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Systematic investigation on the synthesis of androstane-based 3-, 11- and 17-carboxamides via palladium-catalyzed aminocarbonylation

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ABSTRACT

3,17-Dicarboxamido-androst-3,5,16-triene, 3-carboxamido-androst-3,5-dien-17-one, 17-carboxamido-androst-4,16-dien-3-one and 11-carboxamido-androst-5,9(11)-dien-3,17-dione derivatives were synthesized in homogeneous carbonylation reactions from the corresponding 3,17-diiodo-androst-3,5,16-triene, 3-iodo-androst-3,5-diene-17-ethylene ketal, 17-iodo-androst-5,16-dien-3-ethylene ketal, 11-iodo-androst-5,9(11)-diene-3,17-bis(ethylene ketal) derivatives, respectively. A highly chemoselective palladium-catalyzed aminocarbonylation of the corresponding iodo-alkene, carried out under mild reaction conditions, can be considered as the key-step for the introduction of the carboxamide functionalities. The synthesis of the iodo-alkene substrate is based on the transformation of the corresponding keto derivative to hydrazone, which was treated with iodine in the presence of a base (1,1,3,3-tetramethyl guanidine). The aminocarbonylation reaction is highly tolerant towards the *N*-nucleophiles, i.e. various primary and secondary amines including amino acid methyl esters can also be used.

1. Introduction

The homogeneous catalytic reactions are widely used both for the synthesis of simple building blocks and for the functionalization of various skeletons, among them biologically important backbones [1–3]. As for the steroidal skeleton, there is an increasing interest in developing new strategies to introduce functional groups into specific positions (especially into 3-, 11- and 17-positions) of the steroidal framework in order to improve their pharmacological efficacy. Starting from the 1970s, various transition metal catalyzed reactions have been used for the selective modification of the steroidal backbone. As first examples hydrogenation and various carbonylation reactions were used, recently dihydroxylations and several types of coupling reactions proved to sufficient both for the construction of a steroid framework or for the functionalization of the steroidal skeleton [4].

The synthesis of steroidal carboxamides, possessing the amide functionality either at the A- or the D-ring at the distinguished position-3 and 17, respectively [5–11], is in the forefront of the palladium-catalyzed homogeneous reactions. Their importance lies in the chance of tuning their pharmacological activity as 5α-reductase inhibitors [12–15]. Recently, aminocarbonylation with *in situ* formed palladium catalysts was successfully carried out even at the more hindered 12- and 11-positions of the C-ring [16,17]. A seminal work on the transformation of steroidal 11-ketones was carried out by Stéphan et al. Various key intermediates were prepared in methylenation [18], alkinylation [19], aryl- and alkyl-lithium additions [20,21], and allylation by allyl-Grignard reagents [22].

In the present paper, we report on the efficient synthesis of novel androstene derivatives bearing carboxamide functionalities either at 3-, 11- and/or 17-positions. A systematic investigation on the selective synthesis of carboxamides with additional keto functionalities, suitable for further transformations at distinguished positions, was carried out.

2. Experimental

PPh_3, 1,1,3,3-tetramethylguanidine (TMG) and adrenosterone (**16**) were purchased from Aldrich. Androst-4-ene-3,17-dione (**1**), a well-known starting compound for the production of several pharmaceutically active steroids, was produced by bioconversion of fitosterols in Gedeon Richter Plc.

Commercial Et3N, primary and secondary amines including amino acid esters (Aldrich) were used without further purification. Toluene and DMF were dried according to standard procedures.

The steroidal mono- and diketals (**5**, **11** and **10**, **17**, respectively) were synthesized according to modified conventional synthetic

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procedures [23] using the corresponding keto derivatives as starting materials. The transformation of the keto functionality to iodo-alkene moiety was carried out by the modification of the Barton's methodology [24,25]. Owing to differences to the previously published methods, a detailed description of these syntheses will be given below.

The 1H and 13C NMR spectra were recorded on a VARIAN INOVA 400 spectrometer at 400 and 100.58 MHz, respectively. The chemical shifts are given as δ values (ppm) and referenced to tetramethylsilane. TLC analyses were carried out by using Merck TLC sheets (Silica gel 60 F_{254}) and chloroform, chloroform/ethanol, and ethyl acetate/methanol mixtures were used as appropriate eluents. (The exact ratios are given at the corresponding synthetic procedures.) Mass-spectrometry data have been obtained by using a GC–MS system consisting of a Perkin Elmer AutoSystem XL gas-chromatograph and Perkin Elmer TurboMass mass spectrometer.

2.1. Synthesis of 3,17-diiodo-androst-3,5,16-triene (**3**)

Androst-4-en-3,17-dione (**1**) (5 g, 17.5 mmol), freshly distilled hydrazine hydrate (98%, 8.92 g, 178.4 mmol) and barium oxide (100 mg) in 2-methoxy-ethanol (80 mL) were heated for 2 days at 160 °C. After completion of the reaction the mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed with water, and brine. It was dried over sodium sulfate and evaporated to give the 3,17-bis-hydrazone derivative (**2**). The product was used in the next step without further purification.

To a stirred solution of iodine (17.80 g, 70.1 mmol) in dichloromethane (80 mL) solution of **2** (5 g, 15.9 mmol) and 1,1,3,3-tetramethylguanidin (TMG, 16.50 g, 143.3 mmol) in dichloromethane (30 mL) was added drop-wise at room temperature. After the addition was completed, the mixture was stirred for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto water and extracted with ether. The combined organic layer was washed with 1 N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. Purification by column chromatography (silicagel, hexane:EtOAc 99:1) gave pure **3** as a pale yellow solid material. Yield: 1.38 g; 17.1%.

2.2. Synthesis of androst-4-ene-3-one-17-ethylene ketal (**5**)

A solution of androst-4-en-3,17-dione (**1**) (5.98 g, 20.9 mmol) in chloroform (100 mL) and 1.40 mL (1.56 g, 25.1 mmol) of ethylene glycol containing *p*-toluene-sulfonic acid (40 mg) was stirred under reflux for a day in a Dean–Stark water separator. The reaction mixture was cooled neutralized and washed with 5% aqueous NaOH and water. It was dried on sodium sulfate, evaporated and purified by column chromatography (silicagel, petroleum ether (40–70 °C):EtOAc 7:3). Pure **5** as a white solid material was obtained. Yield: 3.12 g; 45.3%.

2.3. Synthesis of androst-5-ene-17-one-3-ethylene ketal (**11**)

A solution of androst-4-en-3,17-dione (**1**) (10 g, 35.0 mmol) in chloroform (150 mL) and 4.70 mL (5.24 g, 84.4 mmol) of ethylene glycol containing *p*-toluene-sulfonic acid (150 mg) was stirred under reflux for a day in a Dean–Stark water separator. The reaction mixture was cooled, neutralized and washed with 5% aqueous NaOH and water. It was dried on sodium sulfate, evaporated and purified by column chromatography (silicagel, petroleum ether 40–70 °C:EtOAc 75:25). Pure 3,17-diketal (**10**) as a white solid material was obtained. Yield: 8.50 g; 65.1%.

To a solution of **10** (5 g, 13.4 mmol) in acetone (500 mL) and water (50 mL), 1 N aqueous HCl (10 mL) was added and stirred overnight at room temperature. After addition of saturated $NaHCO_3$ (200 mL), the mixture was concentrated under reduced pressure. The residue was dissolved in chloroform (150 mL), washed with water and brine, dried on sodium sulfate and evaporated. Purification by column chromatography (silicagel, petroleum ether (40–70 °C):EtOAc 75:25) gave pure **11** as a white solid material. Yield: 1.76 g; 39.8%.

2.4. Synthesis of 3-iodo-androst-3,5-diene-17-ethylene ketal (**7**)

Androst-4-ene-3-one-17-ethylene ketal (**5**) (5 g, 25.2 mmol), freshly distilled hydrazine hydrate (98%, 3.86 g, 77.3 mmol) and barium oxide (100 mg) in 2-methoxy-ethanol (70 mL) were heated for 2 days at 160 °C. After completion of the reaction the mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed with water, and brine. It was dried over sodium sulfate and evaporated to give the 3-hydrazone derivative (**6**). The product was used in the next step without further purification.

To a stirred solution of iodine (6.50 g, 25.6 mmol) in dichloromethane (50 mL) 1,1,3,3–tetramethylguanidin (TMG, 12.05 g, 104.6 mmol) was added slowly and cooled by iced water bath during the addition. The solution of **6** (4 g, 11.6 mmol) in dichloromethane (20 mL) was added drop-wise at room temperature. After the addition was completed, the mixture was stirred for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed with 1 N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. Purification by column chromatography (silicagel, petroleum ether (40–70 °C):EtOAc 7:3) gave pure **7** as a pale yellow solid material. Yield: 1.59 g; 31.1%.

2.5. Synthesis of 17-iodo-androst-5,16-diene-3-ethylene ketal (**13**)

The 17-keto-3-ketal derivative (**11**) (3.3 g, 10 mmol) was transformed to the corresponding 17-iodo-16-ene derivative (**13**) via 17-hydrazone (**12**) according to the procedure described for **7**. Yield: 1.54 g; 35%.

2.6. Synthesis of androst-5-ene-11-one-3,17-bis(ethylene ketal) (**17**)

A solution of adrenosterone (**16**) (5 g, 16.6 mmol) in chloroform (100 mL) and 2.23 mL (2.48 g, 40 mmol) of ethylene glycol containing *p*-toluene-sulfonic acid (40 mg) was stirred under reflux for a day in a Dean–Stark water separator. The reaction mixture was cooled, neutralized and washed with 5% aqueous NaOH and water. It was dried on sodium sulfate, evaporated and purified by column chromatography (silicagel, petroleum ether 70 °C:EtOAc 7:3). Pure **17** as a white solid material was obtained. Yield: 2.82 g; 43.8%.

2.7. Synthesis of 11-iodo-androst-5,9(11)-diene-3,17-bis(ethylene ketal) (**19**)

Androst-5-ene-11-one-3,17-bis(ethylene ketal) (**17**) (5.50 g, 14.2 mmol), freshly distilled hydrazine hydrate (98%, 60.24 g, 1.21 mol) and barium oxide (100 mg) in di(ethylene glycol) methyl ether (80 mL) were heated for 5 days at 195 °C. After completion of the reaction the mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed

with water, and brine. It was dried over sodium sulfate and evaporated to give the 11-hydrazone derivative (**18**). The product was used in the next step without further purification.

To a stirred solution of iodine (5.61 g, 22.1 mmol) in dichloromethane (50 mL) 1,1,3,3–tetramethylguanidin (TMG, 10.90 g, 94.7 mmol) was added slowly and cooled by iced water bath during the addition. The solution of **18** (4.23 g, 10.5 mmol) in dichloromethane (20 mL) was added drop-wise at room temperature. After the addition was completed, the mixture was stirred for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed with 1N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. Purification by column chromatography (silicagel, petroleum ether 70 °C:EtOAc 7:3) gave pure (**19)** as an orange oil. Yield: 0.86 g; 16.4%.

2.8. General procedure for aminocarbonylation at atmospheric pressure

A mixture of **7** (or **13** or **19**) (1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol), and PPh_3 (13.1 mg, 0.05 mmol) were dissolved in 10 mL DMF under argon. NEt_3 (0.5 mL) and *tert*-butylamine (0.30 mL, 3 mmol) (or another *N*-nucleophile) were added. (The amino acid methyl esters (**e**–**g**) were used as hydrochloride salts (1.1 mmol) and were added together with the catalyst.) The atmosphere was changed to CO (1 bar), and the reaction was conducted at 50 °C for the appropriate reaction time (see Table 1). The composition of the reaction mixture was checked by TLC. The solvent was evaporated, and the residue was dissolved in 20 mL of $CHCl_3$. It was washed in turn with 2 mL × 20 mL of water, 20 mL portions of 5% HCl, saturated $NaHCO_3$, and brine. The organic layer was separated, dried over Na_2SO_4 and evaporated. Column chromatography (silica gel, $CHCl_3$/EtOAc 98/2, 95/5, 90/10, or 80/20; the exact ratios are given below) resulted in the target carboxamides (**8**, **14**, and **20**).

The diiodo substrate **3** (0.5 mmol) was dissolved in 10 mL of 2-butanone. The other reagents and precatalysts were used in the amount as given above. The work-up procedure was also identical and resulted in carboxamides **4**.

2.9. Analytical and spectroscopic data of compounds

2.9.1. Ketals

Androst-4-ene-3-one-17-ethylene ketal (**5**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.68 (br s, 1H, 4-C*H*); 3.79–3.91 (m, 4H, O(CH_2)$_2$O); 0.88–2.42 (m, 19H, skeleton protons); 1.16 (s, 3H, 19-CH_3); 0.85 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.3; 171.1; 123.8; 119.0; 65.2; 64.5; 53.6; 49.7; 45.7; 38.6; 35.8; 35.7; 34.0; 33.9; 32.7; 31.3; 30.3; 22.6; 20.4; 17.4; 14.2. MS (*m*/*z*/rel.int.): 330/34 (M^+), 285/4, 266/9, 99/100. IR (KBr, (cm^{-1})): 1672 (C=O), 1619 (C=C). Analysis calculated for $C_{21}H_{30}O_3$ (*M* = 330.47): C, 76.33; H, 9.15; Found: C, 76.21; H, 9.01. R_f = 0.73 (petroleum ether (40–70)/EtOAc = 7/3). Mp. 168–170 °C. White powder-like material (as obtained after column chromatography).

Androst-5-ene-17-one-3-ethylene ketal (**11**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.35 (br s, 1H, 6-C*H*); 3.85–3.95 (m, 4H, O(CH_2)$_2$O); 0.98–2.56 (m, 19H, skeleton protons); 1.02 (s, 3H, 19-CH_3); 0.85 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.9; 140.4; 121.3; 109.3; 64.4; 64.2; 51.8; 49.9; 47.5; 41.8; 36.8; 36.3; 35.8; 31.5; 31.4; 31.0; 30.7; 21.9; 20.3; 18.9; 13.5. MS (*m*/*z*/rel.int.): 330/3 (M^+), 99/100. IR (KBr, (cm^{-1})): 1738 (C=O). Analysis calculated for $C_{21}H_{30}O_3$ (*M* = 330.47): C, 76.33; H, 9.15; Found: C, 76.42; H, 9.41. R_f = 0.79 (petroleum ether (40–70)/EtOAc = 75/25). Mp. 195–1197 °C. White powder-like material (as obtained after column chromatography).

Androst-5-ene-11-one-3,17-bis(ethylene ketal) (**17**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.30 (br s, 1H, 6-C*H*); 3.76–3.94 (m, 9H, 2xO(CH_2)$_2$O + 9-C*H*); 2.50–2.62 (m, 2H, 12-CH_2); 1.14–2.12 (m, 14H, skeleton protons); 1.20 (s, 3H, 19-CH_3); 0.79 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 211.0; 141.2; 120.5; 117.9; 109.1; 65.3; 64.5; 64.3; 64.2; 60.4; 50.1; 48.9; 48.6; 41.6; 37.0; 35.1; 34.3; 33.8; 31.9; 30.8; 22.5; 18.0; 14.8. MS (*m*/*z*/rel.int.): 388/4 (M^+), 99/100. IR (KBr, (cm^{-1})): 1698 (C=O). Analysis calculated for $C_{23}H_{32}O_5$ (*M* = 388.50): C, 71.11; H, 8.30; Found: C, 70.95; H, 8.20. R_f = 0.45 (petroleum ether (40–70)/EtOAc = 7/3). Mp. 180–181 °C. White powder-like material.

2.9.2. Iodoalkenes

3,17-Diiodo-androst-3,5,16-triene (**3**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.55 (br s, 1H, 4-C*H*); 6.12 (br s, 1H, 16-C*H*); 5.36 (br s, 1H, 6-C*H*); 2.58–2.63 (m, 2H, 7-CH_2); 1.01–2.22 (m, 13H, skeleton

Table 1
Palladium-catalyzed aminocarbonylation of androstane-based iodo-alkene substrates **3**, **7**, **13** and **19**.[a]

Entry	Substr.	Amine	Amine:substrate ratio	Reaction time [h]	Conv.[b] [%]	Isolated yield (amide) [%]
1	**3**[d]	*t*-BuNH_2 (**a**)	3	20	>98[c]	78 (**4a**)
2	**3**[d]	piperidine (**c**)	1.5	90	>98[c]	80 (**4c**)
3	**3**[d]	morpholine (**d**)	1.5	200	>98[c]	77 (**4d**)
4	**3**[d]	morpholine (**d**)	1.5	90	>95[c]	74 (**4d**)
5	**3**[d]	ProOMe (**g**)	1.1	200	>98[c]	75 (**4g**)
6	**7**	aniline (**b**)	2	90	>98	80 (**8b**)
7	**7**	piperidine (**c**)	1.5	200	>98	80 (**8c**)
8	**7**	piperidine (**c**)	1.5	48	55	n.d.[e]
9	**7**	morpholine (**d**)	1.5	48	35	30 (**8d**)
10	**7**	ProOMe (**g**)	1.1	48	30	22 (**8g**)
11	**13**	*t*-BuNH_2 (**a**)	3	20	>98	82 (**14a**)
12	**13**	aniline (**b**)	2	20	>98	80 (**14b**)
13	**13**	piperidine (**c**)	1.5	20	60	41 (**14c**)
14	**13**	morpholine (**d**)	1.5	20	40	30 (**14d**)
15	**13**	GlyOMe (**e**)	1.1	20	>98	81 (**14e**)
16	**13**	AlaOMe (**f**)	1.1	20	>98	78 (**14f**)
17	**13**	ProOMe (**g**)	1.1	60	>98	77 (**14g**)
18	**19**	*t*-BuNH_2 (**a**)	3	90	>98	82 (**20a**)
19	**19**	piperidine (**c**)	1.5	90	30	20 (**20c**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol substrate; 10 mL DMF; reaction temp.: 50 °C; *p*(CO) = 1 bar (unless otherwise stated).
[b] Based on the iodoalkene substrate; determined by GC (unless otherwise stated).
[c] Based on the iodoalkene substrate; determined by ^{1}H NMR.
[d] 2-Butanone (10 mL) was used as solvent.
[e] Not determined.

protons); 1.00 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 142.8; 139.3; 137.6; 124.2; 112.8; 95.2; 55.0; 50.3; 48.6; 37.4; 36.5; 36.3; 34.7; 33.9; 31.1; 31.0; 21.0; 19.1; 15.4. MS (*m*/*z*/rel.int.): 506/100 (M^+), 491/3, 364/2, 219/12, 145/21. IR (KBr, (cm^{-1})): 1620, 1601 (C=C). Analysis calculated for $C_{19}H_{24}I_2$ (*M* = 506.21): C, 45.08; H, 4.78; Found: C, 45.23; H, 4.89. R_f = 0.90 (hexán/EtOAc = 99/1). Mp. 135–136 °C. Pale yellow crystalline material.

3-Iodo-androst-3,5-diene-17-ethylene ketal (**7**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.51 (br s, 1H, 4-C*H*); 5.32 (br s, 1H, 6-C*H*); 3.78–3.93 (m, 4H, –O(CH_2)$_2$O–); 2.55–2.63 (m, 2H, 7-CH_2); 0.80–2.24 (m, 15H, skeleton protons); 0.90 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 142.3; 139.3; 124.4; 119.3; 94.8; 65.2; 64.5; 50.7; 47.9; 45.8; 37.3; 36.3; 34.3; 34.2; 31.9; 30.9; 30.5; 22.6; 20.4; 18.9; 14.3. MS (*m*/*z*/rel.int.): 440/41 (M^+), 378/100, 352/66, 337/17, 99/68. IR (KBr, (cm^{-1})): 1620, 1603 (C=C). Analysis calculated for $C_{21}H_{29}O_2I$ (*M* = 440.36): C, 57.28; H, 6.64; Found: C, 57.12; H, 6.82. R_f = 0.83 (petroleum ether (40–70)/EtOAc = 7/3). Mp. 144–147 °C. Pale yellow crystalline material.

3-Iodo-androst-2,4-diene-17-ethylene ketal (**7′**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.17 (br s, 1H, 2-C*H*); 5.68 (br s, 1H, 4-C*H*); 3.80–3.94 (m, 4H, –O(CH_2)$_2$O–); 2.53–2.62 (m, 2H, 1-CH_2); 0.80–2.24 (m, 15H, skeleton protons); 0.90 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 148.7; 131.4; 125.0; 119.2; 88.3; 65.2; 64.5; 54.3; 49.7; 45.8; 36.5; 36.4; 34.2; 34.1; 30.8; 30.5; 30.4; 22.7; 20.9; 17.0; 14.2. MS (*m*/*z*/rel.int.): 440/92 (M^+), 325/12, 395/7, 99/100. Analysis calculated for $C_{21}H_{29}O_2I$ (*M* = 440.36): C, 57.28; H, 6.64; Found: C, 57.07; H, 6.85. R_f = 0.79 (petroleum ether (40–70)/EtOAc = 7/3). Yellow viscous material (as obtained after column chromatography).

17-Iodo-androst-5,16-diene-3-ethylene ketal (13): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.12 (br s, 1H, 16-C*H*); 5.35 (br s, 1H, 6-C*H*); 3.88–3.97 (m, 4H, –O(CH_2)$_2$O–); 2.53–2.60 (m, 2H, 4-CH_2); 0.80–2.18 (m, 15H, skeleton protons); 1.05 (s, 3H, 19-CH_3); 0.75 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 140.6; 137.5; 121.6; 112.7; 109.4; 64.4; 64.2; 54.8; 50.1; 49.9; 41.8; 36.9; 36.2; 36.1; 33.7; 31.1; 31.0 (double intensity); 20.8; 18.8; 15.1. MS (*m*/*z*/rel.int.): 440/5 (M^+), 99/100, 55/8. IR (KBr, (cm^{-1})): 1577 (C=C). Analysis calculated for $C_{21}H_{29}O_2I$ (*M* = 440.36): C, 57.28; H, 6.64; Found: C, 57.01; H, 6.80. Mp. 183–186 °C. Pale yellow crystalline material.

11-Iodo-androst-5,9(11)-diene-3,17-bis(ethylene ketal) (**19**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.57 (d, 6.2 Hz, 1H, 4-C*H*); 3.80-3.98 (m, 8H, O(CH_2)$_2$O); 3.62 (dt, 13.5 Hz, 3.5 Hz, 1H); 3.20 (dd, 16.3 Hz, 3.2 Hz, 1H); 2.70 (d, 16.4 Hz, 1H); 2.58 (d, 13.5 Hz, 1H); 1.22–2.15 (m, 12H, skeleton protons); 1.41 (s, 3H, 19-CH_3); 0.90 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 145.2; 139.6; 121.3; 118.4; 109.1; 93.5; 65.2; 64.4; 64.3; 64.2; 55.2; 51.7; 47.5; 45.3; 42.5; 41.9; 40.8; 34.1; 32.6; 29.4; 23.5; 20.1; 13.9. MS (*m*/*z*/rel.int.): 498/2 (M^+), 371/3, 99/100. Analysis calculated for $C_{23}H_{31}O_4I$ (*M* = 498.40): C, 55.43; H, 6.27; Found: C, 55.23; H, 6.40. R_f = 0.72 (petroleum ether (40–70)/EtOAc = 7/3). Orange oil (as obtained after column chromatography).

2.10. Carboxamides

3,17-Di-(*N*-*tert*-butylcarboxamido)-androst-3,5,16-triene (**4a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.66 (br s, 1H, NH); 6.20 (br s, 1H, 16-C*H*); 5.69 (br s, 1H, NH); 5.52 (br s, 1H, 6-C*H*); 5.45 (br s, 1H, 4-CH); 0.96–2.40 (m, 15H, skeleton protons); 1.34 (s, 9H, *t*Bu); 1.32 (s, 9H, *t*Bu); 1.02 (s, 3H, 19-CH_3); 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 167.7; 165.6; 151.7; 141.2; 134.1; 132.7; 129.6; 129.0; 56.8; 51.1; 48.4; 46.5; 34.9; 34.7; 33.4; 31.7; 31.3; 30.0; 28.9; 28.8; 22.0; 20.7; 18.8; 16.4. MS (*m*/*z*/rel.int.): 452/100 (M^+), 395/21, 380/30, 324/12. IR (KBr, (cm^{-1})): 1645 (CON); 1596 (C=C). Analysis calculated for $C_{29}H_{44}O_2N_2$ (*M* = 452.68): C, 76.95; H, 9.80; N, 6.19; Found: C, 76.81; H, 9.95; N, 5.96. R_f = 0.74 ($CHCl_3$/EtOH = 8/2). Mp. 116–118 °C. White crystalline material (as obtained after column chromatography).

3,17-Bis(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-3,5,16-triene (**4c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.92 (br s, 1H, 16-C*H*); 5.63 (br s, 1H, 6-C*H*); 5.44 (br s, 1H, 4-C*H*); 3.35–3.60 (m, 8H, 2xN(CH_2)$_2$); 0.90–2.30 (m, 21H, skeleton protons+ (CH_2)$_3$ (piperidine)); 1.02 (s, 3H, 19-CH_3); 0.94 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.3; 167.8; 148.9; 140.6; 130.8; 129.3; 128.4; 126.2; 56.8; 48.5; 48.4 (br); 42.3 (br); 34.9; 34.1; 33.3; 32.0; 31.6; 30.1; 26.2 (br); 24.7; 23.8; 20.6; 19.0; 16.7. IR (KBr, (cm^{-1})): 1628 (CON); 1597 (C=C). Analysis calculated for $C_{31}H_{44}O_2N_2$ (*M* = 476.70): C, 78.11; H, 9.30; N, 5.88; Found: C, 78.01; H, 9.46; N, 5.60. R_f = 0.57 ($CHCl_3$/EtOAc = 7/3). Pale-yellow viscous material (as obtained after column chromatography).

3,17-Bis(*N*,*N*-3-oxapentan-1,5-diylcarboxamido)-androst-3,5,16-triene (4d): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.14 (br s, 1H, 16-C*H*); 6.01 (br s, 1H, 4-C*H*); 5.55 (br s, 1H, 6-C*H*); 3.66 (br s, 8H, 2xO(CH_2)$_2$); 3.59 (br s, 8H, 2xN(CH_2)$_2$); 1.00–2.38 (m, 15H, skeleton protons); 0.99 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.7; 170.5; 140.7; 137.6; 130.0; 127.3; 116.2; 112.8; 67.2 (double intensity); 55.1; 54.0 (br); 50.3; 48.7; 46.5 (br); 36.4; 36.3; 35.2; 33.9; 31.5; 31.0; 23.9; 21.0; 19.3; 15.4. IR (KBr, (cm^{-1})): 1610 (v br, CON, C=C). Analysis calculated for $C_{29}H_{40}O_4N_2$ (*M* = 480.65): C, 72.47; H, 8.39; N, 5.83; Found: C, 72.21; H, 8.49; N, 5.62. R_f = 0.73 ($CHCl_3$/EtOAc = 1/1). Orange viscous material (as obtained after column chromatography).

3,17-Bis(*N*,*N*-(1′-Methoxycarbonyl-butan-1,4-diyl)-carboxamido)-carboxamido-androst-3,5,16-triene (4g): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.12 (br s, 1H, 16-C*H*); 6.00 (br s, 1H, 4-CH); 5.58 (br s, 1H, 6-C*H*); 5.52 (br s, 2H, NC*H*); 3.72 (s, 6H, 2x OCH_3); 3.58–3.70 (m, 4H, 2xNCH_2); 0.80–2.45 (m, 23H, skeleton protons+ 2x(CH_2)$_2$ (proline)); 0.98 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.3; 173.1; 170.8; 169.2; 146.8; 141.1; 137.7; 137.6; 116.0; 112.8; 59.0; 55.1; 54.4; 52.4; 50.3; 48.7; 36.4; 35.5; 35.2; 34.0; 33.9; 33.6; 33.5; 31.6; 31.3; 31.1; 31.0; 29.5; 25.6; 23.3; 21.0; 19.2; 15.4. IR (KBr, (cm^{-1})): 1743 (C=O); 1618 (v br, CON, C=C). Analysis calculated for $C_{33}H_{44}O_6N_2$ (*M* = 564.72): C, 70.19; H, 7.85; N, 4.96; Found: C, 70.03; H, 7.96; N, 4.71. R_f = 0.73 ($CHCl_3$/EtOAc = 8/2). Yellow viscous material (as obtained after column chromatography).

3-(*N*-phenylcarboxamido)-androst-3,5-diene-17-(ethylene ketal) (8b): ^{1}H NMR ($CDCl_3$, 400 MHz): 7.52–7.62 (m, 2H, Ph(*ortho*)); 7.30–7.38 (m, 2H, Ph(*meta*)); 7.12 (t, 7.4 Hz, 1H, Ph(*para*)); 6.85 (br s, 1H, 4-CH); 5.80 (br s, 2H, 6-CH + NH); 3.80–3.95 (m, 4H, OCH_2CH_2O); 0.80–2.56 (m, 17H, skeleton protons); 0.91 (s, 3H, 18-CH_3); 0.95 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 166.4; 140.8; 138.1; 134.1; 130.8; 129.9; 124.0; 119.9; 119.3; 114.3; 65.2; 64.5; 54.6; 50.6; 49.8; 47.8; 45.8; 36.5; 34.7; 34.1; 33.4; 30.4; 22.6; 21.1; 20.5; 19.0; 14.3. MS (*m*/*z*/rel.int.): 433/30 (M^+), 371/13; 341/100; 99/28. IR (KBr, (cm^{-1})): 1659 (CON). Analysis calculated for $C_{28}H_{35}O_3N$ (*M* = 433.59): C, 77.56; H, 8.14; N, 3.23; Found: C, 77.37; H, 8.40; N, 3.01. R_f = 0.70 ($CHCl_3$/EtOAc = 95/5). Mp. 137–139 °C. Pale brown solid material.

3-(*N*-phenylcarboxamido)-androst-2,4-diene-17-(ethylene ketal) (8′b): ^{1}H NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): 7.50–7.62 (m, 2H, Ph(*ortho*)); 7.30–7.40 (m, 3H, Ph(*meta*)); 7.10 (t, 7.4 Hz, 1H, Ph(*para*)); 6.81 (br s, 1H, 2-CH); 6.01 (br s, 1H, NH); 5.96 (br s, 1H, 4-CH); 3.80–3.92 (m, 4H, OCH_2CH_2O); 0.80–2.50 (m, 17H, skeleton protons); 0.93 (s, 3H, 18-CH_3); 0.97 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 165.3; 148.4; 140.8; 138.0; 134.3; 131.7; 130.0; 127.3; 119.3; 114.8; 64.5; 63.7; 54.7; 50.8; 48.0; 45.7; 37.3; 35.8; 34.6; 34.1; 31.5; 30.6; 22.0; 21.0; 17.3; 13.7.

MS (*m*/*z*/rel.int.): 433/81 (M^+), 341/40; 281/39; 207/35; 99/100. (Identified in the 15/85 mixture of **8′b**/**8c**.)

3-(*N,N*-pentan-1,5-diylcarboxamido)-androst-3,5-diene-17-(ethylene ketal) (8c): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.89 (br s, 1H, 4-CH); 5.41 (br s, 1H, 6-CH); 3.73–3.90 (m, 4H, OCH_2CH_2O); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.30 (m, 23H, skeleton protons+ $(CH_2)_3$); 0.89 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.3; 140.2; 130.7; 128.6; 119.3; 116.1; 65.1; 64.5; 54.6; 50.7; 49.8; 48.0; 45.8; 37.2; 36.5; 34.7; 34.1; 33.4; 32.0; 31.3; 30.6; 24.7; 23.8; 22.7; 20.4; 19.1; 14.2. MS (*m*/*z*/rel.int.): 425/100 (M^+), 363/14; 324/15; 99/38. IR (KBr, (cm^{-1})): 1633 (CON). Analysis calculated for $C_{27}H_{39}O_3N$ (M = 425.61): C, 76.20; H, 9.24; N, 3.29; Found: C, 76.00; H, 9.41; N, 3.11. R_f = 0.58 ($CHCl_3$/EtOAc = 8/2). Yellow highly viscous material.

3-(*N,N*-pentan-1,5-diylcarboxamido)-androst-2,4-diene-17-(ethylene ketal) (8′c): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.70 (br s, 1H, 2-CH); 5.47 (br s, 1H, 4-CH); 3.75-3.90 (m, 4H, OCH_2CH_2O); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.30 (m, 23H, skeleton protons+ $(CH_2)_3$); 0.89 (s, 3H, 18-CH_3); 0.79 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 170.0; 147.0; 131.9; 126.5; 122.8; 119.2; 65.1; 64.4; 54.6; 50.7; 49.8; 48.0; 45.8; 37.8; 36.5; 34.7; 34.1; 33.4; 32.0; 31.2; 30.5; 24.6; 23.8; 22.6; 21.1; 19.1; 14.2. MS (*m*/*z*/rel.int.): 425/80 (M^+), 424/100; 380/53; 362/13; 99/71. IR (KBr, (cm^{-1})): 1633 (CON). (Identified in the 15/85 mixture of **8′c**/**8c**.)

3-(*N,N*-3-oxapentan-1,5-diylcarboxamido)-androst-3,5-diene-17-(ethylene ketal) (8d): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.97 (br s, 1H, 4-CH); 5.52 (br s, 1H, 6-CH); 3.76–3.92 (m, 4H, OCH_2CH_2O); 3.62 (br s, 4H, $O(CH_2)_2$); 3.55 (br s, 4H, $N(CH_2)_2$); 0.80–2.36 (m, 17H, skeleton protons); 0.90 (s, 3H, 18-CH_3); 0.84 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.7; 140.3; 130.2; 129.8; 119.5; 116.0; 67.2; 67.1; 65.4; 64.7; 54.8; 50.9; 48.2; 46.0; 37.4; 35.0; 34.3; 33.6; 32.2; 31.5; 30.8; 24.0; 22.9; 20.7; 19.3; 14.5. MS (*m*/*z*/rel.int.): 427/71 (M^+), 382/38; 99/100. IR (KBr, (cm^{-1})): 1632 (CON). Analysis calculated for $C_{26}H_{37}O_4N$ (*M* = 427.58): C, 73.03; H, 8.72; N, 3.28; Found: C, 72.88; H, 8.89; N, 3.10. R_f = 0.50 ($CHCl_3$/EtOAc = 7/3). Mp. 106–108 °C. Yellow crystalline material.

3-(*N,N*-3-oxapentan-1,5-diylcarboxamido)-androst-2,4-diene-17-(ethylene ketal) (8′d): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.78 (br s, 1H, 2-CH); 5.52 (br s, 1H, 4-CH); 3.76–3.90 (m, 4H, OCH_2CH_2O); 3.62 (br s, 4H, $O(CH_2)_2$); 3.55 (br s, 4H, $N(CH_2)_2$); 0.80–2.36 (m, 17H, skeleton protons); 0.90 (s, 3H, 18-CH_3); 0.82 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 170.3; 147.8; 132.2; 131.4; 128.7; 119.5; 67.2; 67.1; 65.4; 64.7; 54.8; 50.0; 48.2; 46.0; 38.1; 36.7; 34.4; 33.6; 32.2; 31.6; 30.7; 24.0; 22.8; 21.3; 17.6; 14.5. (Identified in the 22/78 mixture of **8′d**/**8d**.)

3-(*N,N*-(1′-methoxycarbonyl-butan-1,4-diyl)-carboxamido)-androst-3,5-diene-17-(ethylene ketal) (8g): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.12 (br s, 1H, 4-CH); 5.50 (br s, 1H, 6-CH); 4.40–4.49 (m, 1H, NCH); 3.75–3.90 (m, 4H, OCH_2CH_2O); 3.63 (s, 3H, OCH_3); 3.50–3.62 (m, 2H, $N(CH_2)_2$); 0.80–2.36 (m, 21H, skeleton protons+ $(CH_2)_2$); 0.90 (s, 3H, 18-CH_3); 0.82 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.1; 169.3; 140.7; 131.8; 128.1; 119.5; 115.8; 65.4; 64.7; 58.9; 54.8; 50.9; 48.2; 46.0; 37.3; 34.9; 34.3; 33.6; 32.2; 31.6; 30.8; 23.3; 22.9; 22.8; 21.3; 20.8; 19.2; 14.5. MS (*m*/*z*/rel.int.): 469/26 (M^+); 429/17; 341/60; 281/100. IR (KBr, (cm^{-1})): 1740 (C=O); 1628 (CON). Analysis calculated for $C_{28}H_{39}O_5N$ (M = 469.62): C, 71.61; H, 8.37; N, 2.98; Found: C, 71.50; H, 8.59; N, 2.73. R_f = 0.63 ($CHCl_3$/EtOAc = 7/3). Mp. 146–148 °C. Pale yellow crystalline material.

3-(*N*-phenylcarboxamido)-androst-3,5-diene-17-one (9b): ^{1}H NMR ($CDCl_3$, 400 MHz): 7.52–7.60 (m, 2H, Ph(*ortho*)); 7.29–7.38 (m, 2H, Ph(*meta*)); 7.10 (t, 7.4 Hz, 1H, Ph(*para*)); 6.90 (br s, 1H, 4-CH); 6.40 (br s, 1H, NH); 5.80 (br s, 2H, 6-CH); 0.85–2.60 (m, 17H, skeleton protons); 0.92 (s, 3H, 18-CH_3); 0.98 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.9; 166.2; 140.9; 138.0; 134.2; 130.0; 129.0; 124.1; 120.0; 119.3; 54.8; 51.8; 50.9; 49.1; 47.7; 35.8; 34.9; 33.4; 31.3; 31.2; 22.0; 20.4; 19.0; 13.7. MS (*m*/*z*/rel.int.): 389/29 (M^+), 297/100. IR (KBr, (cm^{-1})): 1733 (C=O); 1662 (CON); 1595 C=C). Analysis calculated for $C_{26}H_{31}O_2N$ (*M* = 389.54): C, 80.17; H, 8.02; N, 3.60; Found: C, 80.02; H, 8.25; N, 3.37. R_f = 0.78 ($CHCl_3$/EtOAc = 95/5). Beige viscous material.

3-(*N*-phenylcarboxamido)-androst-2,4-diene-17-one (9′b): MS (*m*/*z*/rel.int.): 389/100 (M^+), 374/25; 297/67; 281/71; 207/85. (Identified in the 8/92 mixture of **9′b**/**9b**.)

3-(*N,N*-pentan-1,5-diylcarboxamido)-androst-3,5-diene-17-one (9c): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.89 (br s, 1H, 4-CH); 5.42 (br s, 1H, 6-CH); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.41 (m, 23H, skeleton protons+ $(CH_2)_3$); 0.90 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.6; 171.2; 140.3; 131.0; 128.3; 125.8; 54.7; 51.7; 50.8; 48.2; 47.5; 37.7; 35.7; 34.7; 33.3; 31.3; 30.7; 26.1; 24.6; 23.7; 21.7; 20.2; 19.0; 17.2; 13.6. MS (*m*/*z*/rel.int.): 381/100 (M^+), 366/15; 297/22. IR (KBr, (cm^{-1})): 1736 (C=O); 1633 (CON); 1608 C=C). Analysis calculated for $C_{25}H_{35}O_2N$ (*M* = 381.56): C, 78.70; H, 9.25; N, 3.67; Found: C, 78.55; H, 9.43; N, 3.44. R_f = 0.49 ($CHCl_3$/EtOAc = 8/2). Mp. 102–103 °C. Yellow crystalline material.

3-(*N,N*-pentan-1,5-diylcarboxamido)-androst-2,4-diene-17-one (9′c): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.70 (br s, 1H, 2-CH); 5.48 (br s, 1H, 4-CH); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.41 (m, 23H, skeleton protons+ $(CH_2)_3$); 0.90 (s, 3H, 18-CH_3); 0.80 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.6; 169.8; 146.3; 131.8; 122.8; 116.4; 51.7; 50.8; 47.8; 47.5; 37.2; 35.7; 34.7; 33.3; 31.4; 31.0; 30.0; 26.1; 24.6; 23.7; 21.7; 20.8; 19.0; 17.2; 13.8. MS (*m*/*z*/rel.int.): 381/77 (M^+), 380/100; 365/40; 281/49; 207/65. (Identified in the 20/80 mixture of **9′c**/**9c**.)

3-(*N,N*-3-oxapentan-1,5-diylcarboxamido)-androst-3,5-diene-17-one (9d): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.00 (br s, 1H, 4-CH); 5.56 (br s, 1H, 6-CH); 3.64 (br s, 4H, $O(CH_2)_2$); 3.58 (br s, 4H, $N(CH_2)_2$); 0.80–2.36 (m, 17H, skeleton protons); 0.95 (s, 3H, 19-CH_3); 0.90 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.9; 171.7; 140.5; 130.2; 130.0; 119.3; 67.2; 52.1; 51.4 (br); 51.2; 48.5; 47.8 (br); 47.9; 42.5 (br); 36.0; 35.1; 34.1; 33.5; 31.6; 31.1; 30.3; 23.9; 22.0; 21.1; 20.5; 19.3; 13.9. MS (*m*/*z*/rel.int.): 383/100 (M^+), 297/70; 207/31. IR (KBr, (cm^{-1})): 1736 (C=O), 1611 (br, CON, C=C). Analysis calculated for $C_{24}H_{33}O_3N$ (*M* = 383.53): C, 75.16; H, 8.67; N, 3.65; Found: C, 75.08; H, 8.82; N, 3.46. R_f = 0.45 ($CHCl_3$/EtOAc = 7/3). Mp. 98–100 °C. Yellow crystalline material.

3-(*N,N*-3-oxapentan-1,5-diylcarboxamido)-androst-2,4-diene-17-one (9′d): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.84 (br s, 1H, 2-CH); 5.72 (br s, 1H, 4-CH); 3.64 (br s, 4H, $O(CH_2)_2$); 3.58 (br s, 4H, $N(CH_2)_2$); 0.80–2.36 (m, 17H, skeleton protons); 0.90 (s, 3H, 18-CH_3); 0.88 (s, 3H, 19-CH_3); MS (*m*/*z*/rel.int.): 383/20 (M^+); 382/23; 281/43; 207/100. (Identified in the 18/82 mixture of **9′d**/**9d**.)

17-(*N-tert*-butylcarboxamido)-androst-5,16-diene-3-ethylene ketal (14a): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.12 (br s, 1H, 16-CH); 5.43 (br s, 1H, NH); 5.24 (br d, 4.2 Hz, 1H, 6-CH); 3.80–3.92 (m, 4H, OCH_2CH_2O); 2.48 (br d, 14.1 Hz, 1H, 7-CH_a); 1.02–2.13 (m, 16H, skeleton protons); 1.30 (s, 9H, *t*Bu); 0.98 (s, 3H, 19-CH_3); 0.94 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 165.9; 152.0; 140.7; 134.3; 121.8; 109.5; 64.5; 64.3; 57.0; 51.2; 50.3; 46.6; 42.0; 36.9; 36.4; 34.9; 31.7; 31.5; 31.2; 30.4; 29.1 (triple intensity); 20.9; 18.9; 16.5. MS (*m*/*z*/rel.int.): 413/6 (M^+), 99/100. IR (KBr, (cm^{-1})): 1652 (CON); 1600 (C=C). Analysis calculated for $C_{26}H_{39}O_3N$ (*M* = 413.60): C, 75.50; H, 9.50; N, 3.39; Found: C, 75.41; H, 9.65; N, 3.21. R_f = 0.42 ($CHCl_3$/EtOAc = 9/1). Mp. 218–219 °C. Off-white crystalline material.

17-(*N*-phenylcarboxamido)-androst-5,16-diene-3-ethylene ketal (14b): ^{1}H NMR ($CDCl_3$, 400 MHz): 7.50–7.58 (m, 3H, NH + Ph(*ortho*)); 7.29 (t, 7.4 Hz, 2H, Ph(*meta*)); 7.05 (t, 7.4 Hz, 1H, Ph(*para*)), 6.41 (br s, 1H, 16-CH); 5.35 (br d, 4.0 Hz, 1H, 6-CH); 3.78–3.96 (m, 4H, OCH_2CH_2O); 2.58 (br d, 14.1 Hz, 1H, 7-CH_a); 1.07–2.30 (m, 16H, skeleton protons); 1.04 (s, 3H, 19-CH_3); 1.05 (s,

3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 164.3; 151.4; 140.9; 138.3; 136.4; 129.2 (double intensity); 124.2; 121.7; 120.0 (double intensity); 109.6; 64.6; 64.4; 56.9; 50.3; 47.0; 42.1; 37.0; 36.4; 34.9; 32.2; 31.6; 31.2; 30.4; 20.9; 19.0; 16.6. MS (*m*/*z*/rel.int.): 433/5 (M^+), 281/4; 207/3; 99/100. IR (KBr, (cm^{-1})): 1663 (CON); 1594 (C=C). Analysis calculated for $C_{28}H_{35}O_3N$ (*M* = 433.59): C, 77.56; H, 8.14; N, 3.23; Found: C, 77.43; H, 8.25; N, 3.07. R_f = 0.74 ($CHCl_3$/EtOAc = 9/1). Mp. 256–257 °C. Beige crystalline material.

17-(*N,N*-pentan-1,5-diylcarboxamido)-androst-5,16-diene-3-ethylene ketal (14c): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.64 (br s, 1H, 16-CH); 5.29 (br d, 4.2 Hz, 1H, 6-CH); 3.80–3.92 (m, 4H, OCH_2CH_2O); 3.40–3.55 (m, 4H, $N(CH_2)_2$); 2.51 (br d, 14.1 Hz, 1H, 7-CH_a); 1.02–2.13 (m, 22H, skeleton protons+ $(CH_2)_3$); 1.01 (s, 3H, 19-CH_3); 1.00 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 168.1; 149.2; 140.8; 129.7; 121.8; 109.6; 64.6; 64.4; 56.9; 51.7; 50.3; 48.7; 42.0; 37.0; 36.4; 34.4; 32.4; 31.7; 31.2; 30.9; 27.9; 26.8 (br); 24.9; 20.8; 19.0; 16.8. MS (*m*/*z*/rel.int.): 425/6 (M^+), 325/2; 99/100. IR (KBr, (cm^{-1})): 1626 (CON); 1593 (br) (C=C, Ph). Analysis calculated for $C_{27}H_{39}O_3N$ (*M* = 425.61): C, 76.20; H, 9.24; N, 3.29; Found: C, 76.03; H, 9.45; N, 3.20. R_f = 0.60 ($CHCl_3$/EtOAc = 7/3). Mp. 212–213 °C. Off-white crystalline material.

17-(*N,N*-3-oxapentan-1,5-diyl-carboxamido)-androst-5,16-diene-3-ethylene ketal (14d): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.73 (br s, 1H, 16-CH); 5.32 (br s, 1H, 6-CH); 3.84–3.95 (m, 4H, OCH_2CH_2O); 3.50–3.66 (m, 8H, 2xNCH_2CH_2O); 2.54 (br d, 14.1 Hz, 1H, 7-CH_a); 1.02-2.25 (m, 16H, skeleton protons); 1.03 (s, 3H, 19-CH_3); 1.01 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 168.2; 148.4; 140.8; 131.3; 121.8; 109.6; 67.3(double intensity); 64.6; 64.4; 56.9; 50.3; 48.8; *ca.* 48.0 (br); 42.0; 37.1; 36.4; 34.4; 32.5; 31.7; 31.2; 30.5; 20.8; 19.0; 16.9. MS (*m*/*z*/rel.int.): 427/3 (M^+), 207/3; 99/100. IR (KBr, (cm^{-1})): 1633 (CON); 1593 (C=C). Analysis calculated for $C_{26}H_{37}O_4N$ (*M* = 427.58): C, 73.03; H, 8.72; N, 3.28; Found: C, 72.88; H, 8.61; N, 3.11. R_f = 0.43 ($CHCl_3$/EtOAc = 1/1). Mp. 171–172 °C. Off-white crystalline material.

17-(*N*-methoxycarbonylmethylcarboxamido)-androst-5,16-diene-3-ethylene ketal (14e): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.41 (br s, 1H, 16-CH); 6.19 (br s, 1H, NH); 5.34 (br s, 1H, 6-CH); 4.08 (d, 4.8 Hz, 2H, NCH_2); 3.88–3.98 (m, 4H, OCH_2CH_2O); 3.75 (s, 3H, OCH_3); 2.47 (br d, 14.2 Hz, 1H, 7-CH_a); 1.06–2.23 (m, 16H, skeleton protons); 1.03 (s, 3H, 19-CH_3); 1.00 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 170.9; 166.0; 150.1; 140.8; 137.0; 121.8; 109.6; 64.6; 64.4; 56.9; 52.5; 50.3; 46.6; 42.0; 41.2; 37.0; 36.4; 34.9; 32.0; 31.5; 31.2; 30.4; 20.9; 19.0; 16.5. MS (*m*/*z*/rel.int.): 429/3 (M^+), 207/6; 99/100. IR (KBr, (cm^{-1})): 1735 (COO); 1646 (CON); 1592 (C=C). Analysis calculated for $C_{25}H_{35}O_5N$ (*M* = 429.56): C, 69.90; H, 8.21; N, 3.26; Found: C, 69.80; H, 8.35; N, 3.03. R_f = 0.48 ($CHCl_3$/EtOAc = 7/3). Mp. 192–193 °C. White crystalline material.

17-(*N*-(1-methoxycarbonylethyl)-carboxamido)-androst-5,16-diene-3-ethylene ketal (14f): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.35 (br s, 1H, 16-CH); 6.25 (br d, 7.1 Hz, 1H, NH); 5.30 (br d, 4.2 Hz; 1H, 6-CH); 4.59 (qi, 7.1 Hz; 1H, NCH); 3.85–3.93 (m, 4H, OCH_2CH_2O); 3.70 (s, 3H, OCH_3); 2.50 (br d, 14.0 Hz, 1H, 7-CH_a); 1.06–2.22 (m, 16H, skeleton protons); 1.39 (d, 7.1 Hz, 3H, CHCH_3); 1.02 (s, 3H, 19-CH_3); 0.98 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.9; 165.5; 150.3; 140.8; 137.0; 121.8; 109.6; 64.6; 64.4; 56.9; 52.6; 50.2; 47.9; 46.6; 42.0; 37.0; 36.4; 34.9; 31.9; 31.5; 31.3; 30.4; 20.9; 19.0; 18.8; 16.5. MS (*m*/*z*/rel.int.): 443/3 (M^+), 341/5; 208/8; 99/100. IR (KBr, (cm^{-1})): 1758 (COO); 1639 (CON); 1586 (C=C). Analysis calculated for $C_{26}H_{37}O_5N$ (*M* = 443.58): C, 70.40; H, 8.41; N, 3.16; Found: C, 70.22; H, 8.30; N, 3.01. R_f = 0.60 ($CHCl_3$/EtOAc = 8/2). Mp. 172–173 °C. Off-white crystalline material.

17-(*N,N*-(1′-methoxycarbonyl-butan-1,4-diyl)-carboxamido)-androst-5,16-diene-3-ethylene ketal (14g) (*ca.* 2/1 mixture of two C(O)N rotamers): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.06/5.98 (minor/major) (br s, 1H, 16-CH); 5.32 (br s, 1H, 6-CH); 4.42–4.52 (m, 1H, NCH); 3.87–3.96 (m, 4H, OCH_2CH_2O); 3.70 (s, 3H, OCH_3); 3.45–3.70 (m, 2H, NCH_2); 2.53 (br d, 8 Hz, 1H, 7-CH_a); 1.03–2.28 (m, 20H, skeleton protons+ CH_2CH_2); 1.03 (s, 3H, 19-CH_3); 1.02 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.2/172.9; 167.3; 149.8/149.5; 140.8; 134.4/133.0; 121.7; 109.5; 64.6; 64.4; 58.8/58.7; 56.7/56.6; 52.3/52.2; 50.3; 49.4; 48.7/48.5; 42.0; 37.0; 36.4; 34.5/34.3; 32.6; 31.8; 31.2; 30.4/30.3; 29.4; 25.6/24.9; 20.8; 19.0; 16.6. MS (*m*/*z*/rel.int.): 469/10 (M^+), 341/9; 207/12; 99/100. IR (KBr, (cm^{-1})): 1752 (COO); 1631 (CON); 1595 (C=C). Analysis calculated for $C_{28}H_{39}O_5N$ (*M* = 469.62): C, 71.61; H, 8.37; N, 2.98; Found: C, 71.44; H, 8.18; N, 2.83. R_f = 0.51 ($CHCl_3$/EtOAc = 9/1). Mp. 185–186 °C. White crystalline material.

17-(*N*-*tert*-butylcarboxamido)-androst-4,16-diene-3-one (15a): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.09 (br s, 1H, 16-CH); 5.63 (br s, 1H, 16-CH); 5.48 (br s, 1H, NH); 0.83–2.40 (m, 17H, skeleton protons); 1.30 (s, 9H, *t*Bu); 1.13 (s, 3H, 19-CH_3); 0.94 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.3; 171.0; 165.5; 151.5; 133.6; 123.8; 55.9; 54.0; 51.0; 46.3; 38.6; 35.4; 34.4; 33.8; 33.7; 32.6; 31.7; 31.3; 29.5; 28.8 (triple intensity); 20.6; 17.1; 16.3. MS (*m*/*z*/rel.int.): 369/100 (M^+), 352/41, 297/82. IR (KBr, (cm^{-1})): 1666 (C=O); 1652 (CON); 1597 (C=C). Analysis calculated for $C_{24}H_{35}O_2N$ (*M* = 369.55): C, 78.00; H, 9.55; N, 3.79; Found: C, 77.81; H, 9.68; N, 3.51. R_f = 0.56 ($CHCl_3$/EtOAc = 9/1). Mp. 221–222 °C. Pale yellow solid material.

17-(*N*-phenylcarboxamido)-androst-4,16-diene-3-one (15b): ^{1}H NMR ($CDCl_3$, 400 MHz): 7.98 (br s, 1H, NH); 7.58 (d, 7 Hz, 2H, Ph(*ortho*)); 7.20–7.25 (m, 2H, Ph(*meta*)); 7.02 (t, 7 Hz, 1H, Ph(*para*)), 6.38 (br s, 1H, 16-CH); 5.68 (br s, 1H, 4-CH); 0.80-2.41 (m, 17H, skeleton protons); 1.12 (s, 3H, 19-CH_3); 1.03 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.7; 171.3; 164.0; 150.6; 138.2; 135.9; 128.8 (double intensity); 123.8; 119.7 (double intensity); 55.7; 54.1; 46.7; 38.7; 35.5; 34.3; 33.8; 33.7; 32.6; 31.8; 31.7; 20.7; 17.1; 16.3. MS (*m*/*z*/rel.int.): 389/44 (M^+), 297/100; 281/20; 207/40. IR (KBr, (cm^{-1})): 1673 (C=O); 1651 (CON); 1595 (C=C). Analysis calculated for $C_{26}H_{31}O_2N$ (*M* = 389.54): C, 80.17; H, 8.02; N, 3.60; Found: C, 80.01; H, 8.22; N, 3.37. R_f = 0.59 ($CHCl_3$/EtOAc = 9/1). Mp. 172–173 °C. Pale brown solid material.

17-(*N,N*-pentan-1,5-diylcarboxamido)-androst-4,16-diene-3-one (15c): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.67 (br s, 2H, 4-CH + 16-CH); 3.48 (br s, 4H, $N(CH_2)_2$); 1.02–2.13 (m, 23H, skeleton protons+ $(CH_2)_3$); 1.18 (s, 3H, 19-CH_3); 1.03 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.4; 171.0; 167.6; 148.7; 129.4; 123.8; 55.9; 54.1; 48.4; 48.2 (br); 42.1 (br); 38.7; 35.5; 33.9; 33.8 (double intensity); 32.7; 32.0; 31.8; 26.7 (br); 25.8 (br); 24.6; 20.6; 17.1; 16.6. MS (*m*/*z*/rel.int.): 381/69 (M^+), 366/100; 258/12. IR (KBr, (cm^{-1})): 1674 (C=O); 1630 (CON); 1596 (C=C, Ph). Analysis calculated for $C_{25}H_{35}O_2N$ (*M* = 381.56): C, 78.70; H, 9.25; N, 3.67; Found: C, 78.55; H, 9.41; N, 3.50. R_f = 0.34 ($CHCl_3$/EtOAc = 9/1). Orange viscous material.

17-(*N,N*-3-oxapentan-1,5-diylcarboxamido)-androst-4,16-diene-3-one (15d): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.73 (br s, 1H, 16-CH); 5.70 (br s, 1H, 6-CH); 3.50–3.68 (m, 8H, 2xNCH_2CH_2O); 0.93–2.43 (m, 17H, skeleton protons); 1.20 (s, 3H, 19-CH_3); 1.08 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.3; 170.7; 167.7; 147.9; 131.0; 123.9; *ca.* 67.2 (br); 67.0 (double intensity); 55.9; 54.1; *ca.* 51.0 (br); 48.4; 38.7; 35.5; 33.9; 33.8 (double intensity); 32.6; 32.0; 31.8; 20.6; 17.1; 16.6. MS (*m*/*z*/rel.int.): 383/100 (M^+), 368/90; 297/31. IR (KBr, (cm^{-1})): 1675 (C=O); 1634 (CON); 1596 (C=C). Analysis calculated for $C_{24}H_{33}O_3N$ (*M* = 383.53): C, 75.16; H, 8.67; N, 3.65; Found: C, 75.01; H, 8.79; N, 3.47. R_f = 0.26 ($CHCl_3$/EtOAc = 8/2). Mp. 154–155 °C. Off-white solid material.

17-(*N*-methoxycarbonylmethylcarboxamido)-androst-4,16-diene-3-one (15e): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.35 (br s, 2H, 16-CH + NH); 5.65 (br s, 1H, 4-CH); 4.01 (d, 4.8 Hz, 2H, NCH_2); 3.70 (s, 3H, OCH_3); 0.90–2.40 (m, 17H, skeleton protons); 1.15 (s, 3H, 19-CH_3); 0.98 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$):

199.5; 171.0; 170.6; 165.7; 149.5; 136.3; 123.9; 55.8; 54.0; 52.3; 46.4; 40.9; 38.7; 35.5; 34.4; 33.9; 33.8; 32.7; 31.7; 31.6; 20.7; 17.2; 16.3. MS (*m*/*z*/rel.int.): 385/77 (M^+), 370/42; 281/100; 265/91; 207/20. IR (KBr, (cm^{-1})): 1739 (COO); 1663 (br, C=O + CON); 1592 (C=C). Analysis calculated for $C_{23}H_{31}O_4N$ (M = 385.50): C, 71.66; H, 8.11; N, 3.63; Found: C, 71.48; H, 8.30; N, 3.43. R_f = 0.28 ($CHCl_3$/EtOAc = 8/2). Mp. 192–193 °C. White crystalline material.

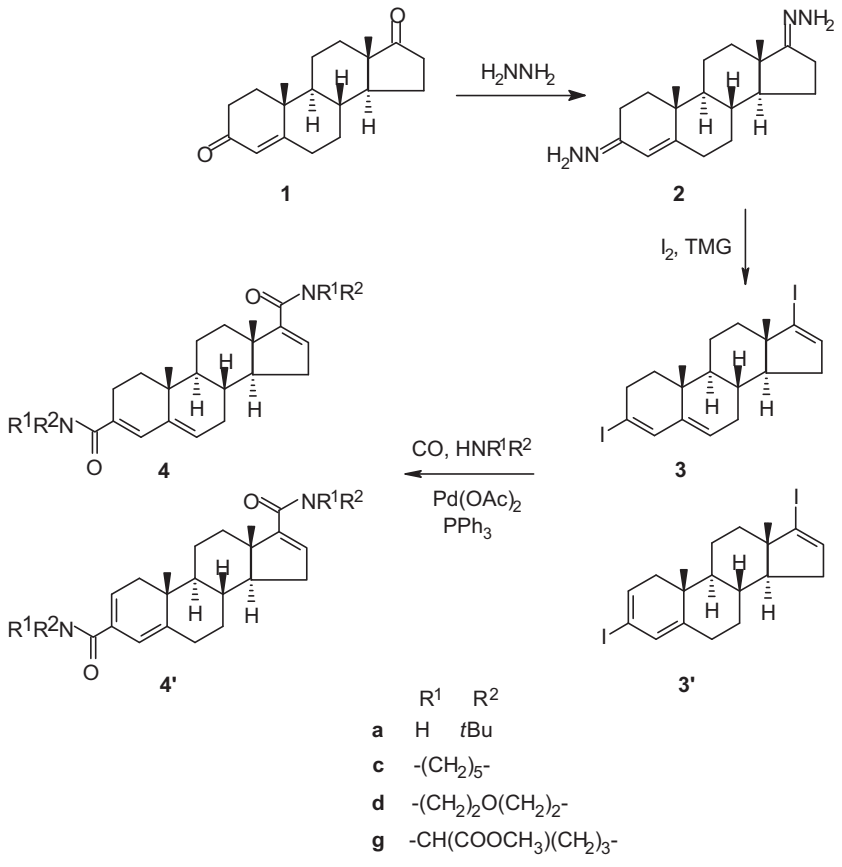
17-(*N*-(1′-methoxycarbonylethyl)-carboxamido)-androst-4,16-diene-3-one (15f): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.35 (br d, 7.1 Hz, 1H, NH); 6.30 (br s, 1H, 16-CH); 5.62 (br s, 1H, 4-CH); 4.53 (qi, 7.1 Hz; 1H, NCH); 3.66 (s, 3H, OCH_3); 0.90–2.40 (m, 17H, skeleton protons); 1.35 (d, 7.1 Hz, 3H, $CHCH_3$); 1.12 (s, 3H, 19-CH_3); 0.94 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.3; 173.5; 170.8; 165.0; 149.5; 135.8; 123.7; 55.6; 53.8; 52.2; 47.5; 46.2; 38.5; 35.3; 34.2; 33.7; 33.6; 32.5; 31.5; 31.4; 20.5; 18.2; 16.9; 16.1. MS (*m*/*z*/rel.int.): 399/42 (M^+), 384/18; 297/100; 282/40. IR (KBr, (cm^{-1})): 1736 (COO); 1675 (C=O); 1655 (CON); 1591 (C=C). Analysis calculated for $C_{24}H_{33}O_4N$ (M = 399.53): C, 72.15; H, 8.33; N, 3.51; Found: C, 72.24; H, 8.51; N, 3.29. R_f = 0.41 ($CHCl_3$/EtOAc = 8/2). Mp. 169–170 °C. Pale yellow solid material.

17-(*N,N*-(1′-methoxycarbonyl-butan-1,4-diyl)-carboxamido-androst-4,16-diene-3-one (15g) (*ca.* 2/1 mixture of two C(O)N rotamers): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.06/5.97 (minor/major) (br s, 1H, 16-CH); 5.68 (br s, 1H, 4-CH); 4.40–4.50 (m, 1H, NCH); 3.70/3.68 (s, 3H, OCH_3); 3.45–3.70 (m, 2H, NCH_2); 0.91–2.42 (m, 21H, skeleton protons+ CH_2CH_2); 1.13 (s, 3H, 19-CH_3); 1.02/1.04 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.3; 172.9/172.6; 170.9; 166.8/166.6; 149.2/148.9; 134.1/132.6; 123.7; 58.5; 55.6/55.4; 54.0; 51.9; 49.1; 48.3/48.1; 38.5; 35.3; 33.9/33.8; 33.7 (double intensity); 33.6; 32.5; 32.0; 31.7; 29.0; 25.3/24.6; 20.5; 17.0; 16.3. MS (*m*/*z*/rel.int.): 425/24 (M^+), 410/8; 366/20; 297/100. IR (KBr, (cm^{-1})): 1747 (COO); 1674 (C=O); 1635 (CON); 1590 (C=C). Analysis calculated for $C_{26}H_{35}O_4N$ (M = 425.57): C, 73.38; H, 8.29; N, 3.29; Found: C, 73.24; H, 8.15; N, 3.11. R_f = 0.35 ($CHCl_3$/EtOAc = 8/2). Yellow viscous material.

11-(*N-tert*-butylcarboxamido)-androst-5,9(11)-dien-3,17-di(ethylene ketal) (**20a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.48 (br d, 1H, 5.1 Hz, 6-C*H*); 5.19 (br s, 1H, NH); 3.80–3.95 (m, 8H, OCH_2CH_2O); 1.20–2.55 (m, 16H, skeleton protons); 1.36 (s, 3H, 19-CH_3); 1.34 (s, 9H, *t*Bu); 0.95 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 174.0; 140.1; 139.4; 127.9; 121.8; 119.0; 108.9; 65.1; 64.4; 64.3; 64.2; 51.2; 47.0; 43.8; 42.0; 41.6; 38.0; 36.6; 34.3; 33.4; 31.3; 28.6; 24.3; 23.9; 14.2; 13.3. MS (*m*/*z*/rel.int.): 471/15 (M^+), 426/8, 399/22, 319/9, 207/21, 99/100. IR (KBr, (cm^{-1})): 1654 (CON). Analysis calculated for $C_{28}H_{41}O_5N$ (M = 471.64): C, 71.31; H, 8.76; N, 2.97; Found: C, 71.18; H, 8.82; N, 2.70. R_f = 0.30 (CH_2Cl_2/EtOAc = 8/2). Pale yellow viscous material.

11-(*N-tert*-butylcarboxamido)-androst-5,11-dien-3,17-di(ethylene ketal) (**20′a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.11 (s, 1H, 12-CH); 5.49 (br d, 1H, 5.1 Hz, 6-C*H*); 5.31 (br s, 1H, NH); 3.82–3.98 (m, 8H, OCH_2CH_2O); 1.20–2.55 (m, 15H, skeleton protons); 1.36 (s, 9H, *t*Bu); 1.06 (s, 3H, 19-CH_3); 0.95 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 172.4; 141.5; 139.7; 136.2; 123.1; 117.9; 109.0; 65.2; 64.3; 64.2; 64.0; 53.3; 51.1; 46.8; 46.0; 42.3; 40.4; 36.9; 34.7; 32.8; 30.8; 28.8; 28.7; 21.6; 18.7; 17.3. MS (*m*/*z*/rel.int.): 471/5 (M^+), 372/5, 207/22, 99/100. IR (KBr, (cm^{-1})): 1649 (CON). Analysis calculated for $C_{28}H_{41}NO_5$ (M = 471.64): C, 71.31; H, 8.76; N, 2.97; Found: C, 71.22; H, 8.87; N, 2.81. R_f = 0.56 (CH_2Cl_2/EtOAc = 6/4). Mp. 253–254 °C. Off-white crystalline material.

11-(*N,N*-pentan-1,5-diylcarboxamido)-androst-5,9(11)-dien-3,17-di(ethylene ketal) (**20c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.50 (br d, 1H, 5.3 Hz, 6-C*H*); 3.80–3.96 (m, 10H,



Scheme 1. Synthesis of 3,17-dicarboxamido-androst-3,5,16-trienes based on androst-4-en-3,17-dione (**1**) via aminocarbonylation of the corresponding iodoalkene derivative as key-intermediate.

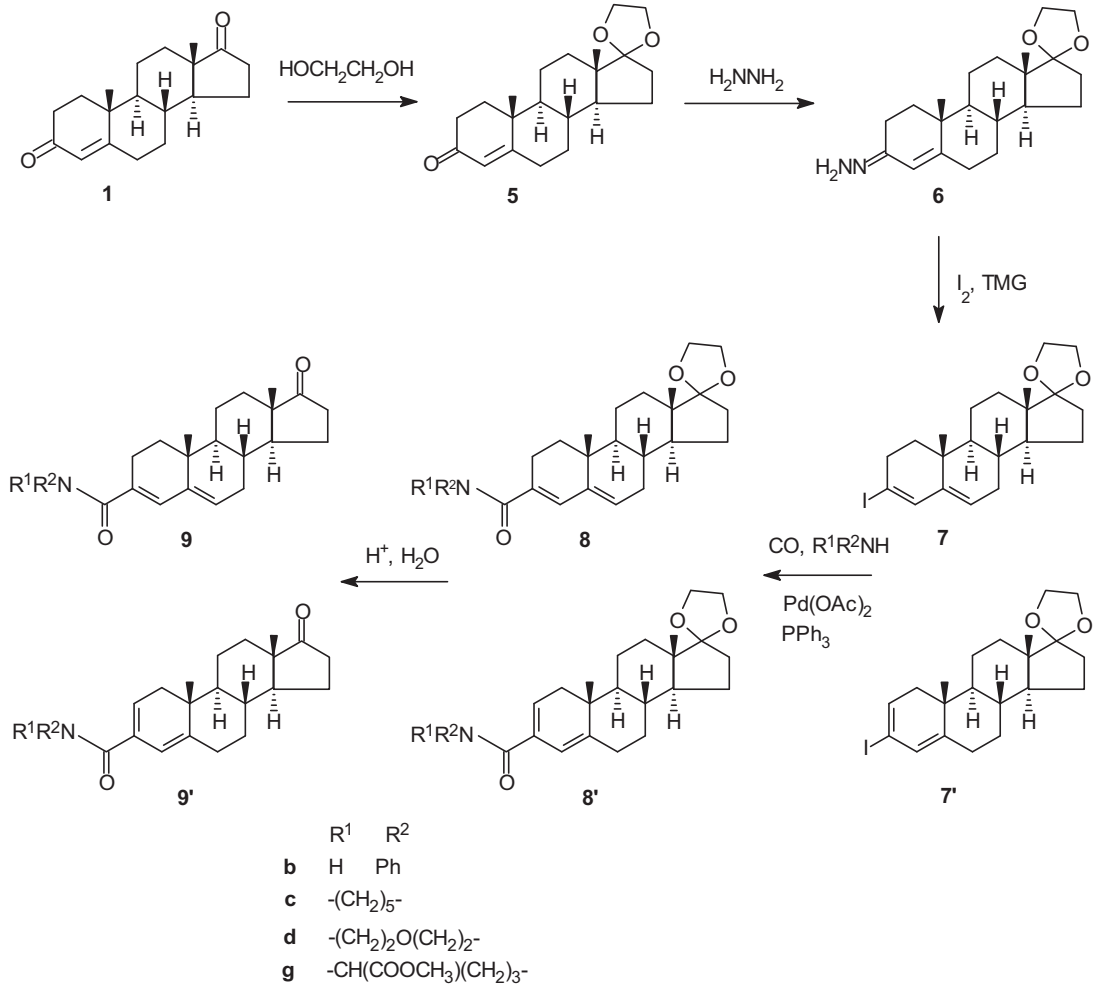
2xOCH$_2$CH$_2$O + NCH_2); 3.10–3.23 (m, 2H, NCH_2); 1.20–2.58 (m, 22H, skeleton protons+ (CH$_2$)$_3$); 1.40 (s, 3H, 19-CH_3); 0.90 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, CDCl$_3$): 173.4; 140.6; 139.7; 125.6; 121.6; 119.2; 109.0; 65.1; 64.6; 64.4; 64.2; 47.6; *ca.* 47 (br); 47.1; 44.0; 41.9; 41.4; *ca.* 41 (br); 37.2; 36.8; 34.4; 32.1; 31.6; 31.2; 26.3; 25.3; 24.6; 23.9; 23.8. MS (*m*/*z*/rel.int.): 483/15 (M$^+$), 440/9, 399/14, 99/100. Analysis calculated for $C_{29}H_{41}O_5N$ (*M* = 483.65): C, 72.02; H, 8.54; N, 2.90; Found: C, 71.90; H, 8.62; N, 2.66. R_f = 0.89 (CH$_2$Cl$_2$/EtOAc = 8/2). Pale yellow viscous material (as obtained after column chromatography).

11-(*N,N*-pentan-1,5-diylcarboxamido)-androst-5,11-dien-3,17-di(ethylene ketal) (**20′c**): ^{1}H NMR (CDCl$_3$, 400 MHz): 5.94 (s, 1H, 12-C*H*); 5.46 (d, 5.7 Hz; 1H, 6-C*H*); 3.80–3.96 (m, 10H, 2xOCH$_2$CH$_2$O + NCH_2); 3.10–3.23 (m, 2H, NCH_2); 1.20–2.50 (m, 21H, skeleton protons+ (CH$_2$)$_3$); 1.25 (s, 3H, 19-CH_3); 0.97 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, CDCl$_3$): 172.4; 142.0; 136.7; 135.4; 122.2; 118.4; 109.2; 65.5; 65.2; 64.4; 64.2; 55.8; *ca.* 53 (br); 47.6; 46.8; 42.2; *ca.* 42 (br); 40.2; 35.4; 34.9; 32.6; 31.4; 30.7; 26.5; 25.3; 24.6; 21.5; 18.0; 17.0. MS (*m*/*z*/rel.int.): 483/10 (M$^+$), 438/2, 364/21, 204/4, 99/100. Analysis calculated for $C_{29}H_{41}O_5N$ (*M* = 483.65): C, 72.02; H, 8.54; N, 2.90; Found: C, 71.81; H, 8.70; N, 2.78. R_f = 0.39 (CH$_2$Cl$_2$/EtOAc = 8/2). Pale yellow viscous material (as obtained after column chromatography).

11-(*N-tert*-butylcarboxamido)-androst-4,9(11)-dien-3,17-dione (**21a**): ^{1}H NMR (CDCl$_3$, 400 MHz): 5.75 (br s, 1H, 4-C*H*); 5.21 (br s, 1H, NH); 1.10–2.60 (m, 16H, skeleton protons); 1.32 (s, 9H, *t*Bu); 1.47 (s, 3H, 19-CH_3); 1.32 (s, 9H, *t*Bu); 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, CDCl$_3$): 219.9; 198.9; 172.6; 168.2; 139.8; 129.2; 124.9; 51.7; 47.1; 45.1; 43.5; 39.6; 38.2; 35.8; 34.1; 33.5; 30.0; 29.7; 28.4; 22.8; 15.2; 13.7. MS (*m*/*z*/rel.int.): 383/9 (M$^+$), 368/11; 311/32, 58/100. IR (KBr, (cm^{-1})): 1739 (C=O); 1646 (br, C=O + CON); 1615 (C=C). Analysis calculated for $C_{24}H_{33}O_3N$ (*M* = 383.53): C, 75.16; H, 8.67; N, 3.65; Found: C, 75.03; H, 8.80; N, 3.44. R_f = 0.48 (CH$_2$Cl$_2$/EtOAc = 1/1). Pale yellow crystalline solid material (as obtained after column chromatography). Mp. 204–205 °C.

11-(*N-tert*-butylcarboxamido)-androst-4,11-dien-3,17-dione (**21′a**): ^{1}H NMR (CDCl$_3$, 400 MHz): 6.48 (s, 1H, 12-CH); 5.76 (br s, 1H, 4-C*H*); 5.44 (br s, 1H, NH); 1.20–2.62 (m, 15H, skeleton protons); 1.32 (s, 9H, *t*Bu); 1.20 (s, 3H, 19-CH_3); 1.02 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, CDCl$_3$): 215.3; 198.8; 171.0; 167.9; 139.6; 135.9; 126.1; 62.5; 54.7; 51.4; 48.9; 46.5; 41.4; 36.2; 35.1; 34.5; 33.9; 29.5; 28.5; 20.8; 18.2; 17.3. MS (*m*/*z*/rel.int.): 383/100 (M$^+$), 368/7; 310/55, 253/22. IR (KBr, (cm^{-1})): 1742 (COO); 1655 (br, C=O + CON); 1613 (C=C). Analysis calculated for $C_{24}H_{33}O_3N$ (*M* = 383.53): C, 75.16; H, 8.67; N, 3.65; Found: C, 75.10; H, 8.82; N, 3.50. R_f = 0.51 (CH$_2$Cl$_2$/EtOAc = 1/1). Pale yellow crystalline solid material (as obtained after column chromatography). Mp. 104–105 °C.

11-(*N,N*-pentan-1,5-diylcarboxamido)-androst-4,9(11)-dien-3,17-dione (**21c**): ^{1}H NMR (CDCl$_3$, 400 MHz): 5.74 (s, 1H, 4-C*H*); 3.80–3.88 (m, 1H, NCH_aH$_b$); 3.39–3.45 (m, 1H, NCH$_a$$H_b$);



Scheme 2. Synthesis of 3-carboxamido-androst-3,5-dien-17-ones based on androst-4-en-3,17-dione (**1**) via aminocarbonylation of the corresponding iodoalkene derivative as key-intermediate.

3.08–3.17 (m, 2H, NCH_2); 1.20–2.60 (m, 22H, skeleton protons+ $(CH_2)_3$); 1.45 (s, 3H, 19-CH_3); 0.93 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 219.9; 198.9; 172.1; 168.3; 140.1; 127.4; 124.9; *ca.* 47 (br); 47.2; 45.1; 43.3; 41.6; *ca.* 41 (br); 38.4; 35.9; 34.3; 33.6; 32.6; 30.0; 26.0; 25.2; 24.4; 24.2; 22.9; 13.9. MS (*m*/*z*/rel.int.): 395/2 (M^+), 380/8, 311/11, 84/100. IR (KBr, (cm^{-1})): 1739 (COO); 1674 (C=O + CON); 1616 (C=C). Analysis calculated for $C_{25}H_{33}O_3N$ (*M* = 395.54): C, 75.91; H, 8.41; N, 3.54; Found: C, 75.80; H, 8.64; N, 3.26. R_f = 0.26 (CH_2Cl_2/EtOAc = 1/1). Mp. 106–107 °C. Orange solid material (as obtained after column chromatography).

11-(*N,N*-pentan-1,5-diylcarboxamido)-androst-4,11-dien-3,17-dione (**21′c**): ^1H NMR ($CDCl_3$, 400 MHz): 6.25 (s, 1H, 12-C*H*); 5.76 (s, 1H, 4-C*H*); 3.10–3.70 (m, 4H, 2xNCH_2); 1.20–2.60 (m, 21H, skeleton protons+ $(CH_2)_3$); 1.23 (s, 3H, 19-CH_3); 1.06 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 215.0; 198.4; 170.8; 167.8; 135.2; 135.0; 126.0; 55.4; 48.8; 48.3; 46.4; 42.5; 41.2; 36.2; 35.3; 34.5; 33.8; 33.7; 29.5; 25.9; 25.2; 24.6; 20.8; 18.8; 17.3. MS (*m*/*z*/rel.int.): 396/100 (M^+), 380/52, 310/45, 274/55, 84/95. IR (KBr, (cm^{-1})): 1742 (C=O); 1673 (C=O + CON); 1609 (C=C). Analysis calculated for $C_{25}H_{33}O_3N$ (*M* = 395.54): C, 75.91; H, 8.41; N, 3.54; Found: C, 75.67; H, 8.61; N, 3.33. R_f = 0.30 (CH_2Cl_2/EtOAc = 1/1). Mp. 106–107 °C. Pale yellow solid material (as obtained after column chromatography).

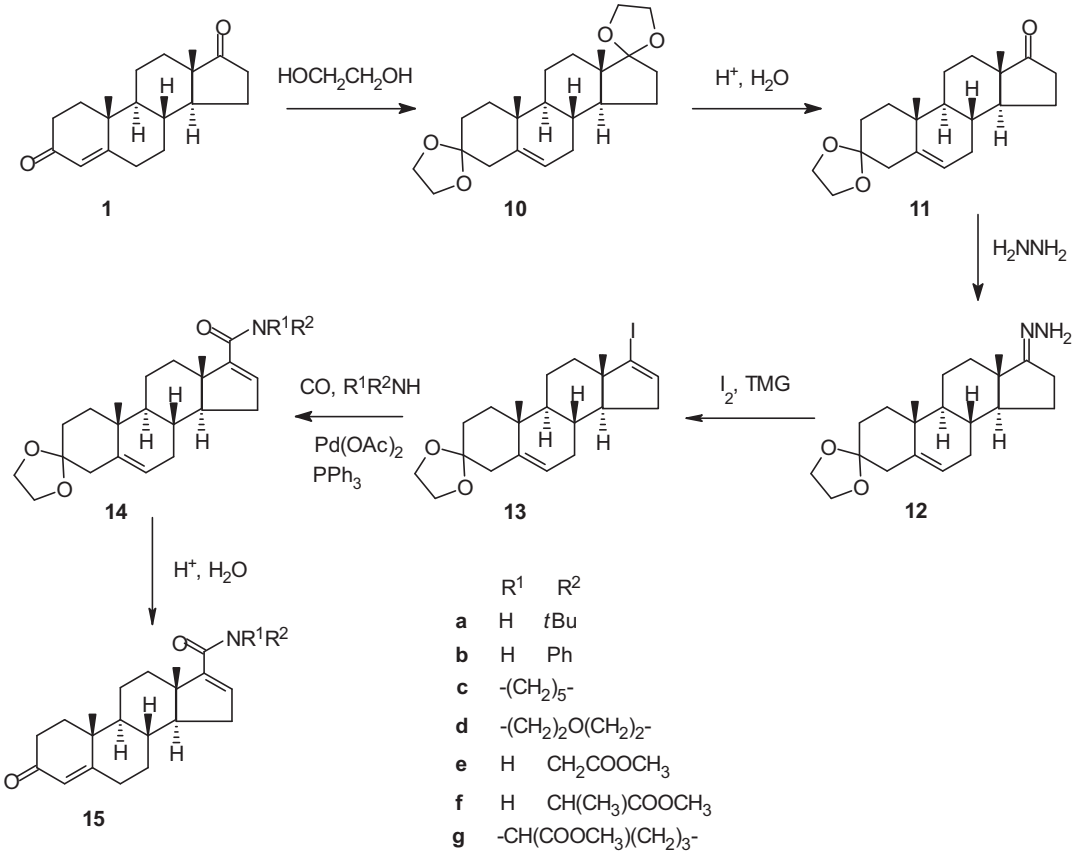
3. Results and discussion

The homogeneous catalytic functionalization of steroids via various carbonylation reactions has been one of our major interest for a long time [4]. The introduction of a carboxamide (or ester, formyl) functionality into the distinguished positions 3, 11 and especially 17 is of pharmacological importance as discussed under Introduction [4,5,12–15]. The transformation of the keto groups at all of the three positions into the corresponding iodo-alkenes, and by using the triiodide (3,11,17-triiodo-androst-3,5,9(11),16-tetraene) as a substrate in palladium-catalyzed carbonylation reaction, the corresponding 3,11,17-tri-carboxamido-androstane was obtained in acceptable yield under mild reaction conditions [17]. The selective aminocarbonylation at one of these distinguished positions, in the presence of a further keto functionality, still remained a challenge.

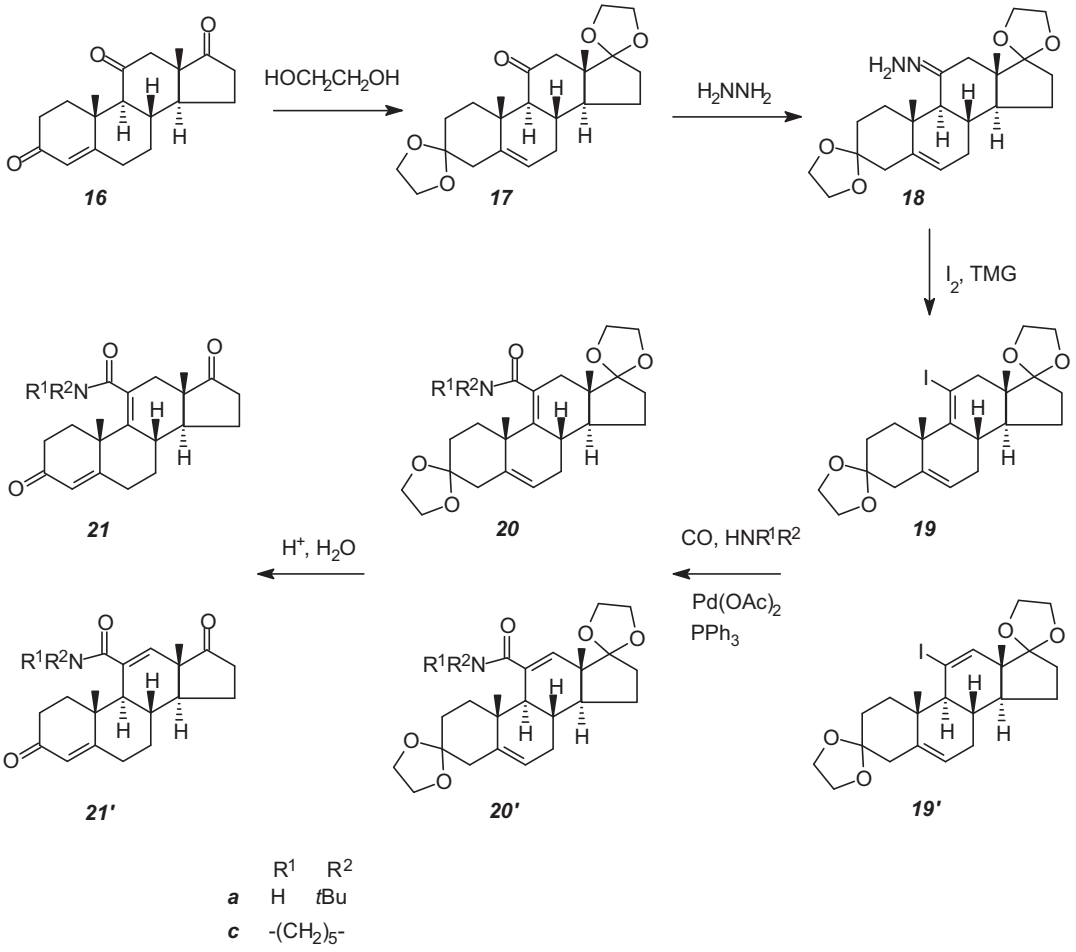
As previously, the appropriate substrates with iodo-alkene functionality(ies) served for the introduction of the carboxamide groups in the present study. The ketone—hydrazone—iodo-alkene reaction sequence was used for the preparation of the substrate. In order to preserve the 3-keto and/or 17-keto functionalities, they were protected as ethylene ketals following conventional synthetic methodologies (See Section 2).

In order to investigate the possibility of the synthesis of steroids containing both keto and carboxamide functionalities from steroids with iodoalkene moieties, 3,17-diiodo-androst-3,5,16-triene (**3**), 3-iodo-androst-3,5-diene-17-ethylene ketal (**7**), 3-iodo-androst-2,4-diene-17-ethylene ketal (**7′**), 17-iodo-androst-5,16-diene-3-ethylene ketal (**13**) and 11-iodo-androst-5,9(11)-diene-3,17-bis(ethylene ketal) (**19**) were synthesized from the corresponding 3,17-diketo-, 3-keto-, 17-keto- and 11-keto derivatives, respectively. In this way, the hydrazones (**2**, **6**, **12** and **18**), obtained after the protection of one or two keto functionalities as ethylene ketal, were transformed to the above iodoalkenes in the presence of TMG and iodine.

The iodoalkenes **3**, **7** (**7′**), **13** and **19** were reacted as substrates in aminocarbonylation reaction (Schemes 1–4). Various primary and secondary amines were used as *N*-nucleophiles (*tert*-butylamine



Scheme 3. Synthesis of 17-carboxamido-androst-4,16-dien-3-ones based on androst-4-en-3,17-dione (**1**) via aminocarbonylation of the corresponding iodoalkene derivative as key-intermediate.



Scheme 4. Synthesis of 11-carboxamido-androst-4,9(11)-dien-3,17-diones based on androst-4-en-3,9,17-trione (**16**) via aminocarbonylation of the corresponding iodoalkene derivative as key-intermediate.

(**a**), aniline (**b**), pyperidine (**c**), morpholine (**d**), methyl glycinate (**e**), methyl alaninate (**f**), methyl prolinate (**g**)) in DMF in the presence of palladium—phosphine '*in situ*' catalysts under carbon monoxide at atmospheric pressure. The '*in situ*' formation of highly active coordinatively unsaturated Pd(0) catalysts with mono- and bidentate phosphines has been published before [26].

It can be stated, that iodoalkene functionalities in all positions (3-iodo-3-ene, 17-iodo-16-ene, 11-iodo-9(11)-ene) reacted quantitatively under mild conditions. In this way, 3,17-dicarboxamido-4,16-diene derivatives (**4**) (Scheme 1), 3-carboxamido-3-ene derivatives (**8**) (Scheme 2), 17-carboxamido-16-ene derivatives (**14**) (Scheme 3) and 11-carboxamido-9(11)-ene derivatives (**20**) (Scheme 4) were synthesized in moderate to high yields depending on the structure of the amine (Table 1).

Using **3** as a substrate, the corresponding carboxamides were isolated in high yields. The secondary amines (**c**, **d** and **g**) have shown diminished reactivity, i.e. longer reaction times were necessary to achieve high yields (entries 1–5).

When the 3/1 mixture of the diiodo compounds **3** and **3′** was used, a complete conversion towards dicarboxamides was obtained (Scheme 1). Two of them, **4a** and **4c** were isolated as pure compounds in acceptable yields using column chromatography, however, **4d**, **4g** were obtained in surprisingly low yields. Although the reaction mixture contained some 2,4-diene isomers (**4′a**, **4′c**, **4′d** and **4′g)** as well, their isolation as pure compound for full characterization was not successful. It is worth noting that the partial isomerization of the 2,4-diene functionality to 3,5-diene was observed during aminocarbonylation, i.e. the original 2,4-diene/3,5-diene ratio of 3-iodo compounds were shifted towards the 3,5-diene structure of 3-carboxamides. The ratio of **4**/**4′** felt in the range of 10/1–12/1. It could be explained by the oxidative addition of the 3-iodo-2,4-diene (**3′**) to Pd(0) forming a Pd(II)-2,4-dienyl intermediate which underwent isomerization to Pd(II)-3,5-dienyl derivative. Its aminocarbonylation provided carboxamides **4**.

The aminocarbonylation of **7** with secondary amines (**c**, **d**, and **g**) resulted in conversion of 55, 35, and 30%, respectively. To achieve higher conversion, and consequently, higher isolated yields, elevated reaction times had to be used (entries 7–10).

As discussed above, the *ca.* 3/1 mixture of the diiodo compounds **7** and **7′** was used, both iodo-dienes were completely converted to the corresponding dicarboxamides **8c**, **8d**, and **8g** (Scheme 2). Again, the isomerization of the conjugated double bond system from 2,4- to 3,5-positions during palladium-catalyzed reaction took place, enabling the isolation of 3-carboxamido-3,5-dienes in good yields. The deprotection at the 17 position led to the corresponding 3-carboxamido-17-keto derivatives (**9c**, **9d** and **9g**) in yields higher than 95%. It is worth noting, that the characterization of 2,4-dienes in both series of compounds (17-ethylene ketals, **8′** and 17-ketones, **9′**) was successful. Unlike the major products (**8** and **9**), the isolation of **8′** and **9′** as pure compounds was failed. However, they could be characterized in two-component mixtures (See Characterization).

The protection of the 3-keto functionality as an ethylene ketal in **1** resulted in the formation of a highly reactive iodo-alkene **13** (Scheme 3). The aminocarbonylation of **13** brought about the high-yielding formation of 17-carboxamides **14a**–**g**. The lowest isolated yield was obtained with secondary amines, while the highest with

tert-butyl-amine (82%) (entries 11–17). The corresponding 3-keto-4-ene derivatives, **15a**–**g**, the potential intermediates for further functionalization, were obtained in high yields (>95%) upon deprotection.

The selective protection of the 3- and 17-keto functionalities of adrenosterone (**16**) and the transformation of the 11-keto functionality to 11-iodo-9(11)-ene by standard synthetic procedures, led to the *ca.* 5/1 mixture of **19** and **19′** (Scheme 4). The palladium-catalyzed aminocarbonylation of the iodo-alkenes resulted in the complete formation of 11-carboxamides **20a**/**20′a** using a primary amine (**a**) while much lower yields have been obtained with a secondary amine (**c**) as *N*-nucleophile (entries 18 and 19). The isomerization of 11-ene to 9(11)-ene during aminocarbonylation took place to a very low extent, i.e., a 4/1 mixture of **20**/**20′** was obtained. The hydrolysis of the ethylene ketal functionalities provided the 11-carboxamido-3,17-dione derivatives **21**/**21′**.

As a summary it can be stated, that conjugated unsaturated steroidal carboxamides, possessing both carboxamide and ketone functionalities, can be synthesized in yields of practical interest in palladium catalyzed carbonylation of the corresponding iodoalkenes. The iodoalkene functionality, easily accessible from ketone, provided a clean, high-yielding aminocarbonylation towards carboxamides. It has been proved that the selective protection of the keto group(s) via ethylene ketals, enables the synthesis of carboxamides with additional keto functionality(ies), which could serve as ideal site for further functionalization of the skeleton. The aminocarbonylation proved to be highly tolerant towards both the structure of the amine nucleophiles and the structural variations of the steroidal backbone.

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