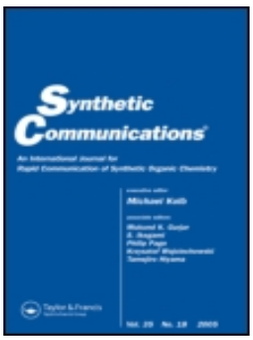

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The First Syntheses of 16β-Chloro- and 16β-Bromo-cyproterone Acetate

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ABSTRACT

The first syntheses of 16β-chloro- and 16β-bromo-cyproterone acetate is described. The preparation of 16β-chlorocyproterone acetate was accomplished in eight steps (6.5% overall yield) from commercially available 16-dehydropregnenolone acetate. 16β-Bromocyproterone acetate was prepared from 16β-chloro-cyproterone acetate with base-induced epoxide formation as the key step.

Key Words: 16β-Bromo-cyproterone acetate; 16β-Chloro-cyproterone acetate; 16-Dehydropregnenolone acetate; Synthesis.

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Synthesis of ideal anti-androgenic molecule is still of interest because it can offer useful treatment for androgen-mediated diseases, such as prostate cancer, acne, seborrhea, androgenic alopecia, precocious puberty and benign prostatic hyperplasia. So modification of steroid structures represents a continuing effort on the part of the steroid chemist to alter biological activity. The alterations in activity, although often predictable, are in some case quite unexpected. A variety of steroids have been synthesized showing higher androgenic activity than testosterone concomitant with several new compounds with anti-androgenic activity. Examples of steroidal molecules with high anti-androgenic effects are cyproterone acetate, which is an antagonist of androgen receptors, and finasteride, which selectively inhibits 5α-reductase isozyme type 2.[1] The 16β-methylene group could increase progestational activity and enhanced the anti-androgenic activity. The 16α- and 16β-methyl group have been described, but assay data is not available.[2] In this connection, it seemed of particular interest to examine derivatives of cyproterone acetate substituted at the 16-position, in view of progestational potentiating effect reported for 16-methylene- and 16α-methyl-cyproterone acetate.[2–4]

Accordingly, we prepared of 16β-chlorocyproterone acetate (**11**) and 16β-bromocyproterone acetate (**14**). Their antiandrogenic and progestational activities will be published in due course.

The synthesis of 16β-chlorocyproterone acetate (**11**) used commercially available 16-dehydropregnenolone acetate (**1**) as the starting material. The preparation of 1,4,6-trienone epoxide (**3**), a key intermediate, was obtained by epoxidation of **1** using 30% H_2O_2/NaOH in methanol to give epoxide (**2**) in 89% yield followed by oxidative-dehydrogenation with 2,4-dichloro-5,6-dicyanobenzoquinone (DDQ)[5,6] in refluxing dioxane to provide the compound **3** in 66% yield. Ketalization of the 20-keto group of **3** with ethylene glycol, ethyl orthoformate and *p*-toluenesulfonic acid[7] provided 16α,17α-epoxy-1,4,6-pregnatriene-20-ethylene ketal-3-one (**4**) in 70% yield. A cyclopropyl group was introduced into the 1,2-position of (**4**) using dimethyl sulfoxonium methylide[8] followed by hydrolysis of 20-ketal with *p*-toluenesulfonic acid in dichloromethane to afford 1α,2α-cyclomethylene-16α,17α-epoxy-1,4,6-pregnatriene-3,20-dione (**5**) in 71% yield (Sch. 1).

Attempts to open the epoxide of **5** using 5 equiv. of *N*,*N*-dimethyl acetamide hydrochloride[9] in chloroform at room-temperature caused cyclopropane ring opening with the formation of a 1-chloromethylene product (**7**) in 55% yield. However, reducing the amount of *N*,*N*-dimethylacetamide hydrochloride to 3.0 equiv. gave the desired compound (**6**) and the 1-chloromethylene product (**7**) in 40 and 34% yields, respectively. Acetylation of **6** using acetic acid, trifluoroacetic

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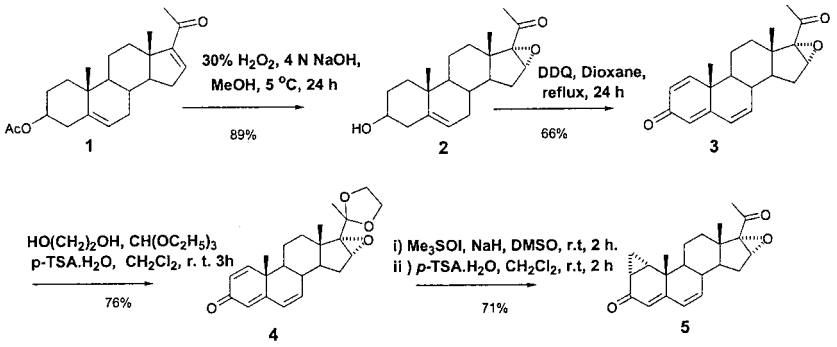

Scheme 1.

anhydride and *p*-toluenesulfonic acid[10] gave the acetate compound (**9**) in 89% yield. Acetate (**9**) was also obtained by acetylation of **7** to give intermediate **8** followed by treatment with pyridine at 100°C for 15 min to afford **9** in 62% yield (Sch. 2).

Epoxidation of **9** using MCPBA provided **10** in 68% yield. When epoxide (**10**) was treated with *N*,*N*-dimethylacetamide hydrochloride in DMSO at 55°C for 30 h, 16β-chlorocyproterone acetate (**11**) was obtained in 60% yield (Sch. 3).

The synthesis of 16β-bromocyproterone acetate (**14**) from 16β-chlorocyproterone acetate (**11**) was accomplished by treatment of **11** with basic Al_2O_3 in benzene to produce 6α,17α-epoxy-1α,2α-cyclomethylene-6-chloro-4,6-pregnadiene-3,20-dione (**12**) in 75% yield followed by epoxide ring opening using a mixture of bromine and PPh_3 in THF to provide 1α,2α-cyclomethylene-6-chloro-16β-bromo-17α-hydroxy-4,6-pregnadiene-3,20-dione (**13**) in 70% yield. 16β-Bromocyproterone acetate (**14**) was obtained after acetylation of **13** in 85% yield (Sch. 4).

EXPERIMENTAL

Melting points were determined on MEI-TEMP capillary melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl anion radical and distilled under a dry N_2 atm immediately prior to use. All other chemicals were obtained from Aldrich Chemical Co. and were used without further purification. Purification of reaction products was carried out by flash

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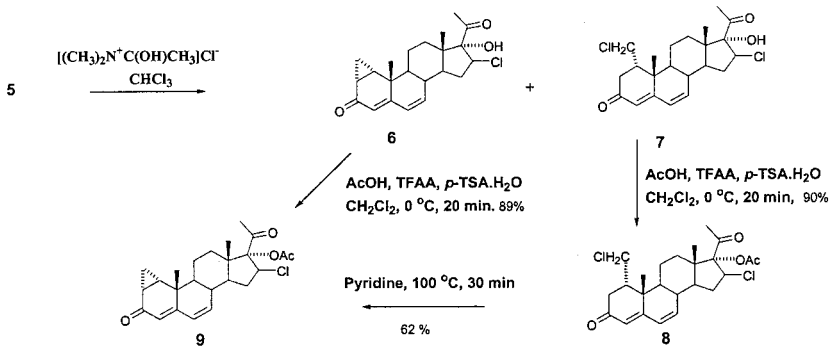
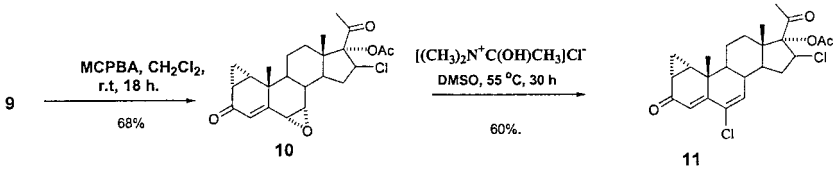
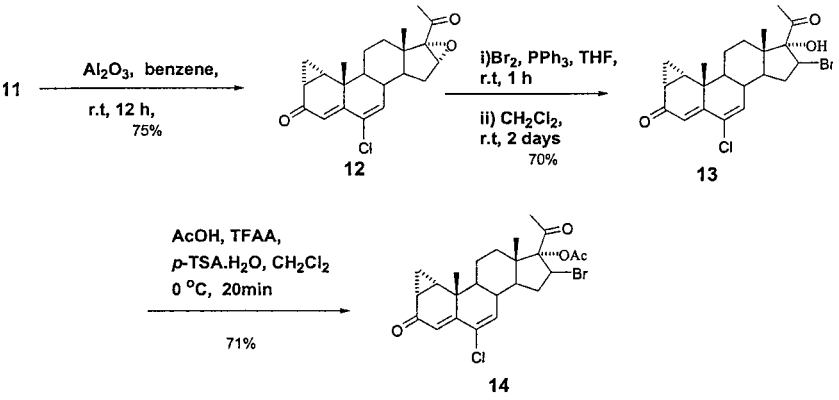


Scheme 2.



Scheme 3.



Scheme 4.

column chromatography using a glass column, dry packed with silica gel (230–400 mesh) according to the method of Still et al.[11] ^{1}H and ^{13}C-NMR spectra were recorded with a Gemini 2000 (300 MHz) spectrometer and Brucker WH 400 (400 MHz) and signals are in δ (ppm) relative to

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TMS at 0.0. Mass spectra were measured on VG7070F mass spectrometer at 6 kV. Elemental analyses were performed by Atlantic Microlab Inc.

3β-Hydroxy-16α,17α-epoxy 5-pregnene-20-one (2): 3β-Acetoxy-5,16-pregnadiene-20-one (**1**) (10 g, 28.09 mmol) was dissolved in methanol (1L). This solution was treated after chilling to 15°C with 4 N sodium-hydroxide (20 mL) and then immediately with 30% hydrogen peroxide (40 mL). The mixture was then stored in the refrigerator at 5°C for 24 h. At this time, examination of sample indicated the absence of an α,β-unsaturated ketone as evidenced by absorption in the ultraviolet. The methanol solution was poured into water (1L) and the resulting white solid separated. The solid, which was washed well with water and dried weighed (8.23 g, 89%); m.p. 175–177°C. The crude product **2** as a white solid was used without further purification.

16α,17α-Epoxy-1,4,6-pregnatriene-3,20-dione (3): A solution of **2** (555 mg, 2.23 mmol) in dry dioxane (45 mL) was added with DDQ (2.5 g) and refluxed under N_2 for 24 h. After removing the precipitate by filtration, the filtrate was concentrated and the residue was dissolved in CH_2Cl_2 (30 mL), then washed with satd. aq. $NaHCO_3$ (20 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated to give crude residue. This residue was purified by flash column chromatography on silica gel (1:1 EtOAc/hexane) to give the compound **3** as a colorless solid (474 mg, 66%); m.p. 175–176°C; IR (KBr): 1697, 1649, 1600, 892 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.0 (d, 1H, -CH=CH-C=O, $J = 3.0$ Hz), 6.2 (m, 2H, -CH=CH-C=CH-C=O, -CH=CH-C=O), 5.98 (s, 1H, -CH=CH-C=CH-C=O), 5.9 (d, 1H, CH=CH-C=CH-C=O, $J =$ 2.4 Hz), 3.7 (s, 1H, -CH-O-(epoxide)), 2.3 (m, 1H), 1.0–2.2 (m, 8H), 2.0 (s, 3H, CH_3C=O), 1.2 (s, 3H, CH_3), 1.1 (s, 3H, CH_3); MS m/z (%) 324 (M^+, 5), 263 (100), 248 (30), 170 (30), 128 (30); HRMS m/z 324.1723 (calcd. for $C_{21}H_{24}O_3$, 324.1725); Anal. calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.58; H, 7.50.

16α,17α-Epoxy-1,4,6-pregnatriene-20-ethylene ketal-3-one (4): A solution of 16α,17α-epoxy-1,4,6-pregnatriene-3,20-dione (**3**) (1.5 g, 4.62 mmol) in CH_2Cl_2 (7.5 mL) was added with ethylene glycol (0.8 mL), ethyl orthoformate (1.1 mL) and *p*-toluenesulfonic acid (150 mg). The reaction mixture was stirred at room temperature for 3 h. Neutralization performed with trimethylamine (0.15 mL). The mixture was washed with water and dried over sodium sulfate anhydrous and evaporated to give a residue. This residue was chromatrographed on silica gel (1:1 EtOAc/hexane) to give **4** as a colorless solid (1.2 g, 72%); m.p. 144–146°C; IR (KBr): 1701, 1658, 1603, 1043, 878 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.05 (d, 1H, C-CH=CH-C=O, $J = 3.0$ Hz), 6.23 (dd, 1H, C-CH=CH-C=O, $J = 3.0$, 0.9 Hz), 6.25 (dd, 1H, CH=CH-C=CH-C=O, $J = 2.4$, 0.56 Hz),

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6.02 (s, 1H, CH=CH-C=CH-C=O), 5.97 (d, 1H, -CH=CH-C=CH-C=O, $J = 2.4$ Hz), 3.9–4.05 (m, 4H, -O-CH_2-CH_2-O-), 3.45 (s, 1H, ^{16}CH-O (epoxide), 1.22 (s, 3H, CH_3), 1.43 (s, 3H, $^{21}CH_3$C-O), 1.12 (s, 3H, CH_3); MS m/z (%) 368 (M^+, 2), 87 (100); HRMS m/z 368.1978 (calcd. for $C_{23}H_{28}O_4$, 368.1988).

1α,2α-Cyclomethylene-16α,17α-epoxy-4,6-prenadiene-3,20-dione (5): A solution of trimethyl sulfoxonium iodide (5.53 g, 24.2 mmol) in DMSO (37 mL) was added to NaH (659 mg of a 50% mineral oil suspension). The reaction mixture was stirred at room temperature. After 1 h a solution of 16α,17α-epoxy-1,4,6-pregnatriene-20-ethylene ketal-3-one (**4**) (1.87 g, 5.07 mmol) in DMSO (24 mL) was added and then the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was added to H_2O (100 mL), the precipitate was collected by filtration. The residue was dissolved with dichloromethane (20 mL) and added *p*-TsOH·H_2O and then the reaction mixture was stirred at room temperature for 2 h. Cold 20% aq. K_2CO_3 was added carefully until the mixture was basic. The mixture was extracted with CH_2Cl_2 (3×20 mL) and washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to afford a thick residue. This residue was purified by flash column chromatography on silica gel (6:5 EtOAc/hexane) to provide **5** as a colorless solid (1.21 g, 71%); m.p. 236–238°C; IR (KBr) 1701, 1657, 1621, 906 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.99 (d, 1H, CH=CH-C=CH-C=O, $J = 3.0$ Hz), 5.83 (d, 1H, -CH=CH-C=CH-C=O, $J = 3.0$ Hz), 5.44 (s, 1H, CH=CH-C=CH-C=O), 3.8 (s, 1H, ^{16}CH-O (epoxide), 1.15 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.98 (s, 3H, $^{21}CH_3$C-O), 0.72 (m, 1H, CH_2 (cyclopropane)); MS m/z (%) 338 (M^+, 8), 295 (80), 278 (100), 263 (27); HRMS m/z 338.1876 (calcd. for $C_{22}H_{26}O_3$, 324.1882).

Conversion of 1α,2α-cyclomethylene-16α,17α-epoxy-4,6-pregnadiene-3,20-dione (5) to 1α,2α-cyclomethylene-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (6): A solution of **5** (493 mg, 1.46 mmol) in chloroform (31 mL) was added with *N*,*N*-dimethyl acetamide hydrochloride (180 mg, 3 equiv.). The reaction mixture was stirred at room temperature for 24 h and then was poured into satd. aq. $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phase was washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude product. The crude product was purified by flash column chromatography on silica gel (2:3 EtOAc/hexane) to give 1α-chloromethyl-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (**7**) as a colorless solid (204 mg, 34%) and 1α,2α-cyclomethylene-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (**6**) as a white solid (217 mg, 40%).

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6: M.p. 217–219°C; IR (KBr): 3421, 1716, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.0 (d, 1H, CH=CH-C=CH-C=O, $J = 3.0$ Hz), 5.87 (d, 1H, -CH=CH-C=CH-C=O, $J = 3.0$ Hz), 5.45 (s, 1H, CH=CH-C=CH-C=O), 3.3 (s, 1H, OH), 4.1 (t, 1 H, ^{16}CH-Cl), 1.25 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.36 (s, 3H, $^{21}CH_3$C-O), 0.72 (m, 1H, CH_2 (cyclopropane)); MS *m/z* (%) 374 (M_+, 91), 338 (53), 332 (36), 320 (30), 312 (62), 294 (60), 43 (100); HRMS *m/z* 374.1651 (calcd. for $C_{22}H_{27}ClO_3$, 374.1749).

7: M.p.180–182°C; IR (KBr): 3422, 1717, 1656, 1625, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.0–6.2 (dd, 2 H, -CH = CH-C=CH-C=O), 5.7 (s, 1H, -CH=CH-C=CH-C=O), 4.1 (m, 1H, ClCH-C-), 3.2–3.75 (dd, 2H, $ClCH_2$-CH-), 3.35 (s, 1H, OH), 2.7–3.0 (m, 2H), 1.0-2.4 (m,10H), 2.45 (s, 3H, CH_3C=O), 1.3 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); MS *m/z* (%) 410 (M^+, 15), 374 (19), 368 (14), 349 (20), 312 (12), 274 (19), 59 (100); HRMS *m/z* 410.1407 (calcd. for $C_{22}H_{28}Cl_2O_3$, 410.1415).

Acetylation of 1α,2α-cyclomethylene-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (6): Under a N_2 atmosphere, acetic acid (0.69 mL, 11.73 mmol) was added to a well stirred mixture of TFAA (1.6 mL, 27.2 mmol) in CH_2Cl_2 (4.5 mL) and the mixture was stirred at room temperature for 30 min. *p*-TsOH·H_2O (93 mg, 0.54 mmol) was then added and the mixture was cooled to 0°C. The 1α,2α-cyclomethylene-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (**6**) (217 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (5 mL), cooled in an ice bath and added to the stirred mixed anhydride and stirring at 0°C for 20 min. Cold 20% aq. K_2CO_3 was added carefully until the mixture was basic. The mixture was diluted with H_2O until the CH_2Cl_2 phase became the lower phase. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to afford a thick syrup. The syrup was purified by flash column chromatography on silica gel (1:10 EtOAc/CH_2Cl_2) to give 1α,2α-cyclomethylene-16β-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione (**9**) as a colorless solid (215 mg, 89%); m.p. 163–165°C; IR (KBr): 1737, 1650, 1613, 1238, 1025 cm^{-1}; MS *m/z* (%) 416 (M^+, 2), 376 (11), 338 (11), 332 (12), 312 (4), 296 (23), 276 (22), 238 (21), 58 (100); HRMS *m/z* 416.1740 (calcd. for $C_{24}H_{29}ClO_4$, 416.1754).

Acetylation of 1α-chloromethyl-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (8): Under a N_2 atmosphere, acetic acid (0.59 mL, 9.97 mmol) was added to a well stirred mixture of TFAA (1.4 mL, 23.8 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 min. *p*-TsOH·H_2O (80 mg, 0.46 mmol) was then added and the mixture was cooled to 0°C. The 1α-chloromethyl-16β-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (**7**) (204 mg, 0.496 mmol)

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was dissolved in CH_2Cl_2 (5 mL), cooled in an ice bath and added to the stirred mixed anhydride and stirring at 0°C for 20 min. Cold 20% aq. K_2CO_3 was added carefully until the mixture was basic. The mixture was diluted with H_2O until the CH_2Cl_2 phase became the lower phase. The mixture was extracted with CH_2Cl_2 (3×20 mL) and washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to give a thick syrup. The syrup was purified by flash column chromatography on silica gel (1:20 EtOAc/CH_2Cl_2) to provide the 1α-chloromethyl-16β-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione (**8**) as a white solid (203 mg, 90%); m.p. 204–206°C; IR (KBr): 1738, 1651, 1614, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.2 (d, 1H, -CH=CH-C=CH-C=O, $J = 3.0$ Hz), 6.06 (d, 1H, -CH=CH-C=CH-C=O, $J = 3.0$ Hz), 5.75 (s, 1H, -CH=CH-C=CH-C=O), 4.3 (t, 1H, ^{16}CH-Cl), 3.7 (t, 1H, ^{1}CH-CH_2Cl), 3.3 (dd, 2H, ClCH_2-CH-), 3.3 (dd, 1H, CH-CH_2Cl, $J = 3.4$, 3.3 Hz), 2.98 (d, 1H, $^2CH_2{}^1$CH-CH_2Cl, $J = 5.3$ Hz), 2.83 (m, 1H, $^2CH_2{}^1$CH-CH_2Cl), 2.22 (s, 3H, CH_3COO-), 2.18 (s, 3H, CH_3C=O), 1.3 (s, 6H, CH_3); MS m/z (%) 452 (M^+, 5), 416 (7), 349 (55), 332 (35), 277 (7), 43 (100); HRMS m/z 452.1508 (calcd. for $C_{24}H_{30}Cl_2O_4$, 452.1521); Anal. calcd. for $C_{24}H_{30}Cl_2O_4$: C, 63.58; H, 6.67. Found: C, 63.57; H, 6.74.

Conversion of 1α-chloromethyl-16β-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione (8) to 1α,2α-cyclomethylene-16β-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione (9): A solution of **8** (205 mg, 0.45 mmol) in pyridine (5 mL) was heated at 100°C for 30 min. After addition to H_2O (10 mL), the precipitate was extracted with CH_2Cl_2 (5×5 mL) and the combined extract was washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:20 EtOAc/CH_2Cl_2) to provide **9** (117 mg, 62%).

Epoxidation of 1α,2α-cyclomethylene-16β-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione (9): MCPBA (460 mg, 68%) was added to a solution of **9** (518 mg, 1.24 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 12 h and then was poured into satd. aq. $NaHCO_3$ (15 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phase was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude product. The crude product was purified by chromatography on silica gel (3:2 EtOAc/hexane) to provide 6α,7α-epoxy-1α,2α-cyclomethylene-16β-chloro-17α-acetoxy-4-pregnene-3,20-dione (**10**) as a white solid (345 mg, 64%); m.p. 185–187°C; IR (KBr): 1737, 1654, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.95 (s, 1H, C=CHC=O), 4.3 (t, 1H, ^{16}CHCl,

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$J = 7.0$ Hz), 3.45 (s, 1H, ^{6}CH-O (epoxide)), 3.25 (s, 1H, ^{7}CH-O (epoxide)) 0.80–2.20 (m, 11H), 0.86–0.94 (m, 2H), 2.17 (s, 3H, $\underline{CH_3}COO$-), 2.15 (s, 3H, $CH_3C{=}O$), 1.25 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.85 (m, 2H, CH_2 (cyclopropane)); MS m/z (%) 432 (M^+, 1), 389 (2), 354 (29), 312 (100); HRMS m/z 432.1726 (calcd. for $C_{24}H_{29}ClO_5$, 432.1704).

16β-Chlorocyproterone acetate (11): A solution of **10** (330 mg, 0.76 mmol) in DMSO (4 mL) was added with dry *N*,*N*-dimethylacetamide hydrochloride (750 mg) and then the mixture was stirred at 55°C under N_2 for 30 h. After addition to H_2O (10 mL), the precipitate was extracted with CH_2Cl_2 (5×10 mL) and the combined extract was washed with water (40 mL), brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 EtOAc/hexane) to afford **11** as a colorless solid (152 mg, 60%); m.p. 190–192°C; IR (KBr): 1737, 1651, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (s, 1H, C=$\underline{CH}$C=O), 6.15 (s, 1H, -$\underline{CH}$=CCl-C=CH-C=O), 4.25 (m, 1H, $^{16}\underline{CH}$Cl), 2.18 (s, 3H, $\underline{CH_3}COO$-), 2.12 (s, 3H, $CH_3C{=}O$), 1.28 (s, 3H, CH_3),1.2 (s, 3H, CH_3), 0.86–0.94 (m, 2H), 0.83 (m, 2H, CH_2 (cyclopropane)); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6, 15.1, 20.4, 21.3, 23.1, 25.4, 26.3, 28.8, 33.6, 37.6, 37.8, 33.9, 46.5, 48.0, 49.1, 61.2, 95.0, 120.9, 130.8, 135.9, 152.1, 170.0, 198.2, 199.8; MS m/z (%) 451 (M^+, 10), 414 (10), 390 (20), 372 (5), 347 (40), 330 (60), 311 (100), 277 (25), 246 (10), 219 (15), 193 (13), 175 (10), 149 (35), 128 (25), 155 (27), 91 (30); HRMS m/z 450.1366 (calcd. for $C_{24}H_{28}Cl_2O_4$, 450.1365).

Conversion of 16β-chlorocyproterone acetate (11) to 1α,2α-cyclomethylene-16α,17α-epoxy-6-chloro-4,6-pregnadiene-3,20-dione (12): A solution of **11** (25 mg, 0.0554 mmol) in benzene (10 mL) was added with basic aluminium oxide (grade I) (500 mg) and stirred at room temperature for 24 h. The mixture was filtered and eluted with CH_2Cl_2 (20 mL). The filtrate was evaporated under reduced pressure to give the residue. This residue was purified by flash column chromatography on silica gel (20:1 EtOAc/CH_2Cl_2) to give **12** as a white solid (15.5 mg, 75%); m.p. 189–190°C; IR (KBr): 1703, 1663, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (s, 1H, CH=CCl-C=$\underline{CH}$-C=O), 6.15 (s, 1H, $\underline{CH}$=CCl-C=CH-C=O), 3.8 (s, 1H, $^{16}\underline{CH}$-O (epoxide)), 2.08 (s, 3H, $\underline{CH_3}C{=}O$), 1.25 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.85 (m, 1H, CH_2 (cyclopropane)); ^{13}C NMR ($CDCl_3$, 100 MHz): 205.0, 198.8, 152.9, 136.9, 130.9, 121.1, 70.9, 60.7, 49.1, 43.5, 42.9, 39.5, 36.6, 31.7, 27.4, 26.7, 26.5, 25.9, 23.4, 21.3, 15.6, 13.0; Anal. calcd. for $C_{22}H_{25}ClO_3$: C, 70.86; H, 6.76. Found: C, 70.86; H, 6.67.

1α,2α-Cyclomethylene-6-chloro-16β-bromo-17α-hydroxy-4,6-pregnadiene-3,20-dione (13): A solution of bromine (0.1 mL) in dry THF

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(5 mL) 1 mL was added to the solution of PPh_3 (125 mg) in dry THF (2 mL). This mixture was stirred for 30 min and the solution of **12** (50 mg, 0.13 mmol) in dry THF (2 mL) was added. The reaction was stirred at room temperature for 30 min and then the solvent was removed under reduced pressure and the residue was dissolved with CH_2Cl_2 (10 mL). The solution was washed with water (5 mL) and dried over anhydrous sodium sulphate. The solution was stored at room temperature for 2 days and then was evaporated under reduced pressure to give the residue. This residue was purified by flash column chromatography on silica gel (20:1 $EtOAc/CH_2Cl_2$) to provide **13** as a white solid (42 mg, 70%); m.p. 180–182°C; IR (KBr): 3443, 1717, 1636, 1606 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.20 (s, 1 H, -CH=CCl-C=CH-C=O), 6.17 (s, 1H, -CH=CCl-C=CH-C=O), 4.15 (m, 1H, ^{16}CH-Br), 3.3 (br, 1H, OH), 2.45 (s, 3H, $^{21}CH_3C$=O), 1.4 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.85 (m, 1H, CH_2 (cyclopropane)); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz): 205.3, 198.7, 153.1, 137.5, 130.4, 120.7, 89.0, 51.6, 48.3, 48.9, 39.3, 38.1, 38.0, 31.5, 28.3, 26.6, 25.8, 23.4, 20.6, 15.6, 13.0; Anal. calcd. for $C_{22}H_{26}BrClO_3$: C, 58.23; H, 5.77. Found: C, 58.24; H, 5.70.

Acetylation of 1α,2α-cyclomethylene-6-chloro-16β-bromo-17α-hydroxy-4,6-pregnadiene-3,20-dione (13): Under a N_2 atmosphere, acetic acid (0.3 mL) was added to a well stirred mixture of TFAA (0.73 mL) in CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature for 30 min. *p*-$TsOH{\cdot}H_2O$ (43 mg) was then added and the mixture was cooled to 0°C. A solution of **13** (30 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) was cooled in an ice bath and added to the stirred mixed anhydride and stirring at 0°C for 20 min. Cold 20% aq. K_2CO_3 was added carefully until the mixture was basic. The mixture was diluted with H_2O until the CH_2Cl_2 phase became the lower phase. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica gel (1:20 $EtOAc/CH_2Cl_2$) to give **14** as a white solid (23.7 mg, 71%); m.p. 165–166°C; IR (KBr): 1738, 1651, 1365, 1239, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.20 (s, 1H, CH=CCl-C=CH-C=O), 6.16 (s, 1H, CH=CCl-C=CH-C=O), 4.25 (t, 1H, ^{16}CHBr), 2.8 (m, 1H), 2.5 (t, 1H), 2.19 (s, 3H, CH_3COO-), 2.17 (s, 3H, CH_3C=O), 1.33 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 0.87 (m, 1H, CH_2 (cyclopropane)); ^{13}C NMR ($CDCl_3$, 100 MHz): 200.0, 198.6, 170.6, 152.5, 136.3, 131.2, 121.4, 94.8, 49.8, 49.1, 48.4, 47.7, 39.3, 38.8, 38.1, 34.2, 28.8, 26.7, 25.9, 23.5, 21.7, 20.9, 16.0, 13.0; Anal. calcd. for $C_{24}H_{26}BrClO_4$: C, 58.14; H, 5.69. Found: C, 58.14; H, 5.68.

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REFERENCES

1. Ramirez, E.; Cabeza, M.; Heuze, I.; Gutierrez, E.; Bratoeff, E. Synthesis and phamocological evaluation of new 16-methyl pregnane derivatives. Chem. Pharm. Bull. **2002**, *50* (1), 15–20.
2. Li, F.; Kumar, N.; Tsong, Y.; Monder, C.; Wayne Bardin, C. Synthesis and progestational activity of 16-methylene-17α-hydroxy-19-norpregn-4-ene-3,20-dione and its derivative. Steroids **1997**, *62*, 403–408.
3. Wiechert, R. 6-Chloro-1,2α-Methylene-Δ^6-17α-Hydroxy-Progesterone Compound and Compositions. US Patent 3,234,093, February 8, 1966.
4. Shapiro, E.L.; Weber, L.; Harris, H.; Miskowicz, C.; Neri, R.; Herzog, H.L. Synthesis and biological activity of 17-esters of 6-dehydro-16-methylene-17α-hydroxyprogesterones. J. Med. Chem. **1972**, *15*, 716–720.
5. Braude, E.A.; Brook, A.G.; Linstead, R.P. Hydrogen tranfer part IV. The use of quinones of high potential as dehydrogenation reagent. J. Chem. Soc. **1954**, 3569–3574.
6. Herz, J.E.; Ocampo, R. Synthesis of 1-hydroxylated bile acid: methyl 1α,3α-dihydroxy 5β-cholan-24-oate. Steroids **1982**, *40*, 661.
7. Hanfried, A. Process for the production of 17α-Acetoxy-1,2-Methylene-4,6-Pregnadiene-3,20-Dione. US Patent 4,599,200, July 8, 1986.
8. Shapiro, E.L.; Popper, T.L.; Weber, L.; Neri, R.; Herzog, H.L. The synthesis and progestational activity of some 1,2α-cyclomethylene-16-methylene progesterone derivatives. J. Med. Chem. **1969**, *12*, 631–636.
9. Harris, H.E.; Miskowicz, J. Novel Process for Preparing Steroid Halohydrins and Vinyl Halides. US Patent 3,766,225, October 16, 1973.

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10. Rao, P.N.; Kirk Acosta, C.; Bahr, M.L.; Burdett, J.E.; Cessac, J.W.; Morrison, P.A.; Kim, H.K. A practical large-scale synthesis of 17α-acetoxy-11α-(4-*N*,*N*-dimethylaminophenyl)-19-norpregna-4,9-dione (CDB-2914). Steroids **2000**, *65*, 395–400.
11. Still, C.W.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. J. Org. Chem. **1973**, *43*, 293–295.

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