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The Synthesis of D-Heteroannulated 3β-Hydroxy-13α-androst-5-ene Derivatives *via* α-Oxoketene Dithioacetal and α-Oxohydroxymethylidene Synthons

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Summary. 16-Ketene dithioacetal derivatives of 3β-hydroxy-13α-androst-5-en-17-one react with amidine, benzamidine, or guanidine to yield novel pyrimido-fused D-heteroannulated steroids. The reactions of 3β-hydroxy-16-hydroxymethylidene-13α-androst-5-en-17-one with N,N′-dinucleophiles furnish heterocycles containing a pyrazole ring fused to positions 16,17 of the sterane skeleton.

Keywords. Steroids; Heterocycles; *Lewis* acids; Pyrazolones; Pyrimidines.

Introduction

The structural modification of steroidal molecules is an important area in organic chemistry. Alteration of the configuration of a stereogenic centre [1–4], aromatization of one ring [5, 6], incorporation of a heteroatom [1, 7–10], and annulation of a heterocycle [11–21] are synthetic methods widely used to obtain novel steroid derivatives. As a consequence of such structural modification, the physiological activities of compounds can be changed, which may result in new biological behaviour [22–24].

The syntheses of some steroidal [16, 17-c]pyrazoles and pyrimidines from α-oxohydroxymethylidene derivatives have been reported earlier [12, 13, 15, 17, 18, 20, 21]. Ring E-modified steroids as novel potent inhibitors of 17β-hydroxysteroid dehydrogenase of type I have also been synthetized from α-oxohydroxymethylidene derivatives, and their inhibitory effects have been studied [25]. α-Oxoketene dithioacetal push–pull activated alkenes are also good synthon equivalents for the synthesis of different heterocycles [26, 27]. The reactions of 3-methoxy-16-bis(methylthio)methylestra-1,3,5(10)-trien-17-one with appropriate dinucleophilic

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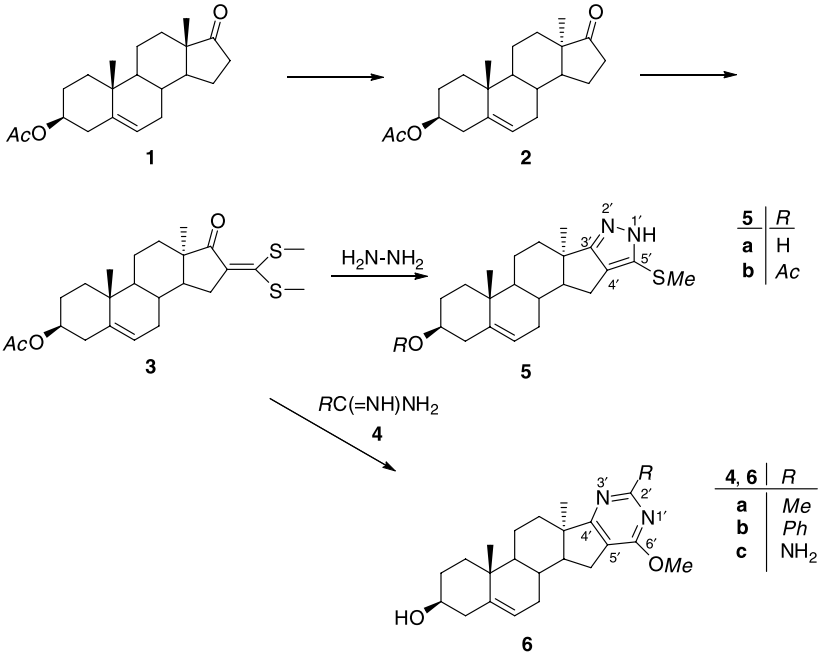
reagents furnish pyrimido-, pyrazolo-, and isoxazoloestrone derivatives [20, 28]. In the presence of hydrazine hydrate, methylhydrazine, or hydroxylamine hydrochloride as dinucleophile, the reaction results in 5′-methylthiopyrazolo or 5′-methylthioisoxazolo androst-5-ene derivatives. With a benzamidinium, acetamidinium, or guanidium salt as dinucleophile in the presence of NaO*Me*, the reaction gives 6′-methoxypyrimido[5′4′:16,17]androst-5-en-3-β-ol derivatives.

3β-Hydroxyandrost-5-en-17-one is a pleiotropic adrenal hormone; it exerts immunoregulatory [29] and antioxidant [30] effects, it functions as a neurosteroid [31], and it may serve as a prognostic factor or therapeutic agent in clinical practice [32, 33]. Since its widespread physiological and pathological functions in the central nervous system have not yet been fully explored, various 3β-hydroxyandrost-5-en-17-one derivatives are subjects for a study of their potential biological effects.

The above-mentioned observations led us to synthesize D-heteroannulated derivatives of 3β-hydroxy-13α-androst-5-en-17-one *via* α-oxoketene dithioacetal and α-oxohydroxymethylidene synthons, to compare the behaviour of these synthons with that of corresponding *normal* (13β) derivatives described in literature under the same reaction conditions, and to study the chemo-, regio-, and stereoselectivities of the reactions.

Results and Discussion

Epimerization of 3β-acetoxyandrost-5-en-17-one (**1**) by the method of *Yaremenko* and *Khvat* [2], which was extended to 3-methoxyestra-1,3,5(10)-trien-17-one by *Schönecker et al.* [3], gave 3β-acetoxy-13α-androst-5-en-17-one (**2**) [34]. This compound was treated with CS_2, *Me*I, and NaH in *DMF* by the method of

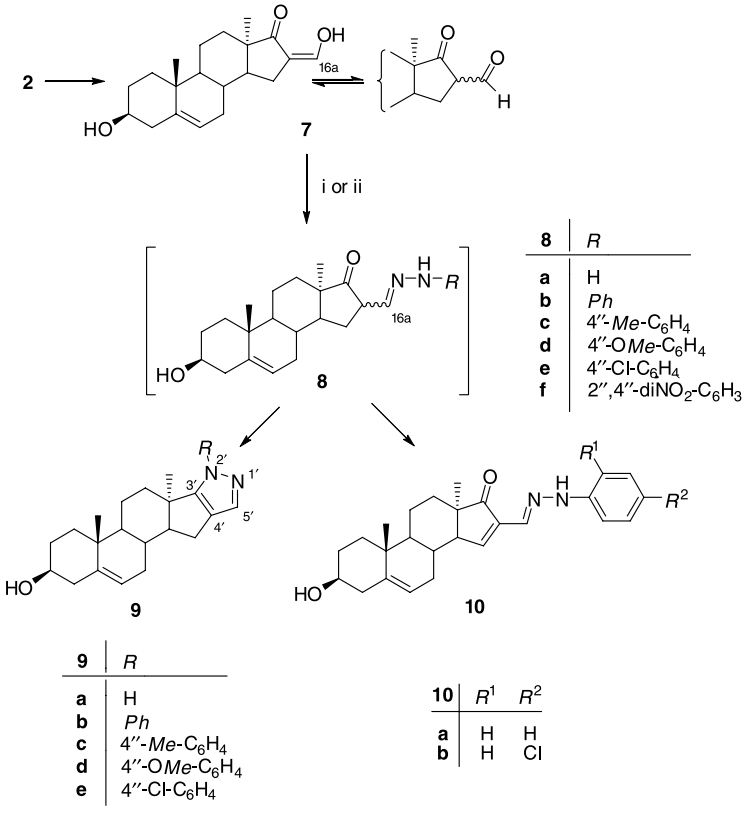


Scheme 1

Rivera et al. [28], which led to the corresponding 3β-acetoxy-16-bis(methylthio)-methylidene-13α-androst-5-en-17-one (**3**) in 58% yield (Scheme 1).

In order to prepare isoxazolo-anellated 3β-hydroxy-13α-androst-5-ene derivatives, the α-oxoketene dithioacetal **3** was reacted with hydroxylamine as dinucleophilic reagent in boiling *Me*OH. In contrast with the similar reaction in the estrone series [20], no reaction was observed. In the case of hydrazine hydrate, the reaction furnished 5′-methylthio-pyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol in 63% yield (**5a**) and 3β-acetoxy-5′-methylthiopyrazolo[4′,3′:16,17]-13α-androst-5-ene (**5b**) in 31% yield. The reaction of α-oxoketene dithioacetal (**3**) with amidinium (**4a**), benzamidinium (**4b**), or guanidinium hydrochloride (**4c**) as dinucleophilic reagent was carried out in anhydrous *Me*OH in the presence of NaO*Me* under reflux. By means of these reactions, the corresponding 2′-methylpyrimido[5′,4′:16,17]-13α-androst-5-en-3β-ol (**6a**), 2′-phenylpyrimido[5′,4′:16,17]-13α-androst-5-en-3β-ol (**6b**), or 2′-aminopyrimido[5′,4′:16,17]-13α-androst-5-en-3β-ol (**6c**) were obtained in 54–95% yields.

The above-mentioned reactions in the 13β-androst-5-ene series furnished the analogous condensed products mainly within reaction times of 8 h, in 62–75% yields [28], whereas our transformations needed only 2 h. Accordingly, we can



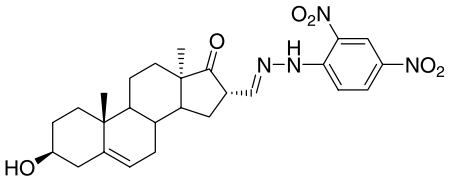
8	*R*
a	H
b	*Ph*
c	4″-*Me*-C_6H_4
d	4″-O*Me*-C_6H_4
e	4″-Cl-C_6H_4
f	2″,4″-diNO_2-C_6H_3

9	*R*
a	H
b	*Ph*
c	4″-*Me*-C_6H_4
d	4″-O*Me*-C_6H_4
e	4″-Cl-C_6H_4

10	R^1	R^2
a	H	H
b	H	Cl

i. hydrazine hydrate or a phenylhydrazine/toluene, reflux
ii. hydrazine hydrate or a phenylhydrazine/$BF_3{\cdot}OEt_2/CH_2Cl_2$ or *Me*OH, *RT*

Scheme 2



8f, 16α-substituted

Fig. 1. The product formed in the reaction of compound **7** and 2,4-dinitrophenylhydrazine

state that the α-oxoketene dithioacetal in the 13α series is more reactive than the analogous push–pull activated alkene in the *normal* series.

We also set out to synthetize N-substituted pyrazolo-anellated derivatives of 3β-hydroxy-13α-androst-5-ene by reacting 3β-acetoxy-16-hydroxymethylidene-13α-androst-5-en-17-one (**7**) with hydrazine and different substituted hydrazine dinucleophilic reagents.

The starting compound **7** was synthetized from 3β-acetoxy-13α-androst-5-en-17-one (**2**) in a *Claisen* condensation reaction. The hydroxymethylidene moiety exists in equilibrium with its formyl tautomer [34]. Reaction of this dicarbonyl compound with hydrazine hydrate in toluene under reflux furnished the condensed pyrazolo derivative **9a** in 64% yield (Scheme 2). The application of phenylhydrazine or substituted phenylhydrazine as nucleophile modified the chemoselectivity of the reaction. Under the same reaction conditions (*Method A*), phenylhydrazine and 2,4-dinitrophenylhydrazine were found to react only as mononucleophiles, yielding 3β-hydroxy-16-formyl-13α-androst-5,15(16)-dien-17-one 16a-phenylhydrazone (**10a**) and 3β-hydroxy-16-formyl-13α-androst-5-en-17-one 16a-(2′,4′-dinitrophenylhydrazone) (**8f**); no anellated compounds were isolated (Fig. 1). The formation of **10a** can be explained by an additional autooxidation of **8a**. We observed hydrolysis of the 3-acetoxy group under the reaction conditions applied, and therefore 3β-hydroxy compounds were isolated in all cases.

We assumed that phenylhydrazine derivatives containing electron-donating groups on their aromatic ring would exhibit an enhanced dinucleophilic character. The reaction of **7** with *p*-tolylhydrazine or *p*-methoxyphenylhydrazine proved this assumption: the transformations led to 1′-tolylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9c**) and 1′-*p*-methoxyphenylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9d**); no monocondensed products (**8**) could be observed. The aromatic *p*-chloro substituent displayed its ambivalent electronic character in this reaction. Treatment of **7** with *p*-chlorophenylhydrazine led to both the monocondensed, oxidized product 3β-hydroxy-16-formyl-13α-androsta-5,15(16)-dien-17-one 16a-(*p*-chlorophenylhydrazone) (**10b**) and the anellated 1′-(*p*-chlorophenyl)-pyrazolo [4′,3′:16,17]-13α-androst-5-en-3β-ol (**9e**).

It is known that slightly acidic conditions favour the condensation reactions of N-nucleophiles with oxo compounds. Hence, we attempted to catalyse these reactions with $BF_3 \cdot OEt_2$ with the aim of obtaining the two missing pyrazolo derivatives. This succeeded in one case; the reaction of **7** with phenylhydrazine in CH_2Cl_2 in the presence of $BF_3 \cdot OEt_2$ at room temperature yielded 1′-phenylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9b**). In contrast, under the same conditions (*Method B*), no reaction was observed with 2,4-dinitrophenylhydrazine.

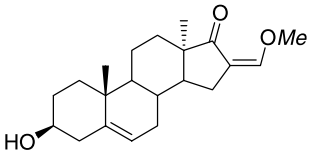


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Fig. 2. The side-product isolated from the reaction of compound **7** with *p*-chlorophenylhydrazine in the presence of $BF_3 \cdot OEt_2$

We additionally carried out the analogous reactions with the other dinucleophilic reagents: hydrazine hydrate, *p*-tolylhydrazine, *p*-methoxyphenylhydrazine, and *p*-chlorophenylhydrazine resulted in the corresponding condensed products (**9a**, and **9c**–**e**). Change of the solvent to *Me*OH in the case of the reaction with *p*-chlorophenylhydrazine led to the appearance of 16-methoxymethylidene-3β-hydroxy-13α-androst-5-en-17-one (**11**) as side-product (28%, Fig. 2).

Our experience demonstrates that electron-donating substituents on the aromatic ring of phenylhydrazine derivatives favour reaction with 1,3-dioxo compounds, whereas electron-withdrawing groups have the opposite effect.

In order to confirm the structures of the synthetized compounds, MS, ^{1}H, and ^{13}C NMR measurements were carried out. To confirm the configurations of the new chiral centres and the regiochemistry, NOESY experiments were performed.

Experimental

All melting points (mp) were determined with a *Kofler* hot-stage apparatus. Optical rotations were measured on a Polamat-A (Zeiss-Jena) polarimeter in CH_2Cl_2 ($c = 1$) at 25°C and are given in units of $10^{-1} \circ cm^2\,g^{-1}$. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm). The spots were detected by spraying with 5% phosphomolybdic acid in 50% aqueous H_3PO_4. The R_f values were determined *via* the spots observed by illumination at 254 and 365 nm. Flash chromatography: Merck silica gel 60, 40–63 μm. All solvents were distilled prior to use. ^{1}H NMR spectra were obtained in $CDCl_3$ or *DMSO*-d_6 solution at 400 or 500 MHz (Bruker DRX 400, DRX 500), and ^{13}C NMR spectra were recorded at 100 or 125 MHz on the same instruments, or at 75 MHz (Bruker AMX 300). Chemical shifts (δ) are reported relative to *TMS*, and are given in ppm; the coupling constants (J) are in Hz. ^{13}C NMR spectra are ^{1}H-decoupled. Mass spectra were measured on a Varian MAT 311A spectrometer.

3β-Acetoxy-16-bis(methylthio)-methylidene-13α-androst-5-en-17-one (**3**, $C_{24}H_{34}S_2O_3$)
NaH (606 mg, 60%, 15.2 mmol), 0.92 cm^3 CS_2 (15.2 mmol), and 0.94 cm^3 *Me*I (15.2 mmol) were added to a stirred solution of 2.00 g **2** (6.10 mmol) in 100 cm^3 anhydrous *DMF*. The reaction mixture was stirred for 1 h at 0°C and for 20 h at room temperature, and the reaction mixture was then poured into ice-H_2O (1 dm^3). The precipitate was collected by filtration, dissolved in CH_2Cl_2, and it was washed with H_2O and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with diisopropyl ether/*n*-hexane (30/70) resulting in 1.54 g (58%) **3**. Mp 62–63°C; $R_f = 0.50$ (*Me*OH/diisopropyl ether = 4/96); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.83$ (s, H_3-19), 1.01 (s, H_3-18), 2.02 (s, CH_3CO), 2.45 and 2.46 (2s, S-CH_3 and S′–CH_3), 2.62 (d, $J = 16.8$ Hz, 1H, H_2-15), 2.88 (dd, $J = 16.8$, 6.6 Hz, 1H, H_2-15), 4.60 (m, H-3), 5.39 (m, $J = 2.4$ Hz, H-6) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.4$ (SCH_3), 19.0 (2C, S- and 19-CH_3), 21.3 (CH_3CO), 22.7, 25.6 (C-18), 27.5, 32.1, 32.9, 34.8, 35.5, 36.6, 36.8 (C-10), 37.8, 47.8, 48.4, 52.1 (C-13), 73.7 (C-3), 121.8 (C-6), 133.8 (C-16), 139.3 (C-5), 151.3 (C-16a), 170.4 (CH_3CO), 204.4 (C-17) ppm; EI-MS (70 eV): $m/z = 434$ (M^+), 374, 327, 311, 84, 49; $[\alpha]_D^{20} = -221\ 10^{-1} \circ cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2).

5′-Methylthiopyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**5a**, $C_{21}H_{30}N_2O_3S$) *and 3β-acetoxy-5′-methylthiopyrazolo[4′,3′:16,17]-13α-androst-5-en-17-one* (**5b**, $C_{23}H_{32}N_2O_2S$)

Compound **3** (150 mg, 0.35 mmol) was dissolved in 40 cm^3 anhydrous *Me*OH, 0.65 cm^3 hydrazine hydrate were added and the reaction mixture was stirred under reflux for 4 h. The reaction mixture was then concentrated, dissolved in CH_2Cl_2, and it was washed with H_2O and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with *Et*OAc/CH_2Cl_2 (10/90) resulting in 45 mg (32%) **5b** and 79 mg (63%) **5a**.

5a. Mp 175–178°C; $R_f = 0.40$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.78$ (s, H_3-19), 1.16 (s, H_3-18), 2.41 (s, SCH_3), 2.89 (dd, $J = 14.7$, 5.8 Hz, H-15) 3.53 (m, H-3), 5.35 (m, H-6) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.9$ (SCH_3), 19.0 (C-19), 22.4, 27.6, 28.9 (C-18), 31.4, 33.4, 33.6, 35.6, 36.9 (C-10), 41.9, 42.4 (C-13), 42.5, 48.4, 60.5, 71.7 (C-3), 121.2 (C-6), 124.5 (C-4′), 129.0 (C-5′), 132.3 (C-5′), 140.3 (C-5), 165.2 (C-3′) ppm; EI-MS (70 eV): $m/z = 358$ (M^+), 343, 325; $[\alpha]_D^{20} = -9\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

5b. Mp 154–158°C; $R_f = 0.70$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.80$ (s, H_3-19), 1.17 (s, H_3-18), 2.03 (s, CH_3CO), 2.41 (s, SCH_3), 2.89 (dd, $J = 14.8$, 5.8 Hz, H-15), 4.60 (m, H-3), 5.39 (m, H-6) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.8$ (SCH_3), 19.0 (C-19), 21.4 (CH_3CO), 22.3, 27.5, 27.6, 28.9 (C-18), 33.4, 33.5, 35.5, 36.6, 37.0 (C-10), 37.8, 42.4 (C-13), 48.3, 60.2, 73.9 (C-3), 122.2 (C-6), 124.4 (C-4′), 132.3 (C-5′), 139.1 (C-5), 165.2 (C-3′), 170.6 (CH_3CO) ppm; EI-MS (70 eV): $m/z = 400$ (M^+), 340, 325, 232, 167, 43; $[\alpha]_D^{20} = -51\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

6′-Methoxy-2′-methylpyrimido[5′,4′:16,17]-13α-androst-5-en-3β-ol (**6a**, $C_{23}H_{32}N_2O_2$)

Compound **3** (100 mg, 0.23 mmol) was dissolved in a solution of 27 mg Na (1.17 mmol) in 50 cm^3 anhydrous *Me*OH, 110 mg acetamidine hydrochloride (1.16 mmol) were added and the mixture was stirred under reflux under nitrogen for 2 h. The mixture was then diluted with H_2O and $(NH_4)_2SO_4$ was added. The precipitate was collected by filtration, dissolved in CH_2Cl_2, and it was washed with water and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with diisopropyl ether, resulting in 72 mg (85%) **6a**. Mp 138–140°C; $R_f = 0.45$ (*Me*OH/diisopropyl ether = 5/95); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.73$ (s, H_3-19), 1.06 (s, H_3-18), 2.62 (CH_3-2′), 2.90 (dd, $J = 15.8$, 6.0 Hz, H-15), 3.52 (m, H-3), 3.97 (s, OCH_3), 5.35 (m, H-6) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.0$ (C-19), 22.8, 25.8 (CH_3-2′), 27.9 (C-18), 29.6, 31.9, 32.9, 33.4, 35.5, 36.8, 36.9 (C-10), 42.0 (C-4), 47.9 (C-13), 48.0, 52.8 (OCH_3), 53.1, 71.6 (C-3), 114.7 (C-5′), 121.1 (C-6), 140.4 (C-5), 166.3 and 166.9 (C-2′, -6′), 179.1 (C-4′) ppm; EI-MS (70 eV): $m/z = 368$ (M^+), 353, 177, 87, 45; $[\alpha]_D^{20} = -109\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

6′-Methoxy-2′-phenylpyrimido[5′,4′:16,17]-13α-androst-5-en-3β-ol (**6b**, $C_{28}H_{34}N_2O_2$)

Compound **3** (100 mg, 0.23 mmol) was dissolved in a solution of 27 mg Na (1.16 mmol) in 50 cm^3 anhydrous *Me*OH, 206 mg benzamidine hydrochloride hydrate (1.15 mmol) were added and the mixture was stirred under reflux under nitrogen for 2 h. The mixture was then diluted with H_2O and $(NH_4)_2SO_4$ was added. The precipitate was collected by filtration, dissolved in CH_2Cl_2, and it was washed with H_2O and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with diisopropyl ether, resulting in 59 mg (60%) **6b**. Mp 195–197°C; $R_f = 0.60$ (*Me*OH/diisopropyl ether = 5/95); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.70$ (s, H_3-19), 1.11 (s, H_3-18), 2.58 (d, $J = 16.1$ Hz, 1H, H_2-15), 3.00 (dd, $J = 16.1$, 6.1 Hz, 1H, H_2-15), 3.51 (m, H-3), 4.10 (s, OCH_3), 5.36 (m, H-6), 7.45 (m, H-3″, -4″, -5″), 8.51 (d, $J = 8.1$ Hz, H-2″, -6″) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 19.0$ (C-19), 22.6, 28.0 (C-18), 30.0, 31.4, 32.5, 33.2, 35.5 36.8 (C-10), 36.9, 41.9, 48.0, 47.9 (C-13), 52.8 (OCH_3), 53.1, 71.6 (C-3), 115.9 (C-5′), 121.0 (C-6), 128.1 and 128.2 (2 × 2C, C-2″, -3″, -4″, -5″), 130.0 (C-4″), 138.3 (C-1″), 140.2 (C-5), 163.5 (C-6′), 166.4 (C-2′), 179.5 (C-4′) ppm; EI-MS (70 eV): $m/z = 430$ (M^+), 415, 319, 251, 239, 118; $[\alpha]_D^{20} = -150\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

2′-Amino-6′-methoxypyrimido[5′,4′:16,17]-13α-androst-5-en-3β-ol (**6c**, $C_{22}H_{31}N_3O_2$)
Compound **3** (100 mg, 0.23 mmol) was dissolved in a solution of 27 mg Na (1.17 mmol) in 50 cm^3 anhydrous *Me*OH, 110 mg guanidine hydrochloride (1.15 mmol) were added, and the mixture was stirred under reflux under nitrogen for 2 h. The mixture was then diluted with H_2O and $(NH_4)_2SO_4$ was added. The precipitate was collected by filtration, dissolved in CH_2Cl_2, and it was washed with water and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with diisopropyl ether/*Me*OH (95/5) resulting in 46 mg (54%) **6c**. Mp 139–141°C; $R_f = 0.45$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, *DMSO*): $\delta = 0.65$ (s, H_3-19), 0.94 (s, H_3-18), 2.28 (d, $J = 14.8$ Hz, 1H, H_2-15), 2.76 (dd, $J = 14.8$, 5.9 Hz, 1H, H_2-15), 3.24 (m, H-3), 3.79 (s, OMe), 4.61 (d, $J = 4.5$ Hz, 3-OH), 5.26 (m, H-6), 6.28 (s, NH_2) ppm; ^{13}C NMR (125 MHz, *DMSO*): $\delta = 18.8$ (C-19), 22.3, 27.6 (C-18), 29.2, 31.2, 32.1, 32.7, 35.2, 36.5, 36.6, 41.9, 47.2, 47.6, 52.0, 52.5, 70.0 (C-3), 104.7 (C-5′), 120.3 (C-6), 140.5 (C-5), 163.7 (C-6′), 166.5 (C-2′), 179.6 (C-4′) ppm; EI-MS (70 eV): $m/z = 369$ (M^+), 354, 178; $[\alpha]_D^{20} = -123\,10^{-1}\,^\circ\,cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2).

16α-Formyl-13α-androst-5-en-3β-ol-17-one 16a-(2,4-dinitro-phenylhydrazone) (**8f** (16α), $C_{26}H_{32}N_4O_6$)
Compound **7** (316 mg, 1.0 mmol) was dissolved in 5 cm^3 toluene and a solution of 218 mg 2,4-dinitrophenylhydrazine (1.1 mmol) in 5 cm^3 *Me*OH was added. The resulting solution was refluxed for 5 h, and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography with *Me*OH/diisopropyl ether (1/99), resulting in 362 mg (73%) **8f**. Mp 149–153°C; $R_f = 0.32$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (s, H_3-19), 1.03 (s, H_3-18), 3.36 (m, H-16), 3.54 (m, H-3), 5.40 (m, H-6), 7.59 (d, $J = 5.2$ Hz, H-16a), 7.91 (d, $J = 9.5$ Hz, H-2′), 8.30 (dd, $J = 9.5$ Hz, $J = 2.5$ Hz, H-5′), 9.12 (d, $J = 2.5$ Hz, H-3′), 11.11 (s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.1$ (C-19), 23.0, 25.0 (C-18), 27.0, 31.3, 32.0, 33.1, 34.5, 36.7, 36.8, 41.8, 47.7, 49.1, 50.2, 50.8, 71.6 (C-3), 116.4 (C-16a), 120.6, 123.4, 129.1 (C-2′), 129.9 (C-5′), 138.1 (C-4′), 140.3 (C-5), 144.9 (C-1′), 148.7 (C-3′), 217.6 (C-17) ppm; EI-MS (70 eV): $m/z = 496$ (M^+), 462, 213, 183, 145, 105, 91, 79; $[\alpha]_D^{20} = -43\,10^{-1}\,^\circ\,cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2).

Pyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9a**, $C_{20}H_{28}N_2O$)
Method A: 158 mg **7** (0.5 mmol) were dissolved in 5 cm^3 toluene and 0.05 cm^3 hydrazine hydrate (1.0 mmol) were added. The resulting solution was refluxed for 12 h, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography with *Me*OH/CH_2Cl_2 (2/98), resulting in 100 mg (64%) **9a**.

Method B: 100 mg **7** (0.3 mmol) were dissolved in 2.5 cm^3 dry CH_2Cl_2 and 0.02 cm^3 hydrazine hydrate (0.4 mmol) and 0.06 cm^3 $BF_3 \cdot OEt_2$ (40% solution in diethyl ether, 0.2 mmol) were added. During the stirring of the solution for 15 min, a precipitate formed. The precipitate was collected by filtration, washed with H_2O, and dried. The crude product was purified by column chromatography with *Me*OH/CH_2Cl_2 (2/98), resulting in 54 mg (58%) **9a**. Mp 276–280°C; $R_f = 0.24$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, *DMSO*): $\delta = 0.66$ (s, H_3-19), 1.05 (s, H_3-18), 2.26 (d, $J = 14.5$ Hz, 1H, H_2-15), 2.80 (dd, $J = 14.5$, 5.9 Hz, 1H, H_2-15), 3.25 (m, H-3), 4.61 (s, 3-OH), 5.27 (m, H-6), 7.20 (s, H-5′) ppm; ^{13}C NMR (75 MHz, *DMSO*): $\delta = 18.7$ (C-19), 21.9, 26.9, 29.0 (C-18), 31.2, 33.0, 33.3, 35.1, 36.4, 36.5, 41.0, 41.9, 48.0, 60.0, 70.0 (C-3), 120.3 (C-6), 120.5 (C-4′), 124.0 (C-5′), 163.1 (C-3′) ppm; EI-MS (70 eV): $m/z = 312$ (M^+), 297, 279, 201, 133, 121; $[\alpha]_D^{20} = -72\,10^{-1}\,^\circ\,cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2).

1′-Phenylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9b**, $C_{26}H_{32}N_2O$)
Method B: 158 mg **7** (0.5 mmol) were dissolved in 2.0 cm^3 *Me*OH, and 0.06 cm^3 phenylhydrazine (0.6 mmol) were added. Then 0.06 cm^3 $BF_3 \cdot OEt_2$ (40% solution in diethyl ether, 0.2 mmol) were added dropwise. The resulting solution was stirred for 2 h. The mixture was next diluted with H_2O, and

$(NH_4)_2SO_4$ was added. The precipitate that formed was collected by filtration, washed with H_2O, and dried. The crude product was purified by column chromatography with *Me*OH/diisopropyl ether (4/96), resulting in 15 mg (10%) **9b**. Mp 126–130°C; $R_f = 0.24$ (*Me*OH/diisopropyl ether = 4/96); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.78$ (s, H_3-19), 1.30 (s, H_3-18), 2.33 (d, $J = 14.4$ Hz, 1H, H_2-15), 2.94 (dd, $J = 14.4$, 6.0 Hz, 1H, H_2-15), 3.50 (m, H-3), 5.35 (m, H-6), 7.34 (s, H-5′), 7.44 (overlapping multiplets, H-2″, -3″, -4″, 5″, 6″) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.8$ (C-19), 22.0, 27.3, 28.6 (C-18), 31.3, 32.6, 33.5, 35.5, 36.8, 36.9 (C-10), 41.9, 44.0 (C-13), 48.5, 62.3, 71.6 (C-3), 121.2 (C-6), 124.9 (2C, C-2′, -6′), 126.6 (C-4″), 127.8 (C-4′), 128.8 (2C, C-3″, -5″), 135.3 (C-5′), 140.2 (C-5), 140.3 (C-1″), 165.4 (C-3′) ppm; EI-MS (70 eV): $m/z = 388$ (M^+), 373, 87, 59, 45.

1′-Tolylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9c**, $C_{27}H_{34}N_2O$)

Method A: 949 mg **7** (3.0 mmol) were dissolved in 5 cm^3 toluene and a solution of 640 mg *p*-tolylhydrazine hydrochloride (4.0 mmol) and 240 mg KOH (4.2 mmol) in 5 cm^3 *Me*OH was added. The resulting solution was refluxed for 12 h and evaporated to dryness in vacuo. The residue was purified by column chromatography with *tert*-butyl methyl ether/*n*-hexane (30/70), resulting in 506 mg (42%) **9c**.

Method B: 316 mg **7** (1.0 mmol) were dissolved in 10 cm^3 *Me*OH and a solution of 175 mg *p*-tolylhydrazine hydrochloride (1.1 mmol) and 44 mg NaOH (1.1 mmol) in 5 cm^3 *Me*OH was added. 0.06 cm^3 $BF_3 \cdot OEt_2$ (40% solution in diethyl ether, 0.2 mmol) were then added dropwise. The resulting solution was stirred for 2 h. The mixture was next diluted with H_2O, and $(NH_4)_2SO_4$ was added. The precipitate was collected by filtration, washed with H_2O, and dried. The crude product was purified by column chromatography with *tert*-butyl methyl ether/*n*-hexane (30/70), resulting in 185 mg (46%) **9c**. Mp 126–130°C; $R_f = 0.24$ (*tert*-butyl methyl ether/*n*-hexane = 50/50); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.77$ (s, H_3-19), 1.27 (s, H_3-18), 2.31 (d, $J = 14.5$ Hz, 1H, H_2-15), 2.91 (dd, $J = 14.5$, 6.0 Hz, 1H, H_2-15), 2.40 (s, 4″-CH_3), 3.49 (m, H-3), 5.36 (m, H-6), 7.22 (d, $J = 8.5$ Hz, H-2″, -6″), 7.31 (d, $J = 8.5$ Hz, H-3″, -5″), 7.31 (s, H-5′) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 18.7$ (C-19), 21.0, 21.9, 27.3, 28.5 (C-18), 31.1, 32.5, 33.4, 35.4, 36.7, 36.8, 41.8, 43.8, 48.4, 62.1, 71.3 (C-3), 121.0 (C-6), 124.7 (2C, C-2″, -6″), 126.1 (C-4′), 129.3 (2C, C-3″, -5″), 135.0 (C-5′), 137.7 and 137.8 (C-1″, 4″), 140.2 (C-5), 153.8 (C-3′) ppm; EI-MS (70 eV): $m/z = 402$ (M^+), 387, 369, 171, 91; $[\alpha]_D^{20} = -208\ 10^{-1}\ ^\circ\ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

1′-p-Methoxyphenylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9d**, $C_{27}H_{34}N_2O_2$)

Method A: 316 mg **7** (1.0 mmol) were dissolved in 5 cm^3 toluene and a solution of 192 mg *p*-methoxyphenylhydrazine hydrochloride (1.1 mmol) and 61 mg KOH (1.1 mmol) in 5 cm^3 *Me*OH was added. The resulting solution was refluxed for 6 h, and next evaporated to dryness *in vacuo*. The residue was purified by column chromatography with *Me*OH/diisopropyl ether (1/99), resulting in 284 mg (68%) **9d**.

Method B: 316 mg **7** (1.0 mmol) were dissolved in 10 cm^3 *Me*OH, and a solution of 192 mg *p*-methoxyphenylhydrazine hydrochloride (1.1 mmol) and 44 mg NaOH (1.1 mmol) in 5 cm^3 *Me*OH was added. 0.06 cm^3 $BF_3 \cdot OEt_2$ (40% solution in CH_2Cl_2, 0.2 mmol) were then added dropwise. The resulting solution was stirred for 2 h. The mixture was next diluted with H_2O, and $(NH_4)_2SO_4$ was added. The precipitate was collected by filtration, washed with H_2O, and dried. The crude product was purified by column chromatography with *Me*OH/diisopropyl ether (1/99), resulting in 163 mg (39%) **9d**. Mp 220–224°C; $R_f = 0.26$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.79$ (s, H_3-19), 1.25 (s, H_3-18), 2.31 (d, $J = 14.5$ Hz, 1H, H_2-15), 2.92 (dd, $J = 14.5$, 5.8 Hz, 1H, H_2-15), 3.49 (m, H-3), 3.85 (s, OCH_3), 5.36 (m, H-6), 6.93 (d, $J = 8.9$ Hz, H-2″, -6″), 7.30 (s, H-5′), 7.33 (d, $J = 8.9$ Hz, H-3″, -5″) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$ (C-19), 22.0, 27.4, 28.6 (C-18), 31.3, 32.6, 33.5, 35.5, 36.8, 36.9, 41.9, 43.7, 48.4, 55.4, 62.1, 71.5 (C-3), 113.9 (2C, C-3″, -5″), 121.2 (C-6), 125.9 (C-4′), 126.4 (2C, C-2″, -6″), 133.5 (C-1″), 134.9 (C-5′), 140.2 (C-5), 154.0 (C-3′), 159.1 (C-4″) ppm; EI-MS (70 eV): $m/z = 418$ (M^+), 403, 385, 187; $[\alpha]_D^{20} = -204\ 10^{-1}\ ^\circ\ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

1′-p-Chlorophenylpyrazolo[4′,3′:16,17]-13α-androst-5-en-3β-ol (**9e**, $C_{26}H_{31}ClN_2O$), *3β-hydroxy-16-formyl-13α-androsta-5,15-dien-17-one 16a-(p-chlorophenylhydrazone)* (**10b**, $C_{26}H_{31}ClN_2O$), *and 16-methoxymethylidene-3β-hydroxy-13α-androst-5-en-17-one* (**11**, $C_{21}H_{30}O_3$)

Method A: 948 mg **7** (3.0 mmol) were dissolved in 10 cm^3 toluene and a mixture of 780 mg *p*-chlorophenylhydrazine hydrochloride (4.4 mmol) and 240 mg KOH (4.2 mmol) in 5 cm^3 toluene was added. The resulting solution was refluxed for 12 h, and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography with *tert*-butyl methyl ether/*n*-hexane (30/70), resulting in 291 mg (23%) **9e** and 223 mg (17%) **10b**.

Method B: 316 mg **7** (1.0 mmol) were dissolved in 10 cm^3 *Me*OH and a solution of 197 mg *p*-chlorophenylhydrazine hydrochloride (1.1 mmol) and 44 mg NaOH (1.1 mmol) in 5 cm^3 *Me*OH was added. 0.06 cm^3 $BF_3 \cdot OEt_2$ (40% solution in diethyl ether, 0.2 mmol) were then added dropwise. The resulting solution was stirred for 2 h. The mixture was next diluted with H_2O, and $(NH_4)_2SO_4$ was added. The precipitate was collected by filtration, washed with H_2O, and dried. The crude product was purified by column chromatography with *tert*-butyl methyl ether/*n*-hexane (30/70) resulting in 194 mg (46%) **9e** and 91 mg (28%) **11**.

9e. Mp 205–207°C; $R_f = 0.28$ (*tert*-butyl methyl ether/*n*-hexane = 50/50); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.77$ (s, H_3-19), 1.29 (s, H_3-18), 2.32 (d, $J = 14.5$ Hz, 1H, H_2-15), 2.92 (dd, $J = 14.5$, 5.5 Hz, 1H, H_2-15), 3.50 (m, H-3), 5.36 (m, H-6), 7.34 (s, H-5′), 7.4 (dd, $J = 16.5$, 8.5 Hz, H-2″, -3″, -5″, -6″) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 18.8$ (C-19), 21.9, 27.2, 28.5 (C-18), 31.2, 32.6, 33.4, 35.3, 36.9, 36.8, 41.8, 44.0, 48.4, 62.3, 71.4 (C-3), 121.1 (C-6), 125.8 (2C, C-2″, -6″), 127.0 (C-4′), 129.0 (2C, C-3″, -5″), 133.4 (C-4″), 135.8 (C-5′), 138.8 (C-1″), 140.2 (C-5), 153.8 (C-3′) ppm; EI-MS (70 eV): $m/z = 422$ (M^+), 407, 119, 57; $[\alpha]_D^{20} = -252\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

10b. Oil; $R_f = 0.24$ (*tert*-butyl methyl ether/*n*-hexane = 50/50); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (s, H_3-19), 1.14 (s, H_3-18), 3.53 (m, H-3), 5.36 (m, H-6), 7.00 (d, $J = 9.0$ Hz, H-2′, -6′), 7.21 (d, $J = 9.0$ Hz, H-3′, -5′), 7.45 (s, H-16a), 7.75 (s, NH), 8.00 (d, $J = 3.0$ Hz, H-15) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.8$ (C-19), 20.2, 29.2 (C-18), 31.2, 32.8, 36.4, 36.8, 37.8, 41.8, 41.9, 46.2, 48.2, 55.0, 71.6 (C-3), 113.9 (2C, C-2′, -6′), 120.4 (C-6), 125.0 (C-15), 129.2 (2C, C-3′, -5′), 135.8 and 138.1 (C-1′, -4′), 141.1 (C-5), 142.7 (C-16), 158.4 (C-16a), 211.8 (C-17) ppm; EI-MS (70 eV): $m/z = 438$ (M^+), 73, 57, 41.

11. Mp 83–89°C; $R_f = 0.43$ (*tert*-butyl methyl ether/*n*-hexane = 80/20); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.82$ (s, H_3-19), 0.98 (s, H_3-18), 2.39 (dd, $J = 16.0$, 1.0 Hz, 1H, H_2-15), 2.62 (dd, $J = 16.0$, 6.5 Hz, 1H, H_2-15), 3.52 (m, H-3), 3.84 (s, OCH_3), 5.36 (m, H-6), 7.26 (s, H-16a) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 19.1$ (C-19), 22.9, 25.5 (C-18), 26.6, 31.3, 31.5, 32.9, 35.2, 36.7, 36.8, 41.9, 47.9, 48.8, 50.7, 61.6, 71.6 (C-3), 114.1 (C-16), 121.0 (C-6), 140.2 (C-5), 156.0 (C-16a), 210.3 (C-17) ppm; EI-MS (70 eV): $m/z = 330$ (M^+), 312, 231, 213, 139, 105, 91, 79, 41; $[\alpha]_D^{20} = -38\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

16-Formyl-13α-androsta-5,15-dien-3β-ol-17-one 16a-phenylhydrazone (**10a**, $C_{26}H_{32}N_2O_2$)

Method A: 949 mg **7** (3.0 mmol) were dissolved in 10 cm^3 toluene and a solution of 0.4 cm^3 phenylhydrazine (3.7 mmol) in 5 cm^3 *Me*OH was added. The resulting solution was refluxed for 15 h, and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography with *Me*OH/diisopropyl ether (1/99) resulting in 373 mg (31%) **10a**. Mp 124–128°C; $R_f = 0.80$ (*Me*OH/diisopropyl ether = 10/90); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (s, H_3-19), 1.14 (s, H_3-18), 3.53 (m, H-3), 5.36 (m, H-6), 6.87 (t, $J = 7.5$ Hz, H-4′), 7.07 (d, $J = 7.5$ Hz, H-2″, -6″), 7.25 (t, $J = 7.5$ Hz, H-3″, -5″), 7.46 (s, H-16a), 7.90 (s, NH), 8.00 (d, $J = 3.5$ Hz, H-15) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 17.8$ (C-19), 20.1, 25.7 (C-18), 29.1, 31.1, 32.6, 36.3, 36.7, 37.7, 41.7, 46.1, 48.1, 54.9, 71.5 (C-3), 112.7 (2C, C-2, -6′), 120.2 and 120.3 (C-6, -15), 128.0 (C-4′), 129.2 (2C, C-3′, -5′), 136.0 (C-1′), 140.1 (C-5), 144.2 (C-16), 157.9 (C-16a), 212.3 (C-17) ppm; EI-MS (70 eV): $m/z = 404$ (M^+), 220, 171, 144, 93, 77; $[\alpha]_D^{20} = +7\ 10^{-1} \circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2).

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