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SYNTHETIC COMMUNICATIONS, 22(13), 1949-1952 (1992)

AN IMPROVED PREPARATION OF AROMATASE INHIBITOR 4-HYDROXYANDROST-4-ENE-3,17-DIONE

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Abstract: The title compound has been prepared in 47% overall yield from androst-4-ene-3,17-dione (**1**) by a two-step sequence comprising hydrox-ylation of **1** with OsO_4 / H_2O_2, followed by dehydration of the resultant diols **3** in alkaline medium.

4-Hydroxyandrost-4-ene-3,17-dione (4-OHA, **4**) and its analogues have been the subject of extensive investigation as steroidal inhibitors of aromatase.[1] In particular, **4** was first reported in 1984 to cause regression of breast cancer metastases[2] and, later, to produce breast cancer remission when used at different drug schedules.[1a] As such, 4-OHA is currently used in the clinical treatment of oestrogen-sensitive breast cancer.

Previous syntheses of **4** have been most commonly achieved by either acid- or base-catalyzed opening of the 4,5-epoxides **2**, in turn obtained by treatment of **1** with alkaline H_2O_2.[3] Overall yields are, however,

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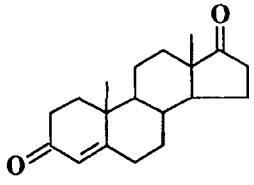
generally low and, in addition, the epoxidation step appears to work rather erratically.[3b]

Recently, Bednarsky and Nelson[4] reported the rearrangement of a mixture of α- and β-epoxyandrost-4-ene-3,17-diones **2** with boron trifluoride etherate in benzene to yield **4** in a 48% yield. In our hands, however, their procedure afforded **4** contaminated, presumably with the keto-aldehydes **6**.[5] Turning to petroleum ether-ethyl ether (3:2) as eluent of the flash chromatography, an average yield of 34% of appreciably pure **4** could be recorded by us over five runs.

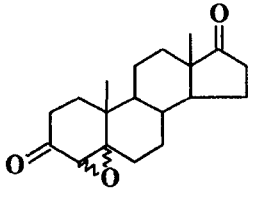
Eventually, the methoxylation of **1** with *o*-iodosylbenzoic acid in methanolic potassium hydroxide has been described to afford a 25% yield of **5**, an obvious precursor of **4**.[6]

In this communication we wish to report that the method used by Camerino *et al.* in 1963 to prepare A-nor analogues of corticosteroids[7] can be adapted to a convenient and reproducible preparation of **4** from **1**.

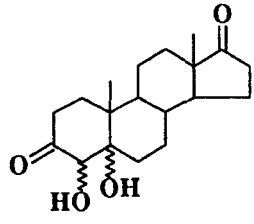
The preparation proceeds *via* the 4,5-diols **3**, formed from **1** using hydrogen peroxide in the presence of a catalytic amount of osmium tetroxide, and brief reaction of these with hot methanolic potassium hydroxide to produce **4** in fair *overall* yield (47%).



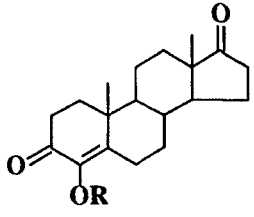
1



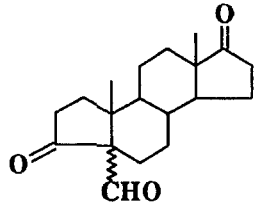
2



3



4, R = H
5, R = CH_3



6

The two diols need not be isolated and the second step of the sequence can be performed directly on the residue of the hydroxylation reaction.

The present procedure competes favourably with existing methods in terms of yield and reproducibility.

Experimental

Melting point was determined on a Kofler hot-stage apparatus and is uncorrected. Optical rotation was measured at 20°C with a Schmidt-Haensch Polartronic D polarimeter (1 dm-cell) in 2% $CHCl_3$ solution. IR spectrum was recorded on a Perkin-Elmer 983 spectrophotometer as 2% solution in $CHCl_3$. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard.

4-Hydroxyandrost-4-ene-3,17-dione (4). A solution of androst-4-ene-3,17-dione (**1**, 1.432 g, 5 mmol) in *tert*-butanol (50 mL) was treated at room temperature with 38 mg (0.15 mmol) of osmium tetroxide pre-dissolved in 2 mL of *tert*-butanol and then with 5 mL of 35% H_2O_2. The resulting solution was stirred at room temperature for 3 days, diluted with brine (100 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The organic phases were washed with brine (100 mL), aqueous 10% sodium bisulfite (50 mL), aqueous 10% Na_2CO_3 (50 mL), brine (100 mL), combined, dried (Na_2SO_4), and evaporated. The residue (1.824 g) was dissolved in MeOH (10 mL), treated with a solution of KOH (393 mg, 7 mmol) in MeOH (3 mL), and stirred at 55°C for 10 min. Acetic acid (0.3 mL) was then added, the solution was diluted with brine (100 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The organic phases were washed with brine (100 mL), combined, dried (Na_2SO_4), and evaporated. Chromatography of the residue (1.727 g) on silica gel (52 g) using hexane-ethyl acetate (7:3) as eluent gave 715 mg (47%) of **4**: mp 200-202°C (from acetone); $[\alpha]_D$ +170° (lit.[3b] mp 202-203°C; $[\alpha]_D$ +181°); IR 3452 (OH), 1730 (C-17 C=O), 1666 (C-3 C=O), 1633 (conjugated C=C)

cm^{-1}; ^1H NMR δ 0.92 (3H, s, 13-Me), 1.21 (3H, s, 10-Me), 6.24 (1H, s, 4-OH); ^{13}C NMR δ 139.078 (C-5), 141.291 (C-4), 193.403 (C-3), 220.490 (C-17).

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