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Application of Ring-Closing Metathesis to the Synthesis of 19-Functionalized Derivatives of 1α-Hydroxyvitamin D_3

Agnieszka Wojtkielewicz and Jacek W. Morzycki*

Institute of Chemistry, University of Bialystok, al. Pilsudskiego 11/4, 15-443 Bialystok, Poland

morzycki@uwb.edu.pl

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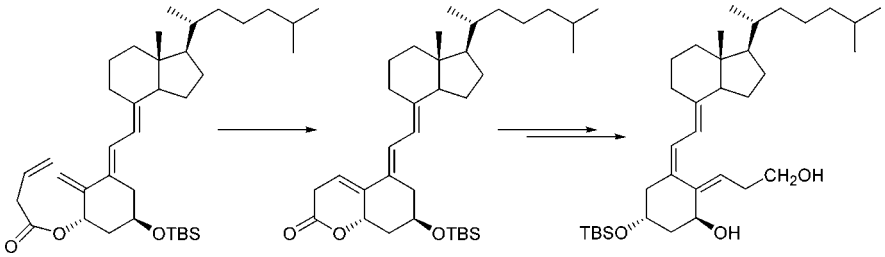
ABSTRACT



The synthesis of the 19-functionalized derivative of vitamin D_3 based on ring-closing metathesis (RCM) is presented.

A hormonally active metabolite of vitamin D_3, 1α,25-dihydroxyvitamin D_3, 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]

The discovery of olefin metathesis and development of well-defined ruthenium and molybdenum alkylidene catalysts[4] 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 D_3 (**1**) with various olefins, such as 1-heptene, allyl alcohol, *trans*-3-hexenedinitrile, and allyl cyanide, were examined. Unfortunately, the CM reactions of vitamin D_3 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

(1) Holick, M. F., Ed. *Vitamin D*: *Physiology, Molecular Biology and Clinical Aplications*; Humana Press: Totowa, NJ, 1999.

(2) (a) Bouillon, R. M.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200. (b) Muralidharan, K. R.; De Lera, A. R.; Isaeff, 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.

(4) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

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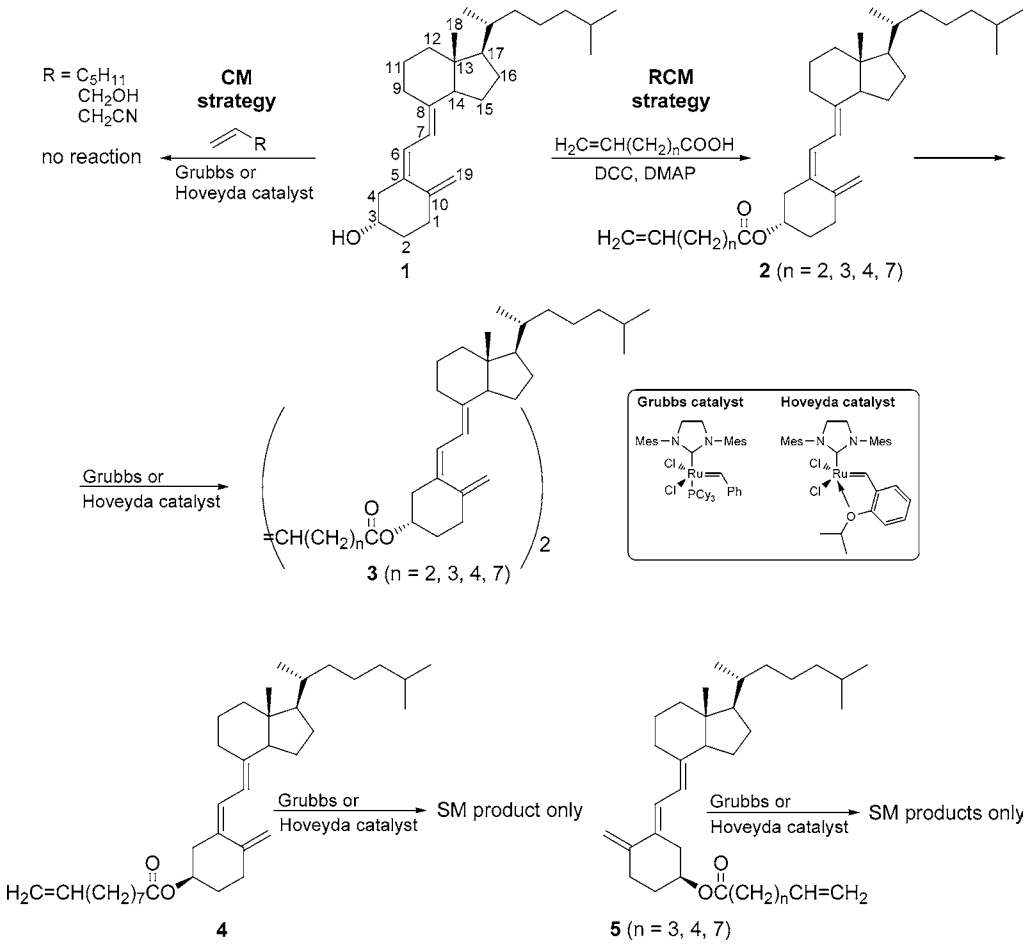
Scheme 1



D_3. According to the synthetic plan, the 3-hydroxyl group in vitamin D_3 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 D_3 esters, the only products were dimers **3**, as a result of self-methatesis (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 D_3 via the Mitsunobu reaction) did not afford the RCM product either. The same results were obtained in the 5,6-*trans*-vitamin D_3 series. The 5,6-*trans*-vitamin D_3 did not undergo the CM reactions, while the corresponding esters (**5**) yielded the SM products only.

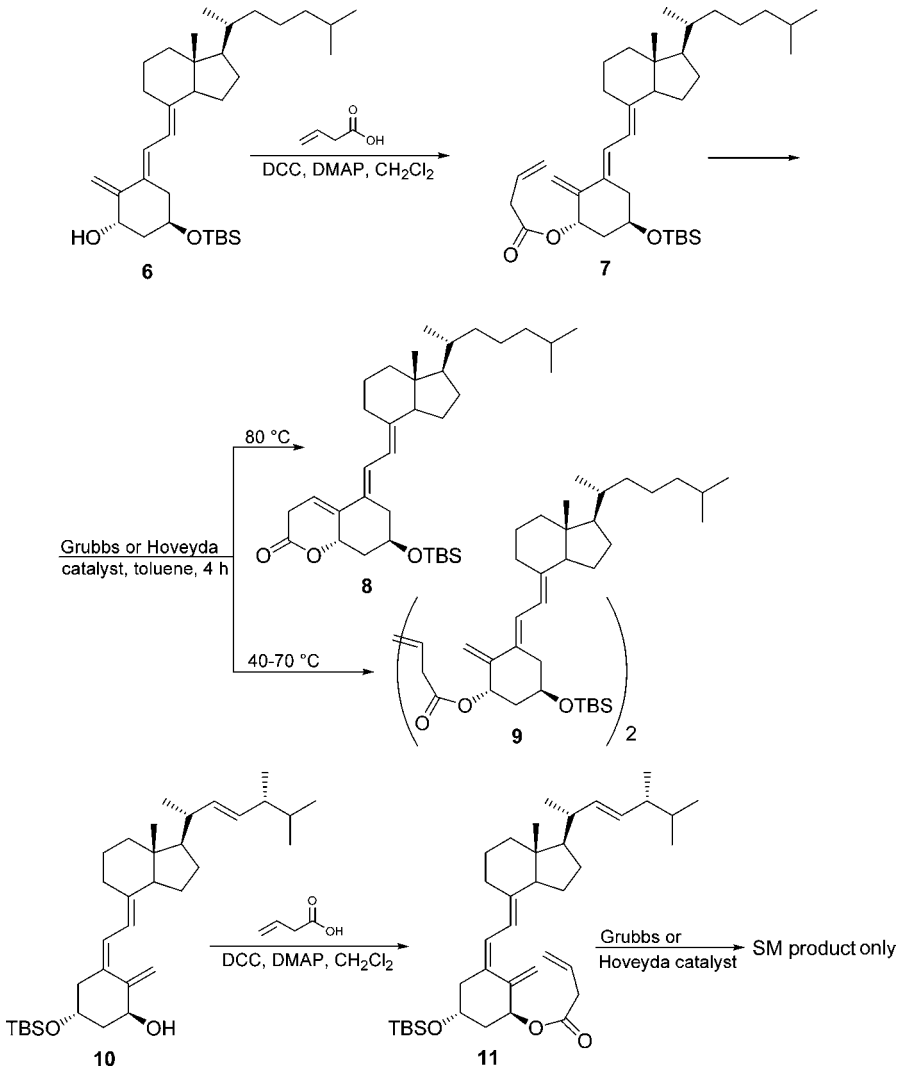
Presumably, the failure of ring closure is due to the lack of sufficient conformational flexibility in ring A, as well as the steric hindrance (5,6-*cis* compounds) caused by the CD ring fragment of the molecule. Additionally, molecular modeling reveals that the cyclization requires the change of A ring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

In the next attempts, the same approach was applied for 1α-hydroxyvitamin D_3 derivatives. The 3-TBS-ether of 1α-hydroxy-5,6-*trans*-vitamin D_3 (**6**) obtained by a known method[6] was analogously transformed into 3-butenoate **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 D_3 (or 1α-hydroxyvitamin D_3) 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.

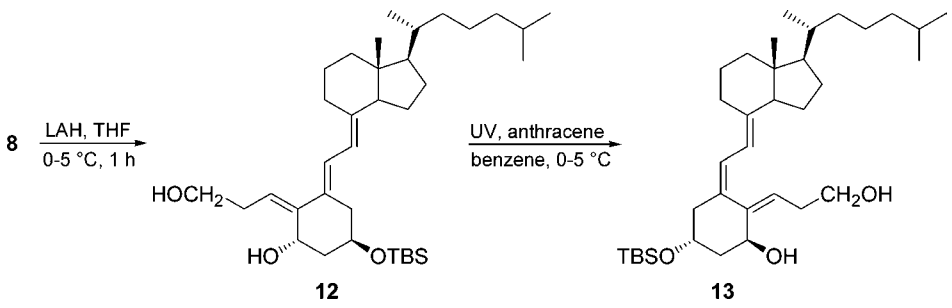
Scheme 2



temperature was not reported earlier for phoshonate or silic analogues of 1α-hydroxy-5,6-*trans*-vitamin D_2.[3f] The influence of other reaction conditions (type of catalyst, dilution, mode of reagent addition) proved much less important. The RCM reaction was not observed (even at higher temperature) for 3-butenoate of 1α-hydroxyvitamin D derivatives (e.g. for compound **11**). The reason for that is presumably the greater steric hindrance caused by the CD ring fragment of the molecule because of the *cis* configuration of the 5,6 double bond in this compound.

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 1α-hydroxy-5,6-*trans*-vitamin D_3 (**12**) in

Scheme 3



the presence of anthracene as triplet sensitizer[7] in degassed and dry benzene at 0−5 °C afforded the desired *cis* isomer **13**. The almost complete conversion to vitamin D_3 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 ^{1}H 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 1α-hydroxyvitamin D was elaborated. In the methodology developed, the synthesis of a cyclic analogue proceeds through RCM of the 1α-hydroxy-*trans*-vitamin D_3 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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