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Novel 13β- and 13α-D-homo steroids: 17a-carboxamido-D-homoestra-1,3,5(10),17-tetraene derivatives via palladium-catalyzed aminocarbonylations

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ABSTRACT

17a-Methoxycarbonyl- and 17a-carboxamido-D-homoestra-1,3,5(10),17-tetraene derivatives were synthesized by palladium-catalyzed carbonylation reactions of the corresponding 17a-iodo-D-homoestra-1,3,5(10),17-tetraene derivatives using methanol and various amines as *O*- and *N*-nucleophiles, respectively. Both the natural (13β) and the epi (13α) series of compounds were isolated. The 17a-iodo-17-ene functionalities in the two 13-epimer series differ in reactivity. While the aminocarbonylations were practically complete in the 13β series in reasonable reaction time under mild conditions and high isolated yields were achieved, the corresponding 13α-17a-iodo-17-ene substrate has shown decreased reactivity resulting in moderate to low yields. However, under high carbon monoxide pressure (40 bar) excellent yields can be obtained even in the 13α series. The aminocarbonylation was completely chemoselective in both series, *i.e.*, the corresponding 17a-carboxamido-17-ene derivatives were formed exclusively.

1. Introduction

The homogeneous catalytic functionalization of steroids with regular skeleton (13β-methyl group and five-membered D-ring) is well-established and was reviewed in 2003 [1]. Among the functionalities introduced, carboxamido group is of special interest due to the high pharmacological importance of 17-carboxamido-androstanes and estra-1,3,5(10)-trienes as 5α-reductase inhibitors. The corresponding 13-epimer, 13α-estra-1,3,5(10)-triene is also known as the framework of 13α-estrone and its derivatives; much less efforts have been made towards its functionalization [2,3].

Palladium-catalyzed aminocarbonylation of steroidal substrates with 3-trifloxy-3-ene or 17-trifloxy/17-iodo-16-ene moieties (where trifloxy stands for trifluoromethylsulphonyloxy, 'TfO' as its acronym used usually) proved to be an efficient tool for the introduction of carboxamide functionalities into positions-3 and -17, respectively [4–10]. Recently, the high reactivity of the iodo-ene moiety in more hindered positions, *i.e.*, 12-iodo-11-ene and 11-iodo-9(11)-ene functionalities, have been utilized for the homogeneous catalytic synthesis of 12-carboxamido-11-spirostenes and 11-carboxamido-androst-9(11)-enes, respectively [11,12]. Furthermore, similar methodology was exploited for the functionalization of estra-1,3,5(10),16-tetraene and androsta-5,16-diene derivatives in the 13α series [13].

The search for steroids with novel pharmacological effects led to the synthesis of D-homo derivatives both in the androstane and estrane series. The isolation from natural sources and the synthetic approaches to D-homosteroids were reviewed recently [14]. An efficient methodology was developed for the synthesis of 16-halogenated D-homoestrone and its 13α-epimer by using Lewis acid-catalyzed intramolecular Prins reaction, that is, the cyclization of the corresponding unsaturated secoestrone aldehyde [15]. D-Homoestrone 3-methyl and 3-benzyl ethers were synthesized both in the natural and 13-epi series and tested *in vitro* in a radioligand-binding assay [16]. Nitrogen-containing D-homo and condensed D-homo compounds belonging to the 13α-estrone series with substituted nitroaniline moieties at position-17a have been described [17]. 2-Phenethyl-D-homoestrone and related compounds were synthesized and tested as 17β-hydroxysteroid dehydrogenase type 1 inhibitors [18].

17-Aminophenyl-17-aza-D-homoestrones were synthesized via δ-alkenyl phenylhydrazones and the corresponding cyclic iminium salts [19]. 3β-Hydroxy-17-oxa-D-homoandrost-5-ene-

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16-one served as a starting compound for the synthesis of novel 4- and 6-nitro D-homo derivatives [20].

Prompted by the pharmacological potential of 17-carboxamides and by the facile palladium-catalyzed carbonylations of the iodoalkene functionality, we report on the synthesis of novel 17a-carboxamido-D-homoestratetraenes from the corresponding 17a-17-ene derivatives.

2. Experimental

PPh_3 and 1,1,3,3-tetramethylguanidine (TMG) were purchased from Aldrich. Commercial NEt3, and primary and secondary amines, including amino acid ester hydrochlorides (Aldrich), were used without further purification. DMF was dried according to a standard procedure. 3-Methoxy-D-homoestra-1,3,5(10)-triene-17a-one (**1**) and 3-methoxy-13α-D-homoestra-1,3,5(10)-triene-17a-one (**2**) were synthesized as described previously in Ref. [16].

3-Methoxy-17a-iodo-D-homoestra-1,3,5(10),17-tetraene (**5**) and 3-methoxy-17a-iodo-13α-D-homoestra-1,3,5(10),17-tetraene (**6**), used as substrates in the present work, were synthesized in a modified conventional three-step synthetic procedure [20,21] from the corresponding 17a-keto derivatives, **1** and **2**, respectively. A detailed description of the synthesis 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 with Merck TLC sheets (Silica gel 60 F_{254}) and $CHCl_3$/EtOAc mixtures (98/2, 95/5, 90/10 or 80/20) as appropriate eluents. Elemental analyses were measured on a 1108 Carlo Erba apparatus. Mass-spectrometric data have been obtained by using a GC–MS system consisting of a Perkin Elmer AutoSystem XL gas chromatograph and a Perkin Elmer TurboMass mass spectrometer.

2.1.1. Synthesis of 3-methoxy-17a-iodo-D-homoestra-1,3,5(10),17-tetraene (*5*) via the corresponding hydrazone

A mixture of 3-methoxy-D-homoestra-1,3,5(10)-triene-17a-one (**1**) (2.60 g, 8.7 mmol), freshly distilled hydrazine hydrate (98%, 2.22 g, 44.5 mmol) and BaO (100 mg) in 2-methoxy-ethanol (50 mL) was heated for 2 days at 110 °C. After completion of the reaction, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic phase was washed successively with water and brine, dried over Na_2SO_4, and evaporated to give the 17a-hydrazone derivative (**3**). This product was used in the next step without further purification.

To a stirred solution of I_2 (4.27 g, 16.8 mmol) in CH_2Cl_2 (50 mL), 1,1,3,3-tetramethylguanidine (TMG, 8.30 g, 72.0 mmol) was added slowly the mixture being cooled in an ice-water bath during the addition. A solution of **3** (2.50 g, 8.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C. After the addition was completed, the mixture was stirred for 1 h. The solvent was then evaporated off and the residue was heated at 90 °C under an argon atmosphere for 3 h, after which the mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed successively with 1N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether (40–60): EtOAc 95:5) resulting in 17a-iodo-17-ene product (**5**) as a white solid material. Yield: 1.20 g; 36.8%. (In order to avoid oxidative and photochemical decomposition, **5** must be kept under argon in a refrigerator. When used in carbonylation reactions, reproducible results can be obtained even after 2 months. No changes either in color or in analytical characteristics were observed within this time interval).

2.1.2. Synthesis of 3-methoxy-17a-iodo-13α-D-homoestra-1,3,5(10),17-tetraene (*6*) via the corresponding hydrazone

3-Methoxy-17a-iodo-13α-D-homoestra-1,3,5(10),17-tetraene (**6**) was prepared according to a known method described above for **5**. The only difference is in the final isolation step, that is, the 17a-iodo-17-ene product (**6**) was purified by column chromatography (silica gel, petroleum ether (40–60): EtOAc 97:3). Yield: 2.05 g; 62.9%.

2.1.3. General procedure for aminocarbonylation at atmospheric pressure

A mixture of **5** (or **6**) (408 mg, 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 alanine and proline methyl ester *N*-nucleophiles were used as hydrochloride salts (1.1 mmol) and 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 off, and the residue was dissolved in 20 mL of $CHCl_3$. It was washed in turn with 2 × 50 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, 98/2, 95/5, 90/10 or 80/20 $CHCl_3$/EtOAc mixtures) resulted in the target 17a-carboxamido-17-ene derivatives (**7a–e**, **8a–e**).

2.1.4. General procedure for aminocarbonylation at high pressure

The DMF solution of the catalyst precursor and reactants (amounts as above) was transferred under argon into a 100 mL stainless steel autoclave. The reaction vessel was pressurized up to 40 bar with CO and the magnetically stirred mixture was heated in an oil bath at 50 °C for the given reaction time. The work-up procedure was identical with that given above for atmospheric aminocarbonylation.

2.1.5. General procedure for methoxycarbonylation at atmospheric pressure

A mixture of **5** (or **6**) (408 mg, 1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol) and PPh_3 (13.1 mg, 0.05 mmol) was dissolved in 10 mL of DMF under argon, and NEt_3 (0.5 mL) and methanol (0.13 mL, 5 mmol). The atmosphere was changed to CO (1 bar), and the reaction was conducted at 50 °C for the appropriate reaction time. The composition of the reaction mixture was checked by TLC. Work-up procedure was identical with that given above for the 17a-carboxamides.

2.1.6. General procedure for methoxycarbonylation at high pressure

A mixture of **6** (408 mg, 1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol) and PPh_3 (13.1 mg, 0.05 mmol) was dissolved in 10 mL of DMF under argon, and NEt_3 (0.5 mL) and methanol (0.13 mL, 5 mmol). The reaction mixture was then transferred under argon into a 100 mL stainless steel autoclave, which was pressurized to 40 bar with CO and the magnetically stirred mixture was heated in an oil bath at 50 °C for 40 h. Work-up

Table 1
Palladium-catalyzed aminocarbonylation of 3-methoxy-17a-iodo-D-homoestra-1,3,5(10),17-tetraene (**5**) and 3-methoxy-17a-iodo-13α-D-homoestra-1,3,5(10),17-tetraene (**6**)[a].

Run	Amine	Substr.	Amine: **5**(**6**) ratio	Reaction time [h]	*p*(CO) [bar]	Conv.[b] [%]	Isolated yield (amide) [%]
1	*t*-BuNH$_2$ (**a**)	**5**	3	20	1	>98	84 (**7a**)
2	*t*-BuNH$_2$ (**a**)	**5**	3	0.25	1	41	ND[c]
3	*t*-BuNH$_2$ (**a**)	**5**	3	0.5	1	83	ND[c]
4	*t*-BuNH$_2$ (**a**)	**5**	3	1	1	89	ND[c]
5	*t*-BuNH$_2$ (**a**)	**6**	3	20	1	45	ND[c]
6	*t*-BuNH$_2$ (**a**)	**6**	3	20	40	87	76 (**8a**)
7	*t*-BuNH$_2$ (**a**)	**6**	3	45	40	97	82 (**8a**)
8	Aniline (**b**)	**5**	2	20	1	>98	80 (**7b**)
9	Aniline (**b**)	**6**	2	20	1	71	55 (**8b**)
10	Piperidine (**c**)	**5**	1.5	20	1	>98	80 (**7c**)
11	Piperidine (**c**)	**5**	1.5	0.25	1	97	ND[c]
12	Piperidine (**c**)	**6**	1.5	20	1	25	20 (**8c**)
13	Piperidine (**c**)	**6**	1.5	20	40	61	55 (**8c**)
14	AlaOMe (**d**)	**5**	1.1	20	1	>98	82 (**7d**)
15	AlaOMe (**d**)	**6**	1.1	20	1	20	16 (**8d**)
16	ProOMe (**e**)	**5**	1.1	20	1	55	40 (**7e**)
17	ProOMe (**e**)	**6**	1.1	20	1	0	–
18	ProOMe (**e**)	**6**	1.1	20	40	66[d]	ND[c]
19	ProOMe (**e**)	**6**	1.1	110	40	98[d]	76 (**8e**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol substrate (**5** or **6**); 10 mL DMF; Reaction temp.: 50 °C.
[b] Determined by GC.
[c] ND = isolated yields were not determined in these runs.
[d] Determined by ^{1}H NMR.

procedure was identical with that given above for the 17a-carboxamides.

2.2. Analytical and spectroscopic data

3-Methoxy-17a-iodo-D-homoestra-1,3,5(10),17-tetraene (**5**): ^{1}H NMR ($CDCl_3$): 7.22 (d, 8.0 Hz, 1H, 1-H); 6.75 (br d, 8.0 Hz, 1H, 2-H); 6.65 (br s, 1H, 4-H); 6.36 (br s, 1H, 17-H); 3.80 (s, 3H, OCH_3); 2.82–2.95 (m, 2H, 6-H_2); 1.95–2.40 (m, 6H, skeleton protons); 1.22–1.60 (m, 7H, skeleton protons); 1.02 (s, 3H, 18–H_3); ^{13}C NMR ($CDCl_3$): 157.8; 138.0; 137.5; 132.9; 126.4; 118.6; 113.7; 111.9; 55.5; 49.1; 44.1; 42.6; 41.6; 39.8; 30.8; 30.4; 27.0; 26.6; 20.2; 18.8. IR (KBr (cm^{-1})): 1610 (C=C); 1576 (A-ring). MS (*m*/*z*/rel. int.): 408/100 (M^+), 281/2; 171/32; 147/14. Analysis calculated for $C_{20}H_{25}OI$ (*M* = 408.32): C, 58.83; H, 6.17; found: C, 58.70; H, 6.36. R_f = 0.71 (petroleum ether (40–60)/EtOAc = 95/5); mp. 108–109 °C. Off-white crystalline material.

3-Methoxy-17a-iodo-13α-D-homoestra-1,3,5(10),17-tetraene (**6**): ^{1}H NMR ($CDCl_3$): 7.22 (d, 8.4 Hz, 1H, 1-H); 6.73 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.63 (d, 2.6 Hz; 1H, 4-H); 6.40 (br d, 3.1 Hz, 1H, 17-H); 3.80 (s, 3H, OCH_3); 2.81–2.91 (m, 2H, 6-H_2); 1.90–2.37 (m, 6H, skeleton protons); 1.20–1.67 (m, 7H, skeleton protons); 1.18 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 157.6; 139.2; 137.9; 133.1; 126.4; 115.0; 113.5; 111.5; 55.3; 45.6; 43.0; 42.2; 42.0; 37.6; 30.3; 29.9; 27.1; 26.9; 26.1; 19.5. IR (KBr (cm^{-1})): 1610 (C=C); 1575 (A-ring). MS (*m*/*z*/rel. int.): 408/100 (M^+), 281/8; 173/44; 147/13. Analysis calculated for $C_{20}H_{25}OI$ (*M* = 408.32): C, 58.83; H, 6.17; found: C, 58.66; H, 6.26. R_f = 0.66 (petroleum ether (40–60)/EtOAc = 97/3); mp. 135–136 °C. White crystalline material.

3-Methoxy-17a-(*N*-*tert*-butylcarboxamido)-D-homoestra-1,3,5(10),17-tetraene (**7a**): ^{1}H NMR ($CDCl_3$): 7.22 (d, 8.4 Hz, 1H, 1-H); 6.73 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.62 (d, 2.6 Hz; 1H, 4-H); 5.83 (br s, 1H, 17-H); 5.48 (br s, 1H, NH); 3.80 (s, 3H, OCH_3); 2.83–2.91 (m, 2H, 6-H_2); 1.88–2.33 (m, 6H, skeleton protons); 1.20–1.60 (m, 7H, skeleton protons); 1.40 (s, 9H, tBu); 1.25 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 170.8; 157.5; 148.0; 137.9; 133.0; 126.6; 126.3; 113.5; 111.5; 55.2; 51.2; 47.5; 43.7; 38.2; 36.6; 35.2; 30.2; 28.9 (triple intensity); 26.4; 26.1; 25.4; 19.8; 19.6. IR (KBr (cm^{-1})): 3412 (NH); 1663 (NCO); 1636 (C=C); 1608 (A-ring). MS (*m*/*z*/rel. int.): 381/100 (M^+), 366/11; 309/22; 280/20. Analysis calculated for $C_{25}H_{35}O_2N$ (*M* = 381.56): C, 78.70; H, 9.25; N, 3.67; found: C, 78.54; H, 9.36; N, 3.49. R_f = 0.80 ($CHCl_3$/EtOAc = 90/10); mp. 184–185 °C. White crystalline material.

3-Methoxy-17a-(*N*-*tert*-butylcarboxamido)-13α-D-homoestra-1,3,5(10),17-tetraene (**8a**): ^{1}H NMR ($CDCl_3$): 7.22 (d, 8.4 Hz, 1H, 1-H); 6.73 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.63 (d, 2.6 Hz; 1H, 4-H); 5.91 (br s, 1H, 17-H); 5.38 (br s, 1H, NH); 3.78 (s, 3H, OCH_3); 2.83–2.90 (m, 2H, 6-H_2); 1.88–2.40 (m, 6H, skeleton protons); 1.08–1.50 (m, 7H, skeleton protons); 1.43 (s, 3H, 18-H_3);1.37 (s, 9H, tBu); ^{13}C NMR ($CDCl_3$): 170.6; 157.5; 144.4; 137.9; 133.0; 128.6; 126.5; 113.4; 111.6; 55.1; 51.0; 46.5; 42.6; 37.6 (double intensity); 36.5; 31.8; 30.4; 28.8; 29.7 (triple intensity); 26.8; 21.0; 18.9. IR (KBr (cm^{-1})): 3451 (NH); 1659 (NCO); 1613 (C=C); 1590 (A-ring). MS (*m*/*z*/rel. int.): 381/100 (M^+), 366/6; 324/10; 309/8; 280/20. Analysis calculated for $C_{25}H_{35}O_2N$ (*M* = 381.56): C, 78.70; H, 9.25; N, 3.67; found: C, 78.60; H, 9.39; N, 3.45. R_f = 0.65 ($CHCl_3$/EtOAc = 95/5); mp. 115–116 °C. Pale yellow crystalline material.

3-Methoxy-17a-(*N*-phenylcarboxamido)-D-homoestra-1,3,5(10),17-tetraene (**7b**): ^{1}H NMR ($CDCl_3$): 7.58 (d, 8.0 Hz, 2H, Ph(*ortho*)); 7.30–7.40 (m, 3H, Ph(*meta*) +NH); 7.22 (d, 7.8 Hz, 1H, 1-H); 7.10 (t, 7.8 Hz, 1H, Ph(*para*)); 6.73 (dd, 7.6 Hz, 2.6 Hz, 1H, 2-H); 6.62 (d, 2.6 Hz; 1H, 4-H); 6.12 (br s, 1H, 17-H); 3.79 (s, 3H, OCH_3); 2.84–2.91 (m, 2H, 6-H_2); 1.92–2.36 (m, 6H, skeleton protons); 1.24–1.61 (m, 7H, skeleton protons); 1.32 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 168.5; 157.6; 147.5; 138.3; 137.8; 132.9; 129.0 (double intensity); 128.7; 126.2; 124.1; 119.8 (double intensity); 113.5; 111.6; 55.2; 47.6; 43.7; 38.3; 36.9; 35.4; 30.1; 26.4; 26.0; 25.6; 19.9; 19.6. IR (KBr (cm^{-1})): 3328 (NH); 1675 (NCO); 1608 (C=C); 1595 (A-ring). MS (*m*/*z*/rel.int.): 401/65 (M^+), 309/100; 281/8; 207/48; 171/61. Analysis calculated for $C_{27}H_{31}O_2N$ (*M* = 401.55): C, 80.76; H, 7.78; N, 3.49; found: C, 80.58; H, 7.86; N, 3.30. R_f = 0.77 ($CHCl_3$/EtOAc = 95/5); mp. 210–211 °C. Off-white crystalline material.

3-Methoxy-17a-(*N*-phenylcarboxamido)-13α-D-homoestra-1,3,5(10),17-tetraene (**8b**): ^{1}H NMR ($CDCl_3$): 7.53 (d, 7 Hz, 2H, Ph(*ortho*)); 7.26–7.32 (m, 3H, Ph(*meta*) +NH); 7.20 (d, 8.4 Hz, 1H, 1-H); 7.08 (t, 7 Hz, 1H, Ph(*para*)); 6.70 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.62 (d, 2.6 Hz; 1H, 4-H); 6.19 (br s, 1H, 17-H); 3.79 (s, 3H, OCH_3); 2.84–2.92 (m, 2H, 6-H_2); 1.90–2.47 (m, 6H, skeleton protons); 1.07–1.50 (m, 7H, skeleton protons); 1.51 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 168.5; 157.6; 143.9; 138.2; 138.0; 133.0; 131.0;

129.0 (double intensity); 126.6; 124.1; 119.7 (double intensity); 113.5; 111.6; 55.2; 46.6; 42.6; 37.9; 37.7; 36.4; 31.9; 30.4; 28.9; 26.9; 21.4; 18.8. IR (KBr (cm^{-1})): 3425 (NH); 1668 (NCO); 1602 (C=C); 1590 (A-ring). MS (*m*/*z*/rel. int.): 401/100 (M^+), 309/86; 281/14; 173/93. Analysis calculated for $C_{27}H_{31}O_2N$ (*M* = 401.55): C, 80.76; H, 7.78; N, 3.49; found: C, 80.50; H, 7.92; N, 3.23. R_f = 0.59 ($CHCl_3$/EtOAc = 98/2); Mp. 223–224 °C. Off-white crystalline material with pinkish tinge.

3-Methoxy-17a-[(*N*,*N*-(1′,5′-pentanediyl)carboxamido)]-D-homoestra-1,3,5(10),17-tetraene (**7c**): ^{1}H NMR ($CDCl_3$): 7.20 (d, 8.4 Hz, 1H, 1-H); 6.72 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.62 (d, 2.6 Hz; 1H, 4-H); 5.52 (br s, 1H, 17-H); 3.78 (s, 3H, OCH_3); 3.40–3.70 (m, 4H, $2NCH_2$); 2.85–2.90 (m, 2H, 6-H_2); 1.20-2.33 (m, 19H, skeleton protons + $(CH_2)_3$); 1.28 (s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): 170.4; 157.6; 143.7; 137.9; 133.0; 126.2; 125.0; 113.5; 111.6; 55.2; 48.5; 47.1; 43.7; 42.1; 38.5; 36.7; 35.4; 30.1; 26.6; 26.4 (double intensity); 25.9; 25.2; 24.8; 20.3; 19.8. IR (KBr (cm^{-1})): 1655 (NCO); 1618 (C=C); 1608 (A-ring). MS (*m*/*z*/rel. int.): 393/49 (M^+), 378/100; 308/5. Analysis calculated for $C_{26}H_{35}O_2N$ (*M* = 393.57): C, 79.35; H, 8.96; N, 3.56; found: C, 79.30; H, 9.14; N, 3.41. R_f = 0.69 ($CHCl_3$/EtOAc = 80/20). Mp. 154–155 °C. White crystalline material.

3-Methoxy-17a-[(*N*,*N*-(1′,5′-pentanediyl)carboxamido)]-13α-D-homoestra-1,3,5(10),17-tetraene (**8c**): ^{1}H NMR ($CDCl_3$): 7.19 (d, 8.4 Hz, 1H, 1-H); 6.70 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.60 (d, 2.6 Hz; 1H, 4-H); 5.63 (br s, 1H, 17-H); 3.76 (s, 3H, OCH_3); 3.20–3.90 (m, 4H, $2NCH_2$); 2.80–2.85 (m, 2H, 6-H_2); 1.30–2.30 (m, 19H, skeleton protons + $(CH_2)_3$); 1.45 (br s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): 169.9; 157.3; 139.6; 137.8; 133.0; 128.7; 126.2; 113.1; 111.3; 54.9; 48.6 (br); 47.1 (br); 42.4 (double intensity); 37.6; 36.5 (br); 33.0 (br); 30.1; 28.4; 26.7; 26.3; 25.6; 24.6 (double intensity); 20.7; 18.7. IR (KBr (cm^{-1})): 1645 (NCO); 1603 (C=C); 1608 (A-ring). MS (*m*/*z*/rel. int.): 393/67 (M^+), 378/100; 308/10. Analysis calculated for $C_{26}H_{35}O_2N$ (*M* = 393.57): C, 79.35; H, 8.96; N, 3.56; found: C, 79.21; H, 9.18; N, 3.40. R_f = 0.59 ($CHCl_3$/EtOAc = 90/10). Mp. 96–97 °C. White crystalline material.

3-Methoxy-17a-[*N*-(1′-methoxycarbonylethyl)carboxamido]-D-homoestra-1,3,5(10),17-tetraene (**7d**): ^{1}H NMR ($CDCl_3$): 7.21 (d, 8.4 Hz, 1H, 1-H); 6.73 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.62 (d, 2.6 Hz; 1H, 4-H); 6.19 (br d, 7.5 Hz; 1H, NH); 6.00 (br s, 1H, 17-H); 4.60 (qi, 7.5 Hz, 1H, NHCH); 3.78 (s, 6H, 2xOCH_3); 2.83–2.90 (m, 2H, 6-H_2); 1.90–2.33 (m, 6H, skeleton protons); 1.20–1.55 (m, 7H, skeleton protons); 1.42 (q, 7.5 Hz, 3H, $CHCH_3$); 1.25 (s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): 173.6; 170.1; 157.4; 146.4; 137.7; 132.9; 128.6; 126.1; 113.4; 111.5; 55.1; 52.3; 47.7; 47.4; 43.5; 38.2; 36.5; 35.1; 30.0; 26.3; 26.0; 25.5; 19.6; 19.4; 18.3. IR (KBr (cm^{-1})): 3347 (NH); 1747 (COO); 1660 (NCO); 1632 (C=C); 1612 (A-ring). MS (*m*/*z*/rel.int.): 411/100 (M^+), 396/10; 309/42; 294/24; 280/18. Analysis calculated for $C_{25}H_{33}O_4N$ (*M* = 411.54): C, 72.96; H, 8.08; N, 3.40; found: C, 72.80; H, 8.22; N, 3.29. R_f = 0.76 ($CHCl_3$/EtOAc = 80/20); Mp. 159–160 °C. White crystalline material.

3-Methoxy-17a-[*N*-(1′-methoxycarbonylethyl)carboxamido]-13α-D-homoestra-1,3,5(10),17-tetraene (**8d**): ^{1}H NMR ($CDCl_3$): 7.20 (d, 8.4 Hz, 1H, 1-H); 6.71 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.61 (d, 2.6 Hz; 1H, 4-H); 6.12 (br s, 1H, 17-H); 6.05 (br d, 7.6 Hz; 1H, NH); 4.60 (qi, 7.4 Hz, 1H, NHCH); 3.78 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 2.83–2.87 (m, 2H, 6-H_2); 1.88–2.35 (m, 6H, skeleton protons); 1.02–1.40 (m, 7H, skeleton protons); 1.42 (s, 3H, 18-H_3); 1.38 (d, 7.4 Hz, 3H, $CHCH_3$). ^{13}C NMR ($CDCl_3$): 173.5; 169.9; 157.5; 142.7; 137.9; 132.9; 130.7; 126.4; 113.4; 111.5; 55.1; 52.2; 47.6; 46.4; 42.6; 37.5; 37.4; 36.5; 31.7; 30.3; 28.7; 26.8; 21.1; 18.7; 18.3. IR (KBr (cm^{-1})): 3392 (NH); 1717 (COO); 1664 (NCO); 1632 (C=C); 1608 (A-ring). MS (*m*/*z*/rel.int.): 411/100 (M^+), 396/5; 309/25; 294/19; 280/23. Analysis calculated for $C_{25}H_{33}O_4N$ (*M* = 411.54): C, 72.96; H, 8.08; N, 3.40; found: C, 72.77; H, 8.23; N, 3.25. R_f = 0.60 ($CHCl_3$/EtOAc = 90/10); Mp. 152–153 °C. Pale yellow crystalline material.

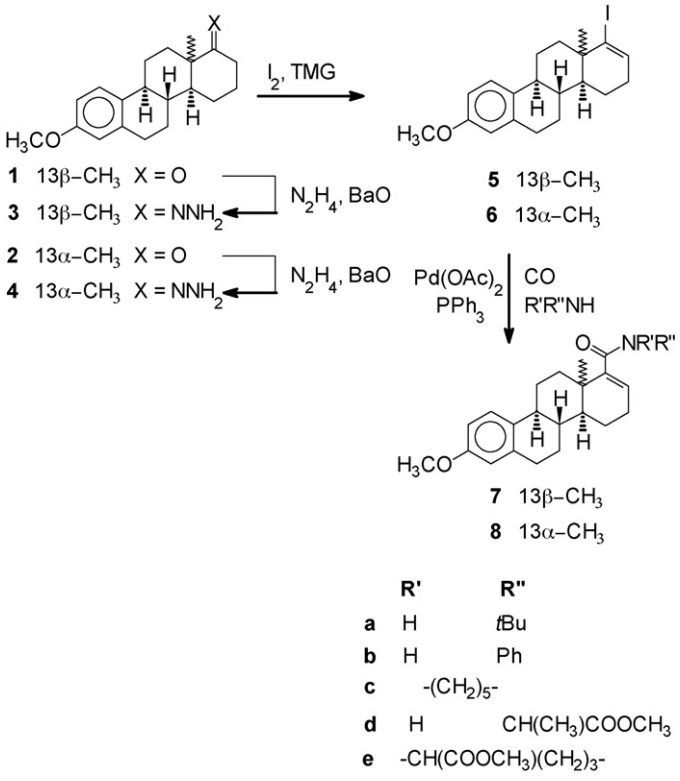
3-Methoxy-17a-[*N*,*N*-(1′-methoxycarbonyl-1′,4′-butanediyl)carboxamido]-D-homoestra-1,3,5(10),17-tetraene (**7e**, 85/15 mixture of two isomers due to C(O)–N hindered rotation): ^{1}H NMR ($CDCl_3$) (major/minor isomer): 7.20 (d, 8.4 Hz, 1H, 1-H); 6.71 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.60 (d, 2.6 Hz; 1H, 4-H); 5.68/5.52 (br s, 1H, 17-H); 4.42 (d, 7.2 Hz, 1H, NCH); 3.78 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 3.50–3.70 (m, 2H, NCH_2); 2.82–2.87 (m, 2H, 6-H_2); 1.80–2.37 (m, 10H, skeleton protons + $(CH_2)_2$); 1.20–1.55 (m, 7H, skeleton protons); 1.24/1.25 (s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$) (major/minor isomer): 172.7/173.3; 170.1/170.3; 157.3; 144.4/144.8; 137.6; 132.8/132.6; 126.3/127.0; 126.0/125.9; 113.3; 111.3; 58.1/57.8; 55.0; 51.8/52.0; 49.3; 47.2/46.9; 43.5/43.4; 38.2; 36.9/36.6; 35.2; 29.9/30.8; 29.3; 26.2; 25.9/25.7; 25.1/24.8; 24.4; 19.9/20.2; 19.5. IR (KBr (cm^{-1})): 1747 (COO); 1657 (NCO); 1614 br (C=C + A-ring). MS (*m*/*z*/rel. int.): 437/70 (M^+), 422/100; 378/15; 309/76. Analysis calculated for $C_{27}H_{35}O_4N$ (*M* = 437.58): C, 74.11; H, 8.06; N, 3.20; found: C, 74.02; H, 8.27; N, 3.11. R_f = 0.61 ($CHCl_3$/EtOAc = 80/20). Yellow highly viscous material.

3-Methoxy-17a-[*N*,*N*-(1′-methoxycarbonyl-1′,4′-butanediyl)carboxamido]-13α-D-homoestra-1,3,5(10),17-tetraene (**8e**, 80/20 mixture of two isomers due to C(O)–N hindered rotation): ^{1}H NMR ($CDCl_3$) (major/minor isomer): 7.18 (d, 8.4 Hz, 1H, 1-H); 6.70 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.60 (d, 2.6 Hz; 1H, 4-H); 5.98/5.86 (br s, 1H, 17-H); 4.58 (t, 7.4 Hz, 1H, NCH); 3.76 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 3.45–3.65 (m, 2H, NCH_2); 2.78–2.87 (m, 2H, 6-H_2); 1.80–2.37 (m, 10H, skeleton protons + $(CH_2)_2$); 0.96–1.50 (m, 7H, skeleton protons); 1.45/1.40 (s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$) (major/minor isomer): 173.1/172.1; 169.7; 157.3; 141.8/140.4; 137.9/137.7; 133.1/132.9; 130.9/129.9; 126.4/126.1; 113.2; 111.4; 58.2/58.5; 55.0; 52.0; 49.8; 46.9; 42.7/42.5; 37.8; 36.5/36.3; 32.5; 30.7/30.2; 29.1; 28.5/27.9; 26.8; 25.6/24.8; 22.2/21.0; 18.7/18.4; 14.1. IR (KBr (cm^{-1})): 1747 (COO); 1679 (NCO); 1611 br (C=C + A-ring). MS (*m*/*z*/rel. int.): 437/65 (M^+), 422/100; 378/10; 309/39. Analysis calculated for $C_{27}H_{35}O_4N$ (*M* = 437.58): C, 74.11; H, 8.06; N, 3.20; found: C, 73.98; H, 8.29; N, 3.01. R_f = 0.72 ($CHCl_3$/EtOAc = 80/20). Mp. 78–80 °C. White crystalline material.

3-Methoxy-17a-methoxycarbonyl-D-homoestra-1,3,5(10),17-tetraene (**9**): ^{1}H NMR ($CDCl_3$): 7.22 (d, 8.4 Hz, 1H, 1-H); 6.66–6.73 (m, 2H, 2-H + 17-H); 6.62 (br s, 1H, 4-H); 3.80 (s, 3H, OCH_3); 3.72 (s, 3H, $COOCH_3$); 2.82–2.91 (m, 2H, 6-H_2); 2.49 (d, 13.0 Hz, 1H, 16-H_a); 1.90–2.35 (m, 5H, skeleton protons); 1.20–1.65 (m, 7H, skeleton protons); 1.21 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 168.0; 157.55; 141.2; 137.6; 133.0; 126.3; 126.21; 113.48; 111.56; 55.2; 51.2; 48.1; 43.6; 39.2; 38.2; 36.6; 35.2; 30.1; 26.5; 26.2; 19.3; 19.0. IR (KBr (cm^{-1})): 1709 (COO); 1612 br (C=C + A-ring). MS (*m*/*z*/rel. int.): 340/100 (M^+), 312/2, 281/10; 228/40; 213/11. Analysis calculated for $C_{22}H_{28}O_3$ (*M* = 340.46): C, 77.61; H, 8.29; found: C, 77.49; H, 8.39. R_f = 0.70 ($CHCl_3$/EtOAc = 98/2). Mp. 95–98 °C. Off-white crystalline material.

3-Methoxy-17a-methoxycarbonyl-13α-D-homoestra-1,3,5(10),16-tetraene (**9′**): ^{1}H NMR ($CDCl_3$): 7.22 (d, 8.4 Hz, 1H, 1-H); 6.73 (dd, 8.4 Hz, 2.6 Hz, 1H, 2-H); 6.62 (br s, 1H, 4-H); 5.82 (br s, 1H, 16-H); 5.61 (br d, 10.0 Hz, 1H, 17-H); 3.80 (s, 3H, OCH_3); 3.71 (s, 3H, $COOCH_3$); 3.00 (br s, 1H, 17a-H); 2.82–2.90 (m, 2H, 6-H_2); 1.90–2.35 (m, 6H, skeleton protons); 1.20–1.65 (m, 7H, skeleton protons); 0.87 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 174.0; 157.57; 137.3; 134.3; 132.7; 126.30; 126.2; 113.50; 111.67; 55.2; 51.2; 45.5; 42.8; 40.1; 39.2; 38.2;35.4; 30.1; 26.7; 26.3; 26.1; 13.5. IR (KBr (cm^{-1})): 1732 (COO); 1612 bar (C=C + A-ring). MS (*m*/*z*/rel. int.): 340/100 (M^+), 312/2, 281/10; 228/40; 213/11. Analysis calculated for $C_{22}H_{28}O_3$ (*M* = 340.46): C, 77.61; H, 8.29; found: C, 77.35; H, 8.44. R_f = 0.70 ($CHCl_3$/EtOAc = 98/2). Mp. 127–129 °C. White crystalline material.

3-Methoxy-17a-methoxycarbonyl-13α-D-homoestra-1,3,5(10),17-tetraene (**10**): ^{1}H NMR ($CDCl_3$): 7.20 (d, 8.4 Hz,



Scheme 1. Synthesis of 3-methoxy-17a-carboxamido-D-homoestra-1,3,5(10),17-tetraene (**7a**–**e**) and 3-methoxy-17a-carboxamido-13α-D-homoestra-1,3,5(10),17-tetraene (**8a**–**e**) derivatives via aminocarbonylation of **5** and **6**, respectively.

1H, 1-H); 6.70–6.76 (m, 2H, 2-H, 6.62 (br s, 1H, 17-H); 3.79 (s, 3H, OCH_3); 3.69 (s, 3H, $COOCH_3$); 2.80–2.90 (m, 2H, 6-H_2); 2.67 (d, 13.0 Hz, 1H, 16-H_a); 1.90–2.37 (m, 5H, skeleton protons); 0.98–1.40 (m, 7H, skeleton protons); 1.39 (s, 3H, 18-H_3); ^{13}C NMR ($CDCl_3$): 167.9; 157.4; 139.1; 137.8; 137.1; 133.1; 126.2; 113.3; 111.9; 55.1; 51.0; 46.8; 42.7; 37.2; 37.1; 36.4; 30.9; 30.2; 27.9; 26.8; 21.9; 18.5. IR (KBr (cm^{-1})): 1708 (COO); 1609 br (C=C + A-ring). MS (*m*/*z*/rel. int.): 340/100 (M^+), 325/3, 293/5; 225/10; 186/32. Analysis calculated for $C_{22}H_{28}O_3$ (*M* = 340.46): C, 77.61; H, 8.29; found: C, 77.40; H, 8.51. R_f = 0.70 ($CHCl_3$/EtOAc = 98/2). Mp. 135–136 °C. Pale-brown crystalline material.

3. Results and discussion

According to a general carbonylation methodology, the iodoalkene functionality undergoes various carbonylation reactions in the presence of amines, alcohols or H_2O as HX-type nucleophiles resulting in a facile synthesis of the corresponding amides, esters or carboxylic acids, respectively. Two 13-epimers of 3-methoxy-17a-iodo-D-homoestra-1,3,5(10),17-tetraene (13β, 'natural', **5** and 13α, 'epi', **6**) were used as substrates in homogeneous carbonylations. They were synthesized from the corresponding 17a-ketone epimers (**1** and **2**, respectively) via their hydrazones (**3** and **4**, respectively) (Scheme 1). A published method based on the ketone–hydrazone–iodoalkene reaction pathway with some modifications was used [21,22]. Using the similar procedure for the synthesis of **5** and **6**, significant differences in yields were observed. Low yields (up to 64%, isolated yields up to 37%) were obtained for **5**. Detailed GC–MS studies revealed that the formation of the target compound (**5**) is always accompanied by that of the four different dehydroiodination products possessing carbon–carbon double bonds in different positions of the D-ring. Furthermore, it turned out that neither the increase of the molar ratio of hydrazine (from 5- to 10-fold related to the starting ketone, **1**) nor the increase in the reaction temperature of hydrazone (**3**) formation (from 110 °C (in 2-methoxy-etanol) to 135 °C (in 2-ethoxy-ethanol)) resulted in higher isolated yield of **5**.

However, the transformation of **2**–**6** (via hydrazone **4**) was practically complete under standard hydrazone formation–iodination conditions and two dehydroiodination products were detected by GC–MS in traces only (less than 2% each). The high-purity iodoalkene (**6**) was isolated by column chromatography in up to 63% yields in a highly reproducible reaction.

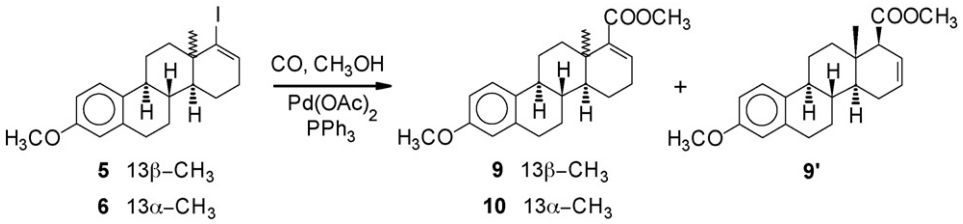
Compound **5** and **6** were reacted with CO at atmospheric pressure and various primary or secondary amines as *N*-nucleophiles (*tert*-butylamine (**a**), aniline (**b**), piperidine (**c**), methyl alaninate (**d**) or methyl prolinate (**e**)) in DMF in the presence of palladium(II) acetate–PPh_3 catalyst formed *in situ* (Scheme 1). The *in situ* formation of highly reactive, coordinately unsaturated palladium(0) complexes from palladium(II) acetate has been investigated in detail [23]. The aminocarbonylation of both **5** and **6** was chemospecific resulting in the exclusive formation of the corresponding 17a-carboxamido-16-ene derivatives, **7a-e** and **8a-e**, respectively. However, the two substrates differ substantially in reactivity: while practically complete conversions were obtained in reasonable reaction times by using **5** (run 1, 8, 10 and 14) except for the case when proline methyl ester was used as *N*-nucleophile (run 16), up to 71% conversions were obtained only with **6** under the same reaction conditions (run 5, 9, 12 and 15) (Table 1).

The smooth work-up procedure of the reaction mixtures, as well as the isolation of the target amides in excellent purity has proved that the substrates with iodo-vinyl functionality are good enol-triflate surrogates. Using the naturally configured **5** (13β), the highest reactivities were observed with sterically less hindered primary and secondary amines such as *tert*-butyl-amine (**a**), aniline (**b**), piperidine (**c**) and methyl alaninate (**d**). The corresponding carboxamides were isolated in yields of up to 84%. The amino acid ester with a sterically hindered secondary amine functionality (methyl prolinate, **e**) resulted in definitely lower yield. Surprisingly, aniline (**b**) with low basicity (usually being less reactive than the other primary amines) reacted with practically complete conversion. It was revealed by detailed GC–MS studies on the aminocarbonylation of **5** with **a** (runs 2–4) and **c** (run 11) as *N*-nucleophiles, that high conversions can be obtained even much shorter reaction times than the normally used 20 h.

Although the order of reactivity is very similar to that of the natural 13β series, that is, **a** being most and **e** less reactive, much lower conversions and, consequently, isolated yields were obtained (Table 1). Under carbon monoxide at atmospheric pressure, 45% conversion was obtained with **a** (run 5), and practically no reaction was observed with **e** (run 17). It is worth noting that the conversions can be increased substantially by applying higher carbon monoxide pressure (40 bar), and as a consequence of that, isolated yields of practical importance were obtained with **a** (runs 6 and 7), with **c** (run 13), and even with the less reactive **e** (run 18).

In addition to the *N*-nucleophiles, methanol as *O*-nucleophile was also used in alkoxycarbonylation of **5** and **6** carried out under carbon monoxide at atmospheric pressure (Scheme 2). Even more pronounced difference in reactivity was observed in methoxycarbonylation than in aminocarbonylations, that is, while **5** was completely converted in 20 h, 6% conversion was achieved with **6** under same conditions. Similarly to aminocarbonylation, the conversion of **6** into the methoxycarbonylated product **10** was efficiently increased to 88% rising the carbon monoxide pressure to 40 bar.

Surprisingly, the product composition differ completely: while the alkoxycarbonylation of **6** (13α-epimer) resulted in the formation of **10** with the expected 17-ene structure exclusively, that of the **5** gave two products in a ratio of 55/45. Detailed NMR

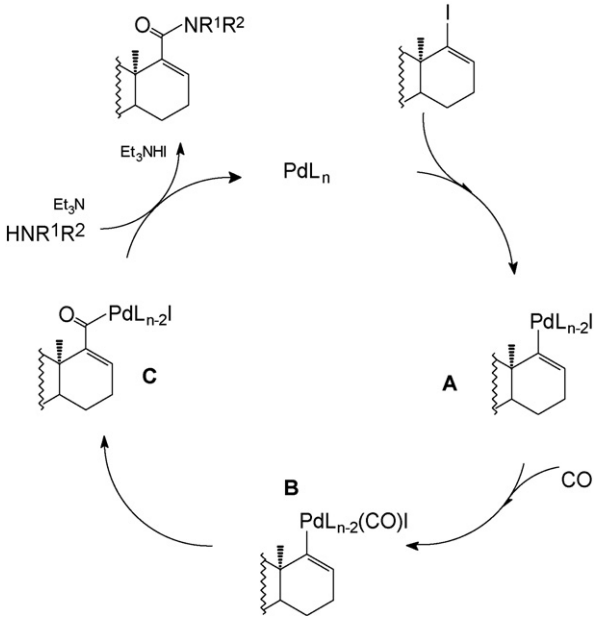


Scheme 2. Synthesis of 3-methoxy-17a-methoxycarbonyl-D-homoestra-1,3,5(10),17-tetraene (**9**) and 3-methoxy-17a-methoxycarbonyl-13α-D-homoestra-1,3,5(10),17-tetraene (**10**) via alkoxycarbonylation of **5** and **6**, respectively.

investigations, including 2D techniques such as NOESY and ROESY, revealed that in addition to the expected α-unsaturated ester (17-ene derivative, **9**) its 16-ene isomer (**9′**) was also formed.

The significant difference between the reactivity of **5** and **6** both in amino- and alkoxycarbonylations can be explained by the different C/D-ring anellations. The *cis*-C/D anellation in **6** resulted in a sterically congested arrangement of ring C and D. The close proximity of the axial 11β-H of the methylene group in position-11 and the axial H atom at C-8, makes the oxidative addition of the 17a-iodo-17-ene moiety to palladium(0)-complex forming an alkenyl-palladium(II) complex (**A**) sterically highly disfavored (Scheme 3). Therefore, the consecutive catalytic steps, the activation and insertion of carbon monoxide, resulting in the terminal carbonyl complex (**B**) and the acyl-palladium(II) complex (**C**), respectively, and the product forming reductive elimination are also much slower than the corresponding elementary steps involving **5.** All of the latter elementary steps are facile reactions due to the *trans* anellation of the C/D-rings and therefore, less steric congestion.

In summary, novel 17a-carboxamido-D-homoestra-1,3,5(10),17-tetraenes were synthesized in palladium-catalyzed carbonylations both in the natural (13β) and in the epi (13α) series. The two iodoalkene substrates, obtained from the corresponding 17a-ketones via the corresponding hydrazones, proved to be excellent enol-triflate surrogates. The *in situ* formed palladium(0) catalysts were highly active in the aminocarbonylation of the normal series resulting in yields of practical interest under mild reaction conditions. The efficacy of the homogeneous carbonylations can be proved also by the acceptable yields in the sterically hindered 13α series which could not be achieved by conventional reactions.



Scheme 3. A simplified reaction mechanism for the aminocarbonylation of a 13α-D-homosteroid.

Acknowledgments

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