Androgen Receptor Affinity of 5′-Acyl Furanosteroids

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Syntheses of 5′-acyl furanosteroids are described from the corresponding unsubstituted [3,2-*b*]furanosteroids using acid anhydrides and acid chlorides in the presence or absence of Lewis acids. New methods have been developed to prepare 5′-acetyl derivatives: reduction of a 5′-trichloroacetyl intermediate either by sodium formaldehyde sulfoxylate or with 10% Pd/C. Most of these 5′-acyl derivatives bind to the rat ventral prostate androgen receptor. However the antiandrogenic activity was diminished when compared with **4**, 5′-methylsulfonyl furanosteroid. Biological studies revealed that 5′-acyl furanosteroids were either androgens or modest antiandrogens. The electrostatic potential maps of the substructures of **3**, **4**, and 5′-acetyl *syn*- and *anti*-furanosteroids showed striking differences which may explain, to some extent, the lack of significant antiandrogenic activity of 5′-acyl furanosteroids.

Introduction

Modulation of androgen biosynthesis or action can be approached through four distinct biochemical pathways: (1) inhibition of gonadotropin synthesis/release at the pituitary/hypothalamic level, (2) gonadal inhibition of androgen biosynthesis, (3) enzymatic inhibition of androgen transformation in target tissues, and (4) androgen receptor antagonism (antiandrogen) in target tissues. Therapeutic intervention through mechanisms 1 and 2 have demonstrable efficacy in the treatment of neoplastic diseases. However when aggressively pursued, they are tantamount to chemical castration and are only suitable to life-threatening conditions such as prostate cancer (PC). In contrast, the agents working through pathways 3 and 4 hold promise for the treatment of non-life-threatening diseases such as benign prostatic hyperplasia (BPH), acne, seborrhea, and hirsutism.[1]

There are a number of pharmacological approaches being sought for the above diseases. These include inhibition of the conversion of testosterone to dihydrotestosterone by inhibiting 5α-reductase by a series of 4-aza steroids,[2-4] inhibition of androgen production by LHRH agonists,[5] inhibition of androgen action by androgen receptor antagonists, and inhibition of the transformation of androgens to estrogens by aromatase inhibitors.[1] In addition to these steroidal antagonists, nonsteroidal antiandrogens such as hydroxyflutamide (**1**) and bicalutamide (Casodex, **2**) which lack the hormonal agonist activity have been reported.[6,7] We are interested in the androgen receptor-based approach to androgen regulation and recently described the novel antiandrogens steroidal (methylsulfonyl)pyrazole (Zanoterone, **3**)[8] and the (methylsulfonyl)furan derivative (**4**) (Figure 1).[9]

Both of these compounds are androgen receptor antagonists and devoid of major ancillary endocrine activity. Structure–activity relationships (SAR) of these sulfonyl A-ring-fused heterocycles revealed potent antiandrogenic compounds which extended the androgen receptor boundary. It was postulated that in this new androgen receptor space the heteroatom attached at C-3 of the steroid nucleus, the position occupied by the oxygen of the natural ligand dihydrotestosterone, carries a partial negative charge to attain androgen receptor affinity. Thus, the bioisosteric replacement of (methylsulfonyl)pyrazole with other methylsulfonyl heterocycles also resulted in the androgen receptor affinity and the androgen antagonist activity.[10] It appears that in these series of compounds the appropriately substituted A-ring-fused heterocycles with a methysulfonyl group and C-17α substitution were an optimal combination for androgen receptor binding and in vivo antiandrogenic potency. Among these, **4**, a 5′-methylsulfonyl [3,2-*b*]-furanosteroid derivative, is more potent as an antiandrogen (ED_{50} = 8 mg/kg) than the other sulfonyl A-ring-fused heterocycles. Furanosteroids also provided avenues to prepare a number of 5′-substituted compounds. In order to explore the SAR for androgen receptor affinity of the [3,2-*b*]furanosteroids, we have introduced substituents at the 5′ position of furanosteroids other than a methylsulfonyl group. Among these, interest was to prepare 5′-acyl derivatives. Herein, we report the preparation, in vitro androgen receptor binding affinity, and in vivo antiandrogenic activity of various 5′-acyl [3,2-*b*]furanosteroids.

Chemistry

The unsubstituted A-ring-fused [3,2-*b*]furanosteroids were prepared as described previously (Scheme 1).[9] The 19-nor- and Δ^4-furanosteroids were also synthesized following the above reaction pathways from dihydronandrolone (19-nordihydrotestosterone) and ethisterone, respectively. The method described here provided a general method for the preparation of unsubstituted

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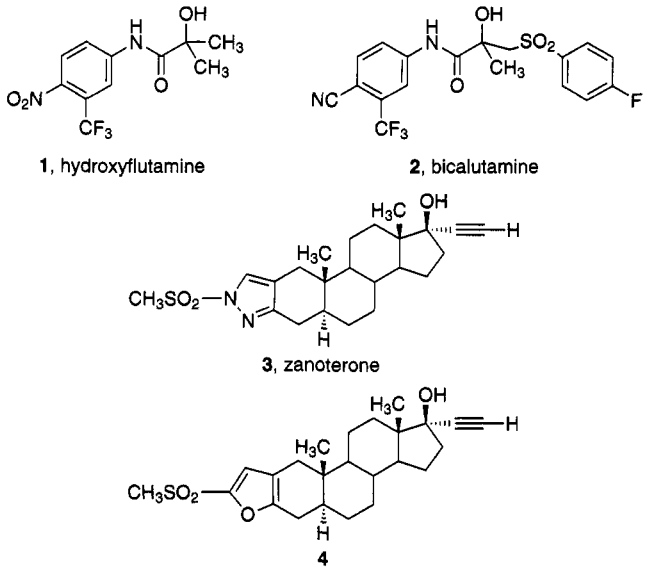
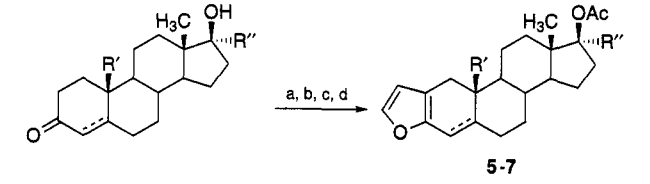
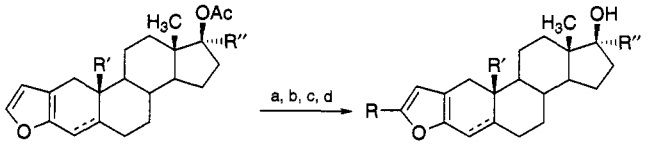


Figure 1. Structures of antiandrogens.

Scheme 1. Acylation[a]

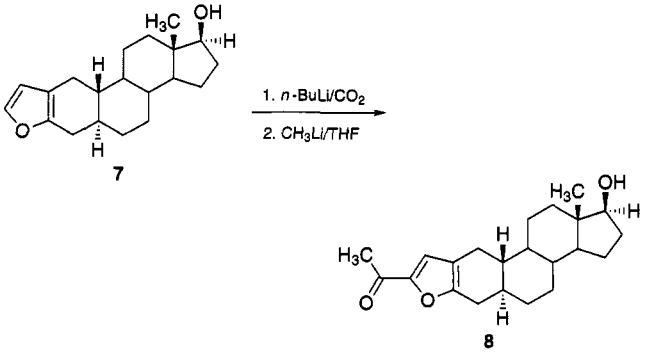


[a](a) $NaOCH_3$/Py, $THPOCH_2CO_2CH_3$; (b) HCl/C_2H_5OH; (c) DIBAL/CH_2Cl_2; (d) Ac_2O/Py/DMAR.



(a) $POCl_3$/DMF or method A; (b) $(RCO)_2O$ or RCOCl with Lewis acids (BF_3·Et_2O or Et_2AlCl); (c) KOH(NaOH) or K_2CO_3/CH_3OH/THF/H_2O; method B; (d) 1. CCl_3COCl/imidazole, 2. $NaSO_2CH_2OH$/EtOH and THF or 10% Pd/C, H_2, 50 psi, 3. K_2CO_3/CH_3OH/THF.

method C



furan derivatives. The 17-hydroxyl group of the furanosteroid was acetylated using the standard procedure (Ac_2O/pyridine/DMAP).

Formylation of either 17-*O*-acetyl or 17-OH furanosteroids were performed by a Vilsmeier–Haack method[11] in dichloroethane at O °C (Scheme 1). The hydrolysis of 17-*O*-acetyl or formyl group with K_2CO_3/CH_3OH gave the 5′-aldehydes **8** (42%), **9** (82%), and **10** (50%) (Table 1).

Acylation was done either using acid chlorides with Lewis acid catalysts such as diethyl aluminum chloride or with the anhydrides in the presence of BF_3·Et_2O (method A). In most instances, the 5′-ketones **11**, **12**, **16–30**, and **35–37** (Table 1) were isolated in reasonable yields (25–90%, Scheme 1). Reactive acid chlorides (trichloroacetyl chloride, Scheme 3) and anhydrides (trifluoacetic anhydride) do not require any catalyst; however, in the former case the yield of the trichloroacetyl derivative was improved with the addition of imidazole to neutralize the HCl generated during the reaction.

Application of the above acetylation procedure to prepare 5′-acetyl derivative **15** (19-norsteroid) resulted in poor yield (<10%) of the compound. Even the mild method described by Pennanen[12] (TsOAc) also gave <20% yield of the desired ketone after extensive purification. In this case the starting material and the resulting ketone appear to be very sensitive to the catalyst used and both tend to decompose during the reaction. We have devised two different methodologies (method B and C, Scheme 1) to overcome this problem.

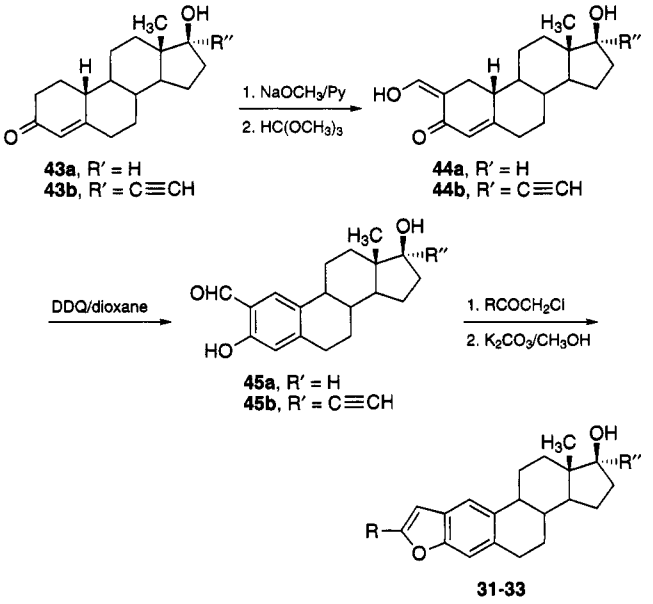
5′-Trichloroacetyl derivative **34** (R′, R″ = H, Scheme 3) was prepared from the corresponding 17-*O*-acetyl furanosteroid and trichloroacetyl chloride/imidazole in 81% isolated yield. On a small scale, the trichloroacetyl group was reduced with Rongalit (sodium formaldehyde sulfoxylate)[13,14] to give the ketone **15** (method B, Scheme 1) after hydrolysis of the 17-*O*-acetyl group in 74% overall yield. Even though this methodology gave the desired compound in respectable yield, it was not applicable to a larger scale due to the evolution of SO_2 gas. After a number of experiments with various reducing agents, we opted to use the catalytic hydrogenation method of reduction (10% Pd/C, DMF/Et_3N) which gave the 5′-acetyl derivative in 88% yield after the usual workup.

The dianion of **7** was quenched with CO_2 gas to give the 5′-carboxyl derivative **39** (R′, R″ = H, Scheme 3) which was then treated with CH_3Li·LiBr solution to give the desired ketone **15** in 47% yield (method C, Scheme 1). Even though these two different approaches were exemplified only for the preparation of ketone **15**, these methods could very well be utilized for the preparation of acetyl derivatives of other compounds.

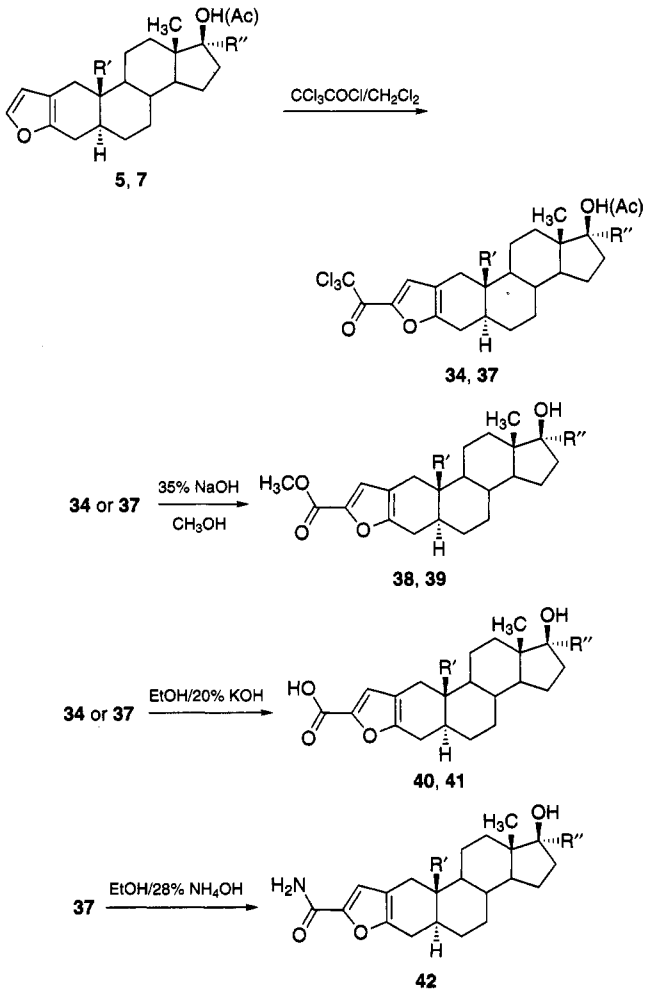
A-ring aromatic furanosteroidal ketones were prepared as depicted in Scheme 2. Most of the literature methods[15] to synthesize A-ring aromatic fused furans gave 5′-substituted [3,2-*b*]furanosteroids. In order to prepare various acylated derivatives, we needed a different route which either could provide these ketones from a common intermediate or gave the unsubstituted furanosteroid which could be derivatized. Thus, steroids **43 a,b** were converted to the 2-hydroxymethylene derivatives **44 a,b** by standard procedures, and the A-ring was aromatized with DDQ in *p*-dioxane to give the hydroxyaldeydes **45 a,b** in 43% and 52% yield, respectively. Reaction of the aldeydes with either chloroacetone or 1-bromo-2-butanone gave ketones **31** (54%), **32** (54%), and **33** (42%).

5′-Acids, -esters, and the -primary amide were prepared from the corresponding 5′-trichloroacetyl derivatives (**34** and **37**, Scheme 3) which were made from furanosteroids and trichloroacetyl chloride as described above. Methanolic sodium hydroxide treatment of these ketones gave the 5′-methyl esters **38** (62%) and **39** (56%)

Scheme 2. A-Ring Aromatic



Scheme 3. Acid/Ester/Amide



(Table 1). On the other hand, heating a solution of ethanolic potassium hydroxide with **34** and **37** resulted in the 5'-carboxylic acids **40** (68%) and **41** (65%). Trichloroacetyl ketone **34** was converted to amide **42** (R' = CH_3, R'' = H) in 73% yield by the treatment with ethanolic ammonium hydroxide.

Biological Results and Discussion

The list of compounds, their androgen receptor relative binding affinity (RBA), and their in vivo antiandrogenic and androgenic activity are presented in Table 1. Receptor affinity was determined following incubation periods with rat ventral prostate cytosol. Values were obtained following 1 h and approximately 18 h since it is characteristic of most androgen antagonists that their affinity for the androgen receptor falls precipitously over this time period.[10] Antiandrogens which lack detectable androgenic activity in vivo usually bind weakly to the receptor compared to androgen agonists. The reference antiandrogens Zanoterone (**3**) and 5'-methylsulfonyl furanosteroid (**4**) are examples of it. In previous papers[8,10] the effects of various 17α substituents on androgen receptor (AR) binding and in vivo antiandrogenic activity of these two compounds were reported. The generalization reported also holds for the acyl furanosteroids as well: maximal AR affinity is achieved with hydrogen and methyl; 17α-C≡CH is the preferred group for in vivo activity.

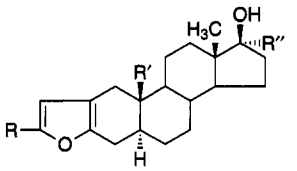
The unsubstituted [3,2-*b*]furanosteriods (**5**–**7**) were estrogenic (increase in uterine weight in the immature female rats; given orally). Formylation (**8**–**10**) and acetylation (**11**–**16**) at the 5' position of the furanosteroids resulted in compounds which lack the estrogenicity and retain the androgen receptor affinity. These acyl compounds including the 19-nor derivatives (**10**, **15**, and **16**) displayed significant androgenic activity rather than antiandrogenic activity when compared to **3** and **4** in vivo. Changing substitutions at C-17 from 17α-H to the corresponding 17α-C≡CH (**9**, **12**, and **16**), 17α-CH=CH_2 (**13**), or 17α-C_2H_5 (**14**) retained the androgen receptor affinity but only led to modest antiandrogenic activity (AA ED_{50} = ≥100). Since the acyl derivatives of 19-norfuranosteroids did not impart the androgenicity, no further derivatives of this series were prepared.

The homologue of acetyl, propionyl derivative **17**, showed compatible affinity for the androgen receptor, but the antiandrogenic activity was nearly 4–5-fold less than that of **4**. The corresponding 17α-C≡CH compound **18** did not bind to the androgen receptor as strongly as **17**, and it did not improve the antiandrogenic activity. Later these compounds were found to have an unacceptable degree of in vivo androgenic activity which halted their development as antiandrogens. Other extended or branched ketones, **19**–**22**, either lost their binding affinity or were androgenic. Similar activities were also displayed by the 5'-cyclic ketones **23**–**27**. On the other hand, the aromatic ketones **28** and **29** lost the binding affinity to the androgen receptor, indicating intolerance to bulky groups at this new receptor space.

A limited number of A-ring aromatic ketones, **31**–**33**, were prepared to balance the androgenicity with estrogenicity in hope to improve the overall profile of this series of compounds as potential antiandrogens. Ketone **31** retained the androgen receptor binding affinity but failed to provide any significant antiandrogenic activity. On the other hand, ketones **32** and **33** lost their affinity to the androgen receptor. The binding affinity of Δ^4-ketone **30** was similar to the A-ring aromatic ketone **31**.

Halogenated ketones, **35**-**37**, did not bind well to the androgen receptor and were either androgenic or estro-

Table 1. Androgen Receptor Binding Affinity of 5′-Acyl Furanosteroids



compound	R	R′	R″	relative binding affinity,[a] androgen receptor 1 h	relative binding affinity,[a] androgen receptor 18 h	AA ED_{50}[b]
testosterone				81.00	25.00	androgenic
Zanoterone				2.20	0.05	15
4	CH_3SO_2	CH_3	C≡CH	2.20	0.21	8
5	H	CH_3	H	2.40	0.32	>100
6	H	CH_3	C≡CH	0.25	<0.01	ND[c]
7	H	H	H	1.30	<0.01	ND
8	HCO	CH_3	H	15.20	3.70	≫100
9	HCO	CH_3	C≡CH	3.70	1.07	100
10	HCO	H	H	5.75	1.80	>100
11	CH_3CO	CH_3	H	22.10	2.10	androgenic
12	CH_3CO	CH_3	C≡CH	1.70	0.18	>100
13	CH_3CO	CH_3	$CH=CH_2$	1.50	0.20	androgenic
14	CH_3CO	CH_3	C_2H_5	0.83	<0.01	androgenic
15	CH_3CO	H	H	8.20	1.30	androgenic
16	CH_3CO	H	C≡CH	0.79	0.07	100
17	C_2H_5CO	CH_3	H	12.30	2.10	33
18	C_2H_5CO	CH_3	C≡CH	0.97	0.15	30
19	C_3H_7CO	CH_3	H	1.90	0.35	>75
20	$(CH_3)_2CHCO$	CH_3	H	3.50	0.20	androgenic
21	$(CH_3)_2CHCO$	CH_3	C≡CH	0.06	<0.01	androgenic
22	$(CH_3)_3CCO$	CH_3	H	0.16	0.04	>100
23		CH_3	H	3.40	0.28	100
24		CH_3	C≡CH	0.50	<0.01	androgenic
25		CH_3	$CH=CH_2$	0.30	<0.01	ND
26		CH_3	H	0.30	<0.01	≫100
27		CH_3	H	0.90	0.30	androgenic
28	C_6H_5CO	CH_3	H	<0.01	<0.01	>100
29	CH_3O-4-C_6H_4CO	CH_3	H	<0.01	<0.01	≫100
30	CH_3CO (Δ^4)	CH_3	H	2.47	0.89	ND
31	CH_3CO (A-aromatic)		H	2.40	1.70	100
32	CH_3CO (A-aromatic)		C≡CH	<0.01	<0.01	ND
33	C_2H_5CO (A-aromatic)		H	0.11	<0.01	ND
35	CF_3CO	CH_3	H	1.43	2.80	androgenic
36	CF_3CO	CH_3	C≡CH	0.16	0.01	estrogenic
37	Cl_3CCO	CH_3	C≡CH	<0.01	<0.01	androgenic
38	CO_2CH_3	CH_3	H	13.60	1.46	≫100
39	CO_2CH_3	CH_3	C≡CH	1.59	0.10	>50
40	CO_2H	CH_3	H	0.14	0.10	≫100
41	CO_2H	CH_3	C≡CH	<0.01	<0.01	≫100
42	NH_2CO	CH_3	C≡CH	1.90	0.20	56

[a] Values represent the mean of at least three separate determinations of rat ventral prostate androgen receptor binding affinity which is defined as ([R1881] at 50% binding inhibition/[competitor] at 50% binding inhibition) × 100. [b] Values represent graphically determined ED_{50} (dose required to inhibit testosterone propionate-induced rate ventral prostate weight gain by 50%). [^{3}H]R1881 is used as the radioligand. [c] ND = not done.

genic in vivo. Methyl esters **38** and **39** bound to the androgen receptor were similar to the ketones and exhibited modest antiandrogenic activity. The corresponding acids, **40** and **41**, proved to be much less active in receptor binding affinity and in vivo antiandrogenic activity. Amide **42** regained the androgen receptor affinity and displayed modest in vivo antiandrogenic activity which was comparable to the propionyl ketone **17**.

From the SAR described above, it was concluded that various 5′-acyl furanosteroids retain the androgen receptor affinity similar to **3** and **4** in this new receptor space. Regardless of electron-withdrawing capabilities of various acyl substituents at the 5′ position of furanosteroids, most lack any significant antiandrogenic activity when compared with 5′-(methylsulfonyl)furanosteroid **4**. The present series of compounds behave more like androgens in vivo than antiandrogens.

The difference in profile of these closely related series of compounds was not obvious. One can assume that the electronic character of these different substituents may play a significant role in introducing antiandrogenic activity in the furanosteroids since the electron-withdrawing capabilities of the methylsulfonyl group are greater than those of the acyl groups. Also acyl

substituents could assume *syn* or *anti* orientations, and one conformation may be favored over the other which may be the cause of reduced antiandrogenic activity.

In order to understand this distinction of the in vivo profile of Zanoterone (**3**), (methylsulfonyl)furan **4**, and acyl furanosteroids, (methylsulfonyl)pyrazole (A) and furan (B) (Figure 2) substructures were modeled in much the same fashion as described by Mallamo and co-workers[10] to permit an appropriate comparison of results. Again 5'-acetylfurans, both *syn* (C) and *anti* (D) substructures, were chosen as representatives for the acyl furanosteroids. The heterocyclic structures were constructed from fragments using the standard tools in the modeling package SYBYL.[17] These individual substructures were then submitted to full geometry optimization in the semiempirical package MOPAC[18] specifying the MNDO method[19] and the "precise" convergence as suggested by Dewar.[20] The new geometry and MOPAC charges were retrieved from these calculations and provided the basis for the electrostatic potential charge comparison (Figures 3 and 4). Dot surfaces were created using the Van der Waals surface and colored by an electrostatic potential method.[21] Three potential ranges were specified and colored differently; surface points with a potential greater than 5 kcal/mol are shown in blue (positive), potentials between −5 and 5 kcal/mol are shown in white (neutral), and points with potentials less than −5 kcal/mol are displayed in red (negative).

These electrostatic potential surface maps of substructures pyrazole (A) and furan (B) show identical overall distribution patterns of the negative charge in the ring and around the methylsulfonyl group (Figure 3). In contrast, the *syn* (C) or *anti*-(D) acetylfuran showed a diminished overall negative charge pattern. When these maps are viewed from the orthogonal positions (Figure 4), a more distinctive picture emerges which may explain the reduced antiandrogenic activity of 5'-acylfurans. These experiments confirm the hypothesis that for androgen receptor activity the partial negative charge is required at the heteroatom attached at the C-3 steroid position. Overall negative charge at the previously unexplored androgen receptor space, exemplified by the in vivo activity of Zanoterone (**3**) and **4**, may be necessary for the antiandrogenic activity.

Experimental Section

Melting points are uncorrected. ^{1}H NMR were recorded on a Varian model HA-100 or Bruker-AC 200 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were measured on a Perkin-Elmer model 467 or Nicolet 20 SX FT IR instrument. Mass spectra were determined using a JOEL JMS-O1SC model instrument. Elemental analyses were performed by Galbraith Laboratories of Knoxville, TN, or Instranal Laboratories of Rensselaer, NY. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was performed on E. Merck 5 × 20, Kieselgel 60 F-254 plates. Column chromatography was performed with Whatman LP52 (37−53 μM) SiO_2 or Kieselgel 60 (230−400 mesh). Preparative HPLC was performed on a Waters Prep 500 instrument using two standard silica Prep-pak cartridges. Most of the yields reported here are from single experiments and are unoptimized.

5α,17α-Pregn-2-en-20-yno[3,2-*b*]furan-17-ol (6). The compound was prepared from dihydroethisterone (500 g, 1.59 mol) following the procedure reported[9] or the procedure described below except pyridine was used as the solvent in the first step

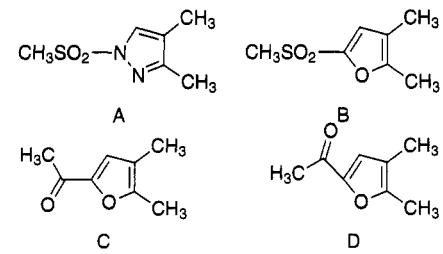


Figure 2. Substructures of (methylsulfonyl)- and acetyl- (*syn* and *anti*) pyrazole and furan.

followed by the treatment with either pTSA·H_2O or 6 N HCl in ethanol to give the corresponding furanone intermediate. The reduction with DIBAL-H and purification on silica gel (from CH_2Cl_2:hexanes, 1:1) afforded **6** (216.7 g, 40% overall): mp 105−107 °C; MS (CI) 339 (MH^+); IR (KBr, cm^{-1}) 3445, 2120, 1510; ^{1}H NMR (DMSO-d_6) δ 0.65 (s, 3 H), 0.70 (s, 3 H), 0.85−2.40 (m, 21 H), 2.50 (s, 1 H), 6.25 (s, 1 H), 7.38 (s, 1 H). Anal. ($C_{23}H_{30}O_2$) C, H.

Alternatively the compound could also be prepared (60% yield) from **5**, 5α,17β-androst-2-eno[3,2-*b*]furan-17-ol,[9] in two steps: oxidation of 17-OH (TFAA/DMSO) followed by the addition of lithium acetylide at −78 °C.

5α,17β-Estr-2-eno[3,2-*b*]furan-17-ol (7). To a suspension of sodium *tert*-butoxide [prepared from sodium (103.7 g, 4.5 mol) and 4.5 L of dry *tert*-butyl alcohol] in 2 L of dry THF was added solid dihydronandralone (552 g, 2 mol). The reaction mixture was stirred at 15−20 °C for 1 h. Methyltetrahydropyranyl acetate[9] (484.5 g, 2.6 mol) was added dropwise over a 30 min period while keeping the temperature of reaction below 20 °C with an ice-bath. The resulting mixture was stirred at room temperature for 18 h. To the thick reaction mixture was introduced 2 L of ethanol to obtain a clear yellow-orange solution which was cooled to 0−5 °C. To this was added 425 mL of 12 N HCl to adjust the pH to 1.5. The resulting suspension was stirred at room temperature for 6 h. Nearly half of the solvent was removed under reduced pressure at below 35 °C and poured into 16 L of water. The solid was filtered, washed with water, and dried to give the furanone as an off-white solid (607.4 g, 96%): mp 121−125 °C; ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.85−2.95 (m, 21 H), 3.50 (t, J = 7.5 Hz, 1 H), 4.25 (bs, 2 H). The furanone was used directly in the next step without any further purification.

To a stirred solution of the furanone (98.10 g, 0.31 mol) in 1.4 L of CH_2Cl_2 at −14 °C under a nitrogen atmosphere was added DIBAL-H [775 mL, 0.775 mol (1.0 M in CH_2Cl_2)] dropwise over a 2 h period. TLC (EtOAc:hexanes, 1:1) showed completion of the reaction. The reaction was quenched by addition of 4 L of water containing 225 mL of concentrated H_2SO_4. After the solution was stirred for 20 min, the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through a plug of Florosil. The Florosil pad was washed with 2 L of CH_2Cl_2 and evaporated to dryness to give **7**, 66.4 g (71%): mp 142−144 °C; IR (KBr, cm^{-1}) 3325, 1515; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 0.80−2.88 (m, 21 H), 3.65 (t, J = 8.0 Hz, 1 H), 6.20 (s, 1 H), 7.25 (s, 1 H). Anal. ($C_{20}H_{28}O_2$) C, H.

General Method for 17-O-Acetylation of [3,2-*b*]Furanosteroids. To a suspension of furanosteroid (0.012 mol) in 50 mL of pyridine and 5 mL of acetic anhydride was added 4-(dimethylamino)pyridine (0.144 g, 0.0012 mol). The mixture was stirred at room temperature for 24 h, poured onto 650 mL of ice−water, and stirred for 30 min. The resulting white solid was collected by filtration, washed with water, and dried. The purity of the product was checked by TLC and ^{1}H NMR before using it.

5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5'-carboxaldehyde (8): prepared from **5** following the procedure below, yield 42% as a pale yellow solid (EtOAc): mp 168−170 °C; MS (m/z) 342 (M^+); IR (KBr, cm^{-1}) 1680, 1510; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 6 H), 0.90−2.70 (m, 21 H), 3.68 (t, J = 7.5 Hz, 1 H), 7.05 (s, 1 H), 9.48 (s, 1 H). Anal. ($C_{22}H_{30}O_3$) C, H.

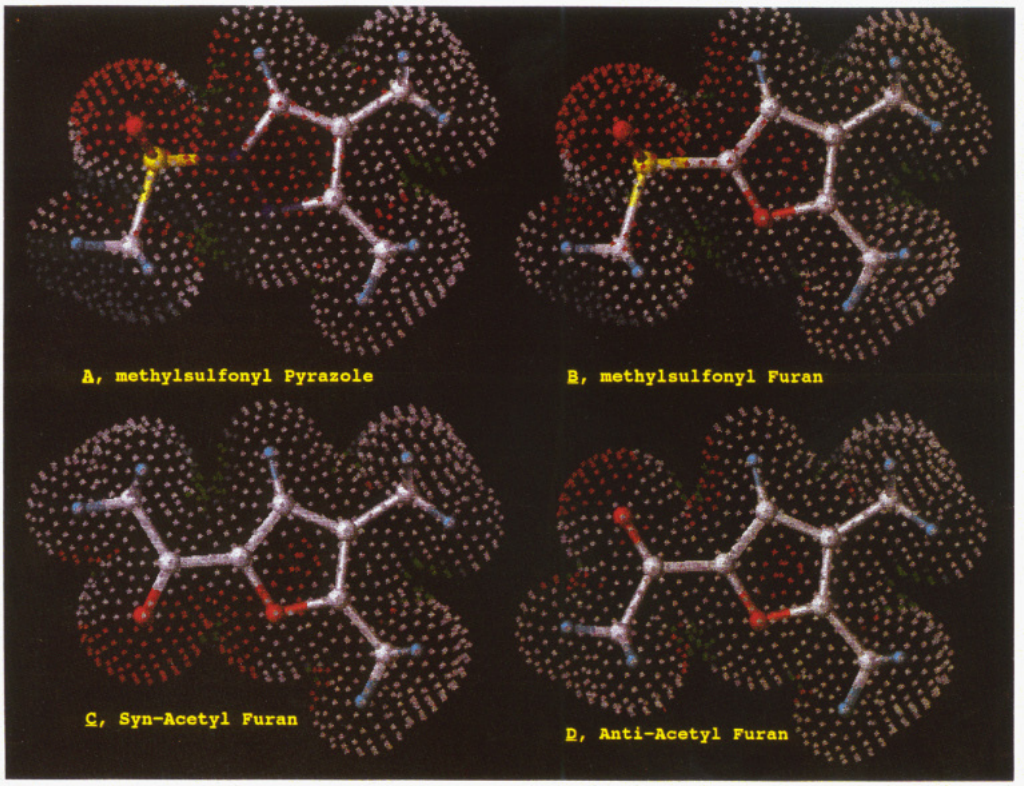


Figure 3. Graphical comparison of electrostatic potential surface maps (MNDO) for substructures A–D coded according to the electrostatic potential (in kcal/mol) experienced at each point on the surface. A potential of >5 kcal/mol is shown as blue (positive), <5 and >−5 kcal/mol is white (neutral), and <−5 kcal/mol is red (negative).

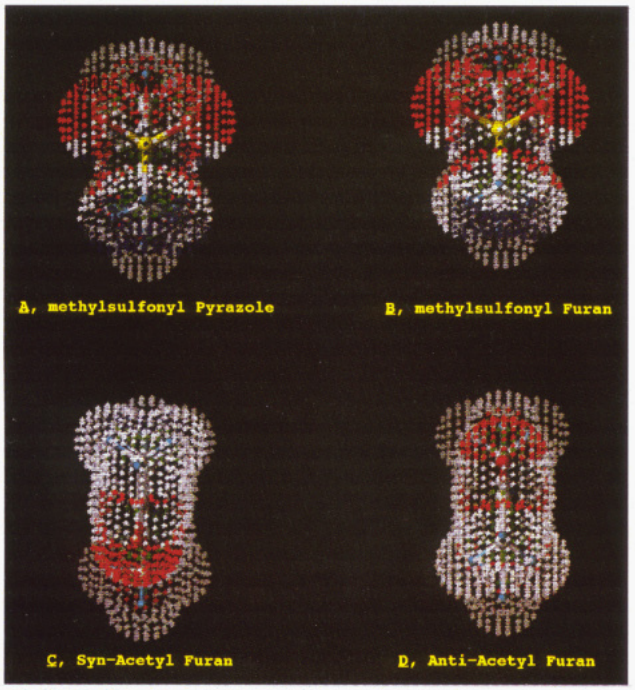


Figure 4. Orthogonal representation of electrostatic potential surfaces (Figure 3).

5α,17α-17-Hydroxypregn-2-en-20-yno[3,2-*b*]furan-5′-carboxaldehyde (9). To a stirred solution of DMF (162 mL, 2.09 mol) in 300 mL of dichloroethane at 0 °C under a nitrogen atmosphere was added $POCl_3$ (111 mL, 1.19 mol) dropwise over a period of 70 min. A solution of **6** (109 g, 0.32 mol) in 250 mL of dichloroethane was added within 5 min while cooling the reaction flask in an ice bath. The reaction mixture was stirred for another 30 min and then poured into 3 L of a stirred 20% NaOAc solution. The organic layer was separated, and the aqueous layer was extracted with 1 L of CH_2Cl_2. The combined organic layer was washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and evaporated to give diformylated product (C-5′ and C-17), 122.8 g (96%): MS (*m*/*z*) 394 (M^+).

To a suspension of the above product in 3 L of ethanol and 200 mL of water was added solid potassium carbonate (44.2 g, 0.32 mol), and the mixture was heated to reflux for 2 h while stirring. The reaction mixture was cooled to room temperature, filtered, and evaporated to dryness under reduced pressure. The resulting solid was triturated with 3 L of water; the solid was filtered, washed thoroughly with water, and dried to give **9**. The product was purified on a silica gel column from CH_2Cl_2:hexanes (1:1) and recrystallized from CH_3CN to give **9**, 96 g (82%) as a pale yellow solid: mp 243–245 °C; IR (KBr, cm^{-1}) 2125, 1690, 1515; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 0.88 (s, 3 H), 0.90–2.70 (m, 21 H), 2.56 (s, 1 H), 7.50 (s, 1 H), 9.50 (s, 1 H). Anal. ($C_{24}H_{30}O_3$) C, H.

5α,17β-17-Hydroxyester-2-eno[3,2-*b*]furan-5′-carboxaldehyde (10). The aldehyde was prepared from **7** as above in 50% yield (EtOAc:hexanes, 1:1): mp 160–162 °C; MS (CI) 329 (MH^+); IR (KBr, cm^{-1}) 1690, 1520; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.80–2.88 (m, 21 H), 3.65 (t, J = 7.8 Hz, 1 H), 7.05 (s, 1 H), 9.48 (s, 1 H). Anal. ($C_{21}H_{28}O_3$) C, H.

Acylation. Method A: RCOCl/Et_2AlCl (Example). 1-(5α,17α-17-Hydroxypregn-2-en-20-yno[3,2-*b*]furan-5′-yl)ethanone (12). To a stirred solution of 17-*O*-acetyl **6** (5.0 g, 0.013 mol) and acetyl chloride (1.51 mL, 0.021 mol) in 50 mL of CH_2Cl_2 at −20 °C under a nitrogen atmosphere was added diethyl aluminum chloride (3.93 mL, 0.039 mol, 1 M in hexane) over a 35 min period. After the reaction mixture was stirred for 2 h at −20 °C, the reaction was quenched by pouring the mixture into 100 mL of ice-cold 3 N HCl. The organic layer was separated, and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combined organic layer was then washed with water, and saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The removal of solvent under reduced pressure gave a crude product which was purified on a silica gel column from EtOAc:hexanes (1:10) to give the diacetate as a white solid, 4.0 g (73%): ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.86 (s, 3 H), 0.95–2.50 (m, 20 H), 1.98 (s, 3 H), 2.30 (s, 3 H), 2.55 (s, 1 H), 6.80 (s, 1 H). The compound was directly used in the next reaction.

A mixture of the diacetate (3.9 g, 9.2 mmol) and milled K_2CO_3 (3.8 g, 27.5 mmol) in 30 mL of methanol and 15 mL of THF was stirred at room temperature for 20 h. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was redissolved in CH_2Cl_2, washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 3.2 g of crude **12**. The product was purified on a silica gel column from CH_2Cl_2:ether (9:1) followed by recrystallization from methanol to give **12**, 2.9 g (84%), as a tan solid: mp 224–226 °C; IR (KBr, cm^{-1}) 2200, 1685, 1510; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3 H), 0.85 (s, 3 H), 0.90–2.70 (m, 21 H), 2.40 (s, 3 H), 2.60 (s, 1 H), 6.95 (s, 1 H). Anal. ($C_{25}H_{32}O_3$) C, H.

Or $(RCO)_2O/BF_3{\cdot}Et_2O$. Alternatively the above compound **12** was prepared in 65% yield from **6** (1 equiv) using acetic anhydride (2.1 equiv) and $BF_3{\cdot}Et_2O$ (1 equiv) in 60 mL of toluene at room temperature followed by the hydrolysis of the diacetate as above.

Method B (Example). 2,2,2-Trichloro-1-(5α,17β-17-acetoxyestr-2-eno[3,2-*b*]furan-5'-yl)ethanone (34, R', R'' = H) and 1-(5α,17β-17-Hydroxyester-2-eno[3,2-*b*]furan-5'-yl)ethanone (15). To a solution of 17-*O*-acetyl **7** (41.1 g, 0.12 mol, prepared from **7**/pyridine/Ac_2O/DMAP) in 210 mL of CH_2Cl_2 under a nitrogen atmosphere at room temperature was added imidazole (12.27 g, 0.18 mol). The amber-colored solution was cooled below 20 °C, and trichloroacetyl chloride (20.1 mL, 0.18 mol) was added slowly over a 1 h period. The reaction mixture was stirred for 20 h at room temperature and then poured onto ice–water. The resultant mixture was made basic from saturated $NaHCO_3$ solution, and the CH_2Cl_2 layer was removed. The aqueous layer was extracted with an additional 100 mL of CH_2Cl_2, and the combined CH_2Cl_2 layer was dried over anhydrous $MgSO_4$. The solvent was concentrated under reduced pressure to a small volume, 150 mL of EtOAc was added and the resulting suspension was heated to 70 °C. The suspension was cooled to 0–5 °C and filtered, washed with Et_2O, and dried. The solid was recrystallized from EtOAc to give **34** (R', R'' = H), 47.4 g (81%), as a white solid: mp 217–219 °C; IR (KBr, cm^{-1}) 1705, 1690; ^1H NMR ($CDCl_3$) 0.80 (s, 3 H), 0.95–2.85 (m, 20 H), 2.05 (s, 3 H), 4.50 (t, J = 7.5 Hz, 1 H), 7.22 (s, 1 H). Anal. ($C_{24}H_{29}Cl_3O_4$) C, H, Cl.

Procedures for the Reduction of the Trichloroacetyl Group. Sodium Formaldehyde Sulfoxylate Reduction, (Rongalit). To a solution of **34** (R', R'' = H) (2.50 g, 5.1 mmol) in 150 mL of EtOH and 50 mL of THF was added solid sodium formaldehyde sulfoxylate (3.84 g, 25.1 mmol). The resulting mixture was stirred under reflux for 12 h (*evolution of SO_2*) and filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was redissolved in CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The removal of solvent under reduced pressure gave a white solid, 1.52 g (96%). The ^1H NMR and TLC of the product were identical to the reduced product available from the catalytic reduction below. The hydrolysis of the 17-*O*-acetyl by the method described gave **15** in 74% overall yield.

Catalytic Reduction. To a solution of **34** (R', R'' = H) (8.00 g, 16.4 mmol) in 100 mL of dry DMF and triethylamine (9.14 mL, 66.0 mmol) was added 10% Pd/C (0.56 g). The mixture was then hydrogenated at room temperature at 50 psi using the Parr apparatus for 15 min. The reaction mixture was passed through a pad of magnesium sulfate, and the pad was washed thoroughly with DMF. The filtrate was concentrated under reduced pressure at 70 °C to a small volume. Addition of hot water followed by cooling to room temperature gave [TLC in EtOAc:cyclohexane (3:7) showed a single product] **15**, 5.7 g (91%), as a cream-colored solid: ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 0.95–2.88 (m, 21 H), 2.05 (s, 3 H), 2.44 (s, 3 H), 4.15 (t, J = 6.8 Hz, 1 H), 7.00 (s, 1 H).

The above product was dissolved in 30 mL of THF and 40 mL of methanol. To this was added milled potassium carbonate (6.28 g, 45.2 mmol), and the mixture was stirred at room temperature for 3 h. The TLC showed completion of the hydrolysis of the 17-*O*-acetyl group. The reaction mixture was cooled to 0–5 °C and filtered, and the filter cake was washed with CH_2Cl_2 thoroughly. The combined organic layer was washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the product which was recrystallized from CH_3CN to give **15**, 4.60 g (88%), as a white solid. The compound has identical IR and ^1H NMR as the product obtained by method C. This methodology was applicable to the large scale preparation of **15** and related compounds.

Method C (Example). 1-(5α,17β-17-Hydroxyester-2-eno[3,2-*b*]furan-5'-yl)ethanone (15). To a stirred solution of **7** (25.0 g, 0.083 mol) in 1.5 L of dry THF at −70 °C under a nitrogen atmosphere was added *n*-BuLi (148 mL, 0.21 mol, 1.4 M in hexane) dropwise over a 10 min period. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 3.5 h. The reaction mixture was cooled with an ice–water bath, and CO_2 was bubbled in until the TLC in EtOAC:hexane (1:1) of the reaction mixture indicated that most of the starting product was consumed. The introduction of the CO_2 was terminated, and 100 mL of 1 N HCl was added slowly; stirring was continued for another 10 min. The reaction mixture was then poured into 1.5 L of 1 N NaOH and 1.0 L of ether and stirred at room temperature for 10 min. The basic aqueous layer was separated and acidified with 3 N HCl. The solid was filtered, washed with cold water, and dried to give the 5'-carboxylic acid derivative. The acid was recrystallized from methanol to give **39** (R', R'' = H), 22.7 g (79%), as a white solid: mp 273–275 °C; IR (KBr, cm^{-1}) 1690, 1520; ^1H NMR (DMSO-d_6) δ 0.70 (s, 3 H), 0.75–2.75 (m, 21 H), 3.45 (t, J = 7.0 Hz, 1 H), 4.38 (bs, 1 H), 6.95 (s, 1 H).

To a stirred solution of acid (50.0 g, 0.145 mol) in 1.5 L of dry THF under an argon atmosphere at ice-bath temperature was added $CH_3Li{\cdot}LiBr$ (500 mL, 0.75 mol, 1.5 M in ether) over a 20 min period. The temperature of the reaction mixture was kept below 20 °C during the addition of the $CH_3Li{\cdot}LiBr$. The cooling bath was removed after completion of addition, and stirring was continued for an additional 1 h. The reaction mixture was cooled to −30 °C in a dry ice/acetone bath, and 120 mL of EtOAc was added dropwise over a 20 min period. The reaction was quenched with 400 mL of saturated NH_4Cl solution and the mixture was stirred for 10 min at −30 °C. The cooling bath was removed, and an additional 1 L of NH_4Cl solution and 1 L of EtOAc were added. The organic phase was separated, and the aqueous layer was extracted several times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, decolorized with charcoal, and evaporated under reduced pressure to give the crude ketone. The ketone was purified on a silica gel column from CH_2Cl_2:Et_2O (4:1) and recrystallized from CH_3CN to give **15**, 23.7 g (47%), as a white solid: mp 198–200 °C; MS (CI) 343 (MH^+); IR (KBr, cm^{-1}) 3480, 1665, 1515; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.90–2.80 (m, 21 H), 2.38 (s, 3 H), 3.60 (t, J = 7.5 Hz, 1 H), 6.98 (s, 1 H). Anal. ($C_{22}H_{30}O_3$) C, H.

1-(5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5'-yl)ethanone (11): method A (acetic anhydride), yield 55% as a pale yellow solid (EtOAc: hexanes, 1:1); mp 76–78 °C; MS (CI) 357 (MH^+); ^1H NMR (DMSO-d_6) δ 0.65 (s, 3 H), 0.74 (s, 3 H), 2.38 (s, 3H), 3.45 (t, J = 8.0 Hz, 1 H), 7.28 (s, 1 H). Anal. ($C_{23}H_{32}O_3$): C, H.

1-(5α,17α-17-Hydroxypregna-2,20-dieno[3,2-*b*]furan-5'-yl)ethanone (13). To a solution of **12** (20.0 g, 0.059 mol) in 150 mL of pyridine was added 30% palladium hydroxide/$SrCO_3$, and the mixture was hydrogenated at room temperature at 50 psi for 1.5 h. The catalyst was removed by filtration and washed with pyridine thoroughly. The combined filtrate was evaporated to dryness under reduced pressure to give the crude product. The compound was purified on a silica gel column from CH_2Cl_2:EtOAc (9:1) and recrystallized from ether to give **13**, 15.6 g (77%), as a off-white solid: mp 210–212 °C; IR (KBr, cm^{-1}) 1690, 1515; MS (m/z) 382 (M^+); ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.90 (s, 3 H), 1.00–2.70 (m, 21 H), 2.40 (s, 3 H), 5.15 (m, 2 H), 6.08 (dd, J = 8.0 Hz, J = 14.0 Hz, 1 H), 7.00 (s, 1 H). Anal. ($C_{25}H_{34}O_3$) C, H.

1-(5α,17α-17-Hydroxypregn-2-eno[3,2-*b*]furan-5'-yl)ethanone (14). To a solution of **13** (18.0 g, 0.047 mol) in 150 mL of pyridine was added 10% Pd/C (0.9 g, 5% by weight). The mixture was hydrogenated in a Parr shaker at room temperature for 6 h. At that time TLC in EtOAc:cyclohexane

(1:3) showed some starting material was left. Therefore more 10% Pd/C (0.5 g) was added, and the hydrogenation was continued for an additional 16 h. TLC showed there was no starting material present. The catalyst was filtered and washed with pyridine, and the combined filtrate was evaporated to dryness under reduced pressure. The resulting solid was recrystallized from CH_3CN to give **14**, 15.6 g (86%), as a white solid: mp 208–210 °C; MS (*m/z*) 384 (M^+); ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.88 (s, 3 H), 0.97 (t, J = 7.0 Hz, 3 H), 0.96–2.70 (m, 23 H), 2.42 (s, 3 H), 7.05 (s, 1 H). Anal. ($C_{25}H_{36}O_3$) C, H.

1-(5α,17α-17-Hydroxy-19-norpregn-2-en-20-yno[3,2-*b*]furan-5′-yl)ethanone (16): method A or B, yield 35% as a pale yellow solid (CH_3CN); mp 153–156 °C; IR (KBr, cm^{-1}) 2125, 1680, 1520; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 0.95–2.88 (m, 21 H), 2.42 (s, 3 H), 2.58 (s, 1 H), 7.25 (s, 1 H). Anal. ($C_{24}H_{30}O_3$) C, H.

1-(5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5′-yl)-1-propanone (17): method A (propionic anhydride), yield 54% as a pale yellow solid (EtOAc:hexanes, 1:1); mp 129–131 °C; ^1H NMR ($CDCl_3$) δ 0.75 (s, 6 H), 0.80–2.65 (m, 21 H), 1.25 (t, J = 8.4 Hz, 3 H), 2.84 (q, J = 8.0 Hz, 2 H), 3.68 (t, J = 7.0 Hz, 1 H), 6.95 (s, 1 H). Anal. ($C_{24}H_{34}O_3$) C, H.

1-(5α,17α-17-Hydroxypregn-2-en-20-yno[3,2-*b*]furan-5′-yl)-1-propanone (18): method A (propionic anhydride), yield 43% as a pale yellow solid (EtOAc:hexanes, 1:1); mp 192–194 °C; IR (KBr, cm^{-1}) 2120, 1670, 1510; ^1H NMR ($CDCl_3$) δ 0.74 (s, 3 H), 0.88 (s, 3 H), 0.98–2.65 (m, 21 H), 1.15 (t, J = 7.6 Hz, 3 H), 2.58 (s, 1 H), 2.77 (q, J = 7.8 Hz, 2 H), 6.95 (s, 1 H). Anal. ($C_{26}H_{34}O_3$) C, H.

1-(5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5′-yl)-butanone (19): method A (butyric anhydride), yield 51% as a pale yellow powder (Et_2O:hexanes, 1:1); mp 93–95 °C; IR (KBr, cm^{-1}) 1675, 1510; ^1H NMR ($CDCl_3$) δ 0.78 (s, 6 H), 0.85–2.55 (m, 23 H), 0.98 (t, J = 7.0 Hz, 3 H), 2.74 (t, J = 7.5 Hz, 2 H), 3.65 (t, J = 7.4 Hz, 1 H), 6.98 (s, 1 H). Anal. ($C_{25}H_{36}O_3$) C, H.

1-(5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5′-yl)-2-methyl-1-propanone (20): method A (isobutyric anhydride), yield 53% as a white solid (pentane); mp 100–102 °C; IR (KBr, cm^{-1}) 1675, 1520; ^1H NMR ($CDCl_3$) δ 0.78 (s, 6 H), 0.85–2.75 (m, 21 H), 1.15 (s, 3 H), 1.20 (s, 3 H), 2.85 (q, J = 6.5 Hz, 1 H), 3.66 (t, J = 6.8 Hz, 1 H), 7.02 (s, 1 H). Anal. ($C_{25}H_{36}O_3$) C, H.

1-(5α,17α-17-Hydroxypregn-2-en-20-yno[3,2-*b*]furan-5′-yl)-2-methyl-1-propanone (21): method A (isobutyric anhydride), yield 40% as a white solid (EtOAc:Et_2O, 1:1); mp 176–178 °C; IR (KBr, cm^{-1}) 1660, 1515; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3 H), 0.84 (s, 3 H), 1.00–2.65 (m, 21 H), 1.10 (s, 3 H), 1.20 (s, 3 H), 2.54 (s, 1 H), 3.25 (q, J = 7.0 Hz, 1 H), 6.84 (s, 1 H). Anal. ($C_{27}H_{36}O_3$) C, H.

1-(5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5′-yl)-2,2-dimethyl-1-propanone (22): method A (trimethylacetic anhydride), yield 53% as a pale yellow solid (CH_2Cl_2:hexanes, 1:1); mp 175–177 °C; IR (KBr, cm^{-1}) 1680, 1515; ^1H NMR ($CDCl_3$) δ 0.77 (s, 6 H), 0.95–2.55 (m, 21 H), 1.32 (s, 9 H), 3.60 (t, J = 6.8 Hz, 1 H), 6.84 (s, 1 H). Anal. ($C_{26}H_{38}O_3$) C, H.

Cyclopropyl(5α,17β-17-hydroxyandrosta-2,4-dieno[3,2-*b*]furan-5′-yl)methanone (23): method A (cyclopropanecarbonyl chloride), yield 34% as a white solid (Et_2O); mp 187–189 °C; IR (KBr, cm^{-1}) 1640, 1510; ^1H NMR ($CDCl_3$) δ 0.78 (s, 6 H), 0.90–2.70 (m, 26 H), 3.65 (t, J = 7.4 Hz, 1 H), 7.05 (s, 1 H). Anal. ($C_{25}H_{34}O_3$) C, H.

Cyclopropyl(5α,17α-17-hydroxypregn-2-en-20-yno[3,2-*b*]furan-5′-yl)methanone (24): method A (cyclopropanecarbonyl chloride), yield 36% as a white solid (cyclohexane:CH_2Cl_2, 1:1); mp 158–160 °C; IR (KBr, cm^{-1}) 1660, 1505; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 0.85 (s, 3 H), 1.00–2.80 (m, 26 H), 2.50 (s, 1 H), 6.88 (s, 1 H). Anal. ($C_{27}H_{34}O_3$) C, H.

Cyclopropyl(5α,17α-17-hydroxypregna-2,20-dieno[3,2-*b*]furan-5′-yl)methanone (25). To a solution of **24** (17.0 g, 0.042 mol) in 100 mL of pyridine was added 2% $Pd(OH)_2$/$SrCO_3$. The mixture was hydrogenated in a Parr apparatus at room temperature at 40 psi for 1 h. The catalyst was filtered, and the filtrate was evaporated to dryness. The product was purified on a silica gel column from EtOAc:CH_2Cl_2 (1:1) and recrystallized from EtOAc to give **25**, 18.1 g (85%), as a white solid: mp 140–142 °C; MS (CI) 409 (MH^+); IR (KBr, cm^{-1}) 1675, 1510; ^1H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.88 (s, 3 H), 0.90–2.85 (m, 26 H), 5.00 (m, 2 H), 5.65 (dd, J = 7.0 Hz, J = 12.0 Hz, 1 H), 6.66 (s, 1 H). Anal. ($C_{27}H_{36}O_3$) C, H.

(5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5′-yl)(1-methyl cyclopropyl)methanone (26): method A (1-methylcyclopropanecarbonyl chloride), yield 47% as an off-white solid (EtOAc:hexanes, 1:1); mp 159–161 °C; IR (KBr, cm^{-1}) 1650, 1515; ^1H NMR ($CDCl_3$) δ 0.75 (s, 6 H), 0.95–2.60 (m, 25 H), 1.48 (s, 3 H), 3.55 (t, J = 6.8 Hz, 1 H), 6.82 (s, 1 H). Anal. ($C_{26}H_{36}O_3$) C, H.

Cyclobutyl(5α,17β-17-Hydroxyandrosta-2,4-dieno[3,2-*b*]furan-5′-yl)methanone (27): method A (cyclobutanecarbonyl chloride), yield 25% (EtOAc:hexanes, 1:1) as a pale yellow solid; mp 153–155 °C; IR (KBr, cm^{-1}) 1665, 1515; ^1H NMR ($CDCl_3$) δ 0.77 (s, 6 H), 0.85–2.70 (m, 27 H), 3.65 (t, J = 7.0 Hz, 1 H), 3.78 (t, J = 6.4 Hz, 1 H), 6.90 (s, 1 H). Anal. ($C_{26}H_{36}O_3$) C, H.

(5α,17β-17-Hydroxyandrosta-2,4-dieno[3,2-*b*]furan-5′-yl)phenylmethanone (28): method A (benzoyl chloride), yield 26% as a white solid (EtOH); mp 239–241 °C; MS (CI) 420 (MH^+); IR (KBr, cm^{-1}) 1640, 1510; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.79 (s, 3 H), 0.85–2.75 (m, 21 H), 3.68 (t, J = 6.8 Hz, 1 H), 6.98 (s, 1 H), 7.55 (m, 3 H), 7.90 (m, 2 H). Anal. ($C_{28}H_{34}O_3$) C, H.

(5α,17β-17-Hydroxyandrosta-2,4-dieno[3,2-*b*]furan-5′-yl)(4-methoxyphenyl)methanone (29): method A (4-methoxybenzoyl chloride), yield 41% as a white solid (EtOAc:hexanes, 1:1); mp 198–200 °C; MS (CI) 449 (MH^+); ^1H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.75 (s, 3 H), 0.85–2.75 (m, 21 H), 3.68 (t, J = 7.3 Hz, 1 H), 3.85 (s, 3 H), 6.98 (d, J = 7.8 Hz, 2 H), 7.00 (s, 1 H), 7.88 (d, J = 8.0, Hz, 2 H). Anal. ($C_{29}H_{36}O_4$) C, H.

1-(5α,17β-17-Hydroxyandrosta-2,4-dieno[3,2-*b*]furan-5′-yl)methanone (30): method B, yield 52% as a pale yellow solid (EtOAc); mp 182–184 °C; IR (KBr, cm^{-1}) 1660, 1500; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 1.05 (s, 3 H), 1.10–2.80 (m, 18 H), 2.45 (s, 3 H), 3.68 (t, J = 7.5 Hz, 1 H), 6.10 (s, 1 H), 7.05 (s, 1 H). Anal. ($C_{23}H_{30}O_3$) C, H.

1-(17β-17-Hydroxyestra-1,3,5(10)-trieno[3,2-*b*]furan-5′-yl)ethanone (31). To a solution of nandrolone **43a** (164.64 g, 0.60 mol) in 1.5 L of toluene under a nitrogen atmosphere was added sodium methoxide (108.0 g, 2.00 mol). The mixture was stirred at room temperature for 30 min. Methyl formate (150 mL, 1.80 mol) was added dropwise, and stirring was continued for 48 h. After addition of 1.2 L of water, the aqueous layer was separated and neutralized by bubbling CO_2. The resulting solid/gummy product was extracted with CH_2Cl_2, washed with water and saturated salt solution, and dried over anhydrous $MgSO_4$. Removal of solvent at reduced pressure gave a yellow foam, 152.1 g (83%): ^1H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 1.00–2.88 (m, 18 H), 3.55 (t, J = 7.9 Hz, 1 H), 5.75 (s, 1 H), 7.05 (bs, 1 H), 7.26 (s, 1 H). The 2-hydroxymethyl compound **44a** was used directly in the next step without any further purification.

To a stirred solution of DDQ (147.5 g, 0.65 mol) in 1.57 L of *p*-dioxane was added a hot solution of 2-hydroxymethyl compound **44a** (196.0 g, 0.65 mol) in 1.05 L of *p*-dioxane under a nitrogen atmosphere. After the mixture was stirred for 2 h at room temperature, 200 mL of 2-propanol was added and stirring was continued for another hour. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was redissolved in CH_2Cl_2 and filtered again. The removal of CH_2Cl_2 under reduced pressure gave the crude A-ring aromatic compound which was purified on a silica gel column from CH_2Cl_2:Et_2O (1:1) to give the hydroxy aldehyde **45a**, 85.0 g (43%): ^1H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 1.00–2.78 (m, 15 H), 3.50 (t, J = 8.0 Hz, 1 H), 6.50 (s, 1 H), 7.38 (s, 1 H), 9.80 (s, 1 H), 10.50 (bs, 1 H). The aldehyde was pure enough for the next reaction.

To a solution of the aldehyde **45a** (14.5 g, 0.048 mol) in 1 L of acetone was added milled potassium carbonate (25.0 g, 0.18 mol) at room temperature with stirring. Freshly distilled chloroacetone (10 mL, 0.12 mol) was added dropwise, and the reaction mixture was heated to reflux with stirring for 18 h.

After cooling to room temperature, the reaction mixture was filtered through a Supercel pad and the solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column from CH_2Cl_2:Et_2O (4:1) to give the ketone which was recrystalized from CH_3CN to give **31**, 10.6 g (54%), as a pale yellow solid: mp 201–203 °C; MS (CI) 339 (MH^+); IR (KBr, cm^{-1}) 1680, 1545; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 1.10–2.45 (m, 14 H), 2.55 (s, 3 H), 3.02 (m, 2 H), 3.75 (t, J = 6.9 Hz, 1 H), 7.25 (s, 1 H), 7.44 (s, 1 H), 7.60 (s, 1 H). Anal. ($C_{22}H_{26}O_3$) C, H.

1-(17α-17-Hydroxy-19-norpregna-1,3,5(10)-trien-20-yno-[3,2-*b*]furan-5'-yl)ethanone (32). Aldehyde **45b** [15.3 g, 0.047 mol, prepared from norethindrone **43b** (19-norethisterone)] was dissolved in 1 L of acetone. Milled potassium carbonate (25 g, 0.18 mol) was added. The reaction mixture was stirred while refluxing, and freshly distilled chloroacetone (11.62 g, 0.12 mol) was added slowly. The reaction mixture was heated to reflux for 20 h and worked up as above. The product was purified on a silica gel column from CH_2Cl_2:Et_2O (4:1) and recrystallized from CH_3CN to give **32**, 9.2 g (54%), as an off-white solid: mp 222–224 °C; MS (CI) 365 (MH^+); ^1H NMR (DMSO-d_6) δ 0.80 (s, 3 H), 1.20–2.55 (m, 14 H), 2.60 (s, 3 H), 2.69 (s, 1 H), 3.05 (m, 2 H), 7.35 (s, 1 H), 7.50 (s, 1 H), 7.65 (s, 1 H). Anal. ($C_{24}H_{26}O_3$) C, H.

1-(17β-17-Hydroxyestra-1,3,5(10)-trieno[3,2-*b*]furan-5'-yl)propanone (33). The compound was prepared following the above procedure from hydroxy aldehyde **45a** and 1-bromo-2-butanone in 42% yield as a light yellow solid (EtOAc): mp 158–160 °C; MS (CI) 353 (MH^+); IR (KBr, cm^{-1}) 1690, 1560; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 1.18–2.50 (m, 14 H), 1.24 (t, J = 6.8 Hz, 3 H), 3.00 (m, 4 H), 3.68 (t, J = 7.0 Hz, 1 H), 7.24 (s, 1 H), 7.42 (s, 1 H), 7.60 (s, 1 H). Anal. ($C_{23}H_{28}O_3$) C, H.

2,2,2-Trifluoro-1-(5α,17β-17-hydroxyandrost-2-eno[3,2-*b*]furan-5'-yl)ethanone (35). To a stirred solution of the 17-*O*-acetyl of **5** (28.0 g, 89.20 mmol) in 140 mL of CH_2Cl_2 was added trifluoroacetic anhydride (38 mL, 270 mmol) over a 5 min period under a nitrogen atmosphere. The reaction mixture was stirred for 2 h and then poured into 500 mL of CH_2Cl_2 and 500 mL of water. The content was stirred for 10 min, and the organic layer was separated, washed with water and saturated NaCl solution, and dried over anhydrous Na_2SO_4. The removal of solvent at reduced pressure gave the crude product as a brown oil. This was used directly in the following reaction.

The above compound was dissolved in 360 mL of THF and 140 mL of methanol, and 15 mL of 10% NaOH solution was added. The reaction mixture was then stirred at room temperature for 30 min, and TLC (EtOAc:cyclohexane, 1:3) showed disappearance of starting material. The reaction mixture was filtered, and the filtrate was diluted with EtOAc, washed with water, and dried over anhydrous $MgSO_4$. The removal of solvent under reduced pressure gave the crude product which was purified on a silica gel column from EtOAc: hexanes (1:6) and recrystallized from EtOAc to give **35**, 11.2 g (31%), as an off-white solid (EtOAc): mp 99–101 °C; IR (KBr, cm^{-1}) 1685, 1515; ^1H NMR ($CDCl_3$) δ 0.78 (s, 6 H), 0.80–2.75 (m, 21 H), 3.68 (t, J = 7.0 Hz, 1 H), 7.32 (s, 1 H). Anal. ($C_{23}H_{29}F_3O_3$) C, H, F.

2,2,2-Trifluoro-1-(5α,17α-pregn-2-en-20-yno[3,2-*b*]furan-5'-yl)ethanone (36): prepared as described above from **6** in 50% yield as a tan solid (EtOAc); mp 101–103 °C; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 0.85 (s, 3 H), 0.90–2.85 (m, 21 H), 2.58 (s, 1 H), 7.35 (s, 1 H). Anal. ($C_{25}H_{29}F_3O_3$) C, H, F.

2,2,2-Trichloro-1-(5α,17α-pregn-2-en-20-yno[3,2-*b*]furan-5'-yl)ethanone (37): prepared from **6** and trichloroacetyl chloride following the procedure described below in 90% yield as an off-white solid (*tert*-butylmethyl ether); mp 172–175 °C; MS (CI) 484 (MH^+); IR (KBr, cm^{-1}) 1680, 1510; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.88 (s, 3 H), 0.90–2.70 (m, 21 H), 2.60 (s, 1 H), 7.48 (s, 1 H). Anal. ($C_{25}H_{29}Cl_3O_3$) C, H, Cl.

Methyl 5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5'-carboxylate (38). To a solution of **5** (14.2 g, 45.2 mmol) in 200 mL of dichloroethane under a nitrogen atmosphere was added dropwise trichloroacetyl chloride (25.41 g, 140 mmol) at room temperature. The resulting reddish solution was stirred at room temperature for 2 h and diluted with Et_2O. The mixture was washed with water and saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4. The removal of solvent and purification of the trichloroacetyl compound on a silica gel column (cyclohexane:EtOAc, 6:1) gave the ketone, 13.25 (64%): MS (CI) 461 (MH^+).

The trichloroacetyl derivative (10.10 g, 22.0 mmol) was dissolved in 100 mL of methanol at room temperature, and 6 mL of 35% aqueous solution of NaOH was added. After the mixture was stirred for 15 min, TLC (cyclohexane:EtOAc, 8:1) showed the disappearance of the starting material. The reaction mixture was diluted with water, and the product was extracted with Et_2O (4 × 100 mL). The combined extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The ester was purified on a silica gel column from cyclohexane: EtOAc (2:1) and recrystallized from hexanes:EtOAc (3:1) to give **38**, 5.1 g (62%), as a pale yellow solid: mp 110–112 °C; IR (KBr, cm^{-1}) 1715, 1530; ^1H NMR ($CDCl_3$) δ 0.78 (s, 6 H), 0.80–2.80 (m, 21 H), 3.65 (t, J = 6.8 Hz, 1 H), 3.83 (s, 3 H), 6.98 (s, 1 H). Anal. ($C_{23}H_{32}O_4$) C, H.

Methyl 5α,17α-17-hydroxypregn-2-en-20-yno[3,2-*b*]furan-5'-carboxylate (39): prepared as above from **37** in 56% yield as a white solid; mp 173–175 °C; MS (*m*/*z*) 396 (M^+); IR (KBr, cm^{-1}) 1705, 1510; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.88 (s, 3 H), 0.90–2.75 (m, 21 H), 2.60 (s, 1 H), 3.85 (s, 3 H), 7.00 (s, 1 H). Anal ($C_{25}H_{32}O_4$) C, H.

5α,17β-17-Hydroxyandrost-2-eno[3,2-*b*]furan-5'-carboxylic acid (40): prepared as below from the corresponding trichloro ketone **34** in 68% yield as a pale yellow solid (DMF: H_2O, 1:1); mp 295–296 °C; MS (CI) 358 (MH^+); IR (KBr, cm^{-1}) 1685, 1515; ^1H NMR (DMSO-d_6) δ 0.72 (s, 3 H), 0.80 (s, 3 H), 0.80–2.80 (m, 21 H), 3.55 (t, J = 7.0 Hz, 1 H), 6.85 (s, 1 H). Anal. ($C_{22}H_{30}O_4$) C, H.

5α,17α-17-Hydroxypregn-2-en-20-yno[3,2-*b*]furan-5'-carboxylic Acid (41). The trichloroacetyl compound **37** (13.30 g, 0.027 mol) was dissolved in 100 mL of EtOH, and 20 mL of 20% aqueous KOH was added. The reaction mixture was heated to reflux with stirring for 16 h, cooled to room temperature, and poured into 2 N HCl. The resulting solid was collected and recrystallized from EtOH to give **41**, 6.90 g (65%), as a colorless solid: mp 303–305 °C; MS (CI) 383 (MH^+); IR (KBr, cm^{-1}) 2120, 1680, 1510; ^1H NMR (DMSO-d_6) δ 0.70 (s, 3 H), 0.75 (s, 3 H), 0.80–2.75 (m, 21 H), 2.55 (s, 1 H), 7.05 (s, 1 H). Anal. ($C_{24}H_{30}O_4$) C, H.

5α,17α-17-Hydroxypregn-2-en-20-yno[3,2-*b*]furan-5'-carboxamide (42). Trichloroacetyl ketone **37** (23.90 g, 0.049 mol) was suspended in 200 mL of EtOH and 100 mL of 28% NH_4OH. The suspension was stirred with refluxing for 20 min, and the resulting solution was poured into a mixture of ice–water. The solid was filtered, washed with water, and dried to give the amide. The recrystallization from CH_3CN gave **42**, 13.70 g (73%), as a white solid: mp 225–227 °C; MS (CI) 382 (MH^+); IR (KBr, cm^{-1}) 1645, 1600, 1520; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.85 (s, 3 H), 0.88–2.55 (m, 21 H), 2.62 (s, 1 H), 6.05 (b, 2 H), 6.95 (s, 1 H). Anal. ($C_{24}H_{31}NO_3$) C, H, N.

Rat Prostate Androgen Receptor Competition Assay.[22] Cytosol was prepared with ventral prostates from castrated adult rats weighing approximately 250 g. Tissues were homogenized in TMDG buffer (10 mM Tris, 20 mM molybdate, 2.0 nM dithiothreitol, 10% glycerol, pH = 7.4) and centrifuged at the equivalent of 105000*g* for 1 h. Aliquots of the supernatant (cytosol) were incubated with [^{3}H]R1881 (methyltrienolone, 5 nM final concentration) in either the absence or presence of increasing concentration (10^{-9}–10^{-5} M) of R1881, reference, or test compounds for 1 h or overnight (approximately 18 h) at 4 °C. Because [^{3}H]R1881 binds weakly to progesterone and glucocorticoid receptors (approximately 5% at 5 nM), cytosols were pretreated with 1 μM triamcinolone acetonide to block these interactions. After a 1 or 18 h incubation period, a suspension of dextran-coated charcoal (1% charcoal, 0.05% dextran T-70) was added to the ligand/cytosol mixture and incubated for 5 min. The charcoal-bound [^{3}H]-R1881, i.e., non-protein-bound, was removed by centrifugation, and the supernatant (protein-bound [^{3}H]R1881) was counted. Relative binding affinities (RBA, used to quantify receptor binding competition) were calculated as the ratio of the concentration required to inhibit [^{3}H]R1881 specific binding

by 50% (with R1881 arbitrarily set at 100). Compounds that did not inhibit binding by 50% at a competitor concentration of 10 μM were considered to be inactive (RBA < 0.01). The interassay coefficient of variation based on 50% inhibition by R1881 was 17.0%.

Androgenic/Antiandrogenic Activity in Castrated Immature Rats.[23,24] Weanling Sprague–Dawley male rats were castrated and, beginning 1 week later, grouped by body weight and medicated orally with the test compound (vehicle was ethanol/cottonseed oil, 1:9 v/v) in the absence or presence of testosterone propionate (0.8 mg/kg sc) for 10 consecutive days. The day following the last medication, the rats were weighed and sacrificed. The ventral prostate of each rat was removed, blotted, and weighed. Antiandrogenic activity was defined by a graphically determined ED_{50} which was defined as the dose required to inhibit testosterone propionate-stimulated prostate weight gain by 50%. Compounds that did not inhibit prostate weight gain by 50% but demonstrated significant inhibition ($p < 0.01$) at a dose of 100 mg/kg were assigned an ED_{50} of >100. Compounds that did not demonstrate a statistically significant inhibition ($p < 0.01$, Dunnett's test) of prostate weight were assigned an ED_{50} of $\gg$100. The interassay coefficient of variation based on the effect of 4.0 mg/kg/day × 10 po of flutamide was 14.2%. Androgenic activity was defined by the percent increase in ventral prostate at a defined dose.

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