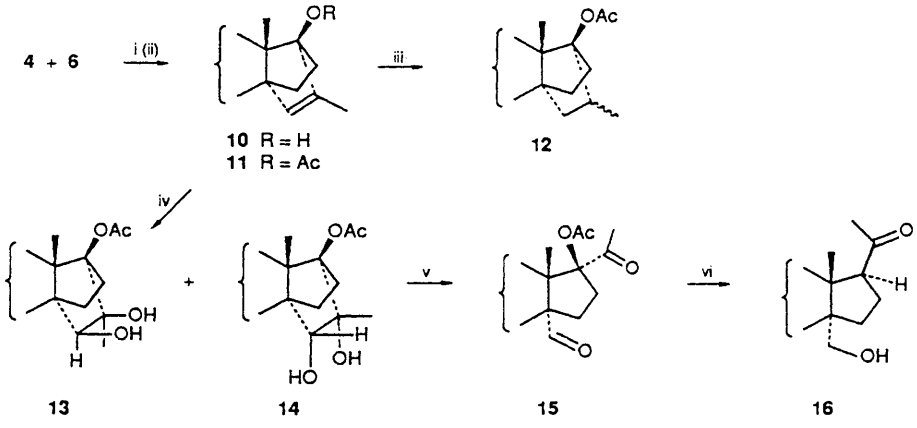
Notwithstanding the overall trend, the result demonstrates a remarkable reduction in the usually clean regio- and stereoselectivity of cycloadditions to 14,16-dienes. It is evident that the presence of a 16-methyl group suppresses the usual *ortho* regioselectivity very strongly, in accordance with FMO principles,[11] but surprisingly, the resultant *meta* regioselectivity is attended by a significant diminution of overall β-face stereoselectivity. Furthermore, the reaction is comparatively slow and appears to be unresponsive to the influence of Lewis acid catalysts. Molecular models show no obvious steric factors which would promote *meta*-directed cycloaddition on the α-face, and explanations are being sought in further model studies on ring D substrates.

In spite of the relative complexity of the cycloaddition result, the purpose in hand was well served by conversion of the major products **4** and **6** into a common intermediate in the overall plan. Thus, small-scale reductive desulphonylations of the individual compounds **4** and **6** with sodium amalgam in methanol–tetrahydrofuran gave satisfactory yields of the identical 14,17-etheno-17[1]-methyl compound **10** (Scheme 2). In practice, the overall efficiency of this process was improved by reducing the mixture of cycloadducts (**4** + **6**), to give the desulphonylated product **10** (81%) accompanied by small amounts of by-products arising from olefinic-bond participation during the reduction.[1] Further work is in progress to clarify aspects of the by-product formation and structures.[12]

The derived 17β-acetate **11** underwent catalytic hydrogenation, but gave an inseparable mixture (*ca.* 1:1) of 17[1]*R* and 17[1]*S* isomers **12**. By contrast, treatment of **11** with osmium tetraoxide–pyridine, and reductive work-up, gave a readily separable mixture (*ca.* 12:1) of 17[1]*S*,17[2]*S* and 17[1]*R*,17[2]*R* diols **13** and **14**, the structures of which were readily distinguished by distinctive NMR properties. The major isomer **13** showed a signal at δ 4.23 (d, *J* 2.1 Hz after D_2O exchange) for the 17[2]-



Scheme 1 *Reagents and conditions:* i, Ac_2O–$CH_3CO_2C(CH_3)=CH_2$–*p*TsOH, 100 °C; ii, $CH_2=CHSO_2Ph$, 140 °C; iii, KOH–MeOH, 25 °C



Scheme 2 *Reagents and conditions:* i, Na–Hg, Na_2HPO_4, 0–25 °C; ii, Ac_2O–*p*TsOH, 0 °C; iii, Pd–C, H_2; iv, OsO_4–C_5H_5N, 25 °C; v, $NaIO_4$, 25 °C; vi, Ca–NH_3, −78 °C

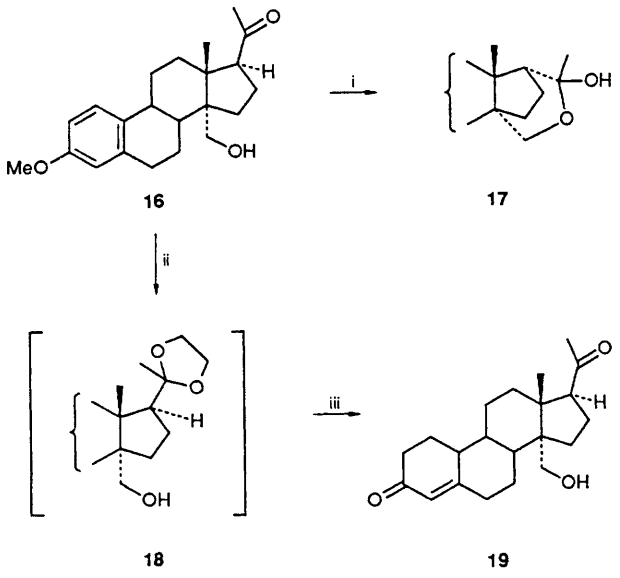
proton, coupled in a near-planar W-conformation with the 15β-proton, thus confirming the *endo* orientation of the 17^1- and 17^2-hydroxy groups. The assignments were further confirmed by diagnostic[1] deshielding of the 9α-proton by the *exo*-17^2-hydroxy group in **14**.

The strongly *endo*-selective hydroxylation of **11** differs significantly from that of the analogous compound lacking a 16-methyl group,[1] in which moderate *exo* stereoselectivity is observed, but an explanation for the difference, based upon purely steric considerations is not obvious.

The stereochemical outcome of the hydroxylation was incidental, since sodium periodate cleavage of the individual diols **13** or **14** or a mixture (**13** + **14**) resulted in efficient conversion into 17β-acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-1,3,5(10)-triene-14-carbaldehyde **15**, the structure of which was evident from infrared absorptions at ν_{max}/cm^{-1} 1736 (17β-OAc) and 1715br (14^1- and 20-CO), and NMR signals for two acetyl methyl groups (3 H, s, at δ 2.05 and 2.1) and an aldehydic proton (1 H, s, at δ 9.87).

The further elaboration of this product into 19-norpregnane analogues required deacetoxylation and inversion at C(17) and, of the many options considered, treatment of **15** with calcium in liquid ammonia proved to be gratifyingly successful. The reaction was conducted at −78 °C in dry tetrahydrofuran, and careful destruction of the excess of calcium with bromobenzene, then addition of ammonium chloride, resulted in 17-deacetoxylation with concomitant 14^1-reduction followed by 17α-protonation of the reaction intermediate, to give 14-hydroxymethyl-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one **16** in 89% yield. The gross structure of **16** was evident from appropriate spectroscopic properties, and the crucial assignment of 17-configuration followed from a CD spectrum ($\Delta\varepsilon_{max}$ +3.25 at 289 nm) typical of 17β-acetyl steroids,[13] and a distinctive NMR signal at δ 3.0 (1 H, t, *J* 8.6 Hz) for the 17α-proton.

It was assumed that the work-up method may have facilitated kinetically controlled (or perhaps, even intramolecular) protonation of the obligatory 17(20)-enolate intermediate and, in an attempt to establish whether the presence of a 14α-hydroxymethyl group might influence the thermodynamic relationship between the 17α- and 17β-acetyl isomers in this series, the compound **16** was treated with methanolic potassium hydroxide. In the event, the purpose of the experiment was not served, since the only product isolated (79%) was formulated as the hemiketal **17** (Scheme 3), arising from intramolecular



Scheme 3 *Reagents and conditions:* i, KOH–MeOH, 60 °C; ii, $(CH_2OH)_2$–*p*TsOH, heat; iii, Li–NH_3–*tert*-BuOH, then HCl–MeOH

entrapment of the 17-epimer of **16** as it was formed. The NMR spectrum of **17** showed the presence of an otherwise undetected impurity (*ca.* 8%), assumed to be the 20-isomer.

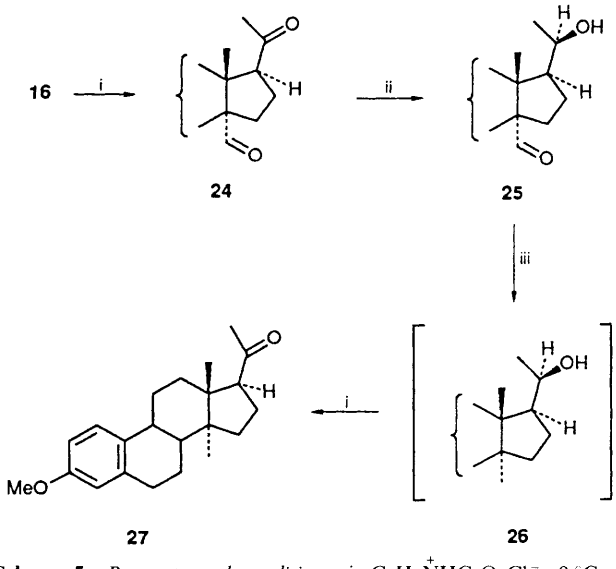
A particular advantage in the efficient conversion of **15** into **16** was the attendant differentiation of functionality at C(14[1]) and C(20), thereby suggesting scope for synthesis of analogues of 19-norprogesterone, variously substituted at C(14). The sensitivity of the 14-hydroxymethyl group in **16** toward strongly acidic reaction conditions demanded care. Ketalisation of **16** in refluxing benzene–ethylene glycol, with sufficient toluene-*p*-sulphonic acid catalyst to allow rapid reaction, was accompanied by losses, but when the reaction was allowed to proceed in the presence of a trace amount of catalyst with slow distillation of solvent, about 90% conversion to the labile 20-ketal **18** was achieved. The product was not purified or fully characterised owing to its lability, but was used directly in subsequent experiments.

Birch reduction of **18**, followed by treatment of the crude product with methanolic hydrochloric acid afforded 14α-hydroxymethyl-19-norprogesterone **19** in 65% yield from **16**. The structure followed from characteristic NMR and chiroptical data.

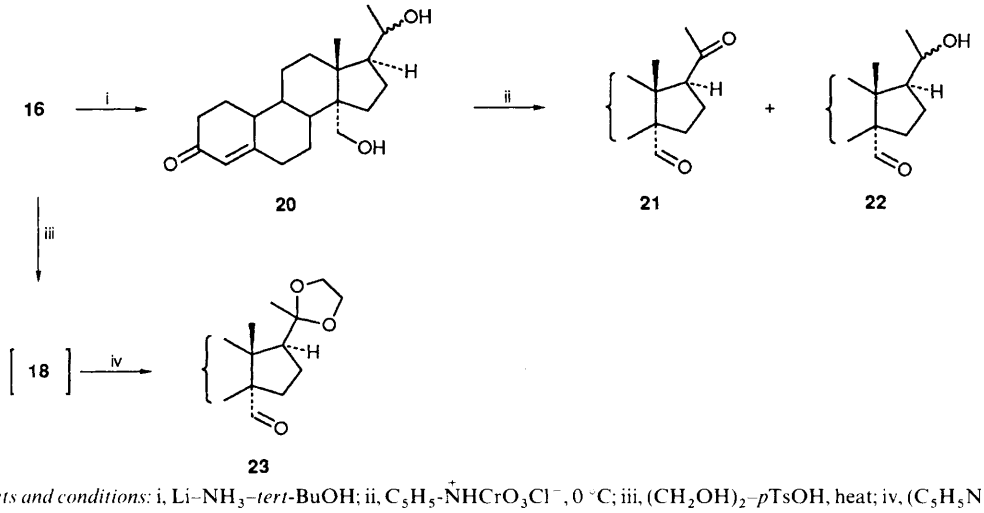
The lability of the ketal **18** invited exploration of an alternative route to **19** and other 14[1],20-differentiated products. Thus, Birch reduction of the hydroxy ketone **16**, and acid treatment of the intermediate gave a crystalline product, assumed to be a mixture of 14[1], 20ξ-diols **20** (MS) (Scheme 4). Attempted chemoselective oxidation of **20** with a slight excess (*ca.* 1.5 mol) of pyridinium chlorochromate showed only moderate selectivity, leading to 3,20-dioxo-19-norpregn-4-ene-14-carbaldehyde **21** (20%) and an inseparable *ca.* 7:3 mixture **22** (44%) of 20*R*- and 20*S*-hydroxy 14α-carbaldehydes. Clearly, this route is amenable to efficient synthesis of the 14-formyl analogue **21** of 19-norprogesterone, if an excess of oxidant is used, but the moderate 14[1],20-differentiation detracted from other applications.

In a complementary investigation, the scope for converting the 14α-hydroxymethyl 20-ketone **16** into 14α-methyl products was examined. The most direct option appeared to be *via* sequential oxidation of the 14α-hydroxymethyl 20-ketal **18** and Wolff–Kishner reduction. However, attempted oxidation of **18** with pyridinium dichromate gave a discouragingly low yield of the corresponding 14α-carbaldehyde **23**.

A reversed differentiation sequence was more successful, and is exemplified by an alternative synthesis of 3-methoxy-14-methyl-19-norpregna-1,3,5(10)-trien-20-one **27**.[14] Thus, oxidation of the 14α-hydroxymethyl 20-ketone **16** gave a moderate yield of 3-methoxy-20-oxo-19-norpregna-1,3,5(10)-triene-14-carbaldehyde **24** (Scheme 5), treatment of which with a small excess of lithium tri(*sec*-butyl) borohydride ('L-Selectride') in tetrahydrofuran at 0 °C resulted in highly



Scheme 5 *Reagents and conditions:* i, $C_5H_5\overset{+}{N}HCrO_3Cl^-$, 0 °C; ii, $LiBu^s_3BH$, 0 °C; iii, N_2H_4–KOH, 215 °C



Scheme 4 *Reagents and conditions:* i, Li–NH_3–*tert*-BuOH; ii, $C_5H_5\overset{+}{N}HCrO_3Cl^-$, 0 °C; iii, $(CH_2OH)_2$–*p*TsOH, heat; iv, $(C_5H_5N^+H)_2C_2O_7^{2-}$, 25 °C

chemoselective reduction of the 20-oxo group, to give a single product (86%). The structure of this product was assigned as **25** on the basis of the expected NMR signals for 14^1-, 20- and 21-protons. Wolff–Kishner reduction of **25**, followed by remethylation (as a result of partial 3-demethylation), and oxidation of the resultant crude product **26**, gave the 14α-methyl 20-ketone **27** (86% from **25**). The structure of **27** was confirmed by comparison with authentic material,[14] and the method constitutes an efficient alternative to this product and hence, to 14α-methyl-19-norprogesterone.

The 14α-hydroxymethyl and 14α-methyl compounds **16** and **27** are key intermediates in our projected synthesis of 14α-substituted analogues of 19-nor-9β,10α-progesterone. Molecular mechanics calculations predict that these target compounds are susceptible to deformation of rings B and C. The 14α-methyl analogue, for example, is expected to display conformational analogy with progesterone, and will thus serve to probe the affinity of conformationally adaptable hormone analogues toward the gestagen receptor.

The synthetic route outlined here provides ready access to the intermediates **16** and **27**, and the derived synthesis of conformational analogues of progesterone is in progress, as part of our ongoing investigation into structure-activity relationships and predictive design of steroid hormones.

Experimental

For general instructions, see ref. 1. Optical rotations are measured in 10^{-1} deg cm^2 g^{-1}. Unless otherwise stated, NMR data refer to 90 MHz spectra. Those determined at 500 MHz are not fully assigned, but all distinctive first-order signals are reported. All *J*-values are in Hz. Accurate mass determinations are employed to characterise those non-crystalline or labile compounds for which reliable microanalytical data could not be obtained.

3-*Methoxy*-16-*methylestra*-1,3,5(10),14,16-*pentaen*-17-*yl Acetate* **3**.—3-Methoxy-16-methylestra-1,3,5(10),15-tetraen-17-one **2**[4] (20 g, 67.5 mmol) was suspended in isopropenyl acetate (400 cm^3), and acetic anhydride (80 cm^3) and toluene-*p*-sulphonic acid (6 g) were added. The mixture was stirred at 100 °C until starting material was absent (TLC) (*ca.* 20 h). The solution was cooled, poured into ice-water, and neutralised by addition of small portions of sodium hydrogen carbonate. The mixture was extracted with benzene (×3), and the combined organic phase was washed with water, dried ($MgSO_4$), and concentrated to give a brown crystalline residue (23.5 g) which was filtered through silica gel (450 g) with ethyl acetate–benzene (1:49) to give a pale-yellow crystalline product (21.8 g), recrystallisation of which from ethyl acetate–methanol gave colourless 14,16-*dien*-17-*yl acetate* **3** (19.8 g, 87%), m.p. 129–130 °C; $[\alpha]_D$ +259 (*c* 0.9); ν_{max}/cm^{-1} 1740; δ 1.04 (3 H, s, 13β-Me), 1.72 (3 H, s, 16-Me), 2.22 (3 H, s, 17-OAc), 3.78 (3 H, s, 3-OMe), 5.75 (1 H, br s, 15-H) and 6.6–7.2 (3 H, m, 1-, 2- and 4-H) (Found: C, 78.1; H, 8.0%; M$^+$, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

Cycloadditon of Phenyl Vinyl Sulphone to the Dienyl Acetate **3**.—A mixture of the dienyl acetate **3** (3.38 g, 10 mmol) and phenyl vinyl sulphone (1.764 g, 10.5 mmol) in dry xylene (6 cm^3) was placed in a pressure vessel, which was flushed with nitrogen, sealed, and heated at 140 °C for 120 h. TLC revealed the presence of some starting material **3**, and three products **4**–**6** [R_f *ca.* 0.38, 0.36 and 0.33 respectively, in ethyl acetate–toluene (1:9)]. Upon cooling, the product of intermediate R_f precipitated and was collected and crystallised from chloroform–benzene to give (17^2R)-3-*methoxy*-16-*methyl*-17^2-*phenylsulphonyl*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*yl acetate* **5** (720 mg, 14%), m.p. 260–262 °C; $[\alpha]_D$ +103 (*c* 0.9); ν_{max}/cm^{-1} 1740; δ(500 MHz) 0.94 (3 H, s, 13β-Me), 1.71 (3 H, d, *J* 1.1, 16-Me), 1.85 (1 H, dt, *J* 2 × 11.8 and 1.9, 8β-H), 2.02 (3 H, s, 17β-OAc), 2.26 (1 H, dd, *J* 12.7 and 4.5, 17^1-H_{endo}), 2.47 (1 H, dd, *J* 12.7 and 9.5, 17^1-H_{exo}), 2.84 (1 H, m, 9α-H), 2.92 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 4.28 (1 H, dd, *J* 9.5 and 4.5, 17^2-H_{exo}), 5.78 (1 H, br s, 15-H), 6.61 (1 H, d, *J* 2.8, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.8, 2-H), 7.19 (1 H, d, *J* 8.6, 1-H) and 7.5–7.95 (5 H, m, SO_2Ph) (Found: C, 71.0; H, 6.9; S, 6.3%; M$^+$, 506. $C_{30}H_{34}O_5S$ requires C, 71.1; H, 6.8; S, 6.3%; *M*, 506).

Flash chromatography of the filtrate on silica gel (300 g), with ethyl acetate–benzene (1:19) as eluent, gave impure starting material **3** (300 mg, 9%) followed by a *ca.* 1:1 mixture (3.8 g, 75%) of the cycloadducts **4** and **6**. A portion of this material was rechromatographed on silica gel to give 3-*methoxy*-17^1-*methyl*-16α-*phenylsulphonyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **4** as a syrup, $[\alpha]_D$ +61 (*c* 1.0); ν_{max}/cm^{-1} 1735; δ(500 MHz) 0.94 (3 H, s, 13β-Me), 1.87 (1 H, dd, *J* 12.0 and 8.9, 15β-H), 1.95 (1 H, dd, *J* 12.0 and 4.6, 15α-H), 1.97 (3 H, s, 17β-OAc), 1.99 (3 H, d, *J* 1.6, 17^1-Me), 2.5 (1 H, br dt, 9α-H), 2.82 (2 H, m, 6-H_2), 3.75 (3 H, s, 3-OMe), 4.92 (1 H, dd, *J* 9.0 and 4.6, 16β-H), 5.87 (1 H, d, *J* 1.6, 17^2-H), 6.6 (1 H, d, *J* 2.7, 4-H), 6.67 (1 H, dd, *J* 8.5 and 2.7, 2-H), 7.16 (1 H, d, *J* 8.5) and 7.53–7.9 (5 H, m, SO_2Ph) (Found: M$^+$, 506.215), followed by 3-*methoxy*-17^1-*methyl*-15α-*phenylsulphonyl*-14,17α-*etheno-estra*-1,3,5(10)-*trien*-17β-*yl acetate* **6** as a colourless foam, $[\alpha]_D$ +37 (*c* 0.9); ν_{max}/cm^{-1} 1740; δ(500 MHz) 0.93 (3 H, s, 13β-Me), 1.68 (1 H, dt, 2 × 11.2, and 2.5, 8β-H), 1.72 (3 H, d, *J* 1.5, 17^1-Me), 2.02 (3 H, s, 17β-OAc), 2.06 (1 H, dd, *J* 13.1 and 9.2, 16β-H), 2.27 (1 H, dd, *J* 13.1 and 5.6, 16α-H), 2.52 (1 H, br m, 9α-H), 2.92 (2 H, m, 6-H_2), 3.05 (1 H, br m, 7β-H), 3.73 (1 H, dd, *J* 9.2 and 5.6, 15β-H), 3.77 (3 H, s, 3-OMe), 5.73 (1 H, d, *J* 1.5, 17^2-H), 6.65 (1 H, d, *J* 2.7, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.18 (1 H, d, *J* 8.6, 1-H) and 7.52–7.85 (5 H, m, SO_2Ph) (Found: M$^+$, 506.214).

Alkaline Treatment of the Cycloadducts **4**, **5** *and* **6**.—(*a*) The compound **4** (202 mg, 0.4 mmol) was dissolved in methanolic potassium hydroxide (1%; 20 cm^3). After 20 h at 25 °C, TLC revealed the absence of starting material, and the mixture was neutralised with solid CO_2 and concentrated under reduced pressure. The residue was extracted with chloroform, and the extract was concentrated. The residue (195 mg) was filtered through silica gel (20 g) with ethyl acetate–benzene (1:5) to give 3-*methoxy*-16-*methyl*-14-(2-*phenylsulphonylethyl*)-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* **7** as a colourless foam (142 mg, 76%), $[\alpha]_D$ +81 (*c* 0.8); ν_{max}/cm^{-1} 1695(CO), and 1305 and 1145(SO_2); λ_{max}/nm 218 (log ε 4.32); δ 0.85 (3 H, s, 13β-Me), 1.78 (3 H, d, *J* 1.4, 16-Me), 3.73 (3 H, s, 3-OMe), 6.55 (1 H, d, *J* 2.6, 4-H), 6.67 (1 H, dd, *J* 8.6 and 2.6, 2-H), 6.83 (1 H, d, *J* 1.4, 15-H), 7.0 (1 H, d, *J* 8.6, 1-H) and 7.55–7.9 (5 H, m, SO_2Ph) (Found: M$^+$, 464.202. $C_{28}H_{32}O_4S$ requires *M*, 464.202).

(*b*) The compound **5** (202 mg, 0.4 mmol) was suspended in methanolic potassium hydroxide (1%; 40 cm^3) and stirred at 45 °C. After 18 h, the suspended material had dissolved and the reaction was complete (TLC). The product was isolated as described in the foregoing experiment and filtered through silica gel (20 g) with chloroform–ethyl acetate (4:1) to give (17^2R)-3-*methoxy*-16-*methyl*-17^2-*phenylsulphonyl*-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17β-*ol* **8** (173 mg, 93%), m.p. 214–215 °C (from methanol); $[\alpha]_D$ +116 (*c* 0.9); ν_{max}/cm^{-1} 3590 (OH), and 1310 and 1150 (SO_2); δ(500 MHz) 0.86 (3 H, s, 13β-Me), 1.39 (1 H, td, *J* 10.6, and 2 × 2.5, 12β-H), 1.7 (3 H, d, *J* 1.6, 16-Me), 1.73 (1 H, dd, *J* 12.3 and 4.3, 17^1-H_{endo}), 1.83 (1 H, dt, *J* 2 × 11.9, and 2.3, 8β-H), 2.0 (1 H, dd, *J* 12.3 and 9.3, 17^1-H_{exo}), 2.14 (1 H, m, 7β-H), 2.83–2.95 (3 H, m, 9α-H and 6-H_2), 3.77 (3 H, s, 3-OMe), 4.23 (1 H, dd, *J* 9.3 and 4.3, 17^2-H), 5.79 (1 H, br s, 15-H), 6.64 (1 H, d, *J* 2.8, 4-H), 6.71 (1 H, dd, *J* 8.6

and 2.8, 2-H), 7.19 (1 H, d, *J* 8.6, 1-H) and 7.5–7.9 (5 H, m, SO_2Ph) (Found: C, 72.4; H, 7.1; S, 7.2%; M^+, 464. $C_{28}H_{32}O_4S$ requires C, 72.4; H, 6.9; S, 6.9%; *M*, 464).

(*c*) Treatment of compound **6** (202 mg, 0.4 mmol) with methanolic potassium hydroxide (1%; 20 cm^3) at 25 °C for 5 h, and work-up and chromatography as described in (*a*), gave 3-*methoxy*-17^1-*methyl*-15α-*phenylsulphonyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* **9** as a colourless foam (175 mg, 94%), $[\alpha]_D$ +55 (*c* 0.8); ν_{max}/cm^{-1} 3590 (OH), and 1305 and 1140 (SO_2); δ(500 MHz) 0.93 (3 H, s, 13β-Me), 1.14 (1 H, dt, 12.7, and 2 × 3.3, 12β-H), 1.31 (1 H, dq, *J* 3 × 13.2, and 3.3, 11β-H), 1.46 (1 H, dd, *J* 12.3 and 5.3, 16α-H), 1.69 (1 H, dt, *J* 2 × 11.4, and 2.4, 8β-H), 1.72 (3 H, d, *J* 1.6, 17^1-Me), 1.76 obsc. (1 H, m, 7α-H), 1.87 (1 H, dd, *J* 12.3 and 9.3, 16β-H), 1.97 (1 H, dt, *J* 2 × 12.6, and 4, 12α-H), 2.2 (1 H, dq, *J* 13.2 and 3 × 3.1, 11α-H), 2.51 (1 H, br dt, *J ca.* 2 × 9, and 3, 9α-H), 2.85–2.95 (2 H, m, 6-H_2), 3.0 (1 H, m, 7β-H), 3.75 (1 H, dd, *J* 9.3 and 5.3, 15β-H), 3.77 (3 H, s, 3-OMe), 5.73 (1 H, d, *J* 1.6, 17^2-H), 6.65 (1 H, d, *J* 2.8, 4-H), 6.7 (1 H, dd, *J* 8.6 and 2.8, 2-H), 7.18 (1 H, d, *J* 8.6, 1-H) and 7.5–7.92 (5 H, m, SO_2Ph) (Found: M^+, 464.202. $C_{28}H_{32}O_4S$ requires *M*, 464.202).

Reductive Desulphonylation of the Cycloadducts **4** + **6**.—The *ca.* 1:1 mixture of cycloadducts **4** and **6** (see above) (22.26 g, 44 mmol) was dissolved in a mixture of dry tetrahydrofuran (80 cm^3) and methanol (320 cm^3), and disodium hydrogen phosphate (predried under high vacuum at 100 °C for 3 h) (31.24 g, 0.22 mol) was added. The mixture was cooled to 0 °C and stirred vigorously whilst sodium amalgam (6%, 83 g) was added. After 2 h, further sodium amalgam (29 g) was added, and stirring was continued at 0 °C for 2 h, and 25 °C for 16 h. Water (50 cm^3) was added carefully to destroy the excess of reagent, and the mixture was concentrated to *ca.* one-third volume under reduced pressure. Water (300 cm^3) was added, and the decanted solution was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The solid residue (13 g) was chromatographed on silica gel (600 g) with ethyl acetate–benzene (1:9) as eluent, to give minor products (500 mg) followed by 3-*methoxy*-17^1-*methyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* **10** (11.5 g, 81%), m.p. 147–149 °C (from aqueous methanol); $[\alpha]_D$ +129 (*c* 0.8); ν_{max}/cm^{-1} 3580; δ(500 MHz) 0.88 (3 H, s, 13β-Me), 1.73 (3 H, d, *J* 1.6, 17^1-Me), 2.8–2.9 (2 H, m, 6-H_2), 5.52 (1 H, d, *J* 1.6, 17^2-H), 6.62 (1 H, d, *J* 2.8, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.2 (1 H, d, *J* 8.6, 1-H) (Found: C, 81.4; H, 8.9%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7% *M*, 324).

3-*Methoxy*-17^1-*methyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl Acetate* **11**.—The hydroxy compound **10** (2 g, 6.2 mmol) was suspended in acetic anhydride (10 cm^3) at 0 °C, and toluene-*p*-sulphonic acid (200 mg) was added with stirring. The suspension cleared rapidly, then slow precipitation ensued. After 1 h, water was added, and the precipitate was collected and filtered through silica gel (50 g) with benzene, to give the 17β-*acetate* **11** (2.06 g, 91%), m.p. 117–119 °C (from dichloromethane methanol); $[\alpha]_D$ +87 (*c* 0.9); ν_{max}/cm^{-1} 1725; δ 0.88 (3 H, s, 13β-Me), 1.72 (3 H, d, *J* 1.7, 17^1-Me), 2.08 (3 H, s, 17β-OAc), 3.78 (3 H, s, 3-OMe), 5.57 (1 H, d, *J* 1.7, 15-H), 6.6–7.22 (3 H, m, 1-, 2- and 4-H) (Found: C, 78.7; H, 8.1%; M^+, 366. $C_{24}H_{30}O_3$ requires C, 78.65; H, 8.25%; *M*, 366).

Catalytic Hydrogenation of the Acetoxy Olefin **11**.—A mixture of the olefin **11** (8 mg) and palladium on charcoal (5%; 6 mg) in ethyl acetate (2 cm^3) was shaken in hydrogen at 25 °C and atmospheric pressure for 24 h. TLC revealed the absence of starting material, and the mixture was filtered through Celite, and the filtrate was evaporated to give a crystalline product (6.5 mg, 81%), m.p. 140–150 °C (from dichloromethane–methanol), *m/z* 368 (M^+), which was shown by NMR to comprise of a *ca.* 55:45 mixture of (17^1*R*)- and (17^1*S*)-3-methoxy-17^1-methyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetates **12**, δ(55% component) 0.91 (3 H, s, 13β-Me), 1.03 (3 H, d, *J* 7.3, 16-Me), 2.05 (3 H, s, 17β-OAc), 3.76 (3 H, s, 3-OMe) and 6.6–7.2 (3 H, m, 1-, 2- and 4-H); δ(45% component) 0.92 (3 H, s, 13β-Me), 1.09 (3 H, d, *J* 6.8, 16-Me), 2.0 (3 H, s, 17β-OAc), 3.75 (3 H, s, 3-OMe) and 6.6–7.2 (3 H, m, 1-, 2- and 4-H).

Hydroxylation of the Acetoxy Olefin **11**.—(*a*) The compound **11** (586 mg, 1.6 mmol) in dry pyridine (10 cm^3) was treated with osmium tetraoxide (500 mg, 1.97 mmol). After 48 h at 25 °C, the mixture was cooled to 0 °C and aqueous sodium disulphite (10%, 20 cm^3) was added. After 30 min, extraction of the mixture with benzene gave a product (690 mg) which was adsorbed on silica gel (70 g). Elution with ethyl acetate–benzene (1:7) gave unidentified material (47 mg), followed by (17^{1}S,17^{2}S)-17^1,17^2-*dihydroxy*-3-*methoxy*-17^1-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **13** (527 mg, 82%), m.p. 209–210 °C (from benzene–hexane); $[\alpha]_D$ +16 (*c* 0.85); ν_{max}/cm^{-1} 3600–3250 (OH) and 1710 (OAc); δ(500 MHz) 1.04 (3 H, d, *J* 0.7, 13β-Me), 1.2 (1 H, tt, *J* 2 × 12.2, and 2 × 2.6), 1.39 (3 H, s, 17^1-Me), 1.95 (1 H, dt, *J* 2 × 13.2 and 3.8), 2.11 (3 H, s, 17β-OAc), 2.64 (1 H, ddd, *J* 12.4, 9.4 and 3.3), 2.8 obsc. (1 H, m, 9α-H), 2.81 (2 H, m, 6-H_2), 3.41 (1 H, d, *J* 7.0, exch. by D_2O, 17^2-OH), 3.75 (3 H, s, 3-OMe), 4.23 (1 H, dd, *J* 7.0 and 2.1→d, *J* 2.1 on D_2O exch., 17^2-H), 4.74 (1 H, s, exch. by D_2O, 17^1-OH), 6.6 (1 H, d, *J* 2.8, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.18 (1 H, d, *J* 8.6, 1-H) (Found: C, 72.1; H, 8.2%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.05%; *M*, 400).

Elution with ethyl acetate–benzene (1:4) gave (17^{1}R,17^{2}R)-17^1,17^2-*dihydroxy*-3-*methoxy*-17^1-*methyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **14** (45 mg, 7%), m.p. 169–170 °C (from benzene–hexane); $[\alpha]_D$ +31 (*c* 0.9); ν_{max}/cm^{-1} 3590 and 3550–3150 (OH), and 1710 (OAc); δ(500 MHz) 0.97 (3 H, s, 13β-Me), 1.45 (3 H, s, 17^1-Me), 1.70 (1 H, td, *J* 13.4, and 2 × 3.3), 2.14 (3 H, s, 17β-OAc), 2.19 (1 H, ddd, *J* 13.6, 8.9 and 4.4), 2.29 (1 H, dq, *J* 13.5, and 3 × 3.2), 2.52 (1 H, dt, 2 × 13.2, and 4.0), 2.8–2.92 (2 H, m, 6-H_2), 3.36 (1 H, d, *J* 6.2, exch. by D_2O, 17^2-OH), 3.53 (1 H, dt, *J* 2 × 11.8, and 4.9, 9α-H), 3.65 (1 H, d, *J* 6.2→s on D_2O exch., 17^2-H), 3.75 (3 H, s, 3-OMe), 4.26 (1 H, s, exch. by D_2O, 17^1-OH), 6.61 (1 H, d, *J* 2.6, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.6, 2-H) and 7.15 (1 H, d, *J* 8.6, 1-H) (Found: C, 72.0; H, 8.2%; M^+, 400).

(*b*) Large scale hydroxylations were carried out using catalytic osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide: these reactions proceeded slowly (up to 10 d) and required further addition of catalyst and co-oxidant, but gave comparable yields of products.

17β-*Acetoxy*-3-*methoxy*-20-*oxo*-19-*nor*-17α-*pregna*-1,3,5(10)-*triene*-14-*carbaldehyde* **15**.—(*a*) Aqueous sodium periodate (6%; 3 cm^3) was added to a stirred suspension of the diol **13** (100 mg, 0.25 mmol) in ethanol (10 cm^3) at 25 °C. After 6 h, the mixture was concentrated to half volume under reduced pressure at 25 °C, water was added, and the product (94 mg, 95%) was isolated by extraction with chloroform and crystallised from ethyl acetate to give the 14-*carbaldehyde* **15** m.p. 212–213 °C; $[\alpha]_D$ +3.5 (*c* 0.9); ν_{max}/cm^{-1} 1736 (OAc) and 1715br (14^1- and 20-CO); δ 1.24 (3 H, s, 13β-Me), 2.05 and 2.1 (each 3 H, s, 17β-OAc and 21-H_3), 3.74 (3 H, s, 3-OMe), 6.56 (1 H, d, *J* 2.7, 4-H), 6.69 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.15 (1 H, d, *J* 8.6, 1-H), and 9.87 (1 H, s, 14^1-H) (Found: C, 72.4; H, 7.85%; M^+, 398. $C_{24}H_{30}O_5$ requires C, 72.3; H, 7.6%; *M*, 398).

(*b*) Similar treatment of the diol **14** or a mixture of diols (**13** + **14**) gave the same product **15**.

14-*Hydroxymethyl*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* **16**.—The compound **15** (250 mg, 0.63 mmol) in dry

tetrahydrofuran (10 cm^3) was added during 15 min to a stirring solution of calcium (150 mg, 3.75 mmol) in liquid ammonia (50 cm^3; distilled from sodium) at −78 °C. The reaction mixture was stirred for a further 20 min at −78 °C, then bromobenzene (1 cm^3) was added slowly followed by solid ammonium chloride (10 g). The ammonia was allowed to evaporate, and the residue was partitioned between water and chloroform. The organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crystalline residue (248 mg) was chromatographed on silica gel, with ethyl acetate–benzene (1:2) as eluent, to give mixed fractions (37 mg) followed by the 14-*hydroxymethyl* 20-*ketone* **16** (192 mg, 89%), m.p. 155–156 °C (from ethyl acetate–hexane); $[\alpha]_D$ +158 (*c* 0.9); ν_{max}/cm^{-1} 3630 (OH) and 1695 (20-CO); $\Delta\varepsilon_{max}$ +3.25 (289 nm); δ(500 MHz) 0.78 (3 H, s, 13β-Me), 1.20 (1 H, t, *J* 5.4, exch. by D_2O, 14^1-OH), 1.35 (1 H, dt, *J* 2 × 12 and 7.6), 1.6 (1 H, dq, *J* 3 × 13.2, and 5.2), 2.11 (3 H, s, 21-H_3), 2.32 (2 H, m, 6-H_2) 3.0 (1 H, t, *J* 8.6, 17α-H), 3.72 and 4.05 (each 1 H, dd, *J* 11.8 and 5.4→d, *J* 11.8 on D_2O exch., 14^1-H_2), 3.75 (3 H, s, 3-OMe), 6.59 (1 H, d, *J* 2.7, 4-H), 6.68 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.17 (1 H, d, *J* 8.6, 1-H) (Found: C, 77.3; H, 8.8%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342).

(20ξ)-20,14-*Hemiketal of* 14-*Hydroxymethyl*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10)-*trien*-20-*one* **17**.—The hydroxy ketone **16** (100 mg, 0.3 mmol) was stirred in methanolic potassium hydroxide (1%, 10 cm^3) at 60 °C for 6 h. Solid carbon dioxide was added to the cold reaction mixture (0 °C), and the methanol was evaporated under reduced pressure. The residue was partitioned between water and chloroform, and the organic phase was washed, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (10 g), with ethyl acetate–benzene (1:9) as eluent, to give the *hemiketal* **17** (79 mg, 79%) m.p. 150–158 °C (from ethyl acetate–hexane); $[\alpha]_D$ +22 (*c* 1.0); ν_{max}/cm^{-1}3580; δ(500 MHz) 0.948 (3 H, d, *J* 0.5, 13β-Me), 1.4 (3 H, s, 20-Me), 1.76 obsc. (1 H, d, *J* 5.9, 17β-H?), 2.04 (1 H, s, exch. by D_2O, 20-OH), 2.63 (1 H, dt, *J* 2 × 12.1, and 5.0), 2.77–2.88 (2 H, m, 6-H_2), 3.18 (1 H, dt, *J* 2 × 13.7, and 4.5, 9α-H), 3.34 (1 H, d, *J* 10.9, 14^1-H_{endo}), 3.75 (3 H, s, 3-OMe), 4.35 (1 H, dd, *J* 10.9 and 1.5, 14^1-H_{exo}), 6.58 (1 H, d, *J* 2.8, 4-H) 6.69 (1 H, dd, *J* 8.6 and 2.8, 2-H) and 7.2 (1 H, d, *J* 8.6, 1-H) (Found: C, 77.3; H, 8.9%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; *M*, 342).

The broad melting range, and an NMR signal at δ 0.947 (s, 13β-Me) (integral, *ca.* 8% of the major 13β-Me signal) indicated the presence of an inseparable impurity, probably the 20-isomer.

14-*Hydroxymethyl*-19-*norpregn*-4-*ene*-3,20-*dione* **19**.—A solution of ethylene glycol (6 cm^3) and toluene-*p*-sulphonic acid (10 mg) was refluxed in dry benzene (120 cm^3), with return of the condensate through 3 Å molecular sieves (6 g). After 2 h, the solution was cooled to 25 °C, the 14-hydroxymethyl 20-ketone **16** (150 mg, 0.44 mmol) was added, and the mixture was refluxed as described above, for 8 h. The benzene solution was cooled, washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated under reduced pressure at 25 °C to give the crude 20-ketal **18** as a colourless glass (190 mg), ν_{max}/cm^{-1} 3600, containing *ca.* 10% starting material (IR and TLC).

The crude ketal **18** (163 mg, 0.42 mmol) in dry tetrahydrofuran (10 cm^3) was added to stirred liquid ammonia (*ca.* 100 cm^3, distilled from sodium) and dry *tert*-butyl alcohol (8 cm^3). Lithium (560 mg) was added in portions, and the mixture was stirred at −35 °C for 2.5 h. Dry methanol (10 cm^3) was added to disperse the blue colour, and the ammonia was allowed to evaporate. Methanol was added to make up the volume of the residual solution to 50 cm^3, and conc. hydrochloric acid (8 cm^3) was added. The acidic solution (pH 1) was stirred at 25 °C for 18 h, then aqueous sodium hydrogen carbonate was added, and the mixture was concentrated under reduced pressure. Extraction of the residue with chloroform gave a solid product (153 mg) which was adsorbed on silica gel (15 g). Elution with ethanol–chloroform (1:19) furnished 14-*hydroxymethyl*-19-*norpregn*-4-*ene*-3,20-*dione* **19** (91 mg, 65%), m.p. 198–200 °C (from chloroform–ethyl acetate); $[\alpha]_D$ +140 (*c* 0.5); ν_{max}/cm^{-1} 3634 (OH), 1700 (20-CO), 1662 (3-CO) and 1620 (C=C); $\Delta\varepsilon_{max}$ −1.69 (321 nm) and +3.14 (283 nm); δ(500 MHz) 0.82 (3 H, s, 13β-Me), 2.09 (3 H, s, 21-H_3), 2.48 (1 H, ddd, *J* 14.4, 3.4 and 2.8), 2.98 (1 H, dd, *J* 9.1 and 8.2, 17α-H), 3.61 and 3.88 (each 1 H, br s, →d, *J* 11.5 on D_2O exch., 14^1-H_2) and 5.79 (1 H, br s, 4-H) (Found: C, 76.6; H, 9.5%; M^+, 330. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.15%; *M*, 330).

Birch Reduction of the 14-*Hydroxymethyl* 20-*Ketone* **16**, *followed by Selective Oxidation*.—The hydroxy ketone **16** (171 mg, 0.5 mmol) in dry tetrahydrofuran (10 cm^3) was reduced with lithium–liquid ammonia–*tert*-butyl alcohol, as described for the corresponding 20-ketal **18**, and the reduction product was similarly treated with methanolic hydrochloric acid. Isolation of the product by extraction with ethyl acetate afforded a crystalline product **20** (120 mg), *m/z* 332 (M^+) and 301 ($M^+ - CH_2OH$). A portion (50 mg, 0.15 mmol) of the material was dissolved in dry dichloromethane (5 cm^3) and treated with pyridinium chlorochromate (50 mg, 0.23 mmol) at 0 °C for 2.5 h. Isopropyl alcohol (0.5 cm^3) was added, and the solution was filtered through silica gel and concentrated to give a slightly discoloured oil (45 mg). Flash chromatography on silica gel (5 g) with ethyl acetate–toluene (2:1) afforded 3,20-*dioxo*-19-*norpregn*-4-*ene*-14-*carbaldehyde* **21** (10 mg, 20%), m.p. 143–150 °C (decomp.) (from benzene–hexane); λ_{max}/nm 239 (log ε 4.23); δ 0.9 (3 H, s, 13β-Me), 2.1 (3 H, s, 21-H_3), 2.54 (1 H, t, *J* 9.0, 17α-H), 5.79 (1 H, t, *J* 1.9, 4-H) and 10.1 (1 H, d, *J* 1.0, 14^1-H); *m/z* 330 (M^+) and 312 ($M^+ - H_2O$), followed by a *ca.* 7:3 mixture (NMR) of (20R)- and (20S)-20-*hydroxy*-3-*oxo*-19-*norpregn*-4-*ene*-14-*carbaldehydes* **22** (22 mg, 44%) as a colourless glass, δ(major component) 1.03 (3 H, s, 13β-Me), 1.11 (3 H, d, *J* 6.1, 21-H_3), 3.76 (1 H, m, 20-H), 5.78 (1 H, m, 4-H) and 10.16 (1 H, d, *J* 1.3, 14^1-H); δ(minor component) 0.95 (3 H, s, 13β-Me), 1.19 (3 H, d, *J* 6.1, 21-H_3), 3.76 (3 H, m, 20-H), 5.78 (1 H, m, 4-H), 10.09 (1 H, d, *J* 1.2, 14^1-H); *m/z* 330 (M^+) and 312 ($M^+ - H_2O$).

20,20-*Ethylenedioxy*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*triene*-14-*carbaldehyde* **23**.—The crude ketal **18** (70 mg, 0.14 mmol) was prepared as described in a previous experiment, and immediately treated with pyridinium dichromate (107 mg, 0.29 mmol) in dry dichloromethane (5 cm^3) at 25 °C for 2 h. Isopropyl alcohol (0.5 cm^3) was added and the mixture was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (10 g), with ethyl acetate–hexane (1:4) as eluent, gave the 14-*carbaldehyde* **23** (14 mg), m.p. 117–119 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1705; δ 1.0 (3 H, s, 13β-Me), 1.27 (3 H, s, 21-H_3), 3.75 (3 H, s, 3-OMe), 3.78–4.05 (4 H, m, OCH_2CH_2O), 6.58–7.20 (3 H, m, 1-, 2- and 4-H) and 10.25 (1 H, s, 14^1-H); *m/z* 384 (M^+).

3-*Methoxy*-20-*oxo*-19-*norpregna*-1,3,5(10)-*triene*-14-*carbaldehyde* **24**.—The hydroxymethyl ketone **16** (30 mg, 0.09 mmol) was treated with pyridinium chlorochromate (70 mg, 0.32 mmol) in dry dichloromethane (3 cm^3) at 25 °C for 20 min. Isopropyl alcohol (0.5 cm^3) was added, followed by water. The organic phase was separated, washed, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (25 mg) on silica gel (5 g), with ethyl acetate–benzene (1:9) as eluent, gave the 14-*carbaldehyde* **24** (16 mg, 54%),

m.p. 145–146 °C (from ethyl acetate–hexane); $[\alpha]_D$ +110 (*c* 0.15); ν_{max}/cm^{-1} 1705br; $\Delta\varepsilon_{max}(\lambda/nm)$ −0.3(325), +2.4(290) and +2.4(286); δ(500 MHz) 0.84 (3 H, s, 13β-Me), 1.37 (1 H, dt, *J* 2 × 11.9, and 7.2), 2.13 (3 H, s, 21-H$_3$), 2.77 (1 H, t, *J* 9.0, 17α-H), 6.59 (1 H, d, *J* 2.7, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.2 (1 H, d, *J* 8.6, 1-H) and 10.16 (1 H, s, 14^1-H) (Found: C, 77.3; H, 8.1%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

(20R)-20-*Hydroxy*-3-*methoxy*-19-*norpregna*-1,3,5(10)-*triene*-14-*carbaldehyde* **25**.—Lithium tri-*sec*-butylborohydride (L-Selectride®) (1 mol dm^{-3} in tetrahydrofuran; 0.24 cm^3) was added during 20 min to a stirred solution of the dioxo compound **24** (65 mg, 0.19 mmol) in dry tetrahydrofuran (6 cm^3) at 0 °C. After a further 2 h, the reaction was essentially complete (TLC), and aqueous sodium hydroxide (10%)–hydrogen peroxide (30%) (1:1, 5 cm^3) was added. The mixture was stirred at 0 °C for 15 min, and then concentrated in a stream of nitrogen. The residue was extracted into chloroform, and the extract was washed, dried ($MgSO_4$), and concentrated to give a crystalline residue (65 mg). Chromatography on silica gel (6 g) with ethyl acetate–toluene (1:2) afforded the 20-*alcohol* **25** (56 mg, 86%), m.p. 157–158 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 3600 (OH) and 1700 (CO); δ(500 MHz) 0.99 (3 H, s, 13β-Me), 1.13 (3 H, d, *J* 6.1, 21-H$_3$), 1.92 (1 H, dt, *J* 2 × 12.2 and 2.5), 2.16 (1 H, ddd, *J* 13.8, 11.5 and 2.3), 2.22 (1 H, t, *J* 9.5), 2.37 (1 H, dt, *J* 2 × 13.6 and 4.8), 2.8 (2 H, m, 6-H$_2$), 2.87 (1 H, dt, *J* 2 × 12.5 and 5.2), 3.75 (3 H, s, 3-OMe), 3.78 (1 H, br m, *W ca.* 23, 20-H), 6.58 (1 H, d, *J* 2.7, 4-H), 6.71 (1 H, dd, *J* 8.6 and 2.7, 2-H), 7.2 (1 H, d, *J* 8.6, 1-H) and 10.29 (1 H, s, 14^1-H); *m*/*z* 342 (M^+).

3-*Methoxy*-14-*methyl*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* **27**.—The 14-carbaldehyde **25** (130 mg, 0.38 mmol) and anhydrous hydrazine (3.5 cm^3) in diethylene glycol (10 cm^3) was heated at 150 °C for 1.5 h. The solution was cooled to 25 °C, potassium hydroxide (0.5 g) was added, and the mixture was heated to 215 °C, allowing excess of hydrazine and water to escape, and kept at 215 °C for 2 h. Aqueous hydrochloric acid was added to the cooled solution, and the product (120 mg) was isolated by extraction with chloroform. TLC revealed that partial 3-*O*-demethylation had occurred, and the product was treated with dimethyl sulphate (0.5 cm^3) and powdered potassium carbonate (1.5 g) in dry acetone (25 cm^3) at 25 °C with stirring for 18 h. Conc. ammonium hydroxide (5 cm^3) was added and, after 30 min, the mixture was concentrated under reduced pressure, and the residue was partitioned between water and chloroform. The organic phase was concentrated, and the residue was filtered through silica gel (10 g) with ethyl acetate–toluene (1:4) to give the 20-alcohol **26** (115 mg), δ 0.90 and 0.91 (each 3 H, s, 13β- and 14α-Me), 1.16 (3 H, d, *J* 6.1, 21-H$_3$), 3.76 (3 H, s, 3-OMe), 3.8 (1 H, br m, 20-H) and 6.6–7.19 (3 H, m, 1-, 2- and 4-H).

The alcohol **26** (115 mg) was treated with pyridinium chlorochromate (280 mg) in dry dichloromethane (30 cm^3) at 25 °C for 1 h. Isopropyl alcohol (0.5 cm^3) was added, the solution was filtered through silica gel, concentrated, and chromatographed on silica gel (10 g) with ethyl acetate–toluene (1:9) to give the 20-ketone **27** (106 mg, 86% from **25**), double m.p. 111–113 and 125–126 °C (from benzene–hexane), identical to authentic material prepared by an unrelated route.[14]

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