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Synthesis of 15β-Hydroxyalkyl-substituted (17*Z*)-Pregn-17-enes, Their Ethers and Esters

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Abstract— Proceeding from Δ^{15}-17-ketosteroids via copper(I)-catalyzed 1,4-addition of Grignard reagent followed by modification of the 15-alkenyl substituent, introduction of a 17-ethylidene component via Wittig reaction, and transformations in the A and B rings of the steroid molecule we obtained a series of 15β-hydroxyalkyl-substituted (17*Z*)-pregn-17-enes, their ethers and esters.

This study was aimed at the synthesis of a series of pregn-17-enes with interesting biological activity and fit as initial compounds for building up side chains of C^{27}–C^{29} steroids via an ene reaction [1–4]. The main feature of the target compounds was the presence of an additional β-substituent in the C^{15} position of the steroid molecule.

As initial compound for the synthesis 15β-substituted pregnenes was chosen 3β-hydroxyandrost-5,15-dien-17-one (**I**) prepared from 3-acetoxydehydroepiandrostrone 17-ethylene ketal [5]. It should be noted that in the course of protecting the hydroxy group in compound **I** by conversion into a *tert*-butyldimethylsilyl ether **II** in tetrahydrofuran [6] an addition of imidazole along Michael reaction was observed with formation of compound **III** in a 5% yield. The imidazole addition across the Δ^{15}-bond was proved by ^{1}H NMR spectroscopy. Alongside the lack of signals from the olefin protons of the C^{15}=C^{16} double bond the spectrum contained resonances characteristic of the protons from the imidazole ring: one-proton singlets at 7.03, 7.08, and 7.64 ppm belonging to protons $H^{4'}$, $H^{5'}$, and $H^{2'}$. The structure of compound **III** was additionally confirmed by the presence in the ^{13}C NMR spectrum of the signals from the imidazole ring carbon atoms appearing as doublets at 118.8, 129.7, and 136.8 ppm. 15β-Configuration was assigned to the substituent both on the strength of the coupling constant of protons linked to C^{16} and by analogy to the most known cases of addition to the Δ^{15}-bond [7]. Obviously only when the imidazole ring is located in the 15β-position the dihedral angle between the protons H^{15a} and H^{16b} would be close to 90° and consequently their coupling constant would be close to zero. At the addition to the 15α-position the 15β-proton would be in an *anti*-periplanar position with respect to both 14α- and 16α-protons. In this case the signals of both protons attached to C^{16} would have appeared as doublet of doublets, and the pattern of the signal from the proton at C^{15} would be still more complicated, also the coupling constants would have been larger that those observed in the spectrum of compound **III**. A case of the Michael addition of imidazole to a cyclopentanone derivative was also reported formerly [8].

The introduction of an alkenyl chain was carried out by adding to unsaturated ketone **II** the Grignard reagent prepared from 5-bromopentene [9] under catalysis with copper bromide complex with dimethyl sulfide [7, 10, 11]. Adding to the reaction mixture the trimethylsilyl chloride (TMSCl) and the hexamethylphosphoramide (HMPA) [12] we raised the yield of adduct **IV** from 85 to 95%. The configuration of the substituent attached to C^{15} in compound **IV** was established in the same fashion as described above for compound **III**.

The modification of the alkenyl substituent at C^{15} in compound **IV** with the goal to introduce oxygen-containing functions first of all involved the formation of a terminal aldehyde group. The hydroxylation was effected in the presence of 4-methylmorpholine N-oxide and a catalytic amount of osmium tetroxide affording diole

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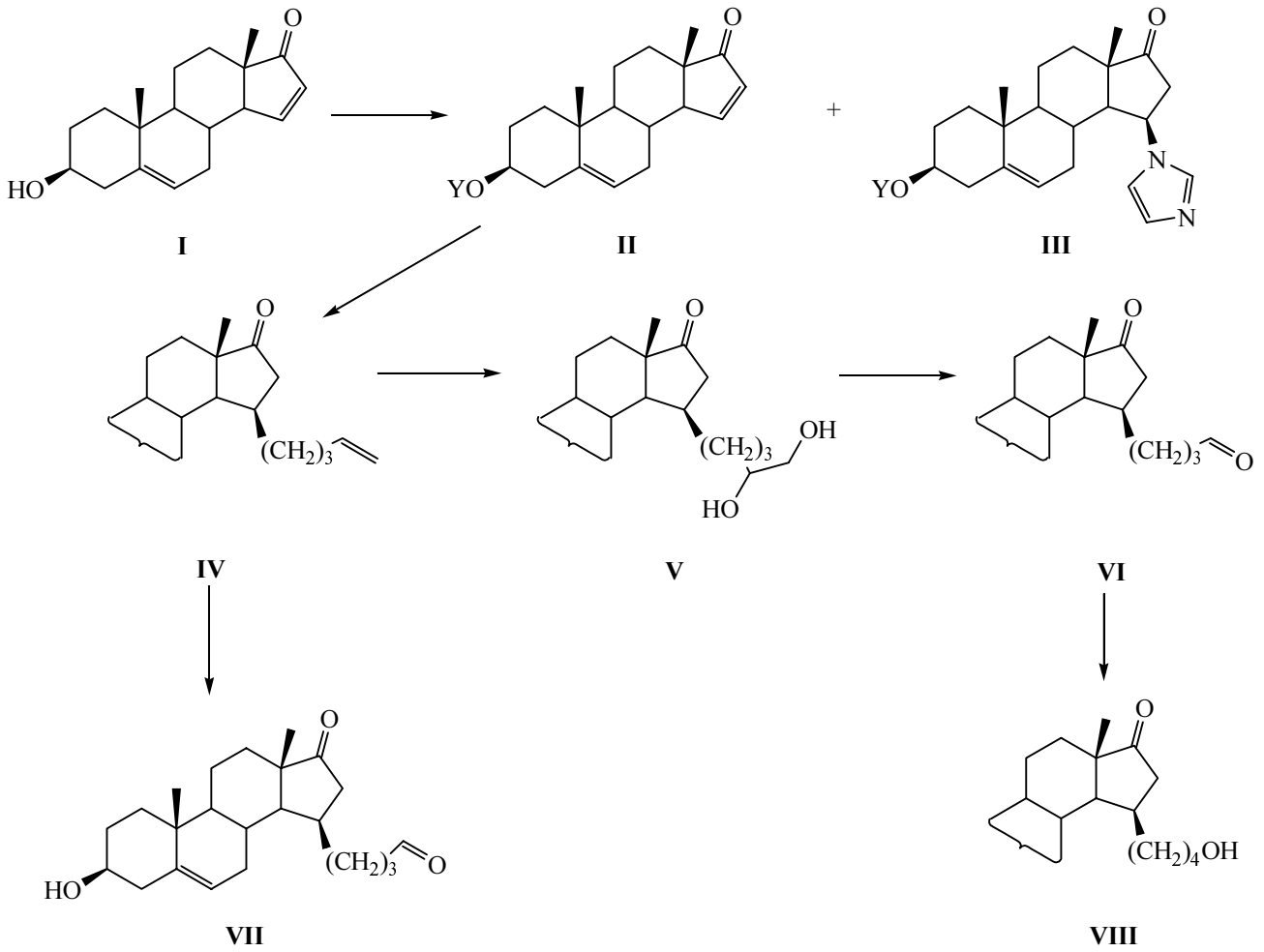


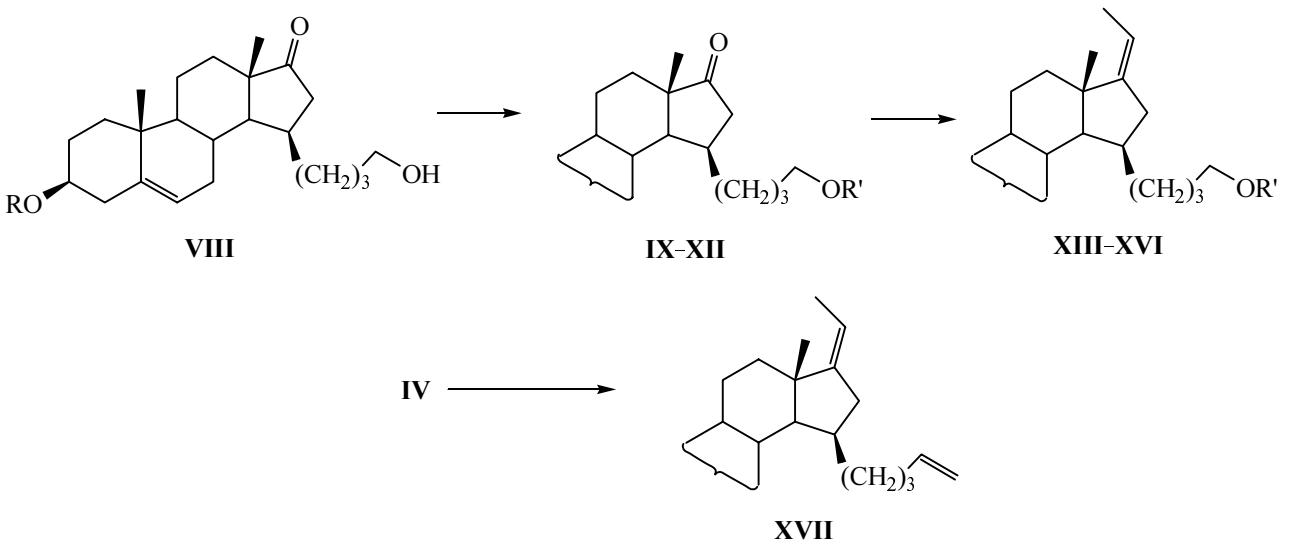
I II III IV V VI VII VIII

YO = *t*-BuMe$_2$Si.

V that underwent cleavage at treating with sodium periodate [13–15] to yield aldehyde **VI**. This procedure was chosen because at selective ozonolysis of the terminal double bond it would be difficult to protect the Δ^5-bond in the B ring of the steroid. Moreover, the yield of aldehyde **VI** proved to be considerably higher (88%) than the one usually obtained by ozonolysis (70–80%). The structure of aldehyde **VI** formation was proved by the appearance in its IR spectrum of an additional absorption band belonging to the stretching vibrations of the aldehyde group (ν 1730 cm^{-1}) and in the ^{1}H NMR spectrum of a one-proton triplet (δ 9.77 ppm) characteristic of aldehydes.

We also attempted to effect the olefin **IV** cleavage with sodium periodate in the presence of catalytic amounts of ruthenium chloride [16, 17]. This method provides aldehyde in one stage, like ozonolysis. However in our case the aldehyde formation was accompanied by the hydrolysis of the protecting group, and instead of the target product aldehyde **VII** was obtained. The attempt at the procedure optimization by decreasing the acidity (addition of sodium hydrogen carbonate) resulted only in decelerating the oxidation. The reaction took 3 days and afforded the same aldehyde **VII**.

The presence of two carbonyl groups in the molecule of steroid **VI** required the use of a selective reagent for reduction of the aldehyde function into an alcohol. The first attempt at reduction with triethylaminoborate complex ($BH_3 \cdot Et_3N$) was not successful [18]. The heating at reflux in THF for 48 h resulted only in partial reduction of the aldehyde into alcohol **VIII**. Much better was the efficiency of lithium tris(*tert*-butoxy)hydroaluminate [19]. However a two-fold excess of the reagent was required to attain an effective reduction of the aldehyde group at low temperature (–70°C). Under these conditions the yield of the target alcohol was 97%. At the use of an equivalent amount of the reductant the yield decreased to 67%. The structure of alcohol **VIII** thus prepared was confirmed by IR spectrum (appearance of the band of hydroxy



R = *t*-BuMe$_2$Si (**VIII–XVI**); R' = *t*-BuMe$_2$Si (**IX, XIII**); THP (**X, XIV**); Piv (**XI, XV**); Ac (**XII**); H (**XVI**).

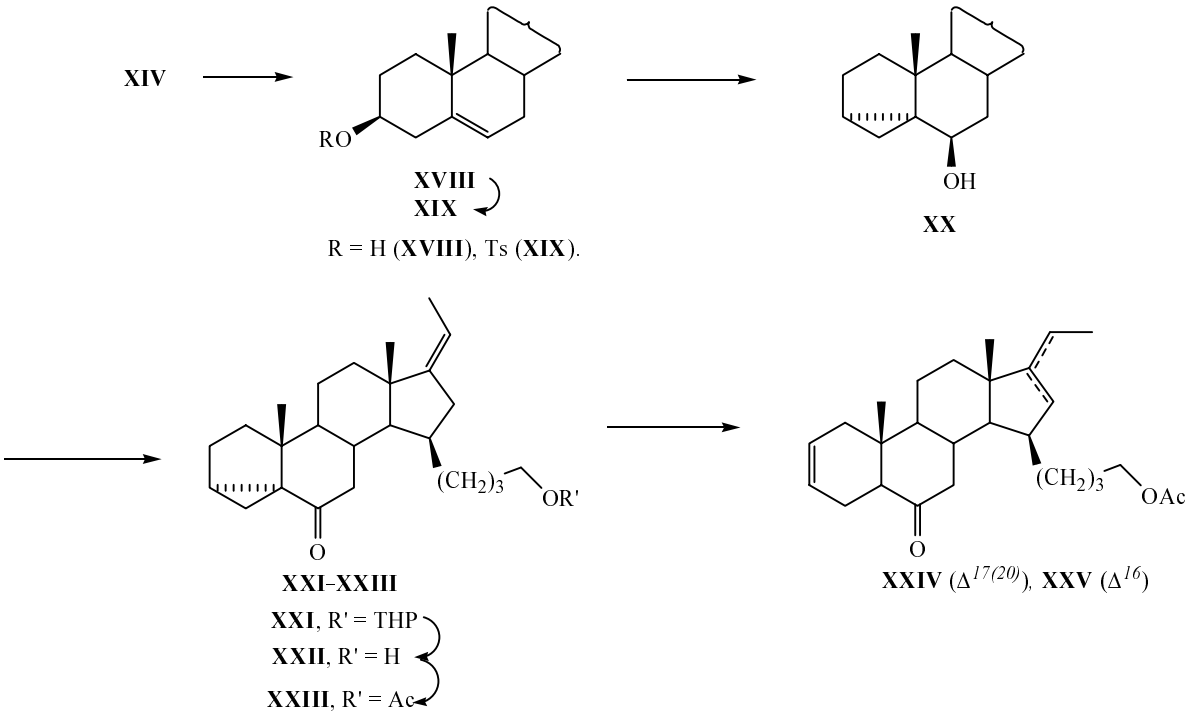
group stretching vibrations at 3480 cm^{-1}) and ^{1}H NMR spectrum [a two-proton triplet of the methylene protons attached to the carbon bearing the hydroxy group (δ 3.65 ppm)].

Further transformations required protection of the hydroxy group, and therefore we synthesized a series of alcohol **VIII** derivatives: *tert*-butyldimethylsilyl **IX** and tetrahydropyranyl **X** ethers, pivaloyl **XI** and acetyl **XII** esters.

The approach to pregnane derivatives was performed by bringing ketones **IX–XI** into Wittig reaction. The presence of an alkyl chain in the *15*β position might affect both the yield and *Z/E*-selectivity of the reaction, therefore we tested various conditions of the reaction using as a rule potassium-containing bases since lithium salts were known [20] to inhibit ylide reaction with 17-ketosteroids. Wittig reaction with ketone **IX** where the ylide was generated from ethyltriphenylphosphonium bromide with the use of potassium bis(trimethylsilyl)amide afforded compound **XIII** in a 77% yield, and with ketone **XI** 17-ethylene derivative **XV** was obtained in a 67% yield. From pivalate **XI** alongside compound **XV** a product of the ester group hydrolysis **XVI** was obtained in 4% yield. The best procedure proved to be that applying potassium *tert*-butylate which had been shown to be the reagent of choice in olefination of 17-ketosteroids lacking alkyl substituents at C^{15} [21, 22]. For instance, boiling the ylide with 17-ketosteroid **X** in benzene in the presence of potassium *tert*-butylate afforded the target compound **XIV** in a 90% yield. It should be mentioned that Wittig reaction with ketone **IV** in the presence of sodium bis(trimethylsilyl)amide proceeded slowly, with low conversion and low yield of target diene **XVII**.

The double bond configuration in 17-ethylidenesteroids **XIII–XVII** was determined by comparing with published ^{1}H NMR spectra of these compounds. A total coincidence was found for the proton signals of the group 21-CH$_3$ and the proton at C^{20} in the known 17*Z*-pregnenes and synthesized compounds **XIII–XVII**. For 17*Z*-olefins a characteristic signal of H^{21} appears at 1.66 ppm [2, 3, 5, 21, 22] whereas ub the spectra of 17*E*-olefins this signal is observed at 1.55 ppm [23]. A similar trend exists in the signals from protons attached to C^{20} (δ 5.15 for *Z*- and 5.05 ppm for *E*-isomer).

By an example of 15β-substituted olefin **XIV** we attempted to perform a transformation in the cyclic part of the steroid molecule in order to prepare Δ^2-6-keto-steroids, intermediates in the synthesis of brassinosteroids and ecdysteroids [24, 25]. The removal of *tert*-butyl-dimethylsilyl protection, tosylation, isosteroid rearrangement, oxidation of 3α,5-cycloalcohol **XX** with pyridinium chlorochromate (PCC), and the replacement of a protective group on the substituent at C^{15} occurred without complications and with high yields. However at isomerization of 3α,5-cycloketone **XXIII** into Δ^2-derivative under treatment with pyridinium hydrobromide in dimethylformamide at 150°C [26] occurred both the isomerization of the C^{20} center and the displacement of the Δ^{17}-bond into the ring furnishing unseparable mixture of isomers **XXIV** and **XXV** in a 1:1 ratio. This unwanted result is proved by the presence in the ^{1}H NMR spectrum of two signals from groups 21-CH$_3$ of intensity cor-



responding to 1.5 proton each with chemical shifts (δ, ppm) of 1.55 d **XXIV** and 1.09 **XXV**, and also by appearance in the downfield region of a multiplet at 5.46 ppm of intensity corresponding to 0.5 proton assigned to H^{20} of compound **XXV**. A similar result of double bond isomerization was obtained at oxidation of (17*Z*)-pregn-17-ene in the presence of a Ru–porphyrin [27].

In this manner a series of 15β-hydroxyalkyl-substituted (17*Z*)-pregn-17-enes, their ethers and esters was prepared by copper-catalyzed Grignard reagent addition to Δ^{15}-17-ketosteroids followed by further modifications of 15-alkenyl substituent, introduction of an ethylene component to atom C^{17} by Wittig reaction, and transformations in the A and B rings of the steroid molecules.

EXPERIMENTAL

Melting points were measured on Koeffler heating block. ^1H and ^{13}C NMR spectra were registered on spectrometer Bruker A-200 (operating frequency for protons 200 MHz) in $CDCl_3$, internal reference TMS. IR spectra were recorded on spectrophotometer UR-20 from samples prepared as films or KBr pellets. Mass spectra (electron impact) were measured on a Hewlett-Packard 5890 instrument with linear temperature programming from 40 to 280°C at a rate 10 deg/min and ionizing electrons energy 70eV. All solvents were prepared for use along standard procedures [28], the reactions were carried out in an argon atmosphere. The reaction progress was monitored by TLC on the plates Merck (Kieselgel 60 F_{254}). The chromatographic separation of reaction mixtures was performed using silica gel 40/60 (Kieselgel 60, Merck).

***tert*-Butyldimethylsilyl ether.** In 20 ml of THF was dissolved 1.26 g (4.45 mmol) of 3β-hydroxy-androst-5,15-dien-17-one (**I**) prepared in 5 stages from dehydroepiandrosterone acetate by the method [5], 0.775 g (11.4 mmol) of imidazole, and 0.863 g (5.75 mmol) of *tert*-butyldimethylsilyl chloride, and the mixture was stirred till disappearance of the original alcohol. The reaction mixture was diluted with hexane (80 ml), washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and dried with Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–ethyl acetate, 9:1). We obtained 1.65 g (94%) of ketone **II** and 0.11 g (5%) of imidazole derivative **III**.

3β-(*tert*-Butyldimethylsilyloxy)androsta-5,15-dien-17-one (II). mp 110–112°C (hexane) (111–112°C [29]). IR spectrum, cm^{-1}: 2930, 1730 (CO), 1250, 1090, 830. ^1H, δ, ppm: 0.04 s (6H, Me_2Si), 0.87 s (9H, *t*-BuSi), 1.05 s (3H, 18-Me), 1.06 s (3H, 19-Me), 3.47 m (1H, $C^3\alpha$, $J_{w/2}$ 32 Hz) 5.35 m (1H, H^6, $J_{w/2}$ 9 Hz), 6.03 d.d (1H, H^{16}, J_1 6.1, J_2 3 Hz), 7.48 d.d (1H, H^{15}, J_1 6.1, J_2 1.2 Hz). Mass spectrum (EI), *m/z* (I_{rel}, %): 385 [*M* – Me]$^+$ (3), 343 [*M*–*t*-Bu]$^+$ (60), 315 [*M* – *t*-Bu-CO]$^+$ (5).

3β-(*tert*-Butyldimethylsilyloxy)-15β-(1*H*-1-imidazolyl)androst-5-en-17-one (III). mp 170–171°C (EtOAc). IR spectrum, cm^{-1}: 2930, 2860, 1750 (CO), 1650, 1260, 1090, 840. ^1H NMR spectrum, δ, ppm: 0.05 s (6H, Me_2Si), 0.81 s (3H, 18-Me), 0.88 s (9H, *t*-BuSi), 1.02 s (3H, 19-Me), 2.84 d.d (1H, H_α^{16}, J_1 19.5, J_2 7.3 Hz), 3.05 d (1H, H_β^{16}, J 19.5 Hz), 3.48 m (1H, H_α^3, $J_{w/2}$ 32 Hz), 4.89 t (1H, H_α^{15}, J 6.1 Hz), 5.34 m (1H, H^6, $J_{w/2}$ 9 Hz), 7.03 s and 7.08 s (2H, $H^{4'}$ and $H^{5'}$), 7.64 s (1H, $H^{2'}$). ^{13}C NMR spectrum, δ, ppm: –4.6 q, 16.5 q, 18.2 s, 19.2 q, 20.1 t, 25.9 q, 29.4 d, 31.1 t, 31.8 t, 34.3 t, 36.9 s, 37.2 t, 42.5 t, 44.3 t, 45.7 s, 51.2 d, 52.9 d, 56.6 d, 72.2 d, 118.8 d, 119.2 d, 129.7 d, 136.8 d, 142.3 s, 217.1 s. Mass spectrum (ESI), *m/z* (I_{rel}, %): 469 $[M+1]^+$ (100).

3β-(*tert*-Butyldimethylsilyloxy)-15β-(4-pentenyl)androst-5-en-17-one (IV). (a) To the cooled at –20°C Grignard reagent solution obtained by adding 1.29 ml (8.64 mmol) of 5-bromopentene in 10 ml of THF to 0.288 g (9.47 mmol) of Mg in 30 ml of THF followed by boiling for 1 h was added in one portion 0.356 g (1.72 mmol) of a complex $CuBr\cdot(CH_3)_2S$. After 5 min to the black solution obtained was added 1.141 g (2.85 mmol) of steroid **II** in 10 ml of THF. The mixture was stirred for15 min, cooled to –50°C, and was treated with a saturated solution of NH_4Cl. The organic substances were extracted into EtOAc, the extract was washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 1.133 g (85%) of ketone **IV**, mp 100–102°C (hexane). IR spectrum, cm^{-1}: 2930, 2860, 1750 (CO), 1650, 1090. ^1H NMR spectrum, δ, ppm: 0.06 s (6H, Me_2Si), 0.88 s (9H, *t*-BuSi), 0.99 s (3H, 18-Me), 1.05 s (3H, 19-Me), 3.49 m (1H, H_α^3, $J_{w/2}$ 32 Hz), 4.95 m (1H, H^5_{cis} $J_{w/2}$ 14 Hz), 5.01 m (1H, H^5_{trans} $J_{w/2}$ 21 Hz), 5.35 m (1H, H^6, $J_{w/2}$ 9 Hz), 5.79 m (1H, $H^{4'}$, $J_{w/2}$ 40 Hz). Mass spectrum (EI), *m/z* (I_{rel}, %): 455 $[M\mathrm{Me}]^+$ (3), 413 $[M-t\text{-Bu}]^+$ (40).

(b) To the cooled at –20°C Grignard reagent solution obtained by adding 0.23 ml (1.95 mmol) of 5-bromopentene in 3 ml of THF to 0.051 g (2.15 mmol) of Mg in 6 ml of THF followed by boiling for 1 h was added in one portion 0.080 g (0.39 mmol) of a complex $CuBr\cdot(CH_3)_2S$. In 5 min the solution was cooled to –78°C, and thereto was added in succession 0.41 ml (3.35 mmol) of TMSCl, 0.565 ml (3.25 mmol) of HMPA, and 0.250 g (0.63 mmol) of steroid **II**. The mixture was stirred for 10 min and then treated with a saturated NH_4Cl solution. The organic substances were extracted into EtOAc, the extract was washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 0.281 g (95%) of ketone **IV**.

3β-(*tert*-Butyldimethylsilyloxy)-15β-(4,5-dihydroxypentyl)androst-5-en-17-one (V). In 40 ml of acetone and 4 ml of water was dissolved 0.959 g (2.04 mmol) of steroid **IV**, and 3.45 ml (0.26 mmol) of 0.075 M OsO_4 solution in *t*-BuOH and 0.33 g (2.44 mmol)of 4-methylmorpholine N-oxide was added thereto. The solution was stirred for 6 h, then a solution of Na_2SO_3 was added, and the stirring was continued for 30 min. Then the reaction mixture was diluted with EtOAc, washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was purified on a column packed with silica gel (eluent toluene–ethyl acetate, 1:1). We obtained 1.005 g (98%) of diol **V**, mp 150–154°C (MeOH–H_2O). IR spectrum, cm^{-1}: 3450, 2940, 2870, 1760 (CO), 1260, 1095. ^1H NMR spectrum, δ, ppm: 0.06 s (6H, Me_2Si), 0.89 s (9H, *t*-BuSi), 0.98 s (3H, 18-Me), 1.04 s (3H, 19-Me), 3.47 m (2H, H_α^3 and $H^{5'}$), 3.69 m (2H, $H^{4'}$ and $H^{5'}$, $J_{w/2}$ 29 Hz), 5.34 m (1H, H^6, $J_{w/2}$ 9 Hz). Mass spectrum (EI), *m/z* (I_{rel}, %): 503 $[M-1]^+$ (10), 447 $[M-t\text{-Bu}]^+$ (100), 429 $[M-t\text{-Bu}-H_2O]^+$ (65), 411 (45).

3β-(*tert*-Butyldimethylsilyloxy)-15β-(4-oxobutyl)androst-5-en-17-one (VI). To 0.898 g (1.78 mmol) of steroid **V** dissolved in 60 ml of ethanol was added 0.514 g (2.4 mmol) $NaIO_4$ in 5 ml of water. The solution was stirred for 30 min, the separated precipitate was filtered off and washed with EtOAc. The filtrate was evaporated without heating to a minimal volume, diluted with EtOAc, washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was purified on a column packed with silica gel (eluent toluene–ethyl acetate, 7:3). We obtained 0.756 g (90%) of aldehyde **VI**, mp 97–98°C (hexane). IR spectrum (film), cm^{-1}: 2940, 2860, 2740 (CHO), 1750 (CO), 1730 (CO), 1260, 1095. ^1H NMR spectrum, δ, ppm: 0.05 s (6H, Me_2Si), 0.88 s (9H, *t*-BuSi), 0.97 s (3H, 18-Me), 1.03 s (3H, 19-Me), 3.47 m (1H, H_α^3, $J_{w/2}$ 32 Hz), 5.33 m (1H, H^6, $J_{w/2}$ 9 Hz), 9.77 t (1H, $H^{4'}$, J 1.3 Hz). ^{13}C NMR spectrum, δ, ppm: –4.6 q, 17.5 q, 18.2 s, 19.3 q, 20.2 t, 21.8 t, 25.9 q, 28.9 d, 30.4 t, 30.8 t, 31.9 t, 33.8 t, 34.3 d, 36.9 s, 37.3 t, 42.3 t, 42.6 t, 43.7 t, 46.6 s, 50.8 d, 54.0 d, 72.4 d, 120.2 d, 142.0 s, 202.0 d, 221.0 s. Mass spectrum (EI), *m/z* (I_{rel}, %): 415 $[M-t\text{-Bu}]^+$ (100).

3β-Hydroxy-15β-(4-oxobutyl)androst-5-en-17-one (VII). To a solution of 0.045 g (0.1 mmol) of steroid **IV** in 6 ml of acetonitrile was added 0.001 g (0.005 mmol) of $RuCl_3$ and 43 mg (0,2 mmol) of $NaIO_4$ in 1 ml of water. The solution was stirred for 3 h, then it was poured into water. The organic substances were extracted into EtOAc, the extract was washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–ethyl acetate, 4:1. We obtained 0.026 g (73%) of steroid **VII**, oily substance. IR spectrum (film), cm^{-1}: 3480, 2940, 2740 (CHO), 1750 (CO), 1730 (CO). ^1H NMR spectrum, δ, ppm: 0.97 s (3H, 18-Me), 1.04 s (3H, 19-Me), 3.53 m 1H, H_α^3, $J_{w/2}$ 32 Hz), 5.39 m (1H, H^6, $J_{w/2}$ 9 Hz), 9.77 t (1H, $H^{4'}$, J 1.3 Hz). Mass spectrum (ESI), *m/z* (I_{rel}, %): 381 $[M + Na]^+$ (40).

3β-(*tert*-Butyldimethylsilyloxy)-15β-(4-hydroxybutyl)androst-5-en-17-one (VIII). To a solution of 0.756 g (1.6 mmol) of steroid **VI** in 35 ml of THF was added at –70°C 0.904 g (3.56 mmol) of $(t\text{-BuO})_3LiAlH$. The solution was stirred for 1 h at–70°C, then thereto was added in succession 1 ml of acetone, 1 ml of saturated NH_4Cl solution, and the mixture was stirred for 30 min. Then it was diluted with $CHCl_3$ and filtered through a bed of Na_2SO_4. On removal of the solvent the residue (0.895 g) was crystallized from hexane to furnish 0.597 g of reaction product. The mother liquor (0.281 g) was subjected to chromatography on a column packed with silica gel (eluent toluene–ethyl acetate, 4:1) to isolate additionally 0.144 g of steroid **VIII**. Overall yield of ketoalcohol **VIII** 0.741 g (97%), mp 109–112°C (hexane). IR spectrum, cm^{-1}: 3480, 2940, 2870, 1750 (CO), 1260, 1095. ^1H NMR spectrum, δ, ppm: 0.05 s (6H, Me_2Si), 0.88 s (9H, *t*-BuSi), 0.99 s (3H, 18-Me), 1.04 s (3H, 19-Me), 3.48 m (1H, H_α^3, $J_{w/2}$ 31 Hz), 3.65 t (2H, $H^{4'}$, J 6.4 Hz), 5.34 m (1H, H^6, $J_{w/2}$ 9 Hz). Mass spectrum (ESI), *m/z* (I_{rel}, %): 497 $[M + Na]^+$ (100).

3β-(*tert*-Butyldimethylsilyloxy)-15β-[(4-*tert*-butyldimethylsilyloxy)butyl]androst-5-en-17-one (IX). To a solution of 0.085 g (0.18 mmol) of alcohol **VIII** in 5 ml of THF was added 0.029 g (0.43 mmol) of imidazole, 0.032 g (0.22 mmol) of $t\text{-BuMe}_2SiCl$, and the mixture was stirred till disappearance of the initial alcohol (TLC monitoring). The reaction mixture was diluted with hexane, washed with a saturated solution of $NaHCO_3$, with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 0.090 g (85%) of reaction product **IX**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1750 (CO), 1260, 1095. ^1H NMR spectrum, δ, ppm: 0.03 s (6H, Me_2Si), 0.05 s (6H, Me_2Si), 0.88 s (18H, *t*-BuSi), 0.98 s (3H, 18-Me), 1.04 s (3H, 19-Me), 3.48 m (1H, H_α^3, $J_{w/2}$ 31 Hz), 3.59 t (2H, $H^{4'}$, J 6.1 Hz), 5.34 m (1H, H^6, $J_{w/2}$ 9 Hz). ^{13}C NMR spectrum, δ, ppm: –5.3 q, –4.6 q, 17.5 q, 18.2 s, 18.3 s, 19.3 q, 20.2 t, 25.8 t, 25.9 q, 28.9 d, 30.7 t, 30.8 t, 31.9 t, 32.7 t, 33.8 t, 34.3 d, 36.9 s, 37.3 t, 42.6 t, 42.7 t, 46.7 s, 50.8 d, 54.2 d, 63.0 t, 72.4 d, 120.3 d, 141.9 s, 221.7 s.

3β-(*tert*-Butyldimethylsilyloxy)-15β-[4-(tetrahydropyran-2-yloxy)butyl]androst-5-en-17-one (X). To a solution of 0.876 g (1.85 mmol) of steroid **VIII** in 25 ml of THF was added 0.418 ml (4.63 mmol) of dihydropyran and 49 mg (0.19 mmol) of pyridinium *p*-toluenesulfonate. The solution was heated at reflux for 30 min, then cooled, diluted with EtOAc, the catalyst was filtered off, the filtrate was washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 0.960 g (93%) of steroid **X**, oily substance. IR spectrum (film), cm^{-1}: 2940, 1750 (CO), 1095. ^1H NMR spectrum, δ, ppm: 0.04 s (6H, Me_2Si), 0.86 s (9H, *t*-BuSi), 0.97 s (3H, 18-Me), 1.02 s (3H, 19-Me), 3.43 m (3H, H_α^3, $H^{4'}$ and $H^{6''}$, $J_{w/2}$ 52 Hz), 3.77 m (2H, $H^{4'}$ and $H^{6''}$, $J_{w/2}$ 46 Hz), 4.54 m (1H, $H^{2''}$), 5.32 m (1H, H^6, $J_{w/2}$ 9 Hz).

3β-(*tert*-Butyldimethylsilyloxy)-15β-(4-pivaloyloxybutyl)androst-5-en-17-one (XI). To a solution of 0.170 g (0.36 mmol) of steroid **VIII** in 2 ml of pyridine was added 0.093 g (0.5 mmol) of trimethylacetic anhydride and 9 mg (0.08 mmol) of dimethylaminopyridine. The solution was stirred for 12 h, then poured into water. The organic substances were extracted into EtOAc, the extract was washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 0.145 g (72%) of steroid **XI**, mp 108–110°C (hexane). IR spectrum, cm^{-1}: 2940, 2870, 1750 (CO), 1260, 1040. ^1H NMR spectrum, δ, ppm: 0.06 s (6H, Me_2Si), 0.89 s (9H, *t*-BuSi), 0.99 s (3H, 18-Me), 1.04 s (3H, 19-Me), 1.18 s (9H, Me_3C), 3.48 m (1H, H_α^3, $J_{w/2}$ 31 Hz), 4.05 t (2H, $H^{4'}$, J 6.4 Hz), 5.34 m (1H, H^6, $J_{w/2}$ 9 Hz). Mass spectrum (EI), *m/z* (I_{rel}, %): 501 $[M - t\text{-Bu}]^+$ (40), 426 (5), 325 (40).

15β-(4-Acetoxybutyl)-3β-(*tert*-butyldimethylsilyloxy)androst-5-en-17-one (XII). To a solution of 0.028 g (0.06 mmol) of steroid **VIII** in 4 ml of

dichloromethane was added 0.012 ml (0.12 mmol) of acetic anhydride and 18 mg (0.15 mmol) of dimethylaminopyridine. The solution was stirred for 12 h, then diluted with dichloromethane, washed with water, with a solution of $NaHCO_3$, a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 24 mg (79%) of steroid **XII**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1750 (CO), 1740 (MeCO), 1260, 1095. ^1H NMR spectrum, δ, ppm: 0.06 s (6H, Me_2Si), 0.89 s (9H, *t*-BuSi), 0.99 s (3H, 18-Me), 1.05 s (3H, 19-Me), 2.03 s (3H, OAc), 3.49 m (1H, H^3_α, $J_{w/2}$ 31 Hz), 4.06 t (2H, $H^{4'}$, *J* 6.4 Hz), 5.35 br.d (1H, H^6, *J* 4.9 Hz).

(17*Z*)-3β-(*tert*-Butyldimethylsilyloxy)-15β-[(4-*tert*-butylsilyldimethyloxy)butyl]-pregna-5,17-diene (XIII). To a solution obtained by adding 1.36 ml (0.68 mmol) of 0.5 M solution of potassium bis(trimethylsilyl)-amide in toluene to 0.303 g (0.81 mmol) of ethyltriphenylphosphonium bromide in 1 ml of THF was added at –78°C 0.080 g (0.14 mmol) of steroid **IX** in 1 ml of THF. The mixture was stirred for 30 min, the cooling was removed, and the solution was heated at reflux for 6 h. Then the solution was cooled and treated with a saturated solution of NH_4Cl. The organic substances were extracted into EtOAc, the extract was washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was dissolved in hexane, 0.5 ml of methyl iodide was added, and the reaction mixture was stirred for 24 h. The precipitate was filtered off, the filtrate was evaporated, and the obtained oily substance was separated on a column packed with silica gel (eluent toluene–petroleum ether, 9:1). We obtained 0.063 g (77%) of reaction product **XIII**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1095. ^1H NMR spectrum, δ, ppm: 0.04 s (6H, Me_2Si), 0.05 s (6H, Me_2Si), 0.88 s (18H, *t*-BuSi), 1.02 s (3H, 18-Me), 1.05 s (3H, 19-Me), 1.65 d (3H, 21-Me, *J* 7.3 Hz), 3.48 m (1H, H^3_α), 3.58 t (2H, $H^{4'}$, *J* 6.4 Hz), 5.15 q.t (1H, H^{20}, J_1 7.3, J_2 1.5 Hz), 5.33 m (1H, H^6, $J_{w/2}$ 9 Hz).

(17*Z*)-3β-(*tert*-Butyldimethylsilyloxy)-15β-[4-(tetrahydropyran-2-yloxy)butyl]-pregna-5,17-diene (XIV). To a solution of ylide prepared by stirring 0.560 g (5 mmol) of potassium *tert*-butylate and 2.4 g (6.5 mmol) of ethyltriphenylphosphonium bromide in 6 ml of benzene at 40°C for 0.5 h was added 0.836 g (1.5 mmol) of steroid **X** in 8 ml of benzene at 10°C. The solution obtained was heated at reflux for 4 h, cooled, and excess acetone was added. In 30 min the solution was treated with 3 ml of saturated NH_4Cl solution, diluted with hexane, and filtered through a bed of Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 9:1). We obtained 0.769 g (90%) of compound **XIV**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1040. ^1H NMR spectrum, δ, ppm: 0.05 s (6H, Me_2Si), 0.88 s (9H, *t*-BuSi), 1.03 s (3H, 18-Me), 1.05 s (3H, 19-Me), 1.65 d (3H, 21-Me, *J* 7.3 Hz), 3.36 m (1H, $H^{4'}$, $J_{w/2}$ 23 Hz), 3.49 m (2H, H^3_α and $H^{6''}$, $J_{w/2}$ 25 Hz), 3.72 m (1H, $H^{4'}$, $J_{w/2}$ 25 Hz), 3.86 m (1H, $H^{6''}$, $J_{w/2}$ 24 Hz), 4.56 m (1H, $H^{2''}$, $J_{w/2}$ 8 Hz), 5.15 q.t (1H, H^{20}, J_1 7.3, J_2 1.8 Hz), 5.33 br.d (1H, H^6, *J* 4.8 Hz).

(17*Z*)-3β-(*tert*-Butyldimethylsilyloxy)-15β-(4-pivaloyloxybutyl)pregna-5,17-diene (XV). Along the procedure applied to the synthesis of compound **XIII** from 0.120 g (0.21 mmol) of ketone **XI** we obtained 0.080 g (67%) of steroid **XV**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1745 (CO), 1040. ^1H NMR spectrum, δ, ppm: 0.05 s (6H, Me_2Si), 0.88 s (9H, *t*-BuSi), 1.03 s (3H, 18-Me), 1.04 s (3H, 19-Me), 1.18 s (9H, Me_3C), 1.66 d (3H, 21-Me, *J* 7 Hz), 3.48 m (1H, H^3_α, $J_{w/2}$ 31 Hz), 4.03 t (2H, $H^{4'}$, *J* 6.4 Hz), 5.15 q.t (1H, H^{20}, J_1 7, J_2 1.5 Hz), 5.32 m (1H, H^6, $J_{w/2}$ 9 Hz). ^{13}C NMR spectrum, δ, ppm: –4.6 q, 13.4 q, 18.3 s, 19.3 q, 20.2 q, 21.1 t, 25.9 q, 26.1 t, 27.2 q, 28.8 t, 28.9 d, 30.9 t, 31.6 t, 32.1 t, 36.8 s, 37.0 d, 37.4 t, 38.7 s, 39.2 t, 39.2 t, 42.7 t, 43.5 s, 50.8 d, 59.3 d, 64.4 t, 72.6 d, 114.1 d, 120.9 d, 141.8 s, 150.7 s, 178.6 s. Further elution with the mixture toluene–petroleum ether, 9:1, furnished 0.004 g (4%) of **(17*Z*)-3β-(*tert*-butyldimethylsilyloxy)-15β-(4-hydroxybutyl)pregna-5,17-diene (XVI)**, oily substance. IR spectrum (film), cm^{-1}: 3500, 2940, 2870, 1040. ^1H NMR spectrum, δ, ppm: 0.06 s (6H, Me_2Si), 0.89 s (9H, *t*-BuSi), 1.04 s (3H, 18-Me), 1.06 s (3H, 19-Me), 1.66 d (3H, 21-Me, *J* 7 Hz), 3.49 m (1H, H^3_α, $J_{w/2}$ 31 Hz), 3.62 t (2H, $H^{4'}$, *J* 6.4 Hz), 5.15 q.t (1H, H^{20}, J_1 7, J_2 1.5 Hz), 5.34 m (1H, H^6, $J_{w/2}$ 9 Hz).

(17*Z*)-3β-(*tert*-Butyldimethylsilyloxy)-15β-(4-pentenyl)pregna-5,17-diene (XVII). To a solution obtained from 0.324 g (0.87 mmol) of ethyltriphenylphosphonium bromide and 0.137 g (0.75 mmol) of sodium bis(trimethylsilyl)amide in 1 ml of THF was added at –78°C 0.115 g (0.24 mmol) of steroid **IV** in 1 ml of THF. After stirring for 1 h the cooling was removed, the solution was heated at reflux for 10 h, then the reaction mixture was cooled, diluted with hexane, washed with a saturated solution of NH_4Cl, a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 9:1). We obtained 0.052 g of

original ketone **IV** and 0.010 g (8%) of reaction product **XVII**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1655, 1270, 1060, 810. ^1H NMR spectrum, δ, ppm: 0.04 s (6H, Me_2Si), 0.86 s (9H, *t*-BuSi), 1.04 s (3H, 18-Me), 1.06 s (3H, 19-Me), 1.65 br.d (3H, 21-Me, *J* 7 Hz), 3.48 m (1H, H^3_α, $J_{w/2}$ 28 Hz), 4.91 d (1H, $H^{5'}_{cis}$, *J* 8 Hz), 4.99 br.d (1H, $H^{5'}_{trans}$, *J* 17 Hz), 5.16 br.q (1H, H^{20}, *J* 7 Hz), 5.33 m (1H, H^6, $J_{w/2}$ 9 Hz), 5.81 m (1H, $H^{4'}$, $J_{w/2}$ 40 Hz).

(17*Z*)-3β-Hydroxy-15β-[4-(tetrahydropyran-2-yloxy)butyl]pregna-5,17-diene (XVIII). To a solution of 0.867 g (1.52 mmol) of steroid **XIV** in 5 ml of THF was added 4.56 ml of 1 M solution of tetrabutylammonium fluoride in THF, and the mixture was stirred. In 2 h additionally 2.28 ml of 1M solution of tetrabutylammonium fluoride in THF was added, and the stirring was continued for 3 h. Then the mixture was diluted with EtOAc, washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene). We obtained 0.683 g (99%) of steroid **XVIII**, oily substance. IR spectrum (film), cm^{-1}: 3480, 2940, 2870, 1040. ^1H NMR spectrum, δ, ppm: 1.04 s (3H, 18-Me), 1.06 s (3H, 19-Me), 1.65 d (3H, 21-Me, *J* 7 Hz), 3.36 m (1H, $H^{4'}$, $J_{w/2}$ 24 Hz), 3.52 m (2H, H^3_α, $H^{6''}$), 3.72 m (1H, $H^{4'}$, $J_{w/2}$ 25 Hz), 3.86 m (1H, $H^{6''}$, $J_{w/2}$ 24 Hz), 4.56 m (1H, $H^{2''}$, $J_{w/2}$ 8 Hz), 5.14 q.t (1H, H^{20}, J_1 7, J_2 1.8 Hz), 5.36 br.d (1H, H^6, *J* 5.1 Hz).

15β-[4-(Tetrahydropyran-2-yloxy)butyl]-3α,5-cyclo-5α-pregn-17-en-6-one (XXI). To a solution of 0.520 g (1.14 mmol) of steroid **XVIII** in 10 ml of pyridine was added 0.724 g (3.8 mmol) of *p*-toluenesulfonyl chloride and 78 mg (0.15 mmol) of dimethylaminopyridine. The solution was stirred for 24 h, then poured into water, the precipitated reaction product was filtered off, washed with water, dried, and dissolved in 90 ml of acetone. To the solution thus obtained was added 0.6 g (6.1 mmol) of potassium acetate in 6 ml of water. The solution was heated at reflux for 48 h, cooled, and acetone was evaporated. The residue was dissolved in EtOAc, washed with a saturated solution of NH_4Cl, a saturated solution of NaCl, and dried on Na_2SO_4. On removing the solvent the residue was dissolved in 10 ml of dichloromethane, and 0.450 g (5 mmol) of potassium acetate and 0.431 g (2 mmol) of pyridinium chlorochromate was added in succession. The mixture was stirred for 2 h, then 0.431 g (2 mmol) of PCC again was added, and the stirring was continued. After 6 h of stirring the reaction mixture was subjected to column chromatography on silica gel (eluent toluene). We obtained 0.325 g (63%) of compound **XXI**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1700 (CO), 1040. ^1H NMR spectrum, δ, ppm: 0.74 t (1H, H^4, *J* 4.9 Hz), 1.03 s (3H, 18-Me), 1.10 s (3H, 19-Me), 1.66 br.d (3H, 21-Me, *J* 7 Hz), 3.35 m (1H, $H^{4'}$, $J_{w/2}$ 24Hz), 3.48 m (1H,$H^{6''}$, $J_{w/2}$ 23 Hz), 3.72 m (1H, $H^{4'}$, $J_{w/2}$ 25 Hz), 3.85 m (1H, $H^{6''}$, $J_{w/2}$ 24 Hz), 4.57 m (1H, $H^{2''}$, $J_{w/2}$ 8 Hz), 5.16 q.t (1H, H^{20}, J_1 7, J_2 1.8 Hz). ^{13}C NMR spectrum, δ, ppm: 11.9 t, 13.3 q, 19.6 t, 19.7 q, 20.5 q, 22.9 t, 25.5 t, 25.8 t, 26.5 t, 29.9 t, 30.7 t, 31.1 t, 31.7 d, 33.5 t, 35.7 d, 37.1 d, 39.1 t, 39.2 t, 43.8 s, 44.5 t, 46.4 s, 46.7 s, 46.8 d, 59.6 d, 62.3 t, 67.6 t, 98.8 d, 114.4 d, 150.0 s, 209.4 s.

(17*Z*)-15β-(4-Acetoxybutyl)-3α,5-cyclo-5α-pregn-17-en-one (XXIII). To a solution of 0.425 g (0.94 mmol) of steroid **XXI** in 15 ml of methanol and 1.5 ml of water was added 0.016 g (0.09 mmol) of *p*-toluenesulfonic acid. The solution was stirred for 12 h, then poured into water, methanol was distilled off, the organic substances were extracted into chloroform, the extract was washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and dried on Na_2SO_4. On removing the solvent the residue was dissolved in 10 ml of dichloromethane, and then were added in succession 0.122 g (1 mmol) of dimethylaminopyridine, 0.24 ml (3 mmol) of pyridine, and 0.3 ml (3 mmol) of acetic anhydride. The solution was stirred for 1 h, diluted with chloroform, washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and dried on Na_2SO_4. On removal of the solvent the residue was separated on a column packed with silica gel (eluent toluene). We obtained 0.288 g (74%) of reaction product **XXIII**, oily substance. IR spectrum (film), cm^{-1}: 2940, 2870, 1750 (MeCO), 1700 (CO), 1250, 1040. ^1H NMR spectrum, δ, ppm: 0.75 t (1H, H^4, *J* 4.9 Hz), 1.04 s (3H, 18-Me), 1.09 s (3H, 19-Me), 1.65 br.d (3H, 21-Me, *J* 7 Hz), 4.02 t (2H, $H^{4'}$, *J* 6.4 Hz), 5.16 q.t (1H, H^{20}, J_1 7, J_2 1.8 Hz).

(17*E*)-15β-(4-Acetoxybutyl)pregna-2,17-diene-6-one (XXIV) and 15β-(4-acetoxybutyl)pregna-2,16-diene-6-one (XXV). To a solution of 0.231 g (0.56 mmol) of steroid **XXIII** in 5 ml of DMF was added 0.358 g (2.24 mmol) of pyridinium hydrobromide The reaction mixture was boiled for 6 h, then cooled and poured in water. The organic compounds were extracted with EtOAc, the extract was washed with a saturated solution of NaCl, and dried on Na_2SO_4. On removing the solvent the residue was separated on a column packed with silica gel (eluent toluene–petroleum ether, 1:1). We obtained 0.095 g (43%) of a mixture of steroids **XXIV** and **XXV**.

IR spectrum (film), cm^{-1}: 3030, 2950, 2860, 1750 (MeCO), 1720 (CO), 1250, 1040. ^1H NMR spectrum, δ, ppm: 0.75 s and 0.77 s (3H, 18-Me and 19-Me), 0.89 s and 0.95 s (3H, 18-Me and 19-Me), 1.09 t and 1.55 br.d (3H, 21-Me, *J* 7 Hz), 2.05 s (3H, OAC), 4.05 t.d (2H, $H^{4'}$, J_1 6.5, J_2 2.2 Hz), 5.08 m (0.5H, H^{20}, $J_{w/2}$ 20 Hz), 5.46 m (0.5H, H^{16}, $J_{w/2}$ 6.7 Hz), 5.57m (1H, H^3, $J_{w/2}$ 16 Hz), 5.70 m (1H, H^2, $J_{w/2}$ 18 Hz). Mass spectrum (EI), *m/z* (I_{rel}, %): 412 $[M]^+$ (60), 397 $[M - Me]^+$ (90), 384 $[M - CO]^+$ (50), 337 $[M$ – Me-AcOH$]^+$ 45), 323 $[M$– CO–AcOH$]^+$ (30), 297 $[M - (CH_2)_4OAc]^+$ (100).

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