

THE SERINI REACTION OF 16,17-DIHYDROXYSTEROID MONOACETATES

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Abstract—The Serini reaction of 16 α -alkyl (or phenyl)-16 β ,17 β -dihydroxysteroid monoacetates **5** and **10** gave stereospecifically 16 β -substituted steroids **6** and **11** in good yields. This rearrangement was shown to proceed through 1,2 hydride shift. It was found that under the same reaction conditions, 16 α -vinyl-16 β ,17 β -diol 17-acetate **5c** rearranged into *Z*-16-ethylidene compound **24** via 1,4 hydride shift.

During hormonal studies on synthetic steroids, it was found¹ that 17 β -hydroxy-16 β -substituted-estr-4-en-3-ones **1** and the corresponding androst-4-en-3-ones **2** showed antiandrogenic activity with very little estrogenic, progestational and androgenic effects. In the previous paper¹ was reported an introduction of β -substituents at position 16 of steroids by a kinetically controlled reaction. This paper describes the Serini reaction^{2,3} of 16,17-dihydroxysteroid monoacetates which provides another highly stereospecific method for the introduction of β -substituents at position 16 (or 17) of steroids.

In estrane series, the starting compounds, 16 α -substituted-16 β ,17 β -diol 17-acetates **5**, were prepared by Grignard reaction of 16-oxo-steroid **3** with alkyl (or phenyl) magnesium halides followed by acetylation of the resulting diols¹ **4** with acetic anhydride in pyridine. Epoxidation of 16 α -vinyl derivative **5c** with *m*-chloroperbenzoic acid in methylene chloride gave 16 α -(1',2'-epoxy)ethyl-16 β ,17 β -diol 17-acetate **5h** in 75% yield.

The solution of **5** in dried toluene was refluxed on an oil bath (at 150°) with freshly activated zinc[†] dust under N₂ for 4–5 h. The zinc dust was removed by filtration and the solvent was evaporated under reduced pressure to give 16 β -substituted-3-

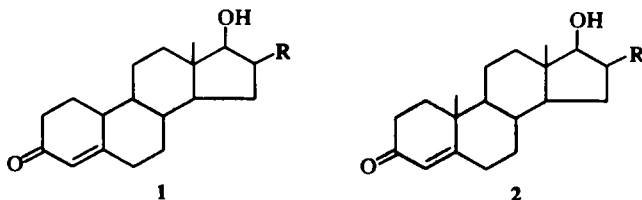
methoxy-estra-1,3,5(10)-trien-17-ones **6**. The summary of some of our results is given in Table 1.

In androstane series, treatment of 16-oxo-3 β ,17 β -bistetrahydropyranyloxy derivative **7** with Grignard reagents yielded 16 α -substituted-3 β ,16 β ,17 β -triol 3,17-bistetrahydropyranyl ethers **8**. Mild acid treatment of **8** gave triols **9** which were acetylated with acetic anhydride-pyridine to afford diacetates **10**. Hydrogenation of **10c** over Raney-Ni in EtOH yielded **10d**. The Serini reaction of **10** gave 3 β -acetoxy-16 β -substituted-androst-5-en-17-ones **11** in excellent yield. The results are summarized in Table 2.

Under the Serini reaction conditions, 16 α -ethyl-estr-4-en-3-one-16 β ,17 β -diol 17-acetate **13**, which was prepared from **4b** by Birch reduction followed by acid treatment to give **12** and then acetylation, was also rearranged into 16 β -ethyl-estr-4-ene-3,17-dione **14** in 94% yield without any interference of an α,β -unsaturated ketonic system in ring A.²

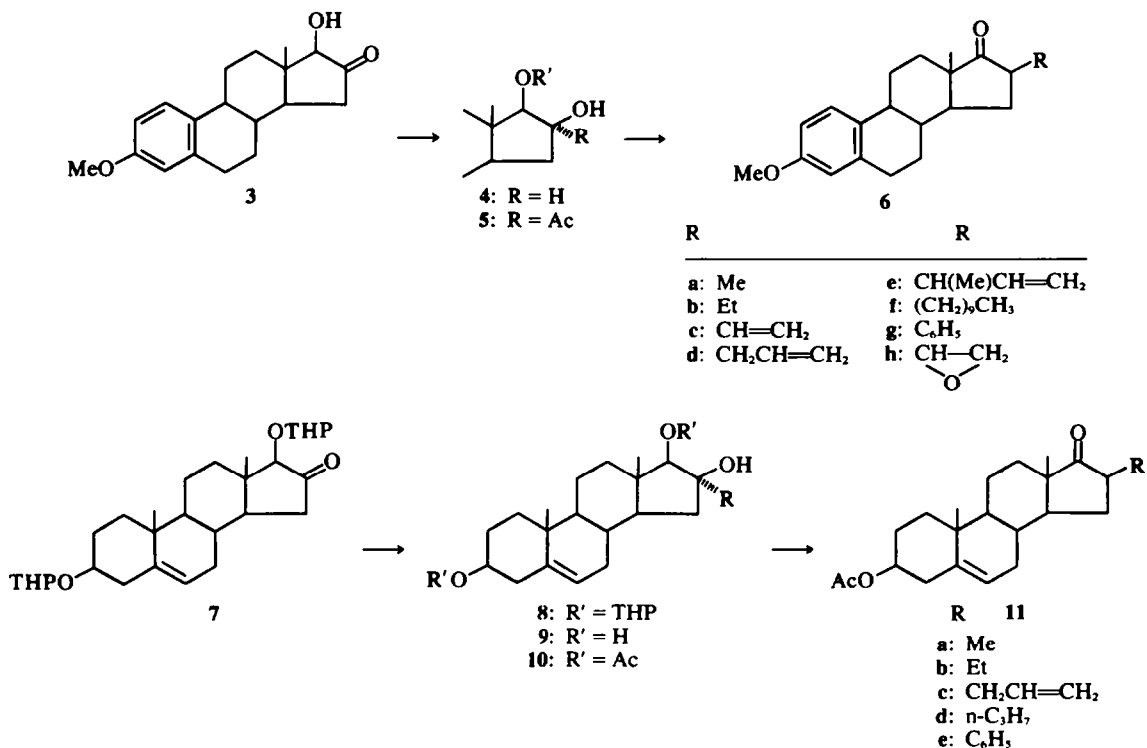
In addition to above-mentioned examples, 17 α -methyl-16 β ,17 β -diol 16-acetate **16**, which was obtained by Grignard reaction of **15**¹⁰ with methyl magnesium iodide, was refluxed with activated zinc dust in dried toluene to afford 17 β -methyl-3-methoxy-estra-1,3,5(10)-trien-16-one **17** in 96% yield.

In order to obtain the mechanistic insight of the Serini reaction, it is worthy to investigate whether 16,17-trans-diol monoacetates undergo the reaction. We prepared the acetates **20** and **22** as follows.

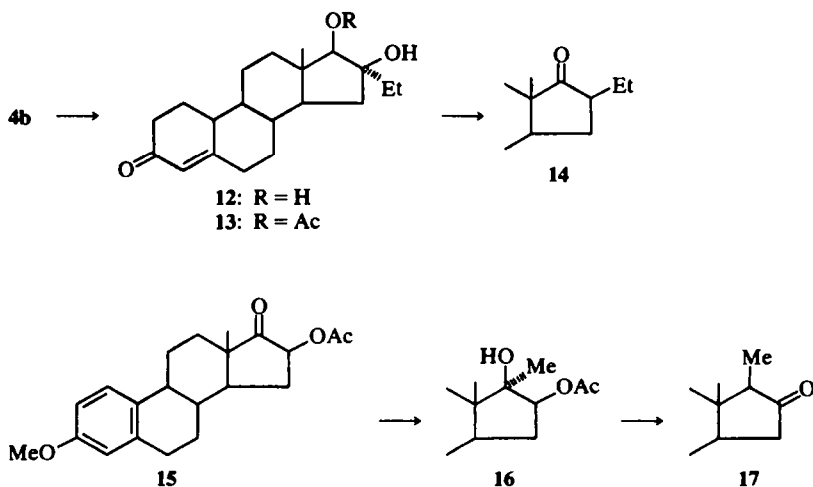


R: Alkyl

SCHEME 1.



SCHEME 2.



SCHEME 3.


4g was oxidized with pyridine-SO₂ complex in DMSO¹¹ to yield an α -ketol **18**. On reduction with LAH* in THF **18** gave trans diol **19** which in turn

*Due to the steric effect of 16 α -phenyl group, 17-ketone was mainly reduced from less hindered β -side to give the 17 α -hydroxy compound.

was acetylated to the corresponding 16 α -phenyl-16 β ,17 α -diol 17-acetate **20**. On the other hand, Grignard reaction of **21**¹⁰ with methyl magnesium iodide in ether-benzene gave 17 α -methyl-16 α ,17 β -diol 16-acetate **22**. Neither **20** nor **22** was affected to the Serini reaction conditions.

These results support the suggestion of the pres-

Table 1. The Serini reaction of 17 β -acetoxy-16 β -hydroxy-16 α -substituted-3-methoxy-estra-1,3,5(10)-trienes

Diol monoacetate R	Reaction time (h)	Product	Yield* (%)
5a ⁶ : Me	3.5	6a ⁶	94
5b : Et	4.0	6b	95
5d : CH ₂ CH=CH ₂	4.0	6d	92
5e : CH(Me)CH=CH ₂	4.0	6e	94
5f : (CH ₂) ₃ CH ₃	4.0	6f	90
5g : C ₆ H ₅	4.5	6g	93
5h : CH—CH ₂ 	4.0	6h	30 [†]

*The yields given are based on recrystallized products from n-hexane-ether (1:1).

[†]Attempted crystallization failed.

Table 2. The Serini reaction of 3 β ,17 β -diacetoxy-16 β -hydroxy-16 α -substituted-androst-5-enes

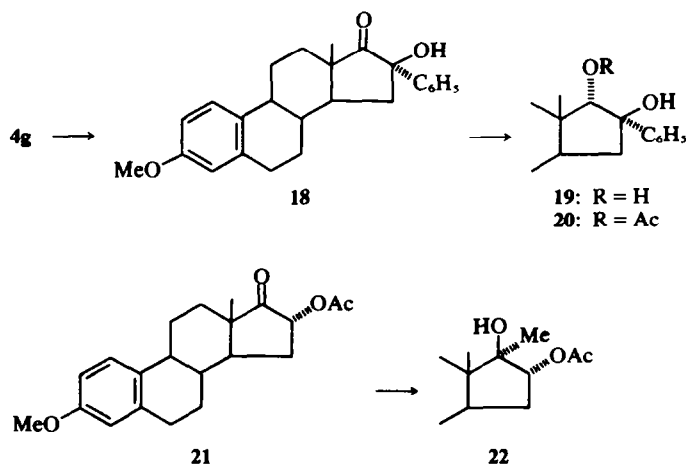
Diol monoacetate R	Reaction time (h)	Product	Yield* (%)
10a : Me	3.0	11a ⁷	92
10b : Et	3.5	11b	93
10c : CH ₂ CH=CH ₂	4.0	11c ⁸	91
10d : n-C ₃ H ₇	4.0	11d ^{8,9}	92
10e : C ₆ H ₅	4.5	11e	94

*The yields given are based on recrystallized products from n-hexane-ether (1:1).

ence of a cyclic orthoacetate intermediate^{3,4} in the Serini reaction.

On a kinetically controlled vinyl-dehydration with H₂SO₄ in MeOH¹, 16 α -vinyl-16 β ,17 β -diol **4c** was converted into *E*-16-ethylidene-3-methoxy-estra-1,3,5(10)-trien-17-one **23**, m.p. 141–142°, in quantitative yield. In contrast, on refluxing with ac-

tivated zinc dust in dried toluene, its 17 β -acetate **5c** was rearranged into *Z*-16-ethylidene isomer **24**, m.p. 117–118°, in 94% yield, together with a small amount of **23** (< 5%). The assignment of configuration of 16-ethylidene groups in **23** and **24** was made by comparison of their NMR spectra. In the NMR spectra of **23** and **24**, vinyl methyl protons appear at



1.85 ($J = 7$ Hz) and 2.14 ppm ($J = 7$ Hz), respectively, and vinyl proton at ca 6.6* and 6.05 ppm ($J = 7$ Hz), respectively. Downfield shift of vinyl methyl protons and upfield shift of vinyl proton of **24** relative to those of **23** indicate that 16-ethylidene groups of **23** and **24** should have *E*- and *Z*-configuration, respectively.

The highly stereospecific formation of *Z*-16-ethylidene isomer **24** prompted us to study the mechanism of the formation. Oxidation of **4** with pyridine-SO₃ complex in DMSO gave **25**. On reduction with NaBD, in MeOH followed by acetylation with acetic anhydride in pyridine, **25** afforded **26** (98% isotope purity†). When treated with activated zinc dust in dried toluene, **26** gave **27** and **23** in a ratio of 3:1. One of the products isolated **27** was partially (33%) deuterated at the vinyl methyl group and no deuteration in **23**.

*Overlapped with aromatic protons.

†Estimated by NMR and mass spectra.

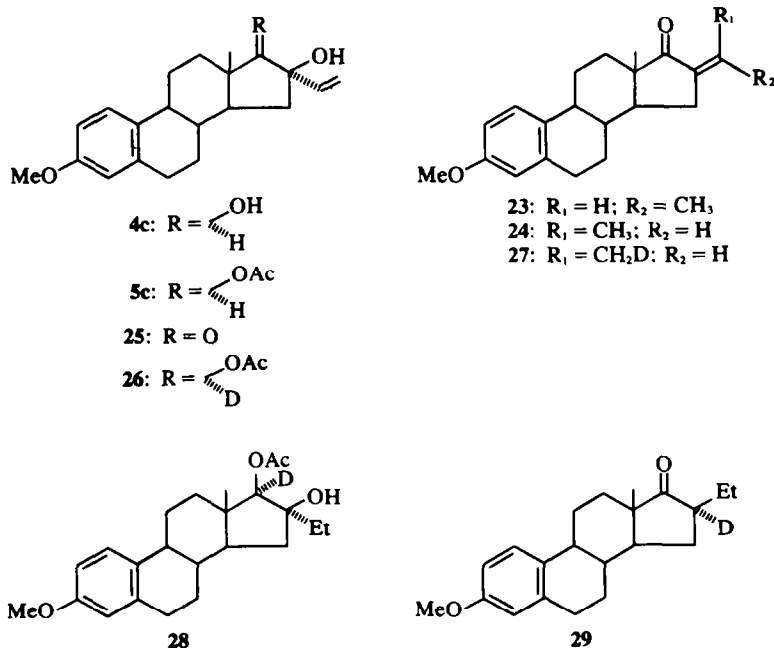
On the other hand, **28** (98% isotope purity), obtained by hydrogenation of **26** over PtO₂ in EtOH, was refluxed with activated zinc dust to afford **29** (97% isotope purity).

These results indicate that the reaction proceeds by a cyclic orthoacetate intermediate^{3,4} **30**, which was rearranged into **27** under 1,4 hydride shift (path a) and into **31** under 1,2 hydride shift³ (path b) which was further isomerized with loss of deuterium to **23**.

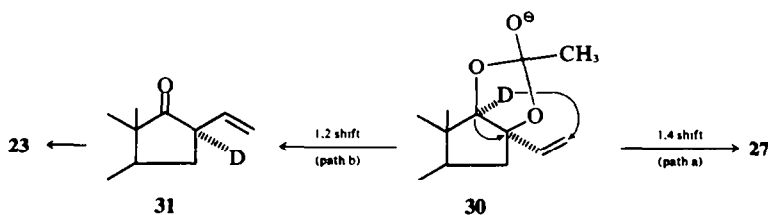
Furthermore, it was found that the addition of catalytic amount of acetic acid accelerated the rearrangement. This suggests that the mechanism of the zinc-catalyzed reaction may be an ionic process.¹

EXPERIMENTAL

All m.ps were uncorrected. UV spectra were measured in EtOH on a Hitachi EPS-3T spectrophotometer. IR spectra were recorded with a Hitachi 215 spectrophotometer. NMR spectra were determined on a Varian HA-100 spectrometer using CDCl₃ as a solvent (unless



SCHEME 5.



SCHEME 6.

otherwise stated); chemical shifts (δ) are given in ppm relative to internal TMS. The mass spectra were determined on a Hitachi RMU-6D mass spectrometer equipped with a direct inlet system. Silicagel GF₂₅₄ (E. Merck) was used for TLC analysis. The organic solns were dried over Na₂SO₄ and evaporated by rotary evaporator.

Grignard reaction of 3. General procedure: To a suspension of Mg ribbon in anhyd ether (or THF) was added dropwise alkyl (or phenyl) halide and the mixture was stirred at room temp for 3 h. To this stirred soln was added dropwise a soln of 3 in anhyd ether (or THF). The mixture was stirred at room temp for 12 h. The excess reagent was decomposed by careful addition of sat NH₄Cl aq and extracted with ether. The extracts were washed with sat NaCl aq, dried, and concentrated to give a resinous material. Recrystallization from n-hexane-ether afforded pure 4. The following compounds were obtained.

16 β ,17 β - Dihydroxy - 16 α - ethyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 4b. Reaction of 3 (15 g) with ethyl magnesium iodide gave 4b (14.8 g), m.p. 131–133°; IR (KBr) 3450 cm⁻¹; NMR 0.84 (3H, s, 18-CH₃), 3.15 (1H, s, 17 α -H), 3.73 (3H, s, OCH₃), 6.5–7.2 (3H, m, Ar); Mass 330 (M⁺), 312. (Found: C, 76.04; H, 8.89. Calc for C₂₇H₃₈O₃: C, 76.32; H, 9.15%).

16 β ,17 β - Dihydroxy - 16 α - vinyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 4c. Reaction of 3 (10 g) with vinyl magnesium bromide gave 4c (8.3 g), m.p. 105°; IR (KBr) 3400, 1635, 910 cm⁻¹; NMR 0.92 (3H, s, 18-CH₃), 3.35 (1H, s, 17 α -H), 3.75 (3H, s, OCH₃), 4.9–5.3 (2H, m, =CH₂), 5.8–6.2 (1H, m, vinyl H), 6.6–7.2 (3H, m, Ar); Mass 328 (M⁺), 310. (Found: C, 76.81; H, 8.62. Calc for C₂₇H₃₆O₃: C, 76.79; H, 8.59%).

16 β ,17 β - Dihydroxy - 16 α - allyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 4d. Reaction of 3 (9.8 g) with allyl magnesium bromide afforded 4d (9.8 g), m.p. 132°; IR (KBr) 3400, 3100, 1635, 910 cm⁻¹; NMR 0.85 (3H, s, 18-CH₃), 3.22 (1H, s, 17 α -H), 3.75 (3H, s, OCH₃), 5.0–5.3 (2H, m, =CH₂), 5.6–6.2 (1H, m, vinyl H), 6.5–7.2 (3H, m, Ar); Mass 342 (M⁺), 301. (Found: C, 77.32; H, 8.94. Calc for C₂₈H₄₀O₃: C, 77.15; H, 8.83%).

16 β ,17 β - Dihydroxy - 16 α - (1' - methyl) allyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 4e. Reaction of 3 (4 g) with crotyl magnesium chloride¹² afforded 4e (3.6 g), m.p. 128–129°; IR (KBr) 3400, 1620 cm⁻¹; NMR 0.86 (3H, s, 18-CH₃), 1.06, 1.08 (total 3H, each d, J = 7 Hz, CH₃), 3.30 (1H, s, 17 α -H), 3.72 (3H, s, OCH₃), 4.9–5.2 (2H, m, =CH₂), 5.8–6.0 (1H, m, vinyl H), 6.5–7.2 (3H, m, Ar); Mass 356 (M⁺), 283. (Found: C, 77.61; H, 9.20. Calc for C₂₉H₄₂O₃: C, 77.49; H, 9.05%).

16 β ,17 β - Dihydroxy - 16 α - n - decyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 4f. Reaction of 3 (6 g) with n-decyl magnesium bromide gave 4f (5.3 g) as a colorless oil. IR (CHCl₃) 3400 cm⁻¹; NMR 0.85 (3H, s, 18-CH₃), 0.88 (3H, t, J = 6 Hz, CH₃), 3.16 (1H, s, 17 α -H), 3.72 (3H, s, OCH₃), 6.5–7.2 (3H, m, Ar); Mass 442 (M⁺), 424.

16 β ,17 β - Dihydroxy - 16 α - phenyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 4g. Reaction of 3 (15.5 g) with phenyl magnesium bromide gave 4g (15.3 g), m.p. 161–162°; IR (KBr) 3400, 1605 cm⁻¹; NMR 0.98 (3H, s, 18-CH₃), 3.12 (1H, s, 17 α -H), 3.73 (3H, s, OCH₃), 6.5–7.6 (8H, m, Ar); Mass 378 (M⁺), 360. (Found: C, 79.29; H, 8.02. Calc for C₂₉H₃₈O₃: C, 79.33; H, 7.99%).

Acetylation of 4. General procedure: A mixture of 4 in Ac₂O and dried pyridine was kept to 40° for 8 h, concentrated, and added 5% NaHCO₃ aq. The mixture was extracted with ether. The extracts were washed with sat NaCl aq, dried, and concentrated to give a resinous ma-

terial. Recrystallization from n-hexane-ether gave pure 5. The following compounds were prepared.

17 β - Acetoxy - 16 β - hydroxy - 16 α - ethyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5b. M.p. 106°; IR (KBr) 3450, 1730 cm⁻¹; NMR 0.89 (3H, t, J = 7 Hz, CH₃), 0.94 (3H, s, 18-CH₃), 2.13 (3H, s, OAc), 3.73 (3H, s, OCH₃), 4.53 (1H, s, 17 α -H), 6.5–7.4 (3H, m, Ar); Mass 372 (M⁺), 312. (Found: C, 74.29; H, 8.55. Calc for C₂₉H₃₈O₄: C, 74.16; H, 8.66%).

17 β - Acetoxy - 16 β - hydroxy - 16 α - vinyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5c. M.p. 133–134°; IR (KBr) 3450, 1730, 1620 cm⁻¹; NMR 0.98 (3H, s, 18-CH₃), 2.10 (3H, s, OAc), 3.69 (3H, s, OCH₃), 4.65 (1H, s, 17 α -H), 4.6–5.3 (2H, m, =CH₂), 5.7–6.1 (1H, m, vinyl H), 6.5–7.2 (3H, m, Ar); Mass 370 (M⁺), 310. (Found: C, 74.33; H, 8.25. Calc for C₂₈H₃₆O₄: C, 74.56; H, 8.16%).

17 β - Acetoxy - 16 β - hydroxy - 16 α - allyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5d. M.p. 113–114°; IR (KBr) 3450, 1735, 1620 cm⁻¹; NMR 0.94 (3H, s, 18-CH₃), 2.11 (3H, s, OAc), 3.73 (3H, s, OCH₃), 4.67 (1H, s, 17 α -H), 5.0–5.3 (2H, m, =CH₂), 5.6–6.0 (1H, m, vinyl H), 6.5–7.2 (3H, m, Ar); Mass 384 (M⁺), 343, 324. (Found: C, 74.79; H, 8.48. Calc for C₂₈H₃₈O₄: C, 74.97; H, 8.39%).

17 β - Acetoxy - 16 β - hydroxy - 16 α - (1' - methyl) allyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5e. A colorless oil; IR (CHCl₃) 3500, 1735, 1640 cm⁻¹; NMR 0.97, 0.98 (total 3H, s, 18-CH₃), 2.23 (3H, s, OAc), 3.71 (3H, s, OCH₃), 4.66 (1H, s, 17 α -H), 5.0–5.2 (2H, m, =CH₂), 5.5–5.8 (1H, m, vinyl H), 6.5–7.2 (3H, m, Ar); Mass 398 (M⁺), 356, 338.

17 β - Acetoxy - 16 β - hydroxy - 16 α - n - decyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5f. A colorless oil; IR (CHCl₃) 3450, 1730 cm⁻¹; NMR 0.88 (3H, t, J = 6 Hz, CH₃), 0.91 (3H, s, 18-CH₃), 2.12 (3H, s, OAc), 3.71 (3H, s, OCH₃), 4.65 (1H, s, 17 α -H), 6.5–7.4 (3H, m, Ar); Mass 484 (M⁺), 424.

17 β - Acetoxy - 16 β - hydroxy - 16 α - phenyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5g. M.p. 187–188°; IR (KBr) 3450, 1730, 1610 cm⁻¹; NMR 1.09 (3H, s, 18-CH₃), 2.07 (3H, s, OAc), 3.74 (3H, s, OCH₃), 5.07 (1H, s, 17 α -H), 6.6–7.6 (8H, m, Ar); Mass 420 (M⁺), 360. (Found: C, 77.19; H, 7.58. Calc for C₂₉H₃₈O₄: C, 77.11; H, 7.67%).

17 β - Acetoxy - 16 β - hydroxy - 16 α - (1',2' - epoxy)ethyl - 3 - methoxy - *estra* - 1,3,5(10) - triene 5h. A mixture of 5c (3 g) and m-chloroperbenzoic acid (3 g) in CH₂Cl₂ (50 ml) was allowed to stand at room temp for 10 h, then added sat NaHCO₃ aq and extracted with ether. The extracts were washed with sat NaCl aq, dried, and evaporated, giving an oil. Recrystallization from n-hexane-ether gave pure 5h (2.3 g), mp 86°; IR (KBr) 3400, 1730 cm⁻¹; NMR 0.98 (3H, s, 18-CH₃), 2.13 (3H, s, OAc), 2.67 (2H, q, J = 4 Hz, 3 Hz, —CH₂—), 3.01 (1H, t, J =

3 Hz, —CH—C—C—), 3.73 (3H, s, OCH₃), 4.70 (1H, s, 17 α -H), 6.6–7.2 (3H, m, Ar); Mass 386 (M⁺), 370, 310. (Found: C, 71.53; H, 7.89. Calc for C₂₉H₃₈O₅: C, 71.48; H, 7.82%).

The Serini reaction of 5. General procedure: To a soln of 5 in dried toluene was added freshly activated zinc dust. The mixture was refluxed on an oil bath (at 150°) with stirring under N₂ for 4 h. The zinc dust was removed by filtration and the solid was washed with toluene thoroughly. The combined filtrates were evaporated under vacuum to give a resinous material. Recrystallization from n-hexane-ether afforded pure 6. The following compounds were obtained.

16 β - Ethyl - 3 - methoxy - *estra* - 1,3,5(10) - triene - 17 - one 6b. M.p. 94°; IR (KBr) 1745 cm⁻¹; NMR 0.84 (3H, s,

18-CH₃), 0.97 (3H, t, J = 7 Hz, CH₃), 3.73 (3H, s, OCH₃), 6.6-7.2 (3H, m, Ar); Mass 312 (M⁺), 283. (Found: C, 80.71; H, 9.09. Calc for C₂₁H₂₆O₂: C, 80.73; H, 9.03%).

16β - *Allyl - 3 - methoxy - estra - 1,3,5(10) - trien - 17 - one* 6d. M.p. 98°; IR (KBr) 1740, 1635, 905 cm⁻¹; NMR 0.80 (3H, s, 18-CH₃), 3.68 (3H, s, OCH₃), 4.8-5.2 (2H, m, =CH₂), 5.5-5.9 (1H, m, vinyl H), 6.4-7.2 (3H, m, Ar); Mass 324 (M⁺), 283. (Found: C, 81.32; H, 8.79. Calc for C₂₂H₂₈O₂: C, 81.44; H, 8.70%).

16β - (1' - *Methylallyl - 3 - methoxy - estra - 1,3,5(10) - trien - 17 - one* 6e. M.p. 65-67°; IR (KBr) 1735, 1640 cm⁻¹; NMR 0.78, 0.80 (total 3H, s, 18-CH₃), 0.99, 1.13 (total 3H, d, J = 6 Hz, CH₃), 3.70 (3H, s, OCH₃), 4.8-5.1 (2H, m, =CH₂), 5.5-6.0 (1H, m, vinyl H), 6.6-7.2 (3H, m, Ar); Mass 338 (M⁺), 283. (Found: C, 81.50; H, 8.99. Calc for C₂₃H₃₀O₂: C, 81.61; H, 8.93%).

16β - *n - Decyl - 3 - methoxy - estra - 1,3,5(10) - trien - 17 - one* 6f. M.p. 98-100°; IR (KBr) 1735 cm⁻¹; NMR 0.86 (3H, s, 18-CH₃), 0.98 (3H, t, J = 6 Hz, CH₃), 3.75 (3H, s, OCH₃), 6.6-7.2 (3H, m, Ar); Mass 424 (M⁺), 409. (Found: C, 82.34; H, 10.68. Calc for C₂₉H₄₄O₂: C, 82.02; H, 10.44%).

16β - *Phenyl - 3 - methoxy - estra - 1,3,5(10) - trien - 17 - one* 6g. M.p. 150-151°; IR (KBr) 1740, 1605 cm⁻¹; NMR 0.91 (3H, s, 18-CH₃), 3.39 (1H, q, J = 10 Hz, 8 Hz, 16α-H), 3.73 (3H, s, OCH₃), 6.5-7.4 (8H, m, Ar); Mass 360 (M⁺). (Found: C, 83.14; H, 7.80. Calc for C₂₂H₂₆O₂: C, 83.29; H, 7.83%).

16β - (1',2' - *Epoxyethyl - 3 - methoxy - estra - 1,3,5(10) - trien - 17 - one* 6h. A colorless oil; IR (CHCl₃) 1735 cm⁻¹; NMR 0.87 (3H, s, 18-CH₃), 3.70 (3H, s, OCH₃), 6.4-7.2 (3H, m, Ar); Mass 326 (M⁺), 310.

Grignard reaction of 7 was performed by the same procedure as used in 4. The following materials were obtained.

3β,17β - *Bistetrahydropyranyloxy - 16β - hydroxy - 16α - ethyl - androst - 5 - ene* 8b. Reaction of 7 (8.1 g) with ethyl magnesium iodide gave 8b (7 g), m.p. 168-170°; IR (KBr) 3500 cm⁻¹; NMR 0.93 (3H, s, 18-CH₃), 1.02 (3H, s, 19-CH₃), 3.92 (1H, s, 17α-H), 5.34 (1H, t, J = 3 Hz, 6-H); Mass 502 (M⁺). (Found: C, 74.25; H, 10.11. Calc for C₃₁H₅₀O₃: C, 74.06; H, 10.03%).

3β,17β - *Bistetrahydropyranyloxy - 16β - hydroxy - 16α - allyl - androst - 5 - ene* 8c. Reaction of 7 (10 g) with allyl magnesium bromide gave 8c (10 g), m.p. 168-170°; IR (KBr) 3500, 3100, 1635, 900 cm⁻¹; NMR 0.93 (3H, s, 18-CH₃), 1.02 (3H, s, 19-CH₃), 3.92 (1H, s, 17α-H), 4.9-5.2 (2H, m, =CH₂), 5.33 (1H, t, J = 3 Hz, 6-H), 5.6-6.2 (1H, m, vinyl H); Mass 514 (M⁺). (Found: C, 76.53; H, 9.80. Calc for C₃₂H₅₀O₃: C, 74.67; H, 9.79%).

3β,17β - *Bistetrahydropyranyloxy - 16β - hydroxy - 16α - phenyl - androst - 5 - ene* 8e. Reaction of 7 (3.5 g) with phenyl magnesium bromide afforded 8e (3.6 g), m.p. 175-177°; IR (KBr) 3500, 1600 cm⁻¹; NMR 1.06 (6H, s, 18-CH₃ and 19-CH₃), 4.15 (1H, s, 17α-H), 5.34 (1H, t, J = 3 Hz, 6-H); Mass 550 (M⁺). (Found: C, 76.47; H, 9.47. Calc for C₃₃H₅₀O₃: C, 76.32; H, 9.15%).

Hydrolysis of 8. General procedure: To a stirred soln of 8 in MeOH was added 0.2% HCl aq. After standing for 30 min at 25° the mixture was added to 5% NaHCO₃ aq and extracted with AcOEt. The AcOEt extracts were washed with sat NaCl aq, dried, and concentrated, giving an amorphous product. Recrystallization from MeOH-ether gave 9. The following compounds were obtained. 3β,16β,17β - *Trihydroxy - 16α - ethyl - androst - 5 - ene* 9b. M.p. 226-227°; IR (KBr) 3500 cm⁻¹; NMR (d₆-DMSO) 0.75 (3H, s, 18-CH₃), 0.86 (3H, t, J = 6 Hz, CH₃), 0.95 (3H,

s, 19-CH₃), 3.1-3.3 (2H, m, 3α-H and 17α-H), 5.26 (1H, t, J = 3 Hz, 6-H); Mass 334 (M⁺), 316. (Found: C, 75.51; H, 10.33. Calc for C₂₁H₃₄O₃: C, 75.40; H, 10.25%). 3β,16β,17β - *Trihydroxy - 16α - allyl - androst - 5 - ene* 9c. M.p. 217-218°; IR (KBr) 3500, 1630, 900 cm⁻¹; NMR (d₆-DMSO) 0.75 (3H, s, 18-CH₃), 0.96 (3H, s, 19-CH₃), 3.1-3.3 (2H, m, 3α-H and 17α-H), 4.9-5.2 (2H, m, =CH₂), 5.28 (1H, t, J = 3 Hz, 6-H), 5.6-6.2 (1H, m, vinyl H); Mass 346 (M⁺), 328. (Found: C, 76.26; H, 9.90. Calc for C₂₂H₃₄O₃: C, 76.26; H, 9.89%). 3β,16β,17β - *Trihydroxy - 16α - phenyl - androst - 5 - ene* 9e. An amorphous powder; IR (KBr) 3500, 1600 cm⁻¹; NMR (d₆-DMSO) 0.92 (3H, s, 18-CH₃), 0.98 (3H, s, 19-CH₃), 3.1-3.3 (2H, m, 3α-H and 17α-H), 5.28 (1H, t, J = 3 Hz, 6-H), 7.3-7.5 (5H, m, Ar); Mass 382 (M⁺), 364.

Acetylation of 9 was performed by the same procedure as used in 5. The following compounds were obtained. 3β,17β - *Diacetoxy - 16β - hydroxy - 16α - methyl - androst - 5 - ene* 10a. M.p. 182-183°; IR (KBr) 3450, 1735 cm⁻¹; NMR 0.93 (3H, s, 18-CH₃), 1.02 (3H, s, 19-CH₃), 1.33 (3H, s, 16α-CH₃), 2.02 (3H, s, OAc), 2.16 (3H, s, OAc), 4.42 (1H, s, 17α-H), 4.4-4.6 (1H, m, 3α-H), 5.39 (1H, t, J = 3 Hz, 6-H); Mass 404 (M⁺), 362, 344. (Found: C, 71.29; H, 8.76. Calc for C₂₆H₃₈O₅: C, 71.25; H, 8.97%). 3β,17β - *Diacetoxy - 16β - hydroxy - 16α - ethyl - androst - 5 - ene* 10b. M.p. 159°; IR (KBr) 3450, 1735 cm⁻¹; NMR 0.88 (3H, t, J = 6 Hz, CH₃), 0.94 (3H, s, 18-CH₃), 1.02 (3H, s, 19-CH₃), 2.01 (3H, s, OAc), 2.13 (3H, s, OAc), 4.48 (1H, s, 17α-H), 4.4-4.6 (1H, m, 3α-H), 5.38 (1H, t, J = 3 Hz, 6-H); Mass 418 (M⁺), 376, 358. (Found: C, 71.80; H, 9.04. Calc for C₂₇H₃₈O₅: C, 71.74; H, 9.15%). 3β,17β - *Diacetoxy - 16β - hydroxy - 16α - allyl - androst - 5 - ene* 10c. M.p. 162-163°; IR (KBr) 3500, 1735, 1630, 900 cm⁻¹; NMR 0.93 (3H, s, 18-CH₃), 1.02 (3H, s, 19-CH₃), 2.02 (3H, s, OAc), 2.13 (3H, s, OAc), 4.50 (1H, s, 17α-H), 4.4-4.6 (1H, m, 3α-H), 4.9-5.3 (2H, m, =CH₂), 5.36 (1H, t, J = 3 Hz, 6-H), 5.6-6.2 (1H, m, vinyl H); Mass 430 (M⁺), 388, 370. (Found: C, 72.64; H, 8.86. Calc for C₂₈H₃₈O₅: C, 72.52; H, 8.90%).

3β,17β - *Diacetoxy - 16β - hydroxy - 16α - n - propyl - androst - 5 - ene* 10d. 10c (2.2 g) in EtOH (40 ml) was hydrogenated over Raney-Ni catalyst (W-3, 0.6 g) at room temp. After H₂ absorption ceased, the catalyst was filtered off, and the solvent was evaporated to give crystals. Recrystallization from n-hexane-ether afforded pure 10d (2.1 g), m.p. 170°; IR (KBr) 3450, 1735 cm⁻¹; NMR 0.93 (3H, s, 18-CH₃), 1.02 (3H, s, 19-CH₃), 2.01 (3H, s, OAc), 2.14 (3H, s, OAc), 4.49 (1H, s, 17α-H), 4.4-4.6 (1H, m, 3α-H), 5.35 (1H, t, J = 3 Hz, 6-H); Mass 432 (M⁺), 390, 372. (Found: C, 72.07; H, 9.55. Calc for C₂₉H₄₀O₅: C, 72.19; H, 9.32%).

3β,17β - *Diacetoxy - 16β - hydroxy - 16α - phenyl - androst - 5 - ene* 10e. M.p. 155°; IR (KBr) 3450, 1735, 1605 cm⁻¹; NMR 1.07 (6H, s, 18-CH₃ and 19-CH₃), 2.00 (3H, s, OAc), 2.04 (3H, s, OAc), 4.4-4.6 (1H, m, 3α-H), 5.01 (1H, s, 17α-H), 5.38 (1H, t, J = 3 Hz, 6-H), 7.2-7.6 (5H, m, Ar); Mass 466 (M⁺), 424, 406. (Found: C, 74.70; H, 8.33. Calc for C₂₉H₃₈O₅: C, 74.65; H, 8.21%).

The Serini reaction of 10 was performed by the same procedure as used in 6. The following compounds were obtained. 3β - *Acetoxy - 16β - ethyl - androst - 5 - en - 17 - one* 11b. M.p. 135°; IR (KBr) 1740, 1715 cm⁻¹; NMR 0.83 (3H, s, 18-CH₃), 0.90 (3H, t, J = 6 Hz, CH₃), 1.04 (3H, s, 19-CH₃), 2.03 (3H, s, OAc), 4.4-4.7 (1H, m, 3α-H), 5.47 (1H, t, J = 3 Hz, 6-H); Mass 358 (M⁺), 298. (Found: C, 77.09; H, 9.48. Calc for C₂₃H₃₄O₃: C, 77.05; H, 9.56%).

3β - *Acetoxy - 16β - phenyl - androst - 5 - en - 17 - one* 11e. M.p. 169-170°; IR (KBr) 1740, 1715, 1605 cm⁻¹; NMR

0.91 (3H, s, 18-CH₃), 1.07 (3H, s, 19-CH₃), 2.03 (3H, s, OAc), 3.39 (1H, q, J = 10 Hz, 8 Hz, 16 α -H), 4.5-4.7 (1H, m, 3 α -H), 5.43 (1H, t, J = 3 Hz, 6-H), 7.28 (5H, s, Ar); Mass 406 (M⁺), 346. (Found: C, 79.80; H, 8.41. Calc for C₂₇H₃₆O₅: C, 79.76; H, 8.43%).

16 β ,17 β -Dihydroxy-16 α -ethyl-estr-4-en-3-one 12. A soln of **4b** (5 g) in 60 ml of 5:1 THF:EtOH was added dropwise to a stirred soln of liquid NH₃ (200 ml). Li ribbon (4 g) in ca 0.3 g portion was added to the mixture which was maintained at -50° by appropriate dry ice-acetone cooling. After an additional 1 h, the NH₃ was evaporated in a slow stream of N₂ and then water (200 ml) was added. The mixture was extracted with ether. The extracts were washed with sat NaCl aq, dried, and concentrated to dryness to give an amorphous powder. To a stirred soln of this material in MeOH (30 ml) was added 6N HCl aq (15 ml). After 30 min water (30 ml) was added and the mixture was extracted with ether and worked up in the usual manner to give an oily product, **12** (4.6 g); UV (EtOH) λ_{max} nm (ϵ) 240 (14,000); IR (CHCl₃) 3400, 1690, 1610 cm⁻¹; NMR 0.89 (3H, s, 18-CH₃), 3.12 (1H, s, 17 α -H), 5.81 (1H, s, 4-H); Mass 318 (M⁺).

17 β -Acetoxy-16 β -hydroxy-16 α -ethyl-estr-4-en-3-one 13. A mixture of **12** (5 g) in Ac₂O (7 g) and pyridine (60 ml) was kept at room temp for 5 h, concentrated and added 5% NaHCO₃ aq. The mixture was extracted with ether and worked up to give **13** (5 g), m.p. 178-180°; UV (EtOH) λ_{max} nm (ϵ) 240 (15,500); IR (KBr) 1735, 1690, 1610 cm⁻¹; NMR 0.87 (3H, t, J = 7 Hz, CH₃), 0.98 (3H, s, 18-CH₃), 2.13 (3H, s, OAc), 4.47 (1H, s, 17 α -H), 5.81 (1H, s, 4-H); Mass 360 (M⁺), 300. (Found: C, 73.47; H, 8.89. Calc for C₂₇H₃₆O₄: C, 73.30; H, 8.95%).

16 β -Ethyl-estr-4-ene-3,17-dione 14. The Serini reaction of **13** (1.3 g) was performed by the same procedure as used in **6**; **14** (1.02 g), m.p. 79-80°; UV (EtOH) λ_{max} nm (ϵ) 240 (14,000); IR (KBr) 1735, 1690, 1605 cm⁻¹; NMR 0.86 (3H, s, 18-CH₃), 5.81 (1H, s, 4-H); Mass 300 (M⁺), 285. (Found: C, 79.93; H, 9.24. Calc for C₂₆H₂₈O₂: C, 79.95; H, 9.39%).

16 β -Acetoxy-17 β -hydroxy-17 α -methyl-3-methoxy-estra-1,3,5(10)-triene 16. To a suspension of Mg ribbon (1.5 g) in anhyd ether was added dropwise methyl iodide (9.4 g) and stirred at room temp for 3 h. To this soln was added dropwise a soln of **15** (3 g) in anhyd ether-benzene. The mixture was stirred at 5° for 3 h and worked up in the usual manner to afford an oil. Recrystallization from n-hexane-ether gave pure **16** (1.2 g), m.p. 117°; IR (KBr) 3400, 1730 cm⁻¹; NMR 0.90 (3H, s, 18-CH₃), 1.23 (3H, s, 17 α -CH₃), 2.07 (3H, s, OAc), 3.73 (3H, s, OCH₃), 4.75 (1H, q, J = 8 Hz, 5 Hz, 16 α -H), 6.6-7.2 (3H, m, Ar); Mass 358 (M⁺), 316. (Found: C, 73.80; H, 8.37. Calc for C₂₇H₃₆O₄: C, 73.71; H, 8.44%).

17 β -Methyl-3-methoxy-estra-1,3,5(10)-trien-16-one 17. The Serini reaction of **16** (500 mg) was performed by the same procedure as used in **6**; **17** (430 mg), m.p. 148-150°; IR (KBr) 1735 cm⁻¹; NMR 0.73 (3H, s, 18-CH₃), 0.90 (3H, d, J = 3 Hz, 17 β -CH₃), 3.76 (3H, s, OCH₃), 6.5-7.2 (3H, m, Ar); Mass 298 (M⁺). (Found: C, 80.41; H, 8.66. Calc for C₂₆H₃₄O₂: C, 80.49; H, 8.78%).

16 β -Hydroxy-16 α -phenyl-3-methoxy-estra-1,3,5(10)-trien-17-one 18. To a stirred soln of **4g** (4.5 g) in DMSO (40 ml) at 10° was added pyridine-SO₂ complex (13 g) and Et₃N (5 ml). After stirring for 10 min water was added, made acidic with 6N HCl aq, to separate the crude crystals. The solid was separated and recrystallization from n-hexane-ether gave pure **18** (4.1 g), m.p. 162-163°; IR (KBr) 3450, 1735, 1605 cm⁻¹; NMR 1.16 (3H, s, 18-

CH₃), 3.21 (3H, s, OCH₃), 6.6-7.3 (8H, m, Ar); Mass 376 (M⁺), 348. (Found: C, 79.63; H, 7.45. Calc for C₂₅H₃₀O₃: C, 79.75; H, 7.50%).

16 β ,17 α -Dihydroxy-16 α -phenyl-3-methoxy-estra-1,3,5(10)-triene 19. A soln of **18** (2.1 g) in anhyd ether (50 ml) was added dropwise to a soln of LAH (2.3 g) in anhyd ether (100 ml) under ice-bath cooling. The mixture was stirred at room temp for 2 h. The excess reagent and the complex were decomposed by careful addition of H₂O (4 ml). The mixture was filtered and the solid was washed with AcOEt thoroughly. The combined filtrates were evaporated to give a residue. Recrystallization from n-hexane-ether afforded pure **19** (1.5 g), m.p. 128-129°; IR (KBr) 3450, 1605 cm⁻¹; NMR 1.19 (3H, s, 18-CH₃), 3.62 (1H, s, 17 β -H), 3.74 (3H, s, OCH₃), 6.5-7.6 (8H, m, Ar); Mass 378 (M⁺), 360. (Found: C, 79.31; H, 8.01. Calc for C₂₅H₃₀O₃: C, 79.33; H, 7.99%).

17 α -Acetoxy-16 β -hydroxy-16 α -phenyl-3-methoxy-estra-1,3,5(10)-triene 20. Acetylation of **19** (1.2 g) was performed by the same procedure as used in **5**; **20** (1.1 g), a colorless oil; IR (CHCl₃) 3450, 1735, 1605 cm⁻¹; NMR 1.27 (3H, s, 18-CH₃), 1.45 (3H, s, OAc), 3.77 (3H, s, OCH₃), 4.93 (1H, s, 17 β -H), 6.6-7.4 (8H, m, Ar); Mass 420 (M⁺), 360.

E-16-Ethylidene-3-methoxy-estra-1,3,5(10)-trien-17-one 23. To a stirred soln at 25° of **4c** (6.5 g) in MeOH (40 ml) was added dropwise (2 min) conc H₂SO₄ (10 ml). After standing for 3 min at 25° the mixture was poured into sat NaHCO₃ aq (100 ml) and extracted with ether. The extracts were washed with sat NaCl aq, dried, and concentrated to dryness to yield **23**. Recrystallization from n-hexane-ether gave pure **23** (6.3 g), m.p. 141-142°; UV (EtOH) λ_{max} nm (ϵ) 231 (13,500); IR (KBr) 1705, 1630 cm⁻¹; NMR 0.92 (3H, s, 18-CH₃), 1.85 (3H, d, J = 7 Hz, =CCH₃), 3.78 (3H, s, OCH₃), ca. 6.6 (1H, vinyl H), 6.5-7.3 (3H, m, Ar); Mass 310 (M⁺), 295. (Found: C, 81.19; H, 8.49. Calc for C₂₁H₂₆O₂: C, 81.25; H, 8.44%).

Z-16-Ethylidene-3-methoxy-estra-1,3,5(10)-trien-17-one 24. The Serini reaction of **5c** (3.1 g) was performed by the same procedure as used in **6**; **24** (2.45 g), m.p. 117-118°; UV (EtOH) λ_{max} nm (ϵ) 231 (13,500); IR (KBr) 1705, 1630 cm⁻¹; NMR 0.90 (3H, s, 18-CH₃), 2.14 (3H, d, J = 7 Hz, =CCH₃), 3.69 (3H, s, OCH₃), 6.05 (1H, q, J = 7 Hz, vinyl H), 6.5-7.2 (3H, m, Ar); Mass 310 (M⁺), 295. (Found: C, 81.22; H, 8.31. Calc for C₂₁H₂₆O₂: C, 81.25; H, 8.44%).

16 β -Hydroxy-16 α -vinyl-3-methoxy-estra-1,3,5(10)-trien-17-one 25. Oxidation of **4c**. Oxidation of **4c** (3.5 g) with pyridine-SO₂ complex in DMSO was performed by the same procedure as used in **18**; **25** (3.1 g), m.p. 109-110°; IR (KBr) 3400, 1740, 1605 cm⁻¹; NMR 1.05 (3H, s, 18-CH₃), 3.72 (3H, s, OCH₃), 5.1-5.4 (2H, m, =CH₂), 5.7-6.1 (1H, m, vinyl H), 6.6-7.2 (3H, m, Ar); Mass 326 (M⁺). (Found: C, 77.31; H, 8.10. Calc for C₂₁H₂₆O₂: C, 77.27; H, 8.03%).

17 β -Acetoxy-17 α -deutero-16 β -hydroxy-16 α -vinyl-3-methoxy-estra-1,3,5(10)-triene 26. To a stirred soln of **25** (1.2 g) in MeOH (15 ml) at 5° under N₂ was added a chilled soln of NaBD₄ (150 mg) in MeOH (3 ml). After 30 min at 5° the mixture was added to water (30 ml) and extracted with ether. The extracts were washed with sat NaCl aq, dried, and concentrated to dryness. The residue was acetylated by the same procedure as used in **5**; **26** (1.0 g), m.p. 134°; IR (KBr) 3450, 1730, 1620 cm⁻¹; NMR no signal of 17 α -H; Mass 317 (M⁺), 329, 311. (Found: C, 74.43; H, 8.33. Calc for C₂₁H₂₆DO₂: C, 74.35; H, 8.41%).

Z - 16 - (2' - Monodeutero)ethylidene - 3 - methoxy - *estra* - 1,3,5(10) - *trien* - 17 - *one* **27**. The Serini reaction of **26** (540 mg) was performed by the same procedure as used in **24**; An oily product was chromatographed on silicagel (20 g) with benzene-AcOEt (5:1). Evaporation of the fractions eluted with benzene-AcOEt (5:1) yielded **27** (125 mg), m.p. 116–118°; UV (EtOH) λ_{\max} nm (ϵ) 231 (13,500); IR (KBr) 1705, 1630 cm^{-1} ; NMR 0.90 (3H, s, 18-CH₃), 2.14 (2H, br. d, J = 7 Hz, =CCH₂D), 3.69 (3H, s, OCH₃), 6.0–6.2 (1H, m, vinyl H), 6.5–7.2 (3H, m, Ar); Mass 311 (M⁺), 295.

17 β - Acetoxy - 17 α - deuterio - 16 β - hydroxy - 16 α - ethyl - 3 - methoxy - *estra* - 1,3,5(10) - *triene* **28**. A soln of **26** (510 mg) in EtOH (30 ml) was hydrogenated at 1 atm and 25° in the presence of PtO₂ (60 mg). After completion of the hydrogenation, the catalyst was removed by filtration and the filtrate was taken to dryness. The residue was recrystallized from n-hexane-ether to give **28** (502 mg), m.p. 106°; IR (KBr) 3450, 1730 cm^{-1} NMR no signal of 17 α -H; Mass 373 (M⁺), 331. (Found: C, 74.11; H, 8.79. Calc for C₂₃H₃₁DO₂: C, 73.95; H, 8.90%).

16 β - Ethyl - 16 α - deuterio - 3 - methoxy - *estra* - 1,3,5(10) - *trien* - 17 - *one* **29**. The Serini reaction of **28** (301 mg) was performed by the same procedure as used in **6**; **29** (285 mg), m.p. 93–94°; IR (KBr) 1745 cm^{-1} ; Mass 313 (M⁺), 284. (Found: C, 80.55; H, 9.37. Calc for C₂₁H₂₇DO₂: C, 80.46; H, 9.32%).

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