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A new facile synthesis of steroid dimers containing 17,17′-dicarboxamide spacers

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ABSTRACT

A set of new steroid dimers linked through ring D–ring D were synthesized via catalytic diaminocarbonylation of 17-iodo-5α-androst-16-ene, in the presence of palladium–phosphine in situ catalysts and aliphatic or aromatic diamines as *N*-nucleophiles. The dimeric steroidal compounds containing 17,17′-dicarboxamide spacers were obtained through highly chemoselective reactions in good isolated yields and completely characterized by spectroscopic techniques.

Steroids are widely found in both plant and animal kingdoms, and play crucial roles in biological systems.[1,2] Among them, dimeric steroids constitute a class of compounds, which have recently attracted much attention due to their remarkable properties as potential cytotoxic, antimalarial, anticancer, and cholesterol lowering drugs as well as molecular umbrellas in drug delivery.[3–9] In addition to their pharmacological importance, several dimeric and oligomeric steroids display micellar activity,[10] they can also act as ligands for proteins and trigger cellular processes or may promote the affinity of ligands to their binding locations by providing extra anchoring points to the active site of certain domains.[11,12] Some of the dimers show liquid-crystal behaviour[13] and play key roles in rate enhancement from hydrophobic binding.[14]

The synthetic approaches reported so far, have led to the preparation of cyclic and acyclic steroidal dimers, by connection between two *cyclopentano-perhydrophenanthrene* skeletons (through A–A, B–B, C–C, D–D or A–D rings).[3–5] The steroidal moieties could be directly linked,[15–17] linked through spacer groups[18–25] and by connection through the steroidal side chains.[26–29] Concerning steroidal D–D ring dimers linked through spacer groups, a number of pollutant multi-step and low-yielding synthetic approaches have been frequently used.[3] Thus, other environmentally sustainable alternatives to promote steroid dimerizations still constitute a great challenge. It is well established that transition-metal-catalyzed reactions are versatile tools to introduce different functionalities into specific positions of the steroidal framework, which can render marked changes in their biological properties.[30] Recently, our groups have reported several examples on the aminocarbonylation of steroidal alkenyl-iodides toward carboxamides.[31] Nevertheless, to the best of our knowledge, there is only one example on the synthesis of dimeric steroids involving Pd-catalyzed carbonylative dimerization of alkenyl-iodide intermediates, to form 17-carboxylic anhydrides, in the presence of carbon monoxide and water.[32] It should be also noted that the application of diamines as *N*-nucleophiles in palladium-catalyzed aminocarbonylation toward dicarboxamides is unprecedented.

Therefore, the iodoalkene-based catalytic synthetic strategy described herein provides a completely new, facile, efficient, and atom economic methodology for the preparation of steroid dimers. A set of dimeric androst-16-enes with structurally different dicarboxamide spacers at C-17 was synthesized via one-pot, one-step palladium-catalyzed aminocarbonylation of 17-iodo-5α-androst-16-ene (**1**), which was obtained by the modified Barton's procedure from the corresponding 17-ketone.[33]

In a typical experiment,[34] 17-iodo-5α-androst-16-ene (**1**) was introduced in the autoclave in the presence of palladium(II) acetate, 2 M equiv of triphenylphosphine, and 0.5 M equiv of the desired diamine (1,2-diaminoethane (**a**), 1,4-diaminobutane (**b**),

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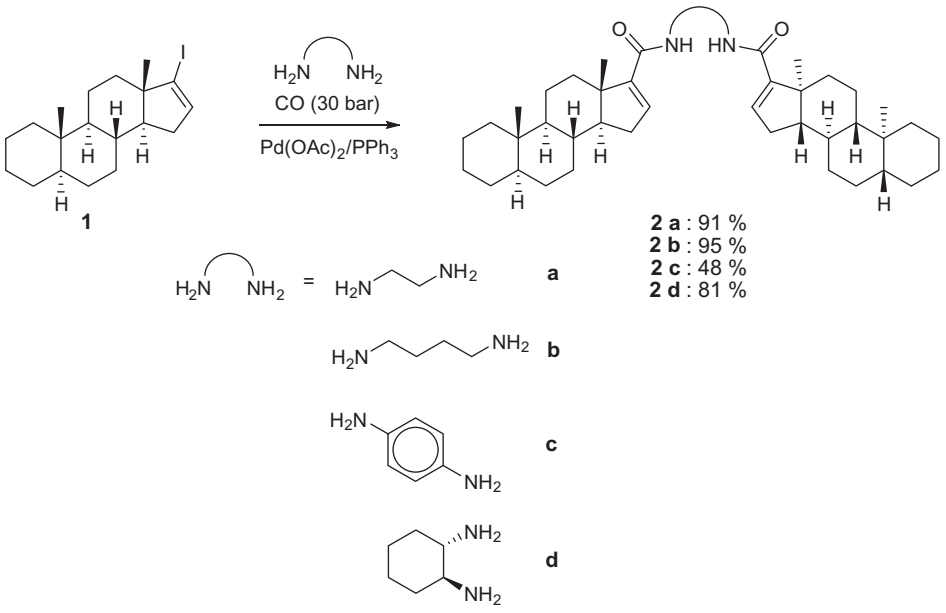

Scheme 1.

1,4-diaminobenzene (**c**), and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (**d**) as *N*-nucleophile), Scheme 1.

The carbonylative dimerization reaction leading to steroidal dicarboxamides (**2a**–**2d**) took place under relatively mild conditions (30 bar CO, 100 °C), with nearly full conversion of the initial iodo alkenyl steroid in 5 h. The symmetric androst-16-ene dicarboxamide dimers **2a**, **2b**, **2c,** and **2d** were obtained in 91%, 95%, 48%, and 81% isolated yields,[35] respectively, after work-up and purification by column chromatography using silica gel, or by simple washing with ethyl acetate. From these results, it was possible to conclude that aliphatic diamines (**a**), (**b**), and (**d**) gave significantly higher yields than that obtained with the aromatic diamine 1,4-diaminobenzene (**c**). It should be noted that the use of optically pure (*1S*,*2S*)-(+)-diaminocyclohexane (**d**) produced a single diastereomeric steroid dimer (**2d**) in 81% isolated yield. However, when a racemic mixture of *trans*-(±)-1,2-diaminocyclohexane was used as nucleophile, a 1:1 mixture of two diastereomeric steroidal dimers was obtained, as evidenced by duplicate signals on ^{1}H and ^{13}C NMR spectra.

Detailed NMR and MS studies carried out on reaction mixtures and raw products (i.e., on isolated products prior to chromatography) revealed that no double carbon monoxide insertion into the Pd-alkenyl species occurred. That is, the formation of 2-ketocarboxamide-type derivatives could not be observed. This observation is in agreement with previous findings showing that iodoalkene substrates undergo double carbon monoxide insertion only under special conditions.[36]

In conclusion, a promising synthetic strategy was developed for the preparation of steroid dimers, via optimized palladium-catalyzed diaminocarbonylation reactions. The versatility of this methodology is demonstrated by the ability to prepare valuable functionalized steroid dimers linked through multiple achiral and a chiral dicarboxamide spacers.

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34. In a typical experiment, $Pd(OAc)_2$ (2.6 mg, 0.0125 mmol), triphenylphosphine (6.6 mg, 0.025 mmol), 17-iodo-androst-16-ene (220 mg, 0.57 mmol), diamine nucleophile (0.285 mmol), and triethylamine (0.25 ml) were dissolved in DMF (5 mL) under argon in a stainless steel autoclave. The atmosphere was pressurized to 30 bar CO. The reaction was conducted for 5 h, upon stirring at 100 °C. The mixture was then evaporated to dryness; the residue was dissolved in chloroform (20 ml) and washed with water (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to a crystalline material or to a waxy residue, which was analyzed by ^1H and ^{13}C NMR. All compounds were purified through column chromatography (Silicagel 60, Merck, 0.063–0.200 mm), EtOAc/$CHCl_3$ (exact ratios are specified for each compound), or simply washed with ethyl acetate (as in the case of **2c**).
35. Characterization of the compounds **2a**–**2d**: *N*,*N*′-(ethane-1,2-diyl)diandrost-16-ene-17-carboxamide (**2a**): Yield: 163 mg (91%), white solid, mp 153–156 °C; R_f (EtOAc/$CHCl_3$ 2:1) 0.16; δ_H (400 MHz, $CDCl_3$) 6.35 (2H, br s, N*H*), 6.23 (2H, s, C=C*H*), 3.45 (2H, d, 9.6 Hz, N-C*H*$_a$H$_b$), 3.33 (2H, d, 9.6 Hz, N-CH$_a$*H*$_b$), 2.03–2.12 (4H, m, 15-*H*$_2$), 1.86 (2H, dd, 12.0 Hz, 15.2 Hz, 14-*H*), 0.88 (6H, s, 19-*H*$_3$), 0.74 (6H, s, 18-*H*$_3$), 0.65–1.60 (38H, m, *skeleton protons*); δ_C (100.6 MHz, $CDCl_3$) 167.4, 150.4, 136.4, 56.9, 55.4, 47.3, 46.7, 39.8, 38.7, 36.6, 35.0, 33.9, 32.1, 31.8, 29.1, 29.0, 26.9, 22.3, 20.8, 16.6, 12.3; IR (KBr (cm^{-1})): 3295 (v br, NH), 1645 (CO), 1591 (C=C); HRMS (ESI): *m*/*z* calcd for $C_{42}H_{65}N_2O_2$ $[M+H]^+$ 629.5041, found 629.5038. *N*,*N*′-(Butane-1,4-diyl)diandrost-16-ene-17-carboxamide (**2b**): Yield: 178 mg (95%), white solid, mp 179–182 °C; R_f (EtOAc/$CHCl_3$ 1:1) 0.15; δ_H (400 MHz, $CDCl_3$) 6.25 (2H, s, C=C*H*), 5.80 (2H, br s, N*H*), 3.26 (4H, br s, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 2.02–2.15 (4H, m, 15-*H*$_2$), 1.88 (2H, dd, 11.6 Hz, 15.2 Hz, 14-*H*), 0.90 (6H, s, 19-*H*$_3$), 0.75 (6H, s, 18-*H*$_3$), 0.66–1.60 (42H, m, *skeleton protons* + NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N); δ_C (100.6 MHz, $CDCl_3$) 166.5, 150.8, 135.8, 57.0, 55.3, 47.4, 46.8, 38.7 (double intensity), 36.6, 35.2, 34.0, 32.1, 31.8, 29.2, 29.1, 27.2, 27.0, 22.3, 20.9, 16.7, 12.3; IR (KBr (cm^{-1})): 3298 (v br, NH), 1639 (CO), 1594 (C=C); HRMS (ESI): *m*/*z* calcd for $C_{44}H_{69}N_2O_2$ $[M+H]^+$ 657.5354, found 657.5347. *N*,*N*′-(1,4-phenylene)diandrost-16-ene-17-carboxamide (**2c**): Yield: 92 mg (48%), beige solid, mp 316–319 °C (dec.); R_f ($CHCl_3$/EtOAc 10:1) 0.45; δ_H (400 MHz, $CDCl_3$) 7.50 (4H, s, aromatic *H*) 7.40 (2H, br s, N*H*), 6.44 (2H, s, C=C*H*), 2.19–2.28 (4H, m, 15-*H*$_2$), 2.02 (2H, dd, 9.4 Hz, 12.2 Hz, 14-*H*), 1.04 (6H, s, 19-*H*$_3$), 0.82 (6H, s, 18-*H*$_3$), 0.76–1.70 (38H, m, *skeleton protons*); δ_C (100.6 MHz, $CDCl_3$) 164.1, 151.3, 136.8, 134.3, 120.4, 56.9, 55.3, 47.4, 47.0, 38.6, 36.6, 35.1, 34.0, 32.1, 32.0, 29.2, 29.0, 26.9, 22.3, 20.8, 16.7, 12.3; IR (KBr (cm^{-1})): 3314 (v br, NH), 1665 (CO), 1594 (C=C); HRMS (ESI): *m*/*z* calcd for $C_{46}H_{65}N_2O_2$ $[M+H]^+$ 677.5041, found 677.5032. *N*,*N*′-(Cyclohexane-(1*S*,2*S*)-diyl)diandrost-16-ene-17-carboxamide (**2d**): Yield: 157 mg (81%), white solid, mp 230–233 °C; $[\alpha]_D^{20}$: + 40.0 (*c* 1.0, CH_2Cl_2); R_f ($CHCl_3$/EtOAc 8:1) 0.8; δ_H (400 MHz, $CDCl_3$) 6.23 (2H, br s, N*H*), 6.20 (2H, s, C=C*H*), 3.72 (2H, br s, N-C*H*$_2$), 2.03–2.16 (6H, m, 15–*H*$_2$ + NCHC*H*$_a$H$_b$, 1.93 (2H, dd, 12.3 Hz, 15.6 Hz, 14-*H*), 0.95 (6H, s, 19-*H*$_3$), 0.80 (6H, s, 18-*H*$_3$), 0.68–1.80 (44H, m, *skeleton protons* + NCHCH$_a$*H*$_b$CH$_2$CH$_2$CH$_a$*H*$_b$CHN); δ_C (100.6 MHz, $CDCl_3$) 167.1; 150.8, 135.2, 56.8, 55.7, 53.6, 47.3, 46.9, 39.0, 36.7, 35.0, 33.9, 32.7, 32.1, 31.8, 29.2, 29.0 26.9, 25.0, 22.3, 20.8, 16.5, 12.3; IR (KBr (cm^{-1})): 3340 (v br, NH), 1642 (CO), 1591 (C=C); HRMS (ESI): *m*/*z* calcd for $C_{46}H_{71}N_2O_2$ $[M+H]^+$ 683.5510, found 683.5528.
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