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Dedicated to Prof. M. Yus on his 60th anniversary

Pd-Catalyzed Alkylation of Halogen-Substituted Steroids with Organozinc Compounds

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Abstract—A general procedure has been developed for the introduction of hydrophobic alkyl groups into positions *6*, *3*, and *17* of steroid molecules via palladium-catalyzed Negishi reaction of halogen-substituted steroids with benzyl- and alkylzinc halides.

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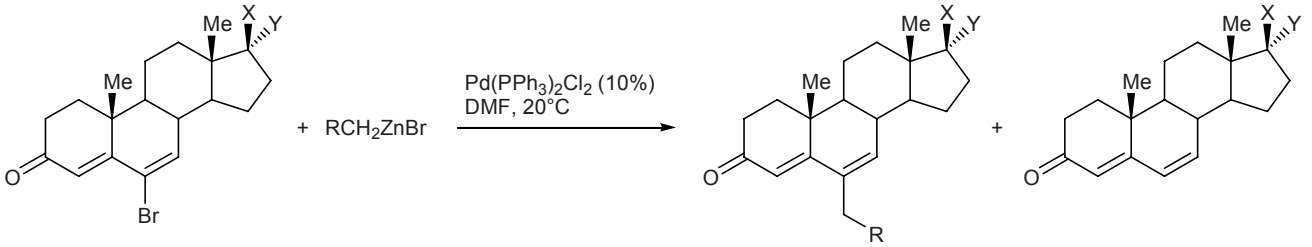
The use of organolithium and organomagnesium compounds for the introduction of alkyl or aryl substituents into various positions of steroid molecules generally requires protection and subsequent deprotection at positions *3*, *17*, or others of the steroid skeleton, where oxo or hydroxy groups are usually present. Recently proposed synthetic approaches to aryl- and vinyl-substituted steroid derivatives, based on Pd-catalyzed cross-coupling reactions [1], do not imply the necessity of introducing protecting groups; however, in this case only the corresponding 3-Δ^3- or 17-Δ^{16}-trifluoromethanesulfonates or halides derived from 17-oxo steroids should be used as initial compounds. Cross-couplings of some related compounds with organozinc [2–5], organoboron [2, 6–11], or organotin compounds [5, 12–15] were reported previously. Such trifluoromethanesulfonates are readily available from the corresponding oxo derivatives according to Stang [16]; 17-iodosteroids can be obtained from 17-oxosteroid hydrazone [17]. The application scope of the above procedures for the introduction of aryl or vinyl groups is strongly restricted; furthermore, mixtures of products can be formed when enolization of the substrate is ambiguous.

It is known that substitution at positions *4* and *6* of androstane skeleton may give rise to enhanced aromatase inhibitor activity [18]. We recently proposed for the first time to use 4-bromo-Δ^4- and 6-chloro(bromo)-$\Delta^{4,6}$-steroids as substrates in Pd-catalyzed arylation with arylboronic acids [19, 20] and Sonogashira ethynylation [21]. Preliminary experiments showed that some of the 6-aryl- and 6-ethynylsteroids thus obtained exhibit a strong inhibitory effect on MCF-7 tumor cells (breast cancer) and revealed a correlation between the size of the hydrophobic substituent on C^6 and antitumor activity.

Taking into account the above stated, we made an attempt to modify steroid molecules via introduction into the 6-position of sterically hindered hydro-

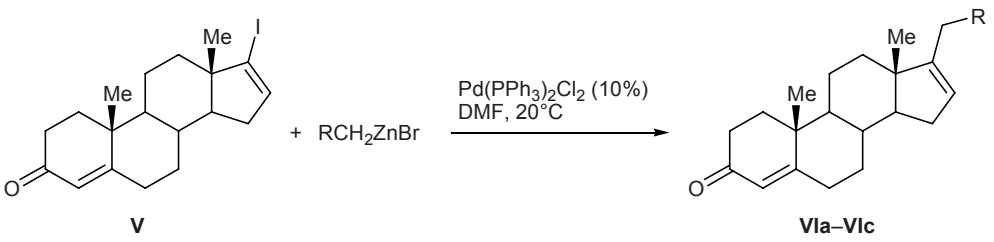
Scheme 1.



I, **II** **IIIa–IIIf** **IV**

I, **IIIa**–**IIIe**, **IV**, XY = O; **II**, **IIIf**, X = Ac, Y = OAc; **III**, R = Ph (**a**), 2-ClC_6H_4 (**b**, **f**), 4-MeC_6H_4 (**c**), 2-$MeOC_6H_4$ (**d**), Me_3Si (**e**).

Scheme 2.



V **VIa–VIc**

R = Ph (**a**), 2-ClC_6H_4 (**b**), Me_3Si (**c**).

phobic substituents, both aryl and alkyl, with a view to estimate antitumor activity of the modified compounds. In the present communication we describe a general procedure for the introduction of hydrophobic alkyl groups into positions *6*, *3*, and *17* of steroid molecules. It is usually very difficult to introduce alkyl groups into molecules of organic halogen compounds in the presence of palladium catalysts and alkylboronic acids, for the latter are much less reactive than aryl- and vinylboronic acids. For this purpose, it is best to use benzylzinc compounds that are readily available from the corresponding benzyl bromides by the action of activated zinc [22].

The best results (the highest yield of compound **IIIa**) in the reaction of 6-bromoandrosta-4,6-diene-3,17-dione (**I**) with benzylzinc bromide (5 mol % of [Pd], 100°C, 6 h) were obtained using polar solvents, dimethylformamide being preferred. The reaction was accompanied by formation of 3–5% of side hydrodehalogenation product, androsta-4,6-diene-3,17-dione (**IV**) (Scheme 1). The most efficient catalyst precursor was $Pd(PPh_3)_2Cl_2$ (see table). Strong electron-donating sterically hindered and bidentate ligands turned out to be weakly effective. Unexpectedly high efficiency was observed in the presence of heterogeneous Pd/C catalyst in combination with PPh_3 (yield 75%).

Raising the amount of $Pd(PPh_3)_2Cl_2$ to 10 mol % allowed us to attain 100% conversion in DMF both at 100°C (6 h) and at room temperature (16 h), and 6-benzylandrosta-4,6-diene-3,17-dione (**IIIa**) was isolated in 88% yield as the only product. Under analogous conditions, we performed reactions with substituted benzylzinc bromides, including those having substituents in the *ortho* position. The reaction with sterically hindered trimethylsilylmethylzinc chloride smoothly afforded 94% of steroid allylsilane **IIIe**. On the other hand, pentafluorobenzylzinc bromide having an electron-withdrawing pentafluorophenyl group and allylzinc chloride failed to react with halosteroids under the same conditions.

Anomalously high sensitivity of the reaction to the nature of bromosteroid should be noted. The reactions with 6-bromosteroids occurred fairly readily, while even traces of the corresponding 4-benzyl derivative were not detected in the reaction with vinylogous 4-bromoandrost-4-ene-3,17-dione under the optimal conditions. No cross-coupling was observed in the reaction of the same substrate in THF with 4-methoxyphenylzinc chloride obtained from the corresponding Grignard compound.

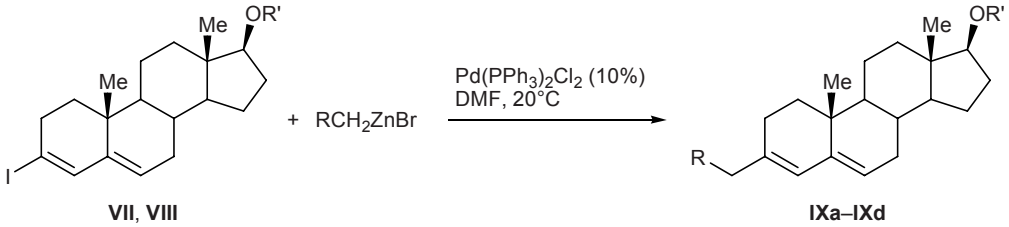
Vinyl iodides are generally more reactive than vinyl bromides in cross-coupling processes. However, the

Yields of compound **IIIa** in the cross coupling of 6-bromoandrosta-4,6-diene-3,17-dione (**I**) with benzylzinc bromide[a]

Catalyst	Yield,[b] %	Catalyst	Yield,[b] %
$Pd(PPh_3)_4$	68	$Pd(dba)_2$/BINAP[c]	1
$Pd(PPh_3)_2Cl_2$	83	$Pd(dppb)Cl_2$[d]	23
$Pd(Cy_3P)_2Cl_2$	48	$Pd(dppf)Cl_2$[e]	11
$Pd(dba)_2$/2 *t*-$Bu_3PH^+ BF_4^-$	45	Pd/C+2 PPh_3	75

[a] 5% [Pd], DMF, 100°C, 6 h; 1–5% of compound **IV** is formed as by-product.
[b] According to the ^1H NMR data.
[c] dba stands for dibenzylideneacetone, and BINAP, for 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.
[d] dppb stands for 1,4-bis(diphenylphosphino)butane.
[e] dppf stands for 1,1′-bis(diphenylphosphino)ferrocene.

Scheme 3.



VII, **VIII** **IXa–IXd**

VII, **IXa**–**IXc**, R′ = Ac; **VIII**, **IXd**, R′ = H; **IX**, R = Ph (**a**), 2-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**, **d**).

reactions of benzylzinc bromides with 17-iodosteroids **V** and **VI** were characterized by a lower rate than with bromosteroids **I**. Even after stirring for 40 h at 20°C, the reaction mixture obtained from iodosteroid **V**, excess benzylzinc bromide, and 10 mol % of $Pd(PPh_3)_2Cl_2$ contained 83% of cross-coupling product **VIa** and 17% of initial steroid **V** (Scheme 2). The conversion of **V** in the reaction with *o*-chlorobenzylzinc bromide in DMF was 70% in 64 h, other conditions being equal. Further increase of the amounts of the catalyst and organozinc reagent or raising the temperature did not result in increased conversion. The conversion of iodide **V** was complete in the reaction with more active Me_3SiCH_2ZnCl, and 17-(trimethylsilylmethyl)androsta-4,16-dien-3-one (**VIc**) was isolated by column chromatography in 98% yield.

Despite the lack of steric hindrances, cross-coupling of 17-acetoxy-3-iodoandrosta-3,5-diene (**VII**) with benzylzinc bromides was fairly slow. Nevertheless, compounds **IXa**–**IXc** were formed as the only products and were isolated in good yields (Scheme 3). Steroid **VIII** possessing a free hydroxy group reacted with excess 4-methylbemzylzinc bromide to give compound **IXd**.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively. The MALDI-TOF spectra were obtained on a Bruker Daltonics Ultra-Flex instrument in dithranol. The products were isolated by column chromatography on silica gel (0.040–0.063 mm, Merck).

Organozinc compounds were prepared by the action of metallic zinc on organic halogen compounds in DMF [22]. Zinc dust, 156 mg (2.4 mmol), was dispersed in DMF, and 50.8 mg (0.2 mmol) of iodine was added. When the yellow color disappeared, the corresponding organic halogen compound was added under argon, and the mixture was stirred for 6 h at 20°C (benzyl bromides) or for 16 h at 80°C (trimethylsilylmethyl chloride).

Halogen-substituted steroids **I**, **II** [20], and **VIII** [23] were synthesized by known methods.

17-Iodoandrosta-4,16-dien-3-one (V). A solution of 5.0 g (16.6 mmol) of 3-methoxyandrosta-3,5-dien-17-one, 4.1 ml of triethylamine, and 11.6 ml (23.9 mmol) of hydrazine hydrate in 96% ethanol was stirred for 2 h on heating under reflux. The mixture was diluted with methylene chloride and washed with water, and the organic phase was dried over Na_2SO_4 and evaporated on a rotary evaporator. 3-Methoxyandrosta-3,5-dien-17-one hydrazone, 4.55 g (87%), thus obtained was then used without additional purification.

Iodine, 6.9 g (27.2 mmol), was added in small portions under vigorous stirring to a solution of 4.04 g (12.9 mmol) of 3-methoxyandrosta-3,5-dien-17-one hydrazone and 18 ml of triethylamine in 81 ml of anhydrous dioxane. The mixture was stirred for 30 min at room temperature, an aqueous solution of Na_2SO_3 was added, the product was extracted into methylene chloride, and the extract was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator. The residue was dissolved in 30 ml of 96% ethanol, 3 ml of 48% hydrobromic acid was added, and the mixture was stirred for 4 h at room temperature, diluted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator. The residue was subjected to chromatography on silica gel using methylene chloride–diethyl ether (20:1) as eluent. Yield 3.31 g (65%), yellow needles, mp 169°C (from MeOH); published data [7]: mp 165–168°C. ^1H NMR spectrum, δ, ppm: 6.12 m (1H), 5.73 m (1H), 2.48–2.24 m (4H), 2.21–2.10 m (1H), 2.06–1.93 m (2H), 1.91–1.82 m (1H), 1.80–1.61 m (4H), 1.56–1.41 m (2H), 1.29–0.93 m (3H), 1.20 s (3H), 0.77 s (3H).

3-Iodoandrosta-3,5-dien-17-yl acetate (VII). A solution of 200 mg (0.5 mmol) of 3-iodoandrosta-3,5-dien-17-ol (**VIII**), 12.2 mg (0.1 mmol) of 4-dimethylaminopyridine, 102 mg (1.0 mmol) of acetic anhydride, and 0.51 g (5.0 mmol) of triethylamine in 2 ml of methylene chloride was stirred for 24 h at room temperature. The mixture was diluted with methylene chloride, washed with three portions of water, dried over Na_2SO_4, and evaporated on a rotary evaporator. The residue was purified by column chromatography using CH_2Cl_2 as eluent. Yield 183.5 mg (83%), colorless crystals. ^{1}H NMR spectrum, δ, ppm: 6.54 m (1H), 5.34 m (1H), 4.60 m (1H), 2.70–2.53 m (2H), 2.23–2.10 m (2H), 2.02 s (3H), 1.81–1.45 m (7H), 1.44–0.98 m (6H), 0.96 s (3H), 0.81 s (3H).

Reactions of alkylzinc halides with halosteroids I, II, V, VII, and VIII (*Negishi reaction. General procedure***).** A solution of the corresponding organozinc compound in DMF, 0.1 ml (0.2 mmol), was added under argon to a suspension of 0.1 mmol of halosteroid **I**, **II**, **V**, **VII**, or **VIII** and 7.0 mg (0.01 mmol, 10 mol %) of $Pd(PPh_3)_2Cl_2$ in 1.9 ml of DMF, and the mixture was stirred for 16–24 h at room temperature. The mixture was diluted with 15 ml of methylene chloride, washed with water (5×10 ml), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in 1.5 ml of methylene chloride, and the solution was subjected to column chromatography on silica gel using methylene chloride–diethyl ether (20:1) as eluent (unless otherwise stated).

6-Benzylandrosta-4,6-diene-3,17-dione (IIIa). Yield 33.0 mg (88%), amorphous substance. ^{1}H NMR spectrum, δ, ppm: 7.19 m (5H), 5.97 br.s (1H), 5.88 s (1H), 3.58 d (1H, J = 15.9 Hz), 3.53 d (1H, J = 15.9 Hz), 2.44 m (4H), 2.16–2.00 m (3H), 1.89 m (1H), 1.70 m (3H), 1.52–1.24 m (4H), 1.11 s (3H), 0.95 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 219.4, 199.6, 162.2, 138.9, 138.0, 134.8, 128.5, 128.2, 126.3, 122.2, 50.8, 48.9, 48.2, 39.2, 36.8, 36.3, 35.6, 33.9, 33.4, 31.2, 21.3, 19.9, 16.2, 13.7. Found, %: C 83.15; H 7.85. $C_{26}H_{30}O_2$. Calculated, %: C 83.38; H 8.07.

6-(2-Chlorobenzyl)androsta-4,6-diene-3,17-dione (IIIb). Yield 34.8 mg (85%), amorphous substance. ^{1}H NMR spectrum, δ, ppm: 7.35 m (1H), 7.16 m (2H), 7.08 m (1H), 5.85 s (1H), 5.80 br.s (1H), 3.65 d (1H, J = 16.7 Hz), 3.59 d (1H, J = 16.7 Hz), 2.60–2.34 m (4H), 2.14–1.87 m (4H), 1.79–1.56 m (3H), 1.49–1.29 m (4H), 1.15 s (3H), 0.94 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 219.4, 199.6, 162.3, 137.8, 136.6, 134.2, 133.3, 129.9, 129.5, 127.9, 126.8, 121.7, 50.8, 48.8, 48.2, 36.8, 36.4 (2C), 35.6, 33.9, 33.5, 31.2, 21.2, 19.9, 16.3, 13.7. MALDI-TOF mass spectrum: m/z 409.18 $[M + H]^+$. $C_{26}H_{30}ClO_2$. Calculated: $[M + H]$ 409.19.

6-(4-Methylbenzyl)androsta-4,6-diene-3,17-dione (IIIc). Yield 36.9 mg (95%), amorphous substance. ^{1}H NMR spectrum, δ, ppm: 7.05 d (2H, J = 8.1 Hz), 7.00 d (2H, J = 8.1 Hz), 5.98 br.s (1H), 5.89 s (1H), 3.54 d (1H, J = 15.7 Hz), 3.48 d (1H, J = 15.7 Hz), 2.55–2.35 m (4H), 2.29 s (3H), 2.16–1.96 m (3H), 1.88 m (1H), 1.69 m (3H), 1.52–1.24 m (4H), 1.10 s (3H), 0.95 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 219.3, 199.5, 162.2, 137.7, 135.8, 135.7, 135.0, 129.1, 128.1, 122.2, 50.8, 49.0, 48.2, 38.8, 36.8, 36.3, 35.6, 34.0, 33.5, 31.3, 21.3, 20.9, 20.0, 16.2, 13.7. MALDI-TOF mass spectrum: m/z 389.23 $[M + H]^+$. $C_{27}H_{33}O_2$. Calculated: $[M + H]$ 389.25.

6-(2-Methoxybenzyl)androsta-4,6-diene-3,17-dione (IIId). Yield 33.8 mg (84%), amorphous substance. ^{1}H NMR spectrum, δ, ppm: 7.17 t.d (1H, J = 7.7, 1.7 Hz), 6.97 d.d (1H, J = 7.7, 1.7 Hz), 6.84 m (2H), 5.92 br.s (1H), 5.89 s (1H), 3.81 s (3H), 3.58 d (1H, J = 16.3 Hz), 3.47 d (1H, J = 16.3 Hz), 2.56–2.36 m (4H), 2.15–1.97 m (3H), 1.88 d.t (1H, J = 12.8, 3.0 Hz), 1.76–1.59 m (3H), 1.50–1.24 m (4H), 1.13 s (3H), 0.94 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 219.4, 200.0, 162.5, 157.1, 137.4, 134.6, 128.9, 127.5 (2C), 122.0, 120.4, 110.3, 55.3, 50.9, 49.0, 48.2, 36.8, 36.4, 35.6, 34.0, 33.5, 32.6, 31.4, 21.3, 20.0, 16.3, 13.8. MALDI-TOF mass spectrum: m/z 405.37 $[M + H]^+$. $C_{27}H_{33}O_3$. Calculated: $[M + H]$ 405.24.

6-(Trimethylsilylmethyl)androsta-4,6-diene-3,17-dione (IIIe) was synthesized using fourfold excess of trimethylsilylmethylzinc chloride. Yield 35 mg (94%), mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 5.85 s (1H), 5.81 br.s (1H), 2.58–2.30 m (4H), 2.10 m (2H), 1.98 m (1H), 1.88 m (1H), 1.75 d (1H, J = 14.5 Hz), 1.70 m (3H), 1.61 d (1H, J = 14.5 Hz), 1.46–1.15 m (4H), 1.10 s (3H), 0.94 s (3H), 0.04 s (9H). Found, %: C 74.33; H 9.36. $C_{23}H_{34}O_2Si$. Calculated, %: C 74.54; H 9.25.

6-(2-Chlorobenzyl)-3,20-dioxopregna-4,6-dien-17-yl acetate (IIIf). Yield 45.7 mg (92%), amorphous substance. ^{1}H NMR spectrum, δ, ppm: 7.34 m (1H), 7.15 m (2H), 7.07 m (1H), 5.84 s (1H), 5.73 s (1H), 3.65 d (1H, J = 16.7 Hz), 3.56 d (1H, J = 16.7 Hz),

2.93 m (1H), 2.60–2.40 m (2H), 2.28 m (1H), 2.10 s (3H), 2.04 s (3H), 1.88–1.57 m (8H), 1.38 m (3H), 1.13 s (3H), 0.69 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 203.7, 199.5, 170.6, 162.5, 139.5, 136.7, 134.3, 132.9, 130.0, 129.6, 127.9, 126.8, 121.6, 96.4, 50.2, 49.1, 47.5, 37.3, 36.4 (2C), 34.1, 33.5, 31.1, 30.3, 26.4, 23.2, 21.2, 20.3, 16.3, 14.3. MALDI-TOF mass spectrum: m/z 494.6 $[M]^+$. Found, %: C 72.64; H 7.11. $C_{30}H_{35}ClO_4$. Calculated, %: C 72.78; H 7.13. M 494.2.

17-(Trimethylsilylmethyl)androsta-4,16-dien-3-one (VIc). Reaction time 48 h. Yield 34.8 mg (98%), mp 118–121°C. ^{1}H NMR spectrum, δ, ppm: 5.71 s (1H), 5.15 m (1H), 2.48–2.21 m (4H), 2.10–1.93 m (2H), 1.91–1.77 m (2H), 1.75–1.55 m (4H), 1.54–1.38 m (2H), 1.33–0.92 m (5H), 1.19 s (3H), 0.74 s (3H), 0.01 s (9H). MALDI-TOF mass spectrum: m/z 356.25 $[M]^+$. Found, %: C 77.27; H 10.18. $C_{23}H_{36}OSi$. Calculated, %: C 77.46; H 10.18. M 356.26.

3-Benzylandrosta-3,5-dien-17-yl acetate (IXa). Reaction time 72 h. The product was purified using methylene chloride as eluent. Yield 32.5 mg (80%), mp 149°C. ^{1}H NMR spectrum, δ, ppm: 7.29–7.10 m (5H), 5.76 s (1H), 5.33 m (1H), 4.59 d.d (1H, J = 7.8, 1.3 Hz), 3.31 s (2H), 2.22–2.10 m (2H), 2.02 s (3H), 1.96–1.85 m (1H), 1.80–1.71 m (2H), 1.70–0.94 m (12H), 0.90 s (3H), 0.81 s (3H). Found, %: C 83.15; H 8.63. $C_{28}H_{36}O_2$. Calculated, %: C 83.12; H 8.97.

3-(2-Chlorobenzyl)androsta-3,5-dien-17-yl acetate (IXb). Reaction time 72 h. The product was purified using methylene chloride as eluent. Yield 37.2 mg (85%), glassy solid. ^{1}H NMR spectrum, δ, ppm: 7.32 d (1H, J = 7.3 Hz), 7.17–7.10 m (3H), 5.64 s (1H), 5.29 m (1H), 4.59 t (1H, J = 8.4 Hz), 3.44 s (2H), 2.20–1.93 m (4H), 2.02 s (3H), 1.78–0.96 m (13H), 0.91 s (3H), 0.81 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 171.2, 141.7, 137.6, 134.5, 134.4, 130.8, 129.4, 127.4, 126.6, 126.0, 121.7, 82.8, 51.3, 48.3, 42.5, 40.7, 36.8, 34.9, 34.1, 31.7, 31.3, 27.5, 26.2, 23.5, 21.1, 20.6, 19.0, 12.0. MALDI-TOF mass spectrum: m/z 437.5 $[M - H]^+$. Calculated: M 437.2.

3-(4-Methylbenzyl)androsta-3,5-dien-17-yl acetate (IXc). Reaction time 40 h. Yield 36.3 mg (87%), glassy solid. ^{1}H NMR spectrum, δ, ppm: 7.06 d (2H, J = 8.1 Hz), 7.03 d (2H, J = 8.1 Hz), 5.76 s (1H), 5.32 m (1H), 4.59 t (1H, J = 8.4 Hz), 3.27 s (2H), 2.30 s (3H), 2.18–0.95 m (17H), 2.02 s (3H), 0.89 s (3H), 0.81 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 171.2, 141.9, 136.9, 136.1, 135.4, 129.0 (2C), 128.7 (2C), 125.5, 121.5, 82.7, 51.3, 48.3, 43.6, 42.5, 36.8, 34.9, 34.2, 31.7, 31.4, 27.6, 25.9, 23.5, 21.1, 21.0, 20.6, 19.0, 12.1. MALDI-TOF mass spectrum: m/z 418.3 $[M]^+$. Calculated: M 418.4.

3-(4-Methylbenzyl)androsta-3,5-dien-17-ol (IXd) was synthesized using fourfold excess of benzylzinc bromide. Reaction time 72 h. Yield 32.6 mg (86%), mp 133–135°C. ^{1}H NMR spectrum, δ, ppm: 7.06 d (2H, J = 8.3 Hz), 7.03 d (2H, J = 8.3 Hz), 5.76 s (1H), 5.33 m (1H), 3.63 t (1H, J = 8.5 Hz), 3.27 s (2H), 2.30 s (3H), 2.18–1.55 m (10H), 1.48–1.23 m (4H), 1.16–0.94 m (4H), 0.90 s (3H), 0.76 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 141.9, 136.9, 136.1, 135.4, 128.9 (2C), 128.7 (2C), 125.5, 121.6, 81.9, 51.6, 48.5, 43.6, 42.9, 36.6, 34.9, 34.2, 31.9, 31.4, 30.5, 25.9, 23.4, 21.0, 20.7, 19.0, 11.0.

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