Preparation of Androst-5-ene-4,7,17-trione and A-Norandrost-5-ene-3,7,17-trione

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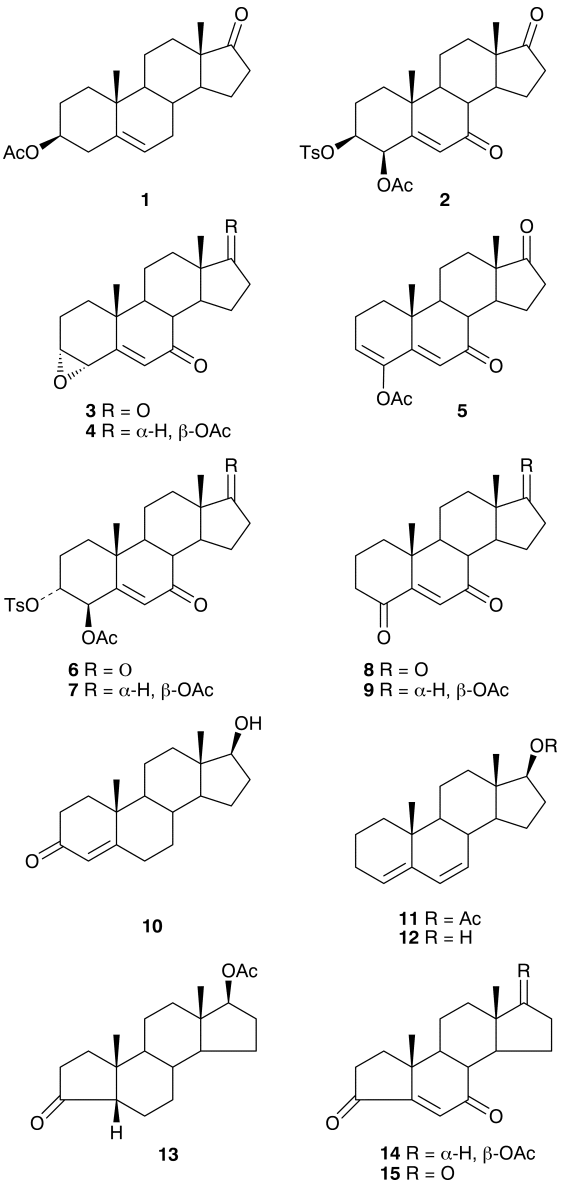
Syntheses are described of the aromatase inhibitor, androst-5-ene-4,7,17-trione, its 17β-acetate and A-nor analogue, A-norandrost-5-ene-3,7,17-trione, starting from dehydroisoandrosterone and testosterone.

Aromatase is a major target enzyme system in the chemotherapy of estrogen dependent breast cancers.[1] Recently a number of steroidal enediones including androst-4-ene-3,6,17-trione and androst-5-ene-4,7,17-trione **8** have been shown to be effective inhibitors.[4,5] The latter has been prepared by the allylic oxidation of androst-5-en-17-one with pyridinium dichromate and *tert*-butyl hydroperoxide[6] in rather low yield.



Scheme

An alternative synthesis of androst-5-ene-4,7,17-trione **8** involved the conversion of 3β-acetoxyandrost-5-en-17-one **1** *via* 3β-*p*-tolylsulfonyloxy-4β-acetoxyandrost-5-en-17-one and allylic oxidation at C-7 with *tert*-butyl chromate to afford the 7,17-diketone **2**.[7] Elimination of the toluene-*p*-sulfonate by solvolysis with sodium acetate in acetic acid followed by hydrolysis of the enol-acetate **5** with hydrochloric acid gave the required enedione **8** (see Scheme).

In another route, the 3α-toluene-*p*-sulfonates, **6** and **7**, were prepared by acetolysis of the 3α,4α-epoxides **3** and **4**[8] and acylation of the 3α-alcohols with toluene-*p*-sulfonyl chloride. Elimination with sodium acetate in acetic acid gave the enediones **8** and **9** directly.

A further synthesis started from testosterone **10** which was converted *via* 17β-acetoxyandrosta-4,6-dien-3-one to the 4,6-diene **11**.[11] Oxidation of the diene **11** and the corresponding 17β-alcohol **12** with chromium trioxide gave the enediones **9** and **8**, respectively. Dehydrogenation of androst-5-ene-4,7,17-trione with DDQ gave a low yield of androsta-2,5-diene-4,7,17-trione.

The A-nor steroid analogue, A-norandrost-5-ene-3,7,17-trione **15**, was prepared from 17β-acetoxy-A-nor-5β-androstan-3-one **13**[13] by bromination, dehydrobromination and allylic oxidation to afford **14**. Hydrolysis of the 17β-acetate and oxidation of the resultant alcohol gave the trione **15**. These synthetic routes afford some potential flexibility for the synthesis of related 5-ene-4,7-diones.

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Techniques used: IR, ^{1}H and ^{13}C NMR, chromatography

References: 18

Table 1: ^{13}C NMR data

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