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An Enantioselective Synthesis of the A-Ring Synthon for Vitamin D_3 Metabolites by Chemicoenzymatic Approach

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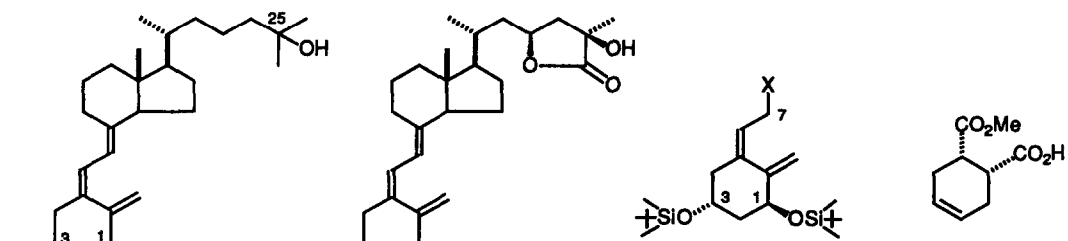
Summary: The A-ring synthon for vitamin D_3 metabolites having 1α-hydroxyl group is synthesized starting from a chiral monoester **6** enzymatically generated.

In addition to the well-recognized role in calcium regulation[1], 1α,25-dihydroxy-vitamin D_3 (**1**) was found to induce cell differentiation of myeloid leukemia cells[2], and a molecular design toward the separation of these potent physiological activities has been a major concern from a medicinal point of view[3]. Structurally, A-ring moiety of **1** is also seen in other interesting vitamin D_3 metabolites such as calcitriol lactone **2**[4]. Thus, the development of an efficient route to the A-ring synthon with 1α-hydroxyl group is indeed demanding for exploitation of the structure-activity relationships of such potent compounds.

Scheme 1



Among several A-ring synthons so far been developed[5], phosphine oxide **3a**, or its equivalent dienol **3b**, is most attractive because of the efficiency in the coupling with CD-ring synthons[6]. We report here the synthesis of dienol **3b**[7] starting from a chiral monoester **4**[8]. Monoester **4** seemed to be an excellent chiral synthon for the synthesis of **3** considering the carbon skeleton (only one carbon corresponding to C-7[9] is missing in **4**) as well as a suitable array of functional groups.

Since introduction of hydroxyl group at C-3 was already established[10], crucial points in the present approach are the stereoselective hydroxylation at C-1 and the construction of dienol group with *Z* stereochemistry.

The synthesis started with the introduction of a hydroxyl group at C-3. Thus, monoester **4** was first converted to lactone **5**[11] in 75% yield. [(1) $ClCO_2Et$, Et_3N/THF, 0°C, then $NaBH_4$/THF-H_2O, 0°C; (2) *p*-TsOH/benzene, r.t.] After hydrolysis of the lactone, resulting sodium carboxylate was directly subjected to an iodolactonization to afford the hydroxyiodolactone **6**, and subsequent silylation of **6** gave iodolactone **7** in 95% overall yield from **5**. [(1) NaOH/H_2O-THF, r.t.; (2) I_2, KI/CH_2Cl_2-H_2O, r.t.; (3) TBDMSCl, imidazole/DMF, r.t.] On heating with DBU in toluene, iodolactone **7** underwent smooth elimination to give olefin **8**[10] in 99% yield.

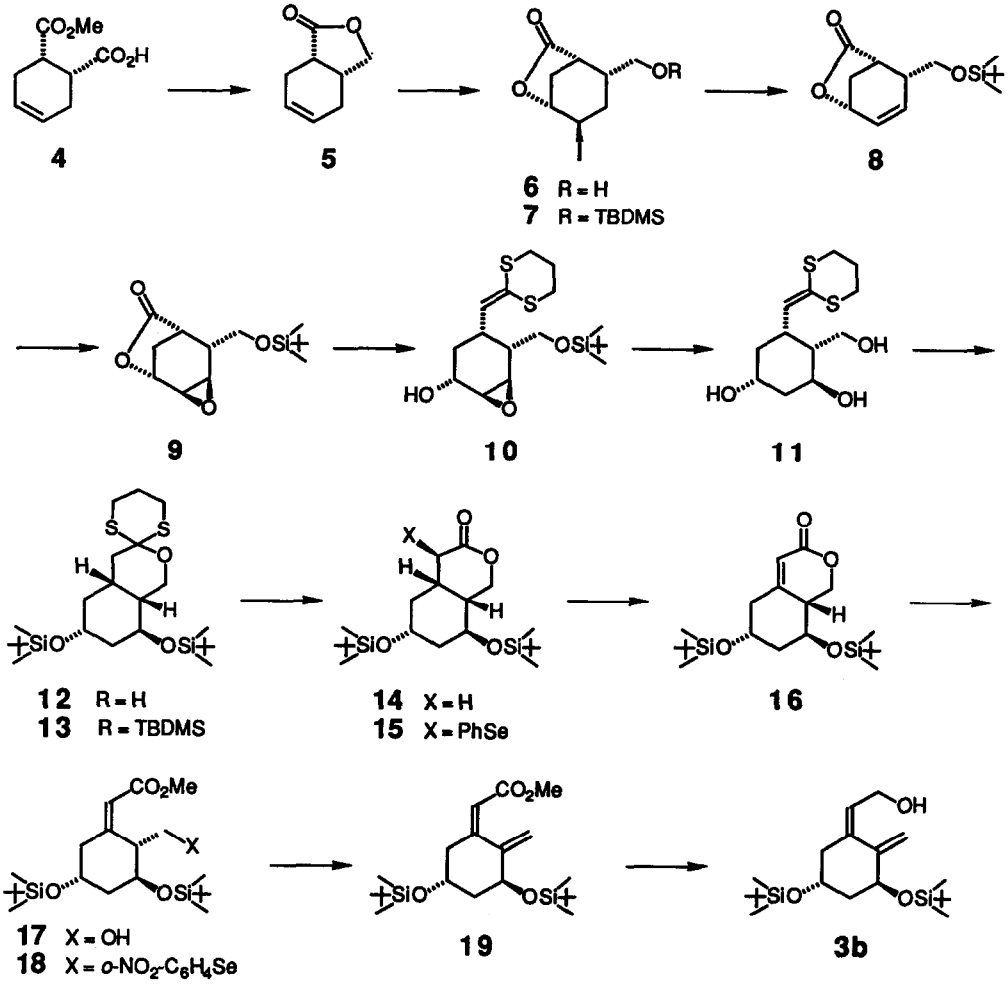
Introduction of 1α-hydroxyl group into **8** was examined next. Initial attempts such as hydroboration or hydrosilylation to the C-C double bond of **8** were all unsuccessful, and alternative epoxidation-reduction approach was then examined. We anticipated that epoxidation of bicyclic **8** would occur from *convex* face, and that reduction of the epoxide would proceed in the desired sense by the participation of a hydroxyl group at C-3 affording 1,3-diol[12].

β-Epoxide **9** was isolated in 89% yield as a single isomer on treatment of **8** with MCPBA. Prior to the reduction of the epoxide, lactone **9** was reduced to a lactol [DIBAL/toluene, -78°C], and the latter was subsequently reacted with 2-lithio-2-trimethylsilyl-1,3-dithiane[13] to obtain ketenedithioacetal **10** (62% yield from **9**) furnishing the carbon skeleton of **3b**. Epoxyalcohol **10** was found to undergo regioselective cleavage by the reaction with $LiAlH_4$[14] in THF at room temperature[15], thereby deprotection of TBDMS group also accompanied giving triol **11**. Crude triol **11** was treated with a catalytic amount of *p*-TsOH in THF affording dithioorthoester **12** in 83% yield from **10**. No formation of 1,2-diol was detected, and the remarkable regioselectivities[14] might be due to both steric reason and neighboring participation described above. Protection of the remaining two hydroxyl groups and subsequent hydrolysis of dithiane group afforded δ–lactone **14**. [(1) TBDMSCl, imidazole/DMF, r.t., 86%; (2) NBS/aq. acetone[16], -15°C, 81%]

With two hydroxyl groups at C-1 and C-3 established, the formation of exocyclic diene with *Z* stereochemistry was attempted next. In the present approach, α,β-unsaturated δ-lactone **16** served as a key intermediate, in which *Z* stereochemistry is already fixed as a part of δ-lactone structure. Unsaturated lactone **16** was obtained in 66% yield from **14** through phenylselenide **15**. [(1) LDA, PhSeBr[17]/THF, -78°C; (2) H_2O_2/THF, 0°C~r.t.]

Unsaturated δ-lactone **16** was cleanly opened by alkaline hydrolysis, and resulting carboxylic acid was methylated with CH_2N_2 to obtain methyl ester **17**. [(1) NaOH/H_2O-MeOH, r.t.; (2) CH_2N_2/Et_2O, 0°C, 81% (two steps)] Treatment with other nucleophiles such as NaOMe or $PhSe^-$ resulted the complex mixture of products. Conversion of alcohol **17** into diene **19** was achieved by means of selenoxide elimination [(1) *o*-NO_2-C_6H_4SeCN, *n*-Bu_3P[18]/THF, r.t. 84%; (2) H_2O_2/THF, 0°C~r.t., 81%], and finally dienol **3b** was obtained as a nicely crystalline material [m.p. 68~69°C,

Scheme 2



$[\alpha]_D^{25}$ +7.9°(*c* 0.4, EtOH); *lit.*[5b]; m.p. 69~71°C, $[\alpha]_D^{25}$ +7.9°(*c* 0.4, EtOH)] by reduction of **19** with DIBAL [toluene, -78°C, 87%]. Spectral data of synthetic **3b** were in good accordance with reported data[5b]. Thus, the A-ring synthon of vitamin D_3 metabolites having 1α-hydroxyl group is synthesized from chiral monoester **6** under complete stereo- and regio- chemical control.

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