

7,8-Dihydro Analogs of Ecdysteroids*

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Abstract—Reactions of 20-hydroxyecdysone, its diacetone, and 24,25(25,26)-anhydro derivative with lithium tetrahydridoaluminate gave the corresponding 6 α - and 6 β -epimeric alcohols and 7,8-dihydro analogs.

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Selective reduction of the double Δ^7 -bonds in ecdysteroids with formation of 7,8-dihydro analogs opens a way to new biologically active structures. Catalytic hydrogenation of ecdysteroids does not produce the desired products because of numerous side reactions [2–4]. Suksamrarn et al. [5] recently reported on stereoselective catalytic hydrogenation of Δ^7 -6-oxo steroids in the presence of sodium nitrite; however, we failed to obtain 7,8-dihydro analogs from 20-hydroxyecdysone and its derivatives according to the procedure described in [5]. Our attempts to hydrogenate the Δ^7 -bond in 20-hydroxyecdysone and its derivatives via reaction with alkali metals in liquid ammonia [6, 7] (which is used for selective reduction of double bond in conjugated ketones of the steroid series) were also unsuccessful.

While studying the reactions of 20-hydroxyecdysone (**I**), its 2,3:20,22-diacetonide **II** and 24,25-(25,26)-anhydro-20-hydroxyecdysone diacetone **III** (a 3:2 mixture of Δ^{24} and Δ^{25} derivatives) with lithium tetrahydridoaluminate we revealed formation of the corresponding 7,8-dihydro analogs **IV–VI** (Scheme 1). In the reaction of compound **I** with LiAlH_4 at a molar ratio of 1:7 (a suspension in diethyl ether) we isolated 21% of 7,8-dihydro analog **IV** which was identical in the IR and NMR (^1H and ^{13}C) spectra to a sample described previously [5]. The reactions of diacetone **II** and **III** with 3 equiv of LiAlH_4 gave the corresponding 7,8-dihydro analogs **V** and **VI** in 35 and 30% yield, respectively. In addition, we isolated mixtures (~1:2)

of previously described [8] 6 α /6 β -epimeric alcohols **VII** and **VIII**, whose yields were 60 and 65%, respectively. When the reaction with diacetone **II** was carried out by adding LiAlH_4 to a solution of **II** (i.e., the order of mixing the reactants was changed), ~10% of compound **IX** was formed together with **V** and **VII**. The reaction with 5 equiv of LiAlH_4 gave rise to a mixture of compounds **V**, **VII**, and **X** (Scheme 2).

It could be presumed that 7,14-diene **IX** is formed via dehydration of alcohol **VII** and that $\Delta^{14(15)}$ -alcohol **X** is the product of reduction and dehydration of 7,8-dihydro derivative **V**. However, compounds **IX** and **X** were not obtained in the reactions of alcohols **VII** and **V** with LiAlH_4 . In these cases, alcohol **VII** was recovered from the reaction mixture, while the reaction of ketone **V** with LiAlH_4 afforded the corresponding alcohol **XI** which failed to react with LiAlH_4 . Therefore, we concluded that compounds **IX** and **X** were formed from a common precursor.

The ^{13}C NMR spectra of saturated ketones **IV–VI** displayed characteristic differences from the spectra of initial conjugated enones **I–III**. The C^7 and C^8 signals appeared in a considerably stronger field, while the C^6 signal was displaced downfield ($\Delta\delta_{\text{C}}$ ~9 ppm) due to the lack of conjugation between the carbonyl group and double bond. Signals in the ^1H and ^{13}C NMR spectra of ketone **V** and alcohol **XI** were assigned using homo- and heteronuclear correlation techniques (COSY, HSQC, HMBC, TOCSY, ROESY). ROESY experiments showed nuclear Overhauser effect between protons of the β -oriented C^{19}H_3 group and 5-H

* For preliminary communication, see [1].

I, IV, $R^1 = R^2 = R^3 = R^4 = H$; II, III, V–VIII, $R^1 R^2 = R^3 R^4 = Me_2C$.

I, II, IV, V, VII, VIII, $R^5 =$
; III, VI, VIII, $R^5 =$

II

LiAlH₄, THF

LiAlH₄, 5 equiv

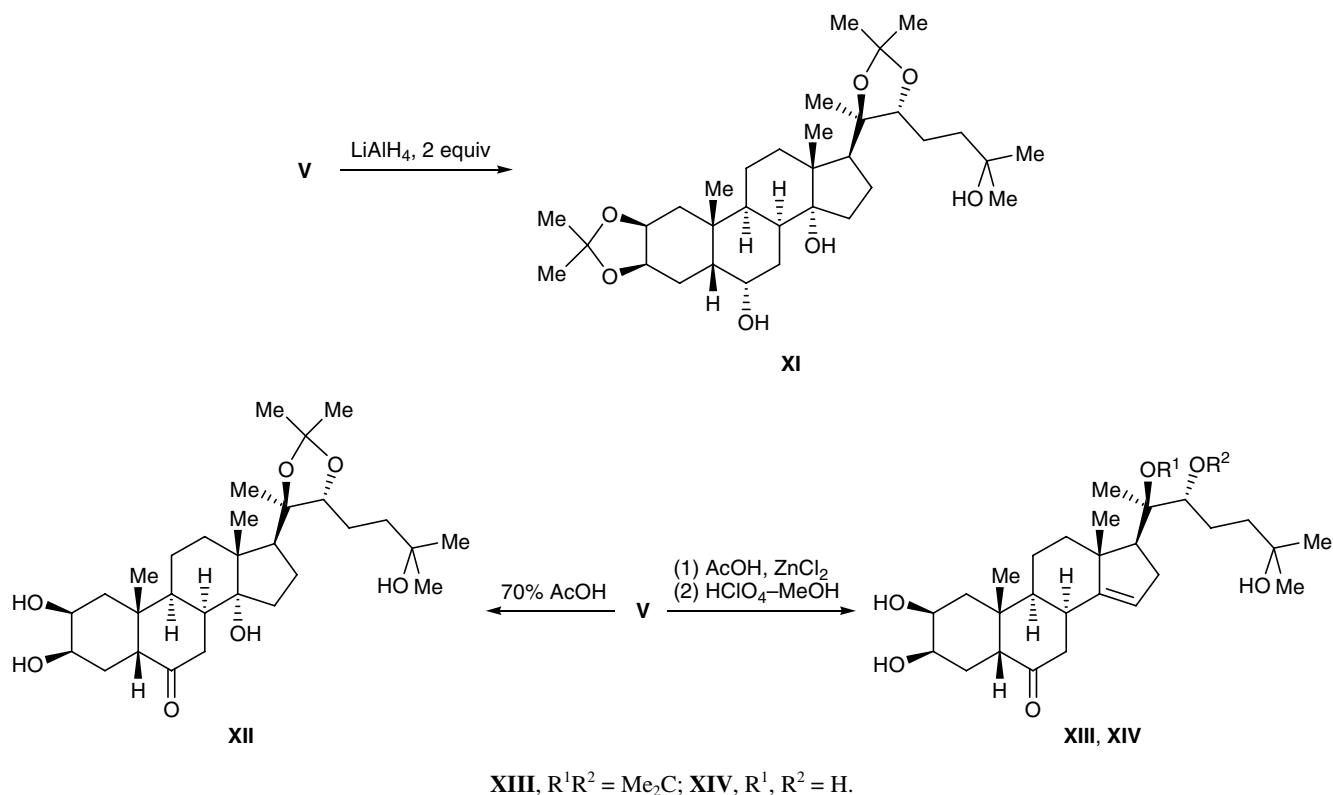
IX

X

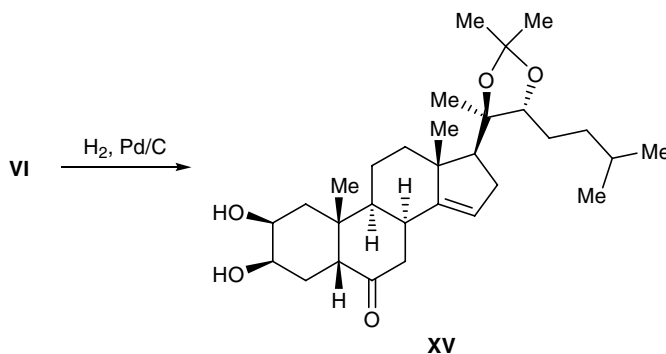
+ V + VII

+ V + VII

Scheme 3.



Scheme 4.

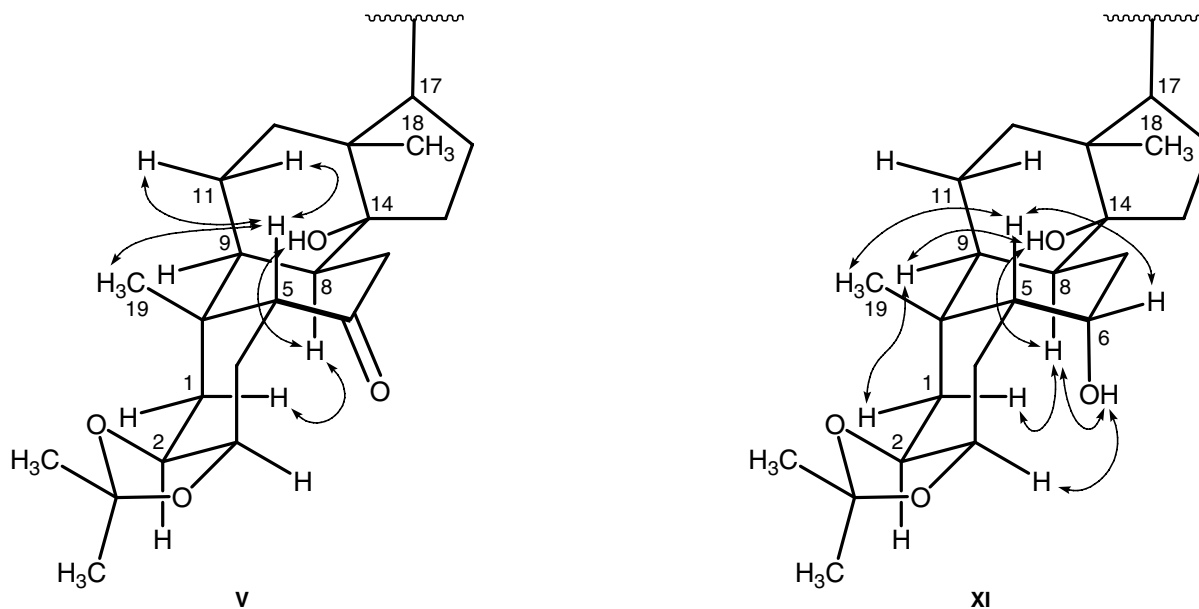


in molecule **V**, indicating *cis*-junction of the A and B rings, i.e., β -orientation of 5-H. The existence of NOE between 8-H and α -14-OH (ROESY) confirmed α -orientation of the former (see figure).

These data show that hydride reduction of the Δ^7 -bond in diacetonide **II** is not accompanied by epimerization at C^5 and that the attack by hydride ion on the double-bonded C^8 atom occurs at the α -side. Unlike α,β -unsaturated ketone **II** [8], no epimerization at C^5 was observed in the hydride reduction of the ketone group in unsaturated ketone **V**. The reduction of ketone **V** with lithium tetrahydridoaluminate is stereospecific, and the product is 6α -alcohol **XI** (Scheme 3),

while the reduction of the 6-oxo group in compound **II** under the same conditions gives a 1:2 mixture of 6α - and 6β -epimeric alcohols **VII** [8].

The structure of alcohol **XI** (see figure) was determined on the basis of NOE cross peaks observed in the ROESY spectra. β -Orientation of the 5-H proton follows from the existence of a correlation between that proton and protons of the C^{19}H_3 group (HMBC). Couplings between the 14-OH proton, on the one hand, and 8-H and 9-H, on the other, suggests α -configuration of the newly formed chiral center at C^8 , and a strong cross peak between 5-H and 6-H unambiguously indicates β -orientation of the latter and hence



Cross couplings (NOEs) in the ROESY experiments for compounds **V** and **XI**.

formation of 6 α -epimeric alcohol **XI**. An additional support to the α -orientation of the 6-OH group is provided by the presence of a cross peak between the 6-OH proton and 8-H. Interaction between the 6 α -OH proton and 3-H was also observed; this means that the latter occupies axial position; correspondingly, the 2-H proton is oriented equatorially.

As follows from our data on the stereochemistry of hydride reduction, the known C⁵-epimerization of ecdysteroids under alkaline conditions [9, 10] accompanies the reduction of the 6-oxo group in Δ^7 -6-oxo ecdysteroids; as a result, 6-hydroxy derivatives of the 5 α -series are formed [8]. The hydride reduction of the Δ^7 -bond in Δ^7 -6-oxo ecdysteroids **I–III** gives rise to 7,8-dihydro derivatives **IV–VI** of the 5 β -series. Likewise, no epimerization at C⁵ is observed in the hydrogenation of the oxo group in saturated ketone **V**. We can conclude that 5 β -epimers of 7,8-dihydro-6-oxo and 7,8-dihydro-6-hydroxy ecdysteroid derivatives with *cis*-junction of the A and B rings are more stable.

The structure of 7,14-dien-6 β -ol **IX** is confirmed by comparison of its ¹H and ¹³C NMR spectra with those of the corresponding 6 α -epimer [8]. Signals from C⁵ and C⁶ in the ¹³C NMR spectrum of the former appear in a weaker field ($\Delta\delta_C = 1.8$ and 4.1 ppm, respectively, while the C⁷ signal is displaced upfield ($\Delta\delta_C = 1.0$ ppm; the C⁷ and C¹⁵ signals were misassigned in [8]). The 6-H signal in the ¹H NMR spectrum of 6 β -dienol **IX** is located in a stronger field ($\Delta\delta = 0.76$ ppm) relative to the corresponding signal of the 6 α -epimer (cf. the data for 6 α - and 6 β -epimeric alcohols **VII** [8]).

The presence of double C¹⁴=C¹⁵ bond in alcohol **X** induces appreciable changes in the ¹H and ¹³C NMR spectral patterns as compared to saturated alcohol **XI**. The ¹H NMR spectrum of **X** contains a signal at δ 5.35 ppm from the vinyl proton on C¹⁵, and the C¹⁴ and C¹⁵ *sp*²-hybridized carbon atoms give rise to downfield signals at δ_C 154.4 and 120.6 ppm, respectively, in the ¹³C NMR spectrum. The C⁸, C¹², C¹⁶, and C¹⁷ signals are displaced downfield ($\Delta\delta_C = 11.5, 7.4, 7.0$, and 9.7 ppm, respectively), while the C⁹ signal is located in a stronger field ($\Delta\delta_C = 11.3$ ppm). As follows from the Dreiding model, the C⁸, C¹⁶, and C¹⁷ atoms in molecule **X** lie in the C¹⁴=C¹⁵ bond plane and are therefore deshielded, while the C⁹ atom falls into the shielded area (out of the double bond plane) [11].

Hydrolysis of diacetone **V** in 70% acetic acid or AcOH/ZnCl₂ [12] resulted in deprotection of only hydroxy groups on C² and C³; the reaction in the presence of ZnCl₂ was accompanied by dehydration to generate $\Delta^{14(15)}$ -bond. As a result, 20,22-acetonides **XII** and **XIII** were obtained, respectively. Deprotection of all four hydroxy groups was achieved using perchloric acid in methanol [13]. In this case, the reaction was also accompanied by dehydration, and the product was enone **XIV** (Scheme 3).

The formation of $\Delta^{14(15)}$ bond also occurred in the catalytic hydrogenation of the side-chain double bond of $\Delta^{24}(\Delta^{25})$ -alkenes **VI**. The reaction was accompanied by deprotection of the hydroxy groups on C² and C³ to give enone **XV** (Scheme 4). An analogous process was

described in [4]. Deprotection of the 2,3-dihydroxy moiety is readily identified by the ^{13}C NMR spectra of compounds **XII**, **XIII**, and **XV**, which contain only one acetal signal at δ_{C} 106.8 ppm. Deshielding effect of the $\Delta^{14(15)}$ -bond leads to downfield shift of the 8-H and 17-H signals in the ^1H NMR spectra of compounds **XIII** and **XV**; as a result, these signals appear in the region free from other signals, and they show a clearly defined fine structure. The 8-H signal is a doublet of triplets ($J_{8,7\beta} = 14.0$, $J_{8,9} = 4.0$ Hz) at δ 3.03 (**XIII**) and 3.04 ppm (**XV**), and the 17-H signal is a doublet of doublets ($J = 14.5$, 11.0 Hz) at δ 2.48 ppm.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument (300.13 for ^1H and 75.46 MHz for ^{13}C) using CDCl_3 and CD_3OD as solvents. Homo- and heteronuclear COSY, TOCSY, ROESY, HSQC, and HBMBC experiments were run on a Bruker DRX-500 spectrometer (500.13 MHz for ^1H and 125.76 MHz for ^{13}C) using DMSO as solvent; to identify hydroxy groups, samples were subjected to lyophilization. The chemical shifts were measured relative to tetramethylsilane as internal reference. The melting points were determined on a Boetius melting point apparatus. The specific rotations were measured on a Perkin–Elmer 141 polarimeter. Thin-layer chromatography was performed on silica gel (Silufol plates); spots were visualized by treatment with a solution of vanillin in ethanol acidified with sulfuric acid.

(20R,22R)-2 β ,3 β ,14 α ,20,22,25-Hexahydroxy-7,8 α -dihydro-5 β -cholestan-6-one (IV, 7,8 α -dihydro-20-hydroxyecdysone). A suspension of 0.5 g (1.04 mmol) of 20-hydroxyecdysone **I** (mp 246°C; prepared according to the procedure described in [14]) in 20 ml of diethyl ether was added under argon to a suspension of 0.277 g (7.29 mmol) of LiAlH_4 in 30 ml of diethyl ether, cooled to $\sim 0^\circ\text{C}$. The mixture was stirred for 30 min at room temperature, 10 ml of methanol was added, the mixture was stirred for 2 h and cooled to 0°C , 5 ml of water was added, and the mixture was neutralized with 5% hydrochloric acid (~ 13 ml) to a weakly acidic reaction. The mixture was evaporated under reduced pressure to a volume of ~ 20 ml and extracted with ethyl acetate (3×50 ml). The extract was evaporated under reduced pressure, and the residue was subjected to chromatography on 15 g of silica gel using chloroform–methanol (10:1) as

eluent. Yield 0.103 g (21%), R_f 0.52 (CHCl_3 –MeOH, 5:1), mp 138–140°C, $[\alpha]_{\text{D}}^{17} = +24.5^\circ$ ($c = 3.47$, MeOH) (cf. [5]). The IR and ^1H and ^{13}C NMR spectra of the product were identical to those given in [5].

(20R,22R)-14 α ,25-Dihydroxy-2 β ,3 β :20,22-bis(isopropylidenedioxy)-5 β ,8 α -cholestan-6-one (V, 7,8 α -dihydro-20-hydroxyecdysone 2,3:20,22-diacetonide). A solution of 0.82 g (1.46 mmol) of diacetonide **II** (mp 234°C; prepared as described in [15]) in 25 ml of diethyl ether was added under stirring in an argon atmosphere to a suspension of 0.16 g (4.39 mmol) of LiAlH_4 in 25 ml of diethyl ether, cooled to $\sim 0^\circ\text{C}$. The mixture was stirred for 1 h at room temperature, cooled to 0°C , and 3 ml of water and ~ 5 ml of 5% hydrochloric acid (to a weakly acidic reaction) were added. The ether layer was separated, and the aqueous layer was extracted with ethyl acetate (3×30 ml). The extracts were combined with the organic phase and evaporated under reduced pressure, and the residue was subjected to chromatography on 5 g of silica gel using chloroform as eluent to isolate 0.29 g (35%) of compound **V**, R_f 0.63 (CHCl_3 –MeOH, 10:1), and 0.49 g (60%) of previously described [8] alcohols **VII** {In the ^{13}C NMR spectrum given in [8], signals from C^{24} , δ_{C} 39.6 and 39.2 ppm, respectively, for the 6 α - and 6 β -epimers of **VII** were missing}.

Compound **V**. mp 275–277°C, $[\alpha]_{\text{D}}^{19} = +14.2^\circ$ ($c = 11.97$, CHCl_3). IR spectrum: $\nu(\text{C}=\text{O})$ 1700 cm^{-1} . ^1H NMR spectrum, δ , ppm: in CDCl_3 : 1.07 s (3H, C^{18}H_3), 1.10 s (3H, C^{21}H_3), 1.19 s (6H, C^{26}H_3 , C^{27}H_3), 1.35 s (3H, C^{19}H_3), 1.26 s, 1.27 s, 1.38 s, 1.47 s (12H, Me_2C), 1.54–2.09 m (17H, CH, CH_2), 2.16 m (1H, 7 α -H), 2.29 m (1H, 17-H), 2.33 d.t (1H, 8-H, $J_{8,7\beta} = 13.5$, $J_{8,7\alpha} = J_{8,9} = 4.0$ Hz), 2.55 br.s (1H, 5-H, $w_{1/2} = 8.9$ Hz), 2.68 t (1H, 7 β -H, $J_{7\beta,7\alpha} = J_{7\beta,8} = 13.4$ Hz), 3.62 m (1H, 22-H, $w_{1/2} = 13.0$ Hz), 4.17 m (1H, 2-H, $w_{1/2} = 12$ Hz), 4.45 m (1H, 3-H, $w_{1/2} = 21$ Hz); in DMSO- d_6 (500.13 MHz): 1.02 s (3H, C^{18}H_3), 1.05 s (3H, C^{21}H_3), 1.07 s (3H, C^{27}H_3), 1.08 s (3H, C^{26}H_3), 1.16 m and 1.76 m (2H, 15-H), 1.19 s and 1.39 s (6H, 2,3- Me_2C), 1.23 s and 1.32 s (6H, 20,22- Me_2C), 1.28 s (3H, C^{19}H_3), 1.34 m and 1.55 m (2H, 24-H), 1.36 m and 1.39 m (2H, 23-H), 1.38 s and 1.99 s (2H, 4-H), 1.52 m and 1.67 m (2H, 1-H), 1.62 m and 1.81 m (2H, 12-H), 1.64 m and 1.77 m (2H, 11-H), 1.69 m and 1.81 m (2H, 16-H), 1.98 d.t (1H, 9-H, $J = 11.0$, 4.0 Hz), 2.06 d.d (1H, 7 α -H, $J_{7\alpha,8} = 4.0$, $J_{7\alpha,7\beta} = 13.0$ Hz), 2.20 m (1H, 17-H), 2.68 br.s (1H, 5-H, $w_{1/2} = 2$ Hz), 2.71 t (1H, 7 β -H, $J_{7\beta,7\alpha} = J_{7\beta,8} = 13.0$ Hz), 3.30 d.t (1H, 8-H, $J_{8,7\beta} = 13.0$, $J_{8,7\alpha} = J_{8,9} = 4.0$ Hz),

3.57 m (1H, 22-H), 3.92 s (1H, 14-OH), 4.13 s (1H, 25-OH), 4.14 m (1H, 2-H), 4.27 m (1H, 3-H). ^{13}C NMR spectrum, δ_{C} , ppm: in CDCl_3 : 18.1 t (C^{11}), 18.4 q (C^{18}), 21.0 t (C^{16}), 21.3 q (C^{21}), 23.5 t (C^{23}), 25.3 t (C^4), 26.7 q (C^{19}), 25.8 q and 28.4 q (2,3- Me_2C), 26.7 q and 28.9 q (20,22- Me_2C), 29.0 q (C^{27}), 29.6 q (C^{26}), 31.3 t (C^{15}), 33.1 t (C^{12}), 34.2 t (C^1), 39.5 s (C^{10}), 41.3 t (C^{24}), 41.3 t (C^7), 41.5 d (C^9), 43.7 d (C^8), 46.8 s (C^{13}), 49.7 d (C^{17}), 50.5 d (C^5), 70.2 s (C^{25}), 70.8 d (C^3), 73.5 d (C^2), 81.8 d (C^{22}), 84.4 s (C^{14}), 84.9 s (C^{20}), 106.8 s (20,22- Me_2C), 107.6 s (2,3- Me_2C), 212.1 s (C^6); in DMSO (500.13 MHz): 17.8 t (C^{11}), 18.0 q (C^{18}), 21.0 t (C^{16}), 21.4 q (C^{21}), 23.1 t (C^{23}), 25.3 t (C^4), 25.9 q (C^{19}), 25.9 q and 28.5 q (2,3- Me_2C), 26.6 q and 29.0 q (20,22- Me_2C), 29.0 q (C^{27}), 29.7 q (C^{26}), 30.1 t (C^{15}), 32.8 t (C^{12}), 33.8 t (C^1), 38.9 s (C^{10}), 40.8 t (C^7), 40.9 d (C^9), 41.1 t (C^{24}), 42.7 d (C^8), 46.3 s (C^{13}), 49.3 d (C^{17}), 49.5 d (C^5), 68.4 s (C^{25}), 70.2 d (C^3), 73.0 d (C^2), 81.3 d (C^{22}), 82.8 s (C^{14}), 84.1 s (C^{20}), 105.8 s (20,22- Me_2C), 106.8 s (2,3- Me_2C), 211.9 s (C^6).

(20R,22R)-14 α -Hydroxy-2 β ,3 β :20,22-bis(isopropylidenedioxy)-5 β ,8 α -cholest-24(25)-en-6-ones [VI, 24,25(25,26)-anhydro-7,8 α -dihydro-20-hydroxyecdysone 2,3:20,22-diacetonides] (mixture of isomers). A solution of 1.3 g (2.40 mmol) of isomeric alkenes **III** (prepared as described in [12, 16]) in 30 ml of diethyl ether was added under stirring in an argon atmosphere to a suspension of 0.27 g (7.2 mmol) of LiAlH_4 in 30 ml of diethyl ether, cooled to -0°C . The mixture was stirred for 3 h at room temperature, cooled to 0°C , 5 ml of water was added, and ~ 10 ml of 5% hydrochloric acid was added to a weakly acidic reaction. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×50 ml). The extracts were combined with the organic phase and evaporated under reduced pressure, and the residue was subjected to chromatography on 30 g of silica gel using chloroform as eluent to isolate 0.39 g (30%) of compound **VI**, R_f 0.5 (CHCl_3 –MeOH, 20:1), and 0.85 g (65%) of previously described [8] alcohols **VIII**.

Compound (**VI**). mp 190 – 192°C , $[\alpha]_{\text{D}}^{19} = +16.1^\circ$ ($c = 8.83$, CHCl_3). IR spectrum, ν , cm^{-1} : 1695 ($\text{C}=\text{O}$). ^1H NMR spectrum (CDCl_3), δ , ppm: 0.91 s and 0.96 s (3H, C^{18}H_3 , $\text{C}^{18'}\text{H}_3$); 0.94 s (3H, C^{19}H_3); 1.11 s and 1.14 s (3H, C^{21}H_3 , $\text{C}^{21'}\text{H}_3$); 1.28 s, 1.38 s, 1.40 s, and 1.50 s (3H each, Me_2C); 1.78–2.20 m (13H, CH, CH_2); 1.62 s ($\sim 2.7\text{H}$, C^{26}H_3); 1.70 s and 1.72 s (3H, C^{27}H_3 , $\text{C}^{27'}\text{H}_3$); 2.22 m (1H, 7 α -H); 2.30 m (1H, 17-H); 2.37 m (1H, 8-H); 2.57 br.s (1H, 5-H, $w_{1/2} = 10.7$ Hz);

2.70 t (1H, 7 β -H, $J = 13.4$ Hz); 3.65–3.71 m (1H, 22-H, 22'-H); 4.20 m (1H, 2-H, $w_{1/2} = 13.0$ Hz); 4.49 m (1H, 3-H, $w_{1/2} = 22.6$ Hz); 4.69 br.s and 4.72 br.s (1.3H, 26-H, $w_{1/2} = 6.8$ Hz); 5.17 t (0.7H, 24'-H, $J = 6.2$ Hz). ^{13}C NMR spectrum (CDCl_3), δ_{C} , ppm: 17.9 q (C^{18}), 18.2 t (C^{11}), 18.6 q ($\text{C}^{27'}$), 21.1 t (C^{16}), 21.4 q (C^{21}), 22.5 q (C^{27}), 25.4 t (C^{23}), 25.7 q (C^{19}), 25.9 q (C^{26}), 26.0 q and 28.5 q (2,3- Me_2C), 26.8 q and 29.6 q (20,22- Me_2C), 27.7 t (C^4), 31.5 t (C^{15}), 33.3 t (C^{12}), 34.4 t (C^{24}), 35.0 t (C^1), 39.6 s (C^{10}), 41.3 t (C^7), 41.6 d and 41.7 d (C^9), 43.8 d and 43.9 d (C^8), 46.9 s (C^{13}), 50.0 d and 50.1 d (C^{17}), 50.6 d (C^5), 70.9 d (C^3), 73.5 d (C^2), 80.6 d and 81.0 d (C^{22}), 84.1 s (C^{20}), 85.0 s (C^{14}), 106.7 s and 106.8 s (20,22- Me_2C), 107.6 s (2,3- Me_2C), 110.0 t (C^{26}), 120.4 d (C^{24}), 133.5 q (C^{25}), 145.3 s (C^{25}), 211.9 s (C^6).

(20R,22R)-2 β ,3 β :20,22-Bis(isopropylidenedioxy)-5 α -cholesta-7,14-diene-6 β ,25-diol (IX). Diacetone **II**, 1 g (1.79 mmol), was dissolved in 50 ml of anhydrous THF, 0.198 g (5.37 mmol) of LiAlH_4 was added, and the mixture was stirred for 1 h at $\sim 25^\circ\text{C}$ under argon. The mixture was cooled to 0°C , 5 ml of water was added, and ~ 7 ml of 5% hydrochloric acid was added to a weakly acidic reaction. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×70 ml). The extracts were combined with the organic phase and evaporated under reduced pressure, and the residue was subjected to chromatography on 40 g of silica gel using chloroform as eluent to isolate 0.1 g (10%) of dienol **IX**, R_f 0.7 (CHCl_3 –MeOH, 10:1), 0.3 g (30%) of **V**, R_f 0.63 (CHCl_3 –MeOH, 10:1), and 0.53 g (53%) of **VII**.

Dienol (**IX**). mp 90 – 92°C , $[\alpha]_{\text{D}}^{19} = -62.8^\circ$ ($c = 7.32$, CHCl_3). ^1H NMR spectrum (CDCl_3), δ , ppm: 1.01 s (3H, C^{18}H_3); 1.04 s (3H, C^{19}H_3); 1.18 s (3H, C^{21}H_3); 1.22 s (6H, C^{26}H_3 , C^{27}H_3); 1.29 s, 1.31 s, 1.41 s, and 1.50 s (3H each, Me_2C); 1.52–2.58 m (15H, CH, CH_2); 3.72 m (1H, 22-H, $w_{1/2} = 15.3$ Hz); 3.81 m (1H, 6-H, $w_{1/2} = 10$ Hz); 4.05 m (1H, 2-H, $w_{1/2} = 20$ Hz); 4.19 m (1H, 3-H, $w_{1/2} = 11$ Hz); 5.62 br.s (1H, 15-H, $w_{1/2} = 8$ Hz); 5.89 br.s (1H, 7-H, $w_{1/2} = 9$ Hz). ^{13}C NMR spectrum (CDCl_3), δ_{C} , ppm: 18.4 q (C^{18}), 20.9 t (C^{11}), 21.1 q (C^{21}), 23.7 t (C^{23}), 24.8 q (C^{19}), 28.3 t (C^4), 29.0 q (C^{27}), 29.6 q (C^{26}), 26.5 q and 28.6 q (2,3- Me_2C), 26.8 q and 28.8 q (20,22- Me_2C), 30.9 t (C^{12}), 34.3 s (C^{10}), 37.2 d (C^9), 39.2 t (C^{16}), 40.4 t (C^{24}), 41.2 t (C^1), 43.3 d (C^5), 47.3 s (C^{13}), 57.6 d (C^{17}), 70.3 s (C^{25}), 70.8 d (C^6), 72.3 d (C^2), 72.8 d (C^3), 81.7 d (C^{22}), 83.6 s (C^{20}), 106.8 s (20,22- Me_2C), 107.9 s (2,3- Me_2C), 120.3 d (C^{15}), 121.2 d (C^7), 135.2 s (C^{14}), 150.0 s (C^8).

(20R,22R)-2 β ,3 β :20,22-Bis(isopropylidenedioxy)-5 β ,8 α -cholest-14-ene-6 β ,25-diol (X). Diacetone II, 0.3 g (0.54 mmol), was dissolved in 20 ml of anhydrous THF, 0.1 g (2.70 mmol) of LiAlH₄ was added, and the mixture was stirred for 1 h at ~25°C under argon. The mixture was cooled to 0°C, 5 ml of water was added, and ~5 ml of 5% hydrochloric acid was added to a weakly acidic reaction. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3×50 ml). The extracts were combined with the organic phase and evaporated under reduced pressure, and the residue was subjected to chromatography on 20 g of silica gel using chloroform as eluent to isolate 0.05 g (17%) of diol X, *R*_f 0.69 (CHCl₃–MeOH, 10:1), 0.088 g (30%) of V, *R*_f 0.63 (CHCl₃–MeOH, 10:1), and 0.15 g (50%) of VII.

Diol (X). mp 75–77°C, [α]_D²⁴ = +35.6° (*c* = 2.74, CHCl₃). ¹H NMR spectrum (CDCl₃), δ , ppm: 1.13 s (3H, C¹⁸H₃); 1.16 s (3H, C¹⁹H₃); 1.18 s (3H, C²¹H₃); 1.22 s (6H, C²⁶H₃, C²⁷H₃); 1.30 s, 1.41 s, and 1.51 s (2:1:1, 12H, Me₂C); 1.60–2.52 m (20H, CH, CH₂); 3.07 m (1H, 8-H); 3.75 m (1H, 22-H, *w*_{1/2} = 21 Hz); 3.95 br.s (1H, 6-H, *w*_{1/2} = 12 Hz); 4.36 m (1H, 2-H, *w*_{1/2} = 13 Hz); 4.63 m (1H, 3-H, *w*_{1/2} = 16 Hz); 5.35 br.s (1H, 15-H, *w*_{1/2} = 13 Hz). ¹³C NMR spectrum (CDCl₃), δ _C, ppm: 17.7 t (C¹¹), 20.8 q (C¹⁸), 23.7 t (C²³), 25.8 q (C²¹), 26.7 q and 28.9 q (2,3-Me₂C), 27.3 q and 28.9 q (20,22-Me₂C), 28.6 q (C¹⁹), 29.7 q (C²⁶, C²⁷), 30.5 t (C¹⁶), 31.0 d (C⁹), 31.6 t (C⁴), 33.4 t (C¹⁰), 36.0 t (C⁷), 37.9 t (C¹), 41.0 d (C⁵), 41.4 s (C¹²), 43.1 t (C²⁴), 46.8 s (C¹³), 48.2 d (C⁸), 59.5 d (C¹⁷), 70.3 s (C²⁵), 71.6 d (C⁶), 72.7 d (C³), 74.6 d (C²), 81.8 d (C²²), 83.7 s (C²⁰), 106.7 s (20,22-Me₂C), 107.0 s (2,3-Me₂C), 120.6 d (C¹⁵), 154.4 s (C¹⁴).

(20R,22R)-2 β ,3 β :20,22-Bis(isopropylidenedioxy)-5 β ,8 α -cholestane-6 α ,14 α ,25-triol (XI). Diacetone V, 0.18 g (0.32 mmol), was dissolved in 7 ml of anhydrous THF, 0.025 g (0.64 mmol) of LiAlH₄ was added, and the mixture was stirred for 0.5 h at ~25°C under argon. The mixture was cooled to 0°C, 5 ml of water was added, and ~7 ml of 5% hydrochloric acid was added to a weakly acidic reaction. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×40 ml). The extracts were combined with the organic phase and evaporated under reduced pressure, and the residue was subjected to chromatography on 8 g of silica gel using chloroform as eluent. Yield 0.16 g (90%), *R*_f 0.34 (CHCl₃–MeOH, 10:1), mp 137–139°C, [α]_D²⁰ = +25.7° (*c* = 9.33, CHCl₃). ¹H NMR spectrum, δ , ppm: in CDCl₃: 1.00 s

(3H, C¹⁸H₃); 1.08 s (3H, C²¹H₃); 1.18 s (9H, C¹⁹H₃, C²⁶H₃, C²⁷H₃); 1.27 s, 1.37 s, and 1.47 s (2:1:1, 12H, Me₂C); 1.60–2.00 m (20H, CH, CH₂); 2.13 m (1H, 17-H, *w*_{1/2} = 19 Hz); 2.32 m (1H, 8-H, *w*_{1/2} = 24 Hz); 3.62 m (1H, 22-H, *w*_{1/2} = 16 Hz); 3.94 br.s (1H, 6-H, *w*_{1/2} = 10 Hz); 4.29 m (1H, 2-H, *w*_{1/2} = 12 Hz); 4.58 m (1H, 3-H, *w*_{1/2} = 16 Hz); in DMSO-*d*₆ (500.13 MHz): 0.92 s (3H, C¹⁸H₃), 1.01 s (3H, C²¹H₃), 1.06 s (C²⁷H₃), 1.07 s (6H, C¹⁹H₃, C²⁶H₃), 1.18 s and 1.37 s (6H, 2,3-Me₂C), 1.22 s and 1.31 s (6H, 20,22-Me₂C), 1.15 m and 1.79 m (2H, 15-H), 1.30 m and 2.33 m (2H, 1-H), 1.34 m and 1.37 m (2H, 23-H), 1.31 m and 1.54 m (2H, 24-H), 1.35 m and 1.39 m (2H, 11-H), 1.51 m and 1.71 m (2H, 12-H), 1.46 m and 1.71 m (2H, 7-H), 1.63 m and 1.68 m (2H, 4-H), 1.37 m (1H, 5-H), 1.66 m and 1.79 m (2H, 16-H), 1.81 m (1H, 9-H), 2.20 m (1H, 17-H), 2.31 m (1H, 8-H), 3.56 m (1H, 22-H), 3.65 s (1H, 14-OH), 3.75 m (1H, 6-H), 4.13 s (1H, 25-OH), 4.19 m (1H, 2-H), 4.39 d (1H, 6-OH, *J* = 3.5 Hz), 4.51 m (1H, 3-H). ¹³C NMR spectrum, δ _C, ppm: in CDCl₃: 18.0 t (C¹¹); 18.3 q (C¹⁸); 21.4 t (C¹⁶); 23.5 t (C²³); 25.9 q (C²¹); 26.7 q (C¹⁹); 27.6 q, 28.6 q, 28.8 q, and 28.9 q (Me₂C); 29.6 q (C²⁶, C²⁷); 31.2 t (C¹⁵); 31.5 t (C⁴); 33.4 s (C⁷, C¹⁰); 34.0 t (C¹²); 36.5 t (C¹); 36.7 d (C⁸); 41.3 t (C²⁴); 42.3 d (C⁵, C⁹); 46.6 s (C¹³); 49.8 d (C¹⁷); 70.2 s (C²⁵); 71.8 d (C⁶); 72.6 d (C³); 74.6 s (C²); 81.8 d (C²²); 84.6 s (C¹⁴); 86.1 s (C²⁰); 106.7 s (20,22-Me₂C); 107.0 s (2,3-Me₂C); in DMSO (500.13 MHz): 17.9 t (C¹¹), 18.1 q (C¹⁸), 21.2 t (C¹⁶), 21.4 q (C²¹), 23.2 t (C²³), 25.9 q and 28.6 q (2,3-Me₂C), 26.7 q and 29.0 q (20,22-Me₂C), 27.3 q (C¹⁹), 29.0 q (C²⁷), 29.6 q (C²⁶), 30.4 t (C¹⁵), 31.7 t (C⁴), 32.8 s (C⁷), 33.0 s (C¹⁰), 33.6 t (C¹²), 35.9 d (C⁸), 36.2 t (C¹), 41.1 t (C²⁴), 41.2 d (C⁵), 41.5 d (C⁹), 46.1 s (C¹³), 49.3 d (C¹⁷), 68.4 s (C²⁵), 70.3 d (C⁶), 71.9 d (C³), 74.2 s (C²), 81.3 d (C²²), 83.9 s (C¹⁴), 84.3 s (C²⁰), 105.8 s (20,22-Me₂C), 106.0 s (2,3-Me₂C).

(20R,22R)-2 β ,3 β ,14 α ,25-Tetrahydroxy-20,22-isopropylidenedioxy-5 β ,8 α -cholestan-6-one (XII, 7,8 α -dihydro-20-hydroxyecdysone 20,22-acetonide (XII)). A mixture of 0.22 g (0.46 mmol) of compound V and 3 ml of glacial acetic acid was stirred for 5.5 h. The mixture was evaporated, and the residue was subjected to chromatography on 9 g of silica gel using chloroform–methanol (20:1) as eluent. Yield 0.1 g (49%), *R*_f 0.60 (CHCl₃–MeOH, 5:1), mp 134–136°C, [α]_D¹⁸ = +7.2° (*c* = 8.67, CHCl₃). IR spectrum: ν (C=O) 1700 cm^{−1}. ¹H NMR spectrum (CDCl₃), δ , ppm: 1.06 s (3H, C¹⁸H₃), 1.11 s (3H, C²¹H₃), 1.21 s (6H, C²⁶H₃, C²⁷H₃), 1.29 s (3H, C¹⁹H₃), 1.39 s (6H, Me₂C), 1.42–2.10 m (19H, CH, CH₂), 2.31 t (1H, 8-H, *J* = 12.5 Hz), 2.43 m

(1H, 5-H, $w_{1/2}$ = 11 Hz), 2.67 t (1H, 7 β -H, J = 14.5 Hz), 3.63 m (1H, 22-H, $w_{1/2}$ = 15 Hz), 3.84 m (1H, 2-H, $w_{1/2}$ = 18 Hz), 3.93 m (1H, 3-H, $w_{1/2}$ = 12 Hz). ^{13}C NMR spectrum (CDCl_3), δ_{C} , ppm: 18.4 q (C^{18}), 20.1 t (C^{11}), 21.1 t (C^{16}), 21.4 q (C^{21}), 23.4 t (C^{23}), 25.0 t (C^4), 26.7 q (C^{19}), 26.9 q and 28.9 q (20,22- Me_2C), 29.1 q (C^{27}), 29.4 q (C^{26}), 31.3 t (C^{15}), 33.5 t (C^{12} , C^1), 39.4 s (C^{10}), 41.0 d (C^9), 41.1 t (C^7), 41.3 t (C^{24}), 43.0 d (C^8), 46.8 s (C^{13}), 49.8 d (C^{17}), 51.1 d (C^5), 70.4 s (C^{25}), 66.7 d (C^3), 69.5 d (C^2), 81.9 d (C^{22}), 84.4 s (C^{20}), 85.0 s (C^{14}), 106.8 s (20,22- Me_2C), 212.8 s (C^6).

(20R,22R)-2 β ,3 β ,25-Trihydroxy-20,22-isopropylidenedioxy-5 β ,8 α -cholest-14-en-6-one (XIII, 7,8 α -dihydrostachysterone B 20,22-acetonide). A mixture of 0.125 g (0.22 mmol) of compound **V** and 3 ml of 70% acetic acid was stirred for 1.5 h, 0.045 g (0.33 mmol) of ZnCl_2 was added, and the mixture was stirred for 2.5 h until the reaction was complete (TLC). The mixture was diluted with 30 ml of water and extracted with butanol (3 $\times$ 20 ml), the extracts were combined and evaporated under reduced pressure, and the residue was subjected to chromatography on 8 g of silica gel using chloroform–methanol (20:1) as eluent. Yield 0.067 g (60%), R_f 0.47 (CHCl_3 –MeOH, 20:1), mp 118–120°C, $[\alpha]_{\text{D}}^{24}$ = –123° (c = 1.18, CHCl_3). IR spectrum: $\nu(\text{C}=\text{O})$ 1700 cm^{-1} . ^1H NMR spectrum (CDCl_3), δ , ppm: 1.16 s (6H, C^{18}H_3 , C^{21}H_3), 1.21 s (6H, C^{26}H_3 , C^{27}H_3), 1.28 s (3H, C^{19}H_3), 1.40 s and 1.41 s (3H each, Me_2C), 1.46–2.21 m (15H, CH, CH_2), 2.15 d.d (1H, 7 α -H, J = 14.5, 4.4 Hz), 2.36 m (1H, 5-H, $w_{1/2}$ = 10 Hz), 2.48 d.d (1H, 17-H, J = 14.5, 11.0 Hz), 2.73 t (1H, 7 β -H, J = 14.5 Hz), 3.03 d.t (1H, 8-H, J = 14.5, 4.0 Hz), 3.72 m (1H, 22-H, $w_{1/2}$ = 5 Hz), 3.87 m (1H, 2-H, $w_{1/2}$ = 24 Hz), 3.97 m (1H, 3-H, $w_{1/2}$ = 11 Hz), 5.33 m (1H, 15-H, $w_{1/2}$ = 8 Hz). ^{13}C NMR spectrum (CDCl_3), δ_{C} , ppm: 17.9 t (C^{11}), 21.0 q (C^{18} , C^{21}), 23.6 t (C^{23}), 24.3 t (C^{16}), 26.7 q (C^{19}), 28.8 q (20,22- Me_2C), 29.0 q (C^{26}), 29.5 q (C^{27}), 30.4 t (C^4), 37.3 d (C^9), 38.4 t (C^1), 39.8 s (C^{10}), 41.2 t (C^{24}), 42.4 t (C^{12}), 44.2 t (C^7), 46.7 s (C^{13}), 47.3 d (C^8), 51.2 d (C^5), 59.3 d (C^{17}), 70.3 s (C^{25}), 66.7 d (C^3), 69.5 d (C^2), 81.6 d (C^{22}), 83.4 s (C^{20}), 106.8 s (20,22- Me_2C), 122.2 d (C^{15}), 151.1 s (C^{14}), 211.9 s (C^6).

(20R,22R)-2 β ,3 β ,20,22,25-Pentahydroxy-5 β ,8 α -cholest-14-en-6-one (XIV, 7,8 α -dihydrostachysterone B). Compound **V**, 0.2 g (0.36 mmol), was dissolved in 3.6 ml of methanol, 1 ml of 10% perchloric acid was added, the mixture was stirred for 3.5 h and cooled to 5°C, 2 ml of water and 1 ml of a saturated

solution of NaHCO_3 were added, and the mixture was extracted with ethyl acetate (3 $\times$ 20 ml). The extracts were combined and evaporated under reduced pressure, and the residue was subjected to chromatography on 8 g of silica gel using chloroform–methanol (20:1) as eluent. Yield 0.07 g (33%), R_f 0.38 (CHCl_3 –MeOH, 5:1), mp 112–114°C, $[\alpha]_{\text{D}}^{18}$ = –56.3° (c = 1.1, MeOH). IR spectrum: $\nu(\text{C}=\text{O})$ 1700 cm^{-1} . ^1H NMR spectrum (CD_3OD), δ , ppm: 1.17 s (3H, C^{18}H_3), 1.19 s (3H, C^{19}H_3), 1.20 s (3H, C^{21}H_3), 1.26 s (3H, C^{26}H_3), 1.42 s (3H, C^{27}H_3), 1.50–2.40 m (17H, CH, CH_2), 2.48 m (1H, 5-H, $w_{1/2}$ = 11 Hz), 2.88 t (1H, 7 β -H, J = 14 Hz), 3.07 m (1H, 8-H, $w_{1/2}$ = 25 Hz), 3.30 m (1H, 22-H), 3.74 m (1H, 2-H, $w_{1/2}$ = 19 Hz), 3.92 m (1H, 3-H, $w_{1/2}$ = 10 Hz), 5.39 br.s (1H, 15-H, $w_{1/2}$ = 8 Hz). ^{13}C NMR spectrum (CD_3OD), δ_{C} , ppm: 19.2 t (C^{11}), 20.1 q (C^{21}), 21.9 q (C^{18}), 25.3 t (C^{23}), 27.3 t (C^{16}), 27.5 q (C^{19}), 28.9 q (C^{26}), 29.4 q (C^{27}), 30.7 t (C^4), 38.9 d (C^9), 40.3 t (C^1), 41.0 s (C^{10}), 42.3 t (C^{12} , S^{24}), 44.5 t (C^7), 45.4 d (C^8), 52.4 d (C^5), 60.8 d (C^{17}), 71.3 s (C^{25}), 68.1 d (C^3), 71.0 d (C^2), 77.2 s (C^{20}), 78.6 d (C^{22}), 123.7 d (C^{15}), 152.9 s (C^{14}), 214.0 s (C^6); the C^{13} signal was obscured by the solvent.

(20R,22R)-2 β ,3 β -Dihydroxy-20,22-isopropylidenedioxy-5 β ,8 α -cholest-14-en-6-one (XV). Hydrogen was passed through a suspension of 0.26 g (0.48 mmol) of compound **VI** and 0.1 g (10%) of Pd/C in 5 ml of ethanol under stirring at at ~25°C. After 3 days, the mixture was filtered, the catalyst was washed with ethanol, and the filtrate was evaporated under reduced pressure. The residue was subjected to chromatography on 6 g of silica gel using chloroform as eluent. Yield 0.094 g (41%), R_f 0.39 (CHCl_3 –MeOH, 20:1), mp 110–112°C, $[\alpha]_{\text{D}}^{23}$ = –18.6° (c = 11.15, CHCl_3). IR spectrum: $\nu(\text{C}=\text{O})$ 1710 cm^{-1} . ^1H NMR spectrum (CDCl_3), δ , ppm: 0.87 d (6H, C^{26}H_3 , C^{27}H_3 , J = 6.5 Hz), 1.14 s (3H, C^{21}H_3), 1.17 s (3H, C^{18}H_3), 1.27 s (3H, C^{19}H_3), 1.40 s and 1.42 s (6H, Me_2C), 1.46–2.22 m (16H, CH, CH_2), 2.15 d.d (1H, 7 α -H, J = 14.5, 3.4 Hz), 2.37 m (1H, 9-H, $w_{1/2}$ = 11 Hz), 2.49 d.d (1H, 5-H, J = 11.7, 14.8 Hz), 2.74 t (1H, 7 β -H, J = 14.5 Hz), 3.04 d.t (1H, 8-H, J = 13.8, 5.1 Hz), 3.69 d.d (1H, 22-H, J = 8.6, 2.5 Hz), 3.91 m (1H, 3-H, $w_{1/2}$ = 24 Hz), 3.99 m (1H, 2-H, $w_{1/2}$ = 11 Hz), 5.35 m (1H, 15-H, $w_{1/2}$ = 6 Hz). ^{13}C NMR spectrum (CDCl_3), δ_{C} , ppm: 17.9 t (C^{11}), 21.0 q (C^{18}), 21.0 q (C^{21}), 22.4 q (C^{26}), 22.4 q (C^{27}), 24.3 t (C^{23}), 26.7 q (C^{19}), 26.8 t (C^{16}), 28.9 s (C^{25}), 28.1 q and 28.9 q (20,22- Me_2C), 30.4 t (C^4), 36.2 t (C^{24}), 37.4 d (C^9), 38.3 t (C^1), 39.8 s (C^{10}), 42.5 t (C^{12}), 44.2 t (C^7), 46.8 s (C^{13}), 47.3 d (C^8),

51.2 d (C^5), 59.5 d (C^{17}), 69.6 d (C^3), 70.7 d (C^2), 81.3 d (C^{22}), 83.2 s (C^{20}), 106.6 s (20,22- Me_2C), 122.3 d (C^{15}), 151.1 s (C^{14}), 212.0 s (C^6).

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