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Synthesis of 11- and 12-Methylestrones *via* the Thermal Elimination of β-Ketosulfoxides

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The bicyclic enones (**3** and **14**) and the triketone (**17**), key intermediates for the synthesis of 11- and 12-methylestrones, were prepared by means of the thermal elimination of the β-ketosulfoxides (**1** and **12**). By a modification of Smith's estrone synthesis, **3** and **14** were transformed to the corresponding 11- and 12-methylestratetraenes (**6** and **26**), which yielded 11β-, 11α- and 12β-methylestrones (**10**, **11** and **32b**) on selective reduction and demethylation, respectively. The triketone (**17**) was also converted into 12β-methylestrone (**32b**) *via* the selective reduction of 12β-methylestrapentaene (**18**). 12α- and 12β-Methylestrones (**32a** and **b**) were synthesized from 12α- and 12β-carboxyestradiol 3-methyl ethers (**28a**, **b**) reported previously.

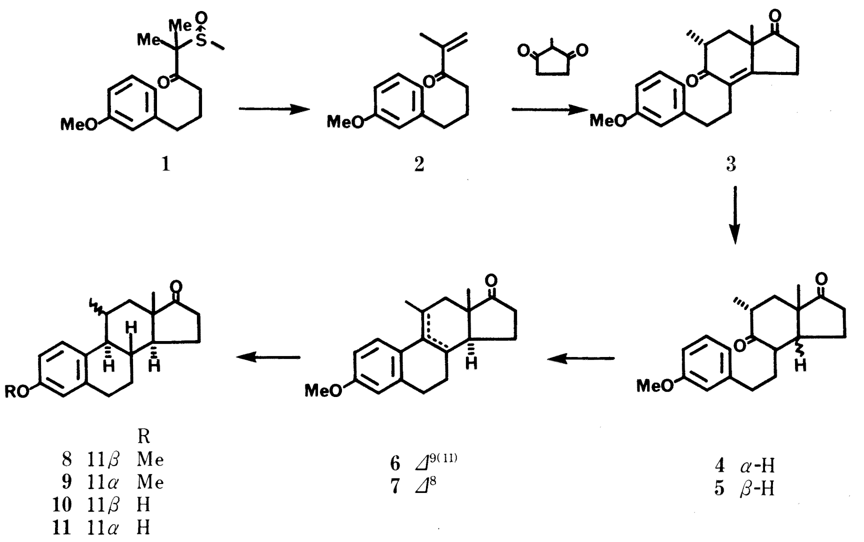
Keywords——β-ketosulfoxide; thermal elimination; Michael reaction; estrogen synthesis; 11-methylestrone; 12-methylestrone

Recently, there have been many attempts to prepare various substituted steroids as tools for the study of molecular interactions between steroidal hormones and their receptors in order to elucidate the molecular mechanisms and also to provide a basis for the design of bioactive compounds.[1] One of the modifications involves introduction of a methyl group into the steroid nucleus, since such derivatives were reported to possess potential hormonal activities.[2] The introduction of a methyl group on ring C was carried out by various methods for the synthesis of 11-methylestrone,[3,4] and attempts were made to synthesize 12-methylestrone.[5,6] However, these methods were not applicable for the synthesis of 12-methylestrones.

In the course of our investigation of synthetic applications of β-ketosulfoxide to aromatic estrogens,[7-9] we now report on the effective synthesis of 11-methylestrones and novel 12-methylestrones.

Synthesis of 11α- and 11β-Methylestrones

In our previous paper,[7] a total synthetic approach to 11-methylequilenine methyl ether was demonstrated by the use of the cyclic enone (**3**) readily prepared by one-pot reaction using the β-ketosulfoxide (**1**) and 2-methylcyclopentane-1,3-dione. For the purpose of the synthesis of 11-methylestrones (**10** and **11**), the cyclic enone (**3**) was chosen as a key intermediate. Initially, catalytic hydrogenation was attempted in order to reduce the enone (**3**) to a desirable C/D-*trans* compound,[10] but it was unsuccessful; the starting material was recovered. Metal–ammonia reduction was known to give a *cis*-fused bicyclic compound in the hydrindan system,[11] but this reduction with the enone (**3**) followed by chromic oxidation unexpectedly afforded the C/D-*trans* fused diketone (**4**) as a major product accompanied with a small amount of its *cis*-isomer (**5**). This result may be attributed to the presence of the 11-methyl substituent, because it must be located in the thermodynamically unfavorable *quasi*-axial configuration in the reaction intermediate affording the *cis*-isomer. The structures of these diketones (**4** and **5**) were determined from their proton nuclear magnetic resonance (^{1}H-NMR) spectra. The angular methyl resonance of the *trans*-diketone (**4**) appeared at 1.20 ppm,



1 2 3

		R
8	11β	Me
9	11α	Me
10	11β	H
11	11α	H

6 $\Delta^{9(11)}$
7 Δ^{8}

4 α-H
5 β-H

Chart 1

whereas that of the *cis*-diketone (**5**) was shifted to lower field at 1.30 ppm. This result suggested that ring D of the *cis*-isomer is deflected down from the plane of molecule[12] and is also in good agreement with the data reported for the hydrindan system.[13] Next, dehydrative cyclization was achieved by the treatment of **4** with methanesulfonic acid to give known $\Delta^{9(11)}$-estratetraene (**6**)[2,4] and Δ^{8}-estratetraene (**7**). The structure of **7** was unequivocally determined on the basis of the spectral data and the transformation to **6** by acid treatment.

Finally, the estratetraene (**6**) was reduced to 11β-methylestrone methyl ether (**8**) by catalytic hydrogenation with palladium on charcoal[2,4] and to 11α-methylestrone methyl ether (**9**) with sodium in liquid ammonia.[4] The demethylation of both compounds (**8** and **9**) by treatment with chlorotrimethylsilane–sodium iodide[14] provided the corresponding 11β- and 11α-methylestrones (**10** and **11**) in reasonable yields.

Synthesis of 12α- and 12β-Methylestrones

To synthesize 12-methylestrone, the cyclic enone (**14**) was assumed to be a possible intermediate, similarly to the case of 11-methylestrones (**10** and **11**). First, a β-ketosulfoxide (**12**) was prepared from methyl 4-(3-methoxyphenyl)butyrate and dipropyl sulfoxide in the presence of lithium diisopropylamide. Then, the thermal elimination reaction of the β-ketosulfoxide (**12**) gave the α,β-unsaturated ketone (**13**) in a good yield. The structure of this compound was defined by its spectral data.

Michael reaction of 2-methylcyclopentane-1,3-dione with the above enone (**13**) was next carried out under the reaction conditions shown in Table I. At high temperature (150 °C), two cyclic enones (**14** and **15**) were formed. The 12β-methylcyclic enone (**14**) was mainly produced under acidic conditions, whereas the 12α-isomer (**15**) was afforded as a major product in the presence of triethylamine. The structures of **14** and **15** were determined from the ^{1}H-NMR spectral data. The diamagnetic shift of the 12-methyl group (0.85 ppm) in the enone (**15**) indicated the axial configuration of the methyl group, *i.e.* α-orientation, reflecting the strong anisotropic effect of the α,β-unsaturated carbonyl group. As shown in Table I, the ketol (**16**) was also produced at lower temperature in the presence of triethylamine accompanied with the above cyclic enone (**15**) and the triketone (**17**). The compound (**16**) was isolated as a diastereoisomeric mixture at the C-14 hydroxyl group. The dehydration of the ketol (**16**) with

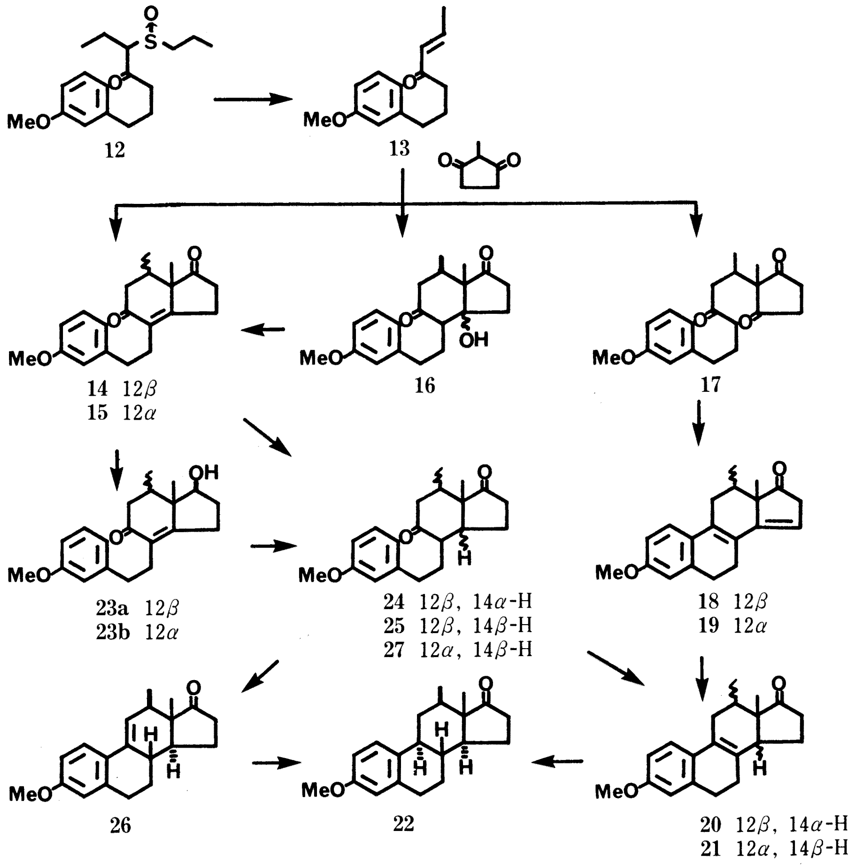


Chart 2

Table I. Results of Michael Reactions of the Unsaturated Ketone (**13**) with 2-Methylcyclopentane-1,3-dione

Reaction conditions			Yields of products (%)[a]			
Solvent	Temperature (°C)	Time (h)	**14**	**15**	**16**	**17**
AcOEt–Et_3N	Reflux	72		6	57	25
AcOEt–Et_3N	150[b]	72	20	63		
AcOH	150[b]	72	53	17		
Toluene[c]	Reflux	11			12	51

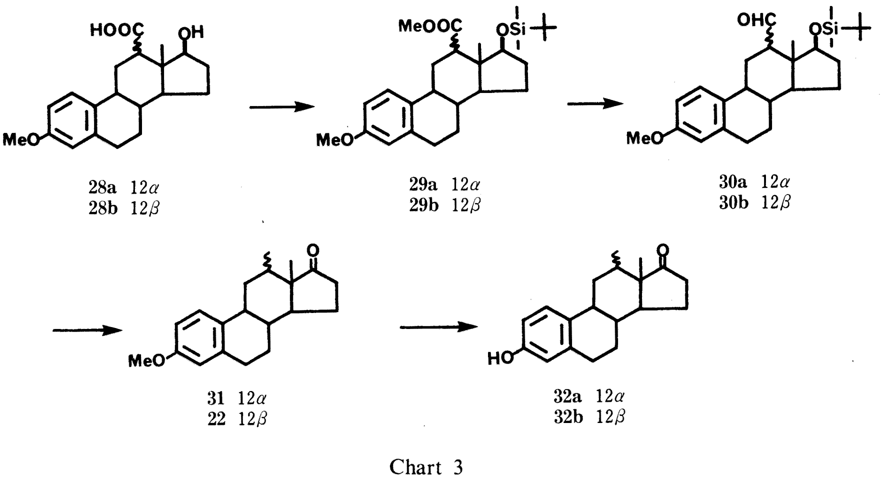
a) Isolated yields. *b*) Reactions were run in a sealed tube. *c*) In the presence of KF and 18-crown-6.

polyphosphate ester gave the 12β-methylcyclic enone (**14**) as a sole product. This fact confirms the β-configuration of the methyl group at C-12 in the ketol (**16**). In the case of neutral conditions with potassium fluoride and 18-crown-6 in toluene, the triketone (**17**) was isolated as a major product along with the ketol (**16**). The infrared (IR) spectrum of **17** showed the characteristic absorption of cyclic carbonyl groups at 1760 cm^{-1}, and in the mass spectrum (MS) the molecular ion peak appeared at *m*/*z* 330.

The transformation into the steroidal skeleton was carried out by acid-catalyzed cyclization of the triketone (**17**) by a modification of Smith's method.[15] The treatment of **17** with methanesulfonic acid afforded the known isomeric 12β- and 12α-methylestrapentaenes (**18**, 55% and **19**, 25%).[6] The 12β-methylpentaene (**18**) was then hydrogenated in the presence of palladium on charcoal to give the 14α-estratetraene (**20**) in spite of a report[6] of the formation of the 8,9,14,15-tetrahydrogenated compound as a major product. In contrast, the hydrogenation of the 12α-isomer (**19**) gave an unfavorable 14β-estratetraene (**21**). The 14α-tetraene (**20**) was then reduced with sodium in liquid ammonia to give 12β-methylestrone methyl ether (**22**) after Jones oxidation.

The conversion of the 12β-methyl cyclic enone (**14**) into 12β-methylestrone (**32b**) was then carried out. In order to avoid the formation of the undesired C/D-*cis* compound,[15] **14** was first reduced to the 17β-alcohol (**23a**) with sodium borohydride prior to catalytic hydrogenation. The β-orientation of the hydroxyl group was assigned on the basis of the ^{1}H-NMR spectrum, which showed the 17α-proton at 4.71 ppm as a doublet of doublets after acetylation.[16] The catalytic hydrogenation of the alcohol (**23a**) gave a novel diketone (**24**) accompanied with a small amount of *cis*-isomer (**25**) after oxidation with chromic acid. The structure assignment of these diketones (**24** and **25**) was achieved in the same manner as described above for the 11-methyl derivatives (**4** and **5**). The *trans*-diketone (**24**) was treated with methanesulfonic acid to give the estratetraene (**26**). The ultraviolet (UV) spectrum showed an absorption maximum at 260 nm, indicating the $\Delta^{9(11)}$-estratetraene structure.[15] The subsequent catalytic hydrogenation of **26** gave 12β-methylestrone methyl ether (**22**).

A total synthetic approach to 12α-methylestrone (**32a**) was attempted from the 12α-methylcyclic enone (**15**). However, the cyclic enone gave only an undesired C/D-*cis* compound (**27**) on catalytic or metal–ammonia reduction, and the catalytic hydrogenation of the 17β-hydroxy compound (**23b**) also afforded **27** after chromic oxidation. The structure of **27** was determined by its conversion into the known C/D-*cis* estratetraene (**21**).[6]



28a 12α
28b 12β

29a 12α
29b 12β

30a 12α
30b 12β

31 12α
22 12β

32a 12α
32b 12β

Chart 3

In order to synthesize 12α-methylestrone (**32a**) and to establish the stereochemistry of synthesized 12β-methylestrone (**32b**), the 12α- and 12β-carboxylated estrone derivatives (**28a, b**) reported in our previous paper[8] were used as intermediates for 12-methylestrones (Chart 3). The 12α- and 12β-carboxylic acids (**28a, b**) were treated with diazomethane and *tert*-butyldimethylchlorosilane in the presence of imidazole to give the 17-silyl ethers (**29a, b**). The silyl ethers (**29a, b**) were reduced with lithium aluminum hydride, followed by oxidation with pyridinium dichromate to yield the 12α- and 12β-aldehydes (**30a, b**), respectively. Wolff–Kishner reduction of the aldehydes (**30a, b**) involving cleavage of the silyl ether and subsequent oxidation with Jones reagent gave 12α- and 12β-methylestrone methyl ethers (**31** and **22**) in reasonable yields. The 12β-methyl derivative (**22**) obtained from compound **28b** was identical with that synthesized from compound **13** (Chart 2). These ethers (**31** and **22**) were finally demethylated in the usual manner[14]) to give 12α- and 12β-methylestrones (**32a, b**) in good yields, respectively.

The synthesized 11- and 12-methylestrogens should be useful for understanding the stereochemical effect of a C-11 or C-12 methyl substituent on the interaction of steroidal hormones with the receptor. A study on the biological activity of these compounds is in progress in our laboratory and details will be reported elsewhere.

Experimental

All melting points were taken on a Mitamura micro hot-stage apparatus and are uncorrected. UV spectra were measured on a Shimadzu UV-200 spectrometer. IR spectra were obtained on a JASCO IR A-200 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-40 spectrometer and JEOL 90-Q spectrometer at 90 MHz using tetramethylsilane as an internal standard (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet). MS measurements were run on a Shimadzu-LKB 9000 spectrometer with the ionizing voltage at 20 eV. For column chromatography, silica gel (70—230 mesh) was used.

(±)-3aα,4,7,7a-Tetrahydro-4-(3-methoxyphenethyl)-6α,7aβ-dimethylindan-1,5(6*H*)-dione (4) and (±)-3aβ,4,7,7a-Tetrahydro-4-(3-methoxyphenethyl)-6α,7aβ-dimethylindan-1,5(6*H*)-dione (5)——Lithium (70 mg, 10 mmol) was added to stirred liquid ammonia (40 ml) at −50 °C. After 5 min, a solution of (±)-7,7a-dihydro-4-(3-methoxyphenethyl)-6α,7aβ-dimethylindan-1,5(6*H*)-dione (**3**)[7]) (550 mg, 1.76 mmol) in tetrahydrofuran (THF) (5 ml) was added dropwise to the above solution and the whole was stirred for 30 min. After the usual work-up, the oily residue was treated with CrO_3 (500 mg, 5 mmol) in pyridine (8 ml) for 1 d at room temperature and then diluted with AcOEt (100 ml). The solution was passed through Al_2O_3 on a sintered glass funnel and the filtrate was evaporated. The residue was subjected to column chromatography (*n*-hexane : AcOEt = 6 : 1). The first eluate gave **4** (490 mg, 88%) as colorless plates from *n*-hexane–isopropyl ether, mp 101—101.5 °C. IR (Nujol): 1740 (C_1-CO), 1700 (C_5-CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, d, J = 6 Hz, C_6-CH_3), 1.20 (3H, s, C_{7a}-CH_3), 3.80 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.15 (1H, m, aromatic). MS *m/z* (%): 314 (M^+, 9), 180 (6), 134 (100). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.49; H, 8.25. The second eluate gave **5** (18 mg) as a colorless oil. IR (neat): 1730 (C_1-CO), 1700 (C_5-CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J = 7 Hz, C_6-CH_3), 1.30 (3H, s, C_{7a}-CH_3), 3.80 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.15 (1H, m, aromatic). MS *m/z* (%): 314 (M^+, 5), 180 (6), 134 (100), 121 (13).

(±)-3-Methoxy-11-methylestra-1,3,5(10),9(11)-tetraen-17-one (6) and (±)-3-Methoxy-11-methylestra-1,3,5(10),8-tetraen-17-one (7)——Methanesulfonic acid (1 ml, 150 mmol) was added to a stirred solution of **4** (314 mg, 1 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After 10 min, the mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH to give **6** (266 mg, 90%) as colorless prisms, mp 123—124 °C. A portion of the above crystals was recrystallized from ether–*n*-hexane to give colorless needles, mp 89.5—90 °C (lit.[4]) mp 88 °C). UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 258 (1800). The other spectral data were identical with the reported values. The mother liquor was subjected to column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **7** (12 mg, 4%) as colorless prisms, mp 107.5—109 °C. IR (Nujol): 1735 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, s, C_{13}-CH_3), 1.13 (3H, d, J = 6 Hz, C_{11}-CH_3), 3.84 (3H, s, OCH_3), 6.6—6.8 (2H, $C_{2,4}$-H), 7.1 (1H, m, C_1-H). UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 270 (11800). *Anal.* Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.00; H, 8.26.

Transformation of 7 into 6——A mixture of **7** (8 mg), concentrated HCl (1 ml) and EtOH (5 ml) was refluxed for 10 min. After evaporation of the solvent *in vacuo*, the residue was recrystallized from MeOH to give **6** (7 mg) as colorless prisms, mp 124—124.5 °C.

(±)-3-Methoxy-11β-methylestra-1,3,5(10)-trien-17-one (8)——A suspension of **6** (296 mg, 1 mmol) and 10% Pd–C (65 mg) in EtOH (40 ml) was stirred at room temperature under an atmosphere of H_2 for 3 h. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was recrystallized from MeOH to give **8** (278 mg, 92%) as colorless needles, mp 165—165.5 °C (lit.[3b]) mp 150—153 °C from aqueous MeOH).

(±)-3-Methoxy-11α-methylestra-1,3,5(10)-trien-17-one (9)——Sodium (80 mg, 3.5 mmol) was added to stirred liquid ammonia (40 ml) at −40 °C. A mixture of **6** (148 mg, 0.5 mmol), aniline (1 ml) and THF (3 ml) was added to the above solution and stirring was continued for 40 min at −40 °C. After the usual work-up, the product was treated with Jones reagent (1 ml) in acetone (5 ml) at 0 °C for 10 min. The mixture was diluted with H_2O and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH three times to give **9** (56 mg, 37%) as colorless columns, mp 99—100 °C (lit. mp 88—90 °C from *n*-hexane[3a]) and 126—127 °C from MeOH–CH_2Cl_2[4])). The spectral data were identical with the reported values and the above crystals were sufficiently pure for the next demethylation step.

(±)-3-Hydroxy-11β-methylestra-1,3,5(10)-trien-17-one (10)——A mixture of **8** (90 mg, 0.30 mmol), chlorotrimethylsilane (500 mg, 4.2 mmol) and NaI (600 mg, 4 mmol) in CH_3CN (8 ml) was heated at 70 °C for 5 h under Ar. The reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed with 5% $Na_2S_2O_3$ and H_2O, then dried (Na_2SO_4) and evaporated. The crude product was recrystallized from acetone to give **10** (78 mg, 91%) as colorless needles, mp 305—309 °C (lit.[4] mp 302—305 °C). The spectral data were identical with the reported values.

(±)-3-Hydroxy-11α-methylestra-1,3,5(10)-trien-17-one (11)——A mixture of **9** (75 mg, 0.25 mmol), chlorotrimethylsilane (500 mg, 4.2 mmol) and NaI (400 mg, 2.7 mmol) in CH_3CN (7 ml) was heated at 70 °C for 5 h under Ar. After the same work-up as described for **10**, the crude product was recrystallized from MeOH to give **11** (68 mg, 95%) as colorless prisms, mp 224—226 °C. IR (Nujol): 3300 (OH), 1720 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.86 (3H, s, C_{13}-CH_3), 1.23 (3H, d, $J=6$ Hz, C_{11}-CH_3), 4.76 (1H, s, OH), 6.60 (1H, d, $J=3$ Hz, C_4-H), 6.64 (1H, dd, $J=8.5$, 3 Hz, C_2-H), 7.00 (1H, d, $J=8.5$ Hz, C_1-H). MS m/z (%): 284 (M^+, 100), 185 (12), 172 (11), 164 (11). *Anal.* Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.24; H, 8.44.

7-(3-Methoxyphenyl)-3-propylsulfinylheptan-4-one (12)——Diisopropylamine (11.2 g, 110 mmol) was added to a stirred solution of *n*-BuLi (7.1 g, 110 mmol, 90% in mineral oil) at −40 °C under Ar and the temperature was gradually raised to 0 °C during 30 min. Dipropyl sulfoxide (6.8 g, 50 mmol) in THF (20 ml) was added dropwise to the above solution and the mixture was stirred for 20 min. Methyl 4-(3-methoxyphenyl)butyrate[7] (10.4 g, 50 mmol) in THF (20 ml) was then added dropwise and the whole was stirred for 20 min at room temperature. The reaction mixture was poured into saturated NH_4Cl solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (AcOEt) to give **12** (14.5 g, 98%) as a colorless oil. IR (neat): 1695 (CO), 1040 (SO) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.85—1.2 (6H, $2\times CH_3$), 1.5—2.0 (6H, methylene), 2.4—2.8 (6H, methylene), 3.40 and 3.62 (0.3H and 0.7H, t, $J=7$ Hz, methine, respectively), 3.72 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic). MS m/z (%): 294 ($M^+ - O$, 2), 218 (14), 134 (100), 121 (30).

7-(3-Methoxyphenyl)-2-hepten-4-one (13)——A solution of the ketosulfoxide **12** (3.0 g, 9.7 mmol) in *n*-butyl ether (10 ml) was refluxed for 3 h and evaporated. The residue was subjected to column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **13** (2.1 g, 95%) as a colorless oil. IR (neat): 1675 (unsaturated CO), 1630 (C=C) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.90 (3H, d, $J=6$ Hz, CH_3), 1.8—2.1 (2H), 2.55 (2H, m), 2.63 (2H, t, $J=7$ Hz), 3.80 (3H, s, OCH_3), 6.12 (1H, d, $J=15$ Hz, olefinic), 6.65—6.86 (3H, aromatic), 6.85 (1H, dd, $J=15$, 6 Hz, olefinic), 7.2 (1H, m, aromatic). MS m/z (%): 218 (M^+, 100), 134 (40), 121 (13), 91 (11).

(±)-7,7a-Dihydro-4-(3-methoxyphenethyl)-7β,7aβ-dimethylindan-1,5(6*H*)-dione (14), (±)-7,7a-Dihydro-4-(3-methoxyphenethyl)-7α,7aβ-dimethylindan-1,5(6*H*)-dione (15), (±)-3,3a,7,7a-Tetrahydro-3a-hydroxy-4-(3-methoxyphenethyl)-7β,7aβ-dimethylindan-1,5(6*H*)-dione (16) and (±)-2-(6-3′-Methoxyphenyl-1-methyl-3-oxohexyl)-2-methylcyclopentane-1,3-dione (17)——(a) A solution of the enone **13** (2.18 g, 10 mmol) and 2-methylcyclopentane-1,3-dione (2 g, 18 mmol) in AcOEt (10 ml) containing 5% triethylamine was refluxed for 3 d. The reaction mixture was evaporated and the residue was subjected to column chromatography (*n*-hexane : AcOEt = 4 : 1) to give three fractions. The first fraction gave **15** (190 mg, 6%) as a colorless oil. IR (neat): 1740 (CO), 1660 (enone) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.85 (3H, d, $J=7$ Hz, C_7-CH_3), 1.22 (3H, s, C_{7a}-CH_3), 3.80 (3H, s, OCH_3), 6.70—6.85 (3H, aromatic), 7.10 (1H, m, aromatic). MS m/z (%): 312 (M^+, 47), 178 (50), 163 (55), 122 (65), 121 (100). The second fraction gave **17** (825 mg, 25%) as a colorless oil. IR (neat): 1760 (CO), 1720 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.85 (3H, d, $J=6$ Hz, C_1-CH_3), 1.00 (3H, s, C_2-CH_3), 3.76 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.2 (1H, m, aromatic). MS m/z (%): 330 (M^+, 1), 178 (5), 134 (100), 121 (24). The third fraction gave **16** (1.9 g, 57%) as colorless needles from *n*-hexane, mp 107—113 °C. IR (Nujol): 3500 (OH), 1750, 1730, 1700 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.86 (3H, d, $J=6$ Hz, C_7-CH_3), 1.00 and 1.10 (each 1.5H, s, C_{7a}-CH_3), 3.72 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.1 (1H, m, aromatic).

(b) A solution of **13** (3.0 g, 13.8 mmol) and 2-methylcyclopentane-1,3-dione (2.8 g, 25 mmol) in AcOEt (10 ml) containing 5% triethylamine was heated at 150 °C in a sealed tube for 3 d. After the same work-up as described above, the residue was subjected to column chromatography to give two fractions. The first fraction gave **14** (860 mg, 20%) as a colorless oil. IR (neat): 1740 (CO), 1660 (enone) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.00 (3H, s, C_{7a}-CH_3), 1.14 (3H, d, $J=6$ Hz, C_7-CH_3), 3.73 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.10 (1H, aromatic). MS m/z (%): 312 (M^+, 100), 178 (64), 163 (63), 122 (60), 121 (76). The second fraction gave **15** (2.7 g, 63%) as a colorless oil.

(c) A solution of **13** (3.2 g, 14.7 mmol) and 2-methylcyclopentane-1,3-dione (3.0 g, 27 mmol) in AcOH (15 ml) was heated at 150 °C under N_2 in a sealed tube for 2 d. The reaction mixture was evaporated and the residue was subjected to column chromatography to give **14** (2.4 g, 53%) and **15** (790 mg, 17%).

(d) A mixture of **13** (500 mg, 2.3 mmol), 2-methylcyclopentane-1,3-dione (210 mg, 1.9 mmol), KF (1.0 g, 17 mmol) and 18-crown-6 (300 mg, 1.1 mmol) in toluene (10 ml) was refluxed with stirring for 11 h. The reaction mixture was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed as described above to give **17** (390 mg, 51%) and **16** (90 mg, 12%).

(e) A solution of **16** (200 mg, 0.69 mmol) and polyphosphate ester (1.0 g) in $CHCl_3$ (20 ml) was refluxed for 3 h. The reaction mixture was washed with 5% Na_2CO_3, H_2O, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **14** (142 mg, 75%).

(±)-3-Methoxy-12β-methylestra-1,3,5(10),8,14-pentaen-17-one (18) and (±)-3-Methoxy-12α-methylestra-

1,3,5(10),8,14-pentaen-17-one (19)——Methanesulfonic acid (1.1 g, 165 mmol) was added dropwise to a stirred solution of the triketone **17** (330 mg, 1 mmol) in CH_2Cl_2 (5 ml) at $-30\,^\circ C$ and the stirring was continued for 20 min. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **18** (163 mg, 55%) as colorless prisms from *n*-hexane–ether, mp 109—110 °C (lit.[6] mp 107—109 °C). The second fraction gave **19** (72 mg, 24%) as colorless needles from *n*-hexane, mp 114—115 °C (lit.[6] mp 109—111 °C).

(±)-3-Methoxy-12β-methylestra-1,3,5(10),8-tetraen-17-one (20)——A mixture of **18** (60 mg, 0.2 mmol) and 10% Pd–C (10 mg) in benzene (10 ml) was stirred under H_2 until 1 mol of H_2 had been taken up. After removal of the catalyst by suction the filtrate was evaporated and the residue was recrystallized from MeOH to give **20** (52 mg, 86%) as colorless prisms, mp 135—137 °C (lit.[6] mp 133—135 °C). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 279 (16500).

(±)-3-Methoxy-12α-methyl-14β-estra-1,3,5(10),8-tetraen-17-one (21)——(a) A mixture of the pentaene **19** (75 mg, 2.6 mmol) and 10% Pd–C (10 mg) in benzene (10 ml) was hydrogenated as described for **20**. After the same work-up as described above, the crude product was recrystallized from MeOH to give **21** (71 mg, 95%) as colorless needles, mp 80.5—83 °C (lit.[6] mp 80—82 °C). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 274 (16100).

(b) Methanesulfonic acid (200 mg, 2.1 mmol) was added to a stirred solution of the diketone **27** (63 mg, 0.2 mmol) in CH_2Cl_2 (5 ml) at 0 °C and the stirring was continued for 20 min. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to give a crude product, which was recrystallized from MeOH to yield **21** (55 mg) as colorless needles, mp 79—81.5 °C.

(±)-3-Methoxy-12β-methylestra-1,3,5(10)-trien-17-one (22)——(a) Sodium (220 mg, 9.6 mmol) was added to liquid ammonia (40 ml) under stirring at $-50\,^\circ C$. After 5 min, a mixture of the tetraene **20** (150 mg, 2 mmol) and aniline (2 ml) in THF (8 ml) was added to the above solution and the whole was stirred for 30 min. Solid NH_4Cl (4 g) was then added in several portions and ammonia was removed at room temperature. The residue was extracted with ether and the extract was washed with 2 N HCl and H_2O, dried (Na_2SO_4) and evaporated. The residue was dissolved in acetone (8 ml) and treated with 8 N H_2CrO_4 (1 ml) in the usual manner. The reaction mixture was extracted with ether, and the extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH to give **22** (104 mg, 69%) as colorless needles, mp 121—123 °C. IR (Nujol): 1740 (CO), 1600 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.81 (3H, s, C_{13}-CH_3), 1.16 (3H, d, $J=7$ Hz, C_{12}-CH_3), 3.73 (3H, s, OCH_3), 6.5—6.7 (2H, $C_{2,4}$-H), 7.10 (1H, d, $J=8$ Hz, C_1-H). MS *m/z* (%): 298 (M^+, 100), 199 (12), 186 (13), 160 (14). *Anal.* Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.44; H, 8.77.

(b) A mixture of the tetraene **26** (200 mg, 0.68 mmol) and 10% Pd–C (55 mg) in EtOH (30 ml) was stirred under H_2. After removal of the catalyst by suction, the filtrate was evaporated to give a crude product, which was recrystallized from MeOH to give **22** (175 mg, 87%) as colorless needles, mp 122—124 °C.

(c) A solution of the 12β-aldehyde (**30b**, 100 mg, 0.23 mmol) and KOH (2 g) in triethylene glycol (10 ml) and hydrazine hydrate (2 ml) was heated at 150 °C for 2 h and then refluxed for 3 h. The mixture was poured into ice-water and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was treated with 8 N H_2CrO_4 (1 ml) in acetone (4 ml) at 0 °C and worked-up in the usual manner to give a crude product, which was recrystallized from MeOH to give **22** (41 mg, 59%) as colorless needles, mp 121—123 °C.

(±)-7,7a-Dihydro-1β-hydroxy-4-(3-methoxyphenethyl)-7β,7aβ-dimethylindan-5(6*H*)-one (23a)——Sodium borohydride (10 mg, 0.26 mmol) was added to a stirred solution of the ketone **14** (312 mg, 1 mmol) in MeOH (10 ml) at 0 °C, and stirring was continued for 5 min. The reaction mixture was evaporated and the residue was extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The crude product was recrystallized from *n*-hexane to give **23a** (298 mg, 95%) as colorless needles, mp 89—91.5 °C. IR (Nujol): 3400 (OH), 1640 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.90 (3H, s, C_{7a}-CH_3), 1.06 (3H, d, $J=7$ Hz, C_7-CH_3), 3.75 (3H, s, OCH_3), 3.76 (1H, t, $J=9$ Hz, C_1-H), 6.6—6.8 (3H, aromatic), 7.10 (1H, m, aromatic). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.30; H, 8.22.

Acetate of the β-Alcohol (23a)——A solution of **23a** (50 mg, 0.16 mmol) in pyridine (2 ml) and Ac_2O (1 ml) was allowed to stand at room temperature for 12 h. The mixture was worked-up in the usual manner to give the acetate of **23a**. IR (neat): 1740 (OAc), 1660 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.93 (3H, d, $J=7$ Hz, C_7-CH_3), 1.00 (3H, s, C_{7a}-CH_3), 2.05 (3H, s, $OCOCH_3$), 3.75 (3H, s, OCH_3), 4.71 (1H, dd, $J=7, 9$ Hz, $C_{1\alpha}$-H), 6.6—6.8 (3H, aromatic), 7.1 (1H, m, aromatic).

(±)-7,7a-Dihydro-1β-hydroxy-4-(3-methoxyphenethyl)-7α,7aβ-dimethylindan-5(6*H*)-one (23b)——Sodium borohydride (18 mg, 0.47 mmol) was added to a stirred solution of the ketone **15** (312 mg, 1 mmol) in MeOH (15 ml) at 0 °C and the stirring was continued for 20 min. The reaction mixture was worked-up as described for **23a** and the crude product was recrystallized from diisopropyl ether to give **23b** (302 mg, 96%) as colorless prisms, mp 124—125 °C. IR (Nujol): 3400 (OH), 1640 (CO), 1610 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.93 (3H, d, $J=7$ Hz, C_7-CH_3), 1.10 (3H, s, C_{7a}-CH_3), 3.75 (3H, s, OCH_3), 4.06 (1H, dd, $J=8, 9$ Hz, $C_{1\alpha}$-H), 6.6—6.8 (3H, aromatic), 7.10 (1H, m, aromatic). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.40; H, 8.31.

(±)-3,3aα,7,7a-Tetrahydro-4-(3-methoxyphenethyl)-7β,7aβ-dimethylindan-1,5(6*H*)-dione (24) and (±)-3,3aβ,7,7a-Tetrahydro-4-(3-methoxyphenethyl)-7β,7aβ-dimethylindan-1,5(6*H*)-dione (25)——A mixture of **23a** (400 mg, 1.27 mmol) and 10% Pd–C (300 mg) in EtOH (25 ml) was stirred under H_2 at room temperature for 6 h. After removal of the catalyst by suction, the filtrate was evaporated. The oily residue was treated with CrO_3 (500 mg, 5 mmol) in pyridine (10 ml) with stirring at 50 °C for 2 h and diluted with AcOEt (30 ml). The suspended solution was passed through Al_2O_3 on a sintered glass funnel and the filtrate was evaporated. The residue was subjected to column chromatography (*n*-hexane : AcOEt = 4 : 1) to give two fractions. The first fraction gave **25** (22 mg) as a colorless oil. IR (neat): 1730 (CO), 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, $J=6$ Hz, C_7-CH_3), 1.14 (3H, s, C_{7a}-CH_3), 3.78 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.15 (1H, m, aromatic). The second fraction gave **24** (340 mg, 85%) as a colorless oil. IR (neat): 1735 (CO), 1705 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, s, C_{7a}-CH_3), 1.15 (3H, d, $J=$ 6 Hz, C_7-CH_3), 3.73 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.10 (1H, m, aromatic). MS *m/z* (%): 314 (M^+, 9), 134 (100), 122 (14), 121 (7).

(±)-3-Methoxy-12*β*-methylestra-1,3,5(10),9(11)-tetraen-17-one (26)——Methanesulfonic acid (700 mg, 7.3 mmol) was added to a stirred solution of **24** (314 mg, 1 mmol) in CH_2Cl_2 (5 ml) and the stirring was continued for 15 min at 0 °C. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with H_2O three times, dried (Na_2SO_4) and evaporated. The residue was recrystallized from MeOH to give **26** (256 mg, 87%) as colorless needles, mp 125—125.5 °C. IR (Nujol): 1735 (CO), 1600, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, s, C_{13}-CH_3), 1.22 (3H, d, $J=7$ Hz, C_{12}-CH_3), 3.75 (3H, s, OCH_3), 5.73 (1H, br s, C_{11}-H), 6.6—7.2 (3H, aromatic). MS *m/z* (%): 296 (M^+, 100), 281 (62), 238 (20), 225 (10). UV λ_{max}^{EtOH} nm (ε): 260 (17700). *Anal.* Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.03; H, 8.14.

(±)-3a*β*,4,7,7a-Tetrahydro-4-(3-methoxyphenethyl)-7*α*,7a*β*-dimethylindan-1,5(6*H*)-dione (27)——(a) A solution of **15** (270 mg, 0.87 mmol) in EtOH (25 ml) was hydrogenated in the presence of 10% Pd–C (150 mg). After removal of the catalyst and evaporation of the solvent, the residue was oxidized with CrO_3 (250 mg, 2.5 mmol) in pyridine (8 ml) by stirring at 50 °C for 2 h. The reaction mixture was worked-up as described for **24** and the crude product was recrystallized from diisopropyl ether to give **27** (248 mg, 84%) as colorless prisms, mp 84.5—86 °C. IR (Nujol): 1725 (CO), 1705 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, $J=6.5$ Hz, C_7-CH_3), 1.23 (3H, s, C_{7a}-CH_3), 3.73 (3H, s, OCH_3), 6.6—6.8 (3H, aromatic), 7.10 (1H, m, aromatic). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.38; H, 8.36.

(b) A solution of **23b** (225 mg, 0.72 mmol) in EtOH (20 ml) was hydrogenated in the presence of 10% Pd–C (140 mg). After work-up as described above, the crude product was recrystallized from diisopropyl ether to give **27** (209 mg, 93%) as colorless prisms, mp 85—86 °C.

(±)-17*β*-*tert*-Butyldimethylsilyloxy-3-methoxy-12*α*-methoxycarbonylestra-1,3,5(10)-triene (29a)——A solution of the 12*α*-carboxylic acid (**28a**)[8] (230 mg, 0.7 mmol) in MeOH (5 ml) was treated with diazomethane–ether and evaporated. The residue was dissolved in *N*,*N*-dimethylformamide (DMF) (4 ml), and *tert*-butyldimethylchlorosilane (280 mg, 1.7 mmol) and imidazole (70 mg, 1.03 mmol) were added to this solution. The mixture was allowed to stand at room temperature for 20 h. The reaction mixture was poured into ice-water and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **29a** (302 mg, 97%) as colorless prisms from diisopropyl ether, mp 141—142 °C. IR (Nujol): 1730 (CO), 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s, $Si(CH_3)_2$), 0.90 (3H, s, C_{13}-CH_3), 0.92 (9H, s, *tert*-butyl), 3.69 (3H, s, $COOCH_3$), 3.80 (3H, s, OCH_3), 3.96 (1H, t, $J=8$ Hz, $C_{17\alpha}$-H), 6.6—6.8 (2H, $C_{2,4}$-H), 7.25 (1H, d, $J=8$ Hz, C_1-H). MS *m/z* (%): 458 (M^+, 2), 401 (100), 326 (5), 267 (8), 265 (8). *Anal.* Calcd for $C_{27}H_{42}O_4Si$: C, 70.70; H, 9.23. Found: C, 70.49; H, 9.17.

(±)-17*β*-*tert*-Butyldimethylsilyloxy-3-methoxy-12*β*-methoxycarbonylestra-1,3,5(10)-triene (29b)——A solution of the 12*β*-carboxylic acid (**28b**)[8] (200 mg, 0.6 mmol) in MeOH (5 ml) was treated with diazomethane–ether and evaporated. The residue was dissolved in DMF (3 ml), and *tert*-butyldimethylchlorosilane (180 mg, 1.1 mmol) and imidazole (68 mg, 1.0 mmol) was added to this solution. The mixture was allowed to stand for 18 h at room temperature. The reaction mixture was worked-up as described for **29a** and the crude product was chromatographed (*n*-hexane : AcOEt = 10 : 1) to give **29b** (252 mg, 95%) as colorless needles from diisopropyl ether, mp 109—110 °C. IR (Nujol): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s, $Si(CH_3)_2$), 0.85 (9H, s, *tert*-butyl), 0.87 (3H, s, C_{13}-CH_3), 3.63 (3H, s, $COOCH_3$), 3.73 (3H, s, OCH_3), 3.87 (1H, m, $C_{17\alpha}$-H), 6.6—6.8 (2H, $C_{2,4}$-H), 7.10 (1H, m, C_1-H). *Anal.* Calcd for $C_{27}H_{42}O_4Si$: C, 70.70; H, 9.23. Found: C, 70.74; H, 9.17.

(±)-17*β*-*tert*-Butyldimethylsilyloxy-12*α*-formyl-3-methoxyestra-1,3,5(10)-triene (30a)——Lithium aluminum hydride (22 mg, 0.58 mmol) was added to a stirred solution of **29a** (210 mg, 0.46 mmol) in THF (5 ml) and the stirring was continued for 30 min at room temperature. The reaction mixture was evaporated and the residue was extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue and pyridinium dichromate (300 mg, 0.8 mmol) were stirred in CH_2Cl_2 (5 ml) for 5 h at room temperature. The reaction mixture was diluted with ether and passed through Al_2O_3 on a sintered glass funnel. The eluate was evaporated and the crude product was recrystallized from diisopropyl ether to give **30a** (176 mg, 90%) as colorless prisms, mp 145—146 °C. IR (Nujol): 1700 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, *tert*-butyl), 0.92 (3H, s, C_{13}-CH_3), 3.80 (3H, s, OCH_3), 4.29 (1H, t, $J=9$ Hz, C_{17}-H), 6.5—6.7 (2H, $C_{2,4}$-H), 7.15 (1H, d, $J=8$ Hz, C_1-H), 10.0 (1H, d, $J=$ 2 Hz, CHO). *Anal.* Calcd for $C_{26}H_{40}O_3Si$: C, 72.85; H, 9.40. Found: C, 72.90; H, 9.31.

(±)-17*β*-*tert*-Butyldimethylsilyloxy-12*β*-formyl-3-methoxyestra-1,3,5(10)-triene (30b)——Lithium aluminum hydride (20 mg, 0.53 mmol) was added to a stirred solution of **29b** (180 mg, 0.39 mmol) in THF (5 ml) at room temperature and the stirring was continued for 30 min. The reaction mixture was worked-up as described for **30a** and the residue was oxidized with pyridinium dichromate (180 mg, 0.48 mmol) in CH_2Cl_2 (5 ml) by stirring for 2 h at room temperature. The crude product was recrystallized from diisopropyl ether to give **30b** (144 mg, 86%) as colorless prisms, mp 128—131 °C. IR (Nujol): 1710 (CO), 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s, $Si(CH_3)_2$), 0.86 (3H, s, C_{13}-CH_3), 3.74 (3H, s, OCH_3), 3.98 (1H, t, $J=9$ Hz, C_{17}-H), 6.6—6.7 (2H, $C_{2,4}$-H), 7.14 (1H, d, $J=8$ Hz, C_1-H), 10.06 (1H, d, $J=2$ Hz, CHO). MS *m/z* (%): 428 (M^+, 1), 371 (100), 279 (29), 265 (11), 211 (55). *Anal.* Calcd for $C_{26}H_{40}O_3Si$: C, 72.85; H, 9.40. Found: C, 72.82; H, 9.13.

(±)-3-Methoxy-12α-methylestra-1,3,5(10)-trien-17-one (31)——A solution of **30a** (180 mg, 0.42 mmol), KOH (2 g) and hydrazine hydrate (2 ml) in triethylene glycol (8 ml) was heated at 150 °C for 2 h. The mixture was then refluxed for 4 h. The reaction mixture was poured into ice-water and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was treated with 8 N H_2CrO_4 (2 ml) in acetone (5 ml) at 0 °C for 1 h and diluted with H_2O. The mixture was extracted with ether twice. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The crude product was recrystallized from MeOH to give **31** (44 mg, 35%) as colorless prisms, mp 118—121 °C. IR (Nujol): 1725 (CO), 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, s, C_{13}-CH_3), 1.09 (3H, d, $J=8$ Hz, C_{12}-CH_3), 3.73 (3H, s, OCH_3), 6.5—6.8 (2H, $C_{2,4}$-H), 7.02 (1H, d, $J=8$ Hz, C_1-H). MS *m/z* (%): 298 (M^+, 100), 241 (11), 200 (14), 186 (55), 160 (53). *Anal.* Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.46; H, 8.75.

(±)-3-Hydroxy-12α-methylestra-1,3,5(10)-trien-17-one (32a)——A solution of **31** (43 mg, 0.104 mmol), trimethylchlorosilane (320 mg, 2.7 mmol) and NaI (500 mg, 3.9 mmol) in CH_3CN (5 ml) was warmed at 60 °C for 6 h under an Ar atmosphere. The reaction mixture was evaporated and the residue was extracted with AcOEt. The extract was washed with 5% $Na_2S_2O_3$ and H_2O, dried (Na_2SO_4) and evaporated. The crude product was recrystallized from MeOH to give **32a** as colorless prisms, mp 227—230 °C. IR (Nujol): 3250 (OH), 1720 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s, C_{13}-CH_3), 1.04 (3H, d, $J=7$ Hz, C_{12}-CH_3), 4.71 (1H, s, OH), 6.55—6.7 (2H, $C_{2,4}$-H), 7.15 (1H, d, $J=8$ Hz, C_1-H). *Anal.* Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.90; H, 8.48.

(±)-3-Hydroxy-12β-methylestra-1,3,5(10)-trien-17-one (32b)——A solution of **22** (65 mg, 0.22 mmol), trimethylchlorosilane (400 mg, 3.4 mmol) and NaI (550 mg, 3.7 mmol) in CH_3CN (6 ml) was warmed at 60 °C under an Ar atmosphere. The reaction mixture was worked-up as described for **32a** and the crude product was recrystallized from MeOH to give **32b** (48 mg, 77%) as colorless needles, mp 245—247 °C. IR (Nujol): 3330 (OH), 1720 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, s, C_{13}-CH_3), 1.20 (3H, d, $J=7$ Hz, C_{12}-CH_3), 4.70 (1H, s, OH), 6.6—6.8 (2H, $C_{2,4}$-H), 7.15 (1H, d, $J=8$ Hz, C_1-H). *Anal.* Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.20; H, 8.43.

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References

1) J. R. Raynaud, T. Ojasoo, M. M. Bouton and D. Philibert, "Drug Design," Vol. 3, ed. by E. J. Ariens, Academic Press, New York, 1977, pp. 170—214; R. B. Gabbard and A. Segaloff, *Steroids*, **41**, 791 (1983); E. W. Bergink, H. J. Kloosterboer, W. H. M. Van der Velden, J. Van der Vies and M. S. DeWinter, *Prog. Cancer Res. Ther.*, **25**, 77 (1983); J. Kirchhoff, X. Wang, R. Ghraf, P. Bull and R. Knuppen, *Brain Res.*, **294**, 354 (1984).
2) J. S. Baran, H. D. Lennon, S. E. Mares and E. F. Nutting, *Experientia*, **26**, 762 (1970).
3) *a*) N. B. Groen and F. J. Zeelen, *Recl. Trav. Chim. Pays-Bas*, **98**, 32 (1979); *b*) F. B. Garland, J. R. Palmer and R. Pappo, *J. Org. Chem.*, **41**, 531 (1976).
4) J. S. Baran, D. D. Langford, I. Laos and C. D. Liang, *Tetrahedron*, **33**, 609 (1977).
5) *a*) L. Nedelec and J. C. Gasc, Ger. Patent 1814304 (1969) [*Chem. Abstr.*, **71**, 81635*b* (1969)]; *b*) A. I. Bross, N. P. Van Vilet and F. J. Zeelen, *J. Chem. Research*, **1981**, 20.
6) R. B. Coombs and R. P. Danna, *J. Chem. Soc.*, **1976**, 1643.
7) *a*) Y. Oikawa, T. Kurosawa and O. Yonemitsu, *Chem. Pharm. Bull.*, **23**, 2466 (1975); *b*) T. Kurosawa, M. Tohma, Y. Oikawa and O. Yonemitsu, *ibid.*, **26**, 1533 (1978).
8) *a*) T. Kurosawa, M. Tohma, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, **29**, 2101 (1981); *b*) T. Kurosawa, U. Niitsu and M. Tohma, *ibid.*, **35**, 587 (1987).
9) S. Ikegawa, T. Kurosawa and M. Tohma, *Chem. Pharm. Bull.*, **36**, 2993 (1988).
10) Steroidal nomenclature was used for convenience in this text.
11) J. d'Angelo, *Tetrahedron*, **32**, 2979 (1976).
12) N. S. Bacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, p. 14.
13) K. H. Baggaley, S. G. Brooks, J. Green and B. T. Redmann, *J. Chem. Soc.* (*C*), **1971**, 2671.
14) G. A. Olah, S. C. Narang, B. G. B. Gupta and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979).
15) G. H. Douglas, J. M. H. Graves, D. Hartley, G. H. Hughes, B. J. McLoughlin and H. Smith, *J. Chem. Soc.*, **1963**, 5072.
16) J. E. Bridgemann, P. C. Cherry, A. S. Clegg, J. M. Evans, Sir Ewart R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards and P. D. Woodgate, *J. Chem. Soc.* (*C*), **1970**, 250.