Synthesis of 15,15-dialkylestradiols

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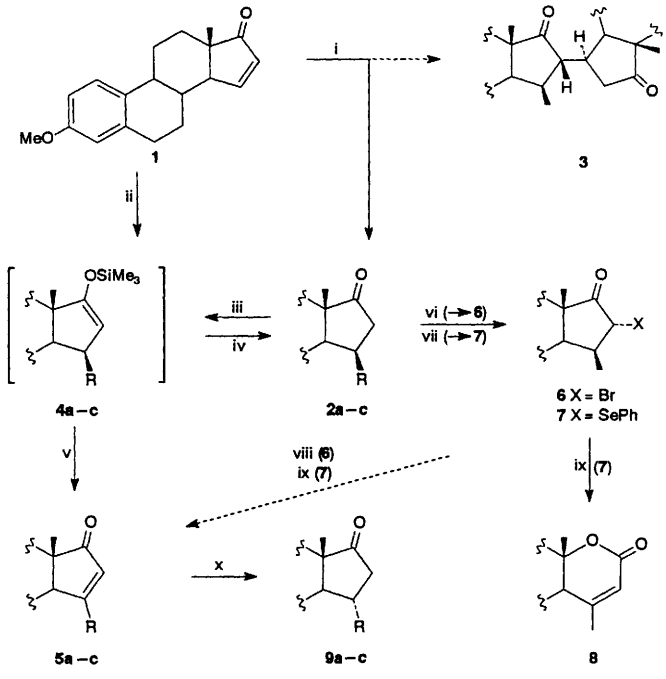
Conjugate alkylation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one 1 leads to 15β-alkyl 17-ketones 2 (Me, Et or Pr^i), which are converted, *via* palladium acetate-mediated dehydrosilylation of their derived silyl enol ethers, into the corresponding 15-alkyl Δ^{15}-17-ketones 5. Conjugate alkylation of these intermediates results in formation of 15,15-dialkyl 17-ketones 10, which undergo stereoselective reduction with lithium aluminium hydride, and deprotection of C-3 to give 15,15-dialkyl analogues 12 of estradiol. Spectroscopic data are presented to demonstrate that substrates 1 and 5 undergo exclusive 15β-alkylation.

Introduction

The finding that a 14α,17α-ethano bridge confers superior oral estrogenicity upon estradiol and estriol analogues,[1,2] has stimulated interest in studying the influence of bridged structures and alkyl residues in ring D upon biological activity of steroidal hormones. Alkyl residues at C-15 feature in numerous recent studies entailing structural modification of steroidal hormones. We were surprised not to find any evidence for previous work on the synthesis of 15,15-dialkyl steroids. As part of an investigation into structure–activity relationships in ring D-modified 19-norsteroids, the synthesis of 15,15-dialkylestradiols was undertaken. In particular, we sought a method for sequential and stereocontrolled introduction of the respective alkyl groups at C-15, in order to synthesize structural variants, upon which the influence of α- and β-face chain extension or branching on biological activity could be evaluated.

The most expeditious route to this objective appeared to require sequential conjugate alkylation–dehydrogenation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **1**. Conjugate alkylation of the resultant 15-alkyl Δ^{15}-17-ketones was expected to lead to stereodefined 15,15-dialkyl analogues of estrone 3-methyl ether and hence the target hormone analogues.

Conjugate methylation of compound **1** has been reported,[3] and there are several accounts of Michael-type additions to steroidal Δ^{15}-17-ketones leading to 15β-substituted 17-ketones.[4] Although the stereoselectivity of these conjugate additions is reportedly high, a recent paper[5] has claimed a significant loss of stereoselectivity accompanying copper-catalysed Grignard reaction of chain-extended nucleophiles to enone **1**. Furthermore, it was argued[5] that the major reaction pathway entails 15α-alkylation, in apparent contradiction of the conclusions reached in earlier investigations.



Scheme 1 *Reagents and conditions:* i, Me_2CuLi, 0 °C (R = Me) or RMgX, CuI, 0–20 °C (R = Et, Pr^i); ii, Me_2CuLi, Me_3SiCl, −78 °C (R = Me); iii, LDA, Me_3SiCl, −78 to 20 °C; iv, 1 mol dm^{-3} HCl, 20 °C; v, $Pd(OAc)_2$, MeCN, reflux; vi, $CuBr_2$, MeOH, C_6H_6, reflux; vii, LDA, Me_3SiCl, −78 to 20 °C; then C_6H_5SeCl, BF_3·Et_2O; viii, LiBr, Li_2CO_3, DMF, reflux; ix, H_2O_2, C_5H_5N, CH_2Cl_2, 0–20 °C; x, Li, NH_3

Results and discussion

In the first instance, we re-examined conjugate methylation of the Δ^{15}-17-ketone **1**, with the intention of applying recent adaptations of organocuprate methodology in order to trap the 15β-methyl enolate intermediate for subsequent dehydrogenation to the 15-methyl Δ^{15}-17-ketone **5a**. Treatment of enone **1** with lithium dimethylcuprate(I) proceeded rapidly in dry tetrahydrofuran (THF) at 0 °C to give the 15β-methyl 17-ketone **2a** (60%) accompanied by a product (31%) formulated as the bisteroid **3** (Scheme 1). The properties of compound **2a** accord with those reported in previous studies,[3] and the assignment of the 15-configuration was rigorously established (see below). The oily bisteroid **3** displayed NMR characteristics consistent with the assigned structure, and was independently synthesized through treatment of the 15β-methyl 17-ketone **2a** with lithium diisopropylamide (LDA) in THF at 0 °C, followed by addition of the Δ^{15}-17-ketone **1**. The configurational assignments at C-16 and C-15′ in dimer **3** could not be verified but are stereoelectronically appropriate.

Competing substrate–product condensations appear to be rare during organocuprate reactions with enones,[6] and the facility of this process here reflects the unusually high Michael electrophilicity of the Δ^{15}-17-ketone **1**. Attempts to suppress formation of this undesired by-product by very slow addition of enone **1** to lithium dimethylcuprate(I) in THF at −78 °C were only partially successful, leading to the required addition product **2a** (82%) and dimer **3** (13%). However, when the reaction was conducted in THF at −78 °C, in the presence of boron trifluoride–diethyl ether complex or chlorotrimethylsilane and triethylamine, conjugate methylation proceeded

cleanly and efficiently ($\geq 90\%$). The silyl enol ether intermediate **4a** obtained in the latter experiment was hydrolysed during work-up in order to simplify comparative studies, but could be used directly for subsequent transformations (see below).

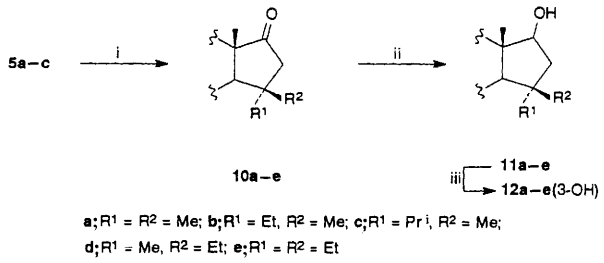
Cognate syntheses of the 15β-ethyl and 15β-isopropyl 17-ketones **2b** and **2c** proceeded efficiently and stereoselectively using appropriate variations of copper-catalysed Grignard methodology on the Δ^{15}-17-ketone **1**. Further conversion of the 15β-alkyl 17-ketones **2** into the corresponding 15-alkyl Δ^{15}-17-ketones **5** was readily achieved through dehydrosilylation[7] of the derived silyl enol ethers **4** (directly isolated in the case of compound **4a**, otherwise ohtained through low-temperature trapping of LDA-generated enolates of compounds **2** with chlorotrimethylsilane) in the presence of palladium(II) acetate in refluxing acetonitrile. The overall efficiency of conversion of the Δ^{15}-17-ketone **1** into the corresponding 15-alkyl Δ^{15}-17-ketones **5** was 75% or better.

Other methods for achieving formal dehydrogenation of the 15β-methyl 17-ketone **2a** were briefly examined and discarded. For example, bromination of compound **2a** proceeded efficiently with copper(II) bromide in refluxing benzene–methanol (1 : 1) to give a single product formulated as the 16α-bromo compound **6** (82%). The structure of product **6** was evident from distinctive ^{1}H NMR signals at δ 2.75 (1 H, quint d, J 4 × 7.7 and 1.8 Hz) and 4.37 (1 H, d, J 1.8 Hz), which defined the relative orientation of the 15- and 16-substituents, and is, incidentally, uniquely compatible with 15β-methyl configuration. However, the unfavourable orientation of the 16-substituent for elimination was confirmed by treatment of compound **6** with lithium carbonate–lithium bromide in refluxing dimethylformamide (DMF), which proceeded slowly to give a poor yield of the 15-methyl Δ^{15}-17-ketone **5a** (13%) accompanied by uncharacterised isomeric material. Since a *syn*-elimination protocol might be expected to proceed more favourably, the silyl enol ether **4a** was treated with benzeneselenenyl chloride and boron trifluoride–diethyl ether complex in dry THF (−78 to 0 °C) to give the non-crystalline 16α-phenylselanyl 17-ketone **7**. However, *in situ* treatment of the reaction mixture with hydrogen peroxide at 25 °C resulted in only a moderate yield of the 15-methyl Δ^{15}-17-ketone **5a** (40%), accompanied by a product formulated as the unsaturated δ-lactone **8** (45%) on the basis of spectroscopic data and analogy.[8] It is noteworthy, however, that selenide **7** appears to be less susceptible to the secondary Baeyer–Villiger oxidation than does the analogous intermediate derived from estrone 3-methyl ether, which gave only the corresponding unsaturated lactone.[8]

The foregoing results clearly demonstrate the superiority of the conjugate alkylation–dehydrosilylation sequence for the preparation of the 15-alkyl Δ^{15}-17-ketones **5**. In an additional series of experiments, it was shown that reduction of these products **5** with lithium in liquid ammonia–THF proceeds efficiently and stereoselectively to give the corresponding 15α-alkyl 17-ketones **9**, which proved useful in comparative spectroscopic studies (see below).

With the 15-alkyl Δ^{15}-17-ketones **5a–c** in hand, conjugate methylations were conducted using lithium dimethylcuprate(I) or methylmagnesium iodide in the presence of copper(I) iodide, to give the corresponding 15,15-dialkyl 17-ketones **10a–c** (Scheme 2). Similarly, conjugate ethylation of the 15-methyl Δ^{15}-17-ketone **5a** and of the 15-ethyl Δ^{15}-17-ketone **5b** gave the 15β-ethyl-15α-methyl 17-ketone **10d** and the 15,15-diethyl 17-ketone **10e** respectively. These reactions proceeded efficiently (80%), and the high stereoselectivity during formation of products **10b–d** was evident from the purity of the products isolated. Spectroscopic evidence (see below) supported the assumption of β-directed alkylation of the 15-alkyl Δ^{15}-17-ketones **5**.

Hydride reduction of the 17-ketones **10a–e** gave the corresponding 17β-alcohols **11a–e**. These reactions were



Scheme 2 *Reagents and conditions:* i, Me_2CuLi, 0 °C (R = Me, **10a–c**) or EtMgBr, CuI (R = Et, **10d–e**); ii, LAH, 0 °C; iii, DIBAH, C_6H_5Me, reflux

uniformly efficient and stereoselective, and the configurational assignments at C-17 were readily deduced from characteristic signals for the 17α-proton at δ 3.54–3.74 (typically, dd, J ~9 and 8 Hz). The 17β-alcohols **11a–e** were deprotected at C-3 [diisobutylaluminium hydride (DIBAH) in refluxing toluene[9]] to give the 15,15-dialkyl analogues **12a–e** of estradiol. These compounds have been subjected to biological evaluation,* which has revealed that not only does the 15,15-dimethyl compound **12a** display highly competitive binding to the estradiol receptor, but that it is also an orally active estrogen. By contrast, the homologues **12b–d** display severely diminished affinity toward the estradiol receptor, a result which has intriguing implications for structure–activity relationships in this series. Further investigations are in progress.

The configurational assignments made in this study rely upon the well established precedent for stereoelectronically favoured 15β-alkylation of the Δ^{15}-17-ketone **1**,[3,4] and the reasonable assumption that this stereoselectivity also prevails during conjugate alkylation of the corresponding 15-alkyl Δ^{15}-17-ketones **5**. The claimed anomaly,[5] of favoured 15α-alkylation during copper(I)-catalysed addition of extended-chain Grignard reagents to compound **1**, prompted an examination of the spectroscopic data for the 15-alkyl 17-ketones **2** and **9** and the corresponding 15,15-dialkyl 17-ketones **10**, for evidence to support the configurational assignments.

A selection of ^{1}H NMR data for the 15-alkyl and 15,15-dialkyl 17-ketones (Table 1) revealed self-consistent patterns of chemical shifts and coupling constants for the 15β- and 15α-alkyl isomers. The 16-H_2 signals of the 15β-alkyl 17-ketones **2a–c** resonated within a narrow range (δ ~2.3–2.5) and, although their near-coalescence and signal overlap in the case of the 15β-methyl 17-ketone **2a** precluded extraction of first-order data, a chemical-shift correlation (COSY) plot revealed the coupling connectivity of the 8-, 14-, 15- and 16-protons and confirmed the assignment of $J_{14\alpha,15\alpha}$ 6.8 Hz. This requires a near-*gauche* relationship between 14α- and 15-H and, necessarily, a β-configuration for the 15-methyl group. By contrast, the 14α-H signals in the 15α-alkyl 17-ketones **9a–c** revealed $J_{14\alpha,15\beta}$-values of ~10.8 Hz arising from the antiperiplanar relationship between 14α- and 15β-H.

The ^{1}H NMR data for the 15,15-dialkyl ketones **10a–e** uncovered no direct evidence for confirmation of the 15-configuration of the isomers **10b–d** and hence, the assumed, β-entry of reagent during conjugate alkylation of the 15-alkyl Δ^{15}-17-ketones **5a–c**. The ^{13}C NMR data for the 15-alkyl 17-ketones (Table 2) were generally self-consistent, and displayed the expected α-, β- and γ-shifts associated with 15-substitution, but were not amenable to additive estimates of ^{13}C chemical shifts in the 15,15-dialkyl 17-ketones. This is probably attributable to variation in rotameric preferences of the 15-ethyl and 15-isopropyl groups in response to mono- or di-substitution at C-15.

The most compelling evidence for the assigned structures of

* Performed at the Institute of Medicinal Chemistry, Schering AG, Berlin.

Table 1 Selected ^{1}H NMR data for 15-alkyl and 15,15-dialkyl 17-ketones

Compound	Signal [a]			
	13β-Me	14α-H	16α-H	16β-H
2a 15β-Me	1.07	168 (dd, 11.3, 6.8)	2.51 obsc.	2.30 obsc.
2b 15β-Et	1.02	1.73 (m)	2.43 (dd, 19.4, 7.8)	2.37 (dd, 19.4, 2.5)
2c 15β-Pr^i	1.08	1.77 (dd, 11.8, 6.0)	2.44 (dd, 19.2, 7.0)	2.38 (dd, 19.2, 3.1)
9a 15α-Me	0.95	1.22 (t, 2 × 10.8)	1.73 (dd, 19.3, 8.4)	2.77 (dd, 19.3, 8.7)
9b 15α-Et	0.97	1.29 (t, 2 × 10.7)	1.79 (dd, 19.4, 7.9)	2.78 (dd, 19.4, 8.8)
9c 15α-Pr^i	0.97	1.45 (t, 2 × 10.8)	1.95 (dd, 18.5, 7.7)	2.42 (dd, 18.5, 8.5)
10a 15,15-Me$_2$	1.10	1.47 (d, 10.9)	2.09 (d, 19.4)	2.61 (d, 19.4)
10b 15α-Et, 15β-Me	1.12	1.48 (d, 11.0)	2.18 (d, 19.4)	2.44 (d, 19.4)
10c 15α-Pr^i, 15β-Me	1.13	1.49 (d, 10.1)	2.20 (d, 19.4)	2.26 (d, 19.4)
10d 15α-Me, 15β-Et	1.09	1.49 (d, 10.1)	1.87 (d, 19.3)	2.80 (d, 19.3)
10e 15,15-Et$_2$	1.10	1.49 (d, 10.1)	1.95 (d, 19.6)	2.64 (d, 19.6)

[a] Given as chemical shift δ/ppm (multiplicity, J/Hz); operational details are described in the Experimental section.

the 15,15-dialkyl compounds was obtained through comparison of the nuclear Overhauser enhancement (NOESY) spectra of the epimers **10b** and **10d**. The 15α-ethyl 15β-methyl 17-ketone **10b** displayed cross-peaks for 16β-H/15β-Me and 16α-H/15α-CH_2Me, whereas the 15β-ethyl 15α-methyl 17-ketone **10d** displayed cross-peaks for 13β-Me/15β-CH_2Me and 16α-H/15α-Me. These NOEs can arise through only *syn*-relationships between the interacting protons.

An examination of the chiroptical properties of the 15-alkyl and 15,15-dialkyl 17-ketones was also undertaken, in search of a diagnostic probe for configurational assignments. However, CD data (Table 3) revealed that the influence of different 15-alkyl groups upon the magnitude of the Cotton effect for the 17-CO group is variable. Thus, the negative increment of $\Delta\Delta\varepsilon$ − 0.59 for the 15β-methyl 17-ketone **2a** accords with the predicted magnitude of an octant-dissignate contribution by a β-removed axial methyl group in conformationally comparable cyclopentanones,[10] whereas that of the 15β-ethyl 17-ketone **2b** is also octant-dissignate but attenuated. By contrast, the increment for the 15β-isopropyl 17-ketone **2c** is strongly octant-consignate. The 15α-alkyl 17-ketones **9a–c** all display *negative*, therefore octant-consignate increments, but that of the 15α-isopropyl 17-ketone **9c** is amplified.

Despite these variations, the summed increments for the appropriate pairs of epimeric 15-alkyl 17-ketones were compared with those observed for the corresponding 15,15-dialkyl 17-ketones, in an attempt to discern an empirically useful trend in support of configurational assignments. However, the correlation is tenuous (Table 3), and clearly inadequate for the intended purpose. The uncertain effect of chain extension or branching upon the 'β-alkyl effect' in cyclopentanones,[10] and the attendant influence of monoalkyl *vs.* dialkyl substitution upon rotameric preferences of the 15-ethyl and 15-isopropyl group, evidently detract from the reliability of this method for configurational assignment in the limited number of compounds examined here.

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; CD, JASCO J-20, methanol solutions. 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)

Conjugate alkylations of 3-methoxyestra-1,3,5(10),15-tetraen-17-one 1

(**a**) Ethereal 1.4 mol dm^{-3} methyllithium (26 cm^3, 36.4 mmol) was added to a stirred slurry of copper(I) iodide (3.43 g, 18.0 mmol) in dry diethyl ether (20 cm^3) at 0 °C. To the resultant clear solution of lithium dimethylcuprate(I) was added a solution of the Δ^{15}-17-ketone **1** (4.24 g, 15.0 mmol) in dry tetrahydrofuran (THF) (100 cm^3). The mixture was stirred at 0 °C for 15 min, then saturated aq. NH_4Cl (60 cm^3) was added. The residue (4.38 g) obtained upon work-up (EtOAc) comprised two components (TLC). Chromatography on silica gel (200 g) with ethyl acetate–hexane (1:4) as eluent gave 3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **2a** (2.70 g, 60%), mp 127–129 °C (from Me_2CO–MeOH) (lit.,[3] 122–124 °C); $[\alpha]_D$ +74 (*c* 1.0, $CHCl_3$) (Found: C, 80.7; H, 8.6; M$^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; M, 298); $\Delta\varepsilon_{max}$ +2.83 (295 nm); ν_{max}/cm^{-1} 1725 (CO); δ_H(400 MHz) 1.07 (3 H, s, 13β-Me), 1.16 (3 H, d, *J*, 7.4, 15β-Me), 1.68 (1 H, dd, *J* 11.3 and 6.8, 14α-H), 1.75 (1 H, qd, *J* 3 × 11.3 and 2.9, 8β-H), 1.89 (1 H, dt, *J* 11.6 and 2 × 2.3, 12β-H), 2.09 (1 H, ddt, *J* 12.7, 5.7 and 2 × 2.9, 7β-H), 2.30 and 2.51 (each 1 H, obsc m, 16-H$_2$), 2.55 (1 H, m, 15α-H), 2.91 (2 H, m, 6-H$_2$), 3.79 (3 H, s, 3-OMe), 6.69 (1 H, d, *J* 2.7, 4-H), 6.73 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H), followed by 3-*methoxy*-16α-[3-*methoxy*-17-*oxoestra*-1,3,5(10)-*trien*-15β-*yl*]-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **3** (1.36 g; 31%) as an oil, $[\alpha]_D$ +131 (*c* 1.0, $CHCl_3$) (Found: C, 80.2; H, 8.4; M$^+$, 580. $C_{39}H_{48}O_4$ requires C, 80.65; H, 8.3%; M, 580); ν_{max}/cm^{-1} 1727 (CO); δ_H(200 MHz) 1.05 and 1.11 (each 3 H, s, 13β- and 13′β-Me), 1.18 (3 H, d, *J* 7.4, 15β-Me), 2.91 (4 H, m, 6- and 6′-H$_2$), 3.81 (6 H, s, 3- and 3′-OMe), 6.69 (2 H, d, *J* 2.7, 4- and 4′-H), 6.73 (2 H, dd, *J* 8.6 and 2.7, 2- and 2′-H) and 7.21 (2 H, d, *J* 8.6, 1- and 1′-H); δ_C(50 MHz) 16.4 (q, 15β-Me) 17.2 and 19.0 (q, C-18 and -18′), 25.6 (t, C-11 and -11′), 26.7 and 26.8 (t, C-7 and -7′), 29.3 and 29.4 (t, C-6 and -6′), 33.9 (d, C-15 and -15′), 34.2 and 35.0 (t, C-12 and -12′), 35.5 and 35.8 (d, C-8 and -8′), 36.2 and 41.6 (t, C-16 and -16′) 44.4 and 44.9 (d, C-9 and -9′), 46.6 and 47.5 (s, C-13 and -13′), 51.9 and 54.5 (d, C-14 and -14′), 55.2 (q, 3- and 3′-OMe), 111.4 and 111.5 (d, C-2 and -2′), 113.9 (d, C-4 and -4′), 125.9 (d, C-1 and -1′), 132.2 and 132.3 (s, C-10 and -10′), 137.6 and 138.0 (s, C-5 and -5′), 157.7 (s, C-3 and -3′) and 221.2 and 221.6 (s, C-17 and -17′).

(**b**) A solution of lithium dimethylcuprate(I) (0.63 mmol) in dry diethyl ether (1 cm^3) [prepared from copper(I) iodide (120 mg, 0.63 mmol) and ethereal 1.6 mol dm^{-3} methyllithium (0.75 cm^3, 1.20 mmol)] was cooled to −78 °C. Triethylamine (0.1 cm^3, 0.8 mmol) and chlorotrimethylsilane (0.1 cm^3, 0.72 mmol) were added, followed by a solution of the Δ^{15}-17-ketone **1** (84 mg, 0.30 mmol) in dry THF (4 cm^3). After 5 min at −78 °C the

Table 2 ^{13}C NMR Data for 15-alkyl and 15,15-dialkyl compounds

Compound	Chemical shift (δ_C)																			
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	3-OMe	Other
17-Ketones																				
2a 15β-Me	126.0	111.4	157.7	113.9	137.8	29.5	26.8	36.0	44.5	132.5	25.6	34.1	47.5	52.3	27.7	44.8	221.3	17.9	55.2	17.0 (15β-Me)
2b 15β-Et	126.0	111.4	157.7	113.9	137.8	29.5	26.8	36.0	44.6	132.4	25.6	34.0	47.1	52.9	36.5	42.2	221.4	17.8	55.2	13.9 (15β-CH_2*Me*), 23.8 (15β-*C*H_2Me)
2c 15β-Pr^i	126.0	111.4	157.7	113.9	137.9	29.5	28.2	32.3	45.0	132.4	25.4	34.8	46.5	55.5	45.5	42.4	220.8	17.4	55.2	21.8, 24.3 (15β-CH*Me*$_2$), 38.0 (15β-*C*HMe$_2$)
9a 15α-Me	126.7	111.7	157.5	113.5	137.4	29.8	26.5	39.6	44.2	131.9	27.7	31.7	50.8	57.2	30.8	47.5	220.1	15.8	55.2	22.0 (15α-Me)
9b 15α-Et	126.8	111.8	157.5	113.5	137.4	29.9	27.8	37.8	44.2	131.9	26.5	31.6	50.3	54.5	39.7	42.7	220.2	15.7	55.2	12.4 (15α-CH_2*Me*), 30.0 (15α-*C*H_2Me)
9c 15α-Pr^i	126.8	111.7	157.5	113.5	137.4	30.1	27.4	39.9	44.4	132.0	26.4	31.8	50.1	50.6	41.7	35.7	220.1	15.6	55.2	14.9, 27.7 (15α-CH*Me*$_2$), 28.5 (15α-*C*HMe$_2$)
10a 15,15-Me$_2$	126.4	111.6	157.6	113.6	137.4	29.8	28.2	37.5	44.9	132.2	26.0	34.2	50.2	58.4	35.5	53.6	221.4	17.9	55.2	24.5, 34.6 (15,15-Me$_2$)
10b 15α-Et, 15β-Me	126.5	111.6	157.6	113.6	137.4	29.9	28.3	37.8	44.9	132.2	26.1	34.2	50.0	56.6	38.9	49.8	220.4	18.2	55.2	9.4 (15α-CH_2*Me*), 21.8 (15α-*C*H_2Me), 30.3 (15β-Me)
10c 15α-Pr^i, 15β-Me	126.4	111.6	157.6	113.6	137.4	30.0	27.8	37.7	45.0	132.3	26.1	34.5	49.9	51.6	41.5	44.6	220.3	17.8	55.2	18.4, 18.8 (15α-CH*Me*$_2$), 23.0 (15β-Me), 36.9 (15α-*C*HMe$_2$)
10d 15α-Me, 15β-Et	126.4	111.6	157.6	113.6	137.4	29.8	28.6	37.3	45.1	132.3	27.4	34.4	49.8	59.8	39.4	48.9	220.3	18.3	55.2	9.0 (15β-CH_2*Me*), 25.9 (15β-*C*H_2Me), 30.3 (15α-Me)
10e 15,15-Et$_2$	126.4	111.6	157.6	113.6	137.4	29.9	27.8	37.5	45.0	132.3	25.9	34.3	49.5	52.6	42.1	44.7	220.5	18.3	55.2	9.1 (2 × 15-CH_2*Me*), 28.1, 32.7 (2 × 15-*C*H_2Me)
Δ^{15}-17-Ketones																				
5a 15-Me	126.1	111.5	157.7	113.6	137.3	29.2	27.7	36.8	45.2	132.0	25.6	29.4	52.6	57.3	175.2	128.7	212.1	21.5	55.2	20.9 (15-Me)
5b 15-Et	126.2	111.6	157.5	113.6	137.3	29.4	27.3	37.0	45.3	132.1	25.6	28.0	52.6	57.0	181.1	125.7	212.2	21.5	55.2	11.6 (15-CH_2*Me*), 29.2 (15-*C*H_2Me)
5c 15-Pr^i	126.3	111.6	157.7	113.6	137.2	29.1	28.1	30.8	45.4	132.2	25.6	29.7	52.6	56.3	185.7	123.9	212.4	21.1	55.2	21.6, 21.7 (15-CH*Me*$_2$), 30.3 (15-*C*HMe$_2$)
17β-Alcohols																				
11a 15,15-Me$_2$	126.3	111.4	157.5	113.6	137.7	29.9	28.5	37.1	44.9	132.9	26.1	38.8	45.6	58.1	36.2	50.1	79.8	13.5	55.2	25.6, 35.0 (15,15-Me$_2$)
11b 15α-Et, 15β-Me	126.3	111.4	157.5	113.6	137.7	29.9	28.6	37.1	45.0	133.0	26.1	38.9	45.3	55.6	39.7	45.6	80.2	13.9	55.2	9.4 (15α-CH_2*Me*), 23.7 (15β-Me), 37.7 (15α-*C*H_2Me)
11c 15α-Pr^i, 15β-Me	126.3	111.4	157.7	113.6	137.6	29.9	28.5	37.3	45.0	133.0	26.2	39.3	44.7	51.8	42.7	40.7	80.8	14.1	55.2	18.2, 18.6 (15α-CH*Me*$_2$), 23.1 (15β-Me), 36.6 (15α-*C*HMe$_2$)
11d 15α-Me, 15β-Et	126.2	111.4	157.5	113.6	137.7	29.9	28.6	36.8	45.2	133.0	25.9	39.0	45.3	59.6	40.0	45.4	80.0	13.9	55.2	8.6 (15β-CH_2*Me*), 29.0 (15α-Me), 30.3 (15β-*C*H_2Me)
11e 15,15-Et$_2$	126.2	111.4	157.5	113.6	137.7	29.8	28.6	36.9	44.7	133.1	26.0	39.2	45.1	51.2	43.1	41.6	80.7	14.2	55.2	8.3, 9.2 (2 × 15-CH_2*Me*), 28.7, 31.9 (2 × 15-*C*H_2Me)

Table 3 CD data for the 15-alkyl and 15,15-dialkyl 17-ketones[a]

Compound	$\Delta\varepsilon(\lambda_{max}/nm)$[a]	Substituent effect ($\Delta\Delta\varepsilon$)	
		Observed[b]	Calculated[c]
2a 15β-Me	+2.83 (295)	−0.59	
2b 15β-Et	+3.22 (294)	−0.20	
2c 15β-Pr^i	+4.69 (296)	+1.27	
9a 15α-Me	+2.70 (295)	−0.72	
9b 15α-Et	+2.94 (292)	−0.48	
9c 15α-Pr^i	+1.70 (293)	−1.72	
10a 15,15-Me_2	+2.08 (295)	−1.34	−1.31
10b 15α-Et, 15β-Me	+2.18 (294)	−1.24	−1.07
10c 15α-Pr^i, 15β-Me	+1.85 (293)	−1.57	−2.31
10d 15α-Me, 15β-Et	+2.30 (294)	−1.12	−0.92
10e 15,15-Et_2	+2.99 (293)	−0.43	−0.68

[a] Measured for solutions in methanol; operational details are given in the Experimental section. [b] Derived by taking the difference from $\Delta\varepsilon$ + 3.42 (296 nm) for 3-methoxyestra-1,3,5(10)-trien-17-one. [c] Derived by adding observed $\Delta\Delta\varepsilon$-values for discrete monoalkyl parents.

mixture was treated with saturated aq. NH_4Cl (5 cm^3) and 1 mol dm^{-3} hydrochloric acid (3 cm^3). The reaction mixture was stirred at 20 °C for 15 min. The residue (72 mg) obtained upon work-up (EtOAc) was chromatographed on silica gel (6 g), eluted with ethyl acetate–toluene (1:4), to give the 15β-methyl 17-ketone **2a** (82 mg, 92%).

(**c**) Copper(I) iodide (119 mg, 0.62 mmol) was added to a solution of ethylmagnesium iodide (6.25 mmol) [prepared from reaction of iodoethane (0.5 cm^3) with magnesium (150 mg)] in dry diethyl ether (1.5 cm^3) at 0 °C. A solution of the Δ^{15}-17-ketone **1** (340 mg, 1.20 mmol) in dry THF (10 cm^3) was added slowly at 20 °C to the stirred solution. After 10 min at 20 °C the mixture was cooled to 0 °C, and saturated aq. NH_4Cl (10 cm^3) was added. Work-up (EtOAc) followed by crystallisation of the residue (341 mg) from $CHCl_3$–MeOH gave 15β-*ethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **2b** (326 mg, 87%), mp 125–129 °C; $[\alpha]_D$ +85 (*c* 0.95, $CHCl_3$) (Found: C, 80.6; H, 8.9; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312); $\Delta\varepsilon_{max}$ +3.22 (294 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H(400 MHz) 0.95 (3 H, t, *J* 2 × 7.5, 15β-CH_2Me), 1.02 (3 H, s, 13β-Me), 1.34 and 1.65 (each 1 H, m, 15β-CH_2Me), 1.73 (1 H, m, 14α-H), 1.90 (1 H, dt, *J* 11.7 and 2 × 2.4, 12β-H), 2.06 (1 H, ddt, *J* 12.6, 5.5 and 2 × 2.9, 7β-H), 2.16–2.25 (1 H, m, 15α-H), 2.29 (1 H, td, *J* 2 × 10.6 and 3.7, 9α-H), 2.37 (1 H, dd, *J* 19.4 and 2.5, 16β-H), 2.43 (1 H, dd, *J* 19.4 and 7.8, 16α-H), 2.92 (2 H, m, 6-H_2), 3.79 (3 H, s, 3-OMe), 6.66 (1 H, d, *J* 2.9, 4-H), 6.72 (1 H, dd, *J* 8.4 and 2.9, 2-H) and 7.20 (1 H, d, *J* 8.4, 1-H).

(**d**) Copper(I) iodide–dimethyl sulfide (215 mg, 0.85 mmol) and hexamethylphosphoric triamide (HMPA) (2.0 cm^3, 11.5 mmol) were added to a solution of isopropylmagnesium bromide (8.50 mmol) [prepared at 0 °C from magnesium (204 mg) and 2-bromopropane (0.8 cm^3)] in dry diethyl ether (10 cm^3) at 0 °C. After 5 min at 0 °C the stirred mixture was slowly treated with a solution of the Δ^{15}-17-ketone **1** (500 mg, 1.77 mmol) and chlorotrimethylsilane (1.6 cm^3, 12.6 mmol) in dry THF (10 cm^3). After 20 min at 0 °C the mixture was treated with saturated aq. NH_4Cl (20 cm^3) and aq. ammonia (10 cm^3). Work-up (EtOAc) and chromatography of the residue (581 mg) on silica gel (50 g) with EtOAc–toluene (1:49) as eluent, gave 15β-*isopropyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **2c** (508 mg, 88%), mp 104–108 °C (from Pr^i_2O); $[\alpha]_D$ +106 (*c* 1.0, $CHCl_3$) (Found: C, 80.5; H, 9.3; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326); $\Delta\varepsilon_{max}$ +4.69 (296 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H(400 MHz) 0.96 and 1.10 (each 3 H, d, *J* 6.4, 15β-$CHMe_2$), 1.08 (3 H, s, 13β-Me), 1.43 (1 H, qd, *J* 3 × 13.1 and 3.8, 7α-H), 1.77 (1 H, dd, *J* 11.8 and 6.0, 14α-H), 1.92 (1 H, dt, *J* 9.6 and 2 × 3.1, 12β-H), 2.22 (1 H, td, *J* 2 × 10.6 and 4.4, 9α-H), 2.30 (1 H, ddt, *J* 13.1, 5.7 and 2 × 2.9, 7β-H), ~2.38 obsc (1 H, dd, *J*, 19.2 and 3.1, 16β-H), 2.44 (1 H, dd, *J* 19.2 and 7.0, 16α-H), 2.89 (2 H, m, 6-H_2), 3.79 (3 H, s, 3-OMe), 6.66 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.4 and 2.8, 2-H) and 7.20 (1 H, d, *J* 8.4, 1-H).

15-Alkyl-3-methoxyestra-1,3,5(10),15-tetraen-17-ones 5

(**a**) A solution of LDA (5.28 mmol) in THF (4 cm^3) [prepared at 0 °C from diisopropylamine (1.5 cm^3, 10.58 mmol) in dry THF (4 cm^3) and 1.6 mol dm^{-3} butyllithium (3.3 cm^3, 5.28 mmol)] was cooled to −78 °C and a solution of the 15β-methyl 17-ketone **2a** (315 mg, 1.05 mmol) in dry THF (5 cm^3) was added slowly. The mixture was stirred at −78 °C for 30 min, then chlorotrimethylsilane (1.4 cm^3, 11.0 mmol) was added and the mixture was allowed to warm to 20 °C. After 15 min at 20 °C the mixture was cooled to 0 °C and saturated aq. NH_4Cl (10 cm^3) was added. Work-up (EtOAc) gave the crude silyl enol ether **4a** (385 mg), which was dissolved in acetonitrile (10 cm^3). Palladium(II) acetate (233 mg, 1.04 mmol) was added, and the mixture was refluxed for 15 min, then cooled to 20 °C, filtered, and concentrated under reduced pressure to give a dark crystalline product (484 mg). Chromatography on silica gel (24 g) with EtOAc–toluene (1:19) as eluent gave 3-*methoxy*-15-*methylestra*-1,3,5(10),15-*tetraen*-17-*one* **5a** (267 mg, 86% from **2a**), mp 156–158 °C (from EtOAc–MeOH); $[\alpha]_D$ −17 (*c* 1.0, $CHCl_3$) (Found: C, 81.3; H, 8.15; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; M, 296); ν_{max}/cm^{-1} 1688 (CO); δ_H(200 MHz) 1.11 (3 H, s, 13β-Me), 2.25 (3 H, s, 15-Me), 2.94 (2 H, m, 6-H_2), 3.79 (3 H, s, 3-OMe), 5.77 (1 H, br s, 16-H), 6.66 (1 H, d, *J* 2.5, 4-H), 6.75 (1 H, dd, *J* 8.6 and 2.5, 2-H) and 7.23 (1 H, d, *J* 8.6, 1-H).

(**b**) A solution of lithium dimethylcuprate(I) (5.41 mmol) in dry diethyl ether (5 cm^3) was prepared as described previously. The reagent was cooled to −78 °C, and triethylamine (0.75 cm^3, 5.40 mmol) and chlorotrimethylsilane (0.7 cm^3, 5.50 mmol) were added, followed by the Δ^{15}-17-ketone **1** (1.0 g, 3.55 mmol) in dry THF (10 cm^3). After the mixture had been kept for 15 min at −78 °C, saturated aq. NH_4Cl (20 cm^3) was added. Work-up (EtOAc) gave crude silyl enol ether **4a** as an oil (1.51 g), which was treated with palladium(II) acetate (770 mg, 3.43 mmol) in acetonitrile (30 cm^3) as described in the foregoing experiment, to yield the 15-methyl Δ^{15}-17-ketone **5a** (861 mg, 82% from **1**).

(**c**) Successive silyl enol ether formation and dehydrosilylation of the 15β-ethyl 17-ketone **2b** (495 mg, 1.58 mmol), as described for compound **2a** [exp. (**a**), above], gave 15-*ethyl*-3-*methoxyestra*-1,3,5(10),15-*tetraen*-17-*one* **5b** (419 mg, 85% from **2b**), mp 103–106 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −14 (*c* 0.9, $CHCl_3$) (Found: C, 81.1; H, 8.5; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; M, 310); ν_{max}/cm^{-1} (CO) 1689; δ_H(400 MHz) 1.11 (3 H, s, 13β-Me), 1.20 (3 H, t, *J* 2 × 7.6, 15-CH_2Me), 2.40 (2 H, m, 15-CH_2Me), 2.94 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 5.79 (1 H, br s, 16-H), 6.64 (1 H, d, *J* 2.8, 4-H), 6.73 (1 H, dd, *J* 8.3 and 2.8, 2-H) and 7.22 (1 H, d, *J* 8.3, 1-H).

(**d**) Similar treatment of the 15β-isopropyl 17-ketone **2c** (521 mg, 1.60 mmol) gave 15-*isopropyl*-3-*methoxyestra*-1,3,5(10),15-*tetraen*-17-*one* **5c** (441 mg, 85% from **2c**), mp 113–116 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ −18 (*c* 1.0, $CHCl_3$) (Found: C, 81.6; H, 8.9; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; M, 324); ν_{max}/cm^{-1} 1690 (CO); δ_H(200 MHz) 1.10 (3 H, s, 13β-Me), 1.16 and 1.22 (each 3 H, d, *J* 2 × 6.6, 15-$CHMe_2$), 2.57 (1 H, dd, *J* 11.2 and 2.7, 14α-H), 2.92 (2 H, m, 6-H_2), 3.79 (3 H, s, 3-OMe), 5.80 (1 H, dd, *J* 2.7 and 1.2, 16-H), 6.65 (1 H, d, *J* 2.7, 4-H), 6.74 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1 H, d, *J* 8.6, 1-H).

(**e**) A mixture of the 15β-methyl 17-ketone **2a** (190 mg; 0.64 mmol) and copper(II) bromide (360 mg; 1.61 mmol) in methanol–benzene (1:1; 20 cm^3) was refluxed for 50 min. The warm reaction mixture was filtered (Celite) and the filtrate was concentrated under reduced pressure. Water (20 cm^3) was added and the standard work-up ($CHCl_3$) gave a yellow-brown crystalline product (222 mg), which was chromatographed on silica gel (10 g) with toluene as eluent, to yield 16α-*bromo*-

3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **6** (198 mg, 82%), mp 162–165 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +71 (*c* 1.0, $CHCl_3$) [Found: C, 63.3; H, 6.6; M^+, 376/378 (1:1). $C_{20}H_{25}BrO_2$ requires C, 63.65; H, 6.7%; M, 377]; ν_{max}/cm^{-1} 1755 (CO); δ_H(200 MHz) 1.11 (3 H, s, 13β-Me), 1.28 (3 H, d, *J* 7.7, 15β-Me), 2.75 (1 H, quint d, *J* 4 × 7.7 and 1.8, 15α-H), 2.95 (2 H, m, 6-H_2), 3.79 (3 H, s, 3-OMe), 4.37 (1 H, d, *J* 1.8, 16β-H), 6.67 (1 H, d, *J* 2.7, 4-H), 6.73 (1 H, dd, *J* 8.5 and 2.7, 2-H) and 7.20 (1 H, d, *J* 8.5, 1-H); δ_C(50 MHz) 16.0 (15β-Me), 18.1 (C-18), 25.4 (C-11), 26.7 (C-7), 29.3 (C-6), 34.85 (C-12), 35.4 (C-8), 41.1 (C-15), 44.25 (C-9), 47.9 (C-13), 49.1 (C-16), 54.0 (C-14), 55.3 (3-OMe), 111.5 (C-2), 113.9 (C-4), 125.9 (C-1), 132.1 (C-10), 137.6 (C-5), 157.7 (C-3) and 221.3 (C-17).

A deoxygenated solution of the bromo ketone **6** (490 mg, 1.30 mmol), lithium bromide (800 mg, 9.22 mmol), and lithium carbonate (690 mg, 9.35 mmol) in dry DMF (15 cm^3) was refluxed for 22 h. The warm solution was poured into aq. 50% acetic acid (14 cm^3). Work-up (EtOAc) gave a residue (370 mg), which was chromatographed on silica gel (35 g) with EtOAc–toluene (1:9) as eluent, to give the 15β-methyl 17-ketone **2a** (90 mg, 23%); the 15-methyl Δ^{15}-17-ketone **5a** (50 mg, 13%), ν_{max}/cm^{-1} 1688 (CO); and material (160 mg, 41%), ν_{max}/cm^{-1} 1741 (CO), assumed to contain the 15-methyl Δ^{14}-17-ketone.

(**f**) The Δ^{15}-17-ketone **1** (114 mg, 0.51 mmol) was converted into the crude silyl enol ether **4a** (150 mg), which was dissolved in dry THF (2 cm^3). Boron trifluoride–diethyl ether complex (0.1 cm^3, 0.79 mmol) was added to the solution at −78 °C, followed by a solution of benzeneselenenyl chloride (191 mg, 1.0 mmol) in dry THF (1 cm^3), and the stirred solution was allowed to warm to 0 °C. The mixture was poured into ice–water and worked up ($CHCl_3$). The residue (181 mg) was chromatographed on silica gel (18 g), with EtOAc–toluene (1:9) as eluent, to give the 15β-methyl 16α-phenylselanyl 17-ketone **7** as a labile, clear oil (145 mg, 80%), δ_H(200 MHz) 1.06 (3 H, 13β-Me) 1.14 (3 H, d, *J* 7.7, 15β-Me), 2.58 (1 H, td, *J* 2 × 7.4 and 2.1, 9α-H), 2.85 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 3.84 (1 H, d, *J* 1.9, 16β-H), 6.63 (1 H, d, *J* 2.6, 4-H), 6.7 (1 H, dd, *J* 8.7 and 2.6, 2-H), 7.15 (1 H, d, *J* 8.7, 1-H) and 7.31–7.63 (5 H, m, SePh); *m/z* 453 (M^+), followed by the 15β-methyl 17-ketone **2a** (12 mg, 10%).

The selenide **7** (145 mg, 0.32 mmol) as a solution in dichloromethane (3 cm^3) and pyridine (1 cm^3) was cooled to 0 °C, and 30% hydrogen peroxide (0.5 cm^3) was added slowly. The solution was stirred for 1.5 h, with slow warming to 20 °C. Saturated aq. $NaHCO_3$ (20 cm^3) was added, and the mixture was worked up ($CHCl_3$). Chromatography of the residue (87 mg) on silica gel (8 g), with EtOAc–toluene (1:9) as eluent, gave the 15-methyl Δ^{15}17-ketone **5a** (38 mg, 40%), followed by 3-*methoxy*-15-*methyl*-17a-*oxa*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17-*one* **8** (45 mg, 45%), mp 185–187 °C (from EtOAc–MeOH); $[\alpha]_D$ −14 (*c* 1.0, $CHCl_3$) (Found: C, 76.7; H, 7.5; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; M, 312); ν_{max}/cm^{-1} 1705 (CO); δ_H(200 MHz) 1.31 (3 H, s, 13β-Me), 2.10 (3 H, t, *J* 2 × 1.5, 15-Me), 2.87 (2 H, m, 6-H_2), 3.79 (3 H, s, 3-OMe), 5.88 (1 H, q, *J* 3 × 1.5, 16-H), 6.68 (1 H, d, *J* 2.7, 4-H), 6.75 (1 H, dd, *J* 8.4 and 2.7, 2-H) and 7.17 (1 H, d, *J* 8.4, 1-H); δ_C(50 MHz) 18.8 (C-18), 23.0 (15-Me), 25.4 (C-11), 28.3 (C-7), 29.2 (C-6), 30.3 (C-12), 38.5 (C-8), 42.9 (C-9), 50.3 (C-14), 55.2 (3-OMe), 83.4 (C-13), 111.4 (C-2), 113.4 (C-4), 119.4 (C-16), 125.2 (C-1), 132.2 (C-10), 137.9 (C-5), 158.0 (C-3), 158.8 (C-17) and 164.1 (C-15).

15α-Alkyl-3-methoxyestra-1,3,5(10)-trien-17-ones 9

(**a**) Freshly cut lithium (11 mg) was dissolved in liquid ammonia (distilled from sodium; 20 cm^3) and the 15-methyl Δ^{15}-17-ketone **5a** (50 mg, 0.17 mmol) as a solution in dry THF (7 cm^3) was added slowly to the stirred mixture. After 15 min the mixture was treated with saturated aq. NH_4Cl (~ 10 cm^3). The ammonia was allowed to evaporate off, and the residue was diluted with water. Standard work-up (EtOAc) gave crude material (40 mg), chromatography of which on silica gel (4 g), with EtOAc–toluene (1:9) as eluent, gave 3-methoxy-15α-methylestra-1,3,5(10)-trien-17-one **9a** (35 mg, 70%), mp 137–140 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +192 (*c* 1.0, $CHCl_3$) (lit.,[3] 135–138 °C; $[\alpha]_D$ +198) (Found: C, 80.3; H, 8.7; M^+, 298. Calc. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8%; M, 298); $\Delta\varepsilon_{max}$ +2.70 (295 nm), ν_{max}/cm^{-1} 1724 (CO); δ_H(400 MHz) 0.95 (3 H, s, 13β-Me), 1.22 (1 H, t, *J* 2 × 10.8, 14α-H), 1.23 (3 H, d, *J* 6.4, 15α-Me), 1.73 (3 H, dd, *J* 19.3 and 8.4, 16α-H), 1.76 (1 H, qd, *J* 3 × 10.8 and 2.4, 8β-H), 1.89 (1 H, dt, *J* 9.6 and 2 × 2.7, 12β-H), 2.22 (1 H, dq, *J* 12.9 and 3 × 2.9, 11α-H), 2.38 (1 H, ddt, *J* 11.6, 4.9 and 2 × 2.4, 7β-H), 2.77 (3 H, dd, *J* 19.3 and 8.7, 16β-H), 2.87 (2 H, m, 6-H_2), 3.76 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.7, 4-H), 6.70 (1 H, dd, *J* 8.7 and 2.7, 2-H) and 7.19 (1 H, d, *J* 8.7, 1-H).

(**b**) Similar treatment of the 15-ethyl Δ^{15}-17-ketone **5b** (50 mg, 0.16 mmol) gave 15α-*ethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **9b** (40 mg, 80%), mp 91–95 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +170 (*c* 1.1, $CHCl_3$) (Found: C, 80.4; H, 8.9; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%, M, 312); $\Delta\varepsilon_{max}$ +2.94 (292 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H(400 MHz) 0.94 (3 H, t, *J* 2 × 7.4, 15α-CH_2*Me*), 0.97 (3 H, s, 13β-Me), 1.22 and 2.02 (each 1 H, m, 15α-CH_2Me), 1.29 (1 H, t, *J* 2 × 10.7, 14α-H), 1.78 (1 H, qd, *J* 3 × 10.7 and 2.9, 8β-H), 1.79 (1 H, dd, *J* 19.4 and 7.9, 16α-H), 1.90 (1 H, dt, *J* 10.9 and 2 × 2.0, 12β-H), 2.23 (1 H, ddt, *J* 12.7, 5.7 and 2 × 2.9, 7β-H), 2.30 (1 H, td, *J* 2 × 10.7 and 4.8, 9α-H), 2.78 (1 H, dd, *J* 19.4 and 8.8, 16β-H), 2.87 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 6.62 (1 H, d, *J* 2.8, 4-H), 6.72 (1 H, dd, *J* 8.7 and 2.8, 2-H) and 7.21 (1 H, d, *J* 8.7, 1-H).

(**c**) Similar treatment of the 15-isopropyl Δ^{15}-ketone **5c** (50 mg, 0.15 mmol) gave 15α-*isopropyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **9c** (35 mg, 72%), mp 128–131 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +173 (*c* 0.45, $CHCl_3$) (Found: C, 80.4; H, 9.2; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326); $\Delta\varepsilon_{max}$ +1.70 (293 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H(400 MHz) 0.83 and 0.92 (each 3 H, d, *J* 6.7, 15α-CH*Me*$_2$), 0.97 (3 H, s, 13β-Me), 1.45 (1 H, t, *J* 2 × 10.8, 14α-H), 1.76 (1 H, qd, *J* 3 × 10.8 and 2.6, 8β-H), 1.90 (1 H, dt, *J* 10.5 and 2 × 2.4, 12β-H), 1.95 (1 H, dd, *J* 18.5 and 7.7, 16α-H), 2.42 (1 H, dd, *J* 18.5 and 8.5, 16β-H), 2.85 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.61 (1 H, d, *J* 2.8, 4-H), 6.71 (1 H, dd, *J* 8.5 and 2.8, 2-H) and 7.20 (1 H, d, *J* 8.5, 1-H).

15,15-Dialkyl-3-methoxyestra-1,3,5(10)-trien-17-ones 10

(**a**) To a solution of lithium dimethylcuprate(I) (0.79 mmol) in dry diethyl ether (2 cm^3) [prepared at 0 °C from copper(I) iodide (150 mg, 0.79 mmol) and ethereal 1.6 mol dm^{-3} methyllithium (1.0 cm^3, 1.6 mmol)] at −78 °C was added boron trifluoride–diethyl ether complex (0.1 cm^3, 0.80 mmol), followed by a solution of the 15-methyl Δ^{15}-17-ketone **5a** (163 mg, 0.55 mmol) in dry THF (2 cm^3). After the mixture had been kept for 30 min at 0 °C, saturated aq. NH_4Cl (10 cm^3) was added. Standard work-up (EtOAc) gave a crystalline residue (132 mg), chromatography of which on silica gel (5 g), with EtOAc–toluene (1:19) as eluent, gave the 3-*methoxy*-15,15-*dimethylestra*-1,3,5(10)-*trien*-17-*one* **10a** (120 mg, 70%), mp 145–148 °C (from EtOAc–MeOH); $[\alpha]_D$ +75 (*c* 1.0, $CHCl_3$) (Found: C, 80.5; H, 8.8; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312); $\Delta\varepsilon_{max}$ +2.08 (295 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H(400 MHz) 1.10 (3 H, s, 13β-Me), 1.28 and 1.29 (each 3 H, s, 15α- and 15β-Me), 1.47 (1 H, d, *J* 10.9, 14α-H), 2.09 (1 H, d, *J* 19.4, 16α-H), 2.23 (1 H, ddt, *J* 12.7, 5.3 and 2 × 2.6, 7β-H), 2.61 (1 H, d, *J* 19.4, 16β-H), 2.93 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 6.63 (1 H, d, *J* 2.7, 4-H), 6.70 (1 H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1 H, d, *J* 8.6, 1-H).

(**b**) Similar treatment of the 15-ethyl Δ^{15}-17-ketone **5b** (150 mg, 0.48 mmol) gave 15α-*ethyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **10b** (127 mg, 81%), mp 110–113 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +90 (*c* 1.0, $CHCl_3$) (Found: C, 81.2; H, 9.5; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326); $\Delta\varepsilon_{max}$ +2.18 (294 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H(400 MHz) 0.89

(3 H, t, J 2 × 7.4, 15α-CH_2Me), 1.12 (3 H, s, 13β-Me), 1.25 (3 H, s, 15β-Me), 1.36 and 1.76 (each 1 H, dq, J 14.8 and 3 × 7.4, 15α-CH_2Me), 1.48 (1 H, d, J 11.0, 14α-H), 2.18 (1 H, d, J 19.4, 16α-H), 2.26 (1 H, ddt, J 12.8, 5.4 and 2 × 2.6, 7β-H), 2.44 (1 H, d, J 19.4, 16β-H) 2.88 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, J 2.9, 4-H), 6.71 (1 H, dd, J 8.6 and 2.9, 2-H) and 7.20 (1 H, d, J 8.6, 1-H).

(c) Similar treatment of the 15-isopropyl Δ^{15}-17-ketone **5c** (200 mg, 0.62 mmol) gave 15α-*isopropyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **10c** (184 mg, 86%), mp 113–115 °C (from Pr^i_2O); $[\alpha]_D$ +87 (*c* 0.9, $CHCl_3$) (Found: C, 81.2; H, 9.6; M^+, 340. $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.5%; M, 340); $\Delta\varepsilon_{max}$ +1.85 (293 nm); ν_{max}/cm^{-1} 1724 (CO); $\delta_H(C_6D_6$; 400 MHz) 0.68 (6 H, d, J 6.0, 15α-$CHMe_2$), 0.87 (3 H, s, 15β-Me) 0.98 (3 H, s, 13β-Me), 1.45 (1 H, td, J 2 × 13.2 and 3.6, 12α-H), 1.62 obsc (1 H, sept, J 6 × 6.0, 15α-C*H*Me_2), 1.95 (1 H, d, J 19.1, 16α-H), 2.08 (1 H, m, 7β-H), 2.15 (1 H, d, J 19.1, 16β-H), 2.68 (2 H, m, 6-H_2), 3.44 (3 H, s, 3-OMe), 6.70 (1 H, d, J 2.6, 4-H), 6.79 (1 H, dd, J 8.8 and 2.6, 2-H) and 7.09 (1 H, d, J 8.8, 1-H); $\delta_H(CDCl_3$; 400 MHz) 0.87 and 0.89 (each 3 H, d, J 6.7, 15α-$CHMe_2$), 1.13 (3 H, s, 13β-Me), 1.32 (3 H, s, 15β-Me), 1.49 (1 H, d, J 10.1, 14α-H), 1.84 (1 H, qd, J 3 × 10.1 and 2.6, 8β-H), 1.94 obsc (1 H, m, 15α-C*H*Me_2), 2.20 (1 H, d, J 19.4, 16α-H), 2.26 (1 H, d, J 19.4, 16β-H), 2.37 (1 H, m, 7β-H), 2.87 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.68 (1 H, d, J 2.8, 4-H), 6.75 (1 H, dd, J 8.8 and 2.8, 2-H) and 7.20 (1 H, d, J 8.8, 1-H).

(d) Treatment of the 15-methyl Δ^{15}-17-ketone **5a** (200 mg, 0.68 mmol) with ethylmagnesium iodide in the presence of copper(I) iodide (*cf.* preparation of compound **2b**) gave 15β-*ethyl*-3-*methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17-*one* **10d** (186 mg, 84%), mp 104–107 °C (from Pr^i_2O); $[\alpha]_D$ +90 (*c* 1.0, $CHCl_3$) (Found: C, 80.9; H, 9.6; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326); $\Delta\varepsilon_{max}$ +2.30 (294 nm); ν_{max}/cm^{-1} 1724; δ_H(400 MHz) 0.94 (3 H, t, J 2 × 7.6, 15β-CH_2Me), 1.09 (3 H, s, 13β-Me), 1.22 (3 H, s, 15α-Me), 1.49 (1 H, d, J 10.1, 14α-H), 1.63 and 1.76 (each 1 H, dq, J 15.2 and 3 × 7.6, 15β-CH_2Me), 1.87 (1 H, d, J 19.3, 16α-H), 2.27 (1 H, ddt, J 12.8, 5.2 and 2 × 2.6, 7β-H), 2.80 (1 H, d, J 19.3, 16β-H), 2.91 (2 H, m, 6-H_2), 3.78 (3 H, s, 3-OMe), 6.64 (1 H, d, J 2.8, 4-H), 6.71 (1 H, dd, J 8.7 and 2.8, 2-H) and 7.21 (1 H, d, J 8.7, 1-H).

(e) Treatment of the 15-ethyl Δ^{15}-17-ketone **5b** (124 mg, 0.4 mmol) with ethylmagnesium iodide in the presence of copper(I) iodide (as in the foregoing experiment) gave 15,15-*diethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **10e** (122 mg, 90%), mp 111–113 °C (from $CHCl_3$–Pr^i_2O); $[\alpha]_D$ +94 (*c* 1.1, $CHCl_3$) (Found: C, 81.2; H, 9.5; M^+, 340. $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.5%; M, 340); $\Delta\varepsilon_{max}$ +2.99 (293 nm); ν_{max}/cm^{-1} 1725 (CO): δ_H(400 MHz) 0.87 and 0.93 (each 3 H, t, J 2 × 7.4, 15α- and 15β-CH_2Me), 1.10 (3 H, s, 13β-Me), 1.42, 1.55, 1.65 and 1.65 (each 1 H, m, 15α- and 15β-CH_2Me), 1.49 (1 H, d, J 10.1, 14α-H), 1.95 (1 H, d, J 19.6, 16α-H), 2.25 (1 H, ddt, J 12.9, 5.3 and 2 × 2.5, 7β-H), 2.64 (1 H, d, J 19.6, 16β-H), 2.87 (2 H, m, 6-H_2), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, J 2.8, 4-H), 6.70 (1 H, dd, J 8.7 and 2.8, 2-H) and 7.20 (1 H, d, J 8.7, 1-H).

15,15-Dialkyl-3-methoxyestra-1,3,5(10)-trien-17β-ols 11

General procedure. Lithium aluminium hydride (3–5 mol equiv.) was added to a solution of the dialkyl ketone **10** (0.15–0.3 mmol) in dry THF (3–6 cm^3) at 0 °C. The mixture was stirred at 0 °C for 5 min. Saturated aq. $NaHCO_3$ was added and the mixture was filtered. Work-up of the filtrate (EtOAc) gave the 17β-alcohol **11**.

(a) 3-*Methoxy*-15,15-*dimethylestra*-1,3,5(10)-*trien*-17β-*ol* **11a** (85%), mp 87–91 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +75 (*c* 1.1, $CHCl_3$) (Found: C, 80.0; H, 9.5; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; M, 314); ν_{max}/cm^{-1} 3606 (OH); δ_H(200 MHz) 0.92 (3 H, s, 13β-Me), 1.06 (1 H, d, J 11.2, 14α-H), 1.11 and 1.14 (each 3 H, s, 15α- and 15β-Me), 1.61 (1 H, dd, J 13.0 and 10.2, 16α-H), 1.9 (1 H, dd, J 13.0 and 7.9, 16β-H), 2.86 (2 H, m, 6-H_2), 3.71 (1 H, dd, J 10.2 and 7.9, 17α-H), 3.77 (3 H, s, 3-OMe), 6.62 (1 H, d, J 2.7, 4-H), 6.71 (1 H, dd, J 8.6 and 2.7, 2-H) and 7.21 (1 H, d, J 8.6, 1-H).

(b) 15α-*Ethyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **11b** (89%), mp 133–136 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +67 (*c* 0.9, $CHCl_3$) (Found: C, 80.0; H, 9.7; M^+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; M, 328); ν_{max}/cm^{-1} 3604 (OH); δ_H(400 MHz) 0.88 (3 H, t, J 2 × 7.2, 15α-CH_2Me), 0.93 (3 H, s, 13β-Me), 1.06 (3 H, s, 15β-Me), 1.10 (1 H, d, J 11.1, 14α-H), 1.32 obsc (2 H, m, 15α-CH_2Me) 1.39 (1 H, dd, J 13.2 and 10.0, 16α-H), 1.73 (1 H, qd, J 3 × 11.1 and 2.3, 8β-H), 1.87 (1 H, dt, J 12.3 and 2 × 2.8, 12β-H), 2.04 (1 H, dd, J 13.2 and 7.9, 16β-H), 2.14 (1 H, ddt, J 12.8, 5.2 and 2 × 2.3, 7β-H), 2.84 (2 H, m, 6-H_2), 3.60 (1 H, dd, J 10.0 and 7.9, 17α-H), 3.77 (3 H, s, 3-OMe), 6.61 (1 H, d, J 2.9, 4-H), 6.70 (1 H, dd, J 8.6 and 2.9, 2-H) and 7.20 (1 H, d, J 8.6, 1-H).

(c) 15α-*Isopropyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **11c** (95%) as an oil, $[\alpha]_D$ +54 (*c* 1.3, $CHCl_3$) (Found: C, 80.4; H, 9.9; M^+, 342. $C_{23}H_{34}O_2$ requires C, 80.65; H, 10.0%; M, 342); ν_{max}/cm^{-1} 3604 (OH); δ_H(200 MHz) 0.88 and 0.92 (each 3 H, d, J 6.8, 15α-$CHMe_2$), 0.96 (3 H, s, 13β-Me), 1.13 (3 H, s, 15β-Me), 1.45 (1 H, d, J, 11.4, 14α-H), 1.73 (1 H, dd, J 13.4 and 10.2, 16α-H), 1.88 (1 H, dt, J 11.2 and 2 × 2.4, 12β-H), 2.13 (1 H, dd, J 13.4 and 7.9, 16β-H), 2.31 (1 H, td, J 2 × 10.1 and 3.5, 9α-H), 3.54 (1 H, dd, J 10.2 and 7.9, 17α-H), 3.78 (3 H, s, 3-OMe), 6.64 (1 H, dd, J 2.7, 4-H), 6.71 (1 H, dd, J 8.5 and 2.7, 2-H) and 7.22 (1 H, d, J 8.5, 1-H).

(d) 15β-*Ethyl*-3-*methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **11d** (90%) as an oil, $[\alpha]_D$ +70 (*c* 1.0, $CHCl_3$) (Found: C, 80.1; H, 9.7; M^+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; M, 328); ν_{max}/cm^{-1} 3604 (OH); δ_H(400 MHz) 0.88 (3 H, t, J 2 × 7.2, 15β-CH_2Me), 0.90 (3 H, s, 13β-Me), 1.10 (3 H, s, 15α-Me), 1.13 (1 H, d, J 11.5, 14α-H), 1.28 (1 H, td, J 2 × 12.8 and 3.2, 12α-H), 1.51 obsc (2 H, m, 15α-CH_2Me), 1.73 obsc (2 H, m, 16α- and 16β-H), 1.87 (1 H, dt, J 12.8 and 2 × 3.2, 12β-H), 2.84 (2 H, m, 6-H_2), 3.74 (1 H, dd, J 9.9 and 8.2, 17α-H), 3.78 (3 H, s, 3-OMe), 6.63 (1 H, d, J 2.8, 4-H), 6.71 (1 H, dd, J 8.4 and 2.8, 2-H) and 7.21 (1 H, d, J 8.4, 1-H).

(e) 15,15-*Diethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* **11e** (94%) as an oil, $[\alpha]_D$ +37 (*c* 0.95, $CHCl_3$) (Found: C, 80.4; H, 9.9; M^+, 342. $C_{23}H_{34}O_2$ requires 80.7; H, 10.0%; M, 342); ν_{max}/cm^{-1} 3603 (CO); δ_H(200 MHz) 0.86 and 0.93 (each 3 H, t, J 2 × 7.5, 15α- and 15β-CH_2Me), 0.91 (3 H, s, 13β-Me), 1.19–1.38 (4 H, m, 15α- and 15β-CH_2Me), 1.88 (1 H, dt, J 11.5 and 2 × 2.7, 12β-H), 2.19 (1 H, m, 7β-H), 2.85 (2 H, m, 6-H_2), 3.62 (1 H, dd, J 9.0 and 7.9, 17α-H), 3.78 (3 H, s, 3-OMe), 6.63 (1 H, d, J 2.7, 4-H), 6.71 (1 H, dd, J 8.5 and 2.7, 2-H) and 7.22 (1 H, d, J 8.5, 1-H).

15,15-Dialkylestra-1,3,5(10)-triene-3,17β-diols 12

General procedure. A toluene solution of 1.5 mol dm^{-3} DIBAH (5 mol equiv.) was added to a solution of the 15,15-dialkyl 17β-alcohol **11** (0.1–0.2 mmol) in dry toluene (5–10 cm^3). The solution was refluxed for 24 h, cooled to 0 °C, and saturated aq. NH_4Cl was added. The aqueous phase was acidified with dil. hydrochloric acid. Standard work-up (EtOAc) gave the 3,17β-diol **12**.

15,15-*Dimethylestra*-1,3,5(10)-*triene*-3,17β-*diol* **12a** (90%), mp 167–170 °C (from EtOAc); $[\alpha]_D$ +49 (*c* 1.1, EtOH) (Found: C, 79.6; H, 9.3; M^+, 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4%; M, 300).

15α-*Ethyl*-15β-*methylestra*-1,3,5(10)-*triene*-3,17β-*diol* **12b** (92%), amorph., $[\alpha]_D$ +59 (*c* 1.0, EtOH) (Found: C, 79.8; H, 9.5%; M^+, 314).

15α-*Isopropyl*-15β-*methylestra*-1,3,5(10)-*triene*-3,17β-*diol* **12c** (90%), mp 201–205 °C (from EtOAc); $[\alpha]_D$ +71 (*c* 1.0, THF) (Found: C, 80.7; H, 9.8; M^+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; M, 328).

15β-*Ethyl*-15α-*methylestra*-1,3,5(10)-*triene*-3,17β-*diol* **12d** (94%), mp 132–136 °C (from EtOAc); $[\alpha]_D$ +54 (*c* 1.0, EtOH)

(Found: C, 80.4; H, 9.5; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; M, 314).

15,15-*Diethylestra*-1,3,5(10)-*triene*-3,17β-*diol* **12e** as a foam (90%), $[\alpha]_D$ +72 (*c* 1.0, EtOH) (Found: C, 80.0; H, 9.7; M^+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; M, 328).

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