Synthesis of 19,19-Difluoro Steroids and of Novel B-Ring-expanded Steroids

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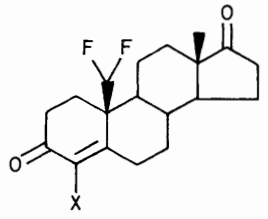
A site-selective fluorination of 10-formylnortestosterone 17-benzoate (**4**) which allows access to 19,19-difluoro steroids is described, and an associated rearrangement reaction yields the novel *abeo*-testosterone derivative (**6**) and thence the homoestradiol derivative (**7**); the *X*-ray structure of (**6**) is reported.

As part of our work concerned with the synthesis of aromatase inhibitors for the treatment of breast cancer,[1] we wished to prepare 19,19-difluoroandrost-4-ene-3,17-dione (**1**) and the corresponding 4-hydroxy-analogue (**2**). These, it was hoped, would inhibit the biosynthesis of estrogens since this is known to involve loss of the 19-methyl group of androst-4-ene-3,17-dione (**3**) *via* an oxidative process.[2]

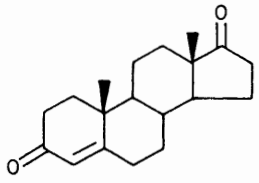
We planned to treat 10-formylnortestosterone 17-benzoate (**4**) with diethylaminosulphur trifluoride (DAST), since this reagent is known to convert aldehyde (and ketone) groups into difluoromethyl groups.[3] Meakins and co-workers have studied the reaction of DAST with numerous keto-steroids[4] under rather forcing conditions (neat DAST at 80 °C), but under milder conditions we were able to achieve a site-selective fluorination of (**4**) and both the keto- and ester-functionalities remained unaffected. Thus, reaction of (**4**) (8.87 mmol) (prepared from the corresponding alcohol by oxidation with pyridinium chlorochromate) with DAST (36.9 mmol) in CH_2Cl_2–$FCCl_3$ (50 ml; 1 : 1) at room temperature for 2 days yielded the desired 19,19-difluoro-compound (**5**) (1.73 g, 60% based on aldehyde consumed, m.p. 174.5—176 °C). In addition to unchanged aldehyde (0.86 g), the rearrangement product (**6**) (0.70 g, m.p. 160 °C) was also isolated.

The structure of this product (**6**) was suggested by ^{13}C and ^{19}F n.m.r. analysis (1 $\succ$CHF, 1 $\equiv$C–F, 8 CH_2, and 5 methine C_1, including one olefinic methine); and was confirmed by *X*-ray structure analysis.

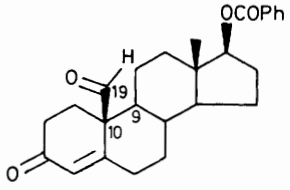
Crystal Data, $C_{26}H_{30}F_2O_3$, M = 428.24, orthorhombic, space group $P2_12_12_1$, a = 8.899(8), b = 13.323(12), c = 18.316(11) Å, U = 2171.6 Å^3, Z = 4, D_m = 1.28, D_c = 1.31 g cm^{-3}, $F(000)$ = 912, λ = 0.7107 Å, μ = 1.03 cm^{-1}. 1359



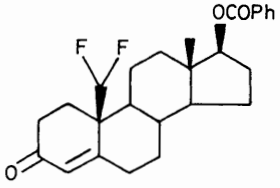
(1) X = H
(2) X = OH



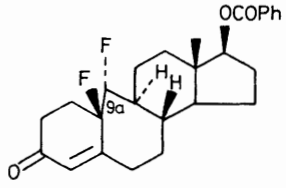
(3)



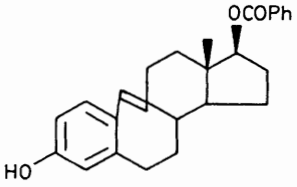
(4)



(5)



(6)



(7)

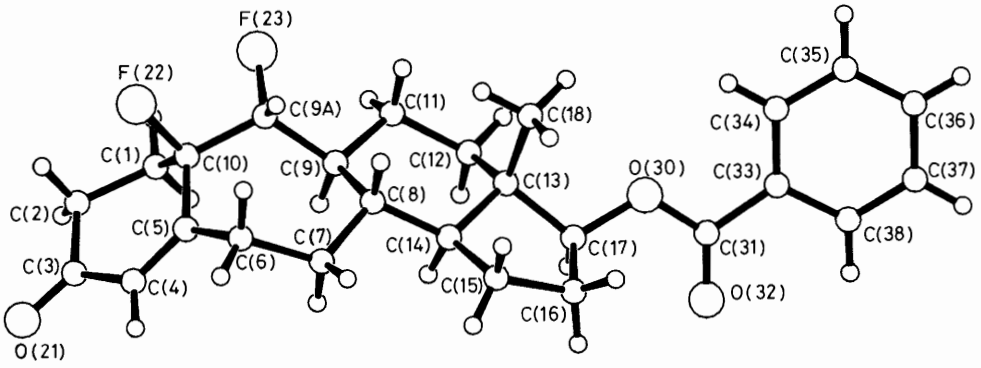
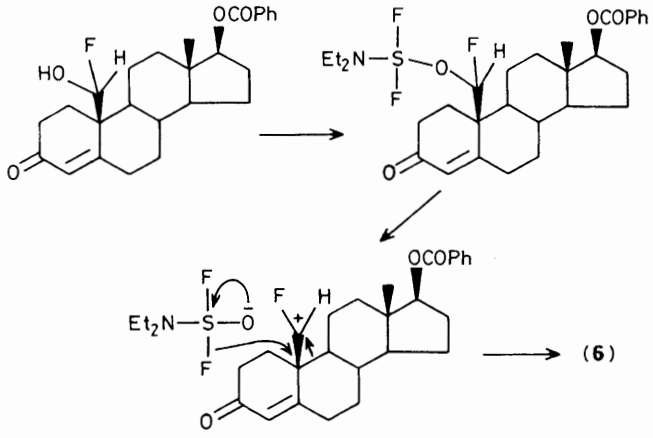


Figure 1. *X*-Ray structure of (**6**).



Scheme 1

Independent above-background data were measured on a diffractometer. The structure was solved by direct methods[5] and refined by full-matrix least-squares to $R = 0.061$. F, O, and C atoms were refined anisotropically. Hydrogen atoms were positioned in trigonal or tetrahedral sites and refined isotropically.† The structure of the molecule is shown in Figure 1. The six-membered ring B has been enlarged to include C(9A) between C(9) and C(10) to give a unique 6:7:6:5 fused ring system. We searched the Cambridge Crystallographic Data Centre files, but found no other structure with this type of fused ring system. The conformation of ring B retains its basic chair shape with atoms C(5), C(6), C(8), and C(9) approximately coplanar (max. deviation 0.10 Å) and atoms C(7) 0.64 Å above and C(9A) and C(10) 1.16 and 0.73 Å respectively below this plane. Rings A, C, and D have the expected conformations. The C(4)–C(5) double bond is retained. The F(22)–C(10)–C(9A)–F(23) torsion angle is −67.0(1)°.

A possible mechanism for this interesting rearrangement is given in Scheme 1, which is analogous to one proposed by Middleton for reactions of DAST with simple aldehydes.[3] To our knowledge the present mode of rearrangement has not been previously described.

The ratio of (**5**) to (**6**) remained at around 2.5:1 over a range of solvent systems (halogenated solvent–ether solvent mixtures) and yields of both species have yet to be optimised.

After 2 weeks at room temperature in dichloromethane (**6**) lost two moles of HF to yield the novel homoestradiol derivative (**7**), which was characterised as its dibenzoate: m.p. 205—206 °C; δ ($CDCl_3$, 220 MHz) 6.29 (s, 1H, 9a olefinic H) and 6.9—8.2 (m, 13H, aromatic H pattern similar to that observed for estradiol di-*O*-benzoate). Given the current interest in novel steroidal ring systems, these two new examples warrant further investigation, not least because of their accessibility.

Finally, the major product (**5**) was successfully converted into 19,19-difluoroandrost-4-ene-3,17-dione (**1**) (ester hydrolysis then Jones' oxidation), and thence into the 4-hydroxy-analogue (**2**) (i, epoxidation; ii, MeOH–NaOH; iii, BBr_3). Both of these compounds were good inhibitors of human placental aromatase (*in vitro*); (**1**) produced a 50% inhibition of enzyme activity at a concentration of 1.3 μM, while (**2**) produced the same effect at 3.3 μM. However, when compared with 4-hydroxyandrost-4-ene-3,17-dione (50% inhibition at 0.2 μM), which is in clinical use, these new analogues can be seen to be much less potent. These results are similar to those reported by Marcotte and Robinson,[6] who have also prepared (**1**), but by a different route.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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