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New Convergent Synthesis of 1α,25-Dihydroxyvitamin D_3 and Its Analogues by Suzuki−Miyaura Coupling between A-Ring and C,D-Ring Parts

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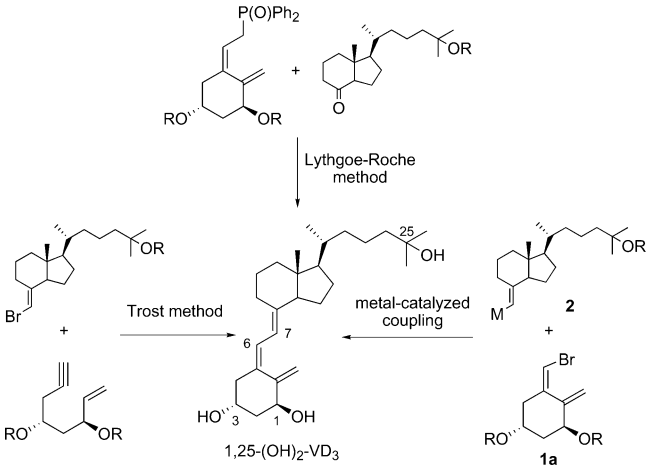
A new convergent method for the synthesis of 1α,25-dihydroxyvitamin D_3 and its analogues has been developed that involves efficient preparation of the A-ring part **1a**, (*Z*)-(3*S*,5*R*)-1-bromomethylene-3,5-bis(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexane, starting from epichlorohydrin (**4**) and its Suzuki−Miyaura coupling reaction with the C,D-ring part **12**. Thus, (*R*)-**4** was converted to (3*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-8-(trimethylsilyl)-oct-1-en-7-yn-3-ol (**3a**) through a ten-step reaction sequence in 49% overall yield. Compound **3a** thus obtained was treated with a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent and then with NBS to afford (*Z*)-(1*S*,2*S*,5*R*)-2-bromomethyl-3-[bromo(trimethylsilyl)methylene]-5-(*tert*-butyldimethylsilyloxy)cyclohexanol (**10a**) in 51% yield, from which **1a** was obtained in 87% yield by sequential treatment with TBSCl/imidazole, DBU, and Cs_2CO_3. The resulting A-ring intermediate **1a** was reacted with alkenylboronate **12** in the presence of a $PdCl_2$(dppf) catalyst to furnish 1α,25-dihydroxyvitamin D_3 in 82% yield after protodesilylation. Similarly, all of the other three possible stereoisomers of A-ring parts **1b**, **1c**, and **1d** were prepared, from which 1-*epi*-, 3-*epi*-, and 1,3-di-*epi*-1α,25-dihydroxyvitamin D_3 were synthesized by coupling with **12** in excellent yield, respectively. Starting from **1a** and **1c**, *des*-C,D-1α,25-dihydroxyvitamin D_3 analogues, retiferol **13** and its 3-epi derivative, were also prepared, respectively.

Introduction

Metabolic activation of vitamin D_3 involves hydroxylation in the liver to form 25-hydroxyvitamin D_3 and the following further hydroxylation in the kidney to produce 1α,25-dihydroxyvitamin D_3 [1,25-$(OH)_2$-VD_3]. The latter metabolite serves as a regulator of calcium homeostasis. In addition to its role, 1,25-$(OH)_2$-VD_3 has recently been shown to promote normal cell differentiation and proliferation as well as to generate a variety of biological responses through nongenomic mechanisms. Because of its important role in human physiology, it 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 extensive research because organic synthesis is the only means of supplying sufficient quantities and creating more effective compounds.[2] Hitherto, two efficient convergent syntheses have been developed and have been used for the preparation of 1,25-$(OH)_2$-VD_3 and its derivatives. As shown in Scheme 1, one is the Lythgoe−Roche method, which uses a connection of the A-ring and C,D-ring parts by the Horner−Wittig reaction,[3] and the other is the Trost method, which involves a Pd-catalyzed carbometalation−cyclization reaction of the acyclic precursor of the A-ring and C,D-ring parts.[4] The coupling approach between the A-ring part **1a** and the C,D-ring part **2** shown in Scheme 1 is anticipated to furnish another efficient convergent synthesis. And, actually, the prepar-

SCHEME 1



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(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) 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.

(4) (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.

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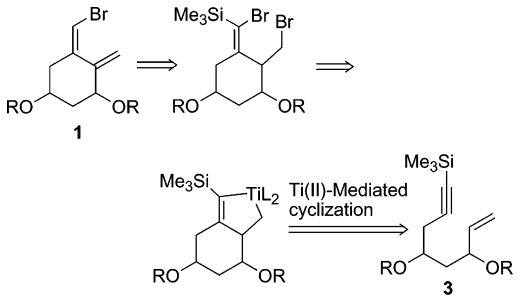
SCHEME 2

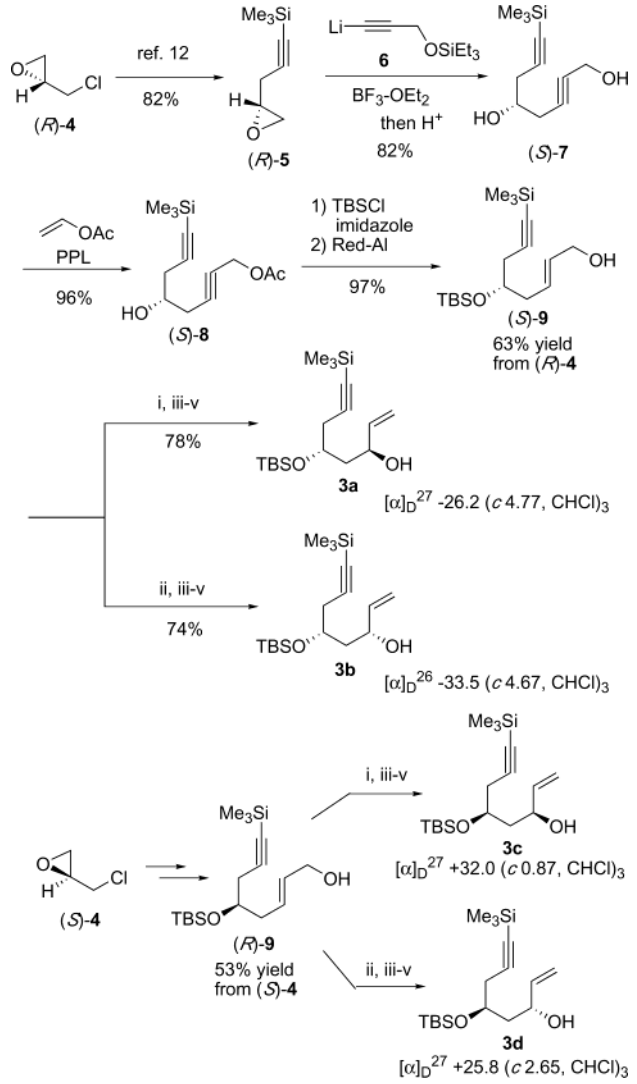


ation of 3-deoxy-1-hydroxyvitamine D_3 by coupling of the corresponding A-ring part with **2** (M = SnR_3 or ZnX), using the Stille coupling or Negishi coupling reaction, was reported by Mouriño and co-workers.[5] We also synthesized 19-*nor*-1,25-$(OH)_2$-VD_3 by Suzuki−Miyaura coupling[6] between the corresponding A-ring part and **2** (M = $B(OR)_2$).[7] However, the preparation of **1a** had not been achieved until our communication reference, and thus the preparation of 1,25-$(OH)_2$-VD_3 through such a coupling pathway has not been reported. Herein we report an efficient method for synthesizing **1a** and its coupling with the C,D-ring part **2** (M = $B(OR)_2$) providing 1,25-$(OH)_2$-VD_3 by Suzuki−Miyaura coupling. We also report the synthesis of three other possible stereoisomers of **1a**, thus consequently, the preparation of all of the A-ring diastereomers of 1,25-$(OH)_2$-VD_3, the unique biological activity of which has been reported.[8,9]

Results and Discussion

We envisaged that the synthesis of **1a** and its stereoisomers could be achieved by Ti(II)-mediated cyclization[10] of the corresponding 1,7-enyne **3** as shown in Scheme 2 by a retrosynthetic method. The synthesis of optically active **3** has been previously reported by Ogasawara and co-workers by starting with optically active epichlorohydrin (**4**).[11] According to this method and with several modifications, we synthesized all four possible stereoisomers **3a**−**d** as shown in Scheme 3. Thus, (*R*)-**4** was converted to epoxide (*R*)-**5**,[12] which in turn was

SCHEME 3[a]



[a] Reaction conditions: (i) Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, *t*-BuOOH, CH_2Cl_2. (ii) Ti(O-*i*-Pr)$_4$, D-(−)-DIPT, *t*-BuOOH, CH_2Cl_2. (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2. (iv) NaI, $NaHCO_3$, acetone. (v) Zn, AcOH, MeOH.

reacted with alkynyllithium **6** in the presence of boron trifluoride etherate[13] to provide, after hydrolysis, diol (*S*)-**7** in 82% yield. Selective acylation of the primary hydroxyl group of (*S*)-**7** to (*S*)-**8** was attained by treatment with vinyl acetate in the presence of porcine pancreatic lipase (PPL) in 96% yield.[14] Protection of the secondary hydroxy group of (*S*)-**8** as *tert*-butyldimethylsilyl (TBS) ether, and the following treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) afforded (*S*)-**9** in 97% yield. From (*S*)-**9**, compounds **3a** and **3b** were prepared in excellent overall yield by the conventional reaction sequence,[11,15] which involves Sharpless catalytic asymmetric epoxidation with L-(+)- or D-(−)-diisopropyl tartrate (DIPT) as a chiral ligand, respectively, conversion of the hydroxy group to iodide, and reductive opening

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(7) Hanazawa, T.; Wada, T.; Masuda, T.; Okamoto, S.; Sato, F. *Org. Lett*. **2001**, *3*, 3975.

(8) For the synthesis of A-ring diastereomers of 1,25-$(OH)_2$-VD_3, see: (a) Konno, K.; Maki, S.; Fujishima, T.; Liu, Z.; Miura, D.; Chokki, M.; Takayama, H. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 151. (b) Muralidharan, K. R.; de Lera, A. R.; Isaeff, S. D.; Norman, A. W.; Okamura, W. H. *J. Org. Chem*. **1993**, *58*, 1895. For their biological activity, see in addition to refs 8a and 8b: (c) Norman, A. W.; Bouillon, R.; Farach-Carson, M. C.; Bishop, J. E.; Zhou, L.-X.; Nemere, I.; Zhao, J.; Muralidharan, K. R.; Okamura, W. H. *J. Biol. Chem*. **1993**, *268*, 20022. (d) Bischof, M. G.; Siu-Caldera, M.-L.; Weiskopf, A.; Vouros, P.; Cross, H. S.; Peterlik, M.; Reddy, G. S. *Exp. Cell. Res*. **1998**, *241*, 194.

(9) The preparation of [1,25-$(OH)_2$-VD_3] by the present method was reported as a preliminary result. Hanazawa, T.; Koyama, A.; Wada, T.; Morishige, E.; Okamoto, S.; Sato, F. *Org. Lett*. **2003**, *5*, 523. See also: *Org. Lett*. **2003**, *5*, 3167 (Additions and Corrections).

(10) Urabe, H.; Sato, F. *Tetrahedron Lett*. **1998**, *39*, 7329.

(11) Tazumi, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1994**, 1903.

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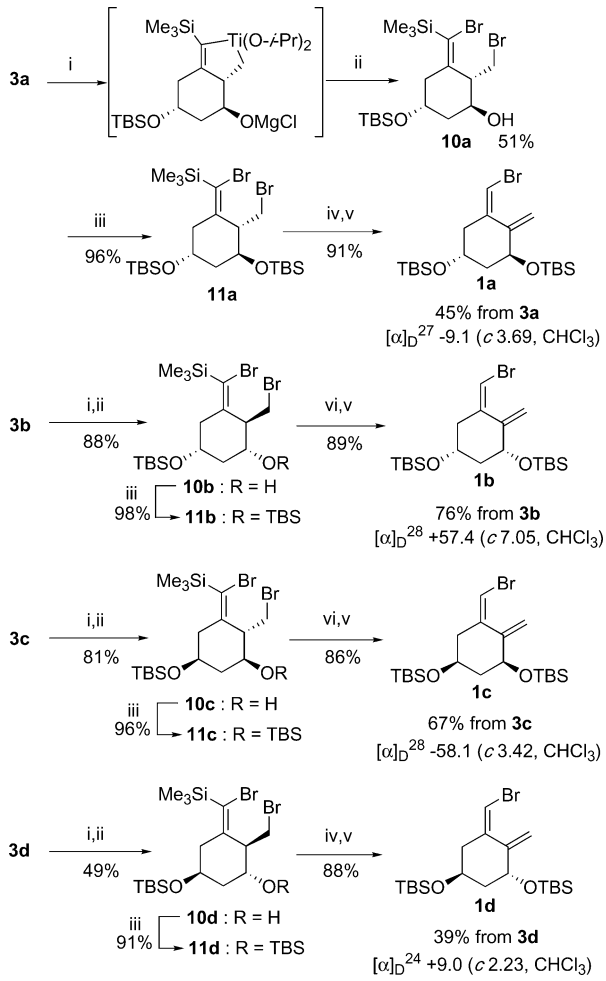
(13) Yamaguchi, M.; Hirano, I. *Tetrahedron Lett*. **1983**, *24*, 391.

(14) Ramaswamy, S.; Morgan, B.; Oehlschlager, A. C. *Tetrahedron Lett*. **1990**, *31*, 3405.

(15) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedoron* **1994**, *50*, 13369.

SCHEME 4[a]

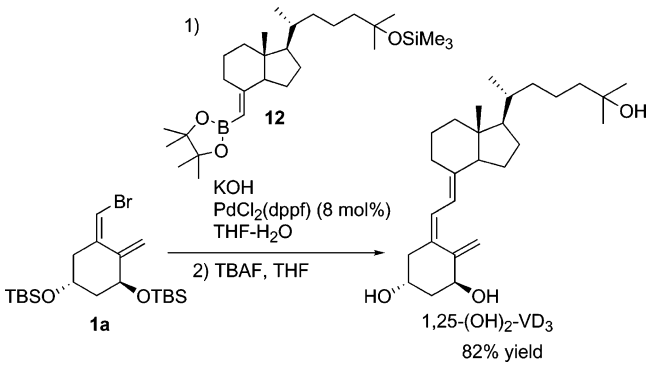


[a] Reaction conditions: (i) *i*-PrMgCl then Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl, ether. (ii) NBS. (iii) TBSCl, imidazole, DMF. (iv) DBU, toluene, 70 °C. (v) Cs_2CO_3, DMF. (vi) DBU, CH_2Cl_2, room temperature.

of the epoxy iodide moiety. Meanwhile, starting with (*S*)-**4** instead of (*R*)-**4** in the reactions mentioned above, two other stereoisomers **3c** and **3d** were prepared similarly via (*R*)-**9**, which is also shown in Scheme 3. The diastereomeric purity of crude **3** thus obtained was found to be more than 97% for **3a** and **3d**, 95% for **3b**, and 96% for **3c**, and in all cases, the corresponding pure **3** was isolated by column chromatography. The isolated yield of pure **3** from **4** was respectively 49, 46, 40, and 43% for **3a**, **3b**, **3c**, and **3d**.

With all four possible stereoisomers of **3** with excellent purity in hand, we proceeded to convert them to the corresponding **1**. As shown in Scheme 4, the titanacyclization of **3**, mediated by a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl,[16] and the following reaction with *N*-bromosuccinimide (NBS) afforded the corresponding dibromo compound **10** in good to excellent yield and in all cases as a single diastereomer in relation to the newly generated stereogenic center. Although the stereochemistry of the carbon center bearing a bromomethyl moiety

SCHEME 5



in **10** thus produced could not be assigned by the ^{1}H NMR analysis, it was tentatively assigned as depicted in Scheme 4 on the basis of our previous results of the cyclization of similar compounds.[10] After protection of the hydroxyl group of **10** as TBS ether, the resulting **11** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene or CH_2Cl_2 and then with Cs_2CO_3 in DMF to provide **1**.[5] In these reaction sequences the following results should be noted: The yield of **10** from **3** is somewhat dependent on the stereochemistry of **3** and it was 49−51% for **3a** (**3d**) and 81−88% for **3b** (**3c**). While dehydrobromination of **11b** (**11c**) with DBU proceeded readily at room temperature in CH_2Cl_2, that of **11a** (**11d**) did not proceed under these reaction conditions and required heating at 70 °C in toluene. The overall yield of **1** from **3** and the $[\alpha]_D$ value of **1a**−**d** thus prepared are shown in Scheme 4.

With the A-ring unit **1** in hand, we carried out the synthesis of 1,25-(OH)$_2$-VD$_3$ and its A-ring diastereomers using the Suzuki−Miyaura coupling reaction. Thus, the reaction of **1a** with **12**[7] in the presence of KOH and $PdCl_2$-(dppf) [8 mol %, dppf = 1,1′-bis(diphenylphosphino)-ferrocene] in aqueous THF furnished, after desilylation, 1,25-(OH)$_2$-VD$_3$ in 82% yield as shown in Scheme 5. Similarly, three other possible A-ring diastereomers of 1,25-(OH)$_2$-VD$_3$ shown in Figure 1, i.e., 1-*epi*-, 3-*epi*-, and 1,3-di-*epi*-1,25-(OH)$_2$-VD$_3$, were prepared from the corresponding **1** and **12** in excellent yield.

Among the analogues of 1,25-(OH)$_2$-VD$_3$, those which lack the C,D-ring structure have recently attracted much interest as potentially therapeutic compounds.[17] The present method for synthesizing 1,25-(OH)$_2$-VD$_3$ with use of **1** is also very efficient for synthesizing other compounds as exemplified by the synthesis of retiferol **13**.[17a] Thus, as shown in Scheme 6, the coupling of **1a** with **14**[7] prepared from the corresponding alkyne by hydroboration reaction afforded retiferol **13** in 78% overall yield after desilylation.[18] Similarly, 3-*epi*-**13** was prepared in excellent yield by starting from **1c** and **14**.

In summary, we have now succeeded in developing a new efficient method for synthesizing 1,25-(OH)$_2$-VD$_3$ and its derivatives. The synthetic method involves practical preparation of the A-ring part of 1,25-(OH)$_2$-VD$_3$ and its

(16) Reviews 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.

(17) (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) Hilpart, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. (d) U.S. Patent 5,969,190, 1998. (e) U.S. Patent 6,184,422, 1999.

(18) For the synthesis of *des*-C,D-VD$_3$-analogues by the Lythgoe−Roche method, see ref 17. Synthesis of *des*-C,D-VD$_3$-analogues by the Trost method was not reported.

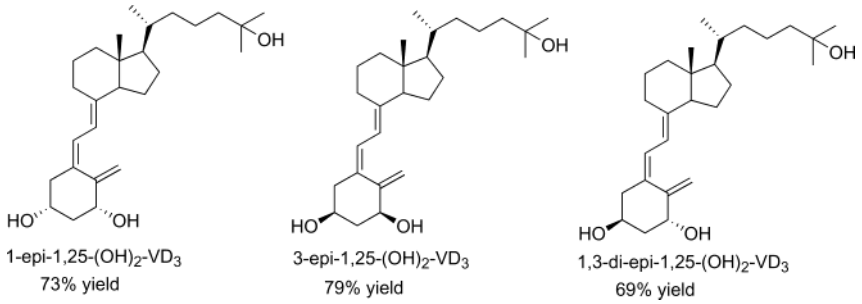
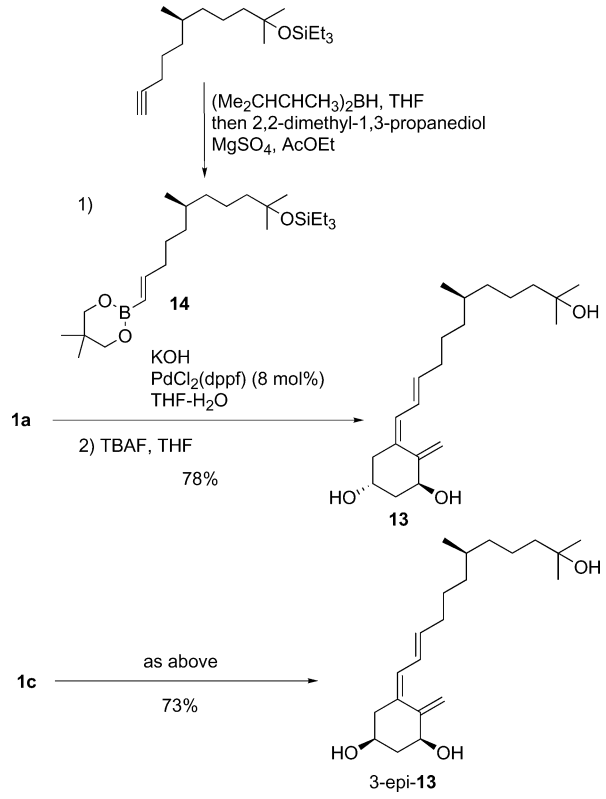


FIGURE 1. A-ring diastereomers of 1,25-$(OH)_2$-VD_3.

SCHEME 6



high yield coupling with the C,D-ring portion by the Suzuki−Miyaura protocol. Thus, in addition to the Trost and Lythgoe−Roche methods, another practical entry to 1,25-$(OH)_2$-VD_3 and its derivatives has now been opened up.

Experimental Section

(*S*)-8-(Trimethylsilyl)octa-2,7-diyne-1,5-diol ((*S*)-7). To a stirred solution of 3-triethylsilyloxy-1-propyne (18.7 g, 110 mmol) in THF (100 mL) was slowly added *n*-BuLi (63.7 mL, 1.57 M in hexane, 100 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, a solution of epoxide (*R*)-**5** (7.71 g, 50.0 mmol) in THF (70 mL) and then boron trifluoride etherate (12.6 mL, 100 mmol) were added. The mixture was stirred for 1 h at −78 °C and warmed to room temperature over 30 min. After addition of saturated aqueous NH_4Cl (100 mL), the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. To a stirred solution of the crude residue in THF (150 mL) was slowly added aqueous 3 N HCl (50 mL) at 0 °C. After being stirred for 1 h at room temperature, the mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexanes−EtOAc) to give (*S*)-**7** (8.61 g, 82%). ^{1}H NMR ($CDCl_3$) δ 4.26 (br s, 2H), 3.86−3.96 (m, 1H), 3.31 (br s, 2H), 2.45−2.60 (m, 4H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 102.4, 87.6, 81.9, 80.9, 68.5, 50.9, 27.6, 26.3, 0.1; IR (neat) 3350, 2959, 2177, 1424, 1249, 1137, 1027, 840, 760 cm^{-1}. $[\alpha]^{28}_D$ −14.0 (*c* 2.69, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_2Si$: C,62.81; H, 8.63. Found: C, 62.56; H, 8.93.

Acetic Acid (*S*)-5-Hydroxy-8-(trimethylsilyl)octa-2,7-diynyl Ester ((*S*)-8). To a solution of (*S*)-**7** (16.5 g, 78.4 mmol) in vinyl acetate (78 mL) was added porcine pancreatic lipase (PPL, 42 units/mg, Sigma-Aldrich, 16.5 g). After being stirred for 3 days at room temperature, the mixture was filtered through a pad of Celite with Et_2O (200 mL). The filtrate was concentrated and chromatographed on silica gel (hexanes−Et_2O) to give (*S*)-**8** (19.0 g, 96%). ^{1}H NMR ($CDCl_3$) δ 4.68 (t, J = 2.1 Hz, 2H), 3.87−3.97 (m, 1H), 2.52−2.58 (m, 4H), 2.36 (s, 1H), 2.10 (s, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.2, 102.0, 88.0, 83.1, 76.7, 68.3, 52.6, 27.7, 26.4, 20.9, 0.1; IR (neat) 3462, 2958, 2176, 1748, 1379, 1250, 1028, 845, 761 cm^{-1}. $[\alpha]^{27}_D$ −0.76 (*c* 2.22, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_3Si$: C, 61.87; H, 7.99. Found: C, 62.24; H, 7.60.

(*S*,*E*)-5-(*tert*-Butyldimethysilyloxy)-8-(trimethylsilyl)-oct-2-en-7-yn-1-ol ((*S*)-9). To a mixture of (*S*)-**8** (22.0 g, 87.2 mmol) and imidazole (13.0 g, 191 mmol) in DMF (180 mL) was added TBSCl (14.4 g, 95.6 mmol) at 0 °C. After the mixture was stirred for 12 h at room temperature, saturated aqueous $NaHCO_3$ (100 mL) at 0 °C was added. The mixture was extracted with hexane (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting pale yellow residue was directly used for the next reaction without purification. To a solution of the residue thus obtained in Et_2O (200 mL) was slowly added Red-Al (63.3 mL, 3.42 M in toluene, 216 mmol) at 0 °C. After the solution was stirred for 1 h at the same temperature, saturated aqueous 1 N HCl (200 mL) was added carefully. The mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane−Et_2O) to give (*S*)-**9** (27.8 g, 97%). ^{1}H NMR ($CDCl_3$) δ 5.68−5.71 (m, 2H), 4.10 (m, 2H), 3.80−3.89 (m, 1H), 2.21−2.40 (m, 2H), 2.33 (d, J = 6.0 Hz, 2H), 1.38 (s, 1H), 0.88 (s, 9H), 0.14 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 131.8, 128.5, 104.4, 86.3, 70.8, 63.7, 39.8, 28.4, 25.9, 18.2, 0.2, −4.3, −4.5; IR (neat) 3326, 2956, 2857, 2178, 1472, 1362, 1250, 1101, 1031, 973, 841, 776 cm^{-1}. $[\alpha]^{28}_D$ 3.39 (*c* 2.82, MeOH) [lit.[11] $[\alpha]^{28}_D$ 3.9 (*c* 0.92, MeOH)].

(3*S*,5*R*)-5-(*tert*-Butyldimethysilyloxy)-8-(trimethylsilyl)oct-1-en-7-yn-3-ol (3a). To a mixture of Ti(O-*i*-Pr)$_4$ (5.00 mL, 17.0 mmol) and 4Å molecular sieves (5.56 g) in CH_2Cl_2 (50 mL) was added diisopropyl L-(+)-tartarate (L-(+)-DIPT) (4.28 mL, 20.4 mmol) at −15 °C and the mixture was stirred for 30 min. To this was slowly added a solution of (*S*)-**9** (27.8 g, 85.1 mmol) in CH_2Cl_2 (30 mL). After being stirred for 40 min at −15 °C, the mixture was cooled to −30 °C and *t*-BuOOH (49.7 mL, 3.41 M in CH_2Cl_2, 169 mmol) was added. The resulting mixture was allowed to warm to −20 °C and stirred

for 24 h. After addition of methyl sulfide (9.34 mL, 127 mmol) and stirring for 1 h at −20 °C, 10% tartaric acid (30 mL) was added to the mixture. The mixture was then warmed to room temperature over 1 h and diluted with Et_2O (500 mL). After addition of NaF (55.6 g) and Celite (55.6 g), the mixture was stirred for 1 h and filtered through a pad of Celite. The resulting filtrate was evaporated to remove solvents. The residue was diluted with Et_2O (300 mL) and aqueous 3 N NaOH (85 mL) and was vigorously stirred for 1.5 h at room temperature. After addition of H_2O (300 mL), the mixture was extracted with Et_2O (3 × 150 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the epoxy alcohol as a pale yellow oil, which was subjected to the next reaction without purification. To a mixture of the epoxide thus obtained and NEt_3 (21.1 mL, 187 mmol) in CH_2Cl_2 (130 mL) was slowly added MsCl (7.88 mL, 102 mmol) at 0 °C. After being stirred for 1 h, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 90 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a colorless residue, which was subjected to the next reaction without purification. To a mixture of the crude mesylate and $NaHCO_3$ (2.13 g, 25.4 mmol) in dry acetone (200 mL) was added NaI (38.2 g, 255 mmol) at room temperature. After being stirred for 20 h, the mixture was concentrated by rotary evaporation and then diluted with saturated aqueous $Na_2S_2O_3$ (200 mL). After extraction with Et_2O (3 × 100 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the corresponding iodide, which was directly used for the next reaction without purification. To a mixture of zinc powder (16.6 g, 254 mmol, activated by washing with diluted HCl and drying in vacuo) in MeOH (20 mL) was added acetic acid (0.273 mL, 4.80 mmol). To this mixture was added a solution of the crude iodide, prepared above, in MeOH (40 mL) under sonication. After 1 h of sonication, acetic acid (4.83 mL, 84.9 mmol) was added. The mixture was filtered with NH_4Cl (200 mL) and CH_2Cl_2 (200 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexanes−Et_2O) to give **3a** (21.7 g, 78% overall yield from (*S*)-**9**). ^{1}H NMR ($CDCl_3$) δ 5.87 (ddd, J = 5.4, 10.5, 17.1 Hz, 1H), 5.26 (dt, J = 1.5, 17.1 Hz, 1H), 5.09 (dt, J = 1.5, 10.5 Hz, 1H), 4.38−4.46 (m, 1H), 4.10−4.18 (m, 1H), 2.92 (s, 1H), 2.48 (d, J = 6.6 Hz, 2H), 1.83 (ddd, J = 3.3, 5.7, 14.4 Hz, 1H), 1.75 (ddd, J = 3.6, 9.3, 14.4 Hz, 1H), 0.89 (s, 9H), 0.13 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.9, 113.9, 103.4, 87.0, 69.5, 69.4, 42.0, 28.2, 25.9, 18.0, 0.1, −4.4, −4.7; IR (neat) 3447, 2957, 2858, 2178, 1647, 1472, 1362, 1251, 1099, 924, 839, 777 cm^{-1}. $[\alpha]^{27}_D$ −26.3 (*c* 4.77, $CHCl_3$) [lit.[11] $[\alpha]^{28}_D$ −26.0 (*c* 1.06, $CHCl_3$)].

(*Z*)-(1*S*,2*S*,5*R*)-2-Bromomethyl-3-[bromo(trimethylsilyl)-methylene]-5-(*tert*-butyldimethylsilyloxy)cyclohexanol (10a). To a solution of **3a** (1.63 g, 4.99 mmol) in Et_2O (50 mL) was added dropwise *i*-PrMgCl (2.51 mL, 1.99 M in Et_2O, 4.99 mmol) at 0 °C. After the solution was stirred for 10 min at the same temperature, Ti(O-*i*-Pr)$_4$ (2.95 mL, 10.0 mmol) was added. The resulting mixture was cooled to −78 °C and *i*-PrMgCl (10.1 mL, 1.99 M in Et_2O, 20.1 mmol) was added slowly. After the solution was stirred for 30 min at −78 °C, the resulting yellow mixture was warmed to −50 °C over 30 min and stirred for 3 h at this temperature. After the mixture was cooled to −78 °C, a solution of NBS (4.90 g, 27.5 mmol) in THF (30 mL) was slowly added and the mixture was allowed to warm to room temperature. After the solution was stirred for 1 h at room temperature, saturated aqueous NH_4Cl (60 mL) was added. The mixture was extracted with Et_2O (3 × 50 mL), washed with saturated aqueous $NaHCO_3$ (80 mL) and H_2O (60 mL), dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane-Et_2O) to give **10a** (1.26 g, 51%). ^{1}H NMR ($CDCl_3$) δ 4.36−4.40 (m, 1H), 3.92−4.04 (m, 1H), 3.65−3.71 (m, 1H), 3.32−3.48 (m, 2H), 2.82 (dd, J = 4.8, 14.1 Hz, 1H), 1.94−2.50 (m, 1H), 1.97 (dd, J = 11.1, 14.1 Hz, 1H), 1.65 (br s, 1H), 1.63 (ddd, J = 2.7, 10.5, 13.8 Hz, 1H), 0.88 (s, 9H), 0.30 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.2, 129.7, 69.2, 66.6, 51.7, 39.9, 37.5, 31.3, 25.8, 18.1, 1.3, −4.4; IR (neat) 3447, 2954, 2857, 1472, 1361, 1251, 1096, 876, 839, 776 cm^{-1}; $[\alpha]^{27}_D$ 0.50 (*c* 2.96, $CHCl_3$). Anal. Calcd for $C_{17}H_{34}Br_2O_2Si_2$: C, 41.98; H, 7.05. Found: C, 42.31; H, 6.85.

(*Z*)-(2*S*,3*S*,5*R*)-2-Bromomethyl-1-[bromo(trimethylsilyl)-methylene]-3,5-bis(*tert*-butyldimethylsilyloxy)cyclohexane (11a). To a mixture of **10a** (1.70 g, 3.49 mmol), imidazole (0.47 g, 6.90 mmol), and DMF (5 mL) was added TBSCl (0.573 g, 3.80 mmol) at 0 °C. After the mixture was stirred for 12 h at room temperature, saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with hexane (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexanes−Et_2O) to give **11a** (2.02 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.34−4.38 (m, 1H), 3.97−4.08 (m, 1H), 3.57−3.63 (m, 1H), 3.27−3.45 (m, 2H), 2.79 (dd, J = 4.5, 13.8 Hz, 1H), 1.92 (dd, J = 10.8, 13.8 Hz, 1H), 1.82−1.90 (m, 1H), 1.58 (ddd, J = 2.4, 10.5, 12.9 Hz, 1H), 0.89 (s, 9H), 0.86 (s, 9H), 0.29 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 148.0, 128.5, 69.3, 66.9, 51.6, 40.1, 38.1, 31.6, 25.9, 25.7, 18.2, 17.9, 1.3, −4.5, −4.6, −4.9; IR (neat) 2953, 2857, 1471, 1361, 1252, 1100, 1018, 837, 775 cm^{-1}; $[\alpha]^{27}_D$ 14.2 (*c* 2.85, $CHCl_3$). Anal. Calcd for $C_{23}H_{48}Br_2O_2Si_3$: C, 45.99; H, 8.05. Found: C, 46.11; H, 7.86.

(*Z*)-(3*S*,5*R*)-1-Bromomethylene-3,5-bis(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexane (1a). To a solution of **11a** (1.70 g, 2.83 mmol) in toluene (5.6 mL) was added DBU (1.68 mL, 11.2 mmol) at 0 °C. The reaction mixture was stirred at 70 °C for 20 h. After addition of saturated aqueous $NaHCO_3$ (15 mL), the mixture was extracted with hexane (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated to give the crude diene product as a yellow oily residue. To a mixture of the crude residue thus obtained and DMF (6 mL) was added Cs_2CO_3 (3.69 g, 11.3 mmol). The reaction mixture was stirred at room temperature for 12 h. After addition of saturated aqueous $NaHCO_3$ (30 mL), the mixture was extracted with hexane (3 × 15 mL) and the combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane−Et_2O) to give **1a** (1.16 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.03 (t, J = 1.5 Hz, 1H), 5.34 (br s, 1H), 5.16 (br s, 1H), 4.39−4.44 (m, 1H), 4.14−4.21 (m, 1H), 2.41 (ddd, J = 1.5, 3.6, 13.5 Hz, 1H), 2.23 (dd, J = 6.3, 13.5 Hz, 1H), 1.73−1.87 (m, 2H), 0.91 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.3, 140.4, 112.1, 100.8, 70.7, 66.8, 44.7, 44.5, 25.9, 25.8, 18.4, 18.2, −4.6, −4.66, −4.71, −5.0; IR (neat) 2950, 1621, 1472, 1361, 1253, 1082, 1006, 776 cm^{-1}; $[\alpha]^{27}_D$ −9.1 (*c* 3.69, $CHCl_3$). Anal. Calcd for $C_{20}H_{39}BrO_2Si_2$: C, 53.67; H, 8.78. Found: C, 53.39; H, 8.80.

(*Z*)-(3*S*,5*R*)-1-Bromomethylene-3,5-bis(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexane (1b). To a solution of **11b** (2.00 g, 3.33 mmol) in CH_2Cl_2 (4 mL) was added DBU (1.60 mL, 10.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. After addition of saturated aqueous $NaHCO_3$ (20 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated to give the crude diene product as a yellow oily residue. To a mixture of the crude residue thus obtained and DMF (4 mL) was added Cs_2CO_3 (4.30 g, 13.2 mmol). The reaction mixture was stirred at room temperature for 20 h. After addition of saturated aqueous $NaHCO_3$ (40 mL), the mixture was extracted with hexane (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$, concentrated ,and chromatographed on silica gel (hexane−Et_2O) to give **1b** (1.32 g, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.11 (d, J = 2.1 Hz, 1H), 5.48 (t, J = 2.1 Hz, 1H), 5.18 (t, J = 2.1 Hz, 1H), 3.93−4.01 (m, 1H), 3.64−3.74 (m, 1H), 2.53 (ddd, J = 2.1, 4.5, 12.9 Hz, 1H), 2.07−2.21 (m, 2H), 1.55 (q, J = 11.4 Hz, 1H), 0.94 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.8,

140.0, 111.4, 101.5, 69.3, 67.8, 46.2, 45.7, 25.94, 25.89, 18.4, 18.2, −4.5, −4.6, −4.8, −5.0; IR (neat) 2951, 2862, 1619, 1471, 1361, 1258, 1080, 911, 835, 675 cm^{-1}; $[\alpha]^{28}_D$ +57.4 (*c* 7.05, $CHCl_3$). Anal. Calcd for $C_{20}H_{39}BrO_2Si_2$: C, 53.67; H, 8.78. Found: C, 54.05; H, 8.52.

1α,25-Dihydroxyvitamin D_3 from 1a and 12. To a mixture of boronate **12**[7] (160 mg, 0.336 mmol), aqueous 3 N KOH (0.11 mL), and THF (0.3 mL) was added dropwise a mixture of bromide **1a** (89.5 mg, 0.200 mmol), $PdCl_2$(dppf) (12.3 mg, 0.0167 mmol), and THF (0.3 mL) at room temperature. The resulting mixture was stirred for 24 h at 60 °C. After addition of Et_2O (20 mL), the mixture was washed with aqueous 1 N HCl (10 mL) and brine (10 mL), dried over $MgSO_4$, concentrated, and purified by passing through a short silica gel column with 1% ether in hexane to provide the corresponding coupling product. To a solution of the coupling product thus obtained in THF (5 mL) was added TBAF (1 mL, 1 M in THF, 1.0 mmol). After the mixture was stirred for 24 h at room temperature, the solvents were removed under reduced pressure. The residue was diluted with H_3O (10 mL) and then extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane−ethyl acetate) to give 1α,25-Dihydroxyvitaminn D_3 (68.3 mg) in 82% yield, the spectral data (^{1}H NMR, IR) and $[\alpha]_D$ value of which were identical with those reported.[3] ^{13}C NMR ($CDCl_3$) δ 147.5, 143.0, 132.8, 124.8, 116.9, 111.7, 71.1, 70.8, 66.8, 56.5, 56.4, 45.9, 45.3, 44.4, 42.9, 40.5, 36.4, 36.1, 29.4, 29.3, 29.1, 27.7, 23.7, 22.3, 20.9, 18.9, 12.1; $[\alpha]^{30}_D$ 47.2 (*c* 1.29, EtOH) [lit.[3] $[\alpha]^{24}_D$ 47.9 (*c* 0.50, EtOH)].

Retiferol 13 from 1a and 14. 13 (55.1 mg) was obtained in 78% yield starting from **1a** (94.0 mg, 0.210 mmol) and **14**[7] (130 mg, 0.306 mmol) under similar reaction conditions as described for the synthesis of 1α,25-dihydroxyvitamin D_3 from **1a** and **12**. The ^{1}H NMR spectroscopic spectra were in full agreement with those reported.[17a] ^{13}C NMR ($CDCl_3$) δ 147.3, 135.4, 133.4, 129.4, 126.6, 112.0, 71.13, 71.09, 66.7, 45.1, 44.2, 42.9, 37.5, 36.4, 33.1, 32.6, 29.8, 29.3, 26.8, 21.8, 19.8; IR (neat) 3373, 2925, 1653, 1458, 1375, 1052, 908, 842, 759 cm^{-1}; $[\alpha]^{27}_D$ +14.7 (*c* 0.65, $CHCl_3$).

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Supporting Information Available: Analytical data for compounds **1c**, **1d**, **3b**−**d**, (*R*)-**9**, **10b**−**d**, **11b**−**d**, and 3-*epi*-13. This material is available free of charge via the Internet at http://pubs.acs.org.

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