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TOTAL SYNTHESIS OF (+)-5α-DIHYDROPREGNENOLONE VIA ACETYLENE-CATION CYCLIZATION

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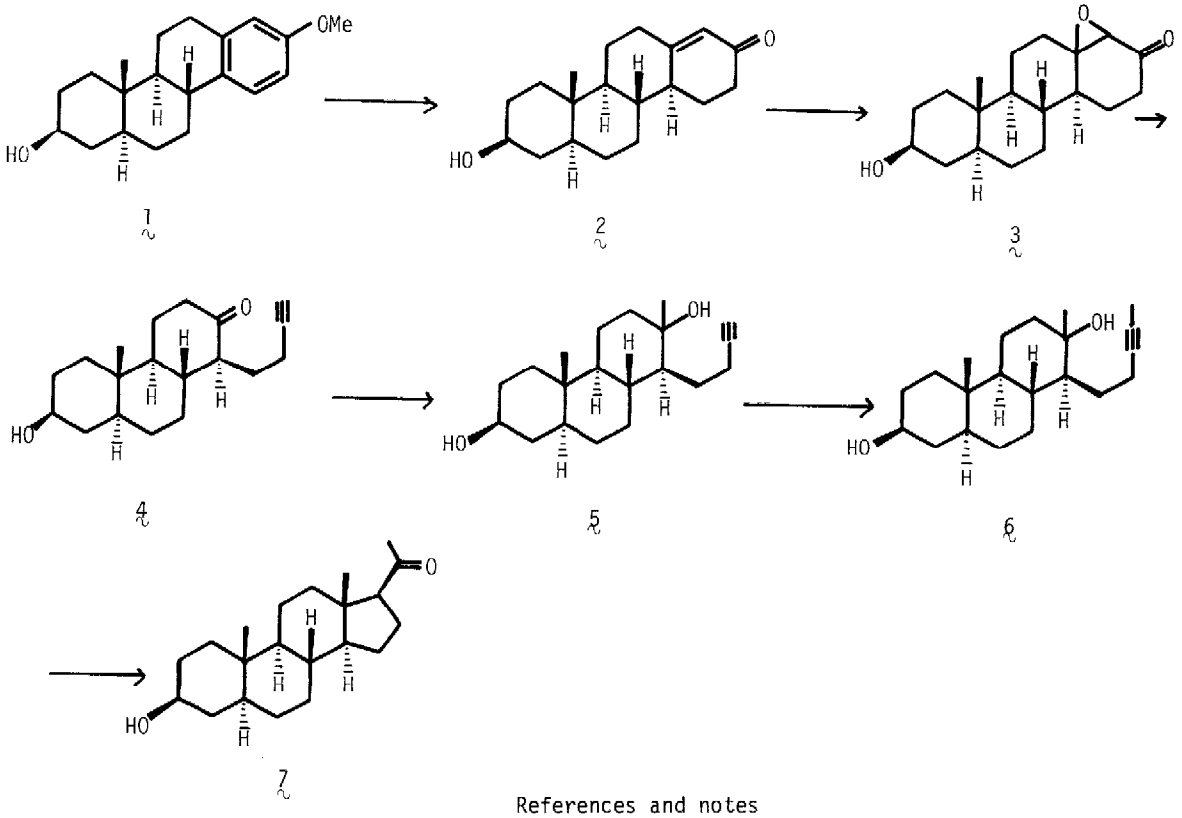
Summary The stereoselective total synthesis of (+)-5α-dihydropregnenolone 7 via acetylene-cation cyclization of 6, which was readily prepared from the optically active D-ring aromatic steroid 1, is described.

Recently, stereocontrolled syntheses of trans-fused hydrindane derivatives have attracted much attention because the latter constitutes the ring portion of steroidal nucleus.[1] Although acetylene-cation cyclization is one of the most promising methods for the construction of the trans-fused hydrindane portion of 20-keto steroids[2], the stereochemical course of this cyclization has been shown to depend on the conformation of the carbonium ion precursors reflecting the nature of substituents on the cyclohexane and acetylene moieties.

Here we wish to report cyclization of compound 6, which has the same stereochemistry —— excepting the C_{13} centre —— as the ring system of the natural steroid 7, and is readily derived from the D-ring aromatic steroid 1 prepared by asymmetric synthesis[3], leading to 5α-dihydropregnenolone (7)[4]. The latter is known to be a metabolite of progesterone[5] and its acetate is an important synthetic intermediate for cholestanol[6]. The requisite acetylenic alcohol 6 was synthesized as follows.

The enone (2) [m.p. 188 - 189°C, $[\alpha]_D$ - 37.3°][8], which was derived in 70.5 % yield from (+)-3-hydroxy-17-methoxy-D-homo-18-nor-5 -androst-13,15,17-triene[4] (1) by Birch reduction (Li, NH_3, tert-BuOH, THF, - 33°C, 5h), followed by acid (10 % HCl, MeOH, room temperature, 4H) treatment and was identical to an authentic racemic sample[7] in its i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra, was converted in 95.2 % yield into epoxide 3 [i.r. ($CHCl_3$) 3600 (OH) and 1700 cm^{-1} (C=O), m/e 304 (M^+), $[\alpha]_D$ - 38.0°][8] by treatment with 30 % hydrogen peroxide in 10 % aqueous sodium hydroxide and methanol at 0°C for 15 min. The acetylenic ketone 4 [i.r. ($CHCl_3$) 3300 (C≡CH) and 1700 cm^{-1} (C=O), m/e 288 (M^+), $[\alpha]_D$ - 6.78°][8] resulting in 59 % yield from Eschenmoser ring opening reaction (p-$TsNHNH_2$, AcOH, CH_2Cl_2, - 20°C, 20 h; room temperature, 4 h) of 3 was treated with methyllithium in THF at 0°C for 1 h to give in 78.7 % yield the acetylenic alcohol 5 [m/e 304 (M^+), $[\alpha]_D$ - 10.8°][8] which was then converted in 63.9 % yield into the requisite acetylenic alcohol 6 [i.r. ($CHCl_3$) 3600 cm^{-1} (OH), n.m.r. ($CDCl_3$) 0.61 (3H, s, Me), 1.20 (3H, s, Me) and 1.77 (3H, s, -C≡C-Me), m/e 316 (M^+), $[\alpha]_D$ - 14.8°][8] by methylation of the terminal acetylene (MeI, $LiNH_2$, NH_3, THF, - 33°C, 5 h). Finally, this acetylenic alcohol 6 was cyclized in 37.4 % yield [CF_3CO_2H, $(CF_3CO_2)_2O$, - 18°C, 2h; 10 % KOH/EtOH, room temperature, 4 h] resulting in formation in 5α-dihydropregnenolone (7)[9] [m.p. 193 - 194°C, $[\alpha]_D$ + 85.0°][8] which was identical to an authentic sample in all aspects except for the value of the optical rotation [$[\alpha]_D$ + 93.0°][8]. This value indicated the optical purity of our product to be 91.4 % i.e., enantiomeric excess to be 95.7 %.



References and notes

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8. All of rotations were determined in chloroform solution at 20°C.
9. The formation of steric isomer of 7 at C_{17} was also recognized in the n.m.r. spectrum of the crude reaction product.

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