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An Improved Synthesis of optically Active Steroids

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17α-Hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-14-one (IIa) which is an intermediate for the total synthesis of estrogens has been optically resolved. The isomer which has unnatural configuration at C-13 has been converted to estrapentaene 3-methyl ether (IVa) *via* the 9,14-epoxy intermediates (XI, XII, XIII, XV).

Wendler, *et al.* reduced[2] 3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene-14,17-dione (Ia)[3] to *rac*-17α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-14-one (IIa) and, after resolution of the product, oxidized the enantiomorf having unnatural configuration at C-13 again to the starting diketone (Ia), thus permitting utilization of the unwanted isomer by circulating it in the resolution process *via* the oxidation-reduction pathway (Ia$\rightleftarrows$(+)IIa +(−)IIa).

We were performing a similar line of work and filed a patent[4] application earlier than Wendler, *et al.*

Treatment of Ia with sodium borohydride (lithium tri-*t*-butoxyaluminum hydride was used by Wendler, *et al.*) gave IIa of mp 72—73° in good yield (77.5%). Wendler, *et al.* blocked the hydroxyl group of IIa as the acetate before cyclization, whereas we performed direct cyclization of IIa into *rac*-3-methoxyestra-1,3,5(10),8,14-pentaen-17α-ol (IVa). IIa afforded a cyclized product (IIIa)[5,6] under a mild acidic condition, *i.e.* treatment with methanolic

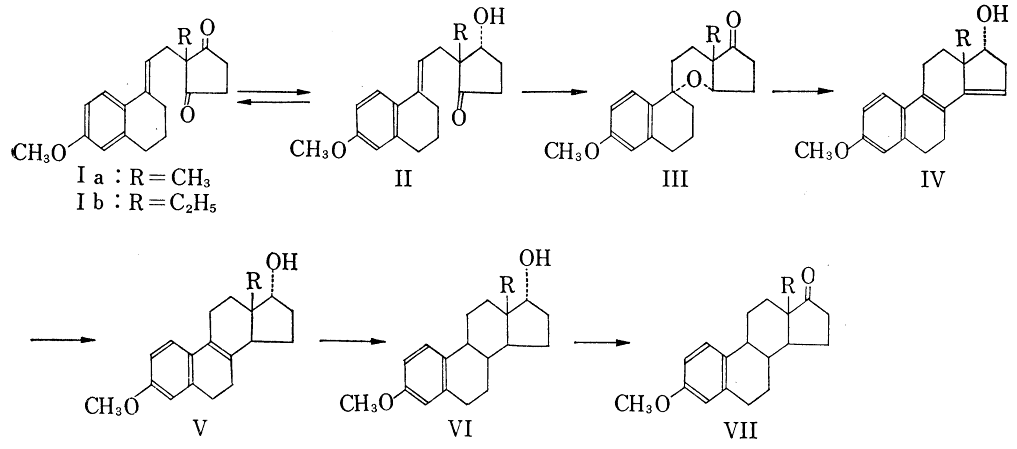

Chart 1

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1) Location: *Juso, Higashiyodogawa-ku, Osaka.*

2) C.H. Kuo, D. Taub, and N.L. Wendler, *Chem. Ind.* (London), **1966**, 1340; *idem*, *J. Org. Chem.*, **33**, 3126 (1968).

3) P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968), and references cited therein.

4) T. Miki and K. Hiraga, J. Patent 14781 (1970) [*C.A.*, **73**, 45688 (1970)].

5) T. Asako, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), in press.

6) H. Gibian, K. Kieslich, H.J. Koch, H. Kosmol, C. Rufer, E. Schröder, and R. Vöslich, *Tetrahedron Letters*, **1966**, 2321.

hydrochloric acid at room temperature or with *p*-toluenesulfonic acid in benzene. IIa and IIIa were converted to IVa on treatment with hydrochloric acid in boiling methanol. IVa can be converted to *rac*-estrone methyl ether (VIIa) following the equation shown in Chart 1.

The same series of reactions as above were also carried out on the 13-ethyl analog of I (Chart 1).

(−) IIa: R=H, $[\alpha]_D=-83.6°$
(−) VIII: R=COCH$_2$CH$_2$COOH, $[\alpha]=-87.8°$
(quinine salt, $[\alpha]_D=+111.8°$)

(+) IIa: R=H, $[\alpha]_D=+83.6°$
(+) VIII: R=COCH$_2$CH$_2$COOH, $[\alpha]_D=+87.2°$
(quinine salt, $[\alpha]_D=+39.6°$)

Chart 2

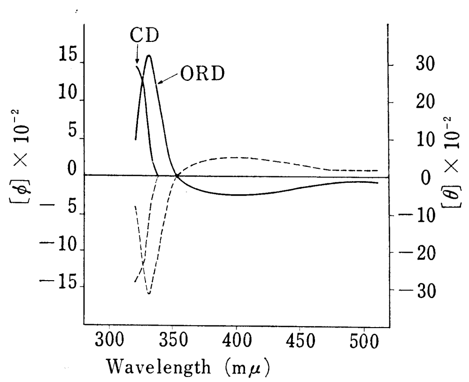

Fig. 1. ORD and CD Curves of IIa (in EtOH)

——: (−)IIa ------: (+)IIa

IIa was converted to its hemisuccinate (VIII) and to the quinine salt for resolution. Removal of the quinine from the crystalline salt of mp 171—172° with sulfuric acid followed by hydrolysis in a KOH solution gave dextrorotatory IIa (mp 102—104°). On the other hand, levorotatory IIa (mp 102—104°) was obtained from the mother liquor of the quinine salt. Fig. 1 shows the optical rotatory dispersion (ORD) and circular dichroism (CD) curves of (−)IIa and (+)IIa.

Both (−)IIa and (+)IIa were respectively converted into estrone methyl ether (VII) and its antipode in the same manner as above, accordingly clarifying that (−)IIa has natural while (+)IIa unnatural configuration. The latter (+)IIa was converted into diketone (Ia) by oxidation with DMSO.

An attempt was then made to transform (+)IIa to a natural steroid skeleton by the route shown in Chart 3. The acetate (IX) of (+)IIa was reduced with sodium borohydride in methanol to afford the 14*β*-ol (X), which was treated with *p*-toluenesulfonic acid in benzene at room temperature. The product was assigned to 13*α*-methyl-9,14*β*-epoxy structure (XI) because of the disappearance of the absorption maximum at 265 mμ characteristic to the 3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene system and the appearance of new absorption maxima at 278 mμ and 286 mμ ascribable to the 3-methoxyestra-1,3,5(10)-triene system in the ultraviolet (UV) spectrum. The structure XI was also supported by the infrared (IR) spectrum which showed no absorption band ascribable to hydroxyl group. After purification by silica gel column chromatography, XI was hydrolyzed to the 17*β*-ol (XII) with potassium hydroxide in methanol. Oxidation of XII with chromium trioxide-pyridine complex afforded 13*α*-methyl-9,14*β*-epoxy-17-one (XIII) which showed an absorption band of a five-membered cyclic ketone at 1740 cm^{-1} in the IR spectrum. Treatment of XIII with hydrochloric acid in refluxing methanol yielded a crystalline material which was proved to be identical in all respects with (−) 3-methoxyestra-1,3,5(10),8,14-pentaen-17*α*-ol (IVa) obtained from (−)IIa by treatment with hydrochloric acid in boiling methanol. The over-all yield from (+)IIa to (−)IVa was 40%.

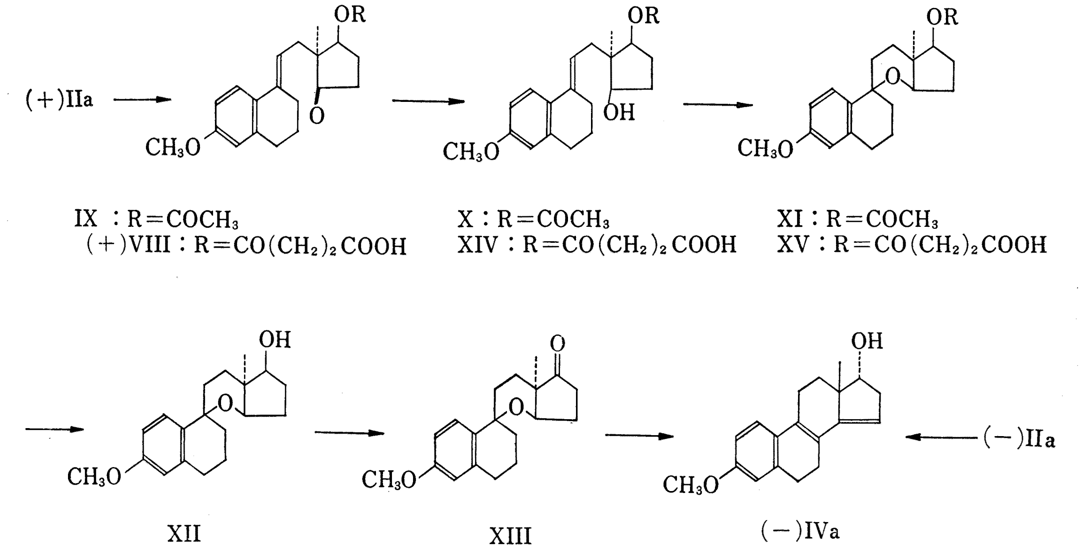

Chart 3

In order to make the pathway shorter we tried to use the hemisuccinate (+)VIII of (+)-IIa mentioned above as a starting material. In this case (—)IVa was obtained in the yield of 30% from (+)IIa in a way similar to that for 17β-acetate series (Chart 3). The above results indicate that total synthesis of natural estrone is possible from both the enantiomeric intermediates, (+)IIa and (—)IIa.

Experimental

***rac*-17α-Hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-14-one (IIa)**——To a solution of 20 g of 3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene-14,17-dione (Ia)[3] in 1 liter of MeOH was added portionwise 0.8 g of $NaBH_4$ with stirring at −20°. After 2 hr, 3 liter of water was added to the reaction mixture and the resulting precipitates were extracted with ether. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to yield 19 g of *rac*-IIa. mp 72—73° (from ether-*n*-hexane). *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.27; H, 7.92. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1725. UV λ_{max}^{EtOH} mμ (ε): 266.5 (1.93×10^4).

rac-17α-Hydroxy-3-methoxy-8,14-seco-13-ethylgona-1,3,5(10),9-tetraen-14-one (IIb) was obtained as an oil from Ib[3] in a manner similar to that for IIa. IR ν_{max}^{film} cm^{-1}: 3400, 1725.

***rac*-3-Methoxy-9α,14α-epoxy-8,14-secoestra-1,3,5(10)-trien-17-one (IIIa)**——A solution of 0.4 g of *rac*-IIa in 30 ml of MeOH and 1 ml of 6N HCl was allowed to stand for 4 hr at room temperature. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, a 5% aqueous $NaHCO_3$ solution and water, dried and concentrated to yield 0.4 g of a yellow oil. When this oil was purified by column chromatography using 20 g of silica gel with the solvent system of benzene-ether (9:1), 0.3 g of *rac*-IIIa was obtained. mp 81—83° (from MeOH). *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.95; H, 7.94. UV λ_{max}^{EtOH} mμ (ε): 276 (1.54×10^3), 283 (1.5×10^3). IR ν_{max}^{Nujol} cm^{-1}: 1742, 1620, 1595, 1509, 836. NMR δ_{ppm} (in CCl_4): 0.92 (3H, singlet, C_{13}-CH_3), 3.67 (3H, singlet, OCH_3), 4.07 (1H, multiplet, C_{14}-H), 6.37 (1H, doublet, C_4-H, $J=2$ Hz), 6.55 (1H, quartet, C_2-H, $J=2$ Hz & 8 Hz), 7.10 (1H, doublet, C_1-H, $J=8$ Hz).

rac-3-Methoxy-9α,14α-epoxy-8,14-seco-13β-ethylgona-1,3,5(10)-trien-14-one (IIIb) was similarly obtained from IIb. mp 64° (from *n*-hexane). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.33. Found: C, 76.51; H, 8.33. IR ν_{max}^{Nujol} cm^{-1}: 1730, no absorption of OH.

***rac*-3-Methoxyestra-1,3,5(10),8,14-pentaen-17α-ol (IVa)**——A solution of 0.15 g of *rac*-IIa in 10 ml of MeOH and 0.5 ml of conc. HCl was refluxed for 40 minutes. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, a 5% aqueous $NaHCO_3$ solution and water, dried and concentrated to yield crude crystals. Recrystallization from MeOH gave 0.12 g of *rac*-IVa. mp 101°. UV λ_{max}^{EtOH} mμ (ε): 311 (2.0×10^4). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1615, 1510.

rac-3-Methoxyestra-1,3,5(10),8-tetraen-17α-ol (Va)——A solution of 3 g of *rac*-IVa in 100 ml of dioxane was shaken under a stream of hydrogen over Raney Ni. After absorption of 265 ml of hydrogen, catalyst was filtered off and filtrate was concentrated to yield 2.2 g of *rac*-Va. mp 159—161° (from AcOEt). *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80.28; H, 8.45. Found: C, 79.97; H, 8.41. UV λ_{max}^{EtOH} mμ (ε): 277 (1.57×10^4).

From 0.8 g of *rac*-IVb was similarly obtained 0.4 g of *rac*-3-methoxy-13β-ethylgona-1,3,5(10),8-tetraen-17α-ol (Vb). mp 141—143° (from AcOEt). *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.36; H, 8.64. IR ν_{max}^{Nujol} cm^{-1}: 3450. UV λ_{max}^{EtOH} mμ (ε): 275 (1.64×10^4).

rac-3-Methoxyestra-1,3,5(10)-trien-17α-ol (VIa)——To a solution of 0.4 g of *rac*-Va in 20 ml of dioxane, 40 ml of ether and 40 ml of liq. NH_3 was added 0.7 g of K at −50° and the resulting mixture was stirred at the same temperature for 2 hr. After addition of 2 g of NH_4Cl, NH_3 was removed at room temperature. To the residue was added water and the mixture was extracted with ether. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to yield 0.4 g of *rac*-VIa. mp 94° (from *n*-hexane). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.92; H, 9.09. Found: C, 79.98; H, 9.15. UV λ_{max}^{EtOH} mμ (ε): 280 (1.98×10^3), 288 (1.9×10^3).

rac-3-Methoxy-13β-ethylgona-1,3,5(10)-trien-17α-ol (VIb) was obtained from *rac*-Vb in a similar manner as *rac*-VIa. mp 71—73° (from MeOH–H_2O). *Anal.* Calcd. for $C_{20}H_{28}O_2 \cdot 1/2\ H_2O$: C, 77.67; H, 9.39. Found: C, 77.51; H, 9.43. UV λ_{max}^{EtOH} mμ (ε): 279 (1.94×10^3), 288 (1.83×10^3).

rac-3-Methoxyestra-1,3,5(10)-trien-17-one (VIIa)——To a solution of 0.2 g of *rac*-VIa in 20 ml of acetone was added 0.3 ml of Jones reagent and the resulting mixture was allowed to stand for 10—15 min at room temperature. When water was added, crystals were precipitated out. mp 140° (from MeOH). Comparison with authentic sample[3] of *rac*-VIIa by mp, IR showed the identity.

rac-3-Methoxy-13β-ethylgona-1,3,5(10)-trien-17-one (VIIb) was obtained from *rac*-VIb in a way similar to that for *rac*-VIIa. mp 126°. Comparison with authentic sample of *rac*-VIIb[3] by mp, IR showed the identity.

Hemisuccinate of _rac_-IIa (_rac_-VIII)——A solution of 6.85 g of *rac*-IIa and 16 g of succinic anhydride in 20 ml of pyridine was stirred at 70—80° for 10 hr. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water, dried and concentrated to yield crude crystals, which were recrystallized from AcOEt to give 5 g of *rac*-VIII as colorless platelet. mp 121—123°. *Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.04. Found: C, 69.20; H, 6.79. UV λ_{max}^{EtOH} mμ (ε): 265 (2.06×10^4).

Quinine Salt of VIII——A solution of 2.43 g of quinine base in 20 ml of acetone and 4 ml of MeOH was added to a solution of 3 g of VIII in 25 ml of acetone. With cooling, 3.5 g of crystals separated out. By recrystallization from MeOH–acetone, 2.1 g of quinine salt of (+)VIII was obtained. $[\alpha]_D^{23}$ +39.6° (c=1.0 in $CHCl_3$). From the first mother liquor, 2.3 g of quinine salt of (−)VIII was obtained as an oil. $[\alpha]_D^{23}$ +111.8° (c=1.0 in $CHCl_3$).

(−)17α-Hydroxy-3-methoxy-8.14-secoestra-1,3,5(10),9-tetraen-14-one 17-Hemisuccinate (VIII)——2.2 g of the oily quinine salt obtained above was dissolved in 30 ml of $CHCl_3$. This solution was washed with 20 ml of a 10% aqueous H_2SO_4 solution three times and then water, dried and concentrated to yield 1.6 g of (−)VIII as an oil. $[\alpha]_D^{24}$ −87.8° (c=1.2 in $CHCl_3$). In a similar manner, 0.9 g of (+)VIII was obtained as an oil from 1.4 g of crystalline quinine salt. $[\alpha]_D$ +87.2° (c=1.2 in $CHCl_3$).

(−)17α-Hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-14-one (IIa)——To a solution of 1.5 g of (−)VIII in 20 ml of MeOH was added 14 ml of 10N aqueous KOH solution with ice cooling. After stirring for 1 hr, the reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, dried and concentrated to afford 0.86 g of (−)IIa as needles. mp 102—103° (from MeOH). $[\alpha]_D^{24}$ −83.6° (c=1.0 in $CHCl_3$). In a similar way, 0.5 g of (+)IIa was obtained by hydrolysis of 0.8 g of (+)VIII as needles. $[\alpha]_D^{24}$ +83.6° (c=1.0 in $CHCl_3$).

(−)3-Methoxyestra-1,3,5(10),8,14-pentaen-17α-ol (IVa)——0.6 g of (−)IIa was dissolved in 16 ml of MeOH and to this solution was added 2.7 ml of conc. HCl. The resulting mixture was refluxed gently with stirring for 40 min, then poured into water, extracted with benzene, washed with water and dried over Na_2SO_4. The solvent was evaporated to afford crude crystals. Recrystallization from a small volume of MeOH gave 0.55 g of (−)IVa as colorless needles. mp 63—64°. $[\alpha]_D^{24}$ −192.6° (c=1.0 in $CHCl_3$). In a similar manner, 0.4 g of (+)IVa was obtained from 0.45 g of (+)IIa. mp 63—64°. $[\alpha]_D^{24}$ +190.8° (c=0.5 in $CHCl_3$).

(−)3-Methoxyestra-1,3,5(10),8-tetraen-17α-ol (Va)——A solution of 0.6 g of (−)IV in 30 ml of dioxane was shaken under a stream of hydrogen over Raney Ni. After 47 ml of hydrogen was absorbed, catalyst was filtered off and the filtrate was concentrated to yield crude crystals. Recrystallization from ether afforded 0.5 g of (−)Va as plates. mp 113—116°. $[\alpha]_D^{24}$ −31.5° (c=1.0 in $CHCl_3$).

In a similar manner, 0.4 g of (+)Va was obtained as an oil. $[\alpha]_D^{24}$ +42.3° (c=1.0 in $CHCl_3$).

(+)3-Methoxyestra-1,3,5(10)-trien-17α-ol (VIa)——To a solution of 0.4 g of (−)Va in 20 ml of dioxane, 40 ml of tetrahydrofurane and 250 ml of liq. NH_3 was added portionwise 2 g of potassium at −30—−50° and the resulting mixture was stirred at the same temperature for 2 hr. Decomposition of excess of potassium with NH_4Cl followed by removal of liq. NH_3 afforded a syrup. To this residue was added water and the resulting mixture was extracted with benzene. The organic layer was washed with water, dried and concentrated to afford 0.35 g of (+)VIa as an oil. $[\alpha]_D^{24}$ +13.5° (c=1.0 in $CHCl_3$). In a similar manner, 0.33 g of (−)VIa was obtained from 0.4 g of (+)Va. mp 96—100°. $[\alpha]_D^{24}$ $-17.6°$ ($c=0.5$ in $CHCl_3$).

(+)3-Methoxyestra-1,3,5(10)-trien-17-one (VIIa)——To a solution of 0.2 g of (+)VIa in 20 ml of acetone was added dropwise 0.25 ml of Jones reagent at room temperature with vigorous stirring. After excess reagent was decomposed with MeOH, water was added into the mixture to give crystals. Recrystallization from EtOH gave 0.18 g of (+)VIIa. mp 165—168°. $[\alpha]_D^{24}$ $+144.2°$. ($c=1.0$ in $CHCl_3$). Comparison of this substance with authentic sample of estrone methyl ether showed an identity. In a similar manner, 0.25 g of (−)VIIa was obtained from 0.3 g of (−)VIa. mp 164—168°. $[\alpha]_D^{24}$ $-147.6°$ ($c=1.0$ in $CHCl_3$).

Reconversion of (+)IIa into I——To a solution of 3.6 g of (+)IIa in 18 ml of benzene, 18 ml of DMSO and 9.6 ml of pyridine were added 0.48 ml of CF_3COOH and 6 g of DCC and the resulting mixture was stirred at room temperature for 14 hr. Then 150 ml of ether was added and subsequent addition of 4 g of oxalic acid, 100 ml of MeOH and water gave precipitates, which were filtered off. The organic layer was separated and washed with an aqueous $NaHCO_3$ solution and water, dried and concentrated. The residue was chromatographed on 100 g of silica gel with the solvent system of benzene–ether (10:1) to afford 2.3 g of I. mp 78°. 0.2 g of (+)IIa was recovered.

(+)17β-Acetoxy-3-methoxy-8,14-seco-13α-estra-1,3,5(10),9-tetraen-17-one (IX)——To a solution of 2.2 g of (+)IIa in 14 ml of pyridine was added 3.2 ml of acetic anhydride and the mixture was kept at 50° for 2 hr. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with dil. HCl, a 5% aqueous $NaHCO_3$ solution and water, dried and evaporated to afford 2.4 g of (+)IX as a pale yellow oil. $[\alpha]_D^{26}$ $+71.0°$ ($c=1.0$ in $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740, 1610, 1500. UV λ_{max}^{EtOH} mμ (ε): 265 (2.6×10^4).

(+)17β-Acetoxy-3-methoxy-8,14-seco-13α-estra-1,3,5(10),9-tetraen-17α-ol (X)——To a solution of 2.4 g of (+)IX in 100 ml of MeOH was slowly added 0.3 g of $NaBH_4$ at −20—−30° and the mixture was stirred at this temperature for 1.5 hr. The reaction mixture was poured into water and extracted with ether. The ether solution was washed with water, dried and evaporated to give 2.4 g of (+)X as an oily material. $[\alpha]_D^{25}$ $+11.1°$ ($c=1.0$ in $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3450, 1730, 1610, 1490.

(+)17β-Acetoxy-3-methoxy-9,14β-epoxy-8,14-seco-13α-estra-1,3,5(10)-triene (XI)——To a solution of 2.4 g of (+)X in 80 ml of benzene was added 0.05 g of *p*-TsOH and the mixture was allowed to stand at room temperature over night. After washing with a sat. aqueous $NaHCO_3$ solution, and then water, the organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on 10 g of silica gel. Elution with benzene gave 2.3 g of an oily material. $[\alpha]_D^{25}$ $+20.8°$ ($c=1.0$ in $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1730, 1610, 1500. UV λ_{max}^{EtOH} mμ (ε): 277 (1.82×10^3), 283 (1.72×10^3).

3-Methoxy-9,14β-epoxy-8,14-seco-13α-estra-1,3,5(10)-trien-17β-ol (XII)——To a solution of 2.3 g of (+)XI in 30 ml of EtOH was added 20 ml of a ethanolic solution of 1N KOH and the reaction mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into water and extracted with ether. The extracts were combined and washed with water, dried and evaporated to give 1.9 g of XII as an oily material. IR ν_{max}^{film} cm^{-1}: 3400, 1610.

(−)3-Methoxy-9,14β-epoxy-8,14-seco-13α-estra-1,3,5(10)-trien-17-one (XIII)——To a suspension of CrO_3–pyridine complex prepared from 1.3 g of CrO_3 and 30 ml of pyridine was added dropwise a solution of 1.9 g of XII in 10 ml of pyridine and the mixture was stirred at room temperature for 2 hr. Then the reaction mixture was poured into ice-water and extracted with ether. The ether solution was washed with dil. H_2SO_4, saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated to give an oily residue which was chromatographed on 30 g of silica gel. Fractions eluted with benzene–ether (50:1) afforded 1.5 g of (−)XIII as an oily material. $[\alpha]_D^{26}$ $-32.7°$ ($c=1.0$ in $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740, 1610, 1500.

(−)3-Methoxyestra-1,3,5(10),8,14-pentaen-17α-ol (IVa)——To a solution of 1.5 g of (−)XIII in 30 ml of MeOH was added 5 ml of conc. HCl and the solution was refluxed for 30 min. The reaction mixture was poured into water and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ solution, water, dried over Na_2SO_4 and evaporated to give 1.5 g of a yellow oil, from which 0.8 g of crude crystals of (−)IVa were obtained. Recrystallization from MeOH afforded the pure sample. mp 59—61°. $[\alpha]_D^{26}$ $-194°$ ($c=1.0$ in $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε): 310 (2.78×10^4).

XII from (+)VIII——To a solution of 2.2 g of (+)VIII in 22 ml of pyridine and 20 ml of water was added 0.4 g of $NaBH_4$ and the mixture was stirred at 0° for 1 hr. The reaction mixture was poured into water. After adjusting the aqueous solution at pH 5.0 with HCl, the mixture was extracted with ether. The ether solution was washed with dil. HCl and water, dried and evaporated. To a solution of the residue (XIV) in dry benzene was added 0.1 g of *p*-TsOH and the solution was allowed to stand overnight at room temperature. The solution was extracted with a saturated $NaHCO_3$ solution and to the water layer was added 10 g of KOH, then 500 ml of water. This mixture was extracted with ether and the ether solution was washed with water, dried and evaporated to give 1.6 g of a yellow oil which was chromatographed on silica gel. Elution with benzene–ether (20:1) gave 1 g of XII as a pale yellow oil.

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