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SYNTHETIC STUDIES TOWARD TO 1α-HYDROXYVITAMIN D_3 —— STEREOSELECTIVE SYNTHESIS OF (±)-(Z)-2-(3β,5α-DIHYDROXY-2-METHYLENECYCLOHEXYLIDENE)ETHYLIDENECYCLOHEXANE

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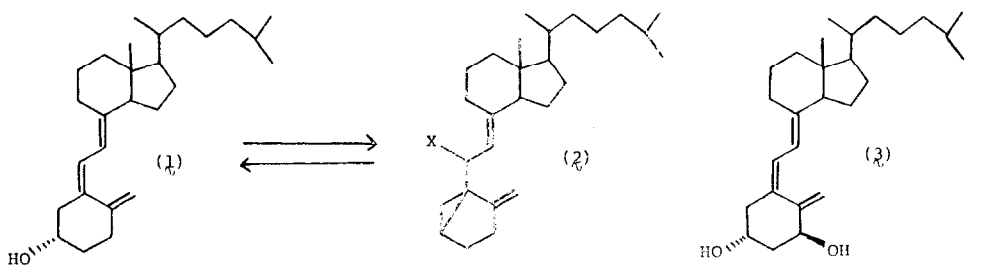
Summary: As a model experiment for a synthesis of 1α-hydroxyvitamin D_3, the title compound (19) was stereoselectively synthesized *via* the solvolysis of (±)-2-hydroxy-2-[(3β-methoxymethoxy-2-methylenebicyclo[3.1.0]hexane)-1]ethylidenecyclohexane (15).

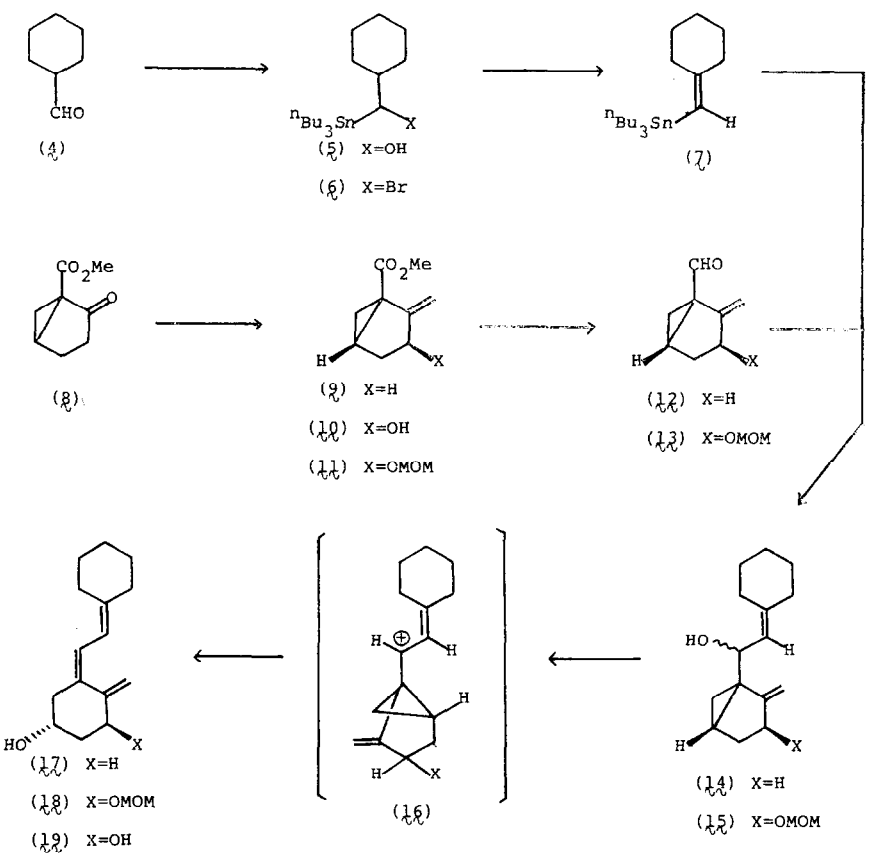
In the course of our synthetic study of vitamin D[1], we attentioned the Mazur's report, the conversion of vitamin D_3 (1) to 3,5-cyclovitamin D_3 (2) and their stereoselective reconversion to the starting vitamin D_3[2]. On the basis of this observation, a stereocontrolled total synthesis of 1α-hydroxyvitamin D_3 (3), the highly biological active analog of cholecalciferol, has been planned *via* the 3,5-cyclo compound. Here we wish to describe a stereoselective synthesis of (±)-(Z)-2-(3β,5α-dihydroxy-2-methylenecyclohexylidene)ethylidenecyclohexane (19) according to this strategy as a model experiment.



Synthesis of bicyclo[3.1.0]hexyl alcohol (15) was achieved by the coupling reaction between the aldehyde (13) having the requisite functionalities of the ring A and the vinyl anion derived from the organostannane (7) according to the Still's method[3]. Thus, treatment of cyclohexanecarboxaldehyde (4) with tributylstannyllithium, prepared by reaction of tributylstannyl chloride and lithium in tetrahydrofuran, at -78°C for 5 min gave the stannylcarbinol (5), which was converted, without purification, into the bromide (6) on the reaction with triphenylphosphine and carbon tetrabromide in methylene chloride at room temperature for 2 h [4,5]. Dehydrobromination of 6 with 1,5-diazabicyclo[5.4.0]undecene-5 in a mixture of dimethylformamide and toluene under reflux for 2 h afforded, in 64 % yield, the olefin (7), ^{1}H-NMR ($CDCl_3$) δ 5.24 (1H, d, J = 4 Hz). The coupling reaction was firstly examined using 2-methylenebicyclo[3.1.0]hexane-1-carboxaldehyde (12), which was prepared from methyl 2-oxo-bicyclo[3.1.0]hexane-1-carboxylate (8)[6] in three steps; Wittig reaction using triphenylmethylphosphonium bromide and n-butyllithium in tetrahydrofuran (47 %), reduction with lithium aluminum hydride and oxidation with pyridinium chlorochromate (PCC) in dichloromethane [85 % from the exomethylene compound (9)]. Coupling proceeded *via* lithiation of 7 with n-butyllithium[3] in tetrahydrofuran at -20°C for 2 h, followed by addition of the aldehyde (12) at -78°C. After stirring for 30 min at -78°C, the product (14), m/e 218 (M^+), was isolated in 76.1 % yield by column chromatography on silica gel. The product was homogeneous on TLC and the ratio of two epimers could not be established by ^{1}H-NMR spectroscopy utilizing shift reagents[7]. Solvolysis was conducted by heating 14 in the presence of catalytic amount of p-toluenesulfonic acid in aqueous dioxane at 55°C for 10 min to give the Z-triene (17) in 66.3 % yield. No formation of E-isomer was observed. The UV spectrum, (MeOH) 260 nm (ε 10,500), of 17, m/e 218 (M^+), indicated the Z-configuration and the ^{1}H-NMR spectrum showed the following signals, ($CDCl_3$) δ 3.89 (1H, m), 4.82 (1H, m, ΔWh/2 = 4 Hz), 5.05 (1H, d, J = 3 Hz), 6.12 (2H, s), which were consistent with the reported ones[8].

The aldehyde possessing a protecting hydroxyl group at C_3 position was obtained *via* the allylic oxidation of 9 with selenium dioxide and t-butyl hydroperoxide[9,10] in methylene chloride. The β-hydroxylated compound (10) was predominantly formed over the α-hydroxy isomer. The oxidation of the α-hydroxy com-

pound to the corresponding ketone was faster than that of the former (10)[10]. Therefore the oxidation for 3 h at room temperature followed by purification of the products by column chromatography gave 10 in 41.3 % yield and the ketone in 33.6 % yield. The hydroxyl group was protected as methoxymethyl (MOM) ether (11) (96 %) by the action of methoxymethyl chloride in the presence of diisopropylethylamine. The ester (11) was transformed, by lithium aluminum hydride reduction (83.4 %) and PCC oxidation (71 %), into the aldehyde (13). Coupling reaction under the same reaction conditions as above gave, in 76.8 % yield, the epimeric alcohols (15), m/e 278 (M^+); NMR ($CDCl_3$) δ 0.56 (1H, t, J = 4 Hz), 3.38 (3H, s), 4.14 (1H, m), 4.68 (2H, s), 4.84 (2H, m), 5.18 (2H, m), which were inseparable. Solvolysis of 15 as above gave the desired Z-triene (18), in 65.3 % yield, m/e 278 (M^+); UV (Et_2O) 265 nm (ε 13,200); ^{1}H-NMR ($CDCl_3$) δ 3.36 (3H, s), 4.16 (1H, m), 4.28 (1H, m), 4.58 (2H, m), 5.20 (2H, m), 6.04 and 6.30 (each 1H, each d, J = 12 Hz), as a sole product. Deprotection of the MOM group by heating



18 in the presence of small amount of conc. hydrochloric acid in methanol at 60°C for 1.5 h produced in 69.5 % yield, the diol (19), mp 118 - 119°C, m/e 234 (M^+); UV (Et_2O) 261 nm (ε 18,400); ^{1}H-NMR ($CDCl_3$) δ 4.20 (1H, m), 4.41 (1H, m), 5.00 (1H, br s), 5.31 (1H, br s), 6.16 and 6.32 (each 1H, each d, J = 12 Hz). Such high stereoselective formation of Z-trienes would be accounted by the solvolysis via the thermodynamically preferred carbonium ion intermediate (16). Thus the above synthetic strategy would provide an efficient synthetic route to 1α-hydroxyvitamin D_3.

References and Notes

1) The previous synthetic study from these laboratories; H. Nemoto, K. Suzuki, M. Tsubuki, K. Minemura, K. Fukumoto, T. Kametani, H. Furuyama, Tetrahedron, 39, 1123 (1983).

2) M. Sheves, Y. Mazur, J. Am. Chem. Soc., 97, 6249 (1975).

3) W. C. Still, J. Am. Chem. Soc., 100, 1481 (1978).

4) R. G. Weiss, E. I. Snyder, J. Org. Chem., 36, 403 (1971).

5) Y. Torisawa, M. Shibasaki, S. Ikegami, Tetrahedron Lett., 22, 2397 (1981).

6) K. Kondo, E. Hiro, D. Tunemoto, Tetrahedron Lett., 4489 (1976).

7) M. Sheves, Y. Mazur, Tetrahedron Lett., 2987 (1976).

8) J. V. Frosch, I. T. Harrison, B. Lythgoe, A. K. Saksena, J. Chem. Soc., Perkin I, 2005 (1974).

9) D. Arigoni, A. Vasella, H. P. Jensen, K. B. Sharpless, J. Am. Chem. Soc., 95, 7917 (1973).

10) H. E. Paaren, H. F. Dehuca, H. K. Schnoes, J. Org. Chem., 45, 3253 (1980).

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