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Synthesis and Biological Activity of 1α-Hydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 and 1α,25-Dihydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3

HIROSHI SAI, SUGURU TAKATSUTO, and NOBUO IKEKAWA*

Department of Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

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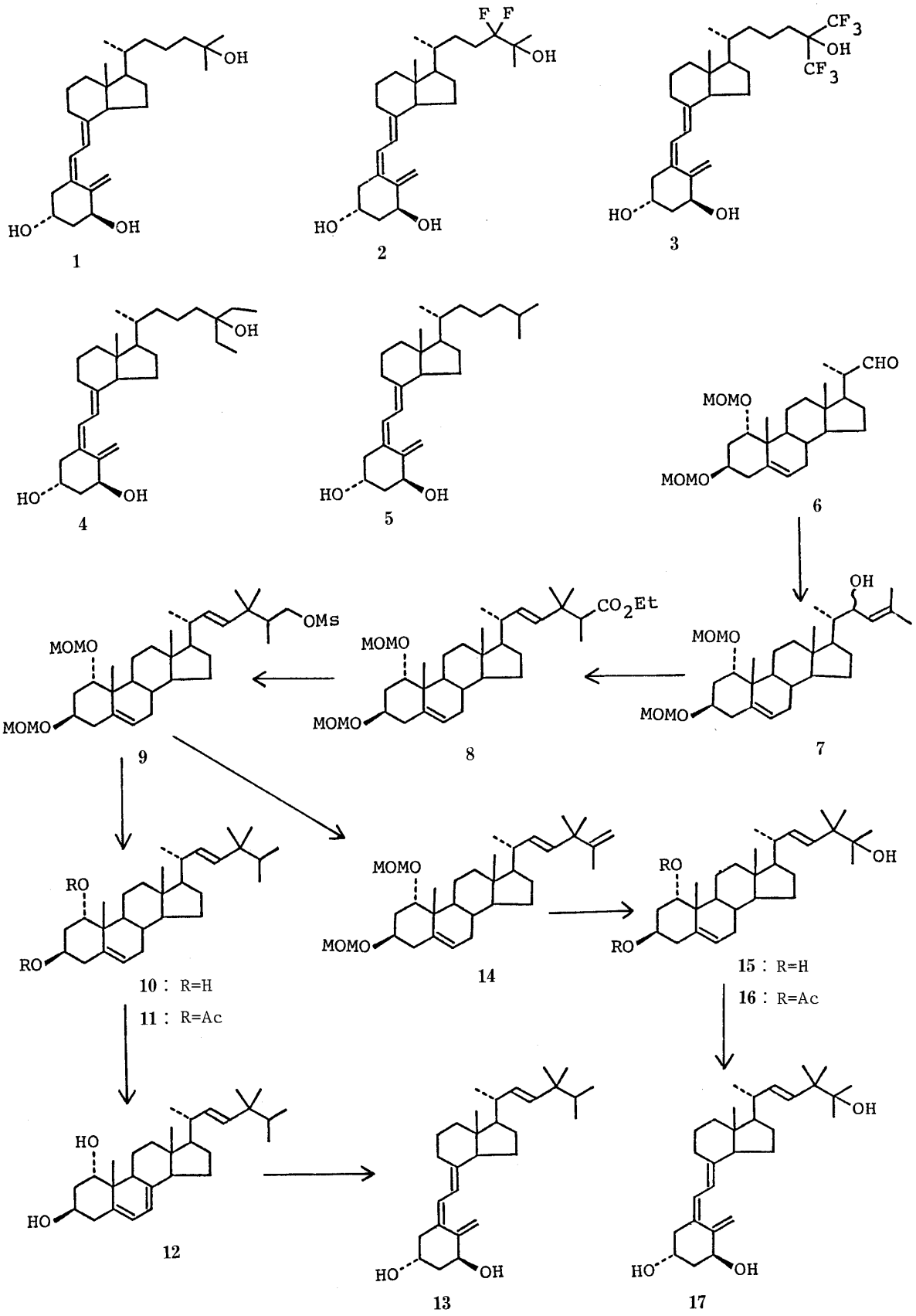
Two new vitamin D_3 analogues, 1α-hydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 (**13**) and 1α,25-dihydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 (**17**), which are blocked for 24-hydroxylation by the methyl groups, were synthesized from 1α,3β-bismethoxymethoxypregn-5-ene-20*S*-carbaldehyde (**6**) by using the orthoester Claisen rearrangement for construction of the carbon skeleton of their side chains. These compounds (**13** and **17**) elicited a rise in serum calcium, but not in serum inorganic phosphorus in rats. In a bioassay for alkaline phosphatase, they were found to show much weaker activity than 1α-hydroxy vitamin D_3 (**5**).

Keywords——1α,25-dihydroxyvitamin D_3; 1α-hydroxyvitamin D_3; 1α-hydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3; 1α,25-dihydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3; orthoester Claisen rearrangement; serum calcium; serum inorganic phosphorus; alkaline phosphatase activity

Vitamin D_3 is converted into the hormonal 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) (**1**) before eliciting its biological function.[1] Since its discovery, much effort has been directed to synthesizing analogues of **1** in order to obtain higher activity or modified actions as compared with $1,25(OH)_2D_3$ (**1**).[2] We have reported 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (**2**)[3] and 26, 26, 26, 27, 27, 27-hexafluoro-1α,25-dihydroxyvitamin D_3 (**3**)[4] which were blocked by the fluorine for 24- and 26-hydroxylation (the deactivation step of **1**). These fluoro compounds were found to be 5—10 times more active than the natural $1,25(OH)_2D_3$ (**1**), probably because of slower metabolism.[5] Recently, we have also reported that 1α,25-dihydroxy-26,27-dimethylvitamin D_3 (**4**) was much more active than $1,25(OH)_2D_3$ (**1**).[6] On the other hand, 1α-hydroxyvitamin D_3 (**5**), a synthetic analogue of **1**, is metabolized to $1,25(OH)_2D_3$ (**1**) and exhibited almost the same activity as **1**.[7] Based on the high biological activity of the 24-difluoro compound **2** and the biotransformation of **5** into **1**, we became interested in the activity of 1α-hydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 (**13**) and 1α,25-dihydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 (**17**).[8] In this paper we describe their synthesis and biological activity.

We planned to construct the side chain of **13** and **17** by means of the following sequence: Grignard reaction of the 22-aldehyde **6**, orthoester Claisen rearrangement, reduction, introduction of a hydroxyl group at the C-25 position in the case of preparation of **17**, and finally formation of the vitamin D analogues **13** and **17** *via* introduction of a 5,7-diene function, followed by photochemical and thermal isomerization.

Our starting material for the target compounds (**13** and **17**) was 1α,3β-bismethoxymethoxypregn-5-ene-20*S*-carbaldehyde (**6**),[6] synthesized from dinorcholenic acid. Treatment of **6** with 1.5 eq of 2-methylpropenylmagnesium bromide gave the allylic alcohol **7** in 83% yield. The mixture of the C-22 epimers **7** was used directly in the ensuing orthoester Claisen rearrangement reaction. The reaction of **7** in refluxing xylene with an excess of triethyl



orthopropionate was carried out in the presence of a catalytic amount of propionic acid. The ethoxycarbonyl group of the resulting 22*E*-dehydro-24,24-dimethyl ester **8**, obtained in 88% yield, was converted into a methyl group by the following successive reactions; lithium aluminium hydride reduction, methanesulfonylation to the sulfonate **9**, and lithium triethylborohydride reduction.[9] Subsequent acid hydrolysis gave 24,24-dimethylcholesta-5,22*E*-diene-1α,3β-diol (**10**) in 54% overall yield from **8**.

Transformation of the diacetate **11** into the vitamin D analogue **13** was carried out as follows. Bromination at C-7 of **11** with *N*-bromosuccinimide was followed by dehydrobromination with tetra-*n*-butylammonium fluoride to give a mixture of the 4,6- and 5,7-diene. Saponification of the mixture with 5% potassium hydroxide in methanol, followed by preparative thin layer chromatography (TLC) provided the pure 5,7-diene **12** in 35% yield. This was irradiated with ultraviolet (UV) light through a Vycor filter in a mixed solvent (benzene–ethanol, 2 : 1) at 0 °C for 5 min and the resulting mixture containing previtamin D was refluxed for 1 h. The target vitamin **13** was isolated by preparative TLC in 23% yield.

We next synthesized the 25-hydroxylated vitamin D_3 **17**. Attempted hydroxylation at the C-25 position of the ester **8** with lithium diisopropylamide and oxygen at −78 °C and then triethyl phosphite was unsuccessful, probably because of the steric hindrance.[10] Thus, we adopted another method *via* the 25-ene compound **14**. Preparation of **14** was effected in 66% yield from the sulfonate **9** by the following successive reactions; displacement reaction with phenylselenyl anion prepared from diphenyl diselenide and sodium borohydride, oxidation with 30% hydrogen peroxide, and fragmentation by heating. Introduction of the 25-hydroxyl group into **14** by oxymercuration–demercuration reaction was fruitless. However, selective epoxidation at the C-25 double bond of **14** with *m*-chloroperbenzoic acid was achieved at 0 °C in 32% yield, along with 39% recovery of **14**. The other by-products isolated were the 5,6-monoepoxide (14%) and the 5,6- and 25, 26-diepoxide (10%). Reduction of the resulting 25,26-monoepoxide with lithium aluminium hydride was followed by removal of the protecting group to afford 24,24-dimethylcholesta-5,22*E*-diene-1α,3β,25-triol (**15**) in 92% yield.[11] Transformation of the diacetate **16** into the second target molecule **17** was accomplished *via* the 5,7-diene as described for **13**.

The synthetic vitamin D_3 analogues **13** and **17** exhibited λ_{max} of 265 nm and λ_{min} of 228 nm in their UV spectra. Their proton nuclear magnetic resonance (^{1}H-NMR) (400 MHz) spectra confirmed the presence of the vitamin D triene systems, *viz.* by the 6, 7, and 19 proton signals and also the 22*E*-geometry ($J = 15.9$ Hz) of the side chains. The mass spectra also supported the structures of **13** and **17**. The homogenity of **13** and **17** was confirmed by high-performance liquid chromatographic analysis.

The biological activities of the synthetic vitamin D_3 analogues **13** and **17** were examined using three different kinds of bioassays (Table I). Increases of serum calcium concentrations in

TABLE I. Increases in Serum Calcium and Inorganic Phosphorus Concentrations and Decrease in Alkaline Phosphatase Activity in Response to 1α-OH-24,24-Me_2-Δ^{22}-D_3 (**13**), 1α,25-$(OH)_2$-24,24-Me_2-Δ^{22}-D_3 (**17**), and 1α-OH-D_3 (**5**)

Compound given	Amount of compound	Serum calcium (mg/100 ml)	Serum inorganic phosphorus (mg/100 ml)	Alkaline phosphatase activity (IU/l)
Ethanol	—	8.67±0.35	8.99±0.26	61.2±4.5
1α-OH-24,24-Me_2-Δ^{22}-D_3 (**13**)	3250 pmol/rat	9.20±0.13	8.84±0.24	58.2±4.0
1α,25-$(OH)_2$-24,24-Me_2-Δ^{22}-D_3 (**17**)	3250 pmol/rat	9.40±0.18	8.86±0.20	54.8±5.9
1α-OH-D_3 (**5**)	3250 pmol/rat	9.99±0.09[a]	10.40±0.52[b]	49.2±3.8

The bioassays were carried out according to the published methods.[5,12] Significance of difference *a*) $p<0.01$, *b*) $p<0.05$.

response to 3250 pmol/rat of **13** and **17** were slightly smaller than those in response to the same dosage of 1α-OH D_3 (**5**). Neither **13** nor **17** increased serum inorganic phosphorus concentrations at a dosage of 3250 pmol/rat. Thus, these dimethyl compounds **13** and **17** were found to possess a discriminating action. In the alkaline phosphatase activity test, compound **13** was inactive. However, its 25-hydroxylated counterpart **17** was found to be slightly active.

Experimental

Melting points were determined on a hot stage microscope and are uncorrected. UV spectra were obtained in ethanol solution with a Shimadzu UV-200 double beam spectrometer. ^{1}H-NMR spectra were taken with a Hitachi R-24A spectrometer unless otherwise noted. All ^{1}H-NMR spectra were taken in deuteriochloroform solution with tetramethylsilane as an internal standard. Electron impact mass spectra (EI-MS) were obtained with a Hitachi M-80 mass spectrometer at 70 eV. Column chromatography was done on silica gel (E. Merck, 70—230 mesh). Preparative TLC was carried out on precoated plates of silica gel (E. Merck, Silica gel 60 F_{254}, 20 cm × 20 cm, 0.25 mm thickness). High-performance liquid chromatography (HPLC) was run with a Shimadzu LC-3A liquid chromatograph. The usual work-up refers to dilution with water, extraction with an organic solvent indicated in parenthesis, washing of the extract to neutrality, drying over $MgSO_4$, filtration, and removal of the solvent under reduced pressure. The following abbreviations are used: THF, tetrahydrofuran; EtOAc, ethyl acetate; ether, diethyl ether.

22ξ-Hydroxy-1α,3β-bismethoxymethoxy-26,27-dinorergosta-5,23-diene (7)——The 22-aldehyde **6**[6] (400 mg, 0.922 mmol) in THF (7 ml) was treated with 1.5 eq of 2-methylpropenylmagnesium bromide THF solution at room temperature. The mixture was stirred for 30 min. The usual work-up (ether) gave a crude product (423 mg), which was applied to a column of silica gel (30 g). Elution with hexane–EtOAc (3 : 1) gave the allylic alcohol **7** (377 mg, 83%), mp 161—163 °C (hexane–EtOAc). ^{1}H-NMR δ: 0.69 (3H, s, 18-H_3), 1.02 (3H, s, 19-H_3), 1.66 (3H, d, J=1 Hz, 25-H_3), 1.72 (3H, d, J=1 Hz, 28-H_3), 3.36 (3H, s, –OCH_3), 3.40 (3H, s, –OCH_3), 3.70 (1H, m, 1β-H), 4.68 (2H, s, 3β-OCH_2O–), 4.64 (2H, ABq, J=7 Hz, J_{AB}=11 Hz, 1α-OCH_2O–), 5.23 (1H, m, 23-H), 5.52 (1H, m, 6-H). *Anal.* Calcd for $C_{30}H_{50}O_5$: C, 73.43; H, 10.27. Found: C, 73.39: H, 10.19.

1α,3β-Bismethoxymethoxy-24,24-dimethylcholesta-5,22*E*-dien-26-oic Acid Ethyl Ester (8)——A mixture of the allylic alcohol **7** (352 mg, 0.718 mmol), ethyl orthopropionate (2 ml), propionic acid (3 drops), and xylene (6 ml) was refluxed for 2 h. Removal of the solvent gave the residue, which was applied to a column of silica gel (30 g). Elution with hexane–EtOAc (5 : 1) gave the ester **8** (362 mg, 88%), mp 104—105 °C (hexane). ^{1}H-NMR δ: 0.70 (3H, s, 18-H_3), 1.23 (3H, t, J=8 Hz, –OCH_2CH_3), 3.36 (3H, s, –OCH_3), 3.40 (3H, s, –OCH_3), 3.70 (1H, m, 1β-H), 4.10 (2H, q, J=8 Hz, –OCH_2CH_3), 4.66 (2H, s, 3β-OCH_2O–),4.64 (2H, ABq, J=7 Hz, J_{AB}=11 Hz, 1α-OCH_2O–), 5.25 (2H, m, 22-H, 23-H), 5.52 (1H, m, 6-H). *Anal.* Calcd for $C_{35}H_{58}O_6$: C, 73.13; H, 10.17. Found: C, 73.22; H, 10.03.

1α,3β-Dihydroxy-24,24-dimethylcholesta-5,22*E*-diene (10)——The ester **8** (140 mg, 0.244 mmol) in THF (4 ml) was treated with lithium aluminium hydride (15 mg, 0.395 mmol) at room temperature for 16 h. The usual work-up (ether) gave the 26-ol (130 mg), which in pyridine (2 ml) was treated with methanesulfonyl chloride (0.1 ml) at room temperature for 1.5 h. The usual work-up (EtOAc) gave the 26-sulfonate **9** (145 mg). ^{1}H-NMR δ: 0.71 (3H, s, 18-H_3), 2.95 (3H, s, mesyl), 3.35 (3H, s, –OCH_3), 3.39 (3H, s, –OCH_3), 3.70 (1H, m, 1β-H), 3.93 (1H, d, J=10 Hz, 26-H), 4.35 (1H, dd, J=10, 4 Hz, 26-H), 4.64 (2H, ABq, J=7 Hz, J_{AB}=11 Hz, 1α-OCH_2O–), 4.66 (2H, s, 3β-OCH_2O–), 5.20 (2H, m, 22-H, 23-H), 5.51 (1H, m, 6-H). The sulfonate **9** (145 mg) in THF (4 ml) was treated with lithium triethylborohydride (1 ml, 1 mmol) at 60 °C for 30 min. The usual work-up (EtOAc) gave a crude product, which in THF (5 ml) was treated with 6 N HCl (3 ml) at 60 °C for 40 min. The usual work-up (dichloromethane) and chromatography on silica gel (30 g) eluting with hexane–EtOAc (2 : 3) gave the 1,3-diol **10** (52 mg, 54% from **8**), mp 180—182 °C (hexane–EtOAc). ^{1}H-NMR δ: 0.70 (3H, s, 18-H_3), 0.80 (6H, d, J=6 Hz, 26-H_3, 27-H_3), 0.90 (6H, s, 24-CH_3), 0.98 (3H, d, J=6 Hz, 21-H_3), 1.02 (3H, s, 19-H_3), 3.82 (1H, m, 1β-H), 3.95 (1H, m, 3α-H), 5.30 (2H, m, 22-H, 23-H), 5.52 (1H, m, 6-H). EI-MS *m/z*: 428 (M^+), 410, 392, 385, 367, 349, 289, 271, 253, 139, 97.

1α,3β-Diacetoxy-24,24-dimethylcholesta-5,22*E*-diene (11)——The 1,3-diol **10** (45 mg, 0.105 mmol) in pyridine (1 ml) was treated with acetic anhydride (1 ml) and 4-dimethylaminopyridine (10 mg) at room temperature for 17 h. The usual work-up (EtOAc) and chromatography on silica gel (10 g) eluting with hexane–EtOAc (10 : 1) gave the diacetate **11** (47 mg, 87%), amorphous. ^{1}H-NMR δ: 0.68 (3H, s, 18-H_3), 0.80 (6H, d, J=6 Hz, 26-H_3, 27-H_3), 0.90 (6H, s, 24-CH_3), 0.96 (3H, d, J=6 Hz, 21-H_3), 1.07 (3H, s, 19-H_3), 2.02 (3H, s, acetyl), 2.05 (3H, s, acetyl), 4.60—5.30 (4H, m, 1β-H, 3α-H, 22-H, 23-H), 5.52 (1H, m, 6-H).

1α,3β-Dihydroxy-24,24-dimethylcholesta-5,7,22*E*-triene (12)——The diacetate **11** (18 mg, 35.2 μmol) in carbon tetrachloride (2 ml) was treated with *N*-bromosuccinimide (6.5 mg, 36.5 mol) under reflux for 20 min. After the mixture had been cooled to 0 °C, the precipitate was filtered off. The filtrate was concentrated below 40 °C to give the crude 7-bromo compound. A solution of this product in THF (4 ml) was treated with tetra-*n*-butylammonium bromide (10 mg) at room temperature for 50 min and then with tetra-*n*-butylammonium fluoride (0.1 ml, 0.1 mmol) at room temperature under argon for 30 min. The usual work-up (EtOAc) gave a mixture of the 4,6-diene and the desired 5,7-diene. The mixture in acetone (10 ml) was treated with *p*-toluenesulfonic acid (10 mg) at room temperature

in the dark for 14 h in order to decompose the 4,6-diene. The usual work-up (EtOAc) gave a crude product, which was applied to three preparative TLC plates. The plates were developed four times with hexane–EtOAc (10 : 1). The band of *Rf* 0.55 was scrapped off and eluted with EtOAc. Removal of the solvent gave the 5,7-diene diacetate (7.5 mg, 42%). UV λ_{max}: 294, 282, 272 nm. The acetate (7.5 mg) in THF (4 ml) was treated with 5% KOH–MeOH (2 ml) at room temperature for 14 h. The usual work-up (EtOAc) gave a crude product, which was applied to three preparative TLC plates; these were developed four times with hexane–EtOAc (2 : 1). The band of *Rf* 0.28 was scrapped off and eluted with EtOAc. Removal of the solvent provided the pure 5,7-diene **12** (5.2 mg, 35% from **11**). UV λ_{max}: 294, 282, 272 nm.

1α-Hydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 (13)——The 5,7-diene **12** (3.3 mg, 7.75 μmol) in benzene (90 ml) and ethanol (40 ml) was irradiated with a medium-pressure mercury lamp through a Vycor filter at 0 °C under argon for 5 min. The reaction mixture (containing previtamin) was refluxed under argon for 1 h. Removal of the solvent gave a crude product, which was applied to three preparative TLC plates; these were developed three times with benzene–EtOAc (2 : 1). The band of *Rf* 0.24 was scrapped off and eluted with EtOAc. Removal of the solvent gave the vitamin D_3 analogue **13** (0.75 mg, 23%). UV λ_{max}: 265 nm, λ_{min}: 228 nm. ^{1}H-NMR (400 MHz) δ: 0.56 (3H, s, 18-H_3), 0.81 (6H, d, J=6.8 Hz, 26-H_3, 27-H_3), 0.89 (6H, s, 24-CH_3), 1.01 (3H, d, J=6.6 Hz, 21-H_3), 4.23 (1H, m, $W_{1/2}$ =18.4 Hz, 3α-H), 4.43 (1H, m, $W_{1/2}$=16.9 Hz, 1β-H), 5.00 (1H, br s, $W_{1/2}$=3.2 Hz, 19-H), 5.10 (1H, dd, J=15.9, 8.6 Hz, 22-H), 5.27 (1H, d, J=15.9 Hz, 23-H), 5.32 (1H, br s, $W_{1/2}$=3.2 Hz, 19-H), 6.02 (1H, d, J=11.5 Hz, 7-H), 6.38 (1H, d, J=11.5 Hz, 6-H). EI-MS *m/z*: 426 (M^+), 408 (M^+-18), 390 ($M^+-2\times18$), 383 (M^+-43, C_{24}–C_{25} cleavage), 365 (383−18), 347 (383−2×18), 287 (M^+-139, $C_{17}-C_{20}$ cleavage), 269 (287−18), 251 (287−2×18), 152 (C_7–C_8 cleavage), 134 (152−18, base peak), 116 (152−2×18).

1α,3β-Bismethoxymethoxy-24,24-dimethylcholesta-5,22*E*,25-triene (14)——Sodium borohydride (100 mg, 2.63 mmol) was added to a suspension of diphenyl diselenide (410 mg, 1.31 mmol) and ethanol (10 ml), and the mixture was stirred at room temperature under argon atmosphere for 10 min. The mesylate **9** (106 mg, 0.174 mmol) in THF (5 ml) was added to this selenide anion solution and the mixture was refluxed for 1 h. The usual work-up (ether) gave a crude product, which was applied to a column of silica gel (20 g). Elution with hexane–EtOAc (5 : 1) provided the selenide (105 mg, 90%). A mixture of the selenide, THF (2.5 ml), ethanol (5 ml), and 30% H_2O_2 (0.15 ml) was stirred at 50 °C for 22 h. The usual work-up (ether) gave a crude product, which was applied to a column of silica gel (10 g). Elution with hexane–EtOAc (10 : 1) provided the triene **14** (59 mg, 66%) as an oil. ^{1}H-NMR δ: 0.70 (3H, s, 18-H_3), 0.98 (3H, d, J=6 Hz, 21-H_3), 1.02 (3H, s, 19-H_3), 1.10 (6H, s, 24-CH_3), 1.67 (3H, s, 27-H_3), 3.83 (1H, m, 3α-H), 4.50—4.85 (6H, m, 27-H_2, 1α-OCH_2O–, 3β-OCH_2O–), 5.22 (2H, m, 22-H, 23-H), 5.52 (1H, m, 6-H). EI-MS *m/z*: 482 (M^+-CH_3OH), 452, 420, 392, 390, 255, 253, 137.

1α,3β,25-Trihydroxy-24,24-dimethylcholesta-5,22*E*-diene (15)——*m*-Chloroperbenzoic acid (20 mg, 0.116 mmol) was added to a solution of the triene **14** (54 mg, 0.105 mmol) in chloroform (5 ml), and the mixture was stirred at 0 °C for 30 min. Then calcium hydroxide (0.2 g) was added to the reaction mixture, and stirring was continued for 30 min. The resulting precipitate was filtered off. The filtrate was evaporated to give the residue, which was applied to a column of silica gel (10 g). Elution with hexane–EtOAc (10 : 1) recovered triene **14** (21 mg, 39%). Further elution with the same solvent provided the 25,26-monoepoxide (18 mg, 32%) as an oil. ^{1}H-NMR δ: 0.69 (3H, s, 18-H_3), 0.99 (6H, s, 24-CH_3), 1.03 (3H, d, J=6 Hz, 21-H_3), 1.24 (3H, s, 27-H_3), 3.35 (3H, s, –OCH_3), 3.39 (3H, s, –OCH_3), 3.70 (1H, m, 1β-H), 3.83 (1H, m, 3α-H), 4.67 (2H, s, 3β-OCH_2O–), 4.67 (2H, ABq, J=7 Hz, J_{AB}=11 Hz, 1α-OCH_2O–), 5.28 (2H, m, 22-H, 23-H), 5.52 (1H, m, 6-H). Further elution with hexane–EtOAc (5 : 1) gave the 5,6-monoepoxide (8 mg, 14%) and the 5,6- and 25,26-diepoxide (6 mg, 10%).

A solution of the 25,26-monoepoxide (12 mg, 22.6 μmol) in THF (2 ml) was treated with lithium aluminium hydride (5 mg, 0.132 mmol) at room temperature for 1 h. The usual work-up (ether) gave a crude product, which was applied to a column of silica gel (6 g). Elution with hexane–EtOAc (5 : 1) gave the 25-ol (11 mg, 92%) as an oil. ^{1}H-NMR δ: 0.70 (3H, s, 18-H_3), 1.02 (3H, d, J=6 Hz, 21-H_3), 1.02 (6H, s, 24-CH_3), 1.17 (6H, s, 26-H_3, 27-H_3), 3.35 (3H, s, –OCH_3), 3.39 (3H, s, –OCH_3), 3.73 (1H, m, 1β-H), 3.80 (1H, m, 3α-H), 4.67 (2H, s, 3β-OCH_2O–), 4.67 (2H, ABq, J=7 Hz, J_{AB}=11 Hz, 1α-OCH_2O–), 5.38 (2H, m, 22-H, 23-H), 5.52 (1H, m, 6-H). The product was converted, as described for **10**, into the triol **15** (11 mg, 99%), mp 175—176 °C (hexane–EtOAc). ^{1}H-NMR δ: 0.67 (3H, s, 18-H_3), 1.01 (9H, s, 19-H_3, 24-CH_3), 1.02 (3H, d, J=6 Hz, 21-H_3), 1.16 (6H, s, 26-H_3, 27-H_3), 3.80 (1H, m, 1β-H), 3.87 (1H, m, 3α-H), 5.33 (2H, m, 22-H, 23-H), 5.50 (1H, m, 6-H). EI-MS *m/z*: 426 (M^+-H_2O), 408, 390, 386, 368, 350, 271, 253, 137, 122, 96, 59.

1α,3β-Diacetoxy-25-hydroxy-24,24-dimethylcholesta-5,22*E*-diene (16)——The triol **15** (10 mg, 22.5 μmol) was converted, as described for **11**, into the diacetate **16** (11.5 mg, 97%) as an oil. ^{1}H-NMR δ: 0.68 (3H, s, 18-H_3), 0.98 (3H, d, J=6 Hz, 21-H_3), 1.02 (6H, s, 24-CH_3), 1.09 (3H, s, 19-H_3), 1.17 (6H, s, 26-H_3, 27-H_3), 2.02 (3H, s, acetyl), 2.05 (3H, s, acetyl), 4.96 (1H, m, 3α-H), 5.06 (1H, m, 1β-H), 5.36 (2H, m, 22-H, 23-H), 5.52 (1H, m, 6-H).

1α,25-Dihydroxy-24,24-dimethyl-22*E*-dehydrovitamin D_3 (17)——The 5,22-diene **16** (11 mg, 20.8 μmol) was converted, as described for **12**, into the 5,7,22-triene (1.6 mg, 17%). UV λ_{max}: 293, 282, 271 nm. The triene (1.2 mg, 2.72 μmol) was converted, as described for **13**, into the vitamin D_3 analogue **17** (0.23 mg, 19%). The spectral data were as follows; UV λ_{max}: 265 nm, λ_{min}: 228 nm. ^{1}H-NMR (400 MHz) δ: 0.56 (3H, s, 18-H_3), 1.02 (3H, s, 24-CH_3), 1.03 (3H, s, 24-CH_3), 1.16 (6H, s, 26-H_3, 27-H_3), 4.23 (1H, m, 3-H), 4.43 (1H, m, 1-H), 5.00 (1H, br s, 19-H), 5.28 (1H, dd,

$J=15.9$, 8.6 Hz, 22-H), 5.32 (1H, br s, 19-H), 5.69 (1H, d, $J=15.9$ Hz, 23-H), 6.02 (1H, d, $J=11.5$ Hz, 7-H), 6.38 (1H, d, $J=11.5$ Hz, 6-H). EI-MS *m/z*: 424 (M^+-18), 406 ($M^+-2\times18$), 383 (M^+-59, C_{24}–C_{25} cleavage), 365 (383 − 18), 347 (383 − 2 × 18), 287 (M^+-155, C_{17}–C_{20} cleavage), 269 (287 − 18), 251 (287 − 2 × 18), 155 (side chain), 152 (C_7–C_8 cleavage), 134 (152 − 18, base peak), 116 (152 − 2 × 18), 96 (155 − 59), 59 (C_{24}–C_{25} cleavage).

References and Notes

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