Stereocontrolled Synthesis of the Ecdysone Side Chain *via* a Furan Derivative

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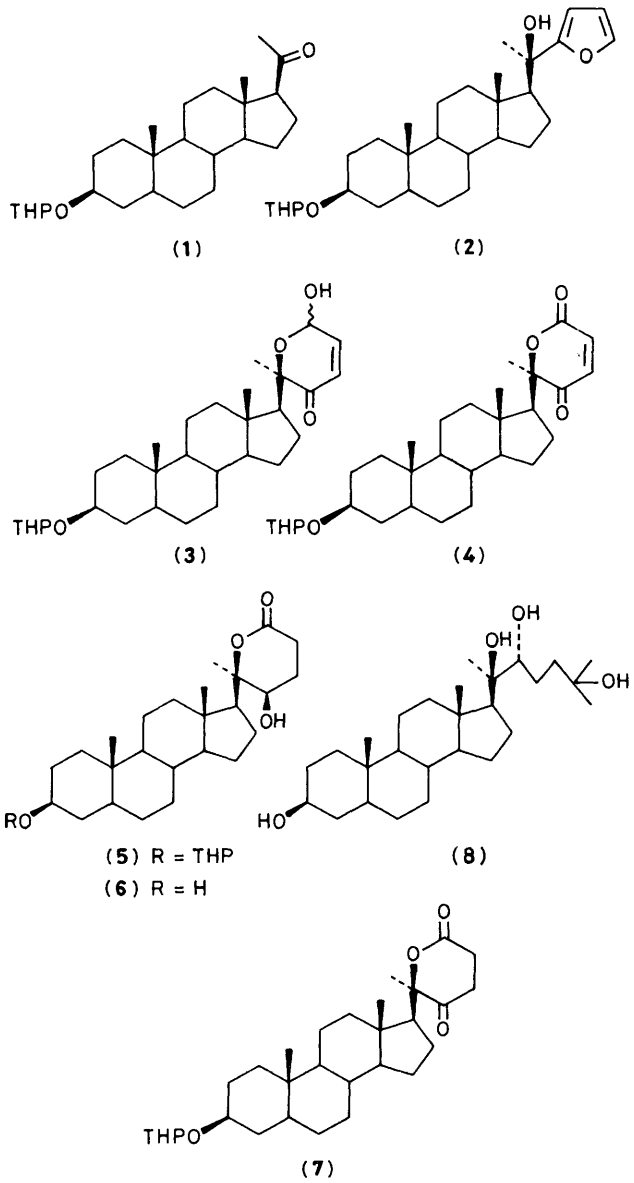
A stereocontrolled synthesis of (20*R*,22*R*)-5β-cholestane-3β,20,22,25-tetraol (**8**) from a furan derivative of pregnanolone is described.

The stereocontrolled synthesis[1] of steroid side chains has been widely investigated because of the significant stereochemical effect of the side chains on the activities of various physiologically interesting steroids, such as insect and crustacean moulting hormones, vitamin D metabolites, and with anolides. Since we have developed a simple and effective methodology[2] for the transformation of pregnenolone to (22*R*)-22,25-dihydroxycholesterol *via* furan derivatives we have also utilized furan derivatives for the introduction of a 20-hydroxyecdysone-type side chain. Here we report a stereocontrolled synthesis of 20*R*,22*R*)-5β-cholestane-3β,-20,22,25-tetraol (**8**).

The synthesis was achieved as outlined in Scheme 1. Reaction of pregnanolone 3-tetrahydropyranyl ether (**1**) and 2-lithiofuran gave the furan derivative (**2**) (M^+, *m/z* 470) which was treated with *m*-chloroperbenzoic acid and sodium acetate in chloroform to afford the isomeric hemiacetal (**3**) [i.r. ν($CHCl_3$) 3595, 3360 (OH), and 1690 cm^{-1} (C=O)] in 81% yield. Oxidation of (**3**) with pyridinium chlorochromate and sodium acetate in dry dichloromethane gave the lactone



Scheme 1. THP = tetrahydropyranyl.

(**4**) which was hydrogenated on a platinum catalyst to yield the 22*R*-compound (**5**) and the keto lactone (**7**) in 77 and 22% yields, respectively. Deprotection of the tetrahydropyranyl ether (**5**) with pyridinium toluene-*p*-sulphonate in ethanol gave the diol (**6**) which was treated with methylmagnesium bromide in tetrahydrofuran to afford (20*R*,22*R*)-5α-cholestane-3β,20,22,25-tetraol (**8**) in 88% yield. The structure including the stereochemistry of the compound (**8**) was determined by comparison with an authentic sample.[3]

Of all the published syntheses, this procedure is one of the most simple and highly stereospecific methods for introducing the 20-hydroxyecdysone-type side chain into a pregnane-type steroid. The remarkable feature of this method is the stereoselective reduction of the enone (**4**) to give the 22*R*-compound (**5**) because the reduction of C-22 ketones by hydrides and/or metal species in solution gives mainly 22*S*-hydroxy compounds.[4]

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