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Synthesis, Antifertility Activity, and Protein Binding Affinity of 7(8→11α)*abeo* Steroids

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A series of 7(8→11α)*abeo* steroids was synthesized by a modification of the previously described total synthesis of this class of compounds and evaluated for biological activity. In general, there was a marked reduction in the relative binding affinities of these compounds for the rabbit uterus estrogen and progestin receptor proteins. None of the compounds which were subjected to uterotropic, antiuterotropic, postcoital, progestational, antiprogestational, or antiandrogenic assays showed any significant activity.

We have previously described the synthesis of a number of 7(8→11α)*abeo*-estranes.[1] The D and L forms of this ring system differ from the natural estranes only by displacement of rings B and D, respectively; other stereochemical relationships are retained (Chart I). As such, 7(8→11α)*abeo* steroids provide an interesting probe of hydrophobic interactions in receptor binding. Here we report the synthesis, antifertility activity, and receptor binding affinity of new 7(8→11α)*abeo*-estranes and -pregnanes.

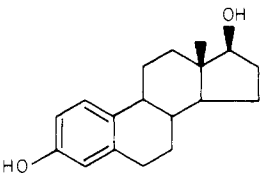
Chemistry. The synthesis of the 7(8→11α)*abeo*-estrane ring system is shown in Scheme I. Several improvements in the original procedure have been made. **2** was obtained in 78% yield, in one step rather than four, by treatment of the acid from **1** with dimethylamine hydrochloride and aqueous formaldehyde in Me_2SO.[2] Cyclization of **4** to **5** was better accomplished using anhydrous hydrogen fluoride in place of polyphosphoric acid.

Demethylation of **6** with boron tribromide in methylene chloride, followed by saponification of the 17-acetate function, gave the diol **7**. Conversion of **6** to the 17β-alcohol and oxidation with Jones reagent gave the ketone **8a**. Demethylation of the latter gave the free phenol **8b** (85%, GC), which was converted to the 17α-ethynyl derivative **9** by treatment with lithium acetylide–ethylenediamine in dioxane.

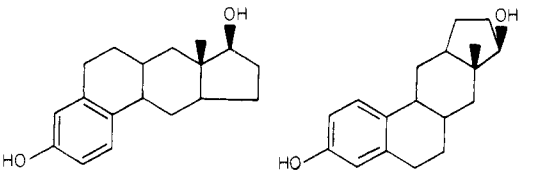
Birch reduction of **6** with lithium in ammonia and *tert*-butyl alcohol proceeded smoothly to give the 3-methoxy-$\Delta^{2,5(10)}$-diene **10** [^{1}H NMR δ 6.45 (1, t, J = 3 Hz, C-2)]. Hydrolysis of **10** with aqueous oxalic acid gave the $\Delta^{5(10)}$-3-ketone **11** (IR 1705 cm^{-1}) in 55% overall yield, while hydrolysis with dilute hydrochloric acid gave the Δ^4-3-ketone **12** (IR 1660 cm^{-1}) in 69% overall yield. Treatment of **10** with ethylene glycol and *p*-toluenesulfonic acid gave the ketal **13**. Oxidation of **13** with pyridine–chromium trioxide gave the ketone **14**. Ethynylation of **14** with freshly prepared[3] lithium acetylide in THF at −78 °C gave **15** which, upon hydrolysis with dilute hydrochloric acid, gave **16** in 42% overall yield from **6**.

The 7(8→11α)*abeo*-estrane skeleton was converted to the 19-nor-7(8→11α)*abeo*-pregnane skeleton by a standard two-step procedure.[4] The reaction of **8a** with excess ethylidenetriphenylphosphorane in Me_2SO[5] yielded **17** as a mixture of cis and trans isomers (71%). Hydroboration of **17** with borane in THF proceeded smoothly to give **18**. Birch reduction of **18** with lithium in ammonia and *tert*-butyl alcohol gave the 3-methoxy-$\Delta^{2,5(10)}$-diene **19**, which was hydrolyzed to the Δ^4-3-ketone **20** with dilute hydrochloric acid. Oxidation of **20** with chromium trioxide and sulfuric acid in DMF[5] gave the Δ^4-3,20-dione **21** in

Chart I. Stereochemical Relationships between D-Estradiol and D- and L-7(8→11α)*abeo*-Estra-1,3,5(10)-triene-3,17β-diol

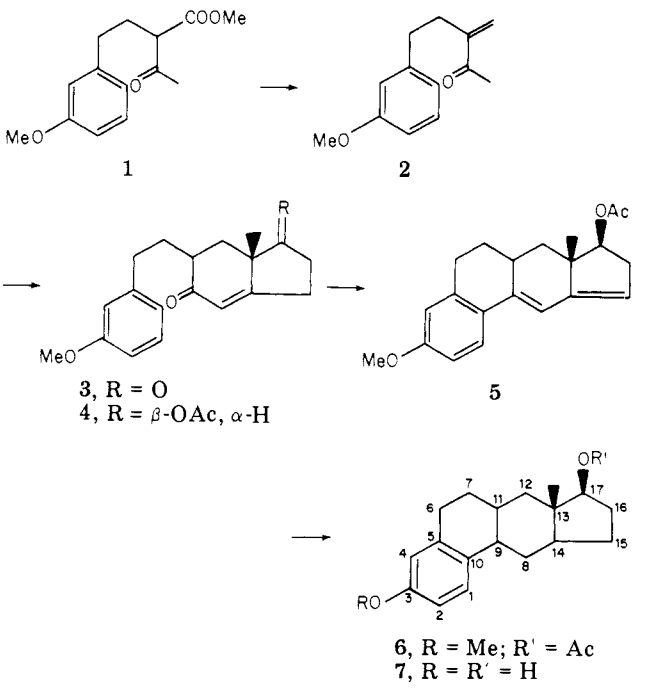


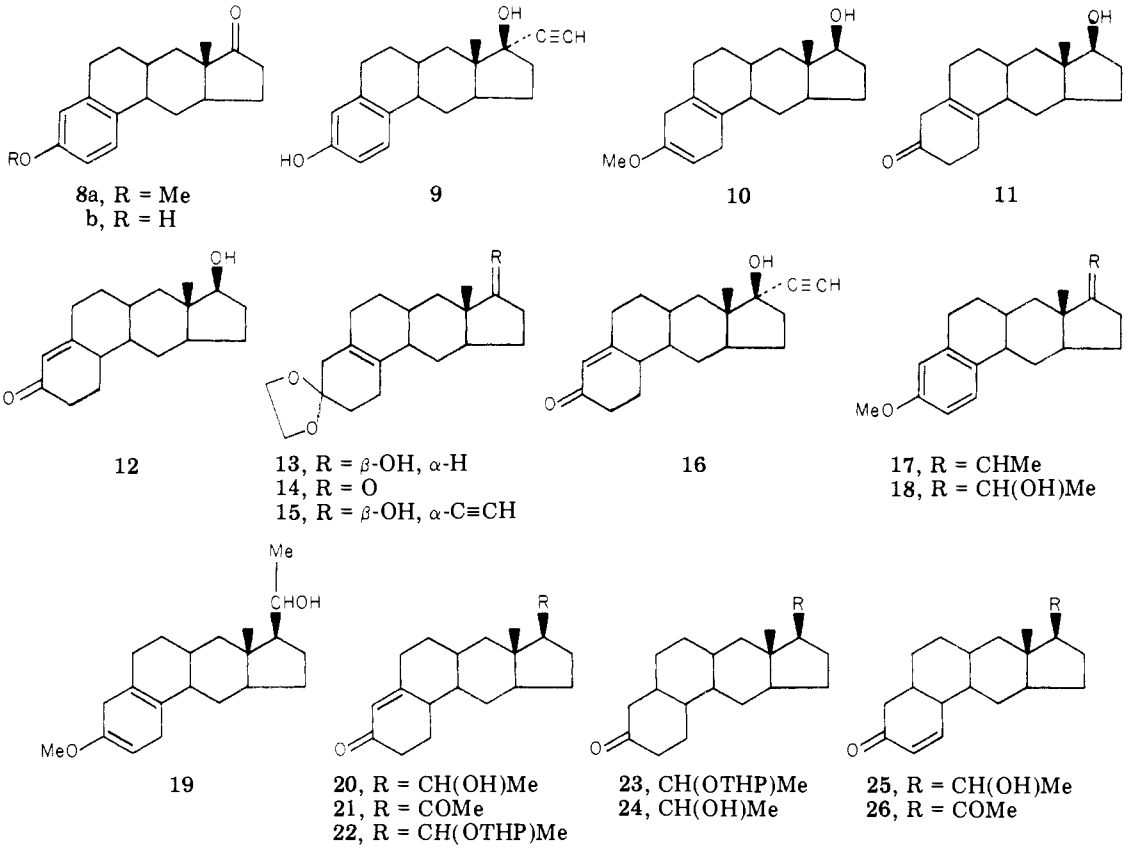
D-estradiol



D- and L-7(8→11α)*abeo*-estra-1,3,5(10)-triene-3,17β-diol

Scheme I





8a, R = Me
b, R = H

9

10

11

12

13, R = β-OH, α-H
14, R = O
15, R = β-OH, α-C≡CH

16

17, R = CHMe
18, R = CH(OH)Me

19

20, R = CH(OH)Me
21, R = COMe
22, R = CH(OTHP)Me

23, CH(OTHP)Me
24, CH(OH)Me

25, R = CH(OH)Me
26, R = COMe

35% overall yield from **17**. The structure of **21** was confirmed by its IR (1700, 1660 cm^{-1}) and ^1H NMR [δ 5.85 (s, C-4)] spectra.

Birch reduction of the unsaturated ketone **20** to the desired 20-hydroxy 3-ketone **24** was complicated by overreduction. Therefore, the tetrahydropyranyl (THP) ether **22** was prepared in quantitative yield by the treatment of **20** with dihydropyran and *p*-toluenesulfonic acid in benzene. Reduction of **22** with lithium and ammonia in THF–*tert*-butyl alcohol (1:1) gave the saturated ketone **23** in 79% yield. Cleavage of the THP group of **23** with *p*-toluenesulfonic acid in 95% aqueous ethanol gave, after chromatography, the crystalline 20α-hydroxy 3-ketone **24** in 63% yield. The assignment of configuration at C-20 is based on literature precedent.[5] Treatment of **24** with phenylselenyl chloride[6] in ethyl acetate, followed by in situ oxidation with hydrogen peroxide gave the Δ^1-3-ketone **25** as a mixture with unchanged **24** and the isomeric ketone **20**, in the ratio of 72:19:9. Oxidation of this mixture with Jones reagent in DMF, followed by chromatography, gave the desired ketone **26** in 29% overall yield from **24**.

Biological Activity. Table I summarizes the relative in vitro binding affinities of the various 7(8→11α)*abeo* steroids for the estrogen and progestin receptor proteins of the rabbit uterus.

The affinities of the 7(8→11α)*abeo* analogues (**7**, **26**) of estradiol and progesterone are ~2% of that of the natural hormones. Introduction of a 17α-ethynyl, as in **9**, does not change this binding affinity significantly and the position of the double bond in ring A is not critical for binding to the progestin receptor (cf. **21** vs. **26**). As with the natural skeleton, the 17α-ethynyl-17β-hydroxy function can replace the 17β-acetyl group without loss in binding activity (cf. **16** vs. **21**).

The free energy of binding of progesterone to the uterine receptor protein is known to be about −12 kcal/mol.[7] Half of this has been attributed to interactions involving the functional groups at C-3 and C-17, the other half to less specific interactions involving the steroid nucleus. The reduced binding affinity of the 7(8→11α)*abeo* steroids represents a decrease of about 1.7 kcal/mol. However, since the 7(8→11α)*abeo* steroids were evaluated as DL mixtures, this is an average value, and it is not possible to determine whether dislocation of ring B or ring D (Chart I) causes the greater loss in binding energy.

Table I also summarizes the uterotropic–antiuterotropic and postcoital antifertility activity of these *abeo* steroids. The uterotropic activity is expressed as precent activity relative to estradiol (sc) or ethynylestradiol (oral). Compounds **7** and **9** both showed limited uterotropic activity, while compounds **11** and **12** were inactive at the highest dose tested. Compounds **9** (oral) and **11** and **12** (sc) did not show any antiuterotropic activity at the highest dose tested. Of the five compounds tested for their postcoital antifertility activity, **9** (oral) and **5**, **11**, and **12** (sc) were ineffective at the highest dose tested. However, compound **7** (sc) did show postcoital antifertility activity at between 1 and 5 mg/kg/day. Thus, even with the low binding activity and even lower uterotropic activity, this compound still retains some postcoital antifertility potential.

Finally, compounds **16** (oral) and **21** and **26** (sc) did not show any progestational or antiprogestational activity at 10, 20, and 10 mg/kg/day, respectively. Compounds **11** and **12** (sc) were tested for their antiandrogenic activity at 30 mg/kg/day and were found to be inactive.

In summary, it is evident that the 7(8→11α)*abeo* skeleton is associated with a marked reduction in the binding affinities and hormonal activities. Since the spatial relationship between substituents at C-3 and C-17 in D- and L-7(8→11α)*abeo* steroids is the same as in the natural

Table I. Individual Test Results from Biological Assays

Assay	Compound							
	5	7	9	11	12	16	21	26
RBA-estrogen receptor	<0.025	2.9 ± 0.4[a]	4.4 ± 0.4[a]	<0.085	0.06 ± 0.01[a]			
RBA-progesterone receptor	<0.4		<0.4	<0.4	<0.4	2.0	1.2 ± 0.6[a]	1.9 ± 0.4[a]
Uterotropic[e]		0.02[b]	0.18[c]	Inact (1)[b,d]	Inact (1)[b,d]			
Antiuterotropic			Inact (10 μg)[c,d]	Inact (5)[b,d]	Inact (5)[b,d]			
Postcoital antifertility[f]	Inact (10)[b,d]	1-5[b]	Inact (6.8)[c,d]	Inact (4)[b,d]	Inact (4)[b,d]			

[a] Average of duplicate measurements. [b] sc administration. [c] Oral administration. [d] Unless otherwise specified number in parentheses refers to highest dose (mg/kg/day). [e] Percent activity relative to estradiol (sc) or ethynylestradiol (oral). [f] ED_{100} in mg/kg/day.

D steroids, it may be concluded that this reduction in activity is due to the dislocation of the B and D rings of the tetracyclic hydrocarbon skeleton.

Experimental Section

Chemical Syntheses. Melting points (Kofler hot-stage microscope) and boiling points are uncorrected. Infrared spectra were measured in $CHCl_3$ (unless otherwise specified) with a Perkin-Elmer 467 spectrophotometer. Ultraviolet spectra were run in methanol on a Cary Model 14 recording spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 using $CDCl_3$ (unless otherwise specified) as a solvent and Me_4Si as an internal standard. Chemical shifts are expressed in δ units. Only significant spectral data are reported. GC analyses were carried out using a Varian Model 1400 with the column containing 3% SE-30 on Variport. Mass spectra were recorded with an Associated Electrical Industries MS-902 instrument. Where analyses are indicated by mass spectra, the homogeneity of these compounds was established by TLC, GC, and other spectral properties. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, III. Analytical results were within ±0.4% of the theoretical values. Each compound had IR, UV, and NMR spectra compatible with its structures. All reactions were carried out under N_2 unless otherwise specified. Worked up in the usual manner means that the solutions of the crude product were washed first, if necessary, with either saturated $NaHCO_3$ or 1 N HCl and then H_2O and brine and dried over anhydrous Na_2SO_4 and solvents were removed under vacuum.

3-(*m*-Methoxyphenethyl)but-3-en-2-one (2).[1] A suspension of **1**[1] (50 g, 0.20 mol) in 1 N NaOH (500 mL) was stirred at room temperature for 3.5 h. The neutral material was removed by extraction with ether. The cooled (0 °C) aqueous layer was carefully acidified (pH 3) and quickly extracted with ether. The ether layer was worked up in the usual manner to give the crude acid (46.2 g) which was dissolved in a cold solution of 37% CH_2O (200 mL, 2.0 mol) and Me_2SO (200 mL). Me_2NH·HCl (16.2 g, 0.20 mol) was quickly added and the reaction mixture stirred at room temperature for 18 h. The mixture was poured into ice water (1 L) and extracted with ether (3 × 400 mL). The ether layer was worked up in the usual manner to give 31.8 g (78%) of **2** (90% pure by GC) which was suitable for use in the next step.

A method due to Miller and Smith[8] for the preparation of **2** from the ester **1** was also evaluated. However, all attempts to prepare the Mannich base from **1** were unsuccessful.

3-Methoxy-7(8→11α)*abeo*-estra-1,3,5(10),8,14-pentaen-17β-yl Acetate (5).[1] A solution of **4**[1] (6.4 g, 18 mmol) in anhydrous HF (30 mL) was stirred at 0 °C for 0.5 h. The red reaction mixture was then cautiously poured onto ice and extracted with C_6H_6 (500 mL). The organic phase was worked up in the usual manner to give the partially hydrolyzed crude product which was reacetylated with pyridine (10 mL) and Ac_2O (10 mL). Removal of the excess reagents followed by crystallization from ethanol afforded **5** (3.02 g, 52%): mp 138–140 °C (lit.[1] mp 131–133 °C).

7(8→11α)*abeo*-Estra-1,3,5(10)-triene-3,17β-diol (7). To a cooled (−78 °C) solution of **6**[1] (250 mg, 0.762 mmol) in CH_2Cl_2 (10 mL) was added a solution of BBr_3 in the same solvent (3 mL, 1.2 M). The reaction mixture was allowed to come to room temperature (15 min) and then stirred for an additional 15 min. The reaction mixture was then cooled to 0 °C, quenched with H_2O (3 mL),, and extracted with $CHCl_3$. The organic phase was shaken with $NaHSO_3$ and then worked up in the usual manner. The crude acetate (235 mg, 91% pure by GC) was dissolved in 0.5 N KOH (10 mL) in 75% aqueous EtOH and stirred at room temperature for 2 h. The cooled reaction mixture was acidified with 3 N HCl and extracted with EtOAc. The organic phase was worked up in the usual manner and the crude product purified by preparative TLC (silica gel, 20% Me_2CO in $CHCl_3$) followed by crystallization from 80% aqueous EtOH at −10 °C (110 mg, 54% yield): mp 192–195 °C; IR (KBr) 1610 cm^{-1} (aromatic C=C); NMR (Me_2CO-d_6) δ 0.78 (s, 3, C-18). Anal. ($C_{18}H_{24}O_2$) *m/e* 272.178.

3-Methoxy-7(8→11α)*abeo*-estra-1,3,5(10)-trien-17-one (8a). The acetate **6**[1] (1.0 g) was saponified quantitatively to the corresponding alcohol by treatment with 0.5 N KOH (15 mL) in 75% aqueous EtOH. Jones reagent (8 N, 1.45 mL) was added dropwise to a solution of the alcohol (0.827 g, 2.89 mmol) in Me_2CO (40

mL). After stirring for 10 min, the reaction mixture was quenched by the addition of *i*-PrOH (2 mL), diluted with H_2O, and extracted with EtOAc. The organic phase was worked up in the usual manner and the product crystallized from EtOAc to yield **8a** (544 mg, 66%): mp 160–163 °C; IR 1725 (C=O), 1600 cm^{-1} (aromatic C=C); NMR δ 0.88 (s, 3, C-18), 3.76 (s, 3, OMe). Anal. ($C_{19}H_{24}O_2$) *m/e* 284.177.

3-Hydroxy-7(8→11α)*abeo*-estra-1,3,5(10)-trien-17-one (8b). The demethylation of **8a** was carried out in exactly the same manner as that of **6**. The phenol **8b** was obtained in 67% yield after preparative TLC (silica gel, 15% Me_2CO in CCl_4): mp 234–236 °C (Et_2O–hexane); IR (KBr) 1715 (C=O), 1600 cm^{-1} (aromatic C=C); NMR (THF-d_8) δ 0.83 (s, 3, C-18). Anal. ($C_{18}H_{22}O_2$) *m/e* 270.162.

17α-Ethynyl-7(8→11α)*abeo*-estra-1,3,5(10)-triene-3,17β-diol (9). To a stirred solution of **8b** (324 mg, 1.20 mmol) in dioxane (35 mL) was added LiC≡CH·$NH_2CH_2CH_2NH_2$ (1.6 g). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated NH_4Cl, diluted with H_2O, and extracted with $CHCl_3$. The organic phase was worked up in the usual manner and the crude product was purified by elution from a silica gel column (20 g; 5% Me_2CO in $CHCl_3$) and crystallization from aqueous EtOH (130 mg, 36%): mp 247–249 °C; IR (KBr) 3280 (C≡CH), 1610 cm^{-1} (aromatic C=C); NMR (MeOH-d_4) δ 0.86 (s, 3, C-18), 2.87 (s, 1, C≡CH). Anal. ($C_{20}H_{24}O_2$) C, H; *m/e* 296.177.

17β-Hydroxy-7(8→11α)*abeo*-estr-5(10)-en-3-one (11). Li ribbon (200 mg, 29 mmol) was added in portions to a rapidly stirred solution of **6** (1.0 g, 3.05 mmol) in distilled NH_3 (150 mL), THF (20 mL), and *t*-BuOH (20 mL). After allowing the mixture to reflux for 1 h, the blue color was discharged with saturated NH_4Cl and the NH_3 allowed to evaporate. The residue was diluted with H_2O (70 mL) and extracted with $CHCl_3$ (3 × 70 mL). The organic phase was worked up in the usual manner to give the $\Delta^{2,5(10)}$-diene **10** (0.91 g). A MeOH solution (150 mL) of **10** was treated with an aqueous solution (30 mL) of $(COOH)_2 \cdot 2H_2O$ (2.3 g). After stirring at room temperature for 1 h, the reaction mixture was diluted with H_2O (200 mL) and extracted with $CHCl_3$ (2 × 200 mL). Usual work-up followed by crystallization from Et_2O gave **11** (460 mg, 55%): mp 145–149 °C (evacuated capillary); IR 1710 cm^{-1} (C=O); NMR δ 0.78 (s, 3, C-18), 2.76 (s, 2, C-4), 3.72 (t, 1, *J* = 8 Hz, C-17). Anal. ($C_{18}H_{26}O_2$) C, H; *m/e* 274.193.

17β-Hydroxy-7(8→11α)*abeo*-estr-4-en-3-one (12). A solution of crude diene **10** (0.60 g, 2.1 mmol) in MeOH (55 mL) and 3 N HCl (35 mL) was heated at 60 °C for 0.5 h. The cooled (0 °C) reaction mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$ and the organic phase worked up in the usual manner. Crystallization of the crude residue yielded **12** (394 mg, 69%): mp 97–99 °C (evacuated capillary); IR 1660 cm^{-1} (C=O); UV 242 nm (ϵ 16 400); NMR δ 0.80 (s, 3, C-18), 3.69 (t, 1, *J* = 8 Hz, C-17), 5.84 (s, 1, C-4). Anal. ($C_{18}H_{26}O_2$) C, H; *m/e* 274.193.

3,3-Ethylenedioxy-7(8→11α)*abeo*-estr-5(10)-en-17β-ol (13). A solution of **10** (275 mg, 0.868 mmol), $HOCH_2CH_2OH$ (0.5 mL), and TsOH (15 mg) in C_6H_6 (8 mL) was refluxed for 2.5 h using Dean–Stark trap. After cooling, the reaction mixture was diluted with C_6H_6 and the organic phase worked up in the usual manner to give **13** in quantitative yield. Even after preparative TLC (silica gel, 5% Me_2CO in $CHCl_3$), attempted crystallization of **13** was unsuccessful: NMR δ 0.73 (s, 3, C-18), 3.63 (t, 1, *J* = 8 Hz, C-17), 3.93 (s, 4, OCH_2CH_2O). Anal. ($C_{20}H_{30}O_3$) *m/e* 318.219.

3,3-Ethylenedioxy-7(8→11α)*abeo*-estr-5(10)-en-17-one (14). A solution of **13** (50 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) was added to a red solution of CrO_3 (96 mg, 0.96 mmol) and pyridine (152 mg, 1.92 mmol) in CH_2Cl_2 (1.5 mL). After stirring at room temperature for 15 min, the supernatant was decanted and the brown gum was triturated with Et_2O. The combined organic extracts were evaporated and the residue was triturated with Et_2O. Usual work-up of the Et_2O phase gave crude **14** (46 mg). Even after preparative TLC (silica gel, 5% Me_2CO in $CHCl_3$), the ketone **14** resisted attempts at crystallization: IR 1735 cm^{-1} (C=O); NMR δ 0.83 (s, 3, C-18), 3.93 (s, 4, OCH_2CH_2O). Anal. ($C_{20}H_{28}O_3$) *m/e* 316.204.

17β-Hydroxy-7(8→11α)*abeo*-19-nor-10-iso-17α-pregn-4-en-20-yn-3-one (16).[9] A solution of *n*-C_4H_9Li (2.5 M, 7.6 mL, 19 mmol) in hexane was added slowly to a saturated solution of dry HC≡CH in THF (35 mL) at −78 °C. After stirring for 10 min under HC≡CH, a solution of **14** (600 mg, 1.89 mmol) in THF (5 mL) was added. The reaction mixture was allowed to come to room temperature (1 h), then cautiously quenched with saturated NH_4Cl, and extracted with EtOAc. Usual work-up of the organic phase gave a dark residue which was purified by elution from basic alumina (activity III) column with C_6H_6 followed by increasing amounts of EtOAc in C_6H_6. The ketal **15** was then hydrolyzed by stirring (7 h) its solution in MeOH (10 mL) and 3 N HCl (2 mL) at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. Usual work-up of the organic phase gave the crude product which was purified by elution from silica gel (50 g) column with $CHCl_3$ to give pure **16** (189 mg, 42% overall yield from **6**): mp 153–156 °C (Et_2O–hexane); IR 3300 (C≡CH), 1710 (C=O), 1620 cm^{-1} (C=C); UV 237 nm (ϵ 16 200); NMR δ 0.89 (s, 3, C-18), 2.56 (s, 1, C≡CH), 5.83 (s, 1, C-4). Anal. ($C_{20}H_{26}O_2$) *m/e* 298.194.

3-Methoxy-7(8→11α)*abeo-cis*-19-norpregna-1,3,5(10),17(20)-tetraene (17). Following a literature procedure[5] for an analogous preparation, **17** was obtained in 71% yield from **8a**: mp 79–84 °C (MeOH–Et_2O); IR (CCl_4) 1610 cm^{-1} (C=C); NMR δ 0.92 (s, 3, C-18), 1.72 (d, 3, *J* = 7 Hz, C-21), 3.78 (s, 3, OMe), 5.18 (m, 1, C-20). Anal. ($C_{21}H_{28}O$) C, H; *m/e* 296.215.

3-Methoxy-7(8→11α)-19-norpregna-1,3,5(10)-trien-20α-ol (18). To a solution of **17** (1.25 g, 4.22 mmol) in THF (50 mL) was added a solution (20 mL) of 1 M BH_3 in THF. After stirring at room temperature for 2 h, 30 mL of 10% NaOH was cautiously added, followed by 10 mL of 30% H_2O_2 at 0 °C. The reaction mixture was refluxed for 1.5 h, diluted with H_2O, and extracted with ether. Usual work-up of the organic phase yielded **18** (1.25 g) as a mixture of isomers at C-20 (TLC and NMR) and was used without purification.

20α-Hydroxy-7(8→11α)*abeo*-19-nor-10-isopregn-4-en-3-one (20). The Birch reduction of **18** to the $\Delta^{2,5(10)}$-diene **19** was carried out in exactly the same manner as that of **6**. The crude diene **19** (1.37 g) was dissolved in a mixture of MeOH (40 mL) and 4 N HCl (25 mL) and refluxed for 1 h. The reaction mixture was diluted with water (70 mL) and extracted with Et_2O (2 × 100 mL). Usual work-up of the organic phase yielded **20** (0.4 g, 32%) as a mixture of isomers at C-20 (TLC and NMR) and was used without purification.

7(8→11α)*abeo*-19-Nor-10-isopregn-4-ene-3,20-dione (21). Following a literature procedure[5] for an analogous preparation, the alcohol **20** was oxidized to the dione **21**. The crude product was purified by elution from an alumina (activity I) column with 10% Me_2CO in C_6H_6 followed by crystallization from Me_2CO–hexane (35% overall yield from **17**): mp 161–162 °C (evacuated capillary); IR (KBr) 1700 (C=O), 1660 cm^{-1} (C=C); UV 238 nm (ϵ 18 100); NMR δ 0.67 (s, 3, C-18), 2.12 (s, 3, C-21), 5.84 (s, 1, C-4). Anal. ($C_{20}H_{28}O_2$) C, H; *m/e* 300.209.

20α-Tetrahydropyranyloxy-7(8→11α)*abeo*-19-nor-10-isopregn-4-en-3-one (22). A solution of **20** (830 mg, 2.75 mmol), dihydropyran (5 mL), and anhydrous TsOH (30 mg) in C_6H_6 (10 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O (50 mL) and worked up in the usual manner. The crude product was purified by elution from the basic alumina (activity III, 80 g) column with C_6H_6 to give **22** (1.03 g, 97%) as a mixture of diastereomers and was used as such in the next step.

20α-Hydroxy-7(8→11α)*abeo*-19-nor-10-isopregn-3-one (24). The Birch reduction of **22** to the saturated ketone **23** (79%) was carried out in exactly the same manner as that of **6**. A solution of the crude ketone **23** (800 mg, 2.06 mmol) and TsOH (400 mg) in 95% EtOH (15 mL) was refluxed for 1 h. The cooled reaction mixture was then diluted with H_2O and extracted with $CHCl_3$ and the organic phase worked up in the usual manner. The crude product was purified by elution from the silica gel (70 g) column with 1% Me_2CO in $CHCl_3$ to give the hydroxy ketone **24** (395 mg, 63%): mp 247–249 °C (Et_2O); IR 1705 cm^{-1} (C=O); NMR δ 0.67 (s, 3, C-18), 1.20 (d, 3, *J* = 6 Hz, C-21), 3.71 (t, 1, *J* = 6 Hz, C-20). Anal. ($C_{20}H_{32}O_2$) *m/e* 304.241.

20α-Hydroxy-7(8→11α)*abeo*-19-nor-10-isopregn-1-en-3-one (25). To a solution of **24** (123 mg, 0.405 mmol) in EtOAc was added C_6H_5SeCl (94 mg, 0.49 mmol) and the orange-red solution was stirred at room temperature until it turned yellow (40 min). The HCl formed during the reaction was removed by extraction with H_2O (3 × 2 mL). A solution of H_2O_2 (30%, 0.5 mL) in THF

(2 mL) was then slowly added to the organic phase and the reaction mixture stirred at room temperature for 1 h. It was then diluted with EtOAc and worked up in the usual manner. The crude product (72% by GC) was used as such in the next step. An analytical sample of **25** was prepared by elution from basic alumina (activity III, 10 g) with C_6H_6 and crystallization from Et_2O: mp 160–163 °C (evacuated capillary); IR 1670 cm^{-1} (C=O); UV 227 nm (ε 9300); NMR δ 0.70 (s, 3, C-18), 2.22 (d, 3, J = 6 Hz, C-21), 3.74 (t, 1, J = 6 Hz, C-20), 5.98 (d, 1, J = 10 Hz, C-2), 7.10 (d, 1, J = 10 Hz, C-1). Anal. ($C_{20}H_{30}O_2$) m/e 302.225.

7(8→11α)abeo-19-Nor-10-isopregn-1-ene-3,20-dione (26). Following a literature procedure[5] for an analogous preparation, the crude alcohol **25** was oxidized to the 3,20-dione **26**. The crude product was purified by elution from a prepacked silica gel column (EM Merck, Size B) with 50% $CHCl_3$ in CCl_4 to give **26** (29% overall yield from **24**). An analytical sample of **26** was prepared by crystallization from Et_2O: mp 142–147 °C (evacuated capillary); IR 1700, 1675 cm^{-1} (C=O); UV 227 nm (ε 10300); NMR δ 0.64 (s, 3, C-18), 2.09 (s, 3, C-21), 5.97 (d, 1, J = 10 Hz, C-2), 7.10 (d, 1, J = 10 Hz, C-1). Anal. ($C_{20}H_{28}O_2$) m/e 300.209.

Biological Procedures. Uterotropic–Antiuterotropic Activity. This assay for uterotropic (estrogenic) activity was carried out by NICHD. Immature, female rats, weighing 45–55 g, were treated daily for three consecutive days with 0.1 mL of the drug suspension (sesame oil). A vehicle control group treated with sesame oil alone was also run. On the day following treatment, the animals were sacrificed and the uteri were excised, cleaned, and weighed to the nearest 0.2 mg. Estradiol was used as a standard for sc administration and ethynylestradiol for oral administration. All values are expressed as percent activity relative to these two compounds.

Antiuterotropic activity was determined in an identical manner with the exception that estradiol and the test compound were administered together. The extent to which D-estradiol stimulated increase in uterine weight was inhibited by the test compound indicated its antiuterotropic activity.

Postcoital Antifertility. This assay was carried out by NICHD. Adult Sprague–Dawley rats were used as the experimental animal. The females were caged with males of proven fertility and checked the next morning for presence of sperm. The day sperm were found was considered day 0 of pregnancy. The test compounds were dissolved or suspended in sesame oil and were administered in a volume of 0.1 mL. The compounds were administered over a 5-day period, starting on day 0 of pregnancy. Autopsy was carried out on day 10 of presumptive pregnancy and the presence and number of normal and resorbing fetuses were determined. ED_{100} is defined as that dose (mg/kg/day) at which no implantation sites were found.

Progestational, Antiprogestational, and Antiandrogenic Activities. Progestational and antiprogestational activities were determined by measuring uterine stimulation in the immature rabbit (Clauberg). Antiandrogenic activity was determined in immature, castrated, male rats by evaluating the ability of the test compound to inhibit androgen stimulation of seminal vesicle, ventral prostate, and levator ani weight.

Relative Binding Activity. These assays were carried out by following previously reported procedures[10] with the following exceptions.

Receptor Source. For both the estrogen and progesterone receptor, the uteri from adult castrate rabbits which had been primed with estradiol were used as the tissue source. The uteri were homogenized in 4–8 vol (w/v) of ice-cold TE buffer (0.05 mM Tris–HCl, 1 mM EDTA, pH 7.4) and the cytosol was obtained by ultracentrifugation.

Competitive Binding Assay. The basic assay used a 0.6-mL incubation volume (0.1 mL of radiolabeled steroid, 0.1 mL of compound, 0.1 mL of cytosol, and 0.3 mL of TE buffer) and was carried out at 4 °C. The competitor concentration was varied from 0.1 nM to 10 mM and the radiolabel was held constant at 6000 cpm for [^{3}H]estradiol (110 Ci/mM) and 20000 cpm of [^{3}H]progesterone (105 Ci/mM). A 24-h incubation was started by addition of the cytosol to the competitor and radiolabel. At the end of the incubation, the bound labeled steroid was isolated and analyzed as previously reported.[10] Standard competition curves for unlabeled estradiol or progesterone were included in the respective assays and the relative binding activity (RBA) was determined.

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Total Syntheses of (±)-1-Carbacefoxitin and -cefamandole and (±)-1-Oxacefamandole

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The total syntheses of the (±)-1-carba analogues of cefoxitin (**11**), 7α-methoxydeacetylcephalothin (**5**) and cefamandole (**31**) and the (±)-1-oxa analogue of cefamandole (**43**) are described. Their bioactivity spectra against 14 typical organisms are similar to those of their natural 1-thia counterparts, with the 1-carba compounds somewhat less active and the 1-oxa compound more active than the natural ones.

Replacement of the sulfur atom at position 1 of the cephalosporin nucleus with oxygen or carbon has been found not to eliminate the antibiotic activity. In fact, (±)-1-carbacephalothin[1] and (±)-1-oxacephalothin,[2] first