A New Synthesis of a Steroid Side Chain *via* Stereocontrolled Protonation: Synthesis of (−)-Desmosterol

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Protonation of the lactone enolate (**9**), obtained from the 20-cyano-steroid (**3**) and (*R*)-benzyl 2,3-epoxypropyl ether (**6**), with saturated aqueous sodium sulphate proceeds in a highly stereoselective manner from the less hindered side to give the (20*R*)-lactone (**10**) which can be converted into the (20*R*)-steroid, desmosterol (**17**).

Since 17-oxo-steroids are readily available *via* the microbial conversion of abundant steroidal precursors,[1] these are promising starting materials for the synthesis of a variety of physiologically active steroids with a C-17 side chain, such as vitamin D metabolites, cholic acid derivatives, and ecdysones. The introduction of the side chain at C-17[2] has been the subject of recent investigation by a number of workers who have developed several new methods including the use of organopalladium,[3] organocopper,[4] and organoborane reagents,[5] Claisen rearrangements,[6] and ene reactions.[7] We report a new highly stereoselective synthesis of a steroid side chain on the 17-oxo-steroid (**1**).

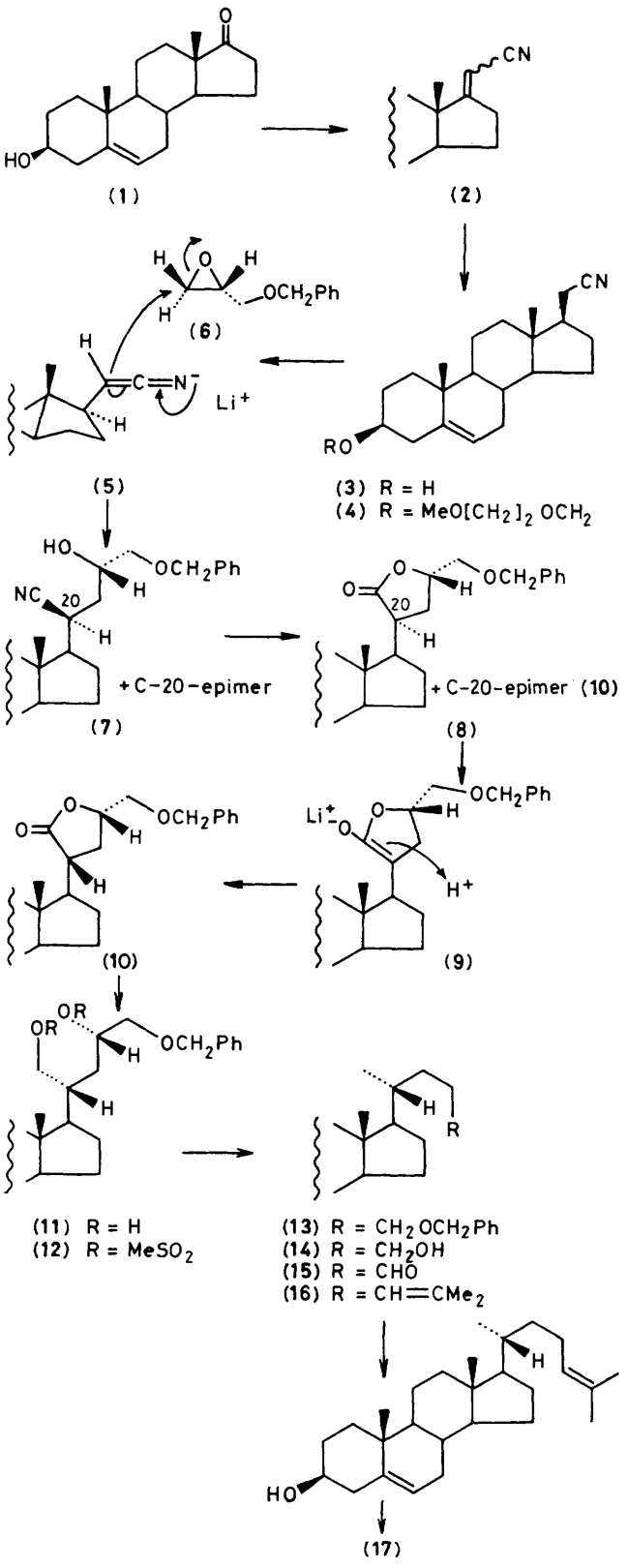
Dehydroepiandrosterone (**1**) was treated with diethylphosphonoacetonitrile[8] (NaH, dimethoxyethane, 10 h) to give the α,β-unsaturated nitrile (**2**),† in 83% yield. Reduction of the α,β-unsaturated system of (**2**) proceeded in a highly stereoselective manner with magnesium in methanol[9] (room temp., 6 h) to form the (17*R*)-acetonitrile (**3**) {m.p. 193—197 °C, $[\alpha]_D$ −74.30° ($CHCl_3$)} quantitatively. The hydroxy group of (**3**) was then alkylated with methoxyethoxymethyl chloride in the presence of *N*,*N*-di-isopropylethylamine (CH_2Cl_2, room temp., 24 h) to give the ether (**4**) {m.p. 57—58·5 °C, $[\alpha]_D$ −58.03° ($CHCl_3$)} in 85% yield. Condensation of the ether (**4**) with (*R*)-benzyl 2,3-epoxypropyl ether (**6**)[10] in the presence of lithium hexamethyldisilazide [$LiN(SiMe_3)_2$] [tetrahydrofuran (THF), 0 °C] gave an inseparable mixture of the cyano-alcohol (**7**) and its C-20-epimer, which without separation was hydrolysed (KOH, aqueous EtOH, reflux, 48 h) to give a mixture (*ca.* 4:1) of the lactone (**8**) and its C-20-epimer (**10**), in 72% overall yield after acid work-up, followed by brief reflux in toluene. Treatment of this epimeric mixture with lithium hexamethyldisilazide at 0 °C (THF), followed by an excess of saturated aqueous sodium sulphate (added in one portion) at −78 °C,[11] resulted in highly stereoselective protonation at C-20 from the less hindered side of the enolate intermediate (**9**) to give the (20*R*)-lactone (**10**) {m.p. 92—92.5 °C, $[\alpha]_D$ −22.80° ($CHCl_3$)} exclusively, in 75% yield.‡ As the (20*R*)-lactone (**10**) was identical to the minor component of the starting mixture (t.l.c.), it was assumed that the addition of (**5**) to the epoxide (**6**) occurred in a fairly selective manner to give (**7**) as the major product as shown in Scheme 1.

The (20*R*)-lactone (**10**) was then reduced with lithium aluminium hydride (THF, 0 °C, room temp.) to give the diol (**11**) {$[\alpha]_D$ −33.66° ($CHCl_3$)} in quantitative yield. Treatment of (**11**) with an excess of mesyl chloride (pyridine, CH_2Cl_2, 0 °C, room temp.) gave the crude dimesylate (**12**), which was then allowed to react with lithium triethylborohydride[12] (THF, room temp. then reflux, 4 h) to give the (20*R*)-methyl derivative (**13**) {$[\alpha]_D$ −31.85° ($CHCl_3$)} in 45% overall yield.§

† Satisfactory spectral (i.r., n.m.r., and mass) and analytical (combustion or high resolution mass spectroscopy) data were obtained for all new compounds.

‡ A small amount of the 20-hydroxy-steroid was obtained as a by-product probably from dissolved oxygen in the solvent.

§ A 20-methyl-steroid with a hydroxy group at C(23) was obtained as a by-product (40% yield). By varying the reduction conditions, the primary mesyloxy group could be removed leaving the secondary group intact (room temp., 1 h).



Reductive debenzylation of (**13**) under Birch conditions (Li, liquid NH_3–THF–EtOH) afforded the primary alcohol (**14**) {$[\alpha]_D$ −39.0° ($CHCl_3$)} in 98% yield, which was identical with an authentic sample {$[\alpha]_D$ −40.07° ($CHCl_3$)} prepared from 3-hydroxy-5-cholenic acid *via* methoxyethoxymethylation, followed by reduction with lithium aluminium hydride. Oxidation of (**14**) under Moffatt–Swern conditions[13] (Me_2SO, oxalyl dichloride, Et_3N, −78 °C) afforded the aldehyde (**15**) which was converted into desmosterol[6a,14] (**17**) {m.p. 118—120 °C, $[\alpha]_D$ 40.3° ($CHCl_3$); lit.[14] m.p. 120—122 °C, $[\alpha]_D$ −42.0° ($CHCl_3$)} *via* (**16**), on treatment with triphenylphosphonium isopropylide, followed by deprotection using zinc bromide in methylene chloride.[15] A method for the conversion of desmosterol (**17**) into cholesterol and precursors of the active vitamin D metabolites has been developed.[2b]

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