(−40 °C) acetone (3 × 25 mL). After drying in vacuo at 140 °C, the product (3) weighed 19.7 g (64% based on 6): mp 171.5–172.5 °C; IR ($CHCl_3$) 2400–2600 (NH^+), 1650 cm^{-1} (C=O); UV λ_{max} 220 nm (ε 24 500), 285 (31 750); NMR (100 MHz) δ 2.08 [4, m, N-(CH_2CH_2)$_2$], 2.72 (3, s, CH_3SO_3), 2.92 (6, m, ArCH_2CH_2 + N-CH_2CH_2O–), 3.67 [4, m, N-(CH_2CH_2)$_2$], 3.69 (3, s, OCH_3), 4.40 (2, t, J = 4.5 Hz, OCH_2-C), 6.68 (2, d, J = 9 Hz, aromatic ortho to –OCH_3), 6.83 (2, d, J = 9 Hz, aromatic ortho to –OCH_2), 6.9–7.3 (4, m, aromatic), 7.20 (s, d, J = 9 Hz, aromatic meta to –OCH_3), 7.83 (2, d, J = 9 Hz, aromatic ortho to C=O), 11.23 (1, br s, NH). Anal. ($C_{31}H_{35}NO_6S$) C, H, N, O, S.

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Synthesis of 11β,13β- and 13β,16β-Propano Steroids: Probes of Hormonal Activity

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Syntheses of 11β,13β- and 13β,16β-propano derivatives of 17α-ethynyl-17β-hydroxygon-4-en-3-one are described. The 13β,16β bridge was constructed by intramolecular alkylation of the C-16 enolate anion from 3-methoxy-13β-[3′-(tosyloxy)propyl]gona-3,5-dien-17-one, the latter being obtained via Birch reduction of both aryl groups of 17β-hydroxy-3-methoxy-13β-(3′-phenoxypropyl)gona-1,3,5(10),8-tetraene (1). The 11β,13β bridge was constructed by Prins cyclization of 17β-acetoxy-3-methoxy-13β-(3′-oxopropyl)gona-1,3,5(10),9(11)-tetraene, itself obtained via Birch reduction of only the side-chain aryl group of 1. Binding affinities of certain of these compounds and substituted 13β-propyl derivatives of 17α-ethynyl-17β-hydroxygon-4-en-3-one for the uterine cytosol receptor of progesterone are reported, and the origin of the high progestational activity of norgestrel and 11β-substituted progestins is discussed.

Introduction of alkyl substituents above the β face of rings C and D of the steroid skeleton can lead to significant enhancement of hormonal activity.[1-3] For example, methylation of C-11β[1] or C-18[2] of 17α-ethynyl-17β-hydroxyestr-4-en-3-one (norethindrone) produces a marked increase in progestational activity, while 11β-methylestradiol is a more potent estrogen than the natural hormone.[2] A priori, these observations might be attributed to enhanced metabolic stability or to an enhanced affinity for the receptor protein. The latter could arise directly from favorable hydrophobic interaction of the alkyl substituent and a cavity in the receptor or indirectly from ring-conformation changes induced by buttressing effects. A recent structure–activity study[3] of a variety of 11β-substituted derivatives of 17α-ethynylestr-4-en-17β-ol (lynestrol) suggested that buttressing effects are dominant. We have sought to identify the origin of the increased potency by synthesis of 11β,13β- and 13β,16β-propano bridged steroids. The conformation of the C-13 substituent in these steroids is rigidly defined and skeletal distortions due to nonbonded interactions of the C-13β substituent with the C-11β and C-16β substituents are eliminated. The starting point for both of these bridge systems was 17β-hydroxy-3-methoxy-13β-(3′-phenoxypropyl)gona-1,3,5(10),8-tetraene (1), obtained by our recently reported procedure.[4]

Chemistry. The synthesis of the 13β,16β-propano bridge system is shown in Scheme I. Birch reduction of 1 with lithium in ammonia and *tert*-butyl alcohol followed by Oppenauer oxidation gave the bisenol ether **2**. Acid hydrolysis provided the 3,17-dione **3** (64%), which was converted to the tosylate **4** along with a minor amount of chloride **5** by treatment with tosyl chloride and pyridine.

Attempts to convert **4** to the 13β,16β-propano bridged compound by intramolecular C alkylation, using potassium *tert*-butoxide (1–2 mol-equiv) in either benzene or benzene/*tert*-butyl alcohol or sodium hydride/Me_2SO to generate the C-17 enolate anion, were totally unsuccessful. It was felt that the presence of the more acidic Δ^4-3-one functionality of **4** might be interfering with the formation of the enolate anion of the C-17 ketone. The tosylate **4** was therefore converted to the enol ether **6** by treatment with trimethyl orthoformate and *p*-toluenesulfonic acid in dioxane. Initial attempts to cyclize **6** by intramolecular C alkylation using potassium *tert*-butoxide in benzene or benzene/*tert*-butyl alcohol were no more successful than with **4**. However, it was then determined that treatment of **6** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for 18 h gave the desired pentacyclic gonane **7** in 80% yield. The IR and ^1H NMR spectra of **7** were in complete agreement with the assigned structure. Since the stereochemistry of the C-13 substitutent in **1** has been rigorously established[4] as β, the configuration of the propano bridge at C-16 must also be β in **7**. Inspection of Dreiding models indicates that it is impossible to construct a 13β,16α-propano bridged system.

Ethynylation of **7** with freshly prepared lithium acetylide[5] afforded **8** which, upon hydrolysis, gave the desired propanogonane **9** in 21% overall yield from **2**.

The 11β,13β-Propano Bridge. The synthesis of this bridge system is shown in Scheme II. It was previously determined that the first step, treatment of **1** with Li/NH_3/THF, effected reduction of the 8,9 double bond and the side-chain phenoxy group without reduction of the A ring. However, the yield of the product **10** was only 12%. Selective reduction of the side-chain aryloxy group is probably promoted by intramolecular protonation of the intermediate radical anion by the 17-hydroxy group. Windholz et al.[6] have reported a similar selectivity for the Birch reduction of 3-methoxy-13β-phenylgona-1,3,5(10)-trien-17β-ol.

In an effort to improve the yield of **10**, this reduction was examined using different conditions. Treatment of

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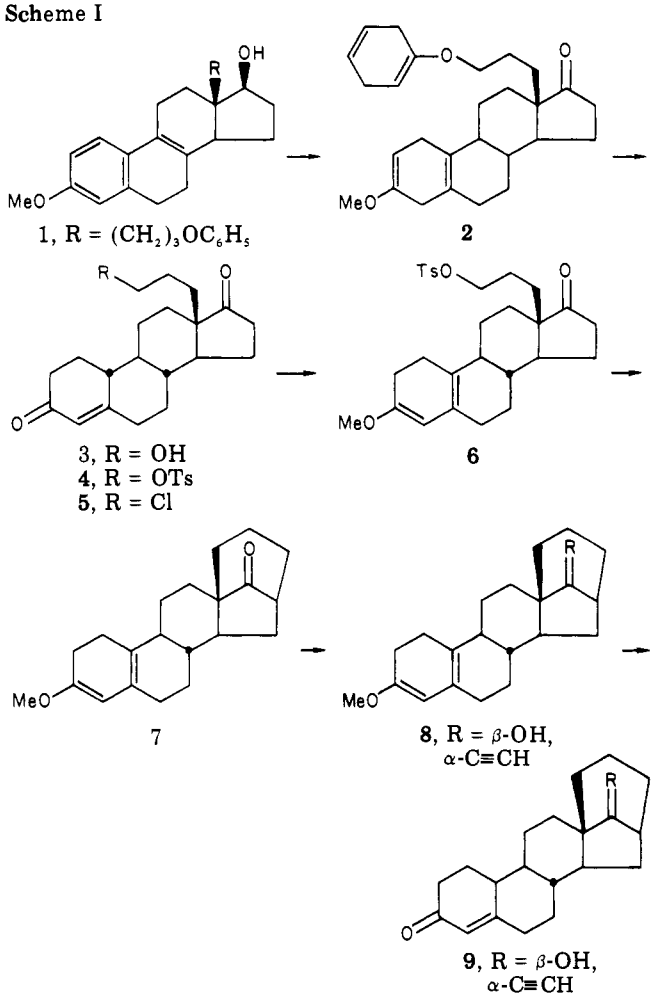
Scheme I



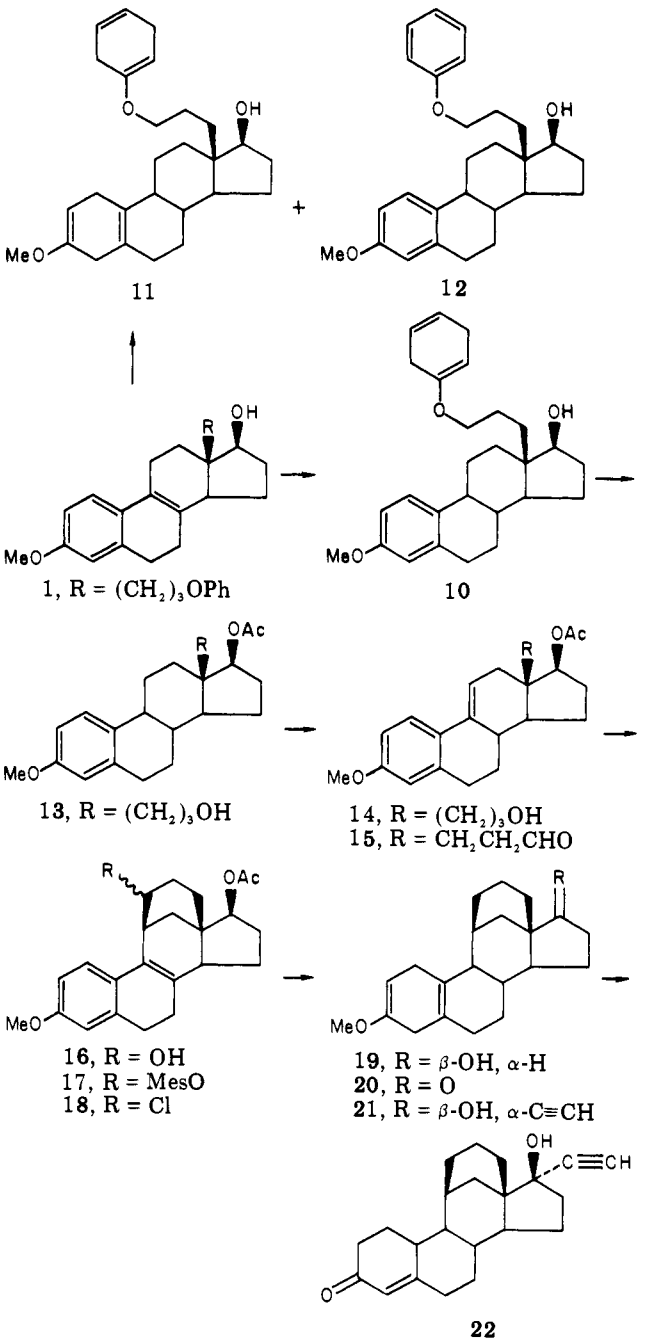
1 with $Li/NH_3/THF/t$-BuOH for 10 min at −33 °C (conditions used by Windholz[6]) resulted in a 1:1 mixture of **10** and the product **11** from reduction of both aryl groups. Repetition in the absence of t-BuOH gave mainly **12** (reduction of only the 8,9 double bond) plus only small amounts of **10**. A longer reaction time (1 h) did not improve the yield of **10**. However, two treatments with $Li/NH_3/THF$, 20 min each, gave a 1:1 mixture of **10** and **12**. This represents the optimum conditions for the preparation of **10**, since recovered **12** can be recycled.

Acetylation of the 17-hydroxy group of **10** to differentiate between this and the latent side-chain hydroxy group, acid-catalyzed hydrolysis of the enol ether group, and purification by elution chromatography and crystallization (CH_2Cl_2/hexane) afforded **13** in 17% overall yield from **1**.

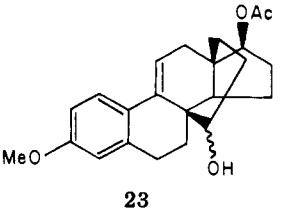
The conversion of **13** to the corresponding $\Delta^{9(11)}$ analogue **14** was accomplished using adamantanol and fluorosulfonic acid.[7] After trial experiments indicated incomplete conversion using literature conditions,[7] 3-methoxyestra-1,3,5(10)-trien-17β-ol acetate was used as a model to establish the appropriate conditions. Treatment with a large excess of fluorosulfonic acid and adamantanol (3.8 equiv) in hexane at −20 °C for 30 min proved optimum for the model system and, when applied to **13**, a 70% yield of **14** was obtained. Oxidation of **14** with pyridine/chromium trioxide or pyridinium chlorochromate[8] gave the aldehyde **15**.

Ring closure, to form the 11β,13β bridge, was accomplished by treatment of **15** with zinc iodide in methylene chloride.[9] The product **16** was isolated by chromatography and characterized by high-resolution mass spectrometry,

Scheme II



UV, and ^1H NMR. In agreement with the assigned structure, the ^1H NMR spectrum showed a multiplet at δ 3.54 attributable to the tertiary proton adjacent to the hydroxyl group and *no* olefinic signals, while the UV spectrum showed the presence of the styrenic chromophore (λ_{max} 278 nm, ε 11 500). The absence of an olefinic signal rules out the alternative cyclization product **23**, which



could have arisen from migration of the 9,11 double bond to the 8,9 position prior to Prins cyclization. The β configuration of the propano bridge at C-11 in **16** is based on the reasoning already applied to the 13,16 bridge (vide

supra). The product **16** was also obtained when a chloroform solution of the aldehyde **15** was passed through a column of silica gel.

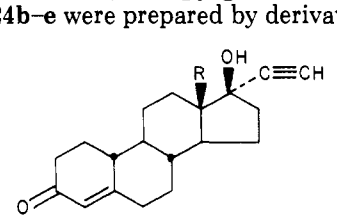
The next step was removal of the hydroxyl function of the propano bridge. To this end, the alcohol **16** was converted to the mesylate[10] and reductive cleavage of the mesyloxy group was attempted using two different literature procedures. Lithium triethylborohydride, reported to be a super nucleophilic reducing agent,[11] failed to effect reductive cleavage, although *O*-acyl cleavage of the 17-acetate group was observed. Treatment with zinc and sodium iodide in dimethoxyethane was equally unsuccessful, despite the precedent for this reducing system.[12]

The failure to effect reduction of the mesylate group of **17** is most likely related to steric inhibition of S_N2 displacement, this being the basis of both of the above procedures. Lithium in ammonia reduction is not subject to the same constraint, although it is better accomplished using the chloride rather than the mesylate group.[13] Not surprisingly, the chloride **18** could not be derived from the mesylate by treatment of the latter with lithium chloride in dimethylformamide;[14] the mesylate was recovered unchanged. This confirmed the inertness of **17** to S_N2 displacement. However, the chloride **18** could be prepared in 60% yield by treatment of the alcohol **16** with triphenylphosphine in CCl_4 and $CHCl_3$.[18] This transformation is not subject to the same steric constraints as S_N2 displacement.[15]

Treatment of **18** with lithium in ammonia and *tert*-butyl alcohol resulted in total reduction of the carbon–halogen bond and at the same time accomplished reduction of the 8,9 double bond and the aromatic ring. The product **19** was oxidized to the 17-ketone **20** using Oppenauer conditions, and the latter was converted to **21** by ethynylation with freshly prepared lithium acetylide.[5] Since **18**–**21** were homogeneous by TLC, it was only after treatment of **21** with aqueous acid, to generate the Δ^4-3-ketone function, that it became apparent that two isomers had been formed in the ratio 7:3 (GLC). After separation by elution chromatography, the spectroscopic properties (IR, UV, MS, and ^1H NMR) of both isomers were found to be essentially identical and consistent with the structure **22**. The isomers must, therefore, differ by the configuration of one or more of the newly created asymmetric centers at C-8, -9, -10, or -17. It is most probable that the steric bulk of the 11β,13β-propano bridge is sufficient to lessen the stereospecificity for the all-trans structure, which is usually observed with metal/ammonia reduction of the 8,9-dehydro derivatives of gona-1,3,5(10)-trienes.[16]

The major isomer can reasonably be assigned the all-trans structure on the basis of precedent[16] plus its greater and significant affinity for the progesterone receptor protein. Thus, relative to progesterone, the binding affinities of the major and minor isomers were 136 and 1%, respectively.

Functionalized 13β-Propylgon-4-en-3-ones. The compounds **24b–e** were prepared by derivatization of the



24a, R = $CH_2CH_2CH_2OH$
b, R = $CH_2CH_2CH_2Cl$
c, R = $CH_2CH_2CH_2OAc$
d, R = CH_2CH_2CHO
e, R = $CH_2CH_2CH_2OCOCH_2Br$

Table I. Binding Affinities of Substituted 17α-Ethynyl-17β-hydroxygon-4-en-3-ones

substituents	binding affinity,[a] %
13β-Me, *d* isomer (norethindrone)	126
13β-Et, racemic (*dl*-norgestrel)	206
11β-Me-13β-Me, *d* isomer	390
11β-Me-13β-Et, racemic	151
13β,16β-propano, racemic (**22**)	1
11β,13β-propano, racemic (**9**)	136

[a] Determined by J. Berg.

corresponding 3′-hydroxypropyl steroid **24a**.[4] These derivatives are potentially capable of alkylating or acylating the receptor protein so acting as irreversible antagonists.[17] The aldehyde **24d** existed exclusively as the internal hemiacetal, as judged by the absence of the aldehydic carbonyl (IR) and proton (NMR) signals.

Structure–Activity Relationships. The binding affinities of the 11β,13β- and 13β,16β-propano gonanes (**9** and **22**, respectively) for the uterine cytosol receptor of progesterone are compared with the affinities of other 11β- and 13β-alkyl substituted gonanes in Table I. Assuming only the natural antipode of the racemate is active, introduction of a methyl group at C-11β or C-18 produces large and comparable increments in the binding affinity relative to norethindrone. This enhanced affinity is largely retained by the 11β-methyl-13β-ethyl and 11β,13β-propano derivatives. Since molecular models demonstrate that the 11β,13β-propano derivative is strain free, distortion of the steroid ring skeleton caused by 11β,13β substituent–substituent interaction is unlikely to be responsible for the activity of either norgestrel or the 11β-alkyl derivatives. Rather, a favorable hydrophobic interaction with a receptor cavity seems probable. In contrast, an unfavorable hydrophobic interaction may be responsible for the greatly diminished activity of the 13β,16β-propano derivative. It seems probable that the conformation adopted by norgestrel in its interaction with the uterine receptor protein is similar to that of the 11β,13β-propano derivative.

The compounds **9** and **24a–e** showed no measurable antiprogestational activity in an anti-Clauberg assay. Compound **24d** had 5% of the progestational activity of progesterone in a standard Clauberg assay. The binding affinities of other compounds for the uterine cytosol receptor protein, relative to progesterone, were **24a**, 2%; **24b**, 1%; **24d**, 21%; and **24e**, 2%.

Experimental Section

Melting points were determined using Kofler hot-stage microscope and are uncorrected. IR spectra were measured with a Perkin-Elmer 267 spectrophotometer. Unless otherwise mentioned, NMR spectra were recorded on a Varian Model A-100, using Me_4Si as an internal standard; chemical shifts are expressed in δ units. Mass spectra were determined using an Associated Electrical Industries MS-902 instrument. UV absorption spectra were obtained using a Cary 14 spectrophotometer. Gas–liquid chromatographic analysis was carried out using a Varian Model 1400 instrument with a column containing 3% SE-30 on Variport. Whenever it was not possible to obtain satisfactory combustion analysis of a compound either due to instability and/or lack of material, the homogeneity of the compound was rigorously established by spectral and physical means and the elemental formula confirmed by high-resolution mass spectrometry. Microanalyses were carried out by Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

13β-(3′-Hydroxypropyl)gon-4-en-3,17-dione (3). A solution of **2**[4] (920 mg, 2.27 mmol) in MeOH (30 mL) and 10% aqueous HCl (15 mL) was refluxed for 1 h, then poured into ice–water (200 mL), and extracted with EtOAc (2 × 300 mL). The residue (711 mg) from the dried (Na_2SO_4) extracts was purified by elution from

silica gel (70 g) with 40% EtOAc in $CHCl_3$, followed by crystallization from CH_2Cl_2–hexane to give **3** (457 mg, 64%): mp 153–155 °C; IR ($CHCl_3$) 3620 and 3500 (free and bonded OH), 1730 (C=O), 1670 (C=O), 1620 (C=C) cm^{-1}; UV (MeOH) λ_{max} 237 nm (ε 16900); ^1H NMR ($CDCl_3$) δ 3.53 (t, 2, J = 5 Hz, CH_2CH_2OH), 5.73 (s, 1, C-4); MS m/e 316.204. Anal. ($C_{20}H_{28}O_3$) C, H.

17α-Ethynyl-17β-hydroxy-13β,16β-propanogon-4-en-3-one (9). A solution of **3** (250 mg, 0.79 mmol) in dry pyridine (2 mL) and *p*-toluenesulfonyl chloride (302 mg, 1.58 mmol) was allowed to stand at 5 °C for 18 h, then poured into ice–water (50 mL), and extracted with EtOAc (2 × 75 mL). The combined extracts were washed with water (2 × 30 mL) containing pyridine to remove excess tosyl chloride, dried (Na_2SO_4), and evaporated to give the tosylate **4**: IR ($CHCl_3$) 1180 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ 3.93 (t, 2, J = 5 Hz, $CH_2CH_2CH_2OTs$). The crude tosylate (351 mg) in dry dioxane (10 mL), trimethyl orthoformate (1.5 mL), and anhydrous *p*-toluenesulfonic acid (10 mg) were stirred at room temperature for 5 h. Pyridine (0.2 mL) was added, and the solvent and excess reagents were removed in vacuo (1 mm) at 0 °C to give **6**: IR ($CHCl_3$) 1655, 1630 cm^{-1} (enol ether); ^1H NMR ($CDCl_3$) δ 3.53 (s 3, OMe). A suspension of this product and potassium *tert*-butoxide (105 mg, 0.938 mmol) in *t*-BuOH (10 mL) was refluxed for 18 h under argon. The reaction mixture was then taken up in CH_2Cl_2 (100 mL), washed with H_2O (3 × 50 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo yielded crude **7** (198 mg, 80%): IR (CH_2Cl_2) 1730 (C=O), 1655, 1630 cm^{-1} (enol ether); ^1H NMR ($CDCl_3$) δ 3.53 (s, 3, OMe), 5.13 (s, 1, C-4), 5.20 (t, 1, J = 6 Hz, C-6). This product (198 mg, 0.631 mmol) in THF (5 mL) was slowly added to a cold (−78 °C) solution of freshly prepared lithium acetylide (6.31 mmol) in THF (35 mL). After stirring for 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature and then stirred for 1 h. The mixture was cooled to 0 °C, treated with saturated NH_4Cl (5 mL) and water (50 mL), and extracted with EtOAc (3 × 50 mL). The organic phase was dried (Na_2SO_4) and evaporated to give 198 mg of crude **8**: IR ($CHCl_3$) 3320 cm^{-1} (C≡CH). This product was dissolved in MeOH (10 mL) and 10% aqueous HCl (5 mL), refluxed for 1 h, and then diluted with water (50 mL) and extracted with EtOAc (3 × 100 mL). The residue (188 mg) from the dried (Na_2SO_4) extracts was purified by elution from silica gel (20 g) with 50% $CHCl_3$ in CCl_4 to give **9** (121 mg, 47%): mp (Et_2O) 107–110 °C; IR ($CHCl_3$) 3600 (OH), 3300 (C≡CH), 1670 (C=O), 1620 (C=C) cm^{-1}; UV (MeOH) λ_{max} 240 nm (ε 14300); ^1H NMR ($CDCl_3$) δ 2.47 (s, 1, C≡CH), 5.84 (s, 1, C-4); MS m/e 324.209. Anal. ($C_{22}H_{28}O_2 \cdot 0.5H_2O$) C, H.

13β-(3′-Hydroxypropyl)-3-methoxygona-1,3,5(10)-trien-17β-ol Acetate (13). Li ribbon (666 mg, 950 mg-atoms) was added to a stirred solution of **1** (5.48 g, 13.5 mmol) in dry THF (40 mL) and NH_3 (120 mL) at −33 °C. After 20 min, the deep-blue color of the mixture was discharged with saturated NH_4Cl (5 mL), and the NH_3 was evaporated with a stream of N_2. Water (500 mL) was then added and the mixture extracted with EtOAc (3 × 500 mL). After evaporation of the dried (Na_2SO_4) extracts, the residue (5.28 g) in dry THF (40 mL) and NH_3 (120 mL) at −33 °C was treated with Li ribbon (333 mg, 47.5 mg-atoms). After stirring for 15 min, saturated NH_4Cl (5 mL) was added. Workup as before gave crude **10** (5.08 g), IR (CCl_4) 1685, 1670 cm^{-1} (enol ether); ^1H NMR ($CDCl_3$) δ 4.58 (m, 1, OC=CH), 5.60 (br s, 2, HC=CH), which was acetylated with Ac_2O (15 mL) and pyridine (15 mL). Concentrated HCl (4.8 mL) was added to a cold (0 °C) solution of the product (5.58 g) in MeOH (600 mL). After stirring at room temperature for 1 h, saturated $NaHCO_3$ (40 mL) was added and the solvent removed in vacuo. Water (300 mL) was added to the residue and the resulting mixture extracted with EtOAc (3 × 500 mL). Evaporation of the dried (Na_2SO_4) organic phase gave 5.40 g of a mixture which was eluted from silica gel (300 g) with 20% hexane in $CHCl_3$, to give the acetate of **12** (2.34 g, 39%), which was recycled, and then **13**. The latter was crystallized from CH_2Cl_2–hexane (0.79 g, 17%): mp 144–147 °C; IR (CCl_4) 3620 (OH), 1735 (C=O), 1610 (aromatic C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3, OAc), 3.53 (t, 2, J = 5 Hz, $-CH_2CH_2OH$), 3.70 (s, 3, O-CH_3), 4.66 (t, 1, J = 6 Hz, C-17), 6.47 (br s, 1, C-4), 6.55 (dd, 1, J = 5 and 2 Hz, C-2), 7.03 (d, 1, J = 5 Hz, C-1); MS m/e 372.230. Anal. ($C_{23}H_{32}O_4$) C, H.

13β-(3′-Hydroxypropyl)-3-methoxygona-1,3,5(10),9(11)-tetraen-17β-ol Acetate (14). Fluorosulfonic acid (18 mL) was added to a cold (−20 °C) suspension of **13** (1.80 g, 4.84 mL) in hexane (24 mL), followed by 1-adamantanol (2.88 g, 18.95 mmol) in portions over a period of 15 min. After stirring for 5 min, the red reaction mixture was cautiously poured onto ice (500 g) and extracted with EtOAc (3 × 500 mL). The residue (4.75 g) from the dried (Na_2SO_4) extracts was purified by elution from silica gel (200 g) with 20% hexane in $CHCl_3$ to yield **14** (1.26 g, 70%): mp (Et_2O–hexane) 152–156 °C; IR (CCl_4) 3620 (OH), 1735 (C=O), 1610 (aromatic C=C) cm^{-1}; UV (MeOH) λ_{max} 263 nm (ε 16900); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3, OAc), 3.56 (t, 2, J = 6 Hz, $-CH_2CH_2OH$), 3.76 (s, 3, OCH_3), 4.84 (t, 1, J = 6 Hz, C-17), 6.07 (br t, 1, J = 4 Hz, C-11), 6.50 (br s, 1, C-4), 6.58 (dd, 1, J = 6 and 2 Hz, C-2), 7.41 (d, 1, J = 6 Hz, C-1); MS m/e 370.214. Anal. ($C_{23}H_{30}O_4$) C, H.

11β,13β-(1′ξ-Hydroxypropano)-3-methoxygona-1,3,5(10),-8-tetraen-17β-ol Acetate (16). Chromium trioxide (2.55 g, 25.8 mmol) was quickly added to a stirred solution of pyridine (4.1 mL, 51.6 mmol) in CH_2Cl_2 (60 mL). After 15 min, the brick-red solution was cooled to 0 °C and a solution of **14** (1.60 g, 4.32 mmol) in CH_2Cl_2 (65 mL) was slowly added. Stirring was continued for an additional 15 min, when the mixture was diluted with water (500 mL) and extracted with EtOAc (3 × 500 mL). Evaporation of the dried (Na_2SO_4) extracts in vacuo yielded crude **15** (1.45 g): IR (CCl_4) 2710, 1735 cm^{-1} (CHO); ^1H NMR ($CDCl_3$) δ 9.63 (br s, 1, CHO). Zinc iodide (182 mg, 0.57 mmol) was added to a solution of crude **15** (1.45 g, 3.93 mmol) in CH_2Cl_2 (25 mL) and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with Et_2O (200 mL), washed with water (2 × 100 mL), and dried. The residue (1.42 g) was eluted from a prepacked silica gel column (Merck size C) with 20% hexane in $CHCl_3$ to give pure **16** (0.21 g, 13%) as a solid unstable at room temperature: mp (CH_2Cl_2–hexane) 121–126 °C; IR (CCl_4) 3580 (OH), 1735 (C=O), 1600 (aromatic C=C) cm^{-1}; UV (MeOH) λ_{max} 278 nm (ε 11500); ^1H NMR ($CDCl_3$) δ 2.04 (s, 3, OAc), 3.54 (m, 1, C-1′), 3.77 (s, 3, OCH_3), 4.71 (t, 1, J = 8 Hz, C-17), 6.66 (d, 1, J = 2 Hz, C-4), 7.70 (dd, 1, J = 5 and 2 Hz, C-2), 7.36 (d, 1, J = 5 Hz, C-1); MS m/e 368.199. Anal. ($C_{23}H_{28}O_4 \cdot 0.5H_2O$) C, H.

11β,13β-(1′ξ-Chloropropano)-3-methoxygona-1,3,5(10),8-tetraen-17β-ol Acetate (18). A solution of **16** (480 mg, 1.30 mmol) and triphenylphosphine (1.36 g, 5.20 mmol) in $CHCl_3$ (5 mL) and CCl_4 (50 mL) was refluxed for 20 h. The solvent was removed in vacuo, and the residue was eluted from silica gel (150 g) using 13% Et_2O in hexane, to yield **18** (311 mg, 60%) as a solid unstable at room temperature: mp (Et_2O–hexane) 104–120 °C; IR (CCl_4) 1735 (C=O), 1610 (aromatic C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3, OAc), 3.76 (s, 3, OCH_3), 4.22 (m, 1, C-1′), 6.65 (br s, 1, C-4), 6.70 (dd, 1, J = 5 and 2 Hz, C-2), 7.06 (d, 1, J = 6 Hz, C-1). Anal. ($C_{23}H_{27}O_3Cl$) requires M^+ 386.165; found 386.165.

17α-Ethynyl-17β-hydroxy-11β,13β-propanogon-4-en-3-one (22). Li wire (182 mg, 26.2 mg-atoms) was added to a solution of **18** (200 mg, 0.518 mmol) in THF (5 mL), *t*-BuOH (5 mL), and ammonia (50 mL). After stirring the solution at −33 °C for 2 h, the blue color was discharged with saturated NH_4Cl (5 mL), and the ammonia was evaporated at room temperature. The residue was diluted with water (200 mL) and extracted with EtOAc (2 × 200 mL) to yield **19** (155 mg): IR (CCl_4) 1690, 1660 cm^{-1} (enol ether); ^1H NMR ($CDCl_3$) δ 3.50 (s, 3, OMe), 6.23 (t, 1, J = 3 Hz, C-2).

A solution of this product (155 mg, 0.52 mmol), distilled aluminum isopropoxide (143 mg, 0.68 mmol), and cyclohexanone (0.73 mL) in toluene (18 mL) was refluxed for 1 h. The mixture was then cooled (50 °C), saturated Rochelle salt (8 mL) was added, and the resulting mixture was steam distilled until the distillate was clear. The residue was then extracted with EtOAc (2 × 300 mL) and purified by elution from silica gel (10 g) with 13% Et_2O in hexane to yield **20** (115 mg): IR (CCl_4) 1730 cm^{-1} (CO). This product (114 mg, 0.340 mmol) in dry THF (2 mL) was added to a cold (−78 °C) solution of freshly prepared lithium acetylide (3.4 mmol) in THF (15 mL). After stirring for 0.5 h at −78 °C, the reaction mixture was allowed to warm to room temperature (1 h) and decomposed with saturated NH_4Cl (2 mL) and water (30 mL). The resulting mixture was extracted with EtOAc (3 × 50

mL) and the organic phase was dried (Na_2SO_4) to give **21**: IR (CCl_4) 3300 cm^{-1} (C≡CH). This product (172 mg) was dissolved in MeOH (10 mL) and 10% aqueous HCl (5 mL) and refluxed for 1 h. The solution was diluted with water (50 mL), extracted with EtOAc (3 × 100 mL), and concentrated. The residue (119 mg) was partially purified by elution from silica gel with 40% $CHCl_3$ in CCl_4 to give 30 mg (16% overall yield from **18**) of a 7:3 mixture of two isomeric products (GC–MS, *m/e* 324). The mixture was partially separated by elution from a prepacked silica gel column (Merck, size A) with 40% $CHCl_3$ in CCl_4 to give the major isomer **22** (11 mg), intermediate fractions with both isomers, and then the minor isomer (4 mg) contaminated with 6% of **22** and 5% of an unknown compound. The major isomer **22** crystallized from ether: mp 162–166 °C; IR ($CHCl_3$) 3580 and 3400 (free and bonded OH), 3300 (C≡CH), 1660 (C=O), 1615 (C=C) cm^{-1}; UV (MeOH) λ_{max} 240 nm (ϵ 14850); ^1H NMR ($CDCl_3$) δ 2.52 (s, 1, C≡CH), 5.84 (s, 1, C-4); MS *m/e* 324.208. Anal. ($C_{22}H_{28}O_2 \cdot 0.25H_2O$) C, H. The minor isomer showed the same spectral characteristics.

13β-(3′-Chloropropyl)-17α-ethynyl-17β-hydroxygon-4-en-3-one (24b). A solution of **24a** (200 mg, 0.602 mmol) and *p*-toluenesulfonyl chloride (346 mg, 1.8 mmol) in dry collidine (4 mL) was allowed to stand at 5 °C for 18 h, poured into ice–water (50 mL) containing pyridine (1 mL), and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with saturated copper nitrate (3 × 20 mL) and water (2 × 20 mL), dried (Na_2SO_4), and then concentrated to obtain the tosylate: IR (CH_2Cl_2) 1180 cm^{-1} (S=O). The crude tosylate (292 mg, 0.60 mmol) and LiCl (83.6 mg, 1.99 mmol) in DMF (4 mL) was stirred at room temperature for 3 h, then poured into water (20 mL), and extracted with EtOAc (3 × 30 mL). Evaporation of the dried (Na_2SO_4) solvent in vacuo and elution of the residue from a prepacked silica gel column (Merck, size A) with 20% hexane in $CHCl_3$ gave **24b** (88 mg, 41%): mp 164–169 °C (CH_2Cl_2–hexane); IR ($CHCl_3$) 3300 (C≡CH), 1660 (C=O), 1625 (C=C) cm^{-1}; UV (MeOH) λ_{max} 239 nm (ϵ 15600); ^1H NMR ($CDCl_3$) δ 2.58 (s, 1, C≡CH), 3.60 (m, 2, C-3′), 5.82 (s, 1, C-4); MS *m/e* 360.186. Anal. ($C_{22}H_{29}O_2Cl \cdot 0.25H_2O$) C, H.

13β-(3′-Acetoxypropyl)-17α-ethynyl-17β-hydroxygon-4-en-3-one (24c). Acetic anhydride (0.14 mL) was added to a solution of **24a** (120 mg, 0.35 mmol) in pyridine (2 mL). After stirring the solution at room temperature for 3.5 h, MeOH (0.5 mL) was added, and the reaction mixture was poured into water (30 mL) and extracted with EtOAc (2 × 50 mL). The residue (136 mg) from the dried (Na_2SO_4) extracts was purified by elution from silica gel (2 g) with $CHCl_3$ to yield **24c** (120 mg, 89%). Although homogeneous by TLC and GLC, attempts at crystallization were unsuccessful: IR ($CHCl_3$) 3600 (OH), 3300 (C≡CH), 1730 (C=O), 1665 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3, OAc), 2.58 (s, 1, C≡CH), 4.07 (t, 2, J = 6 Hz, C-3′), 5.83 (s, 1, C-4); MS *m/e* 384.231. Anal. ($C_{24}H_{32}O_4$) C, H.

17α-Ethynyl-17β-hydroxy-13β-(3′-oxopropyl)gon-4-en-3-one Hemiacetal (24d). To a stirred suspension of pyridinium chlorochromate (189 mg, 0.878 mmol) in CH_2Cl_2 (7 mL) was added a solution of **24a** (200 mg, 0.585 mmol) in CH_2Cl_2 (5 mL). After stirring the mixture at room temperature for 45 min, the solvent was removed in vacuo, and the residue in $CHCl_3$ was passed through Florisil (3 g). The crude product (200 mg) was purified further by elution from silica gel (20 g) with 0.5% MeOH and 5% acetone in $CHCl_3$ to give **24d** (90 mg, 45%) as a mixture of epimers: IR ($CHCl_3$) 3580 (OH), 3300 (C≡CH), 1660 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR δ 2.57 (s, 1, C≡CH), 5.00 and 5.27 (2, m, 1, OCHO), 5.75 (s, 1, C-4). In spite of repeated attempts, satisfactory combustion analysis of **24d** could not be obtained; MS *m/e* 340.203.

17α-Ethynyl-17β-hydroxy-13β-[3′-(bromoacetoxy)-propyl]gon-4-en-3-one (24e). To a cold solution (0 °C) of **24a** (125 mg, 0.377 mmol) in CH_2Cl_2 (7 mL) was added bromoacetic acid (105 mg, 0.754 mmol) in CH_2Cl_2 (4 mL), followed by *N*-(dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (145 mg, 0.754 mmol) in CH_2Cl_2 (4 mL). After 5 min, pyridine (0.037 mL) was added and stirring was continued for 45 min. The reaction mixture was then taken up in $CHCl_3$ (50 mL) and shaken successively with 1% HCl, saturated $NaHCO_3$, and water and dried (Na_2SO_4). Evaporation of the solvent in vacuo and elution of the residue from silica gel (5 g) with 50% Et_2O in hexane, followed by crystallization from CH_2Cl_2/hexane, gave **24e** (96 mg, 51%): mp 148–150 °C (evacuated capillary); IR ($CHCl_3$) 3580 (OH), 3300 (C≡CH), 1730 (C=O), 1660 (C=O), 1610 (C=C) cm^{-1}; NMR δ 2.53 (s, 1, C≡CH), 3.77 (s, 2, $-CH_2Br$), 4.13 (t, 2, J = 6 Hz, C-3′), 5.73 (s, 1, C-4); MS *m/e* 462.140. Anal. ($C_{24}H_{31}O_4Br$) C, H.

Biological Procedures. Progestational and antiprogestational activities were determined by measuring uterine stimulation in the immature rabbit (Clauberg). Both assays were conducted by NICHD. In the anti-Clauberg assay, each compound (10–15 mg) together with progesterone (0.8 mg) in sesame oil was administered subcutaneously once a day for 5 days to rabbits (six) primed for 6 days with estradiol benzoate.

Binding affinities were determined using rabbit uteri as the receptor source, following procedures reported by Berg et al.[19] (11β- derivatives) or by Wani et al.[20]

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