Synthesis of 24,24-Ethanovitamin D₃ Lactones Using Ruthenium-Catalyzed Intermolecular Enyne Metathesis: Potent Vitamin D Receptor Antagonists

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Abstract: Novel vitamin D receptor antagonists, 24,24-ethanovitamin D₃-lactones 6 and 7 and their 2α-functionalized analogues 6α-c and 7α-c were synthesized and their biological activities were evaluated. The triene structure of vitamin D₃ was constructed using Pd-catalyzed alkenylative cyclization of A-ring precursor enynes 12 and 12α-c with the CD-ring bromo-olefin counterpart having 24,24-ethano-α-methylene-γ-lactone on the side chain (21 or 22). The CD-ring precursors 21 and 22 were efficiently synthesized via Ru-catalyzed intermolecular enyne metathesis of 15 with ethylene to give diene 17 followed by cyclopropanation. The VDR antagonistic activity of the newly designed vitamin D₃ lactones 6 and 7 increased to 2.8 times that of TEI-9647 (2) in a HL-60 cell differentiation evaluating system. Moreover, introduction of three substituents, that is, a methyl (6α and 7α), a 3-hydroxypropyl (6β and 7β), or a 3-hydroxypropoxyl group (6c and 7c) into the C2α position of 6 and 7, resulted in marked enhancement, up to 19 times, of the antagonistic activity toward VDR.

Key words: vitamins, antagonist, lactones, ruthenium, metathesis, enynes

1α,25-Dihydroxyvitamin D₃ (1) (Figure 1) is the most physiologically active metabolite of vitamin D₃ and regulates various biological events, including bone metabolism as well as the proliferation and differentiation of various types of tumor cells.1,2 In most cases, the biological responses of 1 are mediated via interaction with its specific nuclear receptor, vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily and acts as a ligand-dependent gene transcription factor with co-activators.3,4 Recently, we have synthesized several 1α,25-dihydroxyvitamin D₃ analogues, which systematically introduced an alkyl, α-hydroxyalkyl, and α-hydroxyalkoxyl group into the C2α position of 1.5–9 Some of these C2α-modified vitamin D₃ analogues showed unique biological profiles. In particular, introduction of the 2α-methyl (1α), 2α-(3-hydroxypropyl) (1β),6 and 2α-(3-hydroxypropoxy) (1c)7 groups led to a 2- to 4-fold higher binding affinity for the bovine thymus VDR relative to the natural hormone 1 with potent agonistic activity.

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lactone ring core structure, and particularly, the effect of the rigid spiro[2.4]ring system on the biological activities (Figure 3). Furthermore, we expected the biological activities of the ethanolate derivatives (6 and 7) to be enhanced by introducing three motifs, that is, the methyl (6a and 7a), the 3-hydroxypropyl (6b and 7b) and the 3-hydroxypropyl group (6c and 7c) as in our previous studies.8,9,14 Here we report the synthesis and biological evaluation of the novel potent VDR antagonists, 24,24-ethano-1α-hydroxyvitamin D₃ lactones and their C2α-modified analogues.

**Synthesis and Biological Evaluation of 24,24-Ethanovitamin D₃ 26,23-Lactones**

First of all, A-ring precursor 12 was synthesized in an improved manner from epoxide 8.15 That is, according to the reported procedure,16 8 was reacted with LiAlH₄ followed by oxidative cleavage of the benzylidene acetal by NBS to give the known compound 9. Pyranose ring-opening of 9 with activated zinc in the presence of NaBH₄CN provided 10 in 75% yield. The primary hydroxyl group of the diol 10 was sulfonated, and the resulting monosulfonate was treated with lithium hexamethyldisilazide to give the epoxide 11. Introduction of the TMS-ethyl group into 11 followed by deprotection under basic conditions gave a diol. The resulting diol was protected by the TBS groups to provide the desired A-ring precursor 12 (Scheme 1).17

![Figure 2](image-url)  
**Figure 2** Structures of 25-dehydro-1α-hydroxyvitamin D₃-26,23-lactones (TEI-9647: 2 and TEI-9648: 3), and their C2α-modified (2a–c and 3a–c), 24-modified (4a and 5), and 2,24-double modified analogues (4a and 5a)

![Figure 3](image-url)  
**Figure 3** Newly designed 24,24-ethanovitamin D₃ lactones 6 and 7 and their 2α-modified analogues (6a–c and 7a–c)

Next, we synthesized the CD-ring counterpart having the ethano-α-methylene-γ-lactone unit on the side chain via Mori’s Ru-catalyzed intermolecular enyne metathesis with ethylene.18 The metathesis precursor 15 was prepared by the addition of lithium siloxymethylacetylide generated from 14 and BuLi to the aldehyde 1314a and the following TPAP oxidation (Scheme 2).

![Scheme 1](image-url)  
**Scheme 1** Improved synthesis of A-ring precursor 12

![Scheme 2](image-url)  
**Scheme 2** Synthesis of alkyne 15

The Ru-catalyzed intermolecular enyne metathesis of 15 with ethylene was investigated for the introduction of a methylene unit into positions C24 and C25 (based on the steroidal numbering), respectively (Table 1). First of all, according to Mori’s procedure, the alkyne 15 was treated with the first generation Grubbs catalyst 16a under ethylene gas (run 1). However, no metathesis product was obtained. The second generation Grubbs catalyst 16b19a was not effective for the intermolecular enyne metathesis of 15, either, and only decomposition of 15 was observed (runs 2 and 3). On the other hand, when the Hoveyda–Grubbs catalyst 16c19b was used, the diene 17 was obtained in 29% (run 4). The same type of Ru catalyst 16d reported by Blechert19c was found to be more effective for the metathesis of 15 with ethylene, and 17 was produced in 55% yield.19d Finally, we disclose that the alkyne-like ethylene metathesis proceeded smoothly in the presence of 10 mol% of 16d at 0 °C to provide the desired diene derivative 17 in high yield (run 6).
Transformation of the dienone 17 into the CD-ring bromo-olefin precursors 21 and 22 is shown in Scheme 3. Cyclopropanation by the 1,4-addition of trimethylsulfoxonium ylide to 17 provided the desired cyclopropyl ketone derivative 18 in good yield. Treatment of 18 with DIBAL-H followed by desilylation of the TBS group using TBAF gave two diol derivatives 19 and 20, which were stereoisomers with respect to the position C23 on the side chain, in 43% yield (2 steps) and in 53% yield (2 steps), respectively. The crystal structure of 20 revealed the absolute configuration of position C23 of 20 to be R (Figure 4). \(^\text{20}\)

From this result, the absolute configuration of position C23 of its stereoisomer 19 was determined to be S. Finally, the diol 19 was converted into the desired CD-ring precursor 21 by oxidation using MnO\(_2\) in 97% yield. Similarly, the lactone 22 was obtained from 20 by MnO\(_2\) oxidation in 92% yield.

The construction of a vitamin D triene skeleton was achieved by Trost’s alkenylative cyclization\(^\text{7,21}\) of the A-ring precursor 12 with the CD-ring counterpart 21 or 22 (Scheme 4). That is, each CD-ring precursor 21 or 22 reacted with enyne 12 in the presence of Pd(0) catalyst, and the protected vitamin D\(_3\) derivative was produced. Acid-mediated deprotection gave the desired 24,24-ethanovitamin D\(_3\) lactone derivatives 6 and 7, respectively.

Biological activities of the synthesized 24,24-ethanovitamin D\(_3\) lactones 6 and 7 were evaluated and the data are shown in Table 2. We also show the data of 24,24-dimethylvitamin D\(_3\) lactones 4 and 5 for comparison. The binding affinity of 6 and 7 for the chick intestinal VDR was examined as described previously. \(^\text{22}\) The binding affinity of (23S)-24,24-ethanovitamin D\(_3\) lactone (6) for the VDR increased remarkably to 13.9 times that of 2 (1.7 times more potent than the natural hormone 1). In the case of TEL-9648 type analogue 7, the binding affinity for the VDR decreased to one tenth that of 3. The antagonistic activities of 6 and 7 were assessed by the NBT-reduction.

### Table 1  Ruthenium-Catalyzed Enyne Metathesis of 15 with Ethylene

<table>
<thead>
<tr>
<th>Run</th>
<th>‘Ru’ (mol%)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16a (5)</td>
<td>r.t.</td>
<td>16</td>
<td>0 (80)</td>
</tr>
<tr>
<td>2</td>
<td>16b (5)</td>
<td>r.t.</td>
<td>24</td>
<td>0 (88)</td>
</tr>
<tr>
<td>3</td>
<td>16b (10)(^b)</td>
<td>reflux</td>
<td>4</td>
<td>0 (44)</td>
</tr>
<tr>
<td>4</td>
<td>16c (20)(^c)</td>
<td>r.t.</td>
<td>24</td>
<td>29 (32)</td>
</tr>
<tr>
<td>5</td>
<td>16d (20)(^d)</td>
<td>r.t.</td>
<td>53</td>
<td>55 (6)</td>
</tr>
<tr>
<td>6</td>
<td>16d (10)</td>
<td>0 °C</td>
<td>1.5</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^a\)The yield in parentheses is that of recovered 15.

\(^b\)5 mol% of 16b was used. After 2 h, 5 mol% of 16b was added.

\(^c\)5 mol% of 16c was used. Additional amounts of 16c were successively added (5 mol%, 5 h, 10 mol%, 19 h).

\(^d\)5 mol% of 16d was used. Additional amounts of 16d were successively added (5 mol%, 24 h, 10 mol%, 48 h).
method\textsuperscript{23} in terms of inhibition of HL-60 cell differentiation induced by 10 nM of the natural hormone 1. Although the antagonistic activity of (23S)-24,24-ethanovitamin D\textsubscript{3} lactone 6 was weaker than that of the corresponding 24,24-dimethyl analogue 4, 6 was 2.8-fold more active than the original 2. On the other hand, the (23R)-isomer 7 showed little antagonistic activity in contrast to (23R)-24,24-dimethylvitamin D\textsubscript{3} lactone 5 which was highly active compared to the original 3.

### Table 2 Biological Activities of 24,24-Ethanovitamin D\textsubscript{3} Lactones 6 and 7

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Binding affinity for VDR\textsuperscript{a}</th>
<th>Antagonistic activity (IC\textsubscript{50}, nM)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 –</td>
<td>–</td>
</tr>
<tr>
<td>TEI-9647 (2)</td>
<td>12</td>
<td>9.4</td>
</tr>
<tr>
<td>4\textsuperscript{c}</td>
<td>37</td>
<td>0.71</td>
</tr>
<tr>
<td>6</td>
<td>167</td>
<td>3.3</td>
</tr>
<tr>
<td>TEI-9648 (3)</td>
<td>7</td>
<td>134.4</td>
</tr>
<tr>
<td>5\textsuperscript{c}</td>
<td>18</td>
<td>51.5</td>
</tr>
<tr>
<td>7</td>
<td>0.7</td>
<td>&gt;3000</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Chick intestinal VDR. The potency of 1 is normalized to 100.

\textsuperscript{b} Antagonistic activity was assessed in terms of IC\textsubscript{50} for the differentiation of HL-60 cells induced by 10 nM of 1.

\textsuperscript{c} See ref.\textsuperscript{14c}

### Effect of C2\textalpha Modification of 24,24-Ethanovitamin D\textsubscript{3} Lactones

Next, we turned our attention to the C2\textalpha-functionalization of the 24,24-ethanovitamin D\textsubscript{3} lactones 6 and 7. We demonstrated that the C2\textalpha-modification of 24-methylvitamin D\textsubscript{3} lactones\textsuperscript{24b} as well as 24,24-dimethyl derivatives\textsuperscript{14c} markedly enhanced their biological activities. From our previous results, we expected a high increase in VDR-binding affinity and marked enhancement of antagonistic activity through the C2\textalpha-functionalization of 6 and 7. The C2\textalpha-modified analogues were similarly synthesized by the coupling reaction of the CD-ring precursors 21 and 22 with the A-ring precursor enynes 12\textalpha\textsuperscript{24} 12\textbeta\textsuperscript{14c} and 12\textepsilon\textsuperscript{7} respectively (Scheme 5).

The evaluation of the biological activities of 6\textalpha–c and 7a–c demonstrated that the C2\textalpha-modification was effective in improving the biological activities of 24,24-ethanovitamin D\textsubscript{3} lactones 6 and 7 (Table 3). Namely, the VDR-binding affinity of (23S)-isomers 6\textalpha–c remained high. In particular, the 2\textalpha-methyl analogue 6a showed 9.3 times stronger VDR-binding affinity than the original TEI-9647 (2). On the other hand, the C2\textalpha-modification of TEI-9648 (3) type analogue 7 increased the low VDR affinity of 7 to 1.9–4.1 times higher than TEI-9648 (3) (7a–c). The antagonistic activity was also enhanced by the C2\textalpha-functionalization. In the case of TEI-9647 type analogues 6\textalpha–c, the VDR antagonistic activity increased to 13–19 times that of 2 (4.5–6.7 times stronger than 6). The antagonistic activity of (23R)-lactone analogue 7 was strongly affected by the substituents at position C2\textalpha (7a–c). That is, (23R)-24,24-ethanovitamin D\textsubscript{3} lactone having the 2\textalpha-methyl group (7a) showed 2.4-times higher VDR antagonistic activity than TEI-9648 (3). On the other hand, the antagonistic activity of the vitamin D\textsubscript{3} lactone derivatives having the longer side-chain at the C2\textalpha position (7b and 7c) decreased to about half that of 8.

### Table 3 Biological Activities of 2\textalpha-Modified 24,24-Ethanovitamin D\textsubscript{3} Lactones 6\textalpha–c and 7a–c

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Binding affinity for VDR\textsuperscript{a}</th>
<th>Antagonistic activity (IC\textsubscript{50}, nM)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEI-9647 (2)</td>
<td>12</td>
<td>9.4</td>
</tr>
<tr>
<td>6a</td>
<td>111</td>
<td>0.49</td>
</tr>
<tr>
<td>6b</td>
<td>83</td>
<td>0.74</td>
</tr>
<tr>
<td>6c</td>
<td>59</td>
<td>0.55</td>
</tr>
<tr>
<td>TEI-9648 (3)</td>
<td>7</td>
<td>134.4</td>
</tr>
<tr>
<td>7a</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>7b</td>
<td>29</td>
<td>240</td>
</tr>
<tr>
<td>7c</td>
<td>13</td>
<td>220</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Chick intestinal VDR. The potency of 1 is normalized to 100.

\textsuperscript{b} Antagonistic activity was assessed in terms of IC\textsubscript{50} for the differentiation of HL-60 cells induced by 10 nM of 1.
usual transcriptionally inactive form.\textsuperscript{27} 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. Namely, 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 antagonist of TEF-9647 (2).\textsuperscript{28,29} Furthermore, the exo-methylene lactone structure is dispensable for the antagonistic action of the vitamin D\textsubscript{3} lactones.\textsuperscript{30} Based on the results, we consider that the nucleophilic thiol groups of the cysteines could attack the α-methylene-γ-lactone of 2 via 1,4-addition to give the corresponding cysteine adduct.\textsuperscript{31} Such interaction between the ligand and the LBD might prevent the positioning of helix 12. As a result, the complex of VDR and antagonist 2 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 novel synthesized vitamin D\textsubscript{3} lactones 6, 6a–c and 7a–c, which showed more potent antagonistic activity, might be situated in a preferable position to interact with the cysteine residues after the binding to the LBD of the VDR. On the other hand, the exo-methylene moiety of the weaker VDR antagonist (23R)-ethanovitamin D\textsubscript{3} lactone (7) is possibly located in an unfavorable position for interaction with the cysteines. Further investigation of the mechanism of antagonistic action is currently in progress.

We have succeeded in the development of novel potent vitamin D receptor antagonists, 24,24-ethano-1α-hydroxyvitamin D\textsubscript{3}, 26,23-lactones 6 and 7 and their C2α-functionalized analogues 6a–c and 7a–c. The VDR antagonists are expected to be potent therapeutic agents for some diseases caused by the hypersensitivity of the VDR to 1α,25-dihydroxyvitamin D\textsubscript{3}, such as Paget’s disease of bone.\textsuperscript{32} We expect these analogues with potent anti-vitamin D activity to contribute to our understanding of the mechanisms involved in the expression of antagonistic activity toward VDR as well as to finding new medicines for treating Paget’s disease of bone.

All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Ethylene gas was used without purification. Column chromatography was performed on silica gel 60 N (Kanto Chemical Co., Inc., 100–210 μm), and flash column chromatography was performed on silica gel 60 (Merck, 40–63 μm). NMR spectra were measured on a JEOL AL-400 magnetic resonance spectrometer. IR spectra were recorded on a JASCO FTIR-8000 spectrometer. MS were measured on a JEOL JMX-SX 102 mass spectrometer. Specific optical rotations were measured on JASCO DIP-370 digital polarimeter.

\textbf{(2S,4S)-4-Benzoyloxy-5-hexene-1,2-diol (10)}

To a solution of 9 (1.5 g, 4.4 mmol) in 1-propanol–H\textsubscript{2}O (9:1, 44 mL) were added activated Zn dust (13 g, 199 mmol) and NaBH\textsubscript{3}CN (1.8 g, 29 mmol) at 95 °C, and the mixture was stirred at the same temperature for 40 min. After the mixture was filtered through a Celite pad, the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel; hexane–EtOAc, 1:1) to give 10.

Yield: 785 mg (75%); colorless oil; [\alpha]\textsubscript{D}\textsuperscript{23} +10.9 (c 1.54, CHCl\textsubscript{3}).

IR (mix): 3381, 1716, 1604, 1275, 1026 cm\textsuperscript{–1}.

1H NMR (400 MHz, CDCl\textsubscript{3}): δ = 1.73–1.89 (m, 2 H), 2.09 (dd, J = 7.3, 4.2 Hz, 1 H), 3.26 (d, J = 3.9 Hz, 1 H), 3.51 (dd, J = 11.1, 6.9, 4.2 Hz, 1 H), 3.64 (ddd, J = 11.1, 7.3, 3.4 Hz, 1 H), 3.75 (m, 1 H), 5.24 (d, J = 10.4 Hz, 1 H), 5.79 (d, J = 17.3 Hz, 1 H), 5.78 (m, 1 H), 5.98 (ddd, J = 17.3, 10.4, 5.9 Hz, 1 H), 7.46 (dd, J = 7.8, 7.8 Hz, 2 H), 7.59 (dd, J = 7.8, 7.8 Hz, 1 H), 8.07 (d, J = 7.8 Hz, 2 H).

13C NMR (100 MHz, CDCl\textsubscript{3}): δ = 38.1, 66.4, 68.1, 72.0, 116.3, 128.2 (2 C), 129.4 (2 C), 129.7, 133.0, 136.1, 166.3.

EI-LRMS: m/z = 236 (M\textsuperscript{+}), 219, 105, 77.

EI-HRMS: m/z calc for C\textsubscript{13}H\textsubscript{16}O\textsubscript{4}: 236.1049; found: 236.1054.

(3S,5R)-Bis(tert-butyldimethyloxyl)oct-1-en-7-yn-1-ene (11)

To a solution of 10 (560 mg, 2.4 mmol) in pyridine (2.4 mL) was added 2-mesitylenesulfonyl chloride (596 mg, 2.7 mmol) at 0 °C, and the mixture was stirred at r.t. for 16 h. The mixture was stirred at r.t. The mixture was washed with sat. aq NaCl, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue was purified by flash column chromatography (silica gel; hexane–EtOAc, 3:1) to give a crude sulfonate compound (827 mg). To a solution of the crude sulfonate (827 mg) in THF (20 mL) was added a solution of LiHMDS in THF (1.0 M, 3.0 mL, 3.0 mmol) at –78 °C, and the mixture was warmed to 0 °C over 1 h. To the mixture was added sat. aq NH\textsubscript{4}Cl, and the mixture was washed with sat. aq NaCl, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue was purified by flash column chromatography (silica gel; hexane–EtOAc, 20:1) to give 11.

Yield: 342 mg (2 steps, 66%); colorless oil; [\alpha]\textsubscript{D}\textsuperscript{23} +14.3 (c 1.12, CHCl\textsubscript{3}).

IR (mix): 1720, 1649, 1603, 1275, 1026 cm\textsuperscript{–1}.

1H NMR (400 MHz, CDCl\textsubscript{3}): δ = 1.94–2.05 (m, 2 H), 2.52 (dd, J = 4.8, 4.8 Hz, 1 H), 2.77 (dd, J = 4.8, 4.8 Hz, 1 H), 3.07 (m, 1 H), 5.25 (ddd, J = 10.6, 1.2, 1.2 Hz, 1 H), 5.39 (ddd, J = 17.1, 1.2, 1.2 Hz, 1 H), 5.73 (ddd, J = 12.1, 6.1, 6.1 Hz, 1 H), 5.97 (ddd, J = 17.1, 10.6, 6.1 Hz, 1 H), 7.45 (dd, J = 7.1, 7.1 Hz, 2 H), 7.57 (dd, J = 7.1, 7.1 Hz, 1 H), 8.07 (d, J = 7.1 Hz, 2 H).

13C NMR (100 MHz, CDCl\textsubscript{3}): δ = 37.9, 47.0, 48.9, 72.6, 116.9, 128.2 (2 C), 129.4 (2 C), 130.0, 132.9, 135.6, 165.3.

EI-LRMS: m/z = 218 (M\textsuperscript{+}), 193, 105, 77.

EI-HRMS: m/z calc for C\textsubscript{13}H\textsubscript{16}O\textsubscript{4}: 218.0949; found: 218.0948.

Ethanovitamin D\textsubscript{3} Lactones with Enzyme Metathesis 2537

Synthesis 2005, No. 15, 2533–2543 © Thieme Stuttgart · New York
Yield: 208 mg (97%); colorless oil; [α]D25 +0.003 (c 1.16, CHCl3). IR (neat): 3374, 3301, 2120, 1645, 1219, 1072 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.74 (ddd, J = 14.5, 7.5, 2.9 Hz, 1 H), 1.83 (ddd, J = 14.5, 8.8, 3.5 Hz, 1 H), 2.05 (t, J = 2.5 Hz, 1 H), 2.35–2.50 (m, 3 H), 2.80 (br d, J = 3.2 Hz, 1 H), 4.11 (m, 1 H), 4.49 (m, 1 H), 5.16 (ddd, J = 10.4, 1.5, 1.5 Hz, 1 H), 5.29 (ddd, J = 17.0, 1.5, 1.5 Hz, 1 H), 5.92 (dd, J = 17.0, 10.4, 5.8 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = 27.2, 42.1, 67.0, 69.8, 70.7, 80.7, 114.4, 140.2.


(4S,6R)-6-[(1R,4E,3aR,7aR)-4-Bromomethylene-7a-methyloctahydropyridine-1-yl]-2-[(tert-butyldimethylsilyl)oxy]-3-methylenehept-1-en-4-one (15)

Yield: 208 mg (97%); colorless oil; [α]D25 +0.003 (c 1.16, CHCl3).

Yield: 96 mg (92%); colorless oil; [α]D25 +64.3 (c 1.21, CHCl3). IR (neat): 1695, 1651, 1632, 1103 cm−1.

1H NMR (400 MHz, CDCl3): δ = 0.061 (s, 6 H), 0.60 (s, 3 H), 0.90 (s, 9 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.23–1.39 (m, 3 H), 1.41–1.73 (m, 5 H), 1.80–2.13 (m, 4 H), 2.44 (dd, J = 16.1, 10.0 Hz, 1 H), 2.70 (dd, J = 16.1, 2.9 Hz, 1 H), 2.88 (m, 1 H), 4.26 (dd, J = 1.4, 1.4 Hz, 2 H), 5.11 (d, J = 1.4 Hz, 1 H), 5.33 (d, J = 1.4 Hz, 1 H), 5.65 (s, 1 H), 5.68 (s, 1 H), 5.76 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = −5.3 (2 C), 11.9, 18.3, 19.9, 22.0, 22.5, 23.9 (3 C), 27.7, 31.0, 33.1, 39.8, 45.6, 46.4, 55.7, 55.8, 65.5, 97.5, 114.2, 122.2, 144.6, 145.4, 149.2, 202.4.

EI-LRMS: mlz = 494 (M+), 479, 437, 415, 345, 253, 211, 183.

EI-HRMS: mlz / c calculated for C24H33O2BrSi: 494.2216; found: 494.2208.

Yield: 86 mg (85%); colorless oil; [α]D25 +70.1 (c 1.15, CHCl3). IR (neat): 1695, 1651, 1632, 1103 cm−1.

1H NMR (400 MHz, CDCl3): δ = 0.13 (s, 6 H), 0.61 (s, 3 H), 0.91 (s, 9 H), 0.99 (d, J = 6.3 Hz, 3 H), 1.25–1.38 (m, 3 H), 1.40–1.72 (m, 5 H), 1.89 (m, 1 H), 1.95–2.03 (m, 2 H), 2.10 (m, 1 H), 2.29 (dd, J = 15.4, 10.1 Hz, 1 H), 2.64 (dd, J = 15.4, 3.4 Hz, 1 H), 2.88 (m, 1 H), 4.46 (s, 2 H), 5.65 (m, 1 H).

13C NMR (100 MHz, CDCl3): δ = −5.2 (2 C), 11.9, 18.2, 19.7, 22.0, 22.4, 25.7 (3 C), 27.7, 30.9, 33.3, 39.6, 45.5, 51.5, 52.3, 55.5, 55.7, 84.1, 90.1, 97.6, 144.5, 187.2.


EI-HRMS: mlz / c calculated for C24H33O2BrSi: 508.2372; found: 508.2366.

(4S,6R)-6-[(1R,4E,3aR,7aR)-4-Bromomethylene-7a-methyloctahydropyridine-1-yl]-2-[(tert-butyldimethylsilyl)oxy]-3,3-ethanohept-1-en-4-one (18)

To a solution of 17 (86 mg, 0.17 mmol) in toluene (1.7 mL) was added a solution of Dibal-H in toluene (1.0 M, 0.25 mL, 0.25 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture were added a few drops of MeOH and sat. aq potassium sodium tartrate at −78 °C, and the mixture was stirred at r.t. for 30 min. To the mixture was added sat. aq NH4Cl at 10 °C and the mixture was extracted with EtO. The organic layer was washed with sat. aq NaCl, dried (Na2SO4) and concentrated. The residue was purified by flash column chromatography (silica gel; hexane−EtOAc, 100:1) to give 18.

Yield: 86 mg (85%); colorless oil; [α]D25 +55.8 (c 1.49, CHCl3).

IR (neat): 3374, 3301, 2120, 1645, 1219, 1072 cm−1.

1H NMR (400 MHz, CDCl3): δ = 0.061 (s, 6 H), 0.60 (s, 3 H), 0.90 (s, 9 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.23–1.39 (m, 3 H), 1.41–1.73 (m, 5 H), 1.80–2.13 (m, 4 H), 2.44 (dd, J = 16.1, 10.0 Hz, 1 H), 2.70 (dd, J = 16.1, 2.9 Hz, 1 H), 2.88 (m, 1 H), 4.26 (dd, J = 1.4, 1.4 Hz, 2 H), 5.11 (d, J = 1.4 Hz, 1 H), 5.33 (d, J = 1.4 Hz, 1 H), 5.65 (s, 1 H), 5.68 (s, 1 H), 5.76 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = −5.3 (2 C), 11.9, 18.3, 19.9, 22.0, 22.5, 23.9 (3 C), 27.7, 31.0, 33.1, 39.8, 45.6, 46.4, 55.7, 55.8, 65.5, 97.5, 114.2, 122.2, 144.6, 145.4, 149.2, 202.4.

EI-LRMS: mlz = 494 (M+), 479, 437, 415, 345, 253, 211, 183.

EI-HRMS: mlz / c calculated for C24H33O2BrSi: 494.2216; found: 494.2208.
**23S-Alcohol**

\[ [\alpha]_{D}^{23} +29.4 (c 0.83, CHCl_{3}) \].

IR (neat): 3424, 1641, 1255, 1042 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.11 \) (s, 6 H), 0.41 (ddd, \( J = 9.3, 5.4, 4.1 \) Hz, 1 H), 0.56 (m, 1 H), 0.57 (s, 3 H), 0.69 (ddd, \( J = 9.3, 5.4, 4.1 \) Hz, 1 H), 0.78 (ddd, \( J = 9.3, 5.4, 4.1 \) Hz, 1 H), 0.93 (s, 9 H), 0.97 (d, \( J = 6.6 \) Hz, 3 H), 1.18–2.05 (m, 15 H), 2.82–2.93 (m, 2 H), 4.13 (d, \( J = 12.3 \) Hz, 1 H), 4.23 (d, \( J = 12.3 \) Hz, 1 H), 5.01 (d, \( J = 19 \) Hz, 1 H), 5.19 (s, 1 H), 5.63 (s, 1 H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = -5.2 \) (2 C), 10.4, 11.5, 11.9, 18.4, 19.8, 22.0, 22.6, 25.9 (3 C), 27.5, 30.3, 31.1, 33.8, 39.9, 42.5, 45.5, 55.8, 56.7, 67.0, 76.9, 97.3, 116.7, 145.0, 147.8.

EI-IRMS: \( m/z = 396 \) (M\(^+\)), 492, 453, 361, 221, 227, 147.

EI-IRMS: \( m/z \) calcd for C\(_{27}\)H\(_{47}\)O\(_2\)BrSi: 510.2528; found: 510.2528.

**23R-Alcohol**

\[ [\alpha]_{D}^{23} +113.7 (c 1.04, CHCl_{3}) \].

IR (neat): 3382, 1634, 1256, 1026 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.11 \) (s, 6 H), 0.43–0.53 (m, 2 H), 0.57 (s, 3 H), 0.64–0.78 (m, 2 H), 0.91 (d, \( J = 6.6 \) Hz, 3 H), 0.92 (s, 9 H), 1.04 (ddd, \( J = 13.8, 10.9, 1.7 \) Hz, 1 H), 1.18–1.72 (m, 11 H), 1.91 (m, 1 H), 1.96 (ddd, \( J = 12.5, 7.1, 1.5 \) Hz, 1 H), 2.01 (dd, \( J = 12.5, 2.3, 2.3 \) Hz, 1 H), 2.80–2.92 (m, 2 H), 4.11 (d, \( J = 12.5 \) Hz, 1 H), 4.21 (d, \( J = 12.5 \) Hz, 1 H), 4.99 (d, \( J = 1.7 \) Hz, 1 H), 5.18 (s, 1 H), 5.63 (s, 1 H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = -5.2 \) (2 C), 11.3, 11.9, 18.4, 18.7, 22.0, 22.6, 25.7, 26.0 (3 C), 27.8, 31.0, 31.1, 32.5, 39.9, 41.8, 45.6, 50.6, 56.0, 66.8, 74.3, 79.7, 116.7, 145.0, 147.9.


EI-IRMS: \( m/z \) calcd for C\(_{27}\)H\(_{47}\)O\(_2\)BrSi (M – H\(_2\)O): 492.2423; found: 492.2423.

To the 23S-alcohol (197 mg, 0.39 mmol) in THF (3.9 mL) was added a solution of TBAF in THF (1.0 M, 0.77 mL, 0.77 mmol) at 0 °C, and the mixture was stirred at r.t. for 15 min. To the mixture was added MnO\(_2\) (346 mg, 4.0 mmol) at r.t., and the mixture was stirred at the same temperature for 30 min. After the mixture was filtered through a short column (silica gel; Et\(_2\)O), the filtrate was concentrated.

**Ethanovitamin D\(_3\) Lacones with Enzyme Metathesis**

**Synthesis 2005, No. 15, 2533–2543 © Thieme Stuttgart · New York**

**(4R,6R)-6-[(1R,4E,3aR,7aR)-4-Bromomethylene-7a-methyl-octahydroinden-1-yl]-3,3-ethano-2-methyleneheptane-1,4-diol (20)**

Similar to the synthesis of 19 from the 23S-alcohol, the crude product, which was obtained from the above 23R-alcohol (269 mg, 0.53 mmol) and TBAF (1.0 M THF solution, 1.1 mL, 1.1 mmol) in THF (3.5 mL) at r.t. for 15 min, was purified by flash column chromatography (silica gel; hexane–EtOAc, 4:1) to give 20.

Yield: 195 mg (93%); colorless solid; mp 167–170 °C (recrystallized from THF–hexane; \( [\alpha]_{D}^{29} +142.9 \) (c 1.19, THF).

IR (KBr): 3382, 1634, 1219, 1014 cm\(^{-1}\).

**Ethanovitamin D\(_3\) Lacones with Enzyme Metathesis**

**Synthesis 2005, No. 15, 2533–2543 © Thieme Stuttgart · New York**
2.7 Hz, 1 H), 2.88 (m, 1 H), 4.50 (dd, J = 11.7, 2.0 Hz, 1 H), 5.02 (s, 1 H), 5.65 (brs, 1 H), 5.94 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 11.9, 14.8, 16.9, 18.4, 22.0, 22.5, 26.1, 27.6, 31.0, 32.5, 39.9, 39.4, 45.6, 55.8, 56.2, 79.4, 97.5, 113.6, 141.0, 144.6, 169.6.

EI-MS: m/z = 392 (M+), 377, 313, 255, 227, 147.

EI-MSR: m/z calcld for C12H16O2BrSi: 392.1351; found: 392.1341.

Vitamin D₃, Lactones; General Procedure

To a solution of an A-ring precursor (1.5 equiv to a CD-ring precursor), and the CD-ring precursor in toluene were added Et₃N and Pd(PPh₃)₃ (30 mol% to the CD-ring precursor) and the mixture was stirred at 110 °C for 1–1.5 h. After the mixture was filtered through a silica gel pad, the filtrate was concentrated. The crude product was dissolved in MeCN (2 mL). To the solution was added a solution of conc HF (10% in MeCN) and the mixture was stirred at r.t. (23 h). The mixture was treated with conc HF in MeCN for 2.5 h. After the usual work-up, the crude product was purified by preparative TLC (silica gel; hexane–EtOAc, 1:1) to give 6a.

Yield: 17 mg (2 steps, 60%); amorphous solid; [α]D = +0.30 (c 1.34, CHCl₃).

IR (film, CHCl₃): 3428, 1755, 2616, 1005, 1242, 1476.5 cm⁻¹.

13C NMR (100 MHz, CDCl₃): δ = 12.0, 12.6, 14.8, 16.5, 20.0, 22.3, 23.5, 27.1, 27.8, 29.1, 34.6, 39.5, 40.4, 42.9, 45.3, 46.0, 56.1, 56.7, 66.8, 70.8, 81.6, 111.7, 113.5, 117.1, 124.8, 133.0, 141.0, 142.7, 147.6, 170.0.

EI-MSR: m/z = 452 (M+), 434, 416, 311, 285, 134, 105.

EI-MSR: m/z calcld for C20H18O4: 452.2926; found: 452.2925.

(23R)-25-Dehydro-24,24-ethano-1α-hydroxyvitamin D₂6,23-Lactone (7a)

According to the General Procedure, the crude product, which was obtained from 22 (21 mg, 52 µmol), 12a (30 mg, 79 µmol), Et₃N (1.5 mL) and Pd(PPh₃)₃ (18 mg, 16 µmol) in toluene (1.5 mL) at 110 °C for 1 h, was treated with conc HF in MeCN for 2.5 h. After the usual work-up, the crude product was purified by preparative TLC (silica gel; hexane–EtOAc, 1:1) to give 7a.

Yield: 12 mg (2 steps, 49%); amorphous solid; [α]D = +118.9 (c 0.85, CHCl₃).

IR (film, CHCl₃): 3441, 1754, 1657, 1604, 1421, 1215, 1055 cm⁻¹.

13C NMR (400 MHz, CDCl₃): δ = 0.57 (s, 3 H), 0.83–1.05 (m, 4 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.15 (dd, J = 10.1, 6.4, 4.9 Hz, 1 H), 1.20–2.08 (m, 17 H), 2.31 (dd, J = 13.4, 6.6 Hz, 1 H), 2.60 (dd, J = 13.4, 3.2 Hz, 1 H), 2.82 (m, 1 H), 4.23 (brs, 1 H), 4.42 (brs, 1 H), 4.51 (dd, J = 11.6, 1.8 Hz, 1 H), 5.00 (s, 1 H), 5.02 (s, 1 H), 5.33 (s, 1 H), 5.94 (s, 1 H), 6.01 (d, J = 11.2 Hz, 1 H), 6.46 (d, J = 11.2 Hz, 1 H).

EI-MS: m/z = 452 (M⁺), 434, 416, 311, 285, 134, 105.

EI-MSR: m/z calcld for C20H18O4: 452.2927; found: 452.2930.

(23S)-25-Dehydro-24,24-ethano-1α-2-methyl-1α-hydroxyvitamin D₂6,23-Lactone (6a)

According to the General Procedure, a crude product, which was obtained from 21 (25 mg, 62 µmol), 12a (36 mg, 94 µmol), Et₃N (1.5 mL) and Pd(PPh₃)₃ (22 mg, 19 µmol) in toluene (1.5 mL) at 110 °C for 1.5 h, was treated with conc HF in MeCN for 2.5 h. After the usual work-up, the crude product was purified by preparative TLC (silica gel; hexane–EtOAc, 1:1) to give 6a.

Yield: 39 mg (71%); amorphous solid; [α]D = +92.0 (c 1.76, CHCl₃).

IR (film, CHCl₃): 3428, 1755, 1657, 1607, 1342, 1215, 1051 cm⁻¹.

13C NMR (400 MHz, CDCl₃): δ = 0.57 (s, 3 H), 0.82–1.05 (m, 4 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.15 (dd, J = 10.1, 6.4, 4.9 Hz, 1 H), 1.20–2.08 (m, 17 H), 2.31 (dd, J = 13.4, 6.6 Hz, 1 H), 2.60 (dd, J = 13.4, 3.2 Hz, 1 H), 2.82 (m, 1 H), 4.23 (brs, 1 H), 4.42 (brs, 1 H), 4.51 (dd, J = 11.6, 1.8 Hz, 1 H), 5.00 (s, 1 H), 5.02 (s, 1 H), 5.33 (s, 1 H), 5.94 (s, 1 H), 6.01 (d, J = 11.2 Hz, 1 H), 6.46 (d, J = 11.2 Hz, 1 H).

C NMR (100 MHz, CDCl₃): δ = 12.0, 14.8, 16.8, 18.4, 22.2, 23.5, 26.4, 27.6, 29.0, 32.5, 39.8, 40.5, 42.8, 45.2, 46.0, 56.3, 57.0, 66.8, 70.8, 79.6, 111.8, 113.7, 117.2, 124.8, 133.1, 141.2, 142.6, 147.6, 169.9.

EI-MSR: m/z = 452 (M⁺), 434, 416, 311, 285, 134, 105.

EI-MSR: m/z calcld for C20H18O4: 452.2927; found: 452.2930.
Hz, 1 H), 5.02 (s, 1 H), 5.28 (s, 1 H), 5.94 (s, 1 H), 6.00 (d, J = 11.2 Hz, 1 H), 6.38 (d, J = 11.2 Hz, 1 H).

1^1C NMR (100 MHz, CDCl$_3$): δ = 12.2, 12.6, 14.9, 16.9, 18.4, 22.3, 23.5, 26.5, 27.6, 29.1, 32.6, 39.8, 40.6, 43.5, 44.2, 46.0, 56.4, 57.0, 71.7, 75.3, 79.5, 113.1, 113.6, 117.1, 124.6, 133.2, 141.1, 142.6, 164.5, 169.7.

EI-MS: mlz = 466 (M$^+$), 448, 430, 265, 166.

EI-HRMS: mlz = calcd for C$_{46}$H$_{50}$O$_3$; 466.3083; found: 466.3075.

(23S)-25-Dehydro-24,24-ethano-2a-(3-hydroxypropyl)-1a-hydroxyvitamin D$_{2,6,23}$-Lactone (6b)

According to the General Procedure, a crude product, which was obtained from 21 (29 mg, 74 mol%), 12b (60 mg, 111 mol%), Et$_3$N (1.5 mL) and Pd(PPh$_3$)$_2$ (26 mg, 22 µmol) in toluene (1.5 mL) at 110 °C for 1.5 h, was treated with concd HF in MeCN for 2.5 h. After the usual work-up, the crude product was purified by preparative TLC (silica gel; EtOAc) to give 6b.

Yield: 23 mg (2 steps 62%); amorphous solid; [α]$_D^{24}$ +20.1 (c 1.78, CHCl$_3$).

IR (film, CHCl$_3$): 3351, 1759, 1655, 1343, 1198, 1055 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): δ = 0.53 (s, 3 H), 0.84 (ddd, J = 9.9, 7.0, 5.0 Hz, 1 H), 0.95 (ddd, J = 9.9, 7.0, 4.6 Hz, 1 H), 1.01 (ddd, J = 9.9, 6.4, 4.6 Hz, 1 H), 1.05 (d, J = 6.6 Hz, 3 H), 1.15–1.75 (m, 17 H), 1.85–2.05 (m, 3 H), 2.13 (br s, 1 H), 2.24 (dd, J = 13.2, 8.3 Hz, 1 H), 2.60 (br s, 2 H), 2.65 (dd, J = 13.2, 4.3 Hz, 1 H), 3.87 (d, J = 8.3, 4.3 Hz, 1 H), 4.36 (br d, J = 2.9 Hz, 1 H), 4.49 (d, J = 8.7, 3.8 Hz, 1 H), 4.98 (d, J = 2.0 Hz, 1 H), 5.01 (s, 1 H), 5.26 (br s, 1 H), 5.93 (s, 1 H), 5.99 (d, J = 11.2 Hz, 1 H), 6.38 (d, J = 11.2 Hz, 1 H).

13C NMR (100 MHz, CDCl$_3$): δ = 12.0, 14.8, 16.5, 20.0, 22.3, 22.8, 23.5, 27.1, 27.8, 28.9, 30.1, 34.6, 39.5, 40.4, 44.1, 46.0, 49.0, 56.1, 56.6, 62.6, 70.2, 73.5, 81.6, 113.4, 113.5, 117.1, 124.5, 133.0, 141.0, 142.7, 146.4, 169.8.

EI-MS: mlz = 510 (M$^+$), 492, 474, 415, 327, 309.

EI-HRMS: mlz = calcd for C$_{46}$H$_{48}$O$_3$; 510.3345; found: 510.3342.

(23R)-25-Dehydro-24,24-ethano-2a-(3-hydroxypropyl)-1a-hydroxyvitamin D$_{2,6,23}$-Lactone (7b)

According to the General Procedure, a crude product, which was obtained from 22 (29 mg, 74 mol%), 12b (60 mg, 111 mol%), Et$_3$N (1.5 mL) and Pd(PPh$_3$)$_2$ (26 mg, 22 µmol) in toluene (1.5 mL) at 110 °C for 1.5 h, was treated with concd HF in MeCN for 2.5 h. After the usual work-up, the crude product was purified by preparative TLC (silica gel; EtOAc) to give 7b.

Yield: 20 mg (2 steps 54%); amorphous solid; [α]$_D^{24}$ +123.4 (c 1.57, CHCl$_3$).

IR (film, CHCl$_3$): 3358, 1757, 1651, 1343, 1196, 1051 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): δ = 0.56 (s, 3 H), 0.82–1.05 (m, 4 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.15 (m, 1 H), 1.20–2.05 (m, 18 H), 2.19 (br s, 1 H), 2.24 (dd, J = 13.2, 8.6 Hz, 1 H), 2.60 (br s, 2 H), 2.65 (dd, J = 13.2, 4.3 Hz, 1 H), 2.83 (m, 1 H), 3.60–3.75 (m, 2 H), 3.88 (dd, J = 8.6, 8.6, 4.3 Hz, 1 H), 4.36 (d, J = 2.7 Hz, 1 H), 4.50 (dd, J = 11.5, 1.5 Hz, 1 H), 4.97 (d, J = 1.7 Hz, 1 H), 5.02 (s, 1 H), 5.27 (d, J = 1.7 Hz, 1 H), 5.94 (s, 1 H), 6.00 (d, J = 11.4 Hz, 1 H), 6.37 (d, J = 11.4 Hz, 1 H).

13C NMR (100 MHz, CDCl$_3$): δ = 12.2, 14.9, 16.9, 18.4, 22.3, 22.8, 23.5, 26.4, 27.7, 29.0, 31.2, 36.5, 39.8, 40.6, 44.3, 46.0, 49.0, 56.3, 56.9, 62.6, 70.2, 73.5, 79.5, 113.5, 113.7, 117.2, 124.4, 133.1, 141.1, 142.4, 146.4, 169.8.

EI-MS: mlz = 510 (M$^+$), 492, 474, 415, 327, 309.

EI-HRMS: mlz = calcd for C$_{46}$H$_{48}$O$_3$; 510.3345; found: 510.3344.
(40%) of distilled H₂O was added to each tube, which was mixed vigorously and centrifuged (2260 × 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 di-oxygen-based scintillation fluid and the radioactivity was measured with a Beckman liquid scintillation counter (Model LS6500). The relative potency of the analogue was calculated from the concentration needed to displace 50% of [26,27-3H]-1α,25-dihydroxyvitamin D₃ from the receptor compared with the activity of 1α,25-dihydroxyvitamin D₃ (assigned a 100% value).

**Assay for HL-60 Cell Differentiation**

Nitro blue tetrazolium (NBT)-reducing assay 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). The cell concentration at seeding was adjusted to 2 × 10⁵ cells/mL and the seeding volume was 1 mL/well. An EtOH solution of 1α,25-dihydroxyvitamin D₃ (final concentration: 10⁻⁸ M) and an analogue (final concentration: 10⁻¹¹ to 10⁻⁶ M) was added to the control culture medium at 0.1% volume and culture was incubated for 96 h at 37 °C in a humidified atmosphere of 5% CO₂–air without a change of medium. The same amount of vehicle was needed to displace 50% of [26,27-3H]-1α,25-dihydroxyvitamin D₃ from the receptor compared with the activity of 1α,25-dihydroxyvitamin D₃ (assigned a 100% value).

**References**


(20) Crystal data of 20 are as follows: C21H34BrO2, space group P2₁2₁2₁, Z = 4, a = 7.785 (6), b = 9.445 (9), c = 27.35 (2) Å, V = 2010 (2) Å³, Dcalcd = 1.313 g/cm³, R1 = 0.063 for 16610 reflections [I > 3.00σ(I)], wR2 = 0.068 [I > 3.00σ(I)]; structure solution and refinement were performed using Direct Methods (SIR92) and full-matrix least-squares on F, respectively. Diffractometer Rigaku RAXIS-RAPID, graphite monochromated CuKα (λ = 1.54187 Å).


(31) It is well known that some biologically active natural products having an α-methylene-γ-lactone structure react with the thiol group of cysteine to give the corresponding cysteine adduct: Kupchan, S. M.; Fessler, D. C.; Eakin, T. J.; Giacobbe, T. J. Science 1970, 168, 376.
