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SYNTHESIS AND ANDROGEN RECEPTOR AFFINITY OF STEROIDAL METHYLSULFONYLFURANS AND A METHYLSULFONYLTHIOPHENE

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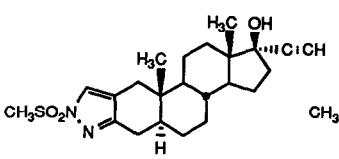
*Abstract: Syntheses of the unsubstituted steroidal [3,2-b]furan (**3a**), thiophene (**3b**) and [2,3-b]furan (**24**) are described. Lithiation of the THP ethers **18a** and **18b** followed by the reaction with methyl disulfide and deprotection gave the 5'-methylsulfide derivatives **19a** and **19b**. Oxidation of the sulfides and ethynylation provided the compounds **2a** and **2b**. Swern oxidation of the [2,3-b]furan **24** with DMSO/TFAA/diisopropylethylamine resulted in oxidation to the 17-ketone and introduction of a 5'-methylthio group to give **25**. Ethynylation at C-17 followed by oxidation of the sulfide group provided the product **27**. 5'-Methylsulfonyl[3,2-b]furanosteroid **2a** bound to the rat ventral prostate androgen receptor. However, the corresponding thiophene **2b** and the [2,3-b]furan **27** lacked affinity for the receptor.*

The 1'-methylsulfonyl steroidal[3,2-c]pyrazole **1** is reported[1,2] to bind to the rat ventral prostate androgen receptor in vitro and to block an androgen-induced response in the



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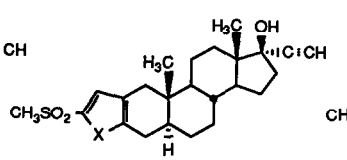
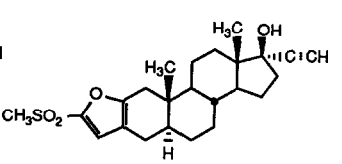


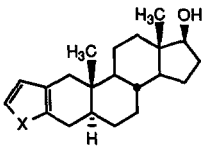
2a, X = O
2b, X = S



27

rat. As part of an effort to define the structural requirements for binding to the androgen receptor we prepared and evaluated the 5'-methylsulfonyl [3,2-b]furan **2a**, the [2,3-b]furan **27**, and the [3,2-b]thiophene **2b**. The compounds **2a**, **2b**, and **27** were chosen as the target compounds since structure-activity relationships among steroidal[3,2-c]pyrazoles[1] revealed that a methylsulfonyl substitution at N-1' and a C-17α substituent were the optimal combination for in vivo antiandrogenic activity.

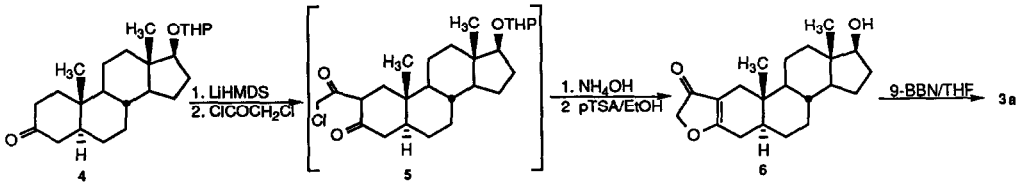
Although syntheses of A-ring fused [3,2-b] furano and thiophene steroids are known in the literature,[3,4,5] none of these synthetic routes could be adopted for the preparation of the required intermediate 4',5'-unsubstituted [3,2-b] furano (**3a**) and thiopheno (**3b**) steroids.



3a, X = O
3b, X = S

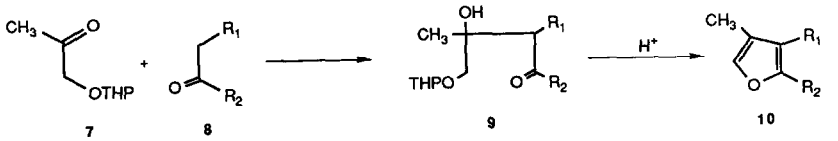
The initial approach (Scheme I) was based on Gariboldi's[6] synthesis of a furanoterpene. The lithium enolate of the ketone 4, prepared with 2 equivalents of lithium hexamethyldisilazane (LiHMDS), was quenched with excess chloroacetyl chloride affording the

SCHEME I



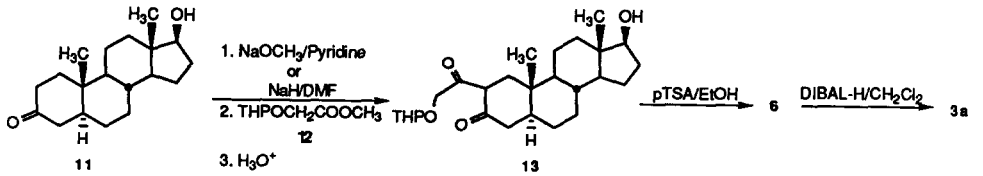
intermediate 5 which, without isolation, was treated with base followed by removal of the protecting group to give the furanone 6. The reduction of 6 with 9-BBN in THF afforded the desired furan 3a in 70% yield However the yield of the furanone 6 falls precipitously when the reaction 4 to 6 is scaled up or the reactants are concentrated. Thus an alternative pathway was required which was amenable to scaleup.

Hagiwara et al.[7] reported a synthesis of the furan 10 that utilized the aldol condensation of protected α-ketols 7 and the ketones 8 to give the intermediate 9 followed by dehydration with pTSA·H_2O as shown below. Application of this strategy for the synthesis of furan 3a is shown in Scheme II.



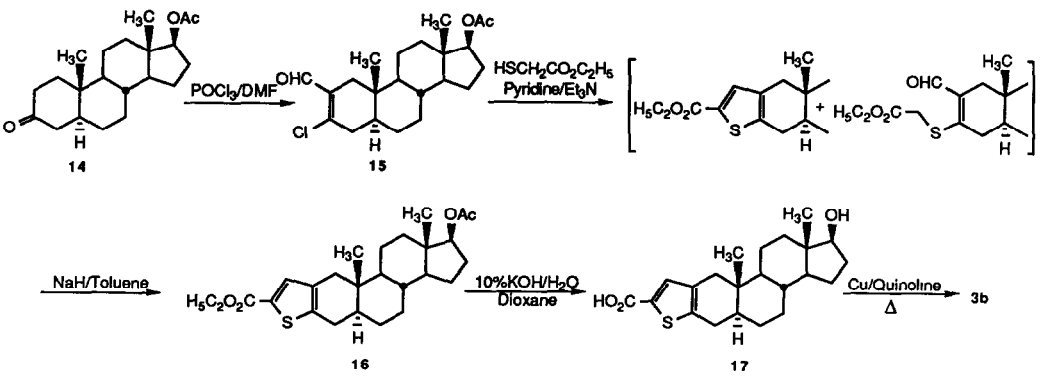
The sodium enolate prepared from androstanolone 11 with either sodium methoxide/pyridine or sodium hydride/DMF was condensed with methyl glycolate tetrahydropyranyl ether 12 to give 13 in 95% yield. Upon treatment with pTSA·H_2O in refluxing EtOH, 13 underwent deprotection, cyclization and dehydration to give 6 in 84% yield The [3,2-b]furanosteroid 3a was isolated in 60% yield after the reduction of furanone 6 with DIBAL-H. This procedure could be used on a large scale to prepare kilogram quantities of 3a.

SCHEME II



For the preparation of the thiophene 3b, 3-chloro-2-aldehyde 15[8] was condensed with ethyl thioglycolate in presence of pyridine/triethylamine to give a mixture of uncyclized and cyclized products (Scheme III). Sodium hydride in refluxing toluene induced complete cyclization to give 16 in 76% yield. Saponification of the ester gave 17 which was decarboxylated in the presence of Cu/quinoline at 200°C resulting in the formation of the [3,2-b]thiophene steroid 3b in 91% yield.

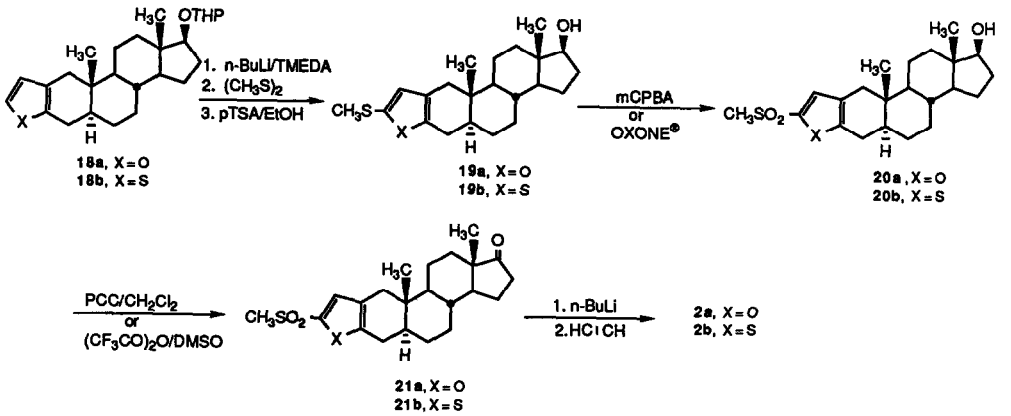
SCHEME III



Lithiation of the tetrahydropyranyl ethers 18a and 18b (Scheme IV) was accomplished with n-Buli/TMEDA. The addition of TMEDA was necessary to ensure complete lithiation (determined by quenching with D_2O and ^1H NMR spectra). After addition of methyldisulfide and deprotection of the tetrahydropyranyl ether with pTSA·H_2O in EtOH the 5'-methylthio derivatives 19a and 19b were isolated in 62% and 95% yield, respectively.

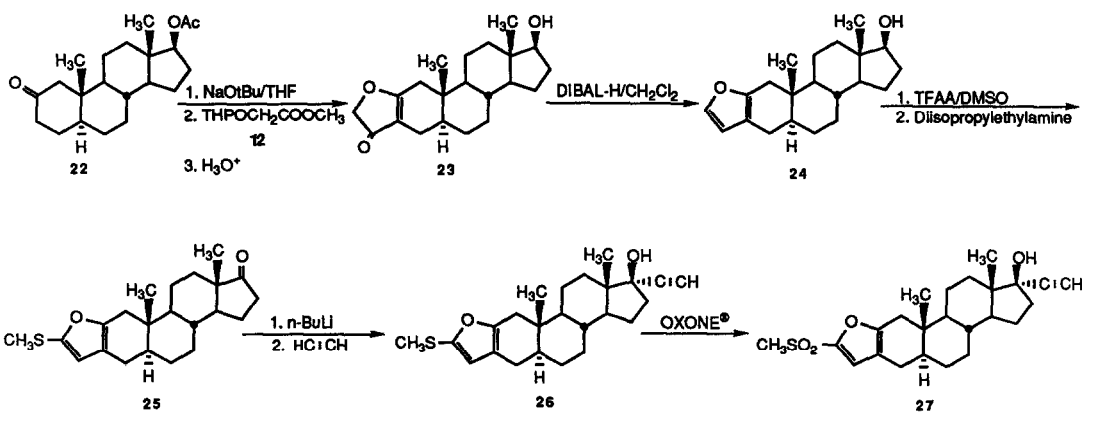
Oxidation of the sulphides (19a and 19b) with either 85% mCPBA at room temperature or preferably with OXONE®[9] afforded the sulfones 20a (70% yield) and 20b (86% yield). The 17-ketosteroids 21a and 21b were prepared with PCC/CH_2Cl_2 or Swern oxidation of 20a and 20b. Ethynylation of the ketones was accomplished by the usual methods[10] to give 2a and 2b.

SCHEME IV



The [2,3-b]furanosteroid 24 was prepared from the known 2-ketosteroid 22[11] (Scheme V). The use of sodium t-butoxide in THF improved the yield (95%) of the furanone 23 when compared to $NaOCH_3$/pyridine or NaH/DMF (yield 60-70%). Swern oxidation of 24 with TFAA/DMSO followed by quenching with diisopropylethylamine and stirring at room temperature resulted not only in oxidation at C-17 but also functionalization at the 5'-position of the furan ring with the methylthio group to give 25 in 90% yield. This unexpected and advantageous result, for which there are precedents[13,14], allowed us to complete the synthesis of the target steroid 27 in just two additional steps: addition of lithium acetylide at -78°C followed by oxidation of the resulting 5'-methylthio 26 with OXONE®.

SCHEME V



Androgen receptor binding affinity (RBA)

Androgen receptor affinity was determined following incubation with rat ventral prostate cytosol. Values were obtained following 1 h and 18 h incubation since it is characteristic of most androgen antagonists that their affinity for the androgen receptor falls precipitously during this time period.[15] Antiandrogens lacking detectable agonist activity in vivo usually bind with less affinity to the receptor than the agonists.[1]

Table I: Androgen receptor binding data

Compound	Relative Binding Affinity (%)*	
	1 h	18h
2a	2.2	0.21
27	0.15	<0.01
2b	<0.01	<0.01
1	2.2	0.05

*Values represent the mean value of at least three separate determinations of rat ventral prostate androgen receptor relative binding affinity which is determined as ([R1881] at 50% binding inhibition/[competitor] at 50% binding inhibition) x 100.

5'-Methylsulfonyl furan derivative **2a** bound to the receptor to the same extent as 1'-methylsulfonylpyrazole steroid 1[1] (Table I). However, the lack of significant binding to the androgen receptor of the 5'-methylsulfonyl[3,2-b]thiopheno **2b** and [2,3-b]furanosteroid **27** is surprising since the methylsulfonyl group occupies nearly the same space as the methanesulfonyl group of 1 and **2a**. This finding suggests that the five-membered ring heterocycle is more than a spacer element between the steroid nucleus and the methylsulfonyl group. The electronic character of the heterocyclic ring may also play a critical role in the binding affinity and will be the subject of a future publication.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B (60 MHz) or Varian Model HA-100 spectrometer or Bruker-AC 200 with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were measured on a JEOL FX 67.8 MHz instrument. IR spectra were measured on a Perkin-Elmer model 467 instrument. Mass spectra were determined using a JEOL JMS-01SC model instrument. Elemental analyses were performed by Galbraith Laboratories of Knoxville, TN or Instranol Laboratories of Rensselaer, NY.

TLC was performed on E. Merck 5x20 cm Kieselgel 60F-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 standard silica Prep-pak cartridges. Most of the yields reported are from single experiments and are unoptimized.

(5α,17β)-17-Hydroxyandrost-2-eno[3,2-b]furan-4'(5'H)-one (6).

To a stirred solution of lithium bis(trimethylsilyl)amide (3.35 g, 20 mmol) in dry THF (50 mL) under a N_2 atmosphere at 0°C is added dropwise the solution of 4 (3.76 g, 10 mmol) in dry THF (100 mL) After 1 h chloroacetyl chloride (10 mL, 62.44 mmol) was added. The cooling bath was removed and stirring was continued for 1 h.

The reaction mixture containing intermediate 5 was poured into a slurry of ammonia and crushed ice, stirred for 30 min, then extracted several times with ether and dried ($MgSO_4$). Evaporation of the Et_2O at reduced pressure gave a brown gum, 3.8 g (94%); ^1H NMR ($CDCl_3$) δ 3.45 (bs, $C\underline{H}_2$, 2H). This was used directly in the next reaction without further purification.

To a stirred suspension of above (11.8 g, 0.029 mol) in 95% EtOH was added pTSA·H_2O (6.0 g, 0.031 mol). Reaction mixture was refluxed for 1 h, cooled to room temperature (RT) and poured into a large volume of ice-water. The resulting precipitate was filtered, washed with water and dried to give 6. The compound was purified on a Florosil® column by elution with EtOAc to give a light yellow solid, 7.3 g (75%); mp 198-200°C; IR (KBr) 1690, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 6H), 3.55 (t, J=8.0Hz, 1H), and 4.36 (s, 2H); MS (m/e) 330 (M^+).

(5α,17β)-Androst-2-eno[3,2-b]furan-17-ol (3a).

To a stirred solution of 6 (1.0 g, 3.03 mmol) in dry THF (25 mL) at 0°C under a N_2 atmosphere was added a solution of 9-BBN (0.5 M solution in THF) (0.64 g, 5.25 mmol). After 1 h at 0°C and overnight at RT, MeOH (4 mL) was added and the solvent was evaporated under reduced pressure to give a foam (1.63 g) which was purified by passing through a Florosil® column using CH_2Cl_2 to give 3a as a foam (1.3 g) (still contaminated with 9-BBN byproducts); ^1H NMR ($CDCl_3$) δ 6.10 (d, J=2.0Hz, 1H), 7.20 (d, J=1.9Hz, 1H).

(2α,5α,17β)-17-Hydroxy-2-[[(tetrahydro-2H-pyran-2-yl)oxy]acetyl]androstan-3-one(13).

To a suspension of 60% NaH (48 g, 1.2 mol) in 100 mL dry DMF under a N_2 atmosphere at RT was added a solution of androstanolone 11 (145.2 g, 0.5 mol) in 500 mL dry DMF. The reaction mixture was stirred at RT for 1 h and was then treated with a solution of methylglycolate tetrahydropyranyl ether 12 (130.5 g, 0.75 mol) in 100 mL dry DMF (slight exotherm). The reaction was stirred for 24 h and 50 mL of MeOH was added. The reaction mixture was poured into 4 L of ice-water and filtered through a SuperCel® pad. The filtrate was neutralized with 6N HCl to give a beige solid which was collected, washed with water and dried to give 13, 206.6 g (95%). A sample was recrystallized from cyclohexane to give 13 as a white solid; mp 128-131°C; IR (KBr) 3480, 1710, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 6H), 0.90-2.40 (m, 30H), 3.60 (m, 2H), 3.75 (m, 1H), 4.75 (m, 1H). Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.16; H, 8.96.

(5α,17β)-17-Hydroxyandrost-2-eno[3,2-b]furan-4'(5'H)-one (6).

To a solution of 13 (190.6 g, 0.44 mol) in 600 mL 95% EtOH was added pTSA·H_2O (15 g, 0.08 mol). The solution was heated to reflux with stirring for 30 min. After cooling to RT, the reaction mixture was poured into ice-water. The resulting solid was filtered, washed with water and dried to give 6 (122.6 g, 84%). A sample was recrystallized from EtOAc:hexane (1:1) to give 6 as a yellow solid; mp 114-117°C (d); IR (KBr) 3460, 1690, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 6H), 0.90-2.50 (m, 21H), 3.60 (t, J=8.0Hz, 1H), 4.50 (s, 2H). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; O, 14.52. Found: C, 76.52; H, 9.03; O, 14.68.

(5α,17β)-Androst-2-eno[3,2-b]furan-17-ol (3a).

To a solution of 6 (122.0 g, 0.37 mol) in 1 L of anhydrous CH_2Cl_2 under a N_2 atmosphere at 0°C was added dropwise a solution of DIBAL-H (1.5 M solution in toluene) (115.6 g, 0.81 mol). The stirring was continued for 1 h then poured into ice-water containing 300 mL of concentrated HCl. The organic layer was separated, washed with water, and dried over $MgSO_4$. Removal of solvent gave a yellow syrup which was purified on a silica gel column by elution with CH_2Cl_2:hexane (1:1). The solid obtained was recrystallized from DMF:water (1:1) to give 3a as a white solid, 69.0 g (60%); mp 156-157.5°C; IR (KBr) 3420, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3H), 0.75 (s, 3H), 0.80-2.50 (m, 21H), 3.45 (t, J=8.5Hz, 1H), 6.20 (d, J=1.8Hz, 1H), 7.40 (d, J=1.9Hz, 1H). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.45; H, 9.56.

Ethyl(5α,17β)-17-(acetoxy)androst-2-eno[3,2-b]thiophene-5'-carboxylate (16).

To a solution of 15 (49.16 g, 0.129 mol) and ethyl 2-mercaptoacetate in 130 mL pyridine heated to reflux was added triethylamine (26 mL, 0.186 mol). After 15 min, the reaction mixture was cooled to RT and poured into ice-water. The product was extracted with toluene (4x250 mL), dried over $MgSO_4$, and concentrated to a volume of 700-800 mL. To this solution was added 60% NaH (7.5 g, 0;187 mol) and the reaction mixture was heated under reflux with stirring under a N_2 atmosphere for 1.5 h. The reaction mixture was poured into ice-water and extracted with EtOAc, washed with saturated salt solution, dried over $MgSO_4$ and evaporated to dryness. Recrystallization of the residue from EtOAc gave 16, 43.31 g (76%); mp 198-200°C; IR (KBr) 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.80 (s, 3H), 1.35 (t, J=8.0Hz, 3H), 2.05 (s, 3H), 4.35 (q, J=7.0Hz, 2H), 4.60 (t, J=7.0Hz, 1H), 7.42 (s, 1H). Anal. Calcd for $C_{26}H_{36}O_4S$. C, 70.23, H, 8.16; S, 7.40. Found: C, 70.34; H, 8.29; S, 7.33.

(5α,17β)-17-Hydroxyandrost-2-eno[3,2-b]thiophene-5'-carboxylic acid (17).

To a solution of 16 (5.9 g, 0.013 mol) in 200 mL of dioxane was added 200 mL of 10% aqueous KOH solution and heated at reflux with stirring for 4 h. The reaction mixture was then poured into ice-water and neutralized with 1N HCl and the resulting solid was filtered and dried. Recrystallization of the solid from acetone gave 17, 4.73 g (97%); mp >300°C; ^1H NMR (d_6DMSO) δ 0.60 (s, 3H), 0.70 (s, 3H), 0.80-2.70 (m, 21H), 3.50 (t, J=7.0Hz, 1H), 7.35

(s, 1H). Anal. Calcd for $C_{22}H_{30}O_3S$: C, 70.85; H, 8.07; S, 8.56. Found: C, 70.93; H, 8.09; S, 8.56.

(5α,17β)-Androst-2-eno[3,2-b]thiophene-17-ol (3b).

A solution of 17 (31.74 g, 0.085 mol) in 300 mL of quinoline was mixed with copper powder (45 g) under a N_2 atmosphere and heated at 200°C for 25 min. The reaction mixture was cooled to RT and filtered. The filtrate was poured into ice-water and neutralized with 6N HCl. The product was extracted with EtOAc and the solvent evaporated after drying over $MgSO_4$. The crude product was recrystallized from cyclohexane to give 3b, 25.4 g (91%); mp 141-141.5°C; IR (KBr) 3450, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.79 (s, 3H), 0.85-2.45 (m, 21H), 3.65 (t, J=7.0Hz, 1H), 6.72 (d, J=7.0Hz, 1H), 7.05 (d, J=7.0Hz, 1H). Anal. Calcd for $C_{21}H_{30}OS$: C, 76.31; H, 9.15; S, 9.70. Found: C, 76.71; H, 9.28; S, 9.70.

(5α,17β)-Androst-2-eno[3,2-b]furan-17-tetrahydropyranyl ether (18a).

To a solution of 3a (16.4 g, 0.052 mol) in 125 mL CH_2Cl_2 was added dihydropyran (6.56 g, 0.078 mol) followed by pyridinium p-toluene sulfonate (1.0 g, 0.004 mol). The reaction mixture was stirred at RT for 1.5 h and was poured into excess ice-water containing 25 mL of saturated $NaHCO_3$ solution. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated to dryness to give **18a** as solid, 20.3 g (98%), which was of sufficient purity to be used in the subsequent step; ^1H NMR ($CDCl_3$, 60MHz) δ 0.72 (s, 3H), 0.79 (s, 3H), 3.55 (m, 2H), 4.50 (4s, 1H), 6.10 (d, J=2.5Hz, 1H), 7.50 (d, J=2.4Hz, 1H). The corresponding [3,2-b]thiophene-17-tetrahydropyranyl ether **18b** was prepared in 95% yield following this procedure.

(5α,17β)-5'-(Methylthio)androst-2-eno[3,2-b]furan-17-ol (19a).

To a solution of **18a** (29.0 g, 0.073 mol) in 600 mL of anhydrous Et_2O under a N_2 atmosphere was added TMEDA (17.43 g, 0.15 mol) followed by n-Buli (2.6 M in hexane) (9.61 g, 0.15 mol) dropwise. The addition of n-Buli was controlled so that only a gentle reflux occurred. After addition was completed, the reaction mixture was stirred an additional 30 min at RT and a solution of methyl disulphide (14.13 g, 0.15 mol) in 10 mL of anhydrous Et_2O was added dropwise. The reaction mixture was stirred for 2 h at RT and quenched by slow addition of saturated NH_4Cl solution. The organic layer was separated, dried over $MgSO_4$ and evaporated to give a gum, 34.1 g; ^1H NMR ($CDCl_3$, 60MHz) δ 0.80 (s, 6H), 2.30 (s, 3H), 3.50 (m, 2H), 4.55 (s, 1H), 6.08 (s, 1H). The compound was used directly in the next step.

To a solution of the above compound in 500 mL EtOH was added pTSA·H_2O (2.5 g) and the reaction mixture was heated on a steam bath for 1 h. After concentration, the residue was poured into ice-water and the product was extracted with CH_2Cl_2. The organic layer was then washed with water, dried over $MgSO_4$ and evaporated to dryness to give a yellow gum which was purified on a silica gel column by elution with EtOAc:CH_2Cl_2 (1:1). Recrystallization from MeOH gave a white solid **19a**, 17.3 g (62%); mp 95-97°C; IR (KBr) 3410, 1500 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 0.75 (s, 6H), 0.80-2.30 (m, 21H), 2.35 (s, 3H), 3.65 (t, J=7.5Hz, 1H), 6.22 (s, 1H). Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.29; H, 8.95; S, 8.89. Found: C, 73.42; H, 8.75; S, 9.10.

Oxidation of Sulphides to Sulfones:

With mCPBA: To a solution of sulphide (1 eq) in CH_2Cl_2 was added 85% mCPBA (2.5 eq) at 0°C under a N_2 atmosphere. The reaction mixture was stirred for an additional 1 h at RT and quenched with 10% sodium sulfite solution. The organic layer was separated, washed with water and dried over $MgSO_4$. Removal of CH_2Cl_2 gave the crude product which was purified on a silica gel column [EtOAc:hexane (3:7)] and recrystallized.

With Oxone®: To a solution of the sulphide (1 eq) in MeOH at 0°C was added an aqueous solution of Oxone® (3 eq) and the reaction mixture was stirred at RT for 24 h. It was then poured into ice-water and extracted with CH_2Cl_2 (3x). The organic layer was dried over $MgSO_4$ and evaporated to dryness and the product was purified on a silica gel column as before.

(5α,17β)-5'-(Methylsulfonyl)androst-2-eno[3,2-b]furan-17-ol (20a).

Prepared from 19a with mCPBA 70% yield (EtOAc:hexane, 1:1); mp 144-146°C; IR (KBr) 3480, 1500, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 6H), 0.85-2.70 (m, 21H), 3.15 (s, 3H), 3.65 (t, J=7.0Hz, 1H), 6.95 (s, 1H). Anal. Calcd for $C_{22}H_{32}O_4S$: C, 67.31; H, 8.21; S, 8.16. Found: C, 67.31; H, 8.30; S, 8.24.

(5α)-5'-(Methylsulfonyl)androst-2-eno[3,2-b]furan-17-one (21a).

To a suspension of pyridinium chlorochromate (9.5 g, 0.044 mol) in 100 mL of CH_2Cl_2 under a N_2 atmosphere was added dropwise a solution of **20a** (11.5 g, 0.03 mol) in 100 mL of CH_2Cl_2. The reaction mixture was then stirred at RT for 4 h. The organic layer was decanted and the tarry residue was triturated with CH_2Cl_2 (2x200 mL). The combined CH_2Cl_2 solution was then washed with 2N HCl, water and dried over $MgSO_4$. The solution was then passed through a Florosil® pad and the pad was washed with CH_2Cl_2. The combined filtrate was evaporated to dryness to give **21a**, 9.1 g (80%). A sample was recrystallized from EtOAc to give a white solid; mp 220-222°C; IR (KBr) 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.90 (s, 3H), 1.00-2.70 (m, 20H), 3.12 (s, 3H), 6.95 (s, 1H). Anal. Calcd for $C_{22}H_{30}O_4S$: C, 67.66; H, 7.74; S, 8.21. Found: C, 67.50, H, 7.56; S, 8.39.

(5α,17α)-5'-(Methylsulfonyl)pregn-2-en-20-yno[3,2-b]furan-17-ol (2a).

Acetylene gas was passed into 80 mL of anhydrous THF at -78°C for 1 h. n-Buli solution (4.03 g, 0.063 mol) in hexane (2.6 M) was added dropwise over 20 min to the above solution with continuous introduction of acetylene gas. After stirring for 10 min, a solution of **21a** (8.4 g, 0 021 mol) in 15 mL of anhydrous THF was added slowly. The reaction mixture was then stirred at -78°C for 1 h and at RT for 2 h. It was quenched by slow addition of saturated NH_4Cl solution. The THF layer was separated, dried over $MgSO_4$ and evaporated to dryness to give a foam. The foam was triturated with Et_2O to give a solid which was recrystallized

from CH_2Cl_2:Et_2O (1:1) to give **2a**, 7.3 g (81%); mp 159-161°C; IR (KBr) 3365, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3H), 0.80 (s, 3H), 1.10-2.50 (m, 21H), 2.58 (s, 1H), 3.10 (s, 3H), 6.94 (s, 1H). Anal. Calcd for $C_{24}H_{32}O_4S$: C, 69.20; H, 7.74; S, 7.70. Found: C, 68.94; H, 7.68; S, 7.90.

(5α,17β)-5'-(Methylthio)androst-2-eno[3,2-b]thiophene-17-ol (19b).

Prepared following the procedure used for the furan derivative **19a** in 95% yield; mp 117-118°C; IR (KBr) 3460, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (s, 3H), 0.78 (s, 3H), 0.90-2.47 (m, 19H), 2.49 (s, 3H), 2.55-2.70 (m, 2H), 3.65 (t, J=7.5Hz, 1H), 6.7 (s, 1H). Anal. Calcd for $C_{22}H_{32}OS_2$: C, 70.16; H, 8.56; S, 17.03. Found: C, 69.94; H, 8.60; S, 17.00.

(5α,17β)-5'-(Methylsulfonyl)androst-2-eno[3,2-b]thiophene-17-ol (20b).

Prepared following the procedure described for the preparation of furan **20a** in 86% yield; mp 242-245°C; IR (KBr) 3600, 3580, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (s, 3H), 0.78 (s, 3H), 0 90-2.85 (m, 21H), 3.15 (s, 3H), 3.66 (t, J=8.0Hz, 1H), 7.35 (s, 1H). Anal. Calcd for $C_{22}H_{32}O_3S_2$: C, 64.67, H, 7.89; S, 15.69. Found: C, 64.59; H, 8.20; S, 16.10.

(5α,17α)-5'-(Methylsulfonyl)pregn-2-en-20-yno[3,2-b]thiophene-17-ol (2b).

To a solution of TFAA (9.4 mL, 0.066 mol) in 40 mL of CH_2Cl_2 at -78°C was added DMSO (6.2 mL, 0.088 mol) dropwise over 15 min and stirred for 30 min at -78°C. A suspension of **20b** (17 45 g, 0.043 mol) in 150 mL of CH_2Cl_2 was added over a 30 min period. After ? h of stirring at -78°C, diisopropylethylamine (38.2 mL, 0.219 mol) was added and the reaction mixture was warmed to RT Removal of solvent under reduced pressure gave a residue which was triturated with water to give a solid. The solid was filtered, dried and suspended in EtOAc with stirring The resulting solid was collected, washed with EtOAc and dried to give **21b**, 15 97 g (91%); MS (CI) 407 (MH^+); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.92 (s, 3H), 1.0-2.85 (m, 20H), 3.15 (s, 3H), 7.35 (s, 1H).

The ketone **21b** was used directly in the ethynylation reaction using the procedure described for the preparation of **2a** to give **2b** in 72% yield; mp 226-228°C; IR (KBr) 2150, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.85 (3H, s), 1.20-2.50 (m, 19H), 2.60 (s, 1H), 2.65-2.75 (m, 2H), 3 15 (s, 3H), 7.35 (s, 1H). Anal Calcd for $C_{24}H_{32}O_3S_2$: C, 66.63; H, 7.46; S, 14.82. Found: C, 66.55; H, 7.43; S, 15.09.

(5α,17α)-5'-(Methylsulfonyl)pregn-2-en-20-yno[2,3-b]furan-17-ol (27).

To a solution of **22** (32 0 g, 0.096 mol) in 300 mL of dry THF under a N_2 atmosphere was added sodium t-butoxide (27.65 g, 0.029 mol). After stirring at RT for 1 h, methylglycolate THP ether **12** (34.89 g, 0.2 mol) was added dropwise and stirring was continued at RT for 20 h. After removal of the solvent under reduced pressure the residue was dissolved in 95% EtOH and concentrated HCl was added to pH ≈2.0 After stirring at RT for 2 h, reaction mixture was poured into excess ice water and the product was extracted with CH_2Cl_2, dried over $MgSO_4$

and the solvent evaporated to dryness to give 23 as a foam, 33.1 g (95%); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.75 (s, 3H), 0.80 (s, 3H), 3.56 (t, 1H), 4.40 (bs, 2H). The compound was used directly in the next step.

The reduction of 23 with the DIBAL-H as before gave the furan 24 as a foam in 25% yield; MS (CI) 315 (MH^+); ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3H), 0.77 (s, 3H), 3.60 (t, J=8.0Hz, 1H), 6.15 (d, J=2.5Hz, 1H), 7.20 (d, J=2.5Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 11.00, 11.97. 20.71, 23.36, 26.95, 28.67, 30.48, 31.27, 35.56, 36.64, 37.18, 37.50, 42.65, 42.81, 50.85, 53.98, 81.75, 109 81, 114 72, 140.29, 150.55.

To a solution of TFAA (27.66 g, 0.132 mol) in 60 mL CH_2Cl_2 at-78°C was added dropwise a solution of DMSO (20.4 g, 0.261 mol) in 60 mL CH_2Cl_2. After stirring for 1 h, a solution of 24 (6.0 g, 0.019 mol) in 150 mL CH_2Cl_2 was added over a 2 h period. After stirring for an additional 1 h at -78°C, diisopropylethylamine (60.12 g, 0.465 mol) was added dropwise. The reaction mixture was then stirred for 20 h at RT and poured into ice water. The organic layer was separated, washed with cold 1N HCl, water, cold saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of solvent gave 25 (6.88 g, 90%) as a foam; IR (KBr) 1738 cm^{-1}; MS (CI) 359 (MH^+); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.80 (s, 3H), 0.89 (s, 3H), 2.30 (s, 3H), 6.10 (s, 1H). This was used directly in the following reaction.

The ethynylation was performed using the procedure described for the preparation of 2a to give 26 (70% yield); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.78 (s, 3H), 0.85 (s, 3H), 2.30 (s, 3H), 2.52 (s, 1H), 6.13 (s, 1H). The oxidation of 26 using Oxone® gave 27 (23%) after recrystallization from Et_2O:hexane (1:1); mp 240-242°C(A); IR (KBr) 3560, 3230, 1505 cm^{-1}; MS (CI) 417 (MH^+); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.89 (s, 3H), 1.30-2.50 (m, 21H), 2 60 (s, 1H), 3.15 (s, 3H), 6.98 (s, 1H). Anal. Calcd for $C_{24}H_{32}O_4S \cdot 0.5H_2O$: C, 67.73; H, 7.82; S, 7.70. Found: C, 67.81; H, 7 67; S, 7.42

Rat Prostate Androgen Receptor Competition Assay. 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 105,000 x 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 concentrations 10^{-9}-10^{-5}M) of R1881 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 the 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).

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References and Notes

1. Christiansen, R. G.; Bell, M. R.; D'Ambra, T. E.; Mallamo, J. P.; Herrmann, J. L.; Ackerman, J. H.; Opalka, C. J.; Kullnig, R. K.; Winneker, R C.; Snyder, B. W.; Batzold, F. H.; Schane, H. P. *J. Med. Chem.* **1990**, *33*, 2094.
2. Snyder, B. W.; Winneker, R. C.; Batzold, F. H. *J. Steroid Biochem.* **1989**, *33*, 1127.
3. Orr, J. C.; Franco, M. L.; Cross, A. D.; Sondheimer, F. *Steroids* **1964**, *3*, 1.
4. Minato (Shionogi) U.S. Patent 3,432,486 (1969).
5. Kaneko, H.; Yamato, Y.; Kurokawa, M. *Chem. Pharm. Bull.* **1968**, *16*, 1200.
6. Gariboldi, P.; Jommi, G.; Sisti, M. *J. Org. Chem.* **1982**, *47*, 1961.
7. Hagiwara, H.; Uda, H. *J. Chem. Soc. Perkin Tran. I* **1984**, 91.
8. Schmitt, J.; Panouse, J. J.; Hallot, A.; Cornu, P.-J.; Pluchet, H.; Comoy, P. *Bull. Soc. Chim (France)* **1964**, 2753.
9. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
10. Christiansen, R. G. U.S. Patent 4,055,562 (1972).
11. Clarke, R. L. U.S. Patent 3,415,816 (1968).
12. Raynaud, J. P.; Bouton, M. M.; Ojasoo, T. *Trends Pharmacol. Sci.* **1980**, *1*, 324.
13. Dimethyl sulfoxide in the presence of HCl is reported to cause introduction of a methylthio group into a reactive nucleus such as an indole. Hocker, J.; Ley, K.; Merten, R. *Synthesis* **1975**, 334.
14. Jain, S.; Shukla, K.; Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Synth. Commun.* **1990**, *20*, 1315 and references cited therein.
15. Winneker, R. C.; Wagner, M. M.; Batzold, F. H. *J. Steroid Biochem.* **1989**, *33*, 1133.