changeable); MS, m/e 398 (M^+). Anal. ($C_{18}H_{22}O_{10}$) H; C: calcd, 54.27; found, 53.74.

Biology. Female BDF_1 and C57BL/6 mice were received from Harlan Industries, Indianapolis, IN. All animals were quarantined for 5 days before being released for use in studies. Prior to study, animals were housed five per cage in suspended gang stainless steel cages. During study, animals were housed individually in suspended stainless steel cages with wire mesh fronts and bottoms. Water and food (Purina Mouse Chow No. 5015) were available ad libitum to all animals at all times.

Tumor. B16 tumor was maintained twice per month by subcutaneous passage in syngenic C57BL/6 mice. On day 0, solid tumor was removed from a donor mouse. Tumor brei was prepared by making a 1:10 dilution (w/v) with HBSS (Hank's balanced salt solution) and then implanted (0.5 mL each) subcutaneously into a shaved dorsoscapular area of BDF_1 mice.

Drug Administration. Drugs were prepared in either normal saline, 0.3% Klucel, or 0.33% Klucel/$NaHCO_3$. Animals were injected for 9 consecutive days after observation of measurable tumor with doses usually ranging from 2.5 to 20 mg/kg injection.

Observations and Calculations. Drug-treated mice were observed daily for no longer than 120 days. Tumor measurements (diameter) and body weights were recorded twice per week. Tumor diameter was calculated in millimeters by using Vernier calipers. Diameters were taken by measuring the long axis (length) and the two short axes (width and depth). Tumor size was expressed as an average of the three diameters.

Median survival time and percent T/C were calculated according to Instruction 14 of the National Cancer Institute (Bethesda, MD). Tumor growth inhibition was calculated as

$$\text{TGI} = 100 - \frac{(\text{change in tumor diameter treated})(100)}{\text{change in tumor diameter control}}$$

Acknowledgment. We gratefully acknowledge support for this work through a grant from the Thomas Edison Program of the State of Ohio and Adria Laboratories, Plain City, OH. One of us (A.M.A.) thanks The University of Palermo for leave of absence. The excellent technical assistance of Ms. Valerie Bell for the biological evaluations is gratefully acknowledged.

Registry No. **3**, 120475-61-8; **4**, 120475-62-9; **5**, 120475-63-0; **6**, 5628-29-5; **7**, 120475-64-1; **8**, 13949-78-5; **9**, 120475-65-2; **10**, 120475-66-3; 11, 120475-67-4; **12**, 120475-68-5; **13**, 120475-69-6; **14**, 40870-55-1; **15**, 120475-70-9; **16**, 120475-71-0; **17**, 120475-72-1; **18**, 120475-73-2; **19**, 120475-74-3; **20**, 120475-75-4; **21**, 120475-76-5; **22**, 20306-76-7; (*Z*)-**23**, 120475-77-6; (*E*)-**23**, 87050-73-5; **24**, 3752-97-4; **25**, 50874-27-6; **26**, 52251-27-1; **27**, 120475-78-7; **28**, 51829-43-7; **29**, 120475-79-8; **30**, 120475-80-1; **31**, 120475-81-2; **32**, 120475-82-3; **33**, 120475-83-4; **34**, 30038-31-4; **35**, 120475-84-5; **36**, 78840-04-7; **37**, 72652-35-8; **38**, 120475-85-6; **39**, 120475-86-7; 2,5-dimethoxybenzyl bromide, 60732-17-4; 2,5-dimethoxyethylbenzene, 1199-08-2; 2,5-dimethoxybenzyl alcohol, 33524-31-1; 2,4,5-trimethoxybenzaldehyde, 4460-86-0.

17-Desoxy Estrogen Analogues

Richard H. Peters, David F. Crowe, Mitchell A. Avery, Wesley K. M. Chong, and Masato Tanabe*

Bio-Organic Chemistry Laboratory, SRI International, Menlo Park, California 94025. *Received March 21, 1988*

A series of 17-substituted, 17-desoxyestratrienes have been synthesized and tested as potential postcoital antifertility agents. Estrogen-relative binding affinities were determined, in vivo assays for estrogenic and postcoital antifertility activity were conducted in rats, and selected candidate compounds were further tested for estrogenic activity in monkeys. In the rat, the 17-desoxyestratriene derivatives **8a**, **8b**, and **30** have shown low estrogenic activity while retaining potent antifertility activity. Structural modifications at the outset included a variety of 17-substituents and an omission of the 17-oxygen functionality, which was previously thought to be necessary for potent activity. The 17β-ethyl side chain exhibited the greatest antifertility activity with the largest separation ratio to estrogenicity. Nuclear modification of 17-desoxyethylestrane derivatives at positions 7 and 11 further increased the desired separation of activity, with the 11-hydroxy moiety enhancing separation more than other features.

For a number of years we have been engaged in an ongoing program for the design of improved antifertility agents. Despite the wide variety of structural modifications that have been realized in the evolution of steroidal drugs, we felt that the role of the C17 oxygen functionality of estrogens had not been fully evaluated. In this regard, we describe herein our examination of structure–activity relationships (SAR) among various 17-desoxy estrogens.

The arrangement of oxygen substituents on a steroid nucleus is well recognized as a key determinant among the variety of biological activities that are modulated by steroids. As each of the specific receptors for progestins, androgens, and estrogens have become better characterized and available in pure form, the direct relationships between binding affinity and the resultant hormonal activities have been verified,[1] although the exact mechanistic details remain obscure. Therefore, it is easy to visualize how the site and geometrical orientation of oxygens on a steroid skeleton can affect its binding affinity for a receptor, and thus the degree of activity.

The estrogen receptor, which elicits a uterotrophic response, has been isolated from rat uterine tissue and used in studies that have defined the connection between binding affinities, structures, and hormonal activity.[2] These studies have suggested that estrogens must have a 17β-hydroxyl and a phenolic 3-hydroxyl in order to have a high binding affinity and, consequently, potent hormonal activity. Different descriptions of the requisite disposition of these two oxygens have been reported;[3a–c] among these are a critical intramolecular distance of 11 Å proposed by Weber and Galantay[4] and an angular dependence examined by Raynaud and co-workers.[3d,e] However, the effects of different numbers of oxygens—either more or fewer—

(1) (a) Gorski, J.; Toft, D.; Shyamala, G.; Smith, D.; Notides, A. *Recent Prog. Horm. Res.* **1968**, *24*, 45. (b) Jensen, E. V.; DeSombre, E. R. *Annu. Rev. Biochem.* **1972**, *41*, 203.

(2) (a) Jensen, E. V.; DeSombre, E. R. *Science* **1973**, *182*, 126. (b) O'Malley, W.; Menns, R. A. *Science* **1974**, *183*, 610.

(3) (a) Korenman, S. G. *Steroids* **1969**, *13*, 163. (b) Hospital, M.; Busetta, B.; Bucort, R.; Weintraub, M.; Baulien, E. E. *Mol. Pharmacol.* **1972**, *8*, 438. (c) Eisenfeld, A. *Endocrinology* **1974**, *94*, 803. (d) Delletrê, J.; Mornon, J. P.; Lepicard, G.; Ojasoo, T.; Raynaud, J. P. *Steroid Biochem.* **1980**, *13*, 45. (e) Ojasoo, T.; Raynaud, J. P. In *Steroid Hormone Receptors: Structure and Function*; Erikson, H., Gustafson, J. A., Eds.; Elsevier: Amsterdam, 1983; p 141.

(4) Weber, H. P.; Galantay, E. *Helv. Chim. Acta* **1972**, *55*, 544.

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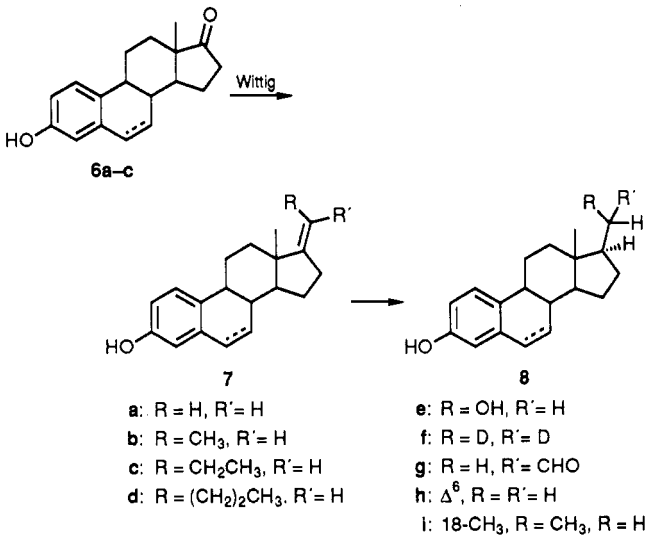
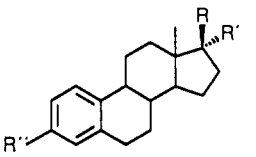
Scheme I



are as yet still unpredictable. In this regard, it was surprising when reports appeared that showed the absence of normally requisite oxygens for corticoids[5] and androgens[6] can prove beneficial. Aligned with this rationale, we wanted to explore these effects on estrogens.

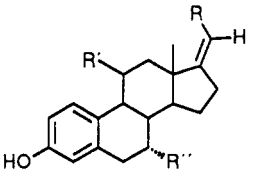
In a precedent relevant to the aims of our program to design better antifertility agents, Kincl and Dorfman[7] found that, relative to mestranol (**2b**), the 3-desoxy derivative 17α-ethynylestra-1,3,5(10)-trien-17-ol (**2a**) had half of the oral postcoital antifertility activity in rats and only 5% of the oral uterotrophic activity in mice and that the 17-desoxy compound estra-1,3,5(10)-trien-3-ol (**1**) had 15% of the oral postcoital antifertility activity in rats and 0.2% of the oral uterotrophic activity in mice.



1: R = R' = H, R'' = OH
2a: R = OH, R' = C≡CH, R'' = H
2b: R = OH, R' = C≡CH, R'' = OMe
3: R = C≡CH, R' = H, R'' = OMe
4: R = CH=CH2, R' = H, R'' = OMe
5: R = CH2CH3, R' = H, R'' = OMe

Therefore, in this case, the removal of either the 3- or 17-oxygen has been shown to provide an improved separation of 10- and 75-fold, respectively, of antifertility to undesired uterotrophic activity. Unfortunately, the estrogenic activity for the similar 17-desoxyestrones **3**, **4**, and **5** synthesized by Oliveto and co-workers[8a] has not yet appeared. These reports led us to prepare other 17-desoxy estrogens in which the oxygen was replaced by other heteroatoms and the 17-alkyl substituents featured different degrees of unsaturation and/or number of heteroatoms. The synthetic 17-desoxy steroids were examined for a separation of uterotrophic and antifertility activity, and other synthetic steroids were then prepared as warranted via customary alterations of the steroidal nucleus,

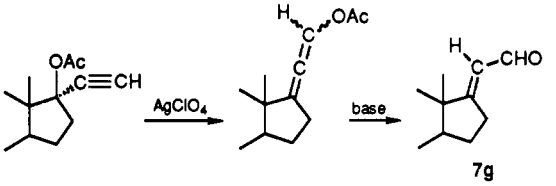
Table I. Changes in the ^1H NMR (60-MHz) Chemical Shifts of the 18-CH_3 as a Result of the Presence of a *Z*-17(20)-Olefin



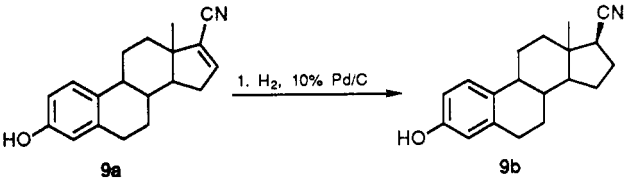
compound	18-CH_3, Hz[a]	Δ18-CH_3, Hz[b]
7b: R = CH_3, R' = R'' = H	56.0	+0.7
7c: R = CH_2CH_3, R' = R'' = H	56.0	+0.7
7d: R = $CH_2CH_2CH_3$, R' = R'' = H	56.0	+0.7
27b: R = CH_3, R' = H, R'' = CH_3	55.0	−0.3
30: R = CH_3, R' = OH, R'' = H	55.0	−0.3

[a] Values of chemical shift (Hz) in $CDCl_3$, relative to tetramethylsilane (TMS) as an internal reference, in a 60-MHz spectrum. [b] Δ18-CH_3 = [chemical shift of 18-CH_3 (Hz) of *Z*-17(20)-olefin] − [chemical shift of 18-CH_3 (Hz) of 17-ketone].

Scheme II



Scheme III



with the intent of further improving the separation of activity.

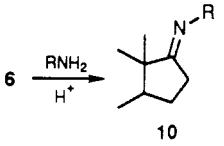
Chemistry

Side-Chain Modifications. As depicted in Scheme I, estrones **6** were elaborated to the corresponding 17-alkylidenes **7**, which were selectively reduced to target 17β-alkyl steroids **8**. The reaction of estrones **6** with Wittig reagents[8b,9] prepared from alkyltriphenylphosphonium bromides afforded 17-olefin isomers of a single geometry, as observed by NMR. Comparison of the NMR spectra of the olefins **7** with the starting estrones **6** revealed chemical shift differences for the C18-methyl that were within a range consistent with the exclusive production of the *Z* isomers, as shown for **7** (Table I). It had previously been reported[10] that, in 60-MHz spectra, the difference from estrones was about 1 Hz for *Z* olefins, versus a larger 7 Hz for *E* olefins. To complete Scheme I, subsequent catalytic hydrogenation of the *Z*-17(20)-olefin occurred stereospecifically from the α-side[8a,11] to afford high yields of the 17β-alkylestratrienes, except in special cases, for which we developed different synthetic methods, as discussed below.

When the 17-methylidene analogue **7a** was treated with diborane and worked up oxidatively, a mixture was ob-

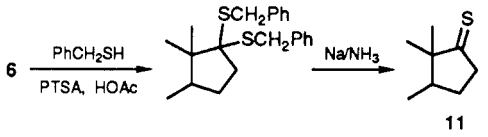
(5) Overbeck, G. A.; Delver, A.; deVesser, J. *Acta Endocrinol. Suppl.* **1962**, *63*, 7.
(6) Bowers, A.; Cross, A. D.; Edwards, J. A.; Carpio, H.; Calzada, M. C.; Denot, E. *J. Med. Chem.* **1963**, *6*, 156.
(7) Kincl, F. A.; Dorfman, R. I. *J. Reprod. Fertil.* **1965**, *10*, 105.
(8) (a) Krubiner, A. M.; Gottfried, N.; Oliveto, E. P. *J. Org. Chem.* **1969**, *34*, 3502. (b) Mills, J. S.; Ringold, H. J.; Djerassi, C. *J. Am. Chem. Soc.* **1958**, *80*, 6118.
(9) Krubiner, A. M.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 24.
(10) (a) Tanabe, M.; Peters, R. H. *J. Org. Chem.* **1971**, *36*, 2403. (b) Benn, W. R.; Dodson, R. M. *J. Org. Chem.* **1964**, *29*, 1142. (c) MacKeller, F. A.; Slomp, G. *Steroids* **1968**, *11*, 787.
(11) Engel, Ch. R.; Bouchard, R.; de Krassny, A. F.; Ruest, L.; Lessard, J. *Steroids* **1969**, *14*, 637.

Scheme IV



a: R = OCH_3
b: R = OH
c: R = NH(2-pyr)
d: R = NH_2

Scheme V



tained, with the 17β-(hydroxymethyl) analogue **8e** as the major product and the 17α isomer as a minor contaminant, which was absent after repeated recrystallization.

As a notable entry for the exploration of the effect of the size of C17-alkyl substituents, the 17-(dideuteriomethylidene) **7f** was prepared in straightforward fashion from estrone via Wittig reaction with (trideuteriomethyl)triphenylphosphonium bromide.

The E-$\Delta^{17(20)}$-aldehyde analogue **7g** was synthesized from ethynylestradiol (EE) via treatment of EE 3,17-diacetate with silver perchlorate in tetramethylguanidine to initially give in situ a 21-acetoxy allene intermediate, which was subsequently heated with base to give the desired α,β-unsaturated aldehyde **7g** (Scheme II).[12]

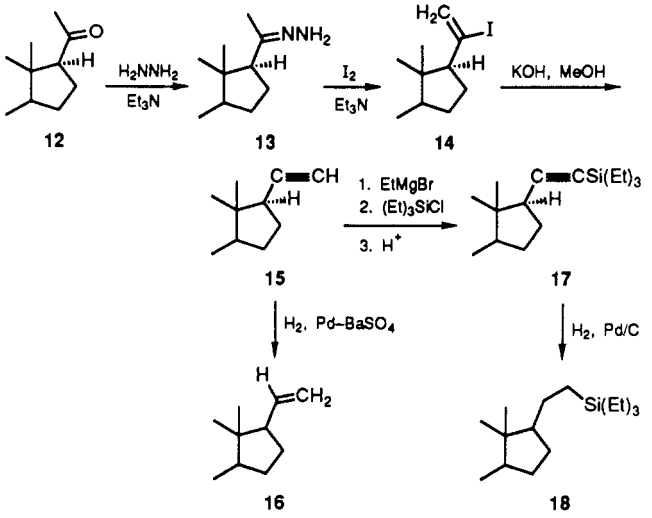
The 17β-nitrile **9b** was prepared from estrone in four steps, as shown in Scheme III. Upon treatment of estrone with potassium cyanide in acetic acid, an addition ensued to give a 17-cyanohydrin, which was subsequently dehydrated to an α,β-unsaturated nitrile **9a**. The acetate of **9a** was hydrolyzed prior to a stereoselective hydrogenation to target 17β-nitrile **9b**.

Several heteroimino analogues were prepared to determine the effect of a stable nitrogen moiety with double-bond character at the 17-position on biological activity, especially for comparison with the 17-methylene analogue **7b**. These analogues were synthesized by treatment of estrone with the appropriate heteroamine hydrochloride in pyridine to afford the methoxime **10a**,[13] oxime **10b**,[13b] and (2-pyridyl)hydrazone **10c**, respectively (Scheme IV). The hydrazone derivative **10d** was prepared from estrone by using hydrazine hydrate in triethylamine and ethanol.

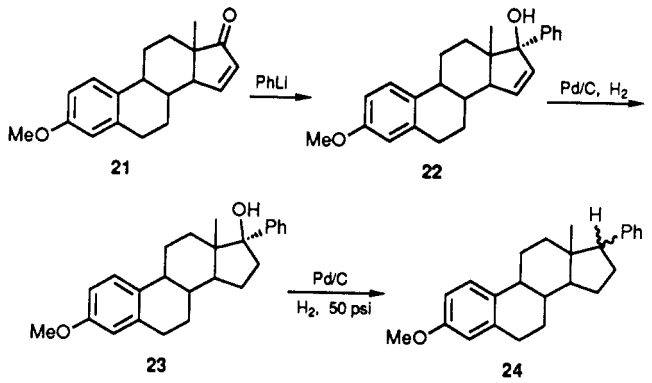
The sulfur isostere **11** of estrone was prepared from estrone 3-acetate by the procedure of Dodson[14] using benzyl mercaptan and *p*-toluenesulfonic acid in acetic acid (Scheme V). Subsequent reduction of the resultant dithioketal with sodium and ammonia afforded thioketone **11**.

The 17β-acetyl compounds served as versatile intermediates for the preparation of several of the target 17-desoxy steroids. The synthetic sequence used by Oliveto and co-workers[8a] in preparing 17β-alkylestranes **3–5** served as protocol for the overall transformation of 17β-acetyl compounds to 17β-alkynyl compounds (Scheme VI). In accordance with this approach, the 17β-acetyl compound **12** was converted to the corresponding hydrazone **13**, which

Scheme VI



Scheme VII

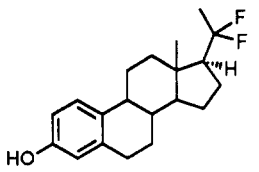


was reacted with iodine under conditions originally described by Barton et al.[15] to give the vinyl iodide **14**. The subsequent exposure of iodide **14** to base completed the preparation of target 17β-ethynyl derivative **15**, which in turn served as an intermediate to other target analogues. The 17β-ethynyl moiety was either reduced, as in **15** or **16**, to provide less unsaturation in the 17β-alkyl group or, alternatively, elaborated via alkylation of the corresponding acetylide anion (from treatment with Grignard reagent) as in **15** to **17**. The incorporation of silicon was forecast by earlier success in our research program with silicon-containing steroids,[16–18] and accordingly, the acetylide **17** was hydrogenated to afford 17β-[2-(triethylsilyl)ethyl] steroid **18**.

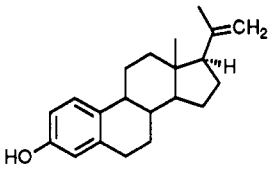
The 17β-acetyl steroid **12** was also used as an intermediate to the 17β-(1,1-difluoroethyl) derivative **19**. The reaction of **12** with the fluorinating agent piperidinosulfur trifluoride[19] and subsequent saponification gave **19**. The 17β-acetyl intermediate **12** was also the precursor for the carbon isostere **20** via a straightforward Wittig reaction.

The 17-desoxy-17-phenylestra-1,3,5(10)-trien-3-ol **24** was prepared from the Δ^{15}-estrone 3-methyl ether (**21**), as shown in Scheme VII. The adduct **23** was not directly

(12) Benn, W. R. *J. Org. Chem.* **1968**, *33*, 3113.
(13) (a) Karkkainen, J.; Ohisalo, J. J.; Ruranen, J.; Luukkainen, T. *Contraception* **1975**, *12*, 505. (b) Wheeler, O. H.; Reyes-Zamora, C. *Can. J. Chem.* **1969**, *47*, 160.
(14) Dodson, R. M.; Sollman, P. B. U.S. Patent 2840577, 1958.
(15) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.
(16) Peters, R. H.; Crowe, D. F.; Tanabe, M.; Avery, M. A.; Chong, W. K. M. *J. Med. Chem.* **1987**, *30*, 646.
(17) Peters, R. H.; Crowe, D. F.; Tanabe, M.; Avery, M. A.; Chong, W. K. M. *J. Med. Chem.* **1988**, *31*, 572.
(18) Crowe, D. F.; Peters, R. H.; Tanabe, M.; Detre, G. U.S. Patent 3946052, 1976.
(19) von Halasz, S. P.; Glemser, O. *Chem. Ber.* **1971**, *104*, 1247.



19



20

available from the 1,2 addition of phenylmagnesium halide or phenyllithium and the corresponding saturated ketone of **21**. Instead, the α,β-unsaturated ketone **21** underwent 1,2 addition to provide allyl alcohol **22**, which was then hydrogenated to the alcohol **23**. The hydroxyl of **23** was removed via catalytic hydrogenolysis at elevated pressure to give target 17-phenylestrane **24**, which was one stereoisomer by TLC and NMR, but without additional data the absolute configuration at C17 remained unassigned.

Nuclear Modifications. On the basis of our biological finding that significant separation of estrogenic from antifertility activity can be attained in the C17-desoxy C17-ethyl side-chain series, we undertook structural modification of the steroid nucleus to further reduce estrogenicity and increase antifertility potency. Our previous structure–activity studies in the EE series have shown that the presence of 7α- and 11β-hydroxy groups or a 7α-methyl group appears to be very effective for reducing estrogenic activity without substantially affecting antifertility activity (see Table II). Therefore, we synthesized the 7α-hydroxyy-17β-ethyl analogue **27a**, the 7α-methyl-17β-ethyl analogue **27b**, and the 11β-hydroxy-17β-ethyl analogue **30** from 7α-hydroxyestrone,[20] 7α-methylestrone, and 11β-hydroxyestrone,[21] respectively, via the corresponding ethylidene intermediates **26** and **29**, as outlined in Scheme VIII.

11β-Methoxy-19-norpregna-1,3,5(10)-trien-3-ol (**32**) was prepared from the 17-ethyl diol **30**. The resultant alkoxide from the C11 alcohol **30** and sodium hydride was alkylated with methyl iodide to give the diether **31**. The aromatic methoxy of **31** was selectively cleaved with lithium diphenyl phosphide[22] to afford the 17β-alkyl target **32**. Another C11 functionality was available from the 11-ketone **33** (Scheme IX). Addition of methyl magnesium bromide to the C11 ketone **33** yielded the 11β-hydroxy-11α-methyl steroid **34** in good yield, with the C11 stereochemistry being assigned by analogy to previous studies.[23] Alternatively, the 11-ketone **33** was subjected to a Peterson methylenation[24] sequence to initially afford adduct **35**, which upon treatment with acid or base gave the 11-*exo*-methylene **36**.

Biological Results and Discussions

Biological studies conducted at the EG&G Mason Research Institute under contract to the National Institute of Child Health and Human Development with rats indicate that our 17-alkyl-17-desoxyestratrienes may be useful as potential postcoital antifertility agents with greatly reduced estrogenicity. The various synthetic steroids and their observed biological activities are summarized in Tables II and III. The overall data from these tables illustrate that the absence of a C17 oxygen in 3-hydroxyestratrienes results in a significant reduction to low levels of estrogenicity, but with retention of potent postcoital antifertility activity. Some noteworthy relationships between structure and activity were found and deserve further mention here.

Low levels of estrogenicity were generally achieved for the 17-desoxyestratrienes **7a–h** and **8a–i**, but whereas most of the C17 alkylidenes **7a–h** had discouragingly low levels of antifertility activity relative to EE, in some cases (highlighted below) the corresponding saturated 17-alkylestratrienes **8a–i** compared favorably with EE: for example, both [17(20)*Z*]-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol (**7b**) and 19-norpregna-1,3,5(10)-trien-3-ol (**8b**) were 1% as estrogenic as EE, but the former (**7b**) was 10% as effective as an antifertility agent whereas the latter (**8b**) attained 66% of the effectiveness of EE.

The impact of the configuration at C17 on antifertility was examined. The C17 diastereomeric mix of 17α,β-ethylpregna-1,3,5(10)-trien-3-ol was effective in rats at a dose of 1000 μg/kg/day (500 μg/kg/day prevented pregnancy in four out of five rats), in contrast to the epimerically pure 17β-ethyl steroid **8b**, which required only 250 μg/kg/day for complete contraceptive efficacy. On the basis of this result, we felt secure in routinely examining only the more readily prepared 17β-alkyl stereoisomer, since it appears to be principally responsible for antifertility activity.

Among the most notable 17-desoxy analogues with substituted steroidal nuclei were the C11 functionalized analogues 17β-ethyl-11β-hydroxy **30**, 17β-ethyl-11β-methoxy **32**, and 17β-ethyl-11-*exo*-methylene **36**. Compound **30** had the largest separation ratio of antifertility to estrogenic activity in rats (A/E = 660) and low estrogenicity in rhesus monkeys. Although it was subsequently found to be ineffective as an antifertility agent in baboons,[25] we will avoid addressing the complicated and controversial issue of extending results between animal species; however, we still feel that the rat and rhesus monkey animal models may be adequate in this case for suggesting parallel behavior in human physiology. The 17β-ethyl-11β-methoxy analogue **32** was a potent oral antifertility agent in rats. This analogue was 20 times (10 μg/kg/day dosage level) more effective than EE in preventing pregnancy, with only 37% of the estrogenicity. Interestingly, the presence of a C11 oxygen was more effective, as observed on comparison to the 11-*exo*-methylene analogue **36**, which had twice the estrogenicity of **32**. Substitution of a methyl group at the 7α-position increases postcoital antifertility activity (2 × EE) while reducing estrogenic activity (15% of EE) for a separation ratio of 14.

For a basis of comparison with our synthetic 11-alkoxy-17-desoxy analogues, we surveyed the known 11-alkoxy EE analogues. For the 17α-ethynyl-17β-hydroxy-11β-methoxy derivative moxestrol (**37**), a patent[26] reported high oral estrogenic potency (20 × EE), which was later confirmed by the NICHD (26 × EE). We felt that this warranted further examination of moxestrol as an antifertility agent and found that it was 10 times more potent than EE and yet only half as potent as 17-desoxy **32**. The initial results with moxestrol were encouraging enough to induce the currently ongoing study of its antifertility activity in

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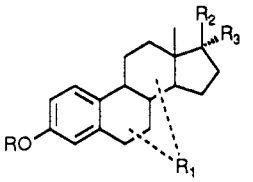
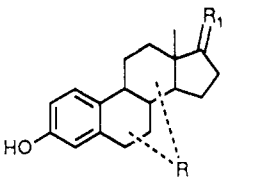
Table II. Oral Estrogenic (Uterotropic) and Antifertility Potencies of 17β-Desoxy Analogues and Other Selected Compounds Relative to Ethynylestradiol in Rats



compd	R	R_1	R_2	R_3	estrogenic potency (*E*)	antifertility potency[a] (*A*)	*A*/*E*	mp, °C	% yield[b]	anal.
EE (**1b**)	H	H	OH	C≡CH	100	100				
estradiol	H	H	OH	H	27	10	0.4			
	H	H	OH	$C{\equiv}CSi(Et)_3$	37	600	16.0			
	H	11β-OH	OH	C≡CH	120	200	1.7			
	H	7α-OH	OH	C≡CH	0.3	66	220.0			
	H	11β-OMe	OH	C≡CH	2000–2641	1000	0.4			
8a	H	H	Me	H	0.3	20	67.0	133–134	70	C, H
8b	H	H	Et	H	1.0	66	66.0	106–108	73	C, H
8c	H	H	Pr	H	0.8	20	25.0	130	79	C, H
8d	H	H	Bu	H	0.4	<10		99–100	76	HRMS
8e	H	H	CH_2OH	H	0.03	≪110		169–171	6	HRMS
8i	H	18-CH_3	Et	H	0.16	<40		115–117	65	C, H
9a	H	Δ^{15}	C≡N	H	<0.1	<4		237–241	38	HRMS
9b	H	H	C≡N	H	0.05	<10		235–239	89	HRMS/C, H
12	H	H	Ac	H	0.01	≪4		240–242		
15	H	H	C≡CH	H	0.07	≪10		149–152	59	HRMS
16	H	H	$CH{=}CH_2$	H	0.26	10		117–118	86	HRMS
17	H	H	$C{\equiv}CSi(Et)_3$	H	0.04	≪4		137–138	53	HRMS
18	H	H	$CH_2CH_2Si(Et)_3$	H	0.27	10	37	64–66	92	HRMS
19	H	H	CF_2CH_3	H	0.09	<20			77	HRMS
20	H	H	$C(CH_3){=}CH_2$	H	0.08	≪10		139	55	HRMS
22	CH_3	Δ^{15}	OH	Ph	0.14	<10		140–141	80	C, H
23	CH_3	H	OH	Ph	0.69	10	14	151–152	70	C, H
24	CH_3	H	Ph	H	<0.1	<4		140–141	57	C, H
27a	H	7α-OH	Et	H	0.04	≪10		215–217	53	C, H
27b	H	7α-Me	Et	H	15	<200		132–133	87	HRMS
30	H	11β-OH	Et	H	0.03	20	660.0	184–185	97	HRMS
32	H	11β-OMe	Et	H	37	>2000	54	229–230	38	C, H
33	H	11-oxo	Et	H		≫1000		202–204	68	C, H
34	H	11β-OH 11α-CH_3	Et	H	0.05	<20		78–79	54	HRMS
36	H	11-$=CH_2$	Et	H	64	400	6.2	85–88	86	C, H

[a] Minimum protective doses for prevention of pregnancy: 200 μg of EE. [b] Yields were not optimized.

Table III. Oral Estrogenic (Uterotropic) and Antifertility Potencies of 17-Alkylidene and Other Analogues Relative to Ethynylestradiol in Rats



compd	R	R_1	estrogenic potency (*E*)	antifertility potency[a] (*A*)	*A*/*E*	mp, °C	% yield[b]	anal.
EE	H	β-OH, α-C≡CH	100	100				
estrone	H	O	12	10	0.8			
7a	H	CH_2	0.5	40	80	116–118	60	C, H
7b	H	$CHCH_3$	0.3	10	33	134–136	45	
7c	H	CHC_2H_5	0.4	<20		140–141	54	C, H
7d	H	CHC_3H_7	0.2	<20		99–100	51	C, H
7f	H	CD_2	0.65	67	103	129–131	32	HRMS
7g	H	CHCHO	0.05	10	200	240–245	73	
7h	Δ^6	CH_2	0.04	<5	125	98–99	52	C, H/HRMS
10a	H	NOMe	0.04	4	>100	250–251	77	
10b	H	NOH	0.28	4	14	240–241	70	C, H, N
10c	H	NNH(2-pyr)	0.1	<4		270	42	C, H, N
10d	H	NNH_2	1.6	<10		245–249	20	C, H, N
11	H	S	2.4			210–212	36	
26c	7α-OH	CH_2	0.1	<20		222–224	23	HRMS
29a	11β-OH	CH_2	0.02	10	500	174–175	84	C, H
29b	11β-OH	$CHCH_3$	0.04	≪7		208–210	85	C, H

[a] Minimum protective doses for prevention of pregnancy: 200 μg of EE. [b] Yields were not optimized.

Scheme VIII

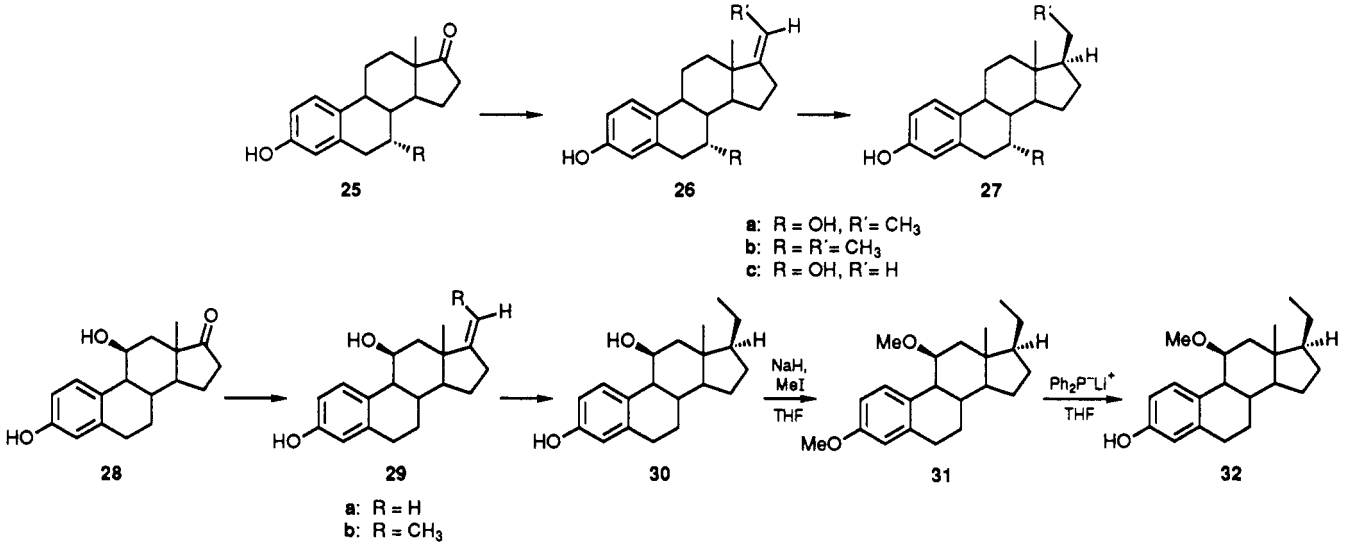
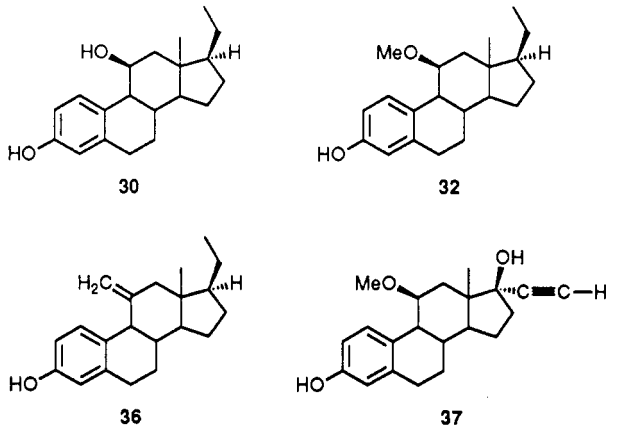


Table IV. Relative Potency of Various Estrogenic Compounds

compound	uterotropic effect in immature rat		antifertility activity in rat	uterotropic effect in mature rat	estrogenic effect in rhesus monkey[a]
EE	100[b]	100[c]	100[d]	100	100[b]
7α-hydroxy-EE	0.1		66	10[e]	100
11β-hydroxy-EE	5.0	110–150	100	19[e]	500
17β-ethyl (**8b**)	1.0		66	11[f]	
11β-hydroxy-17β-ethyl (**30**)	0.04		20	2[f]	≪8

[a] Estrogen withdrawal bleeding. [b] Vehicle, sesame oil. [c] Vehicle, 5% benzyl alcohol–olive oil. [d] 200 μg/kg/day for EE in the rat. Vehicle, sesame oil. [e] At the contraceptive dose; vehicle, sesame oil; relative to EE at 32 μg/kg/day. [f] At the contraceptive dose; vehicle, sesame oil; relative to EE at 64 μg/kg/day.

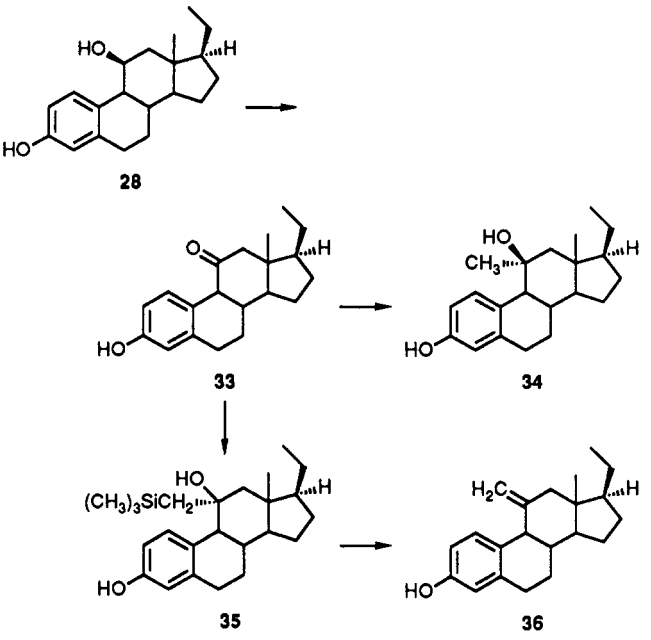
baboons. Similar studies with **32** are now being contemplated.



The foregoing results clearly show that the nature of substitution at C11 of the estratriene nucleus profoundly affects oral antifertility and estrogenic potency. These studies also reinforce the theme that has emerged; that is, significant separations of antifertility activity from estrogenic activity can be achieved, at least in the rat.

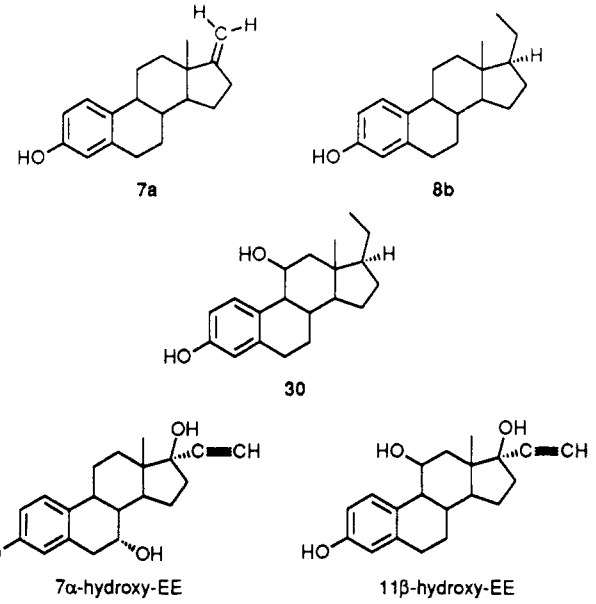
With the 17-desoxy ethyl derivative **30** we have achieved a 660-fold separation of postcoital antifertility activity from estrogenic activity. To our knowledge, this is the largest separation ratio observed to date with any structure. The low estrogenicity is particularly surprising because **30** retains the 3-hydroxyestra-1,3,5(10)-triene structural moiety common to naturally occurring estrogens. This novel finding emphasizes the lack of information about and understanding of the structural features in an estratriene derivative that contribute to the separation of postcoital antifertility activity from estrogenic activity.

Scheme IX



Our findings have established that the selected C17-desoxy analogues **7a**, **8b**, and **30** and the nuclear EE substituted analogues 7α-hydroxy-EE and 11β-hydroxy-EE show good postcoital antifertility characteristics (see Table IV) despite low uterotropic receptor-binding affinities (Table V). This suggests that strong binding to the uterine cytosol receptor may not be the only important criteria necessary for antifertility activity. Therefore, our group of analogues described herein is hopefully only a partial portent of future additional structural modification

Table V. Estrogen Binding Studies for Several Species for Compounds **7a**, **8b**, **30**, 7α-Hydroxy-EE, and 11β-Hydroxy-EE



compound	EC_{50}, μg/mL[a] immature rat	mature rat	immature rabbit	squirrel monkey
estradiol	0.25	0.5	0.5	0.5–0.7
EE	≪2.5 (ca. 0.25)	0.5	0.4	1.0
7a		0.8	1.5	
8b	20	8.0	11.0	60
30	5.6			22
7α-hydroxy-EE	18.0	6.0	36.0	52
11β-hydroxy-EE	5.2	16	8	150

[a] Effective concentration to displace 50% of the bound [^{3}H]estradiol.

of estrogenic compounds, with the promise of even greater separations of estrogenic and antifertility activities.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, Perkin-Elmer 137; NMR, Varian T-60, XL-100, or XL-400) were recorded for all compounds in $CDCl_3$ unless otherwise stated. Either mass spectral or analytical data were determined for all new compounds (see Table II). Mass spectral data were obtained on a CEC 21-110B high-resolution, double-focusing spectrometer. Microanalytical data were determined by Galbraith Labs (Knoxville, TN) for C and H and agreed to within ±0.4% of the calculated values. Woelm silica gel, activity III/30 nm, containing 0.5% fluorescent indicator, was used for all dry-column chromatography[27] with 5% EtOAc in $CHCl_3$ as the developing solvent unless otherwise stated. All other chromatographic purifications were conducted by using 90–200 mesh silica gel on gravity columns with solvents as indicated. Silica gel GF thick-layer plates (20 cm × 20 cm), 1000 μm thick, were used. Tetrahydrofuran (THF) was distilled from methylmagnesium bromide and stored over 4-Å molecular sieves.

General Method for the Preparation of C17 Olefins: 17-Methyleneestra-1,3,5(10)-trien-3-ol (7a). According to the procedure previously described,[9] 4.77 g of estrone gave after chromatography on 400 g of dry-column silica gel 2.8 g of **7a** (60% yield). Recrystallization from MeOH afforded an analytical sample: mp 116–118 °C; NMR δ 4.70 (m, 2 H, $=CH_2$), 0.84 (s, 3 H, 18-CH_3).

[17(20)*Z*]-19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol (7b). The $\Delta^{17(20)}$-olefin **7b** was prepared in the same manner as **7a** except that 37.0 g of ethyltriphenylphosphonium bromide was used. Recrystallization from MeOH afforded 2.1 g of **7b** (45% yield): mp 134–136 °C (lit.[9] 137–139 °C); NMR δ 5.08 (m, 1 H, $=CHCH_3$) 1.68 (m, 3 H, $=CHCH_3$), 0.92 (s, 3 H, 18-CH_3).

[17(20)*Z*]-21-Methyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol (7c). The olefin **7c** was prepared in the same manner as **7a** except that 34.7 g of propyltriphenylphosphonium bromide was used. Recrystallization from MeOH afforded 2.7 g of **7c** (54% yield): mp 140 °C; NMR δ 5.08 (m, 1 H, $=CHCH_2CH_3$), 0.93 (s, 3 H, 18-CH_3).

[17(20)*Z*]-21-Ethyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol (7d). The olefin **7d** was prepared essentially as previously described for **7a** except that 35.9 g of butyltriphenylphosphonium bromide was used. Recrystallization from MeOH afforded 2.7 g of **7d** (51% yield): mp 99 °C; NMR δ 5.08 [m, 1 H, $=CH(CH_2)_2CH_3$], 0.93 (s, 3 H, 18-CH_3).

17-(Dideuteriomethylene)estra-1,3,5(10)-trien-3-ol (7f). A solution of 25.0 g of trideuteriomethyl bromide and 75.0 g of triphenylphosphine in 100 mL of dry benzene was stirred in a stainless steel bomb for 18 h. After cooling, the resultant mass was broken up and dried on a filter funnel. The isolated (trideuteriomethyl)triphenylphosphonium bromide salt (4.10 g) was washed with ether and dried under vacuum for 18 h. To a suspension of 6.33 g of (trideuteriomethyl)triphenylphosphonium bromide in 30 mL of dry THF was added 116 mL of 2.02 M phenyllithium in THF. The reaction was stirred at 65 °C for 2 h and then cooled to room temperature. To the reaction mixture was added 0.94 g of estrone, and stirring was continued for 18 h at 65 °C. After cooling to room temperature, the reaction was poured into water and extracted with ether. The ether was washed with water, dried over Na_2SO_4, and evaporated at reduced pressure to yield 2.16 g of crude olefin **7f**. The crude product was purified via dry-column chromatography with 400 g of silica gel GF. The column was developed with 5% EtOAc in $CHCl_3$. The desired fraction was cut and extracted with EtOAc to yield 0.30 g of **7f** (32% yield). Recrystallization from MeOH afforded pure **7f**, mp 129–131 °C.

[17(20)*E*]-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-al (7g). As previously described,[12] 3.0 g of 3,21-diacetoxy-19-norpregna-1,3,5(10),17(20),20-pentaene was saponified to afford 1.8 g (73%) of aldehyde **7g**. An analytical sample was obtained upon recrystallization from $CHCl_3$/MeOH: mp 240–245 °C (lit.[12] 243–248 °C); NMR (pyridine-d_5) δ 10.07 (d, 1 H, J = 8 Hz, -CHO), 5.94 (m, 1 H, 20-CH), 0.78 (s, 3 H, 18-CH_3).

17-Methyleneestra-1,3,5(10),6-tetraen-3-ol (7h). To a solution of 0.500 g of 6-dehydroestrone in 30 mL of DMSO was added the resultant mixture from 0.54 g of 50% NaH in 8.4 mL of DMSO and 4.11 g of methyltriphenylphosphonium bromide in 16.8 mL of DMSO. After 18 h at 60 °C, the reaction was poured into ice water and extracted with ether. The combined ethereal layers were washed with water and brine, dried over Na_2SO_4, and evaporated to give 1.6 g of crude solid, which was purified via column chromatography with SiO_2 and 10% EtOAc/$CHCl_3$. Subsequent recrystallization from CH_2Cl_2/hexane provided 0.28 g of **7h** (52% yield): mp 98–99 °C; NMR δ 6.41 (m, 1 H, 7-CH), 6.04 (d, 1 H, J = 10 Hz, 6-CH), 4.68 (m, 1 H, 17-$=CH_2$), 0.92 (s, 3 H, 18-CH_3).

General Method for the Preparation of C17 Alkyls: 17-Methylestra-1,3,5(10)-trien-3-ol (8a). A suspension of 0.25 g of 17-methyleneestra-1,3,5(10)-trien-3-ol (**7a**), 10.0 mL of EtOAc, and 15 mg of 10% Pd/C was placed under a hydrogen atmosphere. After 18 h, the resulting suspension was filtered through Celite and the EtOAc was removed at reduced pressure. Recrystallization from hexane afforded 0.175 g of 17-methylestra-1,3,5(10)-trien-3-ol (**8a**) (70% yield): mp 133–134 °C; NMR δ 0.62 (s, 3 H, 18-CH_3). Compounds **8b–d** and **8i** were prepared in a similar manner to **8a**, starting from 0.500 g of **7b–d** and [17(20)*Z*]-18-methyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol, respectively. Analytical samples were furnished from hexane (**8b**) or MeOH (**8c**, **8d**, and **8i**). Yields and physical constants are reported in Table II. NMR of **8a**: δ 0.62 (s, 3 H, 18-CH_3).

17β-(Hydroxymethyl)estra-1,3,5(10)-trien-3-ol (8e). To a solution of 0.500 g of 17-methyleneestra-1,3,5(10)-trien-3-ol (**7a**) in 75 mL of dry THF was added 9.25 mL of 1 M B_2H_6 solution in THF. The reaction was stirred at room temperature for 18 h. To the reaction were added sequentially 10 mL of 10% aqueous NaOH (dropwise at first) and 10 mL of 30% H_2O_2. The resultant

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mixture was stirred for 2 h at room temperature, water was added, and the THF was evaporated. The aqueous phase was extracted with ether. The ether was washed with water, dried over Na_2SO_4, and evaporated at reduced pressure to afford 0.671 g of crude product, which was purified via thick-plate chromatography using benzene/25% ether. The resultant solid, 0.127 g, displayed in the NMR spectrum 18-CH_3 signals at δ 0.66 and 0.80 in a ratio of 4:1, which corresponded to a mixture of C17 epimers with the 17β-(hydroxymethyl) compound **8e** as the major isomer. Compound **8e** selectively accumulated upon repeated recrystallization from $CHCl_3$ to give 0.030 g of crystals: mp 169–171 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 3.68 (m, 2 H, $-CH_2OH$), 0.66 (s, 3 H, 18-CH_3).

17-Cyanoestra-1,3,5(10),16-tetraen-3-ol (9a). To a solution of 4.00 g of 3-acetoxy-17α-cyano-17β-hydroxyestra-1,3,5(10)-triene[12] in 40 mL of pyridine was added dropwise 8.0 mL of phosphorus oxytrichloride. The solution was refluxed for 2.0 h and then poured into ice and water and extracted with ether. The ethereal solution was washed with water, 4% HCl, and water, dried over $MgSO_4$ and evaporated under reduced pressure to afford 3.5 g of crude product, which was dissolved in 10% KOH/MeOH. The resultant solution was stirred for 18 h at room temperature and then poured into EtOAc and water. The organic layer was separated, and the reserved aqueous layer was further extracted with EtOAc. The organic extracts were combined, washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to give 1.9 g of crude product. Purification via thick-plate chromatography with 5% ether in benzene afforded 1.24 g (38% overall yield) of pure nitrile **9a**: mp 237–241 °C; NMR δ 4.62 (s, 1 H, 16-=CH), 0.95 (s, 3 H, 18-CH_3).

17β-Cyanoestra-1,3,5(10)-trien-3-ol (9b). A solution of 0.100 g of tetraene **9a** in 10 mL of EtOAc with 10% Pd/C was stirred under H_2 atmosphere at room temperature for 2.5 h. The catalyst was filtered onto Celite and rinsed well with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated under reduced pressure to provide 0.089 g (89% yield) of triene **9b**. An analytical sample was obtained upon recrystallization from MeOH: mp 235–239 °C; NMR δ 0.96 (s, 3 H, 18-CH_3).

3-Hydroxyestra-1,3,5(10)-trien-17-one 17-Methoxime (10a). **10a** was prepared from estrone according to the procedure cited[13] to yield 1.7 g (77% yield) of crude **10a**. Recrystallization from CH_2Cl_2/MeOH afforded pure **10a**: mp 250–251 °C (lit.[13] 252–254 °C); NMR ($CDCl_3/CD_3OD$, 1:1) δ 3.56 (s, 3 H, $-OCH_3$), 0.76 (s, 3 H, 18-CH_3).

3-Hydroxyestra-1,3,5(10)-trien-17-one 17-Oxime (10b). Analogous to the above procedure, there was obtained 0.368 g (70% yield) of oxime **10b**. An analytical sample was prepared upon crystallization from MeOH: mp 238–240 °C dec (lit.[13b] 231–232 °C); NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.97 (s, 3 H, 18-CH_3).

3-Hydroxyestra-1,3,5(10)-trien-17-one 17-(2-Pyridinyl)-hydrazone (10c). By the above procedure, **10c** was prepared from 0.50 g of estrone and 0.5 g of 2-hydrazinopyridine dihydrochloride in 15 mL of pyridine. Recrystallization from MeOH afforded an analytical sample, 0.28 g (42% yield), of pure **10c**, mp 270 °C dec.

3-Hydroxyestra-1,3,5(10)-trien-17-one 17-Hydrazone (10d). A solution of 0.50 g of estrone, 20 mL of triethylamine, 35 mL of EtOH, and 7.5 mL of hydrazine hydrate was refluxed for 18 h. After cooling, the reaction was poured into water and the resulting precipitate was collected by filtration. The isolated white solid was washed with water and then dissolved in ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated at reduced pressure to yield 0.45 g of crude **10d**. Recrystallization from MeOH afforded 0.10 g (20% yield) of an analytical sample of **10d**, mp 245–249 °C.

3-Hydroxyestra-1,3,5(10)-triene-17-thione (11). According to conditions developed by Dodson and Sollman,[14] a solution of 1.83 g of estrone acetate, 1.53 mL of benzyl mercaptan, and 0.2 g of pTsOH in 10 mL of HOAc was stirred at room temperature for 54 h. The reaction mixture was poured into water, and the precipitate was collected by filtration. The solid was washed with water and dissolved in ether. The ether solution was washed with water and 10% aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated under reduced pressure to give 2.60 g of crude bis(benzylthio)ketal.

A solution of the dithioketal in 8.0 mL of ether was slowly added to a solution of 4.6 g of sodium in 76 mL of liquid ammonia at −80 °C. The reaction was stirred for 2 h while 65 mL of ether was added. The ammonia was allowed to evaporate, the ether was separated, and the remaining solids were dissolved with 3% HCl and ether. The ethereal solutions were combined, washed with 3% HCl and water, dried over Na_2SO_4, and evaporated under reduced pressure to give crude thione **11**. Purification by thick-plate chromatography using 25% ether/benzene and subsequent recrystallization from MeOH provided 0.59 g (36% yield) of pure **11**: mp 210–212 °C (lit.[14] 210–213 °C); NMR ($CDCl_3/CD_3OD$, 1:1) δ 0.96 (s, 3 H, 18-CH_3).

3-Hydroxy-19-norpregna-1,3,5(10)-trien-20-yne (15). A solution of 26.0 g of ketone **12**[8b] in 125 mL of triethylamine, 225 mL of EtOH, and 35 mL of 85% hydrazine hydrate was refluxed for 4 h. After cooling, the solution was poured into water, and the precipitate was collected by filtration. The white solid was washed with water and dried azeotropically with benzene under reduced pressure to yield 19.0 g of the 20-hydrazone of 3-hydroxy-19-norpregna-1,3,5(10)-trien-20-one (**13**), whose infrared spectrum was devoid of the starting material's carbonyl group. Compound **13** was then used without further purification in subsequent conversions.

To a solution of 2.6 g of the crude hydrazone **13** in 200 mL of dry THF and 85 mL of triethylamine was added dropwise a solution of 5.3 g of iodine dissolved in 45 mL of dry THF. At first the iodine color disappeared upon addition, but after 20 mL was added, a precipitate appeared. When the addition was complete, the color of iodine persisted. The reaction was stirred for an additional 1 h at room temperature and concentrated in vacuo. The resultant residue was dissolved in CH_2Cl_2 and washed with 3% HCl and 5% aqueous $Na_2S_2O_3$. The CH_2Cl_2 solution was filtered through 150 g of silica gel, and the filtrate was evaporated under reduced pressure to provide 1.8 g of pure 3-hydroxy-20-iodo-19-norpregna-1,3,5(10),20-tetraene (**14**), which was unstable and was used without further purification.

To a solution of 2.2 g of the vinyl iodide **14** in 100 mL of *tert*-butyl alcohol was added 9.0 g of potassium *tert*-butoxide. The suspension was refluxed for 18 h and then cooled. The reaction was poured into a water–ether mixture. The ether layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated under reduced pressure to yield a residue (1.1 g), which was purified with a dry column of 200 g of silica gel to yield 0.88 g (59% yield), which was recrystallized from CH_2Cl_2/hexane: mp 149–152 °C; NMR δ 2.13 (s, 1 H, ≡C—H), 0.83 (s, 3 H, 18-CH_3).

3-Hydroxy-19-norpregna-1,3,5(10),20-tetraene (16). A solution of 0.50 g of acetylene **15** in 50 mL of pyridine containing 0.125 g of 5% Pd/$BaSO_4$ was hydrogenated at room temperature and atmospheric pressure for 6 h. The suspension was filtered through Celite, and the filtrate was evaporated at reduced pressure. The resulting residue was dissolved in ether, and the ether solution was washed with 3% HCl and water, dried over Na_2SO_4, and evaporated at reduced pressure to yield 0.43 g (86% yield) of vinyl compound **16**. An analytical sample was obtained by sublimation at 95 °C and 0.005 mmHg: mp 117–118 °C; NMR ($CDCl_3$ with a drop of CD_3OD) δ 5.82 (bm, 1 H, =CH), 5.09 (bm, 1 H, =CH), 4.96 (m, 1 H, $-CH$=CH_2), 0.60 (s, 3 H, 18-CH_3).

21-(Triethylsilyl)-19-norpregna-1,3,5(10)-trien-20-yn-3-ol (17). To a solution of 1.12 g of acetylene **15** in 80 mL of dry THF was added 3.2 mL of 3.0 M ethylmagnesium bromide in THF. After the reaction was stirred at room temperature for 0.5 h and at 60 °C for 3 h and then cooled to room temperature, 1.75 mL of triethylchlorosilane was added. The reaction was stirred at room temperature for 2 h and at 60 °C for 18 h, cooled, and poured onto ether and saturated aqueous NH_4Cl. The ether was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated at reduced pressure to give a solid, which was dissolved in methanolic HCl and stirred at room temperature for 4 h. The solution was diluted with ether, washed with water, dried over Na_2SO_4, and evaporated at reduced pressure to yield 1.9 g of crude **17**. Purification by thick-plate chromatography with silica gel GF and benzene/ether (4:1) as the developing solvent gave 0.820 g (53% yield) of silane **17**. An analytical sample was obtained by recrystallization from hexane: mp 137–138 °C; NMR δ 0.82 (s, 3 H, 18-CH_3).

21-(Triethylsilyl)-19-norpregna-1,3,5(10)-trien-3-ol (18). To a solution of 0.14 g of alkyne **17** in 15 mL of 95% EtOH was added 0.03 g of 10% Pd/C. The suspension was hydrogenated on a Parr shaker for 20 h at room temperature and 35–40 psi. The reaction was filtered through Celite, and the EtOH was evaporated at reduced pressure. The remaining water was azeotropically removed with benzene to afford 0.13 g (92% yield) of 17-alkyl compound **18**. An analytical sample was obtained by sublimation at 110 °C/0.025 mmHg to afford a white solid: mp 64–66 °C; NMR δ 0.98 (s, 3 H, 18-CH_3).

Piperidinosulfur Trifluoride. Sulfur tetrafluoride gas (8.5 g) was bubbled through a gas dispersion tube into dry ether (95 mL) at 0 °C. The flask was then equipped with a condenser and a dropping funnel and cooled to −78 °C. Then a solution of *N*-(trimethylsilyl)piperidine (10.0 g) in dry ether (30 mL) was added dropwise over 25 min. The resultant mixture was allowed to slowly warm to ambient temperature and then stirred overnight. The reaction mixture was partially concentrated under reduced pressure and distilled, bp 46–49 °C at 1.4 mmHg (lit.[19] 75–77 °C at 12 mmHg), to afford 9.0 g (82% yield) of the desired reagent.

20,20-Difluoro-19-norpregna-1,3,5(10)-trien-3-ol (19). To a solution of 1.10 g of 3-acetoxy-19-norpregna-1,3,5(10)-trien-20-one in 50 mL of freshly distilled diglyme was added 4.7 mL of piperidinosulfur trifluoride. The reaction was stirred at 85 °C for 18 h, cooled, and slowly poured into water. The mixture was extracted with ether. The ethereal layers were combined, washed with water, dried over Na_2SO_4, and evaporated at reduced pressure to yield 1.35 g of 3-acetoxy-20,20-difluoro-19-norpregna-1,3,5-(10)-triene as an amorphous solid; NMR δ 2.30 (s, 3 H, $-COCH_3$), 1.60 (t, 3 H, J = 19 Hz, $-CF_2CH_3$), 0.89 (t, 3 H, J = 2.0 Hz, 18-CH_3).

A solution of the solid acetate in 50 mL of 10% KOH in MeOH was refluxed for 3 h, the MeOH was removed under reduced pressure, and the resultant solid was partitioned between ether and water. The ethereal layer was separated, washed with additional water, dried over Na_2SO_4, and evaporated at reduced pressure to yield 0.80 g (77% yield) of **19** as an amorphous solid, which was purified via thick-plate chromatography over silica gel. After elution with 10% ether in benzene, difluoride **19** was isolated as a glassy foam. An NMR analysis revealed a strong agreement of observed J_{H-F} coupling values with literature:[28] NMR δ 1.60 (t, 3 H, J = 19 Hz, $-CF_2CH_3$), 0.86 (t, 3 H, J = 2.0 Hz, 18-CH_3).

20-Methylene-19-norpregna-1,3,5(10)-trien-3-ol (20). According to conditions described for the preparation of **7a** using 0.6 g of 3-hydroxy-19-norpregna-1,3,5(10)-trien-20-one (**12**) gave 1.09 g of crude **20**. The sample was purified by thick-plate chromatography with silica gel GF plates and benzene/ether (4:1) as the developing solvent. Recrystallization from CH_2Cl_2/hexane afforded 0.321 g (55% yield) of pure methylene **20**: mp 139 °C; NMR ($CDCl_3$ with a drop of CD_3OD) δ 4.85 (bd, 2 H, J = 8.0 Hz, 20-=CH_2), 1.76 (s, 3 H, 20-CH_3), 0.58 (s, 3 H, 18-CH_3).

3-Methoxy-17α-phenylestra-1,3,5(10),15-tetraen-17β-ol (22). To a solution of 1.19 g of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**21**)[29] in 150 mL of dry THF was added 21.5 mL of 1.86 M phenyllithium in ether/benzene (30:70). After stirring 48 h under N_2 atmosphere, the resultant mixture was poured into water and extracted with EtOAc/ether (1:1). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield 3.4 g of crude adduct **22**, which was purified by column chromatography with SiO_2 and ether/benzene (1:1). Subsequent crystallization from hexane afforded 1.2 g (80% yield) of pure phenylcarbinol **22**: mp 140.5–141.0 °C; NMR δ 3.75 (s, 3 H, OCH_3), 1.13 (s, 3 H, 18-CH_3).

3-Methoxy-17α-phenylestra-1,3,5(10)-trien-17β-ol (23). A solution of 0.250 g of Δ^{15} compound **22** in 30 mL of EtOAc containing 0.2 g of 10% Pd/C was stirred under H_2 atmosphere at room temperature for 2 h and then filtered through Celite. The Celite was rinsed thoroughly with EtOAc, and the filtrate was concentrated at reduced pressure to give 0.27 g of crude **23** as a solid, which was recrystallized to provide 0.176 g (70% yield) of pure 17α-phenylestradiol **23**: mp 151–152 °C; NMR ($CDCl_3$/CD_3OD, 1:1) δ 3.69 (s, 3 H, OCH_3), 1.03 (s, 3 H, 18-CH_3).

3-Methoxy-17-phenylestra-1,3,5(10)-triene (24). A solution of 0.50 g of phenylcarbinol **23** in 100 mL of absolute EtOH containing 0.6 g of 10% Pd/C was shaken in a Parr apparatus with H_2 at 50 psi for 60 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure to give 0.27 g (57% yield) of 17-desoxy analogue **24**: mp 140–141 °C; NMR ($CDCl_3$/CD_3OD, 1:1) δ 3.70 (s, 3 H, OCH_3), 0.50 (s, 3 H, 18-CH_3).

[17(20)*Z*]-19-Norpregna-1,3,5(10),17(20)-tetraene-3,7α-diol (26a). The olefin **26a** was prepared from 7α-hydroxyestrone by the procedure described for compound **7a**. The pure product was obtained by dry-column chromatography on silica gel using benzene/ether (4:1), to afford crystals in 18% yield: mp 218–223 °C; NMR δ 5.10 (m, 1 H, =C*H*CH_3), 4.00 (m, 1 H, C*H*–OH), 1.78 (m, 3 H, =CHC*H*$_3$), 0.94 (s, 3 H, 18-CH_3).

[17(20)*Z*]-7α-Methyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol (26b). The olefin **26b** was prepared in 80% yield from 7α-methylestrone via the procedure described for **7a**. An analytical sample was obtained after column chromatography with silica gel and 5% ether in benzene and subsequent crystallization from pet ether: mp 119–121 °C; NMR δ 5.16 (m, 1 H, =C*H*CH_3), 1.71 (d, 3 H, J = 6 Hz, =CHC*H*$_3$), 0.91 (s, 3 H, 18-CH_3), 0.82 (d, 3 H, J = 7 Hz, 7α-CH_3).

17-Methyleneestra-1,3,5(10)-triene-3,7α-diol (26c). The olefin **26c** was prepared in 23% yield from 7α-hydroxyestrone via the procedure described for **7a**. An analytical sample was obtained after silica gel thick-plate chromatography using 25% EtOAc/$CHCl_3$ and recrystallization from MeOH: mp 222–224 °C; NMR ($CDCl_3$/CD_3OD, 1:1) δ 4.62 (m, 2 H, =CH_2), 4.15 (m, 1 H, C*H*–OH), 0.90 (s, 3 H, 18-CH_3).

19-Norpregna-1,3,5(10)-triene-3,7α-diol (27a). Reduction of 17-alkylidene **26a** by the procedure used for compound **8a** gave the 17β-ethyl analogue **27a** in 53% yield. An analytical sample was prepared by crystallization from MeOH: mp 215–217 °C; NMR (CD_3COCD_3/CD_3OD, 1:1) δ 4.10 (m, 1 H, 7-C*H*OH), 0.68 (s, 3 H, 18-CH_3).

7α-Methyl-19-norpregna-1,3,5(10)-trien-3-ol (27b). Reduction of **26b** by the procedure described for compound **8a** gave **27b** in 87% yield. An analytical sample, mp 132–133 °C, was prepared upon recrystallization from ether/petroleum ether; NMR δ 0.86 (d, J = 7 Hz, 7α-C*H*$_3$), 0.58 (s, 3 H, 18-CH_3).

17-Methyleneestra-1,3,5(10)-triene-3,11β-diol (29a). The olefin **29a** was prepared in 84% yield from 11β-hydroxyestrone via the procedure described for **7a**. An analytical sample was obtained after column chromatography with silica gel with 20% ether in benzene as eluant and subsequent recrystallization from CH_2Cl_2/hexane: mp 174–175 °C; NMR ($CDCl_3$/CD_3OD, 1:1) δ 4.74 (m, 1 H, 11-CH), 4.72 (m, 1 H, 20-=CH_2), 1.07 (s, 3 H, 18-CH_3).

[17(20)*Z*]-19-Norpregna-1,3,5(10),17(20)-tetraene-3,11β-diol (29b). The olefin **29b** was prepared from 11β-hydroxyestrone by the procedure described for compound **7a**. Column chromatography on silica gel and elution with 20% ether in benzene gave pure *Z* ethylidene **29b** in 85% yield. An analytical sample was prepared by crystallization from MeOH: mp 208–210 °C; NMR δ 5.15 (m, 1 H, 20-=CH), 4.80 (m, 1 H, 11-CH), 1.14 (s, 3 H, 18-CH_3).

19-Norpregna-1,3,5(10)-triene-3,11β-diol (30). Reduction of **29b** by the procedure used for compound **8a** gave 17β-ethyl analogue **30** in 97% yield. An analytical sample was prepared by crystallization from acetone: mp 184–185 °C; NMR ($CDCl_3$/CD_3OD, 1:1) δ 4.71 (m, 1 H, 11-CH), 0.82 (s, 3 H, 18-CH_3).

11β-Methoxy-19-norpregna-1,3,5(10)-trien-3-ol (32). To a suspension of sodium hydride (0.6 g of 50% in mineral oil, washed with hexane) in 25 mL of dry THF were successively added 0.75 g of 19-norpregna-1,3,5(10)-triene-3,11β-diol (**30**) and 3.5 mL of methyl iodide. The resultant mixture was heated at 40 °C for 3 h, cooled, then carefully poured into water, and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield 1.0 g of crude 3,11β-dimethoxy-19-norpregna-1,3,5(10)-triene (**31**), which was used without further purification; NMR δ 4.14 (m, 1 H, 11-CH), 3.74 (s, 3 H, $ArOCH_3$), 3.26 (s, 3 H, 11-OCH_3), 1.14 (s, 3 H, 18-CH_3).

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To a solution of 1.22 mL of diphenylphosphine in 30 mL of dry THF at 0 °C was added 10 mL of 1.4 M butyllithium in hexane. The solution was allowed to warm to room temperature, and a solution of 0.8 g of dimethyl ether **31** in 10 mL of dry THF was added. The solution was refluxed for 8.0 h, cooled, poured into 100 mL of 1 N aqueous HCl, and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 1.6 g of crude product. Purification with silica gel thick plates, development with 10% ether in benzene, and extraction into EtOAc afforded 0.300 g (38% yield from **30**) of the desired monomethyl ether **32**. Recrystallization from CH_2Cl_2/hexane gave an analytical sample: mp 229–230 °C; NMR ($CDCl_3/CD_3OD$, 1:1) δ 4.15 (m, 1 H, 11-CH), 3.28 (s, 3 H, $-OCH_3$), 0.79 (s, 3 H, 18-CH_3).

3-Hydroxy-19-norpregna-1,3,5(10)-trien-11-one (33). A solution of 0.700 g of 19-norpregna-1,3,5(10)-trien-3,11β-diol (**30**) in 25 mL of acetone at 0 °C was treated with Jones reagent until an orange color persisted. After stirring at 0 °C for 3 min, the mixture was poured into water and extracted with EtOAc. The organic phase was washed with water and brine and then dried over $MgSO_4$. The solvent was removed at reduced pressure to give 0.640 g of 11-ketone **33** as an amorphous solid, which crystallized from CH_2Cl_2/hexane to afford 0.300 g of analytically pure crystals, mp 202–204 °C. The mother liquor was purified by column chromatography with SiO_2 and 10% ether in benzene as eluant to afford 0.476 g of 11-ketone **33** (total yield of 68.0%); IR (Nujol) 5.86 μm (C=O).

11α-Methyl-19-norpregna-1,3,5(10)-triene-3,11β-diol (34). To a solution of 0.200 g of 3-hydroxy-19-norpregna-1,3,5(10)-trien-11-one (**33**) in 20 mL of dry THF at 0 °C was added 4.25 mmol of methyllithium. After being stirred under N_2 at 0 °C for 45 min, the mixture was poured into 1 N HCl and extracted with EtOAc. The organic phase was washed with water, saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield 0.200 g of crude product. Purification on SiO_2 thick plates using 10% ether/benzene gave 0.120 g (54% yield) of methylcarbinol **34**, which was recrystallized from CH_2Cl_2/hexane to afford crystals: mp 78–79 °C; NMR δ 1.62 (s, 3 H, 11α-CH_3), 0.82 (s, 3 H, 18-CH_3).

11-Methylene-19-norpregna-1,3,5(10)-trien-3-ol (36). A solution of 1.23 g of (chloromethyl)trimethylsilane in 15 mL of dry ether was added dropwise to a suspension of 0.36 g of magnesium turnings in 50 mL of dry ether at a rate that induced a steady reflux. The resultant Grignard solution was then treated with a solution of 0.3 g of 3-hydroxy-19-norpregna-1,3,5(10)-trien-11-one (**33**) in 25 mL of dry ether and refluxed for 5 h. The reaction was allowed to cool, then poured into water, and extracted with ether. The ethereal layers were washed with water and brine, dried over $MgSO_4$, and evaporated to give 0.5 g of crude product. Recrystallization from CH_2Cl_2/hexane afforded 0.114 g (30% yield) of desired adduct 11α-[(trimethylsilyl)methyl]-19-norpregna-1,3,5(10)-triene-3,11β-diol (**35**); NMR δ 7.60–6.50 (m, 3 H, Ar–H), 0.79 (s, 3 H, 18-CH_3), 0.05 [s, 9 H, $-Si(CH_3)_3$].

A solution of 0.3 g of crude 11α-[(trimethylsilyl)methyl]-19-norpregna-1,3,5(10)-triene-3,11β-diol (**35**) in 6 mL of acetone was treated with concentrated HCl (0.025 mL) and stirred under N_2 for 6 h at ambient temperature. The mixture was poured into water and extracted into ether. The ethereal layer was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated under reduced pressure to yield 0.300 g of crude product. Purification on silica gel thick plates after development with 10% ether in benzene afforded 0.200 g (86% yield) of the desired compound **36**: mp 85–88 °C; NMR δ 4.93 (br s, 2 H, 11–CH_2), 0.58 (s, 3 H, 18-CH_3).

Biological Methods. 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 per group. Rats were autopsied 24 h after the last treatment. The uteri were 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 according to standard methods.

Oral Postcoital 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 once daily for 7 consecutive days. A control group received vehicle only. There were 10 animals per group. Rats were sacrificed on or about day 8, and the uteri were examined for the presence of and condition of conceptuses. Results were compared with the regression line established for the standard.

Binding Procedure for Estrogen–Receptor Proteins in Rabbit, Rat, and Squirrel Monkey Uteri. Preparation of Uterine Cytosol. Uteri from the animals were chilled in ice immediately upon removal. After the fat was trimmed off, the uteri were minced and washed for 1 h in Tris-HCl buffer (0.01 M, pH 8.0, containing 0.001 M EDTA and 0.25 M sucrose) at 4 °C. The washed uterine tissue was then homogenized in $^2/_5$ (w/v) volume of the same Tris-HCl buffer. The homogenate was centrifuged at 12000*g* for 15 min, and the resulting supernatant was centrifuged again for 1 h at 270000*g*. Glycerol was added to the final supernatant to give a 45% solution. The prepared cytosol was kept frozen until time of use. The whole procedure was carried out at 4 °C. The protein content of each prepared cytosol is determined by biuret reagent. The following animals were used to prepare cytosol: New Zealand White female rabbits, 5–7 weeks old, weight approximately 2 kg each; immature Sprague-Dawley female rats, 4 weeks old, weight less than 180 g each; mature Sprague-Dawley female rats, 3–6 months old, weight 200–300 g each. The squirrel monkey used was a young female adult; it was sacrificed as a control in another experiment, but the uterus was removed for this estrogen-binding assay.

Binding Procedures.[30] For the binding assay, 100 μL of uterine cytosol was mixed with 0.4 mL of Tris-HCl buffer (described above) containing 0.028 ng (11 000 dpm) of [6,7-^{3}H]estradiol (New England Nuclear Corp., Boston, MA) and 1 μL of DMSO alone or 1 μL of DMSO plus competitors to be tested. The mixtures were incubated at 0–4 °C for 2 h; then the free [6,7-^{3}H]estradiol was separated from bound [6,7-^{3}H]estradiol by charcoal extraction. To the incubated mixture was added 0.5 mL of charcoal solution (300 mg of charcoal and 3 mg of dextran 40 in 50 mL of Tris-HCl buffer used for homogenizing the tissue). The samples were mixed gently and incubated at 4 °C for exactly 10 min. The mixtures then were centrifuged at 4000 rpm for 10 min in a refrigerated centrifuge. The supernatant containing the bound [6,7-^{3}H]estradiol was transferred quantitatively to a counting vial, and 10 mL of scintillation fluid (Scientisol) was added for counting. Counting time was adjusted to give a standard deviation of less than 10%. The counts obtained for samples with competitors relative to those without competitors were then calculated to give the percentage of competition.

Estrogen Withdrawal Bleeding: Rhesus Monkey Test.[31] Adult, female rhesus monkeys were purchased from accredited primate suppliers and housed under standard laboratory conditions. Commercial monkey chow was provided once in the morning and once in the afternoon. Fresh fruit was given at noon. Tap water was available ad libitum between 8:30 a.m. and 5:00 p.m.

Briefly, the procedure is as follows. After a quarantine period, the animals are ovariectomized and allowed to recover from surgery. Four or five animals are used per treatment group. Test substances are dissolved or suspended in recommended vehicles, and one to several dose levels of each test material are evaluated. The animals are treated once a day for a period of 10 days. Before, during, and after the treatment, vaginal swabs are taken daily to determine vaginal bleeding. Changes in the color and swelling of the sex skin are also evaluated every day. When vaginal bleeding is observed, the number of days between the last treatment and the first day of bleeding (latency), as well as the

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duration of bleeding, is recorded. For each dose level, the percent of animals showing bleeding is also calculated. The subsequent evaluation of the compounds depends on the number and form of the dosages. When one or two dose levels are employed, the purpose is to ascertain the estrogenic action of the compound in the monkey. When several dose levels in increasing amounts are tested, the minimum effective dose that will cause withdrawal bleeding in all animals (MED_{100}) can be determined. When several dose levels of two or more compounds are tested, the ratios between their MED_{100} could be used to estimate their relative potencies in this test.

Acknowledgment. This research was supported by Contract NO1-HD-5-2844 from the National Institute of Child Health and Human Development (NICHD), National Institutes of Health. Assays for estrogenic potency and antifertility activity were undertaken at EG&G Mason Research Institute under the direction of Drs. Rehan H. Naqvi and Marjorie C. Lindberg. We express our appreciation to Drs. Marvin Karten and Hyun K. Kim of the NICHD for valuable discussions and guidance.

Registry No. **1b**, 57-63-6; **7a**, 34111-53-0; **7b**, 4736-62-3; **7c**, 120574-27-8; **7d**, 120574-28-9; **7f**, 120476-04-2; **7g**, 16934-51-3; **7h**, 120476-05-3; **8a**, 59452-14-1; **8b**, 59077-04-2; **8c**, 59452-15-2; **8d**, 59452-16-3; **8e**, 65928-98-5; **8e** (17α isomer), 65929-00-2; **8i**, 120476-06-4; **9a**, 102177-29-7; **9b**, 84510-05-4; **10a**, 3342-64-1; **10b**, 5982-51-4; **10c**, 120476-07-5; **10d**, 7628-02-6; **11**, 60037-62-9; **12**, 1667-98-7; **13**, 120475-88-9; **14**, 120475-89-0; **15**, 99898-92-7; **16**, 97560-70-8; **17**, 120475-90-3; **18**, 120475-91-4; **19**, 120475-92-5; **20**, 73271-91-7; **21**, 17748-68-4; **22**, 120475-93-6; **23**, 95943-73-0; **24**, 120475-94-7; **25** (R = OH), 2487-49-2; **25** (R = Me), 10448-96-1; **26a**, 120475-95-8; **26b**, 120476-08-6; **26c**, 120476-09-7; **27a**, 120475-96-9; **27b**, 120476-10-0; **28**, 6803-21-0; **29a**, 120475-97-0; **29b**, 120476-11-1; **30**, 120475-98-1; **31**, 120475-99-2; **32**, 108887-34-9; **33**, 120476-00-8; **34**, 120476-01-9; **35**, 120476-02-0; **36**, 120476-03-1; PhLi, 591-51-5; estrone, 53-16-7; ethyltriphenylphosphonium bromide, 1530-32-1; propyltriphenylphosphonium bromide, 6228-47-3; butyltriphenylphosphonium bromide, 1779-51-7; trideuteriomethyl bromide, 1111-88-2; triphenylphosphine, 603-35-0; (trideuteriomethyl)triphenylphosphonium bromide salt, 1787-44-6; 3,21-diacetoxy-19-norpregna-1,3,5(10),17(20),20-pentaene, 120574-29-0; 6-dehydroestrone, 2208-12-0; methyltriphenylphosphonium bromide, 1779-49-3; (17(20)*Z*)-18-methyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol, 120476-13-3; 3-acetoxy-17α-cyano-17β-hydroxyestra-1,3,5(10)-triene, 120661-79-2; 3-acetoxy-17-cyano-17-chloroestra-1,3,5(10)-triene, 120496-23-3; 2-hydrazinopyridine dihydrochloride, 62437-99-4; estrone acetate, 901-93-9; benzyl mercaptan, 100-53-8; estrone acetate bis(benzylthio) ketal derivative, 117864-98-9; triethylchlorosilane, 994-30-9; piperidinosulfur trifluoride, 33946-34-8; sulfur tetrafluoride, 7783-60-0; *N*-(trimethylsilyl)piperidine, 3768-56-7; 3-acetoxy-19-norpregna-1,3,5(10)-trien-20-one, 67530-18-1; 3-acetoxy-20,20-difluoro-19-norpregna-1,3,5(10)-triene, 120476-12-2; methyllithium, 917-54-4; (chloromethyl)trimethylsilane, 2344-80-1; estradiol, 50-28-2; 21-(triethylsilyl)-19-norpregna-1,3,5(10)-trien-20-yne-3,17β-diol, 50866-95-0; 3,11β,17β-trihydroxy-19-norpregna-1,3,5-(10)-trien-20-yne, 3762-05-8; 3,7α,17β-trihydroxy-19-norpregna-1,3,5(10)-trien-20-yne, 59903-16-1; 11β-methoxy-19-norpregna-1,3,5(10)-trien-20-yne-3,17β-diol, 34816-55-2.

Renin Inhibitors. Synthesis of Transition-State Analogue Inhibitors Containing Phosphorus Acid Derivatives at the Scissile Bond[1]

Mark C. Allen,*[†] Walter Fuhrer,[‡] Brian Tuck,[§] Roy Wade,[†] and Jeanette M. Wood[‡]

Ciba-Geigy Pharmaceuticals Division, Horsham, West Sussex, RH12 4AB England, Research Department, Pharmaceuticals Division, Ciba-Geigy Limited, CH-4002 Basel, Switzerland, and Central Research Laboratories, Ciba-Geigy PLC, Trafford Park, Manchester, M17 1WT England. *Received October 11, 1988*

The synthesis of five amino phosphorus derivatives, **1a–e**, is described. The derivatives were incorporated into a series (18) of analogues of the 5–14 portion of angiotensinogen, in most cases at the scissile Leu–Val bond. The resultant compounds were tested in vitro for their ability to inhibit human plasma renin. Replacement of the scissile bond with the phosphinic analogue of Leu[10]-Val[11] (**1b**) gave the most potent inhibitors, having $IC_{50} = 7.5 \times 10^{-8}$ M for H-Pro-His-Pro-Phe-His-(**1b**)-Ile-His-Lys-OH and $IC_{50} = 1.0 \times 10^{-7}$ M for Z-Arg-Arg-Pro-Phe-His-(**1b**)-Ile-His-NH_2. The shorter phosphonic acid sequence Z-Pro-Phe-His-(**1d**) retained biological activity with an $IC_{50} = 6.4 \times 10^{-6}$ M.

Renin is an aspartyl protease whose specific substrate is angiotensinogen. Cleavage of this substrate produces angiotensin I, which is further cleaved by angiotensin converting enzyme (ACE) to produce the pressor octapeptide hormone angiotensin II.[2] Interruption of this cascade has been shown to provide a means of lowering blood pressure in many hypertensive patients.[3–6] The interruption has been achieved specifically with the development of inhibitors of ACE,[7] and attention has now turned to the initial step in the cascade, the inhibition of renin action. Many laboratories have reported potent angiotensinogen analogue inhibitors of renin,[8] and most of these analogues possess putative transition-state dipeptide type mimics at the site of cleavage.

We report the synthesis and biological activities of a series of transition-state analogue inhibitors of renin,

[†] Ciba-Geigy Pharmaceuticals, England.
[‡] Ciba-Geigy Pharmaceuticals Division, Switzerland.
[§] Central Research Laboratories, Ciba-Geigy PLC, England.

(1) Abbreviations follow the recommendations of the IUPAC–IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides: *Eur. J. Biochem.* **1984**, *158*, 9–31. Additional abbreviations: ACE, angiotensin converting enzyme; DCC, dicyclohexylcarbodiimide; DMF, dimethylformamide; Boc, *tert*-butoxycarbonyl; TFA, trifluoroacetic acid; TEA, triethylamine; HOBT, 1-hydroxybenzotriazole; Sta, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid; LPV or Leu^{P}-(CH_2)Val, 2(*R*,*S*)-[[hydroxy[1(*R*)-amino-3-methylbutyl]phosphinyl]methyl]-3-methylbutanoic acid; LPG or Leu$^{P}(CH_2)$Gly, 3-[hydroxy[1(*R*)-amino-3-methylbutyl]phosphinyl]propanoic acid; Sta^{P}, 2-[hydroxy[1(*R*)-amino-3-methylbutyl]phosphinyl]acetic acid; Leu^{P}onic, [1(*R*)-amino-3-methylbutyl]-phosphonic acid; Leu^{P}inic, [1(*R*)-amino-3-methylbutyl]phosphinic acid; Leu^{Red}Val, *N*-(2-amino-4-methylpentyl)-1-carboxy-2-methylpropylamine; Leu^{C}Val, 2-isopropyl-4-hydroxy-5-amino-7-methyloctanoic acid.

0022-2623/89/1832-1652$01.50/0