An Efficient Solid-Phase Synthesis of the Vitamin D_3 System

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1α,25-Dihydroxyvitamin D_3 (calcitriol) (**1**) is well-known as the hormonally active form of vitamin D_3, whose physiological activities include regulation of cell differentiation and proliferation, intestinal calcium absorption, bone mobilization, and bone formation.[1] These properties have stimulated significant efforts toward the synthesis of various calcitriol analogues having modified side chains and having some A-ring derivatives.[2] However, there is no report of a convenient method for the preparation of a library of vitamin D_3 analogues having modified side chains and modified A-ring moieties at the same time.[3] We anticipated that a key component for constructing a library of vitamin D_3 analogues is the ability to simply and efficiently couple A-ring moieties, CD-rings, and side chains. The combination of a variety of these three components could provide a large array of analogues if this can be performed on solid-phase resins. Recently, solid-phase synthesis has become a powerful tool for the preparation of not only oligopeptides and oligonucleotides but also small molecule libraries.[4] We report here the novel solid-phase synthesis of the vitamin D_3 system, obtained by efficient coupling of the solid-supported CD-ring with modified A-ring moieties, followed by immediate alkylation with a side chain.

The 11-hydroxy CD-ring **8** is a key intermediate, and our strategy is outlined in Scheme 1. The hydroxy group at the 11-position is used for loading to the polymer resin and the attached group should not affect the subsequent two steps, that is:[5] (i) Horner−Wittig reaction of A-ring moieties **5** to the polymer-supported 8-keto CD-ring **4**,[6−8] (ii) alkylation of the polymer-supported tosylate at the 22-position with the Grignard reagent **6**. The trialkylsilane linker was chosen to attach the polymer support because silyl protection has proven to be effective in the synthesis of various vitamin D_3 analogues and is readily cleaved smoothly even in the presence of the unstable triene moiety. To avoid facile epimerization at the 14-position adjacent to the carbonyl group, Horner−Wittig reaction of an A-ring moiety to the polymer-supported 8-keto CD-ring is performed initially, giving rise to the triene system of the vitamin D_3 in the presence of a tosylate. Alkylation of a tosyl group at the 22-position of the polymer-support with a Grignard reagent will afford the vitamin D_3 system,[9] if it can be performed at sufficiently low temperature to avoid isomerization of the triene system. ED-71 (**2**) which has three hydroxy units on the A-ring is a promising candidate for osteoporosis therapy[10] and has regulatory activities for calcium metabolism. Contemplating the construction of a big library of A-ring analogues by changing either the alkoxy group or the stereogenic centers, we attempted solid-phase syntheses of 11-hydroxylated ED-71 analogue **3a** and 1α,25-$(OH)_2$-vitamin D_3 analogue **3b**.

The A-ring moiety **5a** was prepared as follows. Nitrile **9** was synthesized according to our previously reported procedure.[11] Protection of the hydroxy group of **9** by TBS, followed by DIBAL reduction of the nitrile afforded an aldehyde, which was oxidized to acid **10**. Acid **10** was treated with carbonyl diimidazole, followed by the addition of magnesium ethyl malonate, to provide β-keto ester **11**.[12] The (*Z*)-enolate[13] formed by the treatment of **11** with sodium hydride was trapped as a triflate, and the ethyl ester was reduced with DIBAL to yield alcohol **12**. Palladium-(0)-catalyzed cyclization was carried out as previously reported.[14] The reaction proceeded smoothly at room temperature to furnish cyclized (*Z*)-diene **13** in 87% yield, exclusively, without formation of (*E*)-diene.[13] Dienyl alcohol **13** was chlorinated (MsCl/LiCl/DMF), and was converted to the phosphine oxide **5a** according to the literature procedure[6−8,15] (Scheme 2).

The β-hydroxyketone **8** was prepared from the Inhoffen−Lythgoe diol,[16,17] and was loaded on chlorinated PS-DES resin (0.74 mmol/g).[18] The loading yield was determined to be 66% by cleavage with HF·Py in THF from the solid support.[19] Horner−Wittig reaction of resin **4** with lithiated **5a** in THF at −78 °C to −40 °C yielded triene **14**. Acid cleavage gave the corresponding 11-hydroxy compound, whose characterization showed exclusive formation of the triene system and no epimerization at the 14-position. Coupling of tosylate **14** with Grignard reagent **6** at −10

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(9) In most of precedent syntheses of vitamin D_3 derivatives, Grignard coupling reaction was initially carried out with a CD-ring that possesses not 8-keto but 8-hydroxy group. Then, the hydroxy group was oxidized to provide an 8-keto compound, which underwent Horner−Wittig olefination leading to the vitamin D_3 system. There are only a few examples for alkylation of tosylate at the 22-position in the presence of triene system with Grignard reagent. Especially, few examples of alkylation have been reported using 3-alkoxy-3-methylbutyl Grignard reagent for the direct formation of the side chain of vitamin D_3 system; see: Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819.

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(13) NOE (9%) was observed between H_4 and H_6.

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(19) The resin **4** was identified by IR absorption, 1714 (C═O), 1174 (OTs) cm^{-1}, whose bands completely disappeared after acid cleavage.

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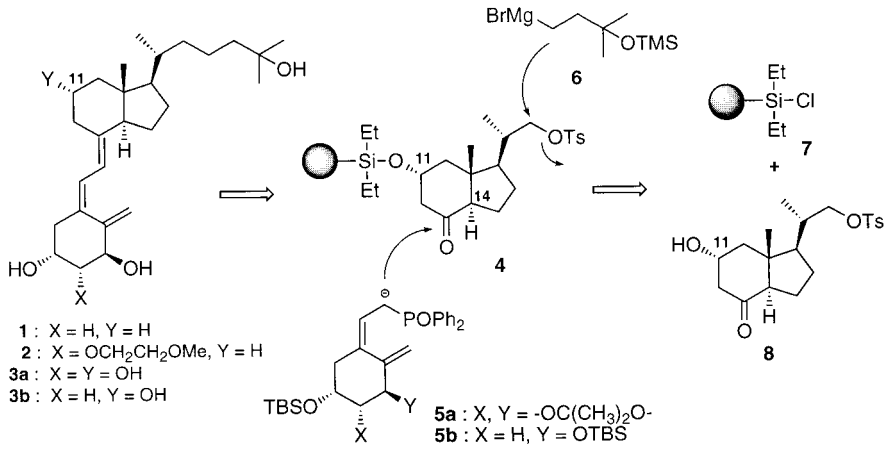
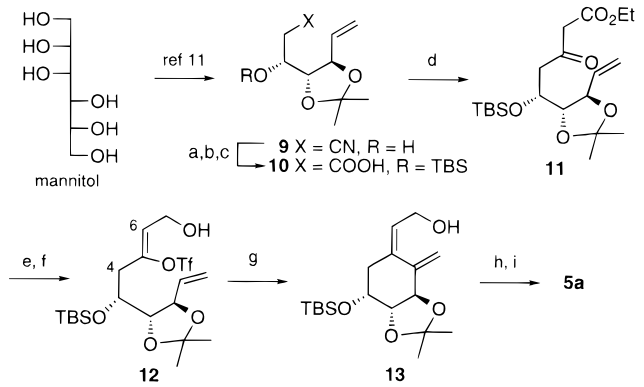
Scheme 1

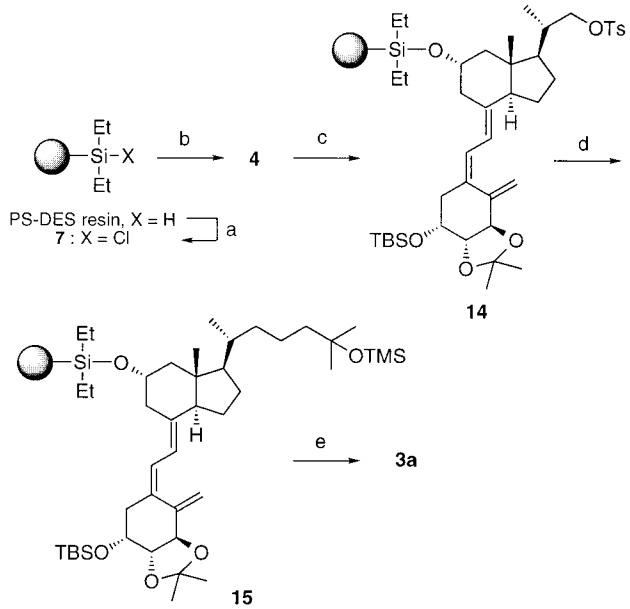


Scheme 2[a]



[a] (a) TBSCl, imidazole, 98%; (b) DIBAL, 83%; (c) $NaClO_4$, NaH_2PO_4, 2-methyl-2-butene, 100%; (d) CDI, $(EtOCOCH_2CO_2)_2Mg$, 99%; (e) NaH, Tf_2NPh, THF, 63%; (f) DIBAL, 96%; (g) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), NEt_3 (2 equiv), DMF, rt, 87%; (h) MsCl, LiCl, lutidine, 85%; (i) *n*-BuLi, Ph_2PH, THF; 5% H_2O_2, 81%.

Scheme 3[a]



[a] (a) 1,3-Dichloro-5,5-dimethylhydantoin (3 equiv), CH_2Cl_2, rt, 1 h; (b) **8** (4 equiv), imidazole (4.5 equiv), CH_2Cl_2, rt, 6 h (66%); (c) **5a** (8 equiv), *n*-BuLi (7.5 equiv), THF −78 to −40 °C, 4 h; (d) **6** (30 equiv, 0.45 M), $CuBr \cdot Me_2S$ (3 equiv), THF, −10 °C, 6 h; (e) HF·Py, THF, rt, 24 h, 62% (from resin **4**).

°C led to the alkylation product **15**.[20] Finally, treatment of **15** with HF·Py in THF at room temperature for 24 h released the desired vitamin D_3 system **3a** (Scheme 3). Simple filtration through silica gel provided a white powder **3a** in 62% overall yield from **4**. The purity of the final product, judging by HPLC analysis, was high, and there is no epimerization at the 14-position of ketone **4** and no triene isomerization under these conditions. This procedure could also be applied to an activated vitamin D_3 analogue. Starting from **5b**,[7,8] the solid-phase synthesis described above (Horner−Wittig reaction with **4**, alkylation with Grignard reagent **6**, and the cleavage from the resin) afforded **3b** (>95% pure) in 61% overall yield.

We have demonstrated an efficient and general strategy for the solid-phase synthesis of vitamin D_3 systems. This strategy promises to overcome the required two carbon−carbon bond-forming steps on the solid-phase, resulting in the consecutive coupling of the CD-ring with the A-ring and side-chain moieties. This solid-phase synthesis will be a powerful method for the preparation of a variety of vitamin D_3 derivatives.

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Supporting Information Available: Experimental information, including experimental procedures for **5a**, **3a**, and **3b**, 270 MHz ^1H NMR and 67.8 MHz ^{13}C NMR spectra of **3a**, **3b**, **5a**, **9**−**13**, IR spectra of resins **4**, **14**, and **15**, and details of the preparation of **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The alkylation by means of the chloride salt of the Grignard reagent instead of the bromide salt **6** was unsuccessful. There are few reports using an alkoxy Grignard reagent in the alkylation at the 22-position on the steroid system, see: Nakagawa, M. Ph.D. thesis, University of Tokyo, 1993 and ref 9.