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Steroids Modified at C^{15}. Synthesis and Spectra-Structure Correlations

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Abstract—A synthesis of 15-benzoyloxybutyl-20-hydroxymethylpregn-16-enes, the intermediates in the synthesis of brassino- and ecdysteroids modified in the D ring was performed starting with 2α,3α-isopropylidenedioxy-6,6-ethylenedyoxy-5α-androst-15-ene-17-one and its 2β,3β-isomer through a sequence of reactions involving Michael addition, Wittig reaction and ene reaction. Structures of the compounds were proved by the methods of two-dimensional NMR spectroscopy.

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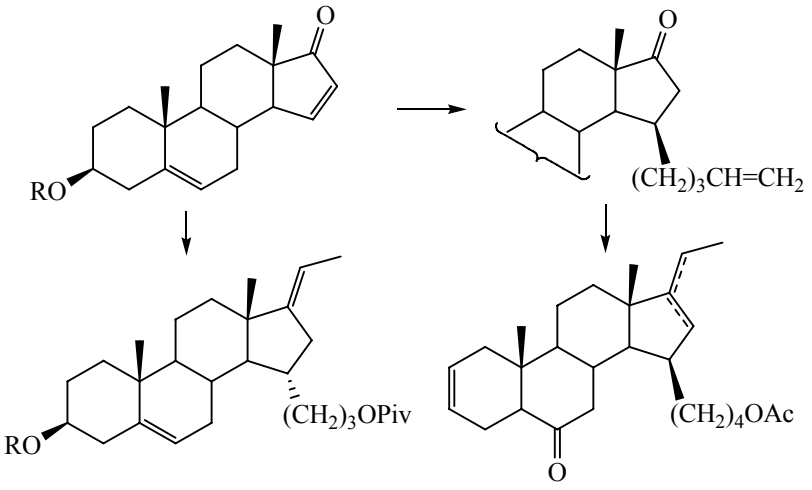
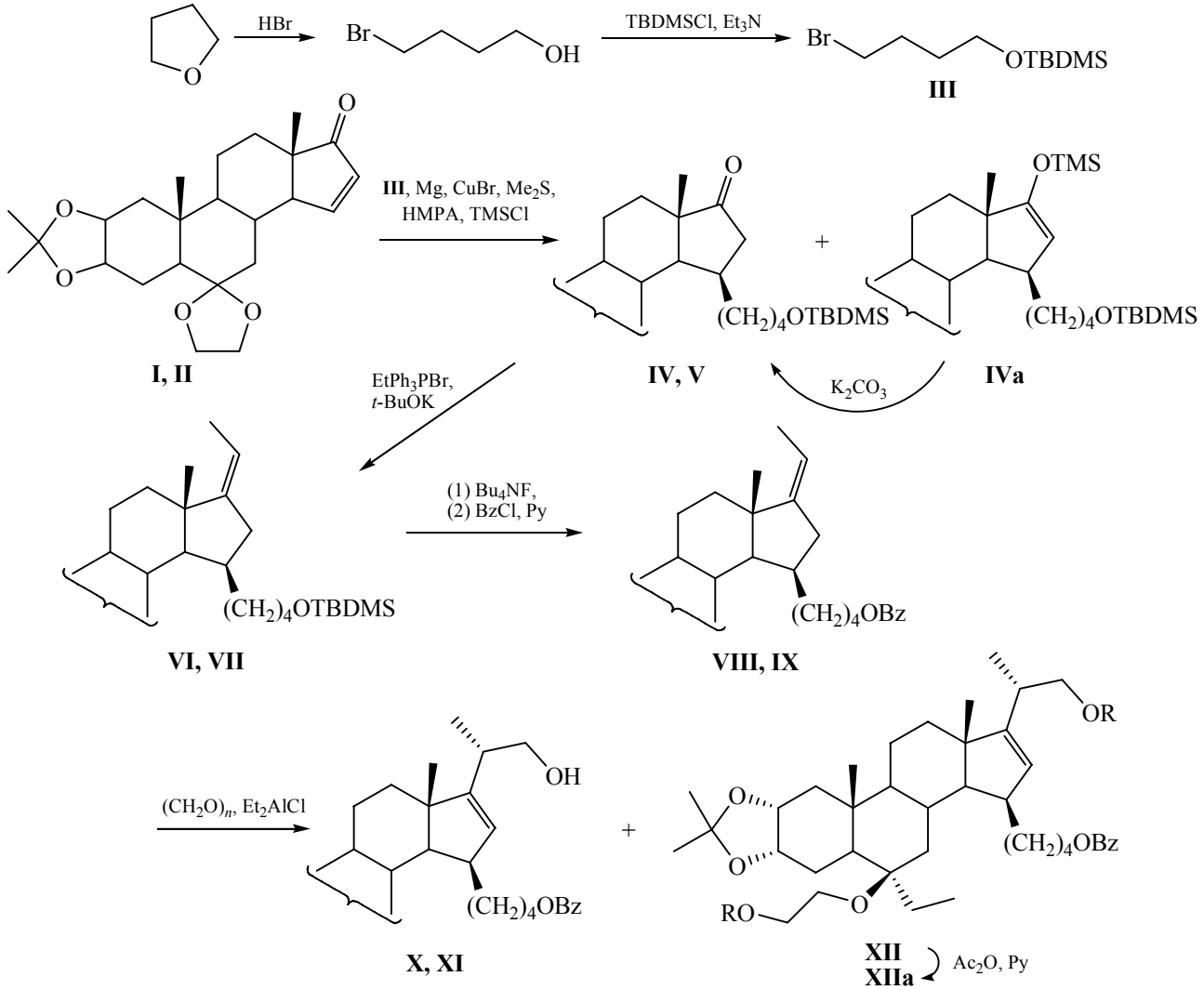
Modified steroids are the most important part of the steroid drugs used in medicine, because the structural modification allows revealing and improving some components of a wide range of physiological effects of steroids, and thus provides a possibility of the focused application of steroids in therapy. Another important area of applications of modified steroids is diagnostics, where they are used as the haptens for immunochemical analysis, tracers for biochemical research, references and labels for studying the mechanism of action. Among the many types of modified steroids, of special interest are the steroids containing an additional carbon substituent in the D ring, since many known compounds of this type, such as 16-alkylsteroids or steroid D-pentaranes [1–6] have valuable pharmacological properties. Among the D-modified steroids, the least studied and very inaccessible are the derivatives containing functionalized carbon substituent at C^{15} [7–11]. Along with the possible validity as a new physiologically active compounds, such derivatives are of interest as haptens in the immunochemical analysis of natural hormones containing pharmacophore features in the ring and the side chain, such as ecdy- and brassinosteroids. Being spatially distant from the structural fragments responsible for biofunctionality of the hormone molecule, such a substituent must not impede its recognition by a receptor or antibody. The recognition



is, in particular, of crucial significance for obtaining adequate information about the structure of the molecule at the immunochemical analysis.

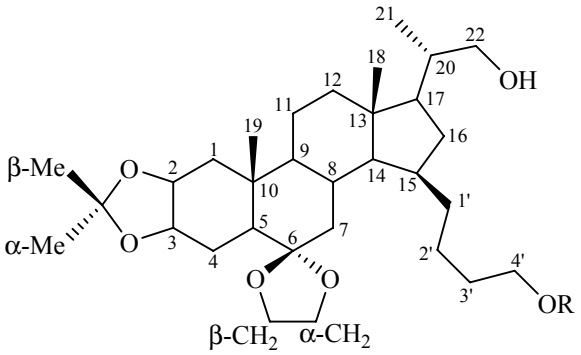
This work continues of our studies on the synthesis of 15-substituted steroids related to brassinosteroid. Initially, our approach to 15-substituted 2,3-dihydroxypregnanes was based on the introduction of the chain in C^{15} position of the unsaturated ketone with a further modification of the rings A and B [12, 13]. This way, as it turned out, has significant limitations due to the instability of pregna-17-ene structure at the modification of rings and due to the competitive reactions involving the protective groups that led to elongation of the reaction scheme and reduced yield of the end product. In this study, we chose another scheme for synthesis, where the cyclic fragment is formed in the early stages, which eliminated such problems. The source ketone **I** and its isomer **II** were prepared along the scheme described in [14], which allowed us to synthesize 2α,3α- and 2β,3β-dihydroxy-derivatives of 15-substituted pregnanes.

Bromide **III**, the reagent for the Michael addition to ketones **I** and **II,** was prepared in two stages from tetrahydrofuran by splitting it with hydrobromic acid [15] and the subsequent protection of the hydroxyl group through silyl ether. Such a procedure reduces the number of stages compared to the previous approach [12], where was used 5-bromopentene while the hydroxyl function in the C^{15} chain was introduced at a later stage.



2α,3α: **I, IV, IVa, VI, VIII, X**; 2β,3β: **II, V, VII, IX, XI**; R = H (**XII**), Ac (**XIIa**); TMSCl is trimethylsilyl chloride, TBDMSCl is *tert*-butylmethylsilyl chloride.

Table 1. [1]H NMR data of compounds **IV–XI**



Atom	Chemical shift, δ, ppm							
	IV[a]	**VI**[a]	**VIII**[b]	**X**[b,c]	**V**[a]	**VII**[a]	**IX**[b]	**XI**[b,c]
1α	1.08	1.06	1.06	1.05	1.34	1.34	1.33	1.32
1β	1.94	1.93	1.93	1.93	2.24	2.24	2.24	2.22
2β(2α)	4.10	4.11	4.10	4.09	4.21	4.21	4.20	4.20
3β(3α)	4.28	4.28	4.27	4.29	4.06	4.06	4.05	4.06
4α	2.16	2.16	2.15	2.14	1.91	1.90	1.89	1.88
4β	1.82	1.83	1.82	1.83	1.54	1.54	1.53	1.53
5α	1.85	1.84	1.83	1.84	1.35	1.33	1.33	1.34
7α	1.13	1.07	1.08	1.12	1.08	1.02	1.03	1.06
7β	1.90	1.84	1.84	1.91	1.91	1.86	1.85	1.91
8β	1.92	1.80	1.81	1.83	1.92	1.82	1.80	1.84
9α	0.89	0.85	0.87	0.90	0.79	0.76	0.77	0.81
11α	1.67	1.59	1.61	1.63	1.65	1.59	1.58	1.61
11β	1.30	1.33	1.34	1.36	1.41	1.44	1.45	1.48
12α	1.23	1.45	1.47	1.33	1.22	1.45	1.45	1.32
12β	1.77	2.18	2.20	1.72	1.78	2.20	2.20	1.73
14α	1.50	1.35	1.37	1.52	1.47	1.33	1.34	1.50
15α	2.14	1.81	1.83	2.32	2.14	1.80	1.82	2.32
16α	2.37	2.47	2.50	5.60	2.37	2.47	2.49	5.60
16β	2.31	2.21	2.23	–	2.31	2.22	2.24	–
18	0.97	1.03	1.04	0.98	0.99	1.05	1.06	0.98
19	0.88	0.87	0.87	0.89	1.17	1.16	1.14	1.16
20	–	5.14	5.15	2.40	–	5.15	5.15	2.40
21	–	1.65	1.65	1.02	–	1.65	1.65	1.03
1'	1.31, 1.50	1.17, 1.36	1.21, 1.49	1.29, 1.52	1.30, 1.51	1.16, 1.37	1.21, 1.50	1.32, 1.50
2'	1.21, 1.42	1.13, 1.36	1.26, 1.50	1.37, 1.50	1.25, 1.43	1.13, 1.37	1.26, 1.50	1.36, 1.50
3'	1.48, 1.54	1.44, 1.52	1.74 (2)	1.76 (2)	1.48, 1.56	1.46, 1.54	1.77 (2)	1.76 (2)
4'	3.60	3.58	4.31	4.32	3.61	3.59	4.31	4.32

Table 1. (Contd.)

Atom	Chemical shift, δ, ppm							
	IV[a]	**VI**[a]	**VIII**[b]	**X**[b,c]	**V**[a]	**VII**[a]	**IX**[b]	**XI**[b,c]
Proton signals of acetonide and dioxolane protecting groups[d]								
α-Me	1.47	1.48	1.47	1.46	1.33	1.33	1.32	1.32
β-Me	1.33	1.32	1.33	1.32	1.55	1.54	1.54	1.54
αA-CH_2	3.76	3.73	3.70	3.72	3.81	3.77	3.74	3.77
αB-CH_2	3.95	3.92	3.86	3.90	3.96	3.93	3.86	3.90
βA-CH_2	4.02	3.99	3.96	3.99	4.03	4.03	3.99	4.01
βB-CH_2	3.88	3.86	3.83	3.89	3.89	3.87	3.85	3.87

[a] *t*-BuMe_2Si, δ, ppm: 0.03 (Me_2Si), 0.88 (Me_3S). [b] Bz, δ, ppm: 7.44 (*meta*), 7.56 (*para*), 8.04 (*ortho*). [c] 20-Hydroxymethyl, δ, ppm: 3.52 and 3.61 (CH_2). [d] (A) indicates the position of the proton CH_2 group in the side of the ring A; (B) indicates the position of the proton CH_2 group in the side of the ring B.

Table 2. ^{1}H and ^{13}C NMR parameters of compounds **XII** and **XIIa**

Atom	^{13}C NMR, δ, ppm		^{13}C NMR, δ, ppm		Atom	^{13}C NMR, δ, ppm		^{13}C NMR, δ, ppm	
	XII[a]	**XIIa**[a,b]	**XII**[a]	**XIIa**[a,b]		**XII**[a]	**XIIa**[a,b]	**XII**[a]	**XIIa**[a,b]
1α	43.73	43.84	1.00	0.99	16	127.19	127.15	5.59	5.59
1β			1.87	1.87	17	157.27	156.51	–	–
2β	73.02	73.16	4.07	4.08	18	22.24	22.11	0.96	0.96
3β	73.27	73.46	4.25	4.26	19	15.25	14.84	0.93	0.92
4α	22.82	22.85	1.99	1.93	20	35.35	31.53	2.38	2.48
4β			2.04	2.04	21	18.27	18.83	1.02	1.05
5α	42.53	42.74	1.51	1.49	22	66.85	68.78	3.51, 3.59	3.93, 4.14
6	77.79	77.70	–	–	1'	29.84	29.92	1.29, 1.50	1.25, 1.50
7α	35.78	35.57	1.07	1.05	2'	25.55	25.70	1.37, 1.50	1.39, 1.50
7β			1.78	1.80	3'	28.99	29.15	1.73 (2)	1.74 (2)
8β	27.21	27.12	1.80	1.84	4'	64.68	64.84	4.30 (2)	4.32 (2)
9α	55.13	55.35	0.80	0.80	^{13}C and ^{1}H signals of acetonide protecting group and substituents at C[6]				
10	37.38	37.52	–	–	α-Me	28.75	28.80	1.45	1.46
11α	20.41	20.48	1.62	1.62	β-Me	26.68	26.76	1.31	1.32
11β			1.34	1.36	$Me_2\underline{C}$	107.54	107.50	–	–
12α	36.97	37.02	1.30	1.30	$\underline{CH_3}CH_2$	9.44	9.42	0.83	0.83
12β			1.71	1.71	$CH_3\underline{CH_2}$	28.90	28.74	1.50 (2)	1.45, 1.55
13	47.32	47.47	–	–	O$\underline{CH_2}CH_2$OR	60.86	58.17	3.34, 3.39	3.44 (2)
14α	57.89	57.77	1.50	1.49	OCH$_2\underline{CH_2}$OR	62.70	64.40	3.65 (2)	4.12, 4.16
15α	43.79	43.91	2.35	2.35					

[a] Bz, δ_H, ppm: 7.44 (*meta*), 7,55 (*para*), 8.03 (*ortho*); δ_C, ppm, 128.5 (C^3), 129.6 (C^2), 130.5 (C^1), 133.0 (C^4), 166.7 (Ph$\underline{C}$O).
[b] Acetonates, δ_H, ppm: 2.01 (6-Me), 2.03 (22-Me); δ_C, ppm: 21.08 (6,22-Me), 171.08 [6-O$\underline{C}$(O)], 171.21 [22-O$\underline{C}$(O)].

The conjugate addition of the Grignard reagent prepared from the bromide **III** to the ketones **I** and **II** in the presence of copper(I) bromide complex with dimethyl sulfide, trimethylsilyl chloride and HMPA [12, 16, 17] gave the products **IV** and **V**, respectively, in almost quantitative yield. However, the reaction involves a two-stage procedure because during the processsing, the intermediate enol silyl ether **IVa** is not completely hydrolyzed. Ether **IVa** was converted to the ketone **IV** by additional treatment with K_2CO_3 in methanol.

Table 3. ^{13}C NMR data of compounds **IV–XI**

Atom	Chemical shift, δ, ppm							
	IV[a]	**V**[a]	**VI**[a]	**VII**[a]	**VIII**[b]	**IX**[b]	**X**[b,c]	**XI**[b,c]
1	42.95	41.05	42.89	41.08	42.91	41.07	42.81	40.99
2	73.00	73.82	73.15	73.82	73.15	73.80	73.11	73.77
3	72.91	75.81	73.03	75.59	73.04	75.56	73.03	75.57
4	22.10	24.01	22.11	24.24	22.14	24.23	22.16	24.31
5	45.95	49.23	45.86	49.17	45.91	49.17	46.18	49.50
6	109.54	109.65	109.82	109.65	109.79	109.60	109.76	109.59
7	39.90	39.79	40.58	40.82	40.71	40.92	40.71	40.91
8	30.21	30.00	30.06	30.06	30.11	30.08	29.81	29.81
9	53.89	55.21	53.77	55.39	53.81	55.37	54.48	56.06
10	38.43	36.65	38.38	36.64	38.40	36.63	38.46	36.73
11	20.13	20.17	20.99	21.19	21.01	21.18	20.54	20.75
12	33.89	33.96	39.20	39.26	39.21	39.24	36.87	36.97
13	46.90	47.03	43.81	43.86	43.82	43.84	47.41	47.47
14	53.26	53.38	58.29	58.37	58.31	58.34	57.62	57.70
15	34.49	34.43	37.12	37.10	37.13	37.09	43.88	43.89
16	42.89	42.71	39.44	39.40	39.45	39.37	127.42	127.43
17	221.37	221.51	150.69	150.73	150.49	150.50	157.21	157.21
18	17.73	17.71	20.44	20.47	20.48	20.48	22.18	22.24
19	13.47	15.17	13.44	15.21	13.45	15.21	13.39	15.14
20	–	–	114.18	114.18	114.37	114.34	35.43	35.47
21	–	–	13.48	13.47	13.48	13.47	18.29	18.28
1'	30.93	30.75	31.26	31.22	31.04	31.00	29.95	29.95
2'	26.08	26.14	26.12	26.12	26.35	26.32	25.82	25.80
3'	33.14	33.35	33.36	33.33	29.07	29.04	29.19	29.19
4'	63.17	63.24	63.46	63.46	65.12	65.12	64.88	64.89
α-Me	28.76	26.29	28.77	26.31	28.78	26.28	28.76	26.28
β-Me	26.71	28.74	26.73	28.82	26.74	28.81	26.72	28.82
Me_2C	107.82	107.96	107.73	107.91	107.75	107.93	107.77	107.93
α-CH_2	64.52	64.47	64.41	64.47	64.44	64.49	64.46	64.52
β-CH_2	65.63	65.24	65.53	65.47	65.61	65.53	65.63	65.58

[a] *t*-$BuMe_2Si$, δ_C, ppm: –5.09 (Me_2Si), 18.46 ($Me_3\underline{C}$), 26.10 ($\underline{Me}_3C$). [b] Bz, δ_C, ppm: 128.49 (C^3), 129.66 (C^2), 130.57 (C^1), 133.0 (C^4), 166.79 (PhCO). [c] 20-Hydroxymethyl, δ_C, ppm: 66.93 (CH_2).

Synthesis of pregnenes **VI** and **VII** is based on the well-developed procedure [18–20]. The Wittig reaction of ketones **IV** and **V** in boiling benzene with the ylide prepared from ethyltriphenylphosphonium bromide led selectively to the 17*Z*-pregnenes in 90–92% yield. Configuration of the 17-center is confirmed according to the NMR data (Tables 1–3), which are quite consistent with the literature.

The next stage of the synthesis required replacement of the protective silyl group, which proved to be unstable under the conditions of ene reaction. The benzoate protection was chosen owing to its stability under the reaction conditions and the need for further discrimination of the two primary hydroxyl groups, (the second is formed in the ene reaction). The two-stage transformation gave esters **VIII** and **IX** in 86% and 92% yield, respectively. Consecutive approach through the formation of C^{22} aldehyde in the synthesis of brassinosteroid side chain was preferred, since the use of functionalized aldehydes for the introduction of the C^{22}–C^{28} fragment has been shown leading to the 20-*unnatural* steroids [21].

Unexpectedly, the carbonyl ene reaction [22–24] required selection of a specific Lewis acid. The typical reagents for a similar conversion were ineffective in the steroid series. For example, boron trifluoride etherate or Me_2AlCl caused partial hydrolysis of the protecting group, and, for example, *t*-$BuMe_2SiCl$ [25] did not even initiated the reaction. We then returned to diethylaluminum chloride [19, 26], which showed good results in our previous work [13]. This reagent was tested initially with compound **IX:** the reaction led to the corresponding alcohol **XI.** Similar good result was obtained with steroid **VIII**. However, further attempts of scaling the experiment under various conditions were complicated by the formation of by-product. The by-product in some cases has been isolated as the main product of the reaction. The isolated by-product was thoroughly analyzed. For this purpose it was acetylated, and according to the data of NMR spectroscopy and mass spectrometry, to the acetate was assigned the structure **XIIa**. It turned out that under the reaction conditions, diethylaluminum chloride can attack the dioxolane ring of the molecule, giving a product **XII** of the ring cleavage. Stereochemistry of addition at C^6 follows from the data of the NOESY spectrum of **XIIa**. The cross-peaks were detected between the methyl protons of ethyl group and 4α- and 7α-protons, whereas the OCH_2 protons interact with 7β,8β protons and weakly with the protons of 19-methyl group.

It could be assumed that the formation of **XII** is associated either with an excess of reagent, or with the temperature factor. However, the change in the ratio of the paraform–diethylaluminum chloride complex, or performing the reaction at different temperatures did not lead to a decrease in the yield of **XII**. So, it was found that the temperature of reaction initiation was about –30°C, but even at this temperature was observed formation of both the products. The compound **X** and **XII** formed in 1:1 ratio and were obtained in a total yield of 75–85%. Solving the problem was quite simple and consisted in the use of strict anhydrous conditions. A slight amount of moisture in the reaction mixture initiates the addition leading to the formation of **XII**. Prolonged pre-drying of substrates allowed us to obtain steroids **X** and **XI** in 73% yield.

Compounds **X–XII** are synthetic precursors of the new D-modified brassino- and ecdysteroids and will be further used in the synthesis of analogues of these hormones to study their physiological activity and use for analytical purposes.

EXPERIMENTAL

Melting points were determined on a Kofler block and were not adjusted. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AVANCE 500-Biospin spectrometer with operating frequencies 500.13 and 125.77 MHz for ^1H and ^{13}C nuclei, respectively, using 5-mm probe (QNP) with Z-gradient. The spectra were recorded at a sample temperature 293 K for solutions in $CDCl_3$, as an internal reference we used the residual solvent signals δ 7.26 (^1H) and 77.16 (^{13}C). The correlation spectra (HSQC, COSY, HMBC, NOESY) were recorded and processed using a standard Bruker-Biospin software. The NMR data are listed in Tables 1–3. The IR spectra were obtained on an UR 20 instrument. The mass-spectra were recorded on an Accela HPLC device with the mass detector LCQ-Fleet (three-dimensional ion trap) using chemical ionization at atmospheric pressure (APCI), detection of positive ions, CID 35%. The *m/z* ratio and relative intensity (%) are given for the most intense peaks.

Preparation of solvent was carried out according to the usual practice [27]. All reactions were performed under argon. The reactions were monitored by TLC on

Merck (Kieselgel 60 F_{254}) plates. Chromatographic separation of reaction mixtures was performed on 40/60 silica gel (Kieselgel 60, Merck).

4-Bromobutoxydimethyl-*tert*-butylsilane (III). A solution of 4-brombutanol [15] (4.59 g, 30 mmol), dimethyl-*t*-butylsilyl chloride (3.8 g, 25 mmol) and triethylamine (68 ml, 50 mmol) in 20 ml of dichloromethane was stirred at room temperature for 72 h. Then the solution was diluted with hexane, washed with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatograpy on a silica gel column (petroleum ether), which gave compound **III** (4.6 g, 70% yield based on dimethyl-*tert*-butylsilyl chloride). Colorless liquid, bp 75–76°C (2 mm Hg). IR (film), cm^{-1}: 2970, 2870, 1260, 1110, 840, 790. ^1H NMR spectrum, δppm: 0.06 (6H, s, Me_2Si), 0.90 (9H, s, *t*-BuSi), 1.65 m (2H, CH_2), 1.94 m (2H, CH_2), 3.45 t (2H, CH_2Br, J = 7 Hz), 3.66 t (2H, CH_2O, J = 7 Hz).

15β-(4-(Dimethyl-*tert*-butylsilyloxy)butyl)-2α,3α-isopropylidenedihydroxy-6,6-ethylenedioxy-5α-androstan-17-one (IV). To a cooled to –20°C solution of Grignard reagent (prepared by adding a solution of bromide **III** (3.12 g, 11.69 mmol) in THF (12 ml) to magnesium chips (0.31 g, 12.89 mmol) in THF (12 ml) followed by reflux for 1 h) was added $CuBr·Me_2S$ complex (0.482 g, 2.35 mmol). After 5 min, the solution was cooled to –78°C and were added subsequently Me_3SiCl (2.47 ml, 19.58 mmol), phosphoric hexamethyltriamide (3.4 ml, 19.58 mmol) and then a solution of steroid **I** (1.362 g, 3.39 mmol) in THF (15 ml). The mixture was stirred for 10 min and then treated with a saturated solution of NH_4Cl. The organic phase was extracted with EtOAc, the resulting solution was washed with saturated NaCl solution and dried over Na_2SO_4. After solvent evaporation, the residue was chromatographed on a silica gel column (EtOAc–petroleum ether, 10:90). The first fraction (0.8 g) contained Me_3Si-derivative **IVa** as the main component. IR (film), cm^{-1}: 2960, 2860, 1640, 1260, 1110, 850, 790, ^1H NMR spectrum (C_6D_6), δppm: 0.06 s (6H, Me_2Si), 0.21 s (9H, Me_3Si), 0.88 s (3H, 19-Me), 0.93 s (3H, 18-Me), 0.98 s (9H, Me_3C), 1.40 s (3H, β-Me, acetonide), 1.59 s (3H, α-Me, acetonide), 3.55 t (2H, 4'-H, J = 6.2), 3.56 m (4H, dioxolane), 4.04 m (1H, 2β-H), 4.19 m (1H, 3β-H), 4.90 d (1H, 16-H, J = 3.0).

Further elution gave ketone **IV** (1.536 g). Fraction of the enol ether was dissolved in methanol (10 ml), K_2CO_3 (0.02 g) was added, and the mixture was stirred for 1 h. After hydrolysis, the solvent was evaporated, the resulting oil was dissolved in EtOAc, the solution was washed successively with saturated solutions of NH_4Cl and NaCl, and dried over Na_2SO_4. After solvent evaporation, the residue was chromatographed on a silica gel column, which gave an additional 0.453 g of ketone **IV**. The overall yield 1.989 g (99%). Colorless oil. IR spectrum (film), cm^{-1}: 2960, 1760, 1250, 1100, 850, 790. Mass spectrum, *m/z*, (*I*, %): 591 ($[M + 1]^+$, 5), 590 ($[M]^+$, 9), 533 ($[M + 1 – (CH_3)_2CO]^+$, 100), 515 ($[M + 1 – (CH_3)_2CO – H_2O]^+$, 25), 471 ($[M + 1 – (CH_3)_2CO – H_2O\text{-}(CH_2)_2O]^+$, 16). Mass spectrum, *m/z* (*I*, %) (MS^2), (590): 575 ($[M – Me]^+$, 61), 532 ($[M – (CH_3)_2CO]^+$, 100), 475 ($[M – t\text{-}BuSiMe_2]^+$, 52).

15β-(4-(Dimethyl-*tert*-butylsilyloxy)butyl)-2β,3β-isopropylidenedihydroxy-6,6-ethylenedioxy-5α-androstan-17-one (V). Along the above procedure, from 0.286 g (0.71 mmol) of steroid **II** after separation was obtained 0.394 g (94%) of steroid **V,** mp 130–133°C (hexane). IR spectrum (KBr), cm^{-1}: 2950, 2870, 1740, 1250, 1110, 850, 790. Mass spectrum, *m/z*, (*I*, %): 591 ($[M + 1]^+$, 100), 533 ($[M + 1 – (CH_3)_2CO]^+$, 61), 515 ($[M + 1 – (CH_3)_2CO – H_2O]^+$, 16). Mass spectrum, *m/z*, (*I*, %) (MS^2) (590): 572 ($[M – H_2O]^+$, 60), 532 ($[M – (CH_3)_2CO]^+$, 100). Found, %: C 69.40, H 9.96. $C_{34}H_{58}O_6Si$. Calculated, %: C, 69.11; H, 9.89.

(17*Z*)-15β-(4-(Dimethyl-*tert*-butylsilyloxy)butyl)-2α,3α-isopropylidenedioxy-6,6-ethylenedioxy-5α-pregna-17-ene (VI). To a solution of ylide (prepared by stirring 30 min a mixture of potassium *t*-butoxide (1.235 g, 3.11 mmol) and triphenylethylphosphonium bromide (4.5 g, 12.13 mmol) in benzene (20 ml) at 40°C was added 2.58 g of steroid **IV** (4.37 mmol) in benzene (20 ml) at 10°C. The resulting solution was refluxed for 2.5 h, then cooled, and acetone (1.5 ml) was added to the mixture. After 30 min it was treated with a saturated solution of NH_4Cl (3 ml), diluted with hexane and passed through a layer of $MgSO_4$. After solvent evaporation, the residue was chromatographed on a silica gel column (EtOAc–petroleum ether, 3:97), which gave 2.42 g of olefin **VI** (92%). Colorless oil. IR spectrum (film), cm^{-1}: 2950, 2870, 1740, 1100, 850, 790. Mass spectrum, *m/z*, (*I*, %), *m/z*: 603 ($[M + 1]^+$, 10), 545 ($[M + 1 – (CH_3)_2CO]^+$, 100). Mass spectrum, *m/z*, (*I*, %) (MS^2) (602): 587 ($[M – Me]^+$, 100), 544 ($[M – (CH_3)_2CO, 13]^+$), 487 ($[M – t\text{-}BuSiMe_2]^+$, 52).

(17*Z*)-15β-(4-(Dimethyl-*t*-butylsilyloxy)butyl)-2β,3β-isopropylidenedioxy-6,6-ethylenedioxy-5α-

pregna-17-ene (VII). Similarly, from 0.361 g (0.61 mmol) of steroid **V** after separation was obtained 0.332 g (90%) of olefin **VII**, mp 157–159°C (hexane). IR spectrum (KBr), cm^{-1}: 2940, 2870, 1110, 850, 790. Mass spectrum, *m/z*, (*I*, %): 603 ($[M + 1]^+$, 100), 545 ($[M + 1 – (CH_3)_2CO]^+$, 100). Mass spectrum, *m/z*, (*I*, %) (MS^2) (603): 544 ($[M – (CH_3)_2CO]^+$, 100), 501 ($[M – Me – MeCH – (CH_3)_2CO]^+$, 33), 485 ($[M – 117]^+$, 34) . Found, %: C 71.87, H 10.02. $C_{36}H_{62}O_5Si$. Calculated, %: C 71.71, H 10.36.

(17*Z*)-15β-(4-Benzoyloxybutyl)-2α,3α-isopropylidenedioxy-6,6-ethylenedihydroxy-5α-pregna-17-ene (VIII). To a solution of 3.393 g of steroid **VI** (5.64 mmol) in THF (20 ml) was added 1M solution of Bu_4NF in THF (11 ml). The resulting mixture was stirred for 2 h, then diluted with EtOAc, washed consecutively with saturated solutions of $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The solvent was evaporated, the residue (3.4 g) was dissolved in methylene chloride (40 ml), then were added consecutively a solution of pyridine (1.1 ml, 13.56 mmol) and benzoyl chloride (1.32 ml, 11.3 mmol). The mixture was stirred at room temperature for 2.5 h, then to it was added methanol (0.6 ml) and stir was continued for 0.5 h. The solution was then diluted with chloroform, washed with saturated solutions of $NaHCO_3$ and NaCl, and dried over $MgSO_4$. After solvent evaporation, the residue was purified by chromatography on a silica gel column (EtOAc–petroleum ether, 10:90), which gave 2.871 g of steroid **VIII** (86%), mp 162–164°C (methanol). IR spectrum (KBr), cm^{-1}: 2950, 2870, 1720, 1280, 720. Mass spectrum, *m/z*, (*I*, %): 593 ($[M + 1]^+$, 39), 535 ($[M + 1 – (CH_3)_2CO]^+$, 100). Mass spectrum, *m/z*, (*I*, %) (MS^2) (592): 577 ([*M* – Me, 100), 549 ([*M* – Me – MeCH, 61) 535 ([*M* + 1 – $(CH_3)_2CO$, 20), 491 ($[M – Me – MeCH – (CH_3)_2CO]^+$, 20). Found, %: C 75.17, H 8.98. $C_{37}H_{52}O_6$. Calculated, %: C 74.96, H 8.84.

(17*Z*)-15β-(4-Benzoyloxybutyl)-2β,3β-isopropylidenedioxy-6,6-ethylenedihydroxy-5α-pregna-17-ene (IX). Similarly, from 0.189 g (0.31 mmol) of compound **VII** after the separation was obtained 0.169 g (92%) of steroid **IX**. Colorless oil. IR spectrum (film), cm^{-1}: 2950, 2870, 1730, 1280, 1120, 720. Mass spectrum, *m/z*, (*I*, %): 593 ($[M + 1]^+$, 100), 535 ($[M + 1 – (CH_3)_2CO]^+$, 35). Mass spectrum, *m/z*, (*I*, %) (MS^2) (593): 549 ($[M – Me – MeCH]^+$, 100), 535 ($[M + 1 – (CH_3)_2CO]^+$, 38), 491 ($[M – Me – MeCH – (CH_3)_2CO]^+$, 49).

(20*S*)-15β-(4-Benzoyloxybutyl)-20-hydroxymethyl-2α,3α-isopropylidenedihydroxy-6,6-ethylenedioxy-5α-pregna-16-ene (X). To a stirred solution of 0.022 g of paraform (0.75 mmol) in methylene chloride (5 ml) was added 1M solution of diethylaluminum chloride in hexane (1 ml) at –78°C. After 5 min, to the resulting complex was added 0.148 g of steroid **VIII** (0.25 mmol) in methylene chloride (3 ml), and the mixture was stirred at riseing temperature to 0°C for 3 h. Then was added a solution of pyridine (0.2 ml) in methanol (1 ml) and, after the cessation of gas evolution, the mixture was poured into a saturated solution of $NaHCO_3$ and NaCl (1: 1) the organic phase was extracted with chloroform, washed with saturated NaCl solution and dried over Na_2SO_4. After solvent evaporation, the residue was separated on a silica gel column (EtOAc–toluene, 20:80), the fraction of alcohol **X** (0.113 g, 73%) was collected. Colorless foam. IR spectrum (film), cm^{-1}: 2950, 2880, 1730, 1280, 1060, 760, 720. Mass spectrum, *m/z*, (*I*, %): 623 ($[M + 1]^+$, 19), 593 ($[M + 1 – CH_2OH]^+$, 7), 565 ($[M + 1 – (CH_3)_2CO]^+$, 100), 535 ($[M + 1 – (CH_3)_2CO – CH_2OH]^+$, 35). Mass spectrum, *m/z*, (*I*, %) (MS^2) (623): 579 ($[M + 1 – (CH_2)_2O]^+$, 100), 565 ($[M + 1 – (CH_3)_2CO]^+$, 48), 547 ($[M + 1 – (CH_3)_2CO – H_2O]^+$, 42), 521 ($[M + 1 – (CH_3)_2CO – (CH_2)_2O]^+$, 34). Further elution gave the product of disclosure dioxolane ring **XII** (0.009 g, 6%). Colorless oil. IR spectrum (film), cm^{-1}: 2950, 2870, 1730, 1280, 750, 720. Mass spectrum, *m/z*, (*I*, %): 653 ($[M + 1]^+$, 0.1), 591 ($[M + 1 – (CH_2OH)_2]^+$, 13), 533 ($[M + 1 – (CH_2OH)_2 – (CH_3)_2CO]^+$, 100), 515 ($[M + 1 – (CH_2OH)_2 – (CH_3)_2CO – H_2O]^+$, 58). Mass spectrum, *m/z*, (*I*, %) (MS^2) (652): 634 ($[M – H_2O]^+$, 97), 622 ($[M – C_2H_6]^+$, 18), 619 ($[M – H_2O – Me]^+$, 38), 594 ($[M – (CH_3)_2CO]^+$, 100), 576 ($[M – (CH_3)_2CO – H_2O]^+$, 60), 532 ($[M – (CH_2OH)_2 – (CH_3)_2CO]^+$, 21).

(20*S*)-15β-(4-benzoyloxybutyl)-20-hydroxymethyl-2β,3β-isopropylidenedihydroxy-6,6-ethylenedioxy-5α-pregna-16-ene (XI). Similarly, from 0.144 g (0.24 mmol) of compound **IX** after the separation was obtained 0.110 g (74%) of the alcohol **XI**, mp 146–147°C (hexane). IR spectrum (film), cm^{-1}: 2950, 2870, 1730, 1280, 1060, 760, 720. Mass spectrum, *m/z*, (*I*, %): 623 ($[M + 1]^+$, 100), 579 ($[M + 1 – C_2H_4]^+$, 13), 565 ($[M + 1 – (CH_3)_2CO]^+$, 15) . Mass spectrum, *m/z*, (*I*, %) (MS^2) (623): 579 ($[M + 1 – C_2H_4]^+$, 100), 565 ($[M + 1 – (CH_3)_2CO]^+$, 79), 547 ($[M + 1 – (CH_3)_2CO – H_2O]^+$, 19), 521 ($[M + 1 – (CH_3)_2CO – (CH_2)_2O]^+$, 95), 503 ($[M + 1 – (CH_3)_2CO – (CH_2)_2O – H_2O]^+$, 75), 485

([M + 1 – $(CH_3)_2CO$ –$(CH_2)_2O$ – $2H_2O$]$^+$, 41). Found, %: C 72.92, H 8.93. $C_{38}H_{54}O_7$. Calculated, %: C 73.28; H 8.74.

(6*R*,20*S*)-20-Acetoxymethyl-6-(2-acetoxyethyloxy)-15β-(4-benzoyloxybutyl)-2α,3α-isopropylidendioxy-6-ethyl-5α-pregna-6-ene (XIIa). To a solution of 0.170 g of steroid **XII** (0.26 mmol) in methylene chloride (3 ml) were added consecutively pyridine (0.15 ml, 1.86 mmol) and acetic anhydride (0.15 ml, 1.47 mmol). The mixture was stirred at room temperature for 24 h, diluted with methylene chloride (15 ml), washed with saturated solutions of $NaHCO_3$ and then NaCl, and dried over Na_2SO_4. After solvent evaporation, the residue was purified by chromatography on a silica gel column (EtOAc–toluene, 20:80), which gave 0.114 g of compound **XIIa** (60%). Colorless oil. IR spectrum (film), cm^{-1}: 2950, 2880, 1755, 1735, 1280, 1250, 1240, 720. Mass spectrum, *m/z*, (*I*, %), *m/z*: 633 ([M + 1 – $AcOCH_2CH_2OH$]$^+$, 7), 575 ([M + 1 – $AcOCH_2CH_2OH$ – $(CH_3)_2CO$]$^+$, 64), 557 ([M + 1 – $AcOCH_2CH_2OH$ – $(CH_3)_2CO$ – H_2O]$^+$, 27), 515 ([M + 1 – $AcOCH_2CH_2OH$ – $(CH_3)_2CO$ – AcOH]$^+$, 100). Mass spectrum, *m/z*, (*I*, %) (MS^2) (736): 721 ([M – Me]$^+$, 30), 678 ([M – $(CH_3)_2CO$]$^+$, 41), 676 ([M – AcOH]$^+$, 28), 650 ([M – $AcOCH{=}CH_2$]$^+$, 100), 618 ([M – AcOH – $(CH_3)_2CO$]$^+$, 65).

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