Heptafluoro-*p*-tolyl as a Selective Protecting Group for the Enone Function of Androst-4-ene-3,17-dione: Application to the Preparation of Deuterium-labelled Testosterone

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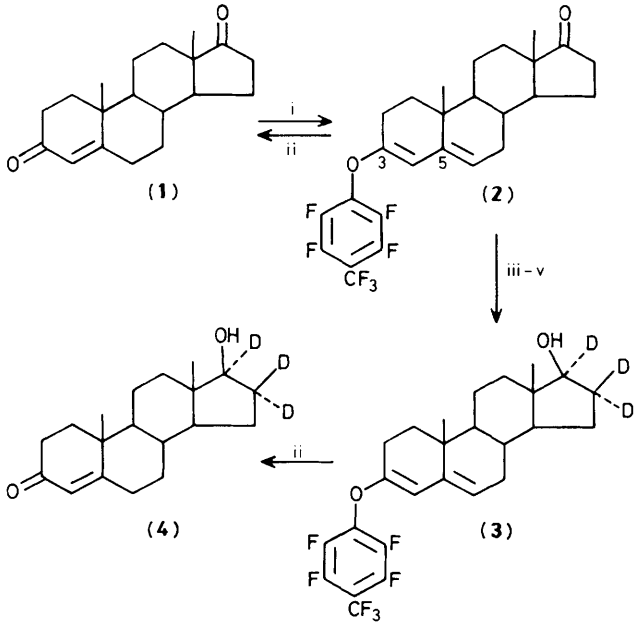
Octafluorotoluene reacts with the enone function of androst-4-ene-3,17-dione in the presence of caesium fluoride to give specifically a 3,5-dienol ether which has been used to prepare deuterium-labelled testosterone.

We have recently demonstrated the use of heptafluoro-*p*-tolyl for the selective protection of phenolic and alcoholic functions[1] and applications in the synthesis of analogues of the anti-cancer drug tamoxifen.[2,3] The phase transfer conditions used for the protection of alcohols and phenols caused the derivatisation of the enol function of 4-hydroxyandrost-4-ene-3,17-dione[1] but ketone functions did not react. We now report that under conditions which promote enolisation of ketones, the enone function in androst-4-ene-3,17-dione (**1**) can be protected selectively. Thus with octafluorotoluene (3.4 equiv.) and anhydrous caesium fluoride (3.2. equiv.) in dimethylformamide at reflux for 6 h, androstenedione (**1**) gives as the sole product the dienol ether derivative (**2**) (86% yield),† m.p. 98—99 °C. The 3,5-diene structure was deduced from the proton n.m.r. spectrum, δ_H 0.92 (3H, s, 18-H), 1.02 (3H, s, 19-H), 1.0—2.7 (17H, methylene envelope), 5.18 (1H, s, 4-H), 5.29 (1H, m, 6-H), in which pre-irradiation of either olefinic proton gave a nuclear Overhauser enhancement of the other, and the u.v. spectrum, $\lambda_{max.}$ (EtOH) 232 (ε 19 950 dm^3 mol^{-1} cm^{-1}), 266sh nm (4500), was typical for a *trans*-diene. Since arylation was exclusively on oxygen, octafluorotoluene is a 'hard' electrophile in hard–soft acid–base (HSAB) theory.[4] This result is paralleled by observations that perfluorotolyl ethers resist attack by 'soft' nucleophiles.[1,3]

† Compound (**2**) gave satisfactory analytical data.



Scheme 1. *Reagents:* i, C_7F_8, CsF, Me_2NCHO, 150 °C; ii, H_2SO_4 (aq.), tetrahydrofuran, 60 °C; iii, D_2O, $(C_7H_{15})_4N^+Cl^-$, NaOD, PhMe, 60 °C; iv, $NaBD_4$, EtOD, 20 °C; v, H_2O.

Sodium methoxide in dimethylformamide, which cleaved the perfluorotolyl ethers of alcohols and phenols,[1] did not regenerate androstenedione from the derivative (**2**) owing to the instability of the enone function under these conditions. However (**2**) behaves as a typical enol ether in that acidic hydrolysis (1 : 1 5 M sulphuric acid–tetrahydrofuran, 60 °C, 12 h) did regenerate the enone (80% yield).

An application of the perfluorotolyl group for the protection of the enone function in synthesis is the preparation of the deuterium-labelled testosterone (**4**) useful as an internal standard in assays of the natural steroid using gas chromatography–mass spectrometry.[5] Thus, base catalysed incorporation of deuterium into the derivative (**2**) under phase transfer conditions[6] followed by reduction of the 17-keto function with sodium borodeuteride gave the testosterone derivative (**3**) (Scheme 1) (58% yield), m.p. 143—144 °C, *m/z* 507 (M^+, 100%), from which the labelled steroid (**4**), m.p. 154—155 °C, *m/z* 291 (M^+, 96%), was released by acidic hydrolysis (93% yield). The isotopic composition, determined by mass spectrometry, was 95.0% [$^2H_3$], 4.7 [$^2H_2$], 0.3 [$^2H_1$]. The labelled testosterone (**4**) has been prepared previously, but from androst-5-en–3β-ol-17-one by a route involving a final enzymatic oxidation step to generate the required 4-ene-3-one.[7]

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