Tetrahedron Letters, Vol. 34, No. 38, pp. 6139-6140, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis of Estrone via a Thallium(III)-mediated Fragmentation of a 19-Hydroxy-androst-5-ene Precursor

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Abstract: Estrone (**6**) has been synthesized from **1**, an industrial precursor of androstane steroids, in seven steps. Key features of the strategy include the functionalization of C-19 (**1** → **2**) and a stereoelectronically controlled, Tl(III)-mediated degradation (**2** → **3**). Oppenauer oxidation of diol **4** then gave the unsaturated hydroxyketone **5**, acid treatment of which induced aromatization affording **6**.

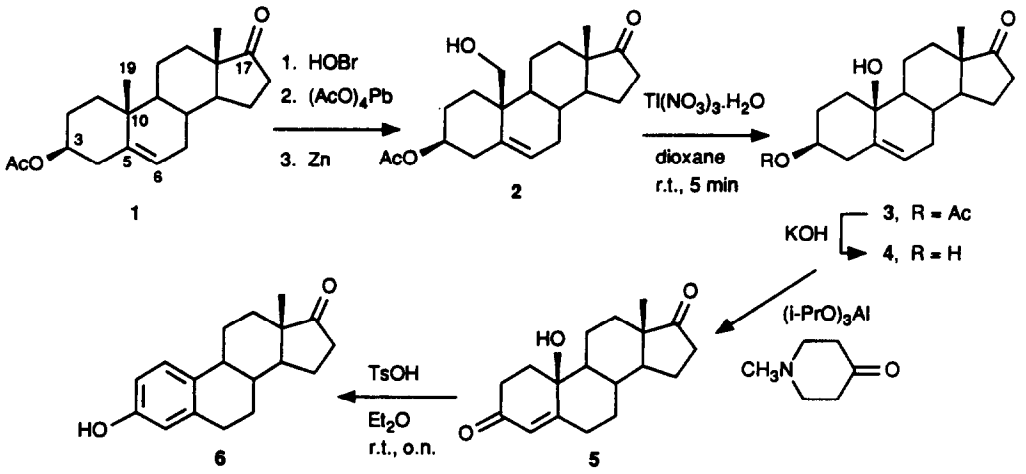
Estrone (**6**) is one of the essential hormones of human reproduction.[1] There has been a considerable synthetic effort aiming at the construction of this molecules and a number of both partial[1-3] and total[4] syntheses have been reported. The partial synthesis starting with common industrial sources must encompass the C-19 removal[2,5,6] which is an elaborate process. Therefore, total syntheses can successfully compete, particularly in view of the recent enantioselective approaches[4] which replaced tedious resolution of synthetic racemates of the early days. We now wish to rekindle interest in the partial synthetic approach. Herein we report on an expedient synthesis of estrone (**6**) starting from a common industrial precursor for steroid synthesis, the androstane derivative **1**.

Functionalization of C-19, an initial step required for removing this carbon,[2,5,6] was developed in the sixties as an efficient and reliable, three-step procedure affording up to ca. 50% overall yield of 19-hydroxy 5-unsaturated derivatives (**1** → **2**).[5,7,8] Using cholestane model compounds, we have recently discovered a unique, thallium(III)-mediated reaction that converts 5-unsaturated 19-hydroxy derivatives directly to 19-nor-10β-alcohols.[9,10] We have now found that this method worked efficiently also with the more functionalized androstane derivative **2**, producing the 19-nor-derivative **3** (69%); TLC analysis revealed a few by-products.

After having accomplished the crucial step, the synthetic strategy followed the procedure initially developed with the cholestane models:[12] the monoacetate **3** was first saponified to give the diol **4** (97%) which on the modified[13] Oppenauer oxidation furnished **5** (78%).[14,18] The latter compound was stable enough to survive the relatively harsh conditions of Oppenauer oxidation (i.e. reflux in toluene for several hours). A quick workup with ice-cold aqueous 1% HCl (to wash out the basic components) was found to be tolerated by the sensitive functionality of **5**. In contrast, treatment of **5** with TsOH at r.t. overnight resulted in a quantitative aromatization of the A-ring to give estrone (**6**).

In summary, starting with the C-19 steroid **1**, we have designed a novel, expedient route to the 19-nor-10β-alcohol **3** which can readily be converted to estrone (**6**) via the reasonably stable hydroxy enone **5**.

Acknowledgment. We thank the ESF and University of Leicester for financial support to R.S.B.



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(Received in UK 30 June 1993; accepted 23 July 1993)