Potent Antagonist for the Vitamin D Receptor: Vitamin D Analogues with Simple Side Chain Structure

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We previously reported that 22S-butyl-25,26,27-trinor-1α,24-dihydroxyvitamin D_3 **2** was a potent VDR antagonist. The X-ray crystal structure of the ligand binding domain of VDR complexed with **2** indicated that this ligand induces an extra cavity within the ligand-binding pocket. The structure also showed that the ligand forms only poor hydrophobic interactions with helix 12 of the protein. Here, to study the effects of the induction of the extra cavity and of insufficient interactions with helix 12 on antagonism, we designed and synthesized a series of vitamin D_3 analogues with or without a 22-alkyl substituent and evaluated their biological potency. We found that the 22-butyl analogues **3c** and **5c** act as full antagonists, the 22-ethyl analogues **3b**, **4b**, **5b**, and 22-butyl analogue **4c** act as partial agonists, and the others (**3a**, **4a**, **5a**, **6a**, **6b**, and **6c**) act as full agonists for VDR. It is intriguing that **6c** is a potent agonist for VDR, whereas its 26,27-dinor analogue **5c** is a potent antagonist. Analogue **6c** recruited coactivator SRC-1 well, but **5c** did not. These results indicate that a combination of induction of the extra cavity and insufficient hydrophobic interactions with helix 12 is important for VDR antagonism in this class of ligands.

The discovery of vitamin D in the 1920s−1930s provided a powerful weapon for the treatment of rickets and osteomalacia. Thereafter, it was found that vitamin D is hydroxylated at the 25-position in the liver and then at the 1α-position in the kidney to produce 1α,25-dihydroxyvitamin D_3 [1,25-$(OH)_2$-D_3,[a] **1**], which is the active form of vitamin D_3. It is now well-known that 1,25-$(OH)_2D_3$ **1** plays an important role in calcium homeostasis, cell differentiation and proliferation, and immunomodulation.[1] 1,25-$(OH)_2D_3$ (**1**) and its active analogues exert these effects by binding to the vitamin D receptor (VDR), which belongs to the nuclear receptor superfamily.[2] VDR is a ligand-dependent transcription factor that forms a heterodimer with another nuclear receptor, retinoid X receptor (RXR).[3] Upon ligand binding, VDR undergoes a conformational change that promotes RXR-VDR heterodimerization.[3] The RXR-VDR heterodimer binds to the vitamin D response elements present in the promoter region of responsive genes, recruits the coactivator, and initiates transcription.

VDR antagonists have been developed by several groups, including ours. ZK compounds[4] and adamantane compounds[5] are antagonists containing a bulky side chain. In contrast, (23S)-25-dehydro-1α-hydroxyvitamin D_3-26,23-lactone (TEI9647)[6] and its derivatives are antagonists lacking a bulky side chain.[6−9] VDR antagonism is thought to be due to VDR adopting a not-fully active conformation upon ligand binding. A VDR−ligand complex with a not fully active

conformation would inhibit heterodimerization with RXR and/or recruitment of coactivators. However, the molecular basis for VDR antagonism is not clearly understood, in part because VDR bound to an antagonist is not stable, so there is no crystal structure to help explain antagonistic activity. Recently, we reported that 22S-butyl-25,26,27-trinor-1α,24-dihydroxyvitamin D_3 **2** is a potent VDR antagonist.[10] The crystal structure of the ligand binding domain (LBD) of VDR complexed with **2** showed insufficient interactions between the ligand and helix 12 of VDR and the formation of an extra cavity.[10] In addition, we found that 22S-butyl-1α,24R-dihydroxyvitamin D_3, which contains the three carbons lacking on the side chain terminal of **2**, recovered agonistic activity, albeit weakly. Furthermore, the crystal structure of the VDR-LBD/22S-butyl-1α,24R-dihydroxyvitamin D_3 complex showed adequate VDR−ligand interactions.[11] In the present study, to investigate the effects of the induction of the extra cavity and of insufficient interactions with helix 12 on VDR antagonism, we synthesized a series of vitamin D_3 analogues with and without a 22-alkyl substituent and evaluated their biological activities.

Design and Synthesis

Design. The crystal structure of the VDR-LBD/**2** complex showed that ligand **2** induces an extra cavity in the ligand-binding pocket (LBP) of the VDR to accommodate the branched butyl group. To investigate the effects of the 22-alkyl substituent, and of the length and hydrophobicity of the side chain, we designed 12 vitamin D analogues, **3**−**6** (Chart 1). The 2-methylene-19-nor structure, instead of the original A-ring structure, was selected because the 19-nor structure is more stable than the conjugated triene structure

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[a] Abbreviations: VDR, vitamin D receptor; LBP, ligand binding pocket; 1,25-$(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; RXR, retinoid X receptor; LBD, ligand binding domain.

Chart 1. Structures of 1,25-(OH)$_2$D$_3$ (**1**) and Vitamin D Analogues
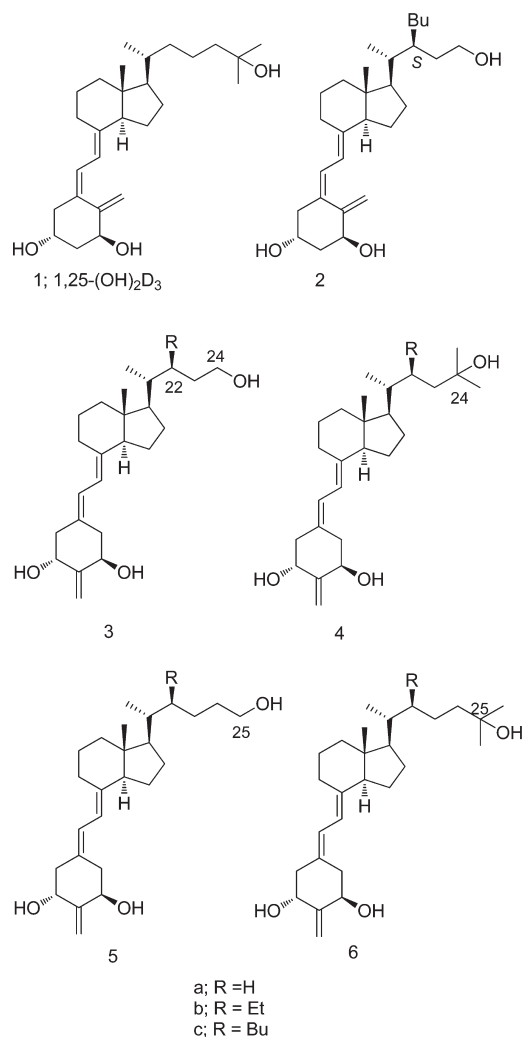
of the hormone and is easily synthesized. In addition, insertion of a methylene group into C(2) was expected to increase the VDR affinity and the biological activity, as in the case of the 2MD compound.[12] 22S-Butyl-2-methylene-19,25,26,27-tetranor-1α,24-dihydroxyvitamin D$_3$ **3c** is a 2-methylene-19-nor type compound corresponding to the parent compound **2**. 1,24-Dihydroxyvitamin D$_3$ derivatives **3a**−**c** and **4a**−**c** were designed to investigate the effects of the 22-alkyl substituent and of the hydrophobicity of the original vitamin D side chain. 1,25-Dihydroxyvitamin D$_3$ derivatives **5a**−**c** and **6a**−**c** were designed to investigate the effects of side chain length in addition to the 22-alkyl substituent.

Synthesis of the 1,24-Dihydroxyvitamin D$_3$ Analogues. As shown in Scheme 1, 1,24-dihydroxyvitamin D$_3$ derivatives **3a** and **4a** were synthesized from aldehyde **8**. The aldehyde (**8**), prepared from the corresponding tosylate **7**, is a convenient synthetic intermediate for various vitamin D side-chain analogues.[5] E-Enoate **9** was obtained by Horner−Emmons reaction using triethyl phosphonoacetate in 79% yield.[13] Selective hydrogenation of α,β-unsaturated ester **9** was achieved by reduction using Mg in MeOH to provide **10** in excellent yield (81%).[14,15] Compound **10** was reduced with DIBAL to give 24-alcohol **11**, which was then treated with camphor sulfonic acid (CSA) to afford the desired compound **3a**. 24,24-Dialkyl analogue **4a** was obtained by treating **10**

with MeLi to provide 24,24-dimethylated compound **12**, which was then treated with CSA to provide **4a**.

Synthesis of 22-Alkyl 1,24-Dihydroxyvitamin D$_3$ Analogues. As shown in Scheme 2, 22-butyl vitamin D derivatives **3c** and **4c** were also synthesized from 22-aldehyde **8**. Compound **8** was treated with ethyl diphenylphosphonoacetate at −78 °C to afford Z-enoate **13** (70%) together with E-isomer **9** (14%).[16] Upon treatment of Z-enoate **13** with n-Bu$_2$CuLi in the presence of HMPA and TMSCl, a diastereofacial-selective conjugate addition of n-Bu$_2$CuLi took place to provide 22S-butyl compound **14** (74%) together with its 22R-isomer (7%). The configuration at C(22) was determined from the stereochemistry of the starting enoate and the reaction conditions based on our previous report.[13] Compound **14** was reduced with DIBAL to give 24-alcohol **16**, which was then treated with CSA to provide the desired 22S-butyl analogue **3c**. On the other hand, 24,24-dimethylated analogue **4c** was obtained upon treatment of **14** with MeLi followed by CSA.

22-Ethyl analogues **3b** and **4b** were synthesized from Z-enoate **13** by procedures analogous to those described above for the synthesis of 22-butyl analogues **3c** and **4c** (Scheme 2). Thus, treatment of **13** with Et$_2$CuLi in the presence of HMPA and TMSCl afforded diastereoselective conjugate addition product **15** (55%). Reduction of the side chain ester followed by deprotection of the A-ring alcohol provided the desired compound **3b**. Treatment of **15** with MeLi provided 24,24-dimethyl compound **19** that was then treated with CSA to give the target compound **4b**.

Synthesis of 1,25-Dihydroxyvitamin D$_3$ Analogues. Synthesis of 1,25-dihydroxyvitamin D$_3$ derivatives **5a** and **6a** was conducted as shown in Scheme 3. The convenient synthetic intermediate **7**[5] was treated with NaI to provide iodide **23**. The iodide (**23**) reacted with sulfone **22**, which was derived from 3-bromo-1-propanol, to give coupling product **24**. Sulfone **24** was reduced with Na−Hg and then deprotected to provide target compound **5a**. 2-Methylene-19-nor-1,25-dihydroxyvitamin D$_3$ **6a** was obtained from tosylate **7** by a coupling reaction with bromide **26** followed by deprotection of the three alcohols.

Synthesis of 22-Alkyl 1,25-Dihydroxyvitamin D$_3$ Analogues. 22-Butyl compounds **5c** and **6c** were synthesized from 22-butyl alcohol **16** (Scheme 4). Tosylate **28** derived from **16** was treated with KCN to give cyanate **30**, which was then reduced with DIBAL to give aldehyde **32**. The aldehyde (**32**) was reduced to alcohol **34** and then deprotected to give **5c**. On the other hand, aldehyde **32** was converted to ester **36** in good yield by alkaline iodine oxidation which was developed by our group.[17] Ester **36** was treated with MeLi to give **38** and deprotected to provide the target compound **6c**. 22-Ethyl compounds **5b** and **6b** were synthesized from 22-ethyl alcohol **17** by procedures analogous to those described above for the synthesis of the 22-butyl compounds **5c** and **6c** (Scheme 4).

Biological Activities

VDR Binding. Binding affinity for the VDR was evaluated by a competitive binding assay using recombinant human VDR-LBD expressed as the C-terminal GST-tagged protein using pGEX-VDR vector[18] in *Escherichia coli* BL21. There are only a few reports in which human VDR was used for competitive binding assays.[6,19] To date, chick, bovine, and rat VDRs have generally been used. Our results are summarized in Table 1. All synthetic compounds showed specific binding to VDR, indicating they are ligands for VDR.

Scheme 1. Synthesis of Analogues **3a** and **4a**
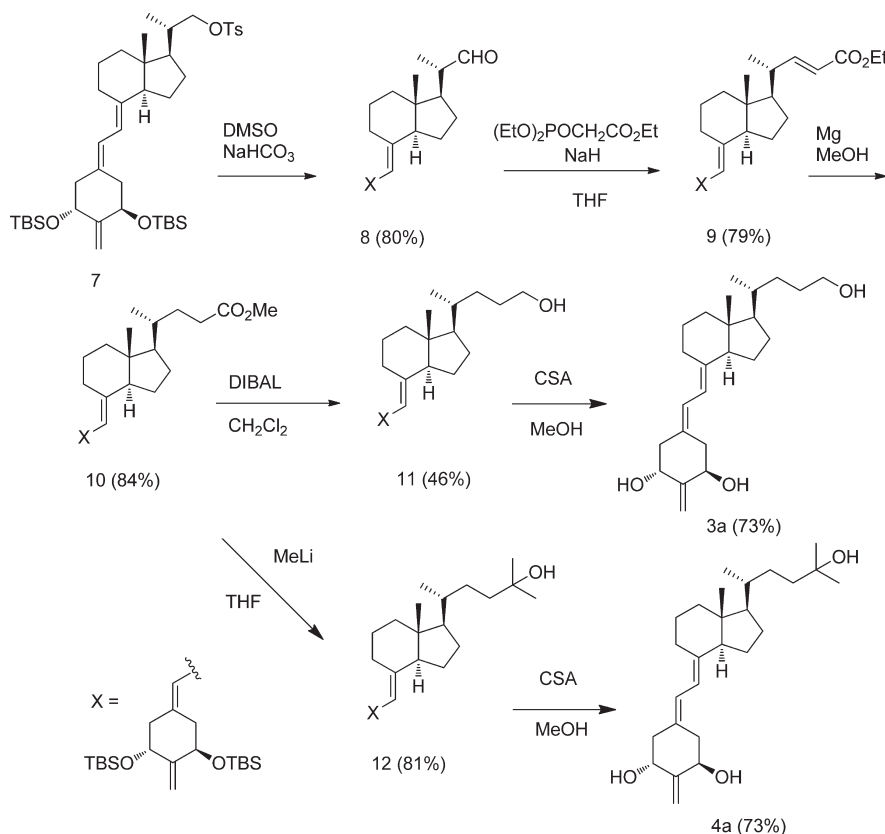
Scheme 2. Synthesis of Analogues **3b**, **3c**, **4b**, and **4c**
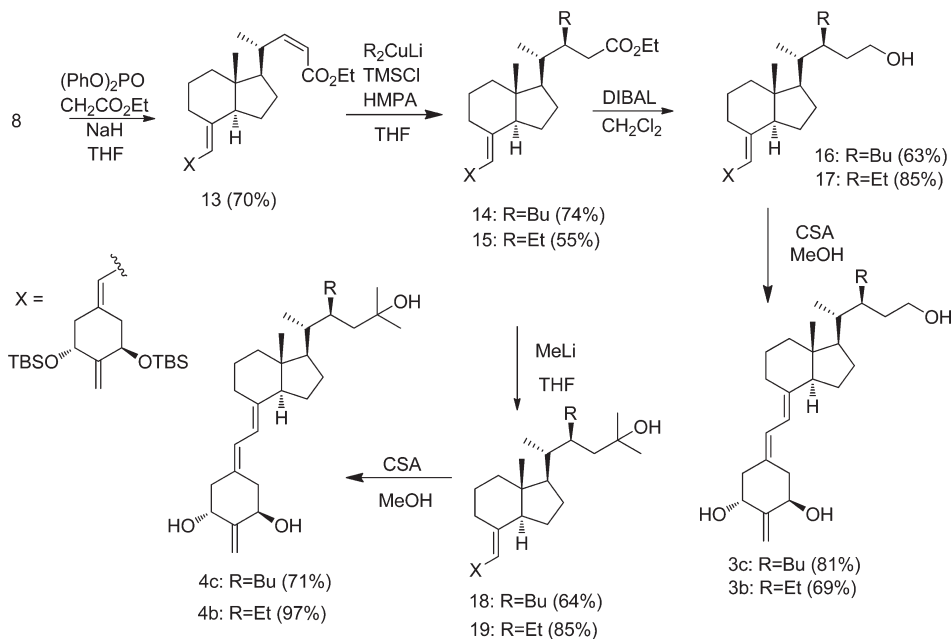
Compounds with the same side chain as that of 1,25-$(OH)_2D_3$ (**6a−c**) showed particularly strong affinity. All 22-butyl analogues (**3c**, **4c**, **5c**, and **6c**) also showed significant affinity.

Transactivation. The ability of synthetic compounds **3−6** to induce transcription of a vitamin D-responsive gene was tested using the mouse osteopontin luciferase reporter gene assay system in Cos7 cells.[10] The results are shown in Figure 1.

Compounds with a 1,25-$(OH)_2D_3$ side chain, **6a−c**, showed particularly strong activity. In addition, all compounds lacking a 22-substituent (**3a**, **4a**, **5a**, and **6a**) showed full agonistic activity. In contrast, compounds **3c**, **4c**, and **5c**, bearing a 22S-butyl group, showed little transactivation potency. Interestingly, 22S-ethyl analogues **3b**, **4b**, and **5b** showed intermediate activity between the corresponding 22-hydrogen and 22-butyl analogues.

Scheme 3. Synthesis of Analogues **5a** and **6a**
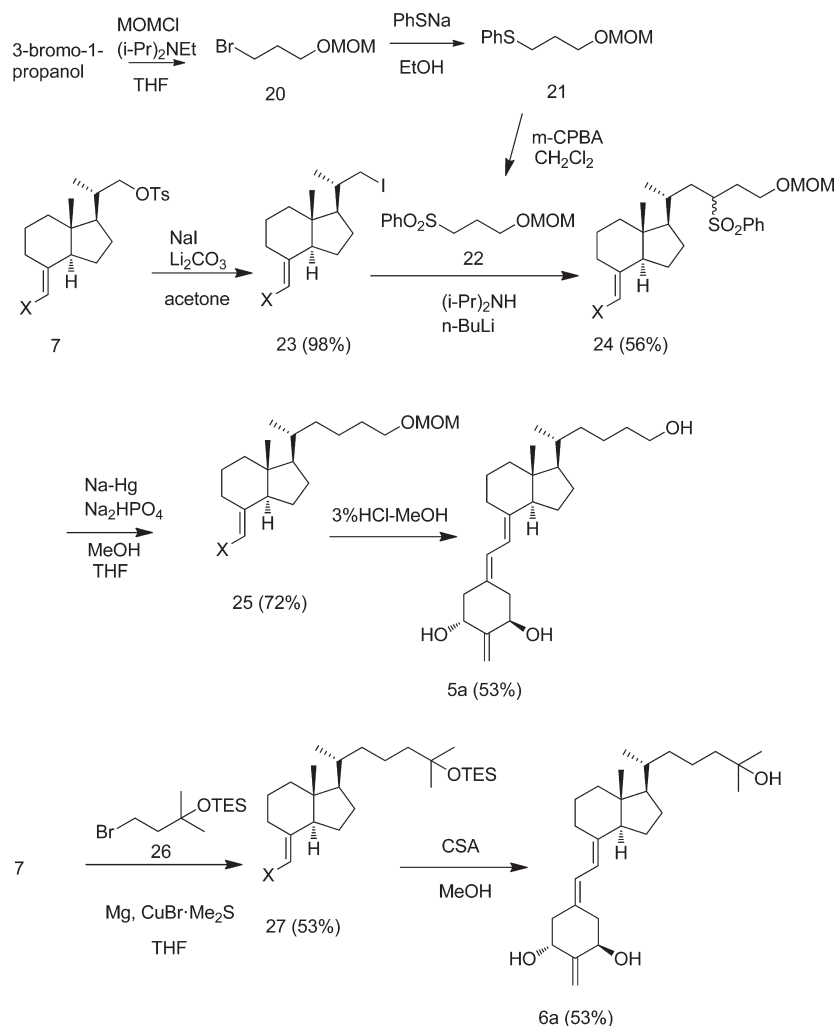
As shown in Figure 2b, compounds **3c**, **4c**, and **5c** concentration dependently inhibited the transactivation induced by 1,25-(OH)$_2$D$_3$ (**1**). In particular, **3c** and **5c**, which have a primary hydroxyl group on the side chain, completely inhibited the transactivation, indicating that these two analogues are full VDR antagonists. 22-Ethyl analogues **3b**, **4b**, and **5b** inhibited the transactivation induced by **1** to their transactivation potency (Figure 2a).

Recruitment of RXR and Coactivator Peptide. We evaluated ligand-dependent recruitment of RXR and a coactivator peptide, SRC-1, to VDR using a mammalian two-hybrid assay similar to that reported previously.[18] As shown in Figure 3, compounds **3a**, **4a**, **5a**, and **6a**, as well as **6b** and **6c**, recruited RXR and SRC-1 concentration dependently. Three 22-butyl analogues **3c**, **4c**, and **5c**, very weakly recruited RXR and SRC-1. 22-Ethyl analogues **3b**, **4b**, and **5b** recruited RXR and SRC-1 moderately.

Discussion

All synthetic analogues with a 24- or 25-hydroxyl group in the side chain showed specific binding for hVDR (Table 1). Therefore, all compounds **3–6** synthesized here are true ligands for hVDR. Compounds **6a–c**, which have the same side chain as the hormone (**1**), showed strong affinity for hVDR regardless of the length of the 22-alkyl substituent. A

similar tendency was observed for the 24-nor-compounds **4a–c**, although their affinity is weaker than that of **6a–c**. For primary alcohols **3a–c** and **5a–c**, hVDR affinity increased in the order: 22-hydrogen, 22-ethyl, and 22-butyl substituent. We reported previously that a primary alcohol side chain has insufficient hydrophobic interactions with helix 12 of VDR and that 22-butyl substituent induces an extra cavity in the native ligand binding pocket.[10] An increase in binding affinity by a 22-alkyl substituent, observed in primary alcohols **3a–c** and **5a–c**, is thought to be caused by newly generated hydrophobic interactions between the 22-alkyl group and amino acid residues lining the extra cavity of VDR. In the case of tertiary alcohols **4a–c** and **6a–c**, hydrophobic interactions with helix 12 appear to be sufficient regardless of the 22-alkyl substituent.

In primary 24-alcohols **3a–c**, transactivation potency is in inverse proportion to the affinity for VDR (Figure 1). Transactivation and inhibition experiments indicated that **3a**, **3b**, and **3c** is an agonist, a partial agonist, and an antagonist, respectively, for VDR (Figures 1 and 2). In primary 25-alcohols **5a–c**, similar results were obtained (Figures 1 and 2). Tertiary 24-alcohols **4a–c** and 25-alcohols **6a–c** showed increased agonistic activity compared to the corresponding primary alcohol (Figure 1). In particular, **6a–c** exhibited completely restored agonistic activity. The results clearly demonstrate that hydrophobicity of the side chain terminal

Scheme 4. Synthesis of Analogues **5b**, **5c**, **6b**, and **6c**
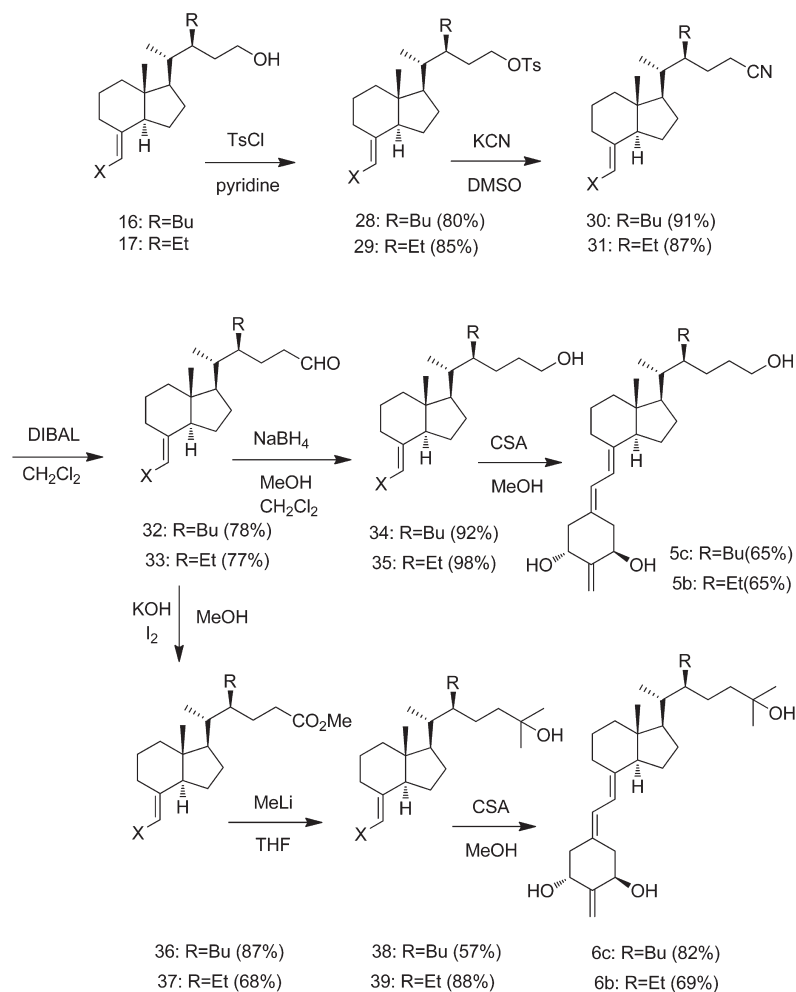
Table 1. VDR Binding Affinity of Synthetic Analogues **3−6** IC$_{50}$ (nM)^a

Compd.	1	3	4	5	6
a: R = H	0.08	2.7	0.10	2.1	0.04
b: R = Et		0.88	0.72	0.42	0.044
c: R = Bu		0.13	0.21	0.19	0.051

^{a} Competitive binding of 1,25-(OH)$_2$D$_3$ (**1**) and synthetic compounds (**3a−c**, **4a−c**, **5a−c**, and **6a−c**) to the human vitamin D receptor. The experiments were carried out in duplicate. The IC$_{50}$ values are derived from dose−response curves and represent the compound concentration required for 50% displacement of radiolabeled 1,25-(OH)$_2$D$_3$ from the receptor protein.

interacting with helix 12 is an important factor for expression of transcriptional activity. Additionally, effects of the alkyl substituent at C(22) are obvious. In **3a−c**, **4a−c**, and **5a−c**, the increased volume of the substituent strengthens inhibitory activity. However, **6a−c**, which have the prototype side chain of hormone **1**, showed strong agonistic activity regardless of the 22-substituent. 22-Ethyl compounds **3b−5b** showed moderate agonistic activity, in between 22-hydrogen compounds **3a−5a** and 22-butyl compounds **3c−5c**. Among the 22-ethyl compounds, **3b−5b** are partial agonists and **6b** is a full agonist. It is striking that primary alcohol **5c** inactivates VDR strongly, whereas corresponding tertiary alcohol **6c** activates VDR strongly. The potency of RXR and SRC-1 recruitments by each ligand correlates well with the transactivation potency of the corresponding ligand.

The above results, combined with our previous study, allow us to suggest a molecular basis for VDR agonistic and antagonistic behaviors of a series of our synthetic side chain analogues as shown in Figure 4. Several research groups have solved crystal structures of VDR-LBD complexed with a variety of ligands.[20−32] All of the crystal structures showed the canonical Moras' conformation of the VDR-LBD and quite similar architectures of the ligand binding pocket (LBP), except for the complex of zebrafish VDR-LBD with "GEMINI",[23,27] an analogue with two identical side chains,[33,34] and the complex of VDR-LBD with 22-butyl analogue **2**.[10] The zebrafish VDR-LBD/GEMINI complex revealed the formation of a new cavity extending the original LBP in order to accommodate the second side chain as well as the VDR-LBD/**2** complex. Figure 4a (conformer A) shows the crystal structure of VDR-LBD/**1**
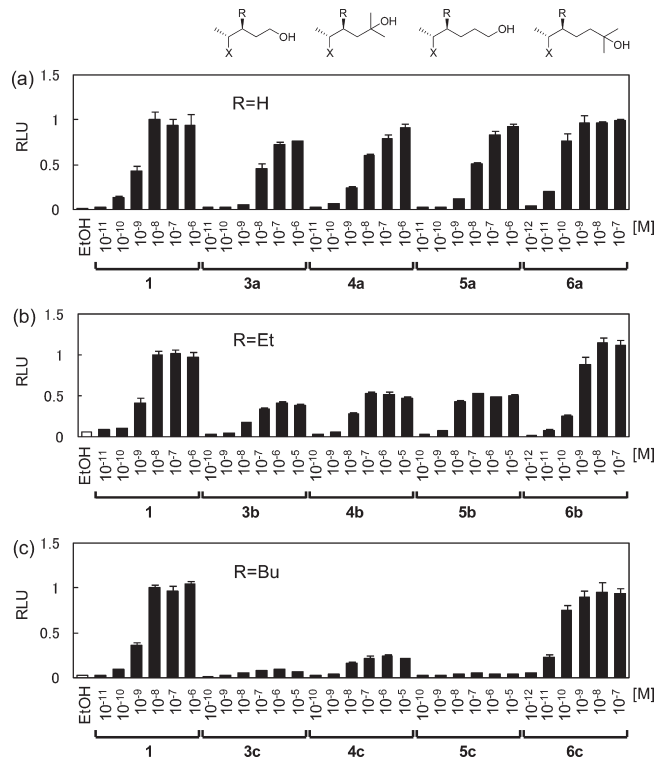
Figure 1. Transactivation of compounds **3**–**6** in Cos7 cells. Transcriptional activity was evaluated by the dual luciferase assay using a full-length human VDR expression plasmid (pCMX-hVDR), a reporter plasmid containing three copies of mouse osteopontin VDRE (SPPx3-TK-Luc), and an internal control plasmid containing sea pansy luciferase expression constructs (pRL-CMV) in Cos7 cells as described previously.[10] Luciferase activity of 10^{-8} M 1,25-$(OH)_2D_3$ (**1**) was defined as 1. (a) Transcriptional activity of **1**, **3a**, **4a**, **5a**, and **6a**. (b) Transcriptional activity of **1**, **3b**, **4b**, **5b**, and **6b**. (c) Transcriptional activity of **1**, **3c**, **4c**, **5c**, and **6c**.
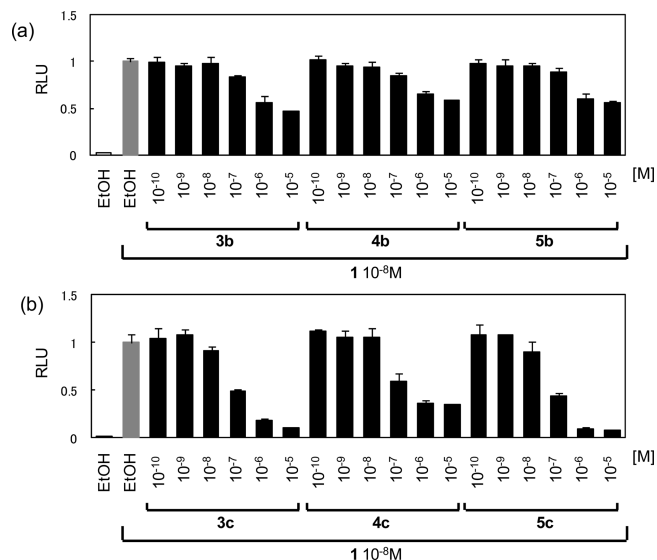

Figure 2. Inhibitory effect on the transactivation induced by 1,25-$(OH)_2D_3$ (**1**) was evaluated using the same assay method described in Figure 1. (a) transcriptional activity of **3b**, **4b**, and **5b** in the presence of 10^{-8} M 1,25-$(OH)_2D_3$ **1**. (b) Transcriptional activity of **3c**, **4c**, and **5c** in the presence of 10^{-8} M 1,25-$(OH)_2D_3$ **1**. All experiments were done in triplicate.

complex[31] in which helix 12 adopts an active conformation. Conformer A is known to be an active conformation of

VDR-LBD. VDR-LBD complexed with a full agonist having no 22-substituent, such as **3a**, **4a**, **5a**, or **6a**, seems to adopt this conformation. Figure 4b (conformer B) shows a docking model of the VDR-LBD/**6c** complex in which the extra cavity is induced to accommodate the branched side chain, but helix 12 still folds back to form an active conformation. This folding back is apparently due to sufficient hydrophobic interactions between helix 12 and the side chain terminal (tertiary alcohol) of the ligand. Thus, it seems that hydrophobic interactions overcome strain caused by the formation of the extra cavity. VDR-LBD complexed with a full agonist such as **6b** and **6c** seems to adopt this conformation. It should be noted that GEMINI could also adopt this conformation.

Figure 4c and 4d (conformers C and D) show docking models in which the extra cavity is induced by the branched side chain, so that helix 12 cannot adopt an active conformation. In contrast to full agonists **6b** and **6c**, full antagonists **2**, **3c**, and **5c** would adopt conformer C and/or D because of insufficient hydrophobic interactions between the side chain terminal (primary alcohol) of the ligand and helix 12. Furthermore, compounds **3b**, **4b**, and **5b** moderately induce the extra cavity and have moderate hydrophobic interactions with helix 12. Therefore, in addition to inactive conformer C and/or D, some proportion of conformer B would also be present in the population.

The 12 compounds synthesized here can form hydrogen bonds between three hydroxyl groups and VDR, as observed in most of the VDR-LBD/ligand complexes. Therefore, in addition to inducing an extra cavity, insufficient hydrophobic interactions would result in inactive VDR.

Conclusions

We performed a systematic study on the synthesis of a series of vitamin D_3 analogues with or without a 22-alkyl substituent and evaluated their biological potency. The present study demonstrated that both the induction of an extra cavity and insufficient hydrophobic interactions with helix 12 are necessary for VDR antagonism by our new class of ligands. A combination of these two structural factors would cause structural strain in VDR, resulting in the unfolding or mis-folding of helix 12. This study showed great promise of ligand design based on the alternative structural basis of VDR agonism and antagonism.

Experimental Section

All reagents were purchased from commercial sources. Unless otherwise stated, NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR in $CDCl_3$ solution with TMS as an internal standard, and the chemical shifts are given in δ values. High and low resolution mass spectra were obtained with a JEOL JMS D-300 and JEOL JMS-HX110A spectrometers. Relative intensities are given in parentheses in low mass. IR spectra were recorded on a SHIMADZU FTIR-8400S spectrophotometer, and data are given in cm^{-1}. UV spectra were recorded on a BECKMAN DU7500 spectrophotometer. All air and moisture sensitive reactions were carried out under argon or nitrogen atmosphere. Purity was determined by HPLC [PEGASIL Silica SP100, 4.6 mm × 150 mm, hexane/$CHCl_3$/MeOH (100:25:8 or 100:25:10), flow rate 1.0 mL/min] and was > 95% for all compounds tested.

Ethyl (2*E*)-4-[(1*R*,3*R*,7*E*,17*β*)-1,3-Bis{[*tert*-butyl(dimethyl)-silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]pent-2-enoate (9). To a suspension of sodium hydride (60% oil suspension, 23.8 mg, 0.546 mmol) in THF (1 mL) at 0 °C was added
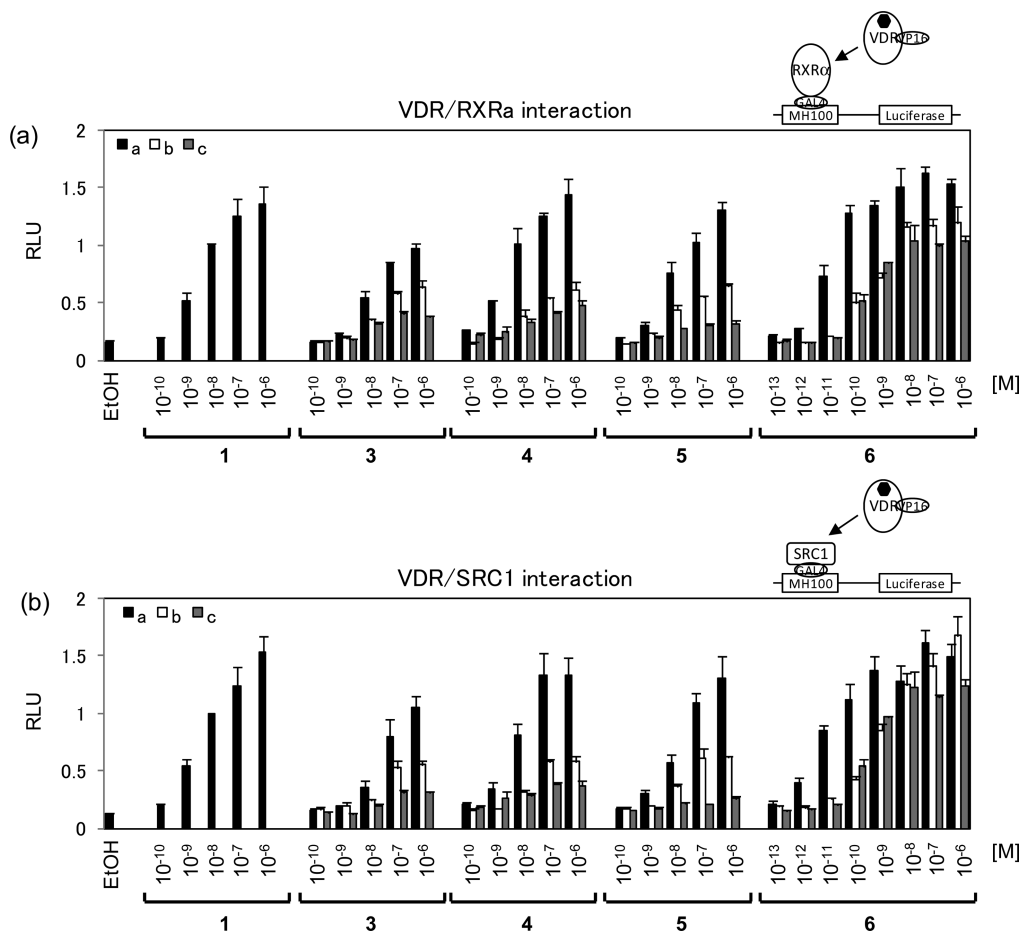
Figure 3. RXRα and SRC-1 recruitment to VDR by 1,25-(OH)$_2$D$_3$ (**1**) and synthetic compounds (**3a**−**c**, **4a**−**c**, **5a**−**c**, and **6a**−**c**) in Cos7 cells. The activities were evaluated by a dual luciferase assay using VP16-VDR expression plasmid (pCMX-VP16-hVDR), RXRα or SRC-1 expression plasmid (GAL4-RXRα or GAL4-SRC-1), a reporter plasmid containing four copies of GAL4 response element (MH100 × 4-TK-Luc), and an internal control plasmid containing sea pansy luciferase expression construct (pRL-CMV). All experiments were carried out in triplicate. Black bars indicate activities of **1**, **3a**, **4a**, **5a**, and **6a**. White bars indicate activities of **3b**, **4b**, **5b**, and **6b**. Gray bars indicate activities of **3c**, **4c**, **5c**, and **6c**. (a) RXRα recruitment, (b) SRC-1 recruitment.

triethyl phosphonoacetate (117 μL, 0.585 mmol), and the mixture was stirred for 10 min. To this solution aldehyde **8** (104 mg, 0.182 mmol) in THF (1 mL) was added, and the mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with water, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/99) to afford **9** (92.8 mg, 79%).

9. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.58 (3 H, s, H-18), 0.86, 0.90 (each 9 H, s, *t*-Bu), 1.10 (3 H, d, *J* = 6.6 Hz, H-21), 1.29 (3H, t, *J* = 7.1 Hz), 2.83 (1 H, m, H-9), 4.18 (2 H, q, *J* = 7.1 Hz, −COOCH$_2$−), 4.43 (2 H, m, H-1, 3), 4.93, 4.97 (each 1 H, s, −C=CH$_2$), 5.75 (1 H, d, *J* = 15.6 Hz, H-23), 5.83 (1 H, d, *J* = 11.4 Hz, H-7), 6.21 (1 H, d, *J* = 11.4 Hz, H-6), 6.84 (1 H, dd, *J* = 15.6, 9.0 Hz, H-22). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.3, 14.2, 18.1, 18.2, 19.3, 22.2, 23.3, 25.7 (3 carbons), 25.8 (3 carbons), 27.5, 28.6, 38.6, 40.0, 40.4, 45.8, 47.6, 55.3, 56.0, 60.0, 71.6, 72.5, 106.3, 116.4, 119.1, 122.2, 133.0, 140.5, 152.9, 154.5, 166.5. MS (EI) *m/z* (%): 642 (M$^+$, 5), 585 (10), 510 (100), 453 (15), 366 (23), 147 (16), 73 (81). HRMS (EI) calcd for C$_{38}$H$_{66}$O$_4$Si$_2$ 642.4500, found 642.4503. IR (neat) 3375, 2954, 2929, 2887, 2856, 1658, 1620, 1461, 1359, 1255, 1101, 1072, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ$_{max}$ 246, 254, 264 nm.

Methyl 4-[(1*R*,3*R*,7*E*,17*β*)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]pentanoate (10). A mixture of ester **9** (122.9 mg, 0.1914 mmol) and magnesium turnings (93.1 mg, 3.83 mmol) in MeOH (2 mL) was stirred at room temperature for 20 h. The reaction was quenched with 1N HCl and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/9) to afford **10** (101.6 mg, 84%).

10. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.86, 0.89 (each 9 H, s, *t*-Bu), 0.93 (3 H, d, *J* = 6.2 Hz, H-21), 2.83 (1 H, m, H-9), 3.67 (3H, s, −COOMe), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, *J* = 11.1 Hz, H-7), 6.21 (1 H, d, *J* = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.0, 18.1, 18.2, 18.4, 22.2, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.5, 28.7, 30.9, 31.0, 35.7, 38.5, 40.5, 45.6, 47.6, 51.5, 56.2 (2 carbons), 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 140.9, 152.9, 174.7. MS (FAB) *m/z* (%): 631 (M$^+$, 5). HRMS (FAB) calcd for C$_{37}$H$_{67}$O$_4$Si$_2$ (M$^+$ + H) 631.4577, found 631.4565.

4-[(1*R*,3*R*,7*E*,17*β*)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]pentan-1-ol (11). Ester **10** (16.2 mg, 0.0257 mmol) in CH$_2$Cl$_2$ (0.5 mL) was treated with DIBALH (160 μL of 1.0 M toluene solution, 016 mmol) at 0 °C for 3 h. The reaction was quenched with water and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/9) to afford **11** (7.1 mg, 46%).

11. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.09 (each 3 H, s, SiMe), 0.55 (3 H, s, H-18), 0.87, 0.89 (each 9 H, s, *t*-Bu), 0.94 (3 H, d, *J* = 6.4 Hz, H-21), 2.82(1 H, m, H-9), 3.62 (2 H, t, *J* = 6.4 Hz, H-24),
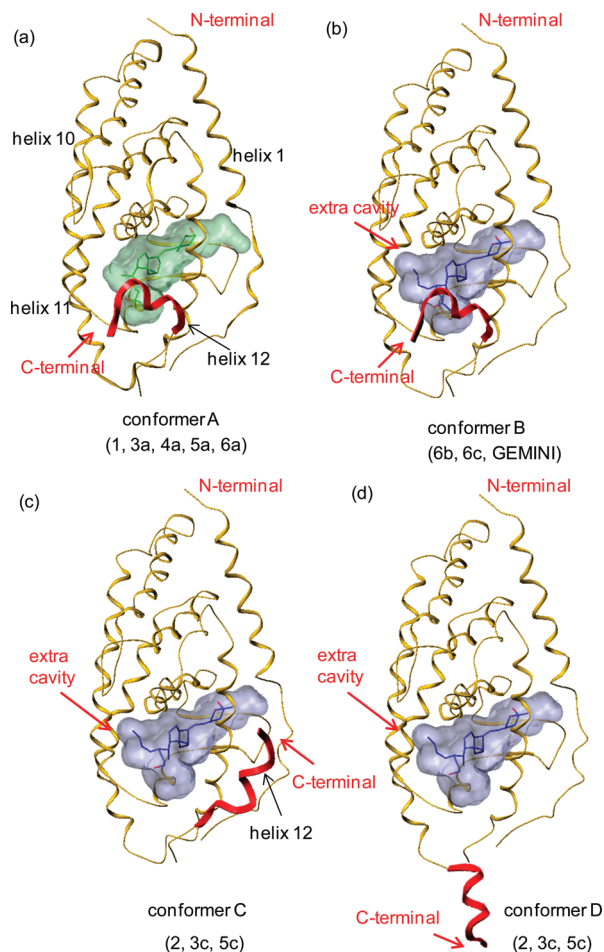
Figure 4. Conformation models of VDR-LBD complexed with agonist and antagonist. (a) Crystal structure of VDR-LBD/**1** complex, (b) docking model of VDR-LBD and 22*S*-butyl-2-methylidene-19-nor-1α,25-dihydroxyvitamin D₃ (**6c**), (c) docking model of VDR-LBD and 22*S*-butyl-2-methylidene-19,26,27-trinor-1α,25-dihydroxyvitamin D₃ (**5c**), (d) docking model of VDR-LBD and 22*S*-butyl-2-methylidene-19,26,27-trinor-1α,25-dihydroxyvitamin D₃ (**5c**).

4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH₂), 5.82 (1 H, d, J = 11.3 Hz, H-7), 6.21 (1 H, d, J = 11.3 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.0, 18.1, 18.2, 18.8, 22.2, 23.4, 25.7 (3 carbons) 25.8 (3 carbons), 27.7, 28.7, 29.4, 31.8, 35.9, 38.5, 40.5, 45.6, 47.6, 56.2, 56.4, 63.6, 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 141.1, 152.9. MS (EI) m/z (%): 602 (M$^+$, 1), 470 (22), 366 (10), 279 (9), 167(26), 149 (83), 73 (100). HRMS (FAB) calcd for $C_{36}H_{67}O_3Si_2$ (M$^+$ + H) 603.4629, found 603.4627. IR (neat) 3344, 2952, 2927, 2833, 2856, 1658, 1620, 1461, 1255, 1101, 1072, 935, 896, 835, 775, 667 cm^{-1}.

2-Methylidene-19,25,26,27-tetranor-1α,24-dihydroxyvitamin D₃ (3a). A solution of **11** (17.1 mg, 0.02841 mmol) and camphor sulfonic acid (19.8 mg, 0.08523 mmol) in MeOH (0.5 mL) was stirred at room temperature for 1 h. Aqueous NaHCO₃ was added, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/1) to afford **3a** (12.3 mg, quant).

3a. ^{1}H NMR (300 MHz, MeOD) δ 0.59 (3 H, s, H-18), 0.97 (3 H, d, J = 6.2 Hz, H-21), 2.83 (1 H, m, H-9), 3.51 (2 H, t, J = 6.4 Hz, H-24), 4.40 (2 H, m, H-1, 3), 5.04, 5.06 (each 1 H, s, −C=CH₂), 5.90 (1 H, d, J = 11.1 Hz, H-7), 6.26 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR (100 MHz, MeOD) δ 12.5, 19.4, 23.3, 24.6, 28.7, 29.9, 30.3, 33.2, 37.4, 39.0, 41.9, 46.8, 46.9, 57.5, 57.9, 63.6, 71.6, 72.5, 107.9, 117.2, 124.1, 133.1, 142.5, 153.9. MS (EI) m/z (%): 374 (M$^+$, 76), 289 (30), 269 (28), 220 (31), 147 (77), 135

(96), 95 (100). HRMS (EI) calcd for $C_{24}H_{38}O_3$ 374.2811, found 374.2821. IR (neat) 3298, 2941, 2925, 2871, 1658, 1620, 1442, 1261, 1070, 1049, 865, 673 cm^{-1}. UV (EtOH) λ_{max} 245, 254, 263 nm.

5-[(1R,3R,7E,17β)-1,3-Bis{[tert-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-2-methylhexan-2-ol (12). To a solution of ester **10** (64.4 mg, 0.102 mmol) in THF (1 mL) at −78 °C was added MeLi (470 μL of 1.09 M Et₂O solution, 0.512 mmol), and the mixture was stirred for 30 min. The reaction was quenched with satd NH₄Cl, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 5/95) to afford **12** (51.9 mg, 0.0824 mmol, 81%).

12. ^{1}H NMR δ 0.02, 0.04, 0.07, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.86, 0.89 (each 9 H, s, *t*-Bu), 0.94 (3 H, d, J = 6.8 Hz, H-21), 1.20 (6 H, s, H-25, 26), 2.80 (1 H, m, H-9), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH₂), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.0, 18.1, 18.2, 18.9, 22.2, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.6, 28.7, 29.0, 29.3, 30.1, 36.2, 38.5, 40.0, 40.5, 45.6, 47.6, 56.2, 56.3, 71.1, 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 141.1, 152.9. MS (EI) m/z (%): 630 (M$^+$, 10), 498 (100), 480 (16), 366 (31), 234 (12), 147(10), 73 (33). HRMS (EI) calcd for $C_{38}H_{70}O_3Si_2$ 630.4864, found 630.4861. IR (neat) 3361, 2952, 2856, 1658, 1620, 1461, 1251, 1101, 1072, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

2-Methylidene-19,24-dinor-1α,25-dihydroxyvitamin D₃ (4a). In a similar manner to that for the synthesis of **3a** from **11**, target compound **4a** (28.2 mg, 0.0702 mmol) was obtained from **12** (51.9 mg, 0.0808 mmol) in 87% yield.

4a. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.92 (3 H, d, J = 6.1 Hz, H-21), 1.21 (6 H, s, H-25, 26), 4.46 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH₂), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). ^{13}C NMR δ 12.1, 18.3, 22.2, 23.4, 27.5, 28.9, 29.0, 29.3, 30.1, 36.1, 38.1, 39.9, 40.4, 45.7 (2 carbons), 56.1, 56.3, 70.6, 71.2, 71.8, 107.7, 115.3, 124.2, 130.5, 143.3, 152.0. MS (EI) m/z (%): 402 (M$^+$, 65), 161 (61), 147(70), 135 (93), 81 (100). HRMS (EI) calcd for $C_{26}H_{42}O_3$ 402.3134, found 402.3135. IR (neat) 3355, 2960, 2871, 1650, 1620, 1440, 1377, 1215, 1074, 1045, 908, 756 cm^{-1}. UV (EtOH) λ_{max} 245, 254, 263 nm.

Ethyl (2Z)-4-[(1R,3R,7E,17β)-1,3-Bis{[tert-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]pent-2-enoate (13). To a solution of ethyl diphenylphosphonoacetate (109 μL, 132.8 mg, 0.415 mmol) in THF (1 mL) was added sodium hydride (50% oil suspension, 18.1 mg, 0.377 mmol) at 0 °C, and the mixture was stirred for 10 min. The mixture was cooled to −78 °C, and then aldehyde **8** (107.9 mg, 0.189 mmol) in THF (1 mL) was added. The mixture was gradually warmed up to −10 °C from −78 °C for 1.5 h. The reaction was quenched with aqueous NH₄Cl, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/99) to afford **13** (85.3 mg, 70%) and *E*-isomer **9** (17.1 mg, 14%).

13. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.62 (3 H, s, H-18), 0.86, 0.90 (each 9 H, s, t-Bu), 1.05 (3 H, d, J = 6.6 Hz, H-21), 1.29 (3 H, t, J = 7.1 Hz, −COOEt), 2.82(1 H, m, H-9), 4.18 (2 H, q, J = 7.1 Hz, −COOCH₂−), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH₂), 5.65 (1 H, d, J = 11.5 Hz, H-23), 5.82 (1 H, d, J = 11.2 Hz, H-7), 5.98 (1 H, dd, J = 11.5, 10.7 Hz, H-22), 6.20 (1 H, d, J = 11.2 Hz, H-6. MS (EI) m/z (%): 642 (M$^+$, 2), 510 (46), 366 (28), 147 (23), 73 (100). HRMS (EI) calcd for $C_{38}H_{66}O_4Si_2$ 642.4500, found 642.4501. IR (neat) 3394, 2952, 2927, 2887, 2856, 1720, 1641, 1461, 1251, 1180, 1099, 1070, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 255, 264 nm.

Ethyl (3S)-3-{1-[(1R,3R,7E,17β)-1,3-Bis{[tert-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}heptanoate (14). A suspension of CuBr/Me₂S (1.5 g, 7.27 mmol) in

THF (6 mL) was cooled to −30 °C, and to this solution was added n-BuLi (8.76 mL, 14.5 mmol, 1.66 M/hexane) and the mixture was stirred for 15 min. To this solution was added TMSCl (1.16 mL, 9.09 mmol), HMPA (1.59 mL, 9.09 mmol), and a solution of enoate **13** (584 mg, 0.909 mmol) in THF (6 mL) in this order. The mixture was stirred at −30 °C for 1.5 h, and the reaction was quenched with satd NH_4Cl. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 5/995) to afford **14** (471 mg, 0.673 mmol, 74%) and its 22*R*-isomer (44.6 mg, 0.06371 mmol, 7.0%).

14. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.52 (3 H, s, H-18), 0.81 (3 H, d, *J* = 6.1 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 1.26 (3 H, t, *J* = 7.1 Hz, −COOEt), 2.82 (1 H, m, H-9), 4.13 (2 H, m, −COOEt), 4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.82 (1 H, d, *J* = 11.1 Hz, H-7), 6.21 (1 H, d, *J* = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.2, 14.1, 14.3, 18.1, 18.2, 22.1, 23.0, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.3, 27.7, 28.8, 30.3, 37.3, 37.8, 38.5, 38.6, 40.7, 45.6, 47.6, 53.9, 56.3, 60.0, 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 141.2, 152.9, 173.9. MS (EI) *m/z* (%): 700 (M$^+$, 1), 568 (44), 511 (11), 366 (34), 351 (11), 234 (17), 147(22), 73 (100). HRMS (EI) calcd for $C_{42}H_{76}O_4Si_2$ 700.5282, found 700.5270. IR (neat) 2954, 2929, 2856, 1735, 1658, 1461, 1251, 1101, 1070, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

22*R*-Isomer of 14. ^{1}H NMR δ 0.03, 0.04, 0.07, 0.08 (each 3 H, s, SiMe), 0.56 (3 H, s, H-18), 0.79 (3 H, d, *J* = 6.7 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 1.26 (3 H, t, *J* = 7.1 Hz, −COOEt), 2.85 (1 H, m, H-9), 4.13 (2 H, q, *J* = 7.1 Hz, −COOEt), 4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.84 (1 H, d, *J* = 11.1 Hz, H-7), 6.21 (1 H, d, *J* = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 14.0, 14.2, 18.1, 18.2, 22.1, 22.8, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.5, 28.8, 29.6, 32.6, 34.8, 37.1, 37.3, 38.6, 40.6, 45.6, 47.5, 54.2, 56.3, 60.1, 71.6, 72.5, 106.2, 116.1, 122.4, 132.8, 140.9, 152.9, 174.5.

(3*S*)-3-{1-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}heptan-1-ol (16). In a similar manner to that for the synthesis of **11** from **10**, target compound **16** (287 mg, 0.436 mmol) was obtained from **14** (440 mg, 0.629 mmol) in 69% yield.

16. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.80 (3 H, d, *J* = 6.2 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.80 (1 H, m, H-9), 3.66 (2 H, m, H-24), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, *J* = 11.1 Hz, H-7), 6.21 (1 H, d, *J* = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.2, 14.2, 18.1, 18.2, 22.1, 23.2, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.8, 28.4, 28.7, 30.7, 35.3, 36.4, 38.0, 38.5, 40.6, 45.6, 47.6, 53.8, 56.3, 61.8, 71.6, 72.5, 106.2, 116.1, 122.4, 132.8, 141.1, 152.9. MS (EI) *m/z* (%): 658 (M$^+$, 1), 526 (28), 366 (5), 279 (13), 167(36), 149 (99), 73 (100). HRMS (EI) calcd for $C_{40}H_{74}O_3Si_2$ 658.5177, found 658.5170. IR (neat) 3301, 2952, 2927, 2893, 2856, 1461, 1380, 1255, 1101, 1072, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

22*S*-Butyl-2-methylidene-19,25,26,27-tetranor-1α,24-dihydroxyvitamin D$_3$ (3c). In a similar manner to that for the synthesis of **3a** from **11**, target compound **3c** (26.3 mg, 0.0609 mmol) was obtained from **16** (49.6 mg, 0.0753 mmol) in 81% yield.

3c. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.80 (3 H, d, *J* = 6.4 Hz, H-21), 0.89 (3 H, t, *J* = 7.0 Hz, CH$_3$ of Bu), 3.64 (2 H, m, H-24), 4.47 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, *J* = 11.3 Hz, H-7), 6.35 (1 H, d, *J* = 11.3 Hz, H-6). ^{13}C NMR δ 11.0, 12.2, 13.2, 21.2, 22.2, 22.5, 26.7, 27.3, 27.9, 29.7, 34.2, 35.4, 36.9, 37.1, 39.5, 44.7 (2 carbons), 52.8, 55.3, 60.8, 69.6, 70.8, 106.7, 114.3, 123.2, 129.4, 142.3, 150.9. MS (EI) *m/z* (%): 430 (M$^+$, 34), 315 (15), 297 (19), 269 (14), 251 (15), 161 (40), 147 (51), 135 (97), 69 (100). HRMS (EI) calcd for $C_{28}H_{46}O_3$ 430.3447, found 430.3447. IR (neat) 3332, 2925, 2869, 1772,

1658, 1620, 1444, 1379, 1263, 1072, 1045, 912, 738 cm^{-1}. UV (EtOH) λ_{max} 246, 254, 263 nm.

(4*S*)-4-{1-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}-2-methyloctan-2-ol (18). In a similar manner to that for the synthesis of **12** from **10**, target compound **18** (34.6 mg, 0.0504 mmol) was obtained from **14** (85.3 mg, 0.122 mmol) in 64% yield.

18. ^{1}H NMR δ 0.03, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.53 (3 H, s, H-18), 0.83 (3 H, d, *J* = 6.4 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 1.23 (6 H, s, H-25, 26), 2.82 (1 H, m, H-9), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, *J* = 11.1 Hz, H-7), 6.21 (1 H, d, *J* = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.0, 13.6, 14.2, 18.1, 18.2, 22.1, 23.2, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.5, 28.8, 29.3, 29.8, 30.5, 30.8, 36.1, 38.6, 40.1, 40.6, 45.6, 45.9, 47.5, 54.4, 56.2, 71.6, 71.9, 72.5, 106.2, 116.1, 122.4, 132.7, 141.2, 152.9. MS (EI) *m/z* (%): 686 (M$^+$, 1), 554 (28), 536 (7), 366 (24), 234 (12), 147 (12), 73 (100). HRMS (EI) calcd for $C_{42}H_{78}O_3Si_2$ 686.5490, found 686.5478. IR (neat) 3440, 2954, 2927, 2856, 1658, 1620, 1461, 1255, 1101, 1072, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 255, 264 nm.

22*S*-Butyl-2-methylidene-19,24-dinor-1α,25-dihydroxyvitamin D$_3$ (4c). In a similar manner to that for the synthesis of **3a** from **11**, target compound **4c** (16.2 mg, 0.0354 mmol) was obtained from **18** (34 mg, 0.0496 mmol) in 71% yield.

4c. ^{1}H NMR δ 0.54 (3 H, s, H-18), 0.82 (3 H, d, *J* = 6.3 Hz, H-21), 0.90 (6 H, t, *J* = 6.8 Hz, CH$_3$ of Bu), 1.22 (6 H, s, H-25, 26), 4.46 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, *J* = 11.2 Hz, H-7), 6.35 (1 H, d, *J* = 11.2 Hz, H-6). ^{13}C NMR δ 12.1, 13.6, 14.2, 22.1, 23.3, 23.5, 27.4, 29.0, 29.3, 29.9, 30.4, 30.8, 36.1, 38.1, 40.0, 40.5, 45.8 (2 carbons), 45.9, 54.4, 56.3, 70.6, 71.8, 71.9, 107.7, 115.3, 124.2, 130.4, 143.4, 152.0. MS (EI) *m/z* (%): 458 (M$^+$, 35), 161 (40), 135 (69), 69 (100). HRMS (EI) calcd for $C_{30}H_{50}O_3$ 458.3760, found 458.3770. IR (neat) 3353, 2952, 2927, 2869, 1612, 1454, 1380, 1074, 1045, 910, 896, 742 cm^{-1}. UV (EtOH) λ_{max} 246, 254, 263 nm.

Ethyl (3*S*)-4-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-3-ethylpentanoate (15). A suspension of CuBr/Me$_2$S (491 mg, 2.31 mmol) in THF (4 mL) was cooled to −30 °C, and to this solution was added EtLi (9.2 mL, 4.6 mmol, 0.5 M solution in benzene/cyclohexane = 90/10) and the mixture was stirred for 15 min. To this solution was added TMSCl (249 µL, 1.95 mmol), HMPA (341 µL, 1.95 mmol), and a solution of enoate **13** (178 mg, 0.278 mmol) in THF (2 mL) in this order. The mixture was stirred at −30 °C for 3.5 h, and the reaction was quenched with satd NH_4Cl. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 3/997) to afford **15** (103 mg, 0.153 mmol, 55%).

15. ^{1}H NMR δ 0.03, 0.05, 0.06, 0.07 (each 3 H, s, SiMe), 0.52 (3 H, s, H-18), 0.81 (3 H, d, *J* = 6.2 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 1.25 (3 H, t, *J* = 7.1 Hz, −COOEt), 2.80 (1 H, m, H-9), 4.13 (2 H, m, −COOEt), 4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, *J* = 11.1 Hz, H-7), 6.21 (1 H, d, *J* = 11.1 Hz, H-6). ^{13}C NMR δ −5.1, −4.9, −4.8 (2 carbons), 11.9, 12.7, 13.2, 14.3, 18.1, 18.2, 20.7, 22.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.3, 28.7, 37.3, 38.5 (2 carbons), 39.4, 40.6, 45.6, 47.6, 53.8, 56.3, 60.0, 71.6, 72.5, 106.2, 116.2, 122.3, 132.8, 141.0, 152.9, 173.8. MS (EI) *m/z* (%): 672 (M$^+$, 1), 540 (24), 366 (17), 234 (9), 147 (12), 129 (16) 73 (100). HRMS (EI) calcd for $C_{40}H_{72}O_4Si_2$ 672.4969, found 672.4959. IR (neat) 2954, 2929, 2883, 2856, 1735, 1658 1614, 1461, 1251, 1101, 1070, 935, 896, 835, 775, 696 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(3*S*)-4-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-3-ethylpentan-1-ol (17). In a similar manner to that for the synthesis of **11** from **10**, target compound **17** (246 mg, 0.390 mmol) was obtained from **15** (307.2 mg, 0.457 mmol) in 85% yield.

17. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.81 (3 H, d, J = 6.3 Hz, H-21), 0.86, 0.89 (each 9 H, s, t-Bu), 2.81 (1 H, m, H-9), 3.67 (2H, m, H-24), 4.42 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.1, 13.3, 18.1, 18.2, 21.1, 22.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.8, 28.7, 34.7, 38.0, 38.5 (2 carbons), 40.6, 45.6, 47.6, 53.9, 56.3, 61.8, 71.6, 72.5, 106.2, 116.1, 122.3, 132.8, 141.1, 152.9. MS (EI) m/z (%): 630 (M$^+$, 2), 498 (51), 366 (28), 351 (11), 234 (16), 147 (19), 73 (100). HRMS (EI) calcd for C$_{38}$H$_{70}$O$_3$Si$_2$ 630.4863, found 630.4863. IR (neat) 3313, 2952, 2927, 2883, 2856, 1658 1612, 1461, 1251, 1101, 1070, 1004, 935, 896, 835, 779 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

22*S*-Ethyl-2-methylidene-19,25,26,27-tetranor-1α,24-dihydroxyvitamin D$_3$ (3b). In a similar manner to that for the synthesis of **3a** from **11**, target compound **3b** (12.4 mg, 0.0307 mmol) was obtained from **17** (28.2 mg, 0.0228 mmol) in 69% yield.

3b. ^{1}H NMR δ 0.54 (3 H, s, H-18), 0.80 (3 H, d, J = 6.4 Hz, H-21), 0.90 (4 H, m), 3.66 (2H, m, H-24), 4.46 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). ^{13}C NMR δ 12.0, 13.1, 13.3, 21.2, 22.2, 23.5, 27.7, 28.9, 34.7, 37.9, 38.1, 38.5, 40.5, 45.7 (2 carbons), 53.9, 56.3, 61.8, 70.6, 71.8, 107.7, 115.3, 124.2, 130.5, 143.3, 151.9. MS (EI) m/z (%): 402 (M$^+$, 55), 315 (20), 297 (27), 251 (26), 173 (30),161 (58), 147 (75), 135 (100), 69 (92). HRMS (EI) calcd for C$_{26}$H$_{42}$O$_3$ 402.3134, found 402.3150. IR (neat) 3336, 2947, 2871, 1726, 1658, 1620, 1440, 1380, 1070, 1045, 1010, 754, 699 cm^{-1}. UV (EtOH) λ_{max} 245, 254, 263 nm.

(4*S*)-5-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-4-ethyl-2-methylhexan-2-ol (19). In a similar manner to that for the synthesis of **12** from **10**, target compound **19** (31.6 mg, 0.0480 mmol) was obtained from **15** (38.1 mg, 0.0567 mmol) in 85% yield.

19. ^{1}H NMR δ 0.03, 0.04, 0.06, 0.07 (each 3 H, s, SiMe), 0.53 (3 H, s, H-18), 0.83 (3 H, d, J = 6.4 Hz, H-21), 0.86, 0.89 (each 9 H, s, t-Bu), 1.24 (6 H, s, H-25, 26), 2.82 (1 H, m, H-9), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.1, −4.9, −4.8 (2 carbons), 12.0, 13.2, 13.6, 18.1, 18.2, 22.1 (2 carbons), 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.5, 28.8, 29.8, 30.5, 38.2, 38.6, 40.2, 40.6, 45.4, 45.6, 47.5, 54.5, 56.3, 71.6, 71.9, 72.4, 106.2, 116.1, 122.4, 132.8, 141.1, 152.9. MS (EI) m/z (%): 658 (M$^+$, 3), 526 (48), 508 (13), 366 (35), 351 (12), 234 (18), 147 (20), 97 (40), 73 (100). HRMS (EI) calcd for C$_{40}$H$_{74}$O$_3$Si$_2$ 658.5177, found 658.5196. IR (neat) 3394, 2954, 2927, 2885, 2856, 1658, 1620, 1469, 1461, 1251, 1101, 1070, 1004, 935, 896, 835, 779 cm^{-1}. UV (hexane) λ_{max} 246, 255, 264 nm.

22*S*-Ethyl-2-methylidene-19,24-dinor-1α,25-dihydroxyvitamin D$_3$ (4b). In a similar manner to that for the synthesis of **3a** from **11**, target compound **4b** (20.1 mg, 0.0467 mmol) was obtained from **19** (31.6 mg, 0.0480 mmol) in 97% yield.

4b. ^{1}H NMR δ 0.54 (3 H, s, H-18), 0.82 (3 H, d, J = 6.2 Hz, H-21), 0.88 (4 H, m), 1.23 (6 H, s, H-25, 26), 4.45 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.1 Hz, H-7), 6.35 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ 12.1, 13.2, 13.6, 22.0, 22.1, 23.5, 27.4, 29.0, 29.8, 30.4, 38.1, 38.2, 40.1, 40.5, 45.4, 45.7 (2 carbons), 54.5, 56.3, 70.6, 71.8, 71.9, 107.7, 115.3, 124.2, 130.5, 143.3, 151.9. MS (EI) m/z (%): 430 (M$^+$, 43), 161 (50), 135 (90), 97 (100). HRMS (EI) calcd for C$_{28}$H$_{46}$O$_3$ 430.3447, found 430.3462. IR (neat) 3373, 2958, 2871, 1726, 1649, 1612, 1461, 1379, 1074, 1045, 900, 865, 756, 669 cm^{-1}. UV (EtOH) λ_{max} 246, 254, 263 nm.

{[3-(Methylperoxy)propyl]sulfonyl}benzene (22). To a solution of 3-bromo-1-propanol (125 μL, 1.39 mmol) and diisopropylethylamine (725 μL, 4.16 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added methoxymethyl chloride (526 μL, 6.93 mmol) at 0 °C and the mixture was stirred for 1 h. The reaction was quenched with 1N HCl, and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was washed with aqueous NaHCO$_3$ and brine,

dried over MgSO$_4$, and evaporated. The residue was added to a solution of sodium thiophenoxide (225 mg, 1.53 mmol) in EtOH (1.7 mL), and the mixture was stirred for 1.5 h at room temperature. The mixture was diluted with 1N NaOH and extracted with benzene. The organic layer was washed with satd NH$_4$Cl and brine and evaporated. The residue was solved in CH$_2$Cl$_2$ (9 mL) and treated with m-chloroperbenzoic acid (195 mg, 2.87 mmol, 65%) for 2 h at room temperature. The mixture was diluted with CH$_2$Cl$_2$ and washed with 1N NaOH, satd NH$_4$Cl, and brine. The organic layer was dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/1) to afford **22** (211 mg, 0.865 mmol, 62% from 3-bromo-1-propanol).

20. ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.13 (2 H, tt, J = 6.3, 6.0 Hz, H-2), 3.37 (3 H, s, −O-CH$_3$), 3.53 (2 H, t, J = 6.3 Hz, H-3), 3.66 (2 H, t, J = 6.0 Hz, H-1), 4.63 (2 H, s, O-CH$_2$-O). ^{13}C NMR (100 MHz, CDCl$_3$) δ 30.8 (C-2), 33.2 (C-3), 55.6 (−O-Me), 65.4 (C-1), 96.9 (−O-CH$_2$-O−).

21. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.92 (2 H, tt, J = 7.1, 6.1 Hz, H-2), 3.03 (2 H, t, J = 7.1 Hz, H-3), 3.36 (3 H, s, −O-Me), 3.63 (2 H, t, J = 6.1 Hz, H-1), 4.61 (2 H, s, O−CH$_2$-O), 7.17 (1 H, td, J = 7.6, 1.2 Hz, arom-H), 7.28 (2 H, dd, J = 7.6, 7.3 Hz, arom-H), 7.34 (2 H, dd, J = 7.3, 1.2 Hz, arom-H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 29.7 (C-2), 30.7 (C-3), 55.6 (−O-Me), 66.3 (C-1), 96.9 (−O-CH$_2$-O−), 126.3, 129.3 (2 carbons), 129.6 (2 carbons), 136.8.

22. ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.01 (2 H, m, H-2), 3.23 (2 H, t, J = 7.8 Hz, H-3), 3.30 (3 H, s, −O-Me), 3.57 (2 H, t, J = 6.0 Hz, H-1), 4.55 (2 H, s, O-CH$_2$-O), 7.58 (2 H, dd, J = 6.9, 7.3 Hz, arom-H), 7.66 (1 H, t, J = 7.3 Hz, arom-H), 7.94 (2 H, d, J = 6.9 Hz, arom-H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 23.8 (C-2), 53.9 (C-3), 55.7 (−O-Me), 65.7 (C-1), 96.8 (−O-CH$_2$-O−), 128.4 (2 carbons), 129.7 (2 carbons), 134.1, 139.5.

(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-17-(1-iodopropan-2-yl)-2-methylidene-9,10-secoestra-5,7-diene (23). A mixture of tosylate **7** (102 mg, 0.141 mmol), sodium iodide (83.7 mg, 0.563 mmol), and lithium carbonate (43.7 mg, 0.591 mmol) in acetone (3 mL) was refluxed for 4 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 5/95) to afford **23** (94.2 mg, 98%).

23. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.58 (3 H, s, H-18), 0.86, 0.96 (each 9 H, s, t-Bu), 1.04 (3 H, d, J = 6.3 Hz, H-21), 2.82 (1 H, m, H-9), 3.18 (1 H, dd, J = 9.7, 5.7 Hz, H-22), 3.35 (1 H, dd, J = 9.7, 2.5 Hz, H-22), 4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.84 (1 H, d, J = 11.3 Hz, H-7), 6.20 (1 H, d, J = 11.3 Hz, H-6). Mass m/z (%): 684 (M$^+$, 10), 552 (100), 424 (28), 366 (28), 73 (49). HRMS calcd for C$_{34}$H$_{61}$O$_2$Si$_2$I 684.3255, found 684.3279. IR (neat) 2952, 2925, 2854, 1461, 1255, 1101, 1070, 835, 777 cm^{-1}.

(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-17-[6-(methoxymethyl)hexan-2-yl]-2-methylidene-9,10-secoestra-5,7-diene (25). To a solution of sulfone **22** (67.2 mg, 0.275 mmol) and diisopropylamine (195 μL, 1.39 mmol) in THF (0.5 mL) was added n-BuLi (481 μL, 0.687 mmol, 1.43 M hexane) at −20 °C and the mixture was stirred for 5 min. A solution of iodide **27** (94.2 mg, 0.138 mmol) and HMPA (479 μL, 2.76 mmol) in THF (0.5 mL) was added, and the mixture was stirred for 1 h. The reaction was quenched with satd NH$_4$Cl, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 10/90) to afford **24** (62.2 mg, 56%). Compound **24** was solved in THF/MeOH (3:2, 1.25 mL) and NaHPO$_4$ (223 mg, 1.57 mmol) and NaHg (368 mg, 1.64 mmol) were added at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction was quenched with 1N HCl and extracted with AcOEt. The organic layer was washed with aqueous NaHCO$_3$ and brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 10/90) to afford **25** (37.2 mg, 72%).

25. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.02, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.86, 0.89 (each 9 H, s, *t*-Bu), 0.93 (3 H, d, J = 6.4 Hz, H-21), 2.81 (1 H, m, H-9), 3.36 (3 H, s, −O-Me), 3.52 (2 H, t, J = 6.6 Hz, H-25), 4.42 (2 H, m, H-1, 3), 4.62 (2 H, s, −O-CH$_2$-O), 4.91, 4.96 (each 1 H, s, −C=CH$_2$ × 2), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). Mass *m/z* (%): 660 (21), 528 (100), 366 (44), 75 (34), 73 (36). HRMS calcd for C$_{39}$H$_{72}$O$_4$Si$_2$ 660.4969, found 660.4953.

2-Methylidene-19,26,27-trinor-1α,25-dihydroxyvitamin D$_3$ (5a). A solution of **25** in 3%HCl−MeOH was stirred at room temperature for 4 h. The mixture was evaporated, and the residue was chromatographed on silica gel (AcOEt/hexane = 80/20) to afford **5a** (8.3 mg, 53%).

5a. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.55 (3 H, s, H-18), 0.93 (3 H, d, J = 6.4 Hz, H-21), 3.65 (2 H, t, J = 6.5 Hz, H-25), 4.47 (2 H, m, H-1, 3), 5.09, 5.11 (each 1 H, s, −C=CH$_2$ × 2), 5.88 (1 H, d, J = 11.5 Hz, H-7), 6.35 (1 H, d, J = 11.5 Hz, H-6). ^{13}C NMR δ 12.1, 18.7, 22.2, 22.3, 23.5, 27.6, 28.9, 33.2, 35.6, 36.0, 38.1, 40.4, 45.8 (2 carbons), 56.3, 56.4, 63.1, 70.7, 71.8, 107.7, 115.3, 124.3, 130.3, 143.4, 151.9. MS (EI) *m/z* (%): 388 (100), 370 (23), 352 (26), 303 (34), 287 (47), 269 (44), 251 (49), 235 (29), 147 (47), 135 (39), 107 (44), 81 (36), 55 (36). HRMS (EI) calcd for C$_{25}$H$_{40}$O$_3$ 388.2977, found 388.2978. IR (neat) 3346, 2993, 2869, 1436, 1375, 1072, 1043, 754 cm^{-1}. UV (EtOH) λ_{max} 246, 254, 263 nm.

(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-17-{6-methyl-6-[(triethylsilyl)oxy]heptan-2-yl}-9,10-secoestra-5,7-diene (27). To a solution of **26** (631 mg, 2.25 mmol) in THF (2.5 mL) was added Mg turnings (54.2 mg, 2.25 mmol), and the mixture was stirred for 0.5 h. The resulting Grignard reagent was added to a solution of CuBr/Me$_2$S (11.3 mg, 0.0550 mmol) in THF (1 mL) at −10 °C, and the mixture was stirred for 15 min. To this solution was added **7** (36.7 mg, 0.0484 mmol) in THF (1 mL), and the mixture was stirred at −10 °C for 1 h. The reaction was quenched with satd NH$_4$Cl and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/99) to afford **27** (31.5 mg, 0.0416 mmol, 86%).

27. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.55 (3 H, s, H-18), 0.56 (6H, dt, J = 7.7, 8.0 Hz, −SiCH$_2$−), 0.86, 0.89 (each 9 H, s, *t*-Bu), 0.92 (3 H, m, H-21), 0.95 (9H, dd, J = 7.7, 8.0 Hz, −SiCH$_2$Me), 1.19 (6H, s, H-26, 27), 2.83 (1 H, m, H-9), 4.42 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6).

2-Methylidene-19-nor-1α,25-dihydroxyvitamin D$_3$ (6a). In a similar manner to that for the synthesis of **3a** from **11**, target compound **6a** (14.6 mg, 0.0351 mmol) was obtained from **27** (31.1 mg, 0.0410 mmol) in 86% yield.

6a. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.94 (3 H, d, J = 6.3 Hz, H-21), 1.21 (6H, s, H-26, 27), 4.47 (2 H, m, H-1, 3), 5.09, 5.11 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). UV (EtOH) λ_{max} 246, 254, 263 nm.

(3S)-3-{1-[(1R,3R,7E,17β)-1,3-bis{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}heptyl 4-methylbenzenesulfonate (28). In a similar manner to that for the synthesis of **29** from **17**, target compound **28** (285 mg, 0.351 mmol) was obtained from **16** (287 mg, 0.436 mmol) in 80% yield.

28. ^{1}H NMR δ 0.04, 0.05, 0.08, 0.09 (each 3 H, s, SiMe), 0.48 (3 H, s, H-18), 0.72 (3 H, d, J = 6.6 Hz, H-21), 0.88, 0.89 (each 9 H, s, *t*-Bu), 2.81 (1 H, m, H-9), 2.45 (3 H, s, Ph-Me), 2.80 (1 H, m, H-9), 4.09 (2 H, m, H-24), 4.44 (2 H, m, H-1, 3), 4.93, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6), 7.33 (2 H, d, J = 8.4 Hz, arom-H), 7.80 (2 H, d, J = 8.4 Hz, arom-H). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 14.1, 18.1, 18.2, 21.6, 22.1, 23.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.6, 28.0, 28.7, 30.5, 31.1, 36.2, 37.6, 38.6, 40.6, 45.6, 47.5, 53.6, 56.2, 69.6, 71.7, 72.3, 106.2, 116.2, 122.4, 127.8 (2 carbons), 129.7 (2 carbons), 132.8, 133.4, 140.9, 144.5, 152.9. MS (EI) *m/z* (%): 812 (M$^+$, 1), 680 (10), 366

(36), 251 (16), 73 (100). HRMS (EI) calcd for C$_{47}$H$_{80}$O$_5$Si$_2$ 812.5265, found 812.5267. IR (neat) 2952, 2927, 2891, 2856, 1361, 1251, 1188, 1099, 1070, 935, 896, 835, 775, 667 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(4S)-4-{1-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}octanenitrile (30). In a similar manner to that for the synthesis of **31** from **29**, target compound **30** (212 mg, 0.318 mmol) was obtained from **28** (284 mg, 0.351 mmol) in 91% yield.

30. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.55 (3 H, s, H-18), 0.79 (3 H, d, J = 6.4 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.83 (1 H, m, H-9), 4.42 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.84 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.0, 12.9, 14.1, 15.7, 18.1, 18.2, 22.1, 23.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.4, 27.7, 28.0, 28.7, 30.5, 36.8, 38.5, 39.3, 40.6, 45.6, 47.6, 53.5, 56.3, 71.6, 72.5, 106.2, 116.2, 119.8, 122.4, 133.0, 140.8, 152.9. MS (EI) *m/z* (%): 667 (M$^+$, 1), 535 (21), 478 (33), 366 (17), 73 (100). HRMS (EI) calcd for C$_{41}$H$_{73}$NO$_2$Si$_2$ 667.5180, found 667.5151. IR (neat) 2952, 2927, 2883, 2856, 2245, 1461, 1251, 1101, 1072, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(4S)-4-{1-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}octanal (32). In a similar manner to that for the synthesis of **33** from **31**, target compound **32** (166 mg, 0.248 mmol) was obtained from **30** (212 mg, 0.318 mmol) in 78% yield.

32. ^{1}H NMR δ 0.02, 0.05, 0.06, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.78 (3 H, d, J = 6.3 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.83 (1 H, m, H-9), 4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.0 Hz, H-7), 6.21 (1 H, d, J = 11.0 Hz, H-6) 9.78 (1 H, t, J = 1.9 Hz, −CHO). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 12.9, 14.2, 18.1, 18.2, 22.1, 23.2, 23.4, 24.0, 25.7 (3 carbons), 25.8 (3 carbons), 27.8, 28.5, 28.7, 30.8, 37.1, 38.5, 39.7, 40.6, 42.6, 45.6, 47.6, 53.7, 56.3, 71.6, 72.5, 106.2, 116.2, 122.4, 132.8, 141.0, 152.9, 203.1. MS (EI) *m/z* (%): 670 (M$^+$, 2), 538 (50), 366 (33), 149 (25), 73 (100). HRMS (EI) calcd for C$_{41}$H$_{74}$O$_3$Si$_2$ 670.5177, found 670.5151. IR (neat) 2952, 2927, 2891, 2856, 1728, 1658, 1620, 1461, 1255, 1101, 1072, 935, 896, 835, 777 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(4S)-4-{1-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}octan-1-ol (34). In a similar manner to that for the synthesis of **35** from **33**, target compound **34** (43.1 mg, 0.0641 mmol) was obtained from **32** (46.7 mg, 0.0697 mmol) in 92% yield.

34. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.78 (3 H, d, J = 5.6 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.83(1 H, m, H-9), 3.63 (2 H, dt, J = 1.7, 6.5 Hz, H-25), 4.45 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.22 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 12.0, 13.0, 14.2, 18.1, 18.2, 22.2, 23.3, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.7, 27.8, 28.7, 28.8, 30.9, 31.3, 37.2, 38.5, 39.8, 40.6, 45.6, 47.6, 53.8, 56.3, 63.5, 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 141.2, 152.9. MS (EI) *m/z* (%): 672 (M$^+$, 2), 540 (46), 366 (30), 147 (19), 73 (100). HRMS (EI) calcd for C$_{41}$H$_{76}$O$_3$Si$_2$ 672.5333, found 672.5326. IR (neat) 3328, 2952, 2927, 2893, 2856, 1612, 1461, 1251, 1101, 1072, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

22S-Butyl-2-methylidene-19,26,27-trinor-1α,25-dihydroxyvitamin D$_3$ (5c). In a similar manner to that for the synthesis of **3a** from **11**, target compound **5c** (18.4 mg, 0.0414 mmol) was obtained from **34** (43.1 mg, 0.0641 mmol) in 65% yield.

5c. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.77 (3 H, d, J = 6.0 Hz, H-21), 0.89 (3 H, t, J = 6.9 Hz, CH$_3$ of Bu), 3.62 (2 H, dt, J = 1.6, 6.5 Hz, H-25), 4.46 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). ^{13}C NMR δ 12.0, 13.0, 14.2, 22.2, 23.3, 23.5, 27.7, 27.8, 28.7, 29.0, 30.9, 31.2, 37.2, 38.1, 39.8, 40.5, 45.7, 45.8, 53.8,

56.4, 63.4, 70.6, 71.8, 107.7, 115.3, 124.2, 130.4, 143.4, 152.0. MS (EI) m/z (%): 444 (M$^+$, 32), 315 (29), 297 (28), 161 (40), 147(52), 135 (100), 69 (89). HRMS (EI) calcd for $C_{29}H_{48}O_3$ 444.3603, found 444.3589. IR (neat) 3346, 2927, 2864, 1448, 1380, 1072, 1045, 756 cm^{-1}. UV (EtOH) λ_{max} 246, 254, 263 nm.

Methyl (4S)-4-{1-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)-silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}oct-anoate (36). In a similar manner to that for the synthesis of **37** from **33**, target compound **36** (96.8 mg, 0.138 mmol) was obtained from **32** (106.5 mg, 0.159 mmol) in 87% yield.

36. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.78 (3 H, d, J = 6.1 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.82 (1 H, m, H-9), 3.67 (3 H, m, −COOMe), 4.43 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 14.2, 18.1, 18.2, 22.1, 23.2, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.0, 27.7, 28.4, 28.7, 30.7, 37.0, 38.5, 39.6, 40.6, 45.6, 47.6, 51.4, 53.7, 56.3, 71.6, 72.5, 106.2, 116.1, 122.4, 132.8, 141.2, 152.9, 174.5. MS (EI) m/z (%): 700 (M$^+$, 3), 568 (61), 366 (45), 147 (27), 73 (100). HRMS (EI) calcd for $C_{42}H_{76}O_4Si_2$ 700.5282, found 700.5270. IR (neat) 2952, 2927, 2891, 2856, 1741, 1461, 1255, 1101, 1070, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(5S)-5-{1-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]ethyl}-2-met-hylnonan-2-ol (38). In a similar manner to that for the synthesis of **12** from **10**, target compound **38** (22.8 mg, 0.0326 mmol) was obtained from **36** (40 mg, 0.0571 mmol) in 57% yield.

38. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.55 (3 H, s, H-18), 0.77 (3 H, d, J = 5.8 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 1.22 (6 H, s, H-26, 27), 2.82(1 H, m, H-9), 4.42 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.82 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.1, −4.9, −4.8 (2 carbons), 12.0, 12.9, 14.2, 18.1, 18.2, 22.1, 23.3 (2 carbons), 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 26.4, 27.7, 28.8, 29.0, 29.3, 31.0, 37.2, 38.5, 40.5, 40.7, 42.3, 45.6, 47.6, 53.8, 56.3, 71.2, 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 141.2, 152.9. MS (EI) m/z (%): 700 (M$^+$, 1), 568 (21), 550 (11), 366 (21), 73 (100). HRMS (EI) calcd for $C_{43}H_{80}O_3Si_2$ 700.5646, found 700.5651. IR (neat) 3381, 2954, 2927, 2894, 2856, 1658, 1616, 1461, 1251, 1101, 1072, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

22S-Butyl-2-methylidene-19-nor-1α,25-dihydroxyvitamin D$_3$ (6c). In a similar manner to that for the synthesis of **3c** from **11**, target compound **6c** (12.6 mg, 0.02700 mmol) was obtained from **38** (22.8 mg, 0.0326 mmol) in 82% yield.

6c. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.77 (3 H, d, J = 6.0 Hz, H-21), 0.90 (3 H, t, J = 6.9 Hz, CH$_3$ of Bu), 1.22 (6 H, s, H-26, 27), 4.47 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). ^{13}C NMR δ 12.0, 12.9, 14.2, 22.2, 23.3, 23.5, 26.3, 27.7, 28.8, 29.0, 29.1, 29.3, 31.0, 37.2, 38.1, 40.5 (2 carbons), 42.3, 45.7, 45.8, 53.8, 56.4, 70.6, 71.2, 71.9, 107.7, 115.3, 124.2, 130.4, 143.4, 152.0. MS (EI) m/z (%): 472 (M$^+$, 29), 161 (36), 147 (42), 135 (78), 69 (100). HRMS (EI) calcd for $C_{31}H_{52}O_3$ 472.3916, found 472.3909. IR (neat) 3365, 2948, 2927, 2869, 1456, 1380, 1199, 1043, 669 cm^{-1}. UV (EtOH) λ_{max} 246, 254, 263 nm.

(3S)-4-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-3-ethylpentyl 4-Methylbenzenesulfonate (29). To a solution of alcohol **17** (222 mg, 0.352 mmol) in pyridine (1.5 mL) was added *p*-toluenesul-fonyl chloride (229 mg, 2.07 mmol) at 0 °C, and the mixture was stirred for 4 h. To this solution was added 1N HCl, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 1/99) to afford **29** (234 mg, 0.298 mmol, 85%).

29. ^{1}H NMR δ 0.04 (6 H, s, SiMe), 0.07, 0.08 (each 3 H, s, SiMe), 0.47 (3 H, s, H-18), 0.72 (3 H, d, J = 6.6 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.44 (3 H, s, Ph-Me), 2.79 (1 H, m, H-9),

4.09 (2 H, m, H-24), 4.43 (2 H, m, H-1, 3), 4.93, 4.96 (each 1 H, s, −C=CH$_2$), 5.85 (1 H, d, J = 11.1 Hz, H-7), 6.20 (1 H, d, J = 11.1 Hz, H-6), 7.33 (2 H, d, J = 8.4 Hz, arom-H), 7.80 (2 H, d, J = 8.4 Hz, arom-H). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 12.8, 13.1, 18.1, 18.2, 21.0, 21.6, 22.1, 23.4, 25.82 (3 carbons), 25.84 (3 carbons), 27.5, 28.7, 30.6, 37.6, 38.3, 38.6, 40.6, 45.5, 47.5, 53.7, 56.3, 69.5, 71.7, 72.4, 106.2, 116.2, 122.4, 127.8 (2 carbons), 129.7 (2 carbons), 132.8, 133.4, 140.9, 144.5, 152.9. MS (EI) m/z (%): 784 (M$^+$, 1), 652 (8), 366 (30), 349 (12), 251 (12), 147 (14), 73 (100). HRMS (EI) calcd for $C_{45}H_{76}O_5SSi_2$ 784.4952, found 784.4974. IR (neat) 2952, 2927, 2883, 2856, 1658 1598, 1461, 1357, 1251, 1188, 1178, 1099, 1070, 935, 896, 835, 775, 665 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(4S)-5-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-4-ethylhexanenitrile (31). A solution of tosylate **29** (239 mg, 0.305 mmol) and KCN (55.8 mg, 0.8579 mmol) in DMSO (7 mL) was stirred at 70 °C for 1 h. The reaction was quenched with water and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromato-graphed on silica gel (AcOEt/hexane = 5/95) to afford **31** (170 mg, 0.2665 mmol, 87%).

31. ^{1}H NMR δ 0.02, 0.04, 0.06, 0.07 (each 3 H, s, SiMe), 0.55 (3 H, s, H-18), 0.79 (3 H, d, J = 6.4 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.81 (1 H, m, H-9), 4.42 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.20 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 12.9, 13.0, 15.7, 18.1, 18.2, 20.9, 22.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 26.9, 27.7, 28.7, 36.8, 38.5, 40.6, 41.3, 45.6, 47.6, 53.6, 56.3, 71.6, 72.5, 106.2, 116.3, 119.9, 122.2, 132.9, 140.7, 152.9. MS (EI) m/z (%): 639 (M$^+$, 1), 507 (33), 450 (51), 366 (19), 147 (16), 73 (100). HRMS (EI) calcd for $C_{39}H_{69}NO_2Si_2$ 639.4867, found 639.4865. IR (neat) 2954, 2929, 2885, 2856, 2244, 1658 1620, 1461, 1251, 1101, 1072, 935, 896, 835, 775 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(4S)-5-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-4-ethylhexanal (33). Cyanide **31** (170 mg, 0.267 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with DIBALH (400 μL of 1.0 M toluene solution, 0.400 mmol) at −20 °C for 1 h. The reaction was quenched with aqueous potassium sodium tartrate and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 5/95) to afford aldehyde **33** (132 mg, 0.205 mmol, 77%).

33. ^{1}H NMR δ 0.02, 0.04, 0.06, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.78 (3 H, d, J = 6.3 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.82 (1 H, m, H-9), 4.42 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.82 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6) 9.78 (1 H, t, J = 1.8 Hz, −CHO). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 13.1, 18.1, 18.2, 21.3, 22.1, 23.4, 23.5, 25.7 (3 carbons), 25.8 (3 carbons), 27.7, 28.7, 37.1, 38.5, 40.6, 41.8, 42.5, 45.6, 47.6, 53.8, 56.3, 71.6, 72.5, 106.2, 116.2, 122.3, 132.8, 140.9, 152.9, 202.9. MS (EI) m/z (%): 642 (M$^+$, 1), 510 (22), 366 (15), 147 (13), 73 (100). HRMS (EI) calcd for $C_{39}H_{70}O_4Si_2$ 642.4864, found 642.4890. IR (neat) 2954, 2929, 2885, 2856, 1726, 1620, 1461, 1251, 1101, 1072, 896, 835, 777, 669 cm^{-1}. UV (hexane) λ_{max} 246, 254, 264 nm.

(4S)-5-[(1R,3R,7E,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-4-ethylhexan-1-ol (35). To a solution of aldehyde **33** (36.7 mg, 0.0572 mmol) in MeOH/CH$_2$Cl$_2$ (1:1, 2 mL) was added NaBH$_4$ (12.0 mg, 0.317 mmol) at 0 °C, and the mixture was stirred for 1 h. To the solution was added water and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 5/95) to afford **35** (36.5 mg, 0.0561 mmol, 98%).

35. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.77 (3 H, d, J = 5.9 Hz, H-21), 0.86, 0.89 (each 9 H,

s, *t*-Bu), 2.80 (1 H, m, H-9), 3.64 (2 H, dt, J = 2.3, 6.6 Hz, H-25), 4.45 (2 H, m, H-1, 3), 4.92, 4.97 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 13.2, 18.1, 18.2, 21.5, 22.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 27.3, 27.7, 28.7, 31.3, 37.2, 38.5, 40.7, 41.9, 45.6, 47.6, 53.9, 56.3, 63.5, 71.6, 72.5, 106.2, 116.3, 122.4, 132.8, 141.1, 152.9. MS (EI) *m/z* (%): 644 (M$^+$, 1), 512 (24), 366 (20), 73 (100). HRMS (EI) calcd for C$_{39}$H$_{72}$O$_3$Si$_2$ 644.5020, found 644.5015. IR (neat) 3352, 2952, 2927, 2883, 2856, 1612, 1461, 1251, 1101, 1070, 835, 775 cm^{-1}. UV (hexane) λ$_{max}$ 246, 254, 264 nm.

22*S*-Ethyl-2-methylidene-19,26,27-trinor-1α,25-dihydroxyvitamin D$_3$ (5b). In a similar manner to that for the synthesis of **3a** from **11**, target compound **5b** (15.1 mg, 0.0366 mmol) was obtained from **35** (36.5 mg, 0.0561 mmol) in 65% yield.

5b. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.77 (3 H, d, J = 6.1 Hz, H-21), 0.88 (4 H, m), 3.63 (2H, m, H-25), 4.46 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). ^{13}C NMR δ 12.0, 13.0, 13.2, 21.5, 22.2, 23.5, 27.3, 27.7, 29.0, 31.2, 37.2, 38.1, 40.5, 41.9, 45.7, 45.8, 53.9, 56.4, 63.4, 70.6, 71.8, 107.7, 115.3, 124.2, 130.4, 143.3, 151.9. MS (EI) *m/z* (%): 416 (M$^+$, 41), 315 (30), 297 (28), 251 (19), 161 (45), 147(61), 135 (100), 69 (84). HRMS (EI) calcd for C$_{27}$H$_{44}$O$_3$ 416.3291, found 416.3310. IR (neat) 3338, 2945, 2871, 1652, 1612, 1442, 1380, 1072, 1045, 912, 756 cm^{-1}. UV (EtOH) λ$_{max}$ 246, 254, 263 nm

Methyl (4*S*)-5-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]-oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-4-ethylhexanoate (37). To a solution of aldehyde **33** (95 mg, 0.148 mmol) in MeOH (10 mL) was added KOH (36 mg, 0.546 mmol) and then iodine (55.5 mg, 0.219 mmol) at 0 °C, and the mixture was stirred for 1 h. The reaction was quenched with 10%Na$_2$SO$_3$, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was chromatographed on silica gel (AcOEt/hexane = 5/95) to afford **37** (67.2 mg, 0.1000 mmol, 68%).

37. ^{1}H NMR δ 0.02, 0.04, 0.06, 0.08 (each 3 H, s, SiMe), 0.54 (3 H, s, H-18), 0.78 (3 H, d, J = 6.2 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 2.82 (1 H, m, H-9), 3.67 (3 H, m, −COOMe), 4.43 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 18.1, 18.2, 21.3, 22.1, 23.4, 25.7 (3 carbons), 25.8 (3 carbons), 26.4, 27.7, 28.7, 32.8, 37.0, 38.5, 40.6, 41.8, 45.6, 47.6, 51.4, 53.8, 56.3, 71.6, 72.5, 106.2, 116.1, 122.3, 132.8, 141.0, 152.9, 174.5. MS (EI) *m/z* (%): 672 (M$^+$, 4), 540 (61), 366 (39), 234 (18), 147 (26), 73 (100). HRMS (EI) calcd for C$_{40}$H$_{72}$O$_4$Si$_2$ 672.4969, found 672.4974. IR (neat) 2952, 2927, 2885, 2856, 1741, 1658, 1620, 1461, 1251, 1101, 1070, 935, 896, 835, 775, 667 cm^{-1}. UV (hexane) λ$_{max}$ 246, 254, 264 nm.

(5*S*)-6-[(1*R*,3*R*,7*E*,17β)-1,3-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylidene-9,10-secoestra-5,7-dien-17-yl]-5-ethyl-2-methylheptan-2-ol (39). In a similar manner to that for the synthesis of **12** from **10**, target compound **39** (29.8 mg, 0.0443 mmol) was obtained from **37** (33.9 mg, 0.0505 mmol) in 88% yield.

39. ^{1}H NMR δ 0.03, 0.05, 0.07, 0.08 (each 3 H, s, SiMe), 0.55 (3 H, s, H-18), 0.77 (3 H, d, J = 5.9 Hz, H-21), 0.86, 0.89 (each 9 H, s, *t*-Bu), 1.22 (6 H, s, H-26, 27), 2.80 (1 H, m, H-9), 4.42 (2 H, m, H-1, 3), 4.92, 4.96 (each 1 H, s, −C=CH$_2$), 5.83 (1 H, d, J = 11.1 Hz, H-7), 6.21 (1 H, d, J = 11.1 Hz, H-6). ^{13}C NMR δ −5.0, −4.9, −4.8 (2 carbons), 11.9, 13.0, 13.3, 18.1, 18.2, 21.6, 22.1, 23.4, 25.7 (3 carbons), 25.8 (4 carbons), 27.7, 28.8, 29.1, 29.3, 37.3, 38.5, 40.7, 42.3, 42.5, 45.6, 47.6, 53.9, 56.3, 71.2, 71.6, 72.5, 106.2, 116.1, 122.4, 132.7, 141.2, 152.9. MS (EI) *m/z* (%): 672 (M$^+$, 1), 540 (24), 522 (12), 366 (20), 234 (13), 147(13), 73 (100). HRMS (EI) calcd for C$_{41}$H$_{76}$O$_3$Si$_2$ 672.5333, found 672.5341. IR (neat) 3357, 2954, 2927, 2891, 2856, 1650, 1612, 1461, 1373, 1251, 1101, 1072, 835, 775 cm^{-1}. UV (hexane) λ$_{max}$ 246, 254, 264 nm.

22*S*-Ethyl-2-methylidene-19-nor-1α,25-dihydroxyvitamin D$_3$ (6b). In a similar manner to that for the synthesis of **3a** from

11, target compound **6b** (12.3 mg, 0.0307 mmol) was obtained from **39** (28.2 mg, 0.0448 mmol) in 69% yield.

6b. ^{1}H NMR δ 0.55 (3 H, s, H-18), 0.77 (3 H, d, J = 6.1 Hz, H-21), 0.89 (4 H, m), 1.25 (6 H, s, H-26, 27), 4.46 (2 H, m, H-1, 3), 5.08, 5.10 (each 1 H, s, −C=CH$_2$), 5.88 (1 H, d, J = 11.2 Hz, H-7), 6.35 (1 H, d, J = 11.2 Hz, H-6). ^{13}C NMR δ 12.0, 13.0, 13.2, 21.6, 22.1, 23.5, 25.7, 27.6, 29.0, 29.1, 29.3, 37.2, 38.1, 40.5, 42.3, 42.5, 45.7, 45.8, 53.9, 56.4, 70.6, 71.2, 71.8, 107.7, 115.3, 124.2, 130.4, 143.4, 152.0. MS (EI) *m/z* (%): 444 (M$^+$, 27), 161 (38), 147(45), 135 (85), 69 (100). HRMS (EI) calcd for C$_{29}$H$_{48}$O$_3$ 444.3603, found 444.3595. IR (neat) 3371, 2960, 2871, 1658, 1612, 1461, 1379, 1215, 1074, 1045, 910, 756 cm^{-1}. UV (EtOH) λ$_{max}$ 246, 254, 263 nm.

Competitive Binding Assay, Human VDR. The human recombinant VDR ligand-binding domain (LBD) was expressed as an N-terminal GST-tagged protein in *E. coli* BL21 (DE3) pLys S (Promega).[18] The cells were lysed by sonication. The supernatants were diluted approximately 500 times in 50 mM Tris buffer (100 mM KCl, 5 mM DTT, 0.5%CHAPS, pH 7.5) containing bovine serum albumin (100 μg/mL). Binding to GST-hVDR-LBD was evaluated according to the procedure reported.[35] The receptor solution (570 μL) in an assay tube was incubated with [^{3}H]-1,25-(OH)$_2$D$_3$ (specific activity, 5.85 TBq/mmol, ca. 2000 cpm) together with graded amounts of each vitamin D analogue (0.001−100 nM) or vehicle for 16 h at 4 °C. The bound and free [^{3}H]-1,25-(OH)$_2$D$_3$ were separated by treating with dextran-coated charcoal for 30 min at 4 °C. The assay tubes were centrifuged at 1000*g* for 10 min. The radioactivity of the supernatant was counted. Nonspecific binding was subtracted. These experiments were done in duplicate.

Transfection and Transactivation Assay. COS-7 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% fetal bovine serum (FBS). Cells were seeded on 24-well plates at a density of 2×10^4 per well. After 24 h, the cells were transfected with a reporter plasmid containing three copies of the mouse osteopontin VDRE (5′-GGTTCAcgaGGTTCA, SPPx3-TK-Luc), a wild-type hVDR expression plasmid (pCMX-hVDR), and the internal control plasmid containing sea pansy luciferase expression constructs (pRL-CMV) by the lipofection method as described previously.[10] After 8 h incubation, the cells were treated with either the ligand or ethanol vehicle and cultured for 16 h. Cells in each well were harvested with a cell lysis buffer, and the luciferase activity was measured with a luciferase assay kit (Promega, WI). Transactivation measured by the luciferase activity was normalized with the internal control. All experiments were done in triplicate.

RXR and SRC-1 Recruitment. Recruitment of RXRα and SRC-1 to VDR by synthetic vitamin D analogues and 1,25-(OH)$_2$D$_3$ (**1**) were assessed using Cos7 cells. The activities were evaluated by a dual luciferase assay using VP16-VDR expression plasmid (pCMX-VP16-hVDR), RXRα or SRC-1 expression plasmid (GAL4-RXRα or GAL4-SRC-1), a reporter plasmid containing four copies of GAL4 response element (MH100 × 4-TK-Luc), and the internal control plasmid containing sea pansy luciferase expression construct (pRL-CMV). All experiments were carried out in triplicate.

Graphical Manipulations and Ligand Docking. Graphical manipulations were performed using SYBYL 8.0 (Tripos, St. Louis, MO). The atomic coordinates of the crystal structure of rVDR-LBD complexed with **1** were retrieved from Protein Data Bank (PDB) (entry 2ZLC).[31] 22-Butyl vitamin D analogues (**6c**, **5c**) were docked into the ligand-binding pocket using Surflex Dock 2.0 (Tripos, St. Louis).

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