Monatshefte für Chemie 137, 1099–1107 (2006)
DOI 10.1007/s00706-005-0500-y

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Synthesis of *D-seco*-13α-Androst-5-ene Derivatives

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Received July 11, 2005; accepted December 7, 2005
Published online July 3, 2006

Summary. 3β-Hydroxy-16,17-*seco*-13α-androsta-5,16-dien-17-al was obtained from 3β-acetoxyandrost-5-en-17-one in six steps with a *Grob* fragmentation as the key step. This *seco*-steroid, containing a formyl group and an unsaturated side-chain in a sterically favourable cis position, is a useful synthon for the synthesis of novel heterocycles condensed to the 3β-hydroxy-13α-androst-5-en-17-one skeleton.

Keywords. 13α-Androst-5-en-17-one; Chirality; *Grob* fragmentation; Natural products; Steroids.

Introduction

We reported that 3β-hydroxy-16,17-*seco*-androsta-5,16-dien-17-al can be formed from *trans*-16-*p*-toluenesulfonyloxymethylandrost-5-ene-3β,17-diol *via Grob* fragmentation [1]. Since that time, the syntheses of 3-methoxy-16,17-*seco*-estra-1,3,5(10),16-tetraen-17-al and 3-methoxy-16,17-*seco*-13α-estra-1,3,5(10),16-tetraen-17-al have been achieved in a similar manner [2, 3]. The resulting *D-seco*-steroid has been utilized for the synthesis of different heterocyclic derivatives. Thus, 13β-estrone tetrahydroquinoline derivatives can be obtained *via* the *Lewis* acid-catalysed hetero *Diels-Alder* cyclization of arylimines derived from *D-seco*-estrone and substituted anilines [4]. The *D-seco*-estrone undergoes an intramolecular 1,3-dipolar cycloaddition with both hydroxylamine and *N*-methylhydroxylamine to produce a single isoxazolidine isomer in each case [5]. Moreover, halogen-containing 13α- and 13β-*D-homo*-estrone derivatives have been synthesized by means of a *Lewis* acid-induced intramolecular *Prins* reaction [6]. The domino *Knoevenagel*-hetero *Diels-Alder* reaction of 13β-*seco*-estrone also led to *D-homo*-estrone derivatives [7].

Several lines of evidence suggest that steroids are implicated in lesion-induced reactions of the nervous system and contribute to its morphological and functional recovery. One of the most extensively studied molecules in this respect is estrone

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[8], but other steroids that precede estrone in its biosynthetic pathway, such as 3β-hydroxyandrost-5-ene (**1a**), also have beneficial effects. It was recently reported, that **1a** regulates the astroglia reaction to the denervation of olfactory glomeruli [9], and various derivatives of **1a** could therefore be compounds with potential neuroprotective effects.

With regard to the above observations and the fact that modifications of the sterane skeleton and of the configuration of the stereogenic center exert appreciable effects on the biological properties of the compound, we set out to epimerize **1b** to 3β-acetoxy-13α-androst-5-en-17-one (**2b**) and to synthesize 3β-hydroxy-16-iodomethyl-13α-androst-5-en-17-ones (**7a**, **8a**), compounds which may potentially afford neuroprotection in the olfactory bulb.

Another approach involved the preparation of 3β-hydroxy-16,17-*seco*-13α-androsta-5,16-dien-17-al (**9**), a potential synthon for novel heterocycles condensed to the 13α-androst-5-ene skeleton, and *D-homo*-13α-androst-5-ene derivatives. The availability of 3β-hydroxy-16,17-*seco*-13β-androsta-5,16-dien-17-al [1] and 3β-hydroxy-16,17-*seco*-13α-androsta-5,16-dien-17-al (**9**) diastereomers allows a comparison of the behavior of these epimers under identical reaction conditions, and study of the chemo-, regio-, and stereoselectivity of various of their reactions.

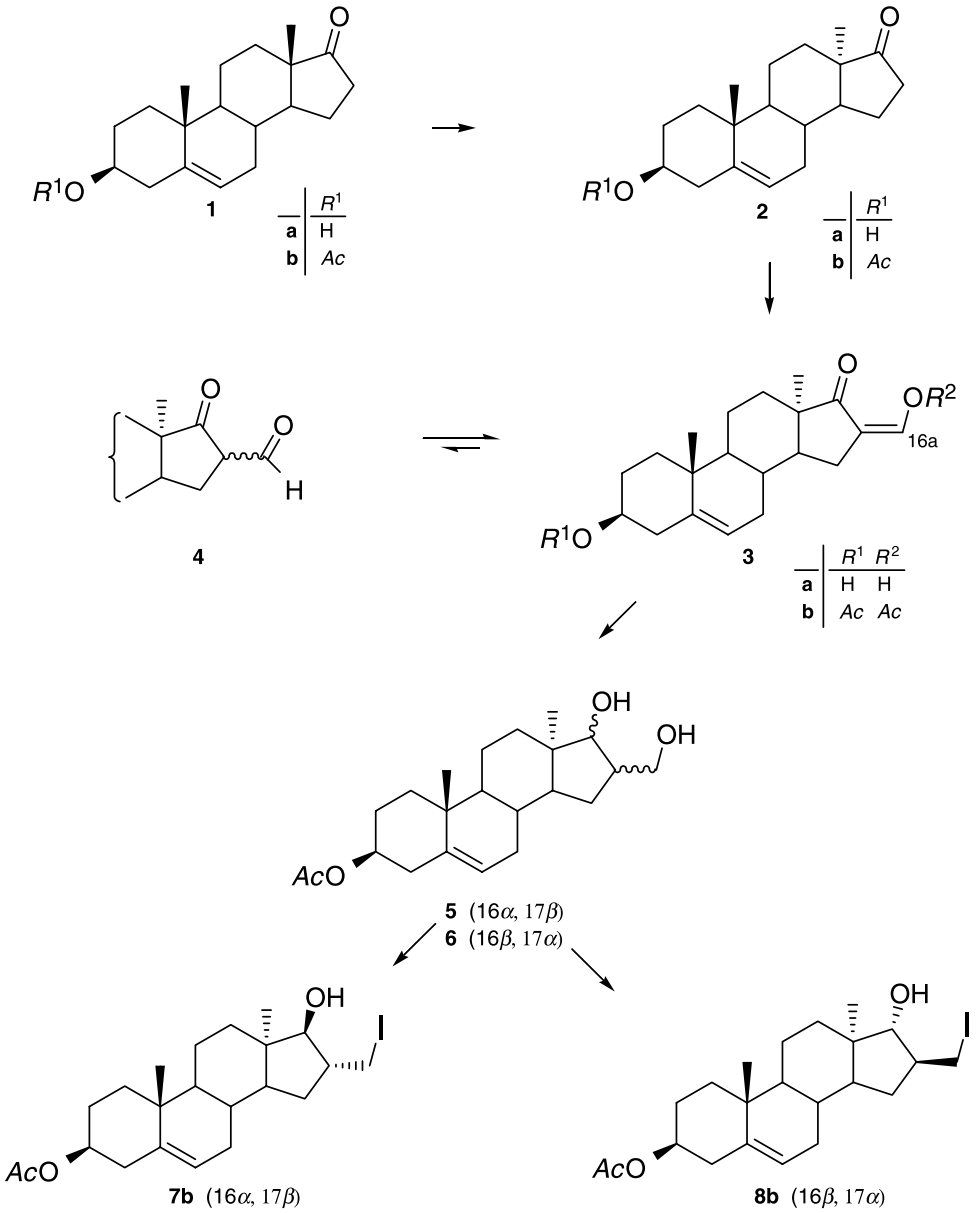
Results and Discussion

1b was epimerized by the method of *Yaremenko* and *Khvat* [10]. The reaction of **1b** with *o*-phenylenediamine in boiling acetic acid furnished 3β-acetoxy-13α-androst-5-en-17-one (**2b**) in 45% yield. This method has been extended by *Schönecker et al.* [11] to 3-methoxy-13α-estra-1,3,5(10)-trien-17-one.

Treatment of **2b** with sodium methoxide and freshly distilled ethyl formate in a *Claisen* condensation gave the sodium salt of 3β-hydroxy-16-hydroxymethylene-13α-androst-5-en-17-one (**3a**) in good yield. The free hydroxymethylene derivative **3a** was obtained by acidification of the aqueous solution of the sodium enolate of **3a**. In principle, **3a** could tautomerize to **4**, or some equilibrium mixture forms of these could be present [12]. The NMR spectrum demonstrated that **3a** was the main form present in $CDCl_3$. The ratio of the formyl proton of **4** at 9.77 ppm and the methylene proton of **3a** at 7.09 ppm is 1:6.7. The structure of **3a** was also proven by acetylation, the resulting 3β-acetoxy-16-acetoxymethylene-13α-androst-5-en-17-one (**3b**) being characterized by NMR spectroscopy and mass spectrometry. The latter was reduced with $NaBH_4$ under controlled conditions, avoiding hydrolysis of the 3-acetyl group. The reduction of 16-hydroxymethylene-17-ketone in the *normal* series leads to three diol isomers. Two isomers containing 17β-hydroxy groups with opposite configurations at C-16 were isolated in nearly identical amounts, while the third isomer was obtained in a significant smaller quantity [13]. In contrast with earlier observations on the 13β-dehydroepiandrosterone series, the reduction of **3b** with $NaBH_4$ selectively produced two *trans* diols, 3β-acetoxy-16α-hydroxymethyl-13α-androst-5-en-17β-ol (**5**) and 3β-acetoxy-16β-hydroxymethyl-13α-androst-5-en-17α-ol (**6**), in 70% overall yield. It is known that reduction of the 13β-steroid 17-ketones normally leads to 17β-hydroxy derivatives [14–16], with a few exceptions [17–19]. In the reduction of **3b**, the ratio of 17β-OH and 17α-OH in both **5** and **6** is 6:1. These results are in good agreement with

those of the 13α-estrane series [3]. Since the separation of **5** and **6** by flash chromatography on silica gel was not possible, the confirmation of the configurations of isomers **5** and **6** is possible only after the formation of their derivatives.

In order to prepare a *D-seco*-steroid in the 13α-dehydroepiandrosterone series, the primary hydroxy group of **5** and **6** was converted into a good leaving group. Since the α,γ-halohydrins and α,γ-diol monosulfonates contain appropriate nucleofugal groups for *Grob* fragmentation [20] we prepared the 16-iodomethyl compounds. The *Appel* reaction is a convenient method for the halogenation of primary and secondary alcohols [21]. On iodination, the yield was high and no

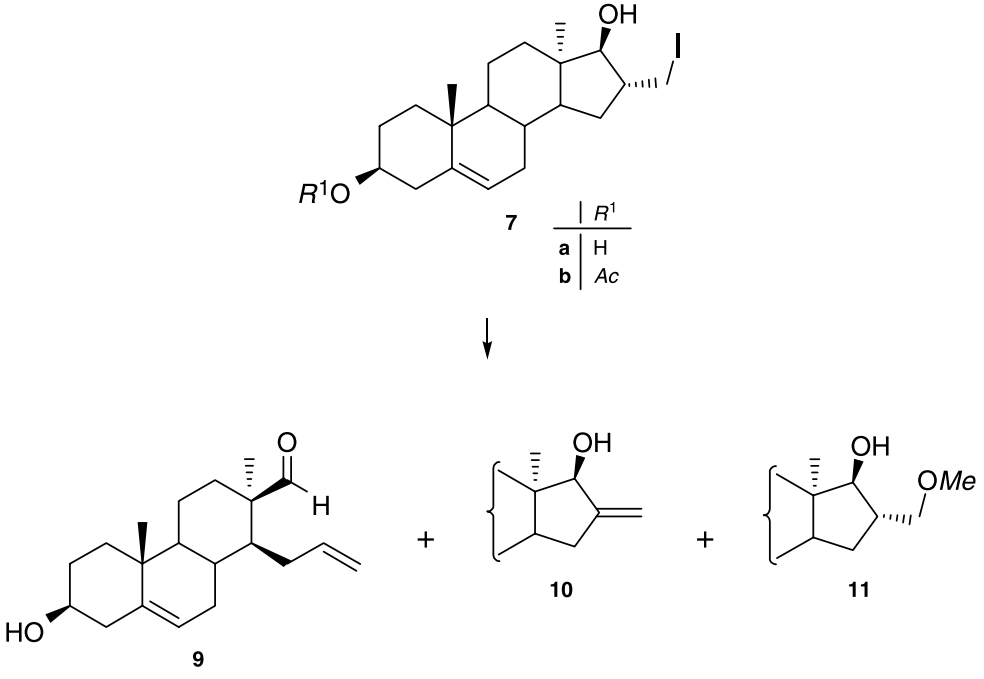


Scheme 1

disubstituted by-products were obtained. Accordingly, the mixture of **5** and **6** was reacted with I_2, Ph_3P, and imidazole in CH_2Cl_2, resulting in 3β-acetoxy-16α-iodomethyl-13α-androst-5-en-17β-ol (**7b**) and 3β-acetoxy-16β-iodomethyl-13α-androst-5-en-17α-ol (**8b**) in an overall yield of 84%, in a ratio of 6:1. After separation of the iodomethyl isomers **7b** and **8b** on silica gel, the configuration of the chiral centres was confirmed by NMR spectroscopy (Scheme 1).

Isomer **7b** was deacetylated with KOH in CH_3OH at 45°C to give **7a**, a compound suitable for neuroprotection examinations. Alkaline solvolysis of **7a** with KOH in CH_3OH under reflux for 6 h furnished the *D-seco*-steroid **9** as the main product. As opposed to the fragmentation of 16-*p*-toluenesulfonyloxy-17-hydroxy compounds in the *normal* series, for the 13α-dehydroepiandrosterone derivatives the fragmentation furnished cis functional groups at C-13 and C-14 in **9**. The fragmentation was accompanied by an elimination reaction: nearly 11% of 3β-hydroxy-16-methylidene-13α-androst-5-en-17β-ol (**10**) was formed. A second type of by-product, 3β-hydroxy-16α-methoxymethyl-13α-androst-5-en-17β-ol (**11**) was obtained in 3% yield by substitution of the leaving group by the solvent CH_3OH (Scheme 2).

The formation of the by-product can readily be explained, since fragmentation reactions are sometimes accompanied by side-reactions such as elimination or substitution [22]. Since the 16-iodomethyl group is located well away from the 17-hydroxy function, cyclization was not expected, though nucleophilic exchange and elimination were not hindered. Since the steric conditions for heterolytic fragmentation exist, the latter takes place as the main process. Thus, fragmentation can occur in all cases where the nucleofugal group is located distantly from the alco-



Scheme 2

Table 1. ^{1}H and ^{13}C chemical shifts (δ/ppm) of **3a**, **3b**, **5**, **7b**, **8b**, and **11** in $CDCl_3$ as the solvent (25°C)

Comp.	$C_{16a}H_x$-Y	16a-H_x	18-H_3	19-H_3	17-H	C-19	C-18
3a	=CH–OH	7.09	0.84	1.04	–	19.1	25.3
3b	=CH–OAc	8.20	0.83	1.01	–	19.0	25.3
5	–CH_2–OH	3.59	0.97	and 0.98		18.5	30.0
7b	α-CH_2–I	3.27, 3.38	0.97	and 0.99	3.44	18.7	30.3
8b	β-CH_2–I	3.34, 3.45	0.92	and 0.96	3.80	19.2	23.2
11	α-CH_2–O*Me*	3.47, 3.54	0.95	and 0.98	3.40	18.6	30.2

holate function formed in the alkaline medium, and therefore cyclization cannot proceed.

In order to confirm the structures of the synthetized compounds, ^{1}H and ^{13}C NMR measurements (including *J*-MOD experiments) were performed. When the similar ^{1}H NMR spectra of the 16-hydroxymethyl (**5**, **6**) and the iodohydrins (**7b**, **8b**) are compared (Table 1), the singlets of the 18- and 19-methyl hydrogens appear at 0.97–0.99 ppm. For **8b**, these singlets appear at 0.92 and 0.96 ppm. In our experience in the 13α-estrone series the singlet of the 18-methyl hydrogens of the analogous halohydrins appear at different chemical shifts, depending on whether it is a 17α- or 17β-substituted compound [3]. In the spectra of the latter derivatives, the singlet is approximately 0.10–0.20 ppm shifted downfield from that in the spectra of 17α isomers. With regard to the above observations the spectra with the singlets at 0.92 and 0.96 ppm can be assigned to the 16β,17α-substituted isomer **8b**. Further, from a comparison of the ^{13}C NMR spectra of the 16-iodomethyl (**7b**, **8b**) and 16-hydroxymethyl compounds (**5**, **6**), it may also be assumed that the signal of the 18-methyl carbon appears with different chemical shifts, depending on whether it is in a 17α- or a 17β-substituted compound. In the spectrum of the latter derivative (**7b**), the signal can be assigned at approximately 30 ppm. This signal is about 7 ppm downfield from that in the spectrum of the 17α derivative (**8b**), which is at 23.2 ppm.

Further, the two double doublets of 16a-H_2 for the 16α-iodomethyl-17β-hydroxy derivative **7b** appear at 3.27–3.38 ppm in the ^{1}H NMR spectrum. The analogous signal for the 16β-iodomethyl-17α-hydroxy compound **8b** is found at higher chemical shift, around 3.34–3.45 ppm. Finally, the triplet assigned to 17-H in the 16α,17β-substituted isomer **7b** appears at 3.43–3.45 ppm. As for the other isomer **8b**, the signal of 17-H is observed at higher chemical shift, $\delta = 3.78$–3.82 ppm, as compared with the other iodomethyl isomer **7b**. Thus, the NMR spectra demonstrated certain interesting features allowing a distinction between the two trans isomers.

In conclusion, the 3β-hydroxy-13α-androst-5-en-17-one (**2a**) and 3β-hydroxy-16α-iodomethyl-13α-androst-5-en-17β-ol (**7a**) obtained are compounds with potential neuroprotective effects. The fragmentation of **7b** *via* a simple pathway led in high yield to the *seco*-steroid **9** containing a formyl group and an unsaturated side-chain in a sterically favourable cis position. Preparation of a *D-seco*-steroid in the 13α series provides a possibility for the construction of various kinds of novel ring-closed steroids, including *D-homo* and heterocyclic compounds. Accordingly, we

have the opportunity to compare the behaviour of the 13α- and the 13β-*D-seco*-steroids under identical reaction conditions and to study the chemo-, regio-, and stereoselectivity of their reactions.

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 or CH_3OH ($c = 1$) 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 for 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. ^1H 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 given in Hz. ^{13}C NMR spectra are ^1H-decoupled. Mass spectra were measured on a Varian MAT 311A spectrometer.

3β-Acetoxy-13α-androst-5-en-17-one (**2b**, $C_{21}H_{30}O_3$)
Compound **1b** (9.91 g, 30 mmol) was dissolved in 100 cm^3 anh. acetic acid, and 5.4 g (50 mmol) *o*-phenylenediamine were added. The mixture was refluxed for 6 h, and then diluted with H_2O. The precipitate that formed was filtered off, dissolved in CH_2Cl_2, 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 3.97 g (40%) **2b**. Mp 144–145°C; $R_f = 0.60$ (diisopropyl ether/*n*-hexane 50/50); $[\alpha]_D^{20} = -165\,10^{-1}{}^{\circ}cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$ (s, 18-H_3), 0.99 (s, 19-H_3), 2.03 (s, CH_3CO), 4.60 (m, H-3), 5.40 (m, 6-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.0$ (C-19), 21.3 ($\underline{C}H_3CO$), 21.9, 22.8, 25.0 (C-18), 27.4, 31.5, 32.9, 33.9, 34.2, 36.5, 36.7 (C-10), 37.6, 47.8, 49.9 (C-13), 50.9, 73.6 (C-3), 121.8 (C-6), 139.1 (C-5), 170.4 ($CH_3\underline{C}O$), 222.1(C-17) ppm; DCI-MS: $m/z = 678$ $[2M + NH_4]^+$, 365 $[M + NH_4 + NH_3]^+$, 348 $[M + NH_4]^+$, 288.

3β-Hydroxy-13α-androst-5-en-17-one (**2a**, $C_{19}H_{28}O_2$)
Compound **2b** (2.77 g, 8.4 mmol) was dissolved in 90 cm^3 methanol and 150 mg KOH (2.7 mmol) dissolved in 10 cm^3 methanol were added. The mixture was refluxed for 1 h, and then diluted with H_2O. The precipitate was filtered off, washed with H_2O, and dried (Na_2SO_4). The crude product was purified by column chromatography with ethyl acetate/CH_2Cl_2 (10/90), resulting in 2.20 g (91%) **2a**. Mp 192–196°C; $R_f = 0.60$ (ethyl acetate/CH_2Cl_2 25/75); $[\alpha]_D^{20} = -164\,10^{-1}{}^{\circ}cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (s, 18-H_3), 0.99 (s, 19-H_3), 3.52 (m, H-3), 5.37 (m, H-6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.0$ (C-19), 22.0, 22.9, 25.1 (C-18), 31.4, 31.6, 33.0, 34.0, 34.1, 36.7 (C-10), 36.8, 42.0, 47.9, 50.0 (C-13), 51.0, 71.6 (C-3), 120.8 (C-6), 140.3 (C-5), 222.2 (C-17) ppm; EI-MS (70 eV): $m/z = 288$ (M^+), 270, 255, 174, 107, 97.

3β-Hydroxy-16-hydroxymethylene-13α-androst-5-en-17-one (**3a**, $C_{20}H_{28}O_3$)
Compound **2b** (33 g, 0.1 mol) was dissolved in 100 cm^3 anh. toluene and 11 g NaO*Me* (0.2 mol) were added, followed dropwise by 120 cm^3 freshly distilled ethyl formate. The mixture was stirred at 50°C for 6 h, left to stand at room temperature overnight, and then diluted with H_2O. The precipitate was filtered off, washed, and dried resulting in 28 g (90%) **3a**. Mp 117–120°C; $R_f = 0.35$ (ethyl acetate/CH_2Cl_2 25/75); $[\alpha]_D^{20} = -120\,10^{-1}{}^{\circ}cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.84$ (s, 18-H_3), 1.04 (s, 19-H_3), 3.52 (m, H-3), 5.35 (m, H-6), 7.09 (m, H-16a) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.1$ (C-19), 22.6, 25.3 (C-18), 26.3, 31.0 (2C), 32.4, 34.8, 36.8 (C-10), 36.9, 41.9, 47.9,

50.3, 50.6 (C-13), 71.6 (C-3), 111.4 (C-16), 120.8 (C-6), 140.3 (C-5), 159.3 (C-16a) ppm; EI-MS (70 eV): $m/z = 316$ (M^+), 298, 283, 213, 125, 105.

3β-Acetoxy-16-acetoxymethylene-13α-androst-5-en-20-one (**3b**, $C_{24}H_{32}O_5$)
Compound **3a** (15.8 g, 50 mmol) was dissolved in a mixture of 35 cm^3 pyridine and 35 cm^3 acetic anhydride, the solution was stirred overnight, and then poured onto a mixture of ice and 15 cm^3 H_2SO_4. The precipitate was collected by filtration, washed neutral, and dried resulting in 18.4 g (92%) **3b**. Mp 160–163°C; $R_f = 0.60$ (CH_2Cl_2); $[\alpha]_D^{20} = -82\,10^{-1}{}^\circ cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.83$ (s, 18-H_3), 1.01 (s, 19-H_3), 2.03 (s, 3-OCOCH_3), 2.24 (s, 16a-OCOCH_3), 4.60 (m, H-3), 5.39 (m, H-6), 8.20 (m, 16a-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.0$ (C-19), 20.6 (16a-OCO$\underline{C}H_3$), 21.3 (3-OCO$\underline{C}H_3$), 22.7, 25.3 (C-18), 27.0, 27.5, 31.3, 32.8, 35.3, 36.6, 36.8 (C-10), 37.8, 47.7, 48.5, 51.0 (C-13), 73.7 (C-3), 120.0 (C-16), 121.6 (C-6), 139.3 (C-5), 141.1 (C-16a), 167.1 (16a-O$\underline{C}OCH_3$), 170.5 (3-O$\underline{C}OCH_3$), 209.7 (C-17) ppm; DCI-MS: $m/z = 818$ $[2M + NH_4]^+$, 418 $[M + NH_4]^+$.

3β-Acetoxy-16α-hydroxymethyl-13α-androst-5-en-17β-ol (**5**, $C_{22}H_{34}O_4$)
and 3β-Acetoxy-16β-hydroxymethyl-13α-androst-5-en-17α-ol (**6**, $C_{22}H_{34}O_4$)
To 4.00 g (10 mmol) **3b** dissolved in 100 cm^3 of a mixture of C_2H_5OH and CH_3OH (1:1), 2.50 g $NaBH_4$ (75 mmol) were added in portions. To maintain *pH* 6, the solution was repeatedly acidified with CH_3OH/acetic acid (1/2), using bromothymol blue as indicator. After completion of the reaction, the mixture was diluted with H_2O, extracted with CH_2Cl_2, and the organic layer was washed to neutrality. After evaporation *in vacuo*, the crude product was purified by column chromatography using *tert*-butyl methyl ether/*n*-hexane (1/1) as solvent, resulting in 2.5 g (70%) of a 6:1 mixture of **5** and **6**, which could not be separated.

5: $R_f = 0.37$ (*tert*-butyl methyl ether/*n*-hexane 80/20); NMR data (assigned from the spectra of the mixture): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ and 0.98 (2s, 18- and 19-H_3), 2.09 (s, $COCH_3$) 3.59 (overlapping m, H-16a and 17-H), 3.77 (dd, $J = 10.1$, 4.9 Hz, H-16a), 4.60 (m, H-3), 5.36 (m, H-6) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.5$ (C-19), 21.0, 21.4 ($\underline{C}H_3CO$), 27.7, 29.4, 30.0 (C-18), 30.5, 33.2, 33.7, 36.5, 37.4 (C-10), 37.6, 43.2 (C-13), 45.9, 48.8, 52.1, 66.4 (C-16a), 73.8 (C-3), 86.1(C-17), 122.1 (C-6), 139.4 (C-5), 170.6 ($CH_3\underline{C}O$) ppm.

3β-Acetoxy-16α-iodomethyl-13α-androst-5-en-17β-ol (**7b**, $C_{22}H_{33}IO_3$)
and 3β-Acetoxy-16β-iodomethyl-13α-androst-5-en-17α-ol (**8b**, $C_{22}H_{33}IO_3$)
To 524 mg P*Ph*$_3$ (2.00 mmol) dissolved in 20 cm^3 CH_2Cl_2 136 mg imidazole (2.00 mmol), 253 mg I_2 (2.00 mmol), and 362 mg (1.00 mmol) of a mixture of **5** and **6** were added in that order. The reaction mixture was stirred at room temperature for 24 h, then poured into H_2O and extracted with CH_2Cl_2. The organic solution was washed with H_2O and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with CH_2Cl_2, resulting in 340 mg (72%) **7b** and 60 mg (12%) **8b**.

7b: Mp 150–153°C; $R_f = 0.55$ (CH_2Cl_2); $[\alpha]_D^{20} = -75\,10^{-1}{}^\circ cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ and 0.99 (2s, 18- and 19-H_3), 2.03 (s, $OCOCH_3$), 3.27 (dd, $J = 9.6$, 6.8 Hz, 16a-H), 3.38 (dd, $J = 9.6$, 6.3 Hz, 16a-H), 3.44 (t, $J = 5.6$ Hz, H-17), 4.60 (m, H-3), 5.37 (m, H-6) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.6$ (CH_2I), 18.7 (C-19), 21.3 (OCO$\underline{C}H_3$), 21.4, 27.6, 30.3 (C-18), 31.3 33.4, 33.5, 34.1, 36.6, 37.4 (C-10), 37.8, 43.9 (C-13), 46.3, 49.7, 52.5, 73.9 (C-3), 87.0 (C-17), 122.1 (C-6), 139.6 (C-5), 170.5 (OCO$\underline{C}H_3$) ppm; DCI-MS: $m/z = 490$ $[M + NH_4]^+$, 430, 381, 364, 304.

8b: Mp 63–64°C; $R_f = 0.40$ (CH_2Cl_2); $[\alpha]_D^{20} = -26\,10^{-1}{}^\circ cm^2\,g^{-1}$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.92$ and 0.96 (2s, 18- and 19-H_3), 2.04 (s, CH_3CO), 3.34 (dd, $J = 9.6$, 6.9 Hz, 16a-H), 3.45 (dd, $J = 9.6$, 5.1 Hz, 16a-H), 3.80 (t, $J = 8.7$ Hz, H-17), 4.61 (m, H-3), 5.37 (m, H-6), ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.4$ (CH_2I), 19.2 (C-19), 20.2, 21.4 ($\underline{C}H_3CO$), 23.2 (C-18), 27.6, 32.4, 33.0, 33.3, 35.9, 36.6, 36.9 (C-10), 37.9, 44.4 (C-13), 45.4, 48.4, 49.7, 73.9

(C-3), 79.0 (C-17), 122.3 (C-6), 139.0 (C-5), 170.6 ($CH_3\underline{C}O$) ppm; DCI-MS: $m/z = 962$ $[2M + NH_4]^+$, 490 $[M + NH_4]^+$, 381, 364, 304.

3β-Hydroxy-16α-iodomethyl-13α-androst-5-en-17β-ol (**7a**, $C_{20}H_{31}IO_2$)
Compound **7b** (2.53 g, 5.35 mmol) was dissolved in 90 cm^3 methanol and 336 mg KOH (6 mmol) dissolved in 30 cm^3 methanol were added. The mixture was warmed up to 45°C, stirred for 20 min, and then diluted with H_2O. The precipitate was filtered off, washed with H_2O, and dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with ethyl acetate/CH_2Cl_2 (5/95), resulting in 1.95 g (84%) **7a**. Mp 200–209°C; $R_f = 0.25$ (ethyl acetate/CH_2Cl_2 10/90); $[\alpha]_D^{20} = -108\ 10^{-1}{}^\circ cm^2\ g^{-1}$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 0.86$ and 0.90 (2s, 18- and 19-H_3), 3.17 (d, $J = 7.1$ Hz, 17-H), 3.24 (m, H-3), 3.29 (t, $J = 8.8$ Hz, 16a-H), 3.51 (dd, $J = 8.8$, 3.9 Hz, 16a-H), 4.63 (d, $J = 4.5$ Hz, 3-OH), 4.84 (d, $J = 5.0$ Hz, 17-OH), 5.25 (m, H-6) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 14.2$ (CH_2I), 18.2 (C-19), 20.6, 30.0, 30.7, 31.1, 32.9, 33.0, 33.2, 36.4, 36.8, 41.8, 43.2, 45.9, 48.5, 51.3, 69.8 (C-3), 84.4 (C-17), 120.0 (C-6), 140.9 (C-5) ppm; EI-MS (70 eV): $m/z = 430$ (M^+), 412, 379, 319, 285, 267.

3β-Hydroxy-16,17-seco-13α-androsta-5,16-dien-17-al (**9**, $C_{20}H_{30}O_2$), *3β-Hydroxy-13α-androsta-5,15-dien-17β-ol* (**10**, $C_{20}H_{30}O_2$) *and 3β-Hydroxy-16α-methoxymethyl-13α-androst-5-en-17β-ol* (**11**, $C_{21}H_{34}O_3$)
Compound **7b** (1.80 g, 3.8 mmol) was dissolved in 50 cm^3 CH_3OH and 400 mg KOH (7.13 mmol) dissolved in 25 cm^3 CH_3OH were added. The mixture was refluxed for 6 h, diluted with H_2O, extracted with CH_2Cl_2, and the extract was dried (Na_2SO_4). After evaporation *in vacuo*, the crude product was purified by column chromatography with ethyl acetate/CH_2Cl_2 (5/95) resulting in 980 mg (70%) **9**, 125 mg (11%) **10**, and 47 mg (4%) **11**.

9: Mp 78–82°C; $R_f = 0.50$ (ethyl acetate/CH_2Cl_2 10/90); $[\alpha]_D^{20} = -77\ 10^{-1}{}^\circ cm^2\ g^{-1}$ ($c = 1$, CH_3OH); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 0.85$ (s, 18-H_3), 1.05 (s, 19-H_3), 3.25 (m, H-3), 4.64 (m, 3-OH), 4.91 (d, $J = 9.3$ Hz, 16a-$H_{16\text{-H}cis}$), 4.98 (d, $J = 17.0$ Hz, 16a-$H_{16\text{-H}trans}$), 5.27 (m, H-6), 5.77 (m, H-16), 9.67 (s, H-17) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 19.4$ (C-19), 21.6, 23.1 (C-18), 31.5, 32.4, 33.1, 34.5, 36.3, 36.7 (C-10), 37.0, 42.6, 49.6, 50.0 (C-13), 50.6, 70.4 (C-3), 115.5 (C-16a), 120.7 (C-6), 139.7 (C-16), 141.0 (C-5), 208.1 (C-17) ppm; DCI-MS: $m/z = 622$ $[2M + NH_4]^+$, 337 $[M + NH_4 + NH_3]^+$, 320 $[M + NH_4]^+$, 283, 134.

10: Mp 184–186°C; $R_f = 0.40$ (ethyl acetate/CH_2Cl_2 10/90); $[\alpha]_D^{20} = -58\ 10^{-1}{}^\circ cm^2\ g^{-1}$ ($c = 1$, CH_3OH); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 0.78$ and 0.83 (2s, 18- and 19-H_3), 3.25 (m, H-3), 3.72 (d, $J = 4.7$ Hz, H-17), 4.61 and 4.70 (2d, $J = 4.6$ Hz, 3- and 17-OH), 4.91 and 5.04 (2s, 16a-H_2), 5.24 (m, H-6) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 18.7$ (C-19), 21.4, 29.5 (C-18), 31.3 (2C), 32.7, 34.0, 34.1, 36.7 (2C), 42.0, 42.9, 46.8, 51.5, 70.0 (C-3), 81.7 (C-17), 108.5 (C-16a), 120.2 (C-6), 140.9 (C-5), 155.5 (C-16) ppm; EI-MS (70 eV): $m/z = (M^+)$, 284, 269, 251, 231, 145, 105, 91.

11: Mp 163–165°C; $R_f = 0.25$ (ethyl acetate/CH_2Cl_2 25/75); $[\alpha]_D^{20} = -72\ 10^{-1}{}^\circ cm^2\ g^{-1}$ ($c = 1$, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ and 0.98 (2s, 18- and 19-H_3), 3.36 (s, OCH_3), 3.40 (d, $J = 8.0$ Hz, H-17), 3.47–3.54 (overlapping m, 16a-H_2), 5.33 (m, H-6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.6$ (C-19), 21.1, 29.6, 30.2 (C-18), 30.4, 31.5, 33.4, 33.6, 36.8, 37.4 (C-10), 42.0, 43.1 (C-13), 46.1, 47.0, 52.3, 59.0 (OCH_3), 76.8 (C-3), 77.3 (C-16a), 86.2 (C-17), 121.2 (C-6), 140.7 (C-5) ppm; EI-MS (70 eV): $m/z = 334$ (M^+), 316, 298, 251, 231, 213, 145, 107, 105.

Acknowledgements

This work was supported financially by the Hungarian Scientific Research Fund (OTKA grant T 049366). The authors thank *P. Forgó* and *I. Simon* (University of Szeged, Hungary) and *R. Machinek* (University of Göttingen, Germany) for the NMR spectra, and *Gy. Udvarnoki* (University of Göttingen, Germany) for the mass spectra.

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