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Synthesis of novel steroid-tetrahydroquinoline hybrid molecules and D-homosteroids by intramolecular cyclization reactions

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Abstract

Steroidal aryliminium salts were prepared from D-*seco*-pregnene aldehyde **2b**, and their $BF_3{\cdot}OEt_2$-catalyzed reactions were studied. The nature of the substituent R^1 in the anilines **3**–**6** essentially influenced the chemoselectivity. Using unsubstituted **3**, 4-methoxy- (**4**) or 4-bromoaniline (**5**), different tetrahydroquinoline derivatives **7a**–**13a** via intramolecular hetero *Diels-Alder* reaction were formed. In the case of 4-nitroaniline (**6**) the *N*-arylamino-D-homopregnane (**14a**) were also obtained. We assume, that an intramolecular *Prins* reaction led to this type of fluoro-D-homosteroid. The main products represent a new class of tetrahydroquinolino-androstenes.

Keywords: Cycloaddition; Hetero *Diels-Alder* reaction; D-Homosteroids; Intramolecular *Prins* reaction; Quinolines

1. Introduction

A significant aim in organic chemistry is the development of new types of pharmacologically active substances. The coupling of two or more natural products to make hybrids leads to an almost inexhaustible reservoir of new types of compounds with diverse structures. We recently made a new type of pharmacologically interesting, hybrid natural product from estrone and the highly biologically active mycotoxin talaromycin B [1], and in vitro tests demonstrated its strong cytotoxic activity against human cells [2]. The combination of a toxin with a steroid was chosen in light of the fact that steroids are able to penetrate the cell membrane and bind the cell nucleus [3].

As part of a program of research on steroid hybrids, we were interested in the synthesis of various kinds of tetrahydroquinolines condensed to the androstane skeleton. Tetrahydroquinolines occur naturally in the human body [4]. One such compound, oxamniquine has an antiarrhythmic effect, while dynemicin, which has a complex structure based on the tetrahydroquinoline system, is a natural antitumor antibiotic [5].

Our goal was to prepare tetrahydroquinoline steroid hybrid molecules via a *Lewis* acid-catalyzed reaction of an aldehyde steroid fragment **2**, containing a substituted allyl and a formyl group in suitable positions, and various anilines **3**–**6**. We planned to perform the reaction in consecutive steps: amine-oxo condensation and a subsequent hetero *Diels-Alder* reaction. Additionally, we intended to investigate the influence of the relatively rigid steroidal skeleton and the different substituents of the aniline on the stereoselectivity of these reactions.

2. Experimental

Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured in chloroform (*c* 1, if not mentioned otherwise) with a POLAMAT-A (Zeiss-Jena) polarimeter and are given in units of 10^{-1} degree $cm^2\ g^{-1}$. Elemental analyses were performed with a Perkin-Elmer CHN analyzer model 2400. Thin-layer chromatography: silica gel 60 F_{254}; layer thickness 0.2 mm (Merck); solvent systems (ss): (A) ethyl acetate/dichloromethane (5:95 v/v); (B) dichloromethane; (C) *tert*-butyl methyl ether/light petroleum (1:1 v/v); (D) ethyl acetate/dichloromethane

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(30:70 v/v); (E) *tert*-butyl methyl ether/dichloromethane (20:80 v/v); (F) ethyl acetate/dichloromethane (10:90 v/v); (G) ethyl acetate/dichloromethane (20:80 v/v); (H) *tert*-butyl methyl ether/dichloromethane (10:90 v/v); detection with iodine or UV (365 nm) after spraying with 50% H_3PO_4 and heating at 100–120 °C for 10 min. Flash chromatography: silica gel 60, 40–63 μm. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ solution with a Bruker DRX-500 instrument, using TMS as the internal standard. ^{13}C NMR spectra were recorded with the same instrument at 125 MHz, using the $CDCl_3$ triplet (δ 77.0) as a reference (if not stated otherwise). EI-MS spectra were recorded on a Varian MAT 311A instrument with an ionization energy of 70 eV.

Diffraction data for compound **7d** were collected on a Stoe-Huber-Siemens four-circle diffractometer at −140 °C and were processed by SMART, SAINT, and SADABS (BrukerAXS, 2002). Intensity data for compound **11c** were collected on a Stoe IPDS II two-circle diffractometer at −140 °C and processed with the program X-Area (Stoe, 2002). In both cases, graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) was used. Compound **14c** was measured on a Bruker rotating anode equipped with Osmic focusing mirrors and a Bruker SMART6000 4K CCD detector using Cu Kα radiation (λ = 1.54178 Å), and the data were processed with Proteum, SAINT, and SADABS (BrukerAXS, 2002). The structures were solved by direct methods using SHELXS [13] and refined against F_o^2 using SHELXL (Sheldrick, G.M., SHELXL-97, Program for Structure Refinement, Universität Göttingen, 1997). All non-hydrogen atoms were refined anisotropically, hydrogen atoms in hydrogen bonds were refined isotropically, and the riding model was used for the remaining hydrogen atoms.

2.1. General procedures

2.1.1. A: Preparation of the Diels-Alder adducts *7a–13a* and the D-homosteroid *14a*

A solution of **2b** (359 mg, 1.0 mmol) and the aniline (**3**–**6**, 1.1 mmol) in dichloromethane (10 ml) was heated under a nitrogen atmosphere in the presence of molecular sieve (4 Å, 150 mg) for 1.5 h at 40 °C. The sieve was filtered off, and $BF_3{\cdot}OEt_2$ (a 1 M solution in CH_2Cl_2, 1 ml, 1 mmol) was added dropwise at 0 °C. The reaction was continued until complete conversion was achieved (TLC). In the next step, saturated $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude products (**7a**–**14a**) were purified by flash chromatography.

2.1.2. B: Alkaline hydrolysis

The steroid derivatives (**7a**–**14a**, **7c**–**14c**, 0.25 mmol) were suspended in methanol (25 ml), and $NaOCH_3$ (25 mg, 0.46 mmol) in methanol (5 ml) was added. The mixture was stirred until completion of the reaction (monitored by TLC) and then worked up. Water (50 ml) was added, and the precipitate was separated, washed with water, and dried. The crude products (**7b**–**14b**, **7d**–**14d**) were purified by flash chromatography or by recrystallization.

2.1.3. C: Preparation of 3β-acetoxy-N-acetyl compounds

The steroid derivatives (**7a**–**13a**, 1.0 mmol) were dissolved in acetic anhydride (10 ml) and KOAc (1.0 g, 10.2 mmol) was added. The solution was heated at 80 °C, which yielded a deep-colored mixture. It was worked up by the addition of water (30 ml) and extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were washed with water (2 × 30 ml), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude products (**7c**–**13c**) were purified by recrystallization or by flash chromatography.

2.1.4. 1′,4′,16,17-Tetrahydro-3β-acetoxy-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (*7a*) and 1′,4′,16,17-tetrahydro-3β-acetoxy-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (*11a*)

D-*seco*-Steroid **2b** (359 mg, 1.0 mmol) was reacted with **3** (0.1 ml, 1.1 mmol) by general procedure A. The resulting crude product was chromatographed on silica gel with dichloromethane as the eluent, yielding pure **11a** (51 mg, 12%), mp 210–222 °C, R_f = 0.4 (ss B), $[\alpha]_D^{20}$ = −82 (Found C, 80.54; H, 8.95; N, 3.41. $C_{29}H_{39}NO_2$ requires C, 80.33, H 9.07, N 3.23%); ^{1}H NMR: δ = 0.82 (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.34 (d, J = 6.9 Hz, 3H, 21-H_3), 2.03 (s, 3H, CH_3CO), 2.10–2.17 (m, 1H), 2.33 (m, 2H, 4-H_2), 2.72 (m, 1H, 20-H), 3.63 (m, 1H, 16-H), 3.68 (br s, 1H, N-H), 4.60 (m, 1H, 3-H), 5.38 (m, 1H, 6-H), 6.49 (dd, J = 7.8, 0.9 Hz, 1H, 6′-H), 6.70 (td, J = 7.3, 0.9 Hz, 1H, 4′-H), 6.97 (m, 1H, 5′-H), 7.09 (d, J = 7.3 Hz, 1H, 3′-H) ppm. ^{13}C NMR: δ = 14.9, 19.3, 20.6, 21.0, 21.4, 27.7, 29.7, 31.2, 32.0, 35.4, 36.7, 37.0, 38.1, 39.4, 43.0, 50.2, 54.1, 54.5, 58.7, 73.9 (C-3), 113.8, 118.2, 122.3 (C-6), 126.1, 126.2, 130.2, 139.8 (C-5), 146.1, 170.5 ($CH_3\underline{C}O$) ppm. EI-MS *m*/*z* (relative intensity): 434 (30), 433 (M^+, 100), 418 (10), 145 (15), 130 (16), 43 (12). Continued elution resulted in **7a** (343 mg, 79%), mp 242–245 °C, R_f = 0.2 (ss B), $[\alpha]_D^{20}$ = +18. (Found C, 80.41; H, 9.14; N, 3.31. $C_{29}H_{39}NO_2$ requires C, 80.33; H, 9.07; N 3.23%); ^{1}H NMR: δ = 0.84 (s, 3H, 18-H_3), 1.05 (s, 3H, 19-H_3), 1.01–1.09 (m, 1H), 1.15 (m, 1H), 1.32 (d, J = 6.4 Hz, 3H, 21-H_3), 1.30–1.40 (m, 2H), 1.44–1.66 (m, 8H), 1.83–1.91 (m, 2H), 2.03 (s, 3H, CH_3CO), 1.94–2.05 (m, 2H), 2.33 (m, 2H, 4-H_2), 3.07 (m, 1H, 20-H), 3.46 (m, 1H, 16-H), 3.92 (br s, 1H, N-H), 4.61 (m, 1H, 3-H), 5.39 (m, 1H, 6-H), 6.58 (d, J = 7.8 Hz, 1H, 6′-H), 6.74 (t, J = 7.8 Hz, 1H, 4′-H), 6.98 (t, J = 7.8 Hz, 1H, 5′-H), 7.22 (d, J = 7.8 Hz, 1H, 3′-H) ppm. ^{13}C NMR: δ = 12.7, 19.1, 19.3, 20.5, 21.4, 27.7, 30.5, 31.6, 31.6, 34.3, 36.6, 36.9, 38.1, 39.0, 42.0, 50.3, 55.2, 56.7, 59.6, 73.9 (C-3), 116.4, 118.7, 122.3 (C-6), 126.4, 128.0, 129.9, 139.9 (C-5), 146.5, 170.5 (CH_3CO) ppm. EI-MS *m*/*z* (relative intensity): 434 (30), 433 (M^+, 100).

*2.1.5. 1′,4′,16,17-Tetrahydro-3β-acetoxy-6′-methoxy-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**8a**) and 1′,4′,16,17-tetrahydro-3β-acetoxy-6′-methoxy-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**12a**)*

D-*seco*-Steroid **2b** (359 mg, 1.0 mmol) was reacted with **4** (135 mg, 1.1 mmol) by general procedure A. Column chromatography of the resulting crude product on silica gel with ethyl acetate/dichloromethane (5:95 v/v) afforded pure **12a** (87 mg, 19%), mp 192–194 °C, R_f = 0.5 (ss A), $[\alpha]_D^{20}$ = −105. (Found C, 77.89; H, 9.02; N, 3.35. $C_{30}H_{41}NO_3$ requires C, 77.71; H, 8.91; N, 3.02%); ^{1}H NMR: δ = 0.89 (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 0.96–1.18 (m, 3H), 1.19–1.32 (m, 2H), 1.35 (d, J = 6.8 Hz, 3H, 21-H_3), 1.45–1.67 (m, 6H), 2.03 (s, 3.H, OAc-H_3), 1.82–2.13 (m, 5H), 2.33 (m, 2H), 2.71 (m, 1H), 3.49 (m, 1H), 3.75 (s, 3H, OMe-H_3), 4.61 (m, 1H, 3-H), 5.38 (m, 1H, 6-H), 6.49 (d, J = 8.4 Hz, 1H, 6′-H), 6.57 (dd, J = 8.4, 2.4 Hz, 1H, 5′-H), 6.76 (d, J = 2.4 Hz, 1H, 3′-H) ppm. ^{13}C NMR: δ = 15.1, 19.2, 19.2, 20.7, 21.3, 27.7, 30.1, 31.1, 32.0, 34.5, 36.6, 36.9, 38.1, 39.8, 43.0, 50.1, 54.2, 55.7, 56.0, 59.2, 73.8, 110.6, 112.4, 114.5, 122.3 (C-6), 133.2, 139.7 (C-5), 140.8, 153.0, 170.4 (OAc-C) ppm. EI-MS *m/z* (relative intensity): 463 (M^+, 100), 464 (30). Continued elution resulted in **8a** (331 mg, 71%), mp 182–185 °C, R_f = 0.2 (ss A), $[\alpha]_D^{20}$ = +28. (Found C, H. $C_{30}H_{41}NO_3$ requires C 77.71, H 8.91, N 3.02, O 10.35%); ^{1}H NMR: δ = 0.83 (s, 3H, 18-H_3), 1.05 (s, 3H, 19-H_3), 0.99–1.09 (m, 1H), 1.15 (m, 1H), 1.31 (d, J = 8.95 Hz, 3H, 21-H_3), 1.27–1.41 (m, 2H), 1.43–1.68 (m, 8H), 1.81–1.92 (m, 2H), 2.03 (s, 3H, CH_3CO), 1.93–2.08 (m, 2H), 2.34 (m, 2H, 4-H_2), 3.04 (m, 1H, 20-H), 3.40 (m, 1H, 16-H), 3.74 (s, 3H, OMe-H_3), 4.61 (m, 1H, 3-H), 5.38 (m, 1H, 6-H), 6.56 (d, J = 8.48 Hz, 1H, 6′-H), 6.60 (dd, J = 8.48, 2.06 Hz, 1H, 5′-H), 6.81 (d, J = 2.06 Hz, 1H, 3′-H) ppm. ^{13}C NMR: δ = 12.7, 19.3 (2C), 20.5, 21.4, 27.7, 30.6, 31.6, 31.6, 34.5, 36.6, 36.9, 38.1, 39.0, 42.0, 50.3, 55.2, 55.7, 57.2, 59.7, 73.9 (C-3), 112.1, 113.8, 117.4, 122.3 (C-6), 131.5, 139.8 (C-5), 140.3, 153.0, 170.4 ($CH_3\underline{C}O$) ppm. EI-MS *m/z* (relative intensity): 463 (M^+, 100), 464 (35).

*2.1.6. 1′,4′,16,17-Tetrahydro-3β-acetoxy-6′-bromo-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**9a**) and 1′,4′,16,17-tetrahydro-3β-acetoxy-6′-bromo-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**13a**)*

D-*seco*-Steroid **2b** (359 mg, 1.0 mmol) was reacted with **5** (189 mg, 1.1 mmol) by general procedure A. The resulting crude product was chromatographed on silica gel with dichloromethane, affording pure **13a** (82 mg, 16%), mp 214–216 °C, R_f = 0.6 (ss B), $[\alpha]_D^{20}$ = −112. (Found C, 68.02; H, 7.62; N, 2.36. $C_{29}H_{38}BrNO_2$ requires C, 67.96; H, 7.47; N, 2.73%); ^{1}H NMR: δ = 0.77 (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.31 (d, J = 6.9 Hz, 3H, 21-H_3), 0.94–1.36 (m, 5H), 1.42–1.67 (m, 6H), 1.81–1.94 (m, 3H), 2.03 (s, 3H, CH_3CO), 1.94–2.07 (m, 1H), 2.15 (m, 1H), 2.33 (m, 2H, 4-H_2), 2.69 (m, 1H, 20-H), 3.63 (m, 1H, 16-H), 3.71 (br s, 1H, N-H), 4.60 (m, 1H, 3-H), 5.38 (m, 1H, 6-H), 6.35 (d, J = 8.3 Hz, 1H, 6′-H), 7.04 (dd, J = 8.3, 1.6 Hz, 1H, 5′-H), 7.16 (d, J = 1.6 Hz, 1H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 19.3, 20.6, 21.3, 21.4, 27.7, 29.7, 31.1, 31.9, 35.5, 36.7, 36.9, 38.1, 39.2, 43.0, 50.2, 53.6, 54.6, 58.0, 73.8 (C-3), 109.6, 115.1, 122.2 (C-6), 128.8, 129.2, 132.1, 139.9 (C-5), 144.8, 170.5 (CH_3CO) ppm. EI-MS *m/z* (relative intensity): 514 (30), 513 ([M + 2]$^+$, 100), 512 (35), 511 (M^+, 98), 210 (16). Continued elution resulted in **9a** (395 mg, 77%), mp 240–242 °C, R_f = 0.1 (ss B), $[\alpha]_D^{20}$ = +60. (Found C, 68.05; H, 7.53; N, 2.86. $C_{29}H_{38}BrNO_2$ requires C, 67.96; H, 7.47; N, 2.73%); ^{1}H NMR: δ = 0.82 (s, 3H, 18-H_3), 1.05 (s, 3H, 19-H_3), 1.00–1.09 (m, 1H), 1.14 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H, 21-H_3), 1.25–1.39 (m, 2H), 1.41–1.67 (m, 8H), 1.81–1.91 (m, 2H), 1.93–2.01 (m, 2H), 2.03 (s, 3H, CH_3CO), 2.27–2.38 (m, 2H, 4-H_2), 3.01 (m, 1H, 20-H), 3.41 (m, 1H, 16-H), 3.94 (br s, 1H, N-H), 4.60 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 6.43 (d, J = 8.7 Hz, 1H, 6′-H), 7.04 (dd, J = 8.7, 1.7 Hz, 1H, 5′-H), 7.29 (d, J = 1.7 Hz, 1H, 3′-H) ppm. ^{13}C NMR: δ = 12.6, 19.0, 19.3, 20.4, 21.4, 27.7, 30.4, 31.5, 31.6, 34.4, 36.6, 36.9, 38.1, 38.9, 42.0, 50.3, 55.3, 56.7, 58.9, 73.8, 110.5, 117.7, 122.2 (C-6), 129.1, 130.7, 132.0, 139.9 (C-5), 145.6, 170.4 (CH_3CO) ppm. EI-MS *m/z* (relative intensity): 514 (28), 513 ([M + 2]$^+$, 100), 512 (32), 511 (M^+, 95).**********

*2.1.7. 1′,4′,16,17-Tetrahydro-3β-acetoxy-6′-nitro-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**10a**) and 3β-acetoxy-16β-[N-(4′-nitro)-phenyl]-amino-17aβ-fluoro-17α-methyl-D-homo-androsta-5-ene (**14a**)*

D-*seco*-Steroid **2b** (359 mg, 1.0 mmol) was reacted with **6** (152 mg, 1.1 mmol) by general procedure A. The resulting crude product was chromatographed on silica gel with *tert*-butyl methyl ether/light petroleum (25:75 v/v), yielding pure **14a** (61 mg, 12%), mp 145–155 °C, R_f = 0.6 (ss C), $[\alpha]_D^{20}$ = +16. (Found C, 69.72; H, 8.02; N, 5.78. $C_{29}H_{39}FN_2O_4$ requires C, 69.85; H, 7.88; N, 5.62%), ^{1}H NMR: δ = 0.93 (s, 3H, 18-H_3), 1.00 (s, 3H, 19-H_3), 1.11 (d, J = 5.2 Hz, 3H, 21-H_3), 2.02 (s, 3H, OAc-H_3), 3.08 (qd, J = 10.5, 4.9 Hz, 1-H, 17-H), 3.47 (s, 1H, N-H), 3.73 (dd, J = 47.9, 10.5 Hz, 1H, 17a-H), 4.47 (m, 1H, 16-H), 4.60 (m, 1H, 3-H), 5.32 (m, 1H, 6-H), 6.50 (d, J = 9.2 Hz, 2H, (2′ + 6′)-H), 8.06 (d, J = 9.2 Hz, 2H, (3′ + 5′)-H) ppm. ^{13}C NMR: δ = 11.9, 15.0, 19.2, 19.5, 21.3, 27.7, 30.4, 30.7, 31.8, 36.5, 36.6, 36.8, 37.8, 38.0, 39.1 (d, J = 18.9 Hz, C-17), 45.8 (d, J = 6.3 Hz), 49.4, 55.9 (d, J = 10.8 Hz), 73.7 (C-3), 103.2 (d, J = 183.7 Hz, C-17a), 111.0 (2C, C-2′ and –6′). 121.7 (C-6), 126.6 (2C, C-3′ and -5′), 137.8 (C-4′), 139.5 (C-5), 153.0 (C-1′), 170.5 (OAc) ppm. EI-MS *m/z* (relative intensity): 498 (M^+, 15), 438 ([M − AcOH]$^+$, 100). Continued elution resulted in **10a** (347 mg, 73%), mp 252–254 °C, R_f = 0.5 (ss C), $[\alpha]_D^{20}$ = +232. (Found C, 72.98; H, 8.21; N, 6.02. $C_{29}H_{38}N_2O_4$ requires C, 72.77; H, 8.00; N 5.85%); ^{1}H NMR: δ = 0.85 (s, 3H, 18-H_3), 1.06 (s, 3H, 19-H_3), 1.01–1.10 (m, 1H), 1.15 (m, 1H), 1.38 (d, J =

6.7 Hz, 3H, 21-H_3), 1.29–1.42 (m, 2H), 1.44–1.76 (m, 8H), 1.86 (m, 2H), 2.04 (s, 3H, CH_3CO), 1.93–2.08 (m, 2H), 2.33 (m, 2H, 4-H_2), 3.06 (m, 1H, 20-H), 3.59 (m, 1H, 16-H), 4.60 (m, 1H, 3-H), 4.84 (s, 1H, N-H), 5.38 (m, 1H, 6-H), 6.45 (d, $J = 8.9$ Hz, 1H, 6′-H), 7.88 (dd, $J = 8.9$, 2.5 Hz, 1H, 5′-H), 8.13 (d, $J = 2.5$ Hz, 1H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.4$, 18.2, 19.3, 20.4, 21.4, 27.7, 30.0, 31.5, 31.5, 34.5, 36.6, 36.9, 38.1, 38.7, 41.9, 50.3, 55.5, 56.4, 57.8, 73.8 (C-3), 114.1, 122.0 (C-6), 123.6, 124.7, 128.3, 138.6, 140.0 (C-5), 152.1, 170.6 (CH_3CO) ppm. EI-MS *m/z* (relative intensity): 478 (M^+, 4), 418 ([M − AcOH]$^+$, 8), 129 (16), 91 (100), 55 (18), 43 (22).

*2.1.8. 1′,4′,16,17-Tetrahydro-3β-hydroxy-4′-methyl-(16β, 17α)-androsta-5,16-dieno [17,16b] quinoline (**7b**)*

7a (108 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from methanol afforded **7b** (169 mg, 70%), mp 216–219 °C, $R_f = 0.4$ (ss D), $[\alpha]_D^{20} = -13$. (Found C, 82.67; H, 9.73, N, 3.67. $C_{27}H_{37}NO$ requires C, 82.81; H, 9.52; N, 3.58%); ^{1}H NMR: $\delta = 0.85$ (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 0.97–1.15 (m, 2H), 1.33 (d, $J = 6.4$ Hz, 1H, 21-H_3), 1.30–1.41 (m, 2H), 1.44–1.69 (m, 8H), 1.85 (m, 2H), 2.00 (m, 2H), 2.20–2.35 (m, 2H), 3.08 (m, 1H, 20-H), 3.46 (m, 1H, 16-H), 3.53 (m, 1H, 3-H), 5.36 (m, 1H, 6-H), 6.59 (d, $J = 7.8$ Hz, 1H, 6′-H), 6.75 (dd, $J = 7.8$, 7.3 Hz, 1H, 5′-H), 6.98 (dd, $J = 7.8$, 7.3 Hz, 1H, 4′-H), 7.23 (d, $J = 7.8$ Hz, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.7$, 19.2, 19.4, 20.6, 30.5, 31.6, 31.6, 31.6, 34.3, 36.6, 37.2, 39.1, 42.1, 42.3, 50.4, 55.4, 56.8, 59.6, 71.7 (C-3), 116.5, 118.8, 121.4 (C-6), 126.4, 128.0, 130.0, 141.0 (C-5), 146.5 ppm. EI-MS *m/z* (relative intensity): 392 (30), 391 (M^+, 100), 390 (10), 144 (8).

*2.1.9. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**7c**)*

7a (434 mg, 1.0 mmol) was acetylated by general procedure C. Column chromatography on silica gel with *tert*-butyl methyl ether/dichloromethane (10:90 v/v) afforded **7c** (428 mg, 90%) mp 202–206 °C, $R_f = 0.6$ (ss E), $[\alpha]_D^{20} = -144$. (Found C, 78.41; H, 8.76; N, 3.05. $C_{31}H_{41}NO_3$ requires C, 78.28; H, 8.69; N 2.94%); ^{1}H NMR: $\delta = 0.88$ (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 0.98–1.07 (m, 1H), 1.13 (td, $J = 13.8$, 3.8 Hz, 1H), 1.35 (d, $J = 6.9$ Hz, 3H, 21-H_3), 1.24–1.43 (m, 2H), 1.44–1.64 (m, 6H), 2.02 (s, 3H, CH_3COO), 1.78–2.04 (m, 5H), 2.17 (s, 3H, CH_3CON), 2.25–2.36 (m, 3H), 2.87 (m, 1H, 20-H), 3.88 (td, $J = 11.0$, 5.8 Hz, 1H, 16-H), 4.60 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 7.08–7.19 (m, 3H, 3′-, 4′- and 5′-H), 7.25 (d, $J = 7.3$ Hz, 1H, 6′-H) ppm. ^{13}C NMR: $\delta = 12.9$, 18.0, 19.2, 20.4, 21.3, 24.7, 27.7, 29.7, 31.3, 31.4, 35.6, 36.6, 36.8, 38.0, 38.5, 40.5, 50.2, 55.8, 60.6, 64.4, 73.8 (C-3), 122.4 (C-6), 124.7, 125.3, 125.5, 126.1, 139.6 (C-5), 139.7, 140.9, 170.3 and 172.4 (2 × CH_3CO) ppm. EI-MS *m/z* (relative intensity): 476 (28), 475 (M^+, 86), 433 (25), 416 (34), 415 ([M − AcOH]$^+$, 100), 373 (70).

*2.1.10. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**7d**)*

7c (119 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from dichloromethane/light petroleum afforded glossy white needles **7d** (101 mg, 93%), mp 215–218 °C, $R_f = 0.4$ (ss E), $[\alpha]_D^{20} = -134$. (Found C, 80.46; H, 8.98; N, 3.46. $C_{29}H_{39}NO_2$ requires C, 80.33; H, 9.07; N 3.23%); ^{1}H NMR: $\delta = 0.88$ (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.35 (d, $J = 6.9$ Hz, 3H, 21-H_3), 2.18 (s, 3H, CH_3CO), 0.96–2.35 (m, 18H), 2.88 (m, 1H, 20-H), 3.52 (m, 1H, 3-H), 3.88 (td, $J = 11.0$, 5.5 Hz, 1H, 16-H), 5.35 (m, 1H, 6-H), 7.09–7.19 (m, 3H), 7.25 (m, 1H, 6′-H) ppm. ^{13}C NMR: $\delta = 12.9$, 18.1, 19.4, 20.4, 24.8, 29.8, 31.4, 31.4, 31.5, 35.6, 36.5, 37.1, 38.5, 40.5, 42.3, 50.3, 55.9, 60.7, 64.4, 71.6 (C-3), 121.5 (C-6), 124.8, 125.3, 125.5, 126.2, 139.8, 140.7 (C-5), 140.9, 172.6 (CH_3CO) ppm. EI-MS *m/z* (relative intensity): 434 (28), 433 (M^+, 100), 391 ([M + H − Ac]$^+$, 40), 296 (25), 144 (10). Crystal data: $C_{29}H_{39}NO_2 \times 0.5$ CH_2Cl_2, $M_r = 476.07$, monoclinic, space group *C*2, $a = 30.218(3)$ Å, $b = 6.050(2)$ Å, $c = 14.218(2)$ Å, $\beta = 100.12(4)°$, $V = 2558.9(10)$ Å^3, $Z = 4$, $\rho_{calc} = 1.236$ g cm^{-3}, $F(000) = 1028$, μ(Mo Kα) = 0.176 cm^{-1}, min/max transmission 0.8867/0.9171, crystal dimensions 0.7 mm × 0.5 mm × 0.5 mm, $2.17° < \Theta < 27.54°$, 12,706 reflections were collected, of which 5032 were independent ($R_{int} = 0.0417$) and 5032 were used for refinement. For the final refinement of 324 parameters, two restraints were used. The *R*-values were: $R_1 = \Sigma|F_o - F_c|/\Sigma F_o = 0.0441$ for $I > 2\sigma(I)$, and $wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum wF_o^4]^{1/2} = 0.1189$ for all data; max/min residual electron density: 0.26/−0.25 eÅ^{-3}.

*2.1.11. 1′,4′,16,17-Tetrahydro-3β-hydroxy-6′-methoxy-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**8b**)*

8a (116 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with *tert*-butyl methyl ether/dichloromethane (20:80 v/v) afforded **8b** (67 mg, 63%), mp 125–127 °C, $R_f = 0.3$ (ss D), $[\alpha]_D^{20} = -34$. (Found C, 79.82; H, 9.45; N, 3.45. $C_{28}H_{39}NO_2$ requires C, 79.76; H, 9.32; N, 3.32%); ^{1}H NMR: $\delta = 0.83$ (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 0.98–1.13 (m, 2H), 1.31 (d, $J = 6.9$ Hz, 3H, 21-H_3), 1.29–1.39 (m, 2H), 1.42–1.68 (m, 8H), 1.80–1.88 (m, 2H), 1.94–2.03 (m, 2H), 2.19–2.34 (m, 2H), 3.04 (m, 1H, 20-H), 3.40 (m, 1H, 16-H), 3.51 (m, 3H), 3.74 (s, 3H, O-CH_3), 5.35 (m, 1H, 6-H), 6.56 (d, $J = 8.5$ Hz, 1H, 6′-H), 6.61 (dd, $J = 8.5$, 2.8 Hz, 1H, 5′-H), 6.81 (d, $J = 2.8$ Hz, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.7$, 19.3, 19.4, 20.5, 30.6, 31.6, 31.6, 31.6, 34.5, 36.5, 37.2, 39.0, 42.0, 42.3, 50.4, 55.2, 55.7, 57.2, 59.7, 71.6, 112.1, 113.8, 117.5, 121.3 (C-6), 131.6, 140.2, 141.0 (C-5), 153.0 ppm. EI-MS *m/z* (relative intensity): 422 (30), 421 (M^+, 100), 404 (6).

*2.1.12. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-6′-methoxy-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**8c**)*

8a (464 mg, 1.0 mmol) was acetylated by the general procedure C. Recrystallization from methanol afforded **8c** (396 mg, 78%), mp 206–209 °C, $R_f = 0.2$ (ss A), $[\alpha]_D^{20} = +106$. (Found C, 75.87; H, 8.68; N, 2.90. $C_{32}H_{43}NO_4$ requires C, 76.00; H, 8.57; N, 2.77%); ^{1}H NMR: $\delta = 0.87$ (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 0.97–1.08 (m, 1H), 1.13 (m, 1H), 1.33 (d, $J = 6.9$ Hz, 3H, 21-H_3), 1.24–1.36 (m, 1H), 1.40 (t, $J = 11.2$ Hz, 1H), 1.46–1.65 (m, 6H), 2.03 (s, 3H, CH_3COO), 1.73–2.06 (m, 5H), 2.15 (s, 3H, CH_3CON), 2.27–2.38 (m, 3H), 2.84 (m, 1H, 20-H), 3.81 (s, 3H, O-CH_3), 3.77–3.88 (m, 1H, 16-H), 4.60 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 6.69 (dd, $J = 8.7$, 2.8 Hz, 1H, 5′-H), 6.79 (d, $J = 2.8$ Hz, 1H, 3′-H), 7.09 (d, $J = 8.7$ Hz, 1H, 6′-H) ppm. ^{13}C NMR: $\delta = 12.9$, 18.2, 19.2, 20.3, 21.3, 24.7, 27.6, 29.5, 31.3, 31.4, 35.7, 36.6, 36.8, 38.0, 38.4, 40.5, 50.1, 55.3, 55.8, 60.5, 64.4, 73.8, 110.0, 112.4, 122.5 (C-6), 126.0, 134.3, 139.5 (C-5), 141.2, 156.7, 170.4 ($CH_3\underline{C}OO$), 172.6 ($CH_3\underline{C}ON$) ppm. EI-MS *m/z* (relative intensity): 506 (36), 505 (M^+, 100), 463 ($[M + H - Ac]^+$, 24).

*2.1.13. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-6′-methoxy-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**8d**)*

8c (126 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from dichloromethane/light petroleum afforded flat crystals **8d** (90 mg, 78%). mp 230–234 °C, $R_f = 0.4$ (ss H), $[\alpha]_D^{20} = -111$. (Found C, 77.85; H, 9.05; N, 2.96. $C_{30}H_{41}NO_3$ requires C, 77.71; H, 8.91; N 3.02%); ^{1}H NMR: $\delta = 0.89$ (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H), 0.95–1.14 (m, 2H), 1.33 (d, $J = 6.4$ Hz, 3H, 21-H_3), 1.22–1.36 (m, 1H), 1.41 (t, $J = 11.2$ Hz, 1H), 1.45–1.66 (m, 6H), 1.70–1.88 (m, 3H), 1.90–2.04 (m, 2H), 2.14 (s, 3H, CH_3CO), 2.18–2.34 (m, 2H), 2.34–2.42 (m, 1H), 2.85 (m, 1H, 20-H), 3.52 (m, 1H, 3-H), 3.80 (s, 3H, OMe), 3.75–3.86 (m, 1H, 16-H), 5.35 (m, 1H, 6-H), 6.69 (dd, $J = 8.7$, 2.4 Hz, 1H, 5′-H), 6.79 (d, $J = 2.4$ Hz, 1H, 3′-H), 7.08 (d, $J = 8.7$ Hz, 1H, 6′-H) ppm. ^{13}C NMR: $\delta = 12.9$, 18.6, 19.4, 20.5, 24.7, 29.4, 31.4, 31.5, 31.6, 35.7, 36.5, 37.1, 38.6, 40.7, 42.3, 50.4, 55.4, 55.9, 60.7, 64.7, 71.6 (C-3), 110.l, 112.7, 121.5 (C-6), 126.1, 134.5, 140.7 (C-5), 141.2, 156.9, 172.7 (CH_3CO). EI-MS *m/z* (relative intensity): 464 (30), 463 (M^+, 100), 42l (20).

*2.1.14. 1′,4′,16,17-Tetrahydro-3β-hydroxy-6′-bromo-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**9b**)*

9a (128 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from acetone afforded **9b** (108 mg, 92%) as clear white crystals. mp 245–247 °C, $R_f = 0.3$ (ss E), $[\alpha]_D^{20} = +74$. (Found C, 69.05; H, 7.65; N, 3.06. $C_{27}H_{36}BrNO$ requires C, 68.93; H, 7.71; N, 2.98%); ^{1}H NMR: $\delta = 0.83$ (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 0.98–1.13 (m, 2H), 1.30 (d, $J = 6.4$ Hz, 3H, 21-H_3), 1.24–1.38 (m, 2H), 1.43–1.68 (m, 8H), 1.84 (m, 2H), 1.93–2.03 (m, 2H), 2.20–2.33 (m, 2H), 3.03 (m, 1H, 20-H), 3.43 (m, 1H, 16-H), 3.52 (m, 1H, 3-H), 5.35 (m, 1H, 6-H), 6.45 (d, $J = 8$, 7 Hz, 1H, 6′-H), 7.05 (dd, $J = 8.7$, 2.3 Hz, 1H, 5′-H), 7.30 (d, $J = 2.3$ Hz, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.6$, 19.0, 19.4, 20.5, 27.0, 30.4, 31.6, 34.4, 36.5, 37.2, 38.9, 42.0, 50.4, 55.3, 56.8, 58.8, 58.9, 71.6, 110.6, 117.8, 121.2 (C-6), 129.2, 130.8, 132.1, 141.0 (C-5), 145.5 ppm. EI-MS *m/z* (relative intensity): 472 (28), 471 ($[M + 2]^+$, 100), 470 (35), 469 (M^+, 100).

*2.1.15. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-6′-bromo-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**9c**)*

9a (523 mg, 1.0 mmol) was acetylated by the general procedure C. Column chromatography on silica gel with ethyl acetate/dichloromethane (5:95 v/v) afforded **9c** (427 mg, 77%), mp 218–220 °C, $R_f = 0.6$ (ss A), $[\alpha]_D^{20} = -113$. (Found C, 67.32; H, 7.34; N, 2.30. $C_{31}H_{40}BrNO_3$ requires C, 67.14; H, 7.27; N, 2.53%); ^{1}H NMR: $\delta = 0.89$ (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 0.98–1.07 (m, 1H), 1.13 (td, $J = 13.9$, 4.1 Hz, 1H), 1.34 (d, $J = 6.9$ Hz, 3H, 21-H_3), 1.24–1.38 (m, 2H), 1.42–1.62 (m, 6H), 1.80–1.90 (m, 3H), 2.03 (s, 3H, CH_3COO), 1.91–2.05 (m, 2H), 2.17 (s, 3H, CH_3CON), 2.14–2.24 (m, 1H), 2.28–2.36 (m, 2H), 2.84 (dq, $J = 10.5$, 6.9 Hz, 1H, 20-H), 3.88 (td, $J = 11.0$, 5.9 Hz, 1H, 16-H), 4.60 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 7.09 (d, $J = 7.9$ Hz, 1H, 6′-H), 7.28 (dd, $J = 7.9$, 1.8 Hz, 1H, 5′-H), 7.35 (d, $J = 1.8$ Hz, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.8$, 17.4, 19.2, 20.3, 21.3, 24.6, 27.6, 30.2, 31.2, 31.3, 35.7, 36.5, 36.8, 38.0, 38.4, 40.5, 50.1, 55.9, 60.3, 64.2, 73.7 (C-3), 117.9, 122.3 (C-6), 126.7, 128.4, 128.9, 139.5, 139.6 (C-5), 141.9, 170.4 (CH_3COO), 172.2 (CH_3CON) ppm. EI-MS *m/z* (relative intensity): 556 (20), 555 ($[M + 2]^+$, 70), 554 (20), 553 (M^+, 66), 496 (30), 495 (98), 494 (32), 493 ($[M - AcOH]^+$, 100), 454 (14), 455 (58), 452 (30), 451 (62), 210 (15), 208 (13), 157 (16), 43 (28).

*2.1.16. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-6′-bromo-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**9d**)*

9c (136 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from dichloromethane/petrolether afforded **9d** (109 mg, 85%), mp 211–214 °C, $R_f = 0.4$ (ss E), $[\alpha]_D^{20} = -113$. (Found C, 68.05; H, 7.62; N, 2.95. $C_{29}H_{38}BrNO_2$ requires C, 67.96, H, 7.47; N, 2.73%); ^{1}H NMR: $\delta = 0.89$ (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.34 (d, $J = 6.9$ Hz, 3H, 21-H_3), 2.17 (s, 3H, CH_3CO), 0.94–2.35 (m, 18H), 2.84 (m, 1H, 20-H), 3.52 (m, 1H, 3-H), 3.88 (td, $J = 11.0$, 6.0 Hz, 1H, 16-H), 5.34 (m, 1H, 6-H), 7.09 (d, $J = 8.7$ Hz, 1H, 6′-H), 7.28 (d, $J = 8.7$ Hz, 1H, 5′-H), 7.35 (s, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.8$, 17.5, 19.3, 20.4, 24.7, 30.2, 31.3, 31.4, 31.5, 35.7, 36.5, 37.1, 38.5, 40.6, 42.2, 50.3, 56.0, 60.3, 64.3, 71.6 (C-3), 118.0, 121.4 (C-6), 126.7, 128.5, 129.1, 139.6, 140.7 (C-5), 142.0, 172.3 (CH_3CO) ppm. EI-MS *m/z* (relative intensity): 514 (26), 513

([M+2]$^+$, 100), 512 (28), 511 (M$^+$, 96), 471 (48), 469 (46), 433 (16), 255 (16), 251 (18), 156 (24), 91 (58), 83 (40), 57 (32), 43 (22).

*2.1.17. 1′,4′,16,17-Tetrahydro-3β-hydroxy-6′-nitro-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**10b**)*

10a (120 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from methanol afforded **10b** (87 mg, 79%), mp 162–165 °C, $R_f = 0.6$ (ss D), $[\alpha]_D^{20} = +217$. (Found C, 74.46; H, 8.45; N, 6.58. $C_{27}H_{36}N_2O_3$ requires C, 74.28, H, 8.31; N, 6.42%); ^{1}H NMR: $\delta = 0.85$ (s, 3H, 18-H$_3$), 1.04 (s, 3H, 19-H$_3$), 0.97–1.14 (m, 2H), 1.37 (d, $J = 6.4$ Hz, 3H, 21-H$_3$), 1.28–1.40 (m, 2H), 1.42–2.35 (m, 15H), 3.05 (m, 1H, 20-H), 3.52 (m, 1H, 3-H), 3.59 (m, 1H, 16-H), 4.81 (br s, 1H, N-H), 5.34 (m, 1H, 6-H), 6.46 (d, $J = 9.2$ Hz, 1H, 6′-H), 7.87 (dd, $J = 9.2$, 2.3 Hz, 1H, 5′-H), 8.12 (d, $J = 2.3$ Hz, 3′-H) ppm. ^{13}C NMR: $\delta = 12.4$, 18.1, 19.4, 20.4, 30.0, 31.5, 31.5, 31.6, 34.5, 36.5, 37.1, 38.8, 41.9, 42.2, 50.3, 55.6, 56.4, 57.8, 71.6 (C-3), 114.1, 121.1 (C-6), 123.6, 124.7, 128.3, 138.6, 141.1 (C-5), 152.1 ppm. EI-MS *m/z* (relative intensity): 436 (M$^+$, 100).

*2.1.18. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-6′-nitro-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**10c**)*

10a (479 mg, 1.0 mmol) was acetylated by general procedure C. Column chromatography on silica gel with *tert*-butyl methyl ether/light petroleum (1:1 v/v) afforded **10c** (427 mg, 82%), mp 212–214 °C, $R_f = 0.3$ (ss C), $[\alpha]_D^{20} = -268$. (Found: C, 51.68; H, 7.92; N, 5.48. $C_{31}H_{40}N_2O_5$ requires C, 71.51; H, 7.74; N, 5.38%); ^{1}H NMR: $\delta = 0.96$ (s, 3H, 18-H$_3$), 1.05 (s, 3H, 19-H$_3$), 1.44 (d, $J = 6.8$ Hz, 3H, 21-H$_3$), 2.03 (s, 3H, CH$_3$COO), 2.27 (s, 3H, CH$_3$CON), 2.33 (m, 2H, 4-H$_2$) 2.90 (m, 1H, 20-H), 4.06 (m, 1H, 16-H), 4.59 (m, 1H, 3-H), 5.37 (m, 1H, 6-H), 7.47 (d, $J = 8.9$ Hz, 1H, 6′-H), 8.05 (dd, $J = 8.9$, 2.2 Hz, 1H, 5′-H), 8.11 (d, $J = 2.2$ Hz, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.7$, 16.4, 19.3, 20.3, 21.3, 24.9, 27.7, 31.3, 31.4, 31.6, 35.9, 36.6, 36.9, 38.1, 38.6, 40.6, 50.3, 56.0, 60.2, 64.1, 73.7 (C-3), 120.8, 121.4, 122.1, 125.1, 139.9, 140.6, 143.9, 145.5, 170.4, 172.0 (2 × CH$_3$CO) ppm. EI-MS *m/z* (relative intersity): 520 (M$^+$, 5), 490 (8), 461 ([M − AcO]$^+$, 33), 460 ([M − AcOH]$^+$, 100), 418 (30), 253 (10).

*2.1.19. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-6′-nitro-4′-methyl-(16β,17α)-androsta-5,16-dieno[17,16-b]quinoline (**10d**)*

10c (130 mg, 0.25 mmol) was hydrolyzed by general procedure B, resulting in a mixture of **10b** and **10d**. Column chromatography on silica gel with *tert*-butyl methyl ether/dichloromethane (10:90 v/v) afforded **10b** (96 mg, 80%, $R_f = 0.5$ (ss H)) and **10d** (11 mg, 9%). **10b** proved to be identical to that mentioned above. **10d** mp 268–270 °C, $R_f = 0.3$ (ss H), $[\alpha]_D^{20} = +245$. (Found C, 72.85, H, 7.93; N, 5.98. $C_{29}H_{38}N_2O_4$ requires C, 72.77; H, 8.00; N, 5.85%); ^{1}H NMR: $\delta = 0.95$ (s, 3H, 18-H$_3$), 1.03 (s, 3H, 19-H$_3$), 1.42 (d, $J = 6.9$ Hz, 3H, 21-H$_3$), 1.82 (d, $J = 10.1$ Hz, 2H), 2.26 (s, 3H, CH$_3$CON), 2.89 (m, 1H, 20-H), 3.51 (m, 1H, 3-H), 4.04 (m, 1H, 16-H), 5.34 (m, 1H, 6-H), 7.47 (d, $J = 8.7$ Hz, 1H, 6′-H), 8.04 (d, $J = 8.7$ Hz, 1H, 5′-H), 8.11 (s, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 12.8$, 16.4, 19.4, 20.3, 24.9, 31.3, 31.5, 31.6, 31.6, 35.9, 36.6, 37.1, 38.6, 40.6, 42.3, 50.4, 56.1, 60.2, 64.2, 71.6 (C-3), 120.85, 121.1, 121.3, 125.1, 140.6, 141.0, 143.9, 145.5, 172.0 (CH$_3$CON) ppm. EI-MS *m/z* (relative intensity): 478 (M$^+$, 100), 436 ([M − Ac]$^+$, 85).

*2.1.20. 1′,4′,16,17-Tetrahydro-3β-hydroxy-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**11b**)*

11a (108 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with ethyl acetate/dichloromethane (10:90 v/v) afforded **11b** (70 mg, 71%), mp 175–176 °C, $R_f = 0.2$ (ss A), $[\alpha]_D^{20} = -95$. (Found C, 82.95; H, 9.31; N, 3.72. $C_{27}H_{37}NO$ requires C, 82.81; H, 9.52; N 3.58%); ^{1}H NMR: $\delta = 0.82$ (s, 3H, 18-H$_3$), 1.02 (s, 3H, 19-H$_3$), 0.93–1.14 (m, 3H), 1.34 (d, $J = 6.9$ Hz, 3H, 21-H$_3$), 1.15–1.37 (m, 2H), 1.44–1.66 (m, 7H), 1.80–1.89 (m, 2H), 1.93 (d, $J = 12.3$ Hz, 1H), 2.02 (m, 1H), 2.14 (m, 1H), 2.18–2.33 (m, 2H), 2.72 (m, 1H, 20-H), 3.51 (m, 1H, 3-H), 3.63 (m, 1H, 16-H), 5.35 (m, 1H, 6-H), 6.49 (d, $J = 7.6$ Hz, 1H, 6′-H), 6.71 (t, $J = 7.6$ Hz, 1H, 4′-H), 6.97 (t, $J = 7.6$ Hz, 1H, 5′-H), 7.09 (d, $J = 7.6$ Hz, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 14.8$, 19.4, 20.8, 21.1, 29.7, 31.2, 31.7, 32.0, 35.5, 36.7, 37.3, 39.5, 42.3, 43.1, 50.4, 54.1, 54.7, 58.8, 71.7 (C-3), 113.8, 118.3, 121.4 (C-6), 126.2, 126.3, 130.3, 141.0 (C-5), 146.0 ppm. EI-MS *m/z* (relative intensity): 392 (30), 391 (M$^+$, 100), 130 (18).

*2.1.21. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**11c**)*

11a (434 mg, 1.0 mmol) was acetylated by general procedure C. Recrystallization from methanol afforded **11c** (423 mg, 89%), mp 277–279 °C, $R_f = 0.1$ (ss A), $[\alpha]_D^{20} = +181$. (Found C, 78.37; H, 8.76; N, 3.12. $C_{31}H_{41}NO_3$ requires C, 78.28; H, 8.69; N 2.94%); ^{1}H NMR: $\delta = 0.09$ (s, 3H, 18-H$_3$), 0.93 (s, 3H, 19-H$_3$), 0.90–1.06 (m, 3H), 1.12 (m, 2H), 1.20 (d, $J = 7.3$ Hz, 3H, 21-H$_3$), 1.35–1.46 (m, 2H), 1.48–1.62 (m, 3H), 1.77–1.97 (m, 4H), 2.01 (s, 3H, CH$_3$COO), 2.12 (s, 3H, CH$_3$CON), 2.06–2.36 (m, 4H), 2.86 (q, $J = 7.3$ Hz, 1H, 20-H), 4.58 (m, 1H, 3-H), 5.22 (m, 1H, 16-H), 5.33 (m, 1H, 6-H), 6.99 (d, $J = 6.9$ Hz, 1H), 7.07–7.21 (m, 3H) ppm. ^{13}C NMR: $\delta = 14.9$ (C-18), 19.1 (C-19), 20.4, 21.4 (CH$_3$COO), 22.2 (C-21), 22.8 (CH$_3$CON), 27.8, 30.2, 32.1, 32.8, 33.5, 36.7, 36.9, 38.0, 38.8, 43.1, 49.9, 53.6, 54.9, 58.5, 73.8 (C-3), 122.4 (C-6), 126.1, 126.1 (2C), 128.9, 137.7, 139.6 (C-5), 140.7, 170.0 and 170.4 (2 × CH$_3$CO). EI-MS *m/z* (relative intensity): 475 (M$^+$, 42), 416 (30), 415 ([M − AcOH]$^+$, 100), 373 (22), 130

(18). Crystal data: $C_{31}H_{41}NO_3$, $M_r = 475.65$, monoclinic, space group $P2_1$, $a = 10.807(2)$ Å, $b = 7.3619(15)$ Å, $c = 16.965(3)$ Å, $\beta = 101.49(3)^\circ$, $V = 1322.6(5)$ Å^3, $Z = 2$, $\rho_{calc} = 1.194\,g\,cm^{-3}$, $F(000) = 516$, $\mu(Mo\,K\alpha) = 0.075\,cm^{-1}$, min/max transmission 0.9421/0.9704, crystal dimensions 0.8 mm × 0.6 mm × 0.2 mm, $1.92^\circ < \Theta < 24.71^\circ$, 10,103 reflections were collected, of which 2441 were independent ($R_{int} = 0.1381$) and 2441 were used for refinement. For the final refinement of 321 parameters, one restraint was used. The *R*-values were: $R_1 = \Sigma|F_o - F_c|/\Sigma F_o = 0.0491$ for $I > 2\sigma(I)$, and $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2} = 0.1126$ for all data; max/min residual electron density: 0.18/−0.19 e Å^{-3}.

*2.1.22. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**11d**)*

11c (119 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with ethyl acetate/dichloromethane (30:70 v/v) afforded **11d** (73 mg, 67%), mp 287–290 °C, $R_f = 0.3$ (ss H), $[\alpha]_D^{20} = +221$. (Found C, 80.54; H, 8.95; N, 3.55. $C_{29}H_{39}NO_2$ requires C, 80.33; H, 9.07; N, 3.23%); ^{1}H NMR: $\delta = 0.09$ (s, 3H, 18-H$_3$), 0.92 (s, 3H, 19-H$_3$), 1.20 (d, $J = 6.9$ Hz, 3H, 21-H$_3$), 2.12 (s, 3H, CH_3CO), 0.84–2.32 (m, 18H), 2.86 (m, 1H, 20-H), 3.50 (m, 1H, 3-H), 5.22 (m, 1H, 16-H), 5.30 (m, 1H, 6-H), 6.99 (d, $J = 7.3$ Hz, 1H, 6′-H), 7.05–7.21 (m, 3H) ppm. ^{13}C NMR: $\delta = 14.9$, 19.2, 20.4, 22.2, 22.8, 30.2, 31.5, 32.0, 32.7, 33.5, 36.6, 37.2, 38.8, 42.2, 43.1, 50.0, 53.6, 54.9, 58.1, 71.5, 121.3 (C-6), 126.0, 126.1 (2C). 128.8, 137.7, 140.6, 140.8, 169.5 (CH_3CO) ppm. EI-MS *m/z* (relative intensity): 434 (30), 433 (M^+, 100), 391 (22), 390 (15), 130 (15), 106 (10).

*2.1.23. 1′,4′,16,17-Tetrahydro-3β-hydroxy-6′-methoxy-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**12b**)*

12a (116 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from dichloromethane/light petroleum afforded **12b** (100 mg, 95%), mp 220–223 °C, $R_f = 0.2$ (ss A), $[\alpha]_D^{20} = -95$. (Found: C, 79.89; H, 9.46; N, 3.45. $C_{28}H_{39}NO_2$ requires C, 79.76; H, 9.32; N, 3.32%); ^{1}H NMR: $\delta = 0.89$ (s, 3H, 18-H$_3$), 1.03 (s, 3H, 19-H$_3$), 0.94–1.16 (m, 3H), 1.17–l.33 (m, 2H), 1.35 (d, $J = 6.9$ Hz, 3H, 21-H$_3$), 1.44–1.68 (m, 6H), 1.80–l.89 (m, 2H), 1.92–2.12 (m, 3H), 2.18–2.33 (m, 2H), 2.71 (m, 1H, 20-H), 3.46–3.57 (m, 2H, 3-H and 16-H), 3.75 (s, 3H, O-CH$_3$), 5.35 (m, 1H, 6-H), 6.48 (d, $J = 8.4$ Hz, 1H, 6′-H), 6.58 (dd, $J = 8.4$, 2.6 Hz, 1H, 5′-H), 6.76 (d, $J = 2.6$, 1H, 3′-H) ppm. ^{13}C NMR: $\delta = 15.2$, 19.3, 19.4, 20.8, 30.1, 31.2, 31.6, 32.1, 34.6, 36.6, 37.3, 39.9, 42.3, 43.1, 50.3, 54.4, 55.8, 56.1, 59.3, 71.7, 110.7, 112.5, 114.5, 121.3 (C-6), 133.2, 140.9, 141.0 (C-5), 153.1 ppm. EI-MS *m/z* (relative intensity): 422 (30), 421 (M^+, 100), 160 (12).

*2.1.24. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-6′-methoxy-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**12c**)*

12a (464 mg, 1.0 mmol) was acetylated by general procedure C. Column chromatography on silica gel with ethyl acetate/dichloromethane (20:80 v/v) afforded **12c** (420 mg, 83%), mp 180–184 °C, $R_f = 0.1$ (ss A), $[\alpha]_D^{20} = +142$. (Found C, 76.22; H, 8.72; N, 2.95. $C_{32}H_{43}NO_4$ requires C, 76.00; H, 8.57; N, 2.77%); ^{1}H NMR: $\delta = 0.14$ (s, 3H, 18-H$_3$), 0.94 (s, 3H, 19-H$_3$), 0.90–1.03 (m, 3H), 1.06–1.16 (m, 2H), 1.19 (d, $J = 7.3$ Hz, 3H, 21-H$_3$), 1.33–1.47 (m, 2H), 1.47–1.61 (m, 3H), 1.76–1.97 (m, 4H), 2.02 (s, 3H, CH_3COO), 2.08 (s, 3H, CH_3CON), 1.99–2.10 (m, 1H), 2.13–2.35 (m, 3H), 2.81 (q, $J = 7.3$, 1H, 20-H), 3.80 (s, 3H, O-CH$_3$), 4.58 (m, 1H, 3-H), 5.22 (m, 1H, 16-H), 5.34 (m, 1H, 6-H), 6.66 (d, $J = 2.8$ Hz, 1H, 3′-H), 6.71 (dd, $J = 8.5$, 2.8 Hz, 1H, 5′-H), 6.91 (d, $J = 8.5$ Hz, 1H, 6′-H) ppm. ^{13}C NMR: $\delta = 14.9$, 19.1, 20.4, 21.4, 22.1, 22.7, 27.7, 30.2, 32.0, 32.6, 33.9, 36.7, 36.8, 38.0, 38.8, 43.1, 49.9, 53.4, 54.7, 55.4, 57.7, 73.8 (C-3), 111.2, 114.0, 122.4 (C-6), 126.9, 130.7, 139.6 (C-5), 142.1, 157.8, 170.0 and 170.4 (CH_3COO and CH_3CON) ppm. EI-MS *m/z* (relative intensity): 506 (35), 505 (M^+, 100).

*2.1.25. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-6′-methoxy-4′-methy-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**12d**)*

12c (126 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with ethyl acetate/dichloromethane (30:70 v/v) afforded **12d** (81 mg, 70%), mp 255–256 °C, $R_f = 0.3$ (ss D), $[\alpha]_D^{20} = +177$. (Found C, 77.85; H, 9.02; N, 2.96. $C_{30}H_{41}NO_3$ requires C, 77.71; H, 8.91; N, 3.02%); ^{1}H NMR: $\delta = 0.14$ (s, 3H, 18-H$_3$), 0.92 (s, 3H, 19-H$_3$), 1.19 (d, $J = 7.3$ Hz, 3H, 21-H$_3$), 2.08 (s, 3H, CH_3CO), 0.84–2.35 (m, 15H), 2.82 (q, $J = 7.3$ Hz, 1H, 20-H), 3.50 (m, 1H, 3-H), 3.79 (s, 3H, O-CH$_3$), 5.22 (m, 1H, 16-H), 5.31 (m, 1H, 6-H), 6.67 (s, 1H, 3′-H), 6.71 (d, $J = 8.7$ Hz, 1H, 5′-H), 6.91 (d, $J = 8.7$ Hz, 1H, 5′-H) ppm. ^{13}C NMR: $\delta = 14.9$, 19.2, 20.4, 22.1, 22.7, 30.2, 31.5, 32.0, 32.5, 33.9, 36.6, 37.2, 38.9, 42.2, 43.1, 50.1, 53.5, 54.7, 55.4, 57.7, 71.5 (C-3), 111.2, 114.1, 121.3 (C-6), 126.9, 130.6, 140.8 (C-5), 142.1, 157.8, 170.0 ($CH_3\underline{C}O$) ppm. EI-MS *m/z* (relative intensity): 464 (30), 463 (M^+, 100), 421 (16), 160 (10).

*2.1.26. 1′,4′,16,17-tetrahydro-3β-hydroxy-6′-bromo-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**13b**)*

13a (128 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with ethyl acetate/dichloromethane (10:90 v/v) afforded **13b** (98 mg, 83%), mp 226–228 °C, $R_f = 0.2$ (ss A), $[\alpha]_D^{20} = -98$. (Found C, 69.05; H, 7.80; N, 3.10. $C_{27}H_{36}BrNO$ requires C, 68.93; H, 7.71; N, 2.98%); ^{1}H NMR (500 MHz, DMSO): $\delta = 0.64$ (s, 3H, 18-H$_3$), 0.94 (s, 3H, 19-H$_3$), 1.20 (d, $J = 5.0$ Hz, 3H, 21-H$_3$), 0.75–1.27 (m, 6H), 1.27–1.86 (m, 9H),

1.86–2.00 (m, 1H), 2.01–2.26 (m, 3H), 2.63 (m, 1H, 20-H), 3.25 (m, 1H, 3-H), 3.58 (m, 1H, 16-H), 4.60 (d, $J = 4.6$ Hz, 1H, OH), 5.27 (m, 1H, 6-H), 5.69 (s, 1H, NH), 6.42 (d, $J = 7.3$ Hz, 1H, 6′-H), 6.94 (d, $J = 6.9$ Hz, 1H, 5′-H), 7.04 (s, 1H, 3′-H) ppm. ^{13}C NMR (75 MHz, DMSO): $\delta = 14.0$, 19.1, 20.1, 23.0, 28.9, 30.7, 31.3 (2C), 35.5, 36.1, 36.9, 38.2, 42.1, 42.4, 49.9, 51.0, 54.2, 56.4, 69.9, 106.4, 114.8, 120.16, 128.3, 128.8, 129.9, 141.3, 144.9 ppm. EI-MS *m/z* (relative intensity): 472 (30), 471 ($[M+2]^+$, 95), 470 (30), 469 (M^+, 100).

*2.1.27. 1′,4′,16,17-Tetrahydro-3β-acetoxy-1′-acetyl-6′-bromo-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**13c**)*

13a (513 mg, 1.0 mmol) was acetylated by general procedure C. Column chromatography on silica gel with ethyl acetate/dichloromethane (20:80 v/v) afforded **13c** (377 mg, 68%), mp 222–225 °C, $R_f = 0.6$ (ss G), $[\alpha]_D^{20} = +154$. (Found C, 67.28; H, 7.35; N, 2.66. $C_{31}H_{40}BrNO_3$ requires C, 67.14,; H, 7.27; N, 2.53%); ^{1}H NMR: $\delta = 0.16$ (s, 3H, 18-H_3), 0.94 (s, 3H, 19-H_3), 1.20 (d, $J = 7.3$ Hz, 3H, 21-H_3), 0.88–1.23 (m, 5H), 1.34–1.62 (m, 5H), 1.70–1.97 (m, 4H), 2.02 (s, 3H, CH_3COO), 2.11 (br s, 3H, CH_3CON), 1.98–2.39 (m, 4H), 2.83 (q, $J = 7.3$ Hz, 1H, 20-H), 4.58 (m, 1H, 3-H), 5.19 (m, 1H, 16-H), 5.34 (m, 1H, 6-H), 6.87 (m, 1H, 6′-H), 7.19–7.34 (m, 2H, 3′- and 5′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.2$, 19.1, 20.3, 21.4, 21.9, 22.8, 27.6, 30.1, 32.0, 32.9, 33.4, 36.6, 36.8, 38.0, 38.6, 43.1, 49.8, 53.5, 54.9, 57.8, 73.7 (C-3), 119.1, 122.3 (C-6), 127.4, 129.2, 131.5, 136.8, 139.6 (C-5), 142.8, 169.7 and 170.4 (CH_3COO and CH_3CON) ppm. EI-MS *m/z* (relative intensity): 556 (18), 555 ($[M+2]^+$, 52), 554 (18), 553 (M^+, 50), 496 ($[M+2-OAc]^+$, 30), 495 ($[M+2-AcOH]^+$, 100), 494 ($[M-OAc]^+$, 36), 493 ($[M-AcOH]^+$, 96), 453 (25), 45l (22), 224 (18), 222 (16), 210 (24), 208 (22).

*2.1.28. 1′,4′,16,17-Tetrahydro-3β-hydroxy-1′-acetyl-6′-bromo-4′-methyl-(16α,17α)-androsta-5,16-dieno[17,16-b]quinoline (**13d**)*

13c (136 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with ethyl acetate/dichloromethane (30:70 v/v) afforded **13d** (88 mg, 69%), mp 245–251 °C, $R_f = 0.3$ (ss D), $[\alpha]_D^{20} = +155$. (Found C, 67.85; H, 7.65; N, 7.55. $C_{29}H_{38}BrNO_2$ requires C, 67.96; H, 7.47; N, 2.73%); ^{1}H NMR: $\delta = 0.16$ (s, 3H, 18-H_3), 0.93 (s, 3H, 19-H_3), 1.19 (d, $J = 7.3$ Hz, 3H, 21-H_3), 2.10 (br s, 3H, NAc), 2.82 (m, 1H, 20-H), 3.50 (m, 1H, 3-H), 5.18 (m, 1H, 16-H), 5.13 (m, 1H, 6-H), 6.86 (m, 1H, 6′-H), 7.23–7.31 (m, 2H, 3′- and 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.2$, 19.2, 20.3, 21.9, 22.8, 30.1, 31.4, 32.0, 32.8, 33.4, 36.5, 37.1, 38.6, 42.1, 43.1, 50.0, 53.5, 54.9, 57.8, 71.5 (C-3), 119.1, 121.3 (C-6), 127.4, 129.2, 131.5, 136.6, 140.7 (C-5), 142.8, 169.8 (NAc) ppm. EI-MS *m/z* (relative intensity): 514 (32), 513 ($[M+2]^+$, 98), 512 (34), 511 (M^+, 100), 471 (26), 469 (28), 224 (14). 222 (16), 210 (18), 43 (20).

*2.1.29. 3β-Hydroxy-16β-[N-(4′-nitro)phenyl]amino-17aβ-fluoro-17α-methyl-D-homo-androst-5-ene (**14b**)*

14a (125 mg, 0.25 mmol) was hydrolyzed by general procedure B. Column chromatography on silica gel with ethyl acetate/dichloromethane (10:90 v/v) afforded **14b** (95 mg, 83%) mp 262–264 °C, $R_f = 0.4$ (ss F), $[\alpha]_D^{20} = +47$. (Found C, 70.96; H, 8.35; N, 6.25. $C_{27}H_{37}FN_2O_3$ requires C, 71.02; H, 8.17; N, 6.14%); ^{1}H NMR: $\delta = 0.94$ (s, 3H, 18-H_3), 1.00 (s, 3H, 19-H_3), 1.12 (d, $J = 5.5$ Hz, 3H, 21-H_3), 3.07 (qd, $J = 10.3$, 4.6 Hz, 1H, 17-H), 3.53 (m, 1H, 3-H), 3.74 (dd, $J = 47.9$, 10.3 Hz, 1H, 17a-H), 4.29 (d, $J = 9.2$ Hz, 1H, 16-H), 5.31 (m, 1H, 6-H), 6.50 (d, $J = 9.2$ Hz, 2H, 2′- and 6′-H), 8.08 (d, $J = 9.2$ Hz, 2H, 3′- and 5′-H) ppm. ^{13}C NMR: $\delta = 11.9$, 15.1, 19.3, 19.6, 30.6, 30.8, 31.6, 31.9, 36.6, 36.8, 36.9, 38.0 (d, $J = 17.1$ Hz, C-13), 39.3 (d, $J = 18.9$ Hz, C-17), 42.0, 46.0 (d, $J = 5.4$ Hz), 49.6, 56.1 (d, $J = 11.7$ Hz), 71.6 (C-3), 103.2 (d, $J = 183.7$ Hz, C-17a), 111.1 (2C, C-2′ and -6′), 120.7 (C-6), 126.7 (2C, C-3′ and -5′), 138.0 (C-4′), 140.7 (C-5), 152.9 (C-1′) ppm. EI-MS *m/z* (relative intensity): 456 (M^+, 100).

*2.1.30. 3β-Acetoxy-N-acetyl-16β-[N-(4′-nitro)phenyl]amino-17aβ-fluoro-17α-methyl-D-homoandrost-5-ene (**14c**)*

14a (113 mg, 0.23 mmol) was dissolved in benzene (15 ml) in a flask equipped with a solvent trap. Benzene (4 ml) was distilled off, and isopropenyl acetate (1 ml) and *p*-toluenesulfonic acid (5 mg) were then added to the mixture. A further amount of benzene (2 ml) was distilled off in 1.5 h. Water (20 ml) was added to the solution, and it was extracted with dichloromethane (3 × 20 ml). The combined organic phases were washed with aqueous $NaHCO_3$ (20 ml), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The resulting deep-brown substance was chromatographed on silica gel with tert-butyl ether/dichloromethane (10:90 v/v) yielding pure **14c** (109 mg, 89%), mp 226–228 °C, $R_f = 0.6$ (ss H), $[\alpha]_D^{20} = -49$. (Found C, 68.98; H, 7.85; N, 5.30. $C_{31}H_{41}FN_2O_5$ requires C, 68.87; H, 7.64; N, 5.18%); ^{1}H NMR: $\delta = 0.56$ (s, 3H, 18-H_3), 0.93 (s, 3H, 19-H_3),1.18 (d, $J = 5.5$ Hz, 3H, 21-H_3), 2.01 (s, 3H, CH_3COO), 3.77 (dd, $J = 48.1$, 9.6 Hz, 1H, 17a-H), 4.57 (m, 1H, 3-H), 4.67 (m, 1H, 16-H), 5.32 (m, 1H, 6-H), 7.32 (d, $J = 8.0$ Hz, 2H, 2′- and 6′-H), 8.31 (d, $J = 8.0$ Hz, 3′- and 5′-H) ppm. ^{13}C NMR: $\delta = 11.6$, 14.9, 19.1, 19.3, 21.3, 23.4, 27.3, 28.5, 30.9, 31.8, 35.5 (d, $J = 19.9$ Hz, C-17), 36.2, 36.5, 36.8, 37.6, 37.8, 45.6 (d, $J = 5.4$ Hz, C-16), 49.2, 55.7, 73.7 (C-3), 103.4 (d, $J = 182.8$ Hz, C-17a), 121.6 (3C, C-6 and -2′ and -6′), 124.8 (2C, C-3′ and -5′), 139.6 (C-5), 145.2 and 147.5 (C-1′ and -4′), 169.5 and 170.4 (CH_3COO and CH_3CON) ppm. EI-MS *m/z* (relative intensity): 480 ($[M-AcOH]^+$, 100). DCI-MS *m/z* (relative intensity): 575 ($[M+NH_3+NH_4]^+$, 16), 558 ($[M+NH_4]^+$, 100), 541 ($[M+H]^+$, 7). Crystal data: $C_{31}H_{41}FN_2O_5$, $M_r = 540.66$, orthorhombic, space group $P2_12_12_1$, $a = 8.1240(10)$ Å, $b = 14.483(2)$ Å, $c = 24.509(4)$ Å, $V = 2883.7(7)$ Å^3, $Z = 4$, $\rho_{calc} = 1.245$ g cm^{-3}, $F(000) = 1160$, μ(Mo Kα) = 0.718 cm^{-1}, min/max transmission 0.8697/0.9316, crys-

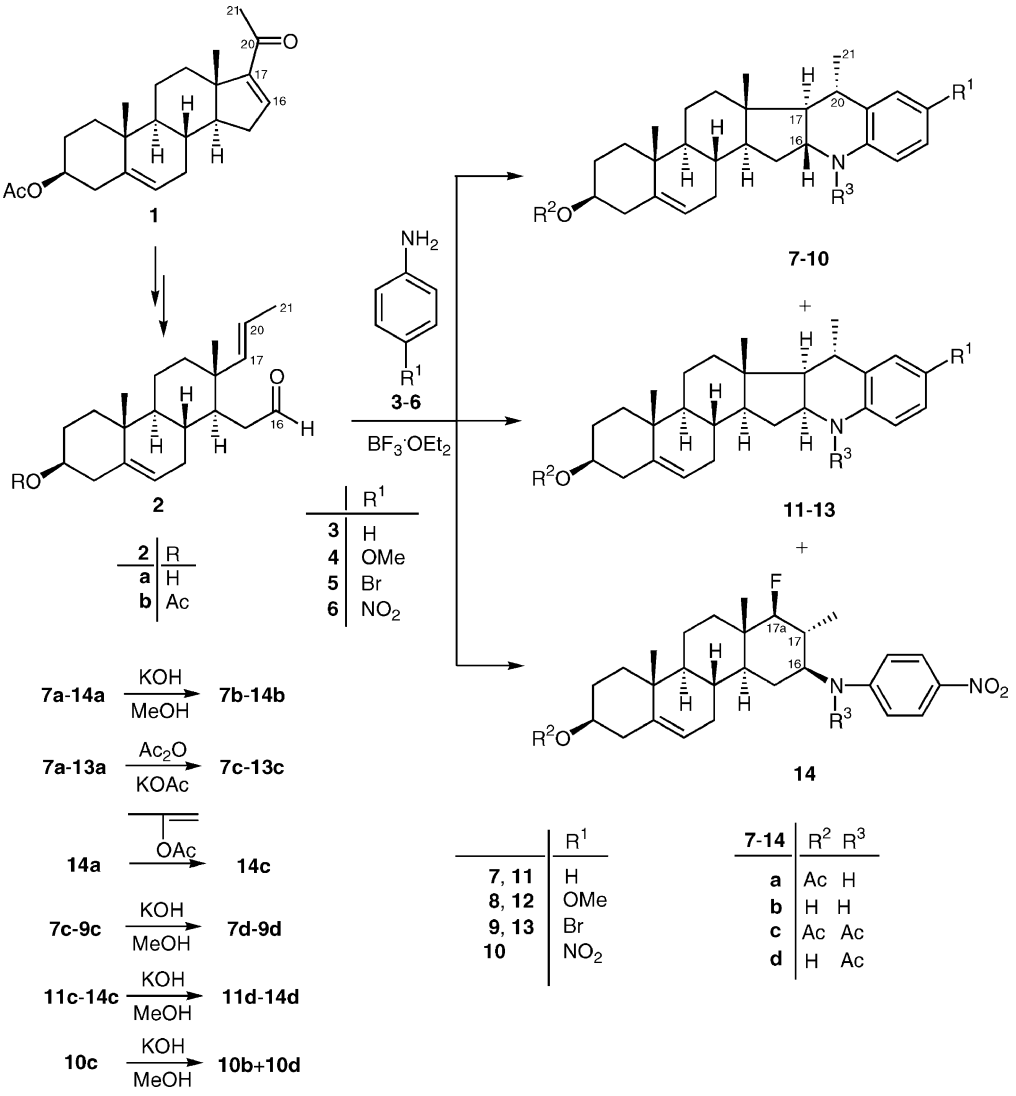
tal dimensions 0.2 mm × 0.2 mm × 0.1 mm, $3.54^\circ < \Theta < 59.09^\circ$, 38,005 reflections were collected, of which 4154 were independent ($R_{int} = 0.0240$) and 4154 were used for refinement. For the final refinement of 358 parameters, no restraints were used. The *R*-values were: $R_1 = \Sigma|F_o - F_c|/\Sigma F_o = 0.0258$ for $I > 2\sigma(I)$, and $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2} = 0.0672$ for all data; max/min residual electron density: 0.19/−0.16 e Å^{-3}.

2.1.31. 3β-Hydroxy-N-acetyl-16β-[N-(4′-nitro)-phenyl]-amino-17aβ-fluoro-17α-methyl-D-homo-androsta-5-ene (14d)

14c (135 mg, 0.25 mmol) was hydrolyzed by general procedure B. Recrystallization from methanol afforded **14d** (110 mg, 88%), mp 157–159 °C, $R_f = 0.3$ (ss D), $[\alpha]_D^{20} = -45$. (Found C, 70.02; H, 7.69; N, 5.71. $C_{29}H_{39}FN_2O_4$ requires C, 69.85; H, 7.88, N, 5.62%); ^{1}H NMR: $\delta = 0.56$ (s, 3H, 18-H$_3$), 0.93 (s, 3H, 19-H$_3$), 1.18 (d, $J = 5.9$ Hz, 3H, 21-H$_3$), 3.50 (m, 1H, 3-H), 3.77 (dd, $J = 48.2$, 9.9 Hz, 1H, 17a-H), 4.67 (m, 1H, 16-H), 5.30 (m, 1H, 6-H), 7.33 (d, $J = 8.0$ Hz, 2H, 2′- and 6′-H), 8.32 (d, $J = 8.4$ Hz, 2H, 3′- and 5′-H) ppm. ^{13}C NMR: $\delta = 11.7$, 15.0, 19.2, 19.4, 23.4, 28.6, 30.9, 31.5, 31.9, 35.6 (d, $J = 18.9$ Hz, C-17), 36.3, 36.8 (2C), 37.7 (d, $J = 16.9$ Hz, C-13), 42.0, 45.8, 49.4, 55.8, 71.5 (C-3), 103.5 (d, $J = 182.2$ Hz, C-17a), 120.7 (3C, C-6 and -2′ and -6′), 124.8 (2C, C-3′ and 5′), 140.7 (C-5), 145.2 and 147.6 (C-4′ and C-1′), 169.6 ($CH_3\underline{C}ON$) ppm. EI-MS *m/z* (relative intensity): 498 (M^+, 50), 478 ($[M-HF]^+$, 100), 318 (35), 300 (65), 285 (48), 207 (32), 180 (44), 43 (32).

3. Results and discussion

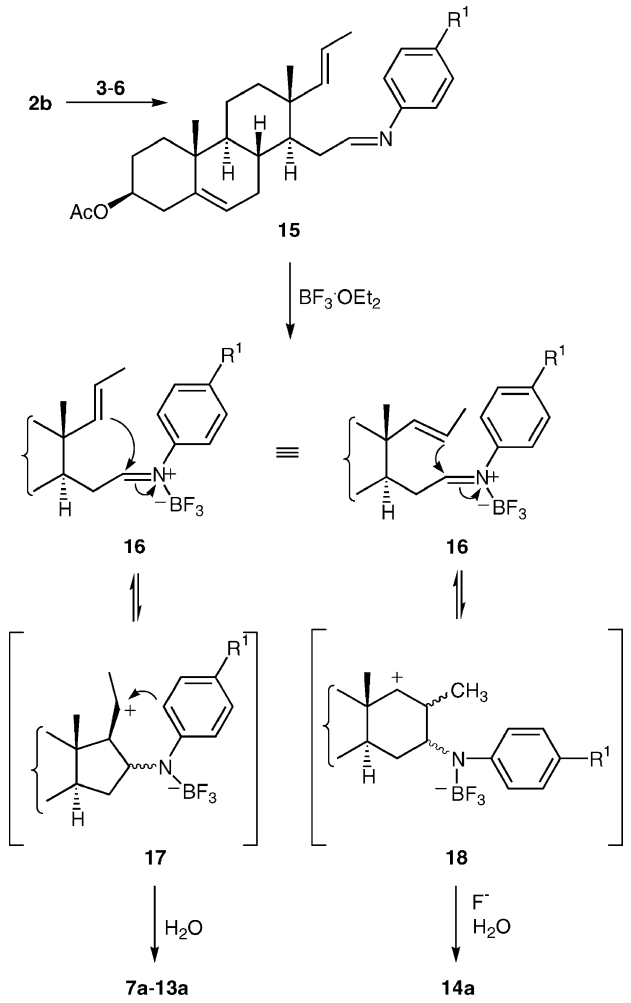
We recently demonstrated that the D-*seco*-steroid **2a** can be obtained in five steps from the readily available pregnadienolone acetate (**1**) [6]. The steroidal aldehyde **2b** was reacted with aniline derivatives **3**–**6** and subsequently treated with $BF_3{\cdot}OEt_2$ as a *Lewis* acid. The reactions resulted in



Scheme 1. Synthesis of steroidal cyclization products **7**–**14** from D-*seco*-pregnene **1**.

Table 1
Products of reactions of **2** with different anilines, and their further derivatives

Entry	Substrates	Reagent	Products	Ratio	Overall yield (%)
1	**2** + **3**	$BF_3{\cdot}OEt_2$	**7a** + **11a**	6.7:1	91
2	**2** + **4**		**8a** + **12a**	3.8:1	90
3	**2** + **5**		**9a** + **13a**	4.8:1	93
4	**2** + **6**		**10a** + **14a**	5.9:1	85
5	**7a**	KOH/MeOH	**7b**		70
6	**8a**		**8b**		63
7	**9a**		**9b**		92
8	**10a**		**10b**		79
9	**11a**		**11b**		71
10	**12a**		**12b**		95
11	**13a**		**13b**		83
12	**14a**		**14b**		83
13	**7a**	Ac_2O/KOAc	**7c**		90
14	**8a**		**8c**		78
15	**9a**		**9c**		77
16	**10a**		**10c**		82
17	**11a**		**11c**		89
18	**12a**		**12c**		83
19	**13a**		**13c**		68
20	**14a**		–		–
21	**14a**	Isopropenyl acetate	**14c**		89
22	**7c**	KOH/MeOH	**7d**		93
23	**8c**		**8d**		78
24	**9c**		**9d**		85
25	**10c**		**10b** + **10d**	8.5:1	89
26	**11c**		**11d**		67
27	**12c**		**12d**		70
28	**13c**		**13d**		69
29	**14c**		**14d**		88

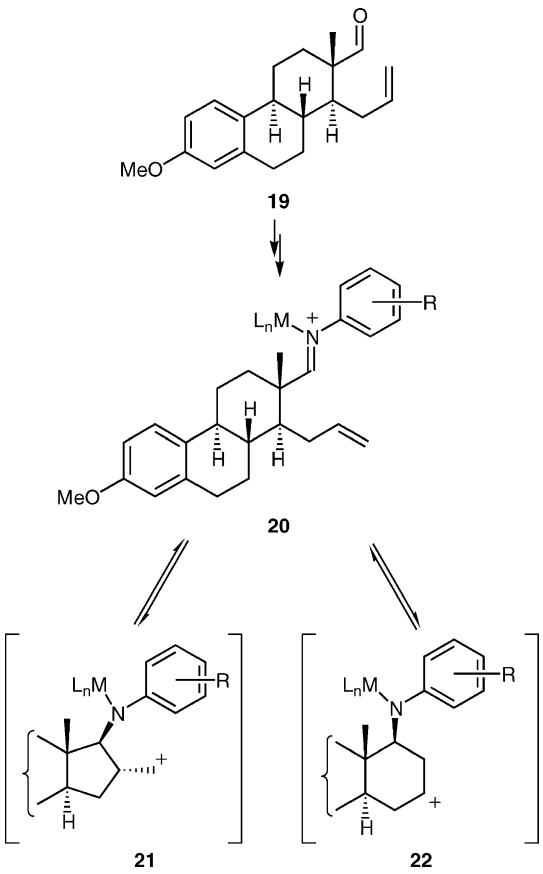


Scheme 2. The assumed formation of carbocations **17** and **18** from **2** by treatment with $BF_3{\cdot}OEt_2$.

the 3-acetoxy steroidal *Diels-Alder* adducts **7a**–**13a** and the D-homosteroid **14a** (Scheme 1). In the cases of the unsubstituted aniline (**3**), *p*-methoxyaniline (**4**), and *p*-bromoaniline (**5**), we isolated two isomeric *Diels-Alder* products: the D/E ring *trans* (16α,17β; **7a**–**9a**) and *cis* (16β,17β; **11a**–**13a**) diastereomers in a ratio of 3.8:1 to 6.7:1 (Table 1, entries 1–3). The total yield was high (90–93%). The best selectivity was observed for **7a** and **11a** (R^1 = H, 6.7:1). The reaction of *p*-nitroaniline (**6**) proceeded with an overall yield of 85%, i.e., lower than for the other three substituents. The corresponding *trans* product **10a** and the product of an aza-*Prins* reaction (**14a**) were obtained in a 5.9:1 ratio.

We assume that the unsaturated aldehyde **2** first condenses with the aniline (**3**–**6**) to yield the imine **15**. Treatment of **15** with $BF_3{\cdot}OEt_2$ results in the iminium ion **16**, which can subsequently give either **17** or **18** in carbocation form. Carbocation **17** can initiate a *Friedel-Crafts* alkylation to give the formally hetero *Diels-Alder* cycloadducts **7a**–**9a** and **11a**–**13a**. In contrast with the normal *Diels-Alder* reaction, cycloaddition of the arylimines follows a two-step ionic reaction mechanism. The cationic forms **17** and **18** can be in equilibrium with each other. However, cyclic carbocation **18** can be stabilized by capture of F^-, giving the arylamino fluoride **14a**. Due to the electron-withdrawing properties of the nitro group the aromatic ring is less suitable to participate in the *Friedel-Crafts* reaction, allowing hereby the other pathway, which serves the aza-*Prins* product (Scheme 2).

The chemoselectivity of these reactions can readily be explained if these results are compared with previous ones. We earlier reported on the transformations of the *seco*-estrone aldehyde **19** by treatment with aniline and subsequently with $BF_3{\cdot}OEt_2$ [7]. The aryliminium salts formed yielded either tetrahydroquinolines condensed to the estrone D ring or *N*-arylamino-D-homosteroids, depending on the substituent on the arylimino group. Using *p*-nitroaniline (**6**), we obtained only the aza-*Prins* product (Scheme 3). With *p*-nitroaniline (**6**) in the present work, we obtained mainly the tetrahydroquinoline condensed steroid (**10a**); indeed, the condensation of **2** with the other anilines **3**–**5** did not give D-homosteroids at all. This behavior can be explained by the difference in the alkene moiety. A comparison of the presumed structures **17** and **21** reveals that the resulting carbocation **17** is secondary in contrast with **21**, which is primary. We assume that this stabilizing effect promotes the *Friedel-Crafts* reaction.



Scheme 3. Formation of carbocations **21** and **22**.

The reactions affording hetero *Diels-Alder*, but not aza-*Prins* adducts (**2b** and anilines **3**–**5**, entries 1–3), also yielded two diastereomeric products: the 16β,17α (*trans*) and 16α,17α (*cis* annulation) compounds (Table 1).

The main (*trans*) product was of the same type as observed exclusively in the estrone series [7,8]. Various investigations have demonstrated that the diastereoselectivity can be influenced by numerous factors. Sabitha et al. synthetized octahydroacridines in a similar way, using $BiCl_3$ as a catalyst. They noted that the selectivity depended on the temperature [9]. Working at 0 °C, they obtained *trans* and *cis* adducts with the *trans* diastereomer (92–100%) as the main product. At room temperature, these two isomers were formed in a 1:1 ratio. Kiselyov and co-workers found that the ratio of the tetrahydrochromano[4,3-b]quinoline diastereomers produced during the intramolecular cyclization of aromatic imines was not influenced by the different solvents (MeCN, THF, or CH_2Cl_2) or catalysts ($Yb(OTf)_3$ or TFA) applied, whereas the overall yield did vary [10,11]. Linkert et al. revealed the dependence of the diastereomeric excess on the catalyzing acid ($SnCl_4$, $EtAlCl_2$ or $BF_3{\cdot}OEt_2$) [12].

The 3-acetoxy derivatives **7a**–**14a** were transformed by alkaline hydrolysis to aminoalcohol compounds **7b**–**14b**, while treatment with acetic acid anhydride/KOAc afforded the *N*,*O*-diacetyl steroids **7c**–**13c**. The *p*-nitro-substituted D-homoandrostane **14a** did not react under the latter conditions. The reaction of **14a** with isopropenyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid gave **14c**. On hydrolysis, these *N*,*O*-diacetyl compounds (**7c**–**14c**) yielded 3-hydroxy-*N*-acetyl products **7d**–**14d**. The *O*-acetyl group underwent selective hydrolysis, while the *p*-nitro-substituted tetrahydroquinolinoandrostane **10c** gave not only the mono hydrolysis product **10d**, but also the aminoalcohol **10b**.

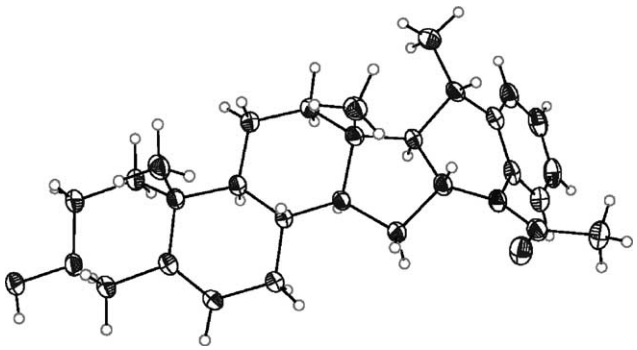


Fig. 1. Molecular structure of **7d**.

The structures of the synthetized compounds were determined by means of ^1H and ^{13}C NMR spectroscopy and NOESY experiments. The starting aldehyde **2b** displayed the 18-CH_3 signal at 0.92 ppm [6], while the main product derivatives **7**–**10** gave a peak in the interval 0.82–0.96 ppm. The 18-CH_3 signal of the-side product derivatives **11c**–**13c** and **11d**–**13d** in the ^1H NMR spectra underwent a strong upfield shift to 0.09–0.16 ppm. The ^1H NMR spectra of **13d**, **14c**, and **14d** exhibited surprisingly broad, insignificant *N*-acetyl signals, though the ^{13}C NMR signals were the expected ones. The configurations of the newly formed stereogenic centers could not be established unambiguously by NMR methods in all cases. X-ray structure analysis of one representative of each type of compound helped to solve this problem. Figs. 1 and 2 depict the crystal structures of a main (**7d**) and a side *Diels-Alder* product (**11c**), respectively.[1] Fig. 3 presents the molecular structure of **14c**, showing the 16β,17α,17aβ orientation of the new D ring substituents.

We have prepared new steroid-tetrahydroquinoline hybrid molecules via *Lewis* acid-catalyzed cyclization reactions. We obtained two types of hetero *Diels-Alder* products: 16,17-*trans* compounds (**7a**–**10a**) as the main product and 16,17-*cis* (**11a**–**13a**) compounds as side-products (entries 1–4). The cyclization of the *p*-nitroarylamino salt af-

[1] Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-224298 for **7d**, CCDC-225031 for **11c** and CCDC-221793 for **14c**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk).

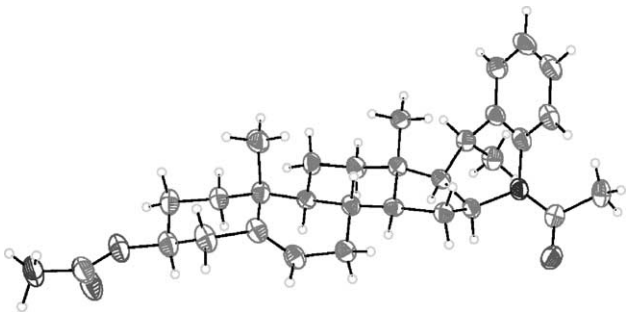


Fig. 2. Molecular structure of **11c**.

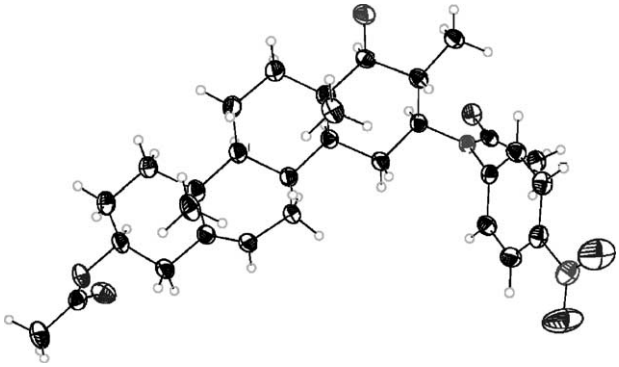


Fig. 3. Molecular structure of **14c**.

forded not only **10a**, but also D-homopregnane **14a** via an intramolecular aza-*Prins* reaction.

Acknowledgements

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