14-Methyl Steroids. Part 4.[1] Synthesis of 14β-Methylestradiol and Related 14β-Methyl-19-norsteroids

James R. Bull, Jan Floor, and Mark A. Sefton*
National Chemical Research Laboratory, Council for Scientific and Industrial Research, P.O. Box 395, Pretoria 0001, Republic of South Africa

3-Methoxy-14-methyl-14β-estra-1,3,5(10),16-tetraen-15-one (**2**) has been converted *via* the derived 16β,17β-epoxy 15-ketone (**3**) into 14-methyl-14β-estra-1,3,5(10)-triene-3,17β-diol (**27**) and the corresponding 3,17α-diol (**28**). The overall course of the reduction of compound (**3**) with lithium aluminium hydride has been elucidated with the aid of the fully assigned 500 MHz ^{1}H n.m.r. spectra of the reduction products and their selectively deuteriated analogues. Reduction of the epoxy alcohol (**14**) to the diol (**15**) with lithium aluminium hydride takes place *via* an unusual epoxide rearrangement.

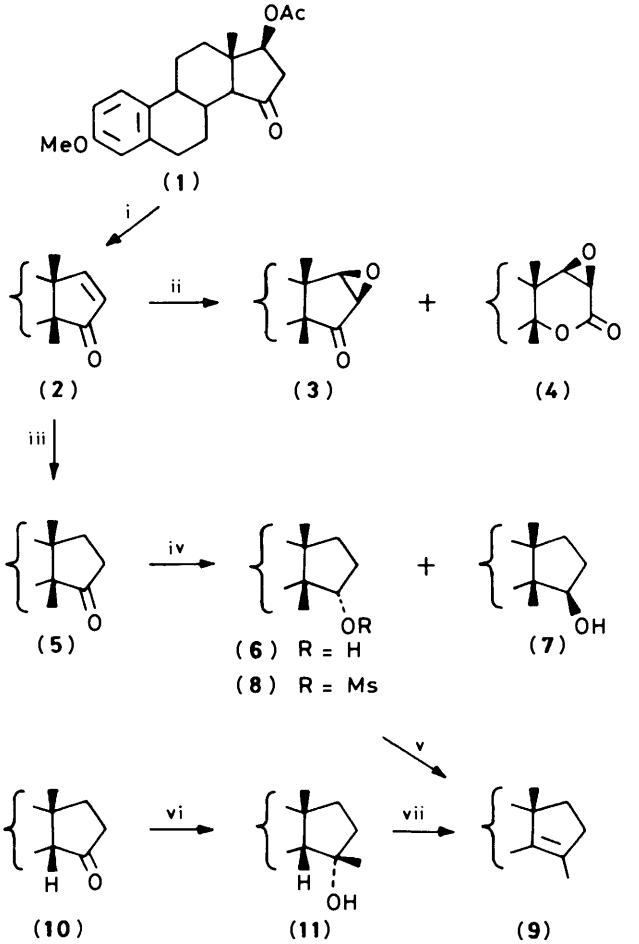
It has previously been shown[2] that base-mediated methylation of 3-methoxy-15-oxoestra-1,3,5(10)-trien-17β-yl acetate (**1**), as first described by Pettit and Brown,[3] affords the 14β-methyl-Δ^{16}-15-ketone (**2**) in high yield. We were interested in converting this product into 14β-methyl analogues of estrone and estradiol as part of an investigation into the influence of 14-alkyl groups upon hormonal activity in 19-norsteroids.

The transposition of functionality from C(15) to C(17) was first envisaged through Michael addition of the elements of benzyl alcohol to the enone (**2**) followed by reductive removal of the 15-oxo group and deprotection of the resultant 17-benzyloxy compound. In the event, attempted addition of benzyl alcohol to enone (**2**) in the presence of potassium hydride failed to give the desired adduct. Instead, a major product, formulated as the 16β,17β-epoxy 15-ketone (**3**), was obtained in variable yields, together with small amounts of the derived epoxy lactone (**4**).

Formation of the epoxy ketone (**3**) under these reaction conditions was unexpected, and is difficult to ascribe to the adventitious presence of hydroperoxide species formed during the reaction, since stringent precautions were taken to exclude oxygen in an attempt to promote the desired reaction course. No attempts were made to optimise the formation of the epoxy ketone (**3**) by this method, since it could be readily prepared from enone (**2**) under more conventional conditions, using alkaline hydrogen peroxide in t-butyl alcohol–tetrahydrofuran (THF). The configuration of the epoxy group in compound (**3**) is compatible with stereoelectronic considerations[4] and may also be influenced by approach of the hydroperoxide anion to the less hindered β-face of the enone (**2**). The assignment was supported by a strongly positive Cotton effect ($\Delta\varepsilon_{max.}$ +4.35) at 320 nm [*cf.* $\Delta\varepsilon_{max.}$ −0.52 (311 nm) for the 15-ketone (**5**)[2]], and was confirmed by subsequent transformations.

In a parallel series of experiments, methods were sought for converting the 15-ketone (**5**) into a 15-olefin for subsequent allylic functionalisation at C(17). The ketone (**5**) failed to form a tosylhydrazone, but treatment with lithium aluminium hydride (LAH) afforded a 4:1 mixture of the 15α- and 15β-alcohol (**6**) and (**7**); the assignments were based on the coupling constants of the respective 15-protons. This epimeric distribution is compatible with reagent attack from the more exposed β-face of ketone (**5**).

Attempted direct dehydration of the 15α-alcohol (**6**) gave complex mixtures. Accordingly, the alcohol (**6**) was treated with methanesulphonyl chloride (MsCl), and the labile product, containing the 15α-mesylate (**8**) together with a less polar component (t.l.c.), was exposed to neutral alumina, which completed the conversion into the latter product (**9**). N.m.r. examination of compound (**9**) revealed the presence of a vinyl methyl group and a tetrasubstituted olefinic bond, and the proposed structure was confirmed by independent synthesis from 3-methoxy-14β-estra-1,3,5(10)-trien-15-one (**10**),[2] through successive methyl-lithium alkylation, and dehydration of the 15α-hydroxy-15β-methyl intermediate (**11**). In view of these

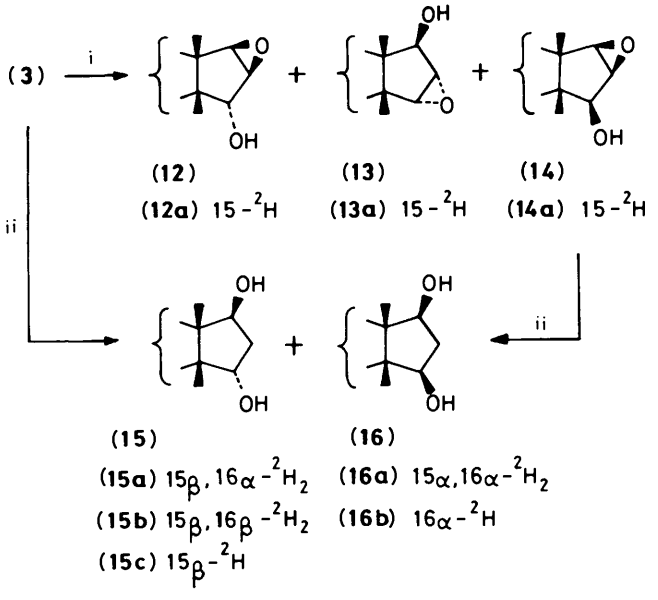


Scheme 1. *Reagents and conditions:* i, MeI–Bu^{t}OK–Bu^{t}OH, 25 °C; ii, KH–$C_6H_5CH_2OH$, 25 °C; iii, 5% Pd–$CaCO_3$, H_2, MeOH–water, 25 °C; iv, LAH–THF, 25 °C; v, MsCl–C_5H_5N, 0 °C, then Al_2O_3–CCl_4, 25 °C; vi, MeLi–Et_2O, 20 °C; vii, MsCl–C_5H_5N, 0 °C

results (Scheme 1), alternative methods were sought for introducing functionality at C(17), and modification of the epoxy ketone (**3**) was considered.

Attempted Wharton rearrangement[5] of compound (**3**) failed, presumably as a result of steric hindrance to formation of a 15-hydrazone. Accordingly, stepwise approaches, based upon formation and rearrangement of a 16β,17β-epoxy 15-alcohol, or formation and differentiation of the hydroxy groups in a 15,17-diol, were investigated.

Reduction of compound (**3**) with LAH in THF at 0 °C afforded a major product (**14**) (86%) accompanied by two isomeric epoxy alcohols (**12**) (1%) and (**13**) (8.4%). The respective yields of the *trans* products (**12**) and (**13**) varied in different preparations, although the sum was consistently about 9%, suggesting that these two isomers might be interconvertible. The structures of the products (**12**)—(**14**) were assigned with the aid of 500 MHz n.m.r. spectroscopy and deuterium labelling (see below).



Scheme 2. *Reagents and conditions:* i, LAH– or LAD–THF, 0 °C; ii, LAH– or LAD–THF, reflux

Forcing reduction of the epoxy ketone (**3**) with LAH in refluxing THF afforded the 15α,17β- and 15β,17β-diol (**15**) (10%) and (**16**) (85%), as expected from hydride attack at C(16) of all the foregoing intermediates (**12**)—(**14**) but, surprisingly, similar forcing reduction of the major, 16β,17β-epoxy 15β-alcohol (**14**) also gave a mixture of both diols (**15**) and (**16**) (Scheme 2).

It is evident from these results that a multi-pathway mechanism of reduction is operational; this is further discussed in the context of the structural assignments (see below) but, for the purpose of the transposition study, further work was carried out upon the major, 16β,17β-epoxy 15β-alcohol (**14**) and its derived 15β,17β-diol (**16**).

Treatment of the 16β,17β-epoxy 15β-alcohol (**14**) with boron trifluoride–diethyl ether and other Lewis acids gave complex mixtures, without evidence of useful conversion into products containing a 17-oxo group. This approach was therefore discarded in favour of one involving differentiation of the 15β- and 17β-hydroxy groups in the diol (**16**).

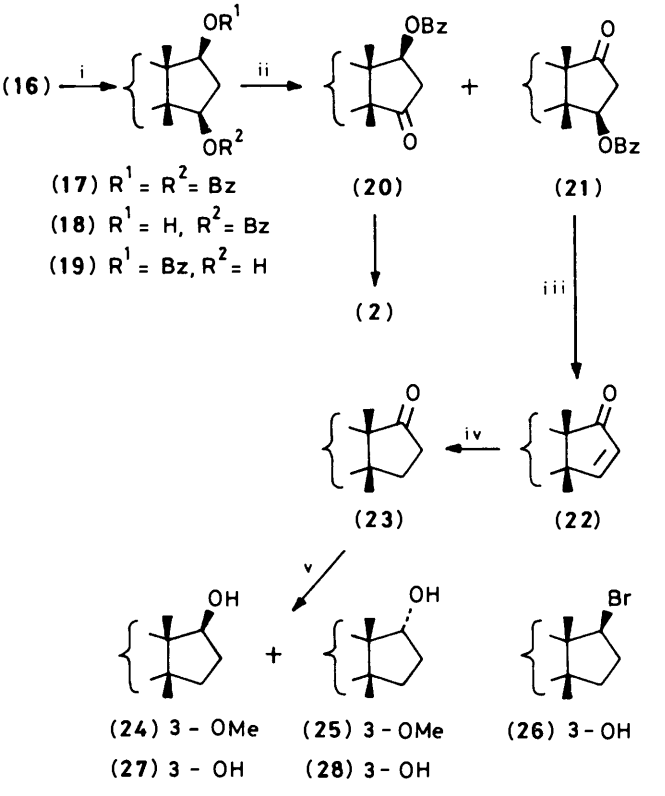
Partial benzoylation of diol (**16**) with benzoyl chloride (1.3 mol) in pyridine at 0 °C gave an inseparable mixture (63%) of monobenzoates (**18**) and (**19**), accompanied by the dibenzoate (**17**) (18%) and some starting material (**16**) (3.6%). N.m.r. examination of the monobenzoate mixture (**18**) + (**19**) revealed that it consisted mainly of the desired 15β-benzoyloxy 17β-alcohol (**18**). The composition of the mixture was estimated by subsequent transformations to be *ca.* 17:1 (**18**):(**19**), resulting from preferential esterification of the less hindered pseudo-equatorial 15β-hydroxy group in compound (**16**).

The mixture (**18**) + (**19**) was subjected to Jones oxidation at 0—5 °C, and the complex product mixture was repeatedly chromatographed to give pure samples of the 15-oxo-17β- and 17-oxo-15β-benzoate (**20**) and (**21**), and their respective β-elimination products (**2**) and (**22**). It is evident that the latter products could have been formed not only during the reaction and work-up but also upon chromatography, and accordingly that the preparative procedure could be improved by first converting the crude oxidation product into the mixture of enones (**2**) and (**22**). Indeed, the major chromatography fraction, comprising compound (**21**) and some derived enone (**22**), was smoothly converted into the latter product upon treatment with sodium isopropoxide in isopropyl alcohol. The estimated overall yield of the Δ^{15}-17-ketone (**22**) from the hydroxy benzoate mixture (**18**) + (**19**) was *ca.* 75%.

The Δ^{15}-17-ketone (**22**) was hydrogenated in the presence of palladium–calcium carbonate to give 14β-methylestrone 3-methyl ether (**23**). We estimate that the overall efficiency of conversion of enone (**2**) into ketone (**23**), taking cognisance of recycling of appropriate intermediates, is *ca.* 45%.

Reduction of the estrone analogue (**23**) with LAH gave a 1:1 mixture of the 17β- and 17α-alcohol (**24**) and (**25**). This result differs notably from those of analogous 14β-*H* and 14β-hydroxy 17-ketones,[6] in which β-face stereoselectivity of reduction exceeds 90%. The 14β-methyl group clearly plays an important steric role in diminishing this stereoselectivity.

Demethylation of the 3-methyl ether (**24**) with boron tribromide under standard conditions gave the 17β-bromo-compound (**26**) as the major product. The estradiol analogues (**27**) and (**28**) were therefore prepared from their respective 3-



Scheme 3. *Reagents and conditions:* i, BzCl–C_5H_5N, 0 °C; ii, 4M-H_2CrO_4–Me_2CO, 0 °C; iii, Pr^iONa–Pr^iOH, 25 °C; iv, 5% Pd–$CaCO_3$, H_2, EtOH, 25 °C; v, LAH–THF, 25 °C

Table 1. ^{1}H N.m.r. data[a] of protons at C(6)—C(12) and angular methyl groups

	Chemical shifts (δ)											
Cmpd.	6α-H	6β-H	7α-H	7β-H	8-H	9-H	11α-H	11β-H	12α-H	12β-H	13β-Me	14β-Me
(12)	2.85	2.79	1.83	2.15	1.20	2.94	2.27	1.30	1.77	1.64	1.09	1.02
(13)	2.87	2.85	1.68	2.20	1.34	2.68	2.19	1.24	2.00	1.35	1.00	1.07
(14)	2.84	2.76	1.45	2.10	1.15	2.37	2.24	1.26	1.38	1.61	1.12	1.10
(15)	2.87	2.83	1.75	2.15	1.33	3.12	2.27	1.45	1.97	1.42	0.98	0.98
(16)	2.84	2.78	1.50	2.15	1.3—1.4	2.61	2.23	1.3—1.4	1.3—1.4	1.3—1.4	1.00	1.12
(24)	2.84	2.84	1.3—1.4	2.06	1.33	2.49	2.22	1.32	1.3—1.4	1.3—1.4	1.00	1.13
(25)	2.82	2.82	1.31	1.97	1.28	2.50	2.31	1.32	1.48	1.50	0.97	0.93

	Coupling constants (Hz)															
	6α,6β	6α,7α	6α,7β	6β,7α	6β,7β	7α,7β	7α,8	7β,8	8,9	9,11α	9,11β	11α,11β	11α,12α	11α,12β	11β,12α	11β,12β	12α,12β
(12)	16.0	6.1	3.7	10.4	5.9	12.7	11.0	3.4	11.3	3.4	11.4	12.5	3.3	3.4	13.5	3.5	13.5
(13)	n.d.	6.5	n.d.	11.8	n.d.	11.8	11.7	2.1	11.6	2.5	12.0	13.0	4.0	3.0	13.8	3.5	13.5
(14)	16.8	5.6	2.4	12.0	5.6	13.0	11.7	2.1	11.2	3.4	11.0	13.1	3.1	3.4	13.4	2.7	13.3
(15)	16.5	6.5	3.7	10.3	6.2	12.7	11.2	3.1	11.8	4.0	12.2	12.8	4.2	3.3	12.8	3.3	12.7
(16)	16.8	5.6	2.2	12.1	5.5	12.8	12.1	2.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

[a] Data were recorded for $CDCl_3$ solution at 500 MHz with $CHCl_3$, δ 7.2400, as internal standard. Assignments were based on proton–proton correlation spectroscopy (COSY) and selective proton-spin decoupling experiments. n.d. = not determined. For all compounds, δ 3.77 ± 0.01 (3 H, s, OMe), 6.61 ± 0.02 (1 H, d, *J* 2.8 Hz, 4-H), 6.71 ± 0.02 (1 H, dd, *J* 2.8 and 8.6 Hz, 2-H), and 7.20 ± 0.03 (1 H, d, *J* 8.6 Hz, 1-H).

Table 2. ^{1}H N.m.r. data[a] of ring-D protons

Cmpd.	15α-H	15β-H	16α-H	16β-H	17-H
(6)*		4.15 (dd, 7 and 1)	n.d.	n.d.	n.d.
(7)*	4.66 (dd, 9.5 and 6.5)		n.d.	n.d.	n.d.
(12)		4.14 (s)	3.24 (br d, 2.7)		3.34 (d, 2.7)
(12a)		exch.	3.24 (d, 2.7)		3.34 (d, 2.7)
(13)		3.35 (d, 2.7)		3.40 (d, 2.7)	3.81 (s)
(13a)		exch.		3.40 (s)	3.81 (s)
(14)	4.22 (d, 1.6)		3.50 (dd, 3.1 and 1.6)		3.17 (d, 3.1)
(14a)	exch.		3.50 (d, 3.1)		3.17 (d, 3.1)
(15)		4.25 (dd, 6.8 and 1.2)	2.25 (ddd, 15.8, 8.0, and 1.2)	2.13 (ddd, 15.8, 6.8, and 3.5)	3.97 (dd, 8.0 and 3.5)
(15a)		exch.	exch.	2.11 (br s, $w_{\frac{1}{2}}$ 7)	3.97 (br d, 3.5)
(15a + b) **(15a)**		exch.	exch. (80%)	2.11 (br s, $w_{\frac{1}{2}}$ 7) (80%)	3.9574 (br d, 3.5) (80%)
(15a + b) **(15b)**		exch.	2.22 (br d, 8.0) (20%)	exch. (20%)	3.9599 (br d, 8.0) (20%)
(15c)		exch.	2.22 (dd, 15.8 and 8.0)	2.13 (dd, 15.8 and 3.5)	3.97 (dd, 8.0 and 3.5)
(16)	4.50 (dd, 8.9 and 8.1)		2.82 (ddd, 14.9, 8.9, and 8.0)	1.53 (ddd, 14.9, 8.1, and 3.1)	3.58 (dd, 8.0 and 3.1)
(16a)	exch.		exch.	1.52 (br s, $w_{\frac{1}{2}}$ 5)	3.57 (d, 3.1)
(16b)	4.49 (d, 8.1)		exch.	1.52 (br d, 8.0)	3.57 (d, 3.1)
(24)	1.87 (ddd, 12.7, 10.2, and 9.8)	1.41 (obsc.)	2.33 (dddd, 14.6, 10.2, 7.9, and 1.9)	1.68 (dddd, 14.6, 9.8, 9.6, and 2.9)	3.75 (dd, 7.9 and 2.9)
(25)	1.99 (ddd, 13.2, 12.3, and 6.3)	1.19 (ddd, 13.2, 10.1, and 3.9)	1.56 (dddd, 13.9, 12.3, 7.7, and 3.9)	2.19 (dddd, 13.9, 10.1, 9.3, and 6.3)	4.17 (dd, 9.3 and 7.7)

[a] Spectra were recorded for $CDCl_3$ *solutions* at 500 MHz. Chemical shifts are in p.p.m. (δ) with $CHCl_3$, 7.2400, as internal standard. Multiplicities and couplings are given in parentheses. exch. = exchanged; obsc. = obscured.
* Determined from 90 MHz spectra. n.d. = not determined. All other signals of deuteriated analogues were identical with those of the parent compound.

Table 3. Reductions with lithium aluminium deuteride in THF

Substrate	Temperature	Products
16β,17β-epoxy 15-ketone (**3**)	0 °C	(**12a**), (**13a**), and (**14a**)
16β,17β-epoxy 15-ketone (**3**)	reflux	(**15a**), (**15b**), and (**16a**)
16β,17β-epoxy 15β-alcohol (**14**)	reflux	(**15c**) and (**16b**)
[15α-^{2}H]-16β,17β-epoxy 15β-alcohol (**14a**)	reflux	(**15a**) and (**16a**)

methyl ethers (**24**) and (**25**) by reduction with di-isobutylaluminium hydride.[7] These reactions are summarised in Scheme 3.

Structural Assignments and Mechanisms.—The course of reduction of the epoxy ketone (**3**) was studied with the aid of 500 MHz ^{1}H n.m.r. spectroscopy of the products and their selectively deuteriated analogues. The operation of a simple mechanism, involving hydride attack at C(15) followed by reductive cleavage of the epoxy group in the resultant epoxy alcohols, could not be assumed in view of the formation of the three intermediates (**12**)—(**14**) under mild conditions, and the reduction of the major epoxy alcohol (**14**) to the minor diol (**15**), as well as the expected product (**16**).

The elucidation of the pathways to the formation of the 15,17-diols necessitated proving the configuration at C(15) and C(17) for each of the epoxy alcohols (**12**)—(**14**) and the diols (**15**) and (**16**). Accordingly, full assignments of the ^{1}H n.m.r. spectra of these compounds were carried out with the aid of comparative evidence for a series of model compounds derived from estrone.[8] Thus, the chemical shifts of all protons and those splittings which could be identified were tabulated (Tables 1 and 2). Spectral changes (Table 2), displayed by selectively deuteriated products arising from reduction of compounds (**3**), (**14**), and (**14a**) with lithium aluminium deuteride (LAD) (Table 3), facilitated the assignments and provided insight into the mechanistic sequences.

Forcing reduction of the epoxy ketone (**3**) with LAD led to a mixture of the diols (**15a**), (**15b**), and (**16a**) (Table 3). Since one of the hydroxymethine protons was retained in each of these products, a prior rearrangement of the epoxy group to a 17-oxo group, or a redox reaction at C(17),[9] could be excluded; the diols were therefore epimeric only at C(15).

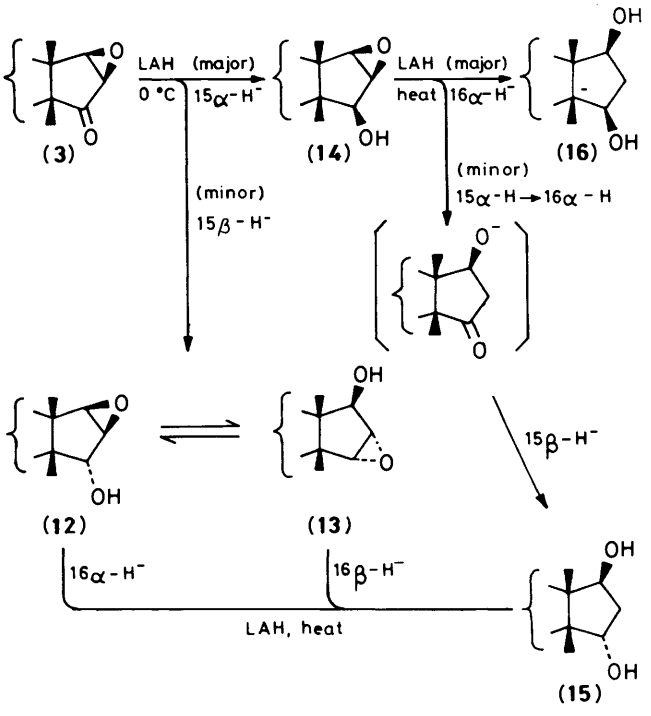
The configurational assignments of the diols (**15**) and (**16**) at C(15) and C(17) could now be based on a correlation of the observed coupling constants with torsional angle relationships of the ring-D protons, as estimated from Dreiding models. The relative chemical shifts of the 16α- and 16β-protons were also predictably influenced by the orientation of the hydroxy groups. An item of additional evidence was the deshielding influence of the 15α-hydroxy group of diol (**15**) upon the 7α-, 9α-, and 12α-proton (Table 1). This effect cannot be ascribed to ring deformations associated with steric crowding since the effect of the 15-hydroxy groups on the chemical shifts of the other ring-B and -C protons, as well as the ring-B and -C proton–proton coupling constants, is minimal.

The assignments of the C(15) protons of the epoxy alcohols (**12**)—(**14**) in their respective ^{1}H n.m.r. spectra were facilitated by the incorporation of deuterium into this position through reduction of the epoxy ketone (**3**) with LAD under mild conditions (Table 2), and the configurations at C(15) were based on the chemical shifts of appropriate ring-B and -C α-face protons. The observed ring-D proton–proton coupling constants were consistent with the assigned configurations.

The rearranged epoxy alcohol (**13**) is presumably formed from isomer (**12**), in which the interacting groups are *trans*-disposed,[10] and the variations in the relative amounts of compounds (**12**) and (**13**), isolated from different reductions of the epoxy ketone (**3**), could be influenced by small changes in the reaction or even work-up conditions. Direct epoxide opening of both deuteriated compounds (**12a**) and (**13a**) by LAD under forcing conditions would then account for the formation of both dideuteriated diols (**15a**) and (**15b**) (Table 3).

The mode of formation of the diol (**15**) as a by-product of the reduction of the epoxy alcohol (**14**) to the diol (**16**) was less obvious. Possible epimerisation at C(15) by a redox mechanism[9] following epoxide opening was discounted as no interconversion between the diols (**15**) and (**16**) was observed, even after prolonged heating with LAD for several days. The isolation of the diols (**15a**) and (**15c**) from reduction with LAD of the epoxy alcohols (**14a**) and (**14**), respectively, showed that the inversion at C(15) is in fact ascribable to a 15α ⟶ 16α hydride shift in the epoxy alcohol (**14**) to give a 17β-alkoxy-15-oxo intermediate which then undergoes stereoselective β-face hydride attack at C(15). Unusual reactions of *cis*-α-epoxy alcohols with hydrogen bromide,[11] or of *cis*-α-epoxy esters with Grignard reagents,[12] have been attributed to analogous rearrangements.

A plausible multi-pathway mechanism for the reduction of the epoxy ketone (**3**) is depicted in Scheme 4. It is interesting to note that the stereoselectivity of reduction of the 15-oxo group in the epoxy ketone (**3**) is reversed relative to that of the isolated 15-ketone (**5**) and also to that implied in the reduction of the 17-alkoxy-15-oxo intermediate in Scheme 4. This finding is compatible with the stereoelectronic requirements associated with 1,2-reduction of cyclic α-epoxy ketones,[4] and is not necessarily only a reflection of changes in steric factors in the environment of the carbonyl group.



Scheme 4. Reduction of epoxy ketone (**3**)

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. Unless otherwise stated, spectra were recorded

as follows: i.r., Perkin-Elmer 257, chloroform solution; ^{1}H n.m.r., Varian EM-390 (tetramethylsilane as internal standard) or Bruker WM-500, deuteriochloroform solutions; mass (electron impact), Varian MAT 212; c. d., JASCO J-20, methanol solutions. Optical rotations were measured for chloroform solutions at 20 °C, with a Perkin-Elmer 241 polarimeter. Silica gel for column chromatography refers to Merck Kieselgel 60.

16β,17β-*Epoxy*-3-*methoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (**3**).—(*a*) A solution of the enone (**2**) (200 mg) in benzyl alcohol (10 ml) was added to potassium benzyloxide in benzyl alcohol [prepared by addition of potassium hydride (50% suspension in oil; *ca.* 500 mg) to benzyl alcohol (10 ml)] at 0 °C under nitrogen. The mixture was stirred without further cooling for 18 h, then acidified with dil. hydrochloric acid and extracted with chloroform. The extract was washed successively with water and aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure, and the residual benzyl alcohol was removed at 80 °C/1 mmHg. Chromatography of the residue on silica gel (50 g) with ethyl acetate–benzene (1:9) as eluant gave the *epoxy ketone* (**3**) (120 mg), m.p. 156—157 °C (from acetone–methanol); $[\alpha]_D$ +226° (*c* 0.8); $\nu_{max.}$ 1 735 cm^{-1} (CO); $\Delta\varepsilon_{max.}$ +4.35 (320 nm); δ (90 MHz) 1.24 and 1.33 (each 3 H, s, 13β- and 14β-Me), 3.31 (1 H, d, *J* 3 Hz, 17α-H), 3.57 (1 H, d, *J* 3 Hz, 16α-H), 3.79 (3 H, s, OMe), and 6.58—7.27 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.9; H, 7.8%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312), followed by starting material (**2**) (53 mg).

Longer reaction times resulted in diminished recoveries of compound (**2**), accompanied by the formation of variable amounts of a more polar product which was isolated by chromatography and shown to be 17β,17aβ-*epoxy*-3-*methoxy*-14-*methyl*-15-*oxa*-D-*homo*-14β-*estra*-1,3,5(10)-*trien*-16-*one* (**4**), m.p. 163—165 °C (from acetone–hexane); $[\alpha]_D$ +118° (*c* 0.5); $\nu_{max.}$ 1 721 cm^{-1} (CO); $\Delta\varepsilon_{max.}$ −0.39 (279 nm) and +12.0 (226 nm); δ (90 MHz) 1.34 (3 H, s, 13β-Me), 1.65 (3 H, s, 14β-Me), 3.30 (1 H, d, *J* 4 Hz, 17aα-H), 3.58 (1 H, d, *J* 4 Hz, 17α-H), 3.78 (3 H, s, OMe), and 6.58—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 73.2; H, 7.45%; M^+, 328. $C_{20}H_{24}O_4$ requires C, 73.1; 7.4%; *M*, 328).

(*b*) Aqueous hydrogen peroxide (30%; 50 ml) was added in 5 ml aliquots, at intervals of 30 min, to a stirred solution of the enone (**2**) (500 mg) in a mixture of THF (100 ml) and t-butyl alcohol (100 ml) containing aqueous potassium hydroxide (20%; 3 ml) at 20 °C. After the addition was complete, the mixture was stirred for a further 1.5 h, then aqueous sodium sulphite (10%; 100 ml) was added and the mixture was stirred for 15 min. Organic solvents were removed under reduced pressure and the product was isolated by extraction with diethyl ether. Crystallisation of the crude product from acetone–methanol gave the epoxy ketone (**3**) (265 mg), and chromatography of the mother-liquor residue on silica gel (45 g) with ethyl acetate–hexane (1:4) as eluant gave a further crop of product (**3**) (170 mg), and starting material (**2**) (13 mg). Yields of up to 5% of the epoxy lactone (**4**) were also isolated after more prolonged reaction times.

Reduction of 3-*Methoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (**5**).—Lithium aluminium hydride (200 mg) was added to a stirred solution of the 15-ketone (**5**)[2] (298 mg) in dry THF (30 ml). The mixture was stirred at 25 °C for 90 min, then ethyl acetate was added, followed by saturated aqueous ammonium chloride. The organic phase was separated, washed successively with water, dil. hydrochloric acid, and brine, dried, and evaporated under reduced pressure. Chromatography of the residue on silica gel (100 g) with ethyl acetate–hexane (3:7) gave 14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,15α-*diol* 3-*methyl ether* (**6**) (240 mg), m.p. 80—103 °C (decomp.) (from acetone–hexane); $[\alpha]_D$ +59° (*c* 0.4); $\nu_{max.}$ 3 610 and 3 460br cm^{-1} (OH); δ (90 MHz) 0.79 and 0.94 (each 3 H, s, 13β- and 14β-Me), 3.76 (3 H, s, OMe), 4.15 (1 H, dd, *J* 7 and 1 Hz, 15β-H), and 6.57—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.3; H, 9.5%; M^+, 300. $C_{20}H_{28}O_2$ requires C, 79.95; H, 9.4%; *M*, 300), followed by 14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,15β-*diol* 3-*methyl ether* (**7**) (60 mg), m.p. 136—138 °C (from acetone–hexane); $[\alpha]_D$ +50° (*c* 0.6); $\nu_{max.}$ 3 600 and 3 440br cm^{-1} (OH); δ (90 MHz) 0.95 (6 H, s, 13β- and 14β-Me), 3.78 (3 H, s, OMe), 4.66 (1 H, dd, *J* 9.5 and 6.5 Hz, 15α-H), and 6.58—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.3; H, 9.6%; M^+, 300).

15-*Methylestra*-1,3,5(10),14-*tetraen*-3-*yl Methyl Ether* (**9**).—(*a*) The 15α-alcohol (**6**) (60 mg) was treated with methanesulphonyl chloride (0.15 ml) in dry pyridine (2 ml) at 0 °C for 2 h. Ice–water and dichloromethane were added and the organic phase was separated, washed successively with ice–water, cold dil. hydrochloric acid, cold aqueous sodium hydrogen carbonate, and brine, and then dried. The solvent was evaporated off under reduced pressure and the residue, showing two major components on t.l.c., was dissolved in tetrachloromethane (3 ml), to which neutral alumina (Woelm Akt.I; 1 g) was added. The mixture was stirred at 25 °C until t.l.c. showed that the initial mixture had undergone conversion into the less polar component. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (10 g) with ethyl acetate–hexane (3:7) as eluant, to give *compound* (**9**) (42 mg), m.p. 85—87 °C (from acetone–methanol); $[\alpha]_D$ +226° (*c* 0.5); δ (90 MHz) 1.06 (3 H, s, 13β-Me), 1.82 (3 H, s, 15-Me), 3.78 (3 H, s, OMe), and 6.57—7.33 (3 H, m, 1-, 2-, and 4-H) (Found: C, 85.3; H, 9.5%; M^+, 282. $C_{20}H_{26}O$ requires C, 85.05; H, 9.3%; *M*, 282).

(*b*) Methyl-lithium (*ca.* 2M in diethyl ether; 70μl) was added to a stirred solution of 3-methoxy-14β-estra-1,3,5(10)-trien-15-one (**10**) (30 mg) in diethyl ether (2 ml) at 20 °C. After 1 h, the mixture was carefully acidified, and the product was isolated by extraction with ethyl acetate, and chromatographed on silica gel (10 g) with ethyl acetate–hexane (3:7) as eluant to give the crude 15α-hydroxy-15β-methyl compound (**11**) (22 mg), δ (90 MHz) 1.03 (3 H, s, 13β-Me), 1.43 (3 H, s, 15β-Me), 3.78 (3 H, s, OMe), and 6.6—7.28 (3 H, m, 1-, 2-, and 4-H); *m/z* 300 (M^+, 25%), 282 (50, $M - H_2O$), 267 (6, $M - H_2O$ − Me), 225 (25), and 187 (100).

Treatment of the alcohol (**11**) with methanesulphonyl chloride (200 μl) in pyridine (1 ml) at 0 °C for 3 h, followed by extraction of the quenched reaction mixture with dichloromethane, gave a product which was dissolved in tetrachloromethane (2 ml) and treated with neutral alumina (Woelm Akt I; 0.5 g) at 20 °C for 16 h. The mixture was filtered, the filtrate was evaporated, and the product was chromatographed on silica gel (5 g) with ethyl acetate–hexane (3:7) as eluant to give the olefin (**9**) (6 mg), identical with the product obtained in the foregoing experiment. Further elution gave the unchanged intermediate (**11**) (10 mg).

Reduction of the Epoxy Ketone (**3**).—(*a*) Lithium aluminium hydride (200 mg) was added to a stirred solution of the epoxy ketone (**3**) (650 mg) in THF (50 ml) at 0 °C. After 1 h at 0 °C and 30 min at 20 °C, the reaction was quenched, and the product was isolated by extraction with ethyl acetate, and adsorbed on silica gel (80 g). Elution with ethyl acetate–benzene (3:7) afforded 16β,17β-*epoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,15α-*diol* 3-*methyl ether* (**12**) (8 mg) as an oil, $\nu_{max.}$ 3 595 and 3 440br cm^{-1} (OH) (Found: M^+, 314.188. $C_{20}H_{26}O_3$ requires *M*, 314.188), followed by 15α,16α-*epoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,17β-*diol* 3-*methyl ether* (**13**) (55 mg),

m.p. 178—180 °C (from acetone–hexane); $[\alpha]_D$ +86° (*c* 0.4); $\nu_{max.}$ 3 610 and 3 450br cm^{-1} (OH) (Found: C, 76.7; H, 8.5; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314). Further elution with the same solvent gave 16β,17β-*epoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,15β-*diol* 3-*methyl ether* (**14**) (560 mg), m.p. 163—165 °C (from acetone–hexane); $[\alpha]_D$ +60° (*c* 0.5); $\nu_{max.}$ 3 590 and 3 435 cm^{-1} (OH) (Found: C, 76.5; H, 8.4%; M^+, 314).

(*b*) Lithium aluminium hydride (50 mg) was added to stirred solution of the epoxy ketone (**3**) (500 mg) in dry THF (10 ml) at 0 °C. The mixture was then refluxed for 1 h and worked up as in the foregoing experiment. Chromatography of the product on silica gel (50 g) with ethyl acetate–benzene (1:1) as eluant gave the 16β,17β-epoxy-15β-alcohol (**14**) (19 mg), followed by 14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,15α,17β-*triol* 3-*methyl ether* (**15**) (50 mg), m.p. 136—139 °C (from diethyl ether–hexane); $[\alpha]_D$ +56° (*c* 0.3); $\nu_{max.}$ 3 605 and 3 450br cm^{-1} (OH) (Found: C, 75.8; H, 9.2%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316), followed by 14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,15β,17β-*triol* 3-*methyl ether* (**16**) (424 mg), m.p. 193—195 °C (from acetone–hexane); $[\alpha]_D$ +51° (*c* 0.3); $\nu_{max.}$ 3 600 and 3 470 cm^{-1} (OH) (Found: C, 76.2; H, 9.2%; M^+, 316).

Reduction of the 16β,17β-*Epoxy* 15β-*Alcohol* (**14**).—Treatment of the epoxy alcohol (**14**) (250 mg) with lithium aluminium hydride (200 mg) in refluxing THF (10 ml) for 4 h, followed by work-up and chromatography as described in the foregoing experiment, gave the 15α,17β-diol (**15**) (15 mg) and the 15β,17β-diol (**16**) (196 mg).

Partial Benzoylation of the 15β,17β-*Diol* (**16**).—Benzoyl chloride (200 μl) was added to a solution of the diol (**16**) (557 mg) in dry pyridine at 0 °C. After 1 h at 0 °C, the reaction was quenched through addition of water, the product was isolated by extraction with diethyl ether, and the solution was chromatographed on silica gel (90 g). Elution with ethyl acetate–hexane (1:2) gave 3-*methoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-15β,17β-*diol* 15,17-*dibenzoate* (**17**) (170 mg) as an oil, $\nu_{max.}$ 1 710 cm^{-1} (CO); δ (90 MHz) 1.11 and 1.49 (each 3 H, s, 13β- and 14β-Me), 3.27 (1 H, ddd, *J* 16, 8, and 8 Hz, 16α-H), 3.76 (3 H, s, OMe), 5.05 (1 H, dd, *J* 8 and 3 Hz, 17α-H), 5.79 (1 H, dd, *J* 8 and 8 Hz, 15α-H), and 6.6—8.2 (13 H, m, ArH); *m/z* 524 (M^+, 3%), 402 (15, $M - C_6H_5CO_2H$), 297 (20, $M - C_6H_5CO_2H - C_6H_5CO$), 280 (25, $M - 2 \times C_6H_5CO_2H$), 187 (100), 186 (20), and 185 (20) (Found: M^+, 524.256. $C_{34}H_{36}O_5$ requires *M*, 524.256), followed by an inseparable mixture (467 mg) of the 17β-hydroxy-15β- and 15β-hydroxy-17β-benzoate (**18**) and (**19**), δ (90 MHz) 1.05 and 1.38 [each 3 H, s, 13β- and 14β-Me of (**18**)], 3.07 [1 H, ddd, *J* 15, 9, and 9 Hz, 16α-H of (**18**)], 3.71 [1 H, obsc. m, 17α-H of (**18**)], 3.76 (3H, s, OMe) 5.67 [1 H, t, *J* 9 Hz, 15α-H of (**18**)], and 6.5—8.2 (8 H, m, ArH). Further elution gave starting material (**16**) (20 mg).

Oxidation of the Hydroxy Benzoates (**18**) *and* (**19**).—4M-Chromic acid (1 ml) was added to the mixture of hydroxy benzoates (**18**) and (**19**) (910 mg) in acetone (100 ml) at 0—5 °C. After 5 min, isopropyl alcohol was added, the mixture was concentrated under reduced pressure, and the residue was extracted with diethyl ether to give a product (875 mg) which was adsorbed on silica gel (330 g). Elution with ethyl acetate–hexane (1:6) gave a mixed fraction (Fraction A, 46 mg), followed by 3-*methoxy*-14-*methyl*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**22**) (20 mg), m.p. 83.5—84.5 °C (from diethyl ether–hexane); $[\alpha]_D$ +263° (*c* 0.3); $\nu_{max.}$ 1 703 cm^{-1} (CO); $\lambda_{max.}$(MeOH) 220 nm (log ε 4.31); δ (90 MHz) 1.02 and 1.09 (each 3 H, s, 13β- and 14β-Me), 3.74 (3 H, s, OMe), 6.13 (1 H, d, *J* 6 Hz, 16-H), 6.5—7.1 (3 H, m, 1-, 2-, and 4-H), and 7.38 (1 H, d, *J* 6 Hz, 15-H); *m/z* 296 (M^+, 20%), 187 (100), and 186 (30) (Found: C, 80.7; H, 8.2. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%), followed by a second mixed fraction (Fraction B, 734 mg).

Rechromatography of Fraction A (46 mg) on silica gel (15 g) with ethyl acetate–benzene (1:19) gave 3-*methoxy*-14-*methyl*-15-*oxo*-14β-*estra*-1,3,5(10)-*trien*-17β-*yl benzoate* (**20**) (11 mg), m.p. 163.5—164.5 °C (from diethyl ether–hexane); $[\alpha]_D$ +102° (*c* 0.2); $\nu_{max.}$ 1 715br cm^{-1} (CO); δ (90 MHz) 1.14 and 1.43 (each 3 H, s, 13β- and 14β-Me), 3.76 (3 H, s, OMe), 5.23 (1 H, br d, *J* 7 Hz, 17α-H), and 6.6—8.2 (8 H, m, ArH); *m/z* 418 (M^+, 5%) 313 (15, $M - C_6H_5CO$), 296 (10, $M - C_6H_5CO_2H$), 187 (100), and 186 (60) (Found: C, 77.2; H, 7.3. $C_{27}H_{30}O_4$ requires C, 77.5; H, 7.2%), followed by a mixed fraction (15 mg) and the Δ^{16}-15-ketone (**2**) (18 mg).

Rechromatography of a portion (73.4 mg) of Fraction B on silica gel (22 g) with ethyl acetate–benzene (1:19) as eluant gave 3-*methoxy*-14-*methyl*-17-*oxo*-14β-*estra*-1,3,5(10)-*trien*-15β-*yl benzoate* (**21**) (35 mg) as an oil, $\nu_{max.}$ 1 733 [C(17)=O] and 1 715 cm^{-1} (PhCO); δ (90 MHz) 1.10 and 1.21 (each 3 H, s, 13β- and 14β-Me), 3.23 (1 H, dd, *J* 19 and 8 Hz, 16α- or 16β-H), 3.76 (3 H, s, OMe), 5.98 (1 H, dd, *J* 8 and 8 Hz, 15α-H), and 6.6—8.2 (8 H, m, ArH); *m/z* 418 (M^+, 10%), 296 (35, $M - C_6H_5CO_2H$), 187 (100), and 186 (25) (Found: M^+, 418.2145. $C_{27}H_{30}O_4$ requires *M*, 418.2144), followed by a mixed fraction (22 mg) and the Δ^{15}-17-ketone (**22**) (8 mg).

The remainder of Fraction B (660 mg) in isopropyl alcohol (17.5 ml) was treated with a solution of sodium isopropoxide in isopropyl alcohol [prepared by adding sodium (37 mg) to isopropyl alcohol (10.5 ml)]. After 1 min, the reaction was quenched with acetic acid, and the mixture was evaporated under reduced pressure. The product was isolated by extraction of the residue with ethyl acetate, and chromatographed on silica gel (65 g) with ethyl acetate–benzene (1:19) as eluant to give the Δ^{15}-17-ketone (**22**) (407 mg).

3-*Methoxy*-14-*methyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**23**).—A solution of the Δ^{15}-17-ketone (**22**) (310 mg) in ethanol (45 ml) was hydrogenated in the presence of palladium–calcium carbonate (5%; 220 mg) for 1 h. The filtered solution was evaporated under reduced pressure to give the 17-*ketone* (**23**) (308 mg), m.p. 171—172 °C (from diethyl ether–methanol); $[\alpha]_D$ +92° (*c* 0.3); $\nu_{max.}$ 1 720 cm^{-1} (CO); $\Delta\varepsilon_{max.}(CH_3CN)$ +1.77 (292 nm); δ (90 MHz) 0.93 and 0.98 (each 3 H, s, 13β- and 14β-Me), 3.76 (3 H, s, OMe), and 6.6—7.3 (3 H, m, 1-, 2-, and 4-H); *m/z* 298 (M^+, 100%), 270 (95, $M - CO$), 187 (80), and 186 (60) (Found: C, 80.5; H, 9.1. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%).

Reduction of the 17-*Ketone* (**23**).—Lithium aluminium hydride (80 mg) was added to a stirred solution of the ketone (**23**) (130 mg) in dry diethyl ether (25 ml). After 30 min, the reaction was quenched with ethyl acetate, and the product was isolated by extraction with diethyl ether and chromatographed on silica gel (7 g) with ethyl acetate–benzene (1:9) as eluant to give 14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,17β-*diol* 3-*methyl ether* (**24**) (60 mg), m.p. 143—144.5 °C (from methanol); $[\alpha]_D$ + 38° (*c* 0.3); $\nu_{max.}$ 3 610 and 3 460br cm^{-1} (OH); *m/z* 300 (M^+, 55%), 282 (25, $M - H_2O$), 254 (45), 187 (70), and 174 (100) (Found: C, 79.7; H, 9.7. $C_{20}H_{28}O_2$ requires C, 79.95; H, 9.4%), followed by 14-*methyl*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* 3-*methyl ether* (**25**) (59 mg), m.p. 104 °C (from methanol); $[\alpha]_D$ + 19° (*c* 0.1); $\nu_{max.}$ 3 600 and 3 430br cm^{-1} (OH); *m/z* 300 (M^+, 100%), 174 (40), and 147 (60) (Found: C, 80.1; H, 9.3%).

17β-*Bromo*-14-*methyl*-14β-*estra*-1,3,5(10)-*trien*-3-*ol* (**26**).—A solution of boron tribromide in dichloromethane (220 mg ml^{-1}; 300 μl) was added to a solution of the methyl ether (**24**) (40 mg) in dichloromethane (2 ml) under nitrogen at −10 °C. The solution was warmed to 0 °C and stirred for 2 h, then quenched with aqueous sodium hydrogen carbonate (4%). The organic

product was extracted with ethyl acetate and chromatographed on silica gel (4 g) with ethyl acetate–benzene (1:19) as eluant to give the *phenol* (**26**) (30 mg), m.p. 152—153 °C (from benzene–hexane); $[\alpha]_D$ +61° (*c* 0.2); $\nu_{max.}$ 3 580 and 3 300br cm^{-1} (OH); δ_H (500 MHz) 1.17 and 1.20 (each 3 H, s, 13β- and 14β-Me), 1.93 (1 H, ddd, *J* 12.7, 10.4, and 9.6 Hz, 15α-H), 2.26 (1 H, dddd, *J* 13.0, 3.3, 3.3, and 3.3 Hz, 11α-H), 2.36 (1 H, dddd, *J* 15.5, 10.4, 9.6, and 4.7 Hz, 16β-H), 2.49 (1 H, m, 9-H), 2.68 (1 H, dddd, *J* 15.5, 9.6, 8.8, and 1.7 Hz, 16α-H), 2.79 (2 H, m, 6-H_2), 4.19 (1H, dd, *J* 8.8 and 4.7 Hz, 17α-H), 6.54 (1 H, d, *J* 2.7 Hz, 4-H), 6.61 (1 H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.12 (1 H, d, *J* 8.6 Hz, 1-H); δ_C (125 MHz) 64.19 (d, *J* 156 Hz, C-17); *m/z* 348/350 (M^+, 70/67%), 269 (20, *M* − HBr), 159 (75), and 133 (100) (Found: C, 65.6; H, 7.4; Br, 22.6. $C_{19}H_{25}BrO$ requires C, 65.3; H, 7.2; Br, 22.9%).

14-*Methyl*-14β-*estra*-1,3,5(10)-*triene*-3,17β-*diol* (**27**).—A solution of di-isobutylaluminium hydride (20% in toluene; 0.5 ml) was added to a solution of the methyl ether (**24**) (48 mg) in dry toluene (2 ml) under nitrogen, and the solution was heated under reflux for 48 h. The reaction mixture was quenched with dil. hydrochloric acid and the crude product, isolated with ethyl acetate, was chromatographed on silica gel (4 g) with methanol–chloroform (1:19) as eluant to give the *diol* (**27**) (35 mg), m.p. 233.5—235 °C (from methanol–benzene); $[\alpha]_D$ +57° (*c* 0.2 in ethanol); *m/z* 286 (M^+, 100%), 160 (80), and 133 (90) (Found: C, 79.7; H, 9.3. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.1%).

14-*Methyl*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**28**).—The methyl ether (**25**) (45 mg) was treated with di-isobutylaluminium hydride, as described in the foregoing experiment. The crude product was crystallised from methanol–benzene to give the *diol* (**28**) (25 mg), m.p. 240—242 °C; $[\alpha]_D$ +24° (*c* 0.2 in ethanol); *m/z* 286 (M^+, 45%), 268 (30, *M* − H_2O), 240 (40), 211 (20), 173 (55), 172 (40), and 160 (100) (Found: C, 79.8; H, 9.3%).

Reductions with Lithium Aluminium Deuteride.—Reductions were carried out using lithium aluminium deuteride under the same conditions as those described in the preparative section (solvent and temperature given in parentheses). Products were separated, and characterised by t.l.c. comparison and mass spectrometry. N.m.r. data are given in Table 2.

(*a*) 16β,17β-Epoxy 15-ketone (**3**) (100 mg) (THF, 0 °C) gave the [15β-^{2}H]-16β,17β-epoxy 15α-ol (**12a**) (6.4 mg), *m/z* 316 (*M* + 1, 4.2%) and 315 (M^+, 20.9), the [15β-^{2}H]-15α,16α-epoxy 17β-*ol* (**13a**) (<0.5 mg), *m/z* 316 (*M* + 1, 2%) and 315 (M^+, 10), and the [15α-^{2}H]-16β,17β-epoxy 15β-*ol* (**14a**) (75 mg), *m/z* 316 (*M* + 1, 22%) and 315 (M^+, 100).

(*b*) 16β,17β-Epoxy 15-ketone (**3**) (200 mg) (refluxing THF) gave a *ca.* 4:1 mixture (90 mg) of the [15β,16α-$^2H_2$]- and [15β,16β-$^2H_2$]-15α,17β-diol (**15a**) and (**15b**), *m/z* 318 (M^+), and the [15α,16α-$^2H_2$]-15β,17β-diol (**16a**) (96 mg), *m/z* 319 (*M* + 1, 20%) and 318 M^+, 100).

(*c*) [15α-^{2}H]-16β,17β-Epoxy 15β-ol (**14a**) (50 mg) (refluxing THF) gave the [15β,16α-$^2H_2$]-15α,17β-diol (**15a**) (1 mg), *m/z* 319 (*M* + 1, 6.5%) and 318 (M^+, 25.7), and the [15α,16α-$^2H_2$]-15β,17β-diol (**16a**) (40.3 mg), identical with that obtained in the foregoing experiment.

(*d*) 16β,17β-Epoxy 15β-ol (**14**) (50 mg) (refluxing THF) gave the [15β-^{2}H]-15α,17β-diol (**15c**) (10 mg), *m/z* 317 (M^+), and the [16α-^{2}H]-15β,17β-*diol* (**16b**) (33 mg), *m/z* 318 (*M* + 1, 21%) and 317 (M^+, 100).

References

1 K. Bischofberger and J. R. Bull, *Tetrahedron*, 1985, **41**, 365.
2 J. R. Bull, J. Floor, and G. J. Kruger, *J. Chem. Res. (S)*, 1979, 224.
3 G. R. Pettit and T. H. Brown, *J. Chem. Soc. C*, 1967, 2024.
4 E. Toromanoff, *Tetrahedron*, 1980, **36**, 2809.
5 P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615.
6 A. F. St André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, 1952, **74**, 5506; J. R. Bull and M. A. Sefton, *S. Afr. J. Chem.*, 1985, **38**, 73.
7 J. C. Hilscher, Ger. P., 2 409 991 (*Chem. Abstr.*, 1976, **84**, 59862v).
8 K. Bischofberger, J. R. Bull, and A. A. Chalmers, submitted for publication in *Tetrahedron*.
9 J. M. Schwab, *J. Org. Chem.*, 1983, **48**, 2105.
10 G. B. Payne, *J. Org. Chem.*, 1962, **27**, 2105; T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham, and F. J. Walker, *ibid.*, 1982, **47**, 1373; M. Yamaguchi and I. Hirao, *J. Chem. Soc., Chem. Commun.*, 1984, 202.
11 S. Greenfield, E. Glotter, D. Lavie, and Y. Kashman, *J. Chem. Soc. C*, 1967, 1460.
12 J. R. Bull, *J. Chem. Soc. C*, 1969, 1128.

Received 8*th November* 1985; *Paper* 5/1968