Synthesis of the Steroid Rubrosterone

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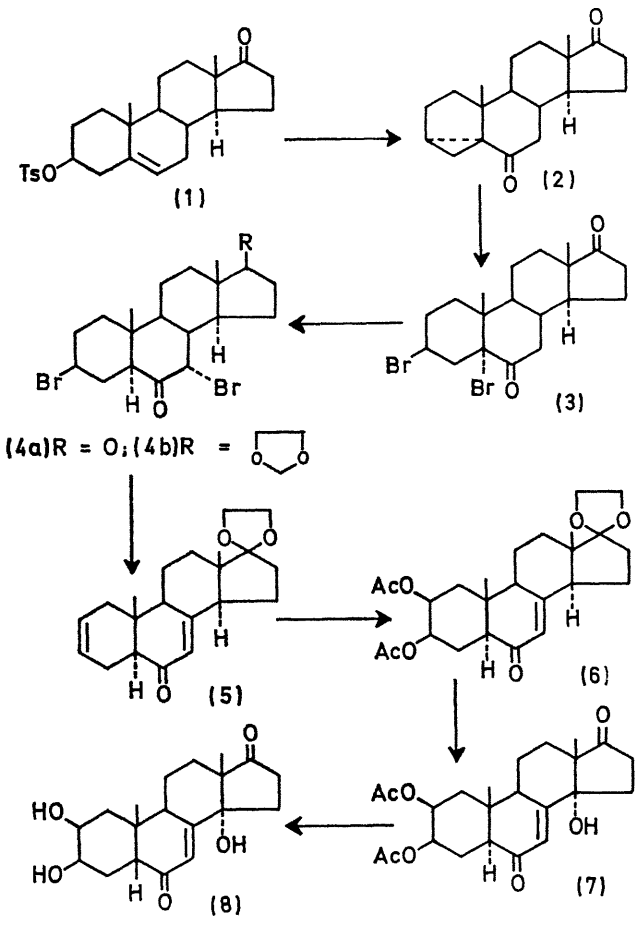
Summary Rubrosterone, a steroid with the ecdysone skeleton, was synthesized from readily available starting material.

RUBROSTERONE, a metabolite of ecdysterols, was isolated from plant sources by Takemoto *et al.* and formulated as



2β,3β,14α-trihydroxy-5β-androst-7-ene-6,17-dione (**8**).[1] The synthesis of (**8**) was recently reported by Takemoto *et al.*[2,3] and by Hocks *et al.*[4] We describe the synthesis of rubrosterone by the *i*-steroid method which is a novel and short approach to the synthesis of the ecdysterone skeleton and related compounds.

Rearrangement of 3β-hydroxyandrost-5-en-17-one tosylate (**1**) in aqueous acetone and potassium acetate, followed by Jones oxidation, gave the known 3α,5-cyclo-5α-androstane-6,17-dione[5] (**2**) in 68% yield. Bromination of (**2**) in acetic acid afforded 3β,5α-dibromoandrostane-6,17-dione (**3**)† (83·4%), m.p. 165—166°, $[\alpha]_D$ −47°, u.v. λ_{max} ($CHCl_3$) 303 nm (ε 221), n.m.r. ($CDCl_3$) δ 0·88 (C-18 CH_3), 1·05 (C-19 CH_3), 4·54 (3α-proton). Acid-catalysed rearrangement of (**3**) (HBr–HOAc) gave the 3β,7α-dibromo-derivative (**4a**) in 50% yield, m.p. 212—213°, $[\alpha]_D$ +131°, u.v. λ_{max} ($CHCl_3$) 306 nm (ε 158), n.m.r. ($CDCl_3$) δ 0·84 (C-19 CH_3), 0·90 (C-18 CH_3), 3·32 (m, 3α- and 5α-protons) and 4·29 (d, *J* 5 Hz, 7β-proton). Dehydrobromination of (**4a**) led to extensive decomposition and inseparable mixtures. However, the 17-ethylenedioxy-derivative (**4b**) readily underwent double dehydrobromination on treatment with $LiCO_3$–$MeCONMe_2$ to give the desired 17,17-ethylenedioxy-5α-androsta-2,7-dien-6-one (**5**) (50%) m.p. 132—133°, $[\alpha]_D$ + 6°, u.v. λ_{max} (EtOH) 242 nm (ε 9700), n.m.r. ($CDCl_3$) δ 0·77 (C-18 CH_3), 0·84 (C-19 CH_3) 3·81 (ethylenedioxy-group), 5·48 (m, C-2 and C-3 vinylic protons), 5·6 (dd, *J* 2·5 Hz, C-7 vinylic proton).‡

cis-Hydroxylation of (**5**) with silver acetate and iodine in moist acetic followed by acetylation led to (**6**), m.p. 155—157°, $[\alpha]_D$ −16·5°, in 37% yield. The 14α-hydroxyl function was introduced directly with SeO_2 in dioxan[6] and the protective group at C-17 removed (tetrahydrofuran–3·5 N-$HClO_4$) to furnish (**7**) (40%), m.p. 270—272°, $[\alpha]_D$ +73°, u.v. λ_{max} (EtOH) 238 nm (ε 10,600), n.m.r. ($CDCl_3$) δ 0·85 (C-18 CH_3), 1·01 (C-19 CH_3), 2·05, 2·11 (acetate functions at positions 2 and 3), 4·71 (m, 3α-proton), 5·17 (m, 2α-proton), 6·20 (d, *J* 2·5 Hz, C-7 vinylic proton).

Hydrolysis of (**7**) and inversion at C-5 under equilibrating conditions (0·033% K_2CO_3) furnished synthetic rubrosterone, (**8**), identical in all respects with an authentic specimen.

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† Structure (**3**) was further confirmed by an alternative synthesis. Addition of hypobromous acid to known 3β-bromoandrost-5-en-17-one, followed by Jones oxidation afforded (**3**) identical in all respects with the product obtained by the addition of bromine to (**2**).

‡ The observed splitting pattern (dd) for the C-7 vinylic proton is consistent with a C/D *trans*-fused system. In a C/D *cis*-fused system the allylic coupling constant between 7-H and 14-H is negligible (0·5 Hz), and a doublet will be observed for 7-H due to the allylic coupling with 9-H.

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