Oxygenation of 2,4-Dibromoestrogens with Nitric Acid: A New Synthesis of 19-Nor Steroids[1)]

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A convenient synthesis of 19-nor steroids 4a, 4b, 12a, and 12c is described. Oxygenation of 2,4-dibromoestrogens 1a, 1b, 8a, and 8b with nitric acid in acetic acid gave the corresponding 2,4-dibromo-10β-hydroxy-1,4-dien-3-one derivatives 2a, 2c, 9a, and 9d in excellent yields. These 10β-hydroxy-dienones were subjected to catalytic hydrogenation over palladium-on-charcoal to afford the saturated 5ξ-3-oxo derivatives 3a, 3b, 10a, and 10b, respectively, in very high yields. These saturated products were then converted into the corresponding 19-nor steroids 4a, 4b, 12a, and 12c by treatment with acid, perchloric acid, *p*-toluenesulfonic acid or Nafion-H.

Keywords 2,4-dibromoestrogen; nitric acid oxidation; 2,4-dibromo-10β-hydroxy-1,4-estradien-3-one; catalytic hydrogenation; 10β-hydroxy-5ξ-estran-3-one; dehydration; perchloric acid; Nafion-H; 19-nor steroid

19-Nor steroids, which are of considerable importance owing to their biological activity, have traditionally been prepared by the Birch reduction of estradiol derivatives.[2)] While this method is useful, it has some limitations.[2)] On the other hand, various approaches for the production of 19-nor steroids from 19-substituted derivatives have also been reported.[3)] It is virtually impossible to compare the efficiency of the various procedures since optimal conditions have usually not been described. Lupon *et al.*[4)] recently reported a short synthesis of 19-nor steroids using the photooxygenation of estrogens as the key reaction.

Recently, we[5)] reported the use of 2,4-dihalogenoestrogens for the synthesis of the major metabolites of estrogens, the 2- and 16α-hydroxy derivatives. In conjunction with our investigation of the utility of the 2,4-dihalogeno compounds, we have developed a new application of the 2,4-dibromides for the synthesis of 19-nor steroids. Our alternative procedure involves the oxygenation of the 2,4-dibromides **1a**, **1b**, **8a** and **8b** with nitric acid and a subsequent hydrogenation followed by treatment with acid.

Reaction of 2,4-dibromo-estrogens **1a** and **1b** with 2.5 mol eq of 70% nitric acid in acetic acid[6)] at room temperature gave the 2,4-dibromo-10β-hydroxy-1,4-dien-3-one derivatives **2a** (95%) and **2c** (96%) (Fig. 1). These structures were determined on the basis of infrared (IR), ultraviolet (UV) and proton nuclear magnetic resonance (^{1}H-NMR) spectral data and elemental analysis. The stereochemistry at C-10 was established on the basis of previous results for the reaction of estrogens with lead(IV) acetate[7)] or thallium(III) trifluoroacetate.[8)] Recently, Galdecki *et al.*[9)] carried out the detailed conformational analysis of compound **2c** by X-ray crystallography, supporting the 10β-hydroxy structure. The 2,4-dibromo steroids **8a** and **8b** having 16α-ketol and 16α,17β-glycol structures were similarly converted into the corresponding 10β-hydroxy-dienone **9a** and **9d** in excellent yields. Treatment of compounds **2a**, **2c**, and **9a** with acetic anhydride–pyridine (room temperature, overnight) gave the 10β-acetoxy derivatives **2b** (53%), **2e** (35%), and **9c** (43%) along

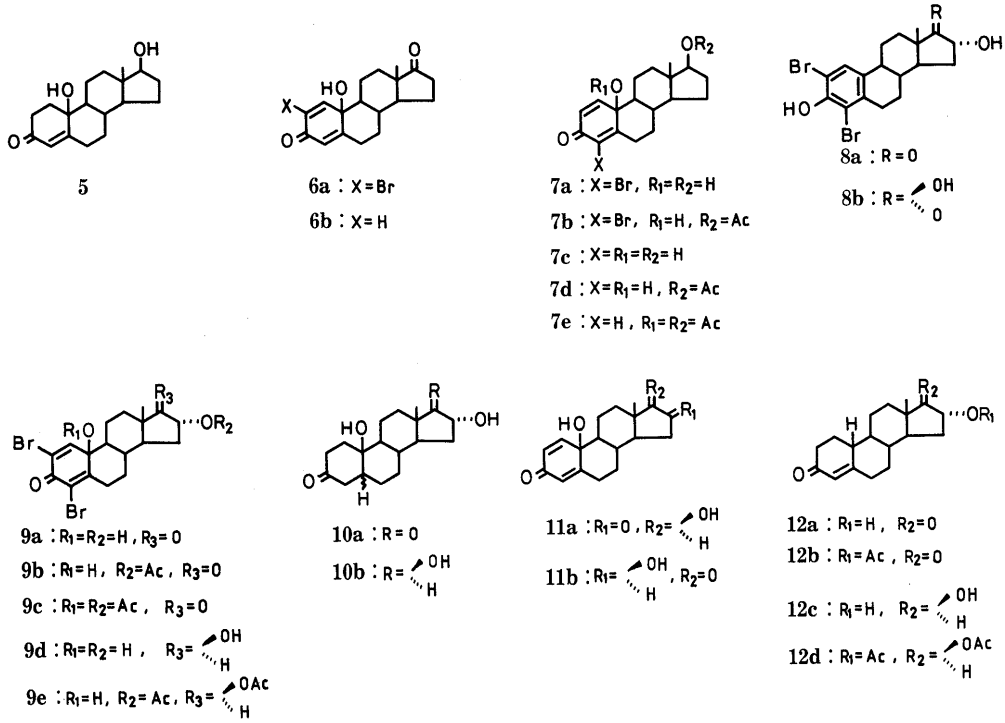
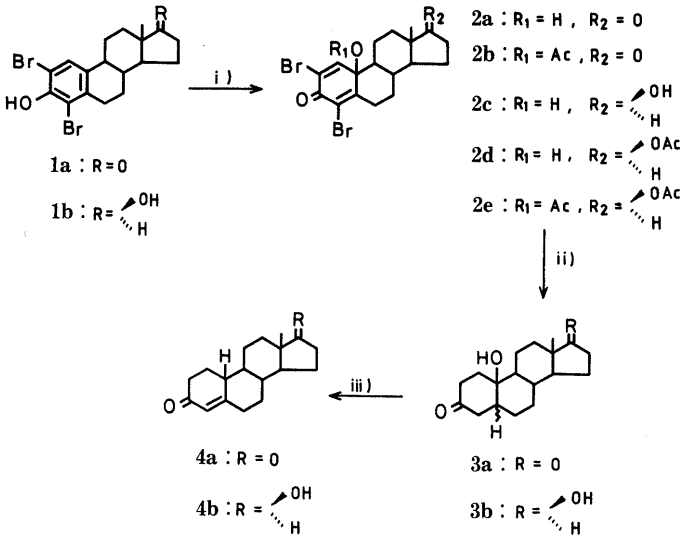


Chart 1



i) HNO_3, AcOH ii) H_2, Pd-C, EtOH–pyridine iii) H^+

Fig. 1

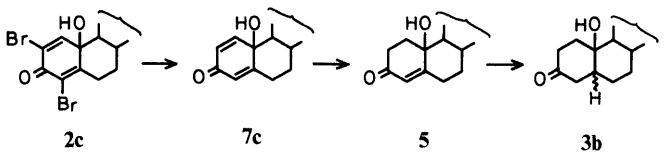


Fig. 2

with the recovered substrate **2a** (37%), the 17β-monoacetate **2d** (58%) from the 17β-alcohol **2c**, and the 16α-monoacetate **9b** (35%) from the 16α-ketol **9a**, respectively, while a similar reaction of compound **9d** having a 16α,17β-glycol structure did not afford its 10β-acetate but solely the 16,17-diacetate **9e** in a quantitative yield.

Compounds **2a**, **2c**, **9a**, and **9d** were catalytically hydrogenated over palladium-on-charcoal in ethanol containing 5% pyridine[10] until absorption of hydrogen (*ca.* 4 mol eq) stopped, yielding the corresponding debrominated tetrahydro derivatives **3a**, **3b**, **10a**, and **10b** in very high yields. On the other hand, the 10β-hydroxy-4-en-3-one **5** was isolated before completion of the reaction with compound **2c**. This suggests that hydrodebromination of the 2,4-dibromides occurs first, and subsequent catalytic hydrogenation proceeds through initial reduction of the double bond at C-1 rather than at C-4 in analogy with the reduction of 1,4-androstadiene-3-ones[11] (Fig. 2). Considering the stereochemistry of the catalytic hydrogenation,[12] compounds **3a**, **3b**, **10a**, and **10b** would be mixtures of the 5α- and 5β-reduced products with the latter isomer formed in the larger amounts.

Hydrodebromination of the 2,4-dibromides **2a** and **2c** was next carried out according to the method[13] previously reported, using formic acid, palladium-on-charcoal, and triethylamine.[14] The course of the hydrodebromination, which was conveniently followed by thin layer chromatography (TLC), indicated that, after *ca.* 8 h, the substrates had almost completely disappeared. Separation of the products by silica gel column chromatography gave compound **6b** (37%) along with the 2-bromide **6a** (35%) from the 17-ketone **2a**, and compound **7c** (26%) along with the 4-bromide **7a** (33%) from the 17β-ol **2b**. When the 16α-hydroxylated steroids **9a** and **9d** were similarly treated, the hydrodebrominated 17β-ketol **11a** (36%), which would be an isomerized product of the 16α-hydroxy-17-one derivative **11b** initially produced,[15] was obtained from the 16α-ketol **9a** while the latter was converted into the tetrahydro compound **10b** (65%), which was identical with the steroid obtained by the above catalytic hydrogenation, along with estriol (21%), which is probably produced in the same way as in the case of catalytic hydrogenation in ethanol (see ref. 10). In these cases, the formation of the 2- or 4-monobromide was not detected by TLC analysis of the reaction mixture.

Table I. Conversion of the Tetrahydro Compounds **3** and **10** into 19-Nor Steroids **4** and **12**

Conditions[a]	19-Nor steroid (yield,[b] %)
Substrate: **3a**	
$HClO_4$	**4a** (60)
p-TsOH	**4a** (35)
Nafion-H	**4a** (65)
Substrate: **3b**	
$HClO_4$	**4b** (21)
p-TsOH	**4b** (20)
Nafion-H	**4b** (61)
Substrate: **10a**	
$HClO_4$	**12a** (60)
p-TsOH	**12a** (15)
Nafion-H	**12a** (28)
Substrate: **10b**	
$HClO_4$	**12c** (45)
p-TsOH	**12c** (5)
Nafion-H	**12c** (15)

a) $HClO_4$: MeOH, $HClO_4$, silica gel, 90 °C. *p*-TsOH: benzene, *p*-TsOH-impregnated silica gel, 60 °C. Nafion-H: $CHCl_3$, Nafion-H, room temperature. *b*) Isolated yield.

Although the exact reason for the different reactivities of the 10β-hydroxy steroids toward the reduction with formic acid as well as the acetylation with acetic anhydride–pyridine is not clear, a conformational transmission of distortion through the D-C-B rings might be in operation.[16]

Conversion of the tetrahydro derivatives **3a** and **3b** into 19-nor steroids **4a** and **4b** was explored under the following chemoselective dehydration reaction conditions: i) perchloric acid, MeOH, silica gel, 90 °C[4]; ii) *p*-TsOH-impregnated silica gel, benzene, 60 °C[17]; iii) perfluorinated ion exchange resin (Nafion-H), chloroform, room temperature[18] (Table I). Among the three reaction conditions, the condition with Nafion-H gave the best yields (*ca.* 60%) of the 19-nor steroids **4a** and **4b**, which were identical with authentic samples. On the other hand, Table I also shows that, in the experiments with the 16α-hydroxy steroids **10a** and **10b**, the highest yields (60 and 45%) of 19-nor steroids **12a** and **12c** were obtained using perchloric acid. The structures of compounds **12a** and **12c** were identified on the basis of the spectral data, elemental analysis, and derivatization to the acetates **12b** and **12d**.

In conclusion, we have developed an efficient synthesis of 19-nor steroids. In this sequence, the 19-nor steroids **4a**, **4b**, and **12a** were each obtained in *ca.* 50% yield from estrone, estradiol and 2,4,16α-tribromoestrone, respectively, while the 19-nor steroid **12c** was obtained in *ca.* 40% yield from

estriol, without isolation of the intermediates. In addition to easier handling, the obvious advantages of this sequence are that it takes place in higher yield and avoids the use of poisonous lead or thallium reagents.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained with JEOL PMX 60 (60 MHz) and JEOL GX 400 (400 MHz) spectrometers using tetramethylsilane as an internal standard and mass spectra (MS) on a JEOL JMS-DX 303 spectrometer. UV spectra were determined on a Hitachi UV 150—20 spectrophotometer, and IR spectra on a Shimadzu IR-430 spectrophotometer. Optical rotation measurements were done on a JASCO DIP-360.

Reaction of 2,4-Dibromoestrogens 1a, 1b, 8a, and 8b with Nitric Acid Compounds **1a**, **1b**, **8a**, and **8b**[5b-d] (3.50 mmol) were dissolved in a mixture of AcOH (93 ml) and $CHCl_3$ (33 ml) (in the case of **1a**) or in AcOH (103 ml) (in the cases of **1b** and **8**), and 70% HNO_3 (0.51 ml, 10.2 mmol) was added to these solutions with stirring at room temperature [reaction time: 45 min (**8a**), 2 h (**1b** and **8b**) or 24 h (**1a**)]. The reaction mixtures were poured into chilled water (1 l). In the experiment with **1a**, the product was extracted with $CHCl_3$ (300 ml × 3) and the organic layer was washed with 5% $NaHCO_3$ solution and water, and dried (Na_2SO_4). After evaporation of the solvent, the solid product obtained was recrystallized to give the 10β-hydroxy derivative **2a**. On the other hand, in the experiments with **1b**, **8a**, and **8b**, the products were collected by filtration, dried under reduced pressure and recrystallized to yield the 10β-hydroxy derivatives **2c**, **9a** and **9d**, respectively.

2,4-Dibromo-10β-hydroxy-1,4-estradiene-3,17-dione (2a) Yield: 95% (1.48 g). mp 230—232 °C (colorless needles, from acetone). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, s, 18-Me), 7.64 (1H, s, 1-H). IR (KBr): 1736, 1653 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 265 (1.08×10^4). $[\alpha]_D^{27}$: 53.0° (c=1.13, $CHCl_3$: MeOH = 9 : 1, v/v). *Anal.* Calcd for $C_{18}H_{20}Br_2O_3$: C, 48.56; H, 4.75. Found: C, 48.32; H, 4.52.

2,4-Dibromo-10β,17β-dihydroxy-1,4-estradien-3-one (2c) Yield: 96% (1.50 g). mp 221—224 °C (dec.) (colorless plates, from MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, s, 18-Me), 3.67 (1H, t, J=8 Hz, 17α-H), 7.67 (1H, s, 1-H). IR (KBr): 3250—3500, 1653 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 266 (1.06×10^4). $[\alpha]_D^{23}$: 54.0° (c=1.0, $CHCl_3$: MeOH = 9 : 1, v/v). *Anal.* Calcd for $C_{18}H_{22}Br_2O_3$: C, 47.99; H, 4.80. Found: C, 48.26; H, 4.97.

2,4-Dibromo-10β,16α-dihydroxy-1,4-estradiene-3,17-dione (9a) Yield: 91% (1.46 g). mp 224—226 °C (dec.) (colorless needles, from AcOEt). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.04 (3H, s, 18-Me), 4.35 (1H, d, J=7.8 Hz, 16β-H), 7.59 (1H, s, 1-H). IR (KBr): 3450, 1740, 1650 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 265 (1.05×10^4). $[\alpha]_D^{22}$: +45.6° (c=1.02, $CHCl_3$: MeOH = 9 : 1, v/v). *Anal.* Calcd for $C_{18}H_{20}Br_2O_4$: C, 46.93; H, 4.38. Found: C, 47.19; H, 4.34.

2,4-Dibromo-10β,16α,17β-trihydroxy-1,4-estradien-3-one (9d) Yield: 89% (1.44 g). mp 198—200 °C (dec.) (colorless needles, from MeOH–H_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, s, 18-Me), 3.70 (1H, d, J=6 Hz, 17α-H), 4.07 (1H, m, 16β-H), 7.63 (1H, s, 1-H). IR (KBr): 3300—3480, 1664 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 266 (1.02×10^4). $[\alpha]_D^{20}$: −23.4° (c=1.03, $CHCl_3$: MeOH = 9 : 1, v/v). *Anal.* Calcd for $C_{18}H_{22}Br_2O_4$: C, 46.78; H, 4.80. Found: C, 46.87; H, 4.77.

Acetylation of the 10β-Hydroxy Steroids 2a, 2c, 9a, and 9d with Acetic Anhydride–Pyridine The steroids (100 mg, 0.215—0.224 mmol) were treated with pyridine (1 ml) and acetic anhydride (0.5 ml) at room temperature overnight. The reaction mixtures were diluted with AcOEt (50 ml) and washed with 5% HCl and 5% $NaHCO_3$ solutions and water and dried (Na_2SO_4). After evaporation of the solvent, the products were purified by preparative TLC (hexane : AcOEt = 3 : 1 or 2 : 1, v/v) and recrystallization to give the acetates **2b**, **2d**, **2e**, **9b**, **9c**, and **9e**.

2,4-Dibromo-10β-acetoxy-1,4-estradiene-3,17-dione (2b) Yield: 53% (58 mg). mp 183—186 °C (colorless needles, from MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, s, 18-Me), 2.15 (3H, s, 10-OCOCH$_3$), 7.39 (1H, s, 1-H). IR (KBr): 1745, 1735, 1665 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 270 (9.68×10^3). *Anal.* Calcd for $C_{20}H_{22}BrO_4$: C, 49.41; H, 4.56. Found: C, 49.11; H, 4.55.

In addition, **2a** (37 mg, 37%), mp 230—232 °C, was recovered from the reaction mixture.

2,4-Dibromo-10β-hydroxy-17β-acetoxy-1,4-estradien-3-one (2d) The more polar product obtained from **2c** was recrystallized from acetone to yield **2d** (64 mg, 58%) as colorless needles: mp 247—248 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-Me), 2.03 (3H, s, 17-OCOCH$_3$), 4.60 (1H, t, J=8 Hz, 17α-H), 7.50 (1H, s, 1-H). IR (KBr): 3490, 1738, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 265 (9.92×10^3). *Anal.* Calcd for $C_{20}H_{26}Br_2O_4$: C, 49.21; H, 4.95. Found: C, 49.21; H, 4.89.

2,4-Dibromo-10β,17β-diacetoxy-1,4-estradien-3-one (2e) Recrystallization of the less polar product, obtained from **2c**, from acetone afforded **2e** (51 mg, 35%) as colorless plates: mp 193—194 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-Me), 2.03 (1H, s, 17-OCOCH$_3$), 2.13 (3H, s, 10-OCOCH$_3$), 4.57 (1H, t, J=8 Hz, 17α-H), 7.36 (1H, s, 1-H). IR (KBr): 1740, 1725, 1660 cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 270 (9.83×10^3). *Anal.* Calcd for $C_{22}H_{26}Br_2O_5$: C, 49.84; H, 4.97. Found: C, 49.93; H, 4.99.

2,4-Dibromo-10β-hydroxy-16α-acetoxy-1,4-estradiene-3,17-dione (9b) The less polar product obtained from **9a** was purified by TLC to give **9b** (38 mg, 35%). Oil. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.07 (3H, s, 18-Me), 2.11 (3H, s, 16-OCOCH$_3$), 5.41 (1H, d, J=7.8 Hz, 16β-H), 7.54 (1H, s, 1-H). IR (KBr): 3450, 1760, 1745, 1680 cm^{-1}. UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε): 264.4 (9.90×10^3). CI-MS m/z: 503 ($M^+ + 1$).

2,4-Dibromo-10β,16α-diacetoxy-1,4-estradiene-3,17-dione (9c) Recrystallization of the more polar product, obtained from **9a**, from acetone yielded **9c** (50 mg, 43%) as pale yellow needles: mp 227—228 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, s, 18-Me), 2.11 (3H, s, 16-OCOCH$_3$), 2.15 (3H, s, 10-OCOCH$_3$), 5.40 (1H, d, J=7.8 Hz, 16β-H), 7.38 (1H, s, 1-H). IR (KBr): 1740, 1665 cm^{-1}. UV λ_{max} nm (ε): 270 (1.12×10^4). *Anal.* Calcd for $C_{22}H_{24}Br_2O_6$: C, 48.55; H, 4.44. Found: C, 48.79; H, 4.53.

2,4-Dibromo-10β-hydroxy-16α,17β-diacetoxy-1,4-estradien-3-one (9e) Yield: 99% (115 mg). mp 263—263.5 °C (dec.) (colorless needles, from acetone). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, 18-Me), 2.03 and 2.06 (3H, s, 16-and 17-OCOCH$_3$), 4.88 (1H, d, J=5.8 Hz, 17α-H), 5.13 (1H, m, 16β-H), 7.57 (1H, s, 1-H). IR (KBr): 3400, 1740 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 265 (9.83×10^3). *Anal.* Calcd for $C_{24}H_{28}Br_2O_7$: C, 48.37; H, 4.80. Found: C, 48.17; H, 4.97.

Catalytic Hydrogenation of 2,4-Dibromides 2a, 2c, 9a and 9d over Palladium-on-Charcoal in EtOH containing Pyridine The 2,4-dibromides (2.2—2.4 mmol) in 200 (**2a** and **2c**) or 60 ml (**9a** and **9d**) of EtOH containing 5% pyridine were hydrogenated over 250 mg of 5% Pd–C at room temperature and atmospheric pressure until *ca.* 4 mol eq of hydrogen was absorbed. The mixtures were filtered, and the filtrates were concentrated to about 20 ml under reduced pressure below 50 °C, diluted with 300 ml of AcOEt, washed with 5% HCl and 5% $NaHCO_3$ solution and water, and dried (Na_2SO_4). After evaporation of the solvent, the residues were recrystallized to afford the pure tetrahydro derivatives **3a**, **3b**, **10a**, and **10b**.

10β-Hydroxy-5ξ-estrane-3,17-dione (3a) Yield: 92% (601 mg). mp 190—192 °C (colorless plates, from ether). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, 18-Me). IR (KBr): 3520, 1741, 1713 cm^{-1}. $[\alpha]_D^{24}$: +97.0° (c=1.00, $CHCl_3$: MeOH = 9 : 1, v/v). High-resolution MS m/z: M^+ Calcd for $C_{18}H_{26}O_3$ 290.1788. Found: 290.1782.

10β,17β-Dihydroxy-5ξ-estran-3-one (3b) Yield: 95% (623 mg). Semisolid. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, s, 18-Me), 3.67 (1H, t, J=8 Hz, 17α-H). IR (KBr): 3400, 1704 cm^{-1}. $[\alpha]_D^{26}$: +8.79° (c=1.08, $CHCl_3$: MeOH = 9 : 1, v/v). High-resolution MS m/z: M^+ Calcd for $C_{18}H_{28}O_3$: 292.2047. Found: 292.2039.

10β,16α-Dihydroxy-5ξ-estrane-3,17-dione (10a) Yield: 83% (553 mg). mp 212—213 °C (colorless needles, from acetone). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s, 18-Me), 4.38 (1H, m, 16β-H). IR (KBr): 3440, 3400, 1745, 1690 cm^{-1}. $[\alpha]_D^{22}$: +100.5° (c=1.00, $CHCl_3$: MeOH = 9 : 1, v/v). High-resolution MS m/z: M^+ Calcd for $C_{18}H_{26}O_4$: 306.1809. Found: 306.1821.

10β,16α,17β-Trihydroxy-5ξ-estran-3-one (10b) Yiled: 91% (608 mg). mp 222—223 °C (colorless needles, from acetone). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, s, 18-Me), 3.41 (1H, d, J=5.9 Hz, 17α-H), 4.03 (1H, m, 16β-H). IR (KBr): 3510, 3420, 3374, 1690 cm^{-1}. $[\alpha]_D^{26}$: +1.08° (c=1.08, $CHCl_3$). High-resolution MS m/z: M^+ Calcd for $C_{18}H_{28}O_4$: 308.1996. Found: 308.1988.

10β,17β-Dihydroxy-4-estren-3-one (5) Compound **2b** (200 mg, 0.45 mmol) was subjected to catalytic hydrogenation as above and the reaction was stopped when *ca.* 3.5 mol eq of hydrogen was absorbed. The crude products were purified by silica gel column chromatography (hexane–AcOEt) to give **5** (56 mg, 43%) along with the tetrahydro compound **3b** (45 mg, 34%). **5**: mp 204—206 °C (colorless plates, from acetone) (lit.[7b] 208—210 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-Me), 3.70 (1H, t, J=8 Hz, 17α-H), 5.85 (1H, br s, 4-H). IR (KBr): 3400, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 236 (9.38×10^3). MS m/z: 290 (M^+). $[\alpha]_D^{23}$: +61.6° (c=0.58, $CHCl_3$: MeOH = 9 : 1, v/v). *Anal.* Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.20; H, 9.14.

Reaction of the 2,4-Dibromides 2a, 2c, 9a, and 9d with Formic Acid in the Presence of Palladium-on-Charcoal and Triethylamine Compound **2a**, **2b**, **9a**, or **9d** (1 mmol) was dissolved in 50 ml of MeOH. Formic acid (85%,

612 mg, 11.3 mmol), triethylamine (2.4 ml, 17.22 mmol) and 5% Pd–C (120 mg) were added to the solution and the mixture was heated under reflux for 10 h with stirring under N_2 gas. After filtration, the filtrate was concentrated to *ca.* 10 ml, diluted with AcOEt (100 ml), washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the hydrodebrominated product **6**, **7a**, **7c**, or **11a** and the tetrahydrocompound **10b** were isolated by silica gel column chromatography (hexane–AcOEt) and recrystallized from an appropriate solvent.

2-Bromo-10β-hydroxy-1,4-estradiene-3,17-dione (6a) The less polar product obtained from **2a** was recrystallized from acetone to afford **6a** (128 mg, 35%) as colorless plates: mp 279—280 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 0.97 (3H, s, 18-Me), 6.14 (1H, s, 4-H), 7.57 (1H, s, 1-H). IR (KBr): 3480, 1640 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 253 (1.11×10^4). *Anal.* Calcd for $C_{18}H_{21}BrO_3$: C, 59.19; H, 5.79. Found: C, 58.88; H, 5.56.

10β-Hydroxy-1,4-estradiene-3,17-dione (6b) Recrystallization of the more polar product, obtained from **2a**, from acetone gave **6b** (103 mg, 37%) as colorless plates: mp 210—213 °C (lit. 210—211.5 °C,[4] 215—217 °C[7a]). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s, 18-Me), 6.00 (1H, m, 4-H), 6.17 (1H, dd, J=2.0, 10.3 Hz, 2-H), 7.15 (1H, d, J=10.3 Hz, 1-H). IR (KBr): 3430, 1726, 1662 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 238 (1.15×10^4).

4-Bromo-10β,17β-dihydroxy-1,4-estradien-3-one (7a) The less polar product produced from **2c** was recrystallized from acetone to yield **7a** (121 mg, 33%) as colorless needles: mp 213—214 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-Me), 3.59 (1H, t, J=8.3 Hz, 17α-H), 6.28 (1H, d, J=10.3, 2-H), 7.15 (1H, d, J=10.3, 1-H). IR (KBr): 3450, 3300, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 250 (9.9×10^3). *Anal.* Calcd for $C_{18}H_{23}BrO_3$: C, 58.86; H, 6.31. Found: C, 59.11; H, 6.55.

10β,17β-Dihydroxy-1,4-estradien-3-one (7c) Recrystallization of the more polar product, formed from **2c**, from acetone afforded **7c** (75 mg, 26%) as colorless needles: mp 227—230 °C (dec.) (lit. 227—230 °C,[4] 247—250 °C[7a]). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-Me), 3.58 (1H, t, J=8.5 Hz, 17α-H), 5.98 (1H, s, 4-H), 6.15 (1H, dd, J=10.0, 2.2 Hz, 2-H), 7.18 (1H, d, J=10.0 Hz, 1-H). IR (KBr): 3450, 3280, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 243 (1.07×10^4). *Anal.* Calcd for $C_{18}H_{24}O_3$: C, 75.15; H, 8.41. Found: C, 74.97; H, 8.31.

10β,17β-Dihydroxy-1,4-estradiene-3,16-dione (11a) The product obtained from **9a** was recrystallized from AcOEt to give **11a** (111 mg, 36%) as colorless prisms: mp 211—212 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 0.85 (3H, s, 18-Me), 3.74 (1H, s, 17α-H), 6.01 (1H, s, 4-H), 6.18 (1H, dd, J=2.0, 10.3 Hz, 2-H), 7.15 (1H, d, J=10.3 Hz, 1-H). IR (KBr): 3450, 3380, 1750, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 238 (9.46×10^3). *Anal.* Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C 71.41; H, 7.46.

4-Bromo-10β-hydroxy-17β-acetoxy-1,4-estradien-3-one (7b) Compound **7a** (25 mg, 0.068 mmol) was acetylated with Ac_2O–pyridine as described above. The product was recrystallized from acetone to yield **7b** (21 mg, 75%) as colorless needles: mp 208—210 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, s, 18-Me), 2.04 (3H, s, 17-$OCOCH_3$), 4.58 (1H, t, J=7.8 Hz, 17α-H), 6.32 (1H, d, J=10.3 Hz, 2-H), 7.09 (1H, d, J=10.3 Hz, 1-H). IR (KBr): 3440, 1710 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 250 (9.80×10^3). *Anal.* Calcd for $C_{20}H_{25}BrO_4$: C, 58.69; H, 6.16. Found; C, 58.88; H, 6.01.

Dehydration of Saturated 10β-Hydroxy Steroids 3 and 10 A) $HClO_4$ Method: The saturated alcohol **3** or **10** (0.17 mmol) was dissolved in MeOH (1.5 ml) and a catalytic amount of 70% $HClO_4$ was added. The solution was spotted on a silica gel plate (Merck F_{254}, particle size 0.063—0.200 mm, 20 cm × 20 cm × 0.50 mm) and heated at 90 °C over a period of 20 min. After standing at room temperature, the plate was developed with hexane : AcOEt (2 : 1, for **3a** and **10a**; 1 : 1 for **3b**, v/v) or hexane: AcOEt: acetone (1 : 1 : 0.5, v/v, for **10b**). The band corresponding to the 4-estren-3-one was scraped off and the compound was extracted with AcOEt. Crystallization from an appropriate solvent afforded pure **4** or **12**.

B) *p*-TsOH Method: Silica gel (Merck, particle size 0.063—0.200 mm, 900 mg) impregnated with *p*-TsOH, prepared according to method of D'Onofrio and Scettri[17] was added to a solution of **3** or **10** (0.14 mmol) in dry benzene (13 ml) and the mixture was stirred at 60 °C for 3.5—7 h. After this time, the reaction mixture was filtered, and the filtrate washed with 5% $NaHCO_3$ solution and water, and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane–AcOEt) and recrystallized to yield the pure 19-nor steroid **4** or **12**.

C) Nafion-H Method: Perfluorinated ion-exchange powder (Nafion-H) (50 mg) was added to a solution of **3** or **10** (0.14 mmol) in dry $CHCl_3$ (ml) and the mixture was stirred at room temperature for 2 d. The resin was filtered off and the filtrate was evaporated to give an oily product, which was purified by preparative TLC (hexane–AcOEt) and recrystallized to give pure **4** or **12**.

4-Estrene-3,17-dione (4a) Yield: 60% (method A, 28 mg), 35% (method B, 14 mg), 65% (method C, 30 mg). mp 170—173 °C (colorless plates, from acetone–hexane) (lit. 162—165 °C,[4] 170—171 °C[19]). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, 18-Me), 5.82 (1H, br s, 4-H). IR (KBr): 1730, 1680 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 240 (1.34×10^4).

17β-Hydroxy-4-estren-3-one (4b) Yield: 21% (method A, 10 mg), 20% (method B, 8 mg), 61% (method C, 24 mg). mp 122—123 °C (colorless needles, from ether) (lit. 114—115 °C,[4] 123.8—124.6 °C[19]). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-Me), 3.70 (1H, t, J=8 Hz, 17α-H), 5.85 (1H, br s, 4-H). IR (KBr): 3400, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 241 (1.64×10^4).

16α-Hydroxy-4-estrene-3,17-dione (12a) Yield: 60% (method A, 30 mg), 15% (method B, 6 mg), 28% (method C, 12 mg). Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, s, 18-Me), 4.38 (1H, m, 16β-H), 5.84 (1H, br s, 4-H). IR (KBr): 1745, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 239 (1.25×10^4). High resolution MS *m/z*: Calcd for $C_{18}H_{24}O_3$: 288.1726. Found: 288.1710.

16α,17β-Dihydroxy-4-estren-3-one (12c) Yield: 45% (method A, 22 mg), *ca.* 5% (method B, *ca.* 2 mg), 15% (method C, 6 mg). Oil. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-Me), 3.45 (1H, d, J=6 Hz, 17α-H), 4.02 (1H, m, 16β-H), 5.87 (1H, s, 4-H). IR (KBr): 3400, 1655 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 241 (1.06×10^4). High-resolution MS *m/z*: Calcd for $C_{18}H_{26}O_3$: 290.1882. Found: 290.1891.

16α-Acetoxy-4-estrene-3,17-dione (12b) Compound **12a** (68 mg, 0.24 mmol) was acetylated in the usual fashion. Purification of the product by repeated TLC (hexane–AcOEt) gave **12b** (39 mg, 51%) as a semi-solid. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, s, 18-Me), 2.12 (3H, s, 16-$OCOCH_3$), 5.43 (1H, d, J=7.8 Hz, 16β-H), 5.86 (1H, s, 4-H). IR (KBr): 1743, 1680 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 239 (1.25×10^4). High-resolution MS *m/z*: Calcd for $C_{20}H_{26}O_4$: 330.1819. Found: 330.1831.

16α,17β-Diacetoxy-4-estren-3-one (12d) Compound **12c** (30 mg, 0.10 mmol) was acetylated as above. Recrystallization of the product from acetone gave **12d** (34 mg, 87%) as pale yellow prisms: mp 160—160.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, s, 18-Me), 2.04 and 2.08 (3H, s, 16- and 17-$OCOCH_3$), 4.92 (1H, d, J=5.9 Hz, 17α-H), 5.16 (1H, m, 16β-H), 5.84 (1H, s, 4-H). IR (KBr): 1730, 1660 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 239 (1.08×10^4). *Anal.* Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: 70.55; H, 8.00

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References and Notes

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