angle between Br and the carbonyl oxygenation is large.[30] However, this is not useful in making the epimeric assignment since both endo and exo arrangements provide for a large dihedral angle.

Ethoxycarbonyl Isothiocyanate. The following procedure was more convenient than that described in the literature.[31] Ethyl chloroformate (10.9 g, 0.100 mmol) was slowly added to a vigorously stirred suspension of potassium thiocyanate (9.70 g, 0.100 mmol) in reagent grade acetonitrile (45 mL) held at 70–75 °C, after which the thick yellow mixture was stirred at 70–75 °C for 15–20 min and then at 25 °C for 10 min. With the temperature at 0 °C, 20 mL of acetonitrile was added just before filtration. The solids were rinsed on the funnel, the combined filtrates were evaporated, and the crude yellow product was distilled through a short Vigreaux column. Colorless ethoxycarbonyl isothiocyanate (9.5 g, 73%) was obtained: bp 50–52 °C (10–12 mm); IR (CCl_4) 1980, 1760 cm^{-1}.[27] The liquid was sealed in amber ampules under argon and was kept no longer than 4 days at −5 °C before use.

***N*-(Ethoxycarbonyl)thiocarbamyl Derivative 22e.** Lithio derivative **22a** was prepared essentially as described before for the synthesis of exo ester **22c** by using 214 mg of lactone **19** (1.00 mmol) in 3 mL of tetrahydrofuran with 2.0 mL of 0.97 M *tert*-butyllithium solution. Drops of ethoxycarbonyl isothiocyanate (0.26 mL, ca. 2.0 mmol) were injected, and the yellow solution was stirred for 10 min at −45 °C and then for 1 min at 0 °C. Acetic acid (0.13 mL, 2.0 mmol) was introduced followed by 90 mL of ether. The precipitate of lithium acetate was removed, the filtrate was concentrated, and the crude residual product was chromatographed through a 30-cm column of silica gel (30 g) with chloroform–acetone (9.5:0.5) as the developing solvent. A small amount of unchanged starting lactone **19** (11 mg, 5% recovery) emerged after the expected product. Solvent-free *N*-(ethoxycarbonyl)thiocarbamyl compound **22e** (mp 167–168 °C) was obtained as a homogeneous (TLC) solid (245 mg, 71%). A sample for analysis, prepared by crystallization from ether at −50 °C, melted at 168.5–169.5 °C.

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 48.69; H, 5.56; N, 4.06; S, 9.28. Found: C, 48.95; H, 5.66; N, 4.29; S, 9.28.

The infrared absorption spectrum (CCl_4) showed peaks at 3445, 3280, 1775, 1740 cm^{-1}. The NMR ($CDCl_3$) spectrum showed the following: δ 9.38 (br s, 1, NH), 5.40 (d, J = 0.5 Hz, 1, bridgehead H vicinal to new group), 5.02–4.05 (m, 8), 1.55–1.20 (m, 9, CH_3's).

The exo configuration was assigned provisionally on the basis of both kinetic and thermodynamic preference for this epimer.

Phenylthio Derivative 22f. Lithio enolate **22a** was obtained from 214 mg (1.00 mmol) of lactone **19** plus 2.1 mL of 0.97 M *tert*-butyllithium solution essentially according to the procedure used in the synthesis of exo ester **22c**. After diphenyl disulfide (240 mg, 1.10 mmol) in dry tetrahydrofuran (3 mL) had been injected, the resulting yellow solution was stirred at −12 °C for 15 min. Adding acetic acid (0.061 mL, 1.0 mmol) by syringe quenched the reaction. The resulting heterogeneous mixture was stirred at 0 °C for 3 min before diluting with ether and filtering. The yellow liquid left after removal of all volatiles from the filtrate was chromatographed through 30 g of silica gel 60 with 9:1 chloroform–acetone as solvent. The solvent-free phenylthio product **22f** was isolated as a white solid (280 mg, 87%), which was taken as a mixture of exo and endo forms. Sublimation at 150 °C (0.01 mm) provided a sample for analysis.

Anal. Calcd for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63. Found: C, 59.63; H, 5.71.

The product developed two spots on a TLC plate, R_f 0.50 and 0.59 (9:1 chloroform–acetone). The spectral data are as follows: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.65–7.15 (m, 5, aromatic H's), 5.07–4.10 (m, 7), 1.52 and 1.45 (2 s, 3, *endo*-*gem*-CH_3), 1.32 (s, 3, *exo*-*gem*-CH_3 in both epimers).

The two singlets at 1.52 and 1.45 ppm were consistent with the presence of *exo*- and *endo*-phenylthio epimers of derivative **22f**. Very little change was noted in the nuclear magnetic resonance curve after the product had been shaken vigorously for 5 min with 10% carbonate or after refluxing the product in pyridine for 24 h. However, the phenylthio derivative **22f** did form a lithio derivative with *tert*-butyllithium.

Formation of the corresponding methylthio compound by treating lithio derivative **22a** with dimethyl disulfide failed.

Acknowledgment. We thank Dr. Somsak Ruchirawat and Donald Humphries for their valuable participation at various stages of the work. We appreciate the cooperation of Professor David A. Forsyth at Northeastern University, who determined several precise 60-MHz ^1H NMR curves for us, that of the NMR center, Institute of Polymer Science, The University of Akron, which provided the 300 MHz spectra, and that of the Mass Spectrometry Facility for Biomedical Research, Massachusetts Institute of Technology, which determined mass spectra for several of our compounds. The following very kindly accepted samples of triazole homo-C-nucleoside **21** for assay: A. B. Foster (Chester Beatty Research Institute, Royal Cancer Hospital), Jack J. Fox (Sloan-Kettering Institute for Cancer Research), Enrico Mihich (Roswell Park Memorial Institute), Edward J. Modest (Sidney Farber Cancer Institute), and John A. Montgomery (Southern Research Institute). The American Cancer Society, through Grant No. T-533, provided the financial support without which this research could not have been performed.

Registry No. **1**, 3238-40-2; **2**, 2043-98-3; **3**, 22555-42-6; **4**, 59482-77-8; **5a**, 77984-40-8; **5b**, 77984-41-9; **7**, 77984-42-0; **10**, 20137-88-6; **11**, 51145-10-9; **12**, 77984-43-1; **13**, 78038-57-0; **14**, 77984-44-2; **15**, 67773-47-1; **17**, 78038-58-1; **18**, 77984-45-3; **19**, 78038-59-2; **20**, 78038-60-5; **21**, 78038-61-6; **22a**, 77984-46-4; **22b** aldehyde (isomer 1), 77984-47-5; **22b** aldehyde isomer 2, 78038-62-7; **22b** (*E*)-hydroxymethylene, 77984-48-6; **22b** (*Z*)-hydroxymethylene, 78038-63-8; *endo*-**22c**, 77984-49-7; *exo*-**22c**, 78038-64-9; *exo*-**22d**, 77984-50-0; *exo*-**22e**, 78003-78-8; *endo*-**22f**, 77984-51-1; *exo*-**22f**, 78038-65-0; *p*-toluenesulfonyl chloride, 98-59-9; methanesulfonyl chloride, 124-63-0; thionyl chloride, 7719-09-7; *exo-cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]octane, 77984-52-2; sodium 2,3-*O*-isopropylidene-β-ribofuranosylacetate, 78038-66-1; aminoguanidine bicarbonate, 2582-30-1; ethyl chloroformate, 541-41-3; potassium thiocyanate, 333-20-0; ethoxycarbonyl isothiocyanate, 16182-04-0; diphenyl disulfide, 882-33-7.

(30) Bellamy, L. J. "The Infrared Spectra of Complex Molecules"; Wiley: New York; 1958, p 139. Bellamy, L. J. "Advances in Infrared Group Frequencies"; Methuen and Co. Ltd.: London, 1968; p 142.

(31) Lamon, R. B. *J. Heterocycl. Chem.* **1968**, *5*, 837. See also: Liotta, D.; Engel, R. *Can. J. Chem.* **1975**, *53*, 907.

Syntheses of Seleno Estrogens

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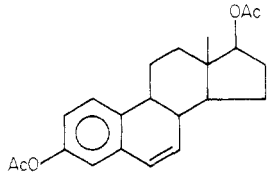
The syntheses of phenylseleno and methylseleno analogues of estradiol are described.

For studies of the noninvasive differentiation of hormone-dependent from hormone-independent mammary tumors, we required seleno analogues of estradiol. The synthesis of several such analogues is the subject of this

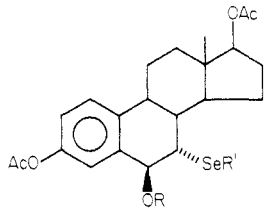
0022-3263/81/1946-3415$01.25/0

paper.

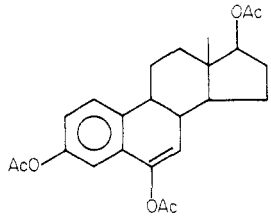
Phenylselenium bromide (generated in situ)[4] was allowed to react with estra-1,3,5(10),6-tetraene-3,17β-diol diacetate (**1**) in the presence of potassium acetate to yield **2a** (80%) and a minor amount of **2b** (5%). The NMR spectrum of **2a** exhibited a doublet at δ 6.12 with a low coupling constant (J = 2 Hz) for the 6α hydrogen and a triplet at δ 3.5, also with a low coupling constant (J = 2 Hz) for the 7β hydrogen. The doublet at low field (δ 6.12) indicated that the acetate group was at C-6. Since the electrophilic addition of an alkyl- or arylseleno bromide or acetate to olefins is known to produce trans isomers[4,5], it follows that the product is 7α-(phenylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol triacetate (**2a**). This assignment was confirmed by chemical evidence. Oxidative elimination of the selenophenyl group, by treating **2a** with hydrogen peroxide in THF, gave the expected enol acetae **3** which was then hydrolyzed to the known 6-oxoestradiol (**4**). The obtained **4** was identical with an authentic sample. Since **3** could be formed only via a syn elimination[6] of the 7α-SeC_6H_5 and 6α-H, these results confirm the 6β location of the acetoxy group in **2a**. The minor product of the above electrophilic addition reaction was 7α-(phenylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol 3,17-diacetate (**2b**). Both seleno acetates **2a** and **2b** were saponified with 5% EtOH–KOH to give 7α-(phenylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol (**5a**).



1



2a, R = Ac; R' = C_6H_5
b, R = H; R' = C_6H_5
c, R = Ac; R' = CH_3
d, R = H; R' = CH_3



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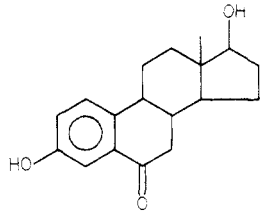

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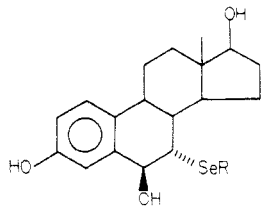
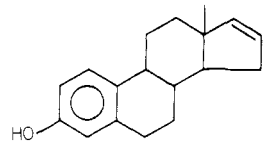


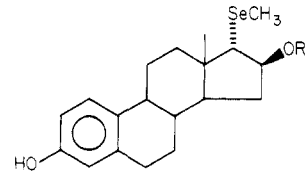
5a, R = C_6H_5
b, R = CH_3

Similarly, electrophilic addition of methylselenium bromide to the Δ^6-estradiol diacetate **1**, in the presence of potassium acetate, gave 7α-(methylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol triacetate (**2c**) (80%) [NMR δ 3.1, (t, J = 2 Hz, 7β-H), 6.04 (d, J = 2 Hz, 6α-H)] and the corresponding 7α-(selenomethyl)-6β-ol **2d** (5%). Saponification of **2c** and **2d** gave 7α-(methylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol (**5b**) in good yield.

Treatment of estra-1,3,5(10),16-tetraen-3-ol (**6**) with methylselenium bromide (generated in situ) in acetic acid furnished 17α-(methylseleno)estra-1,3,5(10)-triene-3,16β-diol 16-acetate (**7a**), which was saponified to **7b**.

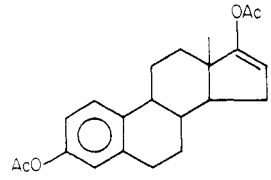


6

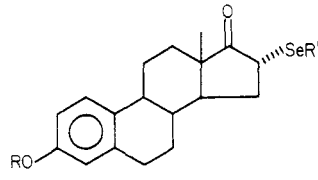


7a, R = Ac
b, R = H

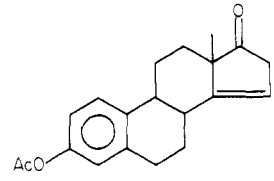
Reaction of estrone enol acetate **8** with phenylselenium bromide in the presence of potassium acetate gave 16α-(phenylseleno)estrone acetate (**9a**). The absence of paramagnetic downfield shift of the C-18 hydrogen atoms in the NMR indicated that the selenide has a 16α rather than a 16β orientation. To demonstrate the C-16 location of the selenide, we treated **9a** with hydrogen peroxide. The oxidative elimination of the 16-seleno moiety is expected to give the Δ^{15}-olefin, which in turn would isomerize to the Δ^{14}-olefin (**10**). Indeed, the Δ^{14}-olefin **10** [NMR δ 1.36 (s, C-18 H), 6.06 (1 H, d of d, J_1 = 10 Hz, J_2 = 2.5 Hz, C-15 H)] was obtained in good yield. The saponification of acetate **9a** gave a mixture of C-16 epimers. However, acid hydrolysis (MeOH–HCl) of **9a** furnished the desired 16α-selenoestrone **9b**.



8



9a, R = Ac; R' = C_6H_5
b, R = H; R' = C_6H_5
c, R = Ac; R' = CH_3
d, R = H; R' = CH_3



10

The 16α-(methylseleno)estrone **9d** was prepared by treating the enol acetate **8** with methylselenium bromide in the presence of potassium acetate, followed by acid hydrolysis of the resulting acetate **9c**. Attempts to prepare 16α-(methylseleno)estradiol **13** via reduction of **9d** with $LiAlH_4$ or $NaBH_4$ resulted in the removal of the selenomethyl group. However, the desired **13** was prepared by an alternative route starting from 16α-bromoestrone acetate **11a**.

Reduction of 16α-bromoestrone acetate **11a** with sodium borohydride in ethanol at 0 °C gave estradiol (13%) and the isomeric bromides A (26%) and B (56%). The mass

(1) Arunachalam, T.; Longcope, C.; Caspi, E. *J. Biol. Chem.* **1979**, *254*, 5900.
(2) Longcope, C.; Arunachalam, T.; Rafkind, I.; Caspi, E. *J. Steroid Biochem.*, in press.
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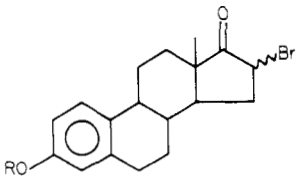
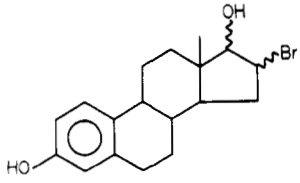
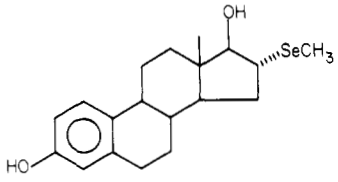
(5) Reich, H. J. *J. Org. Chem.* **1974**, *39*, 428.
(6) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979.



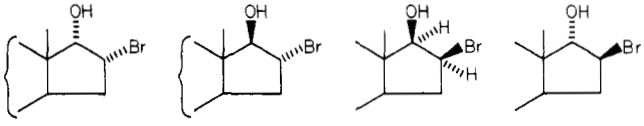
11a, R = Ac; α-Br
b, R = H; α-Br
c, R = H; β-Br



12a, α-OH; α-Br
b, β-OH; α-Br
c, β-OH; β-Br



13



A **B** **C** **D**

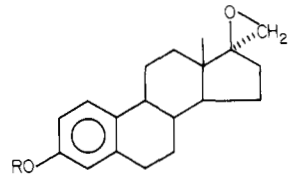
spectra of A and B showed pairs of molecular ions at m/e 350 and 352 (~1:1 ratio), indicating that both compounds are stereoisomers of the 16-bromo-17-ol. Theoretically, four bromohydrins A, B, C, and D could be formed. The isomers C and D could result from the isomerization of 16α-bromide to 16β-bromide prior to reduction. This of course could occur if the rate of isomerization was greater than the rate of reduction of the ketone. The NMR spectrum of compound A showed signals at δ 0.78 (s, 3 H, C-18 H), 3.6 (1 H, d, J = 5 Hz, C-17β H), 4.65 (1 H, m, C-16α H), 6.53 (1 H, s, C-4 H), 6.6 (1 H, d of d, J_1 = 9 Hz, J_2 = 2 Hz, C-2 H), and 7.1 (1 H, d, J = 9 Hz, C-1 H). On the basis of inspection of models, analysis of dihedral angles, and consideration of possible coupling constants of the isomers, the doublet at δ 3.6 was attributed to the 17β-H. The estimated coupling constant for the 17β- and 16β-hydrogen atoms is ~5 Hz. The absence of a downfield shift of C-18 protons, usually influenced by 16β polar substituent, is in accord with the 16α orientation of the bromine. On this basis, compound A was assigned the structure 16α-bromoestra-1,3,5(10)-triene-3,17α-diol (**12a**). As expected for a cis bromohydrin, **12a** on treatment with base gave estrone.

The NMR spectrum of compound B showed signals at δ 0.78 (3 H, s, c-18 H) and 3.7–4.4 (2 H, m for the C-16β and C-17α H). Because the C-18 hydrogen atoms were not shifted downfield (from δ 0.78), the bromine must be in the 16α position. In contrast, the C-17 H was shifted downfield, closer to the C-16 H, and this is consistent with the cis stereochemistry of the C-17α H and the 16α-bromine. It follows, therefore, that compound B is 16α-bromoestra-1,3,5(10)-triene-3,17β-diol (**12b**). As expected for a trans bromohydrin, **12b** on treatment with base gave the 16β,17β-epoxyestra-1,3,5(10)-trien-3-ol. The NMR spectrum [δ 0.85 (3 H, s, C-18 H), 3.23 (1 H, d, J = 3 Hz, C-17α H), 3.5 (1 H, t, J = 3 Hz, C-16α H)] is in accord with the assigned 17β,16β stereochemistry of the epoxide. Our results are in agreement with those of Fishman and Biggerstaff[7] but differ from those of Fajkos et al.[8]

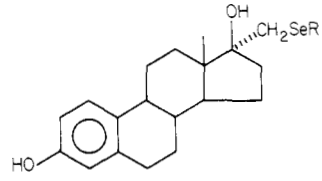
The bromohydrin **12c** can be more conveniently prepared from 16β-bromoestrone **11c**. Acid-catalyzed isomerization of 16α-bromoestrone acetate **11a** gave a 1:3 mixture of 16α- (**11b**) and 16β-bromides (**11c**). The mixture was resolved by high-pressure liquid chromatography. Reduction of **11c** ($NaBH_4$ in ethanol at 0 °C) gave 16β-bromoestradiol **12c** in nearly quantitative yield. Treatment of **12c** with sodium methylselenoate (generated in situ by the reduction of dimethyl diselenide with $NaBH_4$ in ethanol) furnished 16α-(methylseleno)estradiol **13**.

Attempts were made to prepare C-9 or C-11 seleno estrogen analogues by treating estra-1,3,5(10),9-tetraene-3,17β-diol with alkylselenium acetate. However, no reaction took place and the starting material was recovered.

Exposure of the 17β-oxirane **14** to sodium benzeneselenoate[9] gave 17α-[(phenylseleno)methyl]estra-1,3,5-(10)-triene-3,17β-diol (**15a**) in excellent yield. Similarly, treatment of the oxirane **14** with methylselenoate gave 17α-[(methylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (**15b**).



14a, R = H
b, R = CH_3



15a, R = C_6H_5
b, R = CH_3

For the synthesis of radioactive seleno estrogens, a synthesis based on the availability of radioactive ^{75}Se starting materials was developed. Currently, selenous acid ($H_2{}^{75}SeO_3$) and ^{75}Se metal are commercially available. The preparation of radioactive dimethyl diselenide from these starting materials is impractical and technically cumbersome. Consequently, synthetic approaches based on the use of dimethyl diselenide were abandoned.

Instead, the use of (methylseleno)magnesium halide (CH_3SeMgX) was considered. This reagent can be prepared by treating methylmagnesium halide with ^{75}Se metal.

To test the feasibility of this approach, we carried out model experiments with the 17β-oxirane **17** which was prepared by reacting **16** with $(CH_3)_2S{=}CH_2$. The (methylseleno)magnesium iodide was prepared by adding powdered selenium (metal) to methylmagnesium iodide. The oxirane **17** was added to the reagent and the mixture was stirred (12 h) at room temperature. The recovered product was fractionated by preparative TLC to yield 17α-(methylseleno)methyl **18a** in 50% yield. The product was identical with that of an authentic sample prepared by reacting oxirane **17** with sodium methylselenoate. The advantage of the seleno Grignard route is that the entire sequence of reactions is carried out in the same reaction vessel and does not require isolation of intermediates. The selenohydrin moiety is stable under acidic conditions required for the removal of the C-3 ketal. Thus, the selenohydrin **18a** was hydrolyzed with 0.2 N HCl to give the 17α-[(methylseleno)methyl]-3-one **18b**.

For the synthesis of the analogue **15b**, the intermediate silyl ether **20a** was prepared by treating estrone **19** with trimethylsilyl chloride. Treatment of **20a** with dimethylsulfonium methylide gave mainly the 3-methyl ether **14b**, while the required oxide **21a** was obtained in low yield. However, reaction of *tert*-butyldimethylsilyl ether **20b** with $(CH_3)_2S{=}CH_2$ gave a 2:1 mixture of **14a** and **21b**. It was found later that the oxirane **14a** could be converted to **21a** or **21b** by treatment with trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride. Reaction of **21** (a or b) with

(7) Fishman, J.; Biggerstaff, W. *J. Org. Chem.* **1958**, *23*, 1190.
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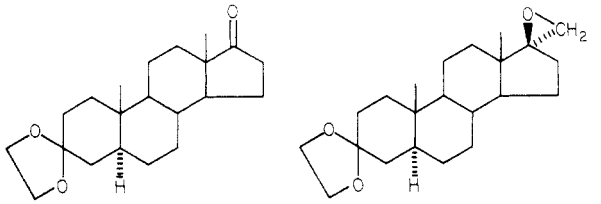

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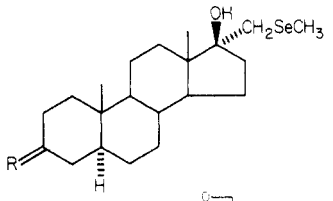
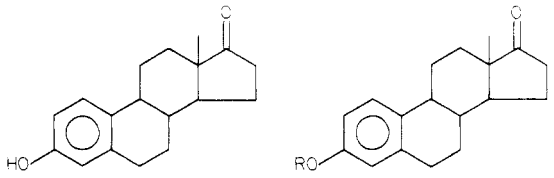


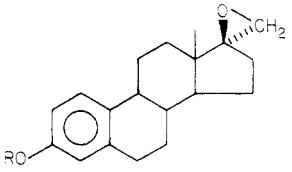
18a, R =

b, R = O

CH_3SeMgI followed by acid hydrolysis yielded the desired 17α-[(methylseleno)methyl]estradiol **15b**.



19 20a, R = $Si(CH_3)_3$
b, R = $Si(CH_3)_2C(CH_3)_3$



21a, R = $Si(CH_3)_3$
b, R = $Si(CH_3)_2C(CH_3)_3$

The method used for the synthesis of **15b** was then adapted for the microscale preparation of [^{75}Se]-(**15b**). The required seleno Grignard reagent was obtained by adding ^{75}Se (1 mCi; sp act. 150 mCi/m mol; 0.6 μ mol) to methylmagnesium iodide (0.65 μmol). The resulting $CH_3{}^{75}SeMgI$ was treated with 1 μmol of oxirane **21a**. After hydrolysis and repeated purification by column chromatography, homogeneous 17α-[(methyl[^{75}Se]seleno)-methyl]estradiol **15b** (100 μCi) was obtained. The results of biological receptor binding studies will be reported elsewhere.

Experimental Section

General. Melting points were taken on a Kofler hot stage. NMR spectra were recorded on a Varian EM 360 or EM 390 spectrometer using tetramethylsilane as internal reference unless otherwise indicated. The spectra were recorded in $CDCl_3$. Mass spectra were determined on a Nuclide Model 12-90-g instrument equipped with Nuclide DA/CS I.2 data acquisition system. The Merck A.G. silica gel 60 (0.06–0.2 mm) was used for column chromatography. Analytical annd preparative TLC was carried out, using plates coated with Merck A.G. silica gel 60 (HF 254 + 366).

7α-(Phenylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol Triacetate (2a). Diphenyl diselenide (80 mg, 0.26 mmol) was added with stirring to a solution of bromine (40 mg, 0.25 mmol) in acetic acid (2 mL). After the solution was stirred for 30 min, a homogeneous dark-red solution was obtained. Then Δ^6-estradiol diacetate[1] 1 (178 mg, 0.5 mmol) and anhydrous potassium acetate (100 mg) were added sequentially, and stirring was continued for 1 h. An immediate mild exothermic reaction occurred and the mixture turned pale brownish yellow.

The reaction was terminated with water (20 mL) and the product(s) was extracted with ethyl acetate. The organic extract was washed with a 10% solution of sodium carbonate and water and dried over Na_2SO_4, and the solvent removed under reduced pressure. The resulting gummy residue (300 mg) was fractionated by preparative TLC [silica gel, hexane–ethyl acetate (3:1)] to yield seleno estrogen **2a** (230 mg), which was recrystallized from hexane–EtOAc: mp 114–116 °C; mass spectrum (calcd for $C_{30}H_{34}O_6Se$, 569), *m/e* 572 (M^+ ^{82}Se), 570 (M^+ ^{80}Se), 568 (M^+ ^{78}Se), 566 (M^+ ^{76}Se), 413 (M^+ - PhSe), 412 (M^+ - PhSeH), 352 (M^+ – (HOAc + PhSeH)); NMR δ 0.9 (3 H, s, 18-H), 2.03 (3 H, s, 6β-OAc), 2.08 (3 H, s, 17β-OAc), 2.30 (3 H, s, 3-OAc), 3.5 (1 H, t, *J* = 2 Hz, 7β-H), 4.77 (1 H, t, *J* = 7 Hz, 17α-H), 6.12 (1 H, d, *J* = 2 Hz, 6α-H), and complex signals between 7.0 and 7.7 (8 H) for aromatic protons.

The 7α-(phenylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol 3,17-diacetate (**2b**) (16 mg) was also isolated from the above TLC: NMR δ 0.88 (s, 3 H, C-18 H_3), 2.07 (s, 17-OAc), 2.3 (s, 3-OAc), 2.3 (t, *J* = 2 Hz, 7β-H), and 4.84 (d, *J* = 2 Hz, 6α-H); mass spectrum, *m/e* 530 (M^+ ^{82}Se), 528 (M^+ ^{80}Se), and 526 (M^+ ^{78}Se).

Estra-1,3,5(10),6-tetraene-3,6,17β-triol Triacetate (3). To a cooled (0–5 °C) and stirred solution of **2a** (57 mg, 0.1 mmol) in THF (3 mL), hydrogen peroxide (35%) (0.1 mL) was added dropwise. The mixture was stirred for 3 h, during which time it was allowed to warm up slowly to ambient temperature. Water (10 mL) was then added and the product was extracted with ethyl acetate. The organic extract was washed with a solution of 10% sodium carbonate and water and dried, and the solvent was removed to yield a gummy residue. Purification by preparative TLC [silica gel, hexane–ethyl acetate (3:1)] gave the enol acetate **3** (36 mg): NMR δ 0.82 (3 H, s, 18-H), 2.01 (3 H, s, 17β-Ac), 2.23 (3 H, s, 3-Ac), 4.63 (1 H, t, 17α-H), and 5.6 (1 H, bs, C-7 H).

3,17β-Dihydroxyestra-1,3,5(10)-trien-6-one (4). A mixture of the 6-enol acetate **3** (30 mg), benzene (3 mL), and 5% EtOH–KOH (2 mL) was stirred for 1 h at 25 °C. The mixture was acidified with acetic acid to pH 5 and diluted with water, and the product was extracted with ethyl acetate. The extract was washed with water and dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield a light-brown solid. Purification by preparative TLC [silica gel, hexane–ethyl acetate (1:1)] gave 6-ketoestradiol **4** (15 mg). The obtained **4** was identical with an authentic sample.[7]

7α-(Phenylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol (5a). A mixture of the triacetate **2a** (32 mg), benzene (2 mL), and 5% ethanolic potassium hydroxide (2 mL) was stirred for 1 h. The mixture was acidified with acetic acid and diluted with water, and the product was extracted with ethyl acetate. After a conventional workup, a gummy residue was obtained. The product was fractionated by preparative TLC [silica gel, hexane–EtOAc (1:1)] to give the selenohydrin **5a** (22 mg): mp 185–187 °C; NMR δ 0.8 (3 H, s, 18-H), 3.54 (t, *J* = 2 Hz, 7β-H), 3.72 (1 H, t, *J* = 6.5 Hz, 17α-H), 4.72 (1 H, d, *J* = 2 Hz, 6α-H), and complex signals for eight aromatic protons; mass spectrum (calcd for $C_{24}H_{28}O_3Se$), *m/e* 440 (M^+ ^{76}Se), 442 (M^+ ^{78}Se), 444 (M^+ ^{80}Se), 446 (M^+ ^{82}Se).

7α-(Methylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol Triacetate (2c). A solution of dimethyl diselenide (100 mg, 0.52 mmol) in acetic acid (2 mL) was added under nitrogen to a stirred solution of bromine (80 mg, 0.5 mmol) in acetic acid (5 mL). The mixture was stirred for 15 more min, during which time the initial orange solution turned dark red (CH_3SeBr). Then, Δ^6-estradiol diacetate **1a** (350 mg, 0.98 mmol) and anhydrous potassium acetate (300 mg) were added sequentially. The mixture was stirred for 3 h at 25 °C, diluted with cold water (100 mL), and extracted with ethyl acetate. The organic extract was washed with 2% aqueous sodium bicarbonate and water and dried (Na_2SO_4), and the solvent was removed under reduced pressure at 40 °C. The resulting white solid was crystallized (ethyl acetate) to give homogeneous 7α-methylseleno **2c** (350 mg, 70%): mp 175–76 °C; NMR δ 0.86 (s, 3 H, C-18 H), 2.05 (s, 6 H, 17-OAc), $SeCH_3$), 2.11 (s, 3 H, 3-OAc), 3.1 (1 H, t, *J* = 2 Hz, 7β-H), 4.74 (1 H, t, *J* = 8 Hz, 17α-H), 6.04 (1 H, d, *J* = 2 Hz, 6α-H), 7.02 (2 H, m, C-2 and C-4 H), and 7.34 (1 H, d, *J* = 8 Hz, C-1 H); mass spectrum, *m/e* 510 (M^+ ^{82}Se), 508 (M^+ ^{80}Se), and 506 (M^+ ^{78}Se).

The mother liquor of the crystallization was fractionated by TLC [silica gel, hexane–ethyl acetate (3:1)] to yield selenohydrin **2d** (40 mg).

7α-(Methylseleno)estra-1,3,5(10)-triene-3,6β,17β-triol (5b). A solution of the triacetate **2c** (100 mg) in benzene (4 mL) was treated with 5% EtOH–KOH (3 mL), and the mixture was stirred for 2 h. It was then acidified with acetic acid diluted with cold water (100 mL), and the product was recovered with ethyl acetate. The extract was washed with 2% aqueous $NaHCO_3$ and water and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a gummy residue. Crystallization from ethyl acetate gave the selenohydrin **5b** (61 mg): mp 216–17 °C; mass spectrum (calcd for $C_{19}H_{28}O_3Se$), *m/e* 384 (M^+ ^{82}Se), 382 (M^+ ^{80}Se), 378 (M^+ ^{78}Se), and 326 (M^+ ^{76}Se).

17α-(Methylseleno)estra-1,3,5(10)-triene-3,16β-diol 16-Acetate (7a). Addition of the Δ^{16}-olefin[1] **6** (60 mg) and of potassium acetate (60 mg) to methylselenium bromide (generated in situ from dimethyl diselenide (25 mg) and bromine (20 mg) in acetic acid) was carried out as described earlier. After the usual workup and purification by preparative TLC [silica gel, hexane–ethyl acetate (2:1)], the selenoacetate **7a** was isolated as white crystalline material (76 mg, 80%): mp 149–50 °C; NMR δ 1.06 (s, 18-H), 2.04 (s, OAc), 2.06 (s, $SeCH_3$), 3.12 (s, 17β-H), 5.3 (m, 16α-H), 6.57 (s, C-4-H), 6.6 (d of d, J_1 = 2 Hz, J_2 = 8 Hz, C-2 H), and 7.14 (d, *J* = 8 Hz, C-1 H); mass spectrum (calcd for $C_{21}H_{28}O_3Se$), *m/e* 410 (M^+ ^{82}Se), 408 (M^+ ^{80}Se), 406 (M^+ ^{78}Se).

17α-(Methylseleno)estra-1,3,5(10)-triene-3,16β-diol (7b). A solution of the 17α-selenomethyl 16β-acetate **7a** (50 mg) in benzene (4 mL) was stirred with 5% EtOH–KOH (2 mL) for 2 h. It was then acidified with acetic acid, diluted with water, and extracted with ethyl acetate. The organic extract was washed with 2% aqueous $NaHCO_3$ and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a fluffy material. Purification by preparative TLC [silica gel, hexane–EtOAc (5:2)] gave crystalline selenohydrin **7c** (33 mg): mp 165–67 °C; NMR δ 1.07 (s, 18-H), 2.03 (s, $SeCH_3$), 3.0 (d, *J* = 1.5 Hz, 17β-H), 4.4 (m, 16α-H), 6.54 (bs, C-4 H), 6.6 (d of d, J_1 = 2 Hz, J_2 = 8 Hz, C-2 H), and 7.1 (d, *J* = 8 Hz, C-1 H); mass spectrum (calcd for $C_{19}H_{26}O_2Se$), *m/e* 368 (M^+ ^{82}Se), 366 (M^+ ^{80}Se), and 364 (M^+ ^{78}Se).

16α-(Phenylseleno)estrone Acetate (9a). Estrone enol diacetate 8 (180 mg, 0.5 mmol) and potassium acetate were added to a solution of phenylselenium bromide[4] [generated in situ from diphenyl diselenide (80 mg, 0.25 mmol) and bromine (40 mg, 0.25 mmole) in acetic acid], as described earlier. After the usual workup and purification by preparative TLC [silica gel, hexane–EtOAc (3:1)], 16α-seleno estrogen (**9a**) (190 mg) was isolated as a white solid: mp 130–133 °C; NMR δ 0.89 (s, 18-H), 2.25 (s, 3-OAc), 4.09 (m, 16β-H), 6.79 (bs, C-4 H), 6.81 (d of d, J_1 = 2 Hz, J_2 = 7.5 Hz, C-2 H), 7.2 (d, *J* = 7.5 Hz, C-1 H), and two multiplets centered at 7.26 (3 H) and 7.6 (2 H) (Se-Ph); mass spectrum (calcd for $C_{26}H_{28}O_3Se$), *m/e* 470 (M^+ ^{82}Se), 468 (M^+ ^{80}Se), and 466 (M^+ ^{78}Se).

16α-(Phenylseleno)estra-1,3,5(10)-trien-3-ol-17-one (9b). To a solution of **9a** (50 mg) in methanol (1 mL) was added concentrated HCl (75 μL), and the mixture was warmed briefly until a clear solution was obtained. The solution was stored for 16 h, and then the solvent removed in a stream of nitrogen and the residue was fractionated by preparative TLC [silica gel, hexane–EtOAc (2:1)]. The obtained 16α-(phenylseleno)estrone (**9b**) (28 mg) showed mp 185–188 °C: NMR δ 0.91 (s, 18-H), 4.1 (m, 16β-H), 6.59 (bs, C-4 H), 6.63 (d of d, J_1 = 2.5 Hz, J_2 = 8 Hz, C-2 H), 7.1 (d, *J* = 8 Hz, C-1 H), 7.1 (3 H, m), and 7.64 (2 H, m) (for the 5 Ar-H in SeC_6H_5).

16α-(Methylseleno)estrone (9d). A solution of dimethyl diselenide (25 mg, 0.125 mmol) in acetic acid (2 mL) was added to a solution of bromine (20 mg, 0.125 mmol) in acetic acid (2 mL). The mixture was stirred for 15 min, and then the enol acetate[1,7] 8 (90 mg, 0.25 mmol) and potassium acetate (150 mg) were added sequentially. The mixture turned from dark brown to pale yellow and then greyish white. The stirring was continued for 3 h and the reaction was worked up as described earlier. The crude residue was fractionated by preparative TLC [silica gel, hexane–EtOAc (3:1)] to give 16α-methylseleno 3-acetate **9c** (55 mg), mp 145–48 °C. This was then hydrolyzed with methanolic hydrochloric acid as described earlier to give 16α-(methylseleno)estrone **9d**, mp 195–98 °C.

3-Acetoxyestra-1,3,5(10),14-tetraen-17-one (10). Hydrogen peroxide (35%) (0.2 mL) was added dropwise to a stirred solution of 16α-selenide **9a** (60 mg) in THF (3 mL) at 0–5 °C. The mixture was stirred for 3 h, during which time it was allowed to warm up to ambient temperature. Then water was added and the product was recovered with ethyl acetate. The extract was washed with 10% aqueous Na_2CO_3 and water and dried, and the solvent was removed. The resulting residue was purified by preparative TLC [silica gel, hexane–EtOAc (3:1)]. The obtained crystalline Δ^{14}-estrone acetate **10** (35 mg) showed mp 113–17 °C: NMR δ 1.35 (s, 18-H), 2.26 (s, 3-OAc), 6.06 (d of d, J_1 = 2.5 Hz, J_2 = 10 Hz, C-15 H).

16β-Bromoestrone (11c). A solution of 16α-bromoestrone acetate (**11a**)[1,7] (500 mg) in 50 mL of 4% ethanolic H_2SO_4 was refluxed for 24 h. The HPLC analysis of an aliquot of the reaction mixture showed two peaks of nearly equal intensity. The NMR spectrum of the mixture had signals at δ 4.15 (t, *J* = 8 Hz, 0.6 H, 16α-H), and 4.6 (t, *J* = 4 Hz, 0.4 H, 16β-H). The results indicated that the product is a (2:3) mixture of 16α- and 16β-bromides. Therefore, the refluxing was continued for a total 140 h. The solution was concentrated to half of its original volume and then diluted with water. The crystalline product was filtered and dried (~450 mg). The residue contained ~75% of 16β-bromide **11c** and ~25% of 16α-bromide **11b**. The isomers were separated by high-pressure liquid chromatography (Partisil ODS, 10/25; 5% ethanol in heptane; flow rate, 1 mL/min; UV detector). The 16β-bromide **11c** was eluted first and its NMR showed signals at δ 1.11 (3 H, s, C-18 H), 4.15 (t, *J* = 8 Hz, 16α-H). The NMR of the 16α-bromide **11b** showed signals at δ 0.95 (s, 3 H, C-18 H), 4.6 (t, *J* = 4 Hz, 16β-H). The 16β-bromide was recrystallized from benzene, mp 217–21 °C.

16β-Bromoestra-1,3,5(10)-triene-3,17β-diol (12c). A solution of 16β-bromoestrone (**11c**) (100 mg) in 5 mL of absolute ethanol was treated with 50 mg of $NaBH_4$ at 0 °C for 20 h. The mixture was diluted with water, neutralized with 1% H_2SO_4, and extracted with ethyl acetate. The extract was washed, dried, and concentrated to give a crystalline residue (74 mg). HPLC analysis indicated that the product was essentially homogeneous **12c**. The product was recrystallized from methanol: mp 178–180 °C; NMR δ 0.93 (s, 3 H, C-18 H), 3.46 (1 H, d, *J* = 8 Hz, 17α-H), 4.6 (1 H, t, *J* = 8 Hz, 16α-H); mass spectrum, *m/e* 350, 352 (M^+ ions), 270 (M^+ - HBr).

$NaBH_4$ Reduction of 16-Bromoestrone Analogues. A. Reduction of 16α-bromoestrone acetate (**11a**) (0.5 g) with $NaBH_4$ in ethanol at 0 °C for 24 h gave a mixture of **12a** and **12b**, which was resolved by preparative TLC (2:1 hexane–ethyl acetate. The 16α-bromo-17α-ol **12a** (0.112 g) showed NMR δ 0.78 (3 H, s, 18-H), 3.6 (1 H, d, *J* = 5Hz, 17β-H), 4.65 (1 H, m, 16β-H). The 16α-bromo-17β-ol **12b** (235 mg) showed NMR δ 0.78 (3 H, s, 18-H), 3.7–4.4 (2 H, m, 16β-H and 17α-H) and estradiol (77 mg).

B. Reduction of a 2:1 mixture of 16β- and 16α-bromoestrone (300 mg) under similar conditions gave, after TLC fractionation, **12a** (45 mg), **12b** (79 mg), and **12c** (140 mg).

Treatment of Bromohydrins 12 with Base. The cis bromohydrins **12a** and **12c**, on refluxing with 5% KOH in ethanol, gave estrone. Under similar conditions, the trans bromohydrin **12b** gave 3-hydroxyestra-1,3,5(10)-triene 16β,17β-oxide (mp 194–197 °C) [NMR δ 0.85 (3 H, s, 18-H)), 3.23 (1 H, d, *J* = 3 Hz, 17α-H), and 3.5 (1 H, t, *J* = 3 Hz, 16α-H)].

16α-(Methylseleno)estra-1,3,5(10)-triene-3,17β-diol (13). 16β-Bromoestradiol **12c** (60 mg) was added to a solution of sodium methylselenoate (CH_3SeNa) in ethanol and kept under argon. The mixture was stirred at room temperature for 20 h, then cold water was added, and the product was recovered with ethyl acetate. The washed and dried extract was concentrated and the residue was fractionated by preparative TLC (hexane–ethyl acetate, 2:1). The obtained 16α-(methylseleno)estradiol **13** was recrystallized from hexane–ethyl acetate (35 mg): mp 247–250 °C dec; NMR δ 0.80 (3 H, s, 18-H), 1.97 (3 H, s, $SeCH_3$), 3.1 (1 H, m, 16β-H), and 3.6 (1 H, d, *J* = 7.5 Hz, 17α-H); mass spectrum (calcd for $C_{19}H_{26}O_2Se$), *m/e* 362 (M^+ ^{76}Se), 364 (M^+ ^{78}Se), 366 (M^+ ^{80}Se), and 368 (M^+ ^{82}Se).

17α-[(Phenylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (15a). To a stirred (under N_2) solution of diphenyl diselenide (40 mg, 0.125 mmol) in absolute ethanol (2 mL), sodium borohydride (10 mg, 0.25 mmol) was added in portions until the bright-yellow solution became colorless. (**Caution**: The reaction is exothermic with vigorous evolution of hydrogen.) The 17-oxirane **14a** (63 mg, 0.24 mmol) was added to the stirred solution, and after 3 h, cold water (30 mL) was added. The products were

recovered with ethyl acetate and processed in the conventional manner to give a gummy residue. Analytical TLC [silica gel, hexane–ethyl acetate (2:1)] indicated the presence of one major and several minor products. The residue was resolved by preparative TLC [silica gel, hexane–ethyl acetate (7:3)] to give 17α-[(phenylseleno)methyl]estradiol **15a** as a fluffy powder (85 mg). This was recrystallized from methanol: mp 237–240 °C; mass spectrum, *m/e* 442 (M^+ ^{80}Se), 440 (M^+ ^{78}Se); NMR δ 0.97 (3 H, s, 18-H), 3.3 (2 H, AB quartet, δ_{AB} = 20 Hz, J_{AB} = 12 Hz, CH_2SePh), 6.57 (1 H, s, C-4 H), 6.63 (1 H, d of d, J_1 = 8 Hz, J_2 = 2 Hz, C-2 H), 7.13 (1 H, d, J = 8 Hz, C-1 H), and two multiplets centered at 7.2 annd 7.55 (SeC_6H_5).

17α-[(Methylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (15b). Method A. To a stirred (under N_2) solution of dimethyl diselenide (24 mg, 0.125 mmol) in absolute ethanol (2 mL), sodium borohydride (10 mg, 0.25 mmol) was added in small portions. When the solution became colorless, the 17-oxirane **14a** (63 mg, 0.24 mmol) was added and the mixture was stirred for 3 h. The reaction was terminated with cold water (20 mL) and extracted with ethyl acetate, and the extract was processed to yield a semisolid residue (85 mg).

Analytical TLC of the product showed one main spot and two minor spots. Following fractionation by TLC [silica gel, hexane–ethyl acetate (2:1)], 17α-[(methylseleno)methyl]estradiol **15b** (70 mg) was obtained. Crystallization (absolute methanol) gave **15b**: mp 210–13 °C; mass spectrum, *m/e* 378 (M^+ ^{78}Se), 380 (M^+ ^{80}Se); NMR δ 0.97 (3 H, s, 18-H), 2.08 (3 H, s, $SeCH_3$), 2.9 (2 H, AB quartet, CH_2SeCH_3), 6.57 (s, C-4 H), 6.63 (d of d, J_1 = 8 Hz, J_2 = 2 Hz, C-2 H), and 7.13 (d, J = 8 Hz, C-1 H).

Method B. A solution of 17β-oxirane **21a** (or **21b**) (0.5 mmol) in ether (2 mL) was added to a solution of (methylseleno)magnesium iodide (~4 mmol) in ether, and the mixture was stirred for 12 h. The reaction was cooled (0 °C), acidified with 10% HCl, and stirred for 15 min. Water was then added, and the product was recovered (ether) and processed, leaving a gummy residue. The residue was fractionated by TLC hexane–ethyl acetate (5:2)] to yield 17α-[(methylseleno)methyl]estradiol **15b** (72 mg, ~60%).

(Methylseleno)magnesium Iodide (CH_3SeMgI). A stock solution of methylmagnesium iodide (10% in ether) was prepared in the conventional manner. The Grignard solution (1 g in 10 mL of ether) was placed in a three-necked, round-bottom flask fitted with an efficient condenser, an inlet for passing dry argon, and a bent side arm, for the addition of powdered selenium. The top of the condenser was fitted with a drying tube (Drierite), which was connected to three scrubbers containing 50% aqueous potassium hydroxide. The last scrubber was vented. Ether (20 mL) was added, and the solution was gently heated to reflux. The heating was stopped and powdered selenium (1 g) was added in small portions at a rate sufficient to maintain the refluxing. After all the selenium was added, the mixture was heated and stirred for 2 h. The flask was cooled to room temperature and the yellowish ethereal solution of CH_3SeMgI was withdrawn with a syringe and transfered to a dry, sealed flask filled with argon. Aliquots of the stock solution of CH_3SeMgI were withdrawn and used as needed.

3,3-(Ethylenedioxy)-17α-[(methylseleno)methyl]-5α-androstan-17β-ol (18a). Method A. A solution of the 17β-oxirane **17** (100 mg) in ether was added to an ether solution of CH_3SeMgI (100 mg) and the mixture was stirred for 10 h at room temperature. The mixture was carefully acidified and diluted with water, and the product was recovered with ether. The ether extract was processed to give a residue, which was resolved by TLC [silica gel, hexane–ethyl acetate (3:1)]. The obtained 17α-(methylseleno)methyl **18a** (55 mg) showed mp 165–169 °C. The product was identical in all respects with an authentic sample prepared by method B.

Method B. Sodium borohydride (20 mg) was added to a stirred solution of dimethyl diselenide (100 μL) in 4 mL of absolute ethanol under nitrogen. The solution was stirred for 15 min, at which time it became colorless. Then the 17β-oxirane **17** (140 mg) was added in one portion and the mixture was stirred for 4 h. Cold water was added and the product was recovered (ethyl acetate) in the usual manner to give nearly homogeneous selenide **18a** (130 mg): mp 167–170 °C; NMR (100 MHz), δ 0.83 (19-H), 0.9 (18-H), 2.04 (s, 3 H, $SeCH_3$), 2.87 (2 H, AB quartet, Δ_{AB} 0.22 ppm, J_{AB} = 12 Hz, CH_2SeMe), and 3.94 (s, 4 H, OCH_2CH_2O); mass spectrum (calcd for $C_{23}H_{38}O_3Se$), *m/e* 438 (M^+ ^{76}Se), 440 (M^+ ^{78}Se), 442 (M^+ ^{80}M), 444 (M^+ ^{82}Se).

17β-Hydroxy-17α-[(methylseleno)methyl]-5α-androstan-3-one (18b). Hydrolysis of the 3-ketal **18a** with 0.2 N HCl in dioxane or acetone gave the title compound **18b** in good yield.

3-(Trimethylsiloxy)estra-1,3,5(10)-trien-17-one (20a). Sylon BTZ (2 mL) was added to a stirred solution of estrone (1.5 g) in a mixture of dry dioxane (15 mL) and dry pyridine (1 mL). The mixture was stirred for 24 h and then 200 mL of 0.1% aqueous K_2CO_3 was added, and the product was recovered with ether. The extract was processed to give crystalline silyl ether **20a** (1.88 g, 98%) (crystallized from isooctane–ether): mp 151–52 °C; NMR δ 0.23 (9 H, s, $Si(CH_3)_3$), 0.87 (3 H, s, C-18 H), 6.53 (1 H, s, C-4 H), 6.57 (1 H, d of d, J_1 = 8 Hz, J_2 = 2.5 Hz, C-2 H), and 7.2 (1 H, d, J = 8 Hz, C-1 H).

3-(*tert*-Butyldimethylsiloxy)estra-1,3,5(10)-trien-17-one (20b). A mixture of estrone (1.6 g, 6 mmol) and imidazole (1.38 g, 20 mmol) in dry DMF (25 mL) was added to *tert*-butyldimethylsilyl chloride (1.35 g, 9 mmol). The mixture was stirred at room temperature for 15 h and then 0.1% aqueous K_2CO_3 (200 mL) was added. The crystalline silyl ether **20b** was filtered and dried (2.21 g, 97%): mp 154–56 °C; NMR δ 0.16 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 3 H, C-18 H), 0.95 (s, 9 H, $SiC(CH_3)_3$).

Reaction of 20a and 20b with $(CH_3)_2S{=}CH_2$. The silyl ether **20a** (1.5 g) was treated with $(CH_3)_2S{=}CH_2$ as described earlier. Fractionation of the residue by column chromatography gave three products: 3-methoxy-17β-oxirane **14b** (70%), **21a** (26%).

Similarly, reaction with **20b** (1.5 g) yielded **14b** (0.9 g) and the oxirane **21b** (0.45 g).

17α-[(Methylseleno)methyl]estra-1,3,5(10)-triene-3,17β-diol (15b). A (5 mL) two-neck round-bottom flask was fitted with an efficient condenser and the other neck was sealed with a septum. The flask was charged with ^{75}Se (1 mCi) (sp act., 150 mCi/mmol) and ether (1 mL). The mixture was brought to gentle reflux and a solution of methylmagnesium iodide (0.65 μmol) in ether (100 μL) was injected. The mixture was refluxed for 2 h and then cooled to room temperature. Then the oxirane **21a** or 21b (1 μmol) in ether (100 μL) was injected and the mixture was stirred (8 h) at 25 °C. The mixture was diluted with water, acidified with 0.1 N HCl (100 μL), and stirred for 15 min. The product was recovered with ether. The ether extract was processed to yield a residue, which was fractionated by column chromatography on silica gel. Elution of the column with hexane–ethyl acetate (2:1) gave the radioactive **15b**. This was rechromatographed to yield homogeneous **15b** (100 μCi). TLC autoradiochromatogram showed a single peak. Dilution experiment with carrier and recrystallization indicated that the sample was at least 93–94% radiochemically pure **15b**.

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Registry No. **1**, 1971-65-9; **2a**, 78149-47-0; **2b**, 78149-48-1; **2c**, 78149-49-2; **2d**, 78149-50-5; **3**, 78149-51-6; **4**, 571-92-6; **5a**, 78149-52-7; **5b**, 78149-53-8; **6**, 1150-90-9; **7a**, 78166-76-4; **7b**, 78149-54-9; **8**, 20592-42-1; **9a**, 78149-55-0; **9b**, 77862-30-7; **9c**, 78149-56-1; **9d**, 78149-57-2; **10**, 34603-43-5; **11a**, 1239-35-6; **11b**, 71765-95-2; **11c**, 1228-71-3; **12a**, 74561-57-2; **12b**, 54982-79-5; **12c**, 51946-42-0; **13**, 78149-58-3; **14a**, 16669-01-5; **15a**, 77862-33-0; **15b**, 78166-87-7; **17**, 78215-26-6; **18a**, 78149-59-4; **18b**, 78149-60-7; **19**, 53-16-7; **20a**, 1839-54-9; **20b**, 57711-40-7; **21a**, 78166-88-8; **21b**, 78166-89-9; 3-hydroxyestra-1,3,5(10)-triene 16β,17β-oxide, 472-57-1.