Stereoselective Routes to 14,15,17-Trisubstituted-3-methoxyestra-1,3,5(10)-trienes

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

An approach to the synthesis of estra-1,3,5(10),8(14)-tetraen-15-one derivatives, based upon stereoselective introduction of functionality into the 14- and 15-positions of Δ^{14}-compounds derived from estrone, is examined. Osmium tetraoxide hydroxylation of 17,17-ethylenedioxy- or 17β-acetoxy-estra-1,3,5(10),14-tetraenes leads exclusively to 14β,15β-diols, whereas epoxidation of the 17β-acetoxy- or 17β-hydroxy-compounds gives mixtures of 14α,15α- and 14β,15β-epoxides. Treatment of these epoxides with sodium phenylselenide leads to 14α-hydroxy-15β- and 14β-hydroxy-15α-phenylselenides respectively. In the presence of aqueous perchloric acid, the 17β-acetoxy-14α,15α- and -14β,15β-epoxides are largely rearranged into 17β-acetoxy-3-methoxy-14β-estra-1,3,5(10)-trien-15-one; small amounts of *trans*-diols are obtained as by-products.

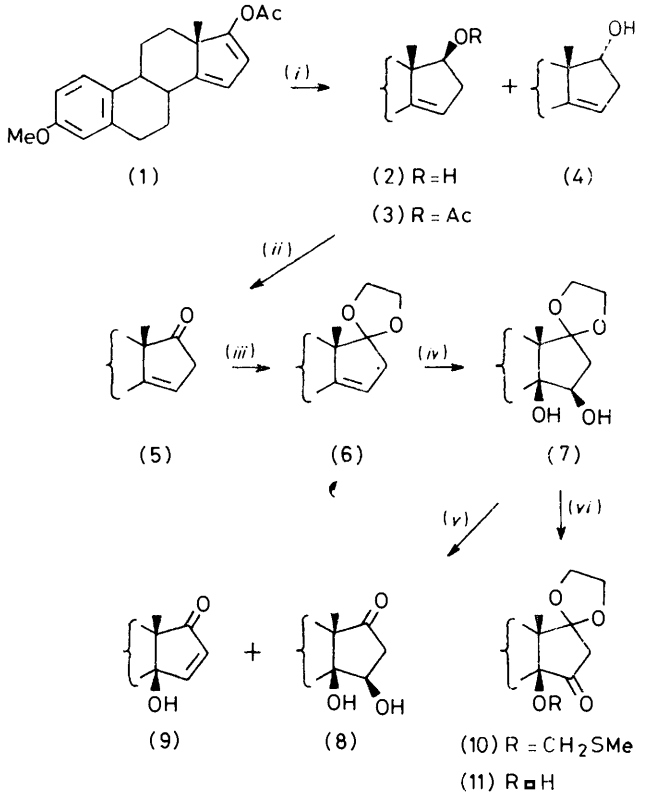
We have recently shown [1] that base-catalysed methylation of estra-1,3,5(10)-trien-15-ones leads stereoselectively to the corresponding 14β-methyl derivatives, whereas the further presence of a Δ^{8}-bond in the substrate results in favoured 14α-methylation.[2] The latter reaction course is analogous to that which obtains during 14-alkylation of $\Delta^{8(14)}$-15-ketones,[3] and provides the key to a synthetic approach to 14α-methyl-19-norsteroids derived from estrone.

The synthesis of hormone analogues by such a route necessitates restoration of the functional elements of estrone after introduction of the 14α-methyl group. For this reason the route to a Δ^{8}-15-ketone, as used previously in the model study,[2] is inappropriate, and a method was sought whereby a Δ^{14}-17-oxygenated derivative could be converted into a Δ^{8}- or $\Delta^{8(14)}$-15-ketone in which protected functionality was retained at C(17). For example, *cis*-hydroxylation of the Δ^{14}-bond, followed by sequential oxidation and dehydration, would lead to the desired system, provided that 14α,15α-diol formation were favoured and thus, that *trans*-elimination of the 14-hydroxy-group were possible. Although a 17-hydroxy- or -acyloxy-group might be liable to undergo β-elimination in the presence of a 15-oxo-group, its subsequent restoration would be facilitated by the resultant Δ^{16}-bond.

Little is known about the factors which influence the stereochemistry of *cis*-hydroxylation of the Δ^{14}-bond. It has been claimed that the major product of osmylation–reduction of a Δ^{14}-cardenolide is the corresponding 14α,15α-diol,[4] whereas that of Δ^{14}-progesterone is the corresponding 14β,15β-diol.[5] This apparent ambiguity emphasises the need for caution in attempting to extrapolate either result to Δ^{14}-compounds lacking a 17β-alkyl side-chain, since it is also known that structural features on or close to ring D influence the stereochemical course of epoxidation of the Δ^{14}-bond.[6,7] Accordingly, our first experiments were aimed at establishing the stereoselectivity of osmylation of 17,17-ethylenedioxy- and 17β-acetoxy-Δ^{14}-compounds derived from estrone methyl ether.

RESULTS AND DISCUSSION

The dienyl acetate (1) derived from 3-methoxyestra-1,3,5(10),15-tetraen-17-one was treated with sodium borohydride in aqueous ethanol, as described by Rasmusson and Arth,[8] to give the desired Δ^{14}-17β-alcohol (2) accompanied by a small amount of the corresponding 17-epimer (4). Careful Jones oxidation of the alcohol (2) afforded the Δ^{14}-17-ketone (5), which was converted



Scheme 1 (*i*) $NaBH_4$–EtOH–H_2O; (*ii*) 8N-CrO_3–Me_2CO, 0 °C; (*iii*) $(CH_2OH)_2$–*p*-TsOH–C_6H_6, heat; (*iv*) OsO_4–C_5H_5N; (*v*) *p*-TsOH–Me_2CO, 25 °C; (*vi*) *N*-chlorosuccinimide–Me_2S–PhMe, −25 °C

cleanly into the Δ^{14}-17-acetal (6) under standard conditions. Although this product could be obtained more directly through treatment of the appropriate 16α-bromo-17-acetal with potassium t-butoxide in dimethyl sulphoxide at 55 °C,[9] the resultant mixture of Δ^{14}- and Δ^{15}-17-acetals was extremely difficult to separate.

The Δ^{14}-compound (6) was treated with osmium

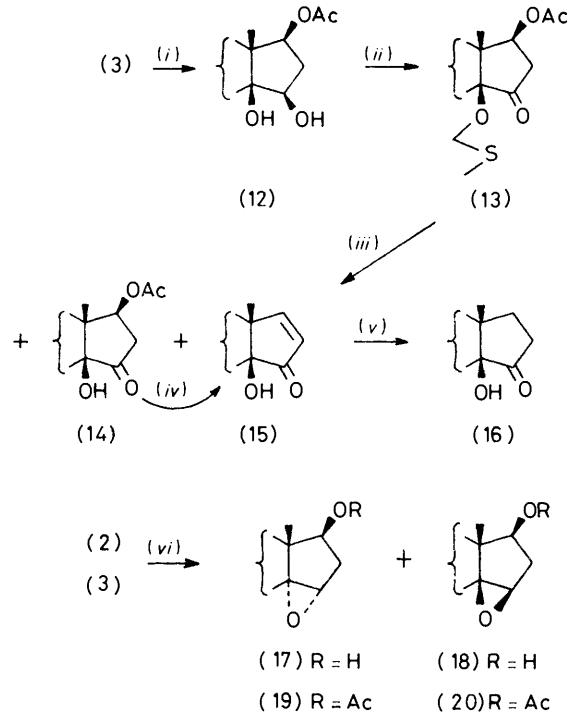
tetraoxide in pyridine at 25 °C and worked up reductively to give a single α-glycol (7). Treatment of this product (7) with toluene-*p*-sulphonic acid in acetone afforded the 17-oxo-14β,15β-diol (8) and the derived 14β-hydroxy-Δ^{15}-17-ketone (9); the structure of the latter compound was confirmed by comparison with material obtained unambiguously from an independent source (see below). Corey oxidation [10] of the α-glycol (7) afforded the 14β-hydroxy-15-ketone (11), accompanied by the corresponding 14β-methylthiomethoxy-15-ketone (10). The c.d. spectrum of (11) in methanol is weakly bisignate (apparent $\Delta\varepsilon_{301}$ + 0.07 and $\Delta\varepsilon_{334}$ − 0.21), suggestive of a degree of conformational mobility in ring D, which may in turn be ascribed to a weak hydrogen-bonding equilibrium between the 14β-hydroxy- and 15-oxo-groups, and the C(17)–β-O bond. Although the effect of introducing a 14β-hydroxy-group cannot therefore be quantified with precision, comparison with the c.d. spectrum of 3-methoxy-14β-estra-1,3,5(10)-trien-15-one (40) [1] in methanol ($\Delta\varepsilon_{302}$ − 2.4) shows that the 14β-substituent does make a consignate contribution to the Cotton effect.

Similar experiments were carried out on the Δ^{14}-17β-acetate (3), in the hope that the change in 17-functionality might modify the ring D conformation or the steric environment of the Δ^{14}-bond favourably for α-attack. In the event, osmylation–reduction of (3) afforded only the 17β-acetoxy-14β,15β-diol (12). Support for the assignment was evident in the n.m.r. signal for the 17α-proton of (12), which appeared as a quartet (*J* 7 and 2 Hz) at δ 4.82, quite unlike the triplet or quartet (*J ca.* 7—8.5 Hz) commonly associated with the 17α-proton of 17β-substituted 14α-steroids.

Corey oxidation [10] of the α-glycol (12) afforded a mixture which, when chromatographed on silica gel, furnished the 17β-acetoxy-14β-methylthiomethoxy-15-ketone (13), followed by fractions from which the primary oxidation product (14) was obtained after recrystallisation; the derived mother-liquor was contaminated with the inseparable β-elimination product (15), whose structure was inferred from spectroscopic data. Filtration of this mixture through neutral active alumina completed the conversion, and the pure 14β-hydroxy-Δ^{16}-15-ketone (15) was obtained; the spectroscopic properties of (15) are comparable with those of related 14β-substituted Δ^{16}-15-ketones.[1] In another experiment, the methylthiomethyl ether (13) was smoothly converted into the enone (15) in the presence of toluene-*p*-sulphonic acid.

Catalytic hydrogenation of (15) gave the 14β-hydroxy-15-ketone (16), shown by c.d. spectroscopy ($\Delta\varepsilon_{318}$ − 1.62) to contain a 14-substituent whose positive contribution to the Cotton effect [$\Delta\Delta\varepsilon$ + 0.78, by comparison with the analogous 14β-H-15-ketone (40) [1]] is compatible with the configurational assignment. Interestingly, the analogous 17β-acetoxy-14β-hydroxy-15-ketone (14) displays a much stronger increment ($\Delta\Delta\varepsilon$ + 1.75), which may be ascribed to a conformational disturbance of ring D, although less pronounced than that of the 17-acetal (11); these quantitative discrepancies obviously restrict the diagnostic application of chiroptical methods in this series.

Furthermore, lanthanoid-induced [11] c.d. spectra [10^{-4}M-Pr(dpm)$_3$ and 10^{-4}M-substrate in dry carbon tetrachloride], determined for the primary hydroxylation products (7) and (12), revealed that the effect for the 17,17-ethylenedioxy-14β,15β-diol (7) ($\Delta\varepsilon_{323}$ − 3.6 and $\Delta\varepsilon_{302}$ + 7.1) is in conflict with the assigned configuration, whereas that of the 17β-acetoxy-14β,15β-diol (12) ($\Delta\varepsilon_{317}$ + 5.2 and $\Delta\varepsilon_{299}$ − 3.6) is in agreement. In view of the available evidence in support of the configurational



SCHEME 2 (*i*) OsO_4–C_5H_5N; (*ii*) *N*-chlorosuccinimide–Me_2S–PhMe, −25 °C; (*iii*) *p*-TsOH–C_6H_6, heat; (*iv*) Al_2O_3; (*v*) Pd–$CaCO_3$–EtOH, H_2; (*vi*) *m*-$ClC_6H_4CO_3H$–$CHCl_3$, 0 °C

assignments, this represents a further example [12] of anomalous chiroptical behaviour, presumably arising from perturbation by a proximate functional group.

The foregoing experiments demonstrate that *cis*-hydroxylation in this series is an impractical approach to the preparation of the corresponding $\Delta^{8(14)}$-15-ketones, since it would entail a difficult *syn*-elimination of the 14β-hydroxy-group.

Attention was turned to possible pathways involving 14,15-epoxides. It is known that 14α,15α-epoxides [5,13–15] and indeed, also 14α,15α-halogenium ion intermediates,[16,17] are prone to Markownikoff attack leading to 14β,15α-disubstituted products, and that those 14β,15β-epoxides which do undergo cleavage without rearrangement are attacked mainly at C(15) [15,17,18] to give products having the same stereochemical arrangement of substituents. Since access to 14α-substituted products from 14,15-epoxides is thus blocked, it was reasoned that C(14) attack upon a 14α,15α-epoxide by a nucleophile,

which could then be induced to undergo *syn*-elimination with the 8β-proton, offers an alternative pathway to $\Delta^{8(14)}$-products. Such an objective may be conceived through the formation and oxidative fragmentation of β-hydroxyselenides from epoxides;[19] a 15α-hydroxy-14β-selenide should be formed, and *syn*-elimination of the derived selenoxide should then occur toward C(8) rather than C(15). Accordingly, an efficient route to a 17-substituted-14α,15α-epoxide was sought.

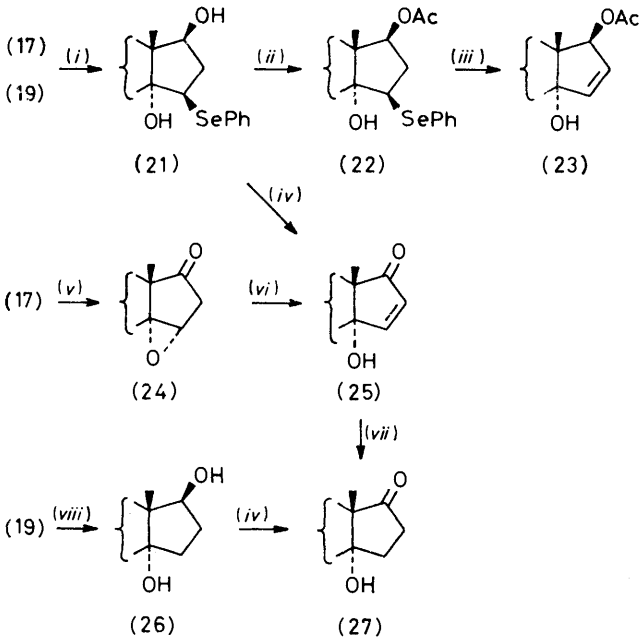
It was considered unlikely that the Δ^{14}-17-ketone (5) or its acetal (6) would be suitable[7] but that some α-face epoxidation could be expected on the Δ^{14}-17β-ol (2) or its acetate (3), since a 17β-substituent, irrespective of steric bulk, is the common feature of all those Δ^{14}-steroids which do give rise to such products.[5,6,13,14,20]

Treatment of the Δ^{14}-17β-alcohol (2) with *m*-chloroperbenzoic acid in chloroform at 0 °C gave a mixture of isomers, separated by chromatography on silica gel. The minor product (17) (41%) was assigned the α-configuration by comparing the chemical shifts of the 15- and 18-protons[21] with those of the major product (18) (55%); these assignments were confirmed by subsequent chemical interconversions (see below).

Interestingly, a similar reaction carried out on the Δ^{14}-17β-acetate (3) gave a much more favourable proportion of the α- (19) (71%) to the β-isomer (20) (24%). This may be ascribed to suppression of the well-known[22] directing influence of a proximate hydroxy-group upon the course of olefin epoxidation. Notwithstanding the rather unfavourable spatial relationship between the 17β-hydroxy-group and the Δ^{14}-bond, it is evident that a measure of participation in (2) can account for the change in isomer distribution. Accordingly, (3) was employed as starting material in order to maximise the yield of the desired 14α,15α-epoxide, despite the superfluity of the acetoxy-group in the following step.

The 14α,15α-epoxy-17β-acetate (19) in dry ethanol–tetrahydrofuran at 80 °C, was treated with sodium phenylselenide, generated *in situ* from diphenyl diselenide and sodium borohydride.[19] The reaction proceeded slowly and, after 16 h, a selenium-containing product (21) had formed in similar amounts to unreacted 14α,15α-epoxy-17β-alcohol (17). Considerable prolongation of reaction times using (17) as starting material led to more complete conversion to (21). The n.m.r. signal for the 17α-proton in the product (21) (triplet, *J* 8 Hz, at δ 4.38) was suggestive of 14α- rather than 14β-stereochemistry, which implied in turn that anti-Markownikoff cleavage had prevailed and consequently, that the phenylselenenyl group was present at C(15) rather than C(14). This was confirmed by acetylation of (21) to give the mono-acetate (22), which underwent oxidative fragmentation by hydrogen peroxide in tetrahydrofuran at 0 °C to give the Δ^{15}-17β-acetoxy-14α-alcohol (23). The formation of a disubstituted olefin, and the simplification of the n.m.r. signal of the 17α-proton in (23) to a weakly-coupled quartet (*J* 2 and 1 Hz), convincingly placed the phenylseleno-group of the cleavage product (21) at C(15) and consequently, also fixed the C(14) stereochemistry. Direct oxidation of the 15β-phenylseleno-14α,17β-diol (21) with Jones reagent afforded a compound taken to be the 14α-hydroxy-Δ^{15}-17-ketone (25). This was confirmed with the aid of a familiar[7] rearrangement of β,γ-epoxy-ketones; thus, the 14α,15α-epoxy-17-ketone (24), obtained through Corey oxidation of the corresponding alcohol (17), was quantitatively converted, during exposure to silica gel, into the identical product (25). Furthermore, catalytic hydrogenation of (25) furnished the known[20] 14α-hydroxy-17-ketone (27), which was also prepared more directly from the 14α,15α-epoxy-17β-acetate (19), through successive reductive cleavage with lithium aluminium hydride and Jones oxidation of the intermediate 14α,17β-diol (26).

For completeness, the reaction of the 14β,15β-epoxy-17β-acetate (20) with sodium phenylselenide was examined; cleavage of the epoxide also proceeded slowly

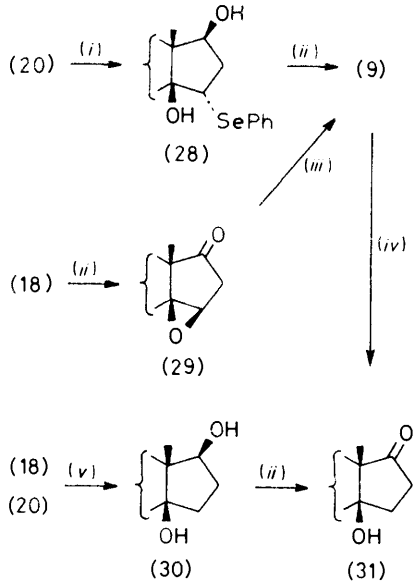


SCHEME 3 (*i*) PhSeNa–EtOH–THF, heat; (*ii*) Ac_2O–C_5H_5N; (*iii*) H_2O_2–THF–K_2CO_3–CO_2, 0 °C; (*iv*) 8N-CrO_3–Me_2CO, 0 °C; (*v*) *N*-chlorosuccinimide–Me_2S–PhMe, −25 °C; (*vi*) SiO_2, 70 °C; (*vii*) Pd–$CaCO_3$–EtOH, H_2; (*viii*) $LiAlH_4$–Et_2O, 25 °C

but eventually afforded the 15α-phenylseleno-14β,17β-diol (28). No other products of epoxide cleavage or rearrangement were detected. The compound (28) underwent direct oxidation with Jones reagent to give the 14β-hydroxy-Δ^{15}-17-ketone (9), identical to the product of β-elimination of the diolone (8) obtained *via* osmylation of the Δ^{14}-17-acetal (6). The structure of (9) is readily inferred by exclusion of the alternative γ-hydroxy-α,β-unsaturated ketone, and by identity with the product of silica-gel-mediated isomerisation[7] of the 14β,15β-epoxy-17-ketone (29).

Catalytic hydrogenation of (9) furnished the 14β-hydroxy-17-ketone (31), also obtained by lithium aluminium hydride reduction of (18) or (20) to the 14β,17β-diol (30), followed by Jones oxidation.

These results demonstrate the apparently unique ability of the phenylselenenyl anion to attack the 14α,15α-epoxides (17) or (19) in an anti-Markownikoff mode, possibly as a consequence of the high nucleophilicity of the reagent, and despite the resultant steric interaction between the 15β-substituent and the 13β-methyl group in the product (21). An additional factor during the reaction may be the absence of any incipient carbocationic character at C(14), as obtains during those acid-mediated cleavages of 14α,15α-epoxides which proceed *via* Markownikoff attack at that position. The result of



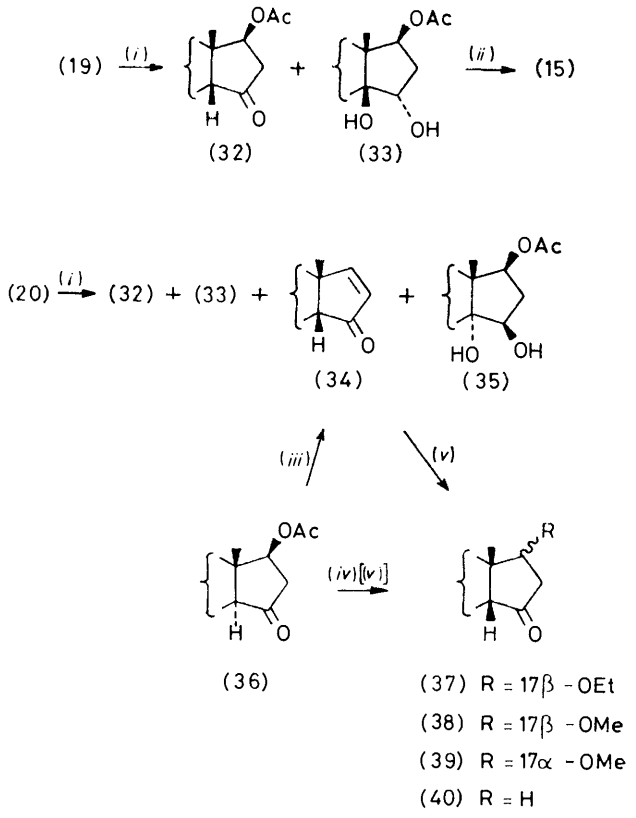
SCHEME 4 (*i*) PhSeNa-EtOH-THF, heat; (*ii*) 8N-CrO_3-Me_2CO, 0 °C; (*iii*) SiO_2, 25 °C; (*iv*) Pd–$CaCO_3$-EtOH, H_2; (*v*) $LiAlH_4$–THF, 25 °C

phenylselenenyl-anion opening of the 14β,15β-epoxide (20) is less surprising, owing to severe steric hindrance toward α-attack at C(14); it has been shown [15,17,18] that less effective nucleophiles react very slowly with 14β,15β-epoxides, thus providing an opportunity for rearrangements to intervene.

In consequence of these findings, it has not been possible to develop a route to $\Delta^{8(14)}$-15-ketones in this series through *syn*-elimination of a 14β-substituent. It was considered necessary, however, to confirm that conventional aqueous acid-mediated cleavage of the 14,15-epoxides (19) and (20) is not a viable route to useful α-glycols.

The 14α,15α-epoxy-17β-acetate (19) in butan-2-one reacted rapidly in the presence of aqueous perchloric acid [23] to give mainly the simple rearrangement product (32), accompanied by a compound (11%), whose spectroscopic properties are in accord with those expected for the 17β-acetoxy-14β,15α-diol (33). An apparent discrepancy between the n.m.r. signal widths for the 15β-protons of (33) (q, *J* 6 and 4 Hz, *W* 10 Hz) and the configurationally related 14β,17β-dihydroxy-15α-phenylselenide (28) (q, *J* 9 and 7 Hz, *W* 16 Hz) may be ascribed to a ring D deformation in the latter compound, occasioned by steric repulsion between the bulky 15α-substituent and the 1,3-disposed elements of ring C; models reveal that such a deformation is indeed possible. The structure of (33) was confirmed through Jones oxidation which resulted, after chromatography on neutral active alumina, in formation of the 14β-hydroxy-Δ^{16}-15-ketone (15), also obtained in earlier experiments though successive *cis*-hydroxylation, oxidation, and β-elimination of the Δ^{14}-17β-acetate (3). In this case, the little epoxide cleavage which does take place must proceed *via* the usual [5,13-15] Markownikoff pathway.

The 14β,15β-epoxy-17β-acetate (20) reacted much more slowly than (19) under similar acidic conditions,[23] and gave the same major product (32), through the presumed intermediacy of the 14α-isomer (36) which was, however, not detected in the reaction mixture. Isomerisation of (36) into (32) under the reaction conditions is



SCHEME 5 (*i*) $HClO_4$-H_2O-EtCOMe; (*ii*) 8N-CrO_3-Me_2CO, 0 °C, followed by Al_2O_3; (*iii*) Bu^tOK–Bu^tOH, 25 °C; (*iv*) 2M-KOH–MeOH–EtOH; (*v*) Pd–$CaCO_3$-EtOH, H_2

expected in view of the well-known [24] thermodynamic relationship between 14α- and 14β-H-15-ketones. The ketone (32) formed in this reaction could not be separated from the accompanying β-elimination product (34), but the mixture was treated with potassium t-butoxide in t-butyl alcohol to give pure (34). A small amount of the 14β,15α-diol (33) was also isolated, together with a further isomer which was not available in sufficient quantity for

complete characterisation, but whose spectroscopic properties suggested that it is the 14α,15β-diol (35). The isolation of both *trans*-diols from a 14β,15β-epoxide has some precedent;[5] mechanistically, the formation of the latter compound (35) implies advanced carbocationic character at C(14) in order to overcome the severe steric demand upon α-attack at that position. Although (35) would serve the intended purpose as an intermediate for the preparation of a derived $\Delta^{8(14)}$-15-ketone, the low yield renders this route impractical.

An incidental feature of these experiments is the use of potassium t-butoxide in t-butyl alcohol to effect conversion of (32) and (36) into the β-elimination product (34). This was necessitated by the observation that treatment of (36) in ethanol with methanolic potassium hydroxide led to the enone (34), accompanied by significant amounts of the artefacts [(37), (38), and (39)] of conjugate addition of alkoxide to the primary reaction product. The ready formation of these products underlines the vulnerability of Δ^{16}-15-ketones to such attack.[1] However, this difficulty was readily circumvented with the aid of the more hindered base.

The foregoing results demonstrate that pathways to *cis*- or *trans*-14,15-disubstituted estrone derivatives of appropriate stereochemistry for subsequent introduction of a $\Delta^{8(14)}$-bond are intractable. New approaches to the synthesis of intermediates for stereoselective synthesis of 14α-methylestrones[2] are receiving attention.

EXPERIMENTAL

For general directions see ref. 1.

Sodium Borohydride Reduction of the Dienyl Acetate (1).—A suspension of sodium borohydride (2.5 g) in aqueous ethanol (75%, 100 ml) was added to a solution of (1) (3.43 g) in ethanol (300 ml) at 0 °C. The mixture was stirred for 6 h, during which time the temperature slowly rose to 25 °C. The excess of reagent was destroyed by the slow addition of acetic acid (2 ml). The mixture was concentrated to *ca.* 200 ml *in vacuo*, and the product was precipitated by addition of water, collected by filtration, washed with water, and dried in a desiccator over phosphorus pentaoxide. Recrystallisation from acetone–hexane gave the Δ^{14}-17β-alcohol (2) (1.85 g), m.p. 117—119 °C, $[\alpha]_D$ +171° (*c* 0.5); $\nu_{max.}$ 3 600 and 1 611 cm^{-1}; δ 1.00 (13-Me), 1.70 (1 H, s, OH), 3.77 (OMe), 4.10 (1 H, t, *J* 8 Hz, 17α-H), 5.21br (1 H, $W_{\frac{1}{2}}$ 5 Hz, 15-H), and 6.57—7.35 (3 H, m, 1-, 2-, and 4-H) (lit.,[8] m.p. 112—114 °C, $[\alpha]_D$ +150°). The mother-liquor residue was adsorbed on silica gel (150 g) and eluted with ethyl acetate–benzene (1 : 9) to give 3-*methoxyestra*-1,3,5(10),14-*tetraen*-17α-*ol* (4) (128 mg), m.p. 104—106 °C (from acetone–hexane), $[\alpha]_D$ +119° (*c* 0.8); $\nu_{max.}$ 3 610 and 1 611 cm^{-1}; δ 1.03 (13-Me), 1.53 (1 H, s, OH), 3.78 (OMe), 4.02 (1 H, d, *J* 5 Hz, 17β-H), 5.26br (1 H, $W_{\frac{1}{2}}$ 6 Hz, 15-H), and 6.60—7.33 (3 H, m, 1-, 2-, and 4-H) (Found: C, 80.0; H, 8.5%; M^+, 284. $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5%; *M*, 284), followed by further 17β-alcohol (2) (846 mg).

3-*Methoxyestra*-1,3,5(10),14-*tetraen*-17β-*yl Acetate* (3).—Acetic anhydride (12 ml) was added to a solution of (2) (4.38 g) in dry pyridine (50 ml). The mixture was stirred at 95 °C for 90 min, after which the solvent and reagent were removed azeotropically with toluene. Crystallisation of the residue from acetone–methanol gave the 17β-*acetate* (3) (4.47 g), m.p. 72—73 °C, $[\alpha]_D$ +105° (*c* 1.0); $\nu_{max.}$ 1 727 and 1 611 cm^{-1}; δ 1.02 (13-Me), 2.07 (OAc), 3.78 (OMe), 5.08 (1 H, t, *J* 8 Hz, 17α-H), 5.22br (1 H, $W_{\frac{1}{2}}$ 6 Hz, 15-H), and 6.60—7.33 (3 H, m, 1-, 2-, and 4-H) (Found: C, 77.3; H, 8.05%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326). The mother-liquor residue was adsorbed on silica gel (60 g) and eluted with ethyl acetate–hexane (3 : 17) to give further (3) (420 mg).

17,17-*Ethylenedioxy*-3-*methoxyestra*-1,3,5(10),14-*tetraene* (6).—8N-Chromic acid (1 ml) was added to a solution of the 17β-alcohol (2) (710 mg) in acetone (50 ml) at 0 °C. After stirring the mixture for 3 min, aqueous sodium sulphite was added, followed by aqueous sodium hydrogencarbonate. The product was extracted with benzene (×2). The extracts were washed with water (×2) and brine, combined, dried, and concentrated to a volume of *ca.* 200 ml *in vacuo*. Ethylene glycol (6 ml) and toluene-*p*-sulphonic acid (200 mg) were added and the mixture was heated under reflux in a Dean–Stark apparatus under nitrogen for 16 h. The mixture was allowed to cool and the product was isolated by extraction with benzene and adsorbed on silica gel (250 g). Elution with ethyl acetate–benzene (7 : 93) gave the 17-ketone (5) (47 mg), m.p. 95—100 °C (from methanol) (lit.,[25] m.p. 103—104 °C), followed by the 17-acetal (6) (424 mg), m.p. 118—120 °C (from acetone–methanol) (lit.,[26] m.p. 121—122 °C).

17,17-*Ethylenedioxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*triene*-14,15β-*diol* (7).—Osmium tetraoxide (300 mg) was added to a solution of (6) (300 mg) in dry pyridine (20 ml) at 25 °C. After 3 days, aqueous sodium hydrogensulphite (10%, 20 ml) was added. The mixture was stirred for 1 h, diluted with water, and extracted with chloroform. The organic phase was washed with water (×2) and brine, dried, and concentrated *in vacuo*. The residual pyridine was removed azeotropically with toluene. The crystalline residue was dissolved in ethyl acetate and adsorbed on a short column of silica gel (40 g). Elution with ethyl acetate gave the *diol* (7) (332 mg), m.p. 124—125 °C (from acetone–hexane), $[\alpha]_D$ +55° (*c* 0.5); $\nu_{max.}$ 3 500br and 1 612 cm^{-1}; δ 0.98 (13-Me), 1.81 (1 H, q, *J* 16 and 4 Hz, 16-H), 2.53 (1 H, q, *J* 16 and 10 Hz, 16-H), 3.32 (1 H, br s, OH), 3.44 (1 H, s, OH), 3.78 (OMe), 3.94 (4 H, m, $W_{\frac{1}{2}}$ 12 Hz, 17-acetal), 4.45 (1 H, q, *J* 10 and 4 Hz, 15α-H), and 6.57—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 70.3; H, 8.1%; M^+, 360. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%; *M*, 360).

14,15β-*Dihydroxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (8).—Toluene-*p*-sulphonic acid (5 mg) was added to a solution of (7) (30 mg) in acetone (6 ml). The mixture was stirred at 25 °C for 18 h. Aqueous sodium hydrogencarbonate was added and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried, and the solvent removed *in vacuo*. Chromatography of the residue on silica gel (10 g) with ethyl acetate–benzene (1 : 1) gave the 14β-hydroxy-Δ^{15}-17-ketone (9) (10 mg), identical with an authentic sample (see below), followed by the *diol* (8) (15 mg), m.p. 200—212 °C (from methanol), $[\alpha]_D$ +121° (*c* 0.1); $\nu_{max.}$ 3 555, 1 735, and 1 612 cm^{-1}; $\Delta\varepsilon$ +1.93 (288 nm); δ 1.15 (13-Me), 1.25 (*ca.* 1 H, s, OH), 3.77 (OMe), 4.82 (1 H, t, *J* 8 Hz, 15α-H), and 6.56—7.18 (3 H, m, 1-, 2-, and 4-H) (Found: C, 72.1; H, 7.8%; M^+, 316. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%; *M*, 316).

17,17-*Ethylenedioxy*-14-*hydroxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (11).—Dimethyl sulphide (500 μl) was added under nitrogen to a stirred solution of *N*-chlorosuccinimide (530 mg) in dry toluene (20 ml) at 0 °C. The

mixture was cooled to −25 °C, after which a solution of the diol (7) (380 mg) in dry toluene (50 ml) was added. After stirring the mixture at −25 °C for 2 h, a solution of triethylamine (700 μl) in toluene (2.5 ml) was added. The mixture was stirred for a further 30 min without further cooling, diluted with aqueous hydrochloric acid (1%), and extracted with benzene (×2). The extracts were washed with water and brine, combined, dried, and evaporated to dryness. The crude product was adsorbed on a short column of silica gel (50 g) and eluted with ethyl acetate–benzene (1 : 1) to give 17,17-ethylenedioxy-3-methoxy-14-methylthiomethoxy-14β-estra-1,3,5(10)-trien-15-one (10) (*m/e*, 418) (120 mg), followed by 17,17-*ethylenedioxy*-14-*hydroxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (11) (265 mg), m.p. 165—187 °C (from acetone–hexane), $[\alpha]_D$ +94° (*c* 0.8); $\nu_{max.}$ 1 753 and 1 611 cm^{-1}; Δε +0.07 (301 nm) and −0.21 (334 nm); δ 1.04 (13-Me), 2.67 (2 H, s, 16-H_2), 3.79 (OMe), 4.04 (4 H, m, $W_{\frac{1}{2}}$ 14 Hz, 17-acetal), and 6.58—7.27 (3 H, m, 1-, 2-, and 4-H) (Found: C, 70.1; H, 7.5%; M^+, 358. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%; *M*, 358).

17β-*Acetoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*triene*-14,15β-*diol* (12).—Osmium tetraoxide (300 mg) was added to a solution of the Δ^{14}-17β-acetate (3) (300 mg) in dry pyridine (30 ml) and the mixture was kept at 25 °C for 3 days. Aqueous sodium hydrogensulphite (10%, 30 ml) was added and the mixture was stirred for 1 h. Water and chloroform were added, the organic phase was separated, washed with water (×2) and brine, dried, and concentrated *in vacuo*. The residual pyridine was removed azeotropically with toluene. Crystallisation of the product from acetone–hexane (×2) gave the *diol* (12) as colourless needles (259 mg), m.p. 134—136 °C, $[\alpha]_D$ +50° (*c* 0.6); $\nu_{max.}$ 3 550br, 1 731, and 1 611 cm^{-1}; δ 1.04 (13-Me), 2.07 (OAc), 3.77 (OMe), 4.46 (1 H, q, *J* 9 and 6 Hz, 15α-H), 4.82 (1 H, q, *J* 7 and 2 Hz, 17α-H), and 6.56—7.30 (3 H, m, 1-, 2-, and 4-H) (Found: C, 69.8; H, 7.85%; M^+, 360. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%; *M*, 360). Chromatography of the combined mother-liquor residues on silica gel (20 g) with ethyl acetate–hexane (1 : 1) afforded further (12) (68 mg).

Oxidation of the 17β-*Acetoxy*-14β,15β-*diol* (12).—Dimethyl sulphide (200 μl) was added under nitrogen to a stirred solution of *N*-chlorosuccinimide (200 mg) in dry toluene (8 ml) at 0 °C. The mixture was cooled to −25 °C, after which a solution of the diol (12) (200 mg) in dry toluene (30 ml) was added. After stirring the mixture at −25 °C for 2 h, triethylamine (280 μl) was added. The cooling bath was removed and the mixture was stirred for a further 30 min. Aqueous hydrochloric acid (1%, 10 ml) was added, and after 15 min, the product was extracted with benzene and isolated in the usual way. Rapid chromatography of the residue on silica gel (40 g) with ethyl acetate–benzene (3 : 7) afforded 17β-*acetoxy*-3-*methoxy*-14-*methylthiomethoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (13) (36 mg), m.p. 150—175 °C (from acetone), $[\alpha]_D$ +99° (*c* 0.2); $\nu_{max.}$ 1 733 and 1 611 cm^{-1}; δ 1.17 (13-Me), 2.10 (OAc), 2.27 (SMe), 3.77 (OMe), *ca.* 4.48—4.83 (2 H, m, SCH_2O), 4.98 (1 H, q, *J* 7 and 2 Hz, 17α-H), and 6.50—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 66.3; H, 7.4%; M^+, 418. $C_{23}H_{30}O_5S$ requires C, 66.0; H, 7.2%; *M*, 418). Further elution with the same solvent system gave mixed fractions (32 mg), followed by 17β-*acetoxy*-14-*hydroxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (14) (139 mg). Recrystallisation from acetone–hexane gave a sample (57 mg), m.p. 183—192 °C, $[\alpha]_D$ +88° (*c* 0.3); $\nu_{max.}$ 3 562, 1 742, and 1 608 cm^{-1}; Δε −0.65 (321 nm); δ 1.11 (13-Me), 2.13 (OAc), 3.78 (OMe), 5.07 (1 H, q, *J* 6.5 and 1 Hz, 17α-H), and 6.58—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 70.7; H, 7.4%; M^+, 358. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%; *M*, 358). The mother-liquor residue of the ketol (14) contained traces of the enone (15) (see following experiment) as shown by t.l.c.

14-*Hydroxy*-3-*methoxy*-14β-*estra*-1,3,5(10),16-*tetraen*-15-*one* (15).—(*a*) A solution of the mother-liquor residue of the ketol (14) (80 mg) (foregoing experiment) in benzene was adsorbed on alumina (Activity I, neutral, 10 g) and eluted with ethyl acetate–benzene (3 : 7) to give the *enone* (15) (54 mg), m.p. 173—175 °C (from acetone–hexane), $[\alpha]_D$ +125° (*c* 1.0); $\nu_{max.}$ 3 553, 1 707, and 1 611 cm^{-1}; $\lambda_{max.}$ 228, 279, and 288 nm (log ε 4.04, 3.30, and 3.27); Δε −7.8 (241 nm), +1.67 (280 nm), +1.49sh (284 nm), and −1.19 (332 nm); δ 1.12 (13-Me), 3.76 (OMe), 6.23 (1 H, d, *J* 6 Hz, 17-H), 6.50—7.05 (3 H, m, 1-, 2-, and 4-H), and 7.75 (1 H, d, *J* 6 Hz, 16-H) (Found: C, 76.3; H, 7.5%; M^+, 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%; *M*, 298).

(*b*) A solution of toluene-*p*-sulphonic acid (2 mg) in water (100 μl) was added to a solution of the methylthiomethyl ether (13) (10 mg) in benzene (2 ml). The mixture was kept at 70 °C for 4 h, diluted with benzene, and worked up in the usual way. P.l.c. of the residue with ethyl acetate–benzene (3 : 7) gave the hydroxy-enone (15) (6 mg), identical (m.p. and mixed m.p.) with the material described in the foregoing experiment.

14-*Hydroxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (16).—Palladium–calcium carbonate (5%, 100 mg) was added to a solution of the enone (15) (55 mg) in ethanol (25 ml). The mixture was stirred under hydrogen for 16 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Chromatography of the residue on silica gel (7 g) with ethyl acetate–benzene (1 : 4) gave the 14β-*hydroxy*-15-*one* (16) (47 mg), m.p. 183.5—185 °C (from acetone-hexane), $[\alpha]_D$ +55° (*c* 0.2); $\nu_{max.}$ 3 590, 1 738, and 1 612 cm^{-1}; Δε −1.62 (318 nm); δ 1.11 (13-Me), 2.18 (*ca.* 1 H, s, OH), 3.78 (OMe), and 6.58—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 75.9; H, 7.9%; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05%; *M*, 300), followed by some starting material (15) (4 mg).

Epoxidation of the Δ^{14}-17-*Alcohol* (2).—A pre-cooled solution of *m*-chloroperbenzoic acid (300 mg) in chloroform (6 ml) was added to a cold (0 °C), stirred solution of the 17-alcohol (2) (284 mg) in chloroform (6 ml). The mixture was stirred at 0 °C for 2 h, diluted with chloroform (100 ml), and washed with aqueous sodium sulphite, aqueous sodium hydrogencarbonate, water, and brine. The organic phase was dried over sodium sulphate and the solvent was removed *in vacuo*. Chromatography of the crystalline residue on silica gel (35 g) with ethyl acetate–benzene (1 : 1) afforded 14,15β-*epoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* (18) (165 mg), m.p. 158–160 °C (from acetone–hexane), $[\alpha]_D$ +131° (*c* 0.6); $\nu_{max.}$ 3 553 and 1 613 cm^{-1}; δ 1.14 (13-Me), *ca.* 3.50 (obscured, 1 H, d, *J ca.* 6 Hz, 17α-H), 3.54 (1 H, s, 15α-H), 3.78 (OMe), and 6.60—7.30 (3 H, m, 1-, 2-, and 4-H); δ (C_6D_6) 1.13 (13-Me), 3.09 (1 H, s, 15α-H), *ca.* 3.43 (obscured, 1 H, d, *J ca.* 6 Hz, 17α-H), 3.44 (OMe), and 6.58—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.0; H, 8.0%; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05%; *M*, 300), followed by 14,15α-*epoxy*-3-*methoxy*-14α-*estra*-1,3,5(10)-*trien*-17β-*ol* (17) (124 mg), m.p. 175—184 °C (from acetone–hexane), $[\alpha]_D$ +97° (*c* 0.8); $\nu_{max.}$ 3 610 and 1 611 cm^{-1}; δ 0.96 (13-Me), 1.75 (1 H, s, OH), 3.56 (1 H, s, 15β-H), 3.74 (obscured, 1 H, t, *J* 8 Hz, 17α-H), 3.79 (OMe), and 6.53—7.33 (3 H, m, 1-, 2-, and 4-H); δ (C_6D_6) 0.78 (13-Me), 3.13

(1 H, s, 15β-H), 3.42 (OMe), 3.63 (1 H, t, *J* 8 Hz, 17α-H), and 6.58—7.17 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.0; H, 8.0%; M^+, 300).

Epoxidation of the Δ^{14}-17-*Acetate* (3).—A pre-cooled solution of *m*-chloroperbenzoic acid (4.4 g) in chloroform (50 ml) was added with stirring to a cold (0 °C) solution of the Δ^{14}-derivative (3) (4.5 g) in chloroform (50 ml). Work-up as described in the foregoing experiment gave a crystalline residue which was dissolved in chloroform and adsorbed on silica gel (800 g). Elution with ethyl acetate–benzene (1 : 4) gave 14,15α-*epoxy*-3-*methoxy*-14α-*estra*-1,3,5(10)-*trien*-17β-*yl acetate* (19) (3.33 g), m.p. 134—135 °C (from acetone–methanol), $[\alpha]_D$ +55° (*c* 1.0); $\nu_{max.}$ 1 732 and 1 612 cm^{-1}; δ 0.96 (13-Me), 2.02 (OAc), 3.59 (1 H, s, 15β-H), 3.76 (OMe), 4.69 (1 H, q, *J* 8.5 and 7.5 Hz, 17α-H), and 6.56—7.33 (3 H, m, 1-, 2-, and 4-H); δ (C_6D_6) 0.80 (13-Me), 1.68 (OAc), 3.14 (1 H, s, 15β-H), 3.43 (OMe), 4.95 (1 H, q, *J* 8.5 and 7.3 Hz, 17α-H), and 6.60—7.13 (3 H, m, 1-, 2-, and 4-H) (Found: C, 74.0; H, 7.8%; M^+, 342. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.7%; *M*, 342), followed by 14,15β-*epoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17β-*yl acetate* (20) (1.15 g), m.p. 178—180 °C (from acetone), $[\alpha]_D$ +104° (*c* 1.0); $\nu_{max.}$ 1 726 and 1 612 cm^{-1}; δ 1.06 (13-Me), 2.05 (OAc), 3.45 (1 H, s, 15α-H), 3.78 (OMe), 4.87 (1 H, d, *J* 6.5 Hz, 17α-H), and 6.58—7.30 (3 H, m, 1-, 2-, and 4-H); δ (C_6D_6) 1.08 (13-Me), 1.75 (OAc), 3.02 (1 H, s, 15α-H), 3.44 (OMe), 4.91 (1 H, q, *J* 5.4 and 2.7 Hz, 17α-H), and 6.53—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 73.5; H, 7.6%; M^+, 342).

3-*Methoxy*-15β-*phenylseleno*-14α-*estra*-1,3,5(10)-*triene*-14,17β-*diol* (21).—(*a*) Sodium borohydride (*ca.* 60 mg) was added in small portions to a stirred solution of diphenyl diselenide (240 mg) in dry ethanol (20 ml) under nitrogen, until the yellow solution just turned colourless. The 17β-acetoxy-14α,15α-epoxide (19) (445 mg) in dry tetrahydrofuran (20 ml) was added and the mixture was kept at 80 °C for 16 h. Benzene (300 ml) was added, followed by water (150 ml). The organic phase was separated, washed with brine, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel (100 g) with ethyl acetate–benzene (1 : 1) gave the *compound* (21) (214 mg) as an oil; $\nu_{max.}$ 3 610, 3 465br, and 1 613 cm^{-1}; δ 1.09 (13-Me), 3.38 (1 H, q, *J* 9 and 3 Hz, 15α-H), 3.78 (OMe), 4.38 (1 H, t, *J* 8 Hz, 17α-H), and 6.58—7.70 (*ca.* 8 H, m, 1-, 2-, 4-H, and PhSe) (Found: M^+, 458.136. $C_{25}H_{30}O_3Se$ requires *M*, 458.136), followed by the 14,15α-epoxide (17) (258 mg), identical (i.r., m.p., mixed m.p.) with authentic material.

(*b*) The 17β-hydroxy-14α,15α-epoxide (17) (1.14 g) in dry tetrahydrofuran (75 ml) was reacted with a solution of sodium phenylselenide [prepared from sodium borohydride (*ca.* 350 mg) and diphenyl diselenide (1.25 g)] in dry ethanol (100 ml) at 80 °C under nitrogen for 64 h to give, after work-up and chromatography on silica gel (250 g) with ethyl acetate–benzene (1 : 1), the 15β-phenylseleno-derivative (21) (1.46 g) and starting material (17) (204 mg).

17β-*Acetoxy*-3-*methoxy*-15β-*phenylseleno*-14α-*estra*-1,3,5(10)-*trien*-14-*ol* (22).—Acetic anhydride (2 ml) was added to a solution of the diol (21) (375 mg) in dry pyridine (8 ml). The mixture was stirred at 90 °C under nitrogen for 60 min and allowed to cool. The solvent and reagent were removed *in vacuo* (azeotropically with toluene). Chromatography of the residue on silica gel (100 g) with ethyl acetate–benzene (1 : 4) gave the 17-*acetate* (22) (330 mg), m.p. 170—172 °C (from ethanol), $[\alpha]_D$ +87° (*c* 0.6); $\nu_{max.}$ 3 610, 3 515br, 1 727, and 1 613 cm^{-1}; δ 1.14 (13-Me), 1.54 (1 H, s, OH), 2.03 (OAc), *ca.* 3.25—3.42 (1 H, m, 15α-H), 3.77 (OMe), 5.26 (1 H, t, *J* 8 Hz, 17α-H), and 6.60—7.63 (*ca.* 8 H, m, 1-, 2-, 4-H, and PhSe) (Found: C, 65.25; H, 6.8%; M^+, 500 and 498. $C_{27}H_{32}O_4Se$ requires C, 64.9; H, 6.5%; *M*, 500 and 498).

17β-*Acetoxy*-3-*methoxy*-14α-*estra*-1,3,5(10),15-*tetraen*-14-*ol* (23).—A solution of the 15β-phenylseleno-derivative (22) (250 mg) in tetrahydrofuran (20 ml) was treated at 0 °C with hydrogen peroxide (30%, 0.8 ml) in the presence of potassium carbonate (100 mg) and a small amount of solid CO_2. The mixture was stirred at 0 °C for 1 h, diluted with water, and worked up by extraction with ethyl acetate. Rapid filtration of the residue through a short column of silica gel (50 g) with ethyl acetate–benzene (1 : 3) gave the Δ^{15}-derivative (23) (90 mg). Recrystallisation of the product from acetone–hexane gave a sample (50 mg), double m.p. 146—150 and 171—173 °C, $[\alpha]_D$ +50° (*c* 0.3); $\nu_{max.}$ 3 605, 3 510br, 1 729, and 1 611 cm^{-1}; δ 0.97 (13-Me), 1.12 (1 H, s, OH), 2.10 (OAc), 3.78 (OMe), 5.80 (1 H, q, *J* 2 and 1 Hz, 17α-H), 6.00 (1 H, q, *J* 6 and 1 Hz, 15-H), 6.39 (1 H, q, *J* 6 and 2 Hz, 16-H), and 6.57—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 73.8; H, 7.8%; M^+, 342.182. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.7%; *M*, 342.183).

14,15α-*Epoxy*-3-*methoxy*-14α-*estra*-1,3,5(10)-*trien*-17-*one* (24).—Dimethyl sulphide (100 μl) was added to a solution of *N*-chlorosuccinimide (135 mg) in toluene (5 ml) at 0 °C under nitrogen. The resulting suspension was cooled to −25 °C and the 17-alcohol (17) (205 mg) in toluene (10 ml) was added dropwise. The mixture was stirred at −25 °C for 3 h, after which triethylamine (150 μl) was added and stirring continued for a further 15 min without further cooling. Saturated aqueous ammonium chloride was added, and the usual work-up gave a product which was filtered rapidly through a short column of silica gel (25 g) with ethyl acetate–benzene (1 : 1), to give the 17-*ketone* (24) (124 mg), m.p. 163—165 °C (from ethanol), $[\alpha]_D$ +103° (*c* 0.5); $\nu_{max.}$ 1 752 and 1 614 cm^{-1}; Δε +3.8 (227 nm), +0.08 (252 nm), −0.13 (278 nm), 0.10 (293 nm), and 0.11 (300 nm); δ 1.14 (13-Me), 3.78 (OMe), 3.93 (1 H, s, 15β-H), and 6.58—7.33 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.4; H, 7.5%; M^+, 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%; *M*, 298).

14-*Hydroxy*-3-*methoxy*-14α-*estra*-1,3,5(10),15-*tetraen*-17-*one* (25).—(*a*) A solution of the epoxy-ketone (24) (30 mg) in benzene was added to a slurry of silica gel (5 g) in benzene. The mixture was evaporated to dryness *in vacuo* and the residue was kept (on the water-bath) at 70 °C for 3 h, then transferred into a short column. The product was eluted with ethyl acetate–benzene (1 : 1). The eluate was concentrated to a small volume and adsorbed on silica gel (5 g). Elution with ethyl acetate–benzene (3 : 7) gave the *enone* (25) (29 mg), m.p. 212—220 °C (from acetone), $[\alpha]_D$ +81° (*c* 0.4); $\nu_{max.}$ 3 600, 3 425br, 1 720, and 1 613 cm^{-1}; $\lambda_{max.}$ 224, 279, and 288 nm (log ε 4.09, 3.29, and 3.23); Δε +2.53 (245 nm), −0.50 (281 nm), +0.20 (321 nm), and −0.12 (364 nm); δ 1.14 (13-Me), 1.49 (1 H, s, OH), 3.78 (OMe), 6.14 (1 H, d, *J* 6 Hz, 16-H), 6.60—7.23 (3 H, m, 1-, 2-, and 4-H), and 7.75 (1 H, d, *J* 6 Hz, 15-H) (Found: C, 76.5; H, 7.6%; M^+, 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%; *M*, 298).

(*b*) 8N-Chromic acid (1.5 ml) was added to a stirred solution of the 15β-phenylseleno-derivative (21) (1.0 g) in acetone (50 ml) at 0 °C. After 3 min aqueous sodium hydrogensulphite (10%, 20 ml) was added, followed by aqueous sodium hydrogencarbonate. The mixture was worked up by extraction with benzene (× 2) and the product was chromatographed on silica gel (130 g) with ethyl acetate–benzene (1 : 1) to give the enone (25) (255 mg),

identical (i.r., m.p., mixed m.p.) with the material obtained in the foregoing experiment.

3-Methoxy-14α-estra-1,3,5(10)-triene-14,17β-diol (26).—Lithium aluminium hydride (200 mg) was added to a solution of the epoxide (19) (200 mg) in dry diethyl ether (20 ml) and the mixture was stirred at 25 °C for 4 h. The excess of reagent was destroyed by careful addition of ethyl acetate and water successively. The mixture was extracted with chloroform (×2). The extracts were washed with water and brine, combined, dried, and the solvent was removed *in vacuo*. Recrystallisation of the product from acetone–hexane gave the diol (26) (103 mg), m.p. 190—192 °C, $[\alpha]_D$ +96° (*c* 0.2); $\nu_{max.}$ 3 605, 3 460br, and 1 610 cm^{-1}; δ 0.89 (13-Me), 1.25 (1 H, s, OH), 1.55 (1 H, s, OH), 3.78 (OMe), 4.38 (1 H, t, *J* 7.5 Hz, 17α-H), and 6.56—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 75.2; H, 8.65%; M^+, 302. Calc. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7%; *M*, 302) (lit.,[20] m.p. 164—165 °C). Chromatography of the mother-liquor residue on silica gel (20 g) with ethyl acetate–benzene (1 : 1) gave a further amount of (26) (35 mg).

14-Hydroxy-3-methoxy-14α-estra-1,3,5(10)-trien-17-one (27).—(*a*) Palladium–calcium carbonate (5%, 60 mg) was added to a solution of the enone (25) (100 mg) in ethanol (25 ml) and the mixture was stirred under hydrogen for 1 h. The catalyst was removed by filtration and the solvent was removed *in vacuo*. Chromatography of the crystalline residue on silica gel (20 g) with ethyl acetate–benzene (1 : 1) gave the hydroxy-ketone (27) (94 mg), m.p. 184—186 °C (from acetone–hexane), $[\alpha]_D$ +130° (*c* 0.4); $\nu_{max.}$ 3 600, 1 740, and 1 612 cm^{-1}; Δε +1.97 (292 nm); δ 1.02 (13-Me), 1.50 (1 H, s, OH), 3.78 (OMe), and 6.60—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.0; H, 8.1%; M^+, 300. Calc. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.05%; *M*, 300) (lit.,[20] m.p. 175—176 °C, $[\alpha]_D$ +152.5°).

(*b*) 8N-Chromic acid (60 μl) was added to a cold (0 °C), stirred solution of the diol (26) (50 mg) in acetone (5 ml). After 2 min aqueous sodium hydrogensulphite (10%, 5 ml) was added, followed by water. Extraction with ethyl acetate followed by chromatography of the residue on silica gel (20 g) with ethyl acetate–benzene (1 : 1) gave the hydroxy-ketone (27), identical (m.p., mixed m.p.) with the material obtained in the foregoing experiment.

3-Methoxy-15α-phenylseleno-14β-estra-1,3,5(10)-triene-14,17β-diol (28).—A solution of sodium phenylselenide was prepared from sodium borohydride (*ca.* 35 mg) and diphenyl diselenide (120 mg) in dry ethanol (10 ml) as described in a previous experiment. The β-epoxide (20) (200 mg) in dry tetrahydrofuran (10 ml) was added and the mixture was kept at 80 °C under nitrogen for 16 h. Benzene (200 ml) was added, followed by water. The organic phase was separated, washed with brine, dried, and concentrated to a small volume *in vacuo*. Chromatography of the residue on silica gel (75 g) with ethyl acetate–benzene (1 : 1) afforded the *compound* (28) (150 mg), m.p. 199—201 °C (from acetone), $[\alpha]_D$ +112° (*c* 0.9); $\nu_{max.}$ 3 600 and 1 608 cm^{-1}; δ 1.10 (13-Me), 3.41 (1 H, s, OH), 3.77 (OMe), 3.83 (obscured, 1 H, t, *J* 5 Hz, 17α-H), 4.04 (1 H, q, *J* 9 and 7 Hz, 15β-H), and 6.58—7.64 (*ca.* 8 H, m, 1-, 2-, 4-H, and PhSe); δ (C_6D_6) 1.02 (13-Me), 3.33 (*ca.* 1 H, s, OH), 3.42 (OMe), 3.29—3.52 (obscured, *ca.* 1 H, m, 17α-H), 4.13 (1 H, q, *J* 9 and 7 Hz, 15β-H), and 6.60—7.60 (*ca.* 8 H, m, 1-, 2-, 4-H, and PhSe) (Found: C, 65.85; H, 6.5%; M^+, 458 and 456. $C_{25}H_{30}O_3Se$ requires C, 65.6; H, 6.6%; *M*, 458 and 456), followed by the epoxy-alcohol (18) (77 mg), identical with authentic material.

14-Hydroxy-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (9).—The 15α-phenylseleno-derivative (28) (45 mg) in acetone (10 ml) was treated at 0 °C with 8N-chromic acid (100 μl). The mixture was stirred for 3 min, then isopropyl alcohol was added, followed by aqueous sodium hydrogencarbonate. The mixture was extracted with benzene, and chromatography of the residue on silica gel (10 g) with ethyl acetate–benzene (1 : 1) gave the *enone* (9) (15 mg), m.p. 183—185 °C (from acetone–hexane), $[\alpha]_D$ +272° (*c* 0.5); $\nu_{max.}$ 3 600, 3 430br, 1 710, and 1 613 cm^{-1}; $\lambda_{max.}$ 220, 279, and 287.5 nm (log ε 4.04, 3.39, and 3.34); Δε −9.8 (240 nm) and +2.53 (331 nm); δ 1.10 (13-Me), 1.88 (1 H, s, OH), 3.76 (OMe), 6.26 (1 H, d, *J* 6 Hz, 16-H), 6.53—7.13 (3 H, m, 1-, 2-, and 4-H), and 7.38 (1 H, d, *J* 6 Hz, 15-H) (Found: C, 76.5; H, 7.4%; M^+, 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%; *M*, 298).

14,15β-Epoxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (29).—8N-Chromic acid (250 μl) was added to a cold (0 °C), stirred solution of the epoxy-alcohol (18) (150 mg) in acetone (25 ml). After 3 min aqueous sodium hydrogensulphite (10%, 10 ml) was added, followed by aqueous sodium hydrogencarbonate. The mixture was worked up in the usual manner, then filtered rapidly through a short column of silica gel (20 g) with ethyl acetate–benzene (1 : 1) to give the *epoxy-ketone* (29) (145 mg), m.p. 152—157 °C (from ethanol), $[\alpha]_D$ +257° (*c* 0.6); $\nu_{max.}$ 1 742 and 1 610 cm^{-1}; Δε +4.7 (291 nm); δ 1.16 (13-Me), 3.74 (1 H, s, 15α-H), 3.79 (OMe), and 6.62—7.22 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.4; H, 7.5%; M^+, 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%; *M*, 298).

Rearrangement of the Epoxy-ketone (29).—A solution of the epoxy-ketone (29) (75 mg) in benzene (5 ml) was adsorbed on a short column of silica gel (15 g) at 25 °C. After 18 h, elution of the column with ethyl acetate–benzene (1 : 1) afforded starting material (29) (16 mg), followed by the 14β-hydroxy-derivative (9) (57 mg), identical with the material obtained in a previous experiment.

3-Methoxy-14β-estra-1,3,5(10)-triene-14,17β-diol (30).[27]—(*a*) Lithium aluminium hydride (300 mg) was added to a solution of the 14β,15β-epoxide (20) (200 mg) in dry tetrahydrofuran (15 ml). The mixture was stirred at 25 °C for 3 h. The excess of reagent was destroyed and the product was isolated by extraction with chloroform. Chromatography of the residue on a short column of silica gel (22 g) with ethyl acetate–benzene (1 : 1) gave the *diol* (30) (165 mg), m.p. 148.5—150 °C (from acetone–hexane), $[\alpha]_D$ +50° (*c* 0.3); $\nu_{max.}$ 3 595, 3 490br, and 1 609 cm^{-1}; δ 1.11 (13-Me), *ca.* 3.78 (obscured, 1 H, d, *J ca.* 6 Hz, 17α-H), 3.78 (OMe), and 6.60—7.18 (3 H, m, 1-, 2-, and 4-H); δ (C_6D_6) 0.99 (13-Me), 3.45 (OMe), 3.52 (1 H, d, *J* 5.5 Hz, 17α-H), and 6.53—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 75.3; H, 8.7%; M^+, 302. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%; *M*, 302).

(*b*) Similar treatment of the epoxide (18) (50 mg) in dry tetrahydrofuran (5 ml) with lithium aluminium hydride (70 mg) for 16 h, afforded the diol (30) (41 mg), identical (m.p., mixed m.p.) with the material described in the foregoing experiment.

14-Hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (31).—(*a*) Palladium–calcium carbonate (5%, 50 mg) was added to a solution of the enone (9) (48 mg) in ethanol (15 ml). The mixture was stirred under hydrogen for 30 min. The catalyst was removed by filtration and the solvent was evaporated to give the hydroxy-ketone (31) (47 mg), m.p. 172—174 °C (from acetone–hexane), $[\alpha]_D$ +102° (*c* 0.3); $\nu_{max.}$ 3 600, 3 450br, 1 735, and 1 611 cm^{-1}; Δε +1.77 (288

nm); δ 1.07 (13-Me), 1.63 (*ca.* 1 H, s, OH), 3.78 (OMe), and 6.60—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: C, 75.8; H, 8.2%; M^+, 300. Calc. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.05%; *M*, 300) (lit.,[28] m.p. 162—163 °C, $[\alpha]_D$ +88°).

(*b*) 8N-Chromic acid (100 μl) was added to a cold (0 °C), stirred solution of the diol (30) (100 mg) in acetone (10 ml). After 3 min, the reaction mixture was worked up and the product was chromatographed on a short column of silica gel (20 g) with ethyl acetate–benzene (1 : 1), to give the 17-ketone (31) (90 mg), identical (m.p., mixed m.p.) with that obtained in the foregoing experiment, followed by starting material (30) (4 mg).

Treatment of the 14α,15α-*Epoxide*(19) *with Perchloric Acid.*—Aqueous perchloric acid (60%, 0.2 ml) was added to a solution of the 14α,15α-epoxide (19) (250 mg) in butan-2-one (20 ml). The mixture was stirred for 5 min, then aqueous sodium hydrogencarbonate was added, followed by ethyl acetate. The organic phase was separated, washed with brine, and dried, and the solvent was removed *in vacuo*. Rapid chromatography of the residue on silica gel (25 g) with ethyl acetate–hexane (3 : 7) gave 17β-*acetoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (32) (210 mg), m.p. 129—132 °C (from acetone-hexane), $[\alpha]_D$ +94° (*c* 0.5); $\nu_{max.}$ 1 735 and 1 613 cm^{-1}; Δε −2.15 (303 nm), −2.00sh (311 nm), and −1.03sh (322 nm); δ 1.17 (13-Me), 2.08 (OAc), 3.77 (OMe), 5.06 (1 H, d, *J* 6 Hz, 17α-H), and 6.55—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 73.8; H, 7.6%; M^+, 342. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.7%; *M*, 342), followed by some minor by-products and 17β-*acetoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*triene*-14,15α-*diol* (33) (30 mg), m.p. 130—132 °C (from acetone–hexane), $[\alpha]_D$ +64° (*c* 0.1); $\nu_{max.}$ 3 570, 1 729, and 1 611 cm^{-1}; δ 0.99 (13-Me), 1.88 (*ca.* 2 H, br s, 2 × OH), 2.07 (OAc), 3.78 (OMe), 4.48 (1 H, q, *J* 6 and 4 Hz, 15β-H), 5.10 (1 H, q, *J* 6 and 4.5 Hz, 17α-H), and 6.60—7.27 (3 H, m, 1-, 2-, and 4-H) (Found: C, 70.05; H, 7.9%; M^+, 360. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%; *M*, 360).

Oxidation of the Diol (33).—8N-Chromic acid (20 μl) was added to a cold (0 °C), stirred solution of the diol (33) (18 mg) in acetone (5 ml). After 2 min aqueous sodium hydrogensulphite (10%, 5 ml) was added, followed by aqueous sodium hydrogencarbonate, and the product was isolated by extraction with ethyl acetate. The crystalline residue was dissolved in a small amount of ethyl acetate–benzene (3 : 7) and adsorbed on alumina (Activity I, *ca.* 5 g). Elution with ethyl acetate–benzene (3 : 7) gave the Δ^{16}-15-ketone (15) (10 mg), identical (m.p., mixed m.p.) with material obtained in a previous experiment.

Treatment of the 14β,15β-*Epoxide* (20) *with Perchloric Acid.*—Aqueous perchloric acid (60%, 0.2 ml) was added to a solution of the epoxide (20) (150 mg) in butan-2-one (20 ml) and the mixture was stirred for 15 h. Aqueous sodium hydrogencarbonate was added, and extraction of the mixture with ethyl acetate gave a product which was adsorbed on silica gel (20 g). Elution with ethyl acetate–hexane (1 : 1) afforded a mixture of the 15-ketone (32) and the Δ^{16}-derivative (34) (*ca.* 2 : 1, 110 mg). Further elution with ethyl acetate gave some unidentified by-products, followed by 17β-*acetoxy*-3-*methoxy*-14α-*estra*-1,3,5(10)-*triene*-14,15β-*diol* (35) (5 mg), m.p. 149—152 °C (from hexane); $\nu_{max.}$ 3 605, 3 480br, 1 725, and 1 610 cm^{-1}; δ 1.25 (13-Me), 2.06 (OAc), 3.77 (OMe), 4.05 (1 H, q, *J* 7.7 and 2.2 Hz, 15α-H), 5.15 (1 H, q, *J* 8.6 and 7.2 Hz, 17α-H), and 6.58—7.20 (3 H, m, 1-, 2-, and 4-H) (Found: M^+, 360; M^+ − 18, 342.184. $C_{21}H_{28}O_5$ requires *M*, 360; $C_{21}H_{26}O_4$ requires *M*, 342.183), and the 14β,15α-diol (33) (10 mg), identical (m.p., mixed m.p.) with the material described previously. The mixture of (32) and (34) (see above) was treated with potassium t-butoxide in t-butyl alcohol (0.5M, 20 ml) at 25 °C under nitrogen for 1 h. The mixture was acidified with dilute aqueous hydrochloric acid, after which water (50 ml) and chloroform (200 ml) were added. The organic phase was separated, washed with water, and dried, and the solvent was removed *in vacuo*. Chromatography of the residue on silica gel (20 g) with ethyl acetate–hexane (1 : 3) gave 3-*methoxy*-14β-*estra*-1,3,5(10),16-*tetraen*-15-*one* (34) (65 mg), m.p. 68—70 °C (from methanol), $[\alpha]_D$ +326° (*c* 1.0); $\nu_{max.}$ 1 695 and 1 612 cm^{-1}; $\lambda_{max.}$ 225, 279, and 287.5 nm (log ε 4.11, 3.30, and 3.25); Δε +9.7 (224 nm), +1.35 (276 nm), and +0.35 (334 nm); δ 1.24 (13-Me), 3.76 (OMe), 6.02 (1 H, d, *J* 6 Hz, 16-H), 6.54—7.15 (3 H, m, 1-, 2-, and 4-H), and 7.51 (1 H, d, *J* 6 Hz, 17-H) (Found: C, 80.6; H, 7.9%; M^+, 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.85%; *M*, 282).

Treatment of the Acetoxy-ketone (36) *with Base.*—(*a*) A solution of the acetoxy-ketone (36) [29] (200 mg) in t-butyl alcohol (5 ml) was treated with potassium t-butoxide in t-butyl alcohol (1M, 5 ml) at 25 °C under nitrogen. After stirring the mixture for 1 h, dilute aqueous hydrochloric acid was added, followed by ethyl acetate. The organic phase was separated, washed with water and brine, dried, and the solvent was removed *in vacuo*. Chromatography of the residue on silica gel (50 g) with ethyl acetate–hexane (3 : 7) gave the enone (34) (125 mg), identical (m.p., mixed m.p.) with the material obtained in the foregoing experiment.

(*b*) A solution of (36) (2.5 g) in ethanol (150 ml) was treated at 25 °C under nitrogen with methanolic potassium hydroxide (2M, 50 ml). After 30 min, acetic acid (6 ml) was added and the mixture was concentrated to a small volume, diluted with water, and the product was isolated by extraction with ethyl acetate (×2). Chromatography of the residue on silica gel (400 g) with ethyl acetate–hexane (3 : 7) gave 17β-*ethoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (37) (443 mg), m.p. 152—154 °C (from acetone–methanol), $[\alpha]_D$ +120° (*c* 0.8); $\nu_{max.}$ 1 731 and 1 611 cm^{-1}; Δε −2.44 (303 nm) and −2.26sh (310 nm); δ 1.26 (13-Me), 1.22 (3 H, t, *J* 7 Hz, CH_2Me), 3.29—3.70 (3 H, m, 17α-H + CH_2Me), 3.81 (OMe), and 6.55—7.23 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.6; H, 8.9%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328), followed by an inseparable mixture (1.69 g) of the enone (34) and a product which was taken to be the 17β-methoxy-15-ketone (38) (see below). Further elution with the same solvent mixture afforded 3,17α-*dimethoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (39) (85 mg), m.p. 158—161 °C (from acetone–methanol), $[\alpha]_D$ +69° (*c* 0.8); $\nu_{max.}$ 1 737 and 1 610 cm^{-1}; Δε −2.07 (303 nm) and −1.96sh (309 nm); δ 1.30 (13-Me), 3.43 (17-OMe), 3.80 (3-OMe), 3.69 (1 H, t, *J* 8 Hz, 17β-H), and 6.56—7.28 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.1; H, 8.5%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314).

Palladium–calcium carbonate (5%, 500 mg) was added to a mixture (1.25 g) of the enone (34) and the 17β-methoxy-15-ketone (38) in dry ethanol (200 ml). The mixture was stirred under a slightly positive pressure of hydrogen for 15 min. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. Chromatography of the residues on silica gel (200 g) with ethyl acetate–hexane (1 : 4) gave the 15-ketone (40) (940 mg), identical with an authentic sample.[1] Further elution with the same solvent mixture afforded 3,17β-*dimethoxy*-14β-*estra*-1,3,5(10)-*trien*-15-*one* (38) (250 mg), m.p. 125—126 °C (from methanol), $[\alpha]_D$ +133°

(*c* 0.7); $\nu_{max.}$ 1 731 and 1 611 cm^{-1}; $\Delta\varepsilon$ −2.30 (303 nm) and −2.14sh (310 nm); δ 1.24 (13-Me), 3.35 (17-OMe), 3.38 (1 H, t, *J ca.* 5 Hz, 17α-H), 3.78 (3-OMe), and 6.56—7.25 (3 H, m, 1-, 2-, and 4-H) (Found: C, 76.4; H, 8.4%; M^+, 314). Similarly, the pure enone (34) (700 mg) in ethanol (100 ml) was hydrogenated over palladium–calcium carbonate (5%, 250 mg) to give, after work-up and chromatography on silica gel (100 g), the 15-ketone (40) (629 mg).

[0/670 *Received*, 7*th May*, 1980]

REFERENCES

[1] J. R. Bull, J. Floor, and G. J. Kruger, *J. Chem. Research*, 1979, (*S*) 224.
[2] J. R. Bull and J. Floor, *J.C.S. Chem. Comm.*, 1980, 270.
[3] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131.
[4] M. Schüpbach, A. F. Krasso, M. Binder, and Ch. Tamm, *Helv. Chim. Acta*, 1971, **54**, 2007.
[5] H. Hasegawa, Y. Sato, and K. Tsuda, *Chem. Pharm. Bull.* (*Japan*), 1963, **11**, 1275.
[6] P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, 1962, **45**, 1041.
[7] F. Sondheimer, S. Burstein, and R. Mechoulam, *J. Amer. Chem. Soc.*, 1960, **82**, 3209.
[8] G. H. Rasmusson and G. E. Arth, *Steroids*, 1973, **22**, 107.
[9] I. M. Clark, W. A. Denny, E. R. H. Jones, G. D. Meakins, A. Pendlebury, and J. T. Pinhey, *J.C.S. Perkin I*, 1972, 2765.
[10] E. J. Corey and C. U. Kim, *Tetrahedron Letters*, 1974, 287.
[11] J. Dillon and K. Nakanishi, *J. Amer. Chem. Soc.*, 1975, **97**, 5417.
[12] J. R. Bull and J. Floor, *J.C.S. Perkin I*, 1977, 724; J. R. Bull and J. H. Harpur, *S. African J. Chem.*, 1977, **30**, 175.
[13] A. Lardon, H. P. Sigg, and T. Reichstein, *Helv. Chim. Acta*, 1959, **42**, 1457.
[14] A. Lardon and T. Reichstein, *Helv. Chim. Acta*, 1962, **45**, 943.
[15] D. Satoh, M. Horie, and J. Morita, *Chem. Pharm. Bull.* (*Japan*), 1966, **14**, 613.
[16] M. Heller, F. J. McEvoy, and S. Bernstein, *Steroids*, 1964, **3**, 193.
[17] Ch. R. Engel and G. Bach, *Steroids*, 1964, **3**, 593.
[18] K. Meyer, *Helv. Chim. Acta*, 1952, **35**, 2444; H. Linde and K. Meyer, *ibid.*, 1959, **42**, 807.
[19] K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1973, **95**, 2697.
[20] T. Kametani, H. Nemoto, M. Tsubuki, G.-E. Purvaneckas, M. Aizawa, and M. Nishiuchi, *J.C.S. Perkin I*, 1979, 2830.
[21] K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, 1964, **29**, 1136.
[22] G. H. Matthews and A. Hassner in 'Organic Reactions in Steroid Chemistry,' vol. 2, eds J. Fried and J. A. Edwards, Van Nostrand–Reinhold, New York, 1972, ch. 9.
[23] J. M. Diggle, M. D. Halliday, A. Kasal, G. D. Meakins, and M. S. Saltmarsh, *J. Chem. Soc.* (*C*), 1970, 2325.
[24] A. R. Van Horn and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89**, 651, and references cited therein.
[25] W. S. Johnson and W. F. Johns, *J. Amer. Chem. Soc.*, 1957, **79**, 2005.
[26] G. C. Buzby, jun., R. A. Edgren, J. A. Fisher, G. A. Hughes, R. C. Jones, K. Ledig, T. W. Pattison, R. Rees, H. Smith, L. L. Smith, D. M. Teller, and G. R. Wendt, *J. Medicin. Chem.*, 1964, **7**, 755.
[27] G. Langbein, H. J. Siemann, E. Menzer, H. S. Seeger, and I. Gruner, Ger. P (East) 128,564 (*Chem. Abs.*, 1978, **88**, 191,241d).
[28] A. Kh. Sharipov and N. K. Abubakirov, *Khim. Prir. Soedin.*, 1967, **3**, 139 (*Chem. Abs.*, 1967, **67**, 44,001p).
[29] E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, 1964, **29**, 64.