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A STEREOSELECTIVE SYNTHESIS OF 1α-HYDROXY-VITAMIN D_3

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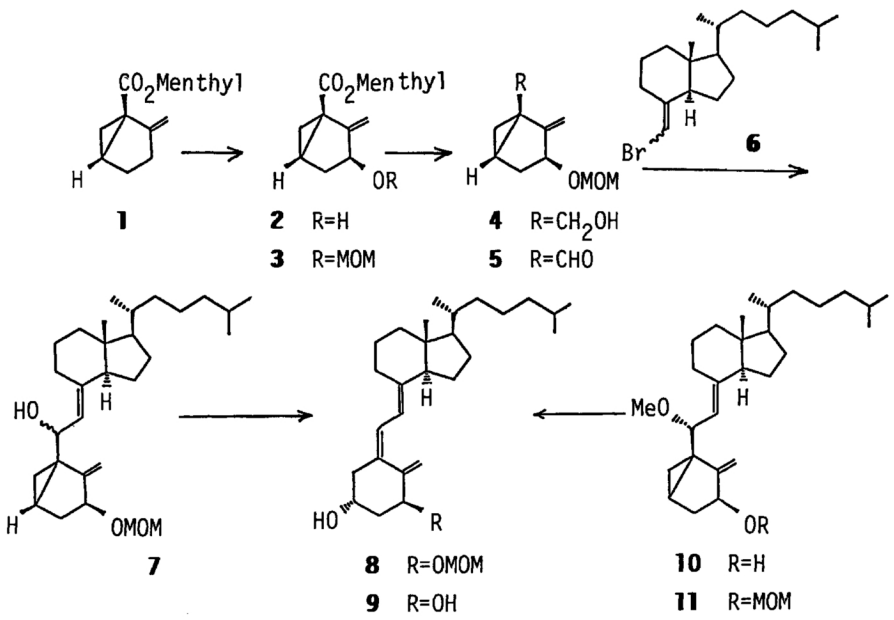
A stereoselective synthesis of 1α-hydroxy-vitamin D_3 was achieved through the solvolysis of the 3,5-cyclovitamin D_3 which was prepared from (-)-(3S,5R)-2-methylene-3-methoxymethyloxybicyclo[3.1.0]hexanecarboxaldehyde and the des-AB-8-bromomethylene-cholestane.

Recently it has been proposed that the primary requirement for activiy in vitamin D analogues is the presence of a 1α-hydroxy group,[1-3] and synthetic 1α-hydroxy-vitamin D_3 (**9**) is now being used in the clinical treatment of nephritic bone disease in humans. These facts prompted us to explore an effective synthetic pathway to 1α-hydroxy-vitamin D_3 (**9**).

Thus, the known optically pure methylene ester (**1**)[4] was firstly oxidized (SeO_2, ^tBuOOH, CH_2Cl_2, room temperature, 1 h) to the allyl alcohol (**2**) [IR ($CHCl_3$) 3600 and 1720 cm^{-1}, ^1H NMR($CDCl_3$) δ 3.85-4.50(1H, m, C_3-H), m/z 292 (M^+), $[\alpha]_D^{20}$ -72.7°(c 2.96, $CHCl_3$)] in 37% yield. The MOM ether (**3**) [m/z 336 (M^+), $[\alpha]_D^{20}$ -80.6°(c 0.96, $CHCl_3$)] prepared in 80% yield by the protection (MOMCl, Hunig base, room temperature, 10 h) of **2** was then subjected to the reduction ($LiAlH_4$, THF, room temperature, 1 h) to give the alcohol (**4**) [IR ($CHCl_3$) 3450 cm^{-1}, m/z 184 (M^+), $[\alpha]_D^{20}$ + 32.6°(c 0.64, $CHCl_3$)] in 92% yield and this alcohol (**4**) was then oxidized (PCC, CH_2Cl_2, room temperature, 2 h) to give the aldehyde (**5**)[5] [m/z 182 (M^+), $[\alpha]_D^{20}$-39.7°(c 0.68, $CHCl_3$)] in 76% yield. Next, the vinyl bromide (**6**)[6] was metallated (^tBuLi, THF, -78 °C, 1 h) and coupled with the chiral aldehyde (**5**) to produce in 34% yield the alcohol (**7**)[7] [m/z 444 (M^+)] as a mixture of stereoisomers. The epimeric alcohols (**7**) thus obtained were subjected to the solvolysis (p-TsOH, aq dioxane, 55 °C, 5 min) to give the protected 1α-hydroxy-vitamin D_3 (**8**)[8] [m/z 444 (M^+), $[\alpha]_D^{20}$+25.5°(c 1.37, $CHCl_3$)] in 77% yield. This compound (**8**) was identical with an authentic sample including optical rotation which was synthesized by the solvolysis (p-TsOH, aq dioxane, 55 °C, 5 min) of the compound (**11**) [m/z 458 (M^+)] prepared in turn by the protection (MOMCl, Hunig base, room temperature, 5 h) of the known alcohol (**10**).[9] Finally, the compound (**8**) was deprotected (conc HCl, MeOH, 60 °C, 3.5 h) to furnish 1α-hydroxy-vitamin D_3 (**9**) in 39% yield.

Thus, we could disclose an effective pathway to 1α-hydroxy-vitamin D_3.



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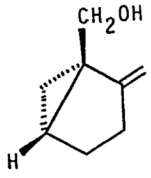

5) **5**: IR($CHCl_3$) 1700, 1650 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.16(1H, t, J=4 Hz), 3.36(3H, s), 4.06-4.50(1H, m), 4.66(2H, s), 5.31, 5.66(2H, each d, J=2 Hz), 9.51(1H, s). Anal. Found: 182.0929(M^+). Calcd for $C_{10}H_{14}O_3$: 182.0941(M).

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7) **7**: IR($CHCl_3$) 3600 cm^{-1}. Anal. Found: 444.3583(M^+). Calcd for $C_{19}H_{48}O_3$: 444.3603(M)

8) **8**: IR($CHCl_3$) 3590 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.50(3H, s), 0.83(6H, d, J=6 Hz), 0.86(3H, d, J=6 Hz), 3.30(3H, s), 3.92-4.35(2H, m), 4,45(1H, d, J=6 Hz), 4.65(1H, d, J=6 Hz), 5.05(1H, d, J=2 Hz), 5.26(1H, d, J=2 Hz), 5.93(1H, d, J=10 Hz), 6.35(1H, d, J=10 Hz). Anal. Found: 444.3568(M^+). Calcd for $C_{19}H_{48}O_3$: 444.3603 (M).

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