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Catalytic Hydrogenation of Substituted 15β-Pregn-16-enes

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Abstract—The catalytic hydrogenation of 15-benzoyloxybutyl-20-hydroxymethylpregn-16-enes under various conditions was studied. It was shown that at the use of a palladium catalyst along with the reduction of the double bond also its shift occurred giving Δ^{14}-derivatives. The reduction over a platinum catalyst is accompanied by the saturation of aromatic ring of the protecting group, but gives the best yield of the desired products and provides a preparative approach to 15-substituted analogs of brassinosteroids. The structures of the obtained compounds were proved by two-dimensional NMR spectroscopy and HPLC-MS.

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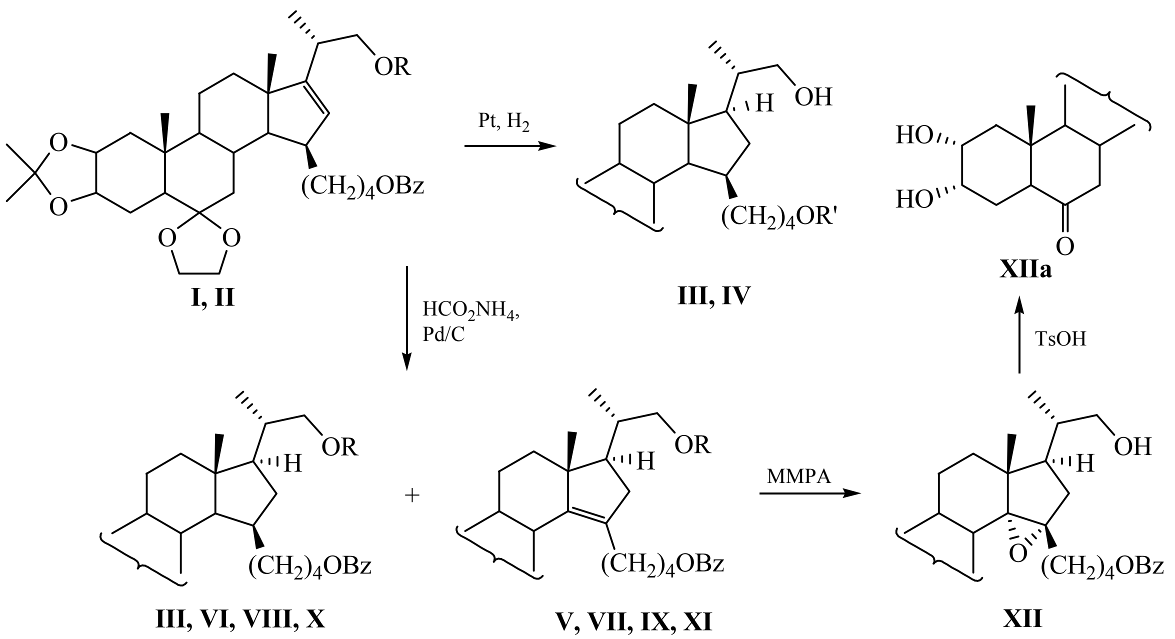
This study is a part of our ongoing studies on the synthesis of steroids with a modified D ring such as analogs of brassinosteroids, ecdysteroids, estradiol, and others [1–4]. In order to approach brassinosteroids analogs functionalized with alkyl substituent at the C^{15} atom we obtained C^2-and C^3-isomeric pregn-16-enes **I**, **II**. Further synthesis scheme involves the formation of side chain of the steroids. The first step includes the reduction of the Δ^{16}-bond. In the literature, there is sufficient information on carrying out this reaction in a series of D-unsubstituted steroids with different side chain length, but the presence of substituent at the C^{15} atom was found to make serious variations in the reaction course. In this work, we present the results of hydrogenation of compounds **I**, **II** under different conditions and the NMR and mass spectrometry data of obtained compounds.

The catalytic hydrogenation of the Δ^{16}-bond of 20-hydroxymethylpregnenes was carried out in the presence of various catalysts, in most cases platinum [5, 6] or palladium on carbon [7, 8], in an appropriate solvent. Initially we used the Adams' catalyst [9, 10], but the reduction of compound **I** in EtOAc after 3 h results in a mixture of two inseparable steroids in a ratio of 2:1. Analysis of the mixture by a two-dimensional NMR spectroscopy and HPLC-MS allowed to conclude that the main product was alcohol **III**, and the minor substance (molecular weight is 630 a. u.) was an analogue of compound **III**, but contained a completely reduced aromatic ring, i.e., it was cyclohexanecarboxylic acid ester **IV**. This result was somewhat unexpected, but not without a precedent [11]. To avoid the formation of the mixture, we performed exhaustive hydrogenation for 7 h (here, reducing the platinum oxide was performed in the presence of steroid). Aromatic ring was fully reduced, but the procedure caused a partial hydrolysis of the acetonide and dioxolane protection groups, decreasing the yields of steroid **IV** up to 35%. According to HPLC data, a ratio of cyclohexanoyl ester **IV**, its 2,3-dihydroxy- and 2,3-dihydroxy-6-ketoderivatives was 45:30:20. Replacing the solvent by ethanol and adding the substrate after reduction of platinum oxide allows us to obtain compound **IV** in a high yield (86%). Scaling the synthesis (> 0.2 mmol of substate) resulted in incomplete reduction of the aromatic ring to give a mixture of compounds **III** and **IV**, wherein the content of **III** ranged from 20 to 40% of the mixture. Neither the increased reaction time to 48 h nor change in the molar substrate–catalyst ratio resulted in the complete reduction of the ring.

The next step of the study was the use of the Pd/C catalyst. Here, however, was a serious probability of the intermediate formation of allylpalladate complex, leading eventually to the epimerization of the C^{20} center. The hydrogenation of compounds **I** and **II** gave a mixture of two products in a 1:1 ratio. Attempts to separate them by column chromatography failed. The



I, **III**, **V**: 2α, 3α, R = H; **Ia**, **VI**, **VII**, 2α, 3α, R = Ac; **II**, **VIII**, **IX**: 2β, 3β, R = H; **III**: 2α, 3α, R' = Bz; **IV**: 2α, 3α, R' = C(O) C_6H_{11}; **X**, **XI**: 2β, 3β, R = Ac; **XII**: 2α, 3α. MMPA is magnesium monoperphthalate.

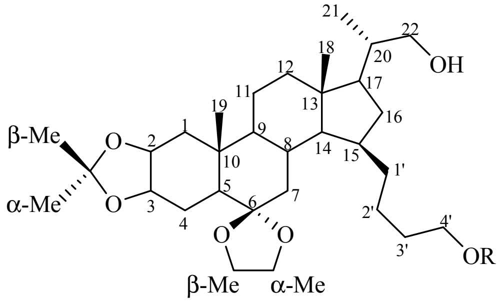
comprehensive analysis of the mixtures by the two-dimensional NMR spectroscopy and HPLC-MS allows a conclusion that the steroids **I** and **II** were partially reduced under the hydrogenation conditions to give alcohols **III** and **VIII** with the “natural” configuration at the C^{20} center as major components of the mixtures. This is confirmed by the signal of the protons of the 21-methyl group at 1.04 ppm in the ^1H NMR spectrum [7]. In the case of compound with the opposite configuration of this center the proton signal would be observed at 0.96 ppm. Chemical shifts of the protons at the C^{22} atom also prove the correctness of the assignment [7]. Minor products were found to be olefins **V** and **IX** with the isomerized double bond, yet with the correct “natural” configuration at C^{17} and C^{20}. This is confirmed by both NMR and mass spectrometry (Tables 2–4). Peaks of the protonated molecules of compounds **V** and **IX** are observed at *m*/*z* 623. Chemical shifts of all protons of the C^{17}-side chain are identical with those of steroids **III** and **VIII**. Additional confirmation of the structure of the hydrogenation products was found by the acetylation of the mixtures. The NMR data and mass spectra of acetates **VI**, **VII**, **X**, and **XI** (Tables 1–4) coincided with the literature data [12].

In order to change the products ratio in favor of alcohols **III** and **VIII**, we performed hydrogenation over a palladium catalyst with *in situ* generation of hydrogen [13, 14]. This method is more convenient instrumentally than the conventional hydrogenation. Compounds **I** and **II** were treated with ammonium formate in the presence of a catalytic amount of palladium on carbon. No starting material was observed after 48 h. The NMR analysis of the reaction mixture showed the presence of alcohols **III**, **VIII** and Δ^{14}-derivatives in a ratio of ~ 2.5:1 with the prevalence of the desired products in each case. The total yield of the products was 80–95%.

According to the reaction mechanism, the retention of the “natural” configuration of the C^{20} center in all products and the formation of Δ^{14}-bond can be explained by the formation of a more stable allylpalladate complex between the C^{15}–C^{17} atoms instead of the C^{16}–C^{20}. Assuming that the addition of hydrogen occurs to the less hindered α-side of the molecule, we obtain the correct stereochemistry of the chiral centers and the substituents in the major (15β,17β,20*S*) and minor (17β,20*S*) products.

Since it was not possible to separate chromatographically compounds **III** and **V**, the mixture was treated with the magnesium salt of monoperphthalic acid. After 5 h the Δ^{14}-derivative **V** was converted into epoxide **XII** without hydrolysis of the protecting groups. The product **III** was easily separated from

Table 1. ^{1}H NMR spectra parameters (δ, ppm) of 2α,3α-dioxyderivatives **Ia**, **III**–**VII**, **XII**, **XIIa**



H	**Ia**[a]	**III**[a]	**IV**[b]	**V**[a]	**VI**[a,c]	**VII**[a,c]	**XII**[b]	**XIIa**[b]
1α	1.07	1.06	1.05	1.06	1.05	1.03	1.08	1.58
1β	1.92	1.94	1.93	1.97	1.94	1.94	1.92	1.78
2β	4.11	4.10	4.11	4.10	4.10	4.10	4.06	3.73
3β	4.28	4.28	4.27	4.28	4.27	4.27	4.23	4.04
4α	2.14	2.13	2.14	2.16	2.14	2.14	2.13	1.89
4β	1.83	1.80	1.83	1.73	1.80	1.80	1.74	1.70
5α	1.85	1.83	1.83	1.81	1.83	1.81	1.78	2.73
7α	1.12	1.03	1.02	1.67	1.02	1.65	1.46	2.47
7β	1.91	1.89	1.88	2.31	1.88	2.31	1.52	2.15
8β	1.82	1.73	1.71	2.39	1.72	2.38	2.39	2.67
9α	0.91	0.81	0.81	0.91	0.82	0.92	1.19	1.81
11α	1.63	1.51	1.52	1.61	1.52	1.62	1.59	1.75
11β	1.35	1.25	1.25	1.36	1.26	1.35	1.38	1.39
12α	1.31	1.11	1.09	1.24	1.12	1.11	1.45	1.54
12β	1.71	1.93	1.92	1.95	1.94	1.94	1.81	1.91
14α	1.50	1.15	1.14	–	1.15	–	–	–
15α	2.31	1.81	1.78	–	1.81	–	–	–
16α	5.59	2.16	2.16	2.16	2.16	2.14	1.90	1.97
16β	–	1.05	1.04	2.16	1.06	2.14	1.38	1.40
17α	–	1.26	1.21	1.47	1.20	1.48	1.15	1.25
18	0.95	0.79	0.79	0.90	0.79	0.90	0.84	0.86
19	0.90	0.85	0.85	0.83	0.85	0.83	0.84	0.77
20	2.47	1.55	1.56	1.66	1.72	1.84	1.44	1.47
21	1.05	1.04	1.04	1.03	1.01	1.00	0.94	0.98
22	3.93; 4.14	3.39; 3.62	3.40; 3.63	3.39; 3.62	3.78; 4.07	3.78 4.07	3.31; 3.56	3.38; 3.58
1'	1.26; 1.50	1.11; 1.51	1.05; 1.44	2.17; 2.33	1.09; 1.51	2.14; 2.34	1.77; 1.91	1.71; 1.87
2'	1.35 1.50	1.24; 1.51	1.12 1.40	1.24; 1.51	1.23; 1.50	1.23; 1.50	1.44; 1.62	1.49; 1.62
3'	1.76 (2)	1.74 (2)	1.54 1.60	1.74 (2)	1.73 (2)	1.73 (2)	1.76 (2)	1.80 (2)
4'	4.31	4.31	4.03	4.31	4.30	4.30	4.30	4.32

Table 1. (Contd.)

H	**Ia**[a]	**III**[a]	**IV**[b]	**V**[a]	**VI**[a,c]	**VII**[a,c]	**XII**[b]	**XIIa**[b]
α-Me	1.47	1.47	1.47	1.45	1.47	1.46	1.44	–
β-Me	1.33	1.32	1.32	1.32	1.33	1.33	1.29	–
αA-CH_2[d]	3.72	3.71	3.73	3.72	3.72	3.72	3.68	–
αB-CH_2[d]	3.90	3.90	3.92	3.90	3.89	3.89	3.85	–
βA-CH_2[d]	3.97	3.95	3.99	3.95	3.94	3.94	3.86	–
βB-CH_2[d]	3.89	3.86	3.85	3.86	3.85	3.85	3.77	–

[a] Bz, δ, ppm: 7.44 (*meta*), 7.56 (*para*), 8.04 (*ortho*). [b] 22-OAc, δ, ppm: 2.04 (Me). [c] Cyclohexanecarbonyl, δ, ppm: 1.25 and 1.78 (C^3H_2, C^5H_2), 1.42 and 1.88 (C^2H_2, C^6H_2), 1.62 (C^4H_2), 2.27 (C^1H). [d] Letters “A” and “B” indicate position of the protons of CH_2-group relative to the ring A and B, respectively.

Table 2. ^1H NMR spectra parameters (δ, ppm) of 2β,3β-dioxyderivatives **VIII**–**XI**

H	**VIII**[a]	**IX**[a]	**X**[a,b]	**XI**[a,b]	H	**VIII**[a]	**IX**[a]	**X**[a,b]	**XI**[a,b]
1α	1.33	1.31	1.32	1.32	16β	1.05	2.14	1.08	2.14
1β	2.23	2.29	2.24	2.23	17α	1.20	1.47	1.21	1.51
2α	4.20	4.20	4.20	4.20	18	0.80	0.90	0.81	0.91
3α	4.05	4.05	4.06	4.06	19	1.13	1.11	1.14	1.10
4α	1.88	1.88	1.88	1.90	20	1.56	1.66	1.73	1.83
4β	1.51	1.51	1.52	1.52	21	1.05	1.02	1.01	1.01
5α	1.32	1.30	1.32	1.31	22	3.38; 3.62	3.38; 3.62	3.79; 4.07	3.79; 4.07
7α	0.97	1.60	0.98	1.60	1'	1.10; 1.50	2.16; 2.30	1.12; 1.51	2.15; 2.32
7β	1.90	2.33	1.90	2.34	2'	1.24; 1.50	1.24; 1.50	1.25; 1.51	1.25; 1.51
8β	1.73	2.40	1.74	2.40	3'	1.74 (2)	1.72 (2)	1.73 (2)	1.73 (2)
9α	0.71	0.82	0.73	0.84	4'	4.31	4.31	4.30	4.30
11α	1.49	1.59	1.50	1.50	α-Me	1.32	1.32	1.33	1.33
11β	1.35	1.46	1.36	1.36	β-Me	1.55	1.55	1.53	1.53
12α	1.09	1.23	1.12	1.12	αA-CH_2[c]	3.74;	3.78	3.75	3.75
12β	1.93	1.97	1.93	1.93	αB-CH_2[c]	3.87	3.92	3.89	3.92
14α	1.12	–	1.14	–	βA-CH_2[c]	4.01	3.95	4.01	4.01
15α	1.80	–	1.81	–	βB-CH_2[c]	3.85	3.85	3.86	3.86
16α	2.16	2.14	2.16	2.14					

[a] Bz, δ, ppm: 7.44 (*meta*), 7.56 (*para*), 8.04 (*ortho*). [b] 22-OAc, δ, ppm: 2.04 (Me). [c] Letters “A” and “B” indicate position of the protons of CH_2-group relative to the ring A and B, respectively.

Table 3. ^{13}C NMR spectra parameters (δ_C, ppm) 2α,3α-dioxyderivatives **Ia**, **III–VII**, **XII**, **XIIa**

C	**Ia**	**III**	**IV**	**V**	**VI**	**VII**	**XII**	**XIIa**
1	42.83	42.93	42.89	42.99	42.95	43.00	42.69	40.28
2	73.14	73.17	73.16	73.10	73.16	73.08	72.94	68.32
3	73.05	73.02	73.00	72.86	73.01	72.84	72.75	68.41
4	22.18	22.13	22.11	22.13	22.12	22.12	21.97	26.49
5	46.19	45.94	45.92	44.62	45.94	44.60	44.38	49.70
6	109.77	109.80	109.81	109.72	109.76	109.67	109.76	212.15
7	40.74	41.02	40.99	40.37	41.00	40.33	36.55	42.85
8	29.81	30.22	30.20	34.83	30.22	34.84	31.59	36.01
9	54.52	53.74	53.70	52.04	53.72	52.00	49.14	50.05
10	38.48	38.33	38.31	38.23	38.32	38.22	38.06	41.96
11	20.55	20.64	20.62	21.48	20.63	21.47	20.58	20.99
12	36.87	41.54	41.51	41.60	41.47	41.54	35.18	35.22
13	47.48	42.71	42.76	50.32	42.77	50.32	43.36	43.58
14	57.40	57.52	57.46	142.38	57.45	142.30	75.50	75.65
15	43.92	36.22	36.20	131.50	36.21	131.55	70.99	71.47
16	127.20	36.55	36.49	41.91	36.46	41.87	35.73	35.47
17	156.44	53.12	52.99	52.04	53.40	52.19	44.30	44.35
18	21.99	15.64	15.62	16.91	15.59	16.87	14.83	14.98
19	13.41	13.47	13.46	13.72	13.47	13.71	13.61	13.39
20	31.55	38.62	38.60	37.07	35.66	34.13	36.83	36.76
21	18.85	17.08	17.11	17.30	17.46	17.70	17.13	17.16
22	68.80	68.05	68.01	68.19	69.56	69.66	67.44	67.44
1'	29.88	32.51	32.50	29.91	32.50	29.95	30.85	30.26
2'	25.79	25.62	25.44	25.87	25.61	25.89	23.39	23.22
3'	29.21	29.04	28.99	28.93	29.03	28.97	29.01	28.92
4'	65.03	65.06	64.27	65.11	65.04	65.10	64.88	64.77
α-Me	28.78	28.77	28.76	28.77	28.77	28.77	28.67	–
β-Me	26.75	26.73	26.73	26.73	26.73	26.73	26.67	–
Me$_2\underline{\text{C}}$	107.78	107.75	107.75	107.72	107.74	107.71	107.72	–
α-CH$_2$	64.47	64.47	64.42	64.36	64.48	64.37	64.38	–
β-CH$_2$	65.64	65.64	65.62	65.75	65.64	65.75	65.61	–
$\underline{\text{Me}}$CO	21.11	–	–	–	21.16	21.16	–	–
Me$\underline{\text{C}}$O	171.23	–	–	–	171.56	171.56	–	–
RCO	166.78	166.79	176.39	166.79	166.78	166.78	166.69	166.79
C1"	130.61	130.58	43.39	130.58	130.56	130.56	130.38	130.39
C2"	129.67	129.65	29.20	129.68	129.64	129.67	129.61	129.70
C3"	128.51	128.51	25.58	128.51	128.51	128.51	128.46	128.52
C4"	133.00	133.02	25.89	133.02	133.01	133.01	133.02	133.06

Table 4. ^{13}C NMR spectra parameters (δ_C, ppm) of 2β,3β-dioxyderivatives **VIII**–**XI**

C	**VIII**	**X**	**IX**	**XI**	C	**VIII**	**X**	**IX**	**XI**
1	41.09	41.13	41.43	41.33	20	38.59	35.66	37.03	34.01
2	73.82	73.82	73.82	73.82	21	17.06	17.44	17.29	17.44
3	75.57	75.58	75.28	75.28	22	68.03	69.57	68.17	69.67
4	24.23	24.23	24.10	24.10	1'	32.46	32.46	29.92	29.93
5	49.21	49.23	47.80	47.82	2'	25.58	25.59	25.86	25.90
6	109.61	109.58	109.50	109.46	3'	29.01	29.01	28.91	28.95
7	41.24	41.23	40.58	40.57	4'	65.06	65.04	65.06	65.04
8	30.19	30.21	34.70	34.77	α-Me	26.28	26.29	26.28	26.29
9	55.31	55.32	53.77	53.76	β-Me	28.81	28.82	28.81	28.82
10	36.57	36.58	36.57	36.58	$Me_2\underline{C}$	107.90	107.91	107.97	107.98
11	20.83	20.84	21.57	20.84	α-CH_2	64.51	64.53	64.45	64.46
12	41.58	41.53	41.61	41.45	β-CH_2	65.54	65.56	65.70	65.72
13	42.73	42.82	50.33	50.35	$\underline{Me}CO$	–	21.16	–	21.16
14	57.55	57.50	142.35	142.29	$Me\underline{C}O$	–	171.57	–	171.57
15	36.18	36.19	131.56	131.55	$Ph\underline{C}O$	166.78	166.78	166.78	166.78
16	36.47	36.40	41.91	41.90	*ipso*-Ph	130.55	130.56	130.55	130.56
17	53.06	53.39	51.95	52.15	*o*-Ph	129.63	129.64	129.68	129.67
18	15.63	15.59	16.90	16.87	*m*-Ph	128.50	128.51	128.50	128.51
19	15.24	15.24	15.61	15.74	*p*-Ph	133.02	133.01	133.02	133.01

epoxide **XII** by column chromatography. The configuration of the epoxide ring in compound **XII** and the hydrolyzed product **XIIa** could not be unambiguously determined by means of analysis of the NOESY spectra. Therefore, we made some attempts to selective opening the epoxide ring that would permit establishing its configuration in the starting compound by the spectral analysis of the products. However, the epoxide ring of steroid **XII** was found to be resistant to the action of many nucleophiles and reducing agents. Thus, treating with acetic, hydrochloric and hydrobromic acids, amines, LiBr, DIBAL, $LiAlH_4$ [15] did not give an expected or unambiguous result. The reactions resulted in the hydrolysis products or in the reduction of the protecting groups. Attempts to rearrange the product into a ketone by the action of $LiClO_4$ [16] or BF_3 also proved unproductive. In the latter case the ring opening was observed, but the reaction product presented a complex mixture. In general, it was expected due to the low differentiation between the C^{14} and C^{15} atoms during the carbocation formation. Ultimately, given the published data on the epoxidation of Δ^{14}-derivatives without substituent at the C^{15} atom and the carbonyl group at the C^{17} [17], we assigned the configuration of the epoxide ring as 14α,15α. The correctness of such assignment can serve the chemical shift of the proton at C^8. For compounds with β-configuration of the epoxide ring it was found at 1.98–2.04 ppm [18–20], whereas in the case of the α-derivatives this proton resonated at 2.28 ppm [21]. The latter value is close to that observed for compound **XII**.

In some works [22, 23] the hydrogenation of the Δ^{16}-bond over palladium catalyst was carried out not with alcohols but with their acetyl derivatives. An attempt to apply the above conditions for the hydrogenation of compound **Ia** has not improved the isomers ratio, moreover, along with compounds **VI** and **VII** the mixture contains also C^{20}-epimer of compound **VI**.

Thus, according to the obtained data, the use of the Adams' catalyst is more preferable for obtaining the 15-substituted brassinosteroids. The formation of a mixture of steroids **III** and **IV** creates some inconveniences in analyzing the spectral data, but it is not a serious problem, since at the further steps of the formation of the side chain the protecting group at C^{15} will be removed. Good to excellent yields and no need for the separation of the products are a significant advantage of the proposed method compared to other tested approaches.

EXPERIMENTAL

Melting points were determined on a Koeffler block and were uncorrected. ^{1}H and ^{13}C NMR spectra were registered on an Avance 500 spectrometer operating at 500.13 and 125.77 MHz, respectively, at 293 K using the signals of the solvent $CDCl_3$ as internal references [δ 7.26 (^{1}H), δ_C 77.16 ppm (^{13}C)]. The correlation spectra (HSQC, COSY, HMBC, NOESY) were recorded and processed using standard software of "Bruker-Biospin". The NMR data are reported in Tables 1–4. IR spectra were obtained on a UR 20 instrument. Mass spectra (MS and MS^2) were registered on a HPLC Accela equipped with a LCQ-Fleet mass detector (three-dimensional ion trap) in chemical ionization mode at atmospheric pressure (APCI), detecting the positive ions (MS^2 – CID 35%). HPLC separation of the mixtures of compounds was performed using a HYPERSIL Gold column (50 mm× 2.1 mm× 1.9 μm), mobile phase acetonitrile–water (100 μl min^{-1} 80% MeCN for alcohols and 95% MeCN for their acetates). Elemental analysis was performed on a Eurovector EA3000 analyzer. The solvents were dried and freshly distilled according to common practice procedure [24]. All the reactions were carried out under argon atmosphere. The reaction progress was monitored by TLC on Merck plates (Kieselgel 60 F254). Chromatographic separation of the reaction mixtures was carried out on 40/60 silica gel (Kieselgel 60, Merck).

(20*S*)-20-Acetoxymethyl-15β-(4-benzoyloxybutyl)-2α,3α-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregn-16-ene (Ia). A mixture of alcohol **I** (0.052 g, 0.08 mmol) in pyridine (1 mL) and acetic anhydride (13 μL, 0.1 mmol) was stirred for 3 h. Then the reaction mixture was treated with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic fractions were dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on a silica gel (EtOAc:petroleum ether = 10:90). Yield 0.047 g (84%), colorless oil, R_f 5.3. Mass spectrum, *m*/*z* (*I*, %): 665 (32) $[M + H]^+$, 607 (100) $[M + H - \text{acetone}]^+$, 563 (13) $[M + H - \text{acetone} - CH_2CH_2O]^+$, 547 (39) $[M + H - \text{acetone} - \text{AcOH}]^+$.

Hydrogenation of olefin I over Pd/C catalyst. A mixture of steroid **I** (0.021 g, 0.03 mmol), Pd/C catalyst (5%, 45 mg) and ammonium formate (0.050 g, 0.8 mmol) in methanol (5 mL) was stirred for 48 h, then the solvent was evaporated. The residue was dissolved in EtOAc, passed through Al_2O_3, and the solvent was evaporated, yielding 0.017 g of an inseparable mixture of alcohols **V** and **III** in a ratio of 1:2.7 (according to HPLC). Colorless oil, IR spectrum (film), ν, cm^{-1}: 3515, 2940, 2870, 1720, 1280.

(20*S*)-15-(4-Benzoyloxybutyl)-20-hydroxymethyl-2α,3α-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregn-14-ene (V). R_f 6.9. Mass spectrum, *m*/*z* (*I*, %): 623 (13) $[M + H]^+$, 622 (11) $[M]^+$, 565 (100) $[M + H - \text{acetone}]^+$, 547 (14) $[M + H - Me_2C(OH)_2]^+$, 503 (20) $[M + H - (CH_2OH)_2 - \text{acetone}]^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (623): 607 (100) $[M - Me]^+$, 564 (62) $[M - \text{acetone}]^+$, 445 (37) $[M - (CH_2)_4OBz]^+$.

Hydrogenation of olefin II over Pd/C catalyst. By the procedure described above from 0.021 g (0.03 mmol) of the compound **II** inseparable mixture (0.020 g) of alcohols, **IX** and **VIII** in a ratio of 1:2.5 (according to HPLC) was obtained. Colorless oil. IR spectrum (film), ν, cm^{-1}: 3520, 2945, 2870, 1720, 1280.

(20*S*)-15-(4-Benzoyloxybutyl)-20-hydroxymethyl-2β,3β-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregn-14-ene (IX). R_f 6.7. Mass spectrum, *m*/*z* (*I*, %): 623 (12) $[M + H]^+$, 565 (100) $[M + H - \text{acetone}]^+$, 547 (13) $[M + H - Me_2C(OH)_2]^+$, 503 (8) $[M + H - (CH_2OH)_2 - \text{acetone}]^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (623): 607 (100) $[M - Me]^+$, 579 (23) $[M + H - CH_2CH_2O]^+$, 565 (36) $[M + H - \text{acetone}]^+$, 521 (26) $[M + H - \text{acetone} - CH_2CH_2O]^+$, 445 (46) $[M - (CH_2)_4OBz]^+$.

(20*S*)-15β-(4-Benzoyloxybutyl)-20-hydroxymethyl-2β,3β-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregnane (VIII). R_f 7.2. Mass spectrum, *m*/*z* (*I*, %): 625 (100) $[M + H]^+$, 581 (18) $[M + H - CH_2CH_2O]^+$, 567 (15) $[M + H - \text{acetone}]^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (625, CID 50): 581 (100) [*M* + H –

$CH_2CH_2O]^+$, 523 (14) $[M + H - \text{acetone} - CH_2CH_2O]^+$, 413 (18) $[M - 211]^+$.

Epoxidation and separation of the mixture of compounds III and XII. To a solution of the mixture of alcohols **V** and **III** (0.133 g) in ethanol (15 mL) was added magnesium monoperphthalate hexahydrate (80%, 0.145 g, 0.23 mmol). After stirring for 5 h, to the mixture a saturated solution of NaCl was added. Then organic phase was extracted with CH_2Cl_2 and dried over Na_2SO_4. After removing the solvent the residue was chromatographed on a silica gel (EtOAc:petroleum ether = 10:90) to give 0.078 g of **(20*S*)-15β-(4-benzoyloxybutyl)-20-hydroxymethyl-2α,3α-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregnane (III)**, mp 110–112°C (hexane), R_f 7.8. IR spectrum (film), ν, cm^{-1}: 3515, 2940, 2870, 1720, 1280. Mass spectrum, *m*/*z* (*I*, %): 625 (21) $[M + H]^+$, 567 (100) $[M + H - \text{acetone}]^+$, 523 (12) $[M + H - \text{acetone} - CH_2CH_2O]^+$. Mass spectrum ($MS^2$), *m*/*z* (*I*, %) (625): 609 (100) $[M - Me]^+$, 566 (10) $[M - \text{acetone}]^+$, 413 (24) $[M - 211]^+$. Found, %: C 73.02; H 8.93. $C_{38}H_{56}O_7$. Calculated, %: C 73.04; H 9.03. *M* 624.

Further elution gave 0.041 g of **(20*S*)-15β-(4-benzoyloxybutyl)-20-hydroxymethyl-2α,3α-isopropylidenedioxy-14α,15-oxo-6,6-ethylenedioxy-5α-pregnane (XII)**, a colorless oil. IR spectrum (film), ν, cm^{-1}: 3520, 2945, 2870, 1720, 1280. Mass spectrum, *m*/*z* (*I*, %): 639 (55) $[M + H]^+$, 622 (100) $[M - O]^+$, 621 (24) $[M + H - H_2O]^+$, 564 (94) $[M - O - \text{acetone}]^+$, 563 (44) $[M + H - H_2O - \text{acetone}]^+$, 547 (18) $[M + H - H_2O - \text{acetone} - O]^+$, 545 (25) $[M + H - 2H_2O - \text{acetone}]^+$. Mass spectrum ($MS^2$), *m*/*z* (*I*, %) (639): 621 (100) $[M + H - H_2O]^+$, 581 (11), 563 (66) $[M + H - H_2O - \text{acetone}]^+$, 545 (32) $[M + H - 2H_2O - \text{acetone}]^+$.

(20*S*)-15β-(4-Benzoyloxybutyl)-20-hydroxymethyl-2α,3α-dihydroxy-14α,15-oxo-5α-pregnan-6-one (XIIa). To a solution of the steroid **XII** (0.038 g, 0.06 mmol) in THF (3 mL) was added toluenesulfonic acid (0.012 g, 0.07 mmol) and water (0.5 mL). The resulting mixture was heated at 50°C for 10 h. After the hydrolysis the mixture was cooled and poured into a saturated solution of NaCl and $NaHCO_3$. The organic phase was extracted with EtOAc and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (EtOAc:toluene = 50:50). Yield 0.023 g, 70%, colorless oil. IR spectrum (film), ν, cm^{-1}: 3450 br, 3071, 2945, 2870, 1720, 1715, 1270. Mass spectrum, *m*/*z* (*I*, %): 555 (5) $[M + H]^+$, 537 (100) $[M + H - H_2O]^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (555): 537 (100) $[M + H - H_2O]^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (537): 519 (100) $[M + H - 2H_2O]^+$, 501 (23) $[M + H - 3H_2O]^+$, 483 (14) $[M + H - 4H_2O]^+$. Found, %: C 71.92; H 8.43. $C_{33}H_{46}O_7$. Calculated, %: C 71.45; H 8.36. *M* 554.

Hydrogenation of olefin I over the Adams' catalyst. To the catalyst, prepared by hydrogen saturation of PtO_2 (0.007 g) in EtOH (4 mL) for 1 h, 0.069 g of olefin **I** (0.11 mmol) was added. The resulting mixture was stirred under a hydrogen atmosphere (1 atm) for 18 h, after which the catalyst was filtered off and washed with EtOH. The combined filtrates were evaporated, and the residue was purified by column chromatography on silica gel yielding 0.060 g (86%) of **(20*S*)-20-hydroxymethyl-2α,3α-isopropylidenedioxy-15β-(4-cyclohexanecarboxybutyl)-6,6-ethylenedioxy-5α-pregnane (IV)**. Colorless oil. IR spectrum (film), ν, cm^{-1}: 2950, 2880, 1730, 1260, 1180, 760. Mass spectrum, *m*/*z* (*I*, %): 631 (39) $[M + H]^+$, 573 (100) $[M + H - \text{acetone}]^+$, 529 (10) $[M + H - 102 - \text{acetone} - CH_2CH_2O]^+$. Mass spectrum ($MS^2$), *m*/*z* (*I*, %) (630): 615 (43) $[sM - Me]^+$, 571 (100) $[M - \text{side chain}]^+$, 553 (16) $[M - Me - (CH_2OH)_2]^+$, 527 (64) $[M - \text{side chain} - CH_2CH_2O]^+$.

Acetylation of the mixture of steroids III and V. To a mixture of 0.004 g (6 μmol) of steroids **V** and **III** in pyridine (0.5 mL) an excess acetic anhydride (2.5 μL, 24 μmol) was added. The resulting mixture was stirred at room temperature for 24 h, and methanol (0.2 mL) was added. After 0.5 h the solvent was evaporated, the residue was dissolved in EtOAc, washed with water, and passed through a layer of Na_2SO_4. The removal of the solvent gave an inseparable mixture of acetates **VII** and **VI** in a ratio of 1:2.5 (according to HPLC). The crude mixture was analyzed by NMR and mass spectrometry. **(20*S*)-20-Acetoxymethyl-15-(4-benzoyloxybutyl)-2α,3α-iso-propylidenedioxy-6,6-ethylenedioxy-5α-pregn-14-ene (VII).** R_f 5.8. Mass spectrum, *m*/*z* (*I*, %): 665 (28) $[M + H]^+$, 664 (31) $[M]^+$, 607 (100) $[M + H - \text{acetone}]^+$, 589 (19) $[M + H - Me_2C(OH)_2]^+$, 547 (23) $[M + H - AcOH - \text{acetone}]^+$, 545 (22) $[M + H - (CH_2OH)_2 - \text{acetone}]^+$. Mass spectrum ($MS^2$), *m*/*z* (*I*, %) (664): 649 (100) $[M - Me]^+$, 606 (89) $[M - \text{acetone}]^+$, 605 (87) $[M - 59]^+$, 604 (42) $[M - AcOH]^+$, 591 (21) $[M - CH_2OAc]^+$, 587 (21) $[M - Me - (CH_2OH)_2]^+$, 551 (28) $[M - Me - \text{side chain}]^+$, 487 (40) $[M - (CH_2)_4OBz]^+$. **(20*S*)-20-Acetoxymethyl-15β-(4-benzoyloxybutyl)-2α,3α-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregnane (VI).** R_f 6.2. Mass spectrum, *m*/*z* (*I*, %): 667 (27) $[M + H]^+$, 666 (24) $[M]^+$, 609 (100) $[M + H - \text{acetone}]^+$, 565 (13) $[M + H -$

acetone – CH_2CH_2O]$^+$, 547 (13) [*M* + H – $(CH_2OH)_2$ – acetone]$^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (667): 651 (100) [*M* – Me]$^+$, 608 (11) [*M* – acetone]$^+$, 455 (36) [*M* – 211]$^+$, the splitting of B ring.

Acetylation of mixture of IX and VIII. By the procedure described above from 0.010 g (16 μmol) of a mixture of compounds **IX** and **VIII,** an inseparable mixture of 0.020 g of acetates **IX** and **VIII** in a ratio of 1:2.6 (according to HPLC) was obtained. The mixture without further purification was subjected to NMR and mass spectrometric analysis. **(20*S*)-20-Acetoxymethyl-15-(4-benzoyloxybutyl)-2β,3β-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregn-14-ene (XI).** R_f 6.2. Mass spectrum, *m*/*z* (*I*, %): 665 (100) [*M* + H]$^+$, 607 (28) [*M* + H – acetone]$^+$, 589 (28) [*M* + H – $Me_2C(OH)_2$]$^+$, 547 (18) [*M* + H – AcOH – acetone]$^+$, 545 (22) [*M* + H – $(CH_2OH)_2$ – acetone]$^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (665): 649 (100) [*M* – Me]$^+$, 487 (54) [*M* – Me – side chain]$^+$. **(20*S*)-20-Acetoxymethyl-15β-(4-benzoyloxybutyl)-2β,3β-isopropylidene-dioxy-6,6-ethylenedioxy-5α-pregnane (X).** R_f 6.6. Mass spectrum, *m*/*z* (*I*, %): 667 (100) [*M* + H]$^+$, 623 (24) [*M* + H – CH_2CH_2O]$^+$. Mass spectrum (MS^2), *m*/*z* (*I*, %) (667, CID 15): 609 (100) [*M* + H – acetone]$^+$, 565 (98) [*M* + H – acetone – CH_2CH_2O]$^+$, 551 (65) [*M* + H – Me – side chain]$^+$, 531 (37) [*M* + H – Me – OBz]$^+$.

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