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Efficient and Practical Synthesis of the A-Ring Precursor of 19-*nor*-1α,25-Dihydroxyvitamin D_3 and Its ^{13}C- or ^{2}H-Labeled Derivative

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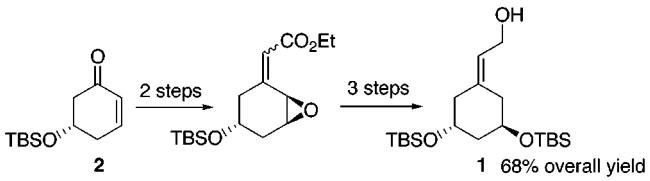
ABSTRACT



The A-ring precursor of 19-*nor*-1α,25-dihydroxyvitamin D_3 (1) and its ^{13}C- or ^{2}H-labeled derivative were efficiently synthesized from readily available, optically active 5-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone (2) through a five-step reaction in 68% overall yield.

1α,25-Dihydroxyvitamin D_3 [1α,25-$(OH)_2VD_3$], the biologically active form of vitamin D_3, is a highly potent regulator of calcium homeostasis, and more recently, its activity in cellular differentiation, inhibition of tumor cell proliferation, and induction of functions related to the immunological system have been established.[1] Many structural analogues have been prepared and tested, and differentiation was made of the respective activities. 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 Ro 65-2299 (Hoffmann La Roche) have attracted much interest as potentially therapeutic agents.[3]

One efficient methods for synthesizing these compounds involves a Wittig olefination of the diphenylphosphine oxide derived from the allyl alcohol **1** via the chloride with the corresponding carbonyl moiety, as exemplified by the synthesis of 19-*nor*-1α,25-$(OH)_2VD_3$ as shown in Scheme 1.[4] Considerable efforts, therefore, have been made toward developing an industrially viable access to **1**, the A-ring precursor of 19-*nor*-1α,25-$(OH)_2VD_3$.

(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. *Biochem. Biophys. Acta* **1993**, *1158*, 279.

(3) Paricalcitol: (a) Graul, A.; Leeson, P. A.; Castaner, J. *Drugs Future* **1998**, *23*, 602. Ro 65-2299: (b) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. Other analogues: (c) 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. (d) Zhou, X.; Zhu, G.-D.; Van Haver, D.; Vandewalle, M.; De Clercq, P. J.; Verstuyf, A.; Bouillon, R. *J. Med. Chem.* **1999**, *42*, 3539. (e) 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. (f) Kubodera, N.; Okano, T.; Nakagawa, K.; Ozono, K.; Mikami, K. *Curr. Pharm. Design* **2000**, *6*, 791.

(4) For the synthesis of 19-*nor*-1α,25-$(OH)_2VD_3$ and its derivatives using **1**, see refs 2b and 3b−e.

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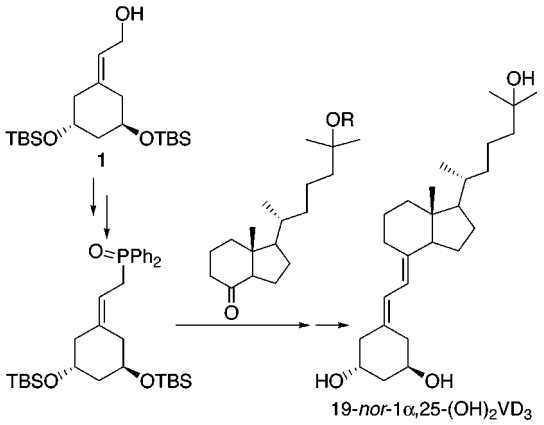
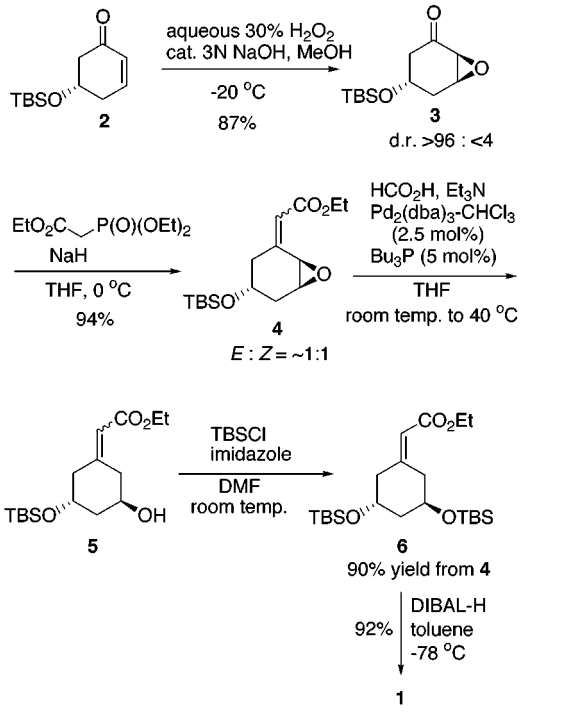
Scheme 1



Scheme 2



Five syntheses of **1** have been reported so far. DeLuca prepared **1** starting from (−)-quinic acid via an eight-step reaction in 16−20% overall yield.[2b] Vandewalle reported a five-step synthesis with 15% overall yield starting from optically active 1,2:4,5-diepoxypentane.[5] Mikami[3c] and Uskokovic[6] independently accomplished the synthesis starting from achiral acyclic precursors and using carbonyl-ene cyclization as a key reaction in 11 steps in 9.7% and 20% overall yield, respectively. Quite recently, Hilpert developed an efficient approach to **1** starting from triacetate of *trans*-cyclohexane-1,3,5-triol, which employs selective enzymatic hydrolysis (63% overall yield).[3b,7]

We have recently developed optically active 5-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone (**2**) as a versatile building block for synthesizing chiral cyclohexane derivatives.[8] The compound **2** can be readily prepared starting from optically active ethyl 3-hydroxy-4-chlorobutyrate[8a] or epichlorohydrin,[8h] both of which are commercially available. In both synthetic approaches, all of the reagents used are readily available, nontoxic, and inexpensive, and the overall yield exceeds 50%. We believe, therefore, that **2** can be easily prepared in quantity and thus might find industrial use. We have, so far, revealed that **2** can be conveniently used as a starting compound for synthesizing several natural products such as penienone,[8d] penihydron,[8d] palitantin,[8e] and the A-ring synthon of 1α,25-$(OH)_2VD_3$.[8f,g] Herein we report the synthesis of **1** from (*S*)-**2**.

The synthesis can be accomplished according to the reaction sequence shown in Scheme 2, which involves highly diastereoselective epoxidation of **2** to **3**, Horner−Wadsworth−Emmons olefination of **3** to **4**, and regioselective reductive ring opening of the epoxide moiety of **4** to **5**. Epoxidation of (*S*)-**2** under various conditions was examined. It was found that the use of H_2O_2/NaOH gives **3** in 87% yield with the highest diastereomeric ratio of 96:4. Oxone at 0 °C (6 h) afforded **3** in 22% yield[9] and 94% dr, whereas TBHP/Triton-B (5 °C, 3 h) gave **3** in 70% yield[10] and 85% d.r. It is noteworthy that *m*-CPBA failed to oxidize **2**.

The Horner−Wadsworth−Emmons olefination reaction of **3** with $(EtO)_2(O)PCH_2CO_2Et$ afforded **4** in 94% yield, which was obtained as a mixture of *E*- and *Z*-isomers and was used for the following reactions without separation. The regiospecific reductive epoxide ring opening of **4** to **5** was effectively carried out with HCO_2H in the presence of a catalytic amount of $Pd_2(dba)_3(CHCl_3)$ (2.5 mol %).[11] Protection of the newly formed hydroxy group as *tert*-butyldimethylsilyl ether followed by column chromatography provided **6**[12] in 90% overall yield from **4**. The compound **1** ($[\alpha]^{29}_D$ +17.8 (*c* 1.02, $CHCl_3$), lit.[3b] $[\alpha]_D$ +18.4 (1%, $CHCl_3$)) was finally synthesized in 92% yield by reduction of **6** with DIBAL-H,[13] the spectral data of which were in good agreement with those reported.[3b,c] Thus, the synthesis of **1**

(5) Zhou, S. Z.; Anné, S.; Vandewalle, M. *Tetrahedron Lett.* **1996**, *37*, 7637.

(6) Courtney, L. F.; Lange, M.; Uskokovic, M. R.; Wovkulich, P. M. *Tetrahedron Lett.* **1998**, *39*, 3363.

(7) Wirz, B.; Iding, H.; Hilpert, H. *Tetrahedron: Asymmetry* **2000**, *11*, 4171.

(8) (a) Hikichi, S.; Hareau, G. P.-J.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8299. (b) Koiwa, M.; Hareau, G. P−J.; Morizono, D.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 4199. (c) Hareau, G. P−J.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2099. (d) Hareau, G. P−J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (e) Hareau, G.; Koiwa, M.; Hanazawa, T.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 7493. (f) Hareau, G. P. J.; Koiwa, M.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2385. (g) Koiwa, M.; Hareau, P. J.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2389. (h) Hanazawa, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.*, in press.

(9) Recovery of **2** was 75%.

(10) Phenol was coproduced in 30% yield.

(11) For reductive epoxide ring opening of diene monoepoxides with a Pd(0)/HCO_2H reagent, see: Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.

(12) $[\alpha]^{29}_D$ + 18.0 (*c* 0.26, $CHCl_3$). Spectral data (^1H NMR and IR) were in good agreement with those reported.[2b,3b]

(13) The reduction of **6** to **1** with Red-Al was reported to proceed in 97% yield; see ref 3b.

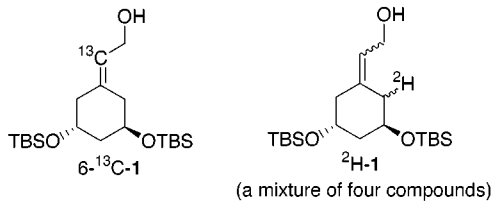


Figure 1.

from **2** was attained in five steps and in 68% overall yield.[14] Although it is difficult to compare the present approach to **1** with the Hilpert method, which appears to be the most practical approach known to date, because the starting compounds and the reagents used for its synthesis are quite different, we believe that this adds another industrially viable approach to **1**.

(14) Thus, **1** was obtained in 35% overall yield in 11 steps from ethyl 3-hydroxy-4-chlorobutyrate.

Another attractive feature of the present approach is the fact that it allows the synthesis of **1** labeled with ^{13}C or ^{2}H (Figure 1). Thus, the use of $(EtO)_2(O)P\text{-}^{13}CH_2CO_2Et$[15] instead of $(EtO)_2(O)PCH_2CO_2Et$ for the conversion of **3** to **4** in Scheme 2 provided **1** labeled with a ^{13}C atom at the C-6 position (steroid numbering). Meanwhile, the use of DCO_2D instead of HCO_2H for the conversion of **4** to **5** afforded a mixture of **1** having a ^{2}H atom on the cyclohexane ring at the C-4 and C-10 positions.[16]

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Supporting Information Available: Experimental procedure and spectral data for compounds **3**−**5** and ^{13}C- or ^{2}H-labeled **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Purchased from Aldrich.

(16) Deuterium incorporation of the resulting ^{2}H-**1** was determined to be >93% by GC/MS analysis.