ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 8, pp. 1151–1157. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © A.V. Baranovskii, R.P. Litvinovskaya, V.A. Khripach, 2007, published in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 8, pp. 1159–1164.

Synthetic Approach to Preparation of Indole Derivatives Fused with a Bicyclo[3.3.1]nonane Framework

A. V. Baranovskii, R. P. Litvinovskaya, and V. A. Khripach

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, 220141 Belarus
e-mail: litvin@iboch.bas-net.by

Received July 12, 2006

Abstract—Starting with Δ^{15}-17-ketosteroids, applying Normant reaction with allylmagnesium bromide and anionic Cope rearrangement of the formed allyl alcohol, 15α-derivatives of androstane series were prepared. The latter were brought into Wittig reaction with an ylide generated from ethyltriphenylphosphonium bromide, and the product was subjected to ene reaction to provide 15α-substituted pregnanes.

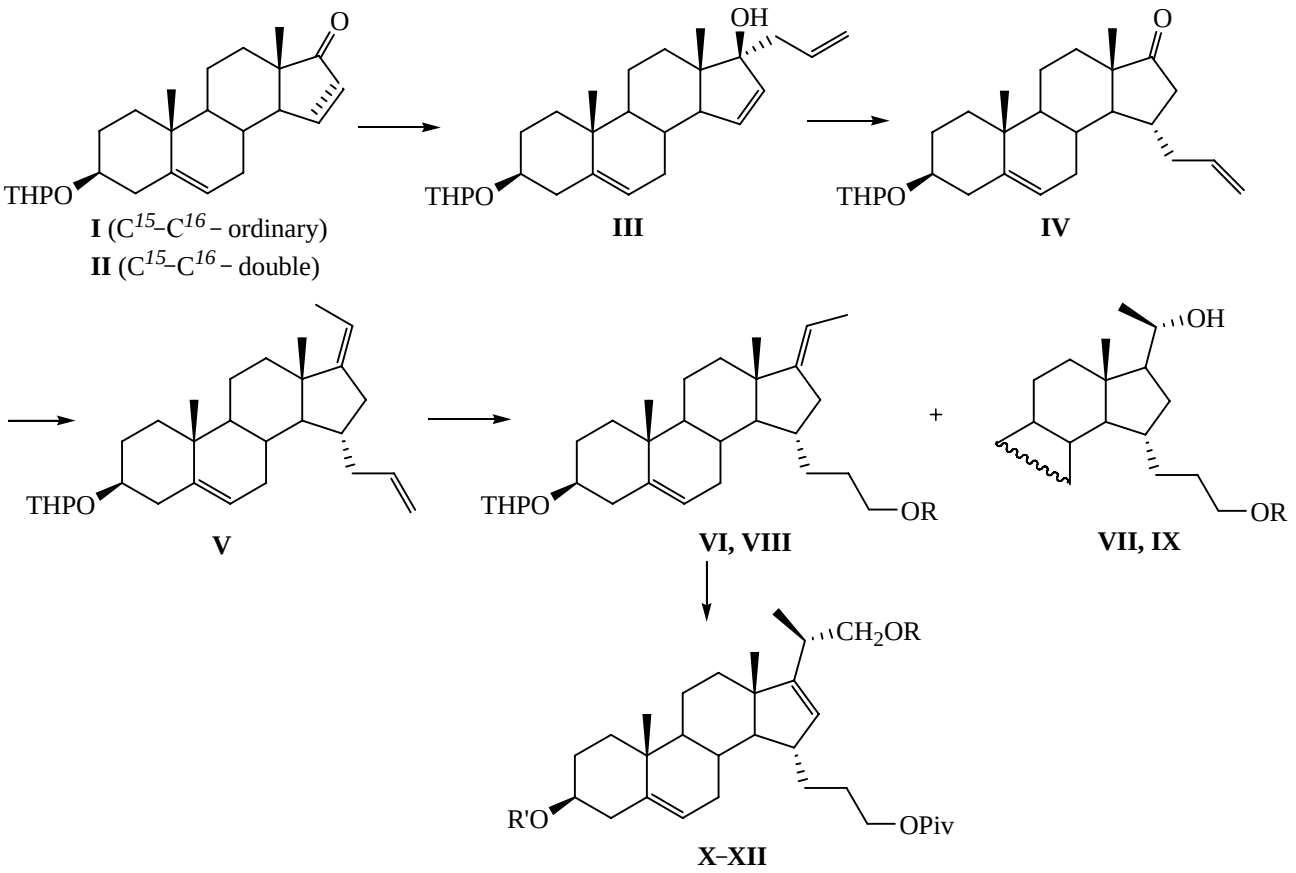
DOI: 10.1134/S1070428007080106

We reported formerly on a synthesis of a series of 15β-substituted 17*Z*-pregnenes [1] proceeding from dehydroepiandrosterone. This communication deals with the synthesis of new 15α-substituted pregnenes and with some their transformations. We selected as an initial substance for the synthesis compound **II** prepared by dehydrosilylation of a silyl enol ether of dehydroepiandrosterone tetrahydropyranyl derivative (**I**) [2]. The conversion of unsaturated ketone **II** into a derivative with a 15α-substituent **IV** was carried out by the method developed for estrone series compounds [3, 4]. To this end Δ^{15}-17-ketosteroid **II** was treated with an organocerium compound prepared from allylmagnesium bromide and cerium chloride to obtain allyl alcohol **III** in a nearly quantitative yield. Its formation was confirmed by the appearance in the ^{1}H NMR spectrum of one-proton and two-proton multiplets at δ 5.94 and 5.14 ppm characteristic of an allyl structure, and also by the disappearance in the IR spectrum of the absorption band belonging to the carbonyl stretching vibration and by the presence of a band at 3500 cm^{-1} from the stretching vibrations of a hydroxy group.

Alcohol **III** under conditions of Cope anionic rearrangement (a treatment with potassium hydride in THF at −78°C in the presence of 18-crown-6 [3]) was converted into ketone **IV** in 56% yield. Regretfully, the use of potassium hexamethyldisilazide [5] as a base did not led to an increased yield of the target ketone, whereas in the series of estrane derivatives the yields attained were up to 90%. The structure of compound **IV** follows from its IR spectrum (the absorption band of hydroxy group stretching vibrations disappears, and the carbonyl group band is observed at 1750 cm^{-1}) and from ^{1}H NMR spectrum (the signals of olefin protons at C^{15} and C^{16} vanish, and the signals of allyl group protons shift upfield to δ 5.79 and 5.02 ppm).

The transition to pregnane derivatives was preformed by subjecting ketone **IV** to Wittig reaction with ylide generated from ethyltriphenylphos-phonium bromide using potassium *tert*-butylate as base. As a result a single product was isolated, triene **V**. It was established by comparison of the spectral characteristics of olefin **V** with those of previously obtained 17*Z*-olefins of 15β-series [1] and 17*Z*-olefins lacking a substituent in the D ring [6] that in the presence of the 15α-substituent also formed an olefin of 17*Z*-configuration. However the signal of the proton at C^{20} being identical in pattern and having the same coupling constants appeared upfield (δ 5.08 ppm) compared with unsubstituted or 15β-substituted 17-ethylidene derivatives (δ 5.15 ppm).

We planned to perform the regioselective hydroxylation of the terminal double bond in compound **V** by hydroboronizing. However we failed to carry out the reaction using 9-BBN or thexylborane. The hydroboronizing was successful only at the use of a complex borane–dimethyl sulfide; therewith the hydroboronizing occurred at the terminal double bond providing alcohol **VI** and also partially at the Δ^{17}-bond with the formation of diol **VII**. Surprisingly under the chosen conditions (in THF at 0°C) an isomerization of Δ^{17}-bond occurred in the main reaction product. The 17*E*-configuration of



R = H (**VI, VII, X, XI**), Piv (**VIII, IX**), Ac (**XII**); R' = THP (**X**), H (**XI**), Ac (**XII**); THP is 2-tetrahydropyranyl, Piv is pivaloyl.

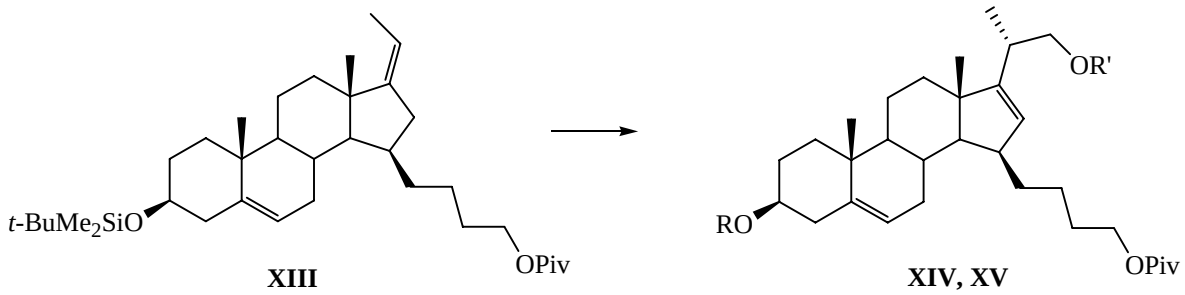
compound **VI** and its ester **VIII** was established from their ^{1}H NMR spectra where the signal of proton at C^{20} was shifted upfield and had a quite different pattern. The protons signal of methyl group at C^{21} was also shifted upfield from 1.66 (**V**) to 1.54 ppm (**VI**) as inherent to 17*E*-pregnenes [7]. ^{13}C NMR spectra of olefins **V** and **VI** also were different. The most sensitive were signals of C^{17} and C^{18} (they shifted downfield by 2 ppm) and signal of C^{20} (it shifted upfield by 3 ppm).

The double bond migration in the course of hydroboronizing was formerly described. It occurs through an equilibrium borane addition to the double bond at a high (up to 160°C) [8] or elevated (from 20 to 60°C) temperature, as in the case of 20-methylpregn-17-ene [9]. Presumably the isomerization we observed was an intramolecular process originating from the fairly close location of the double bonds. 20*S*-Configuration of the C^{20} center in the minor product **VII** was established from the chemical shift of the protons signal of the methyl groups at C^{20} and C^{13} in the ^{1}H NMR spectra. In the spectrum of 20*R*-isomer these signals are observed at 0.80 and 1.15 ppm respectively, and in the spectrum of 20*S*-isomer, at 0.70 and 1.22 ppm [10]. In the spectra of compounds **IX** and **VII** prepared by us the proton signals of methyl groups appeared at 0.71–0.72 (18-Me) and 1.22–1.23 ppm (21-Me).

In order to prove additionally the configuration of the Δ^{17}-bond in compound **VI** we carried out an ene reaction of olefin **VIII** with paraformaldehyde in the presence of diethylaluminum chloride for this process was known [6, 11, 12] to proceed stereoselectively: The 17*Z*-ethylidenes should provide 20β-, and the 17*E*- ethylidenes, 20α-methylderivatives. As a result of the reaction two compounds were obtained: homoallyl alcohol **X** (product of the ene reaction) in 22% yield and diol **XI** (product of ene reaction and of removal of tetrahydropyranyl protection) in 42% yield.

At the same time an analogous ene reaction was performed with 17*Z*- ethylidene **XIII** [1] possessing a 15β-substituent; here a homoallyl alcohol **XIV** was obtained in 51% yield.

The analysis of spectra of compounds **X, XI**, and **XIV** and acetates **XII** and **XV** prepared by acylating the corresponding alcohols with acetic anhydride in pyridine



XIII **XIV, XV**

R = *t*-BuMe$_2$Si (**XIV**), Ac (**XV**); R' = H (**XIV**), Ac (**XV**).

led to the following conclusions. It is known from published data that in the ^{1}H NMR spectra of 20*S*-derivatives free of substituents at C^{15} a characteristic signal of the protons of 21-methyl appears in the region δ 1.01–1.05 ppm [13–16], whereas in the spectra of 20*R*-isomers this signal is observed in the region δ 1.11 ppm [17, 18]. The signal of analogous protons in the ^{1}H NMR spectra of compounds **X–XII** appears at δ 1.11 ppm confirming the assumption on the isomerization of the double bond in the course of hydroboronizing compound **V**. In the ^{1}H NMR spectrum of acetate **XII** signals of an impurity were found (up to 10% according to integral intensity) corresponding to 20*S*-isomer. This fact suggests either an incomplete isomerization of 17*Z*-olefin **V** during hydroboronizing or a certain possibility of the reagent attack from the side of the β-region of the steroid olefin molecule **VIII**; the latter may be due to the presence of the 15α-substituent.

EXPERIMENTAL

Melting points were measured on a Koeffler heating block. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker A-200 (operating frequencies 200 and 50 MHz respectively) in $CDCl_3$ with TMS as internal reference. IR spectra were recorded on a spectrophotometer UR-20 from films or KBr pellets. Mass spectra were taken on a Hewlett Packard-5890 instrument in electron impact (EI) mode or on AMD 402 Intectra device at electrospray ionization (ESI) at ionizing energy 70 eV. The solvents were prepared by known procedures [19], all reactions were carried out under an argon atmosphere. The reaction progress was monitored by TLC on Merck (Kieselgel 60 F_{254}) plates. The chromatographic separation of the reaction mixtures was done using silica gel 40/60 (Kieselgel 60, Merck).

3β-(2-Tetrahydropyranyloxy)androsta-5,16-dien-17-one (II). To a solution of 3.6 mmol of lithium diisopropylamide in 5 ml of THF was added at –78°C 1.116 g (3 mmol) of 3β-(2-tetrahydropyranyloxy)androst-5-en-17-one in 10 ml of THF. The solution was stirred for 20 min, and 0.868 g (1 ml, 8 mmol) of trimethylsilyl chloride was added. The cooling was removed, and the reaction mixture warmed at stirring to 0°C within 30 min. Then the reaction mixture was poured into a mixture of saturated solutions of $NaHCO_3$ and NaCl, 1:1. The organic layer was separated, the water layer was extracted with ethyl acetate, the combined extracts were washed with a saturated solution of NaCl, and dried with anhydrous sodium sulfate. On removing solvent (without heating) the residue (0.575 g) was dissolved in 50 ml of acetonitrile, 0.672 g (3 mmol) of $Pd(OAc)_2$ was added, and the solution obtained was boiled for 20 min. On completion of the reaction the solution was cooled, evaporated, and the residue was subjected to chromatography on silica gel (eluent toluene–ethyl acetate, 95:5). We obtained 0.195 g (17%) of initial ketone **I** and 0.855 g (77%) of dienone **II**, mp 152–154°C (hexane) (132–142°C [20]). IR spectrum (KBr), cm^{-1}: 2950, 2870, 1720 (CO), 1470, 1120, 1040, 820. ^{1}H NMR spectrum, δ, ppm: 1.05 s (6H, 18-Me and 19-Me), 3.51 m (2H, C^{3}H$_\alpha$, C$^{6'}$H, $J_{w/2}$ 28 Hz), 3.91 m (1H, C$^{6'}$H, $J_{w/2}$ 22 Hz), 4.70 m (1H, C$^{2'}$H, $J_{w/2}$ 10 Hz), 5.37 m (1H, C^{6}H, $J_{w/2}$ 9 Hz), 6.03 d.d (1H, C^{16}H, J_1 6.1, J_2 3 Hz), 7.48 d.d (1H, C^{15}H, J_1 6.1, J_2 1.2 Hz).

17α-Allyl-17-hydroxy-3β-(2-tetrahydropyranyloxy)androsta-5,15-diene (III). To a suspension of 1.166 g (4.73 mmol) of anhydrous $CeCl_3$ in 15 ml of THF was added 4.73 ml of 1 M solution of allylmagnesium bromide in THF at –78°C. After 1 h to the solution obtained 0.731 g (1.98 mmol) of steroid **II** in 10 ml of THF was added. The solution was stirred for 15 min at –78°C, and a saturated solution of NH_4Cl was added thereto. The organic phase was extracted with ethyl acetate, the extract was washed with a saturated NaCl solution and dried with anhydrous sodium sulfate. On removing the solvent the residue (0.889 g) was

crystallized from hexane, the crystals were filtered off to obtain 0.631 g of compound **III**. The mother liquor was evaporated, and the residue (0.306 g) was purified by chromatography on silica gel (eluent toluene–ethyl acetate, 95:5). Thus additional 0.168 g of steroid **III** was obtained. Overall yield 0.799 g (98%), mp 149–152°C (hexane). IR spectrum (KBr), cm^{-1}: 3500, 2940, 2870, 1040. ^1H NMR spectrum, δ, ppm: 0.92 s (3H, 18-Me), 1.05 s (3H, 19-Me), 3.52 m (1H, C^3H_α, $C^{6'}H$, $J_{w/2}$ 33 Hz), 3.92 m (1H, $C^{6'}H$, $J_{w/2}$ 23 Hz), 4.71 m (1H, $C^{2'}H$, $J_{w/2}$ 9 Hz), 5.14 m (2H, $C^{3''}H$, $J_{w/2}$ 19 Hz), 5.37 m (1H, C^6H, $J_{w/2}$ 9 Hz), 5.68 d.d (1H, $C^{15}H$, J_1 5.8, J_2 3 Hz), 5.83 d.d (1H, $C^{16}H$, J_1 5.8, J_2 1.2 Hz), 5.94 m (1H, $C^{2''}H$, $J_{w/2}$ 32 Hz). ^{13}C NMR spectrum, δ, ppm: 14.7 q, 19.3 q, 20.0 t, 20.4 t, 25.4 t, 27.9 t, 29.8 d, 30.4 t, 31.2 t, 31.7 t, 36.9 s, 37.0 t, 38.0 t, 40.2 t, 50.6 d, 50.7 s, 57.4 d, 62.8 t, 75.8 d, 85.9 s, 96.8 d, 118.6 t, 120.8 d, 131.0 d, 135.0 d, 137.5 d, 141.4 s. Mass spectrum (ESI), *m/z* (I_{rel}, %): 435 $[M + Na]^+$ (100).

15α-Allyl-3β-(2-tetrahydropyranyloxy)androst-5-en-17-one (IV). To a suspension of 0.120 g (3 mmol) of potassium hydride in 5 ml of THF was added in succession at –78°C 0.290 g (1.1 mmol) of dibenzo-18-crown-6 and 0.241 g (0.59 mmol) of steroid **III**. The solution was stirred for 48 h at 10°C and treated with a saturated NH_4Cl solution, reaction products were extracted into EtOAc, the extract was washed with a saturated NaCl solution and dried with anhydrous sodium sulfate. On removing the solvent the residue was subjected to chromatography on silica gel (eluent cyclohexane–toluene, 1:1). Yield 0.134 g (56%), mp 141–143°C (hexane). IR spectrum (KBr), cm^{-1}: 2940, 2860, 1750. ^1H NMR spectrum, δ, ppm: 0.93 s (3H, 18-Me), 1.06 s (3H, 19-Me), 3.51 m (2H, C^3H_α, $C^{6'}H$, $J_{w/2}$ 38 Hz), 3.92 m (1H, $C^{6'}H$, $J_{w/2}$ 22 Hz), 4.71 br.s (1H, $C^{2'}H$), 5.02 m (2H, $C^{3''}H$, $J_{w/2}$ 22 Hz), 5.35 br.d (1H, C^6H, J 4.9 Hz), 5.70 m (1H, $C^{2''}H$, $J_{w/2}$ 40 Hz). ^{13}C NMR spectrum, δ, ppm: 15.17 q, 19.54 q, 20.19 t, 20.22 t, 25.65 t, 28.12 t, 31.44 t, 31.44 t, 33.03 d, 33.19 t, 37.02 s, 37.08 d, 37.38 t, 40.00 t, 40.18 t, 42.65 t, 50.09 s, 50.16 d, 55.20 d, 63.09 t, 75.93 d, 97.09 d, 116.70 t, 120.88 d, 136.60 d, 141.08 s, 219.99 s. Mass spectrum (ESI), *m/z* (I_{rel}, %): 435 $[M + Na]^+$ (40), 383 (100).

Further elution (eluent cyclohexane–toluene, 1:2) provided 0.031 g (13%) of the initial ketone.

(17*Z*)-15α-Allyl-3β-(2-tetrahydropyranyloxy)-pregna-5,17-diene (V). To a solution of ylide prepared by stirring 0.165 g (1.37 mmol) of potassium *tert*-butylate and 0.599 g (1.62 mmol) of ethyl triphenylphosphonium bromide in 3 ml of benzene at 40°C in 0.5 h was added 0.229 g (0.56 mmol) of steroid **IV** in 5 ml of benzene at 10°C. The solution was boiled for 4 h, cooled, and excess acetone was added. After 30 min the solution was treated with 1 ml of saturated solution of NH_4Cl, diluted with hexane, and filtered through a layer of Na_2SO_4. On removing the solvent the residue was subjected to chromatography on silica gel (eluent toluene–hexane, 1:1). Yield 0.203 g (85%), oily substance. IR spectrum (film), cm^{-1}: 2940, 2860, 1160. ^1H NMR spectrum, δ, ppm: 0.95 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.66 br.d (3H, 21-Me, J 7.1 Hz), 3.51 m (2H, C^3H_α, $C^{6'}H$, $J_{w/2}$ 38 Hz), 3.92 m (1H, $C^{6'}H$, $J_{w/2}$ 22 Hz), 4.72 m (1H, $C^{2'}H$, $J_{w/2}$ 7 Hz), 4.94 d (1H, $C^{3''}H_{cis}$, J 9.1 Hz), 4.99 br.d (1H, $C^{3''}H_{trans}$, J 16.3 Hz), 5.08 q.t (1H, $C^{20}H$, J_1 7.1, J_2 1.6 Hz), 5.34 br.d (1H, C^6H, J 4.8 Hz), 5.77 m (1H, $C^{2''}H$, $J_{w/2}$ 40 Hz). ^{13}C NMR spectrum, δ, ppm: 13.1 q, 17.8 q, 19.3 q, 20.0 t, 20.8 t, 25.5, t 28.0 t, 31.3 t, 32.7 d, 33.0 t, 36.7 t, 36.8 s, 37.2 t, 38.7 d, 39.5 t, 40.0 t, 40.6 t, 46.1 s, 49.9 d, 59.3 d, 62.8 d, 75.9 t, 96.8 d, 112.8 d, 115.1 t, 121.2 d, 138.0 d, 140.7 s, 148.5 s.

Hydroboronizing of triene V. To a solution of 0.156 g (0.37 mmol) of steroid **V** in 5 ml of THF was added 2 ml (0.4 mmol) of 0.2 M solution of $BH_3 \cdot (CH_3)_2S$ at 0°C. The solution was stirred for 30 min, then 1 ml of 4 N solution of NaOH and 1 ml of 30% hydrogen peroxide were added, and the stirring was continued for 2 h more. Then a solution of sodium thiosulfate was added, the organic phase was extracted with ethyl acetate, the extracts were washed with saturated solutions of NH_4Cl and NaCl, and dried with anhydrous sodium sulfate. On removing the solvent the residue was subjected to chromatographic separation on silica gel (eluent toluene–ethyl acetate, 4: 1). We obtained 0.070 g (43%) of diene **VI** and 0.051 g (30%) of alcohol **VII**.

(17*E*)-15α-(3-Hydroxypropyl)-3β-(2-tetrahydropyranyloxy)pregna-5,17-diene (VI), mp 146–149°C (hexane). IR spectrum (KBr), cm^{-1}: 3500, 2940, 2860, 1160. ^1H NMR spectrum, δ, ppm: 0.79 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.53 d (3H, 21-Me, J 5.9 Hz), 3.50 m (2H, C^3H_α, $C^{6'}H$, $J_{w/2}$ 32 Hz), 3.64 t (2H, $C^{3''}H$, J 6.4 Hz), 3.89 m (1H, $C^{6'}H$, $J_{w/2}$ 33 Hz), 4.71 m (1H, $C^{2'}H$, $J_{w/2}$ 6 Hz), 5.02 m (1H, $C^{20}H$, $J_{w/2}$ 30 Hz), 5.32 m (1H, C^6H, $J_{w/2}$ 11 Hz). ^{13}C NMR spectrum, δ, ppm: 13.9 q, 19.5 q, 20.10 q, 20.20 t, 20.80 t, 25.70 t, 28.20 t, 31.50 t, 31.90 t, 32.70 t, 33.10 d, 33.50 t, 34.80 t, 35.80 t, 36.90 s, 37.50 t, 39.70 d, 40.20 t, 45.30 s, 50.60 d, 58.70 d, 63.00 t, 63.50 t, 76.1 d, 97.1 d,

109.80 d, 121.40 d, 140.10 s, 150.90 s. Mass spectrum (ESI), *m/z* (I_{rel}, %): 465 [M + Na]$^+$ (60).

(20*S*)-15α-(3-Hydroxypropyl)-3β-(2-tetrahydropyranyloxy)pregn-5-en-20-ol (VII), mp 176–177°C (EtOAc). IR spectrum (KBr), cm^{-1}: 3500, 2940, 2860, 1160. ^{1}H NMR spectrum, δ, ppm: 0.72 s (3H, 18-Me), 1.01 s (3H, 19-Me), 1.23 d (3H, 21-Me, J 7.3 Hz), 3.49 m (2H, C^{3}H$_\alpha$, C$^{6'}$H, $J_{w/2}$ 25 Hz), 3.62 t (2H, C$^{3''}$H, J 6.1 Hz), 3.74 m (1H, C^{20}H, $J_{w/2}$ 20 Hz), 3.91 m (1H, C$^{6'}$H, $J_{w/2}$ 28 Hz), 4.71 m (1H, C$^{2'}$H, $J_{w/2}$ 9 Hz), 5.33 m (1H, C^{6}H, $J_{w/2}$ 9 Hz). ^{13}C NMR spectrum, δ, ppm: 13.6 q, 19.5 q, 20.2 t, 20.6 t, 24.0 q, 25.7 t, 28.2 t, 31.5 t, 31.8 t, 32.7 d, 33.3 t, 33.5 t, 34.0 t, 37.1 s, 37.4 t, 38.7 t, 38.8 d, 40.2 t, 43.7 s, 50.1 d, 56.4 d, 60.2 d, 63.0 t, 63.4 t, 70.0 d, 76.1 d, 97.0 d, 121.4 d, 141.0 s. Mass spectrum (ESI), *m/z* (I_{rel}, %): 483 [M + Na]$^+$ (100).

(17*E*)-15α-(3-Pivaloyloxypropyl)-3β-(2-tetrahydropyranyloxy)pregna-5,17-diene (VIII). To a solution of 0.070 g (0.16 mmol) of steroid **VI** in 1 ml of pyridine was added 0.060 g (0.32 mmol) of trimethylacetic anhydride and 4 mg (0.04 mmol) of dimethylaminopyridine. The solution was stirred for 12 h, then poured into water, and the products were extracted into ethyl acetate. The combined extracts were washed in succession with saturated solutions of $NaHCO_3$ and NaCl, and dried with anhydrous sodium sulfate. On removing the solvent the residue was subjected to chromatography on silica gel (eluent toluene–ethyl acetate, 9:1). Yield 0.057 g (68%), mp 92–95°C (hexane). IR spectrum (KBr), cm^{-1}: 2940, 2860, 1740, 1160. ^{1}H NMR spectrum, δ, ppm: 0.79 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.20 s (9H, Me_3C) 1.54 d (3H, 21-Me, J 6.7 Hz), 3.50 m (2H, C^{3}H$_\alpha$, C$^{6'}$H, $J_{w/2}$ 30 Hz), 3.92 m (1H, C$^{6'}$H, $J_{w/2}$ 28 Hz), 4.05 t (2H, C$^{3''}$H, J 6.1 Hz), 4.72 m (1H, C$^{2'}$H, $J_{w/2}$ 9 Hz), 5.03 m (1H, C^{20}H, $J_{w/2}$ 28 Hz), 5.31 m (1H, C^{6}H, $J_{w/2}$ 9 Hz).

(20*S*)-15α-(3-Pivaloyloxypropyl)-3β-(2-tetrahydropyranyloxy)pregn-5-en-20-ol (IX). By the above procedure from 0.045 g (0.1 mmol) of alcohol **VII** and 0.026 g (0.15 mmol) of trimethylacetic anhydride we obtained 0.019 g (36%) of ester **IX** as oily substance. IR spectrum (film), cm^{-1}: 3420, 2860, 1745, 1160. ^{1}H NMR spectrum, δ, ppm: 0.71 s (3H, 18-Me), 1.01 s (3H, 19-Me), 1.18 s (9H, Me_3C), 1.22 d (3H, 21-Me, J 6.1 Hz), 3.50 m (2H, C^{3}H$_\alpha$, C$^{6'}$H, $J_{w/2}$ 33 Hz), 3.71 m (1H, C^{20}H, $J_{w/2}$ 26 Hz), 3.91 m (1H, C$^{6'}$H, $J_{w/2}$ 23 Hz), 4.03 t (2H, C$^{3''}$H, J 5.8 Hz), 4.71 m (1H, C$^{2'}$H, $J_{w/2}$ 9 Hz), 5.30 m (1H, C^{6}H, $J_{w/2}$ 10 Hz).

Ene reaction of compound VIII with paraformaldehyde. To a stirred solution of 0.008 g (0.27 mmol) of paraformaldehyde in 1 ml of dichloromethane was added at –78°C 0.54 ml of 1 M solution of diethylaluminum chloride in hexane. After 45 min to the complex obtained was added 0.046 g (0.09 mmol) of steroid **VIII** in 4 ml of dichloromethane, and the mixture was stirred at –30°C. After 3 h to a solution 0.2 ml of pyridine in 1 ml of methanol was added, and the cooling was removed. After the end of gas liberation the mixture was poured into a saturated solution of $NaHCO_3$, the products were extracted with EtOAc, the extract was washed with a saturated NaCl solution, and dried with anhydrous sodium sulfate. On removing the solvent the residue was separated by chromatography on silica gel (eluent toluene–ethyl acetate, 4:1). We obtained 0.011 (22%) of alcohol **X** and 0.018 g (42%) of diol **XI**.

(20*R*)-20-Hydroxymethyl-15α-(3-pivaloyloxypropyl)-3β-(2-tetrahydropyranyloxy)pregna-5,16-diene (X). Oily substance. IR spectrum (film), cm^{-1}: 3420, 2940, 2860, 1750. ^{1}H NMR spectrum, δ, ppm: 0.85 s (3H, 18-Me), 1.06 s (3H, 19-Me), 1.12 d (3H, 21-Me, J 6.7 Hz), 1.19 s (9H, Me_3C), 3.41 d.d (1H, C^{22}H, J_1 10.8, J_2 5.6 Hz), 3.51 m (3H, C^{3}H$_\alpha$, C^{22}H, C$^{6'}$H, $J_{w/2}$ 30 Hz), 3.91 m (1H, C$^{6'}$H, $J_{w/2}$ 23 Hz), 4.06 t (2H, C$^{3''}$H, J 5.4 Hz), 4.71 m (1H, C$^{2'}$H, $J_{w/2}$ 9 Hz), 5.31 m (1H, C^{6}H, $J_{w/2}$ 9 Hz), 5.36 C (1H, C^{16}H). Mass spectrum, *m/z* (I_{rel}, %): 426 (20), 327 (20), 309 (30).

(20*R*)-20-Hydroxymethyl-15α-(3-pivaloyloxypropyl)pregna-5,16-diene-3β-ol (XI), mp 127–130°C (hexane). IR spectrum (KBr), cm^{-1}: 3500, 2940, 2860, 1750. ^{1}H NMR spectrum, δ, ppm: 0.84 s (3H, 18-Me), 1.04 s (3H, 19-Me), 1.11 d (3H, 21-Me, J 6.7 Hz), 1.19 s (9H, Me_3C), 3.41 d.d (1H, C^{22}H, J_1 10.8, J_2 5.6 Hz), 3.56 m (2H, C^{3}H$_\alpha$, C^{22}H, $J_{w/2}$ 31 Hz), 4.04 t (2H, C$^{3'}$H, J 5.4 Hz), 5.31 m (1H, C^{6}H, $J_{w/2}$ 10 Hz), 5.35 C (1H, C^{16}H).

(20*R*)-3β-Acetoxy-20-acetoxymethyl-15α-(3-pivaloyloxypropyl)pregna-5,16-diene (XII). To a solution of 17 mg (0.036 mmol) of steroid **XI** in 4 ml of dichloromethane was added 0.018 ml (0.16 mmol) of acetic anhydride and 0.016 ml (0.2 mmol) of pyridine. The solution was stirred for 12 h, then 0.1 ml of methanol was added, the reaction mixture was diluted with dichloromethane, washed in succession with saturated solutions of $NaHCO_3$ and NaCl, and dried with anhydrous sodium sulfate. On removing the solvent the residue was subjected to chromatography on silica gel (eluent toluene–ethyl acetate, 4:1). Yield 8 mg (40%).

Oily substance. IR spectrum (film), cm^{-1}: 2940, 2860, 1750, 1240. ^1H NMR spectrum, δ, ppm: 0.83 s (3H, 18-Me), 1.06 s (3H, 19-Me), 1.11 d (3H, 21-Me, *J* 6.7 Hz), 1.19 s (9H, Me_3C), 2.03 s (3H, OAc), 2.05 s (3H, OAc), 3.79 d.d (1H, $C^{22}H$, J_1 10.4, J_2 8.5 Hz), 4.04 t (2H, $C^{3'}H$, *J* 5.8 Hz), 4.06 m (1H, $C^{22}H$, $J_{w/2}$ 17 Hz), 4.59 m (1H, C^3H_α, $J_{w/2}$ 23 Hz), 5.32 s (1H, $C^{16}H$), 5.34 m (1H, C^6H, $J_{w/2}$ 10 Hz). ^{13}C NMR spectrum, δ, ppm: 17.7 q, 18.4 q, 19.3 q, 20.5 t, 21.0 q, 21.4 q, 26.6 t, 27.2 q, 27.7 t, 29.7 t, 31.1 d, 31.8 d, 33.0 t, 34.7 t, 36.9 s, 37.0 t, 38.0 t, 38.8 s, 44.5 d, 48.8 C, 50.2 d, 59.7 d, 64.6 t, 68.7 t, 73.8 d, 122.2 d, 127.9 d, 139.7 s, 154.9 s, 170.5 s, 171.1 s, 178.6 s.

(20*S*)-3β-*tert*-Butyldimethylsilyloxy-20-hydroxymethyl-15β-(4-pivaloyloxybutyl)-pregna-5,16-diene (XIV). Along the procedure for the synthesis of steroids **X** and **XI** from 0.072 g (0.12 mmol) of compound **XIII**, 0.011 g (0.36 mmol) of paraformaldehyde, and 0.7 ml of 1 M solution of diethylaluminum chloride in a mixture of hexane isomers we obtained 0.037 g (51%) of compound **XIV**, mp 79–80°C (hexane). IR spectrum (film), cm^{-1}: 3420, 2940, 2860, 1750, 1160, 1100. ^1H NMR spectrum, δ, ppm: 0.05 s (6H, Me_3Si), 0.88 s (3H, 18-Me), 0.98 s (9H, Me_3CSi), 1.03 d (3H, 21-Me, *J* 6.7 Hz), 1.05 s (3H, 19-Me), 1.18 s (9H, Me_3C), 3.54 m, (3H, C^3H_α, $C^{22}H$, $J_{w/2}$ 33 Hz), 4.04 t (2H, $C^{4'}H$, *J* 6.1 Hz), 5.33 d (1H, C^6H, *J* 4.9 Hz), 5.59 d (1H, $C^{16}H$, *J* 2.4 Hz). ^{13}C NMR spectrum, δ, ppm: –4.6 q, 18.1 q, 18.2 s, 19.2 q, 20.6 t, 22.0 q, 25.4 t, 25.9 q, 27.2 q, 28.6 d, 28.9 t, 29.9 t, 31.4 t, 32.0 t, 35.3 d, 36.9 t, 36.9 s, 37.3 t, 38.7 s, 42.7 t, 43.8 d, 47.1 s, 51.3 d, 58.5 d, 64.2 t, 66.7 t, 72.5 d, 120.8 d, 127.3 d, 142.0 s, 156.9 s, 178.6 s.

(20*S*)-3β-Acetoxy-20-acetoxymethyl-15β-(4-pivaloyloxybutyl)pregna-5,16-diene (XV). To a solution of 0.025 g (0.04 mmol) of steroid **XIV** in 1 ml of THF was added 0.56 ml of 1 M solution of *tetra-n*-butylammonium fluoride in THF, and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with EtOAc, washed in succession with saturated solutions of $NaHCO_3$ and NaCl, and dried with anhydrous sodium sulfate. On removing the solvent the residue was dissolved in 1 ml of pyridine, and 0.03 ml (0.32 mmol) of acetic anhydride was added. The solution was stored at room temperature for 12 h, then 0.1 ml of methanol was added, the solution was diluted with EtOAc, washed in succession with saturated solutions of $NaHCO_3$ and NaCl, and dried with anhydrous sodium sulfate. On removing the solvent the residue was subjected to chromatography on silica gel (eluent toluene–ethyl acetate, 9:1). Yield 21 mg (92%), oily substance. IR spectrum (film), cm^{-1}: 2940, 2860, 1750, 1240. ^1H NMR spectrum, δ, ppm: 0.96 s (3H, 18-Me), 1.05 d (3H, 21-Me, *J* 6.9 Hz), 1.07 C (3H, 19-Me), 1.19 C (9H, Me_3C), 2.03 C (3H, OAc), 2.04 C (3H, OAc), 2.45 sextet (1H, $C^{20}H$, *J* 7.5 Hz), 3.93 d.d (1H, $C^{22}H$, J_1 10.5, J_2 8.4 Hz), 4.03 t.d (2H, $C^{4'}H$, J_1 6.5, J_2 1.9 Hz), 4.13 d.d (1H, $C^{22}H$, J_1 10.6, J_2 6.1 Hz), 4.60 m (1H, C^3H_α, $J_{w/2}$ 32 Hz), 5.40 d (1H, C^6H, *J* 4.9 Hz), 5.57 d (1H, $C^{16}H$, *J* 2.6 Hz). ^{13}C NMR spectrum, δ, ppm: 18.7 q, 19.1 q, 20.5 t, 20.9 q, 21.4 q, 21.7 q, 25.4 t, 27.2 q, 27.7 t, 28.6 d, 28.9 t, 29.8 t, 31.4 t, 31.4 d, 36.9 t, 37.0 t, 37.0 s, 38.1 t, 36.1 s, 43.8 d, 47.2 C, 51.2 d, 58.2 d, 64.3 t, 68.7 t, 73.9 d, 122.3 d, 127.0 d, 140.1 s, 156.2 s, 170.5 s, 171.1 s, 178.6 s.

REFERENCES

1. Baranovskii, A.V., Litvinovskaya, R.P., and Khripach, V.A., *Zh. Org. Khim.*, 2004, vol. 40, p. 1656.
2. Bull, J.R. and Loedolff, M., *J. Chem, Soc., Perkin Trans. 2*, 1996, p. 1269.
3. Bojack, G. and Kunzer, H., *Tetrahedron Lett.*, 1994, vol. 35, p. 9025.
4. Dionne, P., Ngatcha, B.T., and Poirier, D., *Steroids*, 1997, vol. 62, p. 674.
5. Paquette, L.A. and Thompson, R.C., *J. Org. Chem.*, 1993, vol. 58, p. 4952.
6. Houston, T.A., Tanaka, Y., and Koreeda, M., *J. Org. Chem.*, 1993, vol. 58, p. 4287.
7. Shull, B.K. and Koreeda, M. *J. Org. Chem.*, 1990, vol. 55, p. 99.
8. Pelter, A., Smith, K., and Brown, H.C., *Borane Reagents, Series Best Synthetic Methods*, Academic Press, 1988, 503 p.
9. Krubiner, A.M., Gottfried, N., and Olivetto, E.P., *J. Org. Chem.*, 1968, vol. 33, p. 1715.
10. Kirk, D.N., Toms, H.C., Douglas, C., White, K.A., Smith, K.E., Latif, S., and Hubbard, R.W.P., *J. Chem, Soc., Perkin Trans. 2*, 1990, p. 1567.
11. Batcho, A.D., Berger, D.E., Uscokovic, M.R., and Snider, B.B., *J. Am. Chem. Soc.*, 1981, vol. 103, p. 1293.
12. Dauben, W.G. and Brookhart, T., *J. Org. Chem.*, 1982, vol. 47, p. 3921.
13. Kobayashi, N., Higashi, T., and Shimada, K., *J. Chem. Soc., Perkin, Trans. 1*, 1994, p. 269.
14. Deng, S., Yu, B., Lou, Y., and Hui, Y., *J. Org. Chem.*, 1999, vol. 64, p. 202.

15. Batcho, A.D., Berger, D.E., Davoust, S.G., Wovkulich, P.M., and Uskokovic, M., *Helv. Chim. Acta*, 1981, vol. 158, p. 1682.
16. Konno, K., Ojima, K., Hayashi, T., and Takayama, H., *Chem. Pharm. Bull*., 1992, vol. 40, p. 1120.
17. Castedo, L., Granja, J.R., Mourino, A., and Pumar, M.C., *Synth. Commun*., 1987, vol. 17, p. 251.
18. Castedo, L., Granja, J.R., and Mourino, A., *Tetrahedron Lett*., 1985, vol. 26, p. 4959.
19. Perrin, D.D. and Armarego, W.L.F., *Purification of Laboratory Chemicals*, Oxford: Pergamon Press, 1988, 391 p.
20. Wicha, J. and Masnyk, M., *Bull. Pol. Acad. Sci. Chem*., 1985, vol. 33, p. 19.