Asymmetric Total Synthesis of Steroid Hormones: An Efficient Route to (+)-3β-Hydroxy-17-methoxy-D-homo-18-nor-5α-androsta-13,15,17-triene

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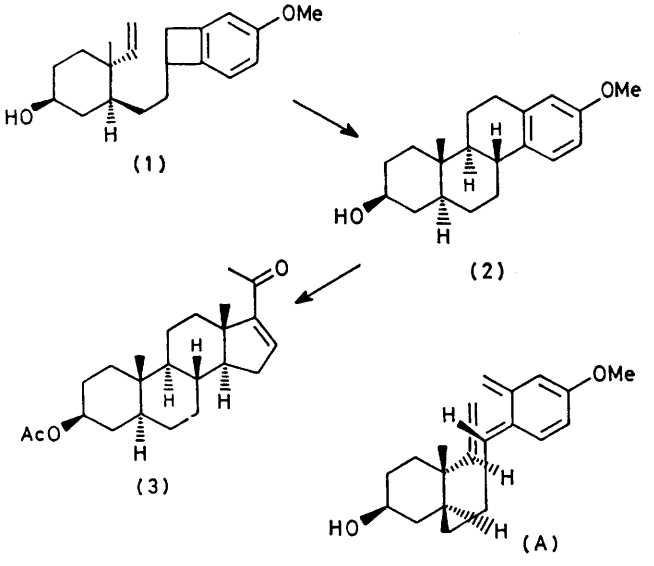
Summary Optically active 3β-hydroxy-17-methoxy-D-homo-18-nor-5α-androsta-13,15,17-triene (**2**), an important intermediate in the synthesis of 5α-Δ^{16}-pregnen-3β-ol-20-one (**3**), has been synthesised by thermolysis of optically active 4-hydroxy-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-1-methyl-1-vinylcyclohexane (**1**).

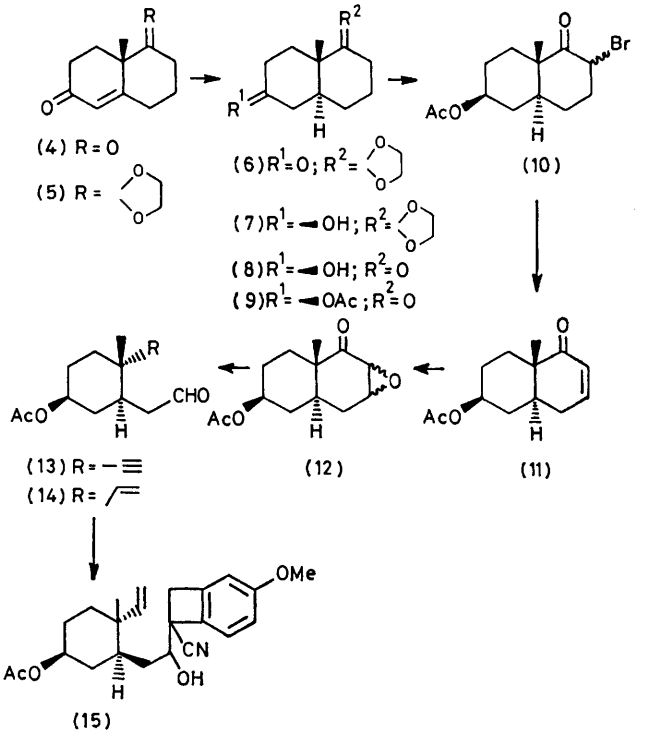
SYNTHETIC approaches to the A-ring aromatic and 19-nor-steroid nuclei based on novel BC ring construction *via* intramolecular cycloaddition to *o*-quinodimethanes derived from benzocyclobutenes or other precursors are of current interest.[1] None of these, however, provides a synthetic route to 5α-pregnane derivatives, in either racemic or optically active form, which constitute an important class of steroid hormones and could be key intermediates in the synthesis of other classes of steroid hormones.[2] Here we report an efficient synthesis of optically active 3β-hydroxy-17-methoxy-D-homo-18-nor-5α-androsta-13,15,17-triene (**2**) [which has been transformed into 5α-Δ^{16}-pregnen-3β-ol-20-one acetate (**3**) in its (±)-form[3]] by asymmetric induction. The synthesis is based on the chiral cyclohexane derivative (**1**), in which the BC rings of the steroidal system are formed in one step by an intramolecular cycloaddition reaction.



SCHEME 1

The key intermediate, optically active 2-benzocyclobutenylethylcyclohexane (**1**), was prepared from (*S*)-8a-methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (**4**) {$[\alpha]_D^{25}$ + 113° ($CHCl_3$)}[4] as follows. The monoacetal (**5**) $[\alpha]_D^{25}$ + 124·2°,† synthesised from (**4**) by a standard procedure,‡ was reduced with Na in liquid NH_3 in the presence of EtOH to give compound (**6**) ($[\alpha]_D^{25}$ + 20·7°),† which was converted, by treatment with $NaBH_4$ in MeOH, into the acetal alcohol (**7**) ($[\alpha]_D^{25}$ −38·5°).† The oxo acetate (**9**) ($[\alpha]_D^{25}$ −61°)† was derived in the usual manner‡ from the oxo alcohol (**8**) ($[\alpha]_D^{25}$ −52·3°),† which was in turn obtained from treatment of (**7**) with 5% HCl in acetone. The enone (**11**) ($[\alpha]_D^{25}$ −38·9°)† was obtained from treatment of (**9**) with Br_2 in $CHCl_3$ in the presence of NaOAc, and elimination of the resulting bromide (**10**) using LiBr and Li_2CO_3 in dimethylformamide.

Oxidation of the enone (**11**) with 30% H_2O_2 in 10% NaOH and MeOH afforded the epoxide (**12**); Eschenmoser ring opening of (**12**) was then examined. The reaction proceeded well on using the Corey modification.[5] Thus, the epoxide (**12**) was treated with 2,4-dinitrophenylsulphonylhydrazine in CH_2Cl_2–$MeCO_2H$ (1 : 1) to give the acetylenic aldehyde (**13**) ($[\alpha]_D^{25}$ −77·2°),† which, on hydrogenation on $PdCO_3$ in acetone under hydrogen, yielded the olefinic aldehyde (**14**) ($[\alpha]_D^{25}$ −14·0°).†



SCHEME 2

† Rotations were determined in chloroform.

‡ Experimental details will be published elsewhere.

Condensation of this olefinic aldehyde (**14**) with 1-cyano-4-methoxybenzocyclobutene[6] in liquid NH_3 in the presence of $NaNH_2$, followed by reductive removal (Na in liquid NH_3) of the cyano and hydroxy groups of the resulting compound (**15**) [*m/e* 383 (M^+)], was achieved by our method[1b] to furnish the key intermediate (**1**) [$\delta(CDCl_3)$ 0·96 (3H, s, Me), 3·84 (3H, s, OMe), 4·8—6·05 (3H, m, olefinic protons), and 6·6—7·2 (3H, m, ArH), *m/e* 300 (M^+)]. Heating the benzocyclobutene (**1**) in *o*-dichlorobenzene at 180 °C for 14 h in a current of nitrogen gave compound (**2**) {$[\alpha]_D^{25}$ −43·64°, δ ($CDCl_3$) 0·85 (3H, s, Me), 3·83 (3H, s, OMe), and 6·7—7·4 (3H, m, ArH), *m/e* 300 (M^+)}.§ The structure, including stereochemistry, of this compound was established by a direct comparison of its i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra with those of an authentic racemic sample.[3]

The stereoselective outcome of this intramolecular cyclisation can be explained by the intervention of the intermediate (**A**) and indeed this is the one expected to be most stable in light of the preceeding papers.[1]

Thus, we have disclosed an efficient asymmetric synthesis of compound (**2**) and the method, in connection with the established method,[3] should provide a general route for the asymmetric synthesis of a wide range of 5α-pregnane steroids.

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§ All reactions in the sequence from compound (**4**) to compound (**2**) proceeded in moderate to high yield.

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