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A NOVEL STEREOCONTROLLED APPROACH TO STEROID SIDE CHAIN CONSTRUCTION : ASYMMETRIC SYNTHESIS OF POTENTIAL SYNTHON OF THE VITAMIN D SERIES

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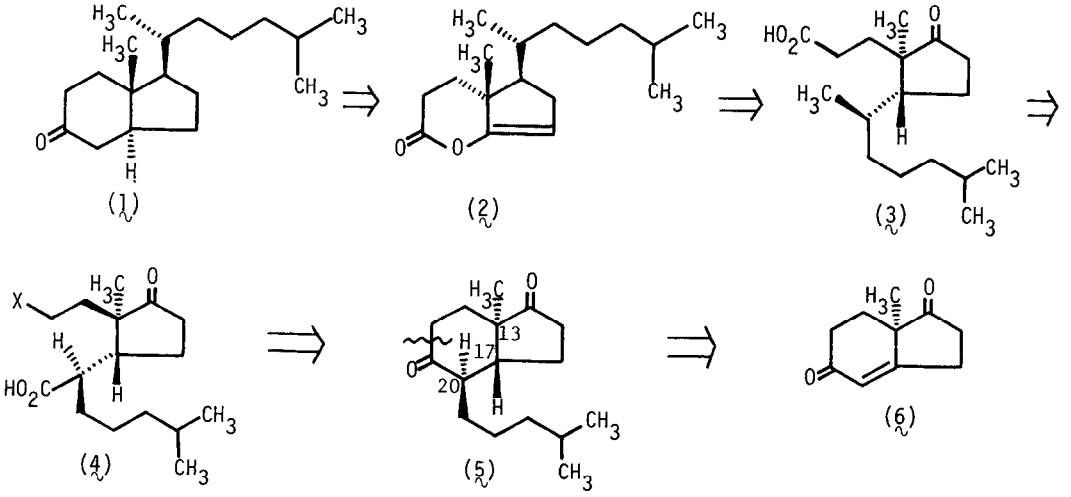
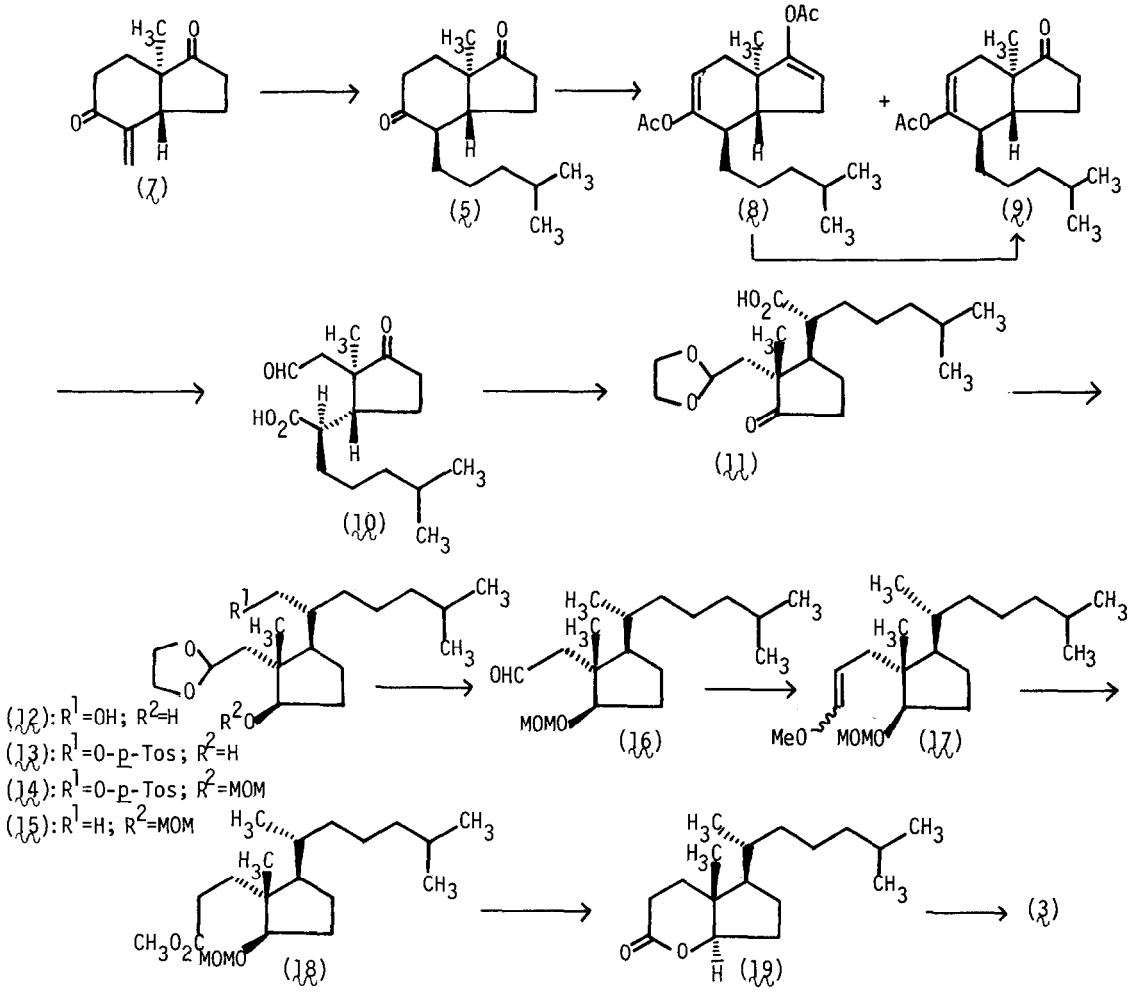
Summary: Stereocontrolled synthesis of (-)-de-AB-8-oxa-cholest-14-en-9-one (2) as an optically active form was achieved starting from the methylene ketone (7). This work constitutes a formal synthesis of de-AB-cholestan (1).

Stereocontrolled construction of steroid side chains including CD-ring system is a major problem in the total synthesis of biologically important steroids and a number of investigations for a solution to this problem have been reported up to date.[1)] In the course of our synthetic study of vitamin D series,[2)] we have investigated the stereocontrolled synthesis of vitamin D synthons and here describe the successful construction of de-AB-8-oxa-cholest-14-en-9-one (2) as an optically active form starting from the methylene ketone (7). The most remarkable feature of our synthetic plan is that the chiralities at C (13), C (17), and C (20) (steroid numbering) are incorporated in the compound 5 as the most stable isomeric form which could be derived from the indenedione (6).



Thus, the methylene ketone (7) [i.r. ($CHCl_3$) 1680 and 1740 cm^{-1}, m/e 178 (M^+)], which was derived from the indenedione (6),[3] was subjected to a 1,4-addition reaction of isoamyl group according to Yamamoto's procedure[4] (isoamylmagnesium bromide, CuI, $BF_3 \cdot Et_2O$, THF, -78°C, 10 min) to give the diketone (5), in 72.8% yield, [i.r. ($CHCl_3$) 1710 and 1740 cm^{-1}, m/e 250 (M^+), $[\alpha]_D$ -95.8° ($CHCl_3$)]. The enol acetylation of 5 (isopropenyl acetate, p-toluenesulfonic acid, reflux, 6 h) afforded the dienol diacetate (8) [i.r. ($CHCl_3$) 1755 cm^{-1}, m/e 334 (M^+), $[\alpha]_D$ -35.2° ($CHCl_3$)] and the enol monoacetate (9) [i.r. ($CHCl_3$) 1740 and 1755 cm^{-1}, m/e 292 (M^+), $[\alpha]_D$ -71.3° ($CHCl_3$)] in a ratio of 2 : 1 in 94% yield, and the diacetate (8) was found to be hydrolysed (LiOH, aqueous THF, 0°C, 3 h) selectively to give the monoacetate (9) in 86% yield. Next, the keto acid (10) which was obtained by the ozonolysis (O_3, CH_2Cl_2, -78°C, 30 min) of 9, followed by the hydrolysis (LiOH, aqueous THF, room temp., 1 h) of the resulting acid anhydride, was converted as usual ($HOCH_2CH_2OH$, camphorsulfonic acid, benzene, reflux, 1.5 h) into the acetal carboxylic acid (11) [i.r. ($CHCl_3$) 1710 and 1740 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 5.15 (1H, d,d J = 4 and 8 Hz, $[\alpha]_D$ -17.6° ($CHCl_3$)] in 70% yield. The transformation of 11 into the methyl derivative (15) was straightforward as follows. The carboxylic acid (11) was subjected to reduction ($LiAlH_4$, THF, room temp., 6 h) to the diol (12) (i.r. ($CHCl_3$) 3450 cm^{-1}, m/e 314 (M^+)] which was converted (p-TsCl, TEA, DMAP, CH_2Cl_2, room temp., 8 h) into the monotosylate (13) [m/e 468 (M^+), $[\alpha]_D$ +21.5°($CHCl_3$)] in 62% yield from 11. The compound (14) [m/e 512 (M^+), $[\alpha]_D$ +11.1° ($CHCl_3$)] prepared in 84.1% yield by the protection (MOMCl, Hünig base, room temp., 10 h) of 13 was then subjected to the reduction ($LiAlH_4$, THF, reflux, 1 h) to give the methyl derivative (15) [m/e 342 (M^+), $[\alpha]_D$ +26.0° ($CHCl_3$)] in 92% yield. The selective deprotection (10% HCl, acetone, room temp., 2 h) of the acetal group of the methyl derivative (15) afforded the aldehyde (16) [i.r. ($CHCl_3$) 1710 cm^{-1}, ^{1}H-NMR (CCl_4) δ 3.25 (3H, s, OCH_3) and 4.47 (2H, s, OCH_2O), $[\alpha]_D$ +10.9° ($CHCl_3$)] in 92% yield and this was transformed into the ester (18) [i.r. ($CHCl_3$) 1730 cm^{-1}, $[\alpha]_D$ +1.3° ($CHCl_3$)] in 72% yield *via* the enol ether (17) [m/e 326 (M^+)] by Wittig reaction[5] ($CH_3OCH_2\overset{\oplus}{P}Ph_2$, LDA, THF, -78°, 10 min, then NaH, THF, room temp., 20 h) followed by oxidation[6] (PCC, CH_2Cl_2, room temp., 20 h) of the resulting enol ether (17). Finally, the lactone (19) [i.r. ($CHCl_3$) 1730 cm^{-1}, m/e 266 (M^+), $[\alpha]_D$ +133.2° ($CHCl_3$)] prepared by the deprotection (10% HCl, acetone, reflux, 4 h) of the ester (18) was hydrolysed (LiOH, aqueous THF, room temp., 1 h) and then oxidized (Jones' reagent, acetone, 0°, 5 min) to afford the keto carboxylic acid (3) ($[\alpha]_D$ -42.3° ($CHCl_3$)] in 81% yield from 18 which was identical by i.r. (neat) and ^{1}H-NMR ($CDCl_3$, 300 MHz) spectral comparison with the authentic sample.[1m] The keto carboxylic acid (3) thus obtained was transformed into the enol lactone (2) ($[\alpha]_D$ -32.5° ($CHCl_3$)) according to the known procedure.[1m]

Thus, the synthetic strategy described above provides a new method for the stereoselective construction of steroid side chains including CD-ring system.



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