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Synthesis and Evaluation of A-Ring Diastereomers of 1α,25-Dihydroxy-22-Oxavitamin D_3 (OCT)[1]

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Abstract—A-ring diastereomers of 1α,25-dihydroxy-22-oxavitamin D_3 (OCT) (**2**), 3-epi-1α,25-dihydroxy-22-oxavitamin D_3 (3-epiOCT) (**3**) and 1,3-diepi-1α,25-dihydroxy-22-oxavitamin D_3 (1,3-diepiOCT) (**4**) were synthesized by the convergent method. In vitro binding affinity for rat vitamin D binding protein and calf-thymus vitamin D receptor, differentiation-inducing activity on HL-60 cells, and transcriptional activity of 3-epiOCT (**3**) and 1,3-diepiOCT (**4**) were evaluated in comparison with OCT (**2**), 1-epi-1α,25-dihydroxy-22-oxavitamin D_3 (1-epiOCT) (**5**) and 1α,25-dihydroxyvitamin D_3 (**1**).

Introduction

The active vitamin D_3, 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) (**1**), is now well recognized as one of the potent regulators of cell proliferation and differentiation processes in addition to possessing a regulatory effect on calcium and phosphorus metabolism.[2] Various analogues of 1,25$(OH)_2D_3$ (**1**) have been synthesized to separate differentiation-induction and antiproliferation activities from calcemic activity with the aim of obtaining useful analogues for the medical treatment of psoriasis, cancer, etc., without risk of hypercalcemia.[3] 1α,25-Dihydroxy-22-oxavitamin D_3 (OCT) (**2**) was obtained in such synthetic studies and **2** has been shown to be highly potent in stimulating monocytic differentiation of human promyelocytic leukemic HL-60 cells but less calcemic than 1,25$(OH)_2D_3$ (**1**).[4–6] OCT (**2**) is now under the process of approval as an injection for the treatment of secondary hyperparathyroidism underlying renal insufficiency[7] and as an ointment for skin disease, psoriasis.[8]

Recently, the epimerization of the 3-hydroxy group of vitamin D_3 compounds has been reported. 3-Epi-1α,25-dihydroxyvitamin D_3 (3-epi-1,25$(OH)_2D_3$) was isolated in human keratinocytes[9] or rat osteosarcoma cells[10] incubated with 1,25$(OH)_2D_3$. 3-Epi-1,25$(OH)_2D_3$ was also found in the serum of rats treated with 1,25$(OH)_2D_3$.[11] In the case of 24,25-dihydroxyvitamin D_3 (24,25$(OH)_2D_3$), the other major natural metabolite of vitamin D_3, 3-epi-24,25-dihydroxyvitamin D_3 was recently identified in the bile of rats administered with 24,25$(OH)_2D_3$.[12] Although the biological characterization of the epimerized vitamin D_3 compounds at 3-position as yet remains to be clarified, we have been interested in the new metabolic pathway of vitamin D_3 compounds at the A-ring part in addition to the classic metabolic pathway at the side chain. It is a matter of no little interest to us to synthesize putative A-ring metabolites of OCT (**2**) and investigate their biological characteristics. In this paper, we describe the synthesis of 3-epi-1α,25-dihydroxy-22-oxavitamin D_3 (3-epiOCT) (**3**) and 1,3-diepi-1α,25-dihydroxy-22-oxavitamin D_3 (1,3-diepiOCT) (**4**) as A-ring diastereomers of OCT (**2**). Their in vitro binding affinity for calf-thymus vitamin D receptor (VDR) and rat vitamin D binding protein (DBP), differentiation-inducing activity on HL-60 cells, and transcriptional activity using rat 24-hydroxylase gene and human osteocalcin gene are also described as the preliminary biological evaluation of synthesized A-ring diastereomers in comparison with 1,25$(OH)_2D_3$ (**1**), OCT (**2**), and 1-epi-1α,25-dihydroxy-

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22-oxavitamin D_3 (1-epiOCT) (**5**), which was previously prepared as 1β-hydroxylated OCT.[13] OCT (**2**), 3-epiOCT (**3**), 1,3-diepi OCT (**4**), and 1-epiOCT (**5**) consist of all possible A-ring diastereomers of OCT (**2**) (Fig. 1).

Results and Discussion

Synthesis of the A-ring fragment (21) of 3-epiOCT (3)

To synthesize 3-epiOCT (**3**) and 1,3-diepiOCT (**4**), we adopted the convergent method, in which the A-ring fragments (**21** and **35**) are coupled with the C/D-ring fragment (**37**) for the construction of the triene system of vitamin D_3 structures. First, we undertook the synthesis of the A-ring fragment (**21**) of 3-epiOCT (**3**). The epoxide (**8a**), obtained by Katsuki–Sharpless epoxidation[14] of the allyl alcohol (**6**) using diisopropyl L-tartrate (L-DIPT) and subsequent iodination of **7a**, was subjected to reductive cleavage using zinc in methanol containing acetic acid to give the alcohol (**9a**) in 92% yield. After protection of the hydroxy group as its *tert*-butyldimethylsilyl (TBS) ether, deprotection of the 4-methoxybenzyl (MPM) group of **10a**, followed by Swern oxidation of the resulting alcohol (**11a**), gave the aldehyde (**12a**) in 63% overall yield. The aldehyde (**12a**) was then reacted with the dianion generated by the action of methyl acetoacetate and lithium diisopropylamide (LDA) to provide the keto-ester (**13**) as a 1:1 epimeric mixture, which, upon silylation, afforded the TBS ether (**14**) and the TBS enol ether (**15**) in 28% and 32% yields from **12a**, respectively. Treatment of **15** with silica gel in methanol resulted in the formation of **14** in 67% yield. Triflation of the sodium enolate of **14** with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]pyridine (2-Py-N-Tf_2)[15] gave the *Z*-vinyl triflate (**16**) in 70% yield, accompanied by the *E*-isomer (6%), which was easily separated out by column chromatography. Upon treatment of **16** with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) ($(Ph_3P)_4Pd$) (0.1 equiv) and silver oxide (Ag_2O) (1 equiv) in boiling tetrahydrofuran (THF), intramolecular Heck reaction[16] took place cleanly to produce the cyclized ester (**17**) in 78% yield. Reduction of **17** with diisobutylaluminum hydride (DIBAL) gave the alcohols (**18** and **19**) each in 40% yield, after separation by column chromatography. The alcohol **18** is the precursor of the A-ring fragment of 3-epiOCT (**3**), whereas **19** corresponds to that of OCT (**2**). According to the established procedure,[17] the A-ring fragment (**21**) of 3-epiOCT (**3**) was finally obtained from **18** via the chloride (**20**) (Fig. 2).

Synthesis of the A-ring fragment (35) of 1,3-diepiOCT (4)

For the synthesis of the A-ring fragment (**35**) of 1,3-diepiOCT (**4**), we selected a more stereoselective route than that employed in the above-mentioned synthesis of the A-ring fragment (**21**) of 3-epiOCT (**3**), in order to construct the C3 asymmetric center of **35** (the vitamin D numbering) without formation of stereoisomers. Horner–Emmons reaction between triethyl phosphonoacetate and the aldehyde (**12b**), obtained from the allyl alcohol (**6**) in the same manner as described for the preparation of the enantiomer (**12a**), produced the ester (**22**) in 86% yield, which was reduced with DIBAL to give the allyl alcohol (**23**) in 87% yield. Katsuki–Sharpless epoxidation of **23** using diisopropyl D-tartrate (D-DIPT) was accomplished quantitatively to afford the epoxide (**24**). Treatment of **24** with bis(2-methoxyethoxy)aluminum hydride (Red-Al)[18] allowed regioselective reductive opening of the epoxy ring to give the alcohol (**25**). Upon monopivaloylation, silylation, and saponification, **25** afforded the anti-diTBS ether (**27**) in 80% yield together with the corresponding syn-diTBS ether (8%). The latter was derived from the minor product of the Katsuki–Sharpless epoxidation of **23** and was easily separated from **27** by column chromatography at this stage. Swern oxidation of **27**, condensation of the resulting aldehyde (**28**) with methyl acetate, and subsequent Dess–Martin oxidation of **29** gave rise to the ketone (**30**). According to the method developed by Takahashi and co-workers,[19] the ketone (**30**) was transformed into the alcohol (**33**) in 51% overall yield by a three-step sequence involving triflation, DIBAL reduction, and intramolecular Heck reaction. The A-ring fragment (**35**) for the synthesis of 1,3-diepiOCT (**4**) was obtained from **33** by the same method as described in the preparation of **21** from **18** (Fig. 3).

Preparation of the C/D-ring fragment (37)

The C/D-ring fragment (**37**) was prepared from OCT (**2**) via **36** in 23% overall yield by a three-step sequence; i) silylation with trimethylsilyl trifluoromethanesulfonate (TMSOTf), ii) ozonolysis followed by sodium borohydride reduction, and iii) oxidation using tetrapropylammonium perruthenate (TPAP)[20] and *N*-methylmorpholine *N*-oxide (Fig. 4).

Coupling of the A-ring fragments (21 and 35) and C/D-ring fragment (37)

Having obtained the A-ring fragments (**21** and **35**) and the C/D-ring fragment (**37**), we performed the coupling

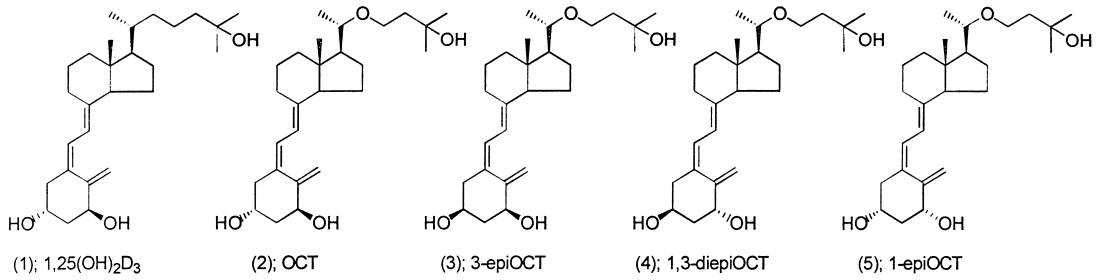

Figure 1. Structures of active vitamin D_3 and OCT analogues.

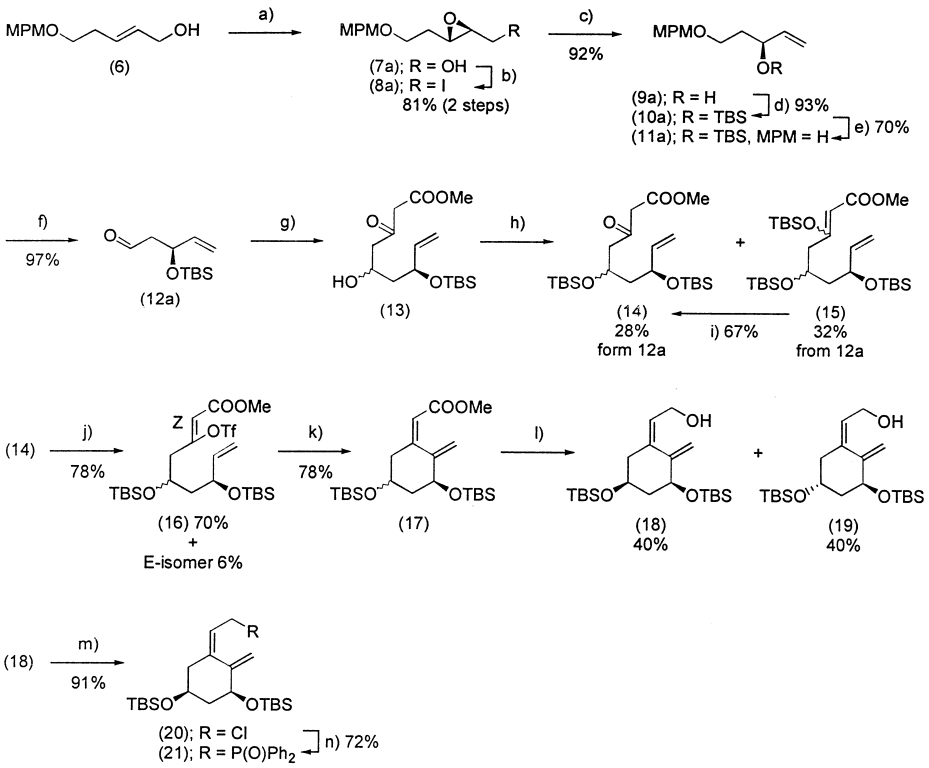

Figure 2. Synthesis of the A-ring fragment (**21**) of 3-epiOCT (**3**). (b)-Series of **7**–**12** correspond to enantiomers of (a)-series for the synthesis of the A-ring fragment (**35**) of 1,3-diepiOCT (**4**); (a) L-DIPT/*tert*-BuOOH/$Ti(O^iPr)_4/CH_2Cl_2$; (b) Ph_3P/I_2/THF–MeOH; (c) Zn/AcOH–MeOH; (d) TBSCl/Et_3N/DMAP/CH_2Cl_2; (e) DDQ/CH_2Cl_2–H_2O; (f) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2; (g) $MeCOCH_2COOMe$/LDA/THF; (h) TBSOTf/Et_3N/CH_2Cl_2; (i) SiO_2/MeOH; (j) 2-Py-N-Tf_2/NaH/THF; (k) $Pd(tpp)_4/Ag_2O$/THF; (l) DIBAL/CH_2Cl_2; (m) NCS/Me_2S/CH_2Cl_2; (n) 1) $HPPh_2$/*n*-BuLi/THF, 2) $H_2O_2/CHCl_3$–H_2O.

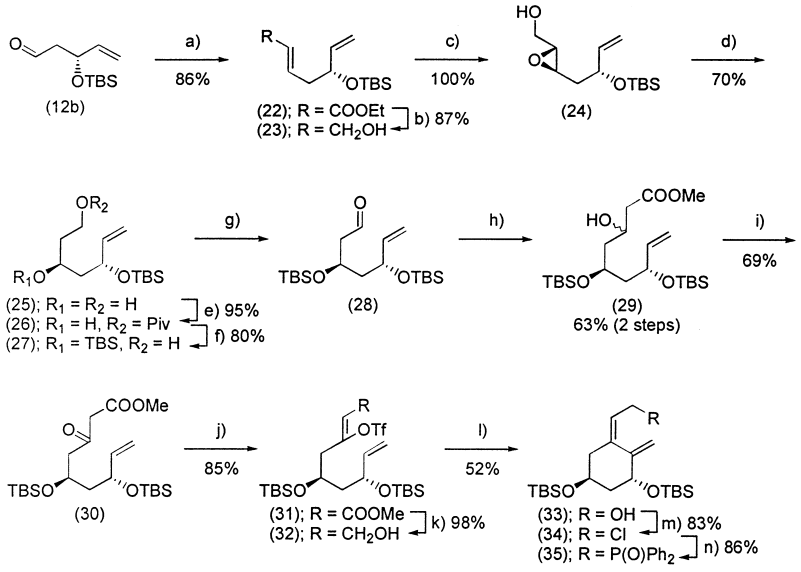

Figure 3. Synthesis of the A-ring fragment (**35**) of 1,3-diepiOCT (**4**); (a) $(EtO)_2P(O)CH_2COOEt$/NaH/THF; (b) DIBAL/CH_2Cl_2; (c) D-DIPT/*tert*-BuOOH/$Ti(O^iPr)_4/CH_2Cl_2$; (d) Red-Al/toluene; (e) PivCl/pyridine/CH_2Cl_2; (f) 1) TBSCl/2,6-lutidine/DMF, 2) 10 N NaOH/MeOH; (g) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2; (h) MeCOOMe/*n*-Buli/diisopropylamine/THF; (i) Dess–Martin reagent/CH_2Cl_2; (j) 2-Py-N-Tf_2/NaH/THF; (k) DIBAL/CH_2Cl_2; (l) $Ph_3P/Et_3N/Pd(OAc)_2$/DMF; (m) NCS/Me_2S/CH_2Cl_2; (n) 1) $HPPh_2$/*n*-BuLi/THF, 2) $H_2O_2/CHCl_3$–H_2O.

reaction[17] in the presence of *n*-butyllithium (*n*-BuLi) to give **38** and **39** in 45% and 33% yields, respectively. Finally, deprotection of the silyl protecting groups of **38** and **39** with tetrabutylammonium fluoride (TBAF) furnished 3-epiOCT (**3**) and 1,3-diepiOCT (**4**), respectively (Fig. 5).

Biological evaluation

The preliminary biological characteristics of 3-epiOCT (**3**) and 1,3-diepiOCT (**4**) were evaluated in comparison with $1,25(OH)_2D_3$ (**1**), OCT (**2**) and 1-epiOCT (**5**). 1-EpiOCT (**5**) was previously synthesized as 1β-hydroxylated OCT[13] taking the relationship between $1,25(OH)_2D_3$ (**1**) and

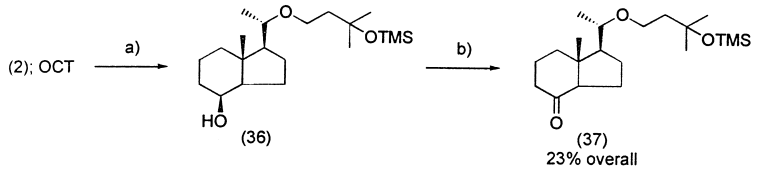

Figure 4. Preparation of the C/D-ring fragment (**37**). (a) 1) $TMSOTf/Et_3N/CH_2Cl_2$, 2) $O_3/MeOH–CH_2Cl_2$, 3) $NaBH_4/MeOH$; (b) $TPAP/NMO/CH_2Cl_2$.

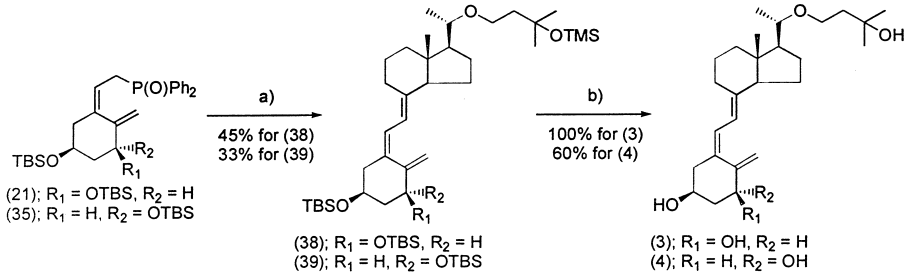

Figure 5. Synthesis of 3-epiOCT (**3**) and 1,3-diepiOCT (**4**). (a) *n*-BuLi/THF; (b) TBAF/THF.

1β-hydroxylated $1,25(OH)_2D_3$, which seemed to be a potent stereospecific antagonist of **1**, into consideration.[21] The results of in vitro binding affinity for rat DBP and calf-thymus VDR, differentiation-inducing activity on human promyelocytic leukemic HL-60 cells, and transcriptional activities on rat 24-hydroxylase gene and human osteocalcin gene in transfected human osteosarcoma MG-63 cells are summarized in Table 1. Among the A-ring diasteromers of OCT, 1,3-diepiOCT (**4**) and 1-epiOCT (**5**) showed weak binding affinity for DBP, although OCT (**2**) and 3-epiOCT (**3**) did not reveal affinity in this experiment, compared to 1,25-$(OH)_2D_3$ (**1**). β-Hydroxy configuration at 1-position of OCT diastereomers might be important to realize binding affinity for DBP. As for binding affinity for VDR, OCT (**2**) showed 1/20 affinity of $1,25(OH)_2D_3$ (**1**), as reported previously.[6] 1-EpiOCT (**5**) did not bind VDR, as also reported before.[13] The VDR binding affinity of both 3-epiOCT (**3**) and 1,3-diepiOCT (**4**) was approximated as 1/200 of OCT (**2**) and 1/4000 of $1,25(OH)_2D_3$ (**1**). The combination between hydroxy substituents at 1- and 3-positions of A-ring diastereomers had a great influence on binding ability for VDR. In differentiation-inducing effects and transcriptional activities, only OCT (**2**) showed more potent effects than $1,25(OH)_2D_3$ (**1**). Slight efficacy was found in 3-epiOCT (**3**); however, it was not found in both 1,3-diepiOCT (**4**) and 1-epiOCT (**5**). This might be explained by the fact that a natural α-hydroxy configuration at 1-position of OCT diastereomers plays an important role in the realization of differentiation-inducing and transcriptional activities. The detailed biological characteristics of A-ring diastereomers of OCT and metabolic epimerization at A-ring moiety incubated with OCT (**2**) will be discussed elsewhere soon.

Table 1. Biological characteristics of $1,25(OH)_2D_3$ (**1**), OCT (**2**) and analogues **3**–**5**

	DBP[a]	VDR[b]	HL-60[c]	Rat 24-OHase[d]	Human osteocalcin[e]
$1,25(OH)_2D_3$ (**1**)	100	100	100	100	100
OCT (**2**)	N.B	5.1	130	433	422
3-EpiOCT (**3**)	N.B.	< 0.1	5	19	10
1,3-DiepiOCT (**4**)	7.2	< 0.1	< 1	< 1	< 1
1-EpiOCT (**5**)	0.9	N.B.	< 1	< 1	< 1.

[a]DBP: Affinity for rat vitamin D binding protein (N.B.: no binding).
[b]VDR: Affinity for calf-thymus vitamin D receptor (N.B.: no binding).
[c]HL-60: Differentiation-inducing effect on HL-60 cells.
[d]Rat 24-OHase: Transcriptional activity on rat 24-hydroxylase gene.
[e]Human osteocalcin: Transcriptional activity on human osteocalcin gene.

Experimental

General

Optical rotations were measured with Horiba SEPA-200 and JASCO DIP-140 polarimeters. Infrared (IR) spectra were obtained using Horiba FT-730, JASCO ET/IR-5300, JEOL JIR-6000, and Hitachi 270-30 spectrophotometers. ^1H and ^{13}C NMR spectra were recorded on VARIAN Gemini-300, JEOL FX-200, and JNM-270EX spectrometers using CDCl3 as a solvent. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane or calibrated from $CHCl_3$. Mass spectra (MS) were measured with JEOL JMS-HX-100, Shimadzu GCMS QP-5050A, and Hitachi M1200H instruments. High resolution mass spectra (HRMS) were recorded on JEOL JMS-AX-500 and VG Auto Spec Q instruments. Ultraviolet (UV) spectra were obtained with a Shimadzu UV-240 spectrometer using EtOH as a solvent. All reactions were carried out under an atmosphere of argon unless otherwise noted. All extracts were dried over $MgSO_4$ and evaporated under reduced pressure with a rotary evaporator. Chromatographic purification was carried out with Merck silica gel 60 (column) or Merck silica gel 60 PF_{254} (peparative TLC).

(2*S*,3*S*)-2,3-Epoxy-5-(4-methoxybenzyl)oxy-1-pentanol (7a). To a stirred solution of L-DIPT (474 mg, 2.03 mmol) and molecular sieves (4 Å, 405 mg) in CH_2Cl_2 (12 mL) at −23 °C was added $Ti(O^iPr)_4$ (468 μL, 1.58 mmol). The resulting mixture was stirred at −23 °C for

10 min and a solution of **6** (5.00 g, 22.5 mmol) in CH_2Cl_2 (11 mL) and *tert*-BuOOH (2.97 M solution in CH_2Cl_2, 15 mL, 45.0 mmol) were added at −23 °C. After being stirred at −15 °C for 2.5 d, the reaction mixture was quenched by the addition of saturated Na_2SO_4 and Et_2O. The mixture was stirred at rt for 2 h, filtered through Celite, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (2:3) gave **7a** (4.92 g, 92%, 91% ee) as a colorless oil. IR (neat) 3426, 1512, 1462, 1248, 1176, 1097 cm^{-1}. ^1H NMR δ: 1.70–1.99 (3H, m), 2.97 (1H, d, t, J = 2.7, 4.2 Hz), 3.10 (1H, d, d, d, J = 2.7, 5.1, 6.6 Hz), 3.58 (2H, t, J = 5.7 Hz), 3.62 (1H, d, d, d, J = 4.2, 7.2, 12.3 Hz), 3.81 (3H, s), 3.90 (1H, d, d, d, J = 2.7, 5.7, 12.3 Hz), 4.45 (2H, s), 6.88 (2H, d, J = 8.7 Hz), 7.26 (2H, d, J = 8.7 Hz). ^{13}C NMR δ: 32.0, 53.7, 55.2, 58.5, 61.8, 66.5, 72.7, 113.8, 129.2, 130.2, 159.1. MS (*m*/*z*) 238 (M^+), 207, 137, 121, 83 (100%). HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1222. $[\alpha]_D^{18}$ −27.7° (*c* 0.90, $CHCl_3$).

(2*R*,3*R*)-2,3-Epoxy-5-(4-methoxybenzyl)oxy-1-pentanol (7b). To a stirred solution of D-DIPT (1.21 g, 5.15 mmol) and molecular sieves (4 Å, 8 g) in CH_2Cl_2 (500 mL) at −25 °C was added $Ti(O^iPr)_4$ (1.18 mL, 3.99 mmol). The resulting mixture was stirred at −25 °C for 30 min and a solution of **6** (12.72 g, 57 mmol) in CH_2Cl_2 (50 mL) and *tert*-BuOOH (2.97 M solution in CH_2Cl_2, 38.4 mL, 114 mmol) at −25 °C were added. After being stirred at −15 °C for 40.5 h, the reaction mixture was quenched by the addition of saturated Na_2SO_4 and Et_2O. The mixture was stirred at rt for 2 h, filtered through Celite, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (2:3) gave **7b** (12.44 g, 92%, 91% ee) as a colorless oil. The results of IR, ^1H NMR, ^{13}C NMR, MS (*m*/*z*), HRMS and optical rotation (opposite) were identical with **7a**.

(2*R*,3*R*)-2,3-Epoxy-1-iodo-5-(4-methoxybenzyl)oxypentane (8a). A mixture of **7a** (4.00 g, 16.8 mmol), imidazole (8.58 g, 126 mmol), Ph_3P (13.2 g, 50.4 mmol), and I_2 (12.8 g, 50.4 mmol) in THF (240 mL) and CH_3CN (60 mL) was stirred at rt for 30 min. The mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, saturated $NaHSO_3$ and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:20) gave **8a** (5.88 g, 100%) as a pale yellow oil. IR (neat) 1612, 1512, 1460, 1361, 1301, 1249, 1174, 1100, 1033 cm^{-1}. ^1H NMR δ: 1.73–1.95 (2H, m), 2.98 (1H, d, d, d, J = 1.8, 5.1, 6.3 Hz), 3.06 (1H, d, d, d, J = 1.8, 6.6, 8.7 Hz), 3.07 (1H, d, d, J = 6.3, 12.6 Hz), 3.22 (1H, d, d, J = 8.7, 12.6 Hz), 3.57 (2H, t, J = 5.7 Hz), 3.81 (3H, s), 6.89 (2H, d, J = 9.0 Hz), 7.27 (2H, d, J = 9.0 Hz). ^{13}C NMR δ: 5.0, 32.2, 55.3, 58.3, 60.3, 66.4, 72.8, 113.8, 129.3, 130.2, 159.2. MS (*m*/*z*) 348 (M^+), 221, 121 (100%). HRMS calcd for $C_{13}H_{17}O_3I$ 348.0222, found 348.0216. $[\alpha]_D^{19}$ +4.3° (*c* 1.04, $CHCl_3$).

(2*S*,3*S*)-2,3-Epoxy-1-iodo-5-(4-methoxybenzyl)oxypentane (8b). A mixture of **7b** (27.9 g, 117 mmol), imidazole (59.8 g, 878 mmol), Ph_3P (92.2 g, 352 mmol), and I_2 (89.3 g, 352 mmol) in THF (680 mL) and CH_3CN (170 mL) was stirred under ice cooling for 30 min. The mixture was diluted with hexane, washed with saturated $NaHCO_3$, saturated $NaHSO_3$ and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:3) gave **8b** (40.5 g, 99%) as a colorless oil. The results of IR, ^1H NMR, ^{13}C NMR, MS, HRMS and optical rotation (opposite) were identical with **8a**.

(3*S*)-5-(4-Methoxybenzyl)oxy-1-penten-3-ol (9a). A mixture of **8a** (5.39 g, 15.5 mmol) and Zn (3.04 g, 46.5 mmol) in MeOH (200 mL) and AcOH (8 mL) was stirred under sonication at 37 °C for 1 h. The mixture was diluted with Et_2O, filtered through Celite, washed with 5% HCl, saturated $NaHCO_3$ and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (2:7) gave **9a** (3.18 g, 92%) as a colorless oil. IR (neat) 3427, 1612, 1513, 1249, 1095, 1033 cm^{-1}. ^1H NMR δ: 1.73–1.92 (2H, m), 2.98 (1H, d, J = 3.6 Hz), 3.56–3.73 (2H, m), 3.81 (3H, s), 4.28–4.38 (1H, m), 4.45 (2H, s), 5.10 (1H, d, t, J = 1.2, 10.8 Hz), 5.27 (1H, d, t, J = 1.2, 17.4 Hz), 5.87 (1H, d, d, d, J = 5.4, 10.8, 17.4 Hz), 6.88 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 8.4 Hz). ^{13}C NMR δ: 36.1, 55.4, 68.1, 72.3, 73.1, 113.9, 114.7, 129.5, 129.8, 140.3, 159.3. MS (*m*/*z*) 222 (M^+), 221, 121 (100%). HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1249. $[\alpha]_D^{20}$ +8.5° (*c* 0.98, $CHCl_3$).

(3*R*)-5-(4-Methoxybenzyl)oxy-1-penten-3-ol (9b). A mixture of **8b** (13.9 g, 40 mmol) and Zn (7.85 g, 120 mmol) in MeOH (400 mL) and AcOH (20.6 mL) was stirred under sonication at 37 °C for 2.5 h. The mixture was diluted with AcOEt, filtered through Celite, washed with 5% HCl, saturated $NaHCO_3$ and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (2:7) gave **9b** (8.79 g, 98%) as a colorless oil. The results of IR, ^1H NMR, ^{13}C NMR, MS, HRMS and optical rotation (opposite) were identical with **9a**.

(3*S*)-3-(*tert*-Butyldimethylsilyl)oxy-5-(4-methoxybenzyl) oxy-1-pentene (10a). To a stirred solution of **9a** (5.15 g, 35.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added Et_3N (5.0 mL, 35.9 mmol), 4-(dimethylamino)pyridine (DMAP) (169 mg, 1.38 mmol), and TBSCl (97%, 5.15 g, 33.1 mmol). The resulting mixture was stirred at rt for 16 h, quenched with saturated $NaHCO_3$, extracted with AcOEt, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave **10a** (4.33 g, 93%) as a colorless oil. IR (neat) 1620, 1515, 1405, 1360, 1300, 1250, 1090, 1040 cm^{-1}. ^1H NMR δ: 0.03 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.77 (2H, q, J = 7.7 Hz), 3.43–3.60 (2H, m), 3.81 (3H, s), 4.28 (1H, q, J = 6.6 Hz), 4.38 (1H, d, J = 11.0 Hz), 4.45 (1H, d, J = 11.0 Hz), 5.01 (1H, d, t, J = 2.0, 10.0 Hz), 5.14 (1H, d, t, J = 2.0, 17.0 Hz), 5.80 (1H, d, d, d, J = 6.6, 10.0, 17.0 Hz), 6.88 (2H, d, J = 8.7 Hz), 7.26 (2H, d, J = 8.7 Hz). ^{13}C NMR δ: −4.8, −4.3, 18.3, 38.2, 55.4, 66.5, 70.9, 72.7, 113.7, 113.8, 129.4, 130.7, 141.7, 159.2. MS (*m*/*z*) 336 (M^+), 279, 122 (100%). HRMS calcd for $C_{19}H_{32}O_3Si$ 336.2121, found 336.2066. $[\alpha]_D^{18}$ +2.0° (*c* 0.99, $CHCl_3$).

(3*R*)-3-(*tert*-Butyldimethylsilyl)oxy-5-(4-methoxybenzyl) oxy-1-pentene (10b). To a stirred solution of **9b** (10.9 g, 49 mmol) in CH_2Cl_2 (250 mL) at 0 °C were added Et_3N

(20.4 mL, 147 mmol), DMAP (600 mg, 5 mmol), and TBSCl (97%, 22.1 g, 147 mmol). The resulting mixture was stirred at rt for 21 h, quenched with saturated AcOEt, washed with 0.5 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:30) gave **10b** (16.5 g, 100%) as a colorless oil. The results of IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS and optical rotation (opposite) were identical with **10a**.

(3*S*)-3-(*tert*-Butyldimethylsilyl)oxy-4-penten-1-ol (11a). To a stirred mixture of **10a** (531 mg, 1.58 mmol) in 5% aqueous CH_2Cl_2 (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (539 mg, 2.38 mmol) at rt. The resulting mixture was stirred for 15 min and saturated $NaHCO_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave **11a** (377 mg, 100%) as a pale yellow oil. IR (neat) 3350, 1467, 1405, 1362, 1254, 1087, 1024 cm^{-1}. ^{1}H NMR δ: 0.06 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.65–1.78 (1H, m), 1.79–1.91 (1H, m), 2.46 (1H, br t, J = 5.4 Hz), 3.66–3.76 (1H, m), 3.78–3.88 (1H, m), 4.42 (1H, br q, J = 6.0 Hz), 5.11 (1H, d, t, J = 1.8, 9.3 Hz), 5.23 (1H, d, t, J = 1.8, 17.4 Hz), 5.85 (1H, d, d, d, J = 5.7, 9.3, 17.4 Hz). ^{13}C NMR δ: −5.0, −4.3, 18.2, 25.9, 39.2, 60.2, 73.3, 114.5, 140.7. MS (m/z) 216 (M^+), 171, 160, 159, 75 (100%). HRMS calcd for $C_9H_{19}OSi$ 171.1205, found 171.1204. $[\alpha]_D^{20}$ +3.3° (c 0.94, $CHCl_3$).

(3*R*)-3-(*tert*-Butyldimethylsilyl)oxy-4-penten-1-ol (11b). To a stirred mixture of **10b** (16.1 g, 48 mmol) in 5% aqueous CH_2Cl_2 (200 mL) was added DDQ (12.0 g, 53 mmol) under ice cooling. The resulting mixture was stirred for 1 h at the same temperature and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ and saturated NaCl, dried, and evaporated. The residue was dissolved in MeOH (150 mL) and treated with $NaBH_4$ (0.875 g, 23 mmol). The resulting mixture was stirred at room temperature for 30 min and extracted with Et_2O. The extract was washed with saturated NH_4Cl and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave **11b** (8.3 g, 81%) as a colorless oil. The results of IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS and optical rotation (opposite) were identical with **11a**.

(3*S*)-3-(*tert*-Butyldimethylsilyl)oxy-4-pentenal (12a). To a stirred solution of $(COCl)_2$ (0.9 mL, 10.3 mmol) in CH_2Cl_2 (40 mL) at −63 °C was added DMSO (1.46 mL, 20.6 mmol). The resulting mixture was stirred at the same temperature for 30 min. To the mixture was added **11a** (1.11 g, 5.16 mmol) in CH_2Cl_2 (5 mL) at −63 °C. The resulting mixture was stirred at the same temperature for 30 min. After addition of Et_3N (5.8 mL, 41.3 mmol) at −63 °C, the resulting mixture was allowed to warm to rt. 0.1 M HCl was added and the mixture was extracted with AcOEt, washed with saturated NaCl, dried, and evaporated to give crude **12a** (1.08 g, 97%) as a pale yellow oil, which was used without further purification. ^{1}H NMR δ: 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 2.50 (1H, d, d, d, J = 2.1, 4.8, 15.6 Hz), 2.62 (1H, d, d, d, J = 2.7, 6.6, 15.6 Hz), 4.65 (1H, br q, J = 5.1 Hz), 5.13 (1H, d, t, J = 1.5, 10.5 Hz), 5.27 (1H, d, t, J = 1.5, 17.1 Hz), 5.88 (1H, d, d, d, J = 5.7, 10.5, 17.1 Hz), 9.79 (1H, br t, J = 2.5 Hz). MS (m/z) 185 (M^+ −CHO), 171, 157, 75 (100%).

(3*R*)-3-(*tert*-Butyldimethylsilyl)oxy-4-pentenal (12b). To a stirred solution of $(COCl)_2$ (7.2 mL, 82 mmol) in CH_2Cl_2 (150 mL) at −63 °C was added DMSO (11.6 mL, 164 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at the same temperature for 15 min. To the mixture was added **11b** (8.0 g, 41 mmol) in CH_2Cl_2 (50 mL) at −63 °C. The resulting mixture was stirred at the same temperature for 40 min. After addition of Et_3N (46 mL, 328 mmol) at −63 °C, the resulting mixture was allowed to warm to rt and the stirring was continued at room temperature for 1 h. To the mixture was added 0.1 M HCl. The mixture was extracted with Et_2O, washed with saturated NaCl, dried, and evaporated to give practically pure **12b** (7.8 g, 97%) as a pale yellow oil, which was used without further purification. The results of ^{1}H NMR and MS were identical with **12a**.

Methyl (5*RS*,7*S*)-5,7-bis(*tert*-butyldimethylsilyl)oxy-3-oxo-8-nonenoate (14). To a stirred mixture of LDA (0.7 M solution in THF, 41.6 mL, 29.1 mmol) at −78 °C was added methyl acetoacetate (1.4 mL, 13.0 mmol). The resulting mixture was stirred at 0 °C for 1.5 h and a solution of **12a** (1.18 g, 5.22 mmol) in THF (2 mL) was added at 0 °C. After being stirred at the same temperature for 40 min, the reaction mixture was quenched with saturated NH_4Cl, extracted with AcOEt, washed with saturated NH_4Cl, dried, and evaporated to give **13** (1.70 g) as a yellow oil, which was used for the next reaction without purification. A sample for ^{1}H NMR spectrum was obtained by preparative TLC developed with AcOEt:hexane (2:5). ^{1}H NMR δ: 0.06 (3H, s), 0.10 (3H, s), 0.90 (4.5H, s), 0.91 (4.5H, s), 1.52–1.79 (2H, m), 2.58–2.78 (2H, m), 3.51 (1H, s), 3.52 (1H, s), 3.74 (3H, s), 4.20–4.28 (0.5H, m), 4.38 (1H, m), 4.46–4.56 (0.5H, m), 5.08 (0.5H, br d, J = 10.5 Hz), 5.12 (0.5H, br d, J = 12.0 Hz), 5.18 (0.5H, br d, J = 17.1 Hz), 5.25 (0.5H, br d, J = 17.1 Hz), 5.74–5.92 (1H, m). To a stirred solution of crude **13** (1.70 g, 5.15 mmol) in CH_2Cl_2 (50 mL) at −78 °C were added Et_3N (1.08 mL, 7.74 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.42 mL, 6.18 mmol). After being stirred at −78 °C for 20 min, the reaction mixture was quenched with saturated $NaHCO_3$ (20 mL), extracted with AcOEt, washed with saturated NH_4Cl and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:15) gave **14** (649 mg, 28% from **12a**) as a colorless oil and the silyl enolate (**15**) (962 mg, 32%) as a colorless oil. Compound **15** was converted to **14** as follows. A mixture of **15** (586 mg, 1.05 mmol) and silica gel (5.90 g) in MeOH (58 mL) was stirred at room temperature for 5 days. The mixture was diluted with AcOEt, filtered through silica gel, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:30) gave **14** (314 mg, 67%) as a colorless oil. ^{1}H NMR δ: 0.00–0.10 (12H, m), 0.86 (4.5H, s), 0.87 (4.5H, s), 0.88 (4.5H, s), 0.89 (4.5H, s), 1.57–1.82 (2H, m), 2.24–2.47 (0.5H, m), 2.69–2.74 (1.5H, m), 3.47 (0.75H,

s), 3.48 (0.75H, s), 4.07–4.35 (2H, m), 5.02 (0.25H, s), 5.05 (1H, br d, $J=10.2$ Hz), 5.14 (0.5H, br d, $J=17.4$ Hz), 5.16 (0.5H, br d, $J=15.9$ Hz), 5.72–5.87 (1H, m).

Methyl (2*Z*,5*RS*,7*S*)-5,7-bis(*tert*-butyldimethylsilyl)oxy-3-(trifluoromethanesulfonyl)oxy-2,8-nonadienoate (16) and methyl (2*E*,5*RS*,7*S*)-5,7-bis(*tert*-butyldimethylsilyl)oxy-3-(trifluoromethanesulfonyl)oxy2,8-nonadienoate (*E*-isomer). A mixture of **14** (393 mg, 0.885 mmol) and NaH (60%, 41 mg, 1.03 mmol) in THF (4.7 mL) was stirred at −5 °C for 1 h. To the stirred mixture was added 2-Py-N-Tf_2 (333 mg, 1.05 mmol) and the mixture was stirred at rt for 19.5 h. The reaction mixture was quenched at 0 °C with H_2O (1 mL), diluted with Et_2O (80 mL), washed with H_2O, 10% citric acid, 10% NaOH and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:50) gave **16** (321 mg, 63%) as a colorless oil, *E*-isomer (28 mg, 6%) as a colorless oil and the recovered **14** (72 mg, 18%).

16. ^{1}H NMR δ: 0.01–0.07 (12H, m), 0.86 (9H, s), 0.89 (9H, s), 1.62–1.88 (2H, m), 2.47 (0.5H, d, d, $J=8.1$, 15.3 Hz), 2.53 (0.5H, d, d, $J=5.3$, 15.3 Hz), 2.63 (0.5H, d, d, $J=5.1$, 15.3 Hz), 2.75 (0.5H, d, d, $J=4.2$, 15.3 Hz), 3.75 (0.5H, s), 3.76 (0.5H, s), 4.06 (1H, m $J=3.3$ Hz), 4.15 (0.5H, q, $J=6.3$ Hz), 4.27 (0.5H, q, $J=4.8$ Hz), 5.09 (1H, br d, $J=10.5$ Hz), 5.14 (0.5H, br d, $J=16.8$ Hz), 5.17 (0.5H, br d, $J=16.8$ Hz), 5.70–5.84 (1H, m), 5.81 (1H, s).

***E*-Isomer.** ^{1}H NMR δ: 0.01–0.07 (12H, m), 0.85 (9H, s), 0.87 (4.5H, s), 0.89 (4.5H, s), 1.62–1.89 (2H, m), 2.96 (0.5H, d, d, $J=5.4$, 14.4 Hz), 3.09 (0.5H, d, d, $J=5.4$, 14.4 Hz), 3.26 (0.5H, d, d, $J=6.0$, 14.4 Hz), 3.28 (0.5H, d, d, $J=6.0$, 14.4 Hz), 3.74 (1.5H, s), 3.75 (1.5H, s), 5.07 (1H, br d, $J=10.2$ Hz), 5.78 (1H, d, d, d, $J=5.4$, 10.2, 16.8 Hz), 5.98 (0.5H, s), 5.99 (0.5H, s).

Methyl (*Z*,3*S*,5*RS*)-[3,5-bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]acetate (17). A mixture of **16** (356 mg, 0.617 mmol), Ag_2O (158 mg, 0.676 mmol), and Pd(tpp)$_4$ (72 mg, 0.063 mmol) in THF (35 mL) was stirred at 60 °C for 24 h. The mixture was filtered through silica gel, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:50) gave **17** (207 mg, 78%) as a colorless oil, which was used without further purification. The analytically pure sample was obtained by preparative TLC.

5*R*-17. IR (neat) 1729, 1643, 1255, 1079 cm^{-1}. ^{1}H NMR δ: 0.06 (6H, s), 0.09 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 0.94 (9H, s), 1.57 (1H, q, $J=11.7$ Hz), 2.15–2.27 (2H, m), 2.38–2.50 (1H, m), 3.63 (3H, s), 3.64–3.80 (1H, m), 4.06–4.12 (1H, m), 4.96 (1H, t, $J=2.1$ Hz), 5.25 (1H, t, $J=2.1$ Hz), 5.67 (1H, d, $J=2.1$ Hz). MS (*m*/*z*) 426 (M^+), 411, 369 (100%).

5*S*-17. IR (neat) 1722, 1641, 1253, 1077 cm^{-1}. ^{1}H NMR δ: 0.05 (6H, s), 0.09 (6H, s), 0.89 (9H, s), 0.90 (9H, s), 1.76 (1H, d, d, d, $J=3.0$, 9.0, 12.1 Hz), 1.93 (1H, d, t, $J=5.1$, 12.1 Hz), 2.26 (1H, d, d, $J=5.6$, 13.1 Hz), 2.34 (1H, br d, $J=13.1$ Hz), 3.63 (3H, s), 4.24 (1H, m), 4.53 (1H, d, d, $J=4.2$, 8.7 Hz), 4.98 (1H, t, $J=1.0$ Hz), 5.18 (1H, t, $J=1.0$ Hz), 5.63 (1H, br s). MS (*m*/*z*) 426 (M^+), 411, 369 (100%).

(*Z*,3*S*,5*S*)-2-[3,5-Bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]ethanol (18) and (*Z*,3*S*,5*R*)-2-[3,5-bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene] ethanol (19). To a stirred solution of DIBAL (1.0 M solution in toluene, 1.3 mL, 1.3 mmol) at −78 °C was added a solution of **17** (206 mg, 0.483 mmol) in CH_2Cl_2 (4.4 mL) dropwise. The resulting mixture was stirred at −78 °C for 30 min, quenched with 10% NaOH at −78 °C, and filtered through Celite. The filtrate was diluted with CH_2Cl_2, washed with 10% citric acid, dried, evaporated, and chromatographed on silica gel. Elution with CH_2Cl_2 gave **18** (77 mg, 40%) as a colorless oil and **19** (77 mg, 40%) as a colorless solid.

18. IR (neat) 3353, 1512, 1467, 1254, 1080 cm^{-1}. ^{1}H NMR δ: 0.06 (6H, s), 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 0.93 (9H, s), 1.56 (1H, q, $J=11.7$ Hz), 2.15–2.21 (2H, m), 2.42 (1H, d, d, d, $J=2.4$, 5.1, 12.9 Hz), 3.73 (1H, t, t, $J=2.1$, 11.1 Hz), 4.14 (1H, br d, $J=12.6$ Hz), 4.28 (1H, d, d, $J=8.4$, 12.6 Hz), 4.76 (1H, t, $J=2.4$ Hz), 5.33 (1H, t, $J=2.4$ Hz), 5.55 (1H, d, d, d, $J=1.8$, 5.1, 7.5 Hz). ^{13}C NMR δ: −4.9, −4.6, 18.2, 18.5, 25.9, 46.4, 46.5, 60.0, 68.3, 70.1, 109.9, 126.9, 138.4, 147.4. MS (*m*/*z*) 398 (M^+), 380, 341, 73 (100%). HRMS calcd for $C_{21}H_{42}O_3Si_2$ 398.2672, found 398.2647.

(*Z*,3*S*,5*S*)-2-[3,5-Bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]-1-chloroethane (20). A mixture of *N*-chlorosuccinimide (NCS, 181 mg, 1.36 mmol) and dimethyl sulfide (DMS, 100 μL, 1.36 mmol) in CH_2Cl_2 (4.4 mL) was stirred at 0 °C for 40 min. This solution (1.2 mL) was then added dropwise to a stirred solution of **18** (74 mg, 0.186 mmol) in CH_2Cl_2 (0.6 mL) at −20 °C. After being stirred at −20 °C for 45 min and at rt for 30 min, the reaction mixture was diluted with hexane, washed with H_2O and saturated NaCl, dried, and evaporated to give **20** (70.6 mg, 91%) as a pale yellow oil, which was used without further purification. IR (neat) 1467, 1377, 1255, 1078 cm^{-1}. ^{1}H NMR δ: 0.07 (6H, s), 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 0.93 (9H, s), 1.56 (1H, q, $J=11.4$ Hz), 2.18 (2H, m), 2.43 (1H, d, d, d, $J=2.1$, 4.8, 12.9 Hz), 3.71 (1H, t, t, $J=4.5$, 11.1 Hz), 3.94 (1H, d, d,t, $J=2.1$, 4.5, 11.7 Hz), 4.10 (1H, d, d, $J=1.5$, 11.1 Hz), 4.18 (1H, d, d, $J=8.1$, 11.1 Hz), 4.96 (1H, t, $J=2.1$ Hz), 5.39 (1H, t, $J=2.1$ Hz), 5.57 (1H, d, t, $J=2.1$, 8.1 Hz). ^{13}C NMR δ: −4.8, −4.6, 18.2, 18.5, 25.9, 41.5, 46.4, 46.5, 68.1, 70.0, 110.1, 123.2, 141.1, 146.9. MS (*m*/*z*) 416 (M^+), 401, 381, 73 (100%), 57. HRMS calcd for $C_{20}H_{38}O_2Si_2$ (M^+-CH_3) 401.2099, found 401.2065.

(*Z*,3*S*,5*S*)-2-[3,5-Bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]ethyl]diphenylphosphine oxide (21). To a stirred solution of $HPPh_2$ (136 mg, 0.728 mmol) in THF (2.4 mL) at 0 °C was added *n*-BuLi (1.58 M solution in hexane, 460 μL, 0.727 mmol) and the stirring was continued for 10 min. The mixture was cooled to −50 °C and a solution of **20** (67.5 mg, 0.162 mmol) in THF (1 mL) was added. The resulting mixture was stirred at

−50 °C for 10 min, and quenched with H_2O. $CHCl_3$ (15 mL) and 5% H_2O_2 (5.4 mL) were added at rt and the mixture was stirred for 1.5 h. The reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and H_2O, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:2) gave **21** (68.0 mg, 72%) as a colorless oil. IR (neat) 1437, 1253, 1120, 1073 cm^{-1}. ^1H NMR δ: 0.03 (6H, s), 0.04 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 0.92 (9H, s), 1.45 (1H, q, J = 11.5 Hz), 2.05–2.15 (2H, m), 2.37 (1H, d, d, d, J = 2.0, 4.5, 12.0 Hz), 3.15 (1H, d, d, d, d, J = 2.5, 5.5, 15.0, 18.0 Hz), 3.32 (1H, br d, t, J = 10.0, 15.0 Hz), 3.40 (1H, t, t, J = 4.0, 11.5 Hz), 3.53 (1H, d, d, t, J = 2.0, 5.0, 9.0 Hz), 4.76 (1H, t, J = 2.5 Hz), 5.28 (1H, t, J = 2.5 Hz), 5.49 (1H, d, d, t, J = 2.0, 5.0, 7.5 Hz), 7.42–7.76 (6H, m). ^{13}C NMR δ: −4.8, −4.7, −4.6, −4.5, 25.8, 25.9, 31.1, 32.2, 46.6, 46.8, 68.3, 69.2, 109.7, 115.7. MS (m/z) 582 (M^+), 525 (100%). HRMS calcd for $C_{33}H_{51}O_3PSi_2$ 582.3115, found 582.3088. $[\alpha]_D^{22}$ −38.0° (c 1.02, $CHCl_3$).

Ethyl (5*R*)-5-(*tert*-butyldimethylsilyl)oxy-2,6-heptadienoate (22). To a stirred mixture of NaH (60%, 3.26 g, 82 mmol) in THF (185 mL) at 0 °C was added dropwise $(EtO)_2P(O)CH_2COOEt$ (13.5 mL, 68 mmol) and the resulting mixture was stirred at rt for 1 h. To the cooled (−78 °C) mixture was added **12b** (7.8 g) in THF (50 mL) dropwise. The resulting mixture was stirred at −78 °C for 30 min, quenched with saturated NH_4Cl at −78 °C, extracted with AcOEt, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:4) gave **22** (10.1 g, 86% from **11b**) as a colorless oil. IR (neat) 1722, 1259, 1083 cm^{-1}. ^1H NMR δ: 0.02 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.27 (3H, t, J = 7.2 Hz), 2.38 (2H, t, J = 7.5 Hz), 4.17 (2H, q, J = 7.2 Hz), 4.21 (1H, m), 5.07 (1H, d, J = 10.5 Hz), 5.19 (1H, d, J = 12.9 Hz), 5.80 (1H, d, d, d, J = 6.0, 10.5, 16.5 Hz), 5.83 (1H, d, J = 16.2 Hz), 6.34 (0.003H, d, t, J = 7.2, 14.4 Hz), 6.92 (0.997H, d, t, J = 7.5, 15.0 Hz). ^{13}C NMR δ: −4.9, −4.4, 14.3, 18.3, 25.9, 41.2, 60.2, 72.7, 114.6, 123.6, 140.6, 145.4. MS (m/z) 269 (M^+-CH_3), 227 (100%). HRMS calcd for $C_{14}H_{25}O_3Si$ (M^+-CH_3) 269.1573, found 269.1558. $[\alpha]_D^{20}$ −6.3° (c 0.82, $CHCl_3$).

(5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-2,6-heptadien-1-ol (23). To a stirred solution of **22** (10.1 g, 35 mmol) in CH_2Cl_2 (296 mL) at −78 °C was added dropwise DIBAL (1 M solution in toluene, 96 mL, 96 mmol). The resulting mixture was stirred at −78 °C for 1 h, quenched with 10% NaOH (4.6 mL), filtered through Celite, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave **23** (7.4 g, 87%) as a colorless oil. IR (neat) 3352, 1253, 1082, 1031 cm^{-1}. ^1H NMR δ: 0.03 (3H, s), 0.04 (3H, s), 0.89 (9H, s), 2.21–2.28 (2H, m), 4.10 (2H, br s), 4.15 (1H, t, J = 6.0 Hz), 5.04 (1H, d, t, J = 5.7, 10.5 Hz), 5.16 (1H, d, t, J = 1.8, 17.1 Hz), 5.64 (2H, m), 5.81 (1H, d, d, d, J = 5.7, 10.5, 17.4 Hz). ^{13}C NMR δ: −4.3, 16.6, 25.0, 41.2, 63.9, 73.5, 114.0, 129.2, 131.6, 141.1. MS (m/z) 241 ($M^+-C_4H_9$), 171 (100%). HRMS calcd for $C_9H_{17}O_2Si$ (M^+) 185.0998, found 185.1000. $[\alpha]_D^{24}$ −10.8° (c 1.01, $CHCl_3$).

(2*R*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-2,3-epoxy-6-hepten-1-ol (24). To a stirred solution of D-DIPT (645 mg, 3 mmol) and molecular sieves (4 Å, 1 g) in CH_2Cl_2 (150 mL) at −30 °C was added $Ti(O^iPr)_4$ (632 mL, 2 mmol) and the resulting mixture was stirred at −30 °C for 30 min. A solution of **23** (7.4 g, 31 mmol) in CH_2Cl_2 (25 mL) and *tert*-BuOOH (2.97 M solution in CH_2Cl_2, 20.5 mL, 61 mmol) were added at −30 °C and the mixture was stirred at −15 °C for 30 h. To the stirred mixture were added saturated Na_2SO_4 and Et_2O. The resulting mixture was stirred at rt for 2 h, filtered through Celite, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:4) gave **24** (8.0 g, 100%) as a colorless oil. IR (neat) 3434, 1468, 1254, 1077 cm^{-1}. ^1H NMR δ: −0.05 (3H, s), −0.02 (3H, s), 1.50–1.70 (2H, m), 2.84 (1H, d, t, J = 2.1, 4.5 Hz), 3.82 (1H, d, d, d, J = 2.7, 6.0, 12.6 Hz), 4.96 (1H, d, t, J = 1.5, 10.5 Hz), 5.11 (1H, d, t, J = 1.5, 17.1 Hz), 5.73 (1H, d, d, d, J = 5.7, 10.5, 17.4 Hz). ^{13}C NMR δ: −4.9, −4.4, 18.2, 25.7, 40.5, 59.2, 61.8, 71.3, 114.1, 127.0, 141.1. MS (m/z) 201 ($M^+-C_4H_9$), 146 (100%). HRMS calcd for $C_9H_{17}O_3Si$ ($M^+-C_4H_9$) 201.0945, found 201.0957. $[\alpha]_D^{25}$ +15.4° (c 1.00, $CHCl_3$).

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-6-hepten-1,3-diol (25). To a stirred solution of **24** (1.4 g, 5.42 mmol) in toluene (28 mL) at −30 °C was added dropwise Red-Al (65% solution in toluene, 3.25 mL, 10.83 mmol). The resulting mixture was stirred at −30 °C for 21 h, quenched with saturated Na_2SO_4, filtered through Celite, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:4) gave **25** (0.99 g, 70%) as a colorless oil. IR (neat) 3365, 1467, 1254, 1072 cm^{-1}. ^1H NMR δ: 0.07 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.52–1.78 (3H, m), 1.85 (1H, d, d, J = 4.5, 10.8 Hz), 2.85 (1H, t, J = 5.0 Hz), 3.82 (1H, d, t, J = 5.1, 6.0 Hz), 3.93 (1H, s), 4.19 (1H, m), 4.57 (1H, m), 5.10 (1H, d, t, J = 1.5, 10.5 Hz), 5.26 (1H, d, t, J = 1.5, 17.4 Hz), 5.87 (1H, d, d, d, J = 4.8, 10.5, 17.1 Hz). ^{13}C NMR δ: −4.6, −3.7, 25.9, 38.8, 44.4, 61.5, 71.4, 75.2, 114.8, 14.1.3. MS (m/z) 229 [$M^+-(H+2CH_3)$], 81 (100%). HRMS calcd for $C_{13}H_{29}O_3Si$ (M^+ + 1) 261.1886, found 261.1933. $[\alpha]_D^{25}$ +1.7° (c 1.03, $CHCl_3$).

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-1-pivaloyloxy-6-hepten-3-ol (26). To a stirred solution of **25** (2.7 g, 10.2 mmol) and pyridine (2.1 mL, 10.2 mmol) in CH_2Cl_2 (130 mL) at 0 °C was added pivaloyl chloride (PivCl, 1.9 mL, 15.3 mmol). The resulting mixture was stirred at rt for 3.5 h, quenched with H_2O, extracted with CH_2Cl_2, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:20) gave **26** (3.3 g, 95%) as a colorless oil. IR (neat) 1722, 1471, 1288, 1254, 1163, 1080 cm^{-1}. ^1H NMR δ: 0.06 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 1.18 (9H, s), 1.59 (1H, d, d, d, J = 2.1, 5.1, 14.1 Hz), 1.67–1.77 (3H, m), 3.94–4.02 (1H, m), 5.12 (1H, d, t, J = 1.5, 10.8 Hz), 5.24 (1H, d, t, J = 1.5, 17.4 Hz), 5.84 (1H, d, d, d, J = 5.4, 10.8, 17.4 Hz). ^{13}C NMR δ: −5.1, −4.5, 18.2 25.9, 27.3, 36.8, 38.8, 43.3, 61.3, 65.1, 72.4, 114.6, 140.2, 178.9. MS (m/z) 287 ($M^+-C_4H_9$), 171, 131, 93 (100%). HRMS calcd for $C_{14}H_{28}O_4Si$ (M^+−C4H9) 287.1678, found 287.1693. $[\alpha]_D^{24}$ −12.8° (c 0.98, $CHCl_3$).

(3*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyl)oxy-6-hepten-1-ol (27). To a stirred solution of **26** (668 mg, 1.94 mmol) in

CH_2Cl_2 (6 mL) at 0 °C were added 2,6-lutidine (0.29 mL, 2.52 mmol) and TBSOTf (0.53 mL, 2.32 mmol). The resulting mixture was stirred at 0 °C for 30 min, quenched with MeOH, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:20) gave the TBS ether of **26** as a colorless oil (860 mg, 97%). IR (neat) 1732, 1157, 1090 cm^{-1}. ^1H NMR δ: 0.03 (3H, s), 0.04 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.88 (18H, s), 1.19 (9H, s), 1.54–1.92 (3H, m), 3.87 (1H, q, $J=6.6$ Hz), 4.04–4.25 (3H, m), 5.04 (1H, d, t, $J=0.9$, 10.2 Hz), 5.11 (1H, d, $J=17.4$ Hz), 5.78 (1H, d, d, d, $J=7.2$, 10.2, 17.4 Hz). ^{13}C NMR δ: −4.5, −4.3, −4.1, 18.1, 25.9, 26.0, 27.3, 36.7, 38.8, 46.8, 61.2, 66.6, 72.0, 114.5, 141.8, 178.6. MS (*m*/*z*) 401 ($M^+-C_4H_9$), 245, 159, 93 (100%). HRMS calcd for $C_{20}H_{41}O_4Si_2$ ($M^+-C_4H_9$) 401.2543, found 401.2517. $[\alpha]_D^{24}$ −30.2° (*c* 1.59, $CHCl_3$). To a stirred solution of the above-mentioned TBS ether of **26** (831 mg, 1.81 mmol) in MeOH (8 mL) at room temperature was added 10 N NaOH (2.4 mL). The stirring was continued for 11 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl, diluted with AcOEt, washed with saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:20) gave **27** (543 mg, 80%) as a colorless oil and the *syn*-alcohol (54 mg, 8%). **27**: IR (neat) 3420, 1470, 1255, 1090, 1035 cm^{-1}. ^1H NMR δ: 0.03 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.09 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 1.65–1.78 (2H, m), 1.78–1.96 (2H, m), 3.66–3.78 (1H, m), 3.79–3.90 (1H, m), 3.92–4.02 (1H, m), 4.10 (1H, q, $J=6.9$ Hz), 5.05 (1H, br d, $J=10.5$ Hz), 5.12 (1H, br d, $J=17.1$ Hz), 5.77 (1H, d, d, d, $J=6.9$, 10.5, 17.1 Hz). ^{13}C NMR δ: −4.5, −4.4, −4.2, −3.9, 18.3, 25.9, 26.0, 38.4, 45.7, 60.3, 69.5, 72.0, 114.6, 141.5. MS (*m*/*z*) 373 (M^+-1), 73 (100%). HRMS calcd for $C_{19}H_{41}O_3Si_2$ (M^+-1) 373.2594, found 373.2627. $[\alpha]_D^{27}$ −14.2° (*c* 0.60, $CHCl_3$).

Methyl (5*S*,7*R*)-bis(*tert*-butyldimethylsilyl)oxy-3-hydroxy-8-nonenoate (29). To a stirred solution of $(COCl)_2$ (0.23 mL, 2.62 mmol) in CH_2Cl_2 (3.6 mL) at −78 °C was added DMSO (0.37 mL, 5.24 mmol). The resulting mixture was stirred at the same temperature for 30 min and a solution of **27** (491 mg, 1.31 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added. After being stirred at the same temperature for 20 min, Et_3N (1.46 mL, 10.48 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with hexane, filtered through Celite, and evaporated to give crude **28** (1.97 g) as a colorless oil, which was used without further purification. To a stirred solution of diisopropylamine (3.7 mL, 26.7 mmol) in THF (55 mL) at −78 °C was added *n*-BuLi (1.53 M in hexane, 17.5 mL, 26.7 mmol). The mixture was stirred at −25 °C for 20 min and then re-cooled to −78 °C. MeCOOMe (2.1 mL, 26.7 mmol) was added at −78 °C and the stirring was continued at the same temperature for 1 h. A solution of **28** (1.97 g) in THF (10 mL) was added dropwise at −78 °C and the mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with saturated NH_4Cl, diluted with Et_2O, dried, evaporated and chromatographed on silica gel. Elution with AcOEt:hexane (1:20) gave **29** (1.50 g, 63% for 2 steps) as a pale yellow oil. IR (neat) 3511, 1736, 1645, 1431, 1169, 1088 cm^{-1}. ^1H NMR δ: 0.00 (3H, s), 0.03 (3H, s), 0.05 (3H, s), 0.06 (3H, s), 0.85 (18H, s), 1.52–1.90 (4H, m), 2.35–2.51 (2H, m), 3.66 (3H, s), 3.96–4.19 (2H, m), 4.30 (1H, t, t, $J=2.7$, 9.9 Hz), 5.02 (1H, d, d, $J=1.5$, 10.2 Hz), 5.09 (1H, d, d, $J=1.5$, 15.6 Hz), 5.74 (1H, d, d, d, $J=6.9$, 10.2, 15.6 Hz). ^{13}C NMR δ: −4.6, −4.4, −4.3, −4.0, 17.9, 18.2, 25.8, 25.9, 42.0, 45.2, 51.6, 65.1, 68.3, 71.8, 114.6, 141.3, 172.5. MS (*m*/*z*) 431 (M^+-CH_3), 389, 317, 243, 203, 171 (100%). HRMS calcd for $C_{21}H_{43}O_5Si_2$ (M^+-CH_3) 431.2649 found 431.2596. $[\alpha]_D^{24}$ −13.9° (*c* 0.82, $CHCl_3$).

Methyl (5*S*,7*R*)-bis(*tert*-butyldimethylsilyl)oxy-3-oxo-8-nonenoate (30). To a stirred solution of **29** (1.50 g, 3.4 mmol) in CH_2Cl_2 (160 mL) at room temperature was added Dess–Martin reagent (8.20 g, 19.4 mmol). The mixture was stirred at room temperature for 15 h, diluted with hexane, and filtered through Celite. The filtrate was diluted with Et_2O, washed with saturated NaCl, dried, evaporated and chromatographed on silica gel. Elution with AcOEt:hexane (1:20) gave **30** (1.00 g, 69%) as a colorless oil. IR (neat) 1751, 1651, 1250, 1084 cm^{-1}. ^1H NMR δ: 0.01 (3H, s), 0.03 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.85 (9H, s), 0.88 (9H, s), 1.58–1.81 (2H, m), 2.69 (2H, d, $J=6.0$ Hz), 3.47 (2H, d, $J=1.8$ Hz), 3.72 (3H, s), 4.06–4.19 (1H, m), 4.24 (1H, q, $J=6.0$ Hz), 5.05 (1H, d, $J=10.8$ Hz), 5.13 (1H, d, $J=17.4$ Hz), 5.77 (1H, d, d, d, $J=6.6$, 10.8, 17.4 Hz). ^{13}C NMR δ: −4.6, −4.5, −4.3, −3.9, 18.0, 18.2, 25.9, 26.0, 46.3, 50.6, 50.9, 66.8, 71.8, 91.1, 114.7, 141.5, 167.5, 175.9. MS (*m*/*z*) 413 (M^+-OCH_3), 387, 243, 201, 171 (100%). HRMS calcd for $C_{21}H_{41}O_4Si_2$ (M^+-OCH_3) 413.2543, found 413.2559. $[\alpha]_D^{24}$ −18.0° (*c* 1.02, $CHCl_3$).

Methyl (*Z*,5*S*,7*R*)-bis(*tert*-butyldimethylsilyl)oxy-3-(trifluoromethanesulfonyl)oxy-2,8-nonadienoate (31). To a stirred solution of **30** (500 mg, 1.1 mmol) in THF (6 mL) at −5 °C was added NaH (60% oil dispersion, 90 mg, 2.2 mmol) and stirring was continued at the same temperature for 1 h. 2-Py-N-Tf_2 (725 mg, 2.0 mmol) was added at −5 °C and the mixture was stirred at room temperature for 7.5 h. The reaction mixture was quenched with H_2O, extracted with Et_2O, washed with 10% citric acid and saturated NaCl, dried, evaporated and chromatographed on silica gel. Elution with Et_2O:hexane (1:50) gave **31** (492 mg, 85%) as a colorless oil. IR (neat) 1736, 1429, 1211, 1136 cm^{-1}. ^1H NMR δ: 0.02 (3H, s), 0.03 (3H, s), 0.05 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 0.88 (9H, s), 1.73 (2H, t, $J=6.0$ Hz), 2.44 (1H, d, d, $J=7.8$, 15.3 Hz), 2.63 (1H, d, d, $J=4.8$, 15.3 Hz), 3.76 (3H, s), 4.01–4.11 (1H, m), 4.54 (1H, q, $J=6.3$ Hz), 5.08 (1H, d, d, $J=0.9$, 10.2 Hz), 5.14 (1H, d, d, $J=0.9$, 17.6 Hz), 5.77 (1H, d, d, d, $J=7.2$, 10.2, 17.6 Hz), 5.82 (1H, s). ^{13}C NMR δ: −4.6, −4.2, −3.8, 18.0, 18.2, 25.8, 25.9, 43.4, 46.4, 52.0, 66.3, 71.5, 113.8, 115.2, 141.3, 156.1, 162.7, 175.9. MS (*m*/*z*) 519 ($M^+-C_4H_9$), 465 (100%). HRMS calcd for $C_{19}H_{34}O_7F_3SSi_2$ ($M^+-C_4H_9$) 519.1516, found 519.1511. $[\alpha]_D^{24}$ +6.5° (*c* 1.02, $CHCl_3$).

(*Z*,5*S*,7*R*)-Bis(*tert*-butyldimethylsilyl)oxy-3-(trifluoromethanesulfonyl)oxy-2,8-nonadien-1-ol (32). To a stirred solution of **31** (45 mg, 0.077 mmol) in CH_2Cl_2 (0.7 mL) at −78 °C was added dropwise DIBAL (1.0 M solution

in toluene, 163 mL, 0.16 mmol). The resulting mixture was stirred at −78 °C for 30 min, quenched with 10 N NaOH, extracted with CH_2Cl_2, and filtered through Celite. The filtrate was washed with 10% citric acid and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with Et_2O:hexane (1:5) gave **32** (41 mg, 98%) as a colorless oil. IR (neat) 3373, 1414, 1217, 1140 cm^{-1}. ^1H NMR δ: 0.02 (3H, s), 0.03 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 0.88 (9H, s), 1.66 (1H, d, t, J = 6.0, 14.1 Hz), 1.75 (1H, d, t, J = 6.3, 13.8 Hz), 2.44 (1H, d, d, J = 7.5, 15.0 Hz), 2.57 (1H, d, d, J = 4.8, 15.0 Hz), 4.00 (1H, quint, J = 6.0 Hz), 4.15 (1H, q, J = 6.6 Hz), 4.22 (1H, d, d, J = 6.9, 13.8 Hz), 4.28 (1H, d, d, J = 7.2, 13.5 Hz), 5.08 (1H, d, J = 10.2 Hz), 5.14 (1H, d, J = 17.4 Hz), 5.61 (1H, t, J = 6.9 Hz), 5.78 (1H, d, d, d, J = 7.2, 10.2, 17.4 Hz). ^{13}C NMR δ: −4.6, −4.5, −4.2, −3.7, 18.2, 25.8, 25.9, 42.5, 46.3, 56.9, 66.3, 71.6, 115.0, 123.1, 141.5, 146.8. MS (m/z) 491 ($M^+-C_4H_9$), 437, 341, 209, 171, 75, 73 (100%). HRMS calcd for $C_{18}H_{34}O_6F_3SSi_2$ ($M^+-C_4H_9$) 491.1567, found 491.1551. $[\alpha]_D^{24}$ +3.9° (c 1.29, $CHCl_3$).

(*Z*,3*R*,5*S*)-[3,5-Bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]ethanol (33). A mixture of **32** (267 mg, 0.486 mmol), Ph_3P (28 mg, 0.107 mmol), Et_3N (136 mL, 0.972 mmol), and $Pd(OAc)_2$ (22 mg, 0.097 mmol) in DMF (10 mL) was stirred at room temperature for 24.5 h. The reaction mixture was extracted with Et_2O, washed with saturated NaCl, dried, evaporated and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave **33** (99.8 mg, 52%) as a colorless oil. IR (neat) 1464, 1254, 1092 cm^{-1}. ^1H NMR δ: 0.05 (6H, s), 0.06 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.43 (1H, br s), 1.74–1.88 (2H, m), 2.18 (1H, d, d, J = 6.6, 12.9 Hz), 2.40 (1H, d, d, J = 6.0, 12.9 Hz), 4.14–4.21 (3H, m), 4.39 (1H, t, J = 5.7 Hz), 4.75 (1H, t, J = 1.2 Hz), 5.16 (1H, br t, J = 1.5 Hz), 5.32 (1H, t, J = 6.9 Hz). ^{13}C NMR δ: −5.0, −4.8, −4.7, 18.2, 18.3, 25.9, 44.7, 45.4, 59.8, 67.4, 71.4, 110.7, 126.7, 139.5, 147.8. MS (m/z) 367 (M^+-CH_2OH), 341, 249, 73 (100%). HRMS calcd for $C_{20}H_{39}O_2Si_2$ (M^+-CH_2OH) 367.2488, found 367.2485. $[\alpha]_D^{24}$ −21.2° (c 0.77, $CHCl_3$).

(*Z*,3*R*,5*S*)-2-[3,5-Bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]-1-chloroethane (34). A mixture of NCS (75 mg, 0.564 mmol) and DMS (43 μL, 0.564 mmol) in CH_2Cl_2 (4.4 mL) was stirred at 0 °C for 40 min. This solution (1.83 mL) was then added dropwise to a stirred solution of **33** (112 mg, 0.282 mmol) in CH_2Cl_2 (0.9 mL) at −20 °C. After being stirred at room temperature for 1 h, the reaction mixture was diluted with hexane, washed with H_2O and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave practically pure **34** (97 mg, 83%) as a pale yellow oil, which was used without further purification.

(*Z*,3*R*,5*S*)-2-[3,5-Bis(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]ethyl]diphenylphosphine oxide (35). To a stirred solution of $HPPh_2$ (195 μL, 1.05 mmol) in THF (3.8 mL) at 0 °C was added *n*-BuLi (1.53 M in hexane, 684 μL, 1.05 mmol) and the stirring was continued for 10 min. The mixture was cooled to −50 °C and a solution of **34** (97 mg, 0.23 mmol) in THF (1.2 mL) was added. The resulting mixture was stirred at −50 °C for 1 h, and quenched with H_2O. $CHCl_3$ (10.6 mL) and 5% H_2O_2 (7.8 mL) were added at room temperature and the mixture was stirred for 30 min. The reaction mixture was diluted with $CHCl_3$, washed with saturated $Na_2S_2O_3$ and H_2O, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:2) gave **35** (117 mg, 86%) as a colorless oil. IR (neat) 1467, 1253, 1083 cm^{-1}. ^1H NMR δ: −0.04 (3H, s), 0.00 (3H, s), 0.02 (3H, s), 0.04 (3H, s), 0.81 (9H, s), 0.88 (9H, s), 1.65–1.75 (1H, m), 1.81–1.91 (1H, m), 2.16 (1H, br d, J = 14.7 Hz), 2.33 (1H, br d, J = 13.2 Hz), 3.15 (1H, d, t, J = 6.6, 15.9 Hz), 3.38 (1H, d, t, J = 8.7, 14.7 Hz), 4.11 (1H, br t, J = 4.2 Hz), 4.35 (1H, br q, J = 4.2 Hz), 4.73 (1H, s), 5.15 (1H, s), 5.33 (1H, q, J = 6.6 Hz), 7.41–7.54 (6H, m), 7.66–7.76 (1H, m). ^{13}C NMR δ: −4.9, −4.7, −4.6, 18.2, 18.3, 25.9, 31.0, 31.9, 44.9, 45.6, 67.5, 70.9, 110.3, 115.1, 115.2, 128.5, 128.7, 131.1, 131.2, 131.8, 132.5, 133.5, 141.0, 141.1, 147.8. MS (m/z) 582 (M^+), 525, 393, 275, 132, 75 (100%). HRMS calcd for $C_{33}H_{51}O_3PSi_2$ 582.3115, found 582.3098. $[\alpha]_D^{24}$ +2.9° (c 1.43, $CHCl_3$).

(1*R*,3a*R*,4*S*,7a*R*)-4-Hydroxy-1-[(*S*)-1-(3-methyl-3-trimethylsilyloxybutyloxy)ethyl] - 7a - methyloctahydro - 1H - indene (36). To a stirred solution of OCT (**2**) (100 mg, 0.239 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C were added Et_3N (266 μL, 1.91 mmol) and TMSOTf (173 μL, 0.96 mmol). The resulting mixture was stirred at 0 °C for 1.5 h, quenched with H_2O, extracted with Et_2O, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave the triTMS ether of OCT (**2**) (186 mg, 75%) as a colorless oil. IR (neat) 1251, 1075 cm^{-1}. ^1H NMR δ: 0.10 (9H, s), 0.12 (18H, s), 0.53 (3H, s), 1.15 (3H, d, J = 6.0 Hz), 1.23 (6H, s), 1.20–2.10 (15H, m), 2.23 (1H, d, d, J = 7.8, 13.8 Hz), 2.46 (1H, d, d, J = 3.8, 13.8 Hz), 2.84 (1H, br d, J = 12.3 Hz), 3.20 (1H, br quint, J = 6.0 Hz), 3.32 (1H, d, t, J = 6.2, 8.7 Hz), 3.65 (1H, d, t, J = 6.6, 8.7 Hz), 4.18 (1H, m), 4.37 (1H, d, d, J = 3.9, 6.6 Hz), 4.90 (1H, d, J = 2.4 Hz), 5.20 (1H, d, J = 1.2 Hz), 6.05 (1H, d, J = 11.1 Hz), 6.27 (1H, d, J = 11.1 Hz). ^{13}C NMR δ: 0.25, 0.3, 2.7, 12.6, 19.4, 22.2, 23.4, 25.8, 30.0, 30.5, 39.8, 44.6, 44.7, 44.9, 45.9, 56.3, 57.5, 65.0, 67.3, 71.7, 73.1, 78.1, 111.6, 118.1, 123.4, 135.0, 141.0, 148.0. $[\alpha]_D^{24}$ +14.9° (c 0.37, $CHCl_3$). O_3 was bubbled into a stirred mixture of the above-mentioned triTMS ether of OCT (**2**) (185 mg, 0.292 mmol) and $NaHCO_3$ (100 mg, 1.19 mmol) in CH_2Cl_2 (4 mL) and MeOH (1 mL) at −78 °C for 30 min. The excess O_3 was removed by bubbling argon. The resulting mixture was diluted with MeOH (5 mL) and $NaBH_4$ (200 mg, 5.263 mmol) was added at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was extracted with CH_2Cl_2, washed with saturated NaCl, dried, evaporated and chromatographed on silica gel. Elution with AcOEt:hexane (1:8) gave **36** (73.4 mg, 72%) as a colorless oil. IR (neat) 3455, 1250, 1169, 1036 cm^{-1}. ^1H NMR δ: 0.09 (9H, s), 0.91 (3H, s), 1.13 (3H, d, J = 6.3 Hz), 1.22 (6H, s), 1.25–2.14 (13H, m), 3.18 (1H, d, q, J = 6.3, 8.7 Hz), 3.32 (1H, d, d, d, J = 6.6, 8.1, 9.0 Hz), 3.64 (1H, d, d, d, J = 6.3, 8.1, 9.0 Hz), 4.08 (1H, br q, J = 2.4 Hz). ^{13}C NMR δ: 2.7, 14.2, 17.4, 19.2, 22.5, 25.7, 30.5, 33.6, 39.7, 41.0, 44.6, 52.6, 57.6, 64.9, 69.3, 73.2, 77.9. $[\alpha]_D^{25}$ +38.4° (c 0.37, $CHCl_3$).

(1*R*,3a*R*,4*S*,7a*R*)-4-Hydroxy-1-[(*S*)-1-(3-methyl-3-trimethylsilyloxybutyloxy)ethyl]-7a-methyloctahydro-1H-inden-4-one (37). To a stirred mixture of **36** (20 mg, 0.056 mmol) and molecular sieves (4 Å, 24 mg) in CH_2Cl_2 (3.1 mL) at room temperature was added NMO (13 mg, 0.107 mmol). The resulting mixture was stirred at room temperature for 1 h. TPAP (1.3 mg, 0.004 mmol) was added. The resulting mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 and filtered with Celite. The filtrate was evaporated and chromatographed on silica gel. Elution with AcOEt:hexane (1:10) gave **37** (24 mg, 96%) as a colorless oil. IR (neat) 1716, 1454, 1369, 1251, 1036 cm^{-1}. ^1H NMR δ: 0.09 (9H, s), 0.62 (3H, s), 1.17 (3H, d, $J=6.0$ Hz), 1.22 (6H, s), 1.48–2.06 (11H, m), 2.15–2.33 (2H, m), 2.44 (1H, d, d, $J=7.5$, 11.4 Hz), 3.22 (1H, d, q, $J=6.0$, 7.5 Hz), 3.31 (1H, d, d, d, $J=6.6$, 8.1, 9.3 Hz), 3.65 (1H, d, d, $J=6.6$, 8.1 Hz). ^{13}C NMR δ: 2.7, 13.3, 19.1, 19.3, 23.9, 25.2, 30.45, 30.5, 38.2, 41.0, 44.5, 48.9, 57.5, 61.9, 65.2, 73.1, 211.9.

(5*Z*,7*E*,1*S*,3*S*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-(3-methyl-3-trimethylsilyloxybutyloxy)-9,10-secopregna-5,7,10(19)-triene (38). To a stirred solution of **21** (43.3 mg, 0.0745 mmol) in THF (0.7 mL) at −78 °C was added *n*-BuLi (1.58 M solution in hexane, 47 μL, 0.075 mmol). The resulting mixture was stirred at −78 °C for 8 min and a solution of **37** (13.1 mg, 0.037 mmol) in THF (2 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 6 h, quenched with saturated NH_4Cl (5 mL), extracted with CH_2Cl_2, washed with H_2O and saturated NaCl, dried, and evaporated. The residue was purified by preparative TLC developed with AcOEt:hexane (1:4) to give **38** (12.6 mg, 45%) as a colorless oil. IR (neat) 1644, 1471, 1370, 1250, 1075 cm^{-1}. ^1H NMR δ: 0.07 (6H, s), 0.08 (3H, s), 0.10 (12H, s), 0.54 (3H, s), 0.89 (9H, s), 0.94 (9H, s), 1.15 (3H, d, $J=6.3$ Hz), 1.23 (6H, s), 1.42–1.76 (12H, m), 1.84–2.04 (3H, m), 2.12–2.26 (2H, m), 2.43 (1H, br d, d, $J=2.7$, 12.3 Hz), 2.83 (1H, br d, $J=11.1$ Hz), 3.12 (1H, q, $J=6.6$ Hz), 3.21 (1H, quint, $J=6.6$ Hz), 3.65 (1H, q, $J=6.6$ Hz), 3.66–3.76 (1H, m), 3.95 (1H, br d, $J=11.1$ Hz), 4.93 (1H, t, $J=2.4$ Hz), 5.38 (1H, t, $J=2.4$ Hz), 6.01 (1H, d, $J=11.4$ Hz), 6.27 (1H, d, $J=11.4$ Hz). ^{13}C NMR δ: −5.0, −4.9, −4.6, 2.7, 12.5, 18.3, 18.6, 19.4, 22.2, 23.5, 25.7, 26.0, 29.1, 29.8, 30.5, 39.7, 44.6, 44.8, 46.6, 47.0, 56.3, 57.5, 65.0, 68.8, 70.3, 78.0, 110.0, 117.9, 123.0, 134.9, 142.0, 148.1. MS (*m*/*z*) 718 (M^+), 703, 75 (100%). HRMS calcd for $C_{41}H_{78}O_4Si_3$ 718.5208, found 718.5201.

(5*Z*,7*E*,1*R*,3*S*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-(3-methyl-3-trimethylsilyloxybutyloxy)-9,10-secopregna-5,7,10(19)-triene (39). To a stirred solution of **35** (44.3 mg, 0.076 mmol) in THF (0.7 mL) at −78 °C was added *n*-BuLi (1.53 M solution in hexane, 50 μL, 0.076 mmol). The resulting mixture was stirred at −78 °C for 15 min and a solution of **37** (14.2 mg, 0.04 mmol) in THF (0.5 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 5 h, quenched with saturated NH_4Cl, extracted with CH_2Cl_2, washed with H_2O and saturated NaCl, dried, evaporated, and chromatographed on silica gel. Elution with AcOEt:hexane (1:30) gave **39** (9.4 mg, 33%) as a colorless oil. IR (neat) 1371, 1252, 1080 cm^{-1}. ^1H NMR δ: 0.01–0.08 (12H, s), 0.10 (12H, s), 0.51 (3H, s), 0.87 (9H, s), 0.88 (9H, s), 1.16 (3H, d, $J=6.0$ Hz), 1.23 (3H, s), 1.25 (3H, s), 1.42–2.03 (15H, m), 2.21 (1H, d, d, $J=3.3$, 12.9 Hz), 2.43 (1H, d, d, $J=3.3$, 12.9 Hz), 2.81 (1H, d, d, $J=4.2$, 12.0 Hz), 3.20 (1H, quint, $J=6.0$ Hz), 3.33 (1H, d, t, $J=6.3$, 15.0 Hz), 3.65 (1H, d, t, $J=6.3$, 15.0 Hz), 4.18 (1H, d, d, t, $J=3.3$, 7.5, 15.0 Hz), 4.38 (1H, d, d, $J=3.9$, 6.6 Hz), 4.87 (1H, d, $J=2.4$ Hz), 5.18 (1H, d, $J=2.4$ Hz), 6.00 (1H, d, $J=11.1$ Hz), 6.22 (1H, d, $J=11.1$ Hz). ^{13}C NMR δ: −5.0, −4.7, −4.6, 2.7, 12.4, 18.4, 19.4, 22.2, 23.5, 29.1, 29.8, 30.5, 40.0, 44.6, 44.8, 44.9, 46.2, 56.3, 57.5, 65.0, 67.6, 72.1, 73.2, 76.7, 77.1, 77.5, 78.1, 111.1, 118.1, 123.3, 135.4, 140.6, 148.6. MS (*m*/*z*) 718 (M^+), 586, 248, 131 (100%). HRMS calcd for $C_{41}H_{78}O_4Si_3$ 718.5208, found 718.5192. $[\alpha]_D^{25}$ +12.9° (*c* 1.60, $CHCl_3$).

(5*Z*,7*E*,1*S*,3*S*,20*S*)-20-(3-Hydroxy-3-methylbutyloxy)-9,10-secopregna-5,7,10(19)-trien-1,3-diol (3). A mixture of **38** (12.6 mg, 0.017 mmol) and TBAF (1.0 M solution in THF, 70 μL, 0.070 mmol) in THF (0.3 mL) was stirred at room temperature for 18 h. The reaction mixture was quenched with H_2O (3 mL), extracted with AcOEt, washed with saturated NaCl, dried, and evaporated. The residue was purified by preparative TLC developed with AcOEt:hexane (1:15) to give **3** (7.7 mg, 100%) as a colorless oil. IR (neat) 3319, 1453, 1371, 1077 cm^{-1}. ^1H NMR δ: 0.53 (3H, s), 1.19 (3H, d, $J=6.0$ Hz), 1.24 (6H, s), 1.44–1.74 (12H, m), 1.84–2.06 (2H, m), 2.12–2.26 (2H, m), 2.25 (1H, br s), 2.44 (1H, d, d, $J=5.1$, 13.2 Hz), 2.56 (1H, br d, d, $J=2.7$, 13.2 Hz), 3.25 (1H, quint, $J=6.3$ Hz), 3.48 (1H, d, t, $J=6.0$, 9.3 Hz), 3.82 (1H, br s), 3.85 (1H, d, t, $J=5.7$, 9.3 Hz), 4.06 (1H, br q, $J=5.1$ Hz), 4.32 (1H, br q, $J=3.9$ Hz), 5.25 (1H, d, $J=1.8$ Hz), 5.55 (1H, br s), 6.28 (1H, d, $J=11.1$ Hz), 6.68 (1H, d, $J=11.1$ Hz). ^{13}C NMR δ: 12.8, 18.9, 19.4, 22.3, 23.3, 25.7, 29.0, 29.2, 29.4, 39.7, 40.7, 41.6, 44.9, 45.6, 56.2, 57.2, 65.6, 68.3, 70.6, 73.3, 78.9, 113.1, 117.5, 125.5, 132.1, 142.4, 147.2. MS (*m*/*z*) 418 (M^+), 400, 44 (100%). HRMS calcd for $C_{26}H_{42}O_4$ 418.3083, found 418.3070. $[\alpha]_D^{17}$ −33.0° (*c* 0.39, EtOH). UV λ_{max} 264 nm λ_{min} 228 nm.

(5*Z*,7*E*,1*R*,3*S*,20*S*)-20-(3-Hydroxy-3-methylbutyloxy)-9,10-secopregna-5,7,10(19)-trien-1,3-diol (4). A mixture of **39** (10.6 mg, 0.014 mmol) and TBAF (1.0 M solution in THF, 209 μL, 0.209 mmol) in toluene (0.5 mL) was stirred at 105 °C for 2 h, diluted with AcOEt, washed with H_2O and saturated NaCl, dried, and evaporated. The residue was purified by preparative TLC developed with CH_2Cl_2:EtOH (9:1) to give **4** (3.5 mg, 60%) as a colorless oil. IR (neat) 3367, 2966, 2933, 2873, 1448, 1375, 1151, 1090, 1055 cm^{-1}. ^1H NMR δ: 0.53 (3H, s), 1.19 (3H, d, $J=6.1$ Hz), 1.23 (6H, s), 2.29 (1H, d, d, $J=7.4$, 13.2 Hz), 2.61 (1H, d, d, $J=3.7$, 13.6 Hz), 2.83 (1H, d, d, $J=3.7$, 11.8 Hz), 3.25 (1H, m), 3.48 (1H, d, t, $J=5.7$, 9.6 Hz), 3.84 (1H, d, t, $J=5.7$, 9.2 Hz), 4.15–4.29 (1H, m), 4.39–4.48 (1H, m), 4.98–5.01 (1H, m), 5.30–5.33 (1H, m), 6.01 (1H, d, $J=11.4$ Hz), 6.38 (1H, d, $J=11.4$ Hz). MS (*m*/*z*) 418 (M^+), 134 (100%). $[\alpha]_D^{24}$ −13.0° (*c* 0.17, EtOH). UV λ_{max} 264 nm λ_{min} 228 nm.

Binding assay for rat plasma DBP. Competitive displacement of [23,24-^{3}H]-25-hydroxyvitamin D_3 (25OHD$_3$)

from vitamin D-deficient rat plasma DBP by $1,25(OH)_2D_3$ (**1**), OCT (**2**) and A-ring diastereomers (**3**, **4**, and **5**) was determined under equilibrium ligand-binding conditions.[22] [23,24-^{3}H]-25OHD$_3$ (specific activity; 3.3 TBq/mmol, obtained from Amersham Co., Buckinghamshire, 82 fmol) in EtOH (50 μL) was mixed with increasing amounts of analogues (0.24–1000 ng) in EtOH (100 μL). Vitamin D-deficient rat plasma (1 mL), diluted 1:70,000 with freshly prepared barbital acetate buffer (3.5 mmol AcOH, 3.5 mmol sodium barbiturate and 0.13 mol NaCl, pH 8.6), was added. The resulting mixtures were incubated at 0 °C for 1 h, treated with dextran charcoal, vortexed, and centrifuged at 3000 rpm for 15 min at 4 °C. Radioactivity of 1 mL of each supernatant was measured with an Aloka LSC-700.

Binding assay for calf-thymus VDR. Displacement of [26,27-^{3}H]-$1,25(OH)_2D_3$ (specific activity; 6.7 TBq/mmol, obtained from Amersham Co., Buckinghamshire) from calf-thymus cytosol receptor (Yamasa Shoyu Co., Ltd., Chiba) by $1,25(OH)_2D_3$ (**1**), or analogues (**2**, **3**, **4**, and **5**) was determined by the reported method.[23] Samples containing calf-thymus cytosol receptor solution (500 μL), prepared with phosphate buffer (0.3 M KCl, 0.05 M K_2HPO_4, pH 7.4), were mixed with increasing amounts of **1** (0.25–256 pg) or **2**, **3**, **4** and **5** (0.25–16384 pg) in EtOH (20 μL) and the samples were incubated at 20 °C for 1 h. [26,27-^{3}H]-$1,25(OH)_2D_3$ (34 fmol) in EtOH (25 μL) was added. The resulting mixture was incubated at 20 °C for 1 h, treated with dextran charcoal, vortexed, and centrifuged at 3000 rpm for 10 min at 4 °C. Radioactivity of 100 μL of each supernatant was measured with an Aloka LSC-700.

Assessment of HL-60 cell proliferation and differentiation. Cells (10^5 cells/well) were placed in 24-well tissue culture plates, and cultured for 3 d in RPMI1640 medium with $1,25(OH)_2D_3$ (**1**), OCT (**2**) and A-ring diastereomers (**3**, **4**, and **5**) (10^{-11}–10^{-7}M). Each group of cells was then collected and washed once with phosphate buffered saline (PBS). Then, the cells (2×10^5) were resuspended in 100 μL of diluent solution containing 1% bovine serum albumin and 1% sodium azide and incubated with 10 μL of human monoclonal FITC conjugated CD11b antibody (Sigma, USA) in the dark for 30 min at room temperature. The cells were washed with diluent solution and then fixed in 300 μL of PBS containing 2% paraformaldehyde. Fluorescence was detected on a Beckton Dickson FACScanTM at an excitation wavelength of 490 nm and emission wavelength of 520 nm. Results were recorded as the mean fluorescence index, which is the product of the fluorescence and the mean fluorescence intensity, with 10^4 cells counted per treatment.

Transfection and luciferase activity assay. Human osteosarcoma MG-63 cells, which are positive for VDR and retinoid X receptor gene expression, were maintained in Dulbecco's modification Eagle medium (Gibco BRL) supplemented with 1% penicillin, 1% streptomycin, and 10% dextran charcoal treated fetal calf serum. Cells (2×10^5) were suspended in 2 mL of the medium and transfected with 0.5 μg luciferase reporter plasmid ($pGVB_2$ vector, Toyo Ink Co., Ltd., Tokyo) inserted with a rat 25-hydroxyvitamin D_3-24-hydroxylase gene promoter (−291/+9) including two vitamin D-responsive elements[24] or a human osteocalcin gene promoter (−848/+10) including vitamin D-responsive element[25] and 0.25 μg of the pRL-CMV vector (Toyo Ink Co., Ltd., Tokyo) as an internal control using the Tfx-50 reagent (Promega Corp., Tokyo). The cells were incubated with $1,25(OH)_2D_3$ (**1**), or analogues (**2**, **3**, **4**, and **5**) (10^{-8} M) for 2 d. The luciferase activities of the cell lysates were measured with a luciferase assay system (Toyo Ink Co., Ltd., Tokyo) according to the manufacturer's instructions. Transactivation measured by luciferase activity was standardized with the luciferase activity of the same cells determined by the Sea Pansy luciferase assay system as a control (Toyo Ink Co., Ltd., Tokyo).[26] Each set of experiments was repeated at least three times, and the results are presented in terms of fold induction as mean ± standard errors.

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