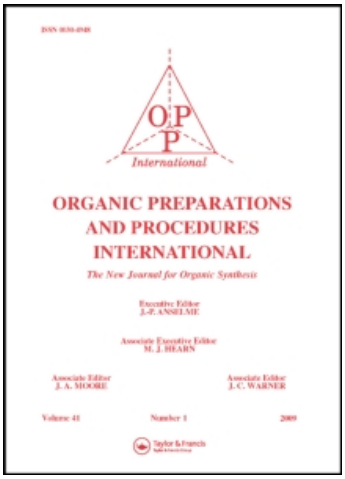


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# HIGH-YIELD SYNTHESIS OF ANDROST-4-ENE-3,6,17-TRIONE AND ANDROST-4-ENE-3B,6B,17B- TRIOL

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# HIGH-YIELD SYNTHESIS OF ANDROST-4-ENE-3,6,17-TRIONE AND ANDROST-4-ENE-3B,6B,17B- TRIOL

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(09/22/07)

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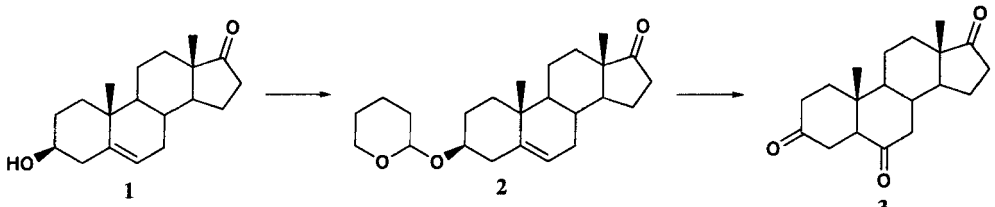
Androst-4-ene-3,6,17-trione (**3**) is a potent inhibitor of estrogen synthetase of the aromatase enzyme system[1-4] and can block the conversion of androst-4-ene-3,17-dione into estrone to adjust the level of estrin in body. During our investigation of the synthesis of androst-4-ene-3,6,17-trione (**3**), a new compound androst-4-ene-3β,6β,17β- triol (**8**) was also obtained by reduction of **3** and it was thought that **8** or its esters might also serve as inhibitors of aromatase to improve the pharmacokinetic properties of **3**.

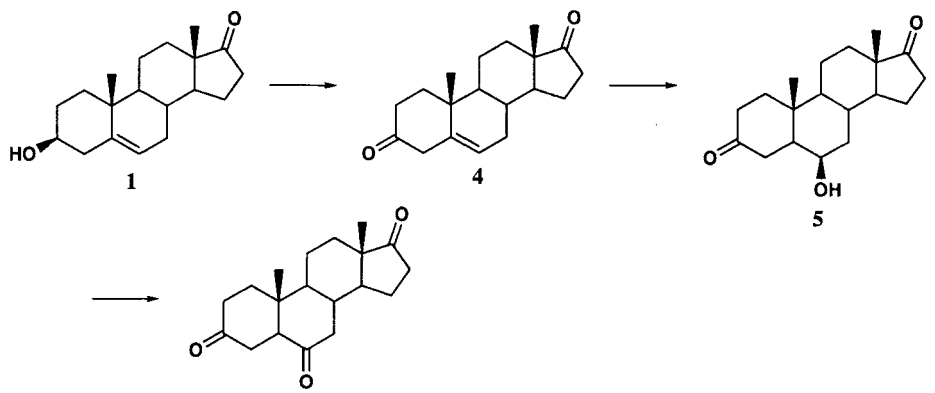
The utilization of pyridinium chlorochromate (PCC) (*Scheme 1*)[5,6] and of Jones reagent




1 2 3

**Scheme 1**

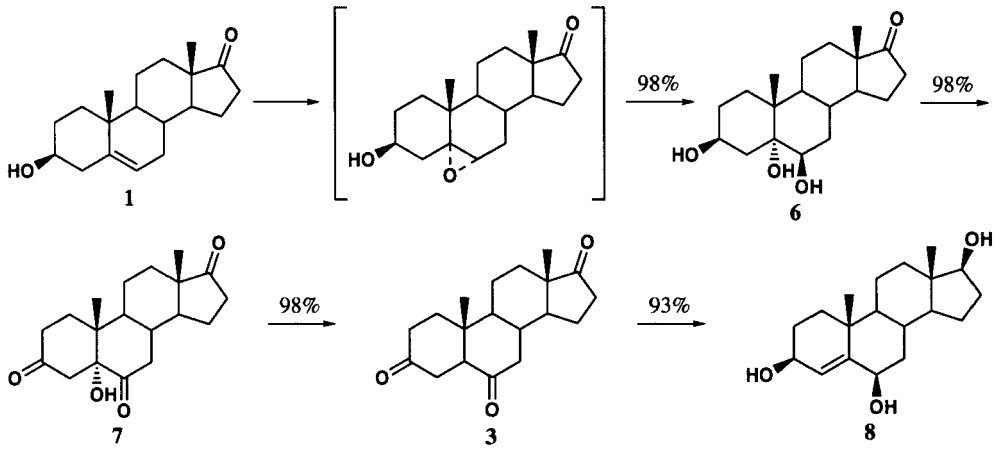
in ether[7] (*Scheme 2*) had been described earlier in the preparation androst-4-ene-3,6,17-trione (**3**) from compound **2** or **4**. However, in our hands the high yields reported by E. J. Parish *et al.*[5] using the PCC reagent could not be reproduced, while the use of the Jones reagent use of




1 4 5 3

**Scheme 2**

required column chromatography to purify the resulting products compounds **3** and **5**. Furthermore, neither method seemed applicable to industrial scale preparation. This paper describes a convenient route to androst-4-ene-3,6,17-trione (**3**) in 76% overall yield and androst-4-ene-3β,6β,17β-triol (**8**) in 88% overall yield from **1** (*Scheme 3*).




**Scheme 3**

The epoxidation-hydrolysis of compound **1** to **6** the key step in this route, had a great influence on the total yield. First, the epoxidation intermediate was difficult to purify but was easily converted to **6** when washed with water. Since there were three hydroxy groups in **6**, it could not be washed with water for further purification. Chloroform in which the epoxide intermediate and some of the impurities formed were fairly soluble while **6** is not, was selected as the solvent for this reaction. The intermediate epoxide was not isolated and treated with ferrous sulfate solution and then, hydrolyzed with sulfuric acid to afford crystals of **6** in excellent yield (98%). At lower temperature (0°C), the oxidation of **6** gave fairly pure **7** in 98% yield. Upon reflux in ethanol in the presence of sulfuric acid, compound **7** gave a 79% yield of **3** as yellow crystals after crystallization from ethyl acetate. Crude **3** was reduced by potassium borohydride and the crude was recrystallized from methanol-chloroform to give a 93% yield of compound **8**.

In summary, a new synthetic route was developed to prepare androst-4-ene-3,6,17-trione **3** and androst-4-ene-3β,6β,17β-triol **8** efficiently with high yields, which seems to have obvious advantages in using general reagents and conventional methods. Thusly, this synthetic route could have great potential for industrial scale synthesis.

## EXPERIMENTAL SECTION

Mass spectrometry was carried out using a Finnigan MAT95XL spectrometer. High pressure liquid chromatography was performed with column $C_{18}$ on a HP1100-Finnigan LCQ (MeOH-$H_2O$ grads system). $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Mercury Plus 400 MHz spectrometer with a TMS as an internal reference. Infrared spectra were obtained by using a Bomen MB spectrometer. Optical rotations were measured on a Horiba SEPA-200. All melting

points were determined in open capillary tubes and are not corrected. Analytical thin layer chromatography was performed on Qingdao silica gel GF-254 pre-coated plates.

**3β,5α,6β-Trihydroxyandrostan-17-one (6).**- To a solution of dehydroepiandrosterone **1** (10.0 g, 34.7 mmol) in chloroform (50 mL), peracetic acid (16%; 30 mL) was added, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was washed with a 10% of aqueous ferrous sulfate (80 mL) and water. Then, a 40% of aqueous sulfuric acid (10 mL) was added to the mixture which was then stirred at room temperature for 12 h. The precipitate formed was collected, washed with chloroform, and dried *in vacuo* to afford **6** as a white solid (11.0 g, 98%), mp 122-123°C.

$^1$H NMR (DMSO-$d_6$): δ 0.73 (s, 3H, $C_{19}$-H), 1.01 (s, 3H, $C_{18}$-H), 1.06-1.46 (m, 9H, $C_{1,8,9,11,12,14}$-H), 1.57-1.64 (m, 2H, $C_{2,7}$-H), 1.72-1.88 (m, 2H, $C_4$-H), 1.92-2.02 (m, 2H, $C_{15}$-H), 2.31-2.38 (dd, 2H, $J_1$ = 10.6, $J_2$ = 8.6, $C_{16}$-H), 3.32 (s, 1H, $C_3$-H), 3.75-3.78 (m, 1H, $C_6$-H), 3.73-3.80 (m, 3H, $C_{3,5,6}$-OH). $^{13}$C NMR (DMSO-$d_6$): δ 13.5 ($C_{19}$), 16.3 ($C_{18}$), 20.0, 21.5, 29.7, 31.1, 31.6, 32.1, 33.4, 35.4, 38.0, 40.9, 44.9, 47.2, 50.6 ($C_{1,2,4,7\text{-}16}$), 65.7 ($C_3$), 73.9 ($C_5$), 74.4 ($C_6$), 200.1 ($C_{17}$). IR(KCl): 3442, 2943, 2865, 1724 cm$^{-1}$. MS: *m/z* = 322 ($M^+$).

*Anal.* Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38; Found: C, 70.73; H, 9.35.

**5α-Hydroxyandrostane-3,6,17-trione (7).**- To a solution of **6** (11.0 g, 34.1 mmol) in acetone (200 mL), chromic acid (6.0 g of chromium trioxide, 4.0 g of sulfuric acid and 10.0 mL of water) was added dropwise, and the mixture was stirred at 0°C for 2 h. The reaction mixture was poured into ice-water containing sodium sulfite. The precipitate formed was collected, washed with water, and dried at 70°C to give **7** as a white solid (10.6 g, 98%), mp 182-185°C.

$^1$H NMR ($CDCl_3$): δ 0.89 (s, 3H, $C_{19}$-H), 1.02 (s, 3H, $C_{18}$-H), 1.36-2.13 (m, 12H, $C_{1,8,9,11,12,14,15,16}$-H), 2.30-2.50 (m, 5H, $C_{2,7,16}$-H), 2.86-3.13 (m, 3H, $C_4$-H, $C_5$-OH). $^{13}$C NMR ($CDCl_3$): δ 13.7 ($C_{19}$), 13.8 ($C_{18}$), 20.1, 31.1, 31.7, 35.6, 36.8, 37.2, 40.5, 43.1, 44.5, 44.7, 48.1, 51.1 ($C_{1,2,4,7\text{-}16}$), 82.6 ($C_5$), 210.5 ($C_6$), 211.3 ($C_3$), 220.3 ($C_{17}$). IR(KCl): 3432, 2939, 1745, 1739, 1720 cm$^{-1}$. MS: *m/z* = 318 ($M^+$).

*Anal.* Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; Found: C, 71.65; H, 8.21.

**Androst-4-ene-3,6,17-trione (3).**- To a solution of **7** (10.6 g, 33.3 mmol) in ethanol (150 mL), sulfuric acid (10% solution; 28 mL) was added, and the mixture was refluxed for 3 h. The reaction solution was concentrated in vacuo and then, poured into water. The precipitate formed was collected, washed with water and dried to give **3** (crude, 9.8 g), mp 220-227°C. Recrystallization from ethyl acetate gave **3** as a white solid (7.9 g, 76% from **1**). Purity: 99.5% (HPLC), mp 228-230°C, *lit.*[7] mp 222-227°C. $[\alpha]_D^{20}$ = 42.5° (c = 1.0 chl), *lit.*[7] $[\alpha]_D^{20}$ = 43.6° (c = 0.94 chl).

$^1$H NMR ($CDCl_3$): δ 0.93 (s, 3H, $C_{18}$-H), 1.20 (s, 3H, $C_{19}$-H), 1.31-1.64 (m, 5H), 1.77-2.17 (m, 8H), 2.42-2.57 (m, 3H, $C_{2,7}$-H), 2.76-2.80 (m, 1H, $C_7$-H), 6.21 (s, 1H, $C_4$-H). IR(KCl): 2955, 1737, 1687, 1671, 1600 cm$^{-1}$. MS: *m/z* = 300 ($M^+$), *lit.*[7] $^1$H NMR ($CDCl_3$): δ 0.93 (s, 3H, $C_{18}$-H), 1.20 (s, 3H, $C_{19}$-H), 2.42-2.61 (m, 5H), 2.70-2.90 (m, 1H), 6.21 (s, 1H, $C_4$-H). IR(KBr): 2956s. 1737s. 1686s. 1600m cm$^{-1}$.

*Anal.* Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; Found: C, 75.94; H, 8.02.

**Androst-4-ene-3β,6β,17β-triol (8)**.- To a solution of **3** (crude, 10 g, 33.3 mmol) and cerium nitrate (2.0 g) in methanol (150 mL), potassium borohydride (1.0 g) was added while stirring, and this mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and poured into water. The precipitate was collected, washed with water, dried, and recrystallized from chloroform to yield 9.50 g (88%) **8** as white crystal (99.7% purity), mp 225-226°C.

$^1$H NMR (DMSO-$d_6$): δ 0.55-0.73 (m, 2H), 0.62 (s, 3H, $C_{18}$-H), 0.82-0.90 (m, 2H), 0.94 (s, 1H, $C_{19}$-H), 1.12-1.71 (m, 11H), 1.78-1.84 (m, 2H, $C_{9,14}$-H), 3.37-3.42 (m, 1H, $C_{17}$-H), 3.90-3.92 (m, 2H, $C_{3,6}$-H), 4.64 (d, 1H, J = 5.09, $C_{17}$-OH), 4.57 (d, 1H, J = 5.08, $C_3$-OH), 4.44 (d, 1H, J = 4.69, $C_6$-OH), 5.54 (s, 1H, $C_4$-H). $^{13}$C NMR ($CD_3OD$): δ 9.8 ($C_{18}$), 18.4 ($C_{19}$), 19.9 ($C_{11}$), 22.5 ($C_{15}$), 27.8 ($C_1$), 28.7 ($C_2$), 34.0 ($C_8$), 35.7 ($C_{16}$), 36.0 ($C_{12}$), 37.1 ($C_{10}$), 40.8 ($C_7$), 42.2 ($C_{13}$), 50.0 ($C_9$), 54.2 ($C_{14}$), 66.8 ($C_3$), 67.2 ($C_6$), 80.5 ($C_{17}$), 119.8 ($C_4$), 147.6 ($C_5$). IR(KCl): 3324, 2930, 2873, 1077, 1060 cm$^{-1}$. MS: $m/z$ = 306 ($M^+$).

*Anal.* Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; Found: C, 74.45; H, 9.87.



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