Cycloaddition-mediated strategies for synthesis of perhydrobenzo[14,15]-14β-19-norsteroids

James R. Bull * and Eugene S. Sickle

Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa.
E-mail: bull@psipsy.uct.ac.za

Received (in Cambridge, UK) 27th June 2000, Accepted 26th September 2000
First published as an Advance Article on the web 7th November 2000

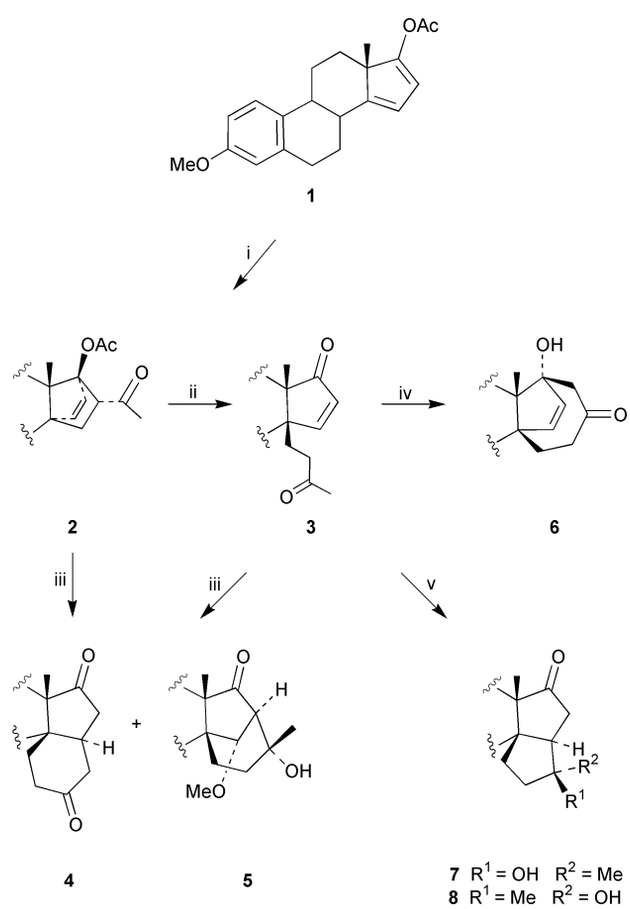
Methods are described for sequential cycloaddition–fragmentation–recombination and cycloaddition–rearrangement-mediated processes for synthesis of the title compounds. Reaction of methyl vinyl ketone with 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **1** gives a cycloadduct **2**, which undergoes retroaldol cleavage followed by intramolecular Michael reaction, to generate 3-methoxy-5′,6′-dihydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-triene-4′(3′*H*),17-dione **4**. Similarly, it is shown that various 16α-alkenyl-14α,17α-etheno-estradiols undergo ready [3,3]-sigmatropic rearrangement to give functional variants of this pentacyclic system. Synthetic routes to novel (perhydrobenzo)[14,15]-14β-analogues of estradiol are described, and aspects of the chemistry of 14β,16β-propano-19-norsteroids derived from alternative intramolecular reaction pathways are outlined.

In further studies to extend the scope of cycloaddition-mediated methodology in the synthesis of new structural variants of bioactive 19-norsteroids, based upon the introduction of hydrophobic and sterically demanding structural elements in ring D, an investigation was undertaken of the cycloaddition of methyl vinyl ketone (MVK) and 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **1**.

We have shown in previous work [1–5] that this substrate is a remarkably versatile source of structurally modified estradiol analogues, mediated by cycloaddition–rearrangement and cycloaddition–fragmentation strategies. Many of these sequences rely on regioselective formation of cycloadducts in which the dienophile-derived functionality is juxtaposed with the bridgehead oxy group at C-17, thus allowing for simple secondary reactions. Thus, cycloaddition of acrolein to **1**, followed by functional-group modification and fragmentation furnished 14-allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one, which served as the key intermediate in stereocontrolled synthesis of the 14α,17α-ethano analogue of estriol [3] and the 14β,17β-propano and 14β,15β-cyclopropa analogues of estradiol.[4,5] The latter structural type revealed the intriguing retention of estrogen receptor-binding affinity in representative hormone analogues, suggesting that the inclusion of sterically demanding hydrophobic substructures in this region of the estradiol template is compatible with the steric demands in the ligand-binding domain of the receptor.[6,7] It was reasoned that the analogous chemistry of an MVK-derived cycloadduct would provide an entry to intermediates for conversion into perhydrobenzo[14,15]-14β-estradiols and perhaps, other expressions of ring D-bridged hormone analogues.

Results and discussion

The reaction of MVK with **1** in THF at 0 °C, in the presence of catalytic boron trifluoride–diethyl ether complex (25 mol%), gave the expected cycloadduct **2** (94%) (Scheme 1), the structure of which was confidently assigned by analogy as well as subsequent transformations. As expected, **2** underwent ready hydrolysis–retroaldol fragmentation in methanolic 1 M KOH at 24 °C, to give the 14β-3′-oxobutyl Δ^{15}-17-ketone **3** (93%). Further treatment of **3** with methanolic 0.03 M KOH under reflux resulted in smooth intramolecular Michael reaction to give the pentacyclic 4′,17-dione **4** (94%), which was also prepared by direct treatment of **2** under similar conditions. An experiment in which **3** was treated in a more concentrated alkaline medium resulted in formation of a reduced yield of **4** (74%), accompanied by a small amount of the product **5** (4%) arising from conjugate addition of methoxide followed by intramolecular aldol reaction.



Scheme 1 *Reagents and conditions*: i, CH_2=$CHCOCH_3$, BF_3·Et_2O, THF, 0 °C; ii, KOH, MeOH, 24 °C; iii, KOH, MeOH, reflux; iv, LiHMDS, $CeCl_3$, THF, −78 °C; v, SmI_2, THF, −78 to 20 °C.

 DOI: 10.1039/b005129m

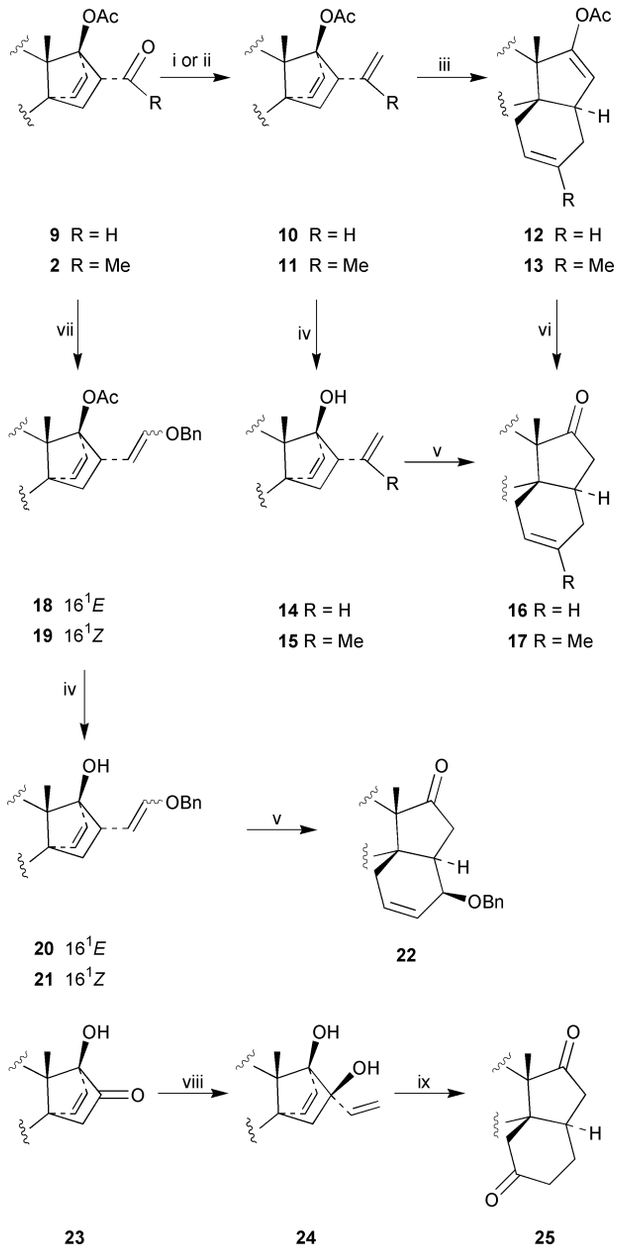
Spectroscopic and analytical data confirmed that the dione **4** is indeed the first example of a novel (perhydrobenzo)[14,15]-14β-steroidal ring system, and provided insight into the connectivity and conformational properties of this product. Although ^{1}H NMR spectroscopy in deuteriochloroform was complicated by some signal overlap, the fully dispersed 400 MHz spectrum in deuteriopyridine, aided by COSY spectroscopy, revealed a pattern of proton signals consistent with the spiro-fused ring system in which ring E adopts a chair ($_{14}C^{4'}$) conformation, and the steroid template is undeformed. Molecular modelling suggested that an alternative chair ($^{14}C_{4'}$) conformation can only be accommodated if ring C adopts a boat conformation, but this is clearly excluded by the presence of the expected[8,9] ring C signals for the ring B half-chair, ring C chair conformation of the 14β-estradiol system.

In the light of earlier work on the synthesis of 14,17-alkano analogues of estradiol,[1,4] it was also of interest to ascertain whether **3** could be induced to undergo an alternative intramolecular closure *via* aldol reaction between C-4′ and C-17. Indeed, low-temperature reaction of **3** with lithium hexamethyldisilazide (LiHMDS) in the presence of cerium(III) chloride, followed by flash chromatography of the crude reaction product, gave a modest yield (≈38%) of impure material, which revealed spectroscopic properties consistent with the 14β,17β-butano 17[2]-ketone **6**. However, attempts to improve the conversion yield and to develop the chemistry of this novel ring system were frustrated by the lability of **6**, which underwent ready retroaldol opening to regenerate the dione **3**.

In another experiment, prompted by the successful intramolecular reductive cyclisation in analogous 14β-formylethyl Δ^{15}-17-ketones,[4] compound **3** was subjected to treatment with samarium(II) iodide in THF at low temperature, to give a separable mixture (≈3:5; 98%) of cyclopenta[14,15] compounds **7** and **8**, arising from exclusive ketyl–olefin coupling at the expense of the alternative, pinacol pathway. This result is complementary to that reported previously,[4] but reveals a distinctive difference in stereoselectivity of closure, associated with the steric influence of the terminal methyl group in **3**. The 3′-configuration of the respective isomers **7** and **8** was confirmed with the aid of nuclear Overhauser effect (NOE) experiments.

The retroaldol–Michael reaction sequence **2** ⟶ **3** ⟶ **4** is well precedented in the analogous conversion of bridgehead-functionalised bicyclo[2.2.2]oct-5-en-2-ones into *cis*-decalins,[10] and in the successful application of this principle in numerous syntheses of target compounds incorporating such substructures.[11] Related target systems are also accessible through [3,3]-sigmatropic processes of structurally similar, functionally modified substrates,[12] and the cycloadducts **9**[3] and **2** invited consideration of this alternative approach to assemble the (perhydrobenzo)[14,15] ring system. Compounds **9** and **2** were readily converted into the 16α-vinyl and 16α-isopropenyl compounds **10** and **11**, respectively, which were heated in toluene at 150 °C (sealed tube) for 48 h, to give the corresponding products **12** (67%) and **13** (64%) of Cope rearrangement (Scheme 2). The obvious expedient of first hydrolysing the bridgehead ester function of **10** and **11** with lithium aluminium hydride (LAH) furnished the respective substrates **14** and **15**, which were amenable to the milder conditions of anionic oxy-Cope rearrangement.[12] The desired reactions proceeded cleanly and efficiently within 2 h in the presence of potassium hydride in refluxing THF, to give the corresponding 17-ketones **16** (87%) and **17** (84%), which were also accessed *via* mild alkaline hydrolysis of the respective enol acetates **14** and **15**. NMR evidence furnished conclusive evidence for the structures of the products **14**–**17**.

The complementarity of the sigmatropic and retroaldol–Michael processes was evident in subsequent synthetic transformations, which provided scope for exploiting alternative pathways for chemodifferentiation of functionality in the



Scheme 2 *Reagents and conditions*: i, $Ph_3\overset{+}{P}CH_3\ I^-$, *t*-BuLi, THF, 25 °C; ii, CH_2Br_2, Zn, $TiCl_4$, THF, CH_2Cl_2, 24 °C; iii, $C_6H_5CH_3$, 150 °C; iv, LAH, THF, 25 °C; v, KH, THF, reflux; vi, KOH, MeOH, 24 °C; vii, $Ph_3\overset{+}{P}CH_2OCH_2C_6H_5\ Cl^-$, *t*-BuLi, THF, 25 °C; viii, CH_2=CHMgBr, THF, 24 °C; ix, KH, THF, −78 °C.

respective products. Furthermore, [3,3]-sigmatropic rearrangement of 2′-functionalised alkenyl systems derived from **9** or **2** could be envisaged, leading to new ring E functional variants of the pentacyclic system. To this end, the 16α-formyl compound **9** was treated with benzyloxymethylene(triphenyl)phosphorane to give a separable mixture (≈1:2; 86%) of the *E*- and *Z*-isomers **18** and **19**. Treatment of the *E*-17-alcohol **20** (derived from **18**) with potassium hydride in refluxing THF was complete within 1 h, and gave the expected rearrangement product **22** (79%), whereas similar treatment of the *Z*-isomer **21** (derived from **19**) required 3 h reaction time, and gave a reduced yield (67%) of the same product **22**. Although the 3′-configuration of **22** was not evident from the NMR signal of the attached proton, an NOE correlation between those of the benzylic and C-16 positions was diagnostic. The reaction times for the respective rearrangements are not necessarily significant, but the formation of a common product implies that they are mediated by a common transition state or that the simpler conversion of **20** proceeds stereospecifically *via* an allowable chair-like transition

state, whereas that of the *Z*-isomer **21** is sterically constrained to proceed non-concertedly.[12]

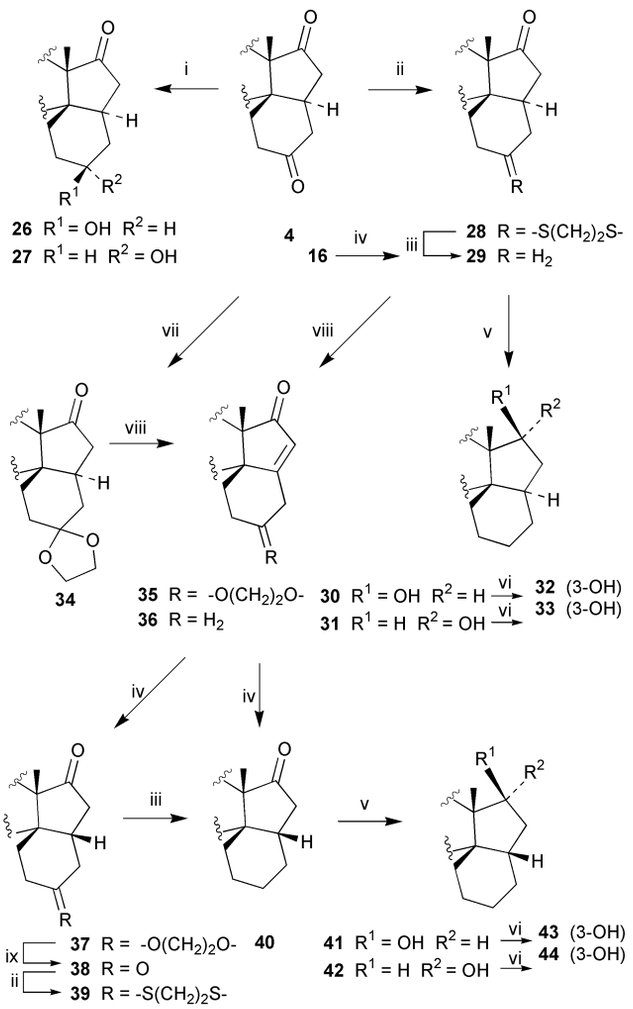
In a further experimental sequence, vinylation of the 16-ketone **23**[13] proceeded efficiently and stereoselectively, to give the 16α-vinyl 16β,17β-diol **24**, which was set up for a doubly potentiated anionic oxy-Cope rearrangement. Indeed, compound **24** underwent impressively convenient rearrangement in the presence of potassium hydride in THF at −78 °C for 15 min, to give the 5′,17-dione **25** in 78% yield.

The foregoing experiments demonstrated that cycloaddition–fragmentation–recombination or cycloaddition–rearrangement reaction sequences provide ready access to an array of variously functionalised (perhydrobenzo)[14,15]-14β-estradiols, and it remained to complete the conversion into the parent estradiol analogues. Chemoselective differentiation of the 4′,17-dione **4** was demonstrated through borohydride reduction, which gave a high yield of the corresponding 4′β- and 4′α-hydroxy 17-ketones **26** (60%) and **27** (30%) (Scheme 3), revealing also the stereoselectivity imposed by the relatively congested β-face environment of the 4′-oxo group.

This chemoselectivity was exploited to realise the purpose in hand, through treatment of **4** with ethanedithiol–boron trifluoride–diethyl ether complex in dichloromethane at 24 °C, to give exclusively the 4′,4′-ethylenedithio 17-ketone **28** (98%). Raney nickel-mediated desulfurisation of **28** proceeded readily to give the 17-ketone **29**. Alternatively, catalytic hydrogenation of the 4′,5′-didehydro 17-ketone **16** furnished **29** directly. Lithium aluminium hydride reduction of **29** displayed slight stereoselectivity in favour of α-face entry of hydride, to give the respective 17β- and 17α-alcohols **30** (49%) and **31** (31%), which were deprotected at C-3 to the corresponding estradiol analogues **32** and **33** by treatment with diisobutylaluminium hydride (DIBAL-H) in toluene under reflux.

A similar approach was adopted for synthesis of 15-isomers of the foregoing hormone analogues. Thus, selective 4′-ketalisation of **4** proceeded as expected, and the derived intermediate **34** was subjected to sequential enol silylation–dehydrosilylation to give the 4′,4′-ethylenedioxy Δ^{15}-17-ketone **35**. Catalytic hydrogenation of **35** proceeded with the expected high β-face selectivity, to give the 4′,4′-ethylenedioxy 15β-17-dione **37**, which was deprotected at C-4′ to furnish the 15β-4′,17-dione **38**. Chemoselective dithioketalisation of **38** proceeded similarly to the 15α-isomer **4**, and Raney nickel desulfurisation of the product **39** gave the 15β-17-ketone **40**. Following optimisation of the oxy-Cope route to the 4′,5′-didehydro-17-ketone **16**, it proved more expedient to access **40** in a shorter, more efficient reaction sequence *via* the 15α-17-ketone **29**. Thus, enol silylation–dehydrosilylation of **29** gave the Δ^{15}-17-ketone **36**, catalytic hydrogenation of which yielded **40** directly, in an overall yield of 87% from **29**. Hydride reduction of **40** gave a separable mixture of the 17β- and 17α-alcohols **41** (46%) and **42** (38%), which were deprotected at C-3 to furnish the respective estradiol analogues **43** and **44**.

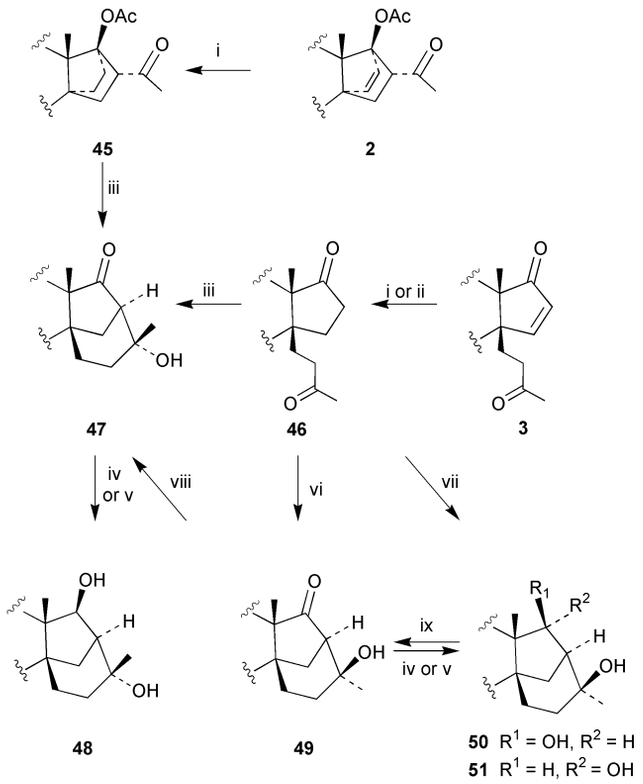
The first objectives of this study were thus achieved, and it remained to explore the scope for elaborating other modes of ring D bridging from the MVK cycloadduct **2** and the derived retroaldol product **3**. For example, the question of a preferred pathway for the intramolecular aldol reaction of the 15,16-dihydro derivative of **3** raises the intriguing prospect of accessing 14β,16β-propano- or 14β,17β-butano-analogues of estradiol. With this in view, the cycloadduct **2** was hydrogenated to give the 14α,17α-ethano compound **45** (Scheme 4). Treatment of **45** with methanolic potassium hydroxide at 0 °C furnished a quantitative yield of a product formulated as the 14β,16β-propano 17-ketone **47**, arising from sequential bridgehead hydrolysis, retroaldol cleavage and subsequent intramolecular aldol reaction. Attempts to intervene in the reaction and isolate any of the obligatory intermediates failed, suggesting that the rate-limiting step may be retroaldol cleavage. Spectroscopic and analytical data for **47** were consistent with



Scheme 3 *Reagents and conditions*: i, $NaBH_4$, THF–MeOH, 0 °C; ii, $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 24 °C; iii, Ra-Ni, EtOH, 50 °C; iv, Pd–C, H_2, EtOAc; v, LAH, THF, 24 °C; vi, DlBAL-H, $C_6H_5CH_3$, reflux; vii, $(CH_2OH)_2$, *p*-TsOH, $C_6H_5CH_3$, reflux; viii, (a) $LiNPr_2$, Et_2O, −78 °C; then Me_3SiCl, 0 °C; (b) $Pd(OAc)_2$, CH_3CN, 25 °C; ix, $C_5H_5N{\cdot}TsOH$, Me_2CO, 25 °C.

the assigned structure, and the configuration at C-16[1] was deduced from NOE correlations. The alternative, stepwise method entailed catalytic hydrogenation of the enedione **3**, which yielded the 3′,17-diketone **46** in moderate yield (61%), but accompanied by significant amounts of the derived aldol product **47**. However, treatment of **3** with methylcopper–DIBAL-H–hexamethylphosphoric triamide (HMPA)[14] proceeded more cleanly to give the 3′-oxobutyl 17-ketone **46** in 84% yield. As expected, **46** underwent intramolecular closure to **47** in the presence of methanolic alkali, but surprisingly, not as readily as the foregoing reaction, **45** ⟶ **47**, implies. This invites questions about the nature of the intermediate during the sequential process; it is conceivable that the primary enolate species arising from retroaldol cleavage is favourably oriented for intramolecular protonation *via* 16β-H, and simple proximity-induced closure. Hydride reduction of **47** proceeded highly stereoselectively to give only the corresponding 17β-alcohol **48**.

The simple and exclusive aldol closure to **47**, mediated by a ring D enolate, is in accordance with the expectation that the product is thermodynamically favoured, but it was of interest to ascertain whether chemoselective enolisation of the 3′-oxo group could be induced under conditions of kinetic control, possibly leading to the elusive 14β,17β-butano product. However, attempts to conduct this step at low temperature, in the presence of various hindered bases and with the aid of trapping



Scheme 4 *Reagents and conditions*: i, Pd–C, H_2, EtOAc; ii, MeCu, DIBAL-H, HMPA, −78 °C; iii, KOH, MeOH, 0 °C; iv, LAH, THF, 21 °C; v, SmI_2, *t*-BuOH, THF, reflux; vi, SmI_2, THF, −78 to 20 °C; vii, SmI_2, THF, reflux; viii, KOH, MeOH, 20 °C; ix, Dess–Martin periodinane, CH_2Cl_2, 20 °C.

agents, were frustrated by poor selectivity, and the only product detected in these experiments was **47**.

Attention was turned to the scope for performing an intramolecular reductive cyclisation upon the 3′,17-diketone **46**, in expectation of generating a 17[1]-methyl 14β,17β-propano 17,17[1]-diol, by analogy with precedent for a 14β-formylethyl 17-ketone.[4] Surprisingly, treatment of **46** with samarium(II) iodide in THF at −78 °C gave a single product (87%), isomeric with starting material, which was assigned the structure **49**. A pattern of NMR signals for product **49**, reminiscent of those assigned to the bicyclo[3.2.1]octanoid substructure of **47**, provided persuasive evidence that it is an isomeric aldol reaction product! The assignment of configuration at C-16[1] was facilitated by transannular NOE correlations and evidence of intramolecular hydrogen bonding. When the experiment was performed on **46** in the presence of an excess of samarium(II) iodide in refluxing THF, the derived 16[1],17-diols **50** (13%) and **51** (68%) were isolated. This reaction outcome was reproduced by similar reaction of the 17-ketone **49**, and demonstrates that the slow reduction favours formation of the 17α-alcohol **51**. By contrast, reduction of **49** with LAH proceeded rapidly and highly stereoselectively through α-face entry of hydride, to give only the 17β-alcohol **50**, paralleling the course of reduction in the isomer **47**. Interestingly, forcing reduction of the isomeric 17-ketone **47** with samarium(II) iodide in refluxing THF followed the course of LAH reduction, to give only the 17β-alcohol **48**.

A decisive experiment entailed treatment of the SmI_2-derived 16[1]-hydroxy 17-ketone **49** with methanolic potassium hydroxide at 20 °C to give, after 5 h, the isomeric product **47**, thus confirming their structural relationship through retroaldol–aldol-mediated equilibration. It remains to speculate upon the unusual course of reaction of **46** with samarium(II) iodide, giving rise to an 'abnormal' aldol reaction product **49**. It is surmised that the expected single-electron-transfer step is sterically hindered, and that samarium(II) 17-enolate formation intervenes, aided by the resultant generation of a chair-like six-membered transition state, in which the strongly oxophilic samarium centre on 17-O coordinates with the 3′-oxo group, and results in 3′,16-bond formation. A closed transition state of this nature would give rise to an aldol reaction under kinetic control, in contrast to the process governed by base-mediated aldol reaction of **46**.

The (perhydrobenzo)[14,15]-14β- analogues of estradiol prepared in this study were assayed for affinity toward the estradiol receptor,[15] which revealed that the 17β-alcohol **32** is highly competitive [competition factor[15] (CF) 1.5], whereas the corresponding 17α-alcohol **33** shows diminished competition (CF 14). These results parallel those of the closely related cyclopenta[14,15]-14β- series.[5] The corresponding data for **43** and **44** reveal that both isomers are unresponsive toward the receptor.

Overall these findings reinforce the trend in observations on analogous compounds,[1,4,5] that the ligand-binding domain (LBD) of the estrogen receptor[6] is relatively accommodating to sterically demanding, hydrophobic substructures in selected sectors of the ring D environment. Although it is premature to speculate on the precise bounds of this region of the LBD, the results contribute toward an emerging picture of the constraints in an idealised ligand for optimum binding, which can be expected to contribute toward predictive design of estrogen agonists and antagonists.

Experimental

For general directions see ref. 5.

16α-Acetyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 2

Boron trifluoride–diethyl ether (0.1 cm^3, 0.82 mmol) was added to a solution of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **1** (648 mg, 2 mmol) and MVK (0.9 cm^3, 10.8 mmol) in dry THF (15 cm^3) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 3 h, then ice–water was added and the mixture was extracted with ethyl acetate. The combined extract was washed successively with aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (756 mg) was chromatographed on silica gel (65 g) using ethyl acetate–hexane (3:7) as eluent to give the *cycloadduct* **2** (740 mg, 94%), mp 141–142 °C (from Me_2CO–MeOH); $[a]_D$ +78 (*c* 1.1) (Found: C, 76.1; H, 7.9%; M^+, 394. $C_{25}H_{30}O_4$ requires C, 76.1; H, 7.7%; *M*, 394); ν_{max}/cm^{-1} 1729 (CO); δ_H (400 MHz) 0.98 (3H, s, 13β-Me), 1.13 (1H, ddd, *J* 13.3, 3.6 and 2.9, 12β-H), 1.36 (1H, ddd, *J* 2 × 11.6 and 2.6, 8β-H), 1.38 (1H, dddd, *J* 2 × 13.3, 11.6 and 3.6, 11β-H), 1.62 (1H, dd, *J* 11.9 and 8.4, 15β-H), 1.74 (1H, dd, *J* 11.9 and 4.3, 15α-H), 2.13 and 2.16 (each 3H, s, 17β-OAc and 16-Ac), 2.20 (1H, dddd, *J* 13.3, 4.4, 3.8 and 2.9, 11α-H), 2.30 (1H, ddd, *J* 2 × 13.3 and 4.4, 12α-H), 2.48 (1H, ddd, *J* 2 × 11.6 and 3.8, 9α-H), 3.40 (1H, dd, *J* 8.4 and 4.3, 16β-H), 3.77 (3H, s, 3-OMe), 6.04 and 6.14 (each 1H, d, *J* 6.1, 17[1]- and 17[2]-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.18 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 14.9 (q, C-18), 21.6 (q, 16-CO*Me*), 23.8 (t, C-7), 27.2 (t, C-11), 29.5 (t, C-12), 30.2 (t, C-6), 30.4 (q, 17-OCO*Me*), 30.6 (t, C-15), 39.4 (d, C-8), 40.2 (d, C-9), 55.3 (d, C-16), 55.4 (q, 3-OMe), 61.8 and 61.9 (each s, C-13 and C-14), 95.9 (s, C-17), 111.8 (d, C-2), 113.8 (d, C-4), 127.1 (d, C-1), 129.9 and 132.3 (each d, C-17[1] and -17[2]), 132.4 (s, C-10), 137.9 (s, C-5), 157.5 (s, C-3), 169.8 (s, 17-O*C*OMe) and 207.6 (s, C-16[1]).

3-Methoxy-14β-(3′-oxobutyl)estra-1,3,5(10),15-tetraen-17-one 3

The cycloadduct **2** (1.94 g, 4.93 mmol) was suspended in methanolic 1 M potassium hydroxide (10 cm^3, 10 mmol) and the suspension was stirred at 24 °C for 2.5 h. Saturated aq. ammonium chloride was added and the mixture was extracted

with ethyl acetate. The combined organic phase was washed (brine, water), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (1.87 g), which was chromatographed on silica gel (100 g) using toluene as eluent, to give *compound* **3** (1.61 g, 93%), mp 114–116 °C (from Me_2CO–MeOH); $[\alpha]_D$ +123 (*c* 1.1) (Found: C, 78.4; H, 8.3%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352); ν_{max}/cm^{-1} 1627 (C=C) and 1709br (CO); δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 2.13 (3H, s, 3′-Me), 2.80 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.20 (1H, d, *J* 5.8, 16-H), 6.59 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.7 and 2.8, 2-H), 7.08 (1H, d, *J* 8.7, 1-H) and 7.33 (1H, d, *J* 5.8, 15-H); δ_C (50 MHz) 19.7 (C-18), 24.7 (3′-Me), 27.4 (C-11), 27.6 (C-7), 30.3 (C-6), 30.9 (C-1′), 32.5 (C-12), 36.4 (C-2′), 39.0 (C-8), 42.2 (C-9), 51.7 and 54.0 (C-13 and -14), 55.2 (3-OMe), 112.2 (C-2), 113.2 (C-4), 127.8 (C-1), 131.3 (C-15), 132.6 (C-10), 137.2 (C-5), 157.5 (C-3), 164.6 (C-16), 207.5 (C-3′) and 213.8 (C-17).

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

(a) The 14β-3′-oxobutyl Δ^{15}-17-ketone **3** (1.32 g, 3.75 mmol) was dissolved in methanol (20 cm^3) and methanolic 0.1 M potassium hydroxide (10 cm^3) was added. The mixture was heated under reflux for 4 h then cooled to 24 °C and saturated aq. ammonium chloride was added. The mixture was extracted with ethyl acetate, and the combined extract was washed (brine, water), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue (1.26 g) was chromatographed on silica gel (50 g), using ethyl acetate–toluene (3 : 7) as eluent, to give the *4′,17-dione* **4** (1.24 g, 94%), mp 86–88 °C (from MeOH–Et_2O); $[\alpha]_D$ +76 (*c* 1.2) (Found: C, 78.5; H, 8.1%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352); ν_{max}/cm^{-1} 1701 (4′-CO) and 1724 (17-CO); δ_H (400 MHz; $CDCl_3$) 1.06 (3H, s, 13β-Me), 1.70 (1H, ddd, *J* 15.4, 9.6 and 6.0, 6′β-H), 1.79 (1H, dd, *J* 19.9 and 9.0, 16β-H), 1.99 (1H, dddd, *J* 15.4, 6.7, 6.4 and 1.4, 6′α-H), 2.18 (1H, dddd, *J* 17.1, 6.4, 6.0 and 1.7, 5′β-H), 2.39 (1H, ddd, *J* 15.9, 2.1 and 1.7, 3′β-H), 2.55 (1H, ddd, *J* 17.1, 9.6 and 6.7, 5′α-H), 2.67 (1H, dd, *J* 15.9 and 5.0, 3′α-H), 2.86 (1H, dd, *J* 19.9 and 10.2, 16α-H), 2.92 (2H, m, 6-H_2), 3.20 (1H, m, 15α-H), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.8, 4-H), 6.68 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_H (400 MHz; C_5D_5N) 1.02 (3H, s, 13β-Me), 1.20 (1H, td, *J* 2 × 13.0 and 3.5, 8β-H), 1.25 (1H, dt, *J* 14.1 and 2 × 3.2, 12β-H), 1.57 (1H, ddd, *J* 15.2, 10.1 and 6.1, 6′β-H), 1.67 (1H, ddd, *J* 14.4, 14.1 and 4.0, 12α-H), 1.73 (1H, ddd, *J* 15.2, 6.6 and 6.1, 6′α-H), 1.95 (1H, dd, *J* 19.4 and 9.0, 16β-H), 2.18 (1H, dtd, *J* 16.9, 2 × 6.1 and 1.9, 5′β-H), 2.37 (1H, ddd, *J* 15.7, 2.4 and 1.9, 3′β-H), 2.55 (1H, ddd, *J* 16.9, 10.1 and 6.6, 5′α-H), 2.67 (1H, dd, *J* 15.7 and 5.1, 3′α-H), 2.73 (1H, ddd, *J* 13.0, 11.1 and 4.0, 9α-H), 2.84 (2H, m, 6-H_2), 2.85 (1H, dd, *J* 19.4 and 10.1, 16α-H), 3.20 (1H, m, 15α-H), 3.74 (3H, s, 3-OMe), 6.81 (1H, d, *J* 2.7, 4-H), 6.96 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.32 (1H, d, *J* 8.5, 1-H); δ_C (100 MHz) 14.8 (q, C-18), 26.6 (t, C-11), 27.1 (t, C-7), 31.0 (t, C-6′), 31.7 (t, C-6), 32.5 (d, C-15), 32.9 (t, C-12), 38.4 (d, C-8), 38.9 (t, C-5′), 40.7 (t, C-16), 43.2 (t, C-3′), 44.5 (s, C-13), 45.8 (d, C-9), 55.2 (s, C-14), 56.1 (q, 3-OMe), 112.3 (d, C-2), 113.3 (d, C-4), 127.5 (d, C-1), 131.4 (s, C-10), 137.1 (s, C-5), 157.7 (s, C-3), 211.7 (s, C-4′) and 218.9 (s, C-17).

(b) The cycloadduct **2** (2 g, 5.1 mmol) was suspended in methanol (10 cm^3) and methanolic 1 M potassium hydroxide (11 cm^3) was added. The resultant mixture was heated under reflux for 4.5 h until all starting material had been consumed (TLC), then was cooled to 24 °C. Saturated aq. ammonium chloride was added and the product (1.97 g) was isolated by extraction with ethyl acetate, and purified by filtration through silica gel (100 g), using ethyl acetate–toluene (3 : 7) as eluent, to give compound **4** (1.88 mg, 94%).

(c) Treatment of the 14β-3′-oxobutyl Δ^{15}-17-ketone **3** (400 mg, 1.14 mmol) with methanolic 0.5 M potassium hydroxide (10 cm^3) under reflux for 2.5 h, followed by work-up and chromatography as described in the foregoing experiments, gave the 4′,17-dione **4** (296 mg, 74%) followed by *(16¹R)-16¹-hydroxy-3,15α-dimethoxy-16¹-methyl-14,16β-propano-14β-estra-1,3,5(10)-trien-17-one* **5** (18 mg, 4%), mp 123–124 °C (from EtOAc–hexane); $[\alpha]_D$ +83 (*c* 1.1) (Found: C, 74.8; H, 8.2%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; *M*, 384); ν_{max}/cm^{-1} 3611 (OH) and 1725 (CO); δ_H (400 MHz; $CDCl_3$), 1.09 (3H, s, 13β-Me), 1.35 (3H, s, 16¹-Me), 2.54 (1H, d, *J* 1.8, 16α-H), 3.16 (1H, td, *J* 2 × 11.8 and 3.7, 9α-H), 3.22 (3H, s, 15α-OMe), 3.78 (3H, s, 3-OMe), 4.19 (1H, s, 15β-H), 6.68 (1H, d, *J* 2.8, 4-H), 6.75 (1H, dd *J* 8.5 and 2.8, 2-H) and 7.10 (1H, d, *J* 8.5, 1-H); δ_H (400 MHz; C_6D_6) 0.88 (1H, ddd, *J* 13.9, 5.5 and 1.8, 16³-H_n), 1.00 (3H, s, 13β-Me), 1.0–1.17 (3H, m, 8β-H and 16²-H_2), 1.14 (3H, s, 16¹-Me), 1.24 (1H, qd, *J* 3 × 13.0 and 3.4, 11β-H), 1.55 (1H, dt, *J* 13.0 and 2 × 3.4, 12β-H), 1.57 (1H, qd, *J* 12.5, 11.5, 11.0 and 6.7, 7α-H), 1.90 (1H, dq, *J* 12.5 and 3.4, 7β-H), 1.93 (1H, ddd, *J* 13.9, 11.8 and 7.5, 16³-H_x), 2.14 (1H, dddd, *J* 13.0, 3.8, 3.7 and 3.4, 11α-H), 2.38 (1H, d, *J* 1.4, 16α-H), 2.41 (1H, td, *J* 2 × 13.0 and 3.8, 12α-H), 2.68–2.74 (2H, m, 6-H_2), 2.89 (3H, s, 15α-OMe), 3.23 (1H, td, *J* 2 × 13.0 and 3.7, 9α-H), 3.39 (3H, s, 3-OMe), 4.06 (1H, s, 15β-H), 6.70 (1H, d, *J* 2.8, 4-H), 6.75 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.10 (1H, d, *J* 8.5, 1-H); δ_C (100 MHz) 17.5 (q, C-18), 23.6 (t, C-7), 25.4 (t, C-11), 28.4 (q, 16¹β-Me), 30.7 (t, C-6), 30.8 (t, C-16³), 33.1 (t, C-12), 34.1 (t, C-16²), 38.4 (d, C-9), 43.4 (d, C-8), 48.4 and 49.2 (each s, C-13 and -14), 55.2 (q, 3-OMe), 56.2 (q, 15α-OMe), 62.3 (d, C-16), 73.5 (s, C-16¹), 85.5 (d, C-15), 111.4 (d, C-2), 113.6 (d, C-4), 125.9 (d, C-1), 134.2 (s, C-10), 137.7 (s, C-5), 157.4 (s, C-3) and 221.9 (s, C-17).

17α-Hydroxy-3-methoxy-14,17β-butano-14β-estra-1,3,5(10),15-tetraen-17²-one 6

Cerium(III) chloride heptahydrate (300 mg, 0.81 mmol) was dried under reduced pressure at 150 °C for 2 h, then cooled under nitrogen to 24 °C, and THF (5 cm^3) was added. A solution of the 14β-3′-oxobutyl Δ^{15}-17-ketone **3** (130 mg, 0.37 mmol) in THF (8 cm^3) was added and the mixture was cooled to −78 °C. A solution of LiHMDS [formed by the addition of 1.6 M *n*-butyllithium (0.3 cm^3, 0.38 mmol) to hexamethyldisilazane (0.15 cm^3, 0.72 mmol) in THF (10 cm^3) at −78 °C, followed by stirring for 30 min at 0 °C], also cooled to −78 °C, was added and the mixture was stirred at −78 °C for 1 h. Saturated aq. ammonium chloride was added, and the mixture was extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (119 mg) on silica gel (15 g), using ethyl acetate–toluene (7 : 13) as eluent, gave starting material **3** (67 mg, 49% recovery) followed by a labile fraction (50 mg, 38%) containing the 14β,17β-butano compound **6**, ν_{max}/cm^{-1} 1702 (CO) and 3567 (OH); δ_H (200 MHz) 1.06 (13β-Me), 2.54 and 2.62 (each 1H, d, *J* 16.9, 17¹α- and 17¹β-H), 3.76 (3-OMe), 5.69 and 5.82 (each 1H, d, *J* 6.7, 15- and 16-H), 6.60 (1H, d, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.8 and 2.7, 2-H) and 7.10 (1H, d, *J* 8.7, 1-H); *m/z* 352 (M^+).

Reductive coupling of the 14β-3′-oxobutyl Δ^{15}-17-ketone 3

Samarium(II) iodide (12 cm^3 of a 0.1 M solution in THF, 1.2 mmol) was added to a solution of compound **3** (178 mg, 0.51 mmol) in THF (15 cm^3) cooled to −78 °C. The mixture was stirred at −78 °C for 30 min, then was allowed to warm to 20 °C and was neutralised by the addition of 0.1 M hydrochloric acid (10 cm^3). The mixture was extracted with chloroform. The combined organic phase was washed successively with hydrochloric acid, aq. sodium thiosulfate, aq. sodium hydrogen carbonate and water, then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (171 mg), which was chromatographed on silica gel (18 g), using ethyl acetate–toluene (3 : 5) as eluent, to give *3′β-hydroxy-3-methoxy-*

3′α-methyl-4′,5′-dihydro-15αH-cyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17(3′H)-one **7** (64 mg, 36%), mp 167–170 °C (from Me_2CO–MeOH); $[\alpha]_D$ −6.6 (*c* 1.3) (Found: C, 77.7; H, 8.2%; M^+, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354); ν_{max}/cm^{-1} 3537 (OH) and 1727 (CO); δ_H (400 MHz; C_6D_6) 0.86 (3H, s, 3′α-Me), 1.17 (3H, s, 13β-Me), 1.82 (1H, dd, *J* 10.7 and 3.9, 15α-H), 2.01 (1H, dd, *J* 19.3 and 10.7, 16α-H), 2.49 (1H, dd, *J* 19.3 and 3.9, 16β-H), 2.27 (2H, m, 6-H_2), 3.37 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.8, 2-H) and 6.90 (1H, d, *J* 8.5, 1-H), followed by *3′α-hydroxy-3-methoxy-3′β-methyl-4′,5′-dihydro-15αH-cyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17(3′H)-one* **8** (111 mg, 62%), mp 143–145 °C (from Me_2CO–MeOH); $[\alpha]_D$ −26.5 (*c* 0.98) (Found: C, 77.9; H, 8.8%; M^+, 354); ν_{max}/cm^{-1} 3564 (OH) and 1728 (CO); δ_H (400 MHz; C_6D_6) 0.94 (3H, s, 3′β-Me), 1.01 (3H, s, 13β-Me), 1.75 (1H, dd, *J* 19.2 and 7.2, 16β-H), 2.03 (1H, dd, *J* 10.6 and 7.2, 15α-H), 2.42 (1H, dd, *J* 19.2 and 10.6, 16α-H), 3.42 (3H, s, 3-OMe), 6.68 (1H, d, *J* 2.8, 4-H), 6.85 (1H, dd, *J* 8.4 and 2.8, 2-H) and 7.14 (1H, d, *J* 8.4, 1-H).

3-Methoxy-16α-vinyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 10

1.7 M *tert*-Butyllithium (0.7 cm^3) was added to a suspension of methyltriphenylphosphonium iodide (485 mg, 1.2 mmol) in THF (5 cm^3) at 0 °C. The mixture was stirred at 0 °C for 1 h. Compound **9** (300 mg, 0.79 mmol) as a solution in dry THF (3 cm^3) was added to the orange solution and the mixture was stirred at 25 °C for 2 h. Water (10 cm^3) was added and the mixture was extracted with ethyl acetate. The combined extract was washed (0.1 M HCl, aq. $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (275 mg) on silica gel (30 g), using ethyl acetate–toluene (1 : 9) as eluent, gave the *16α-vinyl compound* **10** (245 mg, 82%), mp 147–150 °C (from Me_2CO–MeOH); $[\alpha]_D$ +176 (*c* 1.0) (Found: C, 79.3; H, 7.8%; M^+, 378. $C_{25}H_{30}O_3$ requires C, 79.3; H, 7.9%; *M*, 378); ν_{max}/cm^{-1} 1734 (OAc); δ_H (400 MHz) 0.95 (3H, s, 13β-Me), 1.12 (1H, dd, *J* 11.9 and 3.8, 15α-H), 1.16 (1H, ddd, *J* 13.5, 4.3 and 2.7, 12β-H), 1.26 (1H, qd, *J* 2 × 13.5, 11.6 and 4.3, 11β-H), 1.38 (1H, td, *J* 2 × 11.6 and 2.5, 8β-H), 2.08 (3H, s, 17-OAc), 2.21 (1H, dddd, *J* 13.5, 4.4, 3.0 and 2.7, 11α-H), 2.30 (1H, tdd, *J* 2 × 13.5, 4.4 and 0.93, 12α-H), 2.50 (1H, td, *J* 2 × 11.6 and 3.0, 9α-H), 2.83–2.90 (2H, m, 6-H_2), 3.01 (1H, ddd, *J* 8.8, 8.3 and 3.8, 16β-H), 3.77 (3H, s, 3-OMe), 4.98 (1H, ddd, *J* 10.2, 2.0 and 0.8, 2′-H_{cis}), 5.04 (1H, ddd, *J* 17.1, 2.0 and 0.8, 2′-H_{trans}), 5.60 (1H, ddd, *J* 17.1, 10.2 and 8.3, 1′-H), 6.03 and 6.25 (each 1H, d, *J* 6.1, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.5, 1-H).

16α-Isopropenyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 11

Dibromoethane (0.1 cm^3, 1.43 mmol) was added to a stirred suspension of zinc powder (130 mg, 2 mmol) in THF (5 cm^3) under nitrogen. The mixture was cooled to −40 °C (solid CO_2–acetone bath) and titanium(IV) chloride (0.15 cm^3, 1.4 mmol) was added dropwise over a period of 15 min. The mixture was stirred at 5 °C for 2 h, then dichloromethane (5 cm^3) was added to the dark grey slurry. Compound **2** (394 mg, 1.0 mmol) as a solution in dichloromethane (5 cm^3) was added and the resultant mixture was stirred at 24 °C for 1.5 h. The mixture was diluted with pentane (10 cm^3) and aq. sodium hydrogen carbonate was added slowly until effervescence ceased. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed (aq. $NaHCO_3$, water, brine), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (374 mg). Chromatography on silica gel (40 g), using ethyl acetate–toluene (1 : 9) as eluent, afforded *compound* **11** (303 mg, 77%), mp 167–169 °C (from Me_2CO–MeOH); $[\alpha]_D$ +209 (*c* 1.0) (Found: C, 79.4; H, 8.2%; M^+, 392. $C_{26}H_{32}O_3$ requires C, 79.6; H, 8.2%; *M*, 392); ν_{max}/cm^{-1} 1728 (OAc); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.13 (1H, dt, *J* 13.4 and 2 × 3.2, 12β-H), 1.33 (1H, dd, *J* 12.1 and 4.5, 15α-H), 1.39 (1H, td, *J* 2 × 11.5 and 2.6, 8β-H), 1.76 (3H, s, 1′-Me), 1.78 (1H, dd, *J* 12.1 and 8.8, 15β-H), 2.09 (3H, s, 17β-OAc), 2.23 (1H, dtd, *J* 13.4, 2 × 3.7 and 3.2, 11α-H), 2.36 (1H, td, 2 × 13.4 and 3.7, 12α-H), 2.50 (1H, td, 2 × 11.5 and 3.7, 9α-H), 2.85–2.90 (2H, m, 6-H_2), 3.08 (1H, dd, *J* 8.8 and 4.5, 16β-H), 3.77 (3H, s, 3-OMe), 4.64 (1H, dq, *J* 4.1 and 3 × 1.8, 2′-H_{cis}), 4.80 (1H, dq, *J* 4.1 and 3 × 0.8, 2′-H_{trans}), 5.96 and 6.18 (each 1H, d, *J* 6.1, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H).

Cope rearrangement of the 1,5-dienes 10 and 11

(a) A solution of the 16α-vinyl compound **10** (85 mg, 0.22 mmol) in dry toluene (5 cm^3) was purged with nitrogen and then heated in a sealed tube at 150 °C (oil-bath) for 48 h. The cooled reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue (61 mg) was chromatographed on silica gel (7 g), using ethyl acetate–toluene (1 : 9) as eluent, to give *3-methoxy-3′,6′-dihydro-15αH-benzo-[14,15]-14β-estra-1,3,5(10),16-tetraen-17-yl acetate* **12** (57 mg, 67%), mp 163–164 °C (from EtOAc–hexane); $[\alpha]_D$ +278 (*c* 1.0) (Found: C, 79.5; H, 7.9%; M^+, 378. $C_{25}H_{30}O_3$ requires C, 79.3; H, 8.0%; *M*, 378); ν_{max}/cm^{-1} 1729 (CO); δ_H (400 MHz) 1.08 (3H, s, 13β-Me), 2.12 (3H, s, 17β-OAc), 2.76–2.80 (2H, m, 6-H_2), 3.02 (1H, m 15α-H), 3.77 (3H, s, 3-OMe), 4.84 (1H, d, *J* 5.7, 16-H), 5.34 and 5.57 (each 1H, m, 4′- and 5′-H), 6.62 (1H, d, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.19 (1H, d, *J* 8.5, 1-H).

(b) Similar treatment of the 16α-isopropenyl compound **11** (67 mg, 0.17 mmol) gave *3-methoxy-4′-methyl-3′,6′-dihydro-15αH-benzo[14,15]-14β-estra-1,3,5(10),16-tetraen-17-yl acetate* **13** (42 mg, 64%), mp 147–149 °C (from EtOAc–hexane); $[\alpha]_D$ +306 (*c* 0.9) (Found: C, 79.8; H, 8.3%; M^+, 392. $C_{26}H_{32}O_3$ requires C, 79.6; H, 8.2%; *M*, 392); ν_{max}/cm^{-1} 1728 (CO); δ_H (400 MHz) 1.12 (3H, s, 13β-Me), 1.74 (3H, q, *J* 3 × 1.8, 4′-Me), 2.09 (3H, s, 17-OAc), 2.72–2.81 (2H, m, 6-H_2), 3.11 (1H, m, 15α-H), 3.78 (3H, s, 3-OMe), 4.69 (1H, d, *J* 6.1, 16-H), 5.37 (1H, m, 5′-H), 6.61 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.19 (1H, d, *J* 8.5, 1-H).

Preparation of the 17β-alcohols 14 and 15

(a) LAH (106 mg, 2.7 mmol) was added to a solution of the 17β-acetate **10** (250 mg, 0.66 mmol) in dry THF (10 cm^3) at 0 °C under nitrogen, and the mixture was stirred at 25 °C for 20 min. Aq. sodium sulfate was added to the solution at 0 °C until a white precipitate formed. Diethyl ether (10 cm^3) was added and the mixture was stirred for 30 min, then filtered through magnesium sulfate and Celite. The filter pad was washed with chloroform and the filtrate was evaporated under reduced pressure to give *3-methoxy-16α-vinyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol* **14** (182 mg, 82%), mp 237–239 °C (from EtOAc–hexane); $[\alpha]_D$ +156 (*c* 1.0) (Found: C, 82.3; H, 8.3%; M^+, 336. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.3%; *M*, 336); ν_{max}/cm^{-1} 3430 (OH); δ_H (400 MHz) 0.95 (3H, s, 13β-Me), 1.17 (1H, dd, *J* 12.2 and 4.0, 15α-H), 1.23 (1H, ddd, *J* 12.9, 4.3 and 2.7, 12β-H), 1.40 (1H, td, *J* 2 × 11.6 and 2.9, 8β-H), 1.94 (1H, dd, *J* 12.2 and 8.5, 15β-H), 2.10 (1H, td, *J* 2 × 12.9 and 4.3, 12α-H), 2.48 (1H, td, *J* 2 × 11.6 and 4.2, 9α-H), 2.75 (1H, ddd, *J* 8.8, 8.5 and 4.0, 16β-H), 2.83–2.90 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.02 (1H, ddd, *J* 10.1, 2.0 and 0.7, 2′-H_{cis}), 5.12 (1H, ddd, *J* 17.1, 2.0 and 1.0, 2′-H_{trans}), 5.60 (1H, ddd, *J* 17.1, 10.1 and 8.8, 1′-H), 5.80 and 6.08 (each 1H, d, *J* 6.0, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.7, 1-H).

(b) Similar treatment of the 17β-acetate **11** (170 mg, 0.43 mmol) gave *16α-isopropenyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol* **15** (116 mg, 77%), mp 217–220 °C (from

Me_2CO–MeOH); $[\alpha]_D$ +197 (*c* 1.1) (Found: C, 82.2; H, 8.4%; M^+, 350. $C_{24}H_{30}O_2$ requires C, 82.2; H, 8.6%; *M*, 350); ν_{max}/cm^{-1} 3475 (OH); δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 1.25 (1H, dd, *J* 12.7 and 4.6, 15α-H), 1.81 (3H, br s, 1′-Me), 1.83 (1H, dd, *J* 12.7 and 8.5, 15β-H), 3.05 (1H, dd, 8.5 and 4.6, 16β-H), 3.77 (3H, s, 3-OMe), 4.56 and 4.73 (each 1H, m, 2′-H_2), 5.99 and 6.24 (each 1H, d, *J* 8.4, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H).

3-Methoxy-3′,6′-dihydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 16

(a) Potassium hydride (35% suspension in mineral oil; 97 mg, 0.85 mmol) was washed with pentane to remove the oil, then dried by the passage of nitrogen and suspended in THF (3 cm^3). A solution of the 16α-vinyl compound **14** (160 mg, 0.48 mmol) in THF (3 cm^3) was added and the mixture was heated at reflux for 1 h. The mixture was cooled and the reaction was quenched by the slow addition of ethanol (10 cm^3). Water was added and the resultant solution was extracted with ethyl acetate. The combined organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (149 mg) was chromatographed on silica gel (20 g), using ethyl acetate–toluene (1 : 4) as eluent, to give *compound* **16** (140 mg, 87%), mp 176–178 °C (from EtOAc–hexane); $[\alpha]_D$ +213 (*c* 1.1) (Found: C, 82.1; H, 8.4%; M^+, 336. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.3%; *M*, 336); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 2.00 (1H, dd, *J* 19.2 and 11.3, 16α-H), 2.58 (1H, dd, *J* 19.2 and 8.3, 16β-H), 2.76–2.80 (2H, m, 6-H_2), 2.88 (1H, td, *J* 2 × 11.6 and 4.0, 9α-H), 2.96 (1H, m, 15α-H), 3.78 (3H, s, 3-OMe), 5.64 (1H, m, 4′-H), 5.81 (1H, m, 5′-H), 6.60 (1H, d, *J* 2.7, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.5, 1-H).

(b) The enol acetate **12** (20 mg, 0.05 mmol) was suspended in methanol (3 cm^3) and methanolic 0.1 M potassium hydroxide (1 cm^3) was added. The mixture was stirred at 24 °C for 30 min, then saturated aq. ammonium chloride was added. Standard work-up followed by filtration of the crude product (18 mg) through silica gel (2 g), using toluene as eluent, gave **16** (15 mg, 84%).

3-Methoxy-4′-methyl-3′,6′-dihydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 17

(a) Treatment of the 16α-isopropenyl compound **15** (110 mg, 0.31 mmol) with potassium hydride (0.56 mmol) in refluxing THF (5 cm^3) for 2 h, as described in the foregoing experiment (for **14**), followed by similar work-up and chromatography on silica gel (10 g) gave *compound* **17** (90 mg, 82%), mp 211–214 °C (from EtOAc); $[\alpha]_D$ +284 (*c* 0.8) (Found: C, 82.4; H, 8.8%; M^+, 350. $C_{24}H_{30}O_2$ requires C, 82.2; H, 8.6%; *M*, 350); ν_{max}/cm^{-1} 1725 (CO); δ_H (400 MHz) 1.02 (3H, s, 13β-Me), 1.68 (3H, br s, 4′-Me), 2.0 (1H, dd, *J* 19.0 and 11.4, 16α-H), 2.58 (1H, dd, *J* 19.0 and 8.3, 16β-H), 2.88 (1H, td, *J* 11.8 × 2 and 3.6, 9α-H), 2.95 (1H, m, 15α-H), 3.77 (3H, s, 3-OMe), 5.49 (1H, m, 5′-H), 6.60 (1H, d, *J* 2.8, 4-H), 6.74 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H).

(b) Treatment of the enol acetate **13** (23 mg, 0.06 mmol) with methanolic 0.025 M potassium hydroxide (4 cm^3) at 24 °C for 30 min, followed by standard work-up and filtration through silica gel (2 g), gave **17** (18 mg, 87%).

16α-(2′-Benzyloxyethenyl)-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetates 18 and 19

1.7 M *tert*-Butyllithium in pentane (0.8 cm^3) was added to a suspension of benzyloxymethyl(triphenyl)phosphonium chloride (585 mg, 1.4 mmol) in THF (12 cm^3) at 0 °C, and the mixture was stirred at 0 °C for 1 h. A solution of the 16α-carbaldehyde **9** (380 mg, 1 mmol) in dry THF (8 cm^3) was added and the mixture was stirred at 25 °C for 3 h, then diluted with water and extracted with ethyl acetate. The combined organic phase was washed (aq. HCl, aq. $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (478 mg) on silica gel (50 g), using ethyl acetate–toluene (1 : 19) as eluent, gave the *(1′E)-compound* **18** (121 mg, 25%), mp 213–215 °C (from Me_2CO–MeOH); $[\alpha]_D$ +307 (*c* 1.2) (Found C, 79.6; H, 7.2%; M^+, 484. $C_{32}H_{36}O_4$ requires C, 79.3; H, 7.4%; *M*, 484); ν_{max}/cm^{-1} 1734 (OAc); δ_H (400 MHz) 0.93 (3H, s, 13β-Me), 1.02 (1H, dd, *J* 11.9 and 3.6, 15α-H), 1.13 (1H, dt, *J* 13.4 and 2 × 3.1, 12β-H), 1.26 (1H, tdd, *J* 2 × 13.4, 11.6 and 3.1, 11β-H), 1.37 (1H, td, *J* 2 × 11.6 and 2.4, 8β-H), 1.63 and 1.80 (each 1H, m, 7α- and 7β-H), 1.88 (1H, dd, *J* 11.9 and 8.8, 15β-H), 2.05 (3H, s, 17-OAc), 2.20 (1H, ddt, *J* 13.4, 4.2 and 2 × 3.1, 11α-H), 2.32 (1H, td, *J* 2 × 13.4 and 4.2, 12α-H), 2.51 (1H, td, *J* 2 × 11.6 and 3.1, 9α-H), 2.82–2.88 (3H, m, 16β-H, 6-H_2), 3.78 (3H, s, 3-OMe), 4.61 (1H, dd, *J* 12.5 and 9.4, 1′-H), 4.71 (2H, s, $OCH_2C_6H_5$), 6.03 and 6.21 (each 1H, d, *J* 6.3, 17^1- and 17^2-H), 6.38 (1H, d, *J* 12.5, 2′-H), 6.64 (1H, d, *J* 2.7, 4-H), 6.72 (2H, dd, *J* 8.6 and 2.7, 2-H), 7.22 (1H, d, *J* 8.6, 1-H) and 7.29–7.40 (5H, m, $OCH_2C_6H_5$), followed by the *(1′Z)-compound* **19** (296 mg, 61%), mp 231–232 °C (from Me_2CO–MeOH); $[\alpha]_D$ +267 (*c* 1.1) (Found: C, 79.6; H, 7.3%; M^+, 484); ν_{max}/cm^{-1} 1731 (OAc); δ_H (400 MHz) 0.76 (1H, dd, *J* 11.7 and 3.8, 15α-H), 1.0 (3H, s, 13β-Me), 1.60 and 1.78 (each 1H, m, 7α- and 7β-H), 1.97 (1H, dd, *J* 11.7 and 8.9, 15β-H), 2.04 (3H, s, 17-OAc), 2.82–2.90 (2H, m, 6-H_2), 3.60 (1H, ddd, *J* 2 × 8.9 and 3.8, 16β-H), 3.77 (3H, s, 3-OMe), 4.25 (1H, dd, *J* 8.9 and 6.2, 1′-H), 4.70 (2H, s, $OCH_2C_6H_5$), 6.01 (1H, d, *J* 6.2, 2′-H), 6.08 and 6.33 (each 1H, d, *J* 6.2, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8, 2-H), 7.20 (1H, d, *J* 8.6, 1-H) and 7.28–7.30 (5H, m, $OCH_2C_6H_5$).

16α-(2′-Benzyloxyethenyl)-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ols 20 and 21

(a) LAH (15 mg, 0.4 mmol) was added to a solution of the (1′*E*)-17β-acetate **18** (100 mg, 0.21 mmol) in dry THF (5 cm^3) at 0 °C under nitrogen, then the mixture was stirred at 25 °C for 20 min. Aq. sodium sulfate was added to the solution at 0 °C until a white precipitate formed. Diethyl ether (10 cm^3) was added and the mixture was stirred for 30 min, then filtered through magnesium sulfate and Celite. The filter pad was washed with chloroform and the filtrate was evaporated under reduced pressure to give the *(1′E)-17β-alcohol* **20** (79 mg, 85%), mp 254–255 °C (from EtOAc–hexane); $[\alpha]_D$ +311 (*c* 1.0) (Found: C, 81.6; H, 7.8%; M^+, 442. $C_{30}H_{34}O_3$ requires C, 81.4; H, 7.7%; *M*, 442); ν_{max}/cm^{-1} 3467 (OH); δ_H (400 MHz) 0.92 (3H, s, 13β-Me), 1.06 (1H, dd, *J* 12.1 and 3.8, 15α-H), 1.95 (1H, dd, *J* 12.1 and 8.6, 15β-H), 2.59 (1H, ddd, *J* 9.9, 8.6 and 3.8, 16β-H), 2.82–2.88 (2H, 6-H_2), 3.77 (3H, s, 3-OMe), 4.59 (1H, dd, *J* 12.5 and 9.9, 1′-H), 4.71 (2H, s, $OCH_2C_6H_5$), 5.78 and 6.07 (each 1H, d, *J* 6.0, 17^1- and 17^2-H), 6.46 (1H, d, *J* 12.5, 2′-H), 6.62 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7, 2-H), 7.20 (1H, d, *J* 8.6, 1-H) and 7.29–7.40 (5H, m, $OCH_2C_6H_5$).

(b) Similar treatment of the (1′*Z*)-17β-acetate **19** (200 mg, 0.42 mmol) gave the *(1′Z)-17β-alcohol* **21** (150 mg, 81%), mp 217–219 °C (from EtOAc–hexane); $[\alpha]_D$ +212 (*c* 1.1) (Found: C, 81.4; H, 7.9%; M^+, 442); ν_{max}/cm^{-1} 3478 (OH); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.03 (1H, dd, *J* 11.9 and 3.8, 15α-H), 2.01 (1H, dd, *J* 11.9 and 8.2, 15β-H), 2.82–2.91 (2H, m, 6-H_2), 3.32 (1H, ddt, *J* 2 × 8.2, 3.8 and 1.5, 16β-H), 3.77 (3H, s, 3-OMe), 4.20 (1H, dd, *J* 8.2 and 6.2, 1′-H), 4.82 (2H, s, $OCH_2C_6H_5$), 5.86 and 6.0 (each 1H, d, *J* 6.2, 17^1- and 17^2-H), 6.09 (1H, dd, *J* 6.2 and 1.5, 2′-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8, 2-H), 7.20 (1H, d, *J* 8.6, 1-H) and 7.26–7.30 (5H, m, $OCH_2C_6H_5$).

3′β-Benzyloxy-3-methoxy-3′,6′-dihydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 22

(a) Potassium hydride (10.5 mg, 0.26 mmol) in THF (4 cm^3) was

added to a solution of the (1′*E*)-17β-alcohol **20** (60 mg, 0.14 mmol) in THF (5 cm^3) and the mixture was heated at reflux for 1 h. Ethanol (10 cm^3) was added slowly to the cooled reaction mixture, followed by water, and the solution was extracted with ethyl acetate. The combined organic phase was washed with water, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue (57 mg) was chromatographed on silica gel (10 g), using ethyl acetate–toluene (1:9) as eluent, to give *compound* **22** (49 mg, 79%), mp 256–258 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +356 (*c* 0.9) (Found: C, 81.4; H, 7.9%; M^+, 442. $C_{30}H_{34}O_3$ requires C, 81.4; H, 7.7%; *M*, 442); ν_{max}/cm^{-1} 1727 (CO); δ_H (400 MHz) 1.04 (3H, s, 13β-Me), 2.26 (1H, dd, *J* 19.8 and 11.2, 16α-H), 2.60 (1H, dd, *J* 19.8 and 8.3, 16β-H), 2.72–2.90 (2H, m, 6-H_2), 3.24 (1H, m, 15α-H), 3.78 (3H, s, 3-OMe), 4.32 (1H, m, 3′α-H), 4.58 (2H, d, *J* 1.6, $OCH_2C_6H_5$), 5.72 (1H, m, 4′-H), 5.84 (1H, m, 5′-H), 6.61 (1H, d, *J* 2.7, 4-H), 6.75 (1H, dd, *J* 8.5 and 2.7, 2-H), 7.22 (1H, d, *J* 8.5, 1-H) and 7.28–7.35 (5H, m, $OCH_2C_6H_5$).

(b) Reaction of the (1′*Z*)-17β-alcohol **21** (110 mg, 0.25 mmol) with potassium hydride (14 mg, 0.35 mmol) in THF (10 cm^3) at reflux for 3 h, followed by similar work-up and chromatography, gave **22** (74 mg, 67%).

3-Methoxy-16α-vinyl-14,17α-ethenoestra-1,3,5(10)-triene-16β,17β-diol 24

The 14α,17α-etheno 16-ketone **23** (212 mg, 0.65 mmol) was added to a solution of vinylmagnesium bromide [prepared from vinyl bromide (0.1 cm^3, 0.93 mmol) and magnesium turnings (24 mg, 1 mmol)] in THF (10 cm^3) and the mixture was stirred at 24 °C for 3 h. Aq. sodium hydrogen carbonate was added and the mixture was stirred for 15 min, then extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (198 mg) on silica gel (20 g), using ethyl acetate–toluene (3:7) as eluent, gave *compound* **24** (193 mg, 83%), mp 182–184 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +213 (*c* 0.9) (Found: C, 78.1; H, 8.6%; M^+, 354. $C_{23}H_{28}O_3$ requires C, 77.9; H, 8.6%; *M*, 354); ν_{max}/cm^{-1} 3460br (OH); δ_H (400 MHz) 1.19 (3H, s, 13β-Me), 1.84 and 1.95 (each 1H, d, *J* 12.5, 15α- and 15β-H), 2.50 (1H, td, *J* 2 × 11.6 and 3.4, 9α-H), 2.78–2.90 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.11 (1H, dd, *J* 10.6 and 1.2, 2′-H_{cis}), 5.25 (1H, dd, *J* 17.3 and 1.2, 2′-H_{trans}), 5.87 and 5.99 (each 1H, d, *J* 6.1, 17^1- and 17^2-H), 5.97 (1H, dd, 17.3 and 10.6, 1′-H), 6.63 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H).

3-Methoxy-3′,6′-dihydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-triene-5′(4′*H*),17-dione 25

Reaction of the 16α-vinyl-16β,17β-diol **24** (130 mg, 0.37 mmol) with potassium hydride (16 mg, 0.4 mmol) in THF (8 cm^3) at −78 °C for 15 min, followed by standard work-up and flash chromatography of the product (113 mg) on silica gel (10 g), using ethyl acetate–toluene (1:4) as eluent, gave the *5′,17-dione* **25** (105 mg, 78%), mp 106–109 °C (from MeOH–Pr^i_2O); $[\alpha]_D$ +267 (*c* 1.0) (Found: C, 78.4; H, 8.0%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.7; H, 8.0%; *M*, 352); ν_{max}/cm^{-1} 1698 and 1725 (CO); δ_H (400 MHz) 0.98 (3H, s, 13β-Me), 1.61 (1H, dd, *J* 19.7 and 10.3, 16β-H), 1.94 (1H, d, *J* 15.5, 6′α-H), 2.20 (1H, dd, *J* 15.5 and 1.7, 6′β-H), 2.78 (1H, d, *J* 19.7 and 9.9, 16α-H), 3.09 (1H, dddd, *J* 10.3, 9.9, 5.0 and 2.4, 15α-H), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8, 4-H), 6.74 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 13.9 (C-18), 26.1 (C-11), 26.2 (C-3′), 27.4 (C-7), 30.0 (C-6), 31.5 (C-12), 31.7 (C-4′), 34.9 (C-15), 38.1 (C-8), 46.2 (C-9), 48.7 (C-6′), 52.0 (C-13), 55.2 (3-OMe), 55.8 (C-14), 112.4 (C-2), 113.4 (C-4), 127.2 (C-1), 131.2 (C-10), 137.4 (C-5), 157.6 (C-3), 211.4 (C-5′) and 219.4 (C-17).

Hydride reduction of the 4′,17-dione 4

Sodium borohydride (28 mg, 0.74 mmol) was added slowly to a stirred solution of the 4′,17-dione **4** (252 mg, 0.72 mmol) in THF–methanol (3:1; 12 cm^3) at 0 °C under nitrogen. After 10 min at 0 °C the reaction was complete (TLC). Aq. ammonium chloride was added and the mixture was extracted with ethyl acetate. The combined extract was washed (aq. NH_4Cl, water), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (242 mg) on silica gel (25 g), using ethyl acetate–toluene (1:5) as eluent, gave *4′β-hydroxy-3-methoxy-3′,4′,5′,6′-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one* **26** (153 mg, 60%), mp 80–82 °C (from Me_2CO); $[\alpha]_D$ +45 (*c* 1.0) (Found: C, 77.7; H, 8.4%; M^+, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354); ν_{max}/cm^{-1} 3606 (OH) and 1721 (CO); δ_H (400 MHz) 1.01 (3H, s, 13β-Me), 2.76 (1H, dd, *J* 19.2 and 10.4, 16α-H), 3.18 (1H, dd, *J* 19.2 and 7.5, 16β-H), 3.32 (1H, m, 15α-H), 3.77 (3H, s, 3-OMe), 4.22 (1H, q, *J* 3.4, 4′α-H), 6.60 (1H, d, *J* 2.9, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.9, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H), followed by *4′α-hydroxy-3-methoxy-3′,4′,5′,6′-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one* **27** (77 mg, 30%), mp 104–105 °C (from Me_2CO); $[\alpha]_D$ +53 (*c* 1.2) (Found: C, 77.9; H, 8.3%; M^+, 354); ν_{max}/cm^{-1} 3603 (OH) and 1727 (CO); δ_H (400 MHz) 0.98 (3H, s, 13β-Me), 2.20 (1H, dd, *J* 19.9 and 8.8, 16β-H), 2.75 (1H, dd, *J* 19.9 and 10.6, 16α-H), 3.07 (1H, m, 15α-H), 3.78 (3H, s, 3-OMe), 3.88 (1H, tt, *J* 2 × 11.3 and 2 × 5.0, 4′β-H), 6.55 (1H, d, *J* 2.4, 4-H), 6.68 (1H, dd, *J* 8.8 and 2.4, 2-H) and 7.16 (1H, d, *J* 8.8, 1-H).

3-Methoxy-3′,4′,5′,6′-tetrahydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 29

(a) A solution of the 4′,17-dione **4** (120 mg, 0.34 mmol) in dichloromethane (2 cm^3) at 0 °C was treated with ethanedithiol (0.4 cm^3, 4.8 mmol) and boron trifluoride–diethyl ether (0.2 cm^3, 4.7 mmol). The solution was kept at 24 °C for 30 min, then poured into aq. sodium hydrogen carbonate. The mixture was extracted with chloroform and the extract was washed (aq. $NaHCO_3$, water), dried ($MgSO_4$), and evaporated under reduced pressure to yield the *4′,4′-ethylenedithio 17-ketone* **28** (142 mg, 98%), mp 242–244 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +32 (*c* 0.97) (Found: C, 70.2; H, 7.5; S, 14.6%; M^+, 428. $C_{25}H_{32}O_2S_2$ requires C, 70.1; H, 7.5; S, 15.0%; *M*, 428); ν_{max}/cm^{-1} 1727 (CO); δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 3.20–3.40 (2H, m, SCH_2CH_2S), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.9, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.9, 2-H) and 7.18 (1H, d, *J* 8.7, 1-H).

Raney nickel (Aldrich W2, 0.5 g) was washed by decantation with absolute ethanol (×4), then suspended in ethanol (2 cm^3). A solution of dithioketal **28** (158 mg, 0.36 mmol) in ethanol (2 ml) was added and the mixture was stirred at 50 °C for 1 h. Chloroform (3 ml) was added and the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give a solid residue (131 mg), crystallisation of which gave the *17-ketone* **29** (112 mg, 90%), mp 137–138 °C (from Me_2CO–EtOH); $[\alpha]_D$ +23 (*c* 1.1) (Found: C, 81.7; H, 8.7%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; *M*, 338); ν_{max}/cm^{-1} 1728 (CO); δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 3.70 (3H, s, 3-OMe), 6.54 (1H, d, *J* 2.8, 4-H), 6.66 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.15 (1H, d, *J* 8.6, 1-H).

(b) The $\Delta^{4'}$-17-ketone **16** (22 mg, 0.07 mmol) as a solution in ethyl acetate (5 cm^3) at 24 °C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%; 5 mg). After 3 h the mixture was filtered, and the filtrate was evaporated under reduced pressure. Filtration of the residue (19 mg) through silica gel (2 g) using toluene as eluent gave **29** (18 mg, 81%), identical to material obtained in the foregoing experiment.

Hydride reduction of the 17-ketone 29

LAH (100 mg, 2.7 mmol) was added in portions to a stirred solution of the ketone **29** (300 mg, 0.89 mmol) in THF (25 cm^3) at 0 °C under nitrogen, then the mixture was stirred at 24 °C for 10 min. Water was added dropwise until evolution of hydrogen ceased, followed by chloroform. The mixture was filtered and the precipitate was washed repeatedly with chloroform. The chloroform phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (236 mg) was chromatographed on silica gel (30 g), using ethyl acetate–toluene (1:4) as eluent, to give *3-methoxy-3′,4′,5′,6′-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17β-ol* **30** (135 mg, 49%), mp 136–137 °C (from EtOAc–MeOH); $[a]_D$ +77 (*c* 1.2) (Found: C, 81.4; H, 9.2%; M^+, 340. $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.4%; *M*, 340); ν_{max}/cm^{-1} 3578 (OH); δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 3.62 (1H, dd, *J* 6.4 and 5.2, 17α-H), 3.77 (3H, s, 3-OMe), 6.59 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H), followed by *3-methoxy-3′,4′,5′,6′-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17α-ol* **31** (86 mg, 31%), mp 144–145 °C (from CH_2Cl_2–MeOH); $[a]_D$ +56 (*c* 1.0) (Found: C, 81.2; H, 9.6%; M^+, 340); ν_{max}/cm^{-1} 3566 (OH); δ_H (200 MHz) 0.96 (3H, s, 13β-Me), 4.14 (1H, t, *J* 2 × 8.6, 17β-H), 3.77 (3H, s, 3-OMe), 6.59 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.24 (1H, d, *J* 8.6, 1-H).

Deprotection of the 3-methyl ethers 30 and 31

(a) 1.2 M DIBAL-H in toluene (1.5 cm^3, 1.8 mmol) was added to a stirred solution of the 17β-alcohol **30** (100 mg, 0.29 mmol) in dry toluene (10 cm^3) and the mixture was heated at reflux under nitrogen for 48 h. The mixture was cooled, acidified with dil. hydrochloric acid, and extracted with chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a solid residue (81 mg). Recrystallisation (Me_2CO–MeOH) gave *3′,4′,5′,6′-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-triene-3,17β-diol* **32** (72 mg, 75%), mp 179–181 °C; $[a]_D$ +82 (*c* 1.1) (Found: C, 80.8; H, 9.5%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

(b) Similar treatment of the 17α-alcohol **31** (100 mg, 0.29 mmol) gave *3′,4′,5′,6′-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-triene-3,17α-diol* **33** (69 mg, 72%), mp 196–198 °C (from Me_2CO–MeOH); $[a]_D$ +49 (*c* 1.1) (Found: C, 81.0; H, 9.4%; M^+, 326).

4′,4′-Ethylenedioxy-3-methoxy-3′,4′,5′,6′-tetrahydro-15α*H*-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 34

Toluene-*p*-sulfonic acid (21 mg, 0.11 mmol) was added to a solution of the dione **4** (400 mg, 1.13 mmol) in toluene–ethylene glycol (30 cm^3; 9:1) and the mixture was heated under reflux for 7 h with azeotropic removal of water. The solution was cooled to 25 °C and poured into saturated aq. sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the organic phase was washed successively with water and brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (371 mg) on silica gel (30 g), using ethyl acetate–hexane (1:4) as eluent, gave *compound* **34** (353 mg, 79%), mp 189–190 °C (from $CHCl_3$–MeOH); $[a]_D$ +337 (*c* 1.1) (Found: C, 75.6; H, 7.9%; M^+, 396. $C_{25}H_{32}O_4$ requires C, 75.8; H, 8.1%; *M*, 396); ν_{max}/cm^{-1} 1727 (CO); δ_H (200 MHz) 0.98 (3H, s, 13β-Me), 3.12 (1H, m, 15α-H), 3.76 (3H, s, 3-OMe), 3.87–3.93 [4H, m, $O(CH_2)_2O$], 6.62 (1H, d, *J* 2.8, 4-H), 6.75 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.14 (1H, d, *J* 8.5, 1-H).

Dehydrogenation of the 17-ketones 34 and 29

(a) The 4′,4′-ethylenedioxy 17-ketone **34** (300 mg, 0.76 mmol) as a solution in diethyl ether (10 cm^3) was added to a solution of lithium diisopropylamide [formed by the addition of *n*-butyllithium (1.6 M; 0.6 cm^3) to diisopropylamine (0.14 cm^3, 0.80 mmol) in diethyl ether (10 cm^3) at −78 °C, followed by stirring for 30 min at 0 °C] cooled to −78 °C. The mixture was stirred at −78 °C for 1 h then chlorotrimethylsilane (0.2 cm^3, 1.6 mmol) was added and the mixture was allowed to warm to 0 °C. Saturated aq. ammonium chloride was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed successively with water and brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue (327 mg) was dissolved in acetonitrile (12 cm^3) and added to a mixture of palladium(II) acetate (173 mg, 0.76 mmol) and sodium hydrogen carbonate (30 mg, 0.42 mmol) in dry acetonitrile (8 cm^3). The mixture was stirred at 25 °C for 4 h, then filtered through Celite. The Celite was washed with ethyl acetate and the combined filtrate was washed successively with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the crude material (251 mg) on silica gel (20 g), using ethyl acetate–hexane (1:4) as eluent, gave *4′,4′-ethylenedioxy-3-methoxy-3′,4′,5′,6′-tetrahydrobenzo-[14,15]-14β-estra-1,3,5(10),15-tetraen-17-one* **35** (237 mg, 79%), mp 178–180 °C (from $CHCl_3$–MeOH); $[a]_D$ +278 (*c* 1.0) (Found: C, 76.3; H, 7.6%; M^+, 394. $C_{25}H_{30}O_4$ requires C, 76.1; H, 7.6%; *M*, 394); ν_{max}/cm^{-1} 1708 (CO); δ_H (400 MHz) 1.06 (3H, s, 13β-Me), 2.56 (1H, td, *J* 2 × 11.5 and 3.7, 9α-H), 2.69–2.74 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.84–3.88 [4H, m, $O(CH_2)_2O$], 5.82 (1H, s, 16-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.8 and 2.7, 2-H) and 7.08 (1H, d, *J* 8.8, 1-H).

(b) Treatment of the 17-ketone **29** (338 mg, 1 mmol) as described in the foregoing experiment gave *3-methoxy-3′,4′,5′,6′-tetrahydrobenzo[14,15]-14β-estra-1,3,5(10),15-tetraen-17-one* **36** (284 mg, 91%), mp 161–163 °C (from $CHCl_3$–MeOH); $[a]_D$ +202 (*c* 1.0) (Found: C, 82.4; H, 8.4%; M^+, 336. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.3%; *M*, 336); ν_{max}/cm^{-1} 1702 (CO); δ_H (400 MHz) 0.99 (3H, s, 13β-Me), 2.57 (1H, td, *J* 2 × 11.1 and 3.9, 9α-H), 2.68–2.74 (2H, m, 6-H_2), 3.72 (3H, s, 3-OMe), 5.87 (1H, s, 16-H), 6.61 (1H, d, *J* 2.7, 4-H), 6.68 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.08 (1H, d, *J* 8.7, 1-H).

Hydrogenation of the Δ^{15}-17-ketone 35

The enone **35** (200 mg, 0.51 mmol) as a solution in ethyl acetate (5 cm^3) was hydrogenated for 5 h at 24 °C in the presence of palladium on carbon (10%; 81 mg). The mixture was filtered and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue (200 mg) on silica gel (20 g), using ethyl acetate–hexane (1:5) as eluent, gave **34** (10 mg, 5%) followed by *4′,4′-ethylenedioxy-3-methoxy-3′,4′,5′,6′-tetrahydro-15βH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one* **37** (188 mg, 93%), mp 156–157 °C (from $CHCl_3$–MeOH); $[a]_D$ +218 (*c* 1.2) (Found: C, 75.6; H, 8.2%; M^+, 396. $C_{25}H_{32}O_4$ requires C, 75.8; H, 8.1%; *M*, 396); ν_{max}/cm^{-1} 1729 (CO); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.62 (1H, dd, *J* 18.7 and 11.1, 16β-H), 2.52 (1H, td, *J* 2 × 11.1 and 3.9, 9α-H), 2.63 (1H, dd, *J* 18.7 and 8.4, 16α-H), 2.73–2.79 (2H, m, 6-H_2), 3.04 (1H, m, 15β-H), 3.77 (3H, s, 3-OMe), 3.81–3.85 [4H, m, $O(CH_2)_2O$], 6.64 (1H, d, *J* 2.7, 4-H), 6.67 (1H, dd, *J* 8.8 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.8, 1-H).

3-Methoxy-5′,6′-dihydro-15β*H*-benzo[14,15]-14β-estra-1,3,5(10)-triene-4′(3′*H*),17-dione 38

Pyridinium toluene-*p*-sulfonate (59 mg, 0.37 mmol) was added to a solution of the ketal **37** (140 mg, 0.35 mmol) in acetone (10 cm^3) and the mixture was stirred at 25 °C for 4 h. Saturated aq. sodium hydrogen carbonate was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed successively with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (117 mg) was chromatographed on silica gel (15 g), using ethyl acetate–hexane (3:7) as eluent, to give the *dione* **38** (107 mg, 87%), mp 178–

180 °C (from Me_2CO–MeOH); $[\alpha]_D$ +118 (*c* 1.0) (Found: C, 78.5; H, 8.2%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352); ν_{max}/cm^{-1} 1707 (4′-CO) and 1731 (17-CO); δ_H (400 MHz) 1.02 (3H, s, 13β-Me), 1.82 (1H, dd, *J* 19.1 and 11.2, 16β-H), 2.21 (1H, ddd, *J* 16.2, 5.8 and 1.4, 3′β-H), 2.47 (1H, dd, *J* 16.2 and 7.9, 3′α-H), 2.58 (1H, td, *J* 2 × 10.9 and 4.1, 9α-H), 2.69 (1H, dd, *J* 19.1 and 9.3, 16α-H), 2.73–2.92 (2H, m, 6-H_2), 3.01 (1H, m, 15β-H), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.8 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.8, 1-H); δ_C (100 MHz) 16.7 (q, C-18), 26.8 (t, C-11), 27.3 (q, C-7), 30.4, 30.7 and 31.2 (each t, C-6, -6′ and -12), 34.1 (d, C-15), 38.9 (d, C-8), 39.4 (t, C-5′), 43.8 (t, C-3′), 42.2 (t, C-16), 44.7 (d, C-9), 49.5 and 52.8 (each s, C-13 and -14), 55.2 (q, 3-OMe), 112.1 (d, C-2), 113.3 (d, C-4), 127.4 (d, C-1), 131.9 (s, C-10), 137.2 (s, C-5), 157.7 (s, C-3), 209,8 (s, C-4′) and 214.7 (s, C-17).

3-Methoxy-3′,4′,5′,6′-tetrahydro-15β*H*-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 40

(a) A solution of the 4′,17-dione **38** (125 mg, 0.36 mmol) in dichloromethane (5 cm^3) was cooled to 0 °C, and ethanedithiol (0.4 cm^3, 4.8 mmol) was added followed by boron trifluoride–diethyl ether (0.2 cm^3, 4.7 mmol). The solution was stirred at 24 °C for 90 min, then water was added and the resultant mixture was poured into aq. sodium hydrogen carbonate. The mixture was extracted with dichloromethane and the combined organic phase was washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated under reduced pressure to yield a solid residue (158 mg). Recrystallisation gave the *4′,4′-ethylenedithio 17-ketone* **39** (124 mg, 81%), mp 231–234 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +107 (*c* 1.3) (Found: C, 70.1; H, 7.2; S, 14.6%; M^+, 428. $C_{25}H_{32}O_2S_2$ requires C, 70.1; H, 7.5; S, 14.9%; *M*, 428); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 1.13 (3H, s, 13β-Me), 3.27–3.42 [4H, m, $S(CH_2)_2S$], 3.78 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.14 (1H, d, *J* 8.6, 1-H).

Raney nickel (Aldrich W2, 350 mg) was washed (4×) by decantation with absolute ethanol, and suspended in further ethanol (2 cm^3). A solution of the dithioketal **39** (100 mg, 0.23 mmol) in ethanol (3 cm^3) was added and the resultant mixture was heated with stirring at 50 °C for 2.5 h. The mixture was cooled to 25 °C and chloroform (5 cm^3) was added. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to give a solid residue (73 mg). Recrystallisation gave the *17-ketone* **40** (68 mg, 87%), mp 136 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +298 (*c* 0.9) (Found: C, 81.8; H, 9.0%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; *M*, 338); ν_{max}/cm^{-1} 1731 (CO); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 2.09 (3H, dd, *J* 19.1 and 4.3, 16β-H), 2.44 (1H, dd, *J* 19.1 and 7.6, 16α-H), 2.60 (1H, td, *J* 2 × 10.9 and 4.5, 9α-H), 3.13 (1H, m, 15β-H), 3.76 (3H, s, 3-OMe), 6.59 (1H, d, *J* 2.7, 4-H), 6.68 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.19 (1H, d, *J* 8.6, 1-H).

(b) The Δ^{15}-17-ketone **36** (250 mg, 0.74 mmol) as a solution in ethyl acetate (8 cm^3) at 24 °C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%; 78 mg). After 5 h the mixture was filtered, and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue on silica gel (30 g), using ethyl acetate–hexane (1 : 5) as eluent, gave 15α-H ketone **29** (8 mg, 3%) followed by 15β-H isomer **40** (237 mg, 95%).

Hydride reduction of the 17-ketone 40

The 17-ketone **40** (300 mg, 0.89 mmol) was treated with LAH (100 mg, 2.7 mmol) in THF (12 cm^3) at 0 °C for 30 min then at 24 °C for 10 min. Saturated aq. ammonium chloride was added dropwise to the solution until the evolution of hydrogen ceased, and chloroform was added. The mixture was filtered and the precipitate was washed repeatedly with chloroform. The combined filtrate was extracted with chloroform, and the organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (236 mg) was chromatographed on silica gel (30 g), using ethyl acetate–toluene (2 : 8) as eluent, to give *3-methoxy-3′,4′,5′,6′-tetrahydro-15βH-benzo-[14,15]-14β-estra-1,3,5(10)-trien-17β-ol* **41** (139 mg, 46%), mp 172–174 °C (from CH_2Cl_2–MeOH); $[\alpha]_D$ +218 (*c* 1.1) (Found: C, 81.2; H, 9.6%; M^+, 340. $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.4%; *M*, 340); ν_{max}/cm^{-1} 3613 (OH); δ_H (400 MHz) 0.98 (3H, s, 13β-Me), 2.58 (1H, td, *J* 2 × 11.2 and 4.1, 9α-H), 3.09 (1H, m, 15β-H), 3.77 (3H, s, 3-OMe), 3.91 (1H, dd, *J* 9.7 and 3.4, 17α-H), 6.62 (H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.8 and 2.8, 2-H) and 7.2 (1H, d, *J* 8.8, 1-H) followed by *3-methoxy-3′,4′,5′,6′-tetrahydro-15βH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17α-ol* **42** (115 mg, 38%), mp 191–193 °C (from CH_2Cl_2–MeOH); $[\alpha]_D$ +179 (*c* 1.2) (Found: C, 81.0; H, 9.3%; M^+, 340); ν_{max}/cm^{-1} 3609 (OH); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 2.54 (1H, td, *J* 2 × 11.4 and 3.9, 9α-H), 3.17 (1H, m, 15β-H), 3.77 (3H, s, 3-OMe), 3.87 (1H, dd, *J* 10.2 and 8.9, 17β-H), 6.59 (1H, d, *J* 2.6, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.6, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H).

Deprotection of the 3-methyl ethers 41 and 42

(a) 1.2 M DIBAL-H in toluene (1.0 cm^3, 1.2 mmol) was added to a stirred solution of the 17β-alcohol **41** (80 mg, 0.24 mmol) in dry toluene (20 cm^3) and the mixture was refluxed under nitrogen for 48 h. The mixture was cooled to 24 °C, acidified with hydrochloric acid (10%; 10 cm^3), and extracted with chloroform. The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (69 mg). Recrystallisation (Me_2CO–MeOH) gave *3′,4′,5′,6′-tetrahydro-15βH-benzo[14,15]-14β-estra-1,3,5(10)-triene-3,17β-diol* **43** (62 mg, 80%), mp 178–179 °C; $[\alpha]_D$ +286 (*c* 1.0) (Found: C, 80.9; H, 9.0%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 81.0; H, 9.2%; *M*, 326).

(b) Similar treatment of the 17α-alcohol **42** (100 mg, 0.29 mmol) and crystallisation (Me_2CO–MeOH) of the reaction product (83 mg) gave *3′,4′,5′,6′-tetrahydro-15βH-benzo[14,15]-14β-estra-1,3,5(10)-triene-3,17α-diol* **44** (79 mg, 82%), mp 212–214 °C; $[\alpha]_D$ +301 (*c* 1.1) (Found: C, 81.2; H, 9.2%; M^+, 326).

16α-Acetyl-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate 45

The 14α,17α-etheno compound **2** (192 mg, 0.48 mmol) as a solution in ethyl acetate (10 cm^3) at 24 °C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%; 50 mg). After 3 h the mixture was filtered, and the filtrate was evaporated under reduced pressure. Filtration of the residue (195 mg) through silica gel (10 g), using toluene as eluent, gave the *14α,17α-ethano compound* **45** (191 mg, 100%), mp 163–164 °C (from Me_2CO–MeOH); $[\alpha]_D$ +37 (*c* 1.2) (Found: C, 75.5; H, 8.0%; M^+, 396. $C_{25}H_{32}O_4$ requires C, 75.7; H, 8.1%; *M*, 396); ν_{max}/cm^{-1} 1728 (OAc) and 1705 (CO); δ_H (200 MHz) 1.0 (3H, s, 13β-Me), 2.07 (1H, s, 17β-OAc), 2.17 (3H, s, 16α-COMe), 3.34 (1H, ddd, *J* 11.1, 4.4 and 2.6, 16β-H), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.2 (1H, d, *J* 8.5, 1-H).

3-Methoxy-14β-(3′-oxobutyl)estra-1,3,5(10)-trien-17-one 46

(a) The 14β-3′-oxobutyl Δ^{15}-17-ketone **3** (100 mg, 0.28 mmol) as a solution in ethyl acetate (8 cm^3) at 24 °C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%; 30 mg). After 90 min the mixture was filtered, and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue (532 mg) on silica gel (55 g), using ethyl acetate–toluene (1 : 9) as eluent, gave the *dihydro compound* **46** (61 mg, 61%), mp 147–149 °C (from Me_2CO–MeOH); $[\alpha]_D$ −47 (*c* 0.9) (Found: C, 77.7; H, 8.6%; M^+, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354); ν_{max}/cm^{-1} 1727 (CO); δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 2.13 (3H, s, 3′-Me), 2.82–

2.92 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.8, 4-H), 6.67 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H), followed by compound **47** (31 mg, 31%) (see following experiment).

(b) 5% Methyllithium in diethyl ether (0.14 cm^3, 0.3 mmol) was added to a stirred suspension of copper(I) iodide (57 mg, 0.3 mmol) in dry THF (5 cm^3) at 0 °C under nitrogen. The suspension of methylcopper was cooled to −78 °C and HMPA (2 cm^3, 11.4 mmol) and 1.2 M DIBAL-H in toluene (0.3 cm^3, 4 mmol) were added successively. The mixture was stirred at −78 °C for 30 min, then a solution of compound **3** (352 mg, 1 mmol) in dry THF (2 cm^3) was added. The mixture was stirred at −78 °C for 1.5 h, then 1 M hydrochloric acid (5 cm^3) was added and the mixture was extracted with chloroform. The extract was washed (1 M HCl, aq. $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to give a solid residue (310 mg). Filtration through silica gel (30 g) with toluene yielded the 3′,17-dione **46** (296 mg, 84%).

(16¹*R*)-16¹-Hydroxy-3-methoxy-16¹-methyl-14,16β-propano-14β-estra-1,3,5(10)-trien-17-one 47

(a) The 14α,17α-ethano compound **45** (100 mg, 0.25 mmol) was suspended in methanolic 1 M potassium hydroxide (2.5 cm^3, 2.5 mmol) and the mixture was stirred at 0 °C. After 1.5 h 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 (brine, water), dried ($MgSO_4$), and evaporated under reduced pressure. The residue (100 mg) was filtered through silica gel (10 g), using toluene as eluent, to give the *title compound* **47** (99 mg, 99%), mp 195–197 °C (from Me_2CO–MeOH); $[\alpha]_D$ −78 (*c* 1.1) (Found: C, 77.8; H, 8.6%. M^+, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354); ν_{max}/cm^{-1} 3597 (OH) and 1726 (CO); δ_H (400 MHz) 1.08 (3H, s, 13β-Me), 1.26 (1H, dddd, *J* 13.6, 5.8, 3.1 and 2.0, 16^3-H_n), 1.33 (3H, s, 16^1-Me), 1.33 (1H, ddd, *J* 15.0, 13.6 and 5.8, 16^2-H_n), 1.58 (1H, qt, *J* 15.0, 5.9 and 2 × 2.0, 16^2-H_x), 2.04 (1H, ddd, *J* 12.2, 5.6 and 3.1, 15α-H), 2.18 (1H, d, *J* 12.2, 15β-H), 2.24 (1H, td, *J* 2 × 13.6 and 5.9, 16^3-H_x), 2.41 (1H, dd, *J* 5.6 and 2.2, 16α-H), 2.62 (1H, td, *J* 2 × 11.9 and 3.6, 9α-H), 3.20–3.51 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 15.2 (q, C-18), 23.6 (t, C-7), 26.2 (t, C-11), 27.5 (t, C-15), 28.2 (q, 16^1-Me), 29.3 (t, C-16^3), 30.7 (t, C-6), 31.7 (t, C-12), 34.1 (t, C-16^2), 37.3 (d, C-9), 42.6 (d, C-8), 45.3 and 49.2 (each s, C-13 and -14), 55.2 (q, 3-OMe), 57.2 (d, C-16), 71.0 (s, C-16^1), 111.7 (d, C-2), 113.5 (d, C-4), 126.6 (d, C-1), 131.4 (s, C-10), 137.9 (s, C-5), 157.6 (s, C-3) and 221.3 (s, C-17).

(b) The 14β-3′-oxobutyl 17-ketone **46** (100 mg, 0.28 mmol) was suspended in methanolic 1 M potassium hydroxide (10 cm^3, 10 mmol) and the mixture was stirred at 24 °C. After 2.25 h the reaction was complete (TLC), and work-up and chromatography as described in the foregoing experiment gave **47** (85 mg, 85%).

(16¹*R*)-3-Methoxy-16¹-methyl-14,16β-propano-14β-estra-1,3,5(10)-triene-16¹,17β-diol 48

(a) The 16^1-hydroxy 17-ketone **47** (100 mg, 0.28 mmol) was treated with LAH (20 mg, 0.5 mmol) in THF (3 cm^3) at 21 °C for 20 min. The product was isolated by extraction with chloroform and chromatographed on silica gel (10 g), using ethyl acetate–toluene (1 : 1) as eluent, to give the *16¹,17β-diol* **48** (93 mg, 92%), mp 226–227 °C (from Me_2CO) (Found: C, 77.6; H, 8.9%; M^+, 356. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.1%; *M*, 356); ν_{max}/cm^{-1} 3400br (OH); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.12 (1H, tdd, *J* 13.3, 3.6 × 2 and 2.8, 16^2-H_x), 1.24 (1H, td, *J* 11.4 × 2 and 2.4, 8β-H), 1.42 (3H, s, 16^1-Me), 1.60 (1H, ddd, *J* 7.3, 6.8 and 2.8, 16α-H), 1.98 (1H, d, *J* 12.7, 15β-H), 2.07 (1H, dd, *J* 12.7 and 7.3, 15α-H), 2.46 (1H, td, *J* 11.4 × 2 and 2.1, 9α-H), 2.78–2.84 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.99 (1H, d, *J* 6.8, 17α-H), 6.61 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 2.7 and 8.6, 2-H) and 7.2 (1H, d, *J* 8.6, 1-H).

(b) A solution of the 16^1-hydroxy 17-ketone **47** (60 mg, 0.17 mmol) in THF (5 cm^3) and *tert*-butyl alcohol (0.1 cm^3) was treated with 0.1 M samarium(II) iodide (4 cm^3, 0.4 mmol) at reflux for 1 h. 0.1 M Hydrochloric acid (10 cm^3) was added and the mixture was extracted with ethyl acetate. The organic phase was washed (aq. $NaHCO_3$, aq. $Na_2S_2O_3$, water, brine), dried ($MgSO_4$), and evaporated under reduced pressure. The residue (57 mg) was chromatographed on silica gel (6 g), using ethyl acetate–toluene (2 : 3) as eluent, to give the 16^1,17β-diol **48** (59 mg, 82%).

Reaction of the 3′,17-dione 46 with samarium(II) iodide

(a) 0.1 M Samarium(II) iodide (10 cm^3, 1 mmol) was added to a solution of the 3′,17-dione **46** (150 mg, 0.42 mmol) in THF (5 cm^3) at −78 °C. After 6 h at −78 °C the mixture was allowed to warm to 20 °C and was neutralised by the addition of 0.1 M hydrochloric acid (10 cm^3). The mixture was extracted with chloroform and the combined organic phase was washed (0.1 M HCl, aq. $NaHCO_3$, aq. $Na_2S_2O_3$, water) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (129 mg), which was chromatographed on silica gel (12 g), using ethyl acetate–toluene (1 : 4) as eluent, to give *(16¹S)-16¹-hydroxy-3-methoxy-16¹-methyl-14,16β-propano-14β-estra-1,3,5(10)-trien-17-one* **49** (130 mg, 87%), mp 132–134 °C (from EtOAc–MeOH) (Found: C, 77.9; H, 8.5%; M^+, 354. $C_{23}H_{30}O_3$ requires C, 78.0; H, 8.5%; *M*, 354); ν_{max}/cm^{-1} 3530 (OH), 1718 (CO); δ_H (400 MHz) 1.08 (3H, s, 13β-Me), 1.34 (3H, s, 16^1-Me), 1.62 (1H, d, *J* 12.8, 15β-H), 2.24 (1H, ddd, *J* 12.8, 6.2 and 3.2, 15α-H), 2.38 (1H, dd, *J* 6.2 and 1.8, 16α-H), 2.60 (1H, td, *J* 2 × 11.3 and 3.5, 9α-H), 2.84–2.89 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 13.8 (q, C-18), 23.5 (t, C-7), 25.1 (q, 16^1-Me), 26.0 (t, C-11), 29.8 (t, C-16^3), 30.6 (t, C-6), 30.7 (t, C-15), 30.8 (t, C-12), 36.1 (t, C-16^2), 37.4 (d, C-9), 41.95 (d, C-8), 45.9 (s, C-13), 49.7 (s, C-14), 55.2 (q, 3-OMe), 56.6 (d, C-16), 72.5 (s, C-16^1), 111.8 (d, C-2), 113.5 (d, C-4), 126.6 (d, C-1), 132.1 (s, C-10), 137.7 (s, C-5), 157.6 (s, C-3) and 224.4 (s, C-17).

(b) The foregoing reaction was conducted with **46** (200 mg, 0.56 mmol) and samarium(II) iodide (2.4 mmol) in THF (5 cm^3) at reflux for 4.5 h. Similar work-up and chromatography of the product (187 mg) on silica gel (20 g), using ethyl acetate–toluene (3 : 2) as eluent, gave *(16¹S)-3-methoxy-16¹-methyl-14,16β-propano-14β-estra-1,3,5(10)-triene-16¹,17β-diol* **50** (26 mg, 13%), mp 184–186 °C (from Me_2CO–MeOH) (Found: C, 77.6; H, 9.4%; M^+, 356. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.1%; *M*, 356); ν_{max}/cm^{-1} 3400br (OH); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 1.27 (3H, s, 16^1-Me), 1.37 (1H, d, *J* 12.7, 15β-H), 1.74 (1H, ddd, *J* 12.7, 5.7 and 3.3, 15α-H), 2.30 (1H, ddd, *J* 6.8, 5.7 and 1.8, 16α-H), 2.40 (1H, td, 2 × 11.4 and 3.3, 9α-H), 2.80–2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.11 (1H, d, *J* 6.8, 17α-H), 6.61 (1H, d, *J* 2.7, 4-H), 6.7 (1H, dd, *J* 2.7 and 8.6, 2-H) and 7.2 (1H, d, *J* 8.6, 1-H), followed by *(16¹S)-3-methoxy-16¹-methyl-14,16β-propano-14β-estra-1,3,5(10)-triene-16¹,17α-diol* **51** (137 mg, 68%), mp 197–198 °C (from Me_2CO–MeOH) (Found: C, 77.8; H, 9.2%; M^+, 356); ν_{max}/cm^{-1} 3400br (OH); δ_H (400 MHz) 1.08 (3H, s, 13β-Me), 1.23 (1H, d, *J* 12.4, 15β-H), 1.31 (3H, s, 16^1-Me), 1.44 (1H, ddd, *J* 14.1, 6.6 and 3.6, 12β-H), 1.78 (1H, d, *J* 6.0, 16α-H), 2.00 (1H, td, *J* 2 × 14.1 and 3.6, 12α-H), 2.09 (1H, ddd, *J* 12.4, 6.4 and 3.1, 15α-H), 2.29 (1H, dq, *J* 13.1 and 3 × 3.6, 11α-H), 2.46 (1H, td, *J* 2 × 11.6 and 3.6, 9α-H), 2.80 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 4.15 (1H, s, 17β-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 2.8 and 8.6, 2-H) and 7.24 (1H, d, *J* 8.6, 1-H).

Isomerisation of (16¹*S*)-16¹-hydroxy 17-ketone 49

Treatment of compound **49** (10 mg, 0.03 mmol) with methanolic 0.5 M potassium hydroxide (4 cm^3) at 20 °C for 5 h, followed by acidification and isolation by extraction with ethyl acetate, gave the pure (16¹*R*)-16¹-hydroxy 17-ketone **47** (10 mg).

Reduction of the 16¹-hydroxy 17-ketone 49

(a) A solution of the 16¹-hydroxy 17-ketone **49** (100 mg, 0.28 mmol) in THF (5 cm^3) and *tert*-butyl alcohol (0.1 cm^3) was treated with 0.1 M samarium(II) iodide (6 cm^3, 0.6 mmol) at reflux for 1 h. The product was isolated as described in the previous experiment, and chromatographed on silica gel (10 g), using ethyl acetate–toluene (3 : 2) as eluent, to give diols **50** (15 mg, 15%) and **51** (66 mg, 65%).

(b) Treatment of the 16¹-hydroxy 17-ketone **49** (30 mg, 0.08 mmol) with LAH (10 mg, 26 mmol) in THF (3 cm^3) at 21 °C for 20 min, followed by standard work-up and chromatography of the product on silica gel (5 g), using ethyl acetate–toluene (1 : 1) as eluent, gave diol **50** (23 mg, 79%).

Oxidation of the diols 50 and 51

(a) The 16¹,17β-diol **50** (52 mg, 0.14 mmol) as a solution in dry dichloromethane (5 cm^3) was treated with periodinane (650 mg, 1.6 mmol) at 20 °C for 2 h. Diethyl ether (10 cm^3) was added and the mixture was poured into aq. sodium hydrogen carbonate (10 cm^3) containing solid sodium thiosulfate (1 g). The mixture was stirred for 15 min until all the solid material had dissolved. The organic layer was separated and washed successively with aq. sodium hydrogen carbonate (20 cm^3) and water (20 cm^3), dried ($MgSO_4$), and evaporated to dryness to give a solid residue (47 mg). Recrystallisation ($CHCl_3$–MeOH) gave pure compound **49** (42 mg, 79%).

(b) Similar treatment of the 16¹,17α-diol **51** (80 mg, 0.22 mmol) gave compound **49** (69 mg, 85%).

Acknowledgements

We thank the National Research Foundation, the University of Cape Town and Schering AG for financial and material support.

References

1 J. R. Bull and R. I. Thomson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1990, 241.
2 J. R. Bull and L. M. Steer, *Tetrahedron*, 1991, **47**, 7377.
3 J. R. Bull, P. G. Mountford, G. Kirsch, G. Neef, A. Muller-Fahrnow and R. Wiechert, *Tetrahedron*, 1994, **50**, 6363.
4 J. R. Bull, C. Hoadley, P. G. Mountford and L. M. Steer, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 1179.
5 J. R. Bull and P. G. Mountford, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1581.
6 A. M. Brzozowski, A. C. W. Pike, Z. Dauter, R. E. Hubbard, T. Bonn, O. Engstrom, L. Ohman, G. L. Greene, J.-A. Gustaffson and M. Carlquist, *Nature*, 1997, **389**, 753.
7 J.-M. Wurtz, U. Egner, N. Heinrich, D. Moras and A. Muller-Fahrnow, *J. Med. Chem.*, 1998, **41**, 1803.
8 J. R. Bull, J. Floor and M. A. Sefton, *J. Chem. Soc.*, *Perkin Trans. 1*, 1987, 37.
9 J. R. Bull, J. L. M. Dillen and M. A. Sefton, *Tetrahedron*, 1990, **46**, 8143.
10 A. J. Birch and J. S. Hill, *J. Chem. Soc. C*, 1966, 419; 1967, 125; M. L. Elliot and F. J. Urban, *J. Org. Chem.*, 1985, **50**, 1752.
11 G. S. R. Subba Rao, L. Uma Devi and U. J. Sheriff, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 964; G. Mehta, K. S. Rao, M. M. Bhadbhade and K. Venkatesan, *J. Chem. Soc.*, *Chem. Commun.*, 1981, 755; G. S. R. Subba Rao, D. K. Banerjee, L. Uma Devi and U. Sheriff, *Aust. J. Chem.*, 1992, **45**, 187.
12 S. R. Wilson, *Org. React.*, 1993, **43**, 93 and references cited therein.
13 J. R. Bull, C. Grundler, H. Laurent, R. Bohlmann and A. Muller-Fahrnow, *Tetrahedron*, 1994, **50**, 6347.
14 T. Tsuda, T. Hayashi, H. Salori, T. Kawamoto and T. Saegusa, *J. Org. Chem.*, 1986, **51**, 537.
15 Competitive receptor-binding assays were conducted at the Institute of Medicinal Chemistry, Schering AG, Berlin, in accordance with standard protocols for competition with estradiol, as described by K. Lubke, E. Schillinger and M. Topert, *Angew. Chem.*, *Int. Ed. Engl.*, 1976, **15**, 741.