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Type(English)	Doctoral Thesis

Efficient Synthesis of 1α,25-Dihydroxyvitamin D_3, 19-*nor*-1α,25-Dihydroxyvitamin D_3, and Their Derivatives

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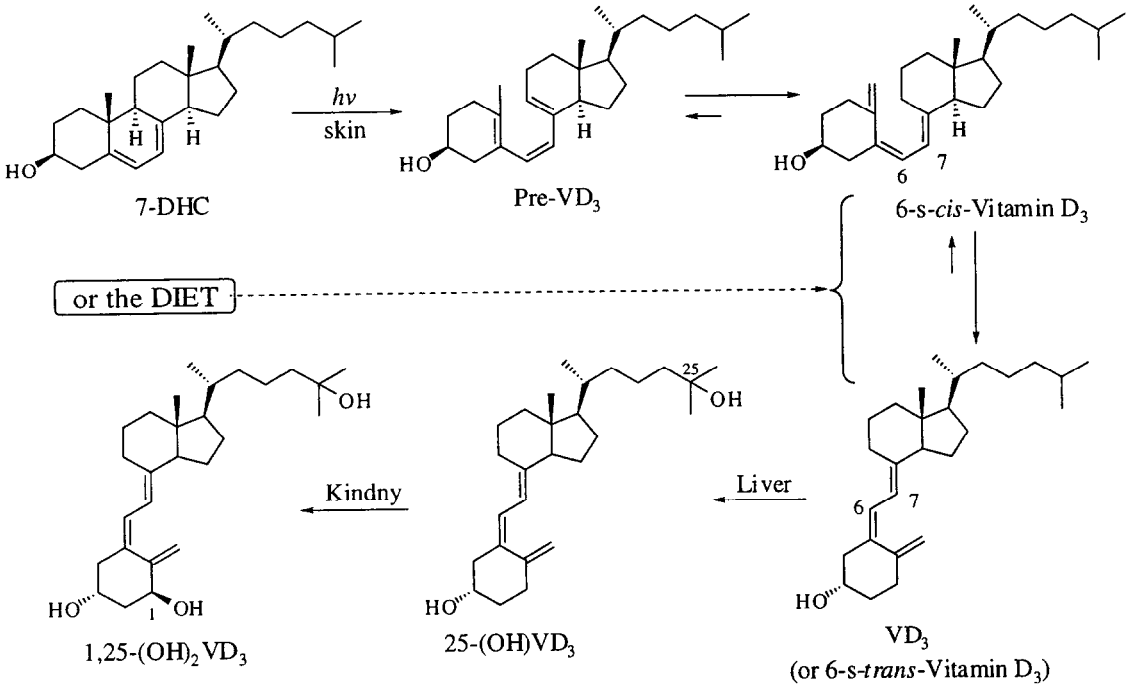
Contents

1. Introdution

1.1 Metabolism of VD_3

1α,25-dihydroxyvitamin D_3 [1,25-$(OH)_2VD_3$], an essential hormonal regulator in higher animals, is produced by the metabolic pathway shown in Figure 1-1.[1,2] The

Figure 1-1



natural vitamin D_3 [VD_3] is produced in skin upon ultraviolet irradiation of 7-dehydrocholesterol [7-DHC; also called provitamin D_3] or is absorbed from the diet. The reaction in skin is believed to be a purely photochemical process, not requiring enzymes or proteins. 7-DHC absorbs ultraviolet light, which effects an electrocyclic rupture of 9,10 bond to produce previtamin D_3 [Pre-VD_3]. The latter is likely a biologically inert compound, which is thought to spontaneously isomerize to VD_3, initially producing the 6-s-*cis*-vitamin D_3 which rapidly rotates about its 6,7 single bond to its more commonly depicted (and more stable) 6-s-*trans*-vitamin D_3. The conversion of VD_3 to 25-hydroxyvitamin D_3 [25-(OH)VD_3] in liver is carried out by a microsomal system. The metabolite 25-(OH)VD_3, the major circulating form of the vitamin D in serum, is then further metabolized to 1,25-$(OH)_2VD_3$ in the kidney. This

1α-hydroxyration occurs exclusively in the renal mitocondorial fraction and involves NADPH, a flavoprotein, an iron sulfur protein, and a cytochrome P-450. The hormone 1,25-$(OH)_2$-VD_3 is transported via the plasma to target cells located for example in the intestine, kidney, and bone. In these target cells, 1,25-$(OH)_2$-VD_3 interacts with specific receptors of the hormone such as the vitamin D_3 receptor [VDR]. The interaction between the ligand and this receptor or other receptors then leads to genomic or nongenomic responses.

1.2 Development of New Analogues of 1,25-$(OH)_2$-VD_3[3]

The discovery of 1,25-$(OH)_2VD_3$ in the early 1970s immediately led to its chemical synthesis for hormone replacement therapy.[4] 1,25-$(OH)_2VD_3$ proved to be valuable calcemic agents capable of the correction of hypocalcemia and bone abnormalities. VD_3 analogues also attracted attention as a more effective substitute for 1,25-$(OH)_2VD_3$.

Although VD_3 analogues attracted interest firstly as calcemic agent, the emergence of the newer nonclassical functions of 1,25-$(OH)_2VD_3$, particularly the discovery of its role in controlling cell proliferation and differentiation, has opened up the possibility as new drugs in other fields such as psoriasis.

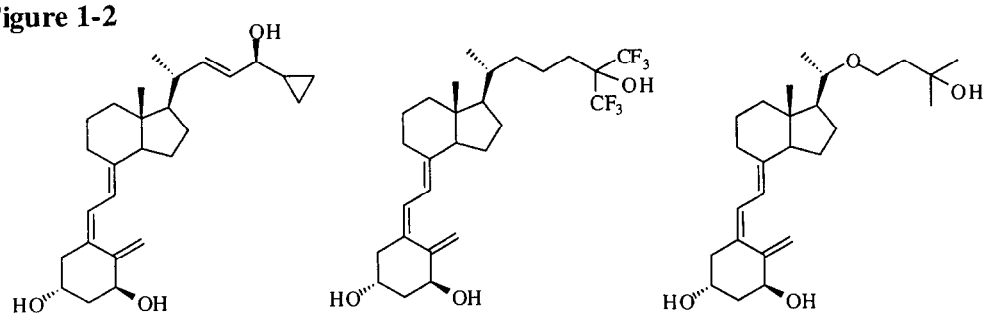
The chemical synthesis of new analogues of 1,25-$(OH)_2VD_3$, therefore, became a major priority with hope that the calcemic properties of 1,25-$(OH)_2VD_3$ might be separated form the antiproliferative cell-differentiating properties. Hundreds of molecules have now been synthesized in pursuit of this goal; these analogues can be classified into three groups as follows.

1) Side-Chain-Modified Analogues

The side chain is an attractive part for modification because of the two major reasons. (Figure 1-2). One is the biological reason that the VDR is relatively tolerant of changes in this part of the molecule, and the other is the synthetic reason that this modification can be easily achieved.[1,5]

Probably the most successful this type of derivatives developed so far is the Leo antipsoriatic drug calcipotriol, also known as MC903, which was the first vitamin D analogue to reach the market for any condition other than hypocalcemia or bone disease.[6]

Figure 1-2

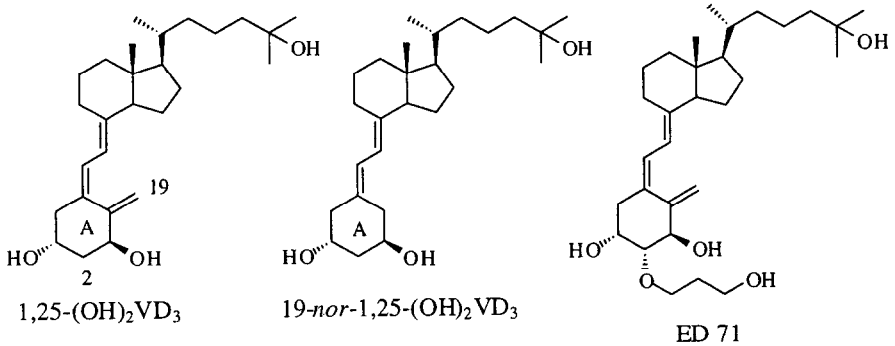


Calciportriol (MC903) 26,27-F_6-1α,25-$(OH)_2VD_3$ 22-Oxacalcitoriol (OCT)

2) A-Ring-Modified Analogues

The analogues with modification in the A-ring have also attracted much interest as potential therapeutical agents. Representative analogues developed so far were 19-*nor*-1,25-$(OH)_2VD_3$ and the Chugai analogue ED 71 as shown in Figure 1-3.[7,8] The former was simplified by the deletion of the 19-metylene group of 1,25-$(OH)_2VD_3$, which increased significantly the stimulation of differentiation and growth inhibition of tumor cells without a parallel increase in hypercalcemia.

Figure 1-3

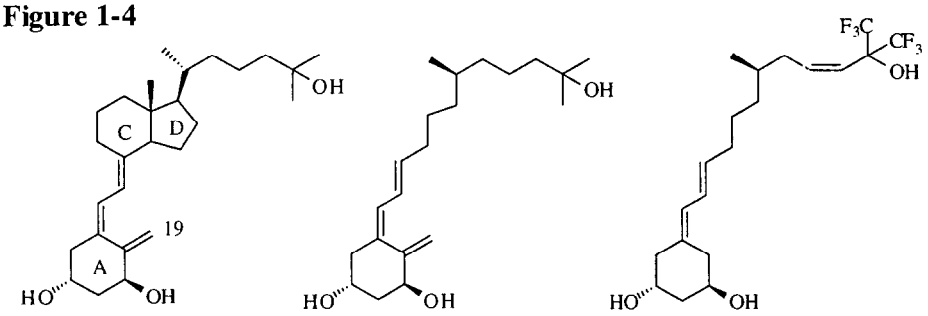


1,25-$(OH)_2VD_3$ 19-*nor*-1,25-$(OH)_2VD_3$ ED 71

3) C,D-Ring-Modified Analogues

The VD_3 analogues modified in the C and/or D rings also have been developed.[9,10] Recently the retiferol **1**, a compound that lacks the C,D-ring substructure, was synthesized (Figure 1-4).[10a] Moreover, the molecular structure of *des*-C,D-VD_3 was further modified in the side chain and simplified in the A-ring segment, which was finally leading to the *des*-C,D-19-*nor*-VD_3 derivative **2** (Ro 65-2299) as a clinical candidate for the evaluation of a potential oral therapy for psoriasis.[10b,c]

Figure 1-4



1,25-$(OH)_2VD_3$ Retiferol **1** RO-65-2229 (**2**)

1.3 General Synthetic Approaches to 1,25-$(OH)_2VD_3$ and its derivatives[1,11]

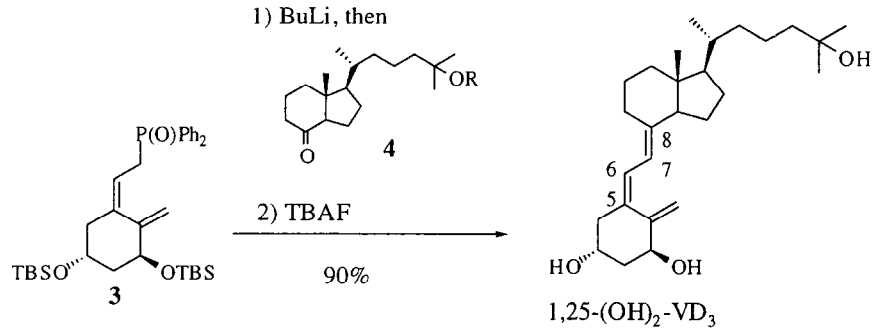
The chemical synthesis of 1,25-$(OH)_2VD_3$ and its analogues has been the subject of extensive research because organic synthesis is the only means of supplying sufficient quantities and creating more effective compounds. Hitherto, the synthesis has been carried out by both linear and convergent methods. The former is the stepwise synthesis from natural steroid hormones such as VD_3. The latter convergent method is the synthetic approach by coupling between A-ring and C,D-ring parts, and is more efficient and suitable for the large scale synthesis.

In this section, two efficient convergent syntheses, which have been widely accepted as practical method by chemists in industry, are introduced.

1) Hoffmann-La Roche Approach

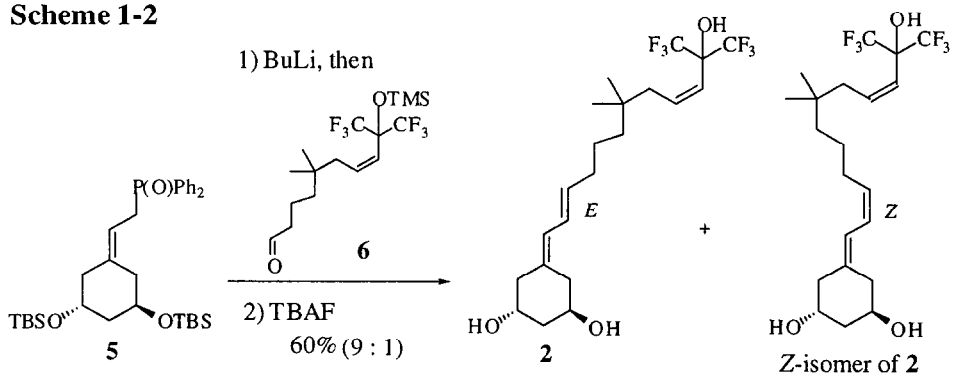
This approach was developed by the Hoffmann-La Roche group to achieve the first total synthesis of 1,25-$(OH)_2VD_3$.[12] As shown in Scheme 1-1, Horner-Wittig reaction between phosphine oxide **3** and C,D-ring ketone **4** produced 1,25-$(OH)_2VD_3$, after deprotection, in 90% overall yield. In this transformation, the newly formed C-7 and C-8 double bond has exclusively the desired natural E-geometry.

Scheme 1-1



One weak point of this method can be seen in the preparation of *des*-C,D-19-*nor*-analogues. As mentioned above, the Wittig olefination reaction with **4** proceeded with excellent stereoselectivity, however, in the case of *des*-C,D-19-*nor*-VD_3s such as **2**, difficulty was incurred in coproducing the stereoisomer in relation to the newly formed olefin moiety (Scheme 1-2).[10c]

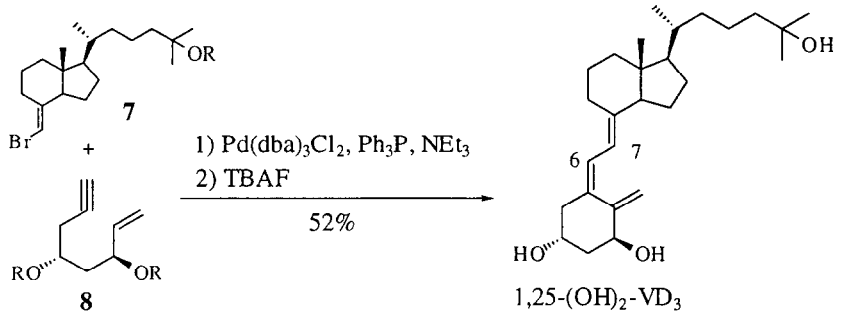
Scheme 1-2



2) Trost Approach

The convergent strategy reported by Trost in 1992, took advantage of a Pd-catalyzed alkylative enyne cyclization to form C-6 and C-7 bond and close the A-ring in one pot from C,D-ring unit **7** and acyclic unit **8** which serves as the precursor of the A-ring (Scheme 1-3).[13] In addition to natural 1,25-$(OH)_2VD_3$, this strategy has been applied to the preparation of several VD_3 analogues. However, the synthesis of 19-*nor*-VD_3 derivatives by this method seems difficult.

Scheme 1-3

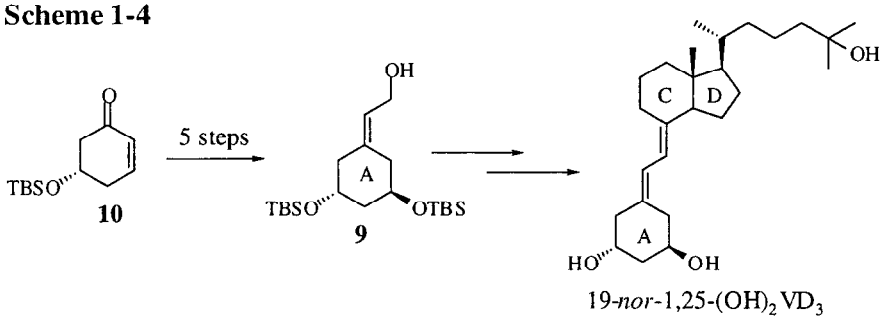


1.4 Aims of the thesis

The main purpose of the present work is to develop another practical synthetic approach to 1,25-$(OH)_2VD_3$ and its derivatives, which might be used complementarily (or which might be complementary) to the Hoffmann-La Roche and Trost methods. The thesis also includes efficient preparation of A-ring part of 19-*nor*-1,25-$(OH)_2VD_3$ which is used in the Hoffmann-La Roche approach (or A-ring intermediate of 19-*nor*-1,25-$(OH)_2VD_3$ reported by the Hoffmann-La Roche group). This thesis consists of five chapters including this introduction chapter, summary of each chapter is as follows:

Chapter 2 "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". In this chapter, it is reported that the known A-ring intermediate of 19-*nor*-1,25-$(OH)_2D_3$, **9**, can be efficiently synthesized from readily available optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**10**) as a versatile building block for synthesizing chiral cyclohexane derivatives.(Scheme 1-4).

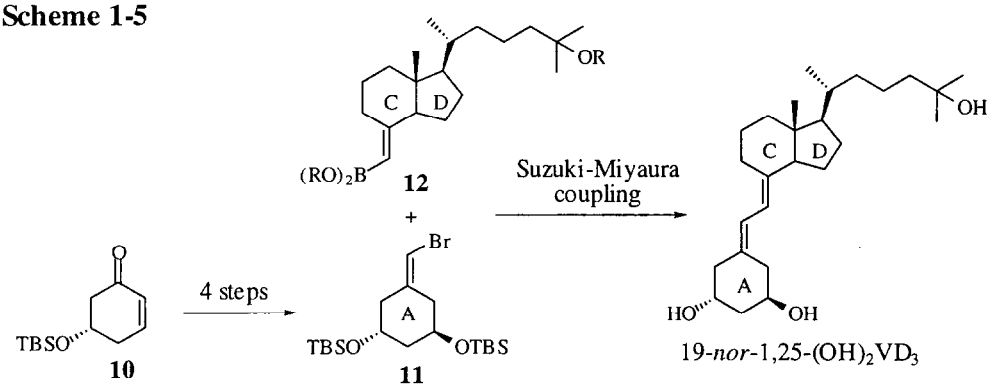
Scheme 1-4



Chapter 3 "Novel Synthetic Approach to 19-*nor*-1α,25-Dihydroxyvitamin D_3 and its

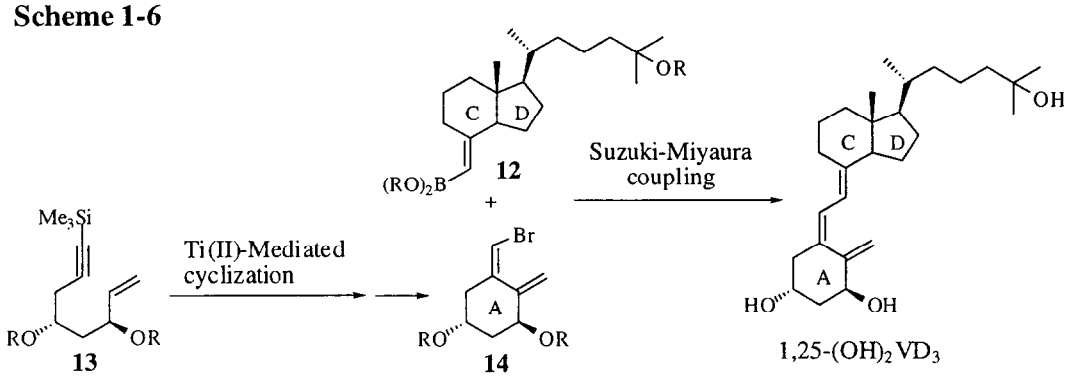
Derivatives by the Suzuki-Miyaura Coupling in Solution and on Solid Support". This chapter describes an efficient and high-yield preparation of the new A-ring intermediate **11** and its utilization for the synthesis of 19-*nor*-1,25-$(OH)_2VD_3$ and *des*-C,D-19-*nor*-VD_3s by the Suzuki-Miyaura coupling under liquid- and/or solid-phase reaction conditions (Scheme 1-5).

Scheme 1-5



Chapter 4 "Efficient Convergent Synthesis of 1α,25-Dihydroxyvitamin D_3 and its Analogues by the Suzuki-Miyaura Coupling". In this chapter, new methodology for synthesizing 1,25-$(OH)_2VD_3$ and its derivatives is reported. This method involves the preparation of A-ring part **14** by the titanacyclization of readily available 1,7-enyne **13** using a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl, and its coupling with C,D-ring portion **12** by the Suzuki-Miyaura protocol (Scheme 1-6).

Scheme 1-6



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2000, *11*, 4171. (c) Hilpart, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681.

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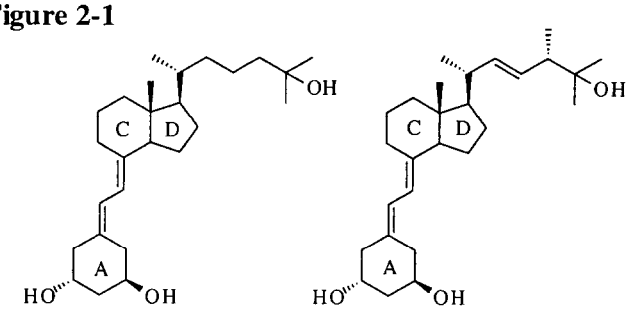
2. Efficient and Practical Synthesis of the A-Ring Precursor of 19-*nor*-1α,25-Dihydroxyvitamin D_3 and its ^{13}C- or ^{2}H-Labeled Derivative

2.1 Introduction

1,25-$(OH)_2VD_3$, the biologically active form of VD_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 1,25-$(OH)_2VD_3$ increased significantly the stimulation of differentiation and growth inhibition of tumor cells without a parallel increase in hypercalcemia.[2] With this finding, 19-*nor*-1,25-$(OH)_2VD_3$ itself and also its derivatives having a different side chain such as paricalcitol have attracted much interest as potential therapeutical agents (Figure 2-1).[3]

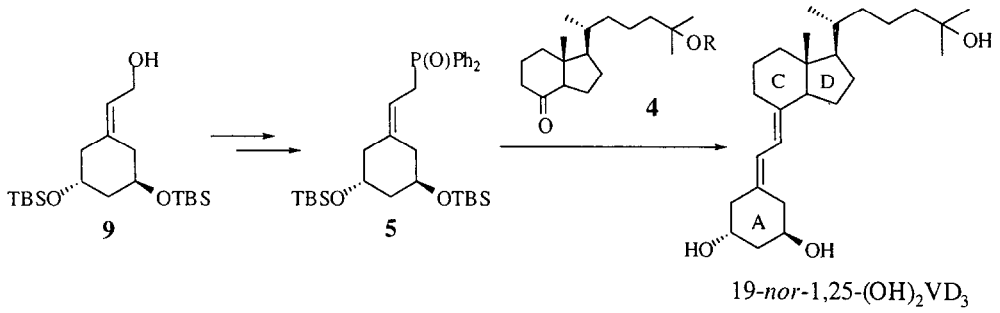
Figure 2-1



19-*nor*-1,25-$(OH)_2VD_3$ Paricalcitol

One efficient method for synthesizing these compounds involves a Wittig olefination of the diphenylphosphine oxide **5** derived from the allyl alcohol **9** via the chloride with the corresponding carbonyl moiety, as exemplified by the synthesis of 19-*nor*-1,25-$(OH)_2VD_3$ as shown in Scheme 2-1.[4] Considerable efforts, therefore, have been made towards developing an industrially viable access to **9**, the A-ring precursor of 19-*nor*-1,25-$(OH)_2VD_3$.

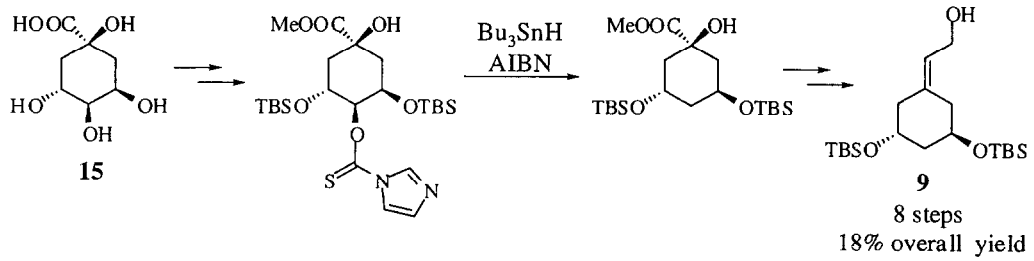
Scheme 2-1



Five syntheses of **9** have been reported so far and representative examples are briefly mentioned below.

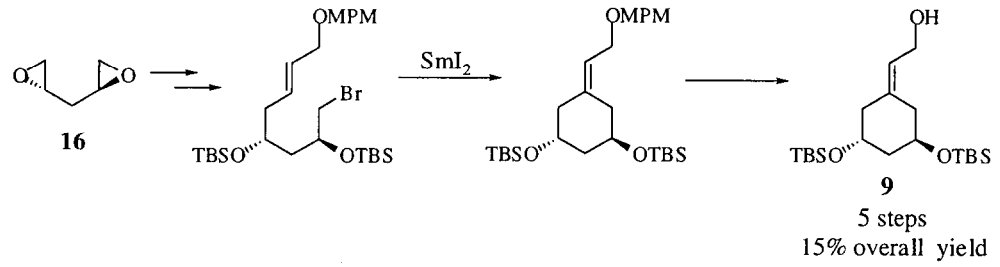
(a) DeLuca et al. prepared **9** starting from (-)-quinic acid (**15**) via an eight-step reaction, including radical deoxygenation with tributyltin hydride in the presence of AIBN, in 18% overall yield (Scheme 2-2).[2b]

Scheme 2-2



(b) Vandewalle et al. reported a five-step synthesis with 15% overall yield starting from readily available (2*S*, 4*S*)-1,2:4,5-diepoxypentane (**16**),[5] where an intramolecular radical cyclization using SmI_2 is the key reaction (Scheme 2-3).[6]

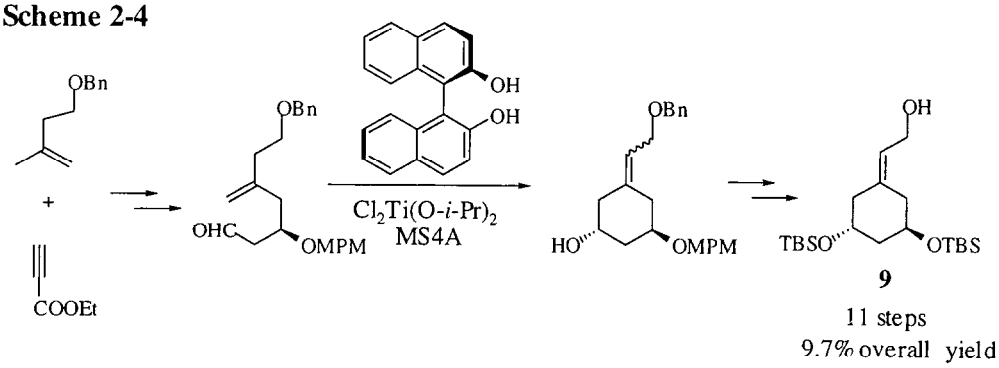
Scheme 2-3



(c) Mikami et al. accomplished the synthesis starting from achiral acyclic precursors

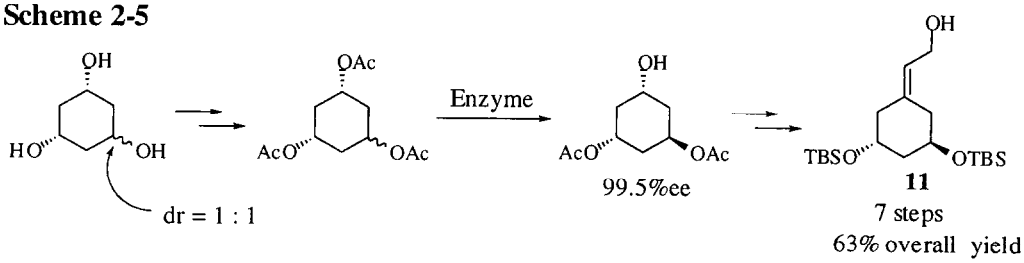
and using carbonyl-ene cyclization as a key reaction in 11 steps in 9.7 % overall yield (Scheme 2-4).[7]

Scheme 2-4



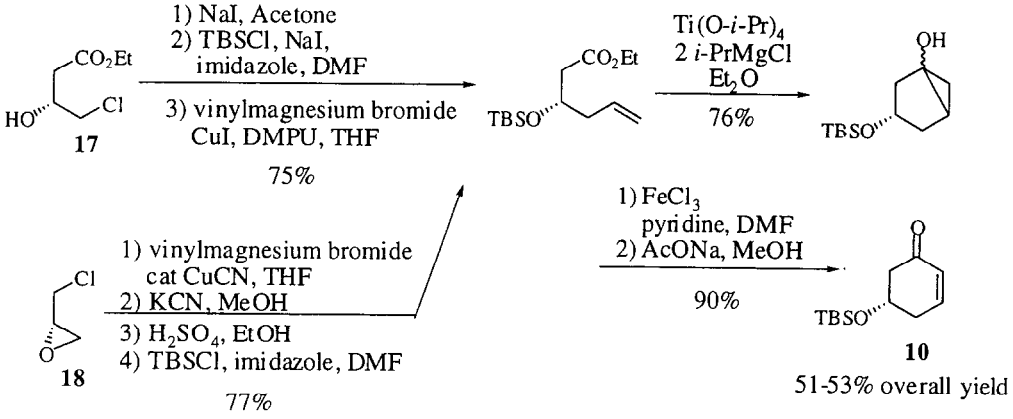
(d) Recetly, Hilpert et al. developed an efficient approach to **9** starting from triacetate of *trans*-cyclohexane-1,3,5-triol, which employs selective enzymatic hydrolysis as shown in Scheme 2-5 (63% overall yield).[3d,e]

Scheme 2-5



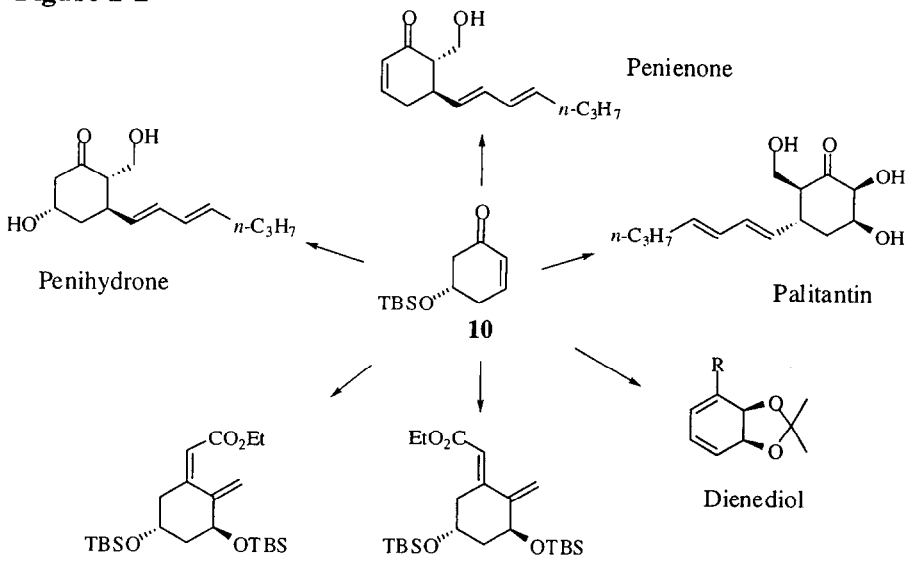
We have recently developed optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**10**) as a versatile building block for synthesizing chiral cyclohexane derivatives.[8] The compound **10** can be readily prepared starting from optically active ethyl 3-hydroxy-4-chlorobutyrate (**17**)[8a] or epichlorohydrin (**18**),[8g] both of which are commercially available. In both synthetic approaches as shown in Scheme 2-6, all of

Scheme 2-6



the reagents used are readily available, non-toxic, and inexpensive, and the overall yield exceeds 50%. We believe, therefore, that **10** can be easily prepared in quantity and thus might find industrial use. We have, so far, revealed that **10** can be conveniently used as a starting compound for synthesizing several natural products and their known intermediates such as penienone,[8c] penihydron,[8c] palitantin,[8d] the A-ring synthon of 1,25-$(OH)_2VD_3$[8e,f] and optically active *cis*-cyclohexane-3,5-dien-1,2-diol acetonides.[8g] (Figure 2-2)

Figure 2-2

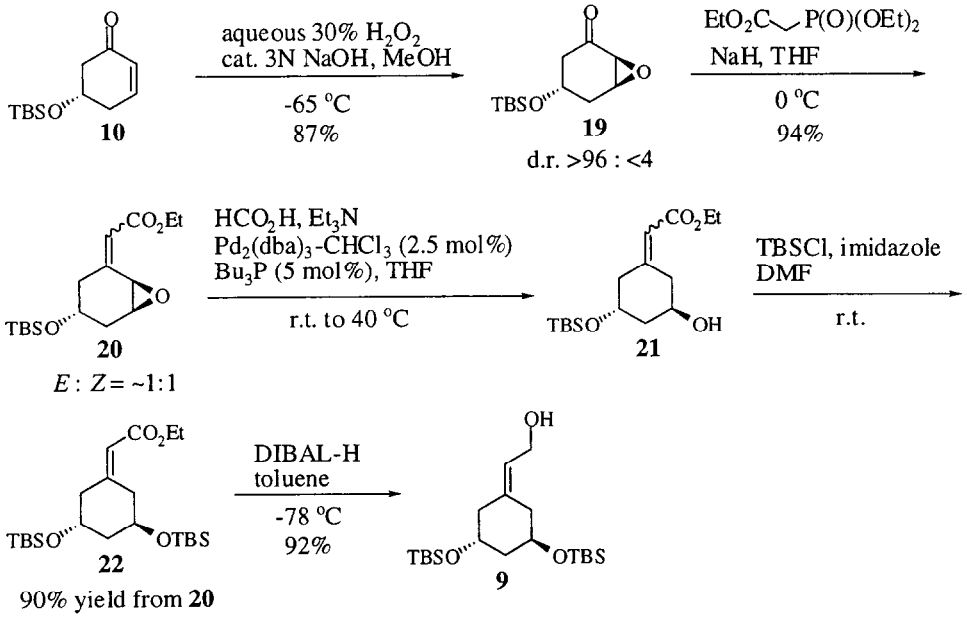


A-ring synthon of 1,25-$(OH)_2VD_3$

2.2 Synthesis of the A-Ring Precursor of 19-*nor*-1,25-$(OH)_2VD_3$

We envisaged that another efficient synthesis of the A-ring intermediate **9** could be accomplished by using readily available **10**. The synthesis of **9** from **10** can be accomplished according to the reaction sequence shown in Scheme 2-7, which involves highly diastereoselective epoxidation of **10** to **19**, Horner-Wadsworth-Emmons

Scheme 2-7



olefination of **19** to **20**, and regioselective reductive ring opening of the epoxide moiety of **20** to **21**. Epoxidation of **10** under various conditions was examined. As shown in Table 2-1, it was found that the use of H_2O_2/NaOH at –65 °C gives **19** in 87% yield with the highest diastereomeric ratio of >96: <4 (entry 2). Phenol was not coproduced under this condition, although we were afraid that **10** could be easily converted to phenol under basic conditions. Oxone at 0 °C (6 h) afforded **19** in 22% yield[9] and 94% d.r (entry 3), whereas TBHP/Triton-B (5 °C, 3 h) gave **19** in 70% yield[10] and 85% d.r (entry 4). It is noteworthy that *m*-CPBA failed to oxidize **10** because of the electronic deficiency of its olefinic part (entry 5).

Table 2-1 Epoxidation of **10** under various conditions

Entry	Reagent	Solvent	Temper-ature	Time	Diastereo-ratio	NMR Yield
1	H_2O_2 10 eq NaOH 0.15 eq	MeOH	0 °C	6 h	90 : 10	85%
2	H_2O_2 10 eq NaOH 0.15 eq	MeOH	-65 °C	30 h	>96 : <4	87%
3	OXONE 2.4 eq	H_2O	2 °C	6 h	94 : 6	22%
4	TBHP 5 eq TritonB 0.06 eq	EtOH-Dioxane	5 °C	3 h	85 : 15	70%
5	m-CPBA 4 eq	CH_2Cl_2	r.t.	50 h		0%

The Horner–Wadsworth–Emmons olefination reaction of **19** with $(EtO)_2(O)PCH_2CO_2Et$ afforded **20** 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 **20** to **21** 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 TBS ether followed by column chromatography provided **22**[12] in 90% overall yield from **20**. The compound **9** ($[\alpha]^{29}_D$ +17.8 (*c* 1.02, $CHCl_3$), lit.,[3d] $[\alpha]_D$ +18.4 (1%, $CHCl_3$)) was finally synthesized in 92% yield by the reduction of **22** with DIBAL-H,[13] the spectral data of which were in good agreement with those reported.[3d,7a] Thus, the synthesis of **9** from **10** was attained in five steps and in 68% overall yield.[14]

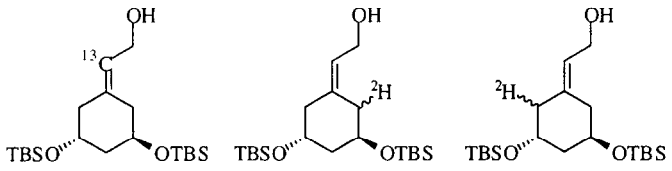
2.3 Synthesis of the ^{13}C or ^{2}H-Labeled A-Ring Precursor

There have been considerable advances in the development of structure-function relationships for VD_3 through syntheses and biological studies of a large number of analogues. However, our understanding of the mode of action at the molecular level remains limited. Isotopically labeled VD_3 compounds are therefore of great importance. Deuterium-labeled VD_3 analogues are useful for studying the enzymatic hydroxylation and the vitamin/previtamin equilibrium, and ^{13}C-labeled VD_3 compounds are useful for direct conformational studies of ligands bound to proteins.

Another attractive feature of the present approach as mentioned above is the fact that it allows the synthesis of **9** labeled with ^{13}C or ^{2}H (Figure 2-3). 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 **19** to **20** in Scheme 2-7 provided **9** 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 **20** to **21** afforded a mixture of **9** having a ^2H atom on the cyclohexane ring at the C-4 and C-10 positions.[16]

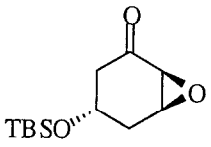
Figure 2-3



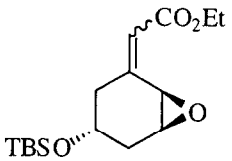
6-^{13}C-**9** ^{2}H-**9**
(a mixture of four compounds)

2.4 Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Gemini-2000 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00). IR spectra were recorded on an FT-IR spectrometer (JASCO FT/IR-230. Elemental analyses were performed on an Elemental automatic analyzer. GC-MS (low-resolution mass spectrum, EI) analyses were performed on a Shimadzu QP-5000 GC-mass spectrometer. All reactions sensitive to oxygen and/or moisture were performed under an argon atmosphere. Dry solvents (THF, ethyl ether, and toluene) were purchased from Kanto Chemicals Co. (Japan). Other chemicals are commercially available, unless otherwise indicated, and were used as received. 5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenone (**10**) was prepared from commercially available ethyl (*R*)-3-hydoxy-4-chlorobutyrate by the reported procedure.[8a,c]

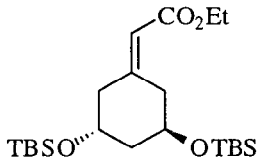


(1*S*,4*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-7-oxa-bicyclo[4.1.0]heptan-2-one (19): To a mixture of **10** (6.14 g, 27.2 mmol) and 35% aqueous H_2O_2 (23.6 mL, 272 mmol) in MeOH (210 mL) was added aqueous 3 N NaOH (4.8 mL, 14.4 mmol) at –78 °C. The resulting mixture was then stirred vigorously for 30 h at –65 °C. After the addition of aqueous saturated NH_4Cl (210 mL) to this mixture, the volume was reduced to half by removing the solvents in vacuo. The residue was extracted with CH_2C1_2 (3 x 150 mL), dried over $MgSO_4$, and concentrated to give a pale yellow oil which was purified by column chromatography (SiO_2, hexane-Et_2O) to yield the corresponding epoxide **19** (5.74 g) in 87% yield. Diasteromeric ratio was found to be >96: <4 by GC analysis [HR-1 capillary column, Shinwa Chemical Industries, Ltd., 0.25 ϕ x 30 m, He 0.5 mL/min, starting at 60 °C (2 min) to 280 °C at the rate of 10 °C/min: retention time = 12.57 min for the major isomer and 12.72 min for the minor isomer]. ^{1}H NMR ($CDCl_3$) δ 4.21-4.30 (m, 1H), 3.55 (br s, 1H), 3.26 (d, J = 3.9 Hz, 1H), 2.76 (dd, J = 3.0, 15.3 Hz, 1H), 2.39 (dd, J = 3.9, 15.3 Hz, 1H), 2.19 (dd, J = 6.6, 15.3 Hz, 1H), 2.00 (br d, J = 15.3 Hz, 1H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.8, 67.3, 55.4, 54.7, 44.9, 32.9, 25.5, 17.8, -5.0, -5.1; IR (neat) 2929, 2888, 2857, 1726, 1472, 1406, 1361, 1331, 1255, 1075, 1031, 985, 935, 871, 837, 778, 715; $[\alpha]^{29}_D$ -12.1 (*c* 0.500, $CHCl_3$); Anal. Calcd. for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.15; H, 8.98.



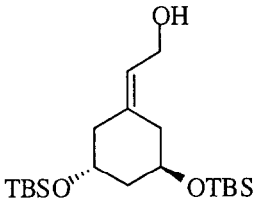
[(1*R*,4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-7-oxa-bicyclo[4.1.0]hept-2-ylidene]acetic acid ethyl ester (20): To a suspension of NaH (0.54 g, 55% in oil, 13 mmol) in THF (20 mL) was slowly added diethylphonoacetic acid ethyl ester (2.6 ml, 13 mmol) at 0 °C with efficient stirring. The mixture was allowed to warm to room temperature and stirred for 30 min. To this mixture was added a solution of **19** (2.42 g, 10 mmol) in

THF (10 ml) at 0 °C. The stirring was continued for 1 h at 0 °C. After the addition of aqueous saturated NH_4Cl (30 ml) at 0 °C, the mixture was extracted with Et_2O (3 x 20 ml). The combined extracts were dried over $MgSO_4$, and concentrated to give a yellow residue, which was purified by flash-chromatography (SiO_2, hexane-Et_2O gradient) to afford **20** (2.99 g) as a colorless oil in 94% yield. A 1: 1 mixture of *E*- and *Z*-**20**: ^1H NMR ($CDCl_3$) δ 6.09 (s, 1H), 5.93 (s, 1H), 4.78 (d, *J* = 3.9 Hz, 1H), 4.07-4.27 (m, 4H), 3.92-4.03 (m, 2H), 3.40-3.48 (m, 2H), 3.37 (d, *J* = 3.6 Hz, 1H), 2.97 (dd, *J* = 7.2, 16.5 Hz, 1H), 2.76 (dt, *J* = 2.7, 16.5 Hz, 1H), 2.50 (d, *J* = 14.7 Hz, 1H), 2.20-2.36 (m, 2H), 2.06 (dd, *J* = 6.6, 14.7 Hz, 1H), 1.76-1.91 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26 (t. *J* = 7.2 Hz, 3H), 0.83 (s, 18H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.4, 165.2, 152.4, 151.9, 123.0, 121.9, 65.4, 64.9, 60.1, 59.9, 56.0, 54.9, 54.6, 49.9, 39.7, 33.8, 33.4, 25.8, 18.0, 14.3, -4.6, -4.7, -4.8, -4.9; IR (neat) 2955, 2856, 1717, 1650, 1471, 1386, 1256, 1153, 1093, 1040, 870, 835, 778 cm^{-1}.

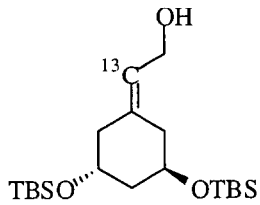


[(3*R*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)cyclohexylidene]acetic acid ethyl ester (22): To a solution of $Pd_2(dba)_3CHCl_3$ (134 mg, 0.13 mmol) in dioxane (5 mL) was added *n*-Bu_3P (0.065 mL, 0.26 mmol) at ambient temperature. To the mixture was added a solution of formic acid (0.98 mL, 25.5 mmol) and Et_3N (1.2 mL, 10.2 mmol) in 1,4-dioxane (10 mL) at room temperature. After the mixture was stirred for 5 min, a solution of the epoxide **20** (1.59 g, 5.1 mmol) in dioxane (15 mL) was added. The reaction was initiated by heating to 40 °C for a few minutes and then the mixture was stirred at room temperature for 30 min. After the addition of H_2O (20 mL), the mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a yellow residue. To a solution of the resulting crude residue and imidazole (1.02 g, 15.0 mmol) in DMF (15 mL) was added TBSCl (1.57 g, 10 mmol) in several portions. After the mixture was stirred for 12 h at room temperature, H_2O (20 mL) was added. The mixture was extracted with hexanes (3 x 25 ml), dried ($MgSO_4$), and concentrated in vacuo to give a residue which was purified by flash chromatography (SiO_2; only hexane) to yield **22** (1.92 g) in 90%

yield. $[\alpha]^{29}_D$ (*c* 0.26, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 166.2, 156.5, 117.3, 68.0, 67.9, 59.6, 46.1, 43.2, 37.5, 25.9, 25.8, 18.1, 14.4, -4.67, -4.71, -4.9, -5.0. Spectroscopic data of ^1H NMR and IR were in good agreement with those reported.[2]

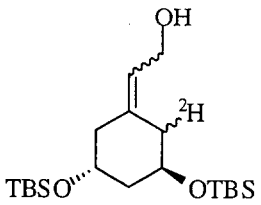


2-[(3*R*,5*R*)-3,5-Bis-(*tert*-butyldimethylsiloxy)cyclohexylidene]ethanol (9): To a stirred solution of **22** (2.14 g, 5 mmol) in toluene (25 mL) was added dropwise diisobutylaluminum hydride (13 mL, 1.14 M in toluene, 15 mmol) over 30 min at –78 °C. After the solution was stirred for 2 h, methanol (5 mL) and H_2O (5 mL) were cautiously added at –78 °C. The mixture was then warmed to room temperature and stirred for 0.5 h. To this were added NaF (5 g) and Celite (5 g), and then the resulting mixture was stirred for 1 h. The mixture was filtered through a pad of Celite with Et_2O (50 mL) and the filtrate was concentrated in vacuo to give a residue which was purified by flash chromatography (SiO_2; hexanes-Et_2O gradient) to yield **9** (1.81 g) as a white solid in 94% yield. mp 63-65 °C (lit.,[2] mp 63-65 °C) $[\alpha]^{29}_D$ +17.9 (*c* 1.02, $CHCl_3$) [lit.,[2] $[\alpha]_D$ +18.4 (*c* 1%, $CHCl_3$)]; ^{13}C NMR ($CDCl_3$) δ 138.2, 125.2, 68.1, 67.9, 58.4, 45.6, 43.4, 36.6, 25.9, 18.2, -4.6, -4.66, -4.70, -4.74. Spectroscopic data of ^1H NMR, EI-MS and IR were in good agreement with those reported.[2,3]



Compound 6-^{13}C-9: Prepared from **10** according to the same procedure for preparation of **9**, except for the use of $(EtO)_2(O)P\text{-}^{13}CH_2CO_2Et$ instead of $(EtO)_2(O)PCH_2CO_eEt$ for conversion of **19** to **20**, in a similar yield. ^{13}C Atom incorporation was calculated to be more than >98% by GC/EI-MS analysis [*m/z* 238 (34), 212 (29.6), 198 (48.8), 172 (100): HR-1 capillary column, Shinwa Chemical Industries, LTD, 0.25 ϕ x 30 m, He 40 kPa, starting at 120 °C (2 min) to 280 °C at the rate of 10 °C/min: retention time = 16.3-20.3 min] ^1H NMR ($CDCl_3$) δ 5.58 (dt, $J_{C\text{-}H}$ = 154.2 Hz and J = 7.2 Hz, 1H), 3.95-

4.18 (m, 2H), 2.26-2.38 (m, 2H), 2.18 (dt, J = 10.5, 3.6 Hz, 1H), 1.99-2.09 (m, 1H), 1.76-1.85 (m, 1H), 1.63 (ddd, J = 3.0, 8.7, 13.0 Hz, 1H), 1.45 (br s, 1H, OH), 0.87 (s, 18H), 0.05 (s, 6H), 0.04 and 0.03 (2s, each 3H); ^{13}C NMR ($CDCl_3$) δ 138.2 (d, $J_{C\text{-}C}$ = 72.8 Hz), 125.2 (^{13}C atom present at the C-6 position, steroid numbering), 68.1 (d, $J_{C\text{-}C}$ = 2.8 Hz), 67.8 (d, $J_{C\text{-}C}$ = 2.6 Hz), 58.4 (d, $J_{C\text{-}C}$= 46.7 Hz), 45.7, 43.4, 36.7, 25.9, 18.2, -4.56, -4.66, -4.6, -4.74.



^{2}H-Labeled 9 (a mixture of 4- and 10-^{2}H-9): Prepared from **10** according to the same procedure for preparation of **9**, except for the use of DCO_2D instead of HCO_2H for conversion of **20** to **21**, in a similar yield; The ^{1}H and ^{13}C NMR spectra of the resulting ^{2}H-**9** indicated that the residue consisted of two regioisomers, each of which consisted of two stereoisomers, the ratio of which (total four isomers) was determined to be approximately 36:28:21:15 based on ^{13}C NMR. Deuterium incorporation was calculated to be more than >93% by GC/EI-MS analysis [*m/z* 238 (28.7), 212 (29), 198 (39.5), 172 (100): HR-1 capillary column, Shinwa Chemical Industries, LTD, 0.25 ϕ x 30 m, He 40 kPa, starting at 120 °C (2 min) to 280 °C at the rate of 10 °C/min: retention time = 16.3-20.3 min (four isomers could not be separated)] and by comparison of the ^{1}H NMR with that of **9** [for **9**: δ 2.25-2.45 (m, 2H), 2.18 (dd, J = 3.0, 10.5 Hz, 1H), 2.05 (dd, J = 8.1, 13.2 Hz, 1H)]. ^{13}C NMR ($CDCl_3$) δ 138.3, 125.4, 68.1, 68.0, 67.84, 67.80, 58.3, 45.54 and 45.47 [observed as main peaks among multiplet (45.8-45.9)], 43.3, 36.57 and 36.50 [observed as main peaks among multiplet (36.0-36.6)], 25.7, 18.0, -4.86, -4.95, -4.99, -5.03.

2.5 References and Notes

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9. Recovery of **10** was 75%.
10. Phenol was co-produced in 30% yield.
11. For reductive epoxide-ring opening of diene mono-epoxides 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.

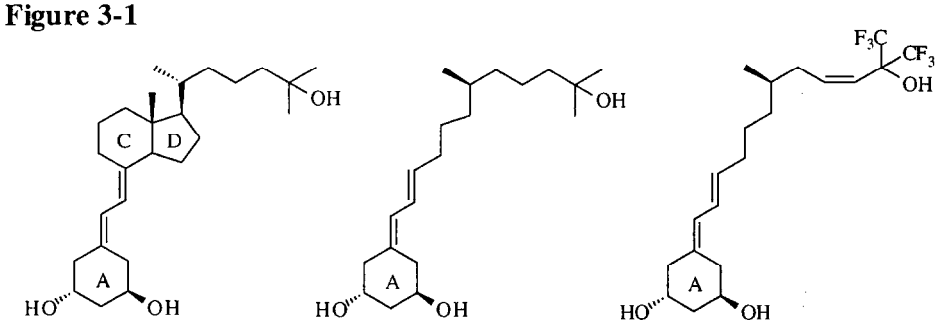
12. $[\alpha]^{29}_{D}$ + 18.0 (*c* 0.26, $CHCl_3$). Spectral data (^1H NMR and IR) were in good agreement with those reported.[2b,3d]
13. The reduction of **22** to **9** with Red-Al was reported to proceed in 95% yield, see ref. 3d.
14. Thus, **9** was obtained in 35% overall yield in 11 steps from ethyl 3-hydroxy-4-chlorobutyrate.
15. Purchased from Aldrich.
16. Deuterium incorporation of the resulting ^2H-**9** was determined to be >93% by GC/MS analysis.

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

3.1 Introduction

1,25-$(OH)_2VD_3$ is a hormonal, biologically active form of VD_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.* synthesized 19-*nor*-1,25-$(OH)_2VD_3$, in which the exocyclic methylene group on the A-ring has been replaced by two hydrogen atoms. This 19-*nor*-analogue showed a selective activity profile, combining high potency in inducing differentiation of malignant cells with very low or no bone calcification activity.[2] With this finding, 19-*nor*-1,25-$(OH)_2VD_3$ 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 **23** and **2** (Ro 65-2299) shown in Figure 3-1 have attracted much interest as potential therapeutical agents.[3]

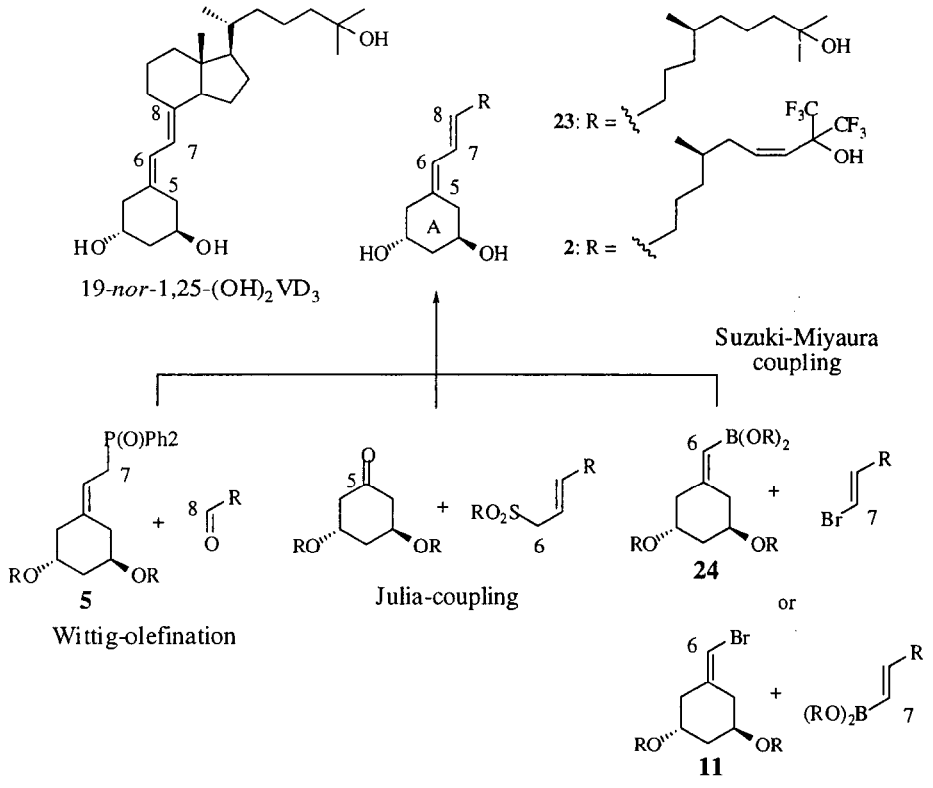
Figure 3-1



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 connection between the C-7 and C-8 positions (see Scheme 3-1), which proceeded with excellent stereoselectivity. However, in the preparation of *des*-C,D-19-*nor*-VD_3s **23** and **2** via a

similar Wittig olefination, difficulty was incurred in coproducing 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 **11** or alkenylboronate **24**, because they failed to prepare **11** and could prepare **24** in only very low yield. This approach, however, is very attractive because it might not only provide another practical approach to the known 19-*nor*-VD_3s, including **23** and **2**, but also open up an entry to new 19-*nor*-VD_3 derivatives that are difficult to prepare through other pathways.[4]

Scheme 3-1

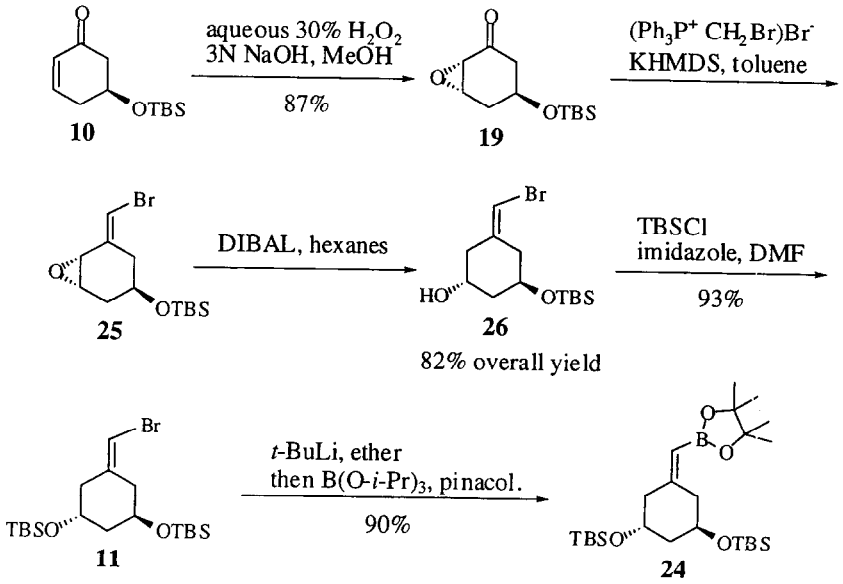


3.2 Novel Synthetic Approach to 19-*nor*-1,25-$(OH)_2VD_3$ and its Derivatives by the Suzuki-Miyaura Coupling in Solution.

We have now found that **11** and **24** can be readily synthesized from **10**[5a,g], which is a versatile chiral building block for synthesizing optically active cyclohexane derivatives[5],

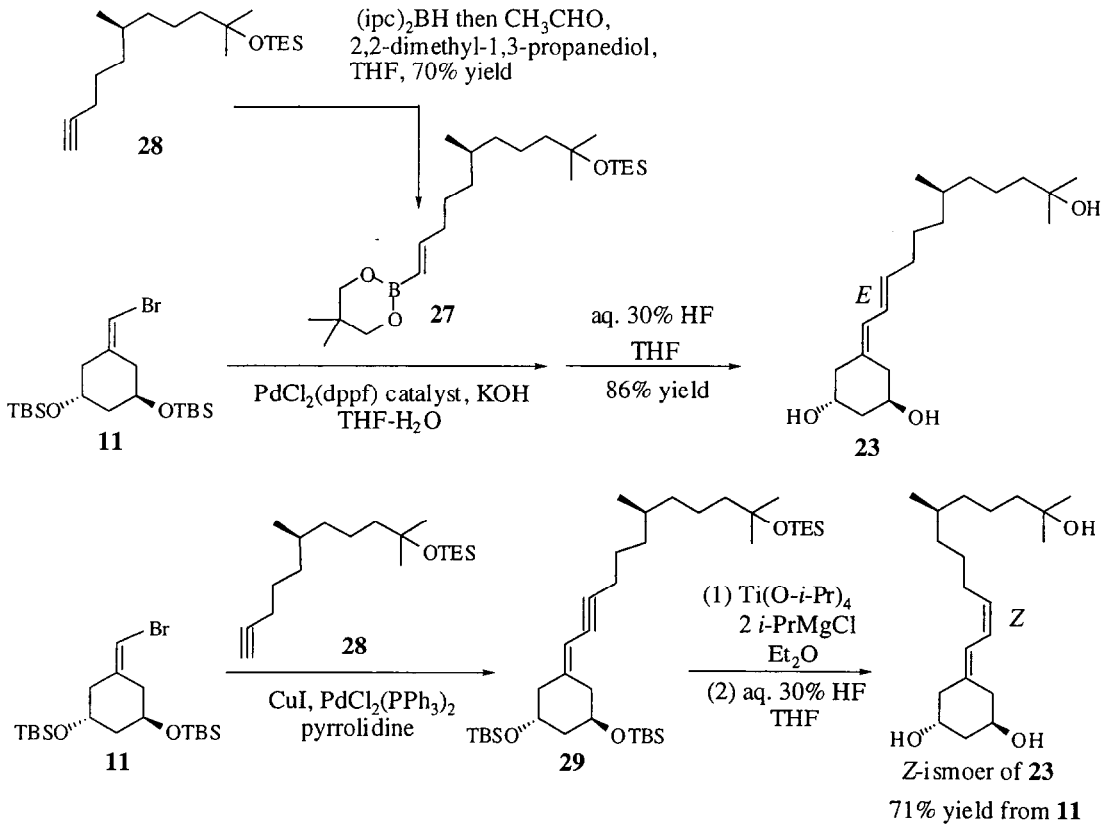
according to the procedure shown in Scheme 3-3. Thus, the compound **10**[6] was converted to (bromomethylidene)cyclohexanol **26** in 71% overall yield by the conventional reaction sequence, which involves stereoselective epoxidation of **10** using a H_2O_2-NaOH reagent,[5h] Wittig olefination reaction of the resulting epoxyketone[7] with $(Ph_3P^+CH_2Br)Br^-$ and KHMDS, and the epoxide-ring opening of the diene mono-epoxide **25**[8] thus produced using DIBAL-H. Silylation of **26**[9] with TBDMSCl/imidazole afforded **11** in 93% yield. The compound **11** thus obtained was readily converted to boronate **24** in 90% yield by sequential treatment with *t*-BuLi, $B(O\text{-}i\text{-}Pr)_3$, aqueous NH_4Cl, and pinacol. Because all the reagents used in the synthesis are readily available, inexpensive and nontoxic and the yield is high (the overall yields of **11** and **24** from **10** were 66% and 60%, respectively), we believe that **11** and **24** can be easily prepared in quantity.

Scheme 3-3



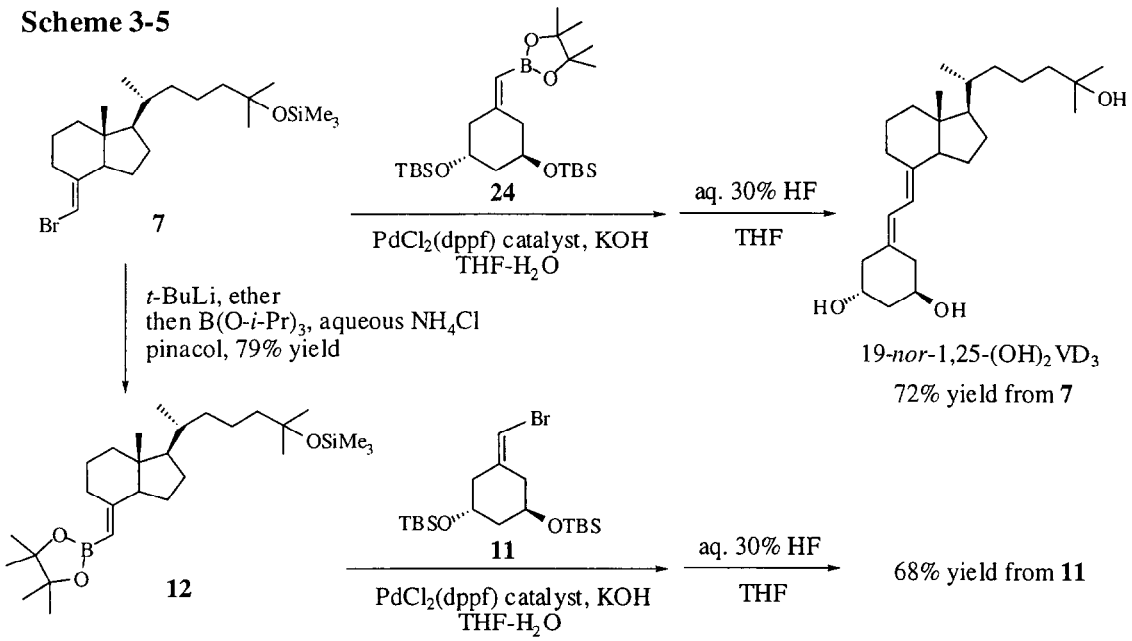
With the A-ring precursors **11** and **24** in hand, we carried out the synthesis of **23** and/or 19-*nor*-1,25-$(OH)_2VD_3$ by the Suzuki-Miyaura coupling reaction[10] (Scheme 3-4). Thus, the coupling reaction of **11** with boronate **27**, prepared by hydroboration of acetylene **28**[11], in the presence of KOH and $PdCl_2$(dppf) (5 mol%) in aqueous THF furnished, after desilylation, **23** in 86% yield. Furthermore, the synthesis of the olefinic isomer of **23** could be accomplished according to the reaction sequence as shown in Scheme 3-4, which involves the Sonogashira coupling[12] of **11** with terminal

Scheme 3-4



alkyne **28** and the reduction of the coupling product **29** mediated by a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent.[13] The ^{1}H and ^{13}C NMR analyses of the crude product by the Suzuki-Miyaura coupling reaction of **11** with **27** indicated that the reaction did not produce the *Z*-isomer of **23** at all. Similarly, 19-*nor*-1,25-(OH)$_2$VD$_3$ was readily synthesized in 68% yield by the coupling reaction between **11** and **12**, the latter of which was prepared from bromide **7**[14] by a lithiation-transmetallation reaction sequence. The Suzuki-Miyaura coupling reaction of boronate **24** and bromide **7** also proceeded smoothly to afford 19-*nor*-1,25-(OH)$_2$VD$_3$ in 72% yield (Scheme 3-5).

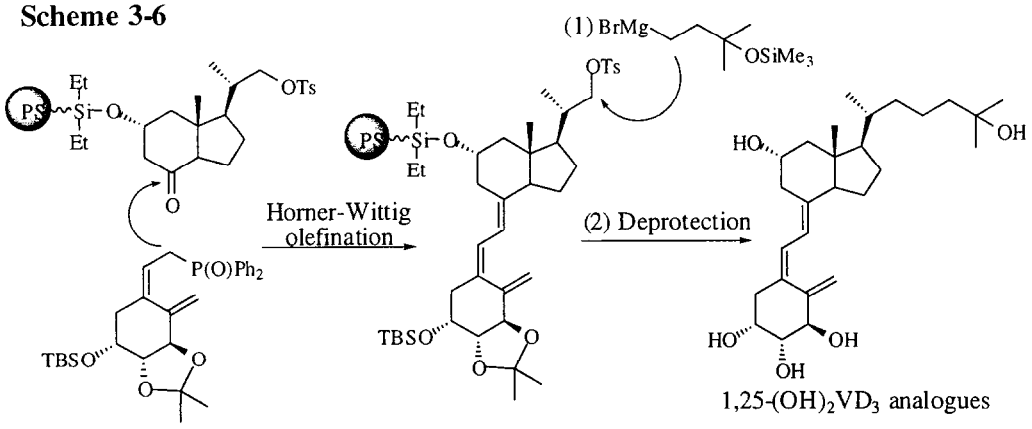
Scheme 3-5



3.3 Novel Synthetic Approach to *Des*-C,D-19-*nor*-VD_3s by the Suzuki-Miyaura Coupling on Solid Support.

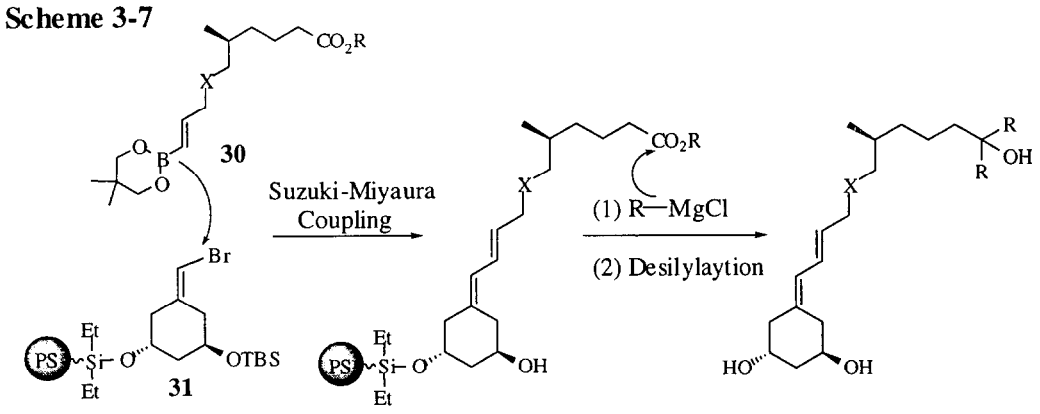
In recent years, it has been proven that applications of solid-phase chemistry, capable of generating combinatorial natural small molecule libraries, to the drug discovery process is extremely effective in terms of searching a wide range of analogues rapidly.[15] Therefore, it seems to be of great value to employ solid-phase chemistry to construct a combinatorial VD_3 library including analogues previously synthesized and to investigate their structure-activity relationships.[16] In 1999, Takahashi et al. reported the solid-phase synthesis of the 11-hydroxy-vitamin D system by combining three component, i.e. the A-ring, the C,D-ring, and the side chain (Scheme 3-6).[16a]

Scheme 3-6



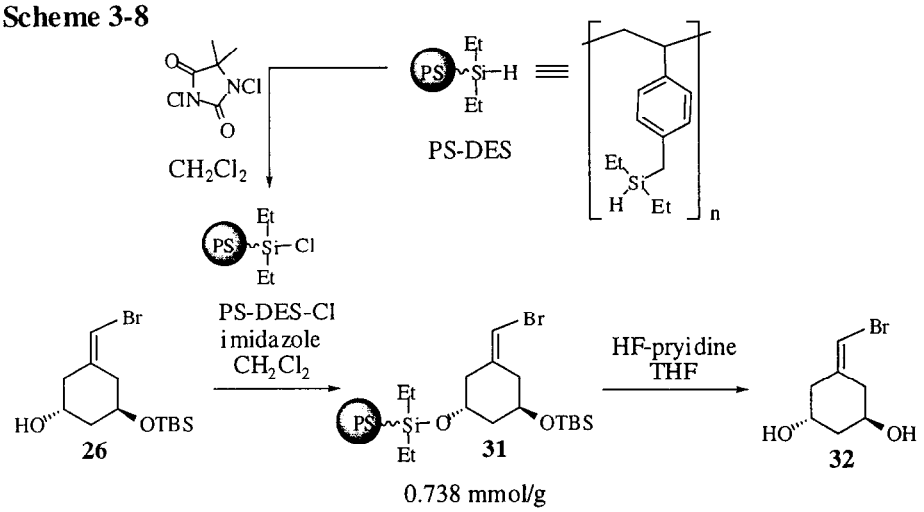
With the results shown in Scheme 3-4, we then devoted our efforts to prepare 19-*nor*-VD_3s in solid phase by utilizing **26**. Our parallel solid-phase synthesis of *des*-C,D-19-*nor*-VD_3s shown in Scheme 3-7 involves coupling of the A-ring **31** with ester boronate **30** and the following Grignard addition to the ester group present in the resulting

Scheme 3-7



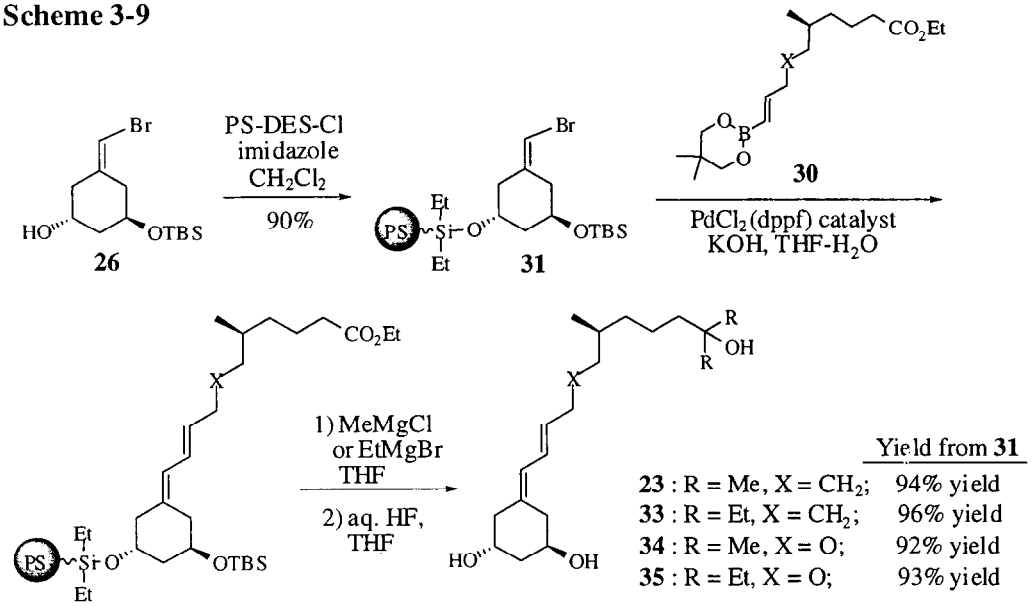
coupling product. Thus, the compound **26** reacted with PS-DES-Cl,[17] which was easily prepared from PS-DES as show in Scheme 3-8, in the presence of imidazole to provide the resin **31**. The loading of **31** was determined to be 0.738 mmol/g by cleavage with HF-pyridine in THF from the resin and quantification of the resulting 5-bromocyclohexane-1,3-diol (**32**) by ^{1}H NMR analysis of the crude mixture using

Scheme 3-8



internal standard. Treatment of the resin **31** thus prepared with boronate **30**[18] where X = CH_2 under similar reaction conditions to those applied in Scheme 3-4 provided the corresponding coupling product, which in turn was treated with an excess amount of MeMgCl or EtMgBr and then aqueous HF to produce **23** and **33** in 94% and 96% yield, respectively (Scheme 3-9).[19] It should be noted that the 26,27-dimethyl-19-*nor*-VD_3 derivative **33**[20] prepared here is a new compound. Similarly, new *des*-C,D-19-*nor*-VD_3 derivatives **34** and **35** were readily synthesized from **31** and **30** (X = O) in 92% and 93% yield, respectively.[19]

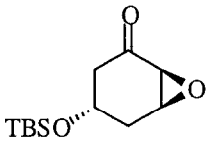
Scheme 3-9



3.4 Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Gemini-2000 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00) or residual $CHCl_3$ (δ 7.26). IR spectra were recorded on an FT-IR spectrometer (JASCO FT/IR-230) and are reported in wave numbers (cm^{-1}). Elemental analyses were performed on an Elemental automatic analyzer. GC/MS and DI/MS (low-resolution mass spectrum, EI) analyses were performed on a Shimadzu QP-5000 GC-mass spectrometer. HPLC analyses were performed on a Shimadzu LC-VP system with a scanning diode array UV-Vis detector (190-370 nm, SPD-M10Avp). Preparative MPLC was performed on a Shimazdu LC-8A system. All reactions sensitive to oxygen and/or moisture were performed under an argon atmosphere. Dry solvents (THF, ethyl ether, and CH_2Cl_2) were purchased from Kanto Chemicals Co. (Japan). Other chemicals are commercially available, unless otherwise indicated, and were used as received. 5-(*tert*-Butyldimethylsilyloxy)-2-cyclohexenone (**10**) was prepared from epichlorohydrine [>99% ee (enantiomeric excess)] by the reported procedure.[5g]

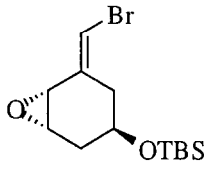
Synthesis of the A-Ring Intermediates 13 and 24



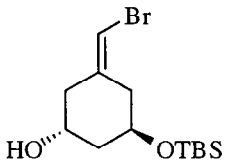
(1*S*,4*S*,6*S*)-4-(*tert*-Butyldimethylsiloxy)-7-oxa-bicyclo[4.1.0]heptan-2-one[5h] (19):

The diastereomerically pure compound (806 mg, 56% yield) could be obtained by recrystallization of **19** (1.44 g, 5.94 mmol) from hexane (5 mL) at -20 °C [conditions and yield were not optimized]. The purity was determined by its GC analysis: $[\alpha]^{29}D$ -14.3 (*c* 3.03, $CHCl_3$).

The following synthesis of **25** was carried out using **19** without recrystallization.



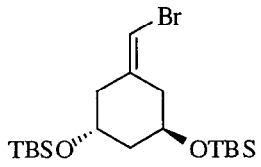
(1*R*,4*R*,6*S*)-(*E*)-2-(Bromomethylene)-4-[(*tert*-butyl)dimethylsiloxy]-7-oxa-bicyclo[4.1.0]heptane (25): To a mixture of $Ph_3P^+(CH_2Br)Br^-$ (11.3 g, 26 mmol) and toluene (50 mL) was added KHMDS (52 mL, 0.5 M in toluene, 26 mmol) at room temperature and the resulting mixture was stirred for 30 min at this temperature. After this mixture was cooled to 0 °C, a solution of epoxy ketone **19** (4.84 g, 20 mmol) prepared above in toluene (10 mL) was added, and the mixture was allowed to warm to room temperature over 30 min. The mixture was concentrated by rotary evaporation. To the resulting residue was added hexane (200 mL). The mixture was filtered through a pad of Celite with hexane (100 mL) and the filtrate was concentrated to give **25**, which was directly used for the next reaction without purification. GC and ^{1}H NMR analyses indicated that the mixture thus obtained consisted of two olefinic isomers in a ratio of >97: <3 and the stereochemistry of the major isomer was conformed by its nOe experiments to be *E*. The following data were recorded for a the crude mixture: ^{1}H NMR ($CDCl_3$) δ 6.49 (t, *J* = 1.8 Hz, 1H) 3.87- 4.02 (m, 1H), 3.49 (d, 3.9 Hz, 1H), 3.38-3.45 (m, 1H), 2.42 (br d, *J* = 15.9 Hz, 1H), 2.27 (dd, *J* = 4.2, 15.0 Hz, 1H), 2.16 (ddd, *J* = 2.1, 8.1, 15.9 Hz, 1H), 1.81 (ddd, *J* = 2.7, 6.9, 15.0 Hz, 1H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.5, 109.2, 64.3, 54.7, 54.1, 35.4, 33.9, 25.8, 18.1, -4.6, -4.7.



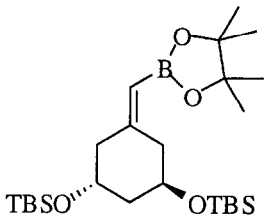
(1*R*,5*R*)-(*Z*)-3-(Bromomethylene)-5-[(*tert*-butyl)dimethylsiloxy]cyclohexanol (26): To a solution of **25** in hexane (50 mL) was added DIBAL-H (26.0 mL, 1.0 M in hexane, 26.0 mmol) at 0 °C. After the mixture was stirred for 1.5 h at 0 °C, water (3.6 mL) was added and the resulting mixture was allowed to warm to room temperature. After the mixture was stirred for 1 h, NaF (10 g) and Celite (10 g) were added. The mixture

was filtered through a pad of Celite with hexane (80 mL) and the filtrate was concentrated and chromatographed to afford **26** (5.25 g) in 82% yield. ^{1}H NMR ($CDCl_3$) δ 6.02 (br s, 1H), 4.04-4.16 (m, 2H), 2.43-2.54 (m, 2H), 2.37 (dd, *J* = 6.9, 13.5 Hz, 1H), 2.15 (dd, *J* = 7.5, 13.5 Hz, 1H), 1.70-1.80 (m, 2H), 1.42 (d, *J* = 5.1 Hz, 1H, OH), 0.88 (s, 9H), 0.07 and 0.09 (2s, each 3H); ^{13}C NMR ($CDCl_3$) δ 139.0, 102.0, 66.9, 66.8, 42.9, 42.3, 39.0, 25.6, 17.9, -5.1, -5.2; IR (neat) 3366, 2928, 1471, 1361, 1254, 1096, 837, 776; $[\alpha]^{26}_D$ +20.2 (*c* 1.12, $CHCl_3$); Anal. Calcd. for $C_{13}H_{25}BrO_2Si$: C, 48.59; H, 7.84. Found: C, 48.92; H, 7.91.

The ee of **26** thus obtained was confirmed to be >99% by ^{1}H NMR analyses after the conversion to the corresponding MTPA esters.

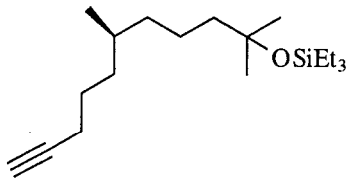


(3*R*,5*R*)-1-(Bromomethylene)-3,5-bis-[(*tert*-butyl)dimethylsiloxy]cyclohexane (11): To a solution of **26** (5.25 g, 16.4 mmol) and imidazole (2.46 g, 36.1 mmol) in DMF (20 mL) was added TBSCl (3.02 g , 20.0 mmol) at 0 °C. After the mixture was stirred for 12 h at room temperature, saturated aqueous $NaHCO_3$ (30 mL) was added. The mixture was extracted with hexane (40 mL), dried over $MgSO_4$, concentrated, and chromatographed on silica gel to provide **11** (6.62 g) in 93% yield. ^{1}H NMR ($CDCl_3$) δ 5.94 (br s, 1H), 4.02-4.15 (m, 2H), 2.30-2.48 (m, 3H), 2.09 (ddd, *J* = 0.9, 7.5, 13.5 Hz, 1H), 1.62-1.84 (m, 2H), 0.87 and 0.89 (2s, each 9H), 0.06 and 0.09 (2s, each 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 139.3, 101.2, 67.4, 67.1, 43.6, 43.2, 39.2, 25.90, 25.87, 18.20, 18.16, -4.64, -4.67, -4.74, -4.86; IR (neat) 2953, 2857, 1637, 1471, 1362, 1255, 1099, 1026, 914, 837, 775; $[\alpha]^{30}_D$ +11.1 (*c* 1.08, $CHCl_3$); Anal. Calcd. for $C_{19}H_{39}BrO_2Si_2$: C, 52.39; H, 9.02. Found: C, 52.31; H, 8.76.



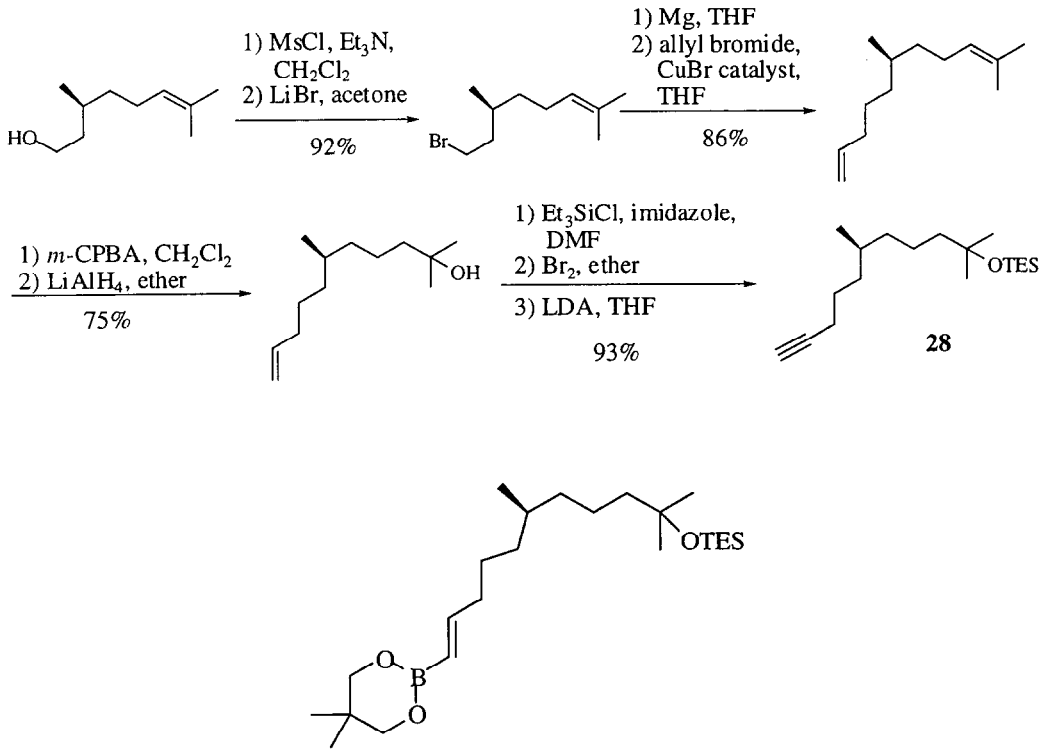
(3'*R*,5'*R*)-2-[3',5'-Bis-(*tert*-butyldimethylsiloxy)cyclohexylidenemethyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (24)[22]: To a solution of **11** (348 mg, 0.80 mmol) in Et_2O (3 mL) was added *t*-BuLi (1.30 mL, 1.35 M in pentane, 1.76 mmol) at –78 °C. After the solution was stirred for 1 h at the same temperature, B(O-*i*-Pr)$_3$ (0.6 mL, 2.0 M in Et_2O, 1.2 mmol) was added. The resulting mixture was allowed to warm to room temperature over 4 h, and then saturated aqueous NH_4Cl (8 mL) and EtOAc (8 mL) were added at 0 °C. After being stirred for 1 h, the mixture was extracted with EtOAc (2 x 6 mL) and the combined extracts were concentrated by rotary evaporation. The residue was dissolved in EtOAc (3 mL), and to this were added pinacol (113 mg, 0.96 mmol) and $MgSO_4$ (1.0 g). The resulting mixture was stirred at room temperature for 12 h, filtered, concentrated in vacuo, and chromatographed on silica gel (hexane-Et_2O with a trace amount of Et_3N) to give **24** (347 mg) in 90% yield. ^{1}H NMR ($CDCl_3$) δ 5.12 (s, 1H), 4.03-4.11 (m, 2H), 2.67 (dd, *J* = 3.6, 13.2 Hz, 1H), 2.54 (dd, *J* = 6.9, 13.2, Hz, 1H), 2.36 (dd, *J* = 3.6, 12.9 Hz, 1H), 2.13 (dd, *J* = 7.5, 12.9 Hz, 1H), 1.62-1.76 (m, 2H), 1.22 (s, 6H), 1.21 (s, 6H), 0.86 (s, 9H), 0.84 (s, 9H), 0.043, 0.036, 0.008 and 0.004 (4s, each 3H); ^{13}C NMR ($CDCl_3$) δ 160.1, 115.6 (br s), 82.5, 68.3, 67.9, 48.0, 43.1, 40.8, 25.8, 25.7, 24.9, 24.6, 18.1, 17.9, -4.9, -5.0, -5.1, -5.2; IR (neat) 2954, 2856, 1645, 1471, 1386, 1256, 1096, 1028, 837, 775; $[\alpha]^{28}_D$ -4.80 (*c* 0.878, $CHCl_3$); Anal. Calcd. for $C_{25}H_{52}BO_4Si_2$: C, 62.21; H, 10.65. Found: C, 62.30; H, 10.54.

Preparation of Boronate Reagents 27 and 14



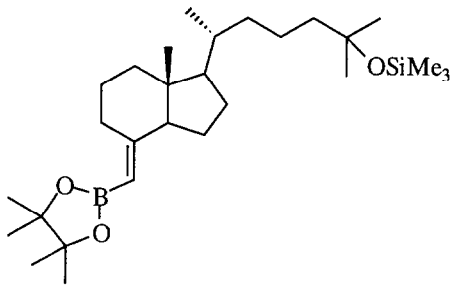
(*R*)-Triethyl-(1,1,5-trimethyldec-9-ynyloxy)silane (28): The compound **28** was

prepared from (*S*)-(-)-citronellol in 55% overall yield according to the conventional reaction sequence shown in the scheme below. ^{1}H NMR ($CDCl_3$) δ 2.16 (dt, *J* = 2.7, 7.2 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.05-1.61 (m, 11H), 1.18 (s, 6H), 0.94 (t, *J* = 8.1 Hz, 9H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.56 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 84.7, 73.4, 68.0, 45.4, 37.5, 36.2, 32.5, 29.98, 29.92, 26.2, 21.8, 19.7, 18.8, 7.22, 6.91; IR (neat) 3315, 2952, 2120, 1459, 1380, 1363, 1236, 1161, 1043, 743; $[\alpha]^{25}_D$ +1.10 (*c* 0.996, $CHCl_3$); Anal. Calcd. for $C_{19}H_{38}OSi$: C, 73.47; H, 12.33. Found: C, 73.34; H, 12.60.



(6'*R*)-(*E*)-2-[6',10'-Dimethyl-10'-(triethylsiloxy)undec-1'-enyl]-5,5-dimethyl[1,3,2]dioxaborinane (27): To a solution of diisopinocampheylborane (2.1 mmol), prepared from BH_3-SMe_2 (0.21 mL, 10 M , 2.1 mmol) and α-pinene (0.70 mL, 4.4 mmol), in THF (1.0 mL) was added a solution of **28** (621 mg, 2.0 mmol) in THF (1.0 mL) at -35 °C. After the solution was stirred for 6.5 h at 0 °C, CH_3CHO (1.1 mL, 20 mmol) was added. The mixture was refluxed for 12 h, cooled to room temperature and concentrated in vacuo. After the addition of 2,2-dimethyl-1,3-propanediol (228 mg, 2.2 mmol), the mixture was stirred for 5 h at room temperature and concentrated in vacuo. The resulting residue was chromatographed on silica gel (hexane-Et_2O-Et_3N) to give **27** (594 mg) in 70% yield. ^{1}H NMR ($CDCl_3$) δ 6.54 (dt, *J* = 17.7, 6.6 Hz, 1H),

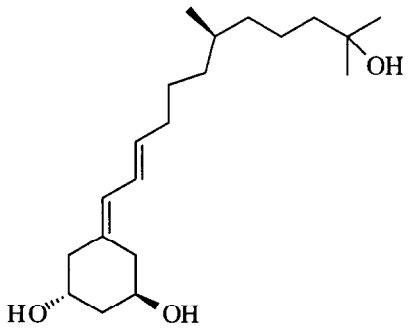
5.33 (d, J = 17.7Hz, 1H), 3.63 (s, 4H), 2.10 (q, J = 6.9 Hz, 2H), 1.00-1.43 (m, 11H), 1.17 (s, 6H), 0.91-0.96 (m, 6H), 0.93 (t, J = 7.8 Hz, 9H), 0.84 (d, J = 6.6 Hz, 3H), 0.55 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 152.0, 122.4 (br s), 73.4, 72.0, 45.3, 37.4, 36.5, 35.8, 32.5, 31.6, 29.79, 29.72, 25.9, 21.71, 21.63, 21.61, 19.5, 6.93, 6.43; IR (neat) 2957, 1718, 1638, 1476, 1413, 1325, 1254, 1044, 813, 743; $[\alpha]^{30}_D$ -0.88 (*c* 1.24, $CHCl_3$); Anal. Calcd. for $C_{24}H_{49}BO_3Si$: C, 67.90; H, 11.63. Found: C, 67.84; H, 11.23.



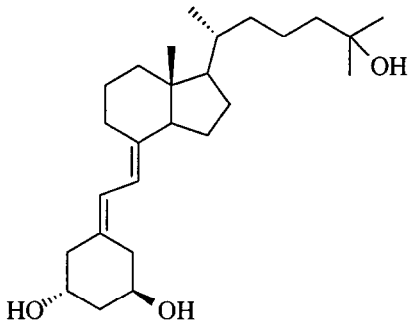
(1'*R*,3a'S,7a'*R*)-(*E*)-2-{1'-[(*R*)-1,5-Dimethyl-5-(trimethylsiloxy)hexyl]-7a'-methylocta hydroinden-4'-ylidenemethyl}-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (12): To a solution of alkenyl bromide **7** (261 mg, 0.61 mmol), prepared according to the reported procedure,[14] in Et_2O (1.8 ml) was added *t*-BuLi (0.99 mL, 1.35 M in pentane, 1.3 mmol) at -78 °C. After the solution was stirred for 1 h at –78 °C, B(O-*i*-Pr)$_3$ (0.45 mL, 2.0 M in Et_2O, 0.9 mmol) was added. The resulting mixture was allowed to warm to room temperature over 4 h, and then saturated aqueous NH_4Cl (5 mL) and EtOAc (5 mL) were added. The mixture was extracted with EtOAc (2 x 10 mL) and the combined extracts were concentrated by rotary evaporation. The residue was dissolved in EtOAc (1.2 mL), and to this were added pinacol (86 mg, 0.73 mmol) and $MgSO_4$ (1.2 g). The resulting mixture was stirred at room temperature for 12 h, filtered, concentrated in vacuo, and chromatographed on silica gel (hexane-Et_2O with a trace amount of Et_3N) to give **12** (228 mg) in 79% yield. ^{1}H NMR ($CDCl_3$) δ 4.90 (s, 1H), 3.17 (br d, J = 6.3 Hz, 1H), 1.94-2.07 (m, 2H), 0.80-1.90 (m, 16H), 1.26 (s, 12H), 1.19 (s, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.54 (s, 3H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.1, 108.2 (br s), 82.5, 74.1, 58.0, 56.9, 46.3, 45.2, 40.5, 36.4, 36.1, 33.3, 30.0, 29.9, 27.6, 25.0, 24.9, 24.4, 22.4, 21.0, 18.9, 12.2, 2.76; IR (neat) 2949, 1639, 1467, 1341, 1249, 1146, 1044, 838, 752; $[\alpha]^{25}_D$ 64.4 (*c* 1.28, $CHCl_3$); Anal. Calcd. for

$C_{28}H_{53}BO_3Si$: C, 70.56; H, 11.21. Found: C, 70.62; H, 11.34.

Synthesis of 19-*nor*-VD_3s by Suzuki-Miyaura Coupling in Solution Phase



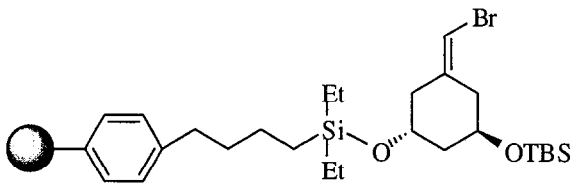
(1*R*,3*R*)-5-[(7*R*)-(*E*)-11-Hydroxy-7,11-dimethyldodec-2-enylidene]cyclohexane-1,3-diol (23)[3b] **from 11 and 27**: To a mixture of boronate **27** (135 mg, 0.32 mmol), aqueous 3 N KOH (0.106 mL) and THF (0.3 mL) was added dropwise a solution of bromide **11** (87.1 mg, 0.20 mmol) and $PdCl_2$(dppf) (11.8 mg, 0.016 mmol) in THF (0.5 mL) at ambient temperature. The resulting mixture was stirred for 8 h at r.t. and then for 12 h at 40 °C. After the addition of Et_2O (10 mL), the mixture was washed with 1N HCl (5 mL) and brine (5 ml), dried over $MgSO_4$, concentrated, passed through a short silica gel column with 1 % ether in hexane, and then concentrated to provide the coupling product. To a solution of the residue thus obtained in THF (1.0 mL) was added aqueous 30% HF (2 drops). After the solution was stirred for 3 h at ambient temperature, aqueous saturated $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, and concentrated to give a crude residue of **23**, the ^1H and ^{13}C NMR of which indicated that no olefinic isomer was produced as shown in page 51. The residue was chromatgraphed on silica gel column with hexane-EtOAc to give **23** (55.8 mg) in 86% yield. The spectroscopic data [^1H NMR (DMSO-d_6) and IR] of **23** thus obtained were in full agreement with those reported.[3b] ^{13}C NMR ($CDCl_3$) δ 134.9, 131.6, 128.2, 125.2, 71.1, 67.4, 67.1, 44.5, 44.2, 42.2, 37.5, 37.1, 36.4, 33.1, 32.6, 29.3, 26.8, 21.8, 19.7; $[\alpha]^{27}_D$ +13.7 (*c* 5.32, $CHCl_3$).



19-*nor*-1,25-Dihydroxyvitamin D_3[2a,b] from 12 and 11: 19-*nor*-1,25$(OH)_2VD_3$ (42 mg) was obtained in 68% yield starting from **11** (67 mg, 0.15 mmol) and **12** (117 mg, 0.24 mmol) under similar reaction conditions described for synthesis of **23** from **11** and **27**. The spectroscopic data [^{1}H NMR, UV, MS (DI, EI) and IR] of 19-*nor*-1,25$(OH)_2VD_3$ thus obtained were in full agreement with those reported.[2a,b] mp 156-157 °C; ^{13}C NMR ($CDCl_3$) δ 143.1, 131.3, 123.8, 115.3, 71.1, 67.3, 67.1, 56.4, 56.2, 45.7, 44.5, 44.3, 42.1, 40.4, 37.1, 36.3, 36.0, 29.2, 29.1, 28.8, 27.5, 23.4, 22.1, 20.7, 18.7, 11.9; $[\alpha]^{27}_D$ 68.7 (*c* 2.16, $CHCl_3$).

19-*nor*-1,25-Dihydroxyvitamin D_3[2a,b] from 24 and 7: 19-*nor*-1,25$(OH)_2VD_3$ (73 mg) was obtained in 72% yield starting from **24** (191 mg, 0.40 mmol) and **7** (106 mg, 0.25 mmol) under similar reaction conditions described for synthesis of **23** from **11** and **27**. After column chromatography, excess amount of **24** was almost recovered. The spectroscopic data of 19-*nor*-1,25$(OH)_2VD_3$ thus obtained were identical with those reported[2a,b] and also with those of 19-*nor*-1,25$(OH)_2VD_3$ prepared above from **12** and **11**.

Preparation of Resin-Supported A-Ring Intermediate 31

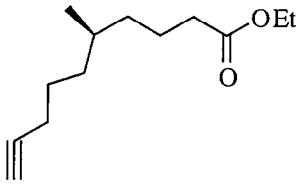


The A-ring precursor supported on polystyrene beads (31): The weight of a 50 mL Schlaker reaction tube (Aldrich) charged with a small magnetic stirring bar was recorded. To this was charged 1.00 g of PS-DES^{TM} resin (Argonaut technologies, 0.6-1.0 mmol / g loading), and then this tube was dried under vacuum for 30 min and

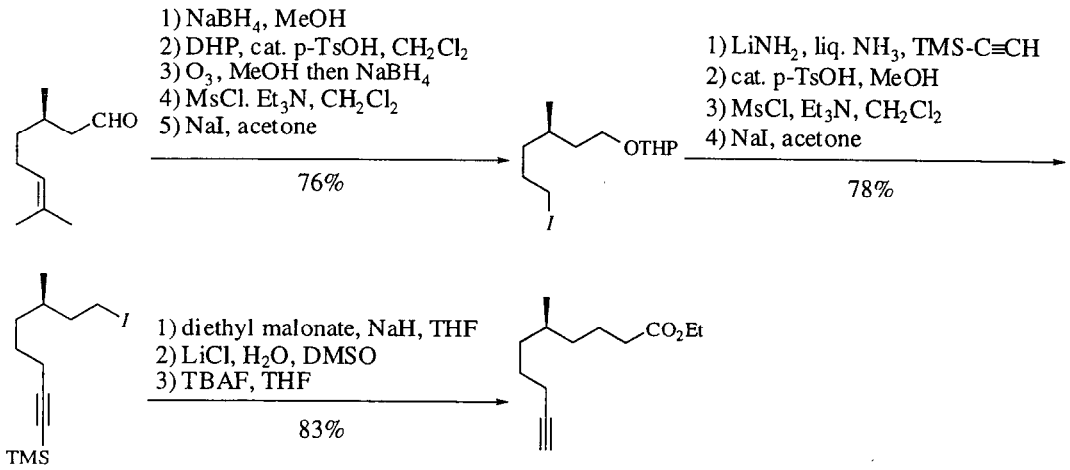
purged with argon. To this was added a solution of 1,3-dichloro-5,5-dimethylhydrantoin (443 mg, 2.25 mmol) in CH_2Cl_2 (11 mL) and the mixture was gently stirred for 2 h at ambient temperature. The mixture was filtered and the residual resin was sequentially washed with CH_2Cl_2 (3 x 20 mL) and THF (3 x 20 mL) under argon and then dried in vacuo. To this reaction tube with the resin was added a solution of alcohol **26** (723 mg, 2.65 mmol) and imidazole (180 mg, 2.63 mmol) in CH_2Cl_2 (25 mL) and the resulting mixture was gently stirred for 4 h at room temperature. The mixture was filtrated and the residual resin was washed with ether (2 x 18 mL). The combined filtrates were washed with water (2 x 20 mL), dried over $MgSO_4$, concentrated, and passed through a short silica gel column to provide the recovered **26** (382 mg, 1.19 mmol). The resin in the tube was sequentially washed with THF-H_2O (3:1, 3 x 12 mL), EtOH (2 x 12 mL), and Et_2O (2 x 18 mL), and then dried in vacuo overnight to afford the A-ring precursor supported on resin **31** (1.31 g). The yield was calculated based on the recovered **26** to be 90%.

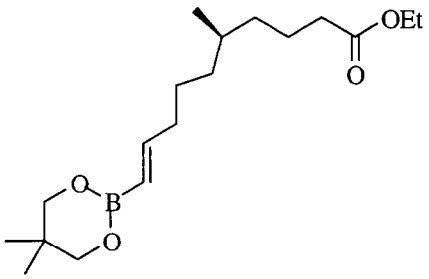
The loading was determined to be 0.738 mmol/g by cleavage with HF-pyridine from the resin and the following quantification of **32** by ^{1}H NMR analysis of the crude mixture using an internal standard: To the mixture of the resin (144 mg) and THF (3 mL) charged in a syringe-shape polypropylene (PP) reaction vessel equipped with a PP-frit (EYELA RT5-S100, Takeda-Rika Co. Ltd., Japan) was added HF(pyr.)$_n$ (0.1 mL) and the mixture was shaken for 6 h at ambient temperature. To the mixture was added 1,4-dibromobenzene (25.6 mg) as an internal standard. The resulting mixture was filtered with THF (3 mL). To the filtrate was added EtOAc (4 mL) and the mixture was washed with aqueous saturated $NaHCO_3$ (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was subjected to ^{1}H NMR analysis which indicated the production of 0.1063 mmol of **32**. Based on the result thus obtained the loading of **31** to the resin was calculated to be 0.738 mmol/g. The authentic sample of **32** was prepared from **26** by treatment with HF(pry.)$_n$ in THF in solution phase: ^{1}H NMR (65 °C, $CDCl_3$) δ 6.09 (s, 1H), 4.09-4.22 (m, 2H), 2.66 (dd, J = 3.9, 13.5 Hz, 1H), 2.50 (dd, J = 3.6, 13.5 Hz, 1H), 2,30 (dd, J = 7.2, 13.5 Hz, 1H), 2.21 (dd, J = 6.9, 13.5 Hz, 1H), 1.88 (t, J = 5.4 Hz, 2H); ^{13}C NMR (65 °C, $CDCl_3$) δ 138.1, 102.8, 66.7, 66.5, 42.9, 41.5, 39.0.

Preparation of Boronate 30

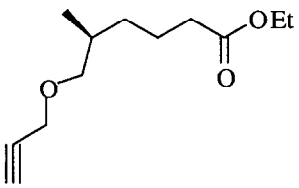


(*R*)-5-Methyldec-9-ynoic acid ethyl ester: 5-Methyldec-9-ynoic acid ethyl ester was prepared from (*R*)-(+)-citronellal according to the procedure shown in the scheme below. ^{1}H NMR ($CDCl_3$) δ 4.11 (q, *J* = 7.2 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.15 (dt, *J* = 2.7, 7.2 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.07-1.69 (m, 9H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 84.6, 68.1, 60.2, 36.3, 36.0, 34.7, 32.2, 26.1, 22.5, 19.5, 18.8, 14.3; IR (neat) 3308, 2941, 1735, 1462, 1375, 1250, 1182, 1099, 1035, 844; $[\alpha]^{30}_D$ +1.21 (*c* 0.906, $CHCl_3$); Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.54; H, 10.46.

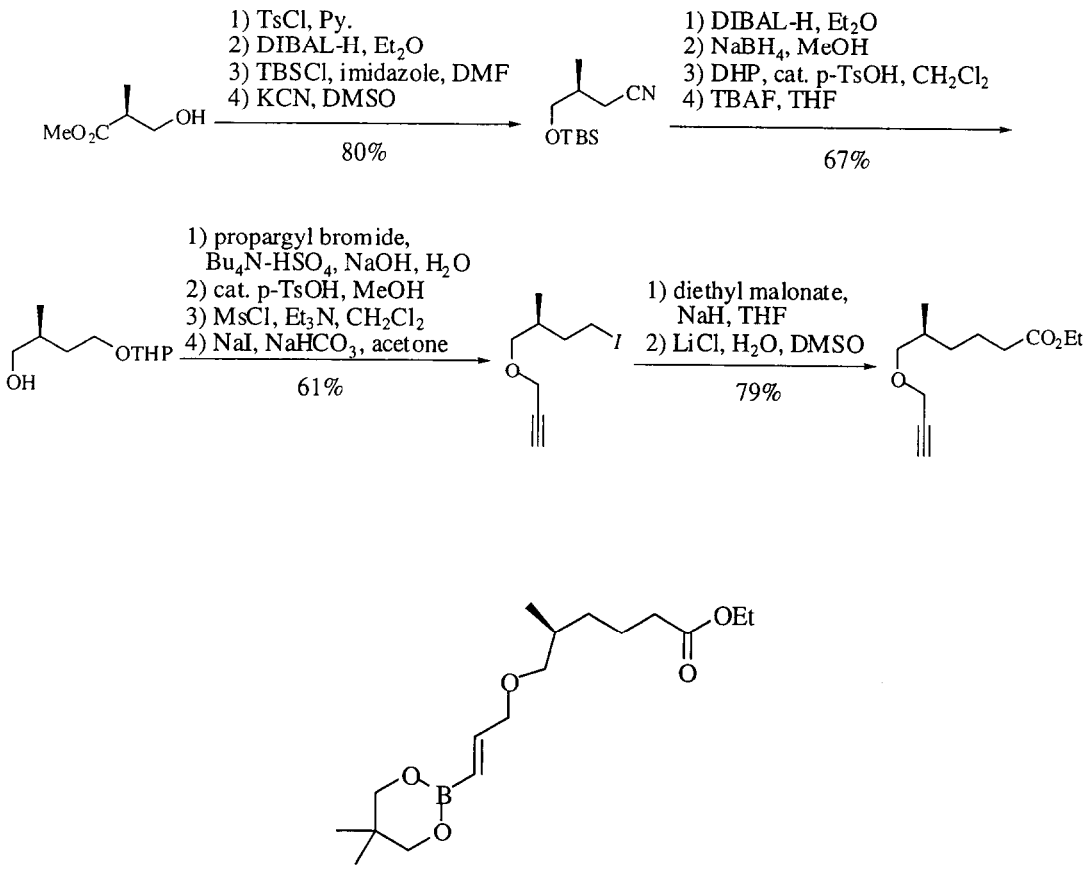




(5*R*)-10-[(*E*)-5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl]-5-methyldec-9-enoic acid ethyl ester (30, X=CH_2): **30** (X=CH_2) (409 mg) was prepared in 63% yield from 5-methyldec-9-ynoic acid ethyl ester (421 mg, 2.0 mmol) prepared above according to a similar procedure to that utilized for synthesizing **27** from **28**. ^{1}H NMR ($CDCl_3$) δ 6.49 (dt, *J* = 17.7, 6.6 Hz, 1H), 5.29 (d, *J* = 17.7 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.58 (s, 4H), 2.21 (t, *J* = 7.5 Hz, 2H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.48-1.64 (m, 2H), 0.98-1.43 (m, 7H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 6H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 151.5, 122.2 (br s), 71.9, 60.0, 36.37, 36.31, 35.8, 34.6, 32.4, 31.6, 25.9, 22.5, 21.8, 19.4, 14.2; IR (neat) 2929, 1735, 1638, 1477, 1414, 1255, 1091, 999, 813; $[\alpha]^{30}_D$ +0.48 (*c* 1.86, $CHCl_3$); Anal. Calcd. for $C_{18}H_{33}BO_4$: C, 66.67; H, 10.26. Found: C, 66.35; H, 10.13.



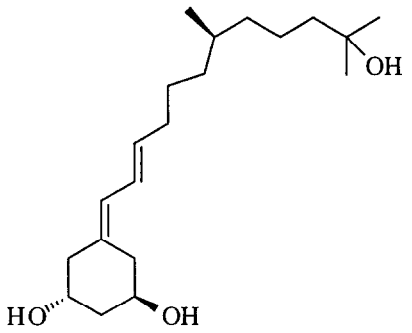
(5*S*)-5-Methyl-6-(prop-2-ynyloxy)hexanoic acid ethyl ester: 5-Methyl-6-prop-2-ynyloxy-hexanoic acid ethyl ester was prepared from (*S*)-3-hydroxy-2-methyl-propionic acid ethyl ester according to the procedure shown in the scheme below. ^{1}H NMR ($CDCl_3$) δ 4.08 (q, *J* = 7.2 Hz, 2H), 4.07 (d, *J* = 2.4 Hz, 2H), 3.32 and 3.26 (2dd, *J* = 9.0, 6.3 Hz and *J* = 9.0, 6.3 Hz, 2H) 2.38 (t, *J* = 2.4 Hz, 1H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.50-1.76 (m, 3H), 1.34-1.48 (m, 1H), 1.05-1.25 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 79.9, 75.2, 74.0, 60.1, 58.1, 34.5, 33.1, 33.0, 22.4, 16.9, 14.2; IR (neat) 3293, 2957, 2878, 1734, 1458, 1375, 1178, 1098, 1034; $[\alpha]^{28}_D$ -1.71 (*c* 4.30, $CHCl_3$); Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.93; H, 9.35.



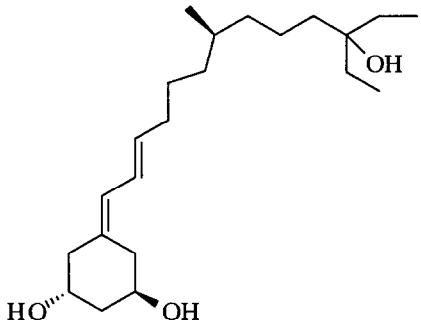
(5*S*)-6-[(*E*)-3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)allyloxy]-5-methylhexanoic acid ethyl ester (30, X=O): **30** (X=O) (1214 mg) was prepared in 93% yield from 5-methyl-6-prop-2-ynyloxy-hexanoic acid ethyl ester (849 mg, 4.0 mmol) prepared above according to a similar procedure to that utilized for synthesizing **27** from **28**. ^{1}H NMR ($CDCl_3$) δ 6.51 (dt, *J* = 18.0, 4.8 Hz, 1H), 5.56 (d, *J* = 18.0 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.99 (d, *J* = 4.8 Hz, 2H), 3.60 (s, 4H), 3.24 and 3.18, (2dd, *J* = 6.3, 9.0 Hz and *J* = 6.3, 9.0 Hz, each 1H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.34-1.80 (m ,5H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.93 (s, 6H), 0.88 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.8, 147.0, 123.6 (br s), 75.8, 72.7, 72.0, 60.0, 34.4, 33.2, 33.0, 31.6, 22.3, 21.7, 16.7, 14.0; IR (neat) 2960, 1733, 1644, 1477, 1416, 1377, 1305, 1255, 1185, 1087, 1015, 814; $[\alpha]^{26}_D$ -2.26 (*c* 3.10, $CHCl_3$); Anal. Calcd. for $C_{17}H_{31}BO_5$: C, 62.59; H, 9.58. Found: C, 62.98; H, 9.32.

Synthesis of 19-nor-VD_3 Derivatives 23 and 33-35 by Suzuki-Miyaura Coupling in Solid Phase

General Procedure: The resin **31** (271 mg, 0.738 mmol/g, 0.20 mmol), $PdCl_2$(dppf) (14.7 mg, 0.02 mmol), alkenylboronate **30** (0.60 mmol) aqueous 50% KOH (0.5 mL) and THF (3.5 mL) were charged in a syringe-shape polypropylene (PP) reaction vessel equipped with a PP-frit (EYELA RT5-S100, Takeda-Rika Co. Ltd., Japan). The mixture was shaken for 8 h at room temperature and for 20 h at 40 °C and then 20 h at 55 °C.[23] After being cooled to room temperature, the resin was washed with THF (20 mL), DMF-H_2O (10 mL, 1/1(v/v)), DMF (10 mL), THF-H_2O (20 mL, 1/1 (v/v)), THF (10 mL), CH_2Cl_2 (10 mL) and Et_2O (20 mL), and then dried in vacuo. To the resulting resin in the vessel were added THF (2.5 mL) and Grignard reagent [EtMgBr (1.46 mL, 1.37 M in Et_2O, 2.0 mmol) or MeMgCl (0.67 ml, 3.0 N in THF, 2.0 mmol)], and then the resulting mixture was shaken for 3 h at room temperature. The resin was washed with THF (20 mL), THF-H_2O (30 mL, 1/1 (v/v)), THF (10 mL), CH_2Cl_2 (10 mL) and Et_2O (10 mL), and then dried in vacuo. To the resulting resin in the vessel were added THF (3 mL) and aqueous 30% HF (ten drops), and then the resulting mixture was shaken for 3 h at room temperature. The mixture was filtered with EtOAc (20 mL) and poured into aqueous saturate $NaHCO_3$ (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was passed through a pad of silica gel to give the product. The crude residue consisted of a desire coupling product (**23**, **33**, **34** or **35**) and a trace amount of 5-bromomethylenecyclohexane-1,3-diol (**32**). The chemical purity of the resulting VD_3 analogue was determined to be >95% by ^1H NMR analysis and HPLC analysis with a scanning diode array UV detector (210-370 nm), as exemplified by the synthesis of **23** as shown in page 51-52 [SI-60 column (silica gel, 4.6 ϕ x 250 mm), *i*-PrOH/hexane (1/6 (v/v)), the resulting VD_3 analogue: λmax 240 - 242 nm, **32**: λmax <210 nm]. Analytically pure sample of VD_3 analogue was obtained by HPLC.

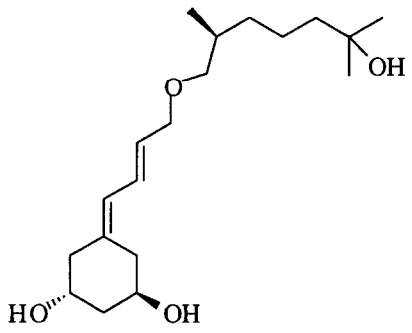


(1*R*,3*R*)-5-[(7*R*)-(*E*)-11-Hydroxy-7,11-dimethyldodec-2-enylidene]cyclohexane-1,3-diol (23)[3b]: **23** (61.0 mg) was obtained in 94% overall yield from resin **31** (271 mg, 0.738 mmol/g, 0.20 mmol), **30** (X=CH_2, 194 mg, 0.60 mmol), and MeMgCl (0.67 ml, 3.0 N in THF, 2.0 mmol). The crude residue consisted of **23** and a trace amount of **32**. The chemical purity of the resulting **23** was determined to be >95% by ^{1}H NMR analysis and HPLC analysis with a scanning diode array UV detector (190-370 nm) [SI-60 column (silica gel, 4.6 ϕ x 250 mm), *i*-PrOH/hexane (1/6 (v/v)), **23**: λmax 242 nm, 14.6 min]. The spectroscopic data of **23** thus obtained were identical with those reported[3b] and also with those of **23** prepared from **11** and **27**.



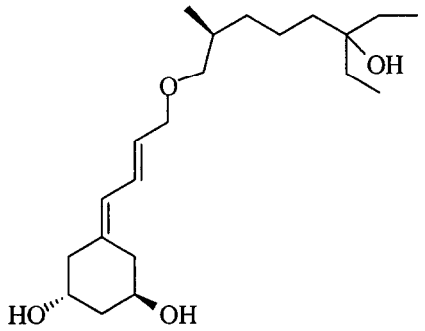
(1*R*,3*R*)-5-[(7*S*)-(*E*)-11-Ethyl-11-hydroxy-7-methyltridec-2-enylidene]cyclohexane-1,3-diol (33): **33** (61.0 mg) was obtained in 96% overall yield from resin **31** (271 mg, 0.738 mmol/g, 0.20 mmol), **30** (X=CH_2, 194 mg, 0.60 mmol), and EtMgBr (1.46 mL, 1.37 M in Et_2O, 2.0 mmol). The crude residue consisted of **33** and a trace amount of **32**. The chemical purity of the resulting **33** was determined to be >95% by ^{1}H NMR analysis and HPLC analysis with a scanning diode array UV detector (190-370 nm) [SI-60 column (silica gel, 4.6 ϕ x 250 mm), *i*-PrOH/hexane (1/6 (v/v)), **33**: λmax 242 nm]: a viscous oil; ^{1}H NMR ($CDCl_3$) δ 6.27 (dd, J = 10.8, 15.0 Hz, 1H), 6.00 (d, J = 10.8 Hz, 1H), 5.68 (dt, J = 15.0, 7.5 Hz, 1H), 4.03-4.16 (m, 2H), 2.61 (dd, J = 3.9, 13.2

Hz, 1H), 2.46 (dd, J = 4.2, 13.2 Hz, 1H), 2.29 (dd, J = 7.5, 13.2 Hz, 1H), 2.03-2.18 (m, 3H), 1.84-1.89 (m, 2H), 1.08-1.51 (m, 15H), 1.46 (q, J = 7.2 Hz, 4H), 0.86 (d, J = 6.3 Hz, 3H). 0.85 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 134.8, 131.7, 128.1, 125.2, 74.7, 67.3, 67.1, 44.5, 42.1, 38.6, 37.7, 37.1, 36.5, 33.1, 32.6, 31.0, 26.8, 20.8, 19.8, 7.91; IR (neat) 3372, 2930, 1458, 1377, 1215, 1050, 963, 940, 814, 756; $[\alpha]^{30}_D$ +12.9 (*c* 7.86, $CHCl_3$); DI/MS(EI) *m/z* : 334 (28, M^+-H_2O), 316 (68), 305 (32), 298 (20), 287 (100), 269 (24), 245 (8), 227 (13), 215 (24), 203 (33), 194 (70), 185 (76), 177 (80). Anal. Calcd. for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44. Found: C, 75.22; H, 11.29.



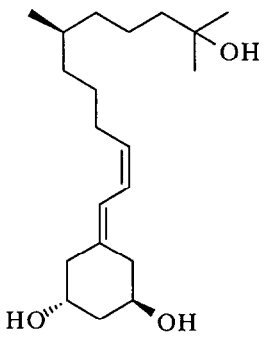
(1*R*,3*R*)-5-[(2'*S*)-(*E*)-4-(6'-Hydroxy-2',6'-dimethylheptyloxy)but-2-enylidene]cyclohexane-1,3-diol (34): **34** (60.0 mg) was obtained in 92% overall yield from resin **31** (271 mg, 0.738 mmol/g, 0.20 mmol), **30** (X=O, 195 mg, 0.60 mmol), and MeMgCl (0.67 ml, 3.0 N in THF, 2.0 mmol). The crude residue consisted of **34** and a trace amount of **32**. The chemical purity of the resulting **34** was determined to be >95% by ^{1}H NMR analysis and HPLC analysis with a scanning diode array UV detector (210-370 nm) [SI-60 column (silica gel, 4.6 ϕ x 250 mm), *i*-PrOH/hexane (1/6 (v/v)), **34**: λmax 240 nm, 17.0 min]: a viscous oil; ^{1}H NMR ($CDCl_3$) δ 6.51 (dd, J = 10.8, 15.0 Hz, 1H), 6.02 (d, J = 10.8 Hz, 1H), 5.73 (dt, J = 15.0, 5.7 Hz, 1H), 4.03-4.13 (m, 2H), 4.00 (d, J = 5.7 Hz, 2H), 3.28 and 3.22 (2dd, J = 6.6, 9.0 Hz and J = 6.6, 9.0 Hz, each 1H), 2.62 (dd, J = 3.9, 13.5 Hz, 1H), 2.46 (dd, J = 3,6, 13.2 Hz, 1H), 2.29 (dd, J = 7.2, 13.2 Hz, 1H), 2.16 (dd, J = 6.9, 13.2 Hz, 1H), 1.82-1.89 (m, 2H), 1.73 (br s, 3H, 3 OH), 1.10-1.48 (m, 7H), 1.20 (s, 6H), 0.91 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.0, 129.7, 127.4, 127.2, 76.0, 71.2, 71.1, 67.3, 67.0, 44.4, 44.1, 41.9, 37.1, 34.3, 33.3, 29.15, 29.11, 21.6, 17.1; IR (neat) 3390, 2935, 1458, 1377, 1297, 1215, 1052, 966, 939, 907, 816, 756; $[\alpha]^{28}_D$ 10.17 (*c* 6.09, $CHCl_3$); DI/MS(EI) *m/z* : 308 (M^+-H_2O, 2),

290 (1), 167 (82), 166 (76), 149 (100), 143 (17). Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.94; H, 10.67.



(1*R*,3*R*)-5-[(2'*S*)-(*E*)-4-(6'-Ethyl-6'-hydroxy-2'-methyloctyloxy)but-2-enylidene]cyclohexane-1,3-diol (35): **35** (65.9 mg) was obtained in 93% overall yield from resin **31** (271 mg, 0.738 mmol/g, 0.20 mmol), **30** (X=O, 195 mg, 0.60 mmol), and EtMgBr (1.46 ml, 1.37 N in Et_2O, 2.0 mmol). The crude residue consisted of **35** and a trace amount of **32**. The chemical purity of the resulting **35** was determined to be >95% by ^{1}H NMR analysis and HPLC analysis with a scanning diode array UV detector (210-370 nm) [SI-60 column (silica gel, 4.6 ϕ x 250 mm), *i*-PrOH/hexane (1/6 (v/v)), **35**: λmax 240 nm, 12.4 min]: a viscous oil; ^{1}H NMR ($CDCl_3$) δ 6.51 (dd, J = 10.8, 15.0 Hz, 1H), 6.02 (d, J = 10.8 Hz, 1H), 5.74 (dt, J = 15.0, 5.7 Hz, 1H), 4.04-4.13 (m, 2H), 4.00 (d, J = 5.7 Hz, 2H), 3.28 and 3.21 (2dd, J = 6.3, 9.3 Hz and J = 6.3, 9.3 Hz, each 1H), 2.63 (dd, J = 3.9, 13.5 Hz, 1H), 2.47 (dd, J = 2.7, 13.2 Hz, 1H), 2.29 (dd, J = 7.8, 13.5 Hz, 1H), 2.17 (dd, J = 6.9, 13.2 Hz, 1H), 1.10-1.90 (m, 9H), 1.60 (br s, 3H, 3OH), 1.46 (q, J = 7.5 Hz, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.85 (t, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 134.7, 129.7, 127.3, 127.0, 76.1, 74.8, 71.2, 67.4, 67.1, 44.5, 42.0, 38.5, 37.3, 34.5, 33.5, 31.0, 20.8, 17.4, 7.9; IR (neat) 3390, 2936, 1459, 1377, 1216, 1052, 967, 939, 816, 757, 666; $[\alpha]^{28}_D$ 11.37 (*c* 2.43, $CHCl_3$); DI/MS(EI) *m/z* : 336 (M^+-H_2O, 0.2), 318 (3), 182 (1), 171 (8), 167 (85), 159 (16), 149 (100). Anal. Calcd. for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 70.92; H, 11.02.

Preparation of the Authentic Sample of Z-isomer of 23.



(1*R*,3*R*)-5-[(7*R*)-(*Z*)-11-Hydroxy-7,11-dimethyldodec-2-enylidene]cyclohexane-1,3-diol (*Z*-isomer of 23): A mixture of bromide **11** (182 mg, 0.418 mmol), acetylene **28** (182 mg, 0.586 mmol), CuI (24 mg, 0.126 mmol), $PdCl_2(PPh_3)_2$ (29 mg, 0.041 mmol) and pyrrolidine (0.54 mL) was stirred for 22 h at 70 °C.[12] After the mixture was cooled to room temperature, water (10 mL) was added. The mixture was extracted with hexane (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, concentrated in vacuo and passed through a short silica gel column to give the corresponding enyne. To a solution of the coupling compound thus obtained and Ti(O-*i*-Pr)$_4$ (0.148 mL, 0.50 mmol) in Et_2O (4 mL) was added *i*-PrMgCl (0.82 mL, 1.26 M in Et_2O, 1.03 mmol) at -50 °C and the resulting mixture was stirred for 3 h at the same temperature. After the addition of water (0.3 mL), the mixture was allowed to warm to room temperature. NaF (0.8 g) and Celite (0.8 g) were added. The mixture was filtered through a pad of Celite with hexane (10 mL) . The filtrate was concentrated in vacuo to give tris-silyl ether of the titled compound, which was desilylated by the reaction with 30% HF (0.1 mL) in THF (5.0 mL) to afford the Z-isomer of **23** (97 mg) in 71% overall yield from **11**. ^{1}H NMR ($CDCl_3$) δ 6.12 -6.32 (m, 2H), 5.43 (dt, *J* = 7.9, 7.5 Hz, 1H), 3.98-4.14 (m, 2H), 2.61 (dd, *J* = 3.6, 13.2 Hz, 1H), 2.48 (dd, *J* = 3.6, 13.2 Hz, 1H), 1.20 (s, 6H), 1.00-2.34 (m, 20H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 134.0, 132.1, 123.14, 123.07, 71.1, 67.2, 67.0, 44.8, 44.2, 42.0, 37.5, 36.8, 36.5, 32.6, 29.28, 29.23, 27.8, 27.0, 21.8, 19.7. As show in page 50, this compound thus obtained was compared with **23** on ^{1}H and ^{13}C NMR analyses.

3.6 References and Notes.

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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. *Biochemica. Et. Biophysica. Acta.*, **1993**, *1158*, 279.
3. Paricalcitol: (a) Graul, A.; Leeson, P. A.; Castaner, J. *Drugs Future* **1998**, *23*, 602. Compound **23**: (b) U. S. Patent **1998**, 5,969,190. Compound **2**: (c) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. (d) U. S. Patent **1999**, 6,184,422. Other 19-*nor*-analogues: (e) Zhou, X.; Zhu, G.-D.; Van Haver, D.; Vandewalle, M.; De Clercq, P. J.; Verstuyf, A.; Bouillon, R. *J. Med. Chem.* **1999**, *42*, 3539. (f) Kubodera, N.; Okano, T.; Nakagawa, K.; Ozono, K.; Mikami, K. *Cur. Pharm. Design* **2000**, *6*, 791.
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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 3-3 and its diastereomer in a ratio of >96: <4, recrystallization of which

from hexane provided the diastereomerically pure compound.

8. >97% *E*.
9. Ee of **26** was confirmed by ^{1}H NMR analyses, after converting to the corresponding MTPA esters, to be >99%.
10. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
11. See Experimental Section.
12. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403 and references cited therein.
13. A Ti(II)-mediated partial reduction of internal alkynes to *cis*-olefins, see: Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. 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. Synthesis & Catalysis* **2001**, *343*, 759. Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 319-354.
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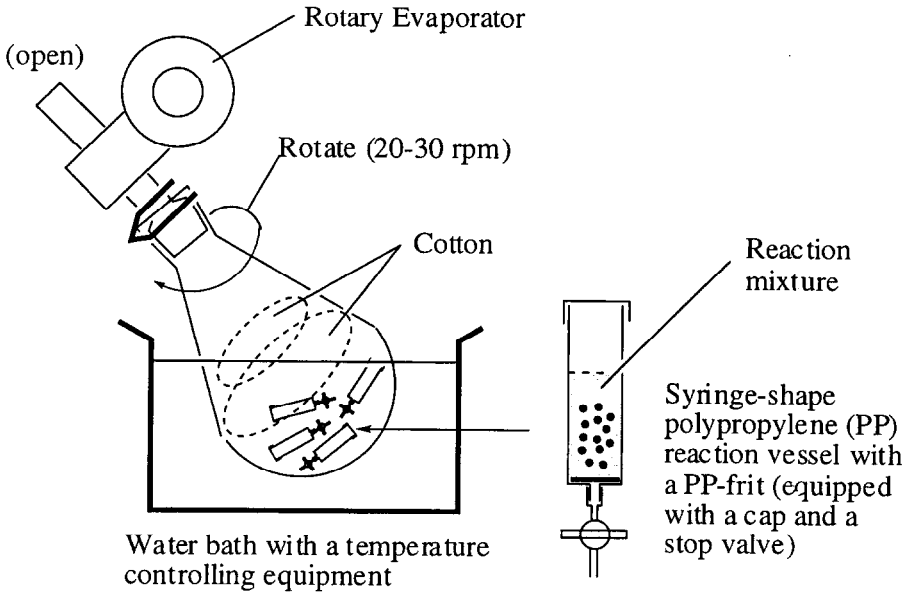
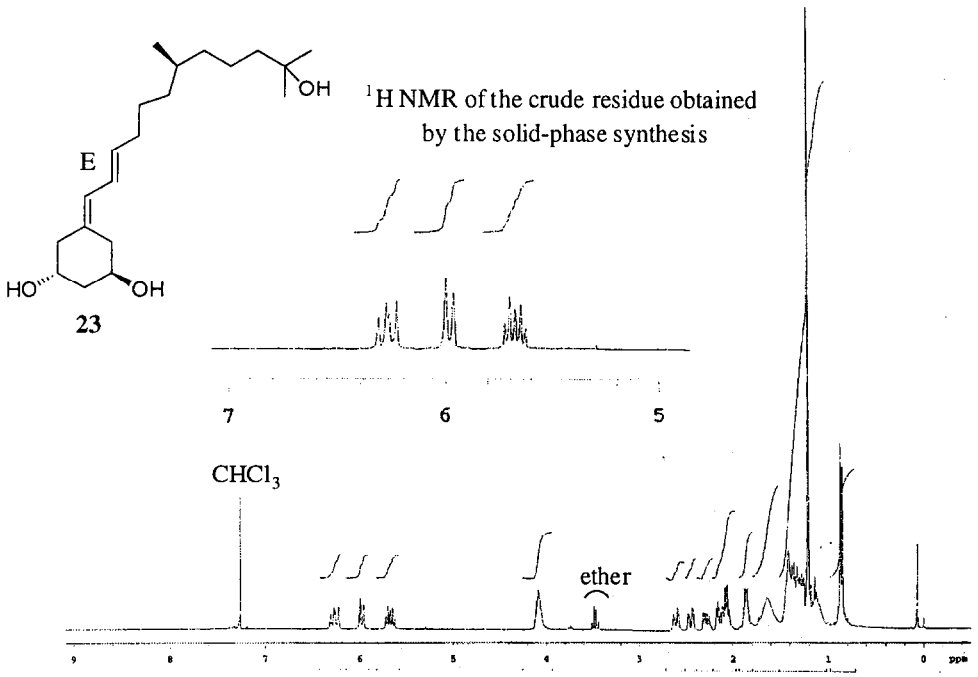
17. Prepared from PS-DES (Argonaut Technologies) by the reported procedure: Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518.
18. Prepared from the corresponding terminal alkynes via hydroboration reaction.[11]
19. Chemical purity of the products **23** and **33-35** was determined by ^{1}H NMR and HPLC analyses to be >95%.
20. Several 26,27-dimethyl derivatives of 1,25-(OH)$_2$VD$_3$, 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$_3$s. Reviews on the synthesis and structure-function relationship of vitamin D analogues: Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocrine Reviews* **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 **34** and **35** by the Julia coupling method developed

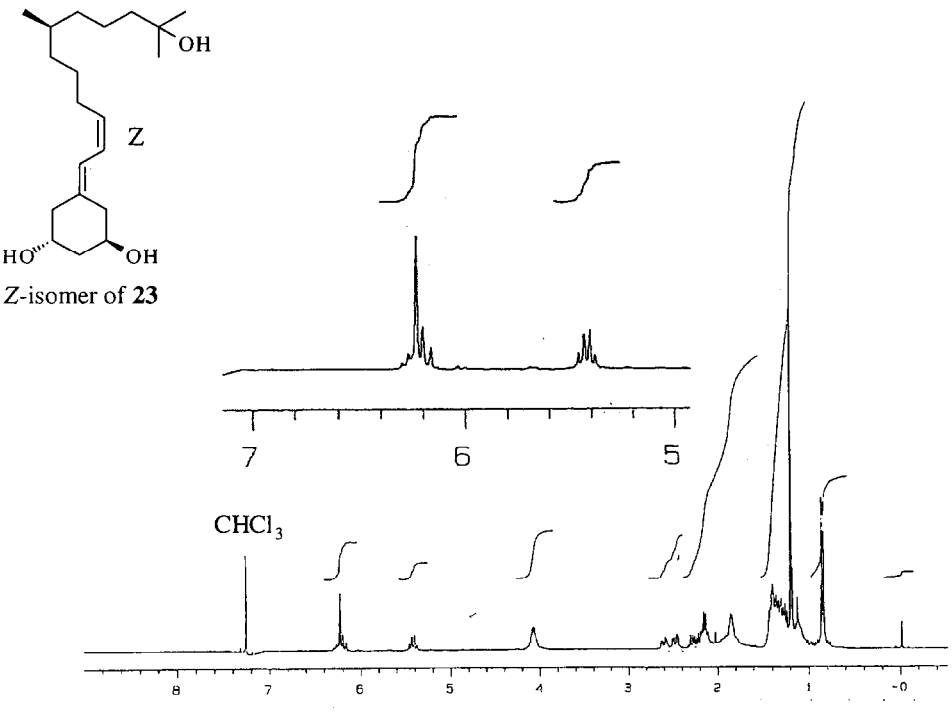
by Hilpert[3c] because the corresponding sulfone reagent might undergo elimination of an alkoxy group by treatment with a base.

22. The compound **24** was reported in the literature, in which the spectral data were not indicated: see 3c.
23. The reaction vessels were placed in a round bottom flask filled with cotton to fix the vessels. The flask was attached to a rotary evaporator (without a vacuum line) and was rotated on a water bath with a temperature controlling equipment, see below:



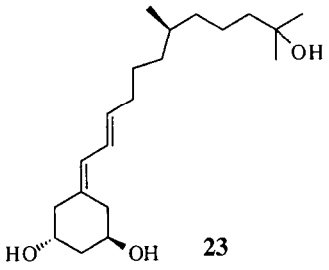
^{1}H NMR Spectra of 23 and its *Z*-isomer (300 MHz, $CDCl_3$)



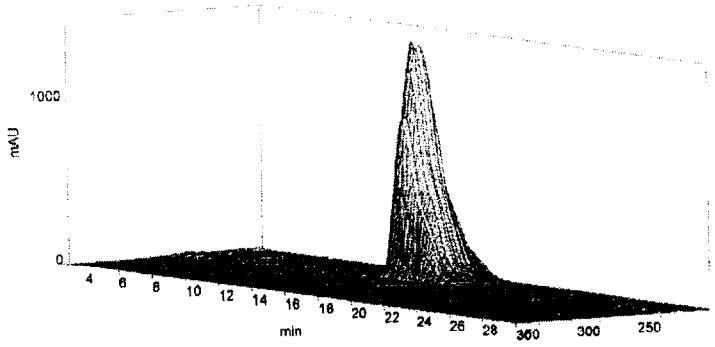


3D-HPLC of Compound 23 obtained by the solid-phase synthesis.

HPLC were performed by using a SI-60 silica gel column [4.6 ϕ x 250 mm, *i*-PrOH/hexane (1/6 v/v] with a photo-diode array UV-detector (Shimadzu, SPD-M10Avp).

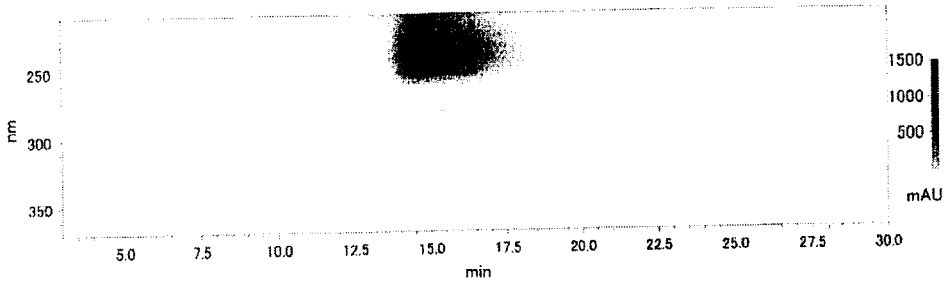


23

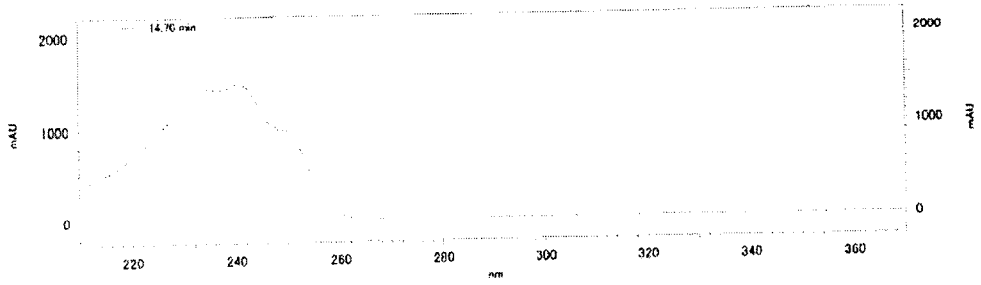


3D Chromatography

2D Chromatography

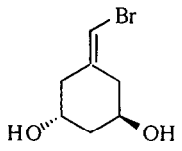


Spectrum at time 14.70 min.

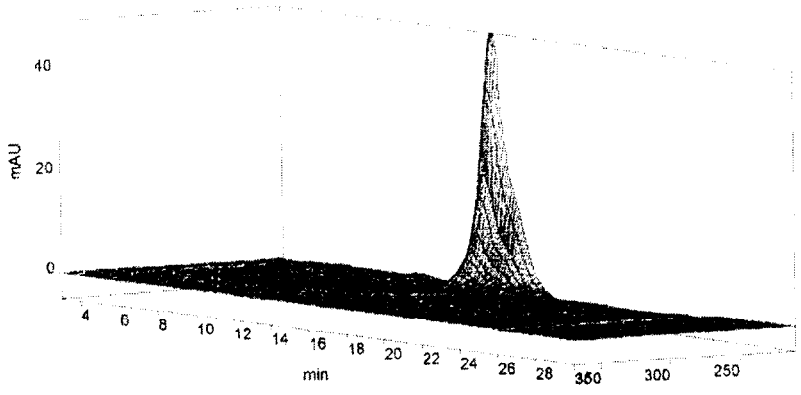


3D-HPLC of 5-Bromomethylene-cyclohexane-1,3-diol (32)

HPLC were performed by using a SI-60 silica gel column [4.6 ϕ x 250 mm, *i*-PrOH/hexane (1/6 v/v] with a photo-diode array UV-detector (Shimadzu, SPD-M10Avp).

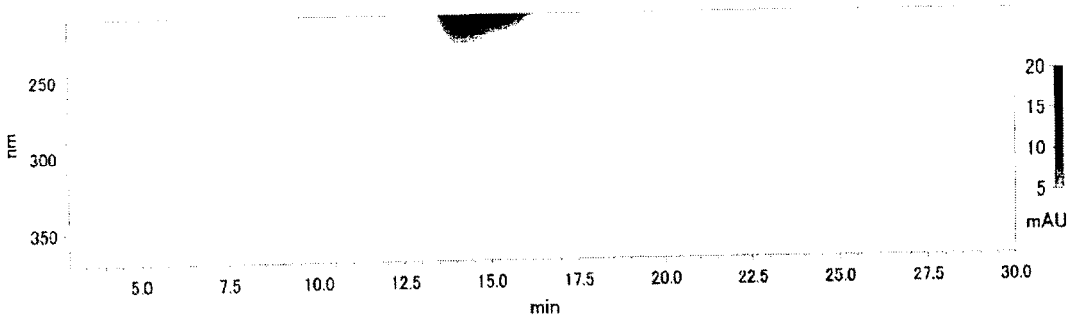


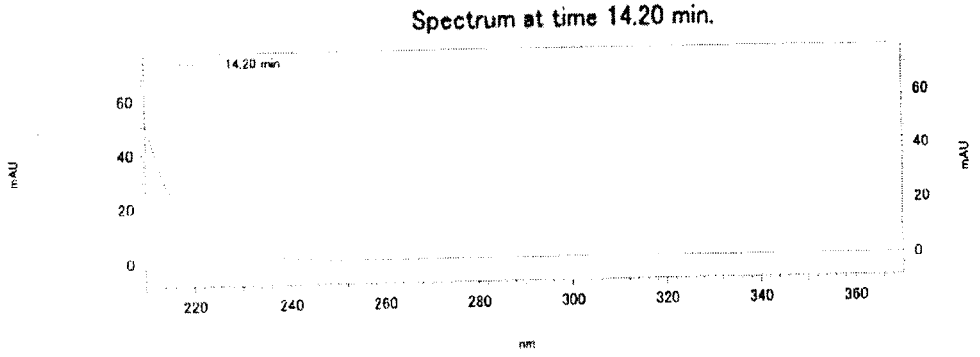
32



3D Chromatography

2D Chromatography



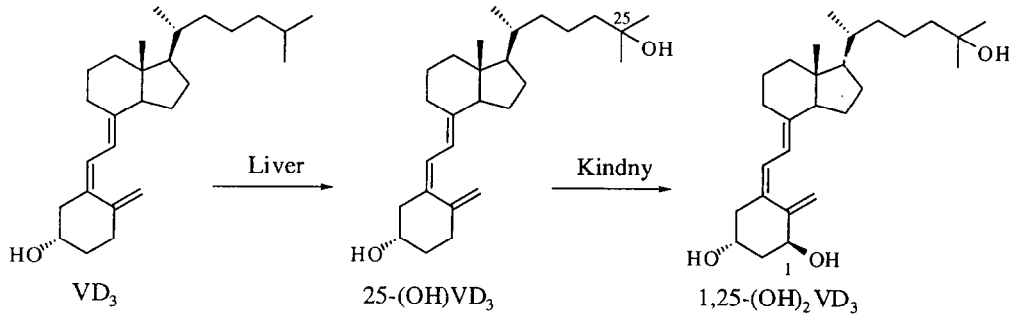


4. Efficient Convergent Synthesis of 1α,25-Dihydroxyvitamin D_3 and its Analogues by the Suzuki-Miyaura Coupling.

4.1 Introduction.

Metabolic activation of VD_3 involves hydroxylation in the liver to form 25-(OH)VD_3 and the following further hydroxylation in the kidney to produce 1,25-$(OH)_2VD_3$ (Figure 4-1). The latter metabolite serves as a regulator of calcium homeostasis. In

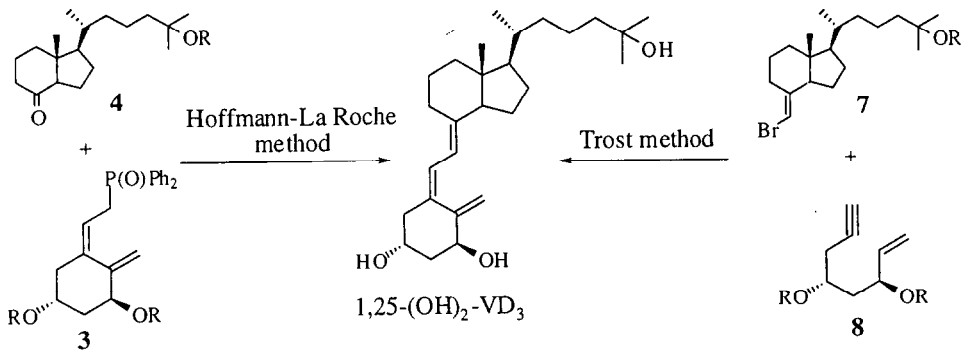
Figure 4-1



VD_3 25-(OH)VD_3 1,25-$(OH)_2VD_3$

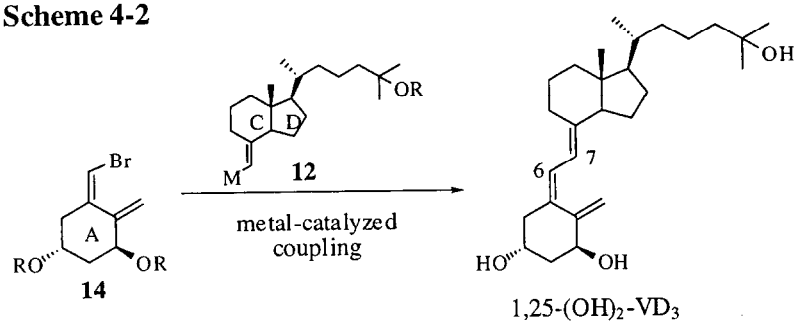
addition to its role, 1,25-$(OH)_2VD_3$ has recently been shown to promote normal cell differentiation and proliferation as well as to generate a variety of biological responses through nongenomic mechanisms. Because of its important role in human physiology, it has attracted substantial interest in its pharmacology and therapeutic potential.[1] The chemical synthesis of 1,25-$(OH)_2VD_3$ 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-$(OH)_2VD_3$ and its derivatives. As shown in Scheme 4-1, one is the Hoffmann-La Roche method which uses a connection of the A-ring **3** and the C,D-ring **4** by the Horner-Wittig reaction,[3] and the other is the Trost method, which involves a Pd-catalyzed carbometallation-cyclization reaction of the acyclic precursor of the A-ring **8**

Scheme 4-1



and the C,D-ring **7**.[4] The coupling approach between the A-ring part **14** and the C,D-ring part **12** shown in Scheme 4-2 is anticipated to furnish another efficient convergent synthesis. And, actually, the preparation of 3-deoxy-1-hydroxyvitamine D_3 by coupling of the corresponding A-ring part with **12** (M = SnR_3 or ZnX) using the Stille coupling or Negishi coupling reaction, was reported by Mouriño and co-workers.[5] However, the preparation of **14** has not been achieved, and thus the preparation of 1,25-$(OH)_2VD_3$ through such a coupling pathway has not been reported.

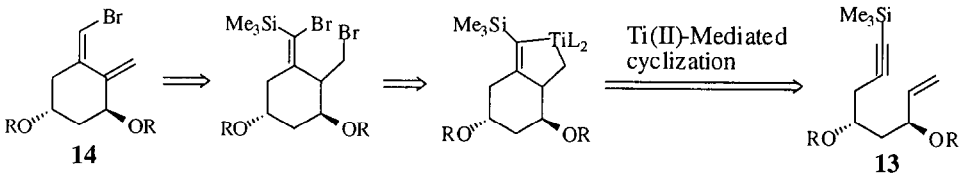
Scheme 4-2



4.2 Synthesis of 1α,25-Dihydroxyvitamin D_3 and its Analogues by the Suzuki-Miyaura Coupling.

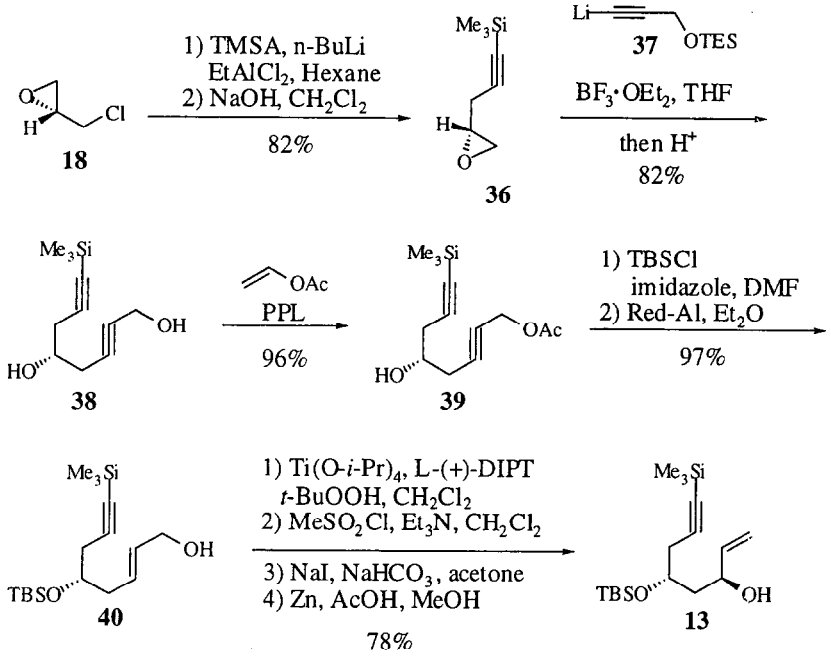
We envisaged that the synthesis of **14** could be achieved by Ti(II)-mediated cyclization[6] of the corresponding 1,7-enyne **13** as shown in Scheme 4-3 by a retrosynthetic method. The synthesis of optically active **13** has been previously reported by Ogasawara and co-workers by starting with optically active epichlorohydrin

Scheme 4-3



(**18**).[7] According to this method and with several modifications, we synthesized **13** as shown in Scheme 4-4. Thus, **18** was converted to epoxide **36**,[8] which in turn was reacted with alkynyllithium **37** in the presence of boron trifluoride etherate[9] to provide, after hydrolysis, diol **38** in 82% yield. Selective acylation of the primary hydroxyl group of **38** to **39** was attained by treatment with vinyl acetate in the presence of porcine pancreatic lipase (PPL) in 96% yield.[10] Protection of the secondary hydroxy group of **39** as TBS ether, and the following treatment with sodium bis(2-methoxy-ethoxy)aluminum hydride (Red-Al) afforded **40** in 97% yield. From **40**, compounds **13** was prepared in excellent overall yield by the conventional reaction sequence,[711] which involves Sharpless catalytic asymmetric epoxidation with L-(+)-diisopropyl tartrate (DIPT) as a chiral ligand, conversion of the hydroxy group to iodide, and

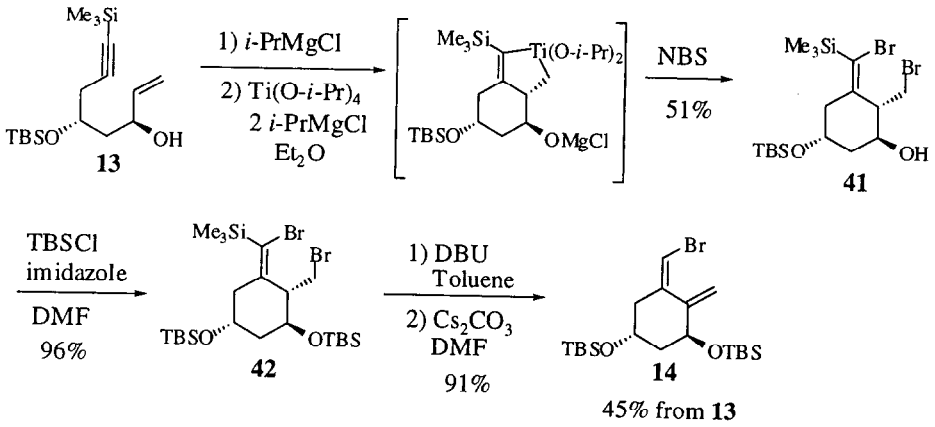
Scheme 4-4



reductive opening of the epoxy iodide moiety. The diastereomeric purity of crude **13** thus obtained was found to be more than 97%, and the corresponding pure **13** was isolated by column chromatography.

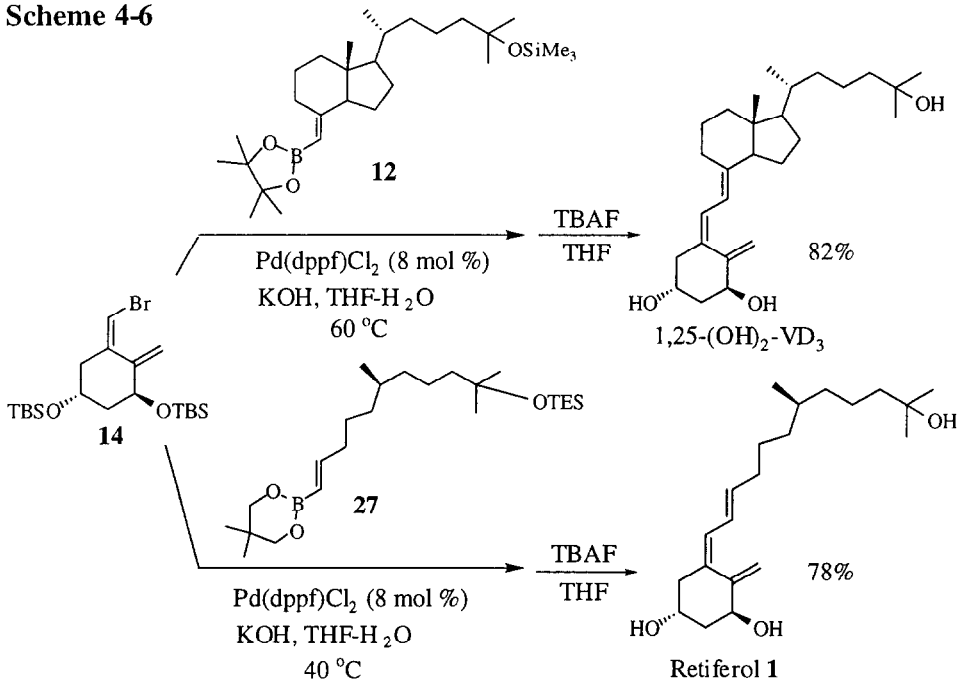
As shown in Scheme 4-5, the titanacyclization of **13**, mediated by a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl,[6] and the following reaction with NBS afforded the corresponding dibromo compound **41** in 51% yield Although the stereochemistry of the carbon center bearing a bromomethyl moiety in **41** thus produced could not be assigned by the ^{1}H NMR analysis, it was tentatively assigned as depicted in Scheme 4-5 on the basis of our previous results of the cyclization of similar compounds.[12] After protection of the hydroxyl group of **41** as TBS ether, the resulting **42** was treated with DBU in toluene and then with Cs_2CO_3 in DMF to provide **14** in excellent yield.[5] Thus, **14** could be obtained in 45% overall yield from **13**.

Scheme 4-5



With the A-ring unit **14** in hand, we carried out the synthesis of 1,25-(OH)$_2$VD$_3$ using the Suzuki-Miyaura coupling reaction.[13] Thus, the reaction of **14** with **12**[14] 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 as shown in Scheme 4-6.

Scheme 4-6

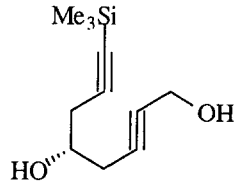


Among the analogues of 1,25-$(OH)_2VD_3$, those which lack the C,D-ring structure have recently attracted much interest as potentially therapeutic compounds.[15] The present method for synthesizing 1,25-$(OH)_2VD_3$ with use of **14** is also very efficient for synthesizing other compounds as exemplified by the synthesis of retiferol **1**.[15a] Thus, as shown in Scheme 4-6, the coupling of **14** with **27**[14] prepared from the corresponding alkyne by hydroboration reaction afforded retiferol **1** in 78 % overall yield after desilylation.[16]

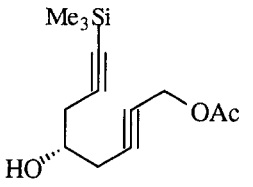
4.4 Experimental Section.

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Gemini-2000 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00), residual $CHCl_3$ (δ 7.26 for ^1H NMR), or $CDCl_3$ (δ 77.0 for ^{13}C NMR). IR spectra were recorded on an FT-IR spectrometer (JASCO FT/IR-230). Elemental analyses were performed on an Elemental automatic analyzer. All reactions sensitive to oxygen and/or moisture were performed under an argon atmosphere. Dry solvents (THF, ethyl ether, dimeythyl-formamide, CH_2Cl_2, and toluene) were purchased from Kanto Chemicals. Other chemicals are commercially available, unless otherwise indicated, and were used as

received.

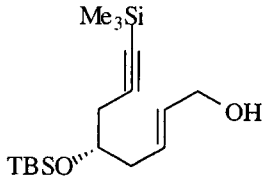


(*S*)-8-(Trimethylsilyl)octa-2,7-diyne-1,5-diol (38): To a stirred solution of 3-triethylsiloxy-1-propyne **37** (18.7 g, 110 mmol) in THF (100 mL) was slowly added *n*-BuLi (63.7 mL, 1.57 M in hexane, 100 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, a solution of epoxide **36** (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 the addition of saturated aqueous NH_4Cl (100 mL), the mixture was extracted with Et_2O (3 × 100 mL). The combined extracts 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 (hexane-EtOAc) to give **38** (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.

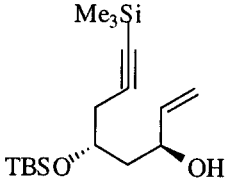


Acetic acid (*S*)-5-hydroxy-8-(trimethylsilyl)octa-2,7-diynyl ester (39): To a solution of **38** (16.5 g, 78.4 mmol) in vinyl acetate (78 mL) was added porcine pancreatic lipase (PPL, 42 units/mg, Sigma-Aldrich, 16.5 g). After being stirred for 3 days at room temperature, the mixture was filtered through a pad of Celite with Et_2O (200 mL). The filtrate was concentrated and chromatographed on silica gel

(hexane–Et_2O) to give **39** (19.0 g, 96%). ^1H 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.



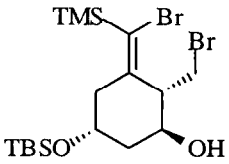
(*S*,*E*)-5-(*tert*-Butyldimethysiloxy)-8-(trimethylsilyl)oct-2-en-7-yn-1-ol (40)[7]: To a mixture of **39** (22.0 g, 87.2 mmol), imidazole (13.0 g, 191 mmol) and DMF (180 mL) was added TBSCl (14.4 g, 95.6 mmol) at 0 °C. After the mixture was stirred for 12 h at room temperature, saturated aqueous $NaHCO_3$ (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 carefully added. 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 **40** (27.8 g, 97%). ^1H 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 (CDCl3) 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.,[7] $[\alpha]^{28}_D$ 3.9 (*c* 0.92, MeOH)].



(3*S*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-8-(trimethylsilyl)oct-1-en-7-yn-3-ol (13)[7]: To

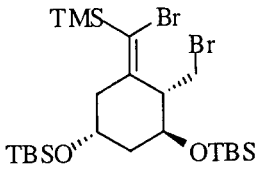
a mixture of $Ti(O\text{-}i\text{-}Pr)_4$ (5.00 mL, 17.0 mmol) and 4A molecular sieves (5.56 g) in CH_2Cl_2 (50 mL) was added diisopropyl L-(+)-tartarate (L-(+)-DIPT) (4.28 mL, 20.4 mmol) at −15 °C and the mixture was stirred for 30 min. To this was slowly added a solution of **40** (27.8 g, 85.1 mmol) 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 the addition of methyl sulfide (9.34 mL, 127 mmol), the mixture was stirred for 1 h at −20 °C, and 10% tartaric acid (30 mL) was added. The mixture was then warmed to room temperature over 1 h and diluted with Et_2O (500 mL). After the 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 with Et_2O (300 mL). 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 the 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 solution 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 the 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, $NaHCO_3$ (2.13 g, 25.4 mmol) and 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 the 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 (hexane-Et_2O) to give **13** (21.7 g, 78% overall yield from **40**). ^1H 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.,[7] $[\alpha]^{28}_D$ –26.0 (*c* 1.06, $CHCl_3$)].

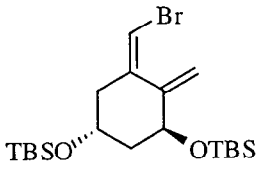


(*Z*)-(1*S*,2*S*,5*R*)-2-Bromomethyl-3-[bromo(trimethylsilyl)methylene]-5-(*tert*-butyldimethylsiloxy)cyclohexanol (41): To a solution of **13** (1.63 g, 4.99 mmol) in Et_2O (50 mL) was added dropwise *i*-PrMgCl (2.51 mL, 1.99 M in Et_2O, 4.99 mmol) at 0 °C. After the solution was stirred for 10 min 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, to this was slowly added a solution of NBS (4.90 g, 27.5 mmol) in THF (30 mL) and the mixture was allowed to warm to room temperature. After the mixture 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 **41** (1.26 g, 51%). ^1H 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.

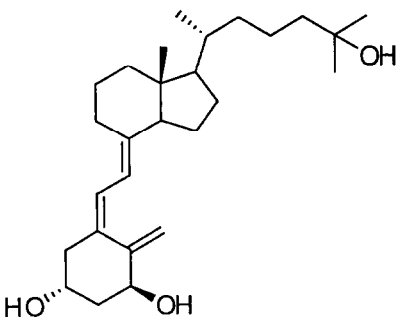


(*Z*)-(2*S*,3*S*,5*R*)-2-Bromomethyl-1-[bromo(trimethylsilyl)methylene]-3,5-bis(*tert*-butyldimethylsiloxy)cyclohexane (42): To a mixture of **41** (1.70 g, 3.49 mmol), imidazole (0.47 g, 6.90 mmol), and DMF (5 mL) was added TBSCl (0.573 g, 3.80 mmol) at 0 °C. After the mixture was stirred for 12 h at 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 (hexane-Et_2O) to give **42** (2.02 g, 96%) as a colorless oil. ^1H 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.



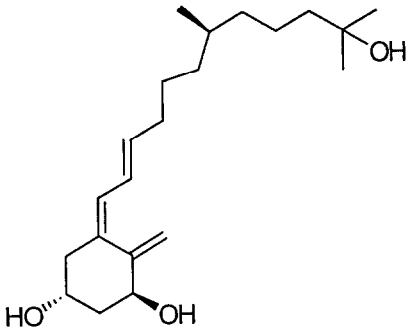
(*Z*)-(3*S*,5*R*)-1-Bromomethylene-3,5-bis(*tert*-butyldimethylsiloxy)-2-methylenecyclohexane (14): To a solution of **42** (1.70 g, 2.83 mmol) in toluene (5.6 mL) was added DBU (1.68 mL, 11.2 mmol) at 0 °C. The reaction mixture was stirred at 70 °C for 20 h. After the addition of saturated aqueous $NaHCO_3$ (15 mL), the mixture was extracted with hexane (3 × 10 mL). 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 the 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 **14** (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.



1α,25-Dihydroxyvitamin D_3 from 14 and 12: To a mixture of boronate **12**[14] (160 mg, 0.336 mmol), aqueous 3 N KOH (0.11 mL), and THF (0.3 mL) was added dropwise a mixture of bromide **14** (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 the 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_2O (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 1 from 14 and 27: 1 (55.1 mg) was obtained in 78% yield starting from **14** (94.0 mg, 0.210 mmol) and **27**[14] (130 mg, 0.306 mmol) under similar reaction conditions as described for the synthesis of 1α,25-dihydroxyvitamin D_3 from **14** and **12**. The ^{1}H NMR spectroscopic spectra were in full agreement with those reported.[15a] ^{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, $CHCl_3$).

4.5 Reference and Notes.

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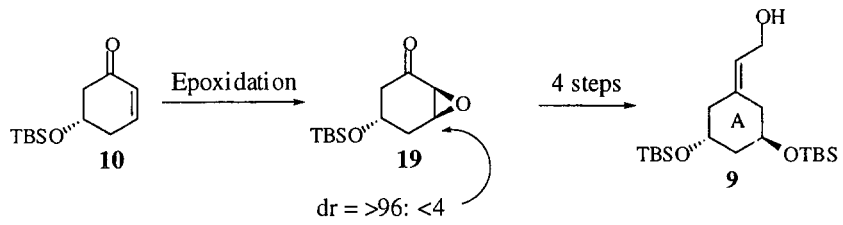
16. For the synthesis of *des*-C,D-VD_3-analogues by Lythgoe-Roche method, see ref 15. Synthesis of *des*-C,D-VD_3-analogues by the Trost method was not reported.

Concluding Remarks

This thesis described the development of new synthetic approach to 1,25-$(OH)_2VD_3$ and its derivatives, and it also included the efficient preparation of the known A-ring part used for the synthesis of 19-*nor*-1,25-$(OH)_2VD_3$. Conclusion of each chapter is as follows:

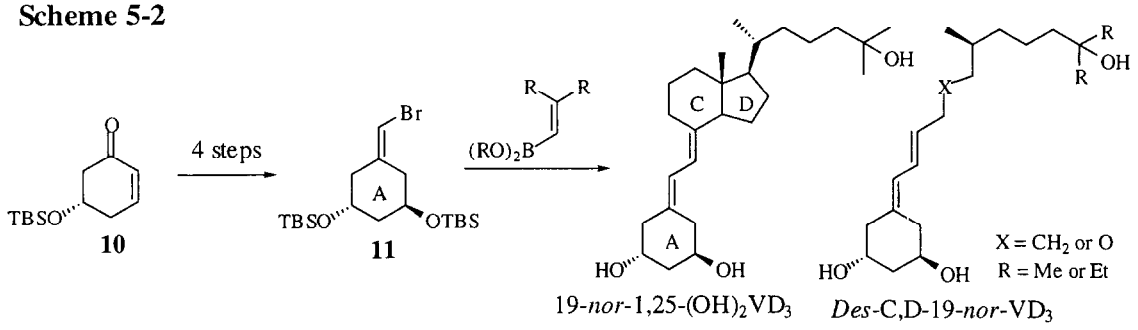
Chapter 2 described the efficient preparation of the known A-ring precursor of 19-*nor*-1,25-$(OH)_2VD_3$, **9**, starting from readily available 5-siloxycyclohexenone **10**. The synthesis of **9** was carried out through a five-step reaction in 68% overall yield, which involves the highly diastereoselective epoxidation of **10** to **19** (Scheme 5-1).

Scheme 5-1



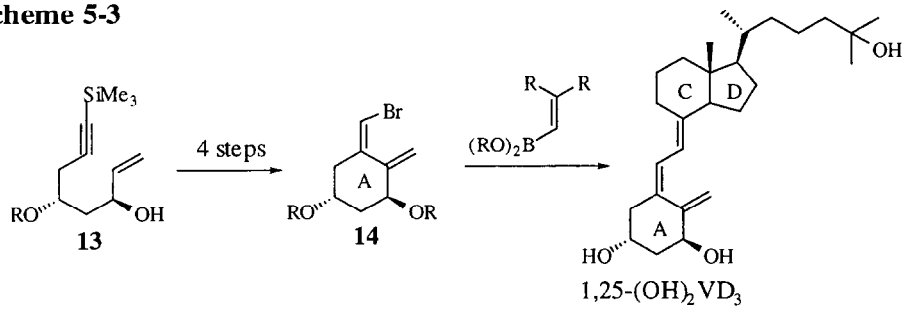
Chapter 3 disclosed the synthesis of new A-ring precursor **11** starting from readily available **10** through a four-step reaction in 66% overall yield. The reaction of the A-ring part **11** with the corresponding C,D-ring portion by the Suzuki-Miyaura coupling in solution and on solid support efficiently proceeded to afford 19-*nor*-1,25-$(OH)_2VD_3$ and its *des*-C,D-analogues (Scheme 5-2). It is noteworthy that this method could allow to synthesize a variety of 19-*nor*-VD_3 derivatives, including those that are difficult to access by other methods.

Scheme 5-2



Chapter 4 described the development of new synthetic methodology for producing 1,25-$(OH)_2VD_3$ and its derivatives. This approach involved the efficient preparation of the A-ring part **14** by the titanacyclization of readily available 1,7-enyne **13** and its coupling with the C,D-ring portion by the Suzuki-Miyaura protocol (Scheme 5-3).

Scheme 5-3



List of Publications

1. Efficient and Practical Synthesis of A-Ring Precursor of 19-*nor*-1α,25-Dihydroxyvitamin D_3 and its ^{13}C- or ^{2}H-Labeled Derivative. Hanazawa, T.; Inamori, H.; Masuda, T.; Okamoto, S.; Sato, F.* *Org. Lett.* **2001**. 3, 2205.

2. Novel Synthetic Approach to 19-*nor*-1α,25-Dihydroxyvitamin D_3 and its Derivatives by the Suzuki-Miyaura Coupling in Solution and on Solid Support. Hanazawa, T.; Wada, T.; Masuda, T.; Okamoto, S.; Sato, F.* *Org. Lett.* **2001**, 3, 3975.

3. Efficient Convergent Synthesis of 1α,25-Dihydroxyvitamin D_3 and its Analogues by the Suzuki-Miyaura Coupling. 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).

4. New Convergent Synthesis of 1α,25-Dihydroxyvitamin D_3 and its Analogues by Suzuki-Miyaura Coupling between A-ring and C,D-ring Parts. Hanazawa, T.; Koyama, A.; Nakata, K.; Okamoto, S.; Sato, F.* *J. Org. Chem.* **2003**, 68, 9767.

Other Publications

5. Asymmetric Synthesis of Palitantin from the (5*R*)-(*tert*-Butyldimethylsiloxy)-2-cyclohexenone. Hareau, G.; Koiwa, M.; Hanazawa, T.; Sato, F.* *Tetrahedron Lett.* **1999**, *40*, 7493.

6. Optically Active *trans*-4-(*tert*-Butyldimethylsiloxymethyl)-5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenone as a Useful Chiral Building Block for Preparation of Substituted Cyclohexane Rings. Hanazawa, T.; Koiwa, M.; Hareau, G; Sato, F.* *Tetrahedron Lett.* **2000**, *41*, 2659.

7. Preparation of Titanated Alkoxyallenes from 3-Alkoxy-2-propyn-1-yl Carbonates and (η^2-Propene)Ti(O-*i*-Pr)$_2$ as an Efficient Ester Homoaldol Equivalent. Hanazawa, T.; Okamoto, S.; Sato, F.* *Org. Lett.* **2000**, *2*, 2369.

8. Chemical Synthesis of Optically Active *cis*-Cyclohexa-3,5-diene-1,2-diols and Their 5-^{2}H-Derivatives. Hanazawa, T.; Okamoto, S.; Sato, F.* *Tetrahedron Lett.* **2001**, *42*, 5455.

9. Efficient and Practical Method for Synthesizing Optically Active Indan-2-ols by the Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl-Mediated Metalative Reppe Raction. Hanazawa, T.; Sasaki, K.; Takayama, Y.; Sato, F.* *J. Org. Chem.* **2003**, 68, 4980.

List of Proceedings

1. Total Synthesis of (-)-Palitantin. Hanazwa, T.; Hareau, G.; Sato, F.* 76th Annual Meeting of the Chemical Society of Japan, March, 1999, Japan.

2. Optically Active Trans-4-(*tert*-butlydimetylsiloxymetyl)-5-(*tert*-butlydimetylsiloxy)-2-cyclohexenone as Useful Chiral Building Block for Preparation of Substituted Cyclohexane Ring. Hanazwa, T.; Koiwa, M.; Hareau, G.; Sato. F.* Workshop on Organic Chemistry for Junior Chemists. December, 1999, Chinese Taipei.

3. Synthesis of New Chiral Building Block for Preparation of Substituted Cyclohexane Ring. Hanazwa, T.; Koiwa, M.; Hareau, G.; Sato. F.* 78th Annual Meeting of the Chemical Society of Japan, March, 2000, Japan.

4. Preparation Of Alkoxyallenes from 3-Alkoxy-2-propyn-1-yl Carbonates and (η^2-Propene)Ti(O-*i*-Pr)$_2$ as an Efficient Ester Homoaldol Equivalent. Hanazawa, T.; Okamoto, S.; Sato, F.* Workshop on Organic Chemistry for Junior Chemists. November, 2000, Japan.

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6. Efficient and Practical Syhthesis of Optically Active *cis*-Cyclohexa-3,5-diene-1,2-diols. Hanazawa, T.; Okamoto, S.; Sato, F.* 79th Annual Meeting of the Chemical Society of Japan, March, 2001, Japan.

7. Efficient and Practical Synthesis of A-Ring Precursor of 1α,25-Dihydroxyvitamin D$_3$ and 19-*nor*-1α,25-Dihydroxyvitamin D$_3$. Inamori, H.; Masuda, T.; Hanazawa, T.; Okamoto, S.; Sato, F.* 79th Annual Meeting of the Chemical Society of Japan, March, 2001, Japan.

8. New Efficient and Practical Synthesis of 19-*nor*-1α,25-Dihydroxyvitamin D_3 Starting from Chiral Building Block, 5-(*tert*-Butyldimetylsiloxy)-2-cyclohexenone. Hanazawa, T.; Wada, T.; Masuda, T.; Okamoto, S.; Sato, F.* 80th Symposium on Organic Synthesis, November, 2001, Japan.

9. Synthesis of 19-*nor*-1α,25-Dihydroxyvitamin D_3 Derivatives by Suzuki-Miyaura Coupling. Hanazawa, T.; Masuda, T.; Wada, T.; Morishige, E.; Okamoto, S.; Sato, F.* 81th Annual Meeting of the Chemical Society of Japan, March, 2002, Japan.

10. Solid-phase Synthesis of 19-*nor*-1α,25-Dihydroxyvitamin D_3 by Suzuki-Miyaura Coupling. Wada, T.; Hanazawa, T.; Masuda, T.; Okamoto, S.; Satǒ, F.* 81th Annual Meeting of the Chemical Society of Japan, March, 2002, Japan.

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12. Synthetic Application of Ti(II)-Mediated Cyclization: Synthesis of New A-ring Intermediate for Preparation of Vitamin D_3 Derivatives. Hanazawa, T.; Koyama, A.; Wada, T.; Morishige, E.; Okamoto, S.; Sato, F.* The 20th IUPAC International conference on Organicmetallic Chemistry (XX ICOMC), July, 2002, Greece.

13. Syntheses of Optical Active 2-Indanoles by a Lowvalent Titanium Reagent. Sasaki, K.; Hanazawa, T.; Takayama, Y.; Sato, F.* 83th Annual Meeting of the Chemical Society of Japan, March, 2003, Japan.

14. Preparation of Polysubstituted Benzene Derivatives by Regioselective Coupling Reaction of Acetylene-Titanium Complexes with Diynes. Wada, T.; Hanazawa, T.; Muraoka, K.; Takayama, Y.; Sato, F.* 83th Annual Meeting of the Chemical Society of Japan, March, 2003, Japan.

15. Synthesis of Pyridine Derivatives by the Cyclotrimerization with the Lowvalent

Titanium Reagent. Hanazawa, T.; Wada, T.; Muraoka, K.; Takahashi, M.; Takayama, Y.; Sato, F.* 83th Annual Meeting of the Chemical Society of Japan, March, 2003, Japan.

16. An Method for Preparation of Fluorine-substituted 19-*nor*-1α,25-Dihydroxyvitamin D_3 Derivatives. Morishige, E.; Hanazawa, T.; Koyama, A.; Okamoto, S.; Sato, F.* 83th Annual Meeting of the Chemical Society of Japan, March, 2003, Japan.

17. Regioselective Reaction of Diethynylpridine Derivatives with a Divalent titanium Reagent. Easy Synthesis of π-Conjugated Oligomers. Hanazawa, T.; Ando, T.; Takahashi, M.; Takayama, Y.; Sato, F.* 84th Annual Meeting of the Chemical Society of Japan, March, 2004, Japan. (To be presented)

18. Design and Synthesis of Vitamin D Antagonists. Yoshimoto, N.; Igarashi, M.; Morizono, D.; Yamagata, S.*; Shimizu, M.; Yamada, S.; Hanazawa, T.; Sato, F. 124th The Pharmaceutical Society of Japan, March, 2004, Japan. (To be presented)

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