171.23, 176.82. Anal. Calcd for $C_{33}H_{32}O_9$: C, 69.2; H, 5.63. Found: C, 69.3; H, 5.59.

4-[2′-Deoxy-B-D-ribo(=arabino)furanosyl]-8-ethenyl-1-hydroxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (2). To a solution of 4-[2′-deoxy-3′,5′-diacetyl-β-D-ribo(=arabino)furanosyl]-8-ethenyl-1-(trimethylacetoxy)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**25**) (80 mg, 0.14 mmol) in 10 mL of methanol was added metallic sodium (3 mg). The suspension was then stirred for 3 h, at which time the reaction mixture was a clear yellow solution. Acetic acid (1 mL) and water (15 mL) was then added, and the resulting precipitate was collected to afford 52 mg (92%) of **2** as a light yellow powder: mp 258–260 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.91 (1 H, ddd, $J_{1',2'\alpha}$ = 7.0 Hz, $J_{2'\alpha,2'\beta}$ = 12.9 Hz, $J_{2'\alpha,3'}$ = 5.8 Hz, H-2′α), 2.70 (1 H, ddd, $J_{1',2'\beta}$ = 7.0 Hz, H-2′β), 3.60 (1 H, dd, $J_{4',5'}$ = 5.3 Hz, $J_{5',5''}$ = 11.6 Hz, H-5′), 3.66 (1 H, dd, $J_{4',5''}$ = 3.8 Hz, H-5″), 3.80 (1 H, m, H-4′), 4.03 (1 H, m, H-3′), 5.46 (1 H, d, J_{cis} = 11.0 Hz), 6.08 (1 H, d, J_{trans} = 17.6 Hz), 6.27 (1 H, dd, H-1′), 6.90 (1 H, dd, vinyl), 6.97 (1 H, d, $J_{2,3}$ = 8.2 Hz, H-2), 7.91 (1 H, d, H-3), 8.06 (1 H, br d, $J_{9,10}$ = 8.3 Hz, H-9), 8.12 (1 H, d, $J_{11,12}$ = 9.0 Hz), 8.22 (2 H, br, H-7, H-11,12), 8.40 (1 H,d, H-10); ^{13}C NMR (DMSO-d_6) δ 44.15, 62.21, 71.05, 77.73, 86.39, 110.27, 114.53, 117.45, 118.94, 119.97, 120.47, 121.84, 124.08, 125.72, 126.40, 127.27, 131.27, 133.05, 134.73, 135.51, 138.47, 147.81, 152.27, 160.61. Anal. Calcd for $C_{24}H_{20}O_6 \cdot 0.5H_2O$: C, 69.7; H, 5.12. Found: C, 69.8; H, 5.09.

Acknowledgment. We thank the American Cancer Society for financial support. Appreciation is expressed to William R. Anderson, Jr., for help with mass and nuclear magnetic resonance spectra and to Terry D. Lee, Beckman Research Institute of the City of Hope, Duarte, CA, for FAB mass spectra.

Convenient Syntheses of Stereoisomeric 1,2-Epoxyestr-4-en-3-ones, Putative Intermediates in Estradiol Metabolism

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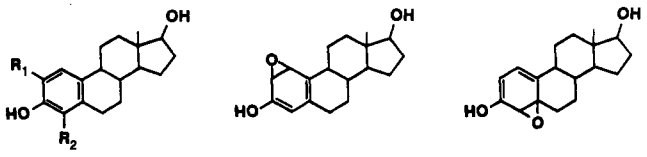
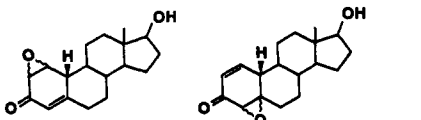
New synthetic sequences are described for 17β-hydroxy-1β,2β- and -1α,2α-epoxyestr-4-en-3-one, which are putative intermediates in the metabolism of estradiol to the 2,3- and 3,4-catecholestrogens, as well as the synthetic precursors of choice for these catechols.

The potent activity of estradiol (**1**) as a female hormone has been known for nearly 60 years. Its use in estrogen replacement therapy in menopausal women has been accompanied by reports of increased risk of cancer,[1] and despite intensive research especially in recent years, no firm connection between the biosynthesis, molecular structure, or catabolism of estradiol and carcinogenic events at the molecular level has yet been established. In 1980 we suggested[2,3] that phenolic arene oxides such as **2** and **3** (or their enone tautomers) might be intermediates in the well-known catabolism of estradiol to the catechols 2-hydroxyestradiol (**4**) and 4-hydroxyestradiol (**5**). Such



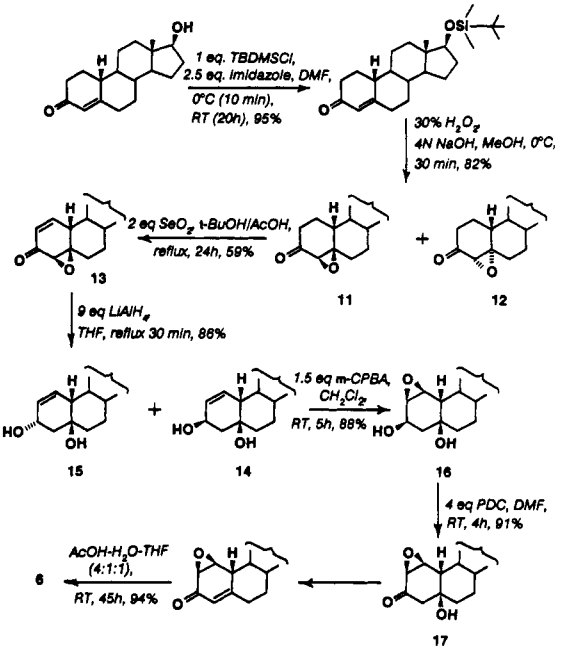
1 $R_1 = R_2 = H$ **2** **3**
4 R_1 = -OH, R_2 = H
5 $R_1 = H$, R_2 = -OH

phenolic arene oxides might also serve as carcinogenic electrophiles in analogy with the dihydrodiol epoxides derived from polycyclic aromatic hydrocarbons. During investigations designed to test this hypothesis, we developed syntheses of four epoxy enones **6–9**,[4] which are



6 1β, 2β-epoxy **8** 4β, 5β-epoxy
7 1α, 2α-epoxy **9** 4α, 5α-epoxy

Scheme I. First Synthesis of Epoxy Enone 6

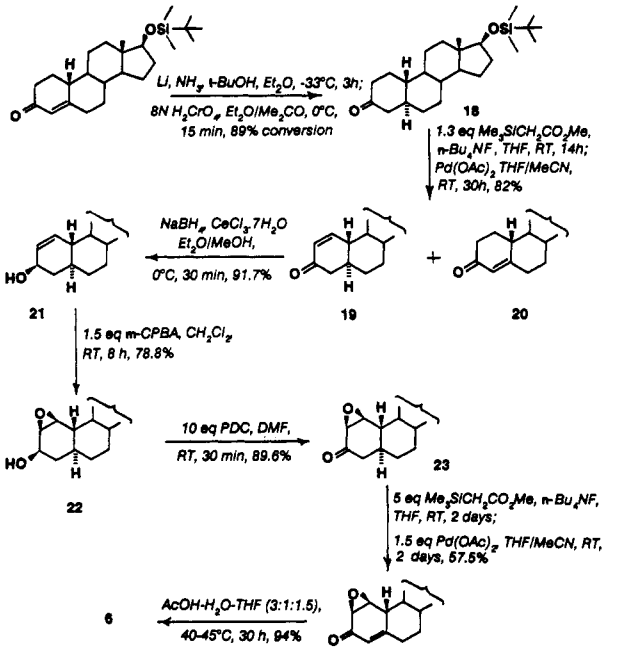


stereoisomeric tautomers of dienol epoxides **2** and **3**. Recently, our attention has focused on epoxy enones **6** and **7**, because **6** was found to accumulate in estradiol-metabolizing MCF-7 cell cultures under conditions where epoxide hydrolysis is inhibited.[4] In this paper we report improved new syntheses of **6** and **7**. The ease with which such epoxy enones can be aromatized to catechols makes these routes also the pathways of choice for synthesis of estrogen-free catechol estrogens **4** and **5**.

(1) Bergkvist, L.; Adami, H. O.; Persson, I.; Hoover, R.; Schairer, C. *N. Engl. J. Med.* **1989**, *321*, 293 and references cited therein.
(2) Le Quesne P. W.; Soloway, A. H.; *J. Theor. Biol.* **1980**, *85*, 153.
(3) Le Quesne, P. W.; Durga, A. V.; Soloway, A. H.; Hart, R. W.; Purdy, R. H. *J. Med. Chem.* **1980**, *23*, 239.
(4) Le Quesne, P. W.; Abdel-Baky. S.; Durga, A. V.; Purdy, R. H. *Biochemistry* **1986**, *25*, 2065.

0022-3263/92/1957-2100$03.00/0

Scheme II. Second Synthesis of Epoxy Enone 6



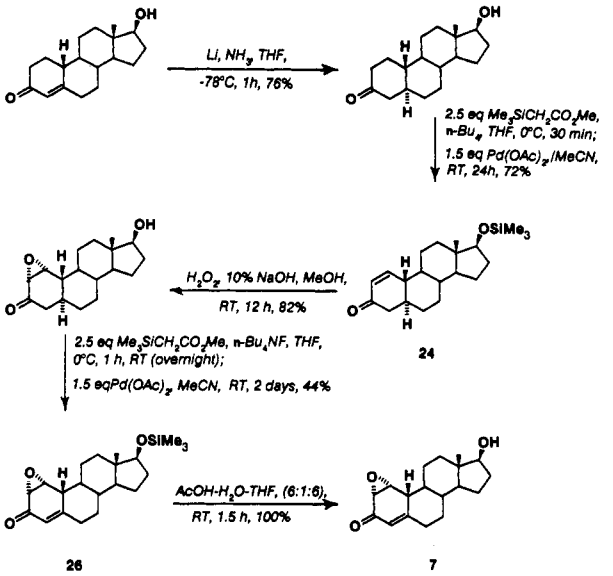
Scheme I depicts the first new synthesis of epoxy enone **6**, starting from 19-nortestosterone **10**. Epoxidation of the TBDMS ether of **10** with alkaline hydrogen peroxide gave almost entirely the 4β,5β-epoxide **11** accompanied by traces of the 4α,5α-isomer **12**. Dehydrogenation of **11** with very pure selenium dioxide included workup via Watanabe's cyanide procedure to give the 4β,5β-epoxy 1-en-3-one **13**.[5] (Aromatization of **13** under acidic or basic conditions gives the 3,4-catechol estrogen **5**).[6] Lithium aluminum hydride reduction of **13** gave enediols **14** and **15**. Each of these could be oxidized to the labile 17β-((*tert*-butyldimethylsilyl)oxy)-5β-hydroxyestr-1-en-3-one (see the Experimental Section). The predominant **14** was epoxidized with *m*-chloroperbenzoic acid to the 1β,2β-epoxy 3β,5β-diol **16**, which in turn was oxidized with pyridinium dichromate to the labile β-hydroxy ketone **17**. Dehydration and silyl ether cleavage gave the desired enone **6** in 29% yield from 19-nortestosterone.

In another approach to epoxy enone **6** (Scheme II), 19-nortestosterone *tert*-butyldimethylsilyl ether was subjected to Birch reduction and Jones oxidation to give the 5α-3-ketone **18**, which on treatment with methyl(trimethylsilyl)acetate–palladium(II) acetate gave mostly the 1-en-3-one **19**, accompanied by a little 4-en-3-one **20**. Compound **19** was reduced with sodium borohydride–cerium(III) chloride to the allylic alcohol **21**, which with *m*-chloroperbenzoic acid gave the 1β,2β-epoxy 3β-ol **22**. Oxidation of **22** with pyridinium dichromate gave epoxy ketone **23**, which by means of a second Kuwajima–Saegusa dehydrogenation followed by desilylation gave the desired epoxy enone **6** in 22% yield from 19-nortestosterone.

Each of these approaches gives the pure epoxy enone **6** conveniently and in good yield. We believe that the second synthesis may be capable of further refinement and might eventually surpass the first in efficiency. The isomeric epoxy enone **7** was prepared according to Scheme III, using analogous chemistry to that in Schemes I and II. The yield of the desired epoxy enone was 20% from 19-nortestosterone **10**.

(5) Watenabe, T.; *Pharm. Bull.* **1957**, *5*, 426.
(6) Abdel-Baky, S. Ph.D. Thesis, Northeastern University, Boston, MA, 1983.

Scheme III. Synthesis of Epoxy Enone 7



These syntheses taken together with earlier work[4] render the isomeric epoxy enones **6**–**9** conveniently available for biochemical study. We plan to report our results in this area in the near future.

Experimental Section

Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Reaction flasks were oven-dried or flame-dried, assembled hot, and cooled under a stream of dry nitrogen. All reactions were carried out under a dry nitrogen atmosphere and monitored by analytical thin-layer chromatography. Solvents were removed under aspirator pressure on a rotary evaporator at 30–40 °C. Reported yields are the yields of isolated products. Solvents were dried according to standard procedures and stored over 4-A molecular sieves unless used for extraction. THF and ether were distilled from the sodium ketyl of benzophenone. All thin-layer chromatography (TLC) plates were oven-activated for a minimum of 1 h at 120 °C prior to use. Flash column chromatography was performed according to the procedure of Still[7] (J. T. Baker, silica gel, 40 μm) and monitored by TLC. High-performance liquid chromatography (HPLC) was performed on Ultrasil columns (silica gel, 10 μm, 250 × 4.6 mm and 250 × 10 mm; ODS-18, 10 μm, 250 × 4.6 mm and 250 × 10 mm).

Proton NMR spectra were, unless otherwise specified, obtained in deuterated chloroform at 300 MHz. Carbon nuclear magnetic resonance (^{13}C NMR) shifts were referenced against the deuterated solvents.

Preparation of 17β-Hydroxy-1β,2β-epoxyestr-4-en-3-one (6). First Approach (Scheme I): (a) 17β-((*tert*-Butyldimethylsilyl)oxy)-4β,5β-epoxyestran-3-one (11). A mixture of 19-nortestosterone (1.1 g, 4 mmol), *tert*-butyldimethylsilyl chloride (0.75 g, 5 mmol), and imidazole (0.68 g, 10 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was magnetically stirred at ambient temperature for 7 h. The reaction mixture was diluted with ether (80 mL) and washed with 5% aqueous hydrochloric acid solution (3 × 30 mL), 5% aqueous sodium bicarbonate solution (3 × 30 mL), and water (30 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness to give a white solid which was purified by flash column chromatography (gradient elution, ethyl acetate in hexane, 10–20% v/v) to give 17β-((*tert*-butyldimethylsilyl)oxy)estr-4-en-3-one (1.476 g, 94.7%). Recrystallization from methanol afforded colorless crystals with mp 137–138 °C: $[\alpha]^{20}_D$ +40.8° (*c* 1.86 in 10% $CHCl_3$/MeOH); MS no M^+, *m*/*z* 331 ($M^+ - t$-Bu).

To an ice-cooled solution of 17β-((*tert*-butyldimethylsilyl)oxy)estr-4-en-3-one (1.4 g, 3.6 mmol) and 6 N aqueous sodium

(7) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

hydroxide solution (0.3 mL) in methanol (150 mL) was added dropwise a 30% aqueous hydrogen peroxide solution (1 mL). The reaction mixture was stirred in an ice bath for 8 h. The solvent was then evaporated to one-fourth of its original volume under reduced pressure. The resulting slurry was poured into cold water to give a white solid which was isolated by suction filtration, washed with several portions of cold water and dried under vacuum. The solid was then subjected to flash column chromatography (10% ethyl acetate in hexane) to give 17β-((*tert*-butyldimethylsilyl)oxy)-4β,5β-epoxyestran-3-one (**11**) (1.19 g, 81.6%; R_f = 0.66 on analytical TLC, hexane–ethyl acetate, 4:1) as colorless crystals from methanol and 17β-((*tert*-butyldimethylsilyl)oxy)-4α,5α-epoxyestran-3-one (**12**) (23.8 mg, 1.6%; R_f +0.59) as colorless needles from methanol. Compound **11**: mp 139–139.5 °C; $[\alpha]^{20}_D$ +63.6° (*c* 1.18 in 10% $CHCl_3$/MeOH); ^1H NMR δ 3.56 (t, 1 H, H-17), 3.04 (s, 1 H, H-4), 0.90 (s, 9 H, Si-*t*-Bu), 0.74 (s, 3 H, H-18); ^{13}C NMR 68.0, 62.0 (epoxide carbons); MS M^+ 404. Compound **12**: mp 137 °C; ^1H NMR ($CDCl_3$) δ 3.56 (t, 1 H, H-17), 2.99 (s, 1 H, H-4), 2.41–2.51 (b dd, 1 H, H-2), 0.86 (s, 9 H, Me_3C), 0.73 (s, 3 H, H-18); ^{13}C NMR ($CDCl_3$) δ 74.0, 61.8 (epoxide carbons); MS (FAB) 405 (M^+ + 1).

(b) 17β-((*tert*-Butyldimethylsilyl)oxy)-4β,5β-epoxyestr-1-en-3-one (13). A solution of 17β-((*tert*-butyldimethylsilyl)-oxy)-4β,5β-epoxyestran-3-one (**11**) (1 g, 2.47 mmol), freshly sublimed selenium dioxide (Aldrich Gold Label) (0.66 g, 5.95 mmol), and glacial acetic acid (2 mL) in *tert*-butyl alcohol (100 mL) was refluxed with stirring for 30 h. The hot mixture was filtered with the aid of Celite, and the residue was washed with several portions of hot ethyl acetate. The filtrate and washings were combined and taken to dryness. The resulting residue was dissolved in ethyl acetate, and the solution was washed with 10% aqueous sodium bicarbonate (3 × 20 mL), water (20 mL), 5% aqueous potassium cyanide solution (20 mL), water (2 × 20 mL), and saturated brine solution (20 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and evaporated under reduced pressure to afford a brown oil, which on flash column chromatography (10% ethyl acetate in hexane) gave 17β-((*tert*-butyldimethylsilyl)-oxy)-4β,5β-epoxyestr-1-en-3-one (**13**) (587 mg, 59%) as colorless crystals from methanol: mp 173–3.5 °C; $[\alpha]^{20}_D$ +299.3° (*c* 1.52 in 10% $CHCl_3$/MeOH); ^1H NMR δ 6.78 (dd, *J* = 4, 4 Hz, H1), 5.96 (d, *J* = 4 Hz, H2), 3.55 (t, 1 H, H17), 3.25 (s, 1 H, H4), 2.64 (1 H, m, H10), 0.90 (s, 9 H, $SiCMe_3$), 0.78 (s, 3 H, 18-Me), 0.02 (s, 6 H, $SiMe_2$). Anal. Calcd for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51; Si, 6.98. Found: C, 71.57; H, 9.46; Si, 6.91.

(c) 17β-((*tert*-Butyldimethylsilyl)oxy)estr-1-ene-3β,5β-diol (14). A solution of 17β-((*tert*-butyldimethylsilyl)oxy)-4β,5β-epoxyestr-1-en-3-one (**13**) (500 mg, 1.24 mmol) in tetrahydrofuran (8 mL) was added dropwise during 30 min to a stirred solution of lithium aluminum hydride (95 mg, 2.5 mmol) in tetrahydrofuran (15 mL) at room temperature. Upon completion of the addition of the hydride, the mixture was refluxed for 1 h and then cooled to room temperature. Ethyl acetate (2 mL) was added followed by water (0.5 mL). The mixture was stirred for 5 min, and then anhydrous magnesium sulfate (500 mg) was added. After stirring for 30 min, the mixture was filtered and the solid was washed with several portions of ether. The filtrate and washings were combined and taken to dryness. The resulting residue was chromatographed (gradient elution, ethyl acetate in hexane, 30–50%) to give first 17β-((*tert*-butyldimethylsilyl)oxy)estr-1-ene-3β,5β-diol (**14**) (434 mg, 85.9%; R_f = 0.32 on analytical TLC, hexane/ethyl acetate, 1:1) as colorless crystals from hexane: mp 155–155.5 °C; $[\alpha]^{20}_D$ +162.2° (*c* 1.48 in 10% $CHCl_3$/MeOH); ^1H NMR δ 5.92 (m, 2 H, H1 and H2), 4.13 (br s, 1 H, H3), 3.50 (t, 1 H, H17), 2.17 (m, 2 H, H4), 0.88 (t, 9 H, Si-*t*-Bu), 0.70 (s, 3 H, 18-Me), 0.01 (s, 6 H, $SiMe_2$). Anal. Calcd for $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41. Found: C, 71.08; H, 10.41.

Subsequently there was eluted 17β-((*tert*-butyldimethylsilyl)oxy)estr-1-ene-3α,5β-diol (**15**) (44 mg, 9%); R_f = 0.08) as colorless needles from hexane: mp 158–9 °C; ^1H NMR ($CDCl_3$) δ 5.87 (ddd, 1 H, H-1, $J_{1,2}$ = 10.2, $J_{1,3}$ = 1.6 Hz), 5.73 (dd, 1 H, H2, $J_{2,1}$ = 10.2, $J_{2,3}$ = 2.2 Hz), 4.49–4.54 (bt, 1 H, H3), 3.51 (dd, 1 H, H17), 0.85 (s, 9 H, Me_3C), 0.73 (s, 3 H, C18).

(d) 17β-((*tert*-Butyldimethylsilyl)oxy)-5β-hydroxyestr-1-en-3-one. To an ice-cooled solution of **14** or **15** (40 mg, 0.1 mmol) in acetone (1 mL) was added dropwise a cold solution of Jones reagent (0.3 mL). The reaction mixture was stirred for 2 min. Excess oxidant was destroyed by addition of 2-propanol until the solution became dark green. The mixture was then partitioned between ether (5 mL) and water (5 mL). The aqueous phase was separated and extracted with ether (3 × 3 mL). The combined ethereal layers were washed with 10% sodium carbonate solution (2 × 2 mL), water (2 × 2 mL), and saturated brine solution (2 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent afforded a crude product which was purified by preparative TLC (hexane/ethyl acetate, 1:1) to give the labile 17β-((*tert*-butyldimethylsilyl)oxy)-5β-hydroxyestr-1-en-3-one (27 mg, 67.8%) as colorless crystals: mp 195–195.5 °C; IR (KBr) 3400, 3015, 2950, 2910, 2850, 1670, 1610, 1470, 1390, 1250, 1130, 1090, 1050, 1020, 900, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (dd, 1 H, H-1, $J_{1,2}$ = 10.2, $J_{1,10}$ = 5.7 Hz), 6.03 (d, 1 H, H-2, $J_{2,1}$ = 10.2 Hz), 3.52 (t, 1 H, H-17), 2.80 (d, 1 H, Hβ-4, *J* = 17.1 Hz, 2.43 (b s, 1 H, OH), 2.22 (d, 1 H, Hα-4, *J* = 17.1 Hz), 2.14 (dd, 1 H, H-10, $J_{10,1}$ = 5.7, $J_{10,9}$ = 11 Hz), 0.85 (s, 9 H, Me_3C), 0.73 (s, 3 H, H18); MS 347 [$M^+ - Me_3C$], 329 [$M^+ - Me_3C - H_2O$].

(e) 17β-((*tert*-Butyldimethylsilyl)oxy)-1β,2β-epoxyestrane-3β,5β-diol (16). To a stirred solution of *m*-chloroperbenzoic acid (260 mg, 1.5 mmol) in methylene chloride (5 mL) was added a solution of 17β-((*tert*-butyldimethylsilyl)oxy)estr-1-ene-3β,5β-diol (**14**) (406 mg, 1 mmol) in methylene chloride (6 mL) over 1 h while a temperature of 10–15 °C was maintained. The reaction mixture was stirred for 8 h. Excess peracid was destroyed by addition of 10% aqueous sodium sulfite solution until a test with starch–iodide paper was negative. The organic layer was separated and washed with 10% aqueous sodium bicarbonate solution (3 × 10 mL), and saturated brine solution (10 mL), dried over anhydrous magnesium sulfate, and filtered. Removal of solvent gave a crude product which was purified by flash column chromatography (gradient elution, ethyl acetate in hexane, 5–10%) to yield 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestrane-3β,5β-diol (**16**) (382 mg, 87.6%) as colorless needles from acetone/*n*-pentane: mp 173.5–174 °C; $[\alpha]^{20}_D$ +88° (*c* 1.0 in MeOH); ^1H NMR δ 4.32 (m, 1 H, H2), 3.69 (m, 1 H, H3), 3.48–3.58 (m, 3 H, H17, 1,3-OH), 0.89 (s, 9 H, Si-*t*-Bu), 0.76 (s, 3 H, 18-Me), 0.01 (s, 6 H, $SiMe_2$). Anal. Calcd for $C_{24}H_{42}O_4Si$·0.25H_2O: C, 67.50; H, 10.01. Found: C, 67.48; H, 10.19.

(f) 17β-Hydroxy-1β,2β-epoxyestr-4-en-3-one (6). To a solution of 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestrane-3β,5β-diol (**16**) (350 mg, 0.83 mmol) in *N*,*N*-dimethylformamide (7 mL) was added at once a solution of pyridinium dichromate (3.115 g, 8.28 mmol) in *N*,*N*-dimethylformamide (7 mL). After stirring at ambient temperature for 4 h, the reaction mixture was diluted with water (60 mL) and extracted with ether (3 × 25 mL). The ethereal layers were combined, washed with water (2 × 10 mL) and saturated brine solution (15 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent to dryness gave a white solid (341 mg). This crude product was dissolved in methylene chloride (25 mL), followed by the addition of neutral aluminum oxide (Woelm, 500 mg) and anhydrous magnesium sulfate (300 mg). The mixture was stirred for 1 h at ambient temperature. After filtration, the solid was washed with several portions of methylene chloride. The combined organic layers were evaporated to dryness to yield a crude product which was crystallized from ethyl acetate/*n*-pentane to give 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestr-4-en-3-one (301 mg, 90.5%) as colorless needles from ethyl acetate/*n*-pentane, mp 103.5–4 °C. This compound (300 mg, 0.74 mmol) in 35 mL of an acetic acid–water–tetrahydrofuran mixture (3:1:1.5) was stirred at 40–45 °C for 30 h. The cooled mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with 5% aqueous sodium bicarbonate solution (2 × 30 mL), water (15 mL), and saturated brine solution (15 mL), dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent gave a crude product which on flash column chromatography (gradient elution, ethyl acetate in hexane, 30–80%) afforded 17β-hydroxy-1β,2β-epoxyestr-4-en-3-one (**6**) (203 mg, 94%) as colorless crystals from dichloromethane/hexane: mp 169–169.5 °C; $[\alpha]^{20}_D$ −238.1° (*c* 1.26 in MeOH); ^1H NMR δ 5.77 (1 H, d, $J_{4,2}$ = 1 Hz, H4), 3.80 (d, $J_{1,2}$ = 4 Hz, H1), 3.65 (1H, t, H17), 3.35 (m, 1 H, H2), 2.68 (d, 1 H, H10), 0.82 (s, 3 H, 18-Me); ^{13}C NMR δ 193.9 (C3), 164.1 (C5), 119.6 (C4), 81.4 (C17), 54.7 (C1), 53.8 (C2). Anal. Calcd for $C_{16}H_{24}O_3$: C, 74.90; H, 8.39. Found: C, 74.79; H, 8.50.

X-ray Structure Determination of Epoxy Enone 6. The steroid epoxide ($C_{18}H_{24}O_3$) crystallized in the noncentrosymmetric, monoclinic space group $P2_1$. The unit cell dimensions, a = 6.837 (1), b = 11.891 (2), and c = 10.070 (2) Å, β = 107.8 (1)°, were determined by least-squares fitting using 15 independent reflections, well-separated in reciprocal space. The cell volume of 779.5 (2) Å^3 contained two asymmetric units yielding a calculated density of 1.23 cm^{-3}. A total of 1323 reflections were recorded in the range $4.0° \leq 2\theta \leq 130°$ with a $P2_1$ automated diffractometer using the $\theta/2\theta$ scanning technique. A total of 1154 unique reflection with $F_o \geq 2.5\sigma(F_o)$ were corrected for Lorentz and polarization factors. The structure was solved by the SHELXTL 4.1 programs. All non-hydrogen atoms were refined anisotropically. All hydrogen atom locations were determined by Fourier difference syntheses. The refinement converged at R = 0.069 over 202 independent parameters. Crystallographic data are tabulated in the supplementary material.

Second Approach (Scheme II). (a) 17β-((*tert*-Butyldimethylsilyl)oxy)estran-3-one. A solution of 17β-((*tert*-butyldimethylsilyl)oxy)estr-4-en-3-one (2 g, 5.15 mmol) and *tert*-butyl alcohol (0.4 mL) in ether (30 mL) was added dropwise to a cold (−78 °C) solution of lithium (0.25 g) in freshly distilled liquid ammonia (200 mL). The reaction mixture was refluxed (−33 °C) with stirring for 3 h. The blue color of the mixture was discharged by the addition of ammonium chloride (0.4 g), and the ammonia was evaporated overnight using a stream of nitrogen. The residual white solid was partitioned between water (75 mL) and ether (75 mL). The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were washed with water (25 mL) and saturated brine solution (25 mL), dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent gave a dark brown oil which was dissolved in a mixture of ether (20 mL) and acetone (10 mL). To this ice-cooled solution was slowly added 8 N aqueous chromic acid solution (2 mL). After the resulting mixture had been stirred at 0 °C for 15 min, isopropyl alcohol was added to destroy the excess oxidant. The mixture was then partitioned between water (30 mL) and ether (30 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the combined ethereal layers were washed with 10% aqueous sodium bicarbonate solution (2 × 25 mL) and saturated brine solution (30 mL), dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent to dryness afforded a brown residue which on flash column chromatography (gradient elution, ethyl acetate in hexane, 5–30%) gave 17β-((*tert*-butyldimethylsilyl)oxy)estran-3-one (**18**) (1.23 g, 89.6%) as colorless needles from methanol: mp 102.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.56 (dd, 1 H, H-17), 0.88 (s, 9 H, Me_3C), 0.73 (s, 3 H, H-18); ^{13}C NMR ($CDCl_3$) δ 211.5, 81.8, 49.6, 45.8, 43.7, 43.4, 41.3, 41.1, 37.0, 33.9, 30.9, 30.6, 30.3, 25.8, 23.4, 18.0, 11.3; MS 333 [M^+ − 57].

(b) 17β-((*tert*-Butyldimethylsilyl)oxy)estr-1-enone (19). To an ice-cooled solution of 17β-((*tert*-butyldimethylsilyl)oxy)-estran-3-one (1.2 g, 3.07 mmol) in tetrahydrofuran (7 mL) was added methyl (trimethylsilyl)acetate (0.65 mL, 3.96 mmol) followed by a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (15 μL). After stirring at ambient temperature overnight, the reaction mixture was taken up in hexane (60 mL), washed with 5% aqueous sodium bicarbonate solution (3 × 10 mL) and saturated brine solution (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated.

To the solution of the colorless silyl enol ether in tetrahydrofuran (15 mL) was added acetonitrile (25 mL) followed by palladium(II) acetate (0.83 g, 3.70 mmol). The reaction mixture was stirred for 30 h and then evaporated to dryness. The resulting dark brown residue was dissolved in a solution of 10% ethyl acetate in hexane (100 mL), and this mixture was filtered through a silica gel bed. The reaction flask and the filter cake were washed with several portions of the ethyl acetate/hexane solution. The filtrate and washings were combined and evaporated to dryness to give a crude product which on flash column chromatography (gradient elution, ethyl acetate in hexane, 5–30%) afforded 17β-((*tert*-butyldimethylsilyl)oxy)estr-1-en-3-one (**19**) (0.98 g, 82%; R_f = 0.55 on analytical TLC, hexane–ethyl acetate, 5:1) as colorless crystals from methanol (mp 82–83 °C) and 17β-((*tert*-butyldimethylsilyl)oxy)estr-4-en-3-one (**20**) (60 mg, 5%; R_f = 0.41).

(c) 17β-((*tert*-Butyldimethylsilyl)oxy)estr-1-en-3β-ol (21). An ice-cooled mixture of 17β-(*tert*-butyldimethylsiloxy)estr-1-en-3-one (**19**) (0.5 g, 1.28 mmol) in ether (4 mL) and cerium trichloride heptahydrate (575 mg, 1.54 mmol) in methanol (10 mL) was stirred for 15 min. To this solution was carefully added small portions of sodium borohydride (97 mg, 2.57 mmol). After stirring at 0 °C for 30 min, the reaction mixture was poured into 5% aqueous sodium hydroxide solution (20 mL). After 15 min of stirring, the mixture was filtered with the aid of Celite and the filter cake was washed with ether (3 × 25 mL). The filtrate and washings were combined. The aqueous phase was separated and extracted with ether (3 × 25 mL). The combined organic layers were washed with water (20 mL) and saturated brine solution (20 mL), dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent to dryness afforded a crude product which was crystallized from methanol to give pure 17β-((*tert*-butyldimethylsilyl)oxy)estr-1-en-3β-ol (**21**) (456 mg, 90.7%) as colorless needles: mp 138–9 °C; ^{1}H NMR δ 5.90 (m, 1 H, H1), 5.62 (m, 1 H, H2), 4.32 (br s, 1 H, H3); ^{13}C NMR δ 131.1 (C1), 130.9 (C2), 81.8 (C17), 68.4 (C3).

(d) 17β-((*tert*-Butyldimethylsilyl)oxy)-1β,2β-epoxyestran-3β-ol (22). To a stirred ice-cooled solution of 17β-((*tert*-butyldimethylsilyl)oxy)estr-1-en-3β-ol (**21**) (376 mg, 0.96 mmol) in methylene chloride (10 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (249 mg, 1.5 mmol) in methylene chloride (8 mL) over 30 min. The reaction mixture was stirred for 8 h. Excess peracid was destroyed by addition of 10% aqueous sodium sulfite solution until a test with starch–iodide paper was negative. The organic layer was separated and washed with 10% aqueous sodium bicarbonate solution (2 × 20 mL) and saturaed brine solution (20 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent afforded a crude product which was purified by flash column chromatography (gradient elution, ethyl acetate in hexane, 20–50%) to give 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestran-3β-ol (**22**) (305 mg, 78.%) as a white powder from acetone/water: mp 147–148 °C; ^{1}H NMR δ 4.0 (m, 2 H, H1,2), 3.55 (m, 2 H, 3-OH, H17), 3.22 (dd, 1 H, H3).

(e) 17β-((*tert*-Butyldimethylsilyl)oxy)-1β,2β-epoxyestran-3-one (23). To a stirred ice-cooled solution of 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestran-3β-ol (**22**) (160 mg, 0.39 mmol) in *N*,*N*-dimethylformamide (3 mL) was added at once a solution of pyridinium dichromate (1.48 g, 3.9 mmol) in *N*,*N*-dimethylformamide (3 mL). After 30 min, the ice bath was removed and the reaction mixture was stirred at room temperature for 2 h, diluted with cold water (70 mL), and extracted with ether (5 × 25 mL). The ethereal layers were combined, washed with water (2 × 25 mL) and saturated brine solution (20 mL), dried over anhydrous magnesium sulfate, and filtered with the aid of Celite. Removal of the solvent to dryness afforded a crude product which was purified by preparative TLC (hexane/ethyl acetate, 5:1) to give pure 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestran-3-one (**23**) (414 mg, 88.6%) as a white powder from ethanol: mp 110.5–111 °C; ^{1}H NMR δ 3.58 (dd, 1 H, H17), 3.55 (d, 1 H, H2), 3.32 (d, 1 H, H1), 0.70 (s, 3 H, 18-Me); ^{13}C NMR δ 207 (C3), 81.6 (C17), 60.9 (C1), 54.9 (C2).

(f) 17β-((*tert*-Butyldimethylsilyl)oxy)-1β,2β-epoxyestr-4-en-3-one. To a stirred solution of 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestran-3-one (**23**) (80 mg, 0.2 mmol) in tetrahydrofuran (1.8 mL) was added methyl (trimethylsilyl)acetate (170 μL, 1 mmol) followed by a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (15 μL). After stirring at ambient temperature for 2 days, the reaction mixture was taken up in hexane (20 mL), washed with 10% aqueous sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated.

To the mixture of the resulting colorless silyl enol ether in tetrahydrofuran (1 mL) and acetonitrile (6 mL) was added palladium(II) acetate (67 mg, 0.3 mmol). The reaction mixture was stirred for 2 days and evaporated to dryness. The residue was subjected to flash column chromatography (25% ethyl acetate in hexane) to give 17β-((*tert*-butyldimethylsilyl)oxy)-1β,2β-epoxyestr-4-en-3-one (45 mg, 56.5%).

Preparation of 17β-Hydroxy-1α,2α-epoxyestr-4-en-3-one (7) (Scheme III). (a) 17β-((Trimethylsilyl)oxy)estr-en-3-one (24). To a cold (−78 °C) solution of lithium wire (0.8 g) dissolved in freshly distilled liquid ammonia (150 mL) was added dropwise a solution of 19-nortestosterone (2 g, 7.28 mmol) in tetrahydro-

furan (40 mL). The reaction mixture was stirred for 1 h. The blue color of the mixture was discharged by the careful addition of ammonium chloride (7 g), and the ammonia was evaporated overnight using a stream of nitrogen. The resulting residue was partitioned between water (60 mL) and ethyl acetate (60 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with water (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The oily crude product was purified by flash column chromatography (gradient elution, ethyl acetate in hexane, 40–60%) to give 17β-hydroxyestran-3-one (1.54 g, 76.4%) as colorless crystals from acetone/hexane, mp 131.5–132 °C.

To an ice-cooled stirred solution of 17β-hydroxyestran-3-one (1.5 g, 5.42 mmol) and methyl(trimethylsilyl)acetate (2.2 mL, 13.50 mmol) in tetrahydrofuran (15 mL) was added a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (80 μL). After 30 min, the ice bath was removed, and the reaction mixture was stirred at ambient temperature for 5 h, taken up in hexane (80 mL), washed with 10% aqueous sodium bicarbonate solution (2 × 20 mL) and saturated brine solution (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated.

The resulting colorless residue was dissolved in acetonitrile (120 mL), and palladium(II) acetate (1.82 g, 8.1 mmol) added. The mixture was stirred at ambient temperature for 24 h and then evaporated to dryness. The resulting residue was dissolved in a mixture of 5% ethyl acetate in hexane (150 mL), and this solution was filtered through a silica gel bed. The clear filtrate was evaporated to dryness to give a colorless oil, which on flash column chromatography (gradient elution, ethyl acetate in hexane, 3–20%) gave 17β-((trimethylsilyl)oxy)estr-1-en-3-one (**24**) (1.36 g, 72.3%; R_f = 0.20 on analytical TLC, hexane–ethyl acetate, 15:1) as colorless needles from methanol/water: mp 96–7 °C; IR (KBr) 3040, 2940, 2860, 1680, 1610, 1440, 1390, 1250, 1140, 1100, 1080, 920, 900, 890, 840, 770; ^{1}H NMR ($CDCl_3$) δ 7.1 (b d, 1 H, H-1, $J_{1,2}$ = 10.2 Hz), 5.97 (ddd, 1 H, H2, $J_{2,1}$ = 10.2, $J_{2,4\alpha}$ = 1.2, J = 2.8 Hz), 3.55–3.60 (dd, 1 H, H-17, J = 7.8 and 8.8 Hz), 2.11–2.20 (dd, 1 H, H-10, J = 16.2 and 13.1 Hz), 0.76 (s, 3 H, H-18), 0.08 (s, 9 H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 199.9, 152.0, 129.4, 81.4, 49.5, 46.7, 45.8, 45.6, 43.2, 41.8, 41.6, 36.6, 32.4, 30.7, 29.7, 25.2, 23.1, 11.3, 0.1; MS: 346 [M^+], 331 [M^+ – Me]. There was also obtained 17β-((trimethylsilyl)oxy)estr-4-en-3-one (0.125 g, 6.6%; R_f = 0.12) as a colorless powder from methanol: mp 105–6 °C; IR (KBr) 3020, 2940, 2840, 1670, 1610, 1260, 1250, 1210, 1140, 1090, 1080, 920, 900, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.83 (b s, 1 H, H-4), 3.53–3.59 (dd, 1 H, H-17, J = 7.8 and 8.8 Hz), 0.77 (s, 3 H, H-18), 0.08 (s, 9 H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 200.1, 167.0, 124.5, 81.5, 49.7, 49.4, 43.1, 42.6, 40.5, 36.7, 36.5, 35.5, 30.7, 26.6, 26.2, 23.3, 11.3, 0.2; MS 346 [M^+], 331 [M^+ – Me], 256 [M^+ – Me_3SiOH].

(b) 17β-((Trimethylsilyl)oxy)-1α,2α-epoxyestr-4-en-3-one (26). To an ice-cooled mixture of 17β-((trimethylsilyl)oxy)estr-1-en-3-one (**24**) (1.2 g, 3.46 mmol) and 10% aqueous sodium hydroxide solution (0.3 mL) in methanol (60 mL) was added dropwise a 30% hydrogen peroxide solution (0.9 mL). After stirring for 12 h the reaction mixture was evaporated to one-fourth of its original volume. The resulting slurry was poured into cold water (100 mL) and extracted with ether (3 × 30 mL). The ethereal layers were combined, washed with water (2 × 25 mL) and saturated brine solution (20 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent afforded a crude product which was crystallized from ethyl acetate/*n*-hexane to give 17β-hydroxy-1α,2α-epoxyestran-3-one (**25**) (0.82 g, 82%) as colorless crystals, mp 131–2 °C.

To an ice-cold solution of 17β-hydroxy-1α,2α-epoxyestran-3-one (**25**) (0.8 g, 2.75 mmol) and methyl (trimethylsilyl)acetate (1.1 mL, 6.88 mmol) in tetrahydrofuran (5 mL) was added a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (41 μL). After 1 h, the ice bath was removed and the reaction mixture was stirred at ambient temperature overnight, taken up in hexane (80 mL), washed with 10% aqueous sodium bicarbonate solution (2 × 20 mL), water (20 mL), and saturated brine solution (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting epoxy silyl enol ether was dissolved in acetonitrile (60 mL), and palladium(II) acetate (0.93 g, 4.14 mmol) was added. The dark brown reaction mixture was stirred at ambient temperature for 2 days and then evaporated to dryness. The residue was dissolved in a mixture of 10% ethyl acetate in hexane, and this solution was filtered through a silica gel bed. Removal of the solvent gave a crude solid, which on flash column chromatography (gradient elution, ethyl acetate in hexane, 10–30%) yielded 17β-((trimethylsilyl)oxy)-1α,2α-epoxyestr-4-en-3-one (290 mg, 29%; R_f = 0.48 on analytical TLC, hexane–ethyl acetate, 6:1): IR (KBr) 2920, 2860, 1720, 1300, 1140, 1120, 1090, 920, 880, 840, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.66 (d, 1 H, H-1, $J_{1,2}$ = 4 Hz), 3.56–3.61 (dd, 1 H, H-17, J = 7.9 and 8.6 Hz), 3.22 (d, 1 H, H-2, $J_{2,1}$ = 4 Hz), 0.77 (s, 3 H, H-18), 0.08 (s, 9 H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 2–5.1, 81.6, 55.43, 55.38, 49.5, 45.0, 44.0, 43.9, 43.1, 41.7, 36.6, 32.6, 30.5, 29.9, 30.5, 29.9, 25.6, 23.3, 11.3, 0.2; MS 362 [M^+], 347 [M^+ – Me].

17β-((Trimethylsilyl)oxy)-1α,2α-epoxyestr-4-en-3-one (**26**) (0.435 g, 44%; R_f = 0.27) was also obtained as colorless needles from hexane: mp 208 °C; IR (KBr) 3010, 2940, 2920, 2860, 1670, 1620, 1450, 1380, 1280, 1280, 1250, 1140, 1100, 910, 900, 880, 840, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.74–5.76 (b d, 1 H, H-4, $J_{4,2}$ = 1.9 Hz), 3.70–3.75 (dd, 1 H, H-1, $J_{1,2}$ = 3.9, $J_{1,10}$ = 3.4 Hz), 3.56–3.61 (dd, 1 H, H-17, J = 7.8 and 8.8 Hz), 3.39 (dd, 1 H, H-2, $J_{2,1}$ = 3.9, $J_{2,4}$ = 1.9 Hz); MS FAB 361 [M^+ + 1].

(e) 17β-Hydroxy-1α,2α-epoxyestr-4-en-3-one (7). A solution of 17β-((trimethylsilyl)oxy)-1α,2α-epoxyestr-4-en-3-one (**26**) (100 mg, 0.27 mmol) in 13 mL of an acetic acid/water/tetrahydrofuran mixture (6:1:6) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic layers were washed with 10% aqueous sodium carbonate (2 × 15 mL) and saturated brine solution (15 mL), dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent afforded a crude product which on flash column chromatography (gradient elution, ethyl acetate in hexane, 30–70%) gave 17β-hydroxy-1α,2α-epoxyestr-4-en-3-one) (**7**) (80 mg, 100%) as colorless needles from methanol, mp. 128–9 °C (lit.[4] mp 123–4 °C).

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Supplementary Material Available: Selected NMR spectra and X-ray data for **11**, **12**, **17**, **18**, **21–24**, and **26** (22 pages). Ordering information is given on any current masthead page.