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Efficient Synthesis of 2-Modified 1α,25-Dihydroxy-19-norvitamin D_3 with Julia Olefination: High Potency in Induction of Differentiation on HL-60 Cells

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Six novel 2-substituted analogues of 1α,25-dihydroxy-19-norvitamin D_3, **6a**,**b**−**8a**,**b**, were efficiently synthesized utilizing (−)-quinic acid as the A-ring precursor. The C2-modified A-rings were prepared as 4-alkylated (3*R*,5*R*)-3,5-dihydroxycyclohexanones **12**−**15** from (−)-quinic acid based on radical allylation at the C4 position of methyl (−)-quinicate. The new type of the CD-ring coupling partner **23** was synthesized from 25-hydroxy Grundmann's ketone **19** to apply to the modified Julia olefination to construct a diene unit between the A-ring and the CD-ring. The coupling yields, including a deprotection step, were 47−62%. After the separation of the diastereomers based on C2 stereochemistry, the structure (2α or 2β) was determined by ^{1}H NMR experiments and compared to DeLuca's 2-methyl- and 2-ethyl-1α,25-dihydroxy-19-norvitamin D_3. Thus, the synthesized 2α-(3-hydroxypropyl)-1α,25-dihydroxy-19-norvitamin D_3 (**8a**) showed almost the same potency in binding to the bovine thymus vitamin D receptor (VDR) as the natural hormone **1**, while its β-isomer **8b** had only a 3% affinity. Both 2α-allyl- and 2α-propyl-1α,25-dihydroxy-19-norvitamin D_3 (**6a** and **7a**) and their 2β-analogues (**6b** and **7b**) possessed a weak affinity for the VDR. The strong VDR ligand **8a** was ca. 36-fold more potent in induction of HL-60 cell differentiation than **1**, and interestingly, even the weaker ligand **8b** showed a 6.7-fold higher potency in the cell differentiation activity than that of **1**.

Introduction

Recently, the A-ring modifications of 1α,25-dihydroxyvitamin D_3 (**1**) have received much attention as potential drugs for the treatment of osteoporosis,[1] psoriasis,[2] hereditary vitamin D-resistant rickets,[3] and chemoprevention of cancer and cancer chemotherapy, especially prostate cancer, colon cancer, and breast cancer.[4] The stereochemistries of both hydroxyl groups at C1 and C3 of the A-ring are essential features for induction of cell differentiation and apoptosis.[5] We previously reported that 2α-substituted analogues of **1** can exhibit enhanced vitamin D receptor (VDR)[6] agonist activities.[7−11] On the other hand, 19-nor A-ring analogues such as 1α,25-dihydroxy-19-norvitamin D_3 (**5**, Figure 1) were first reported in 1990.[12] This 19-nor analogue **5** showed a selective activity profile, combining high potency in inducing differentiation of malignant cells with very low or no bone calcification activity.[13] Further modifications

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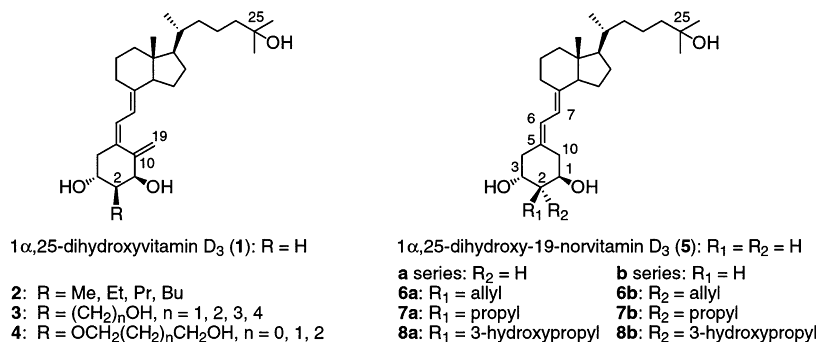

FIGURE 1. Structures of the natural hormone **1** and its 2α-substituted analogues (**2**−**4**),[7−11] 1α,25-dihydroxy-19-norvitamin D_3 (**5**), and its 2-substituted analogues (**6a**,**b**−**8a**,**b**).

to the 19-nor A-ring were also studied, such as the deletion of one of the hydroxyls[14] and the introduction of a 2α-methyl group.[15,16] However, removal of the 10(19)-methylene group reduces the VDR affinity due to its loss of hydrophobic interaction with the ligand-binding domain (LBD) of the VDR. The binding affinity of **5** for the porcine VDR has been reported as 30% of that of **1**,[17] and in our present experiments for the bovine thymus VDR, it was 17%. Recently, we synthesized the stable amide analogues of **5**, which contain a N5−C6 amide bond (similar to the steroidal numbering) instead of the diene system. However, these amide analogues showed almost no affinity to the VDR.[18]

Since we found that the introduction of the 2α-(3-hydroxypropyl) group to **1** resulted in a 3-fold higher binding affinity for the VDR,[8] we expected that 2α-(3-hydroxypropyl)-1α,25-dihydroxy-19-norvitamin D_3 (**8**) might restore the binding affinity for the VDR up to the level of the natural hormone. This type of compound would show a unique biological activity profile of vitamin D. DeLuca's synthetic approach for 19-norvitamin D analogues was based on the Horner−Wadsworth−Emmons coupling reaction to construct the diene system,[15,19] which was developed by Lythgoe et al.[20] However, utilization of this method for our synthetic goal was found to be unsuitable, because a Horner−Wadsworth−Emmons coupling between any of our 2-substituted A-ring phosphine oxides (**16**−**18**) and the known 25-*O*-protected 25-hydroxy Grundmann's ketone **20**[21] was unsuccessful. The CD-ring precursor could be elaborated to incorporate the C6−C7 fragment, such as sulfone **23**, for the subsequent Julia-type coupling with 2-substituted A-ring ketones **12**, **13**, and **15**.

Results and Discussion

Chemistry. Thioimidazolide **9**,[12b] the A-ring precursor, was allylated[22] to afford methyl 4-allylquinicate **10** in 60% yield. Reduction of **10** with $NaBH_4$ in EtOH and the subsequent oxidative cleavage of the resulting vicinal diol using $NaIO_4$ gave ketone **12**, which was the first 2-substituted A-ring precursor, in 82% yield in two steps.[23] Hydrogenation of **12** on 10% Pd/C gave (*R*,*R*)-3,5-dihydroxy-4-propylcyclohexanone **13**, the second 2-substituted A-ring precursor, in 99% yield. When **10** was first submitted to hydroboration, then reduced and cleaved with periodate as before, **14** was produced in 68% overall yield. Protection of the terminal hydroxyl group with TBSCl resulted in a quantitative yield to afford **15**, which was the third 2-substituted A-ring precursor (Scheme 1).

Initially, these three ketones were converted to the corresponding phosphine oxides **16**−**18** using the conventional method,[12b] but all of the Horner−Wadsworth−Emmons coupling reactions with 25-*O*-MOM-protected Grundmann's ketone **20** under basic conditions were

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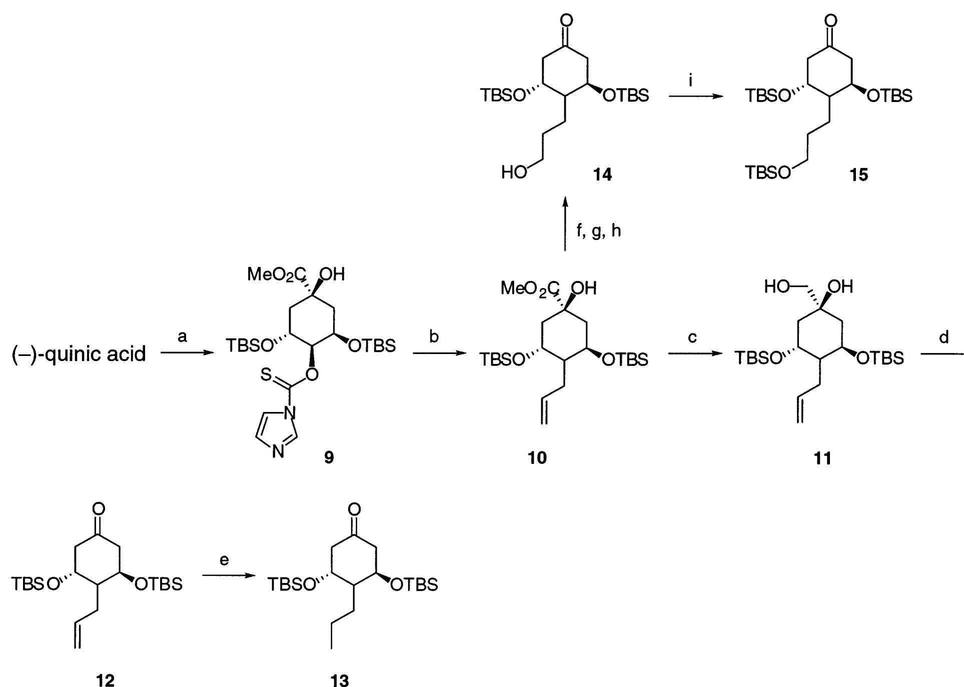
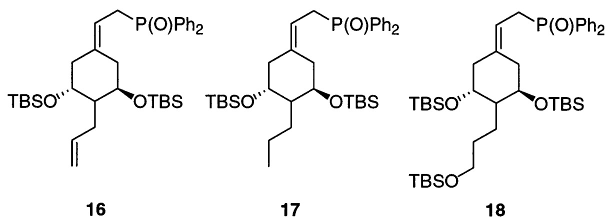
(23) Reduction of **10** using DIBAL-H in toluene at rt gave diol **11** only in 55% yield.

SCHEME 1[a]



[a] Reagents and conditions: (a) see ref 12b; (b) $Bu_3SnCH_2CH{=}CH_2$, AIBN, benzene, reflux, 60%; (c) $NaBH_4$, EtOH, 91%; (d) $NaIO_4$, MeOH−H_2O (2:1), 90%; (e) H_2, Pd/C, MeOH, 99%; (f) BH_3·THF, then 30% H_2O_2, 3 M NaOH; (g) $NaBH_4$, EtOH; (h) $NaIO_4$, MeOH−H_2O (2:1), 68% for three steps; (i) TBSCl, DMAP, Et_3N, CH_2Cl_2, quant.

unsuccessful. It is known that in some cases this coupling reaction results in a very low yield due to the structure of the substituted A-ring phosphine oxide.[13,24] Thus, we changed the synthetic strategy, and we tried a modified Julia olefination recently reported by Hilpert and Wirz for synthesizing retiferol (Ro 65-2299).[25,26]



The tertiary hydroxyl of ketone **19** was protected by a MOM group, and the Horner−Wadsworth−Emmons reaction using triethyl phosphonoacetate and sodium hydride in THF gave the ester **21** (E/Z = 92/8) in 98% yield. Chemical shifts of the vinylic proton of the E- and Z-isomers were 5.45 and 5.65 ppm, respectively. Trost et al. assigned the (E,Z)-stereochemistry of the corresponding bromoolefins using NMR: the vinylic proton of the E-isomer (δ 5.63 ppm) appears in a higher field than that of the Z-isomer (δ 5.93 ppm) due to the anisotropy of the C−C single bond of the five-membered D-ring.[27] (E)-Ethyl ester **21** was reduced to allylic alcohol **22** with DIBAL-H in 99% yield, and sulfonation with 2-mercaptobenzothiazole under Mitsunobu conditions followed by Mo-catalyzed oxidation furnished sulfone **23** in 89% yield, which was the substrate for the modified Julia olefination (Scheme 2).

Each ketone, **12**, **13**, and **15**, and sulfone **23** were coupled using LiHMDS in THF at −78 °C to give the protected 2-substituted 19-norvitamin D_3 as a diastereoisomeric mixture attributed to the C2 stereochemistry. After partial purification through silica gel column chromatography, each mixture was treated with (+)-CSA in MeOH to yield deprotected compounds in 47−62% yields. Diastereomers were separated with reversed-phase HPLC to afford the desired 2α- and 2β-substituted 19-norvitamin D_3 analogues **6a**−**8a** and **6b**−**8b** (Scheme 3).

Previously, conformational analysis on the A-ring of 2α- and 2β-methyl-1α,25-dihydroxy-19-norvitamin D_3,[15] and their ethyl counterparts,[13] was reported in detail. The conformational equilibrium of these 19-nor derivatives

(24) Synthesis of 2,2-dimethyl-1α,25-dihydroxy-19-norvitamin D_3: Posner, G. H.; Woodard, B. T.; Crawford, K. R.; Peleg, S.; Brown, A. J.; Dolan, P.; Kensler, T. W. *Bioorg. Med. Chem.* **2002**, *10*, 2353−2365.

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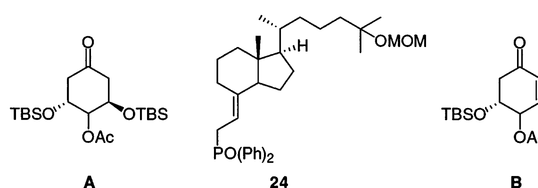
(26) Initially, we tried to connect ketone (**A**) with the two-carbon elongated CD-ring phosphine oxide (**24**); however, only an elimination product (**B**) was obtained under the basic conditions. The resemble elimination reaction was reported in ref 25a. Ketone **A** was prepared through simple acetylation of the corresponding alcohol in ref 19. Data for **B**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.048 (s, 3H), 0.053 (s, 3H), 0.85 (s, 9H), 2.14 (s, 3H), 2.60 (dd, J = 3.2, 16.4 Hz, 1H), 2.71 (dd, J = 6.0, 16.4 Hz, 1H), 4.44 (m, 1H), 5.59 (m, 1H), 6.10 (d, J = 9.6 Hz, 1H), 6.62 (br d, J = 9.6 Hz, 1H).



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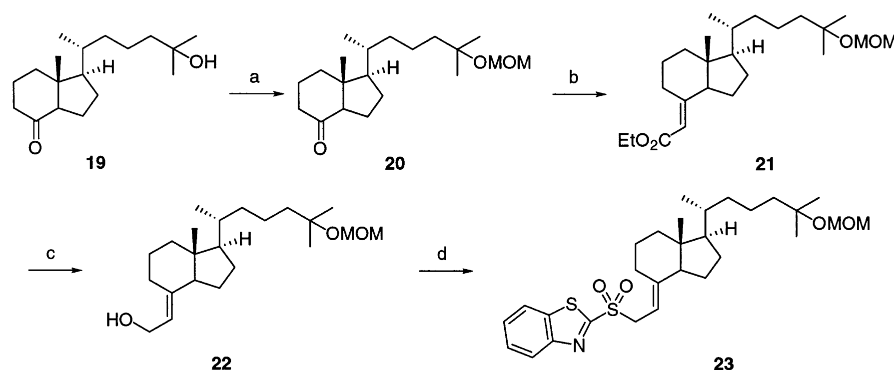
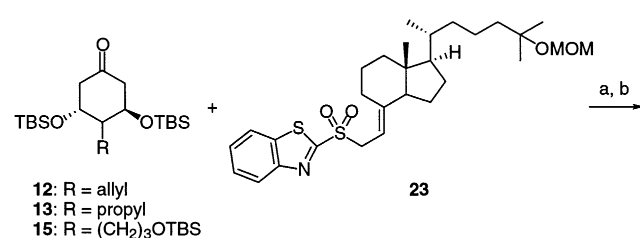
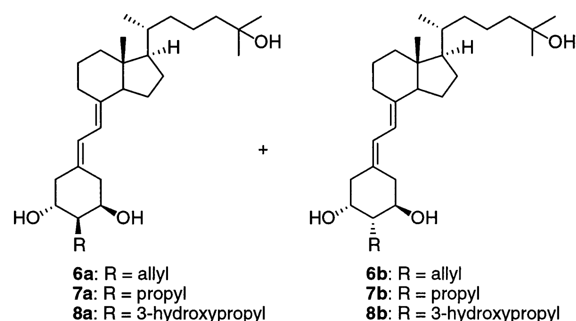
SCHEME 2 [a]



[a] Reagents and conditions: (a) MOMCl, $(^iPr)_2NEt$, CH_2Cl_2, quant; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 98% (*E*/*Z* = 92/8); (c) DIBAL-H, toluene, 99%; (d) 2-mercaptobenzothiazole, $^iPrOCON{=}NCO_2{}^iPr$, Ph_3P, THF, then cat. $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30%$H_2O_2$, EtOH, 89%.

SCHEME 3 [a]

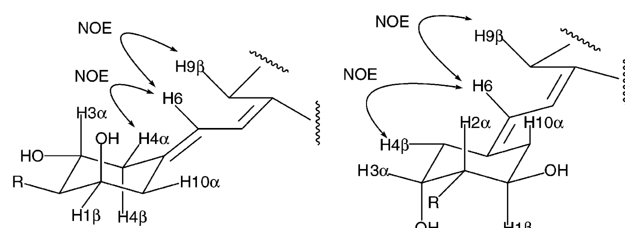




[a] Reagents and conditions: (a) LiHMDS, THF, −78 to 0 °C; (b) (+)-CSA, MeOH, 47−62% in two steps, then reversed-phase HPLC separation of each isomer.

is strongly shifted to one particular chair form (α-chair or β-chair conformation), in which each alkyl group at C2 preferentially takes its equatorial disposition, and the ^1H NMR data and molecular calculations fully supported the structures.[13,15] Preferred conformations of the present 2-substituted 19-norvitamin D_3 **6a**−**8a** and **6b**−**8b** are shown in Figure 2 based on the above discussion and the ^1H NMR experiments including NOEs. The six new analogues were put into two categories: one group had NOE between H6 and H4α, while the other showed NOE between H6 and H4β. The analogues belonging to the former group exhibited a larger (axial−axial) $J_{3\alpha,4\beta}$ = 9.2−9.6 Hz and with a smaller $J_{1\beta,10\alpha}$ = 4.1−4.7 Hz. On the other hand, the later group showed a smaller $J_{3\alpha,4\beta}$ = 3.3−3.8 Hz and a larger (axial−axial) $J_{1\beta,10\alpha}$ = 9.8−10.3 Hz. In this manner, we were able to deduce the stereochemistry of each isomer (Figure 2).

Moreover, the ^1H NMR chemical shifts of representative protons of 2-methyl,[15] 2-ethyl,[13] and 2-allyl analogues are listed in Table 1, in which comparable correlation in



6a-8a: 2α-equatorial chair conformation **6b-8b**: 2β-equatorial chair conformation

FIGURE 2. Preferred conformation of the 2-substituted 19-norvitamin D_3 analogues **6a**−**8a** and **6b**−**8b**. Left (**6a**−**8a** 2α-equatorial chair conformation): NOE between H6 and H4α was observed, 4.6% for R = allyl (**6a**: $J_{3\alpha,4\beta}$ = 9.6, $J_{1\beta,10\alpha}$ = 4.1 Hz), 3.6% for R = propyl (**7a**: $J_{3\alpha,4\beta}$ = 9.2, $J_{1\beta,10\alpha}$ = 4.7 Hz), and 2.4% for R = 3-hydroxypropyl (**8a**: $J_{3\alpha,4\beta}$ = 9.6, $J_{1\beta,10\alpha}$ = 4.3 Hz). Right (**6b**−**8b** 2β-equatorial chair conformation): NOE between H6 and H4β was observed, 1.7% for R = allyl (**6b**: $J_{3\alpha,4\beta}$ = 3.4, $J_{1\beta,10\alpha}$ = 10.3 Hz), 4.2% for R = propyl (**7b**: $J_{3\alpha,4\beta}$ = 3.8, $J_{1\beta,10\alpha}$ = 9.8 Hz), and 3.5% for R = 3-hydroxypropyl (**8b**: $J_{3\alpha,4\beta}$ = 3.3, $J_{1\beta,10\alpha}$ = 10.2 Hz).

TABLE 1. ^1H NMR Chemical Shifts of Representative Protons of 2-Methyl, 2-Ethyl, and 2-Allyl Analogues

	2α-Me[a]	2α-Et[b]	2α-allyl	2β-Me[a]	2β-Et[b]	2β-allyl
1β-H	3.96	4.14	4.08	3.51	3.54	3.64
3α-H	3.61	3.64	3.70	3.90	4.09	4.02
4α-H	2.60	2.60	2.61	2.43	2.34−2.42	2.40
4β-H	2.13	2.14	2.13−2.17	2.34	2.34−2.42	2.34
10α-H	2.80	2.87	2.86			1.88−1.92
10β-H	2.22	2.15	2.13−2.17	3.08	3.10	3.11
7-H	5.82	5.82	5.81	5.87	5.87	5.87
6-H	6.37	6.38	6.35	6.26	6.26	6.26
9β-H	2.80	2.80	2.80	2.80	2.80	2.80
18-H	0.54	0.53	0.53	0.55	0.55	0.55
21-H	0.94	0.94	0.94	0.94	0.94	0.94
26,27-H	1.13	1.22	1.22	1.22	1.22	1.22

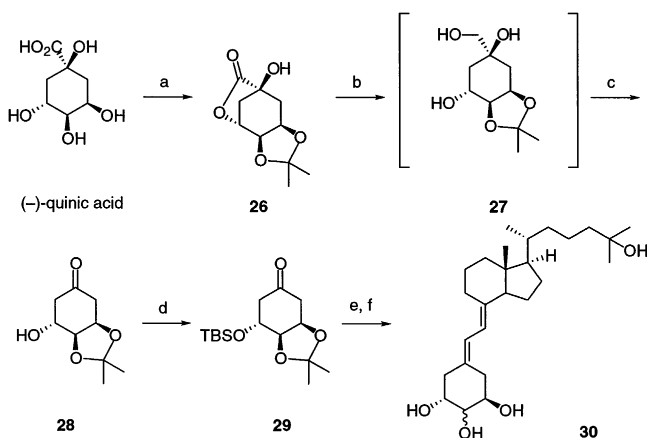
[a] Reference 15. [b] Reference 13.

chemical shift of each proton can be seen in the 2α-series vs 2β-series, respectively.

This C5−C6 Julia-type olefination was found to be applicable to the synthesis of 2-hydroxy-1α,25-dihydroxy-19-norvitamin D_3 (**30**), which was reported by DeLuca's group in 1994 and Yamada's group in 2003.[19,28] As shown in Scheme 4, (−)-quinic acid was converted to 4,5-*O*-isopropylidene lactone **26** in 80% yield. Reduction and

(28) Shimizu, M.; Iwasaki, Y.; Shibamoto, Y.; Sato, M.; DeLuca, H. F.; Yamada, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 809−812.

SCHEME 4[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, (+)-CSA, benzene, 80%; (b) $NaBH_4$, EtOH; (c) $NaIO_4$, $CH_2Cl_2-H_2O$, 92% in two steps; (d) TBSCl, Et_3N, DMF, 95%; (e) **23**, LiHMDS, THF, −78 to 0 °C; (f) (+)-CSA, MeOH, 64% in two steps.

TABLE 2. Relative VDR Binding Affinity and HL-60 Cell Differentiation Activity of 2-Substituted Analogues of 1α,25-Dihydroxy-19-norvitamin D_3

compd	VDR binding affinity[a,b]	HL-60 cell differentiation[a,c]
natural hormone (**1**)	100	100
19-nor (**5**)	17	27
2α-allyl (**6a**)	3	54
2α-propyl (**7a**)	3	84
2α-hydroxypropyl (**8a**)	100	3563
2β-allyl (**6b**)	0.15	20
2β-propyl (**7b**)	0.3	32
2β-hydroxypropyl (**8b**)	3	667

[a] The potency of **1** was normalized to 100. [b] Bovine thymus VDR. [c] Determined by an NBT assay; relative activity was calculated at EC_{50}. Data are the means of three separate experiments.

subsequent oxidative cleavage of the resulting vicinal diol **27** by sodium periodate gave cyclohexanone **28** in 92% yield in two steps.[29] TBS protection of the secondary alcohol furnished a substrate **29** for the Julia-type coupling in 95% yield.[30] Under the same basic conditions as the previous modified Julia olefination, *O*-protected target compounds (a diastereoisomeric mixture) were obtained. Deprotection using (+)-CSA in MeOH gave **30** in 64% yield in the last two steps (overall yield from (−)-quinic acid was 45%).

VDR Binding Affinity and Induction of HL-60 Cell Differentiation. Zhou et al. reported that the binding affinity of 1α,25-dihydroxy-19-norvitamin D_3 (**5**) for the porcine intestinal VDR was 30% of that of the natural hormone.[17] In our experiments using the bovine thymus VDR, it was 17% (Table 2). The introduction of some kind of 2α-substituent, such as the methyl,[7] 3-hydroxypropyl,[8] or 3-hydroxypropoxy group,[9] to the natural hormone **1** increases the binding affinity.[10,11] We anticipated that the introduction of the 3-hydroxypropyl group to **5** would increase the VDR affinity. The results are summarized in Table 2 (bovine thymus VDR).[31] Data of 2α- and 2β-methyl, ethyl, and hydroxymethyl analogues of **5** using the porcine intestinal VDR were reported.[13,15]

In the 2α-alkyl series, the 2α-propyl group in **7a** seemed to be too long to fit in the ligand-binding domain (LBD) of the VDR. The 2α-allyl group in **6a** may have the same effect on binding. As a pure alkyl substituent at the 2α-position, 2α-ethyl analogue of **5** showed high binding affinity (83% of **1**) for the porcine intestinal VDR.[13] From our experiments, the 2α-methyl analogue of **1** was the strongest binder to the bovine thymus VDR in the 2α-alkyl series.[7,8] Introduction of the alkyl group in the 2β-orientation (**6b**, **7b**) decreased the affinity (Table 2). However, **8a** with the 3-hydroxypropyl group at the 2α-position exhibited an equivalent binding affinity to the natural hormone **1**. The terminal hydroxyl group of the 2α-(3-hydroxypropyl) substituent of **8a** would form an additional hydrogen bonding to Arg-274 or Asp-144 of the LBD to stabilize the ligand−VDR complex as in the case of 2α-(3-hydroxypropyl) and 2α-(3-hydroxypropoxy) analogues of **1**.[8a,9a,11] On the other hand, the 2β-isomer **8b** was 33-fold less potent than **1**. From our experiments on the various 2-substituted analogues[7−9] of **1** and DeLuca's 2-substituted 19-nor analogues,[13,15] it can be said that 2α-isomers have a higher VDR affinity than the corresponding 2β-isomers. Recently, Shimizu et al. reported the synthesis of 2-hydroxyethoxy- and 2-(*N*,*N*-diethylcarbamoyl)methoxy active 19-norvitamin D_3, in which the modified A-ring moiety was derived from D-glucose. Interestingly, the 2β-hydroxyethoxy derivative was more potent in the VDR binding than the 2α-hydroxyethoxy counterpart.[28]

Next, we tested the ability of these new 19-nor analogues to induce differentiation of HL-60 cells, which are human promyelocytic leukemia cells, by the NBT reduction method.[32] The results are summarized in Table 2. The analogue **8a** showed ca. 36-fold higher activity in inducing cell differentiation, and **8b** was 6.7-fold more potent than **1**, regardless of its low affinity for the VDR. It is generally accepted that the affinity of a ligand for the VDR and its cell-differentiating activity are not always parallel, because the kinetics of VDR−ligand complex formation to form a transcriptionally active holoform does not directly affect the kinetics in the binding of a coactivator to the active VDR−ligand complex to activate the target gene.[33] The striking differential ability of diastereomeric **8a** and **8b** to induce HL-60 cell differentiation provides new insight into the structure−activity relationships of vitamin D_3 analogues, important for the design of new, more potent drug candidates.

Conclusion

We efficiently synthesized three kinds of 2-substituted active 19-norvitamin D_3 analogues (**6a**,**b**−**8a**,**b**) in 11−14 steps with 38−54% overall yields from (−)-quinic acid

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and 25-hydroxy Grundmann's ketone, utilizing the modified Julia coupling reaction to connect between the C5 and C6 positions. This approach was a short and concise way to introduce a three-carbon unit to the C2 position of 19-norvitamin D_3 (**5**). Further manipulation of the allyl group of intermediate **12** can provide a shorter or longer carbon functional group at C2. The 2α-(3-hydroxypropyl) group in **8a** contributed to a marked increase in both the VDR binding affinity and potency in the induction of HL-60 cell differentiation. As for the VDR binding affinity of **8a**, formation of the new hydrogen bonding between the terminal hydroxyl group of the C2-substituent of **8a** and Arg-274 or Asp-144 would stabilize the ligand (**8a**)−VDR complex. The 2β-counterpart showed 6.7-fold higher activity in cell differentiation despite a lower affinity to the VDR. The 2-propyl and 2-allyl groups were too long as the alkyl substituents to form stable hydrophobic contact with the LBD of the VDR, and analogues with 2-methyl and 2-ethyl groups were better binders to the VDR.[13,15]

The present study implies that the 2α-(3-hydroxypropyl) group in **8a** can compensate for the loss of hydrophobic interaction of the 10(19)-exocyclic methylene group in the LBD, which causes the low VDR affinity of **5**. Further biological testing is underway in our laboratories.

Experimental Section

Methyl (1*R*,3*R*,4*RS*,5*R*)-4-Allyl-3,5-bis[(*tert*-butyldimethylsilyl)oxy]-1-hydroxycyclohexanecarboxylate (10). To a solution of **9**[12b] (1.53 g, 2.81 mmol) in dry benzene (4 mL) was added allyltributyltin (1.9 mL, 8.46 mmol) at rt. To the resulting mixture was added the benzene solution (10 mL) of AIBN (462 mg, 2.81 mmol) over 3 h at a refluxing temperature, and the mixture was further refluxed for 3 h. After cooling, the mixture was concentrated in vacuo, and purification by silica gel column chromatography (hexane/AcOEt = 10:1) afforded 775 mg of **10** as a colorless oil (60%). This was an inseparable mixture of isomers in a ratio of ca. 7:3 and was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 0.06 (s, 6H), 0.07 (s, 6H), 0.88 (s, 9H), 0.89 (s, 9H), 1.24−1.37 (m, 1H), 1.50−1.80 (m, 3H), 1.93−1.99 (m, 2H), 2.09 (dd, *J* = 2.4, 14.6 Hz, 1H), 2.59 (br d, *J* = 14.6 Hz, 1H), 3.76 (s, 3H), 4.22 (m, 1H), 4.45 (ddd, *J* = 4.6, 5.1, 11.2 Hz, 1H), 4.78 (s, 1H), 5.03 (d, *J* = 9.8 Hz, 1H), 5.04 (d, *J* = 17.1 Hz, 1H), 5.74 (m, 1H); minor isomer: 0.10 (s, 6H), 0.13 (s, 6H), 0.88 (s, 6H), 0.91 (s, 9H), 2.19 (dd, *J* = 3.2, 12.9 Hz, 1H), 3.98 (dt, *J* = 4.4, 10.3 Hz, 1H), 4.29 (m, 1H), 4.35 (s, 1H). ^{13}C NMR major isomer: −5.00, −4.92, −4.65, −4.47, 17.8, 18.2, 25.8, 25.9, 28.8, 33.5, 39.6, 46.9, 52.5, 64.4, 71.6, 76.4, 116.3, 137.0, 173.9; minor isomer: −4.81, −4.65, −3.95, −3.65, 17.7, 18.1, 25.96, 26.60, 27.9, 30.6, 39.0, 45.0, 49.9, 66.8, 70.2, 77.2, 115.9, 137.1. IR (neat): 3484, 2955, 2930, 2859, 1740, 1642, 1464, 1389, 1362, 1256, 1103, 876, 837, 777, 669 cm^{-1}. EIMS: 401 (M^+ − ^{t}Bu). HREIMS: calcd for $C_{19}H_{37}O_5Si_2$ (M^+ − ^{t}Bu) 401.2180, found 401.2186.

(1*R*,3*R*,4*RS*,5*R*)-4-Allyl-3,5-bis[(*tert*-butyldimethylsilyl)-oxy]-1-(hydroxymethyl)cyclohexan-1-ol (11). To a solution of **10** (1.52 g, 3.31 mmol) in EtOH (30 mL) was added $NaBH_4$ (375 mg, 9.93 mmol) at 0 °C, and the mixture was stirred at rt for 4 h. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to afford 1.29 g of **11** as a colorless oil (91%). This was an inseparable mixture of isomers in a ratio of ca. 7:3 and was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ −0.02 (s, 3H), −0.01 (s, 3H), 0.00 (s, 6H), 0.80 (s, 9H), 0.82 (s, 9H), 1.15−1.36 (m, 2H), 1.45 (dd, *J* = 2.2, 14.6 Hz, 1H), 1.52−1.68 (m, 2H), 1.84−1.99 (m, 1H), 2.08−2.09 (m, 1H), 2.45−2.49 (m, 1H), 3.23−3.31 (m, 2H), 4.10 (m, 1H), 4.38 (ddd, *J* = 4.6, 5.1, 11.2 Hz, 1H), 4.48 (br s, 1H), 4.91 (m, 2H), 5.60−5.76 (m, 1H); minor isomer: −0.01 (s, 9H), 0.03 (s, 3H), 0.05 (s, 3H), 0.84 (s, 9H), 3.89 (dt, *J* = 4.3, 10.4 Hz, 1H), 4.19−4.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ −5.05, −4.79, −4.77, −4.55, 17.89, 18.23, 25.79, 25.97, 28.94, 32.98, 38.81, 47.40, 65.05, 70.85, 71.78, 74.18, 116.08, 137.23; minor isomer: δ −4.59, −4.43, −3.85, −3.68, 18.13, 18.21, 26.03, 30.82, 38.44, 44.37, 50.66, 67.30, 70.60, 70.74, 74.50, 115.75, 137.37. IR (neat): 3486, 3079, 2932, 2859, 1640, 1470, 1391, 1362, 1226, 1111, 1051, 911, 874, 833, 802, 777, 667 cm^{-1}. EIMS: 430 (M^+). HREIMS: calcd for $C_{22}H_{46}O_4Si_2$ (M^+) 430.2935, found 430.2939.

(3*R*,5*R*)-4-Allyl-3,5-bis[(*tert*-butyldimethylsilyl)oxy]cyclohexanone (12). To a solution of **11** (41 mg, 95 μmol) in MeOH (2 mL) and H_2O (1 mL) was added $NaIO_4$ (31 mg, 0.14 mmol) at 0 °C. After being stirred at rt for 30 min, the reaction mixture was diluted with AcOEt. Brine was added to the mixture, the organic layer was separated, and the aqueous layer was extracted with AcOEt. The organic layer and extracts were combined and washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/AcOEt = 10:1) gave 34 mg of **12** as a colorless oil (90%). $[\alpha]^{24}_{D}$: −33.6 (*c* 1.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 12H), 0.86 (s, 9H), 0.88 (s, 9H), 1.7−1.9 (m, 1H), 2.2−2.3 (m, 1H), 2.3−2.4 (m, 2H), 2.43 (dd, *J* = 3.6, 14.4 Hz, 1H), 2.49 (ddd, *J* = 1.5, 5.7, 14.4 Hz, 1H), 2.64 (ddd, *J* = 1.5, 4.8, 14.4 Hz, 1H), 4.0−4.1 (m, 1H), 4.2−4.3 (m, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 5.09 (br d, *J* = 17.7 Hz, 1H), 5.81 (ddt, *J* = 10.5, 17.7, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7, −4.3, −4.0, 18.1, 25.9, 29.8, 30.9, 48.8, 49.2, 67.9, 69.6, 116.4, 136.9, 212.0. IR (neat): 2955, 2932, 2896, 2859, 2361, 1725, 1641, 1472, 1389, 1362, 1333, 1256, 1161, 1094, 980, 938, 889, 837, 777 cm^{-1}. EIMS: 398 (M^+). HREIMS: calcd for $C_{21}H_{42}O_3Si_2$ (M^+) 398.2673, found 398.2675.

(3*R*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-propylcyclohexanone (13). To a solution of **12** (527 mg, 1.32 mmol) in dry MeOH (15 mL) was added 10% Pd/C (50 mg), and the mixture was stirred at rt in a hydrogen atmosphere (balloon) for 15 h. The reaction mixture was filtered through a silica gel pad, and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/AcOEt = 5:1) afforded 524 mg of **13** as a colorless oil (99%). $[\alpha]^{24}_{D}$: −29.5 (*c* 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.036 (s, 3H), 0.045 (s, 3H), 0.05 (s, 6H), 0.85 (s, 9H), 0.88 (s, 9H), 0.95 (t, *J* = 7.2 Hz, 3H), 1.33 (m, 1H), 1.40−1.54 (m, 3H), 1.71 (ddt, *J* = 5.1, 8.0, 2.6 Hz, 1H), 2.31 (dd, *J* = 8.0, 14.3 Hz, 1H), 2.43 (m, 2H), 2.62 (dd, *J* = 4.7, 14.3 Hz, 1H), 4.02 (dt, *J* = 4.7, 8.0 Hz, 1H), 4.31 (dt, *J* = 2.8, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.9, −4.8, −4.7, −4.3, −4.2, 14.5, 18.1, 20.8, 25.8, 25.9, 28.7, 48.5, 48.8, 49.3, 68.2, 70.3, 207.7. IR (neat): 2957, 2932, 2896, 2859, 1725, 1464, 1362, 1335, 1256, 1171, 1088, 1005, 953, 920, 884, 835, 777, 666 cm^{-1}. EIMS: 400 (M^+). HREIMS: calcd for $C_{21}H_{44}O_3Si_2$ (M^+) 400.2829, found 400.2822.

(3*R*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-(3-hydroxypropyl)cyclohexanone (14). To a solution of **10** (50 mg, 0.11 mmol) in dry THF (1 mL) was added BH_3·THF (1 M solution in THF, 0.27 mL, 0.27 mmol) at 0 °C. After being stirred at rt for 2 h, the reaction was quenched by the addition of 3 M NaOH (1 mL) and 30% H_2O_2 (2 mL). After being stirred at rt for an additional 2 h, the reaction mixture was poured into saturated aqueous Na_2SO_3 and extracted with AcOEt. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in EtOH (1 mL), and $NaBH_4$ (13 mg, 34 mmol) was added to the solution at 0 °C. After being stirred at rt for 2 h, the mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic extracts were combined and washed with saturated aqueous NH_4Cl and brine, dried

over $MgSO_4$, and concentrated in vacuo. The residue containing vicinal diol was dissolved in MeOH (2 mL), and $NaIO_4$ (70 mg, 327 mmol) in H_2O (1 mL) was added to the solution at 0 °C. After being stirred at rt for 14 h, the reaction mixture was diluted with AcOEt, and brine was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The organic layer and extracts were combined and washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to give 31 mg of **14** as a colorless oil (68% in three steps). $[\alpha]^{24}_{D}$: −39.4 (*c* 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.051 (s, 3H), 0.056 (s, 6H), 0.063 (s, 3H), 0.86 (s, 9H), 0.88 (s, 9H), 1.52−1.75 (m, 5H), 2.33 (dd, *J* = 7.9, 14.4 Hz, 1H), 2.46 (m, 2H), 2.64 (dd, *J* = 4.6, 14.4 Hz, 1H), 3.69 (t, *J* = 6.0 Hz, 2H), 4.04 (dt, *J* = 4.6, 7.9 Hz, 1H), 4.33 (dt, *J* = 2.9, 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8, −4.7, −4.3, −4.2, 18.1, 18.2, 22.7, 25.8, 25.9, 30.9, 48.7, 48.8, 49.2, 63.1, 68.3, 70.3, 207.5. IR (neat): 3426, 2955, 2930, 2894, 2859, 1719, 1472, 1362, 1256, 1096, 1061, 835, 775 cm^{-1}. EIMS: 359 (M^+ − ^{t}Bu). HREIMS: calcd for $C_{17}H_{35}O_4Si_2$ (M^+ − ^{t}Bu) 359.2074, found 359.2078.

(3*R*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-[3-(*tert*-butyldimethylsilyloxy)propyl]cyclohexanone (15). To a solution of **14** (204 mg, 0.49 mmol) in dry CH_2Cl_2 (5 mL) were added Et_3N (0.1 mL, 0.72 mmol), DMAP (6 mg, 50 μmol), and TBSCl (88 mg, 0.58 mmol) at 0 °C. After being stirred at rt for 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with AcOEt. The combined organic layer and extracts were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/AcOEt = 10:1) afforded 259 mg of **15** as a colorless oil (quant). $[\alpha]^{27}_{D}$: −29.5 (*c* 1.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.043 (s, 3H), 0.047 (s, 6H), 0.052 (s, 9H), 0.851 (s, 9H), 0.877 (s, 9H), 0.896 (s, 9H), 1.52−1.70 (m, 5H), 2.32 (dd, *J* = 7.9, 14.6 Hz, 1H), 2.44 (m, 2H), 2.63 (dd, *J* = 4.6, 14.6 Hz, 1H), 3.64 (t, *J* = 5.8 Hz, 2H), 4.03 (dt, *J* = 4.6, 7.9 Hz, 1H), 4.32 (dt, *J* = 2.4, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.11, −5.08, −4.78, −4.64, −4.26, −4.20, 18.11, 18.13, 18.52, 23.10, 25.84, 25.93, 26.12, 31.16, 48.82, 48.87, 49.35, 63.52, 68.30, 70.31, 207.7. IR (neat): 2955, 2930, 2894, 2859, 1725, 1472, 1256, 1098, 909, 835, 775 cm^{-1}. EIMS: 530 (M^+). HREIMS: calcd for $C_{27}H_{58}O_4Si_3$ (M^+) 530.3643, found 530.3649.

Ethyl [(1*R*,2*E*,6*R*,7*R*)-7-[(*R*)-6-Methoxymethoxy-6-methylheptan-2-yl]-6-methylbicyclo[4.3.0]nonan-2-ylidene]acetate (21). To a suspension of NaH (675 mg, 20.3 mmol) in THF (20 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (3.7 mL, 23.6 mmol) at 0 °C, and the mixture was stirred at rt for 17 h. Ketone **20** (1.10 g, 3.38 mmol) was dissolved in THF (10 mL), and the solution was added to the mixture above at 0 °C. After being stirred at the same temperature for 14 h, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/AcOEt = 8:1) gave 1.31 g of **21** as a colorless oil (98%). This was an inseparable mixture of *E/Z*-isomers (*E/Z* = 92:8) and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer (*E*): δ 0.57 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.04 (m, 1H), 1.21 (s, 6H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.31−1.46 (m, 7H), 1.48−1.55 (m, 3H), 1.60−1.75 (m, 4H), 1.87−1.89 (m, 1H), 2.01 (br. d, *J* = 15.6 Hz, 1H), 2.09 (dt, *J* = 1.2, 10.0 Hz, 1H), 3.36 (s, 3H), 3.84 (br d, *J* = 14.4 Hz, 1H), 4.14 (dq, *J* = 1.8, 7.2 Hz, 2H), 4.70 (s, 2H), 5.45 (s, 1H); minor isomer (*Z*) selected: δ 0.88 (d, *J* = 6.4 Hz, 3H), 1.26 (s, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 5.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 14.5, 18.9, 20.7, 22.3, 24.0, 26.4, 26.5, 27.6, 29.7, 29.8, 36.1, 36.4, 40.2, 42.4, 47.2, 55.1, 56.8, 56.9, 59.5, 76.3, 91.0, 111.9, 163.1, 166.7. IR (neat): 2944, 2870, 2774, 2124, 2060, 1958, 1717, 1647, 1466, 1381, 1368, 1308, 1271, 1254, 1146, 1096, 1042, 918, 866, 754 cm^{-1}. EIMS: 394 (M^+). HREIMS: calcd for $C_{24}H_{42}O_4$ (M^+) 394.3083, found 394.3091.

2-[(1*R*,2*E*,6*R*,7*R*)-7-[(*R*)-6-Methoxymethoxy-6-methylheptan-2-yl]-6-methylbicyclo[4.3.0]nonan-2-ylidene]ethanol (22). To the (*E/Z*)-mixture of **21** (751 mg, 1.90 mmol) in toluene (14 mL) was added DIBAL-H (1.04 M solution in toluene, 4.6 mL, 4.78 mmol) at −78 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched by adding saturated aqueous Na_2SO_4. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to yield 666 mg of **22** as a colorless oil (99%). ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 0.55 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.03 (m, 1H), 1.22 (s, 6H), 1.25−1.30 (m, 3H), 1.32−1.41 (m, 4H), 1.44−1.56 (m, 5H), 1.65−1.68 (m, 3H), 1.84−2.05 (m, 3H), 2.63 (dd, *J* = 4.2, 12.2 Hz, 1H), 3.37 (s, 3H), 4.21 (d, *J* = 7.2 Hz, 2H), 4.71 (s, 2H), 5.22 (t, *J* = 7.0 Hz, 1H); minor isomer (selected): δ 0.88 (d, *J* = 6.4 Hz, 3H), 5.41 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 18.9, 20.7, 22.3, 23.6, 26.4, 26.5, 27.7, 28.8, 36.2, 36.5, 40.5, 42.3, 45.4, 55.1, 55.7, 56.7, 58.7, 76.4, 90.9, 119.1, 143.5. EIMS: 334 (M^+ − H_2O). HREIMS: calcd for $C_{22}H_{38}O_2$ (M^+ − H_2O) 334.2872, found 334.2876.

(1*R*,2*E*,6*R*,7*R*)-2-[2-(Benzothiazole-2-sulfonyl)ethylidene]-7-[(*R*)-6-methoxymethoxy-6-methylheptan-2-yl]-6-methylbicyclo[4.3.0]nonane (23). To a solution of 2-mercaptobenzothiazole (451 mg, 2.70 mmol) and PPh_3 (707 mg, 2.70 mmol) in dry CH_2Cl_2 (5 mL) were added a solution of **22** (633 mg, 1.80 mmol) in dry CH_2Cl_2 (5 mL) and DIAD (0.52 mL, 1.80 mmol) at 0 °C. After being stirred at the same temperature for 1 h, the mixture was concentrated. The residue was dissolved in EtOH (10 mL), and to the solution were added 30% H_2O_2 (1 mL) and $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (444 mg, 0.36 mmol) at 0 °C. After being stirred at rt for 2 h, the mixture was poured into saturated aqueous Na_2SO_3 and was extracted with AcOEt. The extracts were combined and washed with brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (hexane/Et_2O = 3:1) gave 849 mg of sulfone **23** as a colorless oil (89%). ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 0.26 (s, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 1.00 (m, 1H), 1.20 (s, 6H), 1.22−1.53 (m, 14H), 1.81−1.91 (m, 3H), 2.55 (br d, *J* = 12.4 Hz, 1H), 3.36 (s, 3H), 4.21 (dd, *J* = 6.8, 14.0 Hz, 1H), 4.43 (dd, *J* = 8.8, 14.0 Hz, 1H), 4.70 (s, 2H), 5.02 (dd, *J* = 6.8, 8.8 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H); minor isomer (selected): δ 0.78 (d, *J* = 6.4 Hz, 3H), 1.21 (s, 6H), 3.37 (s, 3H), 4.71 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 18.9, 20.6, 22.2, 23.2, 26.4, 26.5, 27.6, 29.1, 36.0, 36.4, 40.0, 42.3, 45.8, 53.9, 55.1, 56.0, 56.4, 76.3, 90.9, 104.0, 122.0, 125.2, 127.4, 127.7, 136.8, 151.9, 152.6, 165.7. IR (neat): 2948, 2874, 2363, 1657, 1599, 1567, 1472, 1424, 1381, 1327, 1240, 1148, 1090, 1040, 916, 853, 762, 731, 689, 639 cm^{-1}. EIMS: 533 (M^+). HREIMS: calcd for $C_{29}H_{43}O_4NS_2$ (M^+) 533.2634, found 533.2637.

(1*R*,2*E*,6*R*,7*R*)-7-[(*R*)-6-Methoxymethoxy-6-methylheptan-2-yl]-6-methyl-2-[2-(diphenylphosphoryl)ethylidene]bicyclo[4.3.0]nonane (24). To a solution of **22** (133 mg, 0.38 mmol) in dry THF (3 mL) was added BuLi (1.58 M in hexane, 0.28 mL, 0.45 mmol) at 0 °C. After the mixture was stirred at the same temperature for 5 min, freshly recrystallized TsCl (86 mg, 0.45 mmol) was added at the same temperature. To another flask charged with a solution of $HPPh_2$ (0.13 mL, 0.76 mmol) in dry THF (1 mL) was added BuLi (1.58 M solution in hexane, 0.48 mL, 0.76 mmol), and the resulting red solution was added to the above tosylate solution at 0 °C. After being stirred at the same temperature for 1 h, the reaction was quenched by the addition of water. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2 (4 mL). To the solution was added 30% H_2O_2 (2 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The organic layer was separated, and the aqueous layer was extracted with

CH_2Cl_2. The combined organic layer was washed with aqueous 1 M Na_2SO_3, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/AcOEt = 1:1) afforded 178 mg of **24** as an amorphous solid (88%). ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 0.29 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 1.20 (s, 6H), 2.42 (br d, J = 13.2 Hz, 1H), 3.04−3.27 (m, 2H), 3.356 (s, 3H), 4.69 (s, 2H), 5.00 (br dd, J = 6.6, 14.2 Hz, 1H), 7.44−7.49 (m, 6H), 7.68−7.78 (m, 4H); minor isomer: δ 0.83 (d, J = 6.8 Hz, 3H), 1.21 (s, 6H), 3.362 (s, 3H), 4.70 (s, 2H), 5.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 14.9, 18.9, 20.7, 22.3, 23.2, 26.4, 26.5, 27.7, 36.1, 36.5, 40.4, 42.3, 49.7, 55.1, 56.5, 63.4, 76.4, 81.6, 90.9, 128.3, 128.4, 130.7, 130.8, 131.0, 131.1, 131.4, 131.5, 144.5. EIMS: 536 (M^+). HREIMS: calcd for $C_{34}H_{49}O_3P$ (M^+) 536.3420, found 536.3409.

(a*S*,1*R*,3*R*,7*E*)-2-Allyl-9,10-seco-19-norcholesta-5,7-diene-1,3,25-triol (6a) and (a*R*,1*R*,3*R*,7*E*)-2-Allyl-9,10-seco-19-norcholesta-5,7-diene-1,3,25-triol (6b). To a solution of **23** (31.1 mg, 58.3 μmol) in dry THF (200 μL) was added LiHMDS (1 M solution in THF, 55 μL, 55 μmol) at −78 °C. After the mixture was stirred at the same temperature for 1 h, a solution of **12** (17.1 mg, 42.9 μmol) in dry THF (200 μL) was added dropwise to the mixture. After being stirred for 3 h, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 30:1) to yield crude protected 19-norvitamin D_3 (18.0 mg, ca. 59%). To a solution of the crude protected 19-norvitamin D_3 (9 mg, 13 μmol) in dry MeOH (2 mL) was added (+)-CSA (10 mg, 23 μmol) at 0 °C. After being stirred at rt for 19 h, the reaction mixture was diluted with AcOEt. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane/AcOEt = 3:2) afforded 4.0 mg of **6** as a mixture of isomers in a ratio of ca. 1:1 (47%). The isomers were separated by reversed-phase HPLC (YMC-Pack ODS column, 20 × 150 mm, 9.9 mL/min) using CH_3CN/H_2O (85:15) as a solvent system. Data for **6a** (2α-allylated **5**): t_R = 16.6 min. $[\alpha]^{23}_D$: +22.3 (c 0.16, $CHCl_3$). UV (EtOH): λ_{max} 243.5, 252.0, 261.5 nm; λ_{min} 247.5, 258.5 nm. ^1H NMR (600 MHz, $CDCl_3$): δ 0.53 (s, 3H, 18-H_3), 0.94 (d, J = 6.3 Hz, 3H, 21-H_3), 1.06 (m, 1H), 1.22 (s, 6H, 26-H_3 and 27-H_3), 1.24−1.32 (m, 6H), 1.36−1.58 (m, 10H), 1.67 (m, 2H), 1.86−1.93 (m, 2H), 1.99−2.01 (m, 2H), 2.13−2.17 (m, 2H), 2.30 (ddd, J = 6.0, 7.0, 14.2 Hz, 1H, $-CH_2$-$CH{=}CH_2$), 2.50 (ddd, J = 7.0, 8.4, 14.2 Hz, 1H, $-CH_2CH{=}CH_2$), 2.61 (dd, J = 4.7, 12.9 Hz, 1H, 4α-H), 2.80 (dd, J = 4.4, 12.9 Hz, 1H, 9β-H), 2.86 (dd, J = 4.1, 13.8 Hz, 1H, 10α-H), 3.70 (dt, J = 4.7, 9.6 Hz, 1H, 3α-H), 4.08 (dt, J = 4.1, 7.1 Hz, 1H, 1β-H), 5.07 (d, J = 10.2 Hz, 1H, $-CH_2CH{=}CH_2$), 5.15 (d, J = 17.0 Hz, 1H, $-CH_2CH{=}CH_2$), 5.81 (d, J = 11.3 Hz, 1H, 7-H), 5.92 (dddd, J = 6.9, 6.9, 10.2, 17.0 Hz, 1H, $-CH_2CH{=}CH_2$), 6.34 (d, J = 11.3 Hz, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.0, 18.8, 20.8, 22.2, 23.4, 27.6, 28.9, 29.1, 29.3, 32.8, 35.5, 36.1, 36.4, 40.4, 44.4, 45.2, 45.8, 48.9, 56.3, 56.5, 68.7, 71.0, 71.2, 115.2, 116.5, 124.1, 131.2. IR (neat): 3353, 2936, 1644 cm^{-1}. EIMS: 444 (M^+). HREIMS: calcd for $C_{29}H_{48}O_3$ (M^+) 444.3603, found 444.3597. Data for **6b** (2β-allylated **5**): t_R = 16.0 min. $[\alpha]^{22}_D$: +13.8 (c 0.13, $CHCl_3$). UV (EtOH): λ_{max} 243.5, 252.0, 261.5 nm; λ_{min} 247.0, 258.0 nm. ^1H NMR (600 MHz, $CDCl_3$): δ 0.55 (s, 3H, 18-H_3), 0.94 (d, J = 6.6 Hz, 3H, 21-H_3), 1.07 (m, 1H), 1.22 (s, 6H, 26-H_3 and 27-H_3), 1.24−1.33 (m, 5H), 1.37−1.57 (m, 11H), 1.66−1.70 (m, 2H), 1.88−1.92 (m, 2H), 1.99−2.02 (m, 2H), 2.28 (ddd, J = 7.4, 7.7, 14.6 Hz, 1H, $-CH_2CH{=}CH_2$), 2.34 (ddd, J = 1.4, 3.4, 14.0 Hz, 1H, 4β-H), 2.40 (br d, J = 14.0 Hz, 1H,4α-H), 2.53 (ddd, J = 6.7, 7.4, 14.6 Hz, 1H, $-CH_2CH{=}CH_2$), 2.80 (dd, J = 4.2, 12.9 Hz, 1H, 9β-H), 3.11 (ddd, J = 1.4, 4.7, 12.8 Hz, 1H, 10β-H), 3.64 (dt, J = 4.7, 10.3 Hz, 1H, 1β-H), 4.02 (ddd, J = 3.4, 6.3, 6.9 Hz, 1H, 3α-H), 5.07 (d, J = 10.2 Hz, 1H, $-CH_2CH{=}CH_2$), 5.16 (d, J = 17.0 Hz, 1H, $-CH_2CH{=}CH_2$), 5.87 (d, J = 11.3 Hz, 1H, 7-H), 5.93 (dddd, J = 7.3, 7.3, 10.2, 17.0 Hz, 1H, $-CH_2CH{=}CH_2$), 6.26 (d, J = 11.3 Hz, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.0, 18.8, 20.8, 22.3, 23.5, 27.7, 29.0, 29.2, 29.4, 33.2, 36.1, 36.4, 37.7, 40.4, 44.0, 44.4, 45.8, 49.2, 56.3, 56.5, 68.8, 71.0, 71.1, 115.3, 116.5, 123.5, 131.1, 137.6, 143.1. IR (neat): 3420, 2928, 2868, 1640 cm^{-1}. EIMS: 444 (M^+). HREIMS: calcd for $C_{29}H_{48}O_3$ (M^+) 444.3603, found 444.3609.

(a*R*,1*R*,3*R*,7*E*)-2-Propyl-9,10-seco-19-norcholesta-5,7-diene-1,3,25-triol (7a) and (a*S*,1*R*,3*R*,7*E*)-2-Propyl-9,10-seco-19-norcholesta-5,7-diene-1,3,25-triol (7b). These analogues were obtained through the same procedure as described above for the synthesis of **6a** and **6b**. A crude product, which was obtained from **23** (74 mg, 139 μmol), **13** (43 mg, 107 μmol), and LiHMDS (1 M solution in THF, 130 μL, 130 μmol), was partially purified by silica gel column chromatography (hexane/AcOEt = 40:1) to give protected 19-norvitamin D_3 (51 mg, 66%). To a solution of the crude 19-norvitamin D_3 (46 mg, 64 μmol) in dry MeOH (2 mL) was added (+)-CSA (45 mg, 194 μmol) at 0 °C, and the mixture was stirred at rt for 22 h. The usual workup and purification on silica gel column chromatography (hexane/AcOEt = 3:2) afforded 22.0 mg of **7** as a mixture of isomers in a ratio of ca. 1:1 (51%). The isomers were separated by reversed-phase HPLC (YMC-Pack ODS column, 20 × 150 mm, 9.9 mL/min) using CH_3CN/H_2O (90:10) as a solvent system. Data for **7a** (2α-propylated **5**): t_R = 14.2 min. $[\alpha]^{21}_D$: +21.3 (c 0.36, $CHCl_3$). UV (EtOH) λ_{max}: 243.5, 252.0, 262.0 nm; λ_{min} 247.5, 258.5 nm. ^1H NMR (600 MHz, $CDCl_3$): δ 0.53 (s, 3H, 18-H_3), 0.94 (d, J = 6.6 Hz, 3H, 21-H_3), 0.96 (t, J = 7.1 Hz, 3H, $-CH_2CH_2CH_3$), 1.07 (m, 1H), 1.22 (s, 6H, 26-H_3 and 27-H_3), 1.24−1.32 (m, 5H), 1.36−1.40 (m, 4H), 1.45−1.56 (m, 7H), 1.60−1.68 (m, 4H), 1.89 (m, 1H), 1.99−2.01 (m, 2H), 2.12−2.17 (m, 2H), 2.60 (dd, J = 4.5, 12.5 Hz, 1H, 4α-H), 2.80 (dd, J = 4.7, 12.6 Hz, 1H, 9β-H), 2.84 (dd, J = 4.7, 14.0 Hz, 1H, 10α-H), 3.64 (dt, J = 4.5, 9.2 Hz, 1H, 3α-H), 4.09 (br s, 1H, 1β-H), 5.82 (d, J = 11.3 Hz, 1H, 7-H), 6.37 (d, J = 11.3 Hz, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.0, 14.4, 18.8, 20.4, 20.8, 22.2, 23.5, 27.6, 28.9, 29.2, 29.3, 29.4, 35.5, 36.1, 36.4, 40.5, 44.4, 45.2, 45.8, 48.9, 56.3, 56.5, 68.3, 71.1, 71.6, 115.2, 124.0, 131.3, 143.2. IR (neat): 3384, 2955, 2872, 1613 cm^{-1}. EIMS: 446 (M^+). HREIMS: calcd for $C_{29}H_{50}O_3$ (M^+) 446.3760, found 446.3763. Data for **7b** (2β-propylated **5**): t_R = 13.8 min. $[\alpha]^{21}_D$: +15.2 (c 0.32, $CHCl_3$). UV (EtOH): λ_{max} 243.5, 252.0, 261.5 nm; λ_{min} 247.0, 258.0 nm. ^1H NMR (600 MHz, $CDCl_3$): δ 0.55 (s, 3H, 18-H_3), 0.94 (d, J = 6.6 Hz, 3H, 21-H_3), 0.95 (t, J = 7.3 Hz, 3H, $-CH_2CH_2CH_3$), 1.07 (m, 1H), 1.22 (s, 6H, 26-H_3 and 27-H_3), 1.24−1.33 (m, 5H), 1.37−1.53 (m, 11H), 1.66−1.67 (m, 3H), 1.88−1.91 (m, 2H), 1.99−2.02 (m, 2H), 2.35 (ddd, J = 1.2, 3.8, 12.9 Hz, 1H, 4β-H), 2.40 (br d, J = 13.9 Hz, 1H, 4α-H), 2.80 (dd, J = 4.7, 12.6 Hz, 1H, 9β-H), 3.10 (ddd, J = 1.2, 4.4, 12.7 Hz, 1H, 10β-H), 3.54 (dt, J = 4.4, 9.8 Hz, 1H, 1β-H), 4.05 (br s, 1H, 3α-H), 5.87 (d, J = 11.3 Hz, 1H, 7-H), 6.26 (d, J = 11.3 Hz, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.0, 14.4, 18.8, 20.2, 20.8, 22.3, 23.5, 27.7, 29.0, 29.2, 29.4, 29.6, 36.1, 36.4, 37.8, 40.5, 44.1, 44.4, 45.8, 49.1, 56.3, 56.5, 68.0, 71.1, 71.2, 115.3, 123.4, 131.3, 143.0. IR (neat): 3382, 2942, 2872, 1613 cm^{-1}. EIMS: 446 (M^+). HREIMS: calcd for $C_{29}H_{50}O_3$ (M^+) 446.3760, found 446.3757.

(a*R*,1*R*,3*R*,7*E*)-2-(3-Hydroxypropyl)-9,10-seco-19-norcholesta-5,7-diene-1,3,25-triol (8a) and (a*S*,1*R*,3*R*,7*E*)-2-(3-Hydroxypropyl)-9,10-seco-19-norcholesta-5,7-diene-1,3,25-triol (8b). These analogues were obtained through the same procedure as described above for the synthesis of **6a** and **6b**. A crude product, which was obtained from **23** (28.8 mg, 54.0 μmol), **15** (21.8 mg, 41.1 μmol), and LiHMDS (1 M solution in THF, 50 μL, 50 μmol), was partially purified by silica gel column chromatography (hexane/AcOEt = 30:1) to give protected 19-norvitamin D_3 (30.5 mg). To a solution of the crude 19-norvitamin D_3 (30.0 mg, 35.9 μmol) in dry MeOH (1 mL) was added (+)-CSA (42 mg, 180 μmol) at 0 °C, and the mixture was stirred at rt for 38 h. The usual workup and purification on silica gel column chromatography (AcOEt/MeOH = 10:1)

afforded 11.8 mg of **8** as a mixture of isomers in a ratio of ca. 1:1 (62%). The isomers were separated by reversed-phase HPLC (YMC-Pack ODS column, 20 × 150 mm, 9.9 mL/min) using CH_3CN/H_2O (80:20) as a solvent system. Data for **8a** (2α-3-hydroxypropylated **5**): t_R = 10.8 min. $[\alpha]^{22}_D$: +11.4 (*c* 0.19, $CHCl_3$). UV (EtOH): λ_{max} 243.5, 252.0, 261.5 nm; λ_{min} 247.5, 258.5 nm. ^1H NMR (600 MHz, $CDCl_3$): δ 0.53 (s, 3H, 18-H_3), 0.94 (d, *J* = 6.6 Hz, 3H, 21-H_3), 1.07 (m, 1H), 1.22 (s, 6H, 26-H_3 and 27-H_3), 1.24−1.33 (m, 5H), 1.36−1.42 (m, 4H), 1.44−1.56 (m, 5H), 1.59−1.61 (m, 3H), 1.66−1.70 (m, 2H), 1.77−1.78 (m, 2H), 1.89 (m, 1H), 2.00−2.02 (m, 2H), 2.13−2.18 (m, 2H), 2.60 (dd, *J* = 4.7, 12.7 Hz, 1H, 4α-H), 2.80 (dd, *J* = 4.7, 12.6 Hz, 1H, 9β-H), 2.86 (dd, *J* = 4.3, 13.9 Hz, 1H, 10α-H), 3.66 (dt, *J* = 4.7, 9.6 Hz, 1H, 3α-H), 3.70−3.72 (m, 2H, $-CH_2CH_2CH_2OH$), 4.10 (dt, *J* = 4.3, 7.1 Hz, 1H, 1β-H), 5.82 (d, *J* = 11.1 Hz, 1H, 7-H), 6.38 (d, *J* = 11.1 Hz, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.4, 18.8, 20.8, 22.2, 23.5, 27.7, 28.9, 29.2, 29.4, 30.2, 35.6, 36.1, 36.4(2C), 40.5, 44.4, 45.3, 45.8, 48.8, 56.3, 56.5, 63.0, 68.6, 71.1, 71.7, 115.2, 124.1, 131.1, 143.3. IR (neat): 3362, 2924, 2855, 1635 cm^{-1}. EIMS: 462 (M^+). HREIMS: calcd for $C_{29}H_{50}O_4$ (M^+) 462.3709, found 462.3712. Data for **8b** (2β-3-hydroxypropylated **5**): t_R = 10.1 min. $[\alpha]^{21}_D$: +6.8 (*c* 0.16, $CHCl_3$). UV (EtOH): λ_{max} 243.5, 252.0, 261.5 nm. λ_{min} 247.0, 258.0 nm. ^1H NMR (600 MHz, $CDCl_3$): δ 0.55 (s, 3H, 18-H_3), 0.94 (d, *J* = 6.3 Hz, 3H, 21-H_3), 1.07 (m, 1H), 1.22 (s, 6H, 26-H_3 and 27-H_3), 1.24−1.33 (m, 5H), 1.37−1.48 (m, 5H), 1.53−1.60 (m, 6H), 1.66−1.68 (m, 2H), 1.79−1.82 (m, 2H), 1.88−1.92 (m, 2H), 1.99−2.02 (m, 2H), 2.36 (ddd, *J* = 1.5, 3.6, 13.7 Hz, 1H, 4β-H), 2.41 (br d, *J* = 13.7 Hz, 1H, 4α-H), 2.80 (dd, *J* = 4.7, 12.9 Hz, 1H, 9β-H), 3.10 (ddd, *J* = 1.5, 4.8, 12.9 Hz, 1H, 10β-H), 3.56 (dt, *J* = 4.8, 10.2 Hz, 1H, 1β-H), 3.69−3.71 (m, 2H, $-CH_2CH_2CH_2OH$), 4.05 (m, 1H, 3α-H), 5.87 (d, *J* = 11.3 Hz, 1H, 7-H), 6.26 (d, *J* = 11.3 Hz, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.0, 18.8, 20.8, 22.3, 23.5, 23.8, 27.7, 29.0, 29.2, 29.4, 29.9, 36.1, 36.4, 37.9, 40.4, 44.1, 44.4, 45.8, 49.0, 56.3, 56.5, 63.0, 68.3, 71.1, 71.2, 115.2, 123.5, 131.0, 143.2. IR (neat): 3360, 2924, 2855, 1653 cm^{-1}. EIMS: 462 (M^+). HREIMS: calcd for $C_{29}H_{50}O_4$ (M^+) 462.3709, found 462.3723.

(a*RS*,1*R*,3*R*,7*E*)-9,10-Seco-19-norcholesta-5,7-diene-1,2,3,25-tetraol (30). To a solution of **23** (31.8 mg, 59.6 μmol) in dry THF (200 μL) was added LiHMDS (1 M solution in THF, 55 μL, 55 μmol) at −78 °C in an argon atmosphere. After the mixture was stirred at the same temperature for 1 h, a solution of ketone **29** (11.0 mg, 36.6 μmol) in dry THF (200 μL) was added dropwise. This was stirred for 3 h, the resulting mixture was poured into saturated aqueous NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane/AcOEt = 9:1) afforded crude protected 2-hydroxy-19-norvitamin (22.7 mg) as a colorless oil, which was used in the next step without further purification. To a solution of crude protected 19-norvitamin (20.6 mg, 33.3 μmol) in dry MeOH (1 mL) was added (+)-CSA (35 mg, 168 mmol) at 0 °C in an argon atmosphere. After being stirred at rt for 38 h, the reaction mixture was diluted with AcOEt. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (AcOEt/MeOH = 10:1) afforded 9.0 mg of **30** (diastereomer mixture) as white powder in a ratio of ca. 1:1 (64%). ^1H NMR (400 MHz, $CDCl_3$) β-isomer (selected): δ 0.55 (s, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 1.22 (s, 6H), 2.62 (dd, *J* = 4.0, 13.3 Hz, 1H), 2.80 (br d, *J* = 12.7 Hz, 1H), 3.08 (dd, *J* = 4.3, 13.1 Hz, 1H), 3.48−3.54 (m, 1H), 3.68 (m, 1H), 4.08 (m, 1H), 5.84 (d, *J* = 11.0 Hz, 1H), 6.29 (d, *J* = 11.0 Hz, 1H); α-isomer (selected): δ 2.90 (dd, *J* = 4.2, 14.4 Hz, 1H), 3.79 (m, 1H), 5.81 (d, *J* = 11.2 Hz, 1H), 6.38 (d, *J* = 11.2 Hz, 1H). These data are identical with those of ref 19.

Binding Assays to the Bovine Thymus VDR.[31] Bovine thymus 1α,25-dihydroxyvitamin D_3 receptor was obtained from Yamasa Biochemical (Chiba, Japan) and dissolved in 0.05 M phosphate buffer (pH 7.4) containing 0.3 M KCl and 5 mM dithiothreitol just before use. The receptor solution (500 μL, 0.23 mg protein) was preincubated with 50 μL of ethanol solution of 1α,25-dihydroxyvitamin D_3 or an analogue at various concentrations for 60 min at 25 °C. Then, the receptor mixture was left to stand overnight with 0.1 nM [^{3}H]-1α,25-dihydroxyvitamin D_3 at 4 °C. The bound and free [^{3}H]-1α,25-dihydroxyvitamin D_3 were separated by treatment with dextran-coated charcoal for 30 min at 4 °C and centrifuged at 3000 rpm for 10 min. The radioactivity of the supernatant (500 μL) with ACS-II (9.5 mL) (Amersham, UK) was then counted. This experiment was repeated one more time for each analogue to take the mean. The binding curves are shown in the Supporting Information. The relative potency of the analogues was calculated from their concentration needed to displace 50% of [^{3}H]-1α,25-dihydroxyvitamin D_3 from its receptor compared with the activity of 1α,25-dihydroxyvitamin D_3 (assigned a 100% value).

Assays for Induction of HL-60 Cell Differentiation. Activity of the analogues on differentiation of HL-60 cells was estimated by nitroblue tetrazolium (NBT) reduction assay[32] with some modifications. Human promyelocytic leukemia HL-60 cells were grown at 37 °C in RPMI 1640 medium (Asahi Technologlass Co., Chiba, Japan) supplemented with 10% fetal bovine serum (Sigma, St. Louis, MO) in an atmosphere of 95% air and 5% CO_2. Cells were collected, suspended in 1.5 mL of the culture medium containing various concentrations (0, $10^{-10}-10^{-6}$ M) of the analogues at a density of ca. 5×10^5 cells/mL, and then cultivated for 5 days. After the treatment, cells were harvested and suspended in Tyrode's solution (140 mM NaCl, 2.7 mM KCl, 1.1 mM $MgCl_2$, 1 mM $CaCl_2$, 0.45 mM NaH_2PO_4, 5.6 mM D-glucose, pH 7.4) containing 25 mM HEPES and 0.05% NBT (Dojindo Laboratories, Kumamoto, Japan). After preincubation at 37 °C for 7 min, phorbol 12-myristate 13-acetate (4 μM, Sigma, St. Louis, MO) was added to the cell suspension, and the suspension was incubated for 30 min at 37 °C. EDTA (10 mL) was added to stop the reaction, and then the percentage of positive cells (blue-stained cells) was determined using a hemocytometer. This experiment was done for three times for each analogue. EC_{50} value was estimated from the obtained dose−response curve (Supporting Information). Relative differentiation activity was calculated according to the following formula: relative differentiation activity = (EC_{50} of 1α,25-dihydroxyvitamin D_3/EC_{50} of the analogue) × 100.

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Supporting Information Available: General experimental details, ^1H NMR and ^{13}C NMR spectra for all new compounds (**10**−**15**, **21**−**23**, **6a**,**b**−**8a**,**b**), charts of VDR binding assays of compounds **6a**,**b**−**8a**,**b**, and charts for assays of induction of HL-60 cell differentiation activity of compounds **6a**,**b**−**8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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