

A STEREOSELECTIVE SYNTHESIS OF 1 α -HYDROXY-VITAMIN D₃

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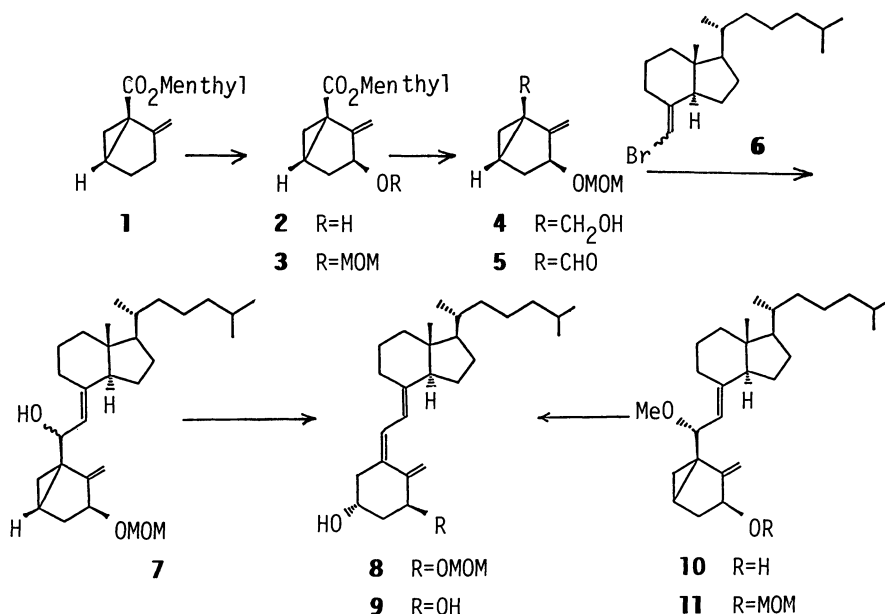
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A stereoselective synthesis of 1 α -hydroxy-vitamin D₃ was achieved through the solvolysis of the 3,5-cyclovitamin D₃ which was prepared from (-)-(3S,5R)-2-methylene-3-methoxymethyloxycyclo[3.1.0]hexanecarboxaldehyde and the des-AB-8-bromomethylene-cholestane.

Recently it has been proposed that the primary requirement for activity in vitamin D analogues is the presence of a 1 α -hydroxy group,¹⁻³⁾ and synthetic 1 α -hydroxy-vitamin D₃ (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 1 α -hydroxy-vitamin D₃ (9).

Thus, the known optically pure methylene ester (1)⁴⁾ was firstly oxidized (SeO₂, ^tBuOOH, CH₂Cl₂, room temperature, 1 h) to the allyl alcohol (2) [IR (CHCl₃) 3600 and 1720 cm⁻¹, ¹H NMR(CDCl₃) δ 3.85-4.50(1H, m, C₃-H), m/z 292 (M⁺), [α]_D²⁰ -72.7°(c 2.96, CHCl₃)] in 37% yield. The MOM ether (3) [m/z 336 (M⁺), [α]_D²⁰ -80.6°(c 0.96, CHCl₃)] prepared in 80% yield by the protection (MOMCl, Hunig base, room temperature, 10 h) of 2 was then subjected to the reduction (LiAlH₄, THF, room temperature, 1 h) to give the alcohol (4) [IR (CHCl₃) 3450 cm⁻¹, m/z 184 (M⁺), [α]_D²⁰ +32.6°(c 0.64, CHCl₃)] in 92% yield and this alcohol (4) was then oxidized (PCC, CH₂Cl₂, room temperature, 2 h) to give the aldehyde (5)⁵⁾ [m/z 182 (M⁺), [α]_D²⁰ -39.7°(c 0.68, CHCl₃)] 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 1 α -hydroxy-vitamin D₃ (8)⁸⁾ [m/z 444 (M⁺), [α]_D²⁰ +25.5°(c 1.37, CHCl₃)] 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 1 α -hydroxy-vitamin D₃ (9) in 39% yield.

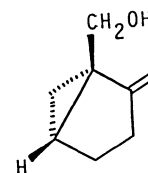
Thus, we could disclose an effective pathway to 1 α -hydroxy-vitamin D₃.



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References

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- 3) A. W. Norman, M. N. Mitra, W. H. Okamura, and R. M. Wing, *Science*, **188**, 1013 (1975).
- 4) S. R. Wilson, M. S. Haque, A. M. Venkatesan, and P. A. Zucker, *Tetrahedron Lett.*, **25**, 3151 (1984). The absolute configuration of this sample was confirmed independently by converting into the olefinic alcohol derivative (i) which had been prepared by us⁶⁾ previously.
- 5) **5**: IR(CHCl_3) 1700, 1650 cm^{-1} ; $^1\text{H NMR}(\text{CDCl}_3)$ 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 $\text{C}_{10}\text{H}_{14}\text{O}_3$: 182.0941(M).
- 6) H. Nemoto, X.-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, **25**, 3095 (1984).
- 7) **7**: IR(CHCl_3) 3600 cm^{-1} . Anal. Found: 444.3583(M^+). Calcd for $\text{C}_{19}\text{H}_{48}\text{O}_3$: 444.3603(M).
- 8) **8**: IR(CHCl_3) 3590 cm^{-1} ; $^1\text{H NMR}(\text{CDCl}_3)$ 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 $\text{C}_{19}\text{H}_{48}\text{O}_3$: 444.3603 (M).
- 9) H. E. Paaren, H. F. DeLuca, and H. K. Schnoes, *J. Org. Chem.*, **45**, 3253 (1980).



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