Intramolecular cyclisation routes to cyclopenta[14,15]-19-norsteroids

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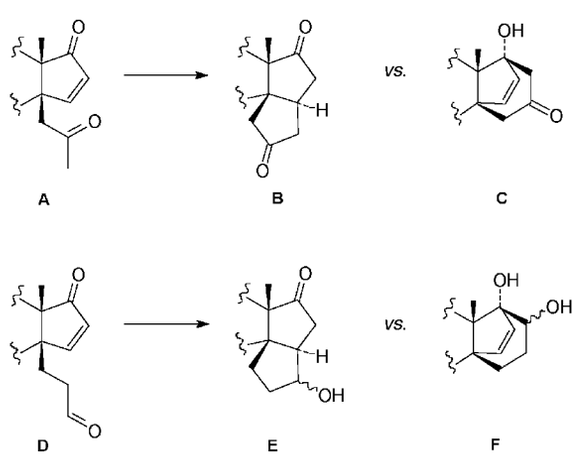
14-Allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one **1** undergoes competitive Wacker oxidation at C-2′ and C-3′ to give the 14β-formylethyl and 14β-acetonyl Δ^{15}-17-ketones **2** and **3** respectively. Alkaline treatment of **3** results in efficient intramolecular Michael reaction, and chemoselective modification of the resultant pentacyclic diketone **6** gives rise to novel cyclopenta[14,15] analogues **11** and **12** of estradiol. Low-temperature reaction of **3** with lithium hexamethyldisilazide–cerium(III) chloride furnishes mainly the product of intramolecular aldol reaction, and hence, the derived 14β,17β-propanoestra-1,3,5(10),15-tetraene-3,17β-diol **21**. Alternative routes to **11** and **12**, *via* intramolecular reductive cyclisation of the 14β-formylethyl Δ^{15}-17-ketone **2**, are described.

Introduction

During the course of investigations into the synthesis of ring D bridged analogues of steroidal hormones, it has been shown that 14β-functionalised-alkyl 17-ketones derived from estrone undergo intramolecular cyclisation leading to 14β,17β-alkano analogues of estradiol.[1,2] Some of these analogues display exceptionally high affinity for the estradiol receptor,[1–3] and represent a novel class of structural variants for probing the nature of the estradiol pharmacophore and the bounds of structure–activity relationships in this family.[4] The emergence of new insights into the molecular basis for estrogen receptor binding[5,6] also adds impetus to the search for predictive design principles associated with estrogen agonists and antagonists.

We now report the results of an investigation into the regioselectivity of intramolecular closure pathways in the corresponding 14β-functionalised-alkyl Δ^{15}-17-ketones, and the ensuing synthesis of a new class of estradiol analogues. It was reasoned that the orientation of interacting centres during base mediated treatment of a 14β-acetonyl Δ^{15}-17-ketone **A** might favour intramolecular Michael reaction, leading to a cyclopenta[14,15] product **B**, rather than the intramolecular aldol pathway to a 14β,17β-propano product **C** (Scheme 1). Further,

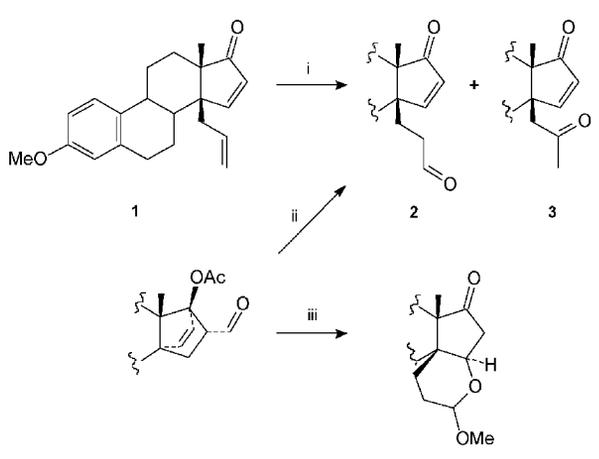


Scheme 1 Intramolecular closure pathways for 14β-acetonyl Δ^{15}-17-ketone **A** and 14β-formylethyl Δ^{15}-17-ketone **D**.

it was expected that intramolecular reductive cyclisation of a 14β-formylethyl Δ^{15}-17-ketone **D** would be amenable to competing ketyl–olefin or pinacol closure routes,[7] leading to products **E** or **F** respectively (Scheme 1); in this case, however, the likely outcome was less obvious. The availability of intermediates **B** and **E** was expected to provide an entry to novel analogues of steroidal hormones.

Results and discussion

The 14β-allyl Δ^{15}-17-ketone **1** is readily available *via* cycloaddition–fragmentation of ring D dienyl precursors,[2] and constituted a convenient starting material for exploring chemo- and regioselective conversion into appropriate 14β-functionalised-alkyl Δ^{15}-17-ketone substrates **A** and **D** for this investigation. In the first instance, **1** was subjected to Wacker oxidation,[8] in the expectation that the corresponding 14β-acetonyl Δ^{15}-17-ketone would thus be formed (Scheme 2). However, treatment of **1** with



Scheme 2 *Reagents and conditions*: i, $PdCl_2$, CuCl, O_2, DMF–H_2O, 65 °C; ii, KOH, MeOH–THF, 20 °C; iii, NaOMe, MeOH, 40 °C.

$PdCl_2$–CuCl–O_2 in aqueous DMF at 65 °C resulted in formation of a mixture (~1 : 1; 91%) of the 14β-formylethyl and 14β-acetonyl compounds **2** and **3**. Since the 15,16-dihydro derivative of **1** undergoes exclusive 2′-oxidation,[2] the diminution of Markovnikov regioselectivity in the reaction of **1** is clearly associated with the presence of the Δ^{15}-bond, and is reminiscent of other Wacker oxidations which have recently been reported to proceed under the influence of intramolecular participation by proximate functionality.[9]

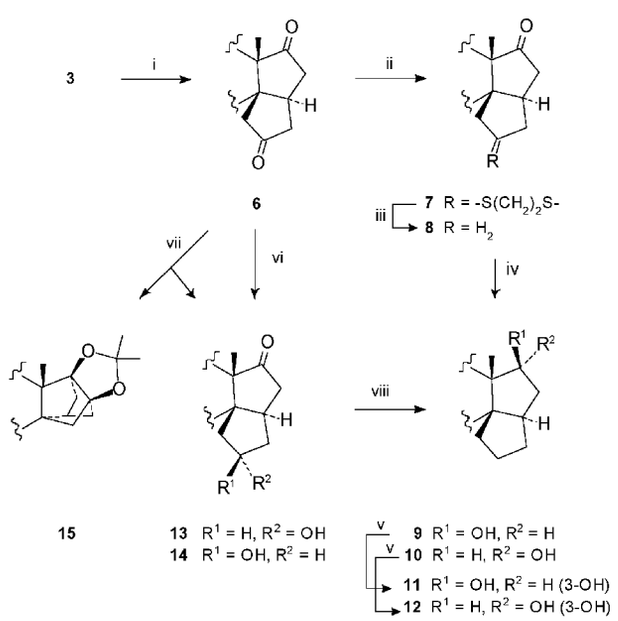
It can be argued that palladium coordination with the allyl group in **1** proceeds with orientationally influential participation of the 1,5-removed Δ^{15}-bond, and that further reaction

of the latter bond is excluded owing to severe steric hindrance, Although the resultant obligatory alignment of the olefinic bonds suggests that the allyl group would be exposed to conventional hydration at C-2′, this position is subject to some steric hindrance by the 13β-methyl group. By contrast, C-3′ may be more favourably disposed to attack through hydrogen-bonded association of water with the proximal 17-oxo group in the coordination complex.

The oxidation products **2** and **3** displayed similar polarity. Furthermore, recovery of the 14β-formylethyl compound **2** was influenced by apparent lability on silica gel, necessitating the use of flash chromatography techniques with minimum contact time, and consequently, reduced separation efficiency. Accordingly, an alternative route to **2** was attempted, *via* retroaldol cleavage of the bridged 16α-formyl compound **4**.[2] Retrograde reactions of similar bridgehead oxygenated cycloadducts incorporating appropriate α-functionality are precedented,[10] but it was recognised that the conditions under which primary bond cleavage of **4** would occur, could also induce secondary reactions. Indeed, treatment of **4** with methanolic KOH at 20 °C resulted in rapid reaction (~2 min), leading to complex mixtures from which the desired product **2** was recovered in poor yield (19%). When the reaction was conducted in the presence of methanolic NaOMe at 40 °C, the only clean product isolated was formulated as **5** (40%), arising from intramolecular capture of a presumed hemiacetal of the primary cleavage product. Attempts to improve these yields or to induce more controlled retroaldol cleavage with the aid of milder reagents have hitherto failed.

Notwithstanding the lack of regioselectivity during Wacker oxidation of the 14β-allyl Δ^{15}-17-ketone **1**, the overall outcome was advantageous for the purpose of this study, since it furnished direct access to both candidate substrates required for intramolecular cyclisation studies (Scheme 1).

Treatment of the 14β-acetonyl Δ^{15}-17-ketone **3** with KOH in THF–MeOH at 65 °C for 2 h gave a single isolable product (64%), formulated as 3-methoxy-3′,15α-dihydro-14β-cyclopenta[14,15]estra-1,3,5,(10)-triene-4′(5′*H*),17-dione **6**, arising from intramolecular Michael reaction (Scheme 3). Although certain diagnostic NMR multiplets for **6** were imperfectly resolved in $CDCl_3$, a spectrum in C_6D_6 revealed a distinctive pattern of multiplets associated with the closed spin systems for



Scheme 3 *Reagents and conditions*: i, KOH, MeOH–THF, 65 °C; ii, $(CH_2SH)_2$, $Zn(OTf)_2$, CH_2Cl_2, 20 °C; iii, Raney Ni, EtOH, Δ; iv, LAH, THF, 0 °C; v, iBu_2AlH, $C_6H_5CH_3$, Δ; vi, $Li(sBu)_3BH$, THF, − 60 °C; vii, SmI_2, THF, Δ, then $HClO_4$, Me_2CO; viii, MsCl, C_5H_5N, 0 °C, then LAH, THF, Δ.

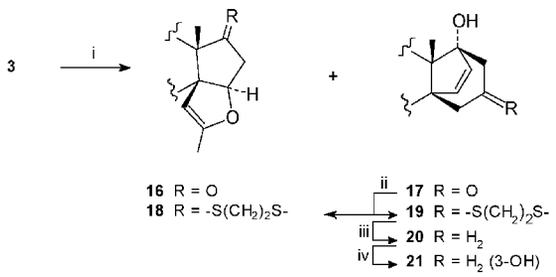
all protons attached to rings D and E. The assignments were verified by various correlation techniques, and facilitated the recognition of 4′,17-chemodifferentiated derivatives in ensuing work (see below). The structure and conformation of **6** have also been verified by X-ray crystallography.[11]

The steric environment of rings D and E in **6** suggested that chemoselective differentiation of the 4′- and 17-oxo groups, *via* preferential reaction at C-4′, would be possible. Indeed, treatment of **6** with $(CH_2SH)_2$ in the presence of zinc triflate[12] at 20 °C resulted in exclusive formation of the 4′,4′-dithioketal **7** (85%), desulfurisation of which with Raney nickel in refluxing EtOH gave the 17-ketone **8**. The identification of downfield NMR multiplets, unambiguously assigned to 16-H_2 by comparison with those present in the 4′,17′-diketone **6**, secured the structural assignment of the 17-ketone **8**, and verified the assumption of 4′-chemoselectivity during dithioketalisation. Treatment of **8** with LAH in THF at 0 °C gave a separable mixture (~1 : 4) of the 17β- and 17α-alcohols **9** and **10**, which were deprotected at C-3 to furnish the respective estradiol analogues **11** and **12**.

An alternative and more direct route to these estradiol analogues was achieved *via* chemoselective reduction of the 4′-oxo group in **6**. Treatment of **6** with LAH or $NaBH_4$ under a variety of conditions gave complex mixtures of partially and completely reduced products, but the reaction with L-Selectride in THF at −60 °C gave a satisfactory yield of an inseparable mixture (~7 : 3, 65%) of the 4′α- and 4′β-hydroxy 17-ketones **13** and **14**, the structures of which were inferred from analogy and subsequent experiments. However, in an unrelated experiment to ascertain the scope for intramolecular coupling, the 4′,17-diketone **6** was treated with SmI_2 in refluxing THF to give an inseparable mixture of polar products, from which the pure 4′α-hydroxy 17-ketone **13** was isolated in 60% yield, after treatment of the reaction mixture with acetone in the presence of perchloric acid. Sequential mesylation–reduction of **13** gave the 17-alcohols **9** and **10**, thereby also confirming chemoselectivity of the reduction step.

The minor product (8%), isolated from the SmI_2-initiated reaction sequence on **6** displayed spectroscopic properties consistent with the acetonide **15** derived from intramolecular reductive coupling. Although intramolecular pinacol closure is precedented in simple bicyclo[3.3.0]octane-3,7-diones,[13] the formation of this exceptionally strained substructure, embedded in a steroidal framework, is remarkable. It is perhaps unsurprising that all attempts to promote this process at the expense of competing chemoselective reduction of the 4′-oxo group in **6** were unsuccessful.

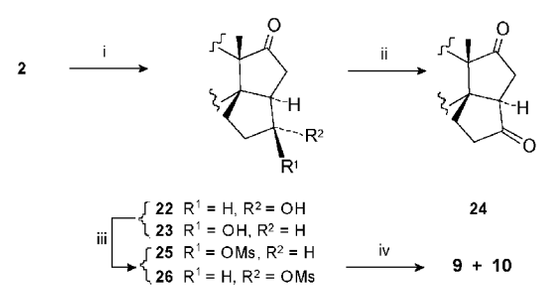
The reaction sequence leading to the skeletally novel cyclopenta[14,15] steroids relies upon Michael regioselectivity during intramolecular reaction of the 14β-acetonyl Δ^{15}-17-ketone **3**. However, when alkaline treatment of **3** was initiated at 20 °C, starting material was rapidly consumed, with formation of a complex mixture (TLC) which underwent progressive simplification to the eventual product **6**, only when the temperature was raised to 65 °C. The possibility that competing but reversible intramolecular aldol reaction (Scheme 1) might be included amongst the early reaction pathways was supported by an experiment in which treatment of **3** with LiHMDS–$CeCl_3$ in THF at −50 °C furnished, after flash chromatography of the reaction mixture, the 14β,17β-bridged compound **17** as the major product (58%) (Scheme 4). Some starting material **6** (14%) was recovered, together with the furan **16** (19%), the structure of which was evident from a distinctive pattern of NMR signals for the ring D environment. The isolation of the latter products suggests scope for optimisation of the reaction conditions, to yield the aldol product **17** exclusively. However, it displayed the expected sensitivity to reaction and work-up conditions, and attempts to introduce methodological improvements were unsuccessful. Nevertheless, the product was highly crystalline and readily characterised; the comparable spectro-



Scheme 4 *Reagents and conditions*: i, LiHMDS, $CeCl_3$, THF, −50 °C; ii, $(CH_2SH)_2$, *p*-TsOH, HOAc, 20 °C; iii, Raney Ni, EtOH, Δ; iv, iBu_2AlH, $C_6H_5CH_3$, Δ.

scopic properties of **17** showed nice correspondence with those of the saturated 14β,17β-propano compound.[1] Further functional group simplification to the estradiol analogue was achieved through dithioketalisation–desulfurisation of **17**, to give 3-methoxy-14β,17β-propanoestra-1,3,5(10),15-tetraen-17α-ol **20**, which was also characterised by analogy,[1] and deprotected to furnish the target compound **21.** The dithioketalisation step proved troublesome in the presence of zinc triflate and, under these conditions, the overall conversion was poor and the major product (34%) was formulated as the 17,17-ethylenedithio derivative **18** of the furan **16,** evidently arising from a retroaldol initiated reaction sequence. Surprisingly, an improvement was achieved through the more protracted treatment of **17** with $(CH_2SH)_2$–AcOH in the presence of catalytic *p*-TsOH, to give the 17^2,17^2-dithioketal **19** in 65% yield.

In accordance with the plan (Scheme 1), complementary experiments were performed to determine the regioselectivity attending intramolecular reductive cyclisation of the 14β-formylethyl Δ^{15}-17-ketone **2**. Initial attempts to exploit SmI_2 for this purpose were frustrated by the formation of complex mixtures, presumably arising from competing coupling and reductive processes. However, the use of McMurry conditions[14] was more successful; treatment of **2** with $TiCl_3$·$(DME)_{1.5}$ and Zn–Cu couple in DME at 0 °C resulted in rapid conversion into a separable mixture (3:7, 85%) of products formulated as the 3′α- and 3′β-hydroxy 17-ketones **22** and **23** (Scheme 5). Com-



Scheme 5 *Reagents and conditions*: i, $TiCl_3$·$(DME)_{1.5}$, Zn–Cu, DME, 0 °C; ii, (a) $(COCl)_2$, DMSO, −78 °C (b) Et_3N, −78 °C; iii, MsCl, C_5H_5N, 0 °C; iv, LAH, THF, Δ.

parative NMR coupling constants of key signals at C-3′, C-15 and C-16 were consistent with the assignments, and a major downfield shift of the 16β-H signal in the 3′β-isomer **23** confirmed a synperiplanar relationship with the OH group. The modest stereoselectivity of the reaction suggests that collinear orientation of the functionality (leading to **23**) is not as decisive a prerequisite as in the analogous intramolecular couplings of saturated 14β-formylalkyl 17-ketones, where formation of the corresponding 14β,17β-alkano 17,17^1-diols occurs with high stereoselectivity.[1,2] Furthermore, it is inferred that the steric influence of the 13β-methyl group upon orientational preference of the 14β-formylethyl chain in **2** must be attenuated during 3′,15-bond formation, in comparison with the alternative 3′,17-cyclisation mode.

The relationship between the isomeric products **22** and **23** was demonstrated through independent Swern oxidations, leading to 3′,17-diketone **24** as the common product, and sequential mesylation–reduction of the mixture **22** + **23** also provided the most direct and efficient route to the 17-alcohols **9** and **10**.

In summary, this investigation has established a practical synthetic route to 3′,4′,5′,15α-tetrahydro-14β-cyclopenta-[14,15]estra-1,3,5(10)-triene-3,17β- and -3,17α-diols **11** and **12**, representing a novel class of skeletally modified analogues of estradiol. The results of competitive assays reveal that the 17β-alcohol **11** has estradiol receptor affinity (competition factor 1.3) comparable to that of the parent hormone, whereas the 17α-alcohol is a relatively uncompetitive binder (competition factor 7.4).[15] The more detailed structure–activity implications of these findings will be analysed elsewhere, in the context of additional structural variants of estradiol and related analogues. However, the trends observed here and in cognate investigations have renewed significance, in the light of recent advances in the understanding of the structural and steric demands of the estradiol receptor.[5,6] The scope for applying these findings to predictive design and synthesis of estrogen agonists and potential antagonists is receiving ongoing attention.

Experimental

Mps were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. Unless otherwise stated, spectra were recorded as follows: IR, Perkin-Elmer 983, chloroform solutions, ^{1}H NMR, Varian VXR (200 MHz) and Varian Unity (400 MHz), deuteriochloroform solutions (*J* values are given in Hz); ^{13}C NMR, Varian VXR (50 MHz) or Varian Unity (100 MHz), deuteriochloroform solutions; mass spectra (electron impact), VG Micromass 16F. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for chloroform solutions at 20 °C, and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. Microanalyses were performed on a Carlo Erba EA 1108 instrument. Silica gel for chromatography refers to Merck Kieselgel 60, 63–200 μm (gravity) or 40–63 μm (flash).

Wacker oxidation of 14β-allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one 1

A mixture of palladium(II) chloride (275 mg, 1.55 mmol) and copper(I) chloride (800 mg, 8.07 mmol) in DMF (75 cm^3) and water (7.5 cm^3) was stirred at 20 °C under an oxygen atmosphere. After 3 h, the 14β-allyl Δ^{15}-17-ketone **1** (1 g, 3.1 mmol) was added and the mixture was stirred vigorously under oxygen at 65 °C. After 90 min, the mixture was poured into water and 5% ammonium hydroxide was added. The mixture was extracted with toluene, and the extract was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure, to yield a yellow oil (1.188 g). Flash chromatography on silica gel (178 g) using ethyl acetate–toluene (1:9) as eluent gave *3-methoxy-14-formylethyl-14β-estra-1,3,5(10),15-tetraen-17-one* **2** (572 mg, 55%) as a colourless oil (Found: M$^+$, 338.188. $C_{22}H_{26}O_3$ requires *M*, 338.188); ν_{max}/cm^{-1} 1720 and 1700 (C=O); δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 2.78–2.85 (2H, m, 6-H_2), 3.74 (3H, s, 3-OMe), 6.22 (1H, d, *J* 6, 16-H), 6.64 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8, 2-H), 7.13 (1H, d, *J* 8.6, 1-H), 7.31 (1H, d, *J* 6, 15-H) and 9.74 (1H, t, *J* 2 × 1, 3′-H). This was followed by mixed fractions (136 mg), and *14-acetonyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one* **3** (244 mg, 23%), mp 132–135 °C (from EtOH); $[\alpha]_D$ +139 (*c* 1.3) (Found: C, 78.1; H, 7.8%; M$^+$, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338); ν_{max}/cm^{-1} 1725br (C=O); δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.2 (3H, s, 2′-Me), 2.68–2.76 (2H, m, 6-H_2), 2.74 and 3.04 (each 1H, d, *J* 18.3, 1′-H_2), 3.73 (3H, s, 3-OMe), 6.22 (1H, d, *J* 5.9, 15-H), 6.52 (1H, d, *J* 2.8, 4-H), 6.67 (1H, dd *J* 8.6 and 2.8, 2-H), 7.1 (1H, d, *J* 8.6, 1-H) and 7.39 (1H, d, *J* 5.9, 16-H).

Retro-aldol reactions of 17β-acetoxy-3-methoxy-14,17α-etheno-estra-1,3,5(10)-triene-16α-carbaldehyde 4

(a). Methanolic 1 M potassium hydroxide (7 cm^3, 7 mmol) was added to a stirred solution of the aldehyde **4** (200 mg, 0.53 mmol) in THF (7 cm^3) at 20 °C under nitrogen. After 2 min, water was added, followed by dilute acetic acid, and the mixture was extracted with chloroform. The organic layer was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give an oil (217 mg). Chromatography on silica gel (22 g) using ethyl acetate–toluene (1:9) as eluent yielded the 14β-formylethyl compound **2** (38 mg, 19%) as a colourless oil followed by an inseparable mixture of more polar material (58 mg).

(b). The aldehyde **4** (100 mg, 0.26 mmol) was added to methanolic 0.5 M sodium methoxide (2.6 cm^3, 1.3 mmol) and the mixture was stirred at 40–50 °C for 2 h. Small portions of dry ice were added, followed by water and 2 M hydrochloric acid until the mixture was acidic. Work-up as in (a) gave a colourless foam (98 mg), which was chromatographed on silica gel (10 g). Elution with ethyl acetate–toluene (1:3) yielded *3,6′β-dimethoxy-4′H,15αH-5′,6′-dihydropyrano[3′,2′:14,15]-14β-estra-1,3,5(10)-trien-17-one* **5** (43 mg, 40%), mp 82–85 °C (from Me_2CO–MeOH); $[\alpha]_D$ +95 (*c* 0.6) (Found: C, 74.35; H, 8.2%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%; *M*, 370); ν_{max}/cm^{-1} 1723 (C=O); δ_H (200 MHz) 1.1 (3H, s, 13β-Me), 2.72–2.82 (2H, m, 6-H_2), 3.35 (3H, s, 6′-OMe), 3.77 (3H, s, 3-OMe), 4.19 (1H, ddd, *J* 10.4, 6.5 and 3.5, 15α-H), 4.36 (1H, d, *J* 5.4, 6′-H), 6.62 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.17 (1H, d, *J* 8.6, 1-H).

3-Methoxy-3′,15α-dihydrocyclopenta[14,15]-14β-estra-1,3,5(10)-triene-4′(5′*H*),17-dione 6

Methanolic 1 M potassium hydroxide (2.43 cm^3, 2.43 mmol) was added to a stirred solution of the 14β-acetonyl Δ^{15}-17-ketone **3** (274 mg, 0.81 mmol) in THF (10 cm^3), and the solution was heated at reflux under nitrogen for 2 h. Water was added and the mixture was acidified with aqueous 3 M hydrochloric acid. The product was extracted into chloroform, and the organic phase was washed successively with aq. $NaHCO_3$, and brine, dried ($MgSO_4$) and evaporated under reduced pressure, to give an oily residue (277 mg) which was chromatographed on silica gel (28 g). Elution with ethyl acetate–toluene (1:9) yielded the *4′,17-diketone* **6** (175 mg, 64%), mp 190–193 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +41 (*c* 1.1) (Found: C, 77.85; H, 7.7%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338); ν_{max}/cm^{-1} 1732br (C=O); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, s, 13β-Me), 1.82–1.92 (1H, m, 16β-H), 2.02 (1H, d, *J* 19, 5′β-H), 2.24 (1H, dd, *J* 19 and 0.9, 5′α-H), 2.26 (1H, d, *J* 19.7, 3′β-H), 2.4 (1H, dq, *J* 13.3 and 3 × 3.2, 11α-H), 2.62 (1H, ddd, *J* 19.7, 6.4 and 1.6, 3′α-H), 2.76–2.86 (3H, m 6-H_2 and 9α-H), 3.09–3.19 (2H, m, 16α- and 15α-H), 3.78 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7, 4-H), 6.75 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.23 (1H, d, *J* 8.7, 1-H); δ_H (400 MHz, C_6D_6) 0.85 (3H, s, 13β-Me), 1.33 (1H, dd, *J* 19.8 and 7.3, 16β-H), 1.38 (1H, m, 7β-H), 1.59 (1H, d, *J* 19.4, 5′β-H), 1.71 (1H, d, *J* 19.3, 3′β-H), 1.76 (1H, dd, *J* 19.4 and 1.1, 5′α-H), 1.88 (1H, dq, *J* 12.6 and 3 × 3.4, 11α-H), 2.08 (1H, ddd, *J* 19.3, 8 and 1.1, 3′α-H), 2.16–2.27 (2H, m, 9α and 15α-H), 2.42–2.48 (2H, m, 6-H_2), 2.52 (1H, dd *J* 19.8 and 10.5, 16α-H), 3.39 (3H, s, 3-OMe), 6.59 (1H, d, *J* 2.8, 4-H), 6.81 (1H, dd *J* 8.7 and 2.8, 2-H) and 7.03 (1H, d, *J* 8.7, 1-H); δ_C (100 MHz, $CDCl_3$) 219.2 (s, C-17), 217.8 (s, C-4′), 157.7 (s, C-3), 137.1 (s, C-5), 130.9 (s, C-10), 127.3 (d, C-1), 113.4 (d, C-4), 112.4 (d, C-2), 55.2 (q, 3-OMe), 54.5 (s, C-13), 53.9 (s, C-14), 48.2 (t, C-5′), 46.4 (t, C-3′), 44.2 (d, C-8), 43.0 (t, C-16), 38.5 (d, C-9), 32.6 (d, C-15), 31.8 (t, C-12), 31.2 (t, C-6), 26.9 (t, C-11), 25.4 (t, C-7) and 15.6 (q, C-18).

4′,4′-Ethylenedithio-3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one 7

(a). A solution of the 4′,17-diketone **6** (50 mg, 0.15 mmol) in dichloromethane (1 cm^3) was added to a mixture of ethane-1,2-dithiol (0.05 cm^3, 0.6 mmol) and zinc trifluoromethanesulfonate (105 mg, 0.3 mmol) in dichloromethane (1 cm^3). The mixture was stirred at 25 °C for 1.5 h, then water was added and the mixture was extracted with dichloromethane. The combined organic phase was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure, to give a pale yellow crystalline residue (82 mg). Flash chromatography on silica gel (8.2 g) using ethyl acetate–toluene (3:97) as eluent, gave the *4′,4′-dithioketal* **7** (52 mg, 85%); mp 160–162 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +138 (*c* 0.8) (Found: M^+, 414.163. $C_{24}H_{30}S_2O_2$ requires *M*, 414.163); ν_{max}/cm^{-1} 1728 (C=O); δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 2.86–2.94 (2H, m, 6-H_2), 3.25 (4H, m, -SCH_2CH_2S-), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H).

(b). Ethane-1,2-dithiol (1.5 cm^3, 18 mmol) and a solution of toluene-*p*-sulfonic acid (15 mg) in glacial acetic acid (2 cm^3) were added successively to a solution of the 4′,17-diketone **6** (270 mg, 0.8 mmol) in glacial acetic acid (6 cm^3). After 18 h at 25 °C, the mixture was poured into water and neutralised with solid $NaHCO_3$. Work-up as in (a) gave a semi-crystalline residue (401 mg), which was flash chromatographed on silica gel (40 g) using ethyl acetate–toluene (1:49) as eluent to give the dithioketal **7** (290 mg, 88%).

3-Methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one 8

Raney nickel (Aldrich, W2, 1 g) was washed by decantation with absolute ethanol (×4), then covered with further ethanol (2 cm^3). A solution of the dithioketal **7** (289 mg, 0.7 mmol) in ethanol (16 cm^3) was added and the mixture was heated at reflux under nitrogen for 2 h, then cooled and filtered through Celite, which was thoroughly rinsed with ethanol. Evaporation of the combined filtrate under reduced pressure yielded a colourless crystalline residue (227 mg) which was flash chromatographed on silica gel (12 g). Elution with ethyl acetate–toluene (3:97) gave material (196 mg) which was hydrogenated with palladium on carbon (10%, 90 mg) in ethyl acetate (25 cm^3) for 90 min. The mixture was filtered and the solvent was evaporated under reduced pressure to yield the *17-ketone* **8** (189 mg, 84%), mp 127–130 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +177 (*c* 1.1) (Found: C, 81.6; H, 8.5%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (3H, s, 13β-Me), 1.76 (1H, dd, *J* 19 and 6.1, 16β-H), 2.34 (1H, dq, *J* 13.3 and 3 × 3.6, 11α-H), 2.7 (1H, td, *J* 2 × 11.2 and 3.5, 9α-H), 2.82–2.86 (3H, m, 15α-H and 6-H_2), 2.87 obsc. (1H, dd, *J* 19 and 10.2, 16α-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); δ_H (400 MHz, C_6D_6) 1.05 (3H, s, 13β-Me), 1.54 (1H, dd, *J* 19.5 and 6.5, 16β-H), 1.98 (1H, dq, *J* 12.5 and 3 × 3.5, 11α-H), 2.27 (1H, dt, *J* 10.3 and 2 × 6.5, 15α-H), 2.34 (1H, td, *J* 2 × 11.6 and 3.2, 9α-H), 2.59 obsc. (1H, dd, *J* 19.5 and 10.3, 16α-H), 2.59–2.64 (2H, m, 6-H_2), 3.43 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.7, 4-H), 6.83 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.11 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 221.7 (s, C-17), 157.5 (s, C-3), 137.7 (s, C-5), 132.0 (s, C-10), 127.3 (d, C-1), 113.5 (d, C-4), 112.1 (d, C-2), 58.1 (s, C-13), 55.4 (s, C-14), 55.2 (q, 3-OMe), 44.4 (t, C-8), 42.3 (d, C-16), 39.2 (d, C-9), 37.5 (d, C-15), 34.3 (t, C-12), 33.6 (t, C-3′), 33.0 (t, C-4′), 31.7 (t, C-6), 27.2 (t, C-11), 25.5 (t, C-7), 23.2 (t, C-5′) and 15.7 (q, C-18).

Hydride reduction of the 17-ketone 8

LAH (75 mg, 1.99 mmol) was added to a stirred solution of the ketone **8** (214 mg, 0.66 mmol) in THF (13 cm^3) at 0 °C under

nitrogen. After 40 min at 0 °C, the reaction was complete (TLC), and saturated aq. ammonium chloride was added. The mixture was extracted with ethyl acetate and the combined organic phase was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$) and concentrated under reduced pressure, to yield a colourless oil (228 mg) which was chromatographed on silica gel (23 g) using ethyl acetate–toluene (1:19) as eluent. First to elute was *3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17β-ol* **9** (39 mg, 18%), mp 67–70 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +72 (*c* 1.2) (Found: M^+, 326.225. $C_{22}H_{30}O_2$ requires *M*, 326.225); ν_{max}/cm^{-1} 3562 (OH); δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 2.15–2.29 (1H, m, 11α-H), 2.44–2.58 (2H, m, 9α- and 15α-H), 2.64 (1H, ddd, *J* 15.1, 11.1 and 7, 16α-H), 2.76–2.86 (2H, m, 6-H_2), 3.68 (1H, dd, *J* 7 and 1.1, 17α-H), 3.77 (3H, s, 3-OMe), 6.6 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 157.3 (s, C-3), 138.1 (s, C-5), 133.1 (s, C-10), 127.2 (d, C-1), 113.4 (d, C-4), 111.9 (d, C-2), 82.3 (d, C-17), 59.7 (2, C-13), 55.2 (q, 3-OMe), 49.4 (s, C-14), 45.1 (d, C-8), 43.2 (d, C-9), 41.5 (t, C-16), 39.7 (d, C-15), 37.1 (t, C-12), 35.1 (t, C-3′), 33.1 (t, C-4′), 31.9 (t, C-6), 27.3 (t, C-11), 25.7 (t, C-7), 23.6 (t, C-5′) and 16.7 (q, C-18). This was followed by *3-methoxy-3′,4′,5′,15α-tetrahydro-14β-cyclopenta[14,15]estra-1,3,5(10)-trien-17α-ol* **10** (145 mg, 67%), mp 67–70 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +66 (*c* 0.6) (Found: C, 80.9; H, 9.1%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326); ν_{max}/cm^{-1} 3596 (OH); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 1.3 (1H, m, 15α-H), 1.98 (1H, ddd, *J* 13.7, 11.5 and 9.5, 16β-H), 2.32 (1H, dq, *J* 12.3 and 3 × 3.5, 11α-H), 2.5–2.58 (1H, m, 9α-H), 2.78–2.87 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 3.93 (1H, dd, *J* 9.5 and 8.9, 17β-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.26 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 157.4 (s, C-3), 137.9 (s, C-5), 133.0 (s, C-10), 127.1 (d, C-1), 113.4 (d, C-4), 111.8 (d, C-2), 80.6 (d, C-17), 58.6 (s, C-13), 55.2 (q, 3-OMe), 47.2 (s, C-14), 44.6 (d, C-8), 40.5 (d, C-9), 39.4 (t, C-16), 39.1 (d, C-15), 35.8 (t, C-12), 33.0 (t, C-3′), 31.6 (t, C-6), 30.2 (t, C-4′), 26.5 (t, C-11), 25.8 (t, C-7), 24.9 (t, C-5′) and 19.7 (q, C-18).

Deprotection of the 3-methyl ethers 9 and 10

(a). Diisobutylaluminium hydride (DIBAL-H) (1.5 M, 2 cm^3, 3 mmol) was added to a stirrred solution of the alcohol **9** (77 mg, 0.24 mmol) in toluene (20 cm^3). The mixture was heated at reflux under nitrogen for 24 h, then cooled and diluted with ethyl acetate. The organic phase was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to yield a non-crystalline residue (96 mg). Chromatography on silica gel (9 g) using ethyl acetate–toluene (1:4) as eluent gave *3′4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-triene-3,17β-diol* **11** (73 mg, 99%), mp 159–161 °C (from $CHCl_3$); $[\alpha]_D$ +66 (*c* 0.5, THF) (Found: C, 81.0; H, 9.1%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

(b). Similar treatment of the alcohol **10** (100 mg, 0.31 mmol) gave, after chromatography, *3′,4′,5′,15α-tetrahydrocyclopenta-[14,15]-14β-estra-1,3,5(10)-triene-3,17α-diol* **12** (97 mg, 99%), mp 213–215 °C (from $CHCl_3$); $[\alpha]_D$ +73 (*c* 0.6, THF) (Found: C, 80.6; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

Selective hydride reduction of the 4′,17-diketone 6

Lithium tri-*sec*-butylborohydride (1 M in THF, 2.22 cm^3, 2.22 mmol) was added to a stirred solution of the 4′,17-diketone **6** (160 mg, 0.44 mmol) in THF (15 cm^3) at −60 °C under nitrogen. After 30 min, saturated aq. ammonium chloride was added and the reaction was warmed to room temperature. Work-up by ethyl acetate extraction yielded a yellow oil (368 mg), which was chromatographed on silica gel (35 g) using ethyl acetate–hexane (3:2) as eluent. First to elute was starting material (24 mg, 16%), followed by an inseparable mixture (~7:3) of the 4′ξ-hydroxy 17-ketones **13** and **14** (94 mg, 62%), ν_{max}/cm^{-1} 3603 (OH) and 1725 (C=O); δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 4.49 obsc. (1H, qd, *J* 3 × 8.7 and 4.7, 4′β-H) (for **13**); 1.06 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 4.6 obsc. (1H, td, *J* 2 × 8.1 and 4.4, 4′α-H) (for **14**); and 6.62 (1H, d, *J* 2.6, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); *m/z* 340 (M^+).

Reaction of the 4′,17-diketone 6 with samarium(II) iodide

The diketone **6** (236 mg, 0.7 mmol) in THF (8 cm^3) was added to samarium(II) iodide (3.3 mmol) in THF (85 cm^3). The mixture was heated at reflux under nitrogen for 1 h, then water (56 cm^3) was added and heating was continued for 16 h. 0.05 M Hydrochloric acid (20 cm^2) was added, and the mixture was extracted with ethyl acetate. The combined organic phase was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to yield pale yellow crystalline material (238 mg). Flash chromatography on silica gel (24 g) using ethyl acetate–hexane (7:3) as eluent gave starting material **6** (9 mg, 4%), followed by a fraction (204 mg) comprising **6** and two inseparable compounds (~1:5 by NMR). Treatment of the mixture (204 mg) in acetone (6 cm^3) with 70% aq. perchloric acid (0.013 cm^3) for 4 h, followed by the addition of aq. $NaHCO_3$ and extraction with $CHCl_3$ gave a non-crystalline residue (228 mg). Chromatography on silica gel (23g) using ethyl acetate–toluene (1:9) as eluent gave *(17²R)-16β,17β-isopropylidenedioxy-3-methoxy-16α,17²-methano-14,17α-ethanoestra-1,3,5(10)-triene* **15** (22 mg, 8%), mp 181–184 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +69 (*c* 0.7) (Found: C, 79.0; H, 8.6%; M^+, 380. $C_{25}H_{32}O_3$ requires C, 78.9; H, 8.5%; M, 380); δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 1.54 and 1.55 (each 3H, s, CMe_2), 2.27 (1H, dq, *J* 13 and 3 × 3.4, 11α-H), 2.78–2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.6, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 157.5 (s, C-3), 138.1 (s, C-5), 132.1 (s, C-10), 127.3 (d, C-1), 119.9 (s, *C*Me_2), 113.7 (d, C-4), 111.8 (d, C-2), 93.2 and 91.9 (each s, C-16 and C-17), 55.2 (q, 3-OMe), 52.7 (s, C-13), 50.4(t, C-17¹), 50.2 (s, C-14) 45.5 and 42.2 (each t, C-15 and C-16¹), 40.8 (d, C-8), 39.3 (d, C-9), 34.9 (t, C-17²), 34.8 (d, C-12), 30.4 (t, C-6), 28.4 and 28.2 (each q, C*Me*$_2$), 28.0 (t, C-11), 24.1 (t, C-7) and 20.6 (q, C-18). Further elution gave starting material **6** (26 mg, 13%) followed by *4′α-hydroxy-3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one* **13** as an oil (123 mg, 60%) (Found: M^+, 340.202. $C_{22}H_{28}O_3$ requires *M*, 340.204); δ_H (200 MHz) 1.05 (3H, s. 13β-Me), 2.02 (1H, dd, *J* 15.5 and 9.8), 2.1 (1H, dd, *J* 13.3 and 7.6), 2.64–2.78 (2H, m, 9α-H and 15α-H), 2.8–2.0 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.49 (1H, dq, *J* 3 × 8.7 and 4.7, 4′-H), 6.62 (1H, d, *J* 2.6, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 220.8 (s, C-17), 157.6 (s, C-3), 137.8 (s, C-5), 131.8 (s, C-10), 127.2 (s, C-1), 113.4 (s, C-4), 112.1 (s, C-2), 56.5 and 55.4 (each s, C-13 and C-14), 55.2 (q, 3-OMe), 44.1 (d, C-8), 43.3 (t, C-16), 43.0 (t, C-3′), 42.1 (t, C-5′), 39.6 (d, C-9), 36.1 (t, C-12), 33.2 (t, C-15), 31.7 (t, C-6), 26.8 (t, C-11), 26.1 (t, C-7) and 15.8 (q, C-18).

4′-Deoxygenation of the 4′-hydroxy 17-ketone 13

Methanesulfonyl chloride (0.1 cm^3, 1.3 mmol) was added to a solution of the hydroxy ketone **13** (110 mg, 0.32 mmol) in pyridine (4 cm^3) at 0 °C. The mixture was stirred at 0 °C under nitrogen for 2 h. Water and 1 M hydrochloric acid were added and the mixture was extracted with ethyl acetate. The organic layer was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellowish oil (163 mg). Flash chromatography on silica gel (16 g) using ethyl acetate–hexane (1:3) as eluent, gave the 4′-mesylate as a colourless oil (107 mg, 80%), *m/z* 418 (M^+) which was dissolved in THF (6 cm^3) and treated with LAH (40 mg, 1 mmol). The mixture was heated at reflux under nitrogen for 2 h, then cooled, quenched (aq. NH_4Cl) and worked-up by extraction

with ethyl acetate. The residue (97 mg) was chromatographed on silica gel (10 g) using ethyl acetate–toluene (1:19) as eluent, to give the 17β-alcohol **9** (19 mg, 18%) followed by 17α-alcohol **10** (49 mg, 47%).

17α-Hydroxy-3-methoxy-14β,17β-propanoestra-1,3,5(10),15-tetraen-17²-one 17

Cerium(III) chloride heptahydrate (560 mg, 1.5 mmol) was dried (2 h at 200 °C/0.5 mmHg) then placed under nitrogen while still hot, and THF (5 cm^3) was introduced. The suspension was stirred overnight, then cooled to −50 °C, and the 14β acetonyl Δ^{15}-17-ketone **3** (200 mg, 0.6 mmol) in THF (10 cm^3) was added, followed by lithium hexamethyldisilazide in THF [from addition of *n*-butyllithium (1.6 M, 3.75 cm^3, 6 mmol) to hexamethyldisilazane (1.6 cm^3, 6 mmol) in THF (10 cm^3) at 0 °C, followed by stirring at 0 °C for 20 min], also cooled to −50 °C. The mixture was stirred at −50 °C for 1 h whereupon starting material was absent (TLC). The reaction was quenched by addition of 1 M hydrochloric acid and the mixture was extracted with chloroform. The extract was washed (brine), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue (175 mg) on silica gel (18 g) using ethyl acetate–toluene (1:9) as eluent, yielded *3-methoxy-5′-methyl-15αH-furano[3′,2′:14,15]-14β-estra-1,3,5(10)-trien-17-one* **16** (38 mg, 19%) as a colourless oil (Found: M^+, 338.188. $C_{22}H_{26}O_3$ requires *M*, 338.188); ν_{max}/cm^{-1} 1732 (C=O) and 1669 (C=C); δ_H (200 MHz) 1.12 (3H, s, 13β-Me), 1.8 (3H, d, *J* 1, 5′-Me), 2.09 (1H, dd, *J* 19.8 and 2.6, 16β-H), 2.46–2.6 (1H, m, 9α-H), 2.78–2.88 (2H, m, 6-H_2), 3.12 (1H, dd, *J* 19.8 and 9.1, 16α-H), 3.77 (3H, s, 3-OMe), 4.31 (1H, br d, *J* 1, 4′-H), 4.95 (1H, dd, *J* 9.1 and 2.6, 15α-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H), followed by diketone **6** (28 mg, 14%), and *17α-hydroxy-3-methoxy-14β,17β-propanoestra-1,3,5(10),15-tetraen-17²-one* **17** (115 mg, 58%), mp 227–230 °C (from $CHCl_3$–MeOH); $[a]_D$ +124 (*c* 1.4) (Found: C, 78.4; H, 7.8%; M^+, 338; $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338) ν_{max}/cm^{-1} 3600 (OH) and 1702 (C=O); δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 1.73 (1H, s, exch. by D_2O, 17α-OH), 1.97–2.14 (1H, m, 11α-H), 2.19 and 2.45 (each 1H, d, *J* 18.7, 17^3-H_2), 2.54 and 2.68 (each 1H, d, *J* 17.9, 17^1-H_2), 2.79–2.87 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.82 and 5.94 (each 1H, d, *J* 6, 15- and 16-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H).

17²,17²-Ethylenedithio-3-methoxy-14β,17β-propanoestra-1,3,5(10),15-tetraen-17α-ol 19

(a). The 17α-hydroxy 17^2-ketone **17** (84 mg, 0.25 mmol) in dichloromethane (7 cm^3) was treated with ethane-1,2-dithiol (0.1 cm^3, 1.2 mmol) and zinc trifluoromethanesulfonate (210 mg, 0.58 mmol) in dichloromethane (2 cm^3), as described for compound **6**. The non-crystalline product (101 mg) was chromatographed on silica gel (10 g) using ethyl acetate–toluene (1:19) as eluent, to give a colourless oil (35 mg, 34%) formulated as 17,17-ethylenedithio-3-methoxy-5′-methyl-15α*H*-furano[3′,2′:14,15]-14β-estra-1,3,5(10)-triene **18**; ν_{max}/cm^{-1} 1676 (C=C); δ_H (200 MHz) 1.19 (3H, s, 13β-Me), 1.82 (3H, d, *J* 1, 5′-Me), 2.77–2.84 (2H, m, 6-H_2), 3.16 (4H, m, $-SCH_2CH_2S-$), 3.77 (3H, s, 3-OMe), 4.26 (1H, d, *J* 1, 4′-H), 4.7 (1H, br d, *J* 7.7, 15α-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H); *m/z* 414 (M^+), followed by the non-crystalline *17²,17²-dithioketal* **19** (24 mg, 23%) (Found: M^+, 414.168. $C_{24}H_{30}O_2S_2$ requires *M*, 414.169); ν_{max}/cm^{-1} 3598 (OH); δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 2.18 and 2.4 (each 1H, d, *J* 14.7, 17^3-H_2), 2.49 and 2.63 (each 1H, d, *J* 13.9, 17^1-H_2), 2.77–2.86 (2H, m, 6-H_2), 3.2 and 3.29 (each 2 H, m, $-SCH_2CH_2S-$), 3.77 (3H, s, 3-OMe), 5.89 and 5.97 (each 1H, d, *J* 6, 15- and 16-H), 6.64 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H).

(b). Ethane-1,2-dithiol (1 cm^3, 12 mmol) and a solution of toluene-*p*-sulfonic acid (60 mg, 0.3 mmol) in glacial acetic acid (2 cm^3) were added successively to a stirred solution of the 17α-hydroxy 17^2-ketone **17** (128 mg, 0.38 mmol) in acetic acid (6 cm^3). The mixture was stirred at 20 °C under nitrogen for 5 h, whereupon further ethane-1,2-dithiol (1 cm^3) was added. After 22 h, the mixture was poured into water, neutralised by portionwise addition of solid $NaHCO_3$, and worked up by chloroform extraction to give a colourless oil (187 mg). Chromatography as in the foregoing experiment yielded the furano 17,17-dithioketal **18** (22 mg, 14%), followed by the hydroxy 17^2,17^2-dithioketal **19** (102 mg, 65%).

3-Methoxy-14β,17β-propanoestra-1,3,5(10),15-tetraen-17α-ol 20

Raney nickel (Aldrich W2, 1 g) was washed by decantation with absolute ethanol (×4), then covered with further ethanol (2 cm^3). The dithioketal **19** (102 mg, 0.25 mmol) was added and the mixture was heated at reflux under nitrogen for 2 h, then cooled and filtered through Celite, which was thoroughly rinsed with ethanol. The combined filtrate was concentrated under reduced pressure to yield a semi-crystalline residue (96 mg) which was chromatographed on silica gel (10 g) with ethyl acetate–toluene (1:9) as eluent, to give the *title compound* **20** (46 mg, 58%), mp 145–148 °C (from $CHCl_3$–MeOH); $[a]_D$ +91 (*c* 0.7) (Found: M^+, 324.2095. $C_{22}H_{28}O_2$ requires *M*, 324.209); ν_{max}/cm^{-1} 3594 (OH); δ_H (200 MHz) 0.97 (3H, d, *J* 0.8, 13β-Me), 2.26 (1H, dq, *J* 13 and 2 × 3.4, 11α-H), 2.36–2.5 (1H, m, 9α-H), 2.77–2.86 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.69 and 5.78 (each 1H, d, *J* 6.1, 15- and 16-H), 6.62 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 157.4 (s, C-3), 138.1 (s, C-5), 135.7 (d, C-16), 133.0 (d, C-10), 132.0 (d, C-15), 126.9 (d, C-1), 113.4 (d, C-4), 111.7 (d, C-2), 86.1 (s, C-17), 55.2 (q, 3-OMe), 54.4 (s, C-13), 50.8 (s, C-14), 41.7 (d, C-8), 39.4 (d, C-9), 30.8 (t, C-12), 30.0 (t, C-6), 27.5 (t, $C\text{-}17^1$), 26.9 (t, C-11), 23.8 (t, C-7), 22.9 (t, $C\text{-}17^3$), 18.5 (t, $C\text{-}17^2$) and 13.7 (q, C-18).

14β,17β-Propanoestra-1,3,5(10),15-tetraene-3,17α-diol 21

Deprotection (DIBAL-H, toluene, reflux, 25 h) of the 3-methyl ether **20** (70 mg, 0.22 mmol), followed by flash chromatography of the product on silica gel (7 g) using ethyl acetate–toluene (3:17) as eluent, gave mixed fractions (7 mg) followed by the *3,17α-diol* **21** (51 mg, 76%), mp 255–257 °C (from EtOAc); $[a]_D$ +75 (*c* 0.5, THF) (Found: C, 81.1; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310).

Intramolecular reductive coupling of the 14β-formylethyl Δ^{15}-17-ketone 2

A mixture of titanium(III) chloride–dimethoxyethane complex (8.0 g, 24 mmol) and zinc–copper couple (4.2g, 65 mmol) was heated at reflux with vigorous stirring in freshly distilled dimethoxyethane (DME) (160 cm^3) for 1.5 h. The black suspension was cooled to 0 °C, and the 14β-formylethyl Δ^{15}-17-ketone **2** (360 mg, 1.07 mmol) in DME (250 cm^3) was added over 10 min. The mixture was stirred at 0–5 °C for 30 min, whereupon the reaction was complete (TLC). Aq. K_2CO_3 (160 cm^3) was added and the mixture was stirred overnight, then concentrated under reduced pressure. The resultant slurry was extracted with ethyl acetate, and the organic phase was washed (2% HCl, water, brine), dried ($MgSO_4$) and concentrated under reduced pressure to yield a colourless foam (419 mg). Chromatography on silica gel (24 g) using ethyl acetate–toluene (1:3) as eluent, gave *3′α-hydroxy-3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta-[14,15]-14β-estra-1,3,5(10)-trien-17-one* **22** (39 mg, 11%), mp 193–194 °C (from $CHCl_3$–MeOH); $[a]_D$ +181 (*c* 0.8) (Found: M^+, 340.203. $C_{22}H_{28}O_3$ requires *M*, 340.204); ν_{max}/cm^{-1} 3607 (OH) and 1726 (C=O); δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 1.77 obsc. (1H, dd, *J* 19.5 and 5.8, 16β-H), 2.62–2.82 (1H, m,

15α-H), 2.82–2.89 (2H, m, 6-H_2), 3.05 (1H, dd, *J* 19.5 and 11.2, 16α-H), 3.78 (3H, s, 3-OMe), 4.24 (1H, dd, *J* 7.6 and 2.6, 3′β-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H), followed by mixed fractions (218 mg, 60%) and *3′β-hydroxy-3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one* **23** (51 mg; 14%), mp 138–139 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +143 (*c* 0.8) (Found: M^+, 340.203. $C_{22}H_{28}O_3$ requires *M*, 340.204); ν_{max}/cm^{-1} 3611 and 3443 (OH) and 1725 (CO); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 2.34 (1H, dq, *J* 13.2 and 3 × 3.5, 11α-H), 2.41 (1H, dd, *J* 20.2 and 6.8, 16β-H), 2.64 (1H, dd, *J* 20.2 and 10, 16α-H), 2.64–2.72 (1H, m, 9α-H), 2.82–2.9 (2H, m, 6-H_2), 2.93 obsc. (1H, dt, *J* 10 and 2 × 6.8, 15α-H), 3.79 (3H, s, 3-OMe), 4.62 (1H, ddd, *J* 8.7, 7.7 and 6.8, 3′α-H), 6.65 (1H, d, *J* 2.7, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.26 (1H, d, *J* 8.6, 1-H).

3-Methoxy-4′,5′-dihydro-15α*H*-cyclopenta[14,15]-14β-estra-1,3,5(10)-triene-3′,17-dione 24

Oxalyl chloride (0.4 cm^3, 4 mmol) in dichloromethane (9 cm^3) under nitrogen was cooled to −78 °C and dimethyl sulfoxide (0.67 cm^3, 8 mmol) in dichloromethane (1.9 cm^3) was added with stirring. After 2 min, a mixture of 3′ξ-hydroxy 17-ketones **22** + **23** (130 mg, 0.38 mmol) [mixed fractions, comprising ~3:7 ratio of **22**:**23** (NMR), obtained during chromatography of the product of the foregoing experiment] in dichloromethane (11 cm^3) was added over 5 min, and the mixture was stirred at −78 °C for 35 min. Triethylamine (2.3 cm^3, 16 mmol) was added, and the mixture was stirred at −78 °C for 5 min then allowed to warm to room temperature. Water was added and the mixture was extracted with dichloromethane. The combined organic phase was washed (aq. $NaHCO_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to yield a solid residue (163 mg). Chromatography on silica gel (16 g) using ethyl acetate–toluene (1:9) as eluent gave the *3′,17-diketone* **24** (114 mg, 89%), mp 177–178 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +154 (*c* 0.9) (Found: C, 78.2; H, 7.9%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338); ν_{max}/cm^{-1} 1732br (C=O); δ_H (400 MHz, $CDCl_3$), 1.1 (3H, s, 13β-Me), 1.8 (1H, m, 5′α-H), 1.93 (1H, ddd, *J* 13.5, 9.6 and 3, 5′β-H), 2.05 (1H, m, 16β-H), 2.38 obsc. (1H, dq, *J* 13.1 and 3 × 3.8, 11α-H), 2.41 obsc. (1H, dd, *J* 20.2 and 9.6, 4′β-H), 2.52 (1H, ddd, *J* 20.2, 11.6 and 3.2, 4′α-H), 2.56–2.62 (1H, m, 9α-H), 2.84–2.89 (2H, m, 6-H_2), 2.95–3.04 (2H, m, 15α-H and 16α-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.6, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 218.4 and 217.6 (each s, C-3′ and C-17), 157.7 (s, C-3),136.9 (s, C-5), 130.8 (s, C-10), 127.0 (d, C-1), 113.4 (d, C-4), 112.2 (d, C-2), 55.2 (q, 3-OMe), 54.4 and 53.8 (each s, C-13 and C-14), 46.9 (d, C-15), 43.8 (d, C-8), 38.2 (d, C-9), 36.9 (t, C-16), 35.8 (t, C-4′), 33.1 (t, C-12), 30.4 (t, C-5′), 30.2 (t, C-6), 26.3 (t, C-11), 24.1 (t, C-7) and 13.8 (q, C-18).

3′-Deoxygenation of the 3′-hydroxy 17-ketones 22 + 23

Reductive coupling of the 14β-formyl Δ^{15}-17-ketone **2** (430 mg, 1.3 mmol) as described in a foregoing experiment, followed by flash chromatography of the product gave a mixture (~3:7 by NMR) of the 3′ξ-hydroxy 17-ketones **22** + **23** (350 mg, 80%), which was treated with methanesulfonyl chloride (0.31 cm^3, 4 mmol) in pyridine (15 cm^3) at 0 °C under nitrogen for 30 min. Water and 1 M hydrochloric acid were added, and the mixture was extracted with ethyl acetate. The combined organic phase was washed (aq. $NaHCO_3$, brine) dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of **25** and **26** as an oil (385 mg). Flash chromatography of a portion of this material using ethyl acetate–toluene (1:9) as eluent gave *3′β-methylsulfonyloxy-3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one* **25** (48%), mp 183–187 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +91 (*c* 0.8) (Found: C, 65.7; H, 7.2%; M^+, 418. $C_{23}H_{30}O_5S$ requires C, 66.0; H, 7.2%; *M*, 418); ν_{max}/cm^{-1} 1729 (C=O) and 1171 (OSO_2); δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 2.31 obsc. (1H, dd, *J* 20.1 and 6.8, 16β-H), 2.74 (1H, dd, *J* 20.1 and 10, 16α-H), 2.86–2.93 (2H, m, 6-H_2), 3.01 (3H, s, 3′β-OMs), 3.18 (1H, dt, *J* 10 and 2 × 6.8, 15α-H), 3.7 (3H, s, 3-OMe), 5.32 (1H, ddd, *J* 14.4, 8.1 and 6.8, 3′α-H), 6.63 (1H, d, *J* 2.6, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H). This was followed by mixed fractions (7%) and *3′α-methylsulfonyloxy-3-methoxy-3′,4′,5′,15α-tetrahydrocyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one* **26** (22%), mp 141–143 °C (from Me_2CO–iPr_2O); $[\alpha]_D$ +164 (*c* 1.0) (Found: C, 65.9; H, 7.3%; M^+, 418); ν_{max}/cm^{-1} 1731 (CO) and 1172 (OSO_2); δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 2.51 (1H, td, *J* 2 × 10.2 and 3.3, 9α-H), 2.83–2.9 (2H, m, 6-H_2), 2.98 (3H, s, 3′β-OMs), 3.78 (3H, s, 3-OMe), 5.0 (1H, dd, *J* 7.7 and 2.7, 3′β-H), 6.63 (1H, d, *J* 2.6, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H). The mixture of 3′-mesylates **25** + **26** (227 mg, 0.56 mmol) in THF (4 cm^3) was refluxed with LAH (30 mg, 0.8 mmol) for 2 h. The product was isolated by extraction with chloroform and chromatographed on silica gel (24 g) using ethyl acetate–toluene (1:19) as eluent, to give the 17β-alcohol **9** (29 mg, 12%), followed by the 17α-alcohol **10** (126 mg, 52%).

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