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## SYNTHESIS AND 2 $\alpha$ -MODIFICATION OF 24-PHENYLVITAMIN D<sub>3</sub> LACTONES: EFFECTS ON VDR ANTAGONISTIC ACTIVITY

Nozomi Saito,<sup>1</sup> Toshihiro Matsunaga,<sup>1</sup> Hiroshi Saito,<sup>2</sup> Miyuki Anzai,<sup>2</sup>  
Kazuya Takenouchi,<sup>2</sup> Daishiro Miura,<sup>2</sup> Seiichi Ishizuka,<sup>2</sup> Hiroaki  
Takayama,<sup>1</sup> and Atsushi Kittaka\*<sup>1</sup>

<sup>1</sup>Faculty of Pharmaceutical Sciences, Teikyo University, Kanagawa 199-0195,  
Japan, <sup>2</sup>Teijin Institute for Bio-Medical Research, Tokyo 191-8512, Japan  
akittaka@pharm.teikyo-u.ac.jp

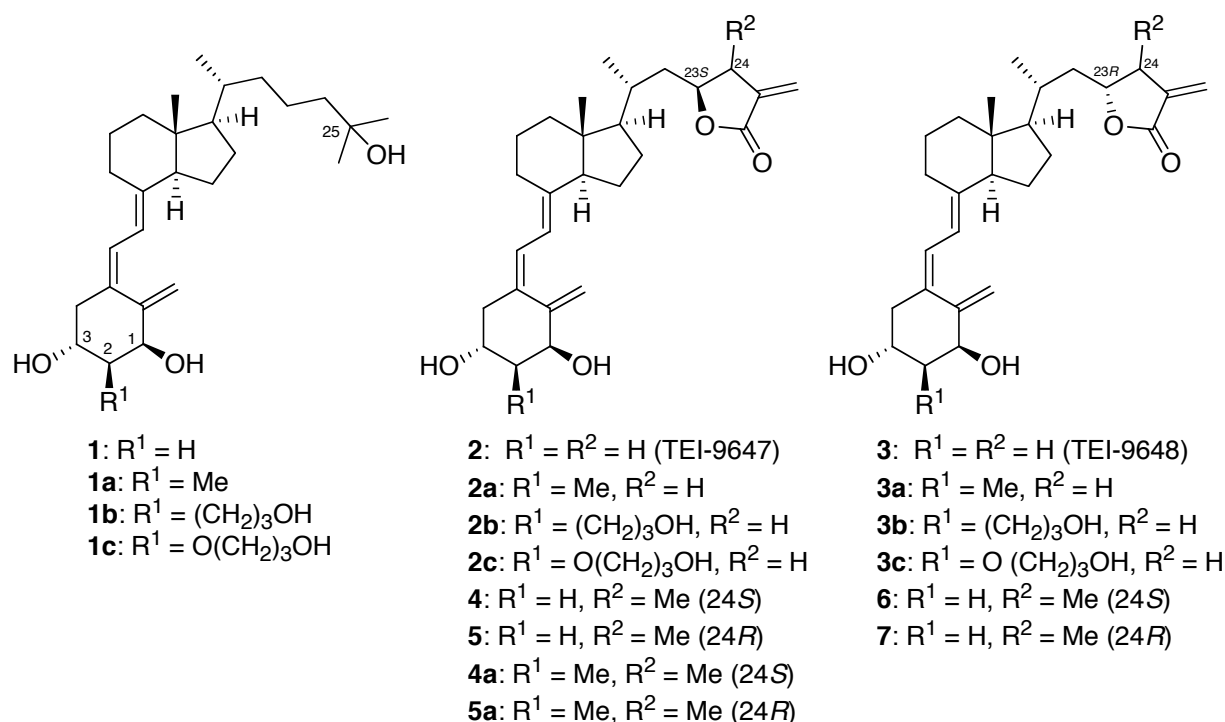
**Abstract** – Novel vitamin D receptor (VDR) antagonists, 1 $\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactones were synthesized by Trost's methodology. The biological evaluation revealed that both the binding affinity for VDR and antagonistic activity were affected by the orientation of the phenyl group on the lactone ring. The modification of the 2 $\alpha$ -position of the 24-phenylvitamin D<sub>3</sub> lactones improved the antagonistic activity up to 41 times higher than that of TEI-9647.

This paper is dedicated to professor Barry M. Trost on the occasion of his 65th birthday.

### INTRODUCTION

It is well known that 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (**1**, Figure 1) regulates not only calcium homeostasis but also differentiation and proliferation of various types of tumor cells and immune reaction.<sup>1,2</sup> Most of the biological responses of **1** are mediated by its specific receptor, vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily and acts as ligand-dependent gene transcriptional factor with coactivators.<sup>3,4</sup> Recently, we reported the systematic synthesis of the vitamin D<sub>3</sub> analogs focused on the A-ring structure.<sup>5-9</sup> During the course of our synthetic studies, we found some functionalization of the C2 $\alpha$  position on the A-ring increased the binding affinity for VDR with potent agonistic activity. That is, introduction of 2 $\alpha$ -methyl (**1a**),<sup>5</sup> 2 $\alpha$ -(3-hydroxypropyl) (**1b**),<sup>6</sup> and 2 $\alpha$ -(3-hydroxypropoxy) (**1c**)<sup>7</sup> groups showed 2- to 4-fold higher VDR binding affinity relative to the natural hormone (**1**).

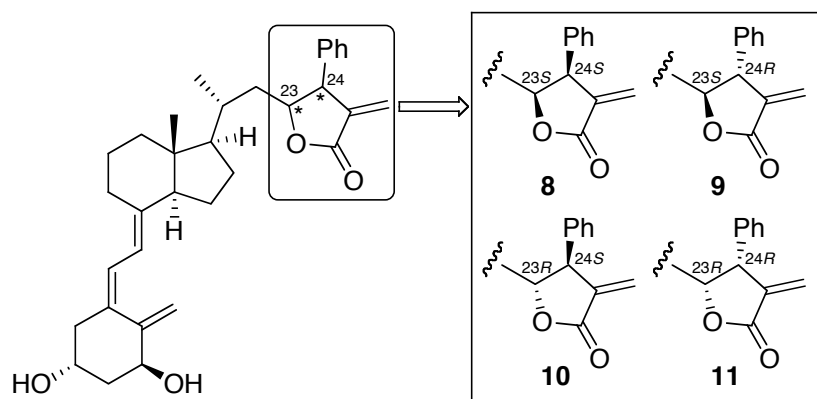
25-Dehydro-1 $\alpha$ -hydroxyvitamin D<sub>3</sub>-26,23-lactones, TEI-9647 (**2**) and TEI-9648 (**3**) are the first VDR antagonists which were discovered through the side-chain modification of the 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>-26,23-lactone metabolite<sup>10</sup> derived from **1**.<sup>11,12</sup> Both of **2** and **3** specifically antagonize the VDR mediated genomic action of the natural hormone (**1**). For example, **2** and **3** inhibit the differentiation of human leukemia cells (HL-60 cells)<sup>11a</sup> as well as 25-hydroxyvitamin D<sub>3</sub>-24-hydroxylase gene expression in human osteosarcoma cells<sup>11b</sup> and in HL-60 cells.<sup>11d</sup> With this background, we set out to conduct a structure-activity relationship study on the vitamin D<sub>3</sub> lactones, and we found some pertinent structural modification of **2** and **3** enhanced their biological activity.<sup>13,14</sup> Namely, introduction of the above three motifs, *i.e.*, the methyl, the 3-hydroxypropyl or the 3-hydroxypropoxy group, into the C2 $\alpha$  position of **2** and **3** (**2a-c** and **3a-c**) raised the potential of the antagonistic activity up to 30-fold.<sup>13a</sup> It was also found that the biological activity of **2** and **3** were affected by lactone ring substituents (**4-7**).<sup>13b</sup> Especially, introducing the methyl group into the C24 position on the lactone ring improved the antagonistic activity to be up to 2.5-fold more potent than that of **2**. Furthermore, we disclosed that **4a** and **5a** with simultaneous double functionalization of the C2 $\alpha$  and C24 positions of **2** possess up to 62-fold improved antagonistic activity over **2**.



**Figure 1.**

We report here synthesis and biological evaluation of newly designed 1 $\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactones (**8-11**) to investigate how an aromatic ring on the lactone ring core structure works for

the antagonism. We were particularly interested in the steric and electronic effects of the aromatic ring on the biological activities (Figure 2).

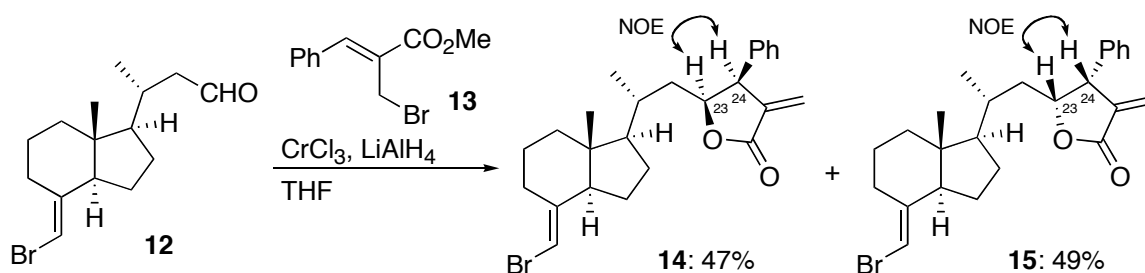


**Figure 2.**

## RESULTS

### SYNTHESIS OF 24-PHENYLVITAMIN D<sub>3</sub>-26,23-LACTONES

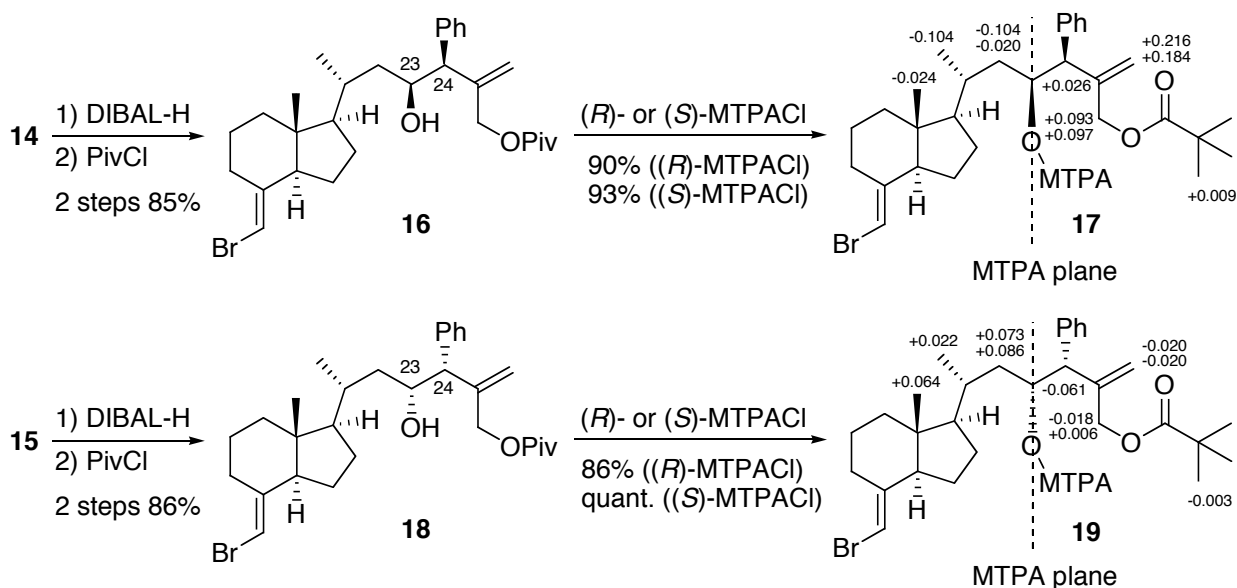
For the construction of the triene-unit of the vitamin D structure, we utilized Trost's alkenylative cyclization<sup>15</sup> of an A-ring precursor with a CD-ring counterpart. First of all, we synthesized CD-ring components having the 23,24-*syn* lactone part, using low-valent Cr-mediated *syn*-selective allylation-lactonization process.<sup>16</sup> The aldehyde (**12**)<sup>13a</sup> reacted with allylic bromide (**13**)<sup>17</sup> in the presence of Cr(II) complex generated from CrCl<sub>3</sub> and LiAlH<sub>4</sub> to give two lactone derivatives (**14**) and (**15**), whose relative stereochemistries on C23 and C24 positions (based on steroidal numbering) were determined by NOE experiments to be *syn*-orientation, respectively.



**Scheme 1.**

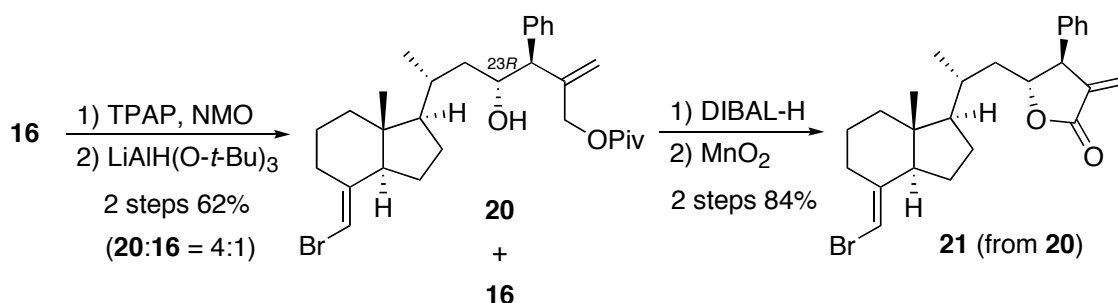
Next, the lactone derivatives (**14**) and (**15**) were transformed into the corresponding MTPA esters (**17**) and (**19**), and the values of  $\Delta\delta = \delta_{(S)\text{-MTPA ester}} - \delta_{(R)\text{-MTPA ester}}$  in the <sup>1</sup>H NMR spectra of **17** and **19** were

calculated, respectively. These data were considered by applying a modified Mosher's method,<sup>18</sup> and the absolute configurations at the C23 position of **17** and **19** were determined to be 23*S* and 23*R*, respectively. From these results and the above NOE experiments shown in Scheme 1, the absolute stereochemistries at the C24 position of **17** and **19** were 24*S* and 24*R*, respectively.



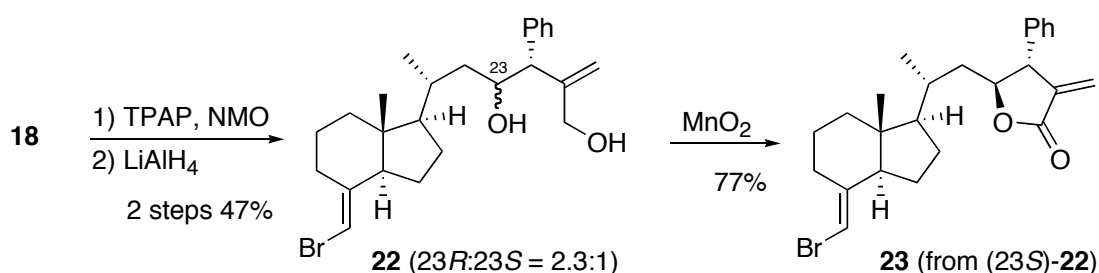
Scheme 2.

The CD ring precursor having 23,24-*anti* lactone unit (**21**) was prepared from **16** derived from the 23,24-*syn* lactone derivative (**14**) (Scheme 3). The oxidation of the secondary hydroxyl group of **16** gave the corresponding ketone derivative, which was reduced by  $\text{LiAlH}(\text{O}-t\text{-Bu})_3$  to give the desired (23*R*)-alcohol (**20**) along with **16** in a ratio of 4 to 1. Deprotection of the pivaloyl group of **20** by DIBAL-H followed by  $\text{MnO}_2$  oxidation provided the *anti* lactone (**21**).



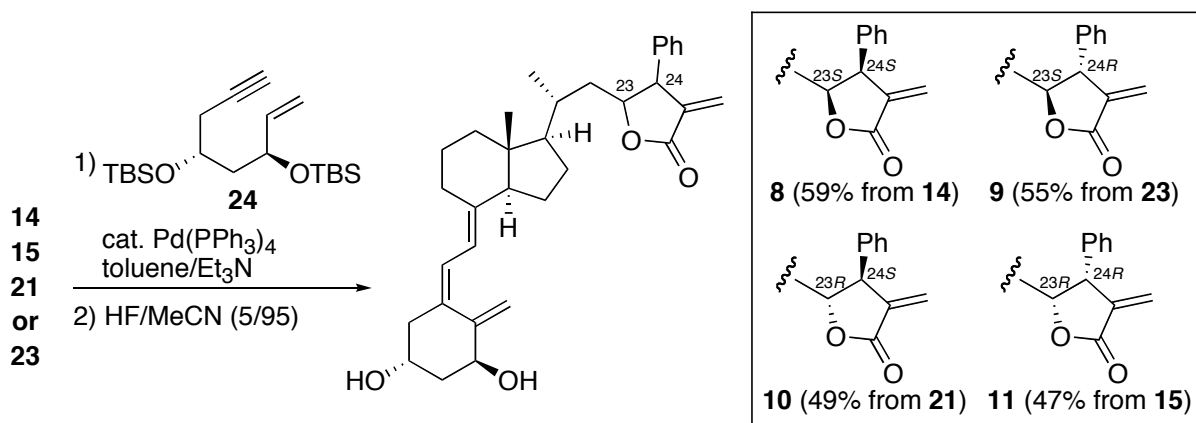
Scheme 3.

On the other hand, another 23,24-*syn* derivative (**18**) was oxidized by TPAP, then the resulting ketone was reduced by  $\text{LiAlH}_4$  to give diol derivative (**22**) ((23*R*)-OH : (23*S*)-OH = 2.3 : 1) (Scheme 4). Then the (23*S*)-isomer of **22** was converted into the 23,24-*anti* lactone derivative (**23**) by  $\text{MnO}_2$  oxidation.



Scheme 4.

Construction of the vitamin D<sub>3</sub> triene skeleton was accomplished by Pd-catalyzed alkenylative cyclization of enyne (**24**)<sup>5a</sup> with the above CD-ring counterparts (**14**, **15**, **21**, or **23**); then acid-mediated deprotection of TBS groups gave the desired 24-phenylvitamin D<sub>3</sub> lactone analogs (**8-11**) (Scheme 5).



Scheme 5.

## BIOLOGICAL EVALUATION OF 24-PHENYLVITAMIN D<sub>3</sub>-26,23-LACTONES

The binding affinities for VDR and antagonistic activity of vitamin D<sub>3</sub> lactones (**8-11**) were evaluated, and these biological activities were found to be affected by the structure of the lactone ring (Table 1). The binding affinity for chick intestinal VDR was examined as described previously.<sup>19</sup> The affinity of (23*S*,24*S*)-lactone (**8**) increased to 2.4-fold more potent than that of TEI-9647 (**2**), and (23*S*,24*R*)-lactone (**9**) showed same affinity as **2**. In the case of (23*R*) lactones, the affinity of (24*S*)-derivative (**10**) was almost same as that of **3**, and the introduction of the (24*S*)-phenyl group (**11**) into **3** raised the affinity to 2.6 times higher compared with that of the original **3**. Next, the antagonistic activities of **8-11** were assessed by the NBT-reduction method<sup>20</sup> in terms of IC<sub>50</sub> for differentiation of HL-60 cells induced by 10 nM of **1**. The antagonistic activity of (23*S*)-lactones (**8**) and (**9**) decreased as compared to **2**. Although (23*R*,24*S*)-lactone (**10**) showed lower antagonistic activity than **3**, the antagonistic activity of (23*R*,24*R*)-lactone derivative (**11**) increased to 4.5 times stronger than that of the original **3**.

**Table 1.** Biological activities of 24-phenylvitamin D<sub>3</sub> lactones (**8-11**).

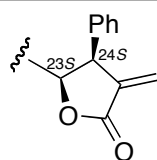
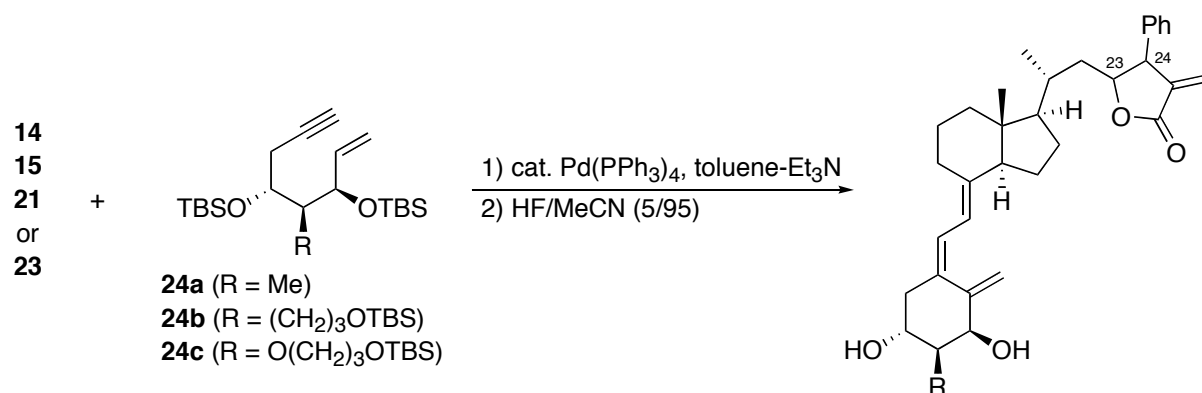
compound	VDR binding affinity <sup>a</sup>	antagonistic activity (IC <sub>50</sub> , nM) <sup>b</sup>
TEI-9647 ( <b>2</b> )	12	9.4
<b>8</b>	29	22
<b>9</b>	12	29
TEI-9648 ( <b>3</b> )	7.0	134
<b>10</b>	5.0	208
<b>11</b>	18	30

<sup>a</sup>The potency of **1** is normalized to 100.

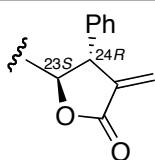
<sup>b</sup>Antagonistic activity was assessed in terms of IC<sub>50</sub> (nM) for differentiation of HL-60 cells induced by 10 nM of **1**.

### EFFECT OF 2 $\alpha$ -MODIFICATION OF 24-PHENYLVITAMIN D<sub>3</sub> LACTONES

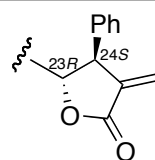
Next, we focused on the 2 $\alpha$ -modification of the four 24-phenylvitamin D<sub>3</sub> lactones (**8-11**). According to our results, 2 $\alpha$ -modification of the vitamin D<sub>3</sub> lactone analogs effectively enhanced both binding affinity for VDR and antagonistic activity.<sup>13,14</sup> Therefore, we expected that introducing the three motifs, *i.e.*, methyl, 3-hydroxypropyl and 3-hydroxypropoxyl groups into the C2 $\alpha$ -position of **8-11** would increase the receptor binding affinity and improve the antagonistic activity. The 2 $\alpha$ -modified 24-phenylvitamin D<sub>3</sub> lactones (**8a-c**, **9a-c**, **10a-c**, and **11a-c**) were similarly synthesized from the corresponding CD-ring unit (**14**, **15**, **21**, and **23**) with the A-ring counterpart (**24a**,<sup>21</sup> **24b**<sup>14</sup> and **24c**<sup>7</sup>), respectively (Scheme 6).



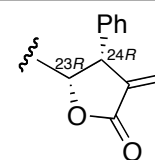
**8a**: 43% (R = Me)



**9a**: 45% (R = Me)



**10a**: 45% (R = Me)



**11a**: 54% (R = Me)

**8b**: 54% (R = (CH<sub>2</sub>)<sub>3</sub>OH)

**9b**: 42% (R = (CH<sub>2</sub>)<sub>3</sub>OH)

**10b**: 45% (R = (CH<sub>2</sub>)<sub>3</sub>OH)

**11b**: 47% (R = (CH<sub>2</sub>)<sub>3</sub>OH)

**8c**: 46% (R = O(CH<sub>2</sub>)<sub>3</sub>OH)

**9c**: 37% (R = O(CH<sub>2</sub>)<sub>3</sub>OH)

**10c**: 41% (R = O(CH<sub>2</sub>)<sub>3</sub>OH)

**11c**: 51% (R = O(CH<sub>2</sub>)<sub>3</sub>OH)

**Scheme 6.**

The biological evaluation of **8a-c** and **9a-c** demonstrated that the 2 $\alpha$ -modification was effective in improving the biological activities of (23*S*)-24-phenylvitamin D<sub>3</sub> lactones (**8**) and (**9**) (Table 2). Namely, the binding affinity of (24*S*)-series (**8a-c**) increased to 1.9-3.3 times as compared to TEI-9647 (**2**). On the other hand, (24*R*)-series (**9a-c**) showed 1.4-2.3 times higher VDR binding affinities than **2**. The antagonistic activity of **8** was enhanced up to 41-fold stronger (**8b**) than that of **2** by 2 $\alpha$ -modification. On the other hand, 2 $\alpha$ -functionalization of (24*R*)-series also exhibited improvement of the antagonistic activity. In particular, 2 $\alpha$ -(3-hydroxypropyl) analog (**9b**) showed 15 times higher antagonistic activity than that of the original **2**.

**Table 2.** Biological activities of 2 $\alpha$ -modified (23*S*)-24-phenyl VD<sub>3</sub> Lactones (**8a-c** and **9a-c**).

compound	VDR binding affinity <sup>a</sup>	antagonistic activity (IC <sub>50</sub> , nM) <sup>b</sup>
TEI-9647 ( <b>2</b> )	12	9.4
<b>8a</b>	23	3.6
<b>8b</b>	34	0.23
<b>8c</b>	40	0.28
<b>9a</b>	17	17
<b>9b</b>	24	0.64
<b>9c</b>	28	2.6

<sup>a</sup>The potency of **1** is normalized to 100.

<sup>b</sup>Antagonistic activity was assessed in terms of IC<sub>50</sub> (nM) for differentiation of HL-60 cells induced by 10 nM of **1**.

The biological activities of 2 $\alpha$ -modified TEI-9648 type analogs (**10a-c** and **11a-c**) were summarized in Table 3. In all 2 $\alpha$ -modified analogs (**10a-c** and **11a-c**), enhancement of binding affinity for VDR was observed. Especially, (23*R*,24*S*)-analog having the 2 $\alpha$ -(3-hydroxypropoxy) group (**10c**) showed 4.0 times higher VDR binding affinity than that of TEI-9648 (**3**) and 5.6 times higher than 2 $\alpha$ -nonsubstituted analog (**10**). It was also demonstrated that the antagonistic activity of the (23*R*)-24-phenylvitamin D<sub>3</sub> lactones (**10** and **11**) was dramatically enhanced by the 2 $\alpha$ -functionalization. Namely, the low antagonistic activity of **10** was improved by such modification. In particular, 2 $\alpha$ -(3-hydroxypropoxy) analog (**10c**) showed 5.8-fold stronger antagonistic activity than that of TEI-9648 (**3**) and 9-fold stronger than **10**. In the case of (24*R*)-series (**11a-c**), the antagonistic activity was markedly increased to 21-37 times more potent than that of the original **3**.

**Table 3.** Biological activities of 2 $\alpha$ -modified (23*R*)-24-phenyl VD<sub>3</sub> Lactones (**10a-c** and **11a-c**).

compound	VDR binding affinity <sup>a</sup>	antagonistic activity (IC <sub>50</sub> , nM) <sup>b</sup>
TEI-9648 ( <b>3</b> )	7	134
<b>10a</b>	13	150
<b>10b</b>	18	88
<b>10c</b>	28	23
<b>11a</b>	19	5.3
<b>11b</b>	26	3.6
<b>11c</b>	24	6.3

<sup>a</sup>The potency of **1** is normalized to 100.

<sup>b</sup>Antagonistic activity was assessed in terms of IC<sub>50</sub> (nM) for differentiation of HL-60 cells induced by 10 nM of **1**.

## DISCUSSION

The VDR-mediated transactivation is triggered by a ligand binding to the ligand-binding domain (LBD) of the apo form of VDR. Then, the ligand-VDR complex changes its conformation into a transcriptionally active holo form, which binds to the coactivators.<sup>22</sup> During conformational change, helix 12, which is the most C-terminal  $\alpha$ -helix of VDR and has the site for interaction with other proteins such as coactivators, plays an important role. That is, it controls whether the function of a ligand is agonism or antagonism.<sup>23</sup> When the VDR antagonist TEI-9647 (**2**) binds to the LBD of a VDR, the conformation of the complex would change into an unusual transcriptionally inactive form.<sup>24</sup> We speculate that some amino acid residues in the LBD participate in the conformational change of the VDR through the interaction of the *exo*-methylene moiety on the lactone ring of **2**. There are two cysteine residues, Cys403 on helix 11 and Cys410 in the hinge region between helix 11 and helix 12 in the LBD of the hVDR. Recently, it was revealed that the two cysteines, Cys403 and Cys410, play an important role in the VDR antagonism of TEI-9647 (**2**).<sup>25,26</sup> Furthermore, the  $\alpha$ -methylene- $\gamma$ -lactone unit is essential for the antagonistic action of the vitamin D<sub>3</sub> lactones.<sup>27</sup> Based on these results, we consider that the nucleophilic thiol groups of the cysteines could attack the  $\alpha$ -methylene- $\gamma$ -lactone of **2** via 1,4-addition to give the corresponding cysteine adduct.<sup>28</sup> Since such interaction between the ligand and the LBD might prevent the well suited positioning of helix 12 for agonism, the VDR-**2** complex could not adopt the transcriptionally active conformation. Therefore, it is thought that the VDR antagonists, whose *exo*-methylene moiety is located at a more favorable position to interact with Cys403 and/or Cys410, show stronger VDR antagonistic activity. The newly synthesized 24-phenylvitamin D<sub>3</sub> lactone analogs,



which exhibited more potent antagonistic activity, might be located in the above preferable position to interact with the cysteines after binding to the LBD of the VDR. Further mechanistic investigation of the antagonism is in progress.

In summary, we synthesized and biological evaluated the novel potent vitamin D receptor antagonists,  $1\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactones (**8-11**) and their  $2\alpha$ -modified analogs (**8a-c**, **9a-c**, **10a-c** and **11a-c**). The VDR antagonists are expected to be potent therapeutic agents for some disease caused by hypersensitivity of the VDR to the natural hormone (**1**) such as Paget's disease of bone.<sup>29</sup> We expected these analogs with potent anti-D activity to contribute to our understanding of the mechanisms involved in the expression of antagonistic activity toward VDR as well as to finding novel medicines for treating Paget's disease of bone.

## EXPERIMENTAL

**General:** All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 N (Kanto Chemical Co., Inc., 100-210  $\mu\text{m}$ ), and flash column chromatography was performed on silica gel 60 (Merck, 40-63  $\mu\text{m}$ ).

**(S)-5-((R)-2-((1R,4E,3aR,7aR)-4-Bromomethylene-7a-methylperhydroindene-1-yl)propyl)-3-methylene-(4S)-phenyldihydrofuran-2-one (14)** and **(R)-5-((R)-2-((1R,4E,3aR,7aR)-4-Bromomethylene-7a-methylperhydroindene-1-yl)propyl)-3-methylene-(4R)-phenyldihydrofuran-2-one (15)**. To a suspension of  $\text{CrCl}_3$  (1.48 g, 9.4 mmol) in THF (38 mL) was added  $\text{LiAlH}_4$  (178 mg, 4.7 mmol) at 0 °C, and the mixture was stirred at rt for 30 min. To the mixture were added a solution of **13** (1.2 g, 4.7 mmol) in THF (20 mL) and a solution of **12** (700 mg, 2.3 mmol) in THF (20 mL) at rt, and the mixture was stirred at the same temperature for 2.5 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with saturated NaCl aq. solution, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by column chromatography on silica gel (toluene/ $\text{CH}_2\text{Cl}_2$  = 9/1) to give **14** (486 mg, 47%) and **15** (513 mg, 49%), respectively. **14**: colorless oil;  $[\alpha]_{\text{D}}^{24}$  -24.8° (*c* 0.69,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  0.38 (s, 3H), 0.52 (m, 1H), 0.97 (d, *J* = 6.0 Hz, 3H), 1.16-1.28 (m, 5H), 1.36-1.42 (m, 2H), 1.48-1.55 (m, 2H), 1.59-1.64 (m, 2H), 1.88 (ddd, *J* = 12.5, 6.6, 1.5 Hz, 1H), 1.91 (br d, *J* = 14.0 Hz, 1H), 2.83 (m, 1 H), 4.26 (ddd, *J* = 7.2, 2.2, 2.2 Hz, 1H), 4.82 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 5.58 (dd, *J* = 1.6, 1.6 Hz, 1H), 5.61 (d, *J* = 2.1 Hz, 1H), 6.41 (d, *J* = 2.1 Hz, 1H), 7.12-7.13 (m, 2H), 7.29 (tt, *J* = 7.3, 1.7 Hz, 1H), 7.33 (br t, *J* = 7.3 Hz, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7, 19.1, 21.8, 22.4, 26.6, 30.9, 33.1, 37.5, 39.7, 45.4, 49.6, 55.6, 55.8, 80.3, 97.5, 124.2, 127.7, 128.7 (2C), 129.0 (2C), 138.4, 139.8, 144.9, 170.5; IR (neat) 2948, 1763, 1144  $\text{cm}^{-1}$ ; EIMS *m/z*

442 ( $M^+$ ), 363, 201, 175, 147; HREIMS calcd for  $C_{25}H_{31}O_2^{79}Br$  442.1507, found 442.1499. **15**: colorless oil;  $[\alpha]_D^{23} +266.7^\circ$  (*c* 1.08,  $CHCl_3$ );  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  0.54 (s, 3H), 0.61 (ddd,  $J = 14.6, 10.7, 2.0$  Hz, 1H), 0.93 (d,  $J = 6.6$  Hz, 3H), 1.09 (dddd,  $J = 9.6, 9.6, 9.6, 9.6$  Hz, 1H), 1.14-1.26 (m, 2H), 1.34 (ddd,  $J = 14.4, 12.0, 2.3$  Hz, 1H), 1.37-1.45 (m, 2H), 1.53 (m, 1H), 1.59-1.65 (m, 3H), 1.70 (m, 1H), 1.87 (ddd,  $J = 12.3, 6.8, 1.6$  Hz, 1H), 1.95 (br d,  $J = 12.4$  Hz, 1H), 2.85 (m, 1H), 4.36 (ddd,  $J = 8.0, 2.6, 2.6$  Hz, 1H), 4.86 (ddd,  $J = 11.8, 8.0, 2.2$  Hz, 1H), 5.615 (s, 1H), 5.617 (d,  $J = 2.6$  Hz, 1H), 6.46 (d,  $J = 2.6$  Hz, 1H), 7.11-7.13 (m, 2H), 7.30 (tt,  $J = 7.3, 1.7$  Hz, 1H), 7.35 (br t,  $J = 7.3$  Hz, 2H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  11.8, 18.3, 21.9, 22.4, 27.4, 30.9, 32.6, 39.0, 39.8, 45.5, 49.6, 55.8, 56.0, 88.8, 97.6, 124.3, 127.7, 128.7 (2C), 129.0 (2C), 137.6, 139.0, 144.8, 170.4; IR (neat) 2951, 1763, 1113  $cm^{-1}$ ; EIMS  $m/z$  442 ( $M^+$ ), 363, 201, 175, 147; HREIMS calcd for  $C_{25}H_{31}O_2^{79}Br$  442.1507, found 442.1506.

**Transformation of 14 into the corresponding (S)- and (R)-MTPA ester (17).** To a solution of **14** (330 mg, 0.74 mmol) in toluene (15 mL) was added a solution of DIBAL-H in toluene (1.04 M, 9.3 mL, 9.7 mmol) at 0 °C, and the mixture was stirred at rt for 32 h. To the mixture was added 10% potassium sodium tartrate aq. solution at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over  $Na_2SO_4$ , and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 5/1) to give a diol (304 mg, 91%) as an amorphous solid.  $[\alpha]_D^{24} +105.1^\circ$  (*c* 1.08,  $CHCl_3$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.55 (s, 3H), 1.05 (d,  $J = 6.6$  Hz, 3H), 1.17 (ddd,  $J = 14.1, 8.9, 6.8$  Hz, 1H), 1.24-1.32 (m, 2H), 1.38 (ddd,  $J = 12.0, 12.0, 5.2$  Hz, 1H), 1.43-1.61 (m, 4H), 1.65-1.83 (m, 6H), 1.93 (dd,  $J = 12.5, 6.8$  Hz, 1H), 2.00 (br d,  $J = 12.5$  Hz, 1H), 2.87 (m, 1H), 3.35 (d,  $J = 6.0$  Hz, 1H), 4.00 (d,  $J = 14.5$  Hz, 1H), 4.07 (d,  $J = 14.5$  Hz, 1H), 4.23 (ddd,  $J = 6.1, 6.1, 6.0$  Hz, 1H), 5.16 (s, 1H), 5.27 (s, 1H), 5.63 (s, 1H), 7.26 (m, 1H), 7.30-7.35 (m, 4H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  11.8, 19.7, 22.0, 22.5, 27.4, 31.0, 34.8, 39.8, 41.5, 45.5, 54.7, 55.8, 56.5, 65.7, 72.0, 97.4, 113.0, 127.1, 128.5 (2C), 129.5 (2C), 138.9, 145.0, 149.5; IR (neat) 3397, 1647, 1557, 1051  $cm^{-1}$ ; EIMS  $m/z$  428 ( $M^+ - H_2O$ ) 331, 254, 227; HREIMS calcd for  $C_{25}H_{33}O^{79}Br$  428.1715, found 428.1718. To a solution of the above diol (379 mg, 0.85 mmol) in  $CH_2Cl_2$  (2.8 mL) were added pyridine (0.27 mL, 3.4 mmol) and PivCl (0.13 mL, 1.0 mmol) at 0 °C, and the mixture was stirred at rt for 23 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with  $Et_2O$ . The organic layer was washed with saturated NaCl aq. solution, dried over  $Na_2SO_4$ , and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 15/1) to give **16** (420 mg, 93%) as a colorless oil.  $[\alpha]_D^{19} +108.5^\circ$  (*c* 0.31,  $CHCl_3$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.55 (s, 3H), 1.05 (d,  $J = 6.6$  Hz, 3H), 1.20 (s, 9H), 1.24-1.34 (m, 4H), 1.44-1.63 (m, 5H), 1.65-1.73 (m, 3H), 1.79 (m, 1H), 1.94 (ddd,  $J = 12.5, 6.8, 1.2$  Hz, 1H), 2.00 (m, 1H), 2.87 (m, 1H), 3.47 (d,  $J = 5.9$  Hz, 1H), 4.22 (m, 1H), 4.40 (d,  $J = 13.3$  Hz, 1H), 4.46 (d,  $J = 13.3$  Hz, 1H), 5.25 (s, 1H), 5.28 (s, 1H), 5.63 (s, 1H), 7.25-7.33 (m, 5H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  11.9, 19.8, 22.1, 22.7, 27.3, 27.6, 31.1, 35.0, 38.9, 39.9, 41.6, 45.6, 54.2,

55.8, 56.5, 66.7, 71.7, 97.4, 114.1, 127.1, 128.4 (2C), 129.4 (2C), 138.0, 144.78, 144.84, 177.8; IR (neat) 1730, 1460, 1154  $\text{cm}^{-1}$ ; EIMS  $m/z$  429 ( $\text{M}^+$ -OPiv) 350, 232, 175; HREIMS calcd for  $\text{C}_{25}\text{H}_{34}\text{O}^{79}\text{Br}$  470.1793, found 429.1792. <Synthesis of (*S*)-MTPA ester (**17**)> To a solution of **16** (26 mg, 49  $\mu\text{mol}$ ) in pyridine (0.49 mL) were added (*R*)-MTPACl (37  $\mu\text{L}$ , 0.15 mmol) and DMAP (9 mg, 74  $\mu\text{mol}$ ) at 0 °C, and the mixture was stirred at rt for 5 days. To the mixture was added water, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with saturated NaCl aq. solution, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 20/1) to give (*S*)-MTPA ester (**17**) (33 mg, 90%) as an amorphous solid.  $[\alpha]_{\text{D}}^{20} +19.6^\circ$  ( $c$  1.15,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  0.48 (s, 3H), 0.88 (m, 1H), 0.96 (d,  $J = 6.3$  Hz, 3H), 1.14 (m, 1H), 1.21 (s, 9H), 1.24-1.45 (m, 5H), 1.52 (m, 1H), 1.60-1.72 (m, 4H), 1.88 (ddd,  $J = 12.5, 6.7, 1.5$  Hz, 1H), 1.94 (br d,  $J = 12.4$  Hz, 1H), 2.86 (m, 1H), 3.31 (s, 3H), 3.63 (d,  $J = 5.9$  Hz, 1 H), 4.46 (d,  $J = 13.4$  Hz, 1H), 4.52 (d,  $J = 13.4$  Hz, 1H), 5.01 (s, 1 H), 5.22 (s, 1H), 5.61 (s, 1H), 5.81 (ddd,  $J = 7.7, 5.9, 5.8$  Hz, 1H), 7.18-7.19 (m, 2H), 7.22-7.25 (m, 3H), 7.31-7.33 (m, 2H), 7.35-7.38 (m, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7, 19.3, 21.9, 22.5, 26.9, 27.2 (3C), 30.9, 33.5, 38.8, 39.0, 39.7, 45.5, 51.5, 55.2, 55.6, 56.4, 66.2, 76.1, 84.5 (q,  $^2J_{\text{C-F}} = 27.6$  Hz), 97.6, 115.5, 123.2 (q,  $^1J_{\text{C-F}} = 288.7$  Hz), 127.3, 127.5, 128.2 (2C), 128.4 (2C), 129.4 (2C), 129.7 (2C), 131.9, 137.5, 143.6, 144.8, 166.0, 177.8; IR (neat) 1738, 1260, 1169  $\text{cm}^{-1}$ ; EIMS  $m/z$  746 ( $\text{M}^+$ ), 669, 513, 434, 333, 256; HREIMS calcd for  $\text{C}_{30}\text{H}_{42}\text{O}_2^{79}\text{Br}$  513.2368, found 513.2369. <Synthesis of (*R*)-MTPA ester (**17**)> Similar to the synthesis of (*S*)-MTPA ester (**17**) from **16**, a crude product, which was obtained from **16** (37 mg, 69  $\mu\text{mol}$ ), (*S*)-MTPACl (37  $\mu\text{L}$ , 0.12 mmol) and DMAP (9 mg, 73  $\mu\text{mol}$ ) in pyridine (0.49 mL), was purified by column chromatography on silica gel (hexane/AcOEt = 20/1) to give (*R*)-MTPA ester (**17**) (34 mg, 93%) as a colorless oil.  $[\alpha]_{\text{D}}^{22} +35.4^\circ$  ( $c$  0.38,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  0.51 (s, 3 H), 0.88 (m, 1H), 1.06 (d,  $J = 6.3$  Hz, 3H), 1.19 (m, 1H), 1.20 (s, 9H), 1.28 (m, 1H), 1.34-1.39 (m, 2H), 1.41-1.47 (m, 2H), 1.54 (m, 1H), 1.60-1.69 (m, 3H), 1.72 (ddd,  $J = 13.3, 9.1, 2.8$  Hz, 1H), 1.91 (ddd,  $J = 12.5, 6.7, 1.5$  Hz, 1H), 1.98 (br d,  $J = 12.9$  Hz, 1H), 2.86 (m, 1H), 3.38 (s, 3H), 3.60 (d,  $J = 4.6$  Hz, 1H), 4.37 (d,  $J = 13.2$  Hz, 1H), 4.43 (d,  $J = 13.2$  Hz, 1H), 4.80 (s, 1H), 5.04 (s, 1H), 5.62 (s, 1H), 5.72 (ddd,  $J = 4.6, 4.5, 4.5$  Hz, 1H), 7.15-7.17 (m, 2H), 7.21-7.25 (m, 3H), 7.33-7.39 (m, 3H), 7.44-7.45 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7, 19.0, 21.9, 22.5, 27.0 (3C), 27.2, 30.9, 33.5, 38.7, 38.8, 39.8, 45.5, 50.4, 55.4, 55.7, 56.4, 66.3, 75.9, 84.2 (q,  $^2J_{\text{C-F}} = 27.6$  Hz), 97.6, 115.5, 123.3 (q,  $^1J_{\text{C-F}} = 285.3$  Hz), 127.2, 127.3, 128.2 (4C), 129.4 (2C), 130.0 (2C), 132.1, 137.0, 143.2, 144.8, 165.9, 177.8; IR (neat) 1738, 1275, 1165  $\text{cm}^{-1}$ ; EIMS  $m/z$  513 ( $\text{M}^+$ -OPiv), 434, 333, 256; HREIMS calcd for  $\text{C}_{30}\text{H}_{42}\text{O}_2^{79}\text{Br}$  513.2368, found 513.2369.

**Transformation of **15** into the corresponding (*S*)- and (*R*)-MTPA ester (**19**).** Similar to the synthesis of a diol from **14**, a crude product, which was obtained from **15** (400 mg, 0.90 mmol) and DIBAL-H (1.04 M toluene solution, 5.3 mL, 5.4 mmol) in toluene (18 mL) at 0 °C for 8.5 h, was purified by column

chromatography on silica gel (hexane/AcOEt = 5/1) to give a diol (373 mg, 92%) as an amorphous solid.  $[\alpha]_D^{22} +45.2^\circ$  ( $c$  1.08,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.58 (s, 3H), 1.02 (d,  $J = 6.4$  Hz, 3H), 1.20-1.36 (m, 5H), 1.41-1.75 (m, 8H), 1.86 (m, 1H), 1.96 (ddd,  $J = 12.2, 6.8, 1.7$  Hz, 1H), 2.03 (m, 1H), 2.88 (m, 1H), 3.23 (d,  $J = 8.3$  Hz, 1H), 3.98 (s, 2H), 4.23 (br dd,  $J = 8.5, 8.3$  Hz, 1H), 5.16 (s, 1H), 5.24 (s, 1H), 5.63 (s, 1H), 7.23-7.35 (m, 5H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.0, 18.7, 22.1, 22.6, 27.8, 31.1, 32.9, 40.0, 41.7, 45.7, 56.0, 56.42, 56.43, 65.8, 69.8, 97.4, 111.5, 127.1, 128.6 (2C), 128.9 (2C), 139.6, 145.0, 149.3; IR (neat) 3430, 1651, 1522, 1065  $\text{cm}^{-1}$ ; EIMS  $m/z$  446 ( $\text{M}^+$ ), 428, 349, 331, 254; HREIMS calcd for  $\text{C}_{25}\text{H}_{31}\text{O}_2^{79}\text{Br}$  446.1820, found 446.1820. Similar to the synthesis of **16**, a crude product, which was obtained from the above diol (460 mg, 1.0 mmol), pyridine (0.33 mL, 4.1 mmol) and PivCl (0.15 mL, 1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.4 mL) at 0 °C for 12 h, was purified by column chromatography on silica gel (hexane/AcOEt = 15/1) to give **18** (513 mg, 94%) as a colorless oil.  $[\alpha]_D^{19} +37.1^\circ$  ( $c$  1.54,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.58 (s, 3H), 1.02 (d,  $J = 6.3$  Hz, 3H), 1.19 (s, 9 H), 1.23-1.38 (m, 5H), 1.41-1.58 (m, 4H), 1.60-1.75 (m, 3H), 1.86 (m, 1H), 1.96 (br dd,  $J = 12.2, 6.6$  Hz, 1H), 2.03 (m, 1H), 2.88 (m, 1H), 3.20 (d,  $J = 8.1$  Hz, 1H), 4.21 (br dd,  $J = 8.7, 8.7$  Hz, 1H), 4.39 (s, 2H), 5.22 (s, 1H), 5.25 (s, 1H), 5.63 (s, 1H), 7.24-7.35 (m, 5H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.1, 18.7, 22.2, 22.7, 27.3 (3C), 27.8, 31.1, 32.9, 38.9, 40.0, 41.7, 45.7, 56.0, 56.2, 56.4, 66.7, 69.6, 97.4, 111.5, 127.2, 128.6 (2C), 128.8 (2C), 138.9, 144.5, 144.8, 177.7; IR (neat) 1732, 1651, 1152  $\text{cm}^{-1}$ ; EIMS  $m/z$  429 ( $\text{M}^+\text{-OPiv}$ ), 411, 332, 255; HREIMS calcd for  $\text{C}_{25}\text{H}_{34}\text{O}^{79}\text{Br}$  429.1793, found 429.1797. <Synthesis of (*S*)-MTPA ester (**19**)> Similar to the synthesis of (*S*)-MTPA ester (**17**) from **16**, a crude product, which was obtained from **18** (34 mg, 64  $\mu\text{mol}$ ), (*R*)-MTPACl (33  $\mu\text{L}$ , 0.13 mmol) and DMAP (8 mg, 64  $\mu\text{mol}$ ) in pyridine (0.64 mL) at rt for 2 days, was purified by flash column chromatography on silica gel (hexane/AcOEt = 20/1) to give (*S*)-MTPA ester (**19**) (41 mg, 86%) as a colorless oil.  $[\alpha]_D^{21} +37.3^\circ$  ( $c$  0.23,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  0.50 (s, 3H), 1.08 (d,  $J = 6.3$  Hz, 1H), 1.21 (s, 9H), 1.26 (m, 1H), 1.30 (m, 1H), 1.38-1.46 (m, 2H), 1.50-1.59 (m, 4H), 1.63-1.69 (m, 2H), 1.81 (m, 1H), 1.87 (m, 1H), 1.96 (ddd,  $J = 12.5, 6.5, 1.5$  Hz, 1H), 2.01 (br d,  $J = 12.5$  Hz, 1H), 2.87 (m, 1H), 3.04 (s, 3H), 3.50 (d,  $J = 9.9$  Hz, 1H), 4.39 (d,  $J = 14.8$  Hz, 1H), 4.42 (d,  $J = 14.8$  Hz, 1 H), 5.19 (s, 1H), 5.22 (s, 1H), 5.64 (s, 1H), 5.98 (br dd,  $J = 9.9, 9.8$  Hz, 1H), 7.16-7.20 (m, 3H), 7.21-7.25 (m, 6 H), 7.32 (m, 1H);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7, 18.4, 22.1, 22.5, 27.2 (3C), 27.6, 31.0, 32.8, 38.8, 39.8, 40.2, 45.5, 53.9, 54.8, 55.8, 56.0, 66.1, 74.9, 84.6 (q,  $^2J_{\text{C-F}} = 27.6$  Hz), 97.6, 113.8, 123.1 (q,  $^1J_{\text{C-F}} = 288.3$  Hz), 127.3, 127.6 (2C), 128.2 (2C), 128.5 (2C), 128.8 (2C), 129.3, 131.5, 138.6, 144.1, 144.9, 166.0, 177.9; IR (neat) 1736, 1256, 1169  $\text{cm}^{-1}$ ; EIMS  $m/z$  513 ( $\text{M}^+\text{-OMTPA}$ ), 434, 333, 256; HREIMS calcd for  $\text{C}_{30}\text{H}_{42}\text{O}_2^{79}\text{Br}$  513.2368, found 513.2372. <Synthesis of (*R*)-MTPA ester (**19**)> Similar to the synthesis of (*S*)-MTPA ester (**19**) from **18**, a crude product, which was obtained from **18** (37 mg, 69  $\mu\text{mol}$ ), (*S*)-MTPACl (72  $\mu\text{L}$ , 0.28 mmol) and DMAP (18 mg, 0.14 mmol) in pyridine (0.70 mL) was purified by column chromatography on silica gel (hexane/AcOEt =

20/1) to give (*R*)-MTPA ester (**19**) (52 mg, quant.) as a colorless oil.  $[\alpha]_D^{19} +46.8^\circ$  (*c* 0.38, CHCl<sub>3</sub>); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  0.44 (s, 3H), 0.99 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.16 (m, 1H), 1.21 (s, 9H), 1.24-1.30 (m, 2H), 1.34 (m, 1H), 1.43-1.50 (m, 2H), 1.55 (m, 1H), 1.62-1.69 (m, 2H), 1.70-1.79 (m, 2H), 1.92 (ddd, *J* = 12.4, 6.5, 1.4 Hz, 1H), 1.98 (br d, *J* = 12.1 Hz, 1H), 2.86 (m, 1H), 3.11 (s, 3H), 3.52 (d, *J* = 10.2 Hz, 1H), 4.42 (s, 2H), 5.21 (br s, 1H), 5.62 (br s, 1H), 6.06 (ddd, *J* = 10.2, 10.2, 0.9 Hz, 1H), 7.07-7.08 (m, 2H), 7.19-7.22 (m, 2H), 7.23-7.31 (m, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  11.8, 18.3, 21.9, 22.5, 27.2 (3C), 27.4, 30.9, 32.7, 38.8, 39.8, 40.3, 45.5, 54.1, 54.8, 55.8, 56.0, 65.9, 74.4, 84.2 (q, <sup>2</sup>*J*<sub>C-F</sub> = 27.6 Hz), 97.5, 113.8, 123.1 (q, <sup>1</sup>*J*<sub>C-F</sub> = 288.7 Hz), 127.2, 127.3, 128.2 (2C), 128.7 (2C), 128.8 (2C), 129.2 (2C), 131.7, 138.9, 144.2, 144.9, 166.1, 177.9; IR (neat) 1738, 1262, 1154 cm<sup>-1</sup>; EIMS *m/z* 667 (M<sup>+</sup>-<sup>79</sup>Br) 566, 497, 333, 256; HREIMS calcd for C<sub>40</sub>H<sub>50</sub>O<sub>5</sub>F<sub>3</sub> 337.3610, found 667.3602.

**(1*R*,4*E*,3*aR*,7*aR*)-4-Bromomethylene-1-[(1*R*,3*R*,4*S*)-3-hydroxy-1-methyl-4-phenyl-6-pivaloyloxy-5-hexenyl]-7*a*-methylperhydroindene (**20**)** To a solution of **16** (405 mg, 0.76 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.8 mL) were added TPAP (42 mg, 0.12 mmol) and NMO (204 mg, 1.7 mmol) at rt, and the mixture was stirred at the same temperature for 7 h. After the mixture was filtered through a silica gel pad, the filtrate was concentrated. The residue was dissolved in THF (7.6 mL). To the solution was added a solution of LiAlH(O*t*-Bu)<sub>3</sub> in THF (1.0 M, 7.6 mL, 7.6 mmol) at 0 °C, and the mixture was stirred at rt for 23 h. To the mixture was added saturated NH<sub>4</sub>Cl aq. solution at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 15/1) to give **20** (202 mg, 50% in 2 steps) and **16** (50 mg, 12% in 2 steps), respectively.  $[\alpha]_D^{27} +85.4^\circ$  (*c* 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.57 (s, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 1.10 (m, 1H), 1.20 (s, 9H), 1.16-1.33 (m, 3H), 1.38-1.49 (m, 3H), 1.51-1.66 (m, 3H), 1.72-1.85 (m, 2H), 1.90 (br dd, *J* = 11.8, 7.0 Hz, 1H), 1.97 (br d, *J* = 12.9 Hz, 1H), 2.36 (br s, 1H), 2.85 (m, 1H), 3.26 (d, *J* = 9.7 Hz, 1H), 4.27 (br dd, *J* = 9.8, 9.7 Hz, 1H), 4.36 (d, *J* = 13.9 Hz, 1H), 4.53 (d, *J* = 13.9 Hz, 1H), 5.25 (s, 1H), 5.34 (s, 1H), 5.62 (s, 1H), 7.16-7.18 (m, 2H), 7.21-7.31 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.0, 18.6, 22.1, 22.6, 27.2 (3C), 27.7, 31.1, 32.8, 38.8, 39.9, 41.1, 45.6, 56.0, 56.2, 58.4, 66.0, 68.9, 97.4, 113.7, 126.9, 128.1 (2C), 128.6 (2C), 139.8, 144.6, 145.0, 178.2; IR (neat) 1730, 1541, 1154 cm<sup>-1</sup>; EIMS *m/z* 512 (M<sup>+</sup>-H<sub>2</sub>O) 427, 411, 332, 255; HREIMS calcd for C<sub>30</sub>H<sub>41</sub>O<sub>2</sub><sup>79</sup>Br 512.2290, found 512.2291.

**(*R*)-5-[(*R*)-2-[(1*R*,4*E*,3*aR*,7*aR*)-4-Bromomethylene-7*a*-methylperhydroindene-1-yl]propyl]-3-methylene-(4*S*)-phenyldihydrofuran-2-one (**21**)** To a solution of **20** (229 mg, 0.43 mmol) in toluene (4.3 mL) was added a solution of DIBAL-H in toluene (1.04 M, 1.7 mL, 1.7 mmol) at 0 °C, and the mixture was stirred at rt for 26 h. To the mixture was added 10% potassium sodium tartrate aq. solution at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.83 mL).

To the solution was added  $\text{MnO}_2$  (2.3 g, 26.4 mmol) at rt, and the mixture was stirred at the same temperature for 2.7 days. After the mixture was filtered through a silica gel pad, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 19/1) to give **21** (161 mg, 84% in 2 steps) as a colorless oil.  $[\alpha]_{\text{D}}^{25} +59.5^\circ$  ( $c$  0.69,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.57 (s, 3H), 0.90 (d,  $J = 6.6$  Hz, 3H), 1.18-1.29 (m, 2H), 1.32-1.40 (m, 2H), 1.43-1.67 (m, 4H), 1.78-1.87 (m, 3H), 1.92-1.99 (m, 2H), 2.86 (m, 1H), 3.71 (m, 1H), 4.46 (br dd,  $J = 8.3, 8.3$  Hz, 1H), 5.37 (d,  $J = 3.1$  Hz, 1H), 5.65 (s, 1H), 6.34 (d,  $J = 3.1$  Hz, 1H), 7.19-7.21 (m, 2H), 7.31-7.40 (m, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.9, 18.5, 22.1, 22.5, 27.6, 31.0, 33.0, 39.9, 41.3, 45.6, 53.5, 55.9, 56.0, 82.8, 97.6, 123.3, 127.8, 128.3 (2C), 129.1 (2C), 138.4, 140.2, 144.7, 169.6; IR (neat) 1765, 1456, 1234, 1140  $\text{cm}^{-1}$ ; EIMS  $m/z$  442 ( $\text{M}^+$ ), 363, 227, 201, 175, 147; HREIMS calcd for  $\text{C}_{25}\text{H}_{31}\text{O}_2^{79}\text{Br}$  442.1507, found 442.1499.

**(1R,4E,3aR,7aR)-4-Bromomethylene-1-[(1R,3S,4R)-3,6-dihydroxy-1-methyl-4-phenyl-5-hexenyl]-7a-methylperhydroindene ((23S)-22)**. To a solution of **18** (700 mg, 1.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (6.6 mL) were added TPAP (324 mg, 0.92 mmol) and NMO (771 mg, 6.6 mmol) at rt, and the mixture was stirred at the same temperature for 1 h. After the mixture was filtered through a silica gel pad, the filtrate was concentrated. The residue was dissolved in THF (10 mL). To the solution was added  $\text{LiAlH}_4$  (82 mg, 2.2 mmol) at 0 °C, and the mixture was stirred at rt for 3.5 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 4/1) to give (23R)-**22** (200 mg, 28% in 2 steps) and (23S)-**22** (136 mg, 19% in 2 steps). (23S)-**22**: colorless oil;  $[\alpha]_{\text{D}}^{25} +44.1^\circ$  ( $c$  2.31,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.45 (s, 3H), 0.99 (d,  $J = 6.6$  Hz, 3H), 1.13-1.38 (m, 5H), 1.40-1.73 (m, 8H), 1.87-1.96 (m, 2H), 2.25 (m, 1H), 2.85 (m, 1H), 3.33 (d,  $J = 8.0$  Hz, 1H), 3.98 (d,  $J = 13.4$  Hz, 1H), 4.04 (d,  $J = 13.4$  Hz, 1H), 4.23 (ddd,  $J = 8.0, 7.7, 4.2$  Hz, 1H), 5.32 (br s, 1H), 5.33 (br s, 1H), 5.60 (br s, 1H), 7.20-7.32 (m, 5H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7, 20.2, 22.1, 22.6, 27.5, 31.0, 35.2, 39.8, 41.8, 45.5, 55.7, 56.4, 57.3, 65.3, 72.4, 97.3, 113.3, 126.9, 128.3 (2C), 128.5 (2C), 140.5, 145.0, 148.8; IR (film,  $\text{CHCl}_3$ ) 3362, 1632, 1453, 1073  $\text{cm}^{-1}$ ; EIMS  $m/z$  446 ( $\text{M}^+$ ), 428, 349, 331, 254; HREIMS calcd for  $\text{C}_{25}\text{H}_{35}\text{O}_2^{79}\text{Br}$  446.1820, found 446.1828.

**(S)-5-[(R)-2-[(1R,4E,3aR,7aR)-4-Bromomethylene-7a-methylperhydroindene-1-yl]propyl]-3-methylene-(4R)-phenyldihydrofuran-2-one (23)**. Similar to the synthesis of **21** from **20**, a crude product, which was obtained from (23S)-**22** (136 mg, 0.30 mmol) and  $\text{MnO}_2$  (2.4 g, 27.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) at rt for 32 h, was purified by column chromatography on silica gel (hexane/AcOEt = 19/1) to give **23** (104 mg, 77%) as a colorless oil.  $[\alpha]_{\text{D}}^{25} +59.5^\circ$  ( $c$  0.69,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.48 (s, 3H), 0.86 (d,  $J = 6.6$  Hz, 3H), 1.17-1.32 (m, 3H), 1.34-1.52 (m, 4H), 1.57-1.72 (m, 3H), 1.80 (ddd,  $J = 14.3, 5.6, 3.5$  Hz, 1H), 1.87-2.00 (m, 3H), 2.86 (m, 1H), 3.72 (ddd,  $J = 6.8, 3.2, 3.2$  Hz, 1H), 4.46 (ddd,  $J$

= 6.8, 6.5, 6.5 Hz, 1H), 5.34 (d,  $J = 3.2$  Hz, 1H), 5.63 (s, 1H), 6.32 (d,  $J = 3.3$  Hz, 1H), 7.19-7.21 (m, 2H), 7.30 (m, 1H), 7.35-7.38 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.9, 18.5, 22.1, 22.5, 27.6, 31.0, 33.0, 39.9, 41.3, 45.6, 53.5, 55.9, 56.0, 82.8, 97.6, 123.3, 127.8, 128.3 (2C), 129.1 (2C), 138.4, 140.2, 144.7, 169.6; IR (neat) 1765, 1456, 1234, 1140  $\text{cm}^{-1}$ ; EIMS  $m/z$  442 ( $\text{M}^+$ ), 363, 227, 201, 175, 147; HREIMS calcd for  $\text{C}_{25}\text{H}_{31}\text{O}_2^{79}\text{Br}$  442.1507, found 442.1499.

**The general procedure for the synthesis Vitamin D<sub>3</sub> lactones.** To a solution of A-ring precursor (1.5 eq. to a CD-ring precursor) and the CD-ring precursor in toluene/ $\text{Et}_3\text{N}$  (ratio of 1 to 3) were added  $\text{Pd}(\text{PPh}_3)_4$  (30 mol% to the CD-ring precursor), and the mixture was stirred at 110 °C for 2 h. The mixture was filtered through a silica gel pad, and the filtrate was concentrated. The residue was dissolved in MeCN (1 mL). To the solution was added a 10% solution of conc. HF in MeCN (1 mL) at 0 °C, and the mixture was stirred at rt. To the mixture was added saturated  $\text{NaHCO}_3$  aq. solution, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by flash column chromatography on silica gel to give the vitamin D<sub>3</sub> analogs. Further purification for biological assays was conducted by reverse-phase recycle HPLC (YMC-Pack ODS column, 20 X 150 mm, 9.9 mL/min, eluent: MeCN/ $\text{H}_2\text{O} = 90/10$ ).

**(23S,24S)-25-Dehydro-1 $\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactone (8).** According to the General Procedure, a crude product, which was obtained from **14** (27 mg, 61  $\mu\text{mol}$ ), **24** (34 mg, 92  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (21 mg, 18  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (4 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1) to give **8** (18 mg, 59% in 2 steps) as an amorphous solid.  $[\alpha]_{\text{D}}^{26} -35.5^\circ$  ( $c$  1.00,  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}} = 265.0$  nm,  $\lambda_{\text{min}} = 230.5$  nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.37 (s, 3H), 0.52 (m, 1H), 0.96 (d,  $J = 5.6$  Hz, 3H), 1.15-1.35 (m, 7H), 1.41 (dd,  $J = 11.4, 7.0$  Hz, 1H), 1.47-1.66 (m, 6H), 1.85-2.04 (m, 4H), 2.30 (dd,  $J = 13.3, 7.0$  Hz, 1H), 2.59 (dd,  $J = 13.3, 3.3$  Hz, 1H), 2.78 (dd,  $J = 12.6, 3.8$  Hz, 1H), 4.22 (m, 1H), 4.26 (ddd,  $J = 7.2, 2.2, 2.2$ , Hz, 1H), 4.23 (m, 1H), 4.82 (ddd,  $J = 14.7, 7.2, 7.2$ , Hz, 1H), 4.98 (s, 1H), 5.32 (s, 1H), 5.60 (d,  $J = 2.2$  Hz, 1H), 5.94 (d,  $J = 11.2$  Hz, 1H), 6.35 (d,  $J = 11.2$  Hz, 1H), 6.40 (d,  $J = 2.2$  Hz, 1H), 7.11-7.13 (m, 2H), 7.29-7.36 (m, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  11.9, 19.2, 22.1, 23.5, 26.8, 29.0, 33.3, 37.6, 40.4, 42.9, 45.3, 45.8, 49.7, 56.1, 56.6, 66.8, 70.9, 80.5, 111.9, 117.0, 124.0, 124.9, 127.6, 128.7 (2C), 128.9 (2C), 132.8, 138.3, 139.8, 142.8, 147.4, 170.4; IR (film,  $\text{CHCl}_3$ ) 3368, 2948, 1757, 1653, 1055  $\text{cm}^{-1}$ ; EIMS  $m/z$  502 ( $\text{M}^+$ ), 484, 466, 451, 278, 251, 209; HREIMS calcd for  $\text{C}_{33}\text{H}_{42}\text{O}_4$  502.3083, found 502.3081.

**(23S,24R)-25-Dehydro-1 $\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactone (9).** According to the General Procedure, a crude product, which was obtained from **15** (16 mg, 36  $\mu\text{mol}$ ), **24** (20 mg, 54  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (12 mg, 10  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (4 mL), was treated with 5% solution of conc. HF in

MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1) to give **9** (10 mg, 55% in 2 steps) as an amorphous solid.  $[\alpha]_D^{26} +7.22^\circ$  (*c* 0.69, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 264.5$  nm,  $\lambda_{\min} = 230.5$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.46 (s, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 1.13-1.40 (m, 3H), 1.46-1.55 (m, 6H), 1.63-1.72 (m, 3H), 1.81 (ddd, *J* = 14.2, 5.6, 3.4 Hz, 1H), 1.87-2.05 (m, 5H), 2.31 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.59 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.80 (m, 1H), 3.72 (ddd, *J* = 7.0, 3.4, 3.4 Hz, 1H), 4.22 (m, 1H), 4.45 (m, 1H), 4.50 (ddd, *J* = 6.9, 6.7, 6.7 Hz, 1H), 4.99 (s, 1H), 5.32 (br.s, 1H), 5.35 (d, *J* = 3.1 Hz, 1H), 6.00 (d, *J* = 11.1 Hz, 1H), 6.33 (d, *J* = 3.1 Hz, 1H), 6.36 (d, *J* = 11.1 Hz, 1H), 7.19-7.21 (m, 2H), 7.29-7.32 (m, 1H), 7.35-7.39 (m, 2H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  11.9, 19.3, 22.3, 23.5, 27.9, 29.1, 34.1, 40.3, 41.7, 42.9, 45.3, 45.9, 53.5, 56.2, 56.5, 66.9, 70.8, 84.3, 111.7, 117.1, 123.4, 124.9, 127.7, 128.3 (2C), 129.1 (2C), 133.0, 139.1, 140.5, 142.7, 147.6, 169.7; IR (film, CHCl<sub>3</sub>) 3358, 2948, 1750, 1651, 1057 cm<sup>-1</sup>; EIMS *m/z* 502 (M<sup>+</sup>), 484, 466, 451, 278, 251, 209; HREIMS calcd for C<sub>33</sub>H<sub>42</sub>O<sub>4</sub> 502.3083, found 502.3077.

**(23R,24S)-25-Dehydro-1 $\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactone (10).** According to the General Procedure, a crude product, which was obtained from **21** (25 mg, 56  $\mu$ mol), **24** (31 mg, 84  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (20 mg, 17  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1) to give **10** (14 mg, 49% in 2 steps) as an amorphous solid.  $[\alpha]_D^{25} +14.6^\circ$  (*c* 1.00, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 264.5$  nm,  $\lambda_{\min} = 230.0$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.55 (s, 3H), 0.90 (d, *J* = 6.3 Hz, 3H), 1.21-1.31 (m, 3H), 1.36 (m, 1H), 1.46-1.56 (m, 5H), 1.64-1.69 (m, 2H), 1.79-2.03 (m, 7H), 2.31 (dd, *J* = 12.8, 6.2 Hz, 1H), 2.60 (br d, *J* = 12.8 Hz, 1H), 2.82 (m, 1H), 3.71 (m, 1H), 4.24 (m, 1H), 4.44-4.49 (m, 2H), 5.00 (s, 1H), 5.33 (s, 1H), 5.37 (d, *J* = 2.7 Hz, 1H), 6.00 (d, *J* = 11.2 Hz, 1H), 6.34-6.38 (m, 2H), 7.19-7.21 (m, 2H), 7.32-7.40 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.1, 18.5, 22.3, 23.5, 27.6, 29.1, 33.0, 40.5, 41.3, 42.9, 45.3, 46.0, 53.5, 56.3, 56.8, 66.9, 70.8, 82.9, 111.8, 117.2, 123.3, 124.8, 127.8, 128.3 (2C), 129.1 (2C), 133.0, 138.5, 140.3, 142.6, 147.5, 169.7; IR (film, CHCl<sub>3</sub>) 3357, 2950, 1750, 1651, 1057 cm<sup>-1</sup>; EIMS *m/z* 502 (M<sup>+</sup>), 484, 466, 451, 278, 251, 209; HREIMS calcd for C<sub>33</sub>H<sub>42</sub>O<sub>4</sub> 502.3083, found 502.3081.

**(23R,24R)-25-Dehydro-1 $\alpha$ -hydroxy-24-phenylvitamin D<sub>3</sub>-26,23-lactone (11).** According to the General Procedure, a crude product, which was obtained from **23** (15 mg, 34  $\mu$ mol), **24** (19 mg, 51  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (12 mg, 10  $\mu$ mol) in toluene/Et<sub>3</sub>N (2 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1) to give **11** (8 mg, 47% in 2 steps) as an amorphous solid.  $[\alpha]_D^{28} +191.6^\circ$  (*c* 0.58, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 264.5$  nm,  $\lambda_{\min} = 230.0$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.52 (s, 3H), 0.61 (ddd, *J* = 14.6, 10.6, 2.0 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.09-1.15 (m, 2H), 1.18-1.43 (m, 5H), 1.47-1.70 (m, 6H), 1.86-2.05 (m, 4H), 2.30 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.59 (dd, *J* = 13.1, 3.4 Hz,



1H), 2.79 (dd,  $J = 12.0, 3.9$  Hz, 1H), 4.22 (m, 1H), 4.36 (ddd,  $J = 7.9, 2.7, 2.7$  Hz, 1H), 4.42 (ddd,  $J = 8.5, 4.3, 4.3$  Hz, 1H), 4.90 (ddd,  $J = 11.8, 7.9, 1.9$  Hz, 1H), 5.00 (br s, 1H), 5.32 (br s, 1H), 5.61 (d,  $J = 2.7$  Hz, 1H), 5.98 (d,  $J = 12.3$  Hz, 1H), 6.35 (d,  $J = 12.3$  Hz, 1H), 6.46 (d,  $J = 2.7$  Hz, 1H), 7.11-7.13 (m, 2H), 7.29-7.37 (m, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  12.0, 18.3, 22.1, 23.5, 27.4, 29.0, 32.7, 39.1, 40.4, 42.8, 45.2, 45.9, 49.7, 56.3, 56.8, 66.8, 70.7, 78.9, 111.7, 117.1, 124.3, 124.8, 127.7, 128.7 (2C), 129.1 (2C), 133.0, 137.6, 139.0, 142.8, 147.6, 170.5; IR (film,  $\text{CHCl}_3$ ) 3418, 2926, 1757, 1653, 1055  $\text{cm}^{-1}$ ; EIMS  $m/z$  502 ( $\text{M}^+$ ), 484, 466, 451, 278, 251, 209; HREIMS calcd for  $\text{C}_{33}\text{H}_{42}\text{O}_4$  502.3083, found 502.3078.

**(23S,24S)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -methyl-24-phenylvitamin D<sub>3</sub>-26,23-lactone (8a).** According to the General Procedure, a crude product, which was obtained from **14** (26 mg, 59  $\mu\text{mol}$ ), **24a** (34 mg, 89  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (20 mg, 17  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (4 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **8a** (13 mg, 43% in 2 steps) as an amorphous solid.  $[\alpha]_{\text{D}}^{25}$  -20.0° ( $c$  0.86,  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}} = 266.5$  nm,  $\lambda_{\text{min}} = 230.0$  nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.35 (s, 3 H), 0.51 (m, 1 H), 0.96 (d,  $J = 5.4$  Hz, 3H), 1.09 (d,  $J = 6.8$  Hz, 3H), 1.17-1.32 (m, 7H), 1.37-1.68 (m, 7H), 1.86-1.92 (m, 3H), 2.22 (dd,  $J = 13.7, 8.3$  Hz, 1H), 2.65 (dd,  $J = 13.7, 3.9$  Hz, 1H), 2.78 (dd,  $J = 12.5, 3.9$  Hz, 1H), 3.82 (m, 1H), 4.26 (ddd,  $J = 7.2, 2.3, 2.1$  Hz, 1H), 4.29 (br s, 1H), 4.82 (ddd,  $J = 7.2, 6.8, 6.8$  Hz, 1H), 4.98 (d,  $J = 2.0$  Hz, 1H), 5.26 (s, 1H), 5.60 (d,  $J = 2.2$  Hz, 1H), 5.93 (d,  $J = 11.1$  Hz, 1H), 6.36 (d,  $J = 11.1$  Hz, 1H), 6.40 (d,  $J = 2.2$  Hz, 1H), 7.11-7.13 (m, 2H), 7.30-7.36 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.9, 12.7, 19.2, 22.1, 23.5, 26.8, 29.0, 33.2, 37.6, 40.4, 43.7, 44.3, 45.8, 49.6, 56.0, 56.6, 71.6, 75.6, 80.5, 113.3, 116.9, 124.1, 124.7, 127.6, 128.7 (2C), 128.9 (2C), 132.9, 138.3, 139.8, 142.8, 146.4, 170.4; IR (film,  $\text{CHCl}_3$ ) 3403, 2938, 1759, 1653, 1034  $\text{cm}^{-1}$ ; EIMS  $m/z$  516 ( $\text{M}^+$ ), 498, 480, 454, 265, 223; HREIMS calcd for  $\text{C}_{34}\text{H}_{44}\text{O}_4$  516.3240, found 516.3243.

**(23S,24R)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -methyl-24-phenylvitamin D<sub>3</sub>-26,23-lactone (9a).** According to the General Procedure, a crude product, which was obtained from **15** (17 mg, 38  $\mu\text{mol}$ ), **24a** (22 mg, 57  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (13 mg, 11  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (4 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **9a** (9 mg, 45% in 2 steps) as an amorphous solid.  $[\alpha]_{\text{D}}^{25}$  +26.7° ( $c$  0.54,  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}} = 266.5$  nm,  $\lambda_{\text{min}} = 230.0$  nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.45 (s, 3 H), 0.84 (d,  $J = 6.3$  Hz, 3H), 1.08 (d,  $J = 6.8$  Hz, 3H), 1.12-1.32 (m, 4H), 1.34-1.71 (m, 11H), 1.80 (ddd,  $J = 14.2, 6.5, 3.3$  Hz, 1H), 1.83-1.94 (m, 3H), 1.98 (br d,  $J = 10.4$  Hz, 1H), 2.23 (dd,  $J = 13.5, 8.0$  Hz, 1H), 2.60 (dd,  $J = 13.5, 4.1$  Hz, 1H), 2.80 (m, 1H), 3.72 (ddd,  $J = 7.0, 3.2, 3.2$  Hz, 1H), 3.84 (ddd,  $J = 8.0, 7.6, 4.1$  Hz, 1H), 4.30 (br.s, 1H), 4.50 (ddd,  $J = 7.0, 6.8, 6.8$  Hz, 1H), 5.00 (d,  $J = 2.0$  Hz, 1H), 5.27 (s, 1H), 5.35 (d,  $J = 3.1$  Hz, 1H), 5.99 (d,  $J = 11.4$  Hz, 1H), 6.32 (d,  $J = 3.1$  Hz, 1H), 6.37 (d,  $J = 11.4$  Hz, 1H), 7.18-7.21 (m, 2H), 7.30 (m, 1H), 7.34-7.39 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.0,

12.6, 19.3, 22.3, 23.5, 26.9, 29.0, 34.0, 40.3, 41.6, 43.5, 44.2, 45.9, 53.5, 56.2, 56.5, 71.7, 75.4, 84.3, 113.2, 117.0, 123.4, 124.6, 127.7, 128.3 (2C), 129.0 (2C), 133.1, 139.1, 140.5, 142.7, 146.5, 169.7; IR (film, CHCl<sub>3</sub>) 3423, 2932, 1761, 1651, 1026 cm<sup>-1</sup>; EIMS *m/z* 516 (M<sup>+</sup>), 498, 480, 454, 265, 223; HREIMS calcd for C<sub>34</sub>H<sub>44</sub>O<sub>4</sub> 516.3240, found 516.3245.

**(23R,24S)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -methyl-24-phenylvitamin D<sub>3</sub>-26,23-lactone (10a).**

According to the General Procedure, a crude product, which was obtained from **21** (27 mg, 61  $\mu$ mol), **24a** (28 mg, 73  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (21 mg, 18  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **10a** (14 mg, 45% in 2 steps) as an amorphous solid.  $[\alpha]_D^{25} +34.6^\circ$  (*c* 0.66, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 266.0$  nm,  $\lambda_{\min} = 230.5$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.54 (s, 3H), 0.90 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.21-1.30 (m, 3H), 1.33-1.41 (m, 2H), 1.44-1.56 (m, 4H), 1.60-1.70 (m, 2H), 1.75-1.82 (m, 2H), 1.84-1.99 (m, 4H), 2.22 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.67 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.81 (m, 1H), 3.71 (ddd, *J* = 7.9, 3.2, 3.2 Hz, 1H), 3.85 (m, 1H), 4.31 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.47 (ddd, *J* = 10.3, 7.9, 2.0 Hz, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 5.28 (s, 1H), 5.37 (d, *J* = 3.1 Hz, 1H), 6.00 (d, *J* = 11.2 Hz, 1H), 6.34 (d, *J* = 3.1 Hz, 1H), 6.37 (d, *J* = 11.2 Hz, 1H), 7.19-7.21 (m, 2H), 7.32 (m, 1H), 7.36-7.40 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.1, 12.6, 18.5, 22.3, 23.5, 27.6, 29.0, 33.0, 40.5, 41.3, 43.5, 44.2, 46.0, 53.5, 56.3, 56.8, 71.7, 75.4, 82.9, 113.2, 117.1, 123.3, 124.6, 127.8, 128.3 (2C), 129.1 (2C), 133.1, 138.5, 140.3, 142.6, 146.5, 169.7; IR (film, CHCl<sub>3</sub>) 3449, 2948, 1750, 1522, 1032 cm<sup>-1</sup>; EIMS *m/z* 516 (M<sup>+</sup>), 498, 480, 454, 265, 223; HREIMS calcd for C<sub>34</sub>H<sub>44</sub>O<sub>4</sub> 516.3240, found 516.3242

**(23R,24R)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -methyl-24-phenylvitamin D<sub>3</sub>-26,23-lactone (11a).**

According to the General Procedure, a crude product, which was obtained from **23** (16 mg, 36  $\mu$ mol), **24a** (21 mg, 55  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (13 mg, 11  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **11a** (10 mg, 54% in 2 steps) as an amorphous solid.  $[\alpha]_D^{25} +262.0^\circ$  (*c* 0.69, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 267.0$  nm,  $\lambda_{\min} = 232.0$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.51 (s, 3H), 0.61 (ddd, *J* = 14.5, 10.7, 2.0 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.21 (ddd, *J* = 12.9, 12.9, 4.0 Hz, 1H), 1.31-1.45 (m, 4H), 1.48-1.72 (m, 9H), 1.86-1.96 (m, 3H), 2.22 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.66 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.79 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.84 (ddd, *J* = 12.0, 7.7, 4.2 Hz, 1H), 4.30 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.35 (ddd, *J* = 7.9, 7.8, 2.7 Hz, 1H), 4.86 (ddd, *J* = 11.7, 7.9, 1.9 Hz, 2H), 4.99 (d, *J* = 2.0 Hz, 1H), 5.27 (s, 1H), 5.61 (d, *J* = 2.6 Hz, 1H), 5.97 (d, *J* = 11.2 Hz, 1H), 6.36 (d, *J* = 11.2 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 7.11-7.13 (m, 2H), 7.29-7.37 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.0, 12.5, 18.4, 22.1, 23.4, 27.4, 29.0, 32.7, 39.1, 40.4, 43.4, 44.1, 45.9, 49.7, 56.3, 56.7, 71.7, 75.3, 78.9, 113.2, 117.1, 124.2, 124.6, 127.7, 128.7 (2C), 129.0 (2C), 133.2, 137.6,

139.0 142.7, 146.5, 170.5; IR (film, CHCl<sub>3</sub>) 3484, 2948, 1750, 1651, 1038 cm<sup>-1</sup>; EIMS *m/z* 516 (M<sup>+</sup>), 498, 480, 454, 265, 223; HREIMS calcd for C<sub>34</sub>H<sub>44</sub>O<sub>4</sub> 516.3240, found 516.3243.

**(23S,24S)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropyl)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (8b).**

According to the General Procedure, a crude product, which was obtained from **14** (31 mg, 70  $\mu$ mol), **24b** (57 mg, 0.11 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (24 mg, 21  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **8b** (22 mg, 54% in 2 steps) as an amorphous solid.  $[\alpha]_D^{25}$  -14.8° (*c* 1.69, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{max}$  = 267.5 nm,  $\lambda_{min}$  = 230.0 nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.35 (s, 3H), 0.51 (m, 1H), 0.95 (d, *J* = 5.4 Hz, 3H), 1.14-1.37 (m, 7H), 1.39-1.52 (m, 3H), 1.60-1.78 (m, 9H), 1.86-1.92 (m, 1H), 2.24 (dd, *J* = 13.2, 8.7 Hz, 1H), 2.66 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.78 (m, 1H), 3.70 (t, *J* = 4.9 Hz, 2H), 3.87 (ddd, *J* = 8.7, 7.5, 4.3 Hz, 1H), 4.25 (ddd, *J* = 7.3, 2.1, 2.1 Hz, 1H), 4.82 (ddd, *J* = 7.5, 6.8, 6.8 Hz, 1H), 4.97 (d, *J* = 1.7 Hz, 1H), 5.27 (d, *J* = 1.7 Hz, 1H), 5.60 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 11.4 Hz, 1H), 6.37 (d, *J* = 11.4 Hz, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 7.11-7.13 (m, 2H), 7.28-7.37 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  11.9, 19.2, 22.1, 22.9, 23.4, 26.8, 29.0, 30.1, 33.2, 37.6, 40.4, 44.4, 45.8, 49.1, 49.6, 56.0, 56.6, 62.7, 70.3, 73.7, 80.5, 113.7, 116.9, 124.1, 124.6, 127.6, 128.6 (2C), 128.9 (2C), 132.8, 138.3, 139.8, 142.9, 146.3, 170.5; IR (film, CHCl<sub>3</sub>) 3391, 2940, 1757, 1047 cm<sup>-1</sup>; EIMS *m/z* 560 (M<sup>+</sup>), 542, 524, 509, 349, 262; HREIMS calcd for C<sub>36</sub>H<sub>48</sub>O<sub>5</sub> 560.3502, found 560.3502.

**(23S,24R)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropyl)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (9b).**

According to the General Procedure, a crude product, which was obtained from **15** (19 mg, 43  $\mu$ mol), **24b** (35 mg, 65  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (15 mg, 13  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **9b** (10 mg, 42% in 2 steps) as an amorphous solid.  $[\alpha]_D^{25}$  +40.8° (*c* 0.77, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{max}$  = 266.0 nm,  $\lambda_{min}$  = 230.0 nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.45 (s, 3H), 0.84 (d, *J* = 6.3 Hz, 3H), 1.13-1.39 (m, 4H), 1.46-1.48 (m, 4H), 1.64-2.04 (m, 14H), 2.24 (dd, *J* = 13.3, 8.5 Hz, 1H), 2.65 (dd, *J* = 13.3, 4.2 Hz, 1H), 2.80 (br d, *J* = 12.2 Hz, 1H), 3.68-3.73 (m, 3H), 3.88 (ddd, *J* = 8.5, 8.1, 4.2 Hz, 1H), 4.37 (s, 1H), 4.50 (ddd, *J* = 6.8, 6.8, 6.8 Hz, 1H), 4.98 (s, 1H), 5.27 (s, 1H), 5.34 (d, *J* = 3.2 Hz, 1H), 5.98 (d, *J* = 11.3 Hz, 1H), 6.32 (d, *J* = 3.2 Hz, 1H), 6.38 (d, *J* = 11.3 Hz, 1H), 7.18-7.20 (m, 2H), 7.28-7.38 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.0, 19.3, 22.3, 22.9, 23.5, 27.9, 29.0, 30.2, 34.0, 40.3, 41.6, 44.3, 45.9, 49.1, 53.5, 56.1, 56.4, 62.8, 70.4, 73.6, 84.3, 113.6, 117.0, 123.4, 124.6, 127.7, 128.2 (2C), 129.0 (2C), 132.8, 139.1, 140.4, 142.8, 146.4, 169.7; IR (neat) 3387, 2948, 1763, 1057 cm<sup>-1</sup>; EIMS *m/z* 560 (M<sup>+</sup>), 542, 524, 509, 349, 262; HREIMS calcd for C<sub>36</sub>H<sub>48</sub>O<sub>5</sub> 560.3502, found 560.3495.

**(23R,24S)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropyl)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (10b).**

According to the General Procedure, a crude product, which was obtained from **21** (21 mg, 47  $\mu\text{mol}$ ), **24b** (38 mg, 70  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (17 mg, 15  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (4 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **10b** (12 mg, 45% in 2 steps) as an amorphous solid.  $[\alpha]_{\text{D}}^{25} +48.5^\circ$  (*c* 0.54,  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}} = 267.0$  nm,  $\lambda_{\text{min}} = 230.0$  nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.54 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 1.20-1.29 (m, 4H), 1.36 (m, 1H), 1.43-1.53 (m, 3H), 1.63-1.98 (m, 14H), 2.24 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.66 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.81 (br.d, *J* = 13.7 Hz, 1H), 3.68-3.73 (m, 3H), 3.90 (ddd, *J* = 8.3, 8.3, 4.4 Hz, 1H), 4.37 (d, *J* = 2.9 Hz, 1H), 4.46 (m, 1H), 4.98 (d, *J* = 1.7 Hz, 1H), 5.27 (d, *J* = 1.7 Hz, 1H), 5.37 (d, *J* = 3.2 Hz, 1H), 6.00 (d, *J* = 11.2 Hz, 1H), 6.34 (d, *J* = 3.2 Hz, 1H), 6.38 (d, *J* = 11.2 Hz, 1H), 7.19-7.21 (m, 2H), 7.32 (m, 1H), 7.36-7.40 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.2, 18.5, 22.3, 22.9, 23.5, 27.6, 29.0, 30.2, 33.1, 40.5, 41.3, 44.3, 46.0, 49.1, 53.5, 56.3, 56.7, 62.9, 70.4, 73.6, 82.9, 113.6, 117.1, 123.3, 124.6, 127.8, 128.3 (2C), 129.1 (2C), 132.9, 138.4, 140.3, 142.7, 146.5, 169.7; IR (film,  $\text{CHCl}_3$ ) 3380, 2940, 1763, 1042  $\text{cm}^{-1}$ ; EIMS *m/z* 560 ( $\text{M}^+$ ), 542, 524, 509, 349, 262; HREIMS calcd for  $\text{C}_{36}\text{H}_{48}\text{O}_5$  560.3502, found 560.3502.

**(23R,24R)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropyl)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (11b).**

According to the General Procedure, a crude product, which was obtained from **23** (17 mg, 38  $\mu\text{mol}$ ), **24b** (31 mg, 57  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (13 mg, 11  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (6 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **11b** (10 mg, 47% in 2 steps) as an amorphous solid.  $[\alpha]_{\text{D}}^{25} +230.3^\circ$  (*c* 0.46,  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}} = 267.0$  nm,  $\lambda_{\text{min}} = 231.0$  nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.50 (s, 3 H), 0.61 (ddd, *J* = 14.4, 10.7, 2.0 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 1.06-1.14 (m, 2H), 1.17-1.40 (m, 4H), 1.45 (m, 1H), 1.57-1.76 (m, 12H), 1.88 (dd, *J* = 11.1, 8.2 Hz, 1H), 1.95 (br d, *J* = 12.7 Hz, 1H), 2.24 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.65 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.79 (br dd, *J* = 12.1, 3.1 Hz, 1H), 3.70 (t, *J* = 5.7 Hz, 2H), 3.90 (ddd, *J* = 8.4, 8.2, 4.3 Hz, 1H), 4.34-4.38 (m, 2H), 4.86 (ddd, *J* = 11.8, 7.9, 2.0 Hz, 1H), 4.97 (d, *J* = 1.5 Hz, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.61 (d, *J* = 2.6 Hz, 1H), 5.96 (d, *J* = 11.5 Hz, 1H), 6.37 (d, *J* = 11.5 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 7.11-7.13 (m, 2H), 7.28-7.37 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.0, 18.4, 22.1, 22.8, 23.4, 27.4, 29.0, 30.2, 32.7, 39.1, 40.4, 44.2, 45.9, 49.0, 49.7, 56.3, 56.7, 62.8, 70.4, 73.6, 78.9, 113.6, 117.0, 124.3, 124.6, 127.7, 128.7 (2C), 129.0 (2C), 132.9, 137.6, 139.0, 142.8, 146.5, 170.5; IR (film,  $\text{CHCl}_3$ ) 3368, 2936, 1757, 1651, 1044  $\text{cm}^{-1}$ ; EIMS *m/z* 560 ( $\text{M}^+$ ), 542, 524, 509, 349, 262; HREIMS calcd for  $\text{C}_{36}\text{H}_{48}\text{O}_5$  560.3502, found 560.3510.

**(23S,24S)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropoxy)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (8c).**

According to the General Procedure, a crude product, which was obtained from **14** (40 mg, 90  $\mu\text{mol}$ ), **24c** (75 mg, 0.14 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (12 mg, 10  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (8 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash

column chromatography on silica gel (hexane/AcOEt = 1/2) to give **8c** (24 mg, 46% in 2 steps) as an amorphous solid.  $[\alpha]_D^{26} -11.3^\circ$  (*c* 1.54, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 268.5$  nm,  $\lambda_{\min} = 231.5$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.35 (s, 3 H), 0.43 (m, 1 H), 0.95 (d, *J* = 5.1 Hz, 3 H), 1.15-1.31 (m, 6H), 1.40-1.52 (m, 3H), 1.59-1.63 (m, 2H), 1.87-1.91 (m, 4H), 2.20-2.25 (m, 2H), 2.47 (br s, 1H), 2.53 (br s, 1H), 2.66 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.77 (br d, *J* = 11.5 Hz, 1H), 3.36 (m, 1H), 3.75-3.92 (m, 4H), 4.04 (m, 1H), 4.25 (m, 1H), 4.44 (s, 1H), 4.82 (m, 1H), 5.07 (s, 1H), 5.38 (s, 1H), 5.60 (s, 1H), 5.93 (d, *J* = 10.7 Hz, 1H), 6.37-6.40 (m, 2H), 7.11-7.12 (m, 2H), 7.30-7.35 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.0, 19.1, 22.1, 23.4, 26.7, 29.0, 31.9, 33.1, 37.5, 40.4, 41.1, 45.8, 49.6, 56.1, 56.6, 61.1, 68.37, 68.41, 72.0, 80.5, 84.6, 116.4, 117.2, 124.0, 125.3, 127.7, 128.7 (2C), 128.9 (2C), 131.5, 138.3, 139.8, 143.1, 144.0, 170.4; IR (film, CHCl<sub>3</sub>) 3387, 2942, 1759, 1075 cm<sup>-1</sup>; EIMS *m/z* 576 (M<sup>+</sup>), 558, 540, 482, 428, 351, 309, 267; HREIMS calcd for C<sub>36</sub>H<sub>48</sub>O<sub>6</sub> 576.3451, found 576.3453.

**(23S,24R)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropoxy)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (9c).**

According to the General Procedure, a crude product, which was obtained from **15** (21 mg, 47  $\mu$ mol), **24c** (40 mg, 72  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (16 mg, 14  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **9c** (10 mg, 37% in 2 steps) as an amorphous solid.  $[\alpha]_D^{28} +25.4^\circ$  (*c* 0.77, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 266.0$  nm,  $\lambda_{\min} = 231.5$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.45 (s, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 1.13-1.38 (m, 3H), 1.46-1.54 (m, 4H), 1.64-1.71 (m, 3H), 1.77-2.00 (m, 6H), 2.23 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.53 (m, 3H), 2.67 (dd, *J* = 13.4, 4.5 Hz, 1H), 2.80 (br d, *J* = 12.9 Hz, 1H), 3.37 (dd, *J* = 7.3, 3.2 Hz, 1H), 3.72 (m, 1H), 3.74-3.91 (m, 3H), 4.05 (ddd, *J* = 8.6, 7.5, 4.5 Hz, 1H), 4.44 (s, 1H), 4.56 (ddd, *J* = 7.5, 6.8, 6.8 Hz, 1H), 5.08 (d, *J* = 2.7 Hz, 1H), 5.34 (d, *J* = 3.1 Hz, 1H), 5.38 (br s, 1H), 5.99 (d, *J* = 11.1 Hz, 1H), 6.32 (d, *J* = 3.1 Hz, 1H), 6.40 (d, *J* = 11.1 Hz, 1H), 7.18-7.20 (m, 2H), 7.30 (m, 1H), 7.34-7.38 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  12.0, 19.3, 22.2, 23.5, 27.9, 29.0, 31.9, 34.0, 40.4, 41.0, 41.6, 45.9, 53.5, 56.2, 56.5, 61.2, 68.4, 68.5, 71.9, 84.3, 84.5, 116.2, 117.2, 123.4, 125.3, 127.7, 128.3 (2C), 129.0 (2C), 131.6, 139.1, 140.5, 143.1, 144.2, 169.7; IR (film, CHCl<sub>3</sub>) 3407, 2936, 1763, 1649, 1076 cm<sup>-1</sup>; EIMS *m/z* 576 (M<sup>+</sup>), 558, 540, 482, 428, 351, 309, 267; HREIMS calcd for C<sub>36</sub>H<sub>48</sub>O<sub>6</sub> 576.3451, found 576.3452.

**(23R,24S)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropoxy)-24-phenylvitamin D<sub>3</sub>-26,23-lactone (10c).**

According to the General Procedure, a crude product, which was obtained from **21** (17 mg, 38  $\mu$ mol), **24c** (32 mg, 57  $\mu$ mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (13 mg, 11  $\mu$ mol) in toluene/Et<sub>3</sub>N (4 mL), was treated with 5% solution of conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **10c** (9 mg, 41% in 2 steps) as an amorphous solid.  $[\alpha]_D^{28} +44.6^\circ$  (*c* 0.27, CHCl<sub>3</sub>); UV (EtOH)  $\lambda_{\max} = 266.0$  nm,  $\lambda_{\min} = 231.5$  nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.54 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 1.18-1.30 (m, 4H), 1.36 (m, 1H), 1.45-1.56

(m, 3H), 1.60-1.68 (m, 2H), 1.75-1.82 (m, 2 H), 1.84-1.89 (m, 2 H), 1.92-1.99 (m, 2 H), 2.15 (br s, 1 H), 2.23 (dd,  $J = 13.7, 8.6$  Hz, 1H), 2.40 (br s, 1H), 2.50 (br s, 1H), 2.68 (dd,  $J = 13.7, 4.3$  Hz, 1H), 2.81 (br d,  $J = 12.5$  Hz, 1H), 3.38 (dd,  $J = 7.2, 3.3$  Hz, 1H), 3.71 (ddd,  $J = 7.7, 3.2, 3.2$  Hz, 1H), 3.75-3.91 (m, 4H), 4.06 (ddd,  $J = 8.6, 8.1, 4.3$  Hz, 1H), 4.44-4.84 (m, 2H), 5.08 (d,  $J = 2.0$  Hz, 1H), 5.37 (d,  $J = 3.2$  Hz, 1H), 5.39 (br s, 1H), 6.00 (d,  $J = 11.5$  Hz, 1H), 6.35 (d,  $J = 3.2$  Hz, 1H), 6.40 (d,  $J = 11.5$  Hz, 1H), 7.19-7.21 (m, 2H), 7.32 (m, 1H), 7.36-7.40 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.1, 18.5, 22.2, 23.4, 27.5, 29.0, 31.9, 33.0, 40.4, 40.9, 41.2, 45.9, 53.4, 56.3, 56.7, 61.2, 68.3, 68.4, 71.8, 82.8, 84.4, 116.0, 117.2, 123.2, 125.3, 127.7, 128.2 (2C), 129.0 (2C), 131.6, 138.4, 140.2, 143.0, 144.1, 169.7; IR (film,  $\text{CHCl}_3$ ) 3423, 2928, 1765, 1647, 1078  $\text{cm}^{-1}$ ; EIMS  $m/z$  576 ( $\text{M}^+$ ), 558, 540, 482, 428, 351, 309, 267; HREIMS calcd for  $\text{C}_{36}\text{H}_{48}\text{O}_6$  576.3451, found 576.3466.

**(23R,24R)-25-Dehydro-1 $\alpha$ -hydroxy-2 $\alpha$ -(3-hydroxypropoxy)-24-phenylvitamin D<sub>3</sub>-26,23-lactone**

**(11c).** According to the General Procedure, a crude product, which was obtained from **23** (18 mg, 41  $\mu\text{mol}$ ), **24c** (34 mg, 61  $\mu\text{mol}$ ) and  $\text{Pd}(\text{PPh}_3)_4$  (17 mg, 15  $\mu\text{mol}$ ) in toluene/ $\text{Et}_3\text{N}$  (4 mL), was treated with 5% solution of conc. HF in MeCN for 2 h. After usual workup, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to give **11c** (12 mg, 51% in 2 steps) as an amorphous solid.  $[\alpha]_{\text{D}}^{25} +217.5^\circ$  ( $c$  0.54,  $\text{CHCl}_3$ ); UV (EtOH)  $\lambda_{\text{max}} = 266.5$  nm,  $\lambda_{\text{min}} = 231.0$  nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.51 (s, 3H), 0.61 (ddd,  $J = 14.4, 10.6, 1.8$  Hz, 1H), 0.91 (d,  $J = 6.3$  Hz, 3H), 1.06-1.14 (m, 2H), 1.21 (ddd,  $J = 12.8, 12.8, 3.7$  Hz, 1H), 1.31-1.39 (m, 2H), 1.42-1.71 (m, 6 H), 1.86-1.90 (m, 3H), 1.95 (br d,  $J = 12.7$  Hz, 1H), 2.19 (br s, 1H), 2.22 (dd,  $J = 13.3, 9.0$  Hz, 1H), 2.39 (br s, 1H), 2.52 (br s, 1H), 2.67 (dd,  $J = 13.3, 4.4$  Hz, 1H), 2.79 (br d,  $J = 12.2$  Hz, 1H), 3.38 (dd,  $J = 7.3, 3.2$  Hz, 1H), 3.74-3.90 (m, 4H), 4.06 (m, 1H), 4.35 (ddd,  $J = 7.8, 2.4, 2.4$  Hz, 1H), 4.43 (br s, 1H), 4.86 (ddd,  $J = 11.6, 7.9, 1.8$  Hz, 1H), 5.07 (d,  $J = 1.5$  Hz, 1H), 5.38 (s, 1H), 5.61 (d,  $J = 2.6$  Hz, 1H), 5.97 (d,  $J = 11.2$  Hz, 1H), 6.39 (d,  $J = 11.2$  Hz, 1H), 6.45 (d,  $J = 2.6$  Hz, 1H), 7.11-7.13 (m, 2H), 7.29-7.37 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.1, 18.4, 22.1, 23.4, 27.3, 29.0, 31.9, 32.7, 39.0, 40.4, 40.9, 45.9, 49.7, 56.3, 56.7, 61.2, 68.3, 68.5, 71.8, 78.9, 84.4, 116.0, 117.2, 124.2, 125.3, 127.7, 128.7 (2C), 129.0 (2C), 131.7, 137.7, 139.0, 143.1, 144.3, 170.5; IR (film,  $\text{CHCl}_3$ ) 3380, 2940, 1763, 1042  $\text{cm}^{-1}$ ; EIMS  $m/z$  576 ( $\text{M}^+$ ), 558, 540, 482, 428, 351, 309, 267; HREIMS calcd for  $\text{C}_{36}\text{H}_{48}\text{O}_6$  576.3451, found 576.3447.

**Vitamin D receptor (VDR) binding assay:** [26,27-Methyl- $^3\text{H}$ ]-1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (specific activity 6.623 TBq/mmol, 15,000 dpm, 15.7 pg) and various amounts of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> and an analog to be tested were dissolved in 50  $\mu\text{L}$  of absolute ethanol in 12 x 75-mm polypropylene tubes. The chick intestinal VDR (0.2 mg) and 1 mg of gelatin in 1 mL of phosphate buffer solution (25 nM  $\text{KH}_2\text{PO}_4$ , 0.1 M KCl, 1 mM dithiothreitol, pH 7.4) were added to each tube in an ice bath. The assay tubes were incubated in shaking water bath for 1 h at 25  $^\circ\text{C}$  and then chilled in an ice bath. Polypropylene glycol 6000 (40%, 1mL) in distilled water was added to each tube, which was the mixed

vigorously and centrifuged at 2,260 x g for 60 min at 4 °C. After the supernatant was decanted, the bottom of the tube containing the pellet was cut off into a scintillation vial containing 10 ml of dioxane-based scintillation fluid and the radioactivity was counted with a Beckman liquid scintillation counter (Model LS6500). The relative potency of the analogs were calculated from their concentration needed to displace 50% of [26,27-*methyl*-<sup>3</sup>H]-1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> from the receptor compared with the activity of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (assigned a 100% value).

**Assay for HL-60 cell differentiation:** Nitro blue tetrazolium (NBT)-reducing activity was used as a cell differentiation marker. HL-60 cells were cultured in RPMI-1640 medium supplemented with 10% heat-inactivated FCS. Exponentially proliferating cells were collected, suspended in fresh medium and seeded in culture plates (Falcon, Becton Dickinson and Company, Franklin Lakes, NJ). Cell concentration at seeding was adjusted to 2 x 10<sup>4</sup> cells/mL and the seeding volume was 1 mL/well. An ethanol solution of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (final concentration: 10<sup>-8</sup> M) and an analog (final concentration: 10<sup>-11</sup> to 10<sup>-6</sup> M) was added to the culture medium at 0.1% volume and culture was continued for 96 h at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub>/air without a change of medium. The same amount of vehicle was added to the control culture. NBT-reducing assay was performed according to the method of Collins.<sup>20</sup> Briefly, cells were collected, washed with PBS, and suspended in serum-free medium. NBT/TPA solution (dissolved in PBS) was added. Final concentrations of NBT and TPA were 0.1% and 100 ng/mL, respectively. Then, the cell suspensions were incubated at 37 °C for 25 min. After incubation, cells were collected by centrifugation and resuspended in FCS. Cytospin smears were prepared, and the counter-staining of nuclei was done with Kemechrot solution. At least 500 cells per preparation were observed.

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