The Angular Trifluoromethyl Group: Synthesis of (±)-3-*O*-Methyl-18,18,18-Trifluoroestradiol

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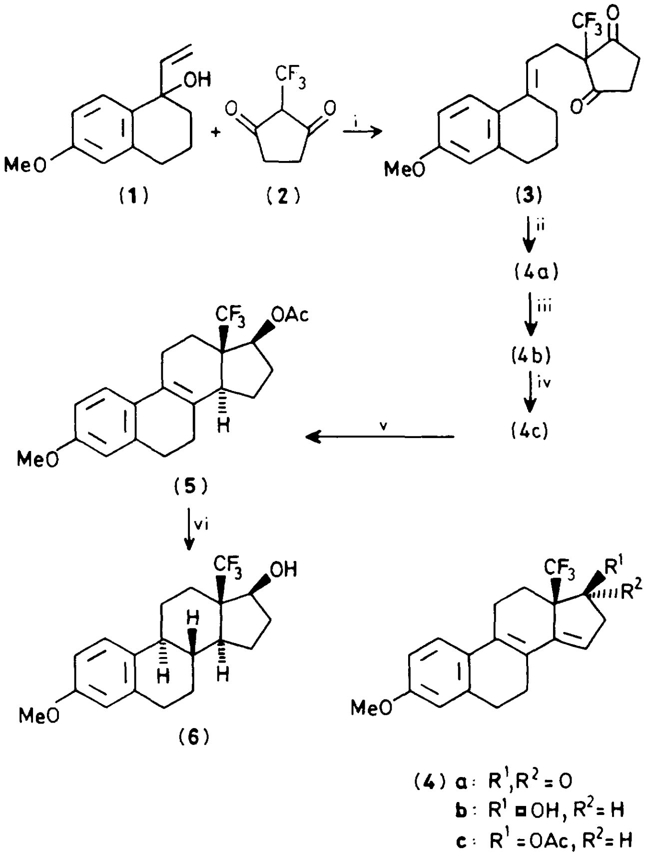
The title compound is prepared in six steps from 2-trifluoromethylcyclopentane-1,3-dione.

Addition of a trifluoromethyl group to drug molecules is known to increase their solubility in lipids and their penetrating ability.[1] So organic molecules bearing this group have become increasingly popular synthetic targets. As far as we



Reagents: i, triethylamine (0.03 mol. equiv.), benzene, room temperature; ii, toluene-*p*-sulphonic acid, benzene, 70 °C; iii, $NaBH_4$, ethanol, 0 °C; iv, Ac_2O, pyridine, room temperature; v, H_2, 5% Pd on Al_2O_3, 2% pyridine in acetone; vi, Na, 10% aniline in liquid ammonia.

know, no steroids with an angular trifluoromethyl group have been characterized.[2] We describe here the synthesis, by a Torgov type reaction,[3] of (±)-3-*O*-methyl-18,18,18-trifluoro-estradiol (**6**) starting from the allyl alcohol (**1**) and 2-trifluoromethylcyclopentane-1,3-dione (**2**).

The main problem is the great instability of the diketone (**2**) towards bases.[4] Fortunately, however, (**2**) is very reactive, and the condensation can be performed at room temperature in the presence of a very small amount of triethylamine to give compound (**3**) in 44% yield [m.p. 57—57.5 °C, δ_F 68.7 p.p.m. ($CDCl_3$, $CFCl_3$ as standard)].

Cyclisation of the diketone (**3**) with toluene-*p*-sulphonic acid proceeded smoothly to give the pentaene (**4a**) (84% yield, m.p. 110—111 °C, δ_F 70.2 p.p.m.). Reduction of (**4a**) by sodium borohydride gave the somewhat unstable alcohol (**4b**) (94% yield, m.p. 133.5—134.5 °C, δ_F 67.8 p.p.m.) which was readily acylated to give (**4c**) (84% yield, m.p. 156—157 °C, δ_F 69.3 p.p.m.).

Selective hydrogenation of the Δ^{14} double bond[5] gave the 14α epimer (**5**) (68% yield, m.p. 173—173.5 °C, δ_F 63.3 p.p.m.). In order to obtain the 'natural' configuration 9α,8β we reduced (**5**) with sodium in liquid ammonia.[6] Under these conditions the tertiary trifluoromethyl group was unaffected; however, during the reduction, the acetoxy group was cleaved and the title compound (**6**) was obtained directly (74% yield, m.p. 131—132 °C, δ_F 57.9 p.p.m.).†

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† All new compounds were fully characterized by analytical and spectral data.