SHORT PAPER

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Efficient synthesis of 16α-methyl cyproterone acetate

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An effective method for synthesis of 16α-methyl cyproterone acetate was accomplished starting from commercially available 16-dehydropregnenolone acetate in eight steps, 11.5% overall yield.

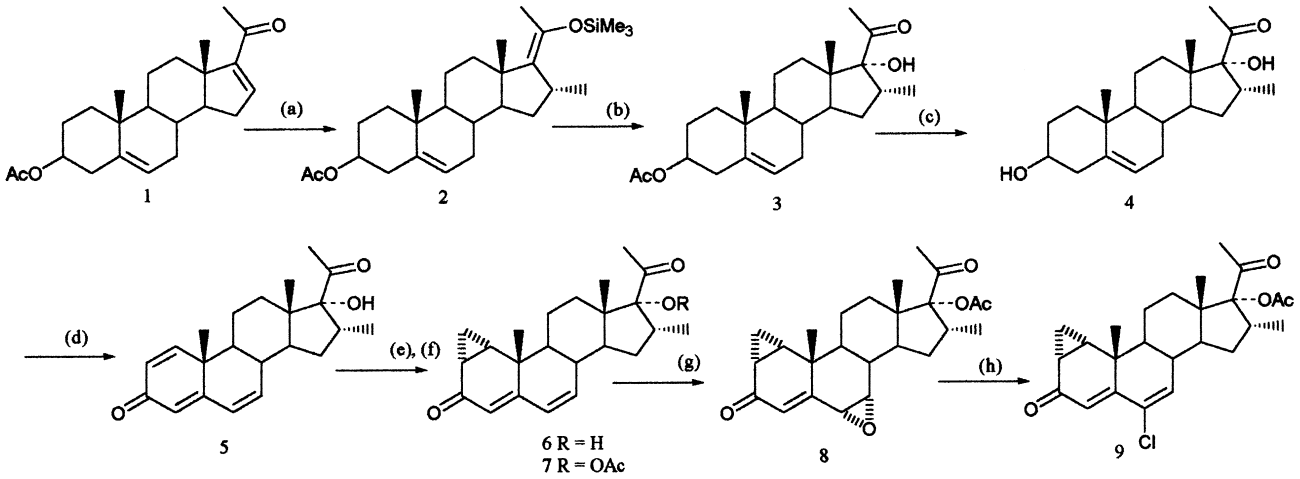
Keywords: cyproterone, progestin, epoxidation, 16-methyl cyproterone, steroids

The use of progestins in female contraception has generated a continuing interest in the development of new and potent progestins with fewer side effects. Many synthetic progestins in clinical use are derived from hydroxyprogesterone or 19-nortestosterone.[1] The synthesis of cyproterone acetate was first reported by Wiechert in 1966.[2] The results of trials of the compound in the treatment of hirsutism and virolism in women and for acne have not been consistent. Cyproterone acetate is the most active antiandrogen so far encountered, but closely related analogues are also active. Furthermore the chemistry and the progestational potentiating effect of the 16-methylene cyproterone acetate have been described indicating that a methylene group at the C-16 position increases the progestational activity. Therefore introduction of substituents on 16-position to enhance biological activity such as methyl group is very interesting.[3,4] The preparation and antiandrogenic effect of 16α-methyl cyproterone acetate has been reported[5] but the synthetic development is still very attractive to steroid chemists.

We report here an efficient route for synthesis of 16α-methyl cyproterone acetate (**9**) by the two-step conjugate addition of methyl magnesium bromide to the C16-position followed by hydroxylation of the resultant silyl enol ether (**2**).[6] Thus the dienone (**1**) was treated with 1.2 equiv. of methyl magnesium bromide (MeMgBr) in the presence of copper cation, trimethylsilyl chloride (TMSCl) and hexamethylphosphoric triamide (HMPA) to obtain a silyl enol ether (**2**) in 84% isolated yield. Oxidation of **2** with 1.1 mol equiv. of *m*-chloroperbenzoic acid (MCPBA) in the presence of 2 mol equiv. of $KHCO_3$ in CH_2Cl_2 at 0 °C followed by desilylation with 1 M HCl produced **3** in 76% yield. Compound **3** was converted to **5** in 41% yield by hydrolysis with 5% NaOH in methanol and then oxidative-dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Introduction of the 1α,2α-cyclopropane moiety into the 1,4,6-triene-3-one (**5**) was accomplished using dimethylsulfoxonium methylide to give **6** in 92% yield after crystallization. Acetylation of **6** using acetic acid, trifluoroacetic anhydride (TFAA) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH.H_2O) afforded the 17-acetate (**7**) in 95% yield after isolation. Subsequent epoxidation of the C-6 double bond with *m*-chloroperbenzoic acid (MCPBA) afforded the 6α,7α-epoxy derivative (**8**) in 93% yield after isolation. When compound **8** was treated with ***N,N***-dimethylacetamide hydrochloride in DMSO at 75 °C, 16α-methylcyproterone acetate (**9**) was obtained in 60% yield[7] (Scheme 1).

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



Scheme 1 Reagents and conditions: (a) MeMgBr, cat. Cu^+, THF, HMPA, TMSCl, –55 to–60 °C, 12 h., 84%; (b) (i)1.1 equiv. MCPBA, 2 equiv. $KHCO_3$, CH_2Cl_2, 0 °C, 15 min.; (ii) 1N HCl, r.t., 15 mim., 76%; (c) 5% aq. NaOH, MeOH, r.t., 12 h., 85%; (d) DDQ, dioxane, reflux, 18 h., 48%; (e) Me_3SOI, NaH, DMSO, r.t., 2 h., 92%; (f) AcOH, TFAA, *p*-TSA.H_2O, CH_2Cl_2, 0 °C, 20 mim., 95%; (g) MCPBA, CH_2Cl_2, r.t., 10 h, 93%; (h) *N,N*-dimethyacetamide hydrochloride, DMSO, 75 °C, 70 h., 60%.

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flash column chromatography using a glass column, dry packed with silica gel (230–400 mesh) according to the method of Still. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ with a Gemini2000 (300 MHz) spectrometer and signals are in δ (ppm) relative to TMS at 0.0. Mass spectra were measured with a VG7070F mass spectrometer at 6 kV. Elemental analyses were performed by Atlantic Microlab Inc.

Silyl enol ether (**2**): Trimethyl silyl chloride (TMSCl) (4ml, 28mmol) was added to a suspension of **1** (5g, 14mmol), cuprous bromide dimethylsulfide complex (142mg) in THF (71ml) and HMPA (5.5 ml) with a stirring at –78 °C. A solution of 1.0 M MeMgBr in THF (17ml, 17mmol) was then added dropwise. The reaction mixture was stirred at –55 to –61 °C for 12 h followed by addition of Et_3N (9ml). The reaction mixture was poured into the mixture of sat. aq $NaHCO_3$ (50ml), ice (50g) and hexane (200ml). The organic phase of the mixture was separated. The aqueous phase was extracted with hexane. The combined organic layer was washed with H_2O (50ml), brine (50ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20:1 EtOAc/hexane) to obtain **2** (5.3g, 84%); m.p. 95–96 °C. ^{1}H NMR ($CDCl_3$) δ: 5.26 (1H, d, *J* = 3.0 Hz), 4.52–4.68 (1H, m), 2.52–2.64 (1H, m), 0.84–2.42 (17H, m), 2.01 (3H, s), 1.79 (3H, s), 1.02 (3H, s), 0.99 (3H, d, *J* = 7.2 Hz), 0.86 (3H, s), 0.19 (9H, s). MS *m/z*: 444.3045 (Calcd for $C_{27}H_{44}O_3Si$: 444.3048)

3β-Acetoxy-16α-methyl-17α-hydroxy-5-pregnene-20-one (**3**): The silyl enol ether **2** (5.3g, 11.95mmol) and dry $KHCO_3$ (179mg, 23.9mmol) in CH_2Cl_2 (129ml) was treated dropwise with 0.5 M MCPBA in CH_2Cl_2 (19.7ml, 1.1 equiv. mol) at 0 °C, and the mixture was stirred for 15 min at 0° C. The reaction mixture was treated with 0.5 M aq. $Na_2S_2O_7$ (20 ml) and stirred for 30 min at room temperature. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phase was concentrated and then the resultant oil was dissolved in THF (31ml) and acidified to pH 1 with 1 N HCl (3ml). After 15 min. at room temperature most of the solvent was removed. The residue was dissolved with CH_2Cl_2 (30ml) and the solution was washed with satd. aq. $NaHCO_3$ (20ml), brine (20ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:3 EtOAc/hexane) to give **3** (3.5 g, 76%); m.p. 182–183 °C. ^{1}H NMR ($CDCl_3$) δ: 5.3 (1H, d, *J* = 3.0 Hz), 4.40–4.60 (1H, m), 3.90–3.05 (1H, m), 2.70 (1H, s), 0.70–2.50 (17H, m), 2.18 (3H, s), 1.96 (3H, s), 0.96 (3H, s), 0.84 (3H, d, *J* = 7 Hz), 0.75 (3H, s). MS *m/z*: 388.2598 (Calcd for $C_{24}H_{36}O_4$: 388.2604)

3β-Hydroxy-16α-methyl-17α-hydroxy-5-pregnene-20-one (**4**): The compound **3** (2.5g, 6.47mmol) was dissolved in MeOH (900ml). The solution was treated with 5% aq. NaOH (20ml) and stirred for 12 h at room temperature. After quenching with satd. aq. NaCl (500ml), the mixture was extracted with CH_2Cl_2 (3 × 200ml). The combined organic phase was washed with H_2O (100ml), brine (100ml), dried over $MgSO_4$, and evaporated under reduced pressure to give product **4** (1.9g, 85%). The product was used without further purification.

16α-Methyl-17α-hydroxy-1,4,6-pregnatrine-3,20-dione (**5**): The solution of **4** (1.74g, 5.02mmol) in dry dioxane (40ml) was added DDQ (3.2g, 14.1mmol) and refluxed under N_2 for 18 h. After removing the precipitate by filtration, the filtrate was concentrated, and the residue was dissolved in CH_2Cl_2 (50 ml), then washed with satd. aq. $NaHCO_3$ (30ml), H_2O (20ml), brine (20ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2:3 EtOAc/hexane) to give compound **5** (820mg, 48 %); m.p. 211–212 °C. ^{1}H NMR ($CDCl_3$) δ: 6.98 (1H, d, *J* = 3.6 Hz), 6.06–6.30 (2H, m), 5.85–5.98 (2H, m), 2.94–3.08 (1H, m), 2.70 (1H, s), 0.72–2.30 (14H, m), 2.20 (3H, s), 1.10 (3H, s), 0.80 (3H, s). Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.62; H, 8.20.

1α,2α-Cyclomethylene-16α-methyl-17α-hydroxy-4,6-pregnadiene-3,20-dione (**6**): Sodium hydride (NaH) (105mg of a 50% mineral oil suspension) was added to a solution of trimethyl sulfoxonium iodide (852mg) in DMSO (6ml) under N_2. After 2 h, a solution of compound **5** (300mg, 0.88mmol) in DMSO (3ml) was added, and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into H_2O, the precipitate was collected by filtration, dried and recrystallised from EtOAc to give **6** (286mg, 92%); m.p. 259–260 °C. ^{1}H NMR ($CDCl_3$) δ: 5.84–6.10 (2H, m), 5.44 (1H, s), 2.94–3.12 (1H, m), 2.79 (1H, s), 0.68–0.75 (2H, m), 0.80–2.23 (13H, m), 2.21 (3H, s), 1.14 (3H, s), 0.87 (3H, d, *J* = 7 Hz), 0.83 (3H, s). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.78; H, 8.52.

1α,2α-Cyclomethylene-16α-methyl-17α-hydroxy-4,6-pregnadiene-3,20-dione-17-acetate (**7**): Under a N_2 atmosphere, acetic acid (1.1ml, 18.4mmol) was added to a well stirred mixture of TFAA (2.5ml, 18.4mmol) in CH_2Cl_2 (7.2ml) and the mixture was stirred for 30 min at room temperature, *p*-TsOH.H_2O (148 mg, 0.86 mmol) was then added, and the mixture was cooled to 0° C. The 17α-hydroxy (**6**) (325mg, 0.918mmol) was dissolved in CH_2Cl_2 (3ml), 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 × 10ml), the combined organic phase was washed with H_2O (20ml), brine (20ml), dried over $MgSO_4$, and evaporated under reduced pressure to afford a thick syrup. The syrup was purified by flash column chromatography on silica gel (1:1 EtOAc/hexane) to give product **7** (320mg, 95%); m.p. 220–223 °C. ^{1}H NMR ($CDCl_3$) δ: 5.86–6.08 (2H, m), 5.46 (1H, s), 3.30–3.45 (1H, m), 0.65–2.60 (11H, m), 2.09 (3H, s), 1.98 (3H, s), 1.12 (3H, s), 0.85 (3H, d, *J* = 7 Hz), 0.76–0.80 (2H, m), 0.72 (3H, s). FAB-MS *m/z*: 397.2387 (Calcd for $C_{25}H_{33}O_4$ $(M + H)^+$: 397.2370)

6α,7α-Epoxy-1α,2α-cyclomethylene-16α-methyl-17α-hydroxy-4,6-pregnadiene-3,20-dione-17-acetate (**8**): MCPBA (177mg, 68%) was added to a solution of compound 7 (190mg, 0.48mmol) in CH_2Cl_2 (5.1ml). The reaction mixture was stirred at room temperature for 10 h and then was poured into satd. aq. $NaHCO_3$ (10ml). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10ml). The combined organic phase was washed with H_2O (20ml), brine (20ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 EtOAc/hexane) to give compound 8 (182mg, 93%); m.p. 235–236 °C. ^{1}H NMR ($CDCl_3$) δ: 5.98 (1H, s), 3.20–3.45 (2H, m), 3.25 (1H, s), 0.80–2.20 (11H, m), 0.86–0.94 (2H, m), 2.18 (3H, s), 2.04 (3H, s), 1.16 (3H, s), 0.93 (3H, d, *J* = 7 Hz), 0.76(3H, s). FAB-HMS *m/z*: 413.2322 (Calcd for $C_{25}H_{33}O_5$ $(M + H)^+$: 413.2319).

16α-Methylcyproterone acetate (**9**): A solution of **8** (130mg, 0.32 mmol) in DMSO (5ml) and dry *N,N*-dimethylacetamide hydrochloride (200mg) was stirred for 70 h under N_2 at 75° C. The reaction mixture was poured into H_2O (10ml), the precipitate was extracted with CH_2Cl_2 (5 x 10ml), and the combined extract was washed with H_2O (40ml), brine (40ml), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 EtOAc/hexane) to give **9** (80mg, 0.19 mmol, 60 %); m.p. 204–205 °C. ^{1}H NMR ($CDCl_3$) δ: 6.12 (2H, s), 3.45 (1H, d, *J* = 7 Hz), 0.74–2.26 (11H, m), 0.84–0.92 (2H, m), 2.09 (3H, s), 1.98 (3H, s), 1.16 (3H, s), 0.86 (3H, d), 0.72 (3H, s). Anal. Calcd for $C_{25}H_{34}O_4Cl$: C, 69.67; H, 7.25. Found: C, 69.51; H, 7.2.

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