Synthesis of 1,11β-Ethanoestra-1,3,5(10)-triene-3,17β-diol: a Novel Bridged Steroid Derivative

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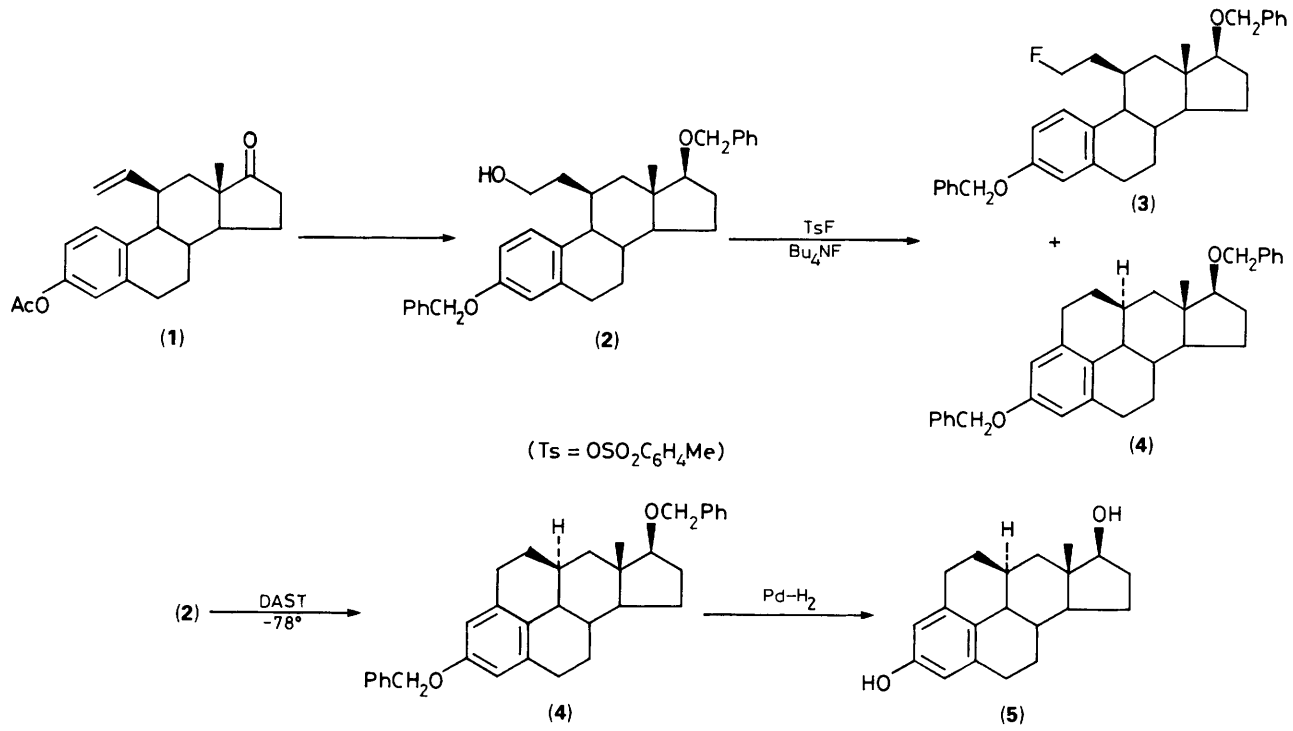
The generation of an electrophilic centre on the 11β-(2-hydroxyethyl) estradiol 3,17β-bis(benzyl ether) (**2**) leads in two steps to the corresponding 1,11β-ethano-estradiol in a 61% overall yield.

As part of our program to prepare high affinity estradiol derivatives as potential radiodiagnostic imaging agents for human breast cancer, we required 11β-(2-hydroxyethyl)-estradiol 3,17β-bis(benzyl ether) (**2**) as an intermediate for the synthesis of the 11β-(2-fluoroethyl)estradiol.[1,2] The introduction of the fluoride to give the protected (2-fluoroethyl)estradiol (**3**) was achieved by the reaction of the alcohol (**2**) with *p*-toluenesulphonyl fluoride and tetrabutylammonium fluoride[3] in refluxing tetrahydrofuran (THF). A careful analysis of the reaction mixture revealed the presence of a minor byproduct whose structure was tentatively assigned as the cyclized estradiol (**4**) based upon the disappearance of the C-1–H in the ^{1}H-n.m.r. spectrum. Inspection of a model of the molecule and an *X*-ray crystallographic analysis of the precursor (**1**),[4] indicated a supraplanar relationship between the terminal carbon of the 11β-substituent and the C-1-position of the *A*-ring. As a result, it appeared that with an appropriate reagent intramolecular cyclization may be the dominant reaction (Scheme 1).

The reagent chosen to effect cyclization was diethylaminosulphur trifluoride (DAST) which, although it activates the carbon–oxygen bond, does not involve the generation of a high concentration of fluoride ion, a condition which favours substitution. Polarization of the terminus with the generation of an incipient electropositive centre on the carbon would lead one to predict intramolecular cyclization as the major reaction pathway. We now report the facile conversion of the alcohol intermediate (**2**) to the novel 1,11β-ethanoestra-1,3,5(10)-triene-3,17β-diol (**5**) by a method which provides only low yields of the corresponding 11β-(2-fluoroethyl) substitution product (Scheme 2).

The addition of DAST to a dichloromethane solution of (**2**)



(0.42 g, 0.86 mmol) at −78 °C for 2 h gave a major product isolated in a 61% yield (0.25 g, m.p. 108—110 °C). The assignment of the structure of 1,11β-ethanoestra-1,3,5(10)-triene-3,17β-diol bis(benzyl ether) was based upon the two benzyl methylenes, and the C-2–H and C-4–H at δ 6.59 and 6.64 respectively (*J* 2.2 Hz). Of particular note was the absence of signals for the CH_2F group and the C-1–H. An analysis of the reaction mixture by t.l.c. indicated the presence of trace quantities of the corresponding fluoroethyl product (**2**) which was identical to that previously obtained.[2]

Removal of the benzylic groups was readily achieved using hydrogen and colloidal palladium, generated *in situ* by the reduction of $PdCl_2(Me_3CN)_2$, in ethanol–ethyl acetate. The desired 1,11β-ethanoestra-1,3,5(10)-triene-3,17β-diol (**5**) was isolated in a quantitative yield (0.12 g, m.p. 212—216 °C).

The product was characterized by optical rotation ($[\alpha]_D^{25}$ −9.59° in THF, *c* 1.77 × 10^{-3}) and ^1H n.m.r. (300 MHz) in [$^2H_6$]Me_2SO; δ 0.69 (s, 3H, C-18–H), 1.06—1.72 (m, 10H), 1.78—1.92 (m, 2H), 2.02—2.16 (m, 2H), 2.44—2.64 (m, 4H), 3.48 (dd, *J* 7.8, 4.8 Hz, 1H, C-17–H), 4.46 (d, *J* 4.8 Hz, 1H, CHOH), 6.28 (d, *J* 2Hz, 1H, C-2–H), 6.35 (d, *J* 2Hz, 1H, C-4–H).

In our opinion, the final product represents the first example of a derivative of estradiol which combines both 1- and 11β-alkyl substituents. The methods employed in the synthesis also illustrate the versatility of the hydroxyalkyl moiety in being converted to either substituted or cyclized products. The determination of the receptor binding properties of this compound and its comparison to the estradiol derivatives is in progress and will be reported elsewhere.

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