

Application of Ring-Closing Metathesis to the Synthesis of 19-Functionalized Derivatives of 1 α -Hydroxyvitamin D₃

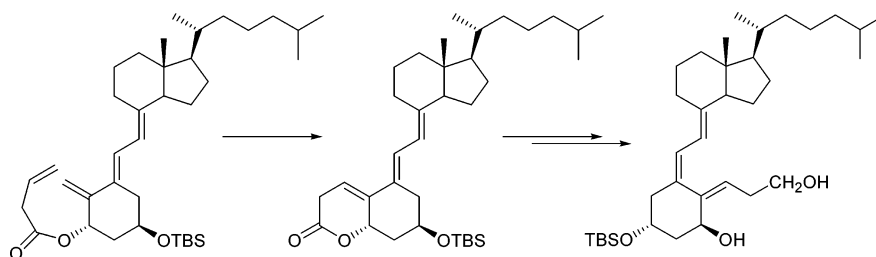
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ABSTRACT



The synthesis of the 19-functionalized derivative of vitamin D₃ based on ring-closing metathesis (RCM) is presented.

A hormonally active metabolite of vitamin D₃, 1 α ,25-dihydroxyvitamin D₃, exhibits, besides the regulation of calcium and phosphorus homeostasis, a variety of biological activities such as cell differentiation and proliferation.¹ Since this discovery, extensive studies to find analogues with selective activity profiles as potential therapeutic agents have been undertaken. Over the past two decades many vitamin D derivatives containing modification in A, C, or D rings as well as in the side chain have been synthesized.² However, only a few methods of synthesis of 19-functionalized compounds have been described so far.³

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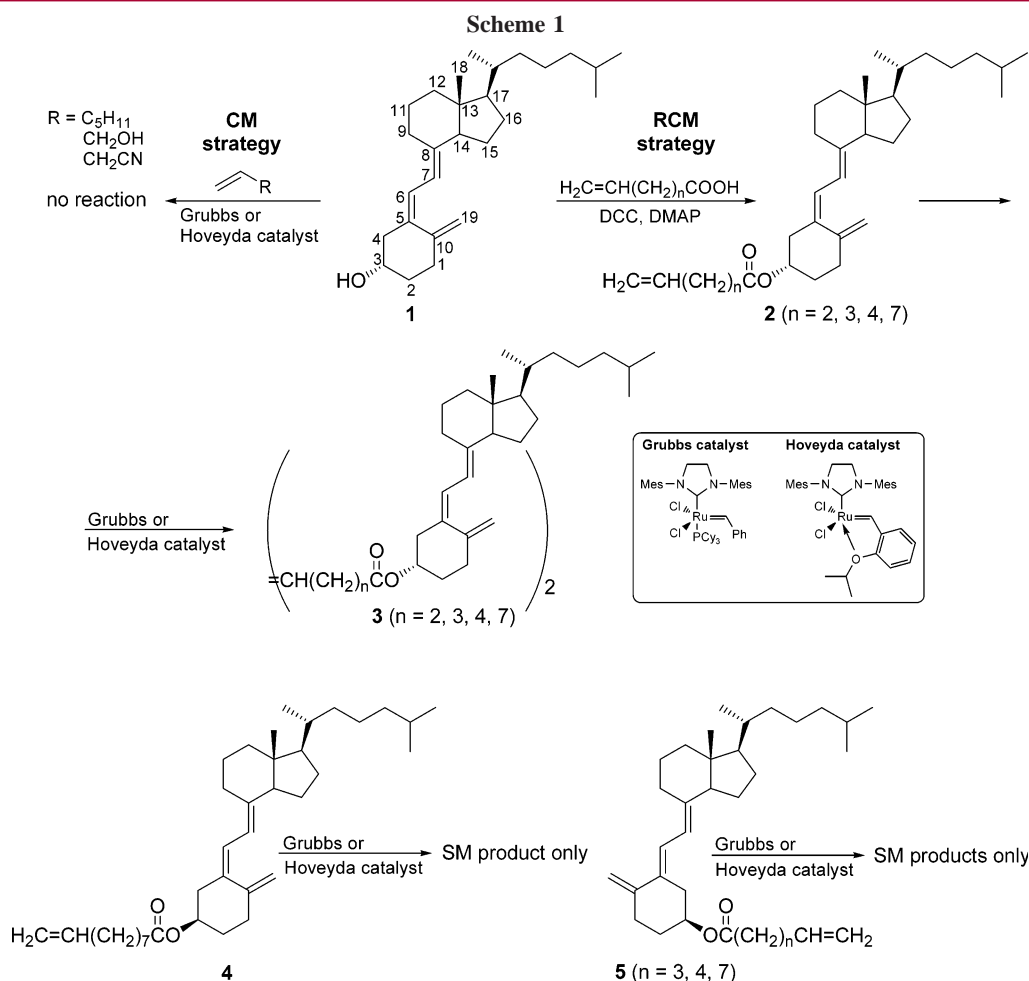
(2) (a) Bouillon, R. M.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200. (b) Muralidharan, K. R.; De Lera, A. R.; Isaef, S. D.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1993**, *58*, 1895. (c) Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823. (d) Kanzler, S.; Halkes, S.; van de Velde, J. P.; Reischel, W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1865. (e) Kroszczynski, W.; Morzycka, B.; Morzycki, J. W. *Wiad. Chem.* **2002**, *56*, 793.

(3) (a) Yamada, S.; Nakayama, K.; Takayama, H.; Itai, A.; Iitaka, Y. *J. Org. Chem.* **1983**, *48*, 3477. (b) Yamada, S.; Suzuki, T.; Takayama, H. *J. Org. Chem.* **1983**, *48*, 3483. (c) Addo, J. K.; Ray, R. *Steroids* **1998**, *63*, 218. (d) Swamy, N.; Addo, J. K.; Ray, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 361. (e) Addo, J. K.; Swamy, N.; Ray, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 279. (f) Ahmed, M.; Atkinson, C. E.; Barrett, A. G. M.; Malagu, K.; Procopiou, P. A. *Org. Lett.* **2003**, *5*, 669.

The discovery of olefin metathesis and development of well-defined ruthenium and molybdenum alkylidene catalysts⁴ has provided a very convenient synthetic route to complex olefins. The preparation of 19-functionalized derivatives of vitamin D based on cross metathesis (CM) seemed to be the shortest and most straightforward way. We have undertaken efforts to synthesize such analogues of vitamin D in our laboratory. The reactions of vitamin D₃ (**1**) with various olefins, such as 1-heptene, allyl alcohol, *trans*-3-hexenedinitrile, and allyl cyanide, were examined. Unfortunately, the CM reactions of vitamin D₃ with these alkenes in the presence of 20 mol % of Grubbs or Hoveyda second generation catalysts in dichloromethane did not work and the starting material was recovered in all cases. There was no reaction even under more drastic conditions (80 °C, 30 mol % of catalyst).

A failure of the CM approach caused alteration of the synthetic strategy and ring-closing metathesis (RCM) was used instead in the next experiments, as an alternative method for the preparation of 19-functionalized derivatives of vitamin

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D₃. According to the synthetic plan, the 3-hydroxyl group in vitamin D₃ was esterified with carboxylic acid containing the terminal double bond (4-pentenoic, 5-hexenoic, 6-heptenoic, and 10-undecenoic acid). The esterification was performed with the DCC method with DMAP as catalyst. The products **2** were obtained in high yields. The esters **2** appeared to be rather unstable and therefore were immediately subjected to RCM reaction.⁵ Although there are many reports of successful application of RCM to the synthesis of medium sized rings,⁴ in the case of metathesis of vitamin D₃ esters, the only products were dimers **3**, as a result of self-methathesis (SM). Despite the change of the reaction conditions—higher temperature (80 °C), more second generation catalyst (Grubbs or Hoveyda, 30 mol %), higher dilution, and slow addition of reagents—the desired RCM products were not formed.

Compound **4** with inverted configuration at C-3 (synthesized from vitamin D₃ via the Mitsunobu reaction) did not afford the RCM product either. The same results were

obtained in the 5,6-*trans*-vitamin D₃ series. The 5,6-*trans*-vitamin D₃ did not undergo the CM reactions, while the corresponding esters (**5**) yielded the SM products only.

Presumably, the failure of ring closure is due to the lack of sufficient conformational flexibility in ring A, as well as the steric hindrance (5,6-*cis* compounds) caused by the CD ring fragment of the molecule. Additionally, molecular modeling reveals that the cyclization requires the change of A ring conformation from the favored chair to the boat conformation.

In the next attempts, the same approach was applied for 1 α -hydroxyvitamin D₃ derivatives. The 3-TBS-ether of 1 α -hydroxy-5,6-*trans*-vitamin D₃ (**6**) obtained by a known method⁶ was analogously transformed into 3-butenolate **7**, which theoretically allows for closure of a six-membered ring in the RCM reaction. In this case the desired cyclic product **8** was obtained in 70% yield with use of 20 mol % of Hoveyda second generation catalyst (worked slightly better than the Grubbs catalyst): dilution, Cm = 0.5–1.5 mM, 80 °C.⁵ The most important factor for successful RCM proved to be reaction temperature. At 40–70 °C the main product appeared to be a dimer **9**, as a result of SM. The higher temperature favored the RCM reaction. Such an effect of

(5) **General procedure for RCM reaction:** To the solution (2 mM) of 20 mol % of Grubbs (or Hoveyda) second generation catalyst in dry toluene in oven-dried Schlenk flask was added the solution (0.5–1.5 mM) of vitamin D₃ (or 1 α -hydroxyvitamin D₃) ester in dry toluene dropwise over 2 h. The reaction mixture was stirred at 80 °C for 4 h under argon atmosphere. Then the reaction mixture was concentrated in vacuo and purified by silica gel column chromatography.

(6) Marshall, J. A.; Grote, J.; Shearer B. J. *Org. Chem.* **1986**, *51*, 1635.

The lactone **8** appeared to be rather unstable, and to avoid its decomposition, it was converted into the corresponding diol **12**. Subsequent photoisomerization of the 19-hydroxyethyl derivative of 1 α -hydroxy-5,6-*trans*-vitamin D₃ (**12**) in



the presence of anthracene as triplet sensitizer⁷ in degassed and dry benzene at 0–5 °C afforded the desired *cis* isomer **13**. The almost complete conversion to vitamin D₃ analogue was observed within 15 min (5 × 3 min) of irradiation with a UV lamp. The two isomers (5*E* and 5*Z*) were distinguished on the basis of their ¹H NMR spectra. The position of two doublets of 6-H and 7-H was diagnostic: for the 5,6-*trans* isomer these signals appeared at 6.46 and 5.89 ppm, while in the case of the 5,6-*cis* compound the first signal was shifted upfield to 6.30 ppm, the second one downfield to 5.91 ppm. Thus the distance between the doublets of 6-H and 7-H in the *trans* isomer is about 0.2 ppm larger than that between analogous signals for the *cis* isomer, what is typical for the *cis/trans* series of vitamin D derivatives.⁸

(7) Gielen, J. W. J.; Koolstra, R. B.; Jacobs, H. J. C.; Havinga, E. *J. R. Neth. Chem.* **1980**, 99, 306.

(8) Paaren, H. E.; DeLuca, H. F.; Schnoes, H. K. *J. Org. Chem.* **1980**, 45, 3253.

In conclusion, a new synthetic strategy for the preparation of 19-functionalized derivatives of 1 α -hydroxyvitamin D was elaborated. In the methodology developed, the synthesis of a cyclic analogue proceeds through RCM of the 1 α -hydroxy-*trans*-vitamin D₃ vinylacetyl derivative. Subsequent reduction of the obtained RCM product followed by photochemical isomerization afforded the 19-functionalized analogue.

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Supporting Information Available: Details of the experiments and characterization of compounds **7**, **8**, **12**, and **13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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