ORGANIC LETTERS

2003
Vol. 5, No. 4
523−525

Efficient Convergent Synthesis of 1α,25-Dihydroxyvitamin D_3 and Its Analogues by Suzuki–Miyaura Coupling

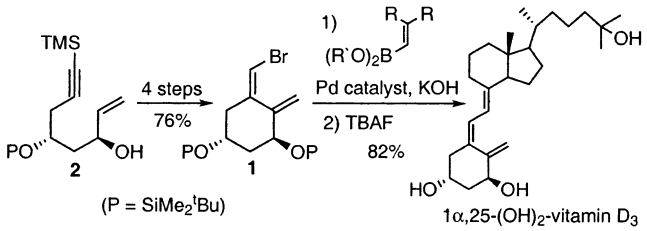
Takeshi Hanazawa, Akiko Koyama, Takeshi Wada, Eiko Morishige, Sentaro Okamoto, and Fumie Sato*

Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

fsato@bio.titech.ac.jp

Received December 4, 2002

ABSTRACT



1α,25-Dihydroxyvitamin D_3 was synthesized by the Suzuki–Miyaura coupling of the A-ring intermediate 1, which was efficiently prepared from readily available 1,7-enyne 2, with the corresponding boronate compound of the C,D-ring portion. The method was applied to prepare *des*-C,D analogues of 1α,25-dihydroxyvitamin D_3.

1α,25-Dihydroxyvitamin D_3 [1,25-$(OH)_2$-VD_3], which plays an important role in human physiology, has attracted substantial interest in its pharmacology and therapeutic potential.[1] The chemical synthesis of 1,25-$(OH)_2$-VD_3 and its analogues, therefore, has been the subject of much research because organic synthesis is the only means of supplying sufficient quantities and creating more effective compounds.[2] Recently, we synthesized 19-*nor*-1α,25-$(OH)_2$-VD_3 by the Suzuki−Miyaura coupling[3] between the corresponding A-ring and C,D-ring parts.[4] Herein we report a new efficient synthetic method of 1,25-$(OH)_2$-VD_3 that involves, as shown in Scheme 1, by a retrosynthetic pathway, the synthesis of A-ring portion **1** from the known starting compound 1,7-enyne **2**[5] by Ti(II)-mediated cyclization reaction[6] and its coupling with C,D-ring unit **3** by the Suzuki−Miyaura coupling.

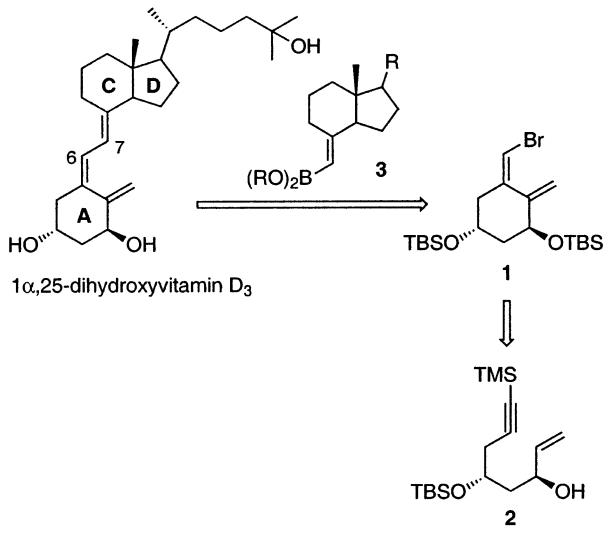
A similar coupling approach to 1,25-$(OH)_2$-VD_3 using the Stille coupling and/or Negishi coupling was proposed by Mouriño and co-workers; however, they only synthesized 3-deoxy-1-hydroxyvitamin D_3 by this approach.[7] It is also noteworthy that the starting enyne **2** can be utilized, after removing the trimethylsilyl group, for producing 1,25-$(OH)_2$-VD_3 by a Pd-catalyzed tandem carbometalation−cyclization reaction (Trost method).[8] The conversion of **2** to [(3*S*)-(1*Z*,3α,5*β*)]-[2-[3,5-bis[[(1,1-dimethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]ethyl]diphenylphosphine oxide, the A-ring intermediate for synthesizing 1,25-$(OH)_2$-VD_3 by the Horner−Wittig reaction (Lythgoe−Roche method[9]) was also reported.[5,10]

Preparation of **2** from optically active epichlorohydrin (**4**) was carried out in 45% overall yield according to the

(1) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: New York, 1997. Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200.
(2) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.
(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(4) Hanazawa, T.; Wada, T.; Masuda, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 3975.
(5) Tazumi, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1903.
(6) Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7329.
(7) García, A. M.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1997**, *62*, 6353.
(8) (a) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836. (b) Trost, B. M.; Hanson, P. R. *Tetrahedron Lett.* **1994**, *35*, 8119.

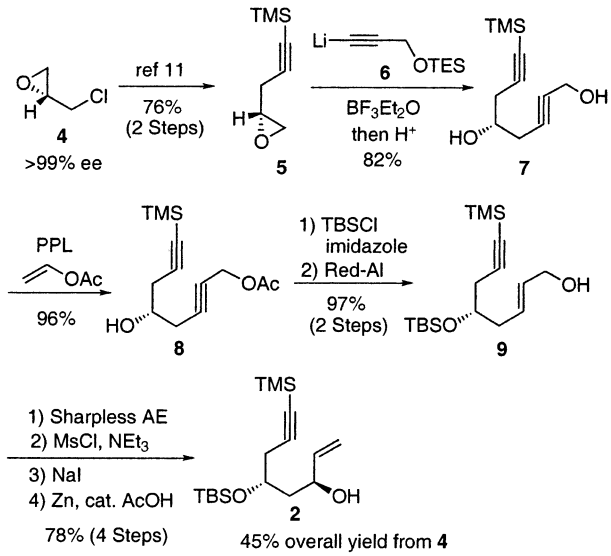
10.1021/ol0274007 CCC: $25.00
Published on Web 01/28/2003

Scheme 1



procedure shown in Scheme 2. Thus, **4** was converted to epoxide **5** according to the procedure reported by Ogasawara

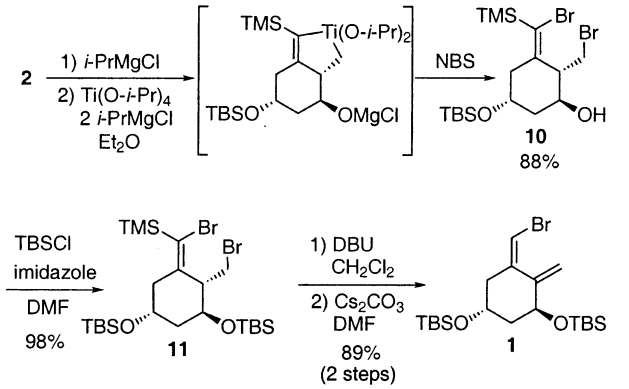
Scheme 2



with minor modifications.[5,11] Epoxide ring-opening of **5** with alkynyllithium **6** in the presence of boron trifluoride etherate provided, after hydrolysis, diol **7** in 82% yield. Selective acylation of the primary hydroxyl group of **7** to **8** was attained by treatment with vinyl acetate in the presence of porcine pancreatic lipase (PPL) in 96% yield. Protection of the secondary hydroxy group of **8** as *tert*-butyldimethylsilyl ether, and the following treatment with sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) provided (*E*)-allyl alcohol **9** in 97% overall yield. Preparation of **2** from **9** was carried out in 78% overall yield by the conventional reaction sequence, which involves Sharpless catalytic asymmetric epoxidation (Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, TBHP, CH_2Cl_2, −20 °C), conversion of the hydroxy group to iodide, and reductive opening of the epoxy iodide moiety.[5]

The titanacyclization of **2** mediated by a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgX, and the following reaction with NBS afforded dibromo compound **10** in 88% yield.[6,12] Although the stereochemistry of the bromomethyl moiety of **10** could not be assigned by the ^{1}H NMR analysis, it was tentatively assigned as depicted in Scheme 3 on the basis of

Scheme 3



our previous results of the cyclization of similar compounds.[6] After protection of the hydroxyl group of **10** as *tert*-butyldimethylsilyl ether, the resulting **11** was treated with DBU in CH_2Cl_2 and then Cs_2CO_3 in DMF to provide **1** in excellent yield.[7] Thus, **1** could be obtained in 76% overall yield from **2**.

With the A-ring unit **1** in hand, we carried out the synthesis of 1,25-(OH)$_2$-VD$_3$ by the Suzuki−Miyaura coupling reaction. Thus, the reaction of **1** with **3**[4] in the presence of KOH and $PdCl_2$(dppf) (8 mol %) in aqueous THF furnished, after desilylation, 1,25-(OH)$_2$-VD$_3$ in 82% yield (Scheme 4).

Among the analogues of 1,25-(OH)$_2$-VD$_3$, those which lack the C,D-ring have recently attracted much interest as potentially therapeutic compounds.[13] The present method for synthesizing 1,25-(OH)$_2$-VD$_3$ using **1** is also very efficient for synthesizing such compounds as exemplified by the synthesis of Retiferol.[13a] Thus, as also shown in Scheme 4, the coupling of **1** with **12**, which was prepared from the corresponding alkyne by hydroboration reaction,[4] afforded, after desilylation, Retiferol in 78% overall yield.[14]

(9) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098 and references therein.

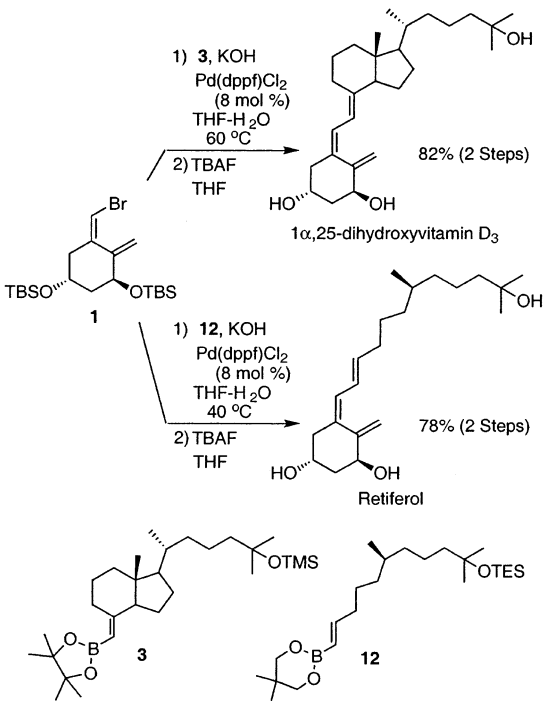
(10) Vrielynck, S.; Vandewalle, M. *Tetrahedron Lett.* **1995**, *36*, 9023.

(11) Subburaj, K.; Okamoto, S.; Sato, F. *J. Org. Chem.* **2002**, *67*, 1024.

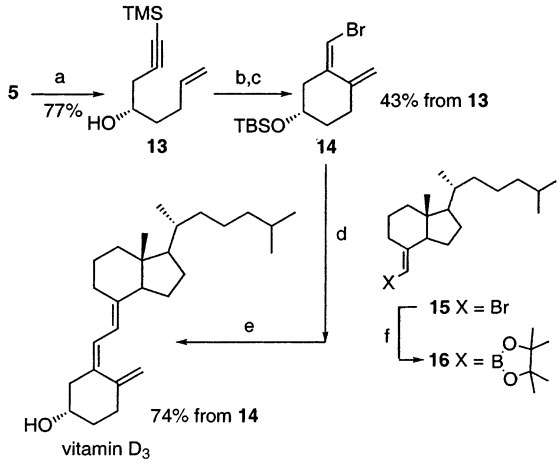
(12) Review for synthetic reactions mediated by a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent: Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759. Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 319−354.

(13) (a) Kutner, A.; Zhao, H.; Fitak, H.; Wilson, S. R. *Bioorg. Chem.* **1995**, *23*, 22. (b) Wirz, B.; Iding, H.; Hilpert, H. *Tetrahedron: Asymmetry* **2000**, *11*, 4171. (c) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. (d) U.S. Patent 5,969,190, 1998. (e) U.S. Patent 6,184,422, 1999.

Scheme 4



Scheme 5[a]



[a] Reaction conditions: (a) allylmagnesium chloride, cat. CuCN (77%). (b) (i) Ti(O-*i*-Pr)$_4$, 2*i*-PrMgCl, NBS; (ii) TBSCl, imidazole (59% for two steps). (c) (i) DBU, CH_2Cl_2; (ii) Cs_2CO_3, DMF (74% for two steps). (d) Pd(dppf)Cl_2 (8 mol %), KOH, THF−H_2O, 60 °C. (e) TBAF, THF (74% for two steps). (f) *t*-BuLi, then B(O-*i*-Pr)$_3$, aqueous NH_4Cl, pinacol, ethyl acetate (76%).

As the synthesis of vitamin D_3 has also attracted much interest, we synthesized vitamin D_3 by a strategy similar to that mentioned above. Epoxide ring-opening reaction of **5** with allylmagnesium bromide in the presence of a catalytic amount of CuCN provided 1,7-enyne **13**, which in turn was converted to **14**, as shown in Scheme 5, according to a procedure similar to the synthesis of **1** from **2**. The Suzuki−Miyaura coupling reaction of **14** with **16**, prepared from **15**, provided vitamin D_3 in 74% yield after deprotection.

In summary, we have developed a new synthetic methodology for synthesizing VD_3, 1,25-$(OH)_2$-VD_3, and their derivatives that involves, as a key reaction, the coupling of the A-ring and C,D-ring portions by Suzuki−Miyaura coupling. Especially noteworthy is the efficient synthesis of **1** that allows easy access to 1,25-$(OH)_2$-VD_3 and its *des*-C,D analogues. Thus, in addition to the Trost[8] and Lythgoe−Roche[9] methods, another practical entry to 1,25-$(OH)_2$-VD_3 and its derivatives has now been established.

Acknowledgment. T.H. thanks the Japan Society for the Promotion of Science for financial support.

Supporting Information Available: Experimental procedure and spectral data for compounds **1**, **2**, **7**−**11**, **13**−**15**, and the final products as shown in Schemes 4 and 5. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0274007

(14) For the synthesis of *des*-C,D-VD_3 analogues by the Lythgoe−Roche method, see ref 13. Synthesis of *des*-C,D-VD_3 analogues by the Trost method was not reported.