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Novel Synthetic Approach to 19-*nor*-1α,25-Dihydroxyvitamin D_3 and Its Derivatives by Suzuki–Miyaura Coupling in Solution and on Solid Support

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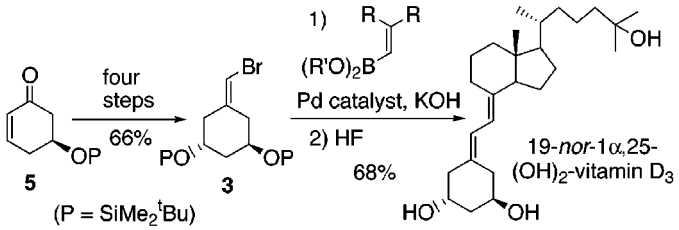
ABSTRACT



19-*nor*-1α,25-Dihydroxyvitamin D_3 was synthesized by the Suzuki–Miyaura coupling of the A-ring intermediate 3, which was efficiently prepared from readily available 5-(*tert*-butyldimethylsilyl)oxycyclohex-2-enone (5), with the boronate compound of the C,D-ring portion. The method could be applied to a solid-phase synthesis to prepare the *des*-C,D derivatives of 19-*nor*-1α,25-dihydroxyvitamin D_3.

1α,25-Dihydroxyvitamin D_3 (1α,25-$(OH)_2VD_3$) is a hormonal, biologically active form of vitamin D_3. Besides its classical role in regulating calcium metabolism, its activities in cellular differentiation, inhibition of tumor cell proliferation, and induction of functions related to the immunological system have been established.[1] In 1990, DeLuca et al. reported that deletion of the 19-methylene group of 1α,25-$(OH)_2VD_3$ increased significantly the stimulation of differentiation and growth inhibition of tumor cells without a parallel increase in hypercalcemia.[2] With this finding, 19-*nor*-1α,25-$(OH)_2VD_3$ itself and also its derivatives having a different C,D-ring portion such as paricalcitol or those lacking the C,D-ring substructure such as the compounds **1** and **2** (Ro 65-2299) shown in Scheme 1 have attracted much interest as potential therapeutical agents.[3]

The synthesis of the 19-*nor*-VD_3s having a C,D-ring portion can be efficiently carried out by the Wittig olefination reaction of the diphenylphosphine oxide of the corresponding A-ring portion with the respective ketone through 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) (a) Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823. (b) Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1991**, *32*, 7663. (c) Yang, S.; Smith, C.; DeLuca, H. F. *Biochim. Biophys. Acta* **1993**, *1158*, 279.

(3) Paricalcitol: (a) Graul, A.; Leeson, P. A.; Castaner, J. *Drugs Future* **1998**, *23*, 602. Compound **1**: (b) U.S. Patent 5,969,190, 1998. Compound **2**: (c) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. (d) U.S. Patent 6,184,422, 1999. Other analogues: (e) Mikami, K.; Osawa, A.; Isaka, A.; Sawa, E.; Shimizu, M.; Terada, M.; Kubodera, N.; Nakagawa, K.; Tsugawa, N.; Okano, T. *Tetrahedron Lett.* **1998**, *39*, 3359. (f) Zhou, X.; Zhu, G.-D.; Van Haver, D.; Vandewalle, M.; De Clercq, P. J.; Verstuyf, A.; Bouillon, R. *J. Med. Chem.* **1999**, *42*, 3539. (g) Verstuyf, A.; Verlinden, L.; Van Baelen, H.; Sabbe, K.; D'hallewyn, C.; De Clercq, P. J.; Vandewalle, M.; Bouillon, R. *J. Bone Miner. Res.* **1998**, *13*, 549. (h) Kubodera, N.; Okano, T.; Nakagawa, K.; Ozono, K.; Mikami, K. *Curr. Pharm. Des.* **2000**, *6*(7), 791.

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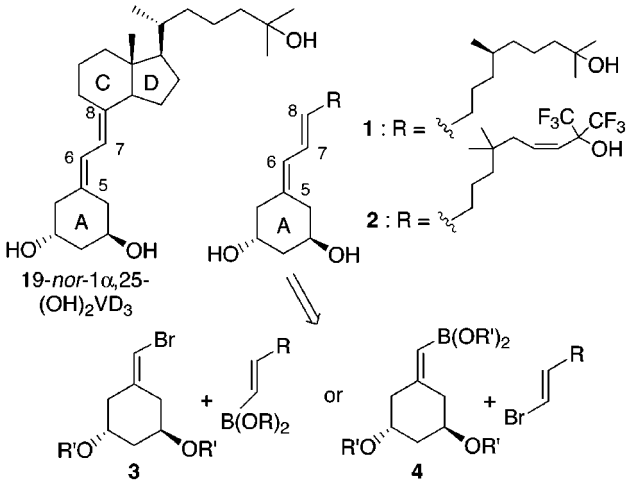
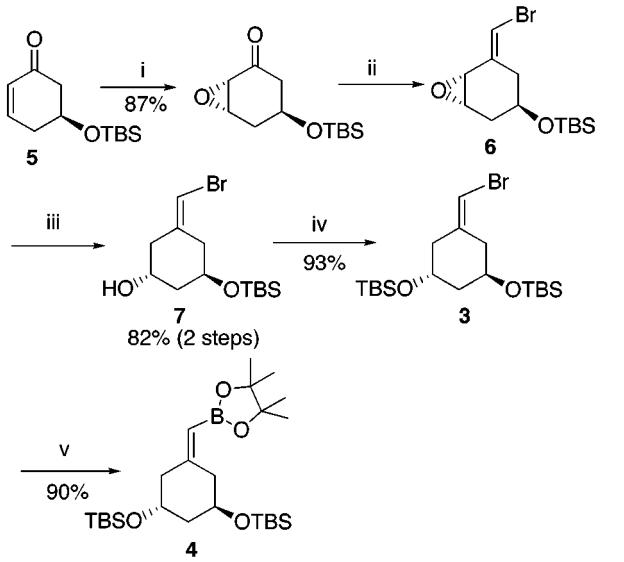
Scheme 1



Scheme 2[a]



[a] (i) Aqueous 30% H_2O_2, 3 N NaOH, MeOH; (ii) $(Ph_3P^+CH_2Br)Br^-$, KHMDS, toluene; (iii) DIBAL, hexanes; (iv) TBDMSCl, imidazole, DMF; (v) *t*-BuLi, ether then B(O-*i*-Pr)$_3$, pinacol.

connection between the C-7 and C-8 positions (see Scheme 1), which proceeded with excellent stereoselectivity. However, in the preparation of *des*-C,D-19-*nor*-VD_3s **1** and **2** via a similar Wittig olefination, difficulty was incurred in co-producing the stereoisomer in relation to the newly formed olefin moiety.[3b−d] To overcome this drawback, preparation of **2** via the connection between the C-5 and C-6 and the C-6 and C-7 positions was pursued by the chemists of Hoffmann-La Roche. They succeeded in the synthesis of **2** via the former connection pathway applying the Julia coupling reaction. However, they gave up the synthesis via the latter pathway by the Suzuki−Miyaura coupling using the intermediate such as alkenylbromide **3** or alkenylboronate **4**, because they failed to prepare **3** and could prepare **4** in only very low yield.[3c] This approach, however, is very attractive because it might not only provide another practical approach to the known 19-*nor*-VD_3s, including **1** and **2**, but also open up an entry to new 19-*nor*-VD_3 derivatives that are difficult to prepare through other pathways.[4] Herein we report an efficient and high-yield preparation of **3** and **4** and their utilization for the synthesis of 19-*nor*-1α,25-$(OH)_2VD_3$ and its derivatives including **1** by the Suzuki−Miyaura coupling under liquid- and/or solid-phase reaction conditions.

We recently reported a practical method for preparation of optically active 5-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone (**5**) and showed that it works as a versatile chiral building block for synthesizing optically active cyclohexane derivatives.[5] We have now found that **3** and **4** can be readily synthesized from (*S*)-**5**[6] according to the procedure shown in Scheme 2. Thus, the compound **5** was converted to bromomethylidenecyclohexanol **7** in 71% overall yield by the conventional reaction sequence, which involves stereoselective epoxidation of **5** using a H_2O_2/NaOH reagent,[5h] Wittig olefination of the resulting epoxyketone[7] with $(Ph_3P^+CH_2Br)Br^-$ and KHMDS, and epoxide-ring opening of the diene monoepoxide **6**[8] thus produced using *i*-Bu_2AlH. Silylation of **7**[9] with TBDMSCl/imidazole afforded **3** in 93% yield. The compound **3** thus obtained was readily converted to boronate **4** in 90% yield by sequential treatment with *t*-BuLi, B(O-*i*-Pr)$_3$, aqueous NH_4Cl, and pinacol. Because all reagents used in the synthesis are readily available, inexpensive and nontoxic and the yield is high (the overall yields of **3** and **4** from **5** were 66% and 60%, respectively), we believe that **3** and **4** can be easily prepared in quantity.

With the A-ring precursors **3** and **4** in hand, we carried out the synthesis of **1** and/or 19-*nor*-1α,25-$(OH)_2VD_3$ by the Suzuki−Miyaura coupling reaction[10] (Scheme 3). Thus, the coupling reaction of **3** with boronate **9**, prepared by hydroboration of acetylene **8**,[11] in the presence of KOH and $PdCl_2$(dppf) (5 mol %) in aqueous THF furnished, after desilylation, **1** in 86% yield. The ^1H and ^{13}C NMR analyses of the crude product indicated that the reaction did not produce the olefinic isomer of **1** at all.[12] Similarly, 19-*nor*-

(4) The synthesis of 19-*nor*-1α-hydroxyvitamin D_3 via the carbon−carbon bond formation between the C-6 and C-7 positions has been reported, although the synthesis did not involve the Csp^2−Csp^2 coupling reaction such as Suzuki−Miyaura coupling: Zhou, S.-Z.; Anné, S.; Vandewalle, M. *Tetrahedron Lett.* **1996**, *37*, 7637.

(5) (a) Hikichi, S.; Hareau, G. P.-J.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8299. (b) Hareau, G. P−J.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2099. (c) Hareau, G. P−J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (d) Hareau, G.; Koiwa, M.; Hanazawa, T.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 7493. (e) Hareau, G. P. J.; Koiwa, M.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2385. (f) Koiwa, M.; Hareau, P. J.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2389. (g) Hanazawa, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **2001**, *42*, 5545. (h) Hanazawa, T.; Inamori, H.; Masuda, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 2205.

(6) Prepared from (*S*)-epichlorohydrine with >99% enantiomeric excess (ee).[5g]

(7) The reaction gave a mixture of the epoxyketone having the structure shown in Scheme 2 and its diastereomer in a ratio of >96:4, recrystallization of which from hexane provided the diastereomerically pure compound.

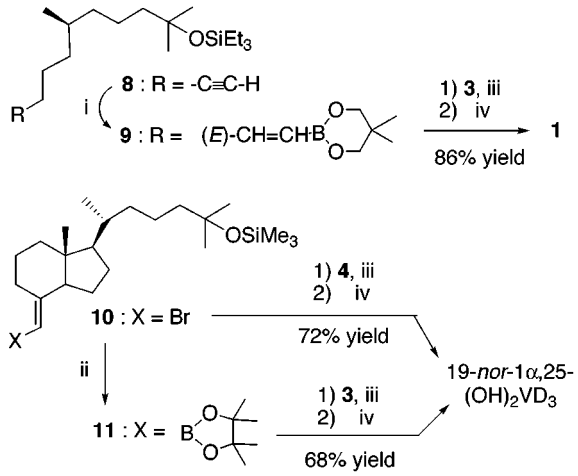
(8) Greater than 97% *E*.

(9) The ee of **7** was confirmed by ^1H NMR analyses, after converting to the corresponding MTPA esters, to be >99%.

(10) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(11) See Supporting Information.

Scheme 3[a]

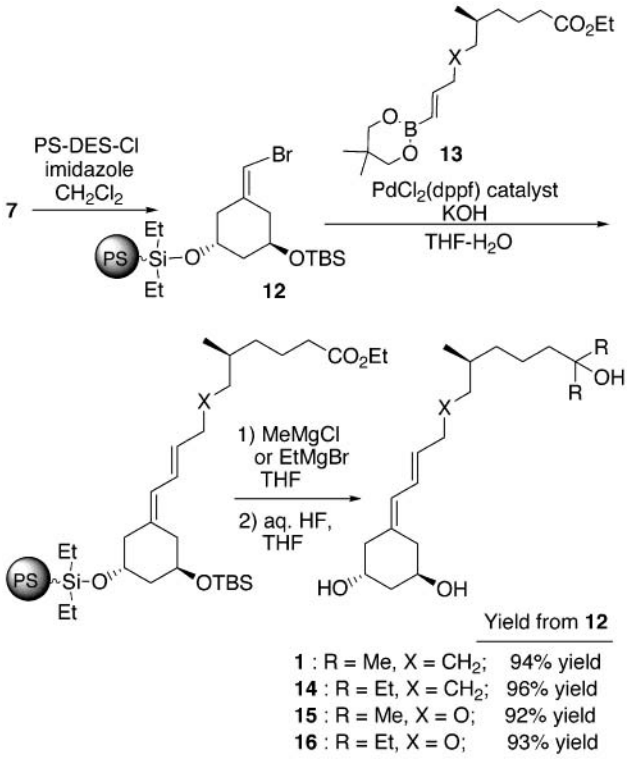


[a] (i) $(ipc)_2BH$, then CH_3CHO, 2,2-dimethyl-1,3-propanediol, THF (70% yield); (ii) *t*-BuLi, then $B(O\text{-}i\text{-}Pr)_3$, aqueous NH_4Cl, pinacol, ether (79% yield); (iii) $PdCl_2(dppf)$ catalyst, KOH, THF/H_2O; (iv) aqueous 30% HF, THF.

$1\alpha,25\text{-}(OH)_2VD_3$ was readily synthesized in 68% yield by coupling reaction between **3** and **11**, the latter of which was prepared from bromide **10**[13] by a lithiation−transmetalation reaction sequence. The Suzuki−Miyaura coupling reaction of boronate **4**[14] and bromide **10** also proceeded smoothly to afford 19-*nor*-$1\alpha,25\text{-}(OH)_2VD_3$ in 72% yield.

With the results shown in Scheme 3, we then devoted our efforts to prepare 19-*nor*-VD_3s in solid phase by utilizing **7**. Synthesis on solid support has recently played an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry.[15] Our parallel solid-phase synthesis of *des*-C,D-19-*nor*-VD_3s shown in Scheme 4 involves coupling of the resin-supported **7** with ester boronate **13** and the following Grignard addition to the ester group present in the resulting coupling product. Thus, the compound **7** reacted with PS-DES-Cl[16] in the presence of imidazole to provide the resin **12**.[17] Treatment of the resin **12** thus prepared with boronate **13**[18] where X = CH_2 under

Scheme 4



reaction conditions similar to those applied in Scheme 3 provided the corresponding coupling product, which in turn was treated with an excess amount of MeMgCl or EtMgBr and then aqueous HF to produce **1** and **14** in 94% and 96% yield, respectively.[19] It should be noted that the 26,27-dimethyl-19-*nor*-VD_3 derivative **14**[20] prepared here is a new compound. Similarly, new *des*-C,D-19-*nor*-VD_3 derivatives **15** and **16** were readily synthesized from **12** and **13** (X = O)[18] in 92% and 93% yield, respectively.[19]

In summary, we have succeeded in developing a new efficient method for synthesizing 19-*nor*-VD_3s, including those that are difficult to access by other known methods, such as **15** and **16**,[21] in solution and on solid support. We believe that the present method can find utility in the fields of drug discovery and manufacturing.

Supporting Information Available: Experimental procedures and spectroscopic data for **3**, **4**, **6**−**9**, **11**, and **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Authentic sample of the cis isomer of **1** was prepared from **3** and **8**, see Supporting Information.

(13) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836.

(14) The corresponding alkenylstannane could be synthesized from **3** via transmetalation using Bu_3SnCl instead of $B(O\text{-}i\text{-}Pr)_3$ (Scheme 2) in 93% yield, which might be useful for 19-*nor*-VD_3 synthesis by Pd-catalyzed coupling reactions: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(15) A leading reference for the Suzuki−Miyaura coupling on solid phase: Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* **2001**, *3*, 803. For solid-phase synthesis of vitamin D_3s, see: Doi, T.; Hijikuro, I.; Takahashi, T. *J. Am. Chem. Soc.* **1999**, *121*, 6749. Hijikuro, I.; Doi, T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716.

(16) Prepared from PS-DES (Argonaut Technologies) by the reported procedure: Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518.

(17) The loading was determined to be 0.738 mmol/g by cleavage with HF-pyridine in THF from the resin and quantification of the resulting 5-bromocyclohexane-1,3-diol by ^1H NMR analysis of the crude mixture using an internal standard.[11]

(18) Prepared from the corresponding terminal alkynes via hydroboration reaction.[11]

(19) Chemical purity of the products **1** and **14**−**16** was determined by ^1H NMR and HPLC analyses to be >95%.

(20) Several 26,27-dimethyl derivatives of $1\alpha,25(OH)_2VD_3$, i.e., the compounds having a 25,25-diethyl structure, have shown a different spectrum of biological activities compared with the corresponding 25,25-dimethyl VD_3s. Reviews on the synthesis and structure−function relationship of vitamin D analogues: Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200. Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877. Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383. Uskokoovic, M., Ed. *Bioorg. Med. Chem. Lett.* **1993**, *3*(9), special issue.

(21) It appears difficult to synthesize **15** and **16** by the Julia coupling method developed by Hilpert[3c] because the corresponding sulfone reagent might undergo elimination of an alkoxy group by treatment with a base.