84, 111436-33-0; 85, 111436-34-1; 86, 111436-35-2; 87, 111436-36-3; 88, 111436-37-4; 89, 111436-38-5; 90, 111436-39-6; 91, 111436-40-9; 92, 24028-59-9; 93, 111436-41-0; 94, 111436-42-1; 95, 111436-43-2; 96, 111436-44-3; 97, 111436-45-4; 98, 111436-46-5; 99, 111436-47-6; 100, 111436-48-7; 101, 111436-49-8; 101·HCl, 111436-53-4; 102, 111436-50-1; 103, 111436-51-2; 104, 111436-52-3; 4-(aminomethyl)piperidine, 7144-05-0; 2-amino-5-(diethylamino)pentane, 140-80-7.

Analogues of [(Triethylsilyl)ethynyl]estradiol as Potential Antifertility Agents

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Various 17α-ethynylsteroids were prepared and derivatized as the corresponding triethylsilyl compounds **2–35**, which were examined for a ratio of antifertility to estrogenic activity that would be more beneficial than that of the presently used agent. Among the triethylsilyl compounds evaluated, only **23** displayed this desired ratio, although two other compounds without the triethylsilyl moiety, **18** and **26**, shared similar characteristics.

We recently described a series of ethynylestradiol (EE) derivatives that featured a systematic variation of trialkylsilyl groups pendant to the ethynyl side chain.[1] The mere presence of silicon was proven to be surprisingly beneficial. Other investigators have assumed the existence of a direct relationship between antifertility and estrogenic activity,[2] but our silyl derivatives displayed a marked reduction in estrogenic activity, with retention of the level of oral antifertility activity. This latter trend is attractive in light of the endocrine disorders and other undesired side effects attributed to the estrogenic activity of prescribed contraceptives.[3] Although we had shown that some remarkable separation of estrogenic from antifertility activities as described above could be achieved by structural variations of the EE side chain, we had heretofore not examined modifications of the EE steroidal nucleus. We have now examined the effects of structural changes in the A, B, C, and D rings of EE while incorporating the C-21 triethylsilyl moiety (for example, see structures **2–35**, Table I).

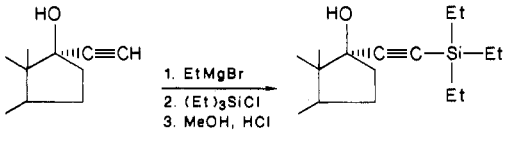
Chemistry Results

The desired analogues **2–35** were synthesized in a straightforward fashion: nuclear-modified ethynylestradiols **3–35** were synthesized from their respective ketones by standard ethynylation procedures. Upon treatment with ethylmagnesium bromide, each was converted to the corresponding acetylide anion, which was capped with chlorotriethylsilane (Scheme I, see the Experimental Section for synthetic details on particular compounds).

Biological Results

Table II shows the compounds, their corresponding antifertility (*A*) and estrogenic (*E*) potencies in rats relative to EE or at maximum dosage levels given, and the ratio of antifertility to estrogenic activity (*A*/*E*). For comparison, ethynylestradiol (EE, **1**) and the unsilylated terminal

Scheme I



17α-acetylenes were examined and included in Table II.

In general, introduction of the triethylsilyl group onto the ethynylestrane derivatives resulted in a decrease of estrogenic activity when the initial estrogenicity of the parent ethynylestranes was greater than 2%. The only exceptions occurred in the 6α- and 11β-hydroxy derivatives (**13** and **27**, respectively), where the introduction of the triethylsilyl group showed an actual increase of 10%–20% in estrogenicity over that of the parent ethynylestrane. However, no parallels could be drawn concerning the antifertility activity.

Ring A substitution at position C-2 with a methoxyl or (di-*n*-propylamino)methyl functionality (**3** and **7**, respectively) drastically reduced both antifertility and estrogenic activity. A lipophilic methyl group retained significant antifertility activity and lost substantial estrogenicity. The presence of a C-4 allyl substituent (as in **8** and **9**) led to an essential void of activity. Antifertility and estrogenicity for the unsubstituted 3-desoxy EE analogue **10** were simultaneously reduced in magnitude. In contrast, the corresponding silylated 3-desoxy EE analogue **11** retained antifertility potency equal to that of EE, with only 13% of the estrogenicity of EE.

Examples with polar hydroxyl substituents on ring B did not exhibit enhanced antifertility activity unless the C-6α hydroxyl was accompanied by a C-17α (triethylsilyl)ethynyl moiety (for example, **12a** compared to **13**). Other types of ring B substituents were also examined—for example, the presence of a C-6β methyl group led to a substantial reduction in overall activity. Unfortunately, a similar lack of activity was observed for ring C and D substituted, triethylsilyl derivatives.

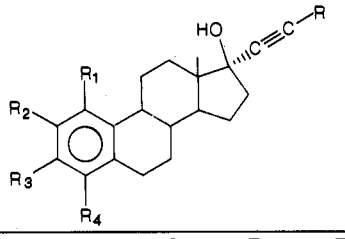
In summary, the best triethylsilyl derivative in Table I was the ring B substituted Δ^6 analogue **23**. Compound **23** had twice the potency of EE as an antifertility agent but only 2% of the estrogenic activity of EE. The 100-fold separation of estrogenic activity and antifertility activity for **23** relative to EE is the greatest that we have observed for any silylethynyl EE derivative.

Surprisingly, two of the intermediate ethynyl compounds, 11β-hydroxy EE (**26**) and 7α-hydroxy EE (**18**),

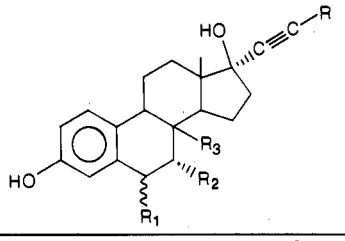
(1) Peters, R. H.; Crowe, D. F.; Tanabe, M.; Avery, M.; Chong, W. K. M. *J. Med. Chem.* **1987**, *30*, 646.
(2) (a) Fishman, J.; Martucci, C. Conference on Estrogen Treatment of the Young, Santa Ynez, California, December 6–9, 1977, p 1228. (b) Fishman, J. *J. Am. Chem. Soc.* **1958**, *80*, 1213.
(3) (a) Bengel, A. S.; Benoit, P. S. *J. Pharm. Sci.* **1973**, *62*, 179. (b) Population Reports, Series A, No. 2, March 1975. Published by Department of Medical and Public Affairs & George Washington University Medical Center, Washington, DC.

0022-2623/88/1831-0572$01.50/0

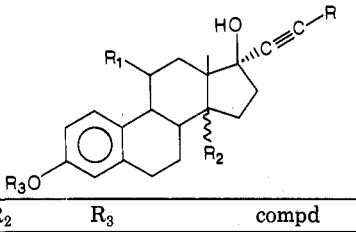
Table I



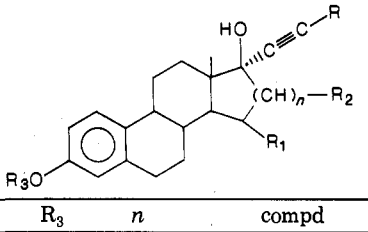
compd	R	R_1	R_2	R_3	R_4	compd	R	R_1	R_2	R_3	R_4
1	H	H	H	OH	H	6	H	H	$CH_2N(n\text{-}Pr)_2$	OH	H
1a	$Si(Et)_3$	H	H	OH	H	7	$Si(Et)_3$	H	$CH_2N(n\text{-}Pr)_2$	OH	H
2	H	H	OMe	OH	H	8	H	H	H	OH	$CH_2CH{=}CH_2$
3	$Si(Et)_3$	H	OMe	OH	H	9	$Si(Et)_3$	H	H	OH	$CH_2CH{=}CH_2$
4	H	H	CH_3	OH	H	10	H	H	H	H	H
5	$Si(Et)_3$	H	CH_3	OH	H	11	$Si(Et)_3$	H	H	H	H



compd	R	R_1	R_2	R_3	compd	R	R_1	R_2	R_3
12a	H	α-OH	H	H	19	$Si(Et)_3$	H	OH	H
13	$Si(Et)_3$	α-OH	H	H	20	H	α-OH	OH	H
14	H	β-OH	H	H	21	$Si(Et)_3$	α-OH	OH	H
15a	$Si(Et)_3$	β-OH	H	H	22	H	Δ^6		H
16	H	β-CH_3	H	H	23	$Si(Et)_3$	Δ^6		H
17	$Si(Et)_3$	β-CH_3	H	H	24	H	Δ^6		Δ^8
18	H	H	OH	H	25	$Si(Et)_3$	Δ^6		Δ^8



compd	R	R_1	R_2	R_3	compd	R	R_1	R_2	R_3
26	H	β-OH	α-H	H	28	H	H	β-H	CH_3
27	$Si(Et)_3$	β-OH	α-H	H	29	$Si(Et)_3$	H	β-H	CH_3



compd	R	R_1	R_2	R_3	n	compd	R	R_1	R_2	R_3	n
30	H	OCH_3	H	CH_3	1	33	$Si(Et)_3$	H	CH_3	H	1
31	$Si(Et)_3$	OCH_3	H	CH_3	1	34	H	H	H	H	2
32	H	H	CH_3	H	1	35	$Si(Et)_3$	H	H	H	2

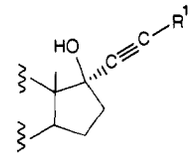
were potent antifertility agents and had extremely weak estrogenic activity in rats. Compound **18** was 66% as effective as EE as an antifertility agent and had only 0.1% of the estrogenic activity of EE (see Table I) for an activity separation of 660. Compound **26** was twice as active as EE in the antifertility test and had only 0.8% of the estrogenic activity of EE for an activity separation of 250. Among the extensive number of compounds that we have screened, **18** showed the greatest separation of antifertility activity and estrogenic activity that we have observed to date.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, Perkin-Elmer 137 instrument; NMR, Varian T-60 and XL-100 or JEOL FX-90Q instruments) were recorded for all compounds in $CDCl_3$ unless otherwise stated. Mass spectral data were obtained with a CEC 21-110B high-resolution, double-focusing spectrometer. Microanalytical data were determined by Galbraith Labs, Knoxville, TN, for C and H on all new compounds and agreed to within ±0.4% of the calculated values. Woelm silica gel, activity III/30 mm, containing 0.5% fluorescent indicator, was used for all dry column chromatography,[4] with 5% EtOAc/$CHCl_3$ as the developing solvent unless otherwise stated. Tetrahydrofuran (THF) was dried by distillation from methylmagnesium bromide and stored over 4-Å molecular sieves.

(4) Loev, B.; Snader, K. M. *Chem. Ind. (London)* **1965**, 15.

Table II. Oral Antifertility and Oral Estrogenic Potencies of Triethylsilyl-Substituted EE Analogues Relative to EE in Rats[a]



compd	steroid substit	R^1	antifertility potency[b] (*A*)	estrogenic potency (*E*)	activity separation (*A*/*E*)	yield,[c] %	mp, °C	anal.
1		H	100	100				
1a		$Si(Et)_3$	600	37	16			
2	2-MeO	H	>2.0 mg/kg per day	0.3				
3	2-MeO	$Si(Et)_3$	>2.8 mg/kg per day	0.06		79	84–86	C, H
4	2-Me	H	40	5.5	7		170–171	
5	2-Me	$Si(Et)_3$	40	2.2	18	53	73–75	HRMS
6	2-CH_2N-(*n*-Pr)$_2$	H	>2 mg/kg per day	1.3		47	gum	C, H
7	2-CH_2N-(*n*-Pr)$_2$	$Si(Et)_3$	>1 mg/kg per day	0.3		59	oil	C, H
8	4-$CH_2CH{=}CH_2$	H	>2 mg/kg per day	0.1		85	oil	HRMS
9	4-$CH_2CH{=}CH_2$	$Si(Et)_3$	>3.0 mg/kg per day	0		51	glass	HRMS
10	3-desoxy	H	33	31	1	65	118–119	
11	3-desoxy	$Si(Et)_3$	100	13	8	71	92–93	C, H
12a	6α-OH	H	>0.2 mg/kg per day	16		57	155–159	C, H
13	6α-OH	$Si(Et)_3$	300	38	8	44	190–192	C, H
14	6β-OH	H						
15a	6β-OH	$Si(Et)_3$	40	16	2	38	glass	HRMS
16	6β-Me	H	>0.5 mg/kg per day	1.8		50	104–110	HRMS
17	6β-Me	$Si(Et)_3$	7.5	0.2	37	51	102–105	HRMS
18	α-OH	H	66	0.1	660	36	234–235	HRMS
19	7α-OH	$Si(Et)_3$	20	0.3	67	10	180–181	HRMS
20	6α,7α-$(OH)_2$	H	>0.5 mg/kg per day	0.3		15	242–244	HRMS
21	6α,7α-$(OH)_2$	$Si(Et)_3$	>0.5 mg/kg per day	0.6		16	192–193	HRMS
22	Δ^6	H	20	2.0	10	64	179–181	HRMS
23	Δ^6	$Si(Et)_3$	200	2.0	100	13	79–87	HRMS
24	$\Delta^{6,8}$	H	10	0.6	17	70	178–179	HRMS
25	$\Delta^{6,8}$	$Si(Et)_3$	66	1	66	23	181–182	HRMS
26	11β-OH	H	200	0.8	250		278–280	
27	11β-OH	$Si(Et)_3$	64	14.4	4	34	95–98	HRMS
28	14β-H, 3-MeO	H	>2 mg/kg per day	0.3		74	100–105	HRMS
29	14β-H, 3-MeO	$Si(Et)_3$	>2 mg/kg per day	1.8		46	82–83	C, H
30	15-MeO, 3-MeO	H	10	0.8	12	41	135–136	C, H
31	15-MeO, 3-MeO	$Si(Et)_3$	>0.2 mg/kg per day	3		57	110–114	C, H
32	16β-Me	H	>2 mg/kg per day	0.5		74	119–120	HRMS
33	16β-Me	$Si(Et)_3$	>0.8 mg/kg per day	0.2		98	152–153	C, H
35	D-homo	$Si(Et)_3$	>2.0 mg/kg per day	0.1		46	161–163	C, H

[a] Testing was conducted by the National Institute of Child Health and Human Development, National Institutes of Health. [b] Minimum protective doses for prevention of pregnancy (200 μg for EE): Numbers given are relative to EE or as maximum dose given in mg/kg per day. [c] Yields were not optimized.

General Method of Ethynylation. Acetylene was purified by bubbling through concentrated sulfuric acid and then successive passage through traps at room temperature and at −78 °C and through a column containing Drierite, KOH pellets, and Drierite. While acetylene was being bubbled into THF at 0 °C, an ether solution of EtMgBr was added in four portions at 15-min intervals. After being stirred for 2.5 h at 0 °C, a solution of the steroid (~1.0 mmol) in THF was added dropwise. The reaction was allowed to warm to room temperature, placed under a nitrogen atmosphere, and stirred for 18 h. The resultant solution was transferred to a round-bottom flask, which was then placed on a rotary evaporator to remove approximately half of the THF under reduced pressure. The resulting suspension was poured into saturated aqueous NH_4Cl solution and extracted with ether. The combined organic phase was washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), and evaporated under vacuum.

General Method of Triethylsilylation. To a solution of 17α-ethynyl steroid in THF under nitrogen was added an ether solution of EtMgBr. The solution was stirred at room temperature for 1 h, heated to 60 °C for 2 h, cooled to room temperature, and treated with triethylchlorosilane. The reaction was allowed to stir at room temperature for 48 h. Then, saturated aqueous NH_4Cl was added, and stirring was continued for 10 min. The mixture was extracted with ether, washed with saturated NH_4Cl solution, and dried (Na_2SO_4), and the solvent was removed under vacuum. To effect hydrolysis of any silyl ethers, the crude product was dissolved in MeOH, treated with a small amount of concentrated HCl, and allowed to stir at room temperature for 1 h. The mixture was extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated under vacuum.

2-Methoxy-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (3). According to the standard procedure, 1.4 g of **2**[5] in 130 mL of THF was reacted with 18 mL of 3.0 M EtMgBr and 19.8 mL of triethylchlorosilane to yield 1.5 g (79% yield) of **3**. An analytical sample, mp 84–86 °C, was prepared by crystallization from MeOH/H_2O: NMR δ 0.90 (s, 18-CH_3), 3.88 (s, OCH_3), 6.68 (s, 1-CH or 2-CH), 6.83 (s, 1-CH or 2-CH).

2-Methyl-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (5). A solution of 0.549 g of 2-methyl-17α-ethynylestradiol[6] in 50 mL of THF was sequentially treated with 2.6 mL of 3.0 M EtMgBr and 13.4 mL of triethylchlorosilane in the manner previously described to yield 1.0 g of crude product. Separation on silica gel thick plates with 5% MeOH in $CHCl_3$ afforded 0.396 g (53% yield) of **5**. Compound **5** resisted crystallization but gave an amorphous solid, mp 73–75 °C, upon lyophilization from benzene: NMR ($CDCl_3$/CD_3OD, 1:1) δ 0.90 (s, 18-CH_3), 2.22 (s, 2-CH_3), 6.52, 7.09 (m, aromatic H).

2-[(Di-*n*-propylamino)methyl]-17α-ethynylestra-1,3,5(10)-triene-3,17β-diol (6). A solution of 1.5 g of 2-[(di-*n*-

(5) Rao, P. N. *Steroids* **1974**, *23*(2), 173.
(6) Ringold, H. J.; Rosenkranz, G. U.S. Patent 3 166 577, January 19, 1965.

propylamino)methyl]estrone[6] in 50 mL of THF was ethynylated by the standard method, employing 10 mL of 3.0 M EtMgBr in 150 mL of THF to yield 1.68 g of crude product. The total crude product was chromatographed on silica gel with CH_2Cl_2 to give 0.747 g (47% yield) of **6** as a clear gum: NMR δ 0.90 (s, 18-CH_3), 2.58 (s, ≡CH), 3.70 (br s, CH_2N).

2-[(Di-*n*-propylamino)methyl]-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (7). A solution of 0.670 g of 2-[(di-*n*-propylamino)methyl]-17α-ethynylestradiol in 50 mL of THF was treated with 3.3 mL of 3.0 M EtMgBr and 14.3 mL of triethylchlorosilane in the manner previously described to yield 1.03 g of crude **7**. Separation on silica gel with CH_2Cl_2 gave 0.502 g (59% yield) of an oil: NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 3.70 (br s, CH_2N).

4-Allyl-17α-ethynylestra-1,3,5(10)-triene-3,17β-triol (8). According to the standard procedure, 1.0 g of 4-allylestrone[7] in 50 mL of THF was reacted with 5 mL of 3.0 M EtMgBr in 150 mL of THF containing acetylene. Chromatography on silica gel with 5% ether/toluene afforded 0.923 g (85% yield) of **19**, which resisted crystallization: NMR δ 0.90 (s, 18-CH_3), 2.60 (s, ≡CH), 5.14 (br s, =CH_2).

4-Allyl-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (9). According to the standard procedures, 0.63 g of **8** in 60 mL of THF was sequentially treated with 5 mL of 3.0 M EtMgBr and 5.5 mL of triethylchlorosilane. Chromatography on silica gel with 5% ether/toluene afforded 0.43 g (51% yield) of **9** as a glass: NMR δ 0.90 (s, 18-CH_3), 5.14 (br s, =CH_2).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-trien-17β-ol (11). A solution of 0.600 g of 3-desoxy-17α-ethynylestradiol[8] in 50 mL of THF was treated with 2.67 mL of 3.0 M EtMgBr and 2.8 mL of triethylchlorosilane in the manner previously described to yield 2.4 g of crude material, which was purified via silica gel column and eluted with CH_2Cl_2 to give 0.603 g (71% yield) of **11**. Crystallization from CH_2Cl_2/hexane gave an analytical sample: mp 92–93 °C; NMR δ 0.90 (s, 18-CH_3), 7.10 (m, aromatic H).

6α-[(*tert*-Butyldimethylsilyl)oxy]-17α-ethynylestra-1,3,5(10)-triene-3,17β-diol (12). According to the standard procedure, 0.55 g of 6α-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxyestra-1,3,5(10)-trien-17-one[5,9,10] in 50 mL of THF was reacted with a solution of 3.0 M EtMgBr (4 mL) and acetylene in 50 mL of THF to yield 0.587 g (82% yield) of **12**. An analytical sample was obtained by recrystallization from MeOH: mp 190–192 °C; NMR δ 0.90 (s, 18-CH_3), 2.70 (s, ≡CH), 4.90 (m, 6-CH).

17α-Ethynylestra-1,3,5(10)-triene-3,6α,17β-triol[5] (12a). A solution of 0.108 g of silyl ether **12** in 25 mL of MeOH containing 2 drops of concentrated HCl was stirred at room temperature for 30 min. The reaction was poured into H_2O and extracted with ether. The organic phase was washed with H_2O and saturated NaCl, dried over Na_2SO_4, and evaporated to dryness under vacuum. The crude product was purified by thick-plate chromatography using 8% MeOH/$CHCl_3$. Recrystallization from CH_2Cl_2 afforded 0.032 g of triol **12a** (52% yield): mp 155–159 °C (lit.[5] mp 158–161 °C); NMR δ 0.90 (s, 18-CH_3), 2.64 (s, ≡CH), 3.38 (br s, 6-CH).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,6α,17β-triol (13). According to the standard procedure, 0.25 g of **12a** in 30 mL of THF was sequentially reacted with 1.6 mL of 3.0 M EtMgBr and 1.8 mL of triethylchlorosilane. Recrystallization from MeOH afforded 0.109 g (44% yield) of **13**: mp 190–192 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 3.38 (br s, 6-CH).

6β-[(*tert*-Butyldimethylsilyl)oxy]-17α-ethynylestra-1,3,5(10)-triene-3,17β-diol (15). According to the standard procedure, 0.542 g of 6β-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxyestra-1,3,5(10)-trien-17-one in 50 mL of THF was reacted with 4 mL of 3.0 M EtMgBr followed by acetylene in 50 mL of THF to yield, after recrystallization from MeOH, 0.300 g (52%) of **15**: mp 168–169 °C; NMR ($CDCl_3/CD_3CD$, 1:1) δ 0.18 (s, $Si(CH_3)_2$), 0.95 (s, 18-CH_3, *t*-BuSi), 2.62 (s, ≡CH), 3.80 (m, 6-CH).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,6β,17β-triol (15a). According to the standard procedure, 0.20 g of **15** in 15 mL of THF was sequentially reacted with 1.3 mL of 3.0 M EtMgBr and 1.4 mL of triethylchlorosilane to yield a crude product, which, after thick-plate silica gel chromatography and developing with 8% MeOH/$CHCl_3$, provided 0.077 g (38% yield) of **15a** as a glass, which resisted crystallization: NMR δ 0.90 (s, 18-CH_3), 4.70 (br s, 6-CH).

17α-Ethynyl-6β-methylestra-1,3,5(10)-triene-3,17β-diol (16). A solution of 0.364 g of 6β-methylestrone[12] in 50 mL of THF was ethynylated by the standard method with 3.34 mL of 3.0 M EtMgBr in 150 mL of THF to yield 0.377 g of crude product, which was purified via dry column chromatography to afford 0.197 g (50% yield) of pure **16**. Recrystallization from CH_2Cl_2/hexane provided an analytical sample: mp 104–110 °C; NMR δ 0.90 (s, 18-CH_3), 1.34 (d, J = 7 Hz, 6-CH_3), 2.60 (s, ≡CH).

6β-Methyl-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (17). A solution of 0.113 g of 6β-methyl-17α-ethynylestradiol in 10 mL of THF was treated with 0.73 mL of 3.0 M EtMgBr and 2.4 mL of triethylchlorosilane in the standard way to yield 0.138 g of crude product. Separation on a silica gel thick plate with 10% 2-propanol/hexane gave 0.078 g (51% yield) of pure product, which upon lyophilization from benzene formed an amorphous powder: mp 102–105 °C; NMR δ 0.90 (s, 18-CH_3), 1.34 (d, J = 7 Hz, 6-CH_3).

17α-Ethynylestra-1,3,5(10)-triene-3,7α,17β-triol (18). According to the standard procedure, 1.0 g of 7α-hydroxyestrone[9,11,13] in 100 mL of THF was treated with 5 mL of 3.0 M EtMgBr in 50 mL of THF saturated with acetylene to afford, after chromatography with silica gel preparative TLC plates developed in 10% MeOH/$CHCl_3$ and crystallization from MeOH, 0.39 g (36% yield) of **18**: mp 234–235 °C; NMR ($CDCl_3/CD_3OD$, 1:1), δ 0.90 (s, 18-CH_3), 2.60 (s, ≡CH), 3.40 (br s, 7-CH).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3β,7α,17β-triol (19). According to the standard procedure, 0.286 g of **18** in 50 mL of THF was reacted with 2.5 mL of 3.0 M EtMgBr and 2.8 mL of triethylchlorosilane to yield, after purification on a dry silica gel column eluting with 10% EtOAc/$CHCl_3$ and recrystallization from MeOH, 0.041 g (10% yield) of **19**: mp 180–181 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90, (s, 18-CH_3), 3.40 (br s, 7-CH).

17α-Ethynylestra-1,3,5(10)-triene-3,6α,7α,17β-tetrol (20). To a solution of 0.075 g of 17α-ethynylestra-1,3,5(10)-triene-3,6α,7α-triol acetonide in 15 mL of MeOH was added 0.5 mL of 2 N HCl. The reaction mixture was stirred overnight at 25 °C and then poured into water, and the product was extracted into ether. Separation on silica gel plates with 8% MeOH/$CHCl_3$ and crystallization from MeOH gave 0.010 g (15% yield) of **20**: mp 242–244 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 2.65 (s, ≡CH), 4.18, 4.60 (br s, 6-CH or 7-CH).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,6α,7α,17β-tetrol (21). According to the standard procedure, 0.422 g of **20** in 50 mL of THF was reacted with 2.5 mL of 3.0 M EtMgBr and 2.8 mL of triethylchlorosilane. Purification by thick-plate chromatography, with 8% MeOH/$CHCl_3$ as the developing solvent, and crystallization from CH_2Cl_2 yielded 0.081 g (16% yield) of **21**: mp 192–193 °C; NMR ($CDCl_3/CD_3OD$, 1:1), δ 0.90 (s, 18-CH_3), 4.00 (m, 7-CH), 4.60 (m, 6-CH).

17α-Ethynylestra-1,3,5(10),6-tetraene-3,17β-diol (22). According to the standard procedure, 2.0 g of 6-dehydroestrone in 75 mL of THF was reacted with 12 mL of 3.0 M EtMgBr in 250 mL of THF saturated with acetylene to yield 1.4 g (64% yield) of **22**. An analytical sample was obtained on recrystallization from MeOH: mp 179–181 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 2.62 (s, ≡CH), 6.00 (d, J = 10 Hz, 6-CH), 6.50 (d, J = 10 Hz, 7-CH).

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17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10),6-tetraene-3,17β-diol (23). By the standard procedure, 0.348 g of acetylene **22** in 60 mL of THF was reacted with 3.2 mL of 3.0 M EtMgBr and 3.5 mL of triethylchlorosilane to afford, after recrystallization from MeOH, 0.062 g (13% yield) of silane **23**: mp 79–81 °C; NMR δ 0.90 (s, 18-CH_3), 5.98 (d, J = 10 Hz, 6-CH), 6.48 (d, J = 10 Hz, 7-CH).

17α-Ethynylestra-1,3,5(10),6,8-pentaene-3,17β-diol (24). According to the standard procedure, 1.00 g of equilenin in 60 mL of THF was reacted with a mix of 8 mL of 3.0 M EtMgBr in 60 mL of THF saturated with acetylene to give, after recrystallization from CH_2Cl_2, 0.775 g (70% yield) of acetylene **24**: mp 178–179 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.87 (s, 18-CH_3), 2.65 (s, ≡CH), 7.00–8.00 (m, aromatic H).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10),6,8-pentaene-3,17β-diol (25). According to the standard procedure, 0.400 g of **24** in 50 mL of THF was sequentially reacted with 1.8 mL of 3.0 M EtMgBr in 60 mL of THF and 3 mL of triethylchlorosilane to give, after recrystallization from MeOH, 0.128 g (23% yield) of **25**: mp 181–182 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 7.00–8.00 (m, aromatic, H).

17α-[(Triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,11β,17β-triol (27). A solution of 0.80 g of 17α-ethynylestra-1,3,5(10)-triene-3,11β,17β-triol[14] in 50 mL of THF was treated with 7.0 mL of 3.0 M EtMgBr and 5.0 mL of triethylchlorosilane in the manner previously described to yield 1.6 g of crude product. Purification via silica gel thick plates developed with 50% ether/benzene and recrystallization from acetone/hexane gave 0.21 g (34% yield) of **27**: mp 95–98 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 1.14 (s, 18-CH_3), 4.80 (br s, 11-CH).

17α-Ethynyl-14β-estra-1,3,5(10)-triene-3,17β-diol 3-Methyl Ether (28). A solution of 1.00 g of 14-isoestrone methyl ether[15] in 50 mL of THF was ethynylated by the standard method with 5.0 mL of 3.0 M EtMgBr in 150 mL of THF to yield 1.20 g of crude product, which separated on a silica gel column with methylene chloride to afford 0.813 g (74.5%) of **28**, which crystallized from CH_2Cl_2/hexane: mp 100–105 °C; NMR δ 1.00 (s, 18-CH_3), 2.60 (s, ≡CH), 3.80 (s, OCH_3).

3-Methoxy-17α-[(triethylsilyl)ethynyl]-14β-estra-1,3,5(10)-trien-17β-ol (29). A solution of 0.542 g of ethynyl-14-isoestradiol 3-methyl ether in 50 mL of THF was treated with 40 mL of 3.0 M EtMgBr and 2.5 mL of triethylchlorosilane in the standard way to yield 0.709 g of crude product, which was purified on a silica gel column with 75% $CHCl_3$/hexane and crystallized from hexane to give 0.331 g (46% yield) of **29**: mp 82–83 °C; NMR δ 1.00 (s, 18-CH_3), 2.58 (s, ≡CH), 3.72 (s, OCH_3).

3,15β-Dimethoxy-17α-ethynylestra-1,3,5(10)-trien-17β-ol (30). A solution of 1.50 g of 3,15β-dimethoxyestra-1,3,5(10)-trien-17-one[16] in 50 mL of THF was ethynylated by the standard method with 8.0 mL of 3.0 M EtMgBr in 150 mL of THF to yield 1.74 g of crude product. Crystallization from acetone/hexane gave 0.660 g (41% yield) of **30**: mp 135–136 °C; NMR δ 1.10 (s, 18-CH_3), 2.60 (s, ≡CH) 3.28 (s, 16-OCH_3), 3.80 (s, 3-OCH_3).

3,15β-Dimethoxy-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-trien-17β-ol (31). A solution of 0.400 g of **30** in 50 mL of THF was sequentially treated with 1.33 mL of 3.0 M EtMgBr and 1.4 mL of triethylchlorosilane by the standard method to yield 1.00 g of crude **31**. Separation on silica gel thick plates with 3% $MeOH/CHCl_3$ as eluent gave 0.304 g (57% yield) of **31** as a clear, colorless oil, which, upon lyophilization from benzene, yielded a white amorphous powder: mp 110–114 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 1.10 (s, 18-CH_3), 3.20 (s, 16-OCH_3), 3.80 (s, 3-OCH_3).

17α-Ethynyl-16β-methylestra-1,3,5(10)-triene-3,17β-diol (32). A solution of 1.00 g of 16β-methylestrone[17] in 50 mL of THF was ethynylated by the standard method with 10 mL of 3.0 M of EtMgBr in 150 mL of THF to yield 1.22 g of crude product. Crystallization from cyclohexane gave 0.230 g of product, and separation of the mother liquid on a silica gel column with CH_2Cl_2 gave an additional 0.574 g of **32** (total yield 74%). Recrystallization from CH_2Cl_2/hexane gave **32**: mp 119–120 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 1.10 (d, J = 7 Hz, 16-CH_3), 2.60 (s, ≡CH).

16β-Methyl-17α-[(triethylsilyl)ethynyl]estra-1,3,5(10)-triene-3,17β-diol (33). A solution of 0.571 g of 16β-methyl-17α-ethynylestradiol in 50 mL of THF was treated with 2.6 mL of 3.0 M EtMgBr and 1.8 mL of triethylchlorosilane by the standard method of triethylsilation to yield 1.30 g of crude oil. Separation on a silica gel column with CH_2Cl_2 gave 0.767 g (98% yield) of **33**. An analytical sample, mp 152–153 °C, was prepared by crystallization from CH_2Cl_2/hexane: NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.90 (s, 18-CH_3), 1.10 (d, J = 7 Hz, 16-CH_3).

17α-Ethynyl-D-homoestra-1,3,5(10)-triene-3,17α-diol (34). A solution of 1.00 g of D-homoestrone[18] in 60 mL of THF was ethynylated by the standard method with 10 mL of 3.0 M EtMgBr and acetylene in 150 mL of THF to yield 1.24 g of crude product, which was an inseparable mixture of α- and β-ethynyl isomers that was purified via silica gel thick-plate chromatography with 5% $MeOH/CHCl_3$ and used without further purification. In this manner, 0.436 g (46% yield) of the isomeric mixture was prepared.

17α-[(Triethylsilyl)ethynyl]-D-homoestra-1,3,5(10)-triene-3,17α-diol (35). A solution of 0.396 g of the mixture **34** in 50 mL of THF was sequentially treated with 5.3 mL of 3.0 M EtMgBr and 3.33 mL of triethylchlorosilane in the manner previously described to yield 1.1 g of crude product. Purification with a silica gel column with benzene and recrystallization from $CHCl_2$/hexane afforded 0.253 g (46% yield) of **35** (a single isomer by NMR analysis): mp 161–163 °C; NMR δ 0.94 (s, 18-CH_3).

Biology. Oral Estrogenic Activity. Immature female rats of the Sprague–Dawley strain (approximately 45–55 g, 21 days of age) received at least three dose levels of the test compound and standard dissolved in sesame oil. All compounds were administered orally (gavage), once daily, for 3 consecutive days. A control group received vehicle only. There were 10 animals/group. Rats were autopsied 24 h after the last treatment and the uteri excised, cleaned of fat and connective tissue, blotted on moist filter paper, and weighed to the nearest 0.2 mg. Regression lines for the standard and the test compound (when possible) were constructed and compared by using standard methods.

Oral Antifertility Activity. Adult, female, cycling rats were cohabited with males during the night of the day of proestrus. Animals with evidence of positive mating (presence of sperm in vaginal washings) received the test compound dissolved in sesame oil by gavage daily for 7 consecutive days. A control group received vehicle only. There were 10 animals/group. Rats were sacrificed on or about day 8, and the uteri were examined for the presence and condition of conceptuses. Results were compared with the regression line established for the standard (EE).

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