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STEREOCONTROLLED SYNTHESIS OF STEROID SIDE CHAINS VIA ORGANOBORANES. STEREOSPECIFIC SYNTHESIS OF 20R- AND 20S-25-HYDROXYCHOLESTEROL.

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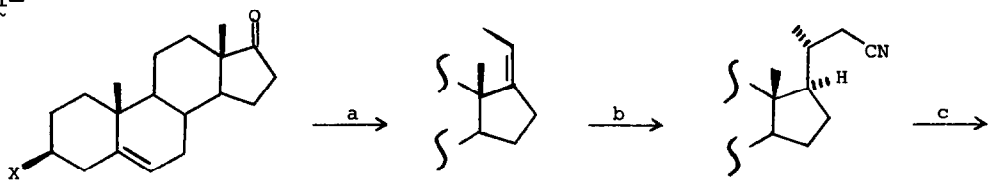
Summary: Both 20R- and 20S-25-hydroxycholesterol have been stereospecially prepared from readily available 3β-hydroxy-5-androsten-17-one.

The discovery of biologically important steroids with modified side chains, such as ecdysone and the metabolites of vitamin D, as well as the discovery of marine steroids with an "unnatural" configuration at C-20, has stimulated the development of many methods for the stereospecific synthesis of steroid side chains.[2] Since 17-keto steroids are becoming readily available via microbial degradation of abundant plant steroids, these are attractive starting materials for further elaboration. Newer methods which have been used to attach a steroid side chain to a 17-keto steroid include the use of organopalladium chemistry,[3] organocopper chemistry,[4] Claisen rearrangements[5] and ene reactions.[6] When considering side-chain elaborations an important transformation would be the conversion of a 17-keto steroid to the biologically important 25-hydroxy steroids. One would also desire the ability to obtain either C-20 epimer selectivity. We report herein methods for achieving these goals.

The synthesis of 20R-25-hydroxycholesterol starts with the conversion of a 17-keto steroid (1)[7] to a Z-17(20)-ethylidene steroid (2) via the Wittig reaction[8] (Scheme 1). Hydroboration of 2 with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds exclusively from the α-face. Subsequent reaction of the organoborane with chloroacetonitrile in the presence of potassium 2,6-di-t-butyl-4-methylphenoxide gave the 22-cyano-steroid (3) with the natural configuration at C-17 and C-20 in 88% yield.[9] Reduction of 3 with diisobutylaluminum hydride (Dibal) gave the 22-aldehyde-steroid (4), which was then reacted with triethylphosphonoacetate to obtain the α,β-unsaturated ester (5). Selective reduction of the side-chain double bond was achieved by catalytic hydrogenation of 5 over 5% palladium on charcoal. Methylation of the saturated ester with methyllithium

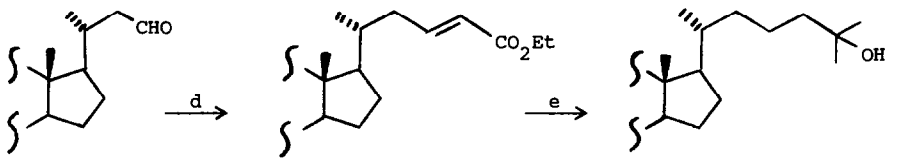
afforded 20R-25-hydroxycholesterol (6), m.p. 176-178° (lit.[10] 178-180°) in 58% overall yield in 6 steps from the 17-keto-steroid (1). H^1 NMR: δ5.33 (m, 1H, H-5), 3.46(m, 1H, H-3), 1.22(s, 6H, 26,27-CH_3's), 1.03(s, 3H, 19-CH_3), 0.93 (d, J = 6Hz, 3H, 21-CH_3), 0.69(s, 3H, 18-CH_3).

Scheme 1[a]



1 2 3

X = OH, OAc, 3α,6α-cyclomethyl ether

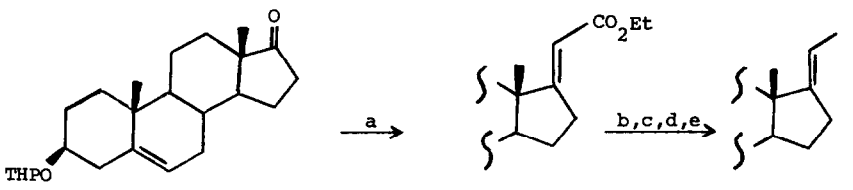


4 5 6

[a]Conditions: (a) Six equivalents of $Ø_3PEtBr$, THF, t-BuOK/t-BuOH, reflux, 12 hr, 83% yield; (b) two equivalents of 9-BBN, (r.t., overnight), two equivalents of potassium 2,6-di-t-butyl-4-methylphenoxide and chloroacetonitrile, 0°, 1 hr, 88% yield; (c) Dibal, -70° → RT, 93% yield; (d) three equivalents of triethylphosphonoacetate/NaH, reflux, 4 hr, 91% yield; (e) H_2, 5% Pd/charcoal, r.t., 15 hr, 95% yield; (f) three equivalents MeLi, reflux, 2 hr, 99% yield.

The stereospecific synthesis of the 20S-25-hydroxycholesterol requires hydroboration of an E-17(20)-ethylidene steroid exclusively from the α-face. Therefore, preparation of an E-17(20)-ethylidene steroid was needed. Olefin inversion[11] of the Z-17(20)-ethylidene steroid through an epoxide was not successful, although ordinary olefins are inverted without difficulty. The traditional method[12] of addition of ethyl magnesium bromide to the 17-keto-steroid (1) and subsequent dehydration of the 17-ethyl-17-hydroxy-steroid gave a mixture of the E-17(20)-ethylidene steroid and a 5(6)-16(17)-diene (2.5:1), which was partially purified by recrystallization (8:1). Unsatisfied with the purity and yield, a stereospecific synthesis of the E-17(20)-ethylidene steroid was performed as shown in Scheme 2.

Scheme 2[a]



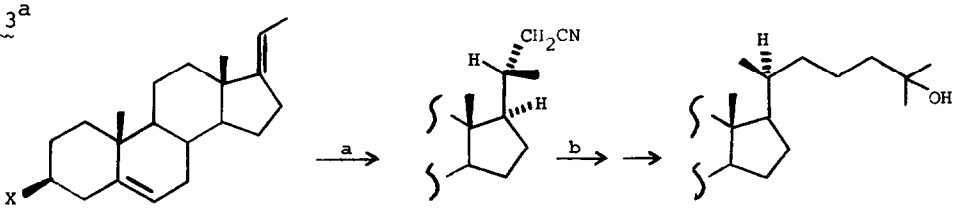
7 8 9

[a]Conditions: (a) Three equivalents of triethylphosphonoacetate, EtONa/EtOH, reflux, 15 hr, 83% yield; (b) LAH, 100%; (c) 1.2 equivalents of PBr_3; (d) LAH; (e) DHP, TsOH, 62% yield in 3 steps.

The reaction of 17-keto-steroid (7) with triethylphosphonoacetate gave 20-carboethoxy - steroid-5(6)-E-17(20)-diene (8).[13] Reduction of 8 with lithium aluminum hydride (LAH) gave an allylic alcohol. Careful bromination of the allylic alcohol with PBr_3, reduction of the resulting allylic bromide with LAH and reprotection of the 3-hydroxy group with dihydropyran gave the desired E-17(20)-ethylidene steroid (9), m.p. 141-143°C. Deprotection of the THPO group (acetic acid, tetrahydrofuran, water; 4:2:1, 40-60°C, 2 hrs) and acetylation (acetic anhydride/pyridine) gave the acetate m.p. 141.5-142°C (lit.[12] 140°) in an overall 51% yield. H^1 NMR: δ5.38 (m, 1H, H-5), 5.03(m, 1H, H-20), 4.58(m, 1H, 3H), 2.01(s, 3H, CH_3CO_2), 1.52(d, J = 7Hz, 3H, 21-CH_3), 1.04(s, 3H, 19-CH_3), 0.76(s, 3H, 18-CH_3).

Hydroboration of the E-17(20)-ethylidene steroid acetate (10) with 9-BBN at room temperature proceeded slower than the Z-isomer.[14] Alkaline oxidation of the steroid-9-BBN adduct gave only the 20R-3β-acetoxy-pregnane-20-ol and 20R-pregnane-3β-20-diol due to the exclusive α addition of 9-BBN (the acetoxy group was partially reduced). The synthesis of 20S-25-hydroxycholesterol began with carbon-carbon bond formation reaction of 10 (Scheme 3). Hydroboration with

Scheme 3[a]



10 11 12

X = THPO, OAc, OH

[a]Conditions: (a) Three equivalents of 9-BBN (r.t. overnight), three equivalents of potassium 2,6-di-t-butyl 4-methylphenoxide and chloroacetonitrile, ethanol, 0°, 1 hr, 94-97% yield; (b) see c-f in Scheme 1.

9-BBN and the subsequent reaction of the steroid-9-BBN adduct with chloroacetonitrile in the presence of potassium 2,6-di-t-butyl-4-methylphenoxide gave the 22-cyano-steroid (11) with the unnatural configuration at C-20 and natural configuration at C-17 in 94-97% yield. Following the sequence of reactions in Scheme 1, the 22-cyano-steroid (20S) was transformed into 20S-25-hydroxycholesterol, m.p. 184-186° (lit.[10] 180-185°). ^{1}H NMR: δ5.33 (m, 1H, H-5), 3.46(m, 1H, H-3), 1.22(s, 6H, 26,27-CH_3's), 1.03(s, 3H, 19-CH_3), 0.84(d, J = 6Hz, 3H, 21-CH_3), 0.69 (s, 18-CH_3). The ^{1}H and ^{13}C NMR spectra of this product were identical with an authentic sample generously supplied by M. Uskokovic of Hoffmann-LaRoche.

Thus a 17-keto steroid may be stereospecifically transformed into either the 20R- or 20S-25-hydroxy steroid. It should be noted that the 5(6)-double bond need not be protected in these reactions.[15]

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