Novel approach to the synthesis of the aromatase inhibitor 4-hydroxyandrost-4-ene-3,17-dione (4-OHA)

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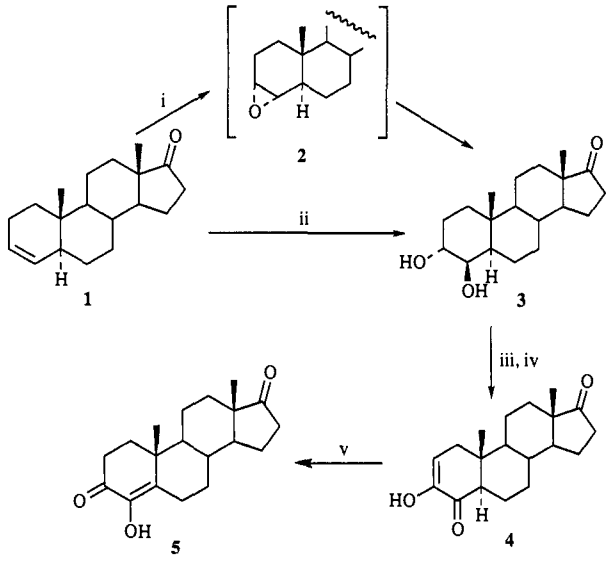
COMMUNICATION

A straightforward synthesis of the title compound is achieved through a novel approach, comprising the oxidation of the easily available 5α-androst-3-en-17-one 1 in two sequential steps to yield the kinetic diosphenol 4, which gives the desired 4-OHA 5 by base-catalysed isomerization.

Since the growth of some hormone-dependent cancers is controlled by estrogens, inhibition of aromatase, the cytochrome P450 enzyme which catalyses the last step in their biosynthesis, can be a logical and efficient approach for therapy on estrogen-dependent diseases.[1] Among the steroid inhibitors, 4-hydroxyandrost-4-ene-3,17-dione (4-OHA) **5**, has proved to be very effective in the treatment of advanced breast cancer[2] and quite recently has found clinical use.[3] A certain number of synthetic methods have been previously described for the preparation of 4-OHA, **5**. Most of the syntheses rely upon acid-catalysed opening of a mixture of 4α,5α- and 4β,5β-epoxides,[4] easily obtained by treatment of androstenedione with alkaline H_2O_2, although a report on the base-catalysed opening of the same mixture has been described.[5] The methoxylation of androstenedione with *o*-iodosylbenzoic acid in methanolic potassium hydroxide has been used to afford the 4-methoxy derivative as a precursor of 4-OHA, **5**.[6] However, the overall yields found in the described methods are generally low. More recently, an improved preparation of 4-OHA **5** *via* alkaline dehydration of a mixture of 4,5-diols, obtained from androstenedione with osmium tetroxide in the presence of hydrogen peroxide, was also reported[7] with a moderate overall yield of 47%. The establishment of 4-OHA as a drug and the recent upsurge on studies towards the elucidation of the active site of aromatase with 4-androstenedione analogues[8] prompted us to explore an alternative synthesis for this compound **5**.

We report herein a novel synthetic strategy for the preparation of 4-OHA, in which the starting material is 5α-androst-3-en-17-one **1**, efficiently prepared by zinc reduction of androstenedione in acetic acid and under sonochemical conditions,[9] followed by crystallization. A two-step oxidative route was then studied and is illustrated in Scheme 1. Treatment of the 3-olefin **1** with performic acid generated *in situ*[10] led, after work-up, to the *trans*-diaxial diol **3** (96%). The 3α,4α-epoxide **2** (Scheme 1) was the only product to be detected and isolated when formic acid was replaced by dichloromethane as a solvent, although under the previously reported conditions it was detected only during TLC control of the reaction. Further oxidation of the 3α,4β-dihydroxy-5α-androstan-17-one **3**, formed with dimethyl sulfoxide activated with trifluoroacetic anhydride,[11] gave quantitatively the kinetic diosphenol 3-hydroxy-5α-androst-2-ene-4,17-dione **4**, which by base-catalysed isomerization with NaOMe–MeOH[12] led to the desired thermodynamic diosphenol, 4-OHA **5**, in high yield (80%).

In summary, the high yield and rapid reactions, the easy availability of the starting material and reagents together with their low cost and non-toxicity render this new synthesis an efficient process. Due to the lack of chirality at C-5 in the target steroid **5**, the use of the whole epimeric mixture of 5α- and 5β-androst-3-en-17-one[9] as starting material for this synthesis is under investigation.



Scheme 1 *Reagents and conditions:* i, H_2O_2, HCO_2H, CH_2Cl_2, RT, 6 h; ii, H_2O_2, HCO_2H, RT, 1 h; iii, DMSO, TFAA, −60 °C, 3 h; iv, Et_3N, −60 °C 15 min; v, Na, MeOH, RT, 1 h

Experimental

3α,4β-Dihydroxy-5α-androstan-17-one 3

A stirred solution of the olefin **1** (67.5 mg, 0.25 mmol) in 90% formic acid (2 cm^3) was treated with 30% hydrogen peroxide (0.05 cm^3, 0.5 mmol) at room temperature for 1 h (TLC). After dilution with methanol (10 cm^3) and basification with aq. sodium hydroxide, the solution was neutralized with 10% aq. HCl and extracted with dichloromethane. The extract was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated to dryness to give compound **3** (75 mg, 96%) as a pure white crystalline solid, mp 232–234 °C (from acetone–hexane) (lit.,[13] 235–237 °C); ν_{max}(KBr)/cm^{-1} 3450 (OH), 1740 (C=O); δ_H(500 MHz; CD_3OD; Me_4Si) 0.86 (3 H, s, 18-H_3), 1.06 (3 H, s, 19-H_3), 3.51 (1 H, ddd, $J_{3\beta,2\alpha}$ 3.0, $J_{3\beta,4\alpha}$ 3.0, $J_{3\beta,2\beta}$ 1.5, 3β-H), 3.76 (1 H, dd, $J_{4\alpha,5\alpha}$ 6.0, $J_{4\alpha,3\beta}$ 3.0, 4α-H); δ_C(75.6 MHz; $CDCl_3$; Me_4Si) 13.8 (C-18), 14.2 (C-19), 70.5 (C-3), 76.1 (C-4), 220.4 (C-17); *m/z* (EI) 306 (M^+, 100%).

3α,4α-Epoxy-5α-androstan-17-one 2

As above, but using dichloromethane as the reaction solvent (1 cm^3), the olefin **1** (67.5 mg, 0.25 mmol) was treated with 30% hydrogen peroxide (0.05 cm^3, 0.5 mmol) and 90% formic acid (0.05 cm^3, 0.5 mmol) at room temperature for 6 h (TLC). The only detected and isolated product was epoxide **2** (75 mg, 96%), mp 158–159 °C (from diethyl ether) (lit.,[13] 156–158 °C); ν_{max}(KBr)/cm^{-1} 1750 (C=O); δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.79 (3 H, s, 19-H_3), 0.86 (3 H, s, 18-H_3), 2.71 (1 H, d, $J_{4\beta,3\beta}$ 4.0, 4β-

H), 3.17 (1 H, dd, $J_{3\beta,4\beta}$ 4.0, $J_{3\beta,2H}$ 2.0, 3β-H); δ_C(50.3 MHz; $CDCl_3$; Me_4Si) 13.4 (C-19), 13.9 (C-18), 52.1 (C-4), 55.6 (C-3), 220.9 (C-17); *m/z* (EI) 288 (M^+, 100%).

3-Hydroxy-5α-androst-2-ene-4,17-dione 4

To a stirred and cooled (−60 °C) mixture of dimethyl sulfoxide (0.15 cm^3, 2.11 mmol) in dichloromethane (9 cm^3) under nitrogen, trifluoroacetic anhydride (0.27 cm^3, 1.91 mmol) was added dropwise. After 10 min a solution of the diol **3** (203 mg, 0.66 mmol) in a mixture of dichloromethane and dimethyl sulfoxide (1 cm^3) was added and stirred until the steroid was consumed (3 h, TLC control). Triethylamine (0.615 cm^3, 4.41 mmol) was then added and after 15 min at −60 °C the temperature was raised to 5 °C. The solution was poured into 2 M hydrochloric acid (25 cm^3) and worked up in the usual manner to yield the crude *diosphenol* **4** (199 mg, 98%) as the only detected product. This pale yellow solid could not be crystallized,† and an analytical sample was purified by column chromatography [silica gel; ethyl acetate–light petroleum (bp 60–80 °C) (1:1)] (Found: C, 75.46; H, 8.97. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%); ν_{max}(KBr)/cm^{-1} 3400 (OH), 1743 (C=O), 1675 (C=O); δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, s, 18-H_3), 0.93 (3 H, s, 19-H_3), 5.85 (1 H, s, 2-OH, disappeared with D_2O), 5.96 (1 H, dd, $J_{2,1}$ 3.0, $J_{2,1}$ 7.0, 2-H); δ_C(50.3 MHz; $CDCl_3$; Me_4Si) 13.2 (C-18), 13.7 (C-19), 113.9 (C-2), 145.9 (C-3), 196.8 (C-4), 220.7 (C-17); *m/z* (EI) 302 (M^+, 100%).

4-Hydroxyandrost-4-ene-3,17-dione 5

To a stirred and cooled (0 °C) solution of **4** (60 mg, 0.2 mmol) in methanol (3 cm^3) under nitrogen, sodium metal (50 mg, 2.2 mmol) was added. After 1 h at room temperature the solution was neutralized with 10% aq. HCl and the usual work-up was followed. The residue was purified by flash chromatography [silica gel; diethyl ether–carbon tetrachloride (1:1)] to give the title compound **5** (48 mg, 80%) as pure colourless needles, mp 202–203 °C (from ethyl acetate) (lit.,[5] 201–203 °C); ν_{max}(KBr)/cm^{-1} 3415, 3390 (OH), 1743 (C=O), 1672 (C=O), 1636 (C=C); δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.92 (3 H, s, 18-H_3), 1.20 (3 H, s, 19-H_3), 3.07 (1 H, m, 6α-**H**), 6.16 (1 **H**, s, 4-OH, disappeared with D_2O); δ_C(125 MHz; $CDCl_3$; Me_4Si) 13.7 (C-18), 17.1 (C-19), 139.2 (C-4), 141.3 (C-5), 193.5 (C-3), 220.7 (C-17).

† Attempts to recrystallize this compound were unsuccessful due to its conversion into 4-OHA.

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