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IMPROVED SYNTHESES OF 3,17β-DIACETOXYESTRA-1,3,5(10)-TRIEN-6-ONE

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Abstract : improved syntheses of 3,17β-Diacetoxyestra-1,3,5(10)-trien-6-one **5** was achieved in 4 steps (respectively in 45% and 56% overall yield) from 19-nortestosterone **1**.

3,17β-Diacetoxyestra-1,3,5(10)-trien-6-one (**5**) is an important precursor of C-6 and C-7 functionalized estrogens.[1-5] Its preparation by benzylic oxidation of 3,17β-diacetoxyestra-1,3,5(10)-triene with chromic oxide in acetic acid gives low and variable yields (usually < 30%).[2,3,6] Marples *et al* performed this benzylic oxidation using the CrO_3/3,5-dimethylpyrazole complex with modest yield

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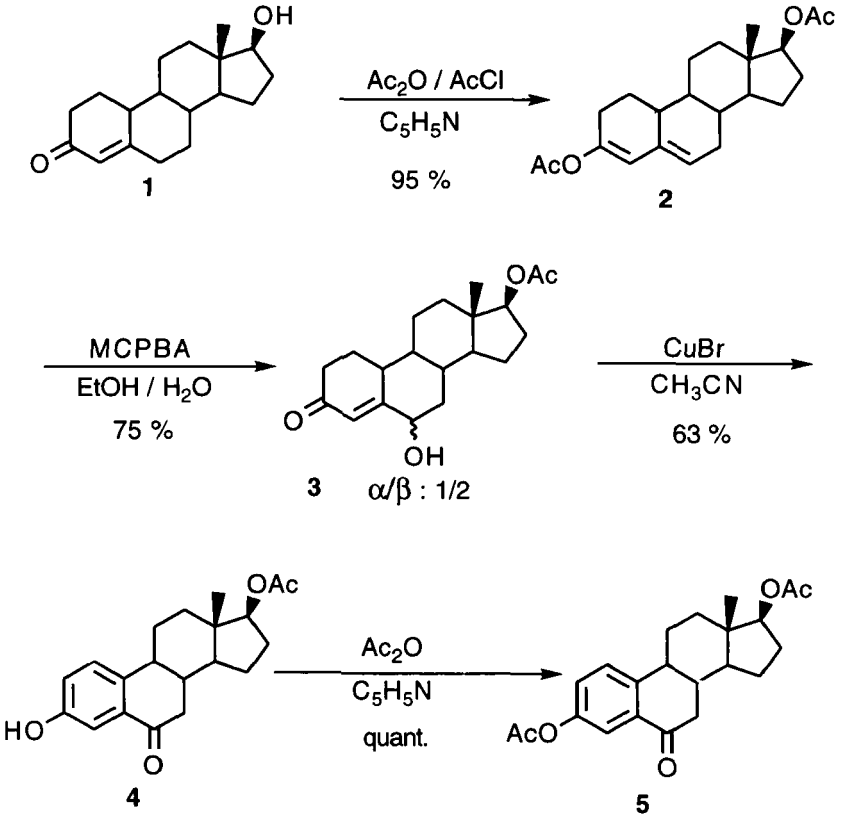
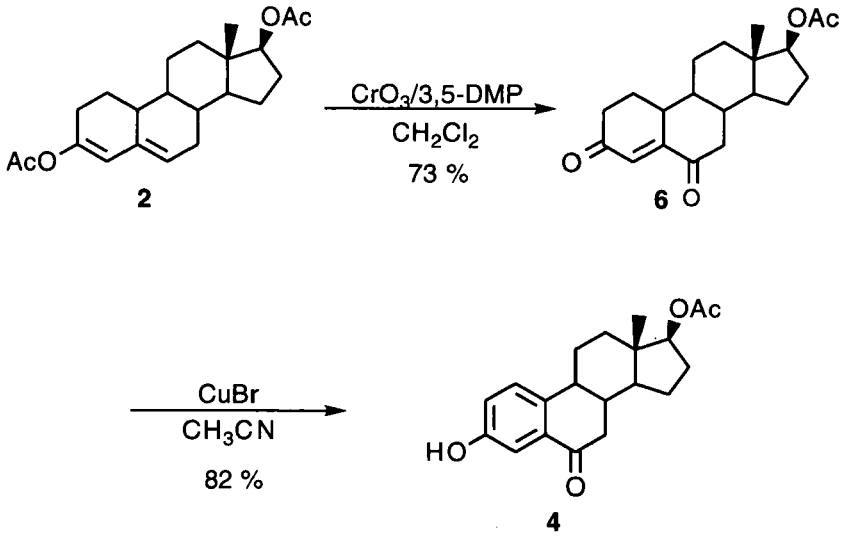
(routinely 40%).[7] The large excess of oxidant (25 equivalents) used to carry out the reaction leads to a tedious work-up and an extensive chromatographic purification. In order to obtain large quantities of this derivative, we devised other routes to improve the overall yield and the easiness of its preparation.



Scheme 1 : first synthesis of **1**.

Our first synthesis of **5** is depicted in scheme 1 and use the commercially available 19-nortestosterone as starting material. Treatment of **1** with a mixture of acetyl chloride and acetic anhydride in the presence of pyridine afforded the dienol ester **2**

in high yield.[8] Epoxidation of **2** using *m*-chloroperbenzoic acid (MCPBA) in ethanol/water[9] gave a mixture of epimeric alcohol **3** in a 2:1 ratio in favor of the β-alcohol. The oxidation of **2** with Oxone®[10] leads to a lower yield (20%) of the mixture but with a better diastereoselectivity (α:β = 1:8). The mixture of alcohols was not separated and was submitted to an aromatization reaction.[11] Thus treatment of **3** with 2.5 equivalents of CuBr in acetonitrile gave in one step 17β-acetoxy-1,3,5(10)-trien-6-one in good yield. This reaction works smoothly to give the intermediate benzylic alcohol which is further oxidized to the ketone **4** under the reaction conditions. Acetylation of **4** in standard conditions completed the synthesis of **5**.



Scheme 2 : alternative synthesis of intermediate **4**.

Interestingly, the oxidation of intermediate **2** with the CrO_3/3,5-dimethylpyrazole complex (scheme 2) give the diketone **6** in good yield (73%). Aromatization of the

A-ring of this compound affords the estradiol derivative **4** in 82 % yield. Thus **5** can be obtained in 56% overall yield from 19-nortestosterone by this alternative synthesis.

We have developped two new syntheses of 3,17β-Diacetoxyestra-1,3,5(10)-trien-6-one (**5**) The overall yield of the first one is 45%. Since most of the intermediates can be used in the following step without chromatographic purification, this sequence should be a rapid alternative to the direct benzylic oxidation of **2**. The modification of the oxidation step permit to reach a 56% overall yield which is definitively better than the classical way but still with the inconvenience of chromic oxidation. In addition, both methodologies allow the discrimination of each hydroxyl groups of estradiol.

Experimental Section

All chemical and reagents were obtained from Aldrich Chemical Company (France) except 19-nor-testosterone which was obtained from Sigma and used as recieved. Acetonitrile was distilled from calcium hydride and pyridine was dried on potassium hydroxide. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. NMRspectra were mesured on a Bruker AC 200 Fourier transform spectrophotometer with proton observation at 200 MHz and carbon observation at 50 MHz. The chemical shifts are reported in ppm downfield from TMS and coupling constant are expressed in Herz.

3,17β-Diacetoxyestra-3,5-diene (2) :

Under a nitrogen atmosphere, acetic anhydride (885 µL, 9.4 mmol), dry pyridine (240 µL, 2.9 mmol) and acetyl chloride (1.96 mL, 27.8 mmol) were added

successively to 19-nor-testosterone (990 mg, 3.6 mmol) at room temperature with stirring. The mixture was stirred at 80°C for 8h. After concentration *in vacuo*, the residue was dilute in ethyl acetate (50 mL), washed with water (2 x 5 mL), sat. aq. $NaHCO_3$ (10 mL), water (5mL) and brine (5 mL) and dried ($MgSO_4$). Recrystallization from ethyl acetate afforded 1.23 g (95%) of **2**.

$[\alpha]_D^{23}$ -155.6° (c = 1.02, $CHCl_3$). mp = 132-135°C.

IR (KBr) : 3020, 2980, 2880, 1770, 1735, 1665, 16400 1250, 1200 cm^{-1}.

^1H NMR ($CDCl_3$) : 5.76 (d, J= 2.0 Hz, 1 H, H-4), 5.47 (t, J = 2.5 Hz, 1 H, H-6), 4.62 (dd, J_1 = 9 Hz and J_2 = 7.4 Hz, 1H, H-17), 2.13 (s, 3H, H-20), 2.04 (s, 3H, H-22), 0.82 ppm (s, 3H, H-18).

^{13}C NMR ($CDCl_3$) : 171.0 (C-21), 169.1 (C-19), 148.7 (C-3), 134.5 (C-6), 123.6 (C-4), 117.5 (C-5), 82.7 (C-17), 50.3 (C-14), 42.6 (C-13), 42.5 (C-10), 40.6 (C-9), 36.6 (C-2), 36.6 (C-8), 30.9 (C-7), 28.0 (C-12), 27.5 (C-1), 27.2 (C-16), 26.2 (C-11), 23.3 (C-15), 21.1 (C-20), 21.0 (C-22), 11.9 ppm (C-18).

The spectral data are identical with the reported value.[8]

17β-Acetoxy-4-estren-6-ol-3-one (3) :

m-Chloroperbenzoic acid (40%, 632 mg, 1.46 mmol) was slowly added to a solution of **2** (350 mg, 0.98 mmol) in a mixture of ethanol and water (5 mL, 95/5) with stirring at room temperature. The stirring was continued for 30 mn at this temperature and the mixture was extracted with dichloromethane (3 x 20 mL). The dichloromethane solution was washed with $Na_2S_2O_3$ 10% (5 mL), sat. $NaHCO_3$ (5 mL) and brine (5mL), dried (Na_2SO_4) and concentrated *in vacuo*. to give 245 mg (75%) of **3** as a mixture of diastereoisomers.

IR (KBr) : 3420, 2920, 2850, 1735, 1675, 1375, 1250, 1050 cm^{-1}.

^1H NMR ($CDCl_3$), deduced from the spectra of the mixture :

6β-isomer : 5.88 (d, J = 1.9 Hz, 1H, H-4), 4.61 (dd, J_1 = 9 Hz et J_2 = 7.4

Hz, 1H, H-17), 4.37 (dd, J_1 = 2.5 Hz et J_2 = 2.5 Hz, 1H, H-6), 2.05 (s, 3H, H-20), 0.87 (s, 3H, H-18).

6α-isomer : 6.21 (d, J = 1.7 Hz, 1H, H-4), 4.61 (dd, J_1 = 9 Hz et J_2 = 7.4 Hz, 1H, H-17), 4.27 (dd, J_1 = 2.5 Hz et J_2 = 2.5 Hz, 1H, H-6), 2.05 (s, 3H, H-20), 0.85 (s, 3H, H-18).

The mixture of both epimers was employed in the next step without further purification.

17β-Acetoxyestra-1,3,5(10)-trien-3-ol-6-one (4) :

Under a nitrogen atmosphere, CuBr (344 mg, 1.54 mmol) was added to a solution of **3** (235 mg, 0.7 mmol) in dry acetonitrile (7 mL) with stirring at room temperature. The stirring was continued for 1h at this temperature and the mixture was decolorized by addition of the minimum of water. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel. Elution with petroleum ether/ethyl acetate (70:30 to 60:40) afforded 145 mg (63%) of **4**.

IR (KBr) : 3400, 3060, 2940, 2920, 2875, 1730, 1670,1610, 1440, 1250, 1030 cm^{-1}.

^1H NMR (DMSO-d_6) : 7.2 (d, J = 2.5 Hz, 1H, H-4), 7.27 (d, J = 8.4 Hz, 1H, H-1), 6.99 (dd, J_1 = 8.4 Hz and J_2 = 2.5 Hz, 1H, H-2), 4.60 (dd, J_1 = 8.3 Hz and J_2 = 8.2 Hz, 1H, H-17), 2.02 (s, 3H, H-20), 0.76 ppm (s, 3H, H-18).

^{13}C NMR (DMSO-d_6) : 198.3 (C-6), 171.8 (C-19), 157.3 (C-3), 139.0 (C-5), 134.4 (C-10), 128.2 (C-4), 122.7 (C-1), 113.4 (C-2), 83.1 (C-17), 50.2 (C-14), 44.7 (C-7), 44.2 (C-13), 43.3 (C-9), 40.8 (C-8), 37.5 (C-12), 28.5 (C-16), 26.5 (C-11), 23.9 (C-15), 22.3 (C-20), 13.2 ppm (C-18).

3,17β-Diacetoxyestra-1,3,5(10)-trien-6-one (5) :

Under a nitrogen atmosphere, acetic anhydride (50 µL, 0.5 mmol) was added to a

solution of **4** (145 mg, 0.44 mmol) in dry pyridine (1 mL) with stirring and ice-cooling. The stirring was continued for 3h at room temperature. The mixture was pourred in ice water and extracted with ethyl acetate (3 x20 mL).The ethyl acetate solution was washed with sat. aq. $CuSO_4$ (5 mL), sat. aq. $NaHCO_3$ (5 mL), water and brine (5mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallzed from ethanol to afford 165 mg (quantitatif) of **5**.

$[\alpha]_D^{23}$ -21.9° (c = 2.1, $CHCl_3$) [lit.[7] $[\alpha]_D$ -22° (c = 2.0, $CHCl_3$)].

mp 174-175°C (lit.[7] mp 173-174°C).

IR (KBr) : 3060, 2920, 2880, 1770, 1740, 1680, 1605, 1485, 1370, 1250, 1200, 1030, 1010 cm^{-1}.

^1H NMR ($CDCl_3$) : 7.74 (d, J = 2.5 Hz, 1H, H-4), 7.44 (d, J = 8.5 Hz, 1H, H-1), 7.25 (dd, J_1 = 8.5 Hz and J_2 = 2.5 Hz, 1H, H-2), 4.70 (dd, J_1 = 8.4 Hz and J_2 = 8.1 Hz, 1H, H-17), 2.75 (dd, J_1 = 16.7 Hz and J_2 = 3.0 Hz, 1H, H-7), 2.30 (s, 3H, H-20), 2.07 (s, 3H, H-22), 0.76 ppm (s, 3H, H-18).

^{13}C NMR ($CDCl_3$) : 198.8 (C-6), 171.1 (C-19), 169.4 (C-21), 149.3 (C-3), 144.3 (C-5), 133.6 (C-10), 127.0 (C-4), 126.7 (C-1), 119.9 (C-2), 82.1 (C-17), 49.7 (C-14), 43.8 (C-7), 42.9 (C-9), 42.7 (C-13), 39.5 (C-8), 36.4 (C-12), 27.4 (C-16), 25.3 (C-11), 22.9 (C-15), 21.1 (C-20), 21.0 (C-22), 11.9 ppm (C-18).

The spectral data are identical with the reported value.[7]

17β-Acetoxy-4-estrene-3,6-dione (6) :

3,5-Dimethylpyrazole (805 mg, 8.4 mmol) was added to a suspension of dry CrO_3 (840 mg, 8.4 mmol) in dry CH_2Cl_2 (8.5 mL) with stirring at -20°C. After 15 mn, a solution of **2** (150 mg, 0.4 mmol) in dry CH_2Cl_2 (2 mL) was added to the complex solution. The mixture was stirred for 20 mn at this temperature after which NaOH solution (5 N, 3.5 mL) was added at -15°C and the resultant mixture was stirred for a further 45 mn at -10°C. The CH_2Cl_2 layer was separated and the

aqueous layer was extracted (2 x 20 mL) with CH_2Cl_2.The combined organic solutions were washed with 2N HCl (2 x 7 mL) and brine (2 x 10 mL) and dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel. Elution with petroleum ether/ethyl acetate (80:20 to 60:40) afforded 101 mg (73%) of **6**.

IR (KBr) : 2980, 2950, 2880, 2850, 1740, 1690, 1680, 1600, 1250, 1045 cm^{-1}.

^1H NMR ($CDCl_3$) : 6.49 (d, J = 1.9 Hz, 1H, H-4), 4.66 (dd, J_1 = 8.8 Hz and J_2 = 8.0 Hz, 1H, H-17), 2.71 (dd, J_1 = 16.5 Hz and J_2 = 2.9 Hz, 1H, H-7), 2.06 (s, 3H, H-20), 0.87 ppm (s, 3H, H-18).

^{13}C NMR ($CDCl_3$) : 199.7 (C-6 et C-3), 170.9 (C-19), 153.9 (C-5), 128.2 (C-4), 82.0 (C-17), 50.0 (C-7), 45.3 (C-9), 43.2 (C-13), 42.6 (C-14), 37.6 (C-17), 37.3 (C-10), 36.0 (C-8), 29.6 (C-12), 28.2 (C-11), 27.2 (C-16), 25.8 (C-1), 23.0 (C-15), 21.0 (C-20), 11.8 ppm (C-18).

17β-Acetoxyestra-1,3,5(10)-trien-3-ol-6-one (4) :

Under a nitogen atmosphere, CuBr (81 mg, 0.33 mmol) was added to a solution of **6** (100 mg, 0.30 mmol) in dry acetonitrile (3 mL) with stirring at room temperature. The stirring was continued for 16h at this temperature and the mixture was decolorized by addition of the minimum of water. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel. Elution with petroleum ether/ethyl acetate (70:30 to 60:40) afforded 92 mg (82%) of **4**.

This product was characterized by comparison of physical data with those described above.

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